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Editorial

Recent Trends in Ocular Genomics

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Ocular genomics is advancing rapidly in parallel with the invention of Genome-Wide Association Studies (GWAS), the application of meta-analysis of multiple GWAS results, and the expansion of GWAS into minority populations. These GWAS methods are based on high-throughput technologies and attempt to associate genetic abnormalities with the diseases they are applied to. The power of GWAS is derived from its sample size, and combining several studies can help identify variants with subtle, but significant effects. Ultimately, understanding the molecular basis of the eye diseases will lead to better diagnosis and treatment.

Three major eye diseases, Age-related Macular Degeneration (AMD), glaucoma, and Diabetic Retinopathy (DR), have been extensively studied in ocular genomics. AMD affects the macula and destroys the central vision. Glaucoma damages the optic nerve and causes loss of peripheral vision. DR produces changes in the retinal blood vessels and instigates blurred vision. These age-related eye diseases diminish the quality of life and cause a significant burden to the society.

There have been many successful and replicable discoveries in AMD genomics. The first successful GWAS study, in 2005, reported the association of a common variant in Complementary Factor H (CFH), a gene that regulates a part of the immune response. Early this year, the AMD Gene consortium identified seven novel loci and confirmed twelve that had been previously reported. These loci are implicated in a wide range of biological functions, including the immune system, lipid metabolism, atherosclerosis, cellular structure, and regulation of blood vessels. Even more recently, three papers reported the association of a rare coding variant in C3, an immune response gene, with AMD by sequencing previously identified regions.

Sample size is a critical factor in GWAS. Small sample sizes can only detect common associations with large effect sizes. This was the case with the discovery of CFH in AMD, which used only 96 cases and 50 controls. Two copies of the common risk variants have about 7-fold increased risk of AMD. Increased sample sizes have since helped uncover common variants with small influences on risk and rare variants. The AMD Gene consortium used 77,100 individuals to unveil the novel loci for AMD. The rare variant in C3, which increases the risk of AMD by about 3-fold, was discovered using thousands of AMD cases and a larger number of controls.

Glaucoma is a group of disorders and its molecular basis is poorly understood. The most common form of glaucoma is Primary Open Angle Glaucoma (POAG). Because POAG presents a range of symptoms, it is difficult to investigate its genetics. The meta-analysis of the Glaucoma Gene Environment Initiative (GLAUGEN) and the NEI Glaucoma Human genetic collaboration (NEIGHBOR) datasets with 3,146 cases and 3,487 controls only revealed two loci for POAG. Recently, researchers have successfully begun to use the quantitative features of glaucoma, such as Intraocular Pressure (IOP), Central Corneal Thickness (CCT), Vertical Cup-Disc Ratio (VCDR), and optic nerve size, to facilitate the search for glaucoma disease-causing genes. For example, both TMCO1, which is associated with elevated IOP, and FNDC3B, which is associated with CCT, are also associated with High-Tension Glaucoma (HTG). Three genetic loci, CDKN2BAS, ATOH7, and SIX1/SIX6, associated with optic nerve parameters are also associated with HTG, with CDKN2BAS associated with both HTG and Normal-Tension Glaucoma (NTG). However, exceptions exist; the CAV1/CAV2 locus is associated with HTG but has not been associated with any quantitative trait and the 8q22 locus is associated with only NTG.

Since POAG disproportionally affects African Americans and Latinos of Mexican origin, GWAS of glaucoma in these populations are now underway. For example, there are now two targeted studies, the African Descent and Glaucoma Study (ADAGES) and Mexican American Glaucoma Genetic Study (MAGGS) (http://projectreporter.nih.gov/). These studies can help uncover population-specific loci different from European ancestry.

GWAS for DR have not yielded consistent risk loci and most of the reported SNPs have not reach genome-wide significance ($P< 5\times10^{-8}$). Different studies have used different cut-offs for defining DR cases and controls, and this has complicated comparisons among studies. Furthermore, traditional risk factors for DR, such as duration of diabetes, glycosylated hemoglobin level, and blood pressure, may explain a lot of its variation. Therefore, the genetic effects are likely to be modest and require large sample sizes to uncover. To address this, a collaborative effort, Multi-ethnic GWAS for DR (http://projectreporter.nih.gov/), combining GWAS results from multiple African American and Caucasian cohorts of individuals with Type 2 diabetes, is ongoing. However, since the prevalence of DR is high among Latinos of Mexican origin, DR studies in this ethnic group may yield more fruitful results, e.g. through admixture mapping. It will also be beneficial to use narrowly-defined phenotypes, such as proliferate DR, to reduce phenotype heterogeneity.

In summary, there have been many GWAS discoveries in ocular genomics since the first success in AMD. More recently, sequencing as an extension of GWAS has helped uncover rare risk variants of AMD. Ocular genomics studies have also expanded from subjects of European ancestry to more diverse populations, which can help fine-mapping of genomic loci and uncover population-specific risk

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variants. Targeted sequencing and admixture mapping should generate promising discoveries in the future, especially in large sample size datasets. However, challenges lay ahead, e.g. how to reduce genetic and phenotypic heterogeneity in genomic investigations, how to gain more understanding in biological pathways building on results from individual variants or genes, and how to distinguish normal eye aging from pathophysiologic changes.

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