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Supplementary information

Mechanisms and disease relevance of mitochondrial translation in humans

In the format provided by the authors and unedited

Supplementary Table 1. **Disease relevance of genes involved in mitochondrial protein synthesis.**

Gene	Known functions	Clinical phenotypes	References
Translation factors			
MTIF3	Translation initiation factor	Polymorphism (rs7669) associated with increased risk of Parkinson's disease (PD).	1–3
TUFM (mtEFTu)	Translation elongation factor-facilitates the delivery of aminoacylated tRNA to the ribosome	Cardiomyopathy; dysplastic leukoencephalopathy; ovarian insufficiency. Common polymorphisms associated with obesity[4].	5–9
TSFM (mtEFTs)	Translation elongation-Nucleotide exchange factor; converts mtEFTu·GDP into mtEFTu·GTP	Cardiomyopathy; childhood-onset ataxia; early-onset chorea; hearing loss; liver failure.	10–16
GFM1 (mtEFG1)	Translation elongation factor-Facilitates the translocation step	Cerebellar hypoplasia; encephalopathy; epilepsy; hepatic disease; hepatomegaly; lactic acidosis; neonatal axial hypotonia and dystonia; West syndrome.	17–24
GFM2 (mtEFG2)	Mitoribosome recycling factor	Abnormalities on cranial MRI; arthrogryposis multiplex congenita; developmental delay; elevated CSF lactate; Leigh syndrome.	25–27
MRRF (mtRRF)	Mitoribosome recycling factor	mRNA expression upregulated in early-stage PD.	28
MTRF-R (C12orf65)	Involved in mitoribosome rescue	Charcot-Marie Tooth disease; encephalomyopathy; intellectual disability; Leigh syndrome; neuropathy; optic atrophy; spastic paraplegia.	29–38
GUF1 (mtEF4)	Involved in mitoribosome fidelity by facilitating back-translocation	West syndrome.	39
TACO1	Alleviates mitoribosome stalling at polyproline stretches	Basal ganglia lesions; Leigh syndrome; U-Fiber Leukoencephalopathy.	40–44
Other proteins involved in posttranscriptional regulation			
COX14 (C12orf62)	Involved in CIV assembly	Neonatal lactic acidosis.	45
COA3 (MITRAC12)	Involved in CIV assembly	Exercise intolerance; neuropathy; obesity; short stature.	46
LRPPRC	mRNA-binding protein; interacts with mitoribosome	Cardiomyopathy; congenital malformations; French-Canadian Leigh syndrome; lactic acidosis.	47–51
ERAL1	GTPase involved in mtSSU biogenesis	Perrault syndrome.	52
MTG2 (GTPBP5)	GTPase involved in mtLSU biogenesis	Congenital malformations.	53
DHX30	RNA helicase,involved in mtLSU assembly	Autism spectrum disorders; dysgenesis of the corpus callosum; global developmental delay; intellectual disability; motor impairment; seizures.	54–58

MRM2	Methyltransferase involved in mtLSU biogenesis	Dystonia; epilepsy; MELAS-like syndrome; strokes.	59,60
TFB1M	Methyltransferase involved in mtSSU biogenesis	Modifier of the mtA1555G mutation and hearing loss. Type 2 diabetes risk gene.	61,62
TRMT10C (MRPP1)	Component of RNaseP; involved in tRNA maturation	Deafness; feeding difficulties; hypotonia; lactic acidosis.	63
HSD17B10 (MRPP2)	Component of RNaseP; involved in tRNA maturation	Cardiomyopathy; HSD10 disease; neurodegeneration; retardation; retinopathy;	64–69
FASTKD2	Involved in mtRNA processing	Cardiomyopathy; encephalomyopathy; epilepsy; lactic acidosis; Lennox-Gastaut syndrome; MELAS-like syndrome; optic atrophy; podocytopathy; sinus tachycardia.	70–76
CLPP	Serine protease; part of the ClpXP complex	Perrault syndrome type 3.	77–79
PNPT1	Together with SUV3 involved in mtRNA degradation	Choreoathetotic movements; encephalomyopathy; hearing loss; Leigh syndrome.	80–83
OXA1L	Inner mitochondrial membrane insertase	Encephalopathy, hypotonia and developmental delay	84,85
Mitoribosomal proteins			
MRPS2 (uS2m)	-	Developmental delays; hypoglycaemia; lactic acidaemia; microcephaly.	86–88
MRPS6 (bS6m)		Polymorphisms associated with increased risk of myocardial infarction.	89
MRPS7 (uS7m)		Hearing loss; kidney disease; lactic acidaemia; liver disease.	90
MRPS9 (uS9m)		Developmental delay; intellectual disability. *	91
MRPS11 (uS11m)		Ankylosing spondylitis.	92
MRPS14 (uS14m)		Elevated lactate; Wolff-Parkinson White Syndrome.	93
MRPS16 (bS16m)		Agenesis of corpus callosum; lactic acidosis.	94,95
MRPS22 (mS22)		Cardiomyopathy; developmental delay; dysmorphism; encephalopathy; hypotonia; oedema; primary ovarian insufficiency; tubulopathy.	96–101
MRPS23 (mS23)		Developmental delay; hypoglycaemia; lactic acidosis; liver disease.	102–104
MRPS25 (mS25)		Agenesis of the corpus callosum; cerebral palsy; encephalomyopathy.	105
MRPS28 (bS1m)		Developmental delay; dysmorphism; hearing loss; intrauterine growth retardation	106

MRPS34 (mS34)		Leigh syndrome.	107–109
MRPS39 (mS39)		Abnormal brain development; Infantile onset Leigh syndrome.	110,111
MRPL3 (uL3m)		Hearing loss; hypertrophic cardiomyopathy; lactic acidosis; liver disease; psychomotor retardation.	112–114
MRPL12 (bL12m)		Growth retardation; kidney disease; neurological deterioration.	115,116
MRPL24 (uL24)		Cerebellar atrophy; choreoatheosis; intellectual disability; lactic acidosis.	117
MRPL44 (mL44)		Hemiplegic migraine hypoglycaemia; infantile onset cardiomyopathy; lactic acidosis; Leigh-like lesions; myopathy; renal insufficiency; steatosis; retinopathy.	118–122
MRPL50 (mL50)		Chronic kidney disease; hearing loss; ovarian insufficiency; ventricular hypertrophy.	123

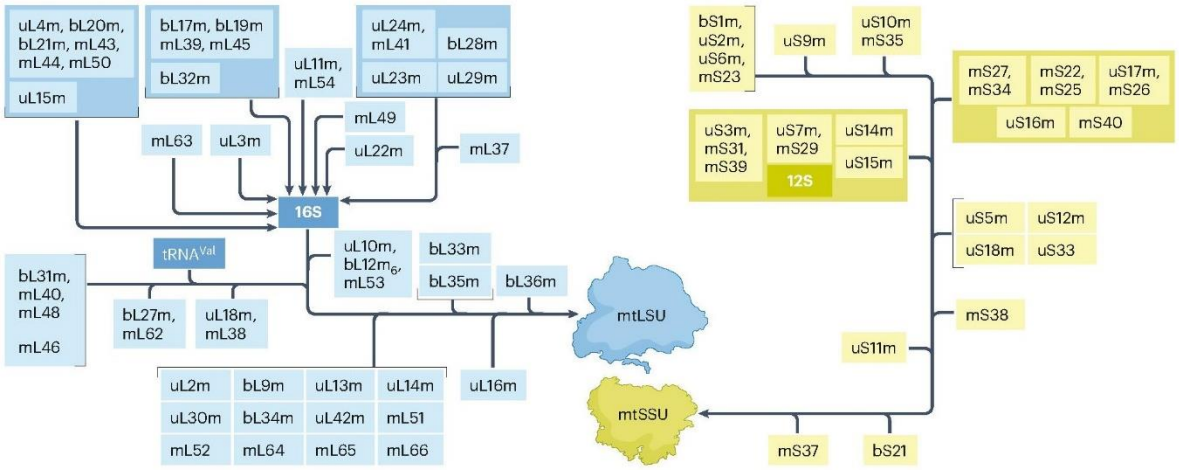
* Present in a microdeletion also containing POU3F3.

Supplementary Box 1. **Ribosome biogenesis in human mitochondria.**

Mitoribosomes are confronted with the challenge to assemble from both mitochondrial and cytoplasmic components. Whereas the mitoribosome RNA moieties (12S, 16S and $tRNA^{Val}$) are encoded by the mitochondrial genome, the 82 mitoribosomal proteins are nuclear encoded, synthesized in the cytosol and subsequently imported into mitochondria. Out of these 82 MRPs, 36 are mitochondria-specific and do not share a homolog with bacteria. The remaining MRPs are homologous of bacterial ribosomal proteins, but they commonly contain significant N-extensions and C-terminal extensions that are absent in their bacterial counterparts[124,125]. These differences in structure and composition compared to bacterial ribosomes are paralleled by distinct ribosome assembly pathways in mitochondria. Mitoribosomes assemble in a modular fashion, forming protein-only subcomplexes, which remain stable upon rRNA depletion[126] (see the figure). These protein-only modules are predominantly clustered according to their spatial proximity within the mitoribosome and are formed in excess as primed building blocks; by contrast, the synthesis of the mitochondrial-encoded RNA components appears to be the rate-limiting step in mitoribosome biogenesis[126].

Mitoribosome assembly is facilitated by a set of specialised biogenesis (or assembly) factors. Currently, our understanding of their functions is limited largely to the late mitoribosome maturation steps, where they facilitate RNA folding and modification and recruitment of MRPs, or inhibit premature subunit joining[127]. These assisting factors include RNA modification enzymes (methyltransferases, pseudouridine synthase), helicases, GTPases and chaperones (recently reviewed ref.[127,128]). Ablation of these factors usually results in the accumulation of immature ribosomal particles and in translation deficiency, highlighting their vital functions. Interestingly, some factors such as malonyl-CoA-acyl carrier protein transacylase (MCAT) and acyl carrier protein, mitochondrial (mtACP) have also metabolic functions, suggesting that metabolic sensing modulates mitoribosome biogenesis [129–131]. MCAT also has a function in mitochondrial fatty acid metabolism, and mtACP is involved in *de novo*

synthesis of fatty acids, Complex I assembly and synthesis of Fe–S cluster[131,132]. However, further investigation is required to elucidate a potential coordination between mitochondrial metabolism and mitoribosome biogenesis. Importantly, mitoribosome biogenesis does not strictly follow a linear pathway; several studies highlight the existence of alternative biogenesis pathways, which makes the system dynamic, flexible and more resilient to disruptions[126,129,133,134]. Especially during late maturation steps, alternative routes ensure efficient, proper maturation of mitoribosome subunits.



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