

**P009** Aberrant splicing of skeletal muscle chloride channel (CIC-1) in proximal myotonic myopathy (PROMM)  
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Proximal myotonic myopathy (PROMM) is an autosomal dominant disorder caused by an untranslated CCTG repeat expansion in intron 1 of the zinc finger 9 gene (ZNF9) on chromosome 3. This disease is characterized by a myotonia, muscle fibers degeneration, cataracts, defective cardiac conduction and insulin resistance. Dysregulation of pre-mRNA alternative splicing has been demonstrated for several genes. Myotonia can be caused by a loss of function of the muscle specific chloride channel (CIC-1). In muscle from patients with PROMM we identified a shorter variant of CIC-1-mRNA with exons 6 and 7 spliced out. The ratio of RT-PCR products suggested that very little of the normal CIC-1 mRNA was produced in PROMM skeletal muscle tissue. This splicing variant contains a premature termination codon at position 236 that prevents expression of full length CIC-1 protein. Heterologous expression does not yield functional channels. Expression of CCTG-repeats in C2C12 cells reproduces the aberrant splicing of CIC-1 observed in PROMM skeletal muscle. We propose that this disruption in alternative splicing regulation of CIC-1 directly correlates with myotonia, a cardinal symptom of myotonic dystrophy.