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Discovery of 42 genome-wide significant loci associated with dyslexia

In the format provided by the authors and unedited

SUPPLEMENTARY INFORMATION

Table of Contents

METHODS

23andMe Genotyping and imputation

Samples were genotyped on one of five genotyping platforms. The V1 and V2 platforms were variants of the Illumina HumanHap550 + BeadChip, including about 25,000 custom SNPs selected by 23andMe, with a total of about 560,000 SNPs. The V3 platform was based on the Illumina OmniExpress + BeadChip, with custom content to improve the overlap with our V2 array, with a total of ~950,000 SNPs. The V4 platform is a fully custom array, including a lower redundancy subset of V2 and V3 SNPs with additional coverage of lower-frequency coding variation, and ~570,000 SNPs. The v5 platform, in current use, is an Illumina Infinium Global Screening Array (~640,000 SNPs) supplemented with ~50,000 SNPs of custom content. Samples that failed to reach 98.5% call rate were excluded from the study.

Individuals were only included if they had > 97% European ancestry, as determined through an analysis of local ancestry (see [1] for further details on the methodology used). Briefly, this analysis first partitions phased genomic data into short windows of ~100 SNPs. Within each window, a support vector machine is used to classify individual haplotypes into one of 31 reference populations. The support vector machine classifications are then fed into a Hidden Markov Model (HMM) that accounts for switch errors and incorrect assignments and gives probabilities for each reference population in each window. Finally, simulated admixed individuals are used to recalibrate the HMM probabilities so that the reported assignments are consistent with the simulated admixture proportions. The reference population data are derived from public data sets (the Human Genome Diversity Project, HapMap and 1000 Genomes) and from 23andMe research participants who have reported having four grandparents from the same country.

A maximal set of unrelated individuals was chosen for each analysis using a segmental identity-by-descent (IBD) estimation algorithm [2]. Individuals were defined as related if they shared more than 700 cM IBD, including regions where the two individuals share either one or both genomic segments identical-by-descent. This level of relatedness (roughly 20% of the genome) corresponds

approximately to the minimal expected sharing between first cousins in an outbred population. For the purposes of GWAS, if a case was found to be related to a control, the case was preferentially kept in the sample.

Participant genotype data were imputed against a single unified imputation reference panel, combining the May 2015 release of the 1000 Genomes Phase 3 haplotypes and the UK10K imputation reference panel. Data for each genotyping platform were phased and imputed separately. Variants that were only genotyped on the 'V1' platform were flagged due to small sample size, and variants on chrM or chrY, because many of these are not currently called reliably. Using trio data, variants that failed a test for parent–offspring transmission were also flagged; specifically, the child's allele count was regressed against the mean parental allele count and variants with fitted $\beta < 0.6$ and $p < 10^{-20}$ for a test of $\beta<1$ were flagged. Variants with a Hardy–Weinberg $p < 10^{-20}$ in Europeans, or a call rate of < 90%, were also flagged. Genotyped variants were also tested for batch effects and variants with $p < 10^{-50}$ by analysis of variance of genotypes against a factor dividing genotyping date into 20 roughly equal-sized buckets were flagged. For imputed GWAS results, variants with average $r^2 < 0.5$ or minimum $r^2 < 0.3$ in any imputation batch were flagged, as well as SNPs that had strong evidence of an imputation batch effect, using an analysis of variance of the imputed dosages against a factor representing imputation batch; results with $p < 10^{-50}$ were flagged. Each variant flagged by QC on genotyped or imputation data were excluded from the GWAS analysis.

Chinese Reading Study sample

Participants

3,127 Grade 3 to Grade 6 primary students aged nine to 14 years were recruited from three cities and four districts in China (Xi'an-YT, Xi'an-CB, Qingyang, and Baotou). In total, 2,476 participants were eligible for subsequent genotyping and association analysis. Ethical approval was obtained for each cohort at the local level and written informed consent was obtained from all the participants' parents.

Phenotypic measures

Reading accuracy: A Chinese character recognition test was employed to measure each child's reading accuracy [3-5]. The test consisted of 150 single Chinese characters selected from China's Elementary School Textbooks (1996). The average frequency of the characters was 182 per million (ranging from 0 to 2,282), and the reliability of this test was 0.95 [3]. Each child was individually tested and was required to read aloud each character at a time.

Reading fluency: A word list reading task [3] was used to measure each child's reading fluency. In this task, children were asked to name a list of 180 two-character words as rapidly and accurately as possible. All these words were from primary school textbooks and have been learned before Grade 3, such as "我们 (we)" and "太阳 (sun)". The mean frequency of these words was 212.77 per million [6].

Since words included in this task were all simple, this task was administrated to test children's reading fluency. The total time for naming the whole word list was recorded as the measurement of reading fluency.

Genotype quality control, imputation, and analysis

DNA was extracted from saliva samples, and individuals were genotyped using the Illumina Asian screening array (650K) by Beijing Compass Biotechnology. Quality control was performed using standard quality control metrics. Eight samples were excluded as they had sex discrepancies between the records and the genetically inferred data [7,8]. Next, we removed 53 samples who had unexpected duplicates or probable relatives (PI-HAT > 0.20). Then, SNPs were filtered out if they showed a variant call rate < 0.95, a minor allele frequency (MAF) < 0.01, a missing genotype data (mind) < 0.90, or a Hardy-Weinberg Equilibrium (HWE) $p < 10^{-5}$ within each dataset.

For imputation, autosomal variants were aligned to the 1000G genomes phase 1v3 reference panel. Imputation was performed using the Michigan imputation Server 4.0 in 5Mb chunks with 500kb buffers, filtering out variants that were monomorphic in the Genome Asia Pilot (GAsP). Chunks with 51% genotyped variants or concordance rate < 0.92 were fused with neighbouring chunks and re-imputed. Finally, imputed variants were filtered out for $r^2 < 0.60$, MAF < 0.02, mind < 0.1, HWE $p < 10^{-}$

[5] using Plink (v1.90). After quality control procedures had been performed, 2,415 children with 4,261,603 SNPs were included in the final analysis. Association analyses were performed using PLINK, fitting an additive model to the linear regression model with adjustment for sex, age, and the first two principal components [8].

Biological annotations

Genome-wide significant variants and the closest gene(s) were annotated using external reference data through FUMA v1.3.6a [9] (unless otherwise specified) and evaluated for functional or regulatory impact. Specifically, we considered the following annotations of SNPs reaching genome-wide significance ($p < 5 \times 10^{-8}$) (Supplementary Table 10):

- **Gene context:**
    - **Distance:** The distance of the variant to the nearest gene in kb. Variants within the gene body or 1 kb up- or downstream of the transcription start site (TSS) or transcription end site (TES) have a value of zero.
    - **Function:** Whether a variant is intergenic or the functional region in which the variant is located within a gene or RNA locus (e.g., 5' UTR).
- **Combined Annotation Dependent Depletion (CADD) score:** A score of the deleteriousness of variants computed from 63 integrated annotations [10]. The higher the score, the more deleterious a variant is: 12.37 is the threshold indicated by the study of potentially actionable exonic pathogenic single-nucleotide variants in European- and African ancestry patients [11].
- **RegulomeDB category (RDB):** A variant classification system in which variants are grouped according to evidence of having a functional consequence from Category 6 (minimal evidence) to Category 1a (likely to affect binding and linked to expression of a gene target) [12].
- **Chromatin state:** The minimum and the most common 15-core chromatin state across 127 tissue/cell types predicted by ChromHMM [13] from 15 (quiescent/low) to 1 (active TSS).

- **GWAS Catalog:** SNP-trait associations reported in the NHGRI-EBI Catalog of human GWAS [14], including for each variant: the trait(s), the effect allele(s), the PubMed ID(s), the study title(s) and the study sample size(s) (Supplementary Table 2).

And the following annotations of genes which were significant in genome-wide gene-based tests (Supplementary Table 12):

- **Probability of Loss-of-function Intolerance (pLI) score:** A score of intolerance to functional mutation from the ExAC database [15] ranging from zero to one. The closer the score is to one, the more intolerant the gene is to loss-of-function mutations. The threshold suggested by Lek, et al. [15] for likely disease-causing variants is ≥ 0.9.
- **Non-coding Residual Variation Intolerance Score (ncRVIS):** A score of intolerance to mutation to non-coding variants [16]. Where ncRVIS is zero, the gene has the average number of non-coding variants given its total mutational burden; when ncRVIS is greater than zero, the gene has less non-coding variation than expected; when ncRVIS is less than zero, it has more. The ncRVIS percentile reflects the rank of the gene amongst all genes. The more negative the ncRVIS, or the lower the percentile, the more intolerant to non-coding variation the gene is.
- **Residual Variation Intolerance Score (ncRVIS) percentile:** As for ncRVIS score but the percentile of the average RVIS score for the whole gene sequence.
- **Non-coding Genomic Evolutionary Rate Profiling (ncGERP) score:** Identifies constraint in non-coding regions by quantifying deficits in substitutions [16]. It is calculated by taking the average GERP++ score (see Davydov, et al. [17]) across the non-coding sequence. The higher the ncGERP score, the fewer substitutions are present than what would be expected as a result of a neutral rate of evolution, and thus the more conserved are the non-coding regions of the gene. The ncGERP percentile reflects the rank of the gene amongst all genes.

- **Protein-coding Genomic Evolutionary Rate Profiling (pcGERP) percentile:** As for ncGERP score but the percentile of the average GERP score for protein-coding sequence [16].
- **Non-coding Combined Annotation Dependent Depletion (CADD) score:** As for CADD score but the average variant score across the non-coding sequence of the gene [16].
- **Non-coding Genome-Wide Annotation of Variants (ncGWAVA) score:** Predicts the combined functionality of non-coding variants across non-coding sequence [16]. It is the average GWAVA score (see Ritchie, et al. [18]) of variants in the non-coding sequence, ranging from zero to one. The closer ncGWAVA is to one, the more likely the variants in non-coding regions of the gene are functional.
- **Expression in the brain:** Average log2 expression in transcripts per million (TPM) per tissue type per gene from the GTEx v8 dataset [19] for 12 brain tissues: Amygdala, Anterior Cingulate Cortex, Caudate Basal Ganglia, Cerebellar Hemisphere, Cerebellum, Cortex, Frontal Cortex, Hippocampus, Hypothalamus, Nucleus Accumbens Basal Ganglia, Putamen Basal Ganglia, and Substantia Nigra (Supplementary Table 15).

Partitioned heritability

Evolutionary analysis

Enrichment of heritability was estimated for the following evolutionary annotations (as described in Tilot, et al. [20]):

- **Human Gained Enhancers and Promoters:** These regulatory regions were identified based on differential H3K27ac and H3K4me2 patterns in the adult and foetal brain tissues of humans, macaques and mice [19, 20], and shown to be present to a significantly lesser degree in macaques and mice. Thus, these regulatory elements were gained in the last 30 million years of human evolution and may be involved in the emergence of human-specific traits [21,22].

- **Ancient selective sweep regions:** These consist of unusually long genomic regions that reached fixation in human populations possibly due to adaptive advantages in the last 250-650 thousand years [23].
- **Neanderthal-introgressed SNPs:** The genomic variants introduced into the human genome by the admixture of *Homo sapiens* and Neanderthal populations around 50-60,000 years ago [24].
- **Neanderthal Depleted Regions:** Large regions in the human genome that are depleted for Neanderthal ancestry, possibly due to the deleterious effect of the archaic sequences in hybrid individuals [25].

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GENLANG QUANTITATIVE TRAIT CONSORTIUM ACKNOWLEDGEMENTS

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Neurodys

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Netherlands Twin Register (NTR)

Funding from the NWO and ZonMW is gratefully acknowledged: Twin family database for behavior genomics studies (NWO 480-04-004); Longitudinal data collection from teachers of Dutch twins and their siblings (481-08-011), Twin-family-study of individual differences in school achievement (NWO-FES, 056-32-010), Genotype-phenotype database for behavior genetic and genetic epidemiological studies (ZonMw Middelgroot 911-09-032); Genetic influences on stability and change in psychopathology from childhood to young adulthood (ZonMW 912-10-020), Why some children thrive (OCW_Gravity program –NWO-024.001.003), Netherlands Twin Registry Repository: researching the interplay between genome and environment (NWO-Groot 480-15-001/674); BBMRI –NL (184.021.007 and 184.033.111): Biobanking and Biomolecular Resources Research Infrastructure; Spinozapremie (NWO- 56-464-14192); Amsterdam Public Health (APH) and Amsterdam Reproduction and Development (AR&D) Research Institutes; European Science Council Genetics of Mental Illness (ERC Advanced, 230374); Aggression in Children: Unraveling gene-environment interplay to inform

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The Philadelphia Neurodevelopmental Cohort (PNC)

Support for the collection of the data sets was provided by grant RC2MH089983 awarded to Raquel Gur and RC2MH089924 awarded to Hakon Hakonarson. All subjects were recruited through the Center for Applied Genomics at The Children's Hospital in Philadelphia. Reading performance was assessed as part of the cognitive test battery and collected by Gur et al. (2012). Genotyping was funded by an Institutional Development Award to the Center for Applied Genomics from The Children's Hospital of Philadelphia and a donation from Adele and Daniel Kubert. We would also like to thank the NIH data repository. The dataset analysed was accessed via dbGaP number 19848 and 12043 (Neurodevelopmental Genomics: Trajectories of Complex Phenotypes (phs000607.v3.p2)).

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Saguenay Youth Study (SYS)

The Canadian Institutes of Health Research (ZP, TP), Heart and Stroke Foundation of Quebec (ZP), and the Canadian Foundation for Innovation (ZP) support the Saguenay Youth Study.

SLI Consortium (SLIC)

SLI Consortium members are as follows: Wellcome Trust Centre for Human Genetics, Oxford: D. F. Newbury, N. H. Simpson, F. Ceroni, A. P. Monaco; Max Planck Institute for Psycholinguistics, Nijmegen: S. E. Fisher, C. Francks; Newcomen Centre, Evelina Children's Hospital, St Thomas' Hospital, London: G. Baird, V. Slonims; Child and Adolescent Psychiatry Department and Medical Research Council Centre for Social, Developmental, and Genetic Psychiatry, Institute of Psychiatry, London: P. F. Bolton; Medical Research Council Centre for Social, Developmental, and Genetic Psychiatry Institute of Psychiatry, London: E. Simonoff; Salvesen Mindroom Centre, Child Life & Health, School of Clinical Sciences, University of Edinburgh: A. O'Hare; Cell Biology & Genetics Research Centre, St. George's University of London: J. Nasir; Queen's Medical Research Institute, University of Edinburgh: J. Seckl; Department of Speech and Language Therapy, Royal Hospital for Sick Children, Edinburgh: H. Cowie; Speech and Hearing Sciences, Queen Margaret University: A. Clark, J. Watson; Department of Educational and Professional Studies, University of Strathclyde: W. Cohen; Department of Child Health, the University of Aberdeen: A. Everitt, E. R. Hennessy, D. Shaw, P. J. Helms; Audiology and Deafness, School of Psychological Sciences, University of Manchester: Z. Simkin, G. Conti-Ramsden; Department of Experimental Psychology, University of Oxford: D. V. M. Bishop; Biostatistics Department, Institute of Psychiatry, London: A. Pickles.

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Toronto

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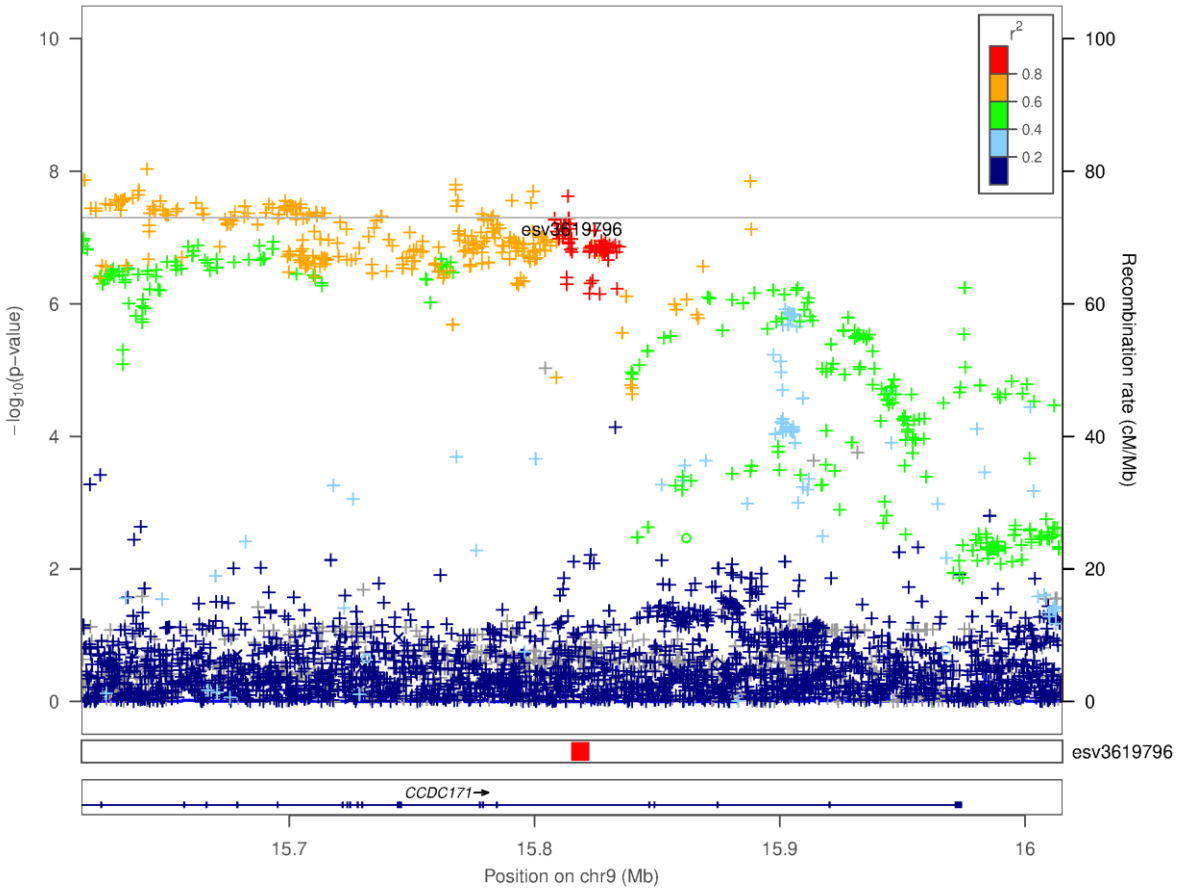
UK Dyslexia

Cohort recruitment and data collection was supported by Wellcome Trust (076566/Z/05/Z and 075491/Z/04) and The Waterloo Foundation (grants to JBTa and SP; 797–1720). Genotype data were generated and analyses funded by the EU (Neurodys, 018696) and the Royal Society (UF100463 grant to SP).

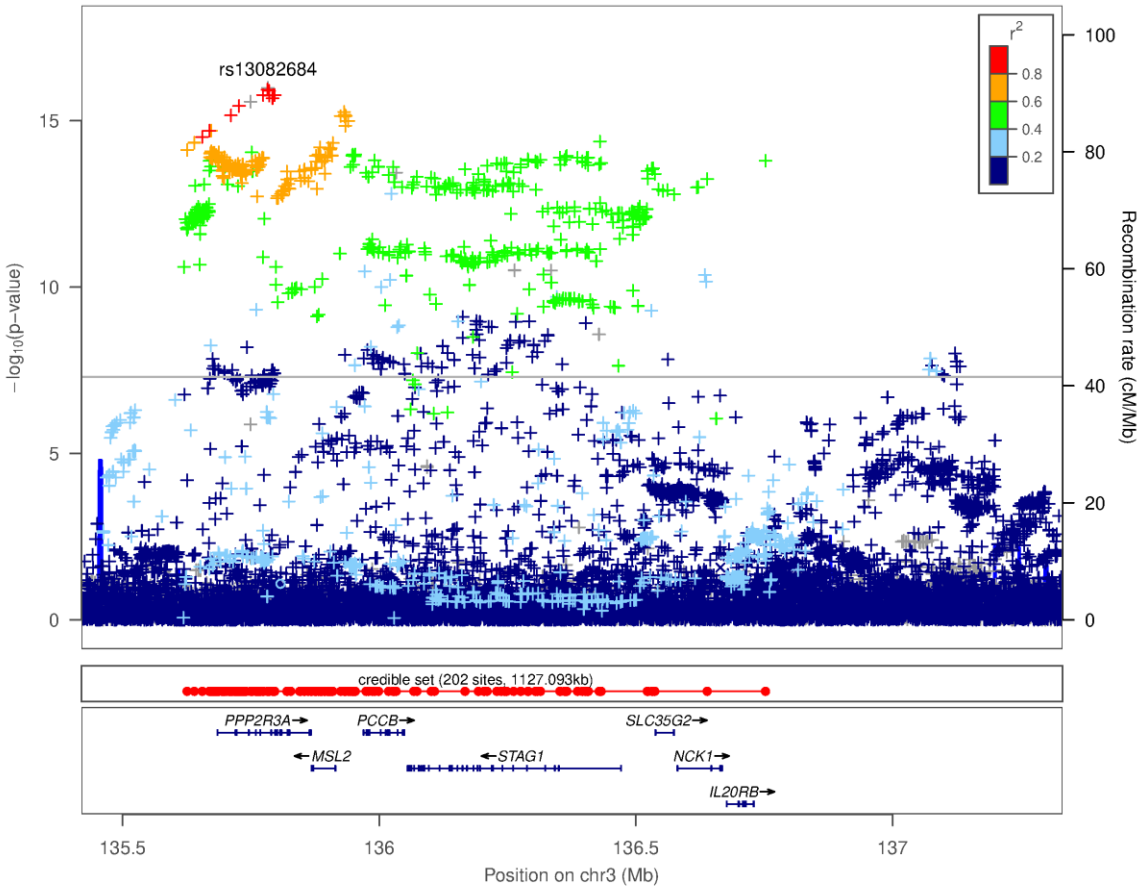
York

The York cohort was funded by Wellcome Trust Programme Grant 082036/B/07/Z.

FIGURES



Supplementary Figure 1.i. Regional association plot which includes information on the credible variant set and known genes in the region for the significant association between dyslexia and chr9p22.3 esv3619796 structural variant nearby rs3122702



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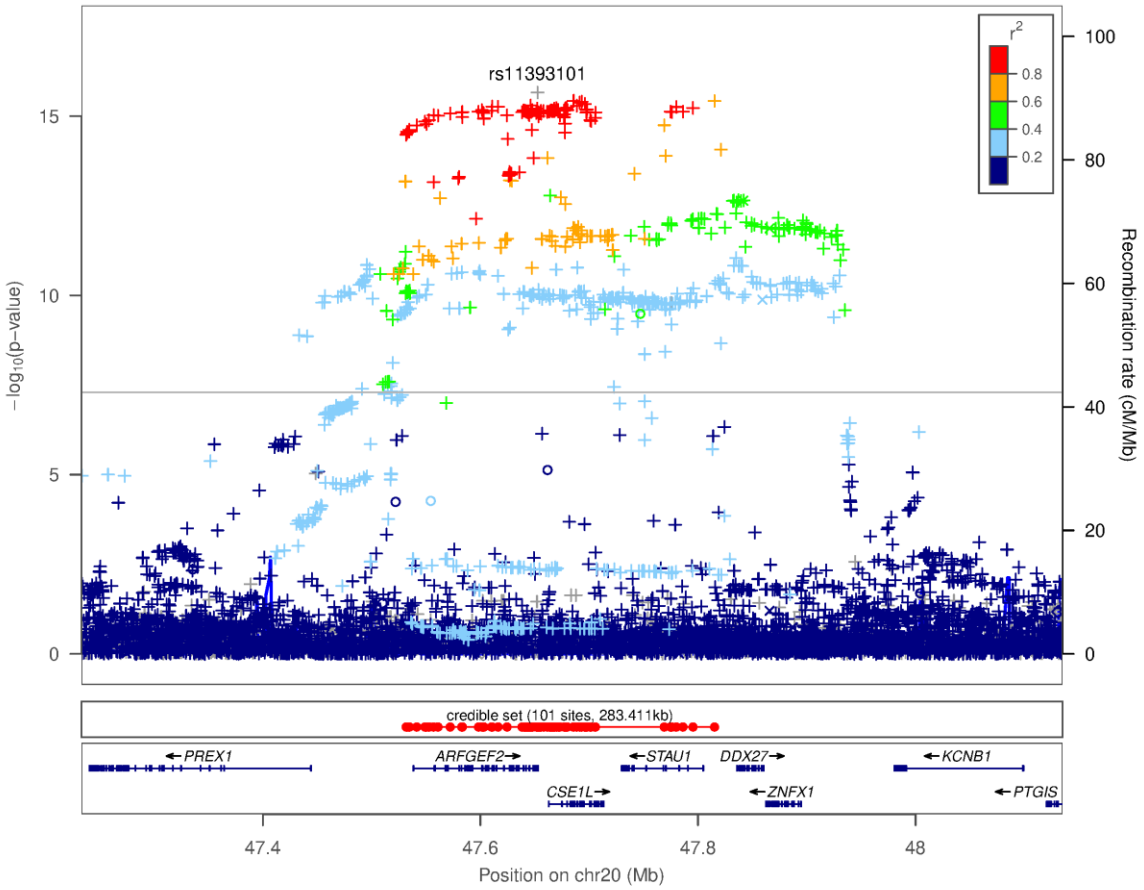

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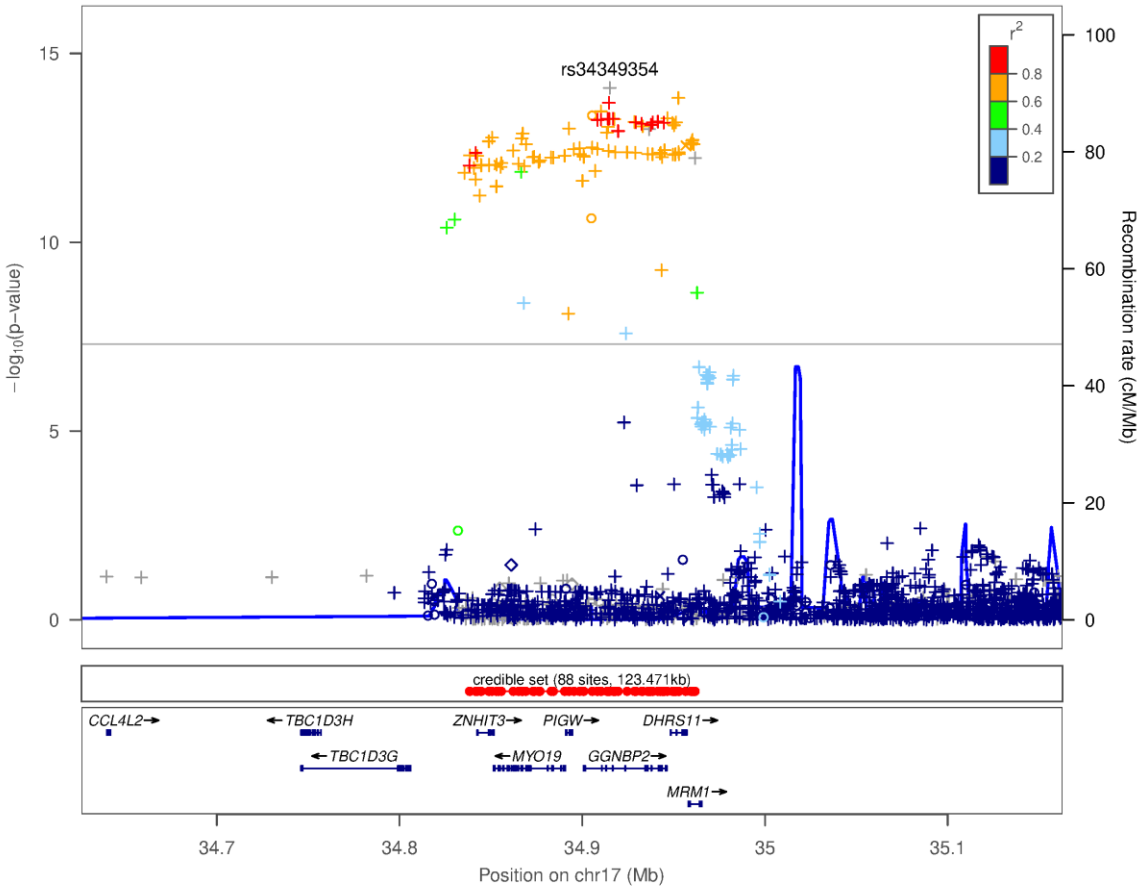

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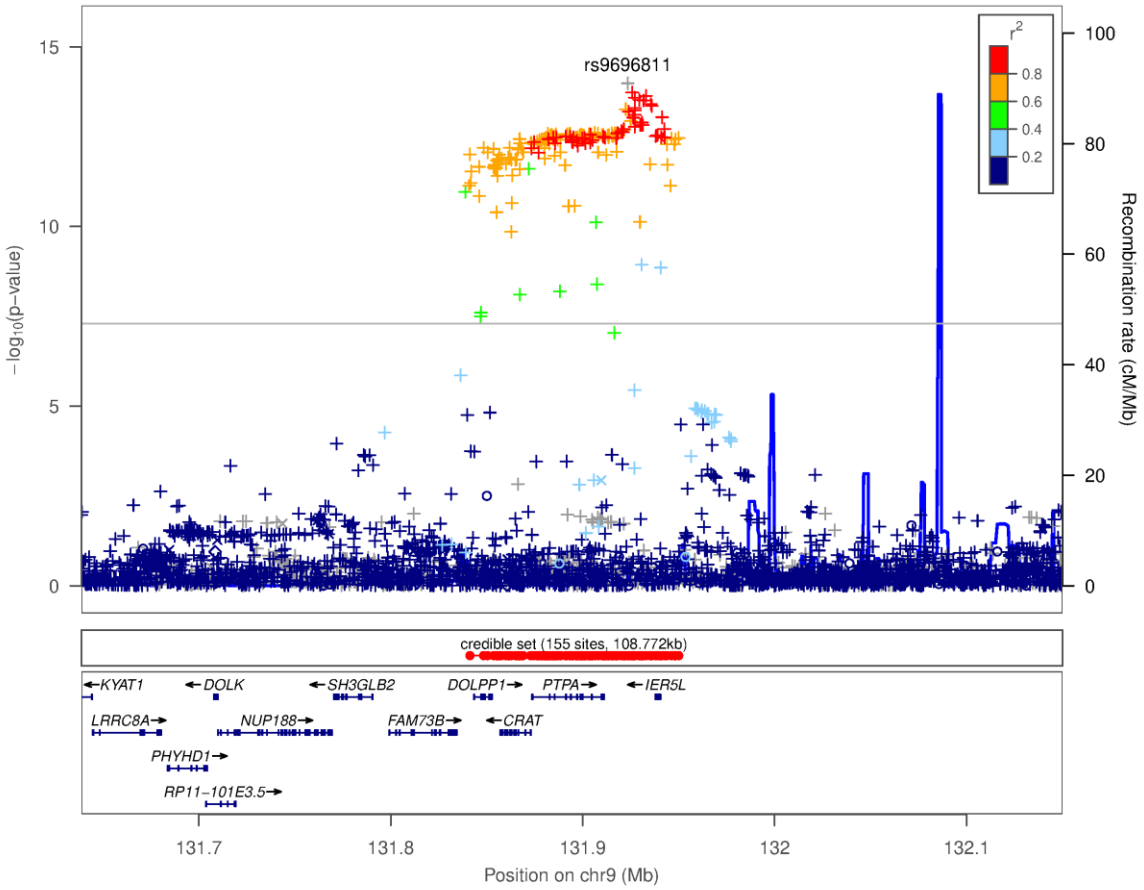

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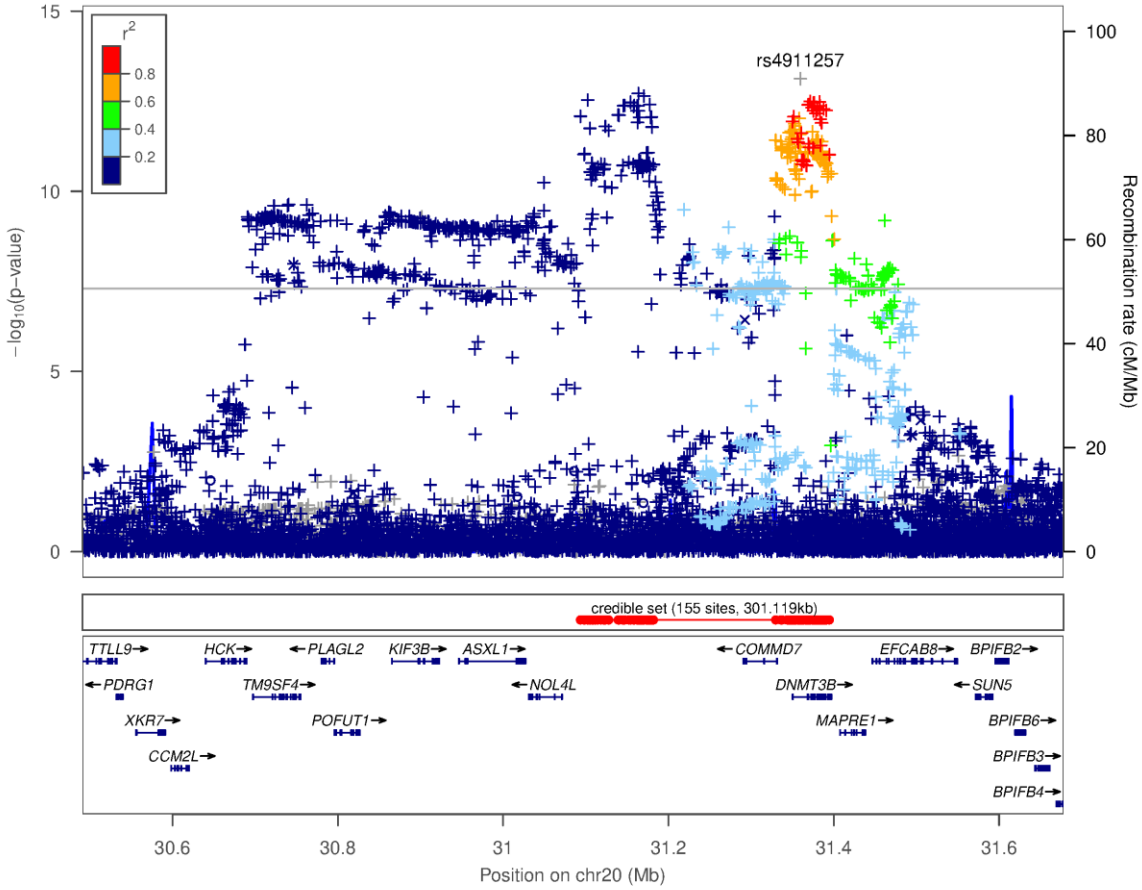

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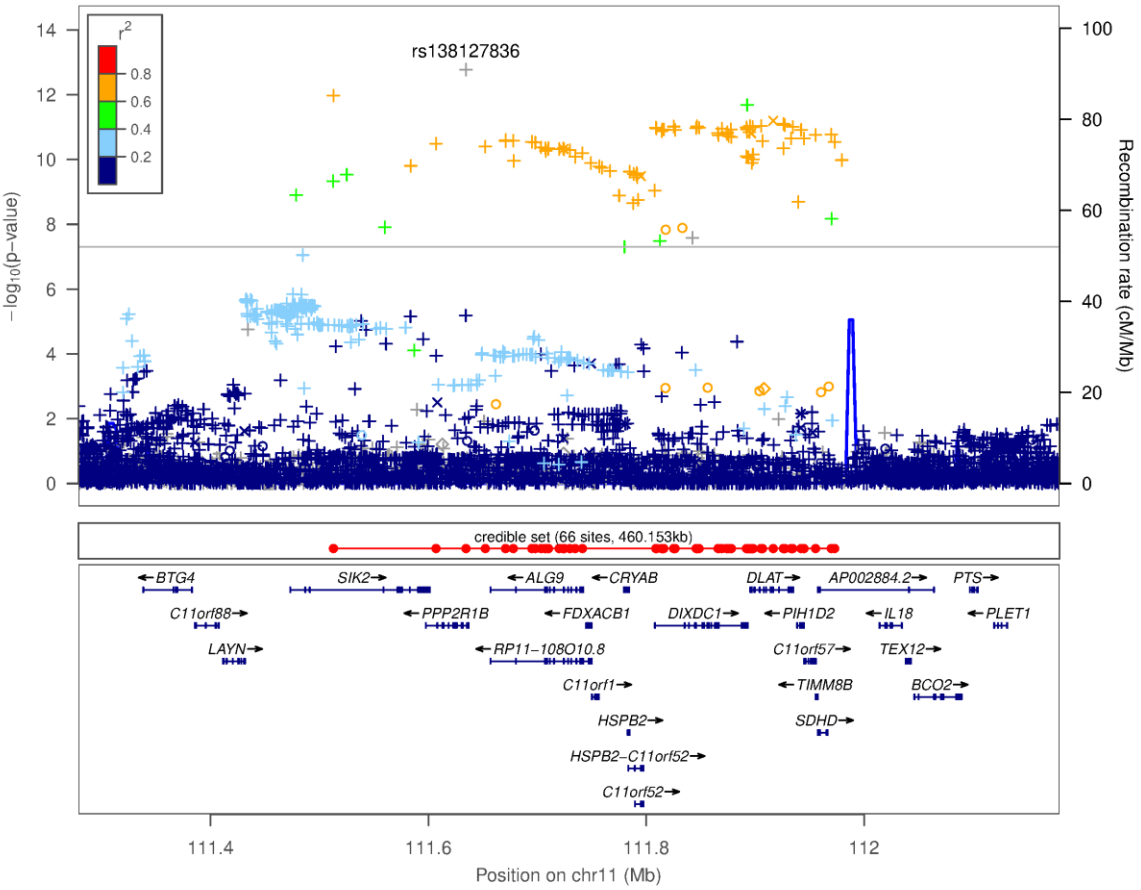

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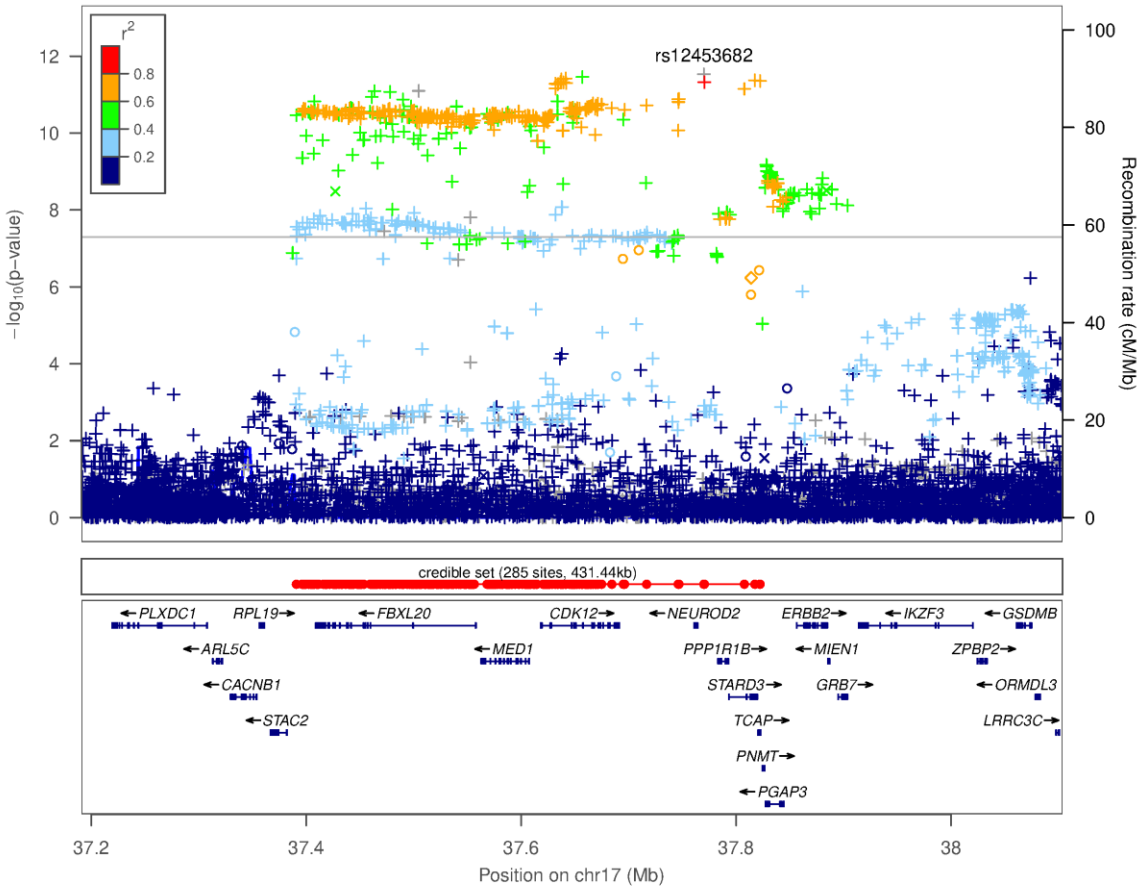

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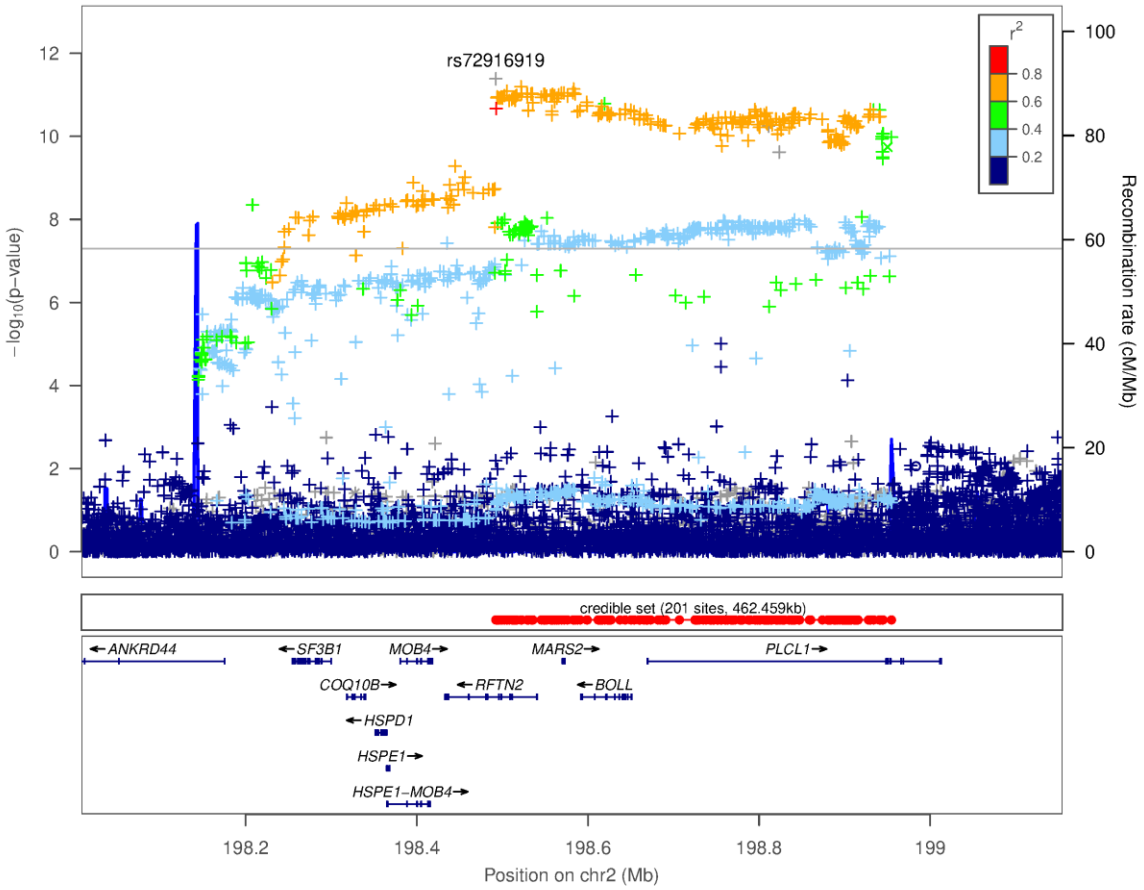
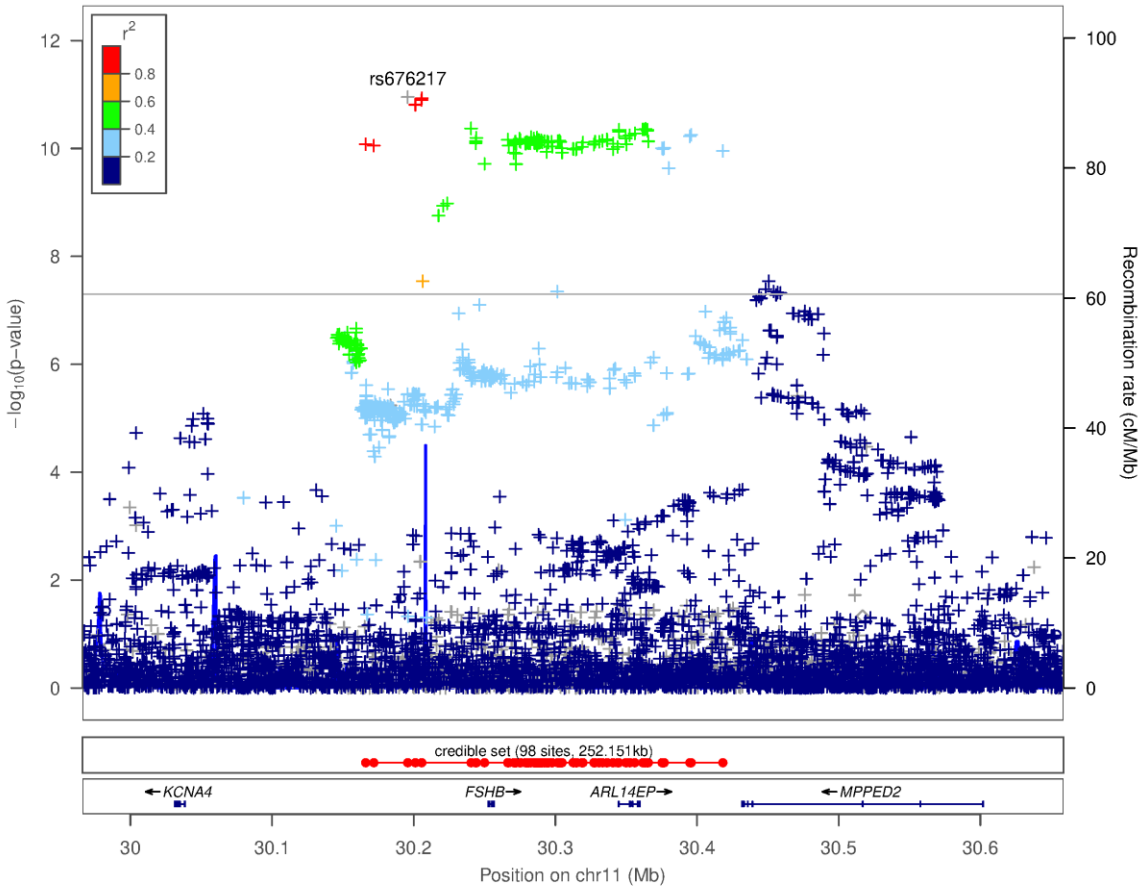
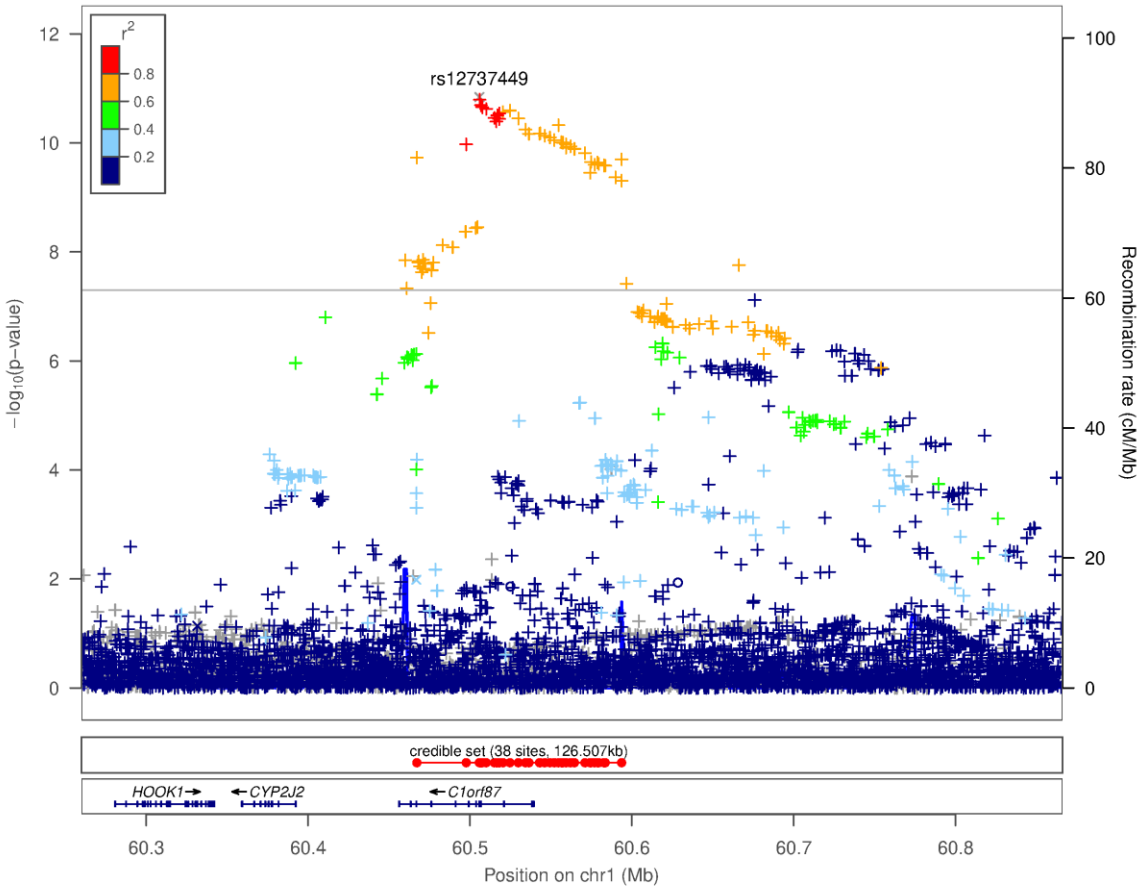


Supplementary Figure 1.ix. Regional association plot which includes information on the credible variant set and known genes in the region for the significant association between dyslexia and chr2q33.1 rs72916919



Supplementary Figure 1.x. Regional association plot which includes information on the credible variant set and known genes in the region for the significant association between dyslexia and chr11p14.1 rs676217



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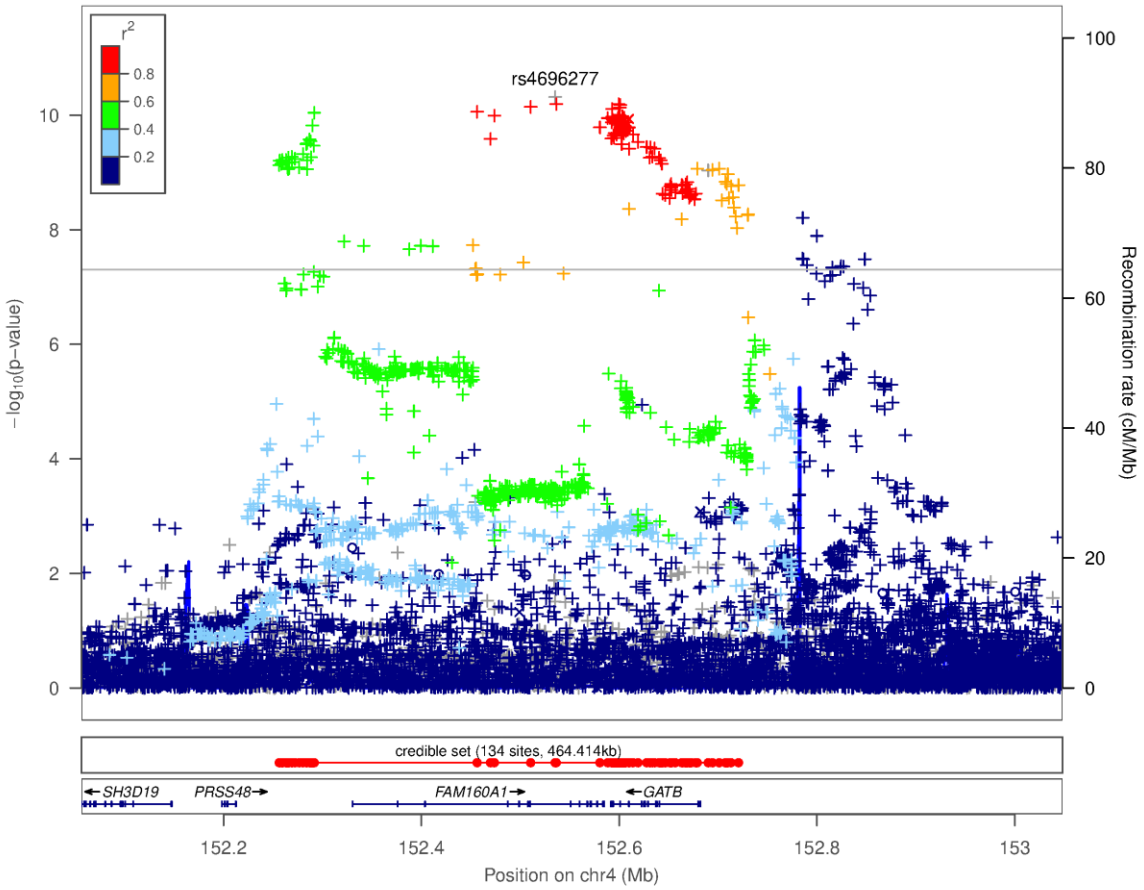

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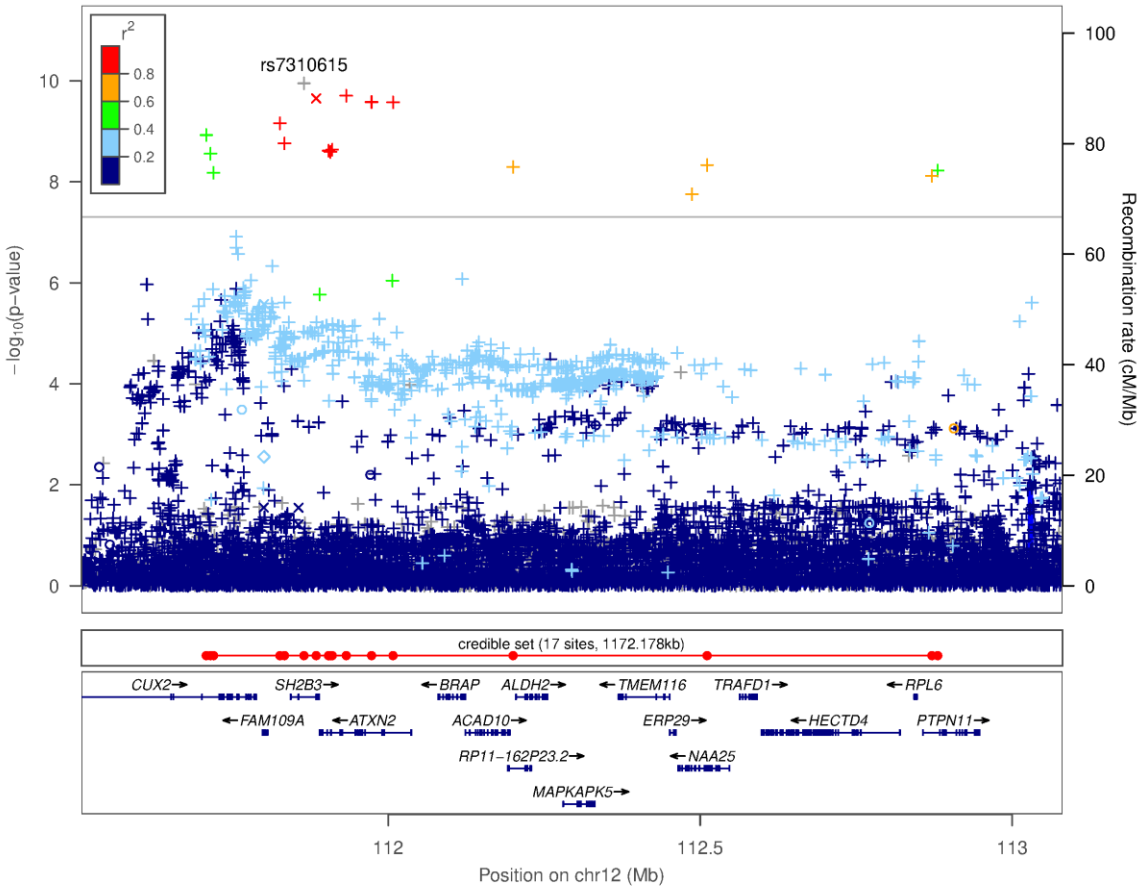

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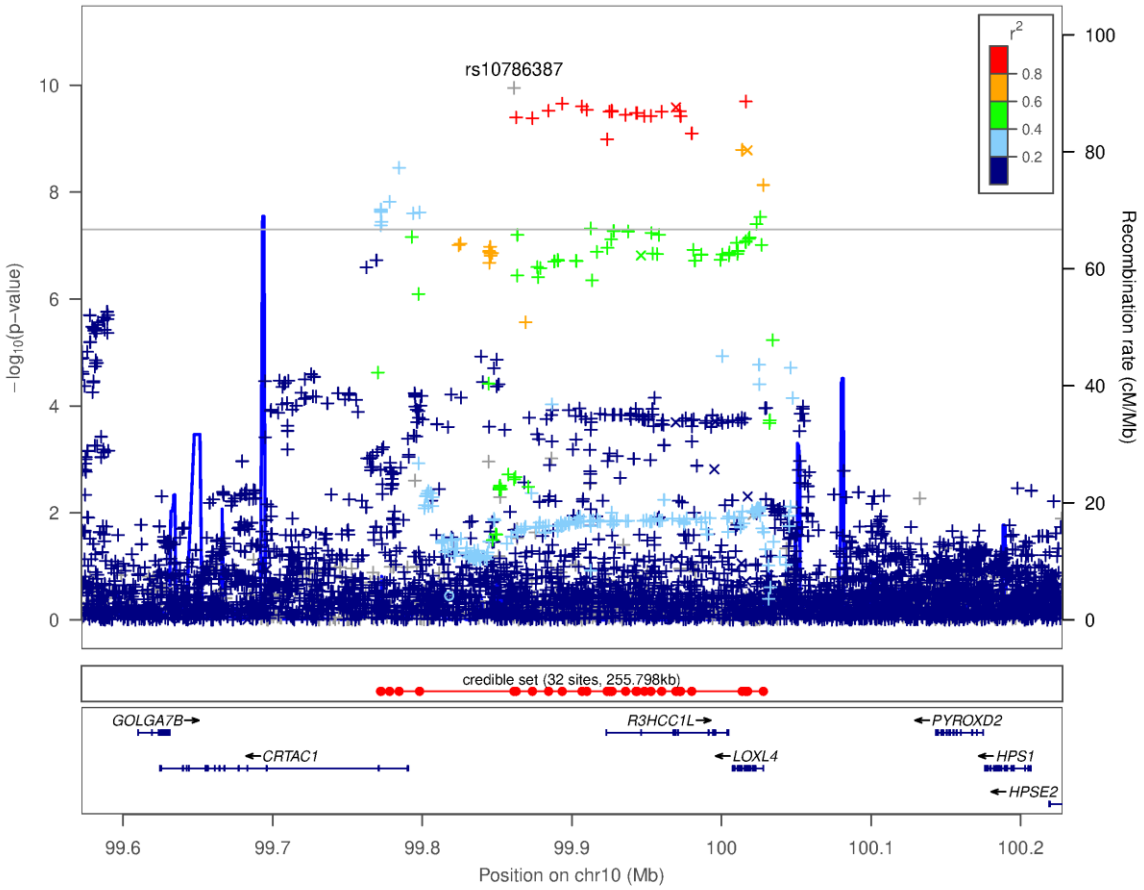

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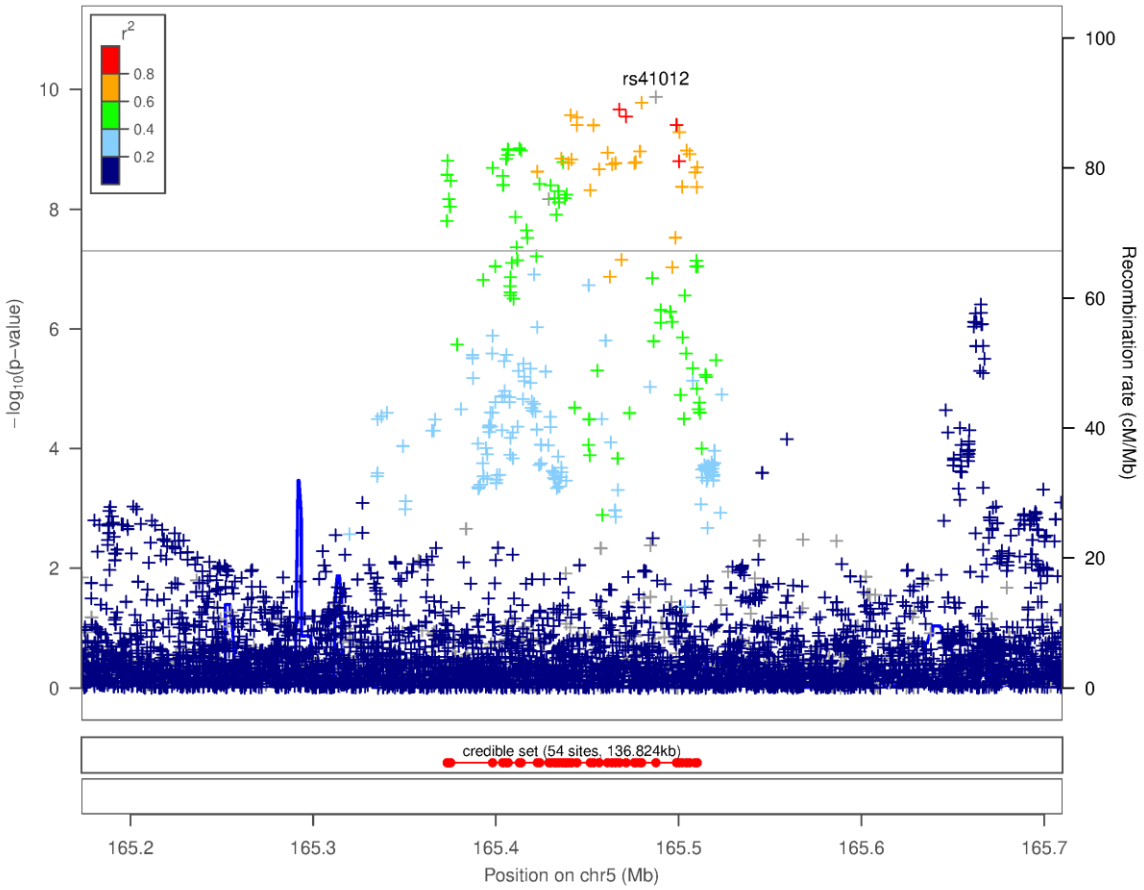

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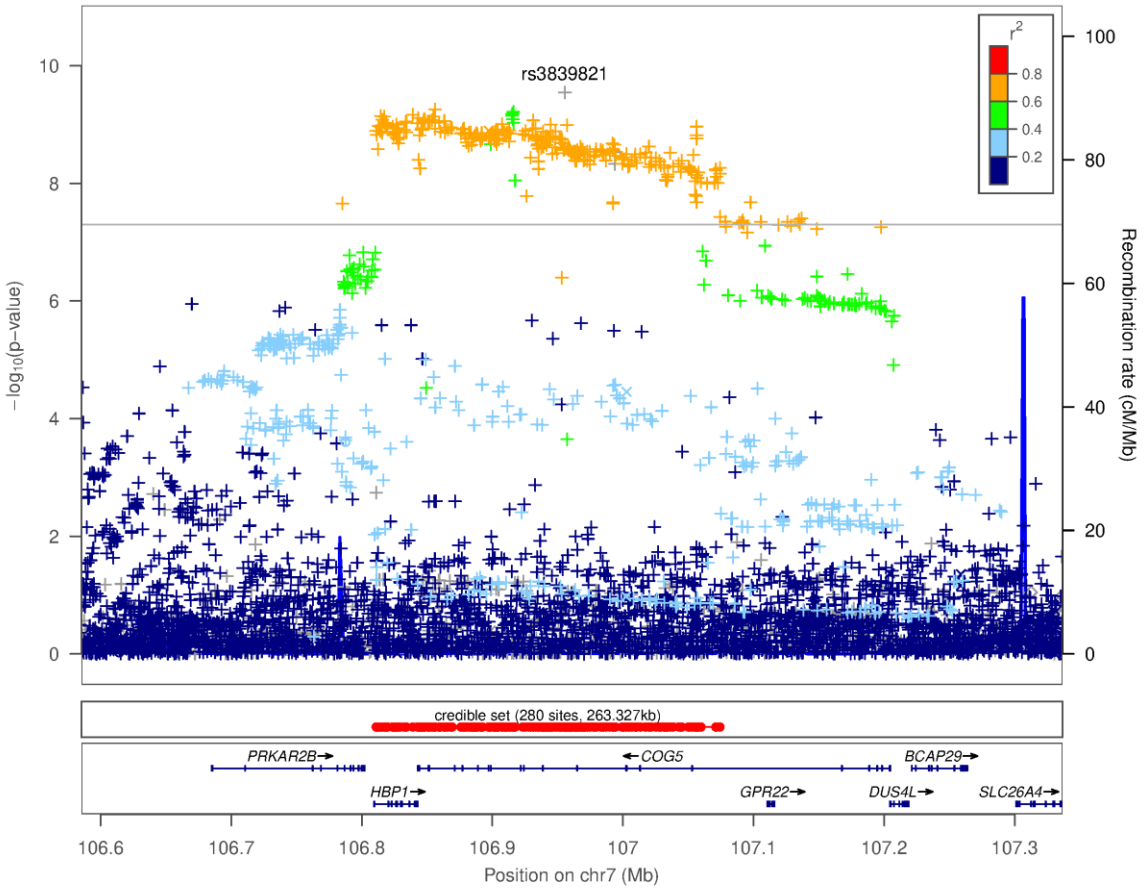

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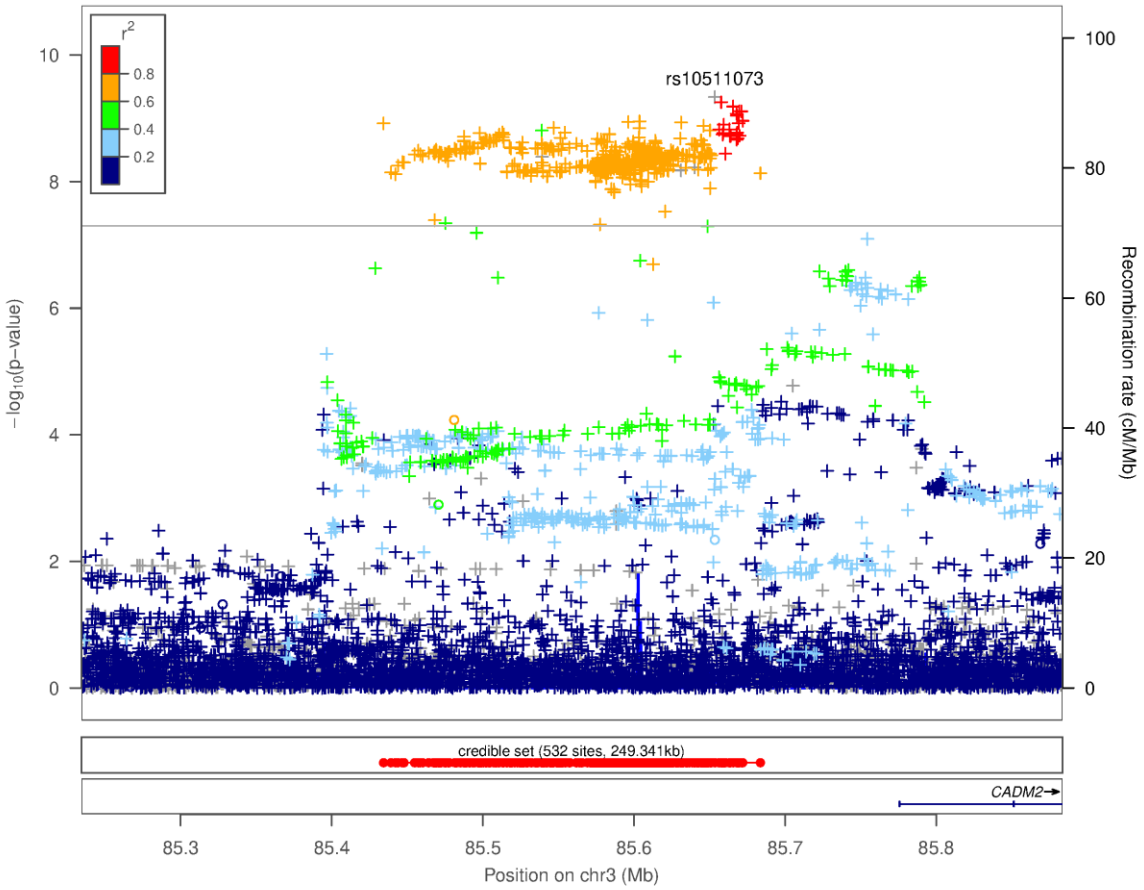

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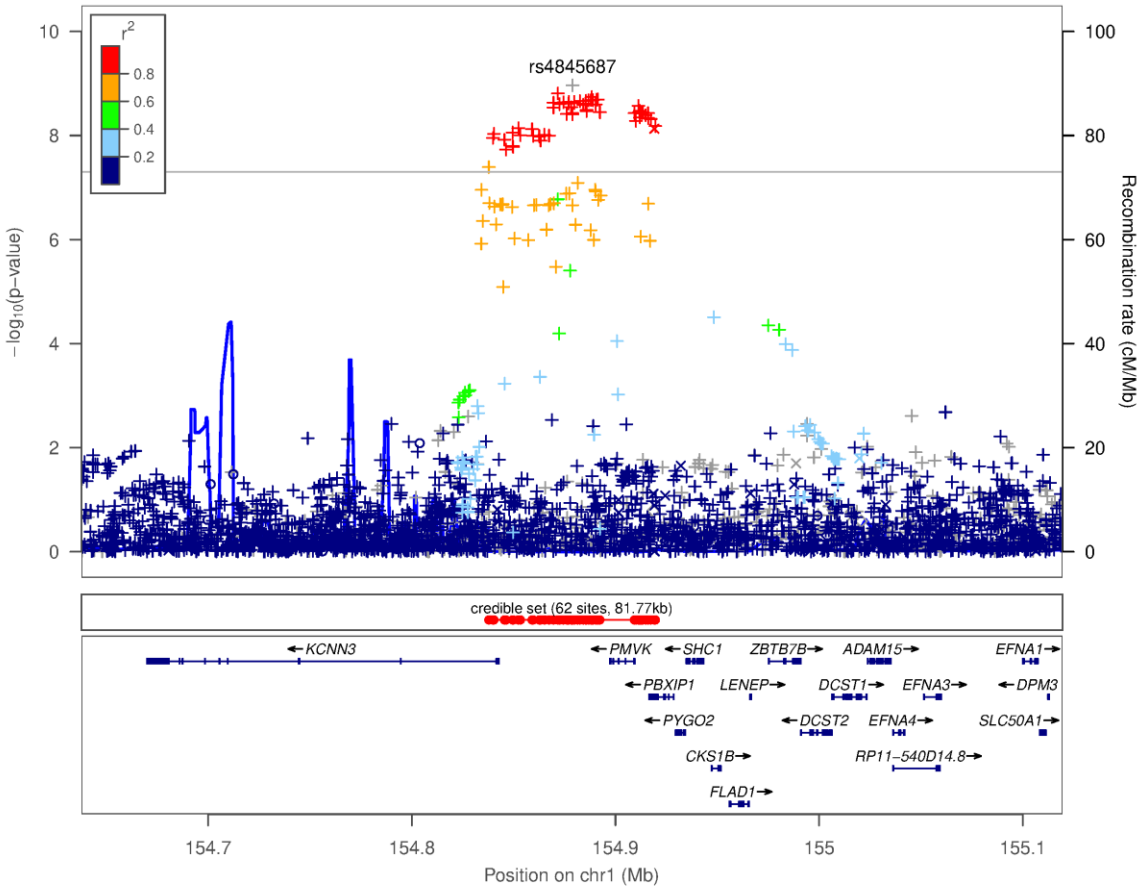

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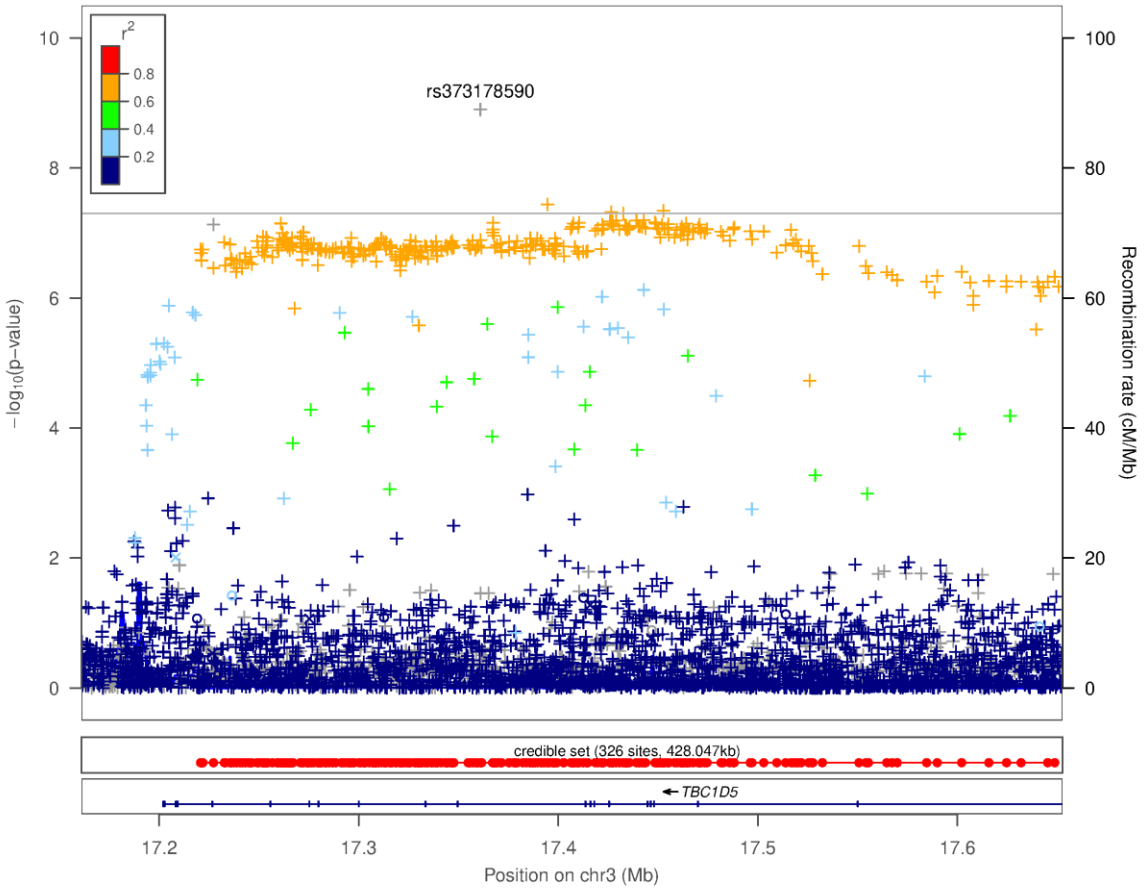

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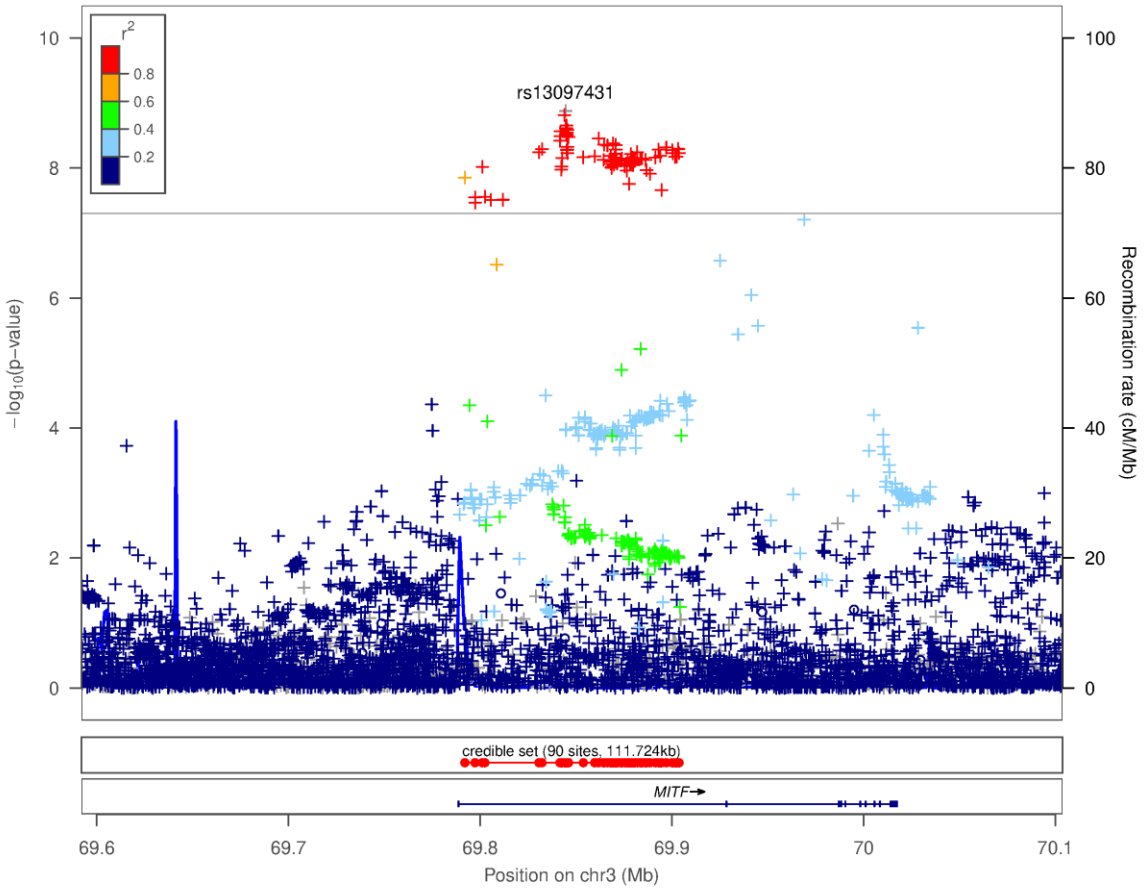

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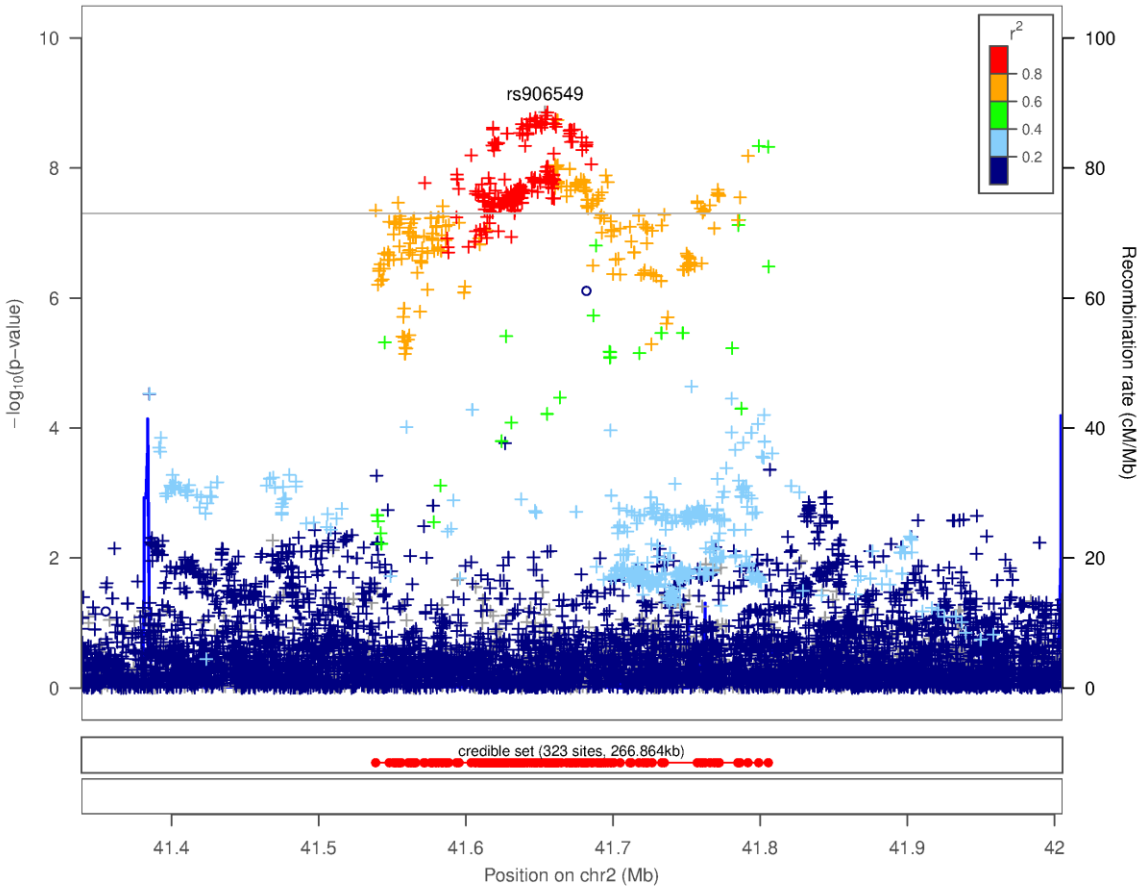

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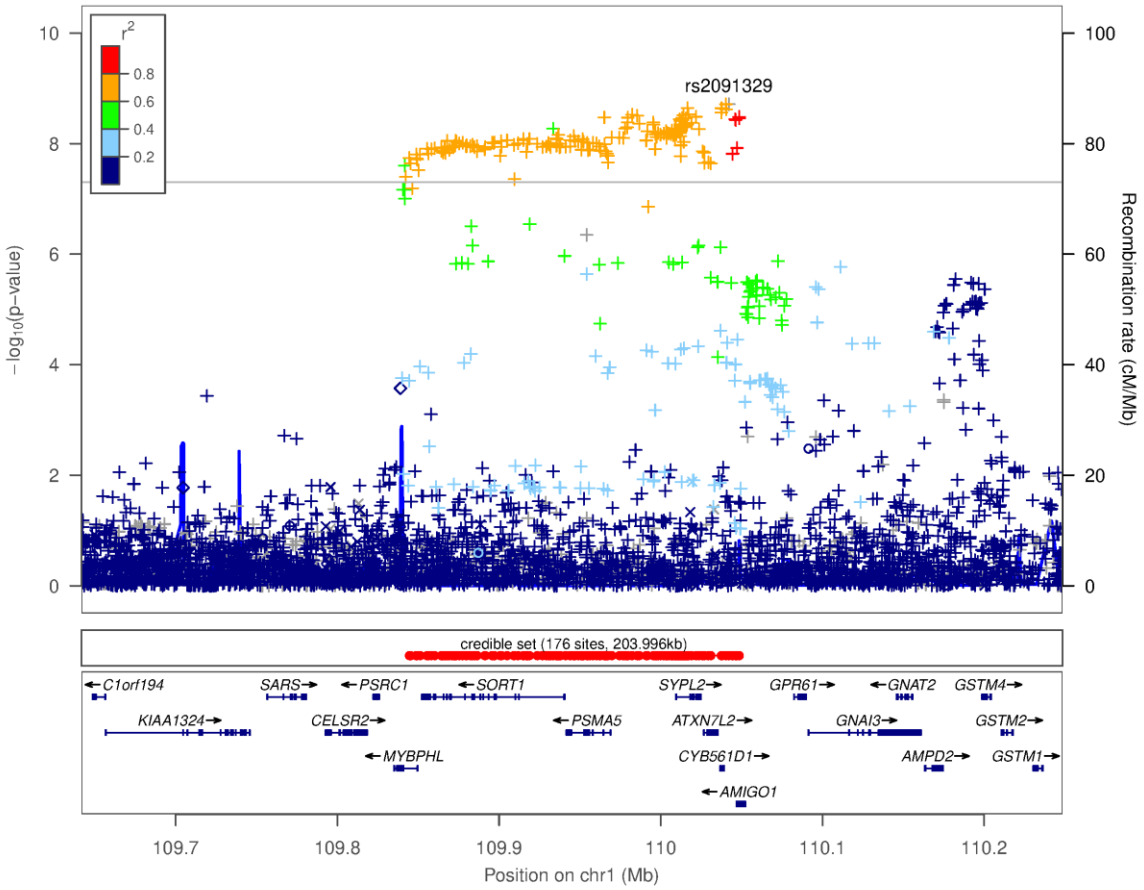

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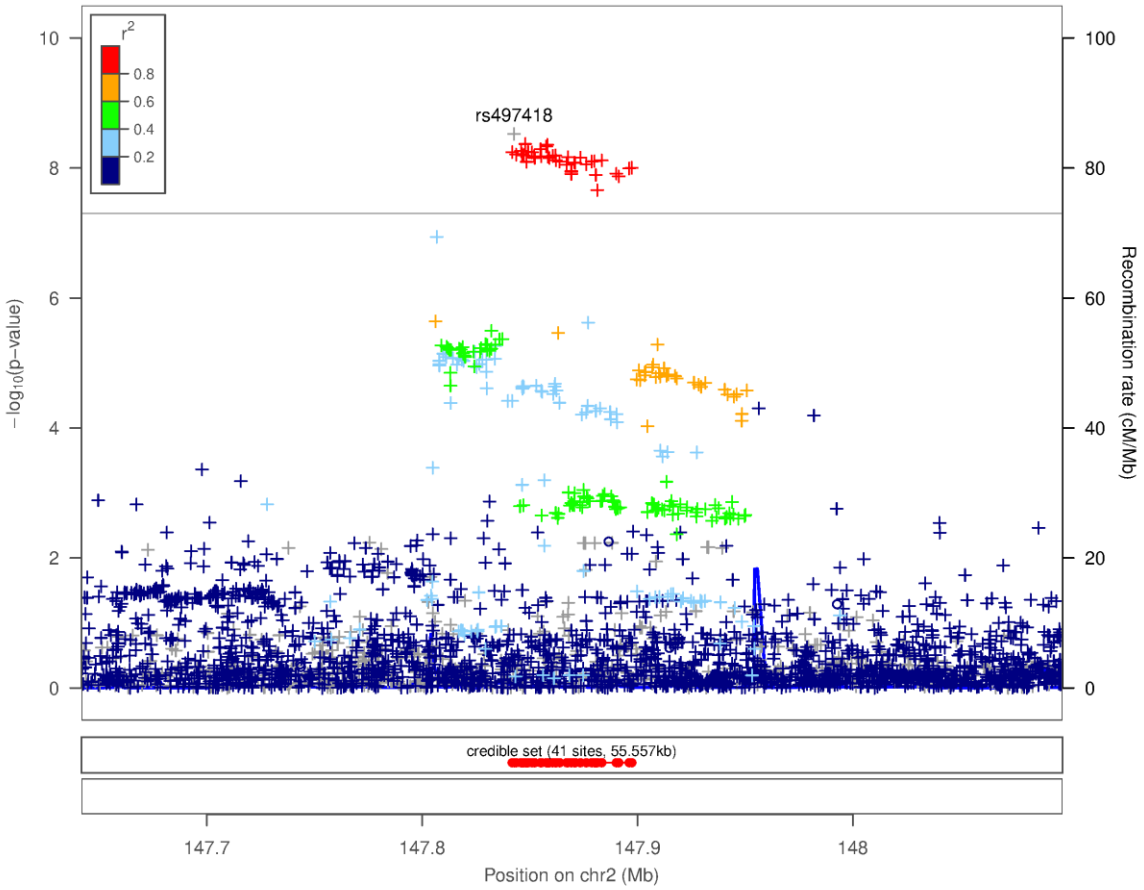

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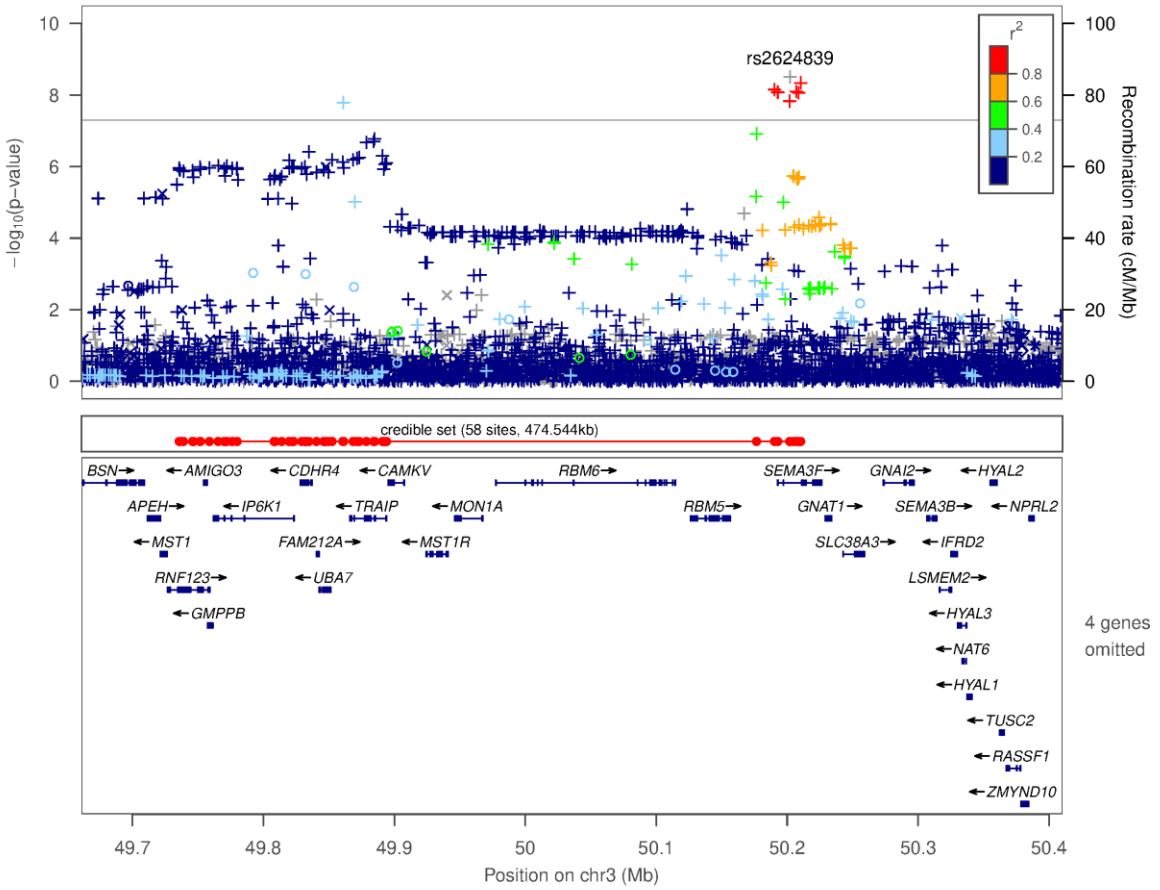

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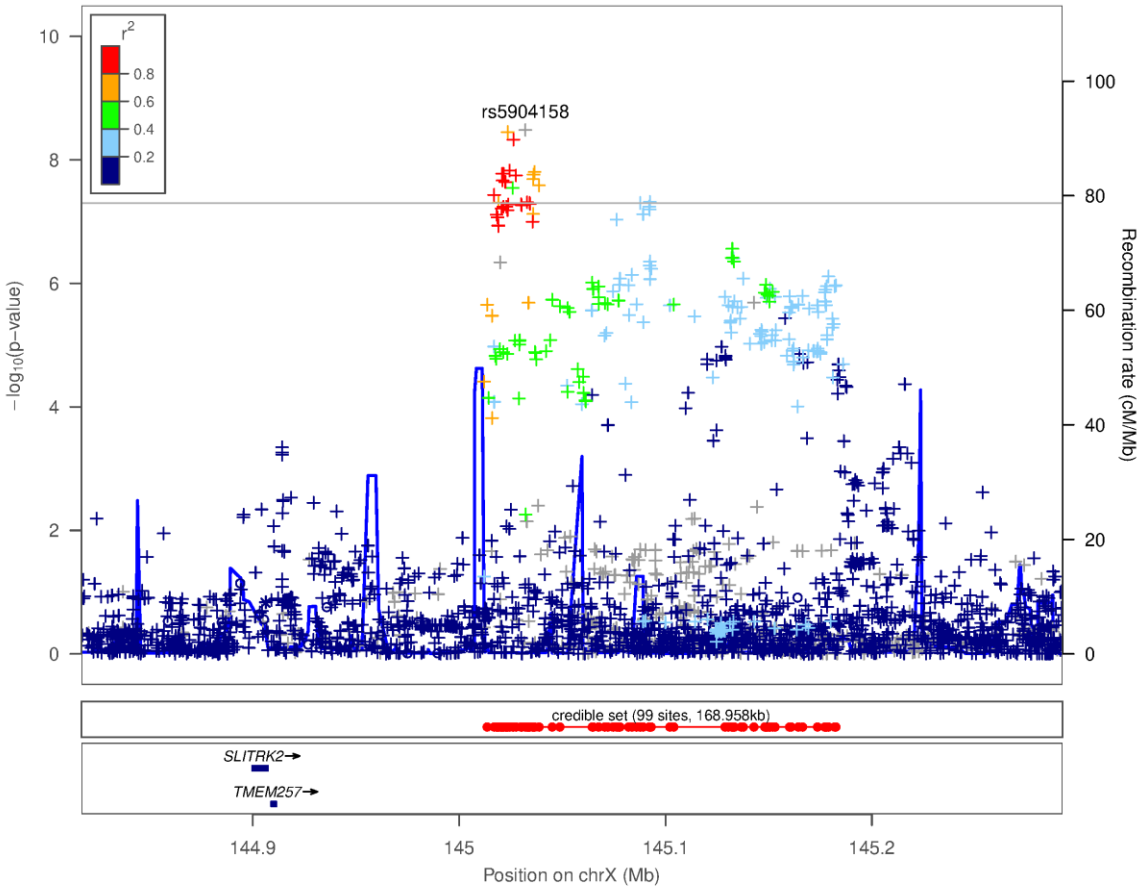

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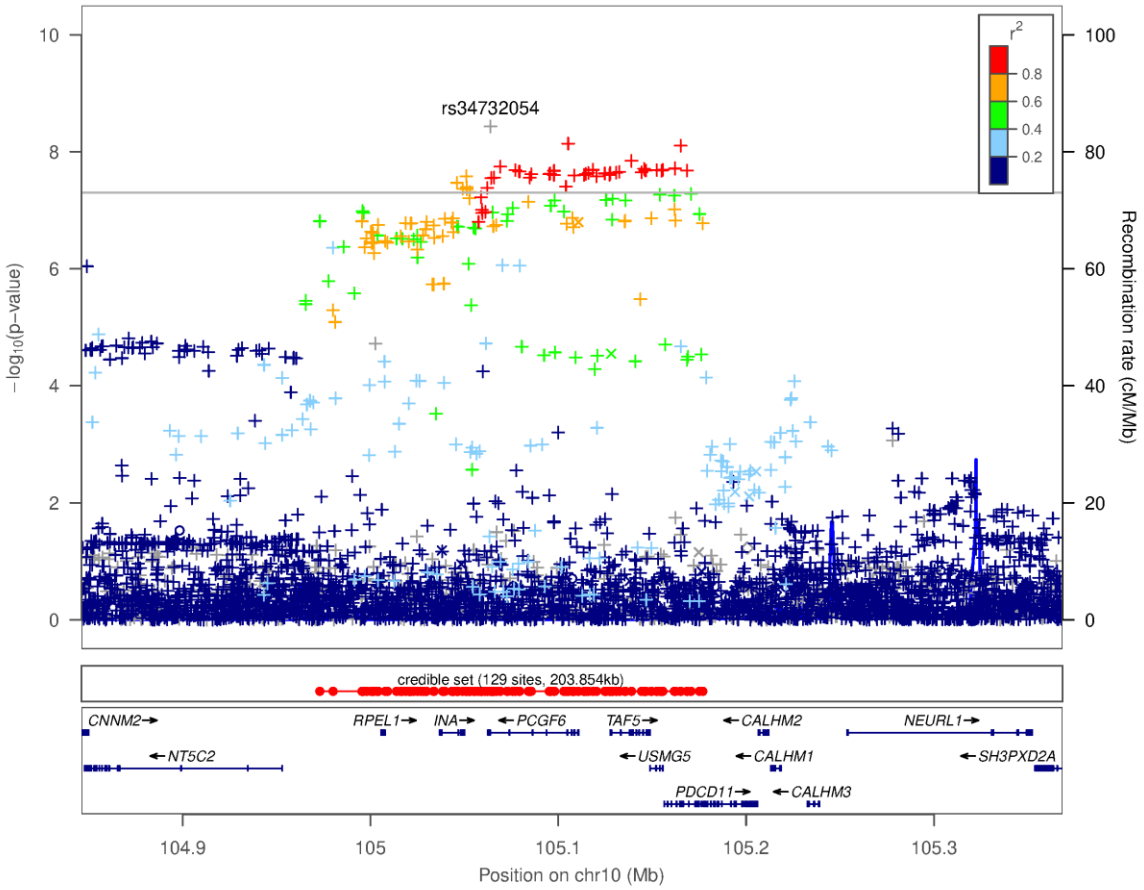

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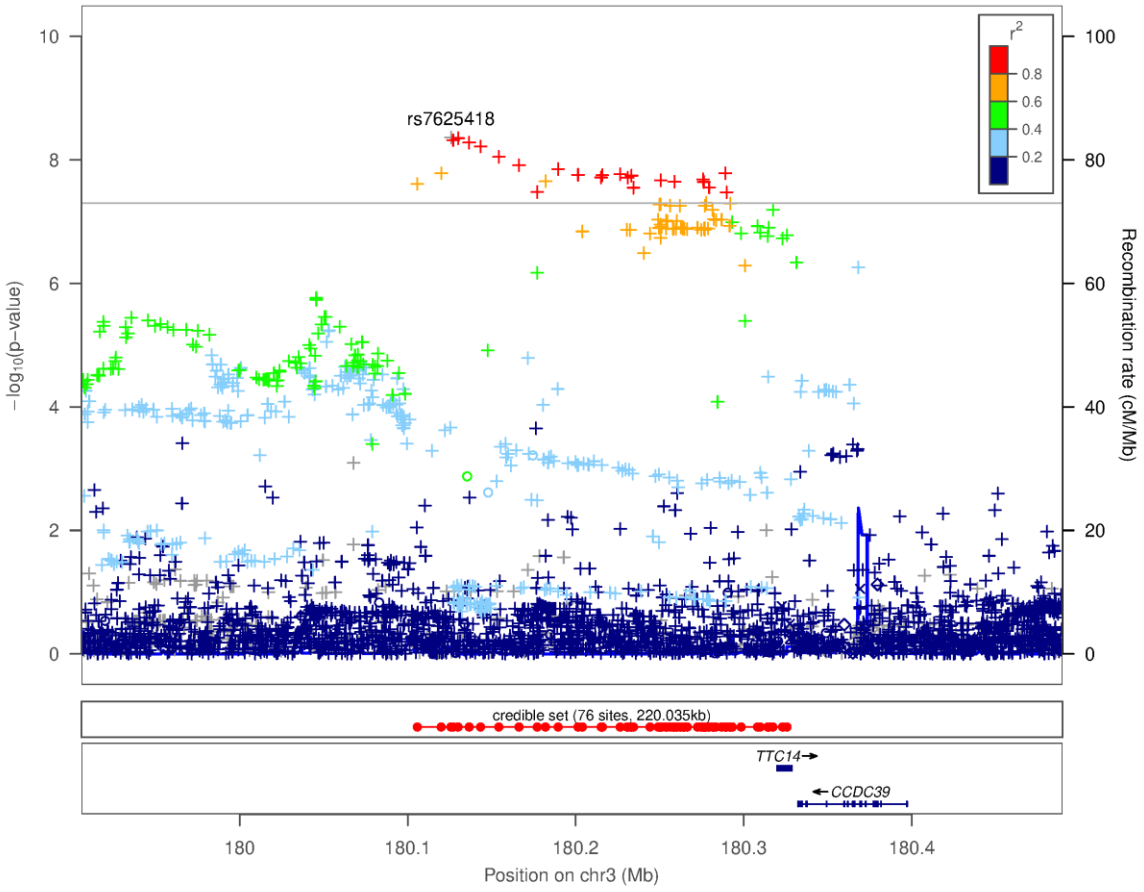

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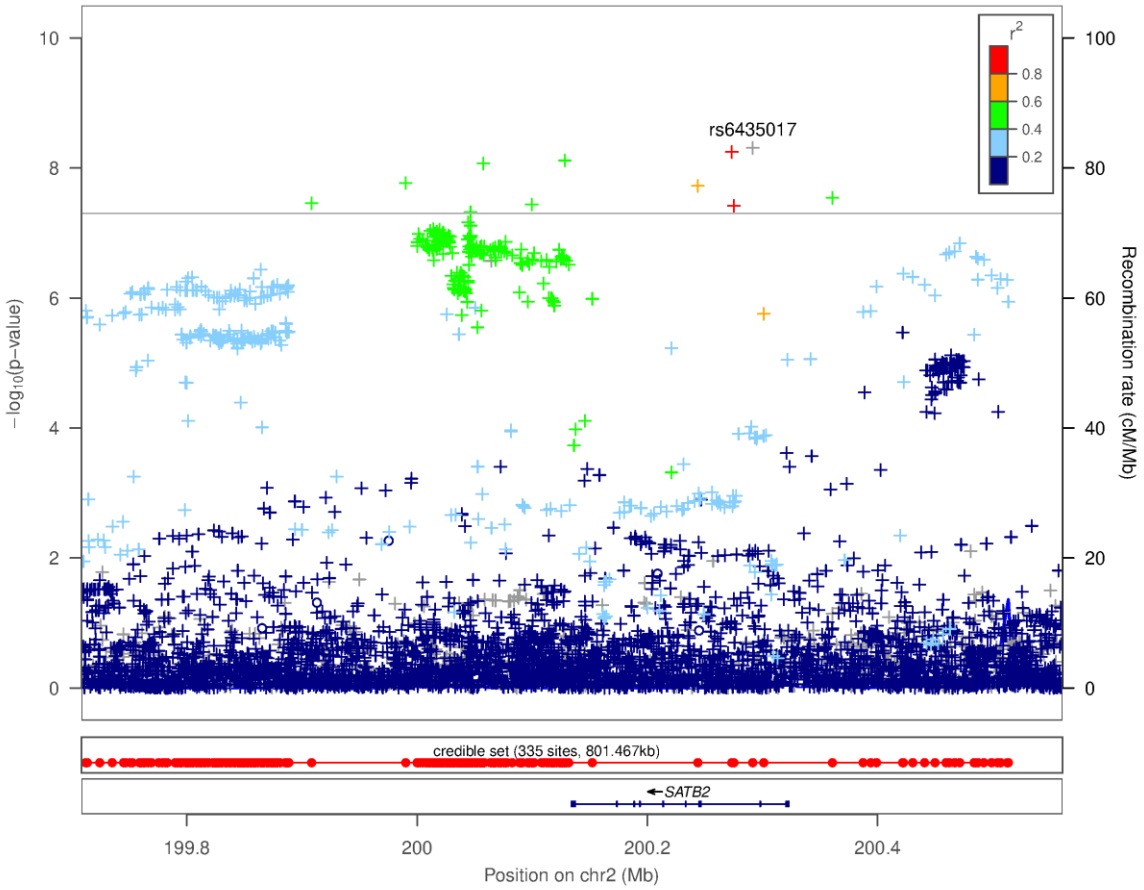

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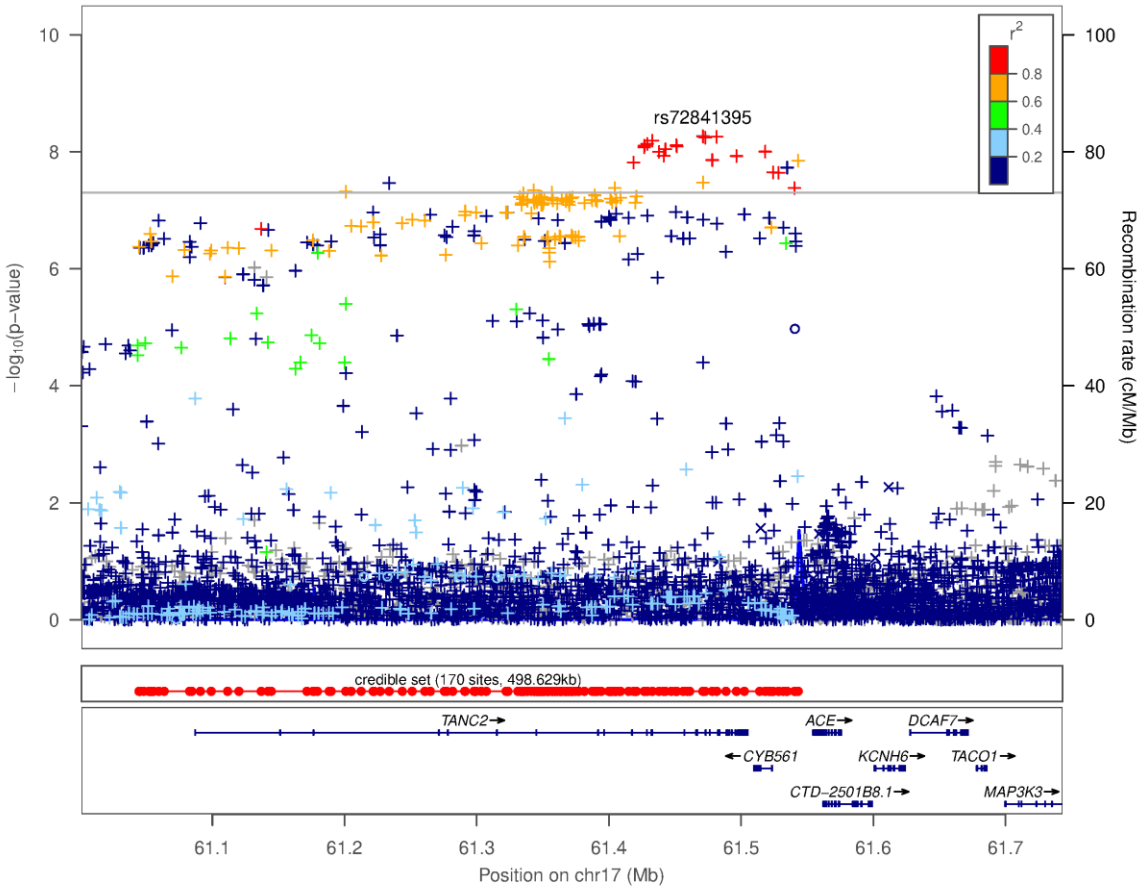

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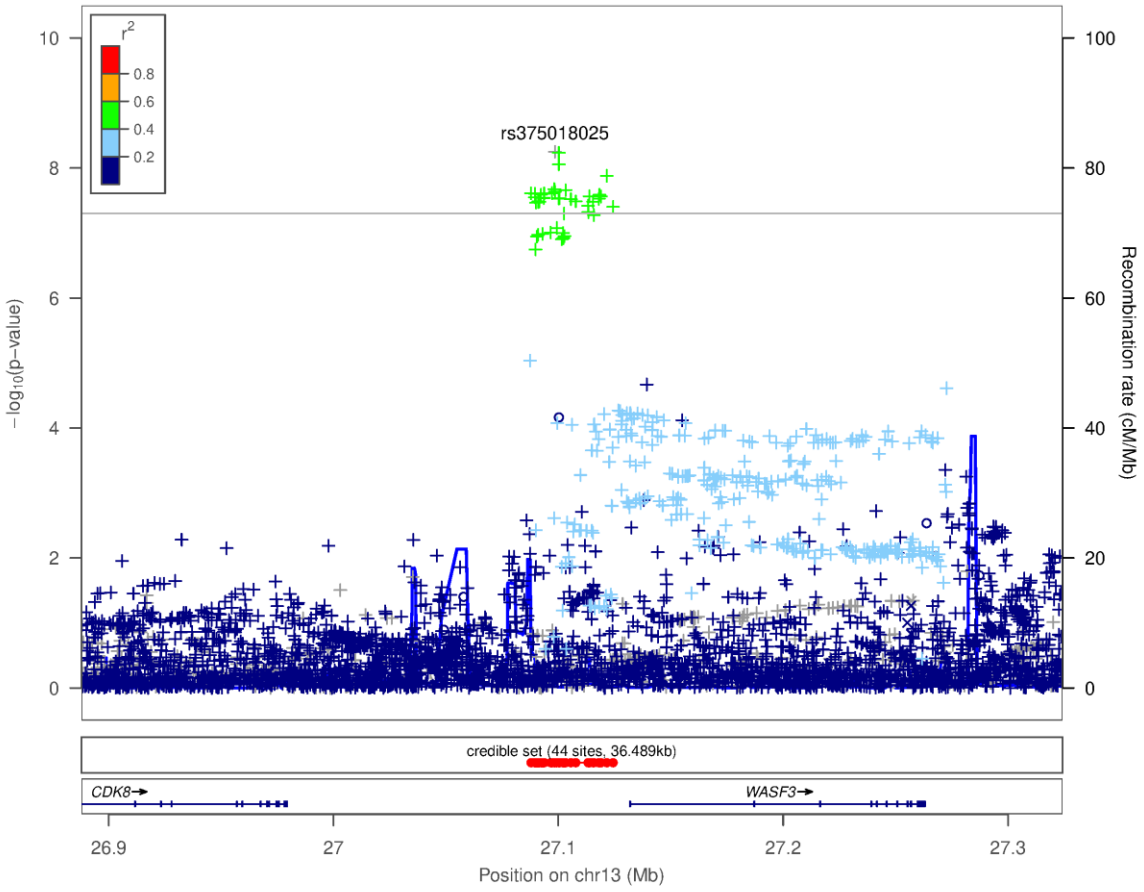

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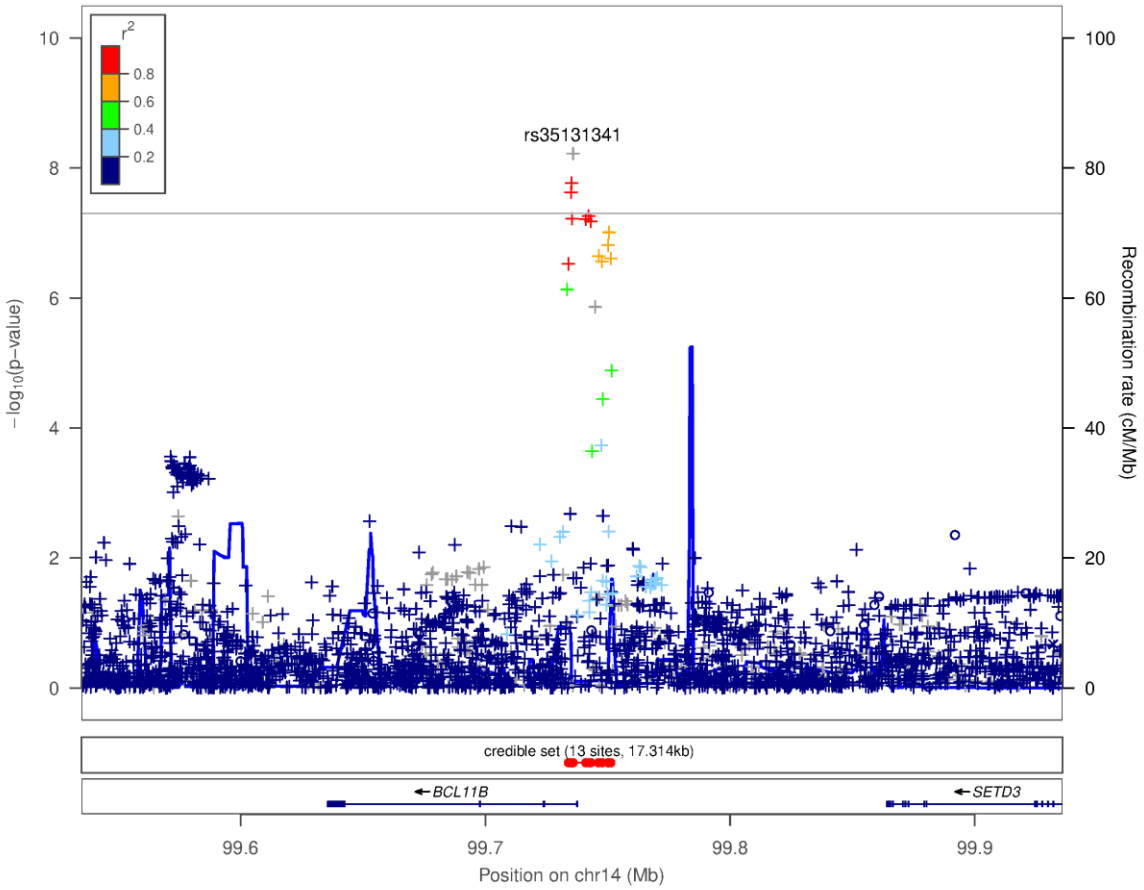

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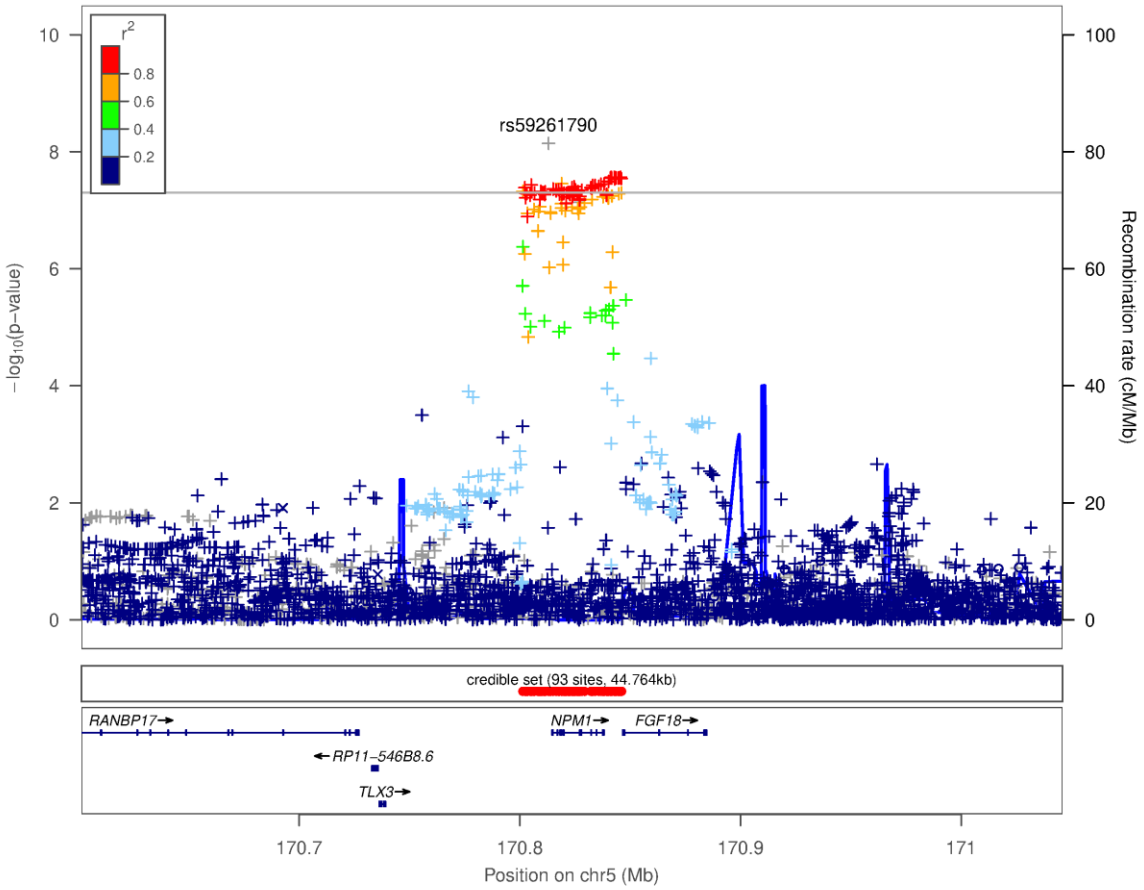

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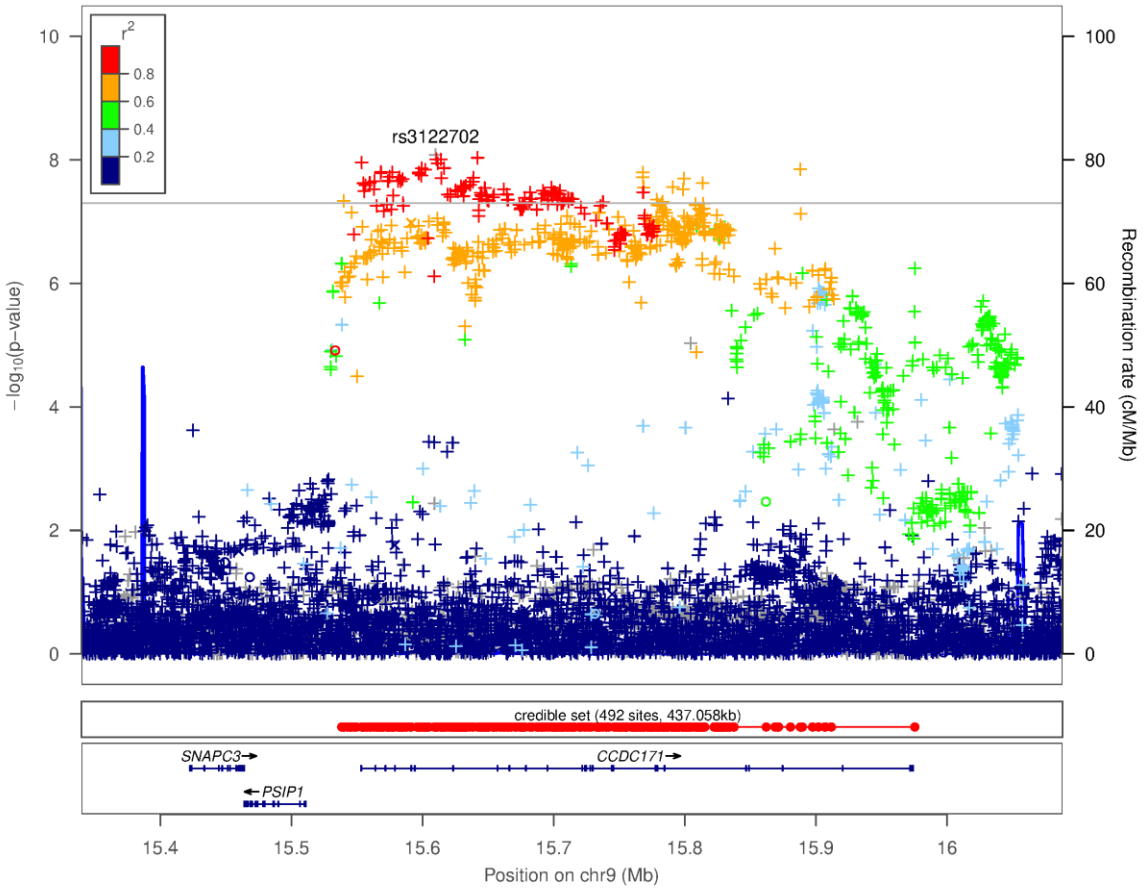
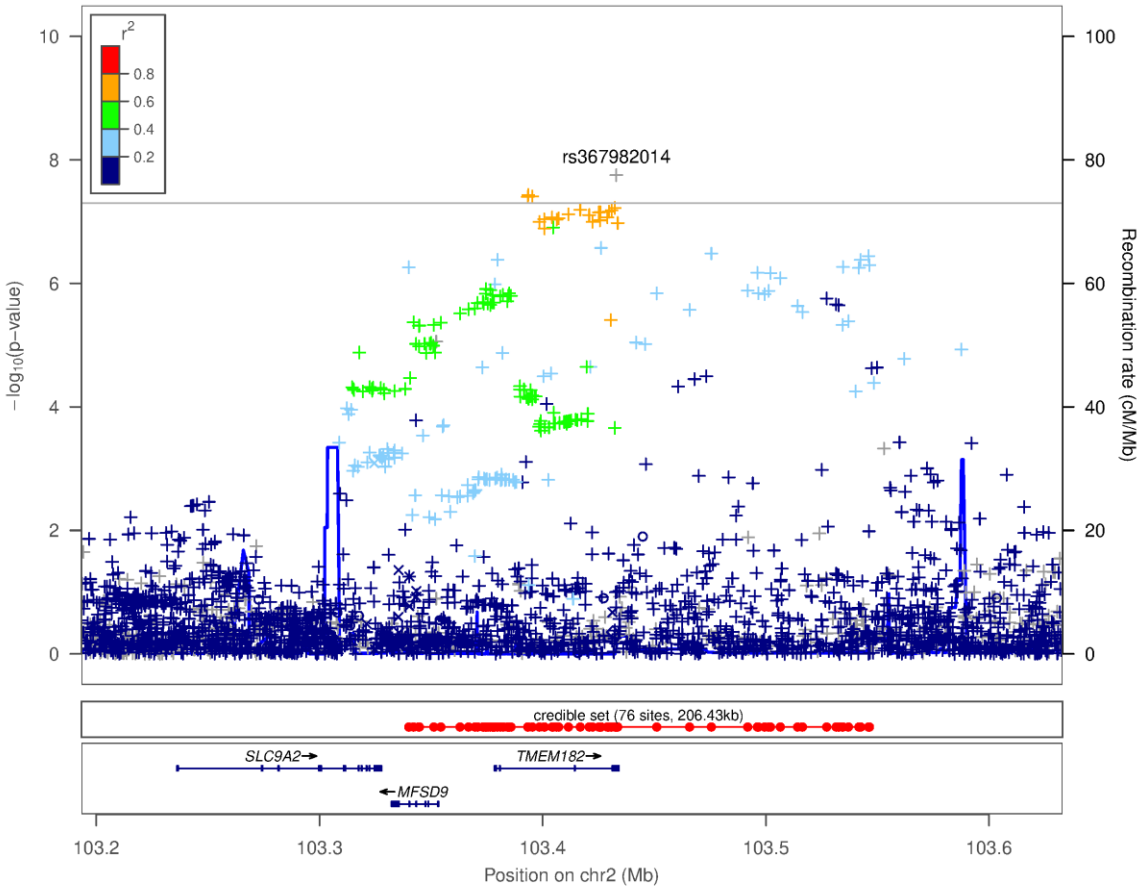
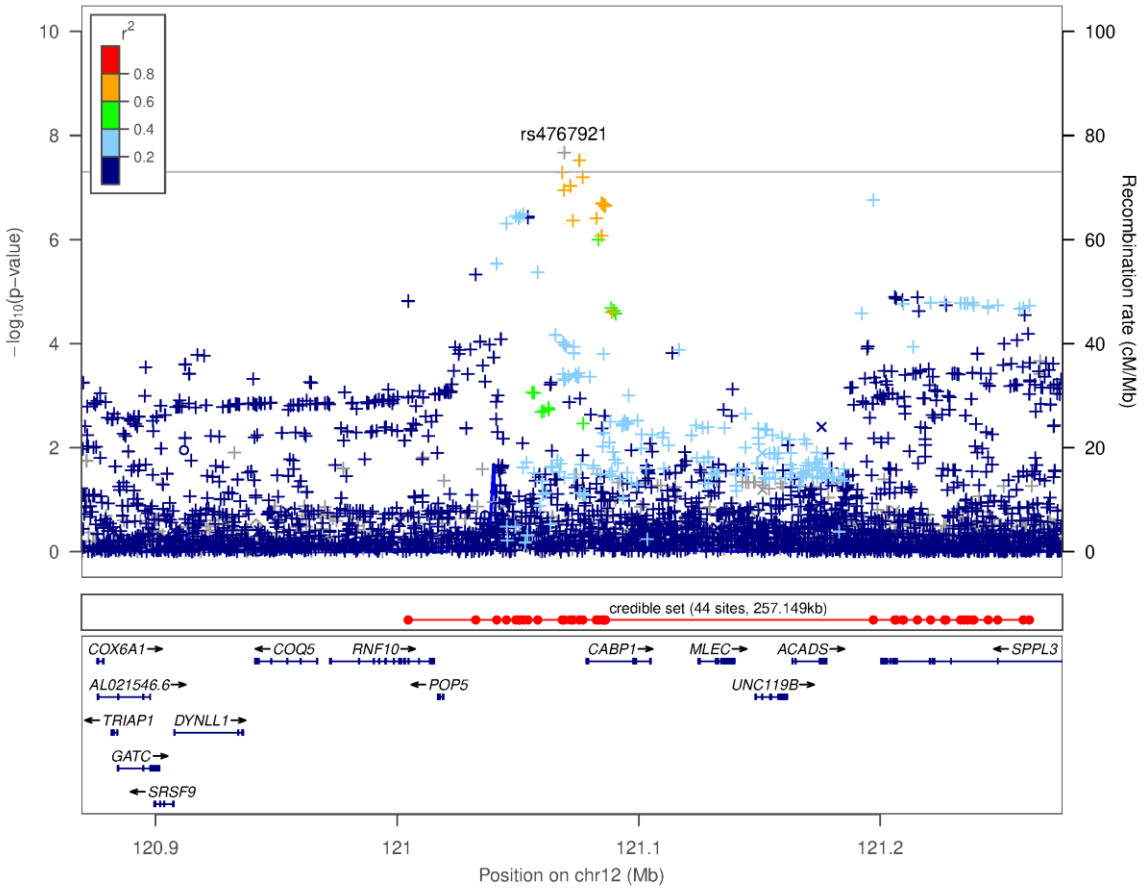


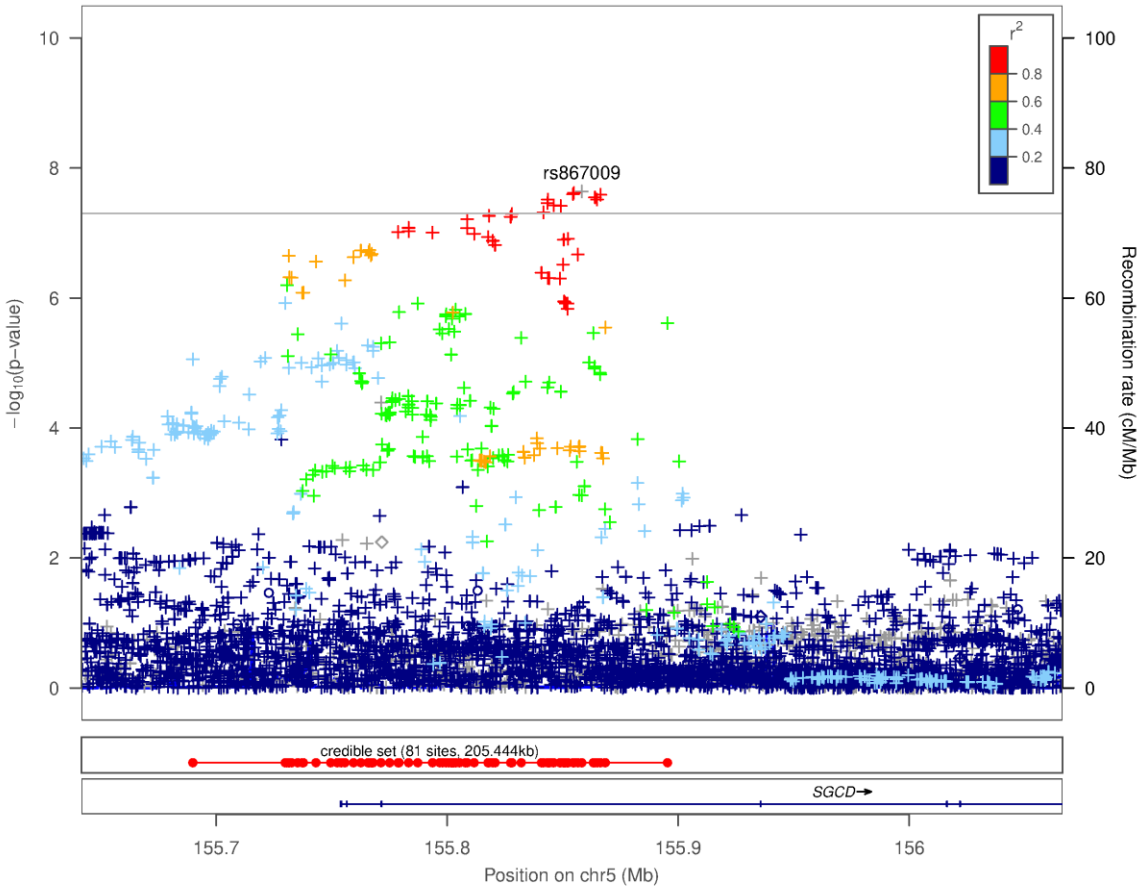
Supplementary Figure 1.xxxiii. Regional association plot which includes information on the credible variant set and known genes in the region for the significant association between dyslexia and chr9p22.3 rs3122702



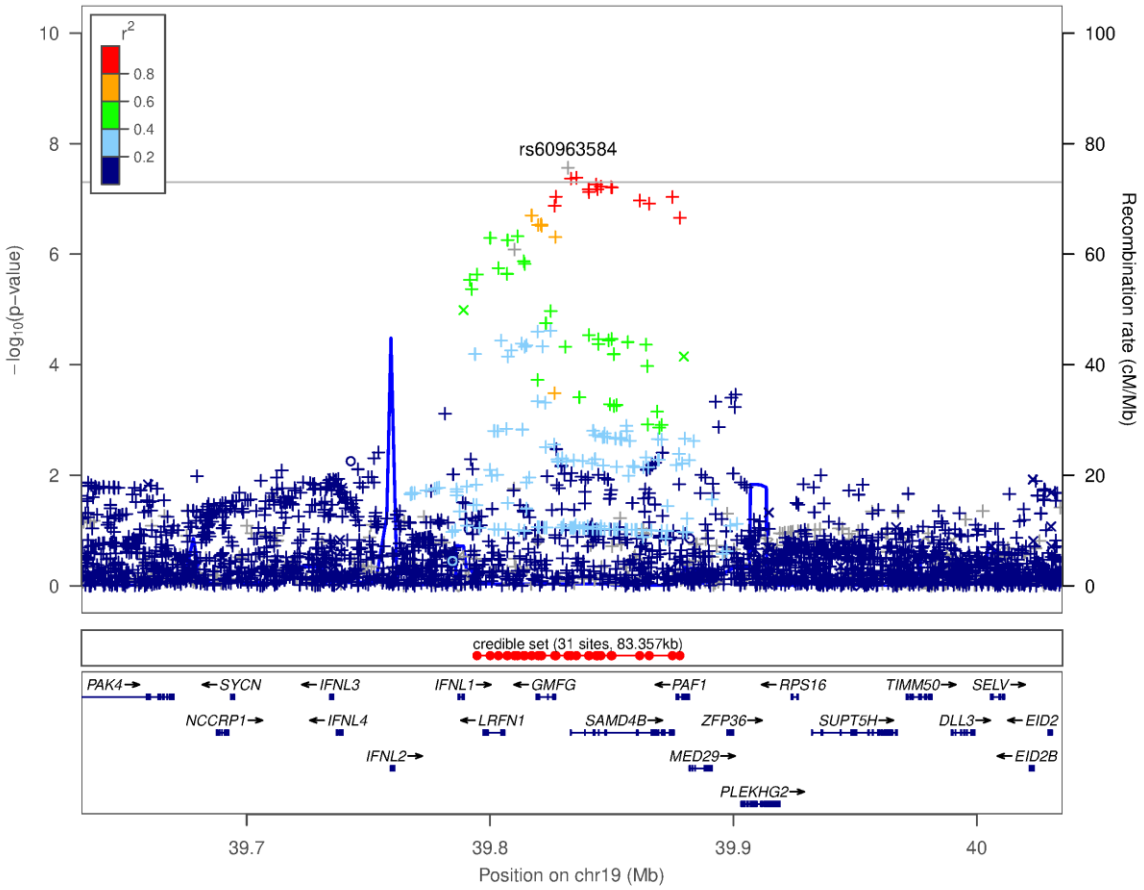
Supplementary Figure 1.xxxiv. Regional association plot which includes information on the credible variant set and known genes in the region for the significant association between dyslexia and chr2q12.1 rs367982014



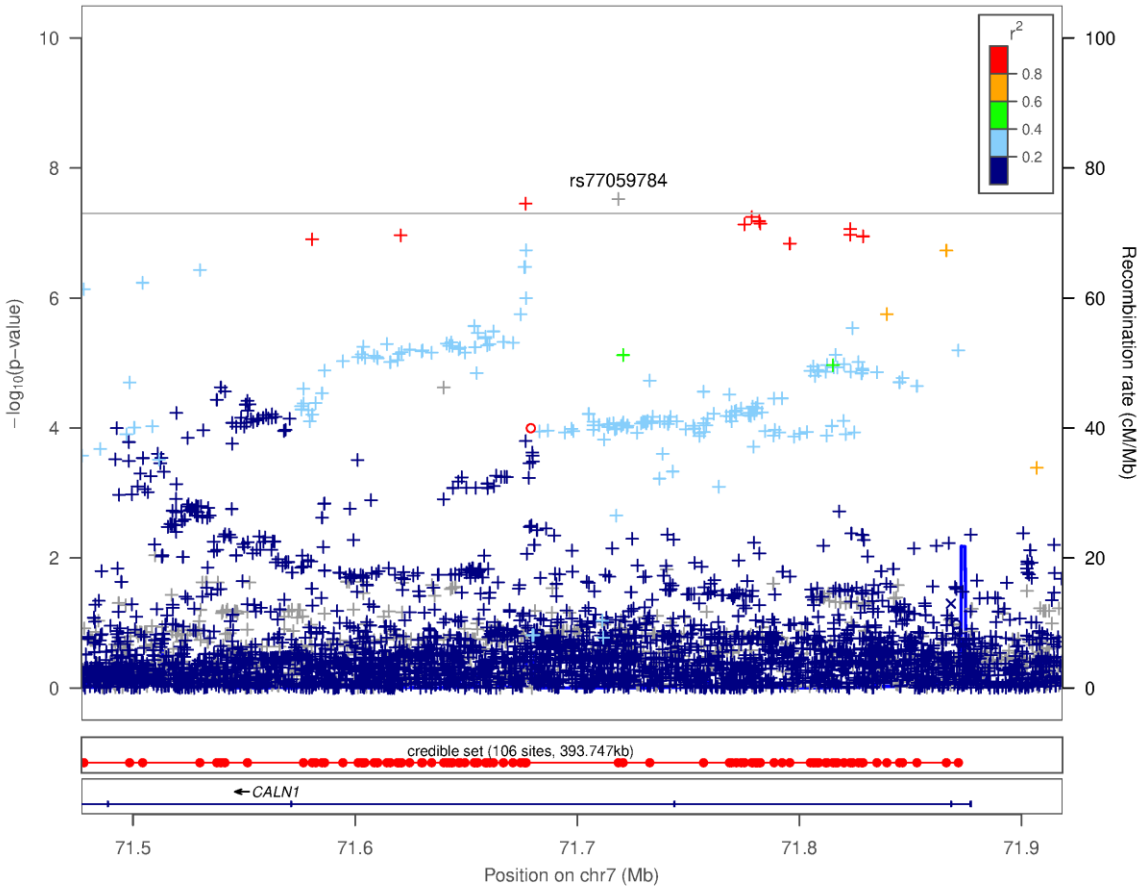
Supplementary Figure 1.xxxv. Regional association plot which includes information on the credible variant set and known genes in the region for the significant association between dyslexia and chr12q24.31 rs4767921



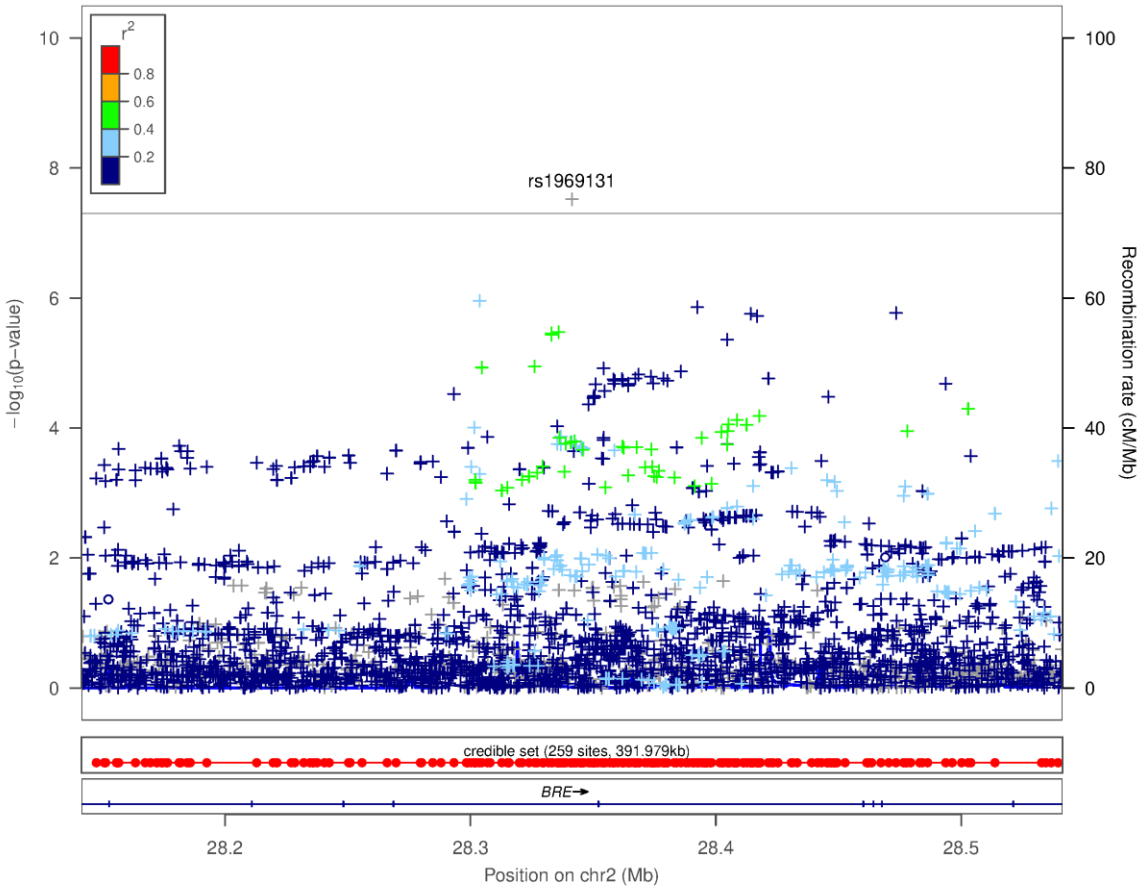
Supplementary Figure 1.xxxvi. Regional association plot which includes information on the credible variant set and known genes in the region for the significant association between dyslexia and chr5q33.3 rs867009



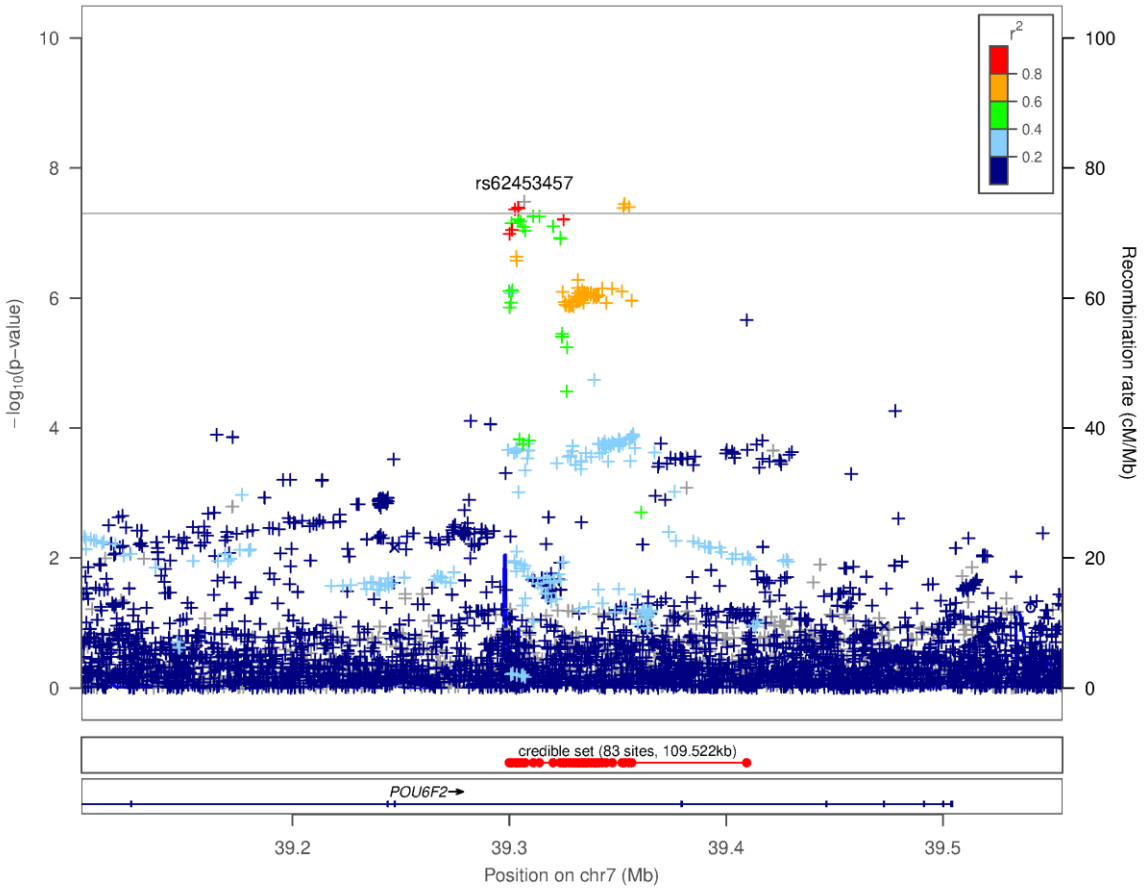
Supplementary Figure 1.xxxvii. Regional association plot which includes information on the credible variant set and known genes in the region for the significant association between dyslexia and chr19q13.2 rs60963584



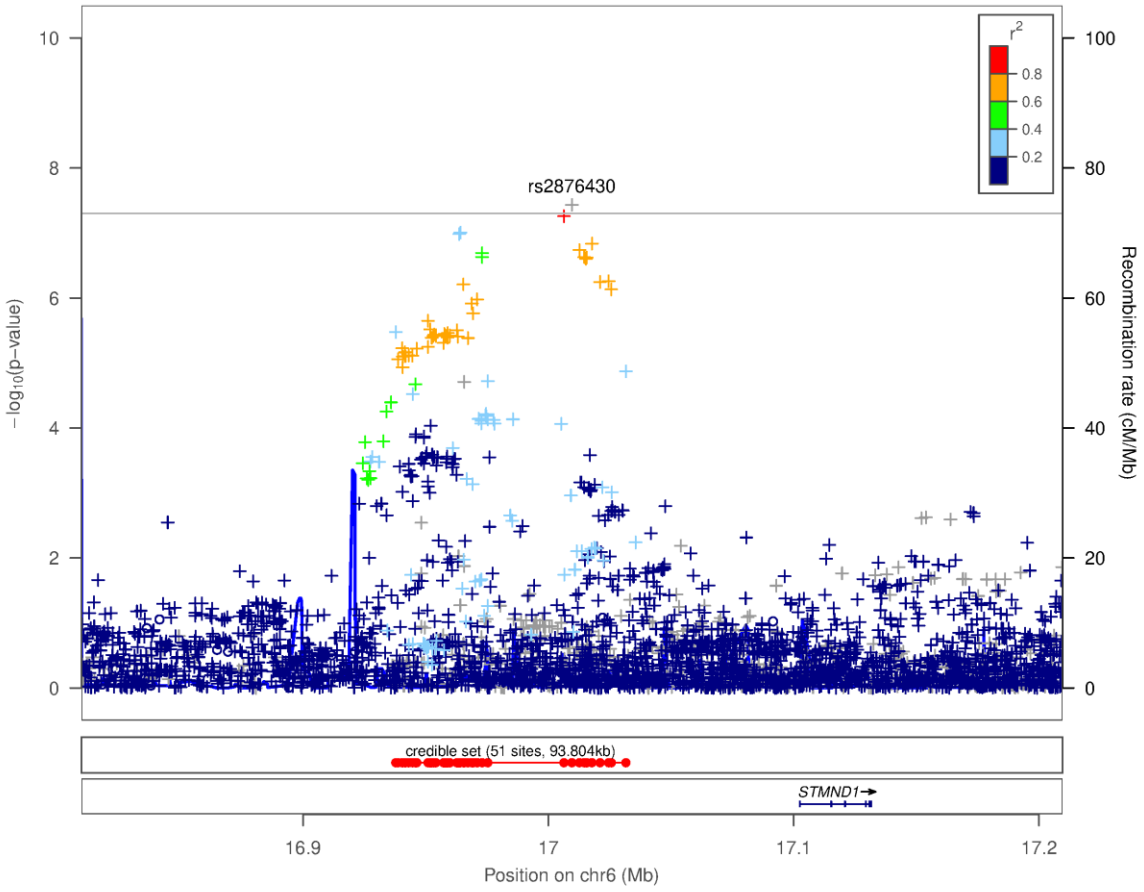
Supplementary Figure 1.xxxviii. Regional association plot which includes information on the credible variant set and known genes in the region for the significant association between dyslexia and chr7q11.22 rs77059784



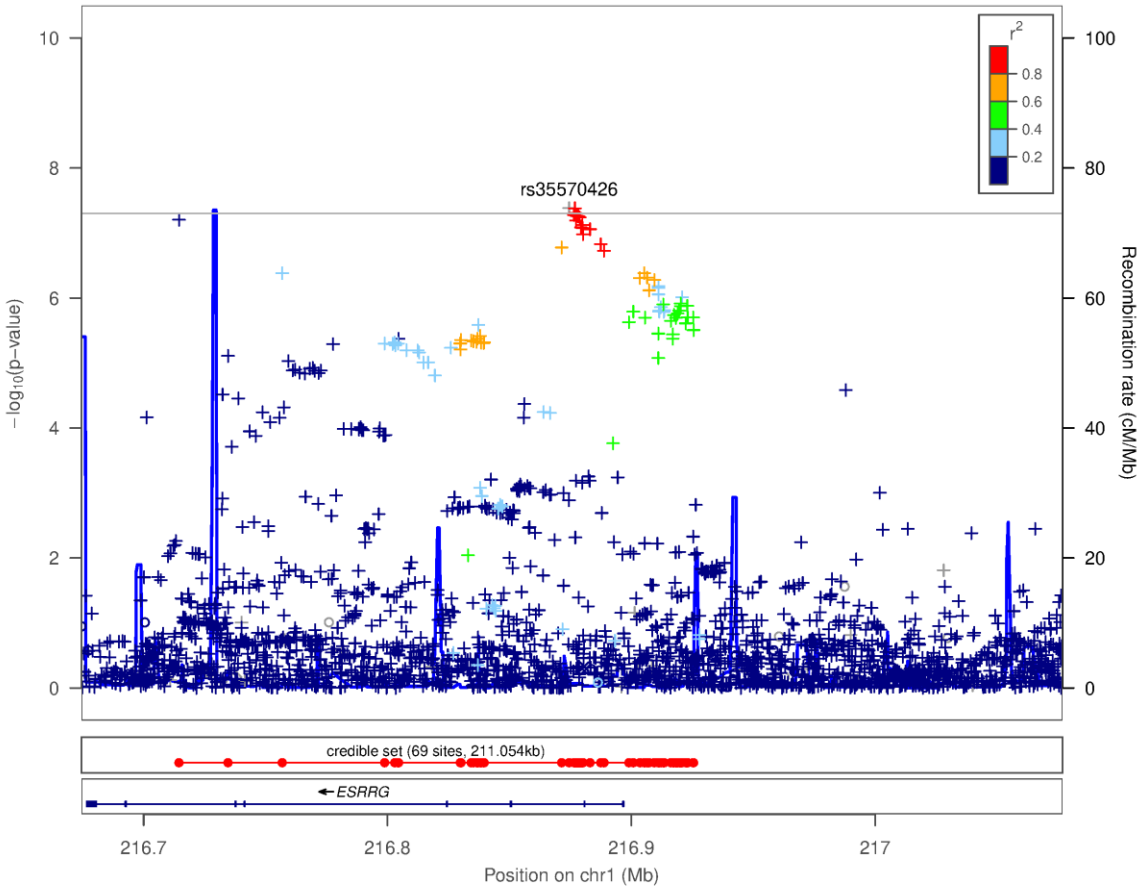
Supplementary Figure 1.xxxix. Regional association plot which includes information on the credible variant set and known genes in the region for the significant association between dyslexia and chr2p23.2 rs1969131



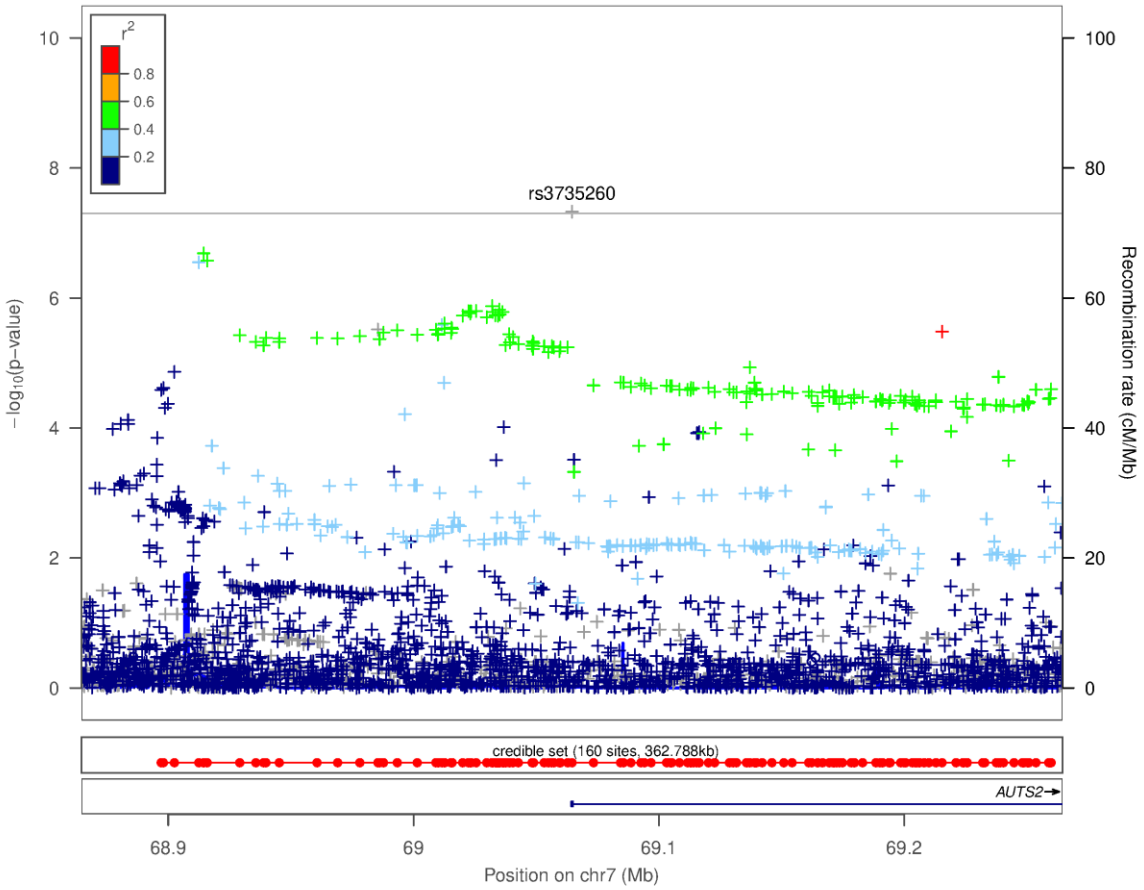
Supplementary Figure 1.xl. Regional association plot which includes information on the credible variant set and known genes in the region for the significant association between dyslexia and chr7p14.1 rs62453457



Supplementary Figure 1.xli. Regional association plot which includes information on the credible variant set and known genes in the region for the significant association between dyslexia and chr6p22.3 rs2876430



Supplementary Figure 1.xlii. Regional association plot which includes information on the credible variant set and known genes in the region for the significant association between dyslexia and chr1q41 rs35570426



Supplementary Figure 1.xliii. Regional association plot which includes information on the credible variant set and known genes in the region for the significant association between dyslexia and chr7q11.22 rs3735260