Studies of a pedigree with limbal dermoid cyst

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Abstract

• AIM: To study clinical features and gene mutations within the paired-like homeodomain transcription factor 2 (PITX2) gene in a pedigree of bilateral limbal dermoids.

• METHODS: Complete eye examinations have been performed on each individual of the family. Exons of paired-like homeodomain transcription factor 2 (PITX2) were amplified by polymerase chain reaction, sequenced, and compared with a reference database.

• RESULTS: We described the phenotype, clinic findings in a family with two affected members. The masses of the proband’s eyes were excised surgically demonstrating a dermoid cyst by histopathological examination. No mutation was detected in the gene PITX2 in this pedigree.

• CONCLUSION: A family of limbal dermoid cyst was reported. In addition, no pathogenic sequence variations were found in PITX2 indicating that this phenotype in this family is a distinctive entity.

• KEYWORDS: Pedigree; dermoid cyst; limbus; PITX2 gene

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INTRODUCTION

Choristomas are composed of normal cells or tissues in an abnormal location [1]. Ocular choristomas include dermoids, lacrimal gland choristomas, osseous choristomas, and complex choristomas. Ocular dermoid is formed by mesodermal tissue and covered by epithelium [2], and presented early in life. Hairs can be seen on its surface. Ocular dermoid is usually the only disorder, but 30% of the cases is associated with other abnormalities of the anterior segment and the ocular adnexae, or with the developmental syndromes of Goldenhar [3]. Ocular dermoids are rarely hereditary. Few cases of limbal or corneal dermoids have been shown to have a genetic basis [4,5]. This report describes a family of limbal dermoid.

PITX2 (paired-like homeodomain transcription factor 2; 4q25; OMIM 601542), a protein with a role in pituitary development, is a member of the bicoid-type homeobox family, expressing in neural crest cells which is necessary for optic stalk and anterior segment structure development [6]. There were a few variances found in introns [7,8]. Most mutations detected in human PITX2 are located in the homeodomain or COOH-terminal domains. Recently, mutations in PITX2 have been linked to ring dermoid of the cornea [9].

The present study reported a family of limbal dermoid. In addition, we also investigated PITX2, a gene related to the corneal ring dermoids and anterior segment abnormality, of this small pedigree. No mutation has been found in the pedigree, indicating that the disorder found in this family may not due to the changes in this gene.

SUBJECTS AND METHODS

Subjects A mother and her son with limbal dermoid cyst were recruited from the clinic of the Department of Ophthalmology at West China Hospital (Sichuan University, Chengdu, China). The immediate family (all numbered individuals in Figure 1) was interested in a genetic analysis of their condition. The study was approved by the medical ethics committee of the West China Hospital of Sichuan University. This study adhered to the tenets of the Declaration of Helsinki.

Figure 1: A: The pedigree of limbal dermoid cyst; B: The proband (II: 4): Temporal corneas were covered by the dermalipoma (arrow); C: Individual III: 5, the proband’s son was born with bilateral limbal and subconjunctival masses (arrow).
Methods The adult patient had undergone detailed clinical examinations including visual acuity, the central corneal thickness, intraocular pressure, A-scan ultrasonography, ultrasound biomicroscope (UBM). Histopathological analysis was performed on the excised masses after surgery. Blood samples were drawn by venipuncture, and genomic DNA was extracted using a Qiamp Blood Kit (Qiagen, Hilden, Germany). All coding exons of PITX2 were amplified by polymerase chain reaction (PCR) using specific primers (Table 1). The PCR fragments were purified and sequenced. Sequence data were compared pair-wise with the published PITX2 sequences.

RESULTS Clinical Findings The proband (II: 2), a 26-year-old woman, presented with the bilateral conjunctival mass and impairment of visual acuity. Her visual acuity was 20/80 on the right side (-12.0D sph-2.5D cyl ax 50°), and 20/100 (-15.0D sph) on the left side. She had developed amblyopia, exotropia and nystagmus (Figure 1A). It was noted that the temporal corneas were covered by the dermal lipoma (Figure 2A). The central corneal thickness was 523μm OD and 544μm OS, and the depth of central anterior chambers was 1.51mm OD and 1.72mm OS. Intraocular pressure was 16mmHg OD and 15mmHg OS. The UBM test of the right eye showed a neoplasm located in the anterior chamber angle (Figure 2C). Slit lamp examinations: In her right eye, there was a large irregular-shaped, yellowish white tumor (6mm×8mm), with hairs protruding from its surface (Figure 2A). As a result, the temporal visual field of the patient was limited. The mass of the left eye appeared very similar to that on the right (Figure 2B), but smaller (3mm×6mm). Both fundi demonstrated high myopic retinal degeneration. Ocular axial lengths, measured by A-scan ultrasonography, were 29.09mm OD and 31.01mm OS. The only clinical manifestation in the affected individual was in the eyes. The tumors were surgically removed and the wounds recovered well. Light microscopy was performed on formalin-fixed paraffin-embedded material provided from the excised masses. Hematoxylin and eosin stain were used for light microscopic studies. Histopathological analysis showed that the neoplasm consisted of the mature fat cells (arrow HEx100); E: Connective tissues, enlongated and spindled cells with a few capillaries (arrow HEx 100); F: The neoplasm was covered by stratified squamous epithelia (HEx100).

Table 1 Primers used in PCR for amplification of PITX2.

<table>
<thead>
<tr>
<th>Exons</th>
<th>Primer sequence (forward/reverse)</th>
<th>Product size (bp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PITX2E1</td>
<td>5'-CAAGAGACGAATGGAAAGG-3' 5'-GTCTGGAGAAAGGAGGTGAC-3'</td>
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<tr>
<td>PITX2E2</td>
<td>5'-GAAGTAAGGCAACTTCCTTCC-3' 5'-CCAGACTCGGATTATCTCAC-3'</td>
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</tr>
<tr>
<td>PITX2E3</td>
<td>5'-TCCCATCTGTGTTACTTCCA-3' 5'-CCTGCCCTCTCTCCACGCTA-3'</td>
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</tr>
<tr>
<td>PITX2E4</td>
<td>5'-CTAGGCTGAGATGTGCTGACT-3' 5'-CGAGTGCTAAGTTCAAGC-3'</td>
<td>874</td>
</tr>
<tr>
<td>PITX2E6</td>
<td>5'-GCTTGCTGCTGTGAGACC-3' 5'-AACGACCTCCTCCACGCA-3'</td>
<td>1190</td>
</tr>
<tr>
<td>PITX2E7</td>
<td>5'-CAGCTCTTCCAGGCTTCTC-3' 5'-CATTCTCTCCTGCTTCAT-TG-3'</td>
<td>376</td>
</tr>
<tr>
<td>PITX2E8</td>
<td>5'-CCCGCAATGGAAGTTTGTAG-3' 5'-TTTCTTATAGGAAGCTGAC-3'</td>
<td>1480</td>
</tr>
</tbody>
</table>
Individual III 1, the proband’s son, a 9-month-old male, was born with bilateral limbal and subconjunctival masses in both eyes which were similar to that of his mother. However, at his young age the masses were somewhat less prominent (Figure 1C). The younger patient was delivered after an uneventful pregnancy at the 37th gestational week. Besides the mother and the son, the examinations of other family members were normal.

Sequencing results The PITX2 genes were all analyzed for intragenic mutations by PCR and sequencing of all coding exons and splice sites. No disease-associated mutation was identified in the pedigree.

DISCUSSION

Limbal dermoids are rarely inherited. Most of the ocular choristomas were sporadic, with few hereditary tendency, despite their presence at a young age. The present pedigree is similar with autosomal dominant inheritance. Annular limbal dermoids of the Ring dermoid syndrome have been shown to have a genetic basis [8]. In our subjects, however, the dermoids did not show the diffuse annular lesions of the Ring dermoid syndrome.

Affected cases were mother and son in our pedigree. The relatively homogenous ocular phenotype includes limbal mass. Exotropia and amblyopia with bilateral involvement were observed in the proband. The UBM test of the proband showed that a neoplasm located in the anterior chamber angle of the right eye. Shields and Shields [24] had mentioned that limbal neoplasms possibly can invade through the corneal epithelium and sclera into the anterior chamber. The younger patient was too young to obtain the UBM test. Future follow-up and careful monitoring as the younger proband will possibly confirm this hypothesis. We also believe that the abnormal phenotype in this family was limited to the eye. Any related dysmorphic physical findings such as facial bone malformations, dental abnormalities, umbilical skin redundancy or posterior embryotoxon were absent.

During embryological development, interaction of the neural epithelium or the surface epithelium with mesenchymal cells of the neural crest is co-mediated by transcription factors encoded by a group of genes. According to previous study, mutations in PITX2 genes were associated with multiple dominantly inherited diseases related to malfunction of the eyes [22], including ring dermoid of the cornea (RDC) [9], Riger syndrome [13], iridogoniodygenesis [14] and Peter’s anomaly [10]. Recently, Doerdelmann et al [10] reported complete chemical shift assignments of the human Pitx2 homedomain and the R24H mutation that induced ring dermoid of the cornea syndrome. Xia et al [9] demonstrated that The PITX2 G185A mutation found in RDC subjects is a novel disease associated mutation resulting in a substitution of arginine by histidine at amino acid 62 (R62H) located in the conserved DNA binding homeodomain.

In the present family, mutations in the coding region of the PITX2 gene were excluded. Genetic mutation involved in limbal dermoid remains unknown. We suggest that limbal dermolipom in addition to nystagmus and strabismus is a new clinical phenotype. The exclusion of the PITX2 gene as likely candidate supports the hypothesis that this phenotype in this family is a distinctive entity in the anterior segment dysgenesis spectrum.

In conclusion, we believe that further studies in this particular family might be needed to determine a possible new gene of primary importance in the embryogenesis of the anterior segment of the eye.

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643