# Corneal Opacity and Genetics

**Review Article**

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## ABSTRACT

The cornea is the outer layer of the eye and has clarity and strength. Its clarity important for vision. The cornea is a transparent avascular connective tissue. The human cornea consists of 5 layers; 3 cellular (epithelium, stroma and endothelium) and 2 interfaces (Bowman's membrane and Descemet's membrane). Corneal opacification is a medical condition that affects the light transmission through the cornea. Corneal opacification may be unilateral or bilateral, in the form of corneal clouding, central, peripheral or diffuse opacity. Corneal opacities may occur in an isolated form or in association with various syndromes and diseases. Corneal opacification may include Congenital Corneal Opacification, Cornea Plana, superficial, stromal and posterior Corneal Dystrophies, keratoendotheliitis fugax hereditaria and Keratoconus. Several genes are implicated in corneal opacification. They may be genetically determined and may show genetic heterogeneity. They may have an autosomal dominant, an autosomal recessive or X-linked inheritance. This review will discuss different gene involvement with corneal opacities.

**Key Words:** Cornea, genetic, opacification, syndromes..

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## INTRODUCTION

The cornea is the outer layer of the eye and has clarity and strength. Its clarity important for vision. The cornea is a transparent, avascular connective tissue that is the basic structure of the eye and forms a barrier against infection. Together with the tear film, it also ensures that the eye has a sufficient preliminary refractive surface. The average horizontal diameter of an adult's cornea is between 11.5 and 12.0mm; which is approximately 1.0mm larger than the vertical diameter. Its thickness is approximately 0.5mm in the center and gradually increases towards the periphery. The peripheral part of the cornea shape is flatter and the central part is steeper, creating an aspherical optical system. The human cornea consists of 5 layers; 3 cellular (epithelium, stroma and endothelium) and 2 interfaces (Bowman's membrane and Descemet's membrane) (Figure 1) (**DelMonte and Kim, 2011**). The cornea is among the most densely innervated and sensitive tissues on the surface of the body. It is richly innervated with sensory nerves that function to detect and clear harmful debris from the surface of the eye, promote growth and survival of the corneal epithelium and hasten wound healing following ocular disease or trauma (**Schwend, 2023**).

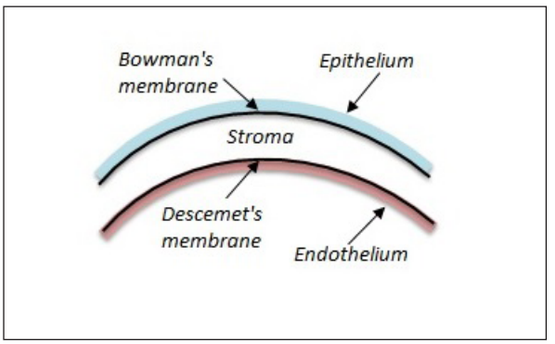


**Figure 1:** The five layers of the cornea. Arranged from anterior to posterior as follow: epithelium, Bowman's membrane, stroma, Descemet's membrane and endothelium.

Corneal opacification is a medical condition that affects the light transmission through the cornea. Corneal opacification may be unilateral or bilateral, in the form of corneal clouding, central, peripheral or diffuse opacity. Corneal opacities may occur in an isolated form or in association with various syndromes and diseases (**Ludwig and Czyz, 2018**).

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**I. Congenital Corneal Opacification:**

Congenital corneal opacification (CCO) embraces of a broad spectrum of disorders with various causes of corneal opacity, which are present at birth, including genetic causes. CCO is considered part of Anterior Segment Developmental Anomalies (ASDA) (**Mataftsi *et al.,* 2011**).

According to the clinical features, CCOs can be divided into Peter's anomaly (PA), sclerocornea with cornea plana (S-CNA) and total "sclerocornea" (S-CCO). PA consists of irido-corneal or kerato-lenticular adhesions, resulting in central or eccentric, localized or total corneal opacifications. S-CNA is characterized by peripheral corneal scleralization and is always accompanying cornea plana. Whereas, S-CCO is characterized by total corneal opacification resembling the sclera (**Mataftsi *et al.,* 2011**).

Several genes are implicated in CCO showing the genetic heterogeneity. These have been known to cause ASDA, including CCO in some patients. However, none of these have been identified as the most common cause of CCO. These include mutations in the paired box 6 (*PAX6*), pituitary homeobox 2 (*PITX2*), forkhead box C1 (*FOXC1*) and forkhead box E3 (*FOXE3*) genes with dominant inheritance pattern. These also include mutations in the genes beta 1,3- galactosyltransferase-like (*B3GALTL*) and keratocan (*KERA*) with recessive inheritance pattern. Additionally, chromosomal abnormalities in CCO may involve genes other than those listed. However, no studies have linked CCO to genetic disruptions on chromosomes 7, 15, 16, 19, and 20 (**Mataftsi *et al.,* 2011**).

Moreover, corneal dermoid and *CYP1B1* cytopathy, or internal corneal ulcer of Von Hippel are considered other types of CCO. Corneal dermoid is considered as choristomas for being a normal tissue in an abnormal site. It is either central or more commonly epibulbar. It may occur either isolated or associated with Goldenhar syndrome. Trisomy 8 mosaicism should be suspected with large central corneal dermoid. Bilateral corneal dermoid are most often seen in MIDAS (Microphthalmia, Dermal Aplasia and Sclerocornea) or MLS (Microphthalmia with Linear Skin defects) syndromes (**Nischal, 2015**).

In *CYP1B1* cytopathy, corneal opacity is caused by central absence of Descemet, endothelium and the Bowman layers. Resistant glaucoma is present with normal corneal diameter. It is associated with *CYP1B1* mutations (**Nischal, 2015; Oliva-Biénzobas *et al.,* 2017**). Biallelic *CYP1B1* pathogenic variants have a variable phenotype. One is termed Peters anomaly type 1 (with iridocorneal adhesions, with or without iridolenticular adhesions) and the other is a limbus-to-limbus opacity, termed *CYP1B1* cytopathy (**Franco *et al.,* 2024**).

A Case Series were done to identify suspected genes responsible for CCO, chromosomal breakpoints in patients with and without CCO were compared in 30 patients with 22q11.2 deletion syndrome seen in an ophthalmology clinic. However, the possible candidate genes for corneal opacification in 22q11.2 deletion syndrome remain elusive (**Franco *et al.,* 2023**).

**II. Cornea Plana:**

Cornea plana (CNA) is a congenital disease, which is described by abnormal flattening of the corneal contour and high secondary hyperopia. There are two types of CNA; an autosomal dominant (CNA1) and an autosomal recessive (CNA2). Both types were assigned to chromosome 12q. No genes had been implicated in CNA1 type. However, mutations in the *KERA* gene located on chromosome 12, have been described in families affected with CNA2. The *KERA* gene encodes the keratocan protein. Keratocan plays an vital part in maintaining the corneal transparency by adjusting the spacing of the collagen fibrils that form the corneal structure (**Pellegata *et al.,* 2000; Lehmann *et al.,* 2001; Khan *et al.,* 2004; Aldave *et al.,* 2007; Liskova *et al.,* 2007a; Nischal, 2015**).

**III. Corneal Dystrophies:**

Corneal dystrophies are a group of heterogeneous, bilateral, genetically determined, non-inflammatory corneal diseases that affect only the cornea. They are characterized by a progressive loss of corneal transparency due to the accumulation of deposits in the various layers of the cornea (**Poulaki and Colby, 2008; Klintworth, 2009; Moshirfar *et al.,* 2024**).

Clinically, corneal dystrophies can be divided into three groups depending on the anatomical location of the abnormalities. Anterior corneal dystrophies are dystrophies that affect the corneal epithelium and its basement membrane or the Bowman layer and the superficial corneal stroma. Stromal corneal dystrophies are caused by corneal stroma affection. However, posterior corneal dystrophies affect Descemet membrane and corneal endothelium. Corneal dystrophies mode of inheritance can be simple autosomal dominant, autosomal recessive or X-linked recessive. Corneal dystrophies should be suspected if there is loss of corneal transparency or it may occur spontaneously, particularly in both corneas with the presence of a positive family history or in the children of consanguineous parents (**Klintworth, 2009; Moshirfar *et al.,* 2024**).

The age of onset of various types of corneal dystrophy varies and may reflect differences in the underlying cause of the defect. Rarely, corneal dystrophies are congenital and represent developmental abnormalities (**Klintworth, 2009**).

*a. Superficial Corneal Dystrophies*

There are six types of corneal dystrophies in this group. These include Meesmann dystrophy (MECD), Thiel-Behnke dystrophy (TBCD), Reis-Bücklers corneal dystrophy (RBCD), Lisch epithelial corneal dystrophy

(LECD), Gelatinous drop-like corneal dystrophy (GDCD), epithelial recurrent erosion dystrophy (ERED) and Sub-epithelial mucinous corneal dystrophy (SMCD). These dystrophies are characterized by abnormalities of the corneal epithelium and Bowman membrane, and they may include also the corneal superficial stroma. Their main clinical features are summarized in table 1. All types of superficial corneal dystrophies have autosomal dominant mode of inheritance except GDCD which is autosomal recessive and LECD which is X-linked recessive (**Klintworth, 2009; Moshirfar *et al.,* 2024**).

**Table 1:** Summary of some Features of Superficial Corneal Dystrophies:

| Superficial Corneal Dystrophies | | | | | | |
|---|---|---|---|---|---|---|
| | **Onset of the disorder** | **Visual acuity** | **Corneal layer affected** | **Main pathology** | **Mode of inheritance** | **Implicated Genes** |
| MECD | Early childhood | Rarely blurred | Epithelial layer | Multiple distinct vesicles | AD | KRT3, KRT12 |
| RBCD | Childhood | Progressive visual impairment | Bowman layer and superficial stroma | Confluent irregular geographic opacities | AD | TGFBI |
| TBCD | 1st/2nd second decade | Progressive visual impairment | Subepithelial layer | Honeycomb opacities in central superficial cornea | AD | TGFBI, unknown gene on 10q23–q24 |
| GDCD | 1st/2nd second decade | Marked visual impairment | Subepithelial layer | Nodular deposits with late staining of fluorescein | AR | TACSTD2 |
| LECD | Childhood | Sometimes impaired | Epithelial layer | Opacities in different patterns | XR | unknown gene on Xp22.3 |
| ERED | 1st decade | Sometimes impaired | Epithelial layer | Erosions | AD | unknown |
| SMCD | 1st decade | Progressive loss of vision | Subepithelial layer | Opacities | AD | unknown |

It is currently known that mutations in *KRT3, KRT12*, *TGFBI*, and *TACSTD2* can cause inherited superficial corneal dystrophies. While mutations in *KRT3* gene, located on 2q13 and *KRT12* gene, located on 17q12 are implicated in MECD. They encode the two units of cytokeratin in the corneal epithelium. P. Arg19Leu amino acid change in the cytokeratin 12 may cause Stocker-Holt corneal dystrophy which is a variant of MECD (**Irvine *et al.,* 1997; Klintworth *et al.,* 1999; Klintworth, 2009**).

It is well-documented that all cases of RBCD (Granular corneal dystrophy type III) are due to precise mutation (p. Arg124Leu) in the *TGFBI* gene, which is located on chromosome 5q31. Additional mutations in the same gene (*TGFBI* gene) have been reported in patients having RBCD or an atypical variant, without histopathologic confirmation (**Li *et al.,* 2008; Klintworth, 2009**).

Also, TBCD was mapped to 5q31, which was associated with TGFBI mutation. Genetic heterogeneity exists and another locus for TBCD has been identified on chromosome 10q23–q24 (**Delpech and Valleix, 2001; Klintworth, 2009**).

Over 20 mutations in the *TACSTD2* gene which is located on 1p32, were assumed to cause GDCD. This gene encodes tumor-associated calcium signal transducer 2. The p. Gln118X mutation is the most commonly detected. Some affected individuals with GDCD do not have *TACSTD2* mutations, suggesting genetic heterogeneity existence in this disease (**Ren *et al.,* 2002; Klintworth, 2009**).

The causative gene for LECD is located to Xp22.3. While, the genes responsible for ERED or SMCD require assignment to a specific chromosomal locus (**Lisch *et al.,* 2000; Klintworth, 2009**).

*b. Corneal Stromal Dystrophies*

Corneal dystrophies include seven types; macular corneal dystrophy (MCD), lattice corneal dystrophies (LCD), granular corneal dystrophy (GCD), fleck corneal dystrophy (FCD), Schnyder corneal dystrophy (SCD), congenital stromal corneal dystrophy (CSCD) and posterior amorphous corneal dystrophy (PACD). These dystrophies are characterized by abnormalities of the stroma of the cornea. Their main clinical manifestations are summarized in table 2. All types of corneal stromal dystrophies have autosomal dominant inheritance except MCD which has autosomal recessive inheritance (**Klintworth, 2009**).

*CHST6* gene mutations are responsible for most cases of MCD. More than 125 *CHST6* gene mutations had been identified. These mutations are in the coding region of *CHST6* either in the form of insertions or major deletions in the upstream region, or splice site mutations. Also insertional or deletional defects in the region between *CHST5* and *CHST6* genes may be the causative mutations in some cases. However, allelic heterogeneity in *CHST6* was reported in various populations. The most recurrent aberrations are in the form of missense and nonsense single nucleotide polymorphisms (SNPs) in *CHST6* gene which in turns change a conserved amino acid (**Liu *et al.,* 2000; Klintworth *et al.,* 2006; Klintworth, 2009**).

**Table 2:** Summary of the most common features of Corneal Stromal Dystrophies:

| **Corneal Stromal Dystrophies** | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | **Onset of the disorder** | **Visual acuity** | **Slit lamp examination** | **Mode of inheritance** | **Implicated Genes** | **common mutation** |
| MCD | | Usually childhood | Ultimately severe visual impairment | Thinner than normal cornea accompanied with diffuse corneal haze and irregular shaped whitish opacities | AR | CHST6 | >125 CHST6 mutations |
| GCD | Type I | Childhood | Progressive visual impairment | Well-defined granules resembling crushed bread crumbs in a crystal clear cornea | AD | TGFBI | p. Arg555Trp |
| | Type II | 1st/2nd decade | | Variable shaped opacities in a clear superficial mid stroma of the cornea. Lattice lines sometimes appear in deeper cornea | | TGFBI | p. Arg124His |
| LCD | Type I | 1st decade | Usually normal until 6th decade | Delicate branching interwoven linear opacities in association with ovoid dots | AD | TGFBI | p. Arg124Cys |
| | Type II | 3rd/4th decade | Progressive visual impairment | Corneal opacities forming lattice lines found mainly in the peripheral cornea | | GSN | p. Asp187Asn, p. Asp187Tyr |
| SCD | | Early in life | Progressive visual impairment | Central corneal haze or Sub-epithelial crystals | AD | UBIAD1 | - |
| FCD | | At birth | Normal | small discrete dandruff or ring-shaped flake like opacities | AD | PIP5K3 | - |
| CSCD | | Before birth | Moderate to severe visual impairment | Diffuse corneal clouding with flake like opacities throughout the stroma | AD | DCN | 1 bp deletion in the DCN gene, DCN frame shift mutation |
| PACD | | Infancy or childhood | Mildly affected | Diffuse sheet-like opacities especially in posterior corneal stroma | AD | Unknown | - |

There are two types of GCD; Type I (GCD1) and Type II (GCD2). Sometimes, GCD2 resemble a combination of GCD and LCD. *TGFB1* gene was implicated in GCD. GCD1 is the consequence of p. Arg555Trp mutation, while GCD2 is due to a p.Arg124His mutation in the *TGFBI* gene (**Korvatska *et al.,* 1998; Akimune *et al.,* 2000; Blanco-Marchite *et al.,* 2007; Klintworth, 2009**).

As for LCD, there are two genetically different inherited disorders. One is due to particular mutations in the TGFBI gene (causing LCD type I and all its variants) (LCD1) that is not associated with systemic manifestations. The most of cases of LCD1 is caused by a p.Arg124Cys mutation in exon 4 of the *TGFBI* gene. The other type of LCD is caused by mutation in the GSN gene (LCD type II) (LCD2) and is always associated with systemic manifestations. GSN gene is located on 9q34 and encodes the actin modulating protein gelsolin. The identified mutations of *GSN* gene that cause LCD2 are p.Asp187Asn and p.Asp187Tyr. However, LCD2 is no longer included among the corneal dystrophies as it is a primarily systemic disorder with ophthalmologic features and recently described as familial amyloid polyneuropathy (FAP) type IV (**Munier *et al.,* 1997; Hotta *et al.,* 1998; Blanco-Marchite *et al.,* 2007; Klintworth, 2009; Moshirfar *et al.,* 2024**).

Mutations in the *UBIAD1* gene is the cause of SCD (**Orr *et al.,* 2007; Weiss *et al.,* 2007**). Mutation in the *PIP5K3* gene is the cause of FCD (**Li *et al.,* 2005**). CSCD is extremely rare. A 1 bp deletion in the *DCN* gene encoding the core protein of decorin was reported in a family having CSCD, whereas a *DCN* frame shift mutation was reported in another family (**Bredrup *et al.,* 2005; Rødahl *et al.,* 2006**). Moreover, a novel heterozygous frameshift deletion in exon 8 of *DCN* (p.His317Thrfs*11), predicted to cause a 33 amino acid truncation and to be the damaging and disease causing were found in 3 of 6 individuals diagnosed with CSCD in 4 consecutive generations of an Armenian family (**Williams *et al.,* 2023**). However, the gene responsible for the PACD is not yet determined (**Klintworth, 2009**).

PACD is a rare genetic disorder of the cornea. A case report on a 12-year-old girl having PACD with a 447-kb deletion that included the small leucine-rich proteoglycan-coding region at 12q21.33 suggesting that PACD may be a contiguous gene syndrome (**Basbus *et al.,* 2022**).

*c. Posterior Corneal Dystrophies*

The posterior corneal dystrophies comprises of four types; Congenital hereditary endothelial corneal dystrophy (CHED), Fuchs corneal dystrophy (FECD), posterior

polymorphous corneal dystrophy (PPCD) and X-linked endothelial corneal dystrophy (XECD). They are described by corneal endothelium and Descemet membrane abnormalities. In the majority, a defective active fluid transport by the corneal endothelium may occur causing excessive edema of the corneal stroma which ruins the corneal clarity and lessens visual acuity. Their main clinical features are summarized in table 3. (**Klintworth, 2009, Guier *et al.,* 2023**).

**Table 3:** Summary of some Features of Posterior Corneal Dystrophies:

| **Posterior Corneal Dystrophies** | | | | | | |
|---|---|---|---|---|---|---|
| | | **Onset of the disorder** | **Visual acuity** | **Slit lamp examination** | **Mode of inheritance** | **Implicated Genes and common mutation** |
| FECD | Early onset | 1st decade progressing through the 2nd to 3rd decades | Progressive visual impairment | Diffuse thickening of Descemet membrane with excrescences (guttae). Endothelial cells sparse and atrophic | AD | COL8A2 p. Leu450Trp, p. Gln455Lys |
| | late onset | 2nd to 3rd decades manifesting at 5th to 6th decades | | | | SLC4A11, TCF8 and unknown gene on 13pTel-13q12.13, 18q21.2-q21.32 |
| PPCD | | Early childhood | Rarely progressive visual impairment | Variable shaped abnormalities of the corneal endothelium | AD | TCF8, unknown gene on 20q11 |
| CHED | Type1 | Occasionally at birth, but usually in 1st/2nd decade | Blurred vision that deteriorates in the morning | Thickened cornea with diffuse clouding with occasional focal gray spots | AD | unknown gene on 20p11.2-q11.2 |
| | Type2 | At birth | Blurred vision | | AR | SLC4A11 |
| XECD | | At birth | Blurred vision in males | Cloudy cornea with moon crater-like endothelial cells | XR | unknown gene on Xq25 |

FECD cause is still unknown. FECD may have an autosomal dominant mode of inheritance with incomplete penetrance. FECD usually affects females more frequently for undetermined reason. Early onset FECD had been linked with *COL8A2* gene mutation which is located on 1p34.3. A p.Leu450Trp mutant in *COL8A2* gene is one of the mutations that had been reported. Moreover, p.Gln455Lys mutation in the *COL8A2* gene was identified in early onset autosomal dominant variant of both FECD and PPCD suggesting that these two disorders are interrelated to each other. Furthermore, late onset FECD have been mapped to 13pTel-13q12.13 and 18q21.2-q21.32. Heterozygous mutations in the *SLC4A11* gene that is located on 20p13-p12, have been also implicated in late-onset FECD. A single unique mutation in the TCF8 gene (located on 10p11.2) causing PPCD type 3, was found in only one patient with FECD (**Biswas *et al.,* 2001; Sundin *et al.,* 2006a; Sundin *et al.,* 2006b; Liskova *et al.,* 2007b; Mehta *et al.,* 2008; Vithana *et al.,* 2008; Klintworth, 2009**).

PPCD is a genetically heterogenous disorder with autosomal dominant inheritance and characterized by extremely variable expression. *VSX1, COL8A2, TCF8* genes had been related to PPCD. Nevertheless, relating *VSX1* and *COL8A2* to PPCD is still undetermined. p.Leu159Met and p.Gly160Asp mutations in *VSX1* had been described, nevertheless studying two large families having PPCD, had excluded the *VSX1* gene. A missense p.Gln455Lys mutation in the *COL8A2* gene was reported in family having PPCD, without histopathologic confirmation. However, suggestion for *TCF8* gene, which encodes transcription factor 8, is more substantial. Moreover, the peri-centromeric region of chromosome number 20 (20q11) has been implicated in PPCD, which is the same region that carries a gene for CHED1. PPCD shares the same clinical, developmental and morphological manifestations with CHED1, and one variant of PPCD is probably linked to CHED1 (**Biswas *et al.,* 2001; Gwilliam *et al.,* 2005; Krafchak *et al.,* 2005; Klintworth, 2009**).

Two types of CHED are documented; CHED1 (which is autosomal dominant) and CHED2 (which is autosomal recessive). CHED1 responsible gene was mapped to the peri-centromeric area of chromosome 20 (20p11.2-q11.2) in an overlapping genetic area for one variant of PPCD as mentioned before. Most cases of CHED2 are caused by homozygous mutations in the *SLC4A11* gene, which encodes bicarbonate transporter-related protein 1 that regulates the intracellular boron concentration. A high degree of mutational heterogeneity has been detected in CHED2 and genetic heterogeneity may exist as no mutations in *SLC4A11* or in its promoter region have been detected in some families (**Toma *et al.,* 1995; Desir *et al.,* 2007; Jiao *et al.,* 2007; Sultana *et al.,* 2007; Hemadevi *et al.,* 2008; Shah *et al.,* 2008; Klintworth, 2009**).

Males having XECD are affected in a more severe form than female XECD patients. Due to the X-linked recessive inheritance, affected fathers are transmitting this disease to their daughters, but not to their sons. XECD was mapped Xq25 (**Schmid *et al.,* 2006; Klintworth, 2009**).

**IV. Keratoendotheliitis fugax hereditaria:**

It is an auto-inflammatory keratitis with autosomal dominant inheritance that intermittently affects the corneal endothelium and stroma. It may lead to opacities and visual acuity deterioration in some cases. It is due to a missense mutation c.61G>C (p. Asp21His) in exon 1 of *NLRP3*, encoding cryopyrin. Cryopyrin is a member of the NLR family of proteins. They are involved in the immune system and they control the reactions to various environmental triggers (**Turunen *et al.,* 2018, Moshirfar *et al.,* 2024**).

This disease was first described in 1964 by the Finnish ophthalmologist as keratitis fugax hereditaria. There are reports on only two Finnish families with 31 affected members till now. Generally, Keratoendotheliitis may occur solely as a sporadic idiopathic finding or in association with various types of viral keratitis. However, there is no other reports of familial keratoendotheliitis. Moreover, no reports were found to exist of keratoendotheliitis fugax hereditaria in other population. However, this disease may also affects other European origin populations (**Valle, 1966; Ruusuvaara and Seta¨la¨, 1987; Inoue, 2014; Turunen *et al.,* 2018**).

The disease is manifested by unilateral attacks of ocular pain, pericorneal injection, and photophobia. Slit-lamp corneal examination shows transiently edematous endothelial cells, mildly edematous stroma, and occasionally a mild anterior chamber reaction. The acute symptoms may vanish in 1-2 days but vision stays blurred for multiple weeks. The attacks begin at the age of 3-12 years and may affect both eye. The frequency decreases and gets milder with age. Oval central stromal opacities may occur, compromising vision in older patients (**Valle, 1966; Ruusuvaara and Seta¨la¨, 1987; Rao *et al.,* 2016**).

**V. Mucopolysaccharidosis:**

Mucopolysaccharidosis (MPS) is a group of genetic disorders that is associated with corneal opacities. It consist with seven types and 13 subgroups. They are characterized by an intrinsic deficiency of the enzymes in charge for the degradation of glycosaminoglycans (GAGs). Failure of degradation of GAG products leads to their extensive accumulation within the lysosomes of various organs including the eye. Its clinical manifestation varies from mild systemic and ocular abnormalities with a normal life span to severe phenotype, fatal in the first few months of life. Visual disability is due to corneal clouding, and other ocular manifestations (**Nagpal *et al.,* 2022**).

MPS is inherited as an autosomal recessive trait except type II, the Hunter's syndrome, which has an X linked inheritance. Several genes are involved such as *IDUA* located on chromosome 4p16 for Type I MPS, *IDS* on chromosome Xq28 for Type II MPS, *SGSH* (chromosome 17q25.3) and *NAGLU* (chromosome 17q. 21.1) for Type III A and B respectively, *GALNS* (chromosome 16q24) and *GLB1* (chromosome 3p21) for Type IV A and B respectively, *ARSB* located on chromosome 5q11 for Type VI, *GUSB* (chromosome 7q11) leads to Type VII and *HYAL1* on chromosome 3p21 leads to Type IX (**Nagpal *et al.,* 2022**).

**VI. Keratoconus:**

Keratoconus (KC) is a Greek word. Keras means cornea and konos means cone. It was firstly described in 1854 (Nottingham). Most KC cases are bilateral, progressive, non-inflammatory localized paraxial stromal thinning of the cornea leading asymmetrical corneal distortion and anterior corneal protrusion. This results in significant impairment of visual acuity due to development of high myopia and irregular astigmatism (**Wheeler *et al.,* 2012; Moussa *et al.,* 2017**).

Keratoconus usually occurs in the teen's age of life. It continues to develop over the next twenty years until it becomes stable. KC affects both men and women. KC affects both men and women. Slit lamp examination may shows Fleischer's ring that is present around the cone at the basal epithelium which may be partial or complete and is due to iron deposition, Vogt's striae which are fine vertical lines due to compression of Descemet's membrane, and Münson's sign which is bulging of the lower lid on downgaze caused by corneal protrusion. Corneal hydrops and acute stromal edema due to breaks in Descemet's membrane leading to stromal scarring may occur in acute KC. Corneal tomography is the most sensitive diagnostic tool to detect keratoconus even in early stages (**Wheeler *et al.,* 2012**).

The cause of KC is not fully known. KC etiology is multifactorial, beside the genetic factors, the environmental factors usually play a significant role. They have a triggering role in genetically predisposed individuals. The relative contribution of the environmental factors such as eye rubbing, atopy against dust, pollen, animal fur or antibiotics and UV exposure is unknown. It is presumed that environmental factors cause oxidative stress in the KC cornea. KC corneas are unable to produce reactive oxygen species (ROS) due to the deficiency of corneal enzymes such as aldehyde dehydrogenase type 3 (ALDH3), catalase, or superoxide dismutase to eliminate or neutralize ROS, leading to the degradation process that leads to corneal thinning and vision loss (**Cristina Kenney and Brown, 2003; Romero-Jiménez *et al.,* 2010; Moussa *et al.,* 2017**).

Although the most common types of KC is sporadic, it occurs in numerous families. Most of familial KC is of autosomal dominant inheritance. However, autosomal recessive pattern was also suggested, particularly in high consanguineous populations. First degree family members are at greater risk than normal individuals. About 6 - 23.5% of KC patients have a positive family history (**Moussa *et al.,* 2017**).

Not less than 17 genomic loci from 12 different studies have been identified in KC patients suggesting genetic heterogeneity. Many chromosomal locations were implicated in KC, such as 5q21.2, 5q23.2, 5q32-33, 14q11.2, 16q23 and 16q22.3-q23.1 (**Tyynismaa *et al.,* 2002; Tang *et al.,* 2005; Li *et al.,* 2006; Bisceglia *et al.,* 2009; Wheeler *et al.,* 2012**).

Large number of candidate genes have been evaluated in relation to KC pathogenesis, but only few genes have been identified. *VSX1* (Visual System Homeobox 1) is located on 20p11–q11. This locus was implicated in PPCD also. It was reported that PPCD is associated with KC. *VSX1* encodes a pairlike homeodomain transcription factors family. It is usually expressed by keratocytes in injured corneas and plays a role in fibroblastic transformation. R166W and L159M mutations in *VSX1* were reported in KC. Another two heterozygous mutations (N151S and G160V) and an intragenic polymorphism were considerably linked to increased risk of KC in Korean population. A missense heterozygotic change (p.Leu268His) was found in five KC patients from two unrelated families. It is unclear whether and how *VSX1* mutations affect KC pathogenesis. (**Wheeler *et al.,* 2012; Moussa *et al.,* 2017**).

*DOCK9* (Dedicator of cytokinesis 9) is a strong candidate gene for keratoconus. *DOCK9* encodes a member of the DOCK family of proteins that has GTP/GDP exchange activity and specifically activates the G protein CDC42. Mutations in *DOCK9* were previously reported by sequencing candidate genes in identified linkage locus at 13q32. This locus was first identified in a large dominant KC Ecuadorian family. However, this finding needs further verification by replication in other keratoconus families (**Gajecka *et al.,* 2009; Czugala *et al.,* 2012**).

A targeted NGS population study identified a total of 167 allelic variants of 22 genes; comparing stable keratoconus and progressive disease. They identified genetic variants of certain pathogenic significance patients with progressive KC; in addition, eight novel genetic variants. Mutations of *FLG, LOXHD1, ZNF469*, and *DOCK9* genes were twice more frequently identified with progressive than stable cases (**Lombardo *et al.,* 2024**).

miR-184 is a microRNA, a small RNA regulatory RNA strands, 19-25 nucleotides long. They usually bind to the 3' untranslated region (UTR) of target gene mRNAs and cause mRNA degradation or translational inhibition. It is expressed in the central corneal epithelial basal and supra-basal cells and in the lens epithelium. Mutations in the miR-184 gene have been reported in families with keratoconus and early frontal pole cataracts. This genomic region, 15q22-q25, was previously mapped as a keratoconus linkage locus. The inheritance was autosomal dominant. However, another study considered mutations in *MIR184*, a rare cause of keratoconus and were found in only 0.25% of cases (**Hughes *et al.,* 2011; Lechner *et al.,* 2013**). Recent study was carried out to identify precursor microRNAs (pre-miRNAs) that differentially expressed in Keratoconus and to characterize mature miRNAs and their target genes suggesting that miRNAs and their target genes might be involved in KC pathogenesis via disruption of crucial molecular processes, including extracellular matrix organization and signal transduction (**Nowak-Malczewska *et al.,* 2024**).

As oxidative stress has been assumed to play a role in KC etiology, *SOD1* (Superoxide dismutase 1) has been investigated as a candidate gene in many KC-related studies. *SOD1* encodes a major cytoplasmic antioxidant enzyme. It metabolizes superoxide radicals and provides a defense against oxygen toxicity. However, no mutations in *SOD1* have been recognized in KC patients. Further investigation is needed to determine whether *SOD1* plays a significant role in the pathogenesis of KC (**Wheeler *et al.,* 2012; Moussa *et al.,* 2017**).

Although most of the keratoconus patients occur as an isolated disorder, keratoconus has been reported to be linked with other ocular, syndromic or systemic disorders such as pigmentary retinopathy, Leber congenital amaurosis, Marfan's syndrome, Down syndrome, mitral valve prolapse and collagen vascular disease. Associations between keratoconus and connective tissue disorders have also been reported; these include osteogenesis imperfecta, GAPO syndrome, type IV Ehlers-Danlos syndrome, and mitral valve prolapse. However, the potential contribution of the associated disorders with keratoconus further highlights the genetic heterogeneity in keratoconus pathogenesis (**Wheeler *et al.,* 2012**).

**Gene therapy and corneal dystrophies**

Corneal blindness is considered the fourth major cause of global blindness which in return leads to an enormous demand for corneal transplantation. Due to the excessive corneal graft failures, the concept of the management of corneal dystrophies changed to correct the underlying genetic cause of the disease (**Salman *et al.,* 2022**).

Gene therapy (GT) consists of 3 possible approaches: gene supplementation, gene silencing, and gene editing with 2 modes of delivery, ex vivo and in vivo in target cells. Gene supplementation involves the delivery of functional wild-type gene employing vectors carrying gene-specific cDNA or codon-optimized to enhance the gene expression. While, gene silencing requires the delivery of molecule in form of antisense RNA, si-RNA, micro-RNA, ribozymes which can inactivate the functionality of a gene involved in disease pathogenicity. Whereas, gene editing includes the delivery of a molecular system that enable targeted alterations in the host gene sequences such as TALEN (transcription activator-like effector nuclease), ZFN (zinc finger nucleases), and recentlye volved CRISPR system (clustered regularly interspaced short palindromic repeats) (**Nidhi *et al.,* 2021; Salman *et al.,* 202**2).

GT and gene editing studies were restricted in preclinical stages and prolonged sustained expression of transgene and could not be succeeded to support clinical trials. Moreover, as the majority of the corneal dystrophies are autosomal dominant, the conventional gene supplementation approach is not operational due to the dominant negative effects of the mutated gene. So, genome editing is a better approach for corneal dystrophies management. The novel approaches in CRISPR genome editing provided prospects for successful GT mangments. Ex vivo and in vivo CRISPR gene corrections in the cornea are possible (**Salman *et al.,* 2022**).

However, GT and gene editing have limitations in the presence of the existing conventional managements. Corneal dystrophies are not sight-threatening in the early stages, slowly progressive with the availability of surgical interventions. While, GT or editing requires long-term extensive research, ethically bound rules, regulations, and multiple follow-ups that does not considered a treatment of choice. In addition, the involved genetic factor of many of the corneal dystrophies, is largely unknown. So, there is no GT and gene editing treatment option available, their clinical trials are very limited, and no FDA-approved corneal GT/editing is achieved so far (**Salman *et al.,* 2022**).

## CONFLICT OF INTEREST

There are no conflicts of interest.

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