

Congenital Myasthenic Syndrome (CMS)

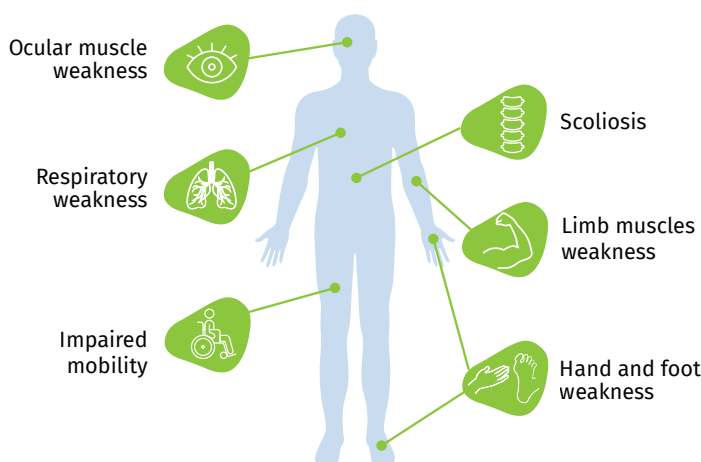
CMS are rare and heterogenous disorders caused by gene variants that impair various aspects of neuromuscular transmission.^{1,2}

Clinical Manifestations

All CMS subtypes cause fatigable weakness, but onset, distribution, symptoms, and treatment response vary with the genetic defect impairing NMJ transmission.³

- Can be characterized by abnormal fatigability, or transitory or permanent weakness of extraocular, facial, bulbar, truncal, respiratory, or limb muscles⁴
- Features may overlap with congenital myopathies, muscular dystrophies, myasthenia gravis, and mitochondrial disorders⁵⁻⁷

Symptoms can include: ⁸⁻¹²



Select Postsynaptic CMS Genetic Subtypes

CMS course of disease and severity are highly variable and may depend on the underlying genetic variant.^{13,14,a} The *DOK7*, *MUSK*, *LRP4*, and *AGRN* genetic subtypes are among the most common forms of postsynaptic CMS; these specific mutations impact postsynaptic AChR clustering.⁴

	DOK7	LRP4	MUSK	AGRN
Synaptic Location 	Postsynaptic ²	Postsynaptic ²	Postsynaptic ²	Synaptic/Postsynaptic ²
Age of Onset 	Birth to early adulthood ⁸	Birth to adolescence ^{9,10}	Birth to adolescence ¹¹	Birth to early adulthood ¹²
Disease Burden 	Wheelchair dependence ¹³ 33% (n=4/12) ventilations ¹⁵ 33% (n=4/12) feeding difficulties ¹⁵	66.7% (n=2/3) wheelchair dependence ^{9,16} 100% (n=2/2) respiratory insufficiency ⁹ 50% (n=1/2) chewing and swallowing difficulties ⁹	50% (n=2/4) difficulties walking ¹¹ 45% (n=9/20) respiratory insufficiency ¹¹ 100% (n=1/1) swallowing impairment ¹³	66.7% (n=4/6) difficulties walking ^{12,17,18} 33.1% (n=2/6) respiratory insufficiency ^{12,17,18} 20% (n=1/5) swallowing impairment ^{12,17,18}

^aDue to the rarity of CMS, level of evidence is limited to smaller case series/case studies; long-term natural history studies in patients with CMS are limited and are descriptive rather than systematic.¹⁵

In a retrospective study of 34 adult patients with CMS, 32 patients were previously misdiagnosed with other disorders¹⁹

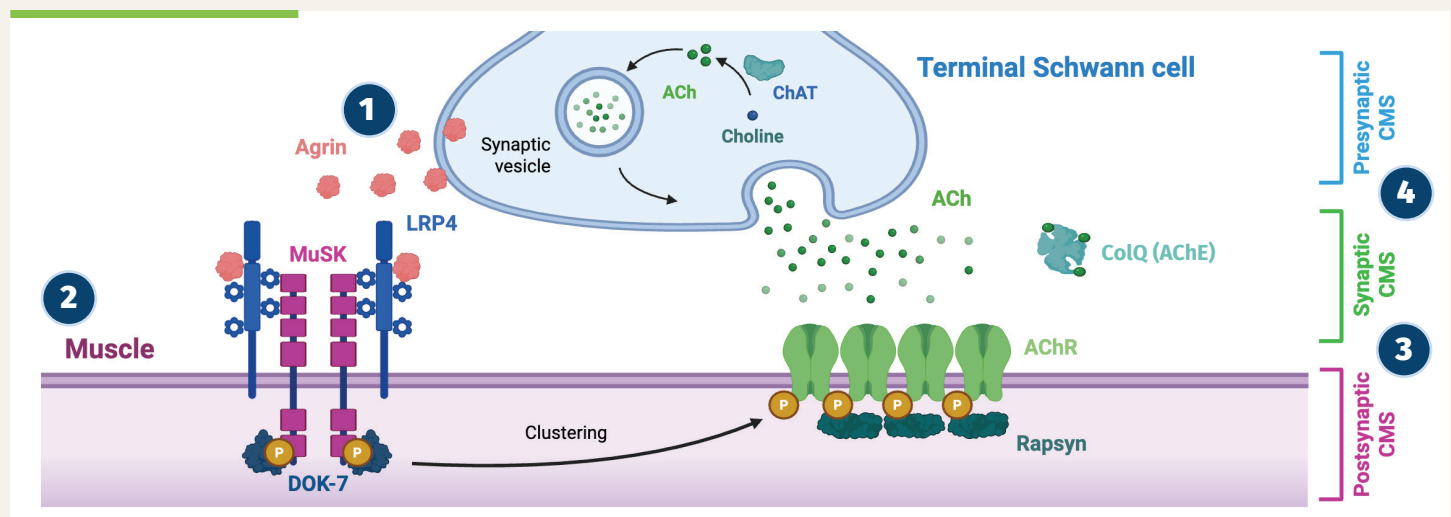


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Sites of Neuromuscular Junction Dysfunction in CMS⁷

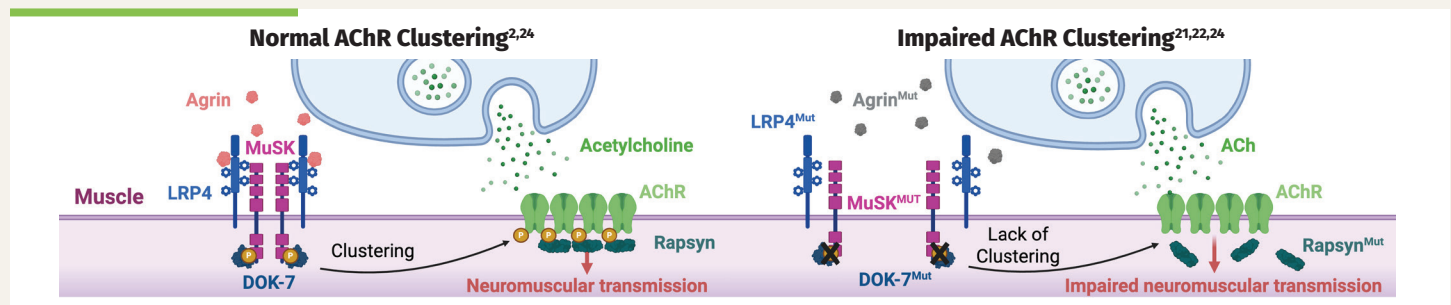
NMJ signal transduction involves complex pathways of many signaling molecules and receptors, and defects in one of these key elements can lead to the muscle fatigability of CMS.⁷

- **Step 1:** During NMJ signaling, AGRIN is secreted from neurons and binds LRP4, which in turn activates MuSK²
- **Step 2:** Recruitment of DOK7 furthers MuSK phosphorylation, resulting in binding of RAPSIN to AChRs^{2,20}
- **Step 3:** RAPSIN causes AChRs to anchor and cluster on the postsynaptic membrane²
- **Step 4:** ColQ interacts with MuSK to anchor AChE in the synapse^{2,21}



General Pathophysiology of Defective AChR Clustering in CMS²

Variants in *DOK7*, *MUSK*, *AGRN*, *LRP4*, or *RAPSN* can impair the MuSK signaling pathway and cause aberrantly small and simplified neuromuscular synapses by impairing AChR clustering^{10,16-18,21-24}



Abbreviations: AChE, acetylcholinesterase; AChR, acetylcholine receptor; AGRN, agrin; CMS, congenital myasthenic syndrome; ColQ, collagen-like tail subunit (of acetylcholinesterase); DOK7, docking protein 7; LRP4, low-density lipoprotein receptor-related protein 4; MUSK, muscle-specific kinase; Mut, mutation; NMJ, neuromuscular junction; RAPSN, receptor-associated protein of the synapse.

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