Supplementary Information

Genome-Wide Association Identifies Diverse Causes of Common Variable Immunodeficiency

Jordan S. Orange, Joseph T. Glessner, Elena Resnick, Kathleen E. Sullivan, Mary Lucas, Berne Ferry, Cecilia E. Kim, Cuiping Hou, Fengxiang Wang, Rosetta Chiavacci, Subra Kugathasan, John W. Sleasman, Robert Baldassano, Elena E. Perez, Helen Chapel, Charlotte Cunningham-Rundles, Hakon Hakonarson

Supplementary Method

Support Vector Machine Method for Possible Prediction of CVID Status and Development of Complications based on a Targeted SNP Panel

A Support Vector Machine (SVM) is a decision-based prediction algorithm which can classify data into several groups. SVM is based on training data mapped to a higher dimensional space and separated by a plane defining the two classes of data, followed by a testing stage where status is predicted based on the model and compared to known status to test the accuracy (1). The implementation of SVM used is LIBSVM software (2,3). Genome-wide SNP microarrays provide 610,000 genotypes which tag the genome in an unbiased way without need for prior hypothesis concerning candidate genes. Classical genome-wide association methods evaluate single SNP significance for difference in allele frequency. Although successful, the reality that many common complex diseases are polygenic in etiology with epistasis of multiple gene combinations makes an integrative model utilizing more of the data content more incisive. The application of SVM to genome-wide SNP data provides a robust framework for clinical disease prediction to evaluate risk and enact preventative measures, as we have demonstrated previously for type 1 diabetes (4).

There are two components to the data: the target value which is the classification of the subject and the corresponding attributes which are more granular characteristics. In the application to CVID, we sought to predict target Values (Class Labels): CVID (yes/no),

Bronchiectasis (yes/no), and OSAI (yes/no). This prediction is based on the attributes (features or observed variables): Genotypes for the top 1,000 SNPs previously identified from case:control genome-wide association (top 0.16% of original data set and all $P<0.0015$).

Phenotype labels were scaled to +1 for affected and -1 for unaffected. Genotype data is scaled with AA=0, AB=0.5 and BB=1. Data is mapped to high dimensional space by the LIBSVM algorithm to differentiate populations (2,3). Iterations of a coarse grid are followed by finer grids to avoid excessive time expenditure of complete grid search. The SVM is based principally on two variables: cost *C* (the penalty parameter of SVMs) and γ= 1/number of variables. The SVM type in our application was C-SVM classification which runs through iterations of minimizing error functions while maintaining a hyperplane with maximum margin to avoid overfitting. The kernal function maps attribute data into a higher dimensional space to improve distinguishing characteristics. The kernel type in this application was a radial basis function (RBF) which is based on distance from an origin. Once the SVM model is established through training and validated for accuracy with an independent dataset in testing, additional data can be mapped and prediction made based on the model.

Support vector machines (SVM) approach is a machine learning approach that can map combinations of genotypes in high dimensional space. The top 1000 significant SNPs from the discovery case:control genotype association studies we used as observed characteristics to form a designation decision between CVID (common variable

immunodeficiency) case and an individual not affected by CVID. The dataset available was separated into a training set of 179 cases and 1,917 controls which the SVM model is based on. In this training set, the case/control label and genotype attributes guide model formation. In the testing set of independent 109 cases and 1,114 controls, only the genotype attributes are supplied to the model established during training which then distinguishes cases or controls based on the genotype profile. The simple diagnostic yes or no question is: based on this person's genotypes do they have CVID? The prediction accuracy turned out well: positive predictive value and negative predictive value of 1.0 and 0.957, respectively.

To demonstrate poor model accuracy based on the same SVM methods, we ran the training stage with randomized testing data. The Bronchiectasis model applied to random affected labels and random genotypes resulted in a prediction accuracy of 27.1%. The Bronchiectasis model applied to random affected labels and correct genotypes resulted in a prediction accuracy of 77.1%. The OSAI model applied to random affected labels and correct genotypes resulted in a prediction accuracy of 67.7%. Given these markedly poorer accuracy results from randomized data compared to our observed data bolsters confidence that our high success rate is less likely due to a confounding factor, bias, or error. Regardless of assurances based on the modeling success rate these results should be taken as preliminary and will require additional data to reach ultimate application in clinical settings.

Supplement References:

1. V. Vapnik. The Nature of Statistical Learning Theory. Springer-Verlag, New York, NY, 1995.

2. Chih-Chung Chang and Chih-Jen Lin, LIBSVM : a library for support vector machines, 2001. Software available at http://www.csie.ntu.edu.tw/~cjlin/libsvm

3. C. W. Hsu, C. C. Chang, C. J. Lin. A practical guide to support vector classification, 2003.

4. Wei Z, Wang K, Qu HQ, Zhang H, Bradfield J, Kim C, Frackleton E, Hou C, Glessner JT, Chiavacci R, Stanley C, Monos D, Grant SF, Polychronakos C, Hakonarson H. From disease association to risk assessment: an optimistic view from genome-wide association studies on type 1 diabetes. PLoS Genet. 2009 Oct;5(10):e1000678. Epub 2009 Oct 9.

Supplemental Tables

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Supplementary Table 1: CVID Subphenotypes and Sample Sizes

CVID Subphenotype	Cases	Controls
Cancer	13	249
Lymphoma	9	253
Lymphadenopathy	30	232
NRH	13	249
LIP	10	252
Bronchiectasis	78	184
Granuloma	34	228
GIEnteropathy	19	243
Malabsorption	13	249
Splenectomy	40	222
Cytopenias	27	235
OSAI	75	187
Low IgM (<50 mg/dL)	206	56
Low IgA (<10 mg/dL)	160	102
CD19 (<1%)	11	251
AgeOnsetSx (<10 yrs)	42	220

Supplementary Table 2. CVID Patients with GI Enteropathy vs CVID Patients without Genotype Association Replication in IBD Based on Single SNP Significance

SNP	Gene	Distance	P_CVID+GIEnteropathy(IBD)	Allele1	F_A	F_U	OR	P_IBD	Allele1	F_A	F_U	OR
rs6532122	*GPRIN3*	3497	0.001204	A	0.2632	0.0947	3.42	9.90E-8	A	0.0786	0.1072	0.7109
rs17041264	*COLQ*	196	0.000368	T	0.1579	0.0350	5.17	3.15E-6	T	0.0049	0.0135	0.3608
rs12889533	*C14orf143*	19903	0.000561	T	0.1316	0.4156	0.21	1.28E-4	T	0.3563	0.3878	0.8736

rs12889533 replicates with allele frequency in the same direction while rs6532122 and rs17041264 are significant in the opposite direction of allele frequency.

Supplementary Table 3: Large Genic CNVs Impacting Single CVID Cases not Observed in Controls

A) Deletions Impacting Immune Genes

CNVR Del Singleton	Count SNPs	Distance From Exon	Gene
chr4:86650109-87684765	209	0	*ARHGAP24,BC038746,**MAPK10***
chr16:75457204-76988778	78	0	*ADAMTS18,AK026469,BC035731,CLEC3A,KIAA1576,MON1B,**WWOX***
chr3:74573112-74866049	66	0	***CNTN3***
chr19:56625454-56761712	64	0	*LOC729767,**SIGLEC12**,**SIGLEC6**,**SIGLEC8***
chr4:103671292-104700248	51	0	*AK093356,BDH2,CENPE,CENPE variant protein,CR604221,LOC133308,MANBA,**NFKB1**,NHEDC1,UBE2D3,UNQ6308,ZCD2*
chr14:43997374-46152755	45	0	*AX748292,BC038722,C14orf106,C14orf155,C14orf28,FANCM,**FKBP3**,KIAA0423,KLHL28,PRPF39*
chr6:29844580-30045812	44	0	*AK097625,BC035647,**HLA-A,HLA-A*0226,HLA-G,HLA-G2.2**,LOC554223,LOC642032,NR_001317,NR_001318,NR_002139*
chr2:86695685-87945980	40	0	*ANAPC1,BC066991,**CD8A**,**CD8B**,DQ576041,LOC285074,MGC4677,PLGLB1,PLGLB2,RGPD1,RGPD2,RMND5A,RNF103*
chr6:22380732-22525808	40	0	***PRL***
chr6:31465923-33432505	34	0	*AF075059,**AGER**,AGPAT1,**AIF1**,AK057104,AL050203,APOM,ATP6V1G2,B3GALT4,**BAT1**,BAT2,BAT3,**BAT4**,**BAT5**,**BF**,**BRD2**,**BTNL2**,**C2**,**C4A**,C4A variant protein,C6orf10,**C6orf21**,**C6orf25**,C6orf26,C6orf27,C6orf31,C6orf47,C6orf48,**CFB**,CLIC1,COL11A2,CREBL1,CS266662,CSNK2B,CYP21A2,**DAXX**,DDAH2,DKFZp313H139,DKFZp547I194,**DKFZp779M0311**,DOM3Z,EGFL8,EHMT2,**FKBPL**,G18.1a,G6E,G6e,G7c,G8,GPSM3,HCP5,**HLA-DMA,HLA-DMB,HLA-DOA,HLA-DOB,HLA-DPA1,HLA-DPB1,HLA-DPB2,HLA-DQA1,HLA-DQA2,HLA-DQB1,HLA-DQB2,HLA-DRA,HLA-DRB1,HLA-DRB5,**HSD17B8,**HSPA1A,HSPA1B**,HSPA1L,LOC401252,LSM2,**LST1,LTA,LTB**,**LY6G5B**,LY6G5C,LY6G6C,LY6G6D,MCCD1,MEGT1,**MICA,MICB,MSH5,NCR3,NEU1**,NFKBIL1,NG36/G9a,NOTCH4,NR_002742,NR_002745,NR_002812,NR_002971,NR_003140,**PBX2,PFDN6,PP199**,PPT2,PRRT1,**PSMB8,PSMB9,RAGE**,RDBP,RGL2,RING1,RNF5,RP,RPS18,RXRB,SKIV2L,SLC39A7,SLC44A4,STK19,**TAP1,TAP2,TAPBP,TNF,TNFa**,TNXB,VARS,VPS52,WDR46,ZBTB12,ZBTB22*
chr2:70616413-71523501	30	0	*ADD2,AF090102,ANKRD53,ATP6V1B1,**CD207**,CLEC4F,FIGLA,KIAA1155,MCEE,MPHOSPH10,N-Acetylglucosamine kinase,NAGK,NP220,OR7E91P,TEX261,**TGFA**,VAX2,ZNF638*
chr8:95257759-96161427	28	0	*AF086017,AX747981,C8orf38,CCNE2,**CDH17**,DPY19L4,FSBP,**GEM**,INTS8,KIAA1429,RAD54B,RBM35A,TP53INP1,p53DINP1*
chr1:184639488-185615061	24	0	*C1orf27,PDC,**PLA2G4A**,**PTGS2***
chr4:124486894-125137357	21	0	*AL833449,BC053945,**SPRY1***
chr1:226522770-226673588	20	0	***KIAA1556,KIAA1639,OBSCN**,TRIM11,TRIM17*
chr21:14806346-14824849	17	0	***HACS1,SAMSN1***
chr7:84542383-84633646	16	0	***SEMA3D***
chr4:162635366-163113553	15	0	***FSTL5***
chr19:48834611-49626859	15	0	*AK090553,AK098175,AK131520,AX748287,BC041923,BC045755,**CADM4**,CR593740,DKFZp564H1322,FLJ12886,HZF19,HZF6,**IRGC**,KCNN4,LYPD5,**PLAUR**,ZNF155,ZNF221,ZNF222,ZNF223,ZNF224,ZNF225,ZNF226,ZNF227,ZNF228,ZNF229,ZNF230,ZNF233,ZNF234,ZNF235,ZNF284,ZNF285A,ZNF404,ZNF45*
chr4:90603695-91299621	14	0	*AK123890,CR605611,KIAA1680,MGC48628,MMRN1,**SNCA***
chr6:138020053-138532047	14	0	*AK124173,PERP,**TNFAIP3***
chr7:30225447-30798217	14	0	*AK096056,AK096687,AK097240,AL137445,BC016976,BC041636,BX648714,C7orf24,CR595731,CRH2R,**CRHR2**,FLJ22374,GARS,INMT,**NOD1**,NR_002186,ZNRF2*
chr12:55685282-	14	0	*ARHGAP9,AVIL,B4GALNT1,BC019026,BC033961,BC073932,CDK4,CENTG1,CR625*

56515644			*050,CS444342,CTDSP2,CYP1,CYP27B1,DCTN2,DDIT3,DTX3,FAM119B,G43318,GEFT,GLI1,INHBC,INHBE,KIAA0286,KIAA1002,KIF5A,**LRP1**,MARCH9,MARS,MBD6,METTL1,MYO1A,NAB2,NDUFA4L2,NXPH4,OS9,PIP5K2C,R3HDM2,RGL1,SHMT2,SLC26A10,STAC3,**STAT6**,TAC3,TSFM,TSPAN31,ZBTB39,ZNEUROK1*
chr16:86267434-86992013	14	0	*AK126852,AX747795,BANP,CA5A,DKFZp434G0522,FLJ00104,JPH3,KLHDC4,**SLC7A5***
chr2:179266611-179839804	13	0	*AK123298,CR624402,**FLJ39502**,SESTD1,**TTN***
chr3:95106214-95125111	12	0	***PROS1***
chr2:36745429-37640775	11	0	*AK001814,BC017652,CCDC75,CEBPZ,**EIF2AK2**,HEATR5B,KIAA1414,PRKD3,PRO1853,QPCT,STRN,SULT6B1,VIT*
chr4:151504432-151570906	11	0	***DKFZp686K03100,LRBA***
chr11:127094060-128138864	11	0	*AX747861,BC039676,DKFZp686D0662,**ETS1**,FLI1*
chr1:31912222-32647867	10	0	*AK096192,BAI2,BAI2,BC069257,BC111382,BSDC1,C1orf90,C1orf91,CCDC28B,COL16A1,CR601100,DCDC2B,DKFZp564C2082,DKFZp686B09139,EIF3S2,**HDAC1**,IQCC,**KHDRBS1**,KPNA6,**LCK**,LOC339483,**MARCKSL1**,PTP4A2,SPOCD1,TMEM39B,TSSK3,TXLNA,UNQ548*
chr3:106447305-107177994	10	0	***ALCAM,CBLB,Nbla00127***
chr6:161278798-161959701	10	0	*AGPAT4,C6orf59,LPAAT-delta,MAP3K4,MTK1,**PARK2**,parkin*
chr7:24205709-24955079	10	0	*DFNA5,ICERE-1,KIAA0704,MPP6,**NPY**,OSBPL3*

B) Deletions Not Impacting Immune Genes

CNVR Del Singleton	Count SNPs	Distance From Exon	Gene
chr3:163785970-165636507	94	0	*BC073807,LOC647107*
chr2:78159130-78549747	86	0	*BC024248,BC030125*
chr3:7053179-7177909	49	0	*GRM7*
chr11:109142987-110423998	48	0	*AK094117,AK124179,ARHGAP20,DKFZp434I0812,FDX1,KIAA1726,NR_001287,RDX*
chr12:27002588-28111983	44	0	*AK000807,ARNTL2,BC043511,DKFZp564O1863,FGFR1OP2,KIAA0965,KIAA1230,KLHDC5,LOC728858,MDS023,MRPS35,PPFIBP1,PTHLH,REP15,STK38L,SURB7,TM7SF3*
chr6:97170276-97625708	39	0	*C6orf66,FHL5,GPR63,KIAA1900,KLHL32*
chr6:163188894-163315053	35	33591	*PACRG*
chr16:9624870-10467886	35	0	*ATF7IP2,DKFZp666E123,DQ587956,DQ595173,GRIN2A,U07199*
chr7:64220284-64795508	34	0	*AK057766,DQ596928,FLJ25037,LOC441242,ZNF92*
chr5:90035491-90386715	33	0	*GPR98,KIAA0686,VLGR1*
chr3:37578530-37705809	32	0	*ITGA9*
chr6:38413748-38630608	32	0	*BTBD9*
chr20:51844911-51931244	28	0	*NR_002189*
chr15:57055702-57917444	26	0	*BNIP2,CCNB2,DKFZp761D081,FAM81A,GCNT3,GTF2A2,LDHAL6B,MYO1E,RNF111*
chr15:54225066-54550705	24	0	*MNS1,TEX9*
chr17:3128134-3194433	23	0	*OR3A1,OR3A2,OR3A4*
chr7:7480856-7819889	22	0	*AK027125,COL28,COL28A1,FLJ20323,RPA3*
chr10:94222227-94754640	22	0	*EXOC6,HHEX,IDE,KIF11*

chr14:91502061-91569101	21	0	*TRIP11,Trip230*
chr2:42398844-43092929	19	0	*COX7A2L,EML4,HAAO,KCNG3,MTA3,OXER1*
chr14:26535543-27350537	19	0	*BX538073*
chr14:92744837-93367366	19	0	*BTBD7,C14orf130,COX8C,KIAA1409,PRIMA1*
chr2:14622841-14924411	18	0	*AX747684,FAM84A*
chr12:10589522-10635183	17	0	*KLRA1*
chr3:99229541-99419735	16	0	*CR749263,OR5AC2,OR5H1,OR5H14,OR5H15*
chr2:132326867-132449751	15	0	*FLJ41821*
chr4:9136858-9881191	15	0	*DKFZp586I2219,DQ581767,DQ583133,DQ584082,DQ585713,DQ589421,DRD5,SLC2A9,WDR1*
chr4:128805691-128920529	15	0	*INTU,SLC25A31*
chr9:16987947-17478111	15	0	*C9orf39,RP11-340N12.1*
chr14:59952568-60075378	15	0	*C14orf39,SIX6*
chr18:5682313-5922670	15	0	*AF301223,TTMA*
chr19:23304120-23389292	15	0	*AK022793,BC038574,BC043213,ZNF91*
chr12:39980210-40809427	14	0	*GLT8D3,PDZRN4*
chr19:19759149-20368239	14	0	*CR593334,CR614976,DKFZp761G18121,FLJ44894,NR_003128,ZNF253,ZNF486,ZNF506,ZNF682,ZNF90,ZNF93*
chr2:98228529-98252357	13	0	*DKFZp434J0326,DKFZp451I0318,MGC26733*
chr2:168309981-169429627	13	0	*AL080192,B3GALT1,BC035245,LASS6,NOSTRIN,STK39*
chr4:22663503-22803604	13	0	*CR607430*
chr5:107695465-109245567	13	0	*AK021888,BC034788,FBXL17,FER,MAN2A1,PJA2*
chr4:20984915-21185852	12	0	*KCNIP4*
chr5:178315216-178514465	12	0	*ADAMTS2,BX648737,CR598488,GRM6,ZNF354C,ZNF454,mGluR6*
chr17:55759021-56436171	12	0	*APPBP2,BCAS3,C17orf64,L32131,PPM1D,USP32*
chr18:60137564-60597211	12	0	*BC036306*
chr5:38305919-38317501	11	11209	*EGFLAM*
chr6:12643097-13219417	11	0	*PHACTR1,RPEL*
chr4:69405358-69494103	10	0	*TMPRSS11E*
chr9:40497792-40617437	10	0	*AK024257*
chr11:102824056-102856185	10	0	*DYNC2H1*
chr11:124360372-124420328	10	0	*CCDC15*
chr12:47817725-47931507	10	0	*TUBA1A,TUBA1B,TUBA1C*
chr14:62671250-62971495	10	0	*GPHB5,PPP2R5E,RHOJ*
chr15:91046103-91378387	10	0	*CHD2,DKFZp781D1727,LOC400451*

C) Duplications Impacting Immune Genes

CNVR Dup Singleton	Count SNPs	Distance From Exon	Gene
chr19:5773490-12007370	827	0	***ACP5***,ACSBG2,ADAMTS10,AF019226,AF075036,AF161365,AK056073,AK097685,AK124717,ALKBH7,ANGPTL4,ANGPTL6,ANKRD25,ANKRD47,AP1M2,ARHGEF18,ASAH3,ATG4D,AX747405,AX747599,AX748210,AY203940,BC007593,BC014506,BC029904,BC033124,BC039523,BC042816,***BGR***,C19orf39,C19orf45,C19orf52,***C19orf59***,***C3***,CAPS,CARM1,***CCL25***,***CD209***,CD320,***CD70***,CDC37,CDKN2D,***CLEC4G***,***CLEC4M***,CLPP,CNN1,COL5A3,CR598956,CRB3,CTXN1,DENND1C,DKFZp547H118,DKFZp564K0223,DKFZp564O1762,DKFZp666A071,DKFZp667O2312,DKFZp761J1410,DKFZp761K0816,DNM2,***DNMT1***,DOCK6,***ECSIT***,EDG5,EDG8,EIF3S4,***ELAVL1***,ELAVL3,ELOF1,EMR1,***EMR4***,***EPOR***,EVI5L,FBN3,FBXL12,***FCER2***,FLJ00153,FLJ11286,FLJ12949,FLJ20079,FLJ22184,FLJ25758,***FUT3***,FUT5,FUT6,GPR108,GTF2F1,HNRPM,HSZFP36,***ICAM1***,***ICAM3***,***ICAM4***,***ICAM5***,***ILF3***,INSR,KEAP1,KHSRP,KIAA0521,KIAA1395,KIAA1518,KIAA1543,KIAA1588,KIAA1776,KIAA1978,LASS4,LDLR,LOC126075,LOC162993,LOC388503,LOC401898,LOC440508,LOC55908,LPPR2,LRRC8E,***MAP2K7***,MARCH2,MBD3L1,MBD3L2,MCOLN1,MGC19604,MGC20983,MGC33407,***MKK7***,MLLT1,MRPL4,***MUC16***,MYO1F,MYO1F variant protein,NDUFA11,NDUFA7,NRTN,OLFM2,OR1M1,OR2Z1,OR7D2,OR7D4,OR7E24,OR7G1,OR7G2,OR7G3,P2RY11,PCP2,***PDE4A***,PEX11G,PIN1,PNPLA6,PPAN,PPAN-P2RY11,PRAM1,PRKCSH,PSPN,QTRT1,RAB11B,RAB3D,RANBP3,RAVER1,RDH8,***RETN***,RFX2,RGL3,RPS28,SH2D3A,SLC25A23,SLC25A41,SLC44A2,SMARCA4,SNAPC2,SPC24,STXBP2,TIMM44,***TMED1***,***TNFSF14***,***TNFSF9***,TRAPPC5,TRIP10,TSPAN16,***TUBB4***,***TYK2***,UBL5,UNQ2443,UNQ501,***VAV1***,VMAC,XAB2,YIPF2,ZNF121,ZNF177,ZNF266,ZNF317,ZNF358,ZNF414,ZNF426,ZNF433,ZNF439,ZNF440,ZNF441,ZNF491,ZNF557,ZNF558,ZNF559,ZNF560,ZNF561,ZNF562,ZNF627,ZNF653,ZNF69,ZNF699,ZNF700,ZNF763,pp10122
chr14:92664804-95787550	448	0	AK125038,ASB2,BC016484,BC037859,BC038791,***BDKRB2***,BTBD7,BX247990,C14orf109,C14orf130,C14orf132,C14orf139,C14orf142,C14orf152,C14orf48,C14orf49,CLMN,COX8C,CR611440,DDX24,***DICER1***,FAM14A,FAM14B,GIG24,GLRX5,GSC,IFI27,***KIAA0928***,KIAA1409,KIAA1622,MOAP1,NM_207443,NR_001459,NR_003002,OTUB2,P27,PRIMA1,SERPINA1,SERPINA10,***SERPINA11***,SERPINA12,SERPINA13,SERPINA3,SERPINA4,***SERPINA5***,***SERPINA6***,***SERPINA9***,***TCL1A***,TCL1B,TCL6,TCL6a1,TCL6d1,TML1
chr11:7678446-10337351	315	0	***ADM***,AK000908,AK055772,AK090613,ASCL3,AX747224,BC017787,BC027619,BC068088,BC073899,BCA3,C11orf16,C11orf17,CMT4B2,CR598129,DKFZp451C1317,DKFZp686I18166,EIF3S5,IPO7,KIAA0298,KIAA1766,LMO1,MGC10850,***NLRP10***,NRIP3,NR_002580,NR_002962,NR_002977,OR10A3,OR10A6,OR5E1P,OR5P2,OR5P3,OVCH2,RAB6IP1,***RIC3***,RPL27A,SBF2,SCUBE2,ST5,STK33,SWAP70,TMEM41B,TMEM9B,TUB,U80769,WEE1,ZNF143
chr13:100600344-103567030	197	0	AK093430,AK096424,AK125748,AX747578,***BIVM***,C13orf27,CR616826,DKFZp434L2319,ERCC5,FGF14,ITGBL1,KDELC1,LOC196541,RP11-430M15.2-003,SLC10A2,TPP2,UNQ1910,VGCNL1
chr14:65357663-66177823	159	0	CR594591,***GPHN***,MGC88374
chr4:119628184-120591177	158	0	AK000709,AK024248,AK097701,AK098126,BC035733,BC070391,CEP170L,DQ574659,DQ575011,DQ575856,DQ576410,DQ582480,DQ599872,***FABP2***,KIAA0755,KIAA1627,LOC401152,MYOZ2,Myopodin,SEC24D,SYNPO2,USP53
chr8:106761674-108458326	156	0	ABRA,***ANGPT1***,CR602836,Nbla00307,OXR1,ZFPM2
chr4:113049611-113759418	129	0	ALPK1,C4orf16,C4orf21,C4orf32,CR590073,DKFZp434C0927,FLJ00302,KIAA1527,LOC91431,NEUROG2,***TIFA***
chr15:40145534-40608559	90	0	***CAPN3***,GANC,KIAA0770,PLA2G4D,PLA2G4F,SNAP23,TMEM87A,VPS39,ZFP106
chr14:43658461-45064383	87	0	AX748292,BC038722,C14orf106,C14orf155,C14orf28,FANCM,***FKBP3***,KIAA0423,KLHL28,PRPF39
chr10:67399581-69536663	75	0	CTNNA3,DNAJC12,HERC4,LRRTM3,***MYPN***,SIRT1
chr3:107041527-108030375	71	0	***CBLB***
chr9:137454076-139460602	70	0	ABCA2,AF161442,AGPAT2,AK023162,AK054908,AK055547,AK090585,AK096249,AK098241,AK128153,AK128864,AL832276,ANAPC2,AX747706,AY952890,BC015688,BC032375,BC034456,BC042667,BC043225,BC061888,BC064596,BC092490,BC101937,BTBD14A,***C8G***,C9orf116,C9orf139,C9orf140,C9orf142,C9orf163,C9orf167,C9orf75,C9orf86,CAMSAP1,***CARD9***,CLIC3,COBRA1,CR614579,CR619051,DKFZp434B205,DKFZp564M173,DKFZp762I052,DPP7,EDF1,EGFL7,ENTPD2,ENTPD8,FAM69B,FBXW5,FLJ20433,FLJ45224,FUT7,GBDR1,GLT6D1,GPSM1,GRIN1,HBE269,INPP5E,KCNT1,KIAA0310,KIAA0649,KIAA1062,KIAA1422,KIAA1984,LCN1,LCN10,LCN12,LCN6,

			LCN8,LCN9,LHX3,LOC389813,LOC389816,LOC401565,LOC441476,LOC728489,MAMDC4,MAN1B1,MGC14327,MGC59937,MGC61598,MRPS2,MRPS2,NDOR1,**NOTCH1**,NOXA1,NPDC1,NPTIIc,NR1,NR_002958,NR_002975,OBP2A,**PAEP**,PHPT1,PMPCA,PTGDS,QSCN6L1,RNF208,RP11-100C15.2,RP11-413M3.10,SDCCAG3,SLC34A3,SNAPC4,SOHLH1,SSNA1,TMEM141,TRAF2,TUBB2C,UAP1L1,UBADC1,UNQ2492,UNQ2541,UNQ747,hNMDAR1-3b,pp8875,ve-statin
chr18:73989470-76116152	60	0	AK056304,ATP9B,AX746671,BC016878,BC017654,BC040056,BX537710,C18orf22,CTDP1,DKFZp434A042,KCNG2,**NFATC1**,PARD6G,PQLC1,SALL3,TXNL4A,ZNF508,hdim1+
chr9:134048500-135886847	54	0	ABO,**ADAMTS13**,ADAMTSL2,AJ011378,AK123314,AX748058,BARHL1,C9orf166,C9orf7,C9orf9,C9orf96,C9orf98,CEL,CELL,CR592591,CR593670,**DBH**,DDX31,EEF1A1,FLJ46082,GBGT1,GFI1B,GTF3C4,GTF3C5,KIAA1308,LOC389827,NR_002783,NTNG2,OBP2B,**RALGDS**,REXO4,RPL7A,SARDH,SETX,**SLC2A6**,SURF1,SURF2,SURF4,SURF5,SURF6,TSC1,**TTF1**,UNQ2513,VAV2,XPMC2H,**vWF-CP**
chr1:2182293-3539057	50	0	**ACTRT2**,AK021767,AK124865,ARHGEF16,BC114358,C1orf93,CR749717,DQ601700,FAM79A,FLJ42875,HES5,MEGF6,**MMEL1**,MORN1,PANK4,PEX10,PLCH2,PRDM16,RER1,RP3-395M20.1,RP3-395M20.10,RP4-740C4.2,SKI,**TNFRSF14**,WDR8
chr1:245537326-245976637	49	0	AB120962,AK130400,BC034303,C1orf150,**CIAS1**,**NLRP3**,OR13G1,OR2B11,OR2C3,OR2G2,OR2G3,OR2W5,OR5AY1,OR6F1,ZNF496
chr14:21582956-21976908	47	0	AK093552,AK125397,AV1S3A1T,AV25S1,AV4S1,**TCR-[alpha] V 33.1,TCR-alpha,TCRA,TCRAV14.1a,TCRAVN1,TCRD,TRA@,V alpha immunoglobulin**,av27s1,**hADV14S1,hADV23S1,hADV29S1,hADV38S2,hDV102S1**
chr7:157944418-158676623	46	0	AX746826,BC041429,BC042556,FAM62B,KIAA1228,NCAPG2,PTPRN2,**VIPR2**,WDR60
chr19:48498399-48562727	46	0	**CD177**
chr22:34946081-35041308	41	0	**APOL1**,APOL2,AX747758,**MYH9**
chr1:113185538-113437683	40	0	AFARP1,AX748125,BC023568,BC037540,BC047723,BX648855,**LRIG2**,**SLC16A1**
chr2:187993955-189286647	39	0	CALCRL,CED-6,GULP1,**TFPI**
chr11:382079-1386192	38	0	AK094678,AK126635,AP2A2,AX747537,AX748330,BC031953,BC048998,BC066355,BRSK2,C11orf35,CD151,CEND1,CHID1,**DEAF1**,DKFZp434K249,DRD4,EFCAB4A,EPS8L2,**HRAS**,**IRF7**,KIAA0899,KIAA1542,LRDD,LRRC56,MG1,MUC5AC,**MUC2**,**MUC5AC**,MUC5B,MUC6,MUCDHL,NR_002585,PDDC1,PEN11B,PKP3,PNPLA2,POLR2L,PTDSS2,RASSF7,RNH1,RPLP2,**SCT**,**SIGIRR**,SLC25A22,TALDO1,TMEM16J,TMEM80,**TOLLIP**,TSPAN4,**tollip**
chr12:98815353-99473749	37	0	ACTR6,ANKS1B,AX746635,BC048272,BC062763,DEPDC4,DKFZp434M0331,DQ579681,DQ583972,DQ595598,DQ598729,EB-1,GOLGA2L1,KIAA0701,**NR1H4**,**SCYL2**,**SLC17A8**,hArpX
chr4:7568079-8105372	36	0	ABLIM2,AFAP1,AJ431609,BC043614,KIAA1808,LOC389199,**SORCS2**
chr14:23995185-24062459	30	0	AK056368,**CMA1**
chr14:103352857-104756910	30	0	**ADSS**,**ADSSL1**,AK057986,AK094143,**AKT1**,AX721091,AX746996,BRF,**BRF1**,C14orf151,C14orf173,C14orf2,C14orf78,C14orf79,CDCA4,CR602005,DKFZp434N0820,DKFZp434N178,DKFZp686J02145,**GPR132**,JAG2,KIAA0284,KIAA0771,KIF26A,LOC374569,LOC400258,MGC23270,NUDT14,PLD4,PPP1R13B,SIVA1,TDRD9,TMEM179,UGPP
chr17:73662981-73765190	23	0	AFMID,BC036810,**BIRC5**,**EPR-1**,SYNGR2,TK1,UNQ464/PRO809,survivin-3B
chr13:45066410-45918722	22	0	AK095119,AK124928,C13orf18,CPB2,FLJ32682,KIAA0853,**LCP1**,LOC220416,LOC283514,RP11-139H14.4-001,RP11-351K3.2-001,SPERT,ZC3H13
chr19:46758119-46863746	21	0	**CEACAM21**,**CEACAM4**,UNQ3098
chr8:6849317-6889488	20	0	AF355799,**DEFA3**
chr20:60320976-62223928	17	0	AK056267,AK128329,AL137301,ARFGAP1,ARFRP1,AX747649,AY940852,BC002534,BC025345,BC069708,BC127852,BHLHB4,BIRC7,C20orf11,C20orf135,C20orf149,C20orf151,C20orf166,C20orf195,C20orf20,C20orf58,C20orf59,CABLES2,**CHRNA4**,COL20A1,COL9A3,DIDO1,DNAJC5,EEF1A2,FLJ00084,FLJ00118,FLJ30313,GATA5,GMEB2,HRIHFB2281,KCNQ2,KIAA1088,KIAA1269,KIAA1510,**LAMA5**,**LIME1**,LOC198437,NPBWR2,NR_003244,NR_003245,NTSR1,OATP-E,OGFR,OK/SW-cl.69,OPRL1,PRIC285,PRPF6,PRR17,PTK6,RGS19,RP4-697K14.11,RPS21,RTEL1,SAMD10,SLC2A4RG,SLCO4A1,SOX18,SRMS,STMN3,Si-1-2-19,TCEA2,TCFL5,**TNFRSF6B**,TPD52L2,UCKL1,URKL1,YTHDF1,ZBTB46,ZGPAT,ZNF512B
chr2:86924985-87026840	16	0	**CD8B**,RGPD1,RMND5A

chr6:128245227-128538250	16	0	***C6orf190*,*PTPRK***
chr1:111628132-111661435	15	0	***CHIA***,*RP11-165H20.1*
chr7:80041654-80110504	13	0	***CD36***
chr12:6085895-6134080	11	0	***VWF***
chr12:17854127-19338878	11	0	***CAPZA3***,*FLJ22655,PIK3C2G,PLCZ1,PLEKHA5*

D) Duplications Not Impacting Immune Genes

CNVR Dup Singleton	Count SNPs	Distance From Exon	Gene
chr8:430424-977192	189	0	*AK128400,BC022082,BC038783,C8orf42,DQ584928,ERICH1,LOC389607*
chr10:2682656-3123648	157	0	*PFKP*
chr19:21575835-22802826	152	0	*BC030765,CR936832,FKSG70,ZNF100,ZNF208,ZNF257,ZNF43,ZNF492,ZNF676,ZNF99*
chr6:63118894-64091007	116	0	*GLULD1,LGS*
chr2:126935385-127317174	98	0	*GYPC*
chr5:169763949-170518986	96	0	*DKFZp666P032,GABRP,KCNIP1,RANBP17*
chr6:1977258-2424512	92	0	*AJ420566,AK023629,AK091028,CR598484,GMDS*
chr1:145196592-145539979	65	0	*BC036212,BCL9,CHD1L*
chr3:62813828-63789968	63	0	*BC043407,C3orf49,CADPS,FLJ44379,SYNPR*
chr5:172824934-173106866	62	0	*BC033564,FAM44B*
chr3:83912925-84849961	54	0	*BC068246*
chr11:106523381-106702850	54	0	*CWF19L2*
chr7:50911090-51127086	50	0	*COBL*
chr9:6557841-7007391	41	0	*AK098534,BC042976,GLDC,JMJD2C,KIAA0780*
chr17:793231-917163	40	0	*ABR,NXN,TIMM22*
chr3:148425802-149211699	39	0	*AK098763,ZIC1,ZIC4*
chr13:62536330-64097876	36	0	*AK057471,AK097490,AK098560,BC128161,NR_002171*
chr4:92669000-94351161	34	0	*GRID2,KIAA1680*
chr3:11041670-11154453	33	0	*SLC6A1*
chr4:141709869-141939520	33	0	*TBC1D9*
chr13:113032851-113140550	30	0	*ADPRHL1,GRTP1*
chr2:148947731-149053581	29	0	*KIAA1461,MBD5*
chr3:141649121-141911988	28	0	*CLSTN2,TRIM42*
chr12:20901315-21459060	27	0	*IAPP,LST-3TM12,LST3,SLCO1A2,SLCO1B1,SLCO1B3*
chr12:130676799-131128244	27	0	*EP400,KIAA1498,KIAA1818,MMP17,NR_002979,PUS1,SFRS8,ULK1*
chr7:34919485-35862821	26	0	*AJ011981,BC049371,BC084560,CR593784,CR595224,DPY19L1,DPY19L2P1,HERPUD2,KIAA0877,SEPT7,TBX20*
chr1:30940148-31013899	25	0	*BC044253,LAPTM5,MATN1*
chr4:63433227-65099386	25	0	*SRD5A2L2*

chr5:12838251-13150705	22	0	*AY328033*
chr6:138653005-138759016	22	0	*KIAA1244*
chr1:103111860-103157198	21	0	*COL11A1*
chr6:34836231-34976532	21	0	*ANKS1A,C6orf107,SNRPC,TAF11*
chr15:27167056-28188067	21	0	*APBA2,BC043570,BC070492,BC071630,BC071855,DQ572986,DQ573498,DQ575284,DQ575742,DQ577333,DQ578370,DQ578838,DQ582641,DQ582940,DQ590322,DQ592322,DQ595055,DQ596303,DQ596319,DQ597873,KIAA0574,NDNL2,TJP1,hXIIL*
chr2:3287465-3327227	20	0	*TSSC1*
chr10:98101269-98152781	19	0	*TLL2,TMEM10*
chr1:79037280-79973037	18	0	*ELTD1*
chr4:68749536-70089270	18	0	*AK123556,TMPRSS11B,TMPRSS11E,UGT2A3,UGT2B10,UGT2B15,UGT2B17,UGT2B7,YTHDC1*
chr2:27584444-28424525	17	0	*AK124439,BC041993,BC048132,BRE,C2orf16,CCDC121,GCKR,MRPL33,RBKS,SLC4A1AP,SUPT7L,XAB1,ZNF512*
chr2:172356838-172528561	17	0	*HAT1,SLC25A12*
chr2:180123158-180216026	16	0	*ZNF533*
chr4:15529521-15552238	15	0	*FGFBP1*
chr18:14805527-14905835	15	0	*ANKRD30B*
chr5:1601764-1621442	14	0	*CR749689*
chr10:88722456-89266679	14	0	*AK091716,BC036645,BC047063,BC065757,BC082979,BC092519,CR609725,CR614919,FAM35A,GLUD1,KIAA1975,KIAA2020,MINPP1*
chr1:225308870-225407413	13	0	*CDC42BPA*
chr7:74674968-74738702	13	0	*LOC441257,PMS2L14*
chr1:193808000-194531039	12	0	*KCNT2,SLICK*
chr2:165344115-165435694	12	0	*COBLL1,KIAA0977*
chr6:123847128-124726881	12	0	*TCBA1,TRDN*
chr16:26961662-26994169	12	0	*TNT*
chr6:102029392-102048325	11	11862	*GRIK2*
chr8:11397047-11414199	11	0	*BLK*
chr8:27689983-27745887	11	0	*ESCO2,PBK*
chr2:77709215-78761206	10	0	*BC024248,BC030125*
chr11:5444172-5454375	10	11939	*HBE1,HBG2,OR51B5*
chr11:19571323-19595111	10	96377	*NAV2*
chr18:68553733-69070964	10	0	*BC013370,BC034583,NETO1*
chr19:34552727-34574348	10	0	*AK094793*
chr4:2059850-2960297	10	0	*AB000464,AB000465,AB000466,ADD1,AK054619,BC010180,BC032331,C4orf10,C4orf15,C4orf8,CR622423,GRK4,KIAA1643,MXD4,Mad4,NOL14,POLN,RNF4,SH3BP2,TETRAN,TNIP2,ZFYVE28*

Supplementary Table 4. Homozygous Deletions Observed Exclusive to Cases

CNVR	Cases Loss	Gene	Distance	Distance From Exon
chr3:100430538-100430538	2	*CLCP1,DCBLD2*	327315	327315
chr2:118777060-118778863	1	*INSIG2*	192993	192993
chr3:146130742-146141275	1	*DQ595575*	883692	883692
chr5:29455914-29488308	1	*AK098570*	247692	247692
chr5:141998044-142000692	1	***FGF1***	0	16953
chr6:32525108-32530999	1	***HLA-DRA***	4306	4306
chr6:62122152-62144592	1	*G43499*	251536	251536
chr6:77159914-77159914	1	*IMPG1*	320859	320859
chr6:128018101-128024702	1	***C6orf190***	46336	46336
chr12:17277311-17282429	1	*LMO3,Nbla03267*	625020	625020

Supplementary Table 5. Genome Global CNV Burden

	Significant Including Common CNV Exonic					
	Locus Exonic Significant Case Enriched	Locus Non-Exonic Case Enriched	Locus Exonic Significant Control Enriched	Locus Non-Exonic Control Enriched	P	DifFreq
Deletion	21	61	8	67	0.022628	0.149431
Duplication	43	173	12	12	0.003336	-0.30093
	Rare CNV Exonic					
	Case CNV Calls Exonic	Case CNV Calls Non-Exonic	Control CNV Calls Exonic	Control CNV Calls Non-Exonic	P	DifFreq
Deletion	527	1149	3970	10290	0.002138	0.036038
Duplication	813	1785	5539	5997	2.45E-55	-0.16722
	Rare CNV >100KB Exonic					
	Case CNV Calls Exonic	Case CNV Calls Non-Exonic	Control CNV Calls Exonic	Control CNV Calls Non-Exonic	P	DifFreq
Deletion	136	83	1012	653	0.768312	0.013197
Duplication	278	146	2263	546	2.46E-11	-0.14996
	Samples w Rare CNV >100KB (Impacting gene or not)					
	Case with large rare CNV	Case without large rare CNV	Control with large rare CNV	Control without large rare CNV	P	DifFreq
Deletion	131	180	1156	1610	0.951669	0.00329
Duplication	186	125	1391	1375	0.001504	0.095178

Supplementary Table 6. TACI Protein TNFRSF13B Gene Amino Acid Variant and Corresponding nsSNP rs ID

nsSNP	DNA position	Alleles	AA Change	Clinical Report (bold-in reports)
rs34562254	16783716	C/T	P (C**C**C) --> L (C**T**C)	P251L
rs72553886	16783732	G/T	V (**G**TC) --> F (**T**TC)	V246F
rs56063729	16783809	A/G	V (G**T**G) --> A (G**C**G)	**V220A**
rs56248318	16784408	A/C	Q (CA**G**) --> H (CA**T**)	Q196H
rs72553885	16784417	A/C	C (TG**C**) --> * (TG**A**)	C193X
rs72553883	16784454	A/C	A (G**C**G) --> E (G**A**G)	**A181E**
rs72553882	16784504	A/C	Y (TA**C**) --> * (TA**A**)	Y164X
rs72553881	16784541	A/G	G (G**G**G) --> E (G**A**G)	G152E
rs72553880	16792777	A/G	A (**G**CT) --> T (**A**CT)	A149T
rs72553879	16792911	A/G	C (T**G**T) --> Y (T**A**T)	C104Y
rs34557412	16792912	C/T	C (**T**GT) --> R (**C**GT)	**C104R**
rs72553877	16792962	A/T	I (A**T**C) --> N (A**A**C)	I87N
rs72553876	16792986	A/G	Y (T**A**T) --> C (T**G**T)	Y79C
rs55916807	16793007	C/T	R (C**G**C) --> H (C**A**C)	**R72H**
rs67951770	16796563	C/G	D (**G**AT) --> H (**C**AT)	D41H
rs67951769	16796563	-/G	frameshift	D41fx
rs72553874	16796566	C/T	W (**T**GG) --> R (**C**GG)	W40R
rs72553884	16784425-16784424	-/G	frameshift	D191G
rs72553878	16792925-16792924	-/T	frameshift	Q99H
rs34182967	16793004-16793003	-/C	frameshift	K73R
rs72553875	16793018-16793017	-/A	frameshift	S68S

Supplementary Table 7. Most Significant Associated Regions Based on Genotype Association

Region Genomic Span	Gene	Count SNPs Top 1000	Distance From Exon	BestP	BestSNP	Allele1	F_A	F_U	P Replication (Discovery SNP)	F_A Replication (Discovery SNP)	F_U Replication (Discovery SNP)	BestP Replication	BestSNP Replication	F_A Replication	F_U Replication
chr6:27236785-32521295	***MHC***	**110**	0	8.62E-10	rs3117426	T	0.3268	0.1907	0.3634	0.1697	0.1468	**0.0004**	rs2156875	0.5734	0.4475
chr8:23746576-24681608	*ADAM28,* ***ADAM7****,ADAMDEC1,STC1*	**4**	0	6.24E-6	rs4872262	A	0.0391	0.0107	**0.03135**	0.0321	0.01346	**0.0314**	rs4872262	0.0321	0.0135
chr4:189671181-189676119	*AK095968*	2	18764	1.78E-5	rs1606234	T	0.2961	0.4124	0.4646	0.4266	0.4524	0.4646	rs1606234	0.4266	0.4524
chr10:73083830-73084583	*CDH23*	2	7287	2.45E-5	rs7087554	A	0.5894	0.4729	0.4591	0.5092	0.4829	0.4591	rs7087554	0.5092	0.4829
chr7:4270929-4287047	***SDK1***	**5**	0	4.70E-5	rs895710	T	0.2905	0.4003	0.4551	0.3578	0.3835	**0.0235**	rs4720301	0.3991	0.4793
chr1:20369369-20490791	*FLJ32784,* ***UBXN10***	**7**	0	9.09E-5	rs7514144	C	0.2654	0.1808	0.3018	0.1560	0.1311	**2.25E-8**	rs6426636	0.4679	0.2857
chr10:27709830-27728115	*PTCHD3*	**7**	0	9.77E-5	rs506659	T	0.4022	0.3026	0.9879	0.2798	0.2793	0.6291	rs493965	0.2844	0.3001
chr1:59987116-59993733	*FGGY*	2	2458	1.52E-4	rs11207520	G	0.3994	0.3026	**0.00148**	0.2569	0.1706	**0.0015**	rs11207520	0.2569	0.1706
chr12:80435676-80444630	*PPFIA2*	2	59900	1.63E-4	rs2400955	T	0.4134	0.3159	0.8687	0.3899	0.3842	0.5347	rs10746192	0.4306	0.4526
chr11:102069786-102079454	*MMP27*	2	0	1.69E-4	rs17099394	T	0.1229	0.0687	0.6947	0.0734	0.06643	0.6947	rs17099394	0.0734	0.0664
chr16:71592439-71594134	*ZFHX3*	2	40845	1.80E-4	rs8056528	C	0.3687	0.2754	0.3698	0.3670	0.3368	0.3698	rs8056528	0.367	0.3368
chr8:124729628-124734756	*KLHL38*	**4**	0	2.05E-4	rs4871402	A	0.0643	0.1325	0.7201	0.1009	0.1088	0.3161	rs7463896	0.1697	0.1979
chr3:7364204-7369287	*GRM7*	**4**	40865	2.96E-4	rs12491592	A	0.1536	0.0939	0.5051	0.0963	0.08318	0.1237	rs7617297	0.3073	0.2592
chr3:8378739-8381919	*BC020876*	2	129448	3.51E-4	rs359030	C	0.1648	0.1033	0.1446	0.1147	0.08535	0.1139	rs358994	0.1055	0.0754
chr6:25570803-25574868	*LRRC16A*	2	0	3.61E-4	rs4320355	T	0.3799	0.2898	0.2219	0.2844	0.2469	0.1896	rs301396	0.445	0.3993
chr6:153354039-153355207	*MTRF1L*	2	0	3.81E-4	rs9322400	T	0.4469	0.3526	0.454	0.3945	0.3688	0.454	rs9322400	0.3945	0.3688
chr3:284363-285747	***CHL1***	2	19083	4.31E-4	rs17273893	T	0.148	0.0908	0.6342	0.0963	0.08678	0.6342	rs17273893	0.0963	0.0868
chr8:121001793-121010709	*DEPDC6*	2	0	4.41E-4	rs869340	C	0.324	0.2402	0.7402	0.3073	0.2966	0.682	rs4871793	0.3113	0.2978
chr2:65518304-65520560	*FLJ16124*	2	784	5.20E-4	rs1194849	G	0.3659	0.4614	**0.01381**	0.3899	0.4771	**0.0119**	rs1876518	0.3853	0.4744
chr21:27713547-27722878	*BC043580*	2	19690	5.51E-4	rs469709	A	0.1704	0.1095	0.9615	0.0963	0.09532	0.6677	rs17631106	0.0688	0.0769

Bold underline: Known immunological function Gene

Supplementary Table 8: Genomic Regions with Multiple SNPs in the 1000 most Significant Associations

Region Genomic Span	Gene	Distance	Distance From Exon	CountSNPs Top1000	BestP	BestSNP	F_A	F_U
chr6:27236785-	***MHC, Many***	**0**	0	110	8.62E-10	rs3117426	0.3268	0.1907

32521295								
chr8:23746576-24681608	*ADAM28,**ADAM7**,ADAMDEC1,STC1*	**0**	0	4	6.24E-6	rs4872262	0.03911	0.01069
chr6:42776382-43502348	*CRIP3,CUL7, GNMT, KLC4,KLHDC3, MEA1,MRPL2,**PARC**,PEAS,PEX6,**PPP2R5D**,PRPH2,PTCRA,**PTK7**,RPL7L1,SLC22A7,SRF,TBCC, **TNRC5**,TTBK1,UNQ1934,ZNF318*	0	0	4	1.22E-5	rs422717	0.2961	0.1982
chr14:39744450-39909619	*BX248273*	584047	584047	4	1.69E-5	rs6571989	0.1927	0.115
chr4:189671181-189676119	***AK095968***	**0**	18764	2	1.78E-5	rs1606234	0.2961	0.4124
chr16:6120908-6137836	*A2BP1*	0	110914	4	1.85E-5	rs12924882	0.1313	0.06915
chr2:224812598-224841089	*FAM124B*	110570	110570	4	1.89E-5	rs4264554	0.3184	0.4353
chr2:45599872-45895169	*PRKCE,SRBD1*	0	0	7	2.12E-5	rs17322265	0.3408	0.4576
chr10:73083830-73084583	***CDH23,KIAA1812***	**0**	7287	2	2.45E-5	rs7087554	0.5894	0.4729
chr2:74996818-75001224	*AK125960*	7650	7650	2	3.25E-5	rs3771781	0.3184	0.4319
chr20:55079605-55083403	***BMP7***	95559	95559	2	4.44E-5	rs6127923	0.2318	0.1498
chr7:4270929-4287047	***SDK1***	**0**	0	5	4.70E-5	rs895710	0.2905	0.4003
chr20:15025030-15074507	*C20orf133*	0	50997	4	5.15E-5	rs6043091	0.2151	0.1367
chr8:8804291-8808564	***MFHAS1***	15750	15750	3	6.80E-5	rs400404	0.3715	0.2726
chr1:158072814-158076453	*CR625159,RP11-190A12.4,SLAMF8*	0	0	2	7.31E-5	rs10494349	0.2067	0.1312
chr18:25213638-25220939	*CDH2*	1202449	1202449	2	7.53E-5	rs9950880	0.2821	0.1943
chr3:106535466-107174255	***ALCAM**,**CBLB**,**Nbla00127***	0	0	5	8.57E-5	rs13062596	0.4358	0.3328
chr6:85682448-85684185	*TBX18*	151830	151830	2	9.07E-5	rs9444253	0.05028	0.1187
chr1:20369369-20490791	***FLJ32784,UBXN10***	**0**	0	7	9.09E-5	rs7514144	0.2654	0.1808
chr10:27709830-27728115	***PTCHD3***	**0**	0	7	9.77E-5	rs506659	0.4022	0.3026
chr12:123259607-123275011	*FAM101A*	64652	64652	4	1.01E-4	rs7972182	0.3855	0.2874
chr13:68136436-68138181	*BC042673*	195237	195237	2	1.09E-4	rs287355	0.2219	0.3213
chr16:69996550-70004357	***CALB2***	14714	14714	2	1.09E-4	rs12102284	0.1676	0.1015
chr11:25128661-25130289	*LUZP2*	67899	67899	2	1.10E-4	rs11028465	0.3352	0.2426
chr12:49729991-49731928	*DKFZp586A011,LETMD1*	0	214	2	1.22E-4	rs4768959	0.1397	0.08033
chr4:25702025-25756263	*LOC389203*	161493	161493	5	1.34E-4	rs2048507	0.257	0.1755
chr7:13858986-13866233	*ETV1*	31148	31148	4	1.35E-4	rs12532319	0.09218	0.04617
chr1:59987116-59993733	***FLJ10986,RP11-242B9.1***	**0**	2458	2	1.52E-4	rs11207520	0.3994	0.3026
chr6:12070732-12073684	***HIVEP1***	47026	47026	2	1.54E-4	rs12193434	0.09777	0.05034
chr19:40814281-40815243	*MGC10433*	0	134	2	1.55E-4	rs2285415	0.352	0.4559
chr6:139472753-139477571	*HECA*	20371	20371	2	1.56E-4	rs17304375	0.2318	0.1549
chr12:80435676-80444630	***PPFIA2***	**0**	59900	2	1.63E-4	rs2400955	0.4134	0.3159

chr12:69717561-69720071	*TSPAN8*	85073	85073	2	1.63E-4	rs6581986	0.2905	0.2053
chr11:102069786-102079454	***MMP27***	**0**	0	2	1.69E-4	rs17099394	0.1229	0.0687
chr3:188168001-188168026	***ST6GAL1***	0	3593	2	1.71E-4	rs12495023	0.2765	0.1934
chr16:71592439-71594134	***ATBF1***	**0**	40845	2	1.80E-4	rs8056528	0.3687	0.2754
chr8:124729628-124734756	***C8ORFK36***	**0**	0	4	2.05E-4	rs4871402	0.06425	0.1325
chr22:42908147-43159207	*KIAA1644,PARVG*	0	0	8	2.27E-4	rs80303	0.3994	0.5013
chr20:44622587-44638545	*NADC3,SLC13A3*	0	0	5	2.49E-4	rs393990	0.09218	0.1664
chr1:9459963-9467504	*SLC25A33*	54611	54611	2	2.57E-4	rs10746490	0.1453	0.2292
chr3:7364204-7369287	***GRM7***	**0**	40865	4	2.96E-4	rs12491592	0.1536	0.0939
chr11:46472478-46855347	*ARHGAP1, CKAP5,CR612190,**F2**, LRP4,MEGF7, ZNF408,coagulation factor II*	0	0	4	3.19E-4	rs2306029	0.3603	0.4593
chr2:181999958-182002374	*AK125001*	27433	27433	2	3.22E-4	rs16867404	0.09497	0.05008
chr7:121184414-121193891	***PTPRZ1***	106504	106504	2	3.24E-4	rs1196493	0.5251	0.4266
chr3:8378739-8381919	***BC020876***	**0**	129448	2	3.51E-4	rs359030	0.1648	0.1033
chr6:25570803-25574868	***LRRC16***	**0**	0	2	3.61E-4	rs4320355	0.3799	0.2898
chr4:131889955-131893245	*BC041448*	793982	793982	2	3.68E-4	rs2125639	0.2905	0.2094
chr15:58159939-58162165	*FOXB1*	74505	74505	2	3.71E-4	rs7168491	0.1648	0.1035
chr6:153354039-153355207	***MTRF1L***	**0**	0	2	3.81E-4	rs9322400	0.4469	0.3526
chr5:172969660-172992688	*FAM44B*	0	0	4	3.83E-4	rs258873	0.2849	0.3798
chr6:55433518-55442340	*HMGCLL1*	0	21202	2	3.86E-4	rs9382494	0.2179	0.3078
chr9:15192417-15195014	*C9orf52*	0	0	2	3.87E-4	rs693196	0.3603	0.2723
chr4:20207250-20210955	*SLIT2*	0	0	2	4.29E-4	rs573118	0.243	0.169
chr3:284363-285747	***CHL1***	**0**	19083	2	4.31E-4	rs17273893	0.148	0.09081
chr11:45198534-45198959	*PRDM11*	0	650	2	4.36E-4	rs12417962	0.06983	0.1351
chr3:138891290-138892064	*SOX14*	74205	74205	2	4.37E-4	rs12637203	0.1844	0.12
chr8:121001793-121010709	***DEPDC6***	**0**	0	2	4.41E-4	rs869340	0.324	0.2402
chr18:74518781-74526115	*SALL3*	315148	315148	2	4.72E-4	rs2931060	0.1257	0.07381
chr4:143965929-143971867	*INPP4B*	0	14945	2	4.81E-4	rs10000770	0.1788	0.1158
chr3:115619659-115623404	*ZBTB20*	0	29017	2	5.19E-4	rs2718419	0.2598	0.1844
chr2:65518304-65520560	***FLJ16124***	**0**	784	2	5.20E-4	rs1194849	0.3659	0.4614
chr5:68236398-68245085	*AK128486*	55041	55041	2	5.27E-4	rs7718291	0.1313	0.2081
chr21:27713547-27722878	***BC043580***	**0**	19690	2	5.51E-4	rs469709	0.1704	0.1095
chr3:5866648-5866856	*EDEM1*	630006	630006	2	5.91E-4	rs2572690	0.1145	0.06602
chr16:7470020-7474240	*A2BP1*	0	33910	2	5.93E-4	rs2191388	0.2709	0.1948
chr6:88936647-	***CNR1***	4366	4366	2	6.35E-4	rs9344757	0.2179	0.3041

88941540								
chr4:32018838-32029980	*PCDH7*	1265004	1265004	3	6.41E-4	rs2130904	0.2458	0.3343
chr1:202125395-202130221	*SNRPE*	18492	18492	2	6.48E-4	rs12145634	0.1369	0.08346
chr7:38733082-38736264	*HVPS41,VPS41*	0	0	2	6.67E-4	rs10255854	0.2179	0.3038
chr11:120260865-120269428	*GRIK4*	0	5023	2	6.67E-4	rs12577638	0.2011	0.1356
chr11:91278373-91283755	*FAT3*	444245	444245	2	6.97E-4	rs10501763	0.03911	0.09207
chr16:20151678-20152281	*GP2*	77031	77031	2	7.14E-4	rs9921767	0.0419	0.09572
chr1:221871750-221882793	***CAPN2***	84031	84031	3	7.29E-4	rs3856154	0.4134	0.3254
chr10:130929688-130931369	***MGMT***	224087	224087	2	7.33E-4	rs538186	0.05307	0.1104
chr5:170727300-170734557	***NPM1***	12168	12168	2	7.52E-4	rs7707008	0.1173	0.1894
chr10:63071553-63080172	*C10orf107*	12553	12553	2	7.69E-4	rs10994852	0.1061	0.06051
chr21:31427707-31432285	*TIAM1*	0	0	2	7.93E-4	rs2833297	0.2095	0.1435
chr4:42434168-42438752	*ATP8A1*	80521	80521	2	8.09E-4	rs6812482	0.2709	0.1965
chr6:161106705-161109328	*PLG*	12377	12377	2	8.78E-4	rs9295131	0.2151	0.2986
chr17:12323188-12325534	*AX747308,BC122562*	68477	68477	2	9.02E-4	rs8069430	0.2584	0.186
chr17:50125991-50127579	*TOM1L1,tom1-like*	205624	205624	2	9.20E-4	rs6504930	0.03371	0.08325
chr16:77330083-77334376	***WWOX***	0	305933	2	9.21E-4	rs1364290	0.1844	0.1231
chr11:5493737-5511794	*HBG2,UBQLNL*	0	0	4	9.28E-4	rs2047456	0.3436	0.2624
chr3:70644812-70648510	*LOC401072*	96929	96929	2	9.91E-4	rs17790790	0.5196	0.4293
chr3:1292289-1302261	***CNTN6***	0	0	2	1.06E-3	rs6799262	0.3571	0.2733
chr3:64977356-64985877	*BC040632*	5173	5173	2	1.15E-3	rs1517927	0.2318	0.1643
chr5:14818187-14825245	*ANKH*	0	0	2	1.15E-3	rs17251715	0.3955	0.3113

Supplementary Table 9. Most Significant Associated Regions Based on Subphenotype Genotype Association

A) Cancer

Significant Region	P-value	SNP	A1	F_A	F_U	OR	Count SNPs	Gene	Distance	Distance From Exon
chr14: 23168471-23169215	4.57E-7	rs222723	C	0.6154	0.1968	6.531	2	*DHRS2*	0	0
chr6:140225308-140225386	1.53E-6	rs12111348	T	0.4231	0.1064	6.157	2	BC039503	2009	2009

B) Lymphoma

Significant Region	P-value	SNP	A1	F_A	F_U	OR	Count SNPs	Gene	Distance	Distance From Exon
chrX:132092989-132095451	5.50E-10	rs5977837	C	0.2778	0.02174	17.31	2	*TFDP3*	82912	82912
chr10:58755852-58767334	1.36E-9	rs16910534	T	0.2222	0.01383	20.37	3	*IPMK*	858286	858286
chr7:90245135-90245280	1.69E-8	rs975004	G	0.3333	0.03953	12.15	2	*KIAA0834*,***PFTK1***	0	12544
chr5:156402979-156407976	3.62E-8	rs10038271	T	0.7222	0.1877	11.25	2	***HAVCR1***	0	651
chr1:55704352-55706323	2.85E-7	rs356086	G	0.1111	0.003953	31.5	2	*FLJ45337*	112975	112975
chr1:106430611-106438079	1.55E-6	rs11184786	T	0.3333	0.05336	8.87	2	*BC043293*	467531	467531

C) Lymphadenopathy

Significant Region	P-value	SNP	A1	F_A	F_U	OR	Count SNPs	Gene	Distance	Distance From Exon
chrX:53035117-53039801	1.90E-7	rs10127016	G	0.3833	0.125	4.351	2	*TMEM29*	0	1409
chr12:30583074-30598457	4.82E-7	rs1905675	C	0.2	0.5453	0.2085	2	*IPO8*	74732	74732
chr14:64723761-64783067	8.09E-7	rs4299072	A	0.1667	0.02802	6.938	4	*BX161428*	0	0
chr5:141916656-141926115	1.13E-6	rs17706715	A	0.2333	0.05603	5.127	2	***FGF1***	27191	27191
chr11:101265604-101266102	1.55E-6	rs17097290	T	0.15	0.02371	7.267	2	*ANGPTL5*	513	513

D) Nodular regenerative hyperplasia of the liver (NRH)

Significant Region	P-value	SNP	A1	F_A	F_U	OR	Count SNPs	Gene	Distance	Distance From Exon
chr1:68153970-68161019	2.29E-10	rs1926283	C	0.2308	0.01807	16.3	3	*AK096081,AK124028*	0	33408
chr21:18188480-18192815	2.84E-7	rs7280675	G	0.1923	0.02008	11.62	2	*CHODL*	2636	2636
chr21:45476504-45476918	3.23E-7	rs4592938	A	0.1154	0.006024	21.52	2	*C21orf89*	1777	1777
chr8:143046590-143055893	1.18E-6	rs12676273	G	0.3462	0.07229	6.794	3	*TSNARE1*	235455	235455

chrX:27453340-27462759	1.29E-6	rs5971431	C	0.3077	0.05823	7.188	3	*AK057304*	55692	55692

E) LIP

Significant Region	P-value	SNP	A1	F_A	F_U	OR	Count SNPs	Gene	Distance	Distance From Exon
chr13:101641990-101673539	5.76E-8	rs1336698	G	0.65	0.168	9.197	6	*FGF14*	0	69139
chrX:143116309-143119321	6.77E-8	rs6649722	A	0.3	0.0377	10.94	3	*UBE2NL*	320286	320286
chrX:47642545-47651320	7.70E-8	rs12387999	A	0.2	0.016	15.38	2	*ZNF81*	0	2262
chr2:109118795-109120561	4.62E-7	rs375099	C	0.25	0.02976	10.87	2	*POSH2*	0	5794
chrX:30122360-30125674	2.52E-6	rs5927496	C	0.7	0.2341	7.633	2	*MAGEB2*	17927	17927

F) Bronchiectasis

Significant Region	P-value	SNP	A1	F_A	F_U	OR	Count SNPs	Gene	Distance	Distance From Exon
chrX:22422160-22428888	5.71E-8	rs5925651	A	0.3462	0.1386	3.291	3	*ZNF645*	219665	219665
chr2:200959722-201175137	2.39E-6	rs13019534	G	0.5064	0.2908	2.503	2	*AOX1,DNAPTP6,KCTD18,SGOL2*	0	0
chr8:15782386-15788801	2.92E-6	rs1563297	A	0.5321	0.3152	2.47	2	*TUSC3*	116020	116020
chr19:51765478-51768118	6.30E-6	rs6509286	C	0.4167	0.2228	2.491	2	*AK094504*	0	27862
chrX:68569536-68573727	1.04E-5	rs7056340	A	0.3141	0.1467	2.663	2	*TMEM28*	68076	68076
chr6:32508322-32510683	1.12E-5	rs2027856	T	0.02564	0.163	0.1351	2	***HLA-DRA***	4942	4942

G) Granuloma

Significant Region	P-value	SNP	A1	F_A	F_U	OR	Count SNPs	Gene	Distance	Distance From Exon
chr11:12182328-12186013	4.83E-6	rs16910765	T	0.2206	0.05921	4.497	3	*KIAA0750,MICAL2,MICAL2PV1,MICAL2PV2*	0	0
chr1:33674005-33683227	1.26E-5	rs12751162	A	0.3824	0.1601	3.248	2	*PHC2*	4803	4803
chr6:88453628-88454474	2.04E-5	rs2250276	G	0.1765	0.04386	4.671	2	***AKIRIN2***	0	5428
chrX:27453340-27462759	3.18E-5	rs5971431	C	0.1912	0.05263	4.255	2	*AK057304*	55692	55692

H) GI Enteropathy

Significant Region	P-value	SNP	A1	F_A	F_U	OR	Count SNPs	Gene	Distance	Distance From Exon
chr12:2531014-2538733	1.21E-7	rs4765961	C	0.4737	0.142	5.439	3	***CACNA1C***	0	0
chr10:26643326-26646318	2.90E-6	rs7903552	G	0.3684	0.107	4.869	2	***GAD2***	9833	9833
chr5:11592622-11597026	6.26E-6	rs2727602	T	0.6053	0.2613	4.334	2	*CTNND2*	0	21030

chr21:42551877-42552623	9.95E-6	rs3787986	T	0.3684	0.1152	4.479	4	*ABCG1*	0	0
chr9:4033590-4039110	1.13E-5	rs676472	C	0.2895	0.07613	4.944	3	*GLIS3*	0	68391
chr4:33014145-33017023	1.43E-5	rs6846113	A	0.1053	0.01029	11.32	2	*AK093205*	552926	552926

I) Malabsorption

Significant Region	P-value	SNP	A1	F_A	F_U	OR	Count SNPs	Gene	Distance	Distance From Exon
chr20:55901032-55985359	3.21E-9	rs8124301	T	0.4231	0.07631	8.877	5	*C20orf85*	174030	174030
chr7:117377201-117382435	9.94E-7	rs17140937	C	0.2692	0.04418	7.971	2	*CTTNBP2*	76404	76404
chr11:124071934-124079438	1.25E-6	rs1784539	G	0.6154	0.2068	6.136	2	***SPA17***	2037	2037
chr10:30255454-30255817	5.18E-6	rs11007812	T	0.3077	0.06426	6.472	2	*CR626438*	85918	85918
chr12:31276546-31281817	6.76E-6	rs12819069	C	0.3846	0.09839	5.727	2	*OVOS2*	26191	26191
chr8:6374232-6376048	8.56E-6	rs2515477	T	0.4231	0.1185	5.456	2	***ANGPT2***,*MCPH1*	0	1213

J) Splenectomy

Significant Region	P-value	SNP	A1	F_A	F_U	OR	Count SNPs	Gene	Distance	Distance From Exon
chr9:130092787-130095025	1.03E-6	rs7026795	A	0.425	0.1802	3.363	2	*C9orf119*	1698	1698
chr3:72044083-72052222	1.11E-6	rs7648163	C	0.55	0.2748	3.226	2	*AK097190*	115138	115138
chr1:73821234-73888127	2.23E-6	rs4606267	G	0.325	0.1194	3.552	3	*BC041341*	244086	244086
chr9:70762083-70815910	2.46E-6	rs2993008	T	0.225	0.06306	4.313	2	*AK057188,PIP5K1B*	0	0
chr8:137069094-137070609	3.13E-6	rs6985828	C	0.0625	0.002252	29.53	2	*KHDRBS3*	340064	340064
chr15:66415767-66419741	3.78E-6	rs6494736	C	0.175	0.04054	5.02	2	*ITGA11*	0	0
chr7:141314419-141314653	2.60E-5	rs11761774	A	0.475	0.2455	2.781	2	*TAS2R38*	4247	4247

K) Cytopenias

Significant Region	P-value	SNP	A1	F_A	F_U	OR	Count SNPs	Gene	Distance	Distance From Exon
chr12:3711033-4573405	4.28E-6	rs241964	C	0.6111	0.3	3.667	6	*C12orf4,C12orf5,CCND2,DYRK4,EFCAB4B,FGF23,FGF6,PARP11,RAD51AP1*	0	0
chr8:2721609-2723174	3.52E-5	rs341672	C	0.2593	0.0812	3.961	2	*CSMD1,KIAA1890*	59615	59615
chr3:2628577-2629597	0.000337	rs1020997	G	0.2407	0.4979	0.3198	2	***CNTN4***	0	40335
chr2:1783619-1783961	0.000426	rs6548056	G	0.1852	0.434	0.2963	2	*MYT1L*	0	514
chr11:2240035-2241166	0.000533	rs17659078	A	0.4444	0.2286	2.699	2	*ASCL2*	5138	5138

chr10:1236883-1237022	0.000603	rs10794730	T	0.4815	0.2596	2.649	2	*ADARB2*	0	583
chr9:1588885-1595735	0.000866	rs1923928	T	0.1852	0.4191	0.315	2	*SMARCA2*	409607	409607
chr1:4222578-4225577	0.000884	rs966321	C	0.2593	0.4979	0.353	2	*AX748168*	146394	146394

L) organ specific autoimmunity (OSAI)

Significant Region	P-value	SNP	A1	F_A	F_U	OR	Count SNPs	Gene	Distance	Distance From Exon
chr8:101728102-101728344	6.89E-8	rs7815950	G	0.2133	0.05615	4.559	2	*SNX31*	0	2334
chrX:39933689-39956544	5.18E-7	rs2948491	A	0.18	0.04545	4.61	4	*BCOR*	12163	12163
chr3:109180117-109186346	6.27E-6	rs709477	A	0.2733	0.4893	0.3926	2	*BC101231*	50156	50156
chr1:37438130-37446852	6.96E-6	rs6426015	A	0.2667	0.1096	2.953	3	*GRIK3*	165699	165699
chr15:84701881-84720707	1.19E-5	rs1431234	C	0.3	0.5108	0.4105	2	*AGBL1*	0	20894

M) Low IgM (<50 mg/dL)

Significant Region	P-value	SNP	A1	F_A	F_U	OR	Count SNPs	Gene	Distance	Distance From Exon
chr1:25735669-25753653	6.02E-8	rs2065970	G	0.06553	0.2411	4.529	5	*LDLRAP1*	0	0
chr4:59393803-59398745	1.77E-5	rs2899130	A	0.2257	0.4286	2.573	2	*BC034799*	1366894	1366894
chr5:76127981-76128963	2.17E-5	rs615986	T	0.4927	0.2679	0.3767	2	***F2RL1***	21647	21647

N) Low IgA (<10 mg/dL)

Significant Region	P-value	SNP	A1	F_A	F_U	OR	Count SNPs	Gene	Distance	Distance From Exon
chrX:30733771-30736604	1.44E-7	rs11095197	T	0.1469	0.3431	3.034	2	***MAP3K7IP3***	18876	18876
chrX:145696682-145751200	3.48E-6	rs6626815	C	0.5656	0.3578	0.4279	5	*CXorf1*	977620	977620
chr15:47024768-47025722	6.75E-6	rs17469978	C	0.2313	0.4167	2.375	2	*SHC4*	0	16198
chrX:32356174-32388539	1.25E-5	rs699457	G	0.2656	0.1078	0.3342	2	*DMD*	0	0
chr1:3915418-3917931	2.69E-5	rs10737395	A	0.1	0.2353	2.769	2	*AK124708*	236	236
chr13:101257602-101258342	3.22E-5	rs1322702	A	0.04375	0.1471	3.768	2	*FGF14*	0	60734

O) Low B cells (CD19+ cells <1%)

Significant Region	P-value	SNP	A1	F_A	F_U	OR	Count SNPs	Gene	Distance	Distance From Exon
chr8:13834782-13842376	7.62E-8	rs2682665	C	0.1818	0.01394	15.71	3	*SGCZ*	149368	149368
chr7:107306707-107314113	2.16E-7	rs9690688	A	0.3636	0.06375	8.393	2	*DLD*	4709	4709

chr9:33103066-33103970	1.40E-6	rs12379501	T	0.3182	0.05578	7.9	2	***B4GALT1***	0	0
chr13:37798435-37846851	2.25E-6	rs4943583	G	0.2273	0.02988	9.549	7	*UFM1*	0	0

P) Young age of symptom onset (<10 yrs)

Significant Region	P-value	SNP	A1	F_A	F_U	OR	Count SNPs	Gene	Distance	Distance From Exon
chrX:152295068-152303019	9.84E-8	rs5987017	A	0.2143	0.04773	5.442	4	*ZNF275*	24829	24829
chrX:37803525-37832251	1.54E-7	rs5918500	C	0.4878	0.2123	3.533	3	*SYTL5*	0	0
chr19:7505735-7508421	2.31E-6	rs604959	C	0.4762	0.2273	3.091	2	*PNPLA6*	0	0

Supplementary Table 10. Most Significant Associated Regions Based on CNV Association

A) Deletions

CNVR Deletion	Count SNPs	Distance From Exon	P Deletion	Cases Del	Controls Del	Gene	MSSM	Oxford	USF	CHOP
chr11:85365857-85381622	5	0	0.01	2	0	***PICALM***,*PICALM variant protein*	0	2	0	0
chr20:57735790-57741780	6	5902	0.026	3	4	*PHACTR3*	2	1	0	0
chr22:17396663-18417315	270	0	0.029	2	1	*ARVCF,C22orf25,C22orf29,CDC45L,CLDN5,CLTCL1,****COMT****,CR618542,CR625276,DGCR14,DGCR2,DKFZp761P1121,DKFZp781E0833,GNB1L,GP1BB,GSCL,HIRA,KIAA1647,L77561,LOC128977,MRPL40,SEPT5,SLC25A1,****TBX1****,TRXR2A,TSSK2,TXNRD2,U84523,UFD1,UFD1L*	2	0	0	0
chr4:10256682-10264316	4	2915	0.029	2	1	***CLNK***	0	1	1	0
chr10:46003146-46042543	8	0	0.029	2	1	*DKFZp566K0524,PTPN20A,PTPN20B*	2	0	0	0

B) Duplications

CNVR Duplication	Count SNPs	Distance From Exon	P Dup	Cases Dup	Controls Dup	Gene	MSSM	Oxford	USF	CHOP
chr2:148396730-148433180	6	0	8.66E-16	15	0	***ACVR2A*****,ORC4L**	10	5	0	0
chr15:35053039-35063531	6	23146	5.72E-13	19	10	*MEIS2*	17	2	0	0
chr10:53044735-53045426	4	79826	9.63E-13	12	0	*PRKG1*	12	0	0	0
chr8:77719805-77720240	3	27377	1.05E-09	10	1	*BC037827*	10	0	0	0
chr7:91789778-91801963	4	0	1.20E-09	12	4	*ANKIB1*	9	3	0	0
chr2:163316298-163316595	3	17100	1.00E-07	7	0	*KCNH7*	6	1	0	0
chr7:87180702-87191931	4	202	7.41E-07	7	1	*RPIB9*	5	2	0	0
chr12:72825720-72832667	3	0	3.04E-06	7	2	*BC061638*	7	0	0	0
chr2:203004035-203017311	5	20466	6.58E-05	6	3	*BMPR2*	6	0	0	0
chr19:9256584-9277749	4	0	0.001	3	0	*ZNF699*	2	0	1	0
chr4:39190766-	6	0	0.004	3	1	*UGDH*	1	2	0	0

39201960										
chr9:112207473-112207708	3	553	0.004	3	1	*SVEP1*	3	0	0	0
chr7:18903915-18905725	4	23171	0.009	3	2	***HDAC9***	1	2	0	0
chr13:64053258-64056530	15	505114	0.01	2	0	*AK057471,AK098560,BC128161*	2	0	0	0
chr14:35408995-35422074	5	0	0.01	2	0	*BRMS1L*	0	2	0	0
chr5:170531269-170536993	4	374	0.01	2	0	*DKFZp666P032,RANBP17*	1	1	0	0
chr4:91413829-91415037	3	33381	0.01	2	0	*KIAA1680,MGC48628*	2	0	0	0
chr7:34685030-34686172	4	4517	0.01	2	0	*AAA1,NPSR1*	1	1	0	0
chr3:176427638-176429297	7	5118	0.01	2	0	*NAALADL2*	2	0	0	0
chr1:170400944-170403742	4	26274	0.01	2	0	*DNM3*	0	1	1	0
chr2:167031393-167045981	4	0	0.01	2	0	*Na+ channel,SCN7A*	2	0	0	0
chr9:28683005-28687679	3	21420	0.01	2	0	***LINGO2***	2	0	0	0
chr9:105860023-105868928	9	27434	0.01	2	0	*OR13C3,OR13C4,OR13C5,OR13C8,OR13F1,SMC2,hCAP-E*	2	0	0	0

Supplemental Figure Legends

Genome-Wide Association Identifies Diverse Causes of Common Variable Immunodeficiency

Jordan S. Orange, Joseph T. Glessner, Elena Resnick, Kathleen E. Sullivan, Mary Lucas, Berne Ferry, Cecilia E. Kim, Cuiping Hou, Fengxiang Wang, Rosetta Chiavacci, Subra Kugathasan, John W. Sleasman, Robert Baldassano, Elena E. Perez, Helen Chapel, Charlotte Cunningham-Rundles, Hakon Hakonarson

Supplementary Figure 1. CVID Clinical Subphenotypes

The core diagnosis of CVID has many clinical progressions with varying frequency. The height and size of subphenotypes signify the frequency of the specific progression. Given significant SNP genotype associations for each CVID subphenotype progression vs. CVID patients without the progression, prediction can be made which may improve clinical outcome.

Supplementary Figure 2. Frequency of Deletion and Duplication Copy Number Variations

Frequency of CNV in cases and controls. CNVs are called on a single sample basis with deletions and duplications in specific genomic regions based on the genotype and intensity signal of contiguous SNPs. These single sample CNV profiles are plotted as a SNP-based statistic to allow for SNP-based association testing. Lastly, neighboring SNPs with similar significance define a CNVR. Red indicates case deletion; Blue indicates case duplication; Black indicates control deletion; Purple indicates control duplication.

Supplementary Figure 3. Duplication of *ORC4L* Found Exclusive to 15 CVID Cases

Vertical blue lines indicate the SNP probe coverage. Green rectangles delineate regions of copy number variation in individual cases. Three exons of *ORC4L* are shown duplicated in 15 cases and 0 controls. It is likely that the duplications could extend to a larger region of *ORC4L* based on coverage.

Supplementary Figure 4. CNV Validation with Illumina Intensity Data Review and Independent Array Technology, Affymetrix 2.7M

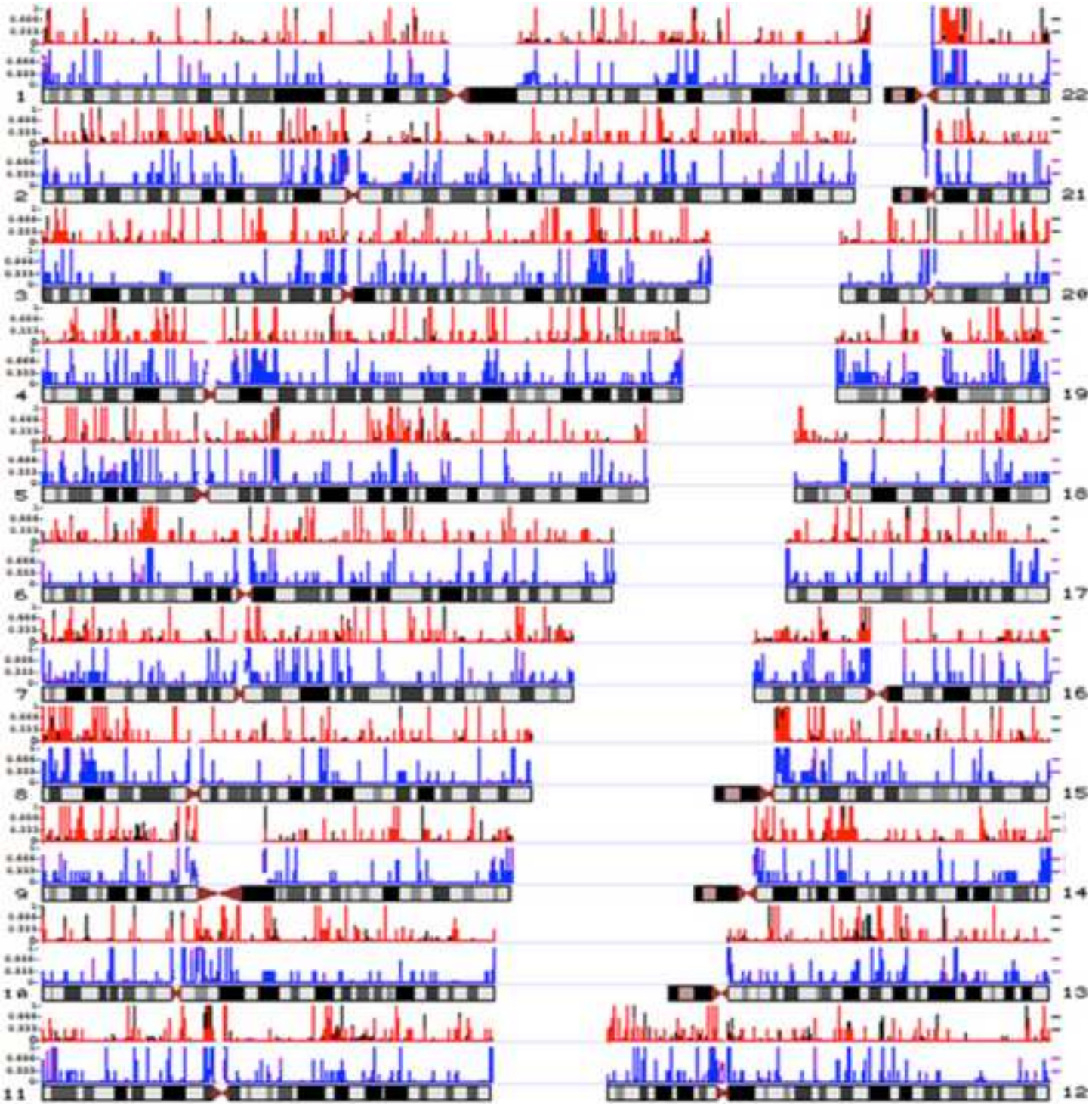
A) **Visual validation of all reported CNV loci using Illumina Quad 610 Intensity Data.** Results from visual inspections are provided. Gray rectangle represents normal diploid two copy state.
B) **Representative experimental validation of two of most significant delections and two duplications, using Affymetrix 2.7M intensity data at a high**

resolution. Intensity values are plotted for each region listed based on samples with copy number variation calls.

C) **Experimental validation of all Table 2 loci using Affymetrix 2.7M intensity data.** Intensity values are plotted for each region listed based on samples with copy number variation calls. Table 2 loci are labeled with corresponding intensity values for contiguous probes in the genomic region.

Repository E Figure No. 1

Repository E Figure No. 2



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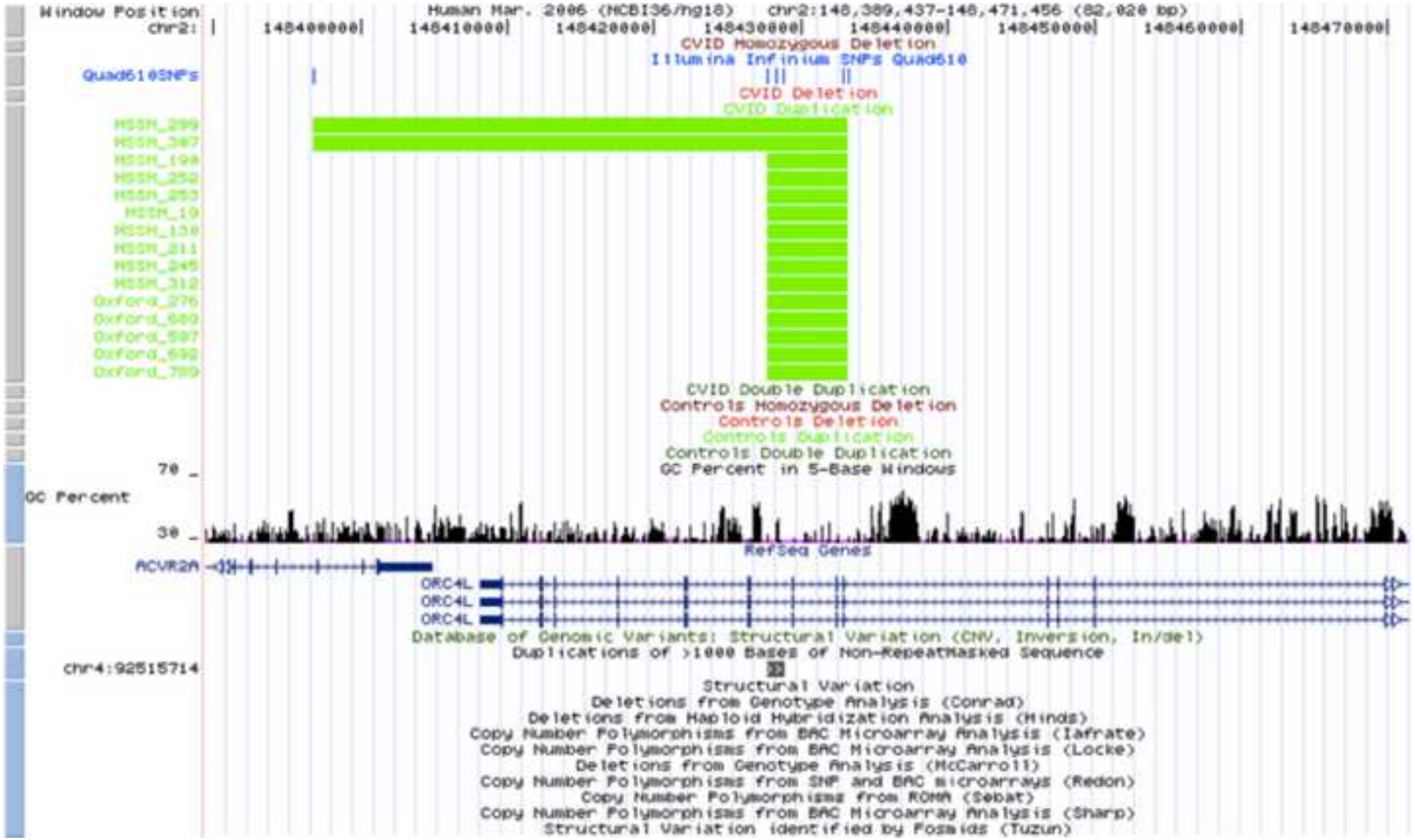

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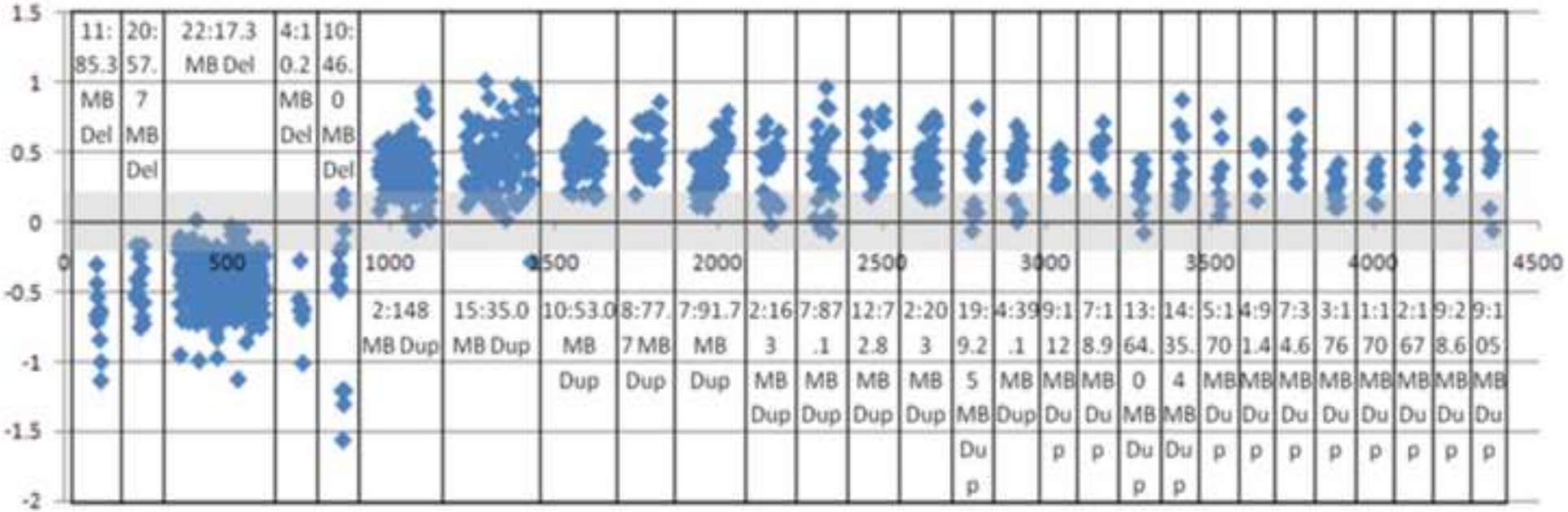

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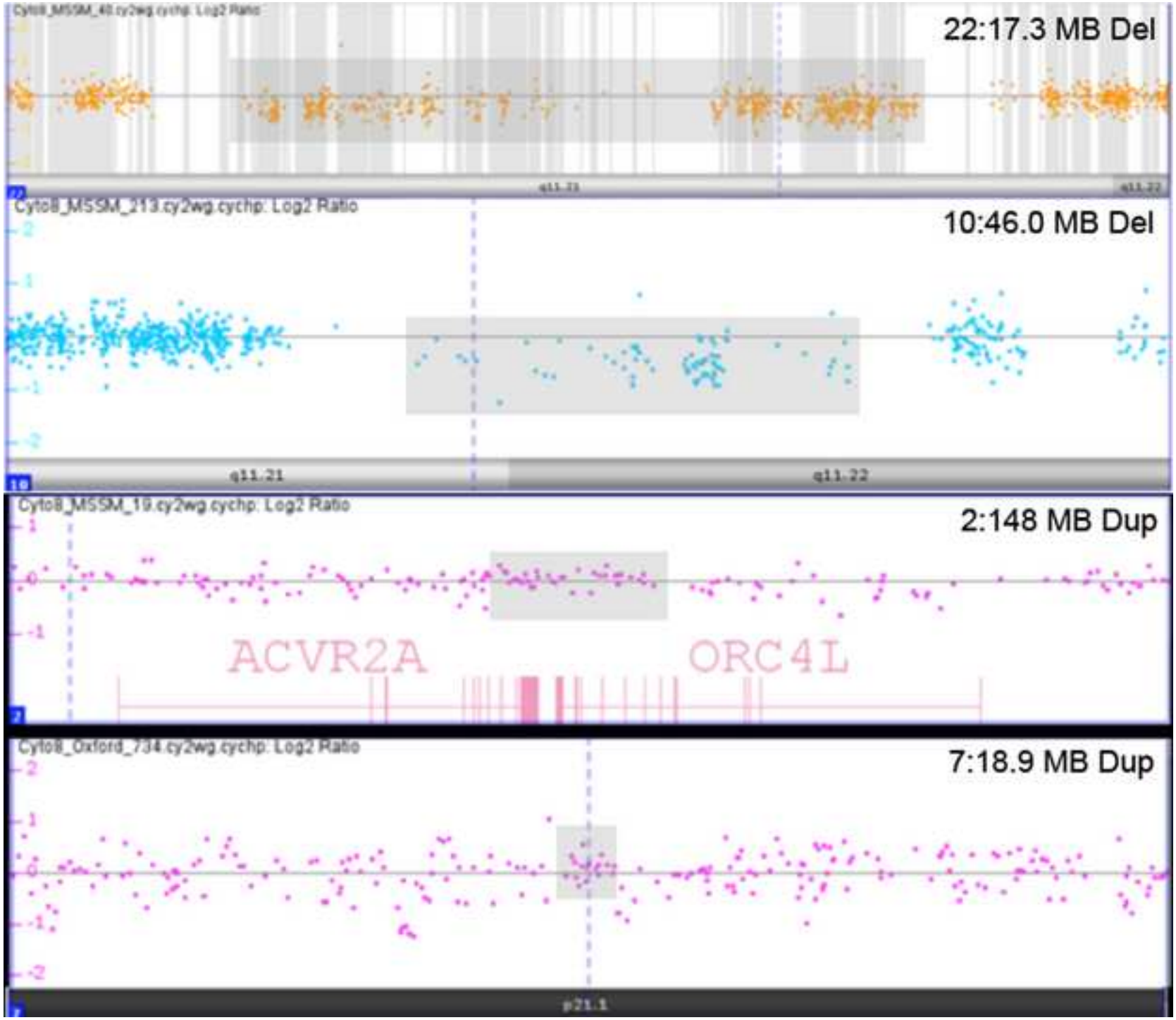

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