An update on the genetics of age-related macular degeneration

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Age-related macular degeneration (AMD) is a genetically complex disorder of the photoreceptor-RPE-Bruch’s membrane-choriocapillaris complex. Family and twin studies have shown that the susceptibility for this disease is genetically influenced. The heritability has been estimated to be up to 71%. Linkage and association studies have identified several chromosomal regions that are likely to contain susceptibility loci with strongest evidence found on chromosome 1q31 and 10q26. Variants in the complement factor H (CFH) gene have been shown by several independent studies to be associated with an increased risk for AMD in Caucasian populations. These findings imply that the innate immune system may play a significant role in AMD pathogenesis. The LOC387715/HTRA1 locus within 10q26 has been identified as a second major locus contributing to AMD pathogenesis. The two late forms of AMD, choroidal neovascularization and geographic atrophy, have not been found to be different in risk allele distribution. Variants within CFH and LOC387715/HTRA1 may contribute to the increased risk of late AMD largely through their impact on precursors, such as drusen and/or other RPE/Bruch’s membrane changes. Considering variants at CFH, LOC387715/HTRA1 and complement component 2-complement factor B (C2-FB), high-risk homozygotes at all three loci may have a 250-fold increased risk compared to baseline. However, the identification of genetic factors has not resulted in therapeutic strategies to modify the disease so far and additional genetic and environmental factors are yet to be discovered in order to influence the onset and the progression of AMD.

Genetic influence on age-related macular degeneration: AMD is a genetically complex disorder of the photoreceptor-retinal pigment epithelium (RPE)-Bruch’s membrane-choriocapillaris complex [1-4]. Early age-related macular degeneration (AMD) is characterized by areas of increased pigment or hyperpigmentation (in the outer retina or choroid) and/or areas of depigmentation or hypopigmentation of the RPE, associated with intermediate or soft drusen [5]. Late AMD includes geographic atrophy (GA) and choroidal neovascularization (CNV). The latter includes any of the following features: subretinal neovascular membranes, intraretinal or subretinal scars, RPE and neurosensory retinal detachments, hard exudates, and retinal hemorrhages [5]. Late AMD is now the most common cause of treatable blindness in the Western world, with a prevalence of 0.05% before the age of 50 years and 11.8% after 80 years of age [6]. Unless effective methods for prevention and treatment are found, the prevalence of AMD is expected to double in the coming decades due to an expected demographic shift towards aging populations [6]. The genetic influence on AMD is well known from family and twin studies [7-14]. First-degree relatives of patients with AMD, as compared with first-degree relatives in families without the disorder, are at increased risk (odds ratio, 2.4) for the condition [10], are affected at a younger age [13,15], and have an increased lifetime risk of late AMD (risk ratio, 4.2) [13]. In order to determine the relative contributions of heredity and environment to the etiology of AMD, Seddon and co-workers performed a population-based twin study of AMD including both concordant/discordant and monozygotic/dizygotic sibling pairs [16]. Heritability estimates for AMD were significant and ranged from 46% to 71%. These results underscore the need to pursue the search for AMD-related genes, despite the initial difficulties encountered with genetic analyses of a complex disease with late onset.

Analysis of candidate genes for age-related macular degeneration: The progress made within the last decade by studying hereditary retinal dystrophies has offered some investigative leads to further study AMD genetics. The similarities that exist between the phenotypic expression in the hereditary early onset diseases and some of the later onset complex traits as seen in AMD suggests a potential involvement of such candidate genes in AMD pathogenesis. In addition, candidate genes were identified based on linkage study results (positional criteria) and knowledge about gene function (functional criteria). However, this approach has not led to a breakthrough (with the exception of complement factor B (FB) and complement component 2 (C2), see below). Table 1 summarizes candidate genes with negative (i.e. no involvement in AMD pathogenesis) results to date [17].

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For other genes, some evidence of an association with AMD has been shown. Genes with at least one result of positive association are summarized in Table 2 [17]. However, variations in those genes either account for only a small fraction of AMD susceptibility or the results are inconclusive.

Fibulin5 represents an example of genes that probably account for only a small fraction of genetic susceptibility to AMD. Stone and colleagues found that the disruption of a gene of the same gene family, EFEMP1 (Fibulin3), is linked to Malattia leventinese/Doyne honeycomb retinal dystrophy [18]. This disorder is characterized by confluent drusen accumulation beneath the RPE, an early hallmark of AMD. EFEMP1 is an extracellular matrix protein. The interaction with other extracellular matrix proteins, such as adhesion molecules, collagens, elastins, fibronectins, laminins, tenascins, hemicentins and vitronectins, suggests an entire group of genes as possible candidates for involvement in drusen formation [18]. Later, the same group systematically evaluated five fibulin genes in a large series of patients with AMD. They demonstrated a significant association between sequence variations in fibulin5 and AMD. However, missense mutations in fibulin5 were estimated to account for only 1.7% of patients with AMD [19].

The photoreceptor cell-specific ATP-binding cassette transporter (ABCA4) gene was identified in 1997 and found to be mutated in patients with Stargardt’s macular dystrophy [20]. ABCA4 has been evaluated as a possible cause for other diseases with similar pathology in the macula including AMD. Two studies by Allikmets and co-workers provided evidence for an association between ABCA4 polymorphisms and AMD [21,22]. While other studies provided support [23,24], a number of studies failed to confirm an association of ABCA4 with AMD [25-32]. The number of patients and controls included in the latter studies appears large enough to rule out a major contribution of mutant ABCA4 alleles in the predisposition to AMD; however, they may not be sufficient to allow minor effects to be discerned. This makes it extremely difficult to determine the significance of individual mutant ABCA4 alleles in the predisposition to AMD, particularly those which are present in low frequency in the general population. The phenotypic similarities between typical juvenile Stargardt’s macular dystrophy and some forms of late atrophic AMD suggest that refined phenotyping may be of value in discerning between the two conditions. Figure 1 shows fundus autofluorescence images of a patient with Stargardt’s macular dystrophy (age, 17 years) and a patient with GA due to AMD (age, 71 years).

The impact of fundus autofluorescence imaging on more precise phenotyping and its potential as a prognostic marker has been demonstrated previously [33-35]. In vivo fundus autofluorescence imaging allows visualization of metabolic changes on the level of the RPE cell monolayer [36-39] and therefore provides information beyond conventional fundus photography or fluorescein angiography. In essence, dominant fluorophores in lipofuscin granules of the RPE cell monolayer are recorded, whereby lipofuscin accumulates with age and in association with various complex and monogenetic retinal diseases. Recently, it has been shown that by means of fundus autofluorescence imaging different phenotypic patterns of abnormal fundus autofluorescence in the junctional zone of late atrophic AMD can be identified [34]. Moreover, there was a high degree of intra-individual symmetry in the fundus autofluorescence pattern in the two eyes of individual patients, but a high degree of inter-individual variability which may suggest genetic heterogeneity. In a preliminary analysis, seven AMD patients exhibiting the fundus autofluorescence pattern “diffuse-fine granular with peripheral punctate spots” (resembling Stargardt’s macular dystrophy; age of onset, 50-84 years) and 14 GA patients exhibiting other fundus autofluorescence patterns were screened for ABCA4 mutations. In the first group, all patients showed at least one mutated allele, and in two patients, two mutated alleles were detected. In the control group of 14 AMD patients exhibiting GA, but a different pattern of abnormal fundus autofluorescence, only two patients showed one mutated allele [40]. We suggest that this distinct AMD phenotype exhibiting “diffuse-fine granular with peripheral punctate spots” reflects genetic alterations in ABCA4 and we

**Table 1. Candidate gene studies for age-related macular degeneration**

| Chromosome | Gene                       |
|------------|----------------------------|
| 1          | ADPR1, EPHX1, GLRX2, LAMC1, LamC2, LAMB3, OCL, PREL1, RG16, TGF2B | 2 EFEMP1 (Fibulin 3), GPR75, IL1A, Fibulin 2, GPX1 | 3 IMPG2 |
| 6          | RDS                        |
| 7          | AhR                        |
| 8          | NAT2                       |
| 10         | CYP2E1                      |
| 11         | CAT, Fibulin 4, VMD2       |
| 12         | AZM, MGST1                 |
| 14         | CKB                        |
| 15         | CYP1A1, CYP1A2              |
| 17         | APOH, ITGB4                |
| 22         | CYP2D6, Fibulin 1, TIMP3    |

Genes with negative results to date. For references, see Haddad et al. [17].

**Table 2. Candidate gene studies for age-related macular degeneration**

| Chromosome | Gene                       |
|------------|----------------------------|
| 1          | ABCA4, HEMICENTIN (Fibulin 6) |
| 3          | CX3CR1                     |
| 6          | HLA genes, VEGF, ELOVL4, SOD2 |
| 7          | PON1                       |
| 9          | VLDLR, TLR4                |
| 12         | LRP6                       |
| 14         | Fibulin 5                  |
| 17         | ACE                        |
| 19         | APOE                       |
| 20         | CST3, MMP9                 |

Genes with at least one positive result to date. For a comprehensive review of these genes including references, see Haddad et al. [17].
speculate this distinct phenotype represents late onset Stargardt’s macular dystrophy mimicking atrophic AMD. These preliminary data suggest that refined phenotyping is paramount in dissecting the role of candidate genes.

**Linkage and association studies in age-related macular degeneration:** Over the past several years, researchers have carried out both linkage studies and association studies in an attempt to identify the genomic regions containing susceptibility loci for AMD. While linkage studies search for genetic markers that segregate with the disease in a familial constellation, association analyses identify genetic marker alleles that either cause disease or are in strong linkage disequilibrium (LD) with the disease-causing alleles.

Fisher and colleagues applied the genome-scan meta-analysis (GSMA) method that allows linkage results from several studies to be combined, providing greater power to identify regions which show only weak evidence for linkage in individual studies [41]. This method has been successful in a number of complex diseases and was applied to six published AMD genome-wide linkage scans: (1) Abecasis et al. [42], (2) Iyengar et al. [43], (3) Majewski et al. [44], (4) Schick et al. [45], (5) Seddon et al. [46], and Weeks et al. [47]. For each study, 120 genomic bins of 30 cM were defined and ranked according to maximum evidence for linkage within each bin. Bin ranks were weighted according to study size and summed across all studies. A high summed rank indicates a region with consistent evidence for linkage across studies. The strongest

| Table 3. Prevalence of the histidine alteration in five different population from different ethnicity |
|-----------------------------------------------|
|       | Caucasian | African-American | Hispanic | Japanese | Somali |
|-------|-----------|------------------|---------|----------|--------|
| C     | 0.34 (0.03) | 0.35 (0.04) | 0.17 (0.03) | 0.07 (0.02) | 0.34 (0.03) |
| T     | 0.66 (0.03) | 0.65 (0.04) | 0.83 (0.03) | 0.93 (0.02) | 0.66 (0.03) |
| CC    | 0.07 (0.02) | 0.11 (0.03) | 0.05 (0.02) | 0.02 (0.02) | 0.07 (0.02) |
| CT    | 0.54 (0.04) | 0.48 (0.06) | 0.25 (0.05) | 0.09 (0.03) | 0.55 (0.05) |
| TT    | 0.39 (0.04) | 0.41 (0.06) | 0.70 (0.05) | 0.89 (0.03) | 0.38 (0.04) |
| Total patients | 148 | 75 | 81 | 82 | 128 |

Values are frequency (standard error) [94].

Figure 1. Phenotyping by means of fundus autofluorescence imaging. Fundus autofluorescence images obtained with a cSLO (Heidelberg retina angiograph, HRA 2, Heidelberg Engineering, Dossenheim, Germany) according to a standard operating procedure. Left: Patient diagnosed with Stargardt’s macular dystrophy (age, 17 years); right: patient diagnosed with atrophic AMD (GA) and a fundus autofluorescence pattern “diffuse-fine granular with peripheral punctate spots” according to Bindewald et al. [34] (age: 71 years).

Figure 2. Two-locus (LOC387715 and CFH) genotype specific disease risks. Two-locus genotype specific disease risks for the two variants: LOC387715 (A69S) and CFH (Y402H) according to Rivera et al. [57].
evidence for an AMD susceptibility locus was found on chromosome 10q26 where genome-wide significant linkage was observed (p=0.00025). Several other regions met the empirical significance criteria for bins likely to contain linked loci including adjacent pairs of bins on chromosomes 1q, 2p, 3p, and 16. Several of the regions identified here showed only weak evidence for linkage in the individual studies. The analysis performed by Fisher and colleagues may help prioritize regions for future positional and functional candidate gene studies in AMD.

Complement factor H gene: Genome-wide linkage analyses and the genome-scan meta-analysis of Fisher and colleagues had pointed to a locus on 1q25-q31 [42-44,46-48]. Case-control studies recently identified complement factor H (CFH) as the responsible gene [49-52]. The CFH Y402H variant, located within a binding site for C-reactive protein (CRP), has consistently been shown to reveal strong association with AMD [53-55].

In a population-based prospective design on a total of 5681 individuals, investigators of the Rotterdam Eye Study have shown that CFH is implicated in all stages of AMD from early hallmarks such as drusen to vision-disabling late AMD [56]. The risk increases with each successive stage to an odds ratio of 11.0 for late AMD. It was calculated that individuals homozygous for the CFH Y402H polymorphism have a 48% risk of developing late AMD by age 95 years while this risk does not exceed 22% for non-carriers. Interestingly, complement factor H was associated with both late AMD subtypes (CNV and GA) in this study. Homozygous CFH Y402H carriers had a higher risk of bilateral than of unilateral late AMD, and risks of GA and mixed AMD were slightly but not significantly higher than neovascular AMD. This is in agreement with other studies that reported higher frequencies of CFH Y402H carriers in persons with GA [54,57] and one study that suggested a lower risk of GA for a CFH haplotype containing the non-risk allele [52]. In a comprehensive survey including variants from three gene loci (CFH, LOC387715/HTRA1, and C2-FB), Maller and co-workers did not find any association with phenotypic subclassifications of late AMD despite good power to detect association [58]. These findings suggest that the high risk for both subtypes of late AMD signifies a common pathogenesis involving the complement system.

CFH is an important regulator of the complement system. Three enzyme cascades exist (see e.g. figure 5 in [59]): the classical complement pathway, initiated by antigen-antibody complexes and surface-bound CRP; the lectin pathway, turned on by mannose groups of microbial carbohydrates; and the alternative complement pathway, activated by surface-bound C3b. The pathways converge at the point where C3 is cleaved into C3a and C3b by C3 convertase, which initiates C5 convertase, finally resulting in the formation of the membrane attack complex with the terminal components (C5b-C9). CFH specifically inhibits the alternative complement cascade but also regulates the common pathway. It binds C3b and acts as a cofactor in the proteolysis of C3b by factor I, resulting in an inactive C3b molecule. This prevents the production of C3 convertase in the alternative cascade as well as the production of C5 convertase in the common pathway. As a result, CFH interferes with the progression of the entire cascade [60-63]. Indeed, Hageman and co-workers showed that CFH and C3b/iC3b colocalize within drusen, suggesting that these regions represent complement activating surfaces within drusen and Bruch’s membrane [52,63]. A recent study suggests that there may be multiple susceptibility alleles in the CFH genomic region with non-coding CFH variants possibly playing a role in disease susceptibility [64]. In this study, Li and co-workers examined the impact of 84 polymorphisms in a region of 123 kb overlapping the CFH gene on disease susceptibility in 544 unrelated affected individuals and 268 unrelated controls. As expected, strong association was observed between disease status and the Y402H-encoding variant (rs1061170). Unexpectedly, 20 other variants showed even stronger association. The strongly associated SNPs fell into two LD groups. The Y402H-encoding variant was included in one of the LD groups. The three SNPs showing strongest association were a synonymous SNP in exon 10, rs2274700, and two intronic SNPs, rs1410996, and rs7535263. The authors conclude that multiple haplotypes in the genomic region seem to modulate the AMD disease risk and that there are multiple disease-predisposing variants. Because the polymorphisms showing the

Figure 3. Progression of geographic atrophy imaged by fundus autofluorescence. Fundus autofluorescence images obtained in 12-month intervals in an AMD patient with a cSLO (Heidelberg retina angiograph, HRA classic and HRA 2, Heidelberg Engineering, Dossenheim, Germany). A large kidney-shaped area of GA was present at baseline (left) corresponding to decreased fundus autofluorescence (dark area). Recovered in yearly intervals, the area of the central atrophic area increased [80].
strongest association with AMD susceptibility appear not to
effect a change in the CFH protein, the authors speculate that
these variants may be important in regulating the expression of
CFH, or other nearby complement genes or both [64].

The region which includes the CFH gene cluster also con-
tains numerous CFH-like genes (e.g., CFHR1, CFHR2, CFHR3, CFHR4, and CFHR5), which reveal high sequence
conservation making any analysis difficult. Hughes and col-
leagues genotyped polymorphisms spanning the CFH gene
cluster in 173 individuals with severe neovascular AMD and
170 controls and found a common haplotype, GTATAAAG,
associated with decreased risk of AMD which was present on
8% of chromosomes of AMD patients and 20% of chromo-
somes of controls [65]. They found that this haplotype carried
a deletion of CFHR1 and CFHR3. Protein blot analysis of se-
rum samples from individuals homozygous for each haplo-
type confirmed the absence of CFHR1 and CFHR3 protein.
CFHR1 and CFHR3 proteins usually are present in the circu-
lation and have the potential to compete with CFH for C3
binding. Possibly, CFH produced from full-length transcripts
is beneficial regarding AMD-risk and other CFH-related pro-
teins interfere with regulation of complement activity [65].

It has long been known that the phenotype spectrum of AMD vari-
ies widely among different ethnicities [66–70]. Moreover, the
phenotypic spectrum of AMD among these groups is quite
heterogeneous [71–75]. For example, in Japanese, soft drusen
are only a moderate risk indicator (18%) for developing CNV
compared with Caucasians, whereas serous pigment epithe-
lial detachments are a very common high risk indicator (58%)
for developing CNV in Japanese [75]. To explore the ethnic
variation of the frequency of the CFH Y402H sequence vari-
ant, Grassi and co-workers analyzed the frequency of the risk
(C) allele in populations from five different ethnicities. Widely
divergent frequencies were noted between some of these popu-
lations (7–35%; Table 3).

These data suggest that there are other as yet unidentified
genetic factors important in the pathogenesis of AMD. These
factors may operate independently or mitigate the effects of
the CFH Y402H sequence variant. Specifically, the findings
suggest the presence of additional genetic risk factors for AMD
in Japanese individuals.

LOC387715/HTRA1: Two recent reports have highlighted the
LOC387715/HTRA1 locus within 10q26 as a second ma-
jor locus contributing to AMD pathogenesis [57,76], Rivera
and co-workers found the strongest association over the
LOC387715 gene conferring a 7.6-fold increased risk for in-
dividuals homozygous for a potential non-synonymous cod-
ing SNP, Ala69Ser. These findings were fully replicated in an
independent case-control cohort. Furthermore, they replicated
the strong association of AMD with the Y402H coding vari-
ant in CFH. The results indicate an independent contribution of the effects of risk alleles at the LOC387715 (Ala69Ser) and
CFH (Tyr402His)-gene locus to the overall disease risk (Fig-
ure 2). Very recently, the findings have been independently
replicated by others [58,77–79].

Patient groups of early high-risk AMD and late AMD were
not different in risk allele distribution in LOC387715. This
was also true for GA and neovascular AMD. So far, it is un-
known, whether risk alleles at LOC387715/HTRA1 as well as
CFH correlate with severity stage of AMD or with a clinical
outcome measure that would be a target of therapeutic inter-
vention. Based on longitudinal data of serial fundus
autofluorescence images from patients with late atrophic AMD,
it has become feasible to determine the progression of GA in
individual patients (Figure 3) [35,80].

The GA progression rate represents both a biologically
based quantitative phenotype of late AMD and the most rel-
vent target for therapeutic intervention. In a preliminary anal-
ysis, we determined whether the risk alleles of both CFH and
LOC387715/HTRA1 are correlated with the progression of GA
in 207 AMD patients with GA (without any signs of CNV).
We found that the risk allele distribution of Y402H in CFH
and A69S in LOC387715/HTRA1 for patients with GA is simi-
lar to those previously reported for pooled AMD samples.
However, no correlation was found between the rate of pro-
gression of GA and CFH and/or LOC387715/HTRA1 geno-
type [81]. These data suggest that both genes contribute to the
increased risk of late AMD largely or entirely through their
impact on precursors (such as drusen and/or other RPE/Bruch’s
membrane changes). This may have implications for therapeu-
tic interventions in patients with late AMD, because the
attempt to modify the respective gene products may not be
promising [81].

DeWan and colleagues performed a genome-wide asso-
ciation study in 96 Chinese patients with neovascular AMD
and 130 controls and confirmed a significant association with
the A69S (rs10490924) polymorphism at the LOC387715/
HTRA1 locus within 10q26 [82]. A more telomeric SNP, rs11200638, was identified to be in almost complete linkage
disequilibrium with rs10490924. SNP rs11200638 is localized
in the putative GC-rich promoter region of the HTRA1 gene
potentially modulating expression levels of the gene [82], Yang
and co-workers provided similar findings in 581 Caucasian
AMD patients and 309 controls [83]. DeWan et al. conclude
that HTRA1 influences specifically CNV formation in AMD
pathogenesis [82], although this conclusion seems unsubstan-
tiated as exclusively wet AMD was included in their study.
Unfortunately, the study of Yang et al. does not provide any
information about the study phenotypes [83]. Obviously, such
studies would considerably benefit from more extensive phe-
notypic analyses.

Factor B/complement component 2: Recent findings have
demonstrated the validity of the candidate gene approach given
the pre-existing knowledge that the complement system plays a
significant role in AMD pathogenesis. Gold and colleagues
reported an association with two other genes that encode regu-
laratory proteins acting along the same biological pathway as
CFH [84]. These two genes are factor B (BF) and comple-
ment component 2 (C2), located 500 base pairs apart on chro-
mosome 6p within the major histocompatibility complex class
III region. The reported association was found in a sample of
898 patients with various forms of AMD and 389 controls.
There was a common risk haplotype across BF and C2 (OR,
1.32), as well as two protective haplotypes (OR, 0.36, and
risk. Fitting an interaction model between and of Rivera et al. indicated that the two risk alleles, in inclusion of interlocus interference [58]. Similarly, the study multiplied to generate a combined risk profile) provided a to detect epistasis. Specifically, a model in which the risk al-
additive interactions were not found despite excellent power LOC387715/HTRA1 and C2-FB among the five common variants at the three loci (approximately 2% of the population) [58].

When evaluating the role of gene-gene interaction (epistasis) at all three loci (approximately 2% of the population) [58]. Conley and co-workers developed a risk model for AMD based on five validated common variants. In contrast to the modest elevation in overall risk to siblings (two- to sixfold [9,10,13]), the predictive value of specific genotype combinations was notable. For example, approximately 10% of the population have a 40-fold greater risk and 1% (high-risk homozygotes at all three loci) have a more than 250-fold increased risk compared to baseline which is observed for individuals carrying the lowest-risk genotypes at all three loci (approximately 2% of the population) [58].

Conclusions: Genetic studies have convincingly demonstrated that there exist common alleles of substantial effect on AMD pathogenesis. The finding of such common alleles with substantial effects makes predictive DNA testing a tempting option although the mechanisms and thus the biological consequences conferred by the common risk alleles at the respective gene loci are not yet understood. Consequently, the knowledge of being carrier of risk alleles is currently not matched by adequate options for preventive strategies or possible treatment modalities.

The finding that variants within and BF are responsible for a large fraction of AMD cases (at least in Caucasians) suggests an important role of the alternative complement pathway in the pathobiology of AMD and further strengthens the notion that inflammation has a major role in this common disease [84].

Several environmental factors have been identified over the past decade including cigarette smoking [85-88], higher body mass index (BMI) [89,90], and nutritional factors [91,92], with smoking being the most consistent in several population based studies worldwide [85,86]. So far, however, there are inconclusive data on gene-environment interactions. In an extended collection of 848 AMD cases, no significant differences in risk allele frequency for either or were detected between smokers and non-smokers despite substantial power by Rivera et al. [57], whereas Schmidt and co-workers observed significant evidence for a statistical interaction between the A69S variant and a history of cigarette smoking [77]. Despretz and colleagues found that the combined effect of homozygosity for the Y402H variant in CFH and smoking exceeds the sum of the independent effects. Compared with no smoking, exposure increased the risk of AMD 3.3 times, the presence of two CFH Y402H alleles increased the risk 12.5 times, while the combination of both determinants increased this risk 34-fold [56]. In contrast, Conley and co-workers excluded a significant interaction of risk allele distribution in CFH or LOC3897715 and cigarette smoking [78]. Similarly, Seddon and co-workers did not find a statistically significant interaction between CFH genotype and cigarette smoking, but the susceptibility to late AMD was modified by the body mass index (BMI; normal values according to WHO, 2000 EK IV: 18.5 kg/m²; -25.0 kg/m²). Compared with lean individuals with the CFH TT genotype, an increased risk of AMD among these lean individuals with BMI lower than 25 was found only for the CC homozygotes. For heavier persons with BMI greater than 25, the risk varied from a non-significant null or slightly protective association for the TT genotype, to a moderately high 2.2-fold increased risk for the heterozygotes, and a very high 5.9-fold increased risk for the CC homozygote state. This interaction between BMI and genotype related risk of late AMD was statistically significant for the CT versus TT genotype [93].
in a detectable phenotype when acting in combination with additional susceptibility alleles either additively or multiplicatively. Additional work exploring these types of interactions should bring us closer to the genes influencing the onset and progression of AMD.

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