# Congenital myasthenic syndromes (CMS)

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Congenital myasthenic syndromes (CMS) form a heterogeneous group of rare diseases characterized by fatigable muscle weakness. They are genetically-inherited and caused by defective synaptic transmission at the cholinergic neuromuscular junction (NMJ). The number of genes known to cause CMS when mutated is currently 30, and the relationship between fatigable muscle weakness and defective functions is quite well-understood for many of them. However, some of the most recent discoveries in individuals with CMS challenge our knowledge of the NMJ, where the basis of the pathology has mostly been investigated in animal models. Frontier forms between CMS and congenital myopathy, which have been genetically and clinically identified, underline the poorly understood interplay between the synaptic and extrasynaptic molecules in the neuromuscular system. In addition, precise electrophysiological and histopathological investigations of individuals with CMS suggest an important role of NMJ plasticity in the response to CMS pathogenesis. While efficient drug-based treatments are already available to improve neuromuscular transmission for most forms of CMS, others, as well as neurological and muscular comorbidities, remain resistant. Taken together, the available pathological data point to physiological issues which remain to be understood in order to achieve precision medicine with efficient therapeutics for all individuals suffering from CMS.

It is a group of conditions characterized by muscle weakness (myasthenia) that worsens with physical exertion. The muscle weakness typically begins in early childhood but can also appear in adolescence or adulthood. Facial muscles, including muscles that control the eyelids, muscles that move the eyes, and muscles used for chewing and swallowing, are most commonly affected. However, any of the muscles used for movement (skeletal muscles) can be affected in this condition. Due to muscle weakness, affected infants may have feeding difficulties. Development of motor skills such as crawling or walking may be delayed. The severity of the myasthenia varies greatly, with some people experiencing minor weakness and others having such severe weakness that they are unable to walk.

Some individuals have episodes of breathing problems that may be triggered by fevers or infection. Severely affected individuals may also experience short pauses in breathing (apnea) that can lead to a bluish appearance of the skin or lips (cyanosis).

The prevalence of congenital myasthenic syndrome is unknown. At least 600 families with affected individuals have been described in the scientific literature.

Mutations in many genes can cause congenital myasthenic syndrome. Mutations in the CHRNE gene are responsible for more than half of all cases. A large number of cases are also caused by mutations in the RAPSN, CHAT, COLQ, and DOK7 genes. All of these genes provide instructions for producing proteins that are involved in the normal function of the neuromuscular junction. The neuromuscular junction is the area between the ends of nerve cells and muscle cells where signals are relayed to trigger muscle movement.

Gene mutations lead to changes in proteins that play a role in the function of the neuromuscular junction and disrupt signaling between the ends of nerve cells and muscle cells. Disrupted signaling between these cells results in an impaired ability to move skeketal muscles,  muscle weakness, and delayed development of motor skills. The respiratory problems in congenital myasthenic syndrome result from impaired movement of the muscles of the chest wall and the muscle that separates the abdomen from the chest cavity (the diaphragm).

Mutations in other genes that provide instructions for proteins involved in neuromuscular signaling have been found to cause some cases of congenital myasthenic syndrome, although these mutations account for only a small number of cases. Some people with congenital myasthenic syndrome do not have an identified mutation in any of the genes known to be associated with this condition.

This condition is most commonly inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

Rarely, this condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. In some cases, an affected person inherits the mutation from one affected parent.  Other cases result from new mutations the gene and occur in people with no history of the disorder in their family.