CLCN1 Mutation is Acting as a Modifier Gene in an Italian DM2 Family with Juvenile Onset

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Introduction: Some unrelated DM2 (Myotonic Dystrophy type 2) families have been reported with heterozygous recessive *CLCN1* mutations and recent data indicate that co-segregation of *CLCN1* mutations in DM2 patients is higher than expected. Aim: The purpose of this study is to investigate if a putative CLCN1 mutation could explain the severe myotonia in an Italian DM2 family with juvenile onset. Methods: We report clinical, histopathological and biomolecular findings on a DM2 14-year-old female with juvenile onset of myotonia and on her affected mother with a more severe phenotype despite a later onset of symptoms. Results: Muscle histopathology correlated with disease severity or age at onset in both patients. Southern blot on both muscle and blood samples revealed only a small increase in the CCTG repeat number through maternal transmission. Fluorescence in situ hybridization, in combination with MBNL1 immunofluorescence on muscle sections, showed the presence of nuclear foci of mutant mRNA and MBNL1. Splicing analysis of the *INSR*, *CLCN1* and *MBNL1* genes in muscle tissue demonstrated that the level of aberrant splicing isoforms was lower in the daughter than in the mother. However, a heterozygous mutation c.501C>G p.F167L in the *CLCN1* gene was present in the daughter's DNA and found to be maternally inherited. Conclusion: Although the age at onset was earlier in the daughter than in the mother, the daughter's histopathological and biomolecular findings did not show greater severity than those observed in her mother thus not explaining the unusual young onset in the daughter. The co-segregation of DM2 with a recessive *CLCN1* mutation provided the explanation for the unusual clinical findings i.e. severe myotonia. In conclusion, this study demonstrates that when clinical features in DM2 are uncommon, additional genes and/or modifying factors need to be explored to account for the phenotype.