review

Mitochondrial ribosomal proteins: Candidate genes for mitochondrial disease

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Most of the energy requirement for cell growth, differentiation, and development is met by the mitochondria in the form of ATP produced by the process of oxidative phosphorylation. Human mitochondrial DNA encodes a total of 13 proteins, all of which are essential for oxidative phosphorylation. The mRNAs for these proteins are translated on mitochondrial ribosomes. Recently, the genes for human mitochondrial ribosomal proteins (MRPs) have been identified. In this review, we summarize their refined chromosomal location. It is well known that mutations in the mitochondrial translation system, i.e., ribosomal RNA and transfer RNA cause various pathologies. In this review, we suggest possible associations between clinical conditions and MRPs based on coincidence of genetic map data and chromosomal location. These MRPs may be candidate genes for the clinical condition or may act as modifiers of existing known gene mutations (mt-tRNA, mt-rRNA, etc.). ***Genet Med* 2004:6(2):73–80.**

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Most of the energy requirements for cell growth, differentiation, and development are met by the mitochondrial ATP produced by the process of oxidative phosphorylation. Mitochondrial DNA encodes 13 essential proteins of this oxidative phosphorylation system. The mRNA for these proteins is translated on mitochondrial ribosomes. Interference with their synthesis, either by deletion or mutation of the mitochondrial genes for these proteins and other components of the mitochondrial translation system, such as mitochondrial tRNAs, is known to cause different mitochondrial diseases of variable severity, including myopathies and sensorineural disorders such as blindness and deafness.[1] By analogy, loss or mutation of any of the 78 proteins required for function of the mitochondrial ribosome[2] might also be expected to result in mitochondrial disease. Kenmochi et al.[3] noted that some of the genes for mitochondrial ribosomal proteins (MRPs) do indeed map to chromosomal loci already associated with human disorders, such as deafness, retinitis pigmentosa, and Usher Syndrome 1E. Now that sequence information is available for essentially all (78) of the human MRPs, and given recent advances in bioinformatics, it is possible to implicate deficiencies in several additional MRPs as candidates for mitochondrial disease.

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THE MITORIBOSOME

Human cells contain two genomes and two protein synthesizing (translation) systems. The first is the nuclear genome of 3×10^9 bp that has 30,000 to 40,000 genes coding a much greater number of proteins whose mRNAs are translated by cytoplasmic ribosomes. The second genome is that found in a cytoplasmic organelle, the mitochondrion (mt). It contains a circular DNA of 16,850 bp (mtDNA) that codes for 2 rRNAs, 22 tRNAs, and 13 mRNAs. At least 1500 (3%) nuclear gene products are translated on cytoplasmic ribosomes and imported by and function in the mitochondrion.[4,5] The cytoplasmic ribosome consists of 4 rRNAs (28S, 18S, 5.8S, and 5S) and 85 ribosomal proteins; the genes for these components are all mapped and reasonably well-studied.[6] Mutations in genes of the cytoplasmic translation machinery (ribosome components plus many interacting factors) that cause various human diseases have been identified (see later). In contrast, genes from both genomes encode the components of the mitochondrion's ribosome. The mitochondrial rRNAs are encoded by mt DNA, whereas the ribosomal proteins are encoded in the nuclear genome, they are synthesized on cytoplasmic ribosomes, and then are imported into the mitochondria. There they assemble with the 2 rRNAs to form mitochondrial ribosomes, and they are responsible for translating the 13 mt mRNAs. Unlike eukaryotic ribosomes and their bacterial ancestors, the mitochondrial ribosome is protein, not RNA, rich. For instance, approximately 7500 bases of rRNA exist in the human cytoplasmic ribosome compared to 2000 bases in the mitochondrial ribosome, whereas both have about 80 ribosomal proteins. A discussion of the evolutionary processes and its association with structure/function relationships of the ribosome is beyond the scope of this review, but see O'Brien 2002.[7]

MITOCHONDRIAL GENETICS

The genes encoded in the nucleus are inherited in a Mendelian fashion, whereas the mitochondrial genome is exclusively maternally inherited, thus making mitochondrial genetics much more complicated. There exist many examples documenting loss of mitochondrial function due to mutations in both genomes and examples where nuclear gene variants can modify the phenotype exerted by a mutation in mt DNA.

Mutations in mitochondrial DNA, being much easier to identify, have been associated with many human diseases.[8] The mutations can be either deletions of much DNA (Kearns-Sayre syndrome, for instance) or point mutations (Lebers Hereditary Optic Neuropathy, for instance); they can occur in every mtDNA of the individual (maternally inherited) or they can occur during replication in the somatic cell. Both of these processes can result in heteroplasmy (more than one type of mtDNA) and may or may not be limited to individual tissues. Because the mitochondria are responsible for energy production through oxidative phosphorylation (OXPHOS), cell types that depend on OXPHOS for a large part of their energy supply such as nerve, brain, heart, and muscle are particularly susceptible to mitochondrial malfunction. Each cell can contain hundreds of mitochondria, each with 2 to 10 mtDNAs; therefore, the degree of heteroplasmy may correlate with the threshold for onset and severity of disease in a tissue specific manner.

Mutations do occur in genes responsible for mitochondrial mRNA translation. The most common examples of mitochondrial disease caused by one of the 30 or so documented point mutations in mt tRNA are MELAS (myopathy, encephalopathy, lactic acidosis and recurrent stroke-like episodes) and MERRF (myoclonic epilepsy with ragged red fibers). Cardiac failure is the serious problem for MELAS patients. Tessa et al.[9] reported cases of a few families in which each of the children had heart problems resulting in the death of one child from cardiac arrest at the age of 15 months. The others were diagnosed with dilated cardiomyopathy. Electron microscopic analysis of a skeletal muscle biopsy from one individual showed increased lipid droplets, subsarcolemmal mitochondrial aggregates, and giant mitochondria. Histochemistry revealed 10% cytochrome c oxidase-negative fibers. Lactate levels were normal. Sequencing of mitochondrial DNA detected a T to C nucleotide change at position 12297 in the $tRNA^{leu}$.[9] Previously, cardiomyopathy has been associated with an A4269G mutation in $tRNA^{ile}$ and a case of fatal infant cardiomyopathy with A4319G also in $tRNA^{ile}$.[10] Also the A1555G mutation in the mt 12S rRNA has been shown to be pathogenic in humans. This mutation appears usually in homoplasmic form and predisposes both to nonsyndromic and antibiotic-induced deafness. Nonsyndromic deafness was initially identified in a large Arab-Israeli pedigree, and subsequently confirmed in populations around the world with the highest recognized frequency in Spain.[11–13] Aminoglycoside ototoxicity is one of the most common causes of acquired deafness. Although vestibulocochlear damage is nearly universal when high drug levels are present for prolonged periods, at lower drug levels there appears to be a significant genetic component influencing susceptibility to aminoglycoside ototoxicity. This was demonstrated in 1993 by the analysis of three Chinese families in which several individuals developed deafness after the use of aminoglycosides. All three of these families had the A1555G mutation in the 12S ribosomal RNA gene, whereas the mutation was not seen in hundreds of controls.[11] This finding was confirmed subsequently in multiple populations around the world.[13]

It appears that the mitochondrial dysfunction induced by the A1555G mutation is primarily a decrease in mitochondrial protein synthesis affecting all proteins similarly.[14] Importantly, the percentage decrease of protein synthesis when compared to ethnically matched cell lines without the mtDNA mutation varies with the clinical status of the individual who provided the cell line. For instance, cell lines from hearing impaired individuals showed an average decrease of 48% in protein synthesis, whereas cell lines from their hearing siblings showed an average decrease of 28%. Similarly, cell lines from deaf individuals also showed more significant decreases in oxygen consumption, and enzymatic activity of OXPHOS complexes I, III, and IV, when compared to cell lines from their unaffected siblings.[14] More recently, this nuclear effect was demonstrated independently by transferring mitochondria from deaf and hearing individuals with the A1555G mutation and those without the mutation into human cells which do not contain any mitochondrial DNA (ρ^o206 cells). With this constant nuclear background, mitochondria containing the A1555G mutation showed significant decreases in the rates of growth in galactose medium, mitochondrial protein synthesis, total oxygen consumption, and complex I–, III–, and IV–dependent respiration, with no significant differences between mitochondria obtained from deaf or from hearing individuals.[15] Because the A1555G mutation in the mitochondrial 12S rRNA gene accounts only for 17% to 33% of patients with aminoglycoside ototoxicity, it appeared possible that other susceptibility mutations can be found in the same gene. DNA from 35 Chinese sporadic patients with aminoglycoside ototoxicity and without the A1555G mutation was analyzed for sequence variations in the 12S rRNA gene. One sequence change, an absence of a thymidine at position 961 with varying numbers of cytosines inserted (δT961insCn), appeared likely to be a pathogenic mutation.[16] More recently, an Italian family with 5 maternally related members who all became deaf after aminoglycoside treatment were found to have the same δT961insCn mutation.[17] This sequence change was not found in 799 control individuals,[16] but Tang et al.[18] found the mutation in 7 out of 1173 random neonatal dried blood spot cards. The real population frequency of this mutation remains thus undetermined, and the existing data are therefore not conclusive on whether this mutation is pathogenic.

An experimentally artificial situation is also very illustrative. The Wallace Lab[19] engineered a mouse cybrid carrying a mitochondrial DNA mutation. Briefly, mouse embryonic stem (ES) cells were depleted of their mitochondria by growing them in Rhodamine-66. New mitochondrial DNA was introduced

such that nuclear DNA and mtDNA originated from different sources (cybrid). Mitochondrial DNA with a mutation at nucleotide position 2443 of the 16S rRNA gene was introduced, the ES cells transferred into a pseudopregnant foster mother, and highly chimeric offspring generated. These offspring had congenital cataracts and functional abnormalities in the retina on electroretinopathy. When these mice were mated, the pups either died in utero or in the very early neonatal period with severe growth retardation and with dilated cardiomyopathy. Large atypical mitochondria were found in both the skeletal and heart muscle tissues. Not surprising, the loss of mitochondrial protein translation was lethal and due to abnormal heart development.

Mutations in nuclear genes, which impact on mitochondrial function, will present as autosomal (or sex-linked) dominant or recessive traits. Obvious examples are those genes that are important for the fidelity of mtDNA replication, repair, or propagation during development. A second example of metabolic disorders would be mutations in those genes coding for proteins that are members of the Tricarbocylic acid (TCA or Krebs cycle) or subunits of the respiratory chain complexes. Other examples include MnSOD (superoxide dismutase)[20] and Frataxin,[21] which appear to protect against oxidative damage to mitochondria by eliminating free radicals and properly regulating iron levels, respectively.[22,23] In fact, mutations may occur in any of the nuclear genes that code for proteins destined to act in or on the mitochondrion.[24,25] Mutations in factors involved in mitochondrial translation have been implicated in age-related respiratory deficiencies.[26] Candidates include genes for aminoacyl-tRNA synthetases, and initiation, elongation, and termination factors for mitochondrial translation. Mutations in yeast MTG1, a protein suggested to be involved in mitochondrial ribosome assembly and thus required for mitochondrial translation[27] compromises mitochondrial protein synthesis, leading to diminished capacity for oxidative phosphorylation and ensuing mitochondrial disease. A human gene homologue, hMTG1, is located at chromosome 10q26.3; however, no known genetic disorders presently map to that position.

RIBOSOMAL PROTEIN DISEASES

In humans, very few diseases have been identified that are caused by defective or aberrantly expressed ribosomal proteins. This is perhaps not surprising because a strong argument could be made for the lethality of such conditions. The best-studied example of a ribosomal protein disease is Diamond-Blackfan anemia (DBA). First reported in the late 1930s,[28] DBA is a rare congenital hypoplastic anemia with a prevalence of 4 to 7 cases per million births,[29–32] and is characterized by absent or decreased erythroid precursors.[33] Frequently, DBA is accompanied by physical defects (41%, $N = 399$),[29,30,34,35] including head and face abnormalities (8–52%), thumb abnormalities (9–18%), and short stature (22%). Although most cases of DBA are sporadic (approximately 75%), both dominant and autosomal recessive patterns of inheritance have been implicated in the remaining 25% of cases[30,36–38] with dominant inheritance being more common.[39]

In 1997, Gustavsson et al.,[39] examined chromosome 19 for linkage to DBA after identifying a DBA patient with a balanced reciprocal translocation (X;19) (p21; q13).[39] (The X chromosome was excluded from consideration based on the observed autosomal transmission of DBA.) Subsequently, the region surrounding the (X;19) (p21; q13) translocation break point was cloned and sequenced allowing the identification of cytoplasmic ribosomal protein S19 (RPS19) as the gene disrupted by the translocation.[40] RPS19 is a component of the small subunit of the cytoplasmic ribosome where it has roles in both the structure of the subunit and in binding of elongation factor 2.[41] Additionally, RPS19 homodimers released from the cell function as chemotactic factors for monocytes during macrophage-dependent apoptotic cell clearance.[42]

Further studies have identified RPS19 mutations in 20% to 25% of both sporadic and unrelated familial DBA patients[30,40,43] (reviewed in Da Costa et al.[44]). In all patients examined, only a single allele of RPS19 has been mutated, suggesting that at least one healthy RPS19 allele is required for viability.[30,40,43] Interestingly, there appears to be little genotype-phenotype correlation between the type of RPS19 mutation and the clinical presentation of DBA or its associated physical anomalies. For example, in a pair of monozygotic twins who present with DBA, share the same RPS19 mutation, and are presumably genetically identical, only one exhibited thumb duplication, whereas their father who contributed the RPS19 missense mutation was healthy except for persistent macrocytosis.[30]

Because mutations in RPS19 are found in only 20% to 25% of all DBA patients, a great deal of effort has been made to identify other candidate genes. In one such study, Gazda et al.[45] analyzed 14 multiplex families in a genome wide search for linkage to DBA and identified a linked loci on chromosome 8. In the same study, they further refined their data by analyzing 38 families with polymorphic markers to chromosome 8. In total, 18 of 38 families were consistent with linkage to chromosome 8, in a region flanked by D8S518 and D8S1825. Interestingly, none of the known ribosomal proteins for which sequence data are available (cytoplasmic or mitochondrial) map to this loci.

MRP CHARACTERIZATION, GENE IDENTIFICATION, AND MAPPING

Analysis of mammalian MRPs by 2D PAGE revealed that mammalian mitochondrial ribosomes contain many more proteins, of vastly different properties, than bacterial ribosomes,[46] and that they are evolving more rapidly than proteins in bacterial or eukaryotic cytoplasmic ribosomes.[47] Early efforts (in the "pregenomic era") to identify coding sequences for mammalian MRPs involved the labor-intensive screening of cDNA libraries with antibodies prepared against individual MRPs or with degenerate oligonucleotides designed from limited amino acid sequence information derived from individual

Table 1
Location of genes for the proteins of the large mitochondrial ribosomal subunit and map positions for candidate associated disorders

Human *MRPL* gene locations			
Protein	Location	Candidate disorder	Map position
MRPL1	4q21.1[a,b,c,d]		
MRPL2	6p21.3[a]–6p21.1[b,c,d]	SCABD[e]	6p23–p21
MRPL3	3q22.1[b,c,d]	DFNA18[f]	3q22
		Moebius syndrome 2	3q21–q22
		DFNB15[g] (digenic)	3q21.3–q25.2
MRPL4	19p13.2[a,b,c,d]	DFNB15[g] (digenic)	19p13.3–p13.1
MRPL9	1q21[a]–q21.3[c,d]	DFNA7[f] diabetes	1q21–q23
MRPL10	17q21.3[a]–17q21.32[c,d]		
MRPL11	11q13.3[a]–q13.32[c]		
MRPL12	17q25[a]–17q25.3[c]	DFNA20[f] NABP[h]	17q25.3
MRPL13	8q22.1–q22.3[a], 8q24.12[b,c,d]		
MRPL14	6p21.3[a]–p21.1[c,d]	SCABD[e]	6p23–p21
MRPL15	8q11.2[a,b]–8q11.23[c,d]		
MRPL16	11q12[a,b]–q13.1[a]		
MRPL17	11p15.5[a]–15.4[a,c,d]		
MRPL18	6q25.3[b,d]–6q26[c]		
MRPL19	2p11.2–q11.2[a], 2p12[c,d]	DFNA43[f]	2p12
MRPL20	1p36.3[a,d]–p36.2[a,b]	Parkinson disease 6 cataract	1p36–p35 1p36
MRPL21	11q13.1[b]		
MRPL22	5q33.1[a]–q33.2[a,c,d]		
MRPL23	11p15.5[a,c,d]–15.4[a,b]		11p15.5
MRPL24	1q21[a]–q22[a,b], 1q23.1[d]	DFNA7[f]	1q21–q23
MRPL27	17q21.3–q22[a,b], q21.33[c,d]	diabetes	17p11.2–q22
MRPL28	16p13.3[b,c,d]		
MRPL30	2q11.2[a,b,c,d]		
MRPL32	7p14[a,b,d]		
MRPL33	2p23.2[b,c]–p21[a]		2p21–23
MRPL34	19p13.1[a,b], p13.12[d]		
MRPL35	2p11.2[b,c,d]		
MRPL36	5p15.3[a,b,d]		
MRPL37	1p32.3[c,d], 1p32.1[a,b]	Parkinson disease 10	1p32
MRPL38	17q25.1[c,d]–q25.3[b]	DFNA20[f] NABP[h]	17q25.3
MRPL39	21q21.3[b,c,d]	Usher syndrome 1E	21q21
MRPL40	22q11.1[d]–q11.2[a,b]	DiGeorge syndrome	22q11
MRPL41	9q34.3[a,b,c,d]	Joubert syndrome	9q34.3
		DNFB33[g]	9q34.3
		Leigh Syndrome	9q34
MRPL42	12q22[a,b]	DFNA25[f]	12q21–24
MRPL43	10q24[1]–q24.3[a,b,c,d]	Alzheimer disease 6	10q24
MRPL44	2q36.1[b,c,d]		
MRPL45	17q12[b,c,d]–q21.2[b]	diabetes	17p11.2–q22
MRPL46	15q25.3[b,c,d]	DFNA30[f]	15q25–q26
MRPL47	3q26.32[d]–3q27.1[b]	Spastic paraplegia 14	3q27–q28
MRPL48	11q13.2–q13.3[b], q13.4[c,d]	Leigh syndrome	11q13
MRPL49	11q13.1[b,c,d]	Leigh syndrome	11q13
MRPL50	9q31.1[b,d]		
MRPL51	12p13.31[b,c,d]		
MRPL52	14q11.1[b]–q11.2[d]		
MRPL53	2p13.1[c,d]–p12[b]	MMDFS[i] Parkinson disease 3 DFNA43[f]	2p14–2p13 2p13 2p12
MRPL54	19p13.3[b,c]	Vacuolar neuromyopathy Leigh syndrome DFNB15[g]	19p13.3 19p13.3 19p13.3–p13.1
MRPL55	1q42.13[b,d]		
MRPL56	15q22.1[b]–q22.2[d]		

—*Continued*

Table 1
Continued

[a]STS-cytogenic mapping.[3]
[b]NCBI Human genome resources, Build 33 (http://www.ncbi.nlm.nih.gov/genome/seq/HsBlast.html).
[c]Human Genome Browser Gateway at UCSC (April 2003 freeze) http://genome.ucsc.edu/cgi-bin/hgGateway?org=human
[d]Rebhan et al.[69] http://bioinformatics.weizmann.ac.il/cards
[e]SCABD Spinocerebellar ataxia with blindness and deafness
[f]DFNA Deafness, autosomal dominant nonsyndromic sensorineural
[g]DFNB Deafness, autosomal recessive
[h]Neuritis, with brachial predilection
[i]MMDFS Multiple mitochondrial dysfunctions syndrome

MRPs. With the advent of the Human Genome Project, and the ensuing flood of expressed sequence information in the databases, it was no longer necessary to isolate MRP cDNA clones for sequence analysis. It was occasionally possible to identify MRP sequences by virtue of their homology to known bacterial ribosomal proteins. However, because the "extra" proteins in mammalian mitochondrial ribosomes have no counterpart in either bacterial or cytoplasmic ribosomes,[7] it was still necessary to obtain amino acid sequence information for each of the MRPs in ribosomes isolated from rat or bovine liver mitochondria. Amino acid sequence information from mammalian mitochondrial ribosomes can be used to identify human MRP coding sequences in the databases, using BLAST (TBLASTN) searches of the nonredundant and EST databases. The recent use of proteomic approaches for sequence analysis of MRPs accelerated the process, and we now have sequences for essentially all (78) of the human MRPs.

Recent advances in bioinformatics and the continuing refinement of the Human Genome Map improve the mapping precision over what was possible with experimental probe hy-

Table 2
Location of genes for the proteins of the small mitochondrial ribosomal subunit and map positions for candidate associated disorders

Human *MRPS* gene locations			
Protein	Location	Candidate disorder	Map position
MRPS2	9q34.3[a,b,c,d]	DNFB33[j] Joubert syndrome Leigh syndrome	9q34.3 9q34.3 9q34
MRPS5	2q11.1[b,c,d]		
MRPS6	21q21.3[a]–q22.1[a,c,d]		21q22/21q22.3
MRPS7	17q25.1[c,d]–q25.2[b]	NAPB[k]	17q25
MRPS9	2q12.1[b]		
MRPS10	6p21.1[b,c,d]	SCABD[l]	6p23–p21
MRPS11	15q25[a]–q25.3[b,c,d]	DFNA30[m]	15q25–q26
MRPS12	19q13.11[a]–q13.2[a,b,c,d]	DFNA4[m]	19q13
MRPS14	1q24[a,b]–q25.1[a,b,c,d]	DFNM1[n] of DFNB26[j]	1q24
MRPS15	1p34.3[b,c,d]	DFNA2[13], 3rd gene; Stuve-Wiedemann syndrome	1p34
MRPS16	10q22.1[a,b]–q22.2[d]		
MRPS17	7p11.2[b,c,d]	Russell-Silver Syndrome	7p11.2
MRPS18A	6p21.1[b,c,d]–6p21.3[a]	SCABD[l]	6p23–p21
MRPS18B	6p21.3[b,d]	SCABD[l]	6p23–p21
MRPS18C	4q21.23[b,c,d]		
MRPS21	1q21.2[a,b,c,d]	DFNA7[m]	1q21–q23
MRPS22	3q23[a,b,c,d]	cataract	3q21–q25
MRPS23	17q23[b]–q23.2[d]	Alzheimer Disease Russell-Silver Syndrome	17q23 17q23–q24
MRPS24	7p14[a,b]–7p13[c]		
MRPS25	3p25.1[a,b,c,d]	Cardiomyopathy, dilated, 1E	3p25–p22
MRPS26	20p13[a,b,c,d]	CDPD1[o]	20p13
MRPS27	5q13.1[b]–q13.2[c,d]		
MRPS28	8q21.1–q21.2[a,b]		
MRPS29	1q21[a,b]–q22[a,b,d]	DFNA7[m] migraine	1q21–q23
MRPS30	5p12[a,d]–5q11[a,b]	Leigh syndrome	5q11
MRPS31	13q13.3[b]–q14.11[d]	moebius syndrome 1	13q12.2–q13
MRPS33	7q34[b,c,d]	DFNB13[j]	7q34–q36
MRPS34	16p13.3[d]–16p13.13[c,d]		
MRPS35	12p11[b]–p11.2[c,d]	Parkinson disease 8 Alzheimer disease 5 Complex 1 deficiency	12p11.2–q13.1 12p11.23–q13.12
MRPS36	5q12.3[b]–q13.2[c,d]		

[a]STS-cytogenic mapping.[3]
[b]NCBI Human genome resources, Build 33 (http://www.ncbi.nlm.nih.gov/genome/seq/HsBlast.html)
[c]Human Genome Browser Gateway at UCSC (April 2003 freeze) http://genome.ucsc.edu/cgi-bin/hgGateway?org=human
[d]Rebhan et al.[69] http://bioinformatics.weizmann.ac.il/cards
[j]DFNB Deafness, autosomal recessive.
[k]Neuritis, with brachial predilection.
[l]Spinocerebellar ataxia with blindness and deafness.
[m]DFNA Deafness, autosomal dominant nonsyndromic sensorineural.
[n]Deafness, nonsyndromic, modifier 1.
[o]Corneal dystrophy and perceptive deafness 1.

bridization techniques. Gene map loci have been determined for all 78 human MRPs (Tables 1 and 2). Many of the MRPs map to loci associated with various developmental and sensorineural disorders. The consequences of mutations in MRPs are expected to range from lethality to marginally impaired energy metabolism. Mutations (or absence) of ribosome assembly proteins or other essential proteins, such as MRPL12, may be lethal due to the absence or inadequate amounts of functional mitochondrial ribosomes. MRPL12 is the initial binding site for elongation factors on the mitochondrial ribosome. Mutations of this protein may so impair ribosome function that products of mitochondrial protein synthesis are insufficient to maintain even a basal metabolic rate. Mutations that do not fully inactivate protein function may have intermediate, "crippling" effects, resulting in diminished oxidative phosphorylation capacity, with attendant growth and developmental anomalies. Mutations may also manifest in a tissue-specific manner, depending on special energy demands, resulting in neuropathies, myopathies, and developmental and sensorineural disorders. Mutations in tissue-specific MRP isoforms[48] may also impact selected tissues, giving rise to a spectrum of disorders.[1]

As inferred earlier, mitochondrial disorders can manifest in various phenotypic classifications. We see in Tables 1 and 2 that MRP genes are candidates for dwarfism, growth retardation, and limb deformity disorders such as Russell-Silver Syndrome,[49,50] Stuve-Wiedemann Syndrome,[51] and Moebius Syndrome I.[52] Metabolic disorders for which MRP genes associate by map position are Multiple Mitochondrial Dysfunctions,[53] Stuve-Wiedemann Syndrome,[51] Leigh Syndrome,[54] and diabetes. Candidate eye and ear disorders include Corneal Dystrophy and Perceptive Deafness,[55] Spinocerebellar Ataxia with blindness and deafness, Moebius Syndrome I,[52] Usher Syndrome, Type 1E,[56] DiGeorge Syndrome,[57] and nonsyndromic hearing losses (15 dominant and 7 autosomal recessive). Failure to maintain adequate ATP levels in cochlear hair cells, in the face of diminished oxidative phosphorylation capacity, may trigger mitochondrial apoptosis or necrosis in some or all of the stimulated hair cells, resulting in hearing loss. In this respect, it may not be surprising that many of the MRPs map to loci associated with nonsyndromic hearing loss. Cardiac disorders for which there may be a mitochondrial involvement are Dilated Cardiomyopathy, Dilated, 1E,[58] and DiGeorge Syndrome.[57] Muscle, nerve, and dementia disorders with mitochondrial involvement include Neuritis with Brachial Predilection,[59] spinocerebellar ataxia, Alzheimer Disease (AD), Parkinson disease, Spastic paraplegia 14,[60] and Vacuolar neuromyopathy.[61] Alzheimer disease and Parkinson disease has been included in our listing because susceptibility to these diseases has been associated with defects in mitochondrial DNA.[62,63] Similarly, there is a form of a maternally transmitted diabetes, with reduced mitochondrial protein synthesis in patients harboring a mitochondrial DNA deletion.[64] The association of reduced mitochondrial energy metabolism with susceptibility to diabetes is strengthened by the development of diabetes with reduced expression of the genes for mitochondrial energy metabolism.[65]

THERAPIES FOR OXIDATIVE PHOSPHORYLATION DISORDERS

There is no cure for disorders of oxidative phosphorylation. The best evidence for therapeutic benefit exists for exercise. Endurance training increases capillarization of muscle and the density of mitochondria in individual cells, whereas resistance training recruits satellite muscle cells into an active state of energy production.[66] In addition, a variety of drugs and dietary supplements have been used in attempts to treat, or at least modulate the course of OXPHOS disorders. In a select group of patients deficient in coenzyme Q10, replacement of coenzyme Q10 or its synthetic analogue idebenone can restore electron flow in the respiratory chain.[67] However, the efficacy of coenzyme Q10 (as an electron transfer mediator or antioxidant) in treating noncoenzyme Q10–deficient patients with OXPHOS disorders remains to be proven.[67] Likewise, the benefit of multiple other agents has been proclaimed in individual cases, but none has demonstrated utility in large, case-controlled studies of OXPHOS disorders. For complex I deficiency, bypass of this complex has been tried using electron transfer mediators such as succinate and triacylglycerol, or a high fat and low carbohydrate diet.[66] Supplement of nicotinamide has been theorized to provide increased NADH for complex I, and vitamin precursors or cofactors (e.g., riboflavin, thiamin, niacin, and vitamin K) may boost production of certain complexes of the respiratory chain.[66,68] Antioxidant use (e.g., vitamin C, vitamin E, or lipoic acid) remains popular to scavenge the free radicals that accumulate in patients with OXPHOS disorders.[68] Carnitine has long been used, as patients with OXPHOS disorders may be secondarily deficient in carnitine, in an attempt to prevent toxicity of acyl-coenzyme A.[66] Newer treatments include creatine monohydrate (potential alternative energy source of phosphocreatine), L-arginine (a vasodilator which may prevent stroke-like episodes inpatients with MELAS), and uridine (to replace a putative pyrimidine deficiency inpatients with oxidative phosphorylation disorders).[66]

CONCLUSION

The literature contains many examples of mitochondrial involvement in the presentation of seemingly diverse clinical situations. Our understanding of the interaction between the nuclear genome, i.e., gene products destined to function directly or indirectly with the mitochondrion, and the mitochondrial genome is increasing dramatically due to the growth in '*omics*: gen*omics*, prote*omics*, metabol*omics*, etc. We have attempted to integrate mitochondrial ribosomal proteins into this picture by suggesting that their expression and requirement for mitochondrial translation must be considered for possible involvement in clinical conditions. Variants in MRP genes should be studied for their association with various phenotypes or as ge-

netic modifiers of existing known gene mutations (mt-tRNA, mt-rRNA, etc.). Initially, this will be best studied in diagnostic in vivo animal models of mitochondrial translation. Lastly, one must consider nontranslational functions for MRPs such as their potential involvement in selective protein import, chaperoning the interactions between imported and locally synthesized mitochondrial subunits during assembly of OXPHOS complexes, and translational control of mitochondrial protein synthesis.

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