

Identifying the Cause of Phenotypic Variability in a Family with Non-Dystrophic Myotonia

D.Raja Rayan¹, A.Haworth², R.Sud², S.McCall², S.V.Tan¹, S.Durran¹, M.Davis² & M.G.Hanna¹

1. MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, Queen Square, London WC1N 3BG,
2. Neurogenetics Unit, National Hospital for Neurology and Neurosurgery, UCLH trust,

Non-dystrophic Myotonia (NDM) is the commonest group of skeletal muscle channelopathies often causing severe myotonia in patients. It is either caused by mutations in the skeletal muscle chloride channel gene, *CLCN1*, or the sodium channel gene, *SCN4A* resulting in increased membrane excitability. An important unexplained issue in NDM is the significant phenotypic variability seen between patients with the same mutation and even within the same pedigree. We investigated the cause of this phenotypic variability in a pedigree with one line of severely affected individuals and another line of mildly affected individuals.

We tested the genes known to be associated with myotonia in both the severely and mildly affected individuals in this pedigree. Sequencing of the sodium channel gene, *SCN4A*, revealed that all affected individuals carried the known mutation c.3917G>T; p.Gly1306Val, consistent with a diagnosis of Paramyotonia Congenita. Sequencing of *CLCN1* in all affected individuals also revealed the presence of a mutation known to cause Myotonia Congenita in exon 8, c.938C>T; p.Ala313Val in the severely affected individuals. This mutation was absent in the mildly affected individuals. In this pedigree the phenotypic variability is therefore most likely due to the double hit of two myotonia-causing mutations in different genes. This suggests that it is important to sequence all myotonia genes in patients with marked phenotypic variability.

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Conflicts of interest

Nothing to declare