Iranian Journal of Basic Medical Sciences

ijbms.mums.ac.ir

IJBMS

# 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

Aliasgar Mohammadi [1], Azam Ahmadi Shadmehri [2], Mahnaz Taghavi [3], Gholamhossein Yaghoobi [4, 5], Mohammad Reza Pourreza [1], Mohammad Amin Tabatabaiefar [1, 6*]

[1] Department of Genetics and Molecular Biology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
[2] Department of Genetics, Islamic Azad University, Science and Research Branch, Tehran, Iran
[3] Zeiss Ophthalmology Clinic, Tabas, South Khorasan, Iran
[4] Department of Ophthalmology, Birjand University of Medical Science, South Khorasan, Iran
[5] Social Detrimental Health Center, Birjand University of Medical Science, South Khorasan, Iran
[6] Pediatric Inherited Diseases Research Center, Research Institute for Primordial Prevention of Non-communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran

**ARTICLE INFO**

***Article type:***
Original article

***Article history:***
Received: Dec 9, 2018
Accepted: Mar 15, 2020

***Keywords:***
Corneal dystrophy
Iran
Next-generation sequencing
Pathogenic variant
*TGFBI*

**ABSTRACT**

***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.

► *Please cite this article as:*
Mohammadi AA, Ahmadi Shadmehri A, Taghavi M, Yaghoobi GhH, Pourreza MR, Tabatabaiefar MA. 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. Iran J Basic Med Sci 2020; 23:1020-1027. doi: 10.22038/ijbms.2020.36763.8757

## 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 *ARSC1, CHST6, COL8A2, GLA, GSN*, *KRT3, KRT12, M1S1* and *UBIAD1* 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 the disease (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). 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 non-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.

*Corresponding author: Department of Genetics, Islamic Azad University, Science and Research Branch, Tehran , Iran, Pediatric Inherited Diseases Research Center, Research Institute for Primordial Prevention of Non-communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran. Tel: +98-31-37929144; Email: tabatabaiefar@med.mui.ac.ir

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 Metods

### *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, FATHMM, SIFT and 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.

Using forward: 5' TCCCTCCTTCTGTCTTCTGC 3' and reverse: 5' CTCGGGGAAGTAAGGCAGTT 3' primers, exon 4 of the *TGFBI* gene was amplified. PCR products were sequenced bi-directionally on an automated Genetic Analyzer ABI 3130XL (Applied Biosystems, Foster City, California, USA) using Big Dye Terminator Cycle Sequencing Kit (Applied Biosystems, Foster City, California, USA) and analyzed with Sequencer 5.4.5 (Gene Codes Corporation). Sequences were compared with reference sequence NM_000358. Variant nomenclature was based on HGVD and variant interpretation was according to the ACMG guideline.

## 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* geneand it was confirmed by Sanger sequencing. *In silico* prediction tools revealed the disruptive effect of the variant (Table 1).

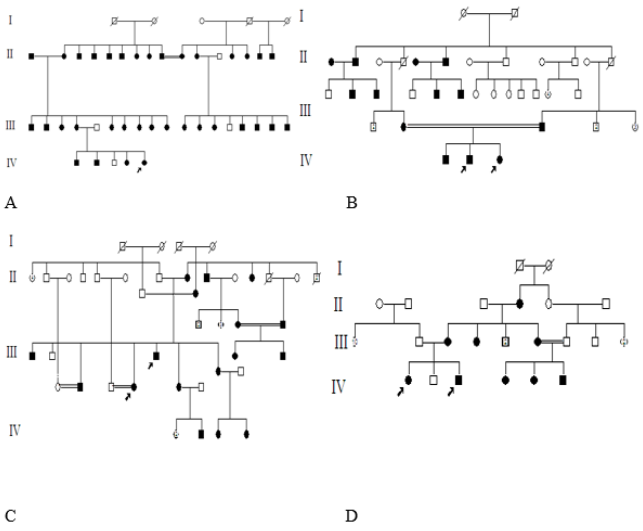


**Figure 1.** Pedigrees. Four large families were investigated. Several patients are available in each generation. Consanguineous marriages with affected individuals are common in the pedigrees, which make pattern of inheritance complicated in some cases

**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

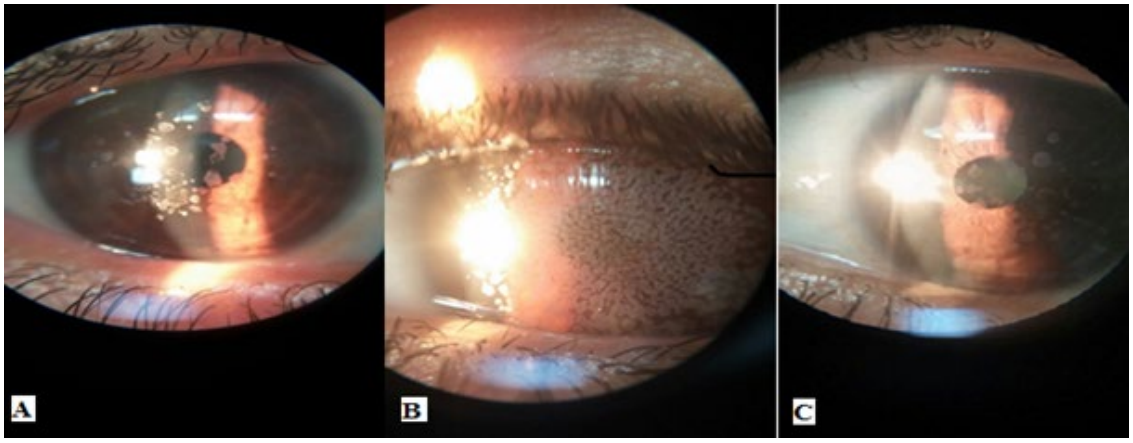


**Figure 2.** Slit-lamp photography. A: 5 years old girl shows granular deposits, B: the cornea of her 11 years old brother shows considerably dense granules. C: their 42 years old mother with no significant problem

***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-years-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.

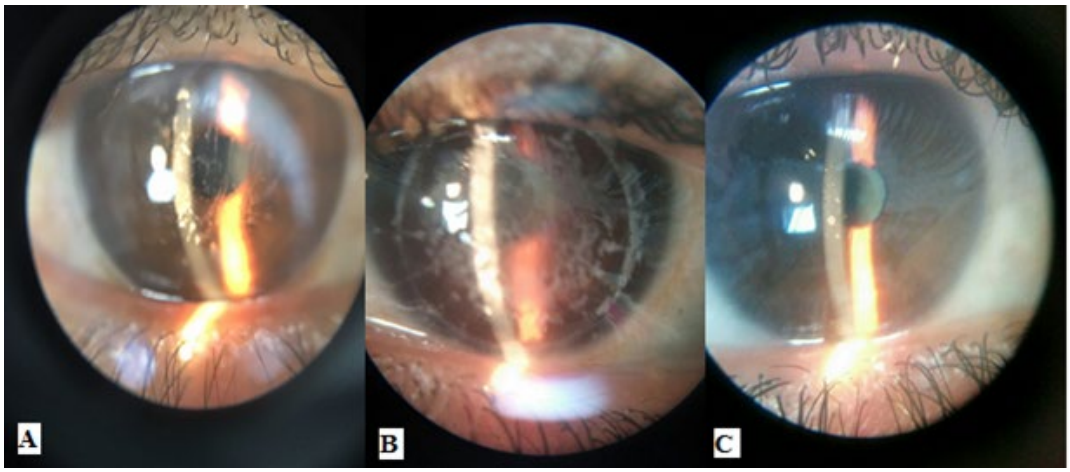


**Figure 3.** Slit-lamp photography, A: a patient with combined Lattice- Granular dystrophy, B: a patient with relatively dense granules, C: a patient with no significant problems

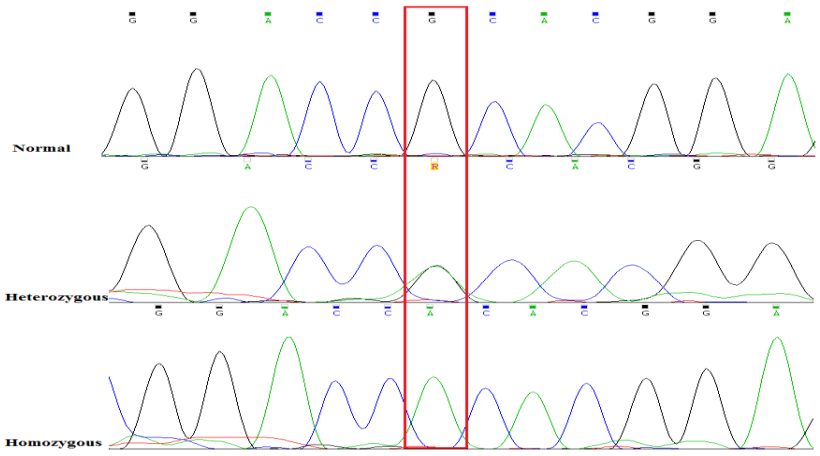


**Figure 4.** DNA sequences for pathogenic variant c.371 G>A (p.R124H) in exon 4. Above: homozygous normal variant, only G at position c.371, middle: Heterozygous state for the variant c.371 G>A, G and A peaks are visible (black and green respectively), below: homozygous pathogenic variant c.371 G>A

## Discussion

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 GCD2 patients with 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

| Row | Coding Position | Protein alteration | Exon | Phenotype | Countries | Ref. No. |
|---|---|---|---|---|---|---|
| 1 | c.337G>A | p.V113I | 4 | GCD | Mexico | (30) |
| 2 | c.367G>C | p.D123H | 4 | Atypical GCD, low penetrance, | Vietnam | (31) |
| 3 | c.370C>T | p.R124C | 4 | LCD1,TBCD,RBCD,GCD2 | China, Korea, Japan | (6) |
| 4 | c.371G>A | p.R124H | 4 | GCD, GCD2 | Japan, Korea, China, UK, Iran, Germany ,India, Hong Kong, ... | (6) |
| 5 | c.371G>A; c.1631A>G | p.R124H;N544S | 4;12 | LCD1 | Japan | (7) |
| 6 | c.371G>A; c.del307- 308delCT | p.R124H; NM | 4 | GCD | Hong Kong | (7) |
| 7 | c.371G>T | p.R124L | 4 | CDRB; Atypical GCD | India, Brazil, USA, Czech, China, France | (32) |
| 8 | c. 371 G > T ;ΔACGGAG | p.R124L ; ΔT125-ΔE126 | 4 | FVGCD( Atypical GCD) | 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.**

| | | | | | | |
|---|---|---|---|---|---|---|
| 11 | | p.A179*, p.R124H | 4 | GCD2 | Korea | (35) |
| 12 | c.895G>A | p.D299N | 7 | Polymorphic LCD | USA | (7) |
| 13 | c.1486C>T | p.R496W | 11 | LCD IV | Japan | (7) |
| 14 | c.1501 C > A | p.P501T | 11 | LCDIIIA | China, Japan | (36) |
| 15 | c.1504 A > G | p.M502V | 11 | Unknown | Mexico | (37) |
| 16 | c.1504 A > G; c.1664 G>A | p.M502V;p.R555Q | 11,12 | Atypical TBCD | France | (7) |
| 17 | c.1514T>A | p.V505D | 11 | LCD I | China | (38) |
| 18 | c.1526 T>C | p.L509P | 11 | GCD2, LCD1 | Germany, France | (7) |
| 19 | c.1526T>G | p.L509R | 11 | LCD1,EBMD | France | (7) |
| 20 | c.1541G>C | p.R514P | 11 | LCD | China | (39) |
| 21 | c. 1545T>A | p.F515L | 11 | LCD1 | China | (39) |
| 22 | c.1548C>G | p.S516R | 11 | GCDI Like | India | (40) |
| 23 | c.1553T>C | p.L518P | 12 | LCD1 (early LCD) | Japan | (41) |
| 24 | c.1553T > G | p.L518R | 12 | LCD1/IIIA | Italy | (8) |
| 25 | c.1565 T > A | p.I522N | 12 | LCD I | China | (42) |
| 26 | c.1580T>G | p.L527R | 12 | LCDIIIA | Japan, Korea | (43) |
| 27 | c.1603G 4 T | G535T | 12 | | | (44) |
| 28 | c.1613 C > G | p.T538R | 12 | LCD1/IIIA | Ukraine, USA | (8) |
| 29 | c.1612A>C | p.T538P | 12 | LCD1 | China, India | (7) |
| 30 | c.1616T>A | p.V539D | 12 | LCD | India | (16) |
| 31 | c.1618-1620delTTG | p.ΔF540 | 12 | CDLI/IIIA first reported as RBCD | Sardinia, | (8, 45) |
| 32 | c.1619T>C | p.F540S | 12 | LCDIII/A | Germany | (46) |
| 33 | c.1625C>G | p.P542R | 12 | LCD | Korea | (7) |
| 34 | c.1631A>G | p.N544S | 12 | LCD | Japan | (47) |
| 35 | c.1637 C > A | p.A546D | 12 | LCD,GCD, Polymorphic LCD | China, Mexico, India, USA, Germany | (48) |
| 36 | c.1637 C > A; c.1652 C > A | p.A546D;P551Q | 12,12 | LCD1 | USA | (7) |
| 37 | c.1636G>A | p.A546T | 12 | LDCIIIA | Brazil ,China, France | (49) |
| 38 | c.1640 T> C | p.F547 S | 12 | Atypical LCD | Hungary | (50) |
| 39 | c.1645G>A;c.1663 C>T | p.A549T;R555W | 12 | GCD1 | Germany | (7) |
| 40 | c.1649 C > T | p.L550P | 12 | GCDII | Mexico, Singapore | (37) |
| 41 | c.1649C>T;c.1877A>G | p.L550P;p. H626R | 12, | Atypical GCD | Mexico | (7) |
| 42 | c.1652 C > A | p.P551Q | 12 | LCD | USA | (48) |
| 43 | c.1664 G>A | p.R555Q | 12 | CDTB, RBCD | Brazil, China, Czech, France, Japan, Singapore, Switzerland, Ukraine, USA | (6) |
| 44 | c.1663 C>T | p.R555W | 12 | GCD1, GCD2,RBCD | Brazil, China, Czech, Mexico, France, Japan, Singapore, Switzerland, Ukraine, USA, Taiwan, Turkey, Vietnam, New Zealand, India, Hong Kong, Spain, UK, Germany, Hungary | (6, 7) |
| 45 | c.1673T> C | p.L558P | 12 | LCDIII | Ukraine | (51) |
| 46 | c.1673T>G | p.L558R | 12 | LCD | Czech Republic | (52) |
| 47 | c.1675T>G | p.L559V | 12 | Atypical GCD | India | (40) |
| 48 | c.1694T> C | p.l565p | 12 | LCD | Poland | (53) |
| 49 | c.1706T>A | p.L569Q | 13 | LCD1 | Korea | (35) |
| 50 | c.1753 T > G | p.L569R | 13 | LCD similar to distinct forms of type I | USA, Korea | (54) |
| 51 | c.1762 A > C | p.H572R | 13 | LCD1,LCDIIIA | Thailand, Singapore, Chile, China, Korea | (55) |
| 52 | c.1761_1763del | p.His572del | 13 | unilateral, late-onset variant of LCD | USA | (56) |
| 53 | c.1681G>T | p.G594V | 13 | late onset , deep stromal LCD | India | (16) |
| 54 | c.1838T>G | p.V613G | 14 | LCDIII | France | (7) |
| 55 | c.1837-1848del12bp GTTGCCGAGCCT | p.del613-616VAEP | 14 | LCD variant | China | (57) |
| 56 | c.1903 T> A | p.M619K | 14 | CGLCD | USA | (58) |
| 57 | c.1859G>A | p.A620D | 14 | Classic LCD | Singapore | (59) |
| 58 | c.1858C>G | p.A620P | 14 | LCDIIIA | Korea | (60) |
| 59 | c.1861C>A | p.T621P | 14 | LCDIIIA | Korea | (35, 61) |
| 60 | c.1866 T>G | p.N622K | 14 | CDLI/IIIA | Italy, South America | (8) |
| 61 | c.1864A>C | p.N622H | 14 | CDLI/IIIA | USA | (7) |
| 62 | c.1868 G > A | p.G623D | 14 | LCD, RBCD | Switzerland, China, USA, Germany | (8) |
| 63 | c.1867C>G | p.G623R | 14 | LCDI, LCDIIA | Germany | (62) |
| 64 | c.1870 G > A | p.V624M | 14 | Unilateral LCD | | (63) |
| 65 | c.1874T>A | p.V625 D | 14 | Early onset of LCD | China | (64) |
| 66 | c.1870-1874del GTGGTC | p.del624-625VV | 14 | Atypical LCD | India | (16) |
| 67 | c.1877A>G; c.1618-1620delTTG | p.H626R; ΔF540 | 14 | CDLI/IIIA | N M | (8) |
| 68 | c.1924 A > C | p.H626P | 14 | CDLI/IIIA, RBCD, TBCD | New Zealand, Czech | (8) |
| 69 | c.1877 A>G | p.H626R | 14 | Asymmetric LCD I/III | China, Mexico, France, Singapore, Ukraine, Vietnam, India, UK, Germany, | (59) |
| 70 | (1885 1886ins9(CCAATGTTC)) | p.(NVP629–630ins) | 14 | LCD III/A | France | (65) |
| 71 | c.1939 T > A | p.V631D | 14 | LCD III/A | Italy | (8) |
| 72 | c.1998G>C | p.R666S | 16 | EBMD | Ireland | (66) |
| 73 | c.1926 del G | premature truncation at amino acid 669 | 14 | CDLI/IIIA | NM | (8) |
| 74 | c.598A>T | p.I200F | 5 | NM | NM | (7) |
| 75 | c.805C>T | p.L269F | 7 | NM | NM | (7) |
| 76 | c.1486C>G | p.R496G | 11 | NM | NM | (7) |

GCD: Granular Corneal Dystrophy; LCD: Lattice Corneal Dystrophy; TBCD: Thiel-Behnke Corneal Dystrophy; RBCD: Reis Bukler Corneal Dystrophy; FVGCD: France Variant Corneal Dystrophy; CGLCD: combined granular-lattice corneal dystrophy; NM: Not Mentioned
* Presented data are arranged based on RefSeq NM_000358; NP_000349

## 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.

## Acknowledgment

We sincerely appreciate the time and assistance of our patients and their families. Here we appreciate Dr. Sedaqhat Eye Clinic for nice collaboration. The study was supported by Isfahan University of Medical Sciences (Grant no. 195122).

## Conflicts of Interest

The authors declare that there are no conflicts of interest.

## References

1. Klintworth GK . Corneal dystrophies. Orphanet J Rare Dis 2009; 4:7-45.
2. Woreta FA, Davis GW, Bower KS. LASIK and surface ablation in corneal dystrophies. Surv Ophthalmol 2015; 60:115-122.
3. Nowinska AK, Wylegala E, Teper S, Lyssek-Boron A, Aragona P, Roszkowska AM, *et al*. phenotype–genotype correlation in patients with schnyder corneal dystrophy. Cornea 2014; 33: 497-503.
4. Fujiki K, Hotta Y, Nakayasu K, Yamaguchi T, Kato T, Uesugi Y, *et al*. Six different mutations of TGFBI (betaig-h3, keratoepithelin) gene found in Japanese corneal dystrophies. Cornea 2000; 19:842-845.
5. Skonier J, Neubauer M, Madisen L, K Bennett, GD Plowman, AF Purchio. cDNA cloning and sequence analysis of beta ig-h3, a novel gene induced in a human adenocarcinoma cell line after treatment with transforming growth factor-beta. DNA Cell Biol 1992; 11:511-522.
6. Munier FL , Korvatska E, Djemaï A, Paslier D Le, Zografos L, Pescia G , *et al*. Kerato-epithelin mutations in four 5q31-linked corneal dystrophies. Nat Genet 1997; 15:247-251.
7. Lakshminarayanan R, Chaurasia SS, Anandalakshmi V, Chai SM, Murugan E, Vithana EN, Beuerman RW, *et al*. Clinical and genetic aspects of the TGFBI-associated corneal dystrophies. Ocul Surf 2014; 12:234-251.
8. Munier FL, Frueh BE, Othenin-Girard P, Uffer S, Cousin P, Wang MX, *et al*. BIGH3 mutation spectrum in corneal dystrophies. Invest Ophthalmol Vis Sci 2002; 43:949-954.
9. Weiss JS, Moller HU, Lisch W, Kinoshita S, Aldave AJ , Belin MW, *et al*. Klintworth. The IC3D classification of the corneal dystrophies. Cornea 2008; 27:1-83.
10. Folberg R, Alfonso E, JO, Croxatto NG Driezen, Panjwani N, Laibson PR, *et al*. Clinically atypical granular corneal dystrophy with pathologic features of lattice-like amyloid deposits. A study of these families. Ophthalmology 1988; 95:46-51.
11. Ferry AP, Benson WH, Weinberg RS. Combined granular-lattice ('Avellino') corneal dystrophy. Trans Am Ophthalmol Soc 1997; 95:61-77.
12. Wu X, Ruan L, Yang Y, Mei Q. Analysis of gene expression changes associated with human carcinoma-associated fibroblasts in non-small cell lung carcinoma. Biol Res 2017; 50:6-14.
13. Han KE, Choi SI, Kim TI, Maeng YS, Stulting RD, Ji YW, *et al*. Pathogenesis and treatments of TGFBI corneal dystrophies. Prog Retin Eye Res 2016; 50:67-88.
14. Choi SI, Kim BY, Dadakhujaev S, Oh JY, Kim TI, Kim JY, *et al*. Impaired autophagy and delayed autophagic clearance of transforming growth factor β-induced protein (TGFBI) in granular corneal dystrophy type 2. Autophagy 2012; 8:1782-1797.
15. Shang D, Liu Y, Yang P, Chen Y, Tian Y. TGFBI-promoted adhesion, migration and invasion of human renal cell carcinoma depends on inactivation of von Hippel-Lindau tumor suppressor. Urology 2012; 79:1-7.
16. Chakravarthi SK, Kannabiran C, Sridhar MS, Vemuganti GK. TGFBI gene mutations causing lattice and granular corneal dystrophies in Indian patients. Invest Ophthalmol Vis Sci 2005; 46:121-125.
17. Poulaki V, Colby K. Genetics of anterior and stromal corneal dystrophies. Semin Ophthalmol 2008; 23:9-17.
18. Mashima Y, Nakamura Y, Noda K, Konishi M, Yamada M, Kudoh J, *et al*. A novel mutation at codon 124 (R124L) in the BIGH3 gene is associated with a superficial variant of granular corneal dystrophy. Arch Ophthalmol 1999; 117:90-93.
19. Alavi A, ElahiE, Rahmati-Kamel M, Karimian F, Rezaei-Kanavi M. Mutation screening of TGFBI in two Iranian avellino corneal dystrophy pedigrees. Clin Exp Ophthalmol 2008; 36:26-30.
20. Sajjadi SH, Javadi MA. Superficial juvenile granular dystrophy. Ophthalmology 1992; 99:95-102.
21. Diaper C, Schorderet D, Chaubert P, Munier F. Clinical and immunopathological corneal phenotype in homozygotes for the BIGH3 R124H mutation. Eye 2005; 19:92-96.
22. Han KE, Choi SI, Chung WS, Jung SH, Katsanis N, Kim TI, *et al*. Extremely varied phenotypes in granular corneal dystrophy type 2 heterozygotes. Mol Vis 2012; 18:1755-1762.
23. Eifrig D, Afshari N, Klintworth G. The clinical spectrum of granular corneal dystrophy caused by the R124H mutation in the TGFB gene. Invest Ophthalmol Vis Sci 2004; 45:1516-1516.
24. Cao W, Ge H, Cui X, Zhang L, Bai J, Fu S, *et al*. Reduced penetrance in familial avellino corneal dystrophy associated with TGFBI mutations. Mol Vis 2009; 15:70-75.
25. Scriver CR, Waters PJ. Monogenic traits are not simple: lessons from phenylketonuria. Trends Genet 1999; 15:267-272.
26. Schacherer J. Beyond the simplicity of Mendelian inheritance. CR Biol 2016; 339:284-288.
27. Poulsen ET, Nielsen NS, Jensen MM, Nielsen E, Hjortdal J, Kim EK, *et al*. LASIK surgery of granular corneal dystrophy type 2 patients leads to accumulation and differential proteolytic processing of transforming growth factor beta-induced protein (TGFBIp). Proteomics 2016; 16:539-543.
28. Lyons CJ, McCartney AC, Kirkness CM, Ficker LA, Steele AD, Rice NS. Granular corneal dystrophy. Visual results and pattern of recurrence after lamellar or penetrating keratoplasty. Ophthalmology 1994 ; 101:1812-1817.
29. Zenteno JC, Ramirez-Miranda A, Santacruz-Valdes C, Suarez-Sanchez R. Expanding the mutational spectrum in TGFBI-linked corneal dystrophies: Identification of a novel and unusual mutation (Val113Ile) in a family with granular dystrophy. Mol Vis 2006; 12:331-335.
30. Ha NT, Cung le X, Chau HM, Thanh TK, Fujiki K, Murakami A, *et al*. A novel mutation of the TGFBI gene found in a Vietnamese family with atypical granular corneal dystrophy. Jpn J Ophthalmol 2003; 47:246-248.
31. Dighiero P, Drunat S, D'hermies F, Renard G, Delpech M, Valleix S. A novel variant of granular corneal dystrophy caused by association of 2 mutations in the TGFBI gene—R124L and ΔT125-ΔE126. Arch Ophthalmol 2000; 118:814-818.
32. Foja S, Hoffmann K, Auw-Haedrich C, Reinhard T, Rupprecht A, Gruenauer-Kloevekorn C. Identfication of two novel mutations in the cornea-specific TGFBI gene causing unique phenotypes in patients with corneal dystrophies. Int Ophthalmol 2016; 36:867-873.

33. Song JS, Lim DH, Chung ES, Chung TY, Ki CS. Mutation analysis of the TGFBI gene in consecutive Korean patients with corneal dystrophies. Ann Lab Med 2015; 35:336-340.
34. Yamamoto S, Okada M, Tsujikawa M, Shimomura Y, Nishida K, Inoue Y, *et al*. A kerato-epithelin (betaig-h3) mutation in lattice corneal dystrophy type IIIA. Am J Hum Genet 1998; 62:719-722.
35. Zenteno JC, Correa-Gomez V, Santacruz-Valdez C, Suarez-Sanchez R,Villanueva-Mendoza C . Clinical and genetic features of TGFBI-linked corneal dystrophies in Mexican population: Description of novel mutations and novel genotype–phenotype correlations. Exp Eye Res 2009; 89:172-177.
36. Tian X, Fujiki K, Wang W, Murakami A, Xie P, Kanai A, *et al*. Novel mutation (V505D) of the TGFBI gene found in a Chinese family with lattice corneal dystrophy, type I. Jpn J Ophthalmol 2005; 49:84-88.
37. Zhong X, Chen S, Huang W, Yang J, Chen X, Zhou Y, *et al*. Novel and known mutations of TGFBI, their genotype-phenotype correlation and structural modeling in 3 Chinese families with lattice corneal dystrophy. Mol Vis 2010; 16:224-230.
38. Paliwal P, Sharma A, Tandon R, Sharma N, Titiyal JS, Sen S, *et al*. TGFBI mutation screening and genotype-phenotype correlation in north Indian patients with corneal dystrophies. Mol Vis 2010; 16:1429-1438.
39. Endo S, Nguyen TH, Fujiki K, Hotta Y, Nakayasu K, Yamaguchi T, *et al*. Leu518Pro mutation of the beta ig-h3 gene causes lattice corneal dystrophy type I. Am J Ophthalmol 1999; 128:104-106.
40. Zhang C, Zeng G, Lin H, Li D, Zhao L, Zhou N, *et al*. A novel mutation I522N within the TGFBI gene caused lattice corneal dystrophy I. Mol Vis 2009; 15:2498-2502.
41. Fujiki K, Hotta Y, Nakayasu K, Yokoyama T, Takano T, Yamaguchi T, *et al*. A new L527R mutation of the betaIGH3 gene in patients with lattice corneal dystrophy with deep stromal opacities. Hum Genet 1998; 103:286-289.
42. Karolak JA, Polakowski P, Szaflik J, Szaflik JP, Gajecka M. Molecular screening of keratoconus susceptibility sequence variants in VSX1, TGFBI, DOCK9, STK24, and IPO5 genes in polish patients and novel TGFBI variant identification. Ophthalmic Genet 2016; 37:37-43.
43. Rozzo C, Fossarello M, Galleri G, Sole G, Serru A, Orzalesi N, *et al*. A common beta ig-h3 gene mutation (delta f540) in a large cohort of Sardinian Reis Bucklers corneal dystrophy patients. Hum Mutat 1998; 12:215-216.
44. Stix B, Leber M, Bingemer P, Gross C, Rüschoff J, M Fändrich, *et al*. Hereditary lattice corneal dystrophy is associated with corneal amyloid deposits enclosing C-terminal fragments of keratoepithelin. Invest Ophthalmol Vis Sci 2005; 46:1133-1139.
45. Mashima Y, Yamamoto S, Inoue Y, Yamada M, Konishi M, Watanabe H, *et al*. Association of autosomal dominantly inherited corneal dystrophies with BIGH3 gene mutations in Japan. Am J Ophthalmol 2000; 130:516-517.
46. Klintworth GK, Bao W, Afshari NA. Two mutations in the TGFBI (BIGH3) gene associated with lattice corneal dystrophy in an extensively studied family. Invest Ophthalmol Vis Sci 2004; 45:1382-1388.
47. Dighiero P, Drunat S, Ellies P, D'Hermies F, Savoldelli M, Legeais JM, *et al*. A new mutation (A546T) of the βig-h3 gene responsible for a French lattice corneal dystrophy type IIIA. Am J Ophthalmol 2000; 129:248-251.
48. Lili T, Gergely L, Klára M, István B, Zoltán S, Károly T, *et al*. TGFBI (BIGH3) gene mutations in Hungary-report of the novel F547S mutation associated with polymorphic corneal amyloidosis. Mol Vis 2007; 13:1976-1983.
49. Pampukha VM, SA, Tereshchenko FA, Livshits LA, Drozhyna GI. Novel L558P mutation of the TGFBI gene found in Ukrainian families with atypical corneal dystrophy. Ophthalmologica 2009; 223:207-214.
50. Dudakova L, Palos M, Jirsova K, Skalicka P, Dundr P, Liskova P. Novel TGFBI mutation p.(Leu558Arg) in a lattice corneal dystrophy patient. Ophthalmic Genet 2016; 37:473-474.
51. M Oldak, JP Szaflik, A Sciezynska, M Udziela, RB Maksym, B Rymgayllo-Jankowska, *et al*. Late-onset lattice corneal dystrophy without typical lattice lines caused by a novel mutation in the TGFBI gene. Cornea 2014; 33:294-299.
52. Warren JF, Abbott RL, Yoon MK, Crawford JB, Spencer WH, Margolis TP. A new mutation (Leu569Arg) within exon 13 of the TGFBI (BIGH3) gene causes lattice corneal dystrophy type I. Am J Ophthalmol 2003; 136:872-878.
53. Atchaneeyasakul LO, Appukuttan B, Pingsuthiwong S, Yenchitsomanus PT, Trinavarat A,Srisawat, C *et al*. A novel H572R mutation in the transforming growth factor-beta-induced gene in a Thai family with lattice corneal dystrophy type I. Jpn J Ophthalmol 2006; 50:403-408.
54. Aldave AJ, Rayner SA, Kim BT, Prechanond A, Yellore VS. Unilateral lattice corneal dystrophy associated with the novel His572del mutation in the TGFBI gene. Mol Vis 2006; :12142-146.
55. Yang J, Han X, Huang D, Yu L, Zhu Y, Tong Y, *et al*. Analysis of TGFBI gene mutations in Chinese patients with corneal dystrophies and review of the literature. Mol Vis 2010; 16:1186-1193.
56. Aldave AJ, Yellore VS, Sonmez B, Bourla N, Salem AK, Khan MA, *et al*. A novel variant of combined granular-lattice corneal dystrophy associated with the Met619Lys mutation in the TGFBI gene. Arch Ophthalmol 2008; 126:371-377.
57. Evans CJ, Davidson AE, Carnt N, López KER, Veli N, Thaung CM, *et al*. Genotype-phenotype correlation for TGFBI corneal dystrophies identifies p.(G623D) as a novel cause of epithelial basement membrane dystrophy. Invest Ophthalmol Vis Sci 2016; 57:5407-5414.
58. Jung JW, ah Kim S, Kang EM, Cho HS, Kim EK. Lattice corneal dystrophy type IIIA with hyaline component from a novel A620P mutation and distinct surgical treatments. Cornea 2014; 33:1324-1331.
59. Lee J, Ji YW, Park SY, Seo KY, Kim TI, Kim EK. Delayed onset of lattice corneal dystrophy type IIIA due to a novel T621P mutation in TGFBI. J Refract Surg 2016; 32:356-358.
60. Gruenauer-Kloevekorn C, Clausen I, Weidle E, Wolter-Roessler M, Tost F, Volcker HE, *et al*. TGFBI (BIGH3) gene mutations in German families: two novel mutations associated with unique clinical and histopathological findings. Br J Ophthalmol 2009; 93:932-937.
61. Afshari N, Bahadur R, Klintworth G. Discovery of novel homozygous mutation in the TGFBI (BIGH3) gene (V624M) in a patient with unilateral lattice corneal dystrophy. Invest Ophthalmol Vis Sci 2004; 45:1517-1517.
62. Tian X, Fujiki K, Zhang Y, Murakami A,Li Q , Kanai A, *et al*. A novel variant lattice corneal dystrophy caused by association of mutation (V625D) in TGFBI gene. Am J Ophthalmol 2007: 144:473-475.
63. Schmitt–Bernard CF, Guittard C, Arnaud B, Demaille J, Argiles A, Claustres M, *et al*. BIGH3 exon 14 mutations lead to intermediate type I/IIIA of lattice corneal dystrophie. Invest Ophthalmol Vis Sci 2000; 41:1302-1308.
64. Boutboul S, Black GC, Moore JE, Sinton J, Menasche M, Munier FL, *et al*. A subset of patients with epithelial basement membrane corneal dystrophy have mutations in TGFBI/BIGH3. Hum Mutat 2006; 27:553-557.
65. Ann T, Abbouda A, Frausto RF, Huseynli S, Gupta K, Alió JL, *et al*. Variant lattice corneal dystrophy associated with compound heterozygous mutations in the TGFBI gene. Br J Ophthalmol 2017; 101:509-513.

66. Sakimoto T, Kanno H, Shoji J, Kashima Y, Nakagawa S, Miwa S, *et al*. A novel nonsense mutation with a compound heterozygous mutation in TGFBI gene in lattice corneal dystrophy type I. Jpn J Ophthalmol 2003; 47:13-17.