Clinical features and possible founder mutation of the 8bp duplication mutation in the SLC4A11 gene causing corneal dystrophy and perceptive deafness in three South American families

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ABSTRACT

Background: Corneal Dystrophy and Perceptive Deafness (CDPD) or Harboyan syndrome is an autosomal recessive rare disorder, characterized by congenital corneal opacities and progressive sensorineural hearing loss, which usually begins after the second decades of life. This study reports the ophthalmic, audiological and genetic features, in five CDPD affected patients from three Chilean families.

Materials and Methods: Five individuals affected with CDPD from three unrelated Chilean families were clinically and genetically examined. To evaluate a putative founder mutation 7 SNPs were analyzed in the three families, an Argentinian patient (carrier of the same mutation previously reported) and 87 Chilean controls.

Results: The ophthalmic symptoms in the five patients were bilateral and symmetric, starting before one year of age, and visual acuity varied from 0.1 to 0.3. In all cases, hearing loss began over 8 years old. The sequence of the 19 exons of SLC4A11 gene of all the affected patients exhibited homozygous eight nucleotide sequence duplication (c.2.233_2.240dup TATGACAC, p.(Ile748Metfs*5)) at the end of exon 16. All the affected patients of the three families were homozygous for a haplotype composed of five SNPs and covering 4.1 Mb. The same haplotype was present in one allele of the heterozygous Argentinian patient and has a frequency of 2.76% in Chilean population.

Conclusions: The five CDPD patients were homozygous for the same mutation in the SLC4A11 gene. Haplotype analysis of all the affected, including the case reported from Argentina was in accordance with a founder mutation.

Introduction

Corneal dystrophies are a group of inherited disorders characterized by loss of corneal transparency and can affect different layers of the cornea (1).

Three forms of endothelial corneal dystrophies are caused by mutations in the solute carrier family 4 sodium borate transporter (NaBC1) member 11 gene, SLC4A11. They are: congenital hereditary endothelial dystrophy (CHED, formerly CHED2, MIM217700) (2), corneal dystrophy with perceptive deafness (CDPD, MIM217400) also known as Harboyan syndrome (3,4) and a late onset form of Fuch’s endothelial corneal dystrophy (FECD, MIM136800) in a small percentage of FECD individuals (3–5). Other FECD forms are caused by mutations in other genes (6).

CHED, CDPD, and FECD corneal dystrophies present degeneration and dysfunction of the corneal endothelial cells, leading to bilateral edematous stroma and thickened Descemet’s membrane. These cause reduced corneal transparency, impaired vision, and blindness (5,7). Corneal transparency is determined by the degree of dehydration of the cornea, which is regulated by pumping out water from the stroma into the aqueous humor.

These three corneal dystrophies differ in some features such as the inheritance pattern, the age at onset of symptoms and hearing loss. While CDPD and CHED exhibit autosomal recessive transmission pattern, the late onset form of FECD has an autosomal dominant inheritance (3–5,8). Corneal opacities are present at birth in both CDPD and CHED; however, CDPD exhibits also progressive sensorineural hearing loss, which usually begins during the second to third decades of life (3,4). Finally, in the late onset form of FECD the symptoms appear most commonly in the fifth or sixth decade of life (5).

The human SLC4A11 gene is located on chromosome 20p12. It encompasses 11,774 base pairs (bp), includes 19
exons and encodes for a protein of 891 amino acids. Approximately 80 mutations have been reported in 17 of the 19 exons of SLC4A11 in individuals with CHED (4,8–17).

The SLC4A11 protein is expressed in the cell membrane of various tissues, with high expression in the corneal endothelium, blood cells, ovary, tongue, lung, skin, and colon (18–20). It contains an extensive cytoplasmic N-terminal domain, 14 transmembrane segments and a small cytoplasmatic C-terminal domain (18–21). It belongs to a group of mammalian bicarbonate transporters, although SLC4A11 does not exhibit bicarbonate transport activity (18,21).

The molecular mechanisms underlying the ophthalmic and hearing symptoms observed in CDPD are not thoroughly understood. In sensory system SLC4A11 protein is expressed in fibrocytes of the spiral ligament, from the basal to the apical portion of the cochlea, in vestibular fibrocytes, and in corneal endothelial cells, playing a role in osmotic balance (22–24). In the cornea, SLC4A11 protein seems to be related to the transport of fluids from the corneal endothelium to the anterior eye chamber, counterbalancing the leaks of fluids into the stroma (24,25).

The main objective of this article is to report the ophthalmic and otolaryngological clinical characteristics, and a genetic mutation in SLC4A11 gene in three Chilean apparently unrelated families with Corneal Dystrophy and Sensorineural Deafness (CDPD). We also explored a putative founder mutation. In Chile, there are no previous reports of mutations in this gene.

Methods

Patients

This study was approved by the ethic committee of the Clinical Hospital of University of Chile and adhered to the tenets of the Declaration of Helsinki. After obtaining informed consent from 11 members of three Chilean families, the pedigrees were constructed (Figure 1). Five affected with CDPD and six unaffected were examined over 5 years. The families have Spanish origin and they are not related to each other. This information was obtained from the interviews of the parents of the probands of families 1 and 3, and to the proband and her mother of family 2. We evaluated whether

![Figure 1. Pedigrees of three families affected by CDPD. (a) A four generation consanguineous family with three living affected subjects. (b) A five generation consanguineous family with one affected subject. (c) A three generation family with no history of consanguinity and with one affected subject. The arrows indicate the probands, open and filled symbols indicate unaffected and affected individuals respectively, squares indicate males, circles indicate females, a diagonal line over circles and squares indicate deceased. Horizontal lines above the squares and circles indicate the subjects clinically examined and asterisks indicate members of the family who underwent genetic analyses of the deletion mutation.]
a founder mutation existed in the three Chilean families and the Argentinean family previously reported (4).

Diagnosis was based on clinical criteria, detailed ophthalmological assessment and audiometry. The diagnostic criteria used for Harboyan syndrome were a congenital disorder characterized by bilateral corneal clouding presents at birth or within the neonatal period and progressive postlingual sensorineural hearing loss based on “IC3D Classification of Corneal Dystrophies – Edition 2” (26). All individuals with distinctive corneal features of endothelial dystrophy and hearing loss were considered clinically affected.

The control population was recruited from subjects attending to ophthalmic service at the same hospital. They were adults without history of corneal dystrophy or hearing defects.

**Ophthalmologic evaluations**

Clinical examination included best corrected visual acuity according to the best line of Snellen acuity, slit lamp biomicroscopy, and color cornea photography. The corneal phenotype was assessed by slit lamp examination and reviewed by an investigator unaware of the patient’s genetic status (Figure 2a).

**Histopathology**

Histological characteristics of one corneal button were evaluated (Patient IV-10 from family 1). Light microscopic studies were performed on sections stained with hematoxylin and eosin (Figure 2b).

**Hearing assessment**

In order to rule out external or middle ear pathologies that could affect audiometric measurements, otoscopic examinations were performed by an otolaryngologist in all individuals, before audiometry testing. The hearing evaluations of subjects were conducted using pure tone and bone audiometry (audiometer Welton 1300, Welton Corporation, Copenhagen, Denmark), in the range of frequencies of 250 through 8000 Hz. The thresholds obtained by air conduction (AC) and bone conduction (BC) were plotted on an audiogram sheet (Figure 3). The pure tone average (PTA) was calculated for each ear.

**Molecular analyses**

Blood samples were collected from 10 participants, 5 affected and five unaffected (subject IV-8 of family 1 did not accept to participate in the genetic study) (Figure 1a). Total DNA was prepared from peripheral blood lymphocytes (27). The 19 exons of the SLCA11 gene were screened for mutations in the three probands. Briefly, the 19 exons were amplified by polymerase chain reaction (PCR) using the primers and conditions described in Supplementary Table 1. The PCR products were sent for sequencing to Macrogen DNA Sequencing Service (Macrogen, Seoul, Korea).

To perform a screening of the 8 bp duplication mutation in a control population sample, we performed a PCR amplification of a fragment of 105 bp. Primers and PCR conditions are described in Supplementary Table 1. This analysis was performed in 87 healthy controls (174 chromosomes) recruited in the Clinical Hospital of the University of Chile.

To evaluate a presumed founder mutation, seven SNPs were genotyped in the 10 family members, in a case previously reported by Desir et al (4) and in 87 healthy control subjects of the population (supplementary Figure 1).

**Results**

**Clinical findings**

The pedigrees of the three families were consistent with autosomal recessive transmission pattern (Figure 1). There was consanguinity in Families 1 and 2 (Figure 1(a and b)). The phenotypic features of the 11 examined individuals of the three families are summarized in Supplementary Table 2.

**Family 1**

This family came from a rural area located at 115 km Northeast of Santiago, Chile. The proband (Figure 1a, IV-7)
was a 23-year-old man affected by CDPD. The parents of the proband were double first cousins. Five relatives of the proband (Figure 1a: III-3, III-11, IV-8, IV-9, and IV-10) were examined clinically. Two of them were affected by CDPD (IV-9 and IV-10) and three were unaffected (Figure 1a: III-3, III-11, and IV-8).

There was a history of twin girls who died in the 1950’s before 1 year of age. The informants reported that the corneas were opaque in both girls and the cause of death was not clear. We could not access the clinical records.

**Family 2**

This family came from Santiago, Chile. The proband (Figure 1b, IV-5) was a 40-year-old woman. Her parents were first cousins. There was no history of other individuals affected with CDPD in this family. The proband (Figure 1b, IV-5) and her mother were examined clinically. We had no access to her father.

**Family 3**

This family came from a city located 400 km South of Santiago. The proband (Figure 1c, III-1), a 12-year-old boy was diagnosed with bilateral corneal endothelial dystrophy at birth. There was no history of CDPD in this family. Both parents (Figure 1c: II-2 and II-3) and the proband (Figure 1c, III-1) were examined clinically.

**Ophthalmologic findings**

All affected patients exhibited bilateral and symmetrical corneal opacities. In three affected individuals, corneal opacities were detected at birth and in two patients at one year of age (Supplementary Table 2). All affected patients showed corneal diameters between 10.0 and 11.5 mm at the moment of the exam. Slit-lamp biomicroscopy of the anterior segment showed, in all affected, whitish corneal opacities extended from limbus to limbus (Figure 2a). Thickening of stroma and endothelium was observed (Figure 2b). All unaffected relatives examined exhibited normal corneal phenotypes.

Patients IV-10, IV-5, and III-1 of families 1, 2, and 3, respectively, showed nystagmus. All affected patients underwent penetrating keratoplasty in both eyes. The first keratoplasties were performed between 3 and 15 years of age. In the affected patients the best visual acuity after keratoplasty varied from 0.1 to 0.3. Patient IV-10 from family 1, an 11-year-old girl, underwent penetrating keratoplasty in the left eye 5 years before this publication. This patient was evaluated before keratoplasty and the cornea of left eye showed typical diffuse opacities and corneal thickening extended from limbus to limbus observed under slit-lamp examination (Figure 2a).

The most ancient corneal graft was performed 26 years earlier (right eye of patient IV-5 of family 2). This graft was rejected in the first year after surgery. In total, 10 graft surgeries were performed and four of them were rejected. So far, no dystrophy recurrence in the grafts has been observed in any of the nonrejected grafts.

Unaffected individuals (III-3, III-11, and IV-8 of family 1; III-6 of family 2, and II-2 and II-3 of family 3), showed normal clinical eye exam (Supplementary Table 2).

Histological corneal examination was performed in the left eye of patient IV-10 of family 1. Hematoxylin-eosin staining revealed an attenuation of the corneal endothelium, increased thickness of Descemet’s membrane and stromal edema (Figure 2b).

**Ear, nose, and throat (ENT) findings**

All affected individuals showed sensorineural hearing loss. The age of onset of hearing loss was variable, ranging from 8 to 18 years (Supplementary Table 2). Severity of hearing loss was also variable, ranging from 20 to 70 decibels (dB) (Figure 3) and was considered moderately severe (between 56 and 70 dB HL) in the worse cases (cases IV-7 from family 1 and IV-5 from family 2) (28). Hearing impairment was progressive with slow changes over time in all cases. For instance, we observed in the patient III-1 of family 3 that hearing level declined 25 dB in 4 years (between 8 and 12 years old) (Figure 3(e and f)). The audiometry of patient IV-5 from family 2 (40 years old), almost did not change in 11 years (Figure 3(c and d)).

The mother of the proband of family 1 (III-11), as expected considering the recessive transmission pattern of CDPD, did not have ocular commitment; but intriguingly she exhibited hearing loss similar to that observed in the affected patients (Figure 3a). In this case, the hearing loss began earlier in life, when she was 3 years old. She has worn hearing aids since age 5.

**Molecular genetics analyses**

The sequence results of the probands of the three families revealed one mutation corresponding to a homozygous 8 bp duplication mutation at the end of exon 16 (c.2233_2240dupTATGACAC) (Figure 4a). The consequence of this mutation would affect the translation of the mRNA by generating a frameshift with the inclusion of four amino acids followed by a stop codon (p.(Ile748Metfs*5)). The parents of the probands of families 1 and 3 and the mother of the proband of family 2 were heterozygous (not shown). This mutation was reported once previously in two brothers of an Argentinean family (4) and was not present in 87 healthy Chilean controls (not shown).

No other variants were detected in any of the 19 exons of the SLC4A11 gene analyzed.

Since all the affected carry the same mutation, a putative founder mutation was explored by the analysis of haplotypes including 7 SNPs. The SNPs were selected based on their position on chromosome 20, surrounding and including the SLC4A11 gene, and having minor allele frequencies (MAF) over than 1% in Mexican and European populations reported in dbSNP (29) (Supplementary Figure 1). This haplotype analysis was performed in all the enrolled subjects, including the Argentinean patient reported (4) (Figure 4b) and the haplotype frequencies were also investigated in 87 controls. The results indicate that one haplotype (C T T C C) composed of the five inner SNPs (rs3729965, rs4815574, rs3827075, rs732923, and rs2326905) is fully conserved in
the three probands and the other two affected of family 1 (Figure 4b). These SNPs covers a region of 4.1 Megabases (Mb). The nonconserved SNPs are located at both extremes of the region (rs459710 and rs6033444). The same haplotype is present in 2.76% of the 87 subjects of the control population. These finding are in accordance with a founder mutation, although more profound genomic analyses are necessary to confirm this hypothesis.

The patients previously reported with the same mutation belong to a family that migrated from Chile to Argentina more than 30 years ago. We performed the haplotype analysis to one of them and we observed heterozygosity in three of the seven polymorphisms analyzed (rs3827075, rs732923, rs2326905). Thus, we inferred two different haplotypes in the Argentinian patient, one of them identical to the one observed in Chilean patients. The shared haplotype between the three Chilean families and the Argentinian patient analyzed supports the founder mutation hypothesis (Figure 4b), although this is not concluding since in the Argentinean patient we did not probe the alleles of the shared haplotype are on the same chromatid as the duplication mutation.

**Discussion**

This report describes the clinical and genetic features of Corneal Dystrophy and Perceptive Deafness (CDPD) in three South American families. The same homozygous small duplication in the SLC4A11 gene was found in the affected of the three families, and has been reported only once worldwide in heterozygosity in two Argentinean brothers having Chilean ancestors (30). This fact, plus a haplotype analysis suggest a founder mutation.

The probands of families 1–3 were genetically studied by DNA sequencing of the 19 exons, detecting one homozygous mutation (c.2233_2240dupTATGACAC) located at the end of exon 16. This duplication would move forward the splicing donor site of exon 16 affecting the RNA splicing and keeping the eight nucleotide duplication in the mRNA after processing. This alteration would affect the translation of the mRNA by generating a frameshift with the inclusion of four amino acids followed by a stop codon (p.(Ile748Metfs*5)). Figure 4c shows a scheme of the normal protein containing the 14 transmembrane domains (TM) and the position of the mutation. This would generate a truncated protein of 751 out of the normal 891 amino acids, the last 4 amino acids being different from the
wild type sequence. This truncated protein would include only the first 9 TM domains and lacks the sequence of the last 5 TM domains (10–14) of the normal protein.

The premature termination would result in nonsense mediated decay (NMD) of the mRNA. NMD is an mRNA quality-control mechanism that accelerates the degradation of abnormal mRNAs harboring a premature termination codon (PTC), preventing the generation and accumulation of truncated proteins that can be toxic (31).

In the probands of the three families studied the c.2233_2240dupTATGACAC mutation was homozygous. Moreover, in all loci of the 19 exons of the SLC4A11 gene sequenced in the three probands we did not find heterozygosity in any of the SNPs reported. There was no evidence that these three families were related. To explore for a potential founder mutation we performed a haplotype analysis including seven SNPs. The results indicate the presence of a haplotype, composed with five of the central SNPs, conserved in all the affected subjects and present with small frequency in control population not carrying the duplication mutation (2.76%). These data support the hypothesis of a founder mutation.

The c.2233_2240dupTATGACAC mutation has been only described once worldwide, as a compound heterozygous associated with the c.2528T>C substitution on the other allele. That was reported in two Argentinean brothers (4) having Chilean ancestors, thereby suggesting a common ancestral mutation. At that time this mutation was named as (p. Thr747ThrfsX6) and it is reported in Leiden open variation database (LOVD) (32). Currently Human Genome Variation Society states that the frameshifts mutations should be designated by "fs" after the amino acid(s) affected by the change. For c.2233_2240dupTATGACAC mutation the first amino acid that changes is Ile748 and no Thr 747, as it was named previously [4].

The five SNPs haplotype was also present in one allele of the Argentinean patient studied [4], supporting the founder mutation hypothesis (Figure 4b). To confirm a founder mutation a more profound genetic analysis would be more certain.

In all patients, the ocular symptoms started before one year of age, and the hearing loss began several years after that, between 8 and 18 years old. This is in agreement with previous reports, which have described similar differences in the timing of onset of the ocular and hearing symptoms. Typically, ocular symptoms initiate at birth or soon after, and are not progressive. In contrast, hearing deficit starts between 10 and 25 years old with a variable degree of hearing loss and slow progression (3,33). In this study, no patient had severe hearing loss (below 71 dB HL) (28) and affected subjects described as progressive hearing loss with subsequent stabilization after 5–10 years of onset. This could be important for of genetic counseling.

All patients underwent penetrating keratoplasty during childhood and no reactivation of dystrophy was observed in any of the nonrejected grafts. Nevertheless, 4 out of 10 grafts were rejected. This high rate could be explained since keratoplasty during childhood regularly present high rejection frequency (34). After keratoplasty best corrected vision in all

Figure 4. (a) DNA sequencing of the exon 16–intron 16 border of the SLC4A11 gene in the proband of family 1 (subject IV-7) and in a control. Nucleotide sequence alignment between the sequence of patient IV-7 of family 1 and a reference sequence. Electropherograms of a healthy control subject (normal sequence), and of patient IV-7 of family 1. (b) Haplotypes of subjects of the three families and of a previously reported subject (4). Seven SNPs were analyzed to construct the haplotypes. Bold characters in a grey box shows a conserved haplotype in all the affected, including the Argentinean compound heterozygous patient (c.2528T>C/c.2233_2240dupTATGACAC) [4]. (c) Illustration of the SLC4A11 protein with the 14 transmembrane (TM) domains (blue) and the location of the c.2233_2240dupTATGACAC duplication mutation.
affected patients was low (between 0.1 and 0.3) (Supplementary Table 1). This poor improvement in the visual acuity could be explained by early life corneal involvement with the consequent development of amблиопia and supported by the high rate of nystagmus observed (3 out of 5 patients).

Another intriguing finding was the hearing problem observed in individual III-11 of family 1. She was heterozygous and did not have ophthalmic symptoms. Her audiometry result was similar to patients with CDPD (Figure 3(a and b)), but the clinic hearing loss started earlier in life. The hearing loss observed in this subject may or may not be related to the mutation described here. If it is not related the deafness may be explained by other genetics or environmental factors. If there is relationship we could speculate that given the SLC4A11 protein forms dimmers (19), mutations in one allele might interfere with the function and/or destination and/or expression of the second allele. These mutations could affect differentially the cornea and the areas related to hearing. Deafness in the heterozygous carrier of the SLC4A11 gene mutation (in III-11 of family 1) raises the possibility that SLC4A11 is a candidate gene for isolated sensori-neural vestibular hearing abnormalities (35). This effect could be also specific for some types of mutations. The hearing problem could be explained by an epistatic effect where SLC4A11 could be interacting with other genes functionally related.

Although the molecular mechanisms underlying the ophthalmic and hearing alterations observed in CDPD are poorly understood, we could speculate that the generation of a truncated protein could hamper the normal functioning of the protein. The dysfunction of the transport of fluid through the endothelium in the eye would lead to the inadequate corneal dehydration and the osmotic imbalance in ear fibrocytes.

Further studies are necessary to explore the actual functional consequences of specific homozygous and heterozygous mutations such as the one presented in this article.

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Disclosure of interest

The authors report no conflicts of interest. The authors are responsible for the content and writing of this article.

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