MEF2 Transcription Factors Regulate Distinct Gene Programs in Mammalian Skeletal Muscle Differentiation*

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SUPPLEMENTAL FIGURE LEGENDS

SUPPLEMENTAL TABLE 1. KEGG pathway analysis of gene sets sensitive to individual MEF2 isoforms.

SUPPLEMENTAL TABLE 2. Gene Ontology term analysis of gene sets sensitive to individual MEF2 isoforms.

SUPPLEMENTAL TABLE 3. Compilation of all overlapping transcription factor binding motifs identified in the Genomatix analysis. Each motif is listed under the relevant overlapping group of significantly overlapping isoforms and a Z-score for each relevant MEF2 isoform is provided. The Z-score threshold for significance is set at greater than or equal to 2. Additionally, characterized binding factors and their binding domains is also provided for each binding motif.

Estrella_SuppTable1

Term	Count	%	p-value	Fold Enrichment
MEF2A				
mmu04142:Lysosome	43	1.33	5.91E-08	2.33
mmu04115:p53 signaling pathway	25	0.77	5.47E-05	2.34
mmu04520:Adherens junction	25	0.77	3.02E-04	2.13
mmu05410:Hypertrophic cardiomyopathy (HCM)	26	0.80	6.24E-04	2.00
mmu05212:Pancreatic cancer	23	0.71	8.81E-04	2.06
MEF2B				
mmu05200:Pathways in cancer	6	4.76	3.55E-02	3.13
mmu04920:Adipocytokine signaling pathway	3	2.38	5.62E-02	7.56
mmu03320:PPAR signaling pathway	3	2.38	7.51E-02	6.41
MEF2C				
mmu04630:Jak-STAT signaling pathway	5	5.05	5.17E-03	6.74
mmu00590:Arachidonic acid metabolism	3	3.03	5.75E-02	7.41
mmu05222:Small cell lung cancer	3	3.03	5.99E-02	7.23
mmu05200:Pathways in cancer	5	5.05	6.22E-02	3.17
MEF2D				
mmu03018:RNA degradation	2	7.14	7.10E-02	23.91

GO Term	Count	%	p-value	Fold Enrichment
MEF2A				
Biological Process				
GO:0006793~phosphorus metabolic process	215	6.65	2.10E-11	1.53
GO:0006796~phosphate metabolic process	215	6.65	2.10E-11	1.53
GO:0016310~phosphorylation	183	5.66	8.30E-11	1.57
GO:0006468~protein amino acid phosphorylation	167	5.16	8.92E-11	1.61
GO:0046907~intracellular transport	119	3.68	1.83E-09	1.70
Cellular Component				
GO:0031974~membrane-enclosed lumen	288	8.91	1.82E-16	1.56
GO:0005739~mitochondrion	315	9.74	3.73E-16	1.52
GO:0043233~organelle lumen	274	8.47	9.38E-15	1.54
GO:0070013~intracellular organelle lumen	272	8.41	2.21E-14	1.53
GO:0005856~cytoskeleton	258	7.98	1.85E-11	1.47
Molecular Function				
GO:0005524~ATP binding	356	11.01	1.26E-19	1.54
GO:0032559~adenyl ribonucleotide binding	358	11.07	2.81E-19	1.53
GO:0030554~adenyl nucleotide binding	367	11.35	6.99E-18	1.49
GO:0001883~purine nucleoside binding	369	11.41	9.22E-18	1.49
GO:0001882~nucleoside binding	370	11.44	1.54E-17	1.48
MEF2B				
Biological Process				
GO:0048514~blood vessel morphogenesis	9	7.14	3.85E-05	7.02
GO:0001568~blood vessel development	9	7.14	1.66E-04	5.70
GO:0001944~vasculature development	9	7.14	1.96E-04	5.56
GO:0007389~pattern specification process	9	7.14	4.62E-04	4.89
GO:0060688~regulation of morphogenesis of a branching structure	4	3.17	5.27E-04	24.71
Cellular Component				
GO:0030018~Z disc	3	2.38	3.02E-02	10.87
GO:0031674~I band	3	2.38	3.92E-02	9.44
GO:0030017~sarcomere	3	2.38	8.13E-02	6.25
GO:0044449~contractile fiber part	3	2.38	9.20E-02	5.82
GO:0042598~vesicular fraction	4	3.17	9.31E-02	3.66
Molecular Function				
GO:0043565~sequence-specific DNA binding	10	7.94	6.59E-03	2.91
GO:0016667~oxidoreductase activity, acting on sulfur group of donors	3	2.38	1.71E-02	14.73
GO:0003700~transcription factor activity	11	8.73	1.92E-02	2.30
GO:0030528~transcription regulator activity	14	11.11	2.99E-02	1.88
GO:0003677~DNA binding	17	13.49	6.96E-02	1.55
MEF2C				
Biological Process				
GO:0046456~icosanoid biosynthetic process	3	3.03	6.27E-03	24.75
GO:0006636~unsaturated fatty acid biosynthetic process	3	3.03	6.73E-03	23.87
GO:0006690~icosanoid metabolic process	3	3.03	9.82E-03	19.65
GO:0033559~unsaturated fatty acid metabolic process	3	3.03	1.10E-02	18.56
GO:0030097~hemopoiesis	5	5.05	2.47E-02	4.44
Cellular Component				
GO:0005783~endoplasmic reticulum	11	11.11	9.67E-03	2.53
GO:0005788~endoplasmic reticulum lumen	3	3.03	5.24E-02	8.02
GO:0044420~extracellular matrix part	3	3.03	8.05E-02	6.27

GO:0005654~nucleoplasm	7	7.07	8.52E-02	2.25
Molecular Function				
GO:0015093~ferrous iron transmembrane transporter activity	2	2.02	1.46E-02	134.22
GO:0005381~iron ion transmembrane transporter activity	2	2.02	3.38E-02	57.52
GO:0008289~lipid binding	5	5.05	8.83E-02	2.92
MEF2D				
Biological Process				
GO:0022402~cell cycle process	5	17.86	1.22E-03	9.60
GO:0000279~M phase	4	14.29	4.90E-03	10.67
GO:0007049~cell cycle	5	17.86	6.03E-03	6.18
GO:0022403~cell cycle phase	4	14.29	7.37E-03	9.21
GO:0000087~M phase of mitotic cell cycle	3	10.71	2.40E-02	11.67
Cellular Component				
none				
Molecular Function				
GO:0000287~magnesium ion binding	4	14.29	1.20E-02	7.64
GO:0030145~manganese ion binding	3	10.71	1.33E-02	15.84

			Z-Score				
TF Module	**Module Description**	**A**	**B**	**C**	**D**	**Known Binding Factor**	**Binding Domain**
A/B							
V$AP1F	AP1, Activating protein 1	3.56	2.41			Batf, Fos, Fosl1, Jdp2, Junb, Batf3, Fosb, Fosl2, Jun, Jund	bZIP
V$BPTF	Bromodomain and PHD domain transcription factors	15.33	3.58			Bptf	not characterized
V$CP2F	CP2-erythrocyte Factor related to drosophila Elf1	5.38	2.17			Tfcp2, Tfcp2l1, Ubp1	not characterized
V$EREF	Estrogen response elements	13.89	3.05			Esr1, Esr2, Esrra, Esrrb, Esrrg	C4 zinc finger domain
V$GFI1	Growth factor independence transcriptional repressor	12.73	2.09			Gfi1, Gfi1b	C2H2 zinc finger domain
V$GZF1	GDNF-inducible zinc finger gene 1	9.43	2.38			Gzf1	BTB-POZ C2H2 zinc fingers
V$HAND	Twist subfamily of class B bHLH transcription factors	10.22	3.98			Hand1, Lyl1, Mesp1, Mesp2, Nhlh1, Nhlh2, Scx, Tal1, Tal2, Tcf12, Tcf15, Tcf3, Tcf4, Twist1, Twist2	bHLH
V$HOXH	HOX - MEIS1 heterodimers	6.78	2.48			Hoxa10, Hoxa11, Hoxa13, Hoxa9,Hoxb13, Hoxb9, Hoxc10, Hoxc11, Hoxc12, Hoxc13, Hoxc9, Hoxd10, Hoxd11, Hoxd12, Hoxd13, Hoxd9, Meis1, Meis2, Meis3	TALE class homeodomain, homeodomain
V$PERO	Peroxisome proliferator-activated receptor	10.92	3.37			Ppara, Ppard, Pparg, Rxra, Rxrb	C4 zinc finger domain
V$RP58	RP58 (ZFP238) zinc finger protein	10.62	3.91			Zbtb18	BTB-POZ C2H2 zinc fingers
V$TEAF	TEA/ATTS DNA binding domain factors	3.83	4.43			Tead1, Tead2, Tead3, Tead4, Tulp1	TEA/ATTS domain
V$YY1F	Activator/repressor binding to transcription initiation site	7.32	2.87			Yy1, Yy2, Zfp42	C2H2 zinc finger domain
V$ZF11	C2H2 zinc finger transcription factors 11	11.69	2.22			ZBTB3 (human)	C2H2 zinc finger domain
A/C							
O$INRE	Core promoter initiator elements	7.14		2.93			
V$AIRE	Autoimmune regulatory element binding factor	10.83		2.19		Aire	SAND domain, PHD domain

V$CAAT	CCAAT binding factors	11.24	2.28		Nfya, Nfyb, Nfyc	heterotrimeric transcription factor
V$CART	Cart-1 (cartilage homeoprotein 1)	21.36	5.43		Alx1, Alx3, Alx4, Arx, Esx1, Hesx1, Isx, Mixl1, Otp, Phox2a, Phox2b, Prop1, Prrx1, Prrx2, Rax, Rhox6, Shox2, Uncx, Vsx1, Vsx2	homeodomain
V$GUCE	GTF2IRDI upstream control element	6.64	2.17		Gtf2i, Gtf2ird1	GTF2I repeat domain
V$LTFM	Lactotransferrin motif	17.14	2.59		Ltf	not characterized
V$NBRE	NGFI-B response elements, nur subfamily of nuclear receptors	3.66	2.96		Nr4a1, Nr4a2, Nr4a3	C4 zinc finger domain
V$NFAT	Nuclear factor of activated T-cells	4.51	2.58		Ilf2, Ilf3, Nfat5, Nfatc1, Nfatc2, Nfatc3, Nfatc4	RHR
V$OSRF	Odd-skipped related factors	7.86	2.07		Osr1, Osr2	C2H2 zinc finger domain
V$PAXH	PAX homeodomain binding sites	8.24	2.16		Pax4, Pax6, Pax7	homeodomain
V$PDX1	Pancreatic and intestinal homeodomain transcription factor	10.18	2.13		Pdx1	homeodomain, LIM domain/homeodomain
V$PLZF	C2H2 zinc finger protein PLZF	20.33	5.87		Zbtb16, Zbtb32	BTB-POZ C2H2 zinc fingers
V$PRDF	Positive regulatory domain I binding factor	4.01	2.47		Prdm1	C2H2 zinc finger domain
V$SIXF	Sine oculis (SIX) homeodomain factors	14.23	3.52		Six1-6	homeodomain, SIX domain
V$SNAP	snRNA-activating protein complex	11.4	3.55		Snapc4	MYB domain
A/D						
V$BRAC	Brachyury gene, mesoderm developmental factor	5.75		4.08	Eomes, Mga, T, Tbr1, Tbx1, Tbx10, Tbx15, Tbx18, Tbx19, Tbx2, Tbx20, Tbx21, Tbx22, Tbx3, Tbx4, Tbx5, Tbx6	T-box
V$CIZF	CAS interating zinc finger protein	4.2		2.51	Zfp384	C2H2 zinc finger domain
V$PPAR	Peroxisome proliferator activated receptor homodimers	12.71		2.59	Pparg	C4 zinc finger domain
B/C						
none						
B/D						
none						
C/D						
none						

A/B/C						
O$VTBP	Vertebrate TATA binding protein factor	35.46	7.38	8.33	Tbp, Tbpl1, Tbpl2	
V$BCDF	Bicoid-like homeodomain transcription factors	32.91	3.9	5.26	Crx, Dmbx1, Gsc, Gsc2, Otx1, Otx2, Pitx1, Pitx2, Pitx3	homeodomain
V$CABL	C-abl DNA binding sites	36.34	4.99	6.76	Abl1	proline-rich region
V$CHRF	Cell cycle regulators: Cell cycle homology element	13.96	4.37	2.51	Lin54	not characterized
V$DMRT	DM domain-containing transcription factors	26.48	5.17	5.08	Dmrt1, Dmrt2, Dmrt3, Dmrta1, Dmrta2, Dmrtb1, Dmrtc1a, Dmrtc1b, Dmrtc1c1, Dmrtc2	DM domain
V$FAST	FAST-1 SMAD interacting proteins	16.54	2.66	2.96	Foxh1	fork head domain (winged helix)
V$GCNR	Germ cell nuclear receptors	26.01	2.39	2.36	Nr6a1	C4 zinc finger domain
V$GREF	Glucocorticoid responsive and related elements	25	3.25	3.05	Ar, Nr3c1, Nr3c2, Pgr	C4 zinc finger domain
V$HAML	Human acute myelogenous leukemia factors	19.54	2.61	2.01	Cbfa2t2, Cbfa2t3, Cbfb, Runx1, Runx1t1, Runx2, Runx3	Runt-domain
V$HMTB	Human muscle-specific Mt binding site	16.7	4.48	4.77	not characterized	not characterized
V$IRFF	Interferon regulatory factors	20.11	2.24	4.01	Irf1, Irf2, Irf3, Irf4, Irf5, Irf6, Irf7, Irf8, Irf9, Stat1, Stat2	IRF-HTH
V$IRXF	Iroquois homeobox transcription factors	25.48	6.21	7.23	Irx1, Irx2, Irx3, Irx4, Irx5, Irx6	homeodomain
V$LEFF	LEF1/TCF	19.81	3.08	5.2	Lef1, Tcf7, Tcf7l1, Tcf7l2	HMG domain
V$MEF2	MEF2, myocyte-specific enhancer binding factor	22.64	4.68	7.08	Mef2a, Mef2b, Mef2c, Mef2d, Myef2	MADS box
V$MITF	Microphthalmia transcription factor	23.36	5.47	2.6	Mitf, Tfe3, Tfeb, Tfec	bHLH-ZIP
V$MYT1	MYT1 C2HC zinc finger protein	18.18	3.6	4.57	Myt1, Myt1l, St18	C2HC zinc finger domain
V$NKX1	NK1 homeobox transcription factors	10.18	3.55	2.53	Nkx1-1, Nkx1-2, Osgin2	homeodomain
V$NKX6	NK6 homeobox transcription factors	15.54	2.33	5.99	Nkx6-1, Nkx6-2, Nkx6-3	homeodomain
V$NKXH	NKX homeodomain factors	20.49	3.86	4.72	Nkx2-1, Nkx2-2, Nkx2-3, Nkx2-4, Nkx2-5, Nkx2-6, Nkx2-7, Nkx2-9, Nkx3-2	homeodomain
V$P53F	p53 tumor suppressor	10.33	3.52	2.84	Trp53, Trp63, Trp73	p53 domain

V$PAX2	PAX-2 binding sites	12.49	2.01	3.2		Pax2	paired box domain, octapeptide, truncated homeodomain
V$PBXC	PBX - MEIS complexes	3.45	2.61	2.71		Meis1, Meis2, Meis3, Pbx1, Pbx2, Pbx3, Pbx4, Pknox1, Pknox2	TALE class homeodomain
V$RXRF	RXR heterodimer binding sites	18.45	4.69	5.43		Nr1h2, Nr1h3, Nr1i2, Nr1i3, Rara, Rarb, Rarg, Rxra, Rxrb, Rxrg, Thra, Thrb, Vdr	C4 zinc finger domain
V$SAL1	Spalt-like transcription factor 1	14.24	3.63	4.57		Sall1	C2H2 zinc finger domain
V$STEM	Motif composed of binding sites for pluripotency or stem cell factors	10.36	3.89	2.92		Pou5f1, Sox2	not characterized
A/B/D							
V$CLOX	CLOX and CLOX homology (CDP) factors	4.79	2.79		3.27	Cphx1, Cux1, Cux2	CUT repeats, homeodomain
A/C/D							
V$EVI1	EVI1-myleoid transforming protein	17.32		7.01	3.67	Bcl11a, Bcl11b, Mecom, Prdm16, Zfp521	C2H2 zinc finger domain
V$PARF	PAR/bZIP family	15.68		3.65	2.62	Dbp, Hlf, Tef, Vbp1	PAR/bZIP family
V$ZF03	C2H2 zinc finger transcription factors 3	8.12		3.45	2.38	Zfp217	C2H2 zinc finger domain
V$ZF10	C2H2 zinc finger transcription factors 10	8.25		2.19	2.28	Prdm14	C2H2 zinc finger domain
B/C/D							
A/B/C/D							
O$PTBP	Plant TATA binding protein factor	25.73	11.48	8.13	2.61		
O$YTBP	Yeast TATA binding protein factor	32.52	12.86	10.71	2.53		
V$ABDB	Abdominal-B type homeodomain transcription factors	28.85	3.98	9.73	3.37	Hoxa10, Hoxa11, Hoxa13, Hoxa9, Hoxb13, Hoxb9, Hoxc10, Hoxc11, Hoxc12, Hoxc13, Hoxc9, Hoxd10, Hoxd11, Hoxd12, Hoxd13, Hoxd9	homeodomain
V$ARID	AT rich interactive domain factor	15.59	2.37	6.34	3.1	Arid3a, Arid3b, Arid5a, Arid5b, Jarid2	ARID domain
V$BCL6	POZ domain zinc finger expressed in B-Cells	19.86	3.84	2.47	2.11	Bcl6, Bcl6b	BTB-POZ C2H2 zinc fingers
V$BRN5	Brn-5 POU domain factors	23.48	4.48	6.22	2.74	Pou6f1, Pou6f2	POU domain

V$BRNF	Brn POU domain factors	31.08	4.27	9.59	3.79	Pou3f1, Pou3f2, Pou3f4, Pou4f1, Pou4f2, Pou4f3	POU domain
V$CDXF	Vertebrate caudal related homeodomain protein	22.98	3.95	5.62	3.21	Cdx1, Cdx2, Cdx4	homeodomain
V$CEBP	Ccaat/Enhancer Binding Protein	7.81	2.66	2.71	2.19	Cebpa, Cebpb, Cebpd, Cebpe, Cebpg, Cebpz	bZIP
V$FKHD	Fork head domain factors	60.68	10.67	11.25	5.29	Ap5z1, Foxa1, Foxa2, Foxa3, Foxb1, Foxb2, Foxc1, Foxc2, Foxd1, Foxd2, Foxd3, Foxd4, Foxe1, Foxe3, Foxf1, Foxf2, Foxg1, Foxi1, Foxj1, Foxj2, Foxj3, Foxk1, Foxk2, Foxl1, Foxl2, Foxm1, Foxn2, Foxn3, Foxo1, Foxo3, Foxo4, Foxo6, Foxp1, Foxp2, Foxp3, Foxp4, Foxq1, Foxs1, Hfh5, Hfh6, Hfh7	fork head domain (winged helix)
V$GABF	GA-boxes	53.93	8.62	17.91	6.36	not characterized	not characterized
V$GATA	GATA binding factors	21.67	3.88	5.58	3.04	Gata1, Gata2, Gata3, Gata4, Gata5, Gata6, Trps1	GATA-C2C2 zinc finger domain
V$HBOX	Homeobox transcription factors	17	2.56	3.98	2.75	Emx2, En1, En2, Evx1, Evx2, Gbx1, Gbx2, Gsx1, Gsx2, Meox1, Meox2, Mnx1, Vax1, Vax2	homeodomain
V$HNF1	Hepatic Nuclear Factor 1	23.19	5.85	6.14	2.43	Hmbox1, Hnf1a, Hnf1b	homeodomain
V$HNF6	Onecut homeodomain factor HNF6	16.09	3.26	6.64	2.08	Onecut1, Onecut2, Onecut3	CUT repeats, homeodomain
V$HOMF	Homeodomain transcription factors	30.98	3.7	6.13	3.28	Barhl1, Barhl2, Barx1, Barx2, Bsx, Hhex, Hmx1, Hmx2, Hmx3, Lbx2, Msx1, Msx2, Msx3, Nobox, Tlx1, Tlx2	homeodomain

V$HOXC	HOX - PBX complexes	34.97	9.23	8.61	5.25	Hoxa1, Hoxa10, Hoxa2, Hoxa3, Hoxa4, Hoxa5, Hoxa6, Hoxa7, Hoxa9, Hoxb1, Hoxb2, Hoxb3, Hoxb4, Hoxb5, Hoxb6, Hoxb7, Hoxb8, Hoxb9, Hoxc10, Hoxc4, Hoxc5, Hoxc6, Hoxc8, Hoxc9, Hoxd1, Hoxd10, Hoxd3, Hoxd4, Hoxd8, Hoxd9, Meis1, Pbx1, Pbx2, Pbx3, Pbx4	TALE class homeodomain, homeodomain
V$HOXF	Paralog hox genes 1-8 from the four hox clusters A, B, C, D	23.43	3.82	7.15	2.94	Hoxa1, Hoxa2, Hoxa3, Hoxa4, Hoxa5, Hoxa6, Hoxa7, Hoxb1, Hoxb2, Hoxb3, Hoxb4, Hoxb5, Hoxb6, Hoxb7, Hoxb8, Hoxc4, Hoxc5, Hoxc6, Hoxc8, Hoxd1, Hoxd3, Hoxd4, Hoxd8, Nanog	homeodomain
V$LHXF	Lim homeodomain factors	23.8	4.26	7.12	2.51	Isl1, Isl2, Lhx1, Lhx2, Lhx3, Lhx4, Lhx5, Lhx6, Lhx8, Lhx9, Lmx1a, Lmx1b	LIM domain/homeodomain
V$NR2F	Nuclear receptor subfamily 2 factors	21.83	3.98	3.11	2.33	Hnf4a, Hnf4g, Nr2c1, Nr2c2, Nr2e3, Nr2f1, Nr2f2, Nr2f6	C4 zinc finger domain
V$OCT1	Octamer binding protein	22.15	4.35	7.13	4.17	Pou2f1, Pou2f2, Pou2f3, Pou3f3	POU domain
V$PAX6	PAX-4/PAX-6 paired domain binding sites	19.98	2.97	2.11	2.24	Pax4, Pax6	paired box domain, homeodomain
V$PIT1	GHF-1 pituitary specific pou domain transcription factor	28.03	5.7	8.74	4.79	Pou1f1	POU domain
V$RORA	v-ERB and RAR-related orphan receptor alpha	15.84	4.35	3.07	2.23	Nr1d1, Nr1d2, Rora, Rorb, Rorc	C4 zinc finger domain
V$RUSH	SWI/SNF related nucleophosphoproteins with a RING finger DNA binding motif	24.56	4.21	5.52	2.08	Hltf	not characterized
V$SATB	Special AT-rich sequence binding protein	17.33	2.71	3.61	2.11	Satb1, Satb2	MAR-binding domain, CUT repeats, homeodomain
V$SIX3	Sine oculis homeobox homolog 3	36.92	3.21	3.9	3	Six3, Six6	homeodomain

V$SORY	SOX/SRY-sex/testis determinig and related HMG box factors	33.64	5.92	8.83	3.88	Cic, Hbp1, Hmga1, Hmga2, Pinx1, Sox1, Sox10, Sox11, Sox12, Sox13, Sox14, Sox15, Sox16, Sox17, Sox18, Sox19, Sox2, Sox21, Sox3, Sox30, Sox4, Sox5, Sox6, Sox7, Sox8, Sox9, Sry, Tox	AT-hook, HMG domain
V$SRFF	Serum response element binding factor	23.26	5.04	4.36	2.28	Srf	MADS box
V$STAT	Signal transducer and activator of transcription	28.25	2.03	4.43	2.79	Stat1, Stat2, Stat3, Stat4, Stat5a, Stat5b, Stat6	STAT domain