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# Multitrait analysis of glaucoma identifies new risk loci and enables polygenic prediction of disease susceptibility and progression

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## **Supplementary Note**

### **1. The UK Biobank (UKBB)**

UK Biobank (UKBB) is a large-scale cohort study that included over 500,000 participants aged between 40-69 years in 2006-2010 from across the United Kingdom. Approximately 488,000 participants were genotyped for 805,426 markers on Axiom arrays (Affymetrix Santa Clara, USA). After standard quality control procedures, ~96M genotypes were imputed using Haplotype Reference Consortium (HRC) and UK10K haplotype resources.<sup>1-3</sup> For the GWASs in UKBB, we only retained SNPs with MAF > 0.01 and imputation quality score > 0.3. Among the 487,409 individuals who passed initial genotyping QC, 409,694 participants had white British ancestry, according to self-reported ethnicity and genetic principal components. To maximize our effective sample size, we also included UKBB participants if their self-reported ancestry was not white British (including a substantial number of individuals reporting their ancestry as 'Irish' or 'any other white background'), but their first two genetic principal components fell within the region of those classified as white British in the n=409,694 set in Bycroft et al.<sup>4</sup> With these criteria, we identified 438,870 individuals for this study who were genetically similar to those of white-British ancestry.<sup>5</sup> For all UKBB analysis except the prediction into the subset of South Asian ancestry (see below, the Supplementary **Figure 12**, **Supplementary Table 11**) we used the 438,870 individuals who were genetically similar to those of white-British ancestry.<sup>5</sup> Detailed information of the genotype data and quality control procedures was reported by Bycroft and colleagues.<sup>4</sup> All participants provided informed written consent, the study was approved by the National Research Ethics Service Committee North West – Haydock, and all study procedures were performed in accordance with the World Medical Association Declaration of Helsinki ethical principles for medical research.

### **2. UKBB VCDR GWAS**

In UKBB, 87,685 left fundus retinal eye images were available (two assessment visits), covering 84,871 participants (UKBB Field: 21015). The VCDR and VDD were assessed from non-stereo fundus images obtained using a Topcon 3D OCT-1000 MKII (Topcon Corporation) by two

fellowship-trained ophthalmologists. Fundus images had a 45° primary field of view and were cropped and enlarged. Images were viewed and graded using a custom Java program, which loads the fundus photographs sequentially, and records the reviewer's grading in time-efficient manner via keyboard input. Two thousand images were randomly selected for quality control, and the Pearson's correlation coefficient of the VCDR measurements between the two ophthalmologists was 0.75 (95%CI: 0.72-0.77), which is in keeping with previous work.<sup>6-8</sup> Bland-Altman plots were also used to investigate the agreement between measurements (Supplementary **Figure 13**).<sup>9</sup> The second visit VCDR measurements were used if available. Otherwise, we used the first visit VCDR measurements (N=50,941, proportion 76%). If the left eye images were ungradable, we used the right eye images instead (N=6,320, proportion 9%, UKBB Field 21016). With data only available on one eye we were unable to assess left-right VCDR asymmetry although this is not relevant to our primary goal of identifying novel genetic associations with VCDR. In VCDR GWAS, we excluded non-white British ancestry participants and glaucoma cases and their relatives ( $\hat{\pi} > 0.2$  calculated using identity by descent determined based on autosomal markers). Finally, 67,040 participants had both VCDR and VDD phenotype data. We used rank-based inverse-normal transformation to ensure VCDR was normally distributed.<sup>10</sup> We used a linear mixed model to account for cryptic relatedness and population stratification in the UKBB samples using BOLT-LMM version 2.3.<sup>11</sup> Association analysis was performed under an additive genetic model, adjusted for the effect of sex, age, the first ten principal components, two indicator variables for ophthalmologists that performed the rating, and VCDR assessment visits. In addition, to adjust for the effect of optic nerve head size, as large optic discs are associated with higher VCDR,<sup>12</sup> VDD was added as a covariate in VCDR GWAS.

### 3. UKBB glaucoma case-control analysis

Glaucoma cases definition and association analysis were described previously.<sup>5</sup> In brief, we identified 7,947 glaucoma cases from ICD-10 diagnosis and self-reported questionnaires, and 119,318 controls who self-reported having no eye disease. We defined glaucoma cases as those who (i) had an ICD-10 diagnosis of 'primary open angle glaucoma', 'other glaucoma' or 'glaucoma, unspecified'; (ii) responded 'glaucoma' to the question 'Has a doctor told you that you have any of the following

problems with your eyes?'; or (iii) responded 'glaucoma' to the question 'In the touch screen you selected that you have been told by a doctor that you have other serious illnesses or disabilities, could you now tell me what they are? (non-cancer illness). Although only a small proportion of the glaucoma cases had documented disease subtype, the proportion of non-POAG glaucoma cases in UKBB would be expected to be small (87% of glaucoma cases were POAG in a recent UK study).<sup>13</sup> In the glaucoma case-control GWAS, we only kept each pair of individuals with  $\hat{\pi} > 0.2$  and used logistic regression in PLINK (version 2.0) for the GWAS analysis.<sup>14</sup> The dosage scores from imputation were used in the logistic regression models adjusted for sex, age, and the first ten principal components.

#### **4. UKBB IOP GWAS**

The IOP GWAS in UKBB was described previously.<sup>5</sup> In the IOP GWAS, we calculated the average corneal-compensated IOP (IOPcc) across both eyes. After excluding non-white British ancestry participants and glaucoma cases and their relatives, 103,914 individuals were included in the GWAS. We used linear mixed model in BOLT-LMM version 2.3 for the association analysis adjusted for sex, age, and the first ten principal components. We conducted a sensitivity analysis either correcting or not correcting for IOP treatment in the <2% of individuals undergoing treatment and results were essentially unchanged.

#### **5. Introduction of linear mixed model**

Linear mixed models (LMM) are widely used in genome-wide association studies to account for relatedness and population structure and increase power.<sup>11,15,16</sup>

In LMM, the simplified model is:

$$Y = u + b_1 X_1 + b_2 X_2 + G + e$$

Where Y is the phenotype (e.g. IOP), u is the mean phenotype value after accounting for covariates and genetic effects. The term  $b_1$  is the fixed effects for covariates (eg. sex, age and principal components),  $X_1$  is the matrix for covariates. The term  $b_2$  is fixed effect for the SNP tested in the association analysis, and  $X_2$  is the SNP genotype (e.g. genetic dosage).<sup>11</sup> The term G is the random

effect from polygenic effect (the accumulated effect from genetic relationship matrix, GRM).<sup>17</sup> The term  $e$  is the residual. In BOLT-LMM, the candidate SNP  $X_2$  was excluded (leave-one-chromosome-out, LOCO) from GRM to avoid modeling that particular SNP effect twice.<sup>11</sup>

## 6. UKBB cumulative risk of glaucoma stratified by PRS

In this subset study of UKBB, after removing relatives and people with other serious eye diseases, data from 382,161 participants were available for analysis. We identified *MYOC* p.Gln368Ter (rs74315329) carriers using imputation. Our previous work has shown that *MYOC* p.Gln368Ter can be imputed with high accuracy from genotyping arrays.<sup>18</sup> In this study, the risk allele (A) dosage of rs74315329 was calculated. We defined *MYOC* p.Gln368Ter carriers by setting the dosage threshold at 0.8. We identified 965 carriers, including 72 glaucoma cases. We gathered the information for age at diagnosis of glaucoma from the UKBB fields 4689 and 20009. In total, age at diagnosis information was available for 4,596 individuals. The training datasets used to construct MTAG PRS are shown in **Extended Data Fig. 1d**. To avoid sample overlap for *MYOC* p.Gln368Ter carriers, we removed all *MYOC* p.Gln368Ter carriers and their relatives from UKBB VCDR and IOP GWAS. A Cox model was used to calculate the cumulative risk of glaucoma for *MYOC* p.Gln368Ter carriers, stratifying by the tertiles of PRS. For analysis examining cumulative risk of glaucoma in the general population (i.e. in *MYOC* p.Gln368Ter non-carriers), we stratified participants by deciles of PRS. For glaucoma cases without age at diagnosis information, we used their age as the age of diagnosis in the survival analysis (for *MYOC* p.Gln368Ter carriers or non-carriers, the cumulative risk was shown until 64 years and 70 years, respectively, due to the small number of cases beyond that age). In the Cox models, we adjusted for sex and the first six genetic principal components. The “survival” package in R was used in analysis.<sup>19</sup>

## 7. South Asian ancestry glaucoma cases and controls

To evaluate the performance of PRS in a population with different ancestry, we selected 192 cases and 6,841 controls of South Asian ancestry (the largest ethnic minority in UK Biobank, defined here as

individuals self describing as Indian or Pakistani ancestry). All included South Asians had homogeneous genetic ancestry which was clearly distinct from UK Biobank participants of European ancestry (Supplementary **Figure 12**).

## **8. The International Glaucoma Genetic Consortium**

Publicly available VCDR and IOP GWAS summary results were downloaded for individuals of European descent from the International Glaucoma Genetic Consortium study (IGGC,  $N_{VCDR}=23,899$ ,  $N_{IOP}=29,578$ ).<sup>20</sup> The GWAS of VCDR and IOP in IGGC were imputed to 1000G and adjusted for age, sex and the first five principal components.<sup>20</sup>

## **9. The Australian & New Zealand Registry of Advanced Glaucoma (ANZRAG) Cohort**

The clinical recruitment and characterisation of ANZRAG has been described previously.<sup>21</sup> We used 3,071 POAG cases and 6,750 historic controls of European descent. Samples were genotyped using Illumina Omni1M, OmniExpress or HumanCoreExome arrays (Illumina, San Diego, USA).<sup>22,23</sup> There were three phases of ANZRAG data collection, whereby the QC, imputation, and association analysis was conducted separately before being meta-analysed. Phase 1 comprised 1,155 advanced POAG cases and 1,992 historic controls genotyped on Illumina Omni1M or OmniExpress arrays.<sup>23</sup> Historic controls were 225 esophageal cancer cases, 317 Barrett's oesophagus cases and their 552 controls, plus 303 inflammatory bowel diseases cases and their 595 controls. Phase 2 comprised 579 additional advanced POAG cases and 946 controls selected from parents of twins, all genotyped on Illumina HumanCoreExome arrays.<sup>22</sup> Phase 3 comprised 1,337 POAG cases and 3,812 controls (selected from an endometriosis study), genotyped on Illumina HumanCoreExome arrays.<sup>24</sup> In phase 3 (but not phases 1 or 2) there was a strong female bias in the control set (the PRS work on advanced glaucoma uses only phases 1 and 2). A subset of the advanced glaucoma cohort had sufficient clinical information to allow us to identify 709 high tension and 330 normal tension cases.<sup>22</sup> Human research ethics approval was obtained from the relevant committees of the Southern Adelaide Clinical Human Research Ethics Committee/Flinders University, the University of Tasmania, QIMR Berghofer

Institute of Medical Research and the Royal Victorian Eye and Ear Hospital. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

As described previously, QC was performed with PLINK.<sup>14</sup> Individuals with >3% missing genotypes, and SNPs with call rate <97%, minor allele frequency (MAF) <0.01, and Hardy-Weinberg equilibrium (HWE)  $P<0.0001$  in controls or  $P<5\times10^{-10}$  in cases were discarded. Identity by descent was estimated using autosomal markers with only one of any pair of individuals with relatedness ( $\hat{\pi}$ ) of >0.2 retained for analysis. Principal components were computed for all participants and reference samples of known Northern European ancestry (1000G British, CEU, Finland participants). Participants with PC1 or PC2 values >6 standard deviations above the mean of the known Northern European ancestry group were removed.

Phasing of genotyped SNPs was undertaken in ShapeIT,<sup>25</sup> with imputation performed using Minimac3 via the Michigan Imputation Server,<sup>26</sup> (HRC reference panel).<sup>2</sup> SNPs with imputation quality ( $r^2$ )>0.3 and MAF >0.01 were retained for analysis.

## **10. The National Eye Institute Glaucoma Human Genetics Collaboration Heritable Overall Operational Database (NEIGHBORHOOD)**

POAG cases and controls and the genotype data were described previously.<sup>27–31</sup> Briefly, in the GWAS of the NEIGHBORHOOD, there are eight independent datasets with 3,853 cases and 33,480 controls. Case and control samples were genotyped on Illumina 660W (Illumina, San Diego, CA, USA), Affymetrix 500K, Affymetrix Mapping 5.0, or Affymetrix 6.0 arrays (Affymetrix, Santa Clara, CA, USA). The genotype imputation was based on 1000 Genomes panel (March 2012). For each dataset, age, sex, and study-specific principal components were adjusted in logistic regression models using ProbABEL.<sup>32</sup> In the meta-analysis, inverse variance weighted method was performed in METAL (2011-03-25 release) with genomic control correction.<sup>33</sup>

## **11. The Blue Mountains Eye Study (BMES)**

Detailed information of the Blue Mountains Eye Study (BMES) study was reported previously.<sup>34</sup> In brief, BMES is a population-based cohort study of common eye diseases among suburban residents aged 49 years or older, living in the Blue Mountains region, west of Sydney, Australia. IOP was measured using Goldmann applanation tonometry (Haag-Streit, Bern, Switzerland).<sup>34</sup> DNA samples were obtained during the 5-year follow-up and ancillary surveys, which were performed between 1997 and 2000. Participants were genotyped with Human610-Quad arrays (Illumina, San Diego, CA, USA). For the PRS prediction, 74 POAG cases and 1,721 controls of European descent with genotype data were included in analysis.

## **12. UK glaucoma replication study (Southampton, Liverpool)**

Detailed information of Southampton samples was reported previously.<sup>35</sup> In brief, POAG patients were recruited from the Southampton University Hospital Trust Eye Clinic and satellite regional glaucoma clinics. Each patient was examined by an experienced glaucoma specialist. Cases with advanced glaucoma (exactly matching that defined for ANZRAG) and of European ancestry were selected for the replication study. 308 cases had trabeculectomy surgery status (yes/no) available. A further set of 50 advanced POAG were recruited as part of Liverpool University study of glaucoma again with the definition of advanced POAG exactly matching the ANZRAG definition.

After quality control, 332 advanced glaucoma cases from Southampton and Liverpool had genotype data available, based on Illumina Infinium Global Screening Array-24 v2.0 array genotyping. Cases were matched to 3,000 European ancestry individuals from the QSkin Sun and Health study,<sup>36</sup> which were genotyped on the same array. Before imputation, we filtered individuals with more than 3% missing genotypes, and SNPs with call rate < 95%, minor allele frequency of <1%, and Hardy-Weinberg P value < 1x10<sup>-6</sup>. The imputation was performed using Michigan Imputation Server.<sup>26</sup> To ensure matching of cases and controls for ancestry, we removed any non-European ethnic outliers based on the first two genetic principal components (> 6 standard deviations), with European

individuals from the 1000 Genomes Project Phase 3 data used as a reference population. Identity by descent was estimated using autosomal markers and only one member of each pair of related individuals ( $\hat{\pi} > 0.2$ ) was retained for analysis.

**13. Progression Risk Of Glaucoma RElevant SNPs of Significant Association (PROGRESSA)  
Study: Early stage glaucoma monitoring through prospective cohort of sequential early manifest glaucoma patients**

Participants were recruited at the various public and private ophthalmology practices in Australia. Inclusion criteria were: age between 18 and 85; the ability to provide written consent; the ability to attend 6-monthly visits for 5 years; and two reliable Humphrey visual field tests separated by less than 12 months, demonstrating early manifest glaucoma at the time of recruitment. Exclusion criteria at recruitment included: an inability to perform reliable visual field testing; mean deviation worse than -6.0 dB; best corrected visual acuity worse than 6/18 in either eye; angle closure, or the presence of other conditions that affect the visual field. Participants were genotyped on HumanCoreExome arrays (Illumina, San Diego, CA, USA).

Patients performed Humphrey Visual Field (HVF) 24-2 SITA Standard at the baseline visit and each follow-up 6-monthly visit. Reliable visual fields were determined by having less than 33% fixation loss, false-positive rates and false-negative rates. A reliable baseline visual field test was considered abnormal if the results of the glaucoma hemifield test (GHT) were outside normal limits, corrected pattern standard deviation (PSD) of  $P < 0.05$  or there was a cluster of at least 3 contiguous points in a glaucoma region, all of which depressed at a  $P < 0.05$  level with at least one depressed at  $P < 0.01$  on the pattern deviation plot (Hodapp-Parrish-Anderson criteria).<sup>37</sup> The glaucoma regions were defined as the paracentral, Bjerum, nasal step and temporal wedge in each hemifield. A second confirmatory HVF test was required to demonstrate a cluster in the same glaucoma region with the same criteria described above. Alternatively, the second HVF test was considered confirmatory if it had an abnormal PSD or GHT (as defined above) and there was a cluster in the same region of at least 3 contiguous points all depressed at  $P < 0.05$ .

Optical coherence tomography (OCT) was performed using a Cirrus HD-OCT (Carl Zeiss Pty Ltd), and used to measure the thickness of peripapillary retinal nerve fibre layer (RNFL). All protocols were approved and monitored by the South Australian Southern Area Clinical Human Research Ethics Committee (SAC HREC; #490.11) and Central Adelaide Local Health Network Human Research Ethics Committee (CALHN HREC), the Bellberry Human Research Ethics Committee (HREC), and NSW Macquarie University Human Research Ethics Committee (HREC). All participants provided written and informed consent once all of the risks and benefits were explained to them.

The PROGRESSA early manifest glaucoma cohort comprised 388 EMG cases with mean OCT follow-up time of 5.1 (SD 1.7) years. There were 159 male and 229 female participants, with a mean age of 67.58 (SD 9.4) years at recruitment. The mean baseline IOP was 15.6 (SD 3.6) mmHg, with mean vertical cup to disc ratio (VCDR) of 0.72 (SD 0.1). The mean baseline OCT peripapillary RNFL thickness was 99.7 (SD 17.6)  $\mu$ m.

#### **14. Definition of independent genome-wide significant loci**

We conducted stepwise model selection procedures in GCTA-COJO (version 1.26)<sup>38</sup> to identify independent genome-wide significant SNPs. GCTA-COJO uses GWAS summary results and estimates LD from a reference sample (randomly selected 5,000 UKBB white British ancestry individuals, considering SNPs within a two megabase window) for the conditional and joint association analysis. Although the joint analysis can uncover SNPs with  $P < 5 \times 10^{-8}$  in the joint test and  $P < 5 \times 10^{-8}$  in the standard (unconditional) test, here we only report SNPs with both unconditional P values and joint P values less than  $5 \times 10^{-8}$ .

To define novel VCDR SNPs, we excluded known VCDR-associated loci, and similarly for novel glaucoma loci, we excluded known glaucoma loci. For glaucoma SNPs, we set IOP SNPs as “known” glaucoma loci if they were replicated in glaucoma GWAS after correction for multiple comparisons in our previous study.<sup>5</sup> To check against the previous literature, we first used HaploReg to identity all the

proxy SNPs ( $r^2 \geq 0.8$ ) of the lead SNPs from GCTA-COJO.<sup>39</sup> The lead SNPs, their proxy SNPs, and the located genes were checked in GWAS Catalog,<sup>40</sup> LDlink<sup>41</sup> and PubMed (last update July 2018).<sup>20,22,29,31,42–46</sup>

## **15. Definition of loci**

Our conditional analysis defined statistically independent SNPs. In some genomic regions, there are multiple independent SNPs. We defined a ‘locus’ as a region containing one or more SNPs, with each locus at least 400 kilobases from the adjacent locus.<sup>47,48</sup>

## **16. Replication of MTAG top loci in independent samples**

We replicated the new glaucoma loci from MTAG in ANZRAG and NEIGHBOURHOOD. Given our replication samples have a much smaller effective sample size than that available from our MTAG analysis, we first examined whether the direction of effect was consistent between discovery and replication cohorts. We calculated the Pearson correlation between the effect sizes estimates from discovery and replication cohorts in R. For the testing of individual putatively novel loci, given our strong prior hypothesis that a risk increasing allele discovered via MTAG would also increase risk in the replication cohorts, we performed one-sided significance tests. We applied a Bonferroni correction to correct for the number of novel loci tested.

## **17. Gene-based and pathway tests**

The gene-based and pathway analysis were conducted in MAGMA (v1.06) as implemented in FUMA (version 1.3.1).<sup>49,50</sup> In gene-based tests, GWAS summary statistics of SNPs were mapped to 18,025 genes, and the association P values for a set of SNPs were calculated. Bonferroni method was used for multiple testing ( $P < 0.05/18,025$ ). In pathway tests, 10,655 predefined gene sets (MsigDB v6.1, curated gene sets: 4,738, GO terms: 5,917) were tested for enrichment.

## 18. Polygenic risk score and prediction

To assess the prediction value of our MTAG method derived PRS, we calculated PRS in PLINK: LD-clumping followed by P value thresholding (PLINK version 1.90 beta, `-clump-p1 1 --clump-p2 1 --clump-r2 0.1 --clump-kb 1000`, and P value thresholds at  $5 \times 10^{-8}$ ,  $1 \times 10^{-5}$ , 0.001, 0.05, 1).<sup>14</sup> LD clumping was based on the overlap SNPs between training and target datasets.

PRS was evaluated in the following training and target samples. There is no sample overlap between each of the training and target datasets:

1. As shown in **Extended Data Fig. 1a**, in the training step, we performed four trait MTAG on UKBB glaucoma GWAS, UKBB VCDR (VDD adjusted), IGGC VCDR and IOP meta GWAS. We used the PLINK LD-clumping and thresholds method to calculate PRS from the MTAG output for UKBB glaucoma. The target outcome was ANZRAG advanced POAG status (1,734 cases and 2,938 controls). We calculated the Nagelkerke's pseudo  $R^2$  and AUC from the logistic regression adjusted for the effects of sex and the first four principal components. We compared the POAG risk between the top and bottom PRS decile groups. We also replicated the OR value for advanced glaucoma in UK samples (Southampton/Liverpool, 332 cases and 3,000 controls).
2. As outlined in point **No.1**, to explore the utility of the PRS, we also evaluated POAG related structural endpoints and the likelihood of progression in PROGRESSA.
3. To further evaluate the prediction ability of MTAG derived PRS over and above the traditional risk factors, we performed three trait MTAG on ANZRAG and UKBB glaucoma meta GWAS, UKBB VCDR (VDD adjusted) GWAS, and UKBB IOP GWAS (**Extended Data Fig. 1b**). Here to avoid the sample overlap between IGGC and BMES, we removed IGGC VCDR and IOP GWAS summary results. The target dataset was 74 POAG cases and 1,721 controls in BMES with IOP and VCDR available. We calculated the AUC for traditional risk factors and PRS.
4. As shown in **Extended Data Fig. 1c**, we performed four trait MTAG from ANZRAG POAG GWAS, UKBB VCDR (VDD adjusted) GWAS, IGGC VCDR GWAS and IOP meta GWAS. In UKBB, we removed 3,000 non-glaucoma participants (selected randomly, we also removed their relatives) with both IOP and VCDR available and reran the VCDR and IOP GWAS. The

target dataset was 1,421 glaucoma cases and the 3,000 controls in UKBB. Both the cases and controls were unrelated and had IOP and VCDR measurements. We calculated the AUC for PRS and its combination with traditional risk factors. To test the performance of the same PRS in UK Biobank samples of non-European ancestry, we selected 192 cases and 6,841 controls of South Asian ancestry (the largest ethnic minority in UK Biobank, defined here as individuals self describing as Indian or Pakistani ancestry, we also removed their relatives). All South Asians had genetic ancestry which was clearly distinct from UK Biobank participants of European ancestry (supplementary **Figure 12**). We also, for the European ancestry samples only (due to limited sample size), evaluated the AUC in 112 ICD-10 defined POAG cases and the 3,000 controls in UKBB.

5. As shown in **Extended Data Fig. 1d**, we performed four trait MTAG from ANZRAG POAG GWAS, UKBB VCDR (VDD adjusted), IGGC VCDR and IOP meta GWAS. To avoid sample overlap for *MYOC* p.Gln368Ter carriers, we removed all *MYOC* p.Gln368Ter carriers and their relatives from UKBB VCDR (VDD adjusted) and IOP GWAS. We used Cox model to calculate the cumulative risk of glaucoma for *MYOC* p.Gln368Ter carriers stratifying by tertiles of the MTAG PRS. For analysis examining cumulative risk (prevalence) of glaucoma in the general population (i.e. in *MYOC* p.Gln368Ter non-carriers), we stratified PRS by deciles. Since the VCDR and IOP GWAS samples are only from non-glaucoma cases, the prediction of glaucoma status in UKBB *MYOC* p.Gln368Ter non-carriers will not be inflated due to sample overlap. In the Cox model, we adjusted for sex and first six genetic principal components.

#### **19. Clinical implications: methods and statistical analysis**

PROGRESSA cohort clinical data used for analysis were recorded at each visit by the treating clinician. OCT scans were obtained using Cirrus HD-OCT (CarlZeiss Meditec, Inc., Dublin, CA) at each visit and any poor quality scans were discarded and repeated on the same day. The Optic Disc Cube 200 X 200 scan generates a 6mm by 6mm square grid by acquiring 200 horizontal lines of 200 A-scans. The peripapillary RNFL thickness is based on a circle of diameter 3.46 mm around the

centre of the optic disc. The average and quadrant thickness data of this circle is displayed under the RNFL Thickness Analysis of the Cirrus OCT software. Poor quality scans as defined by the manufacturer's own inbuilt quality score, and scans with artifacts and segmentation errors were excluded from analysis.

All statistical analysis of PRS and RNFL data, as well as the trabeculectomy surgery analysis, was performed using R statistical software (version 3.4.1). Normality was checked using the Shapiro–Wilk test. Regression analysis adjusted for covariates was performed using linear regression or logistic regression from the base R *stats* package.

## **20. Web resources used**

BOLT-LMM software: <https://data.broadinstitute.org/alkesgroup/BOLT-LMM/>

GCTA software: <http://cnsgenomics.com/software/gcta/>

GWAS Catalog: <https://www.ebi.ac.uk/gwas/>

Haplotype Reference Consortium: <http://www.haplotype-reference-consortium.org/>

International Glaucoma Genetic Consortium dataset: <https://goo.gl/73qHqk>

LOCUSZOOM: <http://locuszoom.sph.umich.edu/>

LDlink: <https://analysis-tools.nci.nih.gov/LDlink/>

LD score regression software: <https://github.com/bulik/ldsc>

METAL software: <http://csg.sph.umich.edu/abecasis/Metal/>

MTAG: Multi-Trait Analysis of GWAS <https://github.com/omeed-maghzian/mtag>

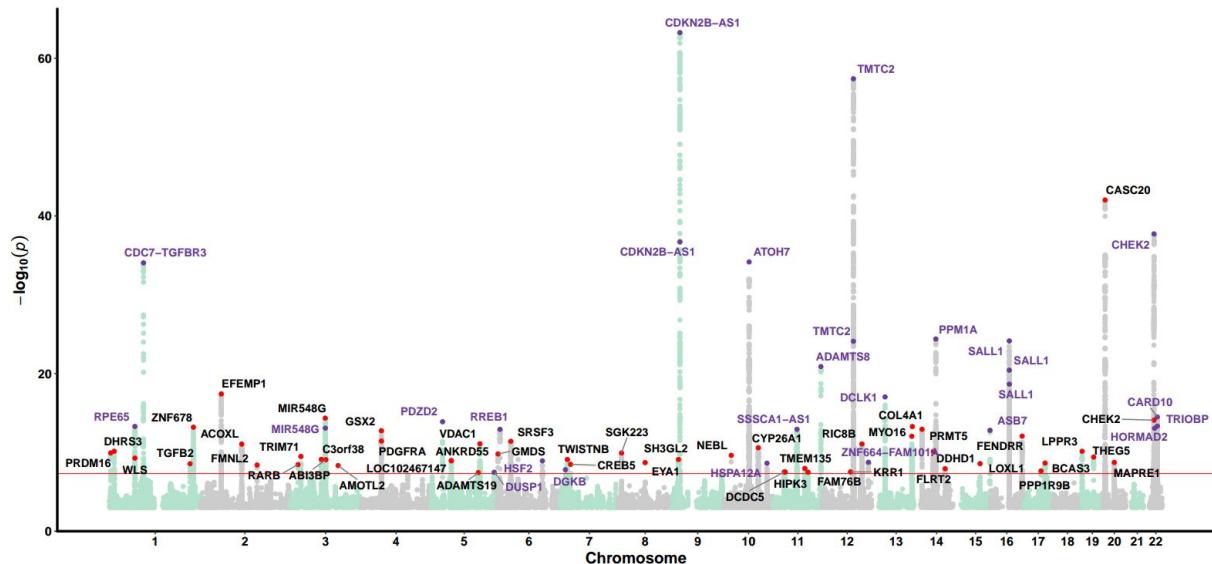
PLINK software: <http://www.cog-genomics.org/plink2>

R: <https://cran.r-project.org/>

UK Biobank: <http://www.ukbiobank.ac.uk/>

## Supplementary Figures

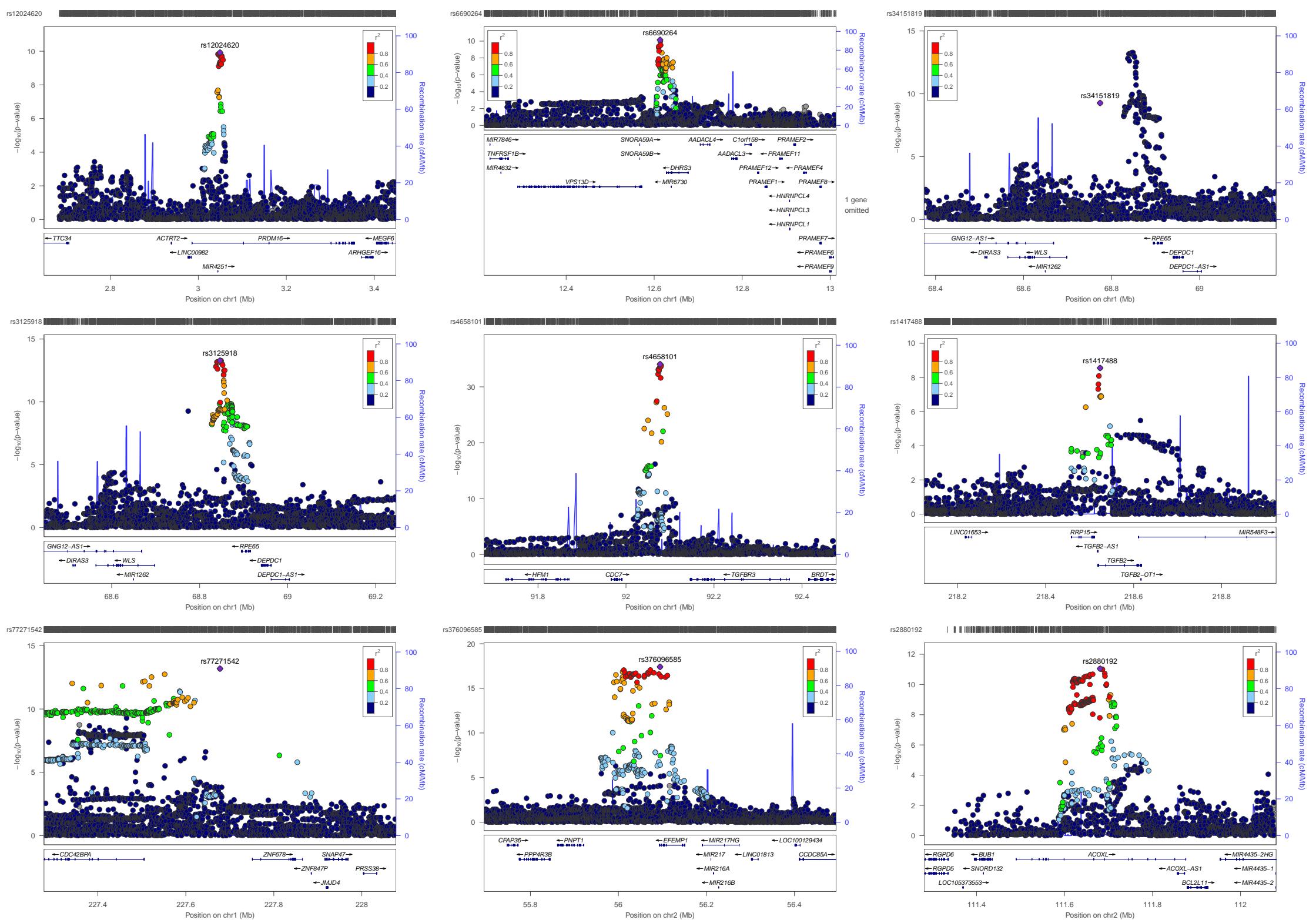
**Supplementary Figure 1. Manhattan plot for the GWAS of UKBB vertical-cup-disc-ratio (adjusted for vertical disc diameter, N = 67,040).**

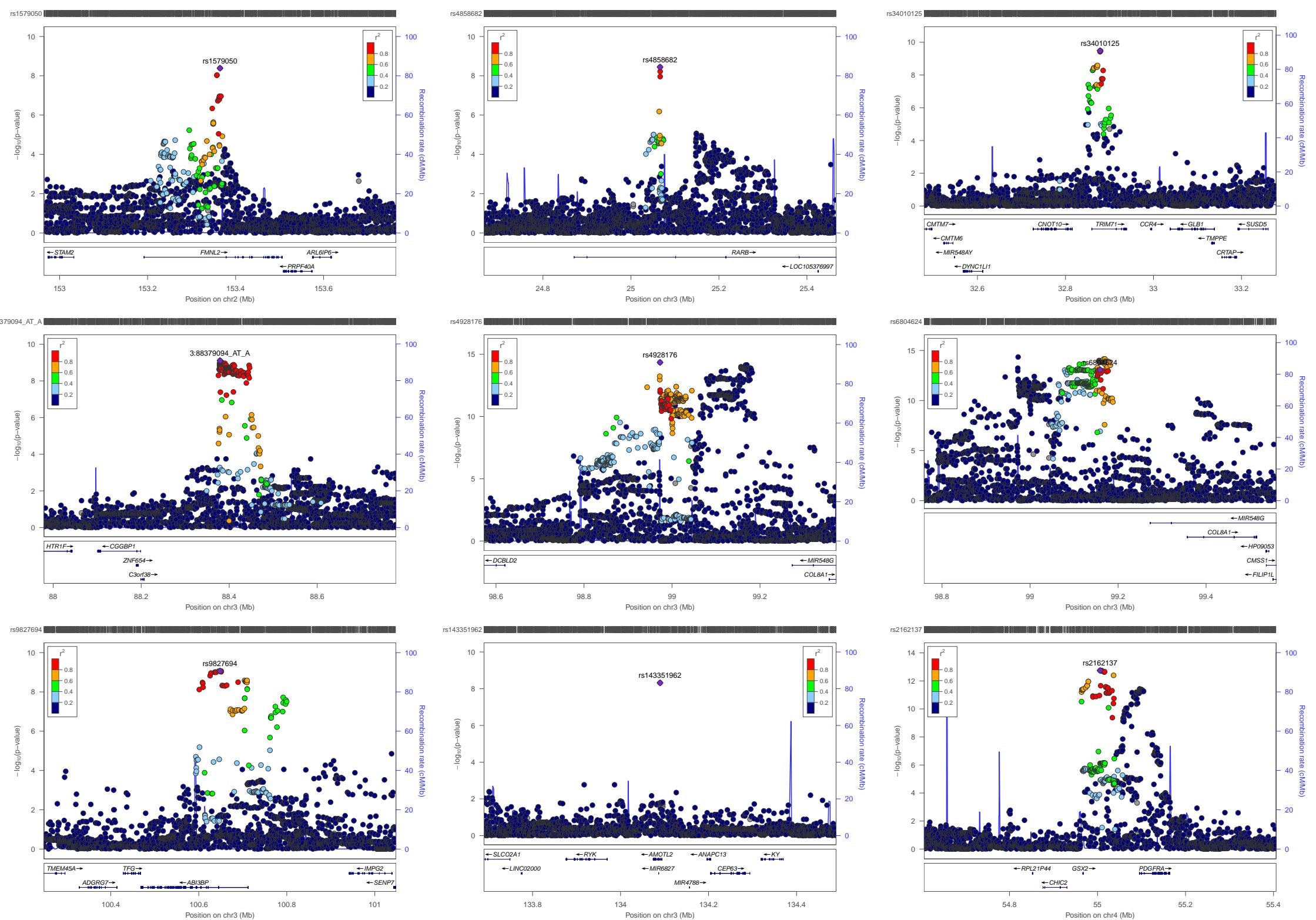


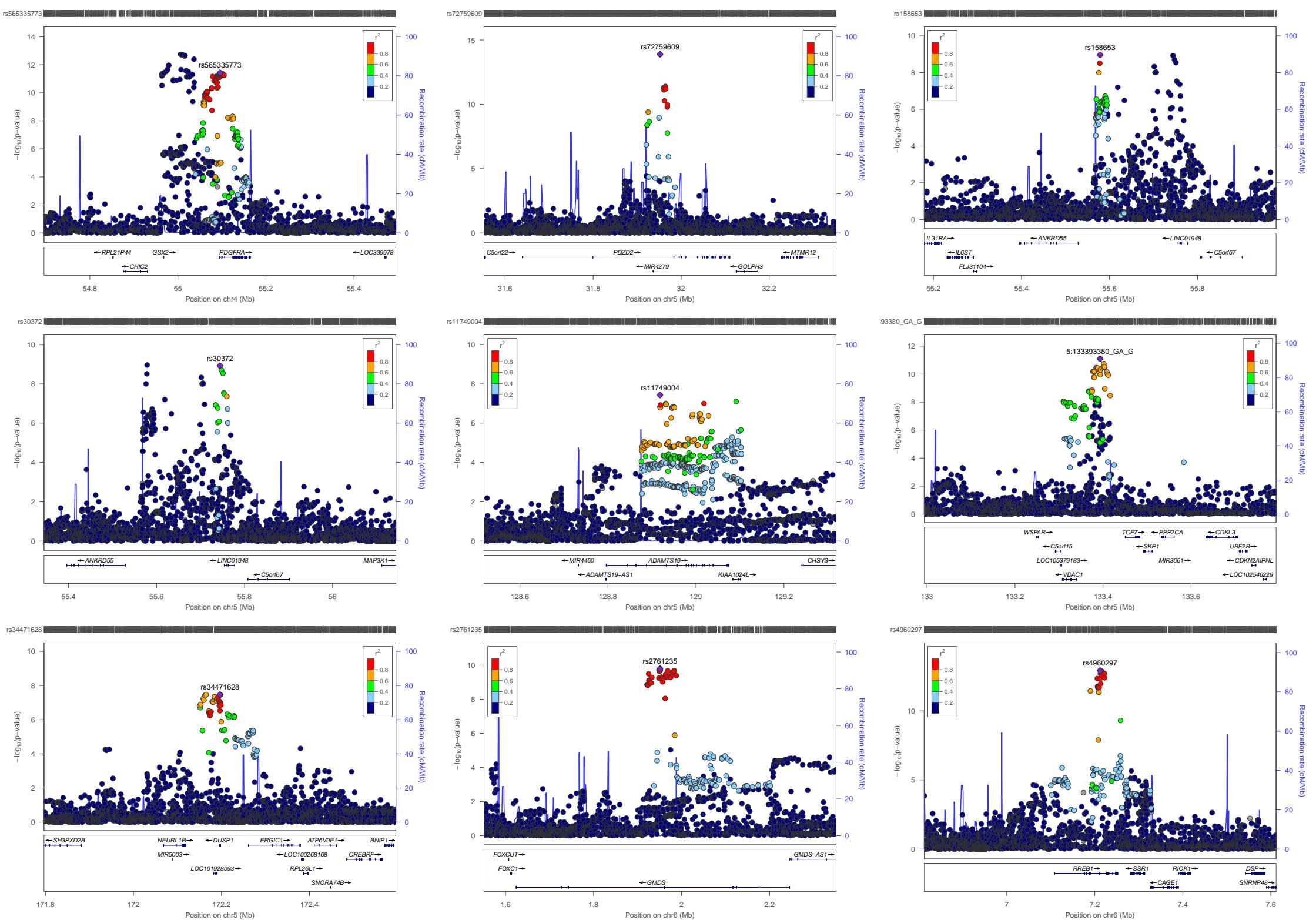
Novel SNPs are highlighted in red dots, with the nearest gene names in black text. Known SNPs are highlighted in purple dots, with the nearest gene names in purple text. The red line is the genome-wide significance level at  $5 \times 10^{-8}$ .

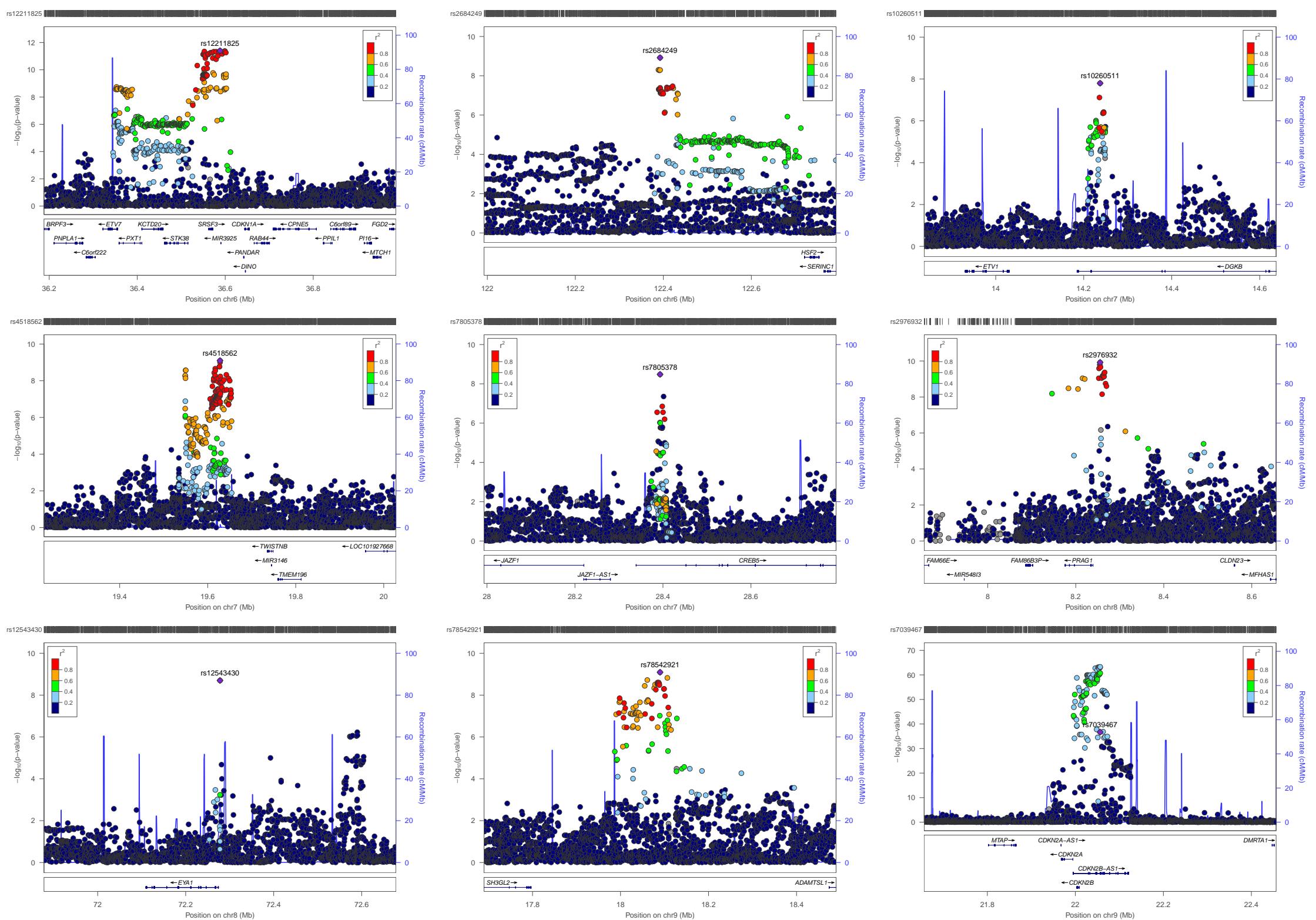
**Supplementary Figure 2. Locuszoom plot of UKBB VCDR (VDD adjusted) lead SNPs (N = 67,040)**

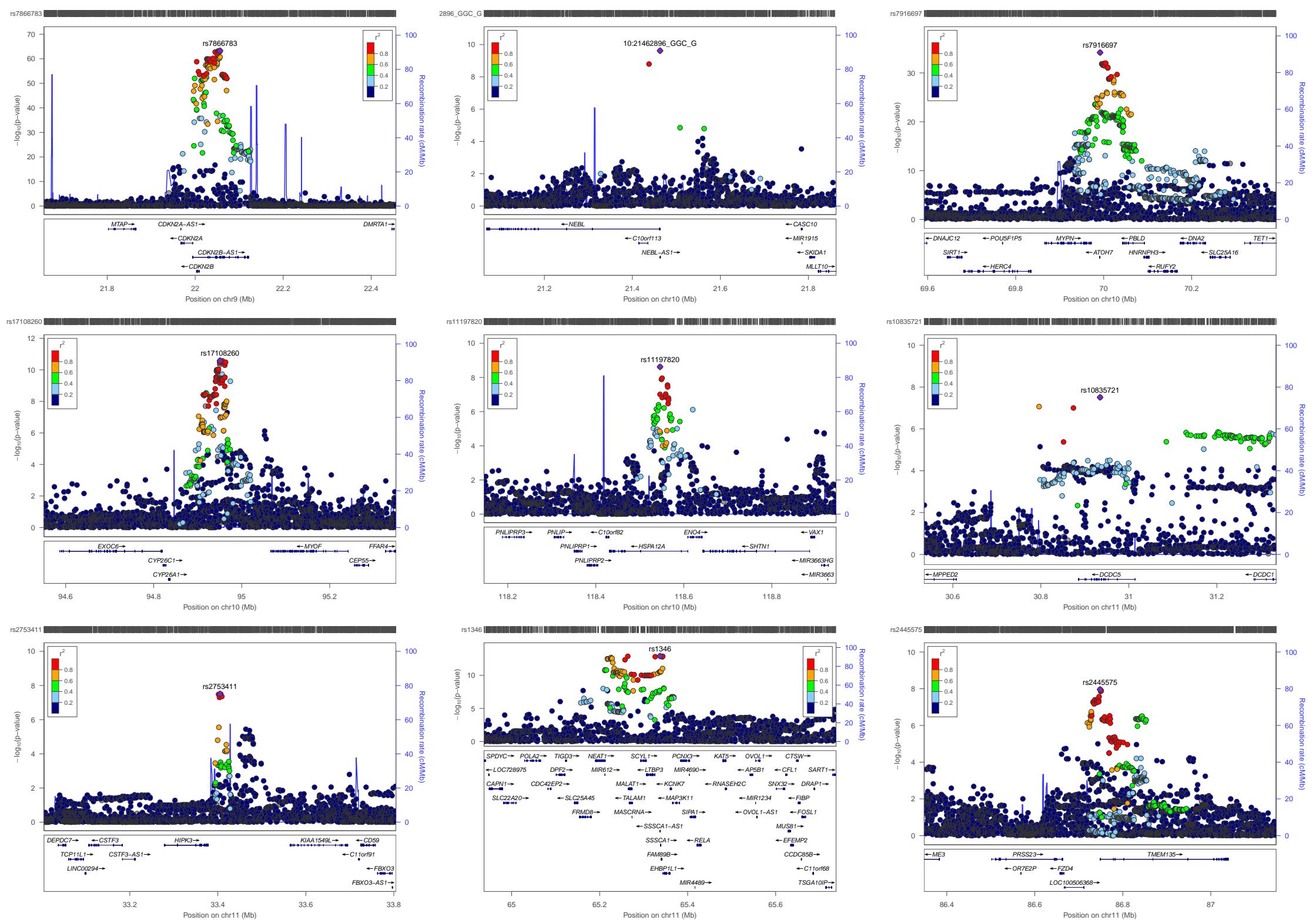
Locuszoom figures are displayed on the following pages.

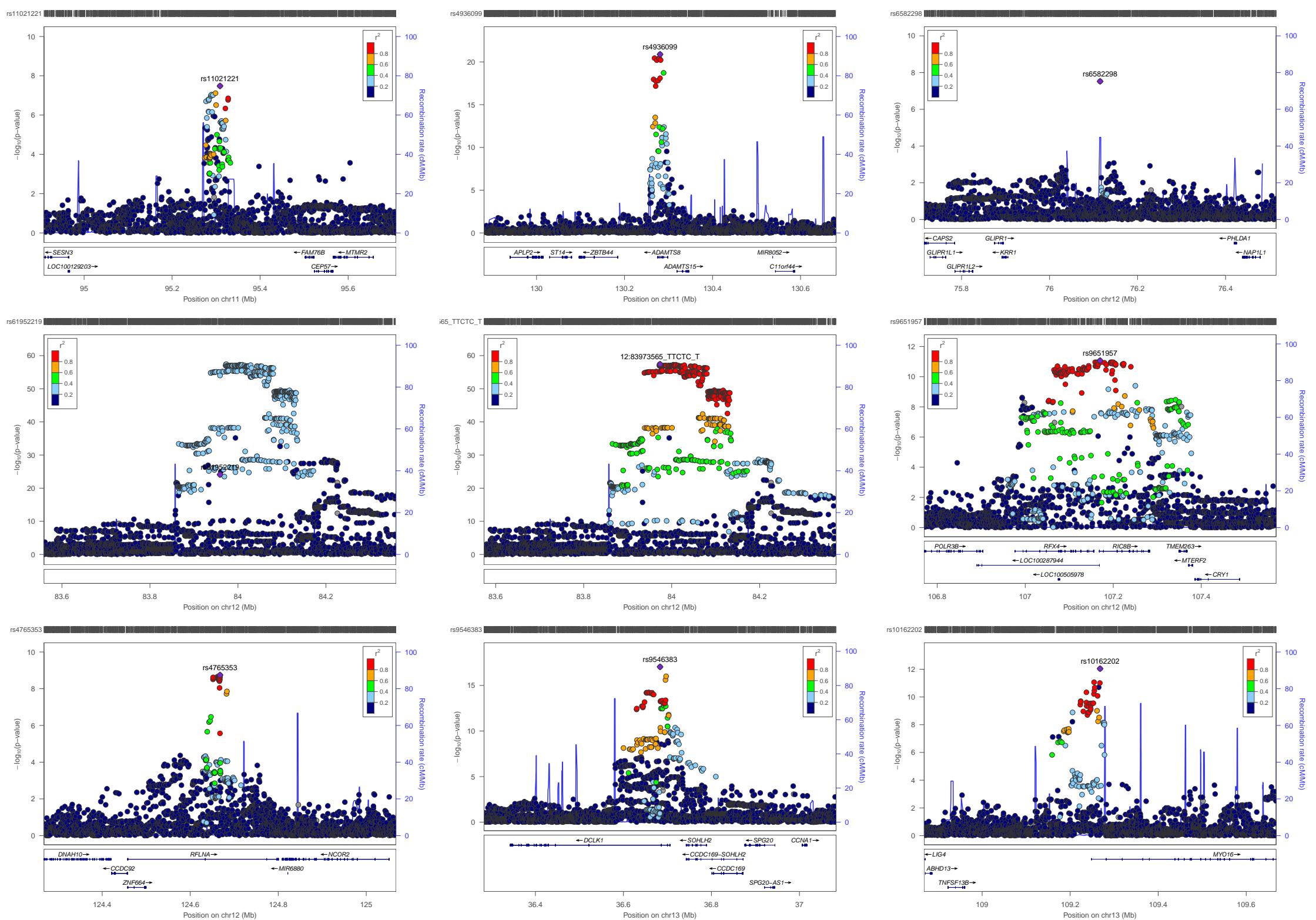


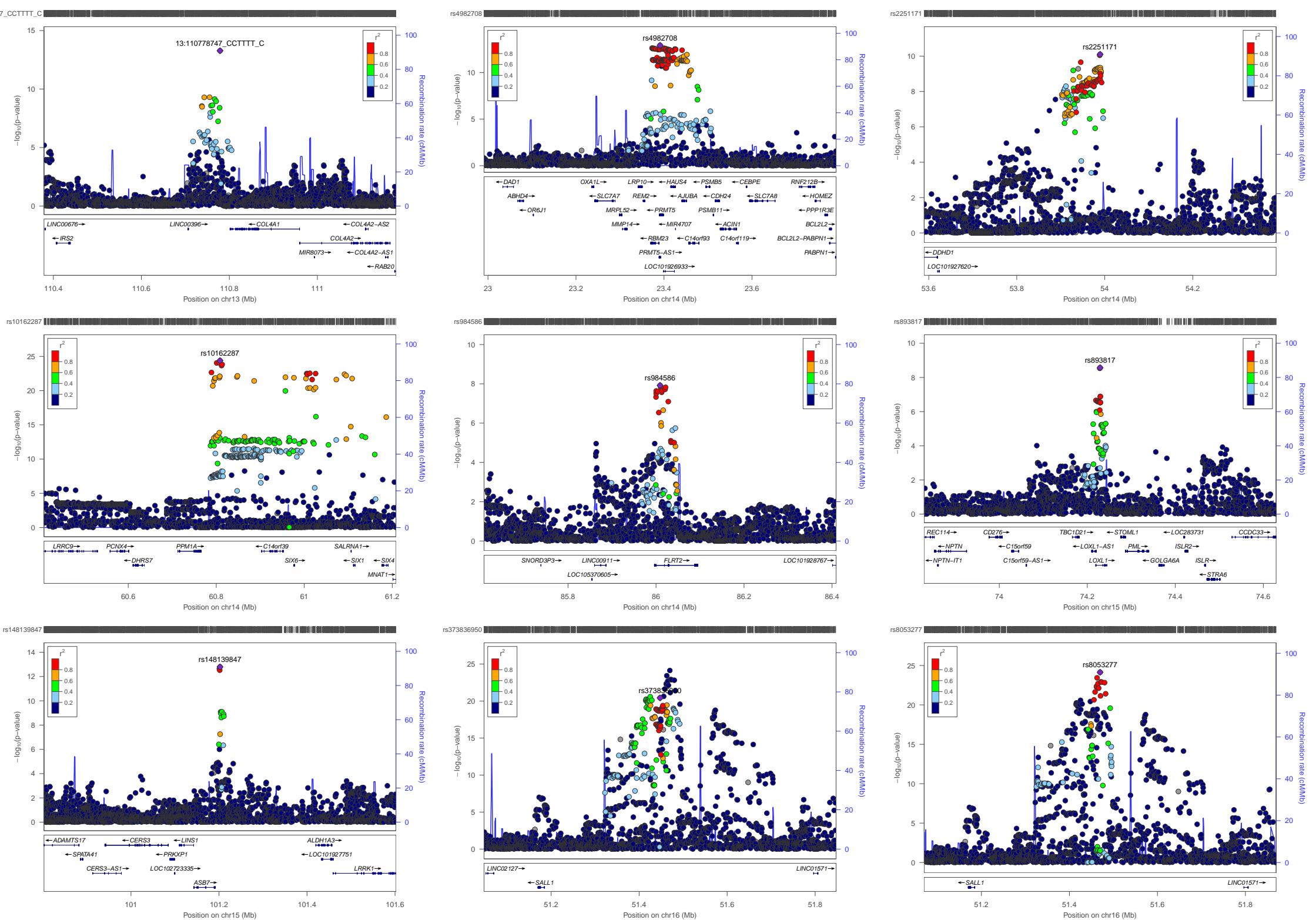


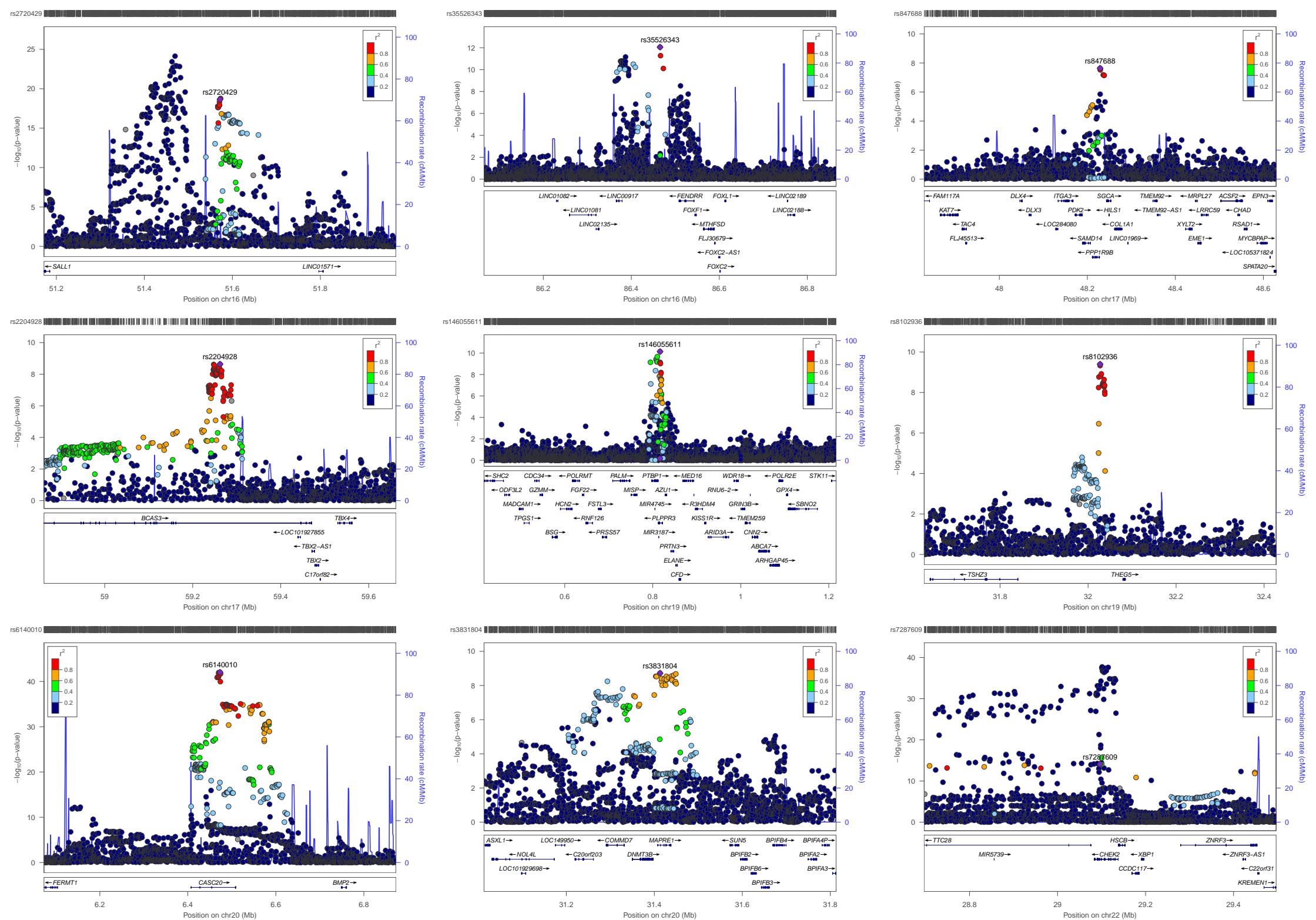


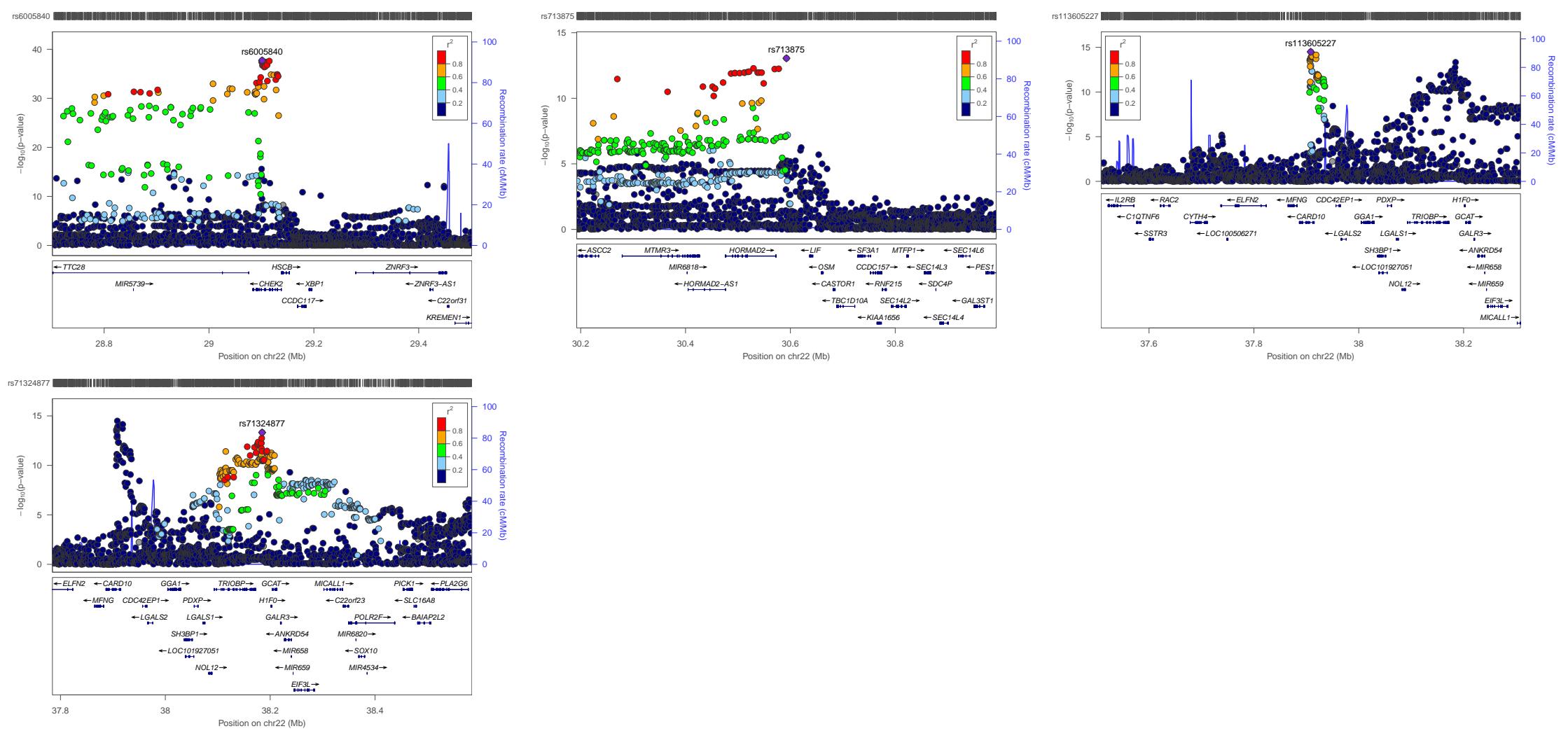




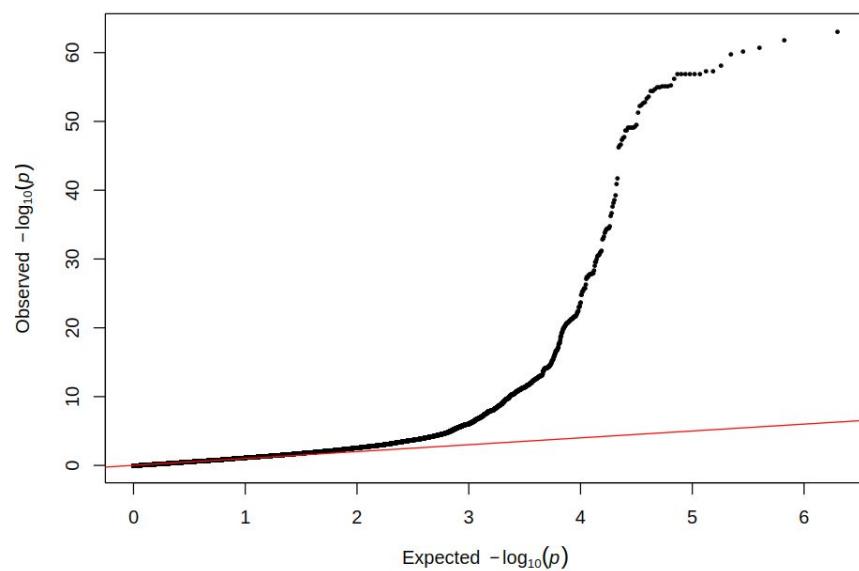






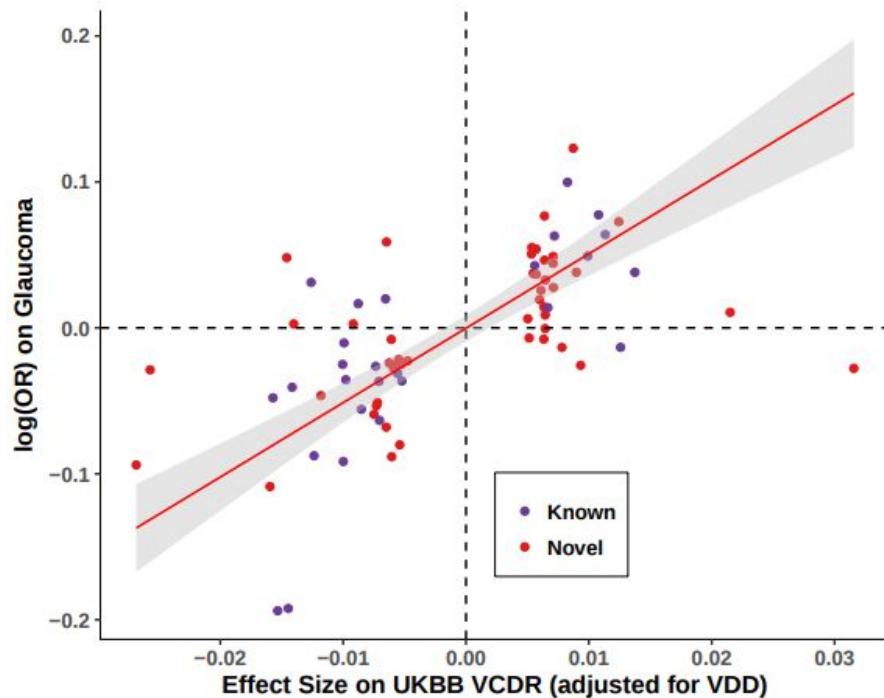


**Supplementary Figure 3. Quantile-quantile plot for UKBB VCDR GWAS (VDD adjusted)**



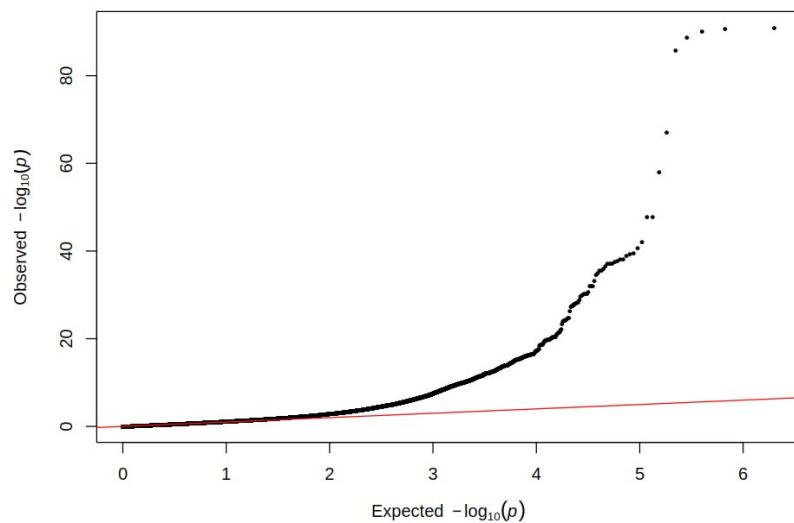
Linkage disequilibrium (LD) score regression intercept is used to assess the genomic inflation, and the intercept is 1.04 (standard error, SE=0.01) with lambda 1.20 and attenuation ratio ((Intercept-1) / ( $\chi^2$  -1)) 0.12 (SE=0.03). The quantile-quantile plot is based on  $1 \times 10^6$  randomly selected SNPs.

**Supplementary Figure 4. Comparison of the effect sizes for 76 UKBB VCDR (VDD adjusted) lead SNPs versus that in independent glaucoma cohorts**



The figure shows the effect sizes for UKBB VCDR (adjusted for VDD) lead SNPs versus log odds ratio in meta-analysis of ANZRAG and UKBB glaucoma GWAS. The Pearson's correlation coefficient is 0.60 (P value= $9.0 \times 10^{-9}$ ). The red line is the best fit line with 95% confidence interval region in grey. Novel VCDR SNPs are highlighted in red and known SNPs in purple.

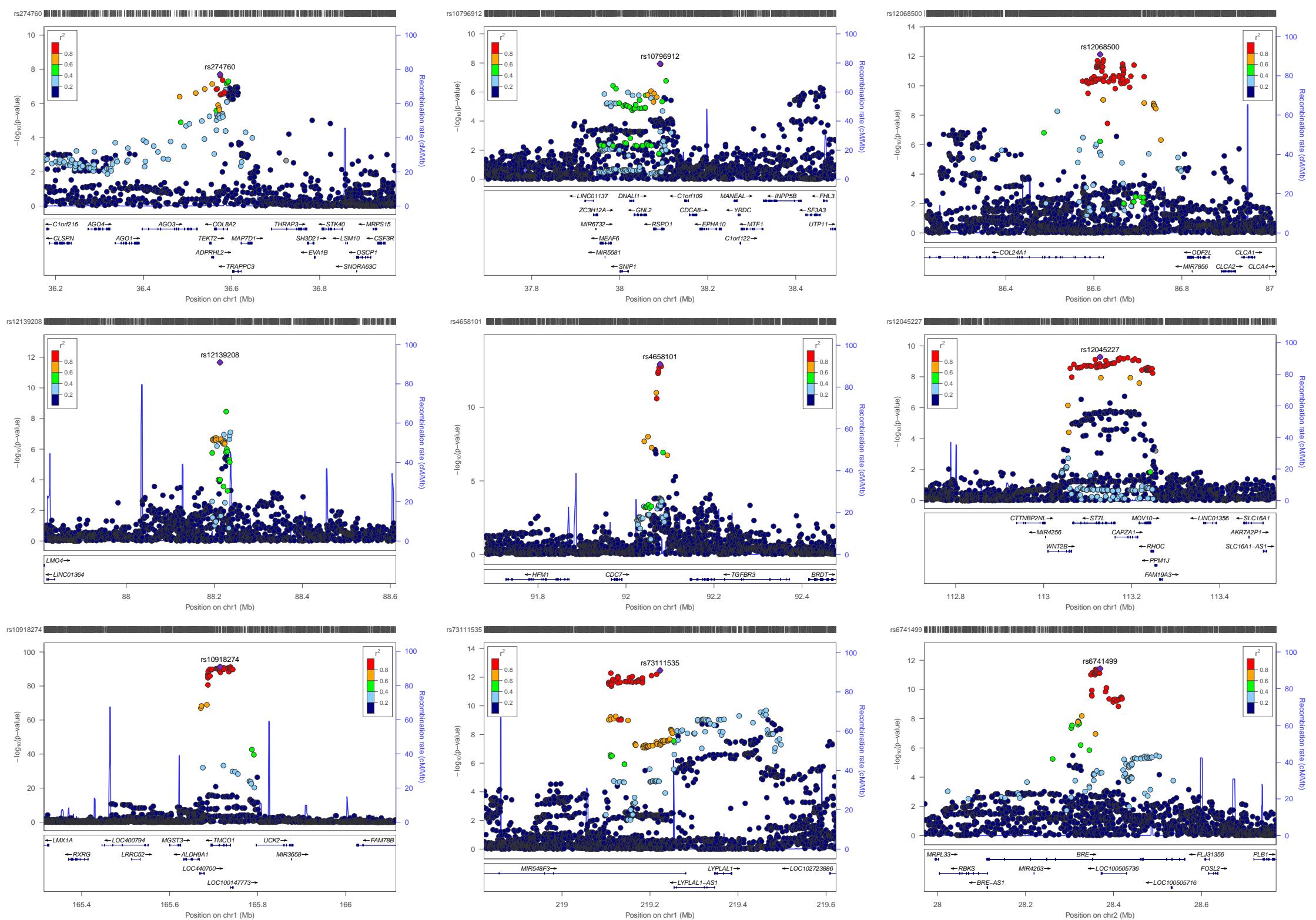
**Supplementary Figure 5. Quantile-quantile plot for MTAG glaucoma GWAS result**

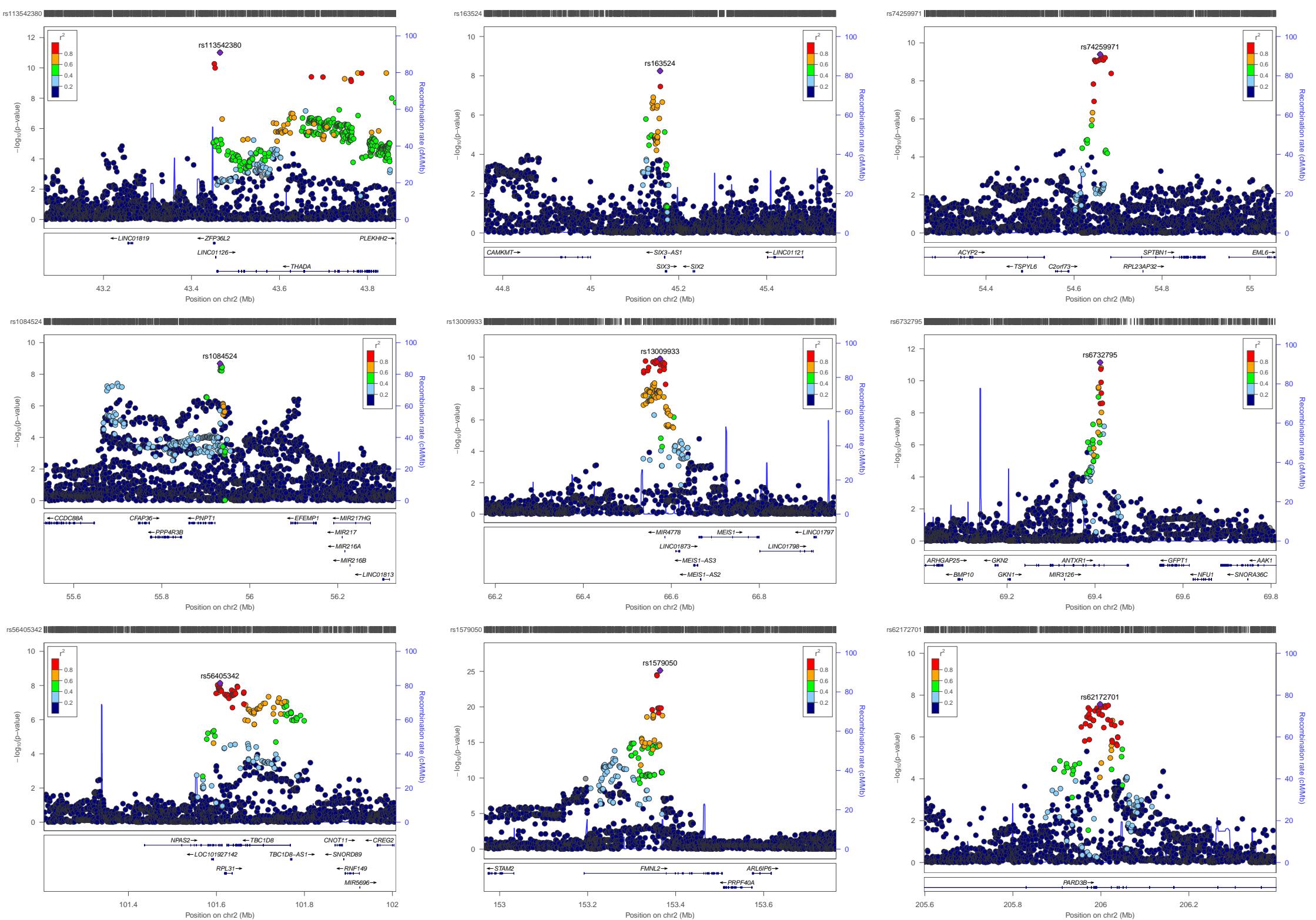


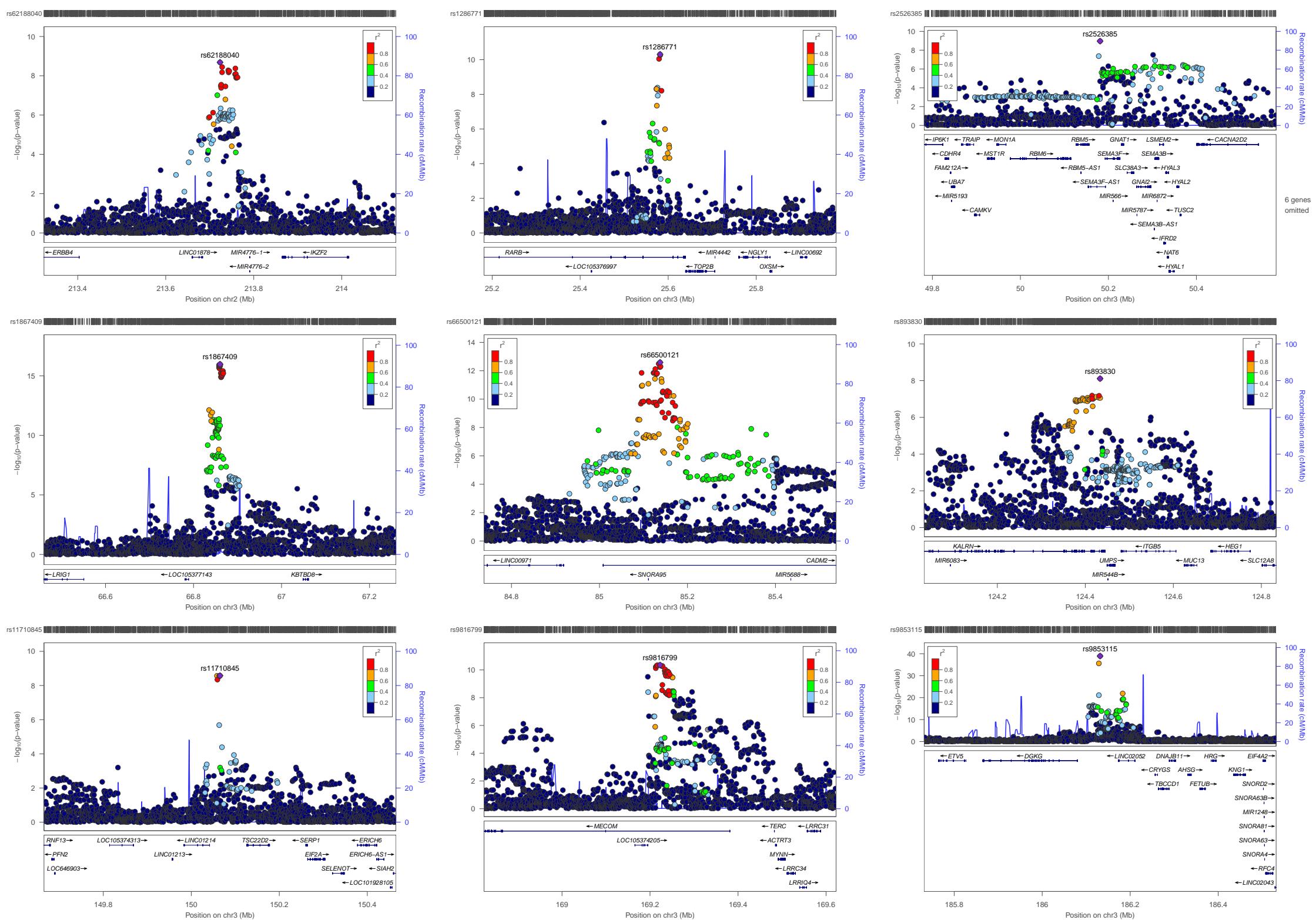
In MTAG GWAS for glaucoma, LD score regression intercept is 0.94 (SE=0.01), and the lambda is 1.19. The quantile-quantile plot is based on  $1 \times 10^6$  randomly selected SNPs.

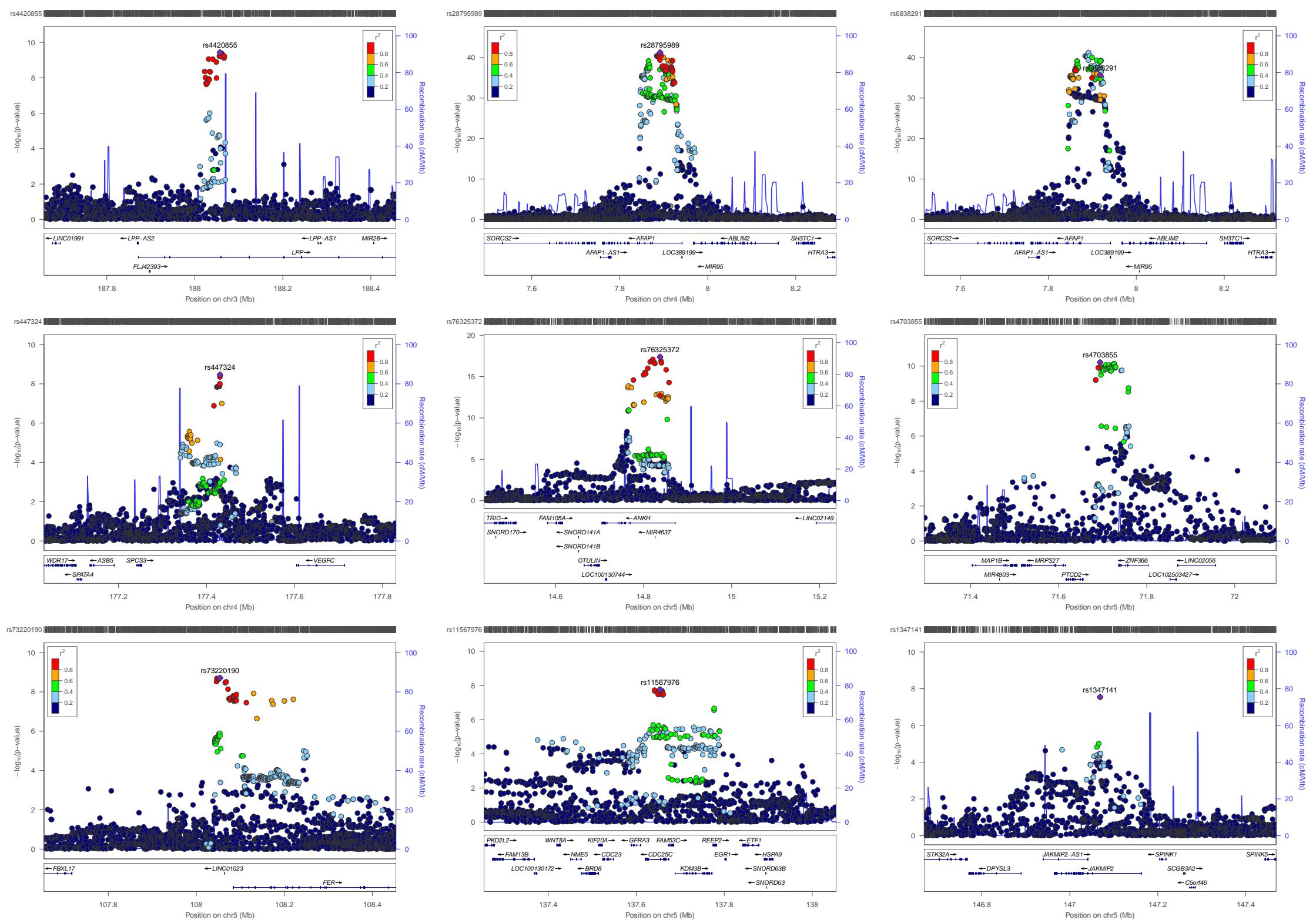
**Supplementary Figure 6. Locuszoom plot of 114 MTAG glaucoma lead SNPs**

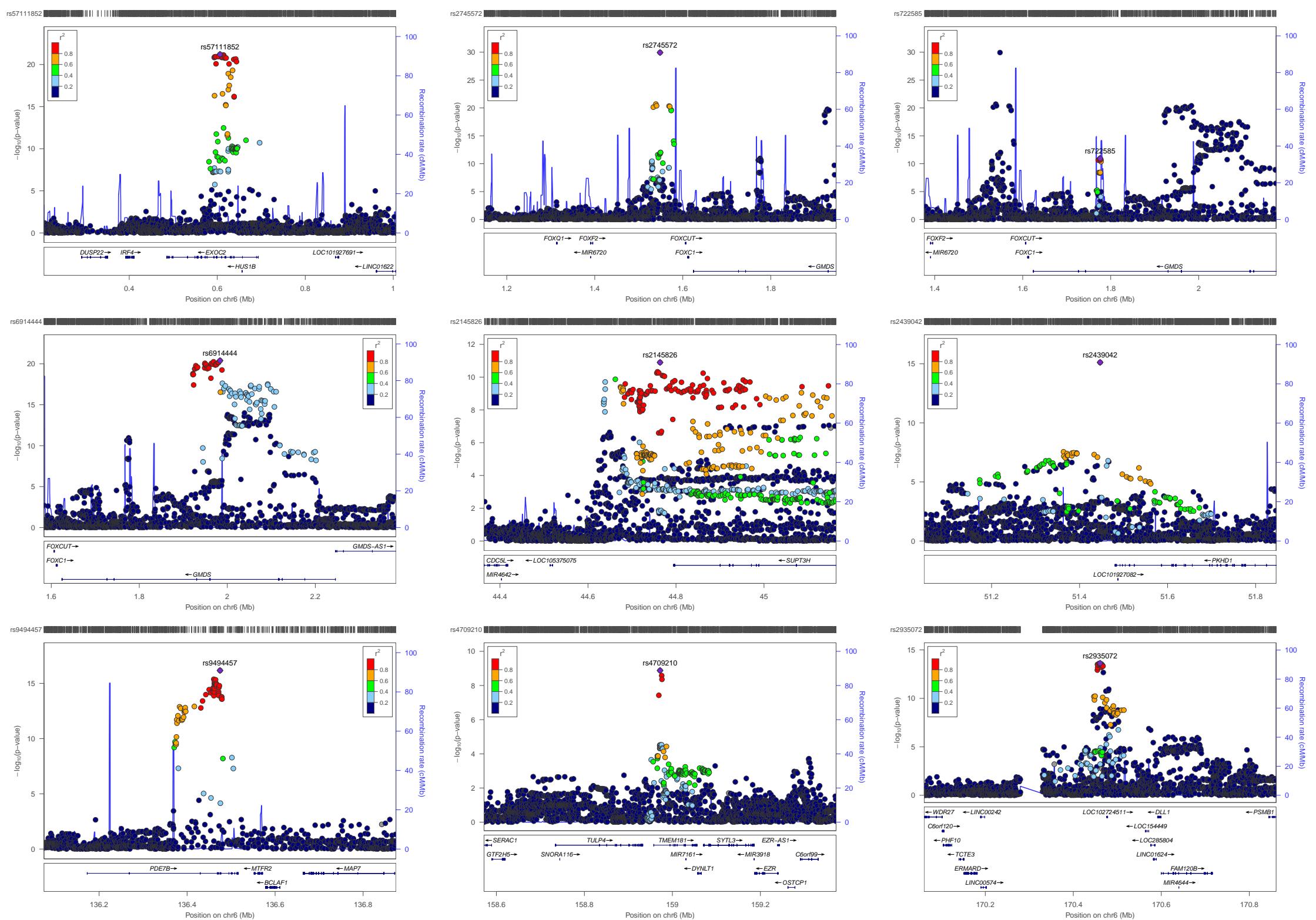
Locuszoom figures are displayed on the following pages.

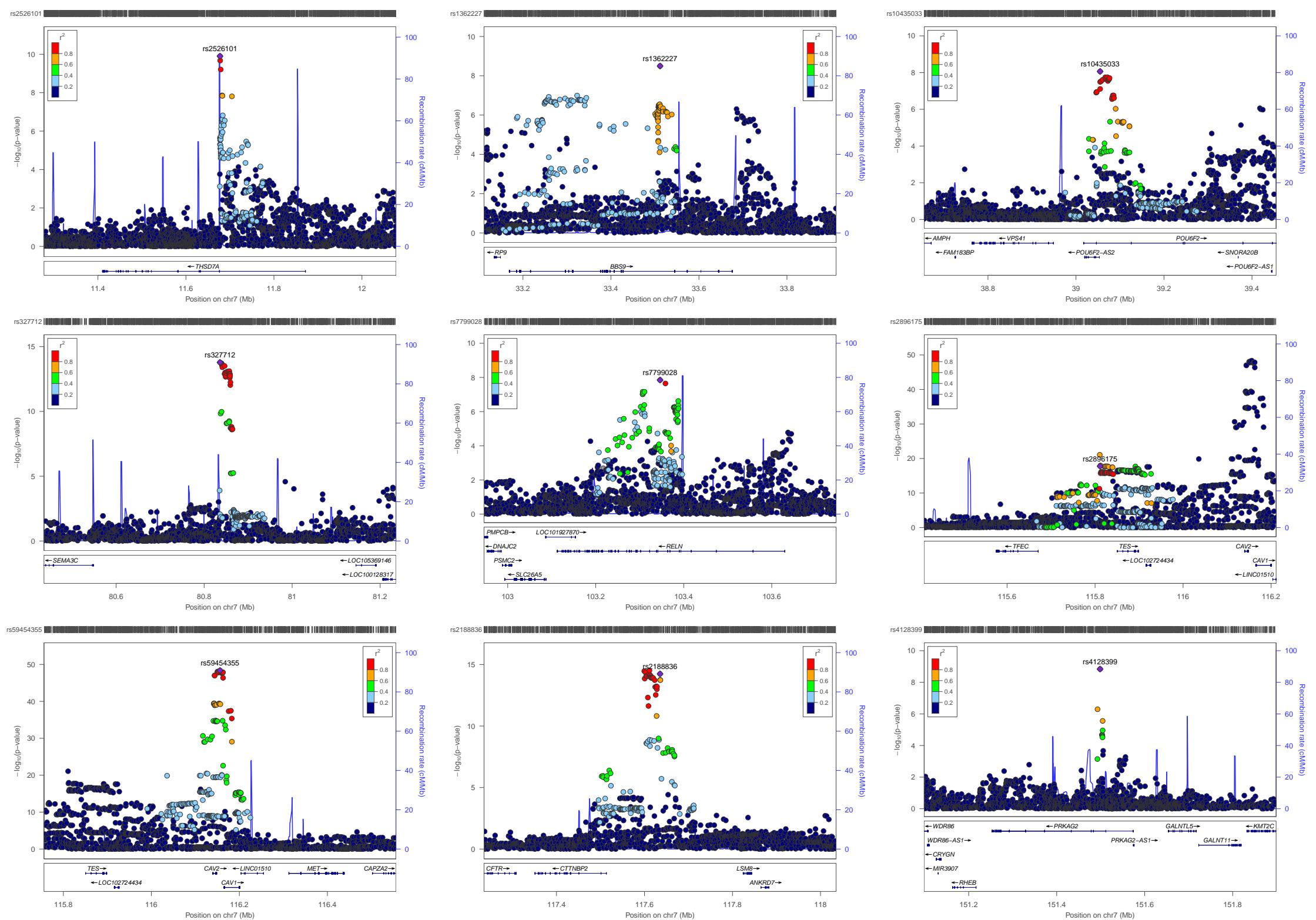


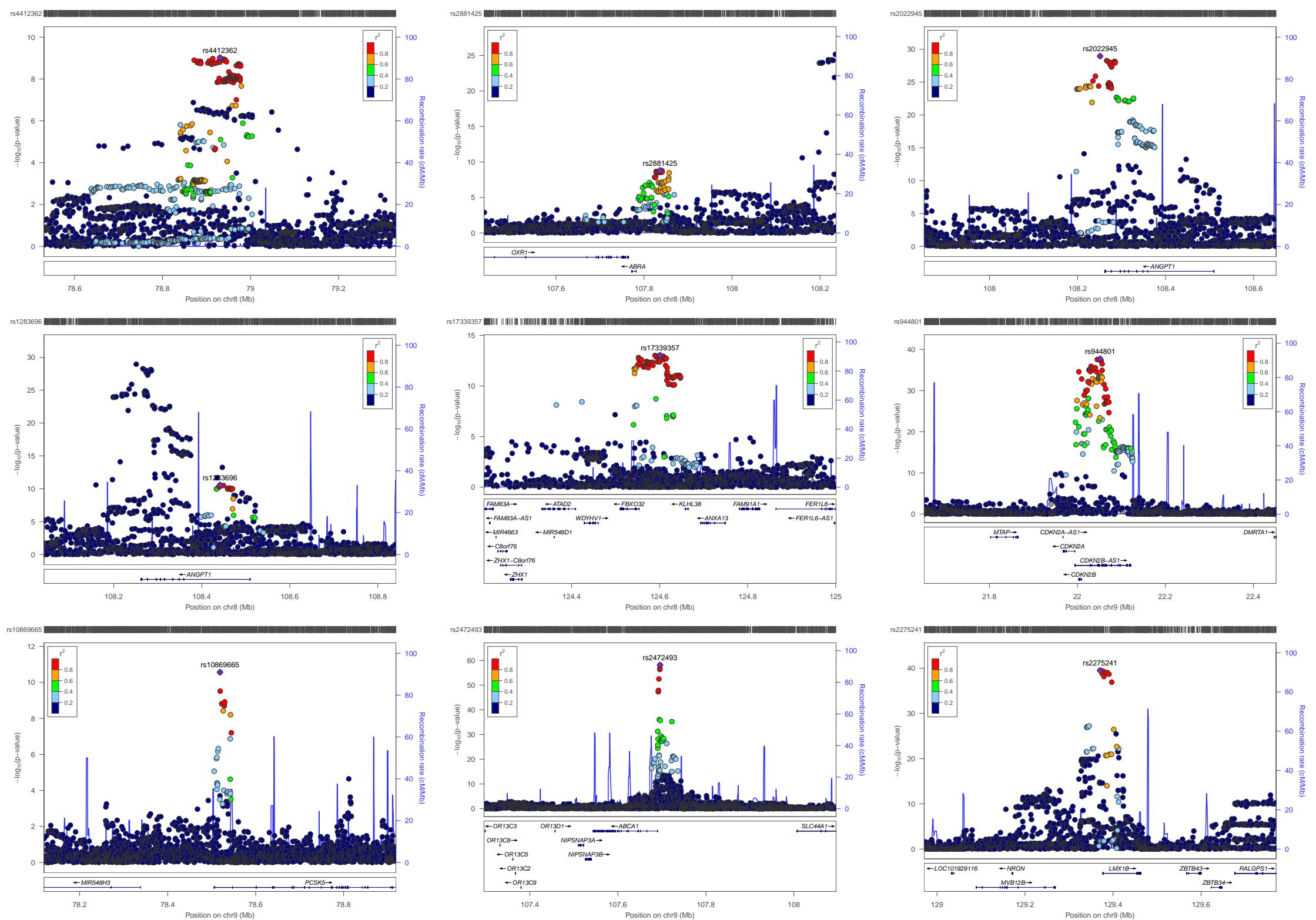


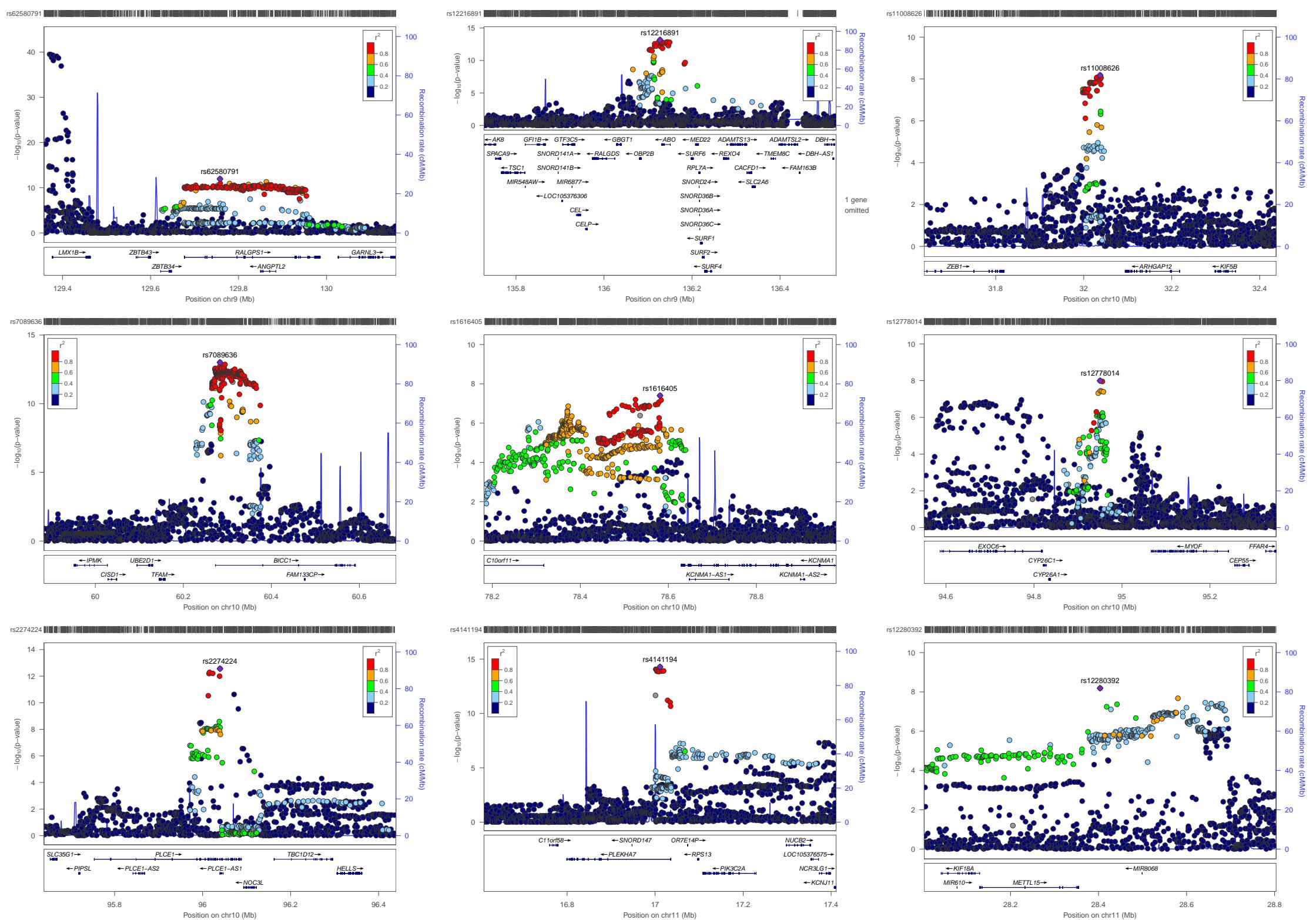


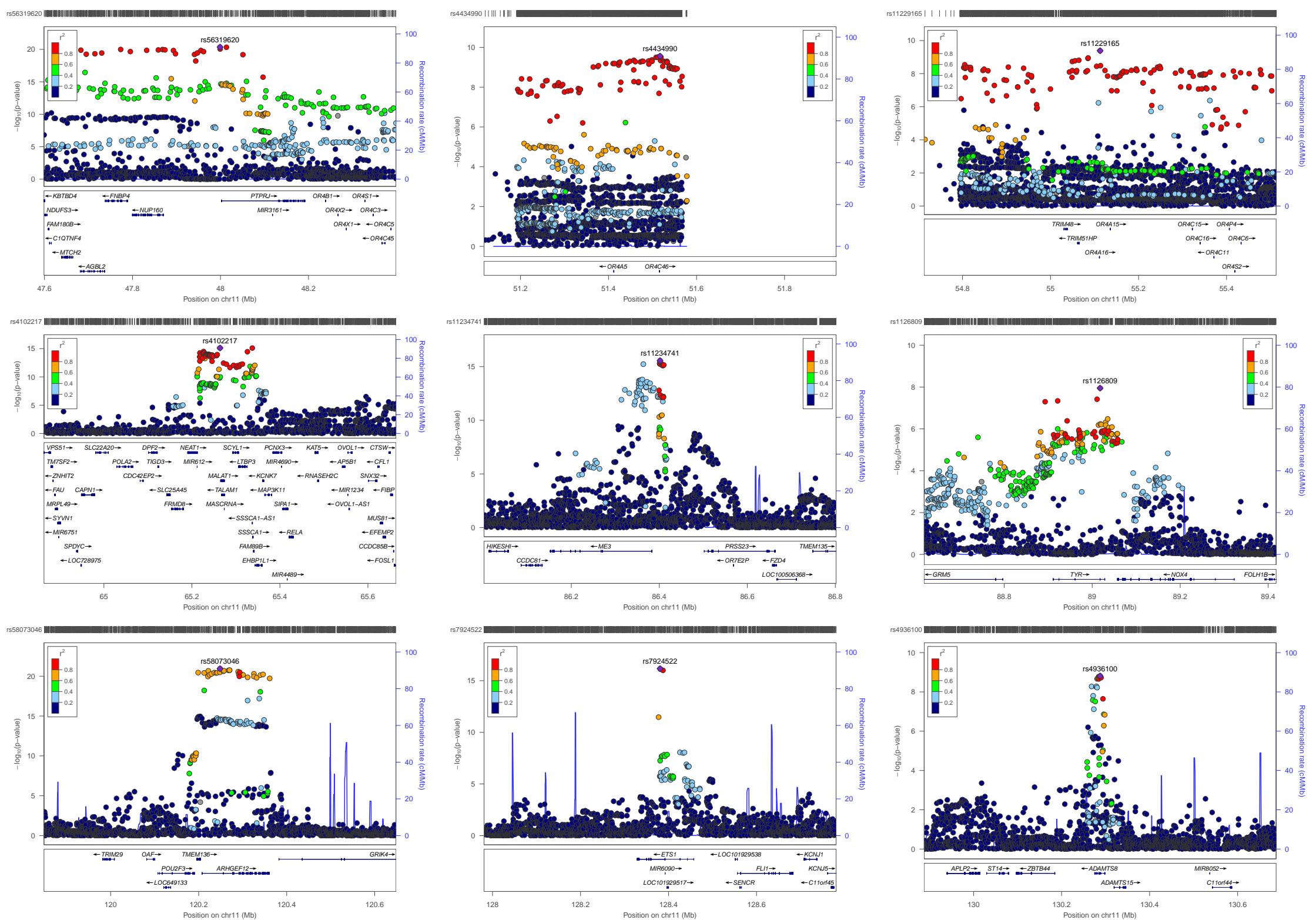


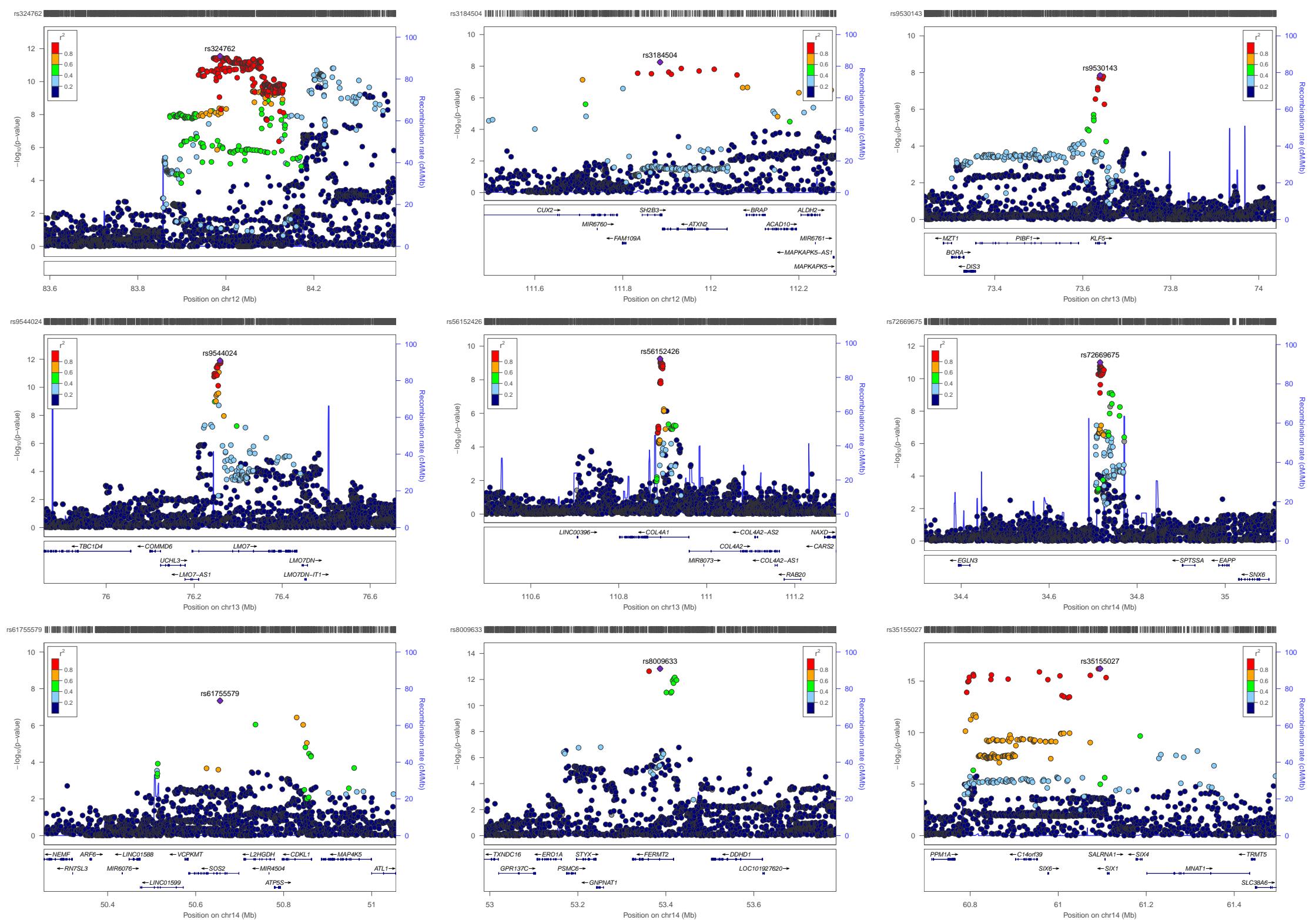


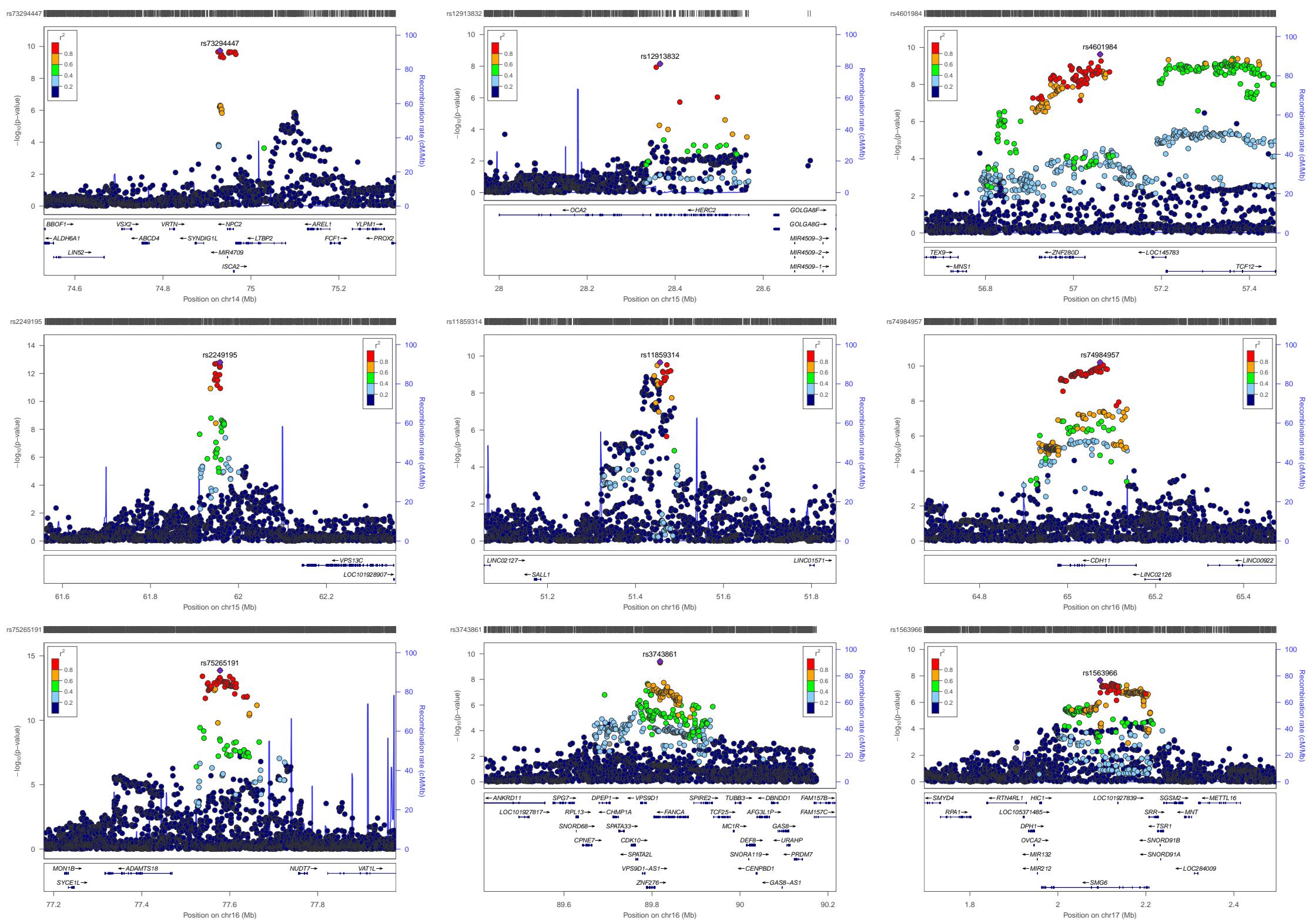


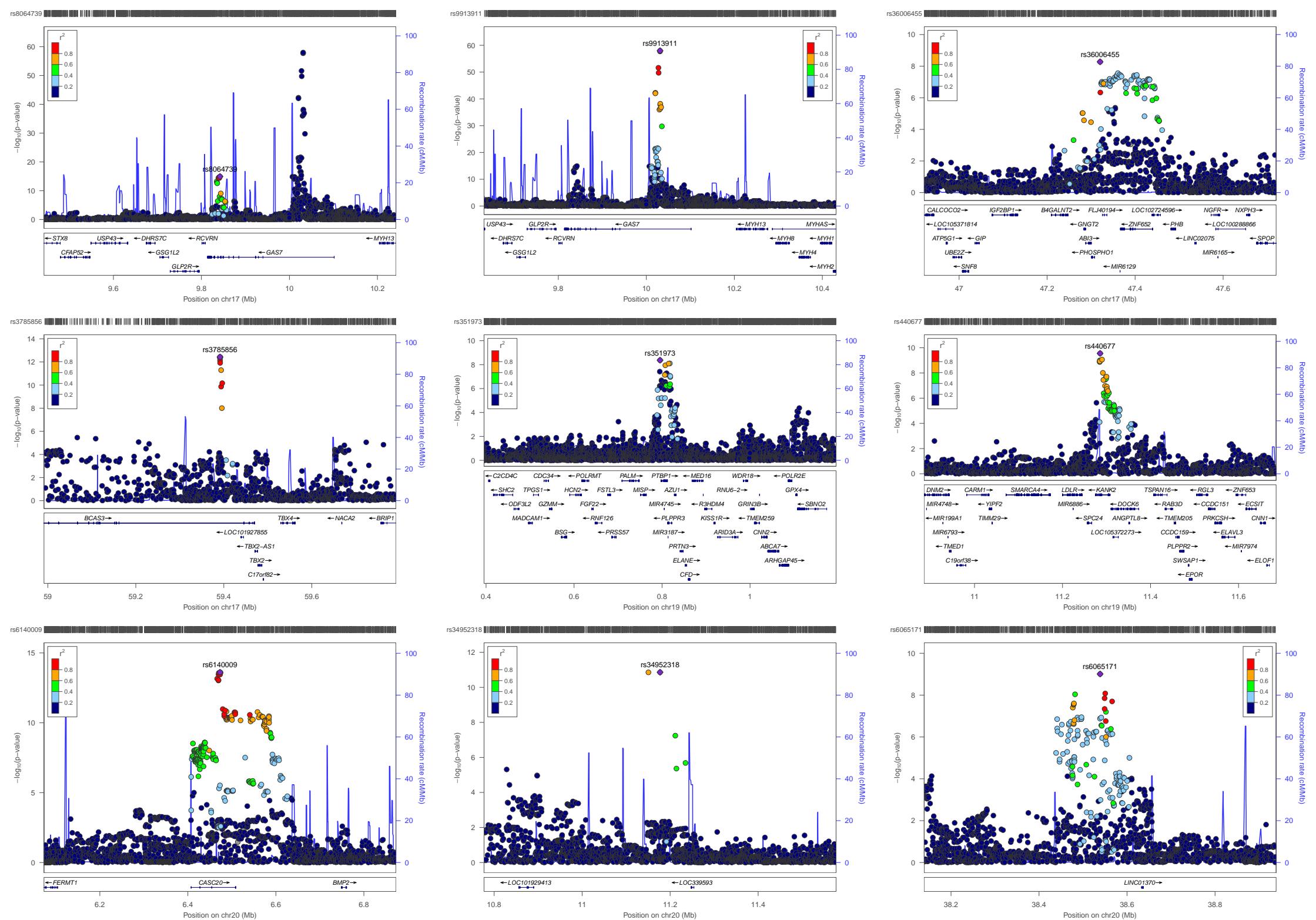


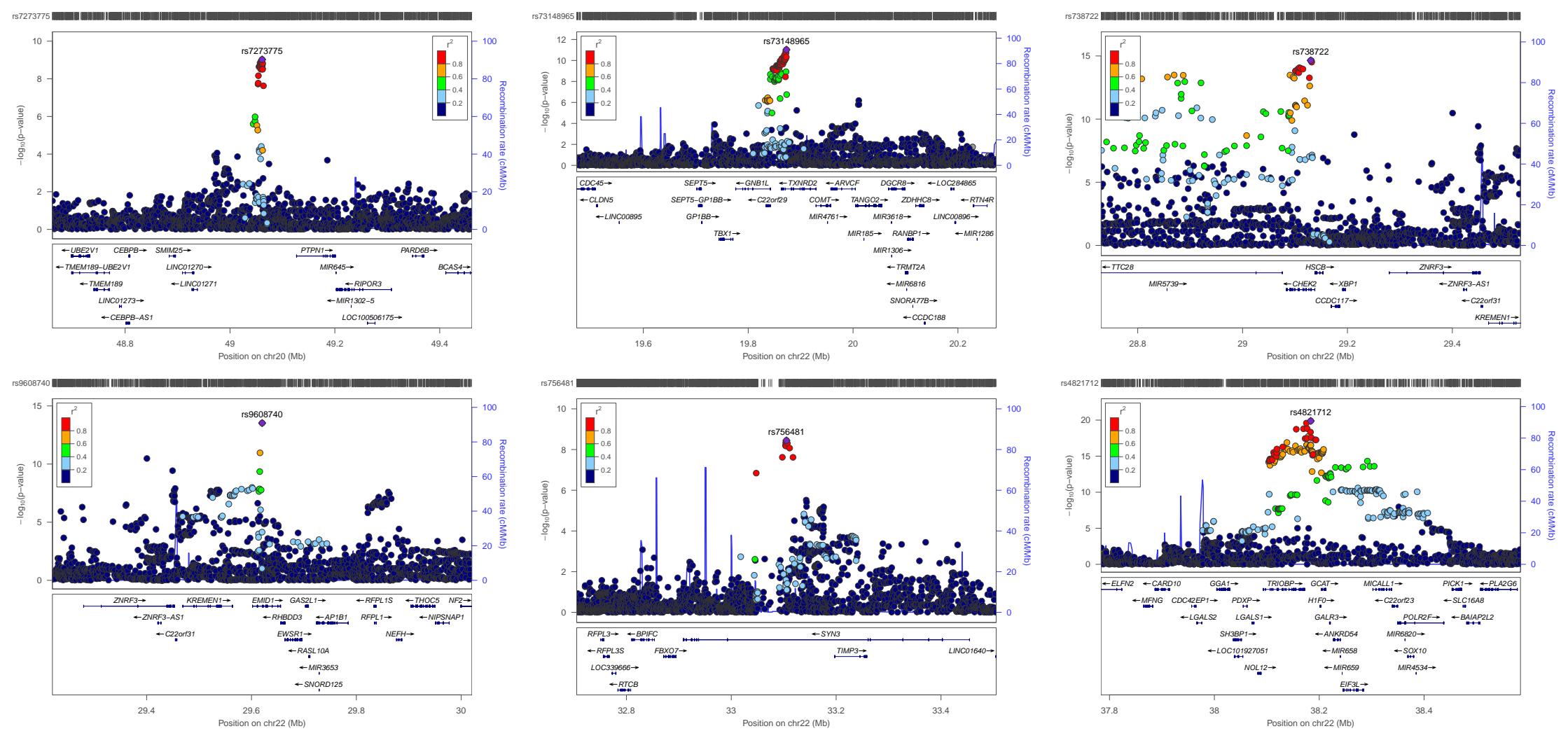




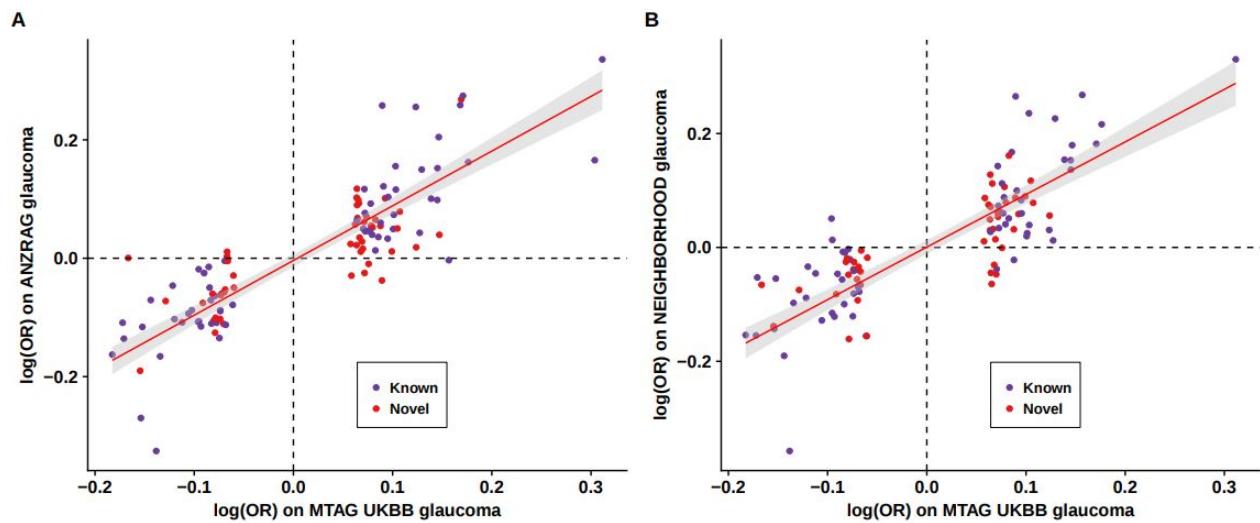






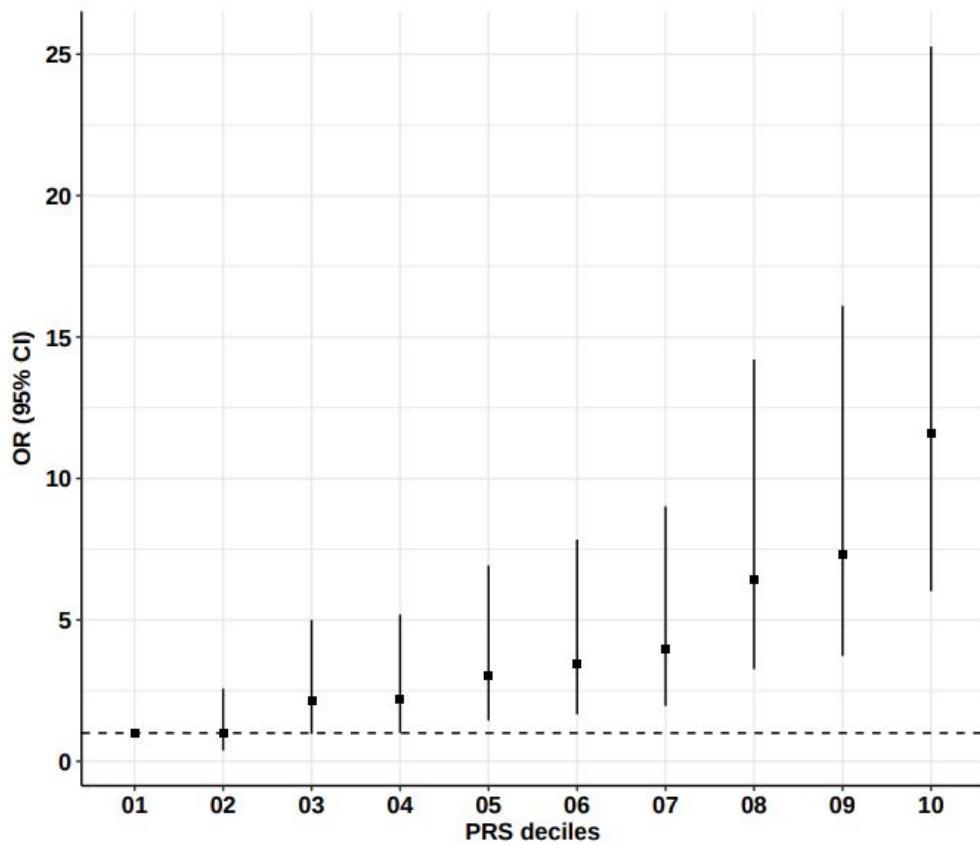


**Supplementary Figure 7. Comparison of the effect sizes for 114 MTAG UKBB glaucoma genome-wide significant independent SNPs versus that in ANZRAG and NEIGHBORHOOD studies.**



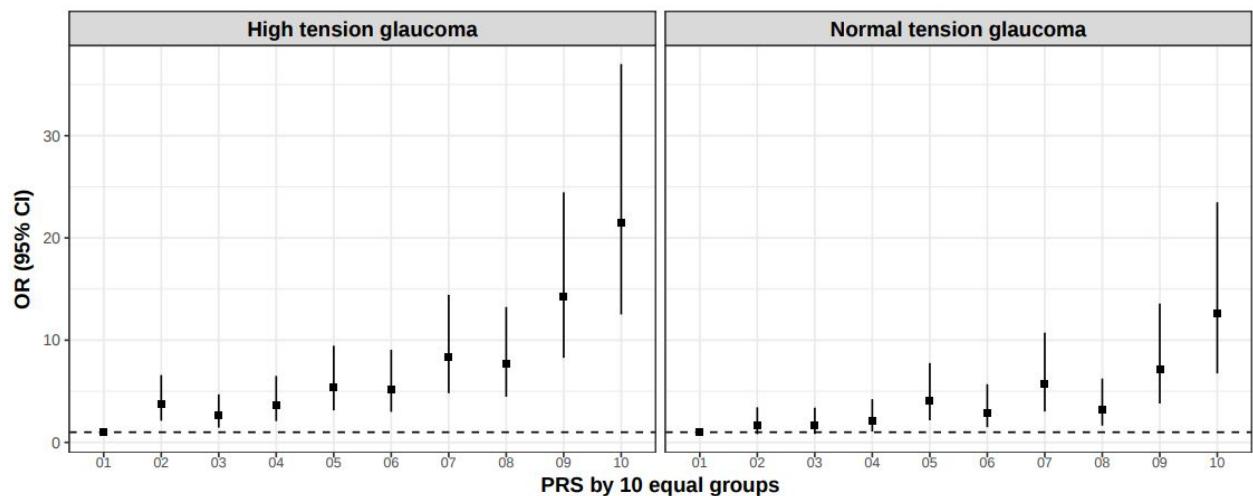
Panel A shows the scatterplot between the effect size (log odds ratio) of MTAG UKBB glaucoma and ANZRAG glaucoma. The Pearson's correlation coefficient is 0.85 ( $P$  value= $1.5 \times 10^{-32}$ ). Panel B displays the scatterplot between the effect size of MTAG UKBB glaucoma and NEIGHBORHOOD glaucoma. The Pearson's correlation coefficient is 0.81 ( $P$  value= $1.8 \times 10^{-26}$ ). In both panels, the red line is the best fit line with 95% confidence interval region in grey. Novel glaucoma SNPs are highlighted in red and known SNPs in purple.

**Supplementary Figure 8. Replication of MTAG PRS prediction in advanced glaucoma**



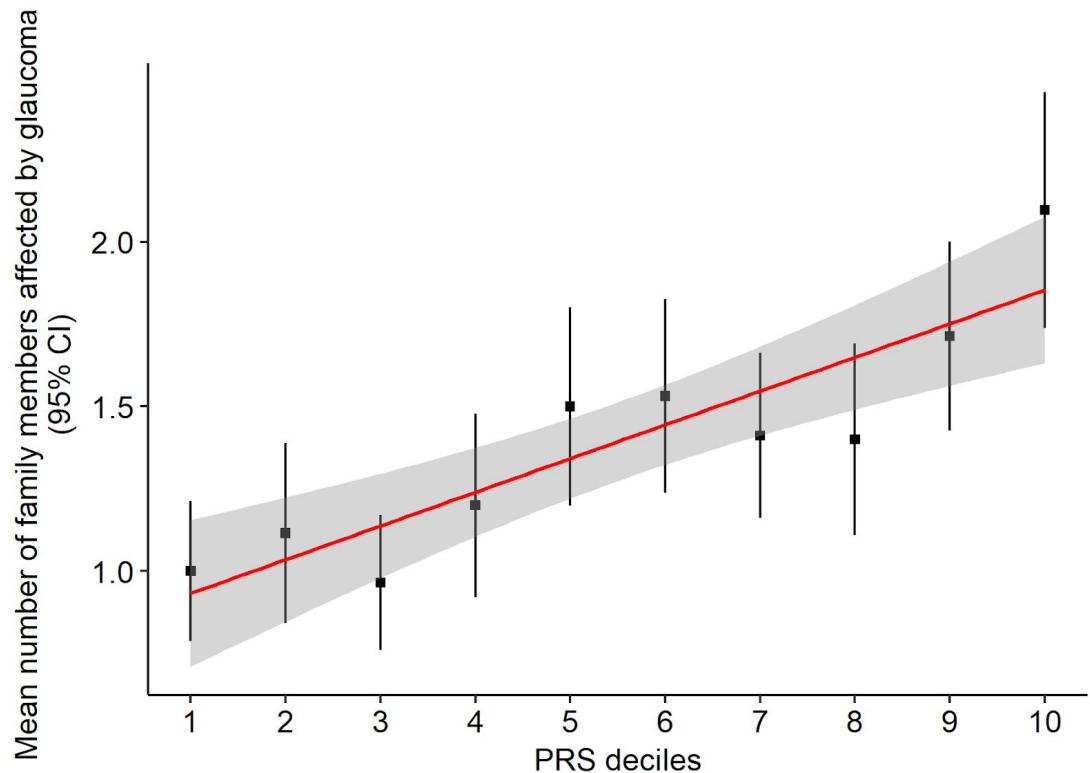
The figure shows the odds ratio (OR) of developing advanced glaucoma in the UK Southampton/Liverpool cohort (with 332 advanced glaucoma cases and 3,000 controls) for each PRS decile. The square dots are the OR values and the error bars are 95% confidence intervals. The dashed line is the reference at the bottom PRS decile (OR=1).

**Supplementary Figure 9. MTAG PRS prediction in high tension glaucoma and normal tension glaucoma**



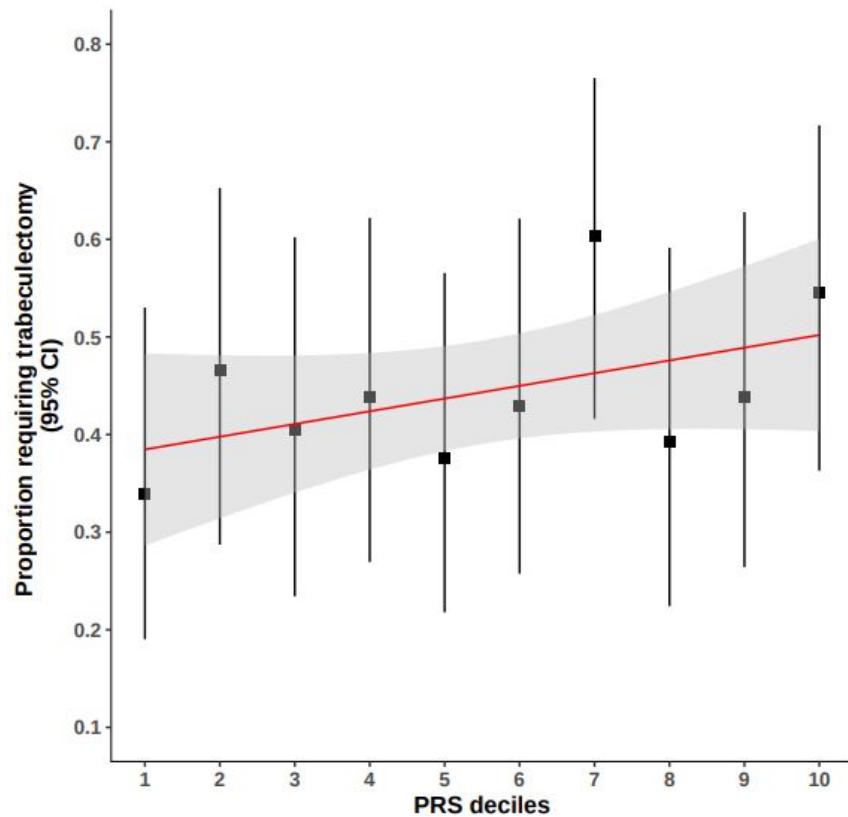
The OR (95%CI) of MTAG PRS in ANZRAG advanced glaucoma cohort (left panel: 709 high tension glaucoma cases and 1,991 controls; right panel: 330 normal tension glaucoma cases and 1,991 controls). The square dots are the OR values and the error bars are 95%CI. The dashed lines are reference at the bottom PRS decile (OR=1). Sex and the first four principal components were adjusted in logistic regressions.

**Supplementary Figure 10. Mean number of family members affected by glaucoma**



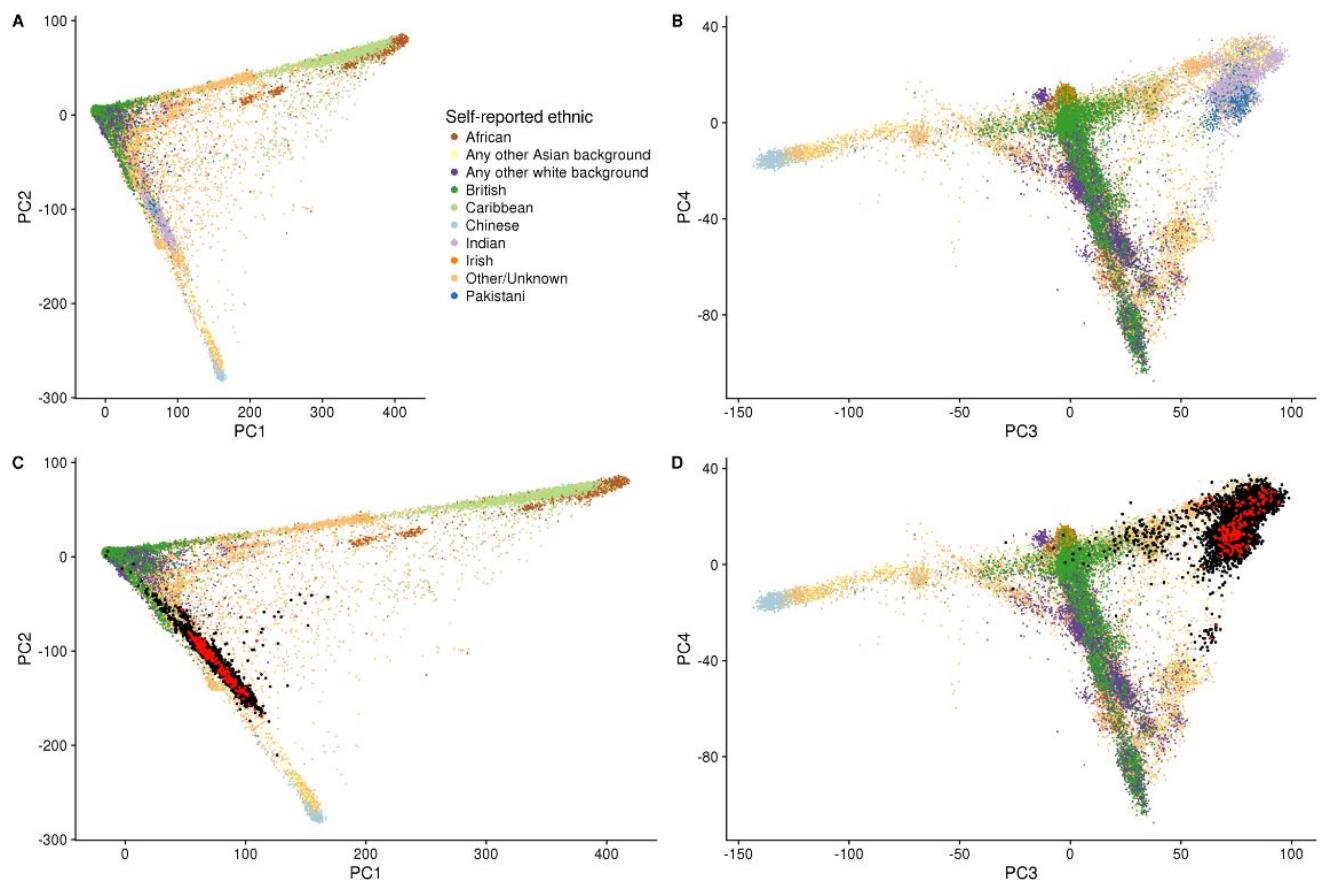
A total of 1,392 ANZRAG cases had accurate family history information. The square dots are the observed mean number of family members affected by glaucoma with error bars reflecting the 95% confidence intervals. The red line is the line of best fit based on linear regression model ( $P = 3.5 \times 10^{-9}$ ).

**Supplementary Figure 11. Replication of MTAG PRS prediction in a proportion of patients requiring trabeculectomy**



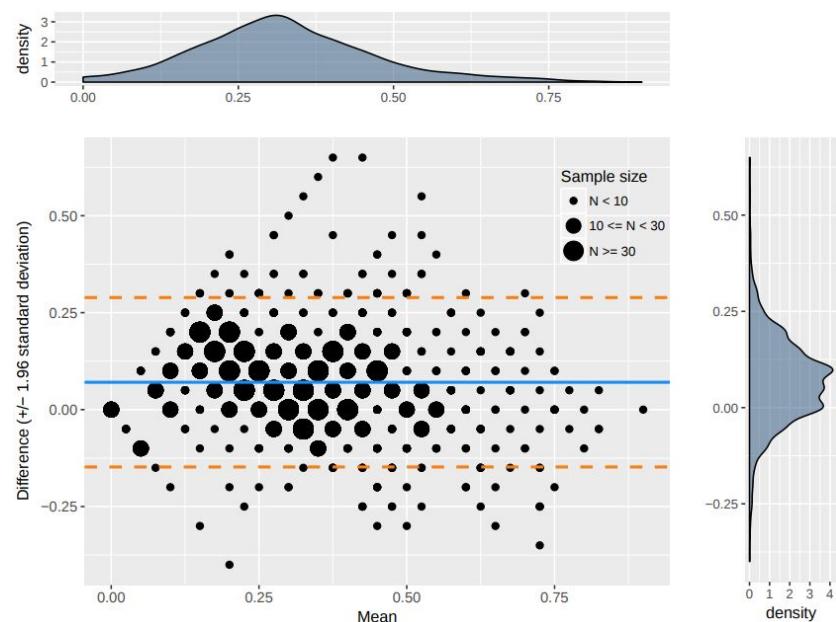
The figure displays the proportion of patients requiring trabeculectomy in either eye in the UK Southampton/Liverpool cohort ( $P=5.7\times 10^{-2}$ ). There were 283 cases with records of surgical treatment status (126 of them have trabeculectomy). The square dots represent the observed average proportion of cases in each decile of PRS who required trabeculectomy, with 95% confidence interval bars. The line of best fit is shown in red, with 95% confidence interval shaded in grey.

**Supplementary Figure 12. Self-report ethnic background in the UK Biobank study.**



The figures display different principal components for UK Biobank samples. Each point is colored based on their self-report ethnic background from UK Biobank Field 21000 (groups with less than 1,000 participants are shown as “Other/Unknown”). Panel A and Panel C are PC 1 vs PC 2, Panel B and Panel D are PC 3 vs PC 4. In Panel C and Panel D, the case-control status of South Asian ancestry (Indian or Pakistani ancestry) is superimposed with red color for glaucoma cases and black color for controls. South Asian samples have genetic ancestry which is clearly distinct from UK Biobank participants of European ancestry; the glaucoma cases of South Asian ancestry are mixed with non-glaucoma cases.

**Supplementary Figure 13. Bland-Altman plot for interobserver variability in VCDR.**



Bland-Altman plots for VCDR ( $n = 2,000$ ), where the x-axis represents the mean value of two gradings by fellowship trained ophthalmologists, the y-axis represents the difference between the two gradings, the blue line is the mean value of difference, and the dashed orange lines are the 95% limits of agreement (95% confidence interval for the mean value of difference). The black dots are scaled by the number of samples. The right and top panels are the density plots for the difference of the measurements and the mean value of measurements, respectively.

## Supplementary Tables

**Supplementary Table 1. Overview of study datasets**

Study	Age Mean ± SD	Sex, male %	Number of participants (cases/controls)	IOP/VCDR Mean ± SD	Genotyping Array	Imputat ion	Imputatio n method
ANZRAG glaucoma (Phase 1)	NA	58%	3,147 (1,155/1,992)	NA	Illumina Omni1M or OmniExpress	1000G phase1	IMPUTE2
ANZRAG glaucoma (Phase 2)	NA	44%	1,525 (579/946)	NA	Illumina HumanCoreExome	HRC r1.1	Minimac3
ANZRAG glaucoma (Phase 3)	NA	26%	5,149 (1,337/3,812)	NA	Illumina HumanCoreExome	HRC r1.1	Minimac3
UKBB glaucoma	56.95± 7.89	46%	127,266 (7,947/119,319)	NA	Affymetrix UK BiLEVE Axiom or UK Biobank Axiom arrays	HRC r1.1	Minimac3
UKBB IOP	57.25± 7.88	47%	103,914	15.98 ± 3.42	Affymetrix UK BiLEVE Axiom or UK Biobank Axiom arrays	HRC r1.1	Minimac3
UKBB VCDR	57.06± 7.89	47%	67040	0.33 ± 0.18	Affymetrix UK BiLEVE Axiom or UK Biobank Axiom arrays	HRC r1.1	Minimac3
IGGC IOP	Varies by sub-study	Varies by sub-study	29,578	Varies by sub-study	Various Illumina and Affymetrix arrays	1000G phase1	IMPUTE2
IGGC VCDR	Varies by sub-study	Varies by sub-study	23,899	Varies by sub-study	Various Illumina and Affymetrix arrays	1000G phase1	IMPUTE2
UK glaucoma (Southampton/Liver pool)	59.03 ± 10.16	47%	3,332 (332/3000)	NA	Illumina Infinium Global Screening Array	HRC r1.1	Minimac3
BMES	64.02 ± 8.24	43%	1,795 (74/1,721)	16.04 ± 2.63 / 0.40 ± 0.12	Illumina Omni1M	HRC r1.1	Minimac3
PROGRESSA	67.5 ± 9.4	41%	388 (388/0)	15.6 ± 3.6 / 0.72 ± 0.1 (baseline)	Illumina HumanCoreExome	HRC r1.1	Minimac3
NEIGHBORHOOD	Varies by sub-study	Varies by sub-study	37,333 (3,853/ 33,480)	Varies by sub-study	Various Illumina and Affymetrix arrays	1000G phase1	Varies by sub-study

Abbreviation: NA, not applicable; SD, standard deviation; IOP, intraocular pressure; VCDR, vertical cup-to-disc ratio.

All samples are of genetically confirmed European ancestry.

**Supplementary Table 2. 76 statistically independent SNPs from UKBB GWAS of VCDR (VDD adjusted)**

SNP	Chr	Position	EA	NEA	Freq	BETA	SE	P	Nearest gene
rs12024620	1	3049362	C	T	0.94	-0.01	1.83E-03	1.2E-10	<i>PRDM16</i>
rs6690264	1	12613422	A	G	0.42	-6.08E-03	9.33E-04	7.2E-11	<i>DHRS3</i>
rs34151819	1	68773910	C	T	0.98	0.02	3.46E-03	5.4E-10	<i>WLS</i>
rs3125918	1	68846246	A	G	0.6	-7.08E-03	9.41E-04	5.2E-14	<i>RPE65</i>
rs4658101	1	92077409	A	G	0.19	0.01	1.12E-03	8.9E-35	<i>CDC7-TGFBR3</i>
rs1417488	1	218523730	C	T	0.75	-6.25E-03	1.05E-03	2.8E-09	<i>TGFB2</i>
rs77271542	1	227677723	A	T	0.94	-0.01	1.87E-03	6.5E-14	<i>ZNF678</i>
rs376096585	2	56094578	C	CT	0.78	9.33E-03	1.08E-03	3.9E-18	<i>EFEMP1</i>
rs2880192	2	111680818	A	G	0.65	6.39E-03	9.36E-04	9.0E-12	<i>ACOXL</i>
rs1579050	2	153364527	A	G	0.42	-5.39E-03	9.17E-04	4.1E-09	<i>FMNL2</i>
rs4858682	3	25066225	C	G	0.47	-5.26E-03	8.92E-04	3.6E-09	<i>RARB</i>
rs34010125	3	32878682	T	C	0.68	5.99E-03	9.53E-04	3.3E-10	<i>TRIM71</i>
3:88379094_AT_A	3	88379094	AT	A	0.45	5.53E-03	8.99E-04	7.8E-10	<i>C3orf38</i>
rs4928176	3	98972835	G	A	0.41	-7.20E-03	9.19E-04	4.5E-15	<i>MIR548G</i>
rs6804624	3	99159147	T	C	0.69	-7.35E-03	9.85E-04	8.5E-14	<i>MIR548G</i>
rs9827694	3	100648298	G	A	0.82	7.09E-03	1.16E-03	8.6E-10	<i>ABI3BP</i>
rs143351962	3	134089758	C	T	0.99	-0.03	4.58E-03	4.8E-09	<i>AMOTL2</i>
rs2162137	4	55005856	C	T	0.34	7.10E-03	9.63E-04	1.8E-13	<i>GSX2</i>
rs565335773	4	55095682	G	GA	0.79	7.81E-03	1.12E-03	3.7E-12	<i>PDGFRA</i>
rs72759609	5	31952051	T	C	0.9	0.01	1.47E-03	1.3E-14	<i>PDZD2</i>
rs158653	5	55578661	G	A	0.48	5.33E-03	8.74E-04	1.1E-09	<i>ANKRD55</i>
rs30372	5	55744230	T	C	0.24	-6.49E-03	1.07E-03	1.2E-09	<i>LOC102467147</i>
rs11749004	5	128918456	T	C	0.25	5.71E-03	1.04E-03	3.7E-08	<i>ADAMTS19</i>
5:133393380_GA_G	5	133393380	GA	G	0.84	8.98E-03	1.31E-03	8.1E-12	<i>VDAC1</i>
rs34471628	5	172196752	A	G	0.96	0.01	2.28E-03	3.4E-08	<i>DUSP1</i>
rs2761235	6	1951135	C	T	0.87	8.72E-03	1.36E-03	1.6E-10	<i>GMDS</i>
rs4960297	6	7212084	C	T	0.55	-6.54E-03	8.82E-04	1.2E-13	<i>RREB1</i>
rs12211825	6	36588140	C	T	0.78	-7.48E-03	1.08E-03	4.0E-12	<i>SRSF3</i>
rs2684249	6	122392511	T	C	0.59	5.59E-03	9.20E-04	1.2E-09	<i>HSF2</i>
rs10260511	7	14237240	C	A	0.84	-7.04E-03	1.25E-03	1.6E-08	<i>DGKB</i>

rs4518562	7	19627952	A	T	0.66	-5.79E-03	9.43E-04	8.0E-10	<i>TWISTNB</i>
rs7805378	7	28393403	A	C	0.56	5.48E-03	9.26E-04	3.3E-09	<i>CREB5</i>
rs2976932	8	8255319	T	C	0.11	-9.18E-03	1.43E-03	1.2E-10	<i>SGK223</i>
rs12543430	8	72278010	T	C	0.39	-5.48E-03	9.14E-04	2.0E-09	<i>EYA1</i>
rs78542921	9	18089832	T	A	0.96	-0.01	2.38E-03	8.1E-10	<i>SH3GL2</i>
rs7039467	9	22056213	A	G	0.69	-0.01	1.13E-03	2.0E-37	<i>CDKN2B-AS1</i>
rs7866783	9	22056359	A	G	0.43	-0.02	9.07E-04	5.4E-64	<i>CDKN2B-AS1</i>
10:21462896_GGC_G	10	21462896	GGC	G	0.99	-0.03	4.06E-03	2.4E-10	<i>NEBL</i>
rs7916697	10	69991853	A	G	0.24	-0.01	1.02E-03	6.8E-35	<i>ATOH7</i>
rs17108260	10	94950713	A	G	0.57	-6.05E-03	9.07E-04	2.6E-11	<i>CYP26A1</i>
rs11197820	10	118546046	G	A	0.58	-5.22E-03	8.75E-04	2.4E-09	<i>HSPA12A</i>
rs10835721	11	30934691	G	A	0.73	-5.48E-03	9.90E-04	3.1E-08	<i>DCDC5</i>
rs2753411	11	33405001	A	T	0.49	-4.74E-03	8.57E-04	3.1E-08	<i>HIPK3</i>
rs1346	11	65337251	A	T	0.8	8.26E-03	1.11E-03	1.2E-13	<i>SSSCA1-AS1</i>
rs2445575	11	86748437	T	C	0.81	6.34E-03	1.11E-03	1.1E-08	<i>TMEM135</i>
rs11021221	11	95308854	T	A	0.83	6.33E-03	1.15E-03	3.3E-08	<i>FAM76B</i>
rs4936099	11	130280725	C	A	0.41	-8.52E-03	8.92E-04	1.3E-21	<i>ADAMTS8</i>
rs6582298	12	76114872	G	A	0.6	5.14E-03	9.28E-04	3.0E-08	<i>KRR1</i>
rs61952219	12	83959231	G	A	0.79	-0.02	1.53E-03	8.0E-25	<i>TMTC2</i>
12:83973565_TTCTC_T	12	83973565	TTCTC	T	0.45	-0.01	8.80E-04	3.9E-58	<i>TMTC2</i>
rs9651957	12	107170128	T	C	0.64	6.11E-03	8.94E-04	8.6E-12	<i>RIC8B</i>
rs4765353	12	124667691	G	C	0.44	-5.57E-03	9.25E-04	1.8E-09	<i>ZNF664-FAM101A</i>
rs9546383	13	36683268	T	C	0.75	-8.77E-03	1.02E-03	9.2E-18	<i>DCLK1</i>
rs10162202	13	109267985	T	C	0.72	7.11E-03	9.95E-04	9.1E-13	<i>MYO16</i>
13:110778747_CCTTTT_C	13	110778747	CCTTTT	C	0.64	-7.29E-03	9.69E-04	5.3E-14	<i>COL4A1</i>
rs4982708	14	23391086	G	A	0.43	6.44E-03	8.69E-04	1.2E-13	<i>PRMT5</i>
rs2251171	14	53989447	G	A	0.6	5.71E-03	8.77E-04	7.9E-11	<i>DDHD1</i>
rs10162287	14	60808553	C	G	0.7	-9.99E-03	9.65E-04	4.1E-25	<i>PPM1A</i>
rs984586	14	86009142	G	A	0.76	-5.90E-03	1.03E-03	1.2E-08	<i>FLRT2</i>
rs893817	15	74229065	G	A	0.37	5.36E-03	9.01E-04	2.7E-09	<i>LOXL1</i>
rs148139847	15	101202269	C	CA	0.87	-9.78E-03	1.33E-03	1.6E-13	<i>ASB7</i>
rs373836950	16	51447492	C	CAA	0.8	0.01	1.14E-03	3.7E-21	<i>SALL1</i>
rs8053277	16	51469726	T	C	0.3	9.91E-03	9.63E-04	7.3E-25	<i>SALL1</i>
rs2720429	16	51571885	G	A	0.77	-0.01	1.12E-03	2.2E-19	<i>SALL1</i>
rs35526343	16	86465334	C	T	0.96	-0.02	2.23E-03	8.8E-13	<i>FENDRR</i>

rs847688	17	48228981	T	C	0.52	5.03E-03	9.00E-04	2.3E-08	<i>PPP1R9B</i>
rs2204928	17	59262040	C	T	0.21	-6.47E-03	1.08E-03	2.3E-09	<i>BCAS3</i>
rs146055611	19	816586	C	CATCT	0.66	6.39E-03	9.82E-04	7.3E-11	<i>LPPR3</i>
rs8102936	19	32027330	G	A	0.66	6.46E-03	1.03E-03	4.0E-10	<i>THEG5</i>
rs6140010	20	6473123	A	G	0.63	0.01	9.07E-04	9.4E-43	<i>CASC20</i>
rs3831804	20	31413015	T	TA	0.78	6.44E-03	1.07E-03	1.9E-09	<i>MAPRE1</i>
rs7287609	22	29096693	C	T	0.99	0.03	4.07E-03	8.2E-15	<i>CHEK2</i>
rs6005840	22	29101357	A	G	0.32	-0.01	9.54E-04	1.9E-38	<i>CHEK2</i>
rs713875	22	30592487	C	G	0.45	6.66E-03	8.93E-04	8.9E-14	<i>HORMAD2</i>
rs113605227	22	37908462	A	AC	0.83	-9.93E-03	1.26E-03	3.2E-15	<i>CARD10</i>
rs71324877	22	38184641	G	GAACA	0.36	7.19E-03	9.54E-04	4.7E-14	<i>TRIOBP</i>

Abbreviations: Chr, Chromosome; EA, effect allele; Freq, allele frequency of effect allele; NEA, non-effect allele; SE, Standard error; SNP, single nucleotide polymorphism; P, P value for VCDR (adjusted for VDD); VCDR, vertical cup-disc ratio; VDD, vertical disc diameter.

**Supplementary Table 3. 107 lead genome-wide significant independent SNPs for VCDR (adjusted for disc diameter) from UK Biobank and IGGC MTAG-analysis**

SNP	Chr	Position	Nearest Gene	EA	NEA	Freq	BETA (MTAG)	P (MTAG)	BETA (UKBB)	P (UKBB)	BETA(IGGC)	P (IGGC)
rs12021948	1	3049381	<i>PRDM16</i>	G	C	0.93	-0.01	1.4E-10	-0.01	4.4E-10	-6.4E-03	0.03
rs302714	1	8486131	<i>RERE</i>	A	C	0.66	-5.2E-03	8.6E-09	-3.9E-03	2.0E-05	-6.0E-03	1.9E-05
rs6690264	1	12613422	<i>VPS13D - DHRS3</i>	A	G	0.42	-6.8E-03	4.1E-15	-6.1E-03	7.2E-11	-6.5E-03	5.9E-06
rs34151819	1	68773910	<i>WLS - RPE65</i>	C	T	0.98	0.02	1.3E-10	0.02	5.4E-10	0.01	0.02
rs1925953	1	68848681	<i>WLS - RPE65</i>	A	T	0.60	-8.1E-03	4.4E-20	-7.1E-03	5.2E-14	-6.7E-03	3.1E-08
rs786914	1	89295765	<i>PKN2</i>	C	A	0.38	-5.1E-03	6.3E-09	-4.6E-03	1.6E-07	-3.8E-03	5.7E-03
rs4658101	1	92077409	<i>CDC7 - TGFBR3</i>	A	G	0.19	0.02	7.2E-51	0.01	8.9E-35	0.01	1.5E-19
rs2187955	1	169536650	<i>F5</i>	G	A	0.52	-5.6E-03	1.0E-10	-3.5E-03	1.7E-05	-6.8E-03	1.0E-08
rs1417488	1	218523730	<i>TGFB2</i>	C	T	0.75	-6.0E-03	1.7E-09	-6.3E-03	2.8E-09	-3.1E-03	0.05
rs77271542	1	227677723	<i>CDC42BPA - ZNF678</i>	A	T	0.94	-0.01	3.1E-16	-0.01	6.5E-14	-0.01	2.7E-04
rs4666465	2	19338691	<i>NT5C1B - MIR4757</i>	C	T	0.64	5.5E-03	1.1E-09	4.3E-03	2.5E-06	5.9E-03	2.8E-05
rs851321	2	19420060	<i>NT5C1B - MIR4757</i>	C	T	0.01	-0.02	7.8E-09	-0.02	2.8E-06	-0.02	3.1E-04
rs2009262	2	56012214	<i>PNPT1 - EFEMP1</i>	T	C	0.79	9.7E-03	1.0E-19	9.4E-03	8.9E-18	5.7E-03	2.8E-04
rs2880192	2	111680818	<i>ACOXL</i>	A	G	0.65	7.1E-03	3.6E-15	6.4E-03	9.0E-12	5.8E-03	2.6E-05
rs74409360	2	239276278	<i>TRAF3IP1</i>	C	T	0.92	8.8E-03	1.6E-08	7.1E-03	1.8E-06	9.6E-03	1.3E-03
rs4858682	3	25066225	<i>MIR4792 - RARB</i>	C	G	0.47	-5.3E-03	7.2E-10	-5.3E-03	3.6E-09	-3.2E-03	0.02
rs56131903	3	32879823	<i>TRIM71</i>	A	T	0.68	6.9E-03	5.9E-14	6.0E-03	3.4E-10	6.1E-03	1.8E-05
rs6764184	3	58006266	<i>FLNB</i>	G	T	0.76	-6.7E-03	2.3E-11	-5.3E-03	2.3E-07	-6.9E-03	4.9E-06
rs9847377	3	66849734	<i>LRIG1 - KBTBD8</i>	T	C	0.52	4.9E-03	1.7E-08	3.8E-03	2.7E-05	5.0E-03	2.4E-05
rs9879264	3	88387796	<i>C3orf38 - EPHA3</i>	A	G	0.44	6.4E-03	1.2E-13	5.5E-03	1.2E-09	5.4E-03	9.2E-06

rs13076500	3	98943479	<i>DCBLD2 - MIR548G</i>	C	T	0.46	-7.4E-03	1.5E-17	-6.6E-03	4.4E-13	-5.7E-03	4.1E-06
rs2880364	3	99156869	<i>DCBLD2 - MIR548G</i>	G	A	0.64	-8.6E-03	7.9E-22	-7.3E-03	1.0E-14	-8.5E-03	1.8E-09
rs17398137	3	100625703	<i>ABI3BP</i>	G	A	0.82	7.6E-03	8.6E-12	7.0E-03	1.5E-09	5.4E-03	7.7E-04
rs2162137	4	55005856	<i>GSX2 - PDGFRA</i>	C	T	0.34	7.3E-03	1.1E-15	7.1E-03	1.8E-13	4.9E-03	6.1E-04
rs4864858	4	55089953	<i>GSX2 - PDGFRA</i>	T	A	0.78	8.1E-03	1.2E-14	7.5E-03	6.4E-12	6.0E-03	1.7E-04
rs1857901	4	126396270	<i>FAT4</i>	G	A	0.64	5.6E-03	2.7E-10	4.8E-03	1.9E-07	5.3E-03	2.5E-04
rs2611206	4	166579647	<i>CPE - TLL1</i>	G	A	0.85	-7.2E-03	2.9E-09	-6.3E-03	3.1E-07	-5.4E-03	1.7E-03
rs1445866	5	3621544	<i>IRX1 - LOC101929153</i>	G	A	0.67	-5.7E-03	6.7E-10	-5.1E-03	1.7E-07	-5.2E-03	5.1E-04
rs72759609	5	31952051	<i>PDZD2</i>	T	C	0.90	0.01	2.2E-21	0.01	1.3E-14	0.01	4.6E-09
rs10072364	5	52064349	<i>ISL1 - PELO</i>	T	C	0.47	-5.1E-03	2.4E-09	-3.9E-03	3.6E-06	-4.9E-03	5.0E-05
rs158653	5	55578661	<i>ANKRD55 - LOC102467147</i>	G	A	0.48	6.3E-03	2.3E-13	5.3E-03	1.1E-09	5.6E-03	2.9E-05
rs30372	5	55744230	<i>ANKRD55 - LOC102467147</i>	T	C	0.24	-7.2E-03	1.2E-12	-6.5E-03	1.2E-09	-6.2E-03	9.8E-05
rs16892523	5	60867273	<i>ZSWIM6 - C5orf64</i>	C	G	0.89	-7.4E-03	3.5E-08	-6.7E-03	3.0E-06	-6.2E-03	2.3E-03
rs12188947	5	82742118	<i>XRCC4 - VCAN</i>	A	C	0.60	5.3E-03	1.7E-09	3.6E-03	9.6E-05	7.1E-03	1.6E-07
rs17421410	5	87836307	<i>LOC102546226 - LINC00461</i>	A	G	0.93	-9.4E-03	1.0E-08	-6.4E-03	7.7E-05	-0.01	1.6E-06
rs13164684	5	129102550	<i>KIAA1024L - CHSY3</i>	A	G	0.08	1.0E-02	8.3E-10	7.4E-03	1.7E-05	0.01	6.9E-07
rs247463	5	133384337	<i>VDAC1 - TCF7</i>	T	G	0.22	7.1E-03	7.4E-12	6.5E-03	5.9E-09	6.1E-03	1.2E-04
rs60111777	5	133402911	<i>VDAC1 - TCF7</i>	C	T	0.90	0.01	4.6E-14	9.6E-03	3.2E-11	8.0E-03	1.7E-04
rs114503346	5	172192350	<i>LOC101928093 - DUSP1</i>	C	T	0.95	0.02	3.9E-14	0.01	4.9E-08	0.02	5.1E-09
rs17756712	6	625071	<i>EXOC2</i>	A	G	0.82	-7.3E-03	5.7E-11	-5.5E-03	3.5E-06	-8.4E-03	2.0E-07

rs56031192	6	1980208	GMDS	T	A	0.87	9.1E-03	6.4E-13	8.7E-03	2.5E-10	6.9E-03	4.0E-04
rs4960295	6	7205796	RREB1	G	A	0.54	-7.8E-03	2.0E-19	-6.3E-03	4.6E-13	-6.9E-03	1.7E-08
rs72852338	6	36554240	STK38 - SRSF3	A	C	0.78	-7.5E-03	8.0E-13	-7.4E-03	8.0E-12	-4.3E-03	8.8E-03
rs9367021	6	39566203	KIF6	G	A	0.59	-5.4E-03	7.5E-10	-4.0E-03	2.0E-06	-5.1E-03	2.8E-05
rs2684249	6	122392511	GJA1 - HSF2	T	C	0.59	6.5E-03	7.2E-14	5.6E-03	1.2E-09	6.5E-03	2.9E-06
rs10260511	7	14237240	DGKB	C	A	0.84	-9.0E-03	2.7E-14	-7.0E-03	1.6E-08	-9.6E-03	4.2E-08
rs12534570	7	19550247	FERD3L - TWISTNB	G	A	0.34	5.5E-03	2.1E-09	5.6E-03	2.7E-09	2.6E-03	0.07
rs7805378	7	28393403	CREB5	A	C	0.56	5.8E-03	2.2E-11	5.5E-03	3.3E-09	4.0E-03	1.1E-03
rs201530	7	101777382	CUX1	A	G	0.47	5.3E-03	6.9E-10	3.8E-03	1.5E-05	6.0E-03	7.5E-07
rs2976932	8	8255319	SGK223 - CLDN23	T	C	0.11	-0.01	8.1E-14	-9.2E-03	1.2E-10	-8.4E-03	7.1E-05
rs12543430	8	72278010	EYA1 - MSC	T	C	0.39	-5.5E-03	6.0E-10	-5.5E-03	2.0E-09	-3.7E-03	0.04
rs67120362	8	72604509	EYA1 - MSC	T	G	0.81	-6.7E-03	6.9E-10	-5.0E-03	8.8E-06	-7.7E-03	2.2E-06
rs78542921	9	18089832	SH3GL2 - ADAMTSL1	T	A	0.96	-0.01	2.0E-11	-0.01	8.1E-10	-0.01	3.0E-03
rs944801	9	22051670	CDKN2B-AS1	G	C	0.43	-0.02	4.7E-91	-0.02	7.6E-64	-0.01	3.8E-32
rs7039467	9	22056213	CDKN2B-AS1	A	G	0.69	-0.01	2.6E-54	-0.01	2.0E-37	-0.01	1.5E-21
rs10512176	9	89252706	ZCCHC6 - GAS1	T	C	0.72	-5.9E-03	8.9E-10	-5.0E-03	7.6E-07	-5.8E-03	1.0E-04
rs8176662	9	136144454	ABO	A	G	0.94	-0.01	4.2E-11	-0.01	6.1E-08	-0.01	6.3E-05
rs190927291	10	21437861	NEBL	C	G	0.99	-0.03	8.9E-12	-0.02	1.6E-09	-0.02	7.2E-04
rs7916697	10	69991853	ATOH7	A	G	0.24	-0.02	2.8E-67	-0.01	6.8E-35	-0.02	8.8E-43
rs72815193	10	94963391	CYP26A1 - MYOF	A	G	0.57	-7.0E-03	8.5E-16	-6.0E-03	3.3E-11	-5.8E-03	2.2E-06
rs2274224	10	96039597	PLCE1; PLCE1-AS1	G	C	0.57	-5.4E-03	4.8E-10	-3.6E-03	1.6E-04	-7.3E-03	5.3E-09
rs11197820	10	118546046	HSPA12A - ENO4	G	A	0.58	-6.4E-03	3.0E-13	-5.2E-03	2.4E-09	-5.8E-03	1.6E-05
rs7952509	11	31599910	ELP4	C	T	0.77	-6.4E-03	3.3E-10	-5.5E-03	6.0E-07	-7.8E-03	4.2E-05

rs2753411	11	33405001	<i>HIPK3 - KIAA1549L</i>	A	T	0.49	-5.2E-03	2.1E-09	-4.7E-03	3.1E-08	-3.6E-03	0.01
rs12789028	11	65326154	<i>LTBP3 - SSSCA1-AS1</i>	G	A	0.80	0.01	1.0E-25	8.3E-03	1.5E-13	0.01	1.1E-16
rs4944662	11	86740573	<i>LOC100506368 - TMEM135</i>	C	T	0.18	-7.6E-03	1.3E-11	-6.1E-03	5.6E-08	-6.9E-03	1.8E-05
rs7949779	11	95282879	<i>LOC100129203 - FAM76B</i>	G	C	0.61	5.6E-03	1.9E-10	4.7E-03	1.7E-07	5.4E-03	9.5E-05
rs4936099	11	130280725	<i>ADAMTS8</i>	C	A	0.41	-9.7E-03	1.6E-28	-8.5E-03	1.3E-21	-8.3E-03	2.8E-09
rs16930371	12	26392080	<i>SSPN - ITPR2</i>	A	G	0.82	6.2E-03	2.0E-08	5.0E-03	7.3E-06	5.8E-03	3.3E-04
rs12821310	12	47963700	<i>PCED1B - RPAP3</i>	C	T	0.82	7.1E-03	1.9E-10	5.0E-03	1.6E-05	8.7E-03	7.5E-08
rs324780	12	84003866	<i>TMTC2 - SLC6A15</i>	G	A	0.46	-0.02	1.6E-75	-0.01	5.4E-58	-0.01	5.7E-21
rs2125948	12	84120798	<i>TMTC2 - SLC6A15</i>	G	C	0.57	0.01	3.5E-36	0.01	1.9E-49	-6.0E-04	0.91
rs73153655	12	84133370	<i>TMTC2 - SLC6A15</i>	A	G	0.81	0.01	1.9E-32	0.01	3.0E-26	9.7E-03	9.2E-09
rs66716938	12	107196825	<i>RIC8B</i>	T	C	0.63	6.9E-03	7.7E-15	6.1E-03	1.1E-11	5.6E-03	7.6E-05
rs4765353	12	124667691	<i>ZNF664-FAM101A</i>	G	C	0.44	-6.7E-03	1.5E-14	-5.6E-03	1.8E-09	-6.2E-03	2.3E-07
rs9546383	13	36683268	<i>DCLK1</i>	T	C	0.75	-9.9E-03	2.3E-23	-8.8E-03	9.2E-18	-8.0E-03	9.4E-08
rs75764673	13	109267466	<i>MYO16</i>	A	G	0.73	6.8E-03	2.1E-12	6.9E-03	9.8E-12	4.2E-03	0.02
rs9521601	13	110766614	<i>IRS2 - COL4A1</i>	G	A	0.47	-5.6E-03	8.4E-11	-5.4E-03	7.2E-10	-3.0E-03	0.01
rs12437151	14	23372913	<i>RBM23</i>	G	A	0.43	7.1E-03	2.0E-16	6.4E-03	2.4E-13	4.8E-03	1.0E-04
rs2251069	14	53988050	<i>LOC101927620 - MIR5580</i>	T	C	0.57	6.7E-03	1.6E-14	5.2E-03	1.9E-09	6.2E-03	2.4E-07
rs2738265	14	54422399	<i>BMP4</i>	C	G	0.46	-4.8E-03	2.9E-08	-3.9E-03	9.4E-06	-4.3E-03	4.2E-04
rs7493429	14	60806759	<i>PPM1A - C14orf39</i>	A	C	0.70	-0.01	9.8E-36	-9.9E-03	8.3E-25	-0.01	4.0E-13
rs28761289	14	65113768	<i>PPP1R36 - PLEKHG3</i>	A	G	0.83	-7.5E-03	4.7E-11	-5.6E-03	1.5E-07	-6.8E-03	3.4E-05
rs984586	14	86009142	<i>FLRT2</i>	G	A	0.76	-7.0E-03	2.5E-12	-5.9E-03	1.2E-08	-6.5E-03	1.6E-05
rs35194812	15	71840327	<i>THSD4</i>	T	C	0.84	-7.5E-03	1.1E-10	-5.5E-03	4.5E-07	-7.4E-03	1.6E-05

rs893817	15	74229065	<i>LOXL1</i>	G	A	0.37	6.1E-03	6.3E-12	5.4E-03	2.7E-09	5.1E-03	1.9E-04
rs28612945	15	99458902	<i>IGF1R</i>	C	T	0.79	6.2E-03	5.7E-09	5.3E-03	5.5E-07	6.6E-03	1.5E-03
rs34222435	15	101200873	<i>ASB7 - ALDH1A3</i>	C	T	0.87	-0.01	2.4E-20	-9.7E-03	2.3E-13	-0.01	3.0E-09
rs1015438	16	51177517	<i>SALL1</i>	G	A	0.81	6.7E-03	1.4E-09	6.1E-03	1.8E-07	5.2E-03	1.4E-03
rs62038917	16	51425823	<i>SALL1 - LOC101927364</i>	G	T	0.78	0.01	1.2E-27	9.9E-03	3.9E-20	9.9E-03	9.3E-10
rs8053277	16	51469726	<i>SALL1 - LOC101927364</i>	T	C	0.30	0.01	6.1E-38	9.9E-03	7.3E-25	0.01	6.1E-16
rs2720429	16	51571885	<i>SALL1 - LOC101927364</i>	G	A	0.77	-9.9E-03	4.5E-22	-0.01	2.2E-19	-6.0E-03	7.3E-05
rs1728367	16	86386888	<i>LINC00917 - FENDRR</i>	C	T	0.09	0.01	9.7E-16	0.01	6.9E-12	9.7E-03	1.2E-05
rs7187191	16	86511858	<i>FENDRR</i>	T	G	0.18	8.2E-03	1.7E-13	7.0E-03	3.0E-09	7.5E-03	2.8E-06
rs847687	17	48229441	<i>PPP1R9B - SGCA</i>	T	G	0.52	6.0E-03	4.2E-12	5.0E-03	3.0E-08	5.8E-03	7.1E-06
rs2204928	17	59262040	<i>BCAS3</i>	C	T	0.21	-7.8E-03	2.2E-13	-6.5E-03	2.3E-09	-6.8E-03	1.0E-05
rs4790993	17	65035215	<i>CACNG4 - CACNG1</i>	T	C	0.70	-5.5E-03	6.9E-09	-5.3E-03	1.4E-07	-3.7E-03	8.5E-03
rs123698	19	807442	<i>PTBP1</i>	G	C	0.40	6.5E-03	9.9E-14	5.6E-03	3.8E-10	8.5E-03	2.3E-05
rs8102936	19	32027330	<i>TSHZ3 - THEG5</i>	G	A	0.66	6.1E-03	1.9E-11	6.5E-03	4.0E-10	3.9E-03	5.7E-03
rs6140009	20	6473054	<i>CASC20</i>	C	T	0.62	0.01	3.2E-48	0.01	1.5E-42	8.3E-03	1.3E-09
rs1819154	20	6528627	<i>CASC20 - BMP2</i>	C	T	0.02	-0.02	3.1E-10	-0.02	7.1E-08	-0.02	6.1E-04
rs6120005	20	31448849	<i>MAPRE1 - SUN5</i>	G	A	0.84	8.5E-03	3.8E-13	7.0E-03	2.1E-09	7.4E-03	1.8E-05
rs143032062	22	28709058	<i>TTC28</i>	T	C	0.98	0.03	1.3E-17	0.03	2.1E-14	0.04	4.2E-05
rs5752776	22	29108229	<i>CHEK2</i>	A	G	0.33	-0.01	2.3E-54	-0.01	3.9E-38	-0.01	5.7E-21
rs1003342	22	30570022	<i>HORMAD2</i>	A	G	0.45	7.7E-03	7.8E-19	6.4E-03	5.9E-13	6.6E-03	4.3E-08
rs6000759	22	37911190	<i>CARD10</i>	T	G	0.78	-9.6E-03	2.8E-20	-8.6E-03	1.0E-14	-8.5E-03	5.2E-08
rs5750494	22	38176979	<i>TRIOBP - H1F0</i>	T	G	0.37	7.3E-03	2.0E-16	6.8E-03	4.4E-13	5.8E-03	4.4E-05

Abbreviations: Chr, Chromosome; EA, effect allele; Freq, allele frequency of effect allele; NEA, non-effect allele; SE, Standard error; P, p value; SNP, single nucleotide polymorphism.

UKBB, UK biobank data; IGGC, International Glaucoma Genetic Consortium; MTAG, meta-analysis results of UKBB and IGGC datasets.

Chromosomal position is based on the NCBI RefSeq hg19 human genome reference assembly.

Supplementary Table 4. 114 statistically independent SNPs for glaucoma risk from MTAG GWAS

SNP	Chr	Position	Nearest Gene	Glaucoma UKBB			P IOP meta (UKBB + IGGC)	Glaucoma MTAG		Glaucoma ANZRAG		Glaucoma NEIGHBORHOOD		Glaucoma meta (ANZRAG + NEIGHBORHOOD)		Glaucoma meta (ANZRAG + NEIGHBORHOOD + UKBB)		Annotation*				
				EA	NEA	Freq		OR	P value	P VCDR (adjust VDD)	OR	P value	OR	P value	OR	P value	OR	P value				
rs274760	1	36573573	COL8A2	C	A	0.94	1.11	4.7E-03	0.22	0.58	1.1E-09	1.13	2.0E-08	1.29	9.8E-04	1.03	0.70	1.16	7.8E-03	1.12	1.5E-04	Known
rs10796912	1	38091597	RSPO1	G	A	0.56	0.96	9.9E-03	0.42	0.12	1.3E-09	0.94	1.1E-08	0.97	0.37	0.86	6.1E-06	0.92	1.8E-04	0.94	1.9E-05	Bonferroni
rs12068500	1	86614151	COL24A1	G	T	0.91	0.93	0.01	1.5E-03	0.06	5.5E-14	0.88	7.3E-13	0.93	0.47	0.93	0.26	0.93	0.18	0.93	4.8E-03	-
rs12139208	1	88213014	LOC100505768	T	C	0.38	1.09	5.5E-07	0.34	0.06	1.4E-08	1.08	2.2E-12	1.05	0.16	1.12	1.4E-03	1.08	1.3E-03	1.09	2.8E-09	Known
rs4658101	1	92077409	HSP90B3P	A	G	0.19	1.05	0.03	8.9E-35	1.5E-19	0.04	1.10	1.2E-13	1.01	0.78	1.09	0.04	1.05	0.11	1.05	7.2E-03	-
rs12045227	1	113128212	ST7L	G	A	0.80	0.97	0.10	2.0E-03	0.05	1.6E-11	0.92	5.3E-10	0.90	7.9E-03	0.98	0.65	0.94	0.02	0.96	8.3E-03	Nominal
rs10918274	1	165714416	TMCO1	T	C	0.12	1.37	4.2E-43	2.4E-06	0.06	3.7E-67	1.37	5.6E-92	1.40	1.4E-13	1.39	3.3E-12	1.40	1.4E-24	1.38	1.4E-65	Known
rs73111535	1	219222850	LOC64372	C	A	0.93	1.17	8.1E-06	0.56	0.39	1.2E-12	1.17	3.4E-13	1.00	0.96	1.31	3.5E-04	1.12	0.02	1.15	6.2E-07	Known
rs6741499	2	28369436	BRE	C	T	0.74	0.94	1.2E-03	5.1E-05	6.7E-03	9.9E-09	0.92	3.8E-12	0.90	2.3E-03	0.99	0.82	0.94	0.02	0.94	5.8E-05	Known
rs113542380	2	43464818	THADA	G	A	0.92	0.90	5.6E-04	0.05	0.06	9.5E-11	0.87	9.7E-12	0.85	8.8E-03	0.91	0.12	0.88	2.9E-03	0.89	6.5E-06	Known
rs163524	2	45157553	SIX3	C	A	0.82	0.92	1.7E-04	0.54	0.90	2.1E-08	0.92	5.7E-09	0.94	0.13	1.00	0.95	0.96	0.24	0.94	1.7E-04	Known
rs74259971	2	54659204	SPTBN1	T	C	0.83	1.11	9.7E-06	0.89	0.61	8.4E-09	1.09	4.0E-10	0.96	0.38	1.09	0.05	1.02	0.49	1.08	6.8E-05	-

<i>rs1084524</i>	2	55932390	<i>PNPT1</i>	G	A	0.15	1.11	5.5E-06	0.07	0.49	2.4E-09	1.09	2.1E-09	1.06	0.32	0.98	0.56	1.00	0.95	1.07	1.9E-04	Known
<i>rs13009933</i>	2	66574390	<i>MIR4778</i>	C	T	0.64	0.94	1.3E-04	9.8E-05	0.68	4.9E-07	0.93	1.3E-10	0.89	0.07	0.95	0.15	0.93	0.03	0.93	1.1E-05	Nominal
<i>rs6732795</i>	2	69411517	<i>ANTXR1</i>	A	C	0.61	0.93	2.9E-05	0.32	0.85	1.8E-11	0.93	7.2E-12	0.92	7.3E-03	0.96	0.25	0.94	5.3E-03	0.93	5.6E-07	Known
<i>rs56405342</i>	2	101608146	<i>NPAS2</i>	C	T	0.86	1.05	0.03	0.02	1.5E-03	5.5E-08	1.09	7.2E-09	1.06	0.25	1.03	0.54	1.05	0.20	1.05	0.01	-
<i>rs1579050</i>	2	153364527	<i>FMNL2</i>	A	G	0.43	0.93	2.0E-05	4.1E-09	0.94	3.9E-26	0.89	7.5E-26	0.90	1.1E-03	0.96	0.19	0.92	9.0E-04	0.93	7.4E-08	Known
<i>rs62172701</i>	2	205998191	<i>PARD3B</i>	A	C	0.78	1.05	0.01	0.77	0.17	1.1E-09	1.07	2.7E-08	1.05	0.20	0.96	0.35	1.01	0.75	1.04	0.02	Known
<i>rs62188040</i>	2	213723345	<i>MIR4776-1</i>	C	A	0.89	1.17	3.3E-08	0.87	0.39	2.6E-05	1.11	2.1E-09	1.08	0.16	1.03	0.64	1.05	0.18	1.12	1.6E-07	Known
<i>rs1286771</i>	3	25581512	<i>RARB</i>	T	C	0.87	1.12	1.9E-05	9.8E-03	0.59	8.0E-08	1.11	4.9E-11	1.05	0.31	1.12	0.03	1.08	0.03	1.11	1.7E-06	Nominal
<i>rs2526385</i>	3	50181135	<i>SEMA3F</i>	T	G	0.20	1.12	8.0E-08	0.05	0.29	1.5E-07	1.08	1.1E-09	1.05	0.20	1.08	0.07	1.07	0.03	1.10	1.6E-08	Nominal
<i>rs1867409</i>	3	66860178	<i>KBTBD8</i>	G	A	0.70	1.07	4.7E-04	2.4E-05	0.03	9.2E-15	1.10	1.1E-16	1.11	3.7E-03	1.06	0.12	1.09	1.3E-03	1.07	2.6E-06	Known
<i>rs66500121</i>	3	85137683	<i>CADM2</i>	A	G	0.41	1.12	2.2E-11	0.03	0.42	1.7E-05	1.08	2.6E-13	1.10	5.0E-03	1.09	0.01	1.09	1.6E-04	1.11	2.3E-14	Known
<i>rs893830</i>	3	124433550	<i>KALRN</i>	G	A	0.84	0.92	3.8E-04	0.41	0.02	6.5E-07	0.92	7.8E-09	0.94	0.17	0.97	0.59	0.96	0.16	0.93	2.1E-04	-
<i>rs11710845</i>	3	150065280	<i>TSC22D2</i>	C	T	0.74	1.11	1.5E-07	0.98	0.42	1.0E-05	1.07	2.7E-09	1.08	0.04	1.08	0.07	1.08	6.2E-03	1.10	4.6E-09	Known
<i>rs9816799</i>	3	169222771	<i>MECOM</i>	T	C	0.56	0.93	3.0E-05	2.5E-04	0.02	7.7E-06	0.93	4.5E-11	0.94	0.08	0.91	6.8E-03	0.93	1.7E-03	0.93	1.8E-07	Bonferroni
<i>rs9853115</i>	3	186131600	3	T	A	0.50	1.11	6.4E-10	0.02	0.03	1.8E-44	1.15	1.1E-39	1.11	2.9E-03	1.17	1.4E-05	1.13	2.4E-07	1.12	1.2E-15	Known
<i>rs4420855</i>	3	188057207	<i>LPP</i>	A	G	0.70	1.10	6.3E-07	0.75	0.49	3.9E-08	1.08	3.8E-10	1.05	0.21	1.03	0.37	1.04	0.12	1.08	7.6E-07	Known
<i>rs28795989</i>	4	7891545	<i>AFAP1</i>	A	G	0.40	1.15	4.1E-17	1.3E-03	0.02	4.1E-33	1.16	5.8E-42	1.16	2.8E-06	1.15	8.3E-05	1.16	7.7E-10	1.15	2.8E-25	Known
<i>rs6838291</i>	4	7917806	<i>AFAP1</i>	C	T	0.82	0.85	1.4E-14	9.1E-03	0.02	4.8E-30	0.84	2.2E-36	0.87	1.0E-03	0.95	0.24	0.91	1.1E-03	0.87	3.2E-16	Known
<i>rs447324</i>	4	177430644	<i>VEGFC</i>	A	G	0.72	1.07	3.6E-04	0.67	0.04	6.4E-08	1.07	3.4E-09	1.03	0.43	1.01	0.71	1.02	0.40	1.05	7.1E-04	-
<i>rs76325372</i>	5	14837332	<i>ANKH</i>	A	C	0.73	1.11	1.7E-08	2.9E-04	0.51	2.5E-12	1.11	4.3E-18	1.12	1.8E-03	1.04	0.31	1.08	2.7E-03	1.10	2.7E-10	Known
<i>rs4703855</i>	5	71693899	<i>PTCD2</i>	C	T	0.70	1.09	5.9E-06	0.05	0.25	2.7E-07	1.08	6.1E-11	0.99	0.79	1.00	0.98	0.99	0.83	1.05	3.9E-04	-

rs73220190	5	108053907	FER	T	C	0.93	1.14	1.7E-04	0.32	0.73	4.4E-09	1.13	1.9E-09	1.02	0.77	1.06	0.39	1.04	0.42	1.10	4.8E-04	-
rs11567976	5	137654218	CDC25C	C	T	0.43	0.95	6.2E-03	0.02	0.07	4.5E-07	0.94	1.7E-08	0.95	0.13	0.98	0.60	0.97	0.14	0.96	2.1E-03	-
rs1347141	5	147068784	JAKMIP2	A	C	0.47	1.06	7.6E-04	0.02	0.01	4.0E-05	1.06	2.9E-08	0.97	0.40	1.09	0.02	1.03	0.29	1.05	6.7E-04	-
<i>rs57111852</i>	<b>6</b>	<b>606263</b>	<i>EXOC2</i>	<b>G</b>	<b>A</b>	<b>0.86</b>	<b>0.87</b>	<b>1.2E-09</b>	<b>5.1E-06</b>	<b>5.8E-06</b>	<b>5.2E-11</b>	<b>0.87</b>	<b>6.2E-22</b>	<b>0.93</b>	<b>0.12</b>	<b>0.83</b>	<b>1.0E-04</b>	<b>0.88</b>	<b>1.5E-04</b>	<b>0.87</b>	<b>8.5E-13</b>	<b>Known</b>
<i>rs2745572</i>	<b>6</b>	<b>1548369</b>	<i>FOXC1</i>	<b>A</b>	<b>G</b>	<b>0.67</b>	<b>1.12</b>	<b>1.2E-10</b>	<b>3.7E-04</b>	<b>5.4E-06</b>	<b>3.6E-22</b>	<b>1.14</b>	<b>1.2E-30</b>	<b>1.16</b>	<b>2.4E-05</b>	<b>1.25</b>	<b>2.4E-09</b>	<b>1.20</b>	<b>6.4E-13</b>	<b>1.15</b>	<b>6.4E-21</b>	<b>Known</b>
<i>rs722585</i>	<b>6</b>	<b>1775863</b>	<i>GMDS</i>	<b>G</b>	<b>A</b>	<b>0.72</b>	<b>1.06</b>	<b>1.8E-03</b>	<b>3.3E-03</b>	<b>0.98</b>	<b>7.3E-12</b>	<b>1.08</b>	<b>1.1E-11</b>	<b>1.04</b>	<b>0.27</b>	<b>1.04</b>	<b>0.31</b>	<b>1.04</b>	<b>0.13</b>	<b>1.05</b>	<b>6.3E-04</b>	<b>Known</b>
<i>rs6914444</i>	<b>6</b>	<b>1983440</b>	<i>GMDS</i>	<b>T</b>	<b>C</b>	<b>0.86</b>	<b>1.11</b>	<b>3.7E-05</b>	<b>2.1E-10</b>	<b>4.2E-04</b>	<b>2.3E-14</b>	<b>1.16</b>	<b>4.1E-21</b>	<b>1.23</b>	<b>4.2E-05</b>	<b>1.20</b>	<b>4.6E-04</b>	<b>1.21</b>	<b>6.3E-08</b>	<b>1.14</b>	<b>1.0E-10</b>	<b>Known</b>
rs2145826	6	44763781	SUPT3H	G	A	0.43	1.08	3.5E-06	0.03	0.48	6.6E-08	1.07	1.3E-11	0.98	0.44	1.06	0.11	1.01	0.61	1.06	4.4E-05	-
<i>rs2439042</i>	<b>6</b>	<b>51446615</b>	<i>PKHD1</i>	<b>T</b>	<b>G</b>	<b>0.90</b>	<b>1.14</b>	<b>1.0E-05</b>	<b>0.14</b>	<b>0.94</b>	<b>1.5E-16</b>	<b>1.15</b>	<b>7.6E-16</b>	<b>NA</b>	<b>NA</b>	<b>NA</b>	<b>NA</b>	<b>NA</b>	<b>NA</b>	<b>1.14</b>	<b>1.0E-05</b>	<b>Known</b>
<i>rs9494457</i>	<b>6</b>	<b>136474794</b>	<i>PDE7B</i>	<b>T</b>	<b>A</b>	<b>0.62</b>	<b>1.08</b>	<b>1.0E-05</b>	<b>0.05</b>	<b>0.27</b>	<b>2.3E-16</b>	<b>1.10</b>	<b>6.9E-17</b>	<b>1.13</b>	<b>4.2E-04</b>	<b>1.10</b>	<b>6.3E-03</b>	<b>1.12</b>	<b>7.6E-06</b>	<b>1.09</b>	<b>7.4E-10</b>	<b>Known</b>
rs4709210	6	158971956	TMEM181	T	A	0.72	1.09	7.4E-06	0.25	0.40	1.3E-06	1.07	1.3E-09	1.06	0.31	1.06	0.11	1.06	0.06	1.08	1.4E-06	Nominal
			<i>LOC15444</i>																			
<i>rs2935072</i>	<b>6</b>	<b>170460912</b>	<b>9</b>	<b>C</b>	<b>T</b>	<b>0.88</b>	<b>0.86</b>	<b>1.8E-09</b>	<b>0.35</b>	<b>0.22</b>	<b>6.1E-09</b>	<b>0.89</b>	<b>2.4E-14</b>	<b>0.90</b>	<b>0.03</b>	<b>0.97</b>	<b>0.51</b>	<b>0.93</b>	<b>0.04</b>	<b>0.89</b>	<b>1.1E-09</b>	<b>Known</b>
<i>rs2526101</i>	<b>7</b>	<b>11677452</b>	<i>THSD7A</i>	<b>A</b>	<b>G</b>	<b>0.55</b>	<b>0.90</b>	<b>1.6E-09</b>	<b>0.54</b>	<b>0.14</b>	<b>6.5E-06</b>	<b>0.93</b>	<b>1.3E-10</b>	<b>0.89</b>	<b>5.2E-04</b>	<b>0.93</b>	<b>0.03</b>	<b>0.91</b>	<b>4.4E-05</b>	<b>0.90</b>	<b>3.7E-13</b>	<b>Known</b>
rs1362227	7	33511631	BBS9	A	C	0.43	1.07	1.3E-04	0.47	0.27	8.8E-08	1.07	3.2E-09	1.02	0.52	1.05	0.17	1.04	0.16	1.06	8.0E-05	-
<i>rs10435033</i>	<b>7</b>	<b>39054837</b>	<i>POU6F2</i>	<b>G</b>	<b>A</b>	<b>0.66</b>	<b>1.05</b>	<b>9.4E-03</b>	<b>0.06</b>	<b>0.02</b>	<b>5.4E-08</b>	<b>1.07</b>	<b>8.7E-09</b>	<b>1.12</b>	<b>7.8E-04</b>	<b>1.14</b>	<b>9.5E-04</b>	<b>1.13</b>	<b>2.2E-06</b>	<b>1.07</b>	<b>1.6E-06</b>	<b>Bonferroni</b>
<i>rs327712</i>	<b>7</b>	<b>80836057</b>	<i>SEMA3C</i>	<b>C</b>	<b>G</b>	<b>0.57</b>	<b>1.10</b>	<b>3.2E-08</b>	<b>0.22</b>	<b>0.70</b>	<b>4.4E-11</b>	<b>1.09</b>	<b>1.7E-14</b>	<b>1.01</b>	<b>0.70</b>	<b>1.05</b>	<b>0.17</b>	<b>1.03</b>	<b>0.23</b>	<b>1.08</b>	<b>1.7E-07</b>	<b>Known</b>
rs7799028	7	103346226	RELN	G	T	0.73	0.94	4.3E-04	1.3E-03	0.63	1.3E-05	0.94	1.4E-08	1.01	0.76	0.96	0.27	0.99	0.59	0.95	1.4E-03	-
<i>rs2896175</i>	<b>7</b>	<b>115811436</b>	<i>TES</i>	<b>A</b>	<b>C</b>	<b>0.62</b>	<b>1.09</b>	<b>8.4E-07</b>	<b>0.06</b>	<b>0.17</b>	<b>3.2E-17</b>	<b>1.10</b>	<b>1.7E-18</b>	<b>1.03</b>	<b>0.32</b>	<b>1.09</b>	<b>0.02</b>	<b>1.06</b>	<b>0.02</b>	<b>1.08</b>	<b>7.4E-08</b>	<b>Known</b>
<i>rs59454355</i>	<b>7</b>	<b>116156023</b>	<i>CAV2</i>	<b>C</b>	<b>G</b>	<b>0.73</b>	<b>0.89</b>	<b>1.0E-09</b>	<b>3.8E-04</b>	<b>4.4E-03</b>	<b>6.7E-57</b>	<b>0.84</b>	<b>4.4E-49</b>	<b>0.90</b>	<b>0.07</b>	<b>0.86</b>	<b>4.1E-05</b>	<b>0.87</b>	<b>8.9E-06</b>	<b>0.89</b>	<b>6.5E-14</b>	<b>Known</b>
<i>rs2188836</i>	<b>7</b>	<b>117635382</b>	<i>CTTNBP2</i>	<b>C</b>	<b>T</b>	<b>0.58</b>	<b>0.92</b>	<b>3.3E-07</b>	<b>0.23</b>	<b>2.9E-03</b>	<b>1.3E-10</b>	<b>0.92</b>	<b>5.8E-15</b>	<b>0.93</b>	<b>0.03</b>	<b>0.91</b>	<b>4.1E-03</b>	<b>0.92</b>	<b>3.6E-04</b>	<b>0.92</b>	<b>5.1E-10</b>	<b>Known</b>
<i>rs4128399</i>	<b>7</b>	<b>151498679</b>	<i>PRKAG2</i>	<b>T</b>	<b>C</b>	<b>0.83</b>	<b>0.89</b>	<b>2.9E-08</b>	<b>0.27</b>	<b>0.90</b>	<b>8.1E-07</b>	<b>0.92</b>	<b>1.5E-09</b>	<b>0.95</b>	<b>0.35</b>	<b>0.99</b>	<b>0.89</b>	<b>0.97</b>	<b>0.44</b>	<b>0.91</b>	<b>2.1E-07</b>	<b>Known</b>

rs4412362	8	78930579	PKIA	C	T	0.39	0.95	1.2E-03	0.17	0.11	6.4E-09	0.94	9.5E-10	1.00	0.89	0.99	0.87	1.00	0.83	0.96	6.1E-03	-
rs2881425	8	107836447	ABRA	A	G	0.68	1.02	0.17	0.37	0.34	2.0E-15	1.07	1.6E-09	1.01	0.85	0.97	0.40	0.98	0.55	1.01	0.38	-
<i>rs2022945</i>	<b>8</b>	<b>108251139</b>	<b>ANGPT1</b>	<b>A</b>	<b>G</b>	<b>0.13</b>	<b>0.84</b>	<b>1.5E-10</b>	<b>0.59</b>	<b>0.03</b>	<b>2.5E-30</b>	<b>0.83</b>	<b>1.1E-29</b>	<b>0.85</b>	<b>1.4E-03</b>	<b>0.86</b>	<b>4.9E-03</b>	<b>0.85</b>	<b>1.8E-05</b>	<b>0.85</b>	<b>1.5E-14</b>	<b>Known</b>
<i>rs1283696</i>	<b>8</b>	<b>108441531</b>	<b>ANGPT1</b>	<b>T</b>	<b>A</b>	<b>0.91</b>	<b>1.14</b>	<b>1.7E-05</b>	<b>0.53</b>	<b>0.99</b>	<b>9.3E-11</b>	<b>1.14</b>	<b>2.7E-11</b>	<b>1.04</b>	<b>0.46</b>	<b>1.01</b>	<b>0.85</b>	<b>1.03</b>	<b>0.50</b>	<b>1.10</b>	<b>1.1E-04</b>	<b>Known</b>
rs17339357	8	124600906	FBXO32	T	A	0.93	0.88	4.0E-05	0.82	0.17	7.2E-15	0.86	9.2E-14	0.83	2.6E-03	0.87	0.04	0.85	3.0E-04	0.87	6.2E-08	Bonferroni
rs944801	9	22051670	CDKN2B-AS1	G	C	0.43	0.85	3.0E-21	7.6E-64	3.8E-32	0.21	0.87	2.0E-38	0.72	3.8E-22	0.70	6.7E-24	0.71	9.9E-45	0.80	6.8E-56	Known
rs10869665	9	78518999	PCSK5	C	T	0.70	1.08	3.0E-05	0.13	0.11	9.9E-09	1.08	2.7E-11	1.05	0.19	1.06	0.11	1.05	0.04	1.07	4.8E-06	Known
rs2472493	9	107695848	ABCA1	G	A	0.45	1.16	1.9E-19	4.1E-03	4.9E-07	3.0E-51	1.19	7.8E-59	1.32	2.9E-16	1.20	1.2E-07	1.26	6.1E-22	1.19	8.5E-38	Known
rs2275241	9	129370576	LMX1B	G	A	0.63	1.14	1.6E-13	2.2E-05	1.3E-03	1.9E-32	1.16	3.2E-40	1.10	4.0E-03	1.17	2.6E-05	1.13	5.9E-07	1.14	5.7E-19	Known
rs62580791	9	129757851	RALGPS1	A	C	0.54	0.94	3.2E-04	0.84	0.04	1.9E-14	0.93	1.1E-12	NA	NA	NA	NA	NA	NA	0.94	3.2E-04	Known
rs12216891	9	136127366	ABO	C	T	0.94	0.90	2.2E-03	5.7E-07	4.2E-05	2.2E-09	0.85	6.7E-14	1.00	1.00	0.94	0.32	0.97	0.49	0.92	4.2E-03	-
rs11008626	10	32037230	ARHGAP12	T	C	0.71	0.93	5.4E-05	0.75	0.01	2.1E-06	0.94	6.6E-09	1.00	0.93	0.94	0.08	0.97	0.25	0.94	7.3E-05	-
rs7089636	<b>10</b>	<b>60283309</b>	<b>BICC1</b>	<b>T</b>	<b>G</b>	<b>0.54</b>	<b>0.92</b>	<b>6.6E-07</b>	<b>5.0E-05</b>	<b>9.5E-05</b>	<b>8.5E-06</b>	<b>0.92</b>	<b>9.8E-14</b>	<b>0.90</b>	<b>0.07</b>	<b>0.85</b>	<b>2.6E-06</b>	<b>0.87</b>	<b>6.8E-07</b>	<b>0.91</b>	<b>1.2E-11</b>	Bonferroni
rs1616405	10	78581153	KCNMA1	A	G	0.49	1.06	4.3E-04	0.30	0.01	9.2E-06	1.06	4.0E-08	1.02	0.68	1.01	0.77	1.01	0.64	1.05	8.9E-04	-
rs12778014	10	94950273	CYP26A1	G	A	0.66	1.07	1.7E-04	4.7E-11	2.1E-05	0.10	1.07	1.0E-08	1.11	2.5E-03	1.03	0.40	1.07	4.8E-03	1.07	3.0E-06	Nominal
<i>rs2274224</i>	<b>10</b>	<b>96039597</b>	<b>PLCE1</b>	<b>G</b>	<b>C</b>	<b>0.57</b>	<b>0.93</b>	<b>6.2E-06</b>	<b>1.6E-04</b>	<b>5.3E-09</b>	<b>3.1E-05</b>	<b>0.93</b>	<b>2.7E-13</b>	<b>0.90</b>	<b>6.8E-04</b>	<b>0.98</b>	<b>0.54</b>	<b>0.93</b>	<b>3.3E-03</b>	<b>0.93</b>	<b>8.2E-08</b>	<b>Known</b>
<i>rs4141194</i>	<b>11</b>	<b>17011176</b>	<b>PLEKHA7</b>	<b>C</b>	<b>A</b>	<b>0.71</b>	<b>0.92</b>	<b>1.1E-05</b>	<b>0.12</b>	<b>0.71</b>	<b>9.9E-16</b>	<b>0.91</b>	<b>5.2E-15</b>	<b>0.98</b>	<b>0.48</b>	<b>0.95</b>	<b>0.22</b>	<b>0.97</b>	<b>0.18</b>	<b>0.94</b>	<b>1.2E-05</b>	<b>Known</b>
rs12280392	11	28403473	METTL15	T	G	0.77	0.95	4.3E-03	0.01	0.10	1.9E-07	0.93	6.5E-09	0.94	0.12	0.96	0.33	0.95	0.07	0.95	7.7E-04	Nominal
rs56319620	11	47998922	PTPRJ	C	A	0.80	0.92	8.0E-05	3.9E-03	0.05	6.1E-23	0.89	4.5E-21	0.95	0.25	0.92	0.04	0.94	0.03	0.93	6.3E-06	Known
rs4434990	11	51517073	OR4C46	G	A	0.87	0.92	6.9E-04	0.76	0.41	2.0E-11	0.91	2.8E-10	0.90	0.03	1.05	0.40	0.95	0.22	0.93	4.4E-04	Known

<i>rs11229165</i>	11	55112643	<i>OR4A16</i>	<i>T</i>	<i>C</i>	0.87	0.92	4.8E-04	0.77	0.75	2.4E-11	0.91	4.1E-10	0.90	0.03	1.01	0.80	0.95	0.13	0.93	1.9E-04	Known
<i>rs4102217</i>	11	65263895	<i>MALAT1</i>	<i>G</i>	<i>C</i>	0.80	1.10	3.6E-06	1.3E-13	3.8E-15	1.9E-03	1.11	7.8E-16	1.08	0.05	1.08	0.08	1.08	9.1E-03	1.10	1.3E-07	Nominal
<i>rs11234741</i>	11	86401678	<i>ME3</i>	<i>A</i>	<i>G</i>	0.80	0.92	1.6E-05	0.18	5.6E-04	2.2E-14	0.90	2.7E-16	0.91	0.02	0.88	3.1E-03	0.90	1.6E-04	0.91	1.3E-08	Known
<i>rs1126809</i>	11	89017961	<i>TYR</i>	<i>G</i>	<i>A</i>	0.69	1.08	6.8E-05	8.2E-04	0.21	2.4E-04	1.07	1.1E-08	1.10	6.0E-03	0.94	0.09	1.02	0.38	1.06	1.8E-04	-
<i>rs58073046</i>	11	120248493	<i>ARHGEF1</i>	<i>A</i>	<i>G</i>	0.88	0.88	1.0E-07	0.47	0.19	6.5E-23	0.86	1.1E-21	0.76	4.4E-08	0.87	6.2E-03	0.81	3.3E-09	0.85	1.3E-14	Known
<i>rs7924522</i>	11	128380742		<i>ETS1</i>	<i>C</i>	<i>A</i>	0.34	0.92	3.0E-06	0.07	0.09	3.1E-15	0.91	6.9E-17	0.89	7.3E-04	0.89	7.4E-04	0.89	1.6E-06	0.91	4.7E-11
<i>rs4936100</i>	11	130287469	<i>ADAMTS8</i>	<i>A</i>	<i>G</i>	0.21	0.95	0.01	5.7E-13	3.2E-04	1.2E-03	0.92	1.5E-09	0.88	2.9E-03	0.95	0.26	0.92	3.2E-03	0.94	1.6E-04	Nominal
<i>rs324762</i>	12	83986665	<i>TMTC2</i>	<i>A</i>	<i>G</i>	0.46	0.96	0.01	1.2E-57	3.2E-20	0.52	0.93	2.9E-12	0.91	6.0E-03	0.92	0.02	0.92	2.6E-04	0.94	3.1E-05	Known
<i>rs3184504</i>	12	111884608	<i>SH2B3</i>	<i>T</i>	<i>C</i>	0.48	0.97	0.10	2.6E-05	9.8E-04	1.9E-07	0.94	5.6E-09	0.92	0.01	0.86	6.2E-06	0.89	1.0E-06	0.94	2.9E-05	Known
<i>rs9530143</i>	13	73639371	<i>KLF5</i>	<i>G</i>	<i>A</i>	0.68	1.08	2.7E-05	0.07	1.00	8.2E-06	1.07	1.4E-08	1.09	9.0E-03	1.07	0.05	1.08	1.1E-03	1.08	1.2E-07	Bonferroni
<i>rs9544024</i>	13	76258720	<i>LMO7</i>	<i>A</i>	<i>G</i>	0.50	0.96	8.0E-03	8.8E-03	4.8E-03	1.1E-12	0.93	1.2E-12	0.87	2.5E-05	0.89	4.4E-04	0.88	3.4E-08	0.93	9.7E-08	Known
<i>rs56152426</i>	13	110893841	<i>COL4A1</i>	<i>A</i>	<i>G</i>	0.82	1.09	7.1E-05	0.33	0.13	5.0E-08	1.09	5.7E-10	1.04	0.42	1.18	3.1E-03	1.09	0.01	1.09	3.0E-06	Known
<i>rs72669675</i>	14	34715771	<i>SPTSSA</i>	<i>A</i>	<i>T</i>	0.63	0.93	4.1E-05	1.8E-05	0.02	3.7E-06	0.93	1.0E-11	0.90	0.06	0.96	0.28	0.94	0.05	0.94	6.5E-06	Nominal
<i>rs61755579</i>	14	50655307	<i>SOS2</i>	<i>C</i>	<i>T</i>	0.97	1.09	0.10	0.08	0.47	1.9E-10	1.18	4.5E-08	1.31	0.03	NA	NA	1.31	0.03	1.11	0.02	Nominal
<i>rs8009633</i>	14	53386836	<i>FERMT2</i>	<i>G</i>	<i>C</i>	0.77	1.05	9.7E-03	0.01	0.15	4.5E-16	1.10	1.5E-13	1.11	0.01	1.06	0.17	1.09	5.0E-03	1.06	2.1E-04	Nominal
<i>rs35155027</i>	14	61095174	<i>SIX1</i>	<i>G</i>	<i>C</i>	0.39	1.12	6.4E-12	6.3E-23	1.1E-09	0.37	1.09	6.2E-17	1.29	3.1E-15	1.30	2.7E-14	1.30	2.5E-28	1.18	6.9E-33	Known
<i>rs73294447</i>	14	74929721	<i>NPC2</i>	<i>T</i>	<i>C</i>	0.99	1.38	9.6E-05	0.03	0.44	3.3E-08	1.36	1.9E-10	1.18	0.25	NA	NA	1.18	0.24	1.33	7.7E-05	Known
<i>rs12913832</i>	15	28365618	<i>HERC2</i>	<i>A</i>	<i>G</i>	0.21	1.07	1.2E-03	9.2E-03	0.24	9.0E-07	1.08	7.1E-09	1.07	0.12	1.06	0.14	1.07	0.03	1.07	1.0E-04	Nominal
<i>rs4601984</i>	15	57060530	<i>ZNF280D</i>	<i>G</i>	<i>T</i>	0.64	0.95	2.9E-03	0.02	0.10	2.3E-09	0.93	2.4E-10	1.00	0.89	0.93	0.05	0.97	0.16	0.96	1.1E-03	Known
<i>rs2249195</i>	15	61958029	<i>VPS13C</i>	<i>A</i>	<i>C</i>	0.57	1.05	3.6E-03	0.96	0.02	7.3E-18	1.08	1.6E-13	1.06	0.09	1.11	2.0E-03	1.08	7.7E-04	1.06	1.6E-05	Bonferroni
<i>rs11859314</i>	16	51455794	<i>SALL1</i>	<i>G</i>	<i>A</i>	0.71	0.94	2.8E-04	2.3E-21	4.8E-12	0.44	0.93	2.2E-10	0.94	0.09	0.97	0.51	0.96	0.08	0.94	7.3E-05	Nominal

<i>rs74984957</i>	16	65073799	<i>CDH11</i>	G	A	0.64	1.07	5.4E-05	0.10	0.25	5.7E-13	1.07	6.2E-11	1.12	0.04	1.15	9.1E-05	1.14	9.9E-06	1.09	1.3E-08	Known
<i>rs75265191</i>	16	77577844	<i>ADAMTS18</i>	G	A	0.93	0.88	3.8E-05	0.03	0.15	2.8E-13	0.86	1.4E-14	0.89	0.05	0.95	0.41	0.91	0.04	0.89	5.8E-06	Known
<i>rs3743861</i>	16	89818340	<i>FANCA</i>	G	C	0.58	1.04	0.02	0.15	0.71	7.0E-13	1.07	4.0E-10	1.04	0.29	1.03	0.36	1.03	0.16	1.04	5.3E-03	-
<i>rs1563966</i>	17	2095954	<i>SMG6</i>	G	A	0.66	1.06	1.2E-03	0.02	0.03	1.0E-05	1.06	2.1E-08	1.06	0.10	1.08	0.04	1.07	8.7E-03	1.06	3.4E-05	Nominal
<i>rs8064739</i>	17	9842264	<i>GAS7</i>	A	C	0.59	0.92	2.7E-07	0.10	0.04	9.8E-12	0.92	1.2E-15	0.99	0.66	0.95	0.10	0.97	0.15	0.93	4.6E-07	Known
<i>rs9913911</i>	17	10031183	<i>GAS7</i>	A	G	0.62	1.16	6.5E-18	0.11	5.6E-06	2.2E-58	1.19	1.1E-58	1.18	1.6E-06	1.24	5.0E-09	1.20	5.6E-14	1.18	6.8E-30	Known
<i>rs36006455</i>	17	47320418	FLJ40194	T	C	0.72	1.06	3.1E-03	0.02	0.08	2.8E-07	1.07	5.3E-09	1.02	0.69	0.95	0.32	0.99	0.74	1.04	0.02	-
<i>rs3785856</i>	17	59391379	<i>BCAS3</i>	A	G	0.20	0.92	5.4E-05	0.80	0.11	1.2E-13	0.91	3.7E-13	0.98	0.64	0.89	6.6E-03	0.94	0.03	0.93	5.1E-06	Known
<i>rs351973</i>	19	795457	<i>PTBP1</i>	A	G	0.36	1.03	0.08	7.5E-08	4.3E-05	1.3E-05	1.07	4.3E-09	1.07	0.11	0.96	0.41	1.03	0.43	1.03	0.06	-
<i>rs440677</i>	19	11285390	<i>KANK2</i>	G	A	0.38	0.94	1.5E-04	1.1E-03	0.03	4.1E-06	0.93	2.8E-10	0.95	0.11	0.97	0.37	0.96	0.07	0.94	3.5E-05	Nominal
<i>rs6140009</i>	20	6473054	<i>CASC20</i>	C	T	0.62	1.07	2.9E-05	1.5E-42	1.3E-09	0.44	1.09	2.4E-14	1.07	0.05	1.17	5.9E-06	1.12	6.1E-06	1.09	1.7E-09	Bonferroni
<i>rs34952318</i>	20	11177055	<i>LOC339593</i>	G	A	0.95	1.17	9.6E-05	0.18	0.17	1.2E-16	1.18	1.4E-11	1.30	0.04	NA	NA	1.30	0.04	1.19	1.5E-05	Known
<i>rs6065171</i>	20	38538768	<i>LOC339568</i>	T	C	0.49	1.06	5.2E-04	0.21	0.10	1.9E-08	1.07	9.8E-10	1.07	0.05	1.03	0.42	1.05	0.04	1.06	6.8E-05	Known
<i>rs7273775</i>	20	49061320	<i>PTPN1</i>	C	T	0.61	1.05	2.8E-03	0.05	0.04	1.3E-08	1.07	9.4E-10	1.10	0.10	1.12	2.2E-03	1.11	5.4E-04	1.07	1.8E-05	Bonferroni
<i>rs73148965</i>	22	19872935	<i>TXNRD2</i>	G	A	0.85	1.13	1.2E-06	0.42	0.40	4.6E-09	1.11	9.4E-12	1.17	1.3E-03	1.27	4.1E-06	1.21	3.5E-08	1.15	9.5E-13	Known
<i>rs738722</i>	22	29130012	<i>CHEK2</i>	T	C	0.30	0.91	3.3E-07	1.4E-35	2.4E-20	0.92	0.91	2.3E-15	0.93	0.03	0.92	0.03	0.92	2.3E-03	0.91	3.3E-09	Nominal
<i>rs9608740</i>	22	29620325	<i>EMID1</i>	A	C	0.81	0.93	1.1E-03	0.26	0.20	2.4E-17	0.90	3.0E-14	0.92	0.06	NA	NA	0.92	0.06	0.93	1.9E-04	Known
<i>rs756481</i>	22	33105227	<i>SYN3</i>	A	G	0.95	1.11	8.5E-03	0.70	0.93	3.1E-12	1.16	3.6E-09	1.04	0.61	NA	NA	1.04	0.60	1.10	0.01	-
<i>rs4821712</i>	22	38183847	<i>TRIOBP</i>	C	T	0.37	1.07	1.4E-04	1.8E-13	1.6E-03	6.1E-14	1.11	1.3E-20	1.05	0.38	1.02	0.57	1.03	0.34	1.06	1.6E-04	Known

Abbreviations: Chr, Chromosome; EA, effect allele; Freq, allele frequency of effect allele; MTAG, multiple trait analysis of GWAS; NEA, non-effect allele; SNP, single nucleotide polymorphism; OR, odds ratio; P, P value for VCDR (adjusted for VDD); VCDR, vertical cup-disc ratio; VDD, vertical disc diameter.

UKBB, UK biobank data; ANZRAG, the Australian & New Zealand Registry of Advanced Glaucoma study; NEIGHBORHOOD, the National Eye Institute Glaucoma Human Genetics Collaboration Heritable Overall Operational Database.

\* Results are highlighted: those which are associated with glaucoma alone or previous reported loci are in bold italics (we also set IOP SNPs as “known” glaucoma loci if they were replicated in glaucoma GWAS after correction for multiple comparisons in our previous study.(MacGregor et al. 2018)), those replicated in ANZRAG and NEIGHBORHOOD after Bonferroni correction ( $P<0.05/49=0.001$ , one-sided test) are in bold, those replicated at a nominal significance level ( $P<0.05$ ) are in italics, with the remainder in normal font. “-”, remain to be confirmed.

Chromosomal position is based on the NCBI RefSeq hg19 human genome reference assembly.

**Supplementary Table 5. Gene-based analysis of glaucoma MTAG GWAS (list of 196 significant genes after Bonferroni correction)**

GENE	CHR	START	STOP	NSNPS	NPARA M	ZSTAT	P	SYMBOL
ENSG00000143183	1	165696032	165796992	136	25	16.106	1.15E-58	<i>TMCO1</i>
ENSG0000007237	17	9813926	10101868	884	154	13.039	3.69E-39	<i>GAS7</i>
ENSG00000196526	4	7760441	7941653	836	53	12.522	2.81E-36	<i>AFAP1</i>
ENSG00000154188	8	108261721	108510283	737	66	10.626	1.12E-26	<i>ANGPT1</i>
ENSG00000136944	9	129376722	129463311	216	36	10.092	3.00E-24	<i>LMX1B</i>
ENSG00000112699	6	1624041	2245926	1258	119	9.9988	7.71E-24	<i>GMDS</i>
ENSG00000105971	7	115927434	116148595	494	49	9.701	1.49E-22	<i>CAV2</i>
ENSG00000157827	2	153191751	153506348	901	72	8.7735	8.66E-19	<i>FMNL2</i>
ENSG00000085276	3	168801287	169381406	1531	132	8.3933	2.36E-17	<i>MECOM</i>
ENSG00000105974	7	116164839	116201233	97	14	8.2351	8.97E-17	<i>CAV1</i>
ENSG00000122870	10	60272900	60591195	564	45	7.7995	3.11E-15	<i>BICC1</i>
ENSG00000134571	11	47352957	47374253	40	11	7.7552	4.41E-15	<i>MYBPC3</i>
ENSG00000135269	7	115850547	115898837	145	12	7.7277	5.48E-15	<i>TES</i>
ENSG00000149187	11	47487496	47587121	104	22	7.6975	6.94E-15	<i>CELF1</i>
ENSG00000154122	5	14704910	14871887	361	50	7.5972	1.51E-14	<i>ANKH</i>
ENSG00000196914	11	120207787	120360645	233	15	7.523	2.68E-14	<i>ARHGEF12</i>
ENSG00000100106	22	38093011	38172563	171	20	7.5211	2.72E-14	<i>TRIOBP</i>
ENSG00000165029	9	107543283	107690518	515	79	7.5088	2.98E-14	<i>ABCA1</i>
ENSG00000213619	11	47586888	47606114	15	6	7.4794	3.73E-14	<i>NDUFS3</i>
ENSG00000100101	22	38077680	38170137	198	23	7.4206	5.83E-14	<i>NOL12</i>
ENSG00000165916	11	47440320	47447993	13	4	7.3928	7.19E-14	<i>PSMC3</i>
ENSG00000183765	22	29083731	29138410	123	20	7.3464	1.02E-13	<i>CHEK2</i>
ENSG00000100116	22	38203912	38213183	19	3	7.3336	1.12E-13	<i>GCAT</i>
ENSG00000110514	11	47290712	47351582	123	14	7.2451	2.16E-13	<i>MADD</i>
ENSG00000181264	11	120195838	120204391	12	2	7.2262	2.48E-13	<i>TMEM136</i>
ENSG00000134574	11	47236493	47260767	51	7	7.2223	2.56E-13	<i>DDB2</i>
ENSG00000134954	11	128328656	128457453	269	50	7.1932	3.16E-13	<i>ETS1</i>
ENSG00000134917	11	130274820	130298888	61	16	7.0756	7.44E-13	<i>ADAMTS8</i>
ENSG00000109919	11	47638867	47664175	22	6	7.0407	9.56E-13	<i>MTCH2</i>
ENSG0000025434	11	47269851	47290396	42	7	7.0056	1.23E-12	<i>NR1H3</i>
ENSG00000196814	9	129089128	129269320	425	41	6.9592	1.71E-12	<i>MVB12B</i>
ENSG00000165917	11	47459308	47470730	31	6	6.914	2.36E-12	<i>RAPSN</i>
ENSG00000112685	6	485133	693117	565	47	6.8764	3.07E-12	<i>EXOC2</i>
ENSG00000168056	11	65306276	65326401	14	4	6.8757	3.08E-12	<i>LTBP3</i>

ENSG00000134575	11	47260853	47270457	24	4	6.8568	3.52E-12	ACP2
ENSG00000175161	3	85008132	86123579	2520	72	6.8394	3.98E-12	CADM2
ENSG00000100124	22	38226862	38245334	18	7	6.8283	4.30E-12	ANKRD54
ENSG00000140937	16	64977656	65160015	437	45	6.8072	4.98E-12	CDH11
ENSG00000110536	11	47586982	47595013	7	3	6.7968	5.35E-12	PTPMT1
ENSG00000100139	22	38301664	38338829	45	8	6.757	7.04E-12	MICALL1
ENSG00000149177	11	48002113	48189670	310	26	6.7299	8.49E-12	PTPRJ
ENSG00000136828	9	129677053	129985445	484	29	6.6688	1.29E-11	RALGPS1
ENSG00000100129	22	38244875	38285414	45	8	6.6577	1.39E-11	EIF3L
ENSG00000176540	11	48387037	48388017	1	1	6.5827	2.31E-11	OR4C5
ENSG00000075420	3	171757418	172119455	751	83	6.5649	2.60E-11	FNDC3B
ENSG00000066336	11	47376411	47400127	58	7	6.5285	3.32E-11	SPI1
ENSG00000142186	11	65292548	65306175	14	5	6.483	4.50E-11	SCYL1
ENSG00000171502	1	86194916	86622626	1297	76	6.4776	4.66E-11	COL24A1
ENSG00000136859	9	129849611	129885162	53	10	6.4641	5.10E-11	ANGPTL2
ENSG00000165915	11	47428683	47438047	20	4	6.4427	5.87E-11	SLC39A13
ENSG00000147883	9	22002902	22009362	6	3	6.4406	5.95E-11	CDKN2B
ENSG00000151376	11	86152150	86383678	815	65	6.4253	6.58E-11	ME3
ENSG00000173442	11	65343509	65360121	24	7	6.377	9.03E-11	EHBP1L1
ENSG00000030066	11	47799639	47870107	105	12	6.364	9.83E-11	NUP160
ENSG00000070366	17	1963133	2207065	542	27	6.3553	1.04E-10	SMG6
ENSG00000136153	13	76194570	76434004	561	53	6.313	1.37E-10	LMO7
ENSG00000140262	15	57210821	57591479	831	29	6.2902	1.59E-10	TCF12
ENSG00000128346	22	38339528	38349676	10	5	6.2606	1.92E-10	C22orf23
ENSG00000124813	6	45295894	45632086	821	80	6.2473	2.09E-10	RUNX2
ENSG00000148737	10	114710009	114927437	394	66	6.2188	2.50E-10	TCF7L2
ENSG00000158019	2	28112808	28561768	815	57	6.1527	3.81E-10	BRE
ENSG00000155363	1	113215763	113243368	54	10	6.1485	3.91E-10	MOV10
ENSG00000178175	5	71738479	71803554	149	18	6.1474	3.94E-10	ZNF366
ENSG00000141376	17	58754814	59470199	825	68	6.1133	4.88E-10	BCAS3
ENSG00000165923	11	47681143	47736941	86	11	6.1109	4.95E-10	AGBL2
ENSG00000105967	7	115575202	115799950	494	45	6.0643	6.63E-10	TFEC
ENSG00000149179	11	46958240	47185936	280	25	6.014	9.05E-10	C11orf49
ENSG00000158955	17	44910567	44964096	95	12	6.0122	9.15E-10	WNT9B
ENSG00000196284	6	44777054	45345690	1544	37	6.0029	9.69E-10	SUPT3H
ENSG00000196159	4	126237554	126414087	433	48	5.9566	1.29E-09	FAT4
ENSG00000086205	11	49168187	49230222	167	16	5.897	1.85E-09	FOLH1
ENSG00000129521	14	34393437	34931980	1553	192	5.8103	3.12E-09	EGLN3

ENSG00000175619	11	48238344	48239314	2	1	5.7915	3.49E-09	OR4B1
ENSG00000160145	3	123798870	124445172	1779	114	5.7898	3.52E-09	KALRN
ENSG00000108379	17	44839872	44910520	86	16	5.7848	3.63E-09	WNT3
ENSG00000049192	5	64444563	64777747	667	46	5.7844	3.64E-09	ADAMTS6
ENSG00000100142	22	38348614	38437922	78	9	5.7716	3.93E-09	POLR2F
ENSG00000137871	15	56922379	57210769	496	35	5.7676	4.02E-09	ZNF280D
ENSG00000126391	11	65154070	65180996	31	9	5.7674	4.02E-09	FRMD8
ENSG00000169604	2	69240310	69476459	550	67	5.7471	4.54E-09	ANTXR1
ENSG00000007341	1	113066140	113163447	189	16	5.7206	5.31E-09	ST7L
ENSG00000138193	10	95753746	96092580	586	55	5.669	7.18E-09	PLCE1
ENSG00000109920	11	47738072	47788995	81	10	5.6557	7.76E-09	FNBP4
ENSG00000134569	11	46878419	46940193	95	12	5.648	8.12E-09	LRP4
ENSG00000116489	1	113161795	113214241	64	11	5.6394	8.53E-09	CAPZA1
ENSG00000176567	11	48285413	48286330	3	2	5.6392	8.54E-09	OR4X1
ENSG00000100154	22	28374004	29075853	1037	43	5.623	9.38E-09	TTC28
ENSG00000173327	11	65365226	65382853	29	6	5.6223	9.42E-09	MAP3K11
ENSG00000138035	2	55861400	55921045	189	24	5.6206	9.52E-09	PNPT1
ENSG00000179008	14	60863187	60982261	216	15	5.6124	9.98E-09	C14orf39
ENSG00000189056	7	103112231	103629963	1814	128	5.5802	1.20E-08	RELN
ENSG00000115970	2	43393800	43823185	936	47	5.5787	1.21E-08	THADA
ENSG00000171408	6	136172834	136516712	482	60	5.5619	1.33E-08	PDE7B
ENSG00000171812	1	36560837	36590821	47	7	5.499	1.91E-08	COL8A2
ENSG00000187498	13	110801318	110959496	591	75	5.476	2.18E-08	COL4A1
ENSG00000156804	8	124510129	124553446	114	27	5.4735	2.21E-08	FBXO32
ENSG00000011304	19	797075	812327	44	9	5.4614	2.36E-08	PTBP1
ENSG00000172733	8	30853321	30891231	46	10	5.4491	2.53E-08	PURG
ENSG00000183762	22	29469066	29564321	247	26	5.4466	2.57E-08	KREMEN1
ENSG00000215012	22	19833661	19842419	29	6	5.4253	2.89E-08	C22orf29
ENSG00000175216	11	46764598	46867847	133	18	5.4176	3.02E-08	CKAP5
ENSG00000143149	1	165631453	165668100	133	14	5.3996	3.34E-08	ALDH9A1
ENSG00000255073	11	58346645	58392112	69	13	5.3878	3.57E-08	ZFP91-CNTF
ENSG00000116117	2	205410516	206484886	2378	168	5.3551	4.28E-08	PARD3B
ENSG00000149182	11	47185848	47198676	21	7	5.3271	4.99E-08	ARFGAP2
ENSG00000174957	11	55944094	55945032	1	1	5.3054	5.62E-08	OR5J2
ENSG00000214891	11	49075266	49080664	15	4	5.2951	5.95E-08	TRIM64C
ENSG00000186660	11	58346584	58388515	67	13	5.2884	6.17E-08	ZFP91
ENSG00000163995	4	7967039	8160559	600	98	5.2871	6.21E-08	ABLIM2
ENSG00000115380	2	56093102	56151274	159	23	5.2786	6.51E-08	EFEMP1

ENSG00000068028	3	50367219	50378411	10	3	5.2726	6.73E-08	RASSF1
ENSG00000116863	1	36554476	36559533	1	1	5.2607	7.18E-08	ADPRHL2
ENSG00000185666	22	32908539	33454358	1371	142	5.25	7.60E-08	SYN3
ENSG00000204634	2	101624079	101869328	513	42	5.2411	7.98E-08	TBC1D8
ENSG00000169218	1	38076951	38100595	60	12	5.2191	8.99E-08	RSPO1
ENSG00000100146	22	38366693	38383429	8	2	5.1909	1.05E-07	SOX10
ENSG00000140873	16	77281710	77469011	903	64	5.189	1.06E-07	ADAMTS18
ENSG00000158805	16	89786808	89807311	94	14	5.1365	1.40E-07	ZNF276
ENSG00000231880	11	47599277	47599823	1	1	5.1199	1.53E-07	KBTBD4
ENSG00000128250	22	29834572	29838444	9	2	5.1175	1.55E-07	RFPL1
ENSG00000143353	1	219347186	219386207	56	11	5.114	1.58E-07	LYPLAL1
ENSG00000198561	11	57520715	57587018	71	11	5.107	1.64E-07	CTNND1
ENSG00000173465	11	65337901	65341413	6	2	5.1008	1.69E-07	SSCA1
ENSG00000001617	3	50192478	50226508	58	9	5.0735	1.95E-07	SEMA3F
ENSG00000198740	17	47366568	47439835	137	14	5.0731	1.96E-07	ZNF652
ENSG00000134697	1	38032417	38061536	58	11	5.0629	2.07E-07	GNL2
ENSG00000064655	20	45523263	45817492	780	92	5.0559	2.14E-07	EYA2
ENSG00000157368	16	70613798	70694585	211	18	5.054	2.16E-07	IL34
ENSG00000070081	11	17229700	17371521	263	22	5.0424	2.30E-07	NUCB2
ENSG00000138041	2	55774428	55846015	186	23	5.0422	2.30E-07	SMEK2
ENSG00000075399	16	89773542	89787394	31	10	5.032	2.43E-07	VPS9D1
ENSG00000189060	22	38201114	38203442	3	1	5.0315	2.43E-07	H1F0
ENSG00000122545	7	35840542	35944917	164	11	5.03	2.45E-07	SEPT7
ENSG00000164463	5	172483355	172566291	173	17	5.0093	2.73E-07	CREBRF
ENSG00000237388	11	48510269	48511332	4	2	5.0045	2.80E-07	OR4A47
ENSG00000129038	15	74218330	74244478	106	16	4.9967	2.92E-07	LOXL1
ENSG00000071575	2	12857015	12882860	49	10	4.9959	2.93E-07	TRIB2
ENSG00000179564	3	50316458	50325545	4	1	4.9869	3.07E-07	LSMEM2
ENSG00000073969	17	44668035	44834830	56	6	4.9754	3.26E-07	NSF
ENSG00000120733	5	137688285	137772717	179	22	4.9715	3.32E-07	KDM3B
ENSG00000197265	8	30435835	30515768	146	17	4.9525	3.66E-07	GTF2E2
ENSG00000187741	16	89803957	89883065	399	21	4.9418	3.87E-07	FANCA
ENSG00000184470	22	19863040	19929341	240	34	4.9377	3.95E-07	TXNRD2
ENSG00000011405	11	17099277	17229530	191	20	4.9241	4.24E-07	PIK3C2A
ENSG00000137834	15	66994566	67074338	197	26	4.9115	4.52E-07	SMAD6
ENSG00000113734	5	172571445	172591390	44	9	4.9083	4.59E-07	BNIP1
ENSG00000254462	11	57480077	57559058	84	11	4.903	4.72E-07	TMX2-CTNND1
ENSG00000158402	5	137620954	137674044	113	14	4.9006	4.78E-07	CDC25C

ENSG00000122507	7	33168856	33645680	1207	66	4.8941	4.94E-07	BBS9
ENSG00000188211	11	17373273	17398888	57	11	4.8896	5.05E-07	NCR3LG1
ENSG00000073712	14	53323986	53419153	172	20	4.8525	6.10E-07	FERMT2
ENSG00000054116	1	36602173	36615098	14	2	4.8271	6.93E-07	TRAPPC3
ENSG00000165912	11	47199076	47207994	18	5	4.8259	6.97E-07	PACSIN3
ENSG00000166689	11	16799842	17035990	689	55	4.8229	7.07E-07	PLEKHA7
ENSG00000178804	3	129262057	129270310	17	4	4.8163	7.31E-07	H1FOO
ENSG00000186998	22	29601840	29655586	140	25	4.8144	7.38E-07	EMID1
ENSG00000160293	9	136627016	136857726	893	102	4.7978	8.02E-07	VAV2
ENSG00000120709	5	137667624	137685416	40	10	4.7956	8.11E-07	FAM53C
ENSG00000106536	7	39017598	39532694	1340	80	4.792	8.26E-07	POU6F2
ENSG00000084636	1	32117848	32169920	83	16	4.7874	8.45E-07	COL16A1
ENSG00000112584	6	170599791	170716153	278	19	4.7803	8.75E-07	FAM120B
ENSG00000102554	13	73629114	73651676	42	10	4.7791	8.80E-07	KLF5
ENSG00000184178	4	53739149	54232242	913	77	4.778	8.85E-07	SCFD2
ENSG00000155366	1	113243728	113250056	15	5	4.7728	9.08E-07	RHOC
ENSG00000214706	3	50325163	50330349	4	2	4.751	1.01E-06	IFRD2
ENSG00000182185	14	68286496	69196935	1929	137	4.7495	1.02E-06	RAD51B
ENSG00000020426	14	61201460	61436671	210	36	4.7477	1.03E-06	MNAT1
ENSG00000142611	1	2985732	3355185	994	157	4.7464	1.04E-06	PRDM16
ENSG00000175806	8	9911778	10286401	1379	88	4.7301	1.12E-06	MSRA
ENSG00000164045	3	48198636	48229892	30	9	4.7297	1.12E-06	CDC25A
ENSG0000005108	7	11409984	11871824	1582	131	4.723	1.16E-06	THSD7A
ENSG00000198877	11	55540914	55541858	2	1	4.7213	1.17E-06	OR5D13
ENSG00000171132	2	45878484	46415129	1716	226	4.7176	1.19E-06	PRKCE
ENSG00000157110	8	30241944	30429778	286	24	4.7101	1.24E-06	RBPM5
ENSG00000163877	1	38000050	38019903	37	9	4.6983	1.31E-06	SNIP1
ENSG00000139624	12	50523575	50561288	49	5	4.6647	1.55E-06	CERS5
ENSG00000167822	11	55904247	55905194	5	2	4.6638	1.55E-06	OR8J3
ENSG00000198252	14	53196898	53241716	73	9	4.6611	1.57E-06	STYX
ENSG00000166979	21	33784314	33887707	257	24	4.6594	1.59E-06	EVA1C
ENSG00000214063	11	842808	867116	42	11	4.6569	1.61E-06	TSPAN4
ENSG00000008197	6	50681541	50740701	82	9	4.6558	1.61E-06	TFAP2D
ENSG00000177830	11	867357	915058	88	13	4.6555	1.62E-06	CHID1
ENSG00000123444	11	47593749	47600567	3	2	4.6521	1.64E-06	KBTBD4
ENSG00000137692	11	102932805	102962944	44	8	4.6427	1.72E-06	DCUN1D5
ENSG00000114302	3	48782030	48885279	71	12	4.6369	1.77E-06	PRKAR2A
ENSG00000156599	11	57435219	57468659	46	9	4.6348	1.79E-06	ZDHHC5

ENSG00000137709	11	120107349	120190653	173	26	4.6344	1.79E-06	<i>POU2F3</i>
ENSG00000163875	1	37958176	37980375	69	12	4.6222	1.90E-06	<i>MEAF6</i>
ENSG00000162804	2	241938255	242034983	246	37	4.6123	1.99E-06	<i>SNED1</i>
ENSG00000079308	2	218664512	218867718	483	84	4.6016	2.10E-06	<i>TNS1</i>
ENSG00000163879	1	38022520	38032458	28	7	4.5882	2.24E-06	<i>DNALI1</i>
ENSG00000177479	3	48956254	49023815	61	11	4.5845	2.28E-06	<i>ARIH2</i>
ENSG00000175592	11	65659520	65668044	20	6	4.5798	2.33E-06	<i>FOSL1</i>
ENSG00000114395	3	50388126	50395891	7	3	4.5797	2.33E-06	<i>CYB561D2</i>
ENSG00000171103	2	29072687	29093167	28	5	4.5509	2.67E-06	<i>TRMT61B</i>
ENSG00000130158	19	11309971	11373157	119	16	4.5488	2.70E-06	<i>DOCK6</i>

**Supplementary Table 6. Pathway analysis of glaucoma MTAG GWAS (list of 14 significant pathways after Bonferroni correction)**

SET	NGE_NES	BETA	BETA_STD	SE	P	FULL_NAME
GO_cc:go_proteinaceous...	335	0.395	0.0534	0.0559	7.99E-13	GO_cc:go_proteinaceous_extracellular_matrix
GO_cc:go_extracellular...	400	0.311	0.0459	0.0507	4.09E-10	GO_cc:go_extracellular_matrix
GO_cc:go_collagen_trimer	84	0.659	0.0449	0.112	1.84E-09	GO_cc:go_collagen_trimer
Curated_gene_sets:reactome...	55	0.781	0.0431	0.137	6.57E-09	Curated_gene_sets:reactome_collagen_formatio
Curated_gene_sets:naba...	41	0.921	0.0439	0.162	7.12E-09	Curated_gene_sets:naba_collagens
GO_bp:go_response_to_laminar...	14	1.56	0.0436	0.298	7.53E-08	GO_bp:go_response_to_laminar_fluid_shear_stress
Curated_gene_sets:pid...	43	0.768	0.0375	0.153	2.79E-07	Curated_gene_sets:pid_syndecan_1_pathway
Curated_gene_sets:naba...	259	0.312	0.0371	0.0643	6.26E-07	Curated_gene_sets:naba_core_matrisome
Curated_gene_sets:kins...	312	0.258	0.0336	0.0555	1.67E-06	Curated_gene_sets:kinsey_targets_of_ewsr1_flii_fusion_dn
GO_bp:go_circulatory_s...	761	0.168	0.0337	0.0363	1.92E-06	GO_bp:go_circulatory_system_development
GO_bp:go_vasculature_d...	452	0.216	0.0338	0.0468	2.02E-06	GO_bp:go_vasculature_development
GO_cc:go_extracellular...	118	0.441	0.0356	0.0958	2.06E-06	GO_cc:go_extracellular_matrix_component
GO_cc:go_complex_of_co...	21	1.03	0.0352	0.227	2.69E-06	GO_cc:go_complex_of_collagen_trimers
GO_mf:go_extracellular...	71	0.571	0.0358	0.129	4.49E-06	GO_mf:go_extracellular_matrix_structural_constituent

**Supplementary Table 7. Discriminatory power of MTAG PRS in the ANZRAG cohort of advanced glaucoma.**

P value thresholds	Nagelkerke R <sup>2</sup>	AUC (95% confidence interval)
$5 \times 10^{-8}$	9.7%	0.66 (0.64,0.67)
$1 \times 10^{-5}$	12.1%	0.68 (0.66,0.69)
0.001	13.2%	0.68 (0.67,0.70)
0.05	9.2%	0.65 (0.63,0.67)
1	6.9%	0.63 (0.62,0.65)

Sex and first four principal components were adjusted when calculated Nagelkerke R<sup>2</sup> and AUC.

We applied the LDpred method alongside the method described in the paper but the predictions were slightly worse than those using the methods described in our manuscript.

**Supplementary Table 8. The prediction value of MTAG PRS and each trait alone in the ANZRAG cohort of advanced glaucoma.**

Methods	Sample size	Nagelkerke R <sup>2</sup>
MTAG method <sup>1</sup>	-	0.13
LDpred <sup>2</sup>	-	0.10
IOP alone <sup>3</sup>	133,492	0.09
Glaucoma alone <sup>4</sup>	Cases = 7,947 Controls = 119,318	0.06
VCDR (DD adjusted) alone <sup>5</sup>	67,040	0.03

<sup>1</sup> The MTAG method with LD-clumping and P value threshold is the main analysis we reported in the manuscript. The training data are based on the MTAG output for glaucoma. We reported the prediction value for SNPs with P values  $\leq 0.001$ .

<sup>2</sup> The LDpred method is based on the summary statistics of MTAG output for glaucoma. We tested the infinitesimal prior (LDpred-inf), and models with different fraction of causal variants (0.1, 0.01, and 0.0001). The best prediction value is at the fraction of causal variants of 0.1.

<sup>3</sup> The training dataset is intraocular pressure meta-analysis of UK biobank (N = 103,914) and IGGC (N = 29,578) GWAS. The best prediction value is at the threshold of P value  $\leq 1 \times 10^{-5}$ .

<sup>4</sup> The training dataset is UK Biobank glaucoma GWAS (7,947 cases and 119,318 controls). The best prediction value is at the threshold of P value  $\leq 1 \times 10^{-5}$ .

<sup>5</sup> The training dataset is UK biobank VCDR (adjusted for disc diameter) GWAS ( N = 67,040). The best prediction value is at the threshold of P value  $\leq 1 \times 10^{-4}$ .

**Supplementary Table 9. The odds ratio of a high polygenic risk score**

High PRS	Reference group	OR	95% CI	P value
Top 50% of distribution	Remaining 50%	2.94	2.60 - 3.34	1.5E-64
Top 20% of distribution	Remaining 80%	3.61	3.11 - 4.20	3.7E-63
Top 10% of distribution	Remaining 90%	4.20	3.43 - 5.17	1.4E-42
Top 5% of distribution	Remaining 95%	4.47	3.36 - 6.00	5.3E-24
Top 2% of distribution	Remaining 98%	5.65	3.55 - 9.37	2.2E-12
Top 1% of distribution	Remaining 99%	8.49	4.16 - 19.69	4.7E-08

CI, confidence interval; OR, odds ratio; PRS, polygenic risk score.

Odds ratios were calculated by comparing the high PRS group with the remainder of the population in a logistic regression model adjusted for the effects of sex and the first four principal components of ancestry.

**Supplementary Table 10. Multivariable logistic regression model in BMES**

<b>Variables</b>	<b>Beta coefficient</b>	<b>Standard error</b>	<b>Z value</b>	<b>P value</b>
(Intercept)	-10.09	1.17	-8.60	8.3E-18
PRS (scaled)	0.77	0.13	6.06	1.4E-09
sex (Male vs Female)	-0.25	0.26	-0.95	0.34
age (Years)	0.10	0.02	6.60	4.1E-11
Family History (have vs. not have )	0.85	0.34	2.53	0.01

**Supplementary Table 11. Prediction value of MTAG PRS in BMES and UKBB**

Target	Models	AUC[95% CI]	P(AUC change)
BMES	Model 1	0.71[0.66,0.77]	
	Model 2	0.72[0.67,0.78]	2.7E-03
	Model 3	0.79[0.75,0.84]	
	Model 4	0.81[0.76,0.86]	5.9E-03
	Model 5	0.86[0.82,0.89]	
	Model 6	0.86[0.82,0.90]	0.02
	Model 7	0.88[0.85,0.92]	
UKBB POAG (European Ancestry)			
	Model 1	0.67[0.63,0.72]	
	Model 2	0.71[0.67,0.76]	2.8E-04
	Model 3	0.76[0.72,0.81]	
	Model 4	0.78[0.74,0.83]	2.2E-03
	Model 5	0.81[0.78,0.85]	
	Model 6	0.88[0.85,0.91]	0.06
UKBB glaucoma (European Ancestry)	Model 7	0.89[0.85,0.92]	
	Model 1	0.66[0.64,0.68]	
	Model 2	0.70[0.68,0.71]	7.9E-20
	Model 3	0.75[0.73,0.76]	
	Model 4	0.76[0.75,0.78]	8.7E-12
	Model 5	0.79[0.78,0.80]	
UKBB glaucoma (South Asian Ancestry)	Model 6	0.82[0.80,0.83]	7.4E-07
	Model 7	0.83[0.81,0.84]	
	Model 1	0.64[0.59,0.68]	
	Model 2	0.73[0.70,0.77]	9.6E-03
	Model 3	0.76[0.73,0.79]	

AUC, area under the curve; CI, confidence interval; P(AUC change), P value from comparing the AUC of two correlated models with and without PRS. Details of the training samples the target datasets to construct PRS are available in **Extended Data Fig. 1**. There was no sample overlap between each of the training and target datasets (**Extended Data Fig. 1**).

Models 1 to 7: Model 1: PRS; Model 2: sex + age; Model 3: PRS + sex + age; Model 4: sex + age + IOP; Model 5: PRS + sex + age + IOP; Model 6: sex + age + IOP + VCDR; Model 7: PRS + sex + age + IOP + VCDR

**Supplementary Table 12. Demographic profile of 1,336 participants with age at diagnosis information in ANZRAG**

PRS percentiles	Number		Sex		Age at Diagnosis (years)		
	bottom	top	M/F bottom	M/F top	Mean bottom (SD)	Mean top (SD)	Median bottom/top
<b>10%</b>	134	134	64/70	65/69	62.83 (15.70)	55.69 (13.02)	65/56
<b>20%</b>	268	267	133/135	135/132	62.15 (14.91)	56.94 (13.79)	65/57

Abbreviations: F, female; M, male; PRS, polygenic risk score; SD, standard deviation.

In 1,734 ANZRAG advanced POAG cases, 398 participants with unknown age at diagnosis.

**Supplementary Table 13. PRS prediction of RNFL progression: Surviving proportion of RNFL**

Dependent variables	Effect size (% loss, 95% CI)	P-value
PRS (per decile)	-0.382 (-0.643, -0.123)	0.004
Age at baseline (years)	-0.026 (-0.107, 0.053)	0.507
IOP at baseline (mmHg)	-0.064 (-0.274, 0.144)	0.543
RNFL thickness at baseline ( $\mu\text{M}$ )	-0.042 (-0.085, -0.001)	0.046

CI: confidence interval; IOP, intraocular pressure; PRS, polygenic risk score; RNFL, retinal nerve fibre layer.

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