Endothelial Dystrophy, Iris Hypoplasia, Congenital Cataract, and Stromal Thinning (EDICT) Syndrome Maps to Chromosome 15q22.1–q25.3

ALBERT S. JUN, MD, PHD, KARL W. BROMAN, PHD, DIANA V. DO, MD, ESEN K. AKPEK, MD, WALTER J. STARK, MD, AND JOHN D. GOTTSCH, MD

• PURPOSE: **To localize a gene causing a newly described autosomal dominant anterior segment dysgenesis characterized by corneal endothelial dystrophy, iris hypoplasia, congenital cataracts, and corneal stromal thinning (EDICT syndrome).**

• DESIGN: **Experimental study.**

• METHODS: **A set of microsatellite markers spanning the 22 human autosomes was used to perform linkage analysis on affected and unaffected individuals within a single family.**

• RESULTS: **Linkage analysis of the anterior segment dysgenesis endothelial dystrophy, iris hypoplasia, congenital cataract, and stromal thinning (EDICT) syndrome in this family revealed a logarithm of the odds (LOD) score of 2.71 on chromosome 15q22.1–25.3 between markers D15993 and D15S202. These results suggest a gene for EDICT syndrome lies in this chromosomal region.**

• CONCLUSIONS: **A LOD score of 2.71 suggests a novel locus associated with the newly described EDICT syndrome lies in a region of chromosome 15 between markers D15S993 and D15S202. Identification of the disease-causing gene in this region may yield insights into a broad range of disorders affecting the corneal stroma, endothelium, iris, and lens. (Am J Ophthalmol 2002; 134:172–176. © 2002 by Elsevier Science Inc. All rights reserved.)**

Accepted for publication Jan 24, 2002.

From the Center for Corneal Genetics, Cornea and External Disease Service, The Wilmer Eye Institute, The Johns Hopkins University School of Medicine (A.S.J., D.V.D., E.K.A., W.J.S., J.D.G.), Baltimore, Maryland; Department of Biostatistics, The Bloomberg School of Public Health, The Johns Hopkins University (K.W.B.), Baltimore, Maryland.

This work was supported by the Deborah Black Research Fund, New York, NY and the Raymond Kwok Research Fund, Hong Kong.

Correspondence to: John D. Gottsch, MD, Maumenee 317, The Wilmer Eye Institute, 600 North Wolfe Street, Baltimore, MD 21287; fax: (410) 614-2816; e-mail: jgottsch@jhmi.edu

ANTERIOR SEGMENT DYSGENESIS REFERS TO A CONstellation of congenital abnormalities of the cornea, iris, trabecular meshwork, and lens. These conditions demonstrate wide phenotypic and genotypic heterogeneity that results from faulty migration or function of neural crest cells during embryologic development.[1] Previously described anterior segment dysgenesis phenotypes are numerous and are associated with a growing number of causative genes. These include aniridia (PAX 6, MIM 106210),[2] anterior segment mesenchymal dysgenesis (PITX3, MIM 601094; FOXE3, MIM 602669),[2] iridocorneal dysgenesis,[3] Peter's anomaly (PAX6, MIM 106210; PITX2, MIM 601542; CYP1B1, MIM 601771),[2] Axenfeld–Rieger syndrome (PITX2, MIM 601542; FKHL7, MIM 601090),[2] iridogoniodysgenesis anomaly (FKHL7, MIM 601090),[2] iridogoniodysgenesis syndrome (PITX2, 601542),[2] and familial glaucoma iridogoniodysplasia (FKHL7, MIM 601090).[2]

We have described the clinical, histopathologic, and ultrastructural features of a three-generation pedigree with an autosomal dominant anterior segment dysgenesis with corneal steepening and thinning, microcornea, endothelial abnormalities resembling posterior polymorphous dystrophy and Fuchs' dystrophy, iris hypoplasia, and congenital anterior polar cataracts.[4] The clinical findings of endothelial dystrophy, iris hypoplasia, congenital cataract, and stromal thinning (EDICT), in addition to the genetic and pathologic features, establish the EDICT syndrome as a novel disease entity. Linkage analysis of this pedigree was performed to further elucidate the genetic basis of this syndrome.

DESIGN

THIS IS AN EXPERIMENTAL STUDY.

0002-9394/02/$22.00
PII S0002-9394(02)01401-0

METHODS

FAMILY MEMBERS WERE INVITED TO PARTICIPATE IN A study to identify the gene causing EDICT syndrome in this family. The study was approved by the Johns Hopkins Joint Committee on Clinical Investigation. Informed consent was obtained from all available family members, including eight affected and six unaffected members of the pedigree (Figure 1 and Table 1). The proband (I-2) and two additional family members (II-2 and III-7) were examined by one or more of the authors. Clinical records of other family members were obtained from their primary ophthalmologists. Detailed clinical findings are described elsewhere[4] and are summarized below (Table 1).

Venous blood (10 ml) was collected from 14 family members and frozen at −20 C. DNA was extracted using standard methods (Qiagen, Santa Clara, California, USA). Genotyping was performed by the University of Utah Genomics Core Facility, Salt Lake City, Utah, USA (http://www.cores.utah.edu/genomics/index.htm). A set of microsatellite markers (MD10 marker set, ABI, Foster City, California, USA) spanning the 22 human autosomes was used to perform linkage analysis of all 14 informative family members. Standard polymerase chain reaction (PCR) conditions (ABI) were used and products were ethanol precipitated and electrophoresed through 5% polyacrylamide gels on an automated DNA sequencer (ABI-Prism 377). Initial data analysis was performed using GeneScan 3.1 and Genotyper 2.1 software programs (ABI).

The method of Broman and Weber was used to verify the relationships in the pedigree.[5] Pedcheck was used in the identification and resolution of Mendelian inconsistencies in the genotype data.[6] Marker allele frequencies were estimated by counting alleles in the observed individuals, ignoring familial relationships. While the resulting estimates were not ideal, the results of multipoint linkage analysis were largely unaffected by these values. Genehunter was used to perform multipoint parametric linkage analysis and to infer haplotypes under the assumption of a dominant completely penetrant locus with disease allele frequency 10^{-6}.[7] The order of genetic markers and intermarker distances were taken from the Marshfield maps.[8]

RESULTS

INITIAL LINKAGE ANALYSIS FAILED TO DISCLOSE A POSItive association between EDICT syndrome and loci previously known to cause anterior segment dysgenesis phenotypes (CYP1B1, FKHL7, FOXE3, PAX6, PITX2, PITX3).[2] Linkage analysis using a set of microsatellite markers spanning the 22 human autosomes with an average 10 cM interval provided evidence for a disease gene on chromosome 15q with a maximum logarithm of odds (LOD) score of 2.71 at marker D15S131. Inferred haplotypes for chromosome 15 are displayed in Figure 1. Breakpoints in individuals III-5 and III-6 narrow the location of the disease gene to the interval between markers D15S117 and D15S127. Based on preliminary linkage analysis, additional genotypes were determined in the region between D15S117 and D15S127 (Figure 1). Note that individual III-5 is a double recombinant over the interval between D15S153 and D15S127, which is approximately 36, 53, and 18 cM long in sex-averaged, female and male genetic distances, respectively.[9] Fine-resolution mapping further narrowed the interval of the putative EDICT gene to the interval between markers D15S993 and D15S202 (Figure 1), a region with an estimated genetic distance of 26 cM.[9]

DISCUSSION

DURING EMBRYOLOGIC DEVELOPMENT, THREE SUCCESSIVE waves of pluripotent neural crest cells migrate into the eye after the basement membrane of the surface ectoderm and the lens vesicle separate.[1] The first wave differentiates into the trabecular meshwork and corneal endothelium, the second wave differentiates into keratocytes, and the third wave differentiates into the iris. Aberrations in this process result in a diverse group of clinical syndromes, including congenital glaucoma, posterior embryotoxon, Axenfeld anomaly and syndrome, Rieger anomaly and syndrome, Peter anomaly, and sclerocornea.[10]

Affected members in this pedigree exhibited autosomal dominant corneal steepening and thinning, microcornea, endothelial abnormalities resembling posterior polymorphous dystrophy and Fuchs' dystrophy, iris hypoplasia, and congenital anterior polar cataracts. Case reports of similar, though not identical, clinical entities include nonfamilial bilateral progressive essential iris atrophy and keratoconus with posterior polymorphous dystrophy,[11] familial keratoconus and Fuchs dystrophy,[12] familial keratoconus with posterior polymorphous dystrophy,[13] and familial congenital cataract with microcornea and Peter anomaly.[14]

This report is the first to suggest an anterior segment dysgenesis locus in the region flanked by markers D15S993 and D15S202 on chromosome 15q22.1–25.3. The LOD score of 2.71, although less than the score of 3.0 commonly accepted as demonstrating linkage, is the maximum that can be obtained in this pedigree as all the known informative members of this family have been genotyped at the putative EDICT locus and across all 22 autosomes. Interestingly, a recent report demonstrates linkage of an autosomal dominant congenital cataract locus to marker D15S117 on chromosome 15q21–22.[15] The "central pouch-like" congenital cataracts described in this report were clearly distinct from the anterior polar cataract seen in our EDICT pedigree. In addition, no other associated anterior segment abnormalities were reported.[15] Despite these differences, linkage of both phenotypes to neighbor-

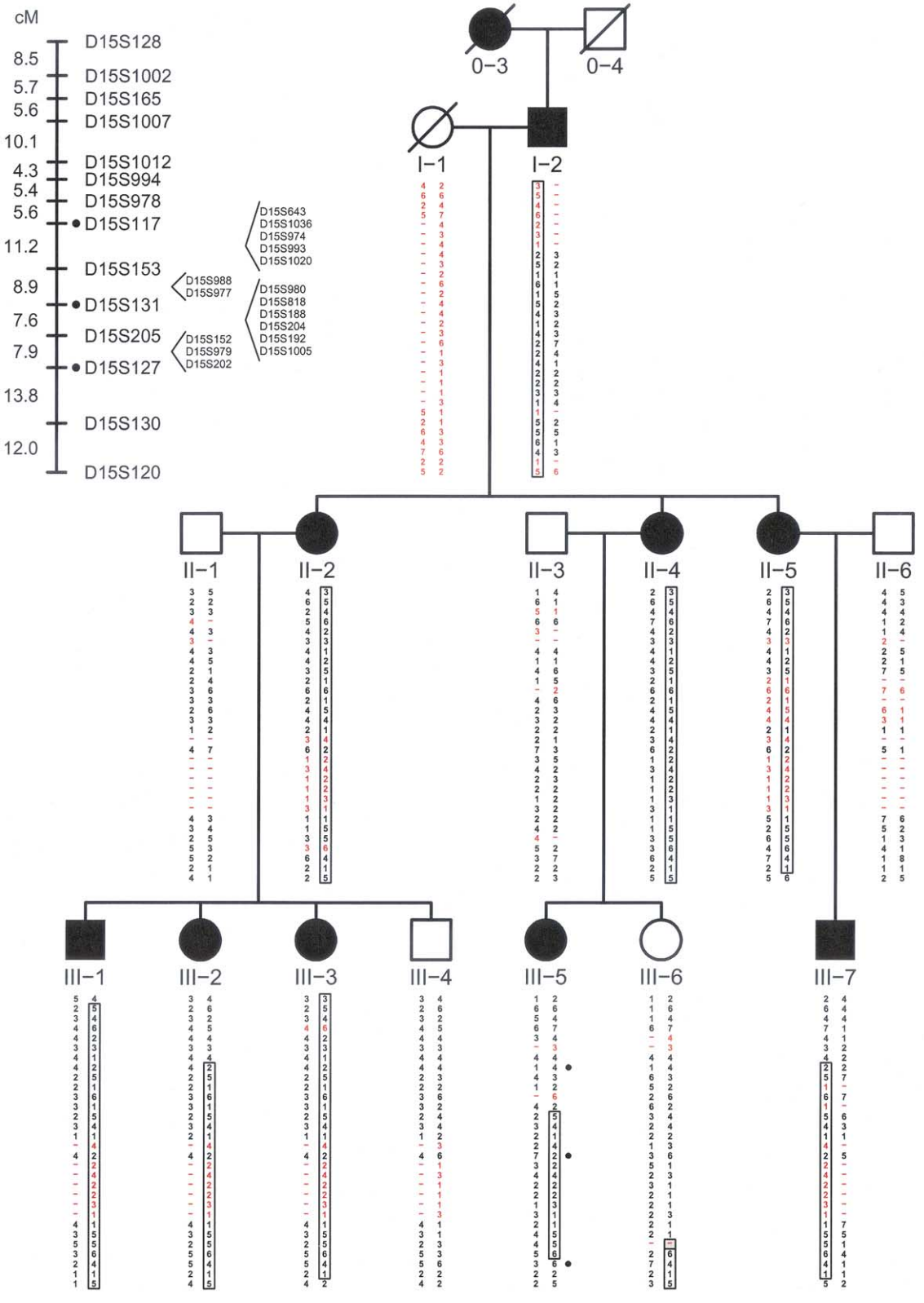

FIGURE 1. Inferred chromosome 15 haplotypes for the endothelial dystrophy, iris hypoplasia, congenital cataract, and stromal thinning syndrome (EDICT) pedigree. Genotypes in red are inferred. Dashes indicate unknown alleles. Boxes indicate alleles on the disease-allele–bearing chromosome. The shaded alleles in individuals III-5 and III-6 are not informative. The genetic map, with sex-averaged distances, is shown in the upper left. Dots indicate the locations of three markers in the haplotypes of individual III-5.

TABLE 1. Phenotypes of Affected EDICT Syndrome Family Members

		Phenotype	
Subject	Age	Right Eye	Left Eye
0-3	Dead	Congenital cataract.	Same
I-2 (proband)	81	Congenital cataract, ICCE; corneal stromal thinning and steepening; small, eccentric pupils and iris defects.	Same
II-2	55	Congenital cataract, ICCE; microcornea; corneal stromal thinning and steepening; small, eccentric pupils.	Same
II-4	48	Congenital cataract, ICCE; microcornea; corneal stromal thinning and steepening, PK.	Same
II-5	43	Congenital cataract, ICCE; corneal stromal thinning and steepening; posterior polymorphous dystrophy, PK.	Same
III-1	32	Congenital cataract, ECCE; corneal stromal thinning and steepening; small, eccentric pupils.	Same
III-2	31	Congenital cataract, ECCE; corneal stromal thinning and steepening.	Same
III-3	30	Congenital cataract, ECCE; corneal stromal thinning and steepening.	Same
III-6	30	Congenital cataract, ECCE; corneal stromal thinning and steepening.	Same
III-7	16	Anterior polar congenital cataract; corneal stromal thinning and steepening; posterior polymorphous dystrophy; small pupils with ectropion pupillae.	Same

ECCE = extracapsular cataract extraction; EDICT = endothelial dystrophy, iris hypoplasia, congenital cataract, stromal thinning; ICCE = intracapsular cataract extraction; PK = penetrating keratoplasty.

ing or possibly overlapping chromosomal loci suggests the interesting possibilities that either EDICT syndrome and central pouch-like cataracts are allelic variants or that at least two genes involved in anterior segment development and function are present in this region of chromosome 15.

Candidate congenital cataract genes within the chromosome 15q21–22 region include fibrillin 1 (FBN1, MIM 134797),[2] fibroblast growth factor 7/keratinocyte growth factor (FGF7/KGF, MIM 148180),[2] and the orphan nuclear receptor ROR alpha (RORA, MIM 600825).[2,15] One additional candidate EDICT syndrome genes include is stromal cell derived factor receptor 1 (SDFR1),[16] which is a transmembrane protein of the Ig superfamily with a putative role in cell-to-cell interaction.[17] Both of these genes are expressed in the eye, though their precise roles in ocular tissues remain unclear.

Sequence analysis of these and other candidate genes is currently underway to identify the gene mutation causing EDICT syndrome. Identification of the disease-causing gene in this region may yield insights into the normal developmental genetics of the anterior segment. Furthermore, discovery of the EDICT syndrome gene may increase our understanding of the genetic causes of a broad range of disorders affecting the corneal stroma, endothelium, iris, and lens.

ACKNOWLEDGMENTS

The authors thank Rebecca Scholl, BS (University of Utah Genomics Core Facility, Salt Lake City, UT), for technical assistance. The generous cooperation of participating family members is greatly appreciated.

REFERENCES

1. Johnston MC, Noden DM, Hazelton RD, Coulombre JL, Coulombre AJ. Origins of avian ocular and periocular tissues. Exp Eye Res 1979;29:27–43.
2. Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/omim.
3. Archer DB, Sharma NK. Irido-corneal dysgenesis. Trans Ophthalmol Soc U K 1978;98:510.
4. Akpek EK, Jun AS, Goodman DF, Green WR, Gottsch, JD. Clinical and ultrastructural features of a novel hereditary anterior segment dysgenesis. Ophthalmol 2002;109:513–519.
5. Broman KW, Weber JL. Estimation of pairwise relationships in the presence of genotyping errors. Am J Hum Genet 1998;63:1563–1564.
6. O'Connell JR, Weeks DE. PedCheck. A program for identification of genotype incompatibilities in linkage analysis. Am J Hum Genet 1998;6:259–266.
7. Kruglyak L, Daly MJ, Reeve-Daly MP, Lander ES. Parametric and nonparametric linkage analysis: a unified multipoint approach. Am J Hum Genet 1996;58:1347–1363.
8. Broman KW, Murray JC, Sheffield VC, White RL, Weber JL. Comprehensive human genetic maps: individual and sex-specific variation in recombination. Am J Hum Genet 1998;63:861–869.
9. Center for Medical Genetics, Marshfield Medical Research Foundation, http://research.marshfieldclinic.org/genetics/.
10. Bahn CF, Falls HF, Varley GA, Meyer RF, Edelhauser HF, Bourne WM. Classification of corneal endothelial disorders based on neural crest origin. Ophthalmology 1984;91:558–563.
11. Blair SD, Seabrooks D, Shields WJ, Pillai S, Cavanagh HD. Bilateral progressive essential iris atrophy and keratoconus with coincident features of posterior polymorphous dystro-

phy: a case report and reported pathogenesis. Cornea 1992; 11:255–261.
12. Lipman RM, Rubenstein JB, Torczynski E. Keratoconus and Fuchs' corneal endothelial dystrophy in a patient and her family. Arch Ophthalmol 1990;108:993–994.
13. Driver PJ, Reed JW, Davis RM. Familial cases of keratoconus associated with posterior polymorphous dystrophy. Am J Ophthalmol 1994;118:256–257.
14. Green JS, Johnson GJ. Congenital cataract with microcornea and Peters' anomaly as expressions of one autosomal dominant gene. Ophthalmic Pediatr Genet 1986;7:187–194.
15. Vanita, Singh JR, Sarhadi VK, et al. A novel form of "central pouch-like" cataract, with sutural opacities, maps to chromosome 15q21–22. Am J Hum Genet 2001;68:509–514.
16. UniGene, http://www.ncbi.nlm.nih.gov/UniGene/.
17. Lopez ND, Kinoshita A, Taniwaki M, et al. Isoform specific expression of the SDR-1 protein, a and b in subregions of the adult rodent brain. Biomed Res 1999;20:43–49.