Title: Congenital Myasthenic Syndromes *GeneReview* – AChR Subunit Genes
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AChR Subunit Genes: *CHRNA1*, *CHRNB1*, *CHRND*, *CHRNE*

CMS with kinetic abnormalities of the acetylcholine receptor (slow-channel syndromes and fast-channel syndromes) is caused by pathogenic variants in the acetylcholine receptor subunit genes *CHRNA1*, *CHRNB1*, *CHRND*, and *CHRNE*. Two major kinetic abnormalities of AChR, resulting in slow-channel syndromes and fast-channel syndromes, have emerged. The two kinetic syndromes are physiologic and morphologic opposites and call for different therapeutic modalities.

Gene structure. The *CHRNA1* reference sequence NM_000079.3 comprises ten exons. The *CHRNB1* reference sequence NM_000747.2 comprises 11 exons. The *CHRND* reference sequence NM_000751.1 comprises 12 exons. The *CHRNE* reference sequence NM_000080.3 comprises 12 exons.

Pathogenic allelic variants

Slow-channel syndrome. Slow-channel syndromes are caused by dominant gain-of-function variants. To date, several autosomal dominant missense variants have been described [Ohno & Engel 2004, Engel & Sine 2005, Navedo et al 2006, Shen et al 2006]. Pathogenic variants have been identified in different AChR subunits and in different functional domains of the subunits. Several pathogenic variants are located in the transmembrane domains (M2 domains of α, β, δ, and ε subunits, and in the M1 domain of the α, β, and ε subunit) or in the extracellular domain of the α and ε subunit (OMIM).

Fast-channel syndrome. The fast-channel CMSs are caused by recessive loss-of-function variants. A number of fast-channel variants have been identified [Ohno & Engel 2004, Engel & Sine 2005, Palace et al 2012]. The pathogenic variants are located in different functional domains of the AChR α, β, and δ subunit. Usually, the mutated allele causing the kinetic abnormality is accompanied by a null variant in the second allele. In all cases, the kinetic mutation dominates the clinical phenotype.

Normal gene product. The five homologous subunits of the adult AChR (two α subunits, and one each of β, δ, and ε) each have a large N terminal extracellular domain and four transmembrane segments (M1-M4); the M2 domain lines the cation-selective pore.

The proteins encoded by these genes:

- *CHRNA1* (NP_000070.1) comprises 457 amino acids.
- *CHRNB1* (NP_000738.2) comprises 501 amino acids.
- *CHRND (*NP_000742.1) comprises 517 amino acids.
- *CHRNE (*NP_000071.1) comprises 493 amino acids.

Abnormal gene product

Slow-channel syndrome. Patch-clamp studies of mutant AChR channels reveal prolonged activation episodes of the AChR in the presence of ACh. This results in prolonged endplate currents and potentials, exceeding the refractory period of the muscle fiber action potential. Therefore, a single nerve stimulus elicits one or more repetitive CMAPs as described in Harper & Engel [1998]. During physiologic activity, the prolonged endplate potentials may undergo staircase summation, producing a depolarization block. Moreover, these factors cause cationic overloading of the junctional sarcoplasm resulting in myopathic changes with loss of AChR from degenerating junctional folds and altered endplate geometry with widening of the synaptic space and subsynaptic alterations.

Fast-channel syndrome. In this subtype of CMS with kinetic abnormalities of the AChR, the channel-opening events are abnormally brief and there are usually fewer activation episodes. Fast-channel pathogenic variants affect one or more of the following functions of AChR: affinity for ACh, efficiency of gating, and stabilization of channel kinetics. Endplate studies reveal normal or reduced AChR numbers. The structural integrity of the postsynaptic membrane is preserved. The common electrophysiologic features are rapidly decaying endplate currents, abnormally brief channel activation periods, and a reduced quantal response owing to the reduced probability of channel opening.

Acetylcholine receptor deficiency with or without minor kinetic abnormality: caused by pathogenic variants in the acetylcholine receptor subunit genes *CHRNA1*; *CHRNB1*; *CHRND*; *CHRNE*

Pathogenic allelic variants. The AChR subunits in individuals with CMS have numerous homozygous or, more frequently, compound heterozygous pathogenic variants that result in a reduced number of functional AChRs at the postsynaptic membrane. These low-expressor or null variants have been reported in all subunits of the adult AChR. However, they are concentrated in the ε subunit and especially in its long cytoplasmic M3/M4 linker.

To date, more than 50 ε subunit pathogenic variants have been reported [Ohno & Engel 2004, Engel & Sine 2005].

Most such pathogenic variants are nonsense, splice site, or frameshift variants resulting in a premature termination of the translational chain.

Missense variants alter residues essential for assembly (e.g., glycosylation sites, the cystine loop) or in the signal peptide, also resulting in reduced gene expression. Some missense variants affecting AChR gene expression also have accompanying kinetic effects.

Single nucleotide variants of a regulatory element (N-box) in the AChRε promoter region have been shown to result in reduced gene expression [Nichols et al 1999, Ohno et al 1999, Abicht et al 2002].

A chromosomal microdeletion of 1290 bp encompassing parts of *CHRNE* has been shown to result in CMS [Abicht et al 2002].

One particular single nucleotide variant in the AChRε subunit (c.1327delG) resulting in endplate AChR deficiency has been shown to be common (~50%) in affected individuals of Romany and/or southeastern European ethnic origin [Abicht et al 1999, Karcagi et al 2001, Morar et al 2004].

Another pathogenic variant in the AChRε subunit (c.1353dupG) is frequent in the Maghreb (especially Algeria and Tunisia), likely because of an ancient founder effect [Beeson et al 2005].

Normal gene product. The five homologous subunits of the adult AChR (two α-subunits, and one each of β, δ, and ε) each have a large N-terminal extracellular domain and four transmembrane segments (M1-M4); the M2 domain lines the cation-selective pore.

Abnormal gene product. Morphologic studies of endplates show an increased number of endplate regions distributed over an increased span of the muscle fiber. The integrity of the junctional folds is preserved, but AChR expression on the folds is patchy and faint. The fetal type γ subunit may partially compensate for absence of the ε subunit, thereby producing a less severe phenotype.

See Table 4. Selected *CHRNE* Pathogenic Allelic Variants.

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