Genetics of Ocular Diseases

H. V. Nema
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Foreword

It is a distinct honor for me to write the foreword for this important and timely book on the genetics of eye diseases that includes the work of several key leaders of eye genetics research. It is a very valuable presentation of the current knowledge that provides and outlines the future potential in the field of eye genetics in combating global blindness.

According to the World Report on Vision (October 2019), at least 2.2 billion people around the world have a vision impairment, of whom at least 1 billion have a vision impairment that could have been prevented or still need to be addressed. Furthermore, 90% of the global burden of eye diseases is shouldered by developing countries, where many treatable diseases often go undiagnosed. A comprehensive research strategy and international research collaborations between the developed and developing worlds are needed to address the prevention of global blindness. A wider collaboration of researchers is needed to advance high-quality science in many areas of vision research as well as improve the standard of care. A coordinated strategy for basic science and translational research, involving the tools of genetics, genetic counseling, and health services research, will help in reducing the global burden of eye diseases.

Indian researchers have played a key role in the development of our knowledge on eye genetics from the beginning of this discipline. Many independent research programs have been developed in India leading to many valuable findings in the field. In addition, by participating in numerous collaborative programs and working with researchers around the world, the Indian laboratories have generated a wealth of knowledge that is helping in the advancement of science. For example, Indian scientists have played key roles in the Global Eye Genetics Consortium (GEGC) that originated as a collaboration between the National Eye Institute (NEI) at the National Institutes of Health (NIH) in the USA and the National Institute of Sensory Organs at Tokyo Medical Center in Japan in 2014. India is one of the few countries in the world at this time that has established a GEGC-India team. In the past five years, the GEGC-India members have conducted several high-quality training programs and established dedicated research labs to advance research in eye genetics. It is a fast growing field of research globally as well as in India that has encouraged many scientists and clinicians to establish new programs in various corners of India. Many Indian eye hospitals have brought geneticists and genetic counselors to work

with the ophthalmologists to expand their services. I expect the field to expand significantly in the coming decade not only in India but in most parts of the world.

The field of eye genetics research is expected to grow significantly in India because not only many next-generation researchers are entering this field of research but also there are many unique populations across the country who are expected to provide useful information for many research developments on biomarkers and therapeutics. Several prominent international collaborative research programs are successfully being conducted in India, which are studying many patient populations with unique phenotypes and genotypes that until now have not been studied.

This book is very timely and expected to serve as a long-term resource for all those interested in working in this field. I am delighted to see that the book not only covers the genetic aspects of various common eye diseases, but it also covers the future applications through gene therapy and genetic counseling as separate chapters. The future programs include training and increased access to the new technologies to many research programs. Undoubtedly, the book will play a key role in providing the required background in training and research. It will further promote and provide guidance to many researchers and clinicians. I wish to congratulate and thank the authors and editors of the book for taking a lead role in expanding our knowledge in the area of eye genetics.

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Abstract

Retinitis pigmentosa (RP) is the most prevalent among the group of rare inherited retinal degenerative diseases (IRDs) leading to vision loss. RP is characterized by night blindness in the initial stages followed by progressive gradual decrease and loss of peripheral vision. The worldwide prevalence of RP is 1:4000 that varies in different geographic location. RP can be inherited as an autosomal dominant (adRP), autosomal recessive (arRP), X-linked (XLRP) or simplex trait; clinically present as isolated condition or syndromic (Bardet–Biedl syndrome, Alstrom syndrome, Ushers syndrome, Senior Loken syndrome, and Jouberts syndrome) with extra ocular abnormalities and partially overlapping genetic/clinical features. Inter and intra familial phenotypic variability, different mutation spectrum in RP explain the genetic heterogeneity in the disease. The overlapping genetic architecture and clinical heterogeneity pose challenge in diagnosis and molecular confirmation and differential diagnosis of the disease. In this book chapter, the current trends in molecular diagnosis of RP using next generation technologies like targeted panel, whole exome and genome sequencing. The implication of genetic diagnosis in checking the eligibility for treatment, future gene therapy trials, pre-implantation genetic diagnosis and thereby management. The other potential treatment strategies applicable in RP patients like optogenetics and cell based therapy that are under clinical trials.

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About the Editors

H.V. Nema post-graduated from GR Medical College, Gwalior. He did his fellowship from the University of Manchester. He is a former Professor and Head, Department of Ophthalmology, Institute of Medical Sciences, Banaras Hindu University, Varanasi. He has a distinguished academic career and is known for teaching, research, and publications. Dr Nema taught ophthalmology to the undergraduate and postgraduate students at Aligarh Muslim University, Aligarh, and Banaras Hindu University, Varanasi, for more than 30 years. He served as a consultant editor, an advisory editor to *Indian Journal of Ophthalmology, Afro-Asian Journal of Ophthalmology*, and *Indian Journal of Optometry*. He has more than 6 dozen publications in national and international journals and authored and edited books. Dr Nema has delivered guest lectures in many universities. He served as an honorary general secretary and a president of UP Ophthalmological Society and was conferred Lifetime Achievement Award.

Nitin Nema is a Professor of Ophthalmology at Sri Aurobindo Medical College and PG Institute, Indore. He is an experienced vitreoretinal surgeon. After his postgraduation from the Institute of Medical Sciences, Banaras Hindu University, he did his fellowship from Aravind Eye Hospital and PG Institute, Madurai. Additionally, he gained clinical and research experience from the University of Illinois at Chicago and University of Wisconsin, Madison, USA. He was awarded a fellowship by the All India Ophthalmological Society to work on a research project on uveitis at Sankara Nethralaya, Chennai. He was also awarded Dr Mohanlal Gold Medal for the best paper by the UP State Ophthalmological Society. He has published and presented many research papers and co-authored *Textbook of Ophthalmology*, *Anatomy of the Eye and Adnexa*, *Manual of Ophthalmology*, and *Diagnostic Procedures in Ophthalmology.*

Genes and Genetics in Ophthalmology

1

Chitra Kannabiran

1.1 Introduction

The knowledge of genes in the pathogenesis of eye diseases is an expanding area that has especially accelerated over the last two decades, ever since the human genome sequence became publicly available. The evolution of the field of genetics in general, and also in ophthalmology, may be traced to the study of disease phenotypes in large families with a disease that affected several members from different generations. The pattern in which the disease was seen in successive generations of a family gave a clue to its genetic character and also showed that manner in which it was inherited from one generation to the next. Though such studies clearly established a genetic transmission of the disease on the basis of a careful examination of all members of the families affected with the disease, the details of the gene itself or the chromosome in which it was located, were unknown. It was not until the latter part of the twentieth century, that molecular techniques became available to map the location of specific genes and later, to read the sequence of the genes to know the changes in the genetic code. The first gene for a human disease that was located on to a specific chromosome was that for Huntington's disease, a neurological disorder, first described by George Huntington in 1872. It is an autosomal dominant disease, usually adult-onset appearing after 30 years of age, with manifestations of loss of motor control leading to jerky movement, changes in personality, and a decline in cognitive function. The gene for Huntington's disease was first mapped in 1983 [1].

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In this study, the investigators showed by evaluating genetic markers on different chromosomes of patients from two large families with the disease, that the Huntington's disease gene was located on chromosome 4. This study was aided by the fact that the families studied were large and had several members available for the study, thus providing statistical support for the results of the mapping experiments.

1.2 Gene Mapping

Using the same type of approach, the gene for an eye disease known as retinitis pigmentosa (RP), was one of the first genes to be mapped for eye diseases, in 1984–1985. Retinitis pigmentosa is a form of blindness that develops in children and young adults due to a defect in the light-sensitive cells in the retina. Using the same mapping approach mentioned above, a few families with X-linked RP were studied, and the disease in these families was tagged to a marker on a specific part of the X chromosome, on the short arm of the chromosome [2]. This was the first report of the mapping of a gene for retinitis pigmentosa and one of the earliest genes mapped for any form of blindness. In the subsequent decade, the mapping and discovery of the gene for glaucoma, specifically primary open-angle glaucoma (POAG), was reported. The first such locus, designated as *GLC1A*, was mapped in a large American family with autosomal dominant inheritance of juvenile open-angle glaucoma (JOAG) to chromosome 1q [3]. JOAG differs from the common late-onset form of POAG in the onset before the age of 20 years, has a more aggressive course and has very high intraocular pressures. The gene for the *GLC1A* locus was identified as the myocilin gene a few years later [4]. In the same decade, genes for other forms of glaucoma such as primary congenital glaucoma were similarly mapped with genetic markers to specific chromosomal regions in large families with multiple members [5, 6].

Perhaps the earliest study to have mapped the genetic locus for an eye disease involves congenital cataract, in which the locus for the disease was linked to the same genetic locus as the blood group antigens known as the Duffy antigens, by Renwick and Lawler [7]. The Duffy blood group antigens were subsequently mapped onto chromosome 1 [8]. The family studied here had zonular, pulverulent cataracts which mapped to this locus, designated as CZP1 (cataract zonular pulverulent 1), was again followed up after several years and spanned eight generations, thus making it suitable to map the disease gene using linkage analysis. The gene on chromosome 1 was identified as the *GJA8* (gap junction protein 8) gene. It encodes a protein connexin 50, and a missense mutation in this gene was found to be associated with the cataract [9]. Gap junction proteins such as connexin 50, form channels within the lens to allow water and ions to pass through from one cell to another, and are thus important for lens homeostasis.

Numerous genes were identified over the next decade for severalother eye diseases including retinal blindness, glaucoma, corneal blindness, etc. using molecular

genetic methodsof gene mapping and sequencing. Another approach commonly used for identifying the genes associated with a disease, is the candidate gene approach, and selection of the gene for mutation screening is based on its functions or expression in the tissue that is affected. It is thus considered plausible that such candidate genes will have disease-associated mutations in a percentage of patients. Candidate gene approaches have also led to the discovery of genes for various disorders of the eye.

1.3 Human Genome Project

At the beginning of this century, a major landmark that shaped the course of human genetics was the Human Genome Project (HGP). This consisted of a megaproject led by teams of scientists from the USA and the UK, and other countries, and involved the process of finding the entire sequence of the human genome, which is made up of about three billion letters that constitute the genetic code. The availability of the entire genome sequence by the year 2003 meant that one knew the sequences of all the genes that are present in the genome. This knowledge catalyzed further discoveries in the genetics of eye diseases.

1.4 Next Generation Sequencing Technologies

There have been significant advances in technology for sequencing the genome in the current time, known as the next generation sequencing technologies (NGS), which are better and many times faster than the technology used by the HGP. We can now directly sequence the genome of individuals with a disease, and find the genes involved in the disease in question by looking for changes in the genome of the patient, as compared with the sequence of the normal genome. Using these methods, we now know many genes that are involved in eye diseases such as cataract, refractive error, macular degeneration, glaucoma, and so on. Genome sequences can be obtained in a matter of days and the procedure is being offered as a diagnostic test for patients with any eye disease, by several clinical laboratories across the world. The costs of these sequencing technologies have been coming down with improvements in capacity of the machines used for the purpose, thus leading to faster results. One can get tests that are based on finding out the sequence of the whole genome (whole genome sequencing or whole exome sequencing if one looks at a part of the genome that encodes proteins). In addition, the NGS technology can be used to test a set of specific genes that are relevant for a particular disease, an approach known as targeted NGS. Even in this method, hundreds of genes can be screened in parallel. This makes it possible to cover much larger ground than conventional genetic testing, in a fraction of the time. These next generation sequencing methods have also led to discovery of many new genes for eye diseases and thus increased our knowledge of the mechanisms of several eye diseases.

1.5 Gene Therapy

Genetic discovery has also led to possibilities of new treatments for genetic diseases that lead to blindness in infants and children. One such example is Leber congenital amaurosis (LCA), a disease affecting the retina and causing blindness at birth or very early childhood. LCA cannot be treated by any conventional form of treatment. One of the types of LCA involves mutations in a gene that encodes the retinal pigment epithelial 65 KDa protein (RPE65), a protein that is abundantly expressed in the retinal pigment epithelium. The RPE65 protein is absent or defective in patients with a mutation in this gene. Through the use of genetic testing methods mentioned above, one can carry out genetic testing and diagnosis of patients, to detect mutations in the *RPE65* gene. Advances in genetics over the last two decades have led to a new treatment for LCA patients with mutation in the *RPE65* gene. It is now possible to replace the mutant gene in these patients with a normal copy of the same gene. This process of gene therapy was developed after extensive research in animals such as mice and dogs that carried mutations in the RPE65 gene. Success in these animal models prompted the process of clinical trials for this gene therapy in human patients. The *RPE65* gene replacement therapy was a first of its kind among eye diseases, and was tried and tested in several patients with mutations in this gene.

Clinical trials of RPE65 gene replacement therapy were initiated in several centers in the USA, and the trials in phases I and II were designed to test safety and efficacy of the gene therapy. Follow-up of patients over time by evaluation of systemic and ocular adverse events and visual recovery indicated no serious adverse effects and treatment outcomes of increased visual field sensitivities and pupillary light responses in the treated eyes of patients. Essentially, the gene therapy with *RPE65* gene replacement was shown to be safe and effective and is under evaluation for further long-term effects on vision. The initial effects, however, peaked within a few weeks of injection, and in certain cases were retained up to 3 years after treatment [10]. Another disease affecting the retina, known as choroideremia, affects mostly males, and is due to a mutation in a particular gene, known as the *CHM* gene, on the X chromosome. The *CHM* gene encodes the Rab Escort Protein 1 (REP1). REP1 is required for adding lipid residues on the Rab small GTPases (RABs). Gene therapy for choroideremia has also been developed such that the mutant gene is replaced with a normal one through the use of the AAV2 vector. Patients administered with this gene therapy in clinical trials showed a mean gain of visual acuity and an increase in retinal sensitivity as compared with baseline [11]. Interestingly, there was a dose-dependent response to this treatment, since patients given a higher dose of the vector had better improvements in retinal sensitivity [12]. Overall, the *CHM* gene therapy has been shown to be safe to be administered into the eyes of affected patients, without any major adverse events noted. Despite these promising results in the therapy trials so far, there are still challenges to be overcome. Of major concern in these cases was the continuing degeneration of the retinal photoreceptors even after the gene therapy was carried out. Other areas to be tackled are in aiming for a better recovery of vision and more long-term benefits of the therapy.

1.6 Gene Editing

Another new tool with potential for therapeutic application that is now being investigated in the area of genetic diseases is a type of molecular scissor. This can be designed to clip out any mutation from a gene of interest and replace the clipped-out part of the gene with a normal copy, a process known as genome editing. Using this technique, researchers in different parts of the world are attempting to design therapies for various eye diseases that have no other treatments available by conventional methods [13]. Here again, investigations are in the process to develop a therapy for a form of LCA that is caused by a specific mutation in another gene known as *CEP290*. The CEP290 gene encodes a centrosomal protein that is a key component of the photoreceptor cells in the retina. There are a few mutations in the *CEP290* gene, which are very common among Caucasian patients with LCA. Thus, the therapy is envisaged to edit these common mutations in the *CEP290* gene in such patients. The results of these trials will provide exciting leads for further progress in treating various forms of blindness by gene therapy.

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Genetics in Corneal Dystrophy

2

Jayesh Vazirani and Mansi Rambhia

Roenouw [1]and Biber [2]introduced the term corneal dystrophy in 1890. Further Fuchs [3], Uhthoff [4], and Yoshida [5] continued to use the term "corneal dystrophy."Corneal dystrophy describes an inherited condition affecting cells, tissues, and organs, singly or in combination. These are inherited disorders that usually present bilaterally, symmetrically, and slowly progressive, and not related to systemic conditions and environmental factors [6].There are exceptions to the above statement, as in clinically unilateral dystrophy—PPCD (posterior polymorphous corneal dystrophy), systemic hypercholesterolemia in SCD (Schnyder corneal dystrophy), EBMD (epithelial basement membrane dystrophy), and central cloudy dystrophy of Francois (CCDF) are likely degenerative rather than hereditary conditions in most of the patients.

The IC3D publication in 2008 contained the traditional anatomic classification that categorized dystrophies according to the corneal layer that was chiefly affected [7, 8].The main limitation of this classification was absence of genetic mapping and genomic associations in corneal dystrophies. At present, genotyping revealed both genotypic heterogeneity (a single dystrophy associated with different genes) and phenotypic heterogeneity (one gene is associated with multiple distinct allelic dystrophy phenotypes).

2.1 Categorization of Corneal Dystrophy on Genetic Basis

Category 1: A well-defined corneal dystrophy,with a well identified mapped gene and the specific mutations are known.

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Category 2: A well-defined corneal dystrophy that has been mapped to one or more specific chromosomal loci, but the gene(s) yet to be identified.

Category 3: A well-defined corneal dystrophy, in which the disorder is yet to be mapped to a chromosomal locus.

Category 4: This category is reserved for a suspected, new, or previously documented corneal dystrophy, although the evidence for it, being a distinct entity is not yet convincing.

IC3D 2015 updated classification (C = Category) is an updated classification system that was proposed in 2015 with alterations of the ancient anatomic level classification to more accurately reflecting involvement of cellular layers. The revised classification removed the extensive table of gene loci and genes with specific mutations as this information is rapidly changing and can be obtained easily on the Internet. The revised classification system included representative histopathology and electron microscopy as well as confocal microscopy. Findings of anterior segment optical coherence tomography (OCT) were added when available.

IC3D 2015 updated classification [9]

Epithelial and subepithelial dystrophies

1. Epithelial basement membrane dystrophy (EBMD) majority degenerative, rarely C1
2. Epithelial recurrent erosion dystrophies (EREDs)—Franceschetti cornealdystrophy (FRCD) C3, Dystrophia Smolandiensis (DS) C3, andDystrophia Helsinglandica (DH) C3
3. Subepithelial mucinous corneal dystrophy (SMCD) C4
4. Meesmann corneal dystrophy (MECD) C1
5. Lisch epithelial corneal dystrophy (LECD) C2
6. Gelatinous drop-like corneal dystrophy (GDLD) C1

Epithelial–stromal TGFBI dystrophies

1. Reis–Bucklers corneal dystrophy (RBCD) C1
2. Thiel-Behnke corneal dystrophy (TBCD) C1
3. Lattice corneal dystrophy
   - Type 1 (LCD1) C1variants (III, IIIA, I/IIIA, IV) of lattice corneal dystrophy C1
4. Granular corneal dystrophy—type 1 (GCD1) C1
5. Granular corneal dystrophy—type 2 (GCD2) C1

Stromal dystrophies

1. Macular corneal dystrophy (MCD) C1
2. Schnyder corneal dystrophy (SCD) C1
3. Congenital stromal corneal dystrophy (CSCD) C1
4. Fleck corneal dystrophy (FCD) C1

5. Posterior amorphous corneal dystrophy (PACD) C1
6. Central cloudy dystrophy of Francois (CCDF) C4
7. Pre-Descemet corneal dystrophy-C1 or C4

Endothelial dystrophies

1. Fuchs endothelial corneal dystrophy—C1, C2, or C3
2. Posterior polymorphous corneal dystrophy (PPCD) C1 or C2
3. Congenital hereditary endothelial dystrophy (CHED) C1
4. X-linked endothelial corneal dystrophy (XECD) C2

Removed dystrophies
Grayson-Wilbrandt corneal dystrophy (GWCD) C4

2.2 Genetics in Corneal Dystrophy

Epithelial and Subepithelial Dystrophies

1. Epithelial basement membrane dystrophy (EBMD)
   Mendelian inheritance in man (MIM) # 121820
   Genetic locus-5q31
   Gene-transforming growth factor beta-induced-TGFB1 in 2 families.
   Inheritance-isolated familial cases have been reported, majority have no documented inheritance hence they are considered to be degenerative or secondary to trauma to eye.
2. Epithelial Recurrent Erosion Dystrophies (EREDs)
   MIM# 122400
   Genetic locus-unknown
   Gene-unknown
   Inheritance-autosomal dominant
3. Subepithelial mucinous corneal dystrophy (SMCD)
   MIM# 612867
   Genetic locus-unknown
   Gene-unknown
   Inheritance-autosomal dominant–most likely, but X-linked recessive inheritance not excluded
4. Meesmann Corneal Dystrophy (MECD)
   MIM #122100
   Genetic locus-Locus 12q13 (KRT3)
   Locus 17q12 (KRT12) Stocker–Holt variant
   Genes-Keratin K3 (KRT3)
   Keratin K12 (KRT12) Stocker–Holt variant
   Inheritance-autosomal dominant

5. Lisch Epithelial Corneal Dystrophy (LECD)
   MIM #300778
   Genetic locus-Xp22.3
   Gene-unknown
   Inheritance-X-chromosomal dominant
6. Gelatinous Drop-like Corneal Dystrophy (GDLD)
   MIM #204870
   Genetic locus-1p32
   Gene-Tumor-associated calcium signal transducer 2 (TACSTD2, previously M1S1)
   Inheritance-autosomal recessive

Epithelial–Stromal TGFBI Dystrophies

1. Reis–Bucklers Corneal Dystrophy
   MIM #608470
   Genetic locus-5q31
   Gene-Transforming growth factor beta-induced-TGFB1
   Inheritance-autosomal dominant
2. Thiel–Behnke Corneal Dystrophy (TBCD)
   MIM #602082
   Genetic locus-5q31
   Gene-Transforming growth factor beta-induced-TGFB1
   Inheritance-autosomal dominant
3. Lattice Corneal Dystrophy, type 1 (Classic) (LCD1) and Variants
   MIM #122200
   Genetic locus-5q31
   Gene-Transforming growth factor beta-induced-TGFB1
   Inheritance-autosomal dominant
4. Granular Corneal Dystrophy, type 1(Classic) (GCD1)
   MIM #121900
   Genetic locus-5q31
   Gene-Transforming growth factor beta-induced-TGFB1
   Inheritance-autosomal dominant
5. Granular Corneal Dystrophy, type 2 (GCD2)
   MIM #607541
   Genetic locus-5q31
   Gene-Transforming growth factor beta-induced-TGFB1
   Inheritance-autosomal dominant

Stromal Dystrophies

1. Macular Corneal Dystrophy (MCD)
   MIM #217800

Genetic locus-16q22
Gene-Carbohydrate sulfotransferase 6 gene—CHST6
Inheritance-autosomal recessive

2. Schnyder Corneal Dystrophy (SCD)
   MIM #21800
   Genetic locus-1p36
   Gene-UbiA prenyltransferase domain containing 1—UBIAD1
   Inheritance-autosomal dominant
3. Congenital Stromal Corneal Dystrophy (CSCD)
   MIM #610048
   Genetic locus-12q21.33
   Gene-Decorin, DCN
   Inheritance-autosomal dominant
4. Fleck Corneal Dystrophy (FCD)
   MIM #121850
   Genetic locus-2q34
   Gene-Phosphoinositide kinase, FYVE finger containing—PIKFYVE
   Inheritance-autosomal dominant
5. Posterior Amorphous Corneal Dystrophy (PACD)
   MIM #612868
   Genetic locus-12q21.33
   Gene-Deletion of keratocan (KERA), lumican (LUM), decorin (DCN), andepiphycan (EPYC)
   Inheritance-autosomal dominant
6. Central Cloudy Dystrophy of Francois
   MlM #217600
   Genetic locus/Gene-None
   Inheritance-unknown, autosomal dominant inheritance is occasionally reported
7. Pre-Descemet Corneal Dystrophy (PDCD)
   MIM: none
   Genetic locus-Isolated PDCD-Unknown
   PDCD associated with X-linked ichthyosis-Xp22.31
   Gene-Isolated PDCD-Unknown
   PDCD associated with X-linked ichthyosis-steroid sulfatase (STS)

Endothelial Dystrophies

1. Fuchs Endothelial Corneal Dystrophy (FECD)
   MIM #136800 (FECD1), MIM#610158 (FECD2), MIM #613267 (FECD3), MIM #613268 (FECD4), MIM #613269 (FECD5), MIM #613270 (FECD6), MIM #613271 (FECD7),MIM #615523 (FECD8)
   Genetic locus
   Early-Onset FECD
   1p34.3–p32 (FECD1)

Late-Onset FECD-Association has been reported to 13pter-q12.13 (FECD2),18q21.2-q21.3 (FECD3), 20p13-p12 (FECD4), 5q33.1-q35.2 (FECD5), 10p11.2 (FECD6), 9p24.1-p22.1 (FECD7), and15q25 (FECD8)

Gene-Early-onset FECD: collagen, type VIII, alpha-2, COL8A2

Inheritance-most commonly unknown, genetic basis of FECD is complex and heterogenous, suggesting incomplete penetrance and variable expressivity

2. Posterior Polymorphous Corneal Dystrophy (PPCD)
   MIM #122000 (PPCD1), MIM #609140 (PPCD2),MIM #609141 (PPCD3)
   Genetic locus-PPCD 1: 20p11.2-q11.2

   - PPCD 2: 1p34.3-p32.3
   - PPCD 3: 10p11.22
   - PPCD 4: 8q22.3-q24.12

   Gene-PPCD1: OVOL2 (ovo-like zinkfinger 2) [10]

   - PPCD2: collagen, type VIII, alpha-2 (COL8A2)
   - PPCD 3: zinc finger E box–binding homeobox 1 (ZEB1)
   - PPCD4: ectopic grainyhead-like transcription factor 2 (GRHL2)

Inheritance-autosomal dominant

3. Congenital Hereditary Endothelial Dystrophy (CHED)
   MIM #217700
   Genetic locus-20p13
   Gene-Solute carrier family 4, sodium borate transporter, member 11—(SLC4A11)

4. X-linked Endothelial Corneal Dystrophy (XECD)
   MIM: none
   Genetic locus-Xq25
   Gene-unknown
   Inheritance-X-chromosomal dominant

Newer Additions After IC3D (2015)

ERED (Epithelial recurrent erosion dystrophy)

In 2015, Swedish authors grouped 5 families and formed a large pedigree with autosomal dominant inheritance [11]. The whole genome sequencing resulted in identification of novel mutation in COL17A1 gene, that encodes collagen type XVII alpha 1 on chromosome 10.

The New Zealand authors screened four families with ERED in 2016 [12]and segregated two variants with ERED on chromosome 10. The COL17A1c.3156C > T variant was segregated in all four epithelial recurrent erosion dystrophy (ERED) families.