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Predicting the pathogenicity of aminoacyl-tRNA synthetase mutations

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ABSTRACT

Aminoacyl-tRNA synthetases (ARSs) are ubiquitously expressed, essential enzymes responsible for charging tRNA with cognate amino acids—the first step in protein synthesis. ARSs are required for protein translation in the cytoplasm and mitochondria of all cells. Surprisingly, mutations in 28 of the 37 nuclear-encoded human ARS genes have been linked to a variety of recessive and dominant tissue-specific disorders. Current data indicate that impaired enzyme function is a robust predictor of the pathogenicity of ARS mutations. However, experimental model systems that distinguish between pathogenic and non-pathogenic ARS variants are required for implicating newly identified ARS mutations in disease. Here, we outline strategies to assist in predicting the pathogenicity of ARS variants and urge cautious evaluation of genetic and functional data prior to linking an ARS mutation to a human disease phenotype.

Contents

1. Mutations in nuclear-encoded ARS enzymes cause human inherited disease

Aminoacyl-tRNA synthetases (ARSs) are ubiquitously expressed, essential enzymes that charge tRNA molecules with cognate amino acids in the cytoplasm and mitochondria. The human nuclear genome harbors 37 ARS loci: 17 that encode a cytoplasmic enzyme, 17 that encode a mitochondrial enzyme, and three that encode a bi-functional enzyme that charges tRNA for both cytoplasmic and mitochondrial protein translation [1]. One of the more interesting, albeit perplexing, findings in ARS research is that mutations in many of the genes encoding these enzymes cause myriad tissue-specific human diseases. As such, determining

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Table 1
ARS Loci implicated in human disease.

Gene	Locus	Location of Protein Function	Mode of Inheritance	Disease Phenotype(s)	References
AARS	16q22	Cytoplasm	Autosomal dominant	CMT2N	[12,34,94]
			Autosomal recessive	EEIE29	
AARS2	6p21.1	Mitochondria	Autosomal recessive	Mitochondrial Infantile CMP	[63,75]
				Leukoencephalopathy with ovarian failure	
CARS2	13q34	Mitochondria	Autosomal recessive	COXPD27	[45]
DARS	2q21.3	Cytoplasm	Autosomal recessive	HBSL	[8]
DARS2	1q25.1	Mitochondria	Autosomal recessive	LBSL	[4]
EARS2	16p12.2	Mitochondria	Autosomal recessive	LTBL	[3]
				COXPD12	
FARS2	6p25.1	Mitochondria	Autosomal recessive	COXPD14	[5,95,96]
				SPG77	
GARS	7p15	Cytoplasm & Mitochondria	Autosomal dominant	CMT2D	[10,97]
			Autosomal recessive	dSMA-V	
				Myalgia, CMP	
HARS	5q31.3	Cytoplasm	Autosomal dominant	CMT2W	[14,98]
			Autosomal recessive	Usher Syndrome 3B	
HARS2	5q31.3	Mitochondria	Autosomal recessive	Perrault Syndrome 2	[6]
IARS	9q22.31	Cytoplasm	Autosomal recessive	Intellectual disability, growth retardation, muscular hypotonia	[47]
IARS2	1q41	Mitochondria	Autosomal recessive	CAGSSS; Leigh Syndrome	[77]
KARS	16q23.1	Cytoplasm & Mitochondria	Autosomal recessive	RI-CMTB	[48,99,100]
				DFNB89	
				Visual impairment, microcephaly, DD, seizures	
LARS	5q32	Cytoplasm	Autosomal recessive	Infantile hepatopathy	[101]
LARS2	3p21.31	Mitochondria	Autosomal recessive	Perrault syndrome 4	[50,64]
				HLASA	
MARS	12q13.3	Cytoplasm	Autosomal dominant	CMT2U[1]	[52,102]
			Autosomal recessive	ILLD	
MARS2	2q33.1	Mitochondria	Autosomal recessive	Spastic Ataxia 3	[53,103]
				COXPD25	
NARS2	11q14.1	Mitochondria	Autosomal recessive	COXPD24	[79]
PARS2	3p21.31	Mitochondria	Autosomal recessive	Alpers syndrome	[78]
QARS	3p21.31	Cytoplasm & Mitochondria	Autosomal recessive	MSCCA	[54]
RARS	5q34	Cytoplasm	Autosomal recessive	HLD9	[7]
RARS2	6q16.1	Mitochondria	Autosomal recessive	PCH6	[55]
SARS2	19q13.2	Mitochondria	Autosomal recessive	HUPRA Syndrome	[56]
TARS2	1q21.2	Mitochondria	Autosomal recessive	COXPD21	[57]
VARS	6p21.33	Cytoplasm	Autosomal recessive	Severe DD, microcephaly, seizures	[104]
VARS2	6p21.33	Mitochondria	Autosomal recessive	COXPD20	[57,105,106]
				Encephaloardiomyopathy	
YARS	1p35.1	Cytoplasm	Autosomal dominant	DI-CMTC	[18,107]
			Autosomal recessive	Multi-system disease, DD, FTT	
YARS2	12p11.21	Mitochondria	Autosomal recessive	MLASA2	[58]

Notes: CAGSSS: Cataracts, growth hormone deficiency, sensory neuropathy, sensorineural hearing loss, and skeletal dysplasia; CMP: Cardiomyopathy; CMT2D: Charcot Marie Tooth disease type 2D; CMT2N: Charcot Marie Tooth disease type 2N; CMT2U: Charcot Marie Tooth disease type 2U; CMT2W: Charcot Marie Tooth disease type 2W; COXPD12: Combined oxidative phosphorylation deficiency 12; COXPD20: Combined oxidative phosphorylation deficiency 20; COXPD21: Combined oxidative phosphorylation deficiency 21; COXPD24: Combined oxidative phosphorylation deficiency 24; COXPD25: Combined oxidative phosphorylation deficiency 25; DD: Developmental delay; DI-CMT: Dominant-intermediate Charcot Marie Tooth disease; dSMA-V: distal spinal muscular atrophy type V; EEIE29: Epileptic encephalopathy, early infantile, 29; FTT: failure to thrive; HBSL: Hypomyelination with brainstem and spinal cord involvement and leg spasticity; HLASA: Hydrops, lactic acidosis and sideroblastic anemia; HLD9: hypomyelinating leukodystrophy 9; HUPRA: Hyperuricemia, pulmonary hypertension, renal failure, and alkalosis; ILLD: Interstitial lung and liver disease; LBSL: Hypomyelination with brainstem and spinal cord involvement and elevated lactate; LTBL: Leukoencephalopathy with thalamus and brainstem involvement and high lactate; MLASA2: myopathy, lactic acidosis, and sideroblastic anemia; MSCCA: Progressive microcephaly, intractable seizures, and cerebral and cerebellar atrophy; PCH6: pontocerebellar hypoplasia type 6; RI-CMTB: Recessive-intermediate Charcot Marie Tooth disease type B; SPG77: spastic paraplegia 77.

[1] While missense variants in *MARS* have been identified in patients with CMT, the genetic evidence is not strong enough to conclude, at this point, that this gene is associated with CMT disease.

the genetic heterogeneity of ARS-related disease and the pathogenic mechanism of each disease-associated ARS mutation will be important for patient diagnosis, prognosis, and treatment. As the number of ARS mutations implicated in human disease rises, it is important to reflect on our current knowledge of the consequences of ARS mutations so that the pathogenicity of newly identified alleles can be carefully evaluated.

To date, mutations in 28 aminoacyl-tRNA synthetase (ARS) genes have been implicated in a spectrum of inherited, single-gene (Mendelian) human disorders (Table 1) [2]. Genes encoding mitochondrial ARSs have been implicated in recessive syndromes, while those encoding cytoplasmic ARSs have been implicated in both recessive and dominant disorders. Not surprisingly, mutations in genes encoding mitochondrial ARS enzymes often cause phenotypes in tissues with high metabolic demands such as the brain, muscle, and liver, similar to pathogenic mutations in mitochondrial genes and in other nuclear genes that encode mitochondrial proteins. For example, mutations in mitochondrial glutamyl-(*EARS2*) and aspartyl-tRNA synthetase (*DARS2*) cause autosomal recessive leukoencephalopathy [3,4], and mutations in mitochondrial phenylalanyl-tRNA synthetase (*FARS2*) have been associated with liver disease, encephalopathy, and lactic acidosis [5]. However, mutations in other mitochondrial ARS enzymes appear to cause tissue-restricted phenotypes; for example, mutations in mitochondrial histidyl-tRNA synthetase (*HARS2*) cause autosomal recessive ovarian dysgenesis and sensorineural hearing loss [6].

Similar to mitochondrial ARSs, mutations in genes encoding cytoplasmic ARS enzymes cause a spectrum of recessive syndromes, many of which include neurological phenotypes (Table 1). For example, arginyl-(*RARS*) and aspartyl-tRNA synthetase (*DARS*) mutations cause autosomal recessive hypomyelination in the