SHORT REPORT

Borate transporter *SLC4A11* mutations cause both Harboyan syndrome and non-syndromic corneal endothelial dystrophy

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Harboyan syndrome, or corneal dystrophy and perceptive deafness (CDPD), consists of congenital corneal endothelial dystrophy and progressive perceptive deafness, and is transmitted as an autosomal recessive trait. CDPD and autosomal recessive, non-syndromic congenital hereditary endothelial corneal dystrophy (CHED2) both map at overlapping loci at 20p13, and mutations of *SLC4A11* were reported recently in CHED2. A genotype study on six families with CDPD and on one family with either CHED or CDPD, from various ethnic backgrounds (in the seventh family, hearing loss could not be assessed because of the proband's young age), is reported here. Novel *SLC4A11* mutations were found in all patients. Why some mutations cause hearing loss in addition to corneal dystrophy is presently unclear. These findings extend the implication of the *SLC4A11* borate transporter beyond corneal dystrophy to perceptive deafness.

Congenital hereditary endothelial dystrophies (CHEDs) are a group of disorders affecting the posterior aspect of the cornea, characterised by bilateral corneal oedema with a thickened stroma and paucity of endothelial cells.¹ In the autosomal recessive form of the disorder, CHED2 (MIM 217700), the condition usually presents at birth and nystagmus often develops.² CHED2 has been linked to 20p13 in consanguineous families^{3–4} with no evidence of locus heterogeneity, and mutations in a candidate gene, *SLC4A11*, have recently been reported.^{5–6} *SLC4A11* (also named *NaBC1* or *BTR1*) is ubiquitously expressed and functions as a membrane-bound electrogenic sodium-borate cotransporter.⁷

Harboyan syndrome, or corneal dystrophy and perceptive deafness (CDPD; OMIM 217400), was first described in 1971⁸ in three siblings from consanguineous, unaffected parents who presented at birth with endothelial dystrophy and later developed sensorineural hearing loss, usually during the second decade of life. The eye phenotype was similar to CHED2, and the syndromic association with teenage-onset perceptive deafness was later reported in other unrelated families.^{9–11} We reported an additional family with the same syndromic association, and mapped an autosomal recessive locus by homozygosity to a 7.73 cM interval on chromosome 20p13,¹² which overlapped the non-syndromic CHED2 locus by >5 cM.^{3–4}

This article reports six families of various ethnic origins with Harboyan syndrome (H1–6) and one family with congenital endothelial dystrophy where deafness could not be assessed because of the proband's young age (C1). We found *SLC4A11* gene mutations in all patients.

PATIENTS AND METHODS

The diagnosis of congenital endothelial corneal dystrophy was made clinically in all patients by an experienced ophthalmologist. Early-onset perceptive hearing loss was observed in all

affected members in six of the seven families (table 1).^{12–13} In family C1 no hearing loss was reported, but the only affected child was too young (2 years old) for this feature to be informative. The parents were asymptomatic in all families. Families H3 and H5 have been described previously.^{12–13} In addition, we studied a subject (not shown in table 1) of the same ethnicity as family H6 (Sephardi Jews from Morocco and Turkey, not consanguineous) who developed sensorineural hearing loss at age 7, and consulted at age 21 with visual symptoms caused by corneal oedema associated with endothelial dystrophy. At age 28, he presented recurrent syncope associated with a prolonged PR interval, a bifascicular block, a transient atrial flutter and significant cardiac pauses, and a cardiac pacemaker was implanted.

Peripheral blood was sampled with informed consent for DNA analysis in all nuclear families, four of which were consanguineous. In family H2, only DNA of the proband was available. DNA was extracted by the standard phenol-chloroform method.¹⁴

In the four consanguineous families, linkage analysis was carried out with microsatellite markers of the 20p13 region to which CDPD1 was mapped.¹² The following markers were studied: D20S864, D20S103, D20S117, D20S199, D20S179, D20S113, D20S198, D20S842, D20S181, D20S473, D20S867, D20S889, D20S116, D20S482, D20S437, D20S95, D20S905, D20S194, D20S156 and D20S851. Marker order was obtained from the Marshfield Comprehensive Human Genetic Maps (<http://research.marshfieldclinic.org/genetics/GeneticResearch/compMaps.asp>) and the UCSC Genome Browser (<http://genome.ucsc.edu/cgi-bin/hgGateway>). DNA was amplified by PCR using 15 ng of DNA from each individual in a final volume of 15 µl, followed by polyacrylamide gel electrophoresis and silver staining.

We used the following primers for amplification and sequencing of the 19 coding exons and adjacent intronic sequences of *SLC4A11*:

SLC4A11EX1D, CCTGCTTCCTTTCTCCC;
SLC4A11EX1R, GTAGGCTATGCACCCTGGAG;
SLC4A11EX2–3D, GAGCCCCTCCTCCTGTG;
SLC4A11EX2–3R, AGGGAAGCCATCACCTCAG;
SLC4A11EX4–5D, ACCAGGCAGTGACAGCATC;
SLC4A11EX4–5R, ATGGGACACCCAGTCCAC;
SLC4A11EX6D, CTAGCAGAGGTCGCCAGG;
SLC4A11EX6R, AAGCAGAGGGCGGGTAAC;
SLC4A11EX7–8D, ATGGGGAGAGCACCTTCAC;
SLC4A11EX7–8R, GATGCAGGACAGGCACAC;
SLC4A11EX9–10D, CTTCACTGATGGTACGTGGC;
SLC4A11EX9–10R, GACACGAATCACTGCAGGC;
SLC4A11EX11–12D, GAGATGGTGCCTGAGACCC;
SLC4A11EX11–12R, AGTGCAAGACCTCCCATCTC;

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

Table 1 Clinical findings and *SLC4A11* mutations in probands and families

Family	H1	H2	H3	H4	H5	H6	C1
Ethnicity/country of origin	Gipsy (Eastern Europe)	Dominican Republic	Morocco	South American Indian	The Netherlands	Sephardi Jewish	India
Visual acuity with correction (age 4/10 left (5) years)	II-3: 3/10 right, 4/10 left (5)	II-1: 20/80 right, 20/30 left (22); first CTx at 13	II-2: 3/10 right, 1/10 left (33); CTx at 14	II-1: CTx at 11	II-1: 2/100 (12); CTx at 12	II-2: 6/30 (24) CTx at age 7	II-2: subnormal (1.5)
Age at diagnosis of hearing loss (age 5 years)	II-3: 5	II-1: 18	II-2: 18	II-1: 19	II-1: 4	II-2: 17	II-2: no hearing deficit (2)
Hearing loss (age 5 years)	II-3: 35 dB (5)	II-1: 40 dB (18)	II-2: 60 dB (33)	II-1: 60 dB (21)	II-1: 30 dB (4)	II-2: 45 dB (24)	
<i>SLC4A11</i> mutation*	Exon 4 (c.473_480del GCTTCGCC) + (c.473_480del GCTTCGCC)	Exon 11 (c.1378_1381del TACGinsA) + (c.1378_1381del TACGinsA)	Exon 11 (c.1463G→A) + (c.1463G→A)	Exon 16 (c.2233_2240dup TATGACAC) + Exon 18 (c.2528T→C)	Exon 17 (c.2423_2454del32 nucleotides) + Exon 18 (c.2528T→C)	Exon 5 (c.637T→C) + Exon 18 (c.2566A→G)	Exon 18 (c.2470G→A)
Protein change (predicted)	p.Arg158ProfsX4	p.Tyr460_Ala461 delinsThr	p.Arg488Lys	p.Thr747ThrfsX6 + p.Leu843Pro	p.Leu808ArgfsX110 + p.Leu843Pro	p.Ser213Pro+ p.Met856Val	p.Val824Met

CTx, conical transposition.

*Nucleotide position in reference to the first ATG of *SLC4A11* cDNA (GenBank NM_032034.2).

SLC4A11EX13-14D, CCTTTCTCCCTGAGATCCCC;
SLC4A11EX13-14R, GGTGTAGCGGAAGTGTGCTC;
SLC4A11EX15-16D, GTGGGTGACGTGGGGTAG;
SLC4A11EX15-16R, ATGTGGCCAGAGGCTCC;
SLC4A11EX17-18D, CTGGCCACATGGGACATAG;
SLC4A11EX17-18R, GCCCATTCTCCACACCTAGAC;
SLC4A11EX19D, GGTGTCCACTGCCTTCTCTC;
SLC4A11EX19R, TACACCTCCCCTCACAGCTC.

PCR products were purified using ExoSAP-IT For PCR Product Clean-Up (USB Corporation, Cleveland, Ohio, USA), sequenced using the Big Dye Terminator cycle sequencing kit v2 (Applied Biosystems, Foster City, California, USA) and analysed on a 3130 Genetic Analyzer sequencing machine (Applied Biosystems). Sequences were inspected in silico for mutations using the SeqScape software V.2.0 (Applied Biosystems).

Control DNA samples were obtained with informed consent from a cohort of volunteers including subjects of European, Moroccan, Indian, South American and non-Ashkenasi Jewish origin. We controlled the absence of each missense mutation observed in this study in a sample of at least 100 unrelated control subjects, including at least 35 ethnically matched subjects, by PCR amplification followed by denaturing high-performance liquid chromatography (dHPLC) analysis and, when indicated, direct sequencing of amplimers, which produced variant dHPLC electrophoregrams.

This study was approved by the ethics committee of University Hospital Erasme – ULB, Brussels, Belgium.

RESULTS

Evidence for linkage was observed at the CDPD1/CHED2 locus in the four consanguineous families, H1, H2, H3 and C1, where we found homozygosity for linked markers in all patients (data not shown). *SLC4A11* mutations were identified in the seven families (table 1, fig 1). All mutations cosegregated with the disease in the families, and none were observed in controls (at least 100 controls, including at least 35 ethnically matched controls tested for each missense mutation). No mutation was found in the patient with hearing loss, non-congenital endothelial dystrophy and cardiac conduction block. In the four consanguineous families (H1, H2, H3 and C1), mutations were homozygous. These consisted of two missense mutations (p.Arg488Lys and p.Val824Met), a 4 bp deletion/1 bp insertion (c.1378_1381delTACGinsA) and an 8 bp deletion (c.473_480delGCTTCGCC) resulting in a truncated protein of 160 residues. Three families were not consanguineous (H4, H5 and H6) and showed compound heterozygosity. One missense mutation (p.Leu843Pro) was common to two families, despite their different ethnic backgrounds (South American Indian and Dutch). The mutation was associated with the same haplotype of contiguous microsatellite markers D20S842, D20S181 and D20S473, which spans 780 kb and encompasses the mutation, consistent with the same ancestral origin. The other mutations in the non-consanguineous families were an 8 bp duplication (c.2233_2240dup TATGACAC) resulting in an aberrantly truncated protein of 751 residues; a 32 bp deletion (c.2423_2454del) resulting in an aberrantly truncated protein of 916 residues; and two missense mutations (p.Ser213Pro and p.Met856Val). All mutations had not been previously reported.

All missense mutations (Ser213, Tyr460, Ala461, Arg488, Val824, Leu843 and Met856) affected amino-acid residues which display high interspecies conservation (fig 2), and the Arg488, Val824 and Leu843 residues also show high conservation across members of the human SLC4 bicarbonate transporter family (fig 2).

Several of the mutations produced frameshifts followed by stop codons, consistent with a loss of function, as suggested by recessive inheritance of CDPD, and as found in CHED2.^{3,6}

Figure 1 Families with Harboyan or corneal dystrophy and perceptive deafness (CDPD) syndrome and *SLC4A11* mutations. The seven nuclear families are shown, with arrows indicating probands for whom *SLC4A11* mutations are shown. Mutation c.2528T→C was found in both families H4 and H5. C, wild-type sequences from unaffected controls; P, sequence electropherograms in probands.

DISCUSSION

We found *SLC4A11* mutations in six families with CDPD from a wide variety of ethnic backgrounds, and in one family with either CHED or CDPD (family C1). All mutations were novel, and segregated with the disease. None were present in a large series of controls. Our findings indicate that CDPD and CHED2 are allelic disorders. CDPD segregated as an autosomal recessive trait, and the patients were homozygotes in consanguineous families and compound heterozygotes in the non-consanguineous families. *SLC4A11* mutations were found in all patients. We found no indication of genetic heterogeneity in our series of patients with CDPD (actually CHED or CDPD in one family). We found no *SLC4A11* mutation in one additional patient with early-onset hearing loss and non-congenital corneal endothelial dystrophy, which is consistent with *SLC4A11* mutations causing congenital eye disease.

SLC4A11 is expressed in the endothelium of the embryonic mouse cornea at E18, equivalent to human gestational month 5, the time at which the CHED2 defect is believed to develop in man.⁵ In CDPD, the patients present with congenital corneal endothelial dystrophy and later develop sensorineural deafness, during the first to third decade of life. Consistent with *SLC4A11* mutations as a cause of hearing loss, this gene is expressed in the cochlea of adult mice, more specifically at the level of the lateral wall, which contains the stria vascularis,¹⁵ the latter being involved in the highly distinctive homeostasis of cochlear fluid and endolymph secretion. In the absence of direct pathological or functional observations from inner ears of patients with Harboyan syndrome, we can only speculate on

the effects of the mutations we report here. Intermediate cells of the stria vascularis share a common neural crest origin with corneal endothelial cells,^{16,17} and a borate-dependent effect on proliferation of these cells, perhaps via a mitogen-activated protein kinase pathway,⁵ might result in deafness. Alternatively, hearing loss might result from fluid imbalance in the inner ear. *SLC4A11* is related to the *SLC4* family of transport proteins, which consists of a functionally diverse group of 11 members that play an essential role in the transport of HCO_3^- .^{18–20} Although *SLC4A11* is a highly selective boron-concentrating transporter, using borate as a physiological substrate in boron-free medium, it functions as a Na^+ and OH^- permeable channel.⁷ Considering the highly specific constitution of the endolymph and the expression of the gene in the stria vascularis, we cannot exclude a role of *SLC4A11* in Na^+ and OH^- homeostasis in the inner ear. Of note, knockout mice lacking the electroneutral sodium bicarbonate cotransporter *SLC4A7* (*NBC3*), a member of this gene family, showed progressive auditory impairment. This was in the form of significantly decreased brainstem auditory evoked responses by the age of 3 months, associated with degeneration of inner and outer hair cells and mild atrophy of the stria vascularis and spiral ligament,^{21,22} while normal at birth,²¹ implicating an ion transporter in the form of hearing loss whose timing is similar to CDPD.

It is unclear why some *SLC4A11* mutations cause CHED2 only^{5,6} while others cause CHED2 and hearing loss (ie, Harboyan syndrome, CDPD). The fortuitous effect of another unlinked gene or of an oligogenic/multigenic set of genes in

Figure 2 Protein sequence alignments around missense mutations. Partial alignment of predicted polypeptide sequences for human SLC4A transporters (six upper lines) and for SLC4A11 from various species (six lower lines). The six missense mutations reported in this study are indicated by arrows. These mutations are located in exons 5 (S213P), 11 (YA460_461T and R488K) and 18 (V824M, L843P and M856V) of SLC4A11.

CDPD is possible but relatively unlikely, considering the number of multiplex families where corneal dystrophy and perceptive deafness cosegregate.^{8–12} Hearing preservation might depend on some residual SLC4A11 activity in patients with CHED2. However, residual activity is unlikely in those patients diagnosed with CHED2 who harboured truncating mutations of both alleles,^{5–6} although it is possible that hearing loss was not yet present, or was overlooked, in at least some of these patients. More plausibly, tissue-specific regulation of gene splicing²³ might explain the differential effect of some mutations on the inner ear. In that respect, our series of patients with CDPD, although limited, seems to indicate some clustering of the mutations around exon 11 and exon 18. Testing a much larger series of patients will be hampered by CDPD being even more rare than non-syndromic CHED2. Our findings nevertheless call for regular screens of hearing acuity in patients with congenital corneal endothelial dystrophy, especially those with no older affected relatives.

In summary, we report mutations of *SLC4A11* in CDPD (Harboyan syndrome), showing allelism with CHED2, and extend the implication of mutations of this borate transporter to perceptive deafness.

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REFERENCES

- 1 Maumenee AE. Congenital hereditary corneal dystrophy. *Am J Ophthalmol* 1960;**50**:1114–24.
- 2 Kirkness CM, McCartney A, Rice NSC, Garner A, Steele ADM. Congenital hereditary corneal oedema of Maumenee: its clinical features, management, and pathology. *Br J Ophthalmol* 1987;**71**:130–44.
- 3 Hand CK, Harmon DL, Kennedy SM, FitzSimon JS, Collum LM, Parfrey NA. Localization of the gene for autosomal recessive congenital hereditary endothelial dystrophy (CHED2) to chromosome 20 by homozygosity mapping. *Genomics* 1999;**61**:1–4.
- 4 Mohamed MD, McKibbin M, Jafri H, Rasheed Y, Woods CG, Inglehearn CF. A new pedigree with recessive mapping to CHED2 locus on 20p13. *Br J Ophthalmol* 2001;**85**:758–9.
- 5 Vithana EN, Morgan P, Sundaresan P, Ebenezer ND, Tan DTH, Mohamed MD, Anand S, Khine KO, Venkataraman D, Yong VHK, Salto-Tellez M, Venkataraman A, Guo K, Hemadevi B, Srinivasan M, Prajna V, Khine M, Casey JR, Inglehearn CF, Aung T. Mutations in sodium-borate cotransporter SLC4A11 cause recessive congenital hereditary endothelial dystrophy (CHED2). *Nat Genet* 2006;**38**:755–7.
- 6 Jiao X, Sultana A, Garg P, Ramamurthy B, Vemuganti GK, Gangopadhyay N, Hejtmancik JF, Kannabiran C. Autosomal recessive corneal endothelial dystrophy (CHED2) is associated with mutations in SLC4A11. *J Med Genet* 2007;**44**:64–8.
- 7 Park M, Li Q, Shcheynikov N, Zeng W, Muallem S. NaBC1 is a ubiquitous electrogenic Na(+)-coupled borate transporter essential for cellular boron homeostasis and cell growth and proliferation. *Mol Cell* 2004;**16**:331–41.
- 8 Harboyan G, Mamo J, Der Kaloustian VM, Karam FA. Congenital corneal dystrophy, progressive sensorineural deafness in a family. *Arch Ophthalmol* 1971;**85**:27–32.
- 9 Nemoto S. Family cases of Harboyan syndrome. *Jibiinkoka* 1986;**58**:161–5.
- 10 Magli A, Capasso L, Foa T, Maurino V, Ventruto V. A further observation of corneal dystrophy and perceptive deafness in two siblings. *Ophthalmic Genet* 1997;**18**:87–91.
- 11 Puga ACS, Nogueira AHH, Felix TM, Kwitko S. Congenital corneal dystrophy and a progressive sensorineural hearing loss (Harboyan syndrome) [letter]. *Am J Med Genet* 1998;**80**:177–9.
- 12 Abramowicz MJ, Albuquerque-Silva J, Zanen A. Corneal dystrophy and perceptive deafness (Harboyan syndrome): CDPD1 maps to 20p13. *J Med Genet* 2002;**39**:110–12.
- 13 Meire FM, Pantelis V, Schuil J. Comment on 'A further observation of corneal dystrophy and perceptive deafness in two siblings'. *Ophthalmic Genet* 1998;**19**:105–6.
- 14 Sambrook J, Fritsch EF, Maniatis T. *Molecular cloning: a laboratory manual*, 2nd edn. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 1989.
- 15 Morris KA, Snir E, Pompeia C, Koroleva IV, Kachar B, Hayashizaki Y, Carninci P, Soares MB, Beisel KW. Differential expression of genes within the cochlea as

- defined by a custom mouse inner ear microarray. *J Assoc Res Otolaryngol* 2005;**6**:75–89.
- 16 **Creuzet S**, Vincent C, Couly G. Neural crest derivatives in ocular and pericocular structures. *Int J Dev Biol* 2005;**49**:161–71.
 - 17 **Bibas A**, Liang J, Michaels L, Wright A. The development of the stria vascularis in the human fetus. *Clin Otolaryngol Allied Sci* 2000;**25**:126–9.
 - 18 **Pushkin A**, Kurtz I. SLC4 base (HCO₃⁻, CO₃²⁻) transporters: classification, function, structure, genetic diseases, and knockout models. *Am J Physiol Renal Physiol* 2006;**290**:F580–99.
 - 19 **Alper SL**. Molecular physiology of SLC4 anion exchangers. *Exp Physiol* 2006;**91**:153–61.
 - 20 **Romero MF**. Molecular pathophysiology of SLC4 bicarbonate transporters. *Curr Opin Nephrol Hypertens* 2005;**14**:495–501.
 - 21 **Bok D**, Galbraith G, Lopez I, Woodruff M, Nusinowitz S, BeltrandelRio H, Huang W, Zhao S, Geske R, Montgomery C, Van Sligtenhorst I, Friddle C, Platt K, Sparks MJ, Pushkin A, Abuladze N, Ishiyama A, Dukkipati R, Liu W, Kurtz I. Blindness and auditory impairment caused by loss of the sodium bicarbonate cotransporter NBC3. *Nat Genet* 2003;**34**:313–9.
 - 22 **Lopez IA**, Acuna D, Galbraith G, Bok D, Ishiyama A, Liu W, Kurtz I. Time course of auditory impairment in mice lacking the electroneutral sodium bicarbonate cotransporter NBC3 (slc4a7). *Brain Res Dev Brain Res* 2005;**160**:63–77.
 - 23 **Cartegni L**, Chew SL, Krainer AR. Listening to silence and understanding nonsense: exonic mutations that affect splicing. *Nat Rev Genet* 2002;**3**:285–98.

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