An animal model for Charcot-Marie-Tooth disease type 4B1

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Charcot-Marie-Tooth disease (CMT) comprises a family of clinically and genetically very heterogeneous hereditary peripheral neuropathies and is one of the most common inherited neurological disorders. We have generated a mouse model for CMT type 4B1 using embryonic stem cell technology. To this end, we introduced a stop codon into the Mtmr2 locus within exon 9, at the position encoding amino acid 276 of the MTMR2 protein (E276X). Concomitantly, we have deleted the chromosomal region immediately downstream of the stop codon up to within exon 13. The resulting allele closely mimics the mutation found in a Saudi Arabian CMT4B1 patient. Animals homozygous for the mutation showed various degrees of complex myelin infoldings and outfoldings exclusively in peripheral nerves, in agreement with CMT4B1 genetics and pathology. Mainly, paranodal regions of the myelin sheath were affected, with a high degree of quantitative and qualitative variability between individuals. This pathology was progressive with age, and axonal damage was occasionally observed. Distal nerve regions were more affected than proximal parts, in line with the distribution in CMT. However, we found no significant electrophysiological changes, even in aged (16-month-old) mice, suggesting that myelin infoldings and outfoldings per se are not invariably associated with detectable electrophysiological abnormalities. Our animal model provides a basis for future detailed molecular and cellular studies on the underlying disease mechanisms in CMT4B1. Such an analysis will reveal how the disease develops, in particular, the enigmatic myelin infoldings and outfoldings as well as axonal damage, and provide mechanistic insights that may aid in the development of potential therapeutic approaches.
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