203 MECHANISMS OF DISEASE IN THE HYPEREKPLEXIAS

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Aims To identify mutations associated with hyperekplexia and to investigate the underlying pathophysiological mechanism of novel mutations identified, whilst providing a genetic diagnosis of hyperekplexia in the cases referred.

Method As part of an ongoing screening program we have analysed the entire coding regions of GLRA1, GLRB and SLC6A5 in 234 hyperekplexia patients referred to our screening project. All sequence variants were regarded as mutations after exclusion from a panel of human controls. The expression and functional properties of novel GLRA1 variants were analysed using immunocytochemistry and patch-clamp electrophysiology.

Results Direct sequencing analysis of GLRA1, GLRB and SLC6A5 revealed mutations in 98 (98/234, 42%) individuals. The majority of mutations were identified in GLRA1 accounting for 60% (59/98) of gene-positive cases. Consistent with previous studies, recessive inheritance was more common. Functional analysis revealed trafficking defects as the major mechanism underlying recessive mutations, whereas dominant mutations primarily affected functional ion channel properties.

Conclusion Novel mutations in GLRA1, GLRB and SLC6A5 were identified contributing to the compendium of reported hyperekplexia mutations. Underlying pathophysiological effects of the novel glycinergic mutations were determined, providing evidence for ion channel disruption, trafficking defects, leaky tonic currents, and loss of function effects.