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 hypotonia 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.  

The glycine receptor (GlyR) is a ligand gated chloride channel which mediates synaptic inhibition in the spinal cord and other brain regions. 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. At present, six missense mutations, P250T, Q266H, R271L, R271Q, K276E, and Y279C, are inherited in a dominant manner. Two mutations, I244N and a deletion of exon 1 to 6 of the GLRA1 gene, can also result in a recessive phenotype, as detected in affected offspring of consanguineous parents. Finally, there are compound mutations (R252H and R392H) which, when inherited from the two parental alleles, give rise to hyperekplexia. In this report, we analysed the GLRA1 gene as the candidate for the disease locus in two families with hereditary hyperekplexia.

Case reports

The first pedigree (Fam-1) contains 20 members over three generations with 10 affected subjects (fig 1A). The female proband (III.13) from family 1 was prone to fall in response to any unexpected stimulus, such as a touch or a sharp sound, from the time she started walking. Falling was the result of momentary generalised stiffness of her trunk and limbs with loss of postural control. This symptom was present in a large number of male and female relatives, as shown in fig 1A, consistent with autosomal dominant inheritance of the disorder. Falling in affected members of the family was sudden, unpredictable, and uncontrollable. Falling was not accompanied by loss of consciousness and affected members were able to rise from the ground immediately after falling. The diagnosis of hyperekplexia was made after publication of the paper by Morley et al. The proband was treated with clonazepam and remained symptomless for over 13 years.

The second pedigree (Fam-2) contains 10 members over three generations with five affected members (fig 1B). The proband (III.10) was a white female who had generalised hypertonia, jerks, irritability, constant crying, and divergent squint during the neonatal period (from 2 days of age). She started to walk at 1 year 2 months with frequent falls, mostly forwards. Nasal percussion or sounds elicited jerks. She is currently aged 12 years and even with 2 mg/day clonazepam still presents with mild hypertonia of the limbs and jerks as before. The proband’s 10 year old brother (III.9) presented at 6 days of age with generalised hypertonia, convergent strabismus (squint), and jerks on percussion of the dorsal nose. He started to walk at the same age as his sister, falling frequently, and has difficulty with fine motor activity. He has learning disabilities for which he is in a special class. He currently is treated with clonazepam but still presents with moderate hypertonia of the limbs and jerks on nasal percussion. The mother of the two children (II.3) is healthy and has never had any of the symptoms observed in either of her children.

Genomic DNA was isolated from peripheral leukocytes from a sample of pedigree members (fig 1). Since the majority of reported hyperekplexia mutations occur in exons 6 and 7 of the GLRA1 gene, we used primers to PCR amplify 332 bp and 280 bp products from genomic DNA templates. PCR products were sequenced directly on both strands using fluorescent Big-Dye terminator chemistry (PE Biosystems, NJ, USA). As shown in fig 1A, the affected subjects of family 1 were heterozygous for a missense mutation at nucleotide position 1192 (G to A), which substitutes an arginine with 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. 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, a subject 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.

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