Letter to the Editor

Mutation in the connexin 50 gene (GJA8) in a Russian family with zonular pulverulent cataract

To the Editor:

Hereditary cataract is a genetically heterogeneous disease. At least nine loci responsible for this disease have been localized, and three genes were clearly identified, namely γC-crystallin (CRYGC), βB2-crystallin (CRYBB2) and connexin 50 (GJA8), as responsible for hereditary cataract in humans. Two mutations have been found in γC-crystallin in families with cataract (1, 2), and one mutation was described in the βB2-crystallin gene (3). In the connexin 50 gene two different mutations were found in large British (4) and Pakistani (5) families, and disease phenotypes in these two families were slightly different. Thus, only a few cataract-causing mutations are known in humans, and every new mutation adds important information about the disease mechanism. Here we describe a new mutation in the connexin 50 gene in a family with zonular pulverulent cataract.

Materials and methods

A three-generation family with three affected individuals was investigated. DNA samples from two affected (mother and son), two unaffected and two spouses were available. Clinical examination revealed pulverulent cataract in all affected. The proband, who is the youngest affected in the family, had onset of the disease at 3 years. At that time, the proband had a normal iris and transparent cornea of 11 mm in diameter. The opacity was not homogeneous, and consisted of opaque particles of different sizes, most of them very small, which identified the cataract as pulverulent (Fig. 1). Opaque particles were distributed unequally in a disc of 5 mm in diameter, which was localized in the center of the lens. Additionally, there was a slightly cloudy inhomogeneous area of 2 mm in diameter in the posterior pole region. Progression of the disease was symmetrical in both eyes. Ultrasound, electrophysiological, biochemical and clinical investigations did not reveal any other pathology of the eye or other organs. The mother of the proband has a similar phenotype.

Results

Because the phenotype of the disease in this family is similar to that of families with described mutations in the connexin 50 gene, we tested the linkage of the disease in the family with two markers tightly flanking the connexin 50 locus, namely D1S2696 and D1S252. The disease segregated perfectly with a specific haplotype in the family (Fig. 2) with a maximal multipoint LOD score of 0.9 at the D1S252. The coding region of the connexin 50

Fig. 1. Photograph of the lens of the proband with zonular pulverulent cataract.
gene was screened by single strand conformation polymorphism (SSCP) for possible DNA alterations. A mobility shift was found in a fragment corresponding to 574–805 nucleotides of the gene (according to sequence with accession number AF217524, also corresponds to nucleotide numbering in (4)). Sequencing revealed a T→G alteration at position 741, which results in Ile247Met substitution.

This alteration destroys the HindI restriction site. This enzyme was used for confirmation of the mutation and for the screening of others. A T741→G nucleotide substitution was found in two available affected members of the family, but in none of their unaffected relatives, nor was it found in 50 chromosomes from 25 healthy unrelated individuals.

Discussion
As with all other connexins, connexin 50 has four transmembrane domains (M1–M4) with both N- and C-ends of the protein oriented to the cytoplasm. The exact positions of the membrane-spanning domains have been predicted by HMM Top Prediction of Transmembrane Helices and Protein Topology server (http://www.enzim.hu/hmmtop/) as amino acids 24–45 (M1), 75–94 (M2), 150–171 (M3) and 202–221 (M4). The first reported connexin 50 mutation, Pro88Ser, is located in the second transmembrane domain. It was found in a large English family with zonular pulvulent cataract (4). The second mutation, Glu48Lys, was found in a large Pakistani family (5). This mutation results in an amino acid change in the first external loop. Patients with this mutation have a phenotype distinct from the English family, with nuclear localization of opaque particles. Ile247Met mutation found in this study falls in the last intracellular domain (Fig. 3). Both the isoleucine and the methionine belong to the same group of neutral amino acids with a nonpolar side chain. However, several mutations of this kind in intra- and extracellular domains in a related connexin 32 gene
were found to cause a disease phenotype (<http://molgen-www.uia.ac.be/CMTMutations/>). To our knowledge, this is the third mutation in the connexin 50 gene described so far.

Fig. 3. Predicted connexin-50 membrane topology indicating location of known mutations. N, amino terminus; M1–M4, membrane-spanning domains; C, carboxyl terminus. Previously described mutations are marked as an open circle, the mutation described in this article is marked as a black circle.

References


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