

## Supplementary information to manuscript:

### Nuclear and cytoplasmatic players in mitochondria-related CNS disorders: from chromatin architecture to subcellular trafficking

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Gene symbol	OMIM gene ID	Phenotype	OMIM ID	Epigenetic function	Inheritance	Mitochondria related gene (pubmed*; Mitominer§)	Function related to mitochondria	Cell type in reference	main findings (ref)
<b>1. Writers</b>									
CREBBP (CBP)	600140	RubinsteinTaybi syndrome 1 (RSTS1)	180849	Histone acetyltransferase (HAT)	AD, de novo	*§	1. an essential regulator for the activation of the MSR and in particular the mitochondrial unfolded protein response	MEF	1. The transcriptional coactivator CBP/p300 is an evolutionarily conserved node that promotes longevity in response to mitochondrial stress
							2. CPB determines mitochondrial dysfunction which leads to impairment of OXPHOX activities and to an increase in ROS production, compromising tissue bioenergetic efficiency.	Human MEF	2. Induction of mitochondrial dysfunction in patients under cardiopulmonary by-pass: preliminary results
DNMT1	126375	Hereditary sensory neuropathy type 1E (HSN1E)	614116	DNA methylation	AD	*	mtDNA methylation	MEF	DNA methyltransferase 1 mutations and mitochondrial pathology: is mtDNA methylated?

DNMT3B	602900	ICF syndrome	242860	DNA methylation	AR	*	DNMT3B null hESCs exhibit a disturbed mitochondrial fission and fusion balance and a switch from glycolysis to oxidative phosphorylation	human embryonic stem cells	DNMT3B deficiency alters mitochondrial biogenesis and $\alpha$ -ketoglutarate levels in human embryonic stem cells
EP300	602700	RubinsteinTaybi syndrome 2 (RSTS2)	613684	Histone acetyltransferase (HAT)	AD, de novo	*	an essential regulator for the activation of the MSR and in particular the mitochondrial unfolded protein response	MEF	The transcriptional coactivator CBP/p300 is an evolutionarily conserved node that promotes longevity in response to mitochondrial stress
EZH2	601573	Weaver syndrome	277590	Lysine N-methyltransferase 6 (KMT6A; H3K27me3)	AD, de novo	*	EZH2 knockdown substantially reduced both oxygen consumption rate and calculated reserve capacity. EZH2 promotes the switch from mitochondrial respiration to glycolysis	Glioblastoma cells	EZH2 promotes metabolic reprogramming in glioblastomas through epigenetic repression of EAF2-HIF1 $\alpha$ signaling
FTO	610966	Growth retardation, developmental delay, coarse facies, and early death	612938	RNA demethylation	AR	*§	FTO down-regulated N6-methyladenosine A levels, decreased mitochondrial content, and increased triglyceride (TG) deposition in hepatocyte.	Hepatocytes	FTO reduces mitochondria and promotes hepatic fat accumulation through RNA demethylation
HUWE1	300697	Mental retardation, X-linked syndromic, Turner type	300706	Histone ubiquitination	XL	*	HUWE1 depletion induces reduction of total mitochondriaubiquitylation following AMBRA1 expression which is a relevant mitophagy eceptor	HeLa cells	HUWE1 E3 liase promotes PINK1/PARKIN-independent mitophagy by eulating AMBRA1 activation via IKKa
KMT2D	602113	Kabuki syndrome	147920	Histone methylation (MLL2)	AD, de novo	*	reduction of the mitochondrial oxygen consumption rate as well as a reduction of the glycolytic flux in both Kmt2d knockout MEFs and skin fibroblasts of Kabuki patients harboring heterozygous KMT2D pathogenic variants.	Kmt2df/f MEFs	Loss of Function of the Gene Encoding the Histone Methyltransferase KMT2D Leads to Deregulation of Mitochondrial Respiration

UBE2A (Rad6a)	312180	X-Linked ID, Nascimento type	300860	Histone ubiquitination	XL	*	RAD6A acts as an E2 ubiquitin-conjugating enzyme that, in combination with an E3 ubiquitin ligase such as Parkin, ubiquitinates mitochondrial proteins to facilitate the clearance of dysfunctional mitochondria in cells. Hence, we identify RAD6A as a regulator of Parkin-dependent mitophagy and establish a critical role for RAD6A in maintaining neuronal function.	mRad6a null MEFs	Mutations in the intellectual disability gene Ube2a cause neuronal dysfunction and impair parkin-dependent mitophagy
<b>2. Erasers</b>									
HDAC4	605314	Brachydactyly- mental retardation syndrome	600430	Histone deacetylase	AD, de novo	*	HDAC inhibitors we examined induced mitochondrial elongation	Hep3B cells	Histone deacetylase inhibitors induce mitochondrial elongation
HDAC8	300269	WilsonTurner syndrome	309585	Histone deacetylase	XL	*	HDAC8 inhibits cytotoxicity induced by cobalt and reoxygenation, in part, through suppressing DRP1 expression and mitochondrial fission.	Human renal proximal tubular HK-2 cells	Histone deacetylase 8 protects human proximal tubular epithelial cells from hypoxia-mimetic cobalt- and hypoxia/reoxygenation- induced mitochondrial fission and cytotoxicity

KDM3B	609373	Diets-Jongmans Syndrome and Rare Genetic Epilepsy	618846	Histone demethylase	AD	*	KDM3B, a histone H3 lysine 9 demethylase, can protect against ferroptosis induced by Erastin, an inhibitor of SLC7A11. (Ferroptosis is a newly discovered form of regulated cell death characterized morphologically by the abnormal mitochondria structure and mechanically by the iron-dependent accumulation of lipid hydroperoxides to lethal concentrations)	Human cell lines (HT-1080)	Histone demethylase KDM3B protects against ferroptosis by upregulating SLC7A11
KDM5C	314690	X-linked syndromic mental retardation; Claes-Jensen type	300534	Histone demethylase (H3K4 tridemethylase)	XL	*	loss of KDM5C protein mediated glycogen reprogramming was essential for resistance to ROS and ferroptosis. Moreover, KDM5C depletion promoted the anchorage-independent cell growth	Cancer cells	Deficiency of the X-inactivation escaping gene KDM5C in clear cell renal cell carcinoma promotes tumorigenicity by reprogramming glycogen metabolism and inhibiting ferroptosis
KDM6A	300128	Kabuki syndrome 2	300867	Histone demethylase (H3K27me3/2)	XL	*	genes involved in mitochondrial oxidative phosphorylation, including Cox5a, Cox7a and Cox8b, were increased in the brown adipose tissue of Kdm6aF/Y mice (Myeloid-specific Kdm6a knockout in Kdm6aF/Y)	adipose tissue (mouse)	Kdm6a suppresses the alternative activation of macrophages and impairs energy expenditure in obesity
PHF8	300560	Siderius X-Linked Mental Retardation Syndrome	300263	Histone demethylase (H4K20me1, H3K9me1/me2)	XL	*	PHF8 and JMJD3 regulate mitochondrial unfolded protein response genes by removing repressive H3K27 methylation marks from their coding regions.	Hypothalamus of the indicated BXD mouse strains	Two Conserved Histone Demethylases Regulate Mitochondrial Stress-Induced Longevity

### 3. Chromatin remodelers (DEAD/H ATPase family)

ACTB	102630	Baraitser Winter syndrome	243310	SWI/SNF, INO80 and ISWI complex	AD, de novo	*	Defects of Mitochondrial Membrane Potential (MMP) Maintenance in Cells Lacking $\beta$ -Actin	MEFs	In Mitochondria $\beta$ -Actin Regulates mtDNA Transcription and Is Required for Mitochondrial Quality Control
ARID1A	603024	Mental retardation, Autosomal dominant 14	614607	DEAD/H ATPase helicase family, SWI/SNF subfamily	AD, de novo	*	ARID1A loss results in increased mitochondrial metabolism and renders ARID1A-mutated cells increasingly and selectively dependent on it. ARID1A loss associated with increase in c-Myc expression and increased mitochondrial number and reduction of their size consistent with a higher mitochondrial cristae/outer membrane ratio.	Ovarian clear cell carcinoma cells	Targeting mitochondrial metabolism in clear cell carcinoma of the ovaries
ATRX	300032	Alpha thalassemia mental retardation syndrome, X-linked (ATRX)	301040	DEAD/H ATPase helicase family resulting in altered coordination of DNA methylation patterns and H3K9me3 binding	XL	*	Expression of MYCN in ATRX-mutant cells leads to metabolic reprogramming and mitochondrial dysfunction	Neuroblastoma	MYCN amplification and ATRX mutations are incompatible in neuroblastoma
SMARCA2	600014	Nicolaidese Baraitser syndrome	601358	DEAD/H ATPase helicase family, SWI/SNF subfamily	AD, de novo	*	SMARCA4/2 deficiency causes reduced IP3R3 expression leading to impaired Ca <sup>2+</sup> transfer from the endoplasmic reticulum to mitochondria required for apoptosis induction	Cancer cell line (H1437 cells)	SMARCA4/2 loss inhibits chemotherapy-induced apoptosis by restricting IP3R3-mediated Ca <sup>2+</sup> flux to mitochondria
SMARCA4	603254	Mental retardation, Autosomal dominant 16	614609	DEAD/H ATPase helicase family, SWI/SNF subfamily	AD, de novo	*	SMARCA4/2 deficiency causes reduced IP3R3 expression leading to impaired Ca <sup>2+</sup> transfer from the endoplasmic reticulum to mitochondria required for apoptosis induction	Cancer cell line (H1437 cells)	SMARCA4/2 loss inhibits chemotherapy-induced apoptosis by restricting IP3R3-mediated Ca <sup>2+</sup> flux to mitochondria

SRCAP	611421	Floating-Harbor syndrome	136140	DEAD/H ATPase helicase family, INO80/SWR subfamily	AD, de novo	*	The SRCAP complex maintains the integrity of mitochondrial morphology, mitochondrial oxidative metabolism and respiratory complexes	mice	The SRCAP chromatin remodeling complex promotes oxidative metabolism during prenatal heart development
<b>4. Other readers and chromatin remodelers</b>									
ASXL1	612990	BohringeOpitz syndrome	605039	PR-DUB complex, histone H2A deubiquitination	AD, de novo	*	provokes dysfunction of HSCs associated with mitochondrial activation, elevated ROS levels, and increased DNA damage.	Vav-Cre ASXL1-MT KI mice	Mutant ASXL1 induces age-related expansion of phenotypic hematopoietic stem cells through activation of Akt/mTOR pathway
BCL11B	606558	Immunodeficiency 49 and Intellectual Developmental Disorder With Speech Delay, Dysmorphic Facies, And T-Cell Abnormalities	618092	transcriptional repressor	AD	*	Bcl11b is a suppressor of apoptosis with knockout cells showing apoptotic pathway activation, mitochondrial membrane potential loss and elevation of BclxL, Caspase 8, and caspase 9.	malignant T cell lines (Jurkat and huT78)	Proteome analysis reveals new mechanisms of Bcl11b-loss driven apoptosis.
CHMP1	164010	pontocerebellar hypoplasia 8	614961	Targets polycomb protein BMI to condensed chromatin	AR	*§	detected elevated amounts of the peroxisomal PEX14 protein and outer mitochondrial membrane protein VOLTAGE-DEPENDENT ANION CHANNEL (VDAC) in chmp1	Plant	The Endosomal Protein CHARGED MULTIVESICULAR BODY PROTEIN1 Regulates the Autophagic Turnover of Plastids in Arabidopsis

CTCF	604167	ID, microcephaly and growth retardation	615502	Chromatin binding factor, insulator	AD, de novo	*	Genome wide expression analysis in Ctf mutant hearts revealed that genes controlling mitochondrial function and protein production, required for cardiomyocyte maturation, were upregulated.	Cardiomyocyte	CTCF counter-regulates cardiomyocyte development and maturation programs in the embryonic heart
EPC2	611000	associated with intellectual disability, seizures, microcephaly, development delay, hypotonia, and behavioral features similar to autism or Angelman syndrome	/	associated with a chromatin repressive complex	AD	*	EPC2 cells also demonstrated decreased mitochondrial ATPB protein expression by immunofluorescence and swollen mitochondria lacking intact cristae by transmission electron microscopy.	human esophageal keratinocyte cell lines	Autophagy mitigates ethanol-induced mitochondrial dysfunction and oxidative stress in esophageal keratinocytes
HCFC1	300019	Mental retardation, X-linked; MRX3/ Methylmalonic acidemia and homocysteinemia (Cobalamin disorder)	309541	Found in repressor and activator complexes	XL	*	The MYC–host cell factor (HCF)–1 interaction influences the expression of genes involved in ribosome biogenesis and mitochondrial pathways.	B lymphocyte cell line (Switchable Ramos cells)	MYC regulates ribosome biogenesis and mitochondrial gene expression programs through its interaction with host cell factor–1

KANSL1	612452	KooleneDe Vries syndrome	610443	NSL1 histone acetyltransferase complex	AD, de novo	*	depletion of KAT8/KANSL1 was shown to cause significant downregulation of mitochondrial DNA transcription and translation, and ultimately impaired mitochondrial respiration. Thus, it is also possible that KAT8/KANSL1-dependent modulation of mitochondrial DNA indirectly regulates PINK1 mitochondrial accumulation and subsequent mitophagy.	POE SH-SY5Y cells	Regulation of mitophagy by the NSL complex underlies genetic risk for Parkinson's disease at Chr16q11.2 and on the MAPT H1 allele
MECP2	300005	RETT syndrome; RTT	312750	Binds to methylated DNA	XL, mainly females	*	Elevated mitochondrial respiration rates and a reduction in coupling were detected in MeCP2-null male mouse brains	Mouse brain	Gene expression analysis exposes mitochondrial abnormalities in a mouse model of Rett syndrome
NIPBL	608667	Cornelia de Lange syndrome 1; CDLS1	122470	Cohesin complex	AD	*	si-NIPBL-induced apoptosis was activated by the intrinsic mitochondrial-mediated caspase pathway. Finally, the findings of this study showed that knockdown of NIPBL promoted apoptosis of breast cancer cells in vitro, possibly via inhibition of autophagosome-lysosome fusion	breast cancer cells	Downregulation of Cohesin Loading Factor Nipped-B-Like Protein (NIPBL) Induces Cell Cycle Arrest, Apoptosis, and Autophagy of Breast Cancer Cell Lines
SATB2	608148	developmental delay, mild to severe intellectual disability, behavioral problems and abnormal craniofacial features, specifically a cleft palate, Glass Syndrome	612313	arranging chromatin packing and organization	AD	*	HDAC1/2 play a conserved role to act in conjunction with SATB2 (mammalian ortholog of DVE-1) to mediate mitochondrial homeostasis.	Human samples, HEK293T cells	Histone deacetylase HDA-1 modulates mitochondrial stress response and longevity

Table S1. Epigenetic-related genes that are involved in cognitive disorders. There were 31 genes selected and distributed over four categories: 1. writers (9 genes), 2. Erasers (6 genes), 3. Chromatin remodelers of the DEAD/H-ATPase family (6 genes), and 4. Other readers and chromatin remodelers (10 genes). Gene names are provided by the official HGNC symbol (HUGO Gene Nomenclature Committee). The column "OMIM Gene ID" was provided according to the OMIM database (Online Mendelian inheritance in Man; <http://www.ncbi.nlm.nih.gov/omim/>). Two different source were used for collecting mitochondria-related genes including pubmed\* and Mitominer\$. The gene function associated with mitochondria are listed which were collected from the reference in the last columns.

AR, autosomal recessive; AD, autosomal dominant; XL, X-linked