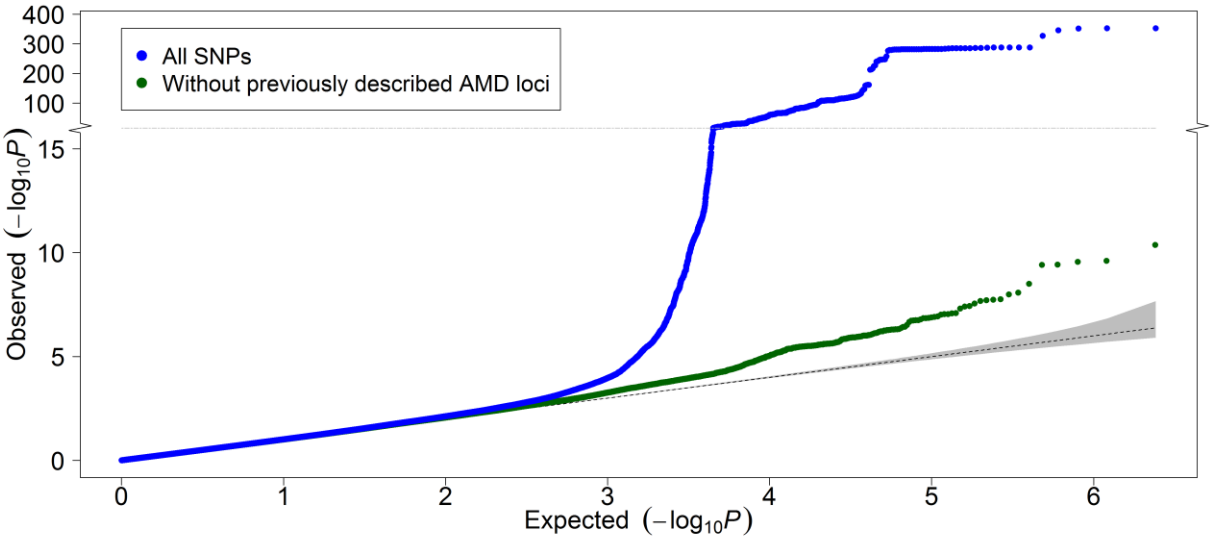
Seven New Loci Associated with Age-Related Macular Degeneration

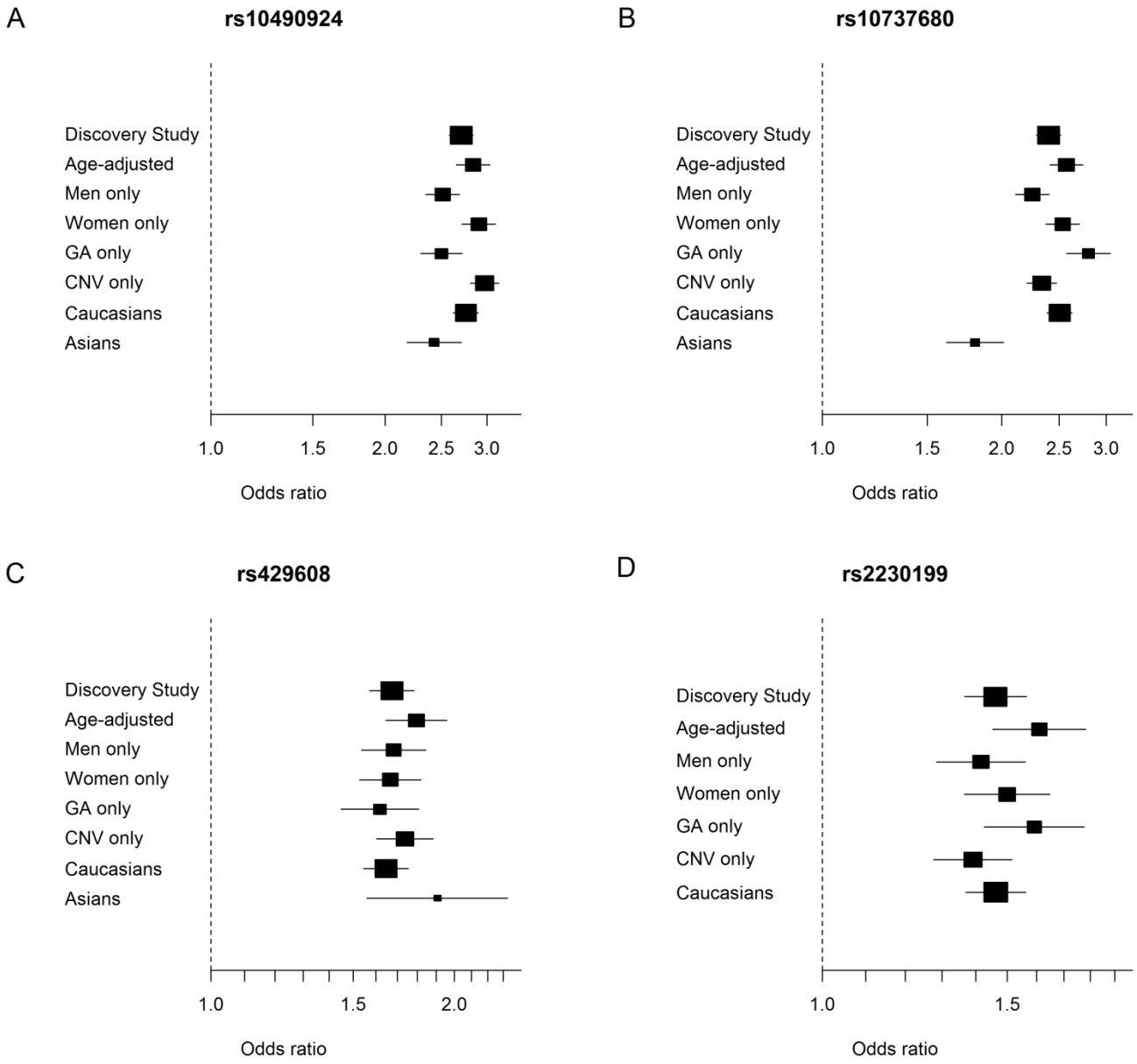
The AMD Gene Consortium

Supplementary Online Material:

SUPPLEMENTARY FIGURE 1. Quantile-Quantile plot. This Q-Q plot compares the actual distribution of p-values with the expected distribution under the null, both for the full set of GWAS results and after excluding variants within 1Mb of known loci.



SUPPLEMENTARY FIGURE 2. Sensitivity analysis for each of the 19 index SNPs. We repeated the original discovery analysis (which compared advanced AMD cases to controls) with an age adjustment (and also excluding subjects whose age was unknown) or stratified by sex, AMD subtype (GA: geographic atrophy; CNV: choroidal neovascularization) or ethnicity. Odds ratios and corresponding 95% confidence intervals are shown with the area of each rectangle representing the precision of the effect estimates ($1/SE^2$).



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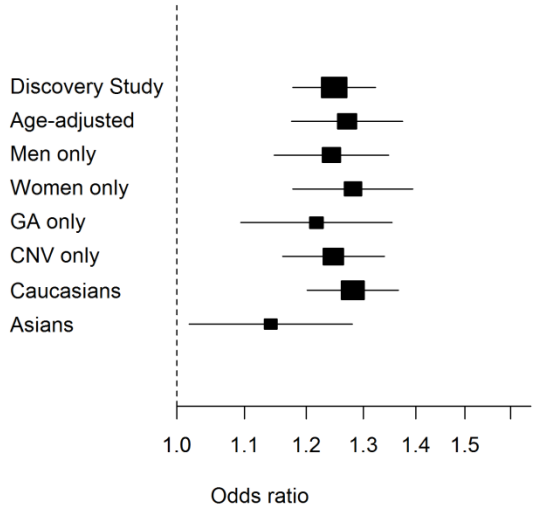
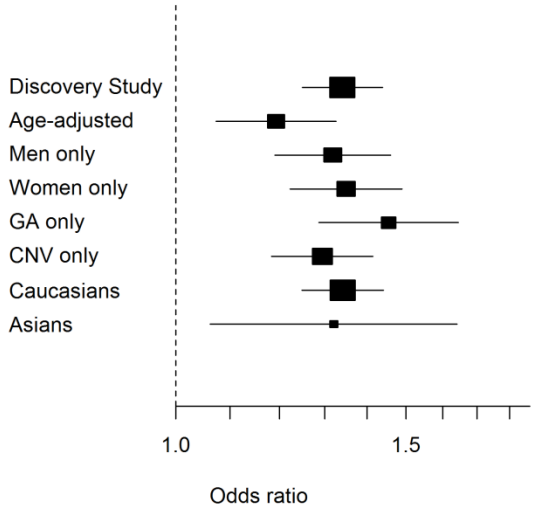
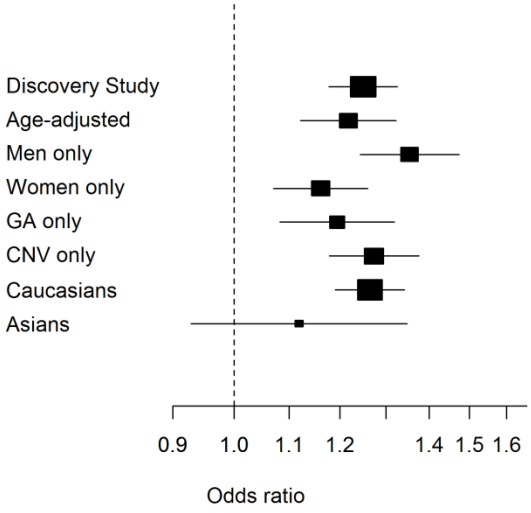

rs5749482
Discovery Study
Age-adjusted
Men only
Women only
GA only
CNV only
Caucasians
Asians
1.0
1.1
1.2
1.3
1.4
1.5
Odds ratio

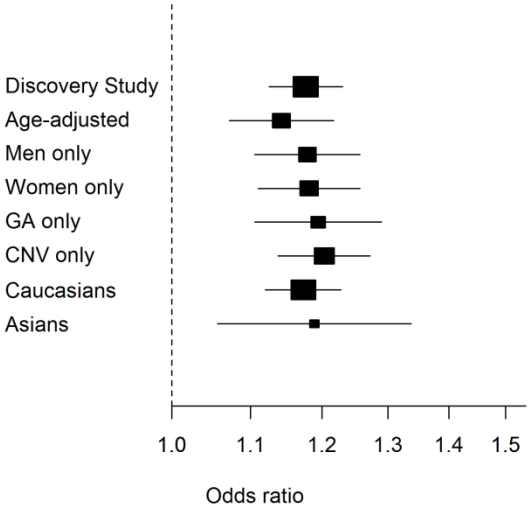
F


rs4420638
Discovery Study
Age-adjusted
Men only
Women only
GA only
CNV only
Caucasians
Asians
1.0
1.5
Odds ratio

G


rs1864163
Discovery Study
Age-adjusted
Men only
Women only
GA only
CNV only
Caucasians
Asians
0.9
1.0
1.1
1.2
1.4
1.5
1.6
Odds ratio

H


rs943080
Discovery Study
Age-adjusted
Men only
Women only
GA only
CNV only
Caucasians
Asians
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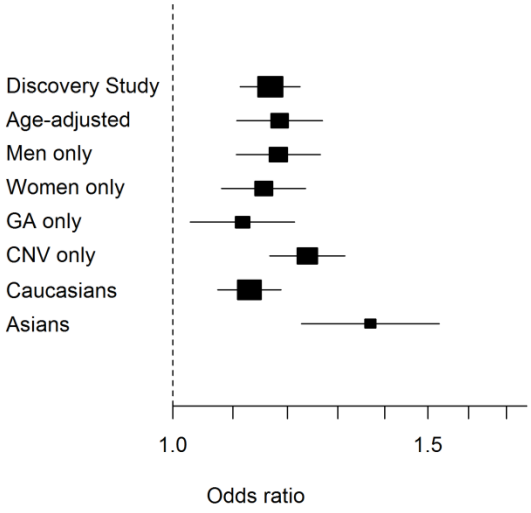
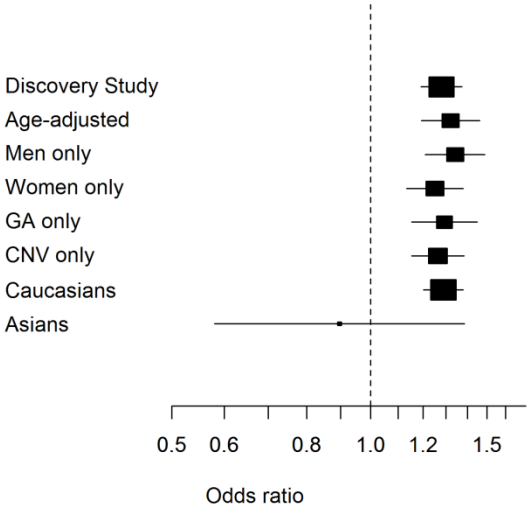
1.1
1.2
1.3
1.4
1.5
Odds ratio

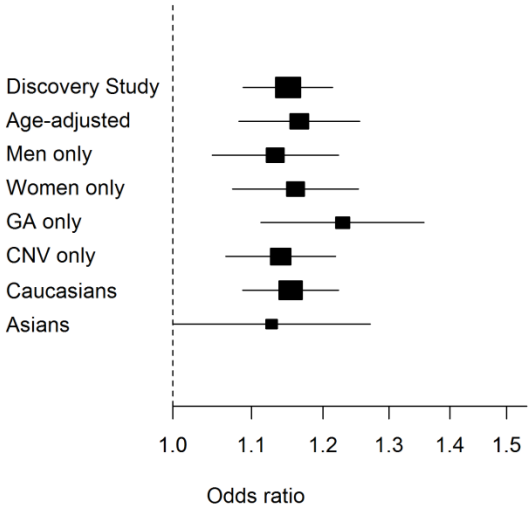
I


rs13278062
Discovery Study
Age-adjusted
Men only
Women only
GA only
CNV only
Caucasians
Asians
1.0
1.5
Odds ratio

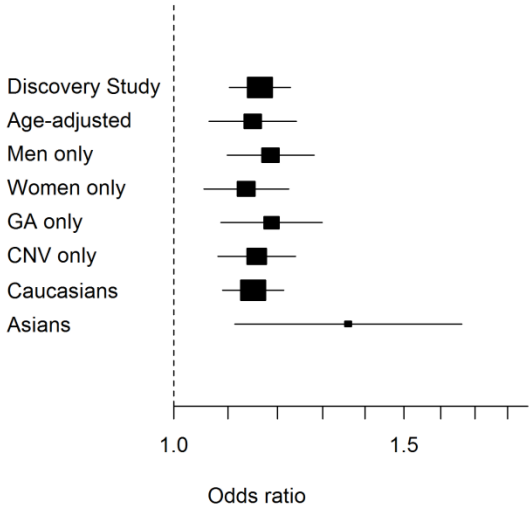
J


rs13081855
Discovery Study
Age-adjusted
Men only
Women only
GA only
CNV only
Caucasians
Asians
0.5
0.6
0.8
1.0
1.2
1.5
Odds ratio

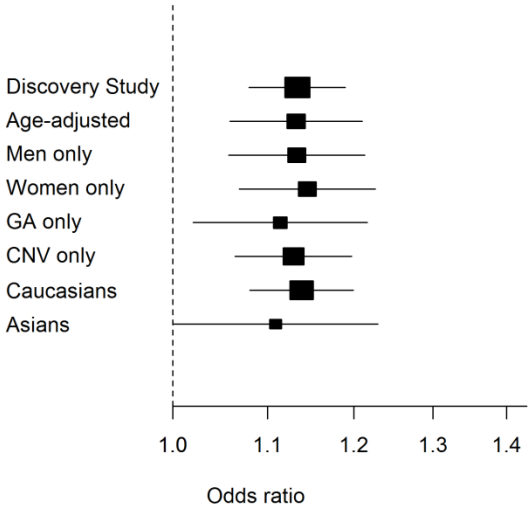
K


rs3130783
Discovery Study
Age-adjusted
Men only
Women only
GA only
CNV only
Caucasians
Asians
1.0
1.1
1.2
1.3
1.4
1.5
Odds ratio

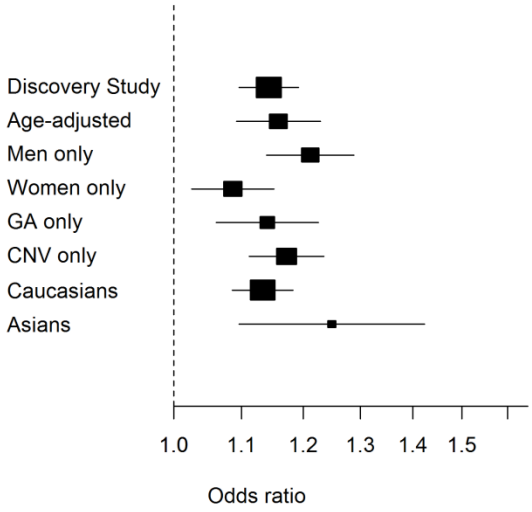
L


rs8135665
Discovery Study
Age-adjusted
Men only
Women only
GA only
CNV only
Caucasians
Asians
1.0
1.5
Odds ratio

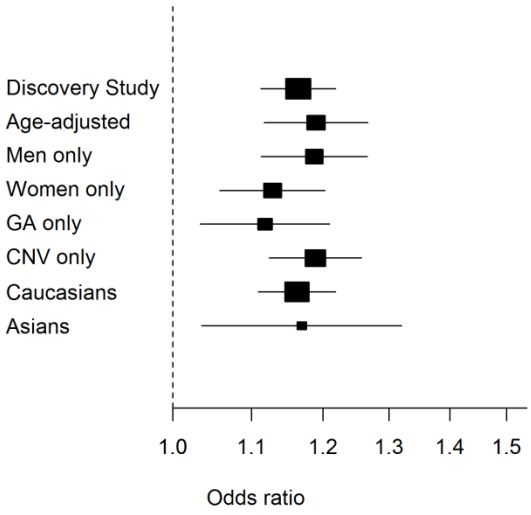
M


rs334353
Discovery Study
Age-adjusted
Men only
Women only
GA only
CNV only
Caucasians
Asians
1.0
1.1
1.2
1.3
1.4
Odds ratio

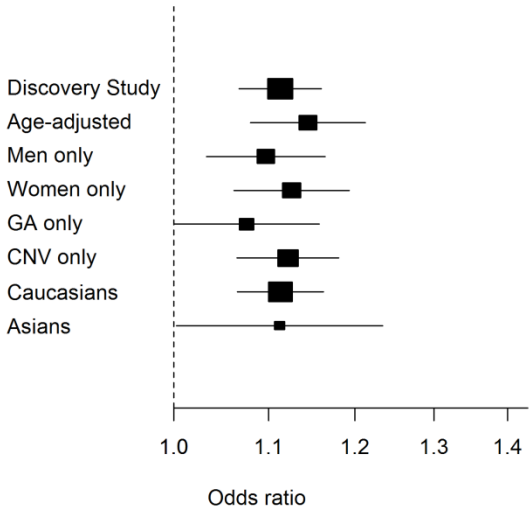
N


rs920915
Discovery Study
Age-adjusted
Men only
Women only
GA only
CNV only
Caucasians
Asians
1.0
1.1
1.2
1.3
1.4
1.5
Odds ratio

O

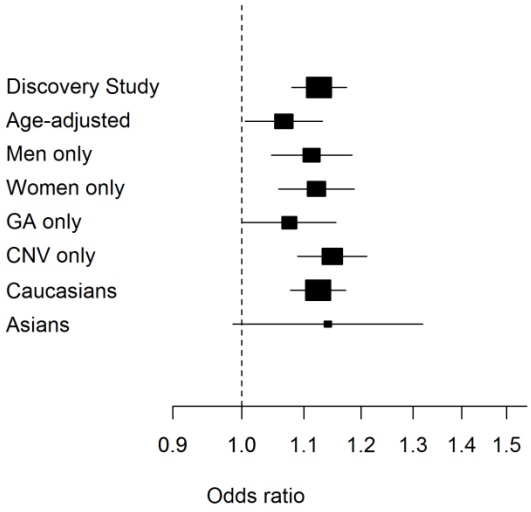

rs4698775
Discovery Study
Age-adjusted
Men only
Women only
GA only
CNV only
Caucasians
Asians
1.0
1.1
1.2
1.3
1.4
1.5
Odds ratio

P


rs8017304
Discovery Study
Age-adjusted
Men only
Women only
GA only
CNV only
Caucasians
Asians
1.0
1.1
1.2
1.3
1.4
Odds ratio

Q

rs6795735



R

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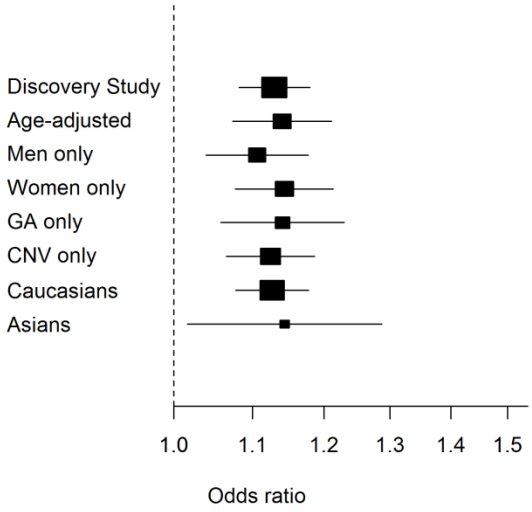
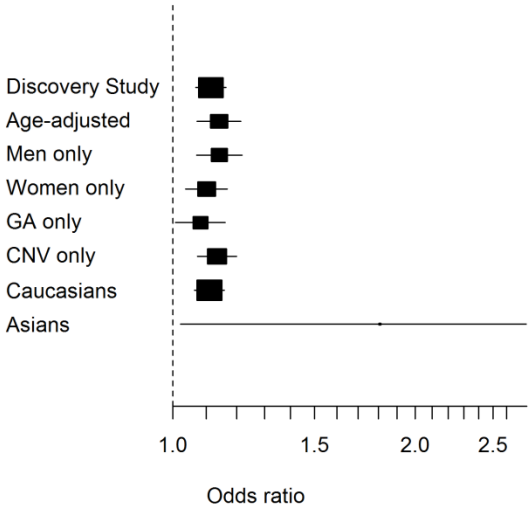
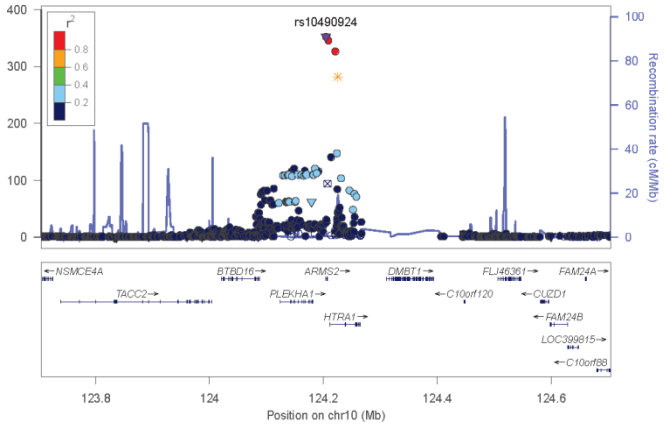


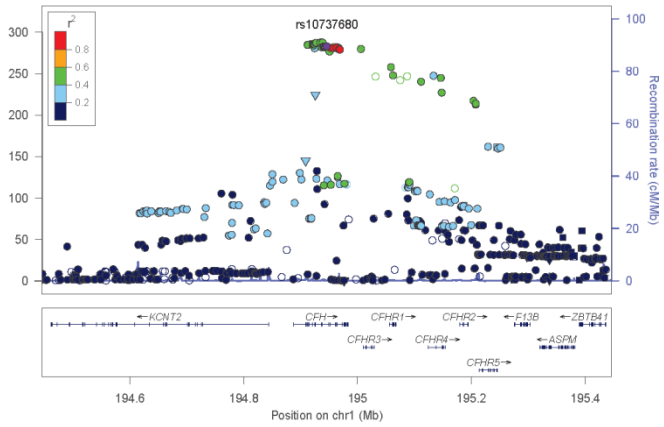
S

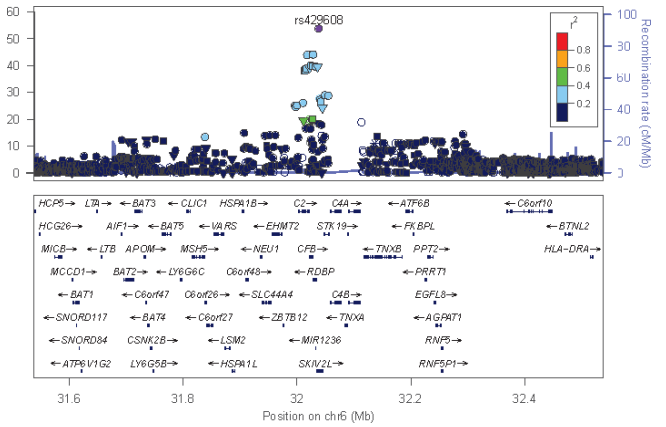
rs9542236

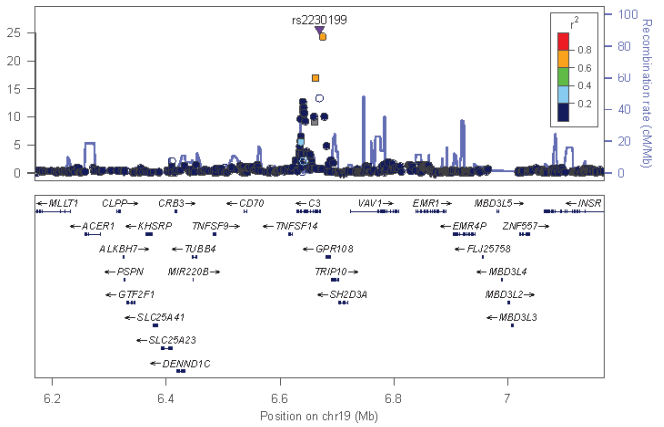


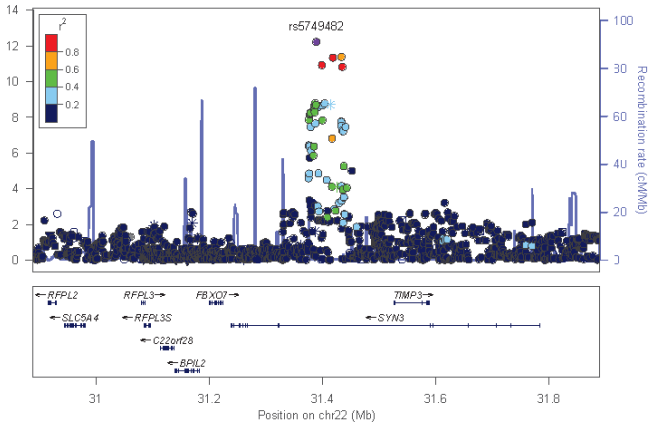
SUPPLEMENTARY FIGURE 3. Zoomplots summarizing association results for each locus. Each panel summarizes association results in the neighborhood of a previously described or confirmed locus. Variants are color coded according to the linkage disequilibrium between them and the most strongly associated SNP in each region. Coding variants are displayed as triangles. For additional details on format, please see Pruim [1].

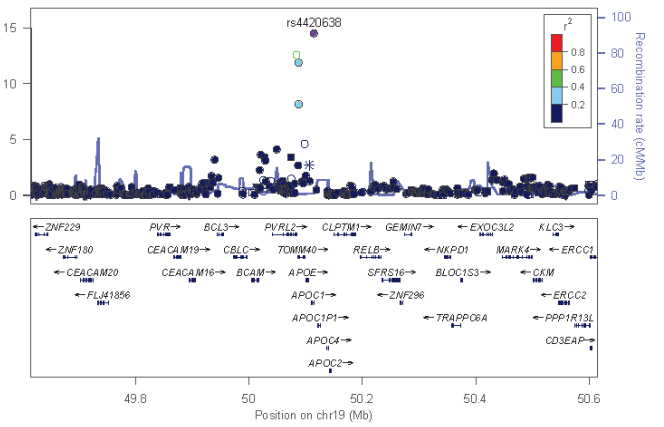


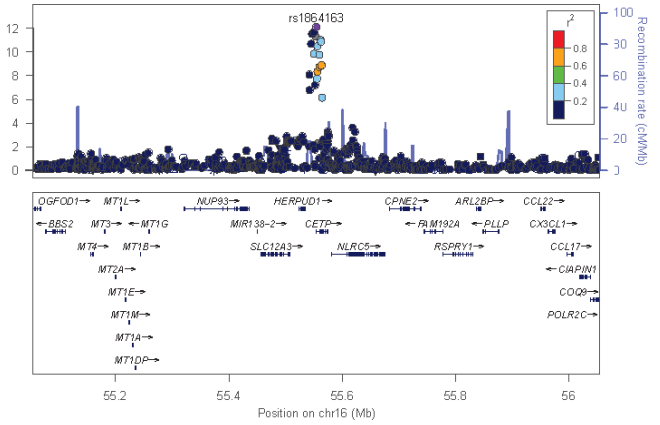








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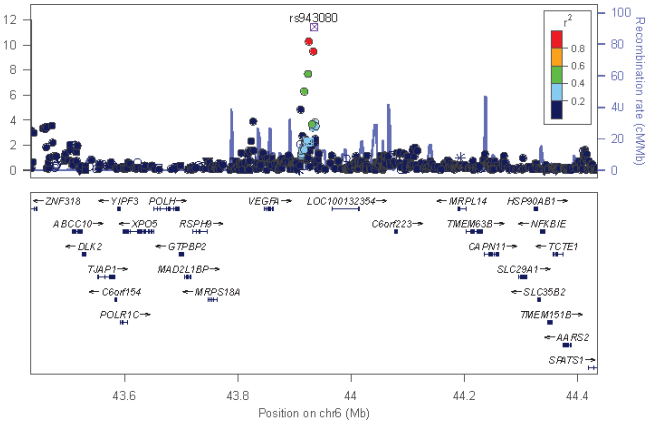
Position on chr16 (Mb)
Recombination rate (cM/Mb)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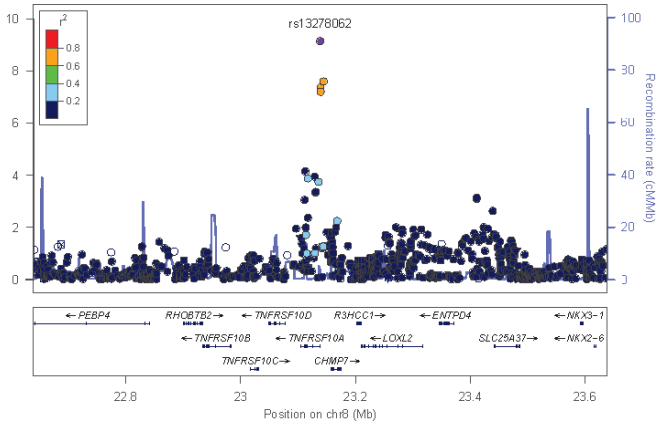
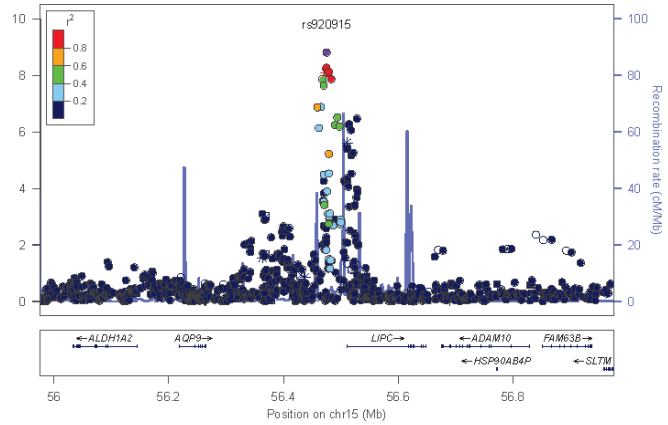
Position on chr6 (Mb)
Recombination rate (cM/Mb)


rs13278062
Position on chr8 (Mb)
Recombination rate (cM/Mb)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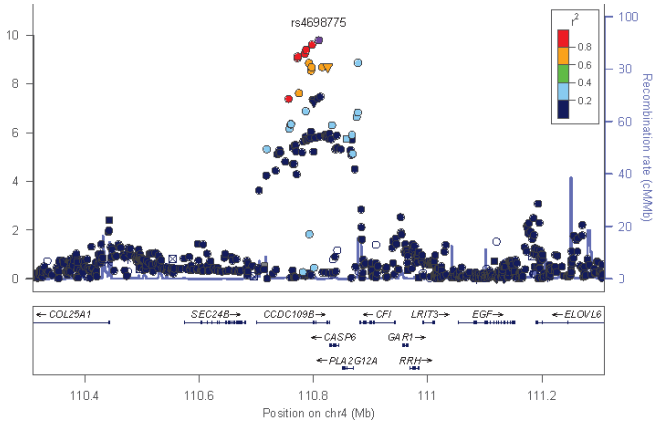
Position on chr15 (Mb)
Recombination rate (cM/Mb)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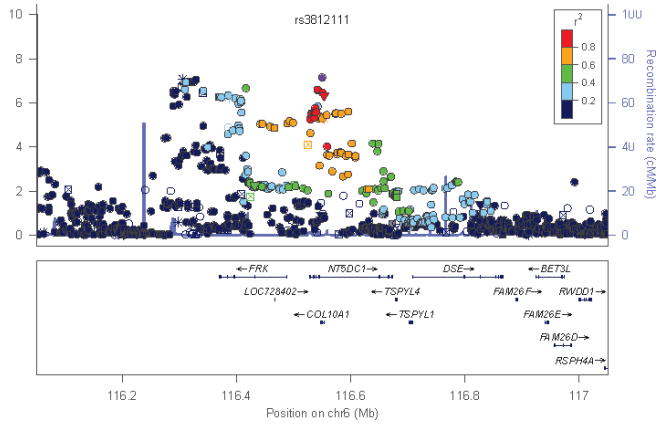
Position on chr4 (Mb)
Recombination rate (cM/Mb)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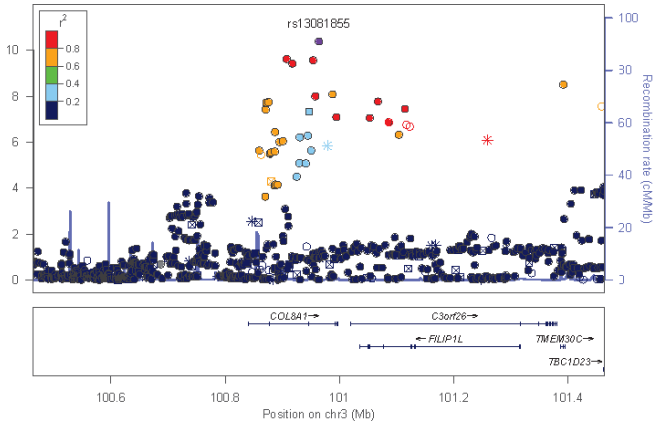
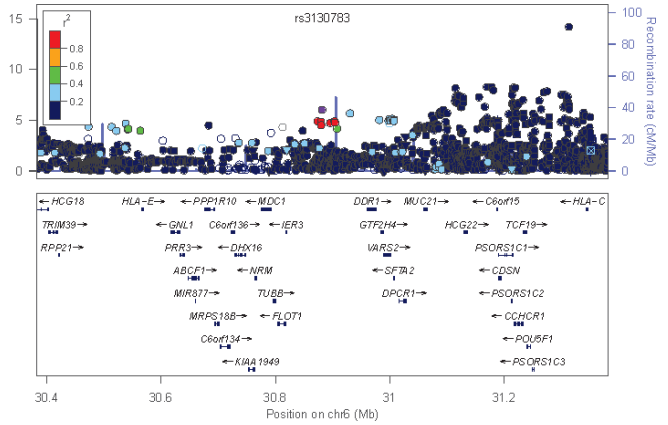
Position on chr6 (Mb)
Recombination rate (cM/Mb)


rs13081855
Position on chr3 (Mb)
Recombination rate (cM/Mb)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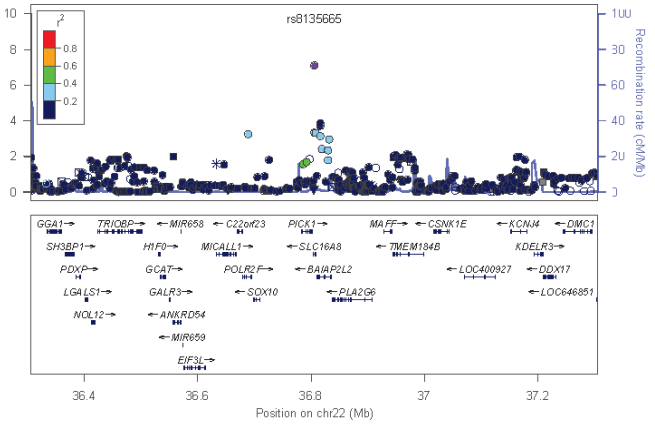
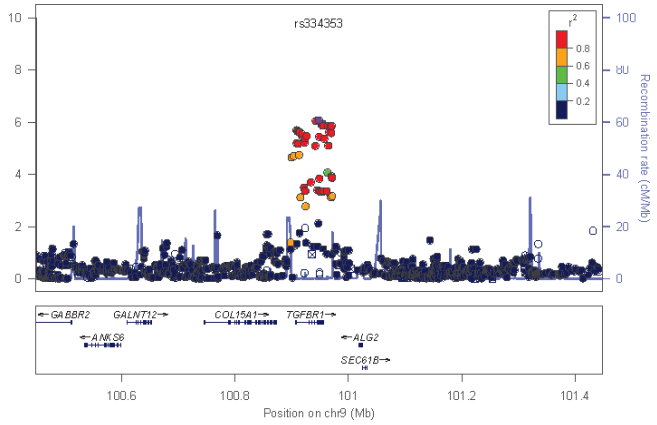
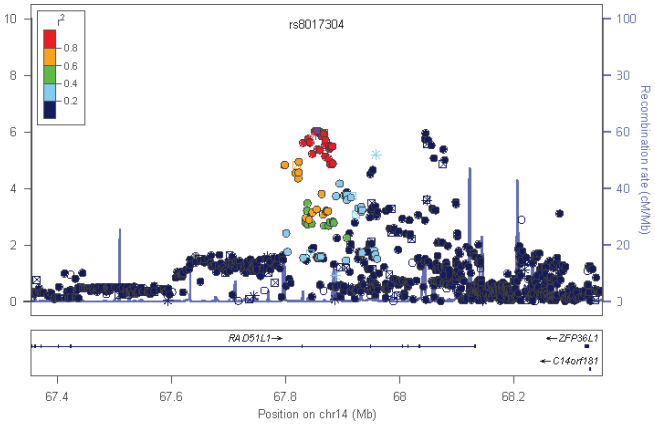
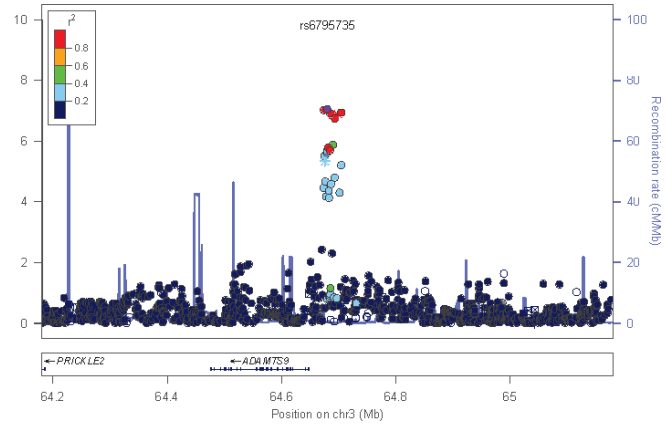
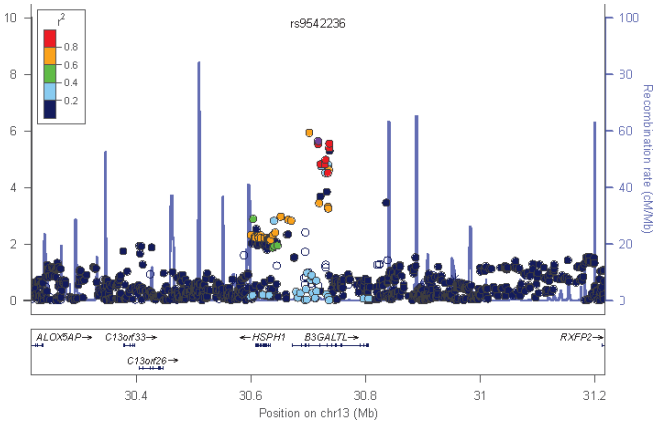
Position on chr6 (Mb)
Recombination rate (cM/Mb)


rs8135665
r²
0.8
0.6
0.4
0.2
Recombination rate (cM/Mb)
GGA1→ TRIOBP→ ←MIR658 ←C22orf23 PICK1→ MAFF→ ←CSNK1E ←KCNJ4 ←DMC1
SH3BP1→ ←HIF0→ MICALL1→ ←SLC16A8 ←TMEM184B KDELR3→
PDXP→ GCAT→ POLR2F→ ←BAIAP2L2 ←LOC400927 ←DDX17
LGALS1→ GALR3→ ←SOX10 ←PLA2G6 ←LOC646851
NOL12→ ←ANKRD54
←MIR659
EIF3L→
36.4 36.6 36.8 37 37.2
Position on chr22 (Mb)

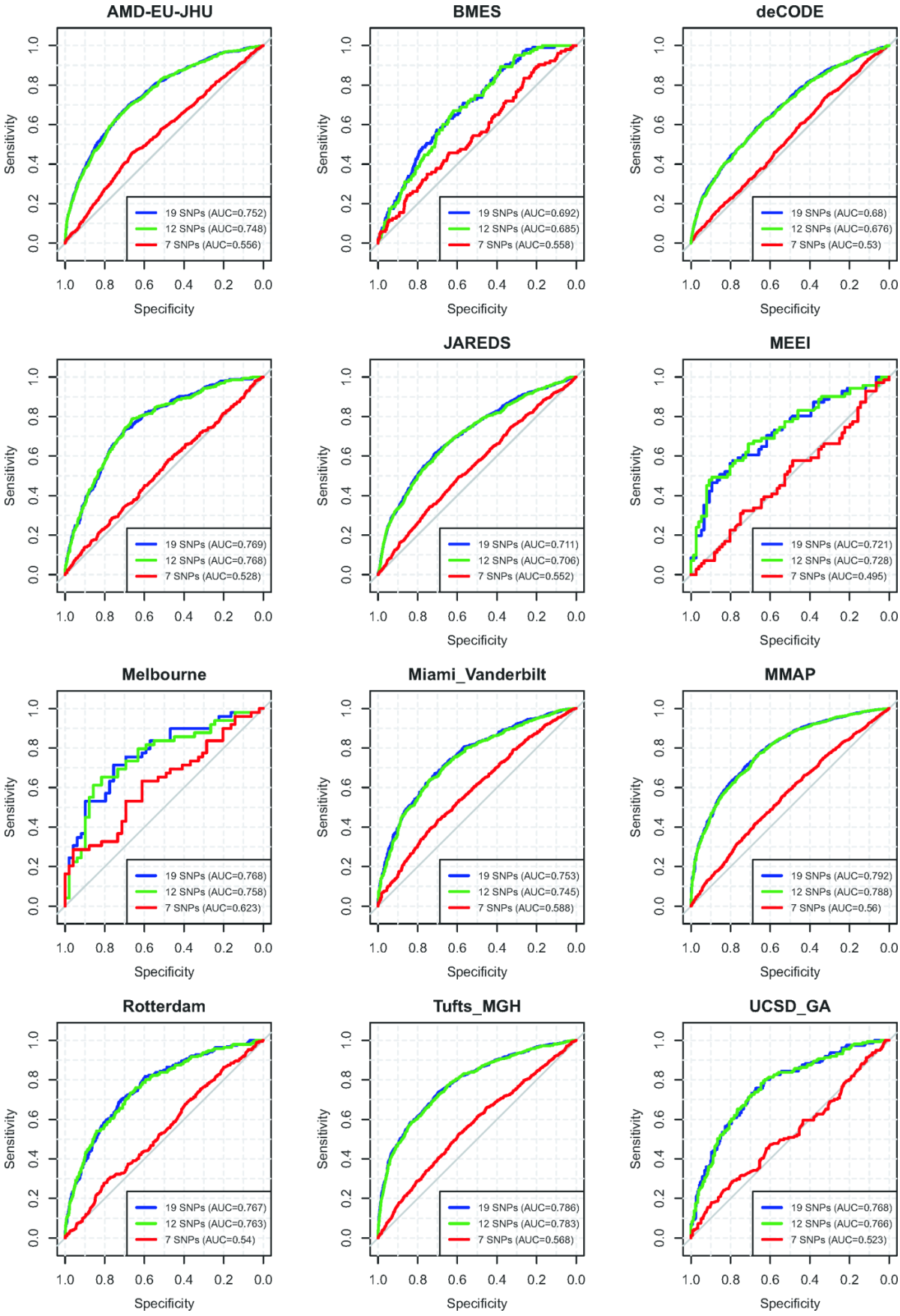

rs334353
r²
0.8
0.6
0.4
0.2
Recombination rate (cM/Mb)
←GABBR2 GALNT12→ COL15A1→ TGFBR1→
←ANKS6 ←ALG2
SEC61B→
100.6 100.8 101 101.2 101.4
Position on chr9 (Mb)


rs8017304
r²
0.8
0.6
0.4
0.2
Recombination rate (cM/Mb)
RAD51L1→ ←ZFP36L1
←C14orf181
67.4 67.6 67.8 68 68.2
Position on chr14 (Mb)


rs6795735
r²
0.8
0.6
0.4
0.2
Recombination rate (cM/Mb)
←PRICKLE2 ←ADAMTS9
64.2 64.4 64.6 64.8 65
Position on chr3 (Mb)


rs9542236
r²
0.8
0.6
0.4
0.2
Recombination rate (cM/Mb)
ALOX5AP→ C13orf33→ ←HSPH1 B3GALTL→ RXFP2→
C13orf26→
30.4 30.6 30.8 31 31.2
Position on chr13 (Mb)

SUPPLEMENTARY FIGURE 4. Risk score analysis of individual samples. 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. The analysis was repeated for each sample and, as shown, gave generally very consistent results in all the samples examined.



SUPPLEMENTARY TABLE 1: Summary of samples contributing to GWAS meta-analysis and follow-up.

Studies	Cases					Controls		Details in Supplementary Note #
	N	% Female	%CNV	%GA	% Mixed (CNV/GA)	*N*	% Female	
Discovery Phase: Samples Contributing to GWAS Meta-Analysis								
AMD-EU-JHU	963[a]	62.9%	40.3%	43.1%	16.6%	4,262[a]	51.7%	1.
VRF (India)	110	33.6%	90.0%	0.0%	10.0%	119	53.8%	2.
BMES	103	64.1%	46.6%	39.8%	13.6%	1,052	55.7%	3.
UK Cambridge/Edinburgh 300k	150[a]	56.7%	72.0%	18.0%	10.0%	601[a]	46.4%	4.
UK Cambridge/Edinburgh 550k	743[a]	55.0%	65.3%	20.9%	13.9%	1,598[a]	52.4%	4.
deCODE AMD	721	32.5%	27.0%	27.9%	45.1%	33,463	42.2%	5.
FAS/KORA	317	72.6%	45.7%	30.0%	24.3%	1,636	50.7%	6.
JAREDS	827	30.5%	100.0%	0.0%	0.0%	3,323	44.4%	7.
MEEI	71	52.1%	100.0%	0.0%	0.0%	76	61.8%	8.
Melbourne	49	63.3%	49.0%	42.9%	0.0%	49	55.1%	9.
Miami/Vanderbilt	867	63.3%	74.0%	17.1%	8.9%	689	55.6%	10.
MMAP	1,464	61.5%	54.4%	28.8%	16.8%	1,150	55.9%	11.
Rotterdam	192	60.4%	35.4%	41.7%	22.9%	1,887	56.5%	12.
Tufts/MGH	912	55.5%	72.7%	27.3%	0.0%	1,679[b]	43.7%	13.
UCSD GA	161	60.9%	0.0%	100.0%	0.0%	260	75.8%	14.

[a] Not included in age adjusted analysis, because age information was not available for most controls.

[b] 29.2% samples included in age adjusted analysis.

SUPPLEMENTARY TABLE 1 (Continued): Summary of samples contributing to GWAS meta-analysis and follow-up.

	Cases					Controls		Details in Supplementary Note #
Studies	***N***	**% Female**	**%CNV**	**%GA**	**% Mixed**	***N***	**% Female**	
Follow-Up Phase: Samples Contributing Genotyping Based Follow-up Of Promising Signals								
AMD-EU-JHU	1,213[d]	62.2%	78.0%	21.3%	0.7%	385[d]	54.8%	15.
BDES	138[d]	65.2%	34.1%c	37.0%	29.0%	932[d]	53.5%	16.
Oregon	598[d]	66.0%	65.0%	25.0%	10.0%	284[d]	54.0%	17.
Greece	156	52.6%	89.7%	0.0%	10.3%	236	54.7%	18.
CCF/VAMC	628	51.1%	64.5%	12.3%	23.2%	568	27.6%	19.
Columbia	736[e]	58.2%	69.4%	16.4%	14.1%	356[f]	55.9%	20.
Univ. of Pittsburgh/UCLA	1,176	62.5%	40.4%	19.1%	40.5%	224	53.6%	21.
Iowa	763	66.7%	84.0%	10.5%	5.5%	562	58.7%	22.
Melbourne	661	62.5%	77.0%	15.9%	7.1%	448	53.6%	23.
Miami/Vanderbilt	103	66.0%	65.0%	19.4%c	15.5%	91	64.8%	24.
NESC	338	62.1%	92.9%	0.0%	7.1%	209	58.4%	25.
NHS/HPFS	164	54.3%	100.0%	0.0%	0.0%	1,344	65.2%	26.
MMAP/NEI	769	58.4%	78.4%	14.0%	7.6%	699	59.8%	27.
SAGe	122	32.8%	100.0%	0.0%	0.0%	151	46.4%	28.
SNUBH	339	47.2%	89.4%	0.0%	10.6%	396	50.3%	29.
Southern Germany	1,136	63.6%	58.6%	20.5%	20.9%	1,054	58.6%	30.
UCSD GA	152	52.0%	0.0%	100.0%	0.0%	135	57.0%	31.
Utah	339	66.4%	72.0%	19.5%	8.6%	156	63.5%	32.

[d] not included in age-adjusted analysis; [e] 92.8% of samples included in age-adjusted analysis; [f] 99.9% of samples included in age-adjusted analysis

SUPPLEMENTARY TABLE 2: Genotyping and imputation methods.

Study	Control Recruitment (Match Criteria)	Genotyping Method / Platform	Genotyping Analysis Software	Inclusion Criteria			SNPs after QC	Imputation Software	SNPs in Meta-Analysis
				MAF[a]	Call Rate	HWE[b]			
GWAS									
AMD-EU-JHU	CEPH/Screened	Illumina HumanHap300 BeadChips or Illumina Human610-Quad BeadChips	MACH2DAT	≥0.01	≥0.98	$>1\times10^{-6}$	259,814	MACH v1.0	2,418,255
Vision Research Foundation (VRF, India)	Screened	Affymetrix 250K *NspI*	Logistic regression on allele dosage using R	≥0.01	≥0.99 for SNPs with MAF <0.05; ≥0.97 for SNPs with MAF <0.10; ≥0.95 otherwise	$>1\times10^{-6}$	167,658	MaCH v1.0	1,663,272
BMES (Blue Mountain Eye Study)	Population Based	Illumina Human670-QuadCustom chip (as part of WTCCC2)	ProbABEL	>0.01	≥95%	$>1\times10^{-6}$	543,846	MACH v1.0.16	2,437,732
UK Cambridge / Edinburgh 300K	Population based (geographic area)	Cases: Illumina Infinium HumanHap300K BeadChip; Controls: Illumina Infinium HumanHap550v1 BeadChip	R package snpStats	≥0.05	≥0.975	$\geq1\times10^{-5}$ (controls)	286,135	R package snpStats	2,244,198
UK Cambridge / Edinburgh 550K	Population based (geographic area)	Cases: Illumina Infinium HumanHap550v3 BeadChip; Controls: Illumina Infinium HumanHap550v3 BeadChip	R package snpStats	≥0.05	≥0.975	$\geq1\times10^{-5}$ (controls)	488,867	R package snpStats	2,251,257
deCODE AMD	Population based (same genotyping platform)	Illumina HumanHap300 or HumanHapCNV370 BeadChips	SNPTEST v2	>0.01	>0.96	$>1\times10^{-6}$	290,447	IMPUTE v1	2,432,355
FAS / KORA	Population based	Affymetrix GeneChip Human Mapping 250k StyI Array	SNPTEST v2.1.1	>0.01	>0.90 for SNPs with MAF >0.1; (1-MAF) for SNPs with MAF ≤0.1	$>1\times10^{-6}$ (controls)	165,770	BEAGLE v3.1.0	2,055,179

Study	Control Recruitment (Match Criteria)	Genotyping Method / Platform	Genotyping Analysis Software	Inclusion Criteria			SNPs after QC	Imputation Software	SNPs in Meta-Analysis
				MAF[a]	Call Rate	HWE[b]			
JAREDS	Population based	Cases: Illumina 610-quad BeadChip; Controls: Illumina HumanHap550v3 BeadChip	MACH2DAT	>0.01	≥0.99	$>1\times10^{-6}$ (controls)	457,489	MACH v1.0	2,398,323
MEEI	Screened (sibling of proband)	Affymetrix 6.0	GEE as implemented in R	>0.02	>0.98	$>1\times10^{-6}$	278,400	MACH v1.0.16	2,040,787
Melbourne	Screened	Affymetrix 6.0	PLINK 1.04	>0.01	>0.95	$>1\times10^{-6}$	324,067	MACH v1.0	2,386,948
Miami/Vanderbilt	Screened	Affymetrix 1M	Logistic regression as implemented in PLINK	>0.05	≥0.95	$>1\times10^{-6}$	668,238	MACH v1.0.16	2,439,893
MMAP	Screened	Illumina HumanCNV370v1	MACH2DAT	≥0.01	≥0.95	$>1\times10^{-6}$	324,067	MACH v1.0	2,455,419
Rotterdam	Screened	Illumina Infinium II HumanHap550	MACH2QTL	>0.01	>0.98	$>1\times10^{-5}$	486,261	MACH v1.0	2,487,441
Tufts / MGH	Screened	Affymetrix 6.0	PLINK 1.07	≥0.01	≥0.98	$>1\times10^{-6}$	644,413	BEAGLE	2,400,051
UCSD GA	Screened	Cases: Illumina 660-Quad v1A; Controls: Illumina 610-Quad	Java	>0.01	>0.95	$>1\times10^{-6}$	383,363	MACH v1.0.16	2,444,727
Follow-up Studies									
AMD-EU-JHU	CEPH/screened	Sequenom	Logistic regression as implemented in PLINK	≥0.01	≥0.98	>0.0013 (controls)	30	n/a	30
BDES	Screened	Kbiosciences (flouroescence based allele-specific PCR)	GEE as implemented in GWAF	>0.01	≥0.95	>0.0013 (controls)	27	n/a	27
Oregon	Screened	Taqman	Logistic regression as implemented in R	>0.01	>0.96	>0.0013 (controls)	12	n/a	12
Greece	Screened	Sequenom	Logistic regression as implemented in R	>0.01	>0.50	>0.0013 (controls)	21	n/a	21
CCF / VAMC	Screened	Taqman	Logistic regression as implemented in PLINK	>0.01	≥0.95	>0.0013 (controls)	27	n/a	27
Columbia	Screened	Taqman	Logistic regression as implemented in PLINK	>0.01	>0.50	>0.0013 (controls)	29	n/a	29

Study	Control Recruitment (Match Criteria)	Genotyping Method / Platform	Genotyping Analysis Software	Inclusion Criteria			SNPs after QC	Imputation Software	SNPs in Meta-Analysis
				MAF[a]	Call Rate	HWE[b]			
Genetics of Age Related-Maculopathy (UCLA/Pittsburgh)	Screened	rs6499777, rs429608, and rs3130783: Taqman; remainder: Sequenom iPLEX MassArray	GEE as implemented in R	>0.01	>0.50	>0.0013 (controls)	25	n/a	25
Iowa	Screened	Sequenom	Logistic regression as implemented in R	>0.01	>0.50	>0.0013 (controls)	21	n/a	21
Melbourne	Screened	Sequenom MassArray	Logistic regression as implemented in PLINK	>0.01	>0.50	>0.0013 (controls)	19	n/a	19
Miami / Vanderbilt	Screened	Taqman	Logistic regression as implemented in PLINK	>0.01	>0.50	>0.0013 (controls)	30	n/a	30
NESC	Screened (sibling of proband)	Sequenom	GEE as implemented in R	>0.01	>0.50	>0.0013 (controls)	21	n/a	21
NHS / HPFS	Screened	Sequenom	Logistic regression as implemented in R	>0.01	>0.50	>0.0013 (controls)	21	n/a	21
MMAP / NEI	Screened	Biotrove	Logistic regression as implemented in R	>0.01	>0.5	>0.0013 (controls)	28	n/a	28
SAGe	Screened	Sequenom, Illumina Human610-Quad chip	Logistic regression as implemented in SNPTEST v2.1.1	>0.05	$\geq$0.95	>0.0013 (controls)	27	n/a	27
SNUBH	Screened	Sequenom iPLEX	Logistic regression as implemented in R	>0.01	>0.50	>0.0013 (controls)	19	n/a	19
Southern Germany	Screened	Sequenom MassARRAY	Logistic regression as implemented in PLINK	>0.01	>0.50	>0.0013 (controls)	29	n/a	29
UCSD GA	Screened	Sequenom MassARRAY	Java	>0.01	>0.50	>0.0013 (controls)	28	n/a	28
Utah	Screened	Sequenom	Logistic regression as implemented in R	>0.01	>0.50	>0.0013 (controls)	21	n/a	21

Note that, because features such as genotyping call rates, accuracy of rare allele genotypes, and the suitability of different methods to account for population stratification all depend on genotyping platform and other study specific features, quality filters necessarily vary between studies (as described in the table above).

[a]minor allele frequency; [b] p value for Hardy-Weinberg Equilibrium.

SUPPLEMENTARY TABLE 3: Genotyped markers of the follow-up study. 32 SNPs that revealed suggestive evidence ($p<10^{-6}$) in the primary discovery analysis were selected for follow-up genotyping. If the index SNP could not be genotyped, a highly correlated proxy ($r^2 > 0.8$) was used with exception of SNP rs10981436 ($r^2 = 0.33$) and SNP rs7499892 ($r^2 = 0.72$).

					Genotyped SNPs per Study[b]																	
Index SNP	**Chr**	**Position (hg19)**	**Gene Label[a]**	**Proxy (r^2)**	**BDES**	**Greece**	**Iowa**	**SNUBH**	**NESC**	**NHS/HPFS**	**Utah**	**Oregon**	**Columbia**	**AMD-EU-JHU**	**Univ. of Pittsburgh/UCLA**	**Melbourne**	**Miami/Vanderbilt**	**MMAP/NEI**	**SAGe**	**Southern Germany**	**CCF/VAMC**	**UCSD GA**
rs10737680	1	196,679,455	*CFH*	rs10922106 (1.0)	X	…	…	…	…	…	…	…	…	X	X	X	X	X	X	X	X	X
rs12084515	1	233,058,437	*NTPCR*	…	X	X	X	X	X	X	X	…	X	X	X	X	X	X	X	…	X	X
rs6795735	3	64,705,365	*ADAMTS9*	…	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
rs13081855	3	99,481,539	*COL8A1 / FILIP1L*	…	X	X	X	X	X	X	X	X	X	X	…	…	X	X	X	X	X	X
rs2172734	3	107,549,462	*BBX / LOC151658*	rs9816888 (1.0)	X	…	…	…	…	…	…	…	X	X	X	…	P	…	X	X	X	X
rs4698775	4	110,590,479	*PLA2G12A/CFI*	rs4698770 (0.959)	X	…	…	…	…	…	…	…	P	X	X	X	…	P	X	X	X	X
rs1605677	5	35,600,210	*SPEF2*	…	X	X	X	…	X	X	X	X	X	X	…	…	X	X	X	X	X	X
rs318042	5	41,474,575	*PLCXD3*	rs318087 (0.983)	X	X	X	X	X	X	X	X	X	X	X	P	X	P	X	X	X	X
rs4279337	5	124,284,656	…	…	X	X	X	X	X	X	X	…	X	X	X	X	X	X	X	X	X	X
rs2863747	5	156,930,784	*NIPAL4/ADAM19*	…	X	X	X	X	X	X	X	X	…	X	X	…	X	X	X	X	X	X
rs3130783	6	30,774,357	*IER3/DDR1*	…	X	X	X	X	X	X	X	…	X	X	X	X	X	X	X	X	X	…
rs429608	6	31,930,462	*C2/CFB*	…	X	…	…	…	…	…	…	…	…	X	X	X	X	X	X	X	X	…
rs943080	6	43,826,627	*VEGFA / LOC100132354*	rs1536304 (0.871)	X	P	P	P	P	P	P	…	P	X	…	X	…	P	X	X	X	X
rs3812111	6	116,443,735	*COL10A1*	…	X	X	X	X	X	X	X	X	X	X	X	…	X	X	X	X	X	X
rs11769700	7	100,090,049	*C7orf51*	…	X	X	X	X	X	X	X	…	X	X	X	X	X	X	…	X	X	X
rs13278062	8	23,082,971	*TNFRSF10A / LOC389641*	…	X	X	X	X	X	X	X	…	X	X	X	…	X	X	X	X	X	X
rs334353	9	101,908,365	*TGFBR1*	…	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Index SNP	Chr	Position (hg19)	Gene Label[a]	Proxy (r^2)	Genotyped SNPs per Study[b]																	
					BDES	Greece	Iowa	SNUBH	NESC	NHS/HPFS	Utah	Oregon	Columbia	AMD-EU-JHU	Univ. of Pittsburgh/UCLA	Melbourne	Miami/Vanderbilt	MMAP/NEI	SAGe	Southern Germany	CCF/VAMC	UCSD GA
rs10981455	9	115,367,155	*KIAA1958*	rs10981436 (0.331)	X	...	...	...	...	...	...	...	...	...	...	...	X	...	X	P	X	...
rs10490924	10	124,214,448	*ARMS2 / HTRA1*	rs3750847 (1.0)	X	...	...	...	...	...	...	...	...	X	X	X	X	X	P	X	X	X
rs6582128	12	73,298,158	...	rs4760851 (1.0)	X	P	P	P	P	P	P	X	P	X	X	P	X	X	X	X	X	X
rs9542236	13	31,819,325	*B3GALTL*	...	X	X	X	X	X	X	X	X	X	X	X	...	X	X	X	X	X	X
rs11158950	14	25,333,115	*STXBP6*	...	...	X	X	X	X	X	X	...	X	X	X	...	X	X	X	...	...	X
rs8017304	14	68,785,077	*RAD51B*	...	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
rs920915	15	58,688,467	*LIPC*	rs443401 (0.88)	...	...	...	...	...	...	...	...	X	X	X	...	P	X	X	X	...	X
rs6499777	16	55,778,536	*CES1P2*	rs11862149 (1.0)	...	X	X	X	X	X	X	...	X	X	X	P	X	X	...	...	...	...
rs1864163	16	56,997,233	*CETP*	rs7499892 (0.719)	X	...	...	...	...	...	...	...	X	X	...	P	X	...	X	X	X	X
rs9973159	18	597,950	*CLUL1*	...	X	X	X	...	X	X	X	X	X	...	X	X	X	X	...	X	X	X
rs2230199	19	6,718,387	*C3*	...	X	...	...	...	...	...	...	...	...	X	X	X	X	X	...	X	X	X
rs4420638	19	45,422,946	*APOE*	...	...	X	X	X	X	X	X	...	X	X	...	...	X	...	X	X	...	X
rs9613841	22	29,622,636	*EMID1*	...	...	...	...	...	...	...	...	...	X	X	...	...	X	X	...	X	...	X
rs5749482	22	33,059,665	*TIMP3*	...	X	...	...	...	...	...	...	...	X	X	X	...	X	X	X	X	X	X
rs8135665	22	38,476,276	*SLC16A8*	...	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Total Number of Genotyped SNPs					**27**	**21**	**21**	**19**	**21**	**21**	**21**	**12**	**26**	**30**	**25**	**19**	**30**	**28**	**27**	**29**	**27**	**28**

[a] Gene label: nearest gene or gene as published for identification. [b] X: Marker genotyped; P: Proxy genotyped

SUPPLEMENTARY TABLE 4: Method for accounting for population structure and genomic control parameter for individual GWAS. Prior to meta-analysis, statistics for each study were corrected using the genomic control method and the correction factor in the last column (except when $\lambda_{GC} < 0$, in which case no correction was applied).

Study	Correction for Population Stratification		λ_{GC} Before Genomic Control
	Software	Method	
AMD-EU-JHU	EIGENSTRAT / EIGENSOFT	PCA, then GC	1.063
BMES	PLINK	PCA, then GC	0.995
deCODE	Custom software	GC	1.167
FAS/KORA	R	GC	1.089
JAREDS	Custom software	GC	1.174
MEEI	R	PCA, then GC	1.012
Melbourne	EIGENSTRAT / EIGENSOFT	PCA, then GC	1.010
Miami/Vanderbilt	EIGENSTRAT / EIGENSOFT	PCA, then GC	1.028
MMAP	EIGENSTRAT / EIGENSOFT	PCA, then GC	1.057
Rotterdam	Custom software	GC	1.039
Tufts/MGH	PLINK	PCA, then GC	1.073
UCSD GA	Java	PCA, then GC	1.108
UK Cambridge / Edinburgh 300k	R, R package snpStats	SA, then GC	1.026
UK Cambridge / Edinburgh 550k	R, R package snpStats	SA, then GC	1.024
VRF (INDIA)	R	GC	1.086

GC: Correction of Output Chi-Square and P-Values by Genomic Controls; PCA: Adjustment for Principal Components of Ancestry; SA: Stratified analysis by geographic origin: single SNP association evaluated using the Mantel extension of the 1-df trend test

SUPPLEMENTARY TABLE 5: Full gene names for genes mapping near one of the 19 index SNPs reaching $p < 5x10^{-8}$

Index SNP	Nearby Gene(s)		
	Symbol	**Name**	**Distance to index SNP [kb] / Location**
rs10490924	*ARMS2*	Age-related maculopathy susceptibility 2	0 / coding sequence
	HTRA1	HtrA serine peptidase 1	6.6 / upstream
rs10737680	*CFH*	Complement factor H	0 / intronic
rs429608	*C2*	Complement component 2	17 / downstream
	CFB	Complement factor B	10.6 / downstream
	SKIV2L	Superkiller viralicidic activity 2-like (S. cerevisiae)	0 / intronic
rs2230199	*C3*	Complement component 3	0 / coding sequence
rs5749482	*TIMP3*	TIMP metallopeptidase inhibitor 3	137.1 / upstream
	SYN3	Synapsin III	0 / intronic
rs4420638	*APOE*	Apolipoprotein E	10.3 / downstream
	APOC1	Apolipoprotein C-I	5.0 / downstream
rs1864163	*CETP*	Cholesteryl ester transfer protein, plasma	0 / intronic
rs943080	*VEGFA*	Vascular endothelial growth factor A	72.4 / downstream
rs13278062	*TNFRSF10A*	Tumor necrosis factor receptor superfamily, member 10a	0.3 / upstream
rs920915	*LIPC*	Lipase, hepatic	35.7 / upstream
rs4698775	*CFI*	Complement factor I	71.4 / downstream
	CCDC109B	Coiled-coil domain containing 109B	0 / intronic
rs3812111	*COL10A1*	Collagen, type X, alpha 1	0 / intronic
rs13081855	*COL8A1*	Collagen, type VIII, alpha 1	0 / intronic
rs3130783	*IER3*	Immediate early response 3	62 / upstream
	DDR1	Discoidin domain receptor tyrosine kinase 1	77.5 / upstream
rs8135665	*SLC16A8*	Solute carrier family 16, member 8 (monocarboxylic acid transporter 3)	0 / intronic
rs334353	*TGFBR1*	Transforming growth factor, beta receptor 1	0 / intronic
rs8017304	*RAD51B*	RAD51 homolog B (S. cerevisiae)	0 / intronic
rs6795735	*ADAMTS9*	ADAM metallopeptidase with thrombospondin type 1 motif, 9	32 / upstream
	ADAMTS9-AS2	ADAMTS9 antisense RNA 2 (non-protein coding)	0 / intronic
	MIR548A2	microRNA 548a-2	0.3 / upstream
rs9542236	*B3GALTL*	Beta 1,3-galactosyltransferase-like	0 / intronic

SUPPLEMENTARY TABLE 6: Independently associated variants near identified loci. We repeated our genome-wide association signal conditioning on the most significantly associated SNPs identified in the first round of analysis. The table summarizes signals peaking at p < .0002 - corresponding to a Bonferroni adjustment for 250 independent tests in each locus and consistent with the average effective number of SNPs in the 1Mb intervals surrounding each of our original signals [2].

Index SNP	Gene	Chr.	Position (hg19)	Alleles	N_{cases}	$N_{controls}$	P-value	r^2 w/lead SNP	D' w/lead SNP	Distance (kb) to lead SNP
rs12045503	*CFH*	1	196,672,473	t/c	7,488	51,549	8.6×10^{-55}	0.41	1.00	7.0
rs9469060	*C2/CFB*	6	31,804,715	a/t	5,698	45,962	2.2×10^{-10}	0.03	0.60	125.7
rs11569520	*C3*	19	6,689,507	a/g	6,501	47,972	1.8×10^{-5}	0.03	0.88	28.9
rs3764261	*CETP*	16	56,993,324	a/c	7,417	51,425	4.7×10^{-6}	0.15	1.00	3.9
rs572410	*LIPC*	15	58,741,384	c/g	7,488	51,522	8.4×10^{-6}	<0.01	0.15	52.9
rs12203852	*FRK/COL10A1*	6	116,206,371	t/c	7,489	51,552	1.3×10^{-4}	0.09	0.42	237.4
rs9262558	*IER3/DDR1*	6	31,006,994	t/c	5,296	45,971	5.8×10^{-7}	<0.01	0.43	232.6
rs2842344	*RAD51B*	14	68,976,971	t/c	7,172	49,915	1.5×10^{-6}	<0.01	0.22	191.9

SUPPLEMENTARY TABLE 7: Non-synonymous coding variants in strong linkage disequilibrium with AMD susceptibility alleles. The table lists all coding variants genotyped in the 1000 Genomes Project data and in strong linkage disequilibrium ($r^2 > 0.60$) with the index SNP for one of our association signals. Where available, association test results at the coding SNP are also listed (some coding SNPs were not part of our imputation reference panel and thus not tested). An analysis of coding variants genotyped by the International HapMap Consortium did not identify additional coding variants in strong linkage disequilibrium with our association signals.

Index SNP	*P* (Index SNP)	Chr	Position [hg19]	Coding SNP	*P* (Coding SNP)	Distance to Index SNP [kb]	Gene Symbol	Exon	Sequence change	Amino acid change	r^2 1000G EUR (N=379)	PolyPhen Prediction
Primary Discover Analysis												
rs4698775	2×10^{-10}	4	110,590,479	rs13846	2×10^{-9}	15.3	*CCDC109B*	6	NM_017918.4:c.758A>T	p.Tyr253Phe	0.89	Possibly Damaging
rs3812111	7×10^{-8}	6	116,443,735	rs1064583	5×10^{-7}	2.8	*COL10A1*	2	NM_000493.3:c.80T>C	p.Met27Thr	0.99	-
rs10490924	4×10^{-353}	10	124,214,448	rs10490924	4×10^{-353}	0.0	*ARMS2*	1	NM_001099667.1:c.205G>T	p.Ala69Ser	1.00	Benign
rs2230199	2×10^{-16}	19	6,718,387	rs1047286	not tested	5.1	*C3*	9	NM_000064.2:c.941C>T	p.Pro314Leu	0.83	Benign
				rs2230199	2×10^{-16}	0.0	*C3*	3	NM_000064.2:c.304C>G	p.Arg102Gly	1.00	Benign
rs4420638	3×10^{-15}	19	45,422,946	rs429358	not tested	11.0	*APOE*	4	NM_000041.2:c.388T>C	p.Cys130Arg	0.63	Benign
Secondary Signal Analysis												
rs12045503	9×10^{-55}	1	196672473	rs1061170	2×10^{-47}	13.2	*CFH*	9	NM_000186.3:c.1204C>T	p.His402Tyr	1.00	Benign
rs9469060	2×10^{-10}	6	31804715	rs36038685	not tested	125.0	*SKIV2L*	10	NM_006929.4:c.970C>T	p.Arg324Trp	0.88	Possibly Damaging
				rs11531	2×10^{-8}	54.2	*VARS*	15	NM_006295.2:c.1876C>T	p.Pro626Ser	0.66	Benign

SUPPLEMENTARY TABLE 8: Gene expression analysis. Retina expression is derived from high throughput and high quality RNA-sequencing data from three young (17-35 yrs age) and two old (75-77 yrs age) human retina. Expression is presented as fragments per kilobase of exon per million fragments mapped (FPKM) value and is highly quantitative (see Brooks [3] for methods and analysis). Low-level expression of retinal genes (such as rhodopsin) in RPE data likely represents photoreceptor contamination. Median normalized signal intensities were computed and signal intensity of >6 was taken as cutoff for expression in microarray data. For comparisons of expression levels, we calculated the log of ratios of estimated RPKM expression levels (for RNA-sequencing data) or of hybridization intensities (for microarray data). These log-ratios were approximately normally distributed with mean zero and evidence for differential expression was evaluated by converting these log-ratios to z-scores (by dividing each by their corresponding standard deviation).

Index SNP	Gene Symbol	RefSeq Transcript Id	Chr.	Gene Position (hg19)		RNA Seq		Microarray		
				Start	End	Young Retina	Old Retina	Probe_set id	Adult RPE	Fetal RPE
rs10737680	*CFH*	NM_000186	1	196,621,007	196,716,634	*	2.58	213800_at	4.82	2.06
	CFHR1	NM_002113	1	196,788.86	196,801.32	*	*	215388_s_at	7.01	4.05
	CFHR3	NM_001166624	1	196,743,929	196,763,203	*	*		**	**
rs6795735	*ADAMTS9*	NM_182920	3	64,501,330	64,673,365	*	*	220287_at	0.84	0.47
	MIR548A2	NR_030317	3	64,705,682	64,941,858	*	*		**	**
rs13081855	*MIR548G*	NR_031662	3	99,273,152	99,717,059	*	*		**	**
	COL8A1	NM_020351	3	99,357,453	99,515,158	*	*	214587_at	0.56	6.24
	C3orf26	NM_032359	3	99,536,677	99,897,476	16.12	14.56		**	**
	FILIP1L	NM_182909	3	99,551,987	99,833,349	*	*	204135_at	1.14	0.53
rs4698775	*SEC24B*	NM_001042734	4	110,354.97	110,461.62	13.85	14.69	202798_at	9.76	15.40
	CCDC109B	NM_017918	4	110,481,354	110,608,872	4.13	3.38	218802_at	1.34	1.05
	CASP6	NM_032992	4	110,609,784	110,624,629	2.35	*	209790_s_at	0.91	2.08
	PLA2G12A	NM_030821	4	110,631,144	110,651,242	8.68	8.51	221027_s_at	2.9	2.91
	CFI	NM_000204	4	110,661,847	110,723,335	14.98	20.74	203854_at	10.27	7.1
rs3130783	*MDC1*	NM_014641	6	30,667,583	30,685,458	13.25	11.01	203061_s_at	1.2	1.98
	TUBB	NM_178014	6	30,688,156	30,693,195	81.64	102.69	209026_x_at	11.83	50.94
	FLOT1	NM_005803	6	30,695,510	30,710,453	39.82	41.32	213819_s_at	0.41	0.41
	FLOT1	NM_005803	6	30,695,510	30,710,453	39.82	41.32	208749_x_at	7.37	10.41
	IER3	NM_003897	6	30,710,975	30,712,327	4.61	2.94	201631_s_at	4.18	9.34
	DDR1	NM_001954	6	30,851,860	30,867,933	25.34	31.89	1007_s_at	3.1	6.32
	GTF2H4	NM_001517	6	30,875,976	30,881,880	10.97	8.06	203577_at	0.38	1.04
	VARS2	NM_001167733	6	30,882,107	30,894,235	10.12	8.02		**	**

Index SNP	Gene Symbol	RefSeq Transcript Id	Chr.	Gene Position (hg19)		RNA Seq		Microarray		
				Start	End	Young Retina	Old Retina	Probe_set id	Adult RPE	Fetal RPE
rs429608	*NEU1*	NM_000434	6	31,826,828	31,830,709	17.22	14.9	208926_at	3.65	9.65
	SLC44A4	NM_001178044	6	31,830,969	31,846,823	*	*	205597_at	0.14	0.26
	EHMT2	NM_006709	6	31,847,536	31,865,464	18.21	15.5	202326_at	1.66	5.12
	ZBTB12	NM_181842	6	31,867,393	31,869,769	5.79	6.04		**	**
	C2	NM_000063	6	31,895,265	31,913,449	*	*	203052_at	1.08	0.26
	CFB	NM_001710	6	31,913,720	31,919,861	*	*	202357_s_at	0.71	0.06
	RDBP	NM_002904	6	31,919,863	31,926,864	23.64	21.66	209219_at	2.17	9.07
	MIR1236	NR_031601	6	31,924,615	31,924,717	*	*		**	**
	SKIV2L	NM_006929	6	31,926,580	31,937,532	9.58	7.7	203727_at	2.41	2.71
	DOM3Z	NM_005510	6	31,937,587	31,940,032	14.92	12.45	215982_s_at	1.24	2.11
	STK19	NR_026717	6	31,938,951	31,949,223	10.72	8.9	204090_at	1.83	2.65
	C4A	NM_007293	6	31,949,833	31,970,457	5.95	11.34	208451_s_at	14.49	2.45
	C4B	NM_001002029	6	31,949,833	31,970,458	4.84	9.79	208451_s_at	14.49	2.45
	CYP21A2	NM_001128590	6	31,973,358	31,976,712	*	*	214622_at	0.16	0.07
	TNXA	NR_001284	6	31,976,196	31,980,800	*	*	208609_s_at	0.28	0.09
	TNXB	NM_032470	6	31,976,196	31,981,050	*	*	206093_x_at	0.62	0.2
rs943080	*VEGFA*	NM_001171626	6	43,737,945	43,754,223	67.21	173.17	210512_s_at	10.6	25.16
	LOC100132354	NR_024478	6	43,858,764	43,905,944	*	*		**	**
rs3812111	*FRK*	NM_002031	6	116,262,692	116,381,921	*	*	207178_s_at	0.41	0.11
	TPI1P3	NR_027338	6	116,359,893	116,361,107	*	*		**	**
	NT5DC1	NM_152729	6	116,421,998	116,566,853	5.82	6.2		**	**
	COL10A1	NM_000493	6	116,440,084	116,447,296	*	*	205941_s_at	0.67	0.2
	TSPYL4	NM_021648	6	116,571,130	116,575,261	18.56	16.92	212928_at	7.06	19.3
rs13278062	*TNFRSF10D*	NM_003840	8	22,993,103	23,021,540	*	*	210654_at	0.13	0.13
	TNFRSF10A	NM_003844	8	23,048,969	23,082,680	*	*		**	**
	LOC389641	NR_033928	8	23,082,733	23,088,439	*	*		**	**
	CHMP7	NM_152272	8	23,101,149	23,119,512	7.98	6.85	212313_at	1.73	3.03
	R3HCC1	NM_001136108	8	23,145,611	23,153,792	68.71	60.16	212866_at	4.67	5.88
	LOXL2	NM_002318	8	23,154,409	23,261,722	2.62	2.3		**	**
rs334353	*COL15A1*	NM_001855	9	101,706,137	101,833,068	*	*	203477_at	0.88	8.12

Index SNP	Gene Symbol	RefSeq Transcript Id	Chr.	Gene Position (hg19)		RNA Seq		Microarray		
				Start	End	Young Retina	Old Retina	Probe_set id	Adult RPE	Fetal RPE
	TGFBR1	NM_004612	9	101,867,411	101,916,473	*	*	206943_at	0.28	0.18
	ALG2	NR_024532	9	101,978,706	101,984,246	6.6	6.21		**	**
	SEC61B	NM_006808	9	101,984,569	101,992,901	35.34	35.8	203133_at	15.02	37.67
rs10490924	*PLEKHA1*	NM_021622	10	124,151,818	124,191,871	7.76	7.71	219024_at	1.71	3.27
	MIR3941	NR_037506	10	124,176,480	124,176,583	*	*		**	**
	ARMS2	NM_001099667	10	124,214,178	124,216,868	*	*		**	**
	HTRA1	NM_002775	10	124,221,040	124,274,424	135.47	163.06	201185_at	28.88	28.84
	DMBT1	NM_007329	10	124,320.18	124,403.25	*	*	208250_s_at	0.89	0.40
rs9542236	*HSPH1*	NM_006644	13	31,710,762	31,736,117	12.24	8.94	206976_s_at	5.74	15.72
	B3GALTL	NM_194318	13	31,774,111	31,906,411	5.57	4.5		**	**
rs8017304	*RAD51B*	NM_133509	14	68,286,495	69,062,738	*	*	210255_at	0.32	0.23
rs920915	*LIPC*	NM_000236	15	58,724,174	58,861,073	*	*	206606_at	0.05	0.05
rs1864163	*SLC12A3*	NM_001126107	16	56,899,118	56,949,762	*	*	208354_s_at	0.34	0.15
	HERPUD1	NM_001010990	16	56,965,747	56,977,793	22.56	18.53	217168_s_at	10.56	14.16
	CETP	NM_000078	16	56,995,834	57,017,756	*	*	206210_s_at	0.09	0.09
	NLRC5	NM_032206	16	57,023,409	57,117,436	*	*		**	**
rs2230199	*TNFSF14*	NM_172014	19	6,663,147	6,670,599	*	*	207907_at	0.06	0.03
	C3	NM_000064	19	6,677,845	6,720,662	3.28	5.25	217767_at	13.19	0.11
	GPR108	NM_001080452	19	6,729,924	6,737,633	39.01	31.95		**	**
	TRIP10	NM_004240	19	6,739,706	6,751,529	18.52	18.89	202734_at	3.38	2.95
	SH2D3A	NM_005490	19	6,752,172	6,767,523	2.23	*	219513_s_at	0.67	0.2
	VAV1	NM_005428	19	6,772,721	6,857,371	*	*	206219_s_at	0.6	0.16
rs4420638	*BCAM*	NM_005581	19	45,312,337	45,324,678	3.31	4.07	203009_at	0.65	1.14
	PVRL2	NM_001042724	19	45,349,392	45,392,485	8.23	8.46	203149_at	2.53	4.01
	TOMM40	NM_006114	19	45,394,476	45,406,946	18.45	19.34	202264_s_at	2.55	2.1
	APOE	NM_000041	19	45,409,038	45,412,650	66.9	99.1	203381_s_at	4.34	14.41
	APOC1	NM_001645	19	45,417,920	45,422,606	7.57	13.43	213553_x_at	2.57	8.23
	APOC1P1	NR_028413	19	45,430,059	45,434,643	*	*		**	**
	APOC4	NM_001646	19	45,445,494	45,448,753	*	*	206738_at	0.58	0.35
	APOC2	NM_000483	19	45,449,238	45,452,822	*	*	204561_x_at	0.24	0.07

Index SNP	Gene Symbol	RefSeq Transcript Id	Chr.	Gene Position (hg19)		RNA Seq		Microarray		
				Start	End	Young Retina	Old Retina	Probe_set id	Adult RPE	Fetal RPE
	CLPTM1	NM_001199468	19	45,458,598	45,496,604	44.7	39.59	201640_x_at	3	2.3
	RELB	NM_006509	19	45,504,706	45,541,456	*	*	205205_at	0.61	0.17
rs5749482	*SYN3*	NM_001135774	22	32,908,539	33,454,377	*	*	206322_at	0.15	0.14
	TIMP3	NM_000362	22	33,196,802	33,259,028	3.39	2.17	201147_s_at	29.05	30.63
rs8135665	*SOX10*	NM_006941	22	38,368,318	38,380,539	*	*	209842_at	5.44	13.09
	SOX10	NM_006941	22	38,368,318	38,380,539	*	*	209843_s_at	0.57	0.78
	PICK1	NM_001039583	22	38,453,261	38,471,708	9.66	8.14	204746_s_at	1.04	0.85
	SLC16A8	NM_013356	22	38,474,143	38,479,170	*	*	220455_at	8.64	32.47
	BAIAP2L2	NM_025045	22	38,480,895	38,506,676	2.23	2.5	221178_at	0.17	0.11
	PLA2G6	NM_003560	22	38,507,501	38,577,761	10.88	8.14	204691_x_at	1.9	1.91
Genes unrelated to AMD Loci	*RHO*[a]	NM_000539	3	129,247,482	129,254,187	5544.14	5287.43	206455_s_at	8.58	0.29
	GNAT1[a]	NM_144499	3	50,229,043	50,235,129	1360.75	1302.89	207514_s_at	3.04	0.04
	PRPH2[a]	NM_000322	6	42,664,333	42,690,358	365.58	432.19	206625_at	12.49	0.22
	PDE6H[a]	NM_006205	12	15,125,956	15,134,799	602.75	529.56	206841_at	11.61	0.15
	RPE65[b]	NM_000329	1	68,894,507	68,915,642	7.7	5.27	207107_at	101.71	85.28
	BEST1[b]	NM_001139443	11	61,717,356	61,731,935	2.38	2.66	207671_s_at	80.03	145.93
	COL8A2[b]	NM_005202	1	36,560,842	36,565,850	*	*	221900_at	1.87	31.15
	GAPDH[c]	NM_002046	12	6,643,657	6,647,536	1774.34	2450.83	212581_x_at	123.31	134.33
	ATF4[c]	NM_001675	22	39,916,569	39,918,691	367.02	280.22	200779_at	42	29.94
	HSP90AA1[c]	NM_001017963	14	102,547,075	102,606,086	777.99	837.2	214328_s_at	140.13	137.67

* represents the genes with FPKM values less than 2 (i.e., low/negligible expression). Human fetal and adult RPE data is derived from Strunnikova et al. *Hum Mol Genet.* 19:2468-2486, 2010; GEO accession number GSE18811. Expression values represented are median normalized signal intensities. Signal intensity of >6 is taken as cutoff for expression in microarray data. ** represents the gene for which either no expression was detected or didn't have probe set id in the chip. Expression values of 10 other genes (unrelated to AMD loci) are included for comparison: [A] =Retina-specific gene, [b] =RPE-specific gene and [C] =housekeeping genes.

SUPPLEMENTARY TABLE 9: Genes in pathway analysis. Genes within 100kb of a SNP in high LD ($r^2 > 0.8$) with one of our replicated signals were flagged as potential AMD disease genes and considered for subsequent pathway enrichment analyses.

Index SNP	Gene Symbol	Chr	Position [kb] (hg19)		Distance to Index SNP [kb]
			Start	End	
rs10737680	*CFH*	1	196,621.01	196,716.63	0
	CFHR3	1	196,743.93	196,763.20	64.48
	CFHR1	1	196,788.86	196,801.32	109.41
rs6795735	*ADAMTS9*	3	64,501.33	64,673.37	32.00
	MIR548A2	3	64,705.68	64,941.86	0.32
rs13081855	*MIR548G*	3	99,273.15	99,717.06	0
	COL8A1	3	99,357.45	99,515.16	0
	C3orf26	3	99,536.68	99,897.48	55.14
	FILIP1L	3	99,551.99	99,833.35	70.45
rs4698775	*SEC24B*	4	110,354.97	110,461.62	128.86
	CCDC109B	4	110,481.35	110,608.87	0
	CASP6	4	110,609.78	110,624.63	19.31
	PLA2G12A	4	110,631.14	110,651.24	40.67
	CFI	4	110,661.85	110,723.34	71.37
rs3130783	*MDC1*	6	30,667.58	30,685.46	88.898
	TUBB	6	30,688.16	30,693.20	81.161
	FLOT1	6	30,695.51	30,710.45	63.90
	IER3	6	30,710.98	30,712.33	62.03
	DDR1	6	30,851.86	30,867.93	77.50
	GTF2H4	6	30,875.98	30,881.88	101.619
	VARS2	6	30,881.98	30,894.24	107.75
rs429608	*NEU1*	6	31,826.83	31,830.71	99.752
	SLC44A4	6	31,830.97	31,846.82	83.64
	EHMT2	6	31,847.54	31,865.46	65.00
	ZBTB12	6	31,867.39	31,869.77	60.692
	C2	6	31,895.27	31,913.45	17.01
	CFB	6	31,913.72	31,919.86	10.60
	RDBP	6	31,919.86	31,926.86	3.60
	MIR1236	6	31,924.62	31,924.72	5.74
	SKIV2L	6	31,926.58	31,937.53	0
	DOM3Z	6	31,937.59	31,940.03	7.13
	STK19	6	31,938.95	31,949.22	8.49
	C4A	6	31,949.83	31,970.46	19.37
	C4B	6	31,949.83	31,970.46	19.37
	CYP21A2	6	31,973.36	31,976.71	42.90
	TNXA	6	31,976.20	31,980.80	45.74
	TNXB	6	31,976.20	31,981.05	45.74
rs943080	*VEGFA*	6	43,737.95	43,754.22	72.40
	LOC100132354	6	43,858.76	43,905.94	32.14
rs3812111	*FRK*	6	116,262.69	116,381.92	61.81
	TPI1P3	6	116,359.89	116,361.11	82.63
	NT5DC1	6	116,422.00	116,566.85	0
	COL10A1	6	116,440.08	116,447.30	0
	TSPYL4	6	116,571.13	116,575,26	127.395

Index SNP	Gene Symbol	Chr	Position [kb] (hg19)		Distance to Index SNP [kb]
			Start	End	
rs13278062	*TNFRSF10D*	8	22,993.10	23,021.54	61.43
	TNFRSF10A	8	23,048.97	23,082.68	0.29
	LOC389641	8	23,082.73	23,088.44	0
	CHMP7	8	23,101.15	23,119.51	18.18
	R3HCC1	8	23,145.61	23,153.79	62.64
	LOXL2	8	23,154.41	23,261.72	71.44
rs334353	*COL15A1*	9	101,706.14	101,833.07	75.30
	TGFBR1	9	101,867.41	101,916.47	0
	ALG2	9	101,978.71	101,984.25	70.34
	SEC61B	9	101,984.57	101,992.90	76.21
rs10490924	*PLEKHA1*	10	124,151.82	124,191.87	22.58
	MIR3941	10	124,176.48	124,176.58	37.86
	ARMS2	10	124,214.18	124,216.87	0
	HTRA1	10	124,221.04	124,274.42	6.59
	DMBT1	10	124,320.18	124,403.25	105.73
rs9542236	*HSPH1*	13	31,710.76	31,736.12	83.21
	B3GALTL	13	31,774.11	31,906.41	0
rs8017304	*RAD51L1*	14	68,286.50	69,062.74	0
rs920915	*LIPC*	15	58,724.17	58,861.07	35.71
rs1864163	*SLC12A3*	16	56,899.12	56,949.76	47.47
	HERPUD1	16	56,965.75	56,977.79	19.44
	CETP	16	56,995.83	57,017.76	0
	NLRC5	16	57,023.41	57,117.44	26.18
rs2230199	*TNFSF14*	19	6,663.15	6,670.60	47.79
	C3	19	6,677.85	6,720.66	0
	GPR108	19	6,729.92	6,737.63	11.54
	TRIP10	19	6,739.71	6,751.53	21.32
	SH2D3A	19	6,752.17	6,767.52	33.79
	VAV1	19	6,772.72	6,857.37	54.34
rs4420638	*BCAM*	19	45,312.34	45,324.68	98.27
	PVRL2	19	45,349.39	45,392.49	30.46
	TOMM40	19	45,394.48	45,406.95	16.00
	APOE	19	45,409.04	45,412.65	10.30
	APOC1	19	45,417.92	45,422.61	0.34
	APOC1P1	19	45,430.06	45,434.64	7.11
	APOC4	19	45,445.49	45,448.75	22.55
	APOC2	19	45,449.24	45,452.82	26.29
	CLPTM1	19	45,458.60	45,496.60	35.65
	RELB	19	45,504.71	45,541.46	81.76
rs5749482	*SYN3*	22	32,908.54	33,454.38	0
	TIMP3	22	33,196.80	33,259. 03	137.14
rs8135665	*SOX10*	22	38,368.32	38,380.54	95.74
	PICK1	22	38,453.26	38,471.71	4.57
	SLC16A8	22	38,474.14	38,479.17	0
	BAIAP2L2	22	38,480.90	38,506.68	4.62
	PLA2G6	22	38,507.50	38,577.76	31.23

Index SNP = Replicated AMD associated SNP; **Gene Symbol** = HUGO Gene ID; **Chr**=Chromosome; **Start/End** = Chromosomal position [kb] of start/end of gene; **Distance to Index SNP**= Distance from index SNP to end or start of gene depending on whether the gene is upstream or downstream of the index SNP, respectively.

SUPPLEMENTARY TABLE 10. INRICH Pathway Analysis. Enriched gene sets with corrected P-value < .10 of the analyzed gene set databases (C2:CP, C5:BP, C5:CC, and C5:MF) are shown. Intervals were defined by the 19 index SNPs +/- 100kb.

Gene Set Source	Gene Set Description	Gene Set Size	Overlapping Genes In AMD Loci	Empirical P-value	Corrected P-value
c2:cp	KEGG Complement and Coagulation Cascades	68	4	1.6×10^{-4}	0.027
c2:cp	Reactome Lipoprotein Metabolism	27	3	2.6×10^{-4}	0.041
c5:bp	Regulation of Apoptosis	335	6	6.4×10^{-4}	0.092
c5:bp	Regulation of Programmed Cell Death	336	6	6.4×10^{-4}	0.092
c5:cc	Collagen	23	4	1.0×10^{-5}	6.0×10^{-4}
c5:cc	Extracellular Matrix	100	5	4.0×10^{-5}	0.0022
c5:cc	Extracellular Matrix Part	57	4	4.0×10^{-5}	0.0022
c5:cc	Extracellular Region	437	11	1.0×10^{-5}	6.0×10^{-4}
c5:cc	Extracellular Region Part	330	10	1.0×10^{-5}	6.0×10^{-4}
c5:cc	Extracellular Space	237	6	4.5×10^{-4}	0.016
c5:cc	Proteinaceous Extracellular Matrix	98	5	4.0×10^{-5}	0.0022
c5:mf	Phospholipid Binding	40	3	9.3×10^{-4}	0.070

SUPPLEMENTARY TABLE 11: Interaction analysis between the 171 pairs of the 19 index SNPs. Nominally significant SNP pairs (p < .05) are shown.

Index SNP A	Gene Label A	Index SNP B	Gene Label B	N_{cases}	$N_{controls}$	Interaction Effect OR	Interaction P-value	Interaction Direction**
rs10737680	*CFH*	rs429608	*C2 / CFB*	6,645	49,367	1.25	5.2×10^{-5}	−−++++−++++
rs10490924	*ARMS2*	rs5749482	*TIMP3*	6,645	49,395	1.15	0.0052	−+++++−−++++
rs5749482	*TIMP3*	rs920915	*LIPC*	6,645	49,401	0.89	0.011	−−−+−−+−−−−+
rs1864163	*CETP*	rs6795735	*ADAMTS9*	6,524	49,244	1.11	0.021	+?++++?−−−++
rs4698775	*CFI*	rs920915	*LIPC*	6,327	47,618	0.92	0.022	+−+−?−−−−−−
rs10490924	*ARMS2*	rs10737680	*CFH*	6,645	49,395	1.09	0.025	−++−−++−+++−
rs5749482	*TIMP3*	rs3130783	*IER3 / DDR1*	6,645	49,399	1.12	0.034	−++−++−++−++
rs920915	*LIPC*	rs9542236	*B3GALTL*	5,818	46,078	0.93	0.038	−−−−+?−−−+−−
rs2230199	*C3*	rs5749482	*TIMP3*	5,219	44,032	0.85	0.041	+?−−??−−−−?

*****For the interaction analysis, an OR>1 implies that individuals carrying risk alleles at both loci are at greater risk of disease than expected assuming a log-additive model for risk. An OR<1 implies that individuals carrying risk alleles at both loci are at lesser risk of disease than expected assuming a log-additive model for risk.

**Plus and minus signs indicate the estimated direction of effect in each study, ordered as follows: BMES, MEEI, deCODE, AMD-EU-JHU, FAS/KORA, JAREDS, Melbourne, Miami/Vanderbilt, MMAP, Rotterdam, Tufts/MGH, UCSD GA. Question marks indicate exclusion of a study due to missing SNP genotypes, extreme effect sizes and/or standard errors.

SUPPLEMENTARY NOTE

GWAS Datasets

All participating GWAS studies were reviewed and approved by local Institutional Review Boards. In addition, subjects gave informed consent prior to enrollment.

1. AMD-EU-JHU

1.1. Baltimore

Cases: All participants were enrolled by the Wilmer Eye Institute in Baltimore. Grading was carried out with a classification system similar to that established by AREDS [4]. Diagnosis of advanced AMD was based on the presence of advanced GA or CNV shown in the submitted stereoscopic color fundus photos. When both GA and CNV were present, the patient was graded as CNV. Intermediate AMD and Early AMD were the same as the AREDS classifications. Patients were also graded as to the certainty of the diagnosis- 100% or less than 100%. Attempts were made to obtain additional follow up photos for all patients for whom certainty was less than 100% or they were at an intermediate or early stage to update diagnoses. Once a patient reached advanced CNV or GA with 100% certainty, no additional photos were obtained and the diagnosis was considered final. This study was approved by the Institutional Review Boards of the Johns Hopkins University. Subjects gave informed consent prior to participation.

1.2. Bonn

Cases: Early AMD, late AMD was defined according to the criteria of the ARM Epidemiological Study Group [5]. Patients below the age 55 years were excluded. Exclusion criteria included any systemic disease known to affect the complement system (e.g. rheumatoid arthritis) ascertained by a standardized case report form derived from the multicenter Fundus Autofluorescence in AMD (FAM) study [6]. Digital fundus photographs were obtained from all participants. In patients with CNV, optical coherence tomography and fluorescein angiography were performed. Fundus autofluorescence imaging was performed in patients with GA due to AMD. All fundus images were evaluated separately by two independent readers.

1.3. Créteil

Cases: Enrolled prospectively at the Department of Ophthalmology at the Hôpital intercommunal de Créteil. Eligible subjects were affected with CNV in one eye and early age-related maculopathy (any drusen or reticular pseudodrusen with or without pigmentary changes) in the fellow eye (not affected by CNV at entry). Inclusion criteria were as follows: 1) age ≥ 55 and < 85 years, 2) signed informed consent, 3) visual acuity ≥ +0.4 LogMAR units in the study eye, and 4) subjects likely to attend follow-up visits during the study period.

The main exclusion criteria were as follows: 1) CNV in both eyes or no CNV in any eye, 2) wide central atrophy encroaching on the fovea of the study eye, 3) progressive ocular diseases (severe glaucoma or other severe retinopathy), 4) corneal or lens opacities precluding retinal evaluation, 5) anticoagulant therapy or bleeding tendency and 6) subjects not covered by the French National Health system or wards of court. The study was reviewed and approved by the relevant IRB (Comité de Protection des Personnes, Paris-Ile de France 5, Paris, France).

1.4. Evry

Controls: Population-based controls were obtained from an anonymized genotype database maintained at the centre d'étude du polymorphisme humain (CEPH). Controls were matched to case samples in the selection based on principal component scores.

1.5. London

Cases: All subjects were of Caucasian descent and were recruited at the Moorfields Eye Hospital in London. Color stereoscopic fundus photography of the macular region with grading of the photographs according to the International Classification System for age-related maculopathy (ICARMS) [5] classification by 2 trained readers independently with any discrepancies being resolved by an ophthalmologist. Cases were excluded if they had retino-choroidal inflammatory disease, diabetic retinopathy, branch retinal vein or artery occlusion or any other cause of visual loss other than amblyopia. The ophthalmic examination included Snellen acuity, slit-lamp examination and biomicroscopic fundoscopy. Auto-fluorescence images were taken of the macula and fluorescein angiography was performed when choroidal neovascularisation was suspected. For patients presenting with visual dysfunction in the second eye, retrospective data was gathered from hospital records concerning previous acuities. Moreover, any color images or fluorescein images relating to previous visual loss were located from the hospital archive.

Controls: Examined in a similar fashion to cases and excluded if drusen > 63 µm was evident, or other signs of age-related maculopathy such as GA. Controls were recruited from spouses or friends of cases, or were from local residential homes for the elderly within 8 km of the hospital. Each participant was interviewed specifically for the study, and a family history, smoking history and other medical history was taken.

1.6. Paris

Cases: Patients were recruited from the Centre Hospitalier National d'Ophtalmologie des Quinze-Vingts à Paris. Grading was carried out with the classification established by AREDS [4]. Digital fundus photographs were obtained from all participants. All images were digitized. Classification was performed by two ophthalmologists. Participants underwent a clinical examination which included visual acuity measurements, color fundus photography, auto-fluorescence imaging and optical coherence tomography. Fluorescein angiography was performed when CNV was suspected.

1.7. Southampton

Cases: Aged older than 55 years, of European descent and ascertained through the Southampton Eye Unit or research clinics undertaken by Andrew Lotery in Guernsey. Classified on the basis of the AREDS classification system [7].

Controls: Same as cases.

2. Vision Research Foundation (VRF, India)

Cases: All cases and controls were of southern Indian ancestry and were aged more than 50 years. AMD was graded using the modified AREDS classification system [8] from fundus photographs. In addition, all subjects underwent a complete ophthalmic examination including recording of the best-corrected visual acuity, subjective refraction, slit-lamp examination, applanation tonometry, binocular indirect ophthalmoscopy and stereoscopic evaluation of disc and macula using the +78 D lens. A 30-degree macula-centered color photograph was taken for each eye after pharmacologic

mydriasis with tropicamide 0.5% and phenylephrine 5%. The Zeiss FF450-plus fundus camera with VISUPAC digital image archiving system (Carl Zeiss, Jena, Germany) was used.

Controls: Control subjects were recruited through the ongoing Chennai Glaucoma epidemiology study [9]. Control subjects had no sign of AMD, in form of drusen or RPE abnormalities.

Study references: Sivakumaran *et al.* 2011, Vijaya *et al.* 2008

3. BMES (Blue Mountains Eye Study)

The BMES is a population-based cohort study of older Australians, aged 49+ years at baseline. Over 98% of 3654 baseline and 1174 BMES extension study participants had 6-field retinal photographs taken of both eyes. Retinal photographs were assessed for AMD lesions following the International Classification and Grading System for AMD. Definitions of early and late AMD closely followed the Wisconsin Age-Related Maculopathy Grading System. [10]

Cases: Early AMD: Presence of large soft indistinct drusen (>125 µm) or reticular drusen alone, RPE depigmentation or increased retinal pigment in combination with large soft distinct drusen in the absence of late AMD. Late AMD: Presence of neovascular AMD (CNV) or pure geographic atrophy (GA). If GA and neovascular ARM were present in the same eye or the same person but different eyes, neovascular ARM was considered the diagnosis for the eye or the person.

Controls: No soft (distinct or indistinct) or intermediate drusen, any retinal pigment abnormalities (either depigmentation or increased pigment), and no signs of early or late AMD. Controls may have hard drusen.

Study references: Bird *et al.* 1995, Klein *et al.* 1991, Mitchell *et al.* 1995, Mitchell *et al.* 2002, Wang *et al.* 2007

4. UK Cambridge/Edinburgh Study

Cases: Selected from existing Cambridge and Edinburgh AMD case-control sample collections [14]. All cases had at least one eye affected by CNV and/or GA. For subjects genotyped using the 300k platform, preference was given to cases with early onset. Cambridge cases were recruited from ophthalmic clinics in London, the South East of England and the North West of England between 2002 and 2006 [14]. All subjects described themselves as “white” rather than “other” on a recruitment questionnaire. Subjects were examined by an ophthalmologist and had colour, stereoscopic fundus photography of the macular region. The images were graded at the Reading Centre, Moorfields Eye Hospital, London using the International Classification of Age-related Maculopathy and Macular Degeneration [5]. The majority of the Edinburgh cases were recruited from ophthalmic clinics in Edinburgh, Dundee and Inverness between 2004 and 2006 and the remainder came from the 1921 Lothian Birth Cohort [15]. All subjects were examined by an ophthalmologist and had colour, stereoscopic fundus photography of the macular region. Images were graded by an ophthalmologist working on the study using the International Classification of Age-related Maculopathy and Macular Degeneration [5]; for validation 100 cases and controls were independently graded at the Moorfields Reading Centre.

Controls: Genotyping data was obtained from the British 1958 Birth Cohort (58BC) [16, 17]. For cases genotyped using the 300k platform, controls matched by geographic area were selected from the 58BC subjects used in the Wellcome Trust Case Control Consortium study [18]. For cases genotyped

using the 550k platform, controls matched by geographic area were selected from the 58BC subjects genotyped as controls for the Type 1 Diabetes Genetics Consortium (T1DGC) study [16].

Study references: Bird *et al.* 1995, Yates *et al.* 2007, Deary *et al.* 2004, Barrett *et al.* 2009, Power and Elliott 2006, Wellcome Trust Case Control Consortium 2007, Cipriani *et al.* 2012

5. deCODE AMD

Cases: Probands were recruited from a list of patients diagnosed with AMD or early AMD at the University Eye Clinic, Reykjavik, or listed in the Icelandic Registry for the Blind during the years 1980-2001, together with their relatives. The AMD cases used in the study went through a standard examination protocol and visual-acuity measurments [21].

Controls: Selected among individuals that have participated in various genetic studies at deCODE genetics and that had been genotyped with the same Illumina chips.

Study references: Magnusson *et al.* 2006.

6. Frankonian AMD study (FAS) / Kooperative Gesundheitsforschung in der Region Augsburg (KORA) Study

Cases: All AMD patients were examined by trained ophthalmologists. Stereo fundus photographs were graded according to standardized classification systems [5] with minor modifications due to the application of 50° digital fundus images and the inclusion of HRA-AF and infrared reflectance images for the evaluation of geographic atrophy and reticular drusen.

Case subphenotypes: Based on the grading of the worse eye (early AMD < GA or NV < Mixed NV/GA).

Controls: Population based without diagnosis based on the KORA platform

Study references: Rivera *et al.* 2005, Holle *et al.* 2005

7. JAREDS (Japanese Age Related Eye Disease Study)

Cases: All AMD cases were diagnosed by comprehensive ophthalmic examination. We classified exudative AMD into 4 subtypes under the established criteria (see references). We did not include dry type AMD.

Controls: For the control subjects, we used genome-wide screening data of BioBank Japan samples, which consists of 2,421 individuals with thirteen diseases and 902 healthy volunteers recruited from Osaka-Midousuji Rotary Club, Osaka, Japan. All control individuals had not had a recent eye examination.

Study references: Arakawa *et al.* 2011, Nakamura 2007

8. MEEI (Massachusetts Eye and Ear Institute) Sibpairs

Cases: All subjects included in this analysis were of Caucasian descent and were recruited from the Retina Service of the Massachusetts Eye and Ear Infirmary in Boston, MA and Associated Retina Consultants at the William Beaumont Hospital in Royal Oak, MI. All probands were at least 50 years of age and had CNV in at least one eye. CNV cases were diagnosed via evaluation of fundus photographs or fluorescein angiograms, and defined as having subretinal hemorrhage, fibrosis, or fluorescein angiographic presence of neovascularization either prior to or at the time of enrollment in the study. Cases were excluded if individuals had any signs of pathologic myopia, presumed ocular

histoplasmosis syndrome, angioid streaks, choroidal rupture, any hereditary retinal diseases other than AMD, previous laser treatment due to retinal conditions other than AMD, and/or if retinal pigment epithelium detachment was the only exudative finding present, as this may not represent definite CNV.

Controls: Controls were excluded if there was evidence of large drusen (>63 μm in diameter), greater than 5 small drusen (<63 μm in diameter), pigment abnormalities, and/or neovascularization or other forms of AMD such as GA. Controls were recruited from siblings of probands and must have had a confirmed diagnosis of normal macula at an age greater than the affected sibling's recorded age of onset for CNV. Disease status of every participant was typically verified by at least 2 investigators, except in instances when an unaffected sibling had to be evaluated by a single investigator during a home visit.

Study references: Deangelis *et al.* 2008

9. Melbourne AMD GWAS

All individuals were of white European ancestry, 60 years of age or older. Study subjects were examined and photographed by trained ophthalmologists; fundus photographs were graded according to standardized classification systems for presence, type, size, location, and number of drusen and pigmentary abnormalities, and also for size and centrality of the late features of AMD, by two independent graders.

Cases: Late AMD: GA (sharply delineated areas of RPE hypopigmentation, larger than 175μm with visible choroidal vessels in its base) or CNV disease, (subretinal hemorrhage, fibrosis or fluorescein angiographic presence of neovascularisation documented at the time of, or prior to, enrolment in the study) in at least one eye. The worst affected eye of each case was used for classification purposes.

Controls: Presented with a normal fundus (<10 hard drusen <63 μm in size) and no altered macular pigmentation in both eyes.

Study references: NONE

10. Miami/Vanderbilt

Study participants were recruited from the Duke University Eye Center (DUEC), the Vanderbilt Eye Institute (VEI), and the Bascom Palmer Eye Institute (BPEI) at the University of Miami Miller School of Medicine. All participants were examined by a retinal specialist by slit-lamp biomicroscopy and dilated fundus examination, including indirect ophthalmoscopy. Fundus imaging was also obtained from all subjects.

Cases: Images were scored using a modified grading system based on the Age-Related Eye Disease Study (AREDS) described in detail elsewhere [27]. Briefly, the grading system was scored from 1 to 5. Early AMD: Grade 3. Late AMD: Grades 4-5.

Controls: Images were scored using a modified grading system based on the Age-Related Eye Disease Study (AREDS) described in detail elsewhere Schmidt *et al.* 2000. Briefly, the grading system was scored from 1 to 5. The 1 and 2 categories corresponded to controls.

Study references: Schmidt *et al.* 2000

11. Michigan/Mayo Clinic/AREDS/UPENN (MMAP)

11.1. Michigan/Mayo Clinic/UPENN

The University of Michigan cohort included affected patients who were enrolled primarily from the retina clinic of the Kellogg Eye Center and control participants were enrolled primarily from the general ophthalmology clinics of the Kellogg Eye Center. For the University of Pennsylvania cohort, subjects were ascertained through the ophthalmology practices of the University of Pennsylvania (Dr. Dwight Stambolian and colleagues) as well as subjects who participated in the clinical trial of the CAPT study. The Mayo subjects were enrolled from the practices of Dr. Albert Edwards and selected colleagues from Dallas, TX and Rochester, MN starting in 1998. All subjects were examined by an ophthalmologist. The study was approved by local Institutional Review Boards and all subjects gave informed consent prior to participation.

Cases: Affected with GA, CNV, or large drusen in at least one eye. If any of the above is only detected in one eye, the evidence of drusen or pigment changes must be found in the fellow eye. Cases were classified with regard to form of disease in the worse eye (neovascularization was considered to be the most severe outcome, large drusen were the least severe).

Controls: Examined and found to have no more than 5 hard drusen and are over the age of 50 (Mayo clinic cohort) or small drusen and pigment changes in one eye only and are over the age of 60 (UMich and UPenn clinic cohorts).

Study references: Abecasis *et al.* 2004, Chen *et al.* 2010, Zareparsi *et al.* 2005

11.2. Age-Related Eye Disease Study Research Group (AREDS)

The AREDS participants had annual fundus photographs for a mean duration of 10 years. These fundus photographs were graded centrally by a reading center with a standardized protocol.

Cases: The cases had evidence of neovascular AMD or geographic atrophy associated with AMD.

Controls: participants with no and minimal small drusen only during the entire 10 years of follow-up.

Study references: Age-Related Eye Disease Study Research Group 2001, Age-Related Eye Disease Study Research Group 2001

12. Rotterdam Study

Prospective population-based study of people aged 55 years and older. All participants have undergone the same examinations. Fundus photographs were graded using the modified International Classification and Grading System.

Cases: Late AMD: CNV and/or GA lesions; Early AMD: Soft distinct drusen and pigmentary changes or soft indistinct drusen with or without pigmentary changes. On request from Consortium: cases with large drusen > 125 µm.

Controls: No AMD lesions or only small hard drusen (<63 µm) and no pigmentary changes.

Study references: Hofman *et al.* 2009, van Leeuwen *et al.* 2003

13. Tufts Medical Center/Massachusetts General Hospital

Cases: All 912 cases participants had European ancestry and were unrelated. Subjects were classified according to the Clinical Age-Related Maculopathy Grading Staging System (CARMS) into 5 stages (as described in Seddon *et al.* 1997, Seddon *et al.* 2006): no age-related macular degeneration (AMD) (stage 1), early AMD (stage 2), intermediate AMD (stage 3), and two advanced stages of AMD:

geographic atrophy (stage 4) and neovascular disease (stage 5) by JMS. For this study, only confirmed cases of advanced AMD including geographic atrophy and neovascular disease (CARMS grades 4 and 5) based on ocular examination and fundus photography as well as other ocular imaging were included. Subject samples were derived from ongoing studies of JMS at Tufts Medical Center.

Controls: Examined control participants (N=491) had European ancestry, were unrelated to other controls and unrelated to cases, and had confirmed lack of signs of age-related macular degeneration based on ocular examination and fundus photography (CARMS grade 1). These subjects were participants in ongoing studies of JMS at Tufts Medical Center. An additional cohort of 1188 controls were analyzed with the same genotyping platform (AFFY 6.0) were derived from the Myocardial Infarction Genetics (MIGEN) project.

Study references: Seddon *et al.* 2006, Yu *et al.* 2011, Sobrin *et al.* 2011, Neale *et al.* 2010, Fagerness *et al.* 2009, Maller *et al.* 2007, Maller *et al.* 2006, Kathiresan *et al.* 2009

14. UCSD GA Study

Cases: Participants underwent a standard examination, which included visual acuity measurements, dilated slit lamp biomicroscopy, and stereoscopic color fundus photography. Grading was carried out with the classification established by AREDS. Diagnosis of advanced AMD was based on the presence of CNV (equivalent to AREDS category 4 or 5).

Controls: > 60 years old, having fewer than 5 small drusen (< 63 μm diameter), and no RPE abnormalities.

Study references: NONE

Replication Datasets

Genetic analyses in all studies were replication was undertaken were reviewed and approved by local Institutional Review Boards. In addition, subjects gave informed consent prior to enrollment.

15. AMD-EU-JHU
See GWAS data set "AMD-EU-JHU"

16. Beaver Dam Eye Study (BDES)
Cases: Late AMD: (CNV, GA or mixed); Early AMD: Drusen size >125 microns with or without pigmentary abnormalities who never developed late AMD during the twenty years of follow-up.

Controls: Did not develop early or late AMD during the twenty years of follow-up. Controls were selected to have been seen at at least one of the follow-up exam and to have only no or small hard drusen in either eye at any time point, thus showing no signs of early or late AMD.

Study references: NONE

17. Oregon
Cases: The sporadic case cohort is recruited through our clinical practice at the Casey Eye Institute, Oregon Health Sciences University. All are >60 years old, unrelated, AREDS category 4 photo verified advanced AMD, either geographic atrophy, neovascular AMD, or both.

Controls: Are based controls (>60 yrs) are recruited from our general ophthalmology clinic. All controls are fundus photo verified as no signs of AMD.

Study references: NONE

18. Central Greece cohort
Cases: This cohort included 24 individuals with AREDS 2, 47 with AREDS 3, 156 with AREDS 4a, b, or c.

Controls: 213 normals with AREDS 0/1.

These patients were recruited from the medical retina outpatient clinic at the University Hospital of Larissa, Greece. The diagnosis of macular degeneration was confirmed by optical coherence tomography and fluorescein angiography. Color fundus photographs and indocyanine green angiography were performed in some cases.

Study references: Silveira *et al.* 2010

19. Cleveland Clinic Foundation/ Veteran Affairs Medical Center Cohort (CCF/VAMC)
Cases: Subjects with large or extensive intermediate drusen, CNV or GA in at least one eye (AREDS severity groups 3, 4, 5).

Controls: Subjects with at most, small, hard drusen and no signs of AMD (AREDS group 1) and no family history of retinal disease.

Study references: NONE

20. Columbia University AMD Genetics Study
Cases: Patients with advanced AMD were subdivided into two phenotypic categories -- geographic atrophy (GA; stage 4) and exudative (CNV; stage 4) AMD – based on the classification of their most

severe eye at the time of their entry into the study. Age > 60. All study subjects were examined by trained ophthalmologists.

Controls: Did not exhibit any distinguishing signs of macular disease or have a known family history of AMD (stage 0). Age > 60. All study subjects were examined by trained ophthalmologists.

Study references: Hageman *et al.* 2005

21. Genetics of Age-related Maculopathy (GARM) (University of Pittsburgh/UCLA)

Cases: The diagnostic criteria were based on a combination of both clinical records and fundus photographs that were provided retrospectively by clinical practitioners unaffiliated with the research group. All records were reviewed and abstracted separately by a single retina specialist (MBG) and the masked photographs were independently graded by the same specialist. Clinical features included drusen (type, quantity, size), pigmentary changes (including pigment epithelial detachments) and/or the presence of end-stage disease (GA and/or CNV membranes). The determination of severity was based on the more severely affected eye. In only a few cases were single eye patients considered and they were treated as if this was the more severely affected eye. In those instances in which there were only photographs of one eye, the records for both eyes were evaluated. GA was excluded if there was evidence of a prior CNV or laser in that eye (by clinical history and/or from retinal photographs). Subjects were classified as exudative AMD based on a lesion in one or both eyes and/or as atrophic AMD based on clear evidence of GA in at least one eye for which there was no prior history of laser or macular surgery.

Individuals in which the photographs and/or records were suboptimal or for whom the disease was so advanced as to obliterate the earlier features of AMD were considered to be AMD cases, unless there was any documentation that was suggestive of an alternative etiology of macular disease.

Controls: Individuals ≥ 65 years old for whom eye-care records and/or fundus photographs indicated either no evidence of any macular changes (including drusen) or a small number (<10) of hard drusen (<=50 micron in diameter) without any other retinal pigment epithelial (RPE) changes.

Study references: Jakobsdottir *et al.* 2005

22. Iowa cohort

Individuals were of European-American descent, over the age of 60, and enrolled under Institutional Review Board (Columbia University and University of Iowa) approved protocols. Patients were examined by trained ophthalmologists. All stereo fundus photographs were graded according to standardized classification systems. Controls did not exhibit any distinguishing signs of macular disease or have a known family history of AMD (stage 0). AMD patients were subdivided into phenotypic categories [eAMD (stages 1a, 1b, 2a, 2b, and 3), geographic atrophy (GA; stage 4) and exudative (choroidal neovascularization; stage 4)] AMD based on the classification of their most severe eye at the time of their recruitment.

Cases: This cohort included 153 individuals with AREDS 2, 83 with AREDS 3, 782 with AREDS 4a, b, or c.

Controls: 426 normals with AREDS 0/1.

Study references: Hageman *et al.* 2005

23. Melbourne AMD GWAS
See GWAS data set "Melbourne AMD GWAS"

24. Miami/Vanderbilt
See GWAS data set "Miami/Vanderbilt"

25. NESC (The New England Sibling Pair Cohort)
Cases: This cohort included 43 subjects with AREDS 2, 63 with AREDS 3, 420 with AREDS 4a, b, or c, and.

All subjects included in this analysis were of Caucasian descent and were recruited from the Retina Service of the Massachusetts Eye and Ear Infirmary in Boston, MA; Associated Retina Consultants at the William Beaumont Hospital in Royal Oak, MI; and Queen's University, Belfast, Northern Ireland, UK. All probands were at least 50 years of age and had CNV in at least one eye. CNV cases were diagnosed via evaluation of fundus photographs or fluorescein angiograms, and defined as having subretinal hemorrhage, fibrosis, or fluorescein angiographic presence of neovascularization either prior to or at the time of enrollment in the study. Cases were excluded if individuals had any signs of pathologic myopia, presumed ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, any hereditary retinal diseases other than AMD, previous laser treatment due to retinal conditions other than AMD, and/or if retinal pigment epithelium detachment was the only exudative finding present, as this may not represent definite CNV.

Controls: 250 normals with AREDS 0/1

These patients were recruited from the Massachusetts Eye and Ear Infirmary in Boston, MA.

Controls were excluded if there was evidence of large drusen (>63 μm in diameter), greater than 5 small drusen (<63 μm in diameter), pigment abnormalities, and/or neovascularization or other forms of AMD such as GA. Controls were recruited from siblings of probands and must have had a confirmed diagnosis of normal macula at an age greater than the affected sibling's recorded age of onset for CNV. Disease status of every participant was typically verified by at least 2 investigators, except in instances when an unaffected sibling had to be evaluated by a single investigator during a home visit.

Study references: DeAngelis *et al.* 2004

26. NHS (Nurses Health Study) and HPFS (Health Professionals Follow Up Study):
Cases: This cohort included 293 individuals with AREDS 2, 164 with AREDS 4a, b, or c.

We used a validated 2-stage procedure to document incident cases of AMD. Briefly, we asked participants on each biennial study questionnaire about the diagnosis of AMD. When AMD was reported, we requested permission to review medical records. If permission was granted, we sent a letter to the participant's ophthalmologist to obtain information on the date of AMD diagnosis, best-corrected visual acuity at the most recent examination, and the chorioretinal lesions present (drusen; retinal pigment epithelium changes including atrophy, hypertrophy and retinal pigment epithelium detachment; geographic atrophy; subretinal neovascular membrane; disciform scar), and other information. We classified cases as neovascular AMD if there was a retinal pigment epithelium detachment, subretinal neovascular membrane, or disciform scar not due to other factors (eg, histoplasmosis, choroidal rupture). Only participants in whom we confirmed the presence

neovascular AMD with a visual acuity of 20/30 or worse attributable to AMD, who were first diagnosed after the date of receipt of the baseline blood specimen and were aged 50 years or older, were selected as cases for the present study. We classified participants based on the most severely affected eye.

Controls: 1070 age and sex-matched normals with AREDS 0/1. Three controls were selected for each case of neovascular AMD at random from study participants in the same cohort as the cases who were still at risk of AMD at the time the case was diagnosed; they were of the same age within 1 year and reported having an eye examination in the past 2 years.

Study references: Schaumberg *et al.* 2010

27. MMAP and National Eye Institute (NEI)
See GWAS data set "MMAP"

The NEI clinical center participants also had fundus photographs in a cross-sectional evaluation.

Cases: Those with CNV AMD and GA associated with AMD.

Controls: Either no drusen or small drusen.

28. Singapore AMD Genetic Study (SAGe)
Cases: Clearly defined CNV secondary to AMD. Choroidal neovascularization secondary to AMD was defined as serosanguineous maculopathy without evidence of PCV in patients 60 years of age or older and no evidence of other neovascular maculopathies. Equivocal cases were not included; patients with a combination of PCV and CNV lesions were not included in this study. All AMD cases in the replication sample were ethnically Chinese.

Controls: Identified from a population-based cohort−Singapore Chinese Eye Study (SCES). We included only subjects who were 60 years of age or older, and had no hard drusen, any soft drusen, any retinal pigment abnormalities, and no signs of early or late AMD.

Study references: Lavanya *et al.* 2009, Sng *et al.* 2011, Cackett *et al.* 2011

29. Seoul National University Bundang Hospital (SNUBH)
Cases: This cohort included 112 individuals with AREDS 3, 352 with AREDS 4a, b, or c.

Controls: 399 normals with AREDS 0/1. These cases and controls were recruited from a hospital-based clinic at the Seoul National University Bundang Hospital in Korea.

Study references: NONE

30. The Southern German AMD study
Consists of AMD patients and controls from the University Eye Clinics of München, Tübingen and Würzburg (Germany).

Cases: All AMD patients were examined by trained ophthalmologists. Stereo fundus photographs were graded according to standardized classification systems [5] with minor modifications due to the application of 50° digital fundus images and the inclusion of HRA-AF and infrared reflectance images for the evaluation of geographic atrophy and reticular drusen. AMD subphenotypes: Based on the grading of the worse eye (early AMD < GA or NV < Mixed NV/GA).

Controls (The Southern German AMD study): Examined by trained ophthalmologists

Study references: Rivera *et al.* 2005

31. UCSD GA Study:
See GWAS data set "UCSD GA Study"

32. Utah cohort:
Individuals were of European-American descent, over the age of 60, and enrolled under Institutional Review Board (Columbia University and University of Iowa) approved protocols. Patients were examined by trained ophthalmologists. All stereo fundus photographs were graded according to standardized classification systems. Controls did not exhibit any distinguishing signs of macular disease or have a known family history of AMD (stage 0). AMD patients were subdivided into phenotypic categories [eAMD (stages 1a, 1b, 2a, 2b, and 3), geographic atrophy (GA; stage 4) and exudative (choroidal neovascularization; stage 4)] AMD based on the classification of their most severe eye at the time of their recruitment.

Cases: This cohort included 45 individuals with AREDS 2, 93 with AREDS 3, 342 with AREDS 4a, b, or c.

Controls: 112 normals with AREDS 0/1. These subjects were recruited from clinics in Utah.

Study references: Hageman *et al.* 2005

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