Mutation in the neuronal voltage-gated sodium channel SCN1A in familial hemiplegic migraine.

BACKGROUND: Familial hemiplegic migraine is an autosomal dominant severe subtype of migraine with aura characterised by some degree of hemiparesis during the attacks. So far, mutations in two genes regulating ion translocation-CACNA1A and ATP1A2-have been identified in pedigrees with this disease.

METHODS: To identify additional genes for familial hemiplegic migraine, we did a genome-wide linkage analysis of two disease pedigrees without mutations in CACNA1A and ATP1A2. Ion channel genes in the candidate interval were analysed for mutations, and the functional consequences of the recorded sequence alteration were determined.

FINDINGS: We identified a novel locus for familial hemiplegic migraine on chromosome 2q24. Sequencing of candidate genes in this region revealed a heterozygous missense mutation (Gln1489Lys) in the neuronal voltage-gated sodium channel gene SCN1A, mutations of which have been associated with epilepsy. This same mutation was present in three families with familial hemiplegic migraine. It results in a charge-altering aminoacid exchange in the so-called hinged-lid domain of the protein, which is critical for fast inactivation of the channel. Whole-cell recordings in transiently transfected tsA201 cells expressing the highly homologous SCN5A sodium channel showed that the mutation...
induces a two-fold to four-fold accelerated recovery from fast inactivation without altering any of the other channel parameters investigated. INTERPRETATION: Dysfunction of the neuronal sodium channel SCN1A can cause familial hemiplegic migraine. Our findings have implications for the understanding of migraine aura. Moreover, our study reinforces the molecular links between migraine and epilepsy, two common paroxysmal disorders.