Title: Congenital Myasthenic Syndromes *GeneReview* – Less Common Genetic Causes
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Less Common Genetic Causes of Congenital Myasthenic Syndromes

AGRN

Gene structure. The complete cDNA of *AGRN* comprises 36 exons. Agrin mRNA undergoes cell-specific alternative splicing at several sites. An amino acid insert of the isoform secreted by motor neurons is required for MuSK activation and for formation of the neuromuscular junction.

Pathogenic allelic variants. A homozygous pathogenic variant, c.5125G>C (p.Gly1709Arg) was identified in two affected sibs from a consanguineous family by Huzé et al [2009]. Subsequently, pathogenic biallelic variants (missense, nonsense, and a genomic deletion) have been reported in a further seven individuals from five families. Determining the pathogenicity of some variants, including c.5023G>A (p.Gly1675Ser) identified homozygous in one affected individual [Karakaya et al 2014], will require further studies.

A 0.48-Mb deletion encompassing the entire gene *AGRN* as well as surrounding genes, was found in *trans* with c.226G>A (p.Gly76Ser) in two affected individuals from one family [Nicole et al 2014].

Table 7. Selected *AGRN* Pathogenic Allelic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.226G>A	p.Gly76Ser	NM_198576.3 NP_940978.2
c.314A>T	p.Asn105Ile	
c.1057C>T	p.Gln353Ter	
c.1362dupC	p.Ser455GlnfsTer8	
c.5023G>A	p.Gly1675Ser	
c.5125G>C	p.Gly1709Arg	
c.5179G>T	p.Val1727Phe	
c.5611G>A	p.Gly1871Arg	
0.48-Mb deletion encompassing all of *AGRN*		

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org). See Quick Reference for an explanation of nomenclature.

1. Variant designation that does not conform to current naming conventions

Normal gene product. The protein (NP_940978.2) has 2045 amino acids. Agrin is a heparan sulfate proteoglycan that has been shown to bind to laminins via its amino-terminal domain 14 and to interact via its carboxy-terminal part with LRP4 and a-dystroglycan. Agrin is a neuronal aggregating factor that induces the aggregation of acetylcholine receptors and other postsynaptic proteins on muscle fibers and is crucial for the formation of the neuromuscular junction. Agrin activates the MuSK by binding and activating the postsynaptic LRP4-MuSK-DOK7 complex to recruit downstream signaling components, which triggers the local aggregation and synthesis of postsynaptic acetylcholine receptors (AChRs) and other postsynaptic proteins, such as the cytoskeletal protein rapsyn.

Abnormal gene product. Missense variants in *AGRN* have been shown to result in production of abnormal agrin protein. The p.Gly1709Arg substitution results in abnormal agrin that is expressed and localized correctly in patient muscle, but results in overall disturbed organization of the neuromuscular junction, affecting both the pre- and postsynaptic regions.

The C-terminal missense variant p.Val1727Phe [Maselli et al 2012] has been shown to impair the ability of agrin to activate MuSK and cluster AChRs, together with increased binding to alpha-dystroglycan but decreased binding to a neural (z+) agrin-specifc antibody. Nicole et al [2014] described two missense variants (p.Gly76Ser and p.Asn105Ile) in the N-terminal agrin domain, which reduced acetylcholine receptors clustering activity of agrin in vitro. Both missense variants are found as compound heterozygotes with a null allele (c.1362dupC; p.Ser455GlnfsTer8 and a 0.48-Mb deletion encompassing all of *AGRN*).

MUSK

Gene structure. *MUSK* comprises 14 exons.

Pathogenic allelic variants. Chevessier et al [2004] identified two heteroallelic pathogenic variants (frameshift and missense) in an individual with CMS. Muscle biopsy showed dramatic pre- and postsynaptic structural abnormalities of the neuromuscular junction and severe decrease in acetylcholine receptor (AChR) epsilon-subunit and MuSK expression [Chevessier et al 2004]. To date, *MUSK* pathogenic variants have been reported in eight individuals with CMS from three families [Chevessier et al 2004, Mihaylova et al 2009, Maselli et al 2010].

Normal gene product. *MUSK* encodes the postsynaptic muscle-specific receptor tyrosine kinase (MuSK; muscle, skeletal receptor tyronsine-protein kinase). MuSK plays an essential role in the agrin-MuSK-rapsyn pathway in organizing the postsynaptic scaffold and in inducing the high concentration of AChR and tyrosine kinases of the ErB family in the postsynaptic membrane.

Abnormal gene product. Expression studies of mutant constructs have indicated that the frameshift prevents MuSK expression; that the missense variant diminishes the expression and stability of MuSK but not its kinase activity; and that overexpression of

the missense mutant in mouse muscle results in decreased EP AChR and aberrant axonal outgrowth [Chevessier et al 2004].

SCN4A

Gene structure. *SCN4A* (NM_000334.4) comprises 24 exons.

Pathogenic allelic variants. One individual with CMS and two heteroallelic *SCN4A* pathogenic variants c.4325T>A and c.737C>T has been identified [Tsujino et al 2003]. An affected individual homozygous for a c.4360C>T missense variant has also been reported [Habbout et al 2016].

Table 8. Selected *SCN4A* Pathogenic Allelic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.737C>T	p.Ser246Leu	NM_000334.4 NP_000325.4
c.4325T>A	p.Val1442Glu	
c.4360C>T	p.Arg1454Trp	

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

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Normal gene product. The reference sequence NP_000325.4 has 1836 amino acids. *SCN4A* encodes the sodium channel protein type 4 subunit alpha ($Na_v1.4$), which mediates the voltage-dependent sodium ion permeability of the postsynaptic membrane to generate and propagate an action potential.

Abnormal gene product. Expression studies in HEK cells revealed that the Na channel with the p.Val1442Glu substitution showed marked enhancement of fast inactivation close to the resting potential and enhanced use-dependent inactivation on high frequency stimulation; that with the p.Ser246Leu substitution showed only minor kinetic abnormalities, suggesting that it is a benign variant. $Na_v1.4$ expression at the endplates and over the sarcolemma was normal by immunocytochemical criteria [Tsujino et al 2003].

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