A New Locus for Autosomal Dominant Congenital Cataracts Maps to Chromosome 3

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PURPOSE. To map a gene for cataracts in a family with congenital nuclear and sutural cataracts and to examine candidate genes in the linked region.

METHODS. A large family with autosomal dominant congenital nuclear and sutural cataracts was identified and characterized. A genome-wide screen was conducted with a set of markers spaced at 10- to 15-cM intervals, and linkage was assessed using standard LOD score analysis.

RESULTS. Fifteen (15) affected individuals were identified. This form of congenital cataracts maps to a 12-cM region on chromosome 3q21.2-q22.3 between markers D3S3674 and D3S3612, with a maximum multipoint LOD score of 6.94 at D3S1273. The crystallin gene, CRYGS, was excluded as a candidate gene for this locus.

CONCLUSIONS. There are now more than 12 different genetic loci that cause congenital cataracts. The most recent locus to be identified is on chromosome 3q21.2-q22.3, in a family with congenital nuclear and sutural cataracts. (Invest Ophthal Vis Sci. 2000;41:36–39)

Cataracts refer to the loss of transparency in the crystallin lens of the eye. The opaque appearance behind the pupil is due to changes in proteins within the lens fibers. Congenital cataracts are among the most prevalent major eye diseases and frequently cause blindness in infants. They can occur as a primary disorder, or secondarily in association with multisystem disorders, such as Down’s syndrome, galactosemia, Wilson’s disease, and myotonic dystrophy.

Approximately half of all cases of congenital cataracts are familial, and autosomal dominant congenital cataracts (ADCC) appear to be the most common form. At least 15 loci have been reported for various primary forms of ADCC. Hejtmancik et al. reviewed nine, and the others were reported more recently. Although some of these forms exhibit distinct phenotypes, there is substantial phenotypic overlap.

We have been studying a family with ADCC, and we present evidence for linkage to chromosome 3q. Three loci in the region are discussed as potential candidate loci for this ADCC locus.

METHODS

Family and Clinical Data

The family comprised 15 affected and more than 15 unaffected individuals across three generations (Fig. 1). Participants gave informed consent to the study protocol, which was approved by the institutional review board of Oregon Health Sciences University and which conforms to the tenets of the Declaration of Helsinki. DNA was available for 31 family members (12 affected, 13 unaffected, and 6 spouses).

Affected family members had congenital nuclear and sutural cataracts that varied in severity among different individuals. Many had had bilateral cataract surgery during early childhood, often at ages 3 to 5 years, but occasionally in the late teens. Several family members never had surgery, even in the presence of moderate sutural and nuclear opacities. One 20-year-old woman with visual acuities of 20/40 OD and 20/30 OS had striking anterior and posterior sutural opacities with some smaller scattered whitish cortical opacities and radially oriented fine vacuoles.

DNA Analysis

Typing with microsatellite markers was performed as previously described. We conducted a full genome scan using a panel of markers spaced at approximately 10-cM intervals (Weber Screening Set 8; Research Genetics, Huntsville, AL; http://www.resgen.com/).

Primers for amplification of a 144-bp segment of CRYGS were designed from the partial cDNA sequence of human CRYGS (GenBank accession number L36869; available at http://ncbi.nlm.nih.gov/). Primer sequences were CRYGS/f: TGTGCAGATTTCATCCAACGCTGGTATTCAG.

Linkage Analysis

Linkage analysis was conducted using the computer program VITESSE. We assumed autosomal dominant inheritance of a rare gene (frequency 0.0001), with nearly complete penetrance (0.95). Because symptoms occur early in childhood, no age correction for penetrance was required. Marker allele frequencies were assumed to be equal. Map locations and distances were based on data obtained at the Genetic Location Database [Southampton, UK (http://cedar.genetics.soton.ac.uk/)].

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FIGURE 1. Pedigree of the ADCC family and haplotypes with chromosome 3 markers from D3S3674 to D3S3612 (the order of the markers is indicated in the box in the upper left corner). (■) Affected individuals; (■□) unaffected individuals; (?) unknown phenotype. The haplotype segregating with the disease is boxed. Critical crossovers in individuals II-6 (D3S1309–D3S3612) and IV-3 (D3S3674–D3S1292) define the region containing the new ADCC locus on chromosome 3q.

FIGURE 2. Results of the chromosome 3 multipoint linkage analysis. The maximum multipoint LOD score (6.94) occurs at D3S1293. Markers and intermarker distances are indicated on the horizontal axis.
RESULTS

After excluding large regions of the genome, we obtained positive LOD scores for markers on chromosome 3q21.2-q22.3 that span approximately 12 cM. The maximum two-point LOD was obtained at D3S1273 (6.65 at $w = 0$). The markers, their map location, and two-point LOD scores are shown in Table 1.

Haplotype data are given in Figure 1. A crossover between D3S3674 and D3S1292 in individual IV-3 defines the proximal border of the region, and one between D3S1309 and D3S3612 in individual II-6 defines the distal border. Results of multipoint analysis are presented in Figure 2. The maximum multipoint LOD score (6.94) occurs across the 0.4-cM region from D3S1292 to D3S1273, and the 1-LOD-unit confidence interval extends from D3S3674 to D3S3612. This region corresponds to 3q21.3-q22.2 on the cytogenetic map (Genetic Location database), illustrated in Figure 3. All affected individuals have an affected parent, and there are no unaffected individuals who carry the disease haplotype. Thus, penetrance appears to be virtually complete in this family.

Crystallin genes are obvious candidate genes for cataracts, because they function as major structural proteins in the lens. Mutations in crystallin genes have been shown to cause ADCC in human families and in several rodent groups.2,5,8–10 Because the $gamma$-crystallin gene $CRYGS$ maps to chromosome 3,11 we considered it a candidate gene for the chromosome 3 ADCC locus. Because regional localization of $CRYGS$ has not been reported, we used radiation hybrid mapping to localize this gene on the chromosome. Mapping was accomplished by screening the Genebridge 4 radiation hybrid panel (Research Genetics) with primers $CRYGS/f$ and $CRYGS/r$. The results are shown in Table 2. $CRYGS$ maps in proximity, but probably distal to WI9695, the most telomeric marker on the framework radiation hybrid map of chromosome 3q. Because this location is more than 60 cM distal to the cataract gene in our family, we excluded it as a candidate gene for this ADCC locus.

DISCUSSION

Hess et al.12 localized a gene, $LIPI-L$, for the protein CP47 to chromosome 3q21-q25. CP47 is a component of the beaded filament, a cytoskeletal structure that is abundant in lens fiber cells and is an excellent candidate gene for ADCC. We are currently mapping this gene on a radiation hybrid panel to localize it more precisely; if it localizes to the critical region for ADCC reported here, we will scan it for mutations.

Recently, Ranum et al.13 mapped a second myotonic dystrophy locus ($DM2$) to an 8-cM region from D3S3674 distal to...
D3S3637 (map position 146.38; Genetic Location Database). This region overlaps our ADCC region and includes D3S1273, the locus with the maximum LOD score. Cataracts are frequently associated with DM (MIM 160900; Online Inheritance in Man, Baltimore, MD, http://www.ncbi.nlm.nih.gov/Omim/), although they are not generally congenital. Although none of the individuals in this ADCC family manifest any other symptoms associated with myotonic dystrophy, it is possible that a particular mutation in the DM2 gene gives rise only to ophthalmologic symptoms.

The murine autosomal dominant cataract mutation Coc maps to a region of mouse chromosome 16 that is syntenic with human chromosome 3q21-q2414; therefore, it may be homologous to the human cataract locus described in this report.

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References