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Advances in the genomics of common eye diseases

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Genome-wide association studies (GWAS) and other genomic technologies have accelerated the discovery of genes and genomic regions contributing to common human ocular disorders with complex inheritance. Age-related macular degeneration (AMD), diabetic retinopathy (DR), glaucoma and myopia account for the majority of visual impairment worldwide. Over 19 genes and/or genomic regions have been associated with AMD. Current investigations are assessing the clinical utility of risk score panels and therapies targeting disease-specific pathways. DR is the leading cause of blindness in the United States and globally is a major cause of vision loss. Genomic investigations have identified molecular pathways associated with DR in animal models which could suggest novel therapeutic targets. Three types of glaucoma, primary-open-angle glaucoma (POAG), angle-closure glaucoma and exfoliation syndrome (XFS) glaucoma, are common age-related conditions. Five genomic regions have been associated with POAG, three with angle-closure glaucoma and one with XFS. Myopia causes substantial ocular morbidity throughout the world. Recent large GWAS have identified >20 associated loci for this condition. In this report, we present a comprehensive overview of the genes and genomic regions contributing to disease susceptibility for these common blinding ocular disorders and discuss the next steps toward translation to effective gene-based screening tests and novel therapies targeting the molecular events contributing to disease.

INTRODUCTION

Common age-related ocular disorders with complex inheritance are responsible for the majority of blindness worldwide. In the United States alone, >3 million individuals over the age of 40 (1) are visually impaired as a consequence of these conditions, and this number is expected to triple by 2020 (2). Effective disease surveillance and treatment will become increasingly important as the population ages. The identification of genetic risk factors contributing to common complex disease is the first step toward the development of gene-based screening tests and novel therapies targeted to the molecular events responsible for disease. Genome-wide association studies (GWAS) and other genomic analyses have successfully identified risk alleles for a large number of common complex human disorders (3), including diseases affecting vision. In this review, we summarize the recent advances in the genomics of the four disorders that are leading causes of visual impairment: age-related macular degeneration (AMD), diabetic retinopathy (DR), glaucoma and myopia (near-sightedness).

AGE-RELATED MACULAR DEGENERATION

AMD is a progressive neurodegenerative disease that diminishes the quality of life for millions of elderly individuals worldwide. In the United States, advanced AMD accounts for more than half of all blindness (4). Phenotypically, macular degeneration progresses from early stages (characterized by abnormalities in the retinal pigment epithelium and accumulation of extracellular deposits called 'drusen' in the macular region of the retina) to advanced or late stages with retinal neovascularization and scarring (especially in the macular region) and atrophy of the retinal pigment epithelium (geographic atrophy) (Fig. 1). AMD has both genetic and environmental contributions; smoking and

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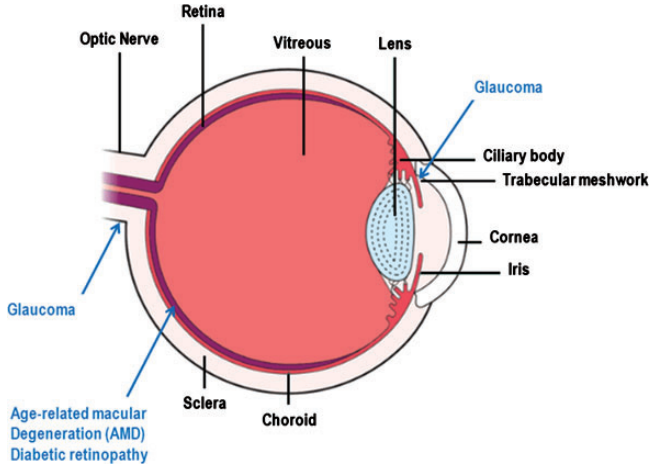

Figure 1. Schematic diagram of the eye. The basic structures of the eye are labeled in black font and the ocular tissues affected by the disorders discussed in this review are labeled in blue font. The function of the eye is to transduce a light signal to an electrical impulse. Light enters the eye through the cornea is focused by the lens and then stimulates the photoreceptors of the retina. The photoreceptors transduce the light signal into an electrical impulse that travels through the optic nerve to the brain. AMD affects the retina, and in particular the macular region of the retina responsible for high acuity vision. The retinal pigment epithelium (also a site of damage in AMD) is the outermost layer of the retina just beneath the photoreceptors. Diabetic retinopathy also affects the retina, frequently causing damage to the macular region and also other parts of the retina. Elevated IOP in glaucoma is caused by a reduction in the rate of removal of intraocular fluid by the trabecular meshwork. The visual compromise in glaucoma is caused by damage to the optic nerve and elevated IOP is a significant risk factor for optic nerve degeneration. Myopia, or near-sightedness, is created when the image focal point occurs in front of the retina (not shown on this figure). This can occur when the eye is too long for it's inherent focusing power.

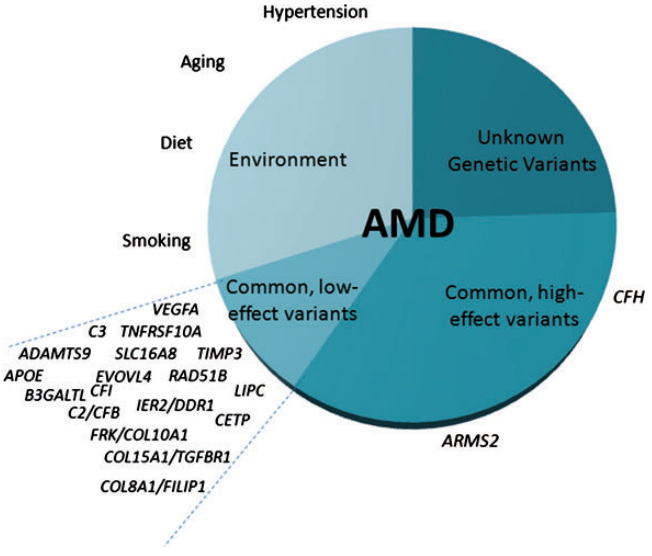

Figure 2. Genes and genomic regions associated with age-related macular degeneration (AMD). Genetic and environmental risk factors are presented. *CFH* (complement factor H) and *ARMS2* (age-related maculopathy susceptibility 2) are major genetic risk factors for the disease.

age are the most consistently observed non-genetic risk factors (5). The genetic component of AMD is significant and has been well established (6–8), with great progress having been made in the past several years toward identifying contributing genetic loci. Significant loci include variants in *CFH* (9–11) and in several additional complement genes including complement 2 (*C2*), complement factor B (*CFB*) (12), complement 3 (*C3*) (13) and complement factor I (*CFI*) (14). Outside the complement genes, the major known genetic contributor to AMD risk resides in the *ARMS2*/*HTRA* region (15–18). More recently, variants near *TIMP3*, *LIPC* and *CETP* have been associated with AMD (19,20). Though several high-effect loci have been identified, these likely account for less than two-thirds of the genetic component of AMD (21). Significant gene–environment interactions have been identified for *CFH* and smoking (22) as well as *CFH* and antibodies to the bacterial pathogen *Chlamydophila pneumonia* (23). Both smoking and *C. pneumonia* would be expected to influence the inflammatory pathways that include *CFH*. The majority of GWAS have been carried out with advanced AMD cases; however, a recent GWAS investigated early-stage AMD cases and confirmed the involvement of *CFH* and *ARMS2/HTRA* in early-stage disease and also provided suggestive evidence for risk alleles specific to early AMD (24). Since preventative therapies would ideally be targeted to early-stage disease, further study of the genetic and environmental risk factors associated with disease onset is warranted. The AMDGene Consortium formed in 2010 (21), performed a genome-wide association study using 7650 advanced AMD cases and 51 844 controls, with follow-up in an additional 9531 cases and 8230 controls. Joint analysis detected 19 loci attaining genome-wide significance at $P < 5 \times 10^{-8}$. Significant loci included 12 previously identified variants in *ARMS2-HTRA1*, *CFH*, *C2-CFB*, *C3*, *TIMP3*, *APOE*, *CETP*, *VEGFA*, *TNFRSF10A*, *LIPC*, *CFI*, *COL10A1*, with odds ratios (ORs) ranging from 1.13 (*COL10A1*) to 2.71 (*ARMS2-HTRA1*). An additional seven variants in *COL8A1-FILIP1L*, *IER3-DDR1*, *SLC16A8*, *TGFBR1*, *RAD51B*, *ADAMTS9* and *B3GALTL* met genome-wide significance for the first time, with ORs ranging from 1.11 (*RAD51B*) to 1.28 (*COL8A10-FILIP1L*) (21). Pathway analyses highlighted lipid metabolism, complement activation, angiogenesis and inflammation (Fig. 2).

The International Age related Macular Degeneration Genomics Consortium (IAMDGC) is currently assessing the ~50 000 person dataset typed on a custom Illumina Exome array, which was designed to bridge the gap between association studies of common variants and sequencing studies of rare variants. Analysis of the ~500 000 markers will provide improved coverage of known disease susceptibility loci through fine-mapping, enhance the power for discovery of disease loci in the largest single-variant analysis yet performed in AMD and facilitate assessment of rare coding variation and copy number variants. These data will also support further exploration of gene–environment interactions and gene association studies in early-stage as well as late-stage disease.

DIABETIC RETINOPATHY

DR is the leading cause of blindness in Americans between 20 and 74 years of age (25) and is rapidly becoming a common cause of visual impairment in developing countries (26). Diabetes causes injury to retinal blood vessels promoting a neovascularization response that causes further retinal damage

especially due to retinal hemorrhage (Fig. 1). The frequency and severity of DR is heterogeneous (27,28). Known risk factors, most notably duration of diabetes and glycemic control, explain some, but not all, of the observed heterogeneity (28–30). Genetic variation may explain some of the remaining heterogeneity in DR development. Heritability has been estimated to be as high as 27% for DR and 52% for proliferative diabetic retinopathy (PDR), the more extreme phenotype (31–33).

Genomic investigations have confirmed and revealed pathways associated with DR. Retinal whole-genome microarray analyses in animal models of diabetes have detected gene expression changes indicating that pro-inflammatory, anti-vascular barrier and neurodegenerative pathways are involved in the disease (34). Candidate gene association studies have explored the contributions from these pathways to disease in humans however; the results have not been reliably reproduced (35–38). For example, strong evidence has been presented for an association between the T allele of rs1617640 in the erythropoietin promoter and PDR (39); however, a second, albeit smaller, study found the opposite allele of this same single nucleotide polymorphism (SNP) to be associated with DR risk (40). *TCF7L2*, a consistent risk locus for type 2 diabetes (T2D), has been studied in DR with both positive (41,42) and negative results (43).

GWAS for DR have also not produced any consistent risk loci. The first two published GWAS for DR, one in a Caucasian type 1 diabetes (T1D) population and the other in a Mexican-American T2D population, generated new candidate loci but these loci did not reach genome-wide significance (44,45). Replication of the loci from the T1D study was subsequently attempted without success (46). A third GWAS for DR reported variants that were associated with genome-wide significant *P* values in a Chinese T2D cohort but there was no independent replication attempted (47). The most recent GWAS of DR in Chinese participants with T2D also did not reveal any genome-wide significant loci (48).

There are several reasons why GWAS have yet to yield consistent findings. The genetic effects are likely to be modest and require large sample sizes to be identified. Data sets from diverse populations have not yet been combined to this end. Another explanation for the inability to replicate DR associations may lie in the heterogeneity among studies with regards to DR case and control definitions, participants' mean duration of diabetes and degree of glycemic control, and the underlying type of diabetes. Larger genomic studies with harmonized phenotyping, particularly examining the extreme and more heritable phenotype of PDR, will be important for uncovering true risk loci.

GLAUCOMA

Glaucoma is a neurodegenerative condition causing irreversible damage to the optic nerve. Most patients with vision loss due to optic nerve degeneration also have elevated intraocular pressure (IOP) caused by abnormal intraocular fluid dynamics (Fig. 1). The most common type of glaucoma, primary-open-angle glaucoma (POAG), has a significant heritability with a sibling risk between 5 and 10 times the population risk (49). Advances in genomic technologies coupled with the formation of consortia contributing appropriate numbers of cases and controls have facilitated genome-wide association studies identifying genes contributing to ocular quantitative traits related to glaucoma pathogenesis (IOP, cup/disc ratio (CDR) optic nerve size and central corneal thickness (CCT)), as well as genes associated with POAG, angle-closure glaucoma and glaucoma associated with exfoliation syndrome (XFS).

Quantitative traits related to glaucoma development are highly heritable and show substantial variation in human populations. IOP is a quantitative trait that is the only modifiable risk factor for glaucoma. Recent genome-wide analyses using normal populations have identified two genes significantly associated with IOP, *GAS7* and *TMCO1* (50). Similar analyses for optic nerve parameters associated with glaucoma risk have identified *CDKN2BAS* and *SIX1SIX6* as genetic risk factors contributing to CDR (51), and *ATOH7* as an important determinant of optic nerve size (52). Populations from around with world have been used to identify genetic factors contributing to CCT, one of the most heritable of the ocular quantitative traits (53–55). A recent study from the International Glaucoma Genetics Consortium identified 16 loci significantly associated with CCT (56) and showed that the collagen and extracellular matrix pathways are important regulators of CCT (Fig. 3).

POAG is the most common type of glaucoma in the Western world. The disease results in a relentless progressive destruction of the optic nerve eventually causing permanent visual loss. Therapeutic strategies are currently limited to reducing optic nerve destruction by lowering IOP. Neuro-protective therapies are not currently available and a major goal of glaucoma genomic research is to identify potential therapeutic targets based on information about genes that influence susceptibility

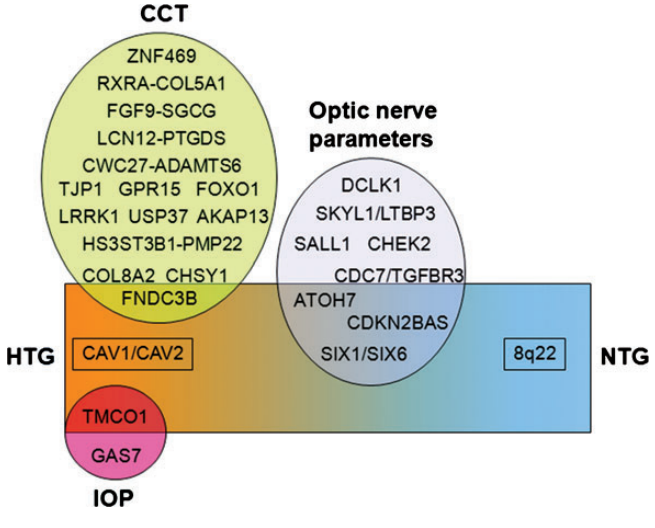

Figure 3. Genes and genomics regions associated with glaucoma and the related quantitative traits. Variants associated with ocular quantitative traits related to glaucoma and (ellipses) and POAG are presented (rectangle). POAG can be divided into high-tension (HTG) and normal-tension (NTG) subgroups. Of the two genes associated with elevated IOP, one (*TMCO1*) is also associated with HTG. One gene associated with thin CCT (*FNDC3B*) is also associated with HTG. Three genomic regions associated with optic nerve parameters (CDKN2BAS, *ATOH7* and *SIX1/SIX6*) are associated with HTG, and one of these, *CDKN2BAS*, is associated with both HTG and NTG. The *CAV1/CAV2* genomic region is associated with HTG but not with any quantitative trait. The 8q22 genomic region is associated with NTG only.

to optic nerve disease. Several GWAS for POAG have been completed. A study from Iceland using 1263 cases and over 34 877 controls identified variants in the *CAV1/CAV2* intergenic region associated with POAG (57). This finding has been replicated in a study of Caucasian cases and controls from the USA (GLAUGEN) (58). Using 590 advanced glaucoma cases and 3956 controls, the *CDKN2BAS* (previously associated with CDR) and *TMCO1* (also associated with IOP) genes were found to be associated with POAG in a study of Australian cases and controls (59). The *CDKN2BAS* and *SIX1/SIX6* genes were also associated with POAG in 3500 cases and controls analyzed in a meta-analysis of the GLAUGEN and NEIGHBOR studies (60). POAG patients affected by the 'normal-tension' subtype of glaucoma (NTG) have increased susceptibility to optic nerve degeneration. The NEIGHBOR/GLAUGEN meta-analysis included a NTG subgroup analysis that showed significant association with *CDKN2BAS* as well as a highly conserved regulatory region 8q22 (60). These results suggest that *CDKN2BAS*, regulating expression of *CDKN2B*, an inhibitor of *CDK4*, and the 8q22 region primarily influence optic nerve degeneration for glaucoma and could be targets for neuroprotective therapies.

Angle-closure glaucoma is a major cause of blindness in Asia. The condition results when intraocular fluid cannot be removed by the trabecular meshwork (Fig. 1) because access is anatomically blocked by an abnormal configuration of the iris and other intraocular structures. Using 1854 angle-closure cases and 9608 controls from five different Asian populations a GWAS identified three associated loci: *PLEKHA7*, *COL11A1* and an intergenic region between *PCMTD1* and *ST18* on chromosome 8q (61). All three of these loci were replicated in a second study using cases and controls from Nepal and Australia (62). *PLEKHA7*, encoding pleckstrin homology domain-containing protein 7, maintains a protein complex that regulates paracellular permeability of several ocular tissues including structures involved in angle-closure glaucoma (iris, trabecular meshwork). *COL11A1* encodes one of the two alpha chains of type XI collagen and mutations in this gene are known to cause Stickler syndrome and other related disorders (63). Interestingly, myopia or near-sightedness is a feature of the Stickler syndromes, and the opposite refractive error (hyperopia) is more commonly associated with angle-closure glaucoma (64). *COL11A1* is expressed in the scleral tissue which is implicated in both myopia and hyperopia (65,66). Little is currently known about the genes flanking the intergenic third locus on chromosome 8q.

XFS is an age-related disease characterized by the progressive accumulation of a fibrillar extracellular material in the trabecular meshwork where it causes a decrease in fluid removal and a corresponding increase inIOP. A GWAS using Icelandic cases and controls identified *LOXL1* (lysyl oxidase like 1) as a major genetic risk factor for XFS (67), a finding that has been replicated in populations worldwide (68). LOXL1 is necessary for development and maintenance of elastin (69). Recent studies suggest that *LOXL1* variants may influence disease development by reducing *LOXL1* gene expression (70,71), causing a compromise of elastic structures in the eye. The frequency of *LOXL1* risk alleles is high in both affected and unaffected individuals arguing that other factors, which could genetic or environmental, must also contribute to the disease (68).

MYOPIA

Myopia is the most common ocular disorder worldwide, with a significant ocular morbidity and impact on global public health. It also carries a huge economic burden, estimated to be $139 billion a year in the United States. The condition develops when the refractive power of the eye is not sufficient to place the focal point in the plane of the retina so that images come into focus in front of the retina (Fig. 1). While temporal and geographical changes in prevalence (affecting >80% young adults in urban East Asia) suggest important environmental influences (72), myopia is highly heritable. Before GWAS, numerous myopia loci were identified, but there were no known non-syndromic myopia genes. GWAS studies have involved either high-grade 'pathological' myopia case–control studies, or analysis of quantitative 'healthy variation' of refractive error using population-based cohorts.

The first high myopia GWAS, published from Japan in 2009, identified a locus on chromosome 11q24, albeit not at genome-wide significance (73). The following year two studies of over 4000 participants in the discovery phase each identified a single locus at genome-wide significance on chromosome 15, at 15q14 near the *GJD2* gene in the Rotterdam Study (74), and near the *RASGRF1* gene at 15q25 in the TwinsUK cohort (75). Both candidate genes, highly expressed in the retina, provide plausible biological candidates for myopia. *GJD2* encodes a neuron-specific protein (connexin36) that is found in retinal photoreceptors, essential in the transmission of rod-mediated visual signals. *RASGRF1* is regulated by muscarinic receptors (76) and retinoic acid, both implicated in myopia development in animal models.

The Consortium on Refractive Error and Myopia (CREAM) published an international meta-analysis using spherical equivalent data from over 45 000 participants, which included 37 382 individuals from 27 populations of European ancestry, and 8376 individuals from five Asian cohorts (77). In all, 26 loci were identified at genome-wide significance, including replication of the chromosome 15 regions. Genes identified were involved in neurotransmission (*GRIA4*), ion transport (*KCNQ5*, *CD55*, *CHNRG*), retinoic acid metabolism (*RDH5*, *RORB*, *CYP26A1*), extracellular matrix remodeling (*LAMA2*, *BMP2*) and eye development (*SIX4*, *PRSS56*, *CHD7*). Despite these discoveries, in common with most complex diseases, the significant associations only explained 3–4% of the variation. At the same time, the personal genomics company 23andMe performed an even larger GWAS with almost 26 000 myopic cases and 20 000 controls, using a Cox proportional hazards model of age of onset of myopia as a proxy for severity (a reasonable assumption), and identified 22 significantly associated loci (78). The similarity of results from two different studies using completely different methodologies was truly remarkable: 16 of the 20 novel loci identified by Kiefer *et al*. were confirmed by CREAM; and of the 22 loci discovered by the CREAM analyses, 14 were replicated by 23andMe and those regions not confirmed had suggestive associations in the other (79).

Further, GWAS meta-analyses have identified *RBFOX1* on chromosome 16 as a candidate gene for refractive error susceptibility in European populations (80), and GWAS have identified genetic variants in high myopia studies in Chinese populations (81,82). Future larger GWAS of myopia will provide further

evidence of genes, each of smaller effect. Exome sequencing holds promise of identifying genes, particularly in highly affected subjects (83,84), and in families with dominantly inherited high-grade myopia (85,86), though the relevance of these findings to 'simple' myopia remains uncertain.

FUTURE DIRECTIONS

A major goal of genomic research is to use genome-wide association findings to develop clinically useful gene-based tests and therapeutic strategies targeted to the disease-related molecular events (87). For AMD, considerable progress has been made in both areas. A SNP risk score combining information from 19 associated loci can distinguish cases and controls reasonably well (area under the receiver operator curve (AUC) = 0.74) (21), suggesting that a SNP score 'test' could be used to identify at risk individuals for preventive or preemptive treatment before the onset of disease (88). Ideally, SNP score tests could be used to identify individuals who would benefit most from specific therapies, such as anti-VEFG injections to control neovascularization (89). However, genetic variants contributing to anti-VEGF responsiveness have only been preliminarily identified (90) and further analyses will be needed before pharmacogenetic-based tests can be clinically useful. Additionally, the identification of *CFH* as a major risk allele for AMD has led to clinical trials investigating the efficacy of anti-complement therapies (91). Other loci associated with AMD could also be targets for novel therapies. The association with lipid pathways suggests that lipid profiles may be clinically useful biomarkers (92); however, these results have not been consistently observed and require further research for confirmation (93). SNP risk scores based on current and new genes associated with glaucoma could also be clinically useful in the future. The identification of novel genes and pathways contributing to glaucoma will also help define disease-specific targets for novel therapeutic approaches. Genomic studies using larger sample sizes, including whole-exome analyses, could lead to the discovery of significant loci for DR. A future area of interest in myopia research is to understand the interaction between associated genes and environmental effects. Through these and other ongoing efforts novel gene-based tests and therapies for common ocular disease can help reduce the global burden of visual impairment.

Conflict of Interest statement. None declared.

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