A pathogenic variant in the transforming growth factor beta I (TGFBI) in four Iranian extended families segregating granular corneal dystrophy type II: A literature review

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Objective(s): Granular and lattice corneal dystrophies (GCDs & LCDs) are autosomal dominant inherited disorders of the cornea. Due to genetic heterogeneity and large genes, unraveling the mutation is challenging.

Materials and Methods: Patients underwent comprehensive clinical examination, and targeted next-generation sequencing (NGS) was used for mutation detection. Co-segregation and in silico analysis was accomplished.

Results: Patients suffered from GCD. NGS disclosed a known pathogenic variant, c.371G>A (p.R124H), in exon 4 of TGFBI. The variant co-segregated with the phenotype in the family. Homozygous patients manifested with more severe phenotypes. Variable expressivity was observed among heterozygous patients.

Conclusion: The results, in accordance with previous studies, indicate that the c.371G>A in TGFBI is associated with GCD. Some phenotypic variations are related to factors such as modifier genes, reduced penetrance and environmental effects.

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Introduction

Granular and lattice corneal dystrophies (GCDs & LCDs) are heterogeneous autosomal dominant disorders. Gradual accumulation of hyaline, amyloid and non-amyloid deposits within anterior stromal layer of the cornea lead to decrement of sight acuity and visual impairment in the first or second decades of life (1). Mutations in at least nine genes ARSCTI, CHST6, COL8A2, GLA, GSN, KRT3, KRT12, M1S1 and UBADI1 have been reported in various types of CDs (2, 3). LCDs and GCDs are transforming growth factor beta induced protein (TGFBI)-linked corneal dystrophies and heterozygous mutations in TGFBI (OMIM 601692, previously called BIGH3), on human chromosome 5q31 is responsible for LCDs and GCDs (4). TGFBI mutations were first identified in human lung adenocarcinoma cell line by Skonier et al. (5). For the first time, four missense mutations in the TGFBI gene were reported by Munier et al., as causative gene in patients with four different types of CD (6). Until now, more than 70 various mutations including missense, non-sense, deletions and insertions have been reported to cause diverse types of CDs (7). Two hot spot codons in TGFBI in relation with LCDs and GCDs are R124 and R555 situated within exons 4 and 12, respectively (8). LCDs and GCDs are epithelial–stromal CDs according to the latest classification of International Committee for the Classification of Corneal Dystrophies (9). LCDs and GCDs are classified by the Committee for the Classification of Corneal Dystrophies (9). GCD type II (Avellino type or ACD; OMIM 607541), was first described by Felborg et al. in patients from Avellino origin, Italy (10). ACD is characterized as granular or combined granular-lattice, grayish-white, crumb-like, superficial and/or amyloid deposits accumulation within anterior third of corneal stroma and/or amyloid lattice opacities in deeper sites of cornea (11). The TGFBI gene encodes a 68-kDa extracellular matrix (ECM) containing 683 amino acid protein called Keratoepithelin (12). The TGFBI protein is expressed in different cell types as well as corneal stromal epithelium cells (13). The protein is involved in many cell processes and functions such as cell adhesion, cell migration, cell differentiation and autophagy phenomenon (14, 15). It has four Fasciclin like (FAS1) domains in C-terminus.
Arginine 124 is situated within the first FAS1 domain, a conserved extracellular domain involved in cell adhesion interactions. Mutations lead to abnormal protein processing and accumulation (16). There are few reports of pathogenic variants in the TGFBI gene in Iranian population. In this study, we applied next-generation sequencing for molecular diagnosis of ACD in an extended Iranian kindred. A known pathogenic variant was co-segregating with the phenotype in the pedigree.

**Materials and Methods**

**Subjects**

Four large isolated pedigrees from a village in South Khorasan province of Iran with several affected members suffering from visual problems were recruited. Precise clinical examinations including slit-lamp examination for available normal and affected members were performed by an ophthalmologist. A complete family history was obtained and the pedigrees were drawn by a medical geneticist. Subsequently, full investigation revealed familial relationship between these four selected pedigrees. After taking informed written consent, peripheral blood samples were obtained in EDTA-containing tubes.

**Molecular analysis**

Genomic DNA was extracted from peripheral blood lymphocytes using Prime Prep Genomic DNA Extraction kit (GeNet Bio, Korea) according to the manufacturer's instruction. Qualitative and quantitative assessment of genomic DNA was checked using 1.2% agarose gel and Nanospec cube biophotometer (Nanolytik®, Dusseldorf, Germany).

A custom designed Nimblegen chip was used to capture exons and exon-intron boundaries of the TGFBI, UBIAD1, CHST6, VSX1, PIKFYVE, DCN, KRT12, and KRT3 genes and sequenced on an Illumina Hiseq 2000 in BGI-Clinical laboratories, Shenzhen, China. BWA was used for mapping short reads to the reference genome (hg19, NCBI Build 37), Picard for removal of duplicate reads and GATK for variant calling. Annotation was performed by ANNOVAR. Heterozygous missense, start codon change, splice site, stop gain, stop loss and nidel variants with MAF < 1%, were filtered in dbSNP version 137, 1000 genomes database, NHLBI GO exome sequencing project (ESP) and exome aggregation consortium (ExAC). We applied online software tools including MutationTaster2, SIFT, PolyPhen-2 to investigate in silico pathogenicity prediction of the missense variant. Candidate variant was investigated in the Human Gene Mutation Database (HGMD) and in the literature to seek the variant novelty and its association with a phenotype.

**Results**

**Clinical and molecular findings**

We examined several affected and normal individuals of four pedigrees, aging 5 to 70 years. History of visual problems was found in more than 60 individuals that apparently were not close relatives. As a result of isolation condition, multiple consanguineous marriages were observed and affected children manifested with a more sever phenotype. A broad spectrum of disease symptoms were observed among affected individuals, from subclinical forms to severe and pure granular and mixed lattice-granular forms of the disease. Some individuals were found with recurrence of dystrophy after bilateral corneal transplantation. NGS revealed a known missense disease-causing variant, c.371G>A (p.R124H), within exon 4 of the TGFBI gene and it was confirmed by Sanger sequencing. In silico prediction tools revealed the disruptive effect of the variant (Table 1).

**Table 1.** In silico analysis of the variant pathogenicity for c.371 G>A in TGFBI

| Software       | MutationTaster2.0 | SIFT   | PolyPhen-2     | FATHMM     |
|----------------|-------------------|--------|----------------|------------|
| Prediction     | Disease causing   | Damaging | Probably damaging | Damaging   |
| Score          | NA                | 0.022  | 0.958          | -2.69      |

NA: Not Available
Pedigree A
Proband was a 27-year-old female with light corneal dystrophy. She belonged to a large family with three generation history of visual impairment. The p.R124H variant was detected in the proposita, her mother and her affected siblings (Figure 1A).

Pedigree B
Probands were two offsprings of a first cousin consanguineous marriage. A 5-year-old girl within a pedigree was diagnosed with mild, slowly progressive CD (Figure 2A). This condition decreased power of vision in both eyes to half at age 5. Slit-lamp examination showed granular deposits within cornea. Her 11-year-old brother was affected by more intensive form with considerable vision loss. He was diagnosed at age 6. The deposits were more aggregated than his 5-year-old sister (Figure 2B). The first offspring of the family was affected by milder form of ACD who was reported to be heterozygous for the mutation. Their 42-year-old mother was affected by a very milder form, with no visual impairment. Light scattering at night was the only problem for the mother. The size and density of deposits were considerably smaller than her offsprings (Figure 2C). Molecular results showed that parents were heterozygous.

Pedigree C
Two mild form affected Probands referred to know about their offspring risk evaluation and genetic counseling. Several affected members were found in their maternal family with a wide spectrum of the disease phenotype. The heterozygous variant co-segregated with the phenotype in the pedigree (Figure 1C).

Pedigree D
A large association with individuals affected with CD in three generations was identified with mild form of the disease (1D). Sequencing results revealed heterozygous pathogenic variant, p.R124H, in all of these patients. Healthy individuals were carrying wild type alleles in homozygous status.
Here we report a disease-causing variant, c.371G>A (p.R124H), at exon 4 of the TGFBI gene, in four large Iranian pedigrees. This position is considered as a hotspot codon in TGFBI (17). The variant affects the first FAS1 domain of the protein, probably by altering protein solubility and stability (18). Although mutations in TGFBI are distributed throughout the gene, there are four exons with the highest rate of missense mutations, including exons 12, 14, 4 and 11, respectively (Table 2). Indeed, TGFBI-linked CDs are the great examples for genotype-phenotype correlation. Specific mutation leads to a specific outcome; furthermore, special mutations in TGFBI-linked CDs are found to be related to the disease severity regardless of homozygous or heterozygous status (18). It seems that mutations in primary exons, especially within exon 4, have more contribution to create granular types of corneal dystrophies and middle exons, especially exon 12 are more responsible for lattice types (Table 2). R124H has the most contribution among GCD2 cases. Mashima and colleagues reported a group of patients affected with GCD2 and reported p.R124H mutation (19). Alavi and colleagues reported a group of patients affected with GCD2 and reported p.R124H in Iranian population and Middle East for the first time. Here we report the largest Iranian group of GCD2 patients with more than 70 affected individuals from four pedigrees living in an isolated village. This position is considered as a hotspot codon in TGFBI (17). The variant affects the first FAS1 domain of the protein, probably by altering protein solubility and stability (18). Although mutations in TGFBI are distributed throughout the gene, there are four exons with the highest rate of missense mutations, including exons 12, 14, 4 and 11, respectively (Table 2). Indeed, TGFBI-linked CDs are the great examples for genotype-phenotype correlation. Specific mutation leads to a specific outcome; furthermore, special mutations in TGFBI-linked CDs are found to be related to the disease severity regardless of homozygous or heterozygous status (18). It seems that mutations in primary exons, especially within exon 4, have more contribution to create granular types of corneal dystrophies and middle exons, especially exon 12 are more responsible for lattice types (Table 2). R124H has the most contribution among GCD2 cases. Mashima and colleagues reported a group of patients affected with GCD2 and reported p.R124H mutation (19). Alavi and colleagues reported a group of patients affected with GCD2 and reported p.R124H in Iranian population and Middle East for the first time. Here we report the largest Iranian group of GCD2 patients with more than 70 affected individuals from four pedigrees living in an isolated village. It seems that GCD2 is the most frequent type of the disease in Iranian population, and p.R124H is considered as the most common cause of the disease (20, 21). More investigations are needed to evaluate the prevalence of TGFBI mutations in CD Iranian patients. The phenotype of homozygous patients were more severe than heterozygous individuals, as earlier age of onset, rapid progression of the disease or more deposits within the cornea in concordance with previous studies (22). Because all patients were sharing the same mutation, we suppose that founder mutation or genetic drift are the responsible mechanisms for high disease prevalence in this isolated village. Clinical variability observed among heterozygous individuals is in concordance with previous investigations (23, 24). However, the reasons of this phenomenon are not completely understood; we hypothesized this results from the effect of modifier genes and other loci on expression of the TGFBI gene. Reduced penetrance, complexity of monogenic traits, epistasis interactions and environmental factors can be other explanations (25-27). Despite enormous advances in genetics, medicine and technology, there are rare successful treatments for monogenic disorders like CDs. In fact, performing procedures such as laser-assisted in situ keratomileusis (LASIK) for GCD2 patients can precipitate the course of the disease (28). We did not find history of LASIK in our patients, although it has a rare indication in such patients. Corneal transplantation had been operated for two of our patients, but disease manifestations were observed few years later in both of them (29).

Table 2. Reported pathogenic variants in the TGFBI gene

| No. | Coding Position | Protein alteration | Exon | Phenotype | Countries | Ref. No. |
|-----|----------------|-------------------|------|-----------|-----------|---------|
| 1 | c.337G>A | p.V113H | 4 | GCD | Mexico | (30) |
| 2 | c.367G>C | p.D123H | 4 | Atypical GCD, low penetrance, LCD1, TBCD, RBCD, GCD2 | Vietnam | (31) |
| 3 | c.370C>T | p.R124C | 4 | GCD, GCD2 | China, Korea, Japan | (6) |
| 4 | c.371G>A | p.R124H | 4 | GCD, GCD2 | Japan, Korea, China, UK, Iran, Germany | (6) |
| 5 | c.371G>A; c.1631A>G | p.R124H/N544S | 4;12 | LCD1 | Japan | (7) |
| 6 | c.371G>A; c.337G>A | p.R124H; NM | 4 | GCD | Hong Kong | (7) |
| 7 | c.371G>T | p.R124L | 4 | CDRB, LCD1, RBCD, GCD2 | Brazil, USA, Czech, China, France | (32) |
| 8 | c.371G>T | p.R124L | 4 | LCD1, RBCD, GCD2 | Brazil, USA, Czech, China, France | (33) |
| 9 | c.370C>T | p.R124S | 4 | GCD1 | UK | (8) |
| 10 | c.393G>T | p.Glu131D | 4 | Schnyder Crystalline like CD phenotype (no mutation in UBIAD gene) | Germany | (34) |
Continued Table 2.

| No. | Sample ID | Sample Type | GCD | Location |
|-----|-----------|-------------|-----|----------|
| 11  | c.1879T>A  | p.A626T     | C   | Mexico   |
| 12  | c.1879T>A  | p.A626T     | C   | Mexico   |
| 13  | c.1879T>A  | p.A626T     | C   | Mexico   |
| 14  | c.1879T>A  | p.A626T     | C   | Mexico   |
| 15  | c.1879T>A  | p.A626T     | C   | Mexico   |
| 16  | c.1879T>A  | p.A626T     | C   | Mexico   |

GCD: Granular Corneal Dystrophy; LCD: Lattice Corneal Dystrophy; TBCD: Thiel-Behnke Corneal Dystrophy; RBDC: Reis Bukler Corneal Dystrophy; FVGGD: France Variant Granular Corneal Dystrophy; GGLCD: combined granular-lattice corneal dystrophy; NM: Not Mentioned

* Presented data are arranged based on RefSeq NM_000358; NP_000349
A pathogenic variant in TGFBI in Iranian families with GCD

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Conclusion

High frequency of TGFBI mutation, p.R124H, in Iranian population can result from a founder mutation or genetic drift. The results are useful for genetic counseling, cascade screening and prenatal diagnosis to reduce disease burden as there is not any treatment for the disease right now.

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Conflicts of Interest

The authors declare that there are no conflicts of interest.

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