The genotypic and phenotypic spectrum of SPG31

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Mutations in the receptor expression enhancing protein 1 (REEP1) have recently been reported to cause autosomal dominant hereditary spastic paraplegia (HSP) type SPG31. In a large collaborative effort, we screened a sample of 535 unrelated HSP patients for *REEP1* mutations and copy number variations. We identified 13 novel and two known *REEP1* mutations in 16 families and sporadic patients by direct sequencing analysis. Twelve out of sixteen mutations were small insertions, deletions, or splice site mutations. These changes would result in shifts of the open-reading-frame followed by premature termination of translation and haploinsufficiency. Copy number variation analysis in a subset of 133 HSP index patients revealed a large duplication of *REEP1* that involved exons 2-7 in an Irish family. Interestingly, we identified two disease associated variations in the 3'-UTR of *REEP1* that fell into highly conserved micro RNA binding sites. Clinically most SPG31 patients present with a pure spastic paraplegia; rare complicating features were restricted to symptoms or signs of peripheral nerve involvement. SPG31 has an early age at onset in the majority of patients. The overall mutation rate in our clinically heterogeneous sample was 3.0%; however, in the sub-sample of pure HSP *REEP1* mutations accounted for 8.2% of all patients. These results firmly establish *REEP1* as a relatively frequent autosomal dominant HSP gene for which genetic testing is warranted. We also establish haploinsufficiency as the main molecular genetic mechanism in SPG31, which should initiate and guide functional studies on *REEP1* with a focus on loss-of-function mechanisms.