A mutation in DOP1B identified as a probable cause for autosomal recessive Peters anomaly in a consanguineous family

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Purpose: Peters anomaly (PA) is a heterogeneous developmental disorder characterized by central corneal opacity and iridocorneal or corneolenticular adhesions. Although many causative genes have been identified, most screened patients do not have mutations in the known genes. We aimed to identify the genetic cause of Peters anomaly in a pedigree with three affected individuals.

Methods: Slit-lamp biomicroscopy and ultrasound biomicroscopy were performed for definitive diagnosis. Exome sequencing was conducted on the DNA of all three patients. After identification of a candidate causative gene, expression of the gene was assessed with real-time PCR in various ocular tissues of three human embryos and three adults.

Results: The patients were affected with isolated PA. The parents of the patients were related to one another. Inheritance of PA was autosomal recessive. After appropriate filtering of the exome data, a homozygous variation in DOP1B remained as the only candidate genetic cause of PA in the pedigree. The variant segregated with disease status in the pedigree and was absent among 800 control Iranians. The variant has been reported in various databases at frequencies of 0.006 or less only in the heterozygous state in some cohorts of African origin. The p.Val1660 amino acid affected by the mutation is completely conserved in mammals and birds during evolution. Expression of DOP1B was shown in all adult and embryonic lens, iris, cornea, sclera, and retina tissues that were tested.

Conclusions: DOP1B that encodes DOP1 leucine zipper like protein B was identified as the putative PA-causing gene in pedigree PA-101. As DOP1B is positioned within the Down syndrome chromosomal region on chromosome 21, until now this gene has mostly been studied with respect to brain functions. However, members of the Dopey gene family have been shown to have roles in development in other organisms. Evidence of the expression of DOP1B in various PA-relevant eye tissues, which, to the best of our knowledge, is shown here for the first time, is to be noted. However, this finding does not necessarily implicate a specific role for DOP1B in eye development as the gene is expressed in many tissues. Ultimately, definitive assessment of the contribution of DOP1B to PA pathology awaits identification of mutations in the gene in unrelated patients with PA and functional studies.

Anterior segment dysgenesis (ASD) includes various developmental disorders that affect the cornea, iris, and lens [1]. Peters anomaly (PA) is a form of ASD which itself is clinically heterogeneous. PA is characterized by central corneal opacity, defects in the posterior stroma, Descemet’s membrane, and endothelium, and iridocorneal or keratolenticular adhesions [2]. The majority of PA cases are bilateral. The disease is usually associated with significant visual loss due to impairment of the central visual axis. Differential diagnosis with respect to related disorders such as sclerocornea is facilitated with ultrasound biomicroscopy [3]. In comparison to optical technologies, ultrasound can travel through opaque media and produce higher-quality images of ocular structures. The developmental mishaps that are thought to culminate in the PA phenotype may involve lens vesicle separation from the surface ectoderm, subsequent invasions of neural crest cells that normally give rise to the corneal endothelium, the corneal stroma, and the iris stroma, or anterior displacement of a normally developed lens [2,4]. Migration of mesenchyme cells initiate at about the sixth week of human gestation [2,5]. Although eye development is well advanced by the time of birth, completion is postnatal [6]. Peters anomaly presentation may be isolated, in conjunction with other ocular anomalies, or part of a broader syndrome; isolated cases are relatively rare (Table 1) [2,7]. Glaucoma is the most frequent accompanying ocular presentation, possibly present in more than 50% of cases [8]. The best-studied syndromic form of PA is Peters plus syndrome (OMIM: 261540) which, in addition
| Gene     | Chromosome position | Selected biologic functions                                                                 | Associated anomalies                                                                 | Inheritance | Peters anomaly-related references |
|----------|---------------------|-------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-------------|----------------------------------|
| B3GLCT  | 13q12               | Beta-1,3-glucosyltransferase                                                            | Peters Plus syndrome                                                                 | AR          | [9,10,20-22]                     |
| CDH2    | 18q12               | Cell-cell adhesion, member of the cadherin superfamily                                   | Eye, heart, brain, and skeletal anomalies, Peters anomaly                              | AD          | [11]                            |
| COL4A1  | 13q34               | Collagen component of basement membrane                                                  | Cerebrovascular disease presentations with ocular, kidney, & muscle anomalies          | AD          | [23]                            |
| CYP1B1  | 2p22                | Cytochrome P450 monoxygenase                                                            | Primary congenital glaucoma                                                           | AR          | [42,43]                         |
| DOP1B   | 21q22               | Developmental roles in various organisms, brain development, member of Dopey gene family | Association with Down syndrome                                                        | AR          | Present study                    |
| FLNA    | Xq28                | Actin-binding protein                                                                    | Otopalatodigital spectrum                                                             | XLR         | [12]                            |
| FOXC1   | 6p25                | Transcription factor                                                                     | Anterior segment dysgenesis, Axenfeld–Rieger syndrome                                 | AD          | [24-27]                         |
| FOXE3   | 1p33                | Transcription factor                                                                     | Microphthalmia, cataract, anterior segment dysgenesis                                 | AD          | [44,45]                         |
| HCCS    | Xp22                | Holocytchrome C-type synthetase cytidylyltransferase-like protein                        | Microphthalmia, MLS syndrome, Peters anomaly, Walker-Warburg syndrome                  | XLD         | [12]                            |
| NCAPG2  | 7q36                | Chromosome condensation, member of condensin II complex                                   | Khan-Khan-Katsanis syndrome, severe neurodevelopmental defects including ocular abnormalities | AR          | [13]                            |
| NDP     | Xp11                | Member of canonical Wnt signaling pathway                                                 | Norrie disease, familial exudative vitreoretinopathy                                  | XLR         | [12]                            |
| PAX6    | 11p13               | Transcription factor                                                                     | Anterior segment dysgenesis, cataract                                                  | AD          | [46]                            |
| PITX2   | 4q25                | Transcription factor                                                                     | Anterior segment dysgenesis Axenfeld–Rieger syndrome                                   | AD          | [28,29]                         |
| POMT2   | 14q24.3             | O-mannosyltransferase2                                                                   | Muscular dystrophy-dystroglycanopathy, Walker-Warburg syndrome                          | AR          | [14]                            |
| PITX3   | 10q24               | Transcription factor                                                                     | Anterior segment dysgenesis, cataract                                                  | AD          | [30]                            |
| PROC    | 2q14                | Inactivator of coagulation factors Va and VIIIa                                          | Hereditary thrombophilia                                                               | AR          | [15]                            |
| PTCH1   | 9q22                | Receptor for secreted hedgehog ligands                                                  | Basal cell Nevus syndrome, holoprosencephaly 7                                         | AD          | [16]                            |
| RERE    | 1p36.23             | Transcriptional regulation, regulator of retinoic acid signaling                         | Neurodevelopment disorder with or without anomalies of brain, eye or heart             | AD          | [17]                            |
| SLC4A1I | 20p13               | SLC4 bicarbonate transporter                                                             | Corneal endothelial dystrophy 2                                                       | AR          | [12]                            |
| TFAP2A  | 6p24                | Transcription factor                                                                     | Branchiooculofacial syndrome                                                           | AD          | [12]                            |
| WDR37   | 10p15               | Member of the WD repeat protein family                                                  | Neuroocularcardiogenitourinary syndrome                                                | AD/AR       | [18]                            |
| WFSI    | 4p16                | Cation-selective ion channel                                                            | Wolfram-like Syndrome                                                                  | AD          | [19]                            |

*From NCBI and the literature; AD, autosomal dominant; AR, autosomal recessive; AD/AR, both autosomal dominant and autosomal recessive; XLD, X-linked dominant; XLR, X-linked recessive
to PA features, is characterized by growth retardation, short stature, brachydactyly, and distinctive facial features [9,10].

In terms of inheritance, Peters anomaly incidence is most often apparently sporadic, although recessive inheritance and dominant inheritance have also been observed (Table 1) [2,8]. Twenty-one PA causative genes that have been reported to date are listed in Table 1. Many of these, including CDH2 (OMIM: 114020; Gene ID: 1000) [11], FLNA (OMIM: 300017; Gene ID: 2316) [12], HCCS (OMIM: 300056; Gene ID: 3052) [12], NCAPG2 (OMIM: 608532; Gene ID: 54892) [13], NDP (OMIM: 300658; Gene ID: 4693) [12], POMT2 (OMIM: 607439; Gene ID: 29954) [14], PROC (OMIM: 612283; Gene ID: 5624) [15], PTC1 (OMIM: 601090; Gene ID: 2296) [24-27], NCAPG2 [13], PITX2 (OMIM: 601542; Gene ID: 5308) [28,29], PITX3 (OMIM: 602669; Gene ID: 5309) [30], RERE [17], SLC4A11 [12], TFAP2A [12], WDR37 [18], and WFSI [19], have been reported only in single patients or families. The majority of the genes, including B3GLCT (OMIM: 610308; Gene ID: 145173) [9,10,20-22], CDH2 [11], COL4A1 (OMIM: 120130; Gene ID: 1282) [23], FLNA [12], FOXC1 (OMIM: 601090; Gene ID: 2296) [24-27], NCAPG2 [13], PITX2 (OMIM: 601542; Gene ID: 5308) [28,29], PITX3 (OMIM: 602669; Gene ID: 5309) [30], RERE [17], SLC4A11 [12], TFAP2A [12], WDR37 [18], and WFSI [19], are associated with syndromic forms of PA. Many of the reported PA causative genes (COL4A1, CYP1B1 (OMIM: 601771; Gene ID: 1545), FOXC1, FOXE3 (OMIM: 601094; Gene ID: 2301), PAX6 (OMIM: 607108; Gene ID: 5080), PITX2, and PITX3) are primarily associated with other conditions that are usually ophthalmic conditions [12]. B3GLCT, the genetic cause of Peters plus syndrome, is an exception in this regard. Notably, mutations in the known PA-associated genes were not observed in most patients of various genetic screenings studies [11-14,16-19]. We report identification of a mutation in DOP1B (OMIM: 604803; Gene ID: 9980) as the possible cause of Peters anomaly in three affected individuals of a pedigree and show expression of the gene in various human embryonic and adult ocular tissues.

METHODS

This research was performed with adherence to the Declaration of Helsinki and the ARVO statement on human subjects. Participants or responsible guardians gave informed consent, and the research was approved by the ethics board of the University of Tehran. Eye globes were obtained from the Central Eye Bank of Iran, a non-profit organization established three decades ago and dedicated mainly to the procurement of eye globes from deceased individuals to be used for corneal transplants and related procedures. Responsible individuals of globe donors gave signed permission for use of the globes or parts for research purposes. Far less frequently, globes of aborted embryos are obtained for research purposes through affiliations of the Eye Bank with the Shahid Beheshti University of Medical Sciences and with informed written consent of the parents. The embryos whose eye globes were used in this study had no gross or apparent anatomic abnormality.

Subjects and eye examinations: Three members of a pedigree diagnosed with PA were referred to us for genetic analysis. Slit-lamp biomicroscopy was performed for all three patients, and ultrasound biomicroscopy (UBM; Eye Cubed™, Ellex, Adelaide, Australia) was performed for two patients. UBM scanning was conducted to a depth of 5 mm, using a 40 MHz transducer and an anterior B-scan time gain control (TGC) probe.

Genetic analysis: Genetic analysis was initiated with whole exome sequencing of the DNA of the three patients using the Sure Select V6-POST kit and an Illumina HiSeq 4000 system (Illumina, Foster City, CA). Exome sequence alignment for each patient was against human reference genome GRCh37/ hg19, and variant callings were done using wANNOVAR. Subsequently, filtering was performed by removing single nucleotide polymorphisms (SNPs) with a minor allele frequency (MAF) of >0.01 in the dbSNP database, the Trans-Omics for Precision Medicine program, the 1000 Genomes database, the NHLBI Exome Sequencing Project, the Exome Aggregation Consortium database, the Genome Aggregation Database, the Greater Middle East Variome Project, ENSEMBL, the Healthy Exomes database, the Sequencing Initiative Suomi database, the VarCards database, or the Iranome database. SNPs observed in in-house exome data belonging to approximately 110 unrelated Iranians affected with non-ocular diseases were also removed. Among the variations that remained, those that did not affect amino acid change or splicing were not considered. Subsequently, a file of homozygous variations and a file of compound heterozygous variations were prepared. The files of the patients were scrutinized to identify retained variations common to the three patients. The single variation identified was screened for segregation with disease status in the pedigree with Sanger sequencing of available members. It was also sought in the Iranome database that contains exome sequence data on 800 healthy Iranians.

Gene expression analysis: Expression of the putative PA-causing gene DOP1B was assessed in lens, iris, cornea, sclera, and retina tissues isolated from the eye globes of three adults and three embryos. The isolation procedure was
Figure 1. Peters anomaly pedigree PA-101. A: Pedigree PA-101. Filled square and circles: PA-affected. Unfilled shapes: not affected with PA. B: Chromatograms showing homozygous and heterozygous mutation c.4978G>A (p.Val1660Ile) in DOP1B, and the wild-type genotype. C: Amino acid sequence alignments showing conservation of Val at positions corresponding to p.1660 in the human DOP1B-encoded protein in orthologous proteins of other organisms.

Figure 2. Slit-lamp biomicroscopy images show the Peters anomaly. A: PA-101-VI4. B: PA-101-VI5. C: PA-101-VII2. The images of PA-101-VI4 and PA-101-VI5 show total corneal opacity and vascularization. The image of PA-101-VII2 shows total corneal opacity and superficial keratinization.
Figure 3. Ultrasound biomicroscopy images show the Peters anomaly. A: PA-101-VI4. B: PA-101-VI5. Images of both patients show irido-corneal adhesion (arrows).

Figure 4. Expression of DOP1B in adult and embryonic ocular tissues as assessed with real-time PCR. Relative expression levels are presented as normalized to glyceraldehyde-3-phosphate dehydrogenase (GAPDH) expression. The average threshold cycle (CT) of GAPDH was 16.21. The expression of DOP1B was assessed in the cornea, lens, retina, sclera, and iris tissues of three adult men and three embryos. Standard deviations are shown.
performed by an expert in ocular pathology (MRK), taking great care to avoid contamination by adjacent tissues. One embryonic retina and two embryonic iris samples were not used because of unsuitable quality. The adults were men aged 20, 25, and 35 years old. The embryos were males aborted at 12, 13, and 14 weeks of gestation. Total RNA extraction was performed using RNX-Plus according to the manufacturer’s instructions (Sinaclon, Tehran, Iran). Complementary DNA (cDNA) was synthesized using random hexamer primers. Real-time PCR was performed on a Corbett Rotor-Gene 6000 machine (QIAGEN, Hilden, Germany) in 20 µl reactions that contained 1 µg of the cDNA, 10 µl SYBR green (BioFACT™, Daejeon, South Korea), and 10 pmol of forward and reverse primers. GAPDH (OMIM: 138400; Gene ID: 2597; glyceraldehyde-3-phosphate dehydrogenase) was used as the control gene. Sequences of forward and reverse primers used for amplification of DOP1B cDNA were 5′-ACT CAA CAA GGC TCT TCA GAG-3′ and 5′-GCA GCT GTA CAG AAA CAA GTC C-3′, respectively. These amplify the two largest alternatively spliced DOP1B cDNAs (NM_001320714.1 and NM_005128.3) that differ only in the 5′ untranslated region (UTR); the lengths of the two transcripts differ by 61 nucleotides. All expression analyses were performed in triplicate.

RESULTS

Subjects and eye examinations: The pedigree (PA-101) of the three related PA-affected individuals is shown in Figure 1A. Slit-lamp examination of PA-101-VI4, who was a 30-year-old woman, showed dense bilateral total corneal opacity and vascularization (Figure 2A). UBM images showed iridocorneal adhesion (Figure 3A). The patient did not have dysmorphic facial features or cognitive anomalies. Growth during childhood was reported to be normal. Her presentation was consistent with isolated PA diagnosis. PA-101-VI5 was a 19-year-old brother of PA-101-VI4. Results of his slit-lamp and UBM examinations were similar to those of his older sister (Figure 2B, Figure 3B). This patient had no other notable presentation. PA-101-VII2 was a 7-year-old girl and a distant relative of siblings. Her slit-lamp examination showed bilateral total corneal opacity and keratinization of the corneal epithelium and conjunctiva (Figure 2C). This young patient was not cooperative for the UBM examination. Nevertheless, considering affiliation with the described siblings, PA diagnosis is also justified for PA-101-VII2. Her facial and body appearance was normal. The mother reported that her daughter had hearing problems, and audiometric testing confirmed the presence of moderate sensorineural hearing loss. Hearing loss has also been reported for PA-affected patients with mutations in TFAP2A and NDP [12].

Genetic analysis: The two affected siblings (PA-101-VI4 and PA-101-VI5) were born to consanguineous parents whose common ancestors were four generations removed (Figure 1A). An affected relative (PA-101-VI2) was also born to consanguineous parents whose common ancestors were two generations removed. In addition to these consanguinities, all four parents were related to one another. The consanguineous parents of the patients were not PA-affected, consistent with autosomal recessive inheritance of the disease. Although consanguinity of the parents suggested that a homozygous sequence variation would most likely be the PA-causative mutation, compound heterozygous variations were also considered for the sake of stringency. After the described filterings and data analysis, a candidate disease causing in known PA-associated genes was not identified. The only homozygous variation or compound heterozygous variations identified that were present in all three patients was the homozygous variation c.G4978A in DOP1B (alias DOPEY2 and C21orf5; Figure 1B). The relatively distant familial relationship between the parents of the siblings and between the two branches of the family were likely important factors in reducing the number of candidate genes after the filterings. The human DOP1 gene is located on chromosome 21q22.12, within the Down syndrome chromosomal region (DSCR) [31-33]. The shared DOP1B variation was within a shared 3.9 Mb homozygous block bordered by positions 34,413,505 and 38,385,585 on this chromosome. DOP1B intragenic variations that define the haplotype associated with the c.G4978A variation in DOP1B on chromosome 21 are T>G, C>A, and G>A at positions 37,617,630, 37,617,724, and 37,661,405, respectively. These are relatively common variations with MAF ≥ 0.14. The specifications of the exome data of all three patients reflected high-quality sequencing (Supplementary Table S1). Sanger sequencing revealed segregation of the variation with disease status, as both pairs of parents and the unaffected sibling of each of the siblings were heterozygous carriers of the variation (Figure 1B). The variation was absent in 800 control Iranians. It was reported in various databases (rs139989297) only in the heterozygous state at low frequencies. The highest reported frequencies were in various cohorts of African origin (ANNOVAR reporting of 0.0015 in Africa cohort of 1000 Genome project, ENSEMBL reporting of 0.006 in cohort of Mende in Sierra Leone, and Exome Sequencing Project reporting of 0.0036 in an African American cohort). Therefore, c.G4978A in DOP1B that causes p.Val1660Ile in the encoded protein, DOP1 leucine zipper like protein B, was considered the best candidate PA-causing mutation in pedigree PA-101. Valine at position p.1660 in the human protein is well conserved among mammals and birds (Figure 1C). Five (fathmm-MKL; LRT; MutationTaster; Polyphen2_HDIV;
Polyphen2_HVAR) of 12 bioinformatics tools predict that the mutation is damaging.

Gene expression analysis: The expression of DOP1B was queried in the eye, as this is the target organ of Peters anomaly. Aborted embryos with gestations that correspond to the time point of the determination and differentiation of ocular tissues were not accessible. Instead, expression analysis at the level of transcription was performed in young male adults and in embryos that were aborted at 12, 13, and 14 weeks of gestation. Expression of DOP1B at the RNA level was shown in all adult and embryonic lens, iris, cornea, sclera, and retina tissues that were tested (Figure 4).

DISCUSSION

Peters anomaly is a clinically heterogeneous developmental eye disorder that has been associated with many genes which together are the cause of disease in a small proportion of patients with PA examined [11]. We have identified DOP1B as a novel putative PA-causing gene. Of course, the possibility that the disease in pedigree PA-101 was caused by mutations in regions of the genome not included in the exome sequencing protocol, including deep intronic variations, cannot be strictly ruled out. Because of the inclusion of DOP1B in the DSCR, the expression of this gene in humans has most often been examined in the brain and with respect to Down syndrome [32,34-36]. DOP1B was shown to be differentially expressed in different brain regions of the normal human fetus and overexpressed in Down syndrome fetal brain tissues. Studies in transgenic mice suggested involvement of DOP1B in brain morphogenesis and mental retardation [32]. An association between DOP1B copy number variations (CNVs) in DNA extracted from brain tissue and late-onset Alzheimer disease has also been reported [37]. In addition to the brain, the expression of DOP1B has been reported in many other tissues, including the eye (ENSG00000142197-DOPEY2/tissue_MGI:1917278). To the best of our knowledge, for the first time, we showed the expression of DOP1B in various specific embryonic and adult ocular tissues, including the cornea, lens, retina, sclera, and iris. These include tissues that are most relevant to Peters anomaly pathology. Although the expression of DOP1B in these tissues is consistent with its potential role in ocular development, the finding does not necessarily implicate such a role because the gene is expressed in many tissues. Ultimately, definitive assessment of the contribution of DOP1B to PA pathology awaits identification of mutations in the gene in unrelated patients with PA and functional studies.

DOP1B is a member of the Dopey gene family whose members contain leucine zipper-like domains with protein–protein interaction functions [32]. Several members of this family, including DOP1B homologous genes Dopa in Aspergillus nidulans, Dop1 in Saccharomyces cerevisiae, and pad1 in Caenorhabditis elegans, have roles in cell differentiation, morphogenesis, and development in the respective organisms [38,39]. The orthologous gene in Drosophila, CG15099 (FlyBase), was suggested to be involved in cell cycle regulation [40]. In addition, as noted above, transgenic studies in mice implicated DOP1B in brain development [32]. Identification of a mutation in DOP1B in Peters anomaly–affected individuals of pedigree PA-101 also implicates the gene in eye development. The leucine-like zipper domains of the encoded protein could promote protein–protein interactions which may, in turn, affect transcriptional regulation. Although the p.Val1660Ile mutation in the PA-101 patients is not within these domains, it may indirectly affect their functions. Unfortunately, the crystalline structure of the DOP1B protein is not available. Interestingly, in a recent bioinformatics study, DOP1B was identified as one of several genes in which disease-causing variants have not been identified, but whose variants are strong candidates for disease causation [41]. It is likely that DOP1B and other yet-to-be-identified PA-causing genes, like several already identified, will each contribute to disease status in only a small minority of patients.

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