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préparée sous la direction du Professeur Daniel Schorderet

et présentée à la Faculté de biologie et de médecine de
l'Université de Lausanne pour l'obtention du grade de

DOCTEUR EN MEDECINE

par

Valéria KHEIR

Médecin diplômée de la Confédération Suisse
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Mutation update: TGFBI pathogenic and likely pathogenic variants in corneal dystrophies

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pour Le Doyen
de la Faculté de Biologie et de Médecine

Monsieur le Professeur John Prior
Vice-Directeur de l'Ecole doctorale

Résumé de la thèse en français:

TGFBI (Human Transforming Growth Factor β-induced) est un gène responsable de plusieurs dystrophies cornéennes. *TGFBI* produit une protéine nommée TGFBI qui joue un rôle dans l'adhésion cellulaire et sert de séquence de reconnaissance certaines intégrines. Une altération des interactions à la surface cellulaire peut être la cause sous-jacente de l'accumulation progressive de dépôts extracellulaires dans les différentes couches cornéennes, avec pour conséquence une atteinte de la transparence et de l'index réfractif de la cornée.

Jusqu'à ce jour, 69 variants pathogéniques ou potentiellement pathogéniques de *TGFBI,* hétérozygotes ou homozygotes, ont été identifiés dans plusieurs dystrophies cornéennes, dont un nouveau variant décrit ici. Toutes les maladies associées à des variants sont héritées de façon autosomique dominante sauf une; cette dernière est héritée de façon autosomique récessive . La plupart des variants associés aux dystrophies cornéennes sont situés au niveau des acides aminés Arg124 et Arg555.

Afin de garder cette liste de variants associés aux dystrophies cornéennes à jour, nous avons généré une base de données spécifique pour *TGFBI* (http://databases.lovd.nl/shared/variants/TGFBI) qui contient tous les variants pathogéniques et potentiellement pathogéniques rapportés dans la littérature à ce jour. Les variants qui ne sont pas associés à une maladie cornéenne sont décrits dans des bases de données spécifiques comme gnomAD et ExAC; par conséquent elles ne sont pas listées ici. Cet article présente la mise à jour la plus récente des variants associés aux dystrophies cornéennes et décrit une nouvelle mutation.

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MUTATION UPDATE

WILEY Human Mutation HGVS HUMAN GENOME VARIATION SOCIETY

Mutation update: *TGFBI* pathogenic and likely pathogenic variants in corneal dystrophies

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Abstract

Human transforming growth factor β-induced (*TGFBI*), is a gene responsible for various corneal dystrophies. *TGFBI* produces a protein called TGFBI, which is involved in cell adhesion and serves as a recognition sequence for integrins. An alteration in cell surface interactions could be the underlying cause for the progressive accumulation of extracellular deposits in different layers of the cornea with the resulting changes of refractive index and transparency. To this date, 69 different pathogenic or likely pathogenic variants in *TGFBI* have been identified in a heterozygous or homozygous state in various corneal dystrophies, including a novel variant reported here. All disease-associated variants were inherited as autosomal-dominant traits but one; this latter was inherited as an autosomal recessive trait. Most corneal dystrophy-associated variants are located at amino acids Arg124 and Arg555. To keep the list of corneal dystrophy-associated variant current, we generated a locus-specific database for *TGFBI* (http://databases.lovd.nl/shared/variants/TGFBI) containing all pathogenic and likely pathogenic variants reported so far. Non-disease-associated variants are described in specific databases, like gnomAD and ExAC but are not listed here. This article presents the most recent up-to-date list of disease-associated variants.

KEYWORDS

BIGH3, inherited corneal dystrophy, TGFBI, variants spectrum

1 | BACKGROUND

Variants in the human transforming growth factor β-induced (*TGFBI*) are responsible for multiple corneal dystrophies. Several variants cause clinically recognizable phenotypes like epithelial basement membrane dystrophy (EBMD), Thiel-Behnke corneal dystrophy (TBCD), Reis-Bücklers corneal dystrophy (RBCD), granular corneal dystrophy, type 1 (GCD1), granular corneal dystrophy, type 2 (GCD2), and classic lattice corneal dystrophy (LCD). Other variants may produce different, overlapping, or mixed phenotypes, often including amyloid deposits. Such dystrophies are called variant LCD by the International classification of Corneal Dystrophies (IC3D) (Weiss et al., 2008, 2015).

1.1 | TGFBI discovery

BIGH3 was first identified by Skonier et al. in 1992 by physical mapping and complementary DNA (cDNA) selection (Skonier et al., 1992, 1994). At that time, these authors were studying the effects of transforming growth factor-β 1 (TGFB1) on the proliferation of different cell types with the aim of identifying new genes, the product of which would mediate cellular response to TGFB1. They treated A549, a lung adenocarcinoma cell line, with TGFB1 and identified

Bigh3. The name *βig-h3* was given because it was the third clone identified after TGFB induction. This gene was then renamed to *TGF-β induced (TGFBI)* by the HUGO gene nomenclature committee, a name that is unfortunately often confused with *TGFB1*. However, *BIGH3* and *β-IgH3* are still used in many publications.

Five years later, we identified *TGFBI* point variants in several forms of corneal dystrophy. This discovery was facilitated by the work of different groups. Linkage analysis in three families affected with GCD1, including a single seven-generation Danish pedigree, allowed the mapping of a locus on chromosome 5q (Eiberg, Moller, Berendt, & Mohr, 1994). The same year, Stone et al. (1994) studying six families with two other forms of CD, LCD1, and the Avellino CD, now known as GCD2, also mapped their loci to the same region on chromosome 5q and confirmed linkage of GCD1 close to D5S393. In the following years, Small et al. (1996) mapped RBCD to the same locus and suggested that all four CDs were the consequence of different variants in the same gene. At the same time, we mapped GCD1 and LCD1 to a 1-cM interval between D5S393 and D5S399 (Korvatska et al., 1996). It took us one more year to generate a physical map of the region using yeast artificial chromosomes and, following cDNA selection, to identify *βig-h3*, as the causative gene of all four CDs (Munier, Korvatska, Djemai et al., 1997). Since this publication, many reports describing *TGFBI* variants in other CDs appeared.

1.2 | Gene structure and protein domain

DNA sequence analysis showed that *TGFBI* encodes a novel protein, TGFBI, also called Keratoepithelin, TGFBIp, p68 β-ig-h3 or RGD-CAP (RGD-containing collagen-associated protein). The gene contains 17 exons and spans 35 kb on 5q31 in human and 30 kb on mouse chromosome 13 (Munier, Korvatska, Djemai et al., 1997; Schorderet et al., 2000; Skonier et al., 1992). Both genomic structures are very similar with identical exon number and two large introns 1 and 2 (Schorderet et al., 2000). TGFBI is an adhesion protein secreted into the extracellular space by the corneal epithelium and keratocytes as well as by mesenchymal cells. It is also secreted in multiple parts of the body and is present in many cell lines (Skonier et al., 1992, 1994). TGFBI is a highly conserved 683-amino acid protein of 68 kDa in humans. Two isoforms of 78 and 68 kDa have been reported (Gibson, Kumaratilake, & Cleary, 1997). It contains an N-terminal secretory signal peptide (residues 1–23), a cysteine-rich EMI domain (residues 45–99), four internal FAS1 domains of approximately 130–140 amino acids each (FAS1–1: residues 134–236, FAS1–2: residues 242–372, FAS1–3: residues 373–501, FAS1–4: residues 502–632) that are homologous to the sea urchin fasciclin protein, a protein involved in nerve cone guidance and an RGD sequence at the C-terminal part (Skonier et al., 1992). The boundaries of each FAS1 domain may vary depending on the alignment program used.

Several regions, including the RGD, the NKDIL in the second FAS1 domain, the 18 amino acids between 563 and 580 (YH18) motif and the EPDIM motifs in the fourth FAS1 domain act as ligand recognition sequences for several integrins including α1β1, α3β1, αvβ3, αvβ5 (Bae et al., 2002; Jeong & Kim, 2004; H. J. Kim & Kim, 2008; Lee et al., 2006; Ohno et al., 1999; Park et al., 2004). Like the RGD motif, NKDIL and EPDIM motifs can adopt a β-turn structure capable of interacting with integrins during cell adhesion (J. E. Kim, Jeong, et al., 2002; Nam et al., 2003; Park et al., 2004). TGFBI binds fibronectin, collagen, and integrins. It covalently binds the collagen-6 microfibrils and can bind to type 1, 2, and 4 collagens, and biglycan and decorin proteoglycans (J. E. Kim, Park, et al., 2002; Reinboth, Thomas, Hanssen, & Gibson, 2006)

2 | INVOLVEMENT IN DISEASE: CLINICAL AND DIAGNOSTIC RELEVANCE

The publication describing the first *TGFBI* pathogenic variants in various forms of CD triggered an important reaction in the community, not only to identify new variants and refine the genotype–phenotype correlations, but also to develop a new classification of CD based on inheritance, molecular genetics and immunohistology (Weiss et al., 2015). The International Conference on 3D Immersion classification describes TGFBI-linked dystrophies by the recognition that they affect multiple layers rather than being confined to one corneal layer.

Initially, variants in *TGFBI* have been associated with four CDs, namely p.Arg555Trp in GCD1 (MIM #121900) and p.Arg555Gln in TBCD (MIM #602082) in the fourth FAS1 domain and p.Arg124Cys in LCD1 (MIM #122200) and p.Arg124His in GCD2 (MIM #607541) in the first FAS1 domain. Interestingly, when additional disease-associated variants were described, most of them were located in the fourth FAS1 domain.

Today, 68 disease-associated variants in *TGFBI* have been reported to cause various types of epithelial and stromal CDs in patients from different ethnic groups. One aspect that all 5q31-linked CDs have in common is the extracellular deposition of insoluble protein aggregates within the cornea that stain with antibodies against TGFBI (Korvatska et al., 1999). Although many variants cause a single well-recognizable phenotype, several produce a heterogeneous phenotype. Reduced penetrance and de novo variants have also been reported (Cao et al., 2009; Hilton, Black, Manson, Schorderet, & Munier, 2007; Hou, Hu, & Wang, 2015; J. W. Kim, Kim, & Song, 2008).

We present an evaluation of all reported *TGFBI* disease-associated variants and describe a novel variant in a two-generation family with RBCD (Table 1). This extensive list of pathogenic and likely pathogenic variants was introduced in a locus-specific database, which is freely accessible at https://databases.lovd.nl/shared/genes/TGFBI.

2.1 | Epithelial basement membrane dystrophy (EBMD; MIM #121820)

Clinical presentation: Epithelial basement membrane dystrophy is the most common anterior dystrophy. It is bilateral, often asymmetric,

TABLE 1 *TGFBI* mutations (NM_000358.2, ENTS00000442011)

Exon	c-Notation	p-Notation	Fas1	Effect	ExAC	Phenotype	Reference
Missense							
4	c.[337G>A]	p.Val113Ile	1	Likely pathogenic	0.1% in Latino	GCD1	Zenteno et al. (2006)
4	c.[367G>C]	p.Asp123His	1	Likely pathogenic	0.1% in East Asian	GCD atypical	Ha et al. (2003)
4	c.[370C>T]	p.Arg124Cys	1	Pathogenic	<<	LCD1	Munier et al. (1997)
4	c.[370C>T]	p.Arg124Cys	1	Pathogenic	<<	GCD2	Edelstein et al. (2010)
4	c.[370C>T]	p.Arg124Cys	1	Pathogenic	<<	RBCD	Ma et al. (2010)
4	c.[370C>T]	p.Arg124Cys	1	Pathogenic	<<	TBCD	Chang (2009)
4	c.[370C>A]	p.Arg124Ser	1	Pathogenic	<<<	GCD1	Stewart et al. (1999)
4	c.[371G>A]	p.Arg124His	1	Pathogenic	<	GCD2	Munier et al. (1997)
4	c.[371G>A]	p.Arg124His	1	Pathogenic	<	GCD2 resembling SVGD	Mashima et al. (1997)
4	c.[371G>A];[371G>A]	p.Arg124His; Arg124His	1	Pathogenic	<	GCD severe type 1	Mashima et al. (1998)
4	c.[371G>A];[371G>A]	p.Arg124His; Arg124His	1	Pathogenic	<	GCD severe type 2	Watanabe et al. (2001)
4	c.[371G>T]	p.Arg124Leu	1	Pathogenic	<<<	SVGD	Okada et al. (1998)
4	c.[371G>T]	p.Arg124Leu	1	Pathogenic	<<<	RBCD with lattice-like lines	Paliwal et al. (2011)
4	c.[393G>T]	p.Glu131Asp	1	Pathogenic	<	Schnyder-like	Foja et al. (2016)
4	c.[535C>T]	p.Arg179*	1	VUS	<<<	Unknown, described as p.Ala179	Song et al. (2015)
11	c.[1486C>T]	p.Arg496Trp	3	Likely pathogenic	<<<	LCD deep, late onset	Kawasaki et al. (2011)
11	c.[1501C>A]	p.Pro501Thr	3	Likely pathogenic	0.4% in East Asian	LCD3A	Yamamoto et al. (1998)
11	c.[1504A>G]	p.Met502Val	4	VUS	0.4% in Latino	Unclassified	Zenteno et al. (2009)
11	c.[1514T>A]	p.Val505Asp	4	Pathogenic	<<<	LCD1	Tian et al. (2005)
11	c.[1526T>C]	p.Leu509Pro	4	Pathogenic	<<<	RBCD-like	Gruenauer-Kloevekorn, Clausen, et al. (2009)
11	c.[1526T>C]	p.Leu509Pro	4	Pathogenic	<<<	LCD1	Niel-Butschi et al. (2011)
11	c.[1526T>G]	p.Leu509Arg	4	Pathogenic	<<<	LCD1 atypical	Niel-Butschi et al. (2011)
11	c.[1526T>G]	p.Leu509Arg	4	Pathogenic	<<<	EBMD	Boutboul et al. (2006)
	c.[1548C>G]	p.Ser516Arg	4	Pathogenic	<<<	GCD1	Paliwal et al. (2010)
12	c.[1553T>C]	p.Leu518Pro	4	Pathogenic	<<<	LCD1	Endo et al. (1999)
12	c.[1553T>G]	p.Leu518Arg	4	Pathogenic	<<<	LCD1/3A	Munier et al. (2002)
12	c.[1565T>A]	p.Ile522Asn	4	Pathogenic	<<<	LCD1	C. Zhang et al. (2009)
12	c.[1580T>G]	p.Leu527Arg	4	Pathogenic	<<<	LCD deep, late onset	Fujiki et al. (1998)
12	c.[1580T>G];[1580T>G]	p.Leu527Arg; Leu527Arg	4	Pathogenic	<<<	LCD3A	Funayama et al. (2006)

(Continues)

TABLE 1 (Continued)

Exon	c-Notation	p-Notation	Fas1	Effect	ExAC	Phenotype	Reference
12	c.[1580T>G];[1580T>G]	p.Leu527Arg; Leu527Arg	4	Pathogenic	<<<	LCD1	Yamada et al. (2005)
12	c.[1612A>C]	p.Thr538Pro	4	Pathogenic	<<<	LCD1	Yu et al. (2006)
12	c.[1613C>G]	p.Thr538Arg	4	Pathogenic	<<<	LCD1/3A	Munier et al. (2002)
12	c.[1616T>A]	p.Val539Asp	4	Pathogenic	<<<	LCD1	Chakravarthi et al. (2005)
12	c.[1619T>C]	p.Phe540Ser	4	Pathogenic	<<<	LCD3A	Stix et al. (2005)
12	c.[1625C>G]	p.Pro542Arg	4	Pathogenic	<<<	LCD1	Cho et al. (2012)
12	c.[1631A>G]	p.Asn544Ser	4	Likely pathogenic	0.1% in East Asian	LCD1/3A	Fujiki et al. (2001)
12	c.[1636G>A]	p.Ala546Thr	4	Pathogenic	<<<	LCD3A	Dighiero, Drunat, Ellies et al. (2000)
12	c.[1637C>A]	p.Ala546Asp	4	Pathogenic	<<<	PCA	Eifrig et al. (2004)
12	c.[1637C>A]	p.Ala546Asp	4	Pathogenic	<<<	GCD1 atypical	Yu et al. (2008)
12	c.[1637C>A]	p.Ala546Asp	4	Pathogenic	<<<	LCD atypical	Correa-Gomez et al. (2007)
12	c.[1640T>G]	p.Phe547Cys	4	Pathogenic	<<<	GCD1 atypical	Foja et al. (2016)
12	c.[1640T>C]	p.Phe547Ser	4	Pathogenic	<<<	PCA	Takács et al. (2007)
12	c.[1643G>C]	p.Arg548Pro	4	Pathogenic	<<<	LCD1	Chae et al. (2016)
12	c.[1649T>C]	p.Leu550Pro	4	Pathogenic	<<<	GCD2	Zenteno et al. (2009)
12	c.[1663C>T]	p.Arg555Trp	4	Pathogenic	<<<	GCD1	Munier et al. (1997)
12	c.[1663C>T]	p.Arg555Trp	4	Pathogenic	<<<	TBCD	Yu et al. (2015)
12	c.[1663C>T];[1663C>T]	p.Arg555Trp; Arg555Trp	4	Pathogenic	<<<	GCD1 severe	Okada et al. (1998)
12	c.[1664G>A]	p.Arg555Gln	4	Pathogenic	<<<	TBCD	Munier et al. (1997)
12	c.[1664G>A]	p.Arg555Gln	4	Pathogenic	<<<	TBCD	El-Ashry et al. (2005)
12	c.[1673T>C]	p.Leu558Pro	4	Pathogenic	<<<	LCD deep	Livshits et al. (2008)
12	c.[1673T>G]	p.Leu558Arg	4	Pathogenic	<<<	LCD1	Dudakova et al. (2016)
12	c.[1675T>G]	p.Leu559Val	4	Pathogenic	<<<	EMBD	Paliwal et al. (2010)
13	c.[1694T>C]	p.Leu565Pro	4	Pathogenic	<<<	LCD1 late onset	Oldak et al. (2014)
13	c.[1706T>G]	p.Leu569Arg	4	Pathogenic	<<<	LCD1	Warren et al. (2003)
13	c.[1706T>A]	p.Leu569Gln	4	Pathogenic	<<<	LCD1	Song et al. (2015)
13	c.[1715A>G]	p.His572Arg	4	Pathogenic	<<<	LCD1	Atchaneeyasakul et al. (2006)
13	c.[1781G>T]	p.Gly594Val	4	Pathogenic	<<<	LCD deep	Chakravarthi et al. (2005)
14	c.[1838T>G]	p.Val613Gly	4	Pathogenic	<<<	LCD late onset	Niel-Butschi et al. (2011)
14	c.[1856T>A]	p.Met619Lys	4	Pathogenic	<<<	GCD2 atypical	Aldave et al. (2008)

(Continues)

TABLE 1 (Continued)

Exon	c-Notation	p-Notation	Fas1	Effect	ExAC	Phenotype	Reference
14	c.[1858G>C]	p.Ala620Pro	4	Pathogenic	<<<	LCD3A	Jung et al. (2014)
14	c.[1859C>A]	p.Ala620Asp	4	Pathogenic	<<<	LCD1	Lakshminarayanan et al. (2011)
14	c.[1861A>C]	p.Thr621Pro	4	Pathogenic	<<<	LCD1	Song et al. (2015)
14	c.[1864A>C]	p.Asn622His	4	Pathogenic	<<<	LCD1/3A	H. S. Stewart et al. (1999)
14	c.[1866T>A]	p.Asn622Lys	4	Pathogenic	<<<	LCD3A	Munier et al. (2002)
14	c.[1866T>G]	p.Asn622Lys	4	Pathogenic	<<<	LCD3A	Munier et al. (2002)
14	c.[1867G>C]	p.Gly623Arg	4	Pathogenic	<<<	CD map-like	Gruenauer-Kloevekorn, Clausen, et al. (2009)
14	c.[1868G>A]	p.Gly623Asp	4	Pathogenic	<<<	LCD1/3A	Munier et al. (2002)
14	c.[1868G>A]	p.Gly623Asp	4	Pathogenic	<<<	LCD atypical	Aldave et al. (2005)
14	c.[1868G>A]	p.Gly623Asp	4	Pathogenic	<<<	SND-like	Auw-Haedrich et al. (2009)
14	c.[1868G>A]	p.G623D	4	Pathogenic	<<<	EBMD	Evans et al. (2016)
14	c.[1870G>A];[1870G>A]	p.Val624Met; Val624Met	4	Likely pathogenic	0.3% in African	LCD atypical	Afshari et al. (2008)
14	c.[1874T>A]	p.Val625Asp	4	Pathogenic	<<<	LCD atypical	Tian et al. (2007)
14	c.[1877A>G]	p.His626Arg	4	Pathogenic	<<<	LCD late onset	H. S. Stewart et al. (1999)
14	c.[1877A>G]	p.His626Arg	4	Pathogenic	<<<	LCD1/3A	Munier et al. (2002)
14	c.[1877A>C]	p.His626Pro	4	Pathogenic	<<<	LCD1/3A	Munier et al. (2002)
14	c.[1892T>A]	p.Val631Asp	4	Pathogenic	<<<	LCD1 with deep deposits	Munier et al. (2002)
16	c.[1998G>C]	p.Arg666Ser	0	Pathogenic	<<	EBMD	Boutboul et al. (2006)
Deletion							
4	c.[310_311delTC]	p.Ser104Lysfs*27	0	Pathogenic	<<<	GCD2	Pang et al. (2002)
12	c.[1618_1620delTTT]	p.Phe540del	4	Pathogenic	<<<	LCD1/3A	Rozzo et al. (1998)
13	c.[1714_1716delCAC]	p.His572del	4	Pathogenic	<<<	LCD late onset	Aldave et al. (2006)
14	c.[1838_1849del12]	p.Val613_Pro616del	4	Pathogenic	<<<	LCD1	Yang et al. (2010)
14	c.[1870_1875delGTGGTC]	p.Val624_Val625del	4	Pathogenic	<<<	LCD atypical	Chakravarthi et al. (2005)
14	c.[1879delG]	p.Val627Serfs*44	4	Pathogenic	<<<	LCD3A	Munier et al. (2002)
Indel							
4	c.[371_378delGCACGGAGinsTC]		1	Pathogenic		GCD1	Dighiero, Drunat, D'Hermeis, et al. (2000)
12	**c.[1556delinsGAGG]**	**p.Val519delinsGlyGly**	**4**	**Pathogenic**	**<<<**	**RBCD**	**This report**

(Continues)

TABLE 1 (Continued)

Exon	c-Notation	p-Notation	Fas1	Effect	ExAC	Phenotype	Reference
14	c.[1868_1869delG CinsAT]	p.Gly623Asp	4	Pathogenic	<<<	RBCD	Afshari et al. (2001)
Insertion							
14	c.[1886_1894dupCC AATGTTC]	p.Thr629insAsnValPro	4	Pathogenic	<<<	LCD1/3A	Schmitt-Bernard et al. (2000)
Complex							
4,12	c.[337G>A];[1673T>C]	p.Val113Ile; Leu558Pro	0,4	Likely pathogenic, pathogenic	0.1% in Latino, <<<	LCD atypical	Ann et al. (2017) Mutations in *trans*
4,12	c.[370C>T];[1637C>A]	p.Arg124Cys; Ala546Asp	1,4	Pathogenic	<<<, <<<	LCD atypical	Cao et al. (2017) Mutations in *cis*
4,12	c.[371G>A;1631A>G]	p.Arg124His; Asn544Ser	1,4	Pathogenic, likely pathogenic	<<<, 0.1% in East Asian	LCD1/GCD2	Yamada et al. (2009) Mutations in *trans*
11,11	c.[1541G>C;1545T>A]	p.Arg514Pro; Phe515Leu	4,4	Pathogenic	<<<, <<<	LCD1	Zhong et al. (2010) Mutations in *cis*
12,12	c.[1637C>A;1652C>A]	p.Ala546Asp; Pro551Gln	4,4	Pathogenic	<<<, <<<	LCD1	Klintworth et al. (2004) Mutations in *cis*
4	c.[371G>T;373_378del]	p.Arg124Leu; Thr125_Glu126del	1,1	Pathogenic	<<<, <<<	CDG atypical	Dighiero, Drunat, D'Hermies et al. (2000) Mutations in *cis*
4, 4	c.[371G>A]?[310_311delTC]	p.Arg124His; p.Ser104Lysfs*27	1,0	Pathogenic	<, <<<		Pang et al. (2002) Phase unknown
4,?	c.[371G>A;535C>T]	p.Arg124His; Arg179*	1,1	Pathogenic	<<, <<<	GCD2	Song et al. (2015) Mutation in *trans*
11,12	c.[1504A>G;1664G>A]	p.Met502Val; Arg555Gln	4,4	VUS, pathogenic	0.4%, <<<		Niel-Butschi et al. (2011) Mutations in *cis*
11,14	c.[1649T>C]?[1877A>G]	p.Leu550Pro? His626Arg	4,4	Pathogenic, pathogenic	<<<, <<<	GCD atypical	Zenteno et al. (2009)
Other phenotype							
	c.[1209T>G]	p.His403Gln		Unknown	<<<	Keratoconus with nonpenetrance	Piret et al. 2016
12	c.[1603G>T]	p.Gly535*	4	Unknown	<<<	Keratoconus	Guan et al. (2012)

Note. Frequency in ExAC: <<<: not reported; <<: <1/10,000; <: <1/1,000; Location: 0: not in FAS1 domain, 1–4: respective FAS1 domain; Variant: [variant;variant]: in *cis*; [variant];[variant]: in *trans*. EBMD: epithelial basement membrane dystrophy; GCD: granular corneal dystrophy; GCD1: GCD, type 1; GCD2: GCD, type 2; LCD: lattice corneal dystrophy; LCD1: LCD, type 1; LCD3: LCD, type 3; PCA: polymorphic corneal amyloidosis; SND-like: Salzmann's nodular degeneration-like; RBCD: Reis-Bücklers corneal dystrophy; SVGD: superficial variant of granular dystrophy; TBCD: Thiel-Behnke corneal dystrophy; VUS: variant of unknown significance.

and occurs more commonly in women over 50 years of age. Clinical findings include four types of lesions: fingerprint lines, map lines that consist of folded strips of the basement membrane, dots or Cogan's dots or microcysts that are debris of collapsed epithelial cells, and Bron's blebs. The majority of patients are asymptomatic but 10% present with transient blurred vision and discomfort from the recurrent erosions.

Histopathology: Maps and fingerprints show aberrant basal membrane. The fingerprint lines consist of thickened basement membrane with fibrillar material and extensions into the epithelium The Cogan's dots are abnormal epithelium with microcysts.

Genetics: Most cases are sporadic but Boutboul et al. (2006) reported two families with EBMD and autosomal-dominant inheritance. They estimated that about 10% of EBMD is due to variants in *TGFBI*. The two reported variants, Arg666Trp and Leu509Arg, are both in the C-terminus of TGFBI. An additional variant causing EBMD, Gly623Asp was reported by Evans et al. (2016).

2.2 | Epithelial-stromal dystrophies

RBCD and TBCD are epithelial-stromal dystrophies as they not only affect the subepithelial area with the destruction of the Bowman layer but also the anterior stroma and later the deeper stroma.

2.2.1 | Reis-Bücklers corneal dystrophy (MIM #608470)

Clinical presentation: Patients are born with normal appearing corneas. Disease becomes symptomatic in the first or second decade of life. Initially, there is potential involvement of the epithelium and superficial part of the stroma. At the level of the Bowman layer and superficial stroma, early confluent and irregular geographic-like opacities with varying densities progressively develop. In the first two decades, RBCD shows more irregular diffuse opacities with clear interruptions. Corneal opacification, as well as bilateral progressive and painful recurrent erosions, develop in childhood, causing vision loss (Paufique & Bonnet, 1966).

Histopathology: Bowman layer, which is acellular, is disrupted and almost completely replaced by band-shaped granular deposits that stained intensely red with Masson trichrome, and which can extend to the subepithelial stroma. In advanced cases, sparse round deposits appear in the middle and posterior stroma.

Genetics: Different variants have been observed with this phenotype. The most frequent variant is the p.Arg124Leu that was observed in many families from various origins (Okada et al., 1998). However, other variants were also identified: p.Arg124Cys in a Chinese family (Ma et al., 2010), p.Leu509Pro in a German family (Gruenauer-Kloevekorn, Clausen et al., 2009), p.Arg555Gln in several families from various origins (Munier, Korvatska, Djemai et al., 1997), Arg555Trp in a heterozygous Mexican patient (Zenteno, Correa-Gomez, Santacruz-Valdez, Suarez-Sanchez, & Villanueva-Mendoza, 2009) and in a homozygous patient of unknown origin (Garg & Jabbar, 2010), and p.Gly623Asp in a patient of unknown origin (Afshari et al., 2001). Two forms of atypical RBCD were found to be associated with two different variants: p.Arg124Leu causing RBCD variant with amyloidogenic phenotype (lattice-like lines) in an Indian family (Paliwal et al., 2011), and p.His626Pro causing a mixed phenotype with RBCD and TBCD patterns in a Caucasian family (Wheeldon et al., 2008). All these variants are dominantly inherited.

2.2.2 | Thiel-Behnke corneal dystrophy (MIM #602082)

Clinical presentation: RBCD and TBCD were misdiagnosed in many scientific journals over decades. They can be particularly confused during the first two decades of life. TBCD exhibits multiple flecks with the reticular formation at the level of Bowman layer, followed by symmetrical subepithelial honeycomb opacities. Peripheral cornea is typically not involved but can be affected with time in older patients. While RBCD has a geographic-like phenotype, TBCD has a honeycomb-like phenotype. Symptoms begin with recurrent corneal erosion during childhood (first and second decade of life) and visual acuity is affected later in life.

Histopathology: Due to the irregularities of the underlying stroma, the epithelium shows alternating irregular thickening and thinning, and there is a focal absence of the epithelial basement membrane. The Bowman layer is replaced by a superficial fibrocellular scar with a pathognomonic wavy saw-toothed pattern or "curly" fibers.

Genetics: The p.Arg555Gln variant is correlated with TBCD. This variant was found in several families from various ethnicities (Cho et al., 2012; El-Ashry, Abd El-Aziz, Hardcastle, Bhattacharya, & Ebenezer, 2005; Munier, Korvatska, Djemai et al., 1997; Takács et al., 2007). Other variants have been shown to be associated with TBCD: Niel-Butschi et al. (2011) reported a French family with an atypical form of TBCD and two variants in *cis*: p.Arg555Gln and p.Met502Val. Based on gnomAD, the Met502Val variant is present in 0.3% of Latinos and 0.2% of non-Finnish European. Therefore, it seems unlikely that it has a direct pathogenic activity. An indirect modifier activity cannot be ruled out at this point.

As discussed above, the p.His626Pro variant has been shown to cause a mixed phenotype between TBCD and RBCD. TBDC has also been linked to a locus on chromosome 10q23-q24, but no gene has been identified so far (Yee et al., 1997). The mode of inheritance of all these variants is dominant.

All pathogenic variants result in the accumulation of insoluble extracellular material in the cornea (Kannabiran & Klintworth, 2006). Accumulation of full length and of fragments of aberrant TGFBI has been demonstrated in corneal deposits (Korvatska et al., 1999).

2.2.3 | Granular corneal dystrophy, type 1 (MIM #121900)

Clinical presentation: GCD1 is one of the most common corneal dystrophies. It is characterized by multiple discrete crumb-like corneal opacities with clear intervening stroma. These gray-white

opacities appear in the first decade of life or at puberty and involve the epithelial and superficial stromal layers of the cornea. These lesions tend to aggregate, expand, and increase in number, spreading both peripherally and more deeply, although, a clear zone around the corneoscleral limbus remains typically unaffected. Central disk-shaped opacities are formed after the third or fourth decade of life. Photophobia is an early symptom. Visual acuity gradually decreases due to progressive corneal opacification and may reach 20/200 after the age of 40 years. Recurrent erosions are frequent. Homozygotes have more severe manifestations.

Histopathology: There is an accumulation of hyaline material subepithelially and between stromal lamellae. This substance stains bright red with Masson's trichrome. Amyloid deposits have been detected in the corneas of older individuals with typical GCD1 (Akiya & Brown, 1970).

Genetics: A great majority of subjects with GCD1 have a C to T transition at nucleotide position 1663 of *TGFBI* exon 12, predicting a p.Arg555Trp change of the protein in heterozygous patients. However, the typical GCD1 phenotype has also been associated with three other variants: G to A transition at position 337 causing p.Val113Ile substitution in a Spanish and Mexican family (Ann et al., 2017; Zenteno et al., 2009), C to A transversion at nucleotide 370 causing a p.Arg124Ser substitution in Asian families (H. S. Stewart et al., 1999), and a C to G transversion at nucleotide 1548 causing a p.Ser516Arg substitution in an Indian family (Paliwal et al., 2010). In the juvenile-confluent form, a defect at p.Arg124His was found to be responsible for the disease in five Japanese homozygous families (Mashima et al., 1998). An atypical form of GCD1 has been linked to the p.Ala546Asp variants in a Chinese family (Yu et al., 2008). p.Leu550Pro and p.His626Arg located in *cis* were inducing an atypical form of granular dystrophy in a Mexican patient (Zenteno et al., 2009). p.Asp123His is another variant responsible for an atypical form of granular dystrophy in a Vietnamese family (Ha et al., 2003). p.Arg555Trp has caused a severe GCD in the homozygous patient (Okada et al., 1998). All variants cited here are dominantly inherited.

Although the Val113Ile variant was described in Spanish/Latino families associated with a peculiar form of CD, it is also in that population that this variant is the most frequent with an observed frequency of 0.1%. Similarly, p.Asp123His variant is most prominent in the East Asian population with a frequency of 0.1%. In addition, this variant has only been described in one family from Vietnam. In these families, segregation of p.Val113Ile and p.Asp123His was not complete. Awaiting reports of additional families, these variants are considered as likely pathogenic.

Edelstein, Huang, Harocopos, and Waltman (2010) described a GCD2 phenotype in a patient with p.Arg124Cys variant. The initial clinical presentation was consistent with LCD1 with diffuse central anterior stromal haze and lattice lines. It is only in the graft that granular deposits were observed. We do not find it appropriate to correlate the p.Arg124Cys variant with the graft phenotype and reclassified this case as LCD1.

A French variant of granular dystrophy was identified in French families bearing a c.371_378delGCACGGAGinsTC heterozygous variant (Dighiero, Drunat, D'Hermies et al., 2000).

2.2.4 | Granular corneal dystrophy, type 2 (MIM# 607541)

Clinical presentation: GCD2 shows both granular and lattice-like deposition in the same cornea. It presents as rings, stars, and granules, often in finger-like appearance. It is epithelial and stromal dystrophy. GCD2 appears to be phenotypically variable, both within and among families. Although affected patients will often demonstrate discrete granular opacities in the first decades of life, stromal lattice-like lines may not appear until later and often do not present as characteristic stromal lattice lines. Dashes in GCD2 appear whiter than in LCD and rarely cross each other, in contrary to lattice lines. With increasing age, the granular lesions become larger and the lattice-like lines, more prominent. Initially, they are found in the mid and deep stroma and later involve the entire stroma. In advanced GCD2 there is also a diffused stromal haze. Visual acuity is rarely worse than 20/70. Corneal erosions cause pain. There are two types of corneal opacities: the more severe type 1 opacity is characterized by a discrete gray-white confluent lesion, which is associated with the p.Arg124His homozygous variants and the type 2 opacity, which is marked by intervening translucent spaces, is associated with the p.Arg124His heterozygous variant.

Histopathology: The presence of both hyaline and amyloid deposits that stain with Masson trichrome and/or Congo red (Aldave et al., 2007; Folberg et al., 1988). Homozygotes show a more severe phenotype.

Genetics: GCD2 is an autosomal-dominant disorder associated with p.Arg124His variant (Munier, Korvatska, Djemai et al., 1997). Other variants have been described with GCD2: p.Arg124Cys in a White male (Edelstein et al., 2010), p.Arg124His in several homozygous families of different ethnicities (Mashima et al., 1998) and in four homozygous Japanese families with reticular opacities (Watanabe et al., 2001), p.Arg124His together with c.307–308delCT in a Chinese patient (Yam et al., 2012), p.Leu550Pro and p.His626Arg in two Mexican families (Zenteno et al., 2009), p.Arg124His together with p.Asn544Ser in a Japanese family that shows GCD2 and LCD (Yamada et al., 2009), and p.Met619Lys in a Hispanic family with an atypical form of GCD2 (Aldave et al., 2008).

2.2.5 | Lattice corneal dystrophy, type 1 (MIM #122200)

Clinical presentations: This disease, also classified as localized amyloidosis, develops early in life. It is characterized by a fine network of linear opacities in the epithelial and anterior stroma of the central and paracentral cornea. These linear branching deposits gradually cause opacification of the visual axis. Central epithelial and subepithelial diffuse corneal opacities cause visual impairment. In the second and third decade of life, diffuse central haze may happen and

may sufficiently reduce vision to necessitate surgical intervention. The disease can be asymmetric between the two eyes or rarely unilateral. Systemic amyloidosis is absent. Recurrent corneal ulceration sometimes occurs.

Histopathology: There is epithelial atrophy, focal thinning or absence of Bowman layer. The eosinophilic amyloid material, which accumulates between the epithelial basement membrane and Bowman layer as well as in the stroma, stains with Congo red and exhibits a birefringence under polarized light.

Genetics: Variants associated with LCD1 are: p.Arg124Cys in many families from different ethnic origins (Munier, Korvatska, Djemai et al., 1997); Val505Asp (Tian et al., 2005), p.Arg514Pro and p.Phe515Leu together (Zhong et al., 2010), p.Ile522Asn (C. Zhang et al., 2009), p.Thr538Pro (Yu et al., 2006), p.Ala620Asp (Lakshminarayanan et al., 2011), and p.Val625Asp (Tian et al., 2007), all in Chinese individuals; p.Leu518Pro was observed in several Japanese families (Endo et al., 1999); p.Val539Asp in an Indian family (Chakravarthi, Kannabiran, Sridhar, & Vemuganti, 2005); p.Ala546Aps/p.Pro551Gln in an Afro-American family (Klintworth, Bao, & Afshari, 2004); p.Leu569Arg in an American family (Warren et al., 2003), p.Leu509Pro in a French family (Niel-Butschi et al., 2011), and p.His572Arg in a Thai and a family of unknown origin (Atchaneeyasakul et al., 2006).

2.2.6 | Lattice dystrophy, type 3 (LCD3)

Clinical presentation: It has a late onset, no recurrent epithelial erosions and the lattice lines are much thicker than those found in type 1.

Genetics: It has been associated with p.Leu527Arg homozygous variant (Funayama, Mashima, Kawashima, & Yamada, 2006).

2.2.7 | Lattice type 3A: (LCD3A; MIM #608471)

Clinical presentation: This disease exhibits clinical characteristics of type 3 and recurrent corneal erosions with the onset of symptoms in the fifth decade of life.

Histopathology: The deposits stain orange-red with Congo red and stain with PAS, Masson's trichrome, and fluorochrome thioflavin T. With a polarizing filter, amyloid deposits demonstrate apple-green birefringence. Metachromasia is apparent with crystal violet staining.

Genetics: LCD3A was associated with P p.ro501Thr variant in several Japanese families (Yamamoto et al., 1998), p.Ala546Thr in French families (Dighiero, Drunat, Ellies et al., 2000), p.Asn622Lys and p.Val627fs in families from Italy or South America (Munier et al., 2002), and p.His572del in a patient of unknown origin that had unilateral LCD (Aldave, Rayner, Kim, Prechanond, & Yellore, 2006). In the following articles, the origin of the patients was not reported: p.Phe540Ser (Stix et al., 2005), p.Asn622His (H. Stewart et al., 1999), and p.His626Arg (H. Stewart et al., 1999).

2.2.8 | Lattice type 4 (LCD4)

Clinical presentation: It has a late onset and shows uncommon forms of lattice deposits with opacities in the deep stroma.

Genetics: Variants that are associated with this phenotype are p.Arg496Trp in a family of unknown origin (Kawasaki et al., 2011), p.Leu527Arg, p.Asn544Ser in Japanese and Korean families (Fujiki et al., 1998; Nakagawa Asahina, Fujiki, Enomoto, Murakami, & Kanai, 2004), p.Leu558Pro in an Ukrainian family (Livshits, Pampukha, Tereshchenko, & Drozhyna, 2008), p.Val631Asp in a European family (Munier et al., 2002), and p.Gly594Val in two Indian families (Chakravarthi et al., 2005). The p.Asn544Ser variant has not been classified as LCD4 but is a LCD of late onset (Mashima et al., 2000). Similarly, the p.Val613Gly variant found in an Algerian patient of 80 years was associated with LCD although it is not indicated in the article whether or not it is a type 4 CD (Niel-Butschi et al., 2011).

2.2.9 | Atypical LCD

Several presentations cannot be strictly classified into a single subtype and have been grouped here. As LCD4, atypical LCD need an extensive clinical and genetic analysis to be confirmed as a unique type of corneal dystrophy.

LCD1/3A is a late-onset disease with anterior/midstromal lattice lines. Variants causing this type of lattice are p.Leu518Arg, p.Thr538Arg, p.Phe540del, p.Gly623Asp, p.His626Pro, and p.His626Arg (Munier et al., 2002), p.Ala546Asp/p.Pro551Gln (Aldave et al., 2004), and p.Thr629_Asn630insAsnValPro (Schmitt-Bernard et al., 2000).

Other atypical LCD is caused by p.Leu509Arg (Niel-Butschi et al., 2011), p.Pro542Arg (Cho et al., 2012), p.Ala546Asp (Correa-Gomez, Villalvazo-Cordero, & Zenteno, 2007), p.Val613_Pro616del (Yang et al., 2010), p.Gly623Asp (Aldave, Rayner, King, Affeldt, & Yellore, 2005), p.Gly623Arg (Gruenauer-Kloevekorn, Braeutigam, Froster, & Duncker, 2009), p.Val624Met (Afshari et al., 2008), and p.Val624_Val625del (Chakravarthi et al., 2005).

A form of inherited polymorphic corneal amyloidosis can also be caused by p.Ala546Asp (Eifrig, Afshari, Buchanan, Bowling, & Klintworth, 2004) and p.Phe547Ser variants (Takács et al., 2007).

2.3 | Concomitant and isolated nonsense variants

Three reports of concomitant nonsense variants are available. Sakimoto et al. (2003) described a family with LCD1 and an p.Arg124Cys variant. In the proband, an additional p.Gly470* variant was observed. This variant was not seen in two other affected family members but was present in her unaffected daughter. A second concomitant nonsense variant was described by Song, Lim, Chung, Chung, and Ki (2015) who presented a patient affected with GCD2 and the classic p.Arg124His variant together with a p.Arg179* variant (reported as p.Ala179* in the publication). The father, also affected with GCD2, only had the classical p.Arg124His variant. A third case was identified in a patient presenting keratoconus and a

p.Gly535* variant (Guan, Liu, Ma, & Ding, 2012). Unfortunately, no segregation analysis was reported and a sequencing error cannot be excluded from the figure provided by the authors.

None of the three nonsense variants are unambiguously associated with a phenotype and additional reports need to be presented before one can conclude on their role.

3 | *TGFBI* EXPRESSION, ROLE, AND PATHOLOGY IN THE EYE OF HUMANS AND ANIMAL MODELS

3.1 | TGFBI expression

During mouse embryogenesis, *Tgfbi* is expressed for the first time at 11.5 days post conception (dpc) in the first and second branchial arches. These structures will give rise to different craniofacial elements including orbita and lower eyelid. Later in embryogenesis, there is a transient expression of *Tgfbi* by the mesenchyme surrounding and composing numerous tissues. These include cranial nerve nuclei (VIII, IX, X), dorsal root ganglia, Rathke pouch, leptomeninges, choroid plexus, submaxillary gland, and connective tissue surrounding the submaxillary acini, developing bones (frontal, parietal, sphenoid, ethmoid, temporal, basio-occipital, chondro-occiput, inner ear, dental, costal and vertebral bone, sternum, and ribs primordium), intervertebral disks, muscular precursor (tongue, pulmonary artery and aorta, and gut walls), vessels, heart, lung, kidney, capsule of the developing adrenal gland, pancreatic primordium (and then connective tissue surrounding the acini and Langerhans islands), peritoneum, capsule of Glisson, thymic primordium, umbilical cord, most of developing cartilages, and derm (Schorderet et al., 2000). In the mouse fetal eye, *Tgfbi* is expressed at 11.5 dpc in the mesenchyme surrounding the optic stalk, at 14.5 dpc in the sclera, choroid, and connective tissue of future eyelids, at 15.5 dpc in the periocular mesenchyme posterior to the developing lens, and finally at 17.5 dpc in the cornea (Schorderet et al., 2000).

In humans, *TGFBI* is widely expressed in many tissues and organs, including spleen, thymus, prostate, testes, ovaries, small intestine, colon, leukocytes, heart, placenta, lung, liver, skeletal muscle, kidneys and pancreas, with highest expression level in leukocytes, heart, and placenta (Ivanov et al., 2008; Skonier et al., 1994). In the brain, *TGFBI* expression was almost undetectable (Ivanov et al., 2008; Skonier et al., 1994). In the human eye, *TGFBI* is expressed almost exclusively in the cornea and in the retinal pigment epithelium (Allaman-Pillet, Oberson, & Schorderet, 2017). This protein is preferentially expressed on the extracellular surface of corneal epithelial cells (Escribano, Hernando, Ghosh, Crabb, & Coca-Prados, 1994). It is more abundant in mature corneas than in the developing cornea. During postnatal development of the cornea, expression, and processing of *TGFBI* change. Between 6 and 14 years of age, the concentration of TGFBI in the cornea increases by about 30% (Karring et al., 2010). This suggests that this protein could have a role in the postnatal development and maturation of the cornea. It could also explain the variation of the age of onset of corneal dystrophies (Karring et al., 2010).

Numerous molecules have been shown to regulate *TGFBI* expression including TGFB1, retinoid (Dokmanovic, Chang, Fang, & Roninson, 2002), interleukin-4 (IL-4; Gratchev et al., 2001), IL-1, tumor necrosis factor (TNF)-α (Nam et al., 2006), TNF-like ligand 1A (S. H. Lee, Kim, Suk, Kim, & Lee, 2010), and the microRNA miR-21 (Liu et al., 2011). Its expression also depends on the accessibility of its promoter to messenger RNA and proteins, and on regulatory elements in the *TGFBI* promoter region that bind transcription factors SP1 and SP3 (Lee et al., 2011).

3.2 | Role of TGFBI

3.2.1 | Physiological role of TGFBI

The role of TGFBI is not fully understood. In addition to an anchoring function between corneal stroma and the adjacent Descemet membrane and subepithelial tissues (Hirano, Klintworth, Zhan, Bennett, & Cintron, 1996), it acts as a membrane-associated growth factor (Escribano et al., 1994; LeBaron et al., 1995) and has been shown to trigger phosphorylation and to activate different intracellular pathways including AKT, extracellular regulated kinase 1/2, focal adhesion kinase, and paxillin, consequently mediating adhesion and migration of vascular smooth muscle cells through interactions with various integrins, although this might be cell-dependent (Klamer et al., 2013; Lee et al., 2006). It has also been shown to play a role in wound healing, corneal growth, and differentiation by mediating cell adhesion via collagen, fibronectin, and integrins (Gibson et al., 1997; Gratchev et al., 2001; Skonier et al., 1992; Yun et al., 2002), in postnatal development and maturation of the cornea (Karring et al., 2010), adhesion and migration of a wide range of cells including fibroblasts (LeBaron et al., 1995), keratocytes, chondrocytes, osteoblasts, and endothelial cells (Thapa, Kang, & Kim, 2005), hematopoietic stem cells and progenitor cells (Klamer et al., 2013), renal proximal tubular epithelial cells (Park et al., 2004), osteoblast adhesion and its differentiation (Bhushan et al., 2013) or absence of it (Monticone et al., 2004; Thapa et al., 2005), and reproduction (Carson et al., 2002; Uekita, Kim, Yamanouchi, Tojo, & Tachi, 2003).

J. E. Kim et al. (2000) proposed that TGFBI mediates cellular activity through interaction between cell adhesion motifs and integrins on different cell types. They reported binding to α3β1 integrins to mediate corneal epithelial cell adhesion through two recognition sites, NKDIL, and EPDIM located in the second and fourth FAS1 domains. All 4 FAS1 domains of TGFBI mediate fibroblastic cell adhesion, in particular by interaction with the αvβ5. In addition, these authors also showed that TGFBI could inhibit angiogenesis (J. E. Kim et al., 2003). This was later confirmed by expressing a recombinant TGFBI containing an RGDRGD modified C-terminal fragment (Ge et al., 2013).

3.2.2 | Pathological role of TGFBI

TGFBI plays a role in pathological conditions, including corneal dystrophies (Munier, Korvatska, Djemai et al., 1997), diabetes (Han et al., 2014), atherosclerotic and restenotic vascular lesions (O'Brien et al., 1996), inflammatory diseases including rheumatoid arthritis (Gratchev et al., 2001; Nam et al., 2006), ovarian endometriosis (Arimoto et al., 2003), and tumorigenesis.

In various cancers TGFBI has an opposite effect, that is, prooncogenic or antioncogenic. On one hand, TGFBI supports the development of tumors in breast, renal, pancreatic, lung, colorectal, intestinal, and brain cancers (Calaf, Echiburu-Chau, Zhao, & Hei, 2008; Golembieski & Rempel, 2002; Hourihan, O'Sullivan, & Morgan, 2003; Ivanov et al., 2008; Sasaki et al., 2002; Yamanaka et al., 2008; Zajchowski et al., 2001). Higher levels of TGFBI have been linked to more aggressive tumors (Ma et al., 2008; Zajchowski et al., 2001) and TGFBI was shown to be indirectly regulated by VHL in VHL-associated cancers such as clear cell carcinoma and hemangioblastoma (Ivanov et al., 2008). It was proposed that upregulation of *TGFBI* in cancer cells could be responsible for their survival via extracellular matrix (ECM)-dependent signaling. The low oxygen situation that prevails in many cancers further supports TGFBI-mediated lymphatic endothelial migration and adhesion to ECM, helping the development of metastases (Irigoyen et al., 2008) and promoting extravasation, an essential step in metastasis (Ma et al., 2008).

On the other hand, many studies reported a tumor suppressor role for TGFBI (Becker et al., 2008; Kang, Dong, & Park, 2010; Wang et al., 2012; Ween et al., 2011; Wen, Hong et al., 2011; Wen, Partridge et al., 2011; Zamilpa et al., 2009; Y. Zhang et al., 2009; Zhao, El-Gabry, & Hei, 2006) and loss-of-function was described in other cancers including ovarian cancer. Y. Zhang et al., (2009) presented evidence that TGFBI had a tumor suppressor role as they showed that mice lacking TGFBI were prone to develop spontaneous tumors, and that *Tgfbi*(−/−) mouse embryonic fibroblasts have increased chromosomal aberrations and enhanced proliferation. However, no spontaneous tumor development was observed in our own knock-out model (Allaman-Pillet et al., 2015). It is only when crossed with a mouse model of retinoblastoma that its antioncogenic activity was revealed (Allaman-Pillet et al., 2017). Decreased *TGFBI* expression in several human leukemia cell lines was correlated with hypermethylation of its promoter, and its demethylation restored expression (Fang, Liu, Guo, Liu, & Zhao, 2014; Kang et al., 2010; Lee et al., 2011; Shah, Shao, Hei, & Zhao, 2008).

3.3 | Pathophysiology in the eye

In 1997, we identified dominant variants in *TGFBI* causing GCD1, LCD1, GCD2, and RBCD (Munier, Korvatska, Djemaï, et al., 1997). Later on, we confirmed the implication of *TGFBI* in several families affected by GCD1, LCD1, and GCD2 (Korvatska et al., 1998). In terms of affected patients, it seems clear that the Arg124 and Arg555 amino acids are hot spots for variants in the 5q31-linked corneal dystrophies. Previously, TGFBI was shown to be present in the corneal epithelium and stromal keratocytes of rabbits as an extracellular protein (Escribano et al., 1994), which was consistent with the hypothesis that the deposits in this pathology originate either in the corneal epithelium or in stromal keratocytes. After these publications, the ophthalmic and genetic community reported additional variants and refined the genotype–phenotype correlation. Therefore new variants were linked to phenotypes like TBCD, LCD3, LCD3A, or atypical corneal dystrophy, as well as LCD deep (Fujiki et al., 1998; Munier, Korvatska, Djemai et al., 1997; Schmitt-Bernard et al., 2000; H. S. Stewart et al., 1999). Lisch and Seitz (2014) showed that in LCD1 both epithelial and stromal cells are involved. They came to this conclusion because patients affected by LCD1, who had a keratoplasty showed recurrences of superficial opacities on the graft, product of the epithelial cells, but no lattice lines, which is an indirect sign that lattice lines are the product of keratocytes.

These TGFBI-linked CDs are characterized by bilateral corneal deposits that usually appear between the first and fourth decade of life, progress over time and could lead to loss of vision by opacification of the central cornea during the third to sixth decades. Phototherapeutic keratectomy or corneal transplantation is necessary in severe cases (Ridgway & Moller, 1992; Rogers, Cohen, & Lawless, 1993). The deposits in GCD1 and RBCD seem identical, but in GCD1 they are localized deeper in subepithelial and stromal layers, whereas in RBCD they are in the epithelial and Bowman layers and occur earlier in life. Histopathology reveals deposits of nonamyloid nature in GCD1 and RBCD and of the amyloid type in LCD1 (Klintworth, 1967). GCD2 show mixed deposits, amyloid and nonamyloid (Folberg et al., 1988).

It is interesting to note that both amyloid-related CDs (LCD1 and GCD2) are due to modifications at Arg124, whereas the nonamyloid-related CDs (GCD1 and RBCD) are due to modifications at Arg555. These four types of CD are inherited as autosomal dominant traits with almost complete penetrance and incomplete dominance as patients with variants on both alleles have a more severe phenotype (Mashima et al., 1998; Okada et al., 1998).

The variants at Arg124 abolish a putative phosphorylation site and could modify the tertiary structure of TGFBI. Variants at Arg555 affect a predicted coiled-coil domain, which could impair binding to stromal proteins. In addition, these variants could also perturb the degradation of TGFBI and be responsible for TGFBI aggregation in corneal deposits. Immunostaining of corneas from patients with GCD1, LCD1, and GCD2 with antisera against the amino and carboxyl termini of TGFBI showed abnormal accumulation of TGFBI and abnormal folding depending on the variant. It was suggested that variants at Arg555 result in accumulation of the whole protein followed by aggregation, whereas the variant at Arg124 was mainly inducing accumulation of a truncated protein, lacking its amino-terminal domain (Korvatska et al., 1999). Thus, the generation of abnormal fragments or increased amount of TGFBI seems to be a common pathogenic mechanism in these corneal dystrophies. Electron microscopy performed on corneal tissue and fibroblasts from patients with GCD2 obtained after keratoplasty showed dilated and degenerative mitochondria (T. I. Kim et al., 2011). It is not clear

whether mitochondrial involvement is an early event in the pathology of CD or it is a secondary result.

Morand et al. (2003) investigated six different variants in an in vitro system and observed that recombinant TGFBI accumulated in the medium regardless of its modified status. However, overexpression of modified *TGFBI* induced a strong apoptotic response in both HeLa and human corneal epithelial cell lines through activation of caspase-3 by a pathway that uses the PDI domain of the fourth TGFBI FAS1 domain (Morand et al., 2003). Overexpression of a carboxyl-truncated *TGFBI* prevented cell apoptosis, suggesting that a region located in the C-terminal domain is necessary to induce cell apoptosis (Morand et al., 2003). In contrast to variants in the RGD domain, modified PDI did not induce apoptosis.

Purified wild-type TGFBI self-assembles to form a fibrillary structure and interacts with matrix proteins such as collagen 1, fibronectin, fibrillin, and laminin. It moderately binds to collagen 2 and 6, and minimally to collagen 4 (Billings et al., 2002; Kim, Jeong, et al., 2002). Recombinant modifications in TGFBI (p.Arg124Cys, p.Arg124His, p.Arg124Leu, p.Arg555Trp, and p.Arg555Gln) did not significantly affect its fibrillary structure, interaction with other extracellular matrix proteins, or adhesion activity in cultured corneal epithelial cells. Degradation products were similar between wild-type and mutated TGFBI (J. E. Kim, Park, et al., 2002). The deleterious impact of altered TGFBI was further evaluated by crystallization experiments. Runager et al. (2009) showed that purified TGFBI variants (p.Arg124Cys, p.Arg124His, and p.Arg124Leu) from human cells did not aggregate (Runager et al., 2009). Whether this is due to different experimental conditions is difficult to establish, but it confirms our unpublished data showing that heterozygous and homozygous p.Arg124Leu knock-in mouse model failed to produce recognizable corneal deposits. These experimental results are in opposition to in vivo analyses showing accumulation of normal and aberrant TGFBI and by-products in corneas from patients.

3.4 | Animal models

The use of animal models has generated conflicting results. Bustamante et al. (2008) generated a transgenic mouse model of GCD1 overexpressing a recombinant *TGFBI* construct containing the Arg555Trp variant under a phosphoglycerate kinase promoter. No expression was detected in the cornea, and no corneal phenotype was observed. However, mutated *TGFBI* was expressed in the retina and induced an age-dependent retinal degeneration both functionally (ERG) and histologically, suggesting that altered *TGFBI* may affect photoreceptor survival. Using an identical promoter but a different transgenesis protocol, Liao, Cui, and Wang (2013) established a transgenic mouse model overexpressing *TGFBI*. These mice displayed central corneal opacities in five out of seven transgenic mice

Yamazoe et al. (2015) reported a transgenic mouse model of GCD2 caused by the p.Arg124His variant, showing granular with or without lattice deposits in the center of the cornea. Histology was similar to that of human-affected corneas. As not all transgenic animals had corneal opacities, the authors concluded that epigenetic and/or environmental factors could influence the phenotype in mice and humans (Yamazoe et al., 2015). As mentioned above, our p.Arg124Leu knock-in animal failed to show any corneal deposits, either at the heterozygous or homozygous state (data not shown).

4 | NOVEL PATHOGENIC VARIANT

An 8-year-old Mexican girl consulted for reduced visual acuity, photophobia, and ocular discomfort. Examination revealed bilateral corneal lesions, granular central subepithelial and paracentral lattice lines in anterior stroma. Visual acuity (VA) and best-corrected visual acuity (BCVA) for the right eye was 20/80 and 20/30 and 20/80 and 20/40 for the left eye. Her mother consulted when she was 15 years of age because of eye redness, photophobia, and blurred vision. At that time she was diagnosed with corneal dystrophy. Her VA and BCVA were 1.5/10 and 8/10 for the right eye and 8/10 and 10/10 for the left. There were superficial bilateral corneal opacities and a central epithelial ulcer was observed in the left eye. Several months later, bilateral lattice lines and epithelial erosions were found in the anterior stroma. Phototherapeutic keratectomy in both eyes was performed. Lamellar keratoplasty followed seven years later in the right eye and 15 years later in the left eye.

Molecular analysis of *TGFBI* revealed a heterozygous c.[1556delinsGAGG], p.[Val519delinsGlyGly] a variant in the mother and her daughter (Figure 1).

5 | VARIANTS IN TGFBI

We have identified, through literature search and our own cases, a total of 69 TGFBI pathogenic or likely pathogenic variants causing various corneal dystrophies. Two additional variants are associated with keratoconus. Pathogenic variants were defined as sequence variants segregating with the disease within the families, which were absent in unaffected individuals and were observed in less than 0.01% of the reported ethnic group in ExAC. Pathogenic variants occur in exons 4, 11–14, and 16. A total of 60 missense variants (86.9%), six deletions (8.6%), one insertion (1.4%), and two small indels (2.9%) have been reported so far in corneal dystrophy.

Certain variants are associated with specific phenotypes, while others can cause various phenotypes (Table 1).

Homozygous p.Arg124His (Diaper, Schorderet, Chaubert, & Munier, 2005; Mashima et al., 1998) and p.Arg555Trp (Kannabiran, Sridhar, Chakravarthi, Vemuganti, & Lakshmipathi, 2005; Okada et al., 1998) are associated with worse prognosis. The Val624Met variant seems to be an exception. CD develops only when the variant is in the homozygous state (Afshari et al., 2008). This is the only publication so far that shows a true recessive inheritance and additional reports are needed to confirm this mode of transmission.

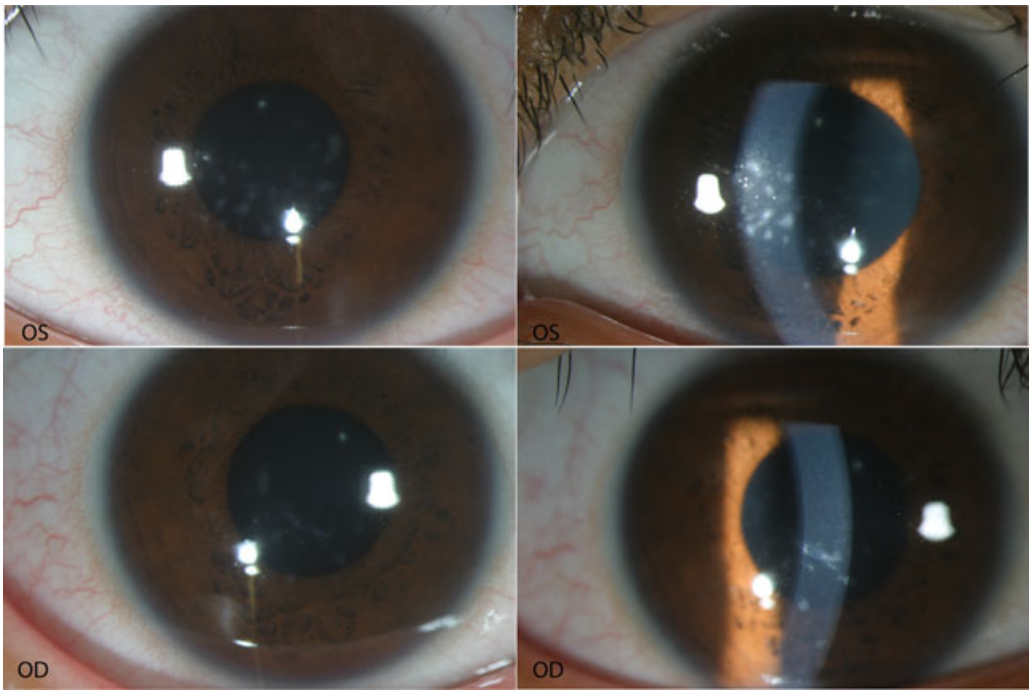

FIGURE 1 Corneal appearance of a patient with the novel *TGFBI*:c.[1556delinsGAGG] pathogenic variant. Slit-lamp microphotographs demonstrate discrete, gray-white subepithelial opacities of various morphologies mainly located at central corneal. The overlying epithelium was intact. OD: right eye, OS: left eye. OD: oculus dextrus; OS: oculus sinister TGFBI: human transforming growth factor β-induced

5.1 | Molecular diagnosis

The correlation between variants and phenotype is such that Sanger sequencing of exons 4 and 12 is still an economically sound procedure. If no pathogenic variant is found in these exons, next-generation sequencing of a panel of genes containing *TGFBI* should be performed.

6 | DATABASE

We have established an up-to-date database describing all the *TGFBI* pathogenic and likely pathogenic variants and associated phenotypes. These variants are listed in Leiden open variation database (LOVD) v.3.0, an open-source database developed by the Leiden University Medical Center in the Netherlands. This database can be found at https://databases.lovd.nl/shared/genes/TGFBI

Sequence variant information include exon–intron location, DNA change, protein change, protein domain, predicted effect, first description of the variant, first description of the phenotypes, original clinical diagnosis, pathogenicity of the sequence variant, mode of inheritance, ethnic origin, and the number of families and patients reported so far.

An accurate list of pathogenic and likely pathogenic variants is important both for medical geneticists and ophthalmologists so that they can correctly diagnose and advise patients carrying a genetic disorder that is the cause of corneal dystrophy.

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