AMD Genetics: Methods and Analyses for Association, Progression, and Prediction

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Abstract

Age-related macular degeneration (AMD) is a multifactorial neurodegenerative disease, which is a leading cause of vision loss among the elderly in the developed countries. As one of the most successful examples of genome-wide association study (GWAS), a large number of genetic studies have been conducted to explore the genetic basis for AMD and its progression, of which over 30 loci were identified and confirmed. In this chapter, we review the recent development and findings of GWAS for AMD risk and progression. Then, we present emerging methods and models for predicting AMD development or its progression using large-scale genetic data. Finally, we discuss a set of novel statistical and analytical methods that were recently developed to tackle the challenges such as analyzing bilateral correlated eye-level outcomes that are subject to censoring with high-dimensional genetic data. Future directions for analytical studies of AMD genetics are also proposed.

Keywords

AMD genetics · GWAS · Machine learning · Progression · Prediction · Statistical methods

7.1 Introduction

Age-related macular degeneration (AMD) is a heritable neurodegenerative disease and a primary cause of vision loss among the elderly in the developed world. AMD is characterized by the loss of photoreceptor and the reduction of retinal pigment epithelium function in the macula. The disease is progressive and irreversible in affecting central vision. The disease process starts with appearance of drusen and progresses to advanced AMD, which is typically classified into two forms: wet AMD (also called choroidal neovascularization (CNV)) and dry AMD (also

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called geographic atrophy (GA)) [1–3]. Dry AMD, characterized by the presence of drusen and thinning of the macula, is the most common type of advanced AMD and affects 85–90% of the AMD patients. Wet AMD, characterized by bleeding or fluid leaking abnormal blood vessels grown underneath the retina and macula, is considered as the more advanced type of AMD. Although affecting only 10–15% of those who have AMD, wet AMD accounts for 90% of the severe vision damage.

7.2 Case–Control Genetic Association Studies on AMD Risk

In 1990s, twin studies and family aggregation studies had shown that genetics played a role in AMD. In a family aggregation study, the prevalence of AMD was much higher in the first-degree relatives of AMD patients (23.7%) than in relatives of healthy individuals (11.6%) [4]. Twin studies indicated that the heritability of AMD range from 46% to 71%, estimated from comparing AMD concordance rates between monozygotic and dizygotic twins [5]. In the effort to explore AMD genetics in early 2000s, association studies and genetic linkage studies had been conducted to identify candidate susceptibility genes. In 2005, a meta-analysis of linkage scans showed that chromosomes 1q25-31 and 10q26 were the most replicated genomic regions [6]. With advances in technology, in addition to candidate gene studies, genome-wide association studies (GWAS) were able to be conducted to examine the association between AMD status and a genome-wide set of single-nucleotide polymorphisms (SNPs). In the same year of 2005, a landmark GWAS revealed an SNP in an intron of *CFH* gene was strongly associated with AMD; the risk allele at the SNP was in linkage disequilibrium (LD) with a tyrosine–histidine change at amino acid 402 of *CFH* [7]. This region of *CFH* binds heparin and C-reactive protein. This was the first GWAS performed for AMD, showing that the effect size was significantly increased by an odds ratio (OR) of 7.4 (95% confidence interval: 2.9–19) under a recessive model. This study recruited 96 AMD patients and 50 controls, and genotyped 116,204 SNPs. Although both the sample size and number of SNPs were small, this study was the first successful GWAS among complex diseases. With its success, an era for GWAS of complex diseases started. Specifically, for AMD, subsequent GWAS identified several susceptibility loci in complement related genes, including *C2/CFB* [8], *CFI* [9], and *C3* [10].

Genes not in the complement pathway had also been identified to be associated with AMD. Of them, the *ARMS2/HTRA1* locus had a strong AMD association with an odds ratio (OR) of 5.0 and population attributable risk of 57% [11, 12]. Since SNPs in both *ARMS2* and *HTRA1* genes in this locus are in strong LD, variants in both genes could be causally relevant to AMD. This is one of the drawbacks of GWAS that one cannot draw a causal conclusion from GWAS results, but a pure association partly due to the fact of LD among SNPs. Thus, post-GWAS functional analysis is required to help understand the biological process. Among other noncomplement genes associated with AMD, *TGFBR1* and *VEGFA* are related to angiogenesis; *COL10A1* and *COL8A1* are related to extracellular collagen matrix; *APOE*, *CETP*, and *LIPC* are related to high-density lipoprotein cholesterol pathway [13–15].

In early 2010, 18 research groups from multiple countries formed the AMD Gene Consortium in order to facilitate the discovery in AMD genetics, with support from the National Eye Institute (NEI) of the U.S. National Institutes of Health (NIH). In 2013, the consortium published a large GWAS for AMD [13] which included 17,181 cases and 60,074 controls, and 2,442,884 genotyped and imputed SNPs. The study reported 19 loci (Table 7.1) with association of AMD reaching the genome-wide significance level ($P = 5 \times 10^{-8}$), where seven loci reached significance for the first time. The proportion of variability in the risk of AMD that is due to heritability had been estimated at 45–70% [5],

Table 7.1 Results for AMD risk genes reported in the two consortium case–control studies and/or the GWAS progression study

SNP	Chr	Position	Major/minor allele	Gene	Fritsche et al. [15]		Yan et al. [32]	
					OR	*P*-value	HR	*P*-value
rs10922109	1	196,704,632	C/A	*CFH*	0.38	9.6×10^{-618}	0.43	3.5×10^{-37}
rs62247658	3	64,715,155	T/C	*ADAMTS9-AS2*	1.14	1.8×10^{-14}		
rs140647181	3	99,180,668	T/C	*COL8A1*	1.59	1.4×10^{-11}		
rs10033900	4	110,659,067	C/T	*CFI*	1.15	5.4×10^{-17}		
rs62358361	5	39,327,888	G/T	*C9*	1.80	1.3×10^{-14}		
rs116503776	6	31,930,462	G/A	*C2-CFB-SKIV2L*	0.57	1.2×10^{-103}	0.56	8.1×10^{-10}
rs943080	6	43,826,627	T/C	*VEGFA*	0.88	1.1×10^{-14}		
rs79037040	8	23,082,971	T/G	*TNFRSF10A*	0.90	4.5×10^{-11}		
rs1626340	9	101,923,372	G/A	*TGFBR1*	0.88	3.8×10^{-10}		
rs3750846	10	124,215,565	T/C	*ARMS2-HTRA1*	2.81	6.5×10^{-735}	2.04	5.3×10^{-42}
rs9564692	13	31,821,240	C/T	*B3GALTL*	0.89	3.3×10^{-10}		
rs61985136	14	68,769,199	T/C	*RAD51B*	0.90	1.6×10^{-10}		
rs2043085	15	58,680,954	T/C	*LIPC*	0.87	4.3×10^{-15}		
rs5817082	16	56,997,349	C/CA	*CETP*	0.84	3.6×10^{-19}		
rs2230199	19	6,718,387	C/G	*C3*	1.43	3.8×10^{-69}	1.45	1.2×10^{-9}
rs429358	19	45,411,941	T/C	*APOE*	0.70	2.4×10^{-42}		
rs5754227	22	33,105,817	T/C	*SYN3-TIMP3*	0.77	1.1×10^{-24}		
rs8135665	22	38,476,276	C/T	*SLC16A8*	1.14	5.5×10^{-11}		
rs11884770	2	228,086,920	C/T	*COL4A3*	0.90	2.9×10^{-8}		
rs114092250	5	35,494,448	G/A	*PRLR-SPEF2*	0.70	2.1×10^{-8}		
rs7803454	7	99,991,548	C/T	*PILRB-PILRA*	1.13	4.8×10^{-9}		
rs1142	7	104,756,326	C/T	*KMT2E-SRPK2*	1.11	1.4×10^{-9}		
rs71507014	9	73,438,605	GC/G	*TRPM3*	1.10	3.0×10^{-8}		
rs10781182	9	76,617,720	G/T	*MIR6130-RORB*	1.11	2.6×10^{-9}		
rs2740488	9	107,661,742	A/C	*ABCA1*	0.90	1.2×10^{-8}		
rs12357257	10	24,999,593	G/A	*ARHGAP21*	1.11	4.4×10^{-8}		
rs3138141	12	56,115,778	C/A	*RDH5-CD63*	1.16	4.3×10^{-9}		
rs61941274	12	112,132,610	G/A	*ACAD10*	1.51	1.1×10^{-9}		
rs72802342	16	75,234,872	C/A	*CTRB2-CTRB1*	0.79	5.0×10^{-12}		
rs11080055	17	26,649,724	C/A	*TMEM97-VTN*	0.91	1.0×10^{-8}		
rs6565597	17	79,526,821	C/T	*NPLOC4-TSPAN10*	1.13	1.5×10^{-11}		
rs67538026	19	1,031,438	C/T	*CNN2*	0.90	2.6×10^{-8}		
rs142450006	20	44,614,991	TTTTC/T	*MMP9*	0.85	2.4×10^{-10}		
rs201459901	20	56,653,724	T/TA	*C20orf85*	0.76	3.1×10^{-16}		

HR, hazard ratio relative to the minor allele (minor allele/major allele); *OR*, odds ratio

while these 19 loci accounted for 15–65% of the total genetic contribution to AMD (corresponding to 7–46% of the total variability in the risk of AMD). To follow up the candidate AMD genes, Zhan et al. performed a sequencing study in 2335 cases and 789 controls in 10 regions including 57 gene [16]. They identified two rare variants p. Arg1210Cys in *CFH* gene and p.Lys155Gln in *C3* gene. In 2016 [15], the International AMD Genomics Consortium (IAMDGC) systematically examined both common and rare variants of AMD association in >12 million SNPs including 163,714 directly genotyped, mostly rare, protein-altering variants in 16,144 cases and

17,832 controls. This study identified 52 independent AMD-associated SNPs ($P < 5 \times 10^{-8}$) including both common and rare variants across 34 loci (Table 7.1). Rare variants were identified in the complement pathway genes, *CFH* and *CFI*, and noncomplement pathway genes, *TIMP3* and *SLC16A8*. In addition, this study was the first study that examined the genetics of advanced AMD subtypes (wet and dry). It reported that *MMP9* was specific to the risk of wet AMD, but not dry AMD (Table 7.2).

A number of studies implied that the same AMD susceptibility loci have different effects in different ethnic groups. A study showed that the frequency of C allele at *CFH* Y402H variant is ~30% in a group of residents of Northern and Western European ancestry from Utah, but only ~5% in Japanese and Chinese individuals [17]. A study in 2014 examined AMD risk across diverse populations and showed both *rs*1061170 (*CFH* Y402H) and *rs*10490924 (*ARMS2* A69S) were associated with AMD in European Americans but not in other populations, including Mexican Americans, African Americans, or Singaporeans [18]. In addition, another study showed that the common *ARMS2* A69S variant was associated with increased risk of AMD in non-Hispanic whites (OR = 2.1) and Mexican Americans (OR = 2.45), but the direction of the effect was surprisingly reversed in non-Hispanic black individuals (OR = 0.43) [19]. The *T* allele of the *ARMS2* variant was the test allele and its frequency was approximately 13% lower in non-Hispanic black patients compared with non-Hispanic black controls. On the contrary, non-Hispanic white and Mexican American patients have a *T* allele frequency 10% higher than their controls. A recent paper emphasized the importance of protective alleles and their roles in AMD, particularly in the population with low prevalence of AMD (e.g., Timor-Leste) [20].

7.3 Genetic Studies on AMD Progression

To date, most AMD genetic studies focused on cross-sectional studies of advanced AMD (wet or dry). AMD is known to be a progressive disease, particularly in elderly population. It starts with a mild AMD condition with small drusen and no vision loss. It then progresses to intermediate AMD with medium sized drusen and minimal vision loss. Then, the disease progresses to the large drusen stage with pigment changes in the retina and some vision loss. Finally, the condition progresses to the advanced AMD stage with significant vision loss. Some AMD patients maintain a good vision for a long time with little disease progression, while others quickly progress to advanced AMD with significant vision loss. Patients can progress to one or both forms of advanced AMD. The genetic effects of disease progression were largely unexplored until recent years. The NEI-sponsored Age-Related Eye Disease Study (AREDS) was designed to assess risk factors for the development and progression of AMD and to evaluate the effects of different oral supplements of minerals and antioxidants in delaying the AMD progression [1]. Then, a subsequent clinical trial, AREDS2, evaluated some modified formulations of oral supplements on AMD progression on a cohort of population with more severe AMD [21, 22]. Both studies collected DNA samples of consented patients and performed genome-wide genotyping.

Recently, multiple research groups studied the AMD progression using the AREDS and/or AREDS2 data. For example, Seddon et al. [23, 24] and Perlee et al. [25] studied the effects of some known AMD risk variants on progression to advanced AMD using one eye per subject, i.e., the faster-progressed eye. Some other studies analyzed the genetic effects on progression status (e.g., no progression, early progression, or late progression) instead of progression time [26]. Furthermore, some studies analyzed the genetics effects on AMD progression to different stages of the disease. For example, Yu et al. [27] used multistate Markov models to assess the effects of 12 AMD risk loci on the AMD multistate progression from normal to intermediate drusen, then to largen drusen, and eventually to wet AMD or dry AMD. They found those known AMD risk genes were associated with progression within certain but not all stages. For example, genes

Table 7.2 Results for risk loci specific to wet AMD but not dry AMD reported in the consortium case–control study and the progression study

Genes	Case–control, 2013	Case–control, 2016	Progression, 2018
MMP9	Not reported	Reported	Reported
TNR	Not reported	Not reported	Reported
ATF7IP2	Not reported	Not reported	Reported

CFH, C3, CFB, and *ARMS2/HTRA1* were found to be associated with progression from intermediate to large drusen and from large drusen to advanced AMD, but not from normal to intermediate drusen. It is well known that the presence and progression of AMD in one eye is strongly correlated with the disease in its fellow eye. For example, Gangnon et al. [28] used the Beaver Dam Eye study to investigate the effects of the AMD severity in one eye on the incidence and progression of AMD in the fellow eye. They found that more severe AMD in one eye was associated with increased incidence of AMD and accelerated progression in its fellow eye. Therefore, to better analyze the AMD progression, more recently, researchers included the progression times of both eyes with appropriate models to account for the between-eye correlation when analyzing the genetic effects on AMD progression. For example, Sardell et al. [29] analyzed the effects of seven SNPs from four known AMD risk regions on AMD progression. Ding et al. [30] evaluated the effects of the top SNPs from the 34 known AMD risk loci on disease progression. In both papers, the progression time was modeled at eye level and the between-eye correlation was incorporated through a Cox proportional hazards (PH) model with the robust variance covariance.

From all the aforementioned studies that investigate a small set of variants on AMD progression, they found that some, but not all of those AMD risk variants are associated with progression. Most reported risk variants associated AMD progression are in the *CFH* and *ARMS* regions [23, 24, 26, 30, 31]. Additional loci such as *C3, COL8A1, CFB,* and *RAD51B* have also been reported to be associated with AMD progression [24, 30].

In 2018, a first GWAS analysis was conducted using the similar robust Cox PH model to test for association of progression to advanced AMD with ~nine million variants on 2721 Caucasians from the AREDS [32]. Four susceptibility loci showed genome-wide significant association ($P < 5 \times 10^{-8}$) with AMD progression, including *ARMS2-HTRA1*, *CFH*, *C2-CFB-SKIV2L*, and *C3* (Table 7.1 and Fig. 7.1). All four loci were also previously reported in AMD case–control studies. Furthermore, variants near *TNR* and *ATF7IP2* were detected to be associated with progression to wet AMD but not dry AMD (Table 7.2). The variants in these two loci are common variants and these two loci were not reported in any AMD case–control genetics study. Moreover, variants in *MMP9* were associated with progression of wet AMD but not dry AMD (Table 7.2). The same locus was reported to be specific to the risk of wet AMD but not dry AMD in a case–control study as well. In the secondary analysis focusing only on the 34 known AMD risk variants, the previously reported *LIPC* and *CTRB2–CTRB1* were also associated with AMD progression under a less stringent *P* cutoff than the GWAS *P* value cutoff (Table 7.1).

Very recently, Sun et al. [33] proposed a novel copula-based bivariate statistical analysis approach to analyze genetic effects on AMD progression using data from both eyes. They specifically analyzed chromosome 10 using AREDS participants with at least one eye at moderate AMD since study enrollment. Besides the *ARMS2-HTRA1* region, they reported a few other regions on chromosome 10 such as *LOC101928913* and *C10orf11* exhibiting potential association with AMD progression. Those regions have not been reported before in previous case–control or progression studies of AMD. Then, Sun and Ding [34] proposed a more flexible copula approach to account for the interval-censoring and performed a GWAS on analyzing

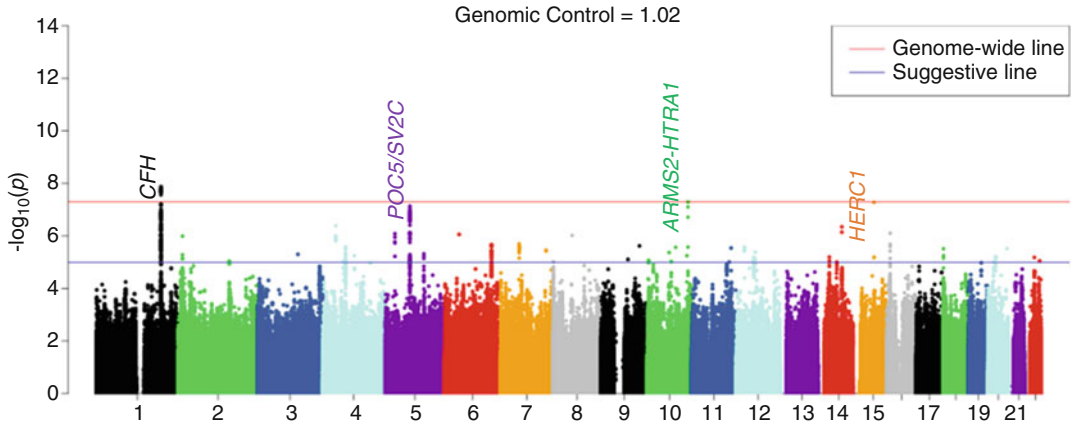

Fig. 7.1 Manhattan plots of GWAS results of AMD progression from Yan et al. [32]. The robust Cox PH model adjusted for baseline AMD severity score (continuous variable), age, smoking status (never, former, and current), and education level (≤high school and >high school). The first two principal components were included to account for population stratification

time-to-late-AMD using AREDS data. Besides confirming the *CFH* and *ARMS2-HTRA1* regions, they also identified the *ATF7IP2* region on chromosome 16 to be associated with AMD progression.

7.4 Prediction Models for AMD Development and Progression

It is known that there are both strong genetic components and important environmental influences on the development and progression of the AMD. Prediction models using demographic, environmental, and genetic factors have been established for AMD prevalence and incidence [35]. Recently, multiple research groups established different prediction models for AMD progression using combination of demographic, environmental, and genetic variables. For example, Seddon et al. [36, 37] established and validated a multivariable prediction model with six variants (in five genes) and other baseline nongenetic variables to predict the progression risk to advanced AMD. Later, the same group expanded their prediction model by adding three new genetic loci and evaluated the effects of those new variants on progression [24]. All these studies used one progression time per subject when developing their prediction models.

Recently, Ding et al. [30] established prediction models with different combinations of nongenetic and genetic factors based on AREDS data and evaluated the model performance using the independent AREDS2 data. Different from the previous approaches, their approach took advantage of all available data by using the progression times from both eyes. They also derived a genetic risk score (GRS) for AMD progression, based on the effects of 34 known AMD risk variants reported from Fritsche et al. [15], and instead of using a set of individual AMD risk variants, they used this composite GRS as a single predictor in the prediction models. They thoroughly evaluated the performance of their prediction models within the AREDS data (using cross-validations) and in an independent cohort from AREDS2 using appropriate measures such as the c-index and Brier score. They found that the prediction model with baseline AMD severity score, age, education level (<= high school or > high school), smoking status (never, former, or current), and the GRS produced satisfactory prediction performance (c-index = 0.89 in AREDS, and = 0.73 in AREDS2). Moreover, adding this GRS to the demographic information alone showed significant improvement in the prediction

performance (c-index increased from 0.62 to 0.75 in AREDS). This work demonstrates the utility and validity of the GRS for AMD prediction.

Fritsche et al. [15] had uploaded ~12 million genetic variants and 35,358 subjects to dbGaP (phs001039.v1.p1) and most of them are Caucasians (32,637). This is by far the largest publicly available AMD genotype dataset, which could be used for predicting AMD risk. Given the large number of sample size and genetic variants, appropriate prediction tools need to be selected. The artificial neural network (NN) method could be a good candidate, since it can learn complex relationship between large number of predictors and outcomes. Several recent developments using NN methods for predicting AMD risks or its progression profiles with large-scale genetics data have seen found in the literature. Furthermore, AMD severity is mainly diagnosed by color fundus images and recent studies have shown the success of machine learning methods in predicting AMD progression using image data [38–45]. Very recently, Yan et al. [46] jointly used large-scale genotypes and fundus images to dynamically predict AMD progression risks with a novel two-stage deep neural network (Fig. 7.2). The results showed that the color fundus photos coupled with genotypes could predict late AMD progression with an averaged area under the curve (AUC) value of 0.85 (95%CI: 0.83–0.86).

7.5 Beyond GWAS

Despite the success of GWAS of AMD, the analysis of other types of omics data beyond DNA has been limited possibly due to the lack of tissue accessibility. Several studies have shown that mitochondrial genetics [47–49], microRNAs [50, 51], and epigenetics [52–54] play roles in AMD pathobiology but they all have small sample size and findings require further investigation. A recent report [55] generated transcriptional profiles of postmortem retinas from 453 controls and AMD cases. The locally expression quantitative trait loci (*cis*-eQTL) analysis revealed 10,474 genetic regulated genes, which include 4541 retina specific eQTLs. They further conducted a transcriptome-wide association study (TWAS) and found three additional AMD-related genes, *RLBP1*, *HIC1,* and *PARP12*. This study indicates that the retina-specific gene expressions could help us understand the genes involved in AMD pathobiology.

7.6 New Statistical Methods Motivated by AMD Data and Research

The wealthy genotype data generated from AMD research, as well as the bilateral nature of the phenotype have motivated comprehensive statistical methodology development in the past few years, which has successfully produced or is producing novel and rigorous statistical methods and software packages for addressing different research objectives.

The newly developed and emerging methods include: (1) Novel copula-based methods and R package ("CopulaCenR") for modeling and testing the bivariate/multivariate data that are subject to right or interval censoring. This is motivated by studying the genetic effects on AMD progression where the outcome data are bivariate time-to-advanced-AMD [33]; (2) Gene-based association tests through functional linear model on (bivariate) time-to-event outcomes [56]; (3) New and robust predictive models for predicting AMD development or progression. In addition to prediction models using genetic risk scores (based on a small group of variants) with traditional logistic model or (robust) Cox PH model [30], new machine-learning-based approaches, such as the random (survival) forest, penalized Lasso regression, and deep neural network using GWAS data are being investigated [46, 57]; (4) Subgroup identification and inference methods for treatment efficacy with time-to-event outcomes. This is highly motivated by the AREDS and AREDS2 studies where the treatment (antioxidant and mineral supplement) showed positive trend in slowing down the AMD progression but did not reach statistical significance level in the entire population. Using various tree-based approaches

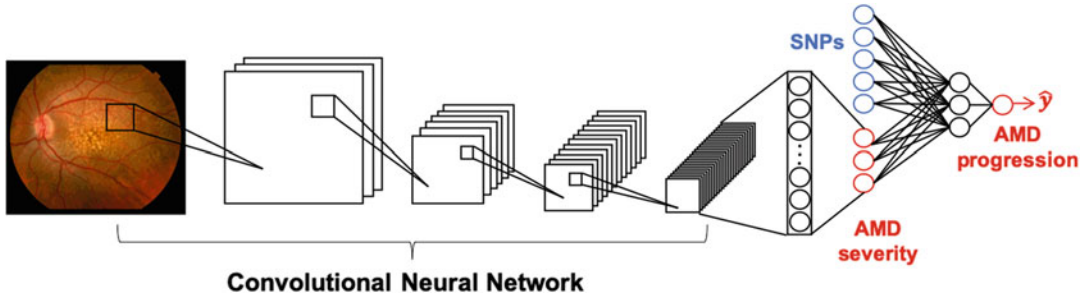

Fig. 7.2 The architecture of the two-stage deep neural network using both fundus image and genetic data for predicting AMD progression risk

and a novel simultaneous inference approach, subgroups (defined by SNPs) with enhanced treatment efficacy have been identified [58]; (5) Other new statistical methods focusing on estimating the association or dependence between two censored variables have been also proposed with motivation from and application on the AMD study [59]. The massive amount and unique features of AMD data become such important assets to statisticians for motivating and applying their novel analytical methods.

7.7 Discussion and Future Direction

Genetic studies of AMD have gained a huge success in the past two decades. Several dozens of AMD-susceptible loci and several pathways have been discovered through GWAS and sequencing studies with international efforts from many countries. However, because classic animal models are not available for AMD and retina tissues are not widely available, the functional roles of discovered loci in AMD biology are still largely unknown. Further collaborations among AMD researches are needed to characterize known AMD variants and to understand the underlying mechanism at transcriptomic or proteomic level. Handa et al. presented a nice perspective to use a system biology approach toward understanding AMD [60]. In addition to the biology research, GWAS of AMD has provided risk factors for disease prediction, which has been shown very accurate in above described studies. To achieve the ultimate goal for personalized medicine, integrative analysis of multilevel data including various omics, environmental, and clinical data with advanced statistical methods is likely to be performed down the road. For example, in the recent two years, several studies have used the AREDS fundus images to perform automated AMD grading by applying convolutional deep learning methods [42, 43, 61]. However, it is more crucial to predict AMD progression profiles over time. In addition to the available genotype data, the AREDS project also includes longitudinal fundus images over 12 years, which allow researchers to collectively use genotypes and fundus images to predict dynamic AMD progression profiles. Besides fundus images, it would be also desirable to have a coherent prediction using multiple types of images (e.g., optical coherence tomography and fundus autofluorescence images). Since late AMD is irreversible, a model that can accurately predict progression profiles over time could urge potential patients to start preventative care early and slow down the disease progression. In the next decade, the genetic studies of AMD will continue growing, likely integrated with many other types of data. With the advance of biological and analytic technology, we anticipate that more genetic variants will be discovered and the functional roles of known loci will be better

understood, leading new therapeutic targets and better diagnosis tools for AMD.

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