The distal hereditary motor neuropathies (dHMNs) are a heterogeneous group of neurodegenerative disorders affecting the lower motoneuron. In a family with both autosomal-dominant dHMN and dHMN type V (dHMN/dHMN-V) present in three generations, we excluded mutations in all genes known to be associated with a dHMN phenotype through Sanger sequencing and defined three potential loci through linkage analysis. Whole-exome sequencing of two affected individuals revealed a single candidate variant within the linking regions, i.e., a splice-site alteration in REEP1 (c.304-2A>G). A minigene assay confirmed complete loss of splice-acceptor functionality and skipping of the in-frame exon 5. The resulting mRNA is predicted to be expressed at normal levels and to encode an internally shortened protein (p.102_139del). Loss-of-function REEP1 mutations have previously been identified in dominant hereditary spastic paraplegia (HSP), a disease associated with upper-motoneuron pathology. Consistent with our clinical-genetic data, we show that REEP1 is strongly expressed in the lower motoneurons as well. Upon exogeneous overexpression in cell lines we observe a subcellular localization defect for p.102_139del that differs from that observed for the known HSP-associated missense mutation c.59C>A (p.Ala20-Glu). Moreover, we show that p.102_139del, but not p.Ala20Glu, recruits atlastin-1, i.e., one of the REEP1 binding partners, to the altered sites of localization. These data corroborate the loss-of-function nature of REEP1 mutations in HSP and suggest that a different mechanism applies in REEP1-associated dHMN.