Autosomal dominant congenital cataract in a Libyan Jewish family: cosegregation with a reciprocal chromosomal translocation \([t(3;5)(p22.3; p15.1)]\)

Emre Zafer, Jeanne Meck, Liora Gerrad, Elon Pras, Moshe Frydman, Orit Reish, Isaac Avni, Eran Pras

1Department of Obstetrics and Gynecology, Georgetown University, Washington, DC; 2Sheba Medical Center, Danek Gartener Institute of Human Genetics, Tel Hashomer, Israel; 4Department of Human Genetics, Assaf Harofeh Medical Center, Zerifin, Israel; 5Department of Ophthalmology, Assaf Harofeh Medical Center, Zerifin, Israel

Purpose: To describe a Jewish family of Libyan ancestry in which autosomal dominant congenital cataract segregates with an apparently balanced reciprocal chromosomal translocation.

Methods: Detailed family history and clinical data were recorded. Cytogenetic studies were performed on 13 family members.

Results: Embryonal cataracts cosegregated through three generations with a balanced chromosomal translocation \([t(3;5)(p22.3; p15.1)]\) while the unbalanced translocation product, 46,XY,-5,+der(5)t(3:5)(p22:p15.1), had multiple congenital anomalies without cataracts.

Conclusions: These observations suggest that an altered function of a gene at one of the translocation breakpoints on chromosome 3p22.3 or 5p15.1 is causally related to cataract development.

Congenital cataracts are common disorders of the eye that often cause visual impairment or blindness in children [1,2]. At least one-third of the cases are familial. Congenital cataracts are most commonly inherited as an autosomal dominant trait, but autosomal recessive and X-linked inheritance patterns have also been reported [3]. Hereditary nonsyndromic congenital cataracts are extremely heterogeneous and are usually considered to be the result of single gene mutations [1]. The presence of associated abnormalities in other organ systems marks the syndromic cataracts, which in turn can be caused by Mendelian disorders, chromosomal abnormalities, or nongenetic factors (e.g., environmental). A unique and rare subgroup among syndromic cataract is associated with chromosomal rearrangements, which are often accompanied by multiple malformations and a family history of recurrent pregnancy losses [4]. While linkage studies in families with hereditary cataracts have been the most fruitful method for the identification of cataract loci, occasionally these were identified by studying families in which cataract cosegregated with marker chromosomes [5-8]. Furthermore, defining the translocation breakpoints in these families may help in cloning the underlying causative gene [9,10], thus providing further insight into normal lens development and cataract formation.

In this report, we present a Libyan Jewish family in which congenital cataracts segregated with a balanced reciprocal chromosomal translocation \((t(3:5)(p22.3;p15.1))\).

METHODS

We have studied a three-generation Libyan Jewish family (56091) manifesting vertical transmission of congenital cataract (adCC; OMIM 604219) and a history of multiple spontaneous abortions and perinatal child deaths (Figure 1). Hospital records indicated that the cataracts were bilateral, presumably present at birth with only a minor effect on visual acuity. Karyotype results from one miscarried 11-week-old fetus (5609133) and two malformed newborns (5609127 and 5609131) with multiple congenital anomalies showed the same unbalanced translocation 46,XY,-5,+der(5)(t(3:5)(p22:p15.1)).

In an attempt to inquire whether the family phenotypes are related to a chromosomal rearrangement, we recruited 10 additional family members for cytogenetic and ophthalmic examinations. The study protocol was approved by the Sheba Medical Center Helsinki Committee and all participants gave informed consent.

Participants underwent a detailed ophthalmologic examination, which included slit lamp biomicroscopy and photography of the cataract lenses (when possible), at Assaf Harofeh Genetic Eye Clinic, Zerifin, Israel.

Correspondence to: Eran Pras, MD, Department of Ophthalmology, Assaf Harofeh Medical Center, Zerifin, Israel, 70300; Phone: 972-8-9779358; FAX: 972-3-6354788; email: eranpras@gmail.com
peripheral blood lymphocytes, amniotic fluid cells, or cultured skin fibroblasts [11]. Twenty metaphases were counted for each individual.

RESULTS
The cataracts (Figure 2) were confined to the embryonic lens nucleus with dense sutural opacity surrounded by white concentric punctuate opacities. Other compartments of the lens were relatively clear. They were evident in 10 members of the family (Figure 1); six of whom (5609108, 5609113, 5609115, 5609116, 5609117, 5609133, 5609106, 5609122, 5609135, 5609123, 5609127, 5609125, and 5609131). Squares: males; circles: females; filled symbols: congenital cataract affected individuals; diagonal lines through symbols: deceased family members; triangles: miscarried embryos.

DISCUSSION
Cosegregation of the cataract and the balanced translocation in this family suggests that a gene located in or remotely influenced by regulatory sites at one of the translocation breakpoints is causally related to the cataract. Previous studies have mapped a recessive congenital cataract gene to chromosome 3p23–3p21.3 and 3p22.1–3p14.2 in both
Palestinian and Lebanese Arab families, respectively [12,13]. A review of their linkage data suggests an overlapping region between polymorphic markers D3S3685 and D3S2409, which correspond to the 3p22.1–3p21.3 segment. A cataract-related gene, glutathione peroxidase (GPX1; OMIM 138320), is located at this region. It was demonstrated that GPX1 knockout mice develop focal lens opacities at an early age that progress to mature cataract after 15 months, indicating a role of GPX1 in lens antioxidant defense mechanism [14]. However, sequencing its coding region failed to reveal any disease-related mutation. Distal 5p does not harbor any known cataract loci. The unbalanced chromosomal rearrangement leads to partial trisomy 3p and partial monosomy 5p without cataract. Thus, the haploinsufficiency of an altered gene product at 3p22 may be a plausible explanation for the observed ocular phenotype in the balanced translocation carriers and the lack of cataract in the unbalanced carriers. Cloning of the translocation breakpoint may allow eventual identification of a novel cataract gene and ascertain whether the previously reported cataract loci and the present one are allelic.

ACKNOWLEDGMENTS

The authors thank the members of the family for their participation.

REFERENCES

1. Hejtmancik JF, Smaoui N. Molecular genetics of cataract. Dev Ophthalmol 2003; 37:67-82. [PMID: 12876830]
2. Robinson GC, Jan JE, Kinnis C. Congenital ocular blindness in children, 1945 to 1984. Am J Dis Child 1987; 141:1321-4. [PMID: 3687875]
3. Foster A, Johnson GJ. Magnitude and causes of blindness in the developing world. Int Ophthalmol 1990; 14:135-40. [PMID: 2188914]
4. Jamieson RV, Gaunt L, Donnai D, Black GC, Kerr B, Steeko O, Black GC. Chromosomal translocation in a family with ocular anomalies: indications for karyotype analysis. Br J Ophthalmol 2003; 87:646-8. [PMID: 12714415]
5. Reese PD, Tuck-Muller CM, Maumenee IH. Autosomal dominant congenital cataract associated with chromosomal translocation. Arch Ophthalmol 1987; 105:1382-4. [PMID: 3662912]
6. Moross T, Vaithilingam SS, Styles S, Gardner HA. Autosomal dominant anterior polar cataracts associated with a familial 2;14 translocation. J Med Genet 1984; 21:52-3. [PMID: 6694185]
7. Monteleone JA, Monteleone PL. Cataracts as a manifestation of chromosomal aberration syndromes, inborn errors of metabolism, and malformation syndromes. Pediatr Ann 1977; 6:115-22. [PMID: 834478]
8. Rubin SE, Nelson LB, Fletcher BA. Anterior polar cataract in two sisters with an unbalanced 3;18 chromosomal translocation. Am J Ophthalmol 1994; 117:512-5. [PMID: 8154535]
9. Jamieson RV, Perveen R, Kerr B, Carette M, Yardley J, Heon E, Wirth MG, Van Heyningen V, Donnai D, Munier F, Black GC. Domain disruption and mutation of the bZIP transcription factor, MAF, associated with cataract, ocular anterior segment dysgenesis and coloboma. Hum Mol Genet 2002; 11:33-42. [PMID: 11772997]
10. Jamieson RV, Farrar N, Stewart K, Perveen R, Mihelec M, Carette M, Grigg JR, McAvoy JW, Lovicu FJ, Tam PP, Scambler P, Lloyd IC, Donnai D, Black GC. Characterization of a familial t(16;22) balanced translocation associated with congenital cataract leads to identification of a novel gene, TMEM114, expressed in the lens and disrupted by the translocation. Hum Mutat 2007; 28:968-77. [PMID: 17492639]
11. Ram SV, Arvind B. Tissue culture techniques and chromosome preparation. In: Ram SV, Arvind B, editors. Human chromosomes: manual of basic techniques. Elmsford(NY): Pergamon Press; 1989. p. 4–44.
12. Pras E, Pras E, Bakhan T, Levy-Nissenbaum E, Lahat H, Assia EL, Garzozi HJ, Kastner DL, Goldman B, Frydman M. A gene causing autosomal recessive cataract maps to the short arm of chromosome 3. Isr Med Assoc J 2001; 3:559-62. [PMID: 11519376]
13. Gal A, Li Y, Angstwurm B, Hartmann C, Ruther K. Mapping the first locus for autosomal recessive cataract on chromosome 3p21 in a large consanguineous Lebanese family. Invest Ophthalmol Vis Sci 2000; 40:S1.
14. Reddy VN, Giblin FJ, Lin LR, Dang L, Unakar NJ, Musch DC, Boyle DL, Takemoto LJ, Ho YS, Knoernschild T, Juennemann A, Lutjen-Drecoll E. Glutathione peroxidase-1 deficiency leads to increased nuclear light scattering, membrane damage, and cataract formation in gene-knockout mice. Invest Ophthalmol Vis Sci 2001; 42:3247-55. [PMID: 11726630]