DOK7

Docking protein 7 encoded by the DOK7 gene is essential for neuromuscular synaptogenesis [1].

The protein functions in aneural activation of MuSK (muscle-specific receptor kinase), which is required for postsynaptic differentiation, and in the subsequent clustering of the acetylcholine receptor in myotubes. This protein can also induce autophosphorylation of muscle-specific receptor kinase. Mutations in this gene are a cause of familial limb-girdle myasthenia autosomal recessive, which is also known as congenital myasthenic syndrome type 1B. Alternative splicing results in multiple transcript variants.

In Congenital Myasthenic Syndromes with Predominant Limb Girdle Weakness (LG-CMS) some of the currently used drugs can either ameliorate or aggravate the symptoms depending on the underlying genetic defect. The drug most frequently used for the treatment of CMS is pyridostigmine an acetylcholinesterase inhibitor. However, pyridostigmine is not effective or is even detrimental in DOK7- and COLQ-related LG-CMS, while beta-adrenergic agonists (ephedrine, salbutamol) show some sustained benefit. Standard clinical trials may be difficult, but standardized follow-up of patients and international collaboration may help to improve the standards of care of these conditions [2].

A 61-year-old female and her older sister showed bilateral ptosis, facial and proximal limb weakness, and scoliosis since childhood. Another female sibling had milder signs, while other family members were asymptomatic. Facial nerve repetitive stimulation in the proband showed decrement of muscle responses. Single fiber EMG revealed increased jitter and blocking. Muscle biopsy showed type 2-fiber atrophy, without tubular aggregates. Mutational analysis in the three affected siblings revealed two compound heterozygous mutations in DOK7: c.1457delC, that predicts p.Pro486Argfs*13 and truncates the protein C-terminal domain, and c.473G>A, that predicts p.Arg158Gln and disruption of the dok7-MuSK interaction in the phosphotyrosine binding (PTB) domain. Unaffected family members carried only one or neither mutation.

Two of the affected sisters showed marked improvement with salbutamol treatment, which illustrates the benefits of a correct diagnosis and treatment of DOK7-CMS [3].

Hua et al., llustrated that the expression of Dok7 was downregulation in human glioma tissues. Dok7 overexpression significantly inhibits proliferation and colony formation in vitro, and the xenograft tumor formation in vivo. In addition, 5-Azacitidine-2'-deoxycytidine (5-Aza), a DNA methylation inhibitor, preventing the loss of Dok7 expression by decreasing aberrant hypermethylation of Dok7 promoter in glioma cells. More importantly, DNMT1 knockdown induced the demethylation of Dok7 promoter, and enhanced the expression of Dok7 in gliomas. These results suggest that epigenetic silencing of Dok7 may provide a novel glioma treatment strategy [4].

References

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