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Review Article

Genetic Perspective of Corneal Endothelial Dystrophies

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Abstract

The corneal endothelium serves primarily in maintaining stromal deturgescence which is essential for transparency of cornea. Any disturbance in its function leads to stromal edema which in turn reduces vision. The genetically heterogeneous nature of four different kinds of corneal endothelial dystrophies represents the involvement of diverse set of genes. Until now, only few genes were identified for a subclass of corneal endothelial dystrophy. Therefore, in this review, elucidated genes and their function involved in different corneal endothelial dystrophies were described to understand the pathogenesis of the disorder.

INTRODUCTION

Corneal dystrophies are defined as primary, inherited, bilateral disorders affecting corneal transparency and refraction, leading to varying degrees of visual disturbances. They are generally said to be of early onset, axial, symmetric, slowly progressive, free from vascularization, and not associated with other systemic conditions. The dystrophies have been traditionally classified according to the layer of involvement into anterior membrane dystrophies (epithelium, epithelial basement membrane, and Bowman layer dystrophies), stromal dystrophies, and endothelial dystrophies (endothelium and Descemet's membrane (DM)). Corneal endothelial dystrophies include congenital hereditary endothelial dystrophy (CHED; MIM# 217700), Fuchs endothelial corneal dystrophy (FECD; MIM# 613267 and 610158), posterior polymorphous dystrophy (PPCD; MIM# 122000), and X- linked endothelial corneal dystrophy (XECD; MIM# 300779). These endothelial dystrophies share many features including, corneal decompensation, altered morphology of endothelial cell, and secretion of an abnormal posterior collagenous layer in the posterior zone of Descemet's membrane, the endothelial basement membrane. Genetics underlying these diseases are being studied, although clinically distinct, corneal endothelial dystrophies share clinical features suggesting that genes implicated in one corneal dystrophy may also harbor mutations liable for other dystrophies (Table 1). This review focuses on the current knowledge of the genetics of corneal endothelial dystrophies.

CONGENITAL HEREDITARY ENDOTHELIAL DYSTROPHY (CHED)

CHED manifests as bilateral, symmetric, noninflammatory corneal clouding involving degeneration of the corneal endothelium without other anterior segment abnormalities, usually evident at birth or in the early postnatal period. It is characterized by diffuse ground glass opacification of the cornea, markedly thickened cornea due to edema, and a thickened DM. CHED has both autosomal dominant (CHED1; OMIM# 121700) as well as autosomal recessive (CHED2; OMIM# 217700) modes of transmission the latter more severe and usually more common. The only difference between clinical features of the dominant and recessive forms of CHED is that the recessive form may manifest earlier and is associated with nystagmus [1]. However, a careful examination of the literature indicated that CHED1 is not sufficiently distinguishable from PPCD1 to consider it a separate corneal endothelial dystrophy [2].

Hand and coworkers localized CHED2 to the short arm of chromosome 20 at 20p13 by homozygosity mapping [3]. Mutations in the sodium bicarbonate transporter-like solute carrier family 4 member 11 (*SLC4A*11, MIM610206) gene present in this locus were found to cause CHED2 [4]. Since the first description of *SLC4A11* mutations, several case reports and small case series have been published [5-17].

The *SLC4A*11 gene belongs to a super family of bicarbonate transporters. The gene has 19 exons spanning 11, 774 bp of genomic DNA, which codes for a protein of 891 amino acids with a calculated molecular mass of 100 kDa. The *SLC4A11* protein has 13 transmembrane domains and intracellular N and C termini. It contains multiple intracellular phosphorylation sites and 2 extracellular N-glycosylation sites [18]. *SLC4A*11 is also known as *BTR1* (bicarbonate transporter related protein-1) or NaBC1 (sodium-coupled borate co-transporter).

Expression of *BTR1/SLC4A*11 gene is seen in several organs and tissues, including the eye, blood, lung, ovary, colon, mouth, embryonic tissue, pancreas, kidney, skin, cranial nerve, ascites, prostate, and brain. Vithana and coworkers by in situ

Table 1: Genetic/allelic heterogeneity of corneal endothelial dystrophies.

Corneal dystrophy	Inheritance	Locus	Location	Gene	Reference	MIM*
Congenital hereditary endothelial dystrophy (CHED)	AD	*CHED1*	20p11-q11	Not known	Toma et al., 1995	121 700
	AR	*CHED2*	20p13-p12	*SLC4A11*	Hand et al., 1999; Vithana et al., 2006	217 700
Fuchs endothelial corneal dystrophy (FECD)	AD	FECD1	1p34.3–p32.3	*COL8A2*	Biswas et al., 2001; Kobayashi et al., 2004	136 800
	AD	FECD2	13pter– q12.13	Not known	Sundin et al., 2006	610 158
	AD	FECD3	18q21.2–q21.3	*TCF4*	Baratz et al., 2010	613 267
	AD	?	18q12–q21	*LOXHD1*	Riazuddin et al., 2012	613 072
	Complex	FECD4	20p13–p12	*SLC4A11*	Riazuddin et al., 2010	613 268
	AD	FECD5	5q33.1–q35.2	unknown	Riazuddin et al., 2009	613 269
	AD	FECD6	10p11.2	*ZEB1*	Riazuddin et al., 2010	613 270
	AD	FECD7	9p24.1–p22.1	unknown	Riazuddin et al., 2010	613 271
	Complex	FECD8	15q25.3	*AGBL1*	Riazuddin et al., 2013	615 523
	AD	SVD	2q37.1	*KCNJ13*	Hejtmancik et al., 2008	193 230
Posterior polymorphous corneal dystrophy (PPCD)	AD	PPCD	20p12.1-20p11.23	unknown	Liskova et al., 2012	122 000
	AD	PPCD1	20p11.2	*VSX1*	Heon et al., 2002	1220 000
	AD	PPCD2	1p34.3–p32.3	*COL8A2*	Biswas et al., 2001	609 140
	AD	PPCD3	10p11.2	*ZEB1*	Krafchak et al., 2005	609 141
		Other	2q36–q37	*COL4A3*	Krafchak et al., 2005	120 070
X-linked endothelial dystrophy (XECD)	X-linked	XECD	Xq25	Not known	Schmid et al., 2006	3009

*MIM - Mendelian inheritance in man
AGBL1 - ATP/GTP-Binding protein –Like1; *COL4A3* - collagen, type IV, alpha 3; *COL8A2*, collagen, type VIII, alpha 2; *KCNJ13* - potassium inwardly-rectifying channel, subfamily J, member 13; *LOXHD1* - lipoxygenase homology domains 1; *SLC4A11* - solute carrier family 4, sodium borate transporter, member 11; SVD - snowflake vitreoretinal degeneration; *TCF4* - transcription factor 4; *VSX1* - visual system homeobox 1; *ZEB1* - zinc finger E-box binding homeodomain 1.

hybridization showed its expression in the mouse cornea at embryonic day 8, which is equivalent to human gestational month 5, the time at which CHED2 pathology develops in humans [4]. *BTR1* is homologous to *BOR1,* a borate transporter in plants [18]. It functions as a ubiquitous electrogenic sodium-coupled borate transporter in the presence of borate, while in the absence of borate it conducts Na^+ and H^+. In view of the requirement for borate in growth and development, *BTR1* may be a mediator for these processes [19]. It is shown that *SLC4A11* prevents severe morphological changes of the cornea caused by increased sodium chloride concentrations in the stroma [20]. However it is established that in corneal endothelium SLC4A11 acts as a Na^+-dependent pH_i modulator transporting OH^- with no significant affinity to $B(OH)^{4-}$ or HCO^{3-} anions [21]. *SLC4A11* also facilitates water movement at a rate similar to AQP proteins and corneal fluid accumulation found in genetic diseases of *SLC4A11* arises at least in part from defective water movement by *SLC4A11* [22].

Mutations in SLC4A11 have also been described in Harboyan syndrome (corneal dystrophy with perceptive deafness; CDPD) which is characterized phenotypically as CHED2 with sensorineural hearing loss appearing in about the second decade of life [6]. The *SlC4A11* knockout model by [23] had a more pronounced phenotype in the ear (i.e., sensorineural deafness) similar to Harboyan syndrome while there were no phenotypic changes in the cornea. However *SlC4A11* KO mouse model by [20] revealed morphological alterations in all layers of the cornea of 12-month-old mice. *SLC4A11* KO mouse model by [24] also successfully represented clinical manifestations of human CHED as well as renal abnormalities. An in vitro study revealed that *SLC4A11* knockdown in human corneal endothelial cells led to suppressed cell growth and reduced cell viability by activating the apoptotic pathway [25].

To date 76 mutations in 17 of the 19 coding exons of *SLC4A11* have been identified indicating the high degree of allelic heterogeneity. Among the 76 mutations 74 are listed in publication by Kodaganur et al. [15], and rest two are in Park et al. [16], & Siddiqui et al. [17], publications. Although 32 of the 136 pedigrees screened to date do not demonstrate coding region mutations in *SLC4A11* [7, 10-12, 14]. Screening of the putative *SLC4A11* promoter region in 20 of these 32 families failed to demonstrate any presumed pathogenic variants [12,14]. Thus, it is possible that locus heterogeneity exists for CHED2.

FUCHS ENDOTHELIAL CORNEAL DYSTROPHY (FECD)

FECD is an adult-onset corneal disorder, which begins at 5th decade. It is a commonly occurring, progressive, bilateral, but often asymmetric, corneal dystrophy. It is characterized by the presence of guttae, which are excrescences in the Descemet's membrane described as a 'focal, refractile accumulation of

collagen posterior to the DM [26]. In later stages of the disease, corneal edema develops due to degeneration of the corneal endothelium, with consequent loss of vision. The prevalence of FECD varies markedly across the world. It affects ~4% of the USA population over the age of 40 years [27] but is less frequent in Asian [28], and Middle-Eastern populations [29]. In Australia, corneal grafting for FECD accounts for ~6% of all corneal grafts performed annually [30].

FECD is a genetically heterogeneous disease. There are two forms defined by the age of onset. Early-onset FECD is rare [31] and is typically inherited as an autosomal dominant disease with high penetrance and almost uniform expressivity [32]. The more common late-onset FECD can either be familial or sporadic, with onset typically after the age of 40 years [33]. The risk of developing the late-onset form increases with age and female sex. Familial late onset FECD shows an autosomal dominant inheritance with high penetrance, but variable expressivity [27].

FECD loci identified by genetic linkage analysis, Genome wide association studies (GWAS), Next generation sequencing & causative genes are shown in Table 1. Linkage analysis of early onset form of FECD identified a 6-7 cM interval on chromosome 1p34.3-p32. Screening of *COL8A2* (collagen, type VIII, alpha 2) gene in this interval revealed a missense mutation p.Q455K [31]. *COL8A2* is an extracellular matrix protein and is a major component of DM [34]. Similarly, Gottsch et al., identified a novel point mutation in the *COL8A2* gene with p.L450W substitution [35]. In addition, Mok et al., also identified the p.Q455V mutation in *COL8A2* in Korean Patients with FECD [36]. However *COL8A2* mutations do not play a role in the phenotypically distinct late onset form of FECD [35].

Mutations in the *ZEB1* (zinc-finger E-box binding homoebox 1) gene also known as *TCF8* can cause both sporadic and familial late-onset FECD [37,38]. *ZEB1* is expressed in the corneal endothelium [39]. It regulates cell proliferation and differentiation by inducing epithelial– mesenchymal transition [40]. Mehta and colleagues screened *ZEB1* in 74 FECD probands including 8 familial and 66 sporadic cases and found two coding region variants one of which was a synonymous substitution and a novel variant, p.N696S. Riazuddin and colleagues reported five presumed causative *ZEB1* missense mutations in 7 of 384 unrelated individuals with FECD. Three of these mutations (p.Q810P, p.Q840P and p.A905T) occurred at sites that are highly evolutionarily conserved in vertebrates, while the remaining two occur at moderately conserved sites.

The *SLC4A11* (solute carrier family 4, sodium borate transporter, member 11) mutations cause sporadic and familial late-onset FECD [41, 42]. Vithana et al., showed that heterozygous mutation in *SLC4A11* is associated with late-onset FECD by analyzing 89 unrelated patients of Chinese and Indian decent [41]. Approximately 5% of FECD in Chinese patients and 4% of FECD in Indian patients attributed to mutations in the *SLC4A11* gene. Four previously unreported mutations were identified, p.S33SfsX18 in a Chinese sporadic case, p.E399K in an Indian sporadic case, p.G709E in a Chinese familial case, and p.T754M in a Chinese sporadic case. The mutations in CHED were inherited in an autosomal recessive fashion [4], the alleles that caused FECD acted in an autosomal dominant pattern [41]. Additional mutations were identified in an American cohort by Riazuddin et al., after sequencing all coding regions of *SLC4A11* in 192 FECD cases [42]. Sorting Intolerant From Tolerant (SIFT) and PolyPhen predicted that among the seven missense mutations p.E167D, p.R282P, p.Y526C, p.V575M, p.G583D, p.G742R and p.G834S identified five of the mutations were pathogenic; p.E176D and p.Y526C were predicted to be benign.

Single-nucleotide polymorphisms (SNPs) in the *TCF4* (transcription factor 4) gene, encoding the E2-2 protein, were reported to be significantly associated with late-onset FECD in Caucasian Americans [43]. Independent replication studies have confirmed association of *TCF4* variants with FECD [44-46]. In particular, the TGC trinucleotide repeat expansion (rs613872) in *TCF4 is* strongly associated with FECD and a repeat length >50 are highly specific for the disease [47] and a predictor of disease risk. Further studies have strengthened the association of *TCF4* polymorphisms in the FECD disease process [48,49] and also suggest a role for clusterin and *TGFBI* polymorphisms [49]. A mutation R162W in the gene potassium inwardly-rectifying channel, subfamily J, member 13 (*KCNJ13*) is described in one family with snowflake vitreoretinal degeneration in which FECD was part of the ocular phenotype [50].

Next-generation sequencing of a FECD family identified a missense mutation, p.R547C in the lipoxygenase homology domains 1 (*LOXHD1*) gene [51]. LOXHD1 is an evolutionarily conserved protein predicted to consist of 15 PLAT (polycystin-1, lipoxygenase, alpha-toxin) domains. The biological function of PLAT domains is not well established, but it is predicted that they target proteins to the plasma membrane [52]. A further cohort of over 200 sporadic FECD patients were sequenced, and a further 15 missense changes identified in this gene [51].

Next-generation sequencing also identified a nonsense mutation (p.R1028*) in *AGBL1* (ATP/GTP-Binding protein – Like1) in the 15q locus [53]. Further sequencing identified a heterozygous missense variant, c.2969G>C that results in nonconserved amino acid substitution (p.C990S). *AGBL1* encodes a glutamate decarboxylase previously identified in serial analysis of gene expression of corneal endothelium, a finding confirmed by immunohistochemical staining [54].

The c.-61G>T (rs1801321) and c.-98G> C (rs1801320) polymorphisms of the *RAD51* gene have a role in the FECD pathogenesis [55]. The RAD51 protein is the central protein involved in homologous recombination and repair of DNA single and double strand breaks (DSBs) in humans [56].

POSTERIOR POLYMORPHOUS CORNEAL DYSTROPHY (PPCD)

PPCD is an autosomal dominant, uncommon, inherited corneal dystrophy which shares some similarities with CHED1. It is characterized by the presence of abnormal corneal endothelial cells which display epithelial features including microvilli and inappropriate cytokeratin expression [57-59]. The age at onset of symptoms is variable and may be in early childhood in severe cases or in adulthood. Clinical outcomes vary from minimal visual impairment to an aggressive course, with development of retrocorneal membranes and corneal opacification requiring keratoplasty [60,61].

PPCD has been associated with a number of other ocular disorders, including primary open angle and secondary angle-closure glaucoma [62], as well as non-keratoconic corneal steepening [63] and keratoconus [64,65]. A number of associated extraocular manifestations, including abdominal hernia and hydrocele formation, distinguish PPCD from the majority of the other corneal dystrophies, which are traditionally considered isolated corneal disorders [66, 67].

To date three genes have been identified as causing PPCD (Table 1). Haplotype analysis in the Czech population points to an as yet unidentified gene at the PPCD1 locus [68]. A locus for PPCD (PPCD1) has been identified in the pericentromeric region of chromosome 20 through linkage analysis [69-71]. Mutation of the visual system homeobox gene 1 (*VSX1*) within this locus was reported as disease-causing in a few PPCD cases [72,73] but this was not replicated in other studies [70,74]. The PPCD1 locus was further reduced to 2.4 cM [75] and subsequently probed with Sanger and next-generation sequencing [76]. The underlying genetic cause within this locus appears to remain elusive. Liskova et al., further explored this locus demonstrating a founder haplotype in the Czech population, but no causative mutation was identified [68]. However recently in the *VSX1* gene a novel change c.173C>T (p.P58L) was found in a patient with PPCD, predicted to be pathogenic, and not seen in 200 ethnically matched control alleles [77].

PPCD2 is caused by mutation of the alpha-2 chain of type VIII collagen gene located on 1p34.3-p32.3. Biswas et al., identified mutations in this gene in two affected members of a single PPCD family [31]. In addition a carrier of L450W mutation in *COL8A2* in an early-onset FECD family was reported to have a phenotype of PPCD [35]. The involvement of *COL8A2* in PPCD has not been substantiated further since no pathogenic mutations were found in additional families screened for mutations [78,79] suggesting this association is questionable or of a low frequency.

The largest percentage of PPCD (approximately one third) is associated with mutations in *ZEB1*, at the PPCD3 locus [67]. Aldave et al., confirmed the role of *ZEB1* in PPCD3 by reporting eight additional frameshift mutations in 32 probands [66]. A study by Liskova et al., also identified *ZEB1* mutations in four out of 10 PPCD families [80]. Further studies increased the number of *ZEB1* mutations associated with PPCD to 24 [81-83].

ZEB1 binds to DNA at a conserved sequence (CACCTG) that is known as an E2 box. In the presence of a truncating mutation in *ZEB1*, *COL4A3* expression has been demonstrated in the corneal endothelium of an individual affected with PPCD3 [67]. These findings, and the identification of six E2 boxes in the 5 kb upstream of the *COL4A3* transcription initiation site, suggest that *ZEB1* participates in the negative regulation of *COL4A3* transcription. Yellore and colleagues tested this hypothesis and found that when *ZEB1* is mutated, there is alteration of either the amount of expression or the temporal expression of the COL4A3 protein. This in turn may influence the endothelial cell to manifest a different phenotype [84].

X-LINKED CORNEAL ENDOTHELIAL DYSTROPHY

X-linked endothelial dystrophy remains the least common of the corneal endothelial dystrophies, reported in only a single family to date [85]. In a 7-generation Austrian family 35 trait carriers were identified in 4 generations. Twenty-two female and 13 male patients demonstrated a wide range of phenotypic features, ranging from 'moon-crater like' changes in the endothelium to congenital corneal edema with variable presence of visual loss ranging from no change in visual acuity to moderate or severe loss of vision. No male-to-male transmission was observed. Given apparent X-linked inheritance pattern, linkage analysis was performed for the X-chromosome, revealing evidence of significant linkage to a 14.79Mb region on Xq25 between markers DXS8057 and DXS1047, although the genetic basis remains unknown [85].

Taken together, studying the various corneal dystrophies and their pathways might be more complex because of genetic heterogeneity. Therefore, bridging the gaps using the high-throughput technique such as next generation sequencing (NGS) helps to identify and unravel the disease causing novel genes. Consequently, understanding the genetics of corneal dystrophies is essential which can provide insights into the various pathways involved in its molecular mechanisms.

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