Clinical Applications of Age-Related Macular Degeneration Genetics

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Understanding genetic causes of age-related macular degeneration (AMD) will eventually yield effective discoveries and improvements in predictive/prognostic methods. These include, but are not limited to, reliable disease prediction (screening for increased discrimination of clinical risk), differential classification of AMD subtypes with biomarkers (development of risk-linked molecular taxonomies), selection of optimal preventive and therapeutic interventions (guided by a biologically meaningful understanding of treatment response), and drug dosing. In this review, we discuss clinical applications informed by key findings in AMD genetics, and provide commentary on leveraging extant and forthcoming evidence to improve AMD risk prediction, AMD classification, and knowledge on the genetic basis of drug activity and toxicity. Advances in translating AMD genetics findings for AMD risk prediction require development of a genetics-based causality for AMD incidence and progression. Molecular subtyping of AMD phenotypes requires a set of dynamic biomarkers presenting prognostic value; although these have yet to be identified, the formation of multidisciplinary teams and their participation in large-scale consortia may yield promising results. Drugs targeting complement and vascular endothelial growth factor (VEGF) systems are under evaluation, and forthcoming work on rare variants and noncoding DNA in AMD pathogenesis will likely reveal biochemical pathways enriched with AMD-associated genetic variants. Pharmacologic targets in these pathways may inform a rational and effective therapeutic approach to preventing and treating this sight-threatening disease.

Age-related macular degeneration (AMD) is a complex sight-threatening disease of public health significance (Miller 2013). Knowledge on the nature of AMD phenotypes and related pathogenic processes (as well as on constraints in approaches to investigation) has influenced our ability to make inferences on a genetics-based causality of this disease. Such inferences are necessary in the development of feasible clinic-based approaches for effective AMD preven-

tion, prognosis, and treatment (Gorin 2012). In this review we discuss clinical applications informed by key findings in AMD genetics, and provide commentary on leveraging extant and forthcoming evidence to improve AMD risk prediction, classification, and knowledge on the genetic basis of drug activity and toxicity. We start with a definition of AMD phenotypes and follow with an overview of what research in AMD genetics has told us about the nature and

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pathogenesis of the disease. These sections are followed by examples of clinical applications in AMD, informed by the aggregate of genetic findings from allied fields of molecular biology, biochemistry, biophysics, cell biology, and bioinformatics. We conclude with commentary on the opportunity for translating existing and emerging results for the purpose of improving clinical care.

AMD PHENOTYPES

Features of advanced, late stages of sight-threatening AMD include pathologic neurodegenerative and/or vasoproliferative changes to the interfaces between the photoreceptors, retinal pigment epithelium (RPE), and choroid vascular network. Neurodegenerative AMD (geographic atrophy) is characterized by one or more notable regions ($\geq 175 \mu\text{m}$) of RPE depigmentation or loss, with concomitant degeneration in the choriocapillaris. Atrophic AMD subtypes are represented by abnormal focal, banded, patchy, or diffuse patterns on fundus autofluorescence measurements (Bindewald et al. 2005). Neovascular AMD involves abnormal development of nascent vessels projecting from the choriocapillaris to the subretinal (Type 1) and/or sub-RPE space (Type 2). Polypoidal choroidal vasculopathy is a subtype of neovascular AMD with clusters of spheroid, choroid-derived vessels typically settling in the sub-RPE space. Retinal angiomatous proliferation is also a discrete neovascular AMD subtype; in this condition, intraretinal neovascular lesions connect with vessels from the choroidal circulations. The Beckman Initiative for Macular Research has published a phenotypic classification of AMD based on consensus of 30 opinion leaders in the field (Ferris et al. 2013). A current goal of AMD genetics is to identify biomarkers that can be used to distinguish these heterogeneous clinical subtypes (Gorin 2012).

STATE OF SCIENCE IN AMD GENETICS

Observations on familial associations in AMD were published by Gass nearly four decades ago (reviewed in Miller 2013), and broadly project-

ed the concept of a hereditary component to the disease. Relative risk of developing AMD among first-degree relatives is 6–12 times higher than in the general population (Klaver et al. 1998), and findings from family-based studies on sibling recurrence risk and disease coincidence in twins suggest that the proportion of variability in AMD risk attributed to heritability ranges from 45% to 70% (Seddon et al. 2005). Details on the large body of results from familial aggregation, segregation, linkage, and twin study approaches are presented by Haddad et al. (2006) and Lim et al. (2012). The key message is that hereditary forms of AMD have shown linkage peaks on at least 17 chromosomes (Gorin 2012); in at least 15 instances, these loci contain common AMD-associated DNA sequence variants present in sporadic (nonfamilial) cases of the disease (Gorin 2012; Fritsche et al. 2013).

Disease–gene relationships in sporadic cases of AMD have been investigated most commonly using the genome-wide association (GWA) study approach paired with linkage disequilibrium mapping. This approach involves broad DNA scans on hundreds of thousands of common sequence variants in thousands of people for the purpose of mapping disease-related loci, and is predicated on the idea that differences between healthy and complex disease states may be partially manifested by multiple common DNA sequence variants—a concept known as the “common disease-common variants hypothesis” (Lander 1996; Manolio et al. 2009). In 2005, the value of the GWA design for efficiently and reliably identifying disease-associated loci (from common sequence variants) was shown in the first set of reports implicating the complement factor H (*CFH*) Y402H variant (chromosome 1q31 locus) in advanced AMD (Klein et al. 2005). These findings, and those describing common variants within another prominent AMD-associated linkage peak on chromosome 10q26, have been replicated in numerous cohorts of subjects with American, Asian, or European ancestry (Haddad et al. 2006; Gorin 2012; Fritsche et al. 2013). In 2013, researchers from a multinational consortium reported results on 19 common susceptibility

loci for AMD from analyses on nearly 80,000 people; in aggregate, these loci explain 10%–30% of phenotypic variation in the disease (Fritsche et al. 2013).

The 19 AMD susceptibility loci were identified with the GWA study approach and have shown characteristics (presented below) of other large-scale efforts noted by Manolio et al. (2009) four years following publication of the initial AMD-Y402H findings. From this study and follow-up commentaries on the topic (Manolio and Green 2011; Manolio 2013), a key message emerges: The many robust relationships elucidated by the GWA approach have offered meaningful guidance on the underlying biology of complex diseases. Furthermore, by amplifying GWA-derived signals with a careful curation process (leading to a more complete annotation of noncoding DNA overlapping regulatory elements, rare/low frequency variants, and structural variants), one may develop meaningful clinical applications. To adequately inform a translation to the clinic, these efforts require extended work (beyond annotation) aimed to identify disease-associated rare, structural, and regulatory variants. Strengths and limitations to inference based on the method are (1) the GWA approach has been successful in identifying novel susceptibility loci for guiding efficient searches on plausible etiologic processes and strengthening insights on phenotypes (Cichon et al. 2009); (2) the magnitude of effects in GWA-based disease-gene associations have been modest (in the range of a 10%–50% change in disease likelihood for the presence of each risk allele) due to aspects of disease biology and chip design constraints—chips carry probes mainly for common single-nucleotide polymorphisms (SNPs), rather than rare SNPs or structural variants, which include copy number variants, inversions, deletions and insertions; (3) individual GWA studies are generally underpowered to detect modest effect sizes typically observed for common variants, which may lead to underestimates of the number of disease–gene relationships, whereas combining data from multiple studies has produced informative and independently replicated findings (Fritsche et al. 2013); (4) positional information

yielded by GWA studies has almost never directly identified a causal variant (Gorin 2012); (5) the range of associated “functional” SNPs (those that lead to changes in processing or expression of the gene transcript or structural and subsequent functional integrity of the protein) coinherited with an AMD-associated SNP may extend 100 kb, and these are candidate regions for fine mapping or resequencing, copy number variants, and promoter regions; and (6) a region may house multiple independent risk variants.

Disease-associated rare variants typically show larger effect sizes and higher predictive value than those of common variants; accordingly, a number of well-funded groups are now directing their efforts to searching for rare variants (McCarthy et al. 2008; Gorin 2012; Manolio et al. 2013). The Seddon group presented the first major finding on a rare and highly penetrant AMD-associated variant in the *CFH* locus (Raychaudhuri et al. 2011). The complement component 3 (*C3*) gene was recently shown to contain a rare AMD-associated variant yielding a greater effect size than those attributed to common AMD-associated variants in the gene; these discoveries were made efficiently after results from GWA studies identified regions for deep sequencing to be used in a cohort large enough to attain stable estimates of effect (Seddon et al. 2013). Gorin offers detailed commentary on the importance of investigating rare variants in complex disease, acknowledging the possibility that genes encoding key etiologic factors may not carry common sequence variants (Gorin 2012).

The central message of this section is that we have been somewhat limited in moving AMD genetics to clinical applications by our dependence on findings from studies designed to interrogate common sequence variants, characterized mainly as SNPs. Imputation and analyses conducted to place these common SNPs into plausible biologic pathways implicated in AMD-related pathology may better guide us toward finding functional DNA sequence variants (that have posttranscriptional and posttranslational effects) in coding or noncoding genomic regions. There is greater appreciation for

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examining the role of rare SNPs, variation in noncoding DNA linked to regulatory elements (microRNA, histone accessibility marks, DNase hypersensitivity clusters, and transcription factor binding sites), and structural variants (copy number variants, inversions, deletions, and insertions) in AMD. Clearly, in developing effective clinical applications of AMD genetics, we must turn to allied fields of biochemistry, biophysics, and cell biology to integrate evidence on AMD-associated exposures, pathogenesis, and pathophysiology in human cohorts and model systems.

KEY DISCOVERIES IN AMD GENETICS: PATHOGENESIS AND PATHOPHYSIOLOGY IN CONTEXT

Recently published works on the state of genomic science in AMD research (Miller 2013) and use of genetics-based findings for inference on AMD causality, risk, and therapeutics (Gorin 2012) provide valuable overviews on systems of genes that encode proteins implicated in AMD pathogenesis and pathophysiology. These systems include the alternative complement pathway, the innate immune response pathway, the chromosome 10q26 locus, extracellular matrix/cell adhesion complex genes, lipid metabolism/transport/signaling-related genes, the mitochondrial genome, vitamin D pathway genes, angiogenesis-related genes, iron metabolism genes, and cellular stress and toxicity genes. Reviews over the past decade have also addressed concepts of pathogenic mechanisms in the context of the human genome (Ambati et al. 2003; Haddad et al. 2006; Hageman et al. 2008; Bird 2010). Initially, family-based and GWA studies applied an empirical (data-driven) approach to identify and characterize mechanisms involved in AMD pathogenesis; hypothesis-driven research is now the mainstay, guided by or supported with evidence from model systems, epidemiologic studies, and clinical observations. There is general consensus that key mechanisms in AMD pathogenesis involve dysregulation of processes leading to (1) abnormal angiogenesis; (2) age-related deposition of amyloid, lipids, or lipofuscin; (3) apoptosis; and

(4) activation or modulation of (a) cellular stress pathway constituents, (b) inflammatory-immune response, or (c) vascular resistance. Lists of AMD-associated genes that drive these processes are provided in recent reviews (Haddad et al. 2006; Gorin 2012; Miller 2013). Pathway and network enrichment analyses are now entering the evidence base (SanGiovanni and Mehta 2009; Silveira et al. 2010; Newman et al. 2012; Fritsche et al. 2013; SanGiovanni and Lee 2013) and may offer meaningful guidance on novel therapies. The majority of targeted therapies for AMD have been directed at inhibiting pathologic angiogenesis through perturbation of VEGF signaling or to alter activity of complement-based systems.

INTERPRETATION AND APPLICATION OF FINDINGS ON GENETICS-BASED CAUSALITY OF AMD

Successful efforts to develop effective clinic-based preventive, prognostic, and therapeutic applications for AMD will require integration of knowledge on AMD-associated genes and their encoded proteins with evidence from genetically modified model systems and epidemiologic, clinical, biochemical studies (Gorin 2012). In this section we discuss aspects of genetic findings essential for designing effective clinical applications (Manolio 2013), while providing commentary on these matters for applied research on interventions for AMD. Key factors influencing the interpretation and application of genetic findings for clinical use include: (1) variant frequency and effect magnitude (based partially on genotyping feature probe sets); (2) the nature of variation (based on genotyping feature probe sets); and (3) alternative explanations for findings (based on coinherited variants with capacity to alter gene activity or protein structure).

Variant Frequency and Effect Magnitude

There is an unmet need to assess the magnitude of disease-gene associations from variants with minor allele frequencies <5%. Both common

and rare variants have yielded useful information with the capacity for improving clinical care in AMD. It is likely that sets of common variants may act in aggregate to produce small but meaningful functional alterations in some people with AMD. The basis for this idea in complex disease etiology has been discussed in detail since the mid-1990s (Lander 1996; Manolio et al. 2009). Ward and Kellis (2012) have commented on works demonstrating the influence of common alleles contributing small but meaningful effects in traits or disease risk (Purcell et al. 2009); these loci, associated with complex traits at *P*-values far below those considered significant on a genome-wide level, have clustered across the genome within DNA sequence encoding constituents of biological pathways implicated in disease pathogenesis (Yang et al. 2010). A central premise is that inference based on a single locus may not elucidate important contributions of genetic variants both manifesting weak associations and the capacity to act together in alteration of disease risk (Lee et al. 2012; SanGiovanni and Lee 2013; Smoller et al. 2013). Robust findings have consistently emerged from the common variant approach to investigation, and such results have been successfully applied to identify systems acting in disease pathogenesis or pathophysiology (Manolio et al. 2009). As mentioned previously, the small proportion of trait heritability contributed by these common variants make them less than optimal for AMD risk prediction or classification (Jakobsdottir et al. 2009).

Disease-associated rare-frequency (minor allele frequency <0.5%) and low-frequency variants (minor allele frequency 0.5%–5.0%) tend to have higher predictive value, and yield point estimates of higher magnitude than the common SNPs contained in most GWA gene chip probe feature sets. Stable estimates of effect (associations) for rare- and low-frequency variants require larger cohorts than those necessary for testing common variants. Efforts to identify rare variants have yielded promising results in AMD genetics (Raychaudhuri et al. 2011; Helgason et al. 2013; Seddon et al. 2013; Zhan et al. 2013). In some instances, high-impact rare causative variants may be resident in genes in

which no common variants exist. If genes harboring common loci (likely detected with the GWA approach) are not proximal to those carrying rare variants, the process of detection is unlikely to be efficient. In this case, a pathway analysis may be useful to identify biologically plausible constituents for follow-up. Regions proximal to and within the 19 susceptibility loci reported by the AMD Genetics Consortium (Fritsche et al. 2013) are being evaluated with fine mapping and exome sequencing methods to expand knowledge on rare- and low-frequency variants associated with a doubling or more of AMD risk. Use of such variants in prediction models is expected to improve accuracy beyond levels explained by clinical, demographic, and lifestyle characteristics.

The Nature of Variation

A more sophisticated understanding of the structural nature of variation and nontranscribed DNA is a necessary condition for efficient translation of meaningful disease-variant findings that may not otherwise indicate obvious functional consequences. This process involves assessing the influence of genomic rearrangements and noncoding SNPs for their capacity to disrupt nontranscribed DNA involved in regulation of transcription. Structural variants and sites overlapping regulatory elements (transcription factor binding sites, DNase hypersensitivity clusters, microRNA-binding domains, and histone promoter or enhancer regions) are potentially important genomic elements in AMD susceptibility for which there is a lack of information. Many (>80%) GWA-defined risk loci fall within noncoding regions of the genome—as these regions are enriched with transcription enhancer elements, it is important to conduct large-scale projects to determine capacity of variation in noncoding and intergenic sequence to induce functional change (e.g., nucleotide changes that alter processing or expression of the gene transcript or structural and functional alterations in integrity of the protein). The ENCODE Project is now archiving such annotations (see <https://www.genome.gov/encode/>) in a public access database.

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Linkage Structure and Coinherited Variants of Functional Significance

We must thoroughly assess disease–SNP relationships for alternative explanations based on coinherited DNA variants—especially those with the capacity to influence gene transcription and protein structure. Disease–SNP relationships often are strongest for variants that have no apparent functional link to the encoded protein. Nonrandom cosegregation (coinheritance of DNA tracts in the genome) is one explanation for such observations—suggesting that the strongly associated SNP marks a susceptibility locus for a causative variant. Gains in accuracy of imputation (supported by the 1000 Genomes Project) and enhancements of annotation databases (supported by the ENCODE Project) have permitted an amplification of GWA study-derived signals with which to identify biologically meaningful findings. The application of whole-exome sequencing within loci identified through projects such as the AMD Gene Consortium (Fritsche et al. 2013) will target candidate functional variants.

The three factors discussed above are inextricably linked, and under certain circumstances may be used to: (1) increase discriminatory power for clinical risk assessment (through the application of predictive models); (2) distinguish clinical cohorts most likely to benefit from specific clinical interventions (through the application biomarkers with clinical information); and (3) assess genetic capacity for drug action and toxicity (through the applications of treatment response studies). We present overviews on these factors below.

Risk Prediction

AMD is a disease of public health significance, and early detection in the presence of an effective preventive intervention would alleviate a great burden of suffering. Most predictive models examining genetics-based causality of AMD are derived from measures of disease status (i.e., AMD prevalence). Gorin presents an astute commentary regarding the application of AMD genetics for risk prediction (Gorin 2012),

stating that clinical applications leading to the most valuable preventive treatments should be informed by prospective studies assessing the genetic component of AMD incidence in people at moderate risk for developing advanced AMD. He notes that prevalent AMD can be predicted well in people carrying many or no susceptibility variants for the disease, but that existing models still lack sensitivity and specificity for the majority of people in the general population (most of whom carry a few risk variants). This point was initially elucidated by Jakobsdottir et al. (2009), who demonstrated that although accurate detection of 80% of AMD cases was possible with three strongly associated loci, prediction was poor for people without the disease (false-positive rates exceeded 40% at a sensitivity of 80%). The second key point is that, until an effective preventive intervention for advanced AMD is developed, risk prediction will offer only limited value in clinical care. AMD is a common disease in the elderly, and costs associated with universal screening are not likely to be supported. With the advent of effective and accessible treatments, positive predictive values may be increased through a screening process focused on people with family histories of AMD and high genetic risk prediction scores. A number of clinical characteristics and lifestyle practices have been identified with AMD risk, and these may be combined with genetic risk scores from common and rare SNPs and structural variants to more accurately predict likelihood of AMD in people who would otherwise show low risks based on demographic or behavioral factors alone.

Disease Classification and Subtyping

Outside of the AMD field, disease–gene relationships and molecular subtyping of disease phenotypes have led to enhanced discrimination of subpopulations likely to benefit from specific treatments (Manolio 2013). This molecular subtyping has elucidated biomarkers that may best be applied in conditions in which other prognostic indicators are less sensitive and more difficult or expensive to obtain. The value of biomarkers is highest for people in preclinical

disease phases and for those at moderate risk for progressing to advanced stages of complex disease (Manolio and Green 2011). AMD may manifest as a number of phenotypes (see *AMD Phenotypes* section) that may not be accurately diagnosed in a clinical examination. The major clinical subtypes of advanced AMD (geographic atrophy and neovascular AMD) carry different risk factors and respond differently to a number of exposures (e.g., smoking) and therapies.

There is currently insufficient evidence to support the idea that the existing panel of serum biomarkers for AMD (C-reactive protein, complement component factors, VEGF, apo-lipoprotein B, antiretinal antibodies, sterol ester levels, anticarboxyethylpyrrole adducts and autoantibodies, and vitamin D) contains effective predictors of AMD incidence or progression (Gorin 2012). Biomarkers have been proposed to support assessment of intervention efficacy, and there is currently an unmet need to demonstrate that long-term alteration of a biomarker by a controlled preventive or therapeutic intervention for AMD will avert subsequent development of AMD. Gorin emphasizes the importance of determining whether a biomarker is constrained to represent the current state of disease (static marker) or whether it may reflect a dynamic response of causal processes to an intervention.

Genetic Basis of Drug Activity and Toxicity

Interventions Based on AMD-Associated Pathway Constituents. Findings from the field of AMD genetics have been integrated with those from biochemical assessments of pathologic specimens in people with moderate or advanced AMD to guide research on the etiologic role of the complement system. Troutbeck et al. (2012) present a background on the complement pathways and their influence on proteolytic cascades that produce the cytolytic membrane attack complex. Complement component inhibitors, antibody-based compounds, and receptor antagonists have been examined as targets for AMD interventions (Table 1). For neovascular AMD, molecular targets within the VEGF system have been proposed and tested on the basis

of biochemical analyses and the existence of related angiogenic and neovascular lesions in numerous blinding retinal diseases. The *VEGFA* gene resides in a susceptibility locus on chromosome 6, and aggregates of genes encoding constituents of the extracellular matrix (altered in vascular remodeling) have supported the decision to target therapies at VEGF (Table 1 contains a list of drugs inhibiting the VEGF system). Details on AMD–VEGF findings from clinical trials are reviewed by Miller (2013).

Drug Development and Drug Safety. Disease–gene relationships have been aimed at identifying novel molecular targets and determining whether DNA sequence variants influence an individual's ability to (1) activate prodrugs and drug-related metabolic or catabolic enzymes, and (2) respond to therapy for the purposes adjusting dosage or switching to alternative agents of higher efficacy. Gorin (2012) has reviewed the AMD pharmacogenomic literature and concluded that there is currently little evidence to support the claim that any DNA sequence variant alters response to treatment with VEGF inhibitors or photodynamic therapy. He further remarks that relationships of susceptibility loci have been additive in nature (each contributing an exclusive aspect of risk); when identified, molecular targets are likely to be heterogeneous and best treated with combined therapies with pharmacologic and non-pharmacologic approaches. Gorin also stresses the point that accurate quantitation of AMD phenotype is paramount in classifying disease progression for drug response studies. A recently published position statement is expected to offer guidance on this matter (Ferris et al. 2013). Finally, regarding constraints to progress in AMD pharmacogenomics, there currently are no established biomarkers with which to monitor response to preventive interventions in AMD-free people at moderate risk for developing the disease. For studies on progression to neovascular AMD, in vivo imaging technologies have been used successfully to identify biomarkers effective for assessing response to anti-VEGF therapies.

The Comparison of AMD Treatments Trials research team recently reported their inves-

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Table 1. Therapeutic agents evaluated for AMD treatment

Therapeutic agent	Target	Administration/Comment
Complement System		
<i>Terminal Components</i>		
POT-4	C3	IVT/Inhibitory cyclic peptide
ARC1905	C5	IVT/Inhibitory anti-C5 aptamer
JSM-7717	C5a receptor	Antagonistic receptor peptidomimetic
JPE-1375	C5a receptor	Antagonistic receptor peptidomimetic
Eculizumab	C5	IV/MAb
CR2-fH	C3d/CFH	Recombinant CFH, animal models
<i>Activation Components</i>		
FCFD4514S	CFD	IVT/Inhibitory MAb
TA106	CFB	INH/Inhibitory MAb
VEGF System		
Pegaptanib (Macugen)	Heparin domain VEGF-A ₁₆₅	IVT/Inhibitory anti-VEGF ₁₆₅ aptamer
Ranibizumab (Lucentis)	All VEGF-A isomers	IVT/Inhibitory MAb fragment
Bevacizumab (Avastin)	All VEGF-A isomers	IVT/Inhibitory MAb
Aflibercept (VEGF Trap)	All VEGF isomers, PlGF	IVT/Fusion protein VEGFR1 + VEGFR2
Pazopanib	VEGF Receptors, PDGFR	Topical/tyrosine kinase inhibitor
AAV-sFLT1	VEGFR	Recombinant VEGFR
E10030	VEGF, PDGF	anti-PDGF aptamer, used w/Lucentis
RetinoStat	Angiostatin, Endostatin	Lentivirus vector
ISONEP	Sphingosine-1-Phosphate	MAb
Sirolimus (Rapamycin)	mTOR/Akt	IVT/Inhibitory macrolide
OT-551	NF-κB constituents	Topical
AAV-PEDF	PEDF	IVT/SR, Recombinant PEDF, models

AAV, adeno-associated virus; C3, complement component 3; C5, complement component 5; CFB, complement factor B; CFD, complement factor D; CFH, complement factor H; INH, inhaled; IVT, intravitreal injection; IV, intravenous injection; Mab, monoclonal antibody; mTOR, mammalian target of rapamycin; PDGF, platelet-derived growth factor; PDGFR, PDGF receptor; PEDF, pigment epithelium-derived growth factor; PlGF, placental growth factor; SR, subretinal; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

tigations on common AMD-associated SNPs (rs1061170 [CFH], rs10490924 [ARMS2], rs11200638 [HTRA1], and rs2230199 [C3]) and response to treatment with ranibizumab or bevacizumab for neovascular AMD (Hagstrom 2013). In no instance did the tested SNPs predict response to the study regimen of anti-VEGF therapy at one year. Endpoints included mean visual acuity (VA), mean change in VA, 15-letter or more increase in VA, retinal thickness, mean change in total foveal thickness, presence of fluid on ocular coherence tomography (OCT), presence of leakage on fluorescein angiography (FA), mean change in lesion size, and mean number of injections administered.

CONCLUDING REMARKS

We have provided an overview on the state of science regarding the potential clinical value of genetic investigations for improving AMD-related risk prediction, disease classification, and the genetic basis of drug activity and toxicity. Research teams are now expanding and improving assessment of rare, structural, and noncoding DNA variants for the purposes of identifying genetic factors that might explain substantial proportions of variation in AMD outcomes. These findings will strengthen processes of prediction and classification. In 2013, an AMD phenotyping consortium published classification schemes that may be applied to assess

changes in AMD associated with preventive and therapeutic interventions. Progress in developing effective clinical applications is dependent on successful integration of evidence from fields of molecular biology, biochemistry, biophysics, cell biology, and bioinformatics. A major constraint on risk prediction is the lack of information with which to characterize a genetics-based causality for AMD incidence and progression. Molecular subtyping of AMD phenotypes requires a set of dynamic biomarkers presenting prognostic value; although these have yet to be identified, the formation of multidisciplinary teams and their participation in large-scale consortia offers promise for a more efficient biomarker characterization. A number of drugs targeting complement and VEGF systems are under evaluation, and forthcoming work on the role of noncoding DNA in AMD pathogenesis will likely lead to the identification of biochemical pathways enriched with genes containing AMD-associated sequence variants. Pharmacologic targets in these pathways may inform a rational and effective therapeutic approach to preventing and treating this sight-threatening disease. In conclusion, while the evidence from studies of AMD genetics is now best suited for informing preclinical research, it is a useful resource that may be effectively applied to improving clinical care.

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