Mitochondrial translation defects and human disease

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Abstract

In eukaryotic cells, mitochondria perform the essential function of producing cellular energy in the form of ATP via the oxidative phosphorylation system. This system is composed of 5 multimeric protein complexes of which 13 protein subunits are encoded by the mitochondrial genome: Complex I (7 subunits), Complex III (1 subunit),Complex IV (3 subunits), and Complex (2 subunits). Effective mitochondrial translation is necessary to produce the protein subunits encoded by the mitochondrial genome (mtDNA). Defects in mitochondrial translation are known to cause a wide variety of clinical disease in humans with high-energy consuming organs generally most prominently affected. Here, we review several classes of disease resulting from defective mitochondrial translation including disorders with mitochondrial tRNA mutations, mitochondrial aminoacyl-tRNA synthetase disorders, mitochondrial rRNA mutations, and mitochondrial ribosomal protein disorders.

Keywords

INTRODUCTION

Mitochondria are double-membrane bound organelles found in most eukaryotic organisms with the important function of generating cellular energy via oxidative phosphorylation, but

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which also function in cellular signaling, cellular differentiation, cell death, and cell cycle regulation. Mitochondria are estimated to be comprised of approximately 1100 proteins and are unique organelles in that they have their own genome and ribosomes that carry out protein synthesis inside the mitochondria[1]. The mitochondrial genome, which is housed in the mitochondrial matrix, encodes 37 genes: 13 which encode protein subunits of respiratory Complexes I, III, IV, and V; 22 which encode mitochondrial tRNAs; and 2 which encode mitochondrial rRNAs. By far the majority of mitochondrial proteins are produced on cytosolic ribosomes and are transported to the mitochondria as precursors via the translocase of the mitochondrial outer membrane (TOM complex), the presequence translocase (TIM23 complex), and presequence-translocase-associated motor located at the inner mitochondrial membrane[2].

Oxidative phosphorylation and generation of cellular ATP requires coordinated biogenesis and assembly of respiratory chain complexes at the inner mitochondrial membrane. Electrons are transferred along the respiratory chain complexes from the reducing equivalents NADH and FADH2 to oxygen to produce water and generate a proton gradient across the inner membrane. This proton gradient enables ATP synthase to generate ATP from ADP and phosphate. In humans, five multi-subunit protein complexes compose the respiratory chain and oxidative phosphorylation system: NADH dehydrogenase (Complex I); succinate dehydrogenase (Complex II); coenzyme Q: cytochrome c-oxidoreductase (Complex III); cytochrome c oxidase (Complex IV); and ATP synthase (Complex V). Complex II is composed of proteins encoded entirely by the nuclear genome, whereas the remaining complexes have protein subunit components encoded by both nuclear and mitochondrial genomes. Additionally, complex assembly is a highly coordinated process involving a number of assembly factors, as well as coordination of nuclear and mitochondrial genes. Defects in mitochondrial translation processes may result in impaired activities of these complexes, resulting in deficient aerobic energy metabolism and clinical disease in humans[3].

Mitochondrial translation is specifically defined as the process within mitochondria whereby mitochondrial mRNA (mt-mRNA) is translated by mitochondrial ribosomes (mitoribosomes) to generate an amino acid polypeptide. Mitochondrial translation is necessary for the generation of thirteen respiratory complex subunits. mt-mRNAs are unique in that they are uncapped, have no or very few 5′-untranslated nucleotides, and contain a poly A tail that immediately follows or forms part of the stop codon[4]. The mitoribosome translates the mt-mRNA by inducing the binding of complementary tRNA anticodon sequences to mt-mRNA codons in a manner analogous to that performed by cytoplasmic ribosomes. The tRNAs carry specific amino acids that are linked together into a polypeptide as the mt-mRNA passes through and is read by the mitoribosome. Mitoribosomes have a higher protein:RNA ratio (2:1 *vs.* 1:2 in cytoplasmic ribosomes) and are less dense (55S *vs.* 80S) than cytoplasmic ribosomes[5]. Additionally, mitoribosomal translation is unique in that there are several differences from the universal genetic code. Human mitochondria translate the conventional UGA stop codon as tryptophan, reprogram the two conventional arginine codons AGA and AGG for termination, and code the conventional isoleucine AUA codon as methionine[6].

Structural studies have established that many mitochondrial ribosome proteins have eubacterial orthologs, but there also exist additional proteins without such orthologs. Mitoriboproteins have traditionally been named by a MRPS (Mitochondrial Ribosomal Protein Small subunit)/MRPL (Mitochondrial Ribosomal Protein Large subunit) nomenclature[5]. Recently, a new naming convention has been proposed based on functional/structural relationships of mitoribosomal proteins across species in order to reduce ambiguity arising from non-orthologous proteins from different species being assigned similar names[7].

Mitochondrial translation defects resulting in human disease may have varying organ involvement, varying age of onset, and varying modes of inheritance. This specific class of mitochondrial disease may be caused by the following mechanisms: mitochondrial tRNA mutations, mitochondrial aminoacyl-tRNA synthetase mutations, mitochondrial rRNA mutations, and mitochondrial ribosomal protein mutations. Additional mechanisms of abnormal mitochondrial translation exist, including impaired translation secondary to mtDNA depletion and defects in mitochondrial RNA synthesis, modification, and degradation, which are beyond the scope of this article but have been recently reviewed[8,9].

MITOCHONDRIAL tRNA MUTATIONS

All 22 mt-tRNAs are encoded by the mitochondrial genome, and the primary function of mt-tRNAs is to deliver amino acids to the nascent polypeptide chain during mitochondrial protein translation. Mitochondrial tRNAs are truncated when compared to their canonical cytosolic tRNA counterparts, and, in some cases, such as in tRNA$^{Ser(AGY)}$, one arm of the classic cloverleaf secondary structure of tRNA is lost[10].

The first report of a mt-tRNA mutation causing human disease was published in 1990 when Kobayashi *et al.*[11] revealed that a mutation in the mitochondrial tRNA^{Leu} gene (*MTTL1*) was causative of mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)[11,12]. Since then, over 300 mutations in mt-tRNA genes have been identified to cause human disease [Table 1]. Most of these mutations prevent tRNA aminoacylation. mt-tRNA mutations have been identified in various structural locations including in the anti-codon wobble position, anti-codon stem, acceptor stem, DHU stem, TYC stem, and the variable loop[12]. Disorders associated with mitochondrial t-RNA mutations are summarized in Table 1.

Interestingly, different point mutations in the same mt-tRNA molecule can result in different human diseases. For example, the point mutation m.14709T>C in *MTTE* (gene that encodes the mitochondrial tRNA^{Glu}) can result in the phenotype of maternally inherited diabetes and deafness, whereas the point mutations m.14674T>G or m.14674T>C in *MTTE* can result in infantile transient mitochondrial myopathy.

Nearly all mitochondrial disease resulting from mt-tRNA mutations display maternal inheritance as mitochondrial DNA is inherited from the mother. However, few instances of paternal inheritance have been reported as well[13,14]. Cells that carry a homogeneous population of the mitochondrial genome, either wild-type or mutant, are termed

homoplasmic. Cells that carry two or more populations of the mitochondrial genome are termed heteroplasmic. With mitochondrial disease due to maternal inheritance, clinical disease severity often correlates with mutation load in affected tissues.

The two most well-known mitochondrial diseases associated with mt-tRNA mutations are MELAS and myoclonic epilepsy with ragged red fibers (MERRF). In approximately 80% of MELAS patients, the causative mutation is the m.3243A>G pathogenic variant in *MTTL₁* (mt-tRNA^Leu). Most patients with MELAS develop symptoms between ages 2 and 40 years old, and these symptoms include stroke-like episodes, encephalopathy with seizures and/or dementia, muscle weakness, exercise intolerance, headaches, vomiting, hearing impairment, peripheral neuropathy, learning disability, and short stature. Treatment for MELAS is supportive and includes treatment with a mitochondrial cocktail. Intravenous arginine is recommended during acute stroke-like episodes, and arginine should be given orally for prophylaxis after a patient has had a first stroke-like episode[15].

The most common mutation causing MERRF in more than 80% of affected patients is the m.8344A>G mutation in *MTTK* (mt-tRNA^Lys). Onset of MERRF is usually in childhood and the first symptom is often myoclonus. Other common symptoms and findings are epilepsy, ataxia, weakness, dementia, hearing loss, short stature, optic atrophy, and cardiomyopathy with Wolff-Parkinson-White syndrome. Treatment is also supportive with antiepileptic medications to treat seizures, mitochondrial cocktail, and physical therapy[16].

MITOCHONDRIAL AMINOACYL-tRNA SYNTHETASE DISORDERS

Mitochondrial aminoacyl-tRNA synthetases (mt-ARSs) are essential for protein synthesis in the mitochondria and generation of oxidative phosphorylation (OXPHOS) system components. mt-ARS proteins are nuclear-encoded and function to charge mitochondrial tRNA molecules, which are mitochondrial-encoded, with their cognate amino acids. While mt-ARS proteins vary in size and oligomeric state (from monomer to tetramer), all contain a catalytic domain and a tRNA anticodon-binding domain[17]. mt-ARS genes are named with an *ARS2* nomenclature (for example, *MARS2* for methionine tRNA synthetase, mitochondrial). For the amino acids glycine and lysine, a separate mt-ARS gene does not exist, and *GARS* and *KARS*, respectively, function as the aminoacyl-tRNA synthetase in both the cytosol and the mitochondria. Additionally, an mt-ARS has not been identified for glutamine (Q), and Q-tRNA is believed to be formed by postconjugation modification of glutamate[18].

The first Mendelian disease reported to be caused by mt-ARS mutations was leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation (MIM #611105) due to autosomal recessive pathogenic variants in *DARS2*, which was reported in 2007[19]. Since then, pathogenic variants in all known mt-ARSs have been identified with the majority being identified by whole exome sequencing studies, and the associated conditions represent a new class of Mendelian disorders [Table 2]. All mt-ARS disorders exhibit autosomal recessive inheritance and most often patients are compound heterozygotes[17]. These Mendelian disorders are extremely rare as deleterious mutations in mt-ARS genes leading to absent mt-ARS function are expected to be lethal. Therefore,

patients most often have at least one allele with a mild mutation leading to some residual mt-ARS gene function.

Interestingly, although pathogenic variants in all mt-ARSs are expected to result in disruption of protein synthesis of OXPHOS system components via impairment of mitochondrial translation, the identified mt-ARS disorders each display strikingly specific clinical phenotypes with specific tissue involvement [Table 2][17,20,21]. Most frequently, mt-ARS disorders display central nervous system involvement, but additional organ systems are specifically involved in certain disorders, such as ovaries in the case of *HARS2* and *LARS2* or kidney in the case of *SARS2* [Table 2][22–24]. Additionally, age of onset is highly variable for the various mt-ARS disorders. The molecular mechanisms behind this selective tissue involvement and disease phenotype for specific mt-ARS disorders are currently poorly understood.

A wide variety of neurological symptoms is also seen with mt-ARS disorders. Leukoencephalopathy may be seen with *AARS2*, *DARS2*, *EARS2*, *NARS2*, *PARS2*, and *WARS2* disorders. Epilepsy may be seen with *CARS2*, *EARS2*, *FARS2*, *NARS2*, *PARS2*, *RARS2*, *TARS2*, *VARS2*, and *WARS2* disorders. Peripheral neuropathy is seen with *IARS2* disorder. Sensorineural hearing loss may be seen with *HARS2*, *IARS2*, *LARS2*, *MARS2*, *NARS2*, and *PARS2* disorders[18].

Pathogenic mutations in *GARS*, which functions in both the cytosol and mitochondria, may cause autosomal dominant Charcot-Marie-Tooth disease, type 2D (MIM #601472) or autosomal dominant neuropathy, distal hereditary motor, type VA (MIM #600794)[25]. Additionally, a few cases of *GARS* variants causing autosomal recessive disease have been reported leading to cardiomyopathy or complex neurological phenotypes [Table 2]. Pathogenic mutations in *KARS* may cause autosomal recessive Charcot-Marie-Tooth disease, recessive intermediate B (MIM #613641) or deafness, autosomal recessive 89 (MIM #613916)[26,27]. Interestingly, Ruzzenente *et al.*[28] recently reported a patient with compound heterozygous *KARS* variants leading to impaired mitochondrial translation, but intact cytosolic translation. This patient had symptoms of sensorineural deafness, developmental delay, hypotonia, and lactic acidosis[28]. Additional case reports have described additional various phenotypes for patients with pathogenic *KARS* mutations including optic neuropathy, progressive leukoencephalopathy, and cardiomyopathy, among others[29–31].

Failure of charging of glutaminyl mt-tRNA (mt-tRNA^{Gln}) has also been identified to cause disease. The GatCAB aminoacyl-tRNA amidotransferase complex provides this function and is composed of three subunits: GATA encoded by *QRSL1*, GATB encoded by *GATB*, and GATC encoded by *GATC*. Patients with defects in glutaminyl mt-tRNA charging present in infancy with lethal cardiomyopathy and lactic acidosis. Pathogenic variants have been identified in *QRSL1*, *GATB*, and *GATC*, and all cause autosomal recessive disease[32,33].

In addition to mt-ARS genes functioning in mitochondrial translation, there is growing evidence that mt-ARS proteins have potential non-canonical roles in immune regulation,

inflammation, and neuronal differentiation[34]. Further work is in progress to further explore the many roles of mt-ARS genes.

MITOCHONDRIAL rRNA MUTATIONS

Mitochondrial 55S ribosomes are composed of two subunits. The small 28S subunit (mtSSU) functions to catalyze the peptidyl-transferase reaction and the large 39S subunit (mtLSU) functions in mt-mRNA binding and decoding[8]. The 28S and 39S mitochondrial ribosome subunits are composed of 12S mt-rRNA (mtSSU) and 16S mt-rRNA (mtLSU) and ribosomal proteins. Both mt-rRNAs are processed from the polycistronic heavy strand transcript, which also encodes tRNA^{Phe} and tRNA^{Val}. Following release of the mature mt-rRNAs by endonucleolytic cleavage, assembly of the functional mitoribosome proceeds via a complex process involving maturation and processing of mt-rRNAs and association with ribosomal proteins[35]. In addition to the 16S mt-rRNA, the large subunit of mammalian ribosomes also include tRNA^{Phe} or tRNA^{Val}[36,37].

The gene *MTRNR1* encodes the mitochondrial 12S ribosomal RNA, and the gene *MTRNR2* encodes the mitochondrial 16S ribosomal RNA. Mutations in *MTRNR1* are associated with hearing impairment with or without aminoglycoside exposure. The *MTRNR1* mutations m.1555A>G[38] and m.1494C>T[39] have been described as a cause of maternally inherited deafness in numerous case reports but the phenotype is variable and not completely penetrant. The identification of a pedigree in which deafness manifested when the m.1555A>G variant was co-inherited with a loss-of-function *SSBP1* variant suggests that SSBP1 may be a phenotypic modifier of m.1555A>G-associated deafness[40]. Additional examples of complex phenotypes involving m.1555A>G include in a pedigree in which the hearing loss co-segregated with familial dilated cardiomyopathy due to mutations in *MT-ATP6*[41]. Recently, expansion of the *MTRNR1* poly-cytidine tract at m.961 has been reported to be associated with non-ophthalmologic manifestations (intellectual disability, epilepsy, and migraine) in a kindred also segregating Leber's hereditary optic neuropathy due to m.3460G>A, although this association is not statistically validated[42]. In contrast to the numerous reports of human disease-associated variants in *MTRNR1*, only a single variant in *MTRNR2*, m.2336C>T, has been identified as a cause of hypertrophic cardiomyopathy in humans[43].

MITOCHONDRIAL RIBOSOMAL PROTEIN DISORDERS

Mammalian mitoribosomes are composed of rRNA and mitochondrial ribosomal protein components. In humans, 30 mitochondrial ribosomal small subunit proteins (MRPSs) assemble with the 12S mt-rRNA to form the small mitoribosomal 28S subunit. Similarly, 50 mitochondrial ribosomal large subunit proteins (MRPLs) assemble with the 16S mt-rRNA along with tRNA to form the large mitoribosomal 39S subunit[44]. MRPS and MRPL proteins are all encoded by the nuclear genome.

At present, nine *MRPS* genes and three *MRPL* genes have been identified to cause mitochondrial disease in humans [Table 3]. All are inherited in an autosomal recessive fashion. Mutations in mitochondrial ribosomal protein genes may destabilize the

mitoribosomal subunits impacting translation, as has been shown via proteomic analysis with *MRPS34* disorder[44]. Despite the presumptive shared pathogenesis of destabilizing either the large or small mitoribosomal subunits, the clinical phenotypes associated with mutations in genes encoding mitoribosomal structural proteins are surprisingly diverse [Table 3]. Most of these disorders present early in life, although missense mutations in *MRPS22* can present with ovarian failure in adolescent females[45]. Neurological deficits have been observed in the majority of patients with this subset of disorders but additional associated clinical phenotypes include hepatopathy, renal dysfunction, deafness, myopathy, and craniofacial or cardiac phenotypes. The neurological features may be variable and range from structural lesions such as agenesis of the corpus callosum to classical Leigh syndrome or functional deficits without apparent structural lesions. Most mitochondrial ribosomal protein subunit disorders cause severe disease often with multi-organ involvement and early death. In the future, additional mitochondrial ribosomal protein disorders are highly likely to be identified via whole exome sequencing of patients with suspected mitochondrial disease.

CONCLUSION

Defects in mitochondrial translation may result in a vast array of clinical disease. Disease mechanisms include, but are not limited to, mitochondrial tRNA mutations, mitochondrial aminoacyl-tRNA synthetase mutations, mitochondrial rRNA mutations, and mitochondrial ribosomal protein mutations. Understanding disease biology of these mitochondrial translation defects is a necessary predecessor to developing effective treatment for these disorders. More research is necessary to further understand this emerging class of mitochondrial disease.

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Table 1.

Clinical phenotypes of mt-tRNA disorders

Gene	Alternative name	Clinical phenotype(s)	PMID[**]
MTTA	mt-tRNA-Ala	Myotonic dystrophy-like myopathy; mitochondrial myopathy	14569122; 16476954
MTTC	mt-tRNA-Cys	MELAS; dystonia	8829635; 9185178; 17724295
MTTD	mt-tRNA-Asp	Myopathy	16059939
MTTE	mt-tRNA-Glu	MIDD; transient infantile mitochondrial myopathy	15048886; 19720722
MTTF	mt-tRNA-Phe	MELAS; MERRF; myopathy; epilepsy; encephalopathy; tubulointerstitial nephropathy	9771776; 15184630; 16769874; 11231339
MTTG	mt-tRNA-Gly	Hypertrophic cardiomyopathy; exercise intolerance; sudden death	8079988; 11971101; 8888049
MTTH	mt-tRNA-His	Cardiomyopathy; RP; MERRF; MELAS; NSHL	11038324; 12682337; 14967777; 21931169
MTTI	mt-tRNA-lle	Cardiomyopathy; familial hypertrophic cardiomyopathy; CPEO	1978914; 11782991; 20149659
MTTK	mt-tRNA-Lys	MERRF; cardiomyopathy and deafness; neurogastrointestinal encephalomyopathy; MIDD; progressive external ophthalmoplegia with myoclonus	2112427; 2124116; 8651277; 9380435; 9571188; 10220860
MTTL1	mt-tRNA-Leu (UUR)	MELAS; MERRF; cardiomyopathy with or without skeletal myopathy; encephalopmyopathy; CPEO; Kearns-Sayre syndrome; sudden infant death syndrome; Leigh syndrome; MIDD; SNHL; FSGS	2102678; 2268345; 8254046; 7906985; 8111377; 8265770; 10519336; 11448301
MTTL2	mt-tRNA-Leu (CUN)	Encephalomyopathy; myopathy; cardiomyopathy	8923013; 9012410; 11313776
MTTM	mt-tRNA-Met	Myopathy	9633749
MTTN	mt-tRNA-Asn	CPEO; myopathy	8254046; 7980504
MTTP	mt-tRNA-Pro	Myopathy; MERFF	7689388; 19273760
MTTQ	mt-tRNA-Gln	Myopathy; sensorineural deafness and migraine; MELAS	10996779; 11424923; 11171912
MTTR	mt-tRNA-Arg	Encephalomyopathy	15286228; 19809478
MTTS1	m-tRNA-Ser (UCN)	MERRF; MELAS; palmoplantar keratoderma with deafness; NSHL; exercise intolerance	7669057; 8019558; 10978361; 14605505
MTTS2	mt-tRNA-Ser (AGY)	Cerebellar ataxia, cataract, and diabetes mellitus; MERRF; MELAS	9792552; 16950817
MTTT	mt-tRNA-Thr	Fatal infantile myopathy; myopathy	1645537; 28187756; 30236074
MTTV	mt-tRNA-Val	Ataxia, progressive seizures, mental deterioration, and hearing loss; Leigh syndrome; hypertrophic cardiomyopathy; MELAS	9443499 ; 9450773; 11799391; 15465092; 21986556
MTTW	mt-tRNA-Trp	Encephalopathy; myopathy; neurogastrointestinal syndrome; encephalocardiomyopathy; Leigh syndrome	7695240; 9673981; 15054399; 18337306; 12776230
MTTY	mt-tRNA-Tyr	Exercise intolerance; CPEO with myopathy; FSGS and dilated cardiomyopathy	11071502; 11756614; 14598342

MELAS: mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MIDD: maternally inherited diabetes and deafness; MERRF: myoclonic epilepsy with ragged red fibers; RP: retinitis pigmentosa; NSHL: nonsyndromic hearing loss; CPEO: chronic progressive external ophthalmoplegia; SNHL: sensorineural hearing loss; FSGS: focal segmental glomerulosclerosis.

[*] Seminal works highlighted including first reports of a gene causing human disease as well as key reports of new phenotypes. References: OMIM (https://omim.org) and MitoMap (https://www.mitomap.org)

Table 2.

Clinical phenotypes of mt-ARS disorders

Gene	Mutation type	Inheritance	OMIM phenotype	Main organ(s) affected	OMIM Phenotype	Age at onset	PMID[#]
AARS2	SNV	Recessive	614096	Heart	Hypertrophic cardiomyopathy	Infancy	21549344
AARS2	SNV	Recessive	615889	Brain, ovaries	Progressive leukoencephalopathy with ovarian failure	Childhood-adulthood	2480803
CARS2	SNV	Recessive	616672	Brain, muscle	Combined oxidative phosphorylation deficiency, 27	Neonatal-childhood	25361775
DARS2	SNV	Recessive	611105	Brain	Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation	Childhood-adulthood	17384640
EARS2	SNV	Recessive	614924	Brain	Combined oxidative phosphorylation deficiency, 12	Infancy	22492562
FARS2	SNV	Recessive	614946	Brain	Combined oxidative phosphorylation deficiency, 14	Infancy	22499341
FARS2	SNV	Recessive	617046	Bran	Spastic paraplegia 77, autosomal recessive	Infancy-childhood	26553276
HARS2	SNV	Recessive	614926	Cochlea, ovaries	Perrault syndrome, 2	Childhood-adulthood	21464306
IARS2	SNV	Recessive	616007	Brain, bone, eyes	Cataracts, growth hormone deficiency, sensory neuropathy, sensiorineural hearing loss, and skeletal dysplasia	Infancy	25130867
LARS2	SNV	Recessive	615300	Cochlea, ovaries	Perrault syndrome, 4	Childhood-adulthood	23541342
LARS2	SNV	Recessive	617021	Brain, blood	Hydrops, lactic acidosis, and sideroblastic anemia	Neonatal	26537577
MARS2	CNV	Recessive	611390	Brain	Spastic ataxia 3, autosomal recessive	Childhood-adulthood	22448145
MARS2	SNV	Recessive	616430	Brain, muscle	Combined oxidative phosphorylation deficiency, 25	Infancy	25754315
NARS2	SNV	Recessive	616239	Brain, muscle, cochlea	Combined oxidative phosphorylation deficiency, 24	Infancy	25385316
NARS2	SNV	Recessive	618434	Cochlea	Deafness, autosomal recessive 94	Infancy	25807530
PARS2	SNV	Recessive	618437	Brain	Epilepetic encephalopathy, early infantile, 75	Neonatal-infancy	25629079
RARS2	SNV	Recessive	611523	Brain	Pontocerebellar hypoplasia, type 6	Infancy-childhood	17847012
SARS2	SNV	Recessive	613845	Kidney	Tubulopathy (hyperuricemia, metabolic alkalosis), pulmonary hypertension, and progressive renal failure (HUPRA syndrome)	Infancy	21255763
TARS2	SNV	Recessive	615918	Brain, muscle	Combined oxidative phosphorylation deficiency, 21	Neonatal	24827421
VARS2	SNV	Recessive	615917	Brain, muscle	Combined oxidative phosphorylation deficiency, 20	Infancy	25058219
WARS2	SNV	Recessive	617710	Brain, muscle	Neurodevelopmental disorder, mitochondria, with abnormal movements and lactic acidosis, with or without seizures	Infancy	28236339
YARS2	SNV	Recessive	613561	Muscle, blood	MLASA	Infancy-childhood	20598274

Gene	Mutation type	Inheritance	OMIM phenotype	Main organ(s) affected	OMIM Phenotype	Age at onset	PMID[#]
GARS[*]	SNV	Dominant	601472	Nerves	Charcot Marie Tooth disease, type 2D	Adulthood	12690580
GARS[*]	SNV	Dominant	600794	Nerves	Neuronopathy, distal hereditary motor, type VA	Adulthood	12690580
GARS[*]	SNV	Recessive	N/A	Brain, heart	Cardiomyopathy or growth retardation and complex neurological presentation	Neonatal-childhood	25058219; 24669931; 28675565
KARS[*]	SNV	Recessive	613641	Nerves	Charcot Marie Tooth disease, recessive intermediate, B	Childhood	20920668
KARS[*]	SNV	Recessive	613916	Cochlea	Deafness, autosomal recessive 89	Infancy-childhood	23768514

mt-ARS: mitochondrial aminoacyl-tRNA synthetases; MLASA: myopathy, lactic acidosis, and sideroblastic anemia; SNV: single nucleotide variation; CNV: copy number variation; HUPRA: Hyperuricemia, pulmonary hypertension, renal failure, and alkalosis.

[*] *GARS* and *KARS* function in both the cytosol and mitochondria;

[#] seminal works highlighted including first reports of a gene causing human disease as well as key reports of new phenotypes. References: OMIM (https://omim.org)

Table 3.

Clinical phenotypes of mitochondrial ribosomal protein disorders

Gene	Inheritance	OMIM number	OMIM phenotype	Clinical phenotype	Age at onset	PMID[*]
Small subunit						
MRPS2	Recessive	617950	Combined oxidative phosphorylation deficiency, 36	Developmental delay, hypoglycemia, lactic acidemia, sensorineural hearing loss	Infancy	29576219
MRPS7	Recessive	617872	Combined oxidative phosphorylation deficiency, 34	Lactic acidemia, hepatorenal failure, sensorineural deafness	Infancy	25556185
MRPS14	Recessive	618378	Combined oxidative phosphorylation deficiency, 38	Hypertrophic cardiomyopathy, growth retardation, hypotonia, lactic acidemia, dysmorphism, intellectual disability	Newborn	30358850
MRPS16	Recessive	610498	Combined oxidative phosphorylation deficiency, 2	Agenesis of corpus callosum, brachydactyly, dysmorphism, lactic acidemia	Newborn	15505824
MRPS22	Recessive	611719	Combined oxidative phosphorylation deficiency, 5	Dysmorphism, hypotonia, hyperammonemia, lactic acidemia, renal tubulopathy, hypertrophic cardiomyopathy, cardiac septal defects	Newborn	17873122; 21189481; 25663021; 28752220
MRPS22	Recessive	618117	Ovarian dysgenesis, 7	Ovarian dysgenesis	Adolescence	29566152; 31042289
MRPS23	Recessive	N/A	N/A	Hepatic disease, combined oxidative phosphorylation deficiency	Childhood	26741492
MRPS28	Recessive	N/A	N/A	Craniofacial dysmorphism, developmental delay, intrauterine growth retardation	Infancy	30566640
MRPS34	Recessive	617664	Combined oxidative phosphorylation deficiency, 32	Dysmorphism, hypotonia, hyperammonemia, lactic acidemia, renal tubulopathy, hypertrophic cardiomyopathy, cardiac septal defects	Infancy	28777931
MRPS39 (PTCD3)	Recessive	N/A	N/A	Intrauterine growth retardation, Leigh syndrome, optic atrophy	Infancy	30607703
Large Subunit						
MRPL3	Recessive	614582	Combined oxidative phosphorylation deficiency, 9	Hypoglycemia, hypertrophic cardiomyopathy, intellectual disability, lactic acidemia, liver fibrosis, renal tubulopathy, sensorineural hearing loss	Infancy	27815843; 21786366
MRPL12	Recessive	N/A	N/A	Dysmorphism, hypotonia, intrauterine and postnatal growth retardation, intellectual disability, lactic acidemia, nystagmus, cerebellar ataxia, basal ganglia/ white matter MRI hyperintensities	Infancy	23603806
MRPL44	Recessive	615395	Combined oxidative phosphorylation deficiency, 16	Hypertrophic cardiomyopathy, lactic acidemia, liver steatosis	Infancy	23315540

[*] Seminal works highlighted including first reports of a gene causing human disease as well as key reports of new phenotypes. References: OMIM (https://omim.org)