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Developments in Ocular Genetics: 2013 Annual Review

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Abstract

Purpose—To highlight major advancements in ocular genetics from the year 2013.

Design—Literature review.

Methods—A literature search was conducted on PubMed to identify articles pertaining to genetic influences on human eye diseases. This review focuses on manuscripts published in print or online in the English language between January 1, 2013 and December 31, 2013. A total of 120 papers from 2013 were included in this review.

Results—Significant progress has been made in our understanding of the genetic basis of a broad group of ocular disorders, including glaucoma, age-related macular degeneration, cataract, diabetic retinopathy, keratoconus, Fuchs' endothelial dystrophy, and refractive error.

Conclusions—The latest next-generation sequencing technologies have become extremely effective tools for identifying gene mutations associated with ocular disease. These technological advancements have also paved the way for utilization of genetic information in clinical practice, including disease diagnosis, prediction of treatment response and molecular interventions guided by gene-based knowledge.

Keywords

Genome-wide association study (GWAS); whole-exome sequencing; epigenetics; meta-analysis; glaucoma; age-related macular degeneration; cataract; diabetic retinopathy; refractive error; Fuchs' endothelial corneal dystrophy; keratoconus; uveal melanoma

Introduction

Vision loss is an important health problem worldwide, affecting an estimated 285 million people¹. In the United States alone, a recent estimate of the direct and indirect costs associated with major adult visual disorders is \$35.4 billion². Development of improved diagnostic and therapeutic measures is essential for reducing the burden of common, potentially blinding disorders that are increasing in prevalence as global populations age.

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Genetic factors play a significant role in all common ocular diseases, including glaucoma, age-related macular degeneration (AMD), cataract, diabetic retinopathy and refractive error. In recent years, there has been a dramatic increase in gene discovery for ocular diseases, driven by large-scale genome-wide association studies (GWAS), powerful meta-analyses, and next generation sequencing technologies (eg: whole exome sequencing). Gene discovery has also fueled translational research geared towards development of gene-based screening tests and targeted gene therapies.

The speed and volume of information in the field of ocular genetics is so great that a full catalog is beyond the scope of this review. Rather, we have highlighted the discoveries with greatest potential for impact on the field. This review includes papers published in the English language between January 1, 2013 and December 31, 2013. The search was conducted on PubMed using the terms “eye” and “gene,” which returned approximately 2050 articles. Publications were considered if they described research on the role of genetic variation in human eye disease or traits. We have summarized the findings of approximately 120 of the papers that best represented areas of substantial progress in the field of ocular genetics. Several additional publications were included to provide context to current or recent discoveries. Publications have been grouped by disease for ease of reference.

Overview of Current Genetic Technologies

Technological advancements have been crucial for the rapid progress made in the field of ocular genetics in the past several years. Important technologies that are heavily utilized include genome-wide association studies (GWAS), whole-exome sequencing, and epigenetic studies.

GWAS involves genotyping of common single nucleotide polymorphisms (SNPs) in diseased individuals and healthy controls. The allele frequencies for these SNPs are compared between the two groups to determine if a given SNP is strongly associated with the disease or trait of interest. An important limitation of GWASs is the fact that they can only identify common variants associated with disease risk, not rare variants³. Moreover, GWASs only provide the genomic location of genetic variants and no information about disease mechanism. Elucidation of the functional effects of identified variants remains an important challenge.

Whole-exome sequencing employs next-generation sequencing technologies to identify variants in protein-coding regions, or exons, of known genes. It enables researchers to screen thousands of loci simultaneously and can be used for the study of both monogenic (Mendelian) diseases and complex inherited disorders⁴. Moreover, it is suitable for identification of both rare and common variants⁴. However, it cannot be used for the study of non-coding, intronic variants. As the cost of next-generation sequencing continues to decline, use of whole-genome sequencing may be a viable alternative and would enable identification of intronic variants.

Epigenetics is the study of heritable modifications in gene expression that do not involve changes in the underlying DNA sequence. These modifications include DNA methylation and histone modifications. Environmental exposures and diet can alter epigenetic

imprinting, which offers a mechanistic link between environmental risk factors and disease development⁵. Methods such as chromatin immunoprecipitation and treatment of genomic DNA with sodium bisulfite have enabled *in vitro* studies of epigenetic imprinting.

Age-Related Cataract (ARC)

Age-related cataract (ARC) results from clouding of the lens and remains the dominant cause of visual impairment and blindness in the world⁶. It is a complex and multifactorial disorder, with both environmental and genetic components. Genetic factors account for approximately 50% of the variation in clinical severity for nuclear cataracts⁷. Genes that have previously been implicated in the pathogenesis of ARC include *PITX3*, *MAF* and *KLC1*⁷.

Given that DNA damage and oxidative stress play critical roles in the pathogenesis of ARC, variants in four DNA repair genes (*BLM*, *WRN*, *ERCC6*, and *OGG1*) were explored for possible association with ARC in the Han Chinese population⁸. SNPs in the *WRN* gene were strongly associated with risk for cataract in this study. Polymorphisms in the glutathione s-transferase omega-1 and 2 genes, which help protect lens cells from oxidative damage, were also examined for association with ARC⁹. SNP rs156697 (Asn142Asp) in the *GSTO2* gene increased risk for ARC in smokers and in individuals with work-related exposure to UV irradiation. A variant in an *HSP70* gene (*HSPA1B* -1267 A/A polymorphism), which acts in cell stress responses, was recently shown to have a protective role against ARC development¹⁰. The role of copy number variants (CNVs) of DNA repair genes has also been studied in the Han Chinese population¹¹. CNVs in heat shock factor protein 4 (*HSF4*) were significantly associated with ARC risk in this population.

Age-Related Macular Degeneration (AMD)

Age-related macular degeneration (AMD) leads to loss of central vision as a result of photoreceptor cell death. It is the leading cause of vision loss among individuals >65 years of age in developed nations¹². There are two forms of the disease: 1) non-neovascular (NNVAMD), characterized by accumulation of drusen, thinning of the macula, and geographic atrophy, and 2) neovascular (NVAMD), characterized by abnormal choroidal blood vessel growth. Risk factors for AMD include age, Caucasian race, family history, female gender, smoking and hypertension¹³. Genes that are associated with AMD risk include *CFH*, *C3*, *C2-CFB*, *CFI*, *HTRA1/LOC387715/ARMS2*, *CETP*, *TIMP3*, *LIPC*, *VEGFA*, *COL10A1*, *TNFRSF10A*, and *APOE*¹³. However, the functional role of genetic variants in disease pathogenesis remains poorly characterized.

Given that most SNPs associated with AMD risk are common variants, the role of rare variants in this disease was recently explored. One study identified rare missense variants in the *CFI*, *C3* and *C9* genes that were strongly associated with advanced AMD¹⁴. The risk allele for the rare variant in *C3* (Gln155) resulted in resistance to proteolytic inactivation by *CFH* and *CFI*, suggesting that this variant may have a functional role in excessive complement activation. A rare, highly penetrant missense variant (p.Gly119Arg) in the *CFI* gene may also play a functional role in AMD pathogenesis¹⁵. Compared to the Gly119 wild-type protein, the Arg119 mutant protein is expressed and secreted at decreased levels.

Moreover, the mutant protein is less effective at mediating degradation of C3b when compared to the wild-type protein. Functional studies in zebrafish found that the Arg119 mutant caused smaller average hyaloid vessel diameter compared to the wild-type, confirming the functional nature of this gene variant.

Additional genetic loci associated with AMD have also been described. For instance, a GWAS in individuals of European and Asian ancestry identified seven novel loci associated with advanced AMD (*COL8A1-FILIP1L*, *IER3-DDR1*, *SLC16A8*, *TGFBRI*, *RAD51B*, *ADAMTS9* and *B3GALT1*)¹². These genes are involved in regulation of complement activity, lipid metabolism, extracellular matrix remodeling, and angiogenesis, all of which are believed to play a role in AMD pathogenesis¹².

Interestingly, genetic variants affect AMD treatment response. For instance, variants in *VEGFA*, *HTRA1*, and *LOC387715/ARMS2* were found to influence visual outcome in patients receiving anti-VEGF injections for NVAMD^{16–18}. Moreover, *CFH* and *ARMS2* variants influence response to zinc and antioxidant treatment for NNVAMD¹⁹. Patients with *ARMS2* risk alleles may benefit most from zinc-only supplementation, whereas patients with *CFH* risk alleles may benefit most from antioxidant-only supplementation. In another study, patients with risk alleles for both the *CFH* rs1061170 and *ARMS2* rs10490924 polymorphisms were found to benefit from dietary antioxidant and fish consumption, whereas individuals who had low genetic risk (one or no risk alleles) did not benefit²⁰. The LDL cholesterol-lowering medication simvastatin has also been shown to slow progression of NNVAMD, especially in those homozygous for the risk allele (CC) for the *CFH* rs1061170 (Y402H) variant²¹.

Two studies recently examined the role of epigenetic factors in AMD pathogenesis and reported conflicting findings. In one study, decreased methylation of the *IL17RC* promoter was found in AMD patients, with accompanying elevation of *IL17RC* mRNA and protein levels in peripheral blood, retina and choroid²². However, a replication study found no evidence of *IL17RC* hypomethylation in AMD patients, highlighting the need for replication of epigenetic association studies prior to clinical application²³.

Central Corneal Thickness (CCT)

There is strong evidence of a role for central corneal thickness (CCT) in ocular diseases. For instance, a thinner CCT is a risk factor for primary open angle glaucoma and is also associated with keratoconus and brittle cornea syndrome²⁴. Increasingly powerful genome-wide association studies (GWAS) have identified multiple loci associated with CCT in both Caucasian and Asian populations. These include *AKAP13*, *COL5A1*, *RXRA-COL5A1*, *COL8A2*, *FAM53B*, *FOXO1*, *IBTK*, *LRRK1*, and *ZNF469*²⁴.

Studies published this past year identified several additional loci associated with CCT. For instance, the *RPN2* gene was found to be associated with CCT in a GWAS designed to identify novel loci for primary open angle glaucoma (POAG) and age-related macular degeneration (AMD)²⁵. In addition, a meta-analysis of approximately 20,000 individuals of European and Asian descent identified 16 novel loci associated with CCT²⁶. Pathway analysis revealed that these CCT-associated loci cluster in collagen and extracellular matrix

(ECM) pathways. To determine whether these loci confer susceptibility to ocular diseases, 26 SNPs were tested in case-control datasets for glaucoma and keratoconus²⁶. The *FOXO1* and *FNDC3B* loci were both significantly associated with keratoconus. The *FNDC3B* locus, which is involved in adipogenesis, was also associated with POAG.

To look for possible ethnic differences in genetic factors associated with CCT, a GWAS was also recently conducted in a Latino population²⁴. The study replicated involvement of the previously identified *RXRA-COL5A1*, *FOXO1*, and *ZNF649* loci in Latinos. Additionally, four novel SNPs found in the uncharacterized LOC100506532 were strongly associated with CCT in this Latino population. Conditional analysis suggested that rs3118515 in LOC100506532 is the dominant contributor to association with CCT in Latinos, as every SNP in the *RXRA-COL5A1* region lost significance after conditioning on rs3118515. This novel SNP is thought to lie in a regulatory region and may be a functional variant.

Diabetic Retinopathy (DR)

Diabetic retinopathy (DR) is the most common microvascular complication of Type I and Type II diabetes mellitus and is a leading cause of blindness worldwide²⁷. It affects up to 80% of individuals who have had diabetes for longer than 15 years²⁷. DR is classified into two subtypes: 1) nonproliferative (NPDR), which is characterized by microaneurysm formation and macular edema, and 2) proliferative (PDR), which is characterized by neovascularization that can result in traction retinal detachment and neovascular glaucoma²⁷.

Several genes are associated with DR, though replication studies in different populations have been inconsistent. Meta-analyses were recently performed to further investigate these associations. One meta-analysis explored the association of paraoxonase (*PON*) gene polymorphisms with DR²⁸. *PON1*-L55M (rs854560) was significantly associated with DR, though *PON1*-Q192R (rs662) and *PON2* gene polymorphisms were not strongly associated in this meta-analysis. The *PON1* gene is a major anti-atherosclerotic component of high-density lipoprotein (HDL)²⁸. Other recent meta-analyses found that the vascular endothelial growth factor (*VEGF*) gene -460T/C and -634G/C polymorphisms are strongly associated with DR, but the -2578C/A polymorphism is not^{29,30}. Interestingly, the CC genotype for the *VEGF* -634G/C polymorphism is also associated with better visual outcome after anti-VEGF treatment for diabetic macular edema³¹. Meta-analyses also found strong associations with DR risk for the *ICAM-1* K469E and the plasminogen activator inhibitor-1 (*PAI-1*) 4G/5G polymorphisms^{32,33}.

The functional roles of selected genes associated with DR have been explored. For instance, variants in the *TCF7L2* gene were found to promote pathological retinal neovascularization via ER stress-dependent upregulation of *VEGFA*³⁴. Moreover, the receptor for advanced glycation end-product (*RAGE*) gene polymorphism -2245G/A was shown to upregulate expression of *NF-κB p65*, plasma *MCP-1*, *AOPP* and pentosidine, all of which are pro-inflammatory, oxidative-glycation markers³⁵. This suggests that *RAGE* gene polymorphisms may play a functional role via modulation of the NF-κB mediated inflammatory pathway.

GWAS and candidate gene studies published this past year identified several novel loci that may play a functional role in DR pathogenesis. For instance, a GWAS conducted in a Chinese population identified three novel loci for DR: *TBC1D4-COMMD6-UCHL3* (rs9565164), *LRP2-BBS5* (rs1399634) and *ARLAC-SH3BP4* (rs2380261)³⁶. These genes are involved in insulin regulation, inflammation, lipid signaling and apoptosis, all of which are involved in DR³⁶. However, these findings were not replicated in an independent cohort of Hispanic patients³⁶. Candidate genes that were also recently found to be associated with DR risk include complement factor H (*CFH*) and complement factor B (*CFB*), the glutathione-S-transferase gene *GSTM1*, adiponectin (*ADIPOQ*), angiotensin-converting enzyme (*ACE*), monocyte-chemoattractant protein-1 (*MCP-1*), osteoprotegerin (*OPG*), the CB1 cannabinoid receptor gene (*CNR1*), transmembrane protein 217 (*TMEM217*), mitochondrial ribosomal protein L14 (*MRPL14*), and the glutamate receptor *GRIK2*^{37–44}.

Recent studies also explored the role of epigenetic factors in DR pathogenesis. For instance, histone methylation of the retinal *SOD2* and *MMP9* genes were reduced in patients with diabetic retinopathy^{45,46}. These data suggest that targeting enzymes involved in histone methylation may serve as a therapeutic strategy for this potentially blinding disorder⁴⁵.

Fuchs' Endothelial Corneal Dystrophy (FECD)

Fuchs' Endothelial Corneal Dystrophy (FECD) is characterized by bilateral, progressive loss of corneal endothelial cells and thickening of Descemet's membrane⁴⁷. It is a leading indication for corneal transplantation. Approximately 50% of patients with FECD have a positive family history, which suggests a strong genetic component in disease pathogenesis⁴⁸. Genes implicated in FECD include *COL8A2*, *SLC4A11*, *ZEB1*, *LOXHD1* and *TCF4*⁴⁹.

Given that genetic variants associated with FECD risk have mainly been studied in Caucasian and Asian populations, these variants were recently explored in African Americans⁴⁹. Variants in the *COL8A2*, *SLC4A11*, and *ZEB1* genes were detected in African American patients. However, similar to the case in Caucasian and Asian populations, these variants were found in only a small fraction of patients examined, suggesting that these genes are not the major contributor to FECD pathogenesis.

Novel loci associated with FECD risk have recently been described. A study of a three-generation family affected by FECD utilized genome-wide linkage mapping and subsequent next-generation sequencing to identify a nonsense mutation in the *AGBL1* gene on chromosome 15q⁵⁰. Whereas wild-type *AGBL1* has cytoplasmic localization, this truncated protein displays predominantly nuclear localization. Moreover, *AGBL1* was shown to interact with the FECD-associated gene *TCF4*, and the *AGBL1* nonsense mutation diminished this interaction. Another study explored a possible connection between oxidative stress response and FECD in a Polish population⁴⁸. Variants in *RAD51*, which encodes a protein involved in homologous recombination and repair of double-stranded breaks, were associated with risk for FECD in this study.

Studies examining the functional roles for genes associated with FECD risk have also been reported. One study demonstrated that *SLC4A11* is involved in Na⁺-coupled OH⁻ transport

in the corneal endothelium, suggesting a role for this gene in regulation of cellular pH⁵¹. Studies of *Col8a2*^{L450W/L450W} and *Col8a2*^{Q455K/Q455K} knock-in mouse models of FECD were also recently performed, which revealed dilation of rough endoplasmic reticulum (RER) consistent with upregulation of the unfolded protein response⁴⁷. Moreover, these mice exhibited increased expression of the autophagy marker *Dram1*, a finding that was confirmed in human FECD endothelium. These data suggest a role for altered autophagy in the pathogenesis of FECD. A whole genome expression analysis was also performed in wild-type and *Col8a2*^{Q455K/Q455K} mutant mice⁵². Compared to wild-type mice, *Col8a2*^{Q455K/Q455K} mutant mice had increased *COX2* and *JUN* expression, both of which are involved in cell stress responses. These findings were confirmed in human FECD samples.

Primary Open Angle Glaucoma (POAG)

Glaucoma refers to a heterogeneous group of disorders that are characterized by progressive loss of retinal ganglion cells and their axons that produces characteristic glaucomatous optic neuropathy. Glaucoma is the leading cause of irreversible blindness in the world. POAG is the most common form, accounting for a majority of glaucoma cases worldwide. Genetic factors play a significant role in POAG. For instance, linkage studies have led to identification of the *MYOC*, *OPTN* and *ASB10* genes⁵³. Genome wide association studies have revealed several POAG-associated loci, including *CDKN2B-AS1*, *TMC01*, *CAVI/CAV2*, *SIX1/SIX6*, *COL5A1/RXRA*, *COL8A2*, *SRBD1*, and *ELOVL5*⁵³.

In some cases, reported genetic associations for POAG have been inconsistent. For instance, TNF α gene polymorphisms were associated with open angle glaucoma in certain populations, though this finding was not replicated in others⁵⁴. A recent meta-analysis identified an association with the TNF α -308G/A polymorphism (rs1800629) in POAG patients⁵⁴. This variant was strongly associated with risk for high-tension glaucoma, but not in normal-tension glaucoma cases. Patients with open angle glaucoma were also found to have higher aqueous humor TNF α levels compared to controls. The TNF α -238G/A, -863C/A, -857C/T polymorphisms were not significantly associated with open angle glaucoma in this meta-analysis. Similar to the case with TNF α polymorphisms, studies of *CAVI/CAV2* variants in different populations have generated inconsistent findings. This year, a study was conducted to explore the association of *CAVI/CAV2* variants with normal-tension glaucoma in Japanese patients⁵⁵. Three SNPs were genotyped in this population. The risk allele for one SNP was reversed in this population, while the others showed no significant association or were monomorphic. These findings suggest that known SNPs in the *CAVI/CAV2* locus are not uniformly associated with normal tension glaucoma among different populations.

Several studies have performed pathway analyses for recently discovered POAG-associated loci. A meta-analysis for caveolin 1/caveolin 2 (*CAVI/CAV2*) and *CDKN2B-AS1* in POAG was done using data obtained from the Glaucoma Genes and Environment (GLAUGEN) study and the National Eye Institute Glaucoma Human Genetics Collaboration (NEIGHBOR) consortium. *CAVI/CAV2* SNPs were found to have greater association with POAG in women and in patients with early paracentral visual field defects⁵⁶. *CAVI* and

CAV2 proteins inhibit endothelial nitric oxide synthase (eNOS), which can alter nitric oxide production and lead to changes in vascular tone and trabecular meshwork function. SNPs in *CDKN2B-AS1*, an antisense noncoding RNA, were found to modulate optic nerve degeneration, as POAG patients with minor alleles for these SNPs had altered cup-to-disk ratios⁵⁷.

Functional studies have also elucidated potential roles for *ASB10* and *SIX6* in POAG. The ankyrin repeat and SOCS box-containing protein-10 (*ASB10*) gene was previously identified through genetic linkage studies at the *GLC1F* locus, though its role in glaucoma is unclear. To determine the biological function of the Asb10 protein, its expression was investigated in human trabecular meshwork (HTM) cells⁵⁸. Asb10 localized to intracellular structures in HTM cells and co-localized with biomarkers of the ubiquitin-mediated proteasomal pathway and the autophagy-lysosomal pathways. Mutations in *ASB10* could potentially affect these pathways and lead to alterations in TM outflow, thereby contributing to the pathogenesis of POAG.

A SNP in the *SIX1-SIX6* locus (rs10483727) was previously identified in a GWAS study and was strongly associated with vertical cup-disk ratio (VCDR) and POAG⁵³. A recent study identified two missense variants in *SIX6*, rs33912345 (His141Asn) and rs146737847 (Glu129Lys), that were associated with VCDR (rs33912345 and rs146737847) and POAG (rs33912345)⁵⁹. Knockdown of *SIX6* in zebrafish led to a small eye phenotype and also led to upregulation of *CDKN2B*. The *SIX6* gene encodes a transcription factor involved in early eye development. In another more recent study, five nonsynonymous coding variants in the *SIX6* gene that were identified in POAG cases resulted in reduced eye size and reduced volume of the optic nerve¹²⁵. Another variant found in the *SIX6* enhancer region resulted in overexpression of *SIX6* in an *in vitro* luciferase assay. Interestingly, in POAG patients who were homozygous for the risk allele for SNP rs33912345 (His 141) were found to have a thinner retinal nerve fiber layer compared to patients homozygous for the non-risk allele (Asn141).

Recent studies have also identified correlations between gene mutations and age of onset/disease severity. For instance, *myocilin* mutations are more prevalent in patients with advanced POAG (defined as more severe visual loss) compared to patients with clinically less severe POAG in an Australasian disease registry⁶⁰. In addition, disease-causing mutations in *COL15A1* and *COL18A1* have been found to influence age of onset of both juvenile and adult open angle glaucoma⁶¹. Patients who carried a *COL15A1* variant had a mean age of onset of 25 years, compared to 44 years for patients without the *COL15A1* variant. Similarly, patients who carried a *COL18A1* variant had a mean age of onset of 32.2 years, compared to 48.8 years for patients without the variant.

A growing number of genes are known to be associated with POAG risk, but they individually explain a relatively small fraction of the heritability of this disease. Studies published this year have identified new loci that may help explain, in part, the heritability gap. For instance, a GWAS identified SNPs in the complement component C7 gene that are strongly associated with POAG risk²⁵. Another study explored the association between estrogen metabolism SNPs and POAG, with analyses conducted for each gender separately

and jointly⁶². The estrogen SNP pathway was associated with POAG in women, but not in men. Gene-based analyses showed strong associations between the catechol-O-methyltransferase gene and both high-tension and normal-tension glaucoma in women. Another study examined the association between copy number variants (CNV) and intraocular pressure (IOP), a key POAG risk factor⁶³. An association was found between IOP and the 5q21.2 CNV locus overlapping the gene *RAB9BP1*. Interestingly, this CNV locus is located near the previously reported and widely replicated *GLC1G* locus for POAG, though the causal gene in this region remains unknown.

Primary Angle Closure Glaucoma (PACG)

Primary angle closure glaucoma (PACG) is characterized by obstruction of the irido-corneal angle by the iris, which leads to impaired aqueous humor outflow and increased intraocular pressure. PACG is associated with increasing age, hyperopia, certain ethnicities, and female gender⁶⁴. A GWAS previously performed on a large cohort of multiple ethnicities (Chinese, Malaysian, Indian, Vietnamese, Saudi Arabian and European) identified three susceptibility loci for PACG: rs11024102 in *PLEKHA7*, rs3753841 in *COL11A1*, and rs1015213 located between *PCMTD1* and *ST18* on chromosome 8q⁶⁴. A fourth association, rs3788317 in *TXNRD2*, did not reach genome-wide significance in the meta-analysis. In a more recent study, these loci were re-examined in Australian Caucasian and Nepalese datasets, which replicated the initial GWAS findings⁶⁴. In a South Indian PACG dataset, however, only one of these associations (rs1015213) was replicated⁶⁵.

Recent studies have also looked for other loci that may be associated with PACG. For instance, SNPs in frizzled-related protein (*MFRP*) and heat shock protein 70 (*HSP70*) showed possible association with primary angle closure in the Han Chinese population, although significance was lost after Bonferroni correction⁶⁶. In an Australian cohort, SNP rs3793342 in the endothelial nitric oxide synthase (*eNOS*) gene showed association with PACG⁶⁷. Variants in serine protease 56 (*PRSS56*) have also been found to be associated with PACG⁶⁸. Lastly, SNPs rs5745718 and rs17427817 in the hepatocyte growth factor (*HGF*) gene were associated with decreased risk of PACG in the Han Chinese population⁶⁹.

Primary Congenital Glaucoma (PCG)

Primary congenital glaucoma (PCG) presents within the first 3 years of life. It is thought to result from developmental defects of the trabecular meshwork, though the exact mechanism remains unknown⁷⁰. Genes that are associated with the disease include *CYP1B1* and *LTBP2*⁷¹. The *GLC3B* and *GLC3C* loci on chromosomes 1p36 and 14q24.3, respectively, have also been linked to PCG, though the associated genes at these loci remain to be determined⁷¹.

Studies published in the past year have identified potential functional roles for *CYP1B1* in PCG pathogenesis. A study examining Cyp1b1-deficient (Cyp1b1 $-/-$) mice found that these mice had elevated diurnal intraocular pressure, irregular collagen distribution in the trabecular meshwork, increased TM oxidative stress, and decreased levels of periostin, which plays an essential role in collagen fibrillogenesis⁷⁰. Taken together, these findings suggest roles for *CYP1B1* in oxidative homeostasis and ultrastructural organization of TM

tissue. *CYP1B1* deficiency also results in attenuation of capillary morphogenesis, increased expression of thrombospondin-2 (an endogenous inhibitor of angiogenesis) and enhanced proliferation/decreased apoptosis of vascular pericytes^{72,73}. These findings support an important role for *CYP1B1* in vascular homeostasis. In addition, *CYP1B1* deficiency leads to sustained activation of NF- κ B, a transcription factor involved in immune and inflammatory responses⁷². Dysregulation of NF- κ B activity has been observed to play a role in a number of disease states, including glaucoma.

CYP1B1 genotype-phenotype correlations are of clinical interest in PCG, as this may help provide more accurate prognosis, guide therapy and assist in genetic counseling. PCG patients with a *CYP1B1* mutation were found to have earlier median age of disease onset in the Han Chinese population⁷¹. Moreover, *CYP1B1* gene mutations were associated with a better surgical outcome in this population, defined as postoperative IOP ≤ 21 mmHg with or without use of glaucoma medications⁷¹.

Keratoconus (KC)

Keratoconus (KC) is a degenerative corneal disorder characterized by localized thinning and protrusion of the corneal stroma. This leads to varying degrees of astigmatism and high myopia. Keratoconus can cause marked visual impairment and is a leading indication for corneal transplantation. Both genetic and environmental factors are known to contribute to this disorder. Candidate genes implicated in the pathogenesis of KC include *VSX1*, *SOD1*, *ZEB1*, *TGFB1*, *HGF*, *RAB3GAP1*, *IL1A*, *IL1B*, and *LOX*⁷⁴.

The visual system homeobox 1 (*VSX1*) has been examined in populations around the world, though significant associations with KC risk have not been observed in all populations. Recently, disease-causing *VSX1* mutations were identified in New Zealand and Han Chinese cohorts^{75,76}. However, studies conducted in South Indian, Iranian, and Greek populations found no significant association between *VSX1* mutations and susceptibility to KC⁷⁷⁻⁷⁹.

A candidate gene study recently performed in Poland found that SNPs rs8177178 and rs8177179 in the transferrin gene were also associated with KC⁸⁰. This suggests a potential role for disturbances in iron homeostasis and oxidative stress in the pathogenesis of this disease. To further explore the connection between oxidative stress and KC, variants in the *RAD51* gene were also studied in a Polish population and found to be associated with disease risk⁴⁸. The *RAD51* gene encodes a protein involved in homologous recombination and repair of double-stranded breaks.

A genome-wide linkage scan previously mapped a KC locus to the genomic region 5q14.3-q21.1⁸¹. The calpastatin (*CAST*) gene is located in this region and was hypothesized to play a role in disease pathogenesis. A recent study further explored this hypothesis by examining whether variants in the *CAST* gene confer susceptibility to KC⁸¹. SNP rs4434401 was found to be strongly associated with KC risk in 2 independent Caucasian cohorts. The *CAST* gene encodes an endogenous inhibitor of the calpains, which are cysteine proteases involved in cellular migration, proliferation and apoptosis⁸¹.

There is also strong evidence for a connection between thinner central corneal thickness (CCT) and risk for keratoconus. A recent meta-analysis that included over 20,000 patients of European and Asian descent identified 16 new loci for CCT and explored whether these loci are associated with keratoconus²⁶. *FOXO1* and *FNDC3B* variants were found to increase risk for keratoconus in two different cohorts. A replication study performed in an Australian cohort found no association between the *FOXO1* and *FNDC3B* variants and KC risk, however⁸². The CCT-associated SNPs rs1324183 (in the *MPDZ-NF1B* gene) and rs9938149 (between *BANP* and *ZNF4659*) were strongly associated with KC risk in the Australian cohort, though the association was via a non-corneal curvature route⁸².

Leber Congenital Amaurosis (LCA)

Leber congenital amaurosis (LCA) is an autosomal recessive disorder that results from dysfunction and degeneration of photoreceptors. In LCA patients with *RPE65* mutations, a recombinant adeno-associated virus vector carrying the human *RPE65* gene has been shown to improve vision without apparent side effects in both animal models and in clinical trials^{83,84}. This is one of the first successes in ocular gene-directed therapy, though the effect of this therapy on the disease process in the long-term is largely unknown.

To explore this question, a recent study evaluated the effects of the gene therapy on retinal degeneration in patients with LCA and in a canine model⁸⁵. In LCA patients, *RPE65* gene therapy resulted in significant visual improvement in the short term, though retinal degeneration continued to progress unabated. Similarly, in a canine model, photoreceptor loss continued unabated if the treatment was given after degeneration had already begun. These findings suggest that a combinatorial treatment strategy is needed to both improve function in the short term and slow retinal degeneration in the long term⁸⁵.

Leber Hereditary Optic Neuropathy (LHON)

Leber hereditary optic neuropathy (LHON) is a mitochondrial-mediated, maternally inherited disease that leads to degeneration of retinal ganglion cells and loss of central vision in early life. It is associated with three point mutations in mitochondrial DNA: m.3460G>A (MT-*ND1*), m.11778G>A (MT-*ND4*), and m.14484T>C (MT-*ND6*)⁸⁶. However, given that LHON predominantly occurs in males and has incomplete penetrance, other genetic and environmental factors may be involved⁸⁷.

SNPs in the *PARL* gene, which encodes a serine protease of the inner mitochondrial membrane, were previously shown to be associated with LHON in a genome-wide linkage analysis performed in Thailand⁸⁷. To determine whether *PARL* may have a role in penetrance of this mitochondrial disease, the *PARL* gene was examined in patients with the m.11778G>A genotype who had LHON and in patients with the m.11778G>A genotype who were unaffected⁸⁷. Two SNPs, rs3749446 and rs1402000, had significantly different frequencies in the two groups, suggesting that *PARL* may be a potential modifier in the pathogenesis of LHON.

Given that point mutations in mitochondrial DNA play an important role in LHON, gene-directed therapy may offer an effective therapeutic approach for this disease. This year, a

recombinant adeno-associated virus (rAAV) expressing *ND1* was constructed and administered as a single intravitreal injection in a murine model of LHON⁸⁸. Adeno-associated virus (AAV)-ND1 administration produced a 1.5-fold reduction in retinal ganglion cell death and a 1.4-fold reduction in optic nerve atrophy. Clinical trials are also currently underway to assess the safety and efficacy of rAAV-*ND4* treatments for patients with the m.11778G>A genotype⁸⁶.

Ocular Malformations

Anophthalmia and microphthalmia (A/M) are heterogeneous congenital disorders that can lead to absence of the eye or to reduced eye size, respectively. These disorders can be inherited as autosomal dominant, autosomal recessive or X-linked traits. *SOX2* gene mutations account for 10–15% of severe A/M cases⁶¹. Although they account for a small percent of cases, mutations in several other genes, including *GDF6*, *FOXE3*, *OTX2*, *PAX6*, *RAX* and *VSX2* have been described in A/M cases⁶¹.

During the past year, two separate studies identified mutations in the *ALDH1A3* as causes of A/M^{89,90}. One study employed a combination of homozygosity mapping, exome sequencing and Sanger sequencing, while the other utilized whole-exome and whole-genome sequencing. Antisense morpholino studies to knockdown *ALDH1A3* gene expression in zebrafish produced a significant reduction in eye size and aberrant axonal connections to the tectum⁹⁰. The *ALDH1A3* gene encodes an enzyme that is involved in the formation of a retinoic acid gradient during ocular development. These studies provide evidence for a connection between dysfunctional retinoic acid synthesis and ocular malformations.

Coloboma results from a delay in closure of the optic fissure and is frequently associated with A/M. Autozygome analysis and exome sequencing was recently used to identify mutations in *C12orf57*, which produced a syndromic form of colobomatous microphthalmia associated with global developmental delay, intractable seizures, and corpus callosum abnormalities⁹¹. Exome sequencing also led to identification of *CYP11B1* as a potential modifier gene in colobomatous microphthalmia⁹². The *CYP11B1* gene regulates retinoic acid signaling, which is a necessary component for proper optic fissure closure. In addition to its potential role in colobomatous microphthalmia, *CYP11B1* also has an established role in primary congenital glaucoma and Peters anomaly⁹².

Studies conducted during the past year have provided a foundation to improve treatment of aniridia, a congenital disorder that results in complete or partial absence of the iris. The vast majority of aniridia cases are due to mutations or deletions of the *PAX6* gene, which encodes a transcription factor necessary for eye and central nervous system development. Recently, postnatal topical application of an ataluren-containing drug formulation was found to reverse corneal, lens and retinal defects in the *Pax6*^{Sev/+} mouse, a model for human aniridia⁹³. ELISA analysis confirmed that treatment promoted synthesis of a full-length Pax6 protein. Ataluren, also known as PTC124, reduces ribosomal sensitivity to stop codons. The efficacy of this drug in a mouse model of aniridia offers promise for a viable therapeutic option for patients with *PAX6* nonsense mutations. Moreover, ataluren administration provides a therapeutic paradigm potentially applicable to other diseases caused by premature

translational termination, including cystic fibrosis, Duchene muscular dystrophy, and certain cancers⁹⁴.

Refractive Error

Refractive error is the most common ocular disorder worldwide, with an estimated 2.3 billion individuals affected⁹⁵. There are three types of refractive error: 1) myopia, which results from increased axial length of the eye, 2) hyperopia, which results from decreased axial length, and 3) astigmatism, which results from irregular corneal curvature⁹⁶. Environmental factors, such as occupations requiring extensive use of close vision and reduced time spent outside play an important role in this disorder. Moreover, heritabilities greater than 50% in several different populations also suggest a strong genetic component⁹⁶. Several genes are associated with refractive error, though each has a very small phenotypic effect, suggesting that yet unidentified genes also play an important role in disease pathogenesis⁹⁵.

Several studies published this past year have identified novel loci that may help explain, in part, the heritability gap. For instance, a GWAS performed using 7,280 samples from five Caucasian cohorts found that SNP rs1050035 in the *RBFOX1* gene was strongly associated with risk for refractive error⁹⁶. The *RBFOX1* gene is a neuron-specific splicing factor that regulates alternative splicing events⁹⁶. A genome-wide meta-analysis in European and Asian populations identified nine novel loci for ocular axial length, five of which were associated in 18 replication cohorts (*LAMA2*, *GJD2*, *CD55*, *ALPPL2*, and *ZC3H11B*)⁹⁷. In the Han Chinese population, a genome-wide meta-analysis found that variants in the *VIPR2* and *SNTB1* genes increase risk for high myopia⁹⁸. Another GWAS performed in a European population found that variants in the platelet-derived growth factor receptor alpha (*PDGFRA*) influence corneal curvature and corneal astigmatism⁹⁹.

Some of the recently identified genetic loci point towards mechanisms that may underlie the development of myopia. For instance, in a genome-wide meta-analysis for refractive error, 16 novel loci were strongly associated in both European and Asian cohorts⁹⁵. These loci include genes that function in neurotransmission (*GRIA4*), ion transport (*KCNQ5*), retinoic acid metabolism (*RDH5*), extracellular matrix remodeling (*LAMA2* and *BMP2*), and eye development (*SIX6* and *PRSS56*)⁹⁵. Another GWAS in Europeans identified 20 novel associations, 10 of which were replicated in an independent cohort¹⁰⁰. These included genes involved in growth of retinal ganglion cells (*ZIC2*, *SFRP1*) and five genes involved in neuronal signaling and development.

Exome sequencing was also recently employed to find genes associated with myopia, which led to identification of mutations in *LRPAP1*, *CCDC111*, *LEPREL1*, and *SCO2* that resulted in disease development^{101–104}. Identification of several novel genetic associations for refractive error in the last year is encouraging. Further studies exploring the functional role of these variants may enable development of improved diagnostic and therapeutic strategies for this common disorder.

Retinal Vascular Disease

Retinal vein occlusion (RVO) causes significant visual morbidity secondary to macular edema and neovascularization. It occurs as a result of intraluminal thrombus formation and is associated with hypertension, hyperlipidemia, diabetes, smoking, oral contraceptive use and hypercoagulable states¹⁰⁵. To explore whether genetic polymorphisms in the coagulation pathway are associated with RVO risk, a candidate gene study was recently conducted in a Turkish population¹⁰⁶. There was a significant association between the *VKORC1* -1639G>A and *VKORC1* -1173 C>T polymorphisms and risk for RVO. The *VKORC1* gene is a component of the vitamin K epoxide reductase complex, which is necessary for gamma carboxylation of clotting factors II, VII, IX, X, and proteins C and S. However, a larger replication study conducted in patients of Caucasian descent found no significant association between the *VKORC1* -1639G>A polymorphism and risk for either central or branch RVO¹⁰⁷.

Matrix metalloproteinases (MMPs) and their endogenous inhibitors (TIMPs) are involved in extracellular matrix turnover and contribute to several pathological processes, including vascular disorders. Notably, MMP expression is elevated during the initial phase of thrombosis, suggesting a possible role in the development of RVO¹⁰⁸. A candidate gene study was recently performed in a Turkish population to further explore this hypothesis¹⁰⁸. The *MMP2*-1306 C/T polymorphism was associated with risk for RVO in this population, though the *TIMP2*G-418C polymorphism was not.

Retinal vascular caliber is an important predictor of subsequent macrovascular disease development, including myocardial infarction and stroke. To identify genetic factors that contribute to variation in retinal arteriolar caliber, a GWAS was recently performed in 18,722 individuals of European ancestry¹⁰⁹. A variant (rs2194025) near the myocyte enhancer factor 2C (*MEF2C*) gene was significantly associated with retinal arteriolar caliber in this cohort and this finding was replicated in a second independent cohort of 3,939 European individuals. However, no significant association was found between this SNP and macrovascular disease outcomes, including coronary artery disease, stroke, myocardial infarction and hypertension¹⁰⁹.

Uveal Melanoma

Uveal melanoma, which arises in the iris, ciliary body and choroid, is the most common ocular malignancy. Prognosis is heavily influenced by chromosome 3 status: loss of one copy (monosomy 3) in the tumor is associated with metastatic disease, which carries a poor prognosis. On the other hand, tumors with two copies of chromosome 3 (disomy 3) rarely metastasize, and therefore have a much more favorable prognosis. Loss of function mutations in the *BAP1* gene have previously been shown to be associated with monosomy 3 and are therefore associated with a poorer prognosis¹¹⁰.

Recently, whole-exome sequencing was utilized to identify other mutations associated with uveal melanoma. Somatic mutations in *EIF1AX* and *SF3B1* were found to occur specifically in uveal melanomas with disomy 3, which are less invasive and have a favorable prognosis¹¹¹. In another study, all *SF3B1* mutations identified in uveal melanomas with

disomy 3 occurred exclusively at codon 625, leading to amino acid changes at this codon¹¹⁰. The *SF3B1* gene encodes subunit 1 of the splicing factor 3b complex; mutations of this gene in uveal melanoma leads to differential alternative splicing of protein coding genes (*ABCC5*, *UQCC*) and long noncoding RNAs (*CRNDE*)¹¹².

Recent studies have also explored epigenetic factors associated with uveal melanoma metastasis. The chemokine factor CXCR4 contributes to invasion and metastatic spread, including liver metastasis of uveal melanomas. Cancer cells constitutively expressing CXCR4 were found to have higher methyltransferase activity after injection into the anterior chamber of the eye when compared to subcutaneously-derived, liver-derived, or wild-type tumor cells¹¹³. This finding suggests that the ocular microenvironment induces methylation and epigenetic downregulation of CXCR4 expression by tumors.

Conclusions

The past year has witnessed numerous advances in ocular genetics. Many of the reported discoveries have been enabled by use of more up-to-date technologies, including genome-wide association studies, whole-exome sequencing, epigenetic studies, and increasingly powerful meta-analyses. Importantly, in the last year, advances have also been made in identifying functional roles genetic variants in disease pathogenesis, paving the way for translation of genetic data into clinical practice. This includes use of genetic signatures for diagnosis and prognosis, prediction of treatment response, and development of targeted gene therapies. Continued research on genetic risk factors for common ocular disorders will be critical in reducing the global burden of visual impairment and blindness.

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Table 1

Ocular Disease Genome Wide Association Studies (GWAS) From 2013

Disease	Population	Number of Cases/ Number of Controls	Significant Association	Chromosomal Location	Gene Function	Reference
Age-Related Macular Degeneration (AMD)	European and Asian	17,100/60,000	<i>COL8A1-FILIPIL</i> , <i>IER3-DDRI</i> , <i>SLC16A8</i> , <i>TGFBR1</i> , <i>RAD51B</i> , <i>ADAMTS9</i> and <i>B3GALT1</i>	Multiple chromosomal loci	Multiple (including regulation of complement activity, lipid metabolism, extracellular matrix remodeling, and angiogenesis)	12
Central Corneal Thickness	U.S. Caucasian	400 POAG Cases and 400 AMD Cases	<i>RPN2</i>	20q12-13.1	Integral membrane protein in rough endoplasmic reticulum	25
	European and Asian	>20,000	<i>USP37</i> , <i>GPR15</i> , <i>TIPARP</i> , <i>CWC27</i> , <i>ADAMTS6</i> , <i>RXRA</i> , <i>COL5A1</i> , <i>COL5A1</i> , <i>LCN12</i> , <i>PTGDS</i> , <i>FGF9-SGCG</i> , <i>FOXO1</i> , Near <i>TIP1</i> (5'), Near <i>AKAP13</i> (5'), <i>LRRK1</i> , <i>CHSY1</i> , <i>BANP</i> , <i>ZNF649</i> , <i>HS3ST3B1-PMP22</i>	Multiple chromosomal loci	Multiple (loci cluster in collagen and extracellular matrix pathways)	26
Diabetic Retinopathy	Latino	1,768	<i>LOC100506532</i>	9q34.3	Long non-coding RNA (lncRNA)	24
Primary Open Angle Glaucoma (POAG)	Chinese, Hispanic	437/570 (Chinese) 585 (Hispanic)	<i>TBC1D4-COMMD6</i> , <i>UCHL3</i> , <i>LRP2-BBS5</i> and <i>ARLAC-SH3BP4</i>	Multiple chromosomal loci	Multiple (including insulin regulation, inflammation, lipid signaling and apoptosis)	36
	U.S. Caucasian	400 POAG Cases and 400 AMD Cases	Complement component C7	5p13	Innate and adaptive immune response	25
	European and Asian	2,979/7,399	<i>FNDC3B</i>	3q26	Adipogenesis	26
Keratoconus	U.S. Caucasian	3,108/3,430	<i>COMT</i> (Associated only in women, not men)	22q11.1-11.2	Metabolism of catecholamines and estrogens	62
	European and Asian	874/6,085	<i>FOXO1</i> , <i>FNDC3B</i>	13q14 (<i>FOXO1</i>) 3q26 (<i>FNDC3B</i>)	Adipogenesis	26
Ocular Behcet's Disease	Korean	379/800 (Discovery cohort) 363/272 (Replication cohort)	<i>GIMAP</i> locus	7q36.1	Immunological functions (thymocyte development, apoptosis regulation in lymphocytes)	114
Refractive Error	Caucasian	7,280	<i>RBFOX1</i>	16p13.3	Alternative splicing events	96
	European and Asian	12,531 (European), 8,216 (Asian)	<i>LAMA2</i> , <i>GID2</i> , <i>CD55</i> , <i>ALPPL2</i> , and <i>ZC3H11B</i>	Multiple chromosomal loci	Multiple (including extracellular matrix and gap junction constituents)	97
	Han Chinese	665/960	<i>VIPR2</i> , <i>SNBT1</i> (High myopia)	7q36.3 (<i>VIPR2</i>), 8q23.4 (<i>SNBT1</i>)	Receptor for vasoactive intestinal peptide (<i>VIPR2</i>), dystrophin-associated protein (<i>SNBT1</i>)	98
	European	2,023	<i>PDGFRA</i> (Corneal curvature and corneal astigmatism)	4q12	Receptor tyrosine kinase	99

Disease	Population	Number of Cases/ Number of Controls	Significant Association	Chromosomal Location	Gene Function	Reference
Retinal Vascular Caliber	European and Asian	37,382 (European), 8,376 (Asian)	<i>GRIA4, KCNQ5, RDH5, LAMA2, BMP2, SIX6 and PRSS56</i>	Multiple chromosomal loci	Multiple (including neurotransmission, ion transport, retinoic acid metabolism, extracellular matrix remodeling, and eye development)	95
	European	45,771	<i>BMP3, BMP4, DLG2, DLX1, KCNMA1, KCNQ5, LAMA2, LRRC4C, PRSS56, RBFOX1, RDH5, RGR, SFRP1, TJP2, ZBTB38, and ZIC2</i>	Multiple chromosomal loci	Multiple (including eye development, extracellular matrix remodeling, growth and guidance of retinal ganglion cells, retinoic acid metabolism, and neuronal signaling)	100
	European	18,722 (Discovery Cohort) 3,939 (Replication Cohort)	<i>MEF2C</i>	5q14.3	Vascular development	109

Table 2

Ocular Disease Gene Discovery in 2013

Disease	Methods	Population	Identified Gene(s)	Gene Function	Reference
Acute anterior uveitis and pediatric uveitis	Candidate gene study	Han Chinese	<i>TRAF5</i>	Mediates tumor necrosis factor (TNF) induced processes	115
Age-Related Cataract (ARC)	Candidate gene studies	Han Chinese	<i>WRN</i>	DNA helicase	8
		Serbian	<i>GSTO2</i>	Metabolism of carcinogens	9
		Han Chinese	<i>HSPA1B</i>	Cell stress responses	10
Anophthalmia/Microphthalmia	Homozygosity mapping + exome sequencing + Sanger sequencing ⁽⁸⁶⁾ ; homozygosity mapping + next-generation sequencing ⁽⁸⁷⁾	Turkish/Moroccan ⁽⁸⁶⁾ ; Egyptian ⁽⁸⁷⁾	<i>ALDH1A3</i>	Formation of a retinoic acid gradient during ocular development	86,87
Anterior uveitis	Candidate gene study	Chinese	<i>CFH</i>	Immune response	116
Autosomal dominant neovascular inflammatory vitreoretinopathy (ADNIV)	Linkage analysis + whole-exome sequencing	U.S. Caucasian	<i>CAPN5</i>	Cysteine protease expressed in retinal photoreceptor cells	117
Autosomal-Recessive Congenital Stationary Night Blindness	Whole-exome sequencing	Various (recruited from clinical centers in Europe, the United States, Canada, Israel, and India)	<i>LRIT3</i>	Regulation of fibroblast growth factor receptors	118
Colobomatous microphthalmia	Autozygome analysis + exome sequencing	Saudi Arabian	<i>CL2orf57</i>	Unknown	91
Cone-Rod Dystrophy	Whole-exome sequencing	Indian	<i>CYP11B1</i>	Retinoic acid signaling	92
	Homozygosity mapping + exome sequencing	Moroccan	<i>RAB28</i>	Ciliary transport in photoreceptor cells	119
Diabetic Retinopathy	Candidate gene studies	Chinese	<i>CFH, CFB</i>	Immune response	37-44
		Iranian	<i>GSTM1</i>	Detoxification of xenobiotics	38
		Korean	<i>ADIPOQ</i>	Glucose regulation and fatty acid oxidation	39
		Han Chinese	<i>ACE</i>	Regulation of fluid- electrolyte balance and blood pressure	40
		Korean	<i>MCP-1</i>	Inflammatory responses	41
		Slovenian	<i>OPG</i>	Inflammatory responses and innate immunity	42
		Polish	<i>CNR1</i>	Cannabinoid receptor	43

Disease	Methods	Population	Identified Gene(s)	Gene Function	Reference
Fuchs' Endothelial Corneal Dystrophy (FECED)	Genome-wide linkage mapping + next-generation sequencing	Chinese	<i>TMEM217, MRPL14, GRIK2</i>	Multiple (neurotransmission, transmembrane proteins, mitochondrial ribosomal protein)	44
	Candidate gene study	Caucasian	<i>AGBL1</i>	Deglutamylation of target proteins	50
Fungal Keratitis	Candidate gene study	Polish	<i>RAD51</i>	Homologous recombination and repair of double-stranded breaks	48
		Han Chinese	<i>TLR2, TLR4</i>	Immune response	120
Keratoconus	Candidate gene studies	Polish	<i>TF</i>	Iron transport	80
		Polish	<i>RAD51</i>	Homologous recombination and repair of double-stranded breaks	48
		Caucasian	<i>CAST</i>	Endogenous inhibitor of the calpains	81
		Australian	<i>MPDZ, NF1B, BANP-ZNF4659</i>	Component of NMDA receptor complex (MPDZ), Tumor suppressor and cell cycle regulator (BANP)	82
Primary Angle Closure Glaucoma (PACG)	Candidate gene studies	Han Chinese	<i>MFRP, HSP70</i>	Eye development (MFRP), protein folding and cell stress response (HSP70)	66
		Australian	<i>eNOS</i>	Modulates vascular tone	67
		Chinese	<i>PKSS56</i>	Eye development	68
		Han Chinese	<i>HGF</i>	Growth factor	69
Proliferative vitreoretinopathy	Candidate gene study	Multiple (Spain, Portugal, UK, Netherlands)	<i>MDM2</i>	E3 ubiquitin ligase, negative regulator of p53	121
Refractive Error	Autozygome analysis + exome sequencing	Saudi Arabian	<i>LRPAP1</i>	LDL receptor trafficking	101
	Whole-exome sequencing	Chinese	<i>CCDC111</i>	Unknown	102
	Whole-exome sequencing	Chinese	<i>LEPREL1</i>	Collagen chain assembly	103
	Whole-exome sequencing	European	<i>SCO2</i>	Oxidative phosphorylation	104
Retinal Vein Occlusion	Candidate gene studies	Turkish	<i>VKORC1</i>	Gamma carboxylation of clotting factors II, VII, IX, X, and proteins C and S	106
		Turkish	<i>MMP2</i>	Extracellular matrix turnover	108
Retinitis Pigmentosa	Homozygosity mapping + exome sequencing	Saudi Arabian, European	<i>ARL2BP</i>	Centromere-associated protein	122
Rod-Cone Dystrophy	Autozygosity mapping + whole-exome sequencing	Caucasian	<i>TUB</i>	Phagocytosis of apoptotic retinal pigment epithelial (RPE) cells	123
Uveal Melanoma	Whole-exome sequencing	Caucasian	<i>SF3B1</i>	RNA splicing	110

Disease	Methods	Population	Identified Gene(s)	Gene Function	Reference
Viteliform Macular Dystrophies	Whole-exome sequencing	Caucasian	<i>EIF1AX, SF3BI</i>	Protein translation (<i>EIF1AX</i>), RNA splicing (<i>SF3BI</i>)	111
	Gene-mapping + whole- exome sequencing	French	<i>IMPG1</i>	Component of rod and cone photoreceptor extracellular matrix domains	124