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The relationship between neurodevelopmental transcriptional programs and insomnia: from Rubinstein-Taybi syndrome into energy metabolism

--Manuscript Draft--

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Abstract:	Neurodevelopmental disorders (NDD) are characterized by cognitive, emotional, and/or motor skills impairment since childhood, and sleep disturbances are a common comorbidity. Rubinstein-Taybi syndrome (RTS), a rare genetic syndrome associated with NDD, is caused by CREBBP haploinsufficiency. This gene encodes an acetyltransferase with crucial role on the establishment of transcriptional programs during neurodevelopment. Although insomnia has been reported in RTS patients, the convergent mechanisms between this sleep disturbance and CREBBP loss-of-function remain unclear. We tested weather the genetic architecture underlying CREBBP regulatory targets and insomnia-associated genes is significantly shared. We then identified the biological pathways enriched among these shared genes. The intersection between CREBBP regulatory targets and genes associated with insomnia included 7 overlapping genes, indicating significantly more overlap than expected by chance. An over-representation analysis on these intersect genes identified pathways related to mitochondrial activity. This finding indicates that the transcriptional programs established by CREBBP might impact insomnia-related biological pathways through the modulation of energy metabolism. The overlapping gene set and biological pathways highlighted by this study may serve as a primer for new functional investigations of shared molecular mechanisms between insomnia and CREBBP regulatory targets.
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July 19th, 2023

Prof. Dr. Winfried Randerath
Editor-in-chief, *Sleep Medicine*

Dear Dr Randerath,

Thank you for considering our manuscript, "**The relationship between neurodevelopmental transcriptional programs and insomnia: from Rubinstein-Taybi syndrome into energy metabolism**," for publication in *Sleep Medicine* as a *Brief Communication Article*.

Although sleep disturbances, such as insomnia and sleep apnea, are known to be highly prevalent on neurodevelopmental disorders (NDD), the convergent molecular mechanisms that link NDD and sleep-related traits are largely unknown. Neural transcriptional programs established during development have been implicated in disease etiology, and chromatin regulators are key effectors of this neuronal epigenetic modulation. The CBP protein, encoded by *CREBBP* gene, is one of the main regulatory hubs responsible for the establishment transcriptional programs during the neurodevelopment. Rare genetic variants affecting *CREBBP* gene were identified causal for Rubinstein-Taybi syndrome, an NDD-related phenotype in which sleep disorders are a frequent comorbidity. The next questions pressing the field revolve around the biological mechanisms underlying the connection between the epigenetic dysregulation followed by *CREBBP* loss-of-function and circadian patterns.

We leveraged gene lists which account for (1) insomnia-associated genes and (2) CBP genomic regulatory targets. After demonstrating significant overlap between those 2 gene lists, we generated functional interaction networks from the set of intersect genes. Our findings suggest that mitochondria function is directly affect by the CBP regulatory targets which are also insomnia-associated genes. These results suggest that the epigenetic modulation of energy metabolism pathways might be a putative factor underlying the clinical association between *CREBBP* haploinsufficiency and insomnia.

The framework used in this study may be applied to other rare NDDs associated with chromatin regulators, leveraging mechanistic insights on the influence of chromatin regulation over circadian patterns.

Thank you for your consideration,

UNIFESP

Mariana Moyses-Oliveira

The relationship between neurodevelopmental transcriptional programs and insomnia: from Rubinstein-Taybi syndrome into energy metabolism

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Highlights

- The Rubinstein-Taybi syndrome (RTS) is a rare genetic syndrome associated with autism spectrum disorder (ASD) and driven by *CREBBP* haploinsufficiency.
- Sleep disturbances have been observed as a common comorbidity in neurodevelopmental disorders (NDD) associated with genes which encode chromatin regulators, as *CREBBP*.
- *CREBBP* direct regulatory targets which are associated with insomnia show enrichment for pathways related to mitochondrial activity.
- Epigenetic modulation of energy metabolism pathways might be a putative factor underlying the clinical association between *CREBBP* haploinsufficiency and insomnia.

Abstract: Neurodevelopmental disorders (NDD) are characterized by cognitive, emotional, and/or motor skills impairment since childhood, and sleep disturbances are a common comorbidity. Rubinstein-Taybi syndrome (RTS), a rare genetic syndrome associated with NDD, is caused by *CREBBP* haploinsufficiency. This gene encodes an acetyltransferase with crucial role on the establishment of transcriptional programs during neurodevelopment. Although insomnia has been reported in RTS patients, the convergent mechanisms between this sleep disturbance and *CREBBP* loss-of-function remain unclear. We tested weather the genetic architecture underlying *CREBBP* regulatory targets and insomnia-associated genes is significantly shared. We then identified the biological pathways enriched among these shared genes. The intersection between *CREBBP* regulatory targets and genes associated with insomnia included 7 overlapping genes, indicating significantly more overlap than expected by chance. An over-representation analysis on these intersect genes identified pathways related to mitochondrial activity. This finding indicates that the transcriptional programs established by *CREBBP* might impact insomnia-related biological pathways through the modulation of energy metabolism. The overlapping gene set and biological pathways highlighted by this study may serve as a primer for new functional investigations of shared molecular mechanisms between insomnia and *CREBBP* regulatory targets.

Keywords: sleep, insomnia, *CREBBP*, neurodevelopmental disorders, energy metabolism, mitochondria.

1. Introduction

Neurodevelopmental disorders (NDD) are a class of conditions characterized by the impairment of personal, social, academic, and/or occupational functioning[1]. Amongst the wide range of clinical manifestations involved with NDD, autism spectrum disorder (ASD) is one the most studied conditions. Even though the ASD diagnosis is dictated by communication and social interaction deficits[1], recent research shows that sleep disturbances are also a prevalent feature in these individuals[2], with sleep problems being predictive of severity of ASD core symptoms[3,4].

A relevant rare genetic condition associated with ASD is the Rubinstein-Taybi syndrome (RTS). Around 50 to 60% of RTS patients present genetic variations in *CREBBP,* resulting in its haploinsufficiency[5]. This gene, which acts as a gene expression regulator, encodes a histone acetyltransferase (HAT) named CBP, which plays a role as co-activator of several transcriptional factors (TF), promoting chromatin remodeling and transcriptional activation[6]. Transcriptional programs established by *CREBBP* play an important role on cell differentiation during the mammalian neurodevelopment[7].

In this context, *CREBBP* haploinsufficiency in RTS can be caused by diverse mutational mechanisms. Chromosomal rearrangements, such as deletion of the 16p13.3 genomic region, which encompasses this gene, are a known RTS underlying genetic factor. Alternatively, RTS can be caused by exonic point mutations on *CREBBP*, which are alterations of a coding nucleotide on the gene´s DNA sequence, such as protein-truncating variants (i.e. abrogation of the protein code sequence) or missense mutations (i.e. nucleotide swap that culminates on an amino acid change). Regardless of the mutational mechanism, the etiology of RTS is generally associated with the functional impairment of the HAT domain coded by *CREBBP*, which is crucial to the protein´s acetyltransferase enzymatic function[5] .

RTS phenotypes encompass atypical facial features, broad and large hallux and/or thumbs, low stature, intellectual impairment and ASD[8]. In addition, sleep alterations, including insomnia, have been reported among RTS patients[6,9]. A recent study with a Swedish cohort of RTS patients submitted to subjective sleep evaluation showed that 52% of these individuals had sleep disturbances[6]. Another study with Dutch patients indicated that sleep problems persist till adulthood in 11% of individuals with RTS[9].

Although the recognition of insomnia as a relevant clinical feature in RTS patients, the convergent molecular mechanisms which link this sleep disturbance to *CREBBP* epigenetic

regulatory function remain unclear. In this study, we dissected the molecular pathways that, when disturbed by *CREBBP* mutation, contribute to the etiology of insomnia phenotypes in these patients.

2. Materials and Methods

Manual curation of gene lists

We manually curated 2 set of genes (Supp. Table S1). The first list contains genes associated with insomnia traits and is a result of the union of hits derived from recent large scale genome wide association studies (GWAS). The second list is composed by genes directly regulated by *CREBBP*, and was generated by mapping previously described *CREBBP* genomic binding sites to gene promoters using Biomart. Lists of *CREBBP* genomic binding sites were obtained from publicly available ChIP-seq experiments from ENCODE database[10].

Gene overlap analysis

We contrasted these 2 gene sets (i.e. genes associated with insomnia traits vs. genes directly regulated by *CREBBP)* to generate an intersection gene list. Using Fisher's Exact Test, we evaluated the statistical significance for the overlapping between these 2 gene lists with a threshold of *p-value*<0.05. This gene overlap analysis pointed to genes associated with insomnia traits among the *CREBBP* regulatory targets.

Pathway enrichment analysis

The Benjamini–Hochberg test was used to identify enriched pathways among the intersection gene list with a significance threshold of adjusted *p-value*<0.05. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) terms were considered in the over-representation analysis.

3. Results

Overlap between gene sets

There were 7 overlapping genes between the insomnia gene set (60 genes total) and the *CREBBP* regulatory targets (238 genes total), demonstrating significantly more overlap than expected by chance (*p-value*=4.8E-06; OR=11.9) (Figure 1A, Supp. Table S1).

Biological pathways enriched among the intersect gene list

Significantly enriched pathways among these 7 shared genes were related to mitochondrial structure (Figure 1B, Supp. Table S2).

4. Discussion

This study suggests that enriched pathways among the intersection between insomnia-associated genes and *CREBBP* regulatory targets are related to mitochondrial structure and functioning. The mitochondrial inner membrane forms a complex structure called mitochondrial cristae, where occurs the tricarboxylic acid cycle (TCA), which is the one of the major processes of the energy metabolism[11]. Conversely, the outer mitochondrial guarantees the integrity of the organelle and forms the intermembrane space[11], where occurs another crucial energetic process: the oxidative phosphorylation[11].

The mitochondrial recycling is essential to the maintenance of brain homeostasis, and this biological pathway is well-established as relevant for the neurodevelopment. In the brain, different mitochondrial shapes and sizes observed in neurons are known to be associated with synaptic activity[12]. Concordantly, during neurodevelopment, these changes in mitochondria forms are relevant for neuroplasticity[12]. In the context of ASD, mitochondrial dysfunction has been implicated in abnormalities related to transsynaptic transmission and brain neurodevelopment[13].

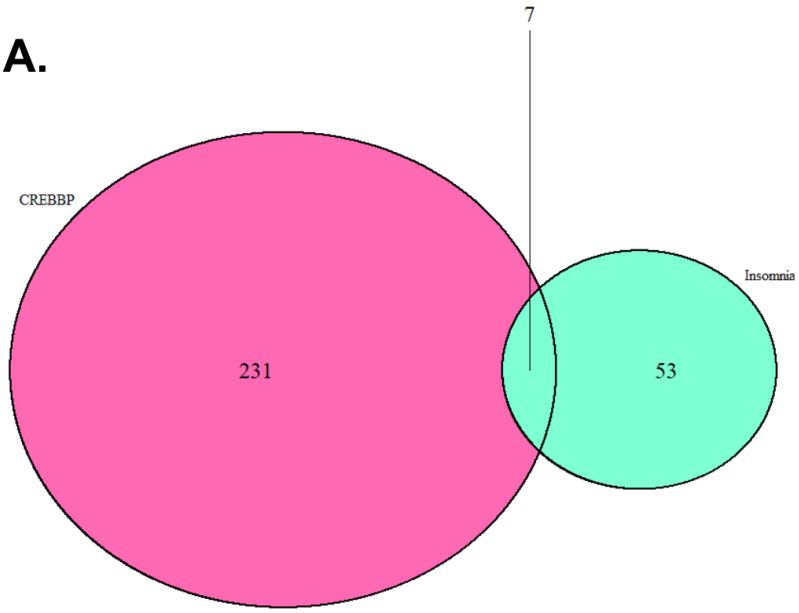
The relationship between insomnia and mitochondria has been previously reported. A bidirectional relationship linking sleep to oxidative stress has been observed, with sleep being relevant for the modulation of reactive oxygen species (ROS) levels[14]. In accordance with this observation, oxidative phosphorylation enzymes, such as cytochrome c oxidase (COX), have been shown to have their activity modulated by sleep deprivation[15]. Additionally, recent research disclosed the interplay between circadian rhythm regulators and mitochondrial structure-related genes[16]. To alter its shape and adapt to the energetic demands in the organism, mitochondria must follow the process of fusion (i.e. when 2 or more mitochondria bind together) or the fission (i.e. when 1 mitochondria is split into 2)[16]. The *MFN1* and *FIS1* genes encode key effectors in these 2 mitochondrial changes, respectively. Both of those genes have their expression regulated by the CLOCK/BMAL1 complex, which are regulators of the circadian rhythm[16]. Concordantly, changes in *Drosophila*'s sleep-awake cycle have been shown to impair mitochondrial activity, leading to an increase in the activity of genes related to oxidative stress and apoptosis[17].

5. Conclusion

The gene overlap and over-representation analysis here performed indicated that *CREBBP* haploinsufficiency might affect the epigenetic regulation processes related to energy metabolism. Oxidative stress and mitochondrial dysfunctions have been previously described as related to sleep disturbances and neurodevelopmental-related processes. The overlapping gene set and biological pathways highlighted by this study may serve as a primer for new functional investigations of shared molecular mechanisms between insomnia´s genetic architecture and epigenetic regulatory programs relevant for the neurodevelopment.

Appendices

A.



B.

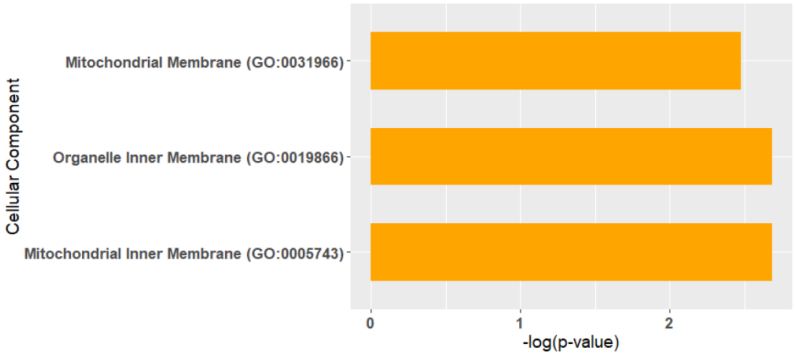


Figure 1. Venn diagram representing the gene list intersection between *CREBBP* regulatory targets and insomnia-associated genes (A) and significant enriched pathways among overlapping genes (B). CREBBP_target = *CREBBP* regulatory genes targets. In_insomnia = Insomnia related genes.

Supplementary Table. List of *CREBBP* regulatory targets, insomnia-associated genes and intersected genes between those 2 gene sets (S1) and enriched pathways between the 7 intersected genes (S2).

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Supp. Table 1 - Gene lists' composition

[1] Zhang, J., Liu, J., Lee, D., Lou, S., Chen, Z
[2] Watanabe, K., Jansen, P. R., Savage, J. E
[3] Jansen, P. R., Watanabe, K., Stringer, S.,

List of *CREBBP* regulatory targets [1]

ADAM12
AK2
ANTXRLP1
APP
ARAP2
ARHGAP22
ARSD
ARVCF
ASMTL
ATP2B2
ATXN1
BCL2
BET1L
BNIP3P11
BSDC1
BVES
C8B
CADPS2
CCDC12
CCR5AS
CD300H
CDYL2
CELF3
CELSR1
CENPU
CGAS
CHCHD3
CHD5
CLTCL1
COG5
COL28A1
COL6A4P1
CRTC3
CSMD1
CYP4F9P
DDR1-DT
DDX60
DENND1B
DLG2
DNAH8
DOCK4
DSCAM

DSCR4
ELAPOR2
ELOVL1
EPHA2
EPS8
ERG
EVPL
EZH2
FAM172A
FAT1
FBXO11
FBXW7
FGF13
FOXJ1
FRMD4A
FSIP2
GABBR2
GABRB2
GAREM1
GFOD1
GLB1
GNB1L
GRB10
GRM4
H2AC25
HIRA
HIVEP3
HNRNPL
HSF2BP
HSPG2
HTR4
HYDIN
IGBP1P2
IGFBPL1
IL2RA
IMMP2L
INPP4B
INSR
INTS7
IPCEF1
IQCA1L
IQSEC1
KANK4
KCNA2
KCNIP4
KCNJ6
KCNMA1
KCNQ1OT1
KCP
KIAA0319

KIF17
KIF6
KLHL22
KLK13
KMT2C
L3MBTL4
LBHD1
LDHB
LMTK3
LRP1B
LRRC2
LRRFIP2
LUZP1
LYPD8
MAML2
MAP4
MARCHF1
MARCHF3
MASP2
MGAT4C
MICAL3
MOCS1
MRPS27
MXRA5
MYLK4
MYT1L
MZF1
NADK2
NEK1
NOS1
NRAV
NRXN1
OSBPL10
PARN
PDE10A
PEBP4
PEPD
PEX5L
PI4KA
PIK3R5
PIN1-DT
PIP5K1C
PKD1L2
PLEC
PLEKHA6
PLXNA4
PPP1R9A
PPP2R2B
PRAME
PREX1

PRKAG2
PRKDC
PROM1
PTPRN2
PUDP
PUM3
PXDN
PXMP4
RCAN1
RCAN2
RELN
RERE
RFX1
RFX3
ROS1
RP1L1
RPS6KA2
RSPH1
RSPH14
RTL10
RTN4R
SBK3
SDCBP2
SEMA6A
SEMA6B
SERINC4
SERPINB1
SESN1
SFPQ
SHANK2
SHISA7
SLC19A1
SLC22A24
SLC25A12
SLC25A16
SLC25A41
SLC30A10
SLC37A3
SLC4A5
SLC6A3
SLC9A9
SMARCD2
SMARCD3
SMCO4
SNX16
SNX8
SRGAP3
SRL
SRSF9
SULT1B1

SUMF1
SUPT3H
SUSD4
SYCE1
SYT2
SYT5
TBC1D16
TCAF1
TCEA3
TEX14
TFEC
TFPI
THAP10
THBS2
THEMIS
TIAM1
TMEM107
TMEM132D
TMEM273
TMEM275
TMEM72
TOP3B
TRAPPC9
TRIM29
TRPV4
TSHZ3
TTC23L
TUBA3FP
TUBB8B
TXNRD2
U3
UBE2H
UNC13A
UNC93B1
USP54
VSTM1
WDR74
WEE2
YPEL1
ZBTB4
ZFPM2
ZNF280B
ZNF423
ZNF445
ZNF585B
ZNF800

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List of gene associated with Insomnia [2,3]

ALKBH8
ANKFY1
ANO10
ATL2
CBX1
CCDC148
CCDC57
CGGBP1
CHMP2A
COG5
CSNK1A1
DCAKD
DIMT1
EGR2
EIF4E
FAM172A
FAM222B
FBXO31
GLO1
GPANK1
HOOK2
IMMP2L
LMBR1L
LYRM2
MED20
MED27
MEX3C
MPHOSPH9
MRPS27
MZF1
NICN1
NTAN1
PAIP1
PAX6
PIK3C2A
PLCH1
POC1B
PPP1R10
PSMC3
RBM39
RC3H2
RPL4

RPS13
SLC25A12
SNAPC5
SNX16
STAU1
TAL1
TBX6
TDRKH
TOB2
TTLL11
UBE2D3
UBE2M
UBE2W
USP49
ZDHHC24
ZNF260
ZNF280D
ZNF784

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C. A., Benjamins, J. S., Muñoz-Manchado, A. B., Nagel, M., Savage, J. E., Tiemeier, H., White, T.,

ntersection gene list of Insomnia-associated genes versus *CREBBP* regulatory gene targets

COG5
FAM172A
IMMP2L
MRPS27
MZF1
SLC25A12
SNX16

https://doi.org/10.1186/s12859-020-03605-3
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ifies new risk loci and functional pathways. Nature Genetics, 51(3), 394–403. https://c

/s41588-022-01124-w
doi.org/10.1038/s41588-018-0333-3

Supp. Table 1 - Pathways enriched among intersect gene list

Database	Term	Overlap	P-value
GO_Cellular_Co	Organelle Inner Membrane (GO:0019866)	3 out of 398	2.08E-04
GO_Cellular_Co	Mitochondrial Membrane (GO:0031966)	3 out of 540	2.58E-04
GO_Cellular_Co	Extrinsic Component Of Endosome Membrane (GO:00	1 out of 6	6.32E-04
KEGG_2021_Hu	Protein export	1 out of 23	8.02E-03
GO_Cellular_Co	Mitochondrial Inner Membrane (GO:0005743)	3 out of 370	2.10E-03
GO_Molecular_F	Mitochondrial Ribosome Binding (GO:0097177)	1 out of 7	2.45E-03
GO_Molecular_F	L-aspartate Transmembrane Transporter Activity (GO:0	1 out of 8	2.80E-03
GO_Molecular_F	siRNA Binding (GO:0035197)	1 out of 9	3.15E-03
GO_Molecular_F	L-glutamate Transmembrane Transporter Activity (GO:	1 out of 12	4.19E-03
GO_Molecular_F	C4-dicarboxylate Transmembrane Transporter Activity	1 out of 14	4.89E-03
GO_Molecular_F	Acidic Amino Acid Transmembrane Transporter Activity	1 out of 15	5.24E-03
GO_Biological_F	Retrograde Transport, Vesicle Recycling Within Golgi (	1 out of 8	2.80E-03
GO_Biological_F	Aspartate Transmembrane Transport (GO:0015810)	1 out of 9	3.15E-03
GO_Biological_F	Mitochondrial Protein Processing (GO:0034982)	1 out of 10	3.50E-03
GO_Biological_F	Aspartate Family Amino Acid Metabolic Process (GO:0	1 out of 12	4.19E-03
GO_Biological_F	C4-dicarboxylate Transport (GO:0015740)	1 out of 12	4.19E-03
GO_Biological_F	Signal Peptide Processing (GO:0006465)	1 out of 13	4.54E-03
GO_Biological_F	L-glutamate Transmembrane Transport (GO:0015813)	1 out of 14	4.89E-03
GO_Biological_F	Respiratory Electron Transport Chain (GO:0022904)	1 out of 14	4.89E-03
GO_Biological_F	Positive Regulation Of Mitochondrial Translation (GO:0	1 out of 14	4.89E-03
GO_Biological_F	L-glutamate Import (GO:0051938)	1 out of 15	5.24E-03
GO_Biological_F	Stem Cell Development (GO:0048864)	1 out of 15	5.24E-03
GO_Biological_F	Neural Crest Cell Differentiation (GO:0014033)	1 out of 18	6.28E-03
GO_Biological_F	Regulation Of Mitochondrial Translation (GO:0070129)	1 out of 22	7.68E-03
GO_Biological_F	Early Endosome To Late Endosome Transport (GO:00	1 out of 24	8.37E-03
GO_Biological_F	Vesicle-Mediated Transport Between Endosomal Comp	1 out of 25	8.72E-03
GO_Biological_F	Protein Targeting To Lysosome (GO:0006622)	1 out of 26	9.07E-03
GO_Biological_F	Alpha-Amino Acid Metabolic Process (GO:1901605)	1 out of 29	1.01E-02
GO_Biological_F	RNA-mediated Gene Silencing (GO:0031047)	1 out of 29	1.01E-02
GO_Biological_F	Heterochromatin Formation (GO:0031507)	1 out of 32	1.12E-02
GO_Biological_F	Gluconeogenesis (GO:0006094)	1 out of 32	1.12E-02
GO_Biological_F	intra-Golgi Vesicle-Mediated Transport (GO:0006891)	1 out of 33	1.15E-02
GO_Biological_F	Protein Targeting To Vacuole (GO:0006623)	1 out of 34	1.18E-02
GO_Biological_F	Hexose Biosynthetic Process (GO:0019319)	1 out of 35	1.22E-02
GO_Biological_F	L-alpha-amino Acid Transmembrane Transport (GO:19	1 out of 40	1.39E-02
GO_Biological_F	Protein Localization To Lysosome (GO:0061462)	1 out of 41	1.43E-02
GO_Biological_F	Amino Acid Transmembrane Transport (GO:0003333)	1 out of 42	1.46E-02
GO_Biological_F	Neural Crest Cell Development (GO:0014032)	1 out of 44	1.53E-02
GO_Biological_F	Regulation Of Alternative mRNA Splicing, Via Spliceos	1 out of 53	1.84E-02
GO_Biological_F	Peptide Metabolic Process (GO:0006518)	1 out of 56	1.94E-02
GO_Biological_F	Endosome To Lysosome Transport (GO:0008333)	1 out of 57	1.98E-02
GO_Biological_F	Protein Targeting To Mitochondrion (GO:0006626)	1 out of 59	2.05E-02
GO_Biological_F	Glucose Metabolic Process (GO:0006006)	1 out of 59	2.05E-02
GO_Biological_F	Response To Metal Ion (GO:0010038)	1 out of 64	2.22E-02

GO_Molecular_F	Dicarboxylic Acid Transmembrane Transporter Activity	1 out of 28	9.76E-03
GO_Molecular_F	Neutral L-amino Acid Transmembrane Transporter Acti	1 out of 41	1.43E-02
GO_Molecular_F	Regulatory RNA Binding (GO:0061980)	1 out of 42	1.46E-02
GO_Molecular_F	Proton Transmembrane Transporter Activity (GO:0015(	1 out of 45	1.57E-02
GO_Molecular_F	rRNA Binding (GO:0019843)	1 out of 46	1.60E-02
GO_Molecular_F	tRNA Binding (GO:0000049)	1 out of 51	1.77E-02
GO_Molecular_F	Amino Acid Transmembrane Transporter Activity (GO:(	1 out of 56	1.94E-02
GO_Molecular_F	L-amino Acid Transmembrane Transporter Activity (GC	1 out of 63	2.19E-02

usted P-va	Odds Ratio	Genes
2.06E-03	40.11	IMMP2L;MRPS27;SLC25A12
2.06E-03	37.21	IMMP2L;MRPS27;SLC25A12
3.37E-03	27.17	SNX16
8.02E-03	151.30	*IMMP2L*
8.39E-03	666.27	IMMP2L;MRPS27;SLC25A12
2.53E-02	555.19	*MRPS27*
2.53E-02	475.86	*SLC25A12*
2.53E-02	416.35	*FAM172A*
2.53E-02	302.76	*SLC25A12*
2.53E-02	256.15	*SLC25A12*
2.53E-02	237.85	*SLC25A12*
2.62E-02	475.86	*COG5*
2.62E-02	416.35	*SLC25A12*
2.62E-02	370.07	*IMMP2L*
2.62E-02	302.76	*SLC25A12*
2.62E-02	302.76	*SLC25A12*
2.62E-02	277.51	*IMMP2L*
2.62E-02	256.15	*SLC25A12*
2.62E-02	256.15	*SLC25A12*
2.62E-02	256.15	*MRPS27*
2.62E-02	237.85	*SLC25A12*
2.62E-02	237.85	*FAM172A*
2.88E-02	195.84	*FAM172A*
2.91E-02	158.51	*MRPS27*
2.91E-02	144.71	*SNX16*
2.91E-02	138.67	*SNX16*
2.91E-02	133.12	*SNX16*
2.91E-02	118.84	*SLC25A12*
2.91E-02	118.84	*FAM172A*
2.91E-02	107.32	*FAM172A*
2.91E-02	107.32	*SLC25A12*
2.91E-02	103.96	*COG5*
2.91E-02	100.81	*SNX16*
2.91E-02	97.84	*SLC25A12*
3.09E-02	85.27	*SLC25A12*
3.09E-02	83.14	*SNX16*
3.09E-02	81.11	*SLC25A12*
3.12E-02	77.33	*FAM172A*
3.52E-02	63.91	*FAM172A*
3.52E-02	60.42	*IMMP2L*
3.52E-02	59.34	*SNX16*
3.52E-02	57.28	*IMMP2L*
3.52E-02	57.28	*SLC25A12*
3.70E-02	52.72	*SLC25A12*

4.04E-02	123.25	*SLC25A12*
4.22E-02	83.14	*SLC25A12*
4.22E-02	81.11	*FAM172A*
4.22E-02	75.56	*SLC25A12*
4.22E-02	73.88	*MRPS27*
4.28E-02	66.48	*MRPS27*
4.34E-02	60.42	*SLC25A12*
4.53E-02	53.58	*SLC25A12*

Figure 1