Asparagine 88 to lysine (N88K), a prevalent congenital myasthenic syndrome mutation of rapsyn, impairs neuromuscular junction by disrupting agrin signaling

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Neuromuscular junctions (NMJ) are a synapse between motoneurons and skeletal muscles, where acetylcholine receptors (AChRs) are concentrated to control muscle contraction. Studies of this synapse have contributed to our understanding of synapse assembly and pathological mechanisms of neuromuscular disorders. Nevertheless, underlying mechanisms of NMJ formation was not well understood. To this end, we took a novel approach – studying mutant genes implicated in congenital myasthenic syndrome (CMS). We showed that knock-in mice carrying N88K, a prevalent CMS mutation of rapsyn, died soon after birth with profound NMJ deficits. Rapsyn is an adapter protein that bridges AChRs to the cytoskeleton and possesses E3 ligase activity. In investigating how N88K impairs the NMJ, we uncovered a novel signaling pathway by which agrin-LRP4-MuSK induces tyrosine phosphorylation of rapsyn, which is required for its self-association and E3 ligase activity. Our results also provide insight into pathological mechanisms of CMS.