Omics in Ophthalmology: Advances in Genomics and Precision Medicine for Leber Congenital Amaurosis and Age-Related Macular Degeneration

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THE GENOMIC REVOLUTION

During the past 20 years, we have witnessed huge technological advancements in the genetics field. Information on genetic variation was gathered, and in 1998 DNA chips were developed that enabled the analysis of genetic variation across the genome. These single nucleotide polymorphism (SNP) microarrays have been instrumental in mapping many disease genes at a genome-wide level. Several years later, the human genome sequence was completed, which greatly facilitated disease gene identification studies. Also, next-generation sequencing techniques were developed, which are much faster and cheaper than the conventional Sanger sequencing techniques. These new technologies now allow the analysis of all coding genes, called the exome, or even the entire genome. Prices for whole genome sequencing have dropped tremendously, estimated at approximately 100 million dollars in 2001, while it now is offered for approximately 4000 dollars. This genomic revolution has had a huge impact on our understanding of the genetic defects and disease mechanisms underlying ophthalmic diseases. Two examples are discussed here. The first is Leber congenital amaurosis (LCA), a severe inherited retinal dystrophy leading to severe vision loss in children, and the second is age-related macular degeneration (AMD), the most common cause of vision loss in the elderly. Twenty years ago, the genetic causes of these diseases were unknown. Currently, more than 20 LCA genes have been identified, and genetic testing can now successfully identify the genetic defects in at least 75% of all LCA cases. Gene-specific treatments have entered the clinical trial phase for three LCA genes, and for seven LCA genes gene-specific therapies have been tested in model systems. Age-related macular degeneration is a multifactorial disease caused by a combination of genetic and environmental factors. Currently, more than 40 loci have been identified for AMD, accounting for 15%-65% of the total genetic contribution to AMD. Despite the progress that has been made so far, genetic testing is not yet recommended for AMD, but this may change if we move to clinical trials or treatments that are dependent on an individual’s genotype. The identification of serum or plasma biomarkers using other “omics” technologies may further improve predictive tests and our understanding of the disease mechanisms of AMD. Ultimately, it is anticipated that predictive tests will help to stratify patients for the most suitable therapy, which will enable the development of precision medicine, tailored to individual needs.

Keywords: age-related macular degeneration, genetic diseases, retinal dystrophy, gene therapy, retinal degeneration

THE GENETIC CAUSES OF LCA

Leber congenital amaurosis is an early-onset retinal dystrophy leading to severe vision loss in children, with an autosomal recessive inheritance pattern. During the past 20 years, various approaches have been used to identify the genetic causes of LCA. In the early years, a common approach for disease gene identification was the analysis of candidate genes. Genes that are expressed specifically in the retina were deemed promising candidate genes, which were isolated by constructing retina-specific cDNA libraries. One of the genes that was identified by this approach is the CRB1 gene, and mutations were identified in patients with LCA. Other LCA genes that were identified by the candidate gene approach include the RPE65, TULP1, CRX, MERTK, RPGRIP1, LRAT, RD3, PRPH2, and GDF6 genes.

The development of genome-wide SNP microarrays greatly facilitated the genome-wide mapping of disease genes. A powerful approach to identify autosomal recessive disease genes
Genetics is homozygosity mapping, a method that identifies regions in the genome that were inherited from a common ancestor. Genome-wide homozygosity mapping in a large French-Canadian family identified an intronic mutation (c.2991+16552→G) in the CEP290 gene, which inserts an aberrant exon into the mRNA and introduces a premature stop codon. This mutation is a common cause of LCA, accounting for 20% to 30% of LCA cases from North European populations. Other LCA genes that have been identified by homozygosity mapping include the GUCY2D, AIPL1, RDH12, LCA5, SPATA7, and IQCB1 genes (Fig. 1).

The field is now shifting to the use of exome sequencing, which allows the analysis of all coding regions of the genome. A major challenge when applying exome sequencing is to identify the causative mutation among the large number of genetic variants that are identified in an individual. The number of candidate variants can be narrowed down by filtering for variants that are absent in control population, and for variants that have functional relevance, for example variants that lead to an amino acid change, introduce a stop codon, or are predicted to affect splicing. This usually leads to a limited number of candidate variants, which can be analyzed further for their relevance to the disease. Genes for LCA that were identified recently by exome sequencing include the KCNJ13, NMNAT1, IFT140, and ALMS1 genes (Fig. 1).

During the past 20 years, more than 20 LCA genes have been identified (Fig. 1). Together, these genes are estimated to account for at least 75% of all LCA cases. Four of these genes, CEP290, GUCY2D, CRB1, and RPE65, account for approximately half of all cases, while the other genes are less frequently mutated. The LCA genes encode proteins with a wide variety of retinal functions, including photoreceptor transduction (e.g., GUCY2D), the visual cycle (e.g., RPE65, LRAT, RDH12), and ciliary transport (e.g., RPGRIP1, CEP290, LCA5, SPATA7, IQCB1, IFT140).

Genetic Testing for LCA

Since the majority of LCA cases can be accounted for by mutations in one of the known LCA genes, genetic testing can be offered effectively to patients and their families. Various approaches are used for genetic testing. One approach is a microarray-based test that can rapidly screen for known mutations in the known LCA genes. An approach that has also been used is to screen for the most frequently mutated exons of known LCA genes. These approaches were used to limit the costs of the genetic tests, but a major disadvantage is that they will miss many mutations in the known genes. With the development of next-generation sequencing, tests have now been developed that can screen the coding regions of all known LCA genes or even all retinal dystrophy genes. Some centers have now switched to offer exome sequencing as a diagnostic test. An advantage of this approach is that if the genetic cause is not identified in one of the known LCA genes, the search can be extended to identify new causative genes. However, one consideration that arises with the use of exome sequencing is the chance of incidental findings in other disease genes that are not related to the disease for which the genetic test was requested. For example, a mutation that predisposes to breast cancer or another form of cancer may surface. Patients should be aware of the risk of such incidental findings and should receive genetic counseling on these issues. The chance of incidental findings can be minimized by first performing an extensive analyses of all LCA or retinal dystrophy genes (gene-panel). Only when this first phenotype-driven gene list analysis does not yield a mutation can a full exome analyses be performed.

Genetic testing for LCA and for retinal dystrophies in general can be important for various reasons, and is recommended by the American Academy of Ophthalmology. First of all, it enables genetic counseling: patients or parents can be informed on recurrence risks, and can make informed career decisions. Furthermore, genetic testing can confirm or establish an accurate diagnosis. Particularly at a young age, certain clinical tests can be difficult to perform, and genetic testing may be a good alternative to establish a rapid diagnosis. In addition, in some rare syndromes, such as Senior-Loken syndrome, a severe retinal dystrophy may be the initial symptom. Genetic testing may identify a syndromic form of the disease, and in the case of Senior Loken syndrome, patients can be referred to a nephrologist at an early age. Currently, it is also becoming more important to establish a genetic diagnosis since gene-specific therapies are being developed, and eligible patients can be enrolled in clinical trials.
TABLE 1. Gene-Specific Therapies for LCA

<table>
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<tr>
<th>Gene</th>
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<tr>
<td>RPE65</td>
<td>Gene supplementation</td>
<td>Human phase I trials completed^49–51</td>
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<tr>
<td>RPE65</td>
<td>Oral synthetic retinoid</td>
<td>Human phase I trial completed^64</td>
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<tr>
<td>LRAT</td>
<td>Oral synthetic retinoid</td>
<td>Human phase I trial completed^64</td>
</tr>
<tr>
<td>MERTK</td>
<td>Gene supplementation</td>
<td>Human phase I trial in progress (clinicaltrials.gov)</td>
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<td>CRB1</td>
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<tr>
<td>RD3</td>
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<tr>
<td>RPGRIP1</td>
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</tr>
<tr>
<td>CEP290</td>
<td>Gene supplementation; splice correction</td>
<td>Preclinical; patient-derived cells^61–63</td>
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**Gene-Specific Therapies for LCA**

During the past years exciting progress has been made in developing gene-specific treatments for LCA (Table 1). Promising results have been obtained in phase I gene supplementation trials in LCA patients with mutations in the RPE65 gene, with significant improvements in visual function after a short period of follow-up. Recent studies on the long-term effect, however, suggested that the visual improvement achieved in the initial trials is temporary and gene supplementation failed to protect against ongoing degeneration. It was suggested that a more efficient delivery of RPE65 at an earlier point in disease progression may have a greater effect on visual function and may protect better against progressive degeneration.

A phase I clinical trial with an oral synthetic retinoid (9-cis retinyl acetate) has led to rapid restoration of visual function in patients with mutations in the RPE65 and LRAT genes, both encoding enzymes involved in the visual cycle. A phase I clinical trial for MERTK gene supplementation currently is in progress (clinicaltrials.gov), and it is expected that gene-specific treatments for several other LCA genes will enter the clinical trial phase in the near future. Preclinical gene supplementation studies have successfully been performed in mice for the AIPL1, CRB1, GUCY2D, LRAT, RD3, and RPGRIP1 genes. A beneficial effect of CEP290 gene replacement on ciliogenesis and splice-correction of the common LCA mutation c.2991+1655A>G using antisense oligonucleotide-based therapy were demonstrated in patient-derived cells.

**LCA – Past, Present, and Future**

To summarize, during the past 20 years, we have witnessed huge progress in understanding the causes of LCA. Twenty years ago, no genetic causes had yet been identified, while currently more than 20 genes are known that account for at least 75% of all LCA cases. Gene supplementation trials and a trial with an oral synthetic retinoid have been performed or are in progress for three LCA genes, and for seven LCA genes a gene-specific therapy has been tested in model systems and may go to clinical trials in the near future. However, several challenges still lie ahead of us. The remaining 25% of LCA cases still must be resolved. These may be caused by mutations in new genes that still await discovery, but it also is possible that they may be caused by variants in introns or regulatory regions in known or new LCA genes. Such variants may be identified using whole genome sequencing, potentially combined with transcriptome analysis in patient-derived cells. In addition, some LCA cases may be caused by digenic or multigenic inheritance models, which may be challenging to identify. Large patient populations would be needed, and, therefore, establishing large databases and sharing of genetic information among research groups and diagnostic labs is required to identify the remaining genetic causes. In the next years the focus should lie on developing or improving gene-specific treatments and designing clinical trials for the most commonly mutated LCA genes: CEP290, GUCY2D, CRB1, and RPE65. Due to the high genetic heterogeneity of LCA and other retinal dystrophies it may not be feasible to develop gene-specific treatments for each gene, particularly for genes that are a rare cause of the disease. Therefore, other more generic therapeutic strategies must be further developed that are independent of the specific genetic defect, such as optogenetics and stem cell therapy.

**AGE-RELATED MACULAR DEGENERATION (AMD)**

**Genetic Causes of AMD**

Age-related macular degeneration is the most common cause of vision loss in the elderly. In contrast to LCA, AMD is not a monogenic disease, but a multifactorial disease caused by a combination of genetic and environmental factors. Based on twin and family studies it has been determined that AMD has a strong genetic component. It has been estimated that up to 71% of AMD risk is attributed to genetic factors. Important nongenetic risk factors for advanced AMD are smoking and a high body mass index (BMI).

To identify the genetic causes of a multifactorial disease, genome-wide association studies (GWASs) can be performed. Genome-wide association studies usually require hundreds to thousands of patients and a similarly sized cohort of control individuals to obtain meaningful results. These individuals are genotyped for common genetic variants across the genome using SNP microarrays, and statistically significant association of all variants with the disease is assessed.

While usually large numbers of patients and controls are required to obtain significant associations with a multifactorial disease, the first GWAS for AMD conducted in 2005 included only 96 AMD patients and 50 control individuals. A genome-wide significant association was identified on chromosome 1, at the *complement factor H* (CFH) gene, encoding a main inhibitor of the alternative complement pathway. This association was successfully identified in this relatively small study, since the effect of genetic variants in the gene is relatively large. Individuals carrying the risk haplotype are 4.6 times more likely to suffer AMD than individuals who do not carry the haplotype (odds ratio [OR], 4.6; 95% confidence interval [CI], 2.0–11).

Since 2005 several other GWASs have been performed for AMD. The largest GWAS to date was performed in 2013,
which included >17,000 AMD patients and >60,000 control individuals. This GWAS identified 19 genome-wide significant loci that are associated with AMD, of which seven loci are novel. The strongest effect sizes are seen at the CFH and ARMS2/HTRA1 loci, with ORs of 2.4 and 2.7, respectively, while the novel loci have smaller effect sizes, with ORs between 1.1 and 1.2. Overall, larger GWASs have identified an increasing number of genes that are associated with AMD, but the effect sizes of variants at the new loci are modest. Most genes identified by GWAS are part of three main pathways: the complement pathway (e.g., CFH, CFI, CFB, and C3), the lipid metabolism (e.g., LIPC, CETP, and APOE), and the extracellular matrix (e.g., COL8A1, COL10A1, and COL15A1).

Because these GWASs have used SNP microarrays, they have mainly interrogated variants that are common in the population. Such common variants usually have relatively small effect sizes. It has been estimated that these common variants detected by GWAS account for approximately 15% to 65% of the total genetic contribution to AMD. Another source of genetic variation may lie in rare variants with large effect sizes. Genetic studies are currently shifting to the use of exome sequencing or whole genome sequencing, which will identify rare, unique variants that segregate within families and, thus, may have even larger effect sizes.

Figure 2. Genetic architecture of AMD. Genome-wide association studies using SNP microarrays have identified variants that are common in the population and generally have small to modest effect sizes. Sequence analysis of candidate genes and GWAS using exome chips have identified variants that occur at a low frequency in the population, but have modest to large effect sizes. Genetic studies are currently shifting to the use of exome sequencing or whole genome sequencing, which will identify rare, unique variants that segregate within families and, thus, may have even larger effect sizes.

The variant was identified in 40 of 2423 AMD patients coding variant, R1210C, that confers high risk of developing a high risk haplotype (H5) at the CFH locus identified a low-frequency variant, G119R, in 3 affected individuals. In a case-control cohort, the G119R variant was identified in 20 of 3567 AMD patients, while it was found in only 1 of 3938 control individuals. Thus, the G119R is a rare allele, but confers high risk of developing AMD (OR, 22.2; 95% CI, 3.0–164.5). Cases with AMD carrying the G119R variant had significantly lower plasma CFI concentrations compared to controls and cases who did not carry the variant, and plasma samples of patients carrying the CFI G119R variant had a significantly lower capacity to degrade C3b compared to control individuals. Sequence analysis of 681 candidate genes in 1676 AMD cases and 745 controls identified a significant burden of rare variants in the CFI gene in patients compared to controls. In addition, rare variants in the C3 (K155Q) and the C9 (P167S) genes have been associated with AMD.

Another approach that is being used to identify rare variants in AMD, is by GWAS using exome chips. An exome chip is a microarray that contains common SNPs, similar to SNP microarrays, in addition to >160,000 low-frequency protein-altering variants. A huge advantage of this approach is that exome chips are much cheaper than exome sequencing, allowing the analysis of larger numbers of samples. Exome chips allow a new wave of GWASs with rare variants. An exome chip analysis in 2119 AMD cases and 5691 controls identified a low-frequency variant in the CETP gene (D442G) and common variants in the C6orf223, SLC44A4, and FGD6 gene to be associated with AMD in East Asians. Recently, a large GWAS for rare variants has been performed by the International AMD Genomics consortium, consisting of 26 groups worldwide. DNA samples of 16,144 AMD patients and 17,852 age-matched control individuals were genotyped with exome chips. Next to the 19 known loci, 16 new loci have
been identified. Of the variants that were associated with AMD, 45 are common variants, and 7 are rare variants, with effect sizes between 1.5 and 47. Besides the four nonsynonymous variants previously found by sequence analysis of candidate genes (CFH R1210C, CFI G119R, C9 P167S, C3 K155Q), three independent noncoding low-frequency variants in CFH were identified (rs148553336, rs191281603, rs35292876). A significant burden of rare, protein-altering variants was identified in the CFH, CFI, TIMP3, and SLC16A8 genes in patients compared to controls.

To further identify rare variants that are associated with AMD, an approach involving exome sequencing or whole genome sequencing can be followed. Since exome sequencing currently is still quite expensive, approaches are being used to enrich for rare variants. One such approach is to analyze AMD families with multiple affected individuals, since such families are more likely to carry rare, highly penetrant variants. A small number of studies have used exome sequencing in AMD families, which identified novel rare variants in the CFH, CFI, HMCN1, and FBN2 genes. Although these variants segregated in most families, a combination of environmental, common, and rare variants may have a role in such families and rare variants, therefore, do not necessarily segregate with the disease. This makes the use of exome sequencing in AMD families more challenging than performing exome sequencing in monogenic diseases. Exome sequencing in an East Asian case-control cohort consisting of 216 AMD patients and 1553 controls identified a coding variant in the UBE3D gene (V379M) to be associated with AMD.

The genetic studies performed to date provide insight into the genetic architecture of AMD (Fig. 2). Genome-wide association studies identified common variants with relatively small effect sizes, with the exception of CFH and ARMS2. Sequencing of candidate genes and exome chip analysis identified several low frequency variants with relatively large effect sizes. Exome sequencing studies in AMD identified rare, unique variants that segregate within families and, thus, may have even larger effect sizes. Additional studies using exome sequencing and whole genome sequencing in large cohorts will provide further insight into the genetic architecture of AMD. Since low-frequency and rare variants may be population-specific, it is necessary to extend such studies to various populations for a comprehensive understanding of genetic variation contributing to AMD pathogenesis.

Genetic Testing for AMD

Based on the currently known environmental, lifestyle, and genetic risk factors, prediction models have been developed for AMD. The area under the curve for these models is between 0.8 and 0.9, and, thus, can distinguish fairly well between those who will and will not suffer AMD. Patients with AMD have a mean probability of >70% for AMD to develop based on the known AMD risk factors, while AMD-free control individuals have a mean probability of <40% (Fig. 3). However, AMD patients at the left end of the distribution have a low probability of developing AMD based on the known AMD risk factors. This suggests that these individuals have accumulated protective factors that may have protected them against development of AMD. Protective factors, and additional risk factors, may be identified using other ‘-omics’ approaches, which may lead to a further improvement of the current prediction models.

Quite some genetic risk factors have been identified for AMD, but are we ready yet for developing and offering predictive tests for AMD? Direct-to-consumer genetic tests have been offered on the internet, which provided consumers with a predicted probability of developing various complex diseases, including AMD. Two studies have evaluated these tests, which for AMD were based on a small number of SNPs (2-6 SNPs in 1-5 genes) and did not take environmental or lifestyle factors into account. Twenty percent of consumers received risks in opposite risk categories; one test would tell them that they had an increased risk of AMD, while another test would tell them that they had a reduced risk of AMD. Overall, direct-to-consumer tests for common diseases are not...
accurate, and have been banned by the Food and Drug Administration. Recently, 23andMe received FDA approval to provide carrier testing for several rare diseases, but approval for common diseases, such as AMD, has not yet been obtained. Genetic tests should be performed by certified labs, and preferably should be ordered by physicians rather than being directly available to consumers. Genetic tests for AMD should be based not only on common genetic factors, but also should include rare variants, for example by sequencing the CFH and CFI genes, and should also include clinical and lifestyle parameters.

What are the benefits, but also risks, of offering genetic tests for AMD? First of all, family members of patients with AMD often want to know if they themselves are at risk for AMD. If genetic tests are offered, they can be counseled on their risk of development of AMD. However, one should keep in mind that the risk prediction might not always be accurate, and some individuals may be told that they have a high risk for AMD, while AMD will not actually develop. Thus, they may be burdened unnecessarily with inaccurate information. However, a benefit of genetic testing is that individuals who have a high predicted risk for AMD will be more motivated to alter their lifestyle. For example, individuals can reduce their risk for advanced AMD by stopping smoking, increasing their physical exercise, and using antioxidant supplements. It recently has been suggested that individuals with the CFH genotype may not benefit from Age-Related Eye Disease Study (AREDS) supplementation, but this was not confirmed by an independent analysis. Currently, genetic testing is not recommended to determine whether an individual should or should not use the AREDS formulation. Therefore, individuals at risk for AMD should still be advised to use antioxidants, irrespective of their genotype. In the future, genetic tests may become important if clinical trials or new treatments are based on genotype. However, as this is not yet the case, genetic testing currently is not recommended by the American Academy of Ophthalmology.

New Treatments for AMD Targeting Molecular Disease Mechanisms

Based on the genes that have been identified to be associated with AMD, we now know that there are at least three main pathways that are involved in AMD: the complement system, lipid metabolism, and extracellular matrix. This provides new targets for treatment of AMD. Several antibodies targeting the complement pathway are currently in the clinical trial phase (Table 2). A phase II clinical trial has been performed with eculizumab, a C5 inhibitor, but has been shown not to be effective. A phase II clinical trial has been performed with lampalizumab, which showed a 20% reduction rate of the atrophic area, and an even higher reduction rate was seen in a subpopulation of patients carrying a CFI variant. Currently, lampalizumab is entering phase III, and it is anticipated that inclusion or analysis will be based on the CFI genotype. In addition, another C5 inhibitor, LFG316, is currently entering a phase II clinical trial.

### Table 2. Clinical Trials in AMD With Antibodies Targeting the Complement Pathway

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Target</th>
<th>Phase</th>
<th>Outcome</th>
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<tr>
<td>Eculizumab</td>
<td>C5</td>
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<td>Ineffective&lt;sup&gt;103&lt;/sup&gt;</td>
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<td>Lampalizumab</td>
<td>CFD</td>
<td>Phase II (MAHALO) completed</td>
<td>20% reduction rate in geographic atrophy area after 18 mos; 44% reduction rate in subpopulation carrying CFI variant&lt;sup&gt;102&lt;/sup&gt;</td>
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### Omics in AMD Research

Research on AMD has focused mainly on genomics, genome-wide approaches to study genetic variation across the genome, but application of other “omics” technologies can further deepen our understanding of AMD pathogenesis and risk factors. Proteomics studies proteins at a large scale, and has been used in AMD research to study the protein content of drusen, macular, retinal, and RPE components, plasma, and eye fluids. Epigenomics studies the methylation state of our DNA, which correlates to altered gene expression levels. These methylation patterns can be altered by our lifestyle, for example by smoking or by our diet. So far, one genome-wide methylation study has been performed in AMD using peripheral blood monocytes. It may be even more interesting to perform such genome-wide methylation studies in DNA isolated locally, in the eye. Metabolomics studies the profile of our metabolites at a large scale. Our metabolic profile is influenced by enzymatic reactions and by our lifestyle, for example our diet. One metabolomics study has been performed so far in AMD, using plasma samples. By generating large datasets using various layers of information, on the genomics levels, but also using proteomics, epigenomics, metabolomics and other “-omics” technologies, we can gain a better understanding of the causes of AMD, and can identify new biomarkers and new targets for treatment.

### AMD – Past, Present, and Future

To conclude, 20 years ago, we knew that AMD had a strong genetic predisposition, but no gene or genomic locus had yet been associated with AMD. Currently, more than 40 loci have been identified for AMD. The currently known risk factors have a moderate-to-high predictive value, with an area-under-the-curve of 0.8 to 0.9. Despite the progress that has been made so far, genetic testing is not yet recommended, but this may change if we move to clinical trials or treatments that are dependent on an individual’s genotype. Next to genetic, clinical, and lifestyle risk factors, the identification of serum or plasma biomarkers may further improve predictive tests for AMD. Several other “omics” technologies can be used to identify such biomarkers, such as epigenomics, metabolomics, and proteomics. Ultimately, it is anticipated that predictive tests will help to stratify patients for the most suitable therapy, which will enable the development of precision medicine, tailored to individual needs.

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for the past seven years. His determination and devotion to research are an inspiration. He invested heavily in establishing the EUgendA database, which is a valuable resource for our current research on AMD. Much of the work I presented here was performed by talented young researchers in our group, whom I have the honor to work with during the past years and gratefully acknowledge for their dedication and hard work. I also acknowledge my valued collaborators from all over the world. Many of them I meet every year at ARVO, and have become dear friends. I look forward to continuing our collaborations and friendships during the years to come. I thank my husband, Tim, and our children, Joost and Liza, for supporting my career, and for being there to share the big and small things in life.

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References


