

Explanation of data presented in tables S1, S2 and S3

Tables S1, S2 and S3 show the results of the Gene Set Analysis (GSA). GSA was performed according to Efron and Tibshirani (Efron B, Tibshirani R. On testing the significance of sets of genes. *Ann Appl Stat.* 2006;1:107-129). In contrast to single gene analysis, GSA assesses the statistical significance of a group of genes in its entirety. The predefined groups of genes that were investigated with GSA were derived from the Biological process Gene Ontology categories (<http://www.geneontology.org/>). Table S1 shows GSA results for the comparison "severe stress/control"; table S2 presents GSA results for the contrast "mild-stress + morphine/mild-stress"; table S3 lists GSA results for the contrast "severe stress + morphine/mild-stress". The information presented in columns A through G in tables S1, S2 and S3 is as follows:

Column A shows the Gene Ontology (<http://www.geneontology.org/>) category number.

Column B provides the enrichment score that was calculated using the GSA method. A positive score indicates that the maxmean statistic is larger in absolute value in the experimental group that is in the numerator relative to the group that is in the denominator. For example, Table 1A lists "behavioral fear response" in row 10 with a positive enrichment score. This means that overall the genes in this gene set showed a more prominent up-regulation in the numerator group (severe stress) relative to the denominator group (control). A negative score indicates that the maxmean statistic is larger in absolute value in the experimental group that is in the denominator relative to the group that is in the numerator. For example, Table 1B lists "endosome to lysosome transport" in row 4 with a negative enrichment score. This means that overall the genes in this gene set showed a more prominent down-regulation in the numerator group (severe stress) relative to the denominator group (control).

Column C provides the p-value generated with the GSA algorithm. p-values and FDRs are generated with the restandardization method in the GSA algorithm (for detailed explanation see Efron B, Tibshirani R. On testing the significance of sets of genes. *Ann Appl Stat.* 2006;1:107-129). p-values of zero are below the smallest p-value value that can be achieved given 3 biological replicates used in the permutation approach in calculating the null distribution of the enrichment.

Column D provides the False Discovery rate (FDR) that was generated with the GSA algorithm. FDR values are generated with the restandardization method in the GSA algorithm (for detailed explanation see Efron B, Tibshirani R. On testing the significance of sets of genes. *Ann Appl Stat.* 2006;1:107-129). FDR values of zero are below the smallest FDR value that can be achieved given 3 biological replicates used in the permutation approach in calculating the null distribution of the enrichment.

Column E shows the Gene Set Length, which is the number of genes in the gene set.

Column F lists the name of the gene set assigned by the Gene Ontology Consortium (<http://www.geneontology.org/>).

Column G lists the gene symbols of all the genes that make up the gene set.

Table S1A. Gene sets up-regulated by severe stress

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0030036	0.1860506	0	0	294	actin cytoskeleton organization and biogenesis	XIRP1,DIAP1,ARPC3,WASF1,BCL6,SPNB3,NEDD9,PFN1,ARPC2,MYH6,PDE4DIP,NEBL,PTK2B,ELN,SYNGAP1,MYH11,ACTR3B,SPNB2,RHOU,WASF3,RAC3,MYH2,CSR1,LMO7,NF2,PPP1R9B,EPB4.9,CAP2,SPNA2,MYBPC3,FSCN1,FMN2,CAPG,NPHP1,AMOT,DRST,TMOD2,WAS,SSH1,GAS7,CDC42BPB,SHROOM1,ARHGEF10L,ABL2,PDPK1,ASB15,ARHGEF17,FGD3,USH1C,CAPN3,GRID2IP,ABI2,BMP10,NEB,TMSB4X,MYL2,EVL,LIMA1,PDGFB,RHOQ,MET,RHOF,FHOD3,TAPBP,PFN3,PDLIM3,TRIOBP,FGD1,ASZ1,MRAS,GHSR,LCP1,ARHGEF11,ACTC1,LTB,CFL1,CDC42EP2,TTN,NCKAP1,CENTG1,CDC42BPA,BIN3,RAC2,FMN1,NRAP,NISCH,PRKCZ,EPB4.1L1,XIRP2,OBSL1,EPB4.1,NF1,PAFAH1B1,TCAP,TMSB10,PARVA,FHL3,ESPN,SSH2,DYNLL1,TNFAIP1,SSX2IP,CORO1A,EHD2,AVIL,PDGFA,SPNA1,TMOD1,ARPC5,WNT2,CORO2B,NCK2,TPM1,RPL9,TRIP10,LIMK1,EZR,CAPZA3,CDC42EP5,DBN1,RND1,CDC88A,PLS3,FMNL3,LST1,DBNL,FAT1,DIAP3,DIAP2,TSC1,CAV2,ACTR3,SHROOM3,PPP1R9A,VILL,4933400A11RIK,TSC2,FGD5,CNN1,NPHP4,SHROOM2,KRT19,WIPF1,BCAR1,CAP1,CAPZA2,MTSS1,CXCL1,FMNL1,DOCK2,GHRL,AKAP2,DSTN,ARHGAP26,DDR1,CALR,FGD4,FSCN2,DAAM1,PLEK2,ARPC4,ATP6V1G2,SDCBP,KRT8,WDR46,FHOD1,CAPZA1,PRKG1,RHOA,ATP2C1,SPNB1,MYH10,LATS1,B3GALT4,DLCL1,ARHGEF2,CDC42BPG,S100A9,POU5F1,WASL,NUAK2,PLA2G1B,PSDC2,ARPC1B,ARF6,ACTN4,PACSIN2
GO:0030048	0.527958	0	0	29	actin filament-based movement	MYL6B,MYH6,MYO5A,MYH2,MYL1,MYBPC3,WAS,APBB1,APBB2,EVL,ACTC1,MYO1E,MYRIP,MYH4,MYH14,WIPF1,MYL6,MYH10,MYO7A,MYH7,MYLK2,MYL7,WASF2,MYH3,TNNT2,MYO9B,MYH9,MYO6,TNNC1
GO:0030029	0.205956	0	0	314	actin filament-based process	XIRP1,MYL6B,DIAP1,ARPC3,WASF1,BCL6,SPNB3,NEDD9,PFN1,ARPC2,MYH6,PDE4DIP,NEBL,PTK2B,ELN,SYNGAP1,MYH11,ACTR3B,MYO5A,SPNB2,RHOU,WASF3,RAC3,MYH2,MYL1,CSR1,LMO7,NF2,PPP1R9B,EPB4.9,CAP2,SPNA2,MYBPC3,FSCN1,FMN2,CAPG,NPHP1,AMOT,DST,TMOD2,WAS,SSH1,GAS7,CDC42BPB,SHROOM1,ARHGEF10L,APBB1,ABL2,PDPK1,FLNC,ASB15,ARHGEF17,FGD3,ENAH,USH1C,CAPN3,APBB2,GRID2IP,ABI2,BMP10,NEB,TMSB4X,MYL2,EVL,LIMA1,PDGFB,RHOQ,MET,RHOF,FHOD3,TAPBP,PFN3,PDLIM3,TRIOBP,FGD1,ASZ1,MRAS,GHSR,LCP1,ARHGEF11,ACTC1,LTB,CFL1,CDC42EP2,TTN,NCKAP1,CENTG1,CDC42BPA,BIN3,RAC2,FMN1,NRAP,NISCH,PRKCZ,EPB4.1L1,XIRP2,OBSL1,MYO1E,EPB4.1,NF1,PAFAH1B1,TCAP,ABCC9,TMSB10,PARVA,FHL3,ESPN,SSH2,DYNLL1,MYRIP,TNFAIP1,SSX2IP,MYH4,CORO1A,EHD2,AVIL,PDGFA,SPNA1,MYH14,TMOD1,ARPC5,WNT2,CORO2B,NCK2,TPM1,RPL9,TRIP10,LIMK1,EZR,CAPZA3,CDC42EP5,DBN1,RND1,CCDC88A,PLS3,FMNL3,LST1,DBNL,FAT1,DIAP3,DIAP2,TSC1,CAV2,ACTR3,SHROOM3,PPP1R9A,VILL,4933400A11RIK,TSC2,FGD5,CNN1,NPHP4,SHROOM2,KRT19,WIPF1,BCAR1,CAP1,CAPZA2,MTSS1,CXCL1,FMNL1,DOCK2,GHRL,AKAP2,DSTN,ARHGAP26,DDR1,CALR,FGD4,FSCN2,DAAM1,PLEK2,ARPC4,ATP6V1G2,SDCBP,KRT8,WDR46,FHOD1,MYL6,CAPZA1,PRKG1,RHOA,ATP2C1,SPNB1,MYH10,LATS1,B3GALT4,DLCL1,ARHGEF2,CDC
GO:0008154	0.3868607	0	0	79	actin polymerization and/or depolymerization	DIAP1,ARPC3,WASF1,SPNB3,PFN1,ARPC2,ELN,ACTR3B,SPNB2,WASF3,EPB4.9,SPNA2,CAPG,WAS,GAS7,ASB15,ENAH,ABI2,TMSB4X,EVL,LIMA1,MET,TRIOBP,ASZ1,GHSR,CFL1,CDC42EP2,FMN1,TMSB10,CORO1A,AVIL,SPNA1,ARPC5,WNT2,NCK2,TPM1,CAPZA3,CDC42EP5,DBNL,DIAP2,CAV2,ACTR3,VILL,SHROOM2,WIPF1,CAPZA2,MTSS1,GHRL,DSTN,ARPC4,CAPZA1,RHOA,SPNB1,LATS1,WASL,ARPC1B,ARF6,ARPC1A,RAC1,ARPC5L,GSN,VIL1,ANG,NCK1,CAPZB,ARHGAP6,RASA1,CLEC2I,SVIL,CXCL12,CIT,SCIN,MAP3K1,TMOD3,RDX,CTTNBP2,TTLL3,PFN2,DLG1
GO:0033275	0.8903944	0	0	12	actin-myosin filament sliding	MYL6B,MYH6,MYH2,MYL1,MYBPC3,MYH4,MYL6,MYH7,MYLK2,TNNT2,MYO9B,TNNC1
GO:0050851	0.2266374	0	0	39	antigen receptor-mediated signaling pathway	BCL10,THY1,CBLB,SLA2,FOX3,TRAT1,TRAF6,ZAP70,PTPN6,UBE2N,CACNB3,PTPN22,IGH-6,LYN,LAX1,SPG21,CD3E,MAPK1,PAWR,BCAR1,ELF1,PSEN1,CD79B,CACNB4,LCK,MAP3K7,CD79A,FYN,NFAM1,UBASH3A,SYK,PTPRC,SH2B2,CD19,MALT1,IKBKG,CLEC2I,PSEN2,LAT2
GO:0031103	0.470885	0	0	19	axon regeneration	KLK8,CHL1,RTN4RL1,RTN4RL2,NTRK3,CHST3,APOA1,NEFL,FXR1,MMP2,MIF,CSPG5,BCL2,VCAN,CTNNA1,APOE,JAK2,LAMB2,SLPP1
GO:0007409	0.3864916	0	0	229	axonogenesis	KLK8,KALRN,SLIT1,NRCAM,CACNA1A,NRP2,ALS2,L1CAM,SLIT3,UNC5C,PVRL1,CHL1,RELN,RTN4RL1,TIAM1,THY1,SYNGAP1,NGF,ROBO1,LMTK2,SLITRK3,EPHA4,NKX2-9,ARTN,NR2E1,RTN4RL2,NRXN1,DPYSL5,PRKCA,SLIT2,RGNEF,POU4F1,CCK,EPHB2,DCC,ANK3,MYCBP2,VAX2,UNC5A,UNC5B,ULK1,FEZF1,POU4F3,RAB3A,MAPT,NTRK3,ISL2,POU3F2,APBB1,NRP1,DPYSL3,RTN4R,ENAH,CNTN2,APBB2,CHST3,PIP5K1C,KIF5C,ERBB2,SEMA5A,APOA1,DCX,ERBB3,EVL,ULK2,SEMA6C,ETV1,DSCAML1,TOP2B,TGFB2,CDH2,SNAP25,FGF8,KLF7,NRN1,EFNB1,PRRX1,EGR2,LHX4,TTL,CDK5R1,MAPK8IP3,BDNF,BAI1,ATOH1,NTNG2,DKL1,PAR6B,UBB,PAFAH1B1,RTN4,POU4F2,GLI2,ABLIM1,STMN1,ACTB,TNR,IGF1R,GFRA3,NTNG1,STK11,EPHA7,BCL11B,NEFL,SLITRK1,CACNA1F,GDF7,EPHB3,TBR1,FOXG1,NTN2,LIMK1,WNT3A,AMIGO1,LHX3,ROBO2,RYK,NUMB,FEZF2,SEMA3B,RXRA,PTPRZ1,SEMA4F,ETV4,PTPN11,PSEN1,NKX2-1,CXCR4,PTK2,TNN,NDEL1,RUNX3,CELSR3,NRXN3,LMX1A,SLITRK6,CYFIP1,DPYSL2,NEUROG2,BAIAP2,BARHL2,WNT7A,PAR63,NFASC,SLITRK5,MMP2,BOC,MYH10,B3GNT2,MIF,CCKAR,FEZ2,HOXA2,SLITRK2,NTF3,STXBP1,FOXD1,HOXA1,CSPG5,SHH,SEMA4D,RAC1,PAX2,GBX2,PLXNA3,BCL2,VASP,APP,CHRN2,VCAN,BMPR1B,TNFRSF12A,SPON2,NOTCH1,PGRMC1,VAX1,S100B,NEFM,LRRCC4,UCHL1,EFNB3,OTX2,CTNNA1,ARX,CSPG4,CDH4,ACHE,METRN,PLXNB2,NUMBL,CREB1,NTN1,GAP43,SLITRK4,NCAM2
GO:0001662	0.8334722	0	0	17	behavioral fear response	NEUROD2,ALS2,GRIN2B,NPY2R,DRD4,CCK,GABRA5,GRM7,GRM2,HCRT,ESR2,VDAC3,BCL2,VDAC1,GRIK2,GNG7,PENK1
GO:0055013	1.0995483	0	0	10	cardiac muscle cell development	XIRP1,BMP10,MYL2,ATG7,ACTC1,TTN,ATG5,OBSL1,MYH10,MYL6B
GO:0048738	0.9575644	0	0	12	cardiac muscle development	MYH6,MYH11,CSR3,PTEN,CXADR,PLN,NKX2-5,ZFPM2,GJC1,MKL2,TBX2,TAZ

Table S1A. Gene sets up-regulated by severe stress

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0048469	0.2515819	0	0	116	cell maturation	XIRP1,NEO1,NRCAM,KCNMA1,IHH,DLG4,FZD5,MYH6,PTK2B,MYH11,BTK,FGFR1,MYBPC3,BHLHB8,GM767,ADAM12,EPAS1,GH RHR,CEBPA,LHX6,NTN4,CAPN3,GNAQ,BMP10,NEB,MECP2,MYL2,PEBP1,EPB4.2,GDF11,KCNIP2,KCNH1,INSL3,ACTC1,TTN,CAP N2,OBSL1,CLN5,TCAP,RUNX2,AGPAT6,VSX1,KLF1,GATA2,TMOD1,RXFP2,TSSK3,NTN2L,CDON,RND1,FOXA1,PPARG,FARP2,AK1 ,KRT19,IRX5,RUNX3,CTNNB1,HESS,CBFB,KRT8,IL21,AGRN,PDE3A,CDC25B,MTCH1,KCNE1,MYH10,PTH2R,CACNA1S,EPO,BCL2, APP,ACTG1,CACNA1H,ANG,DYRK1B,MYLPF,TCFCP2L1,DLG2,CSPG4,NEUURL,EREG,RET,MYOZ1,PGR,BCRA2,RP56KA2,PARK2,IT GB1,FOXO3A,GJA1,PTHR1,VEGFA,SOX10,TNNT2,KDR,FBXO5,CALCA,MAEA,SOX8,CAST,PLP1,ERCC2,TIMP1,HES1,ACTA1,DLD,M YH9,CDKN1C,LGI4,POU2F2,CCNB1,PICK1,SCLT1,SEPT4
GO:0030030	0.2588168	0	0	418	cell projection organization and biogenesis	KLK8,SIPA1L1,KALRN,SLIT1,JUB,NRCAM,BC060632,CELSR2,CACNA1A,MTAP1B,NRP2,ALS2,L1CAM,SLIT3,UNC5C,TUBB4,PVRL1, CHL1,RELN,PTK2B,RTN4RL1,TLX2,MTAP1S,TIAM1,THY1,SYNGAP1,KNDC1,NGF,ITGA8,ROBO1,LMTK2,MTAP2,SLITRK3,EPHA4,N KX2-9,ARTN,NR2E1,RTN4RL2,NRXN1,DPYSL5,RAC3,PRKCA,SLIT2,RGNEF,GPRIN1,POU4F1,WNT7B,FGFR1,GDNF,CCK,ONECUT1,EPH B2,PPP1R9B,DCC,ANK3,CAPG,PTPRF,MYCBP2,VAX2,UNC5A,UNC5B,GAS7,ULK1,FEZF1,POU4F3,RAB3A,MAPT,ATP2B2,PTEN,NT RK3,ISL2,POU3F2,APBB1,CD24A,NRP1,DPYSL3,RTN4R,FGD3,ENAH,CNTN2,APBB2,CHST3,PIP5K1C,KIF5C,ABI2,ERBB2,SEMA5A, APOA1,MECP2,DCX,ERBB3,EVL,LIMA1,GRIN3A,PDGFB,ULK2,SEMA6C,AKAP4,ETV1,LZTS1,VAV2,DSCAML1,TOP2B,AKT1,LIFR,T GFB2,FGD1,CDH2,SNAP25,APC,FGF8,SPAG16,KLF7,NRN1,ATG7,ONECUT2,CFL1,EFNB1,PRRXL1,CDC42EP2,NCKAP1,YWHAH,EG R2,MT3,NRTN,RAC2,TGFB1,LHX4,TTL,CDK5R1,MAPK8IP3,EFHD1,BDNF,BAI1,KLC3,ATOH1,NTNG2,DCLK1,PAR6B,UBB,FRAP1 ,PAK1,PAFAH1B1,RTN4,SH2B1,CLIC5,POU4F2,ALKBH1,GLI2,ABLIM1,STMN1,KIT,ACTB,RPGRI1L,TNR,IGF1R,GFRA3,PTPRK,COR O1A,NTNG1,STK11,EPHA7,TGFB3,TTC30A1,PDGFA,BCL11B,ITGA6,NEFL,SLITRK1,CACNA1F,NCK2,TSGA10,CD44,ITGB4,GDF7,EP HB3,TTC30B,TBR1,FOXG1,NTN2L,LIMK1,WNT3A,CDC42EP5,DBN1,NEURL,CCDC88A,LST1,AMIGO1,ATP7A,BBS4,LHX3,STX3,TSC
GO:0021846	0.6911606	0	0	11	cell proliferation in forebrain	EMX2,POU3F2,ZEB2,POU3F3,FGF8,CCDC100,NCOR2,TACC2,FABP7,TACC1,TACC3
GO:0016337	0.2255664	0	0	325	cell-cell adhesion	PCDH19,PCDH20,NRCAM,CLDN22,BCL10,CELSR2,RGMA,PCDH13,DAB1,CDH26,L1CAM,ICAM1,CLSTN2,UNCX,FAT4,PVRL1,CH L1,HGF,PFN1,CDSN,LGALS7,CYFIP2,RAPGEF1,THY1,ACAN,ITGA8,ROBO1,TNF,THRA,FGF4,DLG5,PCDH19,PCDH88,CADM3,TSTA 3,GATAD2A,PCDH21,CLDN16,LMO7,NF2,PCDH17,COL13A1,NPHP1,PTPRF,B4GALNT2,PCDHA4,AMIGO2,CLDN6,PKD1L1,CLSTN 1,CLDN15,ITGA4,ITGAD,NLGN2,CD24A,TRAF6,ENAH,APOA4,CHAD,OLR1,PVRL3,REG3A,CLDN10,NCAN,CDH12,CLDN14,CTNND 2,CADM2,CDH11,PKHD1,PCDH18,ASTN1,ADA,ZEB2,TCFAP2A,HECTD1,PKP2,DSG1B,NCAM1,DSCAML1,TGFB2,SELPLG,CDH2,P CDHB12,GMDS,PCDH15,CNTN3,NLGN1,COL19A1,NCKAP1,PCDH24,CDH6,CELSR1,CLDN1,DSG4,CDK5R1,CD84,PCDH1,PCDHG A12,CLDN18,PCDH84,DCHS1,OTOR,MUPCDH,COL2A1,AMIGO3,CD209D,CDH15,LAMA3,CADM1,ICAM4,CLSTN3,TGFB3,PCDH B3,JAM2,ITGA6,PCDH16,CDH20,CDH19,CD44,ALX1,PCDH14,JUP,PCDH9,MADCAM1,CDON,LMO4,CLDN2,GPR98,FAT3,AMIG O1,CD34,FAT1,BBS4,TSC1,SNAI1,FAT2,FREM1,SRC,SHROOM3,ROBO2,BARX2,DSC3,ROR2,ZAN,ADAM15,TSC2,ADAM8,CD22,N PHP4,PIK3CB,CLDN9,PDPN,CDH5,PSEN1,TWIST1,PCDH2,CLDN23,GRLF1,CLEC4E,TCAM1,PCDH89,VCAM1,PCDH17,APAF1,PK D1,CDH1,CELSR3,DSC1,CTNNB1,COL8A2,SOX9,DSC2,DSG1A,ITGA5,ITGAM,CLDN8,ICAM5,PCDH8,CTNND1,ITGAL,EMCN,DSG2, CRNN,CLDN20,CLEC7A,DSG3,CERCAM,CD40LG,CLDN7,CLDN3,PARD3,ATP2C1,COBL,PIK3R1,BOC,MYF5,DLC1,COL14A1,CDH18,
GO:0030004	0.340036	0	0	30	cellular monovalent inorganic cation homeostasis	KCNMA1,AQP11,BSND,NR3C2,NEDD4L,ATP1A3,C7,CLCN3,AGTR2,CLN5,TESC,ATP6V0C,CAR2,ATP1A4,CLN6,ATP6V1H,TRP53, LC9A8,ATP1A1,TMPRSS3,SGK1,ATP6V1B2,BCL2,PPT1,MAFG,ATP5B,ATP1A2,CAMK2D,CLN3,AGT
GO:0000904	0.3466066	0	0	282	cellular morphogenesis during differentiation	KLK8,SIPA1L1,KALRN,SLIT1,NRCAM,CELSR2,CACNA1A,NRP2,ALS2,L1CAM,SLIT3,RPGRI1L,UNC5C,PVRL1,CHL1,RELN,RTN4RL1,T LX2,MTAP1S,TIAM1,THY1,SYNGAP1,KNDC1,NGF,ROBO1,LMTK2,ESRRB,SLITRK3,EPHA4,NKX2-9,ARTN,NR2E1,RTN4RL2,NRXN1,DPYSL5,PRKCA,SLIT2,RGNEF,POU4F1,RBP3,CCK,EPHB2,DCC,ANK3,PTPRF,MYCBP2,VAX2,UNC 5A,UNC5B,GAS7,ULK1,CRB1,FEZF1,POU4F3,RAB3A,MAPT,NTRK3,ISL2,POU3F2,APBB1,NRP1,DPYSL3,RTN4R,ENAH,CNTN2,APB B2,CHST3,PIP5K1C,KIF5C,ERBB2,SEMA5A,APOA1,DCX,ERBB3,EVL,ULK2,SEMA6C,ETV1,LZTS1,DSCAML1,TOP2B,LIFR,TGFB2,CD H2,SNAP25,FGF8,KLF7,NRN1,EFNB1,PRRXL1,YWHAH,EGR2,MT3,LHX4,TTL,CDK5R1,MAPK8IP3,BDNF,BAI1,NODAL,ATOH1,NTN G2,DCLK1,PAR6B,UBB,PAFAH1B1,RTN4,POU4F2,GLI2,ABLIM1,STMN1,ACTB,TNR,IGF1R,GFRA3,NTNG1,STK11,EPHA7,BCL11B ,TUG1,NEFL,SLITRK1,CACNA1F,GDF7,EPHB3,TBR1,FOXG1,NTN2L,LIMK1,WNT3A,AMIGO1,ATP7A,BBS4,LHX3,ROBO2,RYK,NUM B,FEZF2,SEMA3B,RORB,RXRA,PTPRZ1,SEMA4F,ETV4,PTPN11,PSEN1,NKX2-1,CXCR4,PTK2,TNN,NDEL1,RUNX3,CELSR3,NRXN3,LMX1A,SLITRK6,CTNNB1,HPRT1,CYFIP1,DMD,DPYSL2,NEUROG2,BAIAP2,KR T8,BARHL2,NR2E3,WNT7A,PARD3,NFASC,SLITRK5,MMP2,BOC,MYH10,B3GNT2,MIF,CCKAR,FEZ2,HOXA2,SLITRK2,NTF3,STXBP 1,FOXD1,DVL1,HOXA1,SGK1,CSPG5,SHH,SEMA4D,RAC1,NTRK2,RPE65,COL18A1,PAX2,GBX2,PLXNA3,BCL2,VASP,APP,CHRN2,
GO:0021795	0.4386939	0	0	13	cerebral cortex cell migration	DAB1,RELN,POU3F2,LHX6,POU3F3,PAFAH1B1,PSEN1,RAC1,PEX13,ARX,LRP8,PEX5,CDK5
GO:0030206	0.4362462	0	0	10	chondroitin sulfate biosynthetic process	CHSY1,CHST3,CHST12,CHST13,CHST11,CHST7,CHST14,CSGALNACT1,DSE,SLC35D1
GO:0050650	0.341358	0	0	13	chondroitin sulfate proteoglycan biosynthetic process	CHSY1,CYTL1,CHST3,CHST12,CHST13,CHST11,CHST7,CHST14,CSGALNACT2,IGF1,CSGALNACT1,DSE,SLC35D1
GO:0002367	0.619157	0	0	17	cytokine production during immune response	BCL10,BCL6,TNF,FOXP3,TRAF6,APOA1,TRAF2,IL10,FCER1G,SASH3,IL21,MAP3K7,NOD2,APOA2,HMOX1,MALT1,DLG1

Table S1A. Gene sets up-regulated by severe stress

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0016358	0.4670373	0	0	55	dendrite development	SIPA1L1,KALRN,CELSR2,CACNA1A,MTAP1B,TLX2,SYNGAP1,KNDC1,MTAP2,PPP1R9B,PTPRF,NRP1,ABI2,MECP2,DCX,GRIN3A,LZTS1,KLF7,YWHAH,MT3,BDNF,DCLK1,PAK1,CACNA1F,DBN1,LST1,ATP7A,BBS4,FEZF2,GHRL,HPRT1,SCARF1,PRKG1,RHOA,PSCD2,ARF6,DVL1,SGK1,RAC1,NTRK2,APP,CHRN2B,SS18L1,ACHE,BBS1,TRAPPC4,CHAT,CIT,CHRNA3,CDK5,KLHL1,SMAD1,IGSF9,MYO6,MCF2
GO:0048813	0.7373899	0	0	23	dendrite morphogenesis	SIPA1L1,CELSR2,CACNA1A,TLX2,KNDC1,PTPRF,DCX,LZTS1,KLF7,YWHAH,MT3,DCLK1,CACNA1F,ATP7A,HPRT1,DVL1,SGK1,CHRN2B,ACHE,CIT,CHRNA3,CDK5,SMAD1
GO:0021700	0.2692413	0	0	138	developmental maturation	XIRP1,NEO1,NRCAM,CACNA1A,KCNMA1,IHH,DLG4,FZD5,MYH6,PTK2B,WNT1,MYH11,MYO5A,BTK,PTGS2,FGFR1,MYBPC3,BHLHB8,GM767,ADAM12,EPAS1,GHRHR,CEBPA,LHX6,NTN4,CAPN3,GNAQ,BMP10,NEB,MECP2,MYL2,SPINK5,PEBP1,EPB4.2,AKT1,TGFB2,GDF11,KCNIP2,KCNH1,INSL3,ACTC1,TTN,DSG4,CAPN2,OBSL1,CLN5,TCAP,RUNX2,AGPAT6,VXS1,KLF1,GATA2,TMOD1,RXFP2,TSSK3,CD44,NTN2L,CDON,RND1,FOXA1,PPARG,BARX2,FARP2,AK1,GRIN1,KRT19,KRTAP16-7,CDH5,IRX5,PSEN1,RUNX3,CTNNB1,HES5,CBFB,KRT8,IL21,AGRN,PDE3A,CDC25B,MTCH1,RECK,KCNE1,MMMP2,MYH10,PTH2R,CACNA1S,RBPJ,EPO,BCL2,APP,ACTG1,CACNA1H,NOTCH1,ANG,DYRK1B,MYLPF,MREG,TCFCP2L1,DLG2,CSPG4,NEURL2,EREG,RET,MYOZ1,PGR,BRCA2,RPS6KA2,PARK2,ITGB1,FOXO3A,GSDMA3,GJA1,PSEN2,PTHR1,VEGFA,PPARD,SOX10,TNNT2,KDR,FBXO5,CALCA,MAEA,SOX8,CAST,PLP1,ERCC2,TIMP1,HES1,ACTA1,DLD,MYH9,CDKN1C,LGI4,POU2F2,CCNB1,PICK1,SCLT1,SEPT4
GO:0001892	0.3846954	0	0	20	embryonic placenta development	ESRRB,CEBPB,HAND1,FOXO3,EPAS1,CEBPA,SPINT1,JUNB,NODAL,GATA2,CITED1,PRDM1,SP3,HIF1A,HSF1,MED1,EGLN1,ARNT,CITED2,SP1
GO:0007032	0.9282034	0	0	10	endosome organization and biogenesis	ALS2,AQP11,VPS18,RAB5B,CLCN3,STX6,RAB22A,ALS2CL,VPS4B,RAB5C
GO:0048821	0.6878335	0	0	14	erythrocyte development	HBA-A2,HBA-A1,BCL6,EPB4.2,ANK1,KLF1,G6PDX,EPO,SOX6,BPGM,MAEA,ERCC2,TIMP1,JMJD6
GO:0042596	0.7559033	0	0	21	fear response	NEUROD2,ALS2,GRIN2B,NPY2R,DRD4,ADRB1,CCK,GABRA5,GRM7,BDNF,GRM2,HCRT,DBH,ESR2,VDAC3,ADRA2A,BCL2,VDAC1,GRIK2,GNG7,PENK1
GO:0021885	0.5287048	0	0	16	forebrain cell migration	EMX2,DAB1,RELN,POU3F2,LHX6,POU3F3,PAFAH1B1,PSEN1,RAC1,PEX13,ARX,LRP8,PEX5,CDK5,DRD1A,DRD2
GO:0015669	1.2730313	0	0	14	gas transport	HBB-B1,HBA-A2,HBA-A1,RPS19,HBA-X,HBB-Y,CYGB,CAR2,HBQ1,KCNK6,F830116E18RIK,MB,NGB,HBB-BH1
GO:0006544	0.6652032	0	0	13	glycine metabolic process	AGXT,A230051G13RIK,SHMT1,SARDH,BAAT,DMGDH,GLDC,DHFR,GCSH,4930402E16RIK,AMT,PPGS,SHMT2
GO:0020027	0.8025053	0	0	9	hemoglobin metabolic process	ALAS2,EIF2AK1,EPB4.2,CAT,LYN,EPO,HIF1A,INHA,INHBA
GO:0002757	0.1316487	0	0	54	immune response-activating signal transduction	BCL10,THY1,CBLB,SLA2,FOXP3,TRAT1,TRAF6,ZAP70,PTPN6,TICAM1,UBE2N,KLRK1,CACNB3,TLR1,TLR6,PTPN22,IGH-6,FCER1G,LYN,MYD88,LAX1,SPG21,CD3E,MAPK1,PAWR,KLRE1,BCAR1,ELF1,PSEN1,CD79B,CACNB4,LCK,TLR7,CLEC7A,MAP3K7,CD79A,NOD2,TLR4,FYN,NFAM1,UBASH3A,SYK,PTPRC,SH2B2,CD19,MALT1,TLR2,IKBK,TLR3,CLEC2I,UNC93B1,PSEN2,LAT2,TLR9
GO:0008286	0.3104239	0	0	46	insulin receptor signaling pathway	PIK3R2,SOC57,FOXO1,PRKCA,EIF4EBP1,GRB2,PTPRF,IRS1,PDPK1,GRB14,INS2,AKT1,EIF4EBP2,AP3S1,ZFP106,SOC53,IRS2,PRKCZ,IGF1R,PTPRA,AHSG,IGFBP1,SRC,PTPN1,TSC2,BCAR1,YBX1,SOC51,BAIAP2,PHIP,STXBPA,INSR,PIK3R1,ENPP1,FOXO2,NR1H3,SZH2B,PTPN2,FOXO4,SORBS1,IGF2,SNF1LK2,GAB1,SLC2A8,GRB10,PIK3R3
GO:0042226	0.5542331	0	0	16	interleukin-6 biosynthetic process	BCL10,CARD9,CEBPB,TRAF6,IL17F,GHSR,TLR1,TLR6,IL19,IL1B,GHRL,TLR4,IFNG,EREG,FOXJ1,INPP5D
GO:0032635	0.4180844	0	0	27	interleukin-6 production	BCL10,TNF,CARD9,CEBPB,FOXP3,TRAF6,IL17F,TICAM1,GHSR,TLR1,TLR6,IL10,FCER1G,IL19,IL1B,GHRL,H47,CHRNA7,UCN,AFAP1L2,NOD2,TLR4,P2RX7,IFNG,EREG,FOXJ1,INPP5D
GO:0035235	0.6976427	0	0	12	ionotropic glutamate receptor signaling pathway	GRIN2B,CAMK2A,GRIN2A,ATP1A3,GRIN3A,CDK5R1,GRIN3B,GRIN1,FYN,APP,CLN3,GRIK1
GO:0007611	0.1417866	0	0	122	learning and/or memory	KLK8,NEUROD2,SHC3,GRIN2B,DLG4,CACNA1C,ATXN1,SYNGAP1,ITGA8,DRD4,PRKCA,GRIN2A,HTT,ATP1A3,EPHB2,GABRA5,TM2OD2,PTEN,PRKAR1B,APBB1,ABI2,DRD5,CTNND2,GRIA1,CACNA1D,GRM7,SNAP25,CHST10,FZD9,EGR2,PRKCZ,BDNF,FOSL2,COMT,ACSL4,NF1,PAFAH1B1,GLUD1,SRF,FOSL1,CRHR1,KIT,PDE4D,RIC8,GLP1R,IL1B,AMPH,JUN,GRIN1,VLDLR,GRM5,PLCB1,GALR2,PSEN1,GHRL,IL1RN,NLGN3,ITGA5,CHRNA7,PCDH8,UCN,AMFR,DBH,RASGRF1,CLN8,FOS,TH,FYN,ADCY8,ESR2,CRHBP,NTAN1,SGK1,KRAS,VDAC3,GM2A,ADAM2,APP,CHRN2B,ITGA3,CASP3,NRAS,GRM4,S100B,GALR3,IGF1,NTF5,EGR1,HMGR,AFF2,VDAC1,PPT1,APOE,SLC6A1,CALB1,IL1RAPL1,PARK2,ATP1A2,HTR2A,ADRA1B,HRH3,ACC2,DRD3,RPS6KB1,PSEN2,LHX8,PTN,GRPR,CRHR,CDK5,PMCH,AAAS,DRD1A,DRD2,BCHE,NOS3,MAN2B1,CLN3,PRKAR2B,FOXP2,IL18,PDE1B
GO:0040011	0.5166664	0	0	19	locomotion	JPH3,CHRM1,MYO5A,GRIN2A,ATP2B2,TTN,SNCA,NEFL,CLN6,GRIN2C,GRM5,PSEN1,GHRL,TSHR,ATP1A2,HTR2C,DRD3,PSEN2,ADORA2A

Table S1A. Gene sets up-regulated by severe stress

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0000165	0.1812122	0	0	243	MAPKKK cascade	TDGF1,BCL10,CAMKK2,MAP3K9,GRIN2B,MAPKBP1,HGF,ADORA1,PTK2B,SYNGAP1,MAP3K10,DOK2,MAPK8IP2,SH3RF1,ADRA2B,TNF,TAOK3,CARD9,DUSP16,PRKCA,ADRA1A,MAP3K6,PDE6G,FGFR1,GRB2,AXIN1,NF2,DUSP19,MUC20,TNFRSF19,MAP3K5,GADD45B,SHANK3,ADRB3,SPRED2,EPGN,CCM2,BRAP,RAPGEF2,DUSP8,CD24A,TRAF6,FGF13,MAP4K3,NDST1,MINK1,ERBB2,MAP2K2,TRIB1,BRAF,INS2,CASR,DUSP9,MET,PEBP1,FLT1,TRAF2,DUSP6,MADD,PTPN6,OSM,ITGB3,FGF8,C5AR1,MAP2K4,MAPK3,MAPBPIP,ADRA2C,AMBP,NRTN,NGG3,TIMP2,MAPK8IP3,LIF,PPP2R1A,MAPK8IP1,MAP2K6,DOK4,MAPKAPK2,PAK1,NF1,TRP73,IGH-6,SH3BP5,DOK1,MAPK10,MYD88,LAX1,PRDX1,TGFB3,DUSP22,NRG1,PRKAA1,CD74,ITPKB,IL1B,ITGAV,IL6,DUSP10,PROK1,WN-T5A,CDC42EP5,MAPK1,DBNL,MAP4K5,SH2D3C,MAP3K2,AKT2,PDE6H,ROR2,MAP3K3,PIK3CB,MAPK8,MAPK14,LRRN3,MAP3K4,PTPN11,PSEN1,GHRL,GRM1,CXCR4,PTK2,IL3,FGD4,PPM1L,SPRED1,CHRNA7,CDC42SE1,BIRC7,SOD1,HIPK2,CARTPT,CAV3,INSR,RGS3,IRAK4,PTPLAD1,SPRED3,EDA2R,IRAK1,MAP3K7,IL11,TIRAP,NOD2,C1QTNF2,MDFI,FRS2,DOK5,MAP2K3,MAP3K7IP1,NRK,TLR4,PLA2G1B,CAV1,NENF,GNAI2,FCER1A,RB1CC1,SYK,KISS1R,LEP,ARRB1,KISS1,ADRA2A,PRKCD,GADD45G,CRK,P2RX7,IL31RA,TRAF7,ARHGFE6,LRK2,FGF2,CD27,PTPRC,MAP2K5,GRM4,MYLK2,PKN1,TNIK,LEPR,MDFIC,SPAG9,NPHS1,RGS4,CSPG4,DUSP
GO:0001578	0.944904	0	0	13	microtubule bundle formation	MARK4,MTAP1B,MTAP1S,MTAP2,NAV1,CLASP1,PSRC1,NEURL,TPPP,GTRGEO22,UBE2B,BBS2,OFD1
GO:0006122	0.5327563	0	0	4	mitochondrial electron transport, ubiquinol to cytochrome c	1110020P15RIK,UQCR,UQCRH,UQCRB
GO:0055067	0.1448824	0	0	53	monovalent inorganic cation homeostasis	KCNMA1,AQP11,BSND,NR3C2,NEDD4L,ATP1A3,SLC9A3,C7,SLC9A2,SLC9A4,SLC26A9,SLC9A1,CLCN3,SLC4A5,AGTR2,CLN5,TESC,SLC9A7,ATP6V0C,EDN1,CAR2,ATP1A4,CLN6,ATP6V1H,KCNA5,ATP6V0A4,TRP53,NHEDC1,SLC9A8,ATP1A1,SLC4A4,TMPRSS3,SLC9A9,AGTR1A,SGK1,ATP6V1B2,BCL2,SLC9A10,NHEDC2,ATP6V1B1,2010110P09RIK,PPT1,SLC4A10,MAFG,ATP5B,EDNRB,ATP1A2,TMCO3,CAMK2D,CLN3,AGT,SLC9A6,SLC9A5
GO:0033555	0.4997569	0	0	41	multicellular organismal response to stress	NEUROD2,CACNA1A,ALS2,GRIN2B,RELN,NPY2R,DRD4,ADRB1,CCK,KCNIP3,GABRA5,SLC6A2,OSM,GRM7,RUNX1,P2RX3,BDNF,COMT,CRHR1,GRM2,HCRT,DBH,ESR2,VDAC3,ADRA2A,TACR1,GJA4,BCL2,SCN9A,NMUR2,VDAC1,PRL,EDNRB,PPARD,GRIK2,CALCA,GNNG7,PENK1,P2RX2,GRIK1,TAC1
GO:0030049	1.0353454	0	0	11	muscle filament sliding	MYL6B,MYH6,MYH2,MYL1,MYBPC3,MYH4,MYL6,MYH7,MYLK2,TNNT2,TNNC1
GO:0048627	0.5044062	0	0	35	myoblast development	XIRP1,NEO1,MYH6,MYH11,MYBPC3,ADAM12,CAPN3,BMP10,NEB,MYL2,KCNH1,ACTC1,TTN,CAPN2,OBSL1,TCAP,TMOD1,NTN2L,CDON,KRT19,KRT8,MYH10,CACNA1S,ACTG1,CACNA1H,DYRK1B,MYLFP,NEURL2,MYOZ1,ITGB1,SOX15,TNNT2,CAST,ACTA1,MYH9
GO:0048628	0.5399496	0	0	34	myoblast maturation	XIRP1,NEO1,MYH6,MYH11,MYBPC3,ADAM12,CAPN3,BMP10,NEB,MYL2,KCNH1,ACTC1,TTN,CAPN2,OBSL1,TCAP,TMOD1,NTN2L,CDON,KRT19,KRT8,MYH10,CACNA1S,ACTG1,CACNA1H,DYRK1B,MYLFP,NEURL2,MYOZ1,ITGB1,TNNT2,CAST,ACTA1,MYH9
GO:0030239	0.6356277	0	0	23	myofibril assembly	XIRP1,MYH6,MYH11,MYBPC3,CAPN3,BMP10,NEB,MYL2,ACTC1,TTN,OBSL1,TCAP,TMOD1,KRT19,KRT8,MYH10,ACTG1,MYLFP,NEURL2,MYOZ1,ITGB1,TNNT2,ACTA1
GO:0051129	0.3101756	0	0	113	negative regulation of cellular component organization and biogenesis	KLK8,SNPH,CLIP2,SPNB3,PFN1,MTAP4,TLX2,THY1,SYNGAP1,MTAP2,SPNB2,EIF4EBP1,MTAP1A,TRIM54,EPB4.9,SPNA2,CAPG,PTPRF,FOX3,ULK1,EIF2AK1,MAPT,PTEN,NRP1,RTN4R,ERCC1,TMSB4X,EVL,LIMA1,ULK2,MET,EIF2AK3,TRIOBP,EIF4EBP2,APC,ASZ1,YWHAH,PACIN1,MT3,CLASP1,RTN4,TMSB10,STMN1,EIF2B3,CORO1A,AVIL,SPNA1,WNT2,TPM1,CAPZA3,DBNL,EIF2B5,CAV2,VILL,SHROOM2,SEMA4F,CAPZA2,HMGB1,TERF2,PSEN1,PAIP2B,PTK2,EIF4EBP3,PACIN3,EIF2B4,CLASP2,CAPZA1,SPNB1,DLC1,KATNB1,ARHGFE2,SET,ARF6,PACIN2,SGK1,RAC1,PLXNA3,GSN,VIL1,HDAC6,CAPZB,S1PR1,CSPG4,BRCA1,ERCC4,MAP6D1,RECL4,EIF2B1,NTN1,CENTD2,TERF2IP,TGFB1,MSX3,PAX5,CDC42,SVIL,MBP,RUFY3,CIT,MAPRE1,SCIN,SEMA3F,MAP3K1,TMOD3,RDX,CTTNBP2,RNF6,ESPL1,SEMA3A,PAIP2,MID1IP1,SPP1,MID1
GO:0051494	0.3320891	0	0	57	negative regulation of cytoskeleton organization and biogenesis	CLIP2,SPNB3,PFN1,MTAP4,MTAP2,SPNB2,MTAP1A,TRIM54,EPB4.9,SPNA2,CAPG,MAPT,TMSB4X,EVL,LIMA1,MET,TRIOBP,APC,ASZ1,CLASP1,TMSB10,STMN1,CORO1A,AVIL,SPNA1,WNT2,TPM1,CAPZA3,DBNL,CAV2,VILL,SHROOM2,CAPZA2,CLASP2,CAPZA1,SPNB1,DLC1,KATNB1,ARHGFE2,SGK1,GSN,VIL1,HDAC6,CAPZB,S1PR1,BRCA1,MAP6D1,CENTD2,SVIL,MAPRE1,SCIN,MAP3K1,TMOD3,RDX,CTTNBP2,MID1IP1,MID1
GO:0045822	0.7333122	0	0	13	negative regulation of heart contraction	ADORA1,ADRA1D,PRKCA,ADRA1A,NOS1,PLN,AGTR2,ADRBK1,ATP1A1,ATP2A2,IL2,ATP1A2,JAK2
GO:0046580	0.6297561	0	0	10	negative regulation of Ras protein signal transduction	BCL6,TNK1,PPP2CB,TIMP2,MFN2,NF1,CENTD3,NUP62,DLC1,STMN3
GO:0048011	0.4402595	0	0	15	nerve growth factor receptor signaling pathway	SOS1,LMTK2,PTPRF,ULK1,SORT1,AGTR2,MAGEH1,SR,BCAR1,PTPN11,BEX1,NDN,RAF1,UTP11L,AGT

Table S1A. Gene sets up-regulated by severe stress

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0031175	0.3793518	0	0	308	neurite development	KLK8,SIPA1L1,KALRN,SLIT1,NRCAM,CELSR2,CACNA1A,MTAP1B,NRP2,ALS2,L1CAM,SLIT3,UNC5C,PVRL1,CHL1,RELN,PTK2B,RTN4RL1,TLX2,MTAP1S,TIAM1,THY1,SYNGAP1,KNDC1,NGF,ROBO1,LMTK2,MTAP2,SLITRK3,EPHA4,NKX2-9,ARTN,NR2E1,RTN4RL2,NRXN1,DPYSL5,RAC3,PRKCA,SLIT2,RGNEF,GPRIN1,POU4F1,WNT7B,FGFR1,GDNF,CCK,EPHB2,PPP1R9B,DCC,ANK3,PTPRF,MYCBP2,VAX2,UNC5A,UNC5B,GAS7,ULK1,FEZF1,POU4F3,RAB3A,MAPT,PTEN,NTRK3,ISL2,POU3F2,APBB1,CD24A,NRP1,DPYSL3,RTN4R,ENAH,CNTN2,APBB2,CHST3,PIP5K1C,KIF5C,ABI2,ERBB2,SEMA5A,APOA1,MECP2,DCX,ERBB3,EVL,GRIN3A,ULK2,SEMA6C,ETV1,LZTS1,DSCAML1,TOP2B,LIFR,TGFB2,CDH2,SNAP25,APC,FGF8,KLF7,NRN1,ATG7,EFNB1,PRRXL1,YWHAH,EGR2,MT3,NRTN,LHX4,TTL,CDK5R1,MAPK8IP3,EFHD1,BDNF,BAI1,ATOH1,NTNG2,DCLK1,PAR6B,UBB,PAK1,PAFAH1B1,RTN4,POU4F2,ALKBH1,GLI2,ABLIM1,STMN1,ACTB,TNR,IGF1R,GFRA3,PTPRK,NTNG1,STK11,EPHA7,BCL11B,NEFL,SLITRK1,CACNA1F,CD44,GDF7,EPHB3,TBR1,FOXG1,NTN2L,LIMK1,WNT3A,DBN1,LST1,AMIGO1,ATP7A,BBS4,LHX3,STX3,LINGO1,PPP1R9A,ROBO2,RYK,NUMB,FEZF2,SEMA3B,MAPK8,RXRA,GALR2,PTPRZ1,SEMA4F,ETV4,PTPN11,PSEN1,GHRL,NKX2-1,CXCR4,PTK2,TNN,NDEL1,RUNX3,CDH1,CELSR3,NRXN3,LMX1A,SLITRK6,HPRT1,UCN,CYFIP1,DMD,DPYSL2,NEUROG2,BAIAP2,RASGRF1,SCARF1,BARHL2,WNT7A,PRKG1,RHOA,PAR3,NFASC,SLITRK5,MMP2,BOC,MYH10,B3GNT2,MIF,CKAR,FEZZ,HOXA2,
GO:0048812	0.396422	0	0	255	neurite morphogenesis	KLK8,SIPA1L1,KALRN,SLIT1,NRCAM,CELSR2,CACNA1A,NRP2,ALS2,L1CAM,SLIT3,UNC5C,PVRL1,CHL1,RELN,RTN4RL1,TLX2,MTAP1S,TIAM1,THY1,SYNGAP1,KNDC1,NGF,ROBO1,LMTK2,SLITRK3,EPHA4,NKX2-9,ARTN,NR2E1,RTN4RL2,NRXN1,DPYSL5,PRKCA,SLIT2,RGNEF,POU4F1,CCK,EPHB2,DCC,ANK3,PTPRF,MYCBP2,VAX2,UNC5A,UNC5B,GAS7,ULK1,FEZF1,POU4F3,RAB3A,MAPT,NTRK3,ISL2,POU3F2,APBB1,NRP1,DPYSL3,RTN4R,ENAH,CNTN2,APBB2,CHST3,PIP5K1C,KIF5C,ERBB2,SEMA5A,APOA1,DCX,ERBB3,EVL,ULK2,SEMA6C,ETV1,LZTS1,DSCAML1,TOP2B,LIFR,TGFB2,CDH2,SNAP25,FGF8,KLF7,NRN1,EFNB1,PRRXL1,YWHAH,EGR2,MT3,LHX4,TTL,CDK5R1,MAPK8IP3,BDNF,BAI1,ATOH1,NTNG2,DCLK1,PAR6B,UBB,PAFAH1B1,RTN4,POU4F2,GLI2,ABLIM1,STMN1,ACTB,TNR,IGF1R,GFRA3,NTNG1,STK11,EPHA7,BCL11B,NEFL,SLITRK1,CACNA1F,GDF7,EPHB3,TBR1,FOXG1,NTN2L,LIMK1,WNT3A,AMIGO1,ATP7A,LHX3,ROBO2,RYK,NUMB,FEZF2,SEMA3B,RXRA,PTPRZ1,SEMA4F,ETV4,PTPN11,PSEN1,NKX2-1,CXCR4,PTK2,TNN,NDEL1,RUNX3,CELSR3,NRXN3,LMX1A,SLITRK6,HPRT1,CYFIP1,DMD,DPYSL2,NEUROG2,BAIAP2,BARHL2,WNT7A,PAR3,NFASC,SLITRK5,MMP2,BOC,MYH10,B3GNT2,MIF,CKAR,FEZZ,HOXA2,SLITRK2,NTF3,STXBP1,FOXD1,DVL1,HOXA1,SGK1,CSPG5,SHH,SEMA4D,RAC1,PAX2,GBX2,PLXNA3,BCL2,VASP,APP,CHRN2,VCAN,BMPR1B,TNFRSF12A,SPON2,NOTCH1,PCACNA1A,CHRM1,EGR3,KIF1B,CHRNA1,RAB3A,CD24A,P2RX3,CHRN4,NTF3,CHRN2,MYLK2,CHAT,DTNA,SLC5A7,CHRNA3,P2RX2
GO:0007274	0.6413776	0	0	17	neuromuscular synaptic transmission	
GO:0048666	0.3671944	0	0	352	neuron development	KLK8,SIPA1L1,KALRN,SLIT1,NRCAM,CELSR2,NEUROD2,CACNA1A,MTAP1B,NRP2,ALS2,L1CAM,SLIT3,UNC5C,CRMP1,DLG4,PVRL1,CHL1,RELN,PTK2B,RTN4RL1,TLX2,MTAP1S,TIAM1,THY1,SYNGAP1,KNDC1,NGF,NEUROD4,ROBO1,LMTK2,MTAP2,SLITRK3,EPHA4,NKX2-9,ARTN,NR2E1,RTN4RL2,NRXN1,DPYSL5,RAC3,PRKCA,SLIT2,RGNEF,DGKG,GPRIN1,POU4F1,WNT7B,HTT,FGFR1,GDNF,CCK,EPHB2,PPP1R9B,DCC,ANK3,PTPRF,MYCBP2,VAX2,UNC5A,UNC5B,GAS7,ULK1,NR2F6,FEZF1,POU4F3,RAB3A,MAPT,PTEN,NTRK3,ISL2,POU3F2,APBB1,CD24A,NRP1,DPYSL3,RTN4R,LHX6,ENAH,NTN4,CNTN2,APBB2,CHST3,PIP5K1C,KIF5C,GNAQ,ABI2,ERBB2,SEMA5A,APOA1,MECP2,DCX,ERBB3,EVL,GRIN3A,ULK2,SEMA6C,ETV1,LZTS1,DSCAML1,TOP2B,LIFR,TGFB2,CDH2,SNAP25,APC,FGF8,KLF7,NRN1,KCNIP2,ATG7,ONECUT2,EFNB1,PRRXL1,RUNX1,YWHAH,EGR2,MT3,NRTN,LHX4,TTL,CDK5R1,MAPK8IP3,LIF,EFHD1,BDNF,EN2,BAI1,ATOH1,NTNG2,DCLK1,PAR6B,UBB,PAK1,CLN5,PAFAH1B1,TRP73,RTN4,POU4F2,ALKBH1,GLI2,ABLIM1,STMN1,ACTB,TNR,VSX1,IGF1R,GFRA3,PTPRK,NTNG1,STK11,EPHA7,BCL11B,ASCL1,NEFL,SLITRK1,CACNA1F,CD44,GDF7,EPHB3,TBR1,FOXG1,NTN2L,LIMK1,WNT3A,DBN1,RND1,LST1,AMIGO1,ATP7A,BBS4,LHX3,STX3,LINGO1,PPP1R9A,ROBO2,FARP2,AK1,RYK,NUMB,FEZF2,SEMA3B,MAPK8,RXRA,GALR2,PTPRZ1,SEMA4F,ETV4,IRX5,PTPN11,PSEN1,GHRL,NKX2-1,CXCR4,PTK2,EN1,TNN,
GO:0030182	0.3249119	0	0	469	neuron differentiation	KLK8,EMX2,SIPA1L1,KALRN,SLIT1,NRCAM,CELSR2,NEUROD2,CACNA1A,MTAP1B,NRP2,ALS2,L1CAM,SOCS2,SLIT3,PTPRU,UNC5C,CRMP1,DLG4,PVRL1,CHL1,RELN,PTK2B,WNT1,RTN4RL1,TLX2,YWHAH,MTAP1S,TIAM1,THY1,SYNGAP1,KNDC1,NGF,NEUROD4,ROBO1,LMTK2,MTAP2,NEUROG1,SLITRK3,EPHA4,NKX2-9,ARTN,NR2E1,RTN4RL2,MDGA1,NRXN1,DPYSL5,RAC3,PRKCA,SLIT2,GPC2,RGNEF,DGKG,GPRIN1,CCND2,PTF1A,POU4F1,CEBPB,BHLHB5,WNT7B,HTT,EFNA3,BRSK1,FGFR1,GDNF,LHX2,CCK,EPHB2,PPP1R9B,DCC,ATN1,ANK3,PTPRF,MYCBP2,VAX2,NEUROD1,HOXC10,UNC5A,UNC5B,GAS7,ULK1,NR2F6,FEZF1,POU4F3,RAB3A,MAPT,ATP2B2,PTEN,NTRK3,ISL2,POU3F2,EMX1,APBB1,CD24A,NRP1,DPYSL3,TUBB3,RTN4R,LHX6,ENAH,NTN4,CNTN2,MNX1,APBB2,CHST3,PIP5K1C,KIF5C,GNAQ,ABI2,ERBB2,SEMA5A,APOA1,MECP2,DCX,ERBB3,EVL,GRIN3A,ULK2,SEMA6C,PHOX2B,ETV1,DBX1,MIB1,LZTS1,DSCAML1,CHRD1,PSD,TOP2B,LIFR,TGFB2,CDH2,SNAP25,APC,FGF8,KLF7,NRN1,KCNIP2,NKX6-2,PTPRR,ATG7,FOXA2,TUBB2A,NLGN1,ONECUT2,EFNB1,PRRXL1,RUNX1,HOXD3,YWHAH,EDN3,EGR2,MT3,NRTN,HELT,TGFBR1,LHX4,TIMP2,TTL,CDK5R1,TLX3,MAPK8IP3,LIF,EFHD1,BDNF,EN2,BAI1,NAPA,ATOH1,NTNG2,DCLK1,AGTR2,PAR6B,TUBB2B,UBB,PAK1,GSX2,CLN5,PAFAH1B1,TRP73,BAG1,ASPM,RTN4,POU4F2,ALKBH1,GLI2,ABLIM1,STMN1,ACTB,TNR,VSX1,IGF1R,GFRA3,PHOX2A,PTPRK,NTNG1,DNMT3B,STK11,EPHA7,BCL11B,GATA2,NR4A2,NRG1,EVX1,ASCL1,NEFL,SLITRK1,CACNA1F,CD44,RTN

Table S1A. Gene sets up-regulated by severe stress

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0007269	0.3515686	0	0	114	neurotransmitter secretion	SNPH,CACNA1A,PCLO,PPFIA3,SPNB3,GRIN2B,STX1A,ADORA1,CPLX2,SEPT5,NGF,CAMK2A,NPY2R,DRD4,UNC13A,NRXN1,VAMP2,RIMS1,CACNA1B,BTK,PRKCB1,SYN1,SYN2,SYN3,APBA1,RAB3A,NRXN2,LIN7C,GRM7,SNAP25,APBA2,NLGN1,CELSR1,EDN3,NISCH,LPHN1,CPLX1,BDNF,DOC2A,ERC2,GRIK5,SYT1,NF1,SNCA,RAB3C,RAB15,NSF,STX7,GRM2,LIN7A,ADRBK1,CACNA1F,IL1B,KCNMB4,STX3,HCRT,PSEN1,LIN7B,CACNB4,IL1RN,NRXN3,CHRNA7,TRIM9,CHRNA4,CARTPT,WNT7A,PINK1,SYT3,YWHAZ,SYT4,CADPS,AP3M2,DVL1,RIMS4,NTRK2,CHRNA2,GRM4,ADORA3,RAB14,TRH,PPT1,CPLX4,PDYN,PARK2,HTR2A,NOS1AP,SYT2,CHRNA6,HRH3,HTR2C,CHRNA4,DRD3,RAB26,SYT12,CHRNA3,STX4A,NPY5R,UNC13B,GIPIC1,CPLX3,SNAPIN,UNC13C,BAIAP3,PLDN,DRD2,SNCAIP,AGT,HTR1B,GRM8,ICA1,MYO6,STXBP2,ADORA2A,GRIK1
GO:0015671	1.2496593	0	0	12	oxygen transport	HBB-B1,HBA-A2,HBA-A1,HBA-X,HBB-Y,CYGB,HBO1,KCNK6,F830116E18RIK,MB,NGB,HBB-BH1
GO:0048008	0.3831692	0	0	14	platelet-derived growth factor receptor signaling pathway	PLAT,RAPGEF1,PTEN,PDGFB,PDAP1,PDGFA,BCR,SRC,BCAR1,PDGFRA,JAK2,VEGFA,PDGFRB,PDGFC
GO:0001956	0.4782583	0	0	13	positive regulation of neurotransmitter secretion	GRIN2B,STX1A,NPY2R,CACNA1B,SNCA,ADRBK1,CARTPT,PINK1,CHRNA2,TRH,HTR2C,ADORA2A,GRIK1
GO:0051092	0.1897712	0	0	35	positive regulation of NF-kappaB transcription factor activity	BCL10,ICAM1,CAMK2A,TNF,CARD9,CARD11,CAT,TICAM1,UBE2N,IKKBK,AMH,MYD88,IRAK2,EDA2R,NPM1,NOD2,TLR4,PLA2G1B,UBE2V1,KRAS,ITGB2,MALTI1,IKKBK,TLR3,RELA,TGFB1,MAP3K13,EDA,NLRC3,PRDX3,AGT,PRKCO,RIPK2
GO:0016540	0.1890862	0	0	92	protein autoprocessing	CAMKK2,MAP3K9,MEX3B,MAP3K10,CAMK2A,LMTK2,TNK1,TAOK3,BTK,MOBK1A,ULK1,PCSK2,EIF2AK1,NTRK3,UHMK1,ZAP70,DYRK1A,ERBB2,FERT2,MET,EIF2AK3,AKT1,ASZ1,CRKRS,CAMK2B,TTN,TGFBR1,CAPN2,PAK1,VRK2,LYN,KIT,HK1,IGF1R,PIM3,BCR,WNT2,MYO3A,TAF1,CDKL5,CLK6,CAV2,IRAK2,JUN,MAP3K3,MAPK14,HATATIP2,PCSK9,PTK2,VEGFC,LCK,CAPN1,INSR,NLK,IRAK1,PAK2,PARP1,FYN,ENPP1,PDGFRA,SYK,PRKCD,NTRK2,LRRK2,PHKA1,PTPRC,PRKACA,ERN1,MAP3K12,CFTFR,JAK2,MAP3K13,GRK1,MAP3K11,EIF2AK2,STK4,KDR,TRPM7,CAMK2D,MAP3K1,CLK3,EGFR,CTTNBP2,PDGFRB,CDK5,YES1,CAMK2G,MAPK15,CLK2,CLK4,CLK1,VRK1
GO:0007265	0.1504347	0	0	293	Ras protein signal transduction	KALRN,GIT1,PLEKHG5,ALS2,IQSEC2,BCL6,SOS1,SHC3,CENTG3,SYDE1,PTK2B,TIAM1,SYNGAP1,ARHGFE10,NGF,DOK2,ARHGDI,GRIT,D10BWG1379E,TNK1,RHOU,IQSEC3,RGNEF,TRIO,ARHGFE5,GRB2,TBC1D16,TBC1D14,TBC1D10C,DEPDC2,CENTB5,FARP1,ARFGEF2,ULK1,ARHGFE12,DOK3,ARHGFE10L,TBC1D10A,ARHGAP20,BRAP,ARHGFE17,FGD3,APOC3,KSR1,ERBB2,RASGRP4,APOA1,IQSEC1,CENTG2,RALGDS,HRAS1,ABR,MAP2K2,ITSN2,SOS2,TBC1D9,ECT2,SHOC2,TBC1D10B,VAV2,D10ERTD610E,RASGRP1,TBC1D5,GBF1,PSCD3,PSD,ARHGFE4,FGD1,CDH2,PSD4,PPP2CB,ARHGAP4,MRAS,RABGAP1L,ARHGFE11,ADPRHL1,MAPK3,CFL1,G3BP1,TTN,SGSM2,CENTG1,RHOB,EVI5L,TIMP2,NISCH,PSCD1,KITL,NET1,MAPK13,TBC1D20,VAV1,RASSF1,MFN2,MAPKAPK2,RASGRF2,PSD3,NF1,PAFAH1B1,TBC1D9B,GNA12,TBC1D24,NTRK1,DOK1,ITSN1,TBC1D30,CENTD3,CENTD1,YWHAB,NRG1,BCR,TBC1D2,RALA,ITPKB,RRAS2,LIMK1,CDC42EP5,MAPK1,DBNL,SMAP1,RHOD,TBC1D13,TSC1,CENTA1,SRC,TIAM2,A630047E20RIK,MAPKAPK3,BC067047,FARP2,TBC1D22B,TBC1D8B,CDC42EP4,FGD5,MAPK14,CNKSR1,PTH,EPS8L2,VAV3,ARHGFE16,ARHGAP1,DOCK2,PLEKHG4,SGSM1,LCK,FGD4,ARHGFE7,DDEF1,TBC1D22A,ARFGEF1,TBC1D21,GNB1,USP36,SDCBP,NUP62,BAIAP2,RASGRF1,SMAP2,PTPLAD1,RHOA,RALB,PLD1,TBC1D15,PLEKHG3,DLG1,ARHGFE2,CENTB1,SYDE2,G3BP2,TBC1D25,CSF1,PSCD2,AR
GO:0032956	0.2615131	0	0	75	regulation of actin cytoskeleton organization and biogenesis	ARPC3,SPNB3,PFN1,ARPC2,NEBL,ELN,ACTR3B,SPNB2,NF2,EPB4.9,SPNA2,CAPG,ARHGFE10L,NEB,TMSB4X,EVL,LIMA1,MET,TRIOBP,ASZ1,CFL1,CDC42EP2,FMN1,TMSB10,CORO1A,AVIL,SPNA1,ARPC5,WNT2,NCK2,TPM1,CAPZA3,CDC42EP5,CCDC88A,DBNL,TSC1,CAV2,ACTR3,VILL,TSC2,SHROOM2,CAPZA2,DSTN,CAPZA1,RHOA,SPNB1,LATS1,DLG1,ARPC1B,ARF6,ARPC1A,KISS1R,RAC1,ARPC5L,GSN,VIL1,NCK1,CAPZB,S1PR1,SORBS3,CENTD2,RASA1,CLEC2I,SVIL,CXCL12,CIT,SCIN,MAP3K1,TMOD3,RDX,C
GO:0030832	0.3250426	0	0	63	regulation of actin filament length	ARPC3,SPNB3,PFN1,ARPC2,NEBL,ELN,ACTR3B,SPNB2,EPB4.9,SPNA2,CAPG,NEB,TMSB4X,EVL,LIMA1,MET,TRIOBP,ASZ1,CFL1,CDC42EP2,FMN1,TMSB10,CORO1A,AVIL,SPNA1,ARPC5,WNT2,NCK2,TPM1,CAPZA3,CDC42EP5,DBNL,CAV2,ACTR3,VILL,SHROOM2,CAPZA2,DSTN,CAPZA1,RHOA,SPNB1,LATS1,ARPC1B,ARF6,ARPC1A,RAC1,ARPC5L,GSN,VIL1,NCK1,CAPZB,RASA1,CLEC2I,SVIL,CXCL12,CIT,SCIN,MAP3K1,TMOD3,RDX,CTTNBP2,PFN2,DLG1
GO:0030833	0.3145465	0	0	26	regulation of actin filament polymerization	ARPC3,PFN1,ARPC2,ELN,ACTR3B,TMSB4X,CDC42EP2,FMN1,TMSB10,ARPC5,NCK2,CDC42EP5,ACTR3,RHOA,LATS1,ARPC1B,ARF6,ARPC1A,RAC1,ARPC5L,NCK1,RASA1,CLEC2I,MAP3K1,PFN2,DLG1
GO:0032970	0.2553534	0	0	78	regulation of actin filament-based process	ARPC3,SPNB3,PFN1,ARPC2,NEBL,ELN,ACTR3B,SPNB2,NF2,EPB4.9,SPNA2,MYBPC3,CAPG,ARHGFE10L,NEB,TMSB4X,EVL,LIMA1,MET,TRIOBP,ASZ1,CFL1,CDC42EP2,FMN1,TMSB10,CORO1A,AVIL,PDGFA,SPNA1,ARPC5,WNT2,NCK2,TPM1,CAPZA3,CDC42EP5,CCDC88A,DBNL,TSC1,CAV2,ACTR3,VILL,TSC2,SHROOM2,CAPZA2,DSTN,CAPZA1,RHOA,SPNB1,LATS1,DLG1,ARPC1B,ARF6,ARPC1A,KISS1R,RAC1,ARPC5L,GSN,VIL1,NCK1,MYLK2,CAPZB,S1PR1,SORBS3,CENTD2,RASA1,CLEC2I,SVIL,CXCL12,CIT,SCIN,MAP3K1,TMOD3,RDX,CTTNBP2,PFN2,DLG1,PRKCO,TNCC1

Table S1A. Gene sets up-regulated by severe stress

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0022603	0.219914	0	0	139	regulation of anatomical structure morphogenesis	KLK8,SIPA1L1,NRCAM,CACNA1A,TLX2,TIAM1,THY1,SYNGAP1,KNDC1,NGF,ROBO1,RHO,SLIT2,PRKCB1,PALM,EPHB2,ANXA7,PTPRF,GAS7,ULK1,RPS29,MAPT,NTRK3,POU3F2,NRP1,RTN4R,FGD3,ULK2,RHO,EPB4.2,LZTS1,GAS2,ITGA7,FGD1,CDH2,CDC42EP2,YWHAH,MT3,TGFBF1,TTL,EPB4.1,SLC26A5,GNA12,RTN4,RUNX2,SPNB4,KIT,DYNLL1,PALM2,CENTD3,PALMD,TGFB3,CNA1,MYH14,PPP6C,SPRR1B,NEFL,LIMK1,EZR,SPRR2A,CDC42EP5,LST1,AMIGO1,BBS4,SHROOM3,ROBO2,CDC42EP4,FGD5,SEMA4F,PDPN,PSEN1,PTK2,GRLF1,HOPX,FGD4,CDC42SE1,CYFIP1,DPYSL2,BARHL2,WNT7A,MYH10,P2RX5,KBTD10,DLCL1,MIF,CSF1,FYN,TNFRSF11B,SGK1,SEMA4D,FERMT2,PLXNA3,CHRN2,TNFRSF12A,ITGB2,NEFM,LRRC4C,CSPG4,CDH4,ACHE,ATP10A,METRNL,PLXNB2,NTN1,CENTD2,FGD6,RASA1,EPB4.1L2,TAOK2,APOE,PLXNB1,ARHGAP15,CFDP1,CDC42,MBP,RUFY3,CIT,FGD2,NGFR,GNA13,ARFIP2,CHRNA3,CDC42EP1,SEMA3F,ARHGEF18,CDC42SE2,TGFB2,RNF6,MYH9,EFNA1,SEMA3A,CDC42EP3,RHOJ,ERMN,SMAD1,FBLIM1,IFT88,PRKCO,SPP1
GO:0050854	0.5967622	0	0	12	regulation of antigen receptor-mediated signaling pathway	BCL10,THY1,CBLB,TRAT1,PTPN6,PAWR,ELF1,LCK,NFAM1,UBASH3A,PTPRC,MALT1
GO:0032012	0.3240896	0	0	40	regulation of ARF protein signal transduction	GIT1,IQSEC2,CENTG3,D10BWG1379E,IQSEC3,CENTB5,ARFGEF2,IQSEC1,CENTG2,GBF1,PSCD3,PSD,PSD4,CENTG1,PSCD1,PSD3,CENTD3,CENTD1,SMAP1,CENTA1,DDEF1,ARFGEF1,USP36,SMAP2,CENTB1,PSCD2,HRBL,PSD2,HRB,CENTB2,ARFGAP3,GIT2,CENTD2,CENTA2,FBXO8,DDEF2,ARFGAP1,DDEF1,ARFGAP2,PSCD4
GO:0050770	0.4455861	0	0	51	regulation of axonogenesis	KLK8,NRCAM,CACNA1A,TIAM1,THY1,SYNGAP1,NGF,ROBO1,SLIT2,EPHB2,ULK1,MAPT,NTRK3,POU3F2,NRP1,RTN4R,ULK2,CDH2,TTL,RTN4,NEFL,LIMK1,AMIGO1,ROBO2,SEMA4F,PSEN1,PTK2,DPYSL2,BARHL2,WNT7A,MIF,SEMA4D,PLXNA3,TNFRSF12A,NEFM,LRRC4C,CSPG4,CDH4,ACHE,METRNL,PLXNB2,NTN1,APOE,PLXNB1,MBP,RUFY3,SEMA3F,RNF6,EFNA1,SEMA3A,SPP1
GO:0050848	0.4088918	0	0	21	regulation of calcium-mediated signaling	L1CAM,DRD4,SLA2,CD4,TRAT1,CD24A,ZAP70,NCAM1,P2RX3,CD8A,CD3E,RGN,ITGAL,P2RX5,FCER1A,SYK,P2RX4,KDR,CDH13,P2RX2,LHCGR
GO:0043370	0.457744	0	0	14	regulation of CD4-positive, alpha beta T cell differentiation	BCL6,IRF4,FOXP3,HLX,IL2RG,RC3H1,IL6,SASH3,IL12RB2,CD86,IL27,IL4RA,CD80,SOC5
GO:0051128	0.1546555	0	0	382	regulation of cellular component organization and biogenesis	KLK8,SIPA1L1,SNPH,NRCAM,ARPC3,CACNA1A,CLIP2,SPNB3,PVRL1,PFN1,ARPC2,NEBL,MTAP4,TLX2,ELN,TIAM1,THY1,SYNGAP1,KNDC1,NGF,ACTR3B,ROBO1,AHR,MTAP2,TNF,SPNB2,RHO,PRKCA,SLIT2,NEDD4L,STON1,EIF4EBP1,PALM,MTAP1A,TRIM54,CK,NF2,EPHB2,EPB4.9,CAND1,ANXA7,SPNA2,MYBPC3,CAPG,PTPRF,MYCBP2,AP2S1,DST,FOXP3,GAS7,ULK1,RPS29,EIF2AK1,RA B3A,MAPT,ARHGEF10L,CALY,PTEN,NTRK3,POU3F2,NRP1,RTN4R,FGD3,DYRK1A,ERCC1,NEB,HCF1,TMSB4X,BIN1,EVL,LIMA1,EIF3E,RAB5B,CBL,ULK2,RHOQ,MET,EIF2AK3,EPB4.2,MIB1,LZTS1,GAS2,ITGA7,TRIOBP,FGD1,EIF4EBP2,CDH2,SNAP25,APC,ASZ1,GHSR,UBE2N,STON2,CFL1,CDKN1B,CDC42EP2,FGF10,YWHAH,PACIN1,MT3,CCDC100,TGFB1,FMN1,TTL,EIF3K,EPB4.1,GRIK5,EIF2C1,EIF4G3,UBB,SLC26A5,CLASP1,GNA12,RTN4,TLK1,TMSB10,IHG-6,SPNB4,FCER1G,STMN1,KIT,EIF3J,DYNLL1,EIF2B3,PALM2,MDN1,DAZL,CENTD3,CORO1A,EIF5A,PALMD,AVIL,TGFB3,PDGFA,SPNA1,PSRC1,MYH14,GATA2,TACC2,FCGR2B,EIF3I,ARPC5,WNT2,PPP6C,SPRR1B,NEFL,NCK2,AHSG,TPM1,TERC,SPACA3,LIMK1,EZR,SPRR2A,CAPZA3,EIF2B2,CD209B,CDC42EP5,CCDC88A,LST1,AMIGO1,DBNL,BBS4,TPPP,EIF2B5,TSC1,EPN2,CAV2,ACTR3,MLL1,SHROOM3,ROBO2,4930503E24RIK,VILL,CDC42EP4,TSC2,FGD5,SHROOM2,MAPK8,EIF4G1,SEMA4F,CAPZA2,PDPN,BZW2,HMGB1,TERF2,PSEN1,GHRL,PAIP2B,PTK2,GRLF1,DSTN,BOLL,DYNC1L1,FGD4,RAB4A,SFTPD,EIF4EBP3,ATF7IP,FCGR3,PACIN3,EIF2B4
GO:0032535	0.3218137	0	0	68	regulation of cellular component size	ARPC3,ALS2,SPNB3,PFN1,ARPC2,NEBL,ELN,ACTR3B,SPNB2,EPB4.9,SPNA2,CAPG,NEB,TMSB4X,EVL,LIMA1,MET,TRIOBP,ASZ1,CFL1,CDC42EP2,FMN1,TMSB10,CORO1A,AVIL,SPNA1,ARPC5,WNT2,NEFL,NCK2,TPM1,CAPZA3,CDC42EP5,DBNL,CAV2,ACTR3,VILL,SHROOM2,CAPZA2,DSTN,CAPZA1,WNT7A,RHOA,SPNB1,LATS1,ARPC1B,ARF6,ARPC1A,RAC1,ARPC5L,VPS24,GSN,VIL1,NCK1,NEFM,CAPZB,RASA1,CLEC2I,SVIL,CXCL12,CIT,SCIN,MAP3K1,TMOD3,RDX,CTTNBP2,PFN2,DLG1
GO:0002718	0.6607299	0	0	12	regulation of cytokine production during immune response	BCL10,BCL6,FOXP3,TRAF6,TRAF2,FCER1G,SASH3,IL21,MAP3K7,NOD2,HMOX1,MALT1
GO:0017157	0.5345379	0	0	37	regulation of exocytosis	CACNA1A,PCLO,SPNB3,STX1A,RAB3D,SEPT5,MYO5A,PRKCA,VAMP2,FREQ,RAB3A,CADPS2,RAB27B,SYCN,SYT1,PRAM1,RAB3C,FCER1G,RPH3AL,TRPV6,TRIM9,SYT4,CADPS,FE22,POU5F1,FCER1A,SYK,TRAF7,FGF2,RAB3B,HMOX1,B4GALT1,RAB26,MS4A2,CDK5,RAPGEF4,EXOC2
GO:0043087	0.1528426	0	0	103	regulation of GTPase activity	JUB,GIT1,ALS2,BCL6,CENTG3,SYDE1,PTK2B,THY1,TBC1D16,TBC1D14,TBC1D10C,CENTB5,CHML,TBC1D10A,RAB3GAP2,FGD3,CENTG2,TBC1D9,TBC1D10B,TBC1D5,FGD1,RABGAP1,ALS2CR12,ADPRHL1,GDI2,SGSM2,CENTG1,EVIS1,TBC1D20,VAV1,NF1,PAFAH1B1,TBC1D9B,TBC1D24,TBC1D30,CENTD3,CENTD1,TBC1D2,AMPH,SMAP1,TBC1D13,TSC1,CENTA1,A630047E20RIK,TBC1D22B,TBC1D8B,TSC2,FGD5,VAV3,ARHGAP1,SGSM1,FGD4,DDEF1,TBC1D22A,TBC1D21,GDI1,RASGRF1,SMAP2,TBC1D15,CENTB1,SYDE2,TBC1D25,HRBL,EVIS,TBC1D7,HRB,STMN3,SGSM3,CENTB2,ARFGAP3,TBC1D17,GIT2,RAB3GAP1,S1PR1,TBC1D23,CHM,ARHGAP6,CENTD2,FGD6,TBC1D12,TBC1D8,CENTA2,RALBP1,FOXJ1,TBC1D4,GRTP1,FGD2,DDEF2,ARFGAP1,RABGAP1,MAP2K1,DOCK7,TBC1D19,ARHGAP27,DDEF1,RA2GRP3,TBC1D2B,TBC1D1,SGS9,WDR67,USP6NL,ARFGAP2,RAPGEF6

Table S1A. Gene sets up-regulated by severe stress

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0051336	0.1023464	0	0	244	regulation of hydrolase activity	JUB,GIT1,BCL10,ALS2,CDKN2D,BCL6,CENTG3,MYH6,SYDE1,PTK2B,THY1,FURIN,MYL4,TNF,PPP1R2,ADRA1A,APOA5,TBC1D16,TBC1D14,TBC1D10C,CKK,AVPR1A,MYBPC3,SAPS2,CENTB5,NOS1,CHML,TBC1D10A,CASP9,RAB3GAP2,FGD3,C6,APOC3,ANGPTL4,GNAQ,RASGRP4,APOA1,CENTG2,HIP1,APOH,CASR,TBC1D9,EIF2AK3,TBC1D10B,BAD,TBC1D5,AVPR1B,BAK1,FGD1,GNAT1,RABGAP1L,HSPA1B,C5AR1,ALS2CR12,FOXL2,SORT1,PDCC6,ADPRHL1,TNFSF15,GDI2,BCL2L10,SGSM2,CENTG1,GSPT1,EVI5L,NLRP2,CASP8AP2,PRKCZ,MYL3,PPP2R4,DNAJB6,TBC1D20,AGTR2,MYC,VAV1,NF1,PAFAH1B1,BBC3,TBC1D9B,CFLAR,PYCARD,TBC1D24,CDKN2A,NMUR1,TPM2,TBC1D30,CENTD3,CENTD1,VCP,TBC1D2,LPAR2,BIRC5,AMPH,TPM1,PTMA,C9,SMAP1,NR4A1,TBC1D13,TSC1,CENTA1,A630047E20RIK,TBC1D22B,TBC1D8B,TSC2,FGD5,SAPS1,VAV3,IFT57,ARHGAP1,SGSM1,NEIL1,APAF1,ADCYA,P1R1,LCK,FGD4,CDH1,GCHFR,DDEF1,TBC1D22A,RGN,TBC1D21,TNNI3,GDI1,FABP1,TRP53,RASGRF1,MTCH1,SMAP2,RHOA,APOC2,ABHD5,ANGPTL3,PML,APOA2,TBC1D15,DLCL1,BAX,PLCB2,CENTB1,CCKBR,SYDE2,GNA15,BCL2L13,TBC1D25,PLA2G1B,CAV1,F2,HRBL,HSPA1A,EVI5,CASP4,PMAIP1,TBC1D7,HRB,GM2A,NOD1,STMN3,FANCG,SGSM3,CENTB2,CYCS,TNNT3,ARFGAP3,COL4A3,ANG,GABARAPL2,TBC1D17,SAPS3,NMUR2,GIT2,IFNB1,RAB3GAP1,S1PR1,TBC1D23,LEPR,MOAP1,SFN,CHM,ERN1,ARHGA
GO:0050994	0.6332206	0	0	10	regulation of lipid catabolic process	ADORA1,MLYCD,APOA5,PPARA,FRAP1,CPT1A,FABP1,CIDEA,ANGPTL3,APOA2
GO:0048169	0.4110225	0	0	28	regulation of long-term neuronal synaptic plasticity	GRIN2B,DLG4,SYNGAP1,LNPEP,RIMS1,GRIN2A,EPHB2,DRD5,HRAS1,BDNF,NF1,SNCA,KIT,GRIN1,GRM5,PLK3,KRAS,NRAS,S100B,EGR1,NPTN,KDR,GRIK2,DRD1A,DRD2,CAMK2G,AGT,GRIK1
GO:0001505	0.2561141	0	0	166	regulation of neurotransmitter levels	SNPH,CACNA1A,PCLO,PPFIA3,SPNB3,GRIN2B,STX1A,ADORA1,CPLX2,SEPT5,NGF,CAMK2A,NPY2R,DRD4,UNC13A,NRXN1,VAMP2,RIMS1,GRIN2A,CACNA1B,BTK,PRKCB1,GDNF,TPH1,SYN1,SLC17A7,SYN2,SYN3,APBA1,RAB3A,EPAS1,GCH1,SLC6A4,NRXN2,LIN7C,PNMT,SNCB,GABRA2,TGFB2,GRM7,SNAP25,APBA2,ARHGFE11,NLGN1,CELSR1,EDN3,COLOQ,NISCH,LPHN1,CPLX1,AGTPBP1,GATA3,BDNF,DOC2A,SV2B,COMT,ERC2,GRIK5,SYT1,NF1,SNCA,RAB3C,RAB15,NSF,STX7,PRIMA1,GRM2,DYNLL1,LIN7A,ADRBK1,SLC1A3,HNMT,NR4A2,CACNA1F,IL1B,NPR1,KCNMB4,ATP7A,STX3,HCRT,GLUL,PSEN1,LIN7B,CACNB4,IL1RN,NRXN3,GCHFR,HPRT1,CHRNA7,TRIM9,CHRN8,DBH,CARTPT,WNT7A,PRG3,PINK1,SYT3,YWHAZ,CLN8,SYT4,CADPS,TH3,AP3M2,DVLI1,RIMS4,NALAD2,NTRK2,CHRN2,GRM4,ADORA3,ACHE,RAB14,TRH,PPT1,ALDH9A1,CPLX4,SLC17A6,SLC25A4,SLC22A3,ALDH5A1,PDYN,MAOB,PARK2,ATP1A2,HTR2A,NOS1AP,CHAT,SYT2,CHRNA6,HRH3,HTR2C,CHRNA4,DRD3,SLC5A7,PARK7,RAB26,MAOA,SLC6A3,SYT12,CHRNA3,STX4A,NPY5R,UNC13B,GIPIC1,CPLX3,SNAPIN,UNC13C,TPH2,BAIAP3,PLDN,DRD1A,DRD2,ABAT,SNCAIP,CLN3,AGT,HTR1B,GRM8,ICA1,MYO6,STXB2,ADORA2A,GRIK1,GAD2,GAD1,DDC
GO:0002700	0.5901303	0	0	15	regulation of production of molecular mediator of immune response	BCL10,BCL6,IL13,FOXP3,TRAF6,TRAF2,FCER1G,SASH3,IL21,MAP3K7,NOD2,FOXP1,HMOX1,MALT1,IL13RA1
GO:0046578	0.2274692	0	0	189	regulation of Ras protein signal transduction	KALRN,GIT1,PLEKHG5,ALS2,IQSEC2,BCL6,SOS1,CENTG3,SYDE1,PTK2B,TIAM1,ARHGFE10,D10BWG1379E,TNK1,IQSEC3,RGNEF,TRIO,ARHGFE5,TBC1D16,TBC1D14,TBC1D10C,DEPDC2,CENTB5,FARP1,ARFGFE2,ARHGFE12,ARHGFE10L,TBC1D10A,ARHGAP20,ARHGFE17,FGD3,ERBB2,RASGRP4,IQSEC1,CENTG2,ABR,ITSN2,SOS2,TBC1D9,ECT2,TBC1D10B,VAV2,D10ERTD610E,TBC1D5,GBF1,PSCD3,PSD,ARHGFE4,FGD1,CDH2,PSD4,PPP2CB,ARHGAP4,RABGAP1L,ARHGFE11,ADPRHL1,TTN,SGSM2,CENTG1,EVI5L,TIMP2,PSCD1,KITL,NET1,TBC1D20,VAV1,MFN2,RASGRF2,PSD3,NF1,PAFAH1B1,TBC1D9B,TBC1D24,ITSN1,TBC1D30,CENTD3,CENTD1,NRG1,BCR,TBC1D2,ITPKB,SMAP1,TBC1D13,TSC1,CENTA1,TIAM2,A630047E20RIK,BC067047,FARP2,TBC1D22B,TBC1D8B,FGD5,VAV3,ARHGFE16,DOCK2,PLEKHG4,SGSM1,FGD4,ARHGFE7,DDEF1,TBC1D22A,ARFGFE1,TBC1D21,USP36,NUP62,RASGRF1,SMAP2,TBC1D15,PLEKHG3,DLCL1,ARHGFE2,CENTB1,SYDE2,TBC1D25,CSF1,PSCD2,ARF6,HRBL,PSD2,4933429F08RIK,EVI5,DNMBP,KRAS,MCF2L,TBC1D7,RAC1,HRB,EPO,CRK,E130112L23RIK,STMN3,SGSM3,NOTCH2,CENTB2,ARPP19,ARHGFE6,ARHGFE9,ARFGAP3,E130306D19RIK,NRAS,TBC1D17,IGF1,SH2B2,GIT2,S1PR1,TBC1D23,PLEKHG1,OBSCN,CENTD2,FGD6,ARHGFE19,PLCE1,TBC1D12,PLEKHG6,ABRA,TBC1D8,CENTA2,RALBP1,FBXO8,FOXJ1,TBC1D4,GRTP1,FGD2,DDEF2,ARHGFE3,ARFGAP1,RABGA
GO:0035023	0.3576424	0	0	85	regulation of Rho protein signal transduction	KALRN,PLEKHG5,ALS2,BCL6,SOS1,SYDE1,PTK2B,TIAM1,ARHGFE10,RGNEF,TRIO,ARHGFE5,DEPDC2,FARP1,ARHGFE12,ARHGFE10L,ARHGAP20,ARHGFE17,FGD3,ABR,ITSN2,SOS2,ECT2,VAV2,D10ERTD610E,ARHGFE4,FGD1,CDH2,ARHGAP4,ARHGFE11,TTN,NET1,VAV1,RASGRF2,PAFAH1B1,ITSN1,CENTD3,BCR,TSC1,TIAM2,BC067047,FARP2,FGD5,VAV3,ARHGFE16,PLEKHG4,FGD4,ARHGFE7,RASGRF1,PLEKHG3,DLCL1,ARHGFE2,SYDE2,4933429F08RIK,DNMBP,MCF2L,RAC1,E130112L23RIK,STMN3,ARHGFE6,ARHGFE9,E130306D19RIK,PLEKHG1,OBSCN,CENTD2,FGD6,ARHGFE19,PLEKHG6,ABRA,RALBP1,FOXJ1,FGD2,ARHGFE3,AKAP13,ARHGFE18,DOCK7,ARHGAP27,9130221D24RIK,SLC26A10,SPATA13,PLEKHG2,ARHGFE1,NGEF,MCF2,ARHGFE15
GO:0051931	0.7458762	0	0	13	regulation of sensory perception	HBA-A2,NPY2R,GRIN2A,CCK,NOS1,IL10,GRM1,GRM3,EDNRB,HTR2C,F2R,ADRB2,GRIN2D

Table S1A. Gene sets up-regulated by severe stress

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0051056	0.1912763	0	0	250	regulation of small GTPase mediated signal transduction	SIPA1L1,KALRN,GIT1,PLEKHG5,ALS2,IQSEC2,BCL6,SOS1,SIPA1L3,CENTG3,RELN,SYDE1,PTK2B,RAPGEF1,TIAM1,SYNGAP1,ARHG EF10,KNDC1,D10BWG1379E,TNK1,IQSEC3,RGNEF,TRIO,ARHGEF5,TBC1D16,TBC1D14,TBC1D10C,DEPDC2,CENTB5,FARP1,IQG AP2,ARFGEF2,DAB2IP,ARHGEF12,CDC42BPB,ARHGEF10L,TBC1D10A,ARHGAP20,RAPGEF2,ARHGEF17,FGD3,ERBB2,RASGRP4,I QSEC1,CENTG2,RALGDS,ABR,ITSN2,SOS2,TBC1D9,ECT2,TBC1D10B,VAV2,D10ERTD610E,RASGRP1,TBC1D5,GBF1,TAPBP,PSCD3 ,PSD,ARHGEF4,FGD1,CDH2,RGL1,PSD4,PPP2CB,ARHGAP4,RABGAP1L,ARHGEF11,LTB,ADPRHL1,TTN,SGSM2,CENTG1,CDC42BP A,EVI5L,TIMP2,PSCD1,KITL,NET1,TBC1D20,VAV1,MFN2,RASGRF2,PSD3,NF1,PAFAH1B1,TBC1D9B,TBC1D24,GARNL4,A430107 D22RIK,ITSN1,TBC1D30,CENTD3,CENTD1,NRG1,BCR,TBC1D2,ITPKB,LST1,SMAP1,TBC1D13,TSC1,CENTA1,RASGEF1C,TIAM2,A6 30047E20RIK,BC067047,FARP2,TBC1D22B,TBC1D8B,TSC2,RASGEF1A,FGD5,VAV3,ARHGEF16,DOCK2,PLEKHG4,SGSM1,A23006 7G21RIK,GARNL3,DDR1,FGD4,ARHGEF7,DDEF1,TBC1D22A,RAPGEF5,RGL3,ARFGEF1,TBC1D21,ATP6V1G2,USP36,NUP62,WDR 46,RASGRF1,B230339M05RIK,SMAP2,RASAL2,RASA3,TBC1D15,B3GALT4,PLEKHG3,DLCL1,ARHGEF2,CDC42BPG,CENTB1,SYDE2, POU5F1,TBC1D25,CSF1,RASAL1,PSCD2,ARF6,HRBL,PSD2,4933429F08RIK,EVI5,DNMBP,KRAS,MCF2L,TBC1D7,ZBTB9,RAC1,HRB
GO:0050803	0.498238	0	0	22	regulation of synapse structure and activity	KLK8,PVRL1,SYNGAP1,PRKCA,PTPRF,USH1C,CYP19A1,SNAP25,GHSR,UBB,GHRL,PTK2,AGRN,WNT7A,COL4A4,SYT10,APP,CHRN B2,PPT1,THBS2,MUSK,PICK1
GO:0048167	0.4365919	0	0	75	regulation of synaptic plasticity	SIPA1L1,PPFIA3,PLAT,GRIN2B,DLG4,ADORA1,YWHAG,SYNGAP1,NCDN,ADRB1,LNPEP,RIMS1,GRIN2A,MMP9,HTT,EPHB2,CAMK 2N2,ATP2B2,DRD5,HRAS1,CTNND2,LZTS1,SYP,P2RX3,YWHAH,EGR2,BDNF,BHLHB2,UBB,NF1,SNCA,CABP1,NFATC4,CRHR1,KIT ,RHEB,DBN1,GSK3B,RNF39,GRIN1,GRIN2C,GRM5,PSEN1,PLK3,RASGRF1,ARC,KRAS,NRAS,MYLK2,S100B,CPEB1,NTF5,EGR1,VGF ,NPTN,PPT1,APOE,CALB1,BCAN,STAR,PSEN2,KDR,GRIK2,GIPC1,CTNNA4,CDK5,PMCH,DRD1A,DRD2,CAMK2G,AGT,BHLHB3,MYO 6,ADORA2A,GRIK1
GO:0045580	0.2253941	0	0	46	regulation of T cell differentiation	BCL6,IRF4,CARD11,IL7R,FOXP3,IL7,IL15,ZAP70,AP3B1,SPINK5,ADA,BAD,IL2RA,H2-OA,HLX,CD1D1,CD74,ITPKB,IL2RG,RC3H1,IL6,SASH3,IL12RB2,AP3D1,H2-AA,CD86,IL27,IL4RA,CD80,LCK,SOC5,SOD1,HSP90AA1,SYK,SHH,CD27,PTPRC,IL2,PNP1,CD2,VNN1,SART1,FOXJ1,TGFBR2,CLPT M1,H2-DMA
GO:0050856	0.8569281	0	0	10	regulation of T cell receptor signaling pathway	BCL10,THY1,CBLB,TRAT1,PTPN6,PAWR,ELF1,LCK,UBASH3A,MALT1
GO:0002026	0.8655894	0	0	16	regulation of the force of heart contraction	MYH6,MYL4,SLC8A1,ADRB1,PRKCA,ADRA1A,CSR3P,PLN,MYL3,ADRBK1,ATP1A1,GAA,ATP2A2,APLN,ATP1A2,ADRA1B
GO:0007266	0.1686133	0	0	125	Rho protein signal transduction	KALRN,PLEKHG5,ALS2,BCL6,SOS1,SYDE1,PTK2B,TIAM1,ARHGEF10,ARHGDI,GRIT,RGNEF,TRIO,ARHGEF5,DEPDC2,FARP1,ARH GEF12,ARHGEF10L,ARHGAP20,ARHGEF17,FGD3,APOC3,APOA1,ABR,ITSN2,SOS2,ECT2,VAV2,D10ERTD610E,ARHGEF4,FGD1,C DH2,ARHGAP4,ARHGEF11,CFL1,TTN,RHOB,NET1,VAV1,RASGRF2,PAFAH1B1,GNA12,ITSN1,CENTD3,BCR,LIMK1,CDC42EP5,RH OD,TSC1,TIAM2,BC067047,FARP2,CDC42EP4,FGD5,CNKSR1,PTH,VAV3,ARHGEF16,ARHGAP1,PLEKHG4,FGD4,ARHGEF7,BAIP2 ,RASGRF1,PTPLAD1,RHOA,PLEKHG3,DLCL1,ARHGEF2,SYDE2,KIFAP3,4933429F08RIK,TAX1BP3,DNMBP,MCF2L,ARHGAP29,ADR A2A,RAC1,E130112L23RIK,STMN3,ARHGEF6,ARHGEF9,E130306D19RIK,ABCA1,PECAM1,PLEKHG1,OBSCN,ARHGAP6,SYNJ2BP, CENTD2,FGD6,ARHGEF19,APOE,PLEKHG6,ABRA,RALBP1,RHOG,CDC42,FOXJ1,FGD2,ROCK1,RTKN,ARHGEF3,GNA13,SRGAP1,C DC42EP1,CDH13,AKAP13,ARHGEF18,DOCK7,ARHGAP5,ARHGAP27,MYO9B,9130221D24RIK,SLC26A10,SPATA13,PLEKHG2,AR HGEF1,RHOJ,NGEF,ARHGDI,ARHGDI,CTNNA1,MCF2,ARHGEF15
GO:0045214	0.8688109	0	0	14	sarcomere organization	XIRP1,MYH6,MYBPC3,CAPN3,BMP10,NEB,TTN,TCAP,KRT19,KRT8,ACTG1,NEURL2,ITGB1,TNNT2
GO:0007268	0.2859138	0	0	451	synaptic transmission	KLK8,SIPA1L1,NPTX1,SNPH,GABBR2,CACNA1A,PCDHB13,SLC6A5,ALS2,GABBR3,PCLO,PPFIA3,SHC3,KCNMA1,PLAT,CLSTN2,SP NB3,GRIN2B,BSN,DLG4,CACNA1E,PVRL1,CHRM1,STX1A,EGR3,ADORA1,KIF1B,CACNA1C,CPLX2,YWHAG,SLC1A2,ATXN1,SYNGA P1,SEPT5,NGF,CAMK2A,MYO5A,NPY2R,NCDN,DRD4,ADRB1,UNC13A,TNF,NRXN1,LNPEP,CHRNE,KCND2,PRKCA,VAMP2,RIMS1 ,GRIN2A,DNAJC5,ADRA1A,CORT,MMP9,NPTX2,KCNQ5,CACNA1B,BTK,PRKCB1,HTT,CHRNA1,SCN1B,GDNF,TPH1,EPHB2,SYNJ1,F REQ,CAMK2N2,PTPRF,DLGAP1,GABRA5,SLC17A7,TMOD2,SYN2,CLSTN1,NPFF,SYN3,CAMK4,APBA1,CHNRG,RAB3A,KIF5A,ATP2 B2,NLGN2,PPP3CA,EPAS1,STRN4,SLC1A6,CHRNA9,CD24A,HTR1F,KCNQ2,GCH1,P14KA,GABRP,USH1C,NTRG1,CHRNA2,SLC6A4, DRD5,KCNQ3,HRAS1,CTNND2,CHRM3,SLC6A2,GRIA1,NRXN2,STX1B,HOMER1,KCNN1,TAC4,LPAR3,LZTS1,LIN7C,PNMT,CYP19A 1,SNCB,GABRA2,GRIK4,TGFB2,GRM7,SNAP25,APBA2,ASZ1,KCNIP2,SYP,GHSR,ARHGEF11,NLGN1,P2RX3,CHRN1,NPBWR1,YW HAH,CELSR1,EDN3,EGR2,SYT5,COLQ,OMP,ACP2,NISCH,PRKCZ,LPHN1,CPLX1,AGTPBP1,GATA3,BDNF,BHLHB2,DOC2A,SV2B,CO MT,PCDHB4,ERC2,GRIK5,UBB,SYT1,NF1,PAFAH1B1,UTS2,SNCA,RAB3C,CABP1,CHRNA5,RAB15,NSF,STX7,NFATC4,PRIMA1,EDN 1,CRHR1,KIT,GRM2,GUC1,DYNLL1,CLSTN3,ACP1,LIN7A,ADRBK1,SLC1A3,HNMT,ACCN1,NR4A2,NRG1,PCDHB3,WNT2,GNAI1,KCN
GO:0016079	0.813515	0	0	30	synaptic vesicle exocytosis	SNPH,PCLO,SPNB3,STX1A,CPLX2,SEPT5,VAMP2,RIMS1,APBA1,RAB3A,SNAP25,APBA2,NLGN1,LPHN1,CPLX1,DOC2A,GRIK5,SYT 1,STX7,STX3,PSEN1,TRIM9,SYT3,SYT2,STX4A,UNC13B,CPLX3,SNAPIN,PLDN,STXB2
GO:0048489	0.6680353	0	0	51	synaptic vesicle transport	SNPH,PCLO,SPNB3,DLG4,STX1A,CPLX2,SEPT5,UNC13A,VAMP2,RIMS1,SH3GL2,SLC18A2,SYNJ1,APBA1,RAB3A,CD24A,BIN1,SN AP25,APBA2,SYP,NLGN1,LPHN1,CPLX1,DOC2A,GRIK5,SYT1,SNCA,STX7,ITSN1,LIN7A,AMPH,STX3,PSEN1,DENND1A,CTNNB1,TR IM9,SYT3,SYT4,STXB1,ZDHHC15,MYLK2,EEA1,SYT2,STX4A,UNC13B,CPLX3,SNAPIN,CDK5,PLDN,DNM2,STXB2

Table S1A. Gene sets up-regulated by severe stress

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0007416	0.3379588	0	0	45	synaptogenesis	NRCAM,CACNA1A,PCDHB13,PVRL1,NRXN1,PRKCA,POU4F1,NLGN2,NRXN2,CDH2,SNAP25,GHSR,NLGN1,PCDHB4,LRP4,UBB,CADM1,NRG1,PCDHB3,PCDHB16,PCDHB14,GLRA2,PCDHB2,GHRL,PTK2,PCDHB9,CDH1,NRXN3,DNER,AGRN,WNT7A,SPOCK2,COL4A4,GJA10,PCDHB5,APP,CHRN2,ACHE,GPHN,PCDHB6,THBS2,PCDHB11,MUSK,MYO6,PCDHB10
GO:0050852	0.3761917	0	0	27	T cell receptor signaling pathway	BCL10,THY1,CBLB,FOXP3,TRAT1,TRAF6,ZAP70,PTPN6,UBE2N,CACNB3,PTPN22,CD3E,MAPK1,PAWR,BCAR1,ELF1,PSEN1,CACNB4,LCK,MAP3K7,FYN,UBASH3A,PTPRC,MALT1,IKBKG,CLEC2I,PSEN2
GO:0042403	0.7474303	0	0	16	thyroid hormone metabolic process	DIO1,CACNA1A,DIO2,RELN,SLCO4A1,KCNJ6,CGA,SULT1B1,TG,DIO3,TPO,SLC5A5,MED1,FOXE1,DUOX2,TTR
GO:0007351	0.8415342	0	0	9	tripartite regional subdivision	TDGF1,HOXB6,TCF3,PCSK6,TBX3,NCKAP1,FRS2,HOXD8,T
GO:0001829	0.5716052	0	0	11	trophectodermal cell differentiation	ESRRB,HAND1,FOXD3,ADA,JUNB,NODAL,SRF,HOPX,SP3,CITED2,SP1
GO:0016055	0.2407138	0	0	144	Wnt receptor signaling pathway	MARK4,CELSR2,KREMEN1,FZD5,WNT1,HHEX,FZD10,WNT10A,BCL9,FRZB,FOXL1,WNT7B,KREMEN2,RSP03,AXIN1,DVL3,AES,TCF3,LRP1,WNT2B,RSP04,TLE3,PYGO1,WNT8B,CSNK1E,DKK3,NKD2,CTNBP1,ZEB2,CSNK1G1,MET,WNT16,SFRP5,WNT5B,DKK1,APC,ASZ1,TLE1,TLE6,WNT8A,FGF10,FBXW2,FZD9,CXXC4,WNT3,FZD1,MACF1,PPP2R1A,APC2,LRP4,WISP1,CSNK1G3,LRP5,FZD4,LEF1,FZD2,CPZ,NDPH,WNT2,SFRP4,PYGO2,NXN,WNT3A,RSP01,WNT5A,CALCOCO1,LRRFIP2,ZBTB33,PIAS4,DACT1,CAV2,GSK3B,ROR2,TSC2,FZD7,LRP6,TGFB1I1,SLC9A3R1,DKK2,CAPZA2,CSNK1G2,WNT10B,DKK4,FRAT2,CTNBP1,WIF1,CTNND1,WNT11,SENP2,WNT4,TCF7,BARX1,WNT7A,FBXW4,PROP1,NLK,AXIN2,HBP1,BTRC,MDFI,CSNK2A2,SOSTDC1,WNT9A,SIX3,CHD8,DVL1,AX1BP3,RSP02,FBXW11,WNT6,CSNK2B,CCDC88C,LDB1,FZD3,CSNK1D,CSNK2A1,MDFIC,PEG12,FZD6,INVS,MITF,GSC,TLE2,FZD8,PPAP2B,TLE4,SFRP1,DIXDC1,HNF1A,FGF9,FRAT1,SFRP2,CBY1,CSNK1A1,PITX2,DVL2,PORCN,PPP2CA,WNT9B,NKD1,CTTNBP2,KLHL12,BRD7,TCF7L2

Table S1B. Gene sets down-regulated by severe stress

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene set description	Gene set genes
GO:0009200	-1.06424	0	0	10	deoxyribonucleoside triphosphate metabolic process	ADA,DUT,NUDT1,PNP1,CMPK2,TBPL1,RRM2B,DTYMK,DGUOK,NUDT15
GO:0045022	-0.9492	0	0	8	early endosome to late endosome transport	IGH-6,LYST,VPS4B,EEA1,SNX16,FLNA,ANKRD27,HAP1
GO:0008333	-0.57461	0	0	8	endosome to lysosome transport	VAMP7,SORT1,RHOB,LYST,M6PR,CHMP5,SNX1,ADRB2
GO:0042462	-0.97505	0	0	17	eye photoreceptor cell development	RPGRI1,THY1,RBP3,CRB1,BBS4,RORB,PSEN1,NTRK2,GABRR2,VEGFA,PRKCI,NRL,CEP290,ALMS1,PAX6,OLFM3,RPGR
GO:0009396	-0.71359	0	0	9	folic acid and derivative biosynthetic process	MTR,MTHFD1L,DHFR,MTHFS,MTHFD1,MTHFSD,ALDH1L1,FPGS,MTHFD2
GO:0006536	-0.61263	0	0	13	glutamate metabolic process	AMDHD1,GLUD1,GOT2,GLUL,NAGS,PRODH,PRODH2,ALDH5A1,GCLM,GOT1,GCLC,GAD2,GAD1
GO:0009065	-0.9563	0	0	17	glutamine family amino acid catabolic process	GLUD1,PADI3,GOT2,FAH,PRODH,GLS,ARG2,ARG1,DDAH1,PRODH2,ALDH4A1,GOT1,DDAH2,ASL,GAD2,GAD1,ASRGL1
GO:0006298	-0.69509	0	0	16	mismatch repair	PMS1,MSH2,MLH3,ANKRD17,MUTYH,PMS2,TDG,ABL1,MLH1,MSH3,MSH4,MSH5,MSH6,TREX1,EXO1,POLD3
GO:0042177	-0.53352	0	0	8	negative regulation of protein catabolic process	GRIN2A,INS2,GRIN2C,SHH,RELA,SERPINB12,MDM4,UCHL5IP
GO:0050805	-0.52291	0	0	19	negative regulation of synaptic transmission	ADORA1,NPY2R,ADRA1A,GRM2,GNAI1,KCNQ4,GNAI2,GRM4,ACHE,SLC6A1,HTR2A,GRIK2,NPY5R,CDK5,PMCH,DRD2,BCHE,HT R1B,GRIK1
GO:0000398	-0.61113	0	0	147	nuclear mRNA splicing, via spliceosome	CPSF2,GEMIN7,TNRC4,POLR2A,POLR2J,HNRNPA0,PRPF8,MYOD1,SNUPN,BRUNOL4,EFTUD2,RNUXA,DBR1,DDX20,TXNL4A,SNRPD2,HNRPUL1,POLR2G,SNRPD3,PPP1R8,SMN1,GTFF2F1,PTBP1,POLR2L,CSTF1,GATC,SF3A1,THOC4,SF3A2,POLR2E,SF3B3,NHP2L1,GEMIN5,U2AF1,CUGBP1,POLR2H,CDC40,YBX1,CLNS1A,LSM7,ASCC3L1,POLR2F,SNRPG,SIP1,CUGBP2,PRMT5,SF3B4,CPSF1,SRPK2,CRNKL1,FUS,NUDT21,DHX9,SF3B2,PCBP1,GEMIN6,RNPS1,KHSRP,PTBP2,GEMIN4,PRPF6,LSM3,POLR2I,DDX23,CPSF3,SF3A1,SF4,POLR2B,SMC1A,GTFF2F2,SFRS10,SLU7,USP39,LSM8,SNRNP,DDX39,POLR2C,HNRNPC,HNRNPL,SNRPA,SNRPB2,HNRNP R,DHX38,HNRNPD,PAPOLA,SFRS2IP,SNRPD1,SNRPE,SFRS11,SF3B5,SF3A3,SNRPF,SFRS2,U2AF2,WDR77,CD2BP2,DHX16,PCF11,PRPF4,TXNL4B,SF1,SNW1,POLR2K,DDX1,PHF5A,MBNL1,CWC15,NCBP2,SFRS9,HNRNPU,CLP1,TGS1,PCBP2,NOVA1,NFX1,PRPF31,PRPF3,SFRS8,RBM8A,RBM5,SFRS6,CSTF3,SNRPA1,SFRS3,HNRNPA2B1,PABPN1,LSM2,BAT1A,SMNDC1,RBM25,CCAR1,GEMIN8,SRRM1,TRA2A,SF3B1,FUSIP1,MAGOH,DNAJC8,HNRNPA1,SFRS1,SFRS5,SNRP70,UPF3B,RBMX,POLR2D,CSTF2,SFRS7
GO:0006779	-0.72847	0	0	18	porphyrin biosynthetic process	ALAS2,TSPO,FECH,IREB2,COX10,ALAD,ALAS1,CPOX,COX15,UROD,HNF1A,NFE2L1,HMB5,SUCLA2,MMAB,UROS,PPOX,RSAD1
GO:0032388	-0.59411	0	0	20	positive regulation of intracellular transport	TNF,GSK3B,GLI3,CDH1,TRIP6,RHOA,SMO,SHH,CD27,TNFSF14,PRKACA,SMAD3,IAK2,EDA,NCBP2,FLNA,EDAR,PRKCQ,CAPN10,UACA
GO:0001522	-0.52902	0	0	14	pseudouridine synthesis	RPUSD3,NOLA2,NOLA3,PUS7L,PUSL1,RPUSD2,TRUB2,DKC1,RPUSD1,PUS1,PUS3,PUS7,RPUSD4,TRUB1
GO:0050764	-0.2518	0	0	20	regulation of phagocytosis	PTEN,FCER1G,GATA2,FCGR2B,AHS6,SPACA3,CD209B,PTK2,SFTPD,FCGR3,PTX3,CLEC7A,MFGE8,SIRPB1,SIRPA,C3,SCARB1,TGFB1,CD47,FCGR1
GO:0008380	-0.54283	0	0	259	RNA splicing	LSM11,CPSF2,GEMIN7,SF2,TNRC4,ARL6IP4,PPP1R9B,PPIL3,LSM4,POLR2A,WBP11,POLR2J,SNRPN,HNRNPA0,PRPF8,MYOD1,RBMY1A1,SNUPN,BRUNOL4,SCNM1,PABPC1,EFTUD2,PPP2R1A,RNUXA,DBR1,6330548G22RIK,DDX20,RBM17,ZRSR2,SCAF1,TXNL4A,PPIL1,SNRPD2,TSEN2,HNRPUL1,POLR2G,SNRPD3,PPP1R8,SMN1,GTFF2F1,PTBP1,POLR2L,CSTF1,RBM4B,GATC,PPP4R2,SF3A1,A2BP1,THOC4,3300001G02RIK,TTF2,RBM22,SF3A2,POLR2E,SF3B3,NHP2L1,GEMIN5,ZMAT5,RRAGC,U2AF1,CUGBP1,TFIP11,MPHOSPH10,POLR2H,CDC40,PPAN,REFBP2,YBX1,WBP4,DHX8,CLNS1A,LSM7,LSM5,ASCC3L1,THOC3,POLR2F,PPARGC1A,LSM6,SNRPG,SIP1,CUGBP2,PRMT5,YTHDC1,SF3B4,CPSF1,SRPK2,LSM10,PRPF38A,CRNKL1,CDC5L,TSEN34,TRPT1,SFRS14,RALY,FUS,NUDT21,DHX9,NONO,PPIG,SF3B2,PRPF40B,PCBP1,ISY1,GEMIN6,RNPS1,KHSRP,PTBP2,LSM1,U2AF1L4,PRPF40A,MAGOHB,GEMIN4,PRPF6,STRAP,SNRPC,SFRS12IP1,LSM3,POLR2I,DDX23,ZCRB1,DDX46,CPSF3,PRPF19,SFRS4,SF4,XAB2,BC003993,POLR2B,NOL3,SMC1A,GTFF2F2,PIIE,SFRS10,SLU7,USP39,LSM8,SNRNP,DDX39,PRPF18,POLR2C,HNRNPC,HNRNPL,SNRPA,1700023B02RIK,RBMXRT,SNRPB2,HNRNPR,DHX38,FRG1,HNRNPD,PAPOLA,SART1,SFRS2IP,6530403A03RIK,SNRPD1,DDX5,PIIH,EIF4A3,1500041N16RIK,SNRPE,SFRS11,SF3B5,SF3A3,2510012J08RIK,SNRPF,SFRS2,U2AF2,WDR77,CD2BP2,RBM4,DHX16,PCF11,PRPF4,

Table S2A. Gene sets up-regulated by mild stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0006519	0.1100191	0.00	0	372	amino acid and derivative metabolic process	PPAT,MOXD1,OA2Z,AARSD1,YARS2,GGH,TTR,INDOL1,PDZD2,ATRN1,ACADM,DND1,ADC,GCAT,ATP7A,HTR2C,D630004A14RIK,K,AARS2,ENPP6,THNSL1,ATP2B2,CLN3,AASS,BCAT1,SLC7A6,DRD2,DIO3,AUH,HPRT1,SHMT1,DARS,PLXNB2,BCKDHB,QDPR,GCLC,ASRGL1,TARSL2,DNMT1,PEMT,BPHL,SDSL,CHRN2,MARS,ETNK1,AK3,GM853,TCF19,ABAT,UROC1,AGXT,PARK2,ACHE,HIBADH,PCBD1,TH,PRG3,OA2Z,ASNSD1,TPR,SMS,SARDH,ACTN3,SAT1,NFS1,PSAT1,CKB,DLAT,SLC7A7,KARS,GATM,PCCB,CTPS2,SLC6A3,DTD1,DHPS,GGT5,DDC,SI,COMT,HDC,GAD2,CAD,RARS2,ACAD8,DDR1,ALDH5A1,SNCB,ASTN1,SLC5A7,SLC22A17,NPR1,GS TZ1,PLOD1,GATA3,GOT2,CKMT1,CDO1,P4HB,PADI4,A230051G13RIK,SMOX,TYRP1,PTS,GAD1,COLQ,FARSA,INS2,PADI2,ODC1,DALRD3,DHFR,GFPT1,GFPT2,DRD1A,CPT1A,FOXE1,DDT,PYCR1,MAT2A,ALDH18A1,POU5F1,DDAH1,ICMT,SEPHS2,CHKA,AFMID,OAT,FRRS1,PCYT2,COL11A2,SULT1B1,DOHH,MTHFR,SLC22A5,HMG20B,SLC7A5,DUS4L,B3GALT4,HAL,AMT,GLUD1,DNMT3A,GOT1,DMGDH,GAMT,TAS1R2,GLS2,DRD4,ATP6V1G2,HDP,DDO,BHMT,TPMT,SLC45A2,ADI1,PCCA,TYR,CTPS,SLC04A1,PHF1,GCLM,LARS2,ARID2,AZIN1,PNMT,SARS2,MAOA,WDR92,IARS,DPYS,FAH,FARSB,DIP2A,AANAT,MCCC1,OA2Z,ACMSD,HARS,MOXD2,HNRPL,ASPA,AMD1,ASPA,DUOX2,SARS,GMPS,ASNS,TOR3A,BCKDK,PAH,LEM1,PHGDH,TPO,SULT1A1,EIF5A,ATF4,EIF2AK4,MTHF
GO:0006520	0.0704953	0.00	0	273	amino acid metabolic process	PPAT,MOXD1,AARSD1,YARS2,GGH,INDOL1,PDZD2,ATRN1,DND1,ADC,GCAT,ATP7A,D630004A14RIK,AARS2,THNSL1,CLN3,AA SS,BCAT1,SLC7A6,AUH,SHMT1,DARS,PLXNB2,BCKDHB,QDPR,GCLC,ASRGL1,TARSL2,SDSL,MARS,AK3,TCF19,UROC1,AGXT,HIBADH,PCBD1,TH,ASNSD1,TPR,SMS,SARDH,ACTN3,NFS1,PSAT1,DLAT,SLC7A7,KARS,PCCB,CTPS2,DTD1,GGT5,SI,COMT,HDC,GAD2,CAD,RARS2,ACAD8,DDR1,ALDH5A1,ASTN1,SLC22A17,GSTZ1,PLOD1,GOT2,CDO1,PADI4,A230051G13RIK,TYRP1,PTS,GAD1,FAR SA,INS2,PADI2,DALRD3,DHFR,GFPT1,GFPT2,DDT,PYCR1,MAT2A,ALDH18A1,POU5F1,DDAH1,SEPHS2,AFMID,OAT,FRRS1,COL11 A2,MTHFR,HMG20B,SLC7A5,DUS4L,B3GALT4,HAL,AMT,GLUD1,GOT1,DMGDH,TAS1R2,GLS2,ATP6V1G2,HDP,DDO,BHMT,SLC4 5A2,ADI1,PCCA,TYR,CTPS,PHF1,GCLM,LARS2,ARID2,SARS2,WDR92,IARS,DPYS,FAH,FARSB,DIP2A,MCCC1,ACMSD,HARS,MOXD 2,HNRPL,ASPA,SARS,GMPS,ASNS,TOR3A,BCKDK,PAH,LEM1,PHGDH,ATF4,EIF2AK4,MTHFD1,LARS,DAXX,GLS,TUBGCP6,KHSR P,PYCR1,POLG2,HARS2,ALDH6A1,BCKDHA,DAO1,DDAH2,PADI6,ARG1,VARS2,GSS,HPDL,IARS2,WARS2,PEPD,GARS,INDO,A530 050D06RIK,MARS2,GOT1L1,0610012D14RIK,PADI1,4933437F05RIK,WDR46,LST1,FARS2,IVD,THNSL2,CARS,KMO,SHMT2,ART4 ,QARS,BHMT2,VARS,ZBTB9,AARS,6530401N04RIK,TARS,HTT,GCH1,SIRT7,SLU7,TARS2,SCYE1,BAAT,SLC25A15,CREG2,PYCR2,M
GO:0006725	0.2091618	0.00	0	145	aromatic compound metabolic process	PPAT,MOXD1,INDOL1,PAICS,FOLR1,AK1,GPHN,ATP7A,MTHFD2,HTR2C,ATP2B2,DRD2,HPRT1,SHMT1,QDPR,MTHFS,ABHD9,AK 2,DNMT1,PEMT,CHRN2,EPHX1,ABAT,CDA,PARK2,PCBD1,TH,GART,MOC51,SLC6A3,MTHFS,DDC,SI,COMT,TYMP,HDC,CAD,A LDH5A1,SNCB,ALDH1L1,NPR1,GSTZ1,GATA3,TYRP1,PTS,ALDH1L2,DHFR,MICAL3,DRD1A,DDT,UMPS,MAT2A,PIPOX,ICMT,AFMI D,CYP1A1,FRRS1,CLYBL,SULT1B1,MTHFR,MOC52,DUS4L,DNMT3A,GAMT,DRD4,HPD,TPMT,SLC45A2,TYR,PNMT,MAOA,FOLH1, DPYS,FAH,AANAT,PRPS1L1,ACMSD,MOXD2,GMPS,TOR3A,PAH,SULT1A1,MTHFD1,TGFB2,COQ6,ALDH6A1,PRHOXNB,HPDL,MA PK1,INDO,VHLH,MTHFD1L,KMO,PRPS1,PCMT1,GNMT,PCBD2,DHODH,ENPEP,MICAL1,GCH1,DPYD,ABHD4,MOC53,GSTM4,CYP 1B1,CYP1A2,MAT1A,TDO2,EPAS1,MAT2B,YWHAH,PSG18,APRT,TAT,IL4I1,TPH1,DBH,GRIN2A,CYP4B1,AOC2,MICAL2,MTPN,SN CA,FPGS,CHRNA7,HGD,MOCOS,AADAT,FTCD,KYNU,MTR,TPH2,DCT,DNMT3B,SPR,NR4A2,SNCAIP,SQLE,ANPEP,1190003J15RIK ,ATF2,EPHX2,CYP2F2,UOX
GO:0046034	0.2626966	0.00	0	47	ATP metabolic process	ATP5F1,AK1,ATP7A,FIGNL1,ATP5J2,MYH7,MYH6,ATP6V0B,ATP5G1,LDHD,ATP5G2,ATP5G3,ATP5A1,ATP5C1,ATP5J,ATP5L,ATP 5D,SLC25A13,MYO9B,ATP5H,ATP6A1,ATP6V1F,NDUFS1,ATP5B,ATP5O,ATP6V0C,TGFB1,ND4L,ATP1A1,ATP5E,ERCC3,ACLY,AT P6V1A,ATP6V1B1,ATP6V1B2,OLA1,NADK,ABCC6,ATP6V0D2,CTNS,AK5,MON2,ATP1A2,CLCA3,ATP2A1,ENTPD1,ATP5K
GO:0046395	0.4086843	0.00	0	45	carboxylic acid catabolic process	DCI,PHYH,ACOX2,ACADM,PEX13,HADHA,HSD17B4,FRAP1,FABP3,PEX7,PPARD,ABAT,PEX5,PCCB,ALDH5A1,CPT2,ACOX3,EHHA DH,ACADS,AKR1A4,CPT1A,HADHB,PCCA,HACL1,ACOT7,ACOXL,MLYCD,CPT1B,ECHS1,ACOX1,LEP,HAO1,ACADS,ACADVL,AKR1 D1,ECH1,BDH2,FAAH,ADIPOQ,CYP39A1,PPARA,LYPLA3,CEL,FABP1,IRG1
GO:0044275	0.221493	0.00	0	104	cellular carbohydrate catabolic process	NUDT5,ADRA1B,GLB1,PGAM2,ALDOART1,OGDHL,CHIA,LDHB,PGAM1,LRR16A,FUT9,GAA,LDHAL6B,OGDH,MDH1,FUCA1,HYA L2,PGD,IGF1,HIF1A,HIBADH,TKTL1,GPI1,H6PD,ALDOA,PGK1,DLAT,6430537H07RIK,GAPDHS,GUSB,PDHB,FUT10,OVGP1,PFKL,I NS2,PYGM,BAD,MLXPL,AGL,TPI1,CHID1,PFKP,CHIT1,PGLS,MDH2,MIF,GNPDA1,LYVE1,ENO3,TREH,PKM2,PKLR,TKT,CTBS,DHT KD1,GBA2,CHI3L3,ENO1,HYAL4,ENO2,PYGL,PDHA1,PFKFB3,HK3,G6PDX,FUT8,CHI3L1,UEVLD,PGK2,GNS,PYGB,GCK,ADPGK,PFK FB1,INSR,PFKM,RPIA,ALDOC,HSD11B1,BPGM,HK1,GAPDH,CHI3L4,PDHA2,LDHC,FUT2,ARNT,HKDC1,3930401K13RIK,MGAM,FG 6PC,LDHA,FUT1,ECD,IDUA,TALDO1,ALDOART2,HYAL1,HK2,FUT4,EG277333,ALDOB,AVPR1A,FUT7

Table S2A. Gene sets up-regulated by mild stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0044242	0.1698676	0.00	0	95	cellular lipid catabolic process	SMPDL3B,DCI,PHYH,ACOX2,ACADM,PEX13,PLCB2,HADHA,PLA2G4A,GM2A,CYP27A1,PLA2G4E,HSD17B4,FRAP1,FABP3,HEXB,P EX7,PPARD,ABAT,PEX5,PCCB,ASAH3,ALDH5A1,CPT2,ACOX3,EHHADH,ACADSB,CPT1A,CYP46A1,NEU3,APOA5,ANGPTL3,SGPL1, TRERF1,HADHB,PPT1,PLA2G4C,LIPE,PLCB3,APOE,PCCA,SMPD1,HACL1,PLA2G1B,SMPD4,GALC,APOC3,ENPP7,SPHK1,PRDX6,HS D17B11,ACOT7,SRD5A2,ACOXL,MLYCD,HEXA,SMPDL3A,SNX17,PNPLA2,SMPD3,CPT1B,ECHS1,HSD11B1,LIPC,ACOX1,LEP,HAO 1,ACADS,ACADVL,AKR1D1,ECH1,AMACR,PLA2G4F,BDH2,PNPLA3,HSD17B14,NAPEPLD,PLA2G4D,GLA,YWHAH,SCARB1,HSD17 B6,FAAH,ADIPOQ,CYP39A1,PPARA,LPL,PLA2G4B,LYPLA3,APOB,CEL,AKR1C18,FABP1,SCARF1,CYP7A1
GO:0031497	0.3585335	0.00	0	109	chromatin assembly	HIST1H4I,ASF1B,HIST3H2BB,HIST1H2BG,SET,HIST1H2BN,HMGB2,HIST1H1D,HIST1H3A,HIST1H2BM,HIST2H3B,HIST1H3G,HIST 2H4,HIST1H2AN,H2AFV,SIRT2,ASF1A,SMARCA5,HIST1H2AO,HIST1H2BL,HIST2H3C1,HIST1H4H,HIST1H4D,NEFH,SIRT3,HIST1H 2AF,H3F3B,HIST2H2AC,HIST1H2BF,1700024P04RIK,HIST2H2BB,TMEM38B,HIST1H1E,H2AFY,HIST2H2AA2,HIST1H4F,HIST1H1 B,HIST1H2BB,NAP1L3,HIST1H2BH,HIST2H2AA1,H3F3A,CENPA,H2AFY2,PKN3,CHAF1B,HIST1H2BP,SIRT6,HIST1H1A,HELLS,NAP 1L5,TSPYL4,RSF1,HIST4H4,HIST1H4J,DNMT3A,SOS2,HIST1H4B,SUV39H1,MBD3,HIST1H2AK,H2AFZ,TSPYL3,HIST1H4M,MYST4, HIST1H2AA,NAP1L1,HIST1H2BC,TSPYL2,1700113O17RIK,HDAC5,HIST1H2AC,TNP1,SMARCA4,NAP1L2,H1FO,HIST2H2BE,HILS1, 1700054O13RIK,SHPRH,HIST3H2BA,SLC22A4,HIST1H3D,CHAF1A,HIST1H2AB,HP1BP3,NAP1L4,SMARCA2,SIRT7,MYST3,HIST2H 3C2,H2AFX,SIRT4,HIST3H2A,HIST1H1T,H1FOO,TSPYL1,H2AFJ,SIRT1,H1FX,HIST1H1C,TSPYL5,DNMT3B,MCM2,HIST1H2BA,CBX 8,HIST1H3F,SIRT5,HIST1H2AE
GO:0051220	0.5500402	0.00	0	11	cytoplasmic sequestering of protein	FAF1,TACC3,MDF1,MXI1,GOPC,NFKBIE,NFKBIL1,IL10,G3BP2,NFKBIA,SUFU
GO:0042994	0.5465605	0.00	0	10	cytoplasmic sequestering of transcription factor	FAF1,TACC3,MDF1,MXI1,NFKBIE,NFKBIL1,IL10,G3BP2,NFKBIA,SUFU
GO:0048813	0.2874463	0.00	0	23	dendrite morphogenesis	SGK1,ATP7A,HPRT1,CHRN2B,CIT,ACHE,SMAD1,KNDC1,CDK5,CHRNA3,DVL1,PTPRF,TLX2,CELSR2,CACNA1F,DCLK1,YWHAH,CAC NA1A,LZTS1,KLF7,SIPA1L1,MT3,DCX
GO:0009582	0.2654092	0.00	0	68	detection of abiotic stimulus	SLC12A2,OPN1MW,PLEKHB1,GNAT2,GUCA1A,ATP2B2,ABCA4,FYN,TACR1,PLCB4,GRIN2D,GPR98,NGFR,RCVRN,TRPC3,PDCL3,P KD1,UNC119,OPN3,ACCN3,SOX2,OPN1SW,TULP1,CHRNA9,PITPNM1,NOX3,GNGT2,NPFFR2,TIMELESS,RGS9BP,PDE6B,PDE6D, TAC1,PCDH15,CDH23,GNB1,OTOP1,GUCA1B,MYC,LXN,TUB,PDCL2,CHRNA10,AIPL1,NR2F6,GRK1,GRM6,CNGB1,GNAT1,OPN4, FECH,PRRXL1,SAG,ACCN1,GRIN2B,PDCL,CACNA1F,TCAP,RGR,CALCA,GJA10,MKKS,GRIN2A,NR2E3,PKD2,RHO,PDC,OPN5
GO:0009581	0.1577807	0.00	0	75	detection of external stimulus	SLC12A2,OPN1MW,PLEKHB1,GNAT2,GUCA1A,ATP2B2,ABCA4,FYN,PLCB4,GRIN2D,GPR98,NGFR,RCVRN,TRPC3,PDCL3,PKD1,U NC119,OPN3,ACCN3,SOX2,OPN1SW,TULP1,CHRNA9,PITPNM1,NOX3,GNGT2,NLRC4,PARG,RGS9BP,PDE6B,PDE6D,CLEC7A,NO D2,PCDH15,CD209B,CDH23,GNB1,OTOP1,GUCA1B,NOD1,MYC,LXN,TUB,PGLYRP4,TLR1,PGLYRP3,PDCL2,CHRNA10,AIPL1,NR2 F6,GRK1,GRM6,CNGB1,GNAT1,OPN4,FECH,PRRXL1,SAG,ACCN1,GRIN2B,PDCL,CACNA1F,TCAP,RGR,CALCA,GJA10,MKKS,GRIN2 A,NR2E3,PGLYRP1,PKD2,RHO,PDC,OPN5,TLR4
GO:0050908	0.2582851	0.00	0	37	detection of light stimulus involved in visual perception	OPN1MW,PLEKHB1,GNAT2,GUCA1A,ABCA4,PLCB4,RCVRN,TRPC3,PDCL3,UNC119,OPN3,OPN1SW,TULP1,PITPNM1,GNGT2,RG S9BP,PDE6B,PDE6D,GNB1,GUCA1B,TUB,PDCL2,AIPL1,GRK1,CNGB1,GNAT1,OPN4,SAG,ACCN1,PDCL,CACNA1F,RGR,GJA10,NR2 E3,RHO,PDC,OPN5
GO:0050974	0.4931055	0.00	0	16	detection of mechanical stimulus involved in sensory perception	SLC12A2,ATP2B2,FYN,GRIN2D,GPR98,ACCN3,SOX2,CHRNA9,PCDH15,CDH23,MYC,CHRNA10,ACCN1,GRIN2B,MKKS,GRIN2A
GO:0006323	0.2834292	0.00	0	143	DNA packaging	HIST1H4I,ASF1B,HIST3H2BB,HIST1H2BG,SET,HIST1H2BN,HMGB2,HIST1H1D,HIST1H3A,HIST1H2BM,HIST2H3B,HIST1H3G,NCA PH,HIST2H4,NUSAP1,HIST1H2AN,H2AFV,SIRT2,ASF1A,NCAPG2,H1FNT,SMARCA5,HIST1H2AO,HIST1H2BL,HIST2H3C1,HIST1H4 H,HIST1H4D,NEFH,SIRT3,HIST1H2AF,H3F3B,HIST2H2AC,HIST1H2BF,1700024P04RIK,HIST2H2BB,HAT1,TMEM38B,NCAPH2,HIS T1H1E,H2AFY,HIST2H2AA2,SEP15,HIST1H4F,HIST1H1B,HIST1H2BB,NAP1L3,HIST1H2BH,HIST2H2AA1,H3F3A,CENPA,AIFM2,H2 AFY2,PRM1,TOP2A,SMC2,PKN3,CHAF1B,HIST1H2BP,SIRT6,HIST1H1A,HELLS,NAP1L5,TSPYL4,RSF1,PRM3,HIST4H4,NCAPD3,HIS T1H4J,DNMT3A,CHMP1A,SOS2,HIST1H4B,SUV39H1,AKAP8,MBD3,HIST1H2AK,H2AFZ,SMARCC1,TSPYL3,HIST1H4M,MYST4,AS H1L,HIST1H2AA,NAP1L1,NCAPD2,HIST1H2BC,TSSK6,TSPYL2,1700113O17RIK,SMC4,HDAC5,HIST1H2AC,TNP1,POLS,SMARCA4, NAP1L2,H1FO,STRA8,ARD1,CDC45,HIST2H2BE,AIFM1,HILS1,PRM2,1700054O13RIK,SHPRH,HIST3H2BA,SYCP3,SLC22A4,NCAP G,HIST1H3D,CHAF1A,HIST1H2AB,HP1BP3,ACIN1,NAP1L4,SMARCA2,SIRT7,MYST3,HIST2H3C2,H2AFX,SIRT4,HIST3H2A,HIST1H 1T,H1FOO,TSPYL1,H2AFJ,MTA2,ENSMUSG00000074355,DFFB,SIRT1,H1FX,HIST1H1C,TSPYL5,DNMT3B,MCM2,HIST1H2BA,RO CK2,PAM,CBX8,HIST1H3F,SIRT5,HIST1H2AE
GO:0042417	0.5473565	0.00	0	22	dopamine metabolic process	ATP7A,HTR2C,DRD2,HPRT1,CHRN2B,PARK2,TH,SLC6A3,DDC,COMT,SNCB,NPR1,DRD1A,DRD4,MAOA,TGFB2,DBH,GRIN2A,SNC A,CHRNA7,NR4A2,SNCAIP
GO:0042756	1.0208784	0.00	0	11	drinking behavior	HRH3,APLN,AGTR1B,HTR1B,PMCH,ACE2,AGT,MIF,CYP11B2,AGTR1A,UCN
GO:0007492	0.272353	0.00	0	20	endoderm development	ANGPT4,MIXL1,EXT1,LHX1,NKX2- 1,HDAC1,LAMC1,CTNNB1,HNF1B,BMPR1A,GATA6,ANKRD17,ANGPT2,NOTCH1,HOXC11,PAX9,ONECUT1,NCKAP1,ARC,ANGPT 1
GO:0008210	0.9095445	0.00	0	9	estrogen metabolic process	BMPR1B,SULT1E1,COMT,H2-KE6,HSD3B1,CYP19A1,HSD17B1,CYP1B1,RDH8

Table S2A. Gene sets up-regulated by mild stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0010458	0.6145452	0.00	0	13	exit from mitosis	UBE2C,CDC23,BIRC5,SIRT2,NPM2,MAD2L1BP,ZW10,NEUROG1,TGFB1,ANLN,PPP1R9B,KNTC1,CLASP1
GO:0006635	0.5406062	0.00	0	28	fatty acid beta-oxidation	DCI,ACOX2,ACADM,HADHA,HSD17B4,FRAP1,FABP3,PEX7,PPARD,PEX5,CPT2,ACOX3,EHHADH,ACADS,ACADSB,CPT1A,HADHB,ACOXL,MLYCD,CPT1B,ECHS1,ACOX1,ACADS,ACADVL,ECH1,BDH2,ADIPOQ,PPARA,FABP1
GO:0009062	0.4892793	0.00	0	41	fatty acid catabolic process	DCI,PHYH,ACOX2,ACADM,PEX13,HADHA,HSD17B4,FRAP1,FABP3,PEX7,PPARD,ABAT,PEX5,PCCB,ALDH5A1,CPT2,ACOX3,EHHA DH,ACADS,ACADSB,CPT1A,HADHB,PCCA,HAACL1,ACOT7,ACOXL,MLYCD,CPT1B,ECHS1,ACOX1,LEP,HAO1,ACADS,ACADVL,ECH1,BDH2,F AAH,ADIPOQ,PPARA,LYPLA3,CEL,FABP1
GO:0019395	0.4625669	0.00	0	50	fatty acid oxidation	DCI,PHYH,ACOX2,ACADM,PEX13,PRKAA2,HADHA,ADIPOR1,SLC25A20,HSD17B4,FRAP1,FABP3,ACACB,PEX7,PPARD,ALOX12,PE X5,CPT2,ACOX3,EHHADH,ACADS,ACADSB,CPT1A,CD36,HADHB,GCDH,PRKAA1,HAACL1,PRKAB2,PPARGC1A,ADIPOR2,ACSL1,ACOXL,ML YCD,CPT1B,ECHS1,PRKAG2,ALOX15,MAPK14,PPARG,ACOX1,HAO1,ACADS,ACADVL,ECH1,BDH2,ADIPOQ,C1QTNF2,PPARA,ADH 7,FABP1
GO:0007631	0.393275	0.00	0	78	feeding behavior	HRH3,NPY,PEX13,GAL,TRH,NTRK2,HTR2C,IAPP,APLN,DRD2,POMC,AGTR1B,FYN,FOS,NKX2-1,CHRN2,HTR1B,PMCH,TH,GCG,CCKAR,MC4R,ACE2,AGT,HCRTR1,CRHR1,PRLHR,GHRL,APLP2,A,GLP1R,LEPR,NPY5R,DRD1A,C PT1A,CARTPT,DMBX1,MCHR1,AGRP,NMUR2,ADORA2A,CRHR2,MIF,BSX,PPYR1,CYP11B2,APP,HCRT,Uchl3,GHSR,STAT3,POU4 F1,GRM7,GALR2,Uchl1,ADM2,GALR3,PHF21A,AGTR1A,LEP,PYY,BDNF,GRIN2B,PRLH,GRIN1,NPW,CALCA,CCK,BRS3,CCKBR,NP Y2R,HCRTR2,CRH,FOSL2,UCN,NMU,NPY1R,NMB
GO:0007565	0.2319559	0.00	0	109	female pregnancy	IGFBP7,CR1L,SULT1E1,CITED2,SOSTDC1,PSG17,CUZD1,IGFBP2,PLEC1,PP11R,EPO,PLA2G4A,EPYC,HPGD,A2M,FOS,STAT5B,PAP PA,NODAL,IGF1,PPARD,HSPG2,CALD1,PSG19,RXRA,ADM,RLN1,OXTR,RPL29,AGT,COMT,GRN,PSG25,CRHR1,PRLHR,GHRL,SP1,OVGP1,FOSL1,LEPR,RAMP2,TRO,BSG,PRSS28,LNPEP,BYSL,BCL2,FKBP4,GNAS,LIPE,PRLR,PSG21,STX2,CEACAM12,IL1RN,MST1,F SHB,SP3,ARG1,GHSR,TPA,PZP,STAT5A,ADIPOR2,INDO,PSG26,CLICS,PRL,PRL8A2,LIF,TGFB2,PSG28,SOD1,MEN1,SCGB1A1,CO L16A1,TPBPA,HSF1,GNRH1,PTHLH,HMX3,CEACAM11,FBLN1,HFE,CALCA,KLF9,PSG18,HSD17B7,CEACAM9,FLT1,CRH,FOSL2,LA MB1-1,PCSK5,ADCYAP1,NAMPT,FCGRT,PSG23,AMBP,CRHBP,UCN,PLAU,EPOR,FOSB,THBD,JUNB,TEAD3,PGF,SFRP4
GO:0006541	0.5935749	0.00	0	20	glutamine metabolic process	PPAT,GGH,PDZD2,ASNSD1,CTPS2,CAD,ALDH5A1,GFPT1,GFPT2,GLS2,CTPS,GMPS,ASNS,LEMED1,GLS,CORO2A,GLULD1,PFAS,CPS 1,GLUL
GO:0030252	0.606153	0.00	0	11	growth hormone secretion	PTPN11,GAL,GHRHR,DRD2,GHRL,GHRH,LTBP4,GHSR,KISS1,CACNA1C,SNAP25
GO:0030201	0.7262516	0.00	0	14	heparan sulfate proteoglycan metabolic process	SULF1,HS6ST1,GLCE,SGSH,EXT1,HS3ST5,NDST2,CSGALNACT1,HS3ST3B1,EXT2,HS2ST1,SULF2,NDST1,LIPC
GO:0046483	0.2934345	0.00	0	113	heterocycle metabolic process	PPAT,SUCLA2,INDOL1,PAICS,FOLR1,AK1,ATP7A,MTHFD2,ATP2B2,BLVRA,HPRT1,SHMT1,MTHFS,AK2,DNMT1,PEMT,ALAS2,LAC TB,DLD,ALAD,CDA,PRG3,GART,RSAD1,GIF,MTHFSD,MMAB,DDC,COMT,TYMP,CAD,HMBS,PNP1,2610209A20RIK,ALDH1L1,PPO X,P4HB,COX15,ALDH1L2,DHFR,HMOX1,UMPS,MAT2A,PIPOX,ICMT,AFMID,CYP1A1,HNF1A,MTHFR,NFE2L1,ALLC,DUS4L,DNMT 3A,GAMT,TPMT,LIAS,PCCA,MYO7B,PNMT,MAOA,FOLH1,DPYS,AANAT,MCCC1,PRPS1L1,ACMSD,ALAS1,GMPS,CPOX,TSPO,MTH FD1,ALDH6A1,CYB5R4,PRHOXNB,UROD,MAPK1,INDO,MTHFD1L,KMO,PRPS1,IRESB2,PCMT1,GNMT,DHODH,FECH,P4HA2,DPYD ,PHF11,CYP1B1,CYP1A2,MAT1A,TD02,MAT2B,PSG18,URO5,APRT,G6PC,TPH1,HEBP1,GRIN2A,HMOX2,FPGS,AADAT,FTCD,KYN U,MTR,TPH2,DNMT3B,COX10,AMBP,1190003J15RIK,P4HA1,UOX
GO:0006547	0.4455427	0.00	0	10	histidine metabolic process	MOXD1,UROC1,HDC,FRRS1,HAL,MOXD2,MTHFD1,AMDHD1,DBH,FTCD
GO:0009755	0.4031593	0.00	0	42	hormone-mediated signaling	SGK1,PTPN11,LHCGR,GNB4,TRH,CUZD1,ADIPOR1,PRKAR2B,ADCY1,PRKAR2A,GCG,GNG5,PRKACB,GNG4,GHRL,PRKACA,A,AGR P,GNAS,GNG8,NUP62,ADCY8,JAK2,GNG13,GHR,GNB3,GCCR,GNB1,GNB2,GNG12,GHSR,JMJD1A,ADIPOR2,PRKAR1A,GNG3,GN G7,LATS2,PRKAR1B,GNG11,GNG10,GNG2,LATS1
GO:0006972	0.9193548	0.00	0	9	hyperosmotic response	TRPV4,SLC12A2,RAC1,PKN1,SLC6A18,PDPK1,TLR3,AVPR1B,TRIP10
GO:0019059	0.4131974	0.00	0	20	initiation of viral infection	WWP1,PVRL1,PSIP1,CD81,HS3ST5,ACE2,XRCC5,CCR5,BANF1,WWP2,LIG4,HS3ST6,ITCH,CD4,HMGA1,PPIA,CXCR4,IFNB1,XRCC4 ,XRCC6
GO:0007007	0.6644553	0.00	0	10	inner mitochondrial membrane organization and biogenesis	FXC1,TIMM10,TIMM9,TAZ,TIMM8A2,TIMM8B,OPA1,BAX,TIMM13,TIMM8A1
GO:0051701	0.5686768	0.00	0	27	interaction with host	SMAD3,DERL1,WWP1,RRAGA,VAPB,PVRL1,TARBP2,HIPK2,CD81,HS3ST5,TLR2,ACE2,WWP2,TLR7,HS3ST6,ITCH,NOD2,TGFB1,T LR1,TLR3,C9,TLR9,INSR,ALB,TLR6,IFNB1,TLR4
GO:0065002	0.2360068	0.00	0	69	intracellular protein transport across a membrane	TRAM2,NUP54,DDX19A,TIMM23,FXC1,TIMM10,SIL1,NUP43,TMEM48,PEX14,1500001M20RIK,TIMM9,TPR,1700034H14RIK,T OMM22,RRBP1,NUP107,NUP155,NUP160,TIMM8A2,RANBP17,TIMM8B,TIMM17B,NUP188,SEC61G,NUP62,TIMM50,NUP88, NUP98,XPO7,POM121,TIMM44,MVP,NUP85,TIMM17A,TIMM22,NUP35,ABRA,SERP2,NUP153,PEX6,D3UCLA1,SENPA2,NUP214 ,MAGMAS,GLE1,RANBP2,NUP133,TIMM13,TIMM8A1,NUP37,CHCHD4,ZMAT3,NUP50,TRAM1L1,DDX19B,NUP210,DNAJC19,S EH11,SEC61A2,NUP11,TRAM1,SEC61B,TKNS,SEC61A1,NUP93,NUPL2,SEC62,NUP205
GO:0051668	0.5515398	0.00	0	15	localization within membrane	SH3GLB1,MAL,CD2,CDH13,TMEM48,PMAIP1,COX18,REEP1,BAX,OXAL1,GRIN3B,EGFR,DOCK2,RTP1,RTP2

Table S2A. Gene sets up-regulated by mild stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0045185	0.3184419	0.00	0	39	maintenance of protein location	FAF1,TACC3,KDELRL1,TLN1,TLN2,SRGN,FLNB,PML,MDFI,GPA1,BBS4,TAF3,TMSB10,MXI1,GOPC,NR5A1,STOPORS,ANK3,NFKBIE,PDIA3,NFKBIL1,KDELRL3,TMSB4X,EZR,DMD,IL10,G3BP2,GYPA,PDIA2,MORC3,SHANK1,NFKBIA,SPNB4,GRIK5,SUFU,PEX5L,PFN1,BCL3,SUPT7L
GO:0032507	0.3583818	0.00	0	34	maintenance of protein location in cell	FAF1,TACC3,KDELRL1,TLN1,TLN2,FLNB,PML,MDFI,GPA1,BBS4,TAF3,MXI1,GOPC,NR5A1,STOPORS,ANK3,NFKBIE,PDIA3,NFKBIL1,KDELRL3,EZR,DMD,IL10,G3BP2,GYPA,PDIA2,MORC3,SHANK1,NFKBIA,SPNB4,GRIK5,SUFU,BCL3,SUPT7L
GO:0000226	0.2356377	0.00	0	131	microtubule cytoskeleton organization and biogenesis	UBE2C,DOCK7,SGK1,TACC3,CKS2,BRCA1,STMN3,DYNC1L1,MARK1,CRYAB,UBE2B,RANBP1,MTAP1A,CNP,KIF2C,NUSAP1,BIRC5,UXT,SMC3,TTK,RNF19A,TUBB1,NDC80,NEFH,TEKT2,ESPL1,TUBGCP5,BBS4,PPP4C,PCM1,DST,PRC1,MAP6D1,CKAP5,CNTROB,NEFL,CETN3,HOOK2,HOOK1,TUBA8,GTRGEO22,UNC84B,TUBGCP2,PAFAH1B1,KIF11,KIF23,TTL,NPM1,CENPJ,ZWINT,AURKA,S,TMN1,CLASP2,MTAP1B,BBS2,TEKT3,TEKT4,BUB1B,CROCC,FBXO5,TBCE,CDC42BPA,MAPRE1,HDAC6,TUBGCP4,FMN2,BRCA2,D,CTN2,GADD45A,TRIM54,NEFM,DYNC1H1,KATNB1,TUBB5,TACC1,CDKN1B,RCC1,OFD1,TUBGCP3,AP1G1,GABARAP,MTAP2,MLH1,TUBGCP6,MID1P1,BBS1,NAV1,RAN,CETN1,TEKTS,MYH9,TUBE1,RANBP9,MID1,SAC3D1,ASZ1,CAV1,KATNA1,NDE1,CCDC100,TPX2,SASS6,HOOK3,TEKT1,NDEL1,1700009N14RIK,TUBG1,PRKCZ,MARK4,CFTR,SPAG5,MTAP4,TPPP,CEP250,SMC1A,MTAP1S,APC,PTK2,PCNT,NEURL,MAPK8,TACC2,CAV2,ARHGFE2,CTTNBP2,PSRC1,CLIP2,CAV3,MAPT,CLASP1,WNT2
GO:0006839	0.2919546	0.00	0	62	mitochondrial transport	MTX2,TIMM23,VDAC1,FXC1,TOMM40,TIMM10,SLC25A32,SLC25A20,SLC25A10,TIMM9,SLC25A17,TOMM22,SLC25A24,SLC25A37,HSPD1,BAK1,SLC25A36,KIF5B,UCP2,CPT2,TOMM20,TIMM8A2,TIMM8B,TIMM17B,SLC25A13,SLC25A12,SLC25A4,SLC25A27,SLC37A2,UCP3,BCL2,IMMP2L,TIMM44,TIMM17A,SLC25A30,MFN2,TSPO,TRNT1,PMPCB,YWHAZ,TIMM13,UCP1,TIMM8A1,BNIP3,BCL2L1,CPT1B,SLC25A14,HSP90AA1,BHLHB8,HTT,GRPEL1,SLC25A15,SLC25A1,DNAJC19,MIEPE,PLEKHF1,AIP,PSEN1,SLC25A2,STAR3,SLC1A3,TOMM34
GO:0007005	0.2742801	0.00	0	133	mitochondrion organization and biogenesis	SH3GLB1,MTX2,NDUFS5,TIMM23,VDAC1,FXC1,SOD2,TOMM40,NDUFS8,MRPL15,SEPT4,ATP7A,TIMM10,GPX1,CASP7,SLC25A32,NRF1,MSTO1,SLC25A20,DNM1L,TFAM,SLC25A10,TIMM9,TAZ,PEX5,SLC25A17,TOMM22,SLC25A24,FIS1,SLC25A37,HSPD1,MFN1,DCTN6,TYMP,BAK1,SLC25A36,KIF5B,UCP2,SFN,PMAIP1,CPT2,AIFM2,TOMM20,TIMM8A2,POLG,TIMM8B,TIMM17B,MRPL39,SLC25A13,SLC25A12,SLC25A4,SLC25A27,COX18,FXN,MAN2A1,SLC37A2,UCP3,SLC22A5,MAP3K1,BCL2,IMMP2L,DNAJA3,TIMM50,OPA1,TIMM44,NDUFS4,TIMM17A,RNF7,SLC25A30,BAX,BID,PPARGC1A,CXADR,MFN2,POLRMT,TSPO,LONP1,1700020C11RIK,AKT1,TRNT1,MRPL12,MYC,NDUFS7,PMPCB,YWHAZ,AIFM1,CASP3,TRP73,RAB3A,TIMM13,UCP1,TIMM8A1,TFB2M,HTRA2,BNIP3,SPG7,BCL2L1,CPT1B,MTERF,SLC25A14,HSP90AA1,BHLHB8,CLN8,DAP3,HTT,GRPEL1,SLC25A15,TRP53,SLC25A1,JUN,DNAJC19,MIEPE,PLEKHF1,MUL1,AIP,EPAS1,CSTAD,CCK,PSEN1,SLC25A2,CAV2,MPV17,STAR3,SLC1A3,TOMM34,CD24A,MRPL17,COX10,RRM2B,PIM2,CDKN2A,BBC3,CEBPA
GO:0000278	0.0961384	0.00	0	421	mitotic cell cycle	UBE2C,PKMYT1,CCNA2,KIF22,CABLES1,DCLRE1A,DBF4,PSMC6,AURKB,SMAD3,EDN1,CCDC5,PAPD5,MAD2L1,1110001A07RIK,BLM,YEATS4,PMF1,PSME2,CDCA8,MPHOSPH6,PSMB7,CDC16,PSMB6,DYNC1L1,E2F5,TPD52L1,BCAT1,ANAPC13,NBN,TIPIN,RPS6KA2,CDC23,E2F6,RAD21,KPNA2,NUF2,CD2AP,MAEA,NCAPH,MYO16,TUBB3,RNF8,KIF2C,FRAP1,CCNE1,NUSAP1,PLK1,BIRC5,STAT5B,SIRT2,SMC3,UBE2E1,CCNB1,PML,TTK,ASPM,CCNB2,NCAPG2,CDK3,CDC20,H1FNT,4922501C03RIK,CENPF,CIT,MAD1L1,IGF1,ID4,NDC80,KHDRBS1,CAMK2D,ESPL1,ITGB1,HMGA2,NEDD9,NCAPH2,PRC1,KIF15,MAPRE2,BUB1,NUDC,RPRM,HUS1,NPM2,UBA3,PSMD9,GPR132,PRKCQ,CCND1,ZWILCH,PSMA4,PSMB2,GML,PSMA6,CETN3,TIMELESS,PRM1,ANAPC7,SMC2,E2F1,POLA1,UBB,FOSL1,PSMD7,CDKN1C,PSMC4,SHC1,PSMD5,CDKN2D,UNC84B,6720463M24RIK,CUL3,EML4,PSMB4,PSMA3,ANAPC11,HELLS,PAFAH1B1,PSME3,PSMF1,ANAPC5,KIF11,DNAJC2,RNF2,CDKN1A,KIF23,PRM3,CCNG1,TCF3,RAD17,CDC2A,CDK2AP1,CAMK2G,SUGT1,CDKN2C,ANP32B,SLFN1,RBM38,PSMB9,BTG3,FOXN3,CUL2,DLG7,CDK4,MAD2L1BP,NEK1,ZW10,SKP1A,BCL2,NCAPD3,CDC25A,ZWINT,TERF1,CHMP1A,AURKA,KIF2B,STMN1,CDC27,CLASP2,TUBB2B,ABL1,AKAP8,WEE1,PSMD12,BUB1B,PSMD6,FBXO5,FSD1,MAPRE1,CCNA1,UBE2I,AURKAIP1,BRCA2,SNF1LK,ANAPC4,ZZEF1,PSME1,CDKN2B,GADD45A,SPC24,DYNC1H1,FOXK1,TNF,NCAPD2,PDS5A,KATNB1,PTTG1,KIF3B,TCFE2A,CDC34,ERCC6L,PARC,SETD8,CDKN1B,NEUROG1,PIN1,RCY1,BL
GO:0006044	0.2235605	0.00	0	28	N-acetylglucosamine metabolic process	SLC35A3,CHIA,B4GALNT2,GNPDA2,EXTL2,HEXB,GNPAT1,OVGP1,DPAGT1,GFPT1,CHID1,GNE,CHIT1,GNPDA1,CHST5,CHST2,C
GO:0030147	0.5856373	0.00	0	10	natriuresis	TBS,PGM3,AMDHD2,CHI3L3,CHST4,CHI3L1,RENBP,UAP1,CHI3L4,CHST7,LARGE,NAGK
GO:0032387	0.2986525	0.00	0	21	negative regulation of intracellular transport	EDN1,DRD2,AGT,NPR1,AGTR2,LNPEP,ADORA2A,NPPB,KNG1,ADORA1
GO:0042992	0.4834805	0.00	0	13	negative regulation of transcription factor import into nucleus	FAF1,TACC3,CRYAB,NLRP3,MDFI,MXI1,GOPC,CDK5,NFKBIE,PKIA,NF1,UACA,NFKBIL1,IL10,G3BP2,BARD1,NFKBIA,SUFU,CRYAA,PKIG,HNF4A
GO:0009112	0.5816332	0.00	0	23	nucleobase metabolic process	FAF1,TACC3,NLRP3,MDFI,MXI1,NFKBIE,NF1,UACA,NFKBIL1,IL10,G3BP2,NFKBIA,SUFU
						PPAT,PAICS,AK1,HPRT1,SHMT1,AK2,CDA,GART,TYMP,CAD,UMPS,DPYS,PRPS1L1,GMPS,ALDH6A1,PRHOXNB,MAPK1,PRPS1,DHODH,DPYD,APRT,1190003J15RIK,UOX

Table S2A. Gene sets up-regulated by mild stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene set description	Gene set genes
GO:0055086	0.0958078	0.00	0	269	nucleobase, nucleoside and nucleotide metabolic process	PPAT,ATP5F1,NUDT5,EDN1,NT5M,PAICS,RRM1,AK1,ERH,GUCA1A,ATP7A,GHRHR,RRM2,UPP1,ADSSL1,ATP2B2,LDHB,ADSL,DCXR,PDE4A,ENTPD3,FIGNL1,HPRT1,SHMT1,CNP,ATP5J2,RXFP2,INSL3,MYH7,PRPS2,AK2,RORA,MDH1,MYH6,MUTYH,ITPA,ADCY5,PGD,DUT,ENPP5,CDA,RP2H,ADCY1,ATP6V0B,HIBADH,ATP5G1,PDE4D,LDHD,GART,H6PD,ABCA1,ADM,ATP5G2,NME5,CTPS2,NUDT7,NPPA,ATP5G3,ADCY7,TYMP,CAD,PNP1,ATP5A1,ATP5C1,ATP5J,NPR1,ADCY2,RBM3,NT5C2,ENPP3,ATP5L,GUCY1A3,ATP5D,UPP2,SLC25A13,NT5C,DHFR,DRD1A,GUCY1B3,GUCY2F,UMPS,NUDT1,AFMID,NUDT4,MYO9B,NMNAT2,GRM8,MSH2,NME4,PDE8A,ENTPD8,TPI1,ADORA2A,PAPSS1,ATP5H,ADCY6,ATP6AP1,ENPP1,ATP6V1F,PNKP,NT5C1B,NME1,PGLS,DTYMK,ARRB1,CMPK1,APOE,NDUFS1,ADCY8,ATP5B,CTPS,GUK1,CACNB4,AMPD3,NT5C3,QPRT,GHRH,DPYS,RP1H,PRPS1L1,IMPDH1,ACMSD,DCK,ATP5O,NCF2,TKT,PDE5A,GUCY1A2,GMPS,ATP6V0C,DRD5,TGFB1,NT5C3L,NUDT3,IMPDH2,ND4L,MTHFD1,ATP1A1,ATP5E,RDH14,GMPR2,NPPB,ALDH6A1,PRHOXNB,ADCY3,ERCC3,ADCY10,DCTD,NT5E,NMNAT1,NAPRT1,ATPIF1,MAPK1,TIMP2,NME7,GUCY2E,ADSS,NME6,CANT1,NPPC,G6PDX,GUCY2C,INDO,ACLY,DGUOK,NUDT9,0610012D14RIK,ATP6V1A,HAOA,SMUG1,NTHL1,ATP6V1B1,AVP,NT5C1A,ENTPD4,NADSYN1,GCK,PRPSAP1,AIPL1,PDE8B,KMO,MPG,FHIT,ADA,PRPS1,CCNO,RP1A,DHODH,TBPL1,HSD11B1,GUCY1B2,SMARCA1,APOBEC1,GMPR,ATP6V1B2,DECR2,DPYD,GUCY2D,ADCY9,OLA1,ATIC,PTH2,DERA,ADK,PTHLH,BC016495,NME2,PRPSAP2,NADK,ABCC6,TDO2,TXNDC3,ATP6V0D2,CTNS
GO:0006753	0.1142313	0.00	0	252	nucleoside phosphate metabolic process	PPAT,ATP5F1,NUDT5,EDN1,NT5M,PAICS,RRM1,AK1,GUCA1A,ATP7A,GHRHR,RRM2,UPP1,ADSSL1,ATP2B2,LDHB,ADSL,DCXR,PDE4A,ENTPD3,FIGNL1,HPRT1,CNP,ATP5J2,RXFP2,INSL3,MYH7,PRPS2,RORA,MDH1,MYH6,MUTYH,ITPA,ADCY5,PGD,DUT,ENPP5,CDA,RP2H,ADCY1,ATP6V0B,HIBADH,ATP5G1,PDE4D,LDHD,GART,H6PD,ABCA1,ADM,ATP5G2,NME5,CTPS2,NUDT7,NPPA,ATP5G3,ADCY7,TYMP,CAD,PNP1,ATP5A1,ATP5C1,ATP5J,NPR1,ADCY2,RBM3,NT5C2,ENPP3,ATP5L,GUCY1A3,ATP5D,UPP2,SLC25A13,NT5C,DHFR,DRD1A,GUCY1B3,GUCY2F,UMPS,NUDT1,AFMID,NUDT4,MYO9B,NMNAT2,GRM8,MSH2,NME4,PDE8A,ENTPD8,TPI1,ADORA2A,PAPSS1,ATP5H,ADCY6,ATP6AP1,ENPP1,ATP6V1F,PNKP,NT5C1B,NME1,PGLS,DTYMK,ARRB1,CMPK1,APOE,NDUFS1,ADCY8,ATP5B,CTPS,GUK1,CACNB4,AMPD3,NT5C3,QPRT,GHRH,RP1H,PRPS1L1,IMPDH1,ACMSD,DCK,ATP5O,NCF2,TKT,PDE5A,GUCY1A2,GMPS,ATP6V0C,DRD5,TGFB1,NT5C3L,IMPDH2,ND4L,MTHFD1,ATP1A1,ATP5E,RDH14,GMPR2,NPPB,ADCY3,ERCC3,ADCY10,DCTD,NT5E,NMNAT1,NAPRT1,ATPIF1,TIMP2,NME7,GUCY2E,ADSS,NME6,CANT1,NPPC,G6PDX,GUCY2C,INDO,ACLY,DGUOK,NUDT9,0610012D14RIK,ATP6V1A,HAOA,SMUG1,NTHL1,ATP6V1B1,AVP,NT5C1A,ENTPD4,NADSYN1,GCK,PRPSAP1,AIPL1,PDE8B,KMO,MPG,FHIT,ADA,PRPS1,CCNO,RP1A,DHODH,TBPL1,HSD11B1,GUCY1B2,SMARCA1,GMPR,ATP6V1B2,DECR2,GUCY2D,ADCY9,OLA1,ATIC,PTH2,DERA,ADK,PTHLH,BC016495,NME2,PRPSAP2,NADK,ABCC6,TDO2,TXNDC3,ATP6V0D2,CTNS
GO:0006334	0.4306467	0.00	0	94	nucleosome assembly	HIST1H4I,ASF1B,HIST3H2BB,HIST1H2BG,SET,HIST1H2BN,HMGB2,HIST1H1D,HIST1H3A,HIST1H2BM,HIST2H3B,HIST1H3G,HIST2H4,HIST1H2AN,H2AFV,ASF1A,SMARCA5,HIST1H2AO,HIST1H2BL,HIST2H3C1,HIST1H4H,HIST1H4D,NEFH,HIST1H2AF,H3F3B,HIST2H2AC,HIST1H2BF,1700024P04RIK,HIST2H2BB,MTMEM38B,HIST1H1E,H2AFY,HIST2H2AA2,HIST1H4F,HIST1H1B,HIST1H2BB,NAP1L3,HIST1H2BH,HIST2H2AA1,H3F3A,CENPA,H2AFY2,PKN3,CHAF1B,HIST1H2BP,HIST1H1A,NAP1L5,TSPYL4,RSF1,HIST4H4,HIST1H4J,SOS2,HIST1H4B,HIST1H2AK,H2AFZ,TSPYL3,HIST1H4M,MYST4,HIST1H2AA,NAP1L1,HIST1H2BC,TSPYL2,1700113O17RIK,HIST1H2AC,SMARCA4,NAP1L2,H1FO,HIST2H2BE,HILS1,1700054O13RIK,SHPRH,HIST3H2BA,SLC22A4,HIST1H3D,CHAF1A,HIST1H2AB,HP1BP3,NAP1L4,SMARCA2,MYST3,HIST2H3C2,H2AFX,HIST3H2A,HIST1H1T,H1FOO,TSPYL1,H2AFJ,H1FX,HIST1H1C,TSPYL5,MCM2,HIST1H2BA,HIST1H3F,HIST1H2AE
GO:0009117	0.1142313	0.00	0	252	nucleotide metabolic process	PPAT,ATP5F1,NUDT5,EDN1,NT5M,PAICS,RRM1,AK1,GUCA1A,ATP7A,GHRHR,RRM2,UPP1,ADSSL1,ATP2B2,LDHB,ADSL,DCXR,PDE4A,ENTPD3,FIGNL1,HPRT1,CNP,ATP5J2,RXFP2,INSL3,MYH7,PRPS2,RORA,MDH1,MYH6,MUTYH,ITPA,ADCY5,PGD,DUT,ENPP5,CDA,RP2H,ADCY1,ATP6V0B,HIBADH,ATP5G1,PDE4D,LDHD,GART,H6PD,ABCA1,ADM,ATP5G2,NME5,CTPS2,NUDT7,NPPA,ATP5G3,ADCY7,TYMP,CAD,PNP1,ATP5A1,ATP5C1,ATP5J,NPR1,ADCY2,RBM3,NT5C2,ENPP3,ATP5L,GUCY1A3,ATP5D,UPP2,SLC25A13,NT5C,DHFR,DRD1A,GUCY1B3,GUCY2F,UMPS,NUDT1,AFMID,NUDT4,MYO9B,NMNAT2,GRM8,MSH2,NME4,PDE8A,ENTPD8,TPI1,ADORA2A,PAPSS1,ATP5H,ADCY6,ATP6AP1,ENPP1,ATP6V1F,PNKP,NT5C1B,NME1,PGLS,DTYMK,ARRB1,CMPK1,APOE,NDUFS1,ADCY8,ATP5B,CTPS,GUK1,CACNB4,AMPD3,NT5C3,QPRT,GHRH,RP1H,PRPS1L1,IMPDH1,ACMSD,DCK,ATP5O,NCF2,TKT,PDE5A,GUCY1A2,GMPS,ATP6V0C,DRD5,TGFB1,NT5C3L,IMPDH2,ND4L,MTHFD1,ATP1A1,ATP5E,RDH14,GMPR2,NPPB,ADCY3,ERCC3,ADCY10,DCTD,NT5E,NMNAT1,NAPRT1,ATPIF1,TIMP2,NME7,GUCY2E,ADSS,NME6,CANT1,NPPC,G6PDX,GUCY2C,INDO,ACLY,DGUOK,NUDT9,0610012D14RIK,ATP6V1A,HAOA,SMUG1,NTHL1,ATP6V1B1,AVP,NT5C1A,ENTPD4,NADSYN1,GCK,PRPSAP1,AIPL1,PDE8B,KMO,MPG,FHIT,ADA,PRPS1,CCNO,RP1A,DHODH,TBPL1,HSD11B1,GUCY1B2,SMARCA1,GMPR,ATP6V1B2,DECR2,GUCY2D,ADCY9,OLA1,ATIC,PTH2,DERA,ADK,PTHLH,BC016495,NME2,PRPSAP2,NADK,ABCC6,TDO2,TXNDC3,ATP6V0D2,CTNS
GO:0006297	0.564268	0.00	0	17	nucleotide-excision repair, DNA gap filling	POLD3,RFC2,PCNA,RFC3,POLD2,RFC5,RPA3,RFC4,LIG4,RFC1,LIG1,POLE,RPA2,POLE2,POLD1,RPA1,POLD4
GO:0031100	0.6251344	0.00	0	29	organ regeneration	CCNA2,GAS6,APOA2,LIFR,HTR2C,CCNE1,HSPG2,ADM,CCND1,LRP2,SHC1,AXL,CDKN1A,CDK4,PHB,APOH,PTPRU,CDK2,LPIN1,LIFR,APOA1,AHSG,TEK,ATIC,AFP,NR4A3,HP,ANGPT1,CEBPA
GO:0001542	0.3385184	0.00	0	17	ovulation from ovarian follicle	PLA2G4A,MMP2,FOXO3A,EDN2,OAS1D,AGT,ADAMTS1,NOS3,LEPR,MMP19,LEP,AFP,NR1P1,CBR1,SIRT1,NOS2,PGR
GO:0014065	0.6251492	0.00	0	11	phosphoinositide 3-kinase cascade	EDN1,IGF1,PPARD,KDR,ERBB3,INS2,ERBB2,CAT,NF1,IGF1R,TSC2
GO:0015914	0.6822411	0.00	0	31	phospholipid transport	NPC2,APOC1,APOA2,ATP11C,ABCA4,ATP11A,ATP10D,ABCG8,ABCA1,ATP8B3,ABCG1,ATP8A2,APOC2,4930417M19RIK,APOA4,ATP11B,PITPNA,APOE,ATP10B,ATP9A,ATP8B2,APOC3,ATP8B4,ATP8B1,APOA1,PCTP,ATP10A,P2RX7,PLSCR1,ATP8A1,ATP9B

Table S2A. Gene sets up-regulated by mild stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0007602	0.3091257	0.00	0	34	phototransduction	OPN1MW,PLEKHB1,GNAT2,GUCA1A,ABCA4,PLCB4,RCVRN,TRPC3,PDCL3,UNC119,OPN3,OPN1SW,TULP1,PITPNM1,GNNGT2,PD E6B,PDE6D,GNB1,GUCA1B,TUB,PDCL2,AIPL1,GRK1,CNGB1,GNAT1,OPN4,SAG,ACCN1,PDCL,RGR,NR2E3,RHO,PDC,OPN5
GO:0046148	0.3980255	0.00	0	36	pigment biosynthetic process	PPAT,PAICS,GPR143,SHMT1,ALAS2,ALAD,GART,SOX2,SI,HMBS,PPOX,TYRP1,A,OCA2,COX15,DDT,HNF1A,NFE2L1,AP3D1,SLC45 A2,TYR,MYO5A,ALAS1,GMPS,IDI2,CPOX,TSPO,MC1R,UROD,IREB2,FECH,4833409A17RIK,UROS,IDI1,DCT,COX10
GO:0042440	0.3300048	0.00	0	43	pigment metabolic process	PPAT,PAICS,GPR143,BLVRA,SHMT1,ALAS2,ALAD,GART,SOX2,SI,HMBS,PPOX,TYRP1,A,OCA2,COX15,HMOX1,DDT,HNF1A,NFE2L 1,BCL2,AP3D1,SLC45A2,TYR,MYO5A,ALAS1,GMPS,IDI2,CPOX,TSPO,CYB5R4,MC1R,UROD,IREB2,FECH,4833409A17RIK,UROS,I DI1,HEBP1,HMOX2,DCT,COX10,AMBP
GO:0006596	0.4817107	0.00	0	8	polyamine biosynthetic process	ADC,GM853,OAZ1,ODC1,AZIN1,AMD1,SRM,AGMAT
GO:0006779	0.4198916	0.00	0	18	porphyrin biosynthetic process	SUCLA2,ALAS2,ALAD,RSAD1,MMAB,HMBS,PPOX,COX15,HNF1A,NFE2L1,ALAS1,CPOX,TSPO,UROD,IREB2,FECH,UROS,COX10
GO:0045840	0.3570086	0.00	0	20	positive regulation of mitosis	UBE2C,EDN1,NUSAP1,BIRC5,IGF1,ESPL1,SHC1,TNF,NEUROG1,TGFB1,BTC,LTA,TGFA,EREG,FGF8,EPGN,HOXA13,CD28,EDN3,EG F
GO:0045669	0.3877688	0.00	0	24	positive regulation of osteoblast differentiation	BMPR1B,BMP6,BMP2,BMP7,IGF1,SMAD1,SMAD5,CTNNB1,ACVR2B,DLX5,BMP4,GNAS,BMPR1A,RUNX2,NPPC,MEN1,BMPR2,J UND,PDLIM7,ACVR1,IFI204,ACVR2A,CD276,WNT7B
GO:0034105	0.463856	0.00	0	23	positive regulation of tissue remodeling	BMPR1B,BMP6,KL,BMP2,PLA2G4A,BMP7,MC4R,CAR2,ACVR2B,BMP4,BMPR1A,TNFSF11,RUNX2,ADRB2,BMPR2,AHSG,P2RX7, CALCA,ACVR1,ACVR2A,SPP1,CD276,THRB
GO:0042993	0.3671963	0.00	0	11	positive regulation of transcription factor import into nucleus	SMAD3,EDA,TNFSF14,PRKCC,RHOA,CD27,TNF,TRIP6,CDH1,FLNA,EDAR
GO:0045039	0.8500958	0.00	0	7	protein import into mitochondrial inner membrane	FXC1,TIMM10,TIMM9,TIMM8A2,TIMM8B,TIMM13,TIMM8A1
GO:0043681	0.4906774	0.00	0	13	protein import into mitochondrion	FXC1,TIMM10,TIMM9,TOMM22,HSPD1,TOMM20,TIMM8A2,TIMM8B,TIMM13,TIMM8A1,GRPEL1,DNAJC19,AIP
GO:0045047	1.2491202	0.00	0	9	protein targeting to ER	SRPR,FOLR1,SRP9,MACF1,FOLR2,SRP19,VCAN,SRP14,SRP72
GO:0006625	0.6180333	0.00	0	13	protein targeting to peroxisome	PEX13,PEX14,PEX3,PEX7,AGXT,PEX19,PEX5,PEX26,PEX1,PEX6,PEX10,PEX16,PEX12
GO:0016567	0.1452386	0.00	0	102	protein ubiquitination	UBE2C,BRCA1,RNF217,WWP1,SIAH2,HERC5,BCL10,SUZ12,UBE2N,NSMCE2,PRPF19,FBXO3,FBXO32,GCLC,SMURF1,STUB1,KC MF1,PARK2,CAND1,RPS27A,PCNP,FBXL5,RBBP6,UBB,SAE1,HUWE1,UBE2V2,RNF11,ANAPC11,TSC1,RNF2,LNX1,FBXL21,TSPAN 17,CDK5,TRIM23,UBE2G1,FBXO9,RNF144B,MAP3K1,BCL2,MGRN1,RBX1,RNF139,FGFR3,ATG3,TRIP12,HDAC6,SUMF1,FBXL3, WDSUB1,GTPBP4,UBE4A,VCP,UBE2V1,NOSIP,DZIP3,BIRC6,RFFL,RING1,ERCC8,AKT1,SIAH1A,UBE4B,CUL5,LRRK2,FBXO4,MDM 2,GSPT1,VHLH,TSG101,SOC5,DDDB2,FBXO11,UBQLN1,UBOX5,UHRF2,TRAF7,FBXW7,UBE3C,BARD1,AMFR,UBE2D1,MIB2,FBX O24,MUL1,LMO7,PPIL2,TRAF6,FBXW11,FBXO10,NEDD4L,CBL,ATG7,FBXO25,CHFR,BMI1,NHLRC1,MYLIP,ATG5,RAB26,CBX8
GO:0018298	0.4838006	0.00	0	15	protein-chromophore linkage	CRY1,OPN1MW,RRH,NID1,OPN3,HMCN1,OPN1SW,CRY2,NID2,HMCN2,OPN4,RGR,RHO,AMBP,OPN5
GO:0042559	0.3254603	0.00	0	11	pteridine and derivative biosynthetic process	GPHN,QDPR,PCBD1,MOCS1,PTS,MOCS2,PCBD2,GCH1,MOCS3,MOCOS,SPR
GO:0042558	0.4630108	0.00	0	15	pteridine and derivative metabolic process	FOLR1,GPHN,SHMT1,QDPR,PCBD1,MOCS1,PTS,MOCS2,PAH,GNMT,PCBD2,GCH1,MOCS3,MOCOS,SPR
GO:0006144	0.8179166	0.00	0	15	purine base metabolic process	PPAT,PAICS,AK1,HPRT1,SHMT1,AK2,GART,PRPS1L1,GMPS,PRHOXNB,PRPS1,DPYD,APRT,1190003115RIK,UOX
GO:0006163	0.194036	0.00	0	94	purine nucleotide metabolic process	PPAT,ATP5F1,PAICS,AK1,ATP7A,ADSSL1,ADSL,FIGNL1,HPRT1,ATP5J2,MYH7,PRPS2,MYH6,MUTYH,RP2H,ATP6V0B,ATP5G1,LD HD,GART,ATP5G2,NME5,ATP5G3,PNP1,ATP5A1,ATP5C1,ATP5J,RBM3,ATP5L,ATP5D,SLC25A13,NUDT1,MYO9B,MSH2,NME4,P APSS1,ATP5H,ATP6AP1,ENPP1,ATP6V1F,NME1,NDUFS1,ATP5B,GUK1,AMPD3,RP1H,IMPDPH1,ATP5O,GMPS,ATP6VOC,TGFB1,I MPDH2,ND4L,MTHFD1,ATP1A1,ATP5E,GMPPR2,ERCC3,NT5E,NME7,ADSS,NME6,ACLY,DGUOK,NUDT9,ATP6V1A,ATP6V1B1,MP G,ADA,PRPS1,ATP6V1B2,DECR2,OLA1,ATIC,NME2,NADK,ABCC6,TXNDC3,ATP6V0D2,CTNS,ADAL,AK5,AMPD2,OGG1,MON2,AT P1A2,CLCA3,AMPD1,NME3,NUDT15,ATP2A1,ENTPD2,ENTPD1,PFAS,ATP5K
GO:0002016	0.7329437	0.00	0	9	regulation of blood volume by renin-angiotensin	ACE,AGTR1B,NKX2-1,ACE2,AGT,AGTR2,MIF,AGTR1A,DRD3
GO:0050773	0.4561024	0.00	0	17	regulation of dendrite development	SGK1,NTRK2,CHRN2,CIT,ACHE,SMAD1,KNDC1,RHOA,CHRNA3,PTPRF,TLX2,DBN1,YWHAH,KALRN,LZTS1,SIPA1L1,MT3
GO:0007096	0.7255034	0.00	0	12	regulation of exit from mitosis	UBE2C,CDC23,BIRC5,SIRT2,NPM2,MAD2L1BP,ZW10,NEUROG1,TGFB1,ANLN,PPP1R9B,KNTC1
GO:0043467	0.5165233	0.00	0	13	regulation of generation of precursor metabolites and energy	ADRA1B,ATP7A,FRAP1,PRKACA,INS2,GFPT1,NKX1-1,ENPP1,CISD2,GCK,DYRK2,C1QTNF2,AVPR1A
GO:0032844	0.3318777	0.00	0	38	regulation of homeostatic process	LHCGR,GPX1,IAPP,PLA2G4A,APLN,EGLN2,LYN,GCLC,TNFRSF11B,VEGFA,MC4R,AGT,CCR5,CCR1,CAR2,BDKRB1,CARTPT,BCL2,ED NRB,TNFSF11,GCLM,THY1,NF1,TGFB1,TGFB2,INPP5D,AHSG,P2RX7,GLRX2,DDIT3,CALCA,EDNRA,CCK,CALCR,TXNDC4,APEX1,M S4A2,SPP1
GO:0032350	0.6498292	0.00	0	13	regulation of hormone metabolic process	BMP6,LHCGR,GAL,STUB1,HIF1A,TCF7L2,TRERF1,KCNMA1,ATP1A1,NR3C1,AOF2,ARNT,CACNA1A

Table S2A. Gene sets up-regulated by mild stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0033157	0.2199275	0.00	0	45	regulation of intracellular protein transport	FAF1,SMAD3,TACC3,PTPN11,NLRP3,MDFI,MBTPS1,EDA,TNFSF14,MXI1,PRKCQ,GSK3B,AGTR2,PRKACA,GOPC,RHOA,CD27,CDK5,NFKBIE,PKIA,SMO,TNF,JAK2,NF1,UACA,GLI3,TGFB1,SHH,NFKBIL1,TRIP6,IL10,G3BP2,NOLC1,BARD1,PRDX1,NFKBIA,CDH1,SUFU,FLNA,EDAR,PKIG,SIRT1,UHMK1,BCL3,HNF4A
GO:0032386	0.165566	0.00	0	56	regulation of intracellular transport	FAF1,SMAD3,TACC3,PTPN11,CRYAB,NLRP3,MDFI,MBTPS1,KHDRBS1,EDA,TNFSF14,CAPN10,MXI1,PRKCQ,GSK3B,AGTR2,PRKACA,GOPC,RHOA,CD27,CDK5,NUDT4,NFKBIE,PKIA,SMO,TNF,JAK2,NF1,UACA,GLI3,TGFB1,SHH,NFKBIL1,TRIP6,AAAS,TNNC1,IL10,G3BP2,NOLC1,MYLK2,BARD1,PRDX1,NFKBIA,NCBP2,ABCA2,CDH1,SUFU,CRYAA,FLNA,EDAR,PKIG,SIRT1,UHMK1,MYBPC3,BCL3,HNF4A
GO:0019216	0.3562091	0.00	0	70	regulation of lipid metabolic process	NPC2,IGFBP7,APOA2,EDF1,BMP6,BRCA1,LHCGR,GAL,PRKAA2,PLA2G4A,SLC25A20,FRAP1,STUB1,STAT5B,ACACB,GCG,BBS4,AGT,ASAH3,ABCG1,MVK,CPT2,CYP51,ACSL4,INS2,CPT1A,APOA5,ANGPTL3,NR5A1,PPAP2A,MLXIPL,ANGPTL4,PRKAA1,DHH,PRKAB2,KCNMA1,PPARGC1A,ATP1A1,APOC3,GHSR,NR3C1,STAT5A,PDGFA,DHCR7,ACSL1,SF1,SOD1,MLYCD,SEC14L2,YY1,CAV1,CPT1B,NR0B1,PDGFB,PRKAG2,ADORA1,L,LEP,CIDEA,LSR,DRD3,SCAP,ADIPOQ,C1QTNF2,PPARA,ABCG4,APOB,STAR,HNF4A,FABP1,THRHB
GO:0007088	0.2388832	0.00	0	47	regulation of mitosis	UBE2C,PKMYT1,EDN1,MAD2L1,CDC16,CDC23,NUSAP1,BIRC5,SIRT2,IGF1,ESPL1,NPM2,SHC1,MAD2L1BP,ZW10,AURKAIP1,ZZF1,TNF,PARC,NEUROG1,PIN1,RCC1,ANAPC10,TGFB1,BTC,LTA,TGFA,NEK2,EREG,FGFR3,HECTD3,EPGN,ANLN,CDC2L1,TUBG1,HOXA13,CD28,PPP1R9B,NEK6,YWHAH,KNTC1,ESR1,EDN3,CDC2L5,PRMT5,EGF,CDC25C
GO:0046822	0.1957474	0.00	0	48	regulation of nucleocytoplasmic transport	FAF1,SMAD3,TACC3,PTPN11,NLRP3,MDFI,MBTPS1,KHDRBS1,EDA,TNFSF14,MXI1,PRKCQ,GSK3B,AGTR2,PRKACA,RHOA,CD27,CDK5,NUDT4,NFKBIE,PKIA,SMO,TNF,JAK2,NF1,UACA,GLI3,TGFB1,SHH,NFKBIL1,TRIP6,AAAS,IL10,G3BP2,NOLC1,BARD1,PRDX1,NFKBIA,NCBP2,CDH1,SUFU,FLNA,EDAR,PKIG,SIRT1,UHMK1,BCL3,HNF4A
GO:0045667	0.3780706	0.00	0	37	regulation of osteoblast differentiation	BMPR1B,SMAD3,TWIST2,BMP6,BMP2,NELL1,BMP7,IGF1,SMAD1,ESRRA,SMAD5,CTNNB1,TOB1,ACVR2B,DLX5,BMP4,GNAS,BMPR1A,RUNX2,FZD1,NPPC,AXIN2,MEN1,BMPR2,HEMGN,OSTN,JUND,TWSG1,PDLIM7,AREG,ACVR1,CHRD,IFI204,CDK6,ACVR2A,CD276,WNT7B
GO:0032881	0.4464129	0.00	0	9	regulation of polysaccharide metabolic process	ADRA1B,FRAP1,INS2,GFPT1,ENPP1,GCK,DYRK2,C1QTNF2,AVPR1A
GO:0042306	0.164954	0.00	0	38	regulation of protein import into nucleus	FAF1,SMAD3,TACC3,NLRP3,MDFI,MBTPS1,EDA,TNFSF14,MXI1,PRKCQ,AGTR2,RHOA,CD27,NFKBIE,PKIA,SMO,TNF,JAK2,NF1,UACA,GLI3,TGFB1,SHH,NFKBIL1,TRIP6,IL10,G3BP2,NOLC1,PRDX1,NFKBIA,CDH1,SUFU,FLNA,EDAR,PKIG,SIRT1,BCL3,HNF4A
GO:0051223	0.1471715	0.00	0	49	regulation of protein transport	FAF1,SMAD3,TACC3,PTPN11,NLRP3,MDFI,MBTPS1,EDA,TNFSF14,MXI1,PRKCQ,GSK3B,AGTR2,PRKACA,GOPC,RHOA,CD27,CDK5,NFKBIE,PKIA,SMO,TNF,JAK2,NF1,UACA,GLI3,TGFB1,SHH,NFKBIL1,LTA,TRIP6,IL10,G3BP2,GAPVD1,NOLC1,BARD1,PRDX1,NFKBIA,PRKCZ,EXOC4,CDH1,SUFU,FLNA,EDAR,PKIG,SIRT1,UHMK1,BCL3,HNF4A
GO:0001976	0.3760557	0.00	0	14	regulation of systemic arterial blood pressure by neurological process	ADRA1B,DRD2,AGTR1B,ACE2,AGT,AGTR2,MIF,P2RX2,AGTR1A,TNNI3,CALCA,ADRA1D,CHRNA7,ADRA1A
GO:0042990	0.3869425	0.00	0	28	regulation of transcription factor import into nucleus	FAF1,SMAD3,TACC3,NLRP3,MDFI,MBTPS1,EDA,TNFSF14,MXI1,PRKCQ,AGTR2,RHOA,CD27,NFKBIE,TNF,NF1,UACA,NFKBIL1,TRIP6,IL10,G3BP2,PRDX1,NFKBIA,CDH1,SUFU,FLNA,EDAR,BCL3
GO:0019229	0.3611183	0.00	0	31	regulation of vasoconstriction	EDN1,ALOX5,ACE,HTR2C,APLN,KCNMB2,EDN2,ADM,ACE2,AGT,PRKCQ,HTR2A,TBXA2R,SHC1,RHOA,TBXAS1,NPPC,MAP2K1,CAV1,CACNA1C,AGTR1A,P2RX1,BDKRB2,HSPA1A,KCNMB4,DBH,ATP1A2,EDN3,ADRA1A,F2R,NPY1R
GO:0009628	0.1008764	0.00	0	352	response to abiotic stimulus	IGFBP7,ADRA1B,SLC24A1,TRPV4,SLC12A2,SGK1,ACADM,ATXN1,SOD2,BLM,PCSK1N,OPN1MW,PLEKH81,IMMT,STX1A,BMP2,GATAT2,TRH,GUCA1A,KRT8,IGFBP2,CYP2R1,DNAJB4,SLC2A1,GPX1,CASP7,RAC1,ATP2B2,PLA2G4A,FOXO2,ABCA4,EIF2B4,CRYAB,DRD2,GTSE2,REV1,MMP2,ABCG5,PDE1B,GCLC,ACCN2,FYN,TACR1,FOS,TSC22D2,PLCB4,SMPD2,KCNA5,TIMP3,CHRN2,PML,GRIN2D,GPR98,NGFR,IGF1,PPARD,PMCH,RCVRN,TRPC3,TSC22D4,PDCL3,ALDOA,ADM,PKD1,POLH,STAT1,UNC119,1200009F1,ORIK,OPN3,ACCN3,STRBP,SOX2,OPN1SW,TULP1,HSPD1,AGT,HUS1,CHRNA9,PITPNM1,NOX3,BAK1,CRHR1,ABCC2,PRKCQ,CCND1,PNP1,IL12B,GNGT2,NPFFR2,GHRL,EIF2B3,CAR2,RBM3,PMAIP1,COL3A1,TIMELESS,TSC22D3,PKN1,COL18A1,FOSL1,HSPA4,LRRP2,CDKN2D,PCYT1A,RGS9BP,CLOCK,DRD1A,SLC6A18,COP3,RHOA,CAT,CDKN1A,MAT2A,SORD,CDK5,LIG4,ELA2,NRAS,EIF2B1,MSH2,PDPK1,MAP3K1,TRPA1,NEK1,BMP4,BCL2,CIRBP,TXNIP,CHD4,PNKP,PDE6B,TGFB11,CASP9,PDE6D,ITGA2,MIF,ABCB1B,MGP,IL12A,SOCS3,BRCC3,MMP13,PKLR,BCRA2,PMP22,ATP1A3,TNF,TAC1,BTG2,FKBP,VGF,OSM,ERCC4,PCDH15,PRKDC,AAAT,BAX,CSDA,NF1,KCNMA1,CDH23,ERCC1,MSH6,PPM1D,NPHP4,TRPV1,IL18,DRD5,UACA,HSPB2,RCAN1,GNB1,HMGN1,HVCN1,ERCC2,TRP53BP2,ACTA1,ABCC8,IL1B,OTOP1,APP,COL1A1,GUCA1B,ERCC8,LTA,AKT1,ADRB2,UBE4B,CDK2,MPZ,ERCC3,MYC,ACADM,PCSK1N,IMMT,TRH,FOS,PMCH,ADM,AGT,RBM3,TRPA1,CIRBP,VGF,CSDA,IL18,ADRB2,P2RX3,TRPM8,GMPR,ADRB1,ADRB3,FOSL2,DIO2
GO:0009409	0.454127	0.00	0	22	response to cold	ADRA1B,DRD2,AGTR1B,ACE2,AGT,AGTR2,MIF,P2RX2,AGTR1A,TNNI3,CALCA,ADRA1D,CHRNA7,ADRA1A
GO:0031960	0.2668145	0.00	0	85	response to corticosteroid stimulus	IGFBP7,APOA2,SGK1,ACADM,PDCD7,BMP6,TRH,IGFBP2,PLA2G4A,PPARGC1B,BCKDHB,A2M,CCNE1,FOS,BIRC5,PIK3R1,PAPPA,HTR1B,AGXT,PARK2,RXRA,ADM,SJ,CPN1,EP300,CCND1,SDC1,FOSL1,SHC1,CDKN1A,BAD,AGL,BMP4,BCL2,GOT1,BCHE,MIF,PTPRU,MGP,FAS,TNF,BAX,KCNMA1,IL1RN,SULT1A1,IL1B,COL1A1,BCKDHA,LCAT,CASP3,IL10,MDK,MAP2K1,CAV1,CNGA3,IL6,SRCDPYD,ABCA3,GNRH1,ABCB4,C1QB,ACADS,IL6RA,KRAS,RPS6KB1,FABP4,ALPL,PRKCA,SERPINA7,TAT,ASL,ADIPOQ,AREG,CALCR,PRSS8,ALDOB,UCN,HP,FOSB,JUNB,PKC2,PTGDS,CEBPA,SLC9A3

Table S2A. Gene sets up-regulated by mild stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0007051	0.431757	0.00	0	36	spindle organization and biogenesis	UBE2C,TACC3,CKS2,DYNC1LI1,RANBP1,SMC3,TTK,TUBB1,NDC80,ESPL1,PRC1,UNC84B,KIF11,KIF23,CENPJ,ZWINT,AURKA,STMN1,BUB1B,FBXO5,DCTN2,DYNC1H1,TUBB5,RCC1,MLH1,RAN,MYH9,SAC3D1,CCDC100,TPX2,1700009N14RIK,TUBG1,SPAG5,SMC1A,PCNT,TACC2
GO:0006614	1.0086467	0.00	0	6	SRP-dependent cotranslational protein targeting to membrane	SRPR,SRP9,SRP19,VCAN,SRP14,SRP72
GO:0042310	0.2926818	0.00	0	39	vasoconstriction	ADRA1B,EDN1,ALOX5,ACE,HTR2C,APLN,KCNMB2,EDN2,ADM,ACE2,AGT,PRKCO,HTR2A,TBXA2R,SHC1,RHOA,EDNRB,TBXAS1,DRD5,NPPC,G6PDX,AVP,MAP2K1,CAV1,CACNA1C,AGTR1A,P2RX1,BDKRB2,HSPA1A,KCNMB4,EDNRA,ADRA1D,DBH,ATP1A2,KEL,EDN3,ADRA1A,F2R,NPY1R
GO:0019058	0.2835242	0.00	0	50	viral infectious cycle	MDFIC,WWP1,VAPB,PVRL1,PSIP1,DEK,TARBP2,OPRK1,CCL2,CD81,HS3ST5,COX11,ACE2,CCL5,XRCC5,CCR5,CCL3,BANF1,TOP2A,RSF1,WWP2,LIG4,MAP3K1,BCL2,CCL4,HS3ST6,ITCH,CD4,TNF,HMGA1,EIF5A,CTBP1,PPIA,HTATSF1,HBXIP,SMARCB1,SUPT5H,APOBEC3,CXCR6,CD28,FURIN,TNIP1,CXCR4,CTBP2,UBP1,IFNB1,XRCC4,XRCC6,PCSK5,NFIA
GO:0016032	0.2768395	0.00	0	64	viral reproduction	MDFIC,SMAD3,DERL1,WWP1,RRAGA,VAPB,PVRL1,PSIP1,DEK,TARBP2,HIPK2,OPRK1,CCL2,CD81,HS3ST5,COX11,ACE2,CCL5,XRCC5,CCR5,CCL3,BANF1,TOP2A,RSF1,WWP2,LIG4,MAP3K1,BCL2,CCL4,HS3ST6,ITCH,CD4,TNF,HMGA1,CALCOCO2,UACA,TGFB1,EIF5A,CTBP1,PARD6A,HCFC1,PPIA,HTATSF1,HBXIP,SMARCB1,OAS1A,SUPT5H,CCL1,INSR,APOBEC3,GF1,HCFC2,CXCR6,CD28,FURIN,TNIP1,CXCR4,CTBP2,UBP1,IFNB1,XRCC4,XRCC6,PCSK5,NFIA
GO:0022415	0.3863451	0.00	0	57	viral reproductive process	MDFIC,SMAD3,DERL1,WWP1,RRAGA,VAPB,PVRL1,PSIP1,DEK,TARBP2,HIPK2,OPRK1,CCL2,CD81,HS3ST5,COX11,ACE2,CCL5,XRCC5,CCR5,CCL3,BANF1,TOP2A,RSF1,WWP2,LIG4,MAP3K1,BCL2,CCL4,HS3ST6,ITCH,CD4,TNF,HMGA1,TGFB1,EIF5A,CTBP1,HCFC1,PPIA,HTATSF1,HBXIP,SMARCB1,SUPT5H,INSR,APOBEC3,CXCR6,CD28,FURIN,TNIP1,CXCR4,CTBP2,UBP1,IFNB1,XRCC4,XRCC6,PCSK5,NFIA
GO:0019048	1.3445012	0.00	0	9	virus-host interaction	SMAD3,DERL1,RRAGA,VAPB,TARBP2,HIPK2,HS3ST6,TGFB1,INSR

Table S2B. Gene sets down-regulated by mild stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene set description	Gene set genes
GO:0055066	-0.1232928	0	0	238	di-, tri-valent inorganic cation homeostasis	HRH3,ADRA1B,TRPV4,EDN1,COMMD1,TRF,HAMP,LHCGR,ITGB3,GNAT2,ATP7A,PTGER3,SLC30A5,ATP2B2,CLN3,CCR2,DRD2,LYN,FTMT,AGTR1B,ITPR3,ALAS2,KCNA5,FXDY1,CCL2,HEXB,TGM2,PMCH,HIF1A,EFHC1,TRFR2,ITGB1,1300017J02RIK,SRPRB,CCKAR,ADM,TPT1,S100B,RSHL1,P2RY4,GNA15,TTCT,OPRL1,CCL5,CCR4,RGN,CRHR1,CCR5,CNTNAP1,CCR10,ABC6,CCR1,GHRL,APLP2,FKBP1B,ATOX1,CCL3,KDR,GRIK2,SLC30A8,GLP1R,CASR,TBXA2R,BDKRB1,PTHR1,HMOX1,HPX,PYGM,GPR6,PLCE1,FXN,CD55,MCHR1,ELA2,IL6ST,NMUR2,SV2A,PLN,BCL2,SLC39A4,PTH2R,EDNRB,NDN,FTL2,ACO1,IL2,APOE,CUTC,CACNB4,GHRH,FTL1,TAC1,THY1,SYPL2,CP,JAK2,ATP2A2,CALCB,HERPUD1,CYSLTR1,TRPC2,LCK,ITGAV,TGFB1,LPAR1,GNB1,IL1B,SLC30A1,TGFB2,APP,SLC8A1,CALR,CCL19,HCRT,TGFA,DMWD,MYC,NUCB2,HSP90B1,PGM1,PRND,C3AR1,CCR9,SLC39A5,CCL28,TRDN,STC1,CCR8,KNG1,SRI,SLC24A3,CXCL13,SCO1,GALR2,SOD1,GNA13,GNG3,AVPR1B,TRPM8,KISS1,CAV1,MT2,BANK1,CACNA1C,ATP2C1,XCL1,TRPV5,IREB2,CCL1,C5AR1,AGTR1A,CCR3,MT1,VDR,CHERP,HTT,BDKRB2,F2,IBTK,ATP7B,MFI2,CLSTN1,ATP2B4,GCM2,RYR2,JPH2,HR,C,FTHL17,TFRC,CACNA1F,PROK2,SLC37A4,PRKCB1,CTRC,HFE,GRIN1,ABC7,TRHR,LPAR3,ANXA7,TNNI3,ITF,PRKCA,CALCA,FZD2,CD52,ITPR1,EDNRA,GPR12,FTH1,RYR3,CCR7,PRNP,CXCR4,EG434729,PSEN1,CACNA1A,PTK2B,CXCR3,CCL7,CCKBR,WFS1,NPY2
GO:0006266	-0.4747065	0	0	9	DNA ligation	HMG2B,TOP2A,LIG4,HMG1B,RAD51,APTX,XRCC4,XRCC6,MGMT
GO:0007204	-0.1986696	0	0	106	elevation of cytosolic calcium ion concentration	HRH3,ADRA1B,TRPV4,EDN1,LHCGR,GNAT2,PTGER3,CCR2,LYN,AGTR1B,ITPR3,TGM2,PMCH,CCKAR,ADM,P2RY4,GNA15,OPRL1,CCR4,CRHR1,CCR5,CNTNAP1,CCR10,CCR1,GHRL,FKBP1B,KDR,GLP1R,TBXA2R,BDKRB1,PTHR1,GPR6,PLCE1,CD55,MCHR1,NMUR2,EDNRB,IL2,GHRH,TAC1,THY1,JAK2,CYSLTR1,TRPC2,LCK,ITGAV,TGFB1,LPAR1,GNB1,IL1B,TGFB2,SLC8A1,HCRT,C3AR1,CCR9,CCL28,CCR8,KNG1,CXCL13,GALR2,GNA13,GNG3,AVPR1B,KISS1,CACNA1C,C5AR1,AGTR1A,CCR3,BDKRB2,F2,IBTK,JPH2,PROK2,TRHR,LPAR3,CALCA,FZD2,CD52,ITPR1,EDNRA,CCR7,CXCR4,CACNA1A,PTK2B,CXCR3,CCKBR,NPY2R,CALCR,TRPC6,CCR6,PTPRC,CAV3,CD24A,GIPR,MS4A2,ADRA1A,F2RL1,F2R,S1PR1,EPOR,XCR1,RXFP3,AVPR1A,NMB,SAAI,LPAR2
GO:0034101	-0.1556556	0	0	58	erythrocyte homeostasis	HEPH,HBA-A1,EPO,HBA-A2,MAEA,LYN,FOXO3A,ALAS2,STAT5B,DNASE2A,HIF1A,SMAP1,SMAD5,TAL1,ANK1,SP1,JMJD6,SOX6,HMOX1,BMP4,SFPI1,CEBP,PG,DYRK3,ERCC2,SP3,STAT5A,G6PDX,SFXN1,ACVR1B,ID2,INPP5D,TIMP1,ACIN1,ETS1,IREB2,KLF1,FOXO3,BPGM,MAPK14,PRDX1,RPS19,LDB1,TCEA1,MAFB,INHBA,EPAS1,ARNT,MB,LMO2,BCL6,INHA,CD24A,CDK6,ACVR2A,RB1,EPB4.2,HCLS1,PKNOX1
GO:0007342	-1.1327216	0	0	11	fusion of sperm to egg plasma membrane	ITGA3,CD9,CATSPER1,IZUMO1,HYAL4,ADAM2,ADAM1A,CRISP1,SERPINA5,HYAL5,SPAM1
GO:0048534	-0.1189614	0	0	340	hemopoietic or lymphoid organ development	TACC3,HEPH,ZFP36,BLM,ATP7A,ACE,CD164,WWP1,HBA-A1,FLT3L,EPO,HBA-A2,SPNA1,MITF,HMG1B,CCR2,CSF1,MEIS1,MAEA,LYN,FOXO3A,CLPTM1,ALAS2,HBB-B1,STAT5B,CD2,PIK3R1,PML,CD74,EBP,DNASE2A,RHOH,MLF1,HIF1A,ESRR,SMAP1,SMAD5,NTRK1,TNFRSF11B,TAL1,KITL,NCA,PH2,KLF6,CLCF1,KIRREL3,TAZ,LTBR,PBX1,CLEC2G,CTNNB1,VPREB1,TTCT,IL4RA,XRCC5,PNP1,ANK1,CCR1,IL12B,MYST1,CAR2,S,P1,FUT10,CD42,KDR,JMJD6,ITPKB,SOX6,HOXB3,ERBB2,IL11,HELLS,HOXB7,CD27,CEBPE,TCF3,TLX1,CARTPT,BAD,LIG4,POU2F2,MSH2,PRDX3,FLT3,CHUK,BMP4,BCL2,DNAJA3,AP3D1,GNAS,FOXP1,NKX3-2,HOXB4,IL2,ZAP70,SFPI1,TNFRSF11A,RTKN2,TNFSF11,SH2B3,FAS,CACNB4,CEBPG,CD4,CSF3,IL2RA,TNF,IL31RA,TCFE2A,PRKD,C,JAK2,NF1,CASP8,IL25,IL7R,ERCC1,DYRK3,NOTCH4,FOXJ1,THOC5,SIX1,PTPN22,LCK,SPN,TGFB1,VAV1,SART1,HDACS,PGM3,S,HH,ERCC2,MLL1,NOTCH2,TGFB2,HS1BP3,RAG2,PAX1,SP3,LTA,PLCG2,TSHR,GMPR2,KLF11,FOXP3,IL17C,POU1F1,IRF8,FGF3,NKX2-5,MED1,H2-DMA,POLM,CD79A,MALT1,H2-AA,STAT5A,MYH9,CSF1R,TERC,CD3D,G6PDX,WNT3A,JAG2,IL10,SOCS5,TLR3,MMP9,IL7,SFXN1,LIF,STAP1,TGFB2,HDAC7,PICALM,CXCL13,TBX1,ACVR1B,ID2,BLNK,CD300LF,TXNRD2,INPP5D,SOD1,IL21,MEN1,TGFB1,CORO1A,RORC,NCOA6,TIMP1,CXCR5,PSEN2,AP3B1,GADD45G,IL3,IRF1,NKX2-3,PURB,LILRB3,CARD11,ADA,ACIN1,ETS1,IL20,KLF1,HHEX,OSTM1,FOXP1,DOCK2,GAB3
GO:0007599	-0.2922338	0	0	106	hemostasis	FBN1,EDN1,F5,ITGB3,EFEMP2,L3MBTL4,FBLN5,VWF,CD9,SCUBE1,P2RY1,GP1BA,AVPR2,FGF,COL3A1,F2R2,SERPINE1,IL11,CD36,EVL,SERPING1,ADORA2A,APOH,GP5,ITGA2,APOE,SERPINF2,FGA,P2RY12,TREML1,OTOG,RAB27A,F13B,ANXA5,F12,F13A1,PLSCR4,F11,MST1,F2RL3,PLAT,PABPC4,PDPN,LMAN1,CPB2,TMPRSS6,IL10RB,C3,PDGFA,KN61,C9,KRT1,ANXA2,GNA13,F8,CAV1,PDGFB,WAS,P2RX1,TFPI2,CD40,PLAUR,F2,VKORC1,FLI1,NFE2,F7,PROS1,ANXA8,PF4,F3,GGCX,HPS4,PROC,ANXA7,HGF,F10,M,MRN1,PLSCR1,TSPAN8,FGG,GNAQ,IL20RA,PPBP,SERPINC1,FOXA2,TFPI,CD40LG,PROZ,ENTPD2,ADAMTS13,F9,PLG,GNA12,F2RL1,HNF4A,F2R,PIK3CB,ENTPD1,SERPIND1,PLAU,PROCR,THBD,GP9,SERPINA5,SAAI
GO:0042090	-1.4235162	0	0	10	interleukin-12 biosynthetic process	IFNG,IRF1,TLR6,REL,TRAF6,NFKB1,MAST2,LTB,RELA,TLR4
GO:0032615	-0.9063338	0	0	16	interleukin-12 production	IFNG,NOD2,G6PDX,IL10,IRF1,PRKCD,CD40,TLR6,REL,TRAF6,NFKB1,CD40LG,MAST2,LTB,RELA,TLR4
GO:0001776	-0.2147443	0	0	37	leukocyte homeostasis	BCL10,STAT5B,TNFSF13B,TNFSF14,TNFRSF13B,EVI1,TNFRSF13C,IFNG,BCL2,DNAJA3,IL2,CD44,FAS,IL2RA,BAX,TGFB1,TGFB2,AKT1,FOXP3,SH2B2,IKKB,CASP3,STAT5A,SOD1,MEN1,CORO1A,IKBK,NKX2-3,LILRB3,BCL2L11,IL6,PPP3CB,SLC37A4,FANCC,PIK3CD,CD24A,FCER1G
GO:0045576	-0.88024	0	0	20	mast cell activation	BCL10,LAT2,TAC4,HMOX1,LAT,THY1,FCER1A,YWHAZ,LCP2,FCGR2B,FYB,FCGR3,BTK,CPLX2,SYK,MS4A2,FCER1G,NDRG1,TLR4,CD48
GO:0007128	-1.1794505	0	0	11	meiotic prophase I	FBXO5,EHMT2,MLH1,SYCP2,SYCE1,RAD1,PIWIL2,PRDM9,OVOL1,SYCE2,FKBP6

Table S2B. Gene sets down-regulated by mild stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0006944	-0.1709414	0	0	73	membrane fusion	EEA1,VAPA,ITGA3,VAMP3,PLA2G4A,CLN3,GM2A,SNAP23,CAST,OTOF,CD9,STXB1,VTI1A,VAV3,MFN1,CADPS,BAK1,RABIF,GCA, RIMS1,NSFL1C,TIE1,CAPN2,VTI1B,CATSPER1,OPA1,CD44,STX2,KCNH1,NAPA,BAX,VAMP2,GOSR2,CACNA1S,VAMP7,MFN2,NP LOC4,IZUMO1,CTBP1,STX11,HYAL4,NAPG,MYH9,RAB3A,SNPH,RABEP1,STAP1,CDON,ADAM2,NEO1,USO1,ANXA7,GNAI3,NSF, GRIK5,CPLX2,BNIP1,ATG7,STX6,CAV2,NTN2L,VCPIP1,LRMP,DYRK1B,PLDN,CACNA1H,ADAM1A,CRISP1,SERPINA5,HYAL5,SPAM 1,ADAM12,SNAP29
GO:0046785	-0.7219618	0	0	17	microtubule polymerization	SGK1,CENPJ,STMN1,FBXO5,MAPRE1,CDKN1B,ASZ1,CAV1,CFTR,TPPP,MAPK8,CAV2,CTTNBP2,PSRC1,CAV3,MAPT,WNT2
GO:0044266	-0.1903085	0	0	24	multicellular organismal macromolecule catabolic process	ACE,MMP2,MMP10,ACE2,MMP8,ADAMTS14,MMP19,MMP13,MMP27,PEPD,MMP9,PRSS2,PRTN3,MMP1B,MMP14,ADAMTS 3,P2RX7,KLK6,MMP16,MMP7,MMP1A,MMP3,MMP11,ADAMTS2
GO:0046716	-0.6349286	0	0	11	muscle maintenance	GAA,HIF1A,MTM1,DMD,SOD1,PPP3CB,SRF,CAV3,LARGE,PLG,GYTL1B
GO:0030099	-0.1913147	0	0	146	myeloid cell differentiation	HEPH,ZFP36,HBA-A1,EPO,HBA- A2,MITF,HMGB3,CSF1,MAEA,LYN,FOXO3A,ALAS2,STAT5B,PIK3R1,PML,DNASE2A,HIF1A,ESRRA,SMAP1,SMAD5,TNFRSF11B,TA L1,KITL,CLEC2G,CTNNB1,ANK1,CCR1,MYST1,CAR2,SP1,CD42,JMJD6,SOX6,IL11,HOXB7,CEBPE,CARTPT,PRDX3,CHUK,BMP4,G NAS,SFP11,TNFSF11,FAS,CEBPG,CSF3,TNF,IL31RA,JAK2,NF1,CASP8,IL25,DYRK3,THOC5,TGFB1,ERCC2,SP3,GMPR2,IL17C,IRF8,S TATS5A,MYH9,CSF1R,G6PDX,TLR3,MMP9,SFXN1,LIF,STAP1,TGFBR2,ACVR1B,ID2,CD300LF,INPP5D,NCOA6,TIMP1,PSEN2,IL3,NK X2- 3,PURB,LILRB3,ACIN1,ETS1,KLF1,OSTM1,GAB3,CSF2,TCFE3,FOXO3,BPGM,SNRK,RUNX1,MAPK14,PPARG,RPS19,RASGRP4,DHR S2,ZBTB7A,LDB1,TCEA1,LEP,MYST3,C8FB,NFKBIA,SPIB,MAFB,JUN,PF4,INHBA,EPAS1,TRAF6,IL4,CCL21A,ARNT,CALCA,MB,LMO 2,PLSCR1,PSEN1,CBFA2T3,IRF4,CALCR,PPBP,JAG1,ZBTB16,VPS33A,BCL6,TIRAP,CLEC2D,TM7SF4,INHA,KLF10,IFI204,CDK6,ADA M10,ACVR2A,RB1,EPB4.2,SCIN,RELB,THPO,SPP1,HCLS1,TLR4,CEBPA,PKNOX1
GO:0002274	-0.2926996	0	0	53	myeloid leukocyte activation	BCL10,LAT2,RORA,CD2,CD74,PRAM1,PRG3,TLR2,TAC4,JMJD6,HMOX1,LAT,TLR7,MIF,SFP11,NOD2,THY1,IL31RA,FCER1A,TGFB1 ,VAMP7,YWHAZ,TLR1,IL10,TLR3,TICAM1,TGFBR2,TLR9,LILRB3,SBNO2,LCP2,SPACA3,CSF2,TLR6,DHRS2,IL8RB,FCGR2B,FYB,FCG R3,CD93,BTK,TRAF6,AIF1,CPLX2,IRF4,SYK,MS4A2,RELB,FCER1G,SLC7A2,NDRG1,TLR4,CD48
GO:0002573	-0.1652394	0	0	69	myeloid leukocyte differentiation	MITF,CSF1,PIK3R1,ESRRA,TNFRSF11B,KITL,CLEC2G,CTNNB1,CAR2,CD42,CEBPE,CARTPT,CHUK,GNAS,SFP11,TNFSF11,CSF3,TN F,IL31RA,NF1,CASP8,IL25,THOC5,TGFB1,SP3,GMPR2,IL17C,MYH9,CSF1R,TLR3,MMP9,LIF,TGFB2,ID2,CD300LF,INPP5D,PSEN2, IL3,NKX2- 3,LILRB3,ACIN1,OSTM1,GAB3,CSF2,TCFE3,RUNX1,PPARG,DHRS2,ZBTB7A,SPIB,JUN,INHBA,TRAF6,IL4,CALCA,PSEN1,CBFA2T3,I RF4,CALCR,CLEC2D,TM7SF4,INHA,KLF10,IFI204,ADAM10,RB1,RELB,TLR4,CEBPA
GO:0050709	-0.39066	0	0	12	negative regulation of protein secretion	APOA2,SRGN,INS2,TNF,FOXP3,SERGEF,IL10,APOA1,CIDEA,TNFRSF4,DPH3,TNFSF4
GO:0001764	-0.3104409	0	0	67	neuron migration	PEX13,ITGA3,FEZF1,FYN,NKX2- 1,PEX2,PEX7,CCKAR,NR2F1,TLX3,PEX5,CCR4,BARHL2,PAFAH1B1,CDK5,NTN1,NR2F2,NDN,ESR2,DNER,GFRA3,PAX6,BARHL1,AL KBH1,MYH10,NAV1,YWHAE,APBB2,DCC,ASZ1,KATNA1,CDK5R1,APBB1,TWIST1,LMX1B,MET,PRRX1,NDEL1,ARX,RELN,NEURO G2,DCLK1,CFTR,TOP2B,GJA1,PHOX2B,CNTN2,MDGA1,PTK2,SOX1,CCK,CXCR4,VAX1,PSEN1,CAV2,NRCAM,CXCL12,CTTNBP2,NE UROD4,DCX,ROBO3,CHL1,DAB1,PRKG1,ATOH1,ASCL1,WNT2
GO:0006911	-0.3281612	0	0	12	phagocytosis, engulfment	GULP1,ELMO1,ABCA1,DOCK1,CLEC7A,VAMP7,FCGR2B,FCGR3,SIRPA,MFGE8,FCGR1,FCER1G
GO:0045026	-0.6569414	0	0	25	plasma membrane fusion	ITGA3,CAST,CD9,TIE1,CAPN2,CATSPER1,CD44,STX2,KCNH1,CACNA1S,IZUMO1,HYAL4,MYH9,CDON,ADAM2,NEO1,NTN2L,DYR K1B,CACNA1H,ADAM1A,CRISP1,SERPINA5,HYAL5,SPAM1,ADAM12
GO:0030168	-0.4012486	0	0	30	platelet activation	L3MBTL4,VWF,CD9,GP1BA,FGF,CD3A1,IL11,EVL,APOE,FGA,P2RY12,TREML1,PDNP,PDGFA,GNA13,PDGFB,P2RX1,CD40,F2,PF 4,PLSCR1,FGG,PPBP,CD40LG,ENTPD2,ADAMTS13,F2R,PIK3CB,ENTPD1,SAA1
GO:0002821	-0.5033375	0	0	24	positive regulation of adaptive immune response	TNFSF13B,PNP1,TNFRSF13C,IL12A,NOD2,FCER1A,TRAF2,FOXP3,MALT1,C3,IL27RA,FCER2A,P2RX7,FCGR3,TRAF6,HSPA1A,MAP 3K7,PTPRC,CD24A,FCGR1,SASH3,CD1D2,CD1D1,FCER1G
GO:0046638	-0.5790531	0	0	17	positive regulation of alpha-beta T cell differentiation	IL4RA,PNP1,ITPKB,AP3D1,ZAP70,FOXP3,SOC5,TGFB2,AP3B1,IL6,SYK,CD80,HLX,SASH3,CD86,IL2RG,CD1D1
GO:0002714	-0.6735315	0	0	8	positive regulation of B cell mediated immunity	NOD2,FCER1A,C3,FCER2A,FCGR3,PTPRC,FCGR1,FCER1G
GO:0032270	-0.1716733	0	0	134	positive regulation of cellular protein metabolic process	DOCK7,BRCA1,AKTIP,DSTN,BMP2,EPO,RAC1,SAMD4,BCL10,UBE2N,IFT88,LYN,PPP2R4,CD42EP2,KRT17,GCLC,PEMT,STUB1,C D81,IGF1,MAPK3,KITL,CLCF1,EP300,BARHL2,CCND1,VEGFC,INS2,IFT52,IL11,RHOA,ARF6,MAP3K1,CDK4,BMP4,TKN2,DAZL,ED NRB,FGFR3,IL2,APOE,IL12A,NCK1,AURKAIP1,CD4,NOD2,TNF,THY1,IL31RA,KATNB1,OSM,FCER1A,CDKN1B,PPARGC1A,SQSTM1 ,TGFB1,EIF5A,IL1B,AKT1,FOXP3,TGFA,TGDF1,LRRK2,MAPK1,SH2D1B1,CD42EP5,FMN1,BOLL,CARD14,LIF,CLN6,MEN1,ASZ1,IL 3,CAV1,BMPR2,EIF2B5,IL20,CSF2,AGTR1A,PDGFRB,IL6,DLG1,F2,CCND3,ADORA1,UBE2D1,P2RX7,CD3E,RGMA,CFTR,NCK2,TPP P,IL5,CD28,FGF2,IL4,PRKCA,DOK7,RB1CC1,SCAP,EDNRA,CCK,TNFRSF14,ATG7,MAPK8,ADIPOQ,PSEN1,PAWR,ATG10,PTK2B,CA V2,SYK,CTTNBP2,NHLRC1,PSRC1,CCND2,CAV3,IGH- 6,CD24A,CD80,DLCL1,CFL1,ACVR2A,BCL3,SH2D1B2,MAP2K4,F2R,UCN,ITLN1,MAPT,HCLS1,TLR4,WNT2

Table S2B. Gene sets down-regulated by mild stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0045807	-0.2712925	0	0	30	positive regulation of endocytosis	CD47,LDLRAP1,GATA2,PPT1,CALY,SFTPD,CD63,CLEC7A,CD209B,CBL1,ACTN4,C3,MIB1,CAV1,KIF3A,SPACA3,AHSG,FCGR2B,FCGR3,SIRPA,PTX3,PTK2,NEDD4L,CBL,FGF10,MFGE8,IGH-6,FCGR1,SIRPB1,FCER1G
GO:0043123	-0.1582868	0	0	93	positive regulation of I-kappaB kinase/NF-kappaB cascade	NDFIP2,VAPA,BCL10,UBE2N,GPR177,TRAF3IP2,TGM2,BST2,TBK1,LGALS9,TSPAN6,LTBR,NDFIP1,ZDHHC17,GPR89,HMOX1,RHOA,BIRC2,ECT2,SLC35B2,TNFSF10,CC2D1A,PPM1A,NUP62,LGALS1,GOLT1B,FKBP1A,RPL17,TMED4,MYD88,TRIM13,NOD2,TNFCASP8,TFG,UBE2V1,LPAR1,IL1B,TMEM9B,NOD1,LTA,MAP3K3,MIER1,RHOC,SLC20A1,MALT1,CANT1,TLR3,TICAM1,PPP5C,SECTM1A,HTR2B,FADD,LITAF,CARD11,SLC44A2,ATP2C1,SHISA5,EEF1D,RIPK1,CD40,TRIM38,ZDHHC13,TLR6,MIB2,TNFRSF10B,FASL,PLK2,MAP3K7IP2,MUL1,RIPK2,REL,TRAF6,NEK6,GJA1,MAP3K7,TRAF5,ADIPOQ,FLNA,IKBKE,TNFRSF1A,TRADD,PLEKHG5,PDCD11,F2R,CFLAR,TICAM2,RELA,ECM1,CARD9,CASP1,TLR4,TMEM101
GO:0002699	-0.5388572	0	0	36	positive regulation of immune effector process	BCL10,PNP1,IL12B,KLRB1C,IL13RA1,IL12A,NOD2,FCER1A,TRAF2,FOXP3,MALT1,C3,SH2D1A,IL21,LAG3,FOXP1,FCER2A,P2RX7,FCGR3,TRAF6,HSPA1A,MAP3K7,KLRK1,CRTAM,SYK,CADM1,PTPRC,CD24A,KLRE1,MS4A2,IL13,FCGR1,SASH3,CD1D2,CD1D1,FCE R1G
GO:0050716	-0.456757	0	0	8	positive regulation of interleukin-1 secretion	NLRP3,PYCARD,IFNG,NOD2,NLRP2,P2RX7,PANX1,SAA1
GO:0001912	-0.5437822	0	0	16	positive regulation of leukocyte mediated cytotoxicity	PNP1,IL12B,KLRB1C,IL12A,SH2D1A,IL21,LAG3,P2RX7,HSPA1A,KLRK1,CRTAM,CADM1,PTPRC,KLRE1,CD1D2,CD1D1
GO:0002705	-0.5285613	0	0	30	positive regulation of leukocyte mediated immunity	PNP1,IL12B,KLRB1C,IL12A,NOD2,FCER1A,TRAF2,FOXP3,MALT1,C3,SH2D1A,IL21,LAG3,FCER2A,P2RX7,FCGR3,TRAF6,HSPA1A,MAP3K7,KLRK1,CRTAM,CADM1,PTPRC,CD24A,KLRE1,FCGR1,SASH3,CD1D2,CD1D1,FCER1G
GO:0002708	-0.5285613	0	0	30	positive regulation of lymphocyte mediated immunity	PNP1,IL12B,KLRB1C,IL12A,NOD2,FCER1A,TRAF2,FOXP3,MALT1,C3,SH2D1A,IL21,LAG3,FCER2A,P2RX7,FCGR3,TRAF6,HSPA1A,MAP3K7,KLRK1,CRTAM,CADM1,PTPRC,CD24A,KLRE1,FCGR1,SASH3,CD1D2,CD1D1,FCER1G
GO:0031116	-1.3615315	0	0	11	positive regulation of microtubule polymerization	CDKN1B,ASZ1,CAV1,CFTR,MAPK8,CAV2,CTTNBP2,PSRC1,CAV3,MAPT,WNT2
GO:0031112	-1.1941082	0	0	12	positive regulation of microtubule polymerization or depolymerization	KATNB1,CDKN1B,ASZ1,CAV1,CFTR,MAPK8,CAV2,CTTNBP2,PSRC1,CAV3,MAPT,WNT2
GO:0050766	-0.4670392	0	0	17	positive regulation of phagocytosis	CD47,GATA2,SFTPD,CLEC7A,CD209B,C3,SPACA3,AHSG,FCGR2B,FCGR3,SIRPA,PTX3,PTK2,MFGE8,FCGR1,SIRPB1,FCER1G
GO:0042327	-0.1861153	0	0	72	positive regulation of phosphorylation	DOCK7,AKTIP,BMP2,EPO,APLN,BCL10,LYN,GLMN,CD81,IGF1,KITL,CLCF1,CCND1,VEGFC,IL11,BMP4,TKN2,EDNRB,FGFR3,IL2,IL12A,CD4,NOD2,TNF,THY1,IL131RA,OSM,FCER1A,SQSTM1,IL1B,TGFA,TDGF1,SH2D1B1,ANG,CARD14,LIF,EREG,EGFR,IL3,GRK1,BMPR2,IL20,CSF2,IL6,CCND3,P2RX7,CD3E,RGMA,IL5,FGF2,IL4,PRKCA,DOK7,RB1CC1,EDNRA,CCK,TNFRSF14,ADIPOQ,PSEN1,AREG,SYK,CCND2,IGH-6,CD24A,CD80,ACVR2A,SH2D1B2,MAP2K4,EGF,ITLN1,HCLS1,TLR4
GO:0001934	-0.2100468	0	0	63	positive regulation of protein amino acid phosphorylation	DOCK7,AKTIP,BMP2,EPO,LYN,CD81,IGF1,KITL,CLCF1,CCND1,VEGFC,IL11,BMP4,TKN2,EDNRB,FGFR3,IL2,IL12A,CD4,NOD2,TNF,THY1,IL131RA,OSM,FCER1A,SQSTM1,IL1B,TGFA,TDGF1,SH2D1B1,CARD14,LIF,IL3,BMPR2,IL20,CSF2,IL6,CCND3,P2RX7,CD3E,RGMA,IL5,FGF2,IL4,PRKCA,DOK7,RB1CC1,EDNRA,CCK,TNFRSF14,ADIPOQ,PSEN1,SYK,CCND2,IGH-6,CD24A,CD80,ACVR2A,SH2D1B2,MAP2K4,ITLN1,HCLS1,TLR4
GO:0051247	-0.1695103	0	0	140	positive regulation of protein metabolic process	DOCK7,FAF1,BRCA1,AKTIP,DSTN,BMP2,EPO,RAC1,SAMD4,BCL10,UBE2N,IFT88,EGLN2,LYN,PPP2R4,CDC42EP2,KRT17,GCLC,PEMT,STUB1,CD81,IGF1,MAPK3,KITL,CLCF1,EP300,BARHL2,CCND1,VEGFC,INS2,IFT52,IL11,RHOA,ARF6,MAP3K1,CDK4,BMP4,TNFK2,DAZL,EDNRB,FGFR3,IL2,APOE,IL12A,NCK1,AURKAIP1,CD4,NOD2,TNF,THY1,IL131RA,KATNB1,OSM,FCER1A,CDKN1B,PPARGC1A,SQSTM1,TGFB1,EIF5A,IL1B,AKT1,FOXP3,TGFA,TDGF1,LRRK2,MAPK1,SH2D1B1,CDC42EP5,FMN1,BOLL,CARD14,LIF,CLN6,MEN1,ASZ1,IL3,CAV1,BMPR2,EIF2B5,IL20,CSF2,AGTR1A,BARD1,PDGFRB,IL6,SGSM3,DLG1,F2,CCND3,ADORA1,UBE2D1,P2RX7,CD3E,RGMA,CFTR,NCK2,TPPP,IL5,CD28,FGF2,IL4,GJA1,PRKCA,DOK7,RB1CC1,SCAP,EDNRA,CCK,TNFRSF14,ATG7,MAPK8,ADIPOQ,PSEN1,PAWR,ATG10,PTK2B,CAV2,WFS1,SYK,CTTNBP2,NHLRC1,PSRC1,CCND2,CAV3,IGH-6,CD24A,CD80,DL1,CFL1,ACVR2A,BCL3,SH2D1B2,MAP2K4,F2R,UCN,ITLN1,MAPT,HCLS1,TLR4,WNT2
GO:0031401	-0.164144	0	0	79	positive regulation of protein modification process	DOCK7,BRCA1,AKTIP,BMP2,EPO,BCL10,UBE2N,LYN,PPP2R4,STUB1,CD81,IGF1,KITL,CLCF1,CCND1,VEGFC,IL11,BMP4,TKN2,EDNRB,FGFR3,IL2,IL12A,CD4,NOD2,TNF,THY1,IL131RA,OSM,FCER1A,PPARGC1A,SQSTM1,TGFB1,IL1B,FOXP3,TGFA,TDGF1,LRRK2,SH2D1B1,CARD14,LIF,MEN1,IL3,BMPR2,IL20,CSF2,IL6,CCND3,ADORA1,UBE2D1,P2RX7,CD3E,RGMA,IL5,FGF2,IL4,PRKCA,DOK7,RB1CC1,EDNRA,CCK,TNFRSF14,ATG7,ADIPOQ,PSEN1,ATG10,SYK,NHLRC1,CCND2,IGH-6,CD24A,CD80,DL1,ACVR2A,SH2D1B2,MAP2K4,ITLN1,HCLS1,TLR4
GO:0002711	-0.6914898	0	0	14	positive regulation of T cell mediated immunity	PNP1,IL12A,TRAF2,FOXP3,MALT1,P2RX7,TRAF6,HSPA1A,MAP3K7,PTPRC,CD24A,SASH3,CD1D2,CD1D1
GO:0051324	-1.2314493	0	0	12	prophase	FBXO5,EHMT2,MLH1,SYCP2,SYCE1,RAD1,PIWIL2,MSH5,PRDM9,OVOL1,SYCE2,FKBP6
GO:0044256	-0.1903085	0	0	24	protein digestion	ACE,MMP2,MMP10,ACE2,MMP8,ADAMTS14,MMP19,MMP13,MMP27,PEPD,MMP9,PRSS2,PRTN3,MMP1B,MMP14,ADAMTS3,P2RX7,KLK6,MMP16,MMP7,MMP1A,MMP3,MMP11,ADAMTS2

Table S2B. Gene sets down-regulated by mild stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0009306	-0.1839066	0	0	70	protein secretion	APOA2,ARFIP1,BACE2,LAX1,LYN,TRAF3IP2,SRGN,NLRP3,GLMN,PYCARD,ACHE,ABCA1,ERP29,TNFSF13B,PRKCO,SCG2,NLRC4,ARL4D,VEGFC,INS2,CD27,POU2F2,IFNG,ADORA2A,GNAS,IL2,PLA2G1B,NOD2,TNF,LTBP2,ARFGAP3,CANX,GNPTAB,TRAF2,FOXP3,TNFSF15,NLRP2,SERGEF,ANG,PPY,IL10,KCNN4,APOA1,LCP2,DNAJC1,AGTR1A,CD40,P2RX7,STEAP3,CIDEA,KRT20,CXCL10,TRAF6,CRTAM,CADM1,NECAB3,PCSK5,TNFRSF4,CD40LG,MS4A2,PDIA4,IL13,PANX1,LMF1,F2RL1,EGF,MON1A,DPH3,TNFSF4,SAI1
GO:0002819	-0.397189	0	0	33	regulation of adaptive immune response	TNFSF13B,PNP1,TNFRSF13C,IL12A,NOD2,STAT6,FCER1A,IL7R,FOXJ1,SPN,TRAF2,FOXP3,MALT1,C3,IL27RA,PPP3CB,FCER2A,FCGR2B,P2RX7,FCGR3,PTPN6,TRAF6,HSPA1A,MAP3K7,DPP4,BCL6,PTPRC,CD24A,FCGR1,SASH3,CD1D2,CD1D1,FCER1G
GO:0046634	-0.6226827	0	0	32	regulation of alpha-beta T cell activation	BLM,BTLA,IL4RA,PNP1,ITPKB,AP3D1,ZAP70,SHH,FOXP3,EBI3,SOC55,TGFBR2,AP3B1,IL27,IL6,CD3E,CD28,TNFRSF14,IL12RB2,IRF4,SYK,BCL6,PTPRC,RC3H1,CD24A,CD80,HLX,SASH3,CD86,IL2RG,CD1D2,CD1D1
GO:0046637	-0.6267105	0	0	23	regulation of alpha-beta T cell differentiation	IL4RA,PNP1,ITPKB,AP3D1,ZAP70,SHH,FOXP3,SOC55,TGFBR2,AP3B1,IL27,IL6,IL12RB2,IRF4,SYK,BCL6,RC3H1,CD80,HLX,SASH3,CD86,IL2RG,CD1D1
GO:0050878	-0.2726188	0	0	140	regulation of body fluid levels	FBN1,EDN1,F5,ITGB3,PTGER3,EFEMP2,APLN,DRD2,L3MBTL4,FBLN5,VWF,CD9,SCUBE1,P2RY1,GP1BA,RLN1,AVPR2,NPPA,TAC4,FGF,PDSS2,NPR1,COL3A1,TSC22D3,F2RL2,HSD11B2,SERPINE1,IL11,OXT,CD36,EVL,SERPING1,ADORA2A,APOH,GP5,ITGA2,APOE,SERPINF2,FGA,P2RY12,TREML1,OTOG,RAB27A,F13B,ANXA5,F12,SCT,KCNMA1,F13A1,PLSCR4,AGTRL1,F11,CYP11B2,MST1,F2RL3,PLAT,GUCA1B,NPPB,PABPC4,PDPN,LMAN1,CPB2,TMPRSS6,IL10RB,C3,TRP73,PDGFA,KCNN4,KNG1,C9,KRT1,SLC22A4,AVP,ANXA2,GNA13,F8,CAV1,PDGFB,WAS,P2RX1,TFPI2,CD40,PLAUR,COPA,F2,VKORC1,FLI1,NFE2,F7,PROS1,ANXA8,PF4,CFTR,F3,GGCX,HPS4,PROC,SCNN1A,ANXA7,HGF,SLC34A1,SLC22A2,F10,MMRN1,PLSCR1,TSPAN8,WFS1,FGG,GNAQ,IL20RA,PPBP,SERPINC1,FOXA2,TFPI,CD40LG,NPR3,PROZ,CEL,ENTPD2,ADAMTS13,F9,PLG,GNA12,F2RL1,HNF4A,F2R,PIK3CB,UCN,ENTPD1,VIP,SERPIND1,PLAU,PROCR,CLCNKA,GUCA2B,THBD,AVPR1A,GP9,SERPINA5,SAI1
GO:0043370	-1.0183523	0	0	14	regulation of CD4-positive, alpha beta T cell differentiation	IL4RA,FOXP3,SOC55,IL27,IL6,IL12RB2,IRF4,BCL6,RC3H1,CD80,HLX,SASH3,CD86,IL2RG
GO:0045595	-0.1301296	0	0	343	regulation of cell differentiation	BMPR1B,SMAD3,TWIST2,RSK2,ZFP36,KLF4,BMP6,PLEKHB1,CDK5RAP3,BMP2,DICER1,IAPP,MITF,MAFF,HMGB3,REST,CRX,PPP2CA,NELL1,CSF1,MEIS1,PRPF19,LMX1A,CCNE1,ISL1,NOTCH3,FOXO3A,CLPTM1,STAT5B,MAF,CD2,ROD1,PIK3R1,CD74,ASPM,NODAL,WNT3,GPR98,BMP7,MYOCD,IGF1,UNCX,PPARD,IGFBP3,IQCB1,ID4,HIF1A,VWV2,ZFH3,SMAD1,ESRRA,HSF4,SMAP1,SMAD5,COMMDS,ITGB1,TNFRSF11B,KITL,TLX3,SOX2,PBX1,CLEC2G,ESRRB,CTNNA1,HES1,IL4RA,BARHL2,PNP1,FGF9,MBNL3,CAR2,WNT9A,APOLD1,ENPP3,NRG1,TBX5,ITPKB,NKX2-2,EPC1,GLP1R,ID3,LBX1,ERBB2,CLU,RHOA,TOB1,ACVR2B,CD27,POU5F1,CNTN4,CARTPT,BAD,LIG4,SIX2,NKX6-2,DLX5,BMP4,BCL2,AP3D1,GNAS,ENPP1,HES5,ZFP488,TGFB11,BEX1,PRLR,NEUROG3,FGFR3,IL2,WNT4,ZAP70,BMPR1A,POU3F2,EZH2,SFPI1,TNFSF11,UNCX2,SOC3,FZD1,SNF1LK,FAS,IRX3,IL2RA,TNF,NOG,HOXA2,TAFA8,JAK2,NF1,IL7R,NOTCH4,ASPA,GHR,FOXJ1,TGFB3,NPHP3,THOC5,CUL7,GDF5,FGF4,SIX1,LCK,PAX6,GLI3,BC054059,SART1,RCAN1,USH2A,SHH,NOTCH2,TGFB2,GDF11,FOXP3,RIF1,LPIN1,LTBP4,PRDM6,SPOCK2,H2-DMA,DLL3,MAPK1,PAX4,TIMP2,PLA2G2A,4930525M21RIK,HOXA7,TCFL5,NPPC,H2-AA,STAT5A,CDKN2B,TRP73,CSF1R,TERC,BOC,FADS1,MIB1,WNT3A,JAG2,SOC55,TLR3,IL7,LIF,TGFBR2,TCL1,ERE,ACVR1B,ID2,ICREM,DRD2,CHRN2B,PMCH,OPN3,TIMELESS,DRD1A,ADORA2A,ADA,OPN4,ALB,IL6,ADORA1,DRD3,CREB1,CSNK1E,NPY2R,PGLYR1,CORT,PTGDS,ARNTL
GO:0042752	-0.5775843	0	0	21	regulation of circadian rhythm	CREM,DRD2,CHRN2B,PMCH,OPN3,TIMELESS,DRD1A,ADORA2A,ADA,OPN4,ALB,IL6,ADORA1,DRD3,CREB1,CSNK1E,NPY2R,PGLYR1,CORT,PTGDS,ARNTL
GO:0043122	-0.1166718	0	0	101	regulation of I-kappaB kinase/NF-kappaB cascade	NDFIP2,VAPA,BCL10,UBE2N,GPR177,TRAF3IP2,RHOH,TGM2,BST2,PPARD,TBK1,LGALS9,SPAN6,LTBR,NDFIP1,ZDHHC17,GPR89,HMOX1,RHOA,BIRC2,ECT2,SLC35B2,TNFSF10,CC2D1A,PPM1A,NUP62,LGALS1,GOLT1B,FKBP1A,RPL17,TMED4,MYD88,TRIM13,NOD2,TNF,CASP8,TFG,UBE2V1,SQSTM1,LPAR1,IL1B,TMEM9B,NOD1,LTA,MAP3K3,MIER1,RHOC,SLC20A1,IL1RL1,IKKB,MAIT1,CANT1,TLR3,TICAM1,PPP5C,SECTM1A,HTR2B,FADD,LITAF,CARD11,CARD6,SLC44A2,ATP2C1,TNFAIP3,SHISA5,EEF1D,RIPK1,CD40,TRIM38,ZDHHC13,TLR6,MIB2,TNFRSF10B,OTUD7B,FASL,PLK2,MAP3K7IP2,MUL1,RIPK2,REL,TRAF6,NEK6,GJA1,MAP3K7,TRAF5,ADIPOQ,FLNA,IKBKE,TNFRSF1A,TRADD,PLEKHG5,PDCC11,F2R,CFLAR,TICAM2,RELA,ECM1,CARD9,CASP1,TLR4,TMEM101
GO:0002889	-0.5098584	0	0	11	regulation of immunoglobulin mediated immune response	NOD2,FCER1A,FOXJ1,C3,FCER2A,FCGR2B,FCGR3,PTPN6,PTPRC,FCGR1,FCER1G
GO:0045088	-0.3182163	0	0	35	regulation of innate immune response	BCL10,NCR1,TLR2,IL12B,ERAP1,KLRB1C,TLR7,IL12A,MYD88,CLEC7A,NOD2,SH2D1B1,H2-BL,TLR1,SH2D1A,TLR3,TICAM1,ERE,IL21,LAG3,TLR9,TLR6,KLRK1,CRTAM,TLR8,KLRB1B,IFNB1,UNC93B1,CADM1,CLEC2D,KLRE1,SH2D1B2,IFNK,CARD9,TLR4
GO:0050704	-0.3897596	0	0	9	regulation of interleukin-1 secretion	NLRP3,PYCARD,IFNG,NOD2,NLRP2,APOA1,P2RX7,PANX1,SAI1
GO:0001910	-0.4567869	0	0	24	regulation of leukocyte mediated cytotoxicity	NCR1,PNP1,IL12B,KLRB1C,IL12A,IL7R,SH2D1B1,H2-BL,SH2D1A,IL21,LAG3,PPP3CB,P2RX7,HSPA1A,KLRK1,CRTAM,KLRB1B,CADM1,CLEC2D,PTPRC,KLRE1,SH2D1B2,CD1D2,CD1D1
GO:0002703	-0.4387959	0	0	43	regulation of leukocyte mediated immunity	NCR1,PNP1,IL12B,KLRB1C,IL12A,NOD2,FCER1A,IL7R,FOXJ1,SPN,TRAF2,FOXP3,SH2D1B1,H2-BL,MALT1,C3,SH2D1A,IL21,LAG3,PPP3CB,FCER2A,FCGR2B,P2RX7,FCGR3,PTPN6,TRAF6,HSPA1A,MAP3K7,KLRK1,CRTAM,KLRB1B,DPP4,CADM1,CLEC2D,PTPRC,CD24A,KLRE1,FCGR1,SH2D1B2,SASH3,CD1D2,CD1D1,FCER1G

Table S2B. Gene sets down-regulated by mild stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0002706	-0.4387959	0	0	43	regulation of lymphocyte mediated immunity	NCR1,PNP1,IL12B,KLRB1C,IL12A,NOD2,FCER1A,IL7R,FOXJ1,SPN,TRAF2,FOXP3,SH2D1B1,H2-BL,MALT1,C3,SH2D1A,IL21,LAG3,PPP3CB,FCER2A,FCGR2B,P2RX7,FCGR3,PTPN6,TRAF6,HSPA1A,MAP3K7,KLRK1,CRTAM,KLRB1B,DPP4,CADM1,CLEC2D,PTPRC,CD24A,KLRE1,FCGR1,SH2D1B2,SASH3,CD1D2,CD1D1,FCER1G
GO:0031114	-0.4114866	0	0	15	regulation of microtubule depolymerization	MTAP1A,MAP6D1,CLASP2,HDAC6,TRIM54,KATNB1,MTAP2,MID1IP1,MID1,MTAP4,APC,ARHGEF2,CLIP2,MAPT,CLASP1
GO:0031113	-0.9310144	0	0	14	regulation of microtubule polymerization	SGK1,STMN1,MAPRE1,CDKN1B,ASZ1,CAV1,CFTR,MAPK8,CAV2,CTTNBP2,PSRC1,CAV3,MAPT,WNT2
GO:0050684	-0.8623286	0	0	6	regulation of mRNA processing	SRPK1,SAFB,BARD1,CDC2L1,MYOD1,FUSIP1
GO:0008593	-0.6599779	0	0	9	regulation of Notch signaling pathway	HEY2,IL6ST,DLL3,NFKBIA,TRP63,JAG1,RFNG,DTX1,KIT
GO:0050730	-0.1916278	0	0	58	regulation of peptidyl-tyrosine phosphorylation	EPO,PPP2CA,LYN,SOCS1,CD81,IGF1,KITL,CLCF1,PDGFC,IL11,TNK2,FGFR3,IL2,IL12A,PDGFD,CD4,NOD2,THY1,IL31RA,IL22RA2,OSM,IL22,TRAF3IP1,FCER1A,TDGF1,SH2D1B1,PDGFA,LIF,EGFR,PPP2R1A,IL3,CAV1,IL20,PDGFB,CSF2,ITGB2,PDGFRB,IL6,NF2,CD3E,IL5,PTPN6,IL4,PRKCA,CKK,TNFRSF14,ADIPOQ,SYK,PTPRC,IGH-6,PRKCE,CD24A,CD80,SH2D1B2,HNF4A,EGF,HCLS1,TLR4
GO:0050926	-0.6888673	0	0	11	regulation of positive chemotaxis	CDH13,VEGFA,SCG2,CXCL9,ARTN,PRKCA,CXCL12,IL16,FGF10,S1PR1,SPP1
GO:0032880	-0.3353678	0	0	11	regulation of protein localization	MYCBP2,SUMO1,CDH2,INS2,BCL2,MYO1A,RABGAP1L,CCDC100,NCKAP1,DDX4,CNPY4
GO:0031399	-0.0942575	0	0	138	regulation of protein modification process	DOCK7,BRCA1,AKTIP,BMP2,EPO,SET,SH2D1B1,PPP2CA,BCL10,UBE2N,LYN,PRKG2,PPP2R4,PRKAR2B,SOCS1,GCLC,STUB1,CD81,IGF1,IGFBP3,PRKAR2A,KITL,CLCF1,PDGFC,IMPACT,CCND1,VEGFC,BDKRB1,IL11,CCDC88A,TSC1,PPP1R14D,CDK5,BMP4,TNK2,ENPP1,RNF139,EDNRB,FGFR3,IL2,IL12A,PDGFD,SOCS3,CD4,NDUFS4,NOD2,TNF,THY1,IL31RA,IL22RA2,OSM,IL22,TRAF3IP1,FCER1A,GTPBP4,PPARGC1A,SQSTM1,CNGA1,TGFB1,IL1B,MLL1,FOXO3,TGFA,TDGF1,LRRK2,YWHAE,SH2D1B1,PDGFA,CARD14,RAPGEF3,LIF,PRKAR1A,UBQLN1,EGFR,PPP2R1A,MEN1,PSEN2,IL3,ARR3,CAV1,APOA1,BMPR2,IL20,PDGFB,CSF2,ITGB2,PDGFRB,IL6,NF2,IL10,BTK,CCND3,ADORA1,UBE2D1,P2RX7,CD3E,PRKAR1B,RGMA,JUN,IL5,PPP1R9B,PTPN6,FGF2,IL4,PRKCA,DOK7,RB1CC1,EDNRA,CK,CD6,TNFRSF14,ARRB2,ATG7,ADIPOQ,PSEN1,ATG10,RAPGEF4,CCDC88C,PAX5,SYK,MSX3,NHLRC1,CCND2,PTPRC,IGH-6,PRKCE,CD24A,ATG5,CD80,DLC1,ACVR2A,SH2D1B2,MAP2K4,HNF4A,EGF,PRKG1,ITLN1,HCLS1,TLR4
GO:0050708	-0.2468467	0	0	41	regulation of protein secretion	APOA2,ARFIP1,SRGN,NLRP3,GLMN,PYCARD,ACHE,PRKCQ,VEGFC,INS2,IFNG,ADORA2A,IL2,PLA2G1B,NOD2,TNF,TRAF2,FOXP3,TNFSF15,NLRP2,SERGEF,ANG,IL10,KCNN4,APOA1,DNAJC1,CD40,P2RX7,CIDEA,KRT20,TRAF6,CRTAM,CADM1,TNFRSF4,CD40LG,IL13,PANX1,EGF,DPH3,TNFSF4,SAA1
GO:0032319	-0.2787008	0	0	20	regulation of Rho GTPase activity	DOCK7,STMN3,ARHGAP27,CENTD2,FGD1,TSC1,PAFAH1B1,FGD2,SYDE1,FOXJ1,FGD5,FGD6,RASGRF1,FGD3,ALS2,PTK2B,BCL6,FGD4,RALBP1,SYDE2
GO:0001914	-0.6538741	0	0	9	regulation of T cell mediated cytotoxicity	PNP1,IL12A,IL7R,PPP3CB,P2RX7,HSPA1A,PTPRC,CD1D2,CD1D1
GO:0002709	-0.5399574	0	0	18	regulation of T cell mediated immunity	PNP1,IL12A,IL7R,SPN,TRAF2,FOXP3,MALT1,PPP3CB,P2RX7,TRAF6,HSPA1A,MAP3K7,DPP4,PTPRC,CD24A,SASH3,CD1D2,CD1D1
GO:0045622	-0.9371438	0	0	11	regulation of T-helper cell differentiation	IL4RA,SOCS5,IL27,IL6,IL12RB2,IRF4,BCL6,RC3H1,CD80,HLX,CD86
GO:0009410	-0.6541819	0	0	33	response to xenobiotic stimulus	NQO1,GSTA4,HAMP,GPX1,GCLC,CYP2E1,EPHX1,UGT1A9,AS3MT,GSTP1,CYP1A1,AOX1,AKR1C12,CYP3A13,FMO4,AHR,ABC4,GSTM4,GSTA2,CYP1B1,CYP1A2,AIP,GSTM2,NR1I2,GSTA3,CYP4B1,HNF4A,ARNT2,AHRR,AKR1C13,EPHX2,CYP2F2,HAMP2
GO:0001523	-0.6851725	0	0	21	retinoid metabolic process	LRAT,ADH4,RETSAT,RARRS2,RBP1,ADH5,RBP2,DHRS3,BCO2,RDH12,DHRS9,ADH1,RDH11,RDH8,ALDH1A7,RDH1,CES6,RPE65,ADH7,DHRS4,ALDH8A1
GO:0007338	-0.2826285	0	0	59	single fertilization	PKDRE1,SPA17,ITGA3,SYT6,HEXB,CD9,SMCP,ATP8B3,GLRA1,SYT8,NHP2L1,NPM2,ZBP2,DNAL1,OVGP1,ZP3,GLRB,ZPBP,PLCD4,AKAP4,CD46,ADAM21,B4GALT1,GNPDA1,CATSPER1,STX2,GM767,TNP1,IZUMO1,ACR,HYAL4,PLCZ1,UBXD6,TRIM36,ZP1,SPACA3,ADAM2,CLGN,IGSF8,AKAP3,TNP2,HIST1H1T,LCNG,ZAN,ADAM3,ZP2,MFGE8,ARSA,FCGBP,ZP4,WBP2NL,SPAG1,ADAM1A,ZP3R,CRISP1,SERPINA5,HYAL5,SPAM1,MST1R
GO:0043403	-0.5379005	0	0	12	skeletal muscle regeneration	GPX1,IGF1,SOX15,PAX7,TGFB2,PLAUR,GJA1,HOPX,MTPN,P2RX5,MYF6,PLAU
GO:0035036	-0.6074821	0	0	19	sperm-egg recognition	SPA17,SMCP,ATP8B3,ZBP2,ZP3,ZPBP,B4GALT1,ACR,SPACA3,TNP2,HIST1H1T,ZAN,ADAM3,ZP2,ARSA,FCGBP,ADAM1A,ZP3R,SPAM1
GO:0002286	-0.7926299	0	0	18	T cell activation during immune response	ATP7A,IL4RA,IL12B,SOCS5,PSEN2,GADD45G,IL27,IL6,IL12RB2,PSEN1,IRF4,BCL6,RC3H1,CD80,BCL3,HLX,CD86,RELB
GO:0006721	-0.6445856	0	0	25	terpenoid metabolic process	LRAT,ADH4,RETSAT,RARRS2,RBP1,ADH5,IDI2,RBP2,DHRS3,4833409A17RIK,BCO2,RDH12,DHRS9,ADH1,RDH11,RDH8,ID1,ALDH1A7,HMGCR,RDH1,CES6,RPE65,ADH7,DHRS4,ALDH8A1
GO:0042093	-0.8419297	0	0	16	T-helper cell differentiation	ATP7A,IL4RA,IL12B,SOCS5,GADD45G,IL27,IL6,IL12RB2,IRF4,BCL6,RC3H1,CD80,BCL3,HLX,CD86,RELB
GO:0019627	-1.5449517	0	0	9	urea metabolic process	ARG1,HTT,SLC25A15,OTC,ASL,NAGS,ARG2,CPS1,CEBPA
GO:0007223	-0.4822387	0	0	26	Wnt receptor signaling pathway, calcium modulating pathway	WNT3,WNT10A,ROR2,CAPZA2,WNT2B,WNT9A,WNT9B,WNT10B,WNT4,WNT1,WNT8B,WNT5B,WNT3A,WNT11,ASZ1,WNT5A,MET,FZD2,WNT6,WNT7A,CAV2,CTTNBP2,WNT16,WNT7B,WNT8A,WNT2
GO:0006805	-0.7046797	0	0	29	xenobiotic metabolic process	NQO1,GSTA4,HAMP,CYP2E1,EPHX1,UGT1A9,AS3MT,GSTP1,CYP1A1,AOX1,AKR1C12,CYP3A13,FMO4,AHR,GSTM4,GSTA2,CYP1B1,CYP1A2,AIP,GSTM2,NR1I2,GSTA3,CYP4B1,HNF4A,AHRR,AKR1C13,EPHX2,CYP2F2,HAMP2

Table S3A. Gene sets up-regulated by severe stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
50:000661	1.353093	0	0	6	SRP-dependent cotranslational protein targeting to membrane	SRP19,SRP9,SRPR,SRP14,SRP72,VCAN
50:000612	1.26807	0	0	39	mitochondrial electron transport, NADH to ubiquinone	NDUFS6,NDUFB4,NDUFB5,NDUFS5,NDUFA1,NDUFAB1,NDUFS2,NDUFA9,NDUFS3,NDUFA2,NDUFB6,NDUFA8,NDUFA7,NDUFA5,NDUFC1,NDUFB2,NDUFB8,NDUFS1,NDUFS4,NDUFB9,NDUFB3,NDUFA10,NDUFB7,NDUFS7,NDUFV1,NDUFC2,NDUFA4,NDUFV2,DLD,NDUFA3,NDUFAF1,NDUFS8,NDUFB10,NDUFA6,ND3,ND1,BDNF,ND4L,ND6
50:000612	1.204142	0	0	4	mitochondrial electron transport, ubiquinol to cytochrome c	UQCRB,UQCRH,UQCR,1110020P15RIK
50:006008	1.152821	0	0	10	membrane hyperpolarization	GRIK2,GLRA1,PARK7,GRIK1,ADORA2A,PRKCZ,NLGN3,ADIPOQ,DRD4,CHRNA4
50:000609	1.140369	0	0	25	tricarboxylic acid cycle	POLR3H,PDHB,SUCLA2,SUCLG1,MDH1,FH1,ATP5G3,IDH3B,ACO2,SDHA,SUCLG2,SDHD,SDHB,MDH1B,SDHC,IDH3A,IDH3G,IDH2,DLST,NNT,CS,MDH2,IDH1,ACO1,2610507B11RIK
50:000661	1.129423	0	0	12	cotranslational protein targeting to membrane	SRP19,SSR3,SRP9,SRPR,SRP14,SRP72,SSR2,SSR1,ARL6IP1,TRAM1,SEC62,VCAN
50:004368	1.124856	0	0	13	protein import into mitochondrion	TIMM8B,TOMM22,TIMM8A1,AIP,DNAJC19,TIMM9,HSPD1,TOMM20,GRPEL1,TIMM10,TIMM8A2,TIMM13,FXC1
50:000920	1.080341	0	0	10	deoxyribonucleoside triphosphate metabolic process	DGUOK,RRM2B,CMPK2,NUDT15,TBPL1,DTYMK,PNP1,NUDT1,DUT,ADA
50:004277	1.036352	0	0	49	organelle ATP synthesis coupled electron transport	NDUFS6,NDUFB4,NDUFB5,NDUFS5,NDUFA1,NDUFAB1,UQCRB,NDUFS2,NDUFA9,NDUFS3,NDUFA2,NDUFB6,NDUFA8,NDUFA7,UQCRH,NDUFA5,NDUFC1,NDUFB2,NDUFB8,NDUFS1,NDUFS4,UQCR,NDUFB9,NDUFB3,NDUFA10,NDUFB7,NDUFS7,NDUFV1,NDUFC2,NDUFA4,NDUFV2,DLD,COX15,NDUFA3,NDUFAF1,NDUFS8,NDUFB10,NDUFA6,ND3,1110020P15RIK,ND1,COX2,COX1,BDNF,TAZ,ND4L,ND6,COX10,COX8B
50:000906	1.034549	0	0	38	aerobic respiration	POLR3H,PDHB,SUCLA2,SUCLG1,MDH1,ME3,UQCRB,OXA1L,FH1,ADSL,UQCRC1,UQCRH,SLC25A14,ATP5G3,IDH3B,UQCRC2,ACO2,SDHA,SUCLG2,SDHD,SDHB,MDH1B,SDHC,IDH3A,IDH3G,IDH2,SURF1,DLST,NNT,CS,MDH2,CAT,COX1,IDH1,ACO1,COX10,2610507B11RIK,FXN
50:000000	1.026994	0	0	10	mitochondrial genome maintenance	MRPL17,RRM2B,TFAM,DNAJA3,MRPL39,MRPL15,SLC25A4,MPV17,POLG,TYMP
50:004277	1.002015	0	0	50	ATP synthesis coupled electron transport	NDUFS6,NDUFB4,NDUFB5,NDUFS5,NDUFA1,NDUFAB1,UQCRB,NDUFS2,NDUFA9,NDUFS3,NDUFA2,NDUFB6,NDUFA8,NDUFA7,UQCRH,NDUFA5,NDUFC1,NDUFB2,NDUFB8,NDUFS1,NDUFS4,UQCR,NDUFB9,NDUFB3,NDUFA10,NDUFB7,NDUFS7,NDUFV1,NDUFC2,NDUFA4,NDUFV2,DLD,COX15,NDUFA3,NDUFAF1,NDUFS8,NDUFB10,NDUFA6,ND3,1110020P15RIK,ND1,ND5,COX2,COX1,BDNF,TAZ,ND4L,ND6,COX10,COX8B
50:000662	0.943617	0	0	26	protein targeting to mitochondrion	TIMM8B,TRNT1,TOMM22,TIMM17A,TIMM8A1,AIP,PMPCB,IMMP2L,DNAJC19,TIMM9,TIMM23,MIPEP,HSPD1,TOMM20,TIMM17B,GRPEL1,TSPO,TIMM10,TOMM40,YWHAZ,TIMM8A2,TOMM34,TIMM13,TIMM44,FXC1,MFN2
50:000659	0.927682	0	0	8	polyamine biosynthetic process	ADC,SRM,OAZ1,ODC1,AMD1,AZIN1,AGMAT,GM853
50:004503	0.910462	0	0	7	protein import into mitochondrial inner membrane	TIMM8B,TIMM8A1,TIMM9,TIMM10,TIMM8A2,TIMM13,FXC1
50:000611	0.89942	0	0	75	oxidative phosphorylation	NDUFS6,NDUFB4,NDUFB5,ATP5L,NDUFS5,NDUFA1,NDUFAB1,UQCRB,ATP6V1F,NDUFS2,ATP5G2,NDUFA9,NDUFS3,NDUFA2,NDUFB6,ATP5B,NDUFA8,UQCRC1,NDUFA7,UQCRH,NDUFA5,ATP5G3,NDUFC1,NDUFB2,NDUFB8,NDUFS1,NDUFS4,UQCR,NDUFB9,NDUFB3,NDUFA10,NDUFB7,NDUFS7,NDUFV1,NDUFC2,NDUFA4,NDUFV2,ATP6AP1,NDUFS7,UQCRC2,NDUFV1,NDUFC2,NDUFA4,NDUFV2,CYC1,ATP5H,DLD,ATP5F1,ATP5A1,COX15,ATP5J,ATP5G1,NDUFA3,NDUFAF1,NDUFS8,ATP5O,ATP5C1,ATP5K,NDUFB10,NDUFA6,ATP5D,CLCA3,ATP5E,ND3,ATP6V0D2,1110020P15RIK,ND1,ND5,COX2,COX1,BDNF,ATP7A,TAZ,ND4L,MSH2,ND6,COX10,FXN,COX8B,MON2
50:002290	0.880845	0	0	58	respiratory electron transport chain	NDUFS6,NDUFB4,NDUFB5,NDUFS5,NDUFA1,NDUFAB1,UQCRB,NDUFS2,NDUFA9,NDUFS3,NDUFA2,NDUFB6,NDUFA8,NDUFA7,UQCRH,NDUFA5,NDUFC1,NDUFB2,NDUFB8,NDUFS1,NDUFS4,UQCR,NDUFB9,NDUFB3,NDUFA10,NDUFB7,NDUFS7,NDUFV1,NDUFC2,NDUFA4,NDUFV2,DLD,PPARGC1A,ALDH5A1,COX15,SLC37A2,NDUFA3,NDUFAF1,NDUFS8,NDUFB10,NDUFA6,SLC25A13,ND3,MYBBP1A,1110020P15RIK,SLC25A12,ND1,ND5,COX2,COX1,CYTB,BDNF,TAZ,ND4L,ND6,COX10,SLC1A3,COX8B
50:004533	0.873657	0	0	52	cellular respiration	POLR3H,PDHB,SUCLA2,SUCLG1,MDH1,ME3,UQCRB,OXA1L,CYCS,FH1,ADSL,UQCRC1,UQCRH,SLC25A14,ATP5G3,IDH3B,NDUFS1,NDUFS4,UQCRC2,ACO2,SDHA,SUCLG2,MTO1,SDHD,SDHB,PPARGC1A,MDH1B,PRKACA,COX15,SDHC,IDH3A,IDH3G,IDH2,SLC25A13,NFATC3,SURF1,BAX,DLST,NNT,CS,CYP1A2,MDH2,CAT,CISD2,COX1,NFATC4,IDH1,ACO1,COX10,2610507B11RIK,FXN,COX4I2
50:002290	0.865593	0	0	59	electron transport chain	NDUFS6,NDUFB4,NDUFB5,NDUFS5,NDUFA1,NDUFAB1,UQCRB,NDUFS2,NDUFA9,NDUFS3,NDUFA2,NDUFB6,NDUFA8,NDUFA7,UQCRH,NDUFA5,NDUFC1,NDUFB2,NDUFB8,NDUFS1,NDUFS4,UQCR,NDUFB9,NDUFB3,NDUFA10,NDUFB7,NDUFS7,NDUFV1,NDUFC2,NDUFA4,NDUFV2,DLD,PPARGC1A,ALDH5A1,COX15,SLC37A2,NDUFA3,NDUFAF1,NDUFS8,NDUFB10,NDUFA6,SLC25A13,ND3,FTSJ3,MYBBP1A,1110020P15RIK,SLC25A12,ND1,ND5,COX2,COX1,CYTB,BDNF,TAZ,ND4L,ND6,COX10,SLC1A3,COX8B
50:000637	0.859432	0	0	8	mRNA cleavage	CSTF1,POP4,CPSF3,CSTF3,NUDT21,CPSF1,CSTF2,PCF11
50:005118	0.854705	0	0	35	cofactor catabolic process	POLR3H,PDHB,BLVRA,SUCLA2,SUCLG1,MDH1,FH1,HMOX2,ATP5G3,IDH3B,ACO2,SDHA,SUCLG2,SDHD,SDHB,MDH1B,SDHC,IDH3A,IDH3G,IDH2,NUDT7,HMOX1,ALDH1L1,DLST,NNT,CS,0610012D14RIK,MDH2,ALDH1L2,NCF1,AMBP,IDH1,NCF2,ACO1,2610507B11RIK
50:004235	0.807868	0	0	10	L-fucose metabolic process	FUT10,FUT8,FUT9,FPGT,GMDS,FUT4,TSTA3,FUT1,FUT7,FUT2

Table S3A. Gene sets up-regulated by severe stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0008333	0.804998	0	0	8	endosome to lysosome transport	CHMP5,M6PR,SNX1,ADRB2,VAMP7,LYST,RHOB,SORT1
GO:000914	0.788918	0	0	17	pyrimidine nucleoside triphosphate metabolic process	CMPK2,NME3,NME7,RBM3,RP2H,TBPL1,NME5,DTYMK,NME1,NME4,TXNDC3,DECR2,CTPS,RP1H,NME6,NME2,DUT
GO:000038	0.773816	0	0	25	spliceosomal snRNP biogenesis	LSM2,SNRPG,CLNS1A,SNRPD2,PRPF31,SNRPE,SNRPF,SNRPB,DDX20,GEMIN8,SNRPD3,NCBP2,TGS1,PRMT5,WDR77,SMN1,FUS1,P1,SNRPD1,SIP1,RNUXA,SNUPN,GEMIN5,GEMIN4,GEMIN6,GEMIN7
GO:0015984	0.766205	0	0	20	ATP synthesis coupled proton transport	ATP5L,ATP6V1F,ATP5G2,ATP5B,ATP5G3,ATP6AP1,ATP5H,ATP5F1,ATP5A1,ATP5J,ATP5G1,ATP5O,ATP5C1,ATP5K,ATP5D,CLCA3,ATP5E,ATP6V0D2,ND4L,MON2
GO:004650	0.76051	0	0	10	S-adenosylmethionine metabolic process	GAMT,PNMT,MAT2B,PCMT1,COMT,MAT2A,TPMT,PEMT,GNMT,MAT1A
GO:000907	0.754444	0	0	9	serine family amino acid biosynthetic process	PSPH,SEPHS2,PSAT1,DHFR,SARDH,AGXT,PHGDH,CTH,CBS
GO:000600	0.734529	0	0	14	fucose metabolic process	FUT10,FUT8,FUT9,FUCA1,FPGT,GMDS,POFUT2,FUT4,B3GALT,LTSTA3,FUT1,FUT7,FUT2,POFUT1
GO:000920	0.73405	0	0	13	pyrimidine ribonucleoside triphosphate biosynthetic process	NME3,NME7,RBM3,RP2H,NME5,NME1,NME4,TXNDC3,DECR2,CTPS,RP1H,NME6,NME2
GO:004225	0.723365	0	0	109	ribosome biogenesis and assembly	EXOSC7,PES1,GNL3L,NOLA3,BXDC5,RRS1,NMD3,GTPBP10,FRG1,RRP1B,BXDC2,MPHOSPH10,MRPL10,MINA,TFB1M,EMG1,UTP18,RRP1,EIF4A3,IMP3,DDX52,BC003885,POP4,5730427N09RIK,EXOSC4,UTP6,RCL1,NGDN,TSR2,UTP11L,GNL2,NHP2L1,EXOSC3,TFB2M,NOL5,NPM1,EBNA1BP2,SBDS,LSM6,KRR1,EXOSC9,WDR36,RNASEL,C1D,ISG20L2,UTP3,DKC1,AATF,RPL7A,IMP4,UTP14A,UTP15,DDX56,RRN3,DDX1,NIP7,TBL3,WBP11,EXOSC5,RPS14,EXOSC2,FTSJ1,D530033C11RIK,DDX51,PA2G4,NPM3,DIMT1,EIF2A,NOL14,GTPBP5,GTPBP4,MRTO4,Z410016O06RIK,WDSOF1,EIF6,TSR1,NOLC1,RNASEN,SDAD1,BYSL,EXOSC10,FBL,WDR3,FTSJ3,RRP9,NOB1,EXOSC1,NOL5A,ARBP,FCF1,NAF1,NOLA2,BMS1,CDKN2A,1110032A13RIK,BOP1,AI595406,PDCC11,DIS3,POPS,EXOSC8,TDRD9,SURF6,NOLA1,GEMIN4,IPO9,FTSJ2,IPO4,HEATR1
GO:000914	0.712045	0	0	46	nucleoside triphosphate biosynthetic process	ATP5L,CMPK2,NME3,ATP6V1F,NME7,ATP5G2,ATP5B,ATP5G3,RBM3,ATP6AP1,RP2H,TBPL1,NME5,ATP6V0B,DTYMK,ATP6V0C,NME1,ATP5H,ATP5F1,ATP5A1,NME4,ATP5J,ATP5G1,ATP5O,ATP5C1,TXNDC3,ATP5K,PNP1,DECR2,ATP6V1B2,SLC25A13,ATP5D,CLCA3,ATP5E,LDHD,ATP5J2,TGFB1,ATP6V1B1,CTPS,ATP6V0D2,RP1H,NME6,ATP6V1A,NME2,ND4L,MON2
GO:000922	0.696524	0	0	17	pyrimidine ribonucleotide biosynthetic process	NME3,NME7,DHODH,RBM3,RP2H,NME5,NME1,CMPK1,NME4,UMPS,TXNDC3,DECR2,CTPS,RP1H,NME6,NME2,AK5
GO:003422	0.696208	0	0	23	transmembrane ion transport	ATP5L,ATP6V1F,ATP5G2,ATP5B,ATP5G3,ATP6AP1,ATP5H,CP,ATP5F1,ATP5A1,ATP5J,ATP5G1,ATP5O,ATP7B,ATP5C1,ATP5K,ATP5D,CLCA3,ATP5E,ATP6V0D2,ATP7A,ND4L,MON2
GO:004594	0.692166	0	0	11	negative regulation of translational initiation	PAIP2,EIF2AK3,EIF2B1,EIF2B3,EIF2B4,EIF2B5,EIF4EBP1,PAIP2B,EIF4EBP3,EIF4EBP2,EIF2AK1
GO:000803	0.690428	0	0	63	tRNA processing	RPP38,RPP14,TRUB1,RPP30,FARS2,DUS4L,TRNT1,ELAC1,RPP25,RPP40,SCAMP4,QTRT1,TSEN2,POP4,PUS3,6720458F09RIK,TRMT12,TYW3,SSB,LSM6,POP7,MTO1,RPP21,PUS7L,TRMU,DKC1,METTL1,LCMT2,1190005F20RIK,TRDMT1,TYW1,KARS,NSUN2,5730449L18RIK,TRMT5,PUS10,DUS2L,THG1L,SARS,TRMT6,ADAT2,TRMT11,D630004A14RIK,AARS,ADAT1,TRPT1,TRUB2,TRIT1,CCDC76,TSEN34,POP1,PUS7,POPS,WDR4,ELAC2,QTRTD1,TRMT1,PUSL1,TSEN54,PUS1,DUS3L,DUS1L,GTPBP3
GO:004298	0.689143	0	0	14	amyloid precursor protein metabolic process	ACHE,PSEN1,ABCG1,BACE2,CLN3,PAWR,PSENEN,AATF,NCSTN,PSEN2,CLK6,APH1A,DHCR24,NECAB3
GO:000636	0.673855	0	0	49	RNA elongation from RNA polymerase II promoter	POLR2J,POLR2I,CCNH,MNAT1,POLR2D,POLR2F,MAP2K1,TAF11,GTF2H3,SUPT4H1,GTF2E2,GTF2A2,GTF2F1,TBP,POLR2B,TAF12,GTF2H2,POLR2G,GTF2H1,TAF9,CDK7,TCEB3,POLR2C,ELP2,TAF13,ADRM1,GTF2F2,CDK9,POLR2E,TAF5,GTF2E1,TCEB2,TAF10,ERCC3,POLR2L,POLR2K,ELL2,GTF2B,GTF2A1,ELL,ELL3,GTF2H4,ERCC2,SUPT5H,POLR2H,TAF6,TAF4B,POLR2A,TAF1
GO:000920	0.667976	0	0	42	purine ribonucleoside triphosphate biosynthetic process	ATP5L,NME3,ATP6V1F,NME7,ATP5G2,ATP5B,ATP5G3,RBM3,ATP6AP1,RP2H,NME5,ATP6V0B,ATP6V0C,NME1,ATP5H,ATP5F1,ATP5A1,NME4,ATP5J,ATP5G1,ATP5O,ATP5C1,TXNDC3,ATP5K,PNP1,DECR2,ATP6V1B2,SLC25A13,ATP5D,CLCA3,ATP5E,LDHD,ATP5J2,TGFB1,ATP6V1B1,ATP6V0D2,RP1H,NME6,ATP6V1A,NME2,ND4L,MON2
GO:000688	0.664031	0	0	43	ER to Golgi vesicle-mediated transport	BET1,ERGIC3,SAR1B,TRAPPC2L,TXNDC1,TRAPPC1,SEC22B,SEC13,TRAPPC3,USE1,SCFD1,LMAN1,TRAPPC4,0610009B22RIK,SEC23B,SAR1A,NRBP1,GOPC,HINT1,LMAN2L,GOSR2,ERGIC2,VAMP7,TRAPPC2,PRES,RAB2A,SEC22C,STX18,SEC22A,RAB1,YKT6,COG3,SEC24D,GOSR1,VCP,SEC24B,SEC23A,ERGIC1,SEC24A,ZW10,SEC24C,SEC31A,HTT
GO:003164	0.657587	0	0	25	negative regulation of neurological system process	GRIK2,ACHE,EIF2AK3,GLRA1,GRM4,GRIK1,DRD2,IFNG,HTR2A,SLC6A1,HTR1B,NPY5R,BCHE,CDK5,NPY2R,CALCA,KCNQ4,GNAI2,PMCH,HCRT,GNAI1,ADRA1A,ADORA1,CLK8,GRM2
GO:004542	0.654695	0	0	11	quinone cofactor biosynthetic process	COQ7,COQ5,VKORC1,COQ6,PDSS2,POLR2C,COQ9,COQ4,COQ3,PDSS1,COQ2
GO:000636	0.648934	0	0	75	rRNA processing	EXOSC7,NOLA3,BXDC5,FRG1,RRP1B,MPHOSPH10,TFB1M,EMG1,UTP18,RRP1,EIF4A3,IMP3,DDX52,POP4,5730427N09RIK,EXOSC4,UTP6,RCL1,NGDN,TSR2,UTP11L,EXOSC3,TFB2M,NOL5,EBNA1BP2,LSM6,KRR1,EXOSC9,WDR36,RNASEL,C1D,UTP3,DKC1,IMP4,UTP14A,UTP15,DDX56,TBL3,WBP11,EXOSC5,RPS14,EXOSC2,FTSJ1,D530033C11RIK,DDX51,PA2G4,NPM3,DIMT1,NOL14,WDSOF1,NOLC1,EXOSC10,FBL,WDR3,FTSJ3,RRP9,NOB1,EXOSC1,NOL5A,FCF1,NAF1,NOLA2,CDKN2A,1110032A13RIK,BOP1,AI595406,PDCC11,DIS3,POPS,EXOSC8,TDRD9,NOLA1,GEMIN4,FTSJ2,HEATR1

Table S3A. Gene sets up-regulated by severe stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene set description	Gene set genes
GO:0009111	0.643225	0	0	20	ribonucleoside metabolic process	ADK,RDH14,DGUOK,QTRT1,NT5E,HPRT1,NT5C2,NT5C3,FHIT,CDA,PNP1,UPP2,PYCRL,NT5C1A,APRT,NUDT3,QTRTD1,UPP1,ADA,APOBEC1
GO:0016077	0.627433	0	0	78	rRNA metabolic process	EXOSC7,NOLA3,BXDC5,FRG1,RRP1B,MPHOSPH10,MKI67IP,TFB1M,EMG1,UTP18,RRP1,EIF4A3,IMP3,DDX52,POP4,5730427N09RIK,EXOSC4,UTP6,RCL1,NGDN,TSR2,UTP11L,EXOSC3,TFB2M,NOL5,EBNA1BP2,LSM6,KRR1,EXOSC9,WDR36,RNASEL,C1D,UTP3,DKC1,IMP4,UTP14A,UTP15,DDX56,TBL3,WBP11,EXOSC5,RPS14,EXOSC2,FTSJ1,D530033C11RIK,DDX51,PA2G4,NPM3,DIMT1,NOL14,WDSOF1,NOLC1,EXOSC10,FBL,WDR3,FTSJ3,RRP9,NOB1,EXOSC1,NOL5A,FCF1,NAF1,NOLA2,CDKN2A,DEDD2,1110032A13RIK,BOP1,AI595406,PDCD11,DIS3,POP5,EXOSC8,ERN2,TDRD9,NOLA1,GEMIN4,FTSJ2,HEATR1
GO:0006754	0.624981	0	0	29	ATP biosynthetic process	ATP5L,ATP6V1F,ATP5G2,ATP5B,ATP5G3,ATP6AP1,ATP6V0B,ATP6V0C,ATP5H,ATP5F1,ATP5A1,ATP5J,ATP5G1,ATP5O,ATP5C1,ATP5K,ATP6V1B2,SLC25A13,ATP5D,CLCA3,ATP5E,LDHD,ATP5J2,TGFB1,ATP6V1B1,ATP6V0D2,ATP6V1A,ND4L,MON2
GO:0042558	0.624618	0	0	11	pteridine and derivative biosynthetic process	PCBD1,GPHH,MOC52,PTS,QDPR,MOC53,MOCOS,GCH1,PCBD2,MOC51,SPR
GO:0006597	0.621056	0	0	16	polyamine metabolic process	ADC,SRM,SAT1,OAZ1,ODC1,SMOX,DHPS,AMD1,SAT2,PAOX,SMS,OAZ2,AZIN1,OAZ3,AGMAT,GM853
GO:0009133	0.616068	0	0	9	nucleoside diphosphate biosynthetic process	CMPK2,ATP5B,DYMK,ATP5A1,ATP5C1,ATP5D,ATP5E,ENTPD8,AK5
GO:0009261	0.614655	0	0	66	ribonucleotide biosynthetic process	ADK,ADSSL1,ATP5L,ADAL,NME3,ATP6V1F,NME7,ATP5G2,ADSL,DHODH,ATP5B,ATP5G3,RBM3,ATP6AP1,RP2H,NME5,ATP6V0B,ATP6V0C,AMPD3,NME1,ATP5H,CMPK1,ATP5F1,ATP5A1,GMPS,PRPS1,NME4,UMPS,ATP5J,ATP5G1,ATP5O,PAICS,ATP5C1,TXNDC3,ATP5K,PRPS2,PNP1,DECR2,ATP6V1B2,SLC25A13,IMPDPH2,ATP5D,CLCA3,ATP5E,LDHD,ATP5J2,PRPS1L1,TGFB1,GART,ATP6V1B1,CTPS,ATP6V0D2,RP1H,ATIC,NME6,ATP6V1A,ADSS,NME2,AMPD1,ND4L,AMPD2,IMPDPH1,ADA,PFAS,AK5,MON2
GO:0048194	0.614511	0	0	11	Golgi vesicle budding	COPB1,COPE,COPB2,PRKCI,COPG,ARCN1,COPZ1,ARF1,ARFGAP1,COPA,GBF1
GO:0034471	0.612452	0	0	147	ncRNA processing	RPP38,EXOSC7,RPP14,TRUB1,NOLA3,RPP30,FARS2,DUS4L,BXDC5,TRNT1,ELAC1,FRG1,RPP25,RPP40,RRP1B,INTS9,MPHOSPH10,TFB1M,EMG1,UTP18,SCAMP4,RRP1,EIF4A3,IMP3,DDX52,QTRT1,TSEN2,POP4,PUS3,5730427N09RIK,EXOSC4,UTP6,RCL1,6720458F09RIK,NGDN,TRMT12,TSR2,UTP11L,EXOSC3,TYW3,TFB2M,SSB,NOL5,EBNA1BP2,LSM6,POP7,MTO1,RPP21,KRR1,PUS7L,TRMU,EXOSC9,WDR36,RNASEL,C1D,UTP3,DKC1,METTL1,LCMT2,IMP4,UTP14A,UTP15,1190005F20RIK,DDX56,TRDMT1,INTS12,TYW1,TBL3,WBP11,KARS,INTS7,NSUN2,EXOSC5,5730449L18RIK,RPS14,EXOSC2,FTSJ1,D530033C11RIK,DDX51,DGCR8,TRMT5,PUS10,PA2G4,NPM3,DIMT1,NOL14,DUS2L,THG1L,SARS,WDSOF1,INTS8,NOLC1,TRMT6,INTS4,EXOSC10,ADAT2,TRMT11,FBL,WDR3,FTSJ3,RRP9,NOB1,INTS2,CPSF3L,D630004A14RIK,AARS,EXOSC1,INTS3,NOL5A,ADAT1,TRPT1,TRUB2,FCF1,NAF1,TRIT1,NOLA2,INTS6,CCDC76,TSEN34,CDKN2A,POP1,PUS7,1110032A13RIK,BOP1,AI595406,PDCD11,DIS3,POP5,EXOSC8,INTS10,WDR4,ELAC2,QTRTD1,TRMT1,TDRD9,NOLA1,GEMIN4,PUSL1,FTSJ2,TSEN54,PUS1,DUS3L,DUS1L,GTPBP3,INTS5,HEATR1,INTS1
GO:0006911	0.612343	0	0	9	phagocytosis, recognition	FCGR3,CD209B,SCARB1,FCGR1,SIRPA,CLEC7A,COLEC12,MFGE8,JMJD6
GO:0051433	0.612175	0	0	65	positive regulation of ubiquitin-protein ligase activity during mitotic cell cycle	PSMB5,PSMD10,PSMB2,SKP1A,PSMA6,CCNB1,BTRC,PSMA2,CDC23,PSMF1,PSMD12,CDC2A,UBE2C,PSMA5,PSMB4,PSMC2,PSMD9,PSMA3,PSMB6,PSMD13,PSMD5,FBXO5,PSMC6,PSMA4,PSMB7,PSMC4,PSMB1,PSMC5,PSME2,PSMA1,PSME1,PSMD14,PLK1,PSMD8,PSMB3,CDCC26,UBE2E1,ANAPC11,ANAPC7,PSMD6,PSMD11,PSMD4,PSMD7,PSMA7,CUL1,PSMC3,CDCC20,ANAPC2,PSMB9,ANAPC10,CDC16,UBB,PSMC1,PSMD1,ANAPC4,ANAPC5,PSMB8,PSMD3,PSME3,UBE2D1,CDC27,PSMD2,PSMB10,ANAPC1,FZR1
GO:0006354	0.611899	0	0	54	RNA elongation	POLR2J,POLR2I,CCNH,MNAT1,POLR2D,POLR2F,MAP2K1,TAF11,GTTF2H3,SUPT4H1,GTTF2E2,GTTF2A2,GTTF2F1,2210012G02RIK,TBP,POLR2B,TAF12,GTTF2H2,POLR2G,GTTF2H1,ERCC6,TAF9,CDK7,TCEB3,POLR2C,ELP2,TAF13,ADRM1,GTTF2F2,CDK9,POLR2E,TAF5,GTTF2E1,TCEB2,TAF10,ERCC3,POLR2L,POLR2K,ELL2,GTTF2B,GTTF2A1,ELL,ELL3,GTTF2H4,ERCC2,TCEA1,SUPT5H,POLR2H,TAF6,TCFA2,TAF4B,TCEA3,POLR2A,TAF1
GO:0006164	0.611345	0	0	65	purine nucleotide biosynthetic process	PPAT,ADSSL1,ATP5L,ADAL,MTHFD1,NME3,ATP6V1F,NME7,ATP5G2,ADSL,ATP5B,NT5E,ATP5G3,RBM3,ATP6AP1,HPRT1,RP2H,NME5,ATP6V0B,ATP6V0C,AMPD3,NME1,ATP5H,ATP5F1,ATP5A1,GMPS,PRPS1,NME4,ATP5J,ATP5G1,ATP5O,PAICS,ATP5C1,TXNDC3,ATP5K,PRPS2,PNP1,DECR2,ATP6V1B2,SLC25A13,IMPDPH2,ATP5D,CLCA3,ATP5E,LDHD,ATP5J2,TGFB1,GART,ATP6V1B1,ATP6V0D2,RP1H,ATIC,NME6,ATP6V1A,ADSS,NME2,AMPD1,ND4L,MSH2,AMPD2,IMPDPH1,ADA,PFAS,AK5,MON2
GO:0031144	0.609226	0	0	62	anaphase-promoting complex-dependent proteasomal ubiquitin-dependent protein catabolic process	PSMB5,BUB3,PSMD10,PSMB2,PSMA6,CCNB1,PSMA2,CDC23,PSMF1,PSMD12,CDC2A,UBE2C,PSMA5,PSMB4,PSMC2,PSMD9,PSMA3,PSMB6,PSMD13,PSMD5,PSMC6,PSMA4,PSMB7,PSMC4,PSMB1,PSMC5,PSME2,PSMA1,PSME1,PSMD14,PSMD8,PSMB3,CDCC26,UBE2E1,ANAPC11,ANAPC7,PSMD6,MAD2L1,PSMD11,PSMD4,PSMD7,PSMA7,PSMC3,CDCC20,ANAPC2,PSMB9,ANAPC10,CDC16,UBB,PSMC1,PSMD1,ANAPC4,BUB1B,ANAPC5,PSMB8,PSMD3,PSME3,UBE2D1,CDC27,PSMD2,PSMB10,ANAPC1
GO:0002671	0.605697	0	0	15	regulation of acute inflammatory response	CCRS5,FCGR3,FCER1G,CCR1,NPY5R,FCGR1,EDNRB,INS2,PIK3CG,C3,FCER1A,SPN,FCGR2B,PLA2G4A,MIF
GO:0006744	0.602003	0	0	10	ubiquinone biosynthetic process	COQ7,COQ5,COQ6,PDSS2,POLR2C,COQ9,COQ4,COQ3,PDSS1,COQ2

Table S3A. Gene sets up-regulated by severe stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:005135	0.601738	0	0	69	positive regulation of ligase activity	PSMB5,PSMD10,XRCC4,PSMB2,SKP1A,PSMA6,CCNB1,BTRC,PSMA2,CDC23,PSMF1,PSMD12,CDC2A,UBE2C,PSMA5,PSMB4,PSMC2,PSMD9,PSMA3,PSMB6,PSMD13,PSMD5,FBXO5,PSMC6,PSMA4,PSMB7,PSMC4,PSMB1,PSMC5,PSME2,PSMA1,PSME1,PSMD14,PLK1,PSMD8,PSMB3,CDC26,UBE2E1,ANAPC11,ANAPC7,PSMD6,PSMD11,GCLM,PSMD4,PSMD7,PSMA7,CUL1,PSMC3,CDC20,ANAPC2,PSMB9,ANAPC10,CDC16,UBB,PSMC1,UBE2N,PSMD1,ANAPC4,ANAPC5,PSMB8,PSMD3,NHEJ1,PSME3,UBE2D1,CDC27,PSMD2,PSMB10,ANAPC1,FZR1
GO:005144	0.600516	0	0	66	positive regulation of ubiquitin-protein ligase activity	PSMB5,PSMD10,PSMB2,SKP1A,PSMA6,CCNB1,BTRC,PSMA2,CDC23,PSMF1,PSMD12,CDC2A,UBE2C,PSMA5,PSMB4,PSMC2,PSMD9,PSMA3,PSMB6,PSMD13,PSMD5,FBXO5,PSMC6,PSMA4,PSMB7,PSMC4,PSMB1,PSMC5,PSME2,PSMA1,PSME1,PSMD14,PLK1,PSMD8,PSMB3,CDC26,UBE2E1,ANAPC11,ANAPC7,PSMD6,PSMD11,GCLM,PSMD4,PSMD7,PSMA7,CUL1,PSMC3,CDC20,ANAPC2,PSMB9,ANAPC10,CDC16,UBB,PSMC1,UBE2N,PSMD1,ANAPC4,ANAPC5,PSMB8,PSMD3,PSME3,UBE2D1,CDC27,PSMD2,PSMB10,ANAPC1,FZR1
GO:000915	0.600454	0	0	21	ribonucleoside monophosphate biosynthetic process	ADK,ADSSL1,ADAL,ADSL,DHODH,AMPD3,GMPS,PRPS1,UMPS,PAICS,PRPS2,IMPDPH2,PRPS1L1,GART,ATIC,ADSS,AMPD1,AMPD2,IMPDPH1,ADA,PFAS
GO:000913	0.592139	0	0	21	nucleoside diphosphate metabolic process	RRM2B,CMPK2,ATP5B,ENTPD3,DTYMK,NME1,NUDT9,ENTPD1,ATP5A1,ENTPD2,CANT1,ATP5C1,NUDT7,NUDT5,ATP5D,ATP5E,ENTPD4,ENTPD8,RRM2,AK5,ENTPD7
GO:000911	0.591469	0	0	39	nucleoside metabolic process	ADK,PPAT,RDH14,DGUOK,CMPK2,PRPSAP2,QTRT1,NT5E,HPRT1,NT5C2,TBPL1,NME5,DTYMK,NT5C3,PRPS1,NME4,UMPS,ERH,FHIT,CDA,PRPS2,PNP1,NT5M,PRPS1L1,UPP2,PYCRL,FPGS,NT5C1A,APRT,NT5C1B,DUT,NUDT3,QTRTD1,UPP1,DPYD,PRPSAP1,TYMP,ADA,APOBEC1
GO:004545	0.59002	0	0	57	cell redox homeostasis	TXNDC13,TXNDC1,GSR,TXNDC4,TXNDC15,TXNL1,TXNDC16,TXNDC12,QSOX2,DNAJC10,TXNDC14,GCLC,GPX1,TXN2,TXN1,TXNDC11,DLD,NXN,GLRX5,2810407C02RIK,APEX1,TXNDC10,TXNDC5,TXNDC3,PRL8A2,PDIA3,P4HB,SEPW1,2700094K13RIK,1700007B13RIK,TXNDC17,PDIA6,PDIA4,GTPBP1,TXNRD2,1810046J19RIK,TXNDC8,TXNRD3,GLRX,PTGES2,TXNDC2,AIFM1,GLRX2,GUCY2G,AIFM3,QSOX1,PDIA2,PDIA5,TXNRD1,ATP10B,NXNL1,MOGAT1,EGLN2,DDIT3,NRP2,SP110,GLRX3
GO:000644	0.583136	0	0	48	regulation of translational initiation	PAIP2,EIF2AK3,4930503E24RIK,EIF4H,EIF1,EIF3H,EIF4B,IMPACT,DAZL,EIF2B1,EIF2B3,EIF2B4,EIF3D,EIF3J,MTIF3,PPP1R15B,EIF2S1,EIF3F,MTIF2,HSPB1,EIF5B,DDX1,EIF3K,EIF2B5,EIF5,BOLL,EIF2B2,EIF2AK4,EIF4A2,EIF1B,EIF3I,EIF3C,EIF3G,TRMT6,EIF5A,EIF4EBP1,EIF3E,BZW1,PAIP2B,BZW2,EIF4EBP3,EIF4G2,EIF4EBP2,EIF2AK1,TNF,EIF4G1,EIF2C1,EIF4G3
GO:000638	0.580027	0	0	27	transcription from RNA polymerase III promoter	POLR3H,GTF3C5,GTF3C6,POLR2F,POLR3G,MAF1,IVNS1ABP,POLR3D,SNAPC2,POLR3C,GTF3C3,SNAPC5,SNAPC3,GTF3C4,POLR3K,POLR2L,POLR2K,POLR3F,TROVE2,CRCP,ZFP143,BRCA1,GTF3C1,GTF3A,GTF3C2,SNAPC4,BRF1
GO:001625	0.578764	0	0	17	preassembly of GPI anchor in ER membrane	PIGH,PIGG,PIGF,PIGA,PIGX,PIGV,PIGQ,PIGL,PIGW,DPM2,PIGB,PIGN,PIGP,PIGO,PIGC,SEMA6D,PIGM
GO:000689	0.576211	0	0	18	retrograde vesicle-mediated transport, Golgi to ER	COG7,PICK1,COPB1,COPE,RER1,COPB2,COPG,ARCN1,COPZ1,COPG2,ARF1,COG3,TAPBP,KIF1C,ARFGAP1,COPA,RAB6B,GBF1
GO:002261	0.575921	0	0	226	ribonucleoprotein complex biogenesis and assembly	PAIP2,EXOSC7,PES1,LSM2,GNL3L,NOLA3,SNRPG,BXDC5,RRS1,NMD3,GTPBP10,FRG1,CLNS1A,EIF1AD,RRP1B,BXDC2,EIF4E,EIF2AK3,MPHOSPH10,4930503E24RIK,MRPL10,MINA,TFB1M,SNRPD2,EMG1,PRPF31,EIF4H,EIF1,SNRPE,UTP18,EIF3H,SF3A3,RRP1,EIF4B,EIF4A3,IMP3,DDX52,BC003885,POP4,5730427N09RIK,IMPACT,CRNKL1,EXOSC4,UTP6,DAZL,SNRPF,RCL1,NGDN,SMNDC1,SNRPB,DDX20,EIF2B1,TSR2,UTP11L,EIF2B3,GNL2,SLU7,EIF1A,NHP2L1,EIF2B4,EXOSC3,TFB2M,EIF3D,EIF3J,GEMIN8,NOL5,PRPF6,NPM1,EBNA1BP2,SBDS,SNRPD3,LSM6,KRR1,PAIP1,MTIF3,PPP1R15B,EXOSC9,WDR36,EIF2S1,RNASEL,C1D,ISG20L2,NCBP2,UTP3,DKC1,AATF,TGS1,EIF3F,LGTN,RPS3A,RPL7A,MTIF2,IMP4,UTP14A,HSPB1,UTP15,EIF5B,DDX56,PRMT5,RRN3,EIF4E2,DDX1,EIF3K,EIF2B5,NIP7,DENR,EIF2S2,TBL3,SFRS9,EIF5,WBP11,USP39,EXOSC5,RPS14,EXOSC2,BOLL,FTSJ1,WDR77,EIF2S3X,EIF2B2,D530033C11RIK,DDX51,EIF2AK4,PA2G4,NPM3,EIF4A2,DIMT1,EIF2A,SMN1,NOL14,GTPBP5,EIF1B,GTPBP4,MRTO4,EIF3I,EIF1AY,EIF3C,SFRS1,EIF3G,FUSIP1,2410016O06RIK,WDSOF1,EIF6,TSR1,NOLC1,RNASEN,TRMT6,SF3A1,SNRPD1,SDAD1,BYSL,SIP1,EXOSC10,EIF5A,EIF5A2,FBL,SF3A2,WDR3,FTSJ3,RRP9,PTBP2,NOB1,MBNL1,EIF4EBP1,SRPK2,EIF3E,BZW1,2410018C20RIK,PAIP2B,TXNL4A,EXOSC1,RNUXA,NOL5A,GATC,BZW2,ARBP,GTF2B,CUGBP1,FCF1,NAF1,NOLA2,BMS1,SFRS2IP,EIF4EBP3,CDKN2A,EIF4G
GO:001834	0.573218	0	0	12	protein amino acid prenylation	FNTA,RABGGTB,ASNSD1,CHM,FNTB,RP2H,WFS1,PGGT1B,SOAT2,RABGGTA,COX10,PTAR1
GO:001028	0.57316	0	0	9	response to lead ion	CDK4,SLC6A1,BCL2L1,STAR,ALAD,CRYAA,HP,NOS3,LCT
GO:000703	0.563853	0	0	23	peroxisome organization and biogenesis	PEX2,PEX7,PEX19,PEX10,ABCD1,PEX26,SCP2,PEX11A,FIS1,PEX11B,LONP2,PEX13,PEX5,AGXT,PEX3,ABCD3,PEX14,PEX6,PEX12,ACOT8,PEX1,PEX16,PEX11C
GO:000616	0.562005	0	0	94	purine nucleotide metabolic process	PPAT,DGUOK,ADSSL1,ATP5L,GUK1,ADAL,MTHFD1,NME3,ATP6V1F,NME7,NUDT15,ATP5G2,ADSL,FIGN1,AK1,ATP5B,NT5E,ATP5G3,RBM3,PAPSS1,NDUFS1,ATP6AP1,HPRT1,RP2H,NME5,ATP6V0B,CTNS,ATP6V0C,AMPD3,NME1,NUDT9,ATP5H,ENTPD1,ATP5F1,ATP5A1,GMPS,ENTPD2,PRPS1,NME4,ATP5J,ATP5G1,ATP2A1,ATP1A1,ATP5O,PAICS,ATP5C1,TXNDC3,OLA1,ATP5K,PRPS2,PNP1,DECR2,ATP6V1B2,SLC25A13,IMPDPH2,ATP5D,NUDT1,MUTYH,MPG,CLCA3,ATP5E,LDHD,ATP5J2,TGFB1,GMPPR2,GART,NADK,ATP6V1B1,ERCC3,ATP6V0D2,RP1H,ATIC,MYH7,NME6,ATP6V1A,ACLY,ENPP1,ADSS,NME2,AMPD1,ATP7A,ND4L,MSH2,ATP1A2,AMPD2,ABCC6,OGG1,MYH6,IMPDPH1,ADA,MYO9B,PFAS,AK5,MON2

Table S3A. Gene sets up-regulated by severe stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0051434	0.555372	0	0	62	negative regulation of ubiquitin-protein ligase activity during mitotic cell cycle	PSMB5,BUB3,PSMD10,PSMB2,PSMA6,PSMA2,CDC23,PSMF1,PSMD12,UBE2C,PSMA5,PSMB4,PSMC2,PSMD9,PSMA3,PSMB6,PSMD13,PSMD5,FBXO5,PSMC6,PSMA4,PSMB7,PSMC4,PSMB1,PSMC5,PSME2,PSMA1,PSME1,PSMD14,PSMD8,PSMB3,CDC26,UBE2E1,ANAPC11,ANAPC7,PSMD6,MAD2L1,PSMD11,PSMD4,PSMD7,PSMA7,PSMC3,CDC20,ANAPC2,PSMB9,ANAPC10,CDC16,UBB,PSMC1,PSMD1,ANAPC4,BUB1B,ANAPC5,PSMB8,PSMD3,PSME3,UBE2D1,CDC27,PSMD2,PSMB10,ANAPC1,FZR1
GO:0009061	0.550486	0	0	16	aspartate family amino acid biosynthetic process	ASNS,ADI1,MTHFD1,MTRR,ASNSD1,GOT1,BHMT2,GOT2,BHMT,0610012D14RIK,THNSL2,PLOD1,MTHFR,ENOPH1,THNSL1,MT R
GO:0048221	0.547594	0	0	10	cis-Golgi to rough ER vesicle-mediated transport	COPB1,COPE,COPB2,COPG,ARCN1,COPZ1,ARF1,ARFGAP1,COPA,GBF1
GO:0009451	0.547022	0	0	34	RNA modification	TRUB1,NOLA3,PARN,TFB1M,QTRT1,PUS3,RPUSD2,DNAJB11,METTL3,RPUSD4,TFB2M,SSB,NOL5,ADAR,PUS7L,DKC1,METTL1,N SUN2,APOBEC3,DIMT1,ADARB1,THG1L,TRUB2,NOLA2,APOBEC2,PUS7,QTRTD1,RPUSD1,A1CF,PUSL1,PUS1,RPUSD3,GTPBP3,A POBEC1
GO:0009141	0.544796	0	0	74	nucleoside triphosphate metabolic process	DGUOK,ATP5L,RRM2B,CMPK2,NME3,ATP6V1F,NME7,NUDT15,ATP5G2,FIGNL1,AK1,ATP5B,ATP5G3,RBM3,NDUFS1,ATP6AP1,RP2H,TBPL1,NME5,ATP6V0B,CTNS,ENTPD3,DTYMK,ATP6V0C,NME1,ATP5H,ENTPD1,ATP5F1,ATP5A1,NME4,ATP5J,ATP5G1,AT P2A1,ATP1A1,ATP5O,ATP5C1,TXNDC3,OLA1,ATP5K,PNP1,DECR2,ATP6V1B2,SLC25A13,ATP5D,NUDT1,CLCA3,ATP5E,LDHD,AT P5J2,TGFB1,NADK,ATP6V1B1,ERCC3,ENPP3,CTPS,ATP6V0D2,RP1H,MYH7,NME6,ATP6V1A,ACLY,ENPP1,NME2,ATP7A,DUT,ND 4L,ATP1A2,ABCC6,MYH6,ADA,MYO9B,AK5,MON2,ENTPD7
GO:0051344	0.544343	0	0	76	regulation of ligase activity	PSMB5,BUB3,PSMD10,XRCC4,PSMB2,SKP1A,PSMA6,CCNB1,BTRC,PSMA2,CDC23,PSMF1,PSMD12,CDC2A,UBE2C,PSMA5,PSM B4,PSMC2,PSMD9,PSMA3,PSMB6,PSMD13,PSMD5,FBXO5,PSMC6,PSMA4,PSMB7,PSMC4,PSMB1,PSMC5,PSME2,PSMA1,PSME 1,PSMD14,PLK1,PSMD8,PSMB3,CDC26,UBE2E1,ANAPC11,ANAPC7,PSMD6,MAD2L1,PSMD11,GCLM,PSMD4,PSMD7,PSMA7,C UL1,PSMC3,CDC20,ANAPC2,PSMB9,ANAPC10,CDC16,FEM1A,UBB,PSMC1,UBE2N,PSMD1,ANAPC4,BUB1B,ANAPC5,PSMB8,PS MD3,NHEJ1,CDKN2A,PSME3,UBE2D1,CDC27,PSMD2,PSMB10,ANAPC1,FEM1B,FZR1,ZER1
GO:0055081	0.542839	0	0	35	transmembrane transport	ATP5L,SLC2A4,ATP6V1F,SLC2A1,ATP5G2,ATP5B,ATP5G3,ATP6AP1,SLC2A13,SLC2A3,ATP5H,CP,ATP5F1,ATP5A1,ATP5J,ATP5G1 ,ATP5O,ATP7B,ATP5C1,SLC2A12,ATP5K,ATP5D,SLC2A2,CLCA3,ATP5E,ATP6V0D2,SLC2A9,SLC2A8,SLC2A5,ATP7A,ND4L,SLC2A1 0,SLC2A7,SLC2A6,MON2
GO:0009151	0.54246	0	0	60	purine ribonucleotide biosynthetic process	ADSSL1,ATP5L,ADAL,NME3,ATP6V1F,NME7,ATP5G2,ADSL,ATP5B,ATP5G3,RBM3,ATP6AP1,RP2H,NME5,ATP6V0B,ATP6V0C,A MPD3,NME1,ATP5H,ATP5F1,ATP5A1,GMPS,PRPS1,NME4,ATP5J,ATP5G1,ATP5O,PAICS,ATP5C1,TXNDC3,ATP5K,PRPS2,PNP1,D ECR2,ATP6V1B2,SLC25A13,IMPDH2,ATP5D,CLCA3,ATP5E,LDHD,ATP5J2,TGFB1,GART,ATP6V1B1,ATP6V0D2,RP1H,ATIC,NME6, ATP6V1A,ADSS,NME2,AMPD1,ND4L,AMPD2,IMPDH1,ADA,PFAS,AK5,MON2
GO:0002671	0.541455	0	0	9	positive regulation of acute inflammatory response	FCGR3,FCER1G,NPY5R,FCGR1,PIK3CG,C3,FCER1A,PLA2G4A,MIF
GO:0009141	0.537865	0	0	64	purine nucleoside triphosphate metabolic process	DGUOK,ATP5L,NME3,ATP6V1F,NME7,NUDT15,ATP5G2,FIGNL1,AK1,ATP5B,ATP5G3,RBM3,NDUFS1,ATP6AP1,RP2H,NME5,AT P6V0B,CTNS,ATP6V0C,NME1,ATP5H,ENTPD1,ATP5F1,ATP5A1,NME4,ATP5J,ATP5G1,ATP2A1,ATP1A1,ATP5O,ATP5C1,TXNDC3, OLA1,ATP5K,PNP1,DECR2,ATP6V1B2,SLC25A13,ATP5D,NUDT1,CLCA3,ATP5E,LDHD,ATP5J2,TGFB1,NADK,ATP6V1B1,ERCC3,AT P6V0D2,RP1H,MYH7,NME6,ATP6V1A,ACLY,NME2,ATP7A,ND4L,ATP1A2,ABCC6,MYH6,ADA,MYO9B,AK5,MON2
GO:0007261	0.536985	0	0	15	nitric oxide mediated signal transduction	MT1,AGT,GUCY1B3,MT2,GUCY1A3,RASD1,DDAH1,FPR1,APOE,NPY2R,DDAH2,PDX1,MAFA,AGTR2,NEUROD1
GO:0051444	0.536951	0	0	63	negative regulation of ubiquitin-protein ligase activity	PSMB5,BUB3,PSMD10,PSMB2,PSMA6,PSMA2,CDC23,PSMF1,PSMD12,UBE2C,PSMA5,PSMB4,PSMC2,PSMD9,PSMA3,PSMB6,PS MD13,PSMD5,FBXO5,PSMC6,PSMA4,PSMB7,PSMC4,PSMB1,PSMC5,PSME2,PSMA1,PSME1,PSMD14,PSMD8,PSMB3,CDC26,UBE 2E1,ANAPC11,ANAPC7,PSMD6,MAD2L1,PSMD11,PSMD4,PSMD7,PSMA7,PSMC3,CDC20,ANAPC2,PSMB9,ANAPC10,CDC16,UB B,PSMC1,PSMD1,ANAPC4,BUB1B,ANAPC5,PSMB8,PSMD3,CDKN2A,PSME3,UBE2D1,CDC27,PSMD2,PSMB10,ANAPC1,FZR1
GO:0009301	0.524083	0	0	15	rRNA transcription	GTF3C5,GTF3C6,MKI67IP,ANG,CD3EAP,GTF3C3,POLR1E,GTF3C4,NPM3,MARS,GTF3C1,GTF3A,GTF3C2,TCOF1,BRF1
GO:0042371	0.518603	0	0	13	quinone cofactor metabolic process	COQ7,COQ5,VKORC1,COQ6,PDSS2,POLR2C,COQ9,ADH4,COQ4,VKORC1L1,COQ3,PDSS1,COQ2
GO:0006661	0.517676	0	0	10	phosphatidylinositol biosynthetic process	IMPA1,CDIPT,CD81,PI4K2A,PIK3C2A,PI4KB,PIP4K2C,PDGFA,PDGFB,PI4KA
GO:0018341	0.517511	0	0	14	protein prenylation	FNTA,RABGGTB,ASNSD1,CHM,FNTB,RP2H,WFS1,COMTD1,PGGT1B,AIPL1,SOAT2,RABGGTA,COX10,PTAR1
GO:0006411	0.510804	0	0	67	translational initiation	PAIP2,EIF1AD,EIF4E,EIF2AK3,4930503E24RIK,EIF4H,EIF1,EIF3H,EIF4B,IMPACT,DAZL,EIF2B1,EIF2B3,EIF1A,EIF2B4,EIF3D,EIF3J,P AIP1,MTIF3,PPP1R15B,EIF2S1,EIF3F,LGTN,RPS3A,MTIF2,HSPB1,EIF5B,EIF4E2,DDX1,EIF3K,EIF2B5,DENR,EIF2S2,EIF5,BOLL,EIF2 S3X,EIF2B2,EIF2AK4,EIF4A2,EIF1B,EIF3I,EIF1AY,EIF3C,EIF3G,TRMT6,EIF5A,EIF5A2,EIF4EBP1,EIF3E,BZW1,2410018C20RIK,PAIP 2B,BZW2,GTF2B,EIF4EBP3,EIF4G2,EIF4EBP2,EIF4E1B,EIF3B,EIF2AK1,EIF4E3,TNF,EIF4G1,EIF2C1,BRF1,DMXL2,EIF4G3

Table S3A. Gene sets up-regulated by severe stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
50:000925	0.507935	0	0	90	ribonucleotide metabolic process	ADK,ADSSL1,ATP5L,ADAL,NME3,ATP6V1F,NME7,ATP5G2,ADSL,FIGNL1,AK1,DHODH,ATP5B,ATP5G3,RBM3,NDUFS1,ATP6AP1,RP2H,NME5,ATP6V0B,CTNS,ATP6V0C,AMPD3,NME1,NUDT9,ATP5H,ENTPD1,CMPK1,ATP5F1,ATP5A1,GMPS,ENTPD2,PRPS1,NME4,UMPS,ATP5J,ATP5G1,ATP2A1,CANT1,ATP1A1,ATP5O,PAICS,ATP5C1,TXNDC3,OLA1,ATP5K,PRPS2,PNP1,NUDT5,DECR2,ATP6V1B2,SLC25A13,IMPDH2,ATP5D,CLCA3,ATP5E,LDHD,ATP5J2,PRPS1L1,TGFB1,GMPT2,GART,NADK,ATP6V1B1,ENTPD4,ERC3,CTPS,ATP6V0D2,RP1H,ATIC,MYH7,NME6,ATP6V1A,ACLY,ADSS,NME2,AMPD1,ATP7A,ND4L,ATP1A2,AMPD2,ABCC6,MYH6,IMPDH1,ADA,MYO9B,PFAS,AK5,MON2,ENTPD7
50:000640	0.506757	0	0	14	tRNA modification	TRUB1,QTTR1,PUS3,SSB,PUS7L,DKC1,METTL1,NSUN2,THG1L,TRUB2,PUS7,QTTRD1,PUS1,GTPBP3
50:000152	0.504692	0	0	14	pseudouridine synthesis	TRUB1,NOLA3,PUS3,RPUSD2,RPUSD4,PUS7L,DKC1,TRUB2,NOLA2,PUS7,RPUSD1,PUSL1,PUS1,RPUSD3
50:000674	0.504445	0	0	30	glutathione metabolic process	GLO1,GSTK1,GSR,MGST1,GSTT2,GCLC,G6PDX,GPX1,GPX4,CTNS,ALDH5A1,HAGH,GCLM,GSTP1,GSTP2,TXNDR3,SOD1,GSTA3,GLRX2,GPX3,GSS,GGT7,GSTT3,GSTA1,IDH1,CTH,GSTT1,GGT1,GGT5,GGT6
50:000920	0.504302	0	0	60	purine ribonucleoside triphosphate metabolic process	ATP5L,NME3,ATP6V1F,NME7,ATP5G2,FIGNL1,AK1,ATP5B,ATP5G3,RBM3,NDUFS1,ATP6AP1,RP2H,NME5,ATP6V0B,CTNS,ATP6V0C,NME1,ATP5H,ENTPD1,ATP5F1,ATP5A1,NME4,ATP5J,ATP5G1,ATP2A1,ATP1A1,ATP5O,ATP5C1,TXNDC3,OLA1,ATP5K,PNP1,DECR2,ATP6V1B2,SLC25A13,ATP5D,CLCA3,ATP5E,LDHD,ATP5J2,TGFB1,NADK,ATP6V1B1,ERC3,ATP6V0D2,RP1H,MYH7,NME6,ATP6V1A,ACLY,NME2,ATP7A,ND4L,ATP1A2,ABCC6,MYH6,MYO9B,AK5,MON2
50:000645	0.503672	0	0	188	protein folding	UXT,ERP29,FUT10,PDRG1,DNAJB9,PIIH,ATF6,PPWD1,H2-DMA,SIL1,TXNDC4,AIP,TTC1,DNAJB1,DNAJC10,PPIL3,DNAJC12,TTC9,TTC9C,CLGN,BAG5,FKBP2,POU5F1,MKKS,DNAJB4,WBSCR18,CCT3,DNAJA3,APOA2,FKBP4,PIN4,AIF1,PPIL1,DNAJA2,CCT6A,LRPAP1,DNAJA1,FKBP3,CLN3,PIGK,PFDN1,RUVBL2,PPIB,DNAJC19,SEP15,NFYC,STUB1,DNAJB11,TCP1,HSPE1,HSP90B1,FKBP1A,FKBP9,PPIL2,LMAN1,DNAJC1,PFDN5,ERO1L,CCT2,DAXX,CCT8,VBP1,DDR1,H2-DMB2,PPIL6,HSPA9,FKBP7,MPDU1,FKBP14,HSPD1,CCT5,CANX,FKBP15,WFS1,LMAN2L,TBCB,PFDN4,B3GALT4,C80913,H2-KE2,PPIL4,TRAP1,HSCB,CDC26,CRYAA,FKBP8,DNAJB12,ATP6V1G2,PPIA,SEC63,WDR46,DNAJC7,BAG4,GRPEL1,DNAJB7,DNAJB13,TCF19,TBCA,DNAJC5B,TOR1B,PDIA6,CLPX,FKBP11,PIIF,AHSA1,FKBP1,CC7,DNAJC18,PTRH1,CALR3,PIIE,DNAJB6,SGTB,TXNDC2,DNAJC17,ST13,TBCD,TBCE,GRPEL2,HSPA4L,GLRX2,PIN1,CCT6B,QSOX1,CD74,ERO1LB,TOR2A,CALR,CRYAB,HSPA8,PPIG,U GCG1L,BBS12,PHF1,SLMAP,PFDN2,AIPL1,PDIA2,PPID,HYOU1,CCT4,BAG2,HSP90AA1,TAPBP,ETF2H4,TBCB,DNAJC2,PDCL,TTC9B,LST1,DNAJC16,PDIA5,DNAJA4,BBS10,HSPH1,FKBP5,ALG12,DNAJB14,VEGFB,COPA,LTB,KRTAP5-1,SDCCAG10,DNAJC5,FKBP1B,RANBP2,A830007P12RIK,DNAJC4,FKBP10,SH3GLB1,APCS,DNAJC14,PPIC,TOR1A,FKBP6,SACS,TOR3A,BAG3,HSP90A1,DNAJC5G,NKTR,COL11A2,DNAJB5,UBE4B,ZBTB9,LTBP4,KRTAP5-2,SYNGAP1
50:000683	0.496107	0	0	62	mitochondrial transport	TIMM8B,TRNT1,TOMM22,KIF5B,TIMM17A,TIMM8A1,AIP,MTX2,PSEN1,PMPCB,IMMP2L,SLC25A14,DNAJC19,TIMM9,VDAC1,TIMM23,SLC25A20,STARD3,CPT2,BCL2L1,SLC25A17,MIPEP,PLEKHF1,HSPD1,TOMM20,BHLHB8,SLC37A2,TIMM17B,SLC25A4,SLC25A15,GRPEL1,TSPO,TIMM10,SLC25A13,TOMM40,SLC25A32,SLC25A1,YWHAZ,TIMM8A2,SLC25A12,UCP2,UCP3,TOMM34,SLC25A30,TIMM13,HSP90AA1,SLC25A27,SLC25A10,SLC25A24,TIMM44,SLC25A37,FXC1,UCP1,CPT1B,BAK1,MFN2,SLC1A3,BNIP3,BCL2,SLC25A36,HTT,SLC25A2
50:004650	0.489999	0	0	14	glycerol ether biosynthetic process	PPAP2A,PEX7,GNPAT,DGAT2,ANG,MOGAT2,PLCE1,PCK1,DGAT1,AGPAT6,CDS1,MOGAT1,PNPLA3,LPL
50:000636	0.486065	0	0	64	transcription initiation from RNA polymerase II promoter	MED27,POLR2J,POLR2I,CCNH,MNAT1,POLR2D,POLR2F,TAF11,ETF2H3,ETF2E2,ETF2A2,ETF2F1,TBP,POLR2B,MED16,TAF12,ETF2H2,TBPL1,POLR2G,MED4,E2F2,ETF2H1,TAF9,MED17,PPARGC1A,CDK7,POLR2C,TAF13,ETF2F2,CDK9,E2F3,POLR2E,TAF5,ETF2E1,MED7,MED26,TBPL2,MED24,TAF10,ETF2A1L,ERC3,POLR2L,POLR2K,MED30,ETF2I,ETF2B,ETF2A1,ETF2H4,ERC2,MED1,MED23,MAZ,TAF2,POLR2H,TAF6,TAF4B,MED14,MED13,CLIP2,POLR2A,TAF1,THRAP3,NCOA6,MED12
50:004316	0.479568	0	0	90	proteasomal ubiquitin-dependent protein catabolic process	PSMB5,BUB3,PSMD10,PSMB2,PSMA6,GCLC,CCNH,MNAT1,PSMA2,CDC23,PSMF1,PSMD12,CDC2A,UBE2C,PSMA5,DERL2,STUB1,PSMB4,UBE2D2,PSMC2,PSMD9,PSMA3,RAD23B,PSMB6,PSMD13,PSMD5,UCHL5IP,UBE2D3,PSMC6,PSMA4,PSMB7,PSMC4,PSMB1,PSMC5,MAN1B1,FAF1,PSME2,SYVN1,PSMA1,PSME1,PSMD14,DERL1,PSMD8,PSMB3,PPP2CB,CDC26,FBXO2,UBE2E1,ANAPC11,ANAPC7,PSMD6,MAD2L1,PSMD11,PSMD4,PSMD7,AMFR,PSMA7,PSMC3,CDC20,ANAPC2,TRIM63,PSMB9,ANAPC10,CDC16,PCNP,DERL3,UBB,PSMC1,RAD23A,PSMD1,ANAPC4,BUB1B,FBXO6,ANAPC5,PSMB8,EDEM3,PSMD3,VCP,PSME3,UBE2D1,SHH,EDEM1,CDC27,PPP2R5C,NPLOC4,UBE2G2,PSMD2,PSMB10,ANAPC1,AKT1,CD2AP
50:000635	0.470241	0	0	79	transcription initiation	MED27,POLR2J,POLR2I,SMARCA5,CCNH,MNAT1,POLR2D,TAF9B,POLR2F,TAF11,ETF2H3,ETF2E2,ETF2A2,NAT14,ETF2F1,SUPT3H,TBP,POLR2B,MED16,TAF12,ETF2H2,TBPL1,POLR2G,MED4,E2F2,ETF2H1,TAF9,MED17,PPARGC1A,CDK7,RRN3,POLR2C,SNAPC5,BRF2,TAF13,ETF3C4,ETF2F2,CDK9,E2F3,POLR2E,PTRF,TAF5,ETF2E1,MED7,MED26,TBPL2,MED24,TAF10,ETF2A1L,ERC3,POLR2L,POLR2K,MED30,ETF2I,ETF2B,ETF2A1,ETF2H4,ERC2,MED1,RF1,MED23,MAZ,MYC,LIPE,TAF2,TAF6L,POLR2H,TAF6,TAF4B,MED14,MED13,CLIP2,POLR2A,TAF1,BRF1,THRAP3,NCOA6,MED12

Table S3A. Gene sets up-regulated by severe stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0009151	0.470219	0	0	80	purine ribonucleotide metabolic process	ADSSL1,ATP5L,ADAL,NME3,ATP6V1F,NME7,ATP5G2,ADSL,FIGNL1,AK1,ATP5B,ATP5G3,RBM3,NDUFS1,ATP6AP1,RP2H,NME5,ATP6V0B,CTNS,ATP6V0C,AMPD3,NME1,NUDT9,ATP5H,ENTPD1,ATP5F1,ATP5A1,GMPS,ENTPD2,PRPS1,NME4,ATP5J,ATP5G1,ATP2A1,ATP1A1,ATP5O,PAICS,ATP5C1,TXNDC3,OLA1,ATP5K,PRPS2,PNP1,DECR2,ATP6V1B2,SLC25A13,IMPDH2,ATP5D,CLCA3,ATP5E,LDHD,ATP5J2,TGFB1,GMPPR2,GART,NADK,ATP6V1B1,ERCC3,ATP6V0D2,RP1H,ATIC,MYH7,NME6,ATP6V1A,ACLY,ADSS,NME2,AMPD1,ATP7A,ND4L,ATP1A2,AMPD2,ABCC6,MYH6,IMPDH1,ADA,MYO9B,PFAS,AK5,MON2
GO:0019888	0.468785	0	0	15	antigen processing and presentation of exogenous peptide antigen via MHC class II	UNC93B1,H2-DMA,FCER1G,H2-DMB2,H2-EA,IFI30,H2-EB2,H2-EB1,CTSE,CD74,FCGR2B,H2-OA,H2-AB1,TRAF6,H2-AA
GO:0043574	0.467514	0	0	14	peroxisomal transport	PEX7,PEX19,PEX10,ABCD1,PEX26,PEX13,PEX5,AGXT,PEX3,PEX14,PEX6,PEX12,PEX1,PEX16
GO:0017144	0.465877	0	0	30	negative regulation of translation	PAIP2,SRP9,EIF2AK3,ANG3,EIF4A3,SRP14,ANG,EIF2B1,EIF2B3,EIF2B4,HBEFG,IGF2BP2,EIF2B5,PTGFRN,EIF2AK4,TIA1,MVK,PRG3,EIF4EBP1,PRKAA1,PAIP2B,NDUFA13,IGF2BP1,EIF4EBP3,TSC1,EIF4EBP2,EIF2AK1,IGF2BP3,PRKCA,YBX2
GO:0007001	0.459165	0	0	10	inner mitochondrial membrane organization and biogenesis	TIMM8B,TIMM8A1,TIMM9,TIMM10,BAX,TIMM8A2,TIMM13,TAZ,OPA1,FXC1
GO:0052571	0.455806	0	0	9	response to host immune response	TLR7,GUCY1A3,TLR3,TLR4,TLR9,TLR1,TLR2,NOD2,TLR6
GO:0052201	0.448942	0	0	11	response to host defenses	TLR7,GUCY1A3,TLR3,TLR4,SMAD3,TLR9,TLR1,TGFB1,TLR2,NOD2,TLR6
GO:0006414	0.448717	0	0	98	translational elongation	RPL10,SRP9,RPS20,RPS18,RPL15,RPS21,RPS13,RPS16,RPS8,RPS7,RPL39,RPS3,SRP14,TUFM,SECISBP2,RPL5,RPL3,RPS25,GSPT2,RPS11,RPL8,RPL36,RPS6,RPL11,RPL23,SEPSECS,RPL7,RPS15A,RPS15,RPS23,RPL12,RPL35A,RPL38,RPS24,RPL31,RPL30,RPS3A,RPL7A,RPL6,GFM1,RPL37,EEFSEC,RPL13A,RPS5,RPS14,RPL9,RPL28,RPL35,RPL17,RPL14,TRSPAP1,RPL10A,RPL21,RPSA,RPL24,RPL18A,EEF1A2,EEF1D,RPL34,RPL36A,RPL4,FAU,RPL19,RPS2,RPL18,RPS10,RPL26,RPS17,EEF1B2,RPS29,RPS27,RPL27A,RPL13,RP59,RPS12,RPL23A,RPL27,RPS26,RPL29,UBA52,ARBP,RPLP1,RPL41,VAR5,RPS4X,EEF1A1,EEF2,RPS19,RPLP2,RPS28,CACNB4,POSTK,DIO2,RPL22,EEF1G,TSFM,EEF2K,RPL3L
GO:0019434	0.44508	0	0	20	aromatic compound catabolic process	EPHX2,GSTZ1,PTS,QDPR,HPD,ABAT,EPHX1,KYNU,INDO,ALDH5A1,INDO1,TD02,AADAT,GCH1,KMO,HGD,PAH,TAT,FAH,AFMID
GO:0008591	0.44469	0	0	9	regulation of Notch signaling pathway	DLL3,HEY2,JAG1,NFKBIA,IL6ST,DTX1,TRP63,RFNG,KIT
GO:0006391	0.442352	0	0	135	tRNA metabolic process	RPP38,RPP14,TRUB1,RPP30,FARS2,DUS4L,TRNT1,ELAC1,RPP25,TARSL2,NARS2,RPP40,LARS2,AAASD1,SCYE1,POU5F1,TARS,DAARS,SCAMP4,AIF1,YARS2,QTRT1,TSEN2,POP4,PUS3,RARS2,6720458F09RIK,TRMT12,PTPLB,TYW3,SSB,DAXX,SLC22A17,DDR1,LSM6,POP7,MTO1,RPP21,PUS7L,TRMU,PARS2,DLAT,LARS,QARS,PLXNB2,DARS2,DKC1,METTL1,LCMT2,POLG2,1190005F20RIK,TRDMT1,RARS,ZMAT2,TYW1,B3GALT4,KARS,NSUN2,5730449L18RIK,WDR92,NARS,ATP6V1G2,EIF2AK4,HARS,TRMT5,WDR46,PUS10,SARS2,FARSB,TCF19,DUS2L,GARS,THG1L,SARS,YARS,TRMT6,WARS,HARS2,ADAT2,TRMT11,TARS2,MARS,D630004A14RIK,AAARS,EARS2,ARID2,ADAT1,TRPT1,TRUB2,IARS2,PHF1,TRIT1,CCDC76,WARS2,DALRD3,VAR5,TAPBP,GTFF2H4,MARS2,TSEN34,4833403I15RIK,EPRS,LST1,KHSRP,POP1,CARS2,PUS7,POP5,WDR4,DUT,LTB,AAARS2,VAR5,IARS,ELAC2,QTRTD1,TRMT1,HMG20B,PUSL1,TSEN54,PUS1,DND1,CARS,DUS3L,ASTN1,DUS1L,GTPBP3,FARSA,CREG2,ZNF1,COL11A2,TPR,ZBTB9,TUBGCP6,SYNGAP1
GO:0046481	0.437128	0	0	41	phosphoinositide biosynthetic process	PIGU,PIGH,IMPA1,PIGG,FRAG1,DPM1,PIGF,PIGA,CDIPT,CD81,PIGK,PI4K2A,PIK3C2A,PIGX,PIGV,PIGQ,PIGL,PIGW,DPM2,PIGB,PI4KB,PIGN,PLAUR,PIGP,PIP4K2C,PGAP1,DPM3,PIGS,GPA1,PIGY,PIGT,C130090K23RIK,PIGO,PDGFA,PIGC,SEMA6D,PIGM,PDGFB,PIGZ,PI4KA,PERLD1
GO:0006091	0.436826	0	0	274	generation of precursor metabolites and energy	POLR3H,PDHB,NDUFS6,NDUFB4,PGAM2,NDUFB5,ATP5L,SUCLA2,NDUFS5,SUCLG1,NDUFA1,MDH1,LDHB,ME3,COX6A2,ENO3,COX17,CYB561,NDUFAB1,UQCRB,PYGL,OGDHL,PPP3R2,ATP6V1F,OXA1L,COX7C,CYCS,MC4R,NDUFS2,MCHR1,SCO1,ATP5G2,FH1,NDUFA9,PGAM1,BPGM,LAMP2,ADSL,ENO2,NDUFS3,GAA,NDUFA2,NDUFB6,ATP5B,PKFB1,BCS1L,NDUFA8,UQCRC1,NDUFA7,UQCRH,NDUFA5,SLC25A14,ATP5G3,NDUFC1,NDUFB2,NDUFB8,IDH3B,NDUFS1,ISL1,NDUFS4,GBE1,UQCR,NDUFB9,NDUFB3,GOT1,NDUFA10,NDUFB7,ATP6AP1,PHKA1,ATPIF1,NDUFS7,UQCRC2,ACO2,NDUFV1,PPP1CA,NRF1,NDUFC2,SDHA,NDUFA4,SUCLG2,MTO1,NDUFV2,COX6C,CYC1,ATP5H,SDHD,SLC25A3,FDX1,SDHB,PPP1CC,DLI,DLAT,PPARGC1A,ECD,PPP1R3D,UEVLD,ALDH5A1,PPP1R2,MDH1B,ALDOC,ATP5F1,ATP5A1,COX4I1,PRKACA,COX15,SLC37A2,LRR16A,ATP5J,ATP5G1,PHKG1,GFPT2,NDUFA3,SDHC,NDUFAF1,PHKB,COX6A1,ALDOB,PGK2,IDH3A,IDH3G,NDUFS8,ATP5O,IDH2,ATP5C1,GNPDA1,SLC25A4,ATP5K,HIF1A,INS2,NDUFB10,GCK,NDUFA6,AASS,PHKG2,SLC25A13,GFPT1,ATP5D,NFATC3,CYB5R4,SURF1,PFKM,ACOX1,CEBPA,ACADVL,CLCA3,ATP5E,LEP,IL6ST,OGDH,ADIPOQ,PKLR,FECH,COX7A1,KL,APOM,BAX,PPP1CB,PGK1,ND3,FTSJ3,ATP6V0D2,ARNT,DLST,PDHA1,EG277333,NNT,CS,MYBBP1A,A,TPI1,1110020P15RIK,CROT,VGF,COX8A,SLC25A12,PKC1,PRKAG3,PPP1R3A,HK2,LDHAL6B,ADRA1B,SLC37A4,6430537H07RIK,ND1,S100B,PPP1R3B,PKM2,LDHC,GNAS,ADPGK,FDXR,CYP1A2,EPM2A,GCGR,PPP1R3C,ALDOA,

Table S3A. Gene sets up-regulated by severe stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:004819	0.436553	0	0	108	Golgi vesicle transport	BET1,SCAMP1,SLC30A6,ERGIC3,COG7,SAR1B,PICK1,TRAPPC2L,D230025D16RIK,TXNDC1,TRAPPC1,SEC22B,GOLGA5,SEC13,COPB1,TRAPPC3,CHIC2,USE1,GABARAPL2,COPE,RER1,COPB2,SCAMP2,PRKCI,SCFD1,LMAN1,TRAPPC4,NAPG,0610009B22RIK,SEC23B,SAR1A,COPG,ARCN1,NRBP1,GOPC,RAB14,TGOLN1,STEAP2,HINT1,BLZF1,LMAN2L,GOSR2,ERGIC2,CUX1,TMED10,COP21,COPG2,VAMP7,VPS29,ARF1,TRAPPC2,PREB,RAB2A,GOLGA7,EXOC5,STX7,SEC22C,STX6,NAPA,STX18,RABEP1,SEC22A,STX16,RAB11,YKT6,OPTN,WIPI1,KRT18,COG1,COG5,COG3,TOM1L2,SEC24D,GGA1,USO1,GOSR1,TAPBP,RAB9B,KIF1C,SPIRE1,ARFGAP1,VCP,SEC24B,ARL1,SCAMP3,PACS1,DOPEY1,COPA,SEC23A,AP2A1,ERGIC1,VPS13A,SNAP23,SEC24A,COG2,ZW10,AP3B2,SEC24C,SEC31A,SORT1,OSBPL5,DOPEY2,RAB6B,GOLGA3,MON2,GBF1,HTT,NBEA
GO:004236	0.433122	0	0	21	water-soluble vitamin biosynthetic process	GSTO1,PSAT1,G6PDX,PNPO,PDXK,NMNAT2,KYNU,NMNAT1,NAPRT1,ITGB1BP3,QPRT,MMAB,BC016495,RFK,0610012D14RIK,AKR1A4,NADSYN1,NMNAT3,NAMPT,GULO,ME1
GO:004603	0.432501	0	0	47	ATP metabolic process	ATP5L,ATP6V1F,ATP5G2,FIGNL1,AK1,ATP5B,ATP5G3,NDUFS1,ATP6AP1,ATP6V0B,CTNS,ATP6V0C,ATP5H,ENTPD1,ATP5F1,ATP5A1,ATP5J,ATP5G1,ATP2A1,ATP1A1,ATP5O,ATP5C1,OLA1,ATP5K,ATP6V1B2,SLC25A13,ATP5D,CLCA3,ATP5E,LDHD,ATP5J2,TGFB1,NADK,ATP6V1B1,ERCC3,ATP6V0D2,MYH7,ATP6V1A,ACLY,ATP7A,ND4L,ATP1A2,ABCC6,MYH6,MYO9B,AKS,MON2
GO:004427	0.418751	0	0	85	nitrogen compound catabolic process	HIBCH,GAD1,ACHE,AUH,6530401N04RIK,HDC,GSTZ1,MPST,MTHFD1,SAT1,GAD2,MOXD1,BCKDHB,DDO,DTD1,CDO1,ARG2,PTS,ASL,MCCC2,QDPR,GOT1,HPD,AHCY,PRODH2,PCCA,BCKDHA,ASRGL1,GOT2,KYNU,INDO,SMOX,GCSH,DHPS,ACAD8,PCCB,MAOA,ALDH6A1,COMT,BCAT1,DDAH1,INDOL1,SARDH,AASS,ASPA,DBH,TDO2,AADAT,PRODH,PAOX,4930402E16RIK,BCKDK,DDAH2,FRRS1,GCH1,DIO3,DMGDH,TST,COLQ,KMO,ARG1,UROC1,A230051G13RIK,GLUD1,CSAD,SLC6A3,DIO2,MCCC1,SHMT1,BCAT2,GLS,HGD,MOXD2,ALDH4A1,PADI3,HAL,AMDHD1,LAO1,GLDC,PAH,AMT,FTCD,TAT,FAH,AFMID
GO:004362	0.418209	0	0	21	cellular protein complex disassembly	MTERFD3,ETF1,MTERF,HRSP12,XRN2,SUPT16H,SMARCE1,MTRF1L,ICT1,PTFR,SET,CEBPB,TNP1,TF2,NRG1,TF1,MTRF1,MAZ,2810006K23RIK,UPF1,HMGA1
GO:001599	0.41762	0	0	12	ATP hydrolysis coupled proton transport	ATP6V1H,ATP6V0E2,ATP6V1E1,ATP6V0E,ATP6V0B,ATP1A1,ATP1A4,ATP6V0A4,ATP1A2,ATP6V1E2,ATP6V1G3,ATP1A3
GO:000911	0.41507	0	0	24	vitamin biosynthetic process	GSTO1,PSAT1,G6PDX,PNPO,PDXK,NMNAT2,VKORC1,KYNU,NMNAT1,NAPRT1,ITGB1BP3,QPRT,MMAB,DHRS9,BC016495,RFK,0610012D14RIK,AKR1A4,CYP27B1,NADSYN1,NMNAT3,NAMPT,GULO,ME1
GO:000649	0.413182	0	0	60	protein amino acid lipidation	PIGU,PIGH,PIGG,FRAG1,DPM1,ZDHHC17,FNTA,PIGF,RABGGTB,PIGA,ASNSD1,PIGK,MTPP,CHM,FNTB,RP2H,HHATL,ZDHHC15,PIGX,PIGV,NMT1,WFS1,COMTD1,PIGQ,PIGL,PIGW,DPM2,ZDHHC2,MAP6D1,ZDHHC1,ZDHHC3,PIGB,PIGN,ATG10,PLAUR,PIGP,ABCA1,PGGT1B,PGAP1,AIPL1,DPM3,PIGS,SOAT2,HHAT,GPA1,PIGY,PIGT,ATG7,C130090K23RIK,PIGO,RABGGTA,PIGC,SEMA6D,PIGM,NMT2,COX10,PIGZ,ZDHHC7,PTAR1,PERLD1
GO:006500	0.412596	0	0	179	protein-DNA complex assembly	H3F3B,MED27,POLR2J,POLR2I,NAP1L5,SMARCA5,CNNH,H2AFV,MNAT1,POLR2D,TAF9B,SLC22A4,POLR2F,HIST1H4M,ASF1A,H3F3A,TAF11,ETF2H3,HIST1H1A,NAP1L2,ETF2E2,ETF2A2,H1F0,NAT14,ETF2F1,TSPYL3,MIS12,TSPYL1,SUPT3H,NAP1L3,HIST4H4,CHAF1B,TBP,POLR2B,HP1BP3,MED16,HIST2H3C1,TAF12,H2AFY,HIST1H4F,ETF2H2,HIST1H3G,HMGB2,TBPL1,POLR2G,HIST1H3A,MED4,HIST2H3B,HIST1H2AB,E2F2,HIST1H4B,HIST3H2A,ETF2H1,H2AFZ,TAF9,MED17,PPARGC1A,TSPYL4,CDK7,HIST1H2AK,H2AFX,HELLS,MCM2,HIST2H4,NAP1L1,HIST1H2AE,RRN3,POLR2C,HIST1H2BG,SNAPC5,HIST1H2AN,HIST3H2BB,H2AFY2,BRF2,HIST1H2BL,H2AFJ,TAF13,HIST2H2AA2,NAP1L4,ETF3C4,HIST2H2AA1,HIST1H1C,ETF2F2,CDK9,E2F3,POLR2E,HIST1H2AO,PTFR,HIST1H2BN,HIST2H2AC,TAF5,HIST1H2AF,ETF2E1,MED7,HIST1H1B,HIST1H3F,HIST1H4H,SET,MED26,PKN3,TBPL2,HIST2H2BB,1700054O13RIK,SOS2,CHAF1A,TMEM38B,HIST1H2BF,ASF1B,MED24,TAF10,ETF2A1L,ERCC3,HIST1H2BH,POLR2L,CENPF,HIST1H2AC,HIST1H1E,POLR2K,MED30,HIST1H2BB,CENPE,HIST1H4J,HMGB1,ETF2I,TF1,HIST1H2BC,HIST1H2BA,ETF2B,1700024P04RIK,ETF2A1,HIST2H2BE,HIST1H1D,HIST1H4D,TSPYL5,ETF2H4,HIST2H3C2,ERCC2,HIST1H3D,MED1,RSF1,HIST1H2BM,MED23,CAND1,HIST3H2BA,SHPRH,HIST1H2AA,HILS1,ATF7IP,HIST1H4I,MAZ,MYC,HIST1H1T,LIPE,TSPYL2,TAF2,TAF6L,H1FOO,POLR2H,PIGU,PIGH,PIGG,FRAG1,DPM1,PIGF,PIGA,PIGK,PIGX,PIGW,PIGQ,PIGL,PIGW,DPM2,PIGB,PIGN,PLAUR,PIGP,PGAP1,DPM3,PIGS,GPA1,PIGY,PIGT,C130090K23RIK,PIGO,PIGC,SEMA6D,PIGM,PIGZ,PERLD1
GO:000650	0.411145	0	0	31	GPI anchor biosynthetic process	PIGU,PIGH,PIGG,FRAG1,DPM1,PIGF,PIGA,PIGK,PIGX,PIGW,PIGQ,PIGL,PIGW,DPM2,PIGB,PIGN,PLAUR,PIGP,PGAP1,DPM3,PIGS,GPA1,PIGY,PIGT,C130090K23RIK,PIGO,PIGC,SEMA6D,PIGM,PIGZ,PERLD1
GO:000918	0.409825	0	0	13	ribonucleoside diphosphate metabolic process	ATP5B,NUDT9,ENTPD1,ATP5A1,ENTPD2,CANT1,ATP5C1,NUDT5,ATP5D,ATP5E,ENTPD4,AK5,ENTPD7
GO:000931	0.409531	0	0	83	amine catabolic process	HIBCH,GAD1,ACHE,AUH,6530401N04RIK,HDC,GSTZ1,MTHFD1,SAT1,GAD2,MOXD1,BCKDHB,DDO,DTD1,CDO1,ARG2,PTS,ASL,MCCC2,QDPR,GOT1,HPD,AHCY,PRODH2,PCCA,BCKDHA,ASRGL1,GOT2,KYNU,INDO,SMOX,GCSH,DHPS,ACAD8,PCCB,MAOA,ALDH6A1,COMT,BCAT1,DDAH1,INDOL1,SARDH,AASS,ASPA,DBH,TDO2,AADAT,PRODH,PAOX,4930402E16RIK,BCKDK,DDAH2,FRRS1,GCH1,DIO3,DMGDH,COLQ,KMO,ARG1,UROC1,A230051G13RIK,GLUD1,CSAD,SLC6A3,DIO2,MCCC1,SHMT1,BCAT2,GLS,HGD,MOXD2,ALDH4A1,PADI3,HAL,AMDHD1,LAO1,GLDC,PAH,AMT,FTCD,TAT,FAH,AFMID

Table S3A. Gene sets up-regulated by severe stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0022618	0.408437	0	0	113	ribonucleoprotein complex assembly	PAIP2,LSM2,SNRPG,EIF1AD,EIF4E,EIF2AK3,4930503E24RIK,SNRPD2,PRPF31,EIF4H,EIF1,SNRPE,EIF3H,SF3A3,EIF4B,IMPACT,CRNKL1,DAZL,SMNDC1,DDX20,EIF2B1,EIF2B3,SLU7,EIF1A,EIF2B4,EIF3D,EIF3J,PRPF6,NPM1,PAIP1,MTIF3,PPP1R15B,EIF2S1,EIF3F,LGTN,RPS3A,MTIF2,HSPB1,EIF5B,EIF4E2,DDX1,EIF3K,EIF2B5,NIP7,DENR,EIF2S2,SFRS9,EIF5,USP39,RPS14,BOLL,EIF2S3X,EIF2B2,EIF2AK4,EIF4A2,EIF2A,SMN1,EIF1B,EIF3I,EIF1AY,EIF3C,SFRS1,EIF3G,FUSIP1,EIF6,TSR1,TRMT6,SF3A1,SNRPD1,SIP1,EIF5A,EIF5A2,SF3A2,PTBP2,MBNL1,EIF4EBP1,SRPK2,EIF3E,BZW1,2410018C20RIK,PAIP2B,TXNL4A,GATC,BZW2,GTF2B,CUGBP1,BMS1,SFRS2IP,EIF4EBP3,EIF4G2,DDX23,EIF4EBP2,EIF4E1B,EIF3B,EIF2AK1,SFRS6,SFRS5,SURF6,EIF4E3,TNF,DICER1,SF1,EIF4G1,GEMIN6,ASCC3L1,BRUNOL4,EIF2C1,CUGBP2,BRF1,ATXN2,SFRS8,DMXL2,EIF4G3
GO:0009061	0.407522	0	0	72	amino acid catabolic process	HIBCH,GAD1,AUH,6530401N04RIK,HDC,GSTZ1,MTHFD1,GAD2,MOXD1,BCKDHB,DDO,DTD1,CDO1,ARG2,PTS,ASL,MCCC2,QDPR,GOT1,HPD,AHCY,PRODH2,PCCA,BCKDHA,ASRGL1,GOT2,KYNU,INDO,GCSH,ACAD8,PCCB,ALDH6A1,BCAT1,DDAH1,INDOL1,SARDH,AASS,ASPA,DBH,TDO2,AADAT,PRODH,4930402E16RIK,BCKDK,DDAH2,FRRS1,GCH1,DMGDH,KMO,ARG1,UROC1,A230051G13RIK,GLUD1,CSAD,MCCC1,SHMT1,BCAT2,GLS,HGD,MOXD2,ALDH4A1,PADI3,HAL,AMDHD1,LAO1,GLDC,PAH,AMT,FTCD,TAT,FAH,AFMID
GO:0000398	0.406435	0	0	147	nuclear mRNA splicing, via spliceosome	SF3B5,LSM2,POLR2J,POLR2I,SNRPG,SNRPA1,CLNS1A,POLR2D,NOVA1,POLR2F,SNRPD2,CSTF1,PRPF31,DNAJC8,SNRPE,MAGOH,SF3A3,HNRNPC,GTF2F1,CPSF3,DDX39,LSM3,HNRNPR,CRNKL1,POLR2B,SNRPF,CLP1,SMNDC1,SNRBP,SNW1,DDX20,SLU7,CCAR1,NHP2L1,POLR2G,DBR1,LSM7,SF3B4,GEMIN8,PRPF6,CWC15,PHF5A,SNRPD3,LSM8,TXNL4B,CSTF3,HNRNPA1,NCBP2,TGS1,HNRNPL,PRMT5,PCBP2,DDX1,POLR2C,NUDT21,FUS,RBM8A,SFRS9,USP39,THOC4,RNPS1,SFRS3,SF3B2,WDR77,CDC40,YBX1,UPF3B,SNRPB2,GTF2F2,PRPF4,SMN1,POLR2E,SMC1A,PTBP1,CPSF1,PRPF3,U2AF1,SNRPA,SFRS1,FUSIP1,DHX38,SFRS10,SF3A1,SNRPD1,SIP1,CSTF2,SF3A2,EFTUD2,PTBP2,POLR2L,NFX1,SF4,MBNL1,SRPK2,BAT1A,POLR2K,TXNL4A,PCF11,RNUXA,PPP1R8,SFRS7,PCBP1,DHX9,GATC,SF3B1,CUGBP1,HNRNPU,DHX16,SF3B3,SRRM1,CD2BP2,U2AF2,SFRS2IP,RBM25,CPSF2,KHSRP,SFRS4,HNRNPD,PAPOLA,DDX23,SNUPN,SFRS2,HNRPUL1,GEMIN5,SFRS6,SFRS5,SFRS11,GEMIN4,POLR2H,RBMX,MYOD1,HNRNPA2B1,SF1,GEMIN6,ASCC3L1,BRUNOL4,RBM5,HNRNPA0,CUGBP2,PABPN1,TRA2A,POLR2A,PRPF8,GEMIN7,SNRP70,SFRS8,TNRC4
GO:0000377	0.406435	0	0	147	RNA splicing, via transesterification reactions with bulged adenosine as nucleophile	SF3B5,LSM2,POLR2J,POLR2I,SNRPG,SNRPA1,CLNS1A,POLR2D,NOVA1,POLR2F,SNRPD2,CSTF1,PRPF31,DNAJC8,SNRPE,MAGOH,SF3A3,HNRNPC,GTF2F1,CPSF3,DDX39,LSM3,HNRNPR,CRNKL1,POLR2B,SNRPF,CLP1,SMNDC1,SNRBP,SNW1,DDX20,SLU7,CCAR1,NHP2L1,POLR2G,DBR1,LSM7,SF3B4,GEMIN8,PRPF6,CWC15,PHF5A,SNRPD3,LSM8,TXNL4B,CSTF3,HNRNPA1,NCBP2,TGS1,HNRNPL,PRMT5,PCBP2,DDX1,POLR2C,NUDT21,FUS,RBM8A,SFRS9,USP39,THOC4,RNPS1,SFRS3,SF3B2,WDR77,CDC40,YBX1,UPF3B,SNRPB2,GTF2F2,PRPF4,SMN1,POLR2E,SMC1A,PTBP1,CPSF1,PRPF3,U2AF1,SNRPA,SFRS1,FUSIP1,DHX38,SFRS10,SF3A1,SNRPD1,SIP1,CSTF2,SF3A2,EFTUD2,PTBP2,POLR2L,NFX1,SF4,MBNL1,SRPK2,BAT1A,POLR2K,TXNL4A,PCF11,RNUXA,PPP1R8,SFRS7,PCBP1,DHX9,GATC,SF3B1,CUGBP1,HNRNPU,DHX16,SF3B3,SRRM1,CD2BP2,U2AF2,SFRS2IP,RBM25,CPSF2,KHSRP,SFRS4,HNRNPD,PAPOLA,DDX23,SNUPN,SFRS2,HNRPUL1,GEMIN5,SFRS6,SFRS5,SFRS11,GEMIN4,POLR2H,RBMX,MYOD1,HNRNPA2B1,SF1,GEMIN6,ASCC3L1,BRUNOL4,RBM5,HNRNPA0,CUGBP2,PABPN1,TRA2A,POLR2A,PRPF8,GEMIN7,SNRP70,SFRS8,TNRC4
GO:0065001	0.399853	0	0	69	intracellular protein transport across a membrane	TIMM8B,TMEM48,TOMM22,1700034H14RIK,TIMM17A,SIL1,TIMM8A1,DDX19A,NUP43,NUP50,TRAM1L1,TIMM22,DNAJC19,TIMM9,TIMM23,SEC61G,RANBP17,SEC61A1,CHCHD4,NUPL2,D3UCLA1,NUP107,MAGMAS,NUP37,NUP35,TRAM1,NUP85,TIMM17B,SEC61B,NUP153,NUP88,TIMM10,NUP62,XPO7,TIMM50,NUP133,GLE1,NUP54,RRBP1,TIMM8A2,SEH1L,DDX19B,ABRA,NUP155,SEC61A2,NUPL1,ZMAT3,PEX14,NUP188,NUP210,SEC62,TIMM13,SEN2,PEX6,TIMM44,NUP205,MVP,NUP93,FXC1,RANBP2,1500001M20RIK,SERP2,NUP98,NUP160,TNKS,TRAM2,NUP214,POM121,TPR
GO:0043521	0.394791	0	0	46	negative regulation of neuron apoptosis	GRIK2,PRDX3,AGT,HRAS1,XRCC4,F2R,PSEN1,GCLC,PPT1,CLN3,ADORA2A,AGTR1B,DLX1,BCL2L1,XRCC2,TGFA,WFS1,RHOA,ROCK1,GCLM,ERBB3,PRDX2,GDF5,SOD1,GDNF,BAX,NEFL,BARHL1,AGTR1A,ADNP,KRAS,SNCA,BDNF,NRAS,BIRC5,MSH2,PCSK6,LIG4,AGTR2,RASA1,FURIN,FGF8,BCL2,TRP73,HTT,CACNA1A
GO:0043241	0.393557	0	0	22	protein complex disassembly	MTERFD3,ETF1,MTERF,HRSP12,XRN2,SUPT16H,SMARCE1,MTRF1L,ICT1,PTRF,SET,CEBPG,TNP1,IRAK3,TTF2,NRG1,TTF1,MTRF1,MAZ,2810006K23RIK,UPF1,HMGA1
GO:0006501	0.391832	0	0	32	GPI anchor metabolic process	PIGU,PIGH,PIGG,FRAG1,DPM1,PIGF,PIGA,PIGK,PIGX,PIGV,PIGQ,PIGL,PIGW,DPM2,PIGB,PIGN,PLAUR,PIGP,GPLD1,PGAP1,DPM3,PIGS,GPA1,PIGY,PIGT,C130090K23RIK,PIGO,PIGC,SEMA6D,PIGM,PIGZ,PERLD1
GO:0006671	0.389478	0	0	37	ceramide metabolic process	PPAP2A,HEXA,PPP2CA,GLA,HEXB,CLN3,CLN8,SMPD1,GM2A,PHCA,ASAH1,ITGB8,UGCG,ASAH2,ALDH5A1,LASS5,GALC,LASS2,N SMAF,CLN6,LYPLA3,GAL3ST1,ASAH3L,SGPL1,PRKAA1,ST6GALNAC6,SMPD2,ST6GALNAC1,CERK,PPP2R1A,ST3GAL5,CEL,LASS6,LASS4,ASAH3,B4GALNT1,NEU3
GO:0032981	0.388094	0	0	25	macromolecular complex disassembly	MTERFD3,ETF1,MTERF,HRSP12,XRN2,SUPT16H,SMARCE1,MTIF3,MTRF1L,ICT1,PTRF,SET,HMOX1,CEBPG,TNP1,APOE,IRAK3,TTF2,NRG1,TTF1,MTRF1,MAZ,2810006K23RIK,UPF1,HMGA1
GO:0015981	0.38608	0	0	14	energy coupled proton transport, against electrochemical gradient	ATP6V1H,ATP6V0E2,ATP6V1E1,ATP6V0E,ATP6V0B,ATP1A1,ATP6V1B2,ATP1A4,ATP6V0A4,ATP6V1B1,ATP1A2,ATP6V1E2,ATP6V1G3,ATP1A3

Table S3A. Gene sets up-regulated by severe stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0006778	0.382338	0	0	18	porphyrin biosynthetic process	SUCLA2,CPOX,UROS,ALAD,NFE2L1,UROD,COX15,RSAD1,TSPO,MMAB,IREB2,FECH,HMBS,ALAS1,ALAS2,HNF1A,PPOX,COX10
GO:0009061	0.379596	0	0	26	serine family amino acid metabolic process	NFS1,PSPH,SEPHS2,PSAT1,GCLC,SHMT2,CDO1,DHFR,SRR,GCSH,SARDH,GCLM,AGXT,4930402E16RIK,PHGDH,FIGS,DMGDH,BAT,AT,A230051G13RIK,CSAD,CTH,SHMT1,SDS,CBS,GLDC,AMT
GO:0016234	0.379043	0	0	16	macroautophagy	PSEN1,CLN3,ATG16L1,ATG4C,ATG5,ATG4D,ATG12,ATG4B,CTSD,BECN1,MAP1LC3A,ATG9A,NPC1,ATG4A,FRAP1,ATG9B
GO:0007001	0.377197	0	0	133	mitochondrion organization and biogenesis	RNF7,TIMM8B,MRPL17,TRNT1,NDUFS5,RRM2B,TOMM22,KIF5B,TIMM17A,TFAM,TIMM8A1,AIP,MTERF,MTX2,PSEN1,GPX1,DNAJA3,PMPCB,MAP3K1,MRPL39,IMMP2L,SLC25A14,CLN8,DNAJC19,TIMM9,VDAC1,NDUFS4,SOD2,TIMM23,SLC25A20,STARD3,NDUFS7,SEPT4,CPT2,NRF1,TFB2M,BCL2L1,DCTN6,SLC25A17,MRPL15,MIPEP,PIM2,FIS1,PLEKHF1,PPARGC1A,HSPD1,TOMM20,BHLHB8,CASP7,SLC37A2,DAP3,CSTAD,MFN1,NDUFS8,MUL1,TIMM17B,SLC25A4,PMAIP1,SLC25A15,MRPL12,GRPEL1,TSPO,1700020C11RIK,TIMM10,SLC25A13,TOMM40,SLC25A32,COX18,TIMM50,HTRA2,CEBPA,MSTO1,PEX5,SLC25A1,TRP53,AIFM1,YWHAZ,BAX,TIMM8A2,MAN2A1,CASP3,MPV17,SLC25A12,DNM1L,UCP2,UCP3,SLC22A5,TOMM34,SLC25A30,TIMM13,RAB3A,HSP90AA1,SLC25A27,AIFM2,CDKN2A,SLC25A10,SLC25A24,TIMM44,BID,ATP7A,TAZ,LONP1,SLC25A37,MYC,SPG7,POLRMT,OPA1,FXC1,CAV2,UCP1,CPT1B,JUN,BAK1,SH3GLB1,POLG,TYMP,COX10,CCK,MFN2,BBC3,FXN,SLC1A3,AKT1,BNIP3,BCL2,CD24A,CXADR,SLC25A36,TRP73,SFN,EPAS1,HTT,SLC25A2
GO:0006878	0.375105	0	0	9	cellular copper ion homeostasis	COMMD1,SCO1,ATP7B,PRND,APLP2,APP,PRNP,ATP7A,ATOX1
GO:0015801	0.369733	0	0	18	acidic amino acid transport	PRAF2,PSEN1,ARL6IP5,CLN8,SLC6A1,SLC17A8,SLC1A1,SLC1A6,SLC25A4,SLC25A13,LTA,SLC25A12,SLC25A22,PRKCD,TNF,SLC1A2,SLC1A3,HTT
GO:0009161	0.366306	0	0	148	nucleotide biosynthetic process	ADK,PPAT,ADSSL1,GUCY2F,ATP5L,RRM2B,ADAL,CMPK2,PRPSAP2,MTHFD1,NME3,ATP6V1F,NME7,G6PDX,ATP5G2,GUCY1B3,ADSL,DHODH,GRM8,ATP5B,NT5E,ATP5G3,GUCY1A3,RBM3,PAPSS1,ADORA2A,NMNAT2,ATP6AP1,HPRT1,DHFR,RP2H,PTHLH,TBPL1,NME5,ATP6V0B,DTYMK,GUCA1A,DRD1A,ATP6V0C,AMPD3,NME1,ATP5H,PTH,ADCY10,KYNU,CMPK1,ATP5F1,ATP5A1,ADCY5,ADCY3,GMPS,NMNAT1,PRPS1,NPPA,GUCY2D,NME4,UMPS,ATP5J,ATP5G1,NAPRT1,ATP5O,PAICS,ATP5C1,TXNDC3,GUCY1B2,ATP5K,PRPS2,ITGB1BP3,PNP1,GUCY2E,DECR2,ATP6V1B2,SLC25A13,RRM1,IMPDH2,QPRT,ATP5D,UCN2,CLCA3,ATP5E,LDHD,ATP5J2,PRPS1L1,TGFB1,RXFP2,GART,ATP6V1B1,BC016495,CTPS,GUCY2G,ATP6V0D2,RP1H,APOE,TYMS,NPY2R,EDN1,0610012D14RIK,ATIC,ABCA1,ARRB2,DRD5,CTPS2,ENTPD8,EDNRA,NME6,NPR1,ATP6V1A,NPPC,ADSS,NME2,ARRB1,AMPD1,THTPA,DCTD,ND4L,NADSYN1,PDZD3,MSH2,ADM,NMNAT3,NAMPT,AMPD2,ADCY2,ADCY8,CAD,PRPSAP1,IMPDH1,ADCY7,ADCY4,PTH2,RLN3,NPR2,NPPB,RRM2,ADCY9,GUCY2C,ADCY1,AVP,ADA,ME1,PFAS,PALM,AK5,MON2,ADCY6,INSL3,GUCA2B,GUCY1A2
GO:0051601	0.356819	0	0	23	protein maturation	ATP6AP2,AIP,SRGN,PSEN1,ADAMTS3,STUB1,PSENE1,WFS1,CPE,PCSK2,PCSK9,NCSTN,ADAM10,DNER,PSEN2,ASPRV1,APH1A,PCSK1,PCSK6,PCSK5,CORIN,FURIN,ADAMTS2
GO:0006741	0.355603	0	0	11	NADPH regeneration	HIBADH,G6PDX,H6PD,PGD,TALDO1,3930401K13RIK,TPI1,HSD11B1,RPIA,TKT,PGLS
GO:0046471	0.348203	0	0	58	glycerophospholipid biosynthetic process	PIGU,PIGH,IMPA1,PIGG,PCYT1A,FRAG1,PTDSS1,DPM1,CHPT1,PIGF,PIGA,CDIPT,CD81,PIGK,FGF7,PHKA1,PI4K2A,PIK3C2A,PIGX,PIGV,PIGQ,PIGL,PIGW,DPM2,AGPAT1,PIGB,FABP5,PI4KB,PIGN,PLAUR,PIGP,FABP3,PIP4K2C,PEMT,PGAP1,DPM3,PIGS,GPA1,PIGY,AGPAT2,PIGT,C130090K23RIK,APOA1,PIGO,TAZ,PTDSS2,PDGFA,CHKA,PIGC,LCAT,PCYT1B,SH3GLB1,SEMA6D,PIGM,PDGFB,PIGZ,PI4KA,PERLD1
GO:0006771	0.347741	0	0	26	porphyrin metabolic process	BLVRA,SUCLA2,CPOX,UROS,HMOX2,ALAD,NFE2L1,UROD,COX15,RSAD1,TSPO,CYB5R4,MMAB,IREB2,HMOX1,FECH,HMBS,ALAS1,CYP1A2,HEBP1,ALAS2,AMBP,HNF1A,GIF,PPOX,COX10
GO:0046511	0.3447	0	0	40	sphingoid metabolic process	PPAP2A,HEXA,PPP2CA,GLA,HEXB,CLN3,CLN8,SMPD1,GM2A,PHCA,ASAHI,ITGB8,UGCG,SGPP1,ASAHD,ALDH5A1,LASS5,GALC,LASS2,NSMAF,CLN6,LYPLA3,GAL3ST1,ASAH3L,SGPL1,PRKAA1,ST6GALNAC6,SMPD2,ST6GALNAC1,CERK,SPHK2,PPP2R1A,ST3GAL5,CEL,LASS6,LASS4,ASAH3,B4GALNT1,SPHK1,NEU3
GO:0051261	0.336586	0	0	26	protein tetramerization	MTMR2,ACHE,PCBD1,ADSL,HPRT1,ATPIF1,ALDH5A1,PDSS2,ACTN2,TH,CDA,AASS,GFPT1,APOE,GPX3,PCBD2,CAT,PDSS1,IGF1R,TRPV5,TGM3,SHMT1,SBF2,TRP63,IDE,INSR

Table S3A. Gene sets up-regulated by severe stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:004425	0.331021	0	0	232	cellular protein catabolic process	CLPP,PSMB5,SMURF2,UFD1L,BUB3,CYLD,USP45,PSMD10,PSMB2,USP21,SKP1A,PSMA6,RBX1,TSG101,FBXO32,GCLC,USP28,PP T1,UBE2L3,UCHL3,CCNB1,BTRC,SMURF1,FBXO7,PSMA2,CDC23,MAP3K1,PSMF1,RNF217,USP8,CUL4B,UBE2B,FBXL4,PSMD12, CDC2A,CLN8,FBXO8,UBE2C,NEDD8,PSMA5,DERL2,STUB1,PSMB4,UBE2D2,PSMC2,PSMD9,PSMA3,RAD23B,UBE2A,TCEB1,PSM B6,USP30,UCHL5,PSMD13,SQSTM1,PSMD5,UCHL5IP,UBE2D3,USP54,CUL5,ZMPSTE24,PSMC6,PSMA4,USP29,UBE1Y1,PSMB7, PSMC4,USP11,BAP1,PSMB1,RNF6,UBE2H,ISG15,PSMC5,MAN1B1,FAF1,PSME2,SYVN1,PSMA1,PSME1,CUL3,PSMD14,DERL1,U SP5,PSMD8,UBE2G1,UHRF2,PLG,CHFR,USP39,USPL1,ARIH2,PSMB3,PPP2CB,CDC26,FBXO2,UCHL4,CUL7,UBE2E1,ANAPC11,AN APC7,LNX1,TOM1L1,USP26,USP33,PSMD6,USP4,MAD2L1,PARK2,USP27X,USP7,USP2,USP47,PSMD11,ATE1,CUL2,PCYOX1,SKP 2,USP18,UBE2K,PSMD4,RNF144B,USP37,USP1,PSMD7,AMFR,USP10,PSMA7,CUL1,PSMC3,CDC20,USP14,ANAPC2,FBXL12,TRI M63,UBE2L6,PSMB9,FBXO22,USP15,USP44,UBE2I,USP35,USP49,ANAPC10,USP13,CDC16,PCNP,DERL3,ARIH1,UBB,UBE3A,FBX W4,PSMC1,RAD23A,FBXO21,UBE2N,RNF11,UCHL1,USP25,DUB1,PSMD1,FBXO11,ANAPC4,2700078E11RIK,BUB1B,SIAH2,FBX O6,ITCH,TAP1,PSMB11,ANAPC5,PSMB8,EDEM3,SIAH1B,PSMD3,CPA2,USP42,PSMA8,VCP,USP9Y,USP46,USP38,USP48,PSME3, UBE2D1,SHH,USP50,EDEM1,HDAC6,CUL4A,CDC27,PPP2R5C,GGNBP1,CBLC,NPLOC4,FBXL7,USP3,USP52,USP16,USP22,SIAH1A,
GO:000641	0.329969	0	0	135	regulation of translation	PAIP2,ETF1,SRP9,1110005A23RIK,F2R,MAPK3,EIF4E,EIF2AK3,4930503E24RIK,RPS18,EIF4H,EIF1,CDK4,NANOS1,EIF3H,ANG3,E IF4B,EIF4A3,HRSP12,IMPACT,DAZL,SRP14,NGDN,SECISBP2,ANG,EIF2B1,EIF2B3,PPP1CA,EIF2B4,DNAJC1,EIF3D,EIF3J,HBEGF,SE PSEC5,PAIP1,MTIF3,PPP1R15B,EIF2S1,EIF3F,IGF2BP2,FMR1,MTIF2,HSPB1,EIF5B,DDX25,RHOA,EIF4E2,DDX1,EIF3K,EIF2B5,EIF5 ,EEFSEC,MIF4GD,MAPK1,PTGFRN,SCAP,BOLL,EIF2B2,IL6,EIF2AK4,NCK1,PA2G4,EIF4A2,PUM2,EIF2A,ZFP36L1,EIF1B,TRSPAP1,E IF3I,MTPN,EIF3C,EIF3G,MYD116,IIEB2,TRMT6,PRKRIR,TIA1,APLP1,QQ,TGFB1,EIF5A,MVK,MKNK1,SAMD4,PRG3,EIF4EBP1,ADA D1,PRKAA1,EIF3E,BZW1,PAIP2B,METAP1,BARHL2,GATC,BZW2,MTRF1,APP,NDUFA13,IGF2BP1,EIF4EBP3,NANOS2,NCK2,EIF4G 2,TSC1,IGF1,F2,EIF4EBP2,UCN,CD28,EIF2AK1,MKNK2,KRT7,PSTK,CPEB1,DIO2,ACO1,BCL3,IGF2BP3,EIF4E3,PTK2B,PUM1,TNF,E IF4G1,PDGFRB,UPF1,AKT1,EIF2C1,CPEB2,KRT17,PRKCA,NANOS3,GCN1L1,ATXN2,EIF4G3,YBX2
GO:003112	0.327893	0	0	20	RNA 3'-end processing	TRNT1,CSTF1,CPSF3,SLBP,GRSF1,PAPOLG,LSM10,CSTF3,CPSF1,APLP1,CSTF2,PABPC2,APP,CSTF2T,PABPC1,PAPOLA,PAPOLB,BA RD1,CSDC2,PABPN1
GO:000640	0.3209	0	0	36	mRNA catabolic process	LSM2,AUH,PARN,DCPS,MAGOH,EIF4A3,LSM7,LSM6,SMG7,RNH1,UPF2,RBM8A,SMG6,LSM5,RNPS1,PNPT1,UPF3B,SMG5,ZFP3 6L1,UPF3A,EXOSC10,DCP1B,MEX3D,ZFP36,DCP1A,PAN3,ZHX2,USP52,GSPT1,MLH1,UPF1,ZFP36L2,HSPA1B,DCP2,ZFP36L3,261 0207I05RIK
GO:004339	0.319954	0	0	21	regulation of protein binding	PCBD1,EIF2AK3,PSEN1,PRMT8,AKTIP,LDLRAP1,ADRB2,SMARCD3,MAP1LC3B,GTPBP4,BAX,ATR,TGFBR3,NRG1,PRMT7,ARRB2, ADRB3,ARRB1,TICAM1,BAK1,BCL2
GO:000651	0.317419	0	0	221	ubiquitin-dependent protein catabolic process	PSMB5,SMURF2,UFD1L,BUB3,CYLD,USP45,PSMD10,PSMB2,USP21,SKP1A,PSMA6,RBX1,TSG101,FBXO32,GCLC,USP28,UBE2L3, UCHL3,CCNB1,BTRC,SMURF1,FBXO7,PSMA2,CDC23,MAP3K1,PSMF1,RNF217,USP8,CUL4B,UBE2B,FBXL4,PSMD12,CDC2A,FBX O8,UBE2C,NEDD8,PSMA5,DERL2,STUB1,PSMB4,UBE2D2,PSMC2,PSMD9,PSMA3,RAD23B,UBE2A,TCEB1,PSMB6,USP30,UCHL5, PSMD13,SQSTM1,PSMD5,UCHL5IP,UBE2D3,USP54,CUL5,PSMC6,PSMA4,USP29,UBE1Y1,PSMB7,PSMC4,USP11,BAP1,PSMB1,R NMF6,UBE2H,PSMC5,MAN1B1,FAF1,PSME2,SYVN1,PSMA1,PSME1,CUL3,PSMD14,DERL1,USP5,PSMD8,UBE2G1,UHRF2,CHFR,U SP39,USPL1,ARIH2,PSMB3,PPP2CB,CDC26,FBXO2,UCHL4,CUL7,UBE2E1,ANAPC11,ANAPC7,LNX1,TOM1L1,USP26,USP33,PSMD 6,USP4,MAD2L1,PARK2,USP27X,USP7,USP2,USP47,PSMD11,ATE1,CUL2,SKP2,USP18,UBE2K,PSMD4,RNF144B,USP37,USP1,PS MD7,AMFR,USP10,PSMA7,CUL1,PSMC3,CDC20,USP14,ANAPC2,FBXL12,TRIM63,PSMB9,FBXO22,USP15,USP44,UBE2I,USP35, USP49,ANAPC10,USP13,CDC16,PCNP,DERL3,ARIH1,UBB,UBE3A,FBXW4,PSMC1,RAD23A,FBXO21,UBE2N,RNF11,UCHL1,USP25 ,DUB1,PSMD1,FBXO11,ANAPC4,2700078E11RIK,BUB1B,SIAH2,FBXO6,ITCH,TAP1,PSMB11,ANAPC5,PSMB8,EDEM3,SIAH1B,PS MD3,USP42,PSMA8,VCP,USP9Y,USP46,USP38,USP48,PSME3,UBE2D1,SHH,USP50,EDEM1,HDAC6,CUL4A,CDC27,PPP2R5C,GG NBP1,CBLC,NPLOC4,FBXL7,USP3,USP52,USP16,USP22,SIAH1A,DUB2,UBE2G2,PSMD2,USP19,PSMB10,UBE4A,ANAPC1,UBC,FZF
GO:000673	0.31741	0	0	179	coenzyme metabolic process	POLR3H,PDHB,COQ7,HIBADH,GLO1,GSTK1,SUCLA2,SUCLG1,MDH1,LDHB,GSR,MGST1,TPK1,GSTT2,MTHFD1,GCLC,G6PDX,FH1, GPX1,PIPOX,GPHN,MOCS2,COQ5,ATP5G3,GPX4,PDXK,LIAS,FOLH1,IDH3B,ACOT5,DBIL5,NMNAT2,DHFR,VNN1,ACO2,H6PD,CT NS,VKORC1,SCP2,DBI,SDHA,SUCLG2,ACOT1,SDHD,COQ6,SDHB,KYNU,DLD,MCEE,ACSS1,DLAT,INDO,MTHFD1L,OXSM,ALDH5A 1,RNASEL,MDH1B,PDSS2,NMNAT1,ACSL6,HAGH,POLR2C,SDHC,NAPRT1,ACOT3,OXCT1,COQ9,IDH3A,IDH3G,IDH2,GBA2,MLYC D,PGD,GCK,ITGB1BP3,NUDT7,MTHFD2,GLYAT,GCLM,QPRT,EHHADH,GSTP1,GSTP2,TXNRD3,MOCS3,TALDO1,SOD1,ALDH1L1,G STA3,TDO2,FOLR1,NADK,CBR2,3930401K13RIK,BC016495,GLRX2,PANK1,DLST,ACOT9,PDHA1,NNT,CS,MTHFS,MOCS,TPI1,AC OT2,HSD11B1,GPX3,0610012D14RIK,COQ4,PANK2,FPGS,GSS,GCDH,SEC16A,GNMT,COQ3,HMGCL,VNN3,ACACB,ACSS2,HAPO, MDH2,MOCS1,ACLY,PANK3,PDSS1,GGT7,KMO,GSTT3,ACMSD,PK4,GSTA1,SLC27A3,RP1A,COASY,HNF4A,ALDH1L2,NADSYN1, NCF1,ACOT8,COQ2,ACSM4,IDH1,CTH,NMNAT3,NAMPT,ACOT12,OXCT2A,NCF2,PANK4,PDHA2,SHMT1,GPD1,C1QL2,ACO1,GST T1,GGT1,MTHFR,CES3,LDHA,PPCDC,2610209A20RIK,MTHFSD,2610507B11RIK,NOX1,TKT,HMGCS1,ME1,HMGCGR,FTCD,GGT5,P GLS,ACACA,ACOT4,MTR,GGT6,DCXR,AFMID

Table S3A. Gene sets up-regulated by severe stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0051188	0.316684	0	0	84	cofactor biosynthetic process	PDHB,COQ7,SUCLA2,TPK1,MTHFD1,GCLC,G6PDX,GPHN,MOCS2,COQ5,CPOX,UROS,PDXK,LIAS,NMNA2,DHFR,VKORC1,ALAD,COQ6,KYNU,DL,ACSS1,DLAT,MTHFD1L,NFE2L1,PDSS2,UROD,NMNA1,COX15,POLR2C,NAPRT1,COQ9,RSAD1,MLYCD,ITGB1B,P3,TSPO,MTHFD2,GCLM,QPRT,MMAB,MOCS3,IRESB2,ALDH1L1,FECH,BC016495,PANK1,HMBS,PDHA1,MTHFS,ALAS1,MOCOS,0610012D14RIK,COQ4,PANK2,FPGS,GSS,GCDH,COQ3,ACSS2,MOCS1,ACLY,PANK3,PDSS1,GGT7,PK4,ALAS2,COASY,NADSYN1,COQ2,HNF1A,NMNA3,NAMPT,PANK4,PDHA2,GGT1,PPOX,PPCDC,2610209A20RIK,COX10,MTHFSD,ME1,GGT5,MTR,GGT6
GO:0043111	0.31367	0	0	40	receptor metabolic process	GRIK2,CHMP5,ACHE,PICK1,FUT8,FNTA,DRD2,PLD2,MUSK,TRAPP4,CLEC2I,GRK4,CDK5,DRD3,SCAP,PAK1,IL10,ACE2,PCSK9,DOK7,APOE,NRG1,LRP4,AGTR1A,TRAT1,DLG2,RAB40C,GRIK5,CAML,DMD,TNF,PPARG,FURIN,DVL1,ULK1,ALS2,GRIA1,AGRN,CACNA1A,SYNGAP1
GO:0006891	0.312598	0	0	22	intra-Golgi vesicle-mediated transport	GOLGA5,COPB1,GABARAPL2,COPE,COPB2,NAPG,CUX1,COPZ1,COPG2,NAPA,STX16,OPTN,COG1,COG5,COG3,TOM1L2,GGA1,USO1,GOSR1,PACS1,COG2,GOLGA3
GO:0051188	0.312343	0	0	216	cofactor metabolic process	POLR3H,PDHB,COQ7,BLVRA,HIBADH,GLO1,GSTK1,NFS1,SUCLA2,SUCLG1,MDH1,LDHB,GSR,MGST1,TPK1,GSTT2,MTHFD1,NFU1,GCLC,G6PDX,PPT1,FH1,GPX1,PIPOX,GPHN,MOCS2,COQ5,CPOX,UROS,HMOX2,ATP5G3,GPX4,PDXK,LIAS,FOLH1,IDH3B,ACOT5,DBIL5,NMNA2,DHFR,VNN1,ACO2,H6PD,CTNS,VKORC1,SCP2,DBI,SDHA,SUCLG2,PCCA,ACOT1,ALAD,SDHD,COQ6,SDHB,KYNU,DL,DL,MCEE,ACSS1,DLAT,INDO,MTHFD1L,OXSM,ALDH5A1,RNASEL,MDH1B,NFE2L1,PDSS2,UROD,NMNA1,ACSL6,HAGH,ISCA1,COX15,POLR2C,SDHC,NAPRT1,ACOT3,OXCT1,COQ9,IDH3A,RSAD1,IDH3G,IDH2,GBA2,MLYCD,PGD,GCK,ITGB1B,P3,NUDT7,TSPO,MTHFD2,GLYAT,GCLM,QPRT,EHHADH,GSTP1,GSTP2,CYB5R4,TXNRD3,MMAB,MOCS3,TALDO1,IRESB2,SOD1,HMOX1,ALDH1L1,GSTA3,TDO2,FECH,FOLR1,NADK,CBR2,3930401K13RIK,BC016495,GLRX2,PANK1,HMBS,DLST,ACOT9,PDHA1,NNAT,CS,MTHFS,ALAS1,MOCOS,TP11,ACOT2,HSD11B1,GPX3,0610012D14RIK,ADH4,COQ4,VKORC1L1,PANK2,FPGS,GSS,GCDH,SEC16A,GNMT,COQ3,HMGCL,VNN3,ISCA2,CYP1A2,ACACB,ACSS2,TST,HAO,MDH2,MOCS1,HEBP1,ACLY,PANK3,PDSS1,GGT7,KMO,GSTT3,ACMSD,PDK4,GSTA1,ALAS2,SLC27A3,RPIA,COASY,HNF4A,ALDH1L2,NADSYN1,NCF1,ACOT8,COQ2,ACSM4,AMBP,IDH1,CTH,HNF1A,NMNA3,NAMPT,ACOT12,OXCT2A,NCF2,MCCC1,PANK4,PDHA2,SHMT1,GPD1,C1QL2,ACO1,GIF,GSTT1,GGT1,PPOX,MTHFR,CES3,LDHA,PPCDC,2610209A20RIK,ISCU,COX10,MTHFSD,2610507B11RIK,FXN,NOX1,TKT,HMGCS1,ME1,HMGCR,FTCD,GGT5,P
GO:0008211	0.312164	0	0	39	protein amino acid alkylation	EZH2,BTG1,SUZ12,EED,PRMT1,METTL5,PRMT8,AI931714,4833442J19RIK,BHMT,LCMT1,LCMT2,PRMT5,SUV39H2,PAX5,PRMT3,RAB3B,PCMT1,PRDM9,ILF3,SUV39H1,MEN1,ICMT,SUV420H1,BTG2,PRMT7,PRMT2,RAB3D,RAB6,CARM1,EHMT1,NSD1,WHSC1L1,HEMK1,SUV420H2,MTR,SATB1,EHMT2,MLL1
GO:0006478	0.312164	0	0	39	protein amino acid methylation	EZH2,BTG1,SUZ12,EED,PRMT1,METTL5,PRMT8,AI931714,4833442J19RIK,BHMT,LCMT1,LCMT2,PRMT5,SUV39H2,PAX5,PRMT3,RAB3B,PCMT1,PRDM9,ILF3,SUV39H1,MEN1,ICMT,SUV420H1,BTG2,PRMT7,PRMT2,RAB3D,RAB6,CARM1,EHMT1,NSD1,WHSC1L1,HEMK1,SUV420H2,MTR,SATB1,EHMT2,MLL1
GO:0006900	0.30824	0	0	18	membrane budding	COPB1,COPE,COPB2,PRKCI,COPG,ARCN1,HINT1,COPZ1,ARF1,P2RX7,CALY,AP2S1,PICALM,ARFGAP1,COPA,SNAP91,HIP1,GBF1
GO:0008654	0.306326	0	0	95	phospholipid biosynthetic process	PIGU,PIGH,IMPA1,PIGG,PCYT1A,FRAG1,PTDSS1,DPM1,CHPT1,PIGF,PIGA,AGPAT5,LYCAT,CEPT1,CDIPT,PGS1,HEXB,CD81,MBOAT5,PIGK,AGPAT9,FGF7,PHKA1,PI4K2A,PIK3C2A,SGMS2,PIGX,PIGV,PBX2,SERINC1,LPGAT1,GPAM,PIGQ,PIGL,AYTL1B,PIGW,ISYN,A1,D5WSU178E,DPM2,DOLK,SERINC5,ETNK1,AGPAT3,AGPAT1,PIGB,FABP5,PI4KB,SGMS1,PIGN,PLAUR,A530057A03RIK,PIGP,FABP3,PIP4K2C,CREBL1,LPCAT2,PEMT,PGAP1,FADS1,DPM3,PIGS,CRLS1,GAAA1,PIGY,AGPAT2,NOTCH4,SAMD8,PIGT,PLA2G4A,CDS2,LPCAT1,AGPAT4,C130090K23RIK,APOA1,PIGO,TAZ,PCYT2,PTDSS2,PDGFA,CHKA,PIGC,LCAT,PCYT1B,CDS1,SH3GLB1,PISD,SEMA6D,PIGM,BTNL7,PDGFB,PIGZ,DGKE,PI4KA,AGER,PERLD1
GO:0046688	0.29825	0	0	16	response to copper ion	MT1,MT2,SOD3,NFKB1,ACADM,ALDOB,ATP7B,SORD,ATP5D,SOD1,BAX,PRNP,ATP7A,LCAT,TFRC,BCL2
GO:0006751	0.293409	0	0	252	nucleoside phosphate metabolic process	ADK,PPAT,HIBADH,RDH14,GMPPR,DGUOK,ADSSL1,DERA,GUCY2F,ATP5L,GUK1,MDH1,LDHB,RRM2B,ADAL,CMPK2,PRPSAP2,MT,HFD1,NME3,DCK,ATP6V1F,NME7,NUDT15,G6PDX,ATP5G2,GUCY1B3,PDE8B,ADSL,FIGNL1,AK1,DHODH,GRM8,ATP5B,NT5E,ATP5G3,GUCY1A3,RBM3,PAPSS1,NDUFS1,ENPP5,ADORA2A,NMNA2,CNP,ATP6AP1,HPRT1,DHFR,ATPIF1,RP2H,NT5C2,H6PD,PTHLH,TBPL1,NME5,ATP6V0B,CTNS,ITPA,ENTPD3,DTYMK,GUCA1A,DRD1A,ATP6VOC,AMPD3,NME1,NUDT9,ATP5H,PTH,ADCY10,KYNU,ENTPD1,NT5C3,INDO,RORA,CMPK1,ATP5F1,ATP5A1,ADCY5,ADCY3,GMPS,NMNA1,ENTPD2,PRPS1,NPPA,GUCY2D,CNGB3,NME4,UMPS,ATP5J,ATP5G1,ATP2A1,CANT1,NAPRT1,ATP1A1,FHIT,ATP5O,PAICS,ATP5C1,CDA,TXNDC3,REXO2,GUCY1B2,OLA1,ATP5K,PGD,GCK,PRPS2,ITGB1B,P3,NUDT7,PNP1,GUCY2E,NUDT5,DECR2,ATP6V1B2,SLC25A13,RRM1,IMPDH2,QPRT,ATP5D,NT5M,NUDT1,UCN2,TALDO1,MUTYH,MPG,NUDT4,CLCA3,ATP5E,LDHD,ATP5J2,PRPS1L1,TDO2,TGFB1,RXFP2,GMPPR2,PDE8A,GART,NADK,CBR2,ATP6V1B1,ENTPD4,3930401K13RIK,BC016495,ERCC3,ENPP3,CTPS,GUCY2G,UPP2,ATP6V0D2,RP1H,APOE,TPIL1,TYMS,NPY2R,HSD11B1,EDN1,0610012D14RIK,PDE5A,ATIC,ABCA1,ARRB2,DRD5,CTPS2,SMARCAD1,TDG,ENTPD8,AIPL1,MYH7,HAAO,EDNRA,NME6,NT5C1A,NPR1,ATP6V1A,ACLY,ENPP1,NPPC,KMO,ADSS,CCNO,NME2,PDE4D,NT5C,ACMSD,ARRB1,AMPD1,THTPA,NT5C3L,RPIA,NT5C1B,ATP7A,DCTD,DUT,ND4L,NADSYN1,NCF1,TIMP2,PDZD3,MSH2,CACNB4,ADM,NMNA3,NAMF
GO:0000184	0.289039	0	0	21	nuclear-transcribed mRNA catabolic process, nonsense-mediated decay	PARN,DCPS,MAGOH,EIF4A3,SMG7,UPF2,RBM8A,SMG6,RNPS1,UPF3B,SMG5,UPF3A,EXOSC10,DCP1B,DCP1A,PAN3,USP52,GSP11,UPF1,DCP2,261020705RIK

Table S3A. Gene sets up-regulated by severe stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:000704	0.288552	0	0	18	lysosomal transport	CHMP5,M6PR,USE1,SNX1,ZFYVE16,ADRB2,LHCGR,VAMP7,AP3M1,LYST,RHOB,ARSB,NPC1,GNPTG,AP3B1,NAGPA,ALS2, SORT1
GO:000649	0.28649	0	0	26	protein amino acid O-linked glycosylation	POMGN1,GALNT1,DPM1,C1GALT1,GALNT2,GALNT13,ST8SIA6,POMT2,GCNT1,DPM2,GALNT10,POMT1,GALNT6,GYPC,GCNT3 ,GALNT7,DPM3,B3GNT6,A4GNT,GALNT9,TRAK2,TRAK1,OGT,GALNT3,POFUT1,LDLR
GO:004636	0.286219	0	0	76	monosaccharide catabolic process	PDHB,FUT10,HIBADH,PGAM2,MDH1,LDHB,ENO3,FUT8,FUT9,OGDHL,G6PDX,PGAM1,BPGM,ENO2,PFKFB1,H6PD,GLB1,DLAT,E CD,UEVLD,ALDOC,LRRC16A,ALDOB,PGK2,FUT4,HIF1A,PGD,INS2,GCK,NUDT5,PFKM,TALDO1,OGDH,PKLR,TKTL1,3930401K13RI K,PGK1,ARNT,PDHA1,EG277333,TPI1,HSD11B1,HK2,LDHAL6B,6430537H07RIK,PKM2,LDHC,ADPGK,ALDOA,MDH2,GAPDH,ALD OART2,MIF,PFKL,IGF1,FUT1,RPIA,PFKP,ALDOART1,ENO1,PFKFB3,PDHA2,HKDC1,LDHA,BAD,GPI1,HK1,FUT7,FUT2,TKT,HK3,ML XIPL,PGLS,GAPDHS,INSR,DHTKD1
GO:004427	0.282414	0	0	104	cellular carbohydrate catabolic process	PDHB,FUT10,HIBADH,PGAM2,MDH1,LDHB,ENO3,FUT8,FUT9,PYGL,OGDHL,CTBS,G6PDX,PGAM1,BPGM,FUCA1,ENO2,GAA,PFK FB1,CHID1,H6PD,GNS,GLB1,DLAT,ECD,UEVLD,ALDOC,GUSB,CHIA,CHI3L4,LRRC16A,HYAL1,ALDOB,PGK2,CHI3L1,HYAL4,FUT4,G NPDA1,HYAL2,GBA2,HIF1A,PGD,INS2,GCK,NUDT5,PFKM,TALDO1,OVGP1,IDUA,OGDH,PKLR,TKTL1,3930401K13RIK,PGK1,ARN T,PDHA1,EG277333,TPI1,HSD11B1,HK2,LDHAL6B,ADRA1B,LYVE1,6430537H07RIK,PKM2,LDHC,ADPGK,ALDOA,MDH2,PYGM,G APDH,ALDOART2,TREH,MIF,PFKL,IGF1,FUT1,RPIA,CHIT1,MGAM,PFKP,ALDOART1,ENO1,PFKFB3,PDHA2,HKDC1,LDHA,G6PC,BA D,GPI1,HK1,CHI3L3,FUT7,FUT2,TKT,HK3,MLXIPL,PYGB,PGLS,GAPDHS,AGL,AVPR1A,INSR,DHTKD1
GO:001599	0.279222	0	0	71	proton transport	SLC30A5,ATP6AP2,ATP5L,ATP6V1D,ATP6V1C1,ATP6V1F,ATP6V1H,ATP5G2,ATP6V0E2,ATP6V1E1,ATP5B,ATP5G3,ATP6V0E,AT P6V0D1,ATP6AP1,ATP6V0B,ATP6V0C,ATP5H,ATP5F1,ATP5A1,ATP5J,ATP5G1,ATP2A1,ATP1A1,ATP5O,ATP5C1,ATP6V1G2,ATP 5K,ATP6V1B2,ATP6V1C2,ATP5D,ATP1A4,ATP6V0A4,ATP5S,CLCA3,ATP5E,ATP5J2,ATP6V1B1,ATP6V0D2,SLC36A2,NNT,SLC9A5, ATP6V0A2,ATP12A,ATP6V1G1,ATP2C1,UCP2,UCP3,ATP2C2,ATP6V1A,NHEDC2,SLC4A11,HVCN1,ATP6,ATP13A2,ND4L,ATP4A,A TP1B4,ATP1A2,ATP2A2,UCP1,ATP6V1E2,ATP6V0A1,ATP6V1G3,NOX1,ATP2A3,TCIRG1,ATP4B,SLC36A1,MON2,ATP1A3
GO:004303	0.271904	0	0	76	tRNA aminoacylation	FARS2,TARSL2,NARS2,LARS2,AARSD1,SCYE1,POU5F1,TARS,DARS,AIF1,YARS2,RARS2,PTPLB,DAXX,SLC22A17,DDR1,PARS2,DLA T,LARS,QARS,PLXNB2,DARS2,POLG2,RARS,ZMAT2,B3GALT4,KARS,WDR92,NARS,ATP6V1G2,EIF2AK4,HARS,WDR46,SARS2,FAR SB,TCF19,GARS,SARS,YARS,WARS,HARS2,TARS2,MARS,D630004A14RIK,AAARS,EAARS2,ARID2,IARS2,PHF1,WARS2,DALRD3,VARS ,TAPBP,GTTF2H4,MARS2,4833403115RIK,EPRS,LST1,KHSRP,CARS2,LTB,AARS2,VARS2,IARS,HMG20B,DND1,CARS,ASTN1,FARSA, CREG2,ZNFX1,COL11A2,TPR,ZBTB9,TUBGCP6,SYNGAP1
GO:000865	0.270546	0	0	51	amino acid biosynthetic process	PSPH,SEPHS2,ASNS,PSAT1,ADI1,MTHFD1,MTRR,CDO1,ASNSD1,MAT2B,ASL,GOT1,DHFR,AK3,PRODH2,BHMT2,GOT2,BHMT,AL DH18A1,UPB1,BCAT1,MAT2A,SARDH,PYCR2,AGXT,PRODH,PHGDH,PYCRL,0610012D14RIK,PYCR1,SIRT7,4933437F05RIK,THNS L2,GLULD1,PLOD1,OTC,GLUL,CTH,BCAT2,NAGS,MTHFR,ALDH4A1,MAT1A,TOR3A,TAS1R2,CBS,PAH,ENOPH1,CORO2A,THNSL1, MTR
GO:004362	0.270529	0	0	84	cellular protein complex assembly	GRIK2,ARL2,CHRNA3,PICK1,NDUFS5,TMEM48,TFAM,PDGFC,SCO1,FKBP4,PSMG2,MIS12,NDUFS4,RANBP17,TCP1,NDUFS7,MU SK,MBD2,PSMG1,ATPAF2,CLEC2I,SMAD3,COX15,PEX13,IPO13,IPO7,ELP2,ADRB2,CDK5,NDUFS8,ADRM1,PAK1,NCK1,IPO11,CO X11,TBCA,COX18,XPO7,DOK7,PRLR,SURF1,SRC,SMAD4,TBCE,CENPF,TGFBF1,XPO6,CSE1L,EID2,ZFYVE9,TGFBF3,CENPE,NUBP1, XPO1,LRP4,FMOD,TAPBP,CD3E,DLG2,NCK2,GRIK5,ANLN,TAZ,PTK2,LONP1,NUP205,MAPK8IP2,TNPO1,IPO9,PTK2B,NUP98,CO X10,IPO4,MLH1,DVL1,TNPO2,KPNB1,IPO8,UNC13B,IPO5,PXN,AGRN,CACNA1A,SYNGAP1
GO:001605	0.248554	0	0	111	carbohydrate catabolic process	PDHB,FUT10,HIBADH,PGAM2,MDH1,LDHB,ENO3,FUT8,FUT9,PYGL,OGDHL,CTBS,G6PDX,PGAM1,BPGM,FUCA1,ENO2,GAA,PFK FB1,CHID1,H6PD,GNS,GLB1,DLAT,ECD,UEVLD,ALDOC,KHK,GUSB,CHIA,CHI3L4,LRRC16A,HYAL1,ALDOB,PGK2,CHI3L1,HYAL4,FU T4,GNPDA1,HYAL2,GBA2,HIF1A,PGD,INS2,GCK,NUDT5,SPACA3,PFKM,TALDO1,OVGP1,IDUA,OGDH,PKLR,TKTL1,3930401K13RI K,PGK1,ARNT,PDHA1,EG277333,LYG1,TPI1,PGLYRP3,HSD11B1,HK2,LDHAL6B,ADRA1B,LYVE1,6430537H07RIK,PKM2,LDHC,AD PGK,ALDOA,MDH2,PYGM,GAPDH,ALDOART2,TREH,MIF,PFKL,IGF1,FUT1,RPIA,CHIT1,PGLYRP4,MGAM,PFKP,ALDOART1,ENO1, PFKFB3,PGLYRP1,PDHA2,HKDC1,LDHA,G6PC,BAD,GPI1,HK1,CHI3L3,LYG2,FUT7,FUT2,TKT,HK3,MLXIPL,PYGB,PGLS,GAPDHS,AG L,AVPR1A,INSR,DHTKD1
GO:003016	0.246876	0	0	36	regulation of proteolysis	IFT52,GCLC,SERPINE2,RAB23,CLN3,CLN8,STUB1,DNAJC1,AURKAIP1,TIMP3,CFH,SERPINB7,CR1L,INS2,SERPINE1,SPINK5,SPINK1 2,KNG1,CLN6,PIK3R1,APOE,PLAUR,TIMP1,SERPINA5,SERPINB13,IFT88,SHH,CD46,TIMP2,CD59B,SERPINB10,AKT1,IDE,WFIKKN 1,LTBP4,EP300

Table S3A. Gene sets up-regulated by severe stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0006488	0.237813	0	0	140	protein amino acid glycosylation	ALG5,FUT10,DPAGT1,COG7,ALG8,ST3GAL4,POMGNT1,B3GALT5,FUT8,GALNT1,TUSC3,DPM1,C1GALT1,FUT9,PSEN1,DDOST,POU5F1,GALNT2,AIF1,GALNT13,MGAT1,ALG1,DAD1,B3GALT6,KRTCAP2,ST8SIA4,ST8SIA6,DAXX,DDR1,ST8SIA3,TSPAN8,MPDU1,B3GNT2,MGAT4A,POMT2,ST6GAL1,ST6GAL2,RPN2,MAN1B1,CD37,B3GALT4,GCNT1,TM4SF5,LRP2,STT3A,B3GALT1,MAGT1,MAN1C1,B3GALNT1,TM4SF4,DPM2,FUT4,ATP6V1G2,ALG3,EDEM2,WDR46,GALNT10,MGAT3,ALG6,POMT1,LIPA,MGAT4B,TCF19,SDF2,RPN1,B4GALT1,IL17A,GANAB,ST6GALNAC2,GALNT6,DOLPP1,GYPC,ST3GAL3,PRKCSH,GAL3ST1,TSPAN7,KEL,MAN2A1,GCNT3,COG3,PMM2,GALNT7,B3GALNT2,UGCGL1,ST6GALNAC6,PHF1,ST3GAL6,DPM3,B3GNT6,ST6GALNAC1,ALK,TAPBP,ABO,MGAT2,GTF2H4,LIPC,MAN1A2,LST1,B4GALNT2,STT3B,A4GNT,FUT1,ALG12,ST3GAL5,MGAT5,B3GNT8,LTB,B3GNT4,GCS1,GNPTG,FUT11,B3GNT7,ST3GAL2,ST8SIA1,ALG2,LARGE,ST6GALNAC3,COG2,ST6GALNAC4,ST8SIA5,FUT7,GALNT9,FUT2,TRAK2,TRAK1,B3GNT5,OGT,B3GALT2,UGCGL2,GALNT3,ST8SIA2,SEC1,COL11A2,ST6GALNAC5,B3GNT3,ST3GAL1,POFUT1,ZBTB9,LDLR,SYNGAP1
GO:0046488	0.235553	0	0	21	phosphatidylinositol metabolic process	PIP4K2A,IMPA1,PTPMT1,CDIPT,CD81,PI4K2A,PIK3C2A,PITPNC1,PIP5K1A,PI4KB,PIP4K2C,PIP5KL1,PDGFA,PIP5K1B,PIP4K2B,IHK3,PIP5K3,PDGFB,PIP5K1C,GALR2,PI4KA
GO:000640	0.23555	0	0	50	RNA catabolic process	EXOSC7,LSM2,AUH,PARN,DCPS,MAGOH,EIF4A3,XRN2,RNASEH2A,LSM7,LSM6,SMG7,RNASE6,RNH1,UPF2,RBM8A,SMG6,LSM5,RNPS1,PNPT1,UPF3B,SMG5,ZFP36L1,UPF3A,EXOSC10,ABCE1,DCP1B,MEX3D,ZFP36,PPP1R8,POP1,DEDD2,DCP1A,HNRNP,DOAS2,PAN3,ZHX2,ERN2,USP52,GSPT1,RNASEH1,MLH1,UPF1,ZFP36L2,PABPC4,HSPA1B,ISG20,DCP2,ZFP36L3,Z610207105RIK
GO:000910	0.234476	0	0	151	glycoprotein biosynthetic process	ALG5,FUT10,DPAGT1,COG7,ALG8,ST3GAL4,POMGNT1,B3GALT5,FUT8,GALNT1,TUSC3,DPM1,C1GALT1,FUT9,PSEN1,DDOST,POU5F1,GALNT2,BACE2,AIF1,GALNT13,MGAT1,ALG1,DAD1,B3GALT6,KRTCAP2,PAWR,ST8SIA4,ST8SIA6,DAXX,DDR1,HBEGF,ST8SIA3,TSPAN8,MPDU1,B3GNT2,MGAT4A,POMT2,AATF,ST6GAL1,ST6GAL2,RPN2,MAN1B1,CD37,B3GALT4,GCNT1,TM4SF5,LRP2,STT3A,B3GALT1,MAGT1,MAN1C1,B3GALNT1,TM4SF4,DPM2,FUT4,TNIP1,ATP6V1G2,ALG3,EDEM2,GAL3ST4,WDR46,GALNT10,MGAT3,ALG6,POMT1,LIPA,MGAT4B,TCF19,SDF2,RPN1,B4GALT1,IL17A,GANAB,ST6GALNAC2,GALNT6,DOLPP1,GYPC,ST3GAL3,PRKCSH,GAL3ST1,TSPAN7,FKRP,KEL,MAN2A1,GCNT3,COG3,PMM2,GALNT7,B3GALNT2,UGCGL1,ST6GALNAC6,PHF1,ST3GAL6,DPM3,B3GNT6,ST6GALNAC1,ALK,TAPBP,ABO,MGAT2,GTF2H4,LIPC,MAN1A2,LST1,B4GALNT2,STT3B,A4GNT,FUT1,ALG12,ST3GAL5,MGAT5,ATP7A,B3GNT8,LTB,B3GNT4,GCS1,GNPTG,FUT11,B3GNT7,ST3GAL2,ST8SIA1,ALG2,NECAB3,LARGE,ST6GALNAC3,COG2,PHLDA1,ST6GALNAC4,ST8SIA5,FUT7,GALNT9,FUT2,TRAK2,TRAK1,B3GNT5,OGT,B3GALT2,BCL2,UGCGL2,GALNT3,ST8SIA2,SEC1,COL11A2,ST6GALNAC5,B3GNT3,ST3GAL1,POFUT1,ZBTB9,LDLR,SYNGAP1
GO:000915	0.232511	0	0	21	purine ribonucleotide catabolic process	ATP5B,AMPD3,NUDT9,ENTPD1,ATP5A1,ENTPD2,ATP2A1,ATP1A1,ATP50,ATP5C1,OLA1,ATP5D,ATP5E,GMPR2,ERCC3,MYH7,ACL1,ATP1A2,ABCC6,MYH6,MYO9B
GO:004616	0.231645	0	0	82	alcohol catabolic process	PDHB,FUT10,HIBADH,PGAM2,MDH1,LDHB,ENO3,FUT8,FUT9,OGDHL,G6PDX,PGAM1,BPGM,ENO2,PFKFB1,H6PD,GLB1,DLAT,ECDC,UEVLD,ALDOC,MIOX,LRRC16A,ALDOB,PGK2,FUT4,HIF1A,PGD,INS2,GCK,NUDT5,PFKM,TALDO1,OGDH,PKLR,TKTL1,3930401K13RIK,PGK1,ARNT,PDHA1,EG277333,TP11,HSD11B1,HK2,LDHAL6B,ADH4,6430537H07RIK,PKM2,LDHC,ADPGK,ALDOA,MDH2,GAPDH,ALDOART2,GPD1L,MIF,PFKL,IGF1,FUT1,RPIA,ADH1,PFKP,ALDOART1,ENO1,PFKFB3,PDHA2,GPD1,ADH7,HKDC1,LDHA,BAD,GPI1,HK1,FUT7,FUT2,TKT,HK3,MLXIPL,PGLS,GAPDHS,INSR,DHTKD1
GO:000652	0.230913	0	0	273	amino acid metabolic process	ADC,HIBCH,PPAT,HIBADH,FARS2,DUS4L,GAD1,NFS1,AUH,TARSL2,NARS2,PSPH,PCBD1,6530401N04RIK,SEPHS2,HDC,ASNS,LARS2,AARSD1,PSAT1,ADI1,SCYE1,GSTZ1,MTHFD1,GAD2,MOXD1,BCKDHB,DDO,GCLC,POU5F1,TARS,DTD1,DARS,MTRR,GOT1L1,SHMT2,CDO1,GGH,AIF1,YARS2,ASNSD1,ARG2,PTS,CLN3,MAT2B,ASL,MCCC2,RARS2,QDPR,GOT1,DHFR,PTPLB,SLU7,HPD,CTNS,STRR,AK3,DAXX,AHXY,PRODH2,BHMT2,SLC22A17,PCCA,DDR1,BCKDHA,ASRGL1,GOT2,PARS2,KYNU,DLAT,INDO,BHMT,LARS,ALDH5A1,QARS,PLXNB2,DARS2,ALDH18A1,SLC7A4,GMPS,POLG2,RARS,HNRPLL,GCSH,TH2MAT2,GFPT2,B3GALT4,ACAD8,GLS2,PCCB,KARS,SLC7A2,ALDH6A1,UPB1,WDR92,COMT,BCAT1,NARS,ATP6V1G2,EIF2AK4,HARS,TYRP1,DDAH1,PEPD,SLC25A15,INDOL1,WDR46,MAT2A,SARS2,INS2,TYR,SARDH,FARSB,AASS,TCF19,ASPA,GCLM,GARS,DDT,GFPT1,PADI2,SARS,DBH,YARS,SLC7A9,PYCR2,WARS,HARS2,AGXT,TDO2,AADAT,3930401K13RIK,CTPS,PRODH,4930402E16RIK,SMS,TARS2,PHGDH,MARS,TPH1,PYCR1,SLC45A2,BCKDK,PADI4,SLC7A7,PDZD2,D630004A14RIK,AARS,OAT,0610012D14RIK,DDAH2,EARS2,FRRS1,SLC6A14,GCH1,ARID2,FPGS,PYCR1,GSS,SLC6A6,SIRT7,IARS2,CTPS2,PADI1,PHF1,4933437F05RIK,HPDL,SI,DCT,DMGDH,ACY1,WARS2,DALRD3,VARS,TAPBP,GTF2H4,MARS2,KMO,4833403115RIK,EPRS,LST1,ARG1,SLC3A1,KHSRP,ATG7,THNSL2,ACMSD,CARS2,GLULD1,PLOD1,BAA
GO:003355	0.227473	0	0	51	cellular response to stress	ASNS,EIF2AK3,PSEN1,CLN3,ATG16L1,EIF2B1,EIF2B3,EIF2B4,KRT20,ATG4C,PPP1R15B,ATG5,EIF2S1,ATG4D,WFS1,ATG12,ATG4B,EIF2B5,SREBF1,CTSD,EIF2AK4,HIF1A,INS2,BECN1,PCSK9,ALB,CARTPT,HMOX1,TRP53,MAP1LC3A,HFE,GLRX2,ARNT,ATG10,HSPA5,ATG9A,FADS1,NPC1,ANGPTL4,PRKCD,JUN,ATG4A,DDIT3,HRK,NUAK2,FOXA3,FRAP1,ATG9B,AVPR1A,EPAS1,GSK3B

Table S3A. Gene sets up-regulated by severe stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:000600	0.221834	0	0	67	glucose catabolic process	PDHB,HIBADH,PGAM2,MDH1,LDHB,ENO3,OGDHL,G6PDX,PGAM1,BPGM,ENO2,PFKFB1,H6PD,DLAT,ECD,UEVLD,ALDOC,LRR16A,ALDOB,PGK2,HIF1A,PGD,INS2,GCK,PFKM,TALDO1,OGDH,PKLR,TKTL1,3930401K13RIK,PGK1,ARNT,PDHA1,E6277333,TP11,HSD11B1,HK2,LDHAL6B,6430537H07RIK,PKM2,LDHC,ADPGK,ALDOA,MDH2,GAPDH,ALDOART2,MIF,PFKL,IGF1,RPIA,PFKP,ALDOART1,ENO1,PFKFB3,PDHA2,HKDC1,LDHA,BAD,GPI1,HK1,TKT,HK3,MLXIPL,PGLS,GAPDHS,INSR,DHTKD1
GO:004646	0.214493	0	0	122	membrane lipid biosynthetic process	PIGU,PIGH,IMPA1,PIGG,PCYT1A,FRAG1,PTDSS1,DPM1,CHPT1,PIGF,PIGA,AGPAT5,LYCAT,CEPT1,CDIPT,PGS1,HEXB,CD81,MBOA,T5,UGT8A,PIGK,AGPAT9,CLN8,FGF7,PHKA1,SMPD1,PI4K2A,ST8SIA6,PIK3C2A,SGMS2,UGCG,PIGX,ST8SIA3,PIGV,PBX2,SERINC1,LPGAT1,A4GALT,GPAM,PIGQ,PIGL,AYT1B,PIGW,ISYNA1,D5WSU178E,DPM2,DOLK,LASS5,SERINC5,LASS2,ETNK1,AGPAT3,AGPAT1,LASS3,PIGB,FABP5,PI4KB,SGMS1,PIGN,GAL3ST1,PLAUR,A530057A03RIK,PRKAA1,PIGP,FABP3,PIP4K2C,CREBL1,LPCAT2,PEMT,PGAP1,ST6GALNAC6,SMPD2,FADS1,DPM3,PIGS,CRLS1,ST6GALNAC1,GPA1,PIGY,AGPAT2,NOTCH4,SAMD8,PIGT,PLA2G4A,CDS2,SPHK2,LPCAT1,AGPAT4,C130090K23RIK,APOA1,ST3GAL5,PIGO,TAZ,PCYT2,PTDSS2,A3GALT2,PDGFA,CHKA,PIGC,LPCAT,PCYT1B,CDS1,ST8SIA1,SH3GLB1,PISD,SEMA6D,LARGE,LASS6,PIGM,BTNL7,LASS4,ST8SIA5,B4GALNT1,B3GNT5,PDGFB,GBGT1,PIGZ,DGKE,PI4KA,AGER,B4GALT6,PERLD1
GO:000690	0.211713	0	0	24	vesicle targeting	PSEN1,COPB1,COPE,COPB2,TMED2,COPG,ARCN1,AP1M2,LRMP,TMED10,COPZ1,ARF1,YKT6,WIPI1,SNAP29,EXOC4,ARFGAP1,COPA,NLGN1,SNAP23,SEPT5,MAP4K2,GBF1,PCLO
GO:000691	0.20343	0	0	34	autophagy	PSEN1,ATG3,CLN3,GABARAPL2,ATG16L1,ATG4C,GOPC,ATG5,ARSA,ATG4D,ATG12,LAMP1,ATG4B,CTSD,RAB24,MAP1LC3B,BECN1,1200002N14RIK,MAP1LC3A,ATG10,WIPI1,ARSB,ATG9A,NPC1,TMEM166,ATG7,ATG16L2,RGS19,ATG4A,ULK1,AMBRA1,FRAP1,ATG9B,IRGM
GO:001060	0.202909	0	0	184	posttranscriptional regulation of gene expression	PAIP2,COG7,ETF1,SRP9,1110005A23RIK,F2R,MAPK3,EIF4E,EIF2AK3,4930503E24RIK,SERBP1,RPS18,EIF4H,EIF1,CDK4,APOA2,MTRR,NANOS1,EIF3H,FBXO7,ANG3,EIF4B,EIF4A3,HRSP12,RBM3,IMPACT,CALCR,DAZL,SRP14,NGDN,SECISBP2,ANG,EIF2B1,EIF2B3,PPP1CA,EIF2B4,DNAJC1,NAPG,EIF3D,EIF3J,HBEGF,SEPSECS,PAIP1,MTIF3,PPP1R15B,PPARGC1A,EIF2S1,EIF3F,IGF2BP2,FMR1,MTIF2,HSPB1,EIF5B,DDX25,APTX,RHOA,EIF4E2,DDX1,MORC3,EIF3K,EIF2B5,EIF5,EEFSEC,MIF4G4,MAPK1,PTGFRN,SCAP,BOLL,EIF2B2,IL6,EIF2AK4,STX12,DGCR8,NCK1,PA2G4,EIF4A2,PUM2,EIF2A,ZFP36L1,EIF1B,TRSPAP1,GTPBP4,EIF3I,MTPN,EIF3C,EIF3G,MYD116,IREB2,TBRG1,TRMT6,PRKRIR,TIA1,APLP1,ELAVL1,QQ,TGFB1,EIF5A,MVK,MKNK1,SAMD4,PRG3,EIF4EBP1,ADAD1,PRKAA1,EIF3E,BZW1,MEX3D,ZFP36,PAIP2B,METAP1,BARHL2,AURKA,COG3,GATC,BZW2,CUGBP1,MTRF1,TNFRSF1B,APP,NDUF A13,IGF2BP1,EIF4EBP3,PABPC1,CDKN2A,NANOS2,APBB1,NCK2,EIF4G2,CPN2,HPS4,TSC1,HNRNPD,IGF1,F2,PEX6,EIF4EBP2,APOA1,MDM4,UCN,CD28,EIF2AK1,ISOC2B,PTEN,MKNK2,KRT7,PSTK,CPEB1,DIO2,ACO1,BCL3,MAPKAPK2,IGF2BP3,EIF4E3,IPO9,PTK2B,PUM1,A1CF,PRKCD,TNF,SND1,DICER1,CCDC88C,NCKAP1,EIF4G1,PDGFRB,UPF1,ZFP36L2,AKT1,BCL2,PRKDC,EIF2C1,CPEB2,APBB2,KRT17,BRF1,RBM38,PRKCA,NANOS3,APOBEC1,GCN1L1,ATXN2,VEGFA,EIF4G3,YBX2
GO:003244	0.20069	0	0	113	protein modification by small protein conjugation	NSMCE2,FBXO25,UBA3,SUZ12,RBX1,TSG101,FBXO32,GCLC,ATG3,FBXO3,SUMO1,SMURF1,SUMO3,FBXL21,MAP3K1,RNF217,SAE1,RBBP6,FBXL3,UBE2C,NEDD8,VHLH,STUB1,RNF2,PPIL2,UBE2V2,UBE2V1,ATG5,CUL5,RPS27A,BMI1,DZIP3,TRIM23,UBE2G1,UHRF2,SUMF1,CHFR,CDK5,SUMO2,KCMF1,MUL1,RFLL,PIAS3,FGFR3,ANAPC11,PIAS2,LNX1,SENP7,PARK2,FBXW11,GTPBP4,RNF144B,ERCC8,UBOX5,AMFR,HERC5,ATG10,BCL10,PCNP,WDSUB1,UBB,FBXO4,FBXL5,UBE2N,PRPF19,RNF11,FBXO11,CBX8,LRRK2,SIAH2,UBQLN1,NAE1,UBE3C,MGRN1,TSPAN17,PIAS4,BRCA1,VCP,RNF139,ATG7,DDB2,MIB2,TSC1,UBE2D1,CAND1,TRAF6,HDAC6,FBXO9,FBXW7,FBXO24,BARD1,WWP1,NHLRC1,GSPT1,RING1,NOSIP,SIAH1A,FBXO10,UBE4A,MDM2,LMO7,TRAF7,AKT1,RAB26,TRIP12,SOC57,BCL2,MYLIP,NEDD4L,UBE4B,CBL,HUWE1,BIRC6
GO:005102	0.193405	0	0	72	mRNA transport	NXT2,TMEM48,DDX19A,MAGOH,NUP43,NUP50,DDX39,RANBP17,MAGOH,NUPL2,SMG7,THOC3,NUP107,HNRNPA1,NUP37,NCBP2,FMR1,UPF2,DDX25,NUP35,G3BP2,RBM8A,THOC4,SMG6,NUP85,NUP153,UPF3B,SMG5,THOC1,NUP88,NUP62,XPO7,UPF3A,NUP133,FUSIP1,GLE1,NXF2,NUP54,NXF3,QK,EIF5A,THOC2,SEH1L,BAT1A,DDX19B,RAE1,NUP155,XPO1,NUPL1,NUP188,NUP210,LRRPRC,NXT1,SENP2,KHSRP,NUP205,MVP,NUP93,REFBP2,RANBP2,NXF1,NUP98,NUP160,TNKS,CASC3,HHEX,UPF1,HRB,NUP214,POM121,TPR,HUWE1
GO:003132	0.180377	0	0	207	regulation of cellular biosynthetic process	PAIP2,AGT,ETF1,SRP9,1110005A23RIK,F2R,MAPK3,EIF4E,EIF2AK3,4930503E24RIK,RPS18,EIF4H,EIF1,CDK4,NANOS1,EIF3H,ARPP19,GRM8,ANG3,GLA,EIF4B,EIF4A3,ARG2,HRSP12,GUCY1A3,IMPACT,DAZL,SRP14,NGDN,SECISBP2,ANG,EIF2B1,EIF2B3,PTHLH,PPP1CA,EGFR,EIF2B4,DNAJC1,EIF3D,EIF3J,HBEGF,GUCA1A,DRD1A,PTH,SEPSECS,PAIP1,MTIF3,PPP1R15B,PPARGC1A,EIF2S1,EIF3F,IGF2BP2,NR3C1,HRH1,FMR1,MTIF2,HSPB1,EIF5B,DDX25,BMP6,RHOA,EIF4E2,DDX1,EIF3K,EIF2B5,EIF5,EEFSEC,MIF4G4,MAPK1,ATP1A1,PTGFRN,LHCGR,SCAP,BOLL,IL10,EIF2B2,IL6,EIF2AK4,DDAH1,NCK1,PA2G4,HIF1A,GCK,EIF4A2,PUM2,EIF2A,ZFP36L1,ITGB2,EIF1B,TRSPAP1,EIF3I,GFPT1,MTPN,EIF3C,AOF2,EIF3G,MYD116,IREB2,TRMT6,LEP,PRKRIR,TIA1,APLP1,PTX3,ADIPOQ,QK,TGFB1,RXFP2,EIF5A,MVK,MKNK1,SAMD4,DYNLL1,ARNT,PRG3,APOE,EIF4EBP1,ADAD1,PRKAA1,EIF3E,BZW1,NPY2R,PAIP2B,GCHFR,METAP1,EDN1,BARHL2,ABCA1,GATC,BZW2,ARRB2,MTRF1,DRD5,EDNRA,NPR1,HSP90AA1,APP,BRCA1,NDUFA13,EINPP1,NPPC,IGF2BP1,PLA2G4A,EIF4EBP3,NANOS2,NCK2,EIF4G2,ARRB1,JAK2,TSC1,IGF1,F2,EIF4EBP2,CAV1,POU1F1,HNF4A,UCN,CD28,NOD2,EIF2AK1,C1QTNF2,MKNK2,PDZD3,KRT7,PSTK,CPEB1,DIO2,AGTR2,KLRK1,ACO1,BCL3,APOA5,IGF2BP3,EIF4E3,PTK2B,PUM1,TICAM1,TNF,TRERF1,RLN3,EIF4G1,PDGFRB,UPF1,AKT1,AVP,HSP90AB1,STK11,MLXIPL,EIF2C1,CPEB2,P2RX4,DYRK2,

Table S3A. Gene sets up-regulated by severe stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0043088	0.174964	0	0	197	negative regulation of catalytic activity	XIAP,PSMB5,BUB3,GPS1,PSMD10,PSMB2,HRH3,LEPROT,PSMA6,GRM4,PSEN1,RGS4,GPX1,PPP2CA,APOA2,CDKN1A,GRM8,PSMA2,CDC23,GLA,ARG2,HERPUD1,PSMF1,PTPRC,CLN3,PSMD12,PTMA,CLN8,GALR1,UBE2C,PSMA5,PRKRIP1,HBXIP,ADORA2A,ATPIF1,PSMB4,PSMC2,PSMD9,PSMA3,PRKCZ,PPP2R4,PSMB6,DRD1A,PKIG,PSMD13,PSMD5,DUSP16,FBXO5,PSMC6,PSMA4,PSMB7,PSMC4,PSMB1,PSMC5,HEXIM2,PSME2,PSMA1,HEXIM1,PSME1,PSMD14,HSPA1A,PDCC4,PSMD8,SPRED1,EDNRB,GNAI3,PSMB3,FABP4,CDC26,UBE2E1,ANAPC11,ANAPC7,INS2,PSMD6,MAD2L1,OAS1D,SNX6,GADD45G,NUP62,PSMD11,TNNT2,TARB2,PCSK9,PAK2,DUSP22,PSMD4,P2RY12,GRM7,PSMD7,DNAJB6,KNG1,SIRT1,ANGPTL3,MEN1,LAX1,PSMA7,PSMC3,NOS1,TNNI3,CDC20,ANAPC2,PSMB9,ANAPC10,APOE,CDC16,UBB,LATS1,DUSP2,CASP3,PSMC1,PKIA,GCHFR,CDKN1B,GALR3,PSMD1,MBIP,ANAPC4,BUB1B,GABBR1,DRD5,HIPK3,ADRA2A,ANAPC5,PSMB8,PKIB,GNAI2,CAV3,CAST,PSMD3,GRM3,CFLAR,ANGPTL4,DUSP8,IL7,CDKN2D,CDKN2A,PSME3,PPP2R1A,GPS2,DUSP9,UBE2D1,LTB4R2,CAND1,APOA1,CAV1,GADD45A,CCR2,RGS3,NOS3,ATP7A,DHCR24,SPRY1,GCKR,CDC27,BIRCS,CBLC,NR4A1,SH3BP5,LEPR,THY1,DUSP19,SPRED2,NOSIP,PSMD2,SPRY2,PSMB10,PIF1,LATS2,ANAPC1,PPARG,NF2,CDK5RAP1,FZR1,PTPN6,TRIB3,TSC2,HMGCN,NPR3,HSPA1B,NEIL1,GADD45B,SPRY4,SORT1,YWHAG,TRIB1,TRP73,SFN,GRM2,APC,NF1,PALM,APOC3,PRKCA,SPRED3,GABBR2,RB1,DUSP6
GO:0030388	0.174705	0	0	72	phosphoinositide metabolic process	PIGU,PIGH,PIP4K2A,IMPA1,PTPMT1,PIGG,FRAG1,PIK3C3,DPM1,PIGV,PIGA,CDIPT,CD81,PIGK,PI4K2A,PIK3C2A,PIGX,PITPNC1,PIGV,PIGQ,IHPK1,PIGL,PIGW,DPM2,PIK3CG,SACM1L,PIP5K1A,PIGB,NUDT4,PI4KB,IHPK2,PIK3R1,PIGN,PIK3C2G,PLAUR,PIGP,PITPNM3,PLCB1,PIP4K2C,GPLD1,PGAP1,DPM3,PIGS,GPA1,PIGY,PIGT,PIP5K1L,C130090K23RIK,PIK3CA,PIGO,PDGFA,PIK3CB,PTEN,PIGC,PLCD4,PIP5K1B,SEMA6D,PIP4K2B,PIGM,IHPK3,PIP5K3,PDGFB,PIP5K1C,PIGZ,GALR2,IPMK,PLCH2,SYNJ1,PIK3CD,PI4KA,PELRLD1,PIK3C2B
GO:0017034	0.159469	0	0	138	protein import	TIMM8B,MBTPS1,NXT2,RBM22,PEX7,PPIH,TOMM22,PTTG1IP,KPNA1,TIMM8A1,AIP,F2R,MAPK3,ARNTL,PEX10,DNAJC19,TIMM9,RANBP17,FYB,PEX26,PRKCC,NOL5,PRICKLE1,PRDX1,RPL23,PKIG,EDAR,TOB1,HSPD1,TOMM20,GLI3,SMAD3,MXI1,FAF1,RHOA,G3BP2,PEX13,PML,MAPK1,FGF9,NFKBIA,IPO13,IPO7,KPNA2,RAN,IL10,KPNA3,PDIA3,NLRP3,IPO11,GRPEL1,IKKBG,TIMM10,CFL1,IL20,TMCO6,XPO7,CRY2,TGFB3,NXF7,NOLC1,FGF2,SIRT1,POLA2,PPP1R10,TRP53,TGFB1,MCM3AP,CEP57,TACC3,TIMM8A2,PEX3,EDA,XPO6,CSE1L,ZFYVE9,PKIA,KPNA4,CD27,ABRA,PRL,XPO1,TRIP6,PEX14,NUTF2,MDF1,TIMM13,PPP3CA,NDUFA13,AK2,KPNA6,F2,PEX6,PEX12,SHH,SNUPN,HNF4A,RPAIN,SUFU,SIX3,GCKR,NUP205,CDH1,NCKIPSD,PEX1,AGTR2,TNPO1,BCL3,NFKBIE,IPO9,FXC1,RANBP2,TNFSF14,TNF,UACA,SMO,NUP98,PEX16,CBLB,NFKBIL1,SIX2,IPO4,AKT1,NUP214,TSC2,TRPS1,TNPO2,KPNB1,FGF10,IPO8,BCL6,NF1,IPO5,TPR,FLNA,RERE,SPNB2,HTT
GO:0016051	0.156853	0	0	53	vesicle organization and biogenesis	SRGN,PSEN1,COPB1,COPE,COPB2,ATG16L1,PRKCI,ZDHHC15,COPG,ARCN1,ATG4C,ATG5,FBXO5,ATG4D,HINT1,ATG12,ATG4B,ZFYVE16,COPZ1,CTSD,SHROOM2,ARF1,TYRP1,LYST,P2RX7,CALY,BECN1,MAP1LC3A,CNO,EPS15,A,SYP,AP2S1,ABCA1,ATG9A,RAB3A,PICALM,ARFGAP1,CAV1,COPA,CAV2,STXBP1,ATG4A,DLG4,CADPS,ALS2,BCL2,SNAP91,ATG9B,SORT1,HIP1,GBF1,UNC13A
GO:0016561	0.144447	0	0	102	protein ubiquitination	NSMCE2,FBXO25,SUZ12,RBX1,TSG101,FBXO32,GCLC,ATG3,FBXO3,SMURF1,FBXL21,MAP3K1,RNF217,SAE1,RBBP6,FBXL3,UBE2C,VHLH,STUB1,RNF2,PPIL2,UBE2V2,UBE2V1,ATG5,CUL5,RPS27A,BMI1,DZIP3,TRIM23,UBE2G1,UHRF2,SUMF1,CHFR,CDK5,KCMF1,MUL1,RFFL,FGFR3,ANAPC11,LNX1,PARK2,FBXW11,GTPBP4,RNF144B,ERCC8,UBOX5,AMFR,HERC5,BCL10,PCNP,WDSUB1,UBB,FBXO4,FBXL5,UBE2N,PRPF19,RNF11,FBXO11,CBX8,LRRK2,SHAH2,UBQLN1,UBE3C,MGRN1,TSPAN17,BRCA1,VCP,RNF139,ATG7,DDDB2,MIB2,TSC1,UBE2D1,CAND1,TRAF6,HDAC6,FBXO9,FBXW7,FBXO24,BARD1,WWP1,NHLRC1,GSPT1,RING1,NOSIP,SIAH1A,FBXO10,UBE4A,MDM2,LMO7,TRAF7,AKT1,RAB26,TRIP12,SOC5,BCL2,MYLIP,NEDD4L,UBE4B,CBL,HUWE1,BIRC6
GO:0006651	0.141477	0	0	104	glycerophospholipid metabolic process	PIGU,PIGH,PIP4K2A,IMPA1,PTPMT1,PIGG,PCYT1A,FRAG1,PTDSS1,PIK3C3,DPM1,CHPT1,PIGF,PIGA,SERINC3,CDIPT,CD81,PIGK,FGF7,PHKA1,PI4K2A,PIK3C2A,LRAT,PIGX,PITPNC1,PIGV,SERINC1,ALDH5A1,PLA1A,PIGQ,IHPK1,PIGL,PIGW,DPM2,SERINC5,PIK3CG,SACM1L,AGPAT1,PIP5K1A,PIGB,NUDT4,LYPLA3,FABP5,PI4KB,IHPK2,PIK3R1,PIGN,PIK3C2G,PLAUR,PIGP,PITPNM3,SERINC2,FABP3,PLCB1,PIP4K2C,PEMT,GPLD1,PGAP1,DPM3,PIGS,GPA1,PIGY,AGPAT2,LIPC,PIGT,PIP5K1L,C130090K23RIK,PIK3CA,APOA1,PIGO,PLA2G1B,TAZ,PTDSS2,PNPLA7,PDGFA,PIK3CB,APOA4,PTEN,PLA2G4B,CHKA,PIGC,LCAT,PIGA,SNAP91,PCYT1B,PLA2G4C,PLCD4,PIP5K1B,SH3GLB1,SEMA6D,PIP4K2B,PIGM,IHPK3,PIP5K3,PDGFB,PIP5K1C,PIGZ,GALR2,IPMK,PLCH2,SYNJ1,PIK3CD,PI4KA,PELRLD1,PIK3C2B

Table S3A. Gene sets up-regulated by severe stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0006644	0.105813	0	0	243	membrane lipid metabolic process	B4GALT4,PPAP2A,PIGU,PIGH,PIP4K2A,IMPA1,PTPMT1,PIGG,PCYT1A,TEX2,FRAG1,PTDSS1,PIK3C3,DPM1,CHPT1,PIGF,HEXA,PP T1,PIGA,PPP2CA,AGPAT5,LYCAT,CEPT1,SERINC3,GLA,CDIPT,PGS1,HEXB,CD81,MBOAT5,UGT8A,CLN3,PIGK,AGPAT9,GPX4,CLN 8,FGF7,PHKA1,SMPDL3B,SMPD1,GM2A,PHCA,ASAH1,PI4K2A,ST8SIA6,ITGB8,PIK3C2A,LRAT,SGMS2,SMPD3,UGCG,PIGX,PITPN C1,ST8SIA3,PIGV,PBX2,SGPP1,ASAH2,SERINC1,LPGAT1,ALDH5A1,PLA1A,PPAP2B,A4GALT,MAN1B1,GPAM,PIGQ,IHPK1,PIGL,PL A2G2A,AYTL1B,PIGW,JSYNA1,DSWSU178E,DPM2,DOLK,PLA2G2C,GBA2,D2HGDH,PRDX6,LASS5,GALC,SERINC5,PIK3CG,PLA2G 2D,LASS2,SACM1L,ETNK1,PCSK9,AGPAT3,AGPAT1,PLCE1,NSMAF,LASS3,PIP5K1A,PIGB,ANGPTL3,NUDT4,CLN6,LYPLA3,FABP5, PI4KB,SMPDL3A,HMOX1,IHPK2,SGMS1,PIK3R1,GRN,PIGN,APOM,GAL3ST1,ENPP7,SPTLC1,ASAH3L,SGPL1,PIK3C2G,PLAUR,AS3 0057A03RIK,PLCB3,PRKAA1,PIGP,PLA2G12B,PITPNM3,SERINC2,FABP3,PLCB1,PIP4K2C,CREBL1,LPCAT2,PEMT,GPLD1,PLA2G4F ,PSAP,PGAP1,ST6GALNAC6,SMPD2,FADS1,ST3GAL6,DPM3,GBA,PIGS,CRLS1,PLA2G6,ST6GALNAC1,OC90,CERK,GPA1,PIGY,AP OC2,SFTPB,AGPAT2,LIPC,NOTCH4,SAMD8,PIGT,PLA2G4A,PSAPL1,PLA2G3,PLA2G4D,PLA2G5,CDS2,SPHK2,PLA2G12A,PPP2R1A ,PIP5KL1,LPCAT1,ARV1,PLAA,AGPAT4,C130090K23RIK,PIK3CA,APOA1,SNCA,PLA2G2F,ST3GAL5,PIGO,PLA2G1B,TAZ,PCYT2,PAF RNF7,XIAP,GLO1,DNAJB9,IL1A,BIRC2,TXNDC1,BNIP1,FRAG1,SPP1,TCF7L2,PSEN1,IL31RA,GCLC,G6PDX,BRE,SERBP1,GPX1,TRIA P1,CFDP1,CDKN1A,SMAD1,RELA,SEMA4D,TAX1BP1,ANXA1,CDC2A,ANXA5,PTMA,DAD1,HBXIP,SOD2,VNN1,SLC9A1,HSP90B1, NME5,HDAC1,BCL2L1,NPM1,PRKCZ,PIM2,CDH13,STAR,ADAM17,TSC22D3,HSPA9,NPY5R,BFAR,TGFA,HSPD1,QARS,IL2,AATF,A VEN,NFKB1,NR3C1,HELLS,HSPB1,SYVN1,HSPA1A,CLU,STAMBP,HDAC3,RTKN,TXNDC5,STAT5B,CBX4,TPT1,SFRP1,CRYAA,IL3,IL1 0,MPO,FOXO1,BNIP3L,BAG4,AMIGO2,ZC3HC1,CFL1,POLB,BECN1,SKP2,EEF1A2,GSTP1,PAX7,PRLR,PRDX2,BAG1,SOD1,FAIM2,B CL2L2,SERPINB2,ARHGDI2,GDNF,ALS2CR2,CIAPIN1,HMOX1,CD40LG,TNFSF13B,PIK3R1,YWHAZ,TNFSF18,NOTCH2,ESR2,SERPI NB9,TRAF2,IL2RB,APOE,BTG2,PRKAA1,CASP2,HTATIP2,BNIP2,BCL2L10,CD27,DDAH2,CCL2,PEA15A,ALOX12,SGK3,ESR1,CRYAB ,FAIM,HMGB1,BIRC3,HIPK3,FOXC2,NOL3,PPID,MKL1,NME6,API5,MCL1,CFLAR,GFRAL,TNFAIP8,EEF1A1,IL7,CDKN2D,FAS,IGF1R ,SPHK2,IGF1,PIK3CA,SNCA,CAV1,PRNP,BDNF,DHCR24,CD28,ERBB4,BIRC5,PROK2,CEBPB,PAFAH2,ADM,FAIM3,MYC,MAPK8IP2, ALOX15,ANGPT1,SOCS3,RASA1,TBX3,TNFRSF18,OPA1,ANXA4,PTK2B,ATF5,FOXC1,TNF,ETS1,SH3GLB1,IER3,MALT1,HGF,STAT5 A,MAPK8IP1,CSF2,AKT1S1,GNRH1,NAIP2,PIK3R2,SNAI2,BRAF,PDGFRB,TRP63,AKT1,BAG3,HRK,BNIP3,GNAQ,BCL2,PAK7,TWIST
GO:0006914	0.102728	0	0	217	anti-apoptosis	PSIP1,TLR7,KPNA1,C1QBP,WDR48,CCR5,MAPK3,EIF4E,PDCL3,SLC25A5,TSG101,ATP6V1H,GPX1,EIF4H,COPB1,APOA2,BTRC,CD 4,CEACAM2,CCDC86,CD81,SMARCB1,GUCY1A3,VDAC1,SLC20A2,TBP,SIVA1,CEACAM1,IFIH1,PSMC2,HS3ST5,EIF3M,TLR3,ATP6 VOC,IVNS1ABP,MAGI3,VAPB,RRAGA,CDC25C,SCARB1,TLR4,KIN,HSPD1,CREB3,CUL5,IFNB1,VCAM1,SGTA,CD86,LTBR,THEM4,IS G15,SMAD3,CD200R1,DERL1,VIM,COPS6,PML,MAPK1,NFKBIA,IPO7,DDX3X,KPNA2,RAN,CXCR7,ITGAV,SF3B2,VPRBP,TNIP1,SL AMF1,FKBP8,TBK1,UBN1,SLC25A4,DLG1,PPIA,BNIP3L,CCR3,KCTD5,EIF4A2,IKBK,POLR2E,USP7,RALA,WAPAL,PRMT6,GADD45 GIP1,TARBP2,RNF216,FYN,ACE2,LYN,PAK2,ALB,SUV39H1,IL2RG,SP1,WWP2,UCLL1,HCK,SRC,STAT1,TLR9,CEBPA,CCNT1,SIRT1, TLR1,EPOR,PSMC3,ITGB1,SYK,RXRA,TGFB1,PIK3R1,UBE2I,MLF1IP,IL2RB,CLDN1,RNGTT,NFX1,FADD,ABCE1,KRT18,YWHAE,UBE 3A,HTATIP2,PVRL1,RTN3,RAD23A,CXCR4,SYNCRIP,BANF1,MFGE8,MDFIC,C9,XPO1,GTf2B,CD247,CREB1,NEDD4,RCOR1,ITCH,F CGR2B,MAP3K5,TLR2,VAC14,KRT19,GRB2,AP1G2,FBLN1,PDCC6IP,CFLAR,STAT3,PIAS4,HAVCR1,PACS1,PVR,CCR2,CRTC2,UNG, CD46,CD93,DDB1,LCK,NOD2,EIF2AK2,PLCG1,ATF7IP,ACOT8,TLR6,AMBIP,CCNT2,KRT7,CARM1,WWP1,MYC,CRTC1,TNPO1,ITGB 3,TNFRSF1A,ANPEP,KRT8,KDR,FDPS,HPX,JMJD2A,TBC1D20,SNDD1,GPX2,NXF1,NUP98,MDM2,ITGA5,CENPA,PRF1,CLDN4,ZYX,EI
GO:0044414	0.093323	0	0	225	interspecies interaction between organisms	PES1,TMEM48,CYCS,PPT1,EMD,ZFP354A,UNC84A,SEP15,MOAP1,TPD52L1,DFFB,ZMPSTE24,DULLARD,RRN3,PML,TOP2A,TMP O,ATXN7,H1FNT,CIDEA,NOLC1,SOD1,AIFM1,BAX,TNP1,CASP3,DFFA,DNASE1L3,UNC84B,NDUFA13,CDKN2A,DEDD2,SYCP3,FO XL2,MYC,LMNA,DNASE1,TSSK6,WBP2NL,CECR2,NUP98,ACIN1,PRM2,SYNE1,BNIP3,PRM1,CD24A,NUMA1,BIRC7,CDAN1,POM1 21
GO:0006991	0.082788	0	0	51	nuclear organization and biogenesis	

Table S3B. Gene sets down-regulated by severe stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0001578	-1.84065	0	0	13	microtubule bundle formation	OFD1,BBS2,UBE2B,TPPP,NEURL,GTRGEO22,PSRC1,MTAP1S,MTAP2,MARK4,CLASP1,MTAP1B,NAV1
GO:0007016	-1.74121	0	0	9	cytoskeletal anchoring at plasma membrane	TLN2,EZR,DMD,GYPA,FLNB,TLN1,ANK3,SPN4,SHANK1
GO:0016079	-1.04183	0	0	30	synaptic vesicle exocytosis	SNAPIN,PLDN,PSEN1,SYT2,SYT3,STX7,CPLX3,SNAP25,RAB3A,LPHN1,STX3,TRIM9,GRIK5,CPLX1,NLGN1,STX4A,STXB2,CPLX2,S EPT5,APBA2,UNC13B,SYT1,SNPH,STX1A,APBA1,VAMP2,DOC2A,SPNB3,RIMS1,PCLO
GO:0030516	-1.00082	0	0	19	regulation of axon extension	CDH4,SEMA3A,NTN1,SEMA3F,RNF6,APOE,TNFRSF12A,BARHL2,LIMK1,TTL,DPYSL2,SEMA4F,RTN4,MAPT,NRCAM,NGF,NRP1,N TRK3,PLXNA3
GO:0042403	-0.98071	0	0	16	thyroid hormone metabolic process	SULT1B1,TTR,SLC5A5,DUOX2,DIO3,DIO1,MED1,TG,CGA,DIO2,TPO,FOXE1,KCNJ6,CACNA1A,SLCO4A1,RELN
GO:0016573	-0.94715	0	0	17	histone acetylation	PPARGC1A,BMI1,SET,MYST1,HTATIP,CPA4,MBD3,MSX3,PCAF,METTL8,FOX3,MYST3,PCGF2,MYST4,CREBBP,TRRAP,EP300
GO:0021766	-0.84135	0	0	17	hippocampus development	BBS4,MKKS,BBS2,ID4,CDK5,YWHAE,CASP3,BBS1,TSC1,PAFAH1B1,LEF1,TRP73,EMX2,ZEB2,LRP8,WNT3A,PLXNA3
GO:0050771	-0.83676	0	0	20	negative regulation of axonogenesis	SPP1,PSEN1,SEMA3A,NTN1,SEMA3F,MBP,RNF6,RUFY3,ULK2,PTK2,THY1,RTN4R,ULK1,SEMA4F,RTN4,CLK8,CSPG4,NRP1,PLXN A3,SYNGAP1
GO:0018409	-0.8233	0	0	10	peptide or protein amino-terminal blocking	ARD1,NAT13,HHATL,NMT1,NARG1,NARG1L,MAP6D1,NMT2,CREBBP,EP300
GO:0018205	-0.81099	0	0	10	peptidyl-lysine modification	DOHH,DHPS,EIF5A,EIF5A2,PLOD1,ATP7A,IVL,TGM2,CREBBP,EP300
GO:0048489	-0.80365	0	0	51	synaptic vesicle transport	SNAPIN,PLDN,PSEN1,SYT2,ZDHHC15,SYT3,CDK5,LIN7A,EEA1,STX7,CPLX3,SYP,CTNNB1,SNAP25,RAB3A,DNM2,LPHN1,STX3,SN CA,AMPH,TRIM9,GRIK5,SYT4,CPLX1,NLGN1,DEPND1A,MYLK2,STXB1,STX4A,STXB2,CPLX2,DLG4,SEPT5,BIN1,APBA2,SH3GL2 ,SLC18A2,CD24A,UNC13B,SYNJ1,SYT1,SNPH,STX1A,APBA1,ITSN1,VAMP2,DOC2A,SPNB3,UNC13A,RIMS1,PCLO
GO:0021795	-0.7981	0	0	13	cerebral cortex cell migration	PSEN1,PEX13,LHX6,CDK5,RAC1,POU3F2,PEX5,ARX,PAFAH1B1,POU3F3,DAB1,LRP8,RELN
GO:0043488	-0.79372	0	0	14	regulation of mRNA stability	SERBP1,CALCR,PAIP1,ZFP36L1,ELAVL1,ZFP36,PABPC1,HNRNP,MAPKAPK2,ZFP36L2,BRF1,APOBEC1,VEGFA,YBX2
GO:0007628	-0.79081	0	0	24	adult walking behavior	GLRB,GLRA1,HEXA,KLHL1,UCHL3,DRD2,CLN8,TRH,DRD1A,EFNB3,SCN1A,HTRA2,UCHL1,CHAT,ATG7,CACNB4,FXN,PCDH15,KCN MA1,CHD7,SCN8A,EPHA4,CACNA1A,CACNA1C
GO:0043113	-0.78335	0	0	14	receptor clustering	GRIK2,PICK1,MUSK,CLEC21,CDK5,PAK1,DOK7,LRP4,DLG2,GRIK5,DVL1,AGRN,CACNA1A,SYNGAP1
GO:0050770	-0.74851	0	0	51	regulation of axonogenesis	ACHE,SPP1,PSEN1,SEMA4D,CDH4,SEMA3A,NTN1,SEMA3F,MBP,PLXNB2,RNF6,LRRC4C,ROBO2,POU3F2,WNT7A,RUFY3,APOE, TNFRSF12A,NEFL,BARHL2,PLXNB1,ULK2,MIF,EFNA1,PTK2,THY1,CDH2,LIMK1,AMIGO1,TTL,NEFM,METRN,RTN4R,DPYSL2,ULK1 ,TIAM1,SEMA4F,RTN4,CLK8,CSPG4,MAPT,NRCAM,NGF,EPHB2,ROBO1,NRP1,SLIT2,NTRK3,CACNA1A,PLXNA3,SYNGAP1
GO:0021885	-0.74148	0	0	16	forebrain cell migration	PSEN1,DRD2,DRD1A,PEX13,LHX6,CDK5,RAC1,POU3F2,PEX5,ARX,PAFAH1B1,POU3F3,DAB1,EMX2,LRP8,RELN
GO:0048675	-0.73554	0	0	30	axon extension	NDN,CDH4,SEMA3A,NTN1,SEMA3F,RNF6,CDK5,CDK5R1,APOE,TNFRSF12A,BARHL2,ULK2,LAMB2,DCLK1,POU4F2,LIMK1,TTL,D PYSL2,CYFIP1,ULK1,SEMA4F,RTN4,POU4F3,MAPT,NRCAM,NGF,DCX,NRP1,NTRK3,PLXNA3
GO:0017157	-0.71009	0	0	37	regulation of exocytosis	POU5F1,FCER1G,RAPGEF4,RAB27B,PRAM1,MS4A2,RAB3B,CDK5,EXOC2,FEZ2,B4GALT1,FGF2,HMOX1,SYK,FCER1A,SYCN,TRPV 6,RAB3A,RAB3D,RPH3AL,RAB3C,TRIM9,SYT4,FREQ,TRAF7,SEPT5,RAB26,CADPS,CADPS2,PRKCA,SYT1,STX1A,VAMP2,SPNB3,CA CNA1A,MYO5A,PCLO
GO:0021543	-0.64195	0	0	37	pallium development	BBS4,TACC1,PSEN1,MKKS,BBS2,PAX6,ID4,PEX13,LHX6,CDK5,RAC1,POU3F2,PEX5,ARX,TACC3,YWHAE,CASP3,BBS1,NR2E1,ATG 7,TSC1,PAFAH1B1,CCDC100,AHSG,LEF1,TACC2,FGF8,POU3F3,DAB1,TRP73,NF1,EMX2,ZEB2,LRP8,WNT3A,PLXNA3,RELN
GO:0043487	-0.64024	0	0	16	regulation of RNA stability	SERBP1,CALCR,PAIP1,ZFP36L1,ELAVL1,MEX3D,ZFP36,TNFRSF1B,PABPC1,HNRNP,MAPKAPK2,ZFP36L2,BRF1,APOBEC1,VEGFA ,YBX2
GO:0016358	-0.63484	0	0	55	dendrite development	MCF2,BBS4,ACHE,CHRNA3,KLHL1,SMAD1,IGSF9,CHRN2,HPRT1,LZTS1,TRAPPC4,PSCD2,SGK1,RHOA,CIT,CDK5,PAK1,RAC1,NT RK2,CACNA1F,MYO6,KNDC1,ABI2,YWHAH,CHAT,BBS1,SCARF1,MT3,APP,ARF6,LST1,MECP2,GHRL,DCLK1,BDNF,ATP7A,SS18L1, PRKG1,TLX2,DVL1,PPP1R9B,PTPRF,FEZF2,GRIN3A,DBN1,DCX,SIPA1L1,MTAP2,NRP1,KALRN,CACNA1A,KLF7,MTAP1B,CELSR2,S YNGAP1
GO:0030252	-0.61733	0	0	11	growth hormone secretion	DRD2,PTPN11,SNAP25,GAL,KISS1,GHRL,GHRHR,GHSR,GHRH,LTBP4,CACNA1C
GO:0031365	-0.61374	0	0	12	N-terminal protein amino acid modification	ARD1,NAT13,HHATL,NMT1,NARG1,METAP2,NARG1L,MAP6D1,METAP1,NMT2,CREBBP,EP300
GO:0045109	-0.61279	0	0	12	intermediate filament organization	KRT9,KRT20,KRT6B,DNAJB6,NEFL,KRT25,KRT6A,NEFM,HRB,KRT17,NEFH,TCHH
GO:0007632	-0.55682	0	0	33	visual behavior	DRD2,PDE1B,CHRN2,DRD1A,ADAM2,SGK1,CDK5,DRD3,NLGN3,DYNLRB1,DBH,ATXN1,ADRA1B,DRD5,GRIN1,APP,NPHP1,APB B1,KRAS,GHRL,NRAS,RIC8,ATP1A2,CRHR1,NPHP4,HMGCR,KIT,NF1,GRIN2A,ATP1A3,HTT,CACNA1C,SYNGAP1
GO:0021533	-0.55372	0	0	14	cell differentiation in hindbrain	RORA,LDB1,MTPN,WNT7A,LHX5,KNDC1,ATP7A,PHOX2B,ATP2B2,AGTPBP1,ULK1,FOXA2,LHX1,CACNA1A
GO:0006473	-0.54429	0	0	24	protein amino acid acetylation	HAT1,ARD1,NAT13,PPARGC1A,NARG1,BMI1,NARG1L,SET,MYST1,HTATIP,CPA4,MBD3,MSX3,PCAF,ING4,METTL8,ING5,FOX3, MYST3,PCGF2,MYST4,CREBBP,TRRAP,EP300

Table S3B. Gene sets down-regulated by severe stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0050885	-0.54388	0	0	35	neuromuscular process controlling balance	HEXA,GAA,HEXB,CLN3,SOX2,CLN8,GM2A,ADCY5,APLP2,NBN,TPP1,CLIC5,GRIN2C,NEFL,RAC3,CDH23,APP,POU4F1,POU4F2,PAFAH1B1,CLRN1,NKX6-2,USH1C,ATP2B2,PUNC,MYH10,MYO7A,POU4F3,USH1G,FOXSI1,PCDH15,KCNMA1,HMX3,CACNA1A,MYO5A
GO:0045429	-0.54158	0	0	14	positive regulation of nitric oxide biosynthetic process	EGFR,HRH1,DDAH1,ITGB2,PTX3,HSP90AA1,JAK2,AGTR2,KLRK1,TICAM1,HSP90AB1,P2RX4,INSR,ICAM1
GO:0045104	-0.53503	0	0	22	intermediate filament cytoskeleton organization and biogenesis	KRT9,CLN8,VP554,ERBB2IP,KRT20,KRT6B,DNAJB6,SOD1,NDEL1,NEFL,KRT25,KRT16,KRT6A,PRPH,NEFM,INA,HRB,RGNEF,KRT17,NEFH,TCHH,DST
GO:0048638	-0.53131	0	0	16	regulation of developmental growth	SPP1,MUSK,COL4A4,ADRB2,MSTN,DLG1,UBB,RPS6KB1,TGFBR2,MIF,HOPX,P2RX5,KLK8,INSR,AGRN,NTRK3
GO:0001756	-0.51883	0	0	33	somitogenesis	DLL3,PSEN1,AXIN2,SFRP2,MEOX1,ABI1,SFRP1,RIPPLY2,RIPPLY1,GCN5L2,IFITM1,PCDH8,MYF5,T,MEOX2,MESP2,PSEN2,PAX1,MYF6,VBX18,HES7,DLL1,MSGN1,LEF1,NCKAP1,PRKDC,MIB1,POFUT1,ZEB2,ROR2,WNT3A,ATM,EP300
GO:0007172	-0.5151	0	0	22	signal complex assembly	GRIK2,PICK1,MUSK,CLEC2I,CDK5,PAK1,NCK1,DOK7,SRC,LRP4,CD3E,DLG2,NCK2,GRIK5,PTK2,MAPK8IP2,PTK2B,DVL1,PXN,AGRN,CACNA1A,SYNGAP1
GO:0007009	-0.50608	0	0	13	plasma membrane organization and biogenesis	A4GALT,SOD1,PLSCR2,PLSCR4,CAV3,S100A9,DYSF,PLSCR1,SYT7,MYH10,PLSCR3,MYH2,AGRN
GO:0001704	-0.50564	0	0	42	formation of primary germ layer	POU5F1,BMPR1A,SMAD1,TRIM15,FGFR2,BMP4,PRKACA,SMAD3,PRKAR1A,SMAD2,ECSIT,EXT2,TWSG1,MIXL1,WNT3,MESP1,CTNNA1,FOXC2,BMP7,ACVR1,TXNRD1,EOMES,HNF1A,KLF4,FOXC1,LEF1,NF2,NCKAP1,EYA2,TLX2,HAND1,NANOG,FOXA2,CHRD,TBX6,LHX1,BMPR2,MACF1,SLIT2,WNT3A,NR4A3,HTT
GO:0051016	-0.50121	0	0	26	barbed-end actin filament capping	GSN,CAPZB,WNT2,SCIN,RDX,CAPZA3,SPNB1,DBNL,CAPZA2,CAPZA1,VILL,ASZ1,SVIL,EVL,SPNA1,CAV2,AVIL,EPB4.9,CAPG,CTTNBP2,TRIOBP,VIL1,MET,SPNB3,SPNB2,SPNA2
GO:0006607	-0.48611	0	0	12	NLS-bearing substrate import into nucleus	KPNA1,FYB,KPNA2,KPNA3,KPNA4,KPNA6,NCKIPSD,CBLB,TRPS1,KPNB1,IPO5,RERE
GO:0016569	-0.46637	0	0	65	covalent chromatin modification	HDAC11,EZH2,SUZ12,PHB,EED,RPS6KAS,PRMT8,RNF2,HDAC1,PPARGC1A,BMI1,HDAC2,HELLS,JMJD1A,HDAC3,SUV39H2,PAX5,PRDM9,SUV39H1,SET,MYST1,SIRT1,MEN1,HTATIP,CPA4,SIRT2,SUV420H1,HDAC8,MBD3,MSX3,UBE2N,PCAF,PRMT7,CBX8,PIM3,METT18,HDAC6,HDAC5,DNMT3A,RBM14,CARM1,EHMT1,RING1,USP22,DNMT3B,JMJD2A,NSD1,FOXP3,WHSC1L1,MYST3,MAP3K12,SUV420H2,PCGF2,HDAC9,HDAC10,MYST4,SATB1,EHMT2,HUWE1,JMJD3,SMARCA4,CREBBP,MLL1,TRRAP,EP300
GO:0035023	-0.46066	0	0	85	regulation of Rho protein signal transduction	MCF2,ARHGFE15,SPATA13,RASGRF1,ARHGFE3,ARHGAP27,NGEF,PLEKHG6,FGD6,SYDE2,DNMBP,RAC1,ARHGFE9,SLC26A10,9130221D24RIK,RALBP1,SOS2,ARHGAP4,ARHGFE16,FOXJ1,ECT2,PLEKHG3,FGD1,STMN3,ABRA,VAV1,ARHGFE5,ARHGFE10,ARHGFE7,E130306D19RIK,ARHGFE2,OBSCN,ARHGAP20,DEPDC2,PLEKHG4,TSC1,ARHGFE6,PLEKHG1,ARHGFE18,NET1,ABR,PAFAH1B1,ARHGFE17,DOCK7,PLEKHG2,ARHGFE11,FGD5,ARHGFE19,VAV3,FGD4,CDH2,PTK2B,E130112L23RIK,FGD2,TIAM2,ARHGFE4,CENTD2,FGD3,ARHGFE10L,DLCL1,CENTD3,4933429F08RIK,FARP2,ALS2,RGNEF,MCF2L,TIAM1,VAV2,RASGRF2,BCL6,BC067047,FARP1,ARHGFE12,BCR,ITSN2,TTN,SOS1,D10ERTD610E,ITSN1,ARHGFE1,AKAP13,PLEKHG5,KALRN,TRIO,SYDE1
GO:0035282	-0.44126	0	0	48	segmentation	DLL3,PSEN1,AXIN2,SFRP2,MEOX1,BMI1,ABI1,FRS2,SFRP1,RIPPLY2,HOXD8,RIPPLY1,GCN5L2,IFITM1,PCDH8,TCF3,MYF5,HOXB6,T,MEOX2,MESP2,PSEN2,EGR2,PAX1,MYF6,VBX18,HOXA2,HES7,PCSK6,DLL1,RPGRI1,MSGN1,TBX3,LEF1,MAFB,NCKAP1,DVL2,ACD,PRKDC,MIB1,POFUT1,TGDF1,ZEB2,MLL3,ROR2,WNT3A,ATM,EP300
GO:0016570	-0.43787	0	0	61	histone modification	HDAC11,EZH2,SUZ12,PHB,EED,RPS6KAS,PRMT8,RNF2,HDAC1,PPARGC1A,BMI1,HDAC2,JMJD1A,HDAC3,SUV39H2,PAX5,PRDM9,SUV39H1,SET,MYST1,SIRT1,MEN1,HTATIP,CPA4,SIRT2,SUV420H1,HDAC8,MBD3,MSX3,UBE2N,PCAF,PRMT7,CBX8,PIM3,METT18,HDAC6,HDAC5,RBM14,CARM1,EHMT1,RING1,USP22,JMJD2A,NSD1,FOXP3,WHSC1L1,MYST3,MAP3K12,SUV420H2,PCGF2,HDAC9,HDAC10,MYST4,SATB1,EHMT2,HUWE1,JMJD3,CREBBP,MLL1,TRRAP,EP300
GO:0048008	-0.43624	0	0	14	platelet-derived growth factor receptor signaling pathway	PDGFC,PDAP1,SRC,JAK2,PDGFA,PTEN,BCAR1,PDGFRA,PLAT,PDGFRB,PDGFB,RAPGEF1,BCR,VEGFA
GO:0051693	-0.43441	0	0	28	actin filament capping	GSN,CAPZB,WNT2,SCIN,RDX,CAPZA3,SPNB1,DBNL,CAPZA2,TPM1,CAPZA1,VILL,ASZ1,SVIL,TMOD3,EVL,SPNA1,CAV2,AVIL,EPB4.9,CAPG,CTTNBP2,TRIOBP,VIL1,MET,SPNB3,SPNB2,SPNA2
GO:0035265	-0.42973	0	0	24	organ growth	AGT,PTPN11,SASH3,SMAD2,RAG2,SOD1,MEN1,ADRA1B,FOXC2,CCNB1IP1,IL7,ACVR2B,PTK2,STRA8,CGA,ADRA1A,FOXC1,FXN,CSDA,BCL2,HLX,EHMT2,BCL2L11,CACNA1C
GO:0045103	-0.42561	0	0	29	intermediate filament-based process	KRT9,CLN8,VP554,ERBB2IP,KRT20,VIM,KRT15,KRT6B,DNAJB6,KRT39,SOD1,NDEL1,NEFL,KRT25,KRT16,KRT76,KRT6A,KRT24,PRPH,NEFM,GFAP,INA,HRB,RGNEF,SYNC,KRT17,NEFH,TCHH,DST
GO:0046854	-0.4205	0	0	14	phosphoinositide phosphorylation	PIK3C3,PIK3C2A,IHPK1,PIK3CG,PI4KB,IHPK2,PIK3R1,PIK3C2G,PIK3CA,PIK3CB,IPMK,PIK3CD,PI4KA,PIK3C2B
GO:0051173	-0.41963	0	0	16	positive regulation of nitrogen compound metabolic process	HPRT1,EGFR,HRH1,COMT,DDAH1,ITGB2,PTX3,HSP90AA1,JAK2,AGTR2,KLRK1,TICAM1,HSP90AB1,P2RX4,INSR,ICAM1
GO:0002483	-0.41632	0	0	22	antigen processing and presentation of endogenous peptide antigen	H2-K1,POU5F1,AIF1,DAXX,DDR1,TAPBPL,B3GALT4,ATP6V1G2,WDR46,TCF19,TRPC4AP,PHF1,TAPBP,GTf2H4,LST1,ERAP1,LTB,H2-Q1,COL11A2,ZBTB9,TAP2,SYNGAP1

Table S3B. Gene sets down-regulated by severe stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0016568	-0.41541	0	0	231	chromatin modification	SUPT4H2,HDAC11,EZH2,SMARCA5,YEATS4,TLK2,CLIC1,SMYD3,HLTF,RBBP7,SUZ12,ASF1A,DMAP1,MORF4L2,RBL1,SMARCA1,PHB,RBBP4,EED,SUPT4H1,RPS6KA5,L3MBTL2,EPC1,CBX3,ACTL6A,HMG20A,CSNK2B,SMARCB1,RUVBL2,BAT4,PRMT8,CHRAC1,SMARCA1,H2AFY,SAP18,RNF2,JMJD2D,MSL31,HDAC1,RUVBL1,INOC1,BCOR,BAZ1A,MORF4L1,JMJD2C,SMARCE1,PPARGC1A,UTP3,C4A,BMI1,SIRT5,NR3C1,HDAC2,HELLS,RCBTB1,JMJD1A,PRMT5,SMARCD1,HDAC3,SUV39H2,SETDB2,PAX5,CBX4,SMARCD3,H2AFY2,DAPK3,ING3,UBN1,EPC2,MYST2,PRDM9,NEU1,TAF5,RBL2,SIRT3,SUV39H1,AOF2,2410016006RIK,SET,ING2,MYST1,SIRT1,MEN1,CFB,BRDT,UTY,ASF1B,JARID1A,HTATIP,CPA4,2210018M11RIK,AEBP2,UTX,CEBP,SMYD1,SIRT2,TNP1,MTA2,BRD8,SUV420H1,WHSC1,HDAC8,TLK1,MBD3,PAD4,MSX3,UBE2N,CBX7,C2,FBXL11,NASP,GF11B,TBL1XR1,NG23,PCAF,TTF1,VPS72,PRMT7,ARID2,CBX8,JARID1D,KLF1,SIRT7,RCOR1,SMARCAD1,RNF20,SMARCC1,SETDB1,GS2,RSF1,PIM3,SYCP3,METTL8,HDAC6,HDAC5,JMJD2B,HILS1,SUDS3,DNMT3A,RBM14,HIRA,HNF1A,CARM1,EHMT1,JARID1C,RING1,JMJD1C,USP22,SETD8,DNMT3B,L3MBTL,STK19,HMG20B,JARID1B,TSPYL2,TAF6L,SETD1B,SIRT6,SUPT5H,JMJD2A,SETMAR,CHD1,PHF21A,CECR2,JMJD1B,NSD1,BAZ1B,FOXP3,WHSC1L1,NPM2,MYST3,MLL5,MAP3K12,SUV420H2,LY6G6C,RNF40,SETD2,SETD1A,SKIV2L,PCGF2,BNIP3,HDAC9
GO:0048628	-0.40771	0	0	34	myoblast maturation	ACTA1,MYLPF,TNNT2,MYOZ1,ITGB1,TMOD1,KCNH1,NEURL2,ACTC1,TCAP,NTN2L,MYL2,KRT19,CDON,CAST,ACTG1,OBSL1,NEB,BMP10,KRT8,CAPN2,CAPN3,MYH6,DYRK1B,MYH10,MYH9,CACNA1S,NEO1,MYH11,ADAM12,TTN,MYBPC3,XIRP1,CACNA1H
GO:0048858	-0.40248	0	0	418	cell projection morphogenesis	MCF2,OFD1,PGRMC1,ARL6,CNTN4,BBS4,ACHE,CHRNA3,BBS5,SPP1,GRM4,PSEN1,TMHS,DYCN2L1,MKKS,NDN,KLHL1,BBS2,MAP2K1,DLX5,PAX6,SMAD1,IGSF9,RASGRF1,FEZ1,SEMA4D,DRD2,GJA1,S100A6,UBE2B,CHRN2B,EPHB1,ISL1,AFG3L2,ADORA2A,CNP,WASF2,TTC8,HPRT1,ERMN,PRKCQ,SLITRK2,LZTS1,CDH4,SEMA3A,EGFR,THBS4,TRAPPC4,EFNA5,CDCA2EP1,KAL1,SPAG6,SLITRK4,BAIAP2,TTYH1,NTN1,CDH13,CAPZB,IFT20,PSCD2,SEMA3F,RYK,MBP,B3GNT2,EFNB1,ALCAM,SLITRK6,CDCA2,PLXNB2,TTN,C30B,SGK1,RNF6,RDX,FGD6,RHOA,NEURL,CLU,ACTN2,CSPG5,LIMA1,PTPN11,E2F4,CIT,CDK5,CTNNA1,EFNB3,GBX2,SEPT2,SDCBP,CEP290,NUP85,PAK1,ATOH1,RAC1,FEZ2,VANGL2,NCK1,NTRK2,TSGA10,SHC1,P2RX7,CFL1,CLIC5,LRRK4C,PAX2,OTX2,ROBO2,TTC30A1,ERBB3,CDK5R1,TGFB3,BCL11B,POU3F2,WNT7A,SOD1,FEZF1,KBTBD10,ALKBH1,NUMB,SH2B1,GDNF,NRXN3,OPHN1,LPIN1,RUFY3,PPP1R9A,RXRA,CACNA1F,TBCE,ARX,PARD6B,FOXJ1,MYO6,BAIAP2L1,SPAG16,APOE,HOXA1,PCM1,TGFB1,TNFRSF12A,NDEL1,UBB,KNDC1,NCAM2,PVRL1,NUMBL,ABI2,NEFL,FGD1,CXCR4,NGFR,MMP2,BARHL2,TEK2,TNR,STMN3,UCHL1,YWHAH,MYO1A,AKAP4,SEMA3B,RUNX3,MAPK8,CXCL12,SNAP25,NTN2L,KIF3A,S100B,CHAT,PPP2R2B,ARFIP2,BMPR1B,CREB1,TTN,C30A2,PARD3,BBS1,PLXNB1,ULK2,SCARF1,CHST3,VAX1,NR2E1,MT3,PCNT,RAC3,NRN1,BMP7,ETV4,RAB3A,WHRN,CDH23,ERBB3
GO:0017156	-0.39176	0	0	39	calcium ion-dependent exocytosis	GLRB,GLRA1,SYT5,POU5F1,VAMP3,RAPGEF4,RIMS2,SYT3,SCIN,SYT6,CDK5,VAMP7,GNDPA1,RIMS3,PKDREJ,B4GALT1,FGF2,SYCN,TRIM36,TRPV6,TNP2,ACR,RPH3AL,STX2,RAB3C,TRIM9,AKAP3,SYT4,SYT8,PLCD4,ARHGAP17,CADPS,SYT1,STX1A,VAMP2,SPN3,CACNA1A,CACNA1C,RIMS1
GO:0030835	-0.37651	0	0	30	negative regulation of actin filament depolymerization	GSN,CAPZB,WNT2,SCIN,RDX,LIMA1,CAPZA3,SPNB1,DBNL,CAPZA2,TPM1,CAPZA1,SHROOM2,VILL,ASZ1,SVIL,TMOD3,EVL,SPNA1,CAV2,AVIL,EPB4.9,CAPG,CTTNBP2,TRIOBP,VIL1,MET,SPNB3,SPNB2,SPNA2
GO:0046834	-0.36353	0	0	15	lipid phosphorylation	PIK3C3,PIK3C2A,IHPK1,PIK3CG,PI4KB,IHPK2,PIK3R1,PIK3C2G,AGK,PIK3CA,PIK3CB,IPMK,PIK3CD,PI4KA,PIK3C2B
GO:0019883	-0.34546	0	0	24	antigen processing and presentation of endogenous antigen	H2-K1,POU5F1,AIF1,DAXX,DDR1,TAPBP1,B3GALT4,ATP6V1G2,WDR46,TCF19,TRPC4AP,CD74,PHF1,TAPBP,ETF2H4,LST1,ERAP1,CD1D1,LTB,H2-Q1,COL11A2,ZBTB9,TAP2,SYNGAP1
GO:0030042	-0.32585	0	0	32	actin filament depolymerization	GSN,CAPZB,WNT2,SCIN,RDX,LIMA1,CAPZA3,SPNB1,DBNL,CAPZA2,TPM1,CAPZA1,SHROOM2,CFL1,VILL,DSTN,ASZ1,SVIL,TMOD3,EVL,SPNA1,CAV2,AVIL,EPB4.9,CAPG,CTTNBP2,TRIOBP,VIL1,MET,SPNB3,SPNB2,SPNA2
GO:0030521	-0.32178	0	0	50	androgen receptor signaling pathway	PPAP2A,POU5F1,AIF1,DNAJA1,MED16,NCOA4,DAXX,MED4,DDR1,MED17,PPARGC1A,PMPEA1,CCNE1,CDK7,JMJD1A,B3GALT4,PIAS1,RAN,PIAS2,ATP6V1G2,WDR46,TCF19,MED24,RNF4,RNF14,MED30,GRIP1,CTNNB1,PHF1,TAPBP,ETF2H4,BRCA1,LST1,MED1,AR,LTB,TGFB11,FHL2,NRIP1,MED14,MED13,COL11A2,NCOA3,THRAP3,ZBTB9,ARID1A,NCOA1,RB1,MED12,SYNGAP1
GO:0043543	-0.32123	0	0	35	protein amino acid acylation	HAT1,ZDHHC17,ARD1,NAT13,HHAT1,ZDHHC15,NMT1,PPARGC1A,NARG1,BMI1,NARG1L,ZDHHC2,MAP6D1,ZDHHC1,SET,ZDHHC3,MYST1,HTATIP,CPA4,MBD3,MSX3,PCAF,HHAT,ING4,METTL8,ING5,NMT2,FOXP3,MYST3,PCGF2,MYST4,ZDHHC7,CREBBP,TRRAP,EP300
GO:0051091	-0.32039	0	0	48	positive regulation of transcription factor activity	PRDX3,AGT,RELA,PRKCQ,NPM1,TLR3,EDA2R,UBE2V1,TLR4,JMY,PYCARD,IKBK,ITGB2,MAP3K13,NLRC3,TGFB1,CEBP,EDA,BCL10,UBE2N,ABRA,CYTL1,CAT,NFAM1,KRAS,IAK2,SHH,CARD9,PLA2G1B,NOD2,RIK2,MYD88,IRAK2,HMGA2,TSSK4,CARD11,TICAM1,TNF,MALT1,IKKB,ERC1,CAMK2A,NCOA3,IL1B,AMH,CREBBP,ICAM1,EP300

Table S3B. Gene sets down-regulated by severe stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0051056	-0.31408	0	0	250	regulation of small GTPase mediated signal transduction	MCF2,TBC1D12,RAPGEF6,TBC1D7,ARHGEF15,POU5F1,RASGRP2,SPATA13,RASGEF1C,MAP2K1,TBC1D2B,TBC1D8,ARPP19,RASGRF1,RAPGEF4,RASGEF1A,AIF1,TBC1D15,RASGEF1B,ARHGEF3,EPO,FBXO8,TBC1D23,ARHGAP27,NGEF,IQGAP3,S1PR1,WDR67,PLEKHG6,DAXX,DDR1,TBC1D22A,RASGRP3,PSCD2,PSCD4,FGD6,B3GALT4,CENTA2,RAPGEF3,PPP2CB,RASA3,SYDE2,DNMBP,RA P1GAP,USP6NL,RAC1,ATP6V1G2,ARHGEF9,WDR46,ITPKB,NUP62,ARFGAP2,TCF19,HRBL,PLCE1,SLC26A10,9130221D24RIK,RALBP1,TBC1D17,SOS2,ARHGAP4,SMAP2,CRK,ARHGEF16,TBC1D22B,TBC1D19,FOXJ1,RABGAP1,NOTCH2,ICMT,ECT2,ARFGAP3,PLEKHG3,TBC1D25,KNDC1,FGD1,RALGDS,TBC1D8B,RAPGEF5,DDEFL1,STMN3,SMAP1,NRG1,ABRA,PSD4,VAV1,RABGAP1L,KITLA,RHGEF5,RASA2,CENTA1,A230067G21RIK,PHF1,ARHGEF10,A630047E20RIK,ARHGEF7,TBC1D9B,SGSM3,TBC1D4,E130306D19RIK,GARNL3,TAPBP,RASGRP4,ERBB2,GT2H4,ARHGEF2,OBSCN,ARF6,ARHGAP20,TBC1D30,DEPDC2,LST1,ARFGAP1,PLEKHG4,KRAS,ADPRHL1,TSC1,TBC1D10A,TBC1D13,IGF1,ARFGEF1,ARHGEF6,PLEKHG1,DAB2IP,TBC1D14,PSD,SIPA1,ARHGEF18,NRAS,NET1,PSCD3,ABR,PAFAH1B1,ARHGEF17,TBC1D21,LTB,CENTB1,DOCK7,PLEKHG2,TIMP2,RASA4,ARHGEF11,PSD2,CENTG1,DOCK2,FGD5,ARHGEF19,VAV3,SGSM2,RAPGEF2,IQGAP1,CENTB2,TBC1D9,A430107D22RIK,GRTP1,SIPA1L2,RASA1,FGD4,GAPVD1,CSF1,C
GO:0000281	-0.30937	0	0	18	cytokinesis after mitosis	POU5F1,AIF1,DAXX,DDR1,NUSAP1,B3GALT4,ATP6V1G2,WDR46,TCF19,PHF1,TAPBP,GT2H4,LST1,LTB,MYH10,COL11A2,ZBTB9,SYNGAP1
GO:0030518	-0.29106	0	0	75	steroid hormone receptor signaling pathway	PPAP2A,POU5F1,AIF1,DNAJA1,MED16,NCOA4,DAXX,MED4,DDR1,NR0B1,MED17,PPARGC1A,PMEP1A,CCNE1,CDK7,NR3C1,PPARGC1B,JMJD1A,B3GALT4,DDX54,PIAS1,KLF9,RAN,PIAS2,ATP6V1G2,WDR46,TCF19,MED24,RNF4,TAZF7,ESR2,RNF14,MED30,YWHAH,ESR1,GRIP1,CTNBNB1,PHF1,RBM9,TAPBP,GT2H4,BRCA1,LST1,MED1,JAK2,AR,PGR,IGF1,LTB,TGFB111,RBM14,CARM1,HMGA2,GHRHR,CALCOCO1,SAFB,FHL2,NRIP1,EGLN2,MED14,MED13,NCOA2,UBR5,NR3C2,COL11A2,NCOA3,THRAP3,NCOA6,ZBTB9,ARID1A,NCOA1,RB1,MED12,GH,SYNGAP1
GO:0030072	-0.28595	0	0	64	peptide hormone secretion	SSTR5,TCF7L2,EIF2AK3,MC4R,GLP1R,RAPGEF4,DRD2,ANXA1,RIMS2,PSMD9,SMPD3,TRH,CAPN10,PTPN11,ENSA,OIT1,GCK,SMAD2,CAMK2G,CPLX3,GCG,CPT1A,CYB5R4,ORF9,LEP,PDE3B,NOS1,SLC30A8,VGF,EDN1,DGAT1,SNAP25,GAL,HNF1B,IL1RN,KISS1,PDX1,PPARD,JAK2,MAFA,GHRL,ACVR2B,GLUD1,HNF1A,CPLX1,GHRHR,KCNQ1,GHSR,GPR119,EDN3,TRPV4,KCNJ11,IRS1,GIP,NEUROD1,GHRH,SIRT4,STX1A,ABCC8,LTBP4,HTT,CACNA1C,MYO5A,PCLO
GO:0051100	-0.26295	0	0	35	negative regulation of binding	DNAJA3,SUMO1,EGLN1,NR0B1,NFKBIA,NLRP3,GTPBP4,MEN1,HMOX1,NARFL,FOXJ1,CEBPG,SIGIRR,PEX14,MDFI,CAT,CDKN2A,RSF1,JAK2,COMM7,HNF4A,NOD2,IRAK2,HR,SMO,ZCCHC11,FOXP3,DDIT3,THRA,ID3,TRIB1,ID2,FLNA,ZFP462,YBX2
GO:0045913	-0.26198	0	0	19	positive regulation of carbohydrate metabolic process	ARPP19,PPARGC1A,HIF1A,INS2,GCK,ARNT,PRKAA1,ADRA1B,MIF,IGF1,POU1F1,HNF4A,C1QTNF2,STK11,MLXIPL,DYRK2,GAPDH,S,AVPR1A,INSR
GO:0006338	-0.26116	0	0	64	chromatin remodeling	SUPT4H2,SMARCA5,RBBP7,ASF1A,RBBP4,SUPT4H1,CBX3,ACTL6A,SMARCB1,CHRAC1,SMARCA1,INOC1,BAZ1A,MORF4L1,SIRT5,HELLS,SMARCD1,SUV39H2,SIRT3,SUV39H1,2410016O06RIK,SIRT1,MEN1,BRD7,CEBPG,SMYD1,SIRT2,TNP1,MTA2,MBD3,NA SP,TF1,CBX8,KLF1,SIRT7,SMARCC1,RSF1,SYCP3,HDAC5,HILS1,DNMT3A,HNF1A,DNMT3B,HMG20B,TAZF6,SIRT6,SUPT5H,CHD1,BAZ1B,FOXP3,NPM2,BNIP3,PBRM1,HMGA1,ARID1B,BPTF,SIRT4,SUPT6H,SMARCC2,ARID1A,RERE,BAZ2A,CHD6,SMARCA4
GO:0043388	-0.25201	0	0	57	positive regulation of DNA binding	PRDX3,AGT,RELA,PRKQC,NPM1,TLR3,EDA2R,UBE2V1,NME1,TLR4,JMY,PYCARD,IKBK,ITGB2,MAP3K13,EDF1,CALM2,NLRC3,TGFB1,CEBPG,EDA,BCL10,UBE2N,ABRA,CYTL1,HIPK3,CAT,NFAM1,KRAS,JAK2,SHH,CARD9,PLA2G1B,NOD2,RIPK2,MYD88,HIPK1,BRD4,IRAK2,HMGA2,TSSK4,CARD11,TICAM1,TNF,CALM1,MALT1,IKBK,CALM3,HIPK2,ERC1,CAMK2A,NCOA3,IL1B,AMH,CREBBP,ICAM1,EP300
GO:0000226	-0.23974	0	0	131	microtubule cytoskeleton organization and biogenesis	UXT,OFD1,BBS4,TEKT5,TUBGCP5,MID1IP1,TACC1,BBS2,TUBGCP4,SMC3,UBE2B,UBE2C,CNP,RNF19A,KIF2C,NPM1,PRKCZ,TUBGCP3,NUSAP1,KIF11,GABARAP,TPPP,PPP4C,WNT2,FBXO5,TTK,SGK1,KATNA1,TUBA8,CFTR,NEURL,MAPRE1,TUBG1,TUBGCP2,MID1,ZWINT,TEKT3,SPAG5,RAN,AP1G1,CETN3,CENPJ,KATNB1,SMC1A,RANBP9,TPX2,PRC1,1700009N14RIK,MAP6D1,SAC3D1,TEKT1,SASS6,TBCE,ASZ1,TACC3,FMN2,CKS2,PCM1,MARK1,NDEL1,CNTROB,NEFL,TEKT2,STMN3,DCTN2,AURKA,UNC84B,RANBP1,CDKN1B,CETN1,RCC1,CRYAB,MAPK8,BUB1B,BBS1,TRIM54,NDC80,ESPL1,PCNT,HOOK1,CAV3,TUBB1,ARHGEF2,BRCA1,TEKT4,CKAP5,BRCA2,CAV1,GADD45A,HDAC6,NDE1,PAFAH1B1,DOCK7,PTK2,BIRC5,KIF23,CCDC100,DYNC1L11,GTRGEO22,CAV2,TUBE1,CLASP2,TTL,PSRC1,TUBB5,NEFM,MLH1,HOOK2,CTTNBP2,TACC2,CROCC,MYH9,STMN1,HOOK3,MTAP1S,CLIP2,MTAP1A,CCDC42BPA,MAPT,APC,MTAP4,MTAP2,NEFH,MARK4,TUBGCP6,CLASP1,DST,MTAP1B,CEP250,DYNC1H1,NAV1

Table S3B. Gene sets down-regulated by severe stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0007507	-0.2383	0	0	200	heart development	IIFT52,BMP2,CHRNA3,CBY1,ADIPOR2,PPP3R1,MNAT1,RXR8,PSEN1,MAP2K5,CALCRL,MKKS,BMPR1A,FGF12,GAA,GJA1,CITED2,CASP8,NOX4,RARB,SOX6,EGLN1,ISL1,ZIC3,FOXP1,FGFR2,ATG5,GLI3,CASP7,BMP4,ACADM,HEXIM1,TH,FGF9,SMARCD3,CENTA2,MYLPF,VANGL2,SRF,HIF1A,IDL1,SHC1,SMAD2,IRX4,TNNT2,SHOX2,PLCE1,ERBB3,NFATC3,TXNRD2,MB,HTR2B,RAF1,MAP3K7IP1,PDLIM5,TBX20,TNNI1,EPOR,TNNI3,ECE2,ITGB1,RXRA,MOSPD3,SMYD1,TGFB1,MIXL1,MESP1,CASP3,CASQ2,EDN1,MSX1,NRG1,ADRA1B,CRKL,PPP3CB,HAND2,ACTC1,CTNNB1,MYL2,MYL3,FOXC2,SLC22A5,TGFB2,SRI,MYH7,EDNRA,MYOCD,PAX3,NKX2-6,ERBB2,COL3A1,PITX2,MKL2,TRP53BP2,RB1CC1,GYS1,MED1,FOXP4,ACVR1,TSC1,PLN,SALL4,ZFPM1,GJA5,PDLIM3,SHH,ACVR2B,VCAN,ALDH1A2,GATA4,TBX5,JMJD6,FOXH1,GLI2,NFATC4,HDAC5,TAZ,NOTCH1,ERBB4,NODAL,PTEN,RBPJ,KCNJ8,TCF25,OSR1,NFATC1,ADM,PCSK5,BMP10,TBX3,HOPX,GNA11,TGFB2,OVOL2,GIC1,ADRA1A,MYLK2,TNNC1,FOXC1,MSX2,SMO,MYH6,ADRBK1,NCKAP1,POU6F1,PTPRJ,DLC1,CSR3,SEMA3C,HHEX,SOX9,NPPB,PKP2,HAND1,TEAD1,DVL2,MYH10,FGF15,DVL1,ITGA4,HDAC9,TSC2,GNAQ,NRP2,FGF8,ID3,PBRM1,ZFPM2,PRKDC,ADAM19,ENG,CXADR,SCUBE1,TBX2,FGFR1,TBX1,PKD1,MEF2C,MYH11,NKX2-5,ALPK3,NF1,INSR,TTN,NCOA6,MIB1,POFUT1,ID2,TGDF1,FBN1,MYBPC3,NRP1,XIRP1,CHD7,WNT3A,LBX1,RARA,DVL3,A
GO:0015833	-0.23173	0	0	81	peptide transport	SSTR5,TCF7L2,EIF2AK3,MC4R,GLP1R,RAPGEF4,DRD2,ANXA1,RIMS2,PSMD9,SMPD3,TRH,CAPN10,PTPN11,ENSA,OIT1,GCK,CDH17,SMAD2,CAMK2G,RPN1,CPLX3,GCG,CPT1A,CYB5R4,ORF9,LEP,PDE3B,NOS1,SLC15A2,SLC15A4,PSMB9,TRPC4AP,SLC30A8,9830102E05RIK,NPY2R,VGF,SLCO3A1,DISP1,EDN1,SLC15A3,ABCA1,DGAT1,SNAP25,GAL,TAP1,HNF1B,IL1RN,KISS1,PDX1,PPARD,JAK2,MAFA,GHRL,ACVR2B,GLUD1,HNF1A,ABCB9,CPLX1,GHRHR,KCNQ1,GHSR,GPR119,EDN3,ADORA1,TRPV4,KCNJ11,IRS1,GIP,NEUROD1,GHRH,SLC15A1,SIRT4,STX1A,ABCC8,LTBP4,HTT,TAP2,CACNA1C,MYO5A,PCLO
GO:0050852	-0.22539	0	0	27	T cell receptor signaling pathway	PSEN1,PTPRC,PAWR,CLEC2I,MAPK1,IKBK, FYN,UBASH3A,BCL10,UBE2N,ZAP70,PSEN2,TRAT1,PTPN22,CD3E,ELF1,TRAF6,MAP3K7,LCK,CACNB4,THY1,BCAR1,MALT1,FOXP3,CBLB,PTPN6,CACNB3
GO:0048469	-0.22391	0	0	116	cell maturation	SCLT1,LGI4,PICK1,MAEA,CCNB1,AK1,FOXO3A,GJA1,EPO,SOX8,ANG,SEPT4,RPS6KA2,KCNIP2,DLD,BHLHB8,PLP1,FBXO5,MTCH1,CDKN1C,LHX6,ACTA1,SOX10,PEBP1,EREG,MYLPF,PARK2,TNNT2,PTH2R,BTK,CEBPA,MYOZ1,ITGB1,RXFP2,RND1,TMOD1,PDE3A,PTHR1,KCNH1,NEURL2,ACTC1,RUNX3,TCAP,CTNNB1,TIMP1,NTN2L,KLF1,MYL2,CALCA,IRX5,VXS1,KRT19,TSSK3,CDON,CAST,A GPAT6,IL21,APP,ERCC2,DLG2,HES1,MECP2,FOXA1,BRCA2,PGR,CBF,EPB4.2,GM767,RET,GDF11,ACTG1,KCNE1,NTN4,OBSL1,NEB,BMP10,GHRHR,KRT8,CAPN2,POU2F2,PTK2B,TCF2L1,KDR,GATA2,CAPN3,MYH6,PPARG,CLN5,DYRK1B,DLG4,MYH10,RUNX2,MYH9,FARP2,GNAQ,BCL2,CACNA1S,FGFR1,NEO1,CSPG4,MYH11,HES5,NRCAM,EPAS1,ADAM12,TTN,FZD5,INSL3,MYBPC3,IHH,XIRP1,CDC25B,KCNMA1,CACNA1H,VEGFA,AGRN
GO:0045767	-0.22238	0	0	34	regulation of anti-apoptosis	G6PDX,BRE,SERBP1,CDKN1A,SMAD1,SLC9A1,BCL2L1,NPM1,STAR,NPY5R,HSPD1,RTKN,HMOX1,PIK3R1,BTG2,PRKAA1,TNFAIP8,IGF1,CAV1,CD28,ERBB4,ADM,MAPK8IP2,ANGPT1,RASA1,OPA1,PTK2B,PIK3R2,PDGFRB,RTN4,ERC1,RARA,LIFR,LRP1
GO:0051099	-0.20702	0	0	61	positive regulation of binding	PRDX3,AGT,EIF2AK3,RELA,AKTIP,PRKCQ,NPM1,TLR3,EDA2R,UBE2V1,NME1,TLR4,JMY,PYCARD,IKBK,ITGB2,MAP3K13,MAP1L,C3B,EDF1,CALM2,NLRC3,DPH3,TGFB1,CEBPG,EDA,BCL10,UBE2N,ABRA,CYTL1,HIPK3,CAT,NFAM1,KRAS,JAK2,SHH,CARD9,PLA2G1B,NOD2,RIPK2,MYD88,HIPK1,BRD4,IRAK2,HMGA2,TSSK4,CARD11,TICAM1,TNF,CALM1,MALT1,IKBK,CALM3,HIPK2,ERC1,CAMK2A,NCOA3,IL1B,AMH,CREBBP,ICAM1,EP300
GO:0030522	-0.20305	0	0	87	intracellular receptor-mediated signaling pathway	PPAP2A,POU5F1,AIF1,DNAJA1,MED16,NCOA4,DAXX,MED4,DDR1,NR0B1,MED17,PPARGC1A,PMPEA1,CCNE1,CDK7,NR3C1,PPARGC1B,JMJD1A,B3GALT4,DDX54,PML,PIAS1,KLF9,RAN,PIAS2,ATP6V1G2,WDR46,TCF19,MED24,CYP26B1,RNF4,TA7,NR1H2,ESR2,RNF14,MED30,PTF1A,YWHAH,ESR1,GRIP1,CTNNB1,PHF1,CREM,RBM9,TAPBP,GTAF2H4,BRCA1,FLT1,LST1,MED1,CYP26A1,JAK2,AR,PGR,IGF1,SLA2,ALDH1A2,LTB,TGFB1I1,RBM14,TGIF1,CARM1,NOS2,HMGA2,GHRHR,CALCOCO1,SAFB,FHL2,NRIP1,EGFN2,DCBLD2,MED14,MED13,NCOA2,UBR5,NR3C2,COL11A2,NCOA3,THRAP3,NCOA6,ZBTB9,ARID1A,NCOA1,RB1,MED12,GH,SYNGAP1
GO:0043470	-0.19957	0	0	15	regulation of carbohydrate catabolic process	ECD,HIF1A,INS2,PFKM,ARNT,HSD11B1,ADRA1B,MIF,PFKL,IGF1,PFKFB3,MLXIPL,GAPDH5,AVPR1A,INSR
GO:0007292	-0.19889	0	0	66	female gamete generation	AGT,PARN,CCNB1,MAGOH,ZSCAN21,FOXO3A,HEXB,DAZL,ANG,RPS6KA2,DMC1,FSHB,FBXO5,FSHR,TOB2,CBR1,EREG,MSH5,OAS1D,AFP,MSH4,FIGLA,SPO11,SIRT1,LEP,RXFP2,FMN2,DYNLL1,PDE3A,MMP2,BCL2L10,DIAP2,BMPR1B,MMP19,PLA2G4A,GLP1,BRCA2,PGR,NOS3,ERCC1,SOHLH2,STRA8,BMP15,LEPR,VMO1,NOS2,PTK2B,SOHLH1,GDF9,GNRH1,NRIP1,LEFTY2,NPM2,ADAMTS1,MLH1,AXIN1,BCL2,NOBOX,EDN2,USP9X,NANOS3,INSL3,CDC25B,WNT4,ATM,YBX2
GO:0051101	-0.19436	0	0	94	regulation of DNA binding	PRDX3,AGT,DNAJA3,SUMO1,RELA,EGLN1,PRKCQ,NPM1,TLR3,EDA2R,UBE2V1,NME1,NR0B1,TLR4,JMY,APEX1,NFKBIA,SIX6OS1,PYCARD,NLRP3,IKBK,ITGB2,MAP3K13,EDF1,MEN1,CALM2,HMOX1,NLRC3,NARF,TGFB1,FOXJ1,CEBPG,EDA,BCL10,TRAF3IP1,UBE2N,SIGIRR,ABRA,CREBZF,PEX14,CYTL1,HIPK3,MDFI,CAT,NFAM1,CDKN2A,RSF1,KRAS,JAK2,SHH,COMMD7,CARD9,HNF4A,PLA2G1B,NOD2,RUNX1T1,RIPK2,MYD88,HIPK1,BRD4,IRAK2,HMGA2,STK36,BCL3,HR,TAF6L,TSSK4,CARD11,TICAM1,TNF,CALM1,SMO,ZCCHC11,MALT1,TAF6,IKBK,FOXP3,DDIT3,CALM3,HIPK2,THRA,ID3,TRIB1,ERC1,CAMK2A,NCOA3,IL1B,ID2,FLNA,ZFP462,AMH,CREBBP,ICAM1,EP300

Table S3B. Gene sets down-regulated by severe stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0030029	-0.18398	0	0	314	actin filament-based process	PFN4,RND3,ARHGDI1,KLHL1,AMOT,ARHGAP6,ELMO1,AIF1,MAP3K1,EPB4.1L3,PFN2,RHO,CSR1,CAP1,WASF2,ERM N,ANG,KPTN,PRKCQ,PRKCI,FHDC1,GSN,ARPC1A,S1PR1,DAXX,PRKCZ,CNN2,DDR1,CAPZB,CAPN10,PSCD2,ARPC1B,WNT2,CDC42 ,SCIN,SIRPA,CORO1C,RACGAP1,RDX,CLEC2I,FGD6,RHOA,TNFAIP1,EPB4.1,LIMA1,CAPZA3,B3GALT4,2610204M08RIK,SPNB1,DB NL,CIT,CDK5,ACTA1,CAPZA2,TPM1,SDCBP,ARPC4,RAC1,MYL7,CAPZA1,ATP6V1G2,SHROOM2,DLG1,MYL6,RPL9,NCK1,WDR46, TESK2,ROCK1,SHC1,TCF19,CF11,CAP2,RHOF,PARVA,TNNT2,ASB15,LLGL1,MYL7,VILL,CNN3,TMSB10,4933400A11RIK,BIN3,FER MT2,KCTD13,XIRP2,OPHN1,LPIN1,MYOZ1,PPP1R9A,ITGB1,PDPK1,ARHGAP8,RND1,DSTN,CRK,ASZ1,FOXJ1,TM0D1,FMN2,MYO 6,ARPC5L,PACSIN2,DYNLL1,PLEK2,ARHGAP26,RHOQ,LATS1,SVIL,ACTR3,ABI2,FGD1,MRAS,TM0D3,ABL1,DIAP2,NEURL2,MYO1 A,WIPF1,CALR,ACTN1,SHROOM4,ACTC1,CORO2B,TCAP,CXCL12,TRPM7,ATP2C1,AKAP2,ARFIP2,KISS1R,MYL2,PHF1,KRT19,WA S,ADRA2A,MYH7,RAC3,MYH4,ACTR3B,TMSB4X,CNN1,PDLIM7,TRIP10,EPB4.1L2,NEBL,TAPBP,CDC42EP2,GTTF2H4,MYH3,ARHG EF2,ARPC5,LIMCH1,ARF6,SHROOM3,CORO1A,PFN1,LST1,EHD2,NPHP1,APBB1,NCK2,KRAS,PLS3,ACTNA4,TSC1,EZR,ROCK2,CDC4 2EP5,PDLIM3,GAS7,GHRL,ARHGFE18,ARPC2,FHOD1,PLA2G1B,NRAS,DIAP3,PAFAH1B1,ARHGFE17,SORBS3,LTB,PDGFA,TTL3,W
GO:0045892	-0.17343	0	0	331	negative regulation of transcription, DNA-dependent	BHLHB3,BMP2,TCEAL1,CBY1,SIN3A,IRF2BP1,RBBP7,IRF8,SUZ12,TSG101,POU5F1,DMAP1,RBL1,SUPT4H1,AIF1,FOXP2,EPC1,ME IS2,MAF1,MBD3L1,ZFP354A,RARB,SOX2,SOX6,S100A1,VHLH,REST,DDX20,PAWR,ZKSCAN17,RNF2,LCOR,GABPA,FOXP1,FOXN3 ,TLE4,DAXX,BCOR,MBD2,DDR1,KLF12,EG237412,PKIG,SMARCE1,NR0B1,TRIM27,ZFP161,IGHMBP2,OLIG2,BMI1,SIRT5,NFKB1, HELLS,SMAD3,CDKN1C,HEXIM2,MX1,HEXIM1,1700023B02RIK,B3GALT4,MDF1,PAX5,CUX1,CBX4,DMBX1,STRAP,DRD3,E2F1, LDB1,RPS14,ATP6V1G2,YBX1,WDR46,PAZG4,ZEB1,INS2,ID1,EGR1,SMAD2,RHOX2A,TCF19,PRRX1,ILF3,JARID2,PAX2,SHOX2,GL IS1,SAP30,GZF1,SIRT3,SUV39H1,TLE1,AOF2,MXD4,DNAJB6,TBPL2,CEBPA,FGF2,SIRT1,TBX20,MEN1,RIPPLY1,E2F6,EID1,NR2F1, TRIM66,SMAD4,TRP53,ZHX1,ZBTB7A,PRDM1,NRIP2,SNF1L,FOXJ1,NOSTRIN,SIRT2,TNP1,MTA2,TRAF3IP1,NFX1,HDAC8,RYBP, EID2,DRAP1,MBD3,MSX3,PKIA,PHF12,MSX1,ZFP148,GFI1B,YWHAQ,HOXB4,SBNO2,TCF3,HMGB1,VPS72,CTNNB1,CBX8,FOX2, CTCF,SIRT7,MLX,IRF7,PEX14,HIPK3,PHF1,TDG,CBFA2T2,VAX1,NR2E1,ORC2L,MDFI,JDP2,CTBP1,OVOL1,PAX3,TAPBP,ALX1,GTTF 2H4,STAT3,PIAS4,NDUFA13,PURB,HES1,PDX1,LST1,RSF1,GLP1,FOXP4,MECP2,BARX2,PPARD,HOXA7,PGR,SALL4,ZFPM1,ING4, HOXA2,SLA2,SOX15,GSC,SIM2,NR2C1,DNMT1,MDM4,FOXH1,GLI2,SUFU,RHOX3A,HDAC5,SIX3,POU4F2,HSF4,DR1,SORBS3,LTB,
GO:0045860	-0.16246	0	0	196	positive regulation of protein kinase activity	AVP1,PPAP2A,CHRNA3,PICK1,ADRA2C,GRM1,F2R,MAP2K1IP1,GRM4,PSEN1,PDGFRC,GNB2L1,MAP2K1,CD4,PTPLAD1,MAP3K1, DRD2,PTPRC,CD81,HTR2A,DGKK,ADORA2A,TPD52L1,MAP3K4,ANG,CEACAM1,EGFR,DAXX,PRKCZ,TLR3,ERCC6,ADORA2B,TLR4, TGFA,DGKB,IL2,PRKD3,BDKRB1,MS4A2,GAB1,TIRAP,VLDLR,PTPN11,FRS2,ADRB2,DBNL,CDK5,PAK1,EREG,INS2,IKBKG,SHC1,M AP3K13,NRK,GADD45G,MAP3K2,PLCE1,TGFB3,PRLR,CARTPT,MAP3K7IP1,SOD1,FGF2,TLR1,ALS2CR2,SDC4,SYK,CRK,FCER1A,SP DYA,TRAF2,FPR1,BCL10,CCND1,PRKAA1,CD74,CXCR4,EDN1,NRG1,MDFIC,KITL,PROK1,EPGN,KISS1R,PARD3,CALCA,MAP3K5,TG FBR2,PDE6G,IGH- 6,LRRN3,ADRA2A,MAPBPIP,GNAI2,EDNRA,MDFI,AGK,CERK,ERBB2,MAP4K5,IL1RN,FLT1,EGF,KRAS,ARRB1,SPHK2,JAK2,C5AR1, ELA2,GNG3,CHRNA7,GHRL,TRAF6,ACVR2B,MAP3K7,SPAG9,DGKQ,PLA2G1B,EFNA1,TNFRSF10B,PIK3CB,MAPKB1,HCRT,CENT G1,C1QTNF2,SPDYB,TLR6,DGKD,PROK2,MAP4K1,GAP43,IRAK2,DGKI,FGD4,CAMKK1,CSF1,MAP2K3,MAP3K6,PTK2B,PRKCD,MA P3K10,TNF,EDN3,TAOK2,CERKL,ADORA1,DGKZ,MALT1,CISH,HGF,CHRM1,IRAK1,CKK,TRAF7,PDE6H,CARD14,CCDC88A,RAB26, ERN1,CARD10,PDGFB,ALS2,MADD,DGKH,CD24A,GADD45B,MUC20,EDN2,SPHK1,ADRA2B,TNFSF15,DGKE,DGKG,DAB1,MAP3K 11,CSPG4,PKN1,MAP2K6,KIT,MAPK8IP3,DGKA,BIRC7,TRP73,CCND3,INSR,MAP3K9,IL1B,TDGF1,ZEB2,CCND2,PXN,CDC25B,LRP8
GO:0033674	-0.15932	0	0	202	positive regulation of kinase activity	AVP1,PPAP2A,CHRNA3,PICK1,ADRA2C,GRM1,F2R,MAP2K1IP1,GRM4,PSEN1,PDGFRC,GNB2L1,MAP2K1,CD4,PTPLAD1,MAP3K1, DRD2,PTPRC,CD81,HTR2A,DGKK,ADORA2A,TPD52L1,MAP3K4,ANG,CEACAM1,EGFR,DAXX,PRKCZ,TLR3,ERCC6,ADORA2B,TLR4, TGFA,DGKB,CD42,IL2,PRKD3,BDKRB1,MS4A2,GAB1,TIRAP,VLDLR,PTPN11,FRS2,ADRB2,DBNL,CDK5,PAK1,EREG,RAC1,INS2,IK BKG,SHC1,MAP3K13,NRK,GADD45G,MAP3K2,PLCE1,TGFB3,PRLR,CARTPT,MAP3K7IP1,SOD1,FGF2,TLR1,ALS2CR2,SDC4,SYK,CR K,FCER1A,SPDYA,TRAF2,FPR1,BCL10,CCND1,PRKAA1,CD74,CXCR4,EDN1,NRG1,MDFIC,KITL,PROK1,EPGN,KISS1R,PARD3,CALCA ,MAP3K5,TGFBR2,PDE6G,IGH- 6,LRRN3,ADRA2A,MAPBPIP,GNAI2,EDNRA,MDFI,AGK,CERK,ERBB2,MAP4K5,IL1RN,FLT1,EGF,KRAS,ARRB1,SPHK2,JAK2,C5AR1, ELA2,GNG3,CHRNA7,GHRL,TRAF6,ACVR2B,MAP3K7,SPAG9,DGKQ,PLA2G1B,EFNA1,TNFRSF10B,PIK3CB,MAPKB1,HCRT,CENT G1,C1QTNF2,SPDYB,TLR6,VAV3,DGKD,PROK2,CLK1B4,MAP4K1,GAP43,IRAK2,DGKI,FGD4,CAMKK1,CSF1,MAP2K3,MAP3K6,PT K2B,PRKCD,MAP3K10,TNF,EDN3,TAOK2,CERKL,ADORA1,DGKZ,MALT1,CISH,HGF,CHRM1,IRAK1,CKK,TRAF7,PDE6H,IRS1,CARD 14,CCDC88A,RAB26,ERN1,CARD10,PDGFB,ALS2,MADD,DGKH,VAV2,CD24A,GADD45B,MUC20,EDN2,SPHK1,ADRA2B,TNFSF15, DGKE,DGKG,DAB1,MAP3K11,CSPG4,PKN1,MAP2K6,KIT,MAPK8IP3,DGKA,BIRC7,TRP73,CCND3,INSR,MAP3K9,IL1B,TDGF1,ZEB2

Table S3B. Gene sets down-regulated by severe stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0043009	-0.15625	0	0	296	chordate embryonic development	DLL3,IFT52,BBS4,CITED1,SLC30A1,XRCC4,FUT8,TCF7L2,RBBP8,PSEN1,AMOT,PAX6,NUP50,AXIN2,PRMT1,GJA1,CITED2,PITPNB,CASP8,ZIC2,SMARCB1,MYB,EGLN1,SFRP2,SOX8,COPS3,COBL,GABPA,BCL2L1,ACVR1C,TAPT1,UBE2A,SBDS,ACVR1B,HBEGF,ZFP830,MEOX1,XRCC2,NMT1,GLI3,HOXA5,GINS1,PSMC4,BMP4,BMI1,PTCH1,SYVNI1,ACVR1,RRN3,ESRRB,APOB,AMOD1,ABI1,FGF9,GNA13,HOXB2,XAB2,GBX2,TCF7,VEZT,SOX10,TPM1,SFRP1,ACVR2A,DLG1,VANGL2,HOXC9,YBX1,SRF,HIF1A,HCN4,EN1,NBN,SMAD2,CDX2,CFL1,PRRX1,TAF8,HOXC5,TBX15,TERF2,DCPP1,AOF2,SFRS1,TGF83,PAX7,SIX4,PTK7,RIPLY2,SP1,MAP3K7IP1,DS3,CELSR1,ADAM10,CEBPA,ALKBH1,MEN1,KEAP1,RIPLY1,PSMC3,HOXB7,ITGB1,TRP53,PRDM1,GRN,GCN5L2,NCAPG2,TCFAP2A,EVI1,ZIC5,ICMT,ARNT,IFITM1,LMO4,BCL10,MBNL1,TGFB1,MAN2A1,SIX1,NDEL1,ASCL2,PCDH8,MBD3,GJB3,HOXD4,EDN1,RUNX1,PRPF19,DMBT1,MSX1,NASP,HOXB4,HAND2,MYF5,HOXB6,GATA6,HOXA6,CUBN,WNT1,GNAS,FOXC2,DNM3T3,TGFB2,HNF1B,CNMB1IP1,T,MEOX2,LIMS1,MESP2,PSEN2,PRRX2,EDNRA,HOXB9,PAX3,NKX2-6,SPINT1,ALX1,SP3,BRCA1,PTPRR,SETDB1,MKL2,SHROOM3,ERCC2,PFN1,PBX1,MED1,PAX1,MYF6,HOXB5,NKX3-2,OSR2,ACVR1,HOXA7,TBX18,BRCA2,AR,TSC1,CDC2L1,SALL4,NLE1,HOXA2,TRAF6,SHH,MAP3K7,GSC,GATA4,TBX5,GLI2,EOMES,ATP7A,NDST1,PLCG1,NODAL,HES7,RIC8,MSH2,CEBPB,TGIF1,FZD3,HNF1A,DAB2,DL1,TWIST1,PCSK5,LIG4,RPGRIP1L,MSGN1,
GO:0009411	-0.15237	0	0	49	response to UV	WRN,GPX1,CDKN1A,RELA,GTF2H2,ERCC6,ERCC5,CASP7,PML,XPA,REV1,PMAP1,ERCC4,FEN1,ERCC8,MEN1,TRP53,FECH,POLH,ERCC3,CASP3,HUS1,MAPK8,SERPINB13,CAT,CDKN2D,ERCC2,DOB2,MC1R,BRCA2,ELA2,XPC,HPAIN,ERCC1,SCARA3,MSH2,IL12B,BCL3,IVL,BRSK2,MSH6,POLD1,UACA,CASP9,HMGN1,IL12A,BCL2,BRSK1,UBE4B
GO:0048646	-0.14926	0	0	289	anatomical structure formation	BTG1,SCYE1,C1GALT1,POU5F1,GPX1,BMPR1A,SCG2,AMOT,DLX5,SMAD1,CYR61,ANG3,ATP5B,CITED2,CASP8,SOX2,DLX6,VHLH,PLXDC1,WASF2,CD9,ATPIF1,IL18,ANG,CEACAM1,TBPL1,JAG1,S1PR1,TRIM15,FGFR2,HBEGF,CDH13,SHB,ANGPT2,CRHR2,ADORA2B,TGFA,NCL,PKNOX1,NARG1,GLI3,RORA,MEIS1,BMP4,CHN2,RNH1,CANX,PRKACA,SMAD3,ARHGAP24,ESRRB,PLG,FRS2,PML,FGF9,GNA13,CDK5,FOXO4,GBX2,ITGAV,CEP290,LDB1,NUS1,EREG,THBS2,LECT1,DDAH1,PRKAR1A,SRF,HIF1A,ID1,PF4,SOX18,SERPINE1,SHC1,ITGB2,SMAD2,ECSIT,B4GALT1,PLXND1,MTPN,FGF6,SPINK5,TXNDC8,4930525M21RIK,SP1,WNT7A,SMAD5,HOXA3,FGF2,TBX20,ANGPTL3,EXT2,DL4,HMOX1,LHX5,TWSG1,NOG,VEZF1,ELK3,PLCD3,COL18A1,APOH,HS6ST1,FABP9,STAB2,HOXA1,RHOB,AGGF1,TNFRSF12A,MIXL1,WNT3,MESP1,KNDC1,HTATIP2,HESX1,CXCR4,EDN1,RUNX1,SERPINA3C,MMP2,EMCN,HAND2,NTF5,CTNNA1,CXCL12,PROK1,EPGN,ENPEP,FOXC2,TGFB2,HNF1B,CCNB1IP1,MEOX2,CASC5,PRL7D1,APOLD1,EDNRA,PMP22,NPR1,BMP7,GATA3,MMP19,ANGPTL4,ERBB2,SP3,EGR2,ANGPTL6,PITX2,PGF,NOTCH4,SH2D2A,FLT1,EGF,ZC3H12A,TEK,COL4A3,NKX3-2,ACVR1,NLE1,TXNRD1,ERAP1,CHRNA7,GHRL,SHH,TMPRSS6,MAP3K7,KLF5,GATA4,NOS3,GLI2,EOMES,VEGFB,ATP7A,STAB1,NOTCH1,PAFAH1B1,EFNA1,PTK2,NODAL,PDGFA,KRT1,ANXA2,PTEN,RBP1,PROK2,LEPR,HNF1A,THY1,SERPINF1,IL15,ANGPT1,TBX
GO:0051347	-0.14499	0	0	207	positive regulation of transferase activity	AVP1,PPAP2A,CHRNA3,PICK1,ADRA2C,GRM1,F2R,MAP2K1IP1,GRM4,PSEN1,PDGFC,GNB2L1,MAP2K1,CD4,SERINC3,PTLAD1,MAP3K1,DRD2,PTPRC,CD81,HTR2A,DGKK,ADORA2A,TPD52L1,MAP3K4,ANG,CEACAM1,EGFR,DAXX,PRKCZ,TLR3,ERCC6,ADORA2B,TLR4,TGFA,SERINC1,DGKB,CDC42,IL2,PRKD3,BDKRB1,MS4A2,GAB1,TIRAP,VLDLR,PTPN11,FRS2,ADRB2,DBNL,CDK5,PAK1,EREG,RAC1,INS2,SERINC5,IKBKG,SHC1,MAP3K13,NRK,GADD45G,MAP3K2,PLCE1,TGF83,PRLR,CARTPT,MAP3K7IP1,SOD1,FGF2,TLR1,ALS2CR2,SDC4,SYK,CRK,FCER1A,SPDYA,TRAF2,FPR1,BCL10,CCND1,PRKAA1,CD74,SERINC2,CXCR4,EDN1,NRG1,MDFIC,KITL,PROK1,EPGN,KISS1R,PAR3,CALCA,MAP3K5,TGFB2,PDE6G,IGH-6,LRRN3,ADRA2A,MAPBP1,GNAI2,EDNRA,MDF1,AGK,CERK,ERBB2,MAP4K5,IL1RN,FLT1,EGF,KRAS,ARRB1,SPHK2,JAK2,C5AR1,ELA2,GNG3,CHRNA7,GHRL,TRAF6,APOA1,ACVR2B,MAP3K7,SPAG9,DGKQ,PLA2G1B,EFNA1,TNFRSF10B,PIK3CB,MAPKB1,HCR,T,CENTG1,C1QTNF2,SPDYB,TLR6,VAV3,DGKD,PROK2,KLK1B4,MAP4K1,GAP43,IRAK2,DGKI,FGD4,CAMKK1,CSF1,MAP2K3,MAP3K6,PTK2B,PRKCD,MAP3K10,TNF,EDN3,TAOK2,CERKL,ADORA1,DGKZ,MALT1,CISH,HGF,CHRM1,IRAK1,CCK,TRAF7,PDE6H,IRS1,CARD14,CCDC88A,RAB26,ERN1,CARD10,PDGFB,ALS2,MADD,DGKH,VAV2,CD24A,GADD45B,MUC20,EDN2,SPHK1,ADRA2B,TNFSF15,DGKE,DGKG,DAB1,MAP3K11,CSPG4,PKN1,MAP2K6,KIT,MAPK8IP3,DGKA,BIRC7,TRP73,CCND3,INSR,MAP3K9,IL1B,TGFB
GO:0007517	-0.14033	0	0	273	muscle development	EZH2,BTG1,ACHE,CBY1,RXR2,F2R,TCF7L2,SGCE,GPX1,GPHN,MORF4L2,CHODL,RXR2,GAA,EMD,FOX2,EPC1,GJA1,FXR1,RARB,CSR2,SOX6,AFG3L2,RCAN1,CACNA2D2,MUSK,SNTA1,JAG1,FOX1,CXCL10,TAGLN2,HBEGF,FKTN,ATG5,BMP4,TAGLN,ACADM,CSF1R,SMAD3,RHOA,NR2F2,PLG,COL4A4,KY,ADRB2,CDK5,FOXO4,ACTA1,SGCA,MSTN,PAK1,MYLPF,ANKRD2,CACNG2,MYL6,MTM1,SRF,HIF1A,ITGB1BP3,CACNB2,TNNT2,CTF1,TCF12,MTPN,ERBB3,EVC,MEF2D,HIST1H1B,DOK7,PAX7,SGCD,SIX4,FGF6,4930525M21RIK,IGFBP5,LGALS1,SOD1,MEF2B,SIRT1,DTNBP1,TNNI1,P2RX2,MYO21,TNNI3,ITGB1,RXRA,TGFB1,PK3R1,TMOD1,SRPK3,SIRT2,CENPF,MBNL1,SIX1,KCNH1,UBB,EID2,FHL1,ACTG2,SVIL,SGCB,DES,NGFR,MRAS,MSX1,NRG1,DNER,NEURL2,PPP3CB,MYF5,CRYAB,SGCG,RPS6KB1,ACTC1,GATA6,TCAP,CTNNA1,NTN2L,LRP4,UNC45B,CHAT,MYL2,MYL3,CALCA,MYEF2,FOXC2,TAGLN3,SRI,KRT19,MEOX2,MYH7,CDON,CAV3,CAST,MYOCD,PAX3,PPP3CA,ERBB2,APP,MYH3,MYL9,PITX2,HSPB2,KREMEN1,MKL2,CHRNA1,UTRN,MYF6,KRAS,BARX2,ACVR1,TSC1,MBNL3,PLN,IGF1,PDLM3,METTL8,SHH,SOX15,CAV1,GSC,BOC,MEF2A,IGSF8,BDNF,NRAS,HDAC5,TAZ,NOTCH1,COL5A3,PTEN,NRD1,ELN,DMD,FOX2,TCF23,ACTG1,CACNB4,MKX,TWIST1,OBSL1,MOV10L1,VAMP5,NEB,BMP10,ITGB1BP2,MYOM2,PITX1,TBX3,HOPX,IFRD1,KRT8,CAPN2,MTSS1,CAV2,GJC1,MYOG,MYLK2,TNNC1,FOXC1

Table S3B. Gene sets down-regulated by severe stress plus morphine

Gene Ontology category	Score	p-value	FDR	Gene set length	Gene_set_description	Gene_set_genes
GO:0045859	-0.12891	0	0	303	regulation of protein kinase activity	AVPI1,BCCIP,PPAP2A,CHRNA3,PICK1,MNAT1,ADRA2C,GPS1,GRM1,F2R,MAP2K1IP1,GRM4,PSEN1,PDGFC,RGS4,GNB2L1,PPP2CA,CDKN1A,MAP2K1,CD4,CDKN2C,PTPLAD1,MAP3K1,DRD2,PTPRC,CD81,HTR2A,DGKK,PRKRIP1,ADORA2A,CDC6,TPD52L1,MAP3K4,ANG,CEACAM1,EGFR,CDC37,DAXX,PRKCZ,TLR3,DRD1A,GTF2H1,PKIG,ERCC6,CDC25C,DUSP16,ADORA2B,TLR4,TGFA,DGKB,CDK7,IL2,PRKD3,BDKRB1,CHEK1,MS4A2,GAB1,CCNE2,CDKN1C,HEXIM2,HEXIM1,TIRAP,PCDC4,SPRED1,VLDLR,PTPN11,FRS2,ADRDB2,DBNL,CDK5,FABP4,PAK1,EREG,CDK5RAP3,INS2,APLP2,IKBK,SHC1,SNX6,MAP3K13,NRK,GADD45G,NUP62,GTPBP4,MAP3K2,TARBP2,PAK2,DUSP22,PLCE1,CDK5R1,TGFB3,PRLR,CARTPT,MAP3K7IP1,KNG1,SOD1,FGF2,CCNT1,MEN1,TLR1,LAX1,ALS2CR2,TRIB2,HERC5,SDC4,ANAPC2,SYK,CRK,FCER1A,SPDYA,CKS2,TRAF2,FPR1,BCL10,APOE,CCND1,PRKAA1,LATS1,DUSP2,CASP3,CD74,PKIA,CXCR4,EDN1,NRG1,BLM,CDKN1B,MDFIC,MBIP,KITL,PROK1,EPGN,KISS1R,CDKN3,DRD5,PARD3,CALCA,HIPK3,MAP3K5,TGFBR2,PDE6G,IGH-6,LRRN3,CDKN2B,ADRA2A,MAPBPPIP,PSEN2,PKIB,GNAI2,EDNRA,MDFI,CAV3,AGK,CERK,ERBB2,MAP4K5,APP,DUSP8,CDKN2D,SSERTAD1,IL1RN,FLT1,EGF,CDKN2A,CKS1B,NCK2,KRAS,ARRB1,SPHK2,PPP2R1A,JAK2,GPS2,C5AR1,TSC1,ELA2,DUSP9,GNG3,CHRNA7,GHRL,TRAF6,ACVR2B,CAV1,GADD45A,MAP3K7,RGS3,SPAG9,DGKQ,PLA2G1B,SPRY1,EFNA1,TNFRSF10B,PIK3CB,MAPKB1
GO:0051098	-0.1271	0	0	120	regulation of binding	PRDX3,AGT,PCBD1,EIF2AK3,PSEN1,DNAJA3,SUMO1,RELA,EGLN1,PRMT8,AKTIP,PRKCO,NPM1,TLR3,EDA2R,UBE2V1,NME1,NR0B1,TLR4,JMY,SMAD3,LDLRAP1,APEX1,NFKBIA,ADRB2,SMARCD3,SIX6OS1,PYCARD,NLRP3,IKBK,ITGB2,SMAD2,MAP3K13,MAP1LC3B,GTPBP4,EDF1,MEN1,CALM2,HMOX1,NLRC3,DPH3,SMAD4,NARFL,TGFB1,FOXJ1,BAX,CEBPG,EDA,BCL10,TRAF3IP1,ATR,UBE2N,SIGIRR,TGFBR3,NRG1,ABRA,BLM,PRMT7,CREBZF,ARRB2,PEX14,CYTL1,HIPK3,MDFI,ADRB3,CAT,NFAM1,CDKN2A,RSF1,KRAS,ARRB1,JAK2,SHH,COMMD7,CARD9,HNF4A,PLA2G1B,NOD2,RUNX1T1,RIPK2,MYD88,HIPK1,BRD4,IRAK2,HMGA2,STK36,BCL3,HR,TAF6L,TSSK4,CARD11,TICAM1,TNF,CALM1,BAK1,SMO,ZCCHC11,MALT1,TAF6,IKBK,FOXPP3,DDIT3,CALM3,HIPK2,THRA,JD3,BCL2,TRIB1,ERC1,CAMK2A,NCOA3,IL1B,ID2,FLNA,ZFP462,AMH,CREBBP,YBX2,ICAM1,EP300
GO:0051338	-0.11236	0	0	320	regulation of transferase activity	AVPI1,BCCIP,PPAP2A,CHRNA3,PICK1,MNAT1,ADRA2C,GPS1,GRM1,F2R,MAP2K1IP1,GRM4,PSEN1,PDGFC,RGS4,GNB2L1,PPP2CA,RBL1,CDKN1A,MAP2K1,CD4,SERINC3,CDKN2C,PTPLAD1,MAP3K1,DRD2,PTPRC,CD81,CLN8,HTR2A,DGKK,PRKRIP1,ADORA2A,CDC6,TPD52L1,MAP3K4,ANG,CEACAM1,EGFR,CDC37,DAXX,PRKCZ,TLR3,DRD1A,GTF2H1,PKIG,ERCC6,CDC25C,DUSP16,ADORA2B,TLR4,TGFA,SERINC1,DGKB,CDC42,CDK7,IL2,PRKD3,BDKRB1,CHEK1,MS4A2,GAB1,CCNE2,CDKN1C,HEXIM2,HEXIM1,TIRAP,PCDC4,SPRED1,VLDLR,PTPN11,FRS2,ADRB2,DBNL,CDK5,FABP4,PAK1,EREG,RAC1,CDK5RAP3,INS2,SERINC5,APLP2,OAS1D,IKBK,SHC1,SNX6,MAP3K13,NRK,GADD45G,NUP62,RBL2,GTPBP4,MAP3K2,TARBP2,PAK2,DUSP22,PLCE1,CDK5R1,TGFB3,PRLR,CARTPT,MAP3K7IP1,KNG1,SOD1,FGF2,CCNT1,MEN1,TLR1,LAX1,ALS2CR2,TRIB2,HERC5,SDC4,ANAPC2,SYK,CRK,FCER1A,SPDYA,CKS2,TRAF2,FPR1,BCL10,APOE,CCND1,PRKAA1,LATS1,DUSP2,CASP3,CD74,PKIA,SERINC2,CXCR4,EDN1,NRG1,BLM,CDKN1B,MDFIC,MBIP,KITL,PROK1,EPGN,KISS1R,CDKN3,DRD5,PARD3,CALCA,HIPK3,MAP3K5,TGFBR2,PDE6G,IGH-6,LRRN3,CDKN2B,ADRA2A,MAPBPPIP,PSEN2,PKIB,GNAI2,EDNRA,MDFI,CAV3,AGK,CERK,ERBB2,MAP4K5,APP,DUSP8,CDKN2D,SSERTAD1,IL1RN,FLT1,EGF,CDKN2A,CKS1B,NCK2,KRAS,ARRB1,SPHK2,PPP2R1A,JAK2,GPS2,C5AR1,TSC1,ELA2,DUSP9,GNG3,CHRNA7,GHRL,TRAF6,APOA1,ACVR2B,CAV1,GADD45A,MAP3K7,RGS3,SPAG9,DGKQ,PLA2G1B,SPRY1,EFNA1,TNFRSF10B,PIK3CB,MAPKB1

Table S4A - Micortubule bundle formation

Gene	Score
OFD1	1.996056396
BBS2	1.233417218
UBE2B	1.125578851
TPPP	0.874182947
NEURL	0.773212169
GTRGEO22	-0.097471853
PSRC1	-0.214113372
MTAP1S	-0.541792902
MTAP2	-0.788067588
MARK4	-1.111905458
CLASP1	-1.171900632
MTAP1B	-1.32341063
NAV1	-2.128027623

Table S4B - Dendrite development

Gene	Score
MCF2	2.316665
BBS4	1.764101
ACHE	1.641147
CHRNA3	1.601749
KLHL1	1.241991
SMAD1	1.198219
IGSF9	1.195423
CHRNA2	1.109888
HPRT1	1.028005
LZTS1	1.000817
TRAPPC4	0.971036
PSCD2	0.889905
SGK1	0.815338
RHOA	0.774777
CIT	0.70722
CDK5	0.7038
PAK1	0.670184
RAC1	0.667283
NTRK2	0.633381
CACNA1F	0.468849
MYO6	0.43411
KNDC1	0.382429
ABI2	0.370328
YWHAH	0.344921
CHAT	0.302209
BBS1	0.283321
SCARF1	0.259185
MT3	0.247251
APP	0.196735
ARF6	0.191648
LST1	0.168843
MECP2	0.152421
GHRL	0.109317
DCLK1	0.098058
BDNF	0.081723
ATP7A	0.068714
SS18L1	-0.0619
PRKG1	-0.25818
TLX2	-0.27854
DVL1	-0.35319
PPP1R9B	-0.45545
PTPRF	-0.4975
FEZF2	-0.50171
GRIN3A	-0.50956
DBN1	-0.58584
DCX	-0.72881
SIPA1L1	-0.73202
MTAP2	-0.78807
NRP1	-0.82315
KALRN	-1.14862
CACNA1A	-1.22864
KLF7	-1.27791
MTAP1B	-1.32341
CELSR2	-1.51836
SYNGAP1	-1.59457

Table S4C - Regulation of axonogenesis

Gene	Score
ACHE	1.641147012
SPP1	1.380656466
PSEN1	1.306903405
SEMA4D	1.15949539
CDH4	0.99509717
SEMA3A	0.988911871
NTN1	0.921794031
SEMA3F	0.886683341
MBP	0.883054004
PLXNB2	0.834097522
RNF6	0.796040426
LRRC4C	0.573494476
ROBO2	0.558065285
POU3F2	0.52763915
WNT7A	0.518874108
RUFY3	0.490270984
APOE	0.417534987
TNFRSF12A	0.407960485
NEFL	0.367509825
BARHL2	0.359643048
PLXNB1	0.261920795
ULK2	0.261141994
MIF	0.146005957
EFNA1	0.054075306
PTK2	0.049376833
THY1	-0.012919509
CDH2	-0.068403515
LIMK1	-0.162577386
AMIGO1	-0.164930427
TTL	-0.197500532
NEFM	-0.250878699
METRNL	-0.255729546
RTN4R	-0.276350039
DPYSL2	-0.325979231
ULK1	-0.380644085
TIAM1	-0.432371467
SEMA4F	-0.433810793
RTN4	-0.448608378
KLK8	-0.539458722
CSPG4	-0.557178817
MAPT	-0.621722674
NRCAM	-0.639936933
NGF	-0.711203576
EPHB2	-0.763462382
ROBO1	-0.790316202
NRP1	-0.823145385
SLIT2	-0.928315056
NTRK3	-1.162799683
CACNA1A	-1.228640639
PLXNA3	-1.27355713
SYNGAP1	-1.594571863

Table S5A - Aerobic respiration

Gene	Score
POLR3H	2.979493079
PDHB	2.766343743
SUCLA2	1.575066443
SUCLG1	1.550458589
MDH1	1.544756007
ME3	1.454191795
UQCRB	1.326788885
OXA1L	1.306376066
FH1	1.257399593
ADSL	1.212541301
UQCRC1	1.13657849
UQCRH	1.131904216
SLC25A14	1.11330701
ATP5G3	1.112117509
IDH3B	1.089403069
UQCRC2	1.018920115
ACO2	1.015636151
SDHA	0.942093473
SUCLG2	0.935235924
SDHD	0.895610294
SDHB	0.882441321
MDH1B	0.835804964
SDHC	0.739816814
IDH3A	0.70710883
IDH3G	0.701619123
IDH2	0.687573659
SURF1	0.530667089
DLST	0.42169367
NNT	0.415837543
CS	0.40631418
MDH2	0.227294699
CAT	0.195949555
COX1	0.09218332
IDH1	0.006997654
ACO1	-0.054939436
COX10	-0.210097949
2610507B11RIK	-0.288809549
FXN	-0.299712072

Table S5B - Cellular response to stress

Gene	Score
ASNS	1.458821
EIF2AK3	1.338014
PSEN1	1.306903
CLN3	1.123042
ATG16L1	1.013702
EIF2B1	1.013152
EIF2B3	0.996263
EIF2B4	0.974435
KRT20	0.9121
ATG4C	0.87095
PPP1R15B	0.860007
ATG5	0.855805
EIF2S1	0.843436
ATG4D	0.823277
WFS1	0.793309
ATG12	0.753368
ATG4B	0.7439
EIF2B5	0.743763
SREBF1	0.684621
CTSD	0.674239
EIF2AK4	0.652226
HIF1A	0.633127
INS2	0.627863
BECN1	0.569986
PCSK9	0.563132
ALB	0.553017
CARTPT	0.529563
HMOX1	0.486094
TRP53	0.468827
MAP1LC3A	0.461529
HFE	0.458487
GLRX2	0.440041
ARNT	0.422939
ATG10	0.422446
HSPA5	0.422116
ATG9A	0.286624
FADS1	0.257263
NPC1	0.221727
ANGPTL4	0.209596
PRKCD	-0.107848
JUN	-0.11344
ATG4A	-0.219351
DDIT3	-0.237319
HRK	-0.335333
NUAK2	-0.383939
FOXA3	-0.453937
FRAP1	-0.454252
ATG9B	-0.512136
AVPR1A	-0.630101
EPAS1	-0.651735
GSK3B	-0.830722

Table S5C - ATP synthesis coupled electra

Gene	Score
NDUFS6	2.094409
NDUFB4	1.859132
NDUFB5	1.691591
NDUFS5	1.558792
NDUFA1	1.549671
NDUFAB1	1.373993
UQCRB	1.326789
NDUFS2	1.27106
NDUFA9	1.244848
NDUFS3	1.193021
NDUFA2	1.182373
NDUFB6	1.179208
NDUFA8	1.140837
NDUFA7	1.133453
UQCRH	1.131904
NDUFA5	1.116749
NDUFC1	1.098126
NDUFB2	1.097799
NDUFB8	1.092862
NDUFS1	1.087287
NDUFS4	1.07959
UQCR	1.05645
NDUFB9	1.056366
NDUFB3	1.042503
NDUFA10	1.040563
NDUFB7	1.037141
NDUFS7	1.019619
NDUFV1	0.989429
NDUFC2	0.957655
NDUFA4	0.935808
NDUFV2	0.914707
DLD	0.86863
COX15	0.777085
NDUFA3	0.740542
NDUFAF1	0.737211
NDUFS8	0.701252
NDUFB10	0.627861
NDUFA6	0.607404
ND3	0.429802
15RIK	0.390586
ND1	0.311259
ND5	0.13161
COX2	0.120325
COX1	0.092183
BDNF	0.081723
TAZ	0.065839
ND4L	0.054199
ND6	-0.108924
COX10	-0.210098
COX8B	-0.313986