Abstract

In 2002, we identified LMNA as the first gene responsible for an autosomal recessive axonal form of Charcot-Marie-Tooth disease, AR-CMT2A. All patients were found to be homozygous for the same mutation in the LMNA gene, p.Arg298Cys. In order to investigate the physiopathological mechanisms underlying AR-CMT2A, we have generated a knock-in mouse model for the Lmna p.Arg298Cys mutation. We have explored these mice through an exhaustive series of behavioral tests and histopathological analyses, but were not able to find any peripheral nerve phenotype, even at 18 months of age. Interestingly at the molecular level, however, we detect a downregulation of the Lmna gene in all tissues tested from the homozygous knock-in mouse Lmna $^{R298C/R298C}$ (skeletal muscle, heart, peripheral nerve, spinal cord and cerebral trunk). Importantly, we further reveal a significant upregulation of Pmp22, specifically in the sciatic nerves of Lmna $^{R298C/R298C}$ mice. These results indicate that, despite the absence of a perceptible phenotype, abnormalities exist in the peripheral nerves of Lmna $^{R298C/R298C}$mice that are absent from other tissues. Although the mechanisms leading to deregulation of Pmp22 in Lmna $^{R298C/R298C}$ mice are still unclear, our results support a relation between Lmna and Pmp22 and constitute a first step toward understanding AR-CMT2A physiopathology