The Corneal Dystrophies
Barry A Weissman, OD, PhD, FAAO (Dip CCL)

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Disclosures:
Professor of Optometry, Marshall B Ketchum University, Southern California College of Optometry

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• Advisor NKCI, Inc
• All comments & errors, however, are completely my own….

Primary references for this discussion:
• Weiss et al. The IC3D Classification of the Corneal Dystrophies. Cornea 2008

“Dystrophy” is currently used to describe an inherited disorder affecting cells, tissues or organs, alone or in combination

• The word dystrophy is derived from the Greek (dys = wrong, difficult; troph = nourishment) & was introduced into the medical literature by Wilhelm Erb in 1884 to describe a disease of the musculature…
• Arthur Groenouw published 2 patients who had “noduli corneae” 125 years ago

We now can recognize granular corneal dystrophy in one of these patients, and macular corneal dystrophy in the other…
• About the same time Biber published his thesis discussing what we now recognize as lattice corneal dystrophy

Groenouw A Arch Augenheilkd 1890
Biber H A Diggleman Zurich 1890

Why should we be interested in the corneal dystrophies?
• Study of the CDs will help understand corneal physiology & genetics
• Enhance differential Dx of other corneal diseases, specifically CL complications
• Curiosity
• Historical perspective
In Ophthalmology & Optometry, the term "corneal dystrophy" – CD – has been used in reference to a group of inherited corneal diseases that are typically central, bilateral, symmetric, slowly progressive, and without relationship to environmental or systemic factors.

Since Bucklers (Klin Monatsbl Augenheilkd 1938) published the first scheme classifying the corneal dystrophies (granular, lattice, & macular), the most commonly used classification systems have been anatomically-based & phenotypic (aided in some cases by light microscopic histopathology) eg, defined by the involved level of the cornea:

- Endothelial & sub-epithelial
- Bowman's membrane (ALL)
- Stroma
- Descemet's membrane (PLL)
- Epithelial

www.allaboutvision.com

Other CD classification schemes are possible…
- Severity
- Histopathological features
- Biochemical characteristics
- Genetic pattern (genotype)

In particular, the development of genotypic analysis is currently revolutionizing medicine, and especially the study of the CDs.

www.edinformatics.com

Example: The CFTR (cystic fibrosis) gene is located on the long arm of chromosome 7 at position 7q31.2


Humane Chromosome 3 from Science

Human Genetic Map

www.edinformatics.com

Genetic characterization of the CDs has revealed both:

Genetic heterogeneity: wherein different gene abnormalities (genotype) cause a single dystrophic phenotype (eg both KRT3 and KRT12 => the same clinical picture of Meesman’s dystrophy)

And

Phenotypic heterogeneity: Wherein a single gene (TGFβ1) causes different allelic dystrophy phenotypes (eg RBCD, TBCD, granular type 1, and type 2, and lattice type 1)
Most CDs are:

- Autosomal dominant
- Bilateral
- Central-Axial (?~avascularity of the cornea)
- Symmetric
- Stable or slowly progressive
- Early onset (congenital or presents during youth)
- Non-inflammtory

Always consider alternative Dx’s

Fabry’s disease & other corneal verticillota

Fabry disease is a rare genetic lysosomal storage disease, inherited in an X-linked manner; results from the buildup of globotriaosylceramide in the body’s cells, including the cornea

a form of sphingolipidosis with pain, renal, & cardiac complications

Genetic testing now available through Genzyme

Other causes of verticillota include systemic medications such as amiodarone, chloroquine, indomethacin, phenothiazines etc

http://www.ojrd.com/

If an “average” eye doctor sees 100 pts/week for 50 weeks/yr…

- 5000 pt-visits per year
- 200,000 pt-visits over a 40 year career
- 1000/1,000,000 = 200/200,000
- Therefore ~200 CD patients seen over a career

Compare to:

- KC prevalence is 50-230/100,000, or 10/10,000 or ~150,000 KC in USA
- CDs also ~10/10,000 but most (>7/10) FECD & EBMD
- Compared to 16 million diabetics in the USA
The IC3D Committee developed a series of descriptive, evidential categories:

<table>
<thead>
<tr>
<th>Category</th>
<th>Defining characteristics</th>
<th>Known gene or known gene locus?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Well-defined dystrophy</td>
<td>Known gene</td>
</tr>
<tr>
<td>2</td>
<td>Well-defined dystrophy</td>
<td>Known gene; no specific gene identified</td>
</tr>
<tr>
<td>3</td>
<td>Well-defined dystrophy</td>
<td>No known gene or gene locus</td>
</tr>
<tr>
<td>4</td>
<td>Poorly defined dystrophy</td>
<td>No known gene or gene locus</td>
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</tbody>
</table>

Epithelial and Subepithelial Dystrophies

- Epithelial basement membrane dystrophy (EBMD), majority degenerative, some C1
- Epithelial recurrent erosion dystrophy (ERED) C4; Smolandiensis variant C3
- Subepithelial mucinous corneal dystrophy (SMED) C4
- Meesmann corneal dystrophy (MECD); Mutation in keratin genes C1
- Lisch epithelial corneal dystrophy (LECD) C2
- Gelatinous drop-like corneal dystrophy (GDLD) C1

Epithelial basement membrane dystrophy (EBMD)
- Also called: Map-dot-fingerprint; Cogan microcystic epithelial; anterior basement membrane
- The vast majority of cases are degenerative, or 2nd trauma, although familial cases have been reported relative to 5q31 (TGFB1)
- Presents late in life and usually asymptomatic; or symptoms of recurrent abrasion and/or blurred vision (due to irregular astigmatism if central lesions)

Meesmann corneal dystrophy (MECD)
- Also called: Juvenile hereditary epithelial dystrophy
- Autosomal dominant: heterozygous missense mutation in either Keratin 3 12q13 (KRT3) or Keratin 12 (Stocker-Holt variant) 17q12 (KRT12)
- Can lead to recurrent erosions, blurred vision
- From irregular surface and/or scarring; Stocker-Holt variant more severe
Lisch epithelial corneal dystrophy (LECD)

- Also called: band-shaped and whorled microcystic dystrophy of the corneal epithelium
- X-chromosomal dominant: Xp22.3
- Asymptomatic or blurred vision (if pupillary zone involved)

Gelatinous drop-like corneal dystrophy (GDLD)

- Also called: subepithelial amylodosis; primary familial amylodosis (Grayson); increased epithelial permeability to NaF; increased epithelial lactoferrin from tears; amyloid
- Autosomal recessive: 1p32, Tumor-associated calcium signal transducer 2 (TACSTD2)
- Significant decrease in vision, photophobia, irritation, redness, tearing
- Increased prevalence in Japan (43% consanguineous marriage)
- Can be pigmented (unusual for CDs)
- Tx bandage SCLs (esp post PKP)

Bowman (ALL) Layer Dystrophies

- Reis-Bucklers corneal dystrophy (RBBCD) (Granular corneal dystrophy type 3) C1
- Thiel-Behnke corneal dystrophy (TBCD) C1; potential variant C2
- Grayson-Wilbrandt corneal dystrophy (GWCD) C4

Reis-Bucklers corneal dystrophy (RBBCD)

- Also called: Corneal dystrophy of Bowman layer, type 1; geographic corneal dystrophy (Weidle); Superficial granular corneal dystrophy; atypical granular corneal dystrophy; granular corneal dystrophy, type 3; anterior limiting membrane dystrophy, type 1
- Autosomal dominant: 5q31 (TGFBI)
- Recurrent corneal erosions and blurred vision

Thiel-Behnke corneal dystrophy (TBCD)

- Also called: Corneal dystrophy of Bowman layer, type II; honeycomb-shaped corneal dystrophy; anterior limiting membrane dystrophy, type II; Curly fibers corneal dystrophy; Waardenburg-Jonkers corneal dystrophy
- Autosomal dominant: 5q31 (TGFBI); 10q24
- Recurrent corneal erosion and later vision impairment
Grayson-Wilbrandt corneal dystrophy (GWCD)
- Autosomal dominant but unknown gene and genetic locus
- Recurrent erosion and perhaps decreased vision

Stromal Dystrophies
- TGFB1 corneal dystrophies
  - Lattice corneal dystrophy: TGFB1 (LCD)
    - Classic lattice corneal dystrophy (LCD) C1
      - Variants III, IIIA, IIIIA & IV C1
    - Granular corneal dystrophy, classic type 1 (GCD1) C1
    - Granular corneal dystrophy, type 2 (granular-lattice) (GCD2) C1
    - [Granular corneal dystrophy, type 3 (GCD3) C1] => see above
    - Macular corneal dystrophy (MCD) C1
    - Schnyder corneal dystrophy (SCD) C1
    - Congenital stromal corneal dystrophy (CSCD) C1
    - Fleck corneal dystrophy (FCD) C1
    - Posterior amorphous corneal dystrophy (PACD) C3
    - Central cloudy dystrophy of Francois (CCDF) C4
    - Pre-Desceemet corneal dystrophy (PDDC) C4

Lattice corneal dystrophy (LCD)
- Also called: Biber-Haab-Dimmer
- Classic Lattice corneal dystrophy (LCD1), Lattice corneal dystrophy, TGFB1 type (LCD), and variants
- Autosomal dominant: 5q31 (TGFB1)
- Beware of 2° trauma, & 2° CA

Lattice corneal dystrophy, Gelsolin Type (LCD2)
- Also part of: Familial amyloidosis, Finish (FAF); Meretoja syndrome; Amyloidosis V; Familial amyloidotic polyneuropathy IV (FAP-IV)
- Autosomal dominant: 9q34 (Gelsolin GSN)
- Onset in third to fourth decade
Granular corneal dystrophy, type 1 or classic (GCD1)
• Also called: Corneal dystrophy Groenouw type 1
• Autosomal dominant: 5q31 (TGFB1)
• Glare & photophobia, frequent recurrent erosions

Granular corneal dystrophy, type 2 Granular-Lattice (GCD2)
• Also called: Combined granular-lattice corneal dystrophy; Avellino corneal dystrophy
• Autosomal dominant: 5q31 (TGFB1)
• Increased prevalence in Korea & Japan
• Genetic testing available through Avellino Lab USA

Prevalence of Granular Corneal Dystrophy Type 1 (Avellino Corneal Dystrophy) in the Korean Population

TABLE 1 Prevalence estimates for type 1 granular corneal dystrophy in the Korean population, 1987–2012

<table>
<thead>
<tr>
<th>Type 1</th>
<th>Heterozygote</th>
<th>Heterozygote (1987)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Korean</td>
<td>0.0691</td>
<td>0.0291</td>
</tr>
</tbody>
</table>

Invasive Surgery

Test for gene mutation that causes corneal dystrophy now available in US

Field 4. Nucleotide and Amino Acid Changes Associated With Variant LCRD, GCD, and ESRD

Field 15. Statistical analysis of the data from the study groups

Macular corneal dystrophy (MCD)

Macular corneal dystrophy is one of the 3 major corneal dystrophies. The first signs are usually noticed in the first decade of life, and progress afterwards, with corneal opacities, thinning, and attacks of pain. MCD is thought to be caused by the lack or abnormal configuration of KS. Most cases are caused by mutations in the gene coding for carbohydrate sulfotransferase 6.


FIGURE 1. The left eye of case 1A, slit-lamp photograph showing multiple granular deposits across the limbus in 4 quadrants of the cornea. B. After 3 months, the same patient as in A, slit-lamp photograph showing scattered granular deposits across the corneal limbus. C. Two months after the visit of B, the deposit cleared progressively and the corneal limbus appeared. D. Three years after the visit of C, the dispersed granular deposits showed recurrance forming from the corneous of middle area. The follow-up period in each white was shown in the same location. From A to D.

FIGURE 2: The left eye of case 2, A, slit-lamp photograph showing multiple granular deposits across the limbus in 4 quadrants of the cornea. B& C. OCT image showing the location first the center of the hemicrani-dental plane, followed with the location of middle area, lastly the location of middle area. D. OCT image showing disappearance of corneal deposit, and these residual white spots under the fundus area. E& F. OCT image with the follow-up period within the same location. From A to D.

FIGURE 14: Macular corneal dystrophy, A, Early macular corneal dystrophy with two central opacities. B, Slit lamp photograph of advanced macular dystrophy with central opacities at multiple level and diffuse stromal haze. C, More advanced macular dystrophy at higher magnification revealing more numerous and diffuse corneal opacities and stromal haze.

Mucopolysaccharidosis syndromes

- Heterogenous group of rare systemic genetic disorders characterized by accumulation of GAGs w/in multiple organ systems
- Result from inherited abnormalities of specific lysosomal enzymes involved in degradation of GAGs
- GAGs accumulate intra- and extracellularly distorting cells and extracellular matrix leading to corneal clouding, among other ocular and non-ocular involvement

MPS I

From Ashworth et al Eye 2006 (corneal opacification esp common in both MPS I* & VI*)

Schnyder corneal dystrophy (SCD)

- Also called: Schnyder crystalline corneal dystrophy; Schnyder crystalline dystrophy sine crystals; hereditary crystalline stromal dystrophy of Schnyder; etc
- Autosomal dominant: 1q36; UBIAD1 prenyltransferase domain containing 1 (UBIAD1)
- Decrease in vision/glare with aging; hyperlipoproteinemia

*** Only 50% show crystals

Mutations in the UBIAD1 Gene on Chromosome Short Arm 1, Region 36, Cause Schnyder Crystalline Corneal Dystrophy

Jaye S. Weiä,1,2 Howard S. Kraus3 Belma Karacanli,4 Gerard Trips,4 Peter S. White5 & Scott Waring6 Walker Eads,7 Wolfgang Horns8 (the Dystrophy)9, Matthias Kranze9, Paul Wann0,11 Neil Ebenzer11 Sauri Mahurde11 and Michael E. Nickerson11

Conclusions: Non-synonymous mutations in the UBIAD1 gene were detected in six SCD families, and a paternal mutation hot spot was observed at amino acid N102. The mutations are expected to interfere with the function of the UBIAD1 protein, since they are located in highly conserved and amino-acid important domains.
Differential Dx of corneal crystals

- Lecithin-cholesterol acyltransferase deficiency (LCAT) & fish eye disease (FED) are rare AR disorders causing anemia, renal insufficiency, atherosclerosis, & cornea opacities similar to non-cystalline SCD & CCDF
- Tangier Dz: AR leading to complete diffuse corneal clouding
- Cystinosis: AR inherited metabolic dz leading to lysosomal storage of cystine => kidney & thyroid dz & fine corneal stroma (including periphery/conjunctival/TM/periph retina polychromatic crystals
- Also tyrosinemia; Bietti crystalline dystrophy; gold corneal crystals; various drugs; Giant mononuclear granulopathy of unknown significance (MGUS)-multiple myeloma (corneal crystals are IgG)

Fleck corneal dystrophy (FCD)

- Also called: Francois-Neetens speckled corneal dystrophy
- Autosomal dominant: 2q35; Phosphatidylinositol-3-phosphate /phosphatidylinositol-3-kinase (PIP5K3)
- Congenital, non-progressive
- “constipated keratocytes” at different levels of the stroma; complex lipids & GAGs in membrane-limited intracytoplasmic vesicles

Congenital stromal corneal dystrophy (CSCD)

- Also called: Congenital hereditary stromal dystrophy; congenital stromal dystrophy of the cornea
- Normal cornea thickness
- Autosomal dominant: 12q13.3 (Decorin-DCN)
- Moderate to severe vision loss
- Klintworth (2009) suggests “very rare” with only 4 families reported

Posterior amorphous corneal dystrophy (PACD)

- Also called: Posterior amorphous stromal dystrophy
- Autosomal dominant; with unknown gene
- Probably congenital, possibly slowly progressive
- Usually corneal thinning; flat Ks => hyperopia; endothelial guttata; iris & angle changes

Corneal dystrophies and genetics in the International Committee for Classification of Corneal Dystrophies era: a review

Andrea L Vincent FRANZCO  Clinical and Experimental Ophthalmology 2014

A similar corneal dystrophy, posterior amorphous corneal dystrophy was classified category 2 to KC 10, with a question as to whether this is a dysgenetic rather than dystrophic. However, an autosomal dominant pedigree investigated has permitted linkage to 12q13.3 with a LOD of 5.6. Although excellent candidate genes existed within this region, (Keratin (KRT16), Lamin C (LAMA3), Decors (DCOR1) and Epithcyn (EPCT1)) no mutations were identified. This finding moves posterior amorphous corneal dystrophy to category 2.14
Always consider masquerade diseases

~50 yr WS, asymptomatic except for “itchy-burnies”
Corneal changes phenotypic of PACD, but...

Only one eye involved
-nil corneal curvature & thickness
Only one patch of endo gutatta (in involved eye)
No iris, angle changes
Upon genetic testing of proband and 5 family members (sister, mother, two daughters, one son) no genetic “hits”

Bareeuwe, Thu, Hilborne, Keravina, unpublished data, 2010

Central cloudy dystrophy of Francois (CCDF)

- Also called: Crocodile shagreen (degeneration), esp if peripheral
- Genetics not yet defined

Pre-Descemet corneal dystrophy (PDCD)
- Some families have been described but unknown genetics
- Asymptomatic
- ?accumulations of cholesterol sulfate

Pre-Descemet Corneal Dystrophy and X-Linked Ichthyosis
Associated With Deletion of Xp22.31 Containing the
373 Gene

Purpose: To report the association of X-linked ichthyosis and pre-Descemet corneal dystrophy with a deletion of the normal skin gene (373a) deleted with microtubule-based conserved genomic hybridizations (aCGH).

Methods: A slit-lamp biomicroscopic examination and cutaneous examinations were performed, after which a skin sample was collected as a source of genomic DNA. Polymorphic chain reaction amplification of each of the 10 exons of the 373a gene was performed, as was aCGH on genomic DNA to detect copy number variation.

Results: The slit-lamp examination revealed punctate opacities in the posterior corneal stroma of each eye. The corneal examination demonstrated scaling and flaking of the skin of the arms and legs. Polymorphic chain reaction amplification using primers designed to amplify each of the 10 exons of 373a failed to produce any amplification. Subsequently, aCGH performed on genomic DNA revealed a microdeletion in the Xp22.31 region approximately 1.2 megabases, containing 373a.

Conclusions: The identification of a microdeletion within Xp22.3 containing 373a with aCGH in an individual with suspected pre-Descemet corneal dystrophy and ichthyosis demonstrates the clinical utility of copy number variation analysis in confirming a presumptive clinical diagnosis.

Aldave AJ, Han J, Frausto RF. Clin Genet 2013

Descemet membrane (PLL) & Endothelial Dystrophies
- Fuchs endothelial corneal dystrophy (FECD) C1, C2, or C3
- Posterior polymorphous corneal dystrophy (PPCD) C1 or C2
- Congenital hereditary endothelial dystrophy 1 (CHED1) ?PPCD
- Congenital hereditary endothelial dystrophy 2 (CHED2) C1
- X-linked endothelial corneal dystrophy (XECD) C2

Genetics of the corneal endothelial dystrophies: an evidence-based review

Aldave AJ, Han J, Frausto RF. Clin Genet 2013

“...linkage, association and familial segregation analyses support a role of only one gene in each corneal endothelial dystrophy:

ZEB1 in PPCD3,
SLC4A11 in CHED2
COL8A2 in FECD (early onset).

In addition, insufficient evidence exists to consider the autosomal dominant form of CHED (CHED1) as distinct from PPCD...”
Fuchs endothelial corneal dystrophy (FECD)

*Also called: Endothelial corneal dystrophy
*Most cases without known inheritance but many familial clusters: autosomal dominant:
  1q24.3-p22; 10q11.22; 13q33-13q12.13; 15q25.3; 18p12.1-q11.23; 20p13 (? SLC4A11, ?COL8A2)
*Usually slowly onset, commonly 4-5% of population >40 years of age; early variant in 1st decade: F 2:3 M 1:1
*Early: endo guttata; late: decreased vision due to stromal swelling, epithelial irregularity, scarring & erosions due to epithelial blisters

Zhu et al
Fuchs Endothelial Corneal Dystrophy
A Neurodegenerative Disorder? 2008 Ophthalmology 115: 1091–1098

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Andrea L Vincent, FRANZCO
Clinical and Experimental Ophthalmology 2014; 42: 6–12

Zhu et al
Fuchs Endothelial Corneal Dystrophy
A Neurodegenerative Disorder? 2008 Ophthalmology 115: 1091–1098

E2-2 Protein and Fuchs’s Corneal Dystrophy
Keith H. Baratz, M.D., Nirubol Tesakulwong, B.S., Fuaijing By, Ph.D., William L. Brown, O.D., Kari Brasham, M.S., Wei Chen, Ph.D., Khoo D. Tran, M.D., Katharina E. Schmidt-Kubista, M.D., John R. Heckenlively, M.D., Anuradha Swaroop, Ph.D., Gwendolyn Amos, Ph.D., Ira Kay J. Baratz, Ph.D., Barbara D. Tschina, Ph.D., William W. Trokel, M.D.

Corneal Classification on the Corneal Dystrophies

Fig. 1. Fuchs’ endothelial dystrophy. Composite showing various major clinical stages in B-K/Fuchs’s changes. Beginning on left, cornea shows anterior axial keratoplasty paracentral region. In the middle stage, corneal guttata changes, epithelial blisters appear and gray, because of new collagen tissue. Endothelial degenerative changes are seen in the subepithelial connective tissue. Collagen tissue posterior to Descemet’s membrane becomes wrinkle. In the late stage, corneal stroma becomes subepithelial and stromal sarcoid increases.

George O. Warloe, M.D., Meryn M. Rodrigues, M.D., Ph.D., and Peter R. Larsson, M.D.

Fig. 2. Endothelial dystrophy. A shows corneal guttata anterior to the Descemet’s membrane, appearing with a center of clear and the surrounding gum. B shows the cornea of the anterior to the Descemet’s membrane, with a center of clear and stromal sarcoid.

Posterior polymorphous corneal dystrophy (PPCD)

- Also called: Schlichting dystrophy
- Autosomal dominant but occl isolated cases: PPCD1 20p1.2-q11.2 (uk gene); PPCD3 10p1.2-q11.2 (2-handed zinc-finger homeodomain transcription factor 8, ZEB1); 17q12
- May be related to endothelial decompensation & corneal edema, 2° glaucoma: TMG 7/12e 1 abdomin lar hernia 1maldevelopment corpus callosum
- Rarely vision changes but can =>PKP, possible slow progression
- May present unilaterally

Classification of Posterior Polymorphous Corneal Dystrophy as a Corneal Ectatic Disorder Following Confirmation of Associated Significant Corneal Steepening

Exclusion of pathogenic promoter region variants and identification of novel nonsense mutations in the zinc finger E-box binding homebox 1 gene in posterior polymorphous corneal dystrophy

Corneal dystrophies and genetics in the International Committee for Classification of Corneal Dystrophies era: a review

Andrea L Vincent FRANZCO  Clinical and Experimental Ophthalmology 2014; 42: 4–12
Congenital hereditary endothelial dystrophy 2 (CHED2)

- Also called: Maumenee corneal dystrophy
- Autosomal recessive: 20p13 (Solute carrier family 4, sodium borate transporter, member 11 SLC4A11)
- Children of consanguineous marriages (rare in USA, common in other countries)
- CHED1 not real? prev reptd families may be PPCD?

Molecular bases of corneal endothelial dystrophies
Thore Schmidt 1,2, Mariana Mazzini Silva 3, Alireza Ziaei 1,2, Uffe Jirkova 1,2, Mads P. Bønder 1,2, Population Eye Research (2002) 22-34

3.1.1. Genetics of CHED1
Genetic study of a large British family with autosomal dominant and fully penetrant inheritance of CHED1 served as the basis for identifying the chromosomal locus (Toma et al., 1995). Two-point linkage analysis of this seven-generation family revealed significant linkage to chromosome 20. The identified locus was within the 30 cM region of the same chromosome linked to posterior polymorphous corneal dystrophy (PPCD) (Heen et al., 1985; Toma et al., 1995). The linkage of both disorders to overlapping regions in chromosome 20 has sparked a debate that the two disorders are allelic variants.

Ideogram of pericentromeric portion of chromosome 20 demonstrating the relationship of the CHED1 locus (D20S48 & D20S471) to the intervals to which PPCD1 has been mapped in 4 families. The common interval to PPCD1 is defined by markers D20S182 & D20S139 Aalavie et al Clin Genet 2013
**X-linked endothelial corneal dystrophy (XECD)**

- X-chromosomal dominant; Xq25
- Congenital onset; males often blurred vision; females asymptomatic
- Variable corneal clouding with “moon-crater” endothelial changes & secondary sub-epithelial band keratopathy

**Comparison of characteristics of corneal dystrophies & degenerations**

<table>
<thead>
<tr>
<th>DEGENERATIONS</th>
<th>DYSTROPHIES</th>
<th>KERATOCONUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNILATERAL</td>
<td>BILATERAL</td>
<td>MOSTLY BILATERAL</td>
</tr>
<tr>
<td>ASYMMETRIC</td>
<td>AXIAL</td>
<td>AXIAL</td>
</tr>
<tr>
<td>PERIPHERAL</td>
<td>INHERITANCE</td>
<td>10-20% INHERITED</td>
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<tr>
<td>LATE ONSET</td>
<td>EARLY ONSET</td>
<td>ONSET @ PUBERTY</td>
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<tr>
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<td>PRIMARY</td>
<td>PRIMARY</td>
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</tr>
<tr>
<td>INFLAMMATORY</td>
<td>NON-INFLAMMATORY</td>
<td>PERHAPS INFLAMMATORY</td>
</tr>
</tbody>
</table>

After Zadnik & Edrington, 2000

**Etiology of Keratoconus**

*UNKNOWN, BUT REPORTS OF ASSOCIATIONS WITH A LARGE NUMBER OF DISEASES (EG DOWN’S, RP, EHLERS-DANLOS SYNDROME ETC) ; NONE CONFIRMED AT CLEK, BUT DOWN’S NOT IN STUDY*

- GENETICS: 14% CLEK PTs REPTD A CLOSE RELATIVE WITH KC DX @ BASELINE & 18% yr 7
- EYE RUBBING: MANY HAVE OBSERVED AN ASSOCIATION, BUT HAS NOT BEEN CONFIRMED
- ATOPY: SIMILARLY, MANY HAVE OBSERVED AN ASSOCIATION (ESP VERNAL) BUT NO CONFIRMATION. 53% CLEK PTs REPAT ATOPIC HX @ BASELINE
- RIGID CONTACT LENS WEAR; ALSO NOT CONFIRMED

**Familial KC studies => a high degree of genetic heterogeneity, & multiple susceptible-disease loci, suggests that mutations in several different genes, involved in related pathways, acting on common targets, are responsible for disease phenotype**

Bisceglia et al IVOS 50(3)2009

Reduced corneal protein w/ incr degradative enzymes & dec inhib enzymes, inc inflammatory markers => complex disorder with a mix of both genetic and non genetic factors

McMahon GSLS 1/2009 (rept of Sorbara CLS 3/2009)

Fig. J. Graphic presentation showing the relationship of retinal keratometric keratometry to the human genome. Black ideograms represent the 22 chromosomes and 2 sex chromosomes. The red box illustrates the positions and orientations of the atrophied lens. The figure was generated using the NCBI Map Viewer.


- Central corneal thickness (CCT) is associated with eye conditions including keratoconus and glaucoma. We performed a meta-analysis on >20,000 individuals in European and Asian populations that identified 16 new loci associated with CCT at genome-wide significance (P < 5 × 10⁻⁸). We further showed that 2 CCT-associated loci, FOXO1 and FNDC3B, conferred relatively large risks for keratoconus in 2 cohorts with 874 cases and 6,085 controls (rs2721051 near FOXO1 had odds ratio (OR) = 1.92, 95% confidence interval (CI) = 1.41-2.62, P = 2.7 × 10⁻⁵); and rs4894535 in FNDC3B had OR = 1.47, 95% CI = 1.29-1.68, P = 4.9 × 10⁻⁷). FNDC3B was also associated with primary open-angle glaucoma (P = 5.6 × 10⁻⁴; tested in 3 cohorts with 2,979 cases and 7,399 controls). Further analyses implicate the collagen and extracellular matrix pathways in the regulation of CCT.

- Summary of Assessment & Treatment

- Anterior dystrophies likely to cause recurrent epithelial erosions & decreased visions through irregular corneal astigmatism &/or central opacification
- Stromal dystrophies likely to eventually decrease vision through opacification; advanced MCD additionally can damage endothelium & lead to increased corneal thickness, epithelial edema, & sub-epithelial scarring
- Endothelial dystrophies can damage the endothelium & lead to increased corneal thickness, epithelial edema, and sub-epithelial scarring
- Observation: if minimal symptoms or loss of function
- Rigid contact lenses can improve vision if corneal irregularity occurs; BSCLs may be particularly protective in GDLD
- AFTs: lubricants, gels, & hyperosmotics
- Antibiotics if erosions
- Corneal transplants (PKP, DSEK, DALK) may be needed in several but not all CDs

- Evaluation of the Association Between Keratoconus and the Corneal Thickness Genes in an Independent Australian Population

- Jinatai Hoshino,1,2 Hiroshi Hoshino,1,2 Yasuyuki Sato,1,2 Haruo Kondo,1,2 Takanori Horiuchi,1,2,3 Shigeru Morisaka,1,2,3 Mark Egli,1 and Paul S. Bird1

- Purpose: A genomewide association study (GWAS) identified six loci associated with central corneal thickness that also conferred a risk of keratoconus (KC). We aimed to assess whether genetic associations found for these loci with KC or corneal curvature in an independent cohort of European ancestry.

- Results: Genotyping data were available for the six SNPs. Genetically significant associations with KC were found for the SNPs rs2115085 (P = 1.27 × 10⁻⁴) and rs800235 (P = 1.95 × 10⁻⁵) in the 1q31 region. The association of rs2115085 with KC was further confirmed in an independent cohort, demonstrating an increased risk of KC for homozygous minor allele carriers (OR = 2.57, 95% CI = 1.57-4.21, P = 1.3 × 10⁻⁴).

- Conclusions: The results of the current study provide evidence for genetic risk factors for KC. The finding of genetic associations with KC for the loci identified in the current study may have important implications for the understanding of KC pathogenesis and the development of KC prevention and treatment strategies.

- Table 2. Logistic Regression Analysis of KC in the Present Study

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