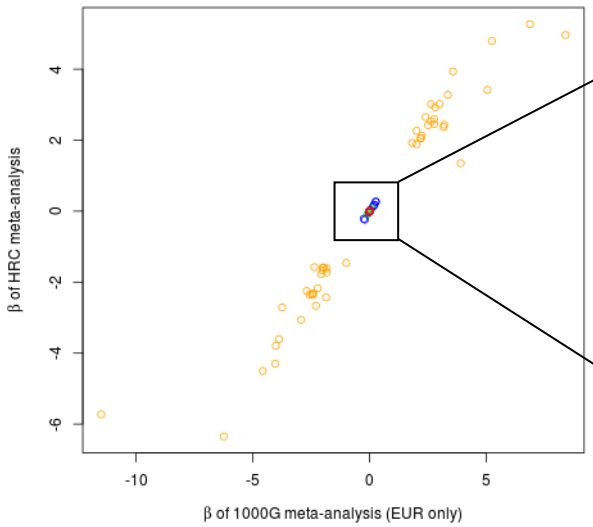
Supplementary Figures

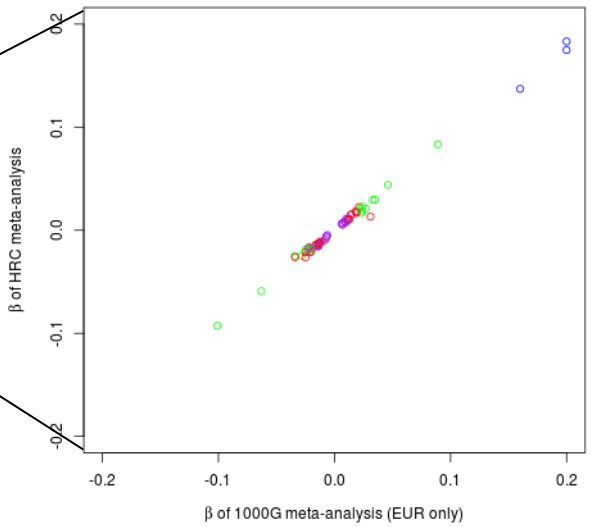
Supplementary Figure 1. The comparison of the results of Springelkamp et al.[1] and Iglesias et al.[2] with the meta-analysis of the discovery cohorts.

Panel (A) shows the comparison of β values, panel (B) shows the zoom in on panel (A), panel (C) shows the comparison of MAF values and panel (D) shows the comparison of p-values. The red circles are the CA loci, the yellow circles are the CCT loci, the green circles are the DA loci, the blue loci are the IOP loci and the purple circles are the VCDR loci.

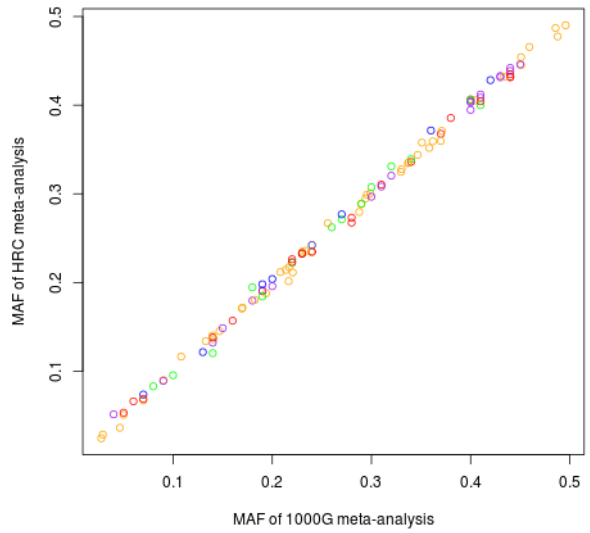
A



B



C



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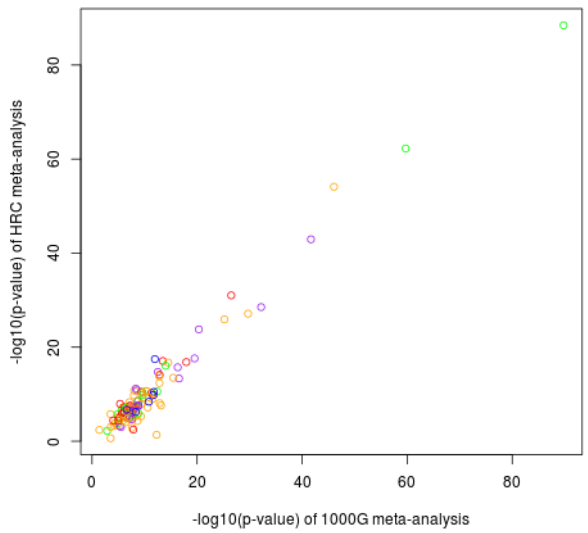
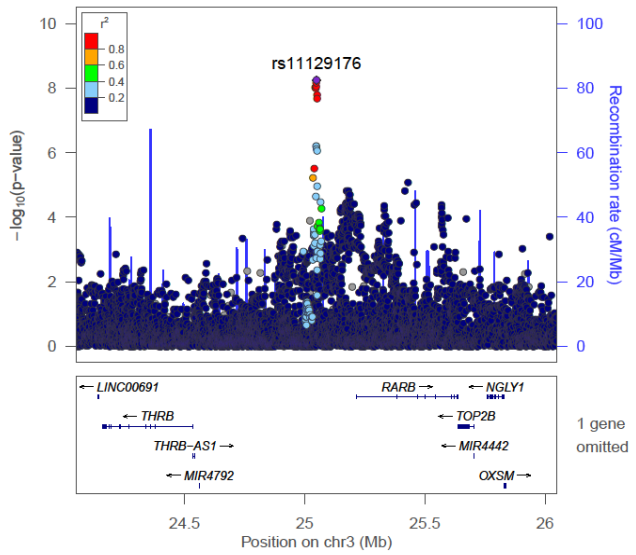


Supplementary Figure 2. Locuszoom plots of all novel identified variants for ONH by CPASSOC

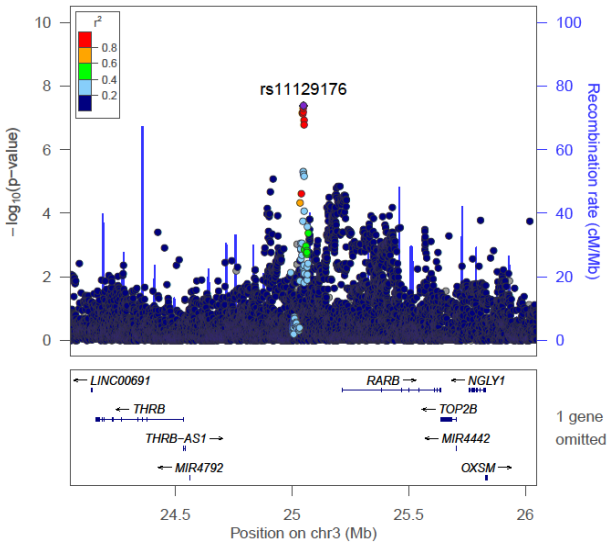
rs551947583(SHet)

SNP not available in Locuszoom

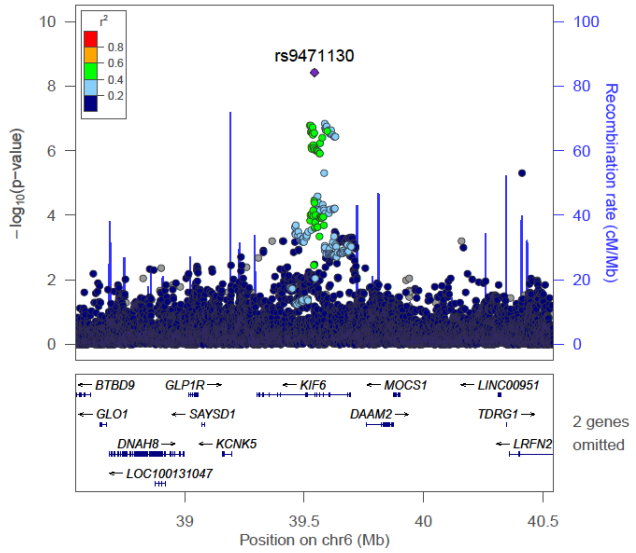
rs11129176 (SHom)



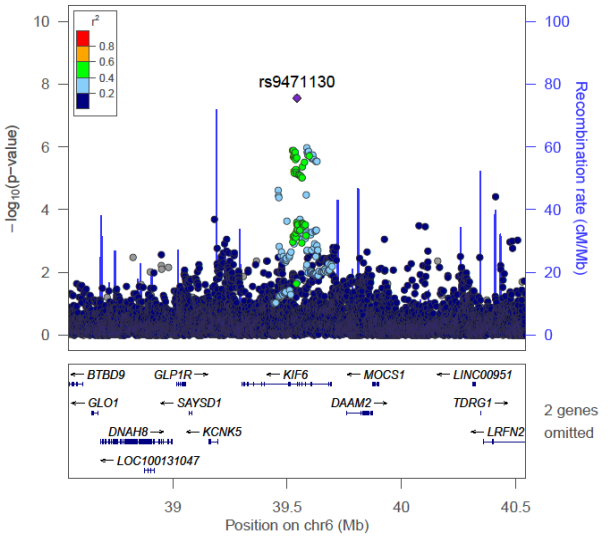
rs11129176 (SHet)



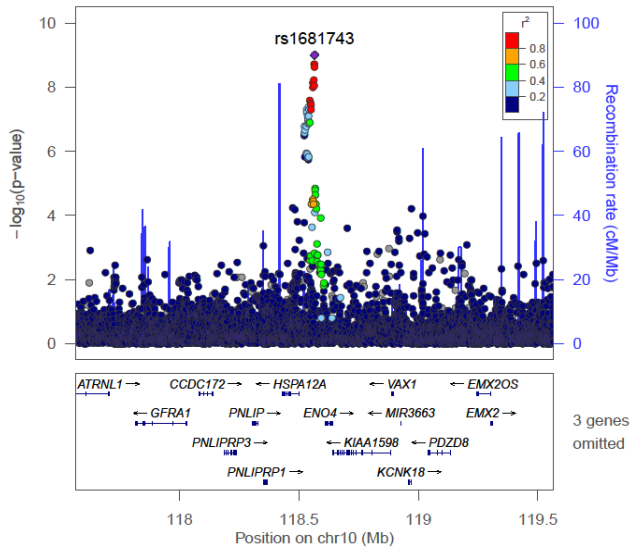
rs9471130 (SHom)



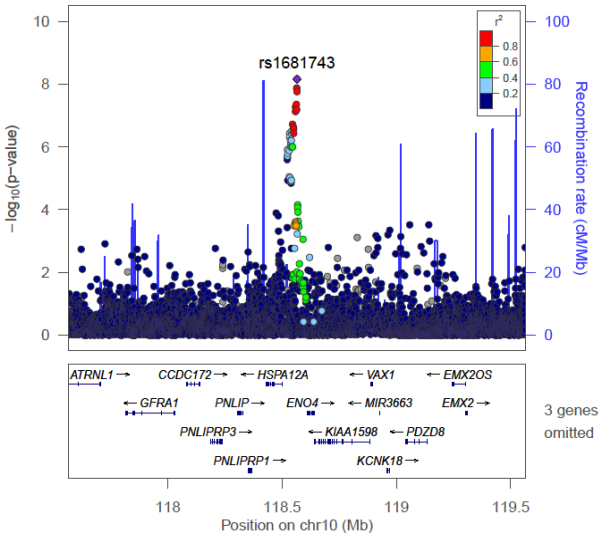
rs9471130 (SHet)



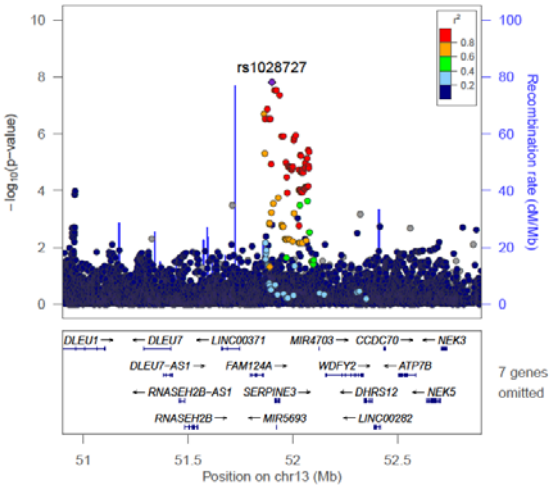
rs1681743 (SHom)



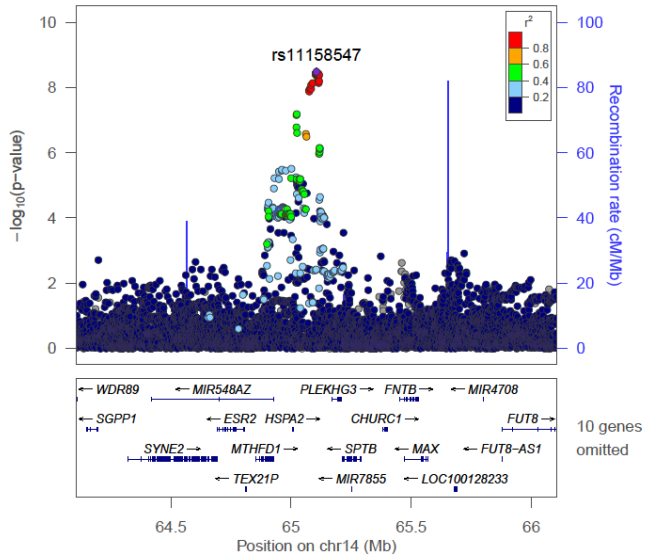
rs1681743 (SHet)



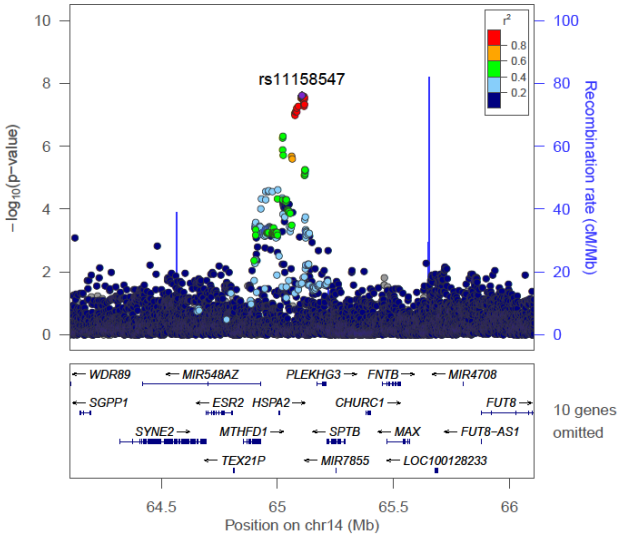
rs1028727



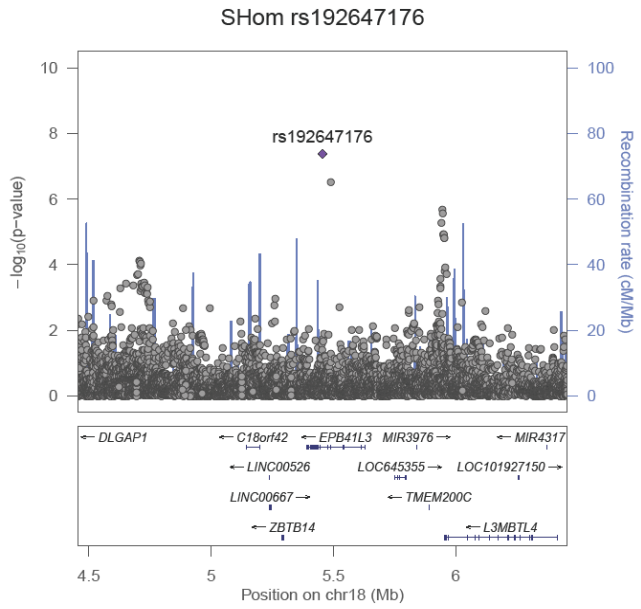
rs11158547 (SHom)



rs11158547 (SHet)

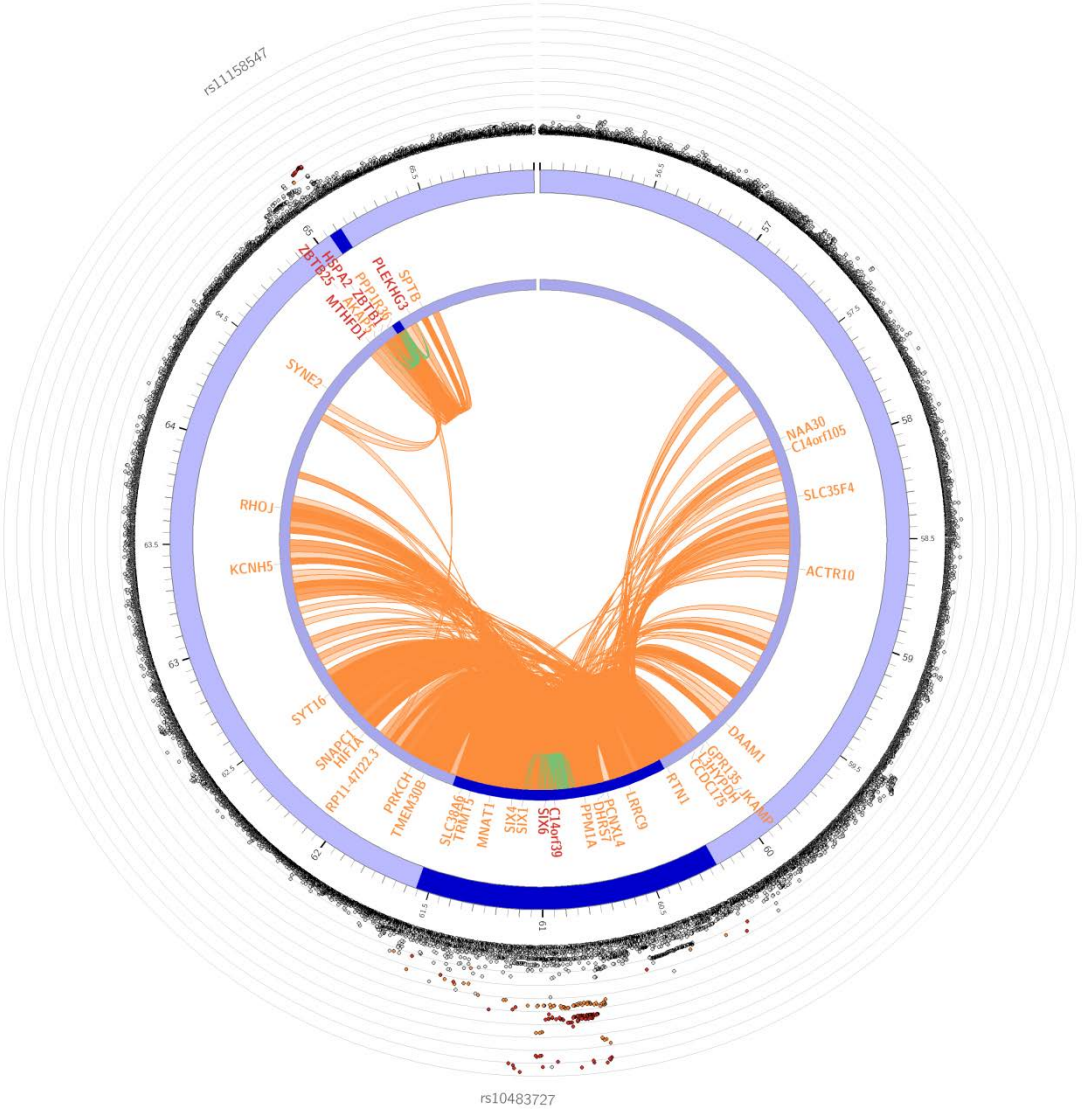


rs192647176 (SHom)


SHom rs192647176
rs192647176
−log10(p−value)
Recombination rate (cM/Mb)
DLGAP1
C18orf42
EPB41L3
MIR3976
MIR4317
LINC00526
LOC645355
LOC101927150
LINC00667
TMEM200C
ZBTB14
L3MBTL4
Position on chr18 (Mb)

Supplementary Figure 3. Circos plot depicting chromatin interactions and eQTL links for chromosome 14

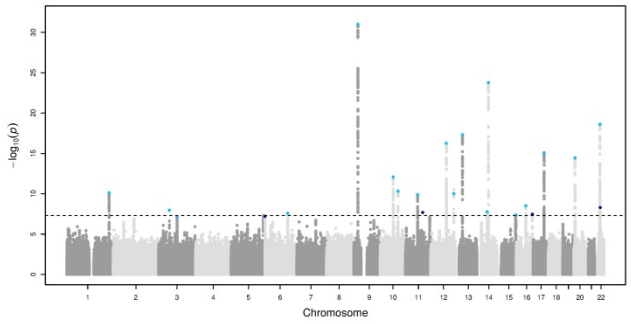
Outer circle: regional association plots for SNPs *P*<0.05 SNPs in genomic risk loci are color-coded as a function of their maximum r2 to the one of the independent significant SNPs in the locus, as follows: red (r2 > 0.8), orange (r2 > 0.6), green (r2 > 0.4) and blue (r2 > 0.2). SNPs that are not in LD with any of the independent significant SNPs (with r2 ≤ 0.2) are grey. Second circle: positional map, genomic risk loci are highlighted in blue.
Third circle: mapped genes by chromatin interactions or eQTLs. Gene mapped only by chromatin interactions or only by eQTLs are colored orange or green, respectively. When the gene is mapped by both, it is colored red.



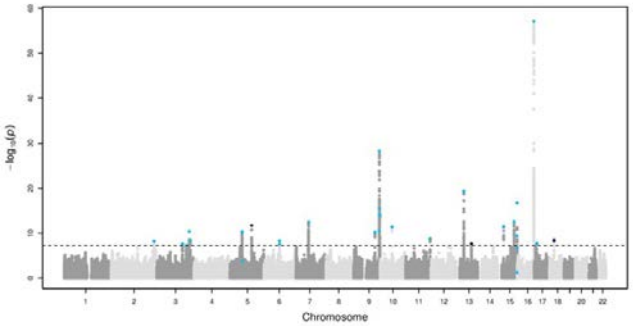
Supplementary Figure 3. Manhattan plots for all traits after the meta-analysis of all discovery cohorts.

Panel (A) shows the manhattan plot for CA, panel (B) shows the manhattan plot for CCT, panel (C) shows the manhattan plot for DA, panel (D) shows the manhattan plot for IOP, panel (E) shows the manhattan plot for VCDR. Variants that passed quality control and that were present in at least 3 cohorts were included. The black dotted line indicates the genome-wide significant line ($5 \cdot 10^{-8}$), the dark blue and the light blue dotes indicate the independent variants which are identified by GCTA within 1 Mb and more than 1 Mb away, respectively, from a published loci for that particular trait. As there are no published loci for RA, all independent loci identified by GCTA are considered new loci.

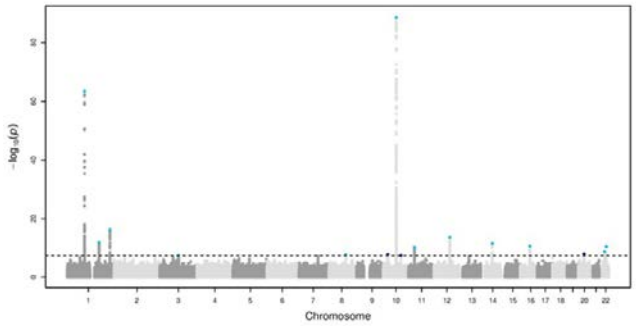
A



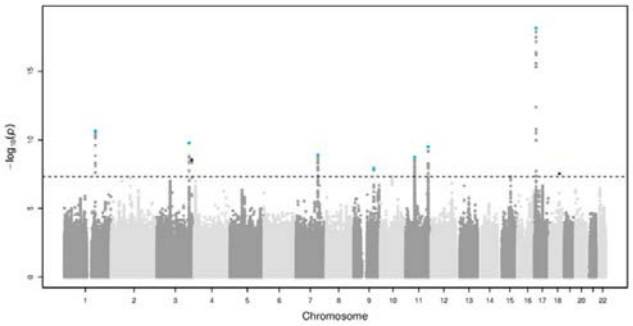
B



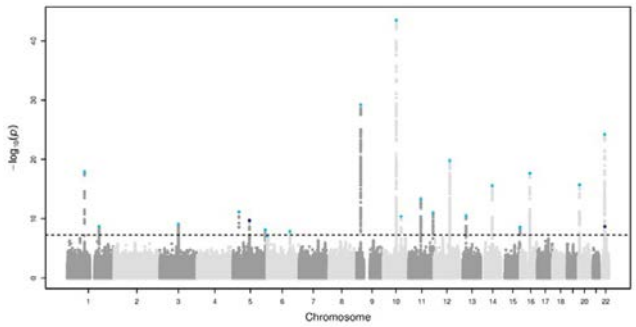
C



D



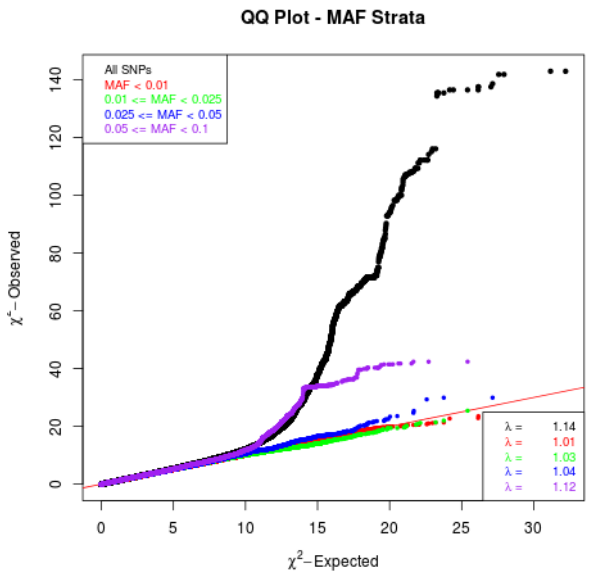
E



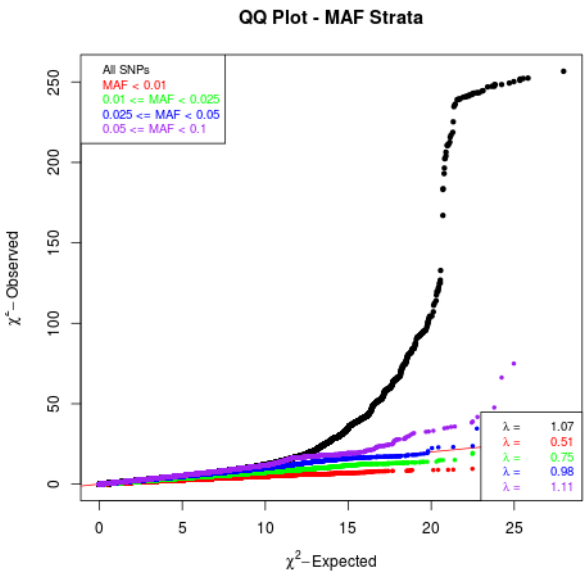
Supplementary Figure 4 QQ-plot for all traits after the meta-analysis of all discovery cohorts.

Panel (A) shows the manhattan plot for CA~DA, panel (B) shows the manhattan plot for CCT, panel (C) shows the manhattan plot for DA, panel (D) shows the manhattan plot for IOP, panel (E) shows the manhattan plot for VCDR. Variants that were present in at least 3 cohorts were included.

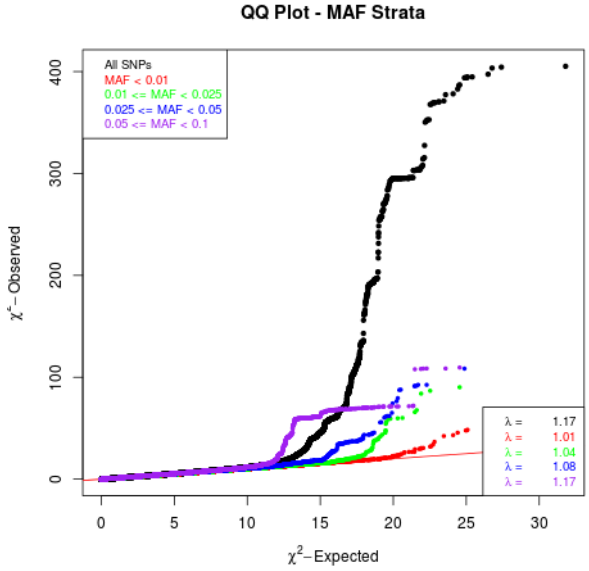
A



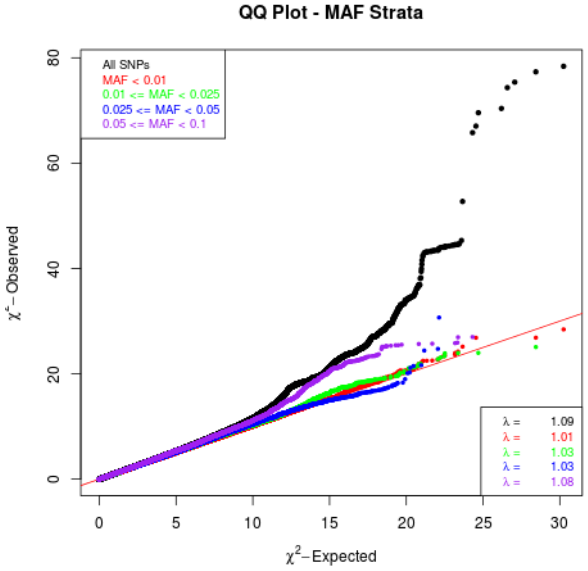
B



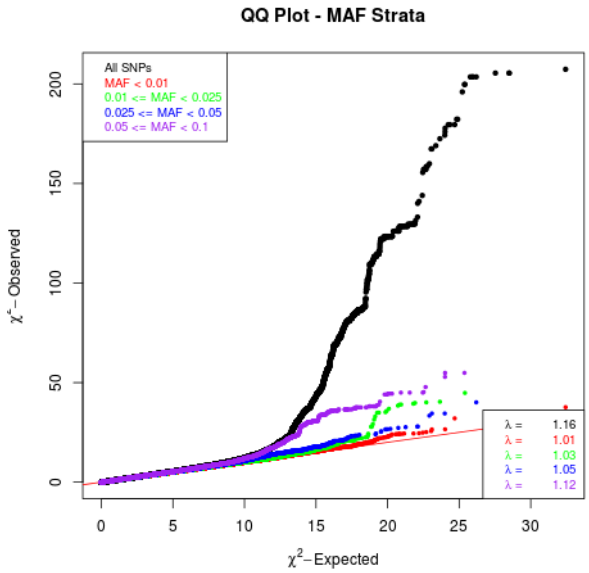
C



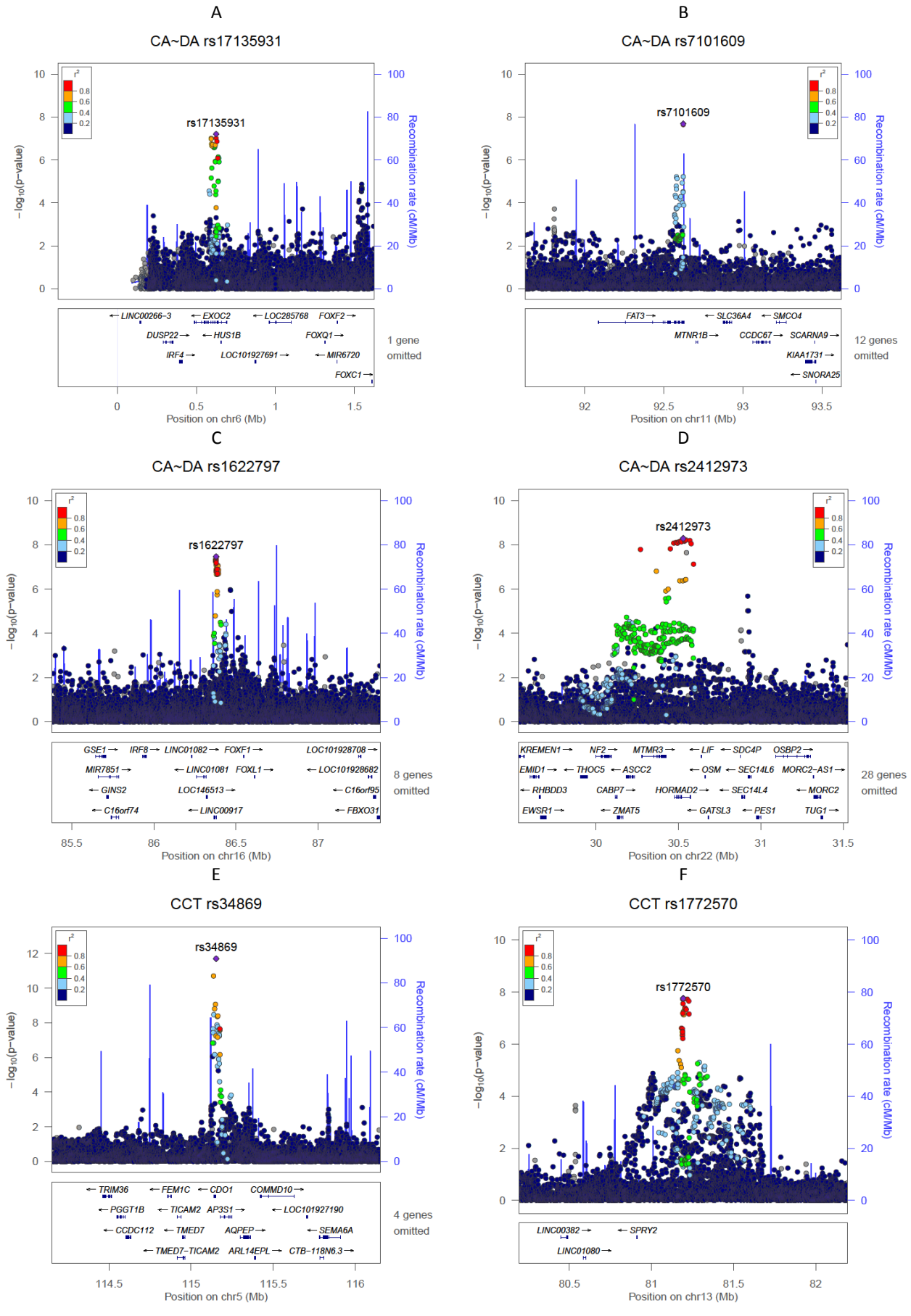
D



E

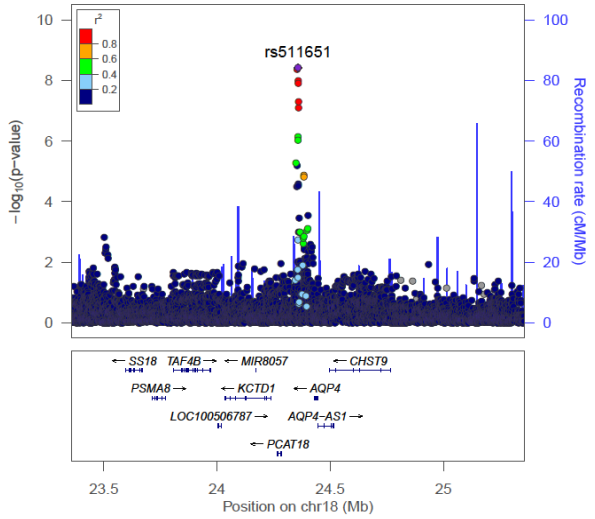

QQ Plot - MAF Strata
All SNPs
MAF < 0.01
0.01 <= MAF < 0.025
0.025 <= MAF < 0.05
0.05 <= MAF < 0.1
λ = 1.16
λ = 1.01
λ = 1.03
λ = 1.05
λ = 1.12
χ2 – Observed
χ2 – Expected
0
50
100
150
200
0
5
10
15
20
25
30

Supplementary Figure 5 Locuszoom plots of all novel identified variants within the single-trait meta-analysis.



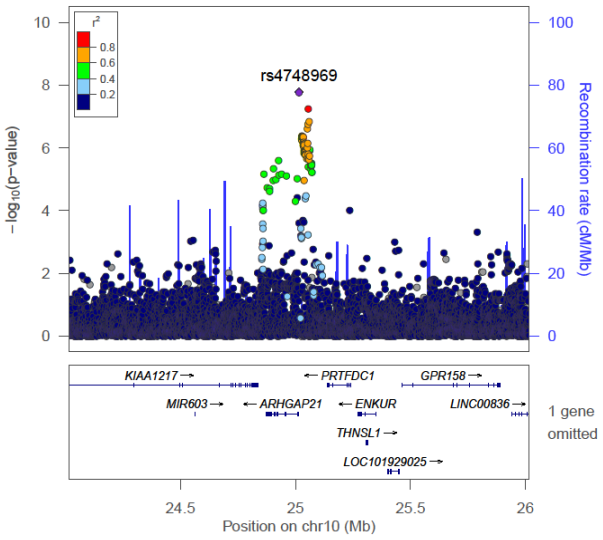
G

CCT rs511651



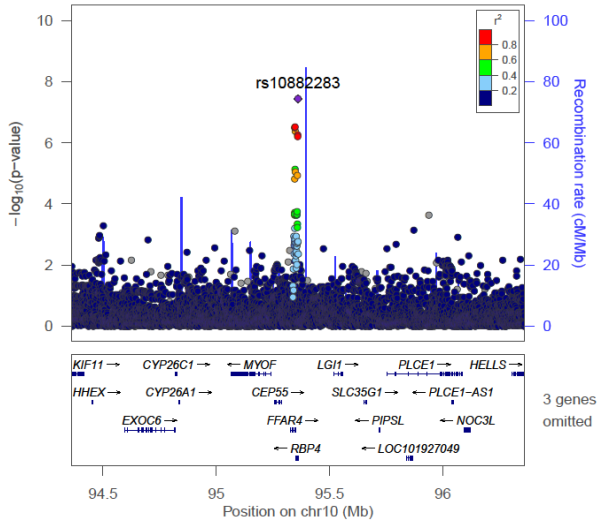
H

DA rs4748969



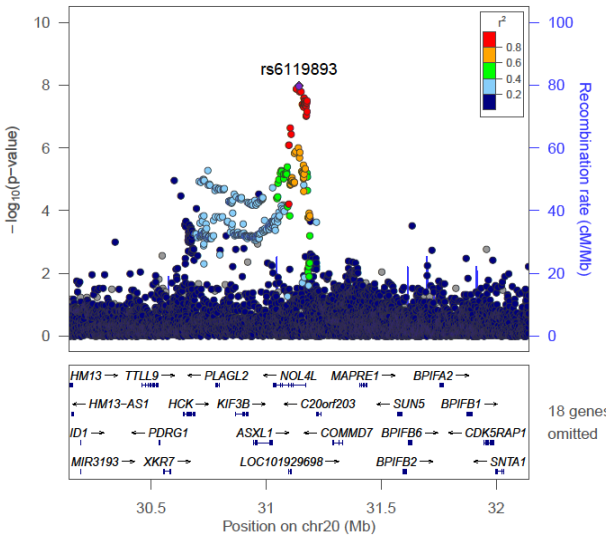
I

DA rs10882283



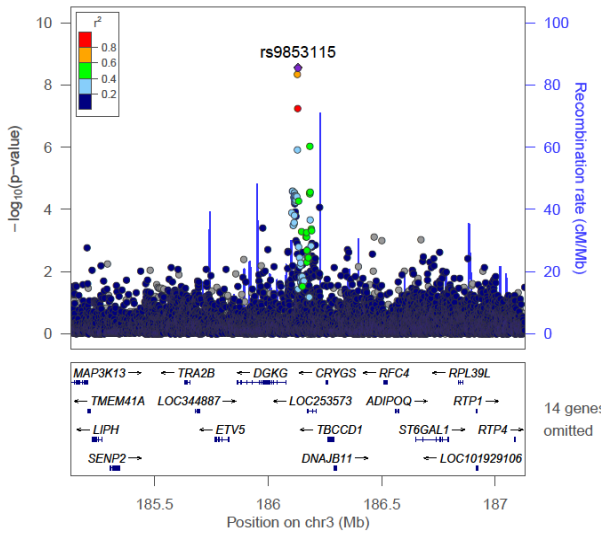
J

DA rs6119893



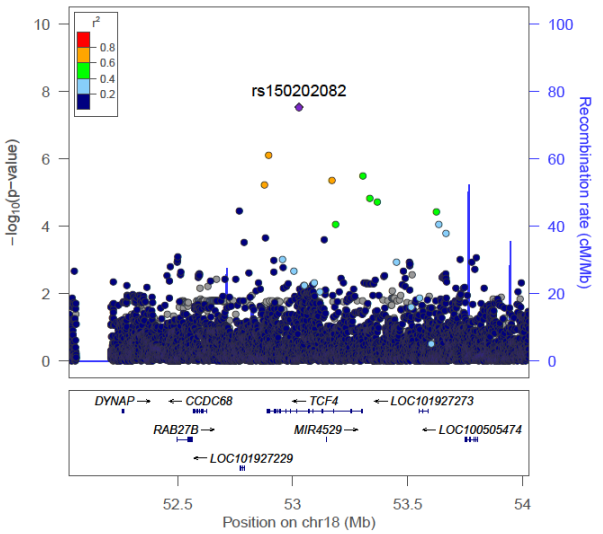
K

IOP rs9853115



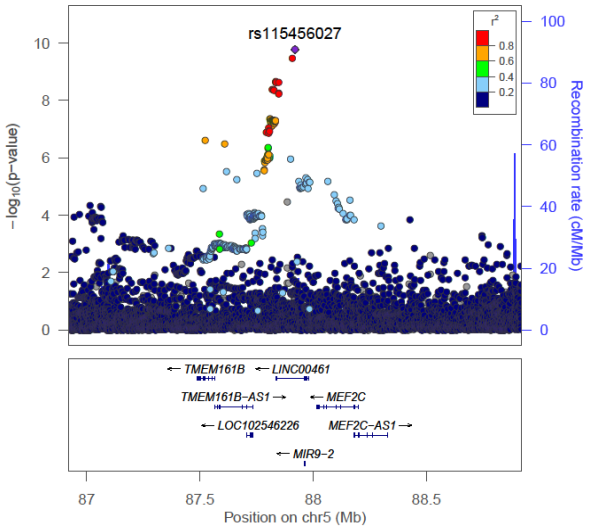
L

IOP rs150202082



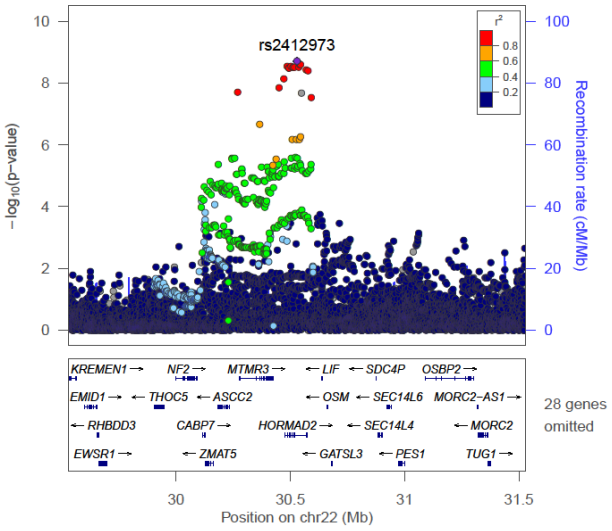
M

VCDR rs115456027



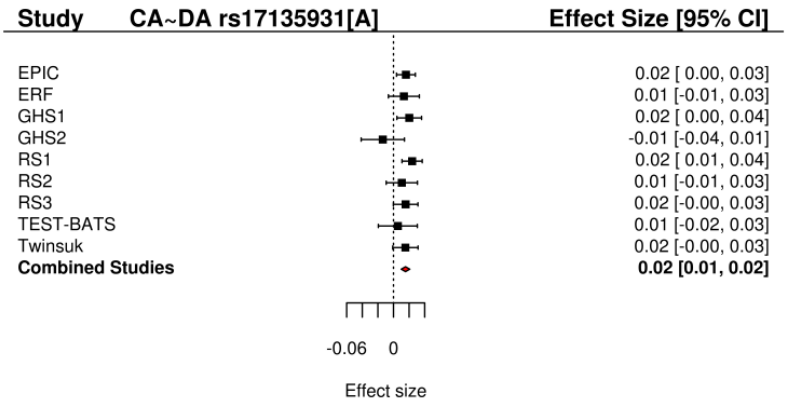
N

VCDR rs2412973

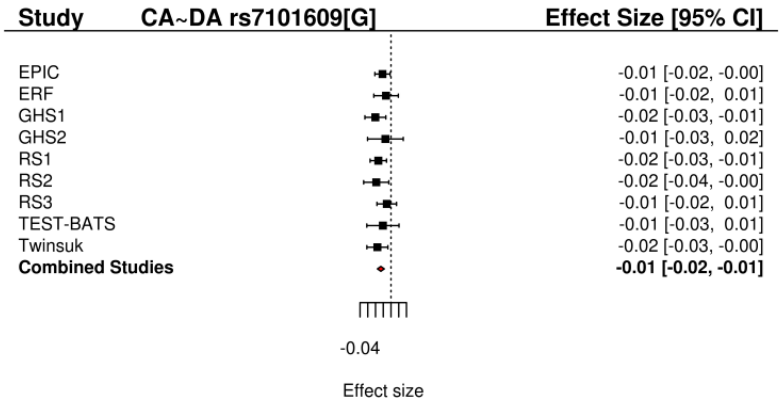


Supplementary Figure 6. Forest plots of all novel identified variants within the single-trait meta-analysis.

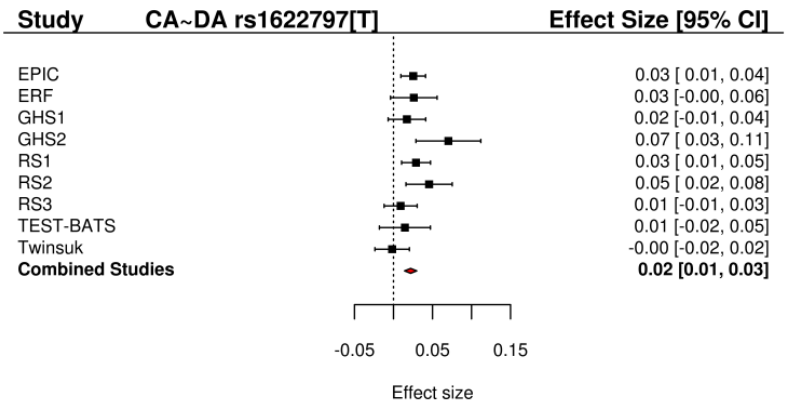
A



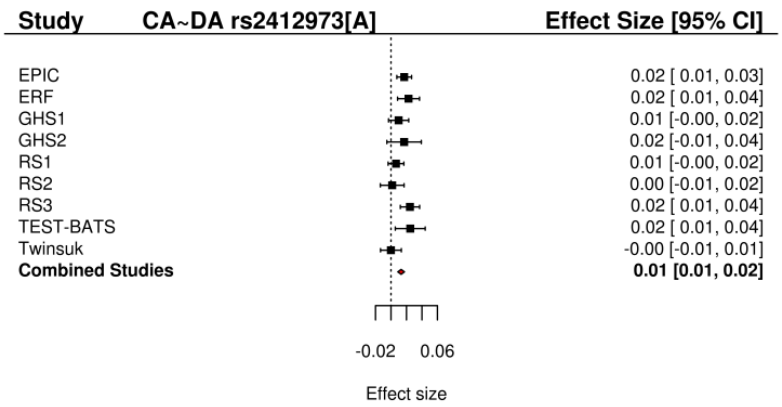
B



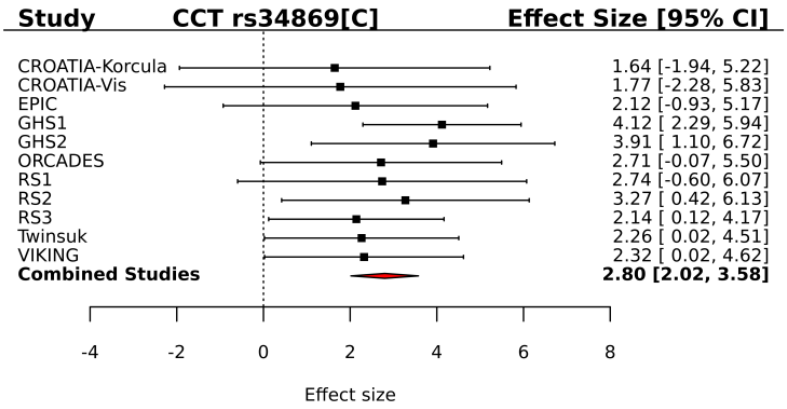
C



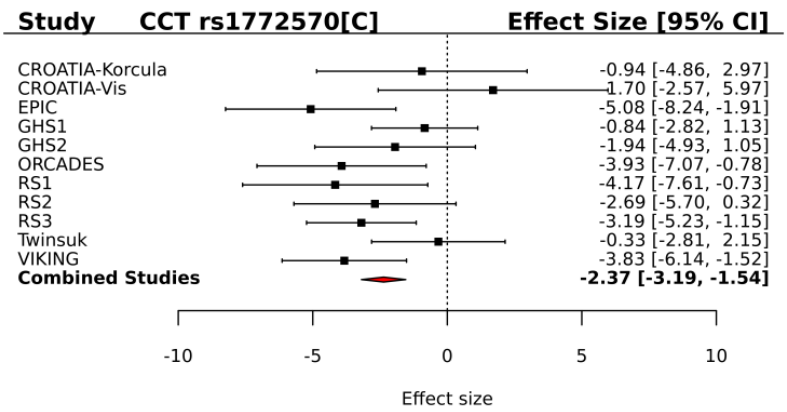
D


Study
CA~DA rs2412973[A]
Effect Size [95% CI]
EPIC 0.02 [0.01, 0.03]
ERF 0.02 [0.01, 0.04]
GHS1 0.01 [-0.00, 0.02]
GHS2 0.02 [-0.01, 0.04]
RS1 0.01 [-0.00, 0.02]
RS2 0.00 [-0.01, 0.02]
RS3 0.02 [0.01, 0.04]
TEST-BATS 0.02 [0.01, 0.04]
Twinsuk -0.00 [-0.01, 0.01]
Combined Studies 0.01 [0.01, 0.02]
-0.02
0.06
Effect size

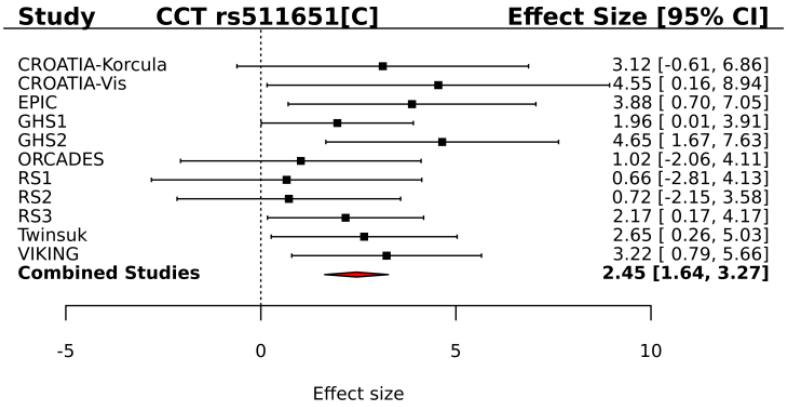
E


Study
CCT rs34869[C]
Effect Size [95% CI]
CROATIA-Korcula 1.64 [-1.94, 5.22]
CROATIA-Vis 1.77 [-2.28, 5.83]
EPIC 2.12 [-0.93, 5.17]
GHS1 4.12 [2.29, 5.94]
GHS2 3.91 [1.10, 6.72]
ORCADES 2.71 [-0.07, 5.50]
RS1 2.74 [-0.60, 6.07]
RS2 3.27 [0.42, 6.13]
RS3 2.14 [0.12, 4.17]
Twinsuk 2.26 [0.02, 4.51]
VIKING 2.32 [0.02, 4.62]
Combined Studies 2.80 [2.02, 3.58]
-4
-2
0
2
4
6
8
Effect size

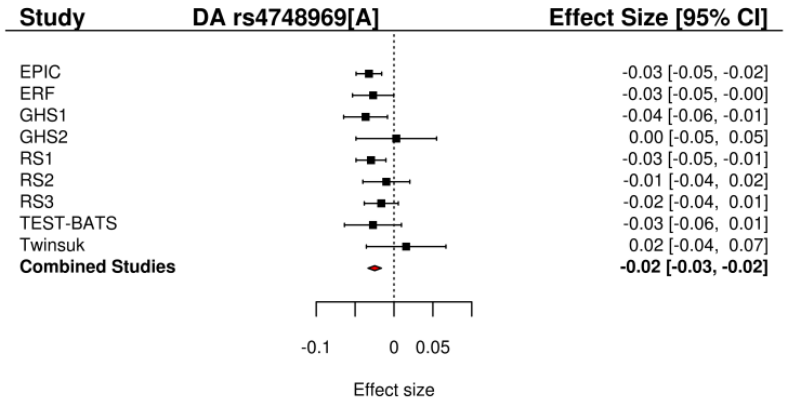
F


Study
CCT rs1772570[C]
Effect Size [95% CI]
CROATIA-Korcula -0.94 [-4.86, 2.97]
CROATIA-Vis 1.70 [-2.57, 5.97]
EPIC -5.08 [-8.24, -1.91]
GHS1 -0.84 [-2.82, 1.13]
GHS2 -1.94 [-4.93, 1.05]
ORCADES -3.93 [-7.07, -0.78]
RS1 -4.17 [-7.61, -0.73]
RS2 -2.69 [-5.70, 0.32]
RS3 -3.19 [-5.23, -1.15]
Twinsuk -0.33 [-2.81, 2.15]
VIKING -3.83 [-6.14, -1.52]
Combined Studies -2.37 [-3.19, -1.54]
-10
-5
0
5
10
Effect size

G


Study
CCT rs511651[C]
Effect Size [95% CI]
CROATIA-Korcula 3.12 [-0.61, 6.86]
CROATIA-Vis 4.55 [0.16, 8.94]
EPIC 3.88 [0.70, 7.05]
GHS1 1.96 [0.01, 3.91]
GHS2 4.65 [1.67, 7.63]
ORCADES 1.02 [-2.06, 4.11]
RS1 0.66 [-2.81, 4.13]
RS2 0.72 [-2.15, 3.58]
RS3 2.17 [0.17, 4.17]
Twinsuk 2.65 [0.26, 5.03]
VIKING 3.22 [0.79, 5.66]
Combined Studies 2.45 [1.64, 3.27]
-5
0
5
10
Effect size

H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Effect Size [95% CI]
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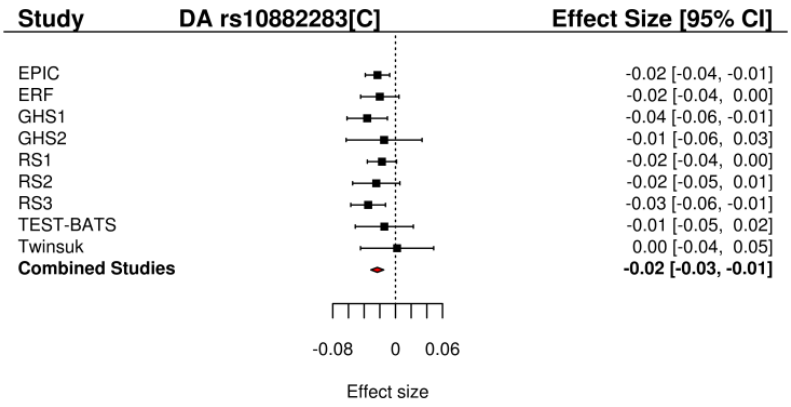
ERF -0.03 [-0.05, -0.00]
GHS1 -0.04 [-0.06, -0.01]
GHS2 0.00 [-0.05, 0.05]
RS1 -0.03 [-0.05, -0.01]
RS2 -0.01 [-0.04, 0.02]
RS3 -0.02 [-0.04, 0.01]
TEST-BATS -0.03 [-0.06, 0.01]
Twinsuk 0.02 [-0.04, 0.07]
Combined Studies -0.02 [-0.03, -0.02]
-0.1
0
0.05
Effect size

I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Effect Size [95% CI]
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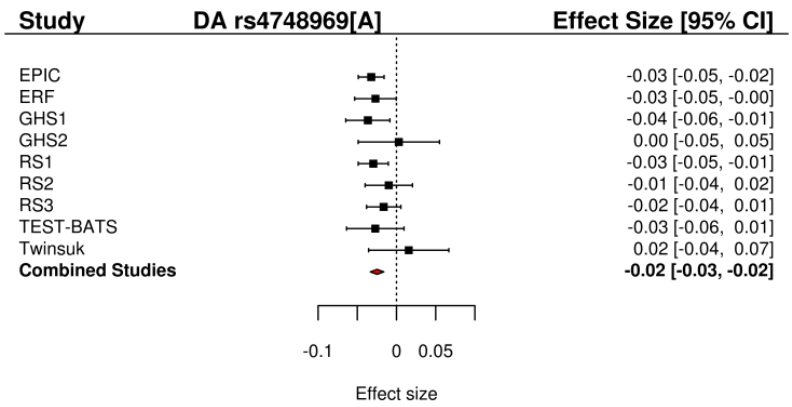
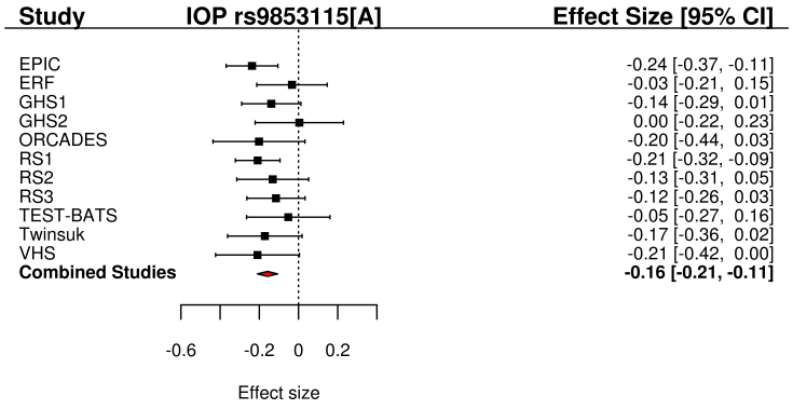
ERF -0.02 [-0.04, 0.00]
GHS1 -0.04 [-0.06, -0.01]
GHS2 -0.01 [-0.06, 0.03]
RS1 -0.02 [-0.04, 0.00]
RS2 -0.02 [-0.05, 0.01]
RS3 -0.03 [-0.06, -0.01]
TEST-BATS -0.01 [-0.05, 0.02]
Twinsuk 0.00 [-0.04, 0.05]
Combined Studies -0.02 [-0.03, -0.01]
-0.08
0
0.06
Effect size

J


Study
DA rs4748969[A]
Effect Size [95% CI]
EPIC
ERF
GHS1
GHS2
RS1
RS2
RS3
TEST-BATS
Twinsuk
Combined Studies
-0.03 [-0.05, -0.02]
-0.03 [-0.05, -0.00]
-0.04 [-0.06, -0.01]
0.00 [-0.05, 0.05]
-0.03 [-0.05, -0.01]
-0.01 [-0.04, 0.02]
-0.02 [-0.04, 0.01]
-0.03 [-0.06, 0.01]
0.02 [-0.04, 0.07]
-0.02 [-0.03, -0.02]
-0.1
0
0.05
Effect size

K


Study
IOP rs9853115[A]
Effect Size [95% CI]
EPIC
ERF
GHS1
GHS2
ORCADES
RS1
RS2
RS3
TEST-BATS
Twinsuk
VHS
Combined Studies
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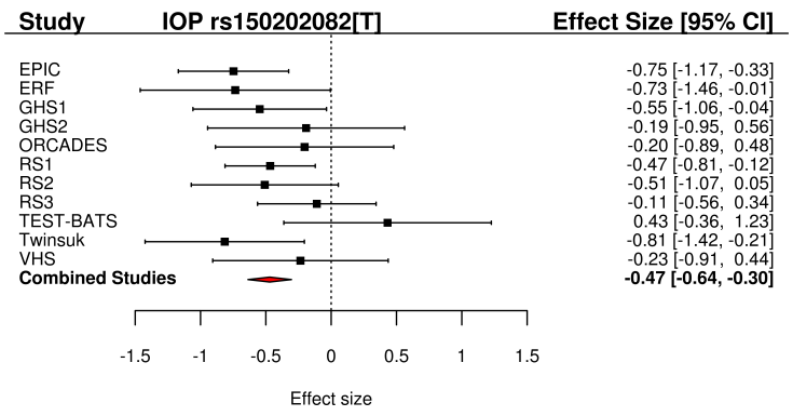
-0.03 [-0.21, 0.15]
-0.14 [-0.29, 0.01]
0.00 [-0.22, 0.23]
-0.20 [-0.44, 0.03]
-0.21 [-0.32, -0.09]
-0.13 [-0.31, 0.05]
-0.12 [-0.26, 0.03]
-0.05 [-0.27, 0.16]
-0.17 [-0.36, 0.02]
-0.21 [-0.42, 0.00]
-0.16 [-0.21, -0.11]
-0.6
-0.2
0
0.2
Effect size

L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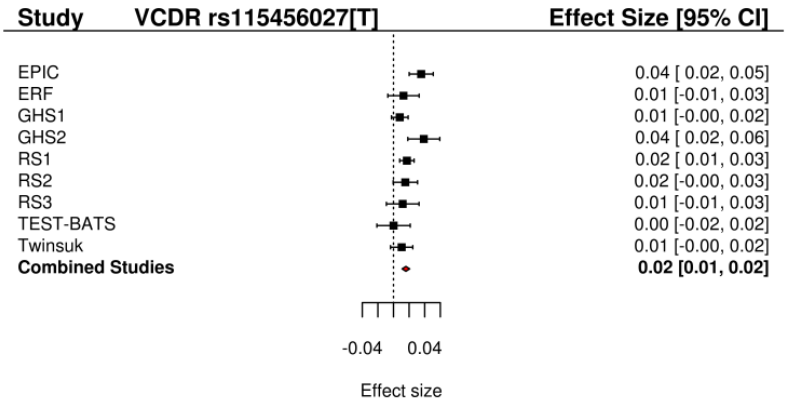
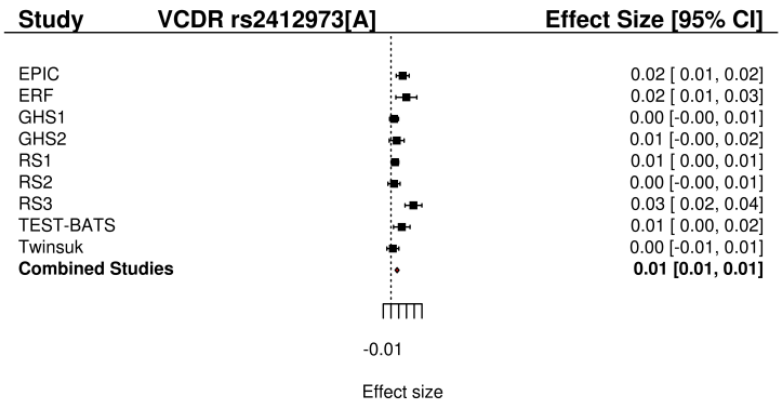
Effect Size [95% CI]
EPIC
ERF
GHS1
GHS2
ORCADES
RS1
RS2
RS3
TEST-BATS
Twinsuk
VHS
Combined Studies
-0.75 [-1.17, -0.33]
-0.73 [-1.46, -0.01]
-0.55 [-1.06, -0.04]
-0.19 [-0.95, 0.56]
-0.20 [-0.89, 0.48]
-0.47 [-0.81, -0.12]
-0.51 [-1.07, 0.05]
-0.11 [-0.56, 0.34]
0.43 [-0.36, 1.23]
-0.81 [-1.42, -0.21]
-0.23 [-0.91, 0.44]
-0.47 [-0.64, -0.30]
-1.5
-1
-0.5
0
0.5
1
1.5
Effect size

M


Study
VCDR rs115456027[T]
Effect Size [95% CI]
EPIC
ERF
GHS1
GHS2
RS1
RS2
RS3
TEST-BATS
Twinsuk
Combined Studies
0.04 [0.02, 0.05]
0.01 [-0.01, 0.03]
0.01 [-0.00, 0.02]
0.04 [0.02, 0.06]
0.02 [0.01, 0.03]
0.02 [-0.00, 0.03]
0.01 [-0.01, 0.03]
0.00 [-0.02, 0.02]
0.01 [-0.00, 0.02]
0.02 [0.01, 0.02]
-0.04
0.04
Effect size

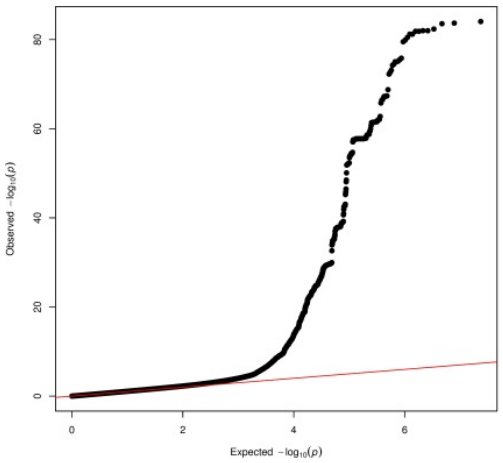
N


Study
VCDR rs2412973[A]
Effect Size [95% CI]
EPIC
ERF
GHS1
GHS2
RS1
RS2
RS3
TEST-BATS
Twinsuk
Combined Studies
0.02 [0.01, 0.02]
0.02 [0.01, 0.03]
0.00 [-0.00, 0.01]
0.01 [-0.00, 0.02]
0.01 [0.00, 0.01]
0.00 [-0.00, 0.01]
0.03 [0.02, 0.04]
0.01 [0.00, 0.02]
0.00 [-0.01, 0.01]
0.01 [0.01, 0.01]
-0.01
Effect size

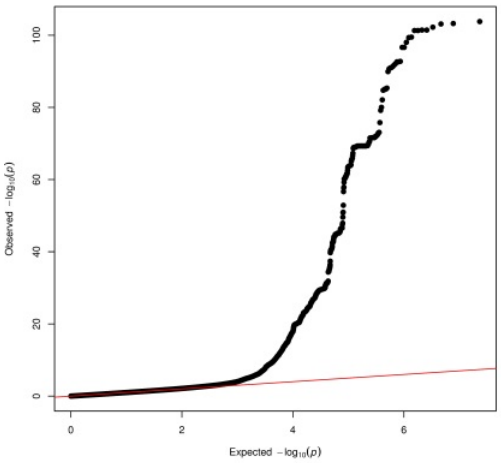
Supplementary figure 7. plot CPASSOC multi-trait analysis for ONH and IOP,CCT.

Panel (A) shows the QQ-plot for SHom ONH, panel (B) shows the QQ-plot for SHet ONH, panel (C) shows the QQ-plot for SHom IOP,CCT panel (D) shows the QQ-plot for SHet IOP,CCT

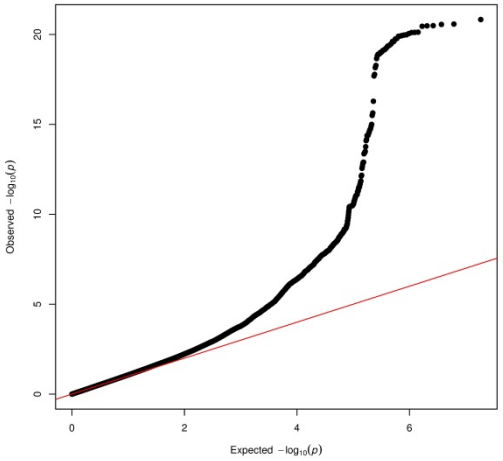
A



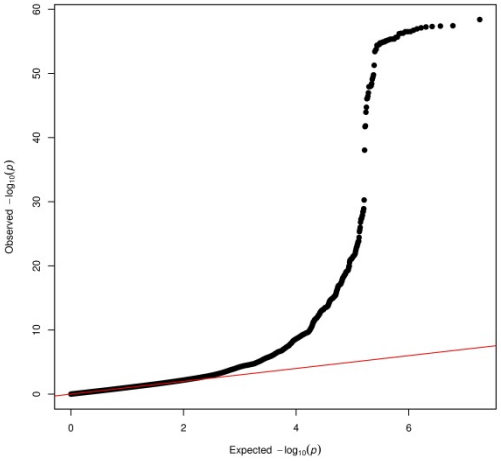
B



C



D



Supplementary Tables

Supplementary Table 1. Baseline characteristics: clinical characteristics.

GAT = Goldmann applanation tonometry. NA = not applicable

Study	Measurement method IOP	Measurement method CA, DA, RA and VCDR	Measurement method CCT
CROATIA-Korcula	NA	NA	Nidek hand held Echoscan US-1800 A- scan
CROATIA-Vis	NA	NA	Nidek hand held Echoscan US-1800 A- scan
EPIC-Norfolk Eye Study	Ocular Response Analyzer (ORA, Reichert, New York, USA; software V.3.01)	HRT3	Pachmate DGH 55, mean of 10 readings per eye; DGH Technology, Exton, PA
ERF	Goldmann applanation tonometry (Haag-Streit, Bern, Switzerland)	Heidelberg Retina Tomograph 2, Heidelberg Engineering, Heidelberg, Germany	NA
GHS1	Noncontact Tonometer (Nidek NT-2000™, Nidek Co., Japan)	Visucam PRO NM™ and Visupac™ (Carl Zeiss Meditec AG, Jena, Germany)	Pachycam™ (Oculus, Wetzlar, Germany)
GHS2	Noncontact Tonometer (Nidek NT-2000™, Nidek Co., Japan)	Visucam PRO NM™ and Visupac™ (Carl Zeiss Meditec AG, Jena, Germany)	Pachycam™ (Oculus, Wetzlar, Germany)
ORCADES	Tonopen	NA	IOPac hand held pachymeter (Heidelberg engineering)
RS-I	Goldmann applanation tonometry (Haag-Streit, Bern, Switzerland)	ImageNet and stereoscopic fundus camera (Topcon TRC-SS2; Tokyo Optical Co., Tokyo, Japan)	Non-contact biometer Lenstar LS900, Haag-Streit, Köniz, Switerzerland
RS-II	Goldmann applanation tonometry (Haag-Streit, Bern, Switzerland)	ImageNet and stereoscopic fundus camera (Topcon TRC-SS2; Tokyo Optical Co., Tokyo, Japan)	Non-contact biometer Lenstar LS900, Haag-Streit, Köniz, Switerzerland
RS-III	Goldmann applanation tonometry (Haag-Streit, Bern, Switzerland)	Heidelberg Retina Tomograph 2, Heidelberg Engineering, Heidelberg, Germany	Non-contact biometer Lenstar LS900, Haag-Streit, Köniz, Switerzerland
TEST-BATS	TONO-PEN XL (Reichert, Inc., New York, USA) and Goldmann applanation tonometry (Haag-Streit, Bern, Switzerland)	Nidek 3-Dx fundus camera with custom planimetric software	ultrasound pachymetry using Tomey SP 2000 (Tomey Corp., Nagoya, Japan)
TwinsUK	Ocular Response Analyzer	Nidek 3-Dx fundus camera with custom planimetric software	Ultrasound pachymetry device
VIKING	Tonopen	NA	IOPac hand held pachymeter (Heidelberg engineering)

Supplementary Table 2. Baseline characteristics for all participating cohorts for the CA analysis.

The unit of CA is mm2.

Study	*N*	Mean age (sd)	Age range	% Men	Mean CA (sd)	CA range
EPIC-Norfolk Eye Study	5853	67.8 (7.7)	48-90	44.60	0.45 (0.33)	0.00-1.81
ERF	2018	48.2 (13.8)	18-85	44.00	0.43 (0.31)	0.00-2.10
GHS1	2372	55.5 (10.7)	35-74	47.85	0.55 (0.34)	0.07-2.63
GHS2	782	54.9 (10.8)	36-74	49.87	0.53 (0.33)	0.07-2.65
RS-I	5555	68.0 (8.4)	55-99	40.90	0.61 (0.34)	0.01-1.98
RS-II	1979	64.7 (7.7)	55-96	46.00	0.57 (0.32)	0.03-1.94
RS-III	2870	57.2 (6.6)	46-90	43.80	0.40 (0.30)	0.00-1.90
TwinsUK	1727	57.1(11.2)	16-83	1.50	0.31(0.24)	0.00-1.45
TEST-BATS	1356	20.4 (9.8)	5-79	45.00	0.45 (0.28)	0.01-1.47

Supplementary Table 3. Baseline characteristics for all participating cohorts for the CCT analysis.

The unit of CCT is µm.

Study	*N*	Mean age (sd)	Age range	% Men	Mean CCT (sd)	CCT range
CROATIA-Korcula	858	56.43(13.72)	18-98	36.00	557.49(35.30)	468-697
CROATIA-Vis	597	56.2 (14.2)	18-86	39.97	560.9 (34.3)	441-662
EPIC-Norfolk Eye Study	1178	70.9 (8.0)	49-92	50.68	555.0 (37.1)	451-680
GHS1	2822	55.9 (10.9)	35-74	48.87	551.2 (35.0)	440-676
GHS2	1133	55.1 (10.8)	36-74	50.04	562.1 (34.0)	436-681
ORCADES	1113	55.1 (14.3)	18-89	37.83	538.0 (32.7)	432-663
RS-I	873	76.3 (6.7)	56-96	47.88	544.4 (33.9)	432-679
RS-II	1215	72.7 (5.3)	65-98	46.50	547.7 (34.2)	433-669
RS-III	2391	62.3 (5.8)	51-94	43.50	550.3 (33.9)	404-691
TwinsUK	2163	56.5 (11.8)	16-83	2.26	545.2 (35.0)	369-658
VIKING	1888	49.7 (15.1)	18-91	40.04	541.9 (33.9)	410-680

Supplementary Table 4. Baseline characteristics for all participating cohorts for the DA analysis.

The unit of DA is mm2.

Study	*N*	Mean age (sd)	Age range	% Men	Mean DA (sd)	DA range
EPIC-Norfolk Eye Study	5856	67.8 (7.7)	48-90	44.70	1.86 (0.40)	0.60-3.51
ERF	2004	48.2 (13.8)	18-85	44.00	1.91 (0.35)	1.07-3.95
GHS1	2372	55.5 (10.7)	35-74	47.85	2.32 (0.45)	1.26-4.65
GHS2	782	54.9 (10.8)	36-74	49.87	2.34 (0.47)	1.07-4.85
RS-I	5563	68.0 (8.4)	55-99	41.00	2.42 (0.47)	0.58-5.13
RS-II	1983	64.7 (7.7)	55-96	46.10	2.33 (0.46)	1.13-5.19
RS-III	2872	57.2 (6.6)	46-90	43.80	1.92 (0.40)	0.75-4.22
TEST-BATS	1356	20.4 (9.8)	5-79	45.00	2.07 (0.39)	1.15-3.56
TwinsUK	1732	57.1 (11.2)	16-83.	1.50	2.59 (0.64)	0.59-5.31

Supplementary Table 5. Baseline characteristics for all participating cohorts for the IOP analysis.

The unit of IOP is mmHg.

Study	*N*	Mean age (sd)	Age range	% Men	Mean IOP (sd)	IOP range
EPIC-Norfolk Eye Study	6472	68.8 (8.0)	48-92	45.22	16.2 (3.8)	5.9-39.8
ERF	2462	49.9 (14.0)	17-87	44.52	15.2 (3.0)	6.5-25.4

GHS1	2720	55.5 (10.8)	35-74	48.67	14.2 (2.8)	7.4-35.8
GHS2	1112	54.9 (10.8)	36-74	50.27	13.9 (2.7)	5.9-27.3
ORCADES	1112	55.1 (14.4)	18-89	37.77	15.0 (2.7)	7.5-29.0
RS-I	6010	69.2 (9.0)	55-101	40.30	14.7 (3.2)	5.0-28.6
RS-II	2095	64.8 (7.9)	55-95	45.90	14.2 (3.1)	7.0-31.5
RS-III	2992	57.2 (6.8)	46-97	43.70	13.6 (2.9)	4.5-30.0
TEST-BATS	1798	22.1 (12.0)	5-81	44.00	15.8 (3.0)	6.0-26.0
TwinsUk	2510	60.0 (11.6)	16-85	2.20	15.6 (3.3)	5.4-33.0
VIKING	1986	49.99 (15.2)	18-91	40.23	14.8 (3.2)	5.0-30.6

Supplementary Table 6. Baseline characteristics for all participating cohorts for the VCDR analysis.

The unit of VCDR is ratio.

Study	*N*	Mean age (sd)	Age range	% Men	Mean VCDR (sd)	VCDR range
EPIC-Norfolk Eye Study	5866	67.8 (7.7)	48-90	44.70	0.34 (0.23)	0.00-1.00
ERF	2008	48.2 (13.8)	18-85	44.00	0.31 (0.20)	0.00-0.87
GHS1	2776	55.8 (10.9)	35-74	48.85	0.44 (0.11)	0.19-0.81
GHS2	1036	54.8 (10.9)	36-74	49.42	0.43 (0.11)	0.19-0.80
RS-I	5573	68.0 (8.4)	55-99	40.90	0.50 (0.13)	0.05-0.87
RS-II	1987	64.7 (7.7)	55-96	46.10	0.50 (0.13)	0.10-0.86
RS-III	2873	57.2 (6.6)	46-90	43.90	0.29 (0.21)	0.00-1.00
TEST-BATS	1330	20.3 (9.7)	5-79	45.00	0.45 (0.13)	0.08-0.88
TwinsUK	1731	57.1 (11.2)	16-83	1.50	0.34(0.11)	0.04-0.70

Supplementary Table 7. SNP genotyping and imputation details of the population based-studies

MAF = minor allele frequency; HWE = Hardy-Weinberg equilibrium

Study	Genotype platform	Pre imputation QC tresholds	Post imputation QC tresholds	HRC version
CROATIA-Korcula	Mix: Illumina CNV370v1,CNV370-Quadv3	MAF > 0.01; SNPcallrate >0.98; HWE> 1x10E-6	Monomorphic, duplicate and triallelic removed ; imputation quality-INFO ≥0.4	HRC r1
CROATIA-Vis	IlluminaHumanHap300v1	MAF > 0.01; SNPcallrate >0.98; HWE> 1x10E-6	Monomorphic, duplicate and triallelic removed ; imputation quality-INFO ≥0.4	HRC r1
EPIC-Norfolk Eye study	Affymetrix UK Biobank Axiom Array	SNP exclusion criteria included: call rate < 95%, abnormal cluster pattern on visual inspection, plate batch effect evident by significant variation in minor allele frequency, and/or Hardy-Weinberg equilibrium P < 10-7. Sample exclusion criteria included: DishQC < 0.82 (poor fluorescence signal contrast), sex discordance, sample call rate < 97%, heterozygosity outliers (calculated separately for SNPs with minor allele frequency >1% and <1%), rare	exclusion: info<0.3, or monomorphic and singletons	HRC r1

		allele count outlier, and impossible identity-by-descent values. Following these exclusions, there were no ethnic outliers.		
ERF	Illumina 6k, Illumina 318K, Illumina 370K and Affymetrix 250K	Sample QC: Sample callrate >97.5%, no excess autosomal heterozygosity (<0.336), no sex-mismatch. SNPs QC: SNP call_rate >98% MAF >0.01, HWE> 1x10E-6	MAF ≥ 0,001 ; imputation quality ≥0,3	HRC r1
GHS1	Affymetrix SNP Array 6.0	None	MAF ≥ 0,001 ; imputation quality ≥0,3	HRC r1.1
GHS2	Affymetrix SNP Array 6.0	none	MAF ≥ 0,001 ; imputation quality ≥0,3	HRC r1.1
ORCADES	Mix: IlluminaHumanHap300v2, HumanCNV370-Quad and HumanOmniExpress-12v1	MAF > 0.01; SNPcallrate >0.98; HWE> 1x10E-6	Monomorphic, duplicate and triallelic removed ; imputation quality-INFO ≥0.4	HRC r1
RS-I	illumina 550 (+duo) Illumina 610 quad	Sample QC: Sample callrate >97.5%, no excess autosomal heterozygosity (<0.336), no sex-mismatch. SNPs QC: SNP callrate >98% MAF >0.01, HWE> 1x10E-6	MAF ≥ 0,001 ; imputation quality ≥0,3	HRC r1
RS-II	illumina 550 duo	As RS-I	MAF ≥ 0,001 ; imputation quality ≥0,3	HRC r1
RS-III	illumina 610 quad	As RS-I	MAF ≥ 0,001 ; imputation quality ≥0,3	HRC r1
TEST-BATS	Human610-Quadv1_B(610K)	mean(GenCall score)>0.7; MAF > 1%; call rate >0.95; HWE> 1x10E-6	MAF ≥ 0.001 ; imputation quality ≥0.3	HRC r1
TwinsUK	Illumina 317K Duo and HumanHap 610K-Quad	MAF > 0.001; SNPcallrate >0.95; HWE> 1x10E-6	NA	HRC r1.1
VIKING	OmniExpressExome-8v1-2_A	MAF > 0.01; SNPcallrate >0.98; HWE> 1x10E-6	Monomorphic, duplicate and triallelic removed ; imputation quality-INFO ≥0.4	HRC r1

Supplementary Table 8 Baseline characteristics: ancestry and study specific covariates.

Study	Ancestry	Study specific covariates used in analysis
CROATIA-Korcula	European,Croatian	Family structure
CROATIA-Vis	European, Croatian	Family structure
EPIC-Norfolk Eye Study	European, English	
ERF	European, Dutch	Family structure
GHS1	European, German	
GHS2	European, German	
ORCADES	European, Orcadian	Family structure
RS-I	European, Dutch	
RS-II	European, Dutch	
RS-III	European, Dutch	
TEST-BATS	European, Australia	Measurement Technique of IOP: Tonopen and GAT
VIKING	European, Shetlandic	Family structure

Supplementary Table 9 SNP genotyping and imputation details of the POAG case-control studies

MAF = minor allele frequency; HWE = Hardy-Weinberg equilibrium

Study	Genotype platform	Pre imputation QC thresholds	Post imputation QC thresholds	HRC version
NEIGHBOR/MEEI	Illumina 660W_Quad_v1 array	MAF > 0.01; SNPcallrate >0.95	MAF > 0.01; imputation quality > 0.7	HRC r1
Southampton	Affymetrix SNP6.0	MAF > 0.05; SNPcallrate > 0.90; HWE > 1x10E-10 (cases)	MAF > 0.01 ; imputation quality ≥0,3	HRC r1.1
UK Biobank	UK BiLEVE Affymetrix Axiom	SNPcallrate >0.95; HWE> 1x10E-6	MAF > 0.005; imputation quality > 0.4	HRC

Supplementary Note

1.1 study descriptives European population-based studies

CROATIA-Korcula and CROATIA-Vis. The CROATIA-Vis study includes unselected adult participants who were recruited in a population-based study during 2003 and 2004 in the villages of Vis and Komiza on the Dalmatian island of Vis. All subjects visited the clinical research center in the region where they were examined in person and where fasting blood was drawn. Biochemical and physiological measurements were performed, detailed genealogies reconstructed, questionnaire of lifestyle and environmental exposures collected, and blood samples stored for further analyses. CROATIA-Korcula participants were recruited in the same manner from the Dalmatian island of Korcula in 2007. All studies received appropriate ethical approval, and all participants gave informed consent.

EPIC-Norfolk Eye Study. The European Prospective Investigation into Cancer (EPIC) study is a pan-European prospective cohort study designed to investigate the etiology of major chronic diseases [3]. EPIC-Norfolk , one of the UK arms of EPIC, recruited and examined 25,639 participants between 1993 and 1997 for the baseline examination[4]. Recruitment was via general practices in the city of Norwich and the surrounding small towns and rural areas, and methods have been described in detail previously[5]. Since virtually all residents in the UK are registered with a general practitioner through the National Health Service, general practice lists serve as population registers. Ophthalmic assessment formed part of the third health examination and this has been termed the EPIC-Norfolk Eye Study [6]. In total, 8,623 participants were seen for the Eye Study, between 2004 and 2011. The EPIC-Norfolk Eye Study was carried out following the principles of the Declaration of Helsinki and the Research Governance Framework for Health and Social Care. The study was approved by the Norfolk Local Research Ethics Committee (05/Q0101/191) and East Norfolk & Waveney NHS Research Governance Committee (2005EC07L). All participants gave written, informed consent.

Erasmus Rucphen Family (ERF) Study. The ERF study has been described in detail previously[7]. A total of approximately 3,000 participants descend from 22 couples who lived in the Rucphen region in The Netherlands in the 19th century. The 2,755 individuals with genotype data and lipid measurements were included in the current analysis.

Gutenberg Health Study I and II (GHS I and GHS II). The GHS is a population-based, prospective, observational cohort study in the Rhine-Main Region in midwestern Germany with a total of 15,010 participants and follow-up after five years. The study sample is recruited from subjects aged between 35 and 74 years at the time of the exam. The sample was drawn randomly from local governmental registry offices and stratified by gender, residence (urban and rural) and decade of age. Exclusion criteria were insufficient knowledge of the German language to understand explanations and instructions, and physical or psychic inability to participate in the examinations in the study center. The study was approved by the Medical Ethics Committee of the University Medical Center Mainz and by the local and federal data safety commissioners. According to the tenets of the Declaration of Helsinki, written informed consent was obtained from all participants prior to entering the study.

Orkney Complex Disease studies (ORCADES). The ORCADES is a family-based, cross-sectional community study of the genetics of complex traits, based in the Orkney Isles in Scotland[8]. All participants gave written informed consent, in accord with the tenets of the declaration of Helsinki, and the study was approved by Research Ethics Committees in Orkney and Aberdeen (North of Scotland REC).

Rotterdam Study cohort I (RS-I). The Rotterdam Study is an ongoing prospective population-based cohort study, focused on chronic disabling conditions of the elderly. The study comprises an outbred ethnically homogenous population of Dutch Caucasian origin. The rationale of the study has been described in detail elsewhere[9]. In summary, 7,983 men and women aged 55 years or older, living in Ommoord, a suburb of Rotterdam, the Netherlands, were invited to participate in the first phase. Fasting blood samples were taken during the participant's third visit to the research center.

Rotterdam Study cohort II (RS-II). The Rotterdam Study cohort II prospective population-based cohort study comprises 3,011 residents aged 55 years and older from the same district of Rotterdam. The rationale and study designs of this cohort is similar to that of the RS-I[9]. The baseline measurements, including the fasting HDL measurements, took place during the first visit.

Rotterdam Study cohort III (RS-III). The Rotterdam Study cohort III prospective population-based cohort study

comprised 3,932 residents aged 45 years and older from the same district of Rotterdam. The rationale and study designs of this cohort is similar to that of the RS-I[9]. The baseline measurements, including the fasting HDL measurements, took place during the first visit.

Twins Eye Study in Tasmania (TEST), Brisbane Adolescent Twin Study (BATS).
The Australian Twin Eye Study comprises participants examined as part of TEST or BATS. The studies were approved by the human ethics committees of the University of Tasmania, Royal Victorian Eye and Ear Hospital, and Queensland Institute of Medical Research.

TwinsUK. The TwinsUK adult twin registry based at St. Thomas' Hospital in London is a volunteer cohort of over 10,000 twins from the general population [10]. Twins largely volunteered unaware of the eye studies, gave fully informed consent under a protocol reviewed by the St. Thomas' Hospital Local Research Ethics Committee. Out of the original 1,951 subjects for whom phenotype and genotype information was available, 1,922 subjects were included in the study; 29 subjects were excluded after failing quality control.

VIKING. The Viking Health Study - Shetland (VIKING) is a family-based, cross-sectional study that seeks to identify genetic factors influencing cardiovascular and other disease risk in the population isolate of the Shetland Isles in northern Scotland. Genetic diversity in this population is decreased compared to Mainland Scotland, consistent with the high levels of endogamy historically. 2105 participants were recruited between 2013 and 2015, each having at least three grandparents from Shetland. All participants gave written informed consent and the study was approved by the South East Scotland Research Ethics Committee.

1.2 study descriptives Asian population-based studies

Beijing Eye Study (BES). The BES is a population-based cohort of Han Chinese in the rural region and in the urban region of Beijing in North China [11,12]. The Medical Ethics Committee of the Beijing Tongren Hospital approved the study protocol and all participants gave informed consent, according to the Declaration of Helsinki. At baseline (2001), 4439 individuals out of 5324 eligible individuals aged 40 years or older participated (response rate: 83.4%). In the years 2006 and 2011, the study was repeated by re-inviting all participants from the survey from 2001 to be re-examined. Out of the 4439 subjects examined in 2001, 3251 (73.2%) subjects returned for the follow-up examination in 2006, and 2695 (60.7%) subjects returned for the follow-up examination in 2011.

Singapore Malay Eye Study (SIMES), Singapore Indian Eye Study (SINDI), and Singapore Chinese Eye Study (SCES)
The three population-based studies were conducted in Singapore: the Singapore Malay Eye Study from 2004 to 2006, the Singapore Indian Eye Study from 2007 to 2009, and the Singapore Chinese Eye Study from 2009 to 2011. The detailed methodology of these three study has been published in previous reports [13,14].In brief, an age-stratified (by 10-year age groups) random sampling in each ethnic group was used to select ethnic Malays, Indians, and Chinese 40 to 80 years of age living across the southwestern part of Singapore during each stipulated study period. The number of selected subjects was 4,168 Malays, 4,497 Indians and 4,606 Chinese. Of these, 3280 Malay persons (response rate 78.7%), 3,400 Indian persons (75.6%) and 3,353 Chinese persons (72.8%) participated in the study. The overall response rate for SEED was 75.6%. This study was approved by the Singapore Eye Research Institute Institutional Review Board and the conduct of the study adhered to the Declaration of Helsinki. All participants gave informed consent. All subjects recruited in the SEED study underwent a standardized interview, and ocular examination at the Singapore Eye Research Institute. An interviewer-administered questionnaire was used to collect demographic data.

1.3 study descriptives & methods European POAG case-controls studies

NEIGHBOR and MEEI
All cases and controls met the clinical criteria used previously by the NEIGHBOR and GLAUGEN studies previously described (Wiggs et al., 2012; Wiggs et al., 2013; Bailey et al., 2016). This study Subjects were enrolled using a protocol was approved by the Massachusetts Eye and Ear Infirmary institutional review board and all subjects signed consent forms approved by the local IRB prior to enrolling in the study. Briefly, POAG cases were defined as individuals for whom reliable visual field (VF) tests showed characteristic VF defects consistent with glaucomatous optic neuropathy. Individuals were classified as affected if the VF defects were reproduced on a subsequent test or if a single qualifying VF was accompanied by a cup-disc ratio (CDR) of 0.7 or more in at least one eye. The majority of cases (over 90%) met this definition, including 96% of the NEIGHBOR cases (Wiggs et al., J of Glaucoma, 2013); and

all of the Mass Eye and Ear, NHS, HPFS, and WGHS cases. A small percentage (less than 10%) of the NEIGHBOR, cases were defined by cup-to-disc ratio only because visual field data was not available, in some cases because of advanced disease (poor visual acuity) or other medical condition. The CDR definition was > 0.7 in both eyes or CDR asymmetry between the two eye of 0.2 (Supplementary Table 2). Patients with signs of secondary causes for elevated IOP such as exfoliation syndrome or pigment dispersion syndrome or critically narrow filtration structures were excluded. Elevation of IOP was not a criterion for inclusion of cases or controls Controls had IOP < 21 mmHg, as measured in a clinical setting, CDR of less than 0.6 and did not have a family history of glaucoma.
Imputed genotypes (Haplotype Reference Consortium) for 2,606 cases and 2,606 controls from 2 independent datasets (NEIGHBOR and MEEI) were used for the replication effort. Quality-control was performed for each data set as described in Bailey et al., 2016 (Supplemental Note).

Southampton. Primary open-angle (POAG) and normal tension glaucoma patients were recruited from the Southampton University Hospital Trust Eye Clinic and satellite regional glaucoma clinics. Ethical approval for the collection of patient information and blood samples was provided by the Southampton and South West Hampshire Local Research Ethics Committee (05/Q1702/8) and Cohort Recruitment commenced in August 2005. Each patient was examined by an experienced glaucoma specialist. Diagnoses were made on the basis of characteristic visual field loss/glaucomatous optic disc damage/increased IOP. Patients presenting with narrow-angle, developmental or secondary glaucoma or any other known abnormalities of the anterior segment were excluded. Patients with unambiguous glaucoma, but normal tension were included in sample collection later. Furthermore, to select for patients with typical POAG or normal-tension glaucoma (NTG), only patients diagnosed over the age of 40 years were included. Both conditions are rare before this age. DNA was extracted according to the standard methods, dissolved in TE buffer, and stored at -20°C. Primary open angle glaucoma patients (n=400) were genotyped on the Affymetrix SNP 6.0 array, all data were exported on the forward strand. These data were combined with the Affymetrix SNP 6.0 data publically available for the WTCCC2 controls. The Genome-wide association data previously described[47] was further filtered to ensure removal of individuals with more than 5% missing genotypes, SNPs with more than 3% missing samples, SNPs with a minor allele frequency of <1% and a Hardy-Weinberg p-value < 1x10-6. SNPs were all on the forward strand and locations were lifted over from hg18 to hg19 using the UCSC liftover tool. SNPs with complementary alleles were also excluded (A/T and G/C).
The data used for imputation included 384 cases and 3389 controls, and 533,774 SNPs. Pre-phasing was carried out using Shapeit (v2, r790) and imputation was carried out using Impute2 (v2.3.1), using 1000 Genomes Phase I integrated haplotypes (produced using SHAPEIT2), b37 Dec 2013, downloaded from the impute2 website. Imputation was carried out over the genome in 5Mb chunks as per the best practices on the impute2 website. The imputed data was then converted to plink format using GTOOL. Case-control analysis was carried out using logistic regressions for the selected replication SNPs and Indels with sex as a covariate, using PLINK (v1.90b3b 64-bit (15 Jan 2015)).

UK biobank
Self-reported glaucoma status was ascertained by participant selection of 'glaucoma' from a list of eye disorders in response to the question "Has a doctor told you that you have any of the following problems with your eyes?". Cases were defined as those reporting "glaucoma." The control group included the non-cases and excluded subjects who reported "Prefer not to answer" or "Do not know." Genotyping was done using two arrays. The first array was the UK BiLEVE [15]. The second array is what was the Affymetrix Axiom® platform with a custom-designed array described in the UK Biobank Axiom® Array Content Summary (http://www.ukbiobank.ac.uk/wp-content/uploads/2014/04/UK-Biobank-Axiom-Array-Content-Summary- 2014.pdf). Phasing on the autosomes was carried out using a modified version of the SHAPEIT22 program modified to allow for very large sample sizes [16]. A total of 806,466 directly genotyped DNA sequence variants were available after variant quality control. The UK Biobank team then performed imputation on Haplotype Reference Consortium (HRC) reference panel; phasing was performed using SHAPEIT3 and imputation was carried out via the IMPUTE4 program [17]. The variant-level quality control exclusion metrics applied to imputed data for GWAS included the following: call rate < 95%, Hardy–Weinberg equilibrium P <1 × 10−6, posterior call probability < 0.9, imputation quality < 0.4, and MAF < 0.005. Sex chromosome and mitochondrial genetic data were excluded from this analysis. In total, 9,061,845 imputed DNA sequence variants were included in our analysis. For sample quality control, we removed individuals with relatedness corresponding to third-degree relatives or closer, and an additional samples with an excess of missing genotype calls or more heterozygosity than expected were excluded.

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EPIC-Norfolk Eye study
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