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Seven New Loci Associated with Age-Related Macular Degeneration

The AMD Gene Consortium

Abstract

Age-related macular degeneration (AMD) is a common cause of blindness in older individuals. To accelerate understanding of AMD biology and help design new therapies, we executed a collaborative genomewide association study, examining >17,100 advanced AMD cases and >60,000 controls of European and Asian ancestry. We identified 19 genomic loci associated with AMD with $p<5\times10^{-8}$ and enriched for genes involved in regulation of complement activity, lipid metabolism, extracellular matrix remodeling and angiogenesis. Our results include 7 loci reaching $p<5\times10^{-8}$ for the first time, near the genes *COL8A1/FILIP1L*, *IER3/DDR1*, *SLC16A8*, *TGFBR1*, *RAD51B*, *ADAMTS9*/*MIR548A2*, and *B3GALTL*. A genetic risk score combining SNPs from all loci displayed similar good ability to distinguish cases and controls in all samples examined. Our findings provide new directions for biological, genetic and therapeutic studies of AMD.

AMD is a highly heritable progressive neurodegenerative disease that leads to loss of central vision through death of photoreceptors[1,2]. In developed countries, AMD is the leading cause of blindness in those >65 years[3]. Genes in the complement pathway[4–11] and a region of chromosome 10 [12,13] have now been implicated as the major genetic contributors to disease. Association has also been demonstrated with several additional loci[14–20], each providing an entry-point into AMD biology and potential therapeutic targets.

To accelerate the pace of discovery in macular degeneration genetics, 18 research groups from across the world formed the AMD Gene Consortium in early 2010, with support from the National Eye Institute (Table 1, Supplementary Table 1, Supplementary Note). To extend the catalog of disease associated common variants, we first organized a meta-analysis of genomewide association scans (GWAS) – combining data for >7,600 cases with advanced disease (geographic atrophy, neovascularization, or both) and >50,000 controls. Each study was first subject to GWAS quality control filters (customized taking into account study specific features[21] as detailed in Supplementary Table 2) and standardized to the HapMap reference panel and statistical genotype imputation[22–25]. Results were combined through meta-analysis[26] and thirty-two variants representing loci with promising evidence of association were genotyped in an additional >9,500 cases and >8,200 controls

Correspondence To: Gonçalo R. Abecasis, University of Michigan School of Public Health, Ann Arbor, MI, USA, goncalo@umich.edu. Iris Heid, University of Regensburg, Regensburg, Germany, iris.heid@klinik.uni-regensburg.de. Lindsay A. Farrer, Boston Universitym, Boston, MA, USA, farrer@bu.edu. Jonathan L. Haines, Vanderbilt University, Nashville, TN, USA, jonathan@chgr.mc.vanderbilt.edu.

(Supplementary Tables 1–3; summary meta-analysis results available online). Our overall analysis of the most promising variants thus included >17,100 cases and >60,000 controls.

Our meta-analysis evaluated evidence for association at 2,442,884 SNPs (Figure 1). Inspection of Q-Q plots (Supplementary Figure 1) and the genomic control value (λ_{GC}=1.06) suggest that unmodeled population stratification does not significantly impact our findings (Supplementary Table 4 for details). Joint analysis of discovery and follow-up studies[27] resulted in 19 loci reaching $p<5\times10^{-8}$ (Figure 1, Table 2, Supplementary Table 5). These 19 loci include all susceptibility loci previously reaching $p<5\times10^{-8}$, except the 4q12 gene cluster for which association was reported in a Japanese population. In addition, the set includes seven loci reaching $p<5\times10^{-8}$ for the first time.

We evaluated heterogeneity between studies using the I^2 statistic, which compares variability in effect size estimates between studies to chance expectations[28]. We observed significant (p<.05/19) heterogeneity only for loci near *ARMS2* (I^2=75.7%, $p<1\times10^{-6}$) and near *CFH* (I^2=85.4%, $p<1\times10^{-6}$). Although these two loci were significantly associated in every sample examined, the magnitude of association varied more than expected. To explore sources of heterogeneity, we carried out a series of sub-analyses: we repeated the genomewide meta-analysis adding an age-adjustment, separating neovascular (NV) and geographic atrophy (GA) cases, in men and women, and in European- and Asian-ancestry samples separately (Figure 3, Supplementary Figure 2). These sub-analyses of the full GWAS dataset did not uncover additional loci reaching $p<5\times10^{-8}$; furthermore heterogeneity near *CFH* and *ARMS2* remained significant in all sub-analyses (I^2>65%, p <. 001). Consistent with previous reports[17,29,30], separate analysis of NV and GA cases showed *ARMS2* risk alleles preferentially associated with risk of NV (OR_{NV}=2.97, OR_{GA}=2.50, $p_{difference}$=.0008) whereas *CFH* risk alleles preferentially associated with risk of GA (OR_{NV}=2.34, OR_{GA}=2.80, $p_{difference}$=.0006). We also observed large differences in effect sizes when stratifying by ethnicity, with variants near *CFH* exhibiting stronger evidence for association among Europeans (p=.0000001) and those near *TNFRSF10A* among East Asians (p=.002). Potential explanations include differences in linkage disequilibrium between populations or differences in environmental or diagnostic factors that modify genetic effects.

Identifying the full spectrum of allelic variation that contributes to disease in each locus will require sequencing of AMD cases and controls. To conduct an initial evaluation of the evidence for multiple AMD risk alleles in the nineteen loci described here, we repeated genomewide association analyses conditioning on the risk alleles listed in Table 2. We then examined each of the 19 implicated loci for variants with independent association (at p<. 0002, corresponding for an estimate of ~250 independent variants per locus). This analysis resulted in the identification of the previously well documented independently associated variants near *CFH* and *C2*/*CFB*[8,10,31,32] and of additional independent signals near *C3*, *CETP*, *LIPC*, *FRK/COL10A1*, *IER3/DDR1*, *RAD51B* (Supplementary Table 6). In four of these loci, the independently associated variants mapped very close (within <60kb) to the original signal. This shows each locus can harbor multiple susceptibility alleles, encouraging searches for rare variants that elucidate gene function in these regions[33,34].

To prioritize our search for likely causal variants, we examined each locus in detail (see LocusZoom[35] plots in Supplementary Figure 3) and investigated whether AMD risk alleles were associated with changes in protein sequence, copy number variation or insertion deletion polymorphisms. One quarter of associated variants altered protein sequence, either directly (N=2) or through linkage disequilibrium (r^2>.6; N=3) with a nearby non-synonymous variant (Supplementary Table 7). Some coding variants point to well-studied genes (*ARMS2*, *C3* and *APOE*) while others help prioritize nearby genes for further study. In chromosome 4q25, index SNP rs4698775 is in strong linkage disequilibrium (r^2=.88) with a potentially protein damaging variant in *CCDC109B*[36], a coiled coil domain containing protein that may be involved in the regulation of gene expression. In chromosome 6q22, index SNP rs3812111 is a perfect proxy for a coding variant in *COL10A1*, a collagen protein that could be important in maintaining the structure and function of the extra-cellular matrix. Interestingly, rs1061170 (NP_000177.2[CFH]:p.His402Tyr) was not in disequilibrium with rs10737680, the most strongly associated SNP in the *CFH* region but, instead, was tagged by a secondary and weaker association signal (Supplementary Tables 6&7). This is consistent with prior haplotype analyses of the locus[10,31,32,34,37].

We used publicly available data[38,39] to check whether any of our index SNPs might be proxies for copy number variants or insertion-deletion polymorphisms (indels), which are hard to directly interrogate with genotyping arrays. This analysis identified a single strong association (r^2=.99), between rs10490924, a coding variant in the *ARMS2* gene which is the peak of association in 10q26, and a 3′ UTR indel polymorphism associated with *ARMS2* mRNA instability[40]. Since index SNP rs10490924 is also in strong disequilibrium (r^2=.90) with a nearby SNP, rs11200638, that regulates *HTRA1*[41], our data does not directly answer whether *HTRA1* or *ARMS2* is the causal gene in this locus. Although a common deletion of the CFHR1 and CFHR3 genes has been proposed[42,43], there was only modest signal in this study which is likely due to linkage disequilibrium with our most significantly associated variants in the locus (r^2=.31 between rs10737680 and 1000 Genomes Project MERGED_DEL_2_6731) as previously suggested[34].

Using RNA-sequencing[44], we examined mRNA levels of 85 genes within 100 kb of our index SNPs in post-mortem human retina (Supplementary Table 8). Of 19 independent risk loci, three had no genes with expressed transcripts in either old or young retina. Two genes showed differential expression between post-mortem retina of young (ages 17–35) and elderly (ages 75 and 77) individuals: *CFH* (p=.009) and *VEGFA* (p=.003), both with increased expression in older individuals. Using previously published data[45], we also examined the expression of associated genes in fetal and adult retinal pigment epithelium (RPE). This revealed increased *C3* expression in adult RPE compared to fetal RPE (p=.0008). *CFH*, *VEGFA* and *C3* are thus up-regulated with aging, and their role in AMD may indicate an accelerated aging process. In addition to *C3* and *CFH*, all the complement genes with detectable expression in the retina or RPE experiments showed higher expression levels in older tissue.

To identify biological relationships among our genetic association signals, we catalogued the genes within 100kb of the variants in each association peak (r^2>0.8 with the index SNP listed in Table 1). Ingenuity Pathway Analysis (Ingenuity Systems, Redwood, CA)

highlighted several biological pathways, particularly the complement system and atherosclerotic signaling, to be enriched in the resulting set of 90 genes (Table 3, Supplementary Table 9). To account for features of genomewide association studies (such as the different number of SNPs in each gene), we carried out two additional analyses. First, we repeated our analysis for 50 sets of 19 control loci drawn from the NHGRI GWAS catalog[46]. In these 50 control sets, Ingenuity enrichment p-values for the complement system and for atherosclerosis signaling genes were exceeded 16% and 32% of the time respectively (although these two specific pathways were never implicated in a control dataset). We also repeated our enrichment analyses using the INRICH tool[47], which is specifically designed for the analysis of genomewide association studies – but accesses a more limited set of annotations. The INRICH analyses showed enrichment for genes encoding collagen and extra-cellular region proteins (both with $p=10^{-5}$ and after adjustment for multiple testing $p_{adjust}=.0006$), complement and coagulation cascades (p=.0002, $p_{adjust}=.03$), lipoprotein metabolism (p=.0003, $p_{adjust}=.04$), and regulation of apoptosis (p=.0009, $p_{adjust}=.09$) (Supplementary Table 10).

To explore the connections between our genetic association signals, we tested for interaction between pairs of risk alleles – looking for situations where joint risk was different than expected based on marginal effects. This analysis resulted in 171 tests of interaction, of which 9 were nominally significant (p<.05, see Supplementary Table 11), consistent with chance expectations. The strongest observed interaction involved risk alleles at rs10737680 (near *CFH*) and rs429608 (near *C2*/*CFB*), the only association that remained significant after adjusting for multiple testing (p=.000052, <0.05/171=.00029). Individuals carrying risk alleles at both these loci where at slightly higher risk of disease than expected.

The proportion of the variability in the risk of AMD that is due to genes, or heritability, has been estimated at 45–70% [2]. Estimating the proportion of disease risk explained by the susceptibility loci identified [48] depends greatly on the disease prevalence - which is difficult to estimate in our sample, as it includes cases and controls of different ages and collected through a variety of ascertainment schemes. Using a model that assumes an underlying normally distributed but unobserved disease risk score or liability[49], the nineteen loci described here account for between 10% (if AMD prevalence is close to 1%) and 30% (if AMD prevalence is closer to 10%) of the variability in disease risk (corresponding to 15–65% of the total genetic contribution to AMD). The variants representing the peak of association at loci previously reaching genomewide significance account for the bulk of this variability: the new loci identified here account for 0.5–1.0% of the total heritability of AMD whereas secondary signals at novel and known loci account for 1.5–3.0% of the total heritability.

We report here the most comprehensive genetic association study of macular degeneration yet conducted, involving 18 international research groups, and a large set of cases and controls. Our data reveal 19 susceptibility loci, including 7 loci reaching $p<5\times10^{-8}$ for the first time, nearly doubling the number of known AMD loci outside the complement pathway. Our results show some susceptibility alleles exhibit different association across ethnic groups and may be preferentially associated with specific subtypes of disease. As with other GWAS meta-analysis, differences in genotyping methods, quality control steps

and imputation strategies between samples might have a minor effect in our results – future studies may document that more uniform approaches across larger sample sizes might uncover more signals. A conundrum of macular degeneration genetics remains that the loci identified to date contribute to both GA and NV, two different phenotypes of advanced disease. In our sample, subtype specific GWAS analyses considering GA or NV cases only did not identify additional loci. Consistent with observations for other complex diseases[39], the majority of common disease susceptibility alleles do not alter protein sequences and are not associated with insertions or deletions of coding sequence or with copy number variation. We expect that the loci identified here will provide an ideal starting point for studies of rare variation[33,34].

In contrast to most other complex diseases, a risk score combining information across our 19 loci, can distinguish cases and controls relatively well (Figure 4, area under the ROC curve [AUC]=.52 including only new loci or AUC=.74 including new and previously reported loci; Supplementary Figure 4). It may be possible to use similar scores to identify and prioritize at risk individuals so they receive preventative treatment prior to the onset of disease[50]. Monotherapies are increasingly utilized to manage neovascular disease, but offer only a limited repertoire of treatment options to patients. Identification of novel genes and pathways enables us to pursue a larger range of disease-specific targets for development of new therapeutic interventions. We expect that future therapies directed at earlier stages of the disease process will allow patients to retain visual function for longer periods, improving the quality of life for individuals with AMD.

ONLINE METHODS

GENOME-WIDE SCAN FOR LATE AMD ASSOCIATION INCLUDING FOLLOW-UP

Study-specific association analysis for discovery—Genotyping was performed on a variety of different platforms summarized in Supplementary Table 2. Each group submitted results from association tests using genotyped and imputed data where the allelic dosages were computed with either MACH[25], IMPUTE[23], BEAGLE[24], or snpStats[52] using the HapMap2 reference panels. The CEU panel was used as a reference for imputation-based analyses for most samples (predominantly of European ancestry), with two exceptions: for the JAREDS samples (predominantly of East Asian ancestry), the CHB+JPT panel was used as a reference; for the VRF samples (predominantly of South Asian ancestry) the combined CEU and CHB+JPT panels were used[22,53]. For most data sets association tests were run under a logistic regression model using either Plink[54], Mach2dat[25], ProbABEL[55], or snpStats[52], though for one dataset containing related individuals the generalized estimating equations algorithm[56] as implemented in R[57,58]. In addition to the primary analysis which tested for SNP associations with advanced AMD unadjusted for age, an age-adjusted sensitivity analysis was conducted by each group with available age. Each group also provided stratified results by sex or AMD subtype (GA or NV) as long as the sample size per stratum exceeded 50 subjects. For all analyses, study-specific control for population stratification was conducted (Supplementary Table 4).

Study-specific association analysis for follow-up—Genotyping of the selected SNPs was performed on different platforms; the same models, sensitivity and stratified

analyses were computed by each follow-up partner, while SNPs with insufficient call rate were excluded based on study-specific thresholds. If the index SNP could not be genotyped, a highly correlated proxy was used whenever possible (Supplementary Tables 2&3).

Quality control before meta-analysis—Before meta-analysis, all study-specific files underwent quality control procedures to check for completeness and plausible descriptive statistics on all variables as well as for compliance of allele frequencies with HapMap[59]. In addition, we excluded SNP results of a study into meta-analysis (i) for discovery: if imputation quality measures were too low (MACH & PLINK <0.3; SNPTEST <0.4) or if effect sizes (|beta|) or standard errors were too extreme (≥5) indicating instability of the estimates, (ii) for follow-up: if Hardy-Weinberg equilibrium was violated ($p<0.05/32$).

Meta-analyses—For both discovery and follow-up, we performed meta-analyses using the inverse variance weighted fixed effect model, which pools the effect size and standard error of each participated GWAS. Using an alternative weighted z-score method, which is based on a weighted sum of z-score statistics, we obtained a very similar set of test statistics (correlation of −log10(p-value) >0.98). All analyses were performed using METAL[26] and R. For the discovery, we applied two rounds of genomic control corrections to each individual GWAS and the combined meta results, respectively [51]. All results were analyzed and validated among four independent teams.

EXTENDED ANALYSES FOR THE IDENTIFIED AMD LOCI

Extended analyses were conducted on the identified loci and particularly on the top SNP of each locus.

Second signal analysis—To detect potential independent signals within the identified AMD loci, each study partner with genotypes for all identified SNPs available re-analyzed their data for all SNPs in the respective loci (index SNP ±1Mb) using a logistic regression model containing all identified index SNPs. Quality control procedures were performed as before. The beta estimates for each SNP were meta-analyzed applying the effective sample size weighted z-score method and two rounds of genomic control correction. The significance threshold ($p<0.05$) for an independent association signal within any of the identified loci was Bonferroni-adjusted using the average effective number of SNPs involved across the identified loci determined by SNPSpD[60]. To this analysis, 13 studies contributed including 7,489 cases and 51,562 controls.

Interaction analysis—Utilizing a pre-specified R-scripts (see URLs), GWAS partners performed 171 logistic regression analyses modeling the pair-wise interaction of the 19 index SNPs assuming an additive model for main and interaction effects. Study-specific covariates were included to the model if required. Per study, quality control included a check for consistency of SNP main effects between discovery and interaction analysis. SNPs with low imputation quality measures and pairs with |beta|>5 or standard errors >5 were excluded before meta-analyzing the interaction effects with the inverse variance weighted fixed effect model in METAL. To this analysis, 12 studies contributed including 6,645 cases and 49,410 controls.

GENETIC RISK SCORE

The meta-analyzed effect sizes, β_j, for each of the 19 SNPs were calculated in the meta-analysis described above and normalized: $\hat{\beta}_j = \beta_j / \sum_{k=1}^{19} \beta_k$, j=1,…,19. Using these as weights, each study partner with all 19 SNPs available computed the individuals' genetic risk score as a normalized weighted sum of the AMD risk increasing alleles among the identified SNPs as

$$S_i = \sum_j \hat{\beta}_j x_{ij},$$

where x_{ij} is the genotype of the ith individual at the jth SNP, so S_i ranges from 0 to 2. This data was available from 12 studies including 7,195 cases and 49,149 controls.

For each study, we used a leave-one-out cross-validation to access the prediction of the risk score. For the kth subject, we fitted a logistic regression model from all subjects in the study excluding the kth subjects: $\log(\frac{y_i}{1-y_i}) = \alpha + \gamma S_i$, i! = k, α is the intercept and γ is the effect of the genetic risk score. The fitted probability of the kth subject was then estimated as $\hat{y}_k = 1/(1+e^{-(\hat{\alpha}+\hat{\gamma}\hat{S}k)})$. We sorted the fitted probabilities and calculated sensitivity and specificity by varying the risk threshold (the value compared with the fitted probability to dichotomize the subject into case or control) from 0 to 1. These were utilized to compute the area-under-the curve (AUC) of the receiver-operating-curve (ROC).

IDENTIFICATION OF CORRELATED CODING VARIANTS AND TAGGED NON-SNP VARIATION

LD estimates were calculated using genotype data of the identified risk loci (index SNPs ±500kb) of individuals with European ancestry from the 1000 Genomes Project (March 2012 release)[61] or from HapMap (release #28)[59]. Variants correlated (r^2>0.6) with one of the GWAS index SNPs were identified using PLINK[54]. To filter coding variants, all correlated variants were mapped against RefSeq transcripts using ANNOVAR[62].

GENE EXPRESSION

We evaluated expression of genes within 100kb of one of the 19 index SNPs, as well as of several retina-specific, RPE-specific and housekeeping genes unrelated to AMD for comparison in retina (RNA-sequencing data from three young [17–35 yrs age] and two old individuals [75 and 77 yrs age]) as well as in fetal and adult retinal pigment epithelium (RPE; published data in the Gene Expression Omnibus database[45]). Expression was analyzed using previously described protocols[44] (Supplementary Table 8).

PATHWAY ANALYSES

Functional enrichment analysis was performed using the Ingenuity Pathway Analysis software (IPA, Ingenuity® Systems). Any gene located within 100kb of a SNP in high LD (r^2>0.8) with one of the index SNPs was considered a potential AMD risk associated gene

and considered for subsequent pathway enrichment analysis. LD estimates were calculated as described above. Applying the above inclusion filters, 90 genes appear to be implicated by our 19 replicated AMD SNPs (Supplementary Table 8). Because genes with related function sometimes cluster in the same locus, we trimmed gene lists during analysis so that only one gene per locus was used to evaluate enrichment for each pathway. The P-value of the association between our implicated gene list and any of the canonical pathways and/or functional gene sets as annotated by IPA's Knowledge Base was computed using a one-sided Fisher's exact test. The Benjamini-Hochberg method was used to estimate False Discovery Rates. To evaluate significance of observed enrichment, we repeated our Ingenuity analysis starting with 50 lists of 19 SNPs randomly drawn from the NHGRI GWAS catalog[46] and, again, using the INRICH tool[63]. When using INRICH, we used gene sets defined in the Broad's Molecular Signatures database[47] (ver3.0) representing manually curated canonical pathway, Gene Ontology biological process, cellular component and molecular function gene sets (C2:CP, C5:BP, C5:CC and C5:MF). We provided INRICH with our full GWAS SNP list and allowed it to carry out 100,000 permutations, matching selected loci in terms of gene count, SNP density and total number of SNPs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

AUTHOR LIST

Lars G Fritsche [1,2, *], Wei Chen [2,3,*], Matthew Schu [4,*], Brian L Yaspan [5,6,*], Yi Yu [7,*], Gudmar Thorleifsson [8], Donald J Zack [9,10,11,12], Satoshi Arakawa [13],

[1]Institute of Human Genetics, University of Regensburg, Regensburg, Germany.
[2]Department of Biostatistics, Center for Statistical Genetics, University of Michigan, Ann Arbor, Michigan, USA.
[*]These authors contributed equally to this work.
[3]Division of Pediatric Pulmonary Medicine, Allergy and Immunology, Department of Pediatrics, Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA.
[4]Department of Medicine (Section of Biomedical Genetics), Boston University Schools of Medicine and Public Health, Boston, Massachusetts, USA.
[5]Center for Human Genetics Research, Vanderbilt University Medical Center, Nashville, Tennessee, USA.
[6]Department of Molecular Physiology and Biophysics, Vanderbilt University School of Medicine, Nashville, Tennessee, USA.
[7]Ophthalmic Epidemiology and Genetics Service, Tufts Medical Center, Boston, Massachusetts, USA.
[8]deCODE genetics, Reykjavik, Iceland.
[9]Department of Molecular Biology and Genetics, Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.
[10]Department of Genetics, Institut de la Vision, UPMC Univ Paris 06, UMR_S 968, Paris, France.
[11]Department of Neuroscience, Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.

Valentina Cipriani [14], Stephan Ripke [15,16], Robert P Igo, Jr. [17,18], Gabriëlle H S Buitendijk [19,20], Xueling Sim [2,21], Daniel E Weeks [22,23], Robyn H Guymer [24], Joanna E Merriam [25], Peter J Francis [26], Gregory Hannum [27], Anita Agarwal [28,29], Ana Maria Armbrecht [30], Isabelle Audo [10,31,32,33], Tin Aung [34,35], Gaetano R Barile [25], Mustapha Benchaboune [36], Alan C Bird [14], Paul N Bishop [37,38], Kari E Branham [39], Matthew Brooks [40], Alexander J Brucker [41], William H Cade [42,43], Melinda S Cain [24], Peter A Campochiaro [11,44], Chi-Chao Chan [45], Ching-Yu Cheng [34,35,46,47], Emily Y Chew [48], Kimberly A Chin [7], Itay Chowers [49], David G Clayton [50], Radu Cojocaru [40], Yvette P Conley [51], Belinda K Cornes [34], Mark J Daly [15], Baljean Dhillon [30], Albert O Edwards [52], Evangelos Evangelou [53], Jesen Fagerness [54,55], Henry A Ferreyra [56], James S Friedman [40], Asbjorg Geirsdottir [57],

[12]Institute of Genetic Medicine, Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.
[13]Laboratory for Genotyping Development, Research Group for Genotyping, Center for Genomic Medicine (CGM), RIKEN, Yokohama, Japan.
[14]Moorfields Eye Hospital and Institute of Ophthalmology, University College London, London, UK.
[15]Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, Massachusetts, USA.
[16]Stanley Center for Psychiatric Research, Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge, Massachusetts, USA.
[17]Department of Epidemiology, Case Western Reserve University, Cleveland, Ohio, USA.
[18]Department of Biostatistics, Case Western Reserve University, Cleveland, Ohio, USA.
[19]Department of Epidemiology, Erasmus Medical Center, Rotterdam, the Netherlands.
[20]Department of Ophthalmology, Erasmus Medical Center, Rotterdam, the Netherlands.
[21]Centre for Molecular Epidemiology, National University of Singapore, Singapore, Singapore.
[22]Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania, USA.
[23]Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania, USA.
[24]Centre for Eye Research Australia, University of Melbourne, Royal Victorian Eye and Ear Hospital, East Melbourne, Australia.
[25]Department of Ophthalmology, Columbia University, New York, New York, USA.
[26]Macular Degeneration Center, Casey Eye Institute, Oregon Health & Science University, Portland, Oregon, USA.
[27]Department of Bioengineering, University of California San Diego, La Jolla, California, USA.
[28]Vanderbilt Eye Institute, Vanderbilt University Medical Center, Nashville, Tennessee, USA.
[29]Department of Ophthalmology & Visual Sciences, Vanderbilt University School of Medicine, Nashville, Tennessee, USA.
[30]Department of Ophthalmology, University of Edinburgh and Princess Alexandra Eye Pavilion, Edinburgh, UK.
[31]INSERM, U968, Paris, France.
[32]CNRS, UMR_7210, Paris, France.
[33]Institute of Ophthalmology, University College London, London, UK.
[34]Singapore Eye Research Institute, Singapore National Eye Centre, Singapore, Singapore.
[35]Department of Ophthalmology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore.
[36]Centre Hospitalier National d'Ophtalmologie des Quinze-Vingts, INSERM-DHOS CIC 503, Paris, France.
[37]School of Biomedicine, Faculty of Medical and Human Sciences, University of Manchester, Manchester, UK.
[38]Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK.
[39]Department of Ophthalmology and Visual Sciences, University of Michigan, Ann Arbor, Michigan, USA.
[40]Neurobiology Neurodegeneration & Repair Laboratory (N-NRL), National Eye Institute, National Institutes of Health, Bethesda, Maryland, USA.
[41]Penn Presbyterian Medical Center, Scheie Eye Institute, Philadelphia, Pennsylvania, USA.
[42]John P. Hussman Institute for Human Genomics, University of Miami Miller School of Medicine, Miami, Florida, USA.
[43]Dr. John T. Macdonald Foundation Department of Human Genetics, University of Miami Miller School of Medicine, Miami, Florida, USA.
[44]Department of Ophthalmology, Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.
[45]Immunopathology Section, Laboratory of Immunology, National Eye Institute, National Institutes of Health, Bethesda, Maryland, USA.
[46]Saw Swee Hock School of Public Health, National University of Singapore, Singapore, Singapore.
[47]Centre for Quantitative Medicine, Office of Clinical Sciences, Duke-NUS Graduate Medical School, Singapore, Singapore.
[48]Division of Epidemiology and Clinical Applications, the Clinical Trials Branch, National Eye Institute, National Institutes of Health, Bethesda, Maryland, USA.
[49]Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel.
[50]Department of Medical Genetics, Cambridge Institute for Medical Research, University of Cambridge, Cambridge, UK.
[51]Department of Health Promotion and Development, School of Nursing, University of Pittsburgh, Pittsburgh, Pennsylvania, USA.
[52]Institute for Molecular Biology, University of Oregon, Eugene, Oregon, USA.
[53]Department of Hygiene and Epidemiology, University of Ioannina Medical School, Ioannina, Greece.
[54]Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts, USA.
[55]Program in Medical and Population Genetics, Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge, Massachusetts, USA.

Ronnie J George [58], Christian Gieger [59], Neel Gupta [40], Stephanie A Hagstrom [60], Simon P Harding [61], Christos Haritoglou [62], John R Heckenlively [39], Frank G Holz [63], Guy Hughes [56,64], John P A Ioannidis [65,66,67], Tatsuro Ishibashi [68], Peronne Joseph [17,18], Gyungah Jun [4,69,70], Yoichiro Kamatani [71], Nicholas Katsanis [72,73,74], Claudia N Keilhauer [75], Jane C Khan [50,76,77], Ivana K Kim [78,79], Yutaka Kiyohara [80], Barbara E K Klein [81], Ronald Klein [81], Jaclyn L Kovach [82], Igor Kozak [56], Clara J Lee [56,64], Kristine E Lee [81], Peter Lichtner [83], Andrew J Lotery [84], Thomas Meitinger [83,85], Paul Mitchell [86], Saddek Mohand-Saïd [31,32,36,87], Anthony T Moore [14], Denise J Morgan [88], Margaux A Morrison [88], Chelsea E Myers [81], Adam C Naj [42,43], Yusuke Nakamura [89], Yukinori Okada [90], Anton Orlin [91], M Carolina Ortube [92,93], Mohammad I Othman [39], Chris Pappas [88], Kyu Hyung Park [94], Gayle J T Pauer [60], Neal S Peachey [60,95], Olivier Poch [96], Rinki Ratna Priya [40], Robyn Reynolds [7], Andrea J Richardson [24], Raymond Ripp [96], Guenther Rudolph [62], Euijung Ryu [97], José-Alain Sahel [10,31,32,33,36,98,99], Debra A Schaumberg [78,100],

[56]Department of Ophthalmology and Shiley Eye Center, University of California San Diego, La Jolla, California, USA.
[57]Department of Ophthalmology, National University Hospital, Reykjavik, Iceland.
[58]Department of Glaucoma, Vision Research Foundation, Sankara Nethralaya, Chennai, India.
[59]Institute of Genetic Epidemiology, Helmholtz Zentrum München, Deutsches Forschungszentrum für Gesundheit und Umwelt, Neuherberg, Germany.
[60]Cole Eye Institute, Cleveland Clinic Foundation, Cleveland, Ohio, USA.
[61]Department of Eye and Vision Science, Institute of Ageing and Chronic Disease, University of Liverpool, Liverpool, UK.
[62]Augenklinik, Ludwig-Maximilians-Universität München, München, Germany.
[63]Department of Ophthalmology, University of Bonn, Bonn, Germany.
[64]Institute for Genomic Medicine, University of California San Diego, La Jolla, California, USA.
[65]Stanford Prevention Research Center, Department of Medicine, Stanford University School of Medicine, Stanford, California, USA.
[66]Department of Health Research and Policy, Stanford University School of Medicine, Stanford, California, USA.
[67]Department of Statistics, Stanford University School of Humanities and Sciences, Stanford, California, USA.
[68]Department of Ophthalmology, Graduate School of Medical Science, Kyushu University, Fukuoka, Japan.
[69]Department of Ophthalmology, Boston University Schools of Medicine and Public Health, Boston, Massachusetts, USA.
[70]Department of Biostatistics, Boston University Schools of Medicine and Public Health, Boston, Massachusetts, USA.
[71]Fondation Jean Dausset, Centre d'Etude du Polymorphisme Humain (CEPH), Paris, France.
[72]Center for Human Disease Modeling, Duke University, Durham, North Carolina, USA.
[73]Department of Cell Biology, Duke University, Durham, North Carolina, USA.
[74]Department of Pediatrics, Duke University, Durham, North Carolina, USA.
[75]Department of Ophthalmology, Julius-Maximilians-Universität, Würzburg, Germany.
[76]Department of Ophthalmology, Royal Perth Hospital, Perth, Australia.
[77]Centre for Ophthalmology and Visual Science, University of Western Australia, Perth, Australia.
[78]Department of Ophthalmology, Harvard Medical School, Boston, Massachusetts, USA.
[79]Massachusetts Eye and Ear Infirmary, Boston, Massachusetts, USA.
[80]Department of Environmental Medicine, Graduate School of Medical Science, Kyushu University, Fukuoka, Japan.
[81]Department of Ophthalmology and Visual Sciences, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, USA.
[82]Bascom Palmer Eye Institute, University of Miami, Miller School of Medicine, Miami, Florida, USA.
[83]Institute of Human Genetics, Helmholtz Zentrum München, Deutsches Forschungszentrum für Gesundheit und Umwelt, Neuherberg, Germany.
[84]Faculty of Medicine, Clinical and Experimental Sciences, University of Southampton, Southampton, UK.
[85]Institute of Human Genetics, Technische Universität München, München, Germany.
[86]Centre for Vision Research, Department of Ophthalmology and the Westmead Millennium Institute, University of Sydney, Sydney, Australia.
[87]Department of Therapeutics, Institut de la Vision, UPMC Univ Paris 06, UMR_S 968, Paris, France.
[88]Department of Ophthalmology and Visual Sciences, University of Utah, John A. Moran Eye Center, Salt Lake City, Utah, USA.
[89]Laboratory of Molecular Medicine, Human Genome Center, Institute of Medical Science, University of Tokyo, Tokyo, Japan.
[90]Laboratory for Statistical Analysis, Center for Genomic Medicine (CGM), RIKEN, Yokohama, Japan.
[91]Department of Ophthalmology Weill Cornell Medical College, Weill Cornell Medical College, New York, New York, USA.
[92]Department of Ophthalmology, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, USA.
[93]Jules Stein Eye Institute, Los Angeles, California, USA.
[94]Department of Ophthalmology, Seoul National University Bundang Hospital, Kyeounggi, Rep. of Korea.
[95]Research Service, Louis Stokes Veteran Affairs Medical Center, Cleveland, Ohio, USA.
[96]Laboratory of Integrative Bioinformatics and Genomics, IGBMC, Illkirch, France.

Hendrik P N Scholl [44,63], Stephen G Schwartz [82], William K Scott [42,43], Humma Shahid [50,101], Haraldur Sigurdsson [57,102], Giuliana Silvestri [103], Theru A Sivakumaran [104], R Theodore Smith [25,105], Lucia Sobrin [78,79], Eric H Souied [106], Dwight E Stambolian [107], Hreinn Stefansson [8], Gwen M Sturgill-Short [95], Atsushi Takahashi [90], Nirubol Tosakulwong [97], Barbara J Truitt [17,18], Evangelia E Tsironi [108], André G Uitterlinden [19,109], Cornelia M van Duijn [19], Lingam Vijaya [58], Johannes R Vingerling [19,20], Eranga N Vithana [34,35], Andrew R Webster [14], H.-Erich Wichmann [110,111,112,113], Thomas W Winkler [114], Tien Y Wong [24,34,35], Alan F Wright [115], Diana Zelenika [116], Li Zhang [56,64,117], Ling Zhao [56,64], Kang Zhang [56,64,117], Michael L Klein [26], Gregory S Hageman [88,118], G Mark Lathrop [71,116], Kari Stefansson [8,102], Rando Allikmets [25,119,+], Paul N Baird [24,+], Michael B Gorin [92,93,120,+], Jie Jin Wang [24,86,+], Caroline C W Klaver [19,20,+], Johanna M Seddon [7,121,+], Margaret A Pericak-Vance [42,43,+], Sudha K Iyengar [17,18,122,123,124,+], John R W Yates [14,50,+], Anand Swaroop [39,40,+], Bernhard H F Weber [1,+], Michiaki Kubo [13,+], Margaret M DeAngelis [88,+], Thierry Léveillard [10,31,32,+], Unnur Thorsteinsdottir [8,102,+], Jonathan L Haines [5,6,+], Lindsay A Farrer [4,69,70,125,126,+], Iris M Heid [59,114,+], Gonçalo R Abecasis [2,+]

AFFILIATIONS

[1]Institute of Human Genetics, University of Regensburg, Regensburg, Germany.

[97]Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, Minnesota, USA.
[98]Fondation Ophtalmologique Adolphe de Rothschild, Paris, France.
[99]Académie des Sciences–Institut de France, Paris, France.
[100]Division of Preventive Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA.
[101]Department of Ophthalmology, Addenbrooke's Hospital, Cambridge, UK.
[102]Faculty of Medicine, University of Iceland, Reykjavik, Iceland.
[103]Centre for Vision and Vascular Science, Queen's University, Belfast, UK.
[104]Division of Human Genetics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA.
[105]Department of Biomedical Engineering, Columbia University, New York, New York, USA.
[106]Hôpital Intercommunal de Créteil, Hôpital Henri Mondor, Université Paris Est, Créteil, France.
[107]Department of Ophthalmology and Genetics, University of Pennsylvania, Philadelphia, Pennsylvania, USA.
[108]Department of Ophthalmology, University of Thessaly School of Medicine, Larissa, Greece.
[109]Department of Internal Medicine, Erasmus Medical Center, Rotterdam, the Netherlands.
[110]Institute of Epidemiology I, Helmholtz Zentrum München, Deutsches Forschungszentrum für Gesundheit und Umwelt, Neuherberg, Germany.
[111]Institute of Medical Informatics, Ludwig-Maximilians-Universität, and Klinikum Grosshadern, München, Germany.
[112]Institute of Biometry, Ludwig-Maximilians-Universität, and Klinikum Grosshadern, München, Germany.
[113]Institute of Epidemiology, Ludwig-Maximilians-Universität, and Klinikum Grosshadern, München, Germany.
[114]Department of Epidemiology and Preventive Medicine, Regensburg University Medical Center, Regensburg, Germany.
[115]Medical Research Council Human Genetics Unit, Institute of Genetics and Molecular Medicine, Edinburgh, UK.
[116]Centre National de Génotypage, CEA - IG, Evry, France.
[117]Molecular Medicine Research Center and Department of Ophthalmology, West China Hospital, Sichuan University, Chengdu, China.
[118]Center for Translational Medicine, University of Utah, John A. Moran Eye Center, Salt Lake City, Utah, USA.
[119]Department of Pathology & Cell Biology, Columbia University, New York, New York, USA.
[+]These authors share starred senior authorship. They directed the project or one of its major component studies.
[120]Department of Human Genetics, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, USA.
[121]Tufts University School of Medicine, Boston, Massachusetts, USA.
[122]Department of Genetics, Case Western Reserve University, Cleveland, Ohio, USA.
[123]Department of Ophthalmology, Case Western Reserve University, Cleveland, Ohio, USA.
[124]Department of Clinical Investigation, Case Western Reserve University, Cleveland, Ohio, USA.
[125]Department of Neurology, Boston University Schools of Medicine and Public Health, Boston, Massachusetts, USA.
[126]Department of Epidemiology, Boston University Schools of Medicine and Public Health, Boston, Massachusetts, USA.

[2]Department of Biostatistics, Center for Statistical Genetics, University of Michigan, Ann Arbor, Michigan, USA.
[3]Division of Pediatric Pulmonary Medicine, Allergy and Immunology, Department of Pediatrics, Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA.
[4]Department of Medicine (Section of Biomedical Genetics), Boston University Schools of Medicine and Public Health, Boston, Massachusetts, USA.
[5]Center for Human Genetics Research, Vanderbilt University Medical Center, Nashville, Tennessee, USA.
[6]Department of Molecular Physiology and Biophysics, Vanderbilt University School of Medicine, Nashville, Tennessee, USA.
[7]Ophthalmic Epidemiology and Genetics Service, Tufts Medical Center, Boston, Massachusetts, USA.
[8]deCODE genetics, Reykjavik, Iceland.
[9]Department of Molecular Biology and Genetics, Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.
[10]Department of Genetics, Institut de la Vision, UPMC Univ Paris 06, UMR_S 968, Paris, France.
[11]Department of Neuroscience, Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.
[12]Institute of Genetic Medicine, Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.
[13]Laboratory for Genotyping Development, Research Group for Genotyping, Center for Genomic Medicine (CGM), RIKEN, Yokohama, Japan.
[14]Moorfields Eye Hospital and Institute of Ophthalmology, University College London, London, UK.
[15]Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, Massachusetts, USA.
[16]Stanley Center for Psychiatric Research, Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge, Massachusetts, USA.
[17]Department of Epidemiology, Case Western Reserve University, Cleveland, Ohio, USA.
[18]Department of Biostatistics, Case Western Reserve University, Cleveland, Ohio, USA.
[19]Department of Epidemiology, Erasmus Medical Center, Rotterdam, the Netherlands.
[20]Department of Ophthalmology, Erasmus Medical Center, Rotterdam, the Netherlands.
[21]Centre for Molecular Epidemiology, National University of Singapore, Singapore, Singapore.
[22]Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania, USA.
[23]Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania, USA.
[24]Centre for Eye Research Australia, University of Melbourne, Royal Victorian Eye and Ear Hospital, East Melbourne, Australia.
[25]Department of Ophthalmology, Columbia University, New York, New York, USA.
[26]Macular Degeneration Center, Casey Eye Institute, Oregon Health & Science University, Portland, Oregon, USA.

[27]Department of Bioengineering, University of California San Diego, La Jolla, California, USA.
[28]Vanderbilt Eye Institute, Vanderbilt University Medical Center, Nashville, Tennessee, USA.
[29]Department of Ophthalmology & Visual Sciences, Vanderbilt University School of Medicine, Nashville, Tennessee, USA.
[30]Department of Ophthalmology, University of Edinburgh and Princess Alexandra Eye Pavilion, Edinburgh, UK.
[31]INSERM, U968, Paris, France.
[32]CNRS, UMR_7210, Paris, France.
[33]Institute of Ophthalmology, University College London, London, UK.
[34]Singapore Eye Research Institute, Singapore National Eye Centre, Singapore, Singapore.
[35]Department of Ophthalmology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore.
[36]Centre Hospitalier National d'Ophtalmologie des Quinze-Vingts, INSERM-DHOS CIC 503, Paris, France.
[37]School of Biomedicine, Faculty of Medical and Human Sciences, University of Manchester, Manchester, UK.
[38]Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK.
[39]Department of Ophthalmology and Visual Sciences, University of Michigan, Ann Arbor, Michigan, USA.
[40]Neurobiology Neurodegeneration & Repair Laboratory (N-NRL), National Eye Institute, National Institutes of Health, Bethesda, Maryland, USA.
[41]Penn Presbyterian Medical Center, Scheie Eye Institute, Philadelphia, Pennsylvania, USA.
[42]John P. Hussman Institute for Human Genomics, University of Miami Miller School of Medicine, Miami, Florida, USA.
[43]Dr. John T. Macdonald Foundation Department of Human Genetics, University of Miami Miller School of Medicine, Miami, Florida, USA.
[44]Department of Ophthalmology, Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.
[45]Immunopathology Section, Laboratory of Immunology, National Eye Institute, National Institutes of Health, Bethesda, Maryland, USA.
[46]Saw Swee Hock School of Public Health, National University of Singapore, Singapore, Singapore.
[47]Centre for Quantitative Medicine, Office of Clinical Sciences, Duke-NUS Graduate Medical School, Singapore, Singapore.
[48]Division of Epidemiology and Clinical Applications, the Clinical Trials Branch, National Eye Institute, National Institutes of Health, Bethesda, Maryland, USA.
[49]Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel.
[50]Department of Medical Genetics, Cambridge Institute for Medical Research, University of Cambridge, Cambridge, UK.

[51]Department of Health Promotion and Development, School of Nursing, University of Pittsburgh, Pittsburgh, Pennsylvania, USA.
[52]Institute for Molecular Biology, University of Oregon, Eugene, Oregon, USA.
[53]Department of Hygiene and Epidemiology, University of Ioannina Medical School, Ioannina, Greece.
[54]Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts, USA.
[55]Program in Medical and Population Genetics, Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge, Massachusetts, USA.
[56]Department of Ophthalmology and Shiley Eye Center, University of California San Diego, La Jolla, California, USA.
[57]Department of Ophthalmology, National University Hospital, Reykjavik, Iceland.
[58]Department of Glaucoma, Vision Research Foundation, Sankara Nethralaya, Chennai, India.
[59]Institute of Genetic Epidemiology, Helmholtz Zentrum München, Deutsches Forschungszentrum für Gesundheit und Umwelt, Neuherberg, Germany.
[60]Cole Eye Institute, Cleveland Clinic Foundation, Cleveland, Ohio, USA.
[61]Department of Eye and Vision Science, Institute of Ageing and Chronic Disease, University of Liverpool, Liverpool, UK.
[62]Augenklinik, Ludwig-Maximilians-Universität München, München, Germany.
[63]Department of Ophthalmology, University of Bonn, Bonn, Germany.
[64]Institute for Genomic Medicine, University of California San Diego, La Jolla, California, USA.
[65]Stanford Prevention Research Center, Department of Medicine, Stanford University School of Medicine, Stanford, California, USA.
[66]Department of Health Research and Policy, Stanford University School of Medicine, Stanford, California, USA.
[67]Department of Statistics, Stanford University School of Humanities and Sciences, Stanford, California, USA.
[68]Department of Ophthalmology, Graduate School of Medical Science, Kyushu University, Fukuoka, Japan.
[69]Department of Ophthalmology, Boston University Schools of Medicine and Public Health, Boston, Massachusetts, USA.
[70]Department of Biostatistics, Boston University Schools of Medicine and Public Health, Boston, Massachusetts, USA.
[71]Fondation Jean Dausset, Centre d'Etude du Polymorphisme Humain (CEPH), Paris, France.
[72]Center for Human Disease Modeling, Duke University, Durham, North Carolina, USA.
[73]Department of Cell Biology, Duke University, Durham, North Carolina, USA.
[74]Department of Pediatrics, Duke University, Durham, North Carolina, USA.
[75]Department of Ophthalmology, Julius-Maximilians-Universität, Würzburg, Germany.
[76]Department of Ophthalmology, Royal Perth Hospital, Perth, Australia.
[77]Centre for Ophthalmology and Visual Science, University of Western Australia, Perth, Australia.
[78]Department of Ophthalmology, Harvard Medical School, Boston, Massachusetts, USA.

[79]Massachusetts Eye and Ear Infirmary, Boston, Massachusetts, USA.
[80]Department of Environmental Medicine, Graduate School of Medical Science, Kyushu University, Fukuoka, Japan.
[81]Department of Ophthalmology and Visual Sciences, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, USA.
[82]Bascom Palmer Eye Institute, University of Miami, Miller School of Medicine, Miami, Florida, USA.
[83]Institute of Human Genetics, Helmholtz Zentrum München, Deutsches Forschungszentrum für Gesundheit und Umwelt, Neuherberg, Germany.
[84]Faculty of Medicine, Clinical and Experimental Sciences, University of Southampton, Southampton, UK.
[85]Institute of Human Genetics, Technische Universität München, München, Germany.
[86]Centre for Vision Research, Department of Ophthalmology and the Westmead Millennium Institute, University of Sydney, Sydney, Australia.
[87]Department of Therapeutics, Institut de la Vision, UPMC Univ Paris 06, UMR_S 968, Paris, France.
[88]Department of Ophthalmology and Visual Sciences, University of Utah, John A. Moran Eye Center, Salt Lake City, Utah, USA.
[89]Laboratory of Molecular Medicine, Human Genome Center, Institute of Medical Science, University of Tokyo, Tokyo, Japan.
[90]Laboratory for Statistical Analysis, Center for Genomic Medicine (CGM), RIKEN, Yokohama, Japan.
[91]Department of Ophthalmology Weill Cornell Medical College, Weill Cornell Medical College, New York, New York, USA.
[92]Department of Ophthalmology, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, USA.
[93]Jules Stein Eye Institute, Los Angeles, California, USA.
[94]Department of Ophthalmology, Seoul National University Bundang Hospital, Kyeounggi, Rep. of Korea.
[95]Research Service, Louis Stokes Veteran Affairs Medical Center, Cleveland, Ohio, USA.
[96]Laboratory of Integrative Bioinformatics and Genomics, IGBMC, Illkirch, France.
[97]Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, Minnesota, USA.
[98]Fondation Ophtalmologique Adolphe de Rothschild, Paris, France.
[99]Académie des Sciences–Institut de France, Paris, France.
[100]Division of Preventive Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA.
[101]Department of Ophthalmology, Addenbrooke's Hospital, Cambridge, UK.
[102]Faculty of Medicine, University of Iceland, Reykjavik, Iceland.
[103]Centre for Vision and Vascular Science, Queen's University, Belfast, UK.
[104]Division of Human Genetics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA.
[105]Department of Biomedical Engineering, Columbia University, New York, New York, USA.

[106]Hôpital Intercommunal de Créteil, Hôpital Henri Mondor, Université Paris Est, Créteil, France.
[107]Department of Ophthalmology and Genetics, University of Pennsylvania, Philadelphia, Pennsylvania, USA.
[108]Department of Ophthalmology, University of Thessaly School of Medicine, Larissa, Greece.
[109]Department of Internal Medicine, Erasmus Medical Center, Rotterdam, the Netherlands.
[110]Institute of Epidemiology I, Helmholtz Zentrum München, Deutsches Forschungszentrum für Gesundheit und Umwelt, Neuherberg, Germany.
[111]Institute of Medical Informatics, Ludwig-Maximilians-Universität, and Klinikum Grosshadern, München, Germany.
[112]Institute of Biometry, Ludwig-Maximilians-Universität, and Klinikum Grosshadern, München, Germany.
[113]Institute of Epidemiology, Ludwig-Maximilians-Universität, and Klinikum Grosshadern, München, Germany.
[114]Department of Epidemiology and Preventive Medicine, Regensburg University Medical Center, Regensburg, Germany.
[115]Medical Research Council Human Genetics Unit, Institute of Genetics and Molecular Medicine, Edinburgh, UK.
[116]Centre National de Génotypage, CEA - IG, Evry, France.
[117]Molecular Medicine Research Center and Department of Ophthalmology, West China Hospital, Sichuan University, Chengdu, China.
[118]Center for Translational Medicine, University of Utah, John A. Moran Eye Center, Salt Lake City, Utah, USA.
[119]Department of Pathology & Cell Biology, Columbia University, New York, New York, USA.
[120]Department of Human Genetics, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, USA.
[121]Tufts University School of Medicine, Boston, Massachusetts, USA.
[122]Department of Genetics, Case Western Reserve University, Cleveland, Ohio, USA.
[123]Department of Ophthalmology, Case Western Reserve University, Cleveland, Ohio, USA.
[124]Department of Clinical Investigation, Case Western Reserve University, Cleveland, Ohio, USA.
[125]Department of Neurology, Boston University Schools of Medicine and Public Health, Boston, Massachusetts, USA.
[126]Department of Epidemiology, Boston University Schools of Medicine and Public Health, Boston, Massachusetts, USA.
[*]These authors contributed equally to this work.
[+]These authors share starred senior authorship. They directed the project or one of its major component studies.

AUTHOR CONTRIBUTIONS

AMD Gene Analysis Committee: L.G.F., W.C., M.S., B.L.Y., Y.Y., L.A.F., I.M.H. (co-lead), G.R.A. (co-lead);

AMD Gene Steering Committee: B.H.F.W. (chair, senior executive committee), G.R.A. (senior executive committee), M.M.D. (senior executive committee), J.L.H. (senior executive committee), S.K.I. (senior executive committee), M.A.P. (senior executive committee), R.A., P.N.Ba., C.C.W.K., B.E.K.K., M.L.K., M.K., T.L., J.M.S., U.T., D.E.W., J.R.W.Y., K.Z.;

AMD-EU-JHU Study: D.J.Z., I.A., M.Be., A.C.B., P.A.C., I.C., F.G.H., Y.Ka., N.K., A.J.L., S.M., O.P., R.Ri., J-A.S., H.P.N.S., E.H.S., A.R.W., D.Z., G.M.L., T.L. contributed phenotype, genotypes and analysis for the AMD-EU-JHU study;

BDES Study: R.P.I., B.E.K.K., R.K., K.E.L., C.E.M., T.A.S., B.J.T., S.K.I. contributed phenotype, genotypes and analysis for the BDES study;

Blue Mountains Eye Study: X.S., P.M., T.Y.W., J.J.W. contributed phenotype, genotypes and analysis for the BMES study;

BU/Utah Study: M.S., G.S.H., G.J., I.K.K., D.J.M., M.A.M., C.P., K.H.P., D.A.S., G.S., E.E.T., M.M.D., L.A.F. contributed phenotype, genotypes and analysis for the BU/UTAH study;

CCF/VAMC Study: S.A.H., P.J., G.J.T.P., N.S.P., G.M.S., R.P.I., S.K.I. contributed phenotype, genotypes and analysis for the CCF/VAMC study;

CEI Study: P.J.F., M.L.K. contributed phenotype, genotypes and analysis for the CEI study;

Columbia Study: J.E.M., G.R.B., R.T.S., R.A. contributed phenotype, genotypes and analysis for the Columbia study;

deCode: G.T., H.Si., H.St., K.S., U.T. contributed phenotype, genotypes and analysis for the deCode study;

Japan Age Related Eye Diseases Study: S.A., T.I., Y.Ki., Y.N., Y.O., A.T., M.K. contributed phenotype, genotypes and analysis for the JAREDS study;

Melbourne Study: R.H.G., M.R.N.C., A.J.R., P.N.Ba. contributed phenotype, genotypes and analysis for the Melbourne study;

Miami/Vanderbilt Study: B.L.Y., A.A., W.H.C., J.L.K., A.C.N., S.G.S., W.K.S., M.A.P., J.L.H. contributed phenotype, genotypes and analysis for the Miami/Vanderbilt study;

MMAP/NEI Study: W.C., K.E.B., M.Br., A.J.B., C-C.C., E.Y.C., R.C., A.O.E., J.S.F., N.G., J.R.H., A.O., M.I.O., R.R.P., E.R., D.E.S., N.T., A.S., G.R.A. contributed phenotype, genotypes and analysis for the MMAP/NEI study;

Rotterdam Study: G.H.S.B., A.G.U., C.M.v.D., J.R.V., C.C.W.K. contributed phenotype, genotypes and analysis for the Rotterdam study;

SAGE Study: T.A., C-Y.C., B.K.C., E.N.V. contributed phenotype, genotypes and analysis for the SAGe study;

Southern German AMD Study: L.G.F., C.G., C.H., C.N.K., P.L., T.M., G.R., H.-E.W., T.W.W., B.H.F.W., I.M.H. contributed phenotype, genotypes and analysis for the Southern German AMD study;

Tufts/Massachussets General Hospital Study: Y.Y., S.R., K.A.C., M.J.D., E.E., J.F., J.P.A.I., R.Re., L.S., J.M.S. contributed phenotype, genotypes and analysis for the Tufts/MGH study;

U.K. Cambridge/Edinburgh Study: V.C., A.M.A., P.N.Bi., D.G.C., B.D., S.P.H., J.C.K., A.T.M., H.Sh., A.F.W., J.R.W.Y. contributed phenotype, genotypes and analysis for the UK Cambridge/Edinburgh study;

University of Pittsburgh/UCLA Study: D.E.W., Y.P.C., M.C.O., M.B.G. contributed phenotype, genotypes and analysis for the Univ. of Pittsburgh/UCLA study;

UCSD Study: G.Ha., H.F., G.Hu., I.K., C.J.L., L.Zhang, L.Zhao, K.Z. contributed phenotype, genotypes and analysis for the USCD study;

VRF Study: R.J.G., L.V., R.P.I., S.K.I. contributed phenotype, genotypes and analysis for the VRF study;

Gene Expression and RNA-Sequencing Data: These data were contributed and analyzed by M.Br., J.S.F., N.G., R.R.P and A.S.

URLs

METAL, http://www.sph.umich.edu/csg/abecasis/Metal/; R, http://www.R-project.org/; gee, http://CRAN.R-project.org/package=gee; Single Nucleotide Polymorphism Spectral Decomposition, http://gump.qimr.edu.au/general/daleN/SNPSpDlite/; Pre-specified R-scripts, http://www.epi-regensburg.de/wp/genepi-downloads; The 1000 Genomes Project, http://www.1000genomes.org/; The HapMap Project, http://www.hapmap.org/genotypes/; PolyPhen-2, http://genetics.bwh.harvard.edu/pph2/; Ingenuity® Systems, http://www.ingenuity.com; NHGRI GWAS catalog, http://www.genome.gov/gwastudies/, INRICH, http://atgu.mgh.harvard.edu/inrich; Full Result Set, http://www.sph.umich.edu/csg/abecasis/public/amdgene2012/

CONFLICT OF INTEREST STATEMENT

A.A., G.R.A., K.E.B., V.C., Y.P.C., M.J.D., A.O.E., L.G.F., M.B.G., J.L.H., A.T.M., D.A.S., W.K.S., J.M.S., A.S., B.H.F.W., D.E.W., and J.R.W.Y. are co-inventors or beneficiaries of patents related to genetic discoveries in AMD. J.L.H. is a shareholder in ArcticDX. S.G.S. is a consultant for Alimera, Bausch + Lomb, and Eyetech; receives

royalties from IC Labs. U.T., K.S., G.T, and H.St. are affiliated and/or employed by deCODE Genetics and own stock and/or stock options in the company. P.M. is on advisory boards for Allergan, Bayer, Novartis, Pfizer and Solvay and has received travel, honorarium and research support from these companies; he has no stocks, equity, contract of employment or named position on company board.

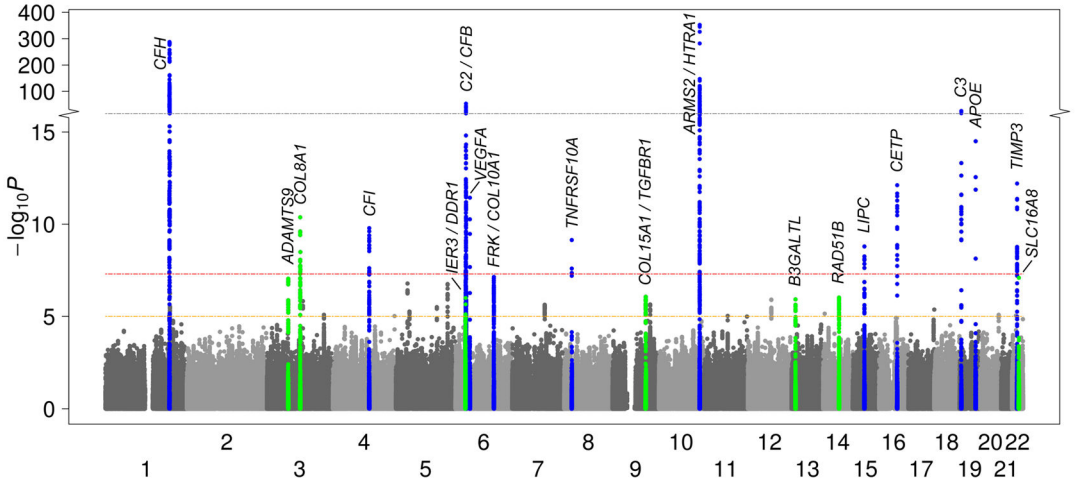

FIGURE 1. Summary of genomewide association scan results

Summary of genomewide association scan results in the discovery GWAS sample. Previously described loci reaching $p < 5\times10^{-8}$ are labeled in blue; new loci reaching $p < 5\times10^{-8}$ for the first time after follow-up are labeled in green.

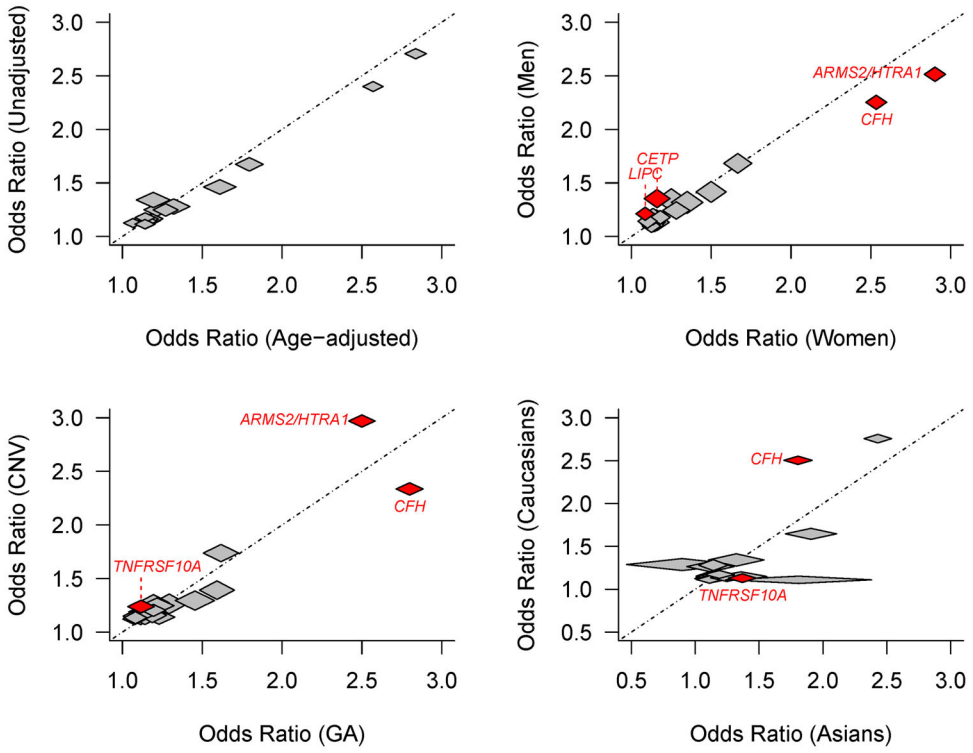

FIGURE 2. Sensitivity analysis

The top left panel compares estimated effect sizes for the original analysis and for an age-adjusted analysis (where age was included as a covariate and samples of unknown age were excluded). The top right panel compares analyses stratified by sex. The bottom left panel evaluates stratification by disease subtype. The bottom right panel evaluates stratification by ethnicity. The size of each marker reflects confidence intervals (with height reflecting confidence interval along the Y axis and width reflecting confidence interval along the X axis). Comparisons reaching $p < 0.05$ are labeled and colored in red.

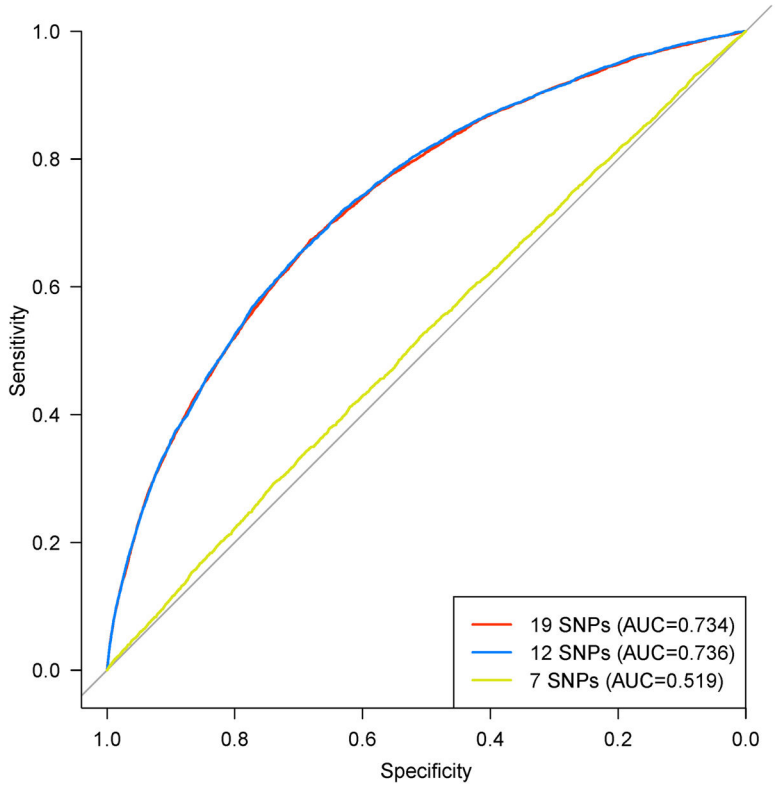

FIGURE 3. Risk score analysis

We calculated a risk score for each individual, defined as the product of the number of risk alleles at each locus and the associated effect size for each allele (measured on the log-odds scale). The plot summarizes the ability of these overall genetic risk scores to distinguish cases and controls.

TABLE 1

Summary of the Samples Used in Genomewide Discovery and Targeted Follow-Up Analyses

For additional details, including a breakdown of the number of cases and controls in individual samples, see Supplementary Table 1. N_{CASES} includes only cases with geographic atrophy, choroidal neovascularization, or both.

Analysis	Contributing Study Groups	N_{CASES}	%Female	%Neovascular Disease	$N_{CONTROLS}$	% Female
Genomewide Discovery	15	7,650	53.9	59.2	51,844	45.2
Targeted Follow-up	18	9,531	56.3	57.8	8,230	53.8
Overall	33	17,181	55.2	58.4	60,074	46.3

TABLE 2

Summary of Loci Reaching Genome-Wide Significance

All results reported here include a genomic control correction for individual studies and also for the final meta-analysis[51].

SNP/Risk Allele	Chromosome, Position	Nearby Genes	EAF	Discovery		Follow-up		Joint		
				P	OR	*P*	OR	*P*	OR	95% CI
Loci Previously Reported With P < 5×10^{-8}										
rs10490924/T	10	124.2 Mb	*ARMS2/HTRA1*	0.30	4×10^{-353}	2.71	2.8×10^{-190}	2.88	4×10^{-540}	2.76	[2.72–2.80]
rs10737680/A	1	196.7 Mb	*CFH*	0.64	1×10^{-283}	2.40	2.7×10^{-152}	2.50	1×10^{-434}	2.43	[2.39–2.47]
rs429608/G	6	31.9 Mb	*C2/CFB*	0.86	2×10^{-54}	1.67	2.4×10^{-37}	1.89	4×10^{-89}	1.74	[1.68–1.79]
rs2230199/C	19	6.7 Mb	*C3*	0.20	2×10^{-26}	1.46	3.4×10^{-17}	1.37	1×10^{-41}	1.42	[1.37–1.47]
rs5749482/G	22	33.1 Mb	*TIMP3*	0.74	6×10^{-13}	1.25	9.7×10^{-17}	1.45	2×10^{-26}	1.31	[1.26–1.36]
rs4420638/A	19	45.4 Mb	*APOE*	0.83	3×10^{-15}	1.34	4.2×10^{-7}	1.25	2×10^{-20}	1.30	[1.24–1.36]
rs1864163/G	16	57 Mb	*CETP*	0.76	8×10^{-13}	1.25	8.7×10^{-5}	1.17	7×10^{-16}	1.22	[1.17–1.27]
rs943080/T	6	43.8 Mb	*VEGFA*	0.51	4×10^{-12}	1.18	1.6×10^{-5}	1.12	9×10^{-16}	1.15	[1.12–1.18]
rs13278062/T	8	23.1 Mb	*TNFRSF10A*	0.48	7×10^{-10}	1.17	6.4×10^{-7}	1.14	3×10^{-15}	1.15	[1.12–1.19]
rs920915/C	15	58.7 Mb	*LIPC*	0.48	2×10^{-9}	1.14	0.004	1.10	3×10^{-11}	1.13	[1.09–1.17]
rs4698775/G	4	110.6 Mb	*CFI*	0.31	2×10^{-10}	1.16	0.025	1.08	7×10^{-11}	1.14	[1.10–1.17]
rs3812111/T	6	116.4 Mb	*COL10A1*	0.64	7×10^{-8}	1.13	0.022	1.06	2×10^{-8}	1.10	[1.07–1.14]
Loci Reaching P < 5×10^{-8} for the First Time										
rs13081855/T	3	99.5 Mb	*COL8A1/FILIP1L*	0.10	4×10^{-11}	1.28	6.0×10^{-4}	1.17	4×10^{-13}	1.23	[1.17–1.29]
rs3130783/A	6	30.8 Mb	*IER3/DDR1*	0.79	1×10^{-6}	1.15	3.5×10^{-6}	1.16	2×10^{-11}	1.16	[1.11–1.20]
rs8135665/T	22	38.5 Mb	*SLC16A8*	0.21	8×10^{-8}	1.16	5.6×10^{-5}	1.13	2×10^{-11}	1.15	[1.11–1.19]
rs334353/T	9	101.9 Mb	*TGFBR1*	0.73	9×10^{-7}	1.13	6.7×10^{-6}	1.13	3×10^{-11}	1.13	[1.10–1.17]
rs8017304/A	14	68.8 Mb	*RAD51B*	0.61	9×10^{-7}	1.11	2.1×10^{-5}	1.11	9×10^{-11}	1.11	[1.08–1.14]
rs6795735/T	3	64.7 Mb	*ADAMTS9/MIR548A2*	0.46	9×10^{-8}	1.13	0.0066	1.07	5×10^{-9}	1.10	[1.07–1.14]
rs9542236/C	13	31.8 Mb	*B3GALTL*	0.44	2×10^{-6}	1.12	0.0018	1.08	2×10^{-8}	1.10	[1.07–1.14]

See Supplementary Table 5 for a summary of all gene name abbreviations used in this Table and elsewhere in the paper. EAF is the allele frequency of the risk increasing allele.

TABLE 3

Pathway Analysis

Ingenuity Canonical Pathways	Enrichment Analysis			
	Nominal p-value	FDR q-value	Molecules	Pathway Size(N_{genes})
Complement System	0.000012	0.0015	*CFI, CFH, C3, CFB**, *C2**,*C4A**, *C4B**	35
Atherosclerosis Signaling	0.00014	0.009	*PLA2G12A, APOC1***, *APOE***, *APOC2***, *APOC4***, *TNFSF14, COL10A1, PLA2G6*	129
VEGF Family Ligand-Receptor Interactions	0.0042	0.150	*VEGFA,PLA2G12A,PLA2G6*	84
Dendritic Cell Maturation	0.0046	0.150	*RELB, ZBTB12, DDR1, COL10A1*	185
Phospholipid Degradation	0.0058	0.151	*PLA2G12A, LIPC, PLA2G6*	102
MIF-mediated Glucocorticoid Regulation	0.0088	0.153	*PLA2G12A, PLA2G6*	42
Inhibition of Angiogenesis by TSP1	0.0093	0.153	*VEGFA,TGFBR1*	39
Fc Epsilon RI Signaling	0.0098	0.153	*VAV1, PLA2G12A, PLA2G6*	111
p38 MAPK Signaling	0.011	0.153	*PLA2G12A, TGFBR1, PLA2G6*	106

* *CFB*, *C2*, *C4A*, and *C4B* all flank rs429608 and thus counted as single hit when determining significance of enrichment.

** *APOC1*, *APOE*, *APOC2*, and *APOC4* all flank rs4420638 and thus counted as single hit when determining significance of enrichment.