MINIREVIEW

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Corneal dystrophies in Japan

Abstract Recent advances in molecular genetics have increased our understanding of the role of genes. Four autosomal dominant corneal dystrophies (CDs); granular CD (GCD), Avellino CD (ACD), lattice CD (LCD), and Reis-Bücklers CD (RBCD) were mapped to the long arm of chromosome 5 (5q31). These four diseases were shown, in a Caucasian series, to result from different missense mutations in the *TGFBI* (*BIGH3*, keratoepithelin) gene. The same mutations were also detected in Japanese patients, from a different ethnic background. Gelatinous drop-like corneal dystrophy (GDLD), on the other hand, which was found in Japanese patients in 1914, is a rare autosomal recessive disorder characterized by corneal amyloidosis. Parents of the patients had a markedly higher frequency of consanguineous marriages than the general population. The gene responsible for GDLD, the membrane component, chromosome 1, surface marker 1 (*M1S1*) gene was mapped to the short arm of chromosome 1(1p). Four deleterious mutations in this gene were detected in Japanese patients. We review here additional studies on mutations of the *TGFBI* and *M1S1* genes found in Japanese patients. In the *TGFBI* gene, nine different mutations were detected in Japanese patients with GCD, ACD, LCD, or RBCD. The codons R124 and R555 of the *TGFBI* gene were hotspots in Japanese patients, of whom many were ACD patients with the R124H mutation. New mutations responsible for LCD were detected in the *TGFBI* gene of patients with LCD, in addition to the P501T mutation in LCD type IIIA found earlier. These studies showed a clear genotype/phenotype correlation associated with the *TGFBI* gene. In the *M1S1* gene, the Q118X mutation was the most common alteration, and a founder mutation in Japanese GDLD patients, as previously reported. Ninety-two percent of the mutated alleles were the Q118X.

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Introduction

Corneal dystrophies (CDs) are inherited, bilateral, primary alterations of the cornea that are not associated with prior inflammation or systemic diseases. Recent advances in molecular genetics have revealed the genes responsible for many corneal dystrophies (Table 1). Three types of autosomal dominant CDs were mapped to the long arm of human chromosome 5 (5q31) (Stone et al. 1994). These are granular Groenouw type I (GCDGI), Avellino CD (ACD), and lattice CD type I (LCDI). In addition, Reis-Bücklers CD (RBCD) was also mapped to the same locus (Small et al. 1996). These four CDs show clinically progressive opacities of the cornea, leading to severe visual impairment. In 1997, missense mutations in the transforming growth factor beta-induced (*TGFBI*, *BIGH3*) gene encoding keratoepithelin were identified in these four CDs in patients of Caucasian background (Munier et al. 1997). The same mutations were also detected in patients from a different ethnic background i.e., Japanese patients (Mashima et al. 1997; Konishi et al. 1998 and 1999; Fujiki et al. 1998a; Okada et al. 1998a; Hotta et al. 1998). Moreover, new mutations in the same gene were reported in Japanese patients (Yamamoto et al. 1998; Fujiki et al. 1998b; Okada et al. 1998b; Endo et al. 1999).

Gelatinous drop-like corneal dystrophy (GDLD), which was detected in Japanese patients by Nakaizumi (1914), is, on the other hand, an autosomal recessive disorder characterized by clinically grayish corneal amyloid deposits that cause severe visual impairment. The prevalence rate was calculated to be 1/33,000 in a nationwide survey of patients and frequencies of consanguineous marriages (Kawano et al. 1992). The disorder was observed mostly in the offspring of consanguineous marriages, with the parents of the

Table 1. Mode of inheritance, gene loci, and genes cloned in herditary corneal dystrophy

Corneal layer	Disease		Inheritance	Gene locus	Gene
Epithelium	Meesmann's dystrophy		AD	12q13	*KRT3*
			AD	17q12–q21	*KRT12*
Stroma	Reis-Bücklers CD				
	Granular CD (Groenouw I)				
	Avellino CD				
	Lattice CD	Type I	AD	5q31	*TGFBI*
		Type IIIA			
		Type IV			
		Type II	AD	9q34	*GSN*
	Gelatinous drop-like CD		AR	1p32–q12	*M1S1*
	Macular CD type I, type II		AR	16q22	*CHST6*
	Schnyder's crystalline dystrophy		AD	1p36–p34.1	
Endothelium	Fuchs' endothelial dystrophy		AD	—	
	Posterior polymorphous dystrophy (PPD)		AD	20q11	
	Congenital hereditary endothelial dystrophy (CHED)		AD	20	
	(CHED 2)		AR	20	

AD, autosomal dominant; AR, autosomal recessive; CD, corneal dystrophy

probands showing a frequency of 43% of consanguineous marriages, higher than that in the general population, which was 6.8% in the marriage year of parents of the probands. It is interesting that the incidence of recessive disorders (Saito 1985 and 1988; Hayakawa et al. 1997), including GDLD (Kawano et al. 1992), has decreased in Japan, because of the marked decrease in consanguineous marriages in recent years in the Japanese population (Imaizumi 1986; Hosoda et al. 1983). The gene responsible for GDLD was mapped to the short arm of chromosome 1 (1p) (Tsujikawa et al. 1998). The membrane component, chromosome 1, surface marker 1 (*M1S1*) gene, the gene responsible for GDLD, was cloned, and four deleterious mutations were detected in this gene in Japanese patients (Tsujikawa et al. 1999).

We present here the findings of our own studies and cite recent advances in findings about two kinds of CDs in Japanese patients. The first is an autosomal dominant CD affected by alterations in the *TGFBI* gene, and includes Avellino CD (ACD), granular CD (GCD), lattice CD (LCD), and Reis-Bücklers CD (RBCD). The second is an autosomal recessive CD, gelatinous drop-like corneal dystrophy (GDLD), which is associated with alterations in the *M1S1* gene.

Materials and methods

In our studies, we analyzed findings in 121 families, including 158 patients and 41 unaffected relatives of patients manifesting GCD, LCD, or RBCD; and 8 families, including 10 patients and 18 unaffected relatives, manifesting the autosomal recessive GDLD. Fifty normal volunteers served as controls. All studies were performed according to the guidelines of the Declaration of Helsinki. Appropriate informed consent was obtained from each subject before the collection of peripheral leukocytes was done. Genomic

DNA was extracted, with a DNA extraction kit (IsoQuick; ORCA Research, Bothell, WA, USA), from peripheral leukocytes. Each exon of the *TGFBI* and *M1S1* genes was amplified by polymerase chain reaction (PCR), using appropriate primers. PCR products were purified using the High Pure PCR Product Purification Kit (Roche Diagnostic, Mannheim, Germany), and directly sequenced with an automated sequencer (model 373A; Perkin Elmer Applied Biosystems, Foster City, CA, USA) in both sense and antisense strands, after termination reaction using a DNA sequencing kit (Dye Terminator Cycle Sequencing, Ready Reaction; Perkin Elmer Applied Biosystems). DNA was digested with restriction enzyme to verify mutation on the *M1S1* gene. Nucleotide sequences for mutation analyses were compared with the nucleotide and deduced amino acid sequences of the *TGFBI* (*βig-h3*) human cDNA (Skonier et al. 1992) and the *M1S1* gene (GA733) (Linnenbach et al. 1989), respectively. Corneas with each mutation were observed histopathologically.

Results and discussion

Autosomal dominant corneal dystrophies caused by mutation of the *TGFBI* (*BIGH3*) gene

In our study, seven different missense mutations were detected in the *TGFBI* gene in 154 patients from 118 families. No mutation was detected in 8 patients from four families with LCD or in the 50 normal volunteers. Table 2 shows the findings of our study including findings from Fujiki et al. (2000), and findings of studies at two widely separated institutions in Japan (Mashima et al. 2000). Codons R124 and R555 are hot spots in Japanese patients. The most frequent mutation in Japanese patients was R124H, which was found in 202 (70.6%) of the 286 families in the studies shown in

Table 2. Mutations of the *TGFBI* gene associated with autosomal dominant corneal dystrophies

Clinical type		Mutation	Present study[a]		Mashima et al. 2000	Total no. of families (%)
			No. of families	No. of patients	No. of families	
Lattice CD	Type I	R124C	13	25	23	36 (12.6)
	Atypical type I	L518P	2[b]	6	—	2 (0.7)
	Type IIIA	P501T	1[c]	4[c]	10	11 (3.8)
	Type IV (late onset)	L527R	9	9	1	10 (3.5)
	LCD (late onset)	N544S	—	—	1	1 (0.3)
	Undetermined		4	8		4 (1.4)
	Subtotal		29	52	35	63
Avellino CD		R124H	84	99	118	202 (70.6)
Granular CD		R555W	5	5	7	12 (4.2)
Reis-Bücklers' CD	Honeycomb-shaped	R555Q	4	6	2	6 (2.1)
	Geographic	R124L	—	—	2	2 (0.7)
	Subtotal		4	6	4	8
Total			122	162	164	286 (100)

[a] Including the findings from Fujiki et al. (2000)

[b] One family and three patients were reported by Hirano et al. (2000)

[c] This is a family with gelatinous drop-like CD. The four members are the proband with GDLD, his father, and the proband's two daughters. They are now aged 59, 85, 32, and 27 years, respectively. They have no symptoms of LCD IIIA; however, symptoms of LCD IIIA may appear in future because this disease has an onset age of 70–90 years (Yamamoto et al. 1998)
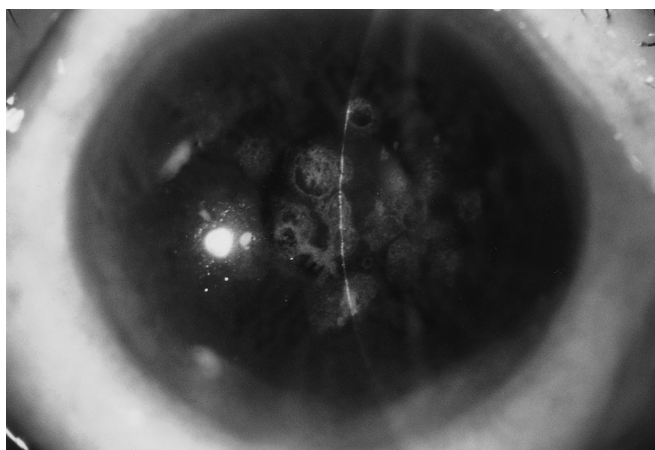

Fig. 1. Photograph of cornea of Avellino corneal dystrophy in patient with the R124H mutation in the *TGFBI* gene

Table 2. This disease is clinically classified as ACD, because it was identified in the Avellino district in Italy. GCD with the R555W mutation was detected in 12 (4.2%) of the 286 families. ACD is a variant of GCD in which there are lattice deposits, in addition to the characteristic granular lesions. The most common appearance of the cornea in patients with the R124H mutation shows evidence of well circumscribed central stromal opacities, as seen in Fig. 1. Interestingly, ACD with the R124H mutation is more common in Japanese patients than in Caucasians, and GCD with the R555W mutation, which is the classic form of GCD without lattice deposits, is rare in Japanese patients (Konishi et al. 1998; Fujiki et al. 2000). Homozygous R124H or R555W mutation of this gene has been reported (Mashima et al. 1997, 1998, and 2000; Fujiki et al. 1998a; Okada et al. 1998a and 1998c). The symptoms in all homozygous patients were more severe than those in heterozygous patients.

The R124C mutation was detected in 36 (12.6%) of the 286 families together with our study, and Mashima et al. 2000. This is clinically LCD type I (LCDI), and is the second most common of the *TGFBI* gene mutations. The L518P, L527R, and N544S mutations were new mutations found in Japanese patients. The L518P mutation belongs to the category of LCDI (Endo et al. 1999; Hirano et al. 2000), the L527R mutation is LCD with deep stromal opacities and of late onset (Fujiki et al. 1998b) and the N544S mutation is also LCD of late onset. LCD with the L527R mutation has now been named LCD type IV (LCDIV) (Klintworth 1999). The P501T mutation, which causes LCD type IIIA (LCDIIIA), was found in Japanese patients (Yamamoto et al. 1998). In our study, four members of a family with GDLD were recorded. However, there were no symptoms of LCDIIIA, even in the 85-year-old father (Ha et al. 2000). Proband with GDLD has two kinds of mutations, homozygous Q118X of the *M1S1* gene and heterozygous P501T of the *TGFBI* gene. The father and two daughters of the proband in our study have the heterozygous Q118X mutation of the *M1S1* gene that is the carrier of GDLD, and the P501T mutation of the *TGFBI* gene. They have no symptoms of LCDIIIA, as shown by careful clinical checking. LCDIIIA with the P501T mutation has an onset age of 70–90 years (Yamamoto et al. 1998). The proband, his father, and the proband's two daughters are now aged 50, 85, 32, and 27 years, respectively. Therefore, symptoms of LCDIIIA may appear in future. Interestingly, all four family members with the P501T mutation have the polymorphism (C → T) at nucleotide position 1411-3 of the *TGFBI* gene, as has been reported in 11 other families with the P501T mutation (Tsujikawa et al. 2000a). Therefore, this family may be related to the other 11 families. It is highly possible that P501T is the founder mutation in Japanese, but this has not yet been confirmed. Although we found

Table 3. Mutations of the *M1S1* gene associated with gelatinous drop-like corneal dystrophy

| Genotype | Tsujikawa et al. 2000 | Present study | |
	No. of families	No. of families	Total no. of families
Q118X/Q118X	31	7	38
Q118X/632delA	1		1
632delA/632delA	1		1
Q207X/Q207X	1		1
S170X/S170X	1		1
Undetermined		1	1
Total	35	8	43

only the R555Q mutation, which is characterized by honeycomb-shaped opacities, in 6 patients from 4 families with RBCD in our study, the R124L mutation has been reported in RBCD patients (Okada et al. 1998b; Mashima et al. 2000).

Autosomal recessive gelatinous drop-like corneal dystrophy caused by mutation of the *M1S1* gene

Tsujikawa et al. (1999) cloned the gene responsible for GDLD and detected four deleterious mutations (Q118X, 632delA, Q207X, and S170X) in the *M1S1* gene, encoding a gastrointestinal tumor-associated antigen. The Q118X mutation was the most common in the GDLD patients, occurring in 77 (91.7%) of the 84 mutated alleles (Table 3). Haplotype analyses using nearby polymorphic markers of the *M1S1* gene in the patients indicated that the Q118X mutation is a Japanese founder mutation and reflects linkage disequilibrium alleles (Tsujikawa et al. 1999 and 2000b). Thus, most patients are Japanese, with few reported cases in other countries. In our study, the homozygous Q118X mutation of the *M1S1* gene was detected in nine patients from seven of eight families with GDLD, and the parents of the probands in four families were consanguineous. Parents and unaffected relatives were found to be heterozygous for this mutation. Our results also supported the findings that the Q118X mutation was a founder mutation. No mutation in the coding region of the *M1S1* gene was detected in one family with GDLD. However, the patient in this family was diagnosed clinically as having GDLD, and histopathological findings showed amyloid deposits in Bowman's membrane and the anterior stromal layer. We examined the promoter region in the *M1S1* gene in this family and found no changes. Although anomalies of the 3′ untranslated region should be considered (Conne et al. 2000), there may be anomalies in other genes that are causative for GDLD.

Conclusion

The two CDs (i.e., autosomal dominant and autosomal recessive CDs) with different modes of inheritance, with different causative genes, *TGFBI* and *M1S1*, show deposits in the stroma. Although the type of mutation is manifested by different histopathological findings, most patients with LCD, ACD, and GDLD showed amyloid deposits in several parts of the subepithelial layer and/or stromal layer. However, amyloid deposits were not observed in GCDGI, which in the classic form of GCD, or in RBCD, in which there are honeycomb-shaped opacities, despite GCDGI and RBCD being caused by a mutation of the same gene, *TGFBI*.

Immunolocalization of βig-h3 protein was strongest in Bowman's layer, then along the stromal interlamellar area and at the sites of attachment of collagen to Descemet's membrane (Streeten et al. 1999). The mechanisms responsible for the occurrence of the diseases and for the appearance of the differing deposits are still not known; however, the variability of form may be related to different amino-acid substitutions at different nucleotide positions, and regional interactions of the protein.

Our studies have shown that codons R124 and R555 of the *TGFBI* gene in autosomal dominant CDs are hotspots in Japanese patients, as they are in other ethnic groups, as reported previously (Korvatska et al. 1998). The most common alteration of the *TGFBI* gene in Japanese patients is ACD, with the R124H mutation, while the second most common is LCDI, with the R124C mutation.

For autosomal recessive GDLD caused by mutation of the *M1S1* gene, 38 families were homozygous for the Q118X mutation. This suggests a specific founder mutation arising from a common ancestor, as already reported (Tsujikawa et al. 2000b).

Histopathological findings were consistent with differences in the positions and/or kinds of deposits, depending on the type of the mutation. Although ACD, LCD, and GDLD show amyloid deposits in specific parts of the stroma, GCD with the R555W mutation, and honeycomb-shaped RBCD with the R555Q mutation, showed absence of these amyloid deposits. These results show a clear genotype/phenotype correlation in genetic corneal dystrophies caused by the *TGFBI* gene.

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