Myotonia congenita

Myotonia congenita (MC) is a skeletal muscle hyper-excitability disorder caused by loss-of-function mutations in the ClC-1 chloride channel. Mutations are scattered over the entire sequence of the channel protein, with more than 30 mutations located in the poorly characterized cytosolic C-terminal domain. In this study, we characterized, through patch clamp, seven ClC-1 mutations identified in patients affected by MC of various severity and located in the C-terminal region. The p.Val829Met, p.Thr832Ile, p.Val851Met, p.Gly859Val, and p.Leu861Pro mutations reside in CBS2 domain, while p.Pro883Thr and p.Val947Glu are in the C-terminal peptide. We showed that the functional properties of mutant channels correlated with the clinical phenotypes of affected individuals. In addition, we defined clusters of ClC-1 mutations within CBS2 and C-terminal peptide sub-domains that share the same functional defect: mutations between 829 and 835 residues and in residue 883 induced an alteration of voltage dependence, mutations between 851 and 859 residues and in residue 947 induced a reduction of chloride currents, whereas mutations on 861 residue showed no obvious change in ClC-1 function. This study improves our understanding of the mechanisms underlying MC, sheds light on the role of the C-terminal region in ClC-1 function and provides information to develop new antimyotonic drugs [1)].

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Altamura C, Lucchiari S, Sahbani D, Ulzi G, Comi GP, D'Ambrosio P, Petillo R, Politano L, Vercelli L, Mongini T, Dotti MT, Cardani R, Meola G, Lo Monaco M, Matthews E, Hanna MG, Carratù MR, Conte D, Imbrici P, Desaphy JF. The analysis of myotonia congenita mutations discloses functional clusters of amino acids within CBS2 domain and C-terminal peptide of ClC-1 channel. Hum Mutat. 2018 Jun 23. doi: 10.1002/humu.23581. [Epub ahead of print] PubMed PMID: 29935101.