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THE MOLECULAR GENETICS OF THE CORNEAL DYSTROPHIES – CURRENT STATUS

Gordon K. Klintworth

Departments of Pathology and Ophthalmology, Duke University Medical Center, Durham, North Carolina

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1. ABSTRACT

The pertinent literature on inherited corneal diseases is reviewed in terms of the chromosomal localization and identification of the responsible genes. Disorders affecting the cornea have been mapped to human chromosome 1 (central crystalline corneal dystrophy, familial subepithelial corneal amyloidosis, early onset Fuchs dystrophy, posterior polymorphous corneal dystrophy), chromosome 4 (Bietti marginal crystalline dystrophy), chromosome 5 (lattice dystrophy types 1 and IIIA, granular corneal dystrophy types 1, 2 and 3, Thiel-Behnke corneal dystrophy), chromosome 9 (lattice dystrophy type II), chromosome 10 (Thiel-Behnke corneal dystrophy), chromosome 12 (Meesmann dystrophy), chromosome 16 (macular corneal dystrophy, fish eye disease, LCAT disease, tyrosinemia type II), chromosome 17 (Meesmann dystrophy, Stocker-Holt dystrophy), chromosome 20 (congenital hereditary endothelial corneal dystrophy types I and II, posterior polymorphous corneal dystrophy), chromosome 21 (autosomal dominant keratoconus) and the X chromosome (cornea verticillata, cornea farinata, deep filiform corneal dystrophy, keratosis follicularis spinulosa decalvans, Lisch corneal dystrophy). Mutations in nine genes (*ARSC1, CHST6, COL8A2, GLA, GSN, KRT3, KRT12, M1S1* and *TGFBI* [*BIGH3*]) account for some of the corneal diseases and three of them are associated with amyloid deposition in the cornea (*GSN, M1S1, TGFBI*) including most of the lattice corneal dystrophies (LCDs) [LCD types I, IA, II, IIIA, IIIB, IV, V, VI and VII] recognized by their lattice pattern of linear opacities. Genetic studies on inherited diseases affecting the cornea have provided insight into some of these disorders at a basic molecular level and it has become recognized that distinct clinicopathologic phenotypes can result from specific mutations in a particular gene, as well as some different mutations in the same gene. A molecular genetic understanding of inherited corneal diseases is leading to a better appreciation of the pathogenesis of these conditions and this knowledge has made it imperative to revise the classification of inherited corneal diseases.

2. INTRODUCTION

Before the end of the nineteenth century Groenouw described a corneal disorder which he designated “noduli corneae” (1,2). As Bücklers (3) pointed out in 1938 Groenouw’s cases were of two types: a nodular one with an autosomal dominant inheritance (Groenouw dystrophy type I, later designated granular corneal dystrophy [GCD]). The other had a recessive inheritance and has come to be known as Groenouw dystrophy type II or macular corneal dystrophy [MCD]. Since Groenouw’s classic paper numerous corneal diseases have attracted attention under the rubric of corneal dystrophies. Particularly during the past decade knowledge about these disorders has increased considerably and much of this information has accumulated since the last review that I wrote on the subject in 1999(4).

The primary defect in all inherited corneal diseases residues in DNA and abnormalities in a gene or in the expression of a gene leads to a disordered chain of biochemical reactions. The timing and sequence of events that follow the specific genetic mutations vary considerably and some of them become manifest during early corneal development.

During the past decade almost thirty corneal diseases have been mapped to specific chromosomal loci and numerous mutations in these genes have been identified (Table 1). These advances in the molecular knowledge of the inherited corneal disorders have enhanced our understanding of them and this may ultimately lead to novel innovative methods for their treatment. Discoveries related to our understanding of the corneal dystrophies at a molecular level by numerous investigators in recent years has made it necessary to revise their classification from the arbitrary ways of the past based on involved structures or the nature of the pathologic process. In this review I have attempted to classify the corneal dystrophies on the basis of a combination of clinical, histopathologic and molecular genetic characteristics. When possible the OMIM* numbers and symbols approved by the human gene nomenclature database committee are given, but many of the conditions covered in the review have not yet received such designations.

Keratoconus, inherited diseases with systemic manifestations that affect the cornea and genetically determined developmental anomalies involving the cornea are not considered in detail in this review, because they have not been traditionally classified as “corneal dystrophies”. Several disorders of the cornea, including recurrent corneal erosions, map-dot-fingerprint and epithelial basement membrane corneal dystrophy, which some authors consider to be corneal dystrophies, are not discussed because they represent non-specific reactions and are not explicit nosological entities.

Eosinophilic material with an affinity for Congo red and other dyes for amyloid accumulates in the cornea under a wide variety of circumstances and is a characteristic of several distinct genetically determined corneal diseases. In all of these conditions the protein deposits possess characteristic randomly dispersed electron-dense fibrils (80 to 100 Å in diameter). Mutations in three genes (*TGFBI GSN, M1S1*) are now known to be associated with some of these inherited corneal amyloidoses. *TGFBI* and *GSN* are responsible for the majority of the lattice corneal dystrophies (LCD types I, IA, II, IIIA, IV and V), while defects in *M1S1* account for most cases of familial subepithelial corneal amyloidosis (gelatinous drop-like corneal dystrophy. Mutations in *TGFBI* also explain the amyloid deposition in corneas with GCD type II. Despite the deposition of amyloid within the cornea in numerous inherited diseases it is noteworthy that this tissue is not affected in many genetically determined forms of amyloidosis that affect other tissues.

The lattice corneal dystrophies are a group of inherited diseases characterized by the presence of a lattice pattern of radially orientated interdigitating branching

Table 1. Inherited Diseases Involving the Cornea

Disease	Inheritance	Gene locus	Gene	Mutations	References
Predominantly Anterior Corneal Dystrophies					
Fabry disease angiokeratoma corporis diffusum	XR	Xq22-24	GLA	56 Mutations	OMIM #301500
Familial subepithelial amyloidosis	AR	1p32	M1S1		5,6
				Base insertions	
				1 base insertion at nt 520	7
				8 base insertion at nt 799	8
				Single base deletions	
				632delA	6
				870delC	8
				1117delA	8
				Single base substitutions	
				M1R	8
				Q118X	6,9-11
				Q118E	8
				C119S	8
				S170X	6
				Q207X	6
				L308R	8
				V194E	8
Keratosis follicularis spinulosa decalvans	XR	Xp22.2-p22.13			12
Meesmann dystrophy	AD	12q13			13
			KRT3		13
				E509K	13
	AD	17q12	KRT12		
				M129T	14
				Q130P	15
				N133K	16
				R135G	17
				R135I	17
				R135T	13,14
				R135L	13
				L140R	17
				V143L	13
				Y429D	17
				1426V	18
Stocker-Holt dystrophy	AD	17q12	KRT12	R19I	19
Subepithelial mucinous dystrophy	AD	Unknown			20
Thiel-Behnke dystrophy	AD	5q22-q32	TGFB1	R555Q	21-25
Predominantly Stromal Dystrophies					
Bietti marginal crystalline dystrophy	AR	4q35	Unknown		26
Congenital hereditary stromal dystrophy	AD	Unknown	Unknown		
Central cloudy dystrophy	AD	Unknown	Unknown		
Central crystalline dystrophy Schnyder dystrophy	AD	1p34.1-p36	Unknown		27
Fleck dystrophy	AD	2q35	Unknown		28
Granular dystrophy					
type I	AD	5q22-q32	TGFB1		29,30
				R555W	23-25,31-38
				R124S	39
type II	AD	5q22-q32	TGFB1	R124H	23-25,33,34, 36,39-50
type III	AD	5q22-q32	TGFB1		31
				R124L	21,23-25, 34,47,51
				R555Q	31,32,34,52 $
				G623N	36 $
				Exon12 ΔF540	53
type IV	AD	5q22-q32		R124L plus ΔT125 and ΔE126	23,25,54 #
Lattice dystrophy					
type I	AD	5q22-q32			30
			TGFB1		31
				R124C	23-25,31,32,34, 36,41, 43,44, 47, 49,55-61
				A546D and P551Q	62
				L518P	32,58,63
type IA	?			R124C	64
type II	AD	9q34			
			GSN		65,66
				D187N	36,66-69
				D187Y	65,70
type III	?AR	unknown			
type IIIA	AD	5q31	TGFB1		37
				Exon11 P501T	34,37,41,71
type IIIB	AD			A622H	72
				H626R	25,72
type IV	AD	5q31	TGFB1		

				L527R	32,34,73-75
type V				A546T	23,25,73
type VI				9bp insertion at nt 1885-1886 and missense at nt 1887	76
type VII				H620R	23
Macular dystrophy					
type I	AR	16q21			77
			CHST6		78
				10 base insertion at nt 707	79
				P31S	80,81
				E71D	80,81
				P72S	80,81
				F107S	80,81
				A128V	79
				R166P	79
				L200R	80,81
				A206V	80,81
type IA	AR	16q21			
			CHST6		
type II	AR	16q21			77
			CHST6		78
				A128V	Φ
unknown types					
				L15P	82
				Q58X	82
				N61T	82
				V66D	83
				F67V	83
				Y68C	82
				M70L	82
				Q82X	82
				C102G	82
				R114C	Φ
				R127C	83
				S131P	82
				C149X	Φ
				L152P	82
				R162G	Φ
				C165S	83
				R166P	82Φ
				L174R	Φ
				L200R	82
				D203E	Φ
				P204G	82
				R211W	Φ
				E274K	Φ
				Q331H	Φ
				deletions	
				deletion of ORF, del of 5' region	83
				deletion GCT>insA	82
				insertions	
				1055-1056 insC	82
Posterior amorphous stromal dystrophy	AD	Unknown	Unknown		
Posterior Corneal Dystrophies					
Congenital hereditary endothelial dystrophy					
CHED type I	AD	20p11.2-q11.2	Unknown		84,85
CHED type II	AR	20p13	Unknown		86
infantile hereditary endothelial dystrophy					
Cornea farinata and deep filiform dystrophy	XR	Xp22.32	STS		
				W372R	87
				W372P	88
				C446Y	87
				S341L	87
				C341L	88
				H444R	88
				IVS8Ds,GT, +1	88
Fuchs dystrophy	AD	1p34.3-p32.3	COL8A2		31
Familial cornea guttae	AD	Unknown	Unknown		
Posterior polymorphous dystrophy					
autosomal dominant type	AD	20q11			89
		1p34.3-p32.3	COL8A2		31
autosomal recessive type	AR	Unknown	Unknown		

X = stop codon, Δ = deletion, Φ Unpublished observation, $ Diagnosis uncertain as characteristic abnormalities not documented by light and electron microscopy. Probably Thiel Behnke dystrophy. # Diagnosis uncertain as characteristic abnormalities not documented by light and electron microscopy. Probably GCD type III. Abbreviations for nucleotides are: Adenine a, Cytosine c, Thymine T and Guanine G. nt = nucleotide

linear filamentous opacities within the corneal stroma. The lattice lines do not coincide with corneal nerves, but relate to linear deposits of amyloid. In cases that have been studied by light microscopy the lattice opacities have been found to correspond with accumulations of amyloid. Since the first description of a lattice corneal dystrophy (LCD) by Biber (90) several different variants of LCD have become recognized. At least two genes (*TGFBI* and *GSN*) account for these disorders and with the exception of mutations in *GSN* (LCD type II), amyloid has not been detected in non-corneal tissues in any of the inherited corneal amyloidoses.

3. CORNEAL DISORDERS DUE TO MUTATIONS IN SPECIFIC GENES

3.1. Corneal dystrophies due to mutations in the TGFB1 (BIGH3) gene

In 1992 Skonier *et al.* discovered a novel gene that was induced in cultured human adenocarcinoma cells by beta transforming growth factor (91). Because the gene was detected in human clone 3 they named the gene *BIGH3, from*(**B**eta transforming growth factor **I**nduced **G**ene in **H**uman clone **3**. Because it is expressed in several species, the label *BIGH3* has become inappropriate and other terms have been proposed, such as *BIG*, but have met with objections. The alternative designation of *TGFB1* used by the human gene nomenclature database committee is a preferable term for this gene because it is applicable to all species. The best designation for the protein product is transforming growth factor beta induced protein. The misnomer kerato-epithelin, coined by Munier *et al.* (92) because of its association with the corneal epithelium is not appealing. The protein is not only present in serum (93), but it is not specific for corneal epithelium.

Following its discovery the *TGFBI* gene was mapped to the long arm of human chromosome 5 (5q31) (94) and three independent laboratories found the protein product or the gene to be expressed in the cornea (95-97). Because three autosomal dominant corneal dystrophies had been mapped to this same locus (30), *TGFBI* became a strong candidate as the gene responsible for these dystrophies and Munier *et al.* (92) identified four specific mutations in *TGFBI* that corresponded with specific phenotypes. Since then numerous investigators have confirmed this observation (21,37,42,44,45,51,59,62,71, 74,98-104) and at least 20 mutations in TGFB1 have been found in 13 clinically and histopathologically distinct phenotypes (GCD types I, II, III and IV, LCD types I, IA,IIIA, IIIB, IV, V, VI and VII, and Thiel-Behnke corneal dystrophy). Several single nucleotide polmorphisms (SNPs) that either do not alter an encoded amino acid or that do not co-segregate with a disease phenotype have also been identified (43,72,103,105).

Evidence from several laboratories indicates that the phenotypes depend upon specific mutations in *TGFBI*. The entire mutated protein, or fragments of it, deposit in the cornea in these different entities (47,71,71,93,106-109). Depending on the mutation the accumulations form rod-shaped crystalloid structures (GCD type I, GCD type III), amyloid (LCD type I, LCD type IIIA, LCD type IV, LCD type V), a combination of rod-shaped bodies with amyloid (GCD type II), or "curly fibers" (Thiel-Behnke dystrophy). The variable appearance of the opacities depends on the location and nature of the corneal deposits and this is presumably influenced by the three dimensional structure of the mutant protein. Patients with homozygous TGFBI mutations develop a more severe corneal dystrophy with larger corneal opacities than those found in heterozygous cases.

3.1.1. Lattice corneal dystrophies

3.1.1.1. Lattice corneal dystrophy type I

LCD type I (CDL1, OMIM #122200) [http://www3.ncbi.nlm.nih.gov/htbin-post/Omin/dispmim?122200] was first described by Biber (90) and its autosomal dominant mode of inheritance was later established by Haab (110) and Dimmer (111). In this disorder foci of amyloid are scattered throughout the corneal stroma and sometimes immediately beneath the epithelium. The corneal endothelium and Descemet's membrane are not involved.

LCD type I usually starts in both eyes towards the end of the first decade of life, but occasionally it begins in middle life and rarely by 2 years of age (112). Delicate interdigitating branching filamentous opacities form a network with the cornea (113,114). These and other shaped opaque areas accumulate particularly within the central corneal stroma producing a superficial haze, while the peripheral cornea remains relatively transparent. The linear opacities may be difficult to identify clinically (115) and are not manifest in all affected members of families with LCD type I (113,116). The opaque interwoven filaments resemble nerves on casual scrutiny and corneal sensation is frequently diminished. Some affected family members may develop a clinical phenotype that resembles GCD type III (discussed later in this review)(117). Recurrent epithelial erosions are common and usually begin during the first decade of life. They may antecede the corneal opacities and in some families recurrent epithelial erosions appear in individuals who lack recognizable stromal disease (118-120). The corneas may be asymmetrically involved, and sometimes one cornea is clear or has discrete rather than linear opacities (121,122). The clinical course varies in different individuals and even within the same family, but the condition is slowly progressive and usually leads to substantial discomfort and visual impairment before the sixth decade. A corneal graft is usually not indicated until after the fourth decade, but may be necessary by 20 years of age (121). The outcome of penetrating keratoplasty is excellent, but amyloid may deposit in the grafted donor tissue some 2-14 years later (121,123-125).

Like nerves the linear deposits are argyrophilic in silver impregnated preparations and can be mistaken for nerves (126), but nerves have not been identified in relation to the deposits. Deposits throughout the corneal stroma that coincide with the lattice pattern of lines and other opacities manifest the light and electron microscopic attributes of amyloid and possess the characteristic tinctorial features.

The majority of cases of LCD type I throughout the world have been associated with a C→ T transition at

nucleotide 417 (417 C→ T) in exon 4 of the *TGFBI* (*BIGH3*) gene. This causes a R124C[#] mutation in the affected codon. In LCD type I the amyloid seems to react mainly with antibodies to the N-terminal sequence of transforming growth factor beta induced protein (47) and not with antibodies to the C-terminal (47). Korvatska *et al.* (127) and Takacs *et al.* (108) have provided evidence that the amyloid in LCD type I results from an accumulation of a 44 kDa N-terminal portion of the mutated transforming growth factor beta induced protein.

3.1.1 2. Lattice corneal dystrophy type IA

Nakamura *et al.* (64) reported five unrelated Japanese individuals with an unusual phenotype, which they called "gelatino-lattice corneal dystrophy". Clinically the disorder resembled a combination of LCD type I and familial subepithelial corneal amyloidosis. The corneas of affected individuals contained fine lattice lines with similarities to those in LCD type I, but in addition the affected corneas had gelatinous mulberry shaped deposits. Painful recurrent corneal erosions occurred during adolescence. The authors claimed that the subepithelial deposits were amyloid, but histopathologic studies were not documented. The only exon of *TGFBI* (exon 4) to be sequenced contained an A124 C mutation. In contrast to Japanese patients with subepithelial corneal amyloidosis no mutation was detected in the entire coding region of *MISI*.

3.1.1.3. Lattice corneal dystrophy type III

When Tetsuo Hida came to Duke University Eye Center for a vitreoretinal fellowship (1984-1986) he brought with him clinical photographs and tissue sections from corneas with an unusual form of lattice corneal dystrophy. The clinical manifestations differed from those of patients with LCD types I and II. Late in life radially orientated lattice lines become apparent in the anterior and mid-stroma. They are much thicker than those in LCD types I and II. We named this disorder, which was not found in more than one generation LCD type III and suggested that it might have an autosomal recessive mode of inheritance (128,129). Usually both eyes are affected, but sporadic unilateral examples have been documented (130). Recurrent epithelial erosions were absent in the first reports (128,129), but present in two sporadic cases (130). The nature of the amyloid is unknown in this type of LCD and the gene has not been mapped.

3.1.1.4. Lattice corneal dystrophy type IIIA

A few years after the documentation of LCD type III cases were reported with a similar phenotype, but with corneal erosions and an autosomal dominant mode of inheritance and named LCD type IIIA (131). Japanese patients with LCD type IIIA are associated with a P501T mutation in *TGFBI (BIGH3*) and the mutated transforming growth factor beta induced protein accumulates and co-localizes with the amyloid (71). The P501T mutation, however, does not cause LCD type IIIA alone as persons with this mutation may be unaffected even by 85 years of age (9). Factors that influence the penetrance of the P501T mutation remain unknown.

3.1.1.5. Lattice corneal dystrophy type IIIB

Stewart *et al.* (72) drew attention to three families with a form of LCD that resembled LCD type IIIA, but which was associated with mutations in codon 622 or 626 of exon 14 in *TGFBI*. This disorder had an onset in middle age (fourth to fifth decade) and hence began later than in LCD type I, but earlier than in LCD types III and IIIA. The majority of corneas were asymmetrically affected and with the exception of one case they were bilateral. In one noteworthy patient the dystrophy first became manifest in the inferior portion of one cornea with an ulcer that was accompanied by a hypopyon. Two years later the other eye became involved following minor corneal trauma suggesting that trauma may be an environmental factor contributing to the expression of the dystrophy.

3.1.1.6. Lattice corneal dystrophy type IV

An atypical form of LCD with deep stromal opacities in the pupillary zone and a late onset has been found in seven unrelated Japanese patients without a positive family history. The deposits are large, nodular and lattice shaped (74). The phenotypic variation in the size and shape of the deposits among affected persons is substantial (74). The disorder is associated with a heterozygous L527R mutation in the TGFBI (34,74,74,75).

3.1.1.7. Lattice corneal dystrophy type V

This type of LCD, which is associated with an A546T mutation in *TGFBI* has also been designated LCD type III-like and the French LCD type IIIA (23).

3.1.1. 8. Lattice corneal dystrophy type VI

Schmitt-Bernard *et al.* documented two families with a type of lattice corneal dystrophy that was intermediate between LCD types I and IIIA (76). This variant was associated with two mutations in exon 14 of *TGFBI* (a 9 base pair insertion in position 1885-1886 or a missense mutation at position 1887).

3.1.1. 9. Lattice corneal dystrophy type VII

Dighiero *et al.* (23) found a H626R mutation in an asymmetric variant of LCD in three individuals from two apparently unrelated families.

3.1.2. Granular corneal dystrophies

In GCD (CDGG1, OMIM #121900) [http://www3.ncbi.nlm.nih.gov/htbin-post/Omin/dispmim?121900] small white sharply demarcated ground glass spots that resemble bread crumbs or snowflakes often become apparent in the central cornea beneath Bowman's zone within the first decade of life and may be identified by 3 years of age (132). By puberty the lesions are obvious, and at the end of a second decade many corneal opacities are perceptible, particularly in the central and superficial cornea (133) but rarely in the deep stroma (134,135). Intervening tissue between the opacities and in the peripheral cornea usually remains clear. The opacities sometimes coalesce and accumulate beneath, or within, the corneal epithelium (136-138). Later the opaque spots extend throughout almost two-thirds of the corneal diameter, while the peripheral 2-3 mm remains clear.

The corneal opacities in GCD result from eosinophilic irregularly lobulated granules with distinct morphologic and staining attributes (136,139). Descemet's

membrane and the corneal endothelium are unremarkable, and so is the cornea between the deposits and in the deeper and peripheral stroma. The deposits are red with the Masson trichrome stain (139) and react with histochemical methods for protein (136,138,140,141) as well as with antibodies to transforming growth factor beta induced protein (93,106). By transmission electron microscopy, discrete, rod-shaped or trapezoid bodies with discrete borders are evident (70,133,142-152). Additional deposits appear moth-eaten with variable-shaped cavities containing fine filaments (148). The accumulations in GCD consist predominantly of an extracellular deposition of mutant transforming growth factor induced protein, but the reason why the protein accumulates remains unknown.

Most patients with GCD do not need a corneal graft or another therapeutic procedure, but in some cases visual impairment may be marked and multiple procedures may be necessary over a lifetime due to recurrent disease. Individuals homozygous for mutations in *TGFBI* may develop an unusually severe form of GCD with an earlier onset (35,153,154).

The accumulations may recur within a year after keratoplasty, but this is sometimes delayed for 10-15 years (133,135,141,148,150,155-159).

Over time it has gradually become apparent that at least four variants of GCD exist.

3.1.2.1. Granular corneal dystrophy type I

GCD type I (classic GCD, R555W mutant TGFBI, OMIM #121900) is characterized by multiple discrete crumb-like corneal opacities and is the most common type of GCD. The condition usually becomes apparent during the first decade of life and is slowly progressive. Visual acuity gradually decreases and painful epithelial erosions are common. This variant of GCD, which almost always has the R555W mutation in exon 12 of *TGFBI* (92,103), is rare in Japan (33). Another mutation in a separate part of TGFBI has been found in a single Asian patient with GCD, who underwent a penetrating keratoplasty at 61years of age. This particular patient, who was diagnosed at 49 years of age as a result of deteriorating vision and who developed recurrent disease in the graft, has been found to have a R124S mutation in TGFBI, but no mutation in exon 12 of this gene (39). Numerous small white granules were present in the cornea and because the phenotype was not significantly different from the usual GCD type I a separate sub-type is not currently warranted. A noteworthy aspect of this case was the lack of amyloid in the corneal stroma, particularly since R124C and R124H mutations in TGFBI are accompanied by amyloid deposition.

3.1.2.2. Granular corneal dystrophy type II

Another variant of GCD that is less common than GCD type I was called GCD type II by Weidel (160) and is also known under other connotations (Avellino corneal dystrophy, GCD with amyloid, combined lattice-granular corneal dystrophy, R124H mutant TGFBI). It is characterized clinically by corneal opacities that are shaped like rings, disks, stars and snowflakes. The condition shares some features of LCD type I. Linear opacities may be present, but the typical lines of LCD are usually absent. Onset is during the second decade. In the absence of a histopathologic evaluation of the cornea or a determination of the molecular genetic defect this variant of GCD can be difficult, if not impossible, to distinguish from GCD type I. Compared to GCD type I progression is delayed and slower and visual acuity is less impaired and often only mildly affected. Painful epithelial erosions occur especially in females and take place less often than in GCD type I (14% of cases compared to 61%). The ancestry of some affected families has been traced to the Avellino region of Italy (hence an earlier, but no longer justifiable, term Avellino dystrophy)(161), but other families have been traced to Germany, Holland, Eastern Europe and other countries. Moreover, most families have been identified in Japan (33,41,45,46,48) and this variant of GCD is the most common type of GCD in Japan (33,41) and Korea (43).

In tissue sections rod shaped crystalloid bodies accumulate in the corneal stroma and deposits of amyloid are also found, but are often small, insignificant and difficult to find (136,143,144,148-151,162). In this disorder most deposits of amyloid probably do not cause lattice lines. To date almost all cases studied with molecular genetic techniques have had the R124H mutation in TGFBI and the phenotype of affected individuals varies markedly in severity from family to family. Most young individuals with the heterozygous R124H mutation do not need treatment (48,163), but visual acuity often becomes severely impaired during childhood in persons when this mutation is homozygous, and a corneal graft is often needed before 25 years of age (40,42,44,45,45,46,102,164,165). Individuals with the homozygous R124H mutation are particularly prone to recurrences which limits the recovery of visual acuity (40,46). Two different clinical phenotypes have been observed in Japanese patients homozygous for the R124H mutation with the phenotype relating to the part of Japan to which the families trace their ancestry, suggesting that it is influenced by other modifier genes (164). In one variant a discrete grayish white opacity covers the anterior stroma and it is confluent in the central and paracentral cornea; in the other type reticular grayish white diffuse opacity in the anterior stroma of the cornea

In corneal tissue from patients with the R124H mutation Korvatska *et al.* (127) found the non-amyloid accumulations to consist of a combination of the 66 kDa and 68 kDa forms of transforming growth factor beta induced protein.

3.1.2.3. Granular corneal dystrophy type III

Deposits morphologically and histochemically indistinguishable from those of typical GCD may be limited to the subepithelial region (137,140,141,143, 166,167) or the epithelium (136) in a disorder that has been termed GCD type III (4). This variant has also been designated superficial GCD, 'true" Reis-Bücklers corneal dystrophy, corneal dystrophy of Bowman's layer type I, geographic corneal dystrophy and R124L mutant of *TGFBI*, OMIM #121900).

It is the bilateral symmetrical dystrophy of the superficial cornea that was reported in 1917 by Reis (168) and demonstrated three decades later by Bücklers (169) to

have an autosomal dominant mode of inheritance. Material that shares the same light and electron microscopic characteristics as in other variants of GCD accumulates mainly in Bowman's layer and immediately beneath the corneal epithelium of affected individuals in the original pedigrees studied by Reis and Bücklers (143,166,167). The literature on GCD type III is extremely confusing mainly because the designation of Reis-Bücklers dystrophy has been used for at least two distinct autosomal dominant entities, which cannot always be differentiated from each other clinically. Some reports on Reis-Bücklers dystrophy have not had this disorder, but a condition that is now called Thiel-Behnke corneal dystrophy and which is characterized by the presence of "curly fibers" that can only be identified by transmission electron microscopy (170-172). To confuse the subject further, individuals in families with LCD may manifest corneal opacities that are similar to those of "Reis-Bücklers" dystrophy (117).

During the first or second decades of life GCD type III usually becomes symptomatic with bilateral recurrent epithelial erosions associated with pain and photophobia. The anterior cornea becomes scarred and acquires an uneven, irregular, and roughened surface. Corneal sensitivity is nearly always diminished, sometimes absent, and, rarely normal (173). The deep corneal stroma and endothelium as well as Descemet's membrane are not affected. Visual acuity gradually deteriorates due to diffuse, asymmetric corneal opacification and an irregular astigmatism. Rings and disc shaped opacities form within the superficial cornea and stellate figures spread into the deeper stroma. Onset is usually at about 4-5 years of age when an opacity consisting of innumerable delicate, cotton-like strands appears in the axial cornea and progressively evolves into a central reticulated ring or geographic shaped pattern (168,169). The opacification eventually extends into the mid-periphery of the cornea with a thinly distributed external stromal haze. In some cases the clinical appearance lacks these characteristics. The condition becomes symptomatic earlier and with a higher frequency of recurrent erosions than most cases of GCD.

The R124L mutation in *TGFBI* identified in most patients with GCD type III, who have undergone a genetic analysis (21,23,34,47,51), differs from those producing other variants of GCD. Haplotype analyses of Japanese families have provided evidence of multiple origins of this mutation (174). A similar clinical phenotype has been detected in Sardinia with a ΔF540 mutation in *TGFBI* (53), but histopathologic studies have not been documented in the affected Sardinians. Reports of a R555Q mutation in *TGFBI* in patients alleged to have Reis-Bücklers dystrophy (32,34,52,92,103) are unacceptable, because they were not accompanied by appropriate documentation of the typical light and electron microscopic findings that characterize this inherited corneal entity. Without an appropriate tissue examination Theil-Behnke dystrophy is commonly misdiagnosed as Reis-Bücklers dystrophy, as pointed out elsewhere in this review. Moreover, the R555Q mutation in *TGFBI* may be specific for Theil-Behnke dystrophy (21-23).

Korvatska *et al.* found that the R124L non-amyloid deposits were all of the 68 kDa form of transforming growth factor beta induced protein. (127).

3.1.2.4. Granular corneal dystrophy type IV

Dighiero *et al.* (23,54) documented a French family with a novel variant of GCD (French variant of GCD) with similarities to GCD type III. Affected members of the family had round snow-flake shaped opacities in the subepithelial and most anterior corneal stroma. Recurrent painful corneal erosions began early in childhood and the phenotype appears to be intermediate between GCD type I and GCD type III. Molecular genetic studies disclosed that the affected persons were heterozygous for the R124L mutation in *TGFBI*, but they were also heterozygous for another mutation in the same gene that predicted the deletion of 2 amino acid residues at codons 125 and 126 (Δ125-ΔE126)(73).

3.1.3. Thiel-Behnke corneal dystrophy

In 1967 Thiel and Behnke (175) drew attention to honeycomb-like opacities at the level of Bowman's layer in association with recurrent erosions and a moderately decreased visual acuity in a large eleven generation pedigree containing 234 members with 26 affected persons. This report did not document light or electron microscopic observations. The disorder, which has become known as Thiel-Behnke dystrophy ("curly" fiber corneal dystrophy, corneal dystrophy of Bowman's layer type II, honeycomb corneal dystrophy, CDB2, OMIM #602082) [http://www3.ncbi.nlm.nih.gov/htbin-post/Omin/dispmim?602082] is a slowly progressive autosomal dominant disorder characterized clinically by the onset of painful corneal erosions during childhood (176). Sub-epithelial corneal opacities with a clear zone at the corneoscleral limbus form a honeycomb-shaped pattern. Like other corneal dystrophies the condition may recur in the graft following penetrating keratoplasty (176,177).

Histopathologically subepithelial fibrous tissue accumulates in a wave-like configuration. Transmission electron microscopy of this tissue discloses the pathognomonic curly filaments. Authors of the early transmission electron microscopic studies of what was probably the same condition (170,178) did not recognize the diagnostic ultrastructural hallmark of Thiel-Behnke dystrophy, which is the presence of curled filaments in a superficial cornea interspersed among normal collagen fibrils in Bowman's zone and the contiguous superficial corneal stroma. These pathognomonic subepithelial "curly" fibers, which can only be identified by transmission electron microscopy, were illustrated in a most elegant study in 1979 by Perry *et al.* (179). Unfortunately the authors did not use the contemporary term that is in vogue, but used the designation Reis-Bücklers dystrophy. However, a detailed study of the original pedigree described by Reis and Bücklers had rod shaped bodies identical to those in GCD (166,167), whereas electron microscopic evaluations of the family originally reported by Thiel and Behnke indicated that these "curly" fibers were a feature of that dystrophy (180). In addition to the "curly" fibers laminin and bullous pemphigoid antigen have been localized in a piebald mosaic distribution through the aberrant subepithelial fibrous tissue suggesting a primarily epithelial disease with the peculiar curly material paralleling the distribution of attachment proteins (181).

Thiel-Behnke dystrophy, which is often confused with GCD type III and inappropriately designated Reis-Bücklers dystrophy, has been mapped to chromosome 5 (5q31)(20) and found to be associated with a R555Q mutation in *TGFBI* (21-23). However, many reports documenting this mutation have based the diagnosis solely on the clinical phenotype and have not taken into account the necessary requirement of a tissue diagnosis (21,32,34). Genetic heterogeneity seems to exist and another locus for Thiel-Behnke dystrophy has also been identified on chromosome 10 (10q23-q24) (182).

The literature related to this dystrophy is chaotic mainly because the disorder has often been called Reis-Bücklers dystrophy, especially in the American literature (176,179,181,183). The confusion stems from several sources: (i) the original description was published in German and illustrated with black and white clinical photographs and not accompanied by light or electron microscopic observations on corneal tissue (ii) the clinical features of Thiel-Behnke corneal dystrophy overlap with Reis-Bücklers corneal dystrophy, (iii) families with the ultrastructural hallmarks of Thiel-Behnke dystrophy have been reported in the literature as Reis-Bücklers dystrophy (20,179), (iv) many reported cases of Reis-Bücklers dystrophy and Thiel-Behnke corneal dystrophy have either not been evaluated by transmission electron microscopy or have not been accompanied by acceptable documentation of the diagnostic ultrastructural characteristics. Because of the confusing nomenclature, the term “corneal dystrophy of Bowman’s layer and superficial stroma” (CDB) has been proposed for both these dystrophies: CDB type 1 for GCD type III and CDB type 2 for Thiel-Behnke dystrophy (183).

A diagnosis of Thiel-Behnke dystrophy can sometimes be suspected by the clinical phenotype, but the identification of the pathognomonic curly fibers within the cornea by transmission electron microscopy in at least some affected family members is essential to establish a precise diagnosis. The molecular composition of the curly filaments remains to be determined. The finding of a R555Q mutation may be diagnostic (22,23), but more families with the characteristic ultrastructural abnormalities need to be documented.

3.2. Corneal dystrophies due to mutations in the GSN gene

3.2.1. Lattice corneal dystrophy type II

Following the recognition that the characteristic lesions of LCD are amyloid (184), a second type of LCD with systemic amyloidosis was discovered in Finland](185-188) [familial amyloid polyneuropathy type IV (Finnish or Meretoja type)(FAP type IV), Meretoja's syndrome, OMIM #105120] [http://www3.ncbi.nlm.nih.gov/htbin-post/Omin/dispmim?105120]. After visiting Meretoja in Finland and seeing affected individuals and pathologic corneal tissue I was convinced that this was a different type of LCD and coined the term LCD type II (189). In this variety of LCD both corneas contain randomly scattered short fine glassy lines, which are less numerous, more delicate and more radially oriented than those in LCD type I. In contrast to LCD type I the peripheral cornea is chiefly affected and the central cornea is almost spared. Corneal sensitivity is reduced and there is a reduction in the long nerve bundles in the subepithelial nerve plexus (190). The cornea in LCD type II has fewer amorphous deposits than LCD type I and epithelial erosions are not a feature. The condition first becomes apparent after 20 years of age (later than in LCD type I). In persons homozygous for the relevant mutant gene the disorder begins earlier. Vision does not usually become significantly impaired before the age of 65 years. A corneal graft is rarely indicated, but when performed a neurotrophic persistent epithelial defect may develop (191) and the histopathologic features can be mistaken for those of LCD type I.

The corneal abnormalities are accompanied by a progressive bilateral neuropathy involving cranial and peripheral nerves, dysarthria, a dry and extremely lax itchy skin with amyloid deposits. A characteristic "mask-like" facial expression, protruding lips with impaired movement, pendulous ears and blepharochalasis are also features.

Two single base substitutions in the *GSN* gene, located on human chromosome 9 (9q34), that encodes the actin-modulating protein gelsolin are known to cause LCD type II (D187N, D187Y). The mutation in many Finnish (192), three American (36,66,68), one Japanese (193) and one English (69) families involves a G to A substitution at nucleotide 654 (codon 187), resulting in an asparagine-187 variant of gelsolin (194). In one Danish and one Czech family a G to T transversion in position 654 at codon 187 results in the substitution of tyrosine for aspartic acid (65,70)**.**

The amyloid in LCD type II is composed of a mutated 71 amino acid long fragment of gelsolin and it accumulates in the corneal stroma and between the epithelium and Bowman’s layer. It also deposits in scleral, choroidal and adnexal blood vessels as well as in the lacrimal gland and perineurium of ciliary nerves. The amyloid is also found in the heart, kidney, skin, nerves, wall of arteries, and other tissues (185). The amyloid within the cornea in LCD type II reacts with the anti-gelsolin antibody (195), but not with the antibodies produced to the amino and carboxy terminals of gelsolin (196).

3.3 Corneal dystrophies due to mutations in the M1S1 gene

3.3.1. Primary familial subepithelial corneal amyloidosis

The designation primary familial subepithelial corneal amyloidosis is recommended for a specific serious inherited autosomal recessive disorder characterized by an accumulation of mounds of amyloid primarily in the central subepithelial cornea and in Bowman’s layer (197,198). The condition is also termed primary familial amyloidosis of the cornea (199,200) and gelatinous drop-like corneal dystrophy (142,201-205,205)(GDLD, OMIM #204870) [http://www3.ncbi.nlm.nih.gov/htbin-post/Omin/dispmim?204870]. During the first decades of life multiple nodules of amyloid deposit in the subepithelial corneal tissue of both corneas producing multiple prominent milky-white gelatinous nodules that resemble a mulberry in shape. Fusiform

deposits similar to those in LCD may also form in the deeper stroma (206). Other features are severe photophobia, tearing, a corneal foreign body sensation and a severe progressive loss of vision. The response to both lamellar and penetrating keratoplasty as well as to a superficial keratectomy is unsatisfactory as amyloid recurs in the graft within about 5 years (207,208).

The amyloid within the cornea contains lactoferrin (209), but the disease is not linked to the lactoferrin gene (210).

This dystrophy has been mapped to the short arm of human chromosome 1 (51) and at least 11 mutations in the M1S1 (formerly *TROP2, GA733-1*) gene that encodes a gastrointestinal tumor-associated antigen have been found to cause this disorder (9). The Q118X mutation has been detected most often (6,211). Some affected individuals have been found not to have mutations in TGFBI (212).

3.4.1. Corneal dystrophies due to mutations in the CHST6 gene

3.4.1.1. Macular corneal dystrophy

"Macula" is Latin for a spot and the adjective "macular" was introduced as the name for a specific corneal dystrophy characterized by white spots within a cloudy cornea. Unfortunately, the designation macular corneal dystrophy (MCD) has lead to misunderstanding because "macular" is also applicable to disorders of the macula in the retina, such as macular degenerations and retinal macular dystrophies. Nevertheless, the designation refers to an autosomal recessive disorder characterized by bilateral diffuse clouding of the corneal stroma and aggregations of irregular shaped grayish-white spots with indistinct edges, especially in the superficial cornea (MCDC1, OMIM #217800) [http://www3.ncbi.nlm.nih.gov/htbin-post/Omin/dispmim?217800]. The opacities usually first appear within a hazy stroma of both corneas during adolescence, but may become apparent in early infancy or even as late as the sixth decade. The non-transparent areas progressively merge over time as the entire corneal stroma gradually becomes cloudy causing severe visual impairment usually before the fifth decade. In addition to corneal opacification the cornea is thinner than normal (213,214). Fortunately, corneal grafting can restore vision. MCD rarely recurs in a corneal graft after many years, but the recurrence is usually not clinically significant (123,123,215-219).

Material that stains positively with histochemical methods for glycosaminoglycans (GAGs) accumulates within the cytoplasm of keratocytes and extracellularly within the corneal stroma between collagen fibers, in Bowman's zone, and in Descemet's membrane (139,220-225). The endoplasmic reticulum within keratocytes and some corneal endothelial cells is dilated and filled with delicate fibrillogranular material (139,220,221,223,225-227,227,228). Numerous electron-lucent lacunae are randomly distributed throughout corneas with MCD. Some lacunae are filled with clusters of abnormal sulfated chondroitinase ABC susceptible proteoglycan filaments (229).

The collagen fibrils have a normal diameter, but the interfibrillar spacing of these fibrils in affected corneas is less than that in the normal cornea (229,230). This close packing of collagen fibrils seems to be responsible for the reduced corneal thickness in MCD (230).

The anterior banded fetal portion of Descemet's membrane is normal, but the posterior layer contains corneal guttae. These focal excrescences as well as the contiguous portions of the posterior layer of Descemet's membrane contain electron-lucent vacuoles (225-227).

Because of features analogous to the systemic mucopolysaccharidoses, we once postulated that MCD was a localized mucopolysaccharidosis due to a defective enzyme needed for the degradation of certain corneal GAGs (221). The assumption that the intra- and extracellular deposits in the cornea were GAGs conformed with the known ability of the keratocyte to synthesize these macromolecules (231,232). Keratan sulfate (KS), the major corneal sulfated GAG, seemed the most likely substance, and this possibility was consistent with the histochemical findings (189,220,233). Other GAGs were unlikely candidates in view of the resistance of the accumulations to digestion by certain enzymes. The persistence of the staining qualities of the accumulations after testicular hyaluronidase digestion argued against hyaluronic acid and chondroitin-4-sulfate being significant components, whereas their resistance to chondroitin ABC lyase digestion attested against dermatan sulfate (221). By exclusion, KS seemed most likely to be the accumulated substance, and this theory was supported by the affinity of both the material and KS for alcian blue at low pH with magnesium chloride concentrations with a molarity of up to 0.8 (233). Moreover, of the methods which aid in the visualization of the accumulations in tissue sections, periodic acid-Schiff may react with KS, whereas, chondroitin sulfates, hyaluronic acid, and other GAGs usually do not (233). Further studies revealed that in contrast to the systemic mucopolysaccharidoses, MCD was not a lysosomal storage disease due to an impaired degradation of corneal GAGs. Lysosomal abnormalities were reported in cultured MCD keratocytes (234), but this observation was not confirmed (235). Surprisingly organ cultures of MCD corneas synthesized considerably less KS than normal corneas (233) and failed to synthesize lumican presumably as a consequence of a defect in an enzyme needed for the sulfation of lactosaminoglycans (233,236). Corneas with MCD synthesized dissimilar proteoglycans and lactosaminoglycan-glycoproteins (237), but produced excessive amounts of variably sulfated glycopeptides (238,239). Both cartilage and cornea contain reduced KS side chains (240).

Subsequently we discovered that KS is lacking in the serum and corneas of some patients with MCD (241-243) and that the serum KS levels correlate positively with the presence or absence of immunohistochemically detectable antigenic KS (AgKS) in the cornea. Also, a determination of the serum KS levels was not helpful in carrier detection. Three immunophenotypes of MCD (MCD types I, IA, and II) could be distinguished based on the immunohistochemical reactivity of serum and corneal

tissue to anti-KS antibodies (244,245). The commonest variety (MCD type I) has no detectable AgKS in the serum or cornea. MCD type II has normal amounts of AgKS in the serum and the abnormal intracytoplasmic accumulations and corneal stroma in MCD type II react with a monoclonal antibody that recognizes sulfated KS epitopes. In MCD type IA, the serum lacks detectable AgKS, but the keratocytes react with antibodies to KS.

MCD was once thought to be restricted to the cornea, because the clinical manifestations only affect the cornea. The observation that serum of patients with one variant of MCD (MCD type I) lacks detectable AgKS led to the prediction that the cartilage must be involved (242,243) and direct evidence for this was later established in MCD type I (246,247) as well as MCD type II (247). The AgKS content of the cartilage is at least 800 times lower than normal (246). However, chondrocytes and the extracellular matrix of the nasal cartilage do not manifest abnormalities comparable to those in the cornea. Also, lesions similar to those in the cornea have not been observed in non-corneal tissues.

It became apparent based mainly on biochemical studies, in which corneal organ cultures were incubated in medium containing radioactive isotopes, that a fundamental defect in at least one type of MCD (MCD type I) involved the sulfation of KS in the biosynthesis of corneal KS containing proteoglycans (PGs) (233,237,248) and that MCD corneas fail to synthesize normal KS containing proteoglycans (236,249). This led to the belief that a basic defect involved a specific sulfotransferase that attaches sulfate moieties to lactosamino-glycan (non-sulfated KS) (236,242,243).

The serum from patients with MCD has normal values for sulfotransferases (250,251) suggesting that the responsible sulfotransferase is not secreted into the serum. Analyses of sulfotransferase activities in extracts of corneas with MCD disclosed normal levels of galactose-6-sulfotransferase (Gal6ST), but lower than normal levels of N-acetylglucosamine 6-O-sulfotransferase (GlyNAc6ST) thus providing a biochemical basis for MCD at an enzymatic level (252).

In addition to the biochemical investigations, the gene responsible for MCD was linked to the human chromosome 16 (77), the relevant region was fine mapped (253,254) and the *TAT* and *LCAT* genes, which cause corneal disease when mutated, were excluded as candidate genes (254). While it was initially uncertain whether the immunophenotypes were genetically different, it later became more likely that they were genetically related. Linkage studies indicated that MCD type II was probably at the same locus as MCD type I (77). In addition, different immunophenotypes were detected in the same families (244,255) and even in the same sibship (256).

By finding sulfotransferase (ST) motifs in expressed tags (ESTs) two adjacent ST genes (CHST5 and *CHST6*) were discovered within the region of human chromosome 16 to which the MCD gene had been fine mapped (78). Knowing that an enzyme for transferring sulfate moieties to keratan sulfate was suspected of being deficient in MCD type I (236,242,243) *CHST5* and *CHST6* became obvious candidates as the MCD disease gene. Subsequently, nucleotide changes as well as insertions within *CHST6* were found to alter the encoded protein in patients with MCD type I (78,79) strongly implicating *CHST6*. In some families with MCD type II major nucleotide insertions or rearrangements were found upstream of the *CHST6* gene by Akama *et al.* (78), suggesting a defect in a regulatory element of *CHST6*. Other patients with MCD type II have had nucleotide changes in *CHST6* in the coding region of *CHST6*. Mutations in *CHST6* presumably result in lumican, keratocan, mesican and perhaps other less abundant proteoglycans and glycoproteins, with considerably less sulfation than normal and the absence of this negative charge undoubtedly has a profound affect on these proteins. At present at least 26 different mutations have been identified in *CHST6*. They include base insertions and single base substitutions.

Despite the strong evidence that mutations in the *CHST6* gene are responsible for MCD numerous questions remain unanswered. For example, why does a defective sulfotransferase involved in the biosynthesis of a normal component of the cornea lead to an intracytoplasmic accumulation of GAGs within keratocytes and the corneal endothelium? Why can the normal degradative enzymes not degrade the storage material? Why do GAGs accumulate in the corneal endothelium of a corneal graft many years later apparently within donor tissue as documented by Klintworth *et al.* (218)?

Even if MCD types I, IA and II are allelic and caused by mutations in *CHST6*, or in upstream regulatory elements, an adequate explanation for the differences between the various immunophenotypes is still needed.

3.5. Corneal dystrophies due to mutations in the KRT3/KRT12 gene

The intermediate filaments within the cytoskeleton of the corneal epithelium are composed of pairs of specific cytokeratins that are co-expressed during epithelial differentiation. In the cornea one member of the duo (cytokeratin 12) is an acid cytokeratin with a molecular weight of 40-56.5 kD (type I cytokeratin); the other (cytokeratin 3) is a neutral or basic cytokeratin with a molecular weight of 53-67 kD (type II cytokeratin). The genes for cytokeratin 3 (*KRT3*) and cytokeratin 12 (*KRT12*) are located on human chromosomes 12 (12q13) and 17 (17q12), respectively.

3.5.1. Meesmann corneal dystrophy

Although first reported clinically in 1935 by Pameijer of the Netherlands (257), Meesmann dystrophy (juvenile familial epithelial dystrophy, OMIM #122100) *} [http://www3.ncbi.nlm.nih.gov/htbin-post/Omin/dispmim?122100] was best characterized as a distinct entity by Meesmann (258,259). The disorder has an autosomal dominant mode of inheritance and begins in infancy with symptoms of mild ocular irritation, photophobia and blurred vision. The course is slowly progressive. Bubble-like, round-to-oval punctate opacities are present in the corneal epithelium of

both eyes. They affect the central corneal epithelium more than the periphery and occur in the absence of a systemic disorder. Removal of the abnormal corneal epithelium is not curative as the basic defect recurs in the regenerated epithelium. This results in a focal aggregation of keratin within the cytoplasm of the corneal epithelium detected in transmission electron micrographs of affected tissue (260-263). The corneal epithelium is irregular in thickness, and the cells often lack normal stratification. Numerous intraepithelial cysts contain degenerated cellular debris and manifest autofluorescence in ultraviolet light (263). Bowman's layer and the corneal stroma are unremarkable. Patients with this dystrophy have a mutation in either the *KRT3* or *KRT12* gene (13,17,18,264). The mutations have been in extremely conserved keratin boundary motifs. For example, in the K12 polypeptide they involve the helix termination (17) or initiation motif (13,14). Dominant mutations affecting this part of the molecule in other keratins severely impair cytoskeletal function (13). In the cornea the mutations disturb keratin filament assembly and result in fibrogranular aggregates of clumped keratin (the characteristic "peculiar substance" of Kuwabara and Ciccarelli) (260).

3.5.2. Stocker-Holt dystrophy

Stocker and Holt (265,266) drew attention to unusual corneal opacities in descendants of Moravians from Dresden in Saxony between the ages of 7 months to 70 years. Affected individuals have numerous small, clear or whitish-gray, closely packed punctate opacities within the epithelium that are usually not discernible with the naked eye, but they are noted on slit lamp biomicroscopy, especially in the interpalpebral zone. The corneal spots, which represent microcysts, are uniform in size and shape. They are usually bilaterally symmetrical and most often become apparent during the first two years of life. In neonates asymptomatic epithelial opacities can be detected. By the end of the first decade of life visual impairment, as well as episodic photophobia and lacrimation may develop. Older individuals complain of a foreign body sensation and mildly decreased visual acuity. Similarities to Meesmann dystrophy led to the belief that Stocker-Holt dystrophy was the same disorder, but the peculiar substance characteristic of the latter entity has not been identified in affected corneas. However, a R19I mutation in the *KRT12* gene has been detected in affected members of the family documented by Stocker and Holt (19).

3.6. Corneal dystrophies due to mutations in the GLA gene

3.6.1 Cornea verticillata

The designation vortex corneal dystrophy (corneal verticillata) was applied to a corneal disorder characterized by the presence of innumerable tiny brown spots arranged in curved whirlpool-like lines in the superficial cornea (267,268). An autosomal dominant mode of transmission was initially suspected, but later it was realized that these individuals were affected hemizygous males and asymptomatic female carriers of an X-linked systemic metabolic disease caused by a deficiency of α-galactosidase (267) (Fabry disease, Anderson-Fabry disease, ceramide trihexosidase deficiency, hereditary dystopic lipidosis, α-galactosidase deficiency, GLA deficiency, OMIM #301500) [http://www3.ncbi.nlm.nih.gov/htbin-post/Omin/dispmim?301500]. Some, but not all cases are due to mutations in the *GLA* gene. Non-familial whorl-like corneal opacities also form in individuals on chloroquine, amiodarone, phenothiazine, or indomethacin therapy and striate melanokeratosis.

3.7. Corneal dystrophies due to mutations in the STS gene

3.7.1. Deep filiform dystrophy and cornea farinata

Small gray punctate opacities accumulate in the central deep corneal stroma immediately anterior to Descemet's membrane, or in a ring around the middle of the cornea in entities known as deep filiform dystrophy and cornea farinata (269,270). The opacities are of variable shape and may resemble commas, circles, lines, threads (filiform), flour (farina) or dots. Terms that have been applied to these disorders include deep filiform dystrophy and cornea farinata (271). Deep filiform dystrophy consists of small multiple threadlike, gray opacities in the pre-Descemet's membrane area that affect the entire width of the cornea except for the perilimbal region (271). It has been noted in association with keratoconus (271) and X-linked ichthyosis (steroid sulfatase deficiency, OMIM #308100) [http://www3.ncbi.nlm.nih.gov/htbin-post/Omin/dispmim?308100] (272). The opacities in ichthyosis may also have the appearance of cornea farinata (273). In X-linked ichthyosis abnormal depositions of basement membrane protein have been identified in the anterior stroma (272). In this disorder the corneal subepithelial and anterior stromal layers may contain white-gray granular opacities associated with irregular overlying corneal epithelium and a thickened basement membrane including irregular extensions into Bowman's layer (274). Small punctate or filiform opacities may also form in the deep corneal stroma (272). Immunoglobulin deposits may generate deep filiform opacities in hypergammaglobulinemia (275).

The opacities in cornea farinata (276,277), which is common in elderly individuals, resemble flour and do not usually decrease visual acuity. In this condition keratocytes anterior to Descemet's membrane contain membrane-bound intracytoplasmic vacuoles that include fibrillogranular material and electron-dense lamellar bodies (270). These manifestations have been observed in X-linked ichthyosis (278). The phenotype of deep filiform dystrophy can also result from immunoglobulin deposition (279).

Cornea farinata and deep filiform dystrophy may result from mutations in the *STS* (steroid sulfatase gene). At least 6 mutations in *STS* have been identified, but they have not been correlated with the presence or absence of corneal abnormalities.

3.8. Corneal dystrophies due to mutations in the COL8A gene

3.8.1. Fuchs corneal dystrophy

Fuchs dystrophy (late hereditary endothelial dystrophy) (OMIM #136800 [http://www3.ncbi.nlm.nih.gov/htbin-post/Omin/dispmim?136800] is a bilateral corneal disorder named after the ophthalmologist, who first described

epithelial edema, stromal clouding, and impaired corneal sensitivity in elderly individuals in 1910 (280). Later it became recognized that hyaline excrescences form centrally on Descemet's membrane (corneal guttae) in this condition. As a rule Fuchs dystrophy presents clinically during the fifth or sixth decade of life and seldom before the sixth decade of life (281-285). Women are affected much more often than men and comprise about 75% of the cases (286). Population studies have shown a marked difference in the prevalence of Fuchs dystrophy in different parts of the world. Fuchs dystrophy is common in the USA, uncommon in Saudi Arabia (287) and extremely rare in Japan (205,285). Most patients with Fuchs dystrophy lack a positive family history, but blood relatives sometimes manifest corneal guttae (288). Familial Fuchs dystrophy may involve siblings (289,290) and two or more successive generations (281,282,288,291-293), apparently as an autosomal dominant disorder with greater expressivity in the female (288,293).

Aside from the guttae, Descemet's membrane is multilayered and often irregularly thickened (two to four times normal) due to an excessive accumulation of collagen especially where the guttae are most abundant.

The cardinal defect affects the corneal endothelium, which degenerates prematurely and produces excessive amounts of an abnormal Descemet's membrane of a type analogous to that assembled *in utero*. Sequential observations on numerous patients have disclosed that the endothelial alterations precede the epithelial changes.

A missense Q455K mutation in the gene encoding the alpha2 chain of type VIII collagen (*COL8A2*) located on human chromosome 1 (1p34.3-p32) has been identified in some patients with a rare autosomal dominant early onset Fuchs corneal dystrophy (31). Moreover, the same mutation has been found in posterior polymorphous corneal dystrophy suggesting that the two disorders are related to each other and that they involve type VIII collagen (31).

3.8.2. Posterior polymorphous corneal dystrophy

The cells lining the posterior surface of the cornea possess the morphologic attributes of epithelial cells in posterior polymorphous corneal dystrophy (PPCD, OMIM #122000) [http://www3.ncbi.nlm.nih.gov/htbin-post/Omin/dispmim?122000] and this is evident clinically by a varied appearance of the corneal endothelial cells. PPCD is usually asymptomatic and hence most cases do not require treatment. However, in those that do PPCD can recur in the graft following perforating keratoplasty (294,295). Corneal tissue has only been examined in cases severe enough to require penetrating keratoplasty. Instead of an endothelial monolayer the posterior cornea is lined by variable numbers of stratified squamous epithelial cells having tonofilaments, cytokeratin and desmosomes (296-299). These cells have numerous microvilli (300,301), but unlike normal corneal epithelium, microplicae are not a feature. Cells on the posterior corneal surface of Descemet's membrane may also have a fibroblast-like appearance (296).

An irregularly thickened, multilaminar Descemet's membrane, occasionally contains focal nodular excrescences (296,301). The normal non-banded portion is thinner than normal and a layer posterior to it contains numerous delicate collagen fibrils (10-20 nm in diameter with a normal cross-striational periodicity) as well as long spacing collagen (with a banding of 55-110 nm) interspersed with fine granular homogeneous basement membrane-like material.

The abnormalities of the corneal endothelium presumably represent anomalous development secondary to a genetic mutation. Failure to produce a continuous anterior banded zone indicates that the cornea is affected before the twelfth week of gestation (302). In other cases the morphologically unremarkable anterior banded portion of Descemet's membrane indicates that the corneal endothelium synthesizes normal basement membrane until late in gestation. Because PPCD is usually not associated with corneal edema, the corneal endothelium presumably maintains a normal state of corneal hydration in most affected individuals.

Although the morphologically abnormal cells may have been displaced during ocular development, it seems more likely that they underwent metaplasia after lining the posterior surface of the cornea. Other pathologic mesothelial cells sometimes possess epithelial or fibroblastic features.

A gene for autosomal dominant CHED is also located in this region (85). More than one gene in this region could be responsible for both these dystrophies, conceivably because of a cluster of genes with related function; alternatively, the two phenotypes may be allelic (85). However, because blood relatives of individuals with PPCD may have CHED (303,304) it seems more likely that the two conditions are due to a mutation in the same gene.

A gene for autosomal dominant PPCD has been mapped to the pericentromeric region of human chromosome 20 (20q)(89). This gene remains to be identified, but PPCD shares developmental, morphological and clinical similarities with CHED1 and is probably related to it. CHED1 and PPCD have not only both been identified in the same family (303,304), but have also been mapped to the same region of human chromosome 20 (85). A missense Q455K mutation in the gene encoding the alpha2 chain of type VIII collagen (COL8A2) located on human chromosome 1 (1p34.3-p32) has been identified in some patients with PPCD indicating that the condition involves type VIII collagen (31).

4. CORNEAL DYSTROPHIES MAPPED TO SPECIFIC CHROMOSOMES BUT WITHOUT IDENTIFIED GENES

4.1. Central crystalline dystrophy (Schnyder dystrophy)

The presence of crystalline opacities in the anterior central portion of both corneas was described by van Went and Wibaut in 1924 (305). Five years later Schnyder (306,307) established this autosomal dominant

condition as a distinct entity, which is now known as central crystalline dystrophy (Schnyder dystrophy, OMIM #121800) [http://www3.ncbi.nlm.nih.gov/htbin-post/Omin/dispmim?121800]. Birefringent cholesterol crystals and associated neutral fats accumulate within keratocytes and extracellularly and correspond to the crystals observed clinically. The lipid is also present in Bowman's layer, between the superficial corneal lamellae and dispersed within the stroma midst the collagen fibrils.

Over time an initially unremarkable corneal stroma acquires small white opacities and a diffuse haze. Occasionally crystals are not evident clinically and only parts of the central corneal opacity may contain crystals (308). Typically a ring-shaped yellow-white opacity composed of innumerable fine needle-shaped crystals forms beneath the epithelium in Bowman's layer and the adjacent anterior stroma of the central cornea. The crystals usually remain in the anterior third of the cornea. The remaining stroma is unremarkable initially, but with time it may acquire small white opacities and a diffuse haze (309). While sometimes appearing dull white, the crystals are frequently scintillating with variegated red and green hues. The epithelium, Descemet's membrane and the endothelium are spared. In some cases crystals are only seen in parts of the central corneal opacity (308). The condition is usually bilateral, but one eye may become affected earlier than the other. Central crystalline dystrophy usually becomes apparent early in life, but has not been observed at birth. Although usually stationary after childhood, the corneal opacification may progress over time and form a dense, disc of corneal crystals and diminish vision of both eyes (310). Visual acuity is usually good, but it may become sufficiently impaired to demand keratoplasty (308,311).

The lipid deposits within the cornea are predominantly phospholipid and cholesterol (esterified and unesterified) (312,313) and probably reflect defective lipid metabolism. The predominant phospholipid is sphingomyelin (313). Most cases lack an apparent systemic disorder (314), but hypercholesterolemia is common (315-320), and so is an arcus lipoides (305,307,309,311,321), xanthelasma {905,786,907}. familial hypercholesterolemia (322,323), familial dysbetalipoproteinemia (322) or hypertriglyceridemia (324) and other manifestations of hypercholesterolemia (322) have been reported. An ultrastructural study of a skin biopsy and cultured fibroblasts from an affected person has disclosed lipid containing membrane-bound spherical vacuoles (314). Because the disorder usually stabilizes with time, only occasional patients with severe impairment require corneal grafting.

A yet to be identified gene for central crystalline corneal dystrophy has been mapped to human chromosome 1 (1p34.1-p36) (27). The *B120* gene, which is involved in lipid transport and metabolism is a strong candidate (325).

4.2. Congenital hereditary endothelial dystrophy

Bilateral corneal opacification ranging from a diffuse haze to a ground glass milk appearance characterizes two types of congenital hereditary endothelial dystrophy (CHED)(hereditary corneal edema, infantile hereditary endothelial dystrophy). The autosomal dominant type of CHED (CHED1) (OMIM #121700) [http://www3.ncbi.nlm.nih.gov/htbin-post/Omin/dispmim?121700] is slowly progressive and becomes manifest during the first two years of life with photophobia and tearing. A gene for this form of CHED has been mapped to chromosome 20 (20q11) (85). Autosomal recessive CHED (CHED2) (OMIM #217700) [http://www3.ncbi.nlm.nih.gov/htbin-post/Omin/dispmim?217700] becomes evident at or shortly after birth. Nystagmus is absent in CHED1, but is a feature of the non-progressive CHED2. CHED1 has been mapped to the pericentromeric region of chromosome 20 (20p11.2-q11.2) (85) in an area overlapping a gene for autosomal dominant posterior polymorphous dystrophy (89). A different gene for CHED2 is located close to the telomere on human chromosome 20 (84,326).

4.3. Bietti marginal crystalline dystrophy

A rare autosomal recessive condition characterized by multiple delicate glistening crystals in the peripheral cornea and retina was first recognized in Italy by Bietti (327). The disorder known as Bietti marginal crystalline dystrophy (OMIM #210370) [http://www3.ncbi.nlm.nih.gov/htbin-post/Omin/dispmim?210370] is relatively common in China and most reported cases have been in persons of Oriental extraction. A systemic disorder of lipid metabolism is suspected and affected individuals sometimes have hyperlipoproteinemia (Fredrickson's type II phenotype) (328).

Very fine crystals that are difficult to see even by slit-lamp biomicroscopy gather in the peripheral paralimbal anterior corneal stroma in persons with areas of retinal pigment epithelial atrophy. Similar crystals are present in all layers of the retina, especially at the posterior pole. This condition has a slowly progressive loss of visual function resulting in night blindness and a constriction of the visual field. The retina undergoes degeneration and the choroidal blood vessels become sclerotic (329). Many cases retain good vision, but become symptomatic because of poor dark adaptation and paracentral scotomas (330). Corneal (330,331) and conjunctival fibroblasts contain crystals and complex osmiophilic inclusions indicating that the disorder is not limited to the cornea (330). The nature of the crystals and inclusions has not been identified with certainty, but a systemic disorder of lipid metabolism is suspected. The condition, which has been associated with abnormalities in fatty acid metabolism and the absence of fatty-acid binding by two cytosolic proteins (332), has been mapped to human chromosome 4 (4q35-4qtel) (26).

4.4. Lisch corneal dystrophy

Lisch corneal dystrophy (band-shaped whorled microcystic dystrophy of the corneal epithelium is a rare inherited disorder of the cornea characterized by the presence of band-shaped and whorled microcysts in the corneal epithelium (333-335). The condition, which was first described by Lish *et al.* in 1992 (333), has clinical similarities to Meesmann corneal dystrophy, but is histopathologically and genetically distinct and is not linked to the KRT3 and KTR12 loci. The gene has been

mapped to the short arm of the X chromosome (Xp22.3) at a maximum likelihood of odds (LOD) score of 2.93 (336).

4.5. Fleck corneal dystrophy

In 1956, François and Neetens (337,338) described two different corneal dystrophies (dystrophie mouchetée and dystrophie nuageuse)(central cloudy and fleck dystrophy) (OMIM #121850) [http://www3.ncbi.nlm.nih.gov/htbin-post/Omin/dispmim?121850]. This condition is known by several names, including hereditary fleck corneal dystrophy. These two phenotypes are almost certainly expressions of a single genetic mutation since they have both been detected in the same family (337) and even in the same individual (339).

In fleck dystrophy some corneal fibroblasts contain fibrillogranular material within intracytoplasmic vacuoles or pleomorphic electron-dense and membranous intracytoplasmic inclusions. The stored material has the histochemical attributes of glycosaminoglycans and lipids and a storage disease involving these compounds is suspected. Extracellular alterations are rare, but foci of broad spaced collagen have been observed. Comparable abnormalities have not been found in other tissues.

The opacities are scattered symmetrically throughout a clear stroma usually in both corneas, but unilateral cases have been reported. One type of opacity consists of numerous small oval, round, wreath-like or semicircular-shaped flattened grayish particles with distinct borders ("flecks"); others that resemble clouds or snowflakes are small and grayish with ill-defined margins and are most numerous in the central third of the cornea and are occasionally most dense in the vicinity of Descemet's membrane. Rarely, mild photophobia is present. Fleck dystrophy does not require specific treatment, but the disorder did not recur in a corneal graft within 10 years of a patient who underwent a penetrating keratoplasty for an associated keratoconus (340).

Fleck dystrophy is characterized by multiple, non-progressive symmetric asymptomatic minute opacities disseminated throughout the corneal stroma (341). In the central cloudy phenotype asymptomatic cloudy stromal opacities with clear intervening stroma are found predominantly in the posterior axial corneal stroma (342,343). Both corneas are usually affected, but there are reports of unilateral cases (344). One type consists of numerous small oval, round, wreath-like or semicircular-shaped flattened grayish particles with distinct borders ("flecks"); others that resemble clouds or snowflakes are small and grayish with ill-defined margins and are most numerous in the central third of the cornea and are occasionally most dense in the vicinity of Descemet's membrane. Both phenotypes occur in the same family and even in the same individual. The disorder affects males and females equally and has been observed throughout life and even in children as young as 2-years (345). The condition has been mapped to the long arm of human chromosome 2 (2q35) (28).

4.6. Keratosis follicularis spinulosa decalvans

Keratosis follicularis spinulosa decalvans (OMIM #308800) [http://www3.ncbi.nlm.nih.gov/htbin-post/Omin/dispmim?308800] is a rare inherited X-linked disorder that affects the skin and cornea. It was first described by Siemens in 1926 in the Netherlands (346,347) and is characterized by cutaneous follicular papules and alopecia (especially involving scalp, eyebrows and eyelashes). Numerous punctate opacities are found beneath the corneal epithelium. Marked photophobia is common. Female carriers may manifest the disorder usually in a mild form. One report documents the findings on a corneal biopsy (348). The disorder has been mapped to Xp22-2-p22.13 (12).

5. CORNEAL DYSTROPHIES THAT HAVE NOT BEEN MAPPED TO SPECIFIC CHROMOSOMES

5.1. Congenital hereditary stromal dystrophy

One large family with descendants in Germany and France is known to have congenital hereditary stromal dystrophy (349). This is a congenital autosomal dominant non-progressive disorder that is limited to the corneal stroma and it is characterized by flaky or feathery clouding of the corneal stroma. The abnormalities consist of a peculiar arrangement of tightly packed lamellae having highly aligned collagen fibrils of unusually small diameter (349). The cornea is of normal thickness and both Descemet's membrane and the corneal endothelium are relatively normal. The responsible gene remains to be identified and has not been mapped to a specific chromosome. Nothing is known about the biochemical alterations, but the abnormally small stromal collagen fibrils and disordered lamellae suggest a disturbance in collagen fibrogenesis.

5.2. Subepithelial mucinous corneal dystrophy

The term subepithelial mucinous corneal dystrophy was coined by Feder *et al* (350) for a unique autosomal dominant anterior corneal dystrophy in which subepithelial mucinous material accumulates in the cornea. The condition, which differs from other corneal dystrophies, has only been recognized in one family of Slovak descent (350).

5.3. Familial corneal guttae

Corneal guttae are common and are not specific for Fuchs dystrophy. They may be a sequel to interstitial keratitis (351-354), aging (292) and MCD (discussed elsewhere in this review). They have been detected clinically in as many as 70% of individuals over the age of 40 years in one part of the United States of America (Gainesville, Florida)(292). They are most often observed after the age of 50 years and are most extensive in the elderly. Corneal guttae are more common in females than males in some reviews (286,355), but not in others (292). Corneal guttae rarely form at an early age, but have been noted at birth (356-358). Congenital corneal guttae seem to be non-progressive and frequently have an autosomal dominant inheritance (357-359). Family studies also support an autosomal dominant mode of inheritance of some guttae that are not apparent early in life. Corneal guttae have been described in monozygotic twins (360), in siblings (361,362), and in two or more successive generations (361,362). Familial corneal guttae may co-

exist with anterior polar cataracts (358). In Japan patients with the R124H mutation in TGFBI have been found to have significantly more corneal guttae than controls (163).

5.4. Posterior amorphous stromal dystrophy

Carpel, Sigelman and Doughman (363) reported a family with irregular symmetric gray-white, sheet like opacities in the deep central posterior corneal stroma that spread peripherally towards the corneoscleral limbus. They coined the term posterior amorphous stromal dystrophy for this autosomal dominant disorder. Transparent stroma may intervene between the corneal opacities, which sometimes indent Descemet's membrane and the endothelium, which may have focal endothelial abnormalities. Both centroperipheral and peripheral forms are recognized (364). Visual acuity is usually minimally impaired, but may be severe enough to warrant a penetrating keratoplasty (365). Families with this condition have apparently only been detected in the USA (363-365).

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Footnotes: *: Online Mendelian Inheritance in Man Number. #: Throughout the text the standard one letter abbreviations are used for amino acids: alanine (A), arginine (R), asparagine (N), aspartic acid (D), cysteine (C), glutamic acid (E,), glutamine (Q), glycine (G), histidine (H), isoleucine (I), leucine (L), lysine (K), methionine (M), phenylalanine (F), proline (P), serine (S), threonine (T), tryptophan (W), tyrosine (Y) and valine (valine (V).

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Send correspondence to: Gordon K. Klintworth, M.D., Ph.D. Professor of Pathology and Joseph A.C. Wadsworth Research Professor of Ophthalmology, Room 255 Medical Science Research, Building, Duke University Medical Center, Box 3802, Durham, NC 27710, Tel: 919-684-3550, Fax: 919-684-9225, E-mail: klint001@mc.duke.edu