The IC3D Classification of the Corneal Dystrophies

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Background: The recent availability of genetic analyses has demonstrated the shortcomings of the current phenotypic method of corneal dystrophy classification. Abnormalities in different genes can cause a single phenotype, whereas different defects in a single gene can cause different phenotypes. Some disorders termed corneal dystrophies do not appear to have a genetic basis.

Purpose: The purpose of this study was to develop a new classification system for corneal dystrophies, integrating up-to-date information on phenotypic description, pathologic examination, and genetic analysis.

Methods: The International Committee for Classification of Corneal Dystrophies (IC3D) was created to devise a current and accurate nomenclature.

Results: This anatomic classification continues to organize dystrophies according to the level chiefly affected. Each dystrophy has a template summarizing genetic, clinical, and pathologic information. A category number from 1 through 4 is assigned, reflecting the level of evidence supporting the existence of a given dystrophy. The most defined dystrophies belong to category 1 (a well-defined corneal dystrophy in which a gene has been mapped and identified and specific mutations are known) and the least defined belong to category 4 (a suspected dystrophy where the clinical and genetic evidence is not yet convincing). The nomenclature may be updated over time as new information regarding the dystrophies becomes available.

Conclusions: The IC3D Classification of Corneal Dystrophies is a new classification system that incorporates many aspects of the traditional definitions of corneal dystrophies with new genetic, clinical, and pathologic information. Standardized templates provide key information that includes a level of evidence for there being a corneal dystrophy. The system is user-friendly and upgradeable and can be retrieved on the website www.corneasociety.org/ic3d.

Key Words: corneal dystrophy, inherited corneal disease, genetic corneal disease, corneal histopathology, gene, mutation, key reference, eponym, epithelial basement membrane dystrophy, epithelial recurrent erosion dystrophy, subepithelial mucinous corneal dystrophy, Meesmann corneal dystrophy, Lisch epithelial corneal dystrophy, gelatinous drop-like corneal dystrophy, Grayson-Wilbrandt corneal dystrophy, lattice corneal dystrophy, lattice gelsolin type dystrophy, granular corneal dystrophy 1, granular corneal dystrophy 2, Avellino corneal dystrophy, Reis–Bücklers corneal dystrophy, Thiel-Behnke corneal dystrophy, macular corneal dystrophy, Schnyder corneal dystrophy, Schnyder crystalline corneal dystrophy, congenital stromal corneal dystrophy, fleck corneal dystrophy, posterior amorphous corneal dystrophy, central cloudy dystrophy of François, pre-Descemet corneal dystrophy, Fuchs endothelial corneal dystrophy, posterior polymorphous corneal dystrophy, congenital hereditary endothelial dystrophy 1, congenital hereditary endothelial dystrophy 2, X-linked endothelial corneal dystrophy

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HISTORY

The word dystrophy is derived from the Greek (dys = wrong, difficult; trophe = nourishment) and was introduced into the medical literature by Wilhelm Erb (1840–1921) in 1884, in describing a disease of the musculature. In 1890, Arthur Groenouw (1862–1945) published his classic paper describing 2 patients with “noduli corneae,” with 1 patient having granular corneal dystrophy and the other, macular corneal dystrophy. At the same time, Biber was also publishing his thesis on lattice corneal dystrophy.

In that pre-slit lamp era, the extent of corneal examination was limited. But although Groenouw did not initially...
appreciate the differences between granular and macular dystrophy or recognize the familial predisposition, the 2 diseases subsequently became known as corneal dystrophies. Fuchs used the word dystrophy to refer to ophthalmologic disease and postulated that dystrophic tissues resulted from lack of nourishment, hormones, blood, and nerve supply. Uhthoff and later Yoshida continued to use the term in their publications.

CORNEAL DYSTROPHY DEFINITION

Although many definitions of the word “dystrophy” have appeared in the medical literature, the term is most commonly used to describe an inherited disorder affecting cells, tissues, or organs, alone or in combination. In ophthalmology, the term “corneal dystrophy” has been used to refer to a group of inherited corneal diseases that are typically bilateral, symmetric, slowly progressive, and without relationship to environmental or systemic factors. As knowledge has increased, exceptions to each of these definitions have been noted. Thus, most patients with epithelial basement membrane dystrophy do not have a hereditary pattern. Some patients with posterior polymorphous corneal dystrophy only manifest unilateral changes. In macular dystrophy, the level of antigenic serum keratan sulfate correlates with the immunophenotypes of the disease, indicating that systemic abnormalities are integral to the development of the characteristic corneal changes. Likewise, there are a number of hereditary, bilateral diseases of the cornea, such as cornea plana, which have not been traditionally classified as corneal dystrophies and may be alternatively accommodated among the congenital anomalies affecting the cornea.

Consequently, experience has demonstrated that the separation of entities into the category called corneal dystrophies may have more historical than practical meaning. There remains no consensus as to the precise definition of corneal dystrophy, but, according to custom, we have chosen to primarily deal with entities formerly called corneal dystrophies.

CORNEAL DYSTROPHY LITERATURE

Bücklers, whose name was later attached to Reis–Bücklers corneal dystrophy (RBCD), published the first classification of the corneal dystrophies when he described the differences between granular, lattice, and macular corneal dystrophies. Although the dystrophies can be classified according to genetic pattern, severity, histopathologic features, or biochemical characteristics, the most commonly used classification system has been anatomically based. The dystrophies are typically classified by level of the cornea that is involved, which separates these entities into epithelial and subepithelial, Bowman layer, stromal, Descemet membrane, and endothelial dystrophies.

SHORTCOMINGS OF CORNEAL DYSTROPHY CLASSIFICATION

Critical review of the corneal dystrophy literature reveals numerous apparent misconceptions and errors. For example, many publications emphasize the necessity of demonstrating corneal crystals to make the diagnosis of Schnyder crystalline corneal dystrophy (SCD). However, examination of large pedigrees of patients with SCD demonstrates that only 50% of affected patients actually have corneal crystals. Nevertheless, publications over the past decades erroneously emphasize that crystals are necessary for the diagnosis of SCD.

The direct consequence is that in some patients with SCD who lack stromal crystals, the diagnosis may be delayed for decades. Once established in textbooks, it is exceedingly difficult to purge incorrect information about rare diseases. Many myths are perpetuated because very few ophthalmologists have seen a substantial number of the unusual corneal dystrophies.

Another difficulty in the literature is the tendency to place too much emphasis on a new or rare observation rather than wait for a full analysis of a new disorder. For example, some of the early papers describing the ultrastructure of RBCD had actually analyzed tissue from patients with Thiel–Behnke corneal dystrophy (TBCD). In a publication, the known entity of RBCD was renamed as an unusual variant of granular dystrophy. These inconsistencies in the literature have confounded our understanding of precise findings in specific corneal dystrophies.

DOES EVERY SINGLE DYSTROPHY ACTUALLY EXIST?

Before the 1970s, new corneal dystrophies were identified and characterized almost exclusively by their clinical appearance aided, in some cases, by light microscopic histopathology. In some cases, the description of a dystrophy was based on a report of a single family. In other cases, a new dystrophy could be misclassified as a variant of a previously described dystrophy. For years, the dystrophy of Waardenburg and Jonkers appeared in references and textbooks. In actuality, these patients had Thiel–Behnke corneal dystrophy.

Often, it is impossible to either confirm or exclude every corneal dystrophy that has made its way into textbooks as an independent entity. Moreover, misunderstandings that became prevalent have often persisted long after they could be resolved. For example, what did Reis and Bücklers actually see when they described what is now called Reis–Bücklers corneal dystrophy? The original pedigree is lost to follow up, and their clinical description is sketchy concerning the specific signs and symptoms. Nevertheless, we still presume that the entity they described is probably what is now established as Reis–Bücklers dystrophy (RBCD), but the original patients could have had what is now called TBCD.

Before honeycomb-shaped corneal dystrophy was described by Thiel and Behnke in 1967, and even afterwards, patients affected with this dystrophy were instead reported as examples of RBCD. It took more than 30 years before the literature had separated these 2 dystrophies. On the other hand, Grayson and Wilbrandt described a family with a Bowman layer dystrophy they initially reported as RBCD but actually provided insufficient evidence to determine definitively whether the unique findings, subsequently called Grayson–Wilbrandt corneal dystrophy (GWCD), indicated...
a distinct entity or a variant of a different Bowman layer dystrophy.

Although the original publication on central cloudy dystrophy of François described a hereditary corneal opacification, there have been only a few other publications that have described an entire family with this disease. Both articles were written before the advent of genotyping so no genetic information is available. Central cloudy dystrophy of François appears clinically indistinguishable from the degenerative condition, posterior crocodile shagreen. It is not possible to determine whether previous publications describing an individual patient with central cloudy dystrophy of François were actually describing patients with posterior crocodile shagreen. In the absence of additional affected pedigrees or genetic studies confirming inheritance, it is possible that central cloudy dystrophy of François and posterior crocodile shagreen are the same entity. Without genotypic information, it may be impossible to determine whether rare or newly described dystrophies are actually unique diseases or represent phenotypic variations of previously described entities.

GENETICS

The development of genotypic analyses has revolutionized our knowledge of the corneal dystrophies and further elucidated additional inaccuracies in the dystrophy nomenclature. The genetic characterization of corneal dystrophies revealed both genetic heterogeneity, that is, different genes (KRT3 and KRT12) causing a single dystrophy phenotype (Meesmann dystrophy), and phenotypic heterogeneity with a single gene (TGFBI) causing different allelic dystrophy phenotypes (RBCD, TBCD, granular type 1, granular type 2, and lattice type 1). Consequently, by enhancing our understanding of the dystrophies, newer genetic information has made the phenotypic classification system archaic.

CURRENT CLASSIFICATION OF THE CORNEAL DYSTROPHIES

The knowledge base has exploded since the first descriptions of granular, macular, and lattice dystrophies over a century ago. Not only has the word dystrophy lost importance but also the distinctive name of many of the individual dystrophies has become less meaningful. The basis of the nomenclature system seems to be more historic than scientific.

As the classification system of these disorders has taken on historic implications, it has been proposed that these conditions be classified “under the rubric of inherited corneal diseases,” although acknowledging that “the popular designation of corneal dystrophy will probably keep its place.”

RECLASSIFICATION OF THE NOMENCLATURE IN OTHER MEDICAL SPECIALTIES

Ophthalmology is not the only medical field that has discovered that the nomenclature of certain diseases has become archaic. Rapid advances in genotyping have challenged the nomenclature of other diseases in other specialties. Some of these specialties have met the challenge by devising new nomenclature systems. In 2001, the European Academy of Allergy and Clinical Immunology published a position paper proposing a new nomenclature in allergy after discussion with “many pediatricians in Europe for several years.” One of the authors wrote that he “set up a reference panel of pediatricians within different areas of pediatrics and at intervals I asked them for their opinion on the proposal.” Subsequent articles in that field have underscored the importance on nomenclature of atopy, atopic disease, and allergy on classifying the individual patient diseases and directing future therapy.

The disconnect between the language of basic scientists and the language of clinicians has also presented challenges in the muscular dystrophy nomenclature. Dubowitz wrote about his concern regarding a “major problem, within the field of therapy for muscular dystrophy, that has arisen from inappropriate nomenclature,” namely that it “… has had a negative impact on the whole field.” Klein wrote that “From a historical perspective, 2 golden ages have shaped the current and evolving classification schemes: 1. the definition of clinical pathological entities in the early twentieth century; and 2. the application of molecular neurogenetics in the past 10–15 years.” He concluded that the shortcoming of the current classification systems resulted not only because of the complex nature of the disorders but also that “modern classification schemes was based on clinical, pathologic and genetic/molecular criteria … attempt to integrate all three levels” and although “genetic classifications are now widely used … expert clinical diagnosis remains an important step in correct diagnosis and classification.” The author proposed classification schemes based on clinical features, genetic features, and molecular mechanisms or protein functions.

THE FORMATION OF THE INTERNATIONAL COMMITTEE FOR CLASSIFICATION OF CORNEAL DYSTROPHIES (IC3D)

In April 2005 at the World Cornea Congress meeting, the session on corneal dystrophies clearly elucidated that nomenclature problems vexed not only SCD but also many other dystrophies. That evening, J.S.W. approached the other members of the board of directors of the Cornea Society to request their support for the creation of an international committee to revise the corneal dystrophy nomenclature. The goal was the recruitment of an international panel of interested world experts possessing firsthand experience with the clinical, genetic, and histopathologic findings of all the corneal dystrophies. In this way, the literature could be critically evaluated to distill the facts and recognize and then remove outdated inaccurate information. With the support of the Cornea Society President (M.W.B.), international ophthalmologic societies were contacted representing 5 continents to recruit representation of corneal specialists, ophthalmic pathologists, and geneticists for this collaborative effort.

The International Committee for Classification of Corneal Dystrophies (IC3D) held its first meeting in Chicago in October 2005 at the American Academy of Ophthalmology, followed by meetings in San Paulo in February 2006 at the World Ophthalmology Congress, in Ft. Lauderdale in May 2006 at the Association for Research in Vision and Ophthalmology, in Las Vegas in October 2006 at the American
Academy of Ophthalmology, and in San Diego in April 2007 at the Association of Cataract and Refractive Surgeons. In between, thousands of e-mails provided online discussion to move the project forward.

CHARACTERISTICS OF THE NEW NOMENCLATURE

At the initial meeting, the group discussed the necessary characteristics of a new nomenclature that definitely would improve accuracy, would be more informative, and could be easy to use, so that it truly could replace the nomenclature that had been used for over a century—a gargantuan task, the successfulness of which only time will tell. The new nomenclature had to reflect current clinical, pathologic, and genetic knowledge, be easily adaptable to advances in understanding from the continued discovery of new genes and mutations and be linked to the old nomenclature for ease of use.

THE IC3D TEMPLATES

The development of a series of templates, which would assemble accurate and up-to-date information about each dystrophy and facilitate the development and maintenance of a revised nomenclature, was undertaken. Each dystrophy template was a brief summary of the current genetic, clinical, and pathologic information about the disease and included representative clinical images. This approach also offered the opportunity to correct errors in the literature and “set the record straight.” Published information was reviewed by all members of the committee, particularly those who had experience with a particular dystrophy. Although there were some dystrophies with which no member of the committee had personal experience, such dystrophies were exceedingly rare and sometimes had only 1 case report in the literature. The process, therefore, was found to be very effective.

CLASSIFICATION AND THE EVOLUTION OF A CORNEAL DYSTROPHY

The largest challenge to the committee was how to devise a classification that would be flexible enough to facilitate the expansion of knowledge from other sources, including genotyping. Evidence for the existence of a corneal dystrophy starts with the identification of a clinical phenotype and may proceed to the characterization of the causative gene mutation. When a corneal dystrophy is first described, there is usually a predictable chain of events. Initially, an entity is identified and characterized clinically. With corneal disorders that impair vision severely enough to warrant keratoplasty, tissue evaluations of the diseased cornea lead to the establishment of distinct clinicopathologic entities. Even in the absence of tissue evaluations, the next phase involves genetic linkage studies that lead to the mapping of the chromosomal locus of the disorder, especially if the condition has a simple Mendelian inheritance pattern. This task is much more tedious and time consuming when more than 1 gene is involved or if there is an interaction between genetic and environmental factors. Gene mapping is followed in due course by the identification of the relevant gene and particular mutations that are responsible for different phenotypical forms of the disorder. Eventually, identification of the gene product provides a better understanding of the mechanism of the disorder and may present some therapeutic possibilities.

To indicate the level of evidence supporting the existence of a given dystrophy, the IC3D committee developed a series of descriptive, evidential categories as follows:

Categories

Category 1: A well-defined corneal dystrophy in which the gene has been mapped and identified and specific mutations are known.
Category 2: A well-defined corneal dystrophy that has been mapped to 1 or more specific chromosomal loci, but the gene(s) remains to be identified.
Category 3: A well-defined corneal dystrophy in which the disorder has not yet been mapped to a chromosomal locus.
Category 4: This category is reserved for a suspected new, or previously documented, corneal dystrophy, although the evidence for it, being a distinct entity, is not yet convincing.

The category assigned to a specific corneal dystrophy can be expected to change over time as knowledge progressively advances. Eventually, all valid corneal dystrophies should attain the classification of category 1; macular corneal dystrophy is an example of a category 1 dystrophy. Conversely, over time and with further information, some entities that are category 4 may be shown not to be distinct entities and may be removed. For example, “Central Discoid Corneal Dystrophy”38 (CDCD), a category 4 dystrophy was found to be indistinguishable phenotypically from SCD sine crystals. Consequently, the IC3D committee further reviewed a case report of CDCD to determine whether this was a unique dystrophy or a variant of SCD. When the causative gene for SCD was found to be UBIAD1,39,40 genetic testing of the proband with CDCD could be performed. Interestingly, the CDCD proband did demonstrate a unique mutation in the UBIAD1 gene (personal correspondence J.S.W.), which was not found in 100 control individuals. With a mutation in the UBIAD1 gene and corneal histopathology, which demonstrated stromal vacuoles consistent with dissolved lipid, it seemed that CDCD was actually SCD. Consequently, this category 4 dystrophy was removed and CDCD was re-classified as SCD. This case clearly illustrates the importance and utility of the IC3D classification system. If an entity is initially categorized as a level 4 dystrophy, new information can be used to determine whether the entity is indeed new or unique or is perhaps a variant of a previously described disease.

THE NEW CLASSIFICATION SYSTEM

Our proposed corneal dystrophy classification system is anatomically based, with dystrophies classified according to the layer chiefly affected (www.corneasociety.org/ic3d). Thus, they are epithelial and subepithelial, Bowman layer, stromal and those affecting Descemet membrane and the endothelium. The majority of the dystrophy names are identical or similar to those in the current nomenclature. However, dystrophies with a known common genetic basis, that is, TGFBI dystrophies, have been grouped together.
THE IC3D CLASSIFICATION (C = CATEGORY)

Epithelial and Subepithelial Dystrophies

1. Epithelial and subepithelial dystrophies (EBMD) — majority degenerative, some C1
2. Epithelial recurrent erosion dystrophy (ERED) C4, (S摸索)landiensi variant) C3
3. Subepithelial mucinous corneal dystrophy (SMCD) C4
4. Mutation in keratin genes: Meesmann corneal dystrophy (MECD) C1
5. Lisch epithelial corneal dystrophy (LECD) C2
6. Gelatinous drop-like corneal dystrophy (GDLD) C1

Bowman Layer Dystrophies

1. Reis–Bücklers corneal dystrophy (RBCD) — Granular corneal dystrophy type 3 C1
2. Thiel–Behnke corneal dystrophy (TBCD) C1, potential variant C2
3. Grayson –Wilbrandt corneal dystrophy (GWCD) C4

Stromal Dystrophies

1. TGFB1 corneal dystrophies

A. Lattice corneal dystrophy
   a. Lattice corneal dystrophy, TGFB1 type (LCD): Classic lattice corneal dystrophy (LCD1) C1, variants (III, IIIA, I/IIIA, and IV) are C1
   b. Lattice corneal dystrophy, gelsolin type (LCD2) C1 (This is not a true corneal dystrophy but is included here for ease of differential diagnosis)

B. Granular corneal dystrophy C1
   a. Granular corneal dystrophy, type 1 (classic) (GCD1) C1
   b. Granular corneal dystrophy, type 2 (granular-lattice) (GCD2) C1
c. Granular corneal dystrophy, type 3 (RBCD) = Reis–Bücklers C1
2. Macular corneal dystrophy (MCD) C1
3. Schnyder corneal dystrophy (SCD) C1
4. Congenital stromal corneal dystrophy (CSCD) C1
5. Fleck corneal dystrophy (FCD) C1
6. Posterior amorphous corneal dystrophy (PACD) C3
7. Central cloudy dystrophy of François (CCDF) C4
8. Pre-Descemet corneal dystrophy (PDCD) C4

Descemet Membrane and Endothelial Dystrophies
1. Fuchs endothelial corneal dystrophy (FECD) C1, C2, or C3
2. Posterior polymorphous corneal dystrophy (PPCD) C1 or C2
3. Congenital hereditary endothelial dystrophy 1 (CHED1) C2
4. Congenital hereditary endothelial dystrophy 2 (CHED2) C1
5. X-linked endothelial corneal dystrophy (XECD) C2

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TABLE 1. The IC3D Classification—Abbreviations and MIM Number

<table>
<thead>
<tr>
<th>MIM Abbreviation</th>
<th>IC3D Abbreviation</th>
<th>MIM #</th>
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<tr>
<td>Epithelial basement membrane dystrophy</td>
<td>EBMD</td>
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<td>Epithelial recurrent erosion dystrophy</td>
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<td>GDLD, CDGDL</td>
<td>GDLD</td>
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<td>Thiel–Behnke CD</td>
<td>CDB2, CDTB</td>
<td>TBCD</td>
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<td>Grayson –Wilbrandt CD</td>
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CD, corneal dystrophy; MIM, Mendelian Inheritance in Man.
Transmission Electron Microscopy

Map: Thick epithelial basement membrane that extends into the epithelium as multilamellar, 2- to 6-nm-thick sheets.
Fingerprint line: Fine fibrillogranular substance in addition to basement membrane. The fibrils are about 17 nm in diameter and the granular material about 8 nm.
Dot: Intraepithelial pseudocyst contains degenerating cells with pyknotic nuclei and cytoplasmic debris.
Bleb pattern: The anterior surface of this material forms discrete mounds, which dent the overlying basal epithelial cells. May mimic cysts clinically but no cysts present histologically.

Confocal Microscopy


Category
Most cases are sporadic and may be degenerative. Category 1 in a minority of cases.

REFERENCES

Epithelial Recurrent Erosion Dystrophy (ERED)
MIM #122400

Alternative Names, Eponyms
Corneal erosions, recurring hereditary (Franceschetti).

Variants
Dystrophia Smolandiensis.

Inheritance
Autosomal dominant.

Genetic Locus
Unknown.

Gene
Unknown; COL8A2, TGFBI, GSN, KRT3 and KRT12 excluded in Smolandiensis variant.

Onset
First decade of life.

Signs (Fig. 2)
Recurrent corneal erosions appear typically at 4–6 years of age but occasionally as early as 8 months of age. They are...
precipitated by minimal trauma or are spontaneous. The cornea may show subepithelial haze or blebs between attacks. In the Smolandiensis variant, half of the patients develop single to a few permanent central subepithelial corneal opacities, which appear at as early as 7 years of age. These vary from subepithelial fibrosis to protruding keloid-like nodules.

**Symptoms**

Most patients have attacks of redness, photophobia, epiphora, and ocular pain. Some experience a burning sensation and report sensitive eyes for years. Exposure to sunlight or draught, dust and smoke and lack of sleep can precipitate attacks. In the Smolandiensis variant, a quarter of patients eventually need corneal grafts at mean age of 44 years. The opacities recur within 15 months in the graft periphery, but the central graft can remain clear for many years.

**Course**

Attacks generally decline in frequency and intensity and cease by the age of 50 years. In the Smolandiensis variant, central subepithelial opacities will progress.

**Light Microscopy**

No changes consistent with either EBMD or known dystrophy of Bowman layer are reported for the Smolandiensis variant.

**Transmission Electron Microscopy**

Not reported.

**Confocal Microscopy**

Not reported.

**Category**

4, 3 (Smolandiensis variant).

**REFERENCES**


**Subepithelial Mucinous Corneal Dystrophy (SMCD)**

**MIM**: None.

**Alternative Names, Eponyms**

None.

**Inheritance**

Autosomal dominant.

**Genetic Locus**

Unknown.

**Gene**

Unknown.

**Onset**

First decade of life.

**Signs (Fig. 3)**

Bilateral subepithelial opacities and haze, most dense centrally, involving the entire cornea.

**Symptoms**

Painful episodes of recurrent corneal erosions, which decrease during adolescence (only 1 publication of a single family).

**Course**

Progressive loss of vision in adolescence.

**Light Microscopy**

Subepithelial band of eosinophilic, periodic acid–Schiff–positive, Alcian blue–positive, hyaluronidase-sensitive material is present anterior to Bowman layer.

**Transmission Electron Microscopy**

Subepithelial deposits of fine fibrillar material.

**Immunohistochemistry**

Combination of chondroitin-4-sulfate and dermatan sulfate.

**Confocal Microscopy**

Not reported.

**Category**

4.

**REFERENCES**


**Mutations in Keratin Genes: Meesmann Corneal Dystrophy (MECD)**

**MIM**: #122100

**Alternative Names, Eponyms**

Juvenile hereditary epithelial dystrophy.
Variant
Stocker–Holt variant.

Inheritance
Autosomal dominant.

Genetic Loci
Locus 12q13 (KRT3).
Locus 17q12 (KRT12) Stocker–Holt variant.

Genes
Keratin K3 (KRT3).
Keratin K12 (KRT12) Stocker–Holt variant.

Onset
Early childhood.

Signs (Fig. 4)
Multiple, tiny epithelial vesicles extend to the limbus and are most numerous in the interpalpebral area with clear surrounding epithelium. Whorled and wedge-shaped epithelial patterns have been reported. The cornea may be slightly thinned and corneal sensation may be reduced.

Indirect illumination shows varying diffuse gray opacities in different patterns, which may have a distinct border. Areas of the central or peripheral cornea may be unaffected. The gray opacities appear as transparent cysts on indirect illumination. Coalescence of several cysts may result in refractile linear opacities with intervening clear cornea.

Stocker–Holt Variant
The entire cornea demonstrates fine, grayish punctate epithelial opacities that stain with fluorescein and fine linear opacities that may appear in a whorl pattern.

Course
Slowly progressive.

Symptoms
Patients are typically asymptomatic or may have mild visual reduction, although some patients complain of glare and light sensitivity. Recurrent painful punctiform epithelial erosions may occur. Rarely, blurred vision results from corneal irregularity and scarring.

Stocker–Holt Variant
Patients demonstrate more severe signs and symptoms with earlier onset compared with classic Meesmann corneal dystrophy.

Light Microscopy
The epithelium always demonstrates intraepithelial cysts. Cysts are filled with periodic acid–Schiff–positive cellular debris, which fluoresces. The epithelium may be thickened and disorganized. Thickened multilaminar basement membrane with projections into the basal epithelium.

Stocker–Holt Variant

Transmission Electron Microscopy
Intracytoplasmic “peculiar substance” represents a focal collection of fibrogranular material surrounded by tangles of cytoplasmic filaments. Cystic round and well-delineated lesions (10–50 μm across). Some lesions with reflective points in the cytoplasm probably correspond to cell nuclei.

Stocker–Holt Variant
Not reported.

Confocal Microscopy
Hyporeflective areas in the basal epithelium ranging from 40 to 150 μm in diameter, with potential reflective spots inside.

Stocker–Holt Variant
Not reported.

Category
1, including Stocker–Holt Variant

FIGURE 4. Meesmann corneal dystrophy. A, Multiple solitary microcysts that are most prominent in the interpalpebral region are seen in retroillumination. B, Diffuse gray opacity with broad oblique illumination, and multiple solitary microcysts in retroillumination.
REFERENCES


Lisch Epithelial Corneal Dystrophy (LECD)

MIM: None.

**Genetic locus**

Xp 22.3.

**Gene**

Unknown.

**Alternative Names, Eponyms**

Band-shaped and whorled microcystic dystrophy of the corneal epithelium.

**Inheritance**

X-chromosomal dominant.

**Onset**

Childhood.

**Signs (Fig. 5)**

Direct illumination shows localized gray opacities in different patterns: whorl-like, radial, band shaped, flame/feathery shaped, and club shaped. Indirect illumination demonstrates multiple, densely crowded clear cysts. The surrounding epithelium is clear. Similar degree of opacities observed in men and women.

**Symptoms**

Asymptomatic or blurred vision if the pupillary zone is involved.

**Course**

Slow progression of opacities with possible deterioration in vision.

**Light Microscopy**

Diffuse cytoplasmic vacuolization of all cells in the affected area.

**Transmission Electron Microscopy**

Extensive vacuolization of the cytoplasm of the affected corneal epithelium. The vacuoles are either optically empty or contain weakly osmiophilic, partly homogenous, and partly lamellar material eventually due to collapsing and coalescing of vacuoles.

**Immunohistochemistry**

Scattered staining on Ki67 immunohistochemistry indicates no evidence of increased mitotic activity.

**Confocal Microscopy**

Many solitary dark and well-demarcated lesions (50–100 μm) with round and oval configuration. Some lesions demonstrate central reflective points, which probably correspond to the cell nuclei.

**Category**

2.

REFERENCES


Gelatinous Drop-Like Corneal Dystrophy (GDLD)
MIM #204870.

Alternative Names, Eponyms
- Subepithelial amyloidosis.
- Primary familial amyloidosis (Grayson).

Genetic Locus
1p32.

Gene
- Tumor-associated calcium signal transducer 2 (TACSTD2, previously M1S1).

Inheritance
- Autosomal recessive.

Onset
- First to second decade.

Signs (Fig. 6)
Initially, the subepithelial lesions may appear similar to band-shaped keratopathy or there may be groups of small multiple nodules, that is, mulberry configuration. These lesions demonstrate late staining with fluorescein, indicating extremely hyperpermeable corneal epithelium. Superficial vascularization is frequently seen. In later life, patients may also develop stromal opacification or develop larger nodular lesions, that is, kumquat-like lesions.

Symptoms
- Significant decrease in vision, photophobia, irritation, redness, and tearing.

Course
- Progression of protruding subepithelial deposits and stromal opacity. Almost all patients develop recurrence after superficial keratectomy, lamellar keratoplasty, or penetrating keratoplasty, typically within a few years.

Light Microscopy
- Subepithelial and stromal amyloid deposits.

Transmission Electron Microscopy
- Disruption of epithelial tight junctions in the superficial epithelium. Amyloid is noted in the basal epithelial layer.

Confocal Microscopy
- Not reported.

REFERENCES

BOWMAN LAYER DYSTROPHIES

Reis–Bücklers Corneal Dystrophy (RBCD)
MIM #608470

Alternative Names, Eponyms
- Corneal Dystrophy of Bowman layer, type I (CDB I).
- Geographic corneal dystrophy (Weidle).
- Superficial granular corneal dystrophy.
- Atypical granular corneal dystrophy.
- Granular corneal dystrophy, type 3.
- Anterior limiting membrane dystrophy, type I (ALMD I).

Genetic Locus
- 5q31.

Gene
- TGFBI.

Inheritance
- Autosomal dominant.

Onset
- Childhood.

Signs (Fig. 7)
Confluent irregular and coarse geographic-like opacities with varying densities develop at the level of Bowman layer and superficial stroma, initially separated from one another. Opacities may extend to the limbus and deeper stroma with time. Can be confused with TBCD.

Symptoms
Vision is impaired from childhood. Recurrent corneal erosions cause ocular discomfort and pain in the first decade but may become less severe from the end of the second decade. Erosions are typically more frequent and severe than in TBCD.

Course
Slowly progressive deterioration of vision. Recurrent corneal erosions may resolve with time. Similar but frequently more aggressive course than TBCD but may not be able to distinguish in an individual case.

Light Microscopy
Bowman layer is replaced by a sheet-like connective tissue layer with granular Masson trichrome–red deposits, which in advanced cases can extend to subepithelial stroma.

Transmission Electron Microscopy
Subepithelial electron-dense, rod-shaped bodies identical to those in GCD1, but not the curly fibers of TBCD, are observed on electron microscopy. Electron microscopy is necessary for definitive histopathologic diagnosis to distinguish from TBCD.

Confocal Microscopy
Distinct deposits are found in the epithelium and Bowman layer. The deposits in the basal epithelial cell layer show extremely high reflectivity from small granular material without any shadows. Bowman layer is replaced by highly reflective irregular material, even more reflective than in TBCD (5q31). Fine diffuse deposits may be noted in the anterior stroma.

Immunohistochemistry
Rod-shaped bodies are immunopositive for transforming growth factor beta–induced protein (keratoepithelin).

Category
1.

REFERENCES

Thiel–Behnke Corneal Dystrophy (TBCD)
MIM #602082

Alternative Names, Eponyms
Corneal dystrophy of Bowman layer, type II (CDB2). Honeycomb-shaped corneal dystrophy.
Anterior limiting membrane dystrophy, type II.
Curly fibers corneal dystrophy.
Waardenburg–Jonkers corneal dystrophy.

Genetic Loci
5q31. 10q24.

Gene
5q31: TGFBI. 10q24: Unknown.

Inheritance
Autosomal dominant.

Onset
Childhood.

Signs (Fig. 8)
Symmetrical subepithelial reticular (honeycomb) opacities with peripheral cornea typically uninvolved. Variety of opacification patterns may make it impossible to distinguish from RBCD in early or individual cases. Opacities can progress to deep stromal layers and corneal periphery.

Symptoms
Recurrent corneal erosions cause ocular discomfort and pain in the first and second decade. Gradual visual impairment develops later. Erosions are less frequent, and the onset of visual impairment is later than in RBCD.

Course
Slowly progressive deterioration of vision from increasing corneal opacification. Recurrent corneal erosions may resolve with time. Similar but frequently less aggressive course than RBCD but may not be able to distinguish in an individual case.

Light Microscopy
Irregular thickening of the epithelial layer to allow for ridges and furrows of underlying stroma, with focal absences of epithelial basement membrane. Bowman layer is replaced by a fibrocellular layer between epithelium and stroma with a pathognomonic wavy saw-toothed pattern.

Transmission Electron Microscopy
Presence of curly collagen fibers with a diameter of 9–15 nm is pathognomonic and distinguishes this dystrophy from RBCD.

Confocal Microscopy
Distinct deposits are found in the epithelium and Bowman layer. The deposits in the basal epithelial cell layer show homogeneous reflectivity with round edges accompanying dark shadows. Bowman layer is replaced with reflective irregular material that is less reflective than in RBCD.

Immunohistochemistry
Curly fibers are immunopositive for transforming growth factor beta–induced protein (keratoepithelin) in TBCD (5q31).


REFERENCES

Grayson–Wilbrandt Corneal Dystrophy (GWCD)
MIM: None.

Alternative Names, Eponyms
None.

Genetic Locus
Unknown.

Gene
Unknown.

Inheritance
Autosomal dominant.

Onset
First to second decade.
Signs (Fig. 9)

Bowman layer demonstrates variable patterns of opacification from diffuse mottling to diffuse gray-white opacities, which extend anteriorly into the epithelium. The cornea between the deposits is clear. Refractile bodies are described in corneal stroma.

Symptoms

Decreased to normal visual acuity. Recurrent corneal erosions are less severe than in RBCD and TBCD.

Course

Progressive.

Light Microscopy

Homogeneous eosin-staining material between Bowman layer and the epithelium, which does not stain with Alcian blue or Masson trichrome stains but is positive for Periodic acid–Schiff.

Transmission Electron Microscopy

Not reported.

Confocal Microscopy

Not reported.

Category

4.

Note: There is only 1 publication describing a single family. The report does not allow definitive diagnosis or exclusion of the theory that this dystrophy may have been a dystrophy of Bowman layer or a variant of EBMD.

REFERENCES


STROMAL DYSTROPHIES

TGFBI Dystrophies

Lattice Corneal Dystrophy, TGFBI Type (LCD): Classic Lattice Corneal Dystrophy (LCD1) and Variants

MIM #122200.

Alternative Names, Eponyms

Classic LCD.

LCD, type 1.

Biber-Haab-Dimmer.

Genetic Locus

5q31.

Gene

TGFBI

Inheritance

Autosomal dominant.

Onset

First decade.

Signs (Fig. 10)

Thin branching refractile lines and/or subepithelial, whitish, ovoid dots usually appear by the end of the first decade. The lines start centrally and more superficially, spreading centrifugally and deeply, but leaving the peripheral 1 mm, and Descemet membrane and endothelium clear. A diffuse stromal, ground-glass haze usually develops later, accompanied by recurrent erosions. The number of lattice lines may differ between the 2 eyes (unilateral cases are described), and the dystrophy may be difficult to diagnose in some younger patients.

Symptoms

Ocular discomfort, pain, and visual impairment, sometimes starting as early as in the first decade of life. Recurrent erosions are frequent. Visual impairment within the fourth decade.

Course

Progressive, often leading to keratoplasty within the fourth decade of life.

Light Microscopy

Epithelial atrophy and disruption with degeneration of basal epithelial cells; focal thinning or absence of Bowman layer, progressively increasing with age; eosinophilic layer between epithelial basement membrane and Bowman layer; and stromal deposition of amyloid substance distorts the architecture of corneal lamellae. Amyloid deposits have characteristic staining. Deposits stain positive with Congo red. Green birefringence is visible with a polarizing filter and...
red-green dichromiasis when a green filter is added with this stain. Metachromasia is noted with crystal violet and fluorescence is noted with use of thioflavin T staining.

**Transmission Electron Microscopy**

Extracellular masses of fine, electron-dense, randomly aligned fibrils with a diameter of 8–10 nm. There are fewer keratocytes in the areas of amyloid deposition: Some are degenerated with cytoplasmic vacuolization, whereas others appear metabolically active. Descemet membrane and endothelium are normal.

**Confocal Microscopy**

Linear and branching structures in the stroma with changing reflectivity and poorly demarcated margins. Lines must be differentiated from other similar images (ie, fungi).

**Category**

1. Note: Historically, multiple subtypes of lattice were created on the basis of phenotypic and genotypic variations. The LCD variants are caused by more than 2 dozen distinct heterozygous amyloidogenic mutations, nearly all of which are located in the fourth FAS1 domain of TGFBI. LCD variants (type IIIA, I/IIIA, IV, and polymorphic amyloidosis) have a delayed onset compared with classic LCD (LCD, type 1). The lattice lines may be larger, with a limbis to limbus ropy appearance (type IIIA), thinner (type I/IIIA), or even absent (polymorphic amyloidosis), although one has to keep in mind that the lattice pattern is very much dependent on age. Corneal erosions are a typical presenting sign of LCD, type IIIA and I/IIIA, but are virtually absent in LCD, type IV and polymorphic corneal amyloidosis. This erosive semiology likely reflects the anterior to posterior (type IIIA and I/IIIA) or posterior to anterior (type IV) progression of the dystrophy.

**REFERENCES**

Lattice Corneal Dystrophy, Gelsolin Type (LCD2) (see note below)
MIM #105120

Genetic Locus
9q34.

Gene
Gelsolin GSN (See note below).

Alternative Names, Eponyms
Part of
Familial amyloidosis, Finnish (FAF).
Meretoja syndrome.
Amyloidosis V.
Familial amyloidotic polyneuropathy IV (FAP-IV).

Inheritance
Autosomal dominant.

Onset
Third to fourth decade.

Signs (Fig. 11)
Lattice lines, more peripheral and less numerous than those of lattice dystrophy, type I, appear in the corneal stroma, spreading centripetally from the limbus. The central cornea is relatively spared. Pronounced dermatochalasis is typical and lagophthalmos common later in life. Risk of open angle glaucoma may be increased.

Systemic signs
Cranial neuropathy, manifesting as facial paresis, bulbar palsy, and laxity of the facial skin. Gradual onset of facial drooping, causing eyebrows to fall over eyes, lagophthalmos, drooping of lower lip with drooling. Peripheral polyneuropathy affects mainly senses of vibration and touch. Carpal tunnel syndrome. Autonomic disturbance includes orthostatic hypotension, cardiac conduction abnormalities, and dysfunction of perspiration.

Symptoms
Ocular: Corneal sensitivity is reduced or absent. Visual acuity is usually normal until the sixth decade because the dystrophy progresses from the peripheral to central cornea. Dry eye symptoms are frequent, and corneal erosions may occur late in life.

Course
Slowly progressive, the majority are in good health still in the seventh decade.

Variant
In rare homozygotes, the systemic component is severe, manifesting with nephrotic syndrome and renal failure from heavy glomerular amyloid deposits.

Light Microscopy
Amyloid is deposited in the cornea in lattice lines, as a discontinuous band under Bowman layer and within the sclera. Streak-like deposits are seen between corneal lamellae, especially in the limbal cornea.

Immunohistochemistry
Deposition of mutated gelsolin is detected in the conjunctiva, in the sclera, in the stroma of the ciliary body, along the choriocapillaris, in the perineurium of ciliary nerves, in the walls of ciliary vessels, and in the optic nerve. Extraocularly, amyloid is found in arterial walls, peripheral nerves and glomeruli.
Confocal Microscopy

Prominent deposits, presumably amyloid, are seen contiguous to basal epithelial cells and stromal nerves. In severely affected corneas, sub-basal and stromal nerves are reduced or absent. Anterior stroma shows fibrosis and abnormal extracellular matrix. Thick anterior and midstromal filaments corresponding to lattice lines and thin undulating structures are visible.

Category

1.

Note: This is not a true corneal dystrophy but is listed here because it can be confused with true lattice dystrophies, which in turn may delay diagnosis of the underlying systemic amyloidosis for many years, especially in populations in which this type of familial amyloidosis is rare.

REFERENCES


Granular Corneal Dystrophy, Type 1 (Classic) (GCD1)

MIM #121900.

Alternative Names, Eponyms

Corneal dystrophy Groenouw type I.

Genetic Locus

5q31.

Gene

TGFBI

Inheritance

Autosomal dominant.

Onset

Childhood, may be seen as early as 2 years of age.

Signs (Fig. 12)

Slit lamp examination reveals well-defined granules that appear white on direct illumination. On retroillumination, these granules are composed of extremely small, translucent dots with the appearance of vacuoles, glassy splinters, or crushed bread crumbs. Opacities do not extend to the limbus. In children, there may be a vortex pattern of brownish granules superficial to Bowman layer. In later life, granules may extend into the deeper stroma down to Descemet membrane. Homozygotes have more severe manifestations.

Symptoms

Glare and photophobia are early symptoms. Visual acuity decreases as opacification progresses with age. Recurrent erosions are seen frequently. Homozygote has more severe symptoms.

Course

As the condition progresses, the opacities become more confluent in the superficial cornea, resulting in a significant reduction of visual acuity.

Light Microscopy

Multiple stromal deposits may extend from deep epithelium to Descemet membrane. The hyaline opacities stain with Masson trichrome.

Transmission Electron Microscopy

Rod-shaped bodies are found, which are similar in appearance to those in RBCD.

Immunohistochemistry

Abnormal deposits react with antibodies to transforming growth factor beta–induced protein (keratoepithelin).

Confocal Microscopy

Hyper-reflective opacities.

Category

1.

REFERENCES


Granular Corneal Dystrophy, Type 2 (Granular-Lattice) (GCD2)
MIM #607541.

Alternative Names, Eponyms

For close to 100 years, this entity was considered a mild variety of granular corneal dystrophy (Groenouw type I). Bücklers, as early as 1938, described a large family with illustrative pictures of this phenotype. Fifty years later, Weidle published the same patients and subdivided granular dystrophy according to subtle differences of clinical appearance. In 1988, Folberg et al described the histopathology of deposition of both amyloid and hyaline deposits in these patients. In 1992, the clinical findings of these patients were published. The combined granular corneal dystrophy—LCD was now called Avellino dystrophy. Avellino, which is the Italian district of the progenitor of the pedigree, became the popular name that appears in most modern textbooks to describe the granular-lattice findings.

Genetic Locus
5q31.

Gene
TGFBI

Inheritance
Autosomal dominant.

Onset
Homozygous patients have earlier onset with dystrophy diagnosed, as early as 3 years of age, compared with heterozygote patients, who may be diagnosed as early as the age of 8 years. Most often, GCD2 is diagnosed during teens or during early adulthood.

Signs (Fig. 13)
Initial slit lamp signs are subtle superficial stromal tiny whitish dots. In the next stage, rings or stellate-shaped...
snowflake stromal opacities appear between the superficial stroma and the mid stroma. Some patients may also demonstrate lattice lines in deeper cornea. Typically, these lines are located deeper than the snowflake stromal opacity. In the final stage, there is a more superficial, translucent flattened breadcrumb opacity, which may coalesce in the anterior stroma. Some patients only manifest multiple white dots. Patients with GCD2 have fewer opacities than those with GCD1. Homozygote patients initially demonstrate numerous small dots in the superficial cornea in early childhood. By adulthood, there are larger, very dense subepithelial irregularly shaped opacities, which may become deeper with time.

**Symptoms**
Vision decreases with age as the central visual axis becomes affected. Pain may accompany mild corneal erosions.

**Course**
Slowly progressive. Homozygotes demonstrate more rapid progression.

**Light Microscopy**
Corneal opacities extend from the basal epithelium to the deep stroma. Although there is deposition of both typical GCD1 deposits and amyloid; individual opacities stain with either Masson trichrome or Congo red. Homozygotes demonstrate more severe findings.

**Transmission Electron Microscopy**
Anterior stromal rod-shaped, very electron-dense deposits are similar to the deposits noted in GCD1. On higher magnification, the rod-shaped deposit is composed of extracellular masses of fine, electron-dense, highly aligned fibrils.
An extremely common ultrastructural finding is the presence of randomly aligned fibrils of amyloid (see LCD template).
Homozygotes demonstrate more severe findings.

**Confocal Microscopy**
Findings are a combination of GCD1 and LCD. Reflective, breadcrumb-like round deposits with well-delineated borders or highly reflective, irregular trapezoidal deposits are present in the anterior stroma (similar to GCD1). Linear and branching deposits with changing reflectivity are observed (similar to LCD).

**Category**
1. Note: Injury to the central cornea results in exacerbation of the corneal dystrophy with increased opacification. LASIK is contraindicated in this dystrophy.

**REFERENCES**

**Macular Corneal Dystrophy (MCD)**
MIM #217800.

**Alternative Names, Eponyms**
Groenouw corneal dystrophy type II. Fehr spotted dystrophy.

**Genetic Locus**
16q22.

**Gene**
Carbohydrate sulfotransferase 6 gene—*CHST6*.

**Inheritance**
Autosomal recessive.

**Onset**
Childhood.

**Signs (Fig. 14)**
Initially, diffuse stromal haze extending to the limbus; later, superficial, central, elevated, irregular whitish opacities (macules) develop and give the condition its name. Unlike granular dystrophy, there are no clear areas between corneal opacities. There are also more posterior peripheral white lesions. The cornea is thinner than normal in early disease. In the advanced stage, the corneal endothelium is affected and Descemet membrane develops guttate excrescences. In addition, the stroma thickens from the inhibition of water from endothelial decompensation.

**Symptoms**
Severe visual impairment occurs between 10 and 30 years of age. Reduction of corneal sensitivity. Photophobia. Painful attacks can sometimes occur due to recurrent erosions.

**Course**
Slowly progressive.

**Light Microscopy**
Glycosaminoglycans (GAGs) accumulate intracellularly and extracellularly in the corneal stroma, corneal endothelium,
and Descemet membrane (stain positively with Hale colloidal iron or Alcian blue). Guttae are commonly present on Descemet membrane.

Transmission Electron Microscopy
Keratocytes and endothelial cells stain positively for GAGs and contain vacuoles and lamellar bodies. The extracellular matrix contains clumps of fibrillogranular material that stain positively for GAGs.

Confocal Microscopy
Blurred limited accumulations of light reflective material are located in the anterior part of the corneal stroma.

Additional Findings
There are 3 variants of macular corneal dystrophy, which are based on the immunoreactivity of the macular deposits. These variants are indistinguishable from each other clinically.
The immunophenotype of macular corneal dystrophy determines the reactivity of the abnormal deposits with an antibody that is specific for the sulfated epitopes on antigenic keratan sulfate (AgKS).
The serum AgKS correlates with the immunophenotypes in the corneal tissue.
Macular corneal dystrophy type I: No AgKS reactivity in the cornea or in the serum.
Macular corneal dystrophy type IA: Keratocytes manifest AgKS reactivity but the extracellular material does not. Serum lacks AgKS.
Macular corneal dystrophy type II: All the abnormal accumulations react positively with AgKS and the serum has normal or lower levels of AgKS.

Category
1.

REFERENCES

Schnyder Corneal Dystrophy (SCD)
MIM #21800.

Alternative Names, Eponyms
Schnyder crystalline corneal dystrophy (SCCD).
Schnyder crystalline dystrophy sine crystals.
Hereditary crystalline stromal dystrophy of Schnyder.
Crystalline stromal dystrophy.
Central stromal crystalline corneal dystrophy.
Corneal crystalline dystrophy of Schnyder.
Schnyder corneal crystalline dystrophy.

Genetic Locus
1p36.

Gene
UbiA prenyltransferase domain containing 1—UBIAD1.

Inheritance
Autosomal dominant.

Onset
Maybe as early as childhood, but diagnosis usually made by the second or third decade. Diagnosis may be further delayed in patients who have the acrystalline form of the disease.

Signs (Fig. 15)
Corneal changes are predictable on the basis of age. Patients aged 23 years or younger have central corneal haze and/or subepithelial crystals. Between 23 and 38 years of age, arcus lipoides is noted. After age 38, mid-peripheral panstromal haze develops causing the entire cornea to appear hazy. Despite the name, only 50% of patients demonstrate
corneal crystals. Crystals may be unilateral, may rarely regress, and can occur late in the disease.

**Symptoms**

Visual acuity decreases with age. Complaints of glare increase with age. Although scotopic vision may be remarkably good (considering the slit lamp appearance), photopic vision may be disproportionately decreased. Corneal sensation decreases with age. Both affected and unaffected members of the pedigrees may have hyperlipoproteinemia (type IIa, III, or IV).

**Course**

Slowly progressive, although majority of patients older than 50 years may require keratoplasty for decreased photopic vision.

**Light Microscopy**

Abnormal deposition of intra- and extracellular esterified and unesterified phospholipids and cholesterol in basal epithelial cells, Bowman layer, and stroma. Organic solvents and resins can dissolve lipids. Consequently, to process the corneal specimen to allow special lipid stains such as oil red O or Sudan black to be performed, the ophthalmologist should inform the pathologist before placing corneal specimen in fixative that lipid stains are requested.

**Transmission Electron Microscopy**

Abnormal accumulation of intracellular and extracellular highly reflective deposits are deposited in epithelium, in Bowman layer, and throughout the stroma. Endothelial lipid has rarely been reported.

**Confocal Microscopy**

Intracellular and extracellular highly reflective deposits may lead to eventual disruption of the basal epithelial/subepithelial nerve plexus.

**Category**

1.

Note: Although Schnyder crystalline corneal dystrophy has been the more commonly used name for this entity, this name has led to confusion in diagnosis because only 50% of the patients have crystals. Consequently, the name Schnyder corneal dystrophy should be the preferred name. If the ophthalmologist does not suspect Schnyder corneal dystrophy when performing penetrating keratoplasty, the opportunity to perform lipid stains may be lost if the corneal specimen is not preserved correctly and lipid is dissolved. In addition, there has been 1 published report of positive Congo red staining, suggesting amyloid deposition in a corneal specimen from a patient with Schnyder corneal dystrophy. More recently, a patient with an entity previously called central discoid corneal dystrophy was found to have a mutation in the **UBIAD1** gene, which causes Schnyder corneal dystrophy. Although the corneal pathology demonstrated GAGs, the phenotype was identical to Schnyder corneal dystrophy sine crystals and the genotype demonstrated the **UBIAD1** mutation, and there was autosomal dominant inheritance. The entity called central
discoid corneal dystrophy is actually Schnyder corneal dystrophy, although GAGs were found on histopathology.

REFERENCES


Congenital Stromal Corneal Dystrophy (CSCD)

MIM #610048.

Alternative Names, Eponyms
Congenital hereditary stromal dystrophy.
Congenital stromal dystrophy of the cornea.

Genetic Locus
12q21.33.

Gene
Decorin—DCN.

Inheritance
Autosomal dominant.

Onset
Congenital.

Signs (Fig. 16)
Diffuse, bilateral, corneal clouding with flake-like, whitish stromal opacities throughout the stroma. The changes are equally pronounced in all areas of the cornea. There are no signs of vascularization or staining with fluorescein. Pachymetry demonstrates increased thickness.

Symptoms
Moderate to severe visual loss.

Course
Nonprogressive or slowly progressive.

Light Microscopy
The stromal lamellae are separated from each other in a regular manner, may have areas of deposition of amorphous material.

Transmission Electron Microscopy
Abnormal lamellar layers consisting of thin filaments randomly arranged in an electron-lucent ground substance separate lamellae of normal appearance. The changes can be seen at all levels of the stroma. The collagen fibril diameter in all lamellae is roughly half that of normal collagen fibrils. The abnormal layers are broader in the posterior stroma. The keratocytes and endothelium are normal, although absence of the anterior banded zone of Descemet membrane has been reported.

Confocal Microscopy
Epithelial cells appear normal. Increased reflectivity from the anterior stroma prevents further studies.

Category
1.

REFERENCES


**Fleck Corneal Dystrophy (FCD)**

MIM #121850.

**Alternative Names, Eponyms**

François-Neetens speckled corneal dystrophy.

**Gene Locus**

2q35.

**Gene**

Phosphatidylinositol-3-phosphate/phosphatidylinositol 5-Kinase type III—**PIP5K3**.

**Inheritance**

Autosomal dominant.

**Onset**

Congenital.

**Signs (Fig. 17)**

Distinctive appearance, with “small, translucent, discoid opacities” or “discrete, flat, gray-white, dandruff-like (sometimes ring-shaped)” opacities scattered sparsely throughout any level of the otherwise clear stroma. Flecks may be present up to the limbus. Epithelium, Bowman layer, Descemet membrane, and the endothelium are not involved. There may be asymmetric or unilateral corneal involvement.

**Symptoms**

Asymptomatic.

**Course**

Nonprogressive.

**Light Microscopy**

Swollen, vacuolated keratocytes, which contain GAG and complex lipids (excess GAG stains with Alcian blue and colloidal iron; lipids are demonstrated by Sudan black and oil red O).

**Transmission Electron Microscopy**

Some keratocytes show membrane-based inclusions with delicate granular material.

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**FIGURE 17.** Fleck corneal dystrophy: Dandruff-like opacities seen in 2 different patients throughout the stroma using (A) broad oblique illumination and indirect illumination, and (B) at varying depths in the slit-lamp photograph.
Confocal Microscopy
Accumulation of pathologic material in stromal cells and inclusions in the basal nerves.

Category
1.

REFERENCES

Posterior Amorphous Corneal Dystrophy (PACD)
MIM: None.

Alternative Names, Eponyms
Posterior amorphous stromal dystrophy.

Gene
Unknown.

Inheritance
Autosomal dominant.

Onset
Often occurs in the first decade of life; it has been noted as early as 16 weeks, suggesting a congenital nature.

Signs (Fig. 18)
PACD presents as diffuse gray-white, sheet-like opacities that can involve any layer of the stroma but are most prominent posteriorly. The lesions can be centroperipheral, extending to the limbus, or peripheral, the latter with less pronounced findings and symptoms. There are often transparent stromal breaks in the opacification. Corneal thinning to as low as 380 μm, a flattened corneal topography (≤41.00 D) and hyperopia are present particularly in the centroperipheral form. Descemet membrane and endothelium may be indented by the opacities and focal endothelial abnormalities have been observed. Prominent Schwalbe line, fine iris processes, pupillary remnants, iridocorneal adhesions, corectopia, pseudopolycoria, and anterior stromal tags have been reported, particularly in patients with a centroperipheral pattern. No association with glaucoma is noted.

Symptoms
The visual acuity is mildly affected, usually better than 20/40.

Course
None or slowly progressive. Usually no treatment is needed, although sometimes penetrating keratoplasty is required.

Light Microscopy
Irregular stromal architecture just anterior to a thin Descemet membrane and focal attenuation of endothelial cells.

Transmission Electron Microscopy
There are abnormally oriented collagen fibers and abnormal keratocytes with disorganization of the posterior stromal lamellae. A fibrillar layer resembling stromal collagen fibers interrupts Descemet membrane. These findings are not pathognomonic of this dystrophy and may be found in other abnormalities. In a patient with more pronounced changes, additional subepithelial deposits and a thick collagenous layer posterior to Descemet membrane were present.

Confocal Microscopy
Microfolds and a hyper-reflective layer in the posterior stroma are present.

Category
3.

Note: The possible congenital onset, lack of progression, and association with iris abnormalities have raised the question whether this may in fact be a mesodermal dysgenesis rather than a corneal dystrophy.

REFERENCES


Central Cloudy Dystrophy of François (CCDF)

MIM: #217600.

*Alternative Names, Eponyms*
None.

*Gene/Genetic Locus*
None.

*Inheritance*
Unknown. Autosomal dominant inheritance is reported in a few articles describing the entity. This entity may be phenotypically indistinguishable from posterior crocodile shagreen, which is a corneal degeneration.

*Onset*
First decade (youngest affected patient was 8 years old).

*Signs (Fig. 19)*
Fortuitous finding of cloudy central polygonal or rounded stromal opacities that fade anteriorly and peripherally and are surrounded by clear tissue. The changes are very similar to Vogt posterior crocodile shagreen.

*Symptoms*
Mostly asymptomatic.

*Course*
Nonprogressive.

*Light Microscopy*
No description in familial cases. Faint undulating appearance of the deep stroma and positive staining for GAGs.

*Transmission Electron Microscopy*
No description in familial cases. One publication described an elderly patient with no familial history. Corneal pathology revealed extracellular vacuoles, some of which contained fibrillogranular material and electron-dense deposits. Endothelial vacuoles with fibrillogranular material. A saw-toothed lamellar pattern has been reported.

FIGURE 19. Central cloudy dystrophy of François. A, Axially distributed, polygonal gray-white stromal opacities separated by linear areas of clear cornea. B, Broad beam slit lamp photograph demonstrating central stromal opacities with linear clear areas and “cracked ice” appearance.

Confocal Microscopy
No description in familial cases. In 2 unrelated patients, there were small highly refractile granules and deposits in the anterior stroma. Multiple dark striae in the extracellular matrix with increased intensity in the posterior stroma, which is adjacent to the corneal endothelial layer.

*Category*
4.

Note: Many of the publications referenced did not provide documentation that the corneal disease was familial. Consequently, it is entirely possible that these cases of CCDF were actually posterior crocodile shagreen.

**REFERENCES**


Pre-Descemet Corneal Dystrophy (PDCD)

MIM: None.

*Alternative Names, Eponyms*
None.

*Gene*
Unknown.

*Inheritance*
Pre-Descemet dystrophy is not a well-defined entity. Although there is no definite pattern of inheritance, it has been described in families over 2–4 generations. The subtype punctiform and polychromatic pre-Descemet dystrophy...
reported to be autosomal dominant in 1 pedigree may represent a specific dystrophy.

**Onset**

Usually after 30 years of age but has been found in children as young as 3 years (punctiform and polychromatic pre-Descemet dystrophy).

**Signs (Fig. 20)**

Pre-Descemet dystrophy has several subgroups; many of these may represent sporadic, age-related degenerative, and secondary changes. There are focal, fine, gray opacities in the deep stroma immediately anterior to Descemet membrane with a variety of shapes. Larger lesions occur. The opacities may be central, annular, or diffuse. In the subtype, punctiform and polychromatic pre-Descemet dystrophy, the changes are more uniform and polychromatic. The rest of the cornea is normal. Similar opacities have been noted in association with other ocular and systemic diseases, such as pseudoxanthoma elasticum, X-linked and recessive ichthyosis, keratoconus, PPCD, EBMD, and CCDF.

**Symptoms**

The vision is usually unaffected and the patients are asymptomatic.

**Course**

Punctiform and polychromatic pre-Descemet dystrophy is nonprogressive. Other forms show progression.

**Light Microscopy**

Histopathologic studies are not consistent. Normal cornea except enlarged keratocytes in the posterior stroma with vacuoles and intracytoplasmic inclusions containing lipid-like material has been described.

**Transmission Electron Microscopy**

Membrane-bound intracellular vacuoles containing electron-dense material suggestive of secondary lysosomes and inclusions consistent with lipofuscin-like lipoprotein suggesting a degenerative process. No extracellular deposits noted.

**Confocal Microscopy**

Hyper-reflective dots located anterior to Descemet membrane; in 1 case reported to be present throughout the stroma.

**Category**

4.

Note: Similar deep corneal opacities are frequently seen in patients with ichthyosis and in carriers of X-linked ichthyosis (MIM #308100). It is unclear whether pre-Descemet dystrophy is a hereditary or a degenerative disorder.

**REFERENCES**


**Fuchs Endothelial Corneal Dystrophy (FECD)**

MIM #136800.

**Alternative Names, Eponyms**

Endoepithelial corneal dystrophy.

**Inheritance**

Cases without known inheritance are most common. Some cases with autosomal dominant inheritance reported.

**FIGURE 20.** Pre-Descemet corneal dystrophy: punctate opacities anterior to Descemet membrane demonstrated with indirect illumination and slit lamp beam.
Genetic Locus
Fuchs endothelial corneal dystrophy 13pTel –13q12.13,
15q, 18q21.2 –q21.32.
Early-onset variant Fuchs endothelial corneal dystrophy
1p34.3 – p32
Gene
None.
Early-onset variant collagen type VIII, Alpha 2—COL8A2.
Onset
Cases without known heredity as early as fifth decade.
Fuchs endothelial corneal dystrophy fourth decade and later.
Early-onset variant FECD first decade. Most cases begin in
the fourth decade or later but the early variant starts in the first
decade.
Signs (Fig. 21)
Cornea guttata accompanied by stromal edema: central
beaten metal-like endothelial changes with or without pigment
dusting. Corneal guttata in adult-onset Fuchs endothelial
corneal dystrophy are larger than those seen in early-onset
Fuchs endothelial corneal dystrophy. Stromal edema due to
endothelial decompensation. Intra- and interepithelial edema
(epithelial bullae); bullous keratopathy. Subepithelial fibrous
scarring and peripheral superficial vascularization may occur
in longstanding cases from chronic edema.
Symptoms
Intermittent reduced vision from epithelial/stromal
edema. Visual acuity worse in the morning due to increased
epithelial/stromal edema. Pain, photophobia, and epiphora due
to epithelial erosions resulting from burst epithelial bullae.
Progressive visual loss.
Course
Progressive.

Light Microscopy
Diffuse thickening and lamination of Descemet mem-
brane. Sparse and atrophic endothelial cells, hyaline excres-
cences on thickened Descemet membrane (guttae). Guttae become
buried or confluent or may be absent. Degeneration, thinning,
and reduction of endothelial cells. Increasing waviness of the
stromal collagen lamellae. Thickening of Descemet membrane
is noted.
Transmission Electron Microscopy
Multiple layers of basement membrane–like material on
the posterior part of Descemet membrane. Degeneration of
endothelial cells. Stromal thickening with severe disorganiza-
tion and disruption of the lamellar pattern.
Confocal Microscopy
Polymegathism and pleomorphism of the endothelial
cells. Early-onset variant Fuchs endothelial corneal dystrophy
has smaller guttata than typical Fuchs endothelial corneal
dystrophy.
Category
3 Fuchs endothelial corneal dystrophy in patients with
no known inheritance.
2 Fuchs endothelial corneal dystrophy with known
genetic loci but gene not yet localized.
1 Early-onset Fuchs endothelial corneal dystrophy.

REFERENCES
2. Fuchs E. Erkrankung der Hornhaut durch Schädigung von hinten. Albrecht
collagen distribution in an L450W mutant of the COL8A2 gene. Invest

FIGURE 21. Fuchs endothelial corneal dystrophy. A, Central guttata viewed
in retroillumination and in the slit beam. B, Cornea guttata as seen in specular
reflection. C, Advanced stromal edema. D, Advanced endothelial decompensation
with epithelial microcystic and bul-
loedema.
Posterior Polymorphous Corneal Dystrophy (PPCD)

MIM PPCD1 #122000, PPCD2 #609140, PPCD3 #609141.

Alternative Names, Eponyms
- Posterior polymorphous dystrophy (PPMD).
- Schlichting dystrophy.

Inheritance
- Autosomal dominant.
- Isolated unilateral cases, with similar phenotype but no heredity.

Genetic Locus
- PPCD 1—20p11.2–q11.2.
- PPCD 2—1p34.3–p32.3.
- PPCD 3—10p11.2.

Gene
- PPCD 1—unknown.
- PPCD 2—collagen type VIII alpha 2, COL8A2
- PPCD 3—two-handed zinc-finger homeodomain transcription factor 8—ZEB1.

Onset
- Early childhood.

Signs (Fig. 22)

Often asymmetric. Deep corneal lesions of various shapes including nodular, vesicular (isolated, in clusters, or confluent) and blister-like lesions. “Railroad tracks” appearance (multiple and isolated). Varying gray tissue at the level of Descemet membrane. Rarely stromal and epithelial edema ranging to ground-glass, milky appearance due to endothelial decompensation. Peripheral iridocorneal adhesions in about 25% of cases. In about 15% of cases, intraocular pressure (IOP) was elevated. Rarely, secondary subepithelial band keratopathy.

Symptoms

Endothelial alterations often asymptomatic. Rarely extensive and progressive visual impairment due to stromal clouding.

Course

Rarely congenital corneal clouding. Endothelial changes often unchanged over years. Possible slow progression of polymorphic vesicles and greater thickness of Descemet membrane over years occasionally causing endothelial decompensation.

Light Microscopy

Descemet membrane with multiple layers of collagen on its posterior surface manifesting focal fusiform or nodular excrescences.

Transmission Electron Microscopy

Extreme thinning or absence of the posterior nonbanded layer of Descemet membrane. Two types of collagenous tissue posterior to Descemet membrane form layers up to 25 nm thick. Multilayered epithelial-like cells with microcilia and desmosomes.

Confocal Microscopy


Immunohistochemistry

PPCD 1: Positive with anti-CK7 antibodies.

Category

PPCD 1—2.
PPCD 2—1.
PPCD 3—1.

REFERENCES


Congenital Hereditary Endothelial Dystrophy 1 (CHED1)

MIM #121700.

Alternative Names, Eponyms

None.

Genetic Locus

20p 11.2–q11.2 (pericentromeric region).

Gene

Unknown.

Inheritance

Autosomal dominant.

Onset

First or second year, occasionally congenital.

Signs (Fig. 23A)

Often asymmetric. Corneal clouding ranging from a diffuse haze to a ground-glass, milky appearance with occasional focal gray spots. Thickening of the cornea (can be 2–3 times normal thickness). Rarely subepithelial band keratopathy. Asymptomatic patients have only endothelial changes in form of moon crater–like appearance and peau d’orange texture. Rarely elevated IOP.

Symptoms

Corneal clouding with blurred vision, photophobia, and tearing. Worsening of vision in the morning. Exclusively peau d’orange–like endothelial alterations with no or little objective reduction of vision.

Course

Progression of corneal clouding over 1–10 years. Slow progression of endothelial alterations with the possibility of endothelial decompensation over a prolonged period.

Light Microscopy

Diffuse thickening and lamination of Descemet membrane. Sparse and atrophic endothelial cells. Parts of the endothelium are replaced by keratin containing stratified squamous epithelium.

Transmission Electron Microscopy

Multiple layers of basement membrane–like material on the posterior part of Descemet membrane. Degeneration of endothelial cells with many vacuoles. Stromal thickening with severe disorganization and disruption of the lamellar pattern.

Confocal Microscopy

Not reported.

REFERENCES

**Congenital Hereditary Endothelial Dystrophy 2 (CHED2)**

**MIM #217700.**

**Alternative Names, Eponyms**
Maumenee corneal dystrophy.

**Genetic Locus**
20p13 (telomeric portion).

**Gene**
Solute carrier family 4, sodium borate transporter, member 11—SLC4A11.

**Inheritance**
Autosomal recessive.

**Onset**
Congenital.

**Signs (Fig. 23B)**
Often asymmetric. More common and severe than CHED1. Corneal clouding ranging from a diffuse haze to ground-glass, milky appearance with occasional focal gray spots. Thickening of the cornea (can be 2–3 times normal thickness). Rarely secondary subepithelial band keratopathy. Rarely elevated IOP.

**Symptoms**
Corneal clouding with blurred vision often accompanied by nystagmus. Minimal to no tearing or photophobia.

**Course**
Relatively stationary.

**Light Microscopy**
Diffuse thickening and lamination of Descemet membrane. Sparse and atrophic endothelial cells.

**Transmission Electron Microscopy**
Multiple layers of basement membrane–like material on the posterior part of Descemet membrane. Degeneration of endothelial cells with many vacuoles. Stromal thickening with severe disorganization and disruption of the lamellar pattern.

**Confocal Microscopy**
Not reported.

**Immunohistochemistry**
Distribution of collagen types I and III–V, and laminin within the posterior collagenous layer of Descemet membrane. SLC4A11 encodes Bicarbonate transporter-related protein-1 (BTR1). BTR1 mutants remain in cytoplasm, whereas wild-type BTR1 localizes mostly to the plasma membrane.

**Category**
1.

---

**REFERENCES**

---

**X-linked Endothelial Corneal Dystrophy (XECD)**

**MIM: None.**

**Alternative Names, Eponyms**
None.

**Genetic Locus**
Xq25.

**Gene**
Unknown.

**Inheritance**
X-chromosomal dominant.

**Onset**
Congenital.

---

**FIGURE 24.** X-linked endothelial corneal dystrophy. Seven-year-old boy with milk glass appearance of the cornea.
Signs (Fig. 24)

Males
Congenital clouding ranging from a diffuse haze to a ground-glass, milky appearance. Possible nystagmus.
Only moon crater–like endothelial changes.
Secondary subepithelial band keratopathy combined with moon crater–like endothelial changes.

Females
Only moon crater–like endothelial changes.

Symptoms
Males: Often blurred vision.
Females: Asymptomatic.

Course

Light Microscopy
Moon crater endothelial changes and subepithelial band keratopathy. Irregular thinning of the epithelium and Bowman lamella. Anterior stroma with irregularly arranged collagen lamellae. Irregular thickening of Descemet membrane with small excavations and pits. Loss of endothelial cells or atypical appearance.

Transmission Electron Microscopy
Moon crater endothelial changes and subepithelial band keratopathy. Subepithelial accumulations of an amorphous granular material. Irregular thinning of Bowman layer (up to 0.5 μm) with many interruptions and gaps. Thickening of Descemet membrane (20–35 μm) consisting of an abnormal anterior and posterior banded zone. Complete absence of the posterior nonbanded zone. Discontinuous endothelial layer with partly normal and partly degenerative appearing cells. No evidence of desmosome-like adherent junctions between the cells or tonofilament bundles within the cytoplasm.

Confocal Microscopy
Not reported.

Category
2.

REFERENCES

RECOMMENDATIONS OF THE IC3D-THE ESTABLISHMENT OF ACCEPTED CRITERIA FOR PUBLICATION OF POTENTIAL NEW OR VARIANT CORNEAL DYSTROPHIES

We have attempted to present a revision of corneal dystrophy nomenclature that is accurate, is easy to use, and can be updated with new discoveries. For over a century, the corneal dystrophy nomenclature has been confounded by the reports of new corneal dystrophies or corneal dystrophy variants with inadequate factual substantiation. Sometimes, these “new” diseases have been variants of previously described dystrophies. However, the advent of genetic testing has provided the opportunity to obtain genetic information to accurately substantiate whether or not a corneal dystrophy is actually new. Ophthalmologists should adopt a more scientific approach to the field of genetic corneal disease by both detailed characterization of phenotypic changes and obtaining genetic testing when indicated. We hope the IC3D nomenclature classification will effectively endorse a more scientific and objective criteria for determining whether a “new” corneal dystrophy or dystrophy variant has indeed been discovered. We urge authors and reviewers alike that more stringent criteria must be met before publication of these entities.

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APPENDIX

Table of Genes and Mutations Associated with the Corneal Dystrophies

The tables are grouped into four categories:
• Epithelial and subepithelial dystrophies
• Bowman layer dystrophies
• Stromal dystrophies
• Descemet membrane and Endothelial dystrophies

Each table is organized into columns:
• Gene (locus)—The abbreviation and chromosomal location for each gene are provided.
• RefSeq (reference sequence)—The reference sequence used to determine the nucleotide and amino acid position of each mutation is listed.
• Exon—The exon in which each mutation is located is given.
• Nucleotide change—Each mutation is described at the nucleotide level. All nucleotide changes are numbered according to the Human Genome Variation Society (HGVS) mutation nomenclature system, in which nucleotide 1 is the A of the ATG-translation initiation codon.
• AA change (amino acid change)—Each mutation is given at the amino acid level. The HGVS mutation nomenclature system is used, employing the three letter amino acid abbreviations, with the translation initiator methionine numbered as +1.
• Original—Each mutation, as originally reported, is listed to allow the reader to correlate the mutations listed in the nucleotide and amino acid change columns with the nomenclature utilized by the original authors.
• Reference—References are provided for each reported mutation.
# Epithelial Dystrophies

## Epithelial Basement Membrane Dystrophy (EBMD)

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## Meesmann Corneal Dystrophy (MECD)

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*Reported as c.4046T>G (GenBank accession number AF137286).*

## Gelatinous Drop-Like Corneal Dystrophy (GDLD)

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### Bowman Layer Dystrophies

Reis–Bücklers Corneal Dystrophy (RBCD) = Granular Corneal Dystrophy, type 3 (see TGFBI corneal dystrophies)
Thiel–Behnke Corneal Dystrophy (TBCD) (see TGFBI corneal dystrophies)

### Stromal Dystrophies

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*Nucleotide and codon numbering system used by the authors who first reported mutations in gelsolin gene,28 with the amino acid numbering starting at the 28th translated residue Ala, preceded by a 27-residue signal peptide. If the initiation Met is designated codon +1, the mutations would be documented as c.640G>A (p.Asp214Asn) and c.640G>T (p.Asp214Tyr).

### TGFBI Corneal Dystrophies

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### Granular Corneal Dystrophy—Variants

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**Macular Corneal Dystrophy (MCD)**

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*Note: c.148C>A translates to p.Arg50Ser. Authors reported Arg50Cys as amino acid change, which would mean that nucleotide change is actually c.148C>T.*

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**Schnyder Corneal Dystrophy (SCD)**

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**Congenital Stromal Corneal Dystrophy (CSCD)**

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**Fleck Corneal Dystrophy (FCD)**

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**Descemet membrane and Endothelial Dystrophies**

**Early-Onset Variant of Fuchs Endothelial Corneal Dystrophy (FECD)**

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### Posterior Polymorphous Corneal Dystrophy 3 (PPCD3)

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### Congenital Hereditary Endothelial Dystrophy 2 (CHED2)

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### REFERENCES


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