Drosophila and human transcriptomic data mining provides evidence for therapeutic mechanism of pentylenetetrazole in Down syndrome

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Running head: Pentylenetetrazole mechanism in Down syndrome

Abstract

Pentylenetetrazole (PTZ) has recently been found to ameliorate cognitive impairment in rodent models of Down syndrome (DS). The mechanism underlying PTZ's therapeutic effect is however not clear. Microarray profiling has previously reported differential expression of genes in DS. No mammalian transcriptomic data on PTZ treatment however exists. Nevertheless, a *Drosophila* model inspired by rodent models of PTZ induced kindling plasticity has recently been described. Microarray profiling has shown PTZ's downregulatory effect on gene expression in fly heads. In a comparative transcriptomics approach, I have analyzed the available microarray data in order to identify potential mechanism of PTZ action in DS. I find that transcriptomic correlates of chronic PTZ in *Drosophila* and DS counteract each other. A significant enrichment is observed between PTZ downregulated and DS upregulated genes, and a significant depletion between PTZ downregulated and DS dowwnregulated genes. Further, the common genes in PTZ downregulated and DS upregulated sets show enrichment for MAP kinase pathway. My analysis suggests that downregulation of MAP kinase pathway may mediate therapeutic effect of PTZ in DS. Existing evidence implicating MAP kinase pathway in DS supports this observation.

Introduction

Chronic treatment with nonconvulsive dosage of PTZ has recently been found to ameliorate cognitive impairment in rodent models of DS (*1*, *2*, *3*, *4*). The mechanism underlying PTZ's potential therapeutic effect in DS is however unclear. Genome scale expression analysis offers a promising approach to identify genes and pathways relevant in pathophysiological and therapeutic mechanisms in complex CNS disorders (*5*). Microarray gene expression profiling has previously been reported in the analysis of control versus DS astrocyte cell line and cerebrum or apical frontal pole (*6*), prefrontal cortex (*7*), and neural progenitor cells (*8*). However, transcriptomic analysis of PTZ treatment effect in mammalian system has not been undertaken yet. This precludes understanding drug's potential mechanism using functional genomic data.

A *Drosophila* model inspired by rodent models of chronic subconvulsive PTZ induced kindling plasticity has recently been developed (*9*). In this model PTZ causes a decreased speed in startle-induced climbing in flies. Antiepileptic drugs, used in treating epilepsy and other neurological and psychiatric disorders, suppress development of this behavioral deficit. Microarray profiling has shown PTZ's downregulatory effect on gene expression in fly heads. This effect has been found to mimic transcriptome and proteome scale changes reported previously in human epilepsy patients and mammalian models of epileptogenesis.

The fly model thus provides a systems level framework for understanding potential disease and drug mechanisms (*9*). In a comparative transcriptomics approach, I examine here if mining of the available fly (*9*) and human (*6, 7, 8*) microarray data could uncover potential mechanism of PTZ action in DS.

<u>Results</u>

I first examined if PTZ regulated genes in *Drosophila* (*9*) counteract differentially expressed genes in DS (*6, 7, 8*). The three diverse DS studies reported differentially expressed genes with insignificant overlap. Genes in DS studies were thus pooled together for matching with human homologs of PTZ regulated genes (**Table S1 supporting material)**. Strikingly, a significant enrichment was found between PTZ downregulated and DS upregulated genes, and a significant depletion between PTZ downregulated and DS dowwnregulated genes (**Fig. 1**). Enrichment for MAP kinase pathway in DS upregulated genes has previously been reported (*8*). In contrast, downregulated genes in *Drosophila*, the only regulated genes in the PTZ model, have been found to enrich MAP kinase pathway (*9*). Thus, I next predicted that significant overlap between PTZ downregulated and DS upregulated genes may result from counteracting effect on MAP kinase signaling. Remarkably, the counteracting commonality genes between PTZ downregulated and DS upregulated sets were found to enrich the MAP kinase pathway (**Fig. 2**). Together, my unbiased transcriptomic analysis provided evidence for the involvement of MAP kinase pathway in the mechanism of action of PTZ.

Discussion

The present functional genomic analysis suggests that potential therapeutic effect of PTZ in DS may be mediated by downregulation of MAP kinase signaling pathway. This is supported by existing evidence from diverse studies. For example, protein analysis of fetal brain cortex has previously identified dysregulation of MAP kinase pathway related components in DS (*10*). Also, comparative genomics analysis has predicted perturbation in MAP kinase pathway in DS (*11*). Further, biochemical analysis has suggested a role of activated MAP kinase signaling in brain pathogenesis in mouse DS model (*12*). Besides, bioinformatic analysis of genes located in the candidate DS region in chromosome 21 has implicated MAP kinase pathway in the disease (*13*). Biochemical, genomic and computational evidence thus exist to support the plausibility of MAP kinase signaling as PTZ's therapeutic target in DS.

Materials and Methods

Chronic PTZ regulated *Drosophila* genes, all downregulated, listed in additional file (*9*) were used in the analysis. Literature on relevant microarray profiling in DS was searched in PubMed (http://www.ncbi.nlm.nih.gov/pubmed). For DS versus control microarrays, list of differentially expressed genes provided in the supplementary tables or data (*3*, *7*, *8*) was used. Overlap between gene sets and pathway enrichment was examined using hypergeometric distribution probability. Human homologs (gene symbols) of *Drosophila* genes were retrieved using Homologene option in FLIGHT (http://www.flight.licr.org/search/batch_homology.jsp). Gene IDs described in human studies were converted to gene symbols using DAVID (http://david.abcc.ncifcrf.gov/summary.jsp), NCBI (http://www.ncbi.nlm.nih.gov/unigene/) and SOURCE (http://smd.stanford.edu/cgi-bin/source/sourceBatchSearch). Genes were depicted in the KEGG pathway for *Homo sapiens* (http://www.genome.jp/kegg/tool/color_pathway.html).

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Figure legends

Figure 1.

Venn diagram showing overlaps among PTZ and DS genes. Of the 716 total up- and down-regulated genes in DS, 56 are common to the PTZ downregulated set. Of the 419 upregulated DS genes, 41 are common to the PTZ set. Of the 301 downregulated DS genes, 16 are common to the PTZ set. Note significant enrichment in PTZ and DS total versus PTZ and DS upregulated (hypergeometric distribution, $p = 0.011$) and depletion in PTZ and DS total versus PTZ and DS downregulated (hypergeometric distribution, $p = 0.008$).

Figure 2.

MAP kinase pathway showing counteracting commonality genes. Of the 419 DS upregulated genes, 9 mapped on to the pathway. Of the 41 counteracting commonality genes, i.e., genes common between PTZ downregulated and DS upregulated sets, 3 figured in the pathway map (BRAF, PAK1 and PRKCA; represented by the three orange color boxes). Note significant enrichment of MAP kinase pathway in counteracting commonality genes ($p = 0.041$).

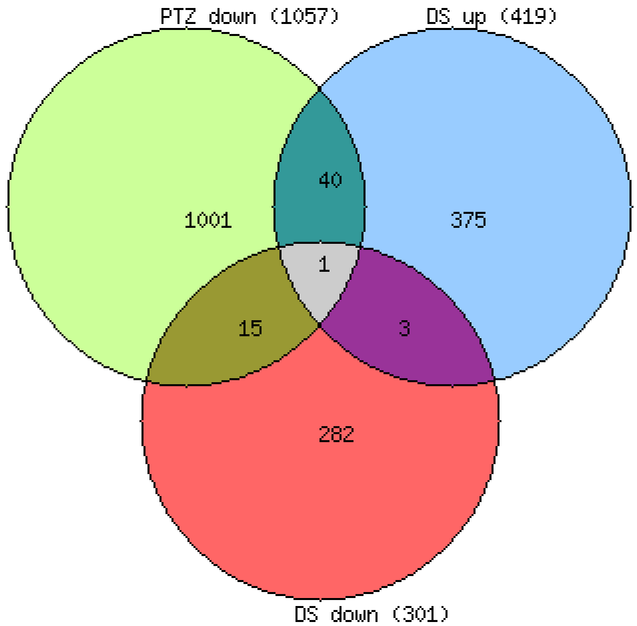

Figure 1

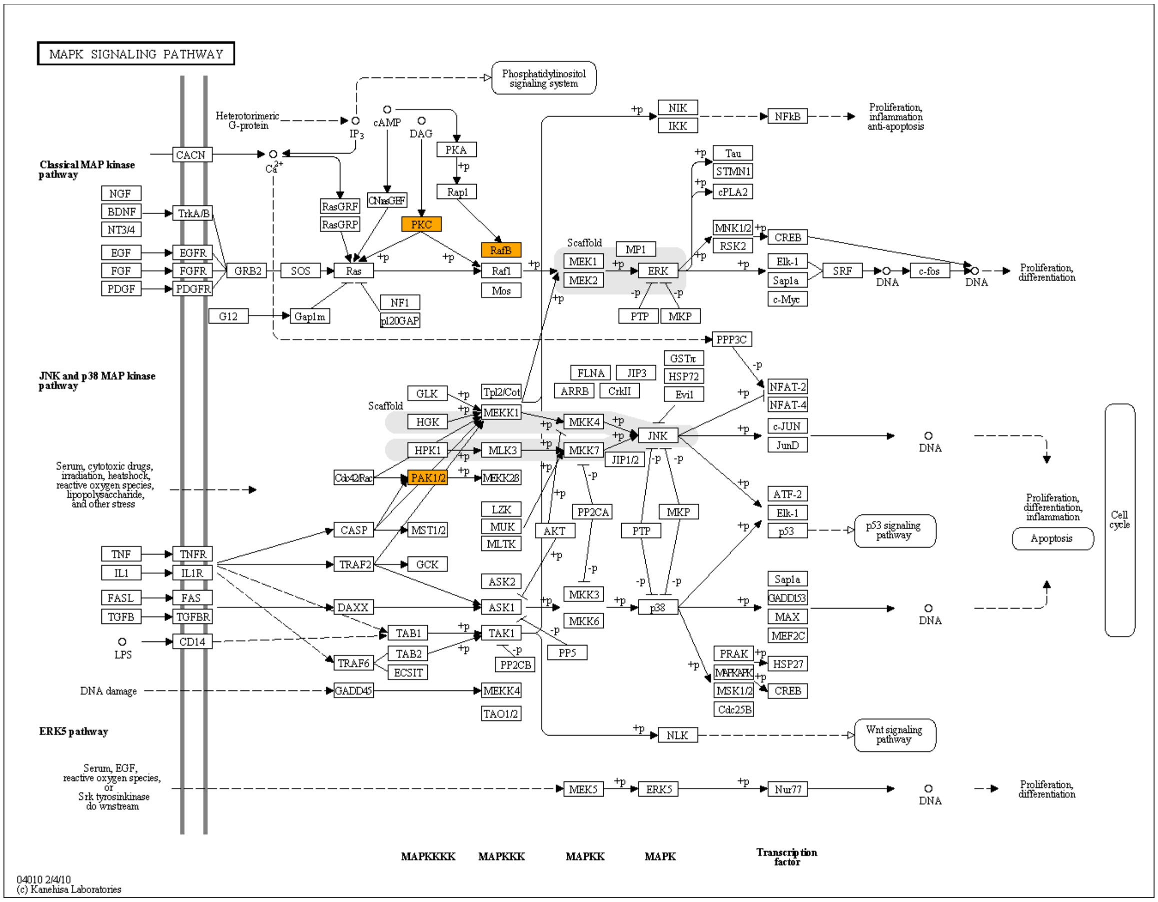
MAPK SIGNALING PATHWAY
Classical MAP kinase pathway
JNK and p38 MAP kinase pathway
ERK5 pathway
Phosphatidylinositol signaling system
Heterotrimeric G-protein
cAMP
DAG
PKA
Rap1
CACN
NGF
BDNF
NT3/4
TrkA/B
EGF
FGF
PDGF
EGFR
FGFR
PDGFR
GRB2
SOS
Ras
RasGRF
RasGRP
CNrasGEF
PKC
RafB
Raf1
Mos
NF1
p120GAP
G12
Gap1m
Scaffold
MP1
MEK1
MEK2
ERK
PTP
MKP
NIK
IKK
NFkB
Proliferation, inflammation anti-apoptosis
Tau
STMN1
cPLA2
MNK1/2
RSK2
CREB
Elk-1
Sap1a
c-Myc
SRF
c-fos
DNA
Proliferation, differentiation
PPP3C
NFAT-2
NFAT-4
Serum, cytotoxic drugs, irradiation, heatshock, reactive oxygen species, lipopolysaccharide, and other stress
GLK
HGK
HPK1
Cdc42/Rac
PAK1/2
Tpl2/Cot
MEKK1
MLK3
MEKK2/3
FLNA
JIP3
ARRB
CrkII
GSTπ
HSP72
Evi1
MKK4
MKK7
JNK
JIP1/2
c-JUN
JunD
ATF-2
p53
p53 signaling pathway
Proliferation, differentiation, inflammation
Apoptosis
Cell cycle
LZK
MUK
MLTK
AKT
PP2CA
CASP
MST1/2
TRAF2
GCK
ASK2
ASK1
TNF
IL1
FASL
TGFB
LPS
TNFR
IL1R
FAS
TGFBR
CD14
DAXX
TAB1
TAB2
TAK1
TRAF6
ECSIT
PP2CB
MKK3
MKK6
PP5
p38
GADD153
MAX
MEF2C
PRAK
MAPKAPK
MSK1/2
Cdc25B
HSP27
DNA damage
GADD45
MEKK4
TAO1/2
NLK
Wnt signaling pathway
Serum, EGF, reactive oxygen species, or Srk tyrosinkinase do wnstream
MEK5
ERK5
Nur77
MAPKKKK
MAPKKK
MAPKK
MAPK
Transcription factor
04010 2/4/10
(c) Kanehisa Laboratories

Figure 2

Table S1. Differentially expressed genes reported in *Drosophila* model and DS studies.

Mohammad et al.	Esposito et al.		Lockstone et al.		Mao et al.	
Downregulated	**Up**	**Dn**	**Up**	**Dn**	**Up**	**Dn**
6-Sep	ABCA2	ABCB4	ACTR3	CLTC	ABI1	ABR
ABCC1	ABCC1	AMFR	ALDH4A1	DNM1	ACVR1	ADAM17
ABCC4	ACTC	ANGPTL1	ALDH7A1		ADFP	ADAM22
ABCF2	ACTR8	APXL2	CAP1		AIM2	ADRA1A
ABCG1	ADCK4	ATP8B1	CAPG		AKAP8	AIP
ABHD2	ADCY2	ATPAF2	CNTN1		AKR1C3	ALOX12B
ABI1	AGPAT3	B3GALT3	DNM2		ALDH2	AOF2
ABLIM1	AHCYL1	B3GAT2	EEF1G		APP	API5
ACAA2	ALS2CR8	BANP	ENO1		AQP3	APOBEC1
ACADSB	ANKFY1	BCAT1	GFAP		ASAH1	AQP9
ACE	ANKRD10	BCAT2	GLUD1		ASB4	ARAF
ACO2	AP3B1	C11orf2	GLUL		ATP5J	ARHGEF1
ACPP	APP	C14orf2	MSN		ATP5O	ARNT
ACSBG2	APTX	C1QTNF5	VIL2		B3GALT2	ASNA1
ACSS2	AQP4	C20orf58			BLVRA	ATP10B
ACTA1	ARFIP1	C20orf64			BMP6	BAZ2B
ACTA2	ARHGAP18	C2orf3			BRP44	BRCA1
ACTG1	ARHGDIA	C3orf6			BTG3	CALCOCO2
ACTN1	ARHU	C6orf194			C21ORF33	CALR
ACTR1A	ATF2	C6orf66			CASK	CCL25
ACTR2	ATP11A	CCNB1			CAV1	CCND2
ACTR3	ATP6V1A	CGI-09			CCR1	CD44
ACTR6	ATRX	CGI-112			CCT8	CDC2L1
ACVR2A	BAIAP3	CHST11			CD200	CDH18
ADAM9	BBP	CPT1B			CD6	CHMP2A
ADAR	BC022889	CYP2R1			CDC23	CLCN6
ADARB1	BCAT2	Cab45			CDC2L6	COLEC10
ADCY2	BM-009	D2S448			CDK10	CYP2A13
ADCY5	BRAF	DAZAP1			CENTB2	CYP2D6
ADCY6	BRD4	DBC-1			CHMP2B	DKFZP547J0410
ADD1	C14orf2	DKFZP727G051			COX11	DNASE2
ADHFE1	C14orf44	DKFZP761M1511			CREB3L2	DSG1

ADRM1	C21orf33	DKFZp434C1714	CROCC	EEA1
ADSSL1	C21orf4	DKFZp547B1713	CSPG5	EFNB1
AGR2	C21orf66	DKFZp727G131	CSTB	EIF5AL1
AKAP1	C21orf86	DPP9	CYLD	FANCG
ALDH3B1	C3orf6	DUSP16	CYP1B1	FARSA
ALDH6A1	C6orf69	E2F3	DCTD	FAS
AMMECR1	CACNA2D2	ECGP	DDT	FMO2
AMPD2	CBX5	EPHA2	DLEU2	FMO3
AMPH	CBX7	EPOR	DLGAP2	FMO6P
ANAPC2	CDC14B	ETV4	DOK1	GAPDH
ANK3	CDC42EP3	ETV5	DSCR3	GCDH
ANKH	CHD4	FBXO10	DYRK1A	GCN5L2
ANKRD13B	CITED2	FEM1A	EED	HLF
ANKRD39	CKMT1	FKBP1B	EIF4H	IFI35
ANP32A	COL6A1	FKBP5	ETF1	INPP4A
AP1M1	COLEC12	FLJ10359	EXT2	KANK1
AP2A2	CPE	FLJ10378	FBLN1	KIAA0753
AP2S1	CPEB1	FLJ10904	GCNT1	KIAA1024
APC	CRYZL1	FLJ14494	GLT8D1	KIAA1539
APC2	CSNK1A1	FLJ20189	GPATCH8	KIAA2013
APEX1	CSTB	FLJ20485	GPR31	KLF1
APOD	CTNNA2	FLJ22021	GSTT1	KLK10
APPBP1	CUGBP1	FLJ22729	GSTT2	LHX1
ARC	DIP2	FLJ23476	HAPLN1	LOC283079
ARF1	DJ159A19.3	FLJ23749	HEMK1	MAGEA12
ARIH1	DKFZP586A0522	FLJ23765	HSPA13	MAP2
ARL4A	DKFZP586L151	FLJ32356	IFI44	MAPK10
ARL6IP2	DKFZP586N0721	FLJ37078	IFNAR2	MAPK8
ARL8B	DLK1	FLJ38464	IL10RB	MAPKAPK2
ARMET	DPYSL3	FOXM1	IL7R	MAST1
ARNTL	DRCTNNB1A	FTH1	INPP5E	MCRS1
ARS2	DTNBP1	FTHFSDC1	INTS10	MYH2
ASAH3L	DTX1	FZD8	ITGA6	NCDN
ASIP	ECM2	GCLM	IVNS1ABP	NCK2
ASPH	EDNRA	GGH	KCNJ15	NENF
ATAD3A	EGLN1	GMNN	KCTD7	NFATC2IP
ATAD3B	EIF4G1	GPX6	KIAA0152	NKX3-2
ATF6	EIF5A	GRB10	KIAA0355	NPPA
ATG5	ELMO2	GTF3C3	LAMP2	NPPB

ATM	ENTPD1	HADHA	LIMK2	NPTX2
ATP13A3	EPRS	HCA127	LOC100288372	NRL
ATP1A3	FAM13C1	HCAP-G	LTA4H	OVOL2
ATP2A1	FGD3	HM13	MATR3	PAX8
ATP2B3	FGF1	HSPC023	MFGE8	PCDH17
ATP5A1	FGF12	HSPC111	MOAP1	PDE3B
ATP5G3	FHOD2	HSPC128	MTERFD1	PDE5A
ATP5H	FLJ10074	HTATIP2	NAE1	PDGFRB
ATP5L	FLJ11467	IDI1	NEK9	PIGO
ATP6V0A1	FLJ20097	IHPK2	NKX2-2	PLIN
ATP6V0A4	FLJ21924	IMPA2	NOTCH4	POLD2
ATP6V0C	FLJ23451	IRAK1	NPFF	POLR2J
ATP6V0D1	FLJ23861	KAPPA-200	NRIP1	POLR2J3
ATP6V1C1	FLJ25082	KCNJ4	NUPL1	PPP3R1
ATP6V1D	FLJ30973	KHK	OCRL	PRKACA
ATP6V1E1	FLJ32499	KIAA0117	OTOR	PTPN1
ATP6V1G1	FLJ32535	KIAA0173	PDXK	RAD23A
ATP6V1H	FLJ32569	KIAA0469	PENK	RASA4
ATP7A	FLJ32731	KIAA1951	PFDN1	RCE1
ATP8A1	FLJ33215	KLF15	PHOX2B	RGS10
ATXN2	FNBP3	KRT10	PIAS2	RIF1
B4GALT1	G3BP2	L3MBTL2	PLOD2	RIMS1
B4GALT2	GABPA	LGN	POLR2B	RND2
BAG2	GALNT7	LIG3	POMZP3	RP1-127D3.2
BAIAP3	GAP43	LOC114971	POP5	RPL21P4
BCAS3	GART	LOC126295	PPP6C	SBF1
BCDIN3	GLS	LOC144997	PTTG1IP	SCAPER
BCR	GLUL	LOC348094	PVRIG	SERPINH1
BEST1	GNAI3	LOC56901	PYGL	SH3BGRL
BEST2	GOLGIN-67	LOC91942	RAB5A	SLC27A2
BIN3	GRIA3	LYSAL1	RAP1A	SLC28A2
BIRC3	H-plk	LZIC	RNF103	SMARCC2
BLCAP	HIBADH	MAP2K2	RP11-540L11.1	SNX26
BLM	HIPK3	MBD1	RSU1	SPTB
BLVRB	HLA-DMB	MCAM	SCG5	SPTBN2
BMPR1A	HLA-DOA	MFNG	SDF2	ST20
BOLL	HMGCS1	MGC22793	SEPP1	STOML2
BRAF	HNLF	MGC24039	SERP1	TACSTD1
BSG	HOXA3	MGC24381	SETD4	TAF6L

C10orf9	HOXB7	MGC25062	SGMS1	TFDP2
C11orf54	HRB2	MGC26885	SH3BGR	TIMP2
C13orf21	HRMT1L1	MGC9850	SLC11A2	TMCC2
C14orf111	HSF1	MGST1	SLC16A1	TNPO3
C14orf122	HSPA4	MMD	SLC4A8	TPM3
C14orf130	HSPH1	MPPE1	SNRPB2	USP52
C14orf4	HT036	MRPS34	SOD1	VAT1
C16orf5	HTATSF1	MSH5	SP100	VCP
C1QBP	HTR2A	MYBL2	SSTR1	ZRSR1
C1orf55	JAK1	NAGA	TAF4B	
C2	JAM2	NDE1	TLR6	
C20orf20	JMJD2	NDST1	TMEM5	
C20orf45	KIAA0217	NDUFB10	TMPO	
C20orf59	KIAA0241	NETO1	TP53AP1	
C22orf5	KIAA0318	NFX1	TPM1	
C3orf21	KIAA0367	NICE-3	TTC3	
C6orf166	KIAA0551	NICE-4	U2AF1	
C7orf20	KIAA0570	NID	UBE2E4P	
CAB39L	KIAA0841	NR2F6	UCHL3	
CACNA1A	KIAA0888	NT5C2	YAP1	
CACNA1D	KIAA1006	NXT1	ZEB1	
CACNA2D3	KIAA1041	OPN3	ZFYVE9	
CADPS	KIAA1107	OSAP	ZNF294	
CALB2	KIAA1685	PACSIN3		
CALM2	KIF3A	PAO		
CAMK2D	KLF7	PCTK1		
CAMSAP1L1	LANCL1	PDCD2		
CAP1	LEAP-2	PEX14		
CAPN9	LHX3	PIP3-E		
CAPS	LIMK2	PLAB		
CASK	LOC114987	POLG		
CAT	LOC151242	PPP1R15A		
CCDC109A	LOC201191	PRPF4		
CCDC12	LOC283177	PSPHL		
CCK	LOC284121	PX19		
CCT3	LOC284723	RFC4		
CD74	LOC285103	RNF123		
CDAN1	LOC340481	RPL12		
CDC20	LOC57795	RPL31		

CDC27	LOC90624	SBBI26
CDC73	LOC91947	SCARB1
CDK10	LRP1	SDCBP2
CDK5RAP1	LSS	SDK1
CDKN2B	MADHIP	SHANK3
CDON	MAP6	SNAPC5
CELSR1	MAPK1	SNRPA
CENTG2	MARCKS	SNRPA1
CHAT	MASP2	SNRPG
CHD4	MBNL1	STK6
CHD7	MBNL2	SURF1
CHEK1	MCM3AP	TAF9
CHEK2	MEF2A	TAGLN2
CHIC2	MFAP3	TM4SF11
CHMP4B	MGC10198	TOP3A
CHMP5	MGC20255	TRAF2
CHRD	MGC20446	TRIM35
CHRNA4	MGC20553	TReP-132
CHST11	MGC24180	TTYH1
CIB1	MGC34032	TUBB-5
CKAP5	MGC43306	TUBGCP3
CLASP1	MGC4730	U5-200KD
CLGN	MLL	UMPK
CLK2	MLLT3	UXT
CLOCK	MYH11	VGLL2
CLSTN1	MYL4	VIP32
CLTA	MYO1B	VRK1
CNIH	NCKAP1	WDR20
CNN3	NDRG3	WFS1
CNO	NEBL	ZNF259
CNOT1	NFE2L2	p30
CNOT2	NFIB	
CNOT3	NMNAT2	
CNOT7	NPAS2	
COL18A1	NXP2	
COL4A5	OSF-2	
COQ7	OXR1	
COX4I2	P2RY1	
CP	PAK1	

CPD	PANK2
CPEB4	PCDH18
CPSF6	PDE4DIP
CREBL2	PENK
CRK	PFTK1
CRKL	PGPEP1
CRP	PICALM
CRYAB	PIGO
CS	PKD1
CSAD	PLXN3
CSK	PLXNA4
CSNK1A1	PNN
CSNK1E	PPP1R12B
CSNK2A1	PRDM1
CSTF2T	PRDX3
CTBP1	PRKAA1
CTSB	PRKCA
CUGBP1	PRODH
CXYorf3	PSMB2
CXorf9	PURA
CYB5A	PURB
CYCS	PWCR1
CYFIP2	RAB11B
CYP3A4	RAB27A
DAD1	RDH10
DAP	RNF38
DARS2	RPS21
DAXX	RPS6KB1
DAZAP1	RUNX2
DBF4	SCAMP1
DBT	SCDGF-B
DCHS1	SDC3
DCK	SEC14L1
DCST2	SEC22L3
DDC	SEC8
DDEF2	SERPINB8
DDOST	SFRP4
DDX3X	SGCD
DDX54	SH3BP5

DEADC1	SIX1
DEK	SLC16A1
DENND4A	SLC4A7
DEPDC5	SLC7A8
DGAT1	SMARCA2
DGCR6L	SMT3H1
DGKI	SNAP25
DHFR	SNRP70
DHX35	SOD2
DIAPH2	SP1
DIP2C	SP4
DKC1	SPTBN1
DMAP1	SRC
DNAI1	SRRM2
DNAJA4	SSBP3
DNAJB4	SSTR2
DNAJB6	STAT2
DNAJC12	STAT3
DNAJC13	STAT5B
DNAJC17	STC1
DNAJC5	STXBP6
DNALI1	SULF1
DNHD3	TA-WDRP
DNM1	TACC1
DOCK1	TAF15
DOHH	TAP1
DPF2	TBC1D4
DRAP1	TCF8
DSC1	TCP10L
DSCAM	TDRKH
DSCAML1	TGOLN2
DTNB	TIA1
DUSP10	TMEM1
DUSP7	TNRC6
DYNC1I2	TPR
DYNC1LI1	TRAP1
DYNLL2	TRIO
DYNLT1	TRIP11
E2F1	TTC11

E2F5
EBF2
ECE2
EEF1A1
EEF1B2
EEF1D
EHD1
EHMT2
EIF1
EIF2AK3
EIF2C1
EIF2C2
EIF2S3
EIF3S1
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