SHORT REPORT

Corneal dystrophy and perceptive deafness (Harboyan syndrome): *CDPD1* maps to 20p13

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The association of congenital corneal dystrophy with teenage onset perceptive hearing loss (Harboyan syndrome) has been reported in two sibships, one with consanguineous parents, which were consistent with autosomal recessive transmission. We have observed a Moroccan sibship where four girls and one boy were affected with this rare syndrome. The parents were first cousins once removed and unaffected. Genome wide homozygosity mapping using 386 microsatellite markers linked the locus to 20p13. A maximum multipoint lod score of 4.20 was obtained at marker D20S179. The minimal critical region is 7.73 cM between markers D20S199 and D20S437. These results confirm the syndromic association of congenital corneal dystrophy and teenage onset hearing loss, and further increase the genetic heterogeneity of recessive deafness.

Developmental defects of the endothelium of the cornea are thought to be the primary cause of a heterogeneous group of disorders called congenital hereditary endothelial dystrophy (CHED). Patients display a cloudy, oedematous cornea, with the oedema extending up to the periphery and into the epithelium of the cornea.¹ Families have been described where the CHED phenotype is transmitted as an autosomal dominant (MIM 121700) or autosomal recessive (MIM 217700) trait, with loci reported in the pericentromeric region of chromosome 20² and in the telomeric region of 20p,³ respectively.

A distinct phenotype of congenital corneal dystrophy, endothelial type, with progressive sensorineural hearing loss of teenage onset (corneal dystrophy with perceptive deafness, CDPD (MIM 217400)) has been reported in a consanguineous Lebanese family consistent with autosomal recessive transmission.⁴ This very rare syndrome was later reported in two Italian sibs⁵ and in an isolated Brazilian patient.⁶ We report here a third, previously undescribed family with Harboyan syndrome.

PATIENTS AND METHODS

The proband, a 28 year old female, presented at birth with corneal clouding and horizontal nystagmus. Bilateral glaucoma was treated surgically at the age of 12 years. Corneal transplantation was performed at 14 years (left eye) and 17 years (right eye) of age. Hearing loss became symptomatic at the age of 18. Tonal audiometry showed perceptive deafness of –35 dB bilaterally at 21 years and of –50 dB at 27 years. Intelligence is normal. Agensis of the left kidney, with absence of compensatory hypertrophy of the right kidney, was found by abdominal ultrasound scanning performed for non-specific digestive symptoms. The proband is the seventh of nine children of Moroccan parents, who are first cousins once removed. Four sisters and one brother are affected with congenital corneal dystrophy and progressive hearing loss. A 42 year old

affected sister was referred to our Ophthalmology Department. Corneal clouding and epithelial oedema were present, and slit lamp examination showed a thickened cornea with milky stroma (fig 1). Corneal transplantation was performed. The explanted cornea displayed an extreme reduction in the number of endothelial cells. Tonal audiometry showed perceptive deafness of –50 dB bilaterally (fig 1). MRI of the temporal bones and pontocerebellar angles was normal. Renal ultrasound scanning was normal.

Rare autosomal recessive disorders in consanguineous families are amenable to homozygosity mapping, a genetic linkage method which assumes that a rare mutation is inherited from a common ancestor via both parents, so that affected sibs are homozygous by descent for polymorphic markers that are close to the disease locus.⁷ Blood samples were obtained with informed consent from the proband, sibs, and parents, and DNA was extracted from peripheral leucocytes using standard techniques. A genome wide screen was performed using 396 microsatellite markers from the Cooperative Human Linkage Consortium human screening set, Weber version 9 (Research Genetics). Marker order was obtained from the Cooperative Human Linkage Centre map (<http://www.chlc.org/HomePage.html>), NCBI Genemap'99 (<http://www.ncbi.nlm.nih.gov/genemap99/>), and the Genetic Location Database (http://cedar.genetics.soton.ac.uk/public_html).

Multipoint linkage analysis was performed using the MAPMAKER/HOMOZ algorithm software⁸ assuming a fully penetrant disease with an allele frequency of 0.001, the parents being first cousins once removed with two common ancestors. Allele frequencies for each polymorphic marker of the candidate region were evaluated from genotyping 30 unrelated people from the same ethnic population.

RESULTS AND DISCUSSION

An initial screen was performed on DNA pooled from affected sibs versus DNA pooled from the parents and unaffected sibs as reported elsewhere.⁹ Markers D1S1677, D3S1304, D4S2368, D9S301, D11S912, ACTC, D17S2196, D17S789, D21S1446, and D22S420 could not be amplified by PCR and were discarded from the analysis. Of the remaining 386 markers, three markers, D7S817, D10S189, and D20S473, were found to be homozygous by state in the affected sibs, while heterozygous in the parents' DNA pool. Subsequent analysis of DNA from each subject, with additional, closely spaced markers (<2 cM) from each of the three regions identified a single genomic segment at 20p13 (fig 2) where all informative markers were homozygous in the affected sibs while heterozygous in the parents, indicating identity by descent and homozygosity for a common haplotype. A brother (empty square in fig 2) was observed who shared homozygosity for markers D20S864 to

Abbreviations: CDPD, corneal dystrophy and perceptive deafness; CHED, congenital hereditary endothelial dystrophy

Figure 1 Clinical phenotype. (Top left) Direct illumination: the whole cornea appears cloudy, partially masking the intraocular structures. The reflection of the flashlight, on the left side of the cornea, is irregular owing to epithelial oedema. (Top right) Slit lamp examination showing milky and increased thickness of the corneal stroma. (Bottom) Tonal audiometry of the right and left ear, respectively: the solid and broken lines represent air and bone sound stimulation, respectively.

D20S199 and was not affected, indicating a critical recombination event between the latter marker and D20S842. This curtailed the minimal critical region to a 7.73 cM segment between markers D20S199 and D20S437 at 20p13.

Multipoint linkage analysis was performed separately on the five affected sibs and on the unaffected brother bearing the critical recombination event, the whole pedigree being too large to be computed in a reasonable time. Addition of the lod^s⁷⁻⁸ yielded a maximum total multipoint lod score of 4.20 at markers D20S889/D20S179 (fig 3). This locus is named *CDPD1* by the Human Gene Nomenclature Database (<http://www.gene.ucl.ac.uk/nomenclature/>), for corneal dystrophy and perceptive deafness, as in MIM 217400.

The 7.73 cM *CDPD1* critical region contains many genes and ESTs and no obvious candidate to account for a developmental defect of the eye endothelium and postlingual hearing loss. Our mapping interval overlaps the linkage region of *CHED2*, a locus for non-syndromic autosomal recessive *CHED*.³ The smallest region of overlap between *CHED2* and *CDPD1*, however, remains larger than 5.0 cM, from D20S113 to D20S437, and still contains many possible candidates. While *CDPD1* and *CHED2* might be allelic disorders, it is noteworthy that, in spite of the vast genetic heterogeneity of hearing loss reported in OMIM (<http://www.ncbi.nlm.nih.gov/omim>), no locus for autosomal recessive hearing loss has been mapped to 20p, making *CDPD1* a distinct locus for genetic deafness.

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Figure 2 Haplotypes in the family. Two unaffected older brothers are not represented for clarity. The proband is indicated by an arrow. The region of homozygosity in affected sibs is boxed. A recombination event is observed between D20S199 and D20S842 in an unaffected brother (open square) who shares homozygosity with patients for markers D20S864 to D20S199. The minimal critical region (black bar) is 7.73 cM. Genetic location of the markers is shown in cM, lower left.

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Figure 3 MAPMAKER/HOMOZ multipoint linkage analysis. A maximum total lod score of 4.20 is observed at markers D20S889/D20S179.

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