The Genetic Mysteries of the Corneal Dystrophies

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Detection: Biomicroscopic Examination Techniques
• Diffuse Illumination
  – How many and what type of opacities
• Parallelepiped/Optic Section
  – What layer(s) of the cornea are involved
• Indirect illumination/Retroillumination
  – Are more opacities visible

Features of Corneal Dystrophies and Degenerations

Corneal Degenerations
• A deposition of abnormal elements due to corneal cellular changes
• Signifies a degradation, deterioration, change in structure, secondary inflammation, metabolic change, aging

Corneal Degenerations (Examples)
• Arcus senilis
• Vogt’s limbal girdle
• Salzmann’s nodular degeneration
• Marginal furrow degeneration
• Terrien’s degeneration
• White ring of Coats
• Pterygium
• Band keratopathy

Corneal ectasias: Dystrophy or Degeneration?
  – Keratoconus
    a. Multifactorial etiology
    b. Genetic predisposition
      1. VSX1 (visual system homeobox 1) mutations in autosomal dominant pedigrees
      2. SOD1
– Pellucid Marginal Degeneration

**Corneal Dystrophies**

- Mostly autosomal dominant inheritance
- Bilateral and usually symmetric
- Affects the central cornea early on
- No associated vascularity
- No associated inflammation
- Rarely associated with systemic disease

**Classification of the Corneal Dystrophies**

- Traditionally, classified by the affected corneal layer
- Molecular genetics are changing this classification
  - Chromosome 1  Chromosome 4
  - Chromosome 5  Chromosome 9
  - Chromosome 12  Chromosome 16
  - Chromosome 17  Chromosome 20
  - Chromosome 21  X-chromosome

**Epithelial Dystrophies**

- Epithelial Basement Membrane Dystrophy
- Meesman’s Dystrophy
- Band-shaped/Whorled Microcystic Dystrophy (Lisch dystrophy)

**Epithelial Basement Membrane Dystrophy (MAP-DOT)**

- Most common anterior dystrophy
- Not always a true dystrophy (may be acquired as opposed to inherited)
- Maplike, dot-like (microcysts), fingerprint and bleb (putty) opacities
- Painful recurrent epithelial erosions (RCEs) after 3rd decade-50% of pts with RCEs have EBMD

**Meesman’s Dystrophy (Juvenile Epithelial Dystrophy)**

Opacities consist of epithelial uniform grey-white intraepithelial microcysts seen early in life; increase in number over time causing an irregular surface; relatively rare dystrophy

- Microcysts contain intracellular keratin; thickened basement membrane
- RCEs can occur causing further visual deterioration
- Linkage studies identify mutations in two cornea-specific genes: KRT3 on chromosome 12q13 and KRT12 on chromosome 17q12)
Band-Shaped/Whorled Microcystic Dystrophy (Lisch)

- Grey band-shaped, feathery opacities
- Intraepithelial, densely crowded clear microcysts
- Diffuse vacuolization of the cellular cytoplasm
- Reduced visual acuity but no RCEs have been reported
- Opacities may diminish with gas permeable contact lens wear
- Linkage of the gene (as yet unidentified) maps to the X chromosome

Autosomal Dominant Recurrent Corneal Erosion Dystrophy

- Autosomal dominant; genetic locus unknown
- Attacks of RCEs usually by age 5
  - Subside by 30-40 years
  - Attacks last for a few days to months
  - Can be triggered by URI, dry air, lack of sleep, trauma, smoke
- Subepithelial fibrotic opacities (keloids)
  - Thickened subepithelium with chondroitin and dermatan sulfate
  - Hudson-Stahli line
- Treatment: Problematic- ointments and PTK=marginal success; rest in dark rooms during attacks

Bowman’s Layer Dystrophies

TGFB1 Dystrophies

- TGFB1 plays a role in corneal development and healing; it also interacts with collagen and other structural elements; it is expressed in the cornea and in other parts of the body.

  - The majority of mutations are Arg 124 and Arg 555 on chromosome 5q31

  - Reis-Buckler’s Dystrophy (Bowman’s Type I)
    - Ring-shaped opacities confined to Bowman’s membrane=honey-comb or fish-net appearance
      - Made up of collagen fibrils
      - Thickened epithelium
        - Irregular astigmatism, less corneal sensation, RCEs
        - Vision good until later decades-PTK beneficial
Mutation maps to the transforming growth factor beta induced TGFB1 (BIGH3) gene on chromosome 5 (5q31 - same site as some stromal dystrophies)

- Some refer to this dystrophy as “Granular dystrophy III”

Thiel Behnke Dystrophy (Bowman’s type II)
- More prevalent than RBD; Develops later in life than RBD
- Similar findings and links to the TGFB1 gene and to the mutations on chromosome 10q23-24 (Arg555Gln)

Stromal Corneal Dystrophies

TGFB1 Dystrophies

1-Granular Dystrophy
- Common stromal dystrophy
- Opacities consist of white, round, crumb-like spots and/or rings
- Stroma in between opacities is clear early on
- Good visual acuity until 7th or 8th decade when spots coalesce and stroma between the spots is affected
- Most common mutation on TGFB1: Arg555Trp. Arg124Ser identified in pts with later onset

2- Granular Dystrophy Type II (Formerly Avellino Corneal Dystrophy)
- Granular and lattice type changes in the same eye
- Hyaline and amyloid deposits in stroma
- Granular changes early onset; lattice changes occur later
- Good vision in early stages; VA rarely worse than 20/70; RCEs infrequent
- Associated with the Arg124His mutation, with genotypic and phenotypic variations
- Opacities consist of an eosinophilic hyaline type deposition in the anterior stroma
- Pts do well with PTK when VA deteriorates

3-Lattice Dystrophy
Type I
- Opacities consist of thin, translucent lines composed of amyloid; deposits in mid-
stroma
• Good vision until later in life—may need PK
• Changes are central but extend to the periphery over time
• Is bilateral, but can be asymmetric and unilateral
• Epithelial erosions can occur
• Mutation localized to the TGFBI gene (5q31)

Lattice Dystrophy
Type III and IIIA
• Type III
  – Thick lattice lines extending to the periphery
  – Occurs later in life
  – Inheritance pattern is autosomal recessive
  – No recurrent epithelial erosions
  – Mutation is on the TGFBI (BIGH3) gene on chromosome 5 same site (5q3)
• Type IIIA
  – Autosomal dominant
  – Recurrent epithelial erosions
  – Same phenotypic presentation as Type III but different mode of inheritance and corneal erosions

Lattice Dystrophy
Type IV
• Another late-onset lattice dystrophy
• Deep stromal opacities made of amyloid
• Mutation localized to the TGFBI gene on chromosome 5 (5q3)
• Other atypical forms of LCD have been described that combine characteristics of the other types.

Other Stromal Dystrophies (Not TGFBI)

Lattice Dystrophy Type II
• Associated with systemic amyloidosis
• Deposition of amyloid in many tissues of the body including skin, arteries, sclera and peripheral nerves
• Corneal changes occur later in life
• Mutation localized to the gelsolin (GSN) gene on chromosome 9 (9q34)
-Gelsolin modulates removal of actin in inflammation and injury; mutations result in the build-up of amyloid

**Macular Dystrophy**
- Autosomal recessive; least common and most severe; early onset
- Three types have been described based upon the presence of antigenic keratan sulfate
- Vision more severely affected than in other stromal dystrophies
- Characterized by stromal haze, and milky white opacities (glucosaminoglycans; descemet’s membrane and the endothelium can be involved –with gutatta)
- Progresses to corneal periphery by ages 20-30
- By age 40, PK may be required
- Mutation localized to the carbohydrate sulfotransferase (CHST6) gene on chromosome 16 (16q22) resulting in an impairment in a major step in the production of keratin sulfate

**Gelatinous Drop-Like Dystrophy**
- Rare, autosomal recessive dystrophy that resembles band keratopathy initially and then progresses into mulberry-like gelatinous deposits made up of amyloid below the epithelium and stroma
- Symptoms include photophobia, foreign body sensation and decreased vision.
- Mutations in the M1S1 gene on chromosome 1p31 that encodes for protein kinase C substrate

**Central Crystalline Dystrophy of Schnyder**
- Characterized by central crystalline stromal cholesterol deposits, sometimes with an arcus
- Visual acuity only reduced if opacities are dense
- Only dystrophy associated with a systemic disorder
- Rule out hyperlipidemia
- Mutation localized to chromosome 1 (1p34-36)

**Fleck Dystrophy (Francois-Neetans)**
- Subtle grey opacities consist of small, wreath-like opacities in the stroma
  - Represent engorged keratocytes
- Usually asymptomatic
  - Cases with photophobia, ocular surface irritation and blepharospasm have been recently reported
- Opacities extend to the periphery
- Visual acuity good throughout life since stroma between flecks remains clear
- Maps to chromosome 2q35 and associated with mutations in the PIP5K3 gene, which encodes for an enzyme that has protein and lipid kinase activity.
Central Cloudy Dystrophy

- Central opacity in stroma looks like cracked-ice or crocodile skin
- Visual acuity is usually normal
- Appearance similar to crocodile shagreen, an age-related corneal change resulting in posterior stromal deposition
- Difficult to differentiate from crocodile shagreen in the late course of disease, especially if bilateral

Endothelial Dystrophies

Fuch’s Endothelial Dystrophy

- Characterized by three stages
  - guttata- localized excresences or thickenings in Descemet’s membrane
  - stromal and epithelial edema
  - corneal fibrosis or scarring
- Results in corneal edema, usually greatest upon awakening
- Women affected more frequently than men
- Affects older individuals, greater than 40 years

Treatment of Fuch’s Dystrophy

- Monitor
- If edema is present, treat with hyperosmotic agents, such as Muro 128
- Watch the ocular hypertensive: Higher IOP=More corneal edema
- In later stages, penetrating keratoplasty or DSAEK may be required
  - DSAEK: Descemet’s Stripping and Automated Endothelial Keratoplasty: New corneal endothelial cells attached to a thin layer of donor corneal tissue is transplanted through a single incision, rapid recovery; no associated astigmatism
- What about Fuch’s dystrophy and cataract?
  - Complicated procedure: cataract extraction and DSAEK/PK at the same time

Posterior Polymorphous Dystrophy

- Characterized by
  - isolated and coalesced posterior vesicles
  - wide areas of thickening of Descemet’s membrane
  - bandlike figures and lines
  - diffuse stromal and epithelial edema
  - peripheral anterior synechiae
- Treatment similar to Fuch’s dystrophy
- An unidentified gene has been mapped to the 20q11 locus of chromosome 20
Congenital Hereditary Endothelial Dystrophy (CHED)

- CHED 1
  - Autosomal dominant
  - Manifests as diffuse corneal edema a few years after birth
  - May be associated with hearing loss
  - Photophobia, tearing
  - Is progressive
  - Mutation for CHED1 has also been mapped to 20p11-20q11 on chromosome 20-overlaps the location of the mutation causing PPD!

- CHED 2
  - Autosomal recessive
  - Central corneal edema from birth
  - Nystagmus
  - Non-progressive but more severe edema than CHED1

Summary of the Molecular Genetics of the Corneal Dystrophies

- Meesmann’s
  - KRT 3, KRT 12 genes on chromosomes 12, 17

- Lisch (Whorled)
  - Unidentified gene on X chromosome

- Reis-Buckler’s (Granular Type III)
  - TGFBI gene on chromosome 5

- Granular Dystrophy
  - TGFBI chromosome 5

- Lattice I,III,IV
  - TGFBI,chromosome 5

- Lattice II
  - GSN,chromosome 9

- Macular Dystrophy
  - CHST6 gene,chromosome 16

- Crystalline Dystrophy
  - Unidentified gene, chromosome 1

- CHED1 and PPD
  - Unidentified gene on chromosome 20
Consider Classification by Affected Chromosome

- **Chromosome 1**
  - Central crystalline dystrophy
  - Early onset Fuch’s dystrophy
  - Posterior polymorphous dystrophy
- **Chromosome 2**
  - Fleck dystrophy
- **Chromosome 5**
  - Lattice dystrophy (Types 1, III and IV)
  - Granular dystrophy Type I
  - Granular Dystrophy Type II (Avellino Dystrophy)
  - Reis-Buckler’s dystrophy (GCDIII)
- **Chromosome 9**
  - Lattice dystrophy Type II
- **Chromosome 12**
  - Meesman dystrophy (and 17)
- **Chromosome 16**
  - Macular corneal dystrophy
- **Chromosome 20**
  - Congenital Hereditary Endothelial Dystrophy Types I and II
  - Posterior Polymorphous Dystrophy
- **X-chromosome**
  - Lisch corneal dystrophy

**Implications of Molecular Genetics for the Future**

- Knowledge of mutations enables researchers to identify the pathways that synthesize abnormal proteins which are deposited in the cornea
- This knowledge can lead to the development of new drugs designed to interfere with these pathways to decrease abnormal protein synthesis
- **Less deposition = less affect on vision = less need for treatment**