Mutations in the glycine receptor α1 subunit (GLRA1) gene in hereditary hyperekplexia pedigrees: evidence for non-penetrance of mutation Y279C

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Editor—Hereditary hyperekplexia, or familial startle disease (OMIM 149400), is a rare neurological disease that is characterised by marked muscular hypertonia in affected infants and an exaggerated response or “startle” reflex to an unexpected stimulus. Positional candidate analysis has successfully identified the gene coding for the α1 subunit of the inhibitory glycine receptor (GLRA1) on chromosome 5q33-35 as the disease gene.1 The glycine receptor (GlyR) is a ligand gated chloride channel which mediates synaptic inhibition in the spinal cord and other brain regions.2 The majority of inherited mutations have been found in exons 6 and 7 of the GLRA1 gene, which code for the first and second transmembrane (TM) domains of the receptor.3 At present, six missense mutations, P250T,4 Q266H,4 R271L,4 R271Q4,5 K276E,5 and Y279C,6 are inherited in a dominant manner. Two mutations, I244N7 and a deletion of exon 6 to 6 of the GLRA1 gene,8 can also result in a recessive phenotype, as detected in affected offspring of consanguineous parents. Finally, there are compound mutations (R252H and a glutamine residue at codon position 271 (R271Q). This mutation is located at the extracellular end of the chloride channel domain of the receptor and results in a marked decrease in sensitivity to glycine.11–13 The mutation was inherited in an autosomal domi-
nant manner and with complete penetrance of the mutant GLRA1 allele, as all the R271Q mutation carriers were affected. In family 2, affected subjects had a missense mutation at nucleotide position 1216 (A to G), which substitutes a tyrosine with a cysteine residue at codon position 279 (Y279C). This mutation is situated in the short extracellular domain between transmembrane domains 2 and 3 and has been reported to disrupt the ability of the receptor to convert agonist binding to channel activity. In contrast to the R271Q mutation in family 1, there appeared to be incomplete penetrance of the Y279C mutation as one clearly unaffected subject, II.3, carried the mutation and transmitted it to her affected children (III.9 and III.10).

**Discussion**

This is the first report of a non-penetrant hyperekplexia mutation and only the second non-penetrant mutation described for the ligand gated ion channel receptor superfamily. Incomplete penetrance has also been observed in autosomal dominant nocturnal frontal lobe epilepsy, which is caused by the S284F missense mutation in the neuronal nicotinic acetylcholine receptor α4 subunit. The presence of four obligate carriers of the S284F mutation in a large pedigree with 21 affected members suggests that there are compensatory mechanisms which can override the receptor defect. In the mouse, the inheritance of a homozygous microdeletion of the Ghr1 gene (oscillator mutation) leads to the complete lack of GlyRα1 protein in the spinal cord of the animal and is lethal. A similar deletion mutation has been described in humans. However, the homozygous offspring of a consanguineous mating suffered only from typical hyperekplexia symptoms suggesting that the loss of the GlyR α1 protein can also be compensated for to some degree in humans. The observation of the escapee in the family 2 pedigree supports this hypothesis. In the postsynaptic membrane, the glycine receptor exists as a complex with other molecules such as the cytoskeletal protein gephyrin, which may modulate the effect of agonist binding and channel activity. The actions of the other major inhibitory neurotransmitter γ-aminobutyric acid (GABA) may also partially compensate for the loss of GlyR function as hyperekplexia is effectively treated with benzodiazepines. Thus, it is possible that environmental or genetic factors effectively compensate for the pathogenic effects of the Y279C mutation in the observed non-penetrant escapee. The elucidation of these factors will have important implications for the understanding of synaptic neurotransmission.

This work was supported by the Australian National Health and Medical Research Council (Block Grant 993050).

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**Figure 1** Sequence analysis of the GLRA1 gene in two hereditary hyperekplexia pedigrees. The probands (indicated by arrows) are part of two complex three generational pedigrees. Asterisks indicate family members screened for the presence of missense mutations in the GLRA1 gene. (A) A missense mutation (R271Q) in the GLRA1 gene of Fam-1 pedigree. The presence of the mutation is indicated by a double peak (G and A) in the sequence electropherograms of affected (Aff) subjects and not in normal (Norm) members. (B) Missense mutation (Y279C) in the GLRA1 gene of the Fam-2 pedigree. Sequence analysis of exon 7 of the GLRA1 gene showed an unaffected obligate carrier (II.3) of the mutation.


