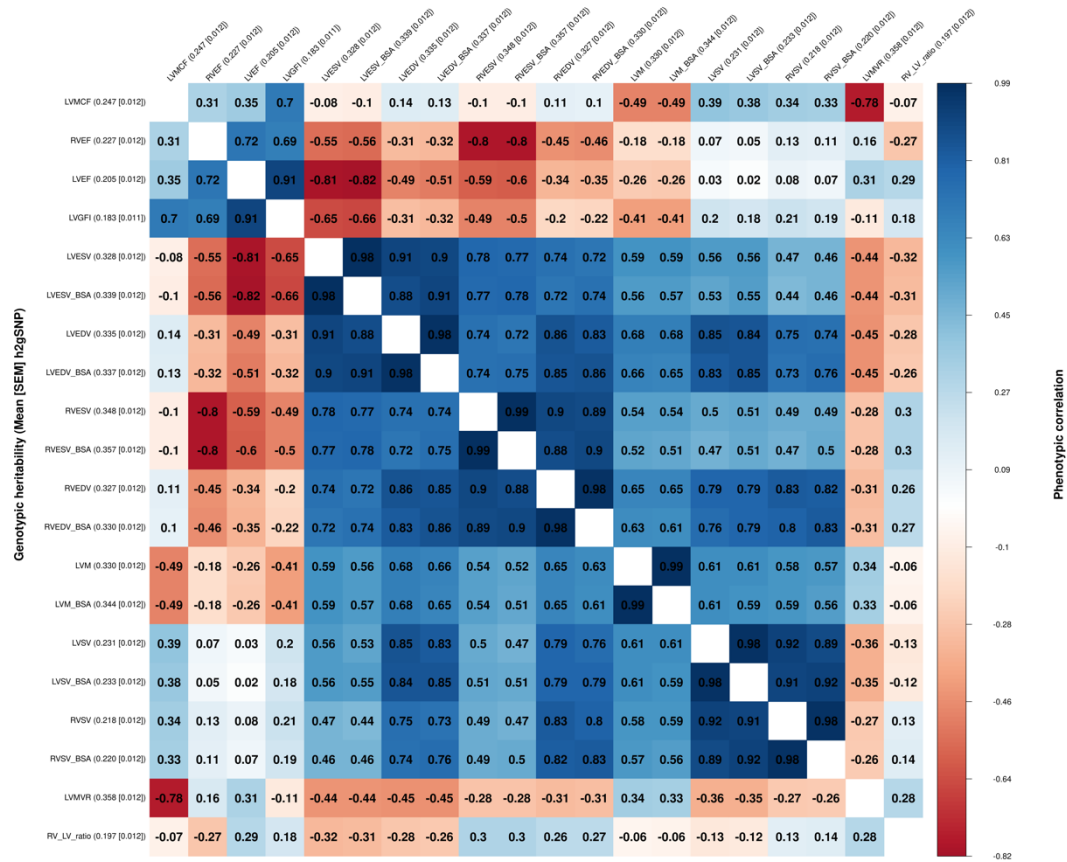
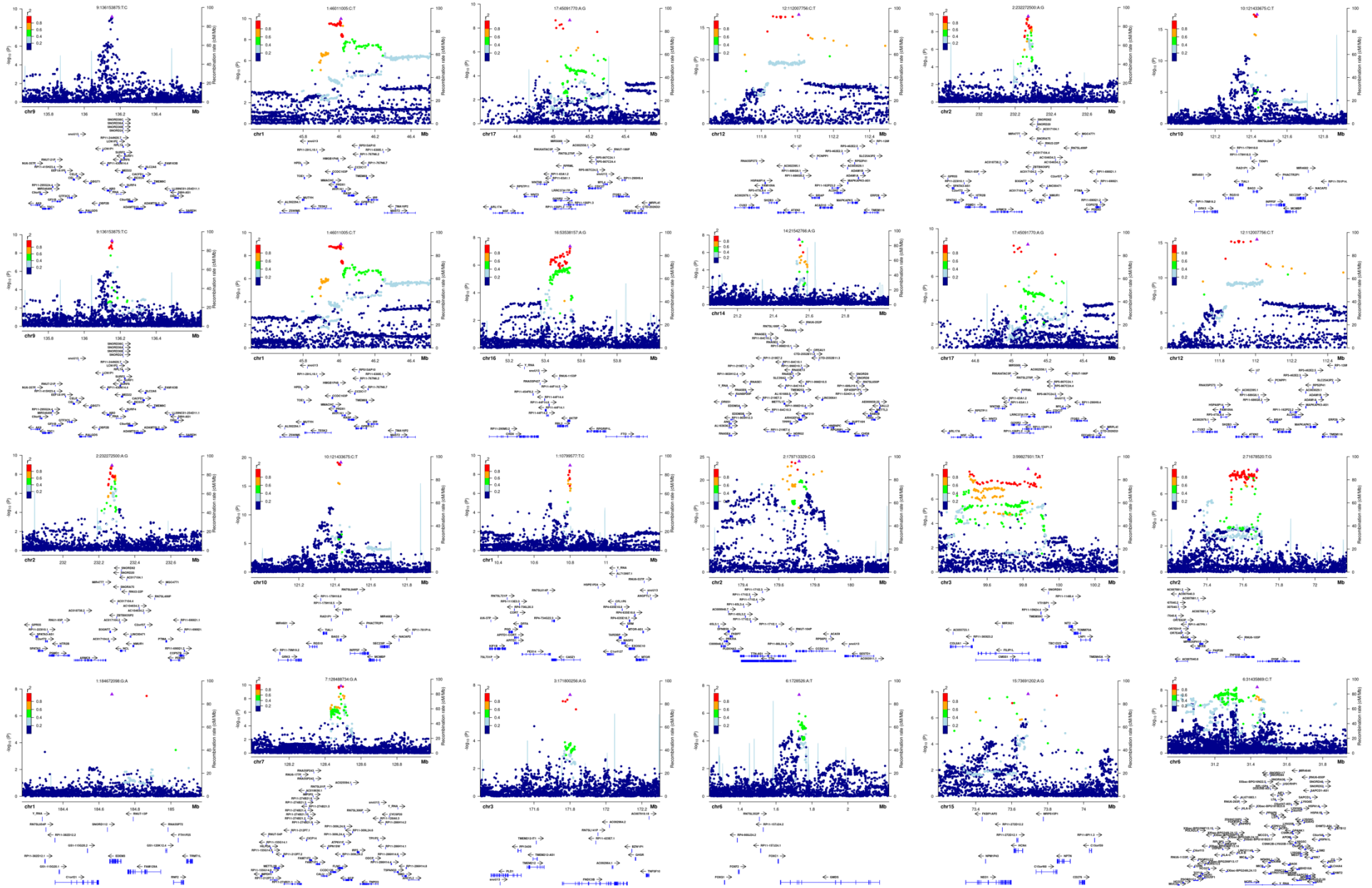


Article Title: Genome-wide analysis of cardiac ventricular phenotypes reveals novel loci and therapeutic targets for heart failure

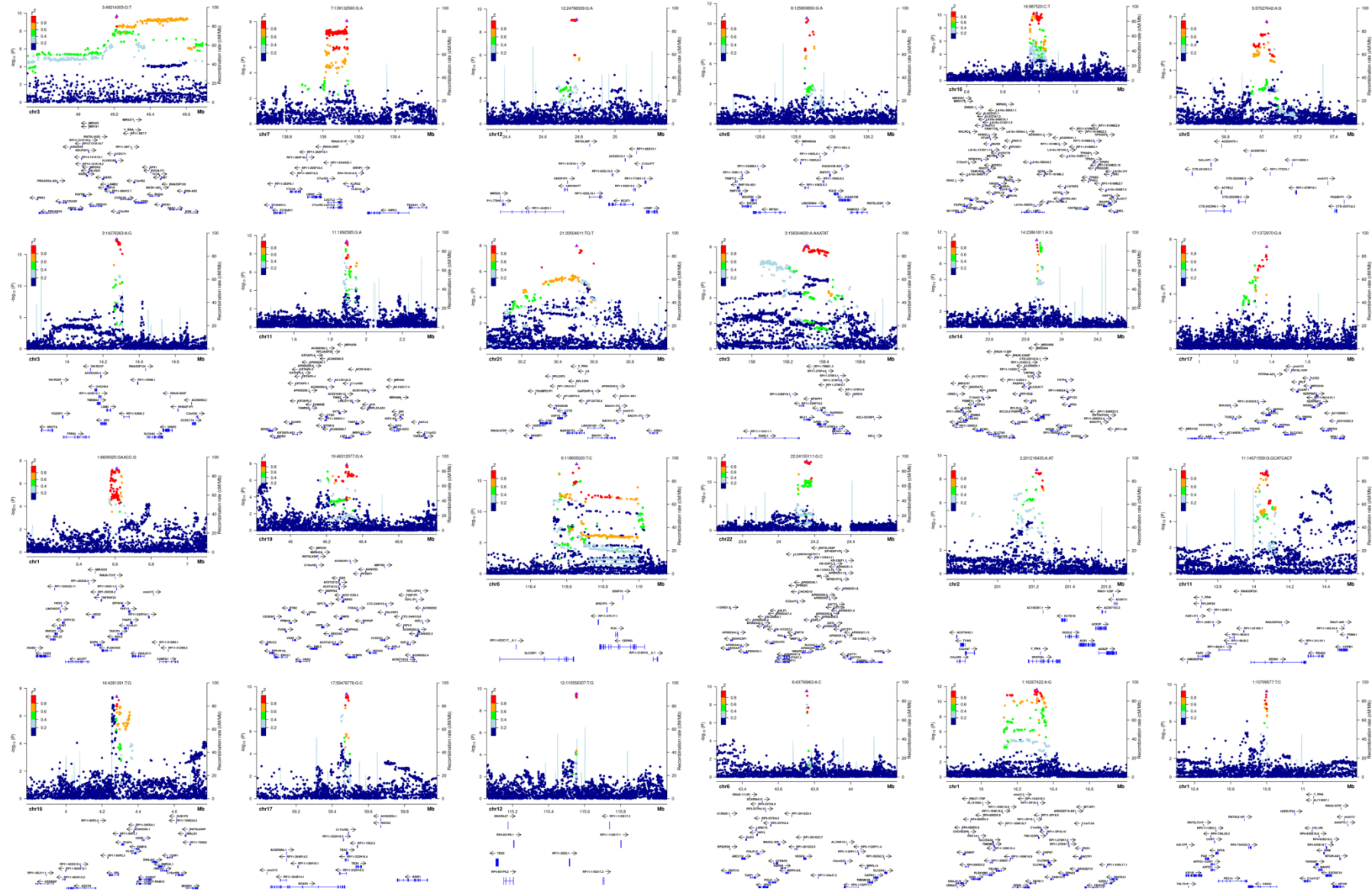


Supplementary Fig 1. Correlogram for left and right ventricular traits. Single-nucleotide polymorphism (SNP) heritability and phenotype correlation between all left and right ventricular traits. Heritability estimated from genotyped SNPs is presented along the axes per each trait. Source data are provided as a Source Data file. SNP, single nucleotide polymorphism; LVEDV, Left Ventricular End-Diastolic Volume; LVESV, Left Ventricular End-Systolic Volume; LVSV, Left Ventricular Stroke Volume; LVEF, Left Ventricular Ejection Fraction; LVGFI, Left Ventricular Global Function Index; LVMCF, Left Ventricular Myocardial Contraction Fraction; LVM, Left Ventricular Mass; LVMVR, Left Ventricular Mass-to-Volume Ratio; LVEDV BSA, Left Ventricular End-Diastolic Volume Indexed to Body Surface Area; LVESV BSA, Left Ventricular End-Systolic Volume Indexed to Body Surface Area; LVSV BSA, Left Ventricular Stroke Volume Indexed to Body Surface Area; LVM BSA, Left Ventricular Mass Indexed to Body Surface Area; RVEDV, Right Ventricular End-Diastolic Volume; RVESV, Right Ventricular End-Systolic Volume; RVSV, Right Ventricular Stroke Volume; RVEF, Right Ventricular Ejection Fraction; RV LV ratio, Right Ventricular to Left Ventricular Ratio; RVEDV BSA, Right Ventricular End-Diastolic Volume Indexed to Body Surface Area; RVESV BSA, Right Ventricular End-Systolic Volume Indexed to Body Surface Area; RVSV BSA, Right Ventricular Stroke Volume Indexed to Body Surface Area; SEM, standard error of the mean.

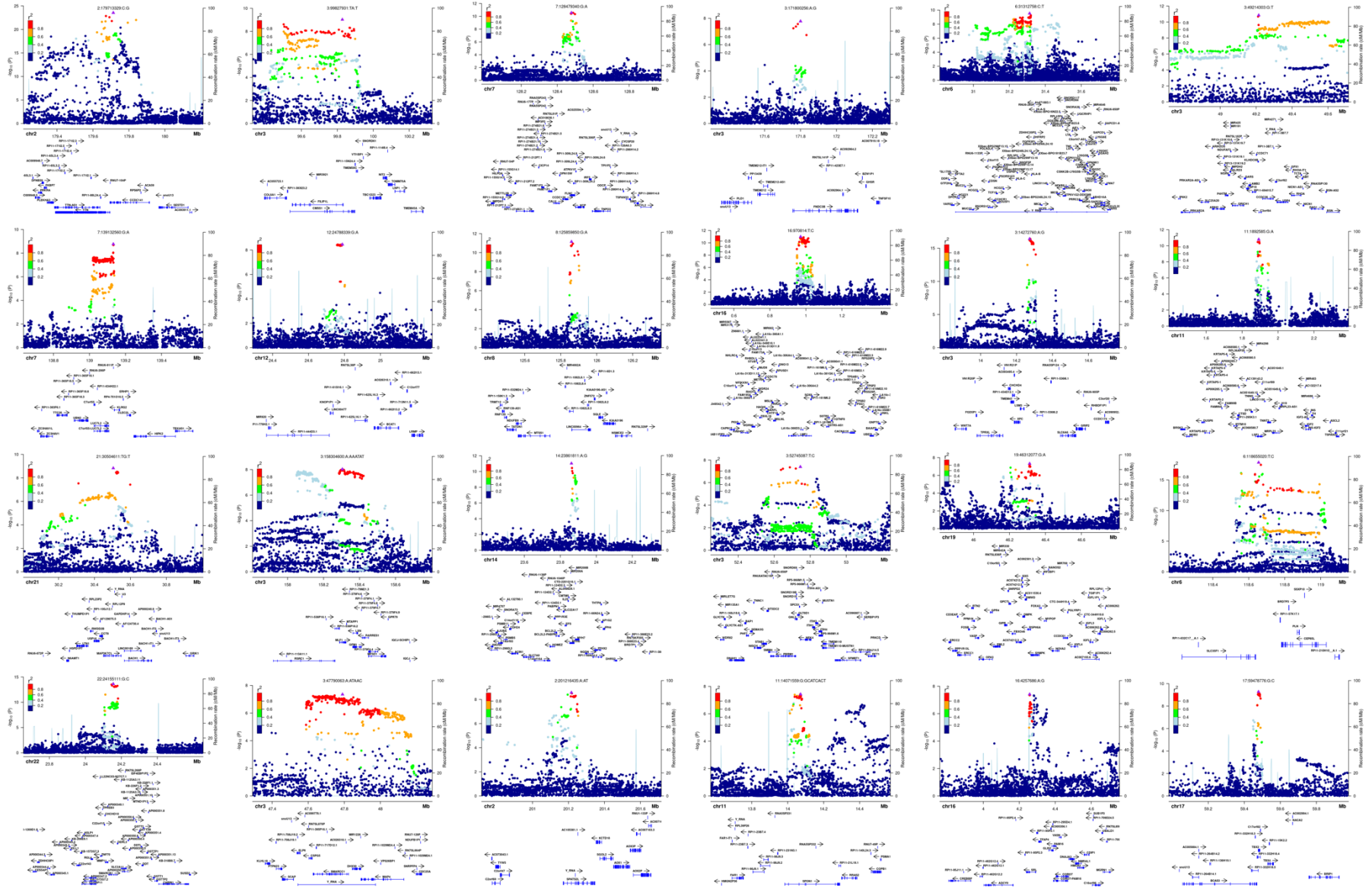
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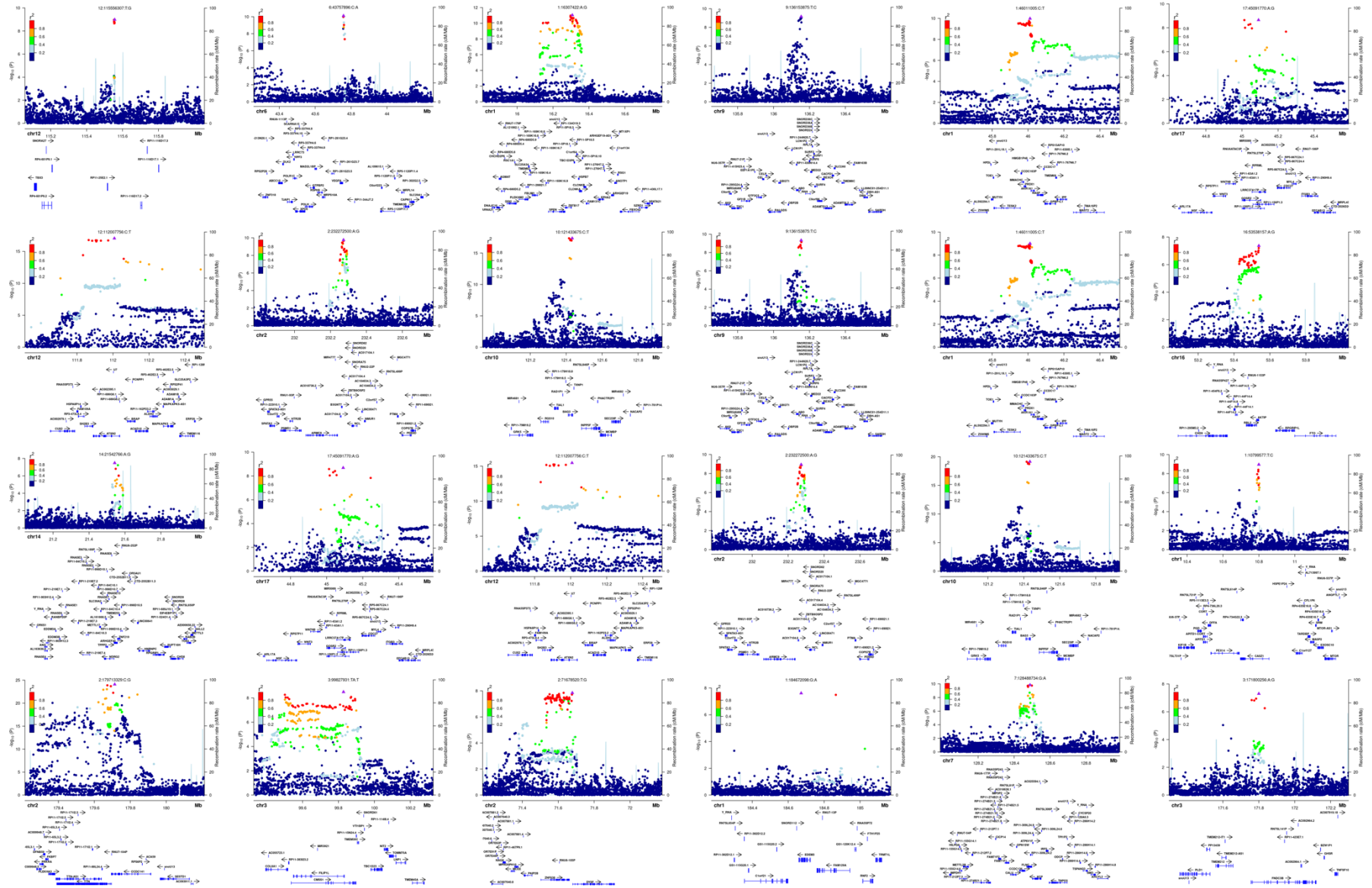
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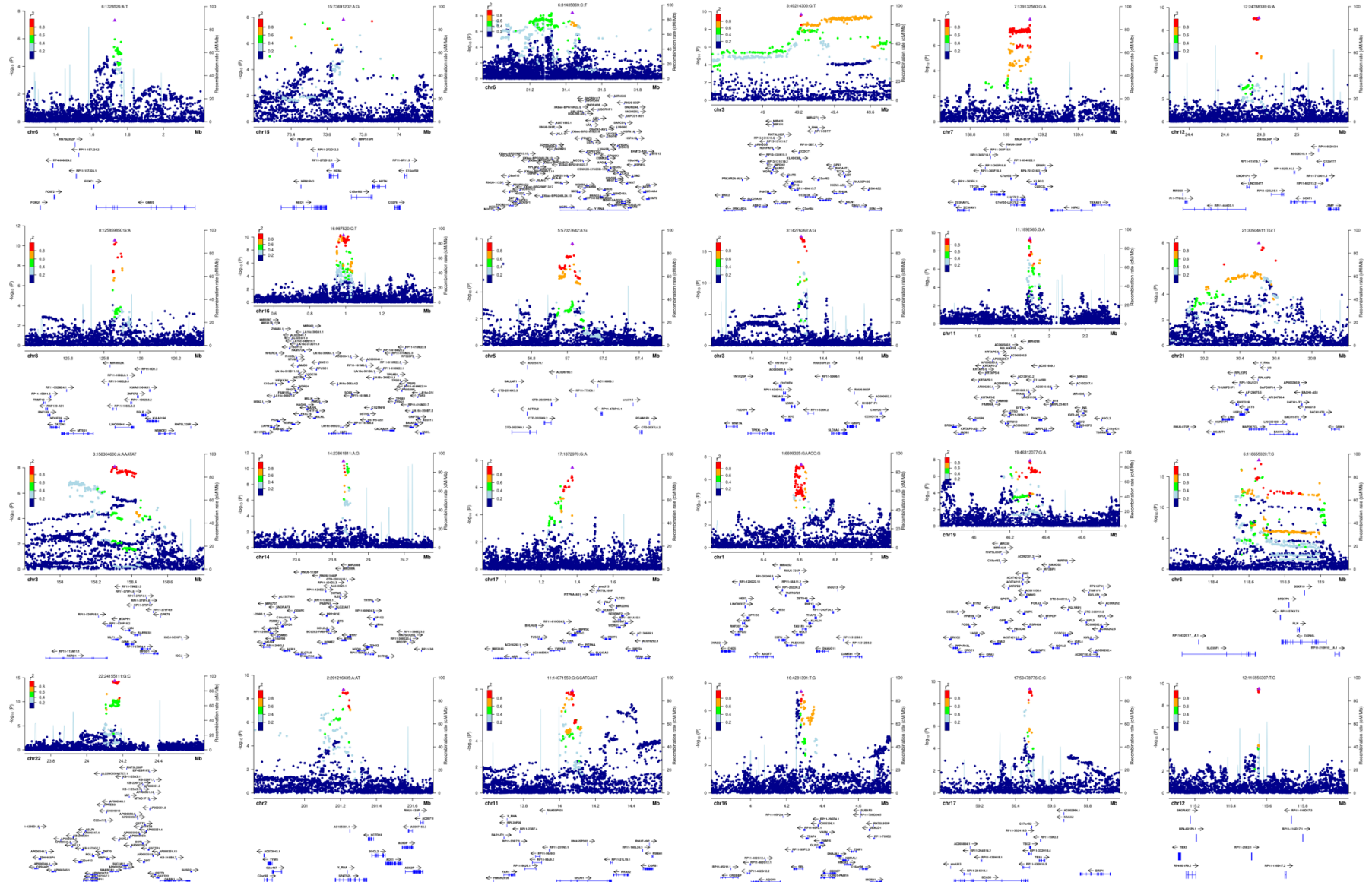
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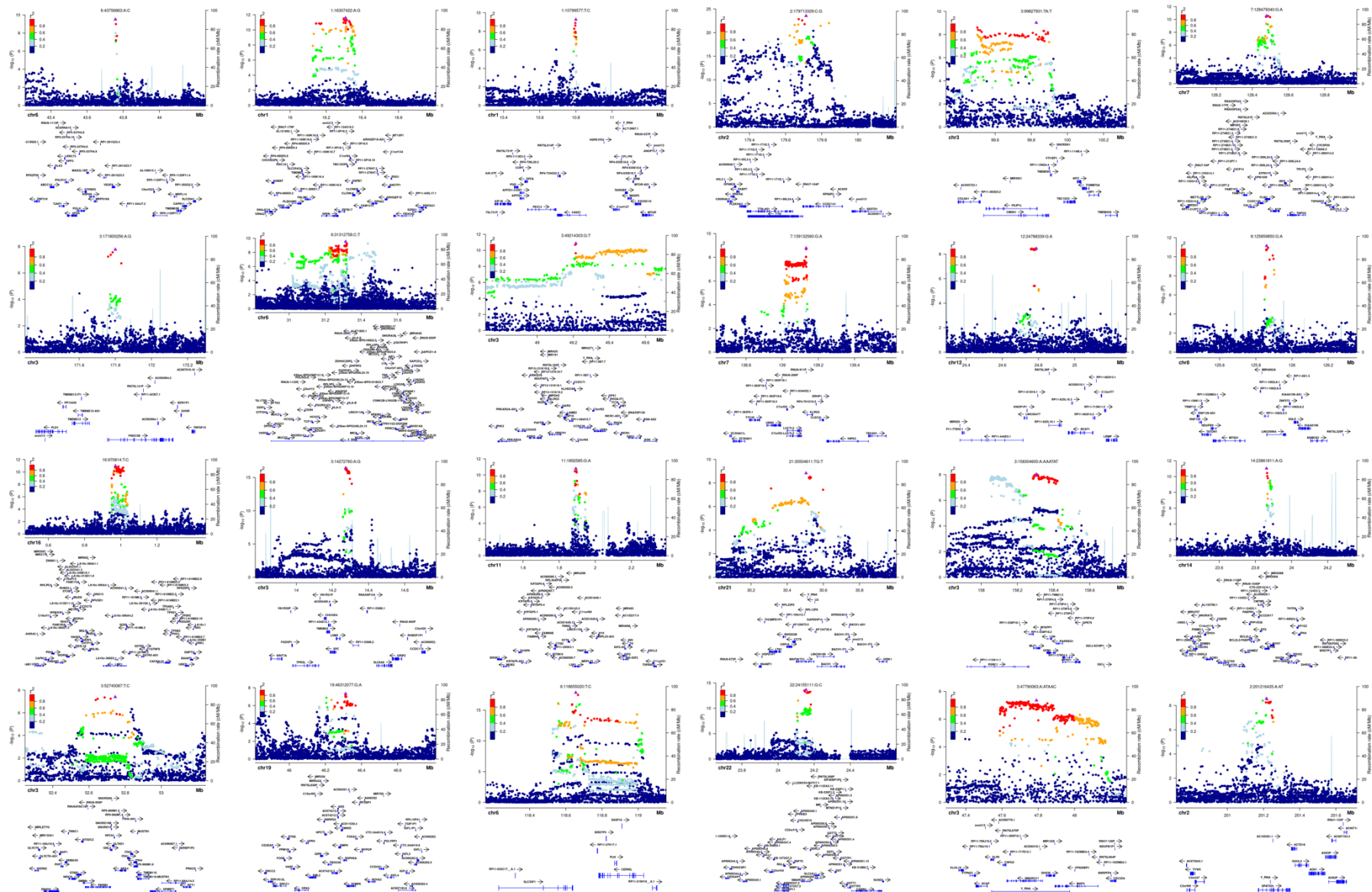
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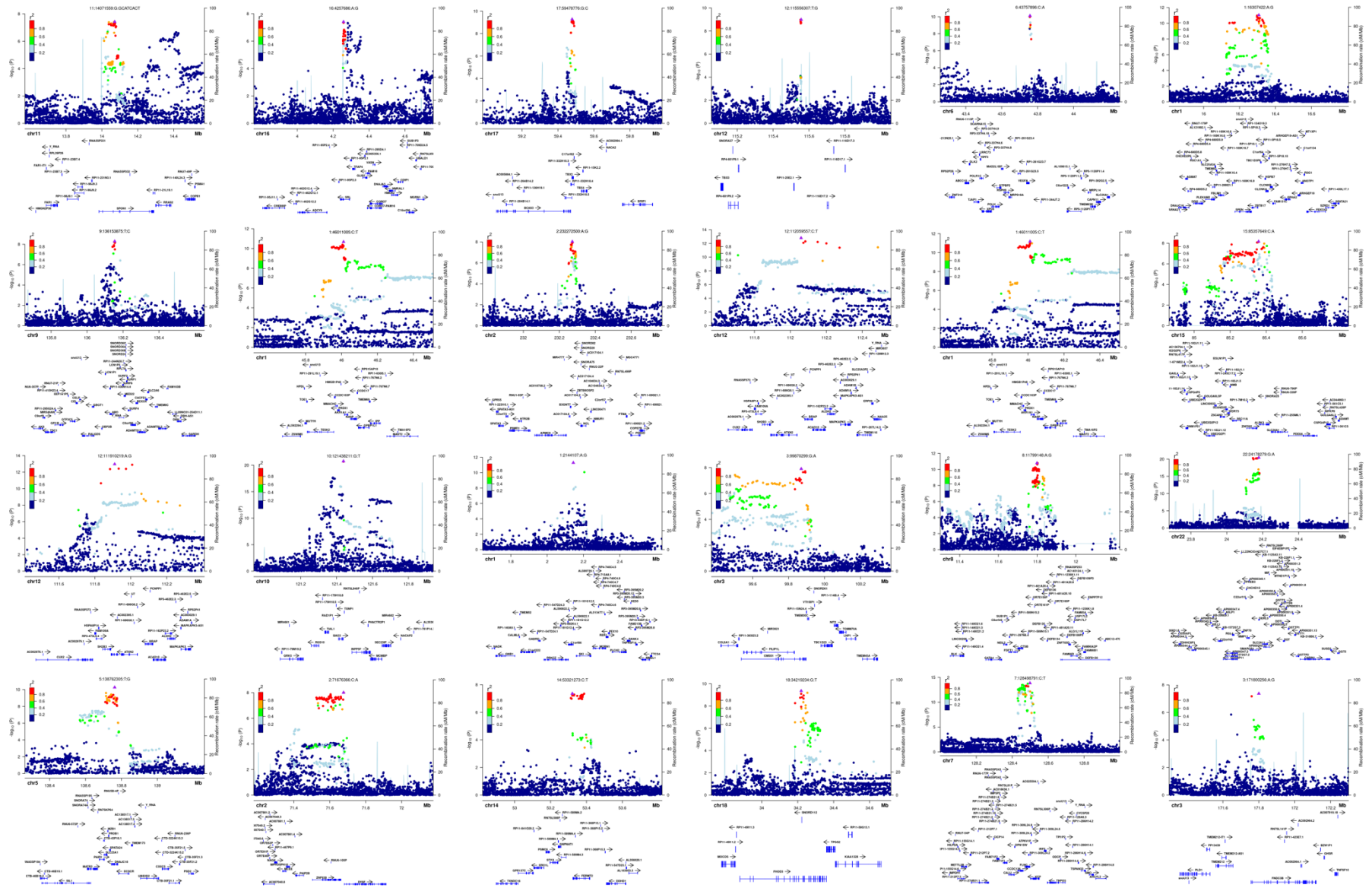
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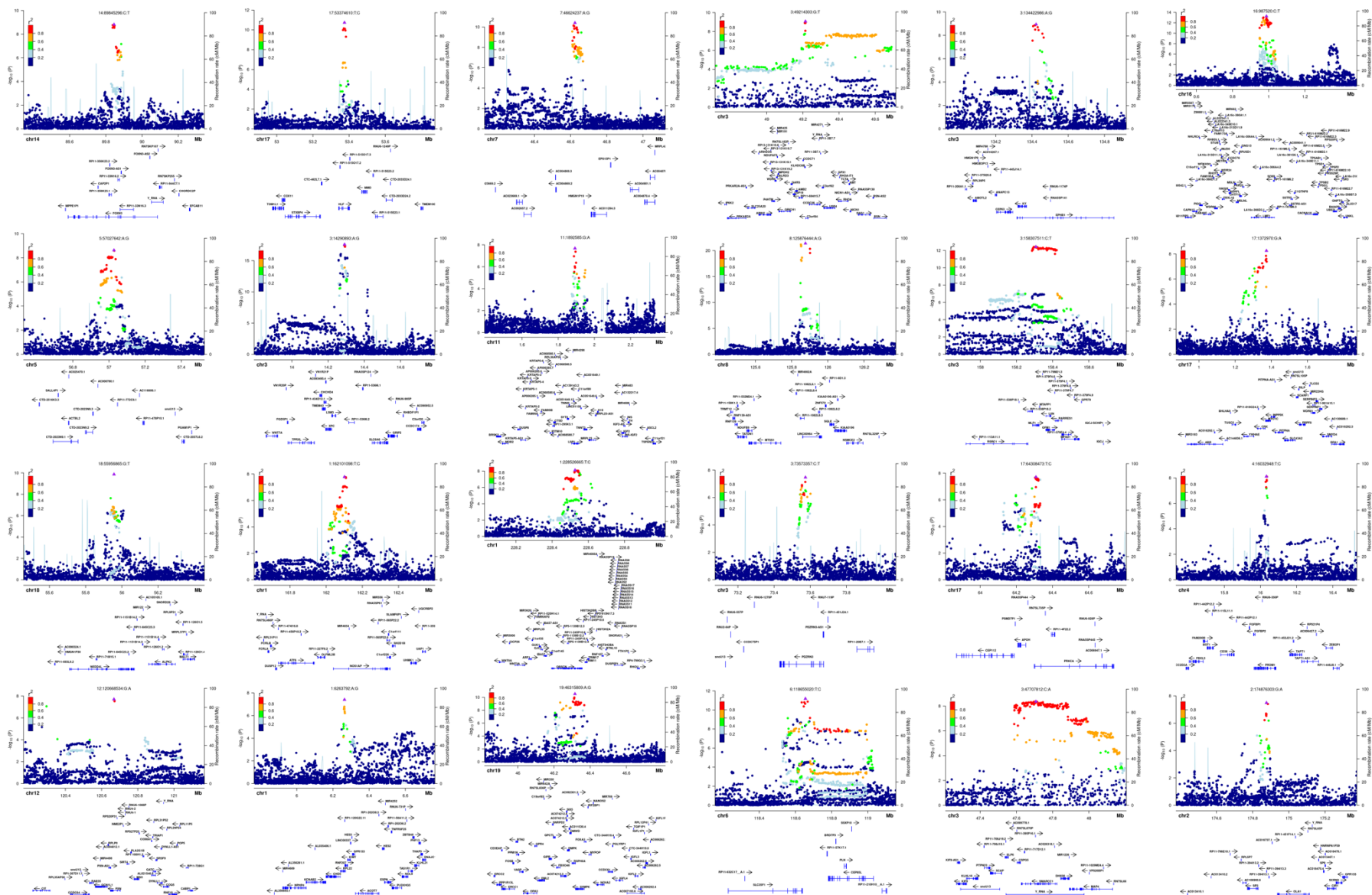
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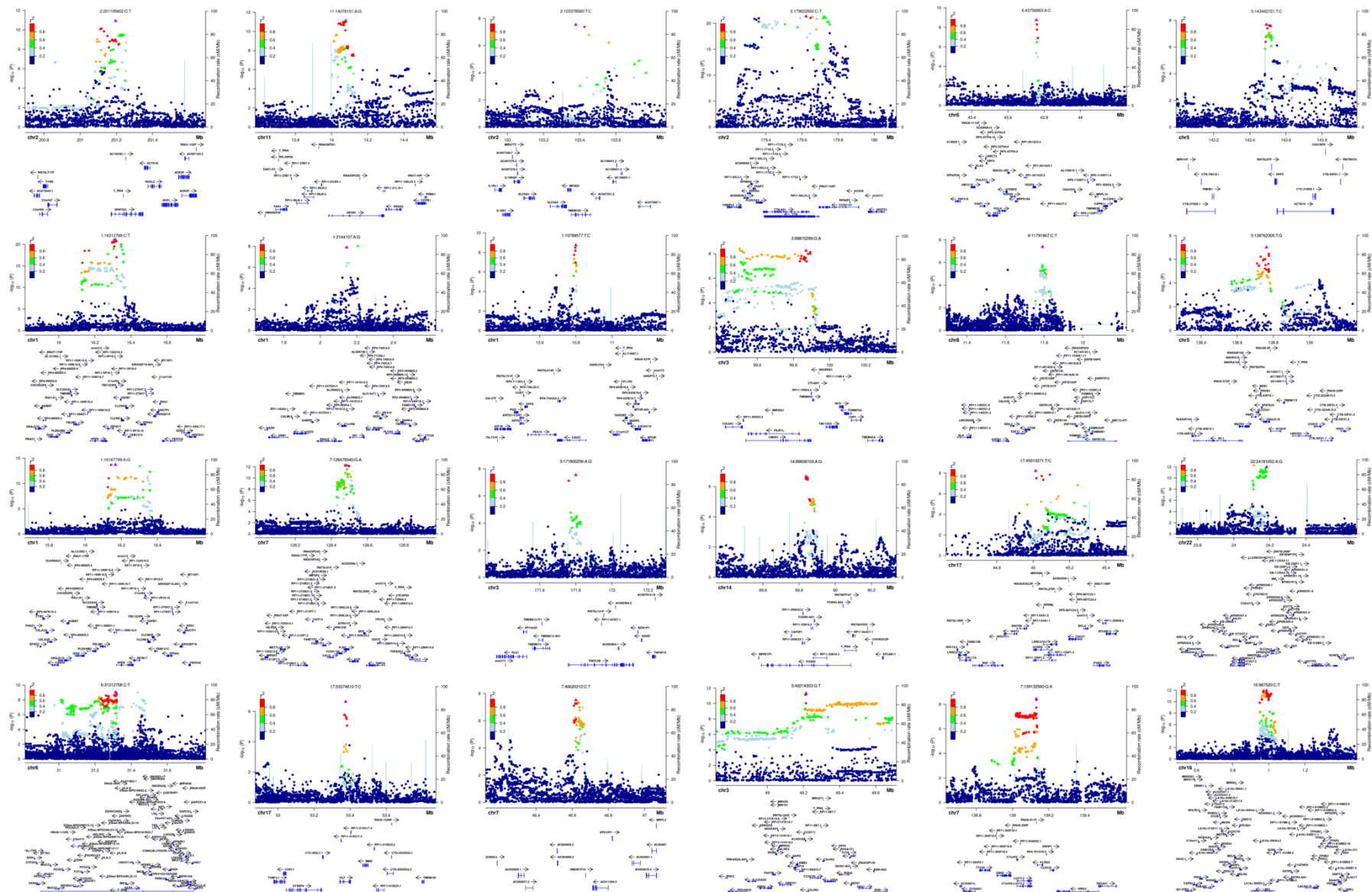
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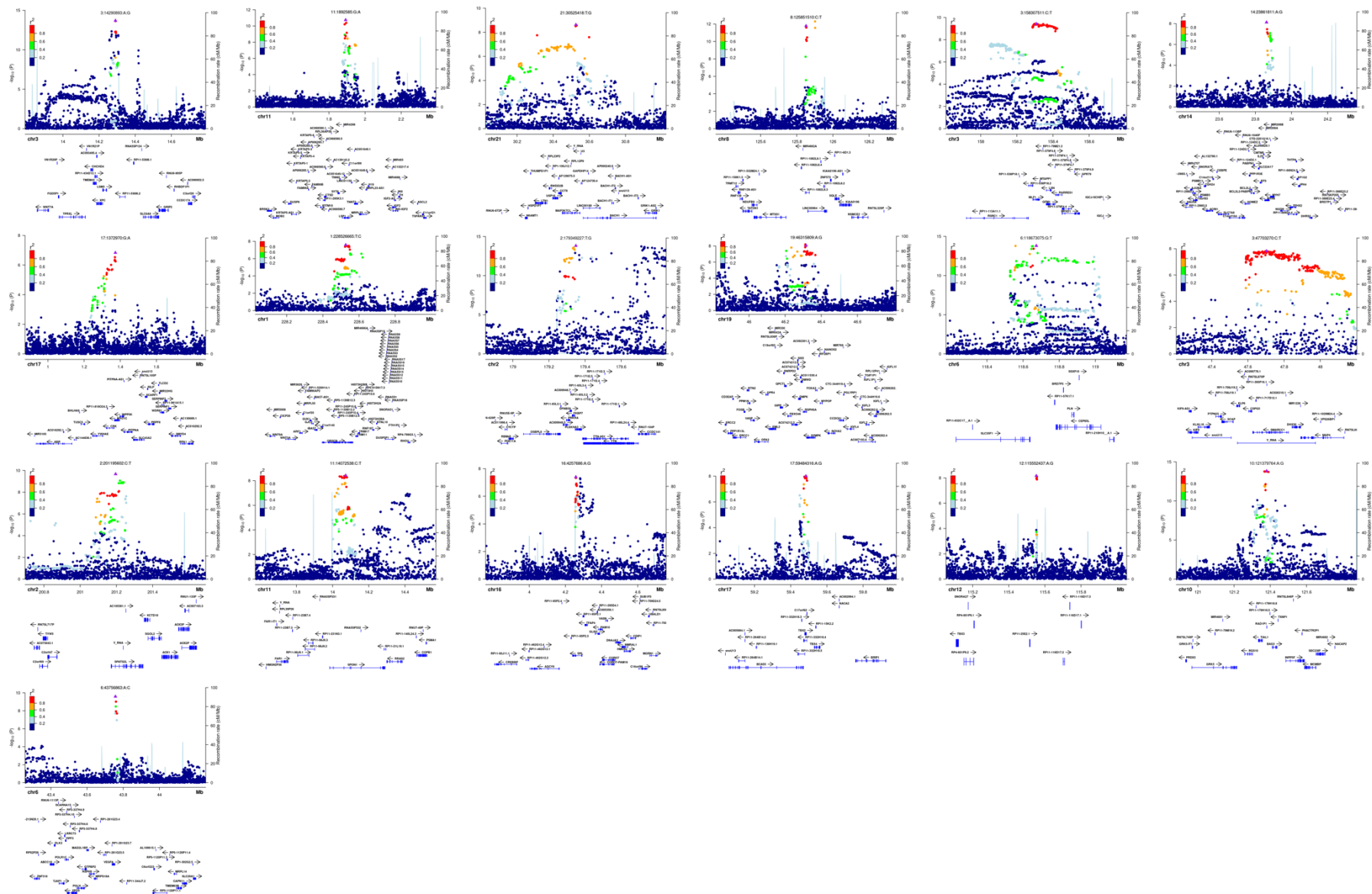
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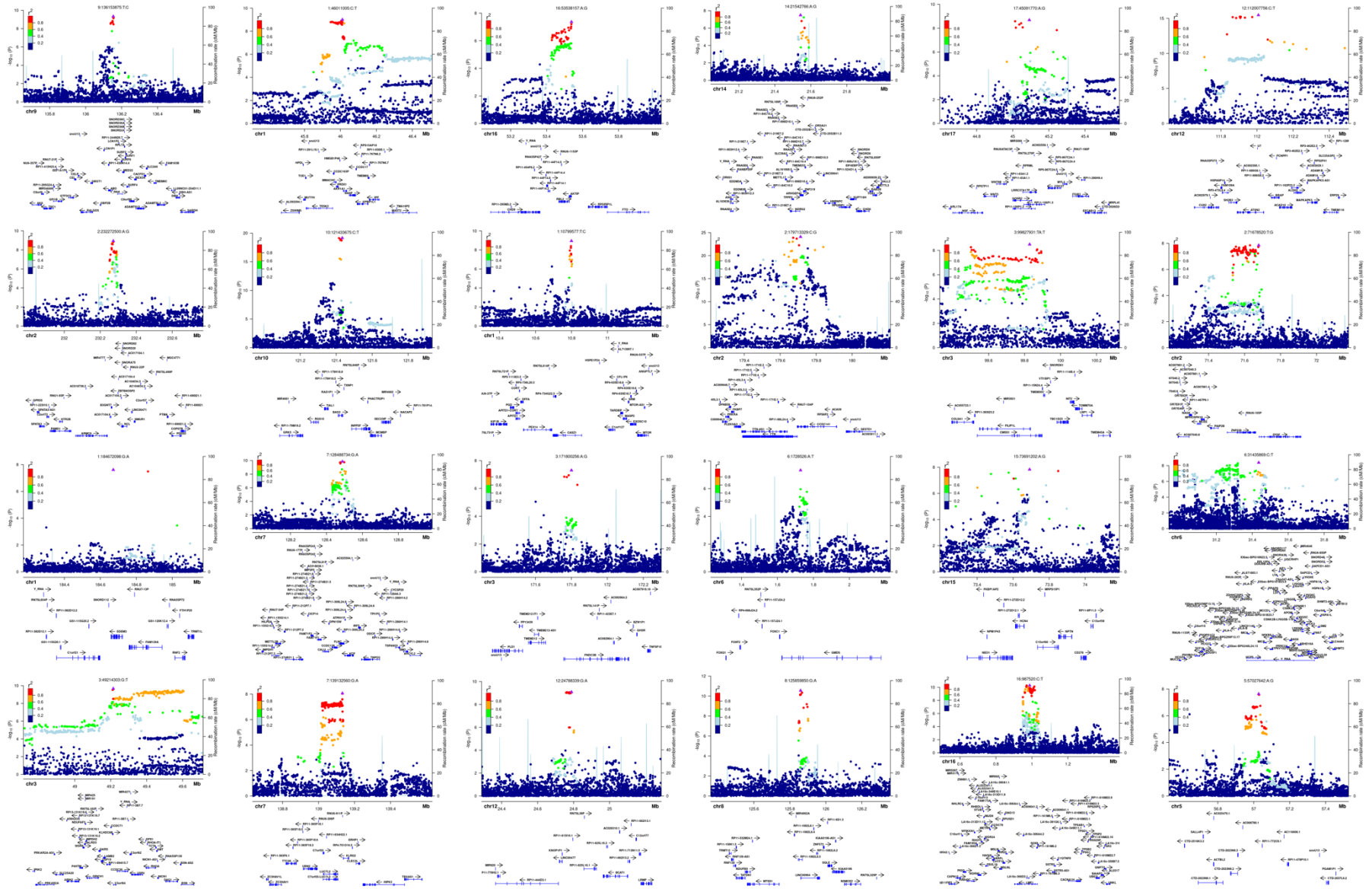
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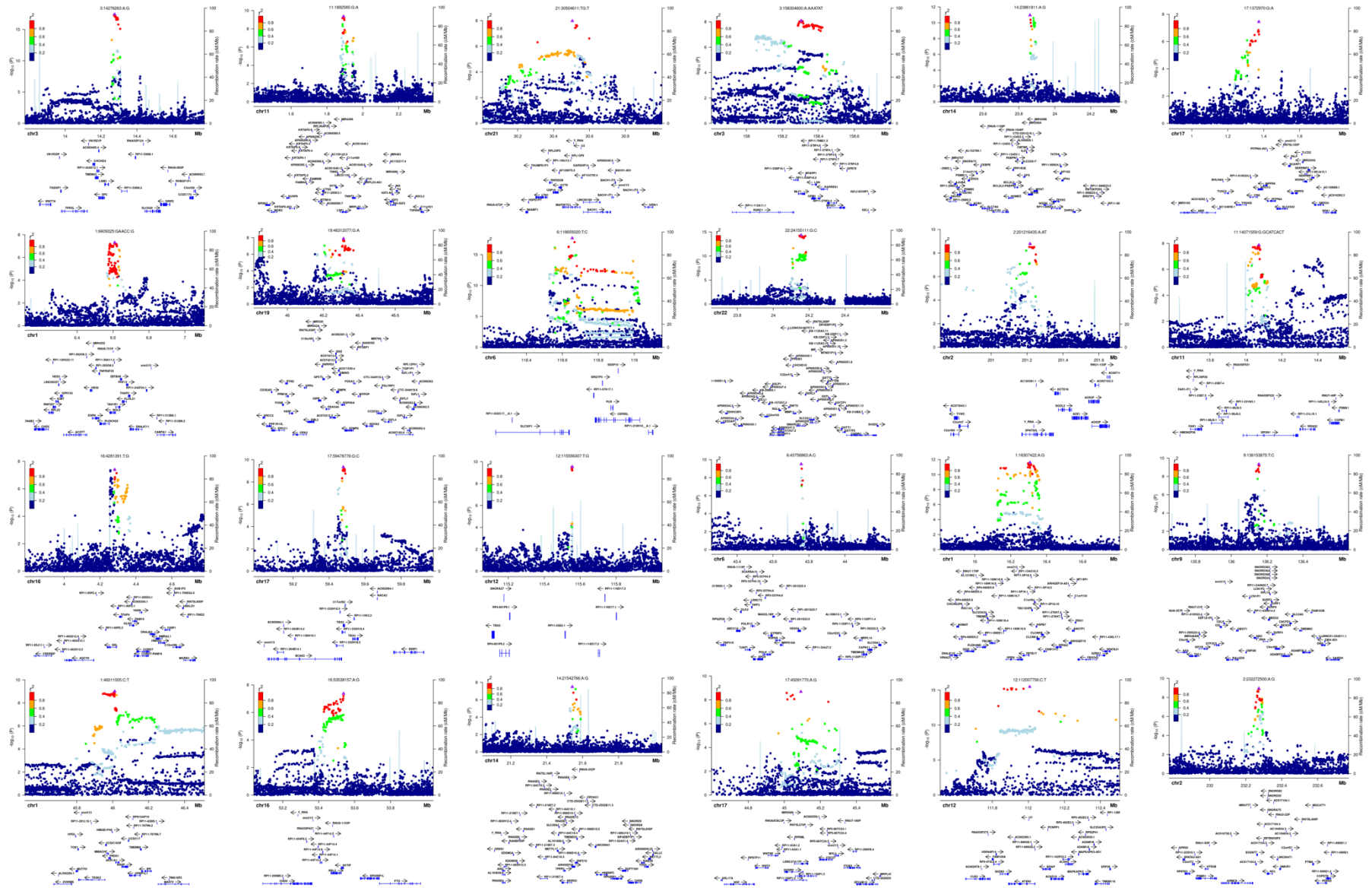
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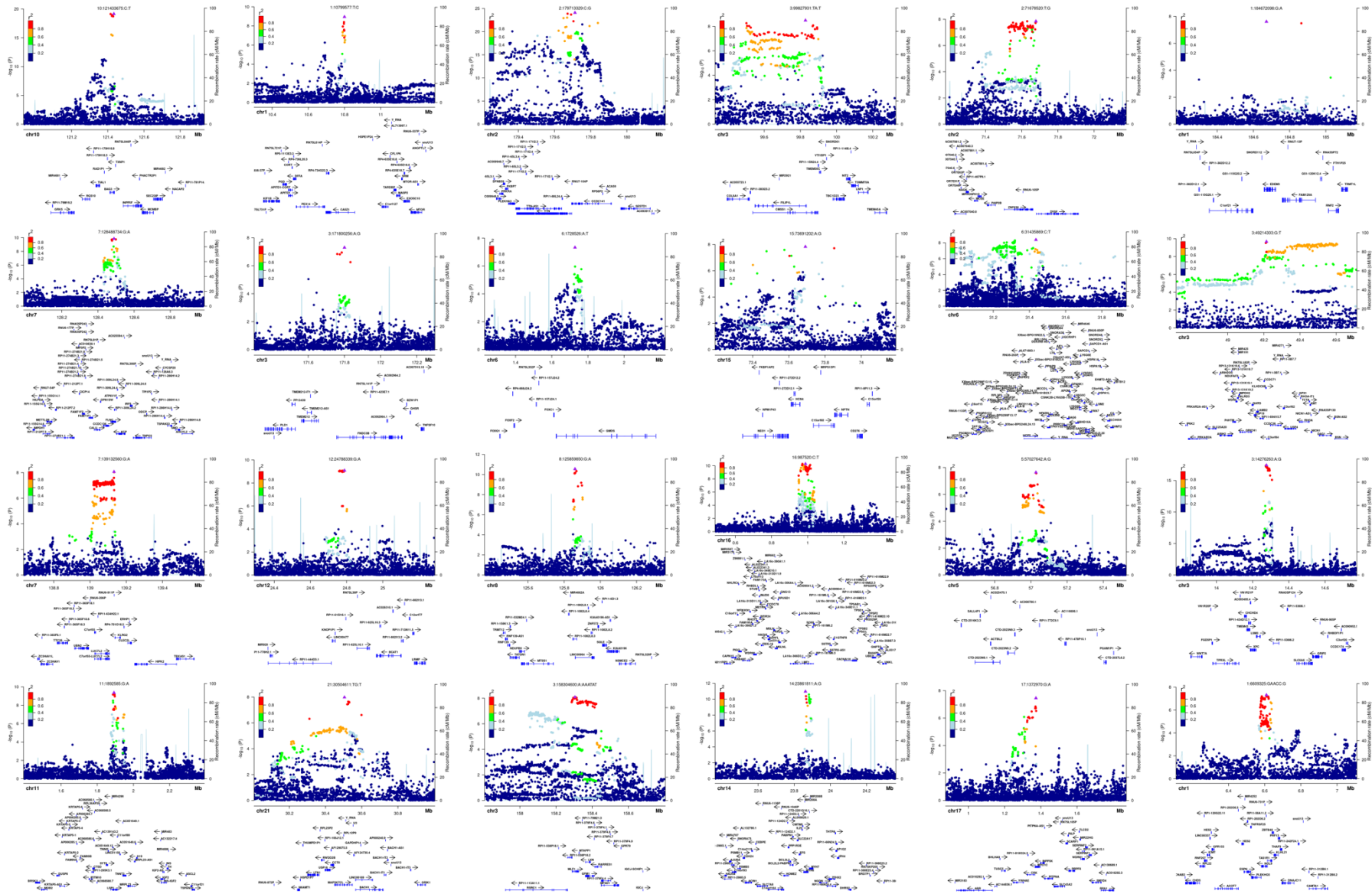
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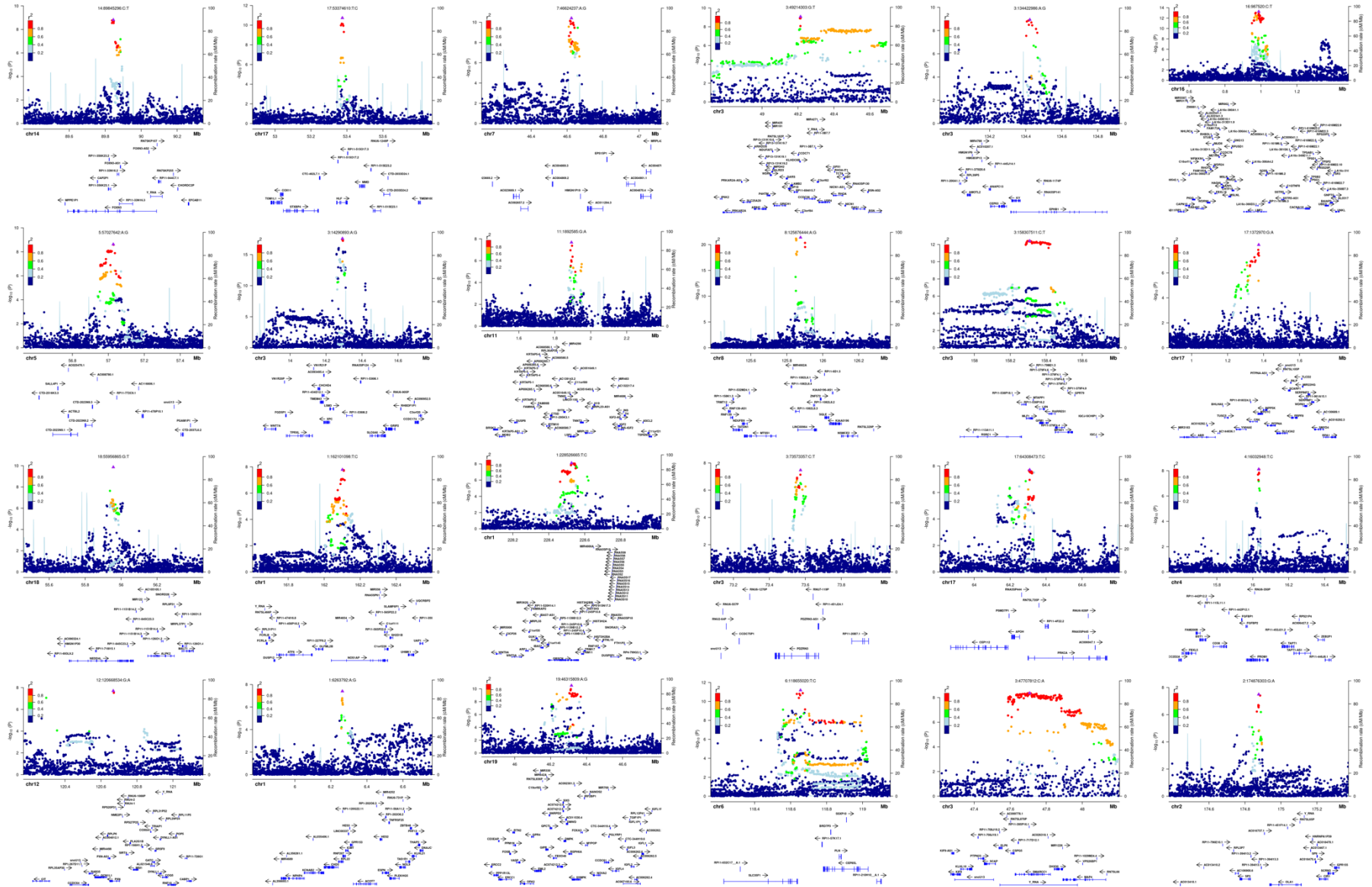
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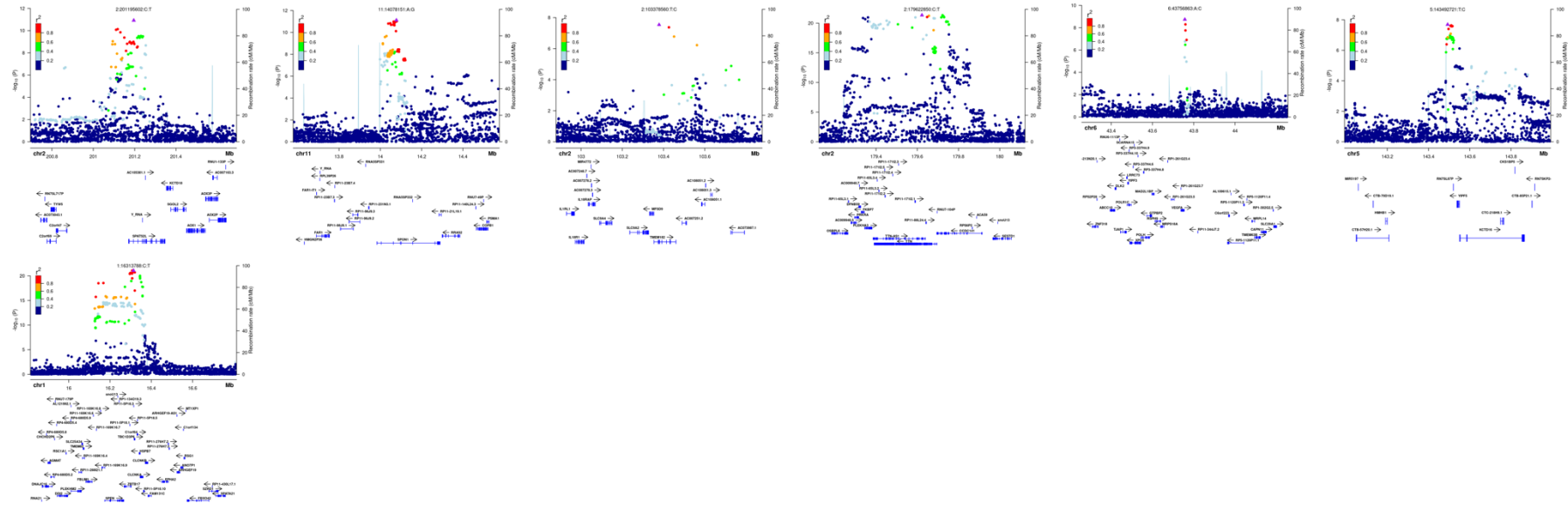


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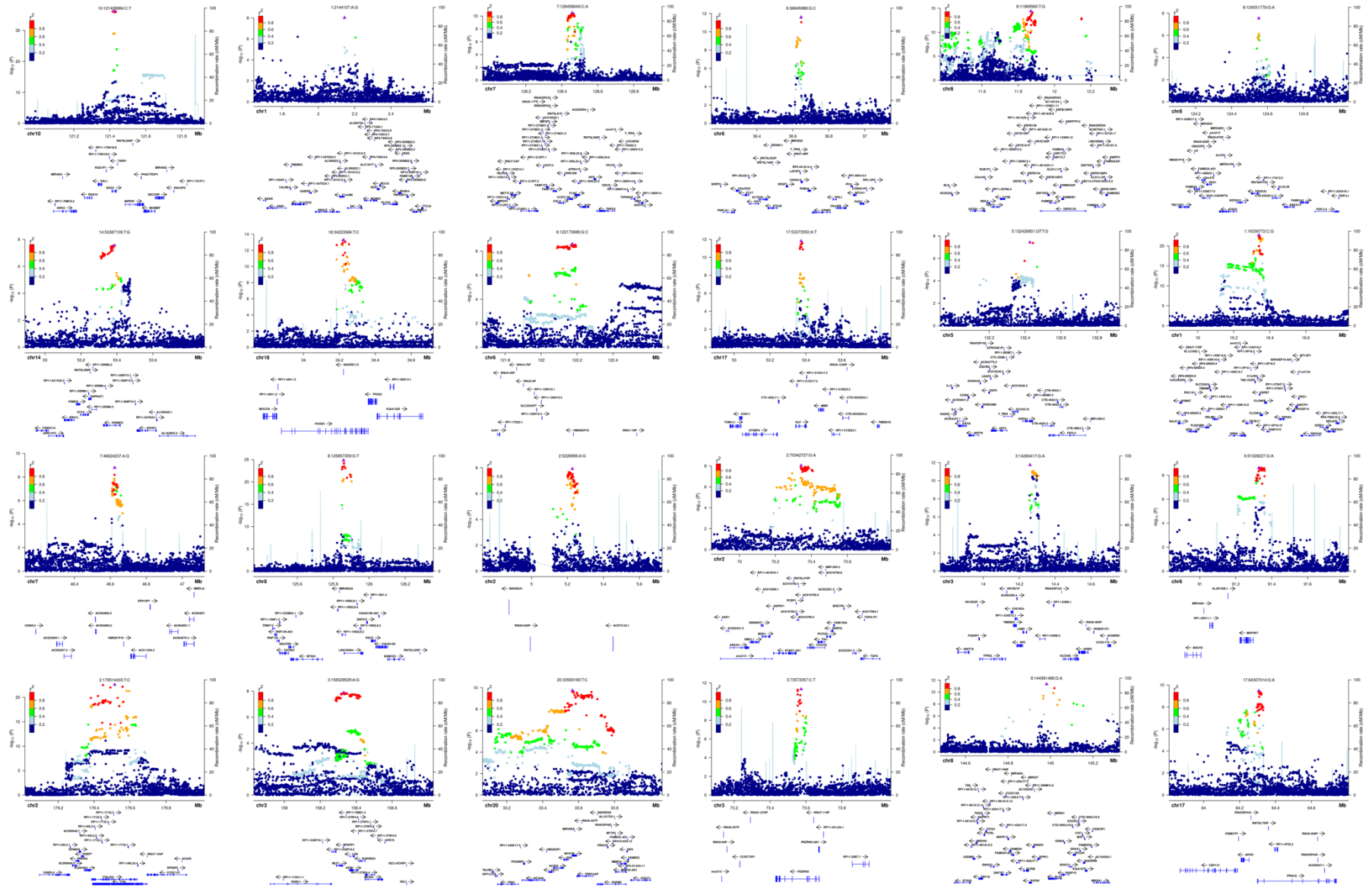


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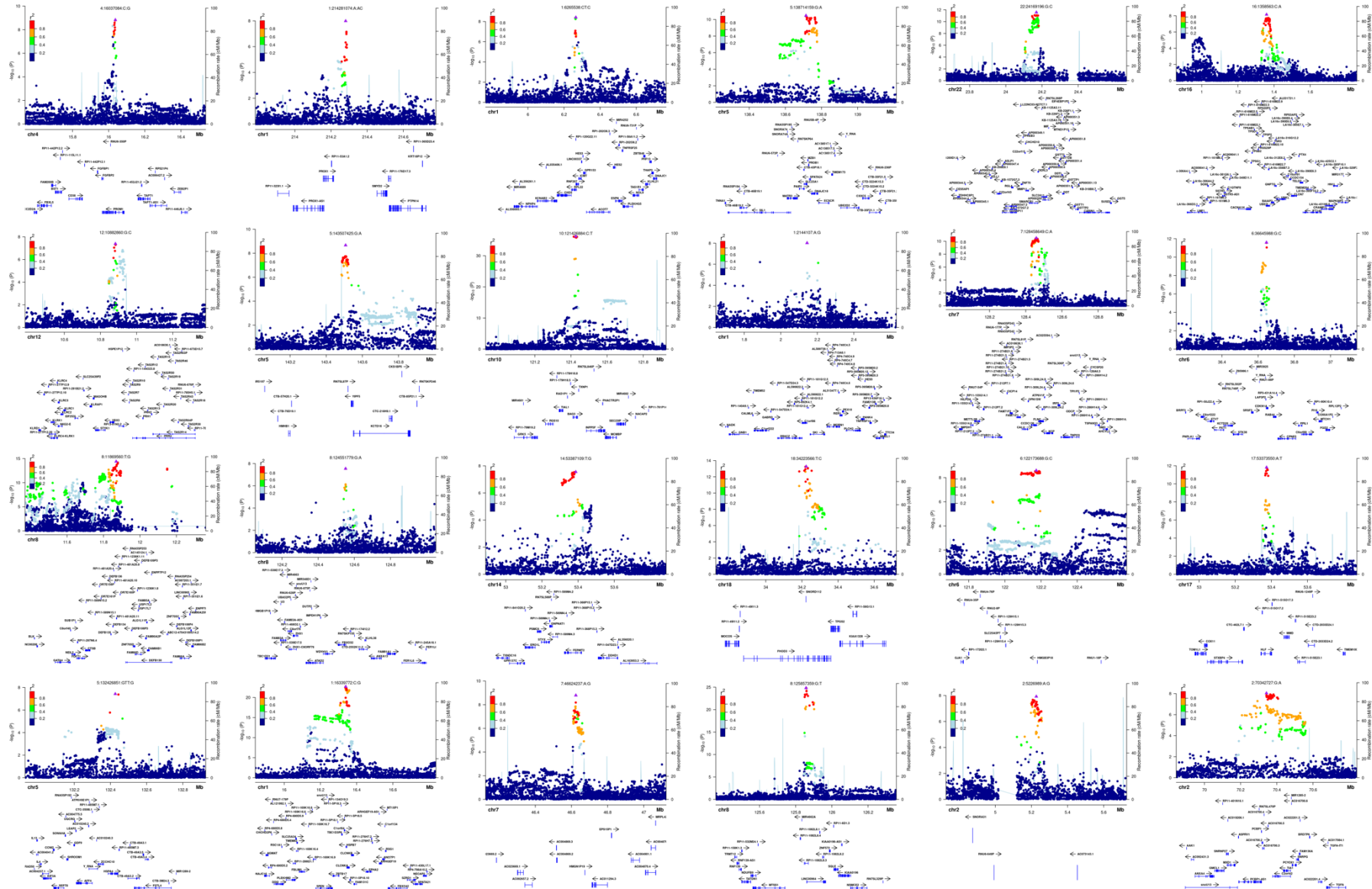


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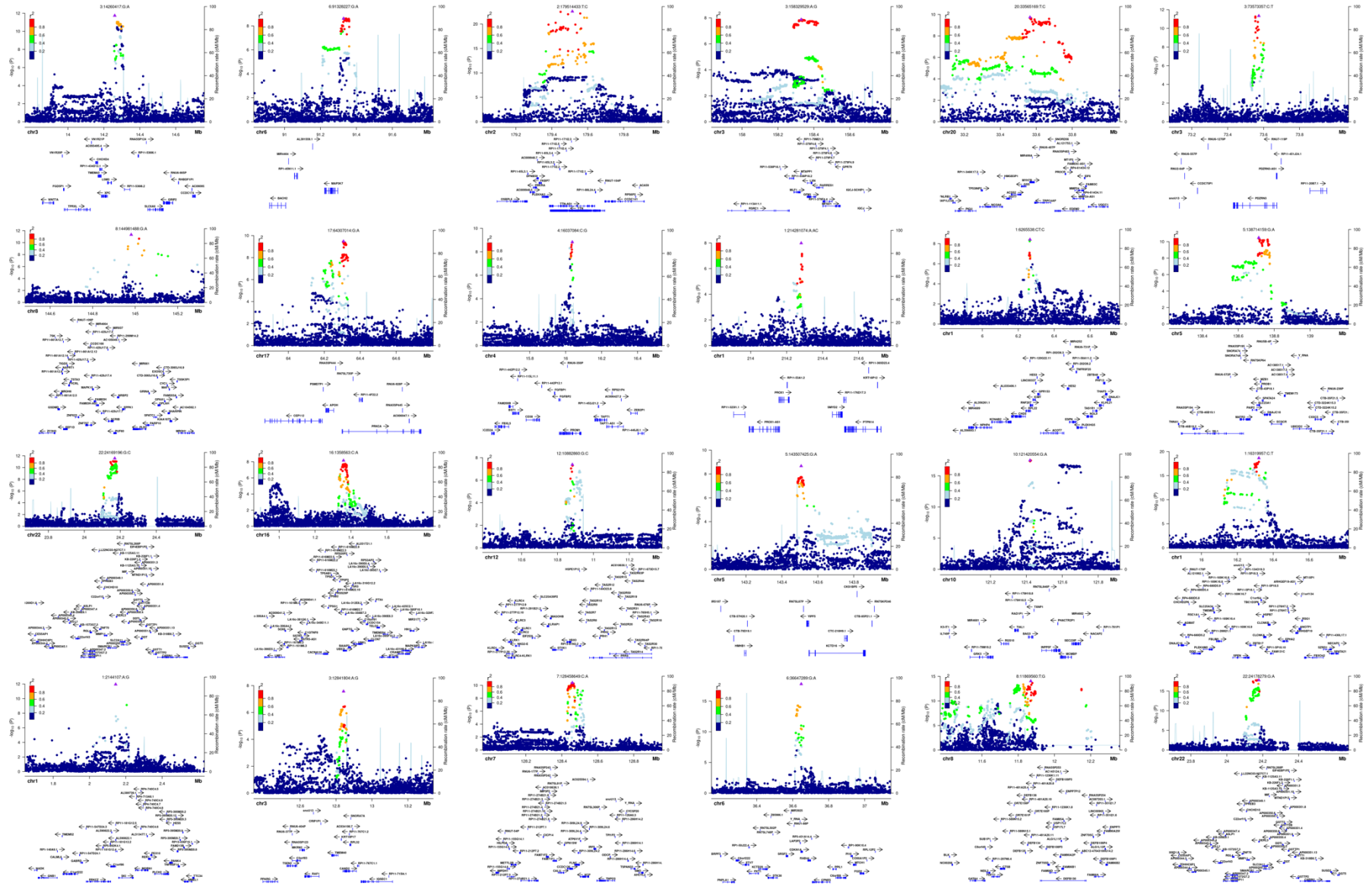
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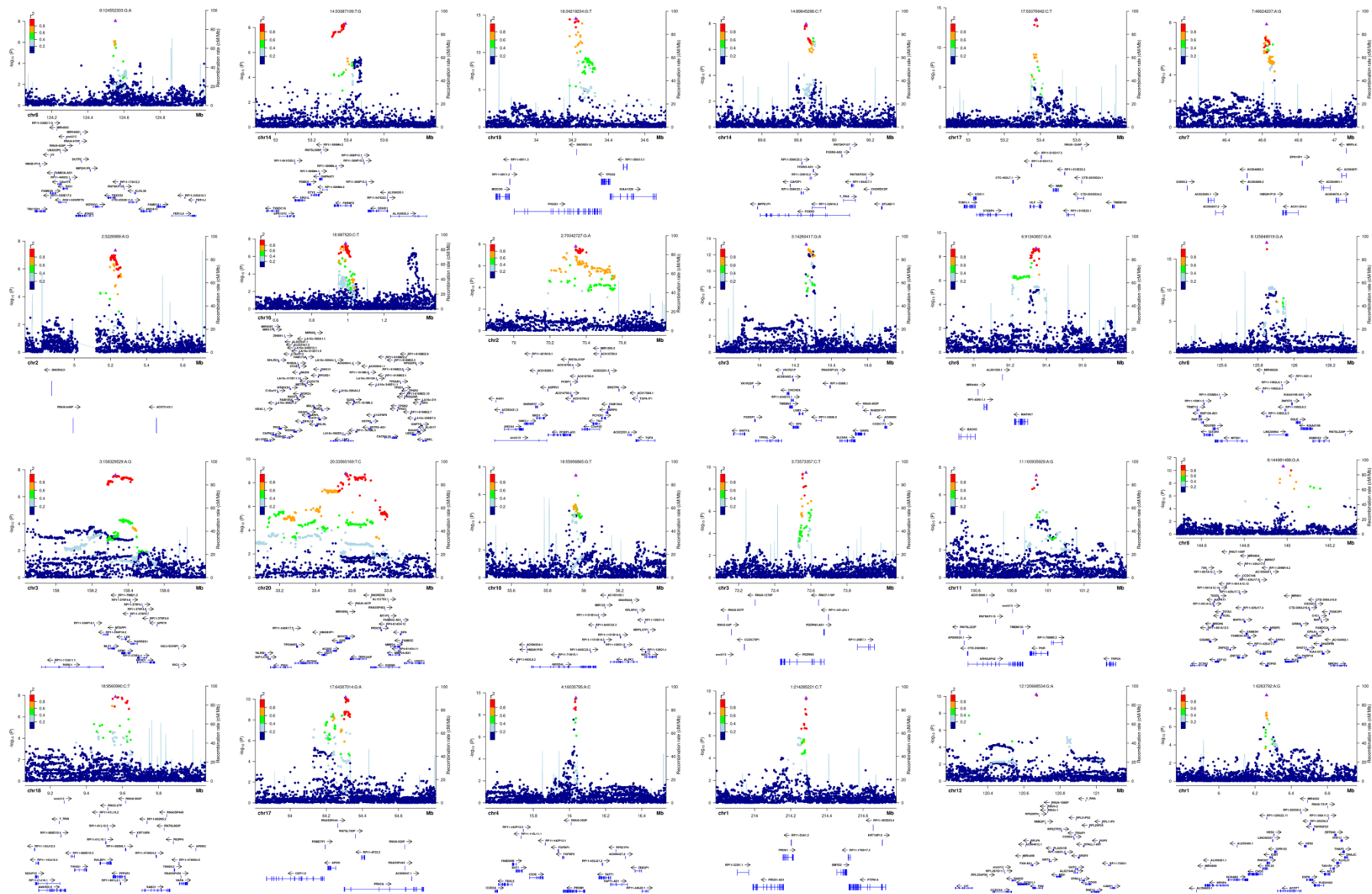
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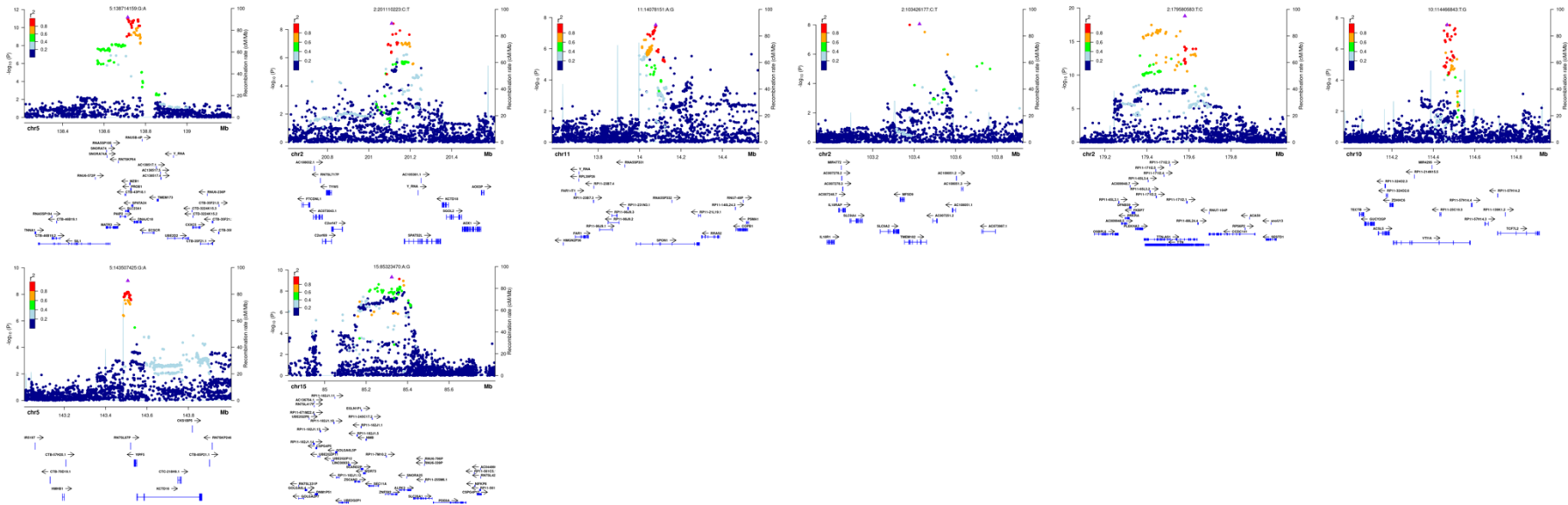
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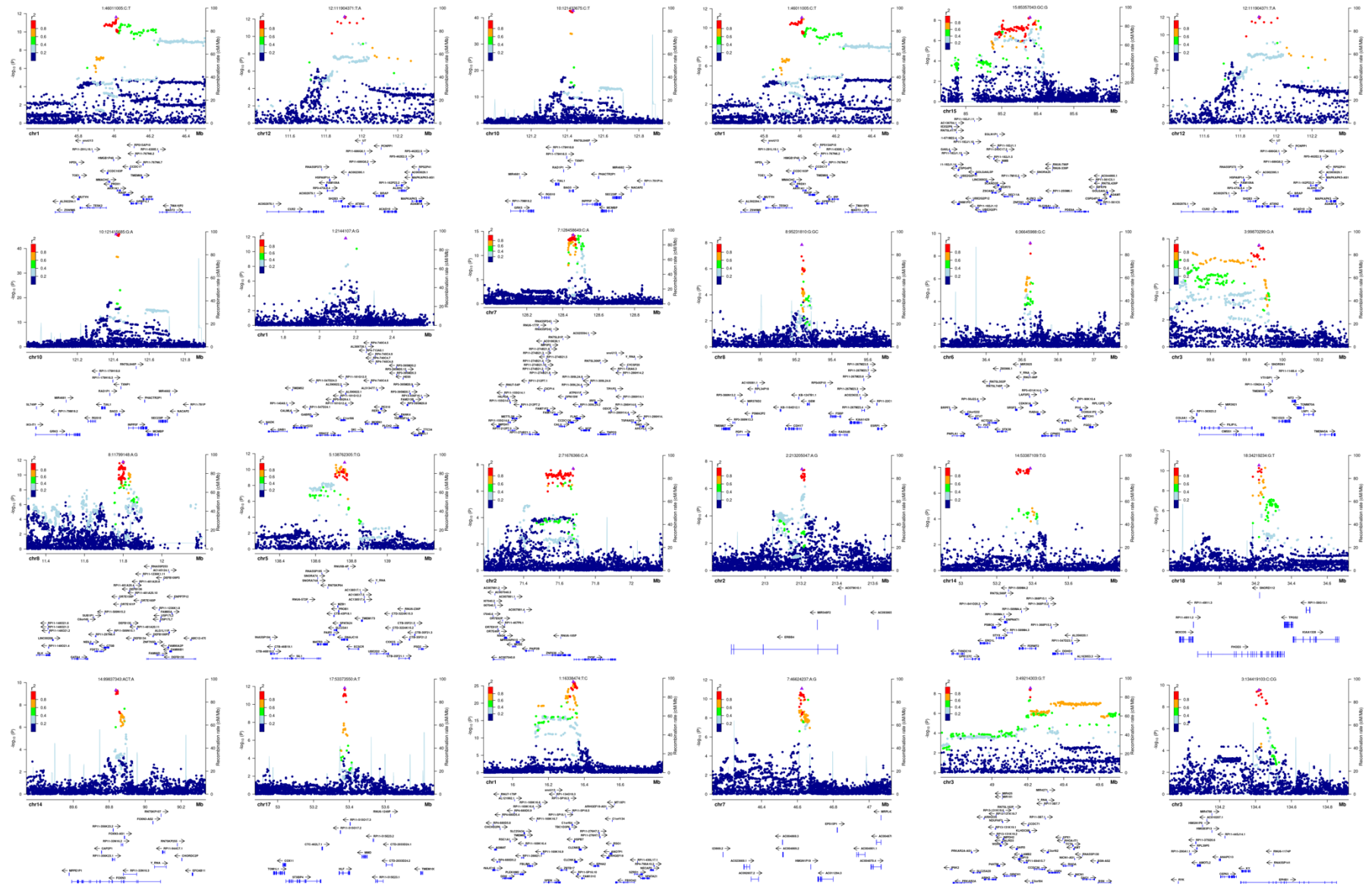
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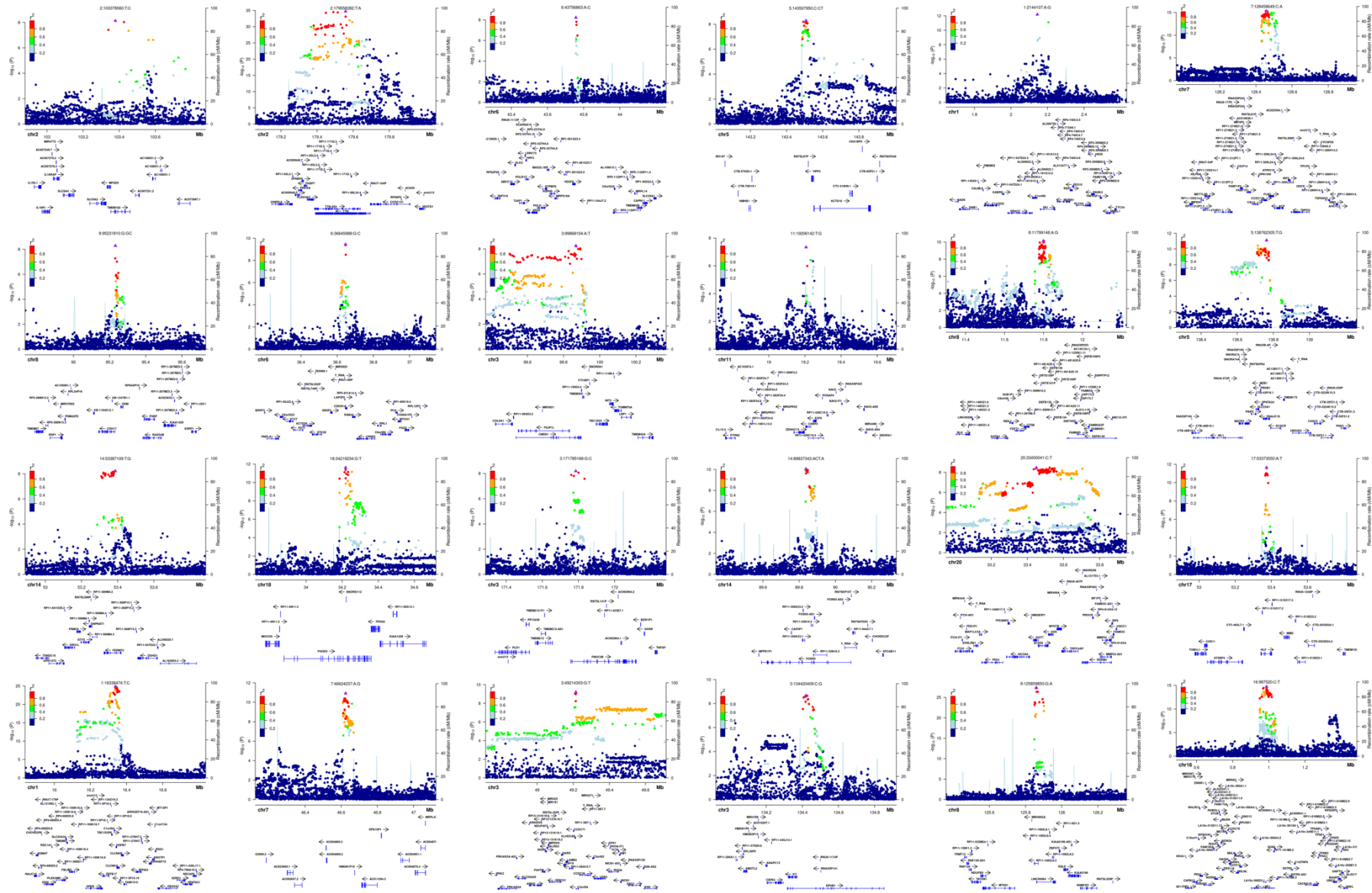
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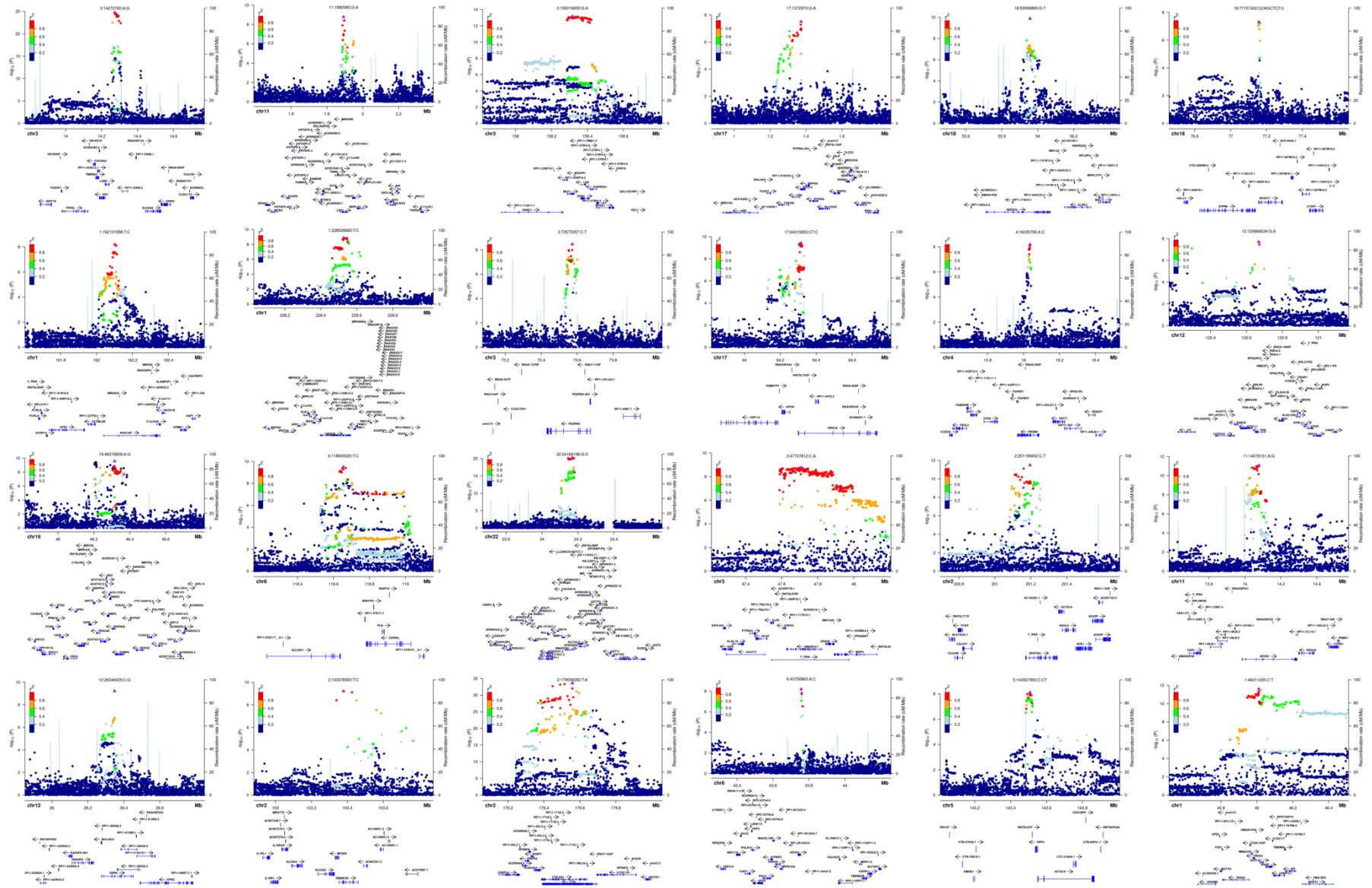
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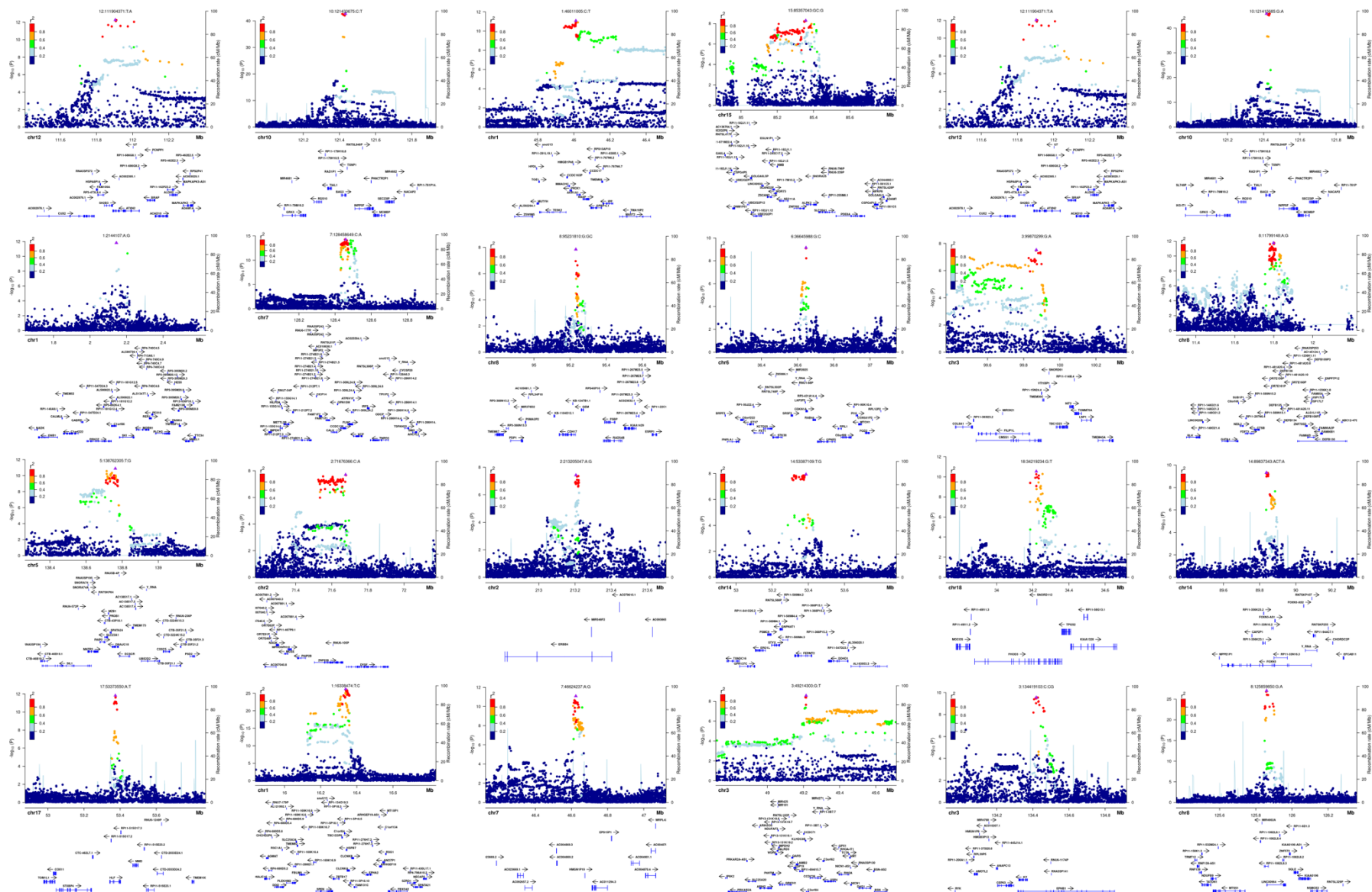
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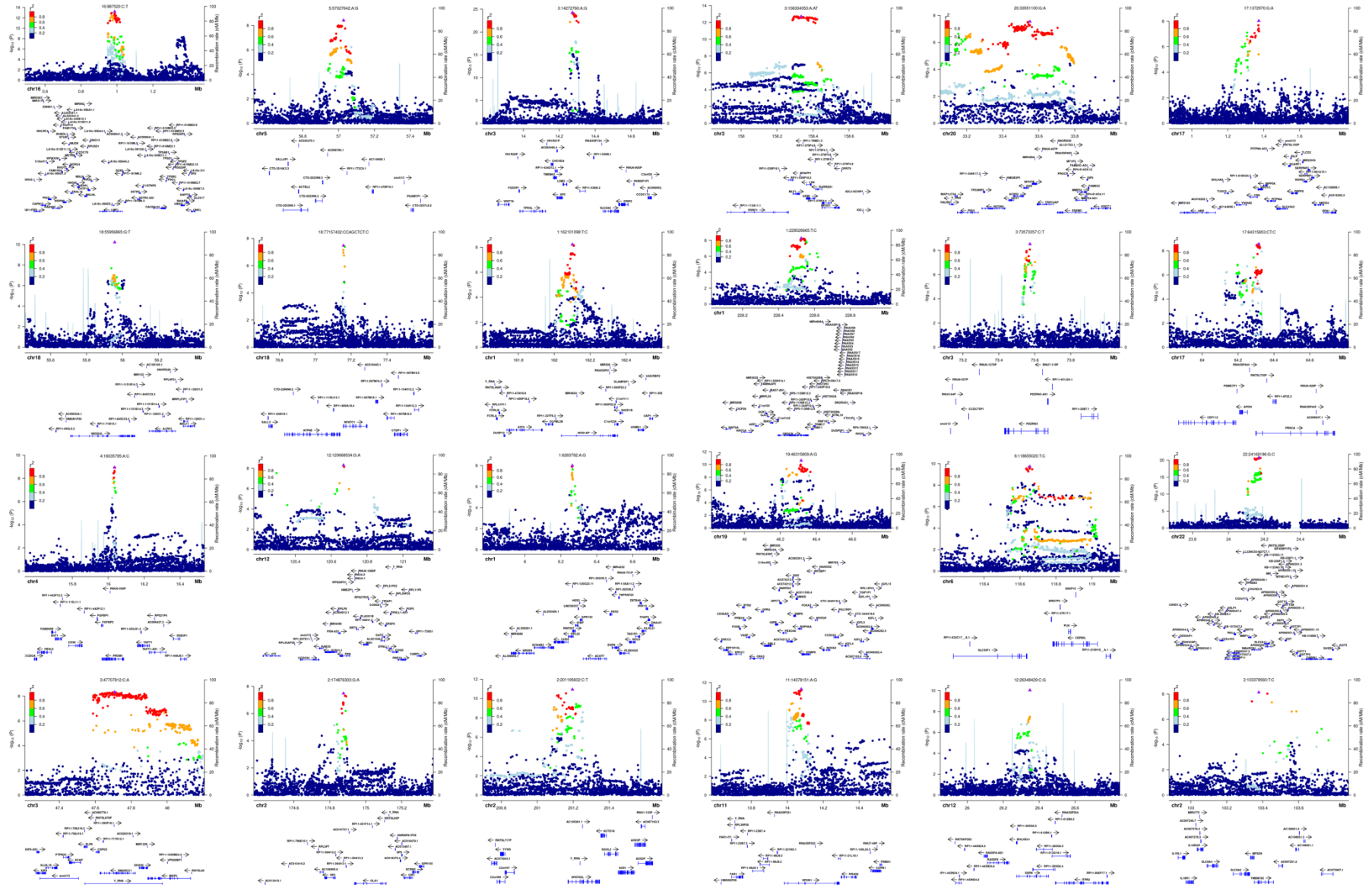
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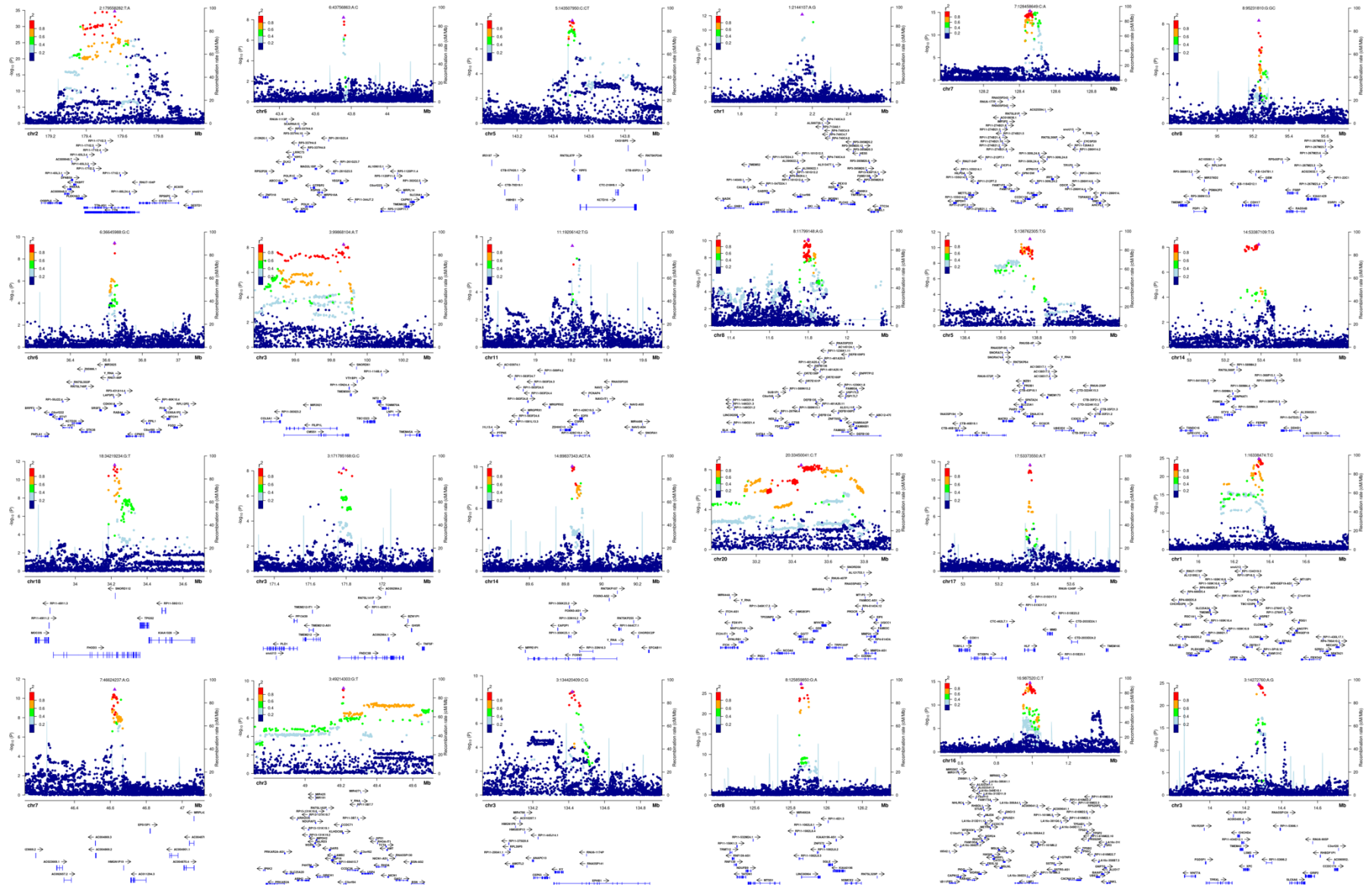
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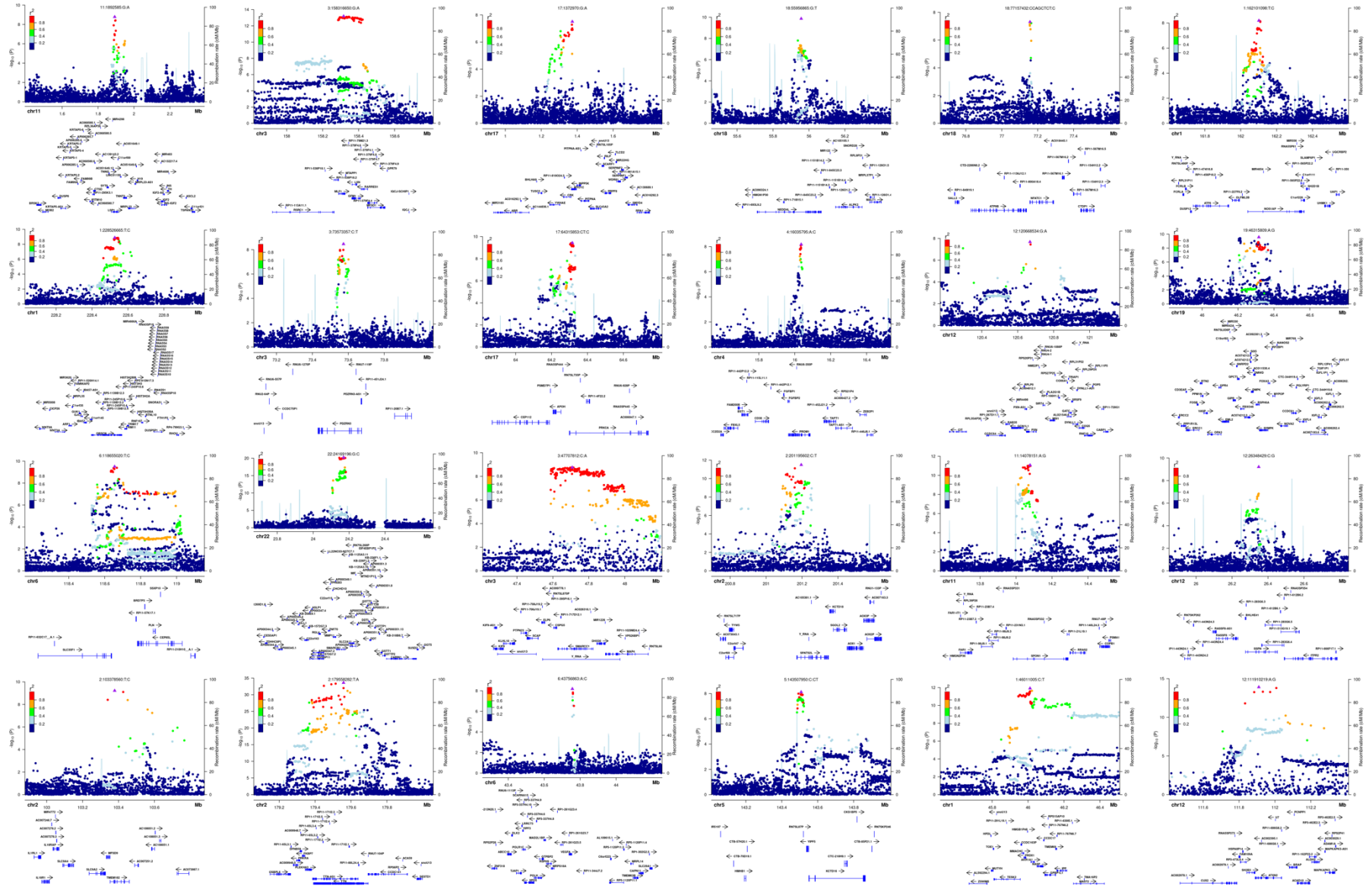
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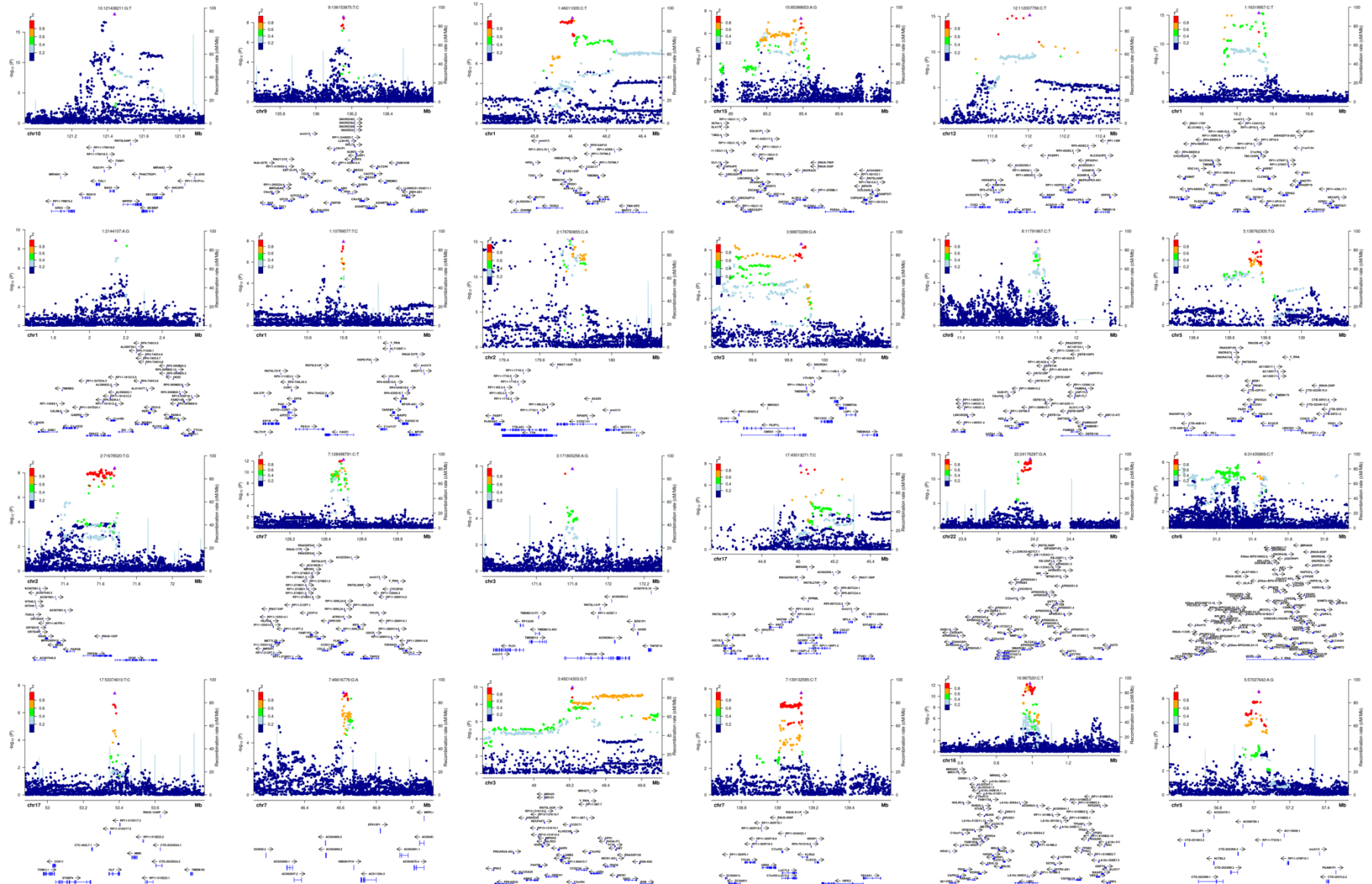
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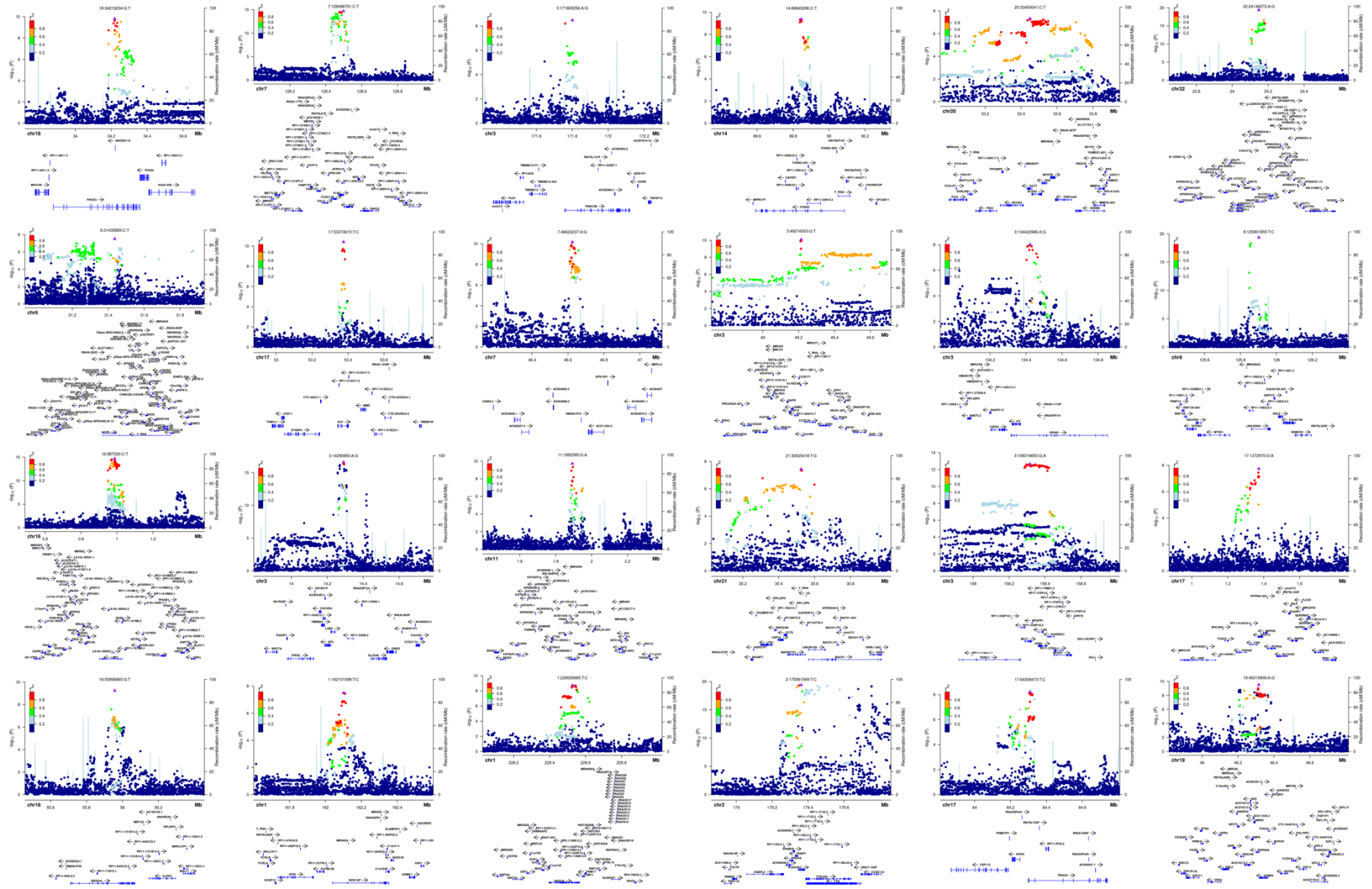
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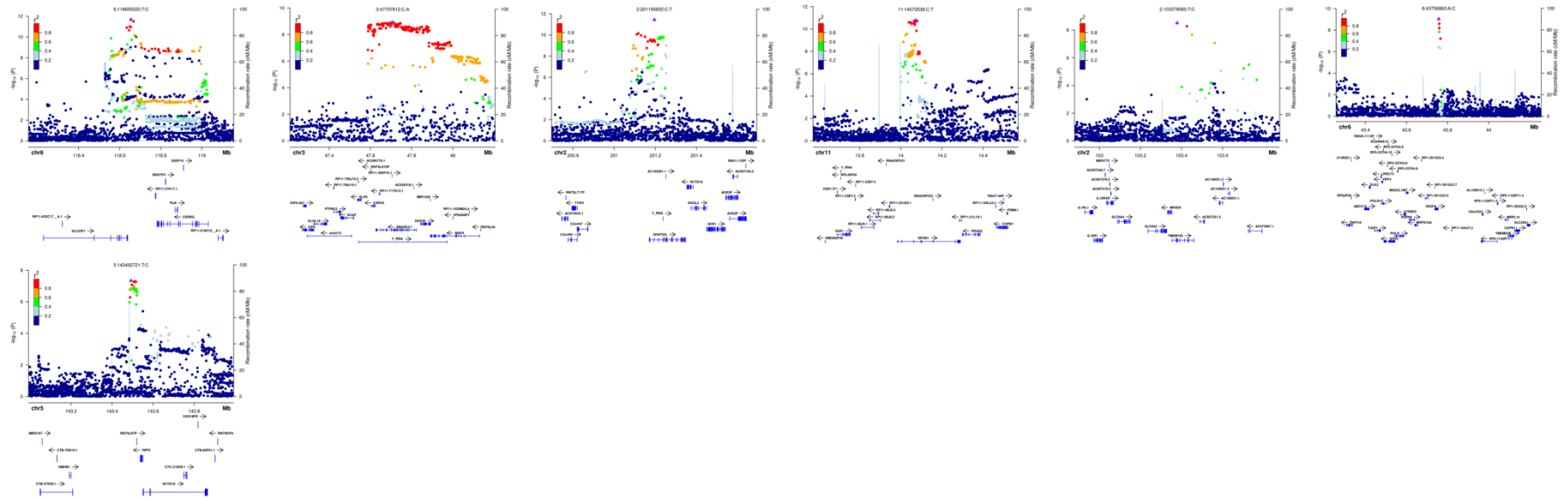


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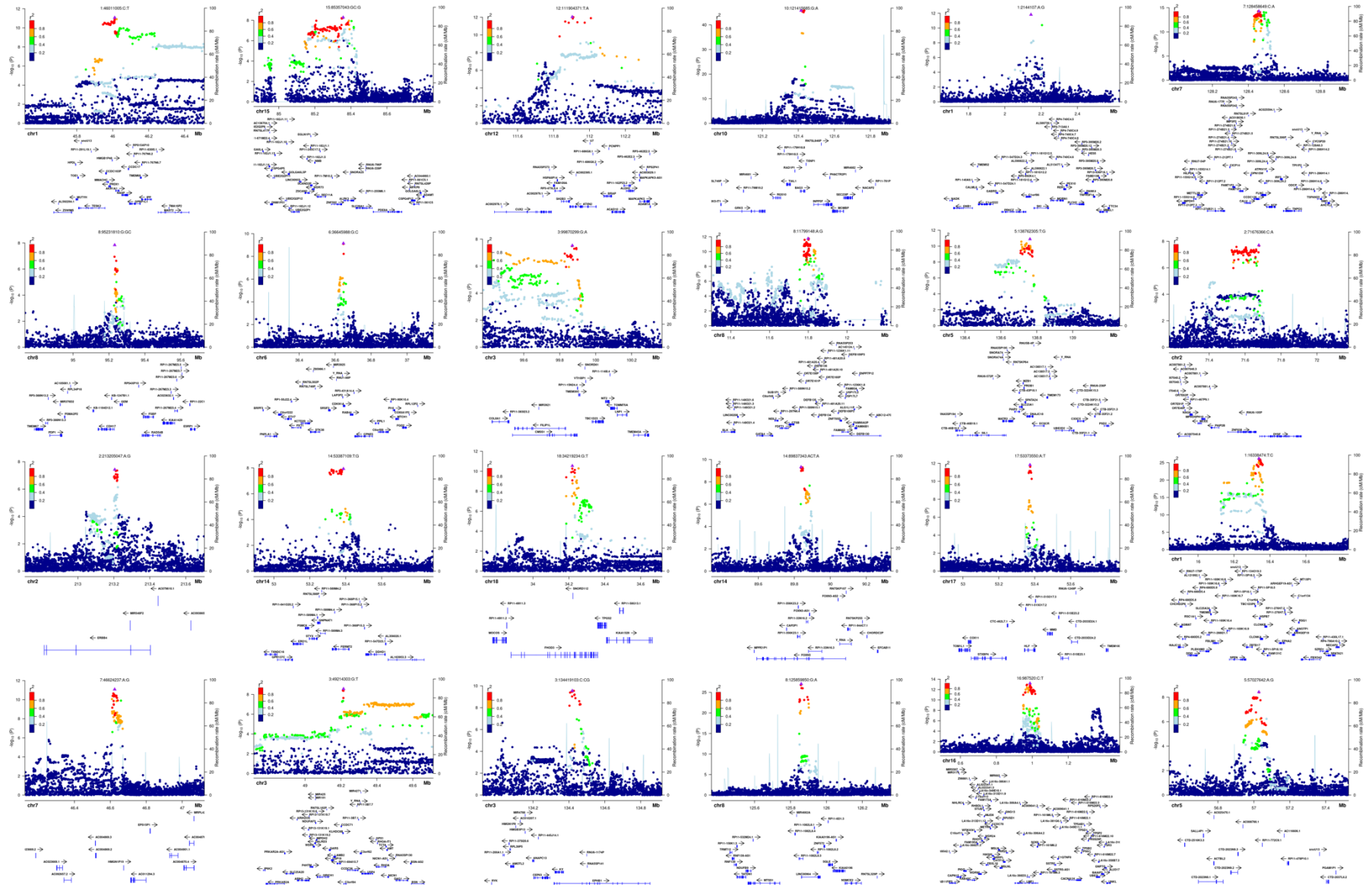


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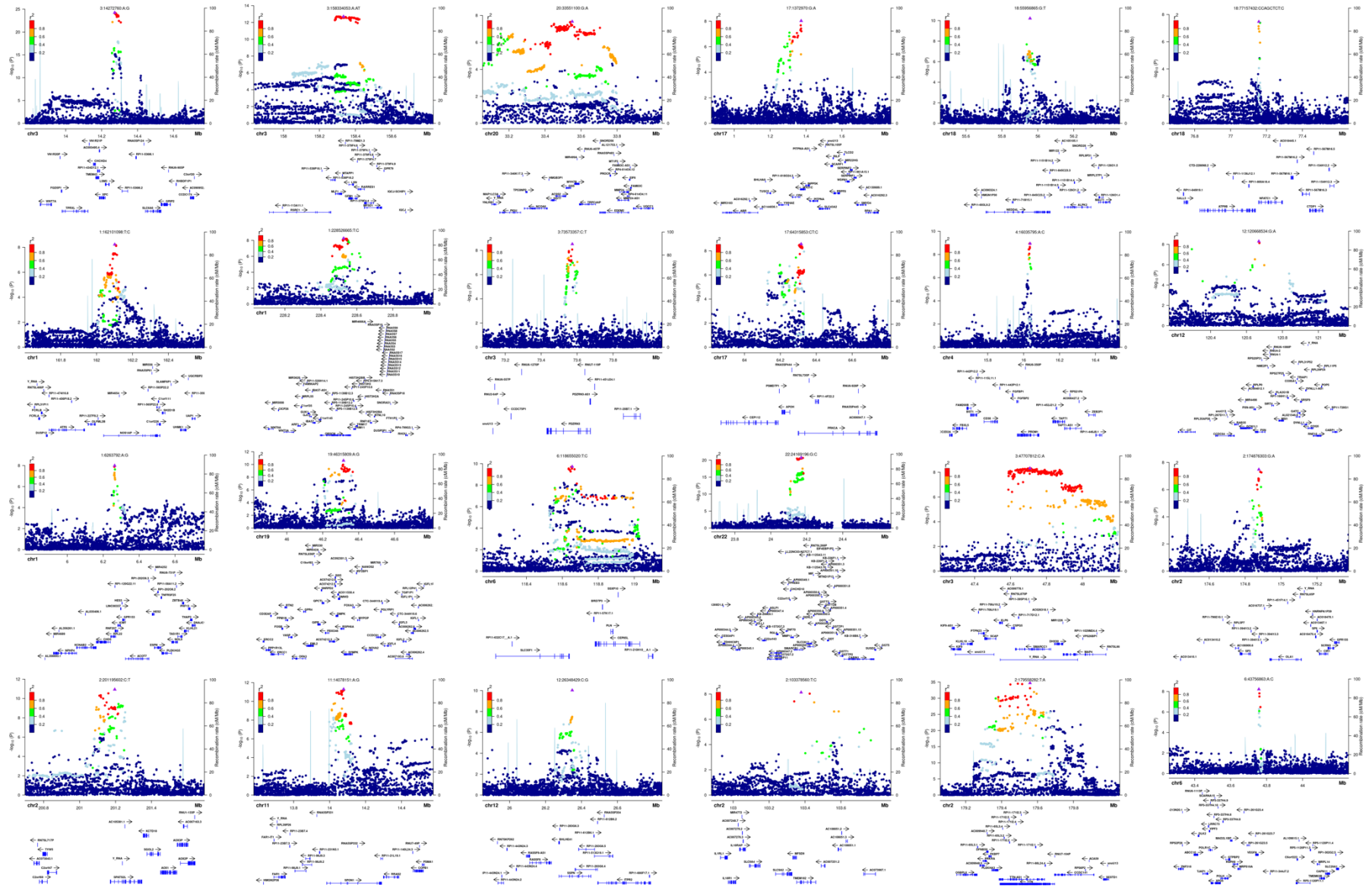


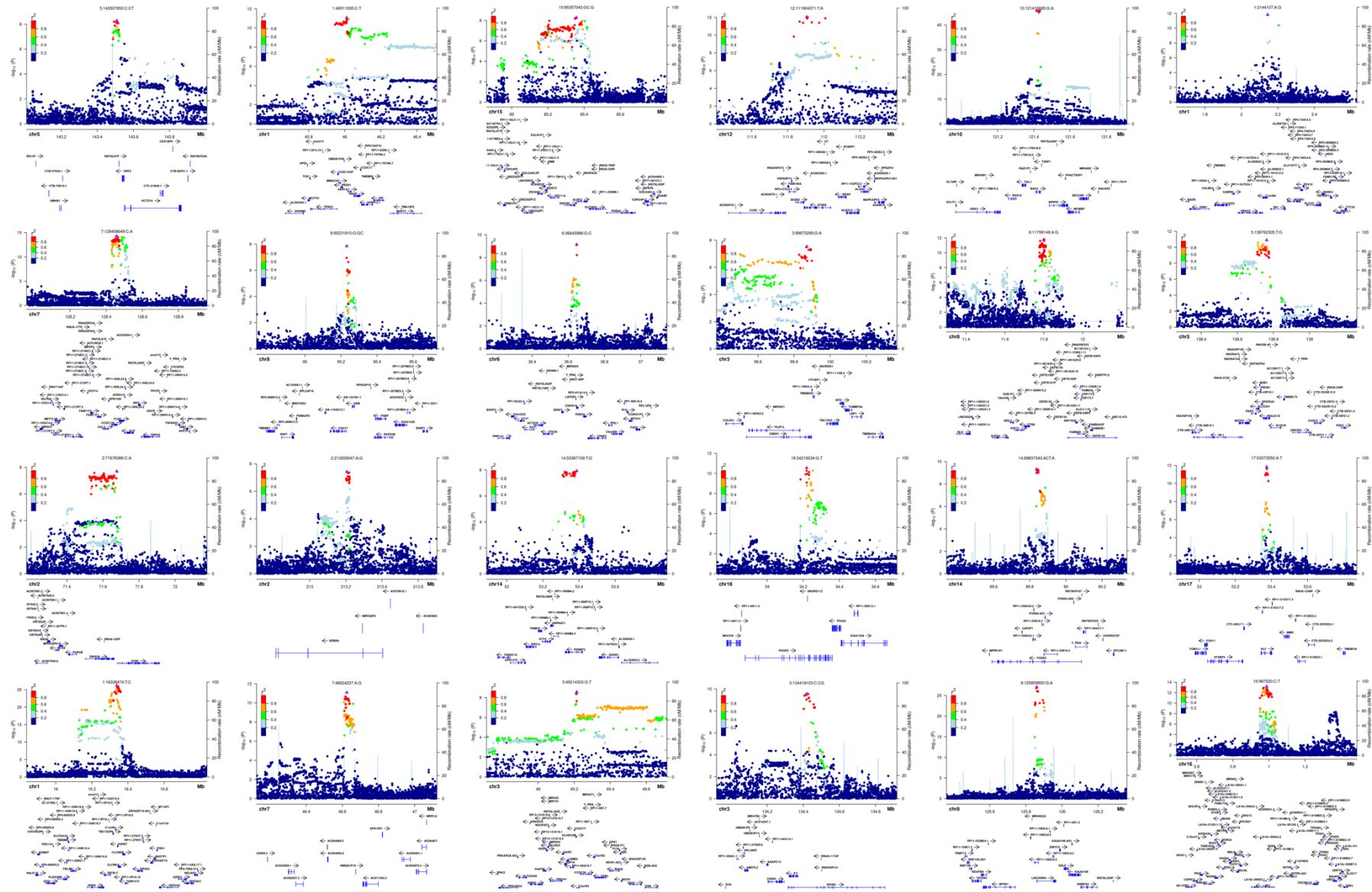
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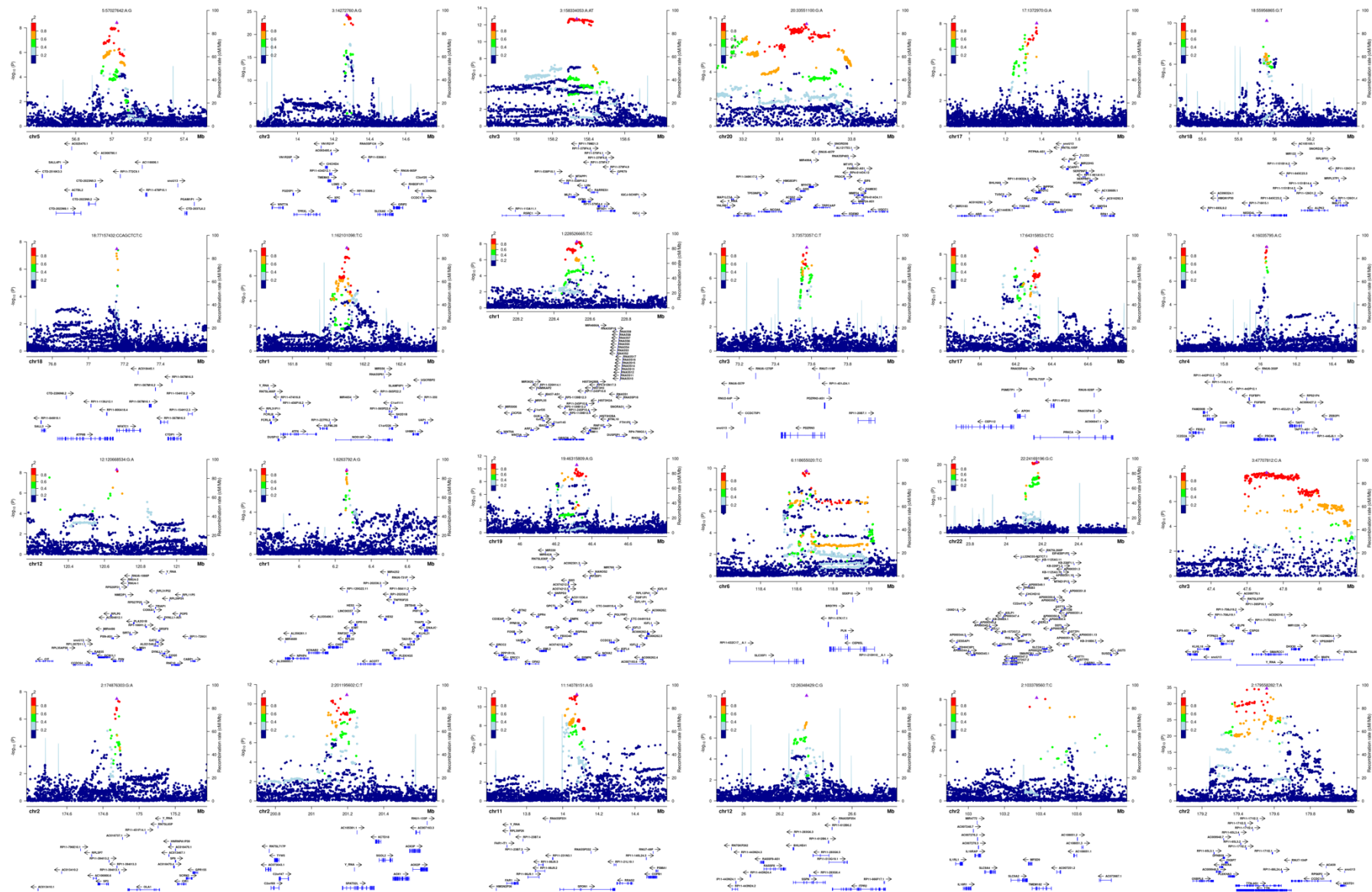


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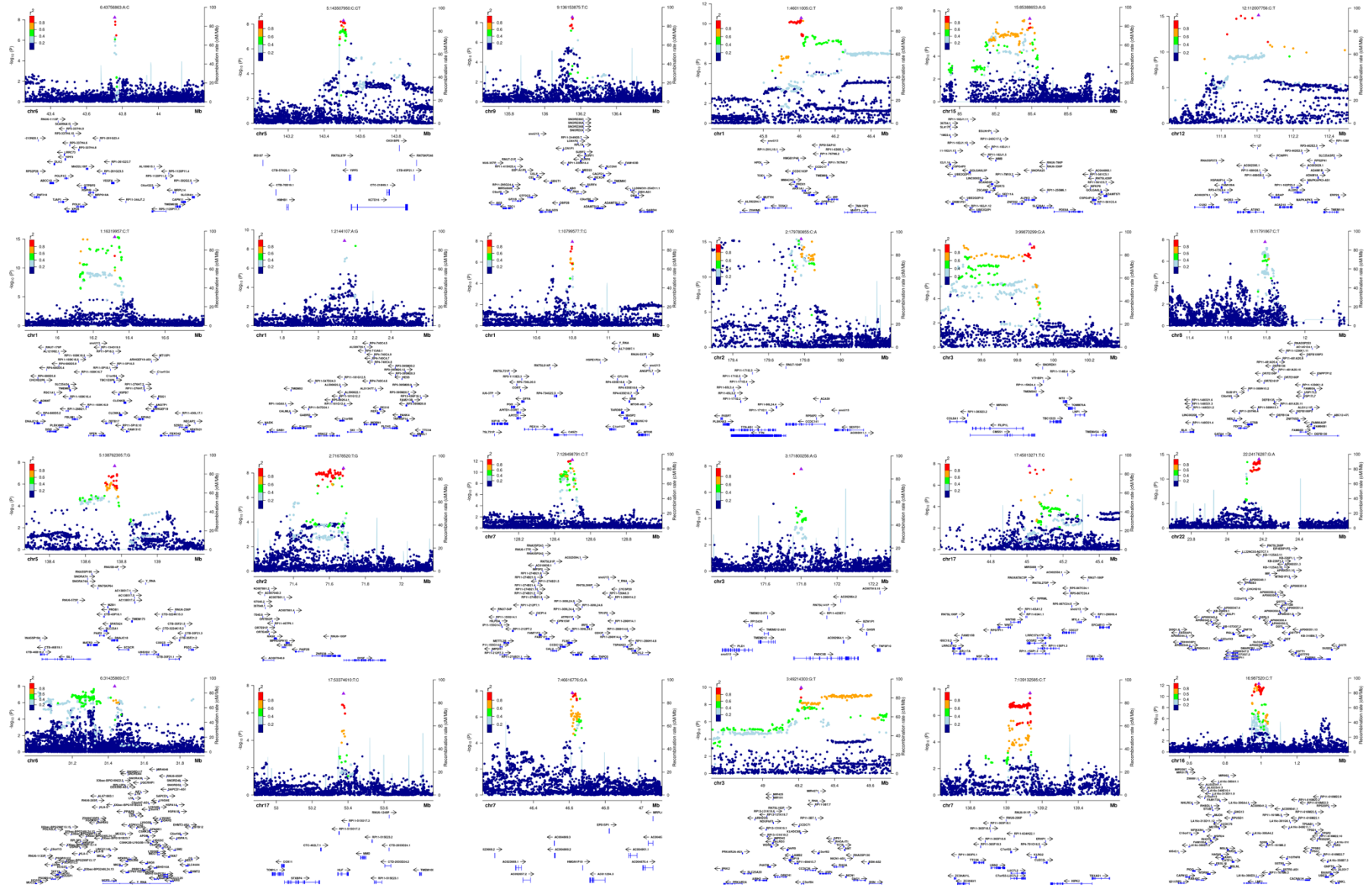


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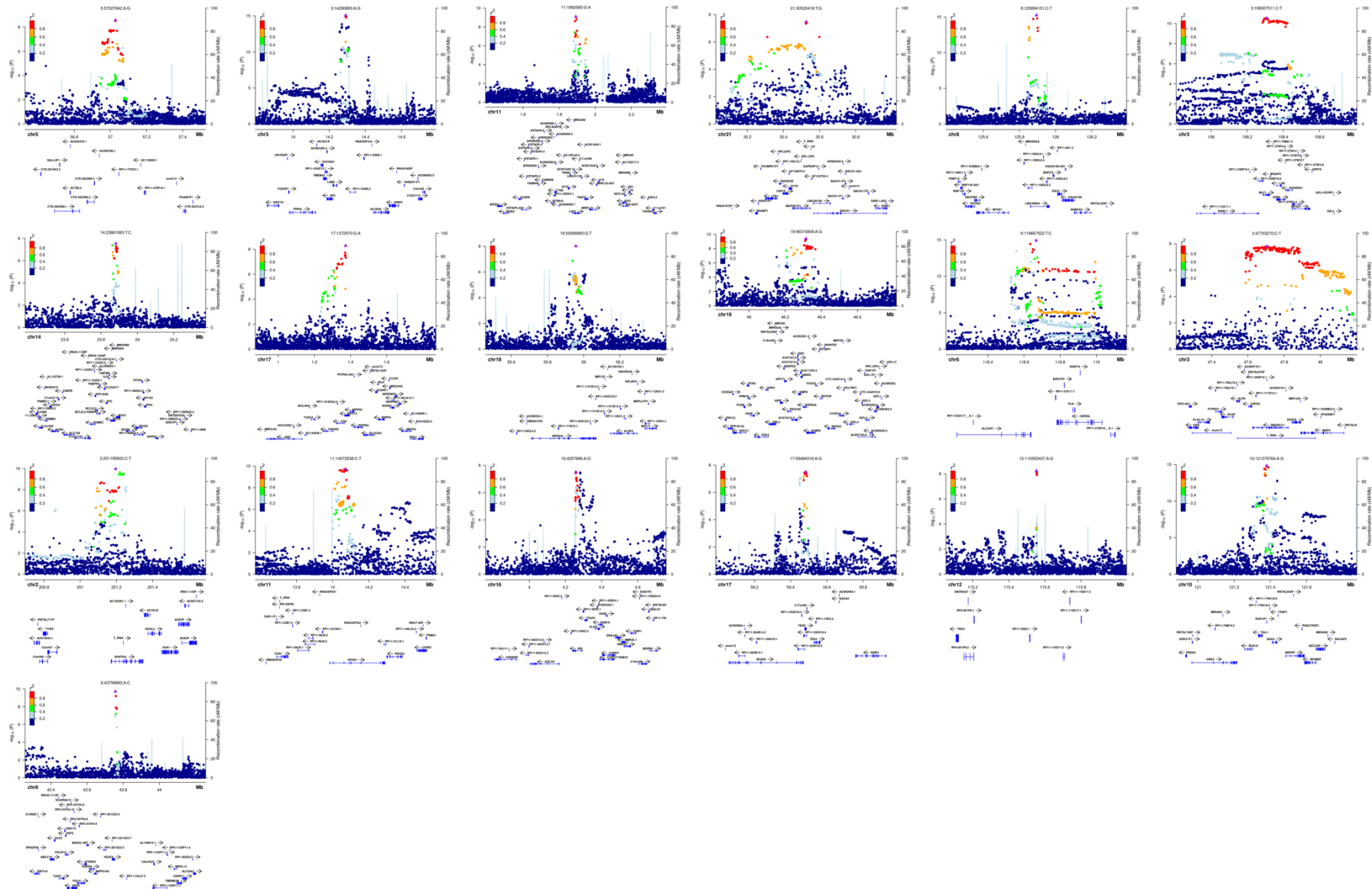
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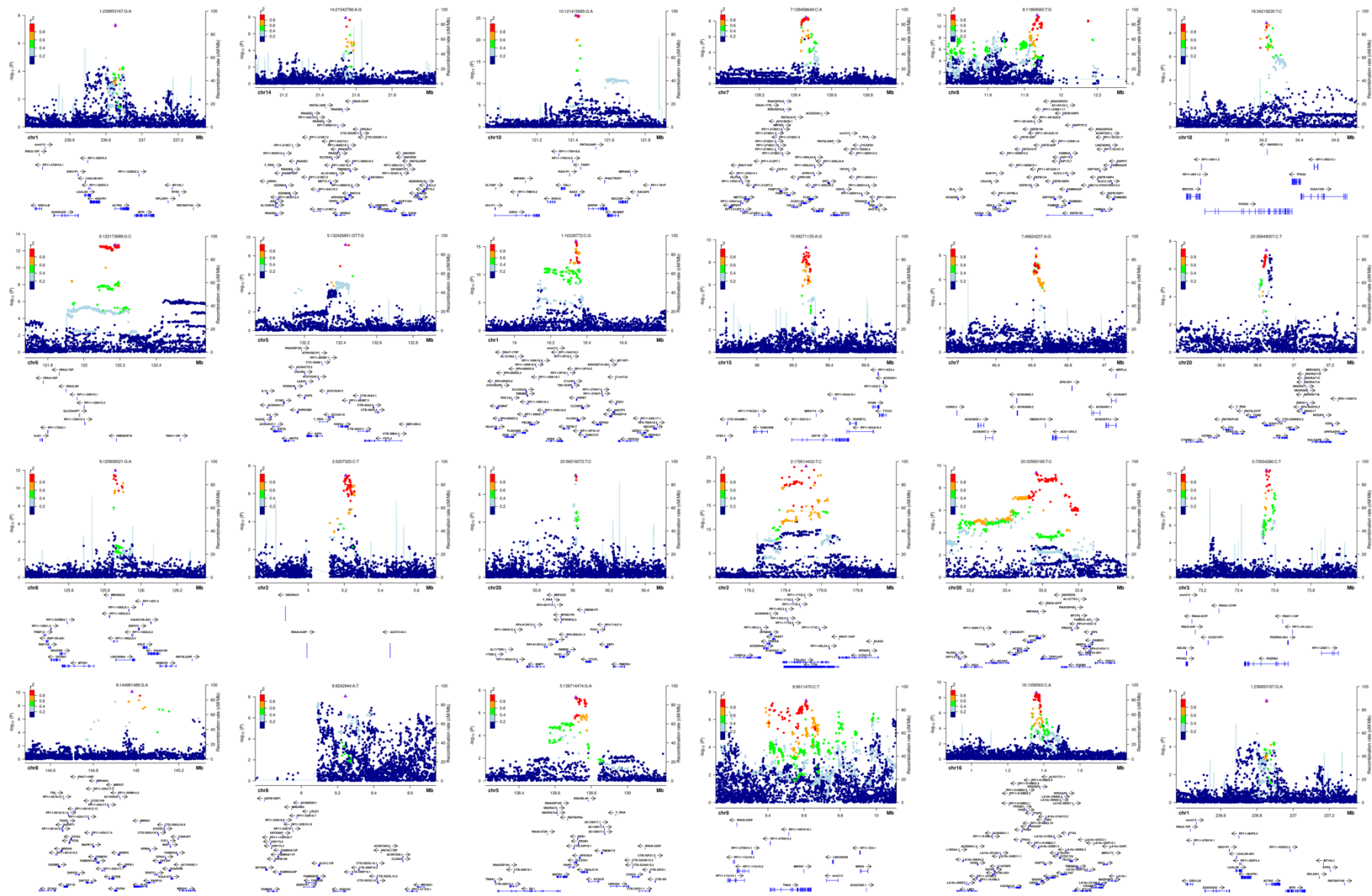
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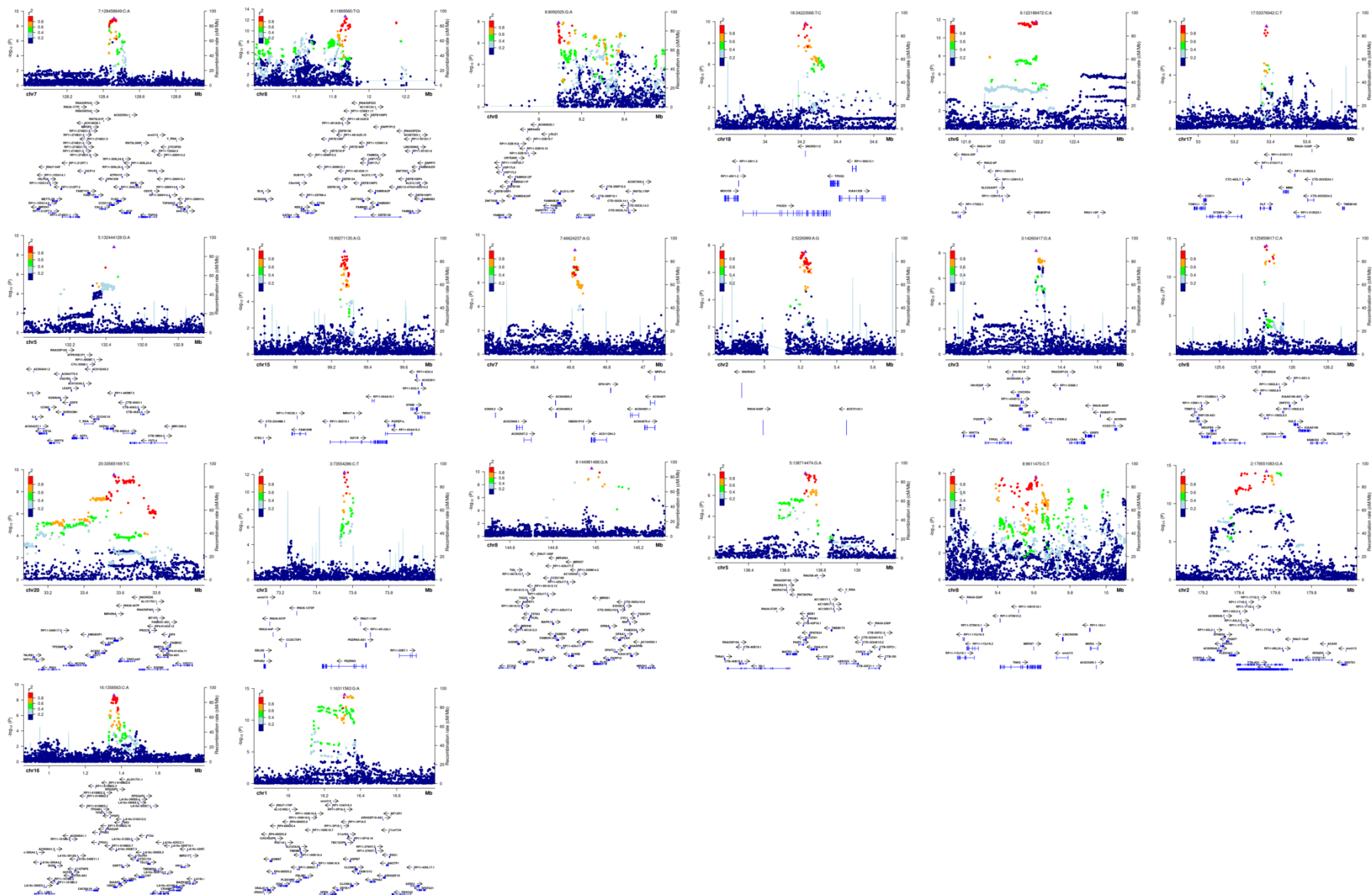
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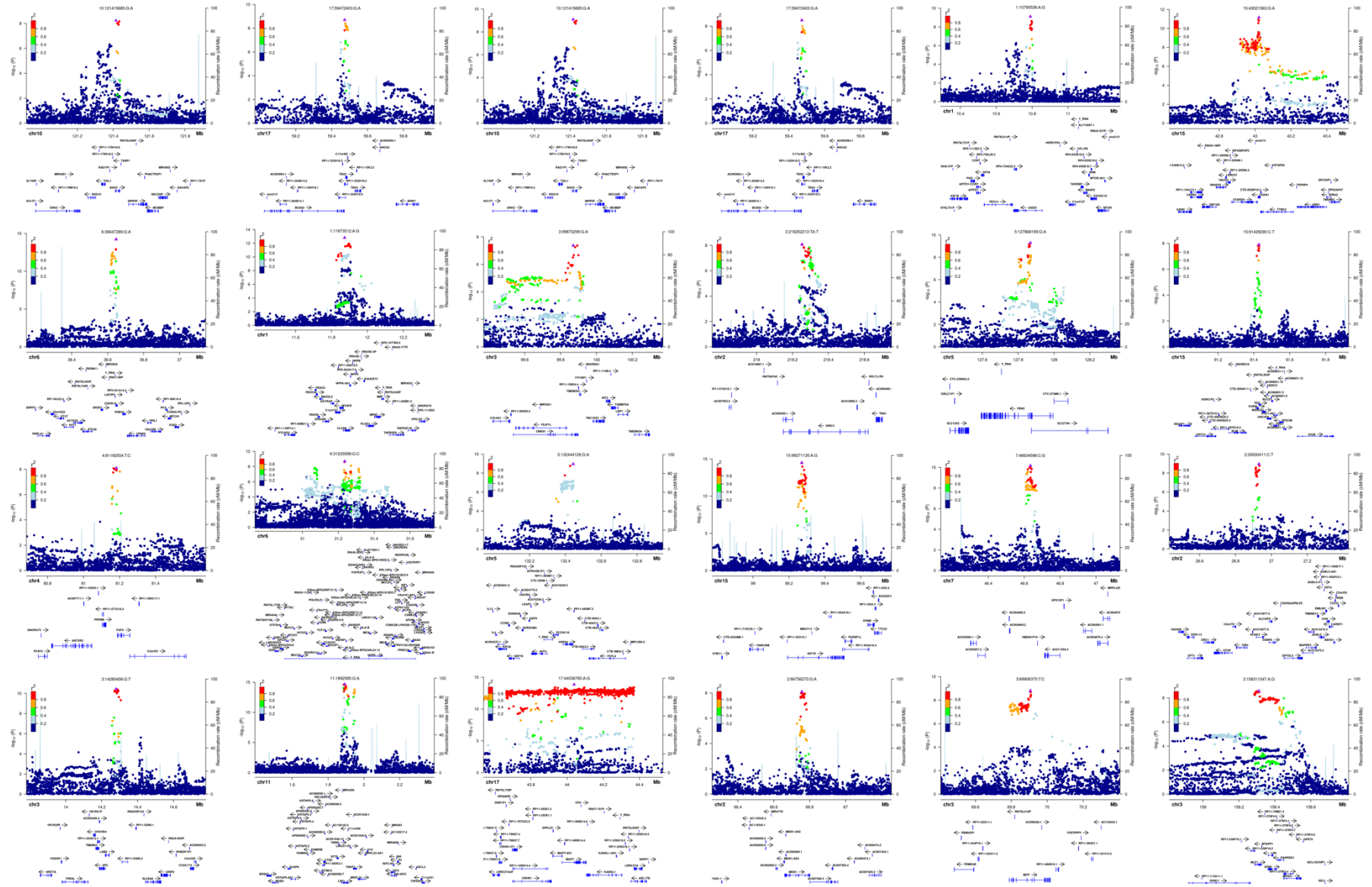
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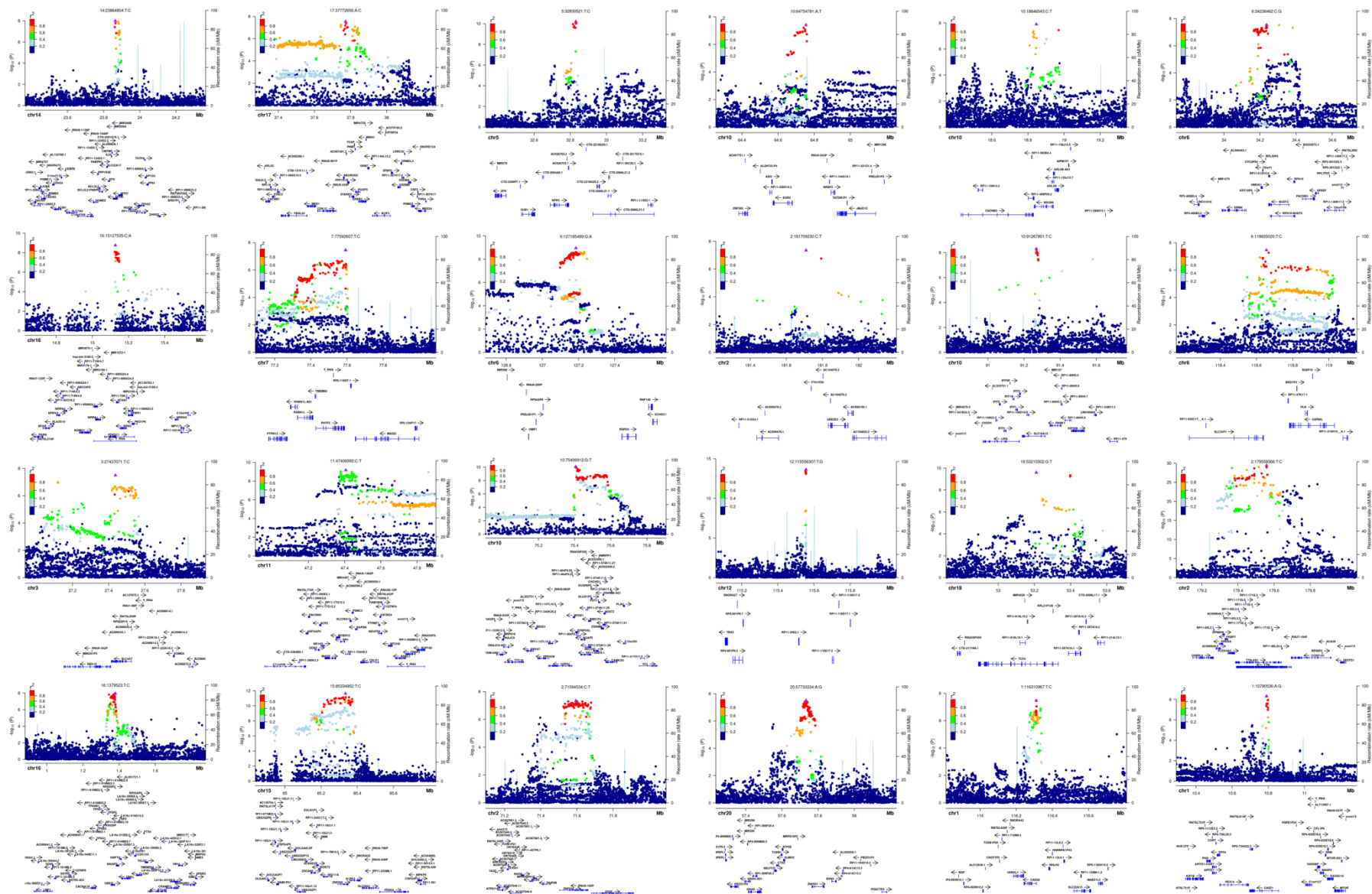
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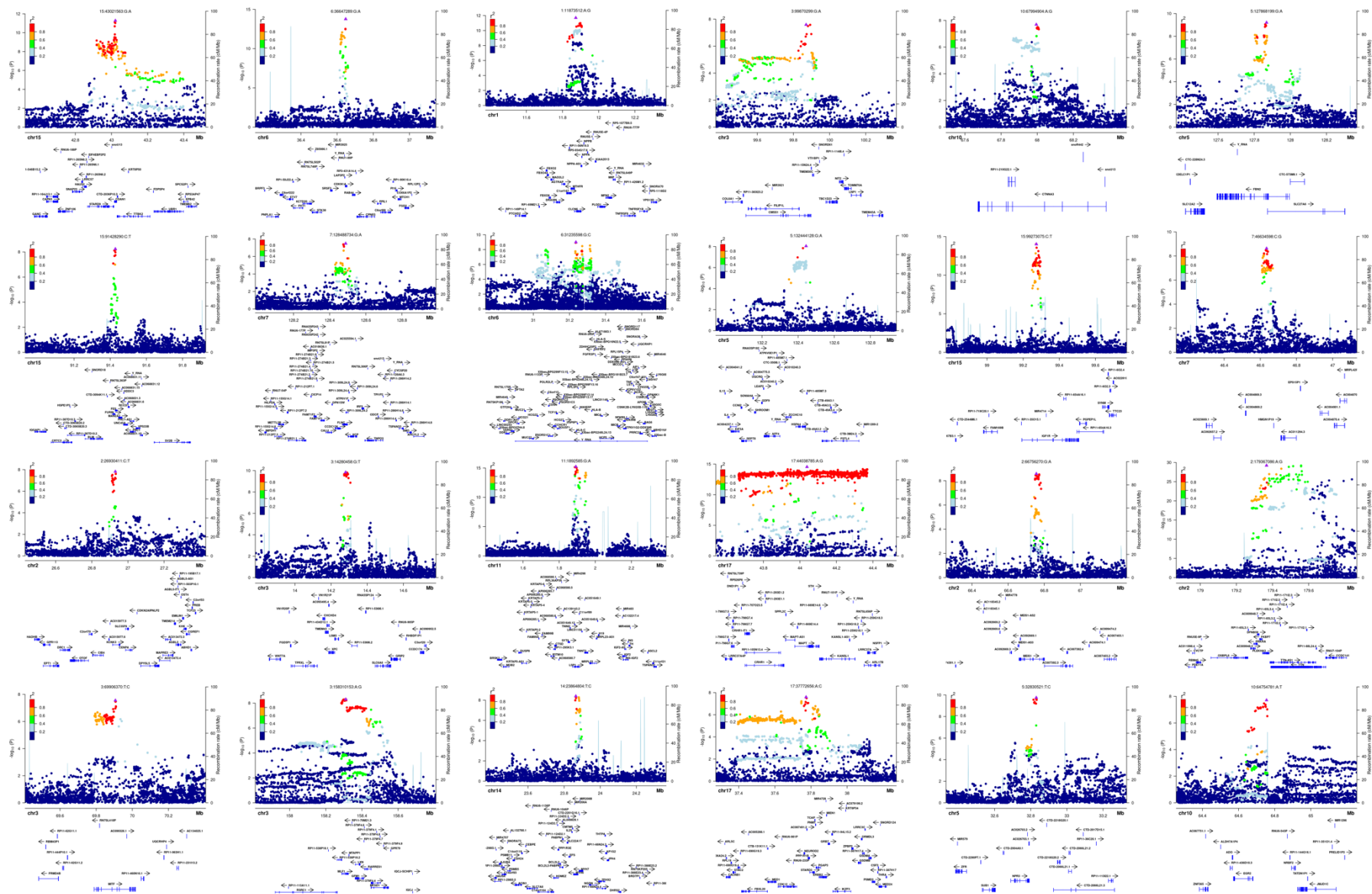
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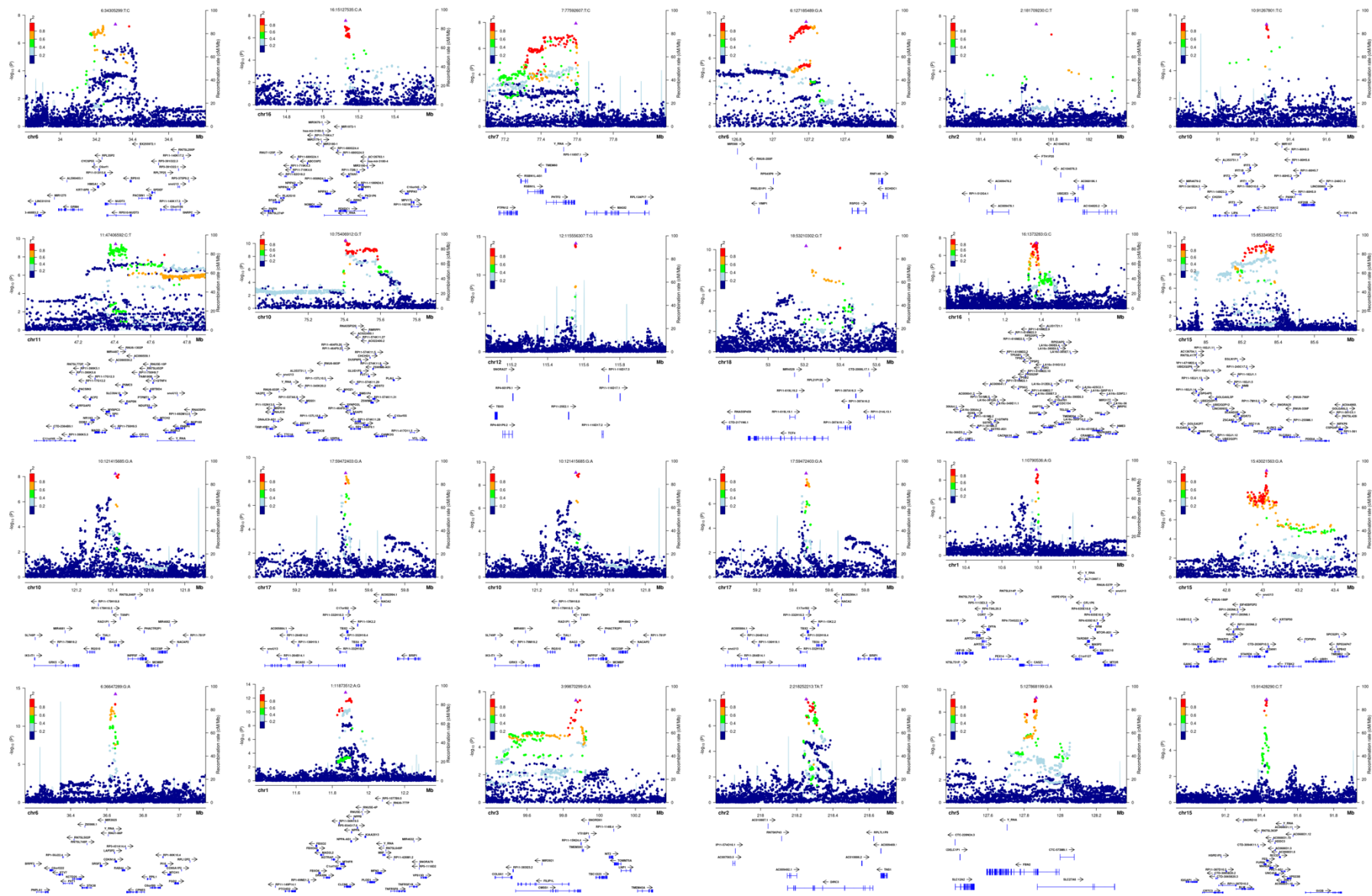
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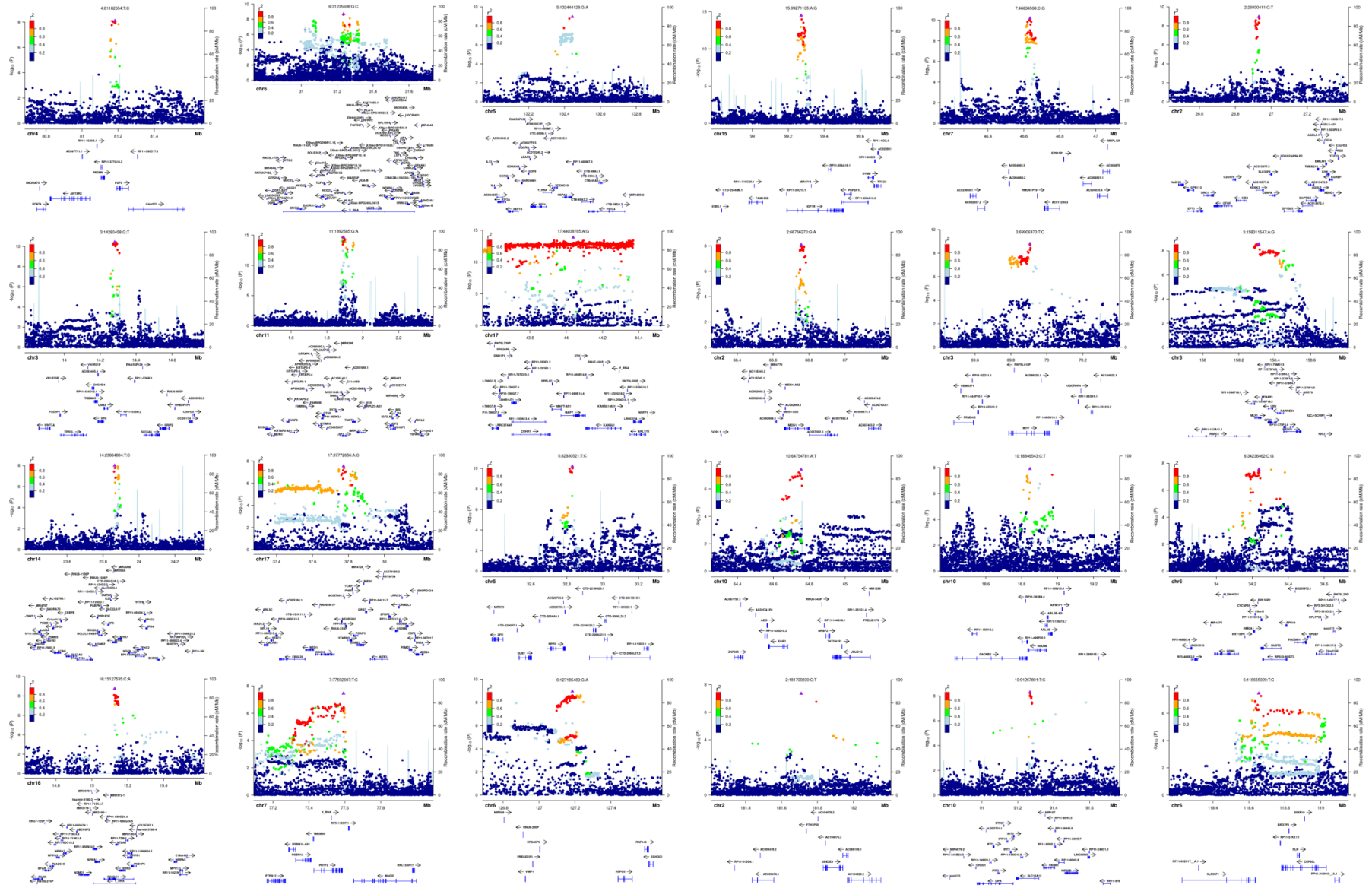
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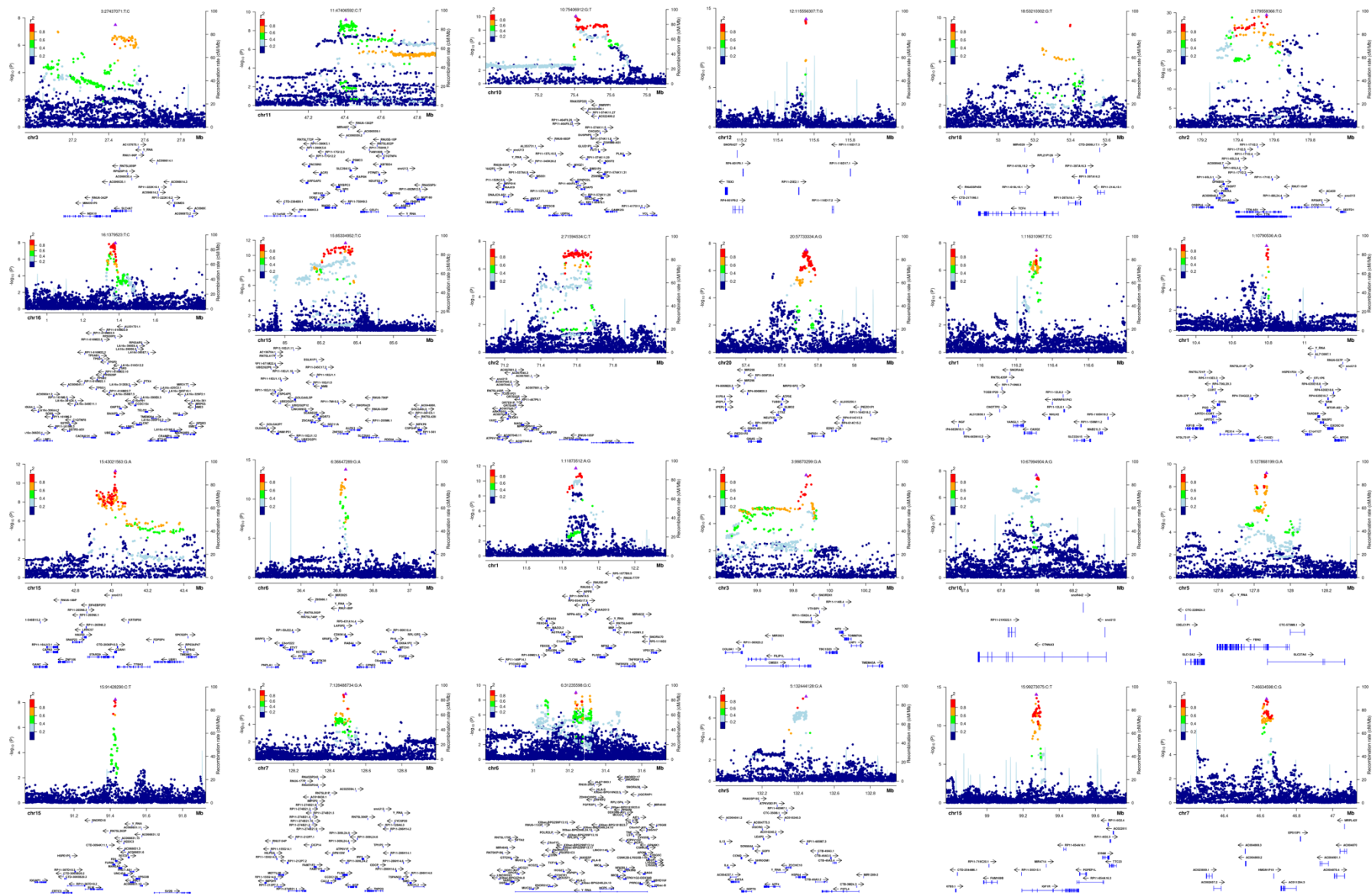
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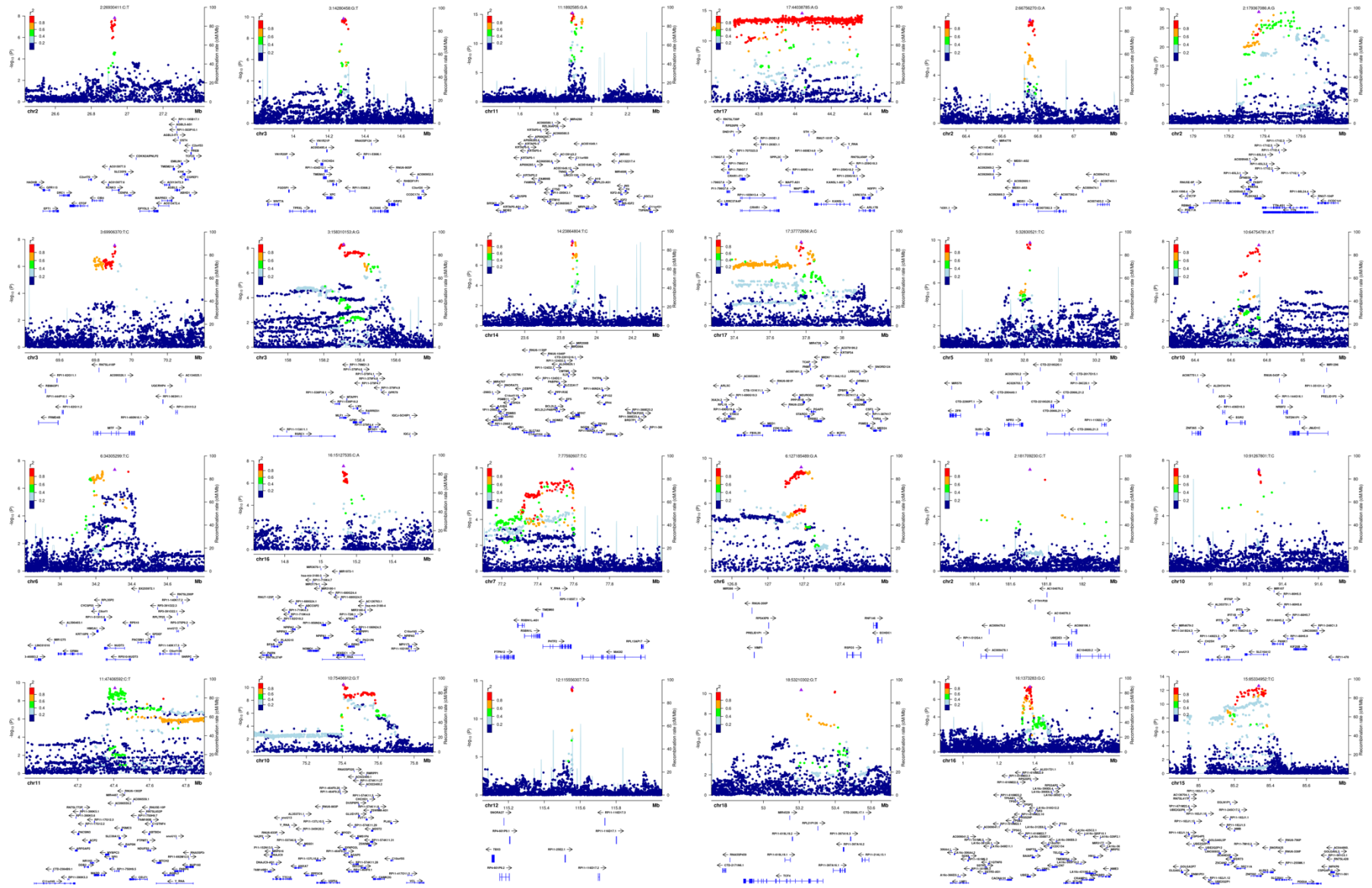
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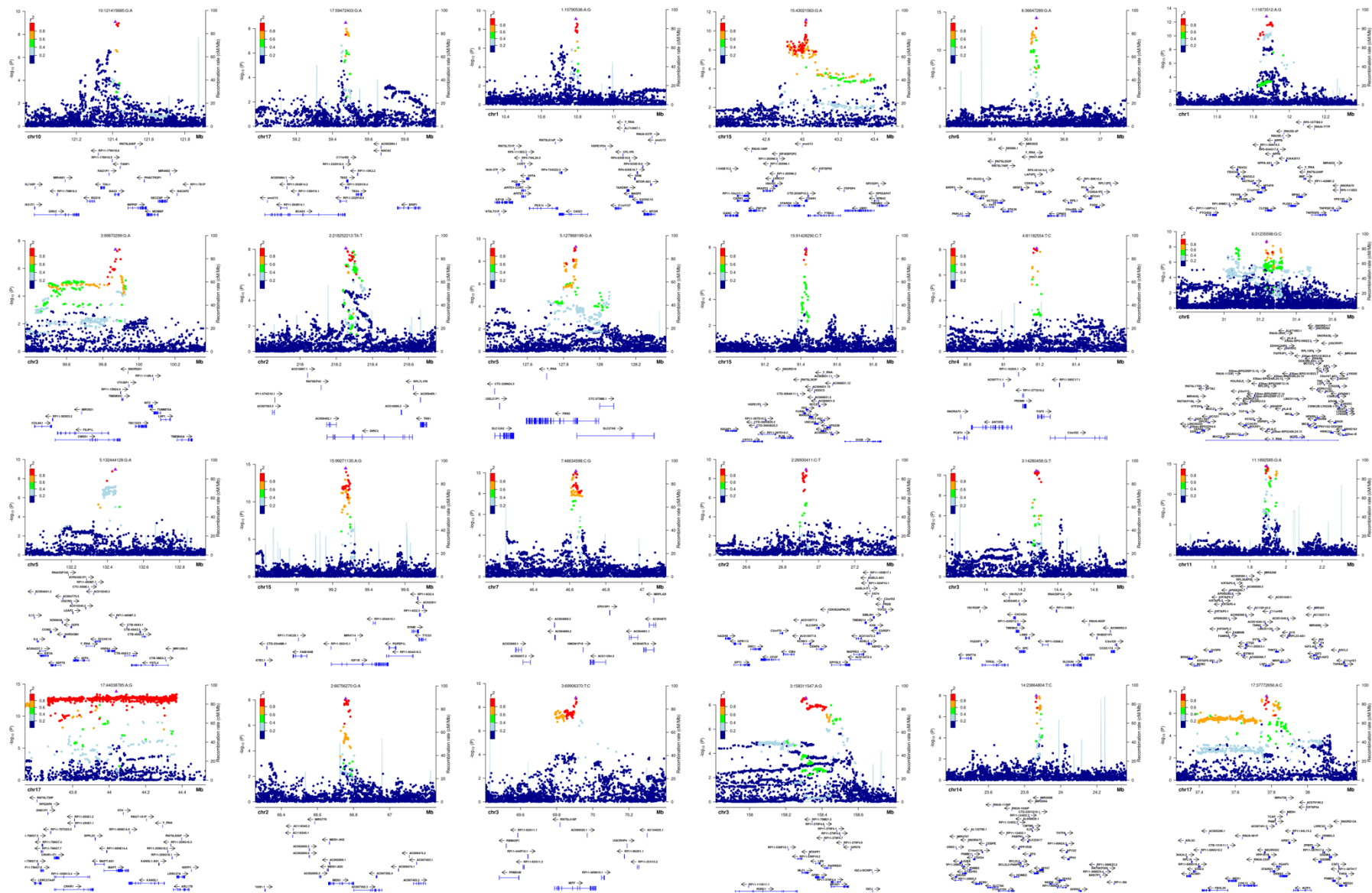
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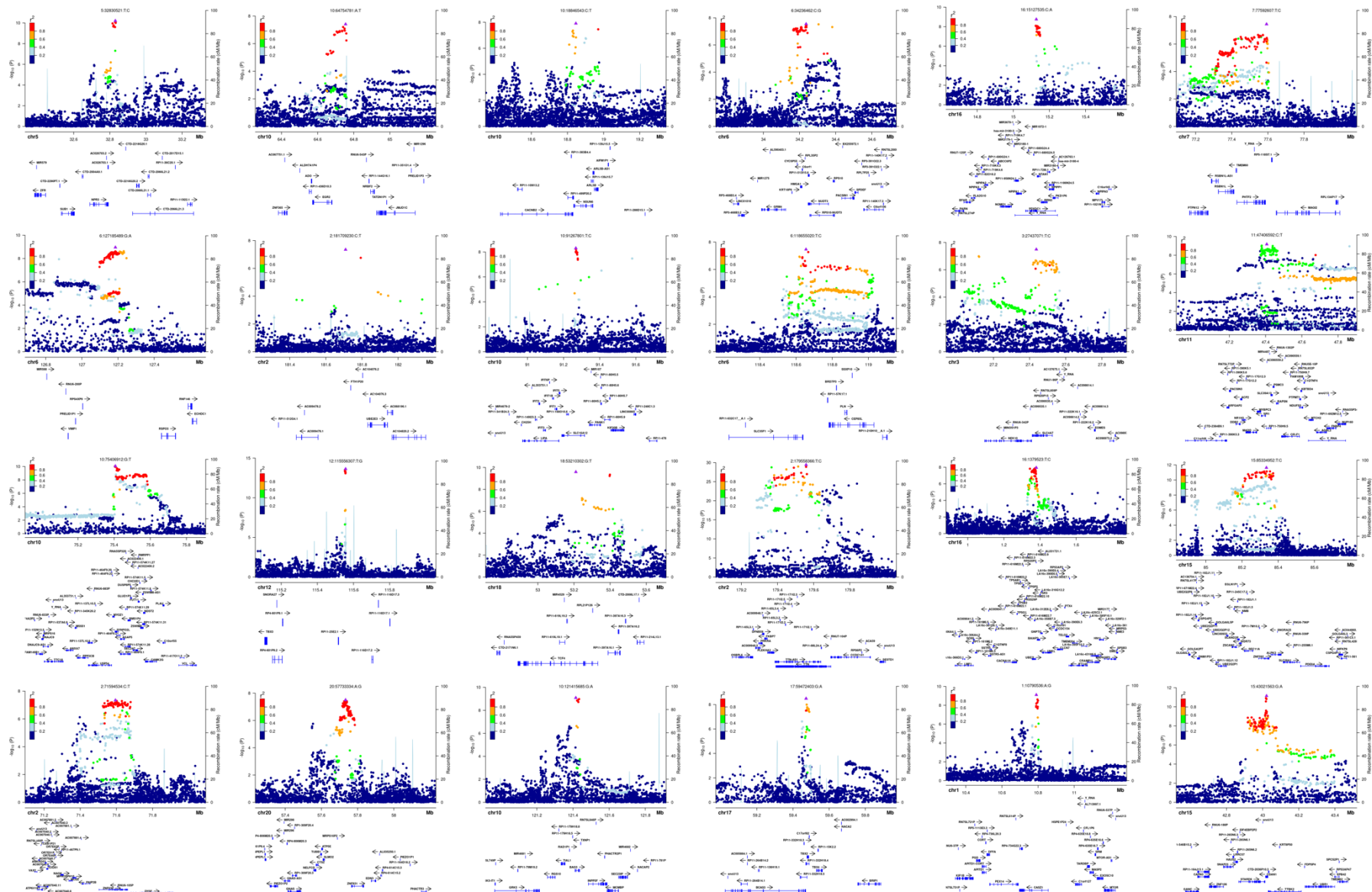
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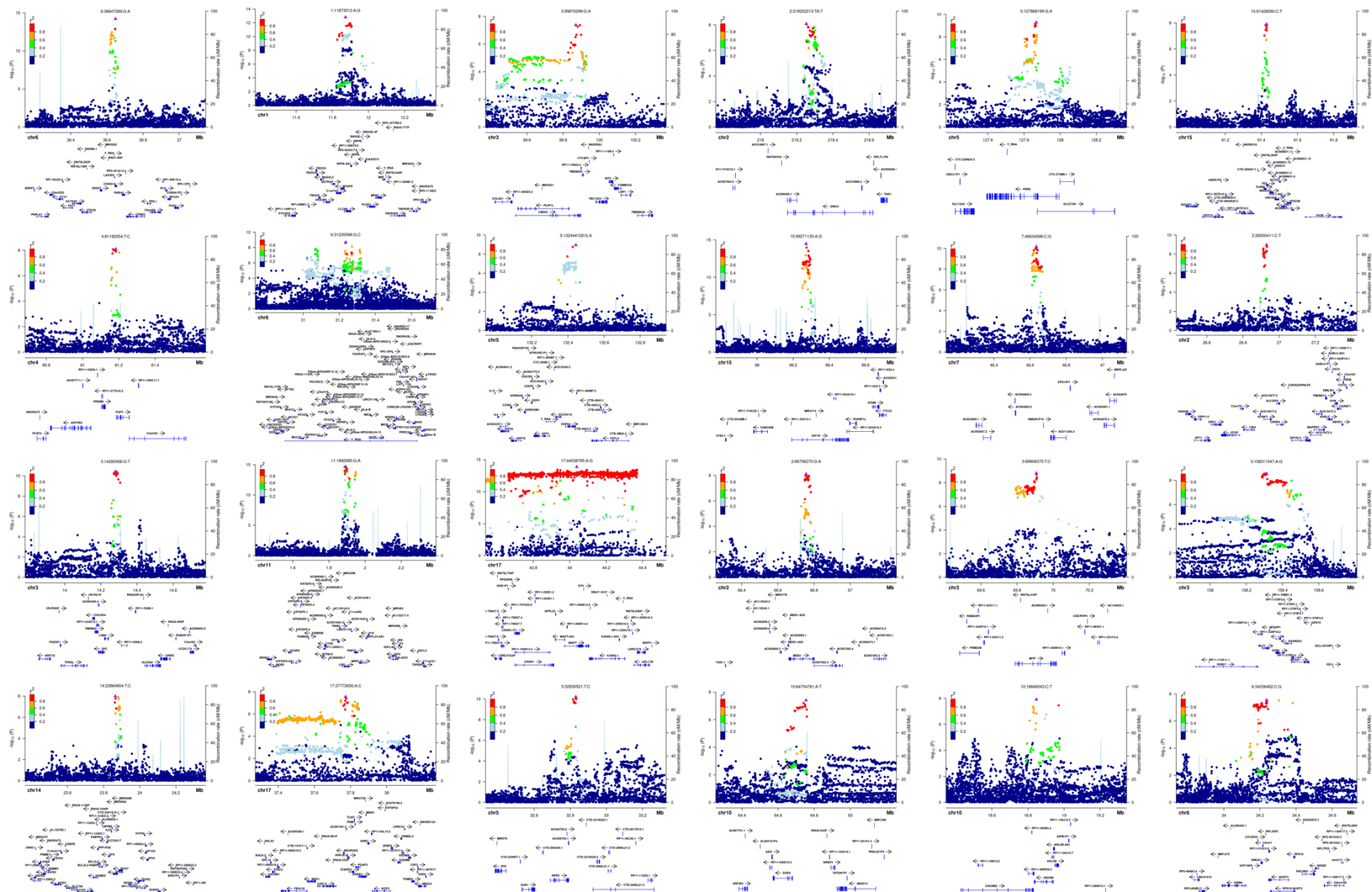
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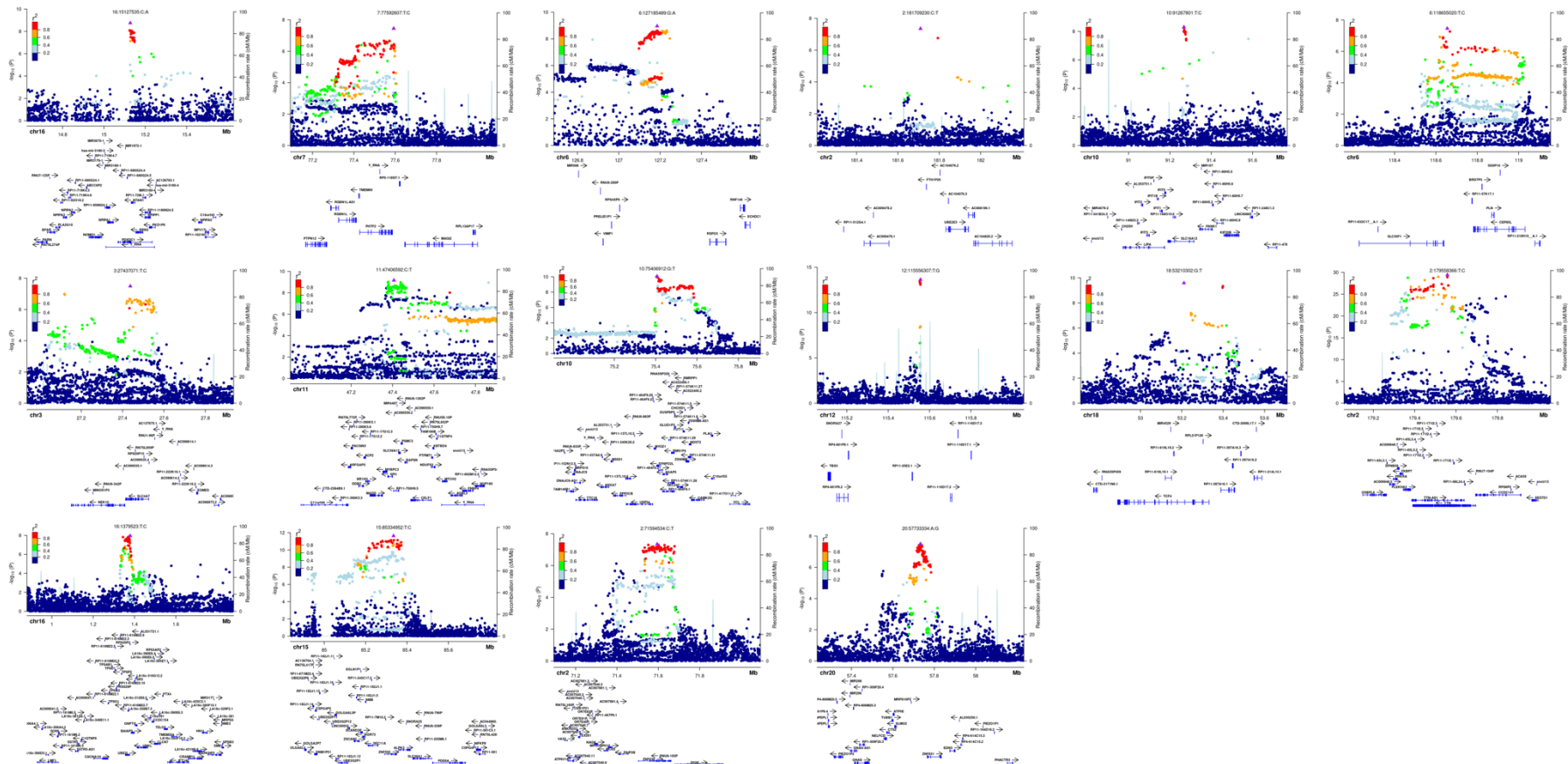
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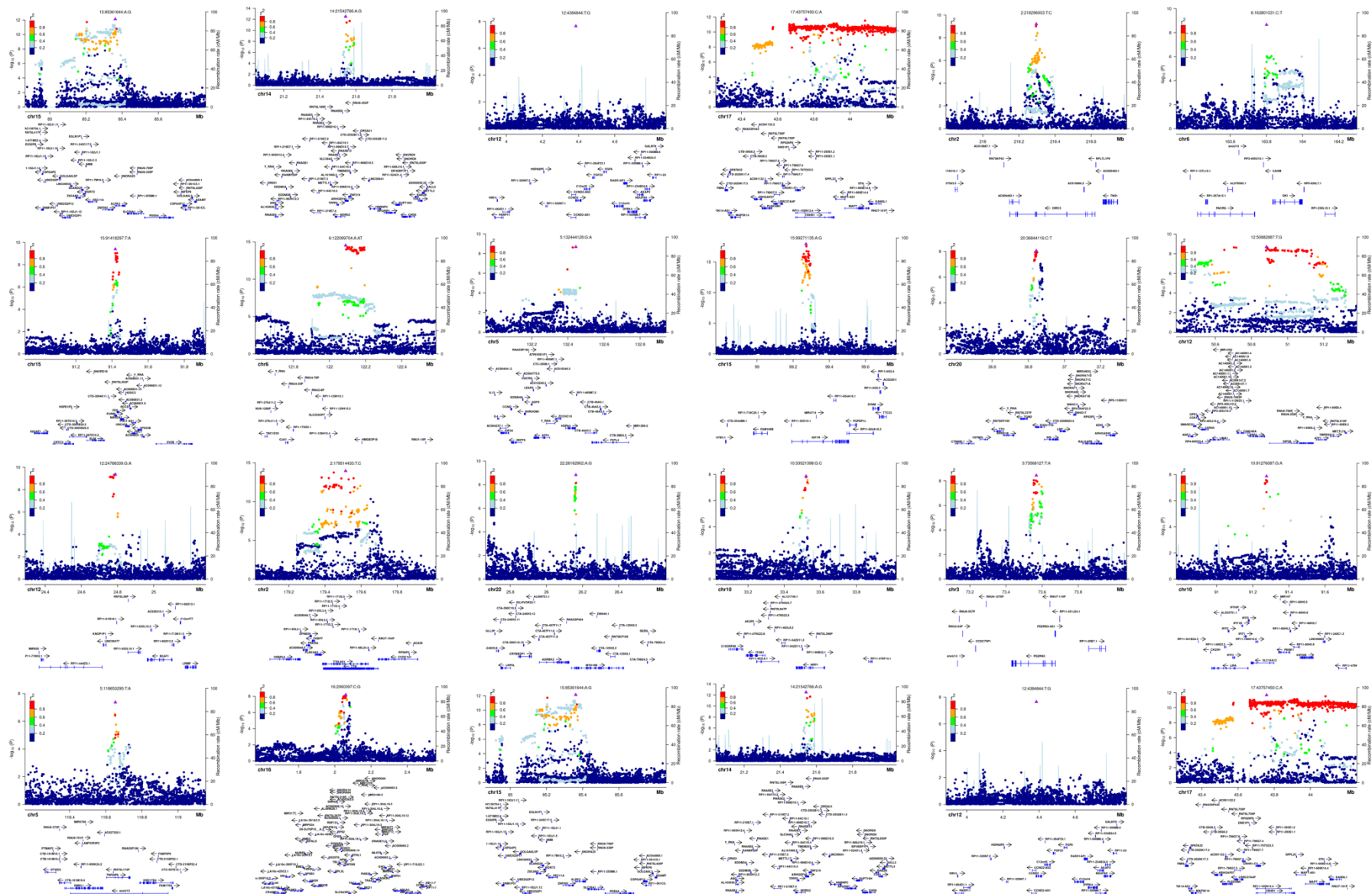
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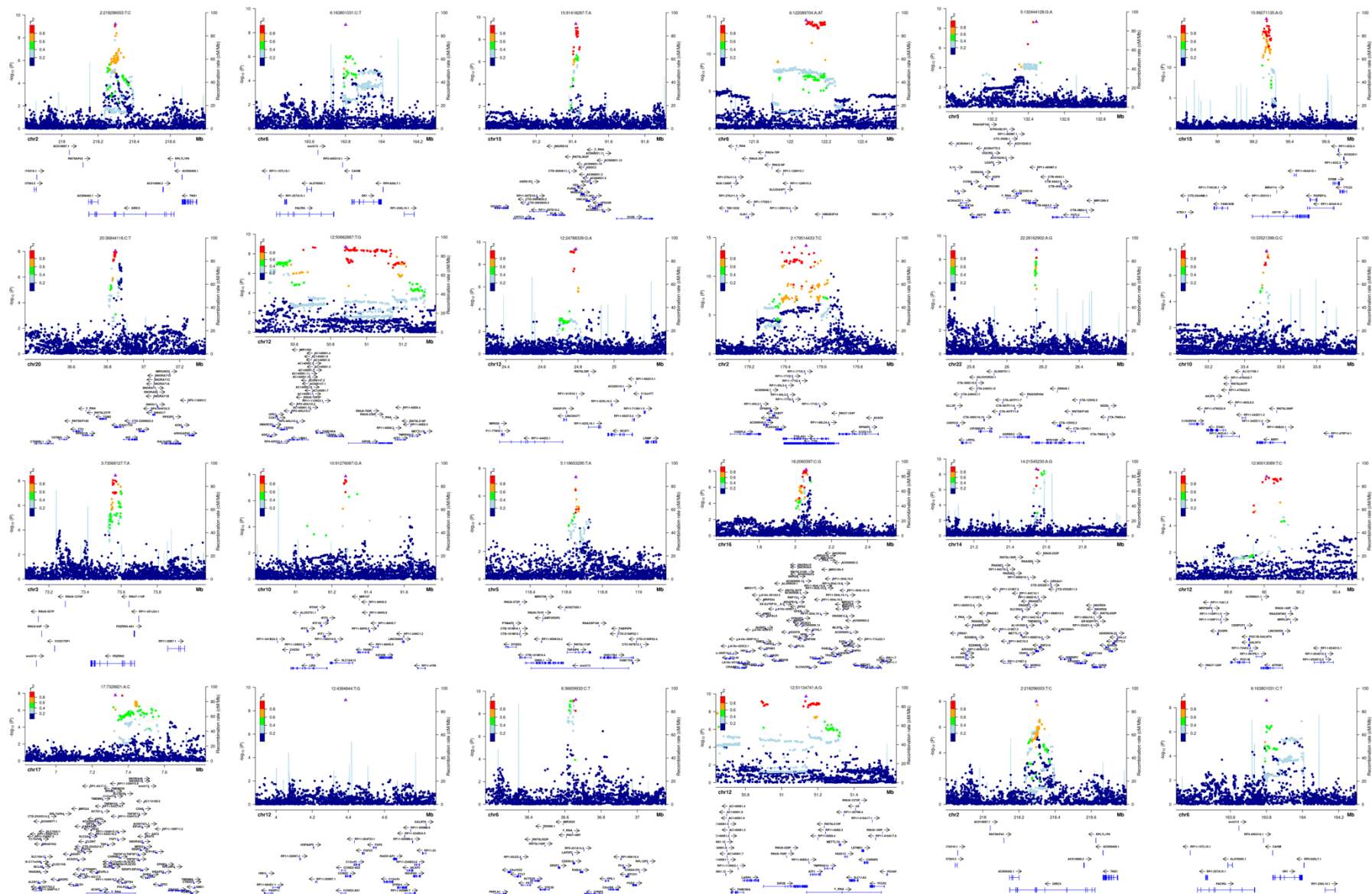
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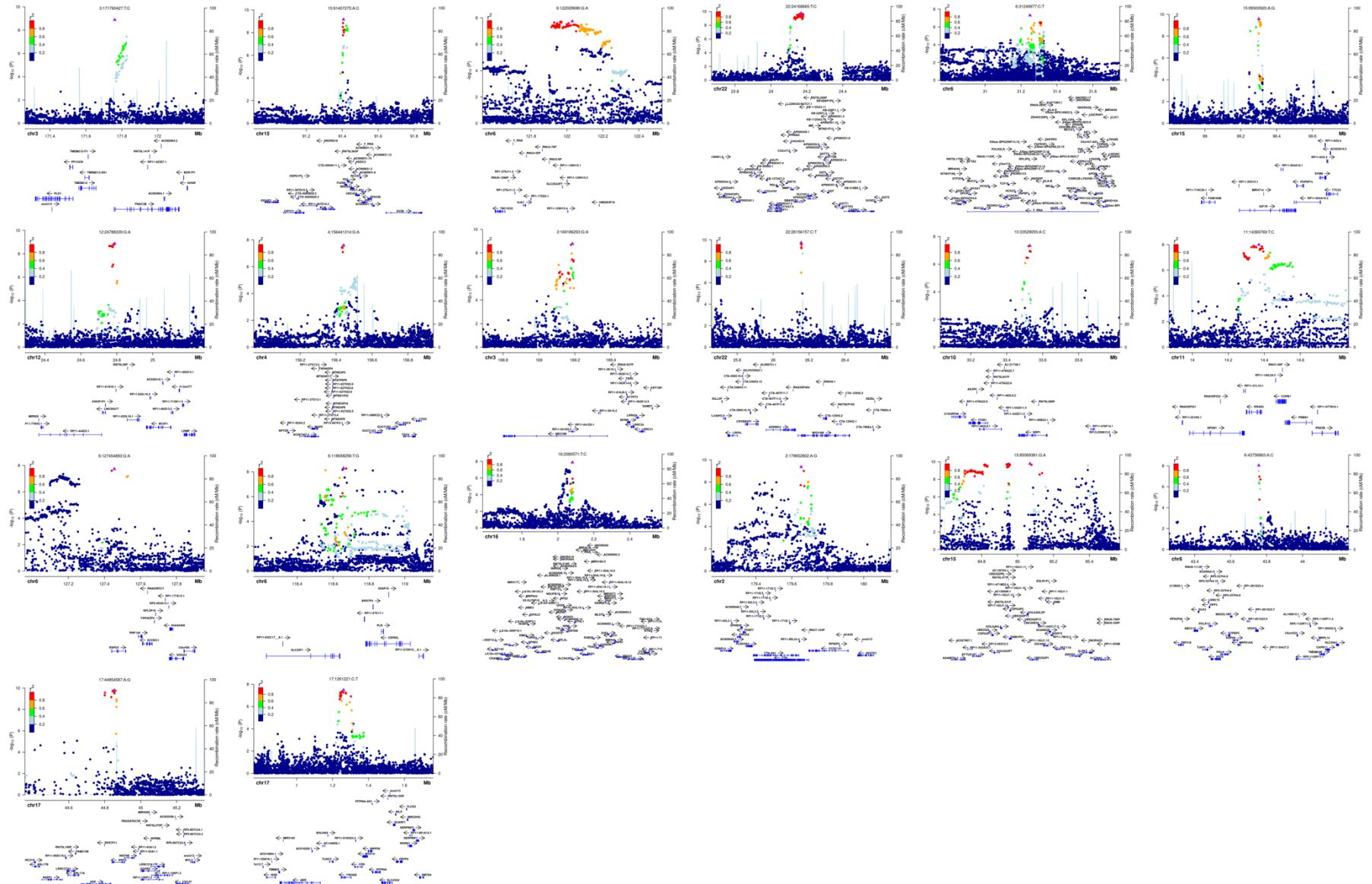
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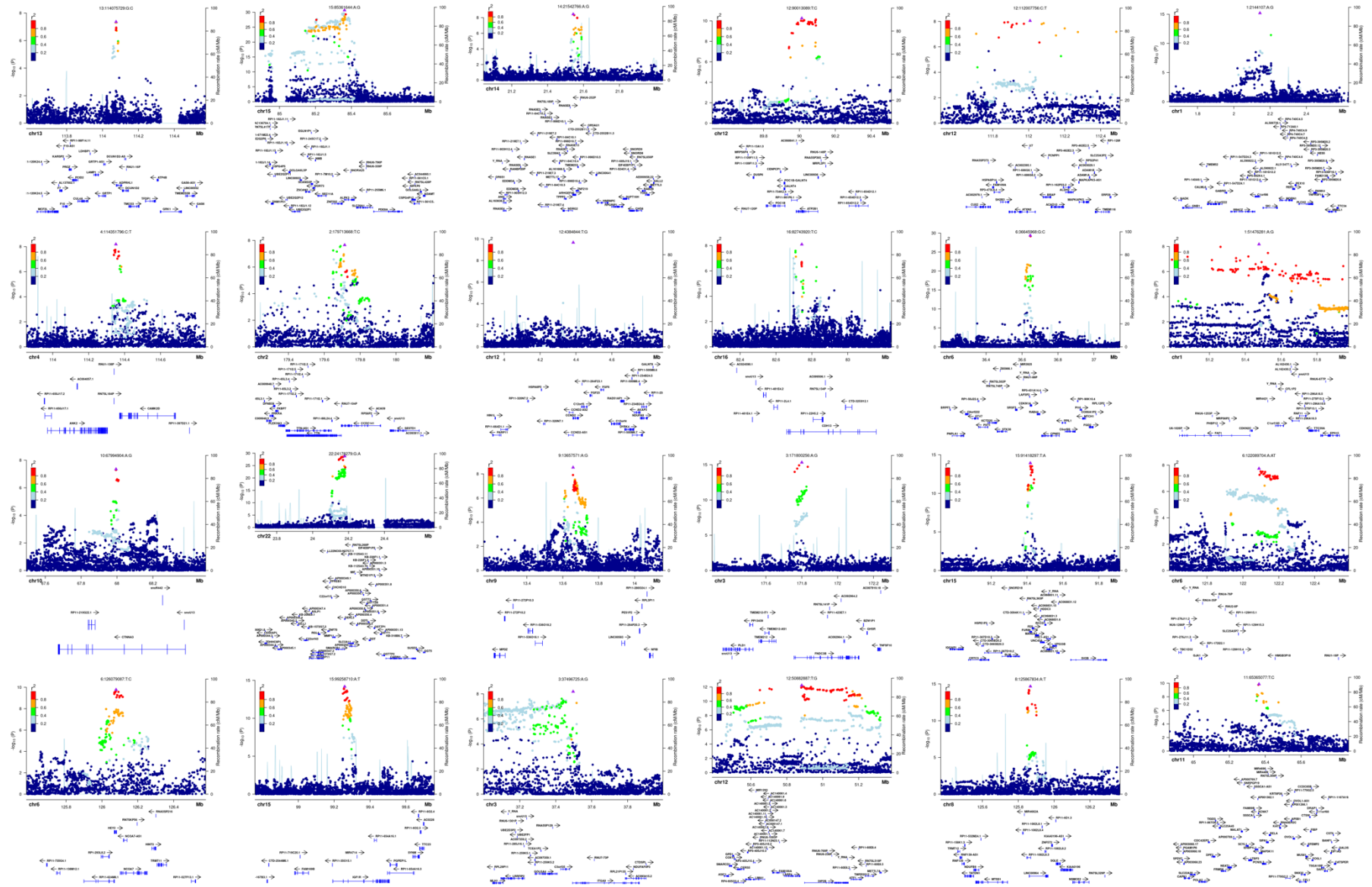
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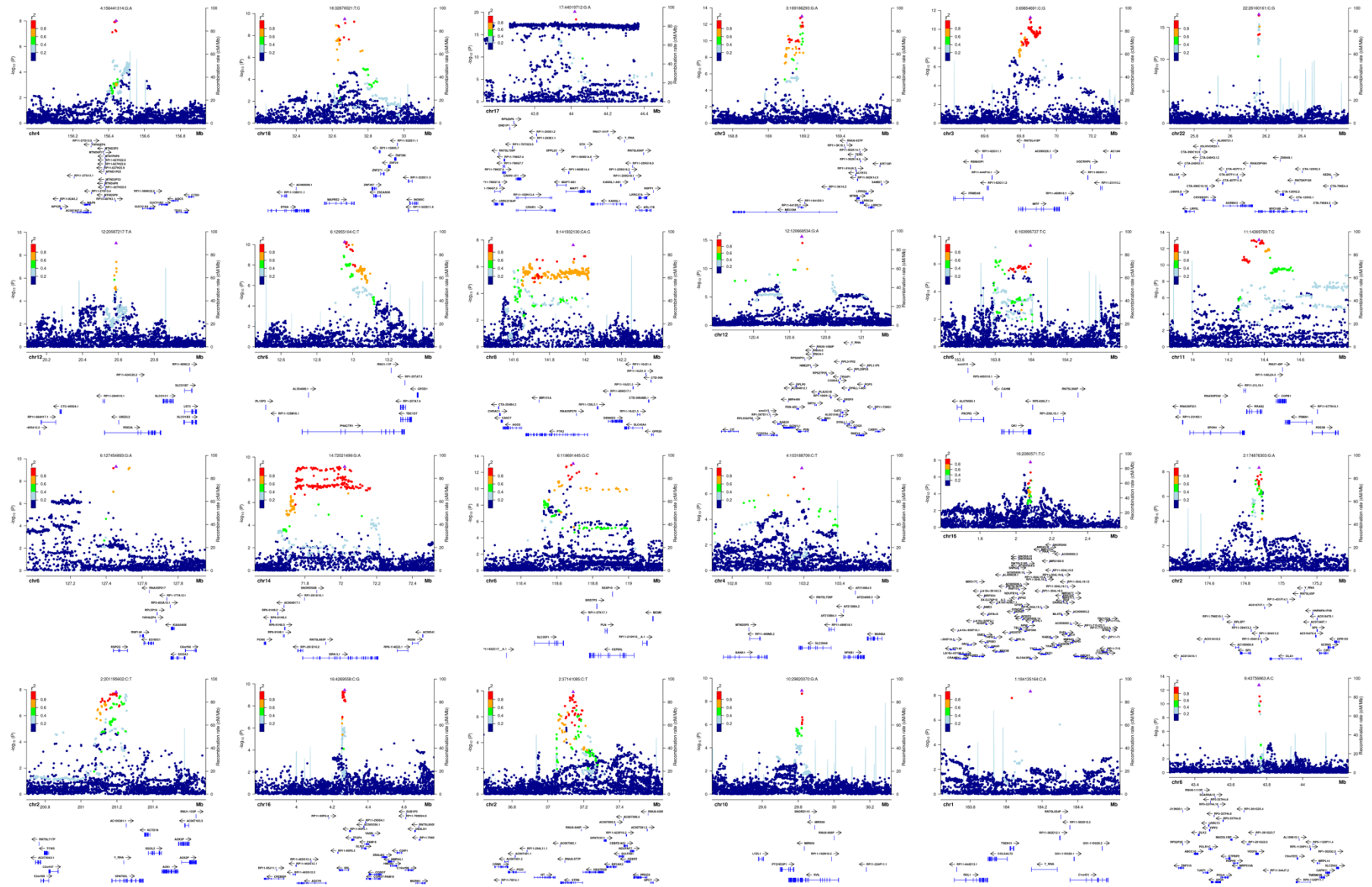
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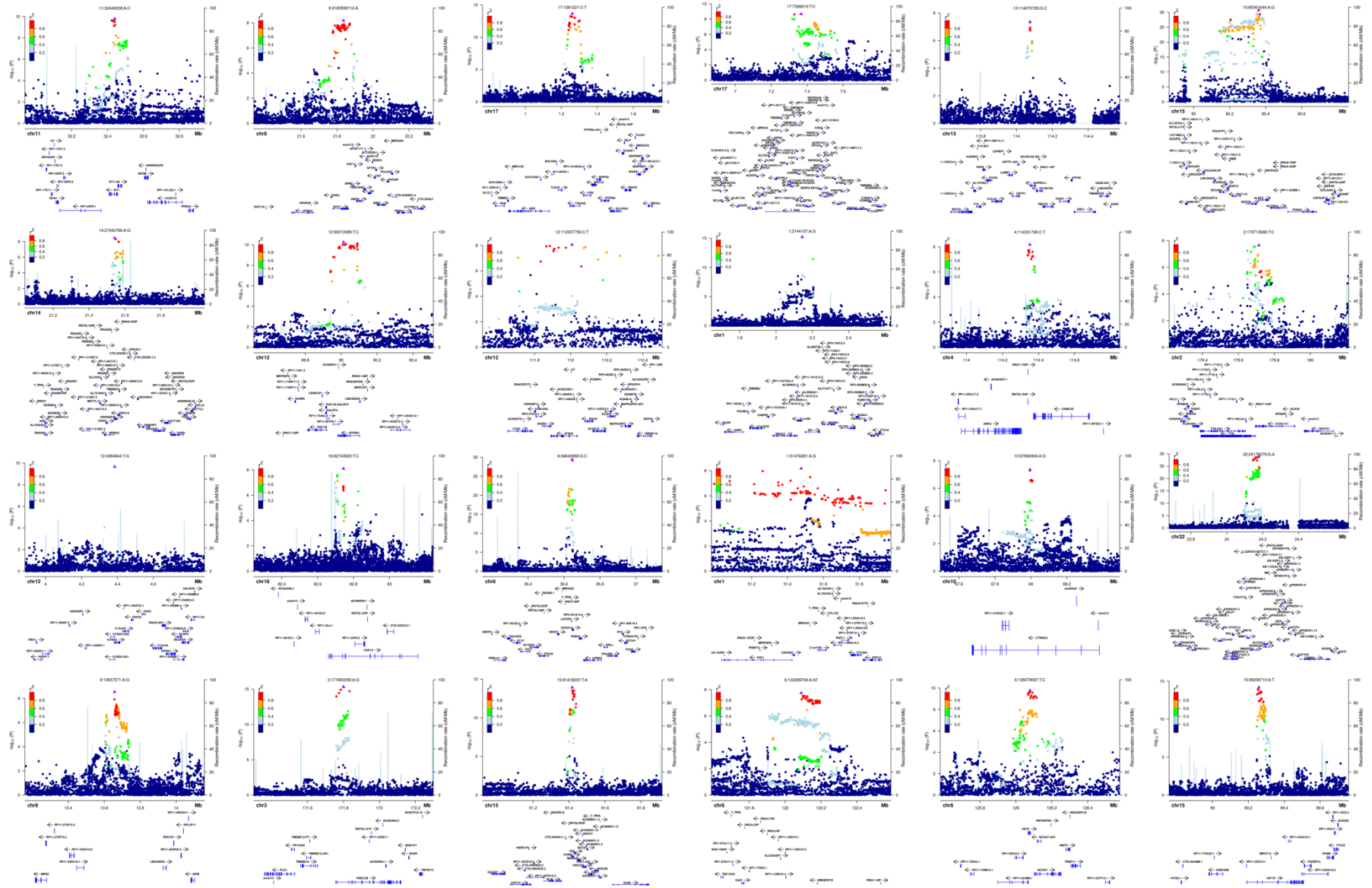
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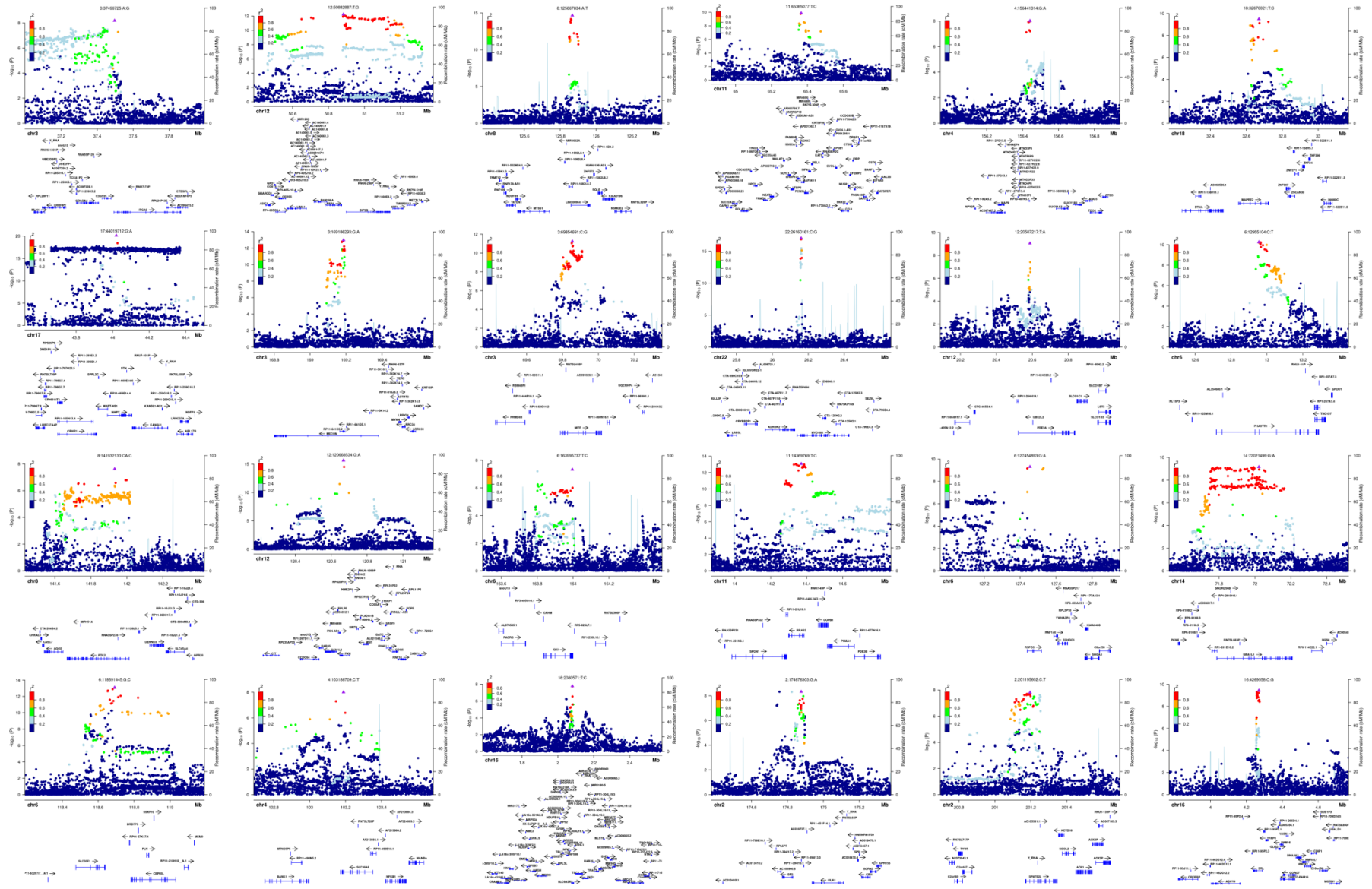
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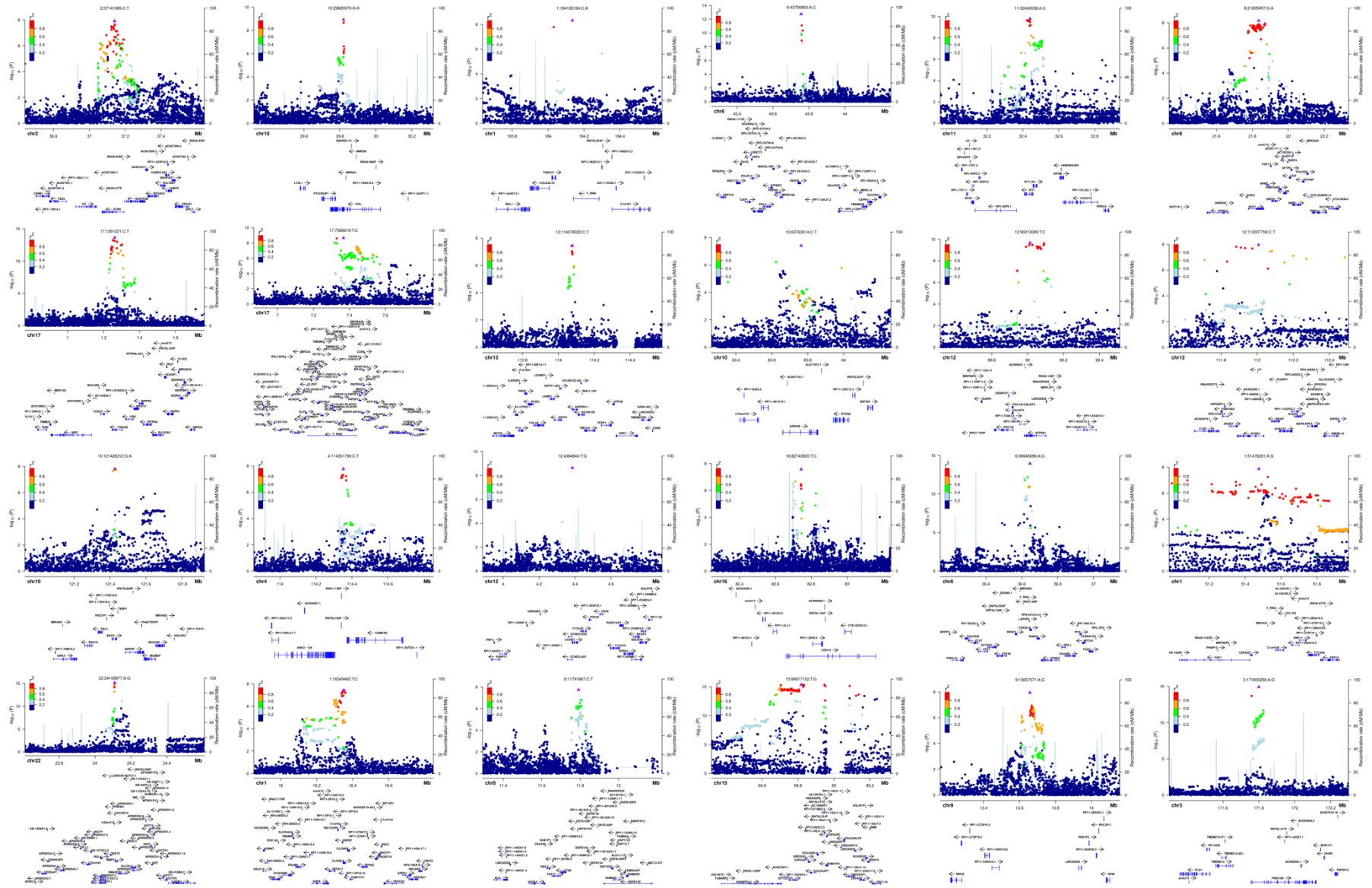
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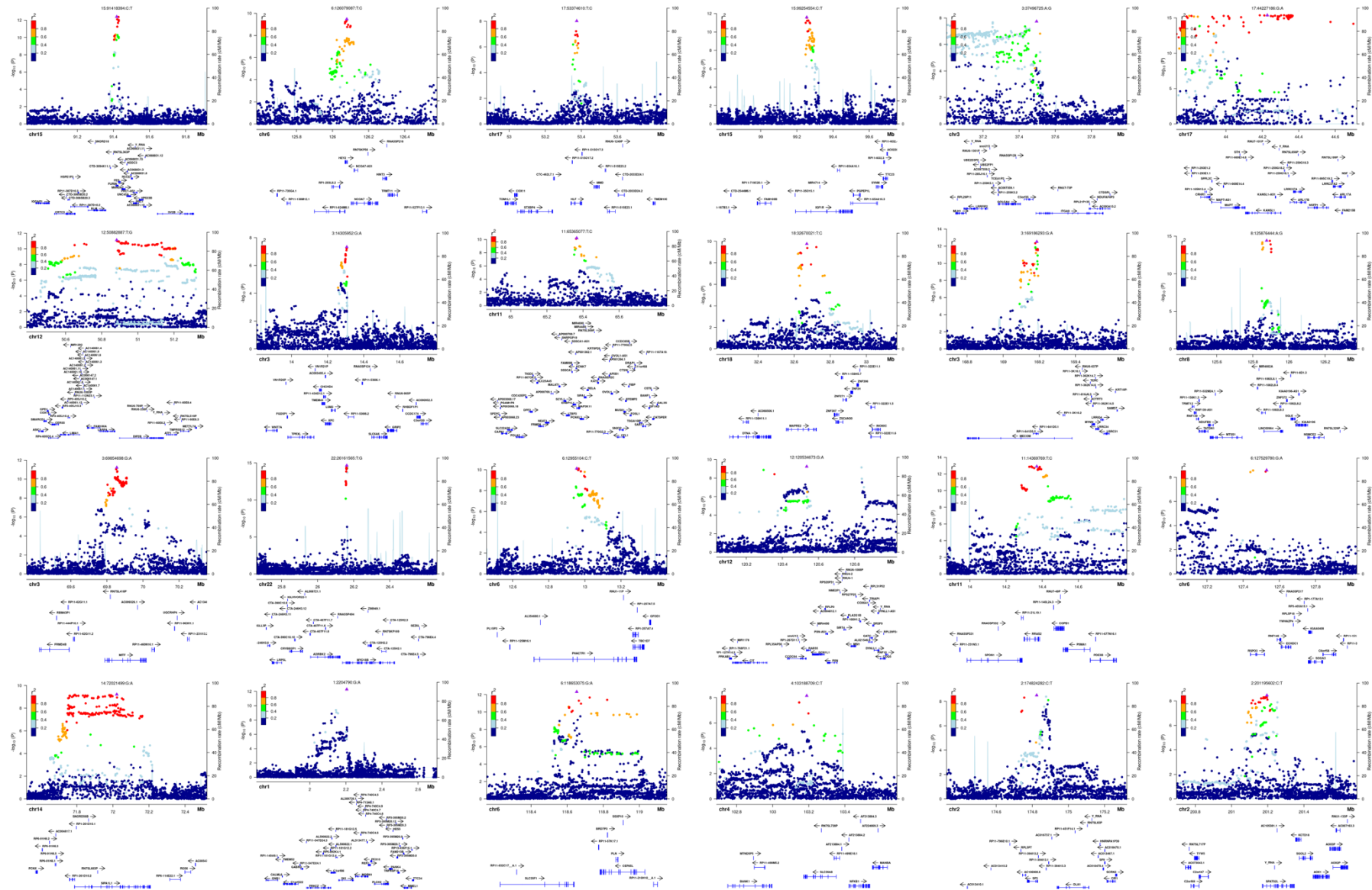


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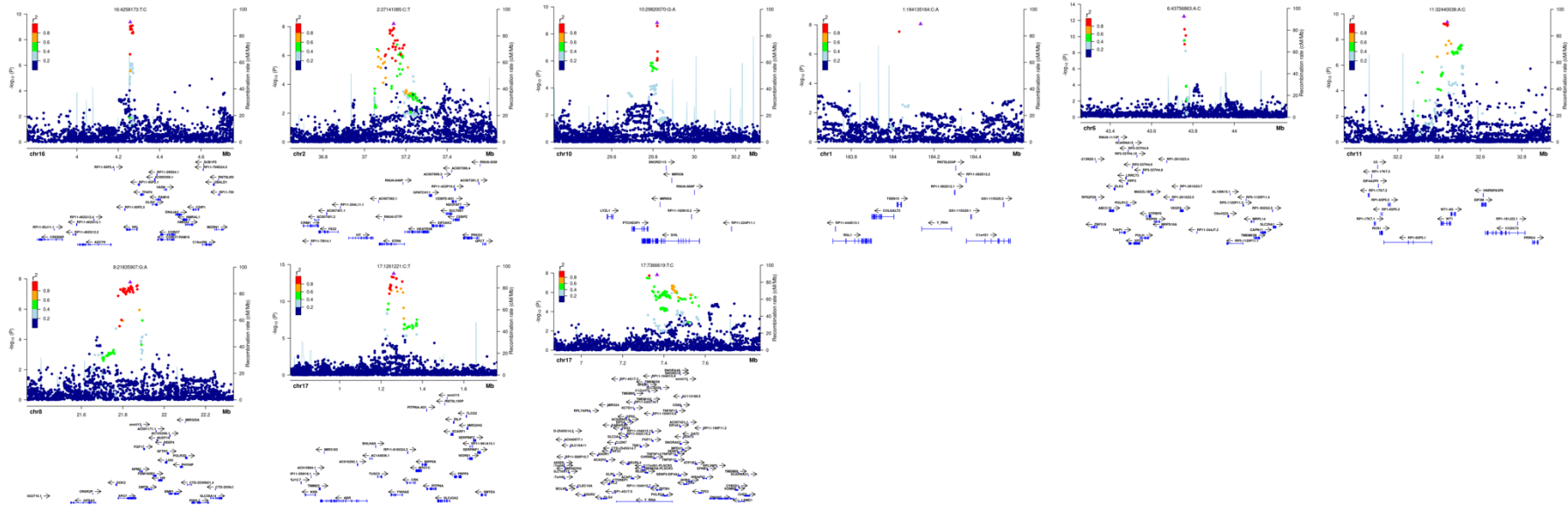


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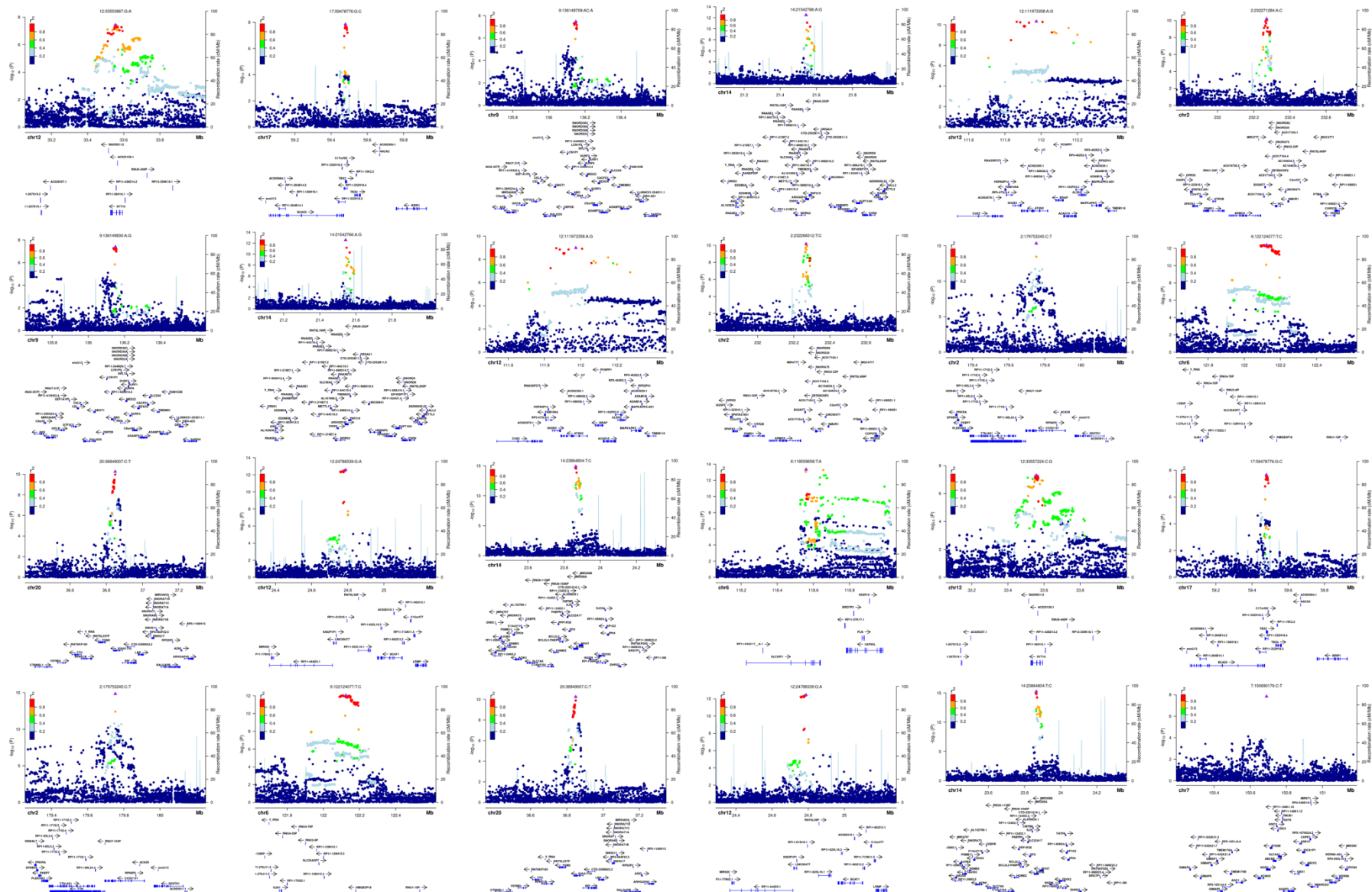


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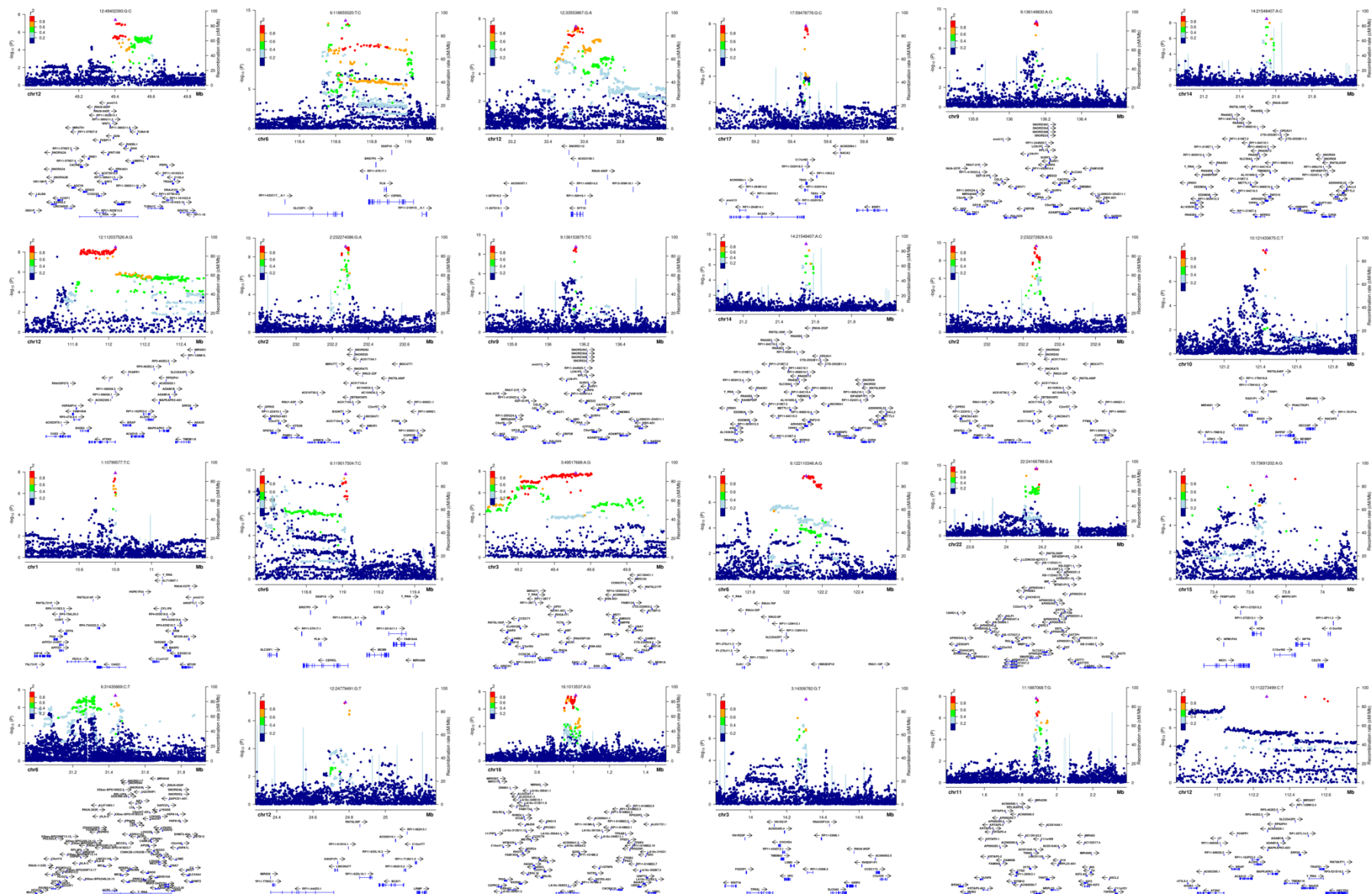
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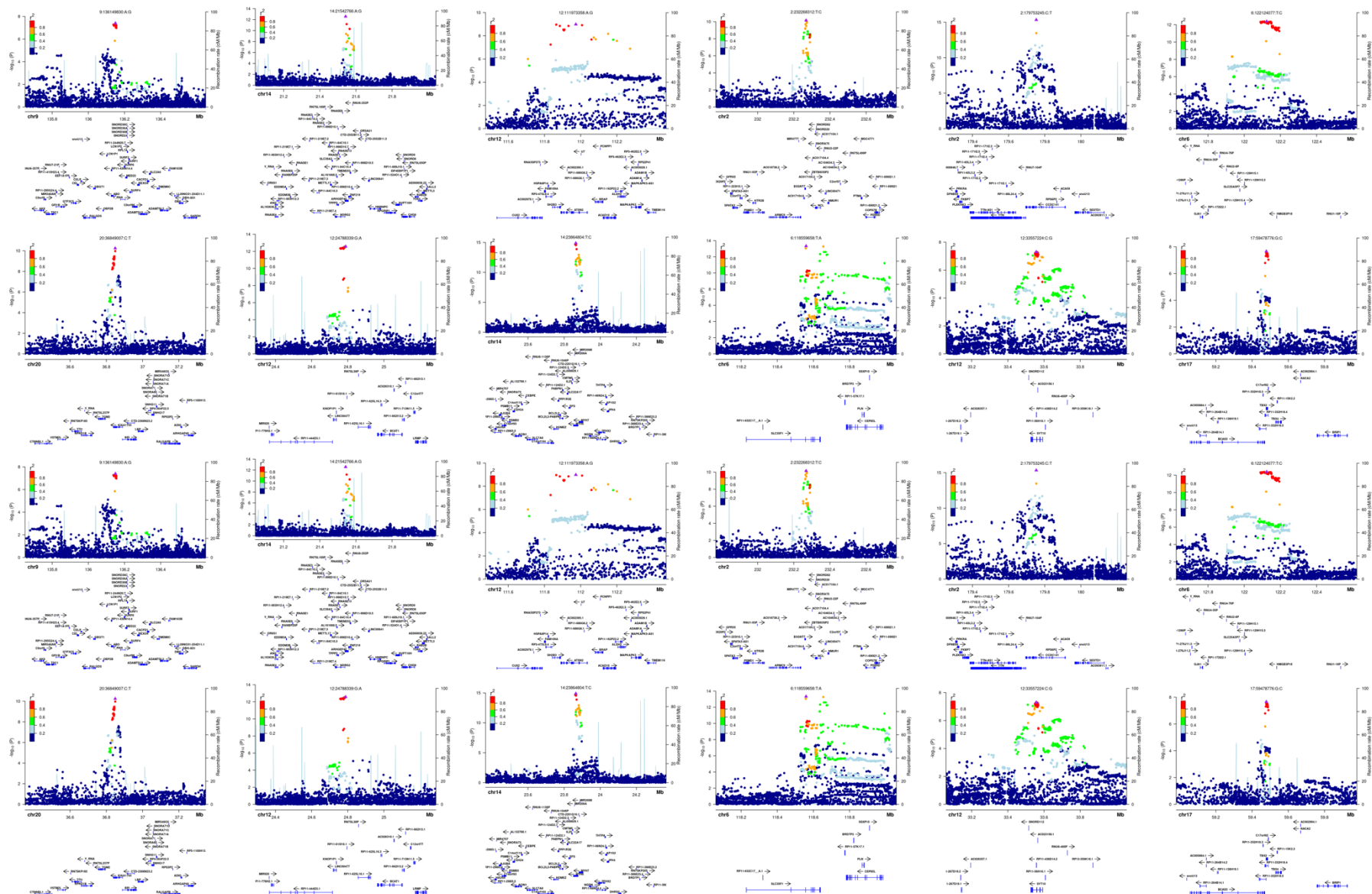
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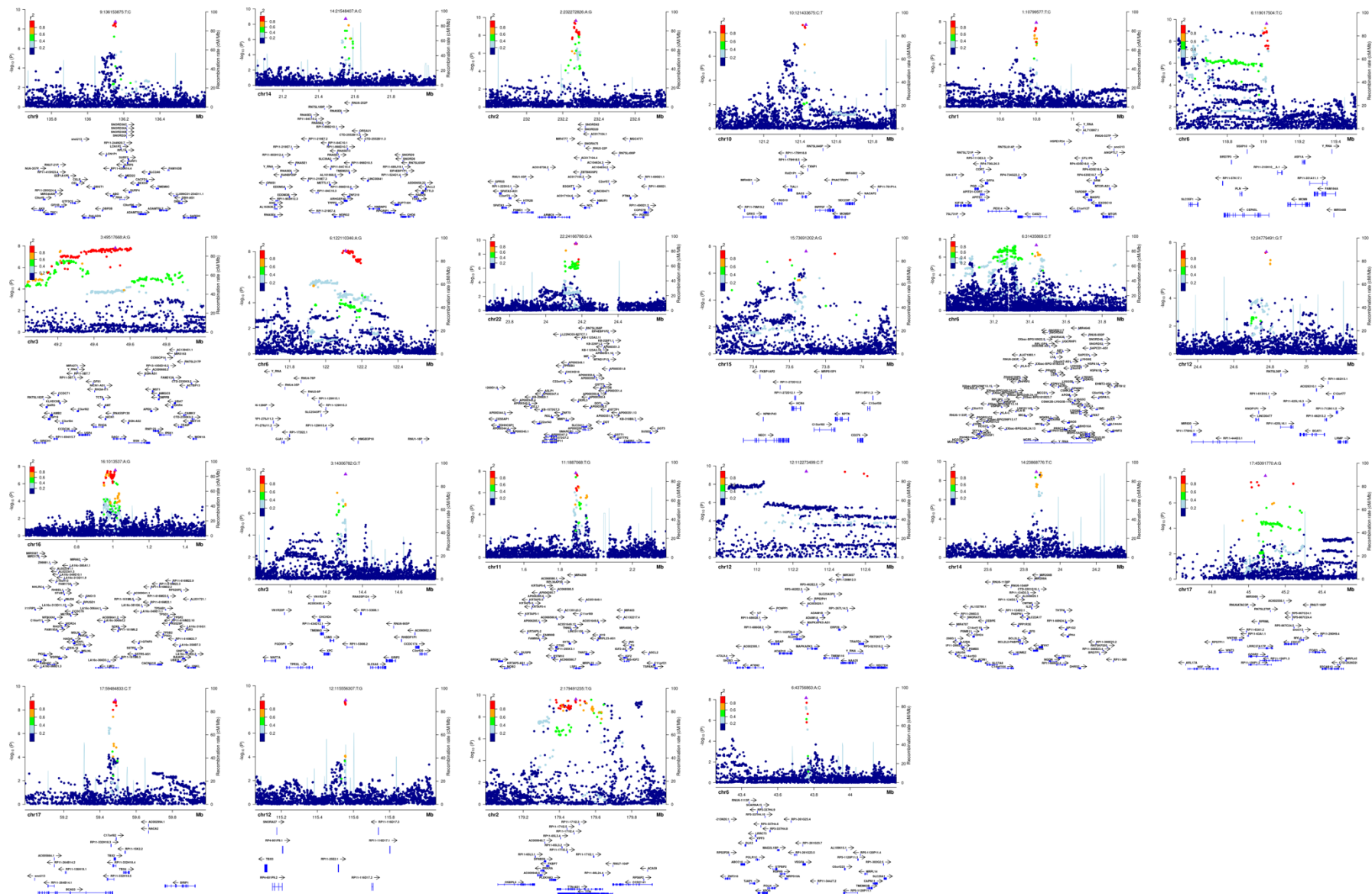
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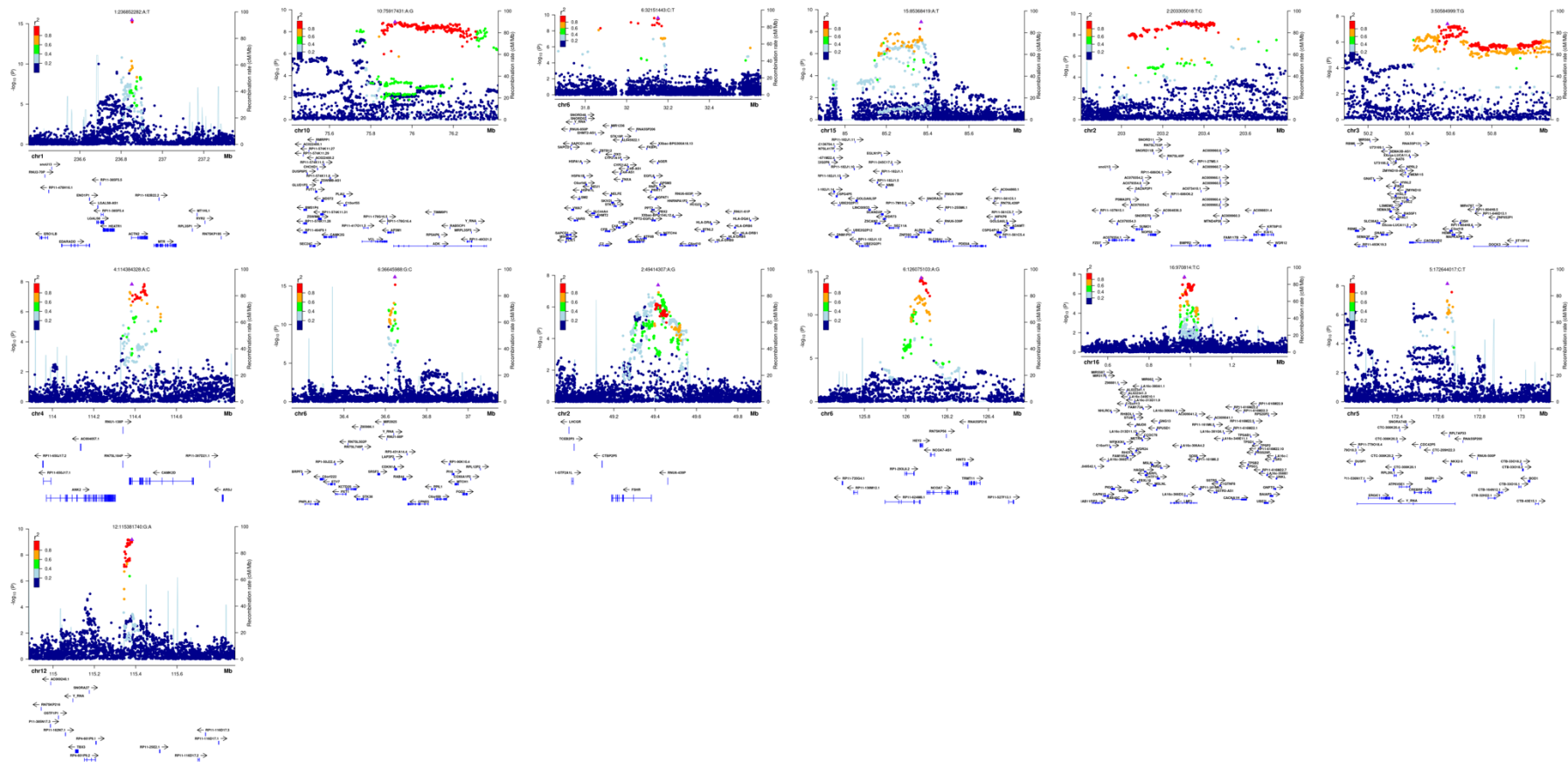
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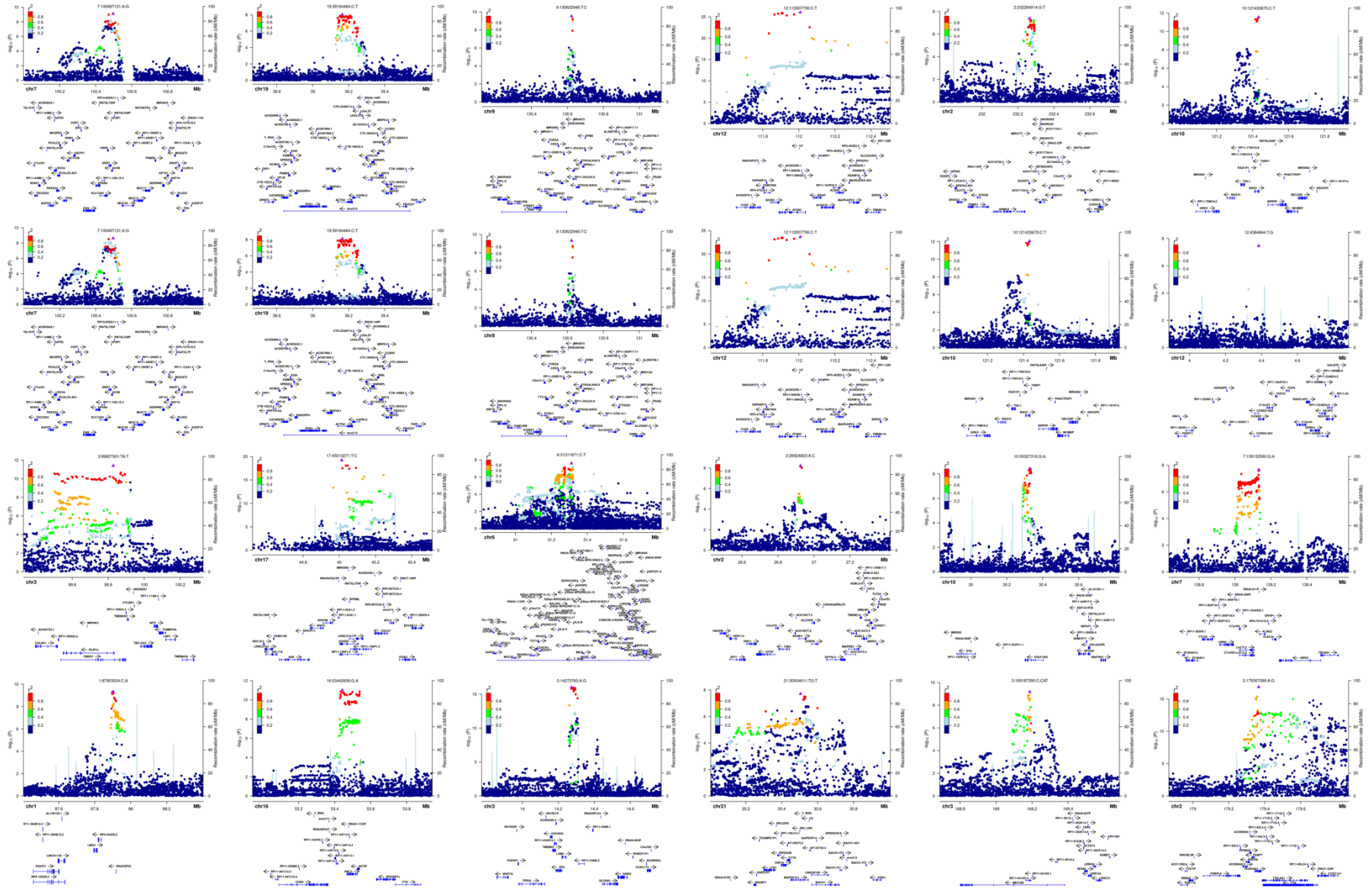
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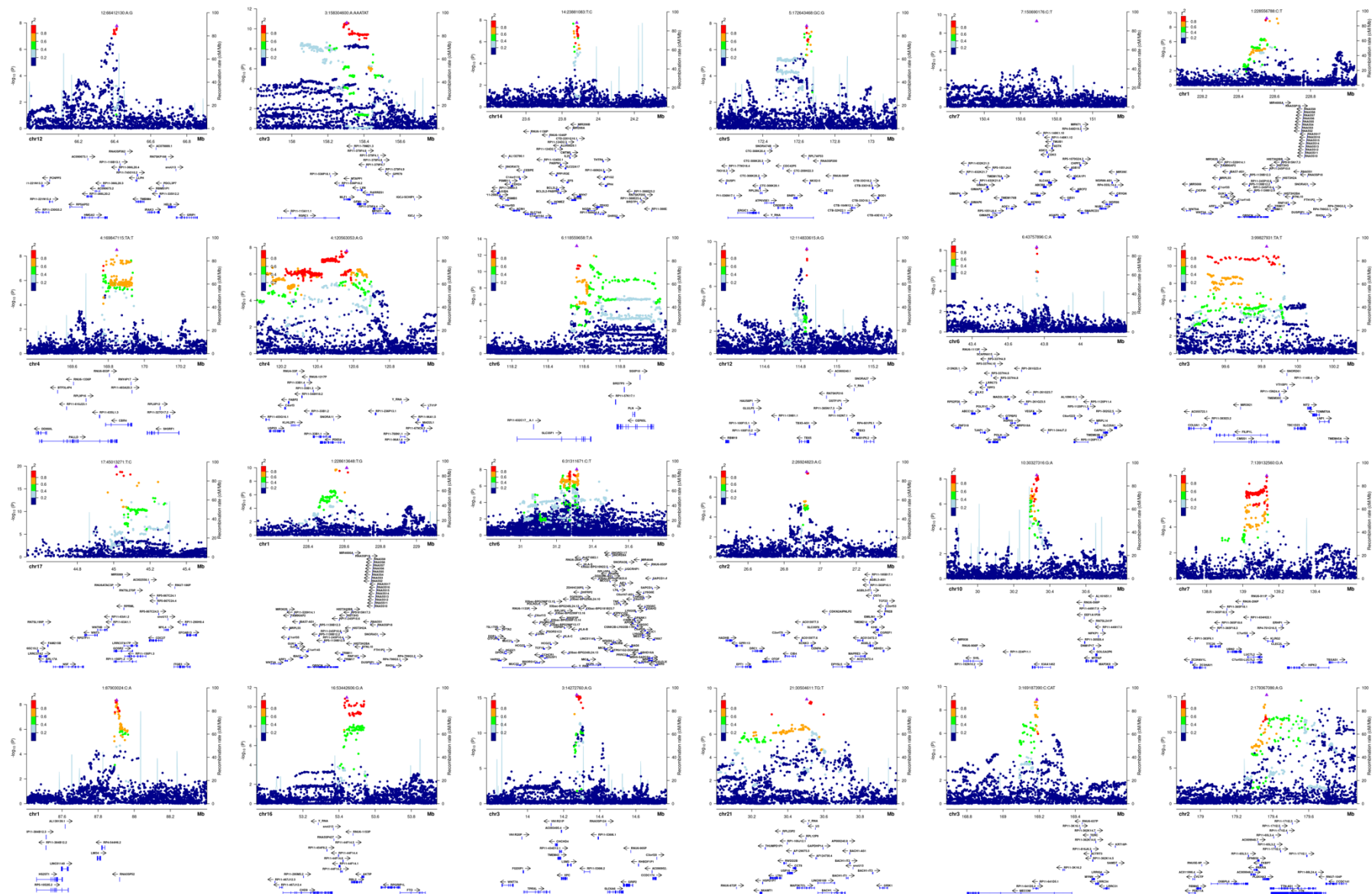


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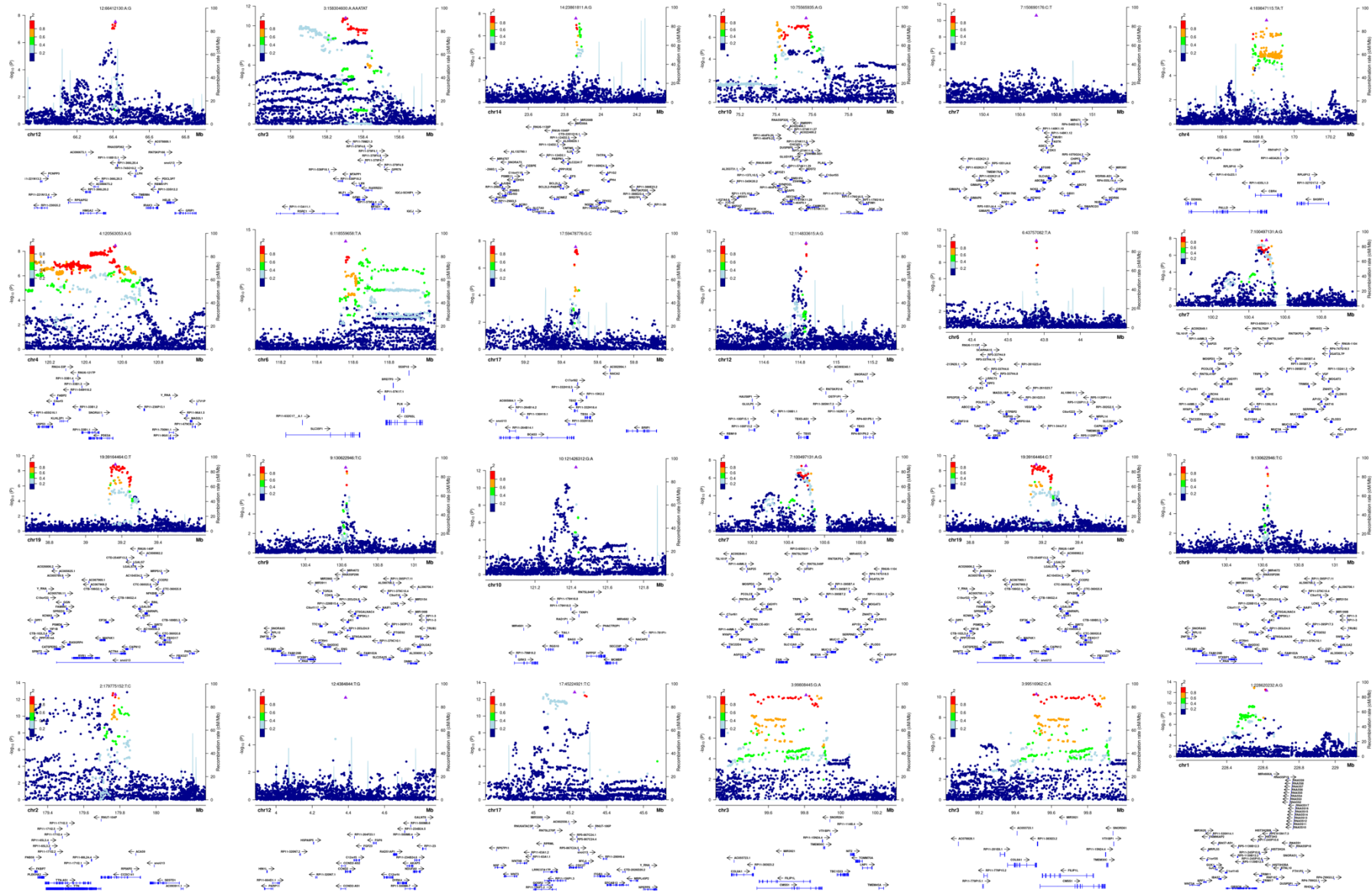


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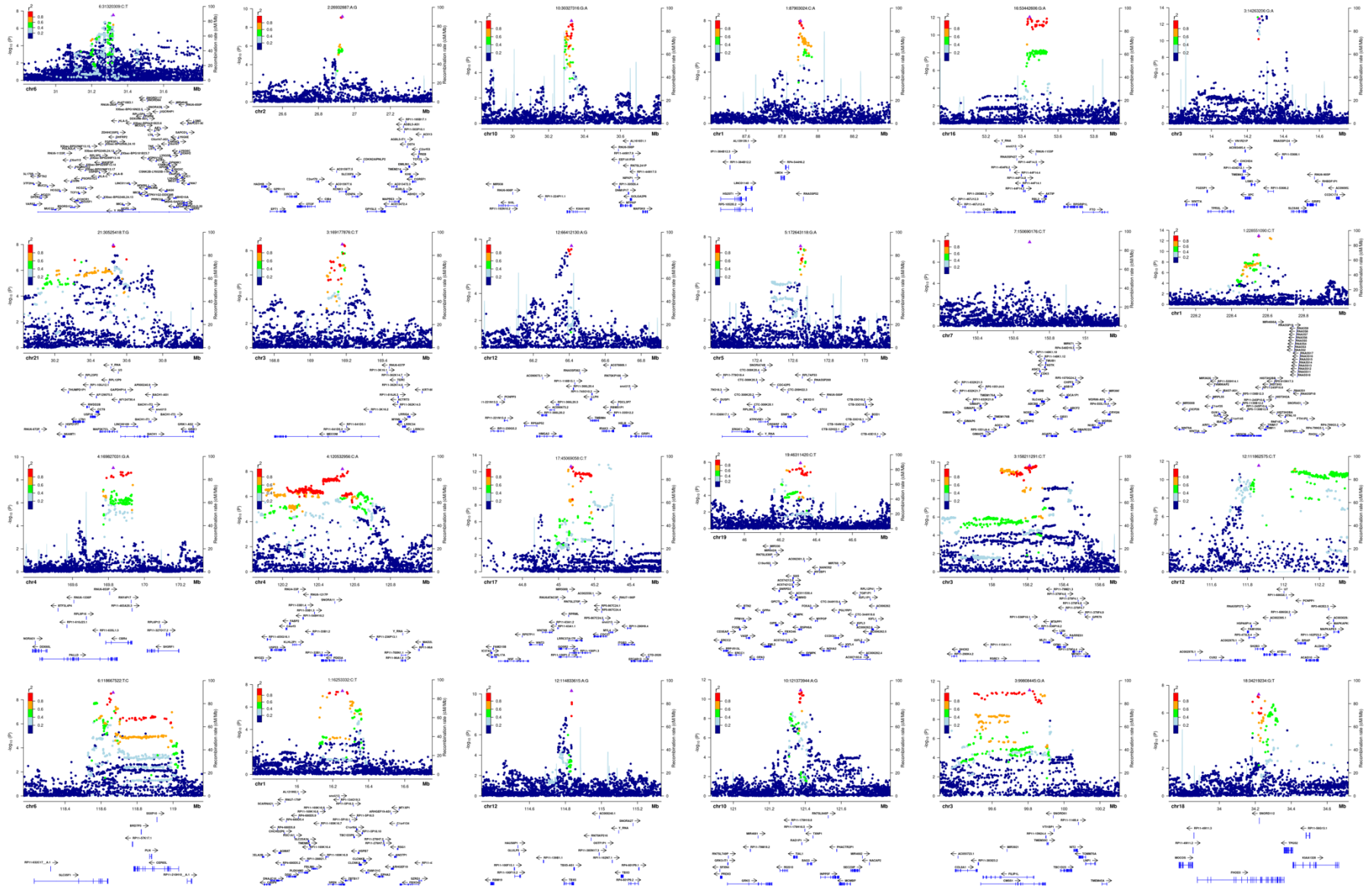


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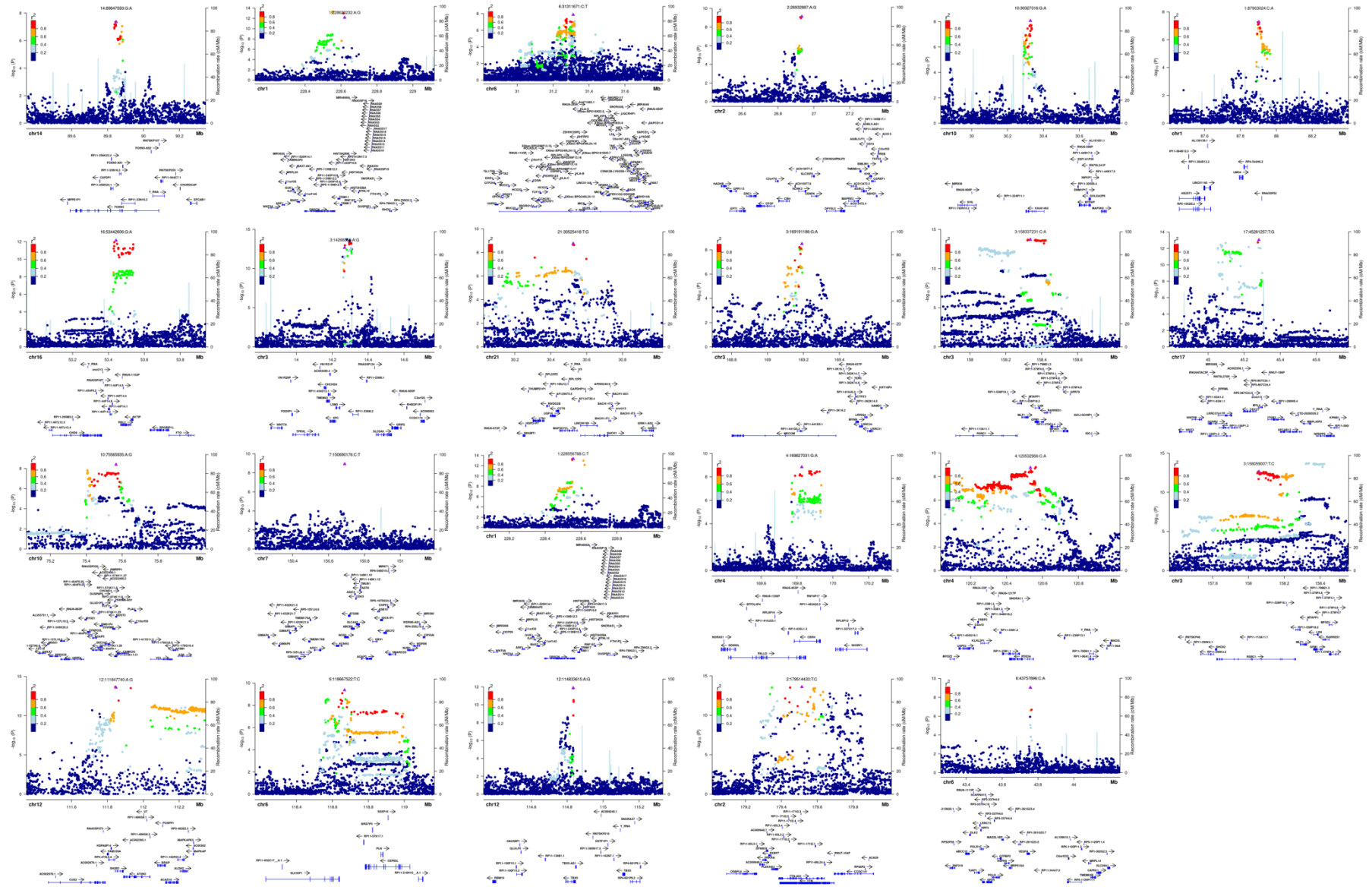
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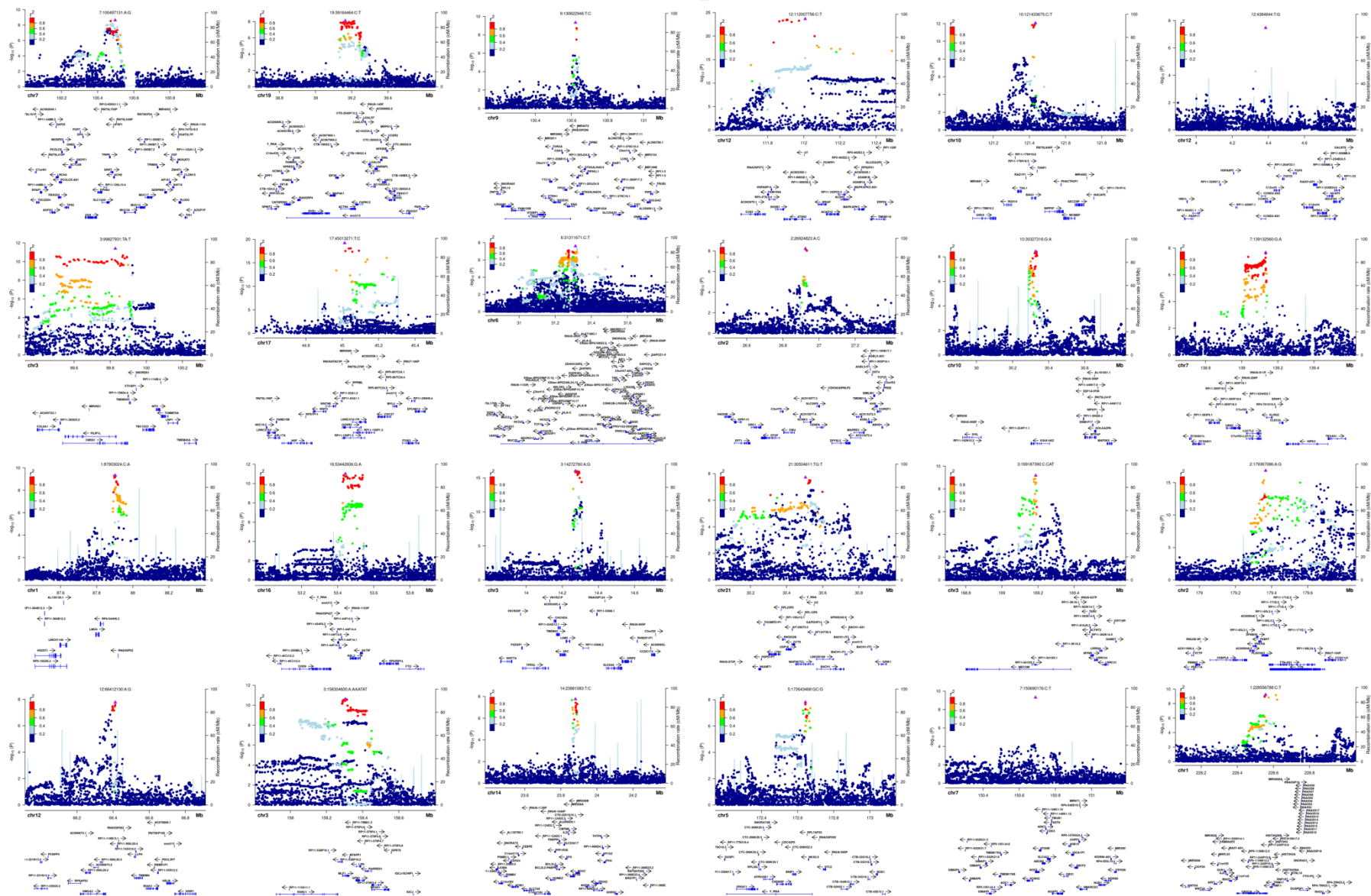
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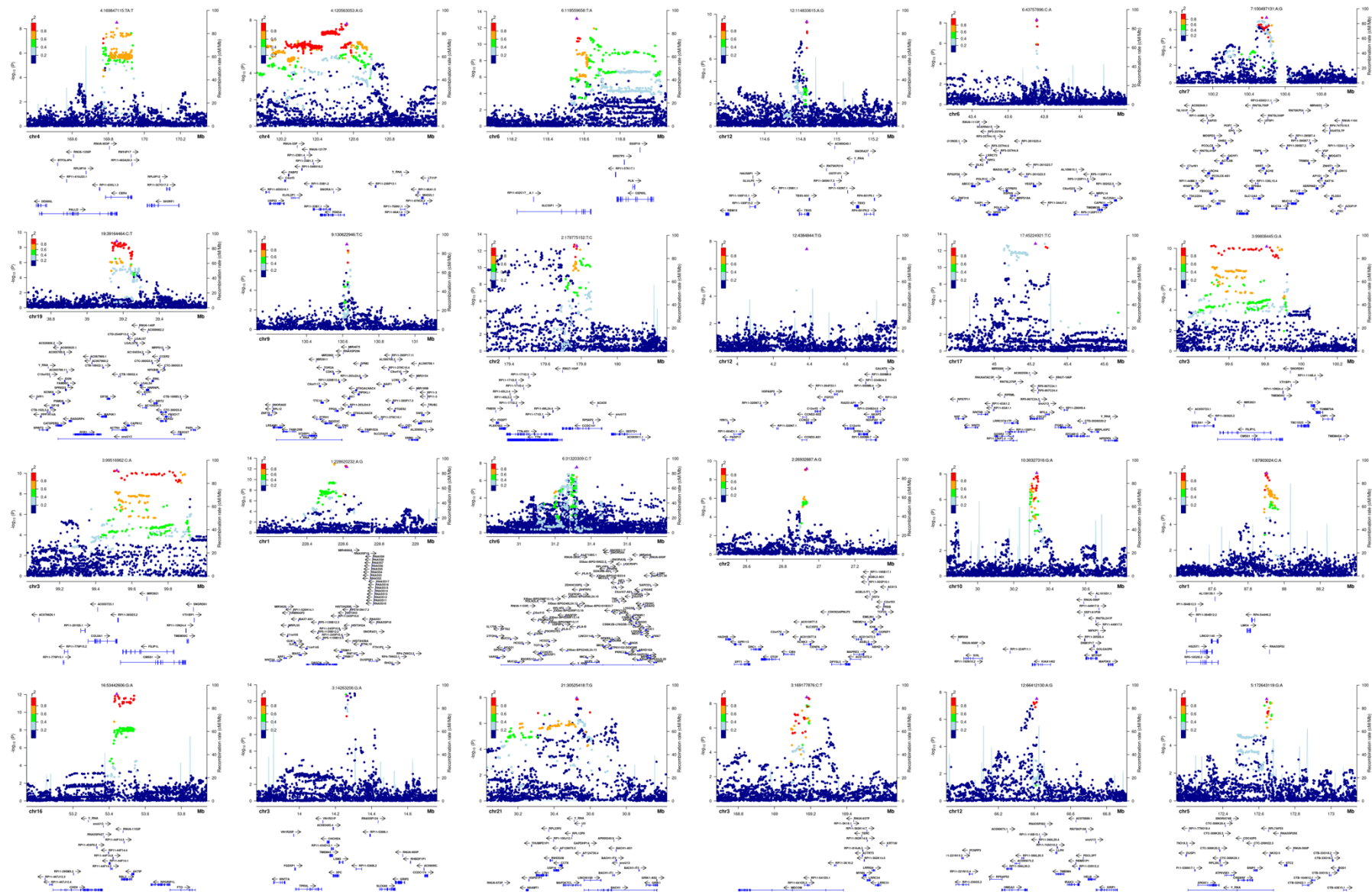
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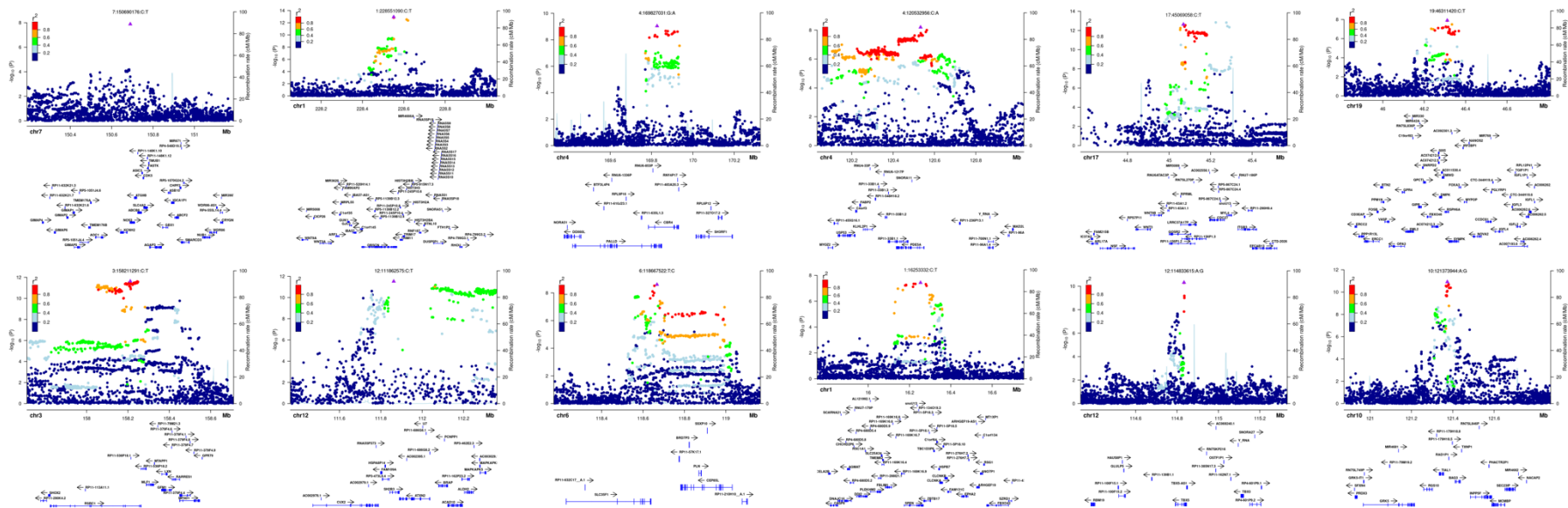
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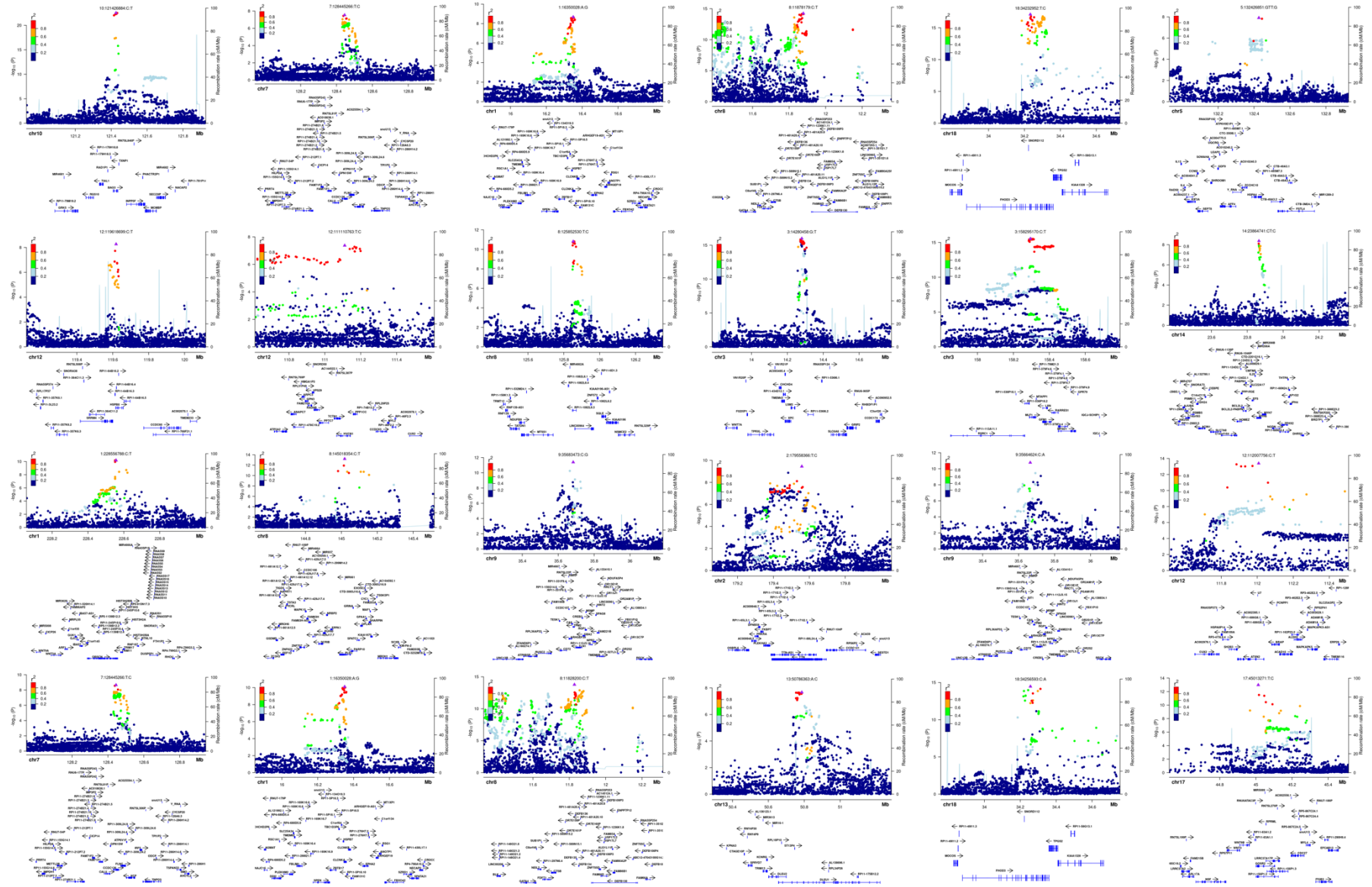
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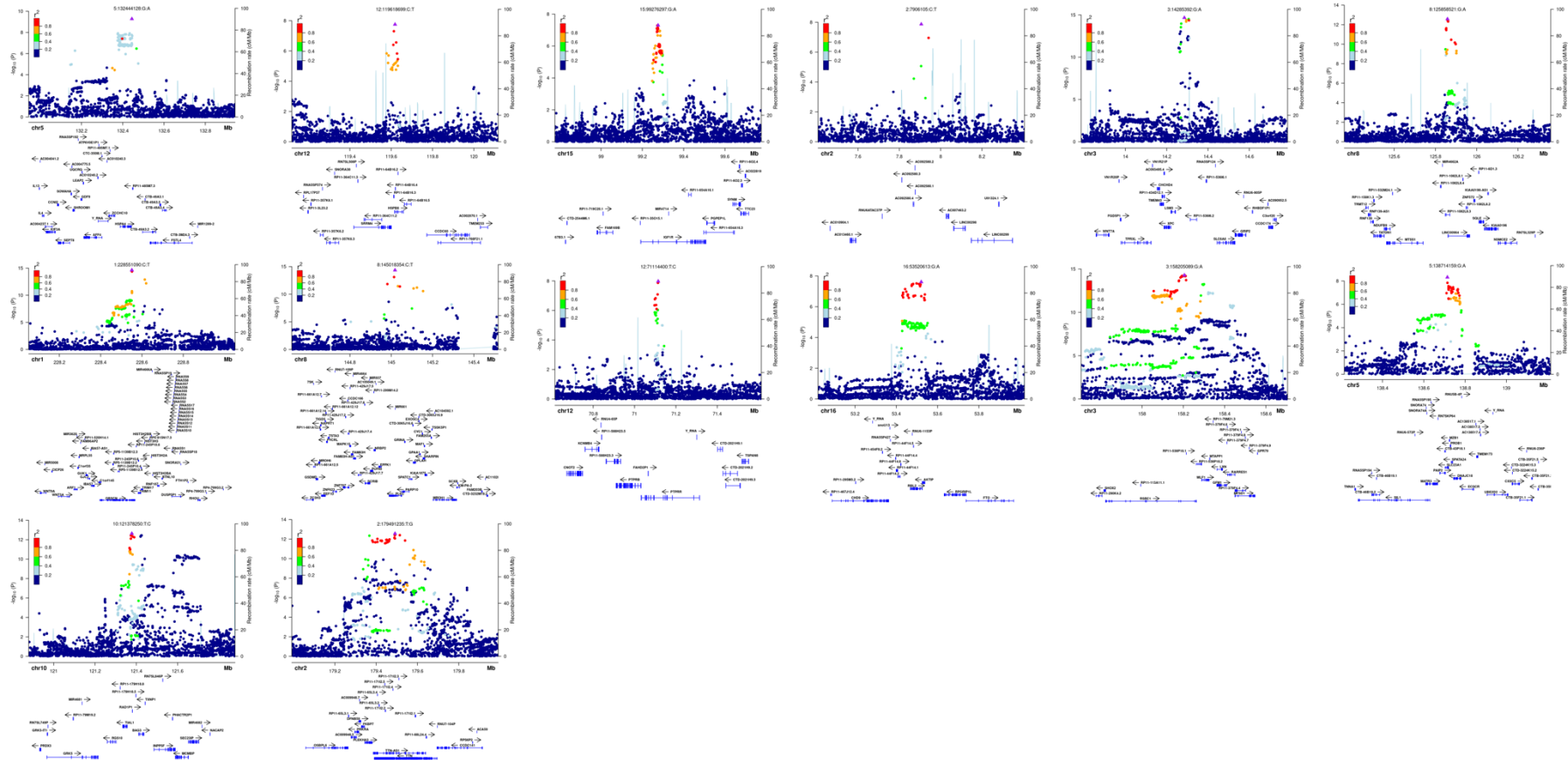
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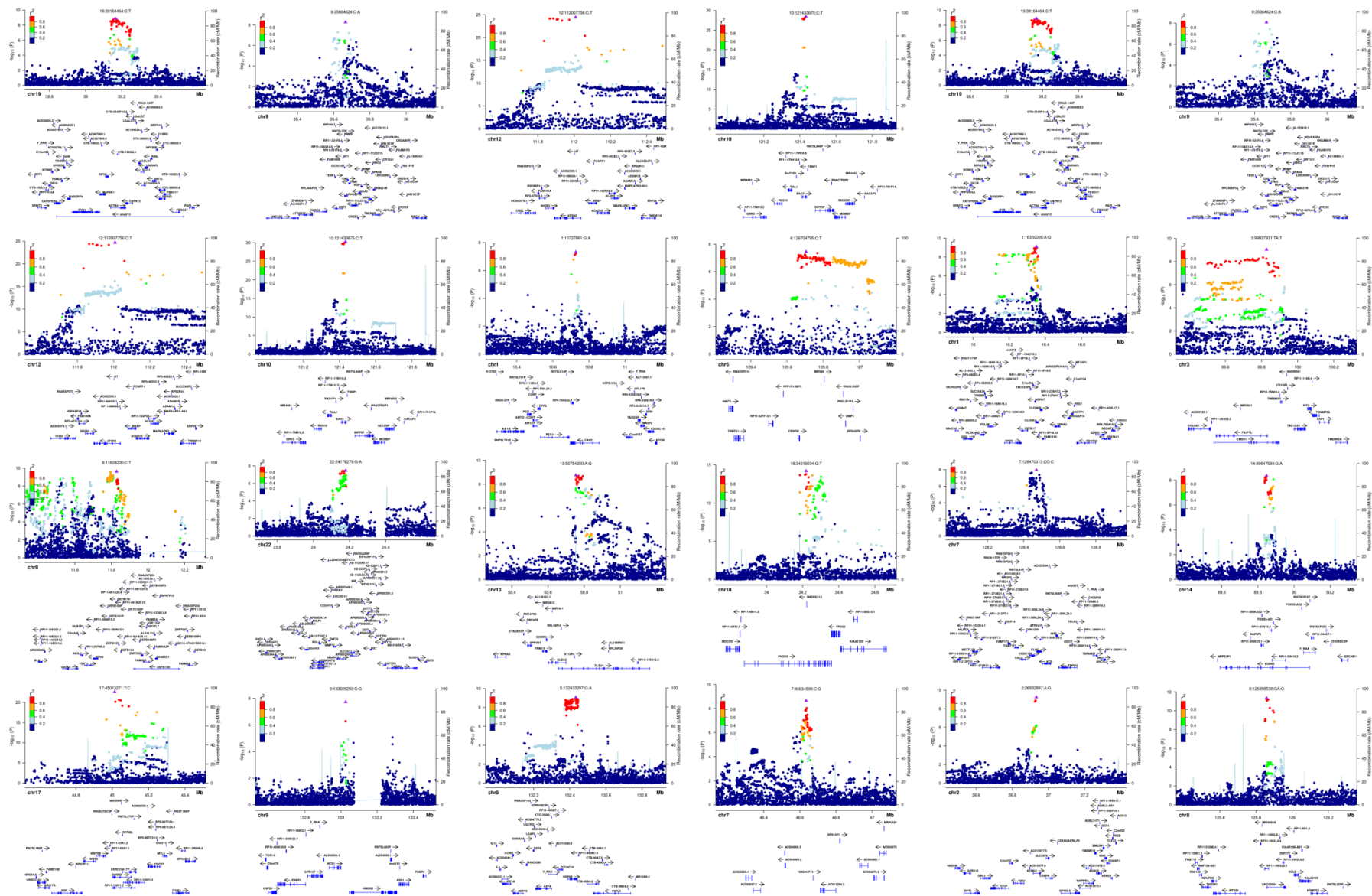
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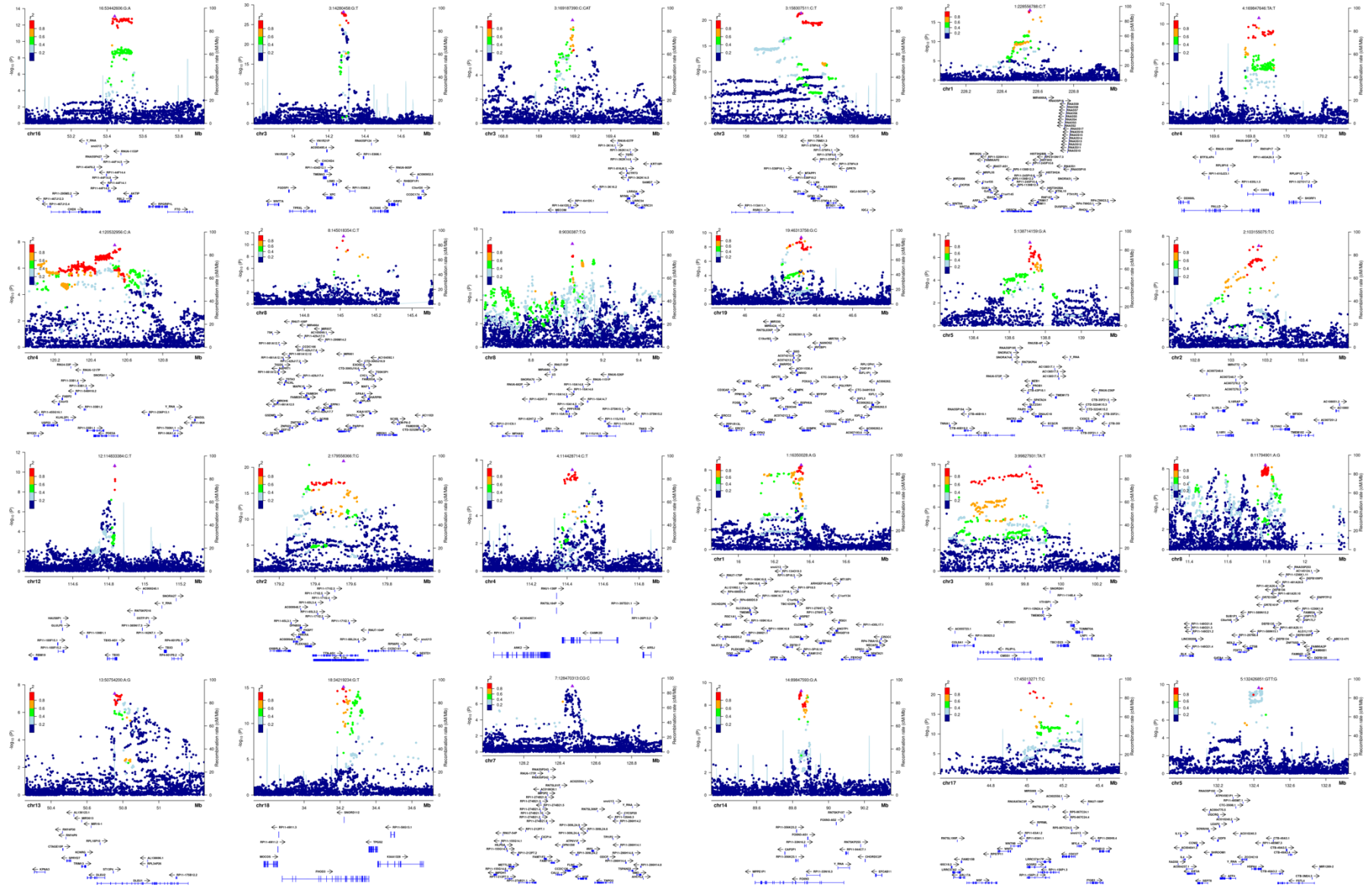
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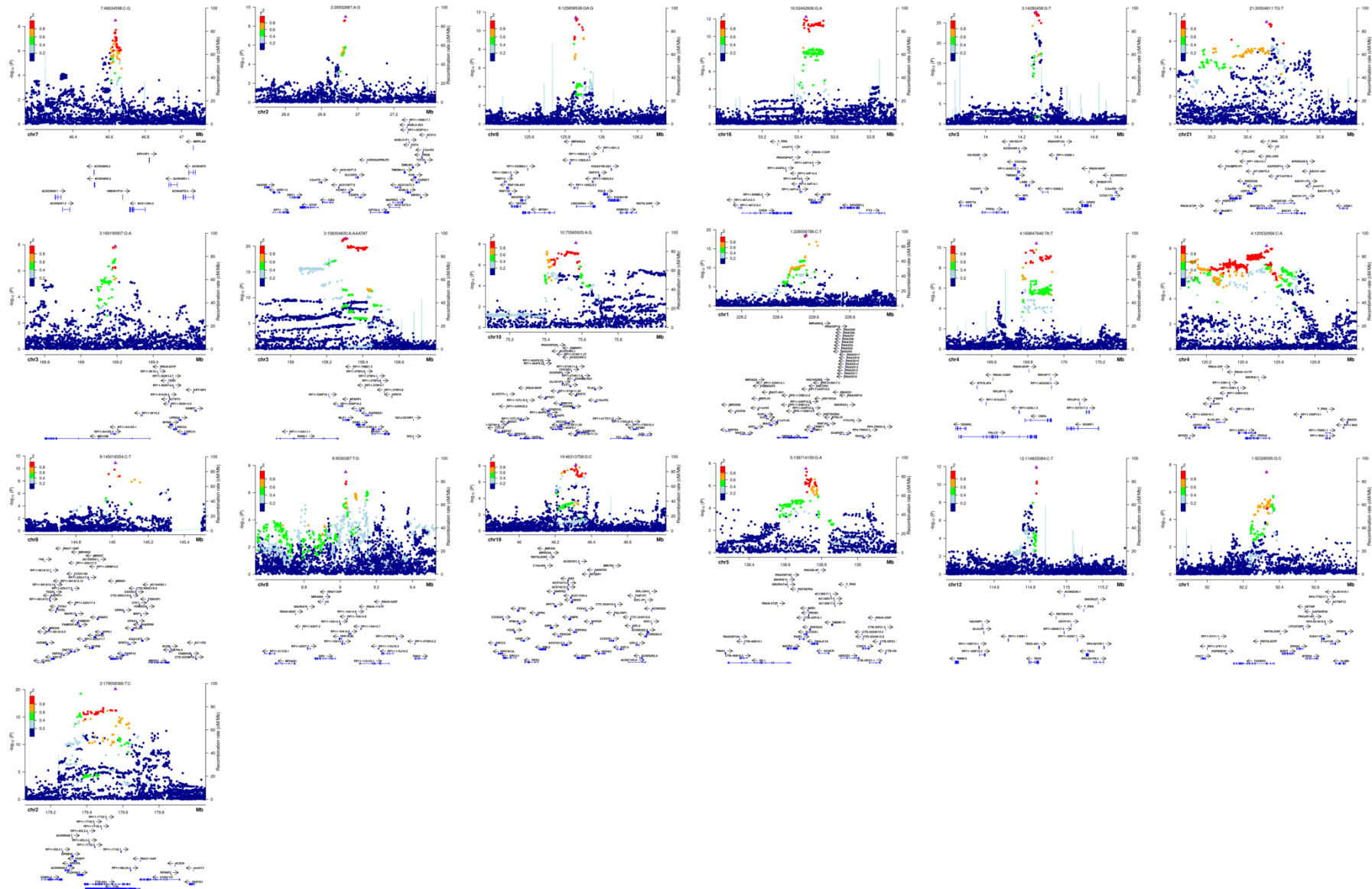
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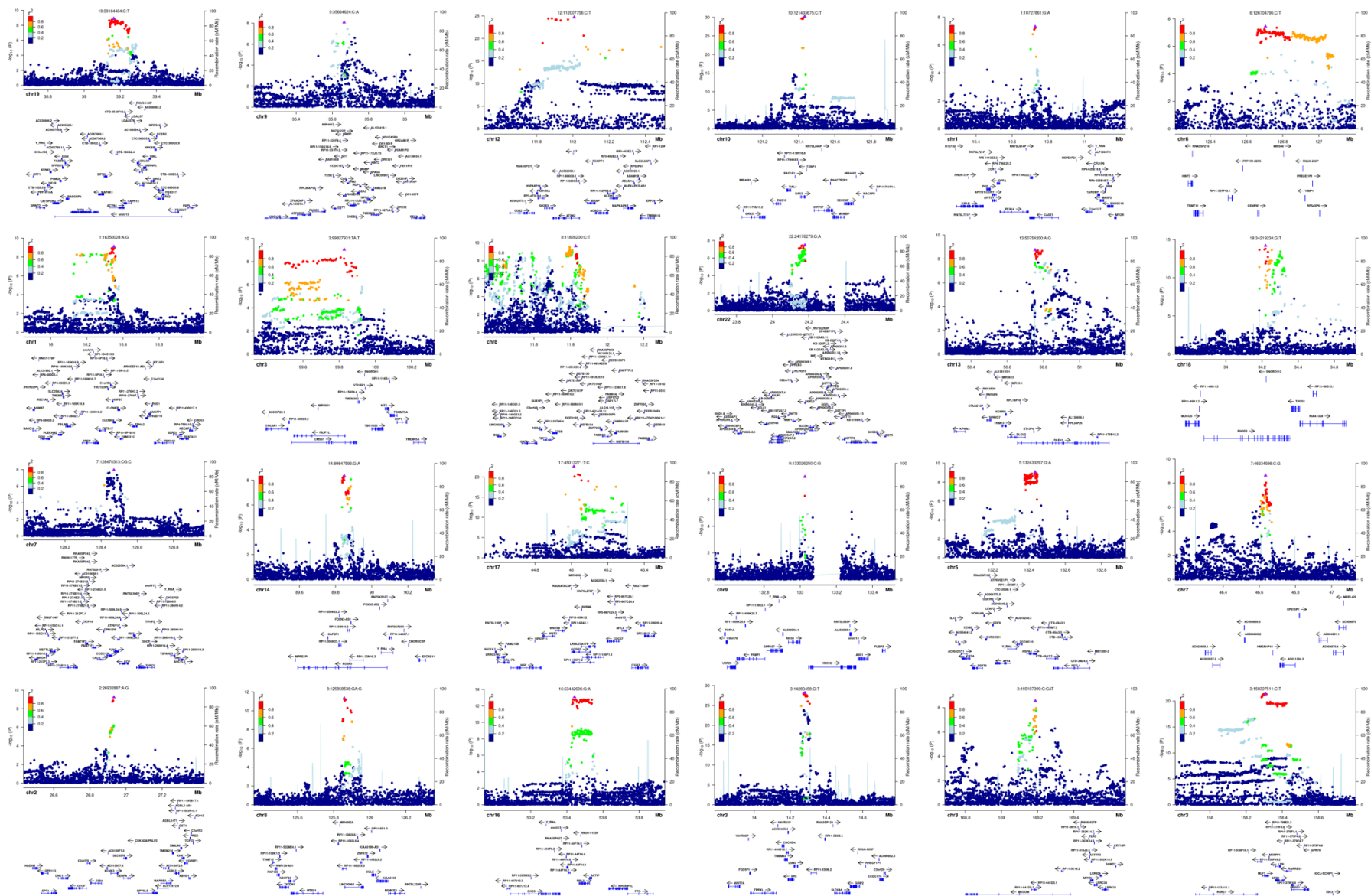
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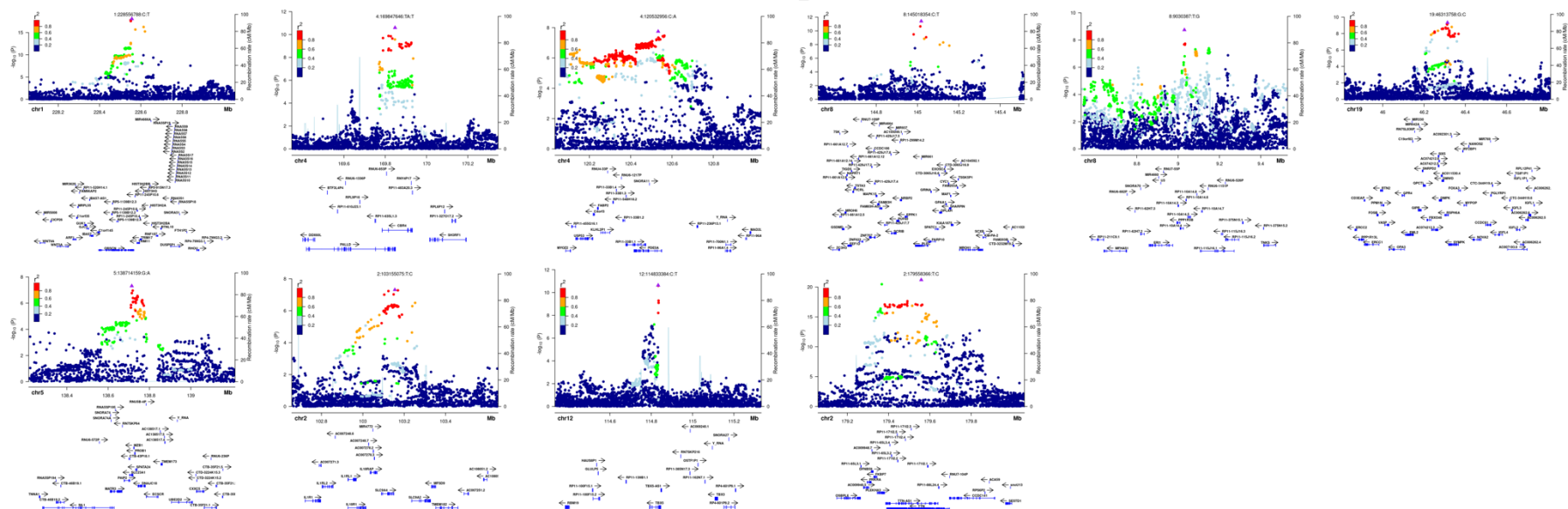
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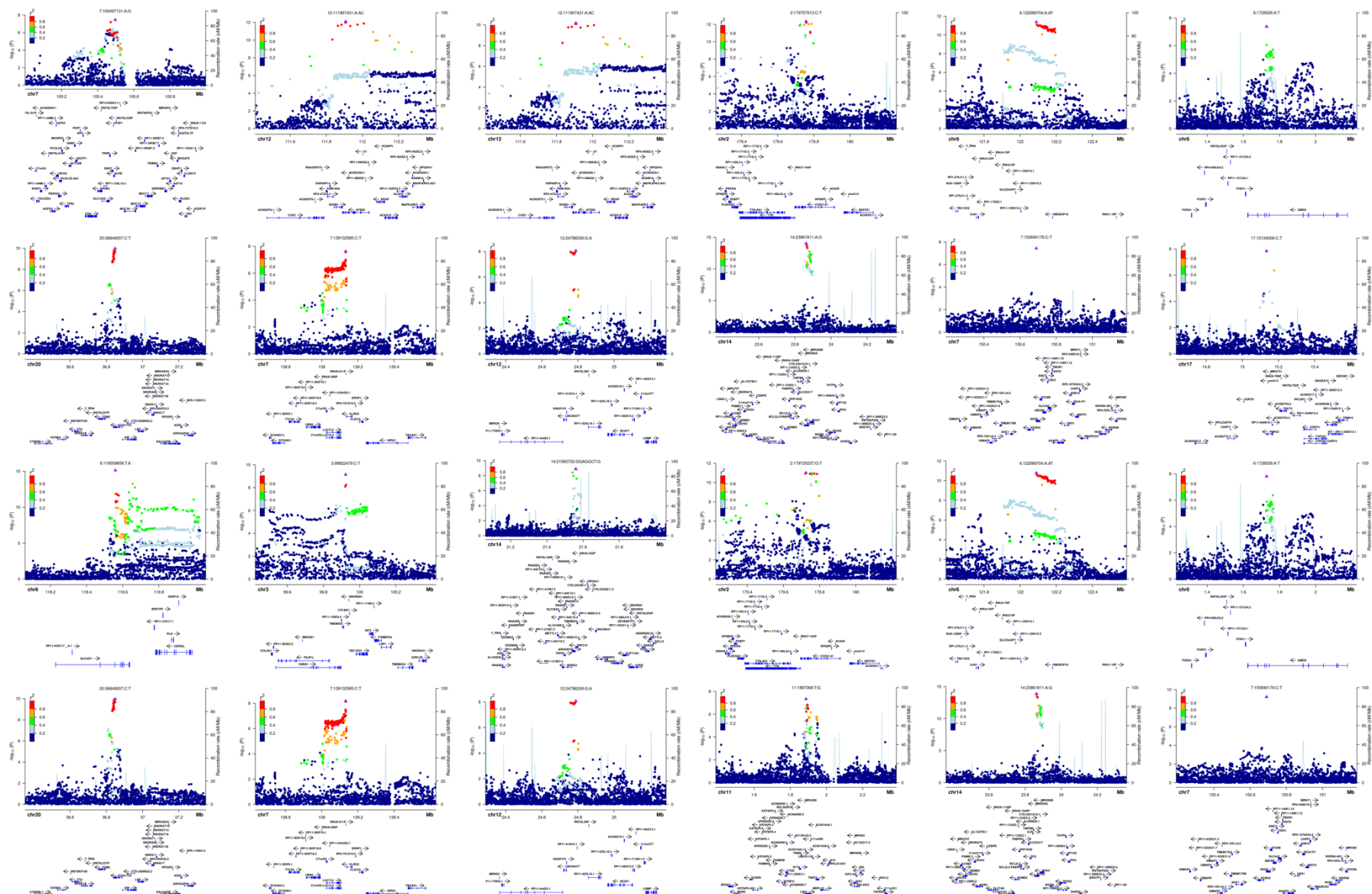
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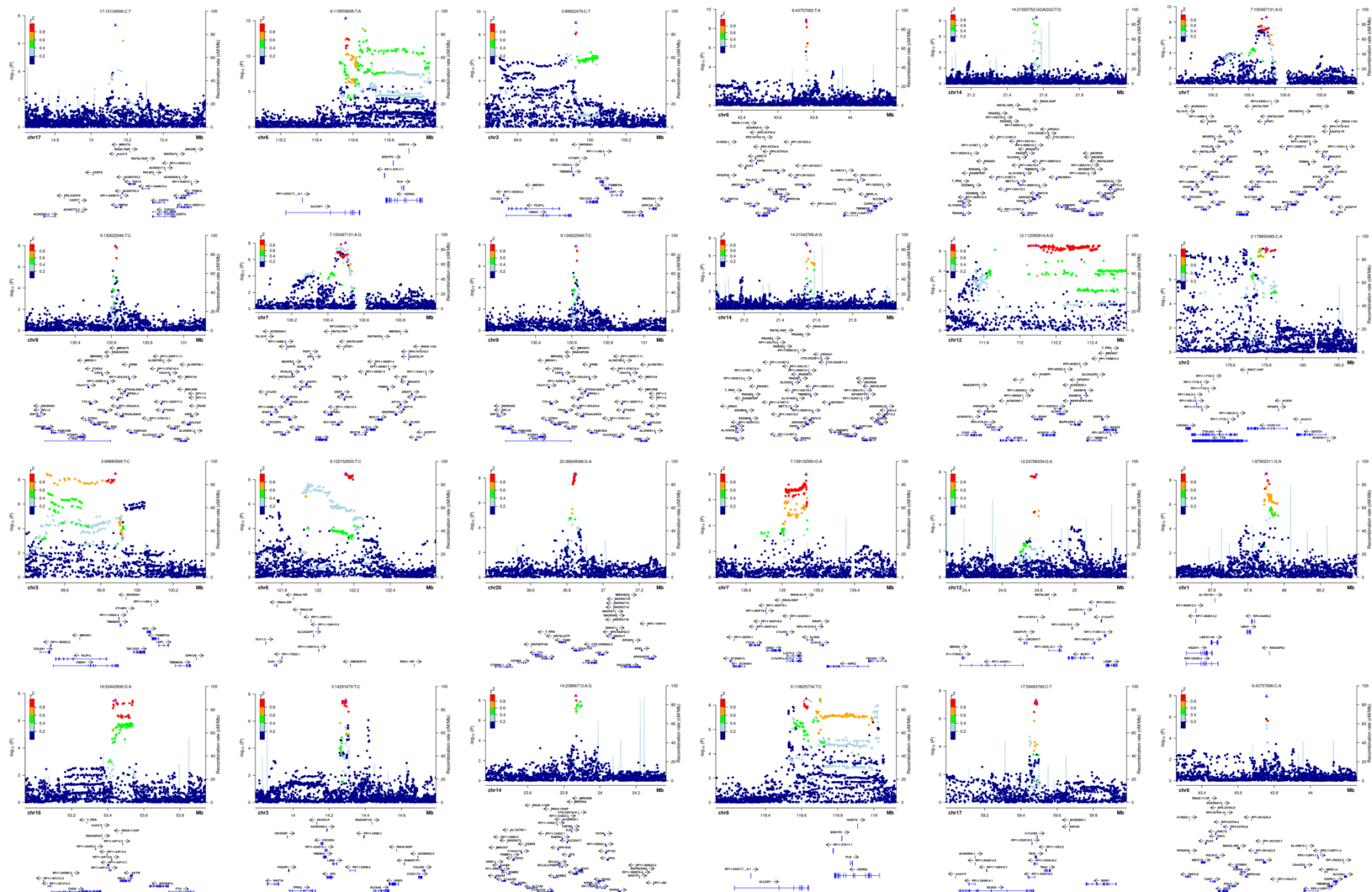
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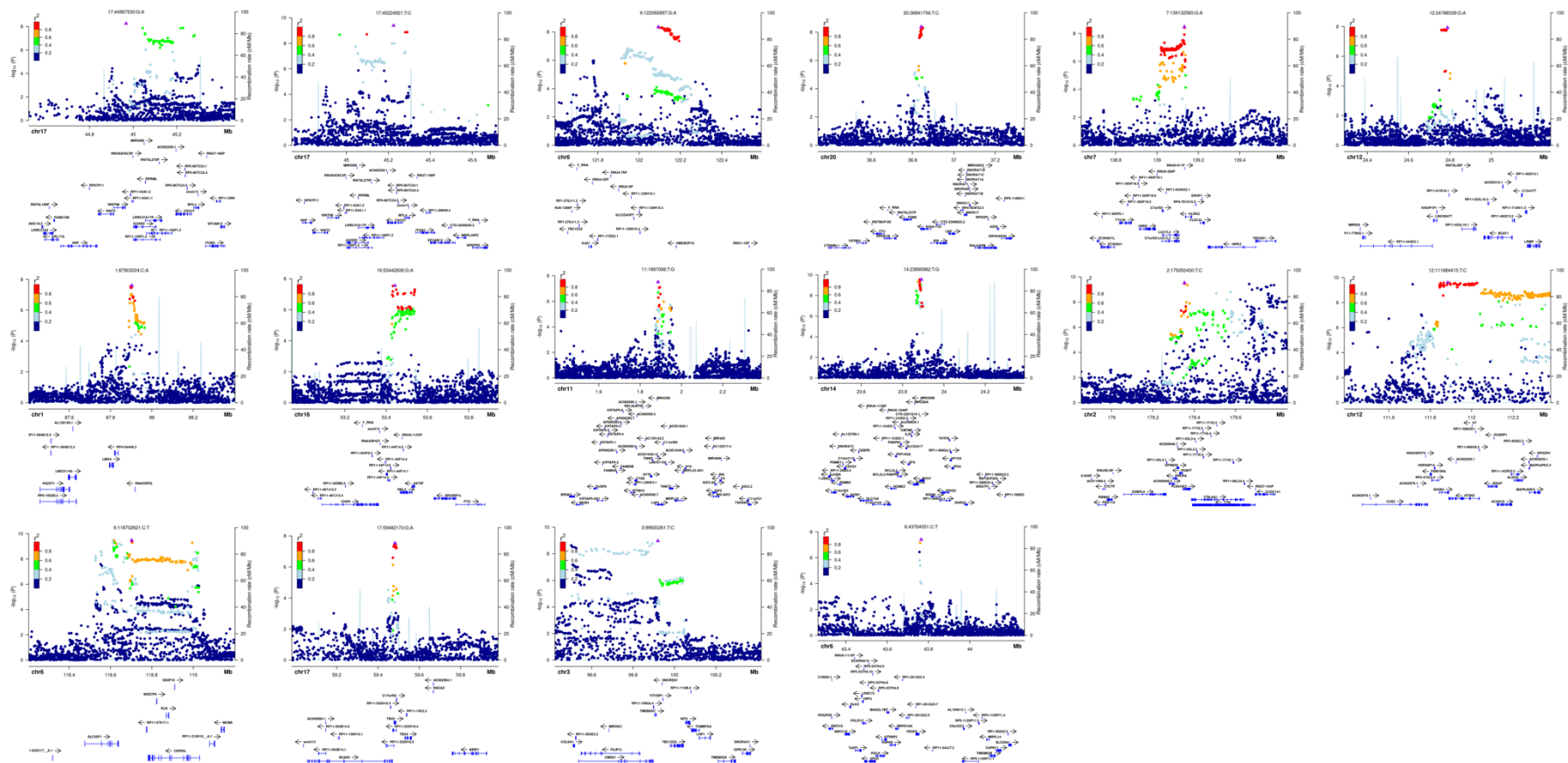
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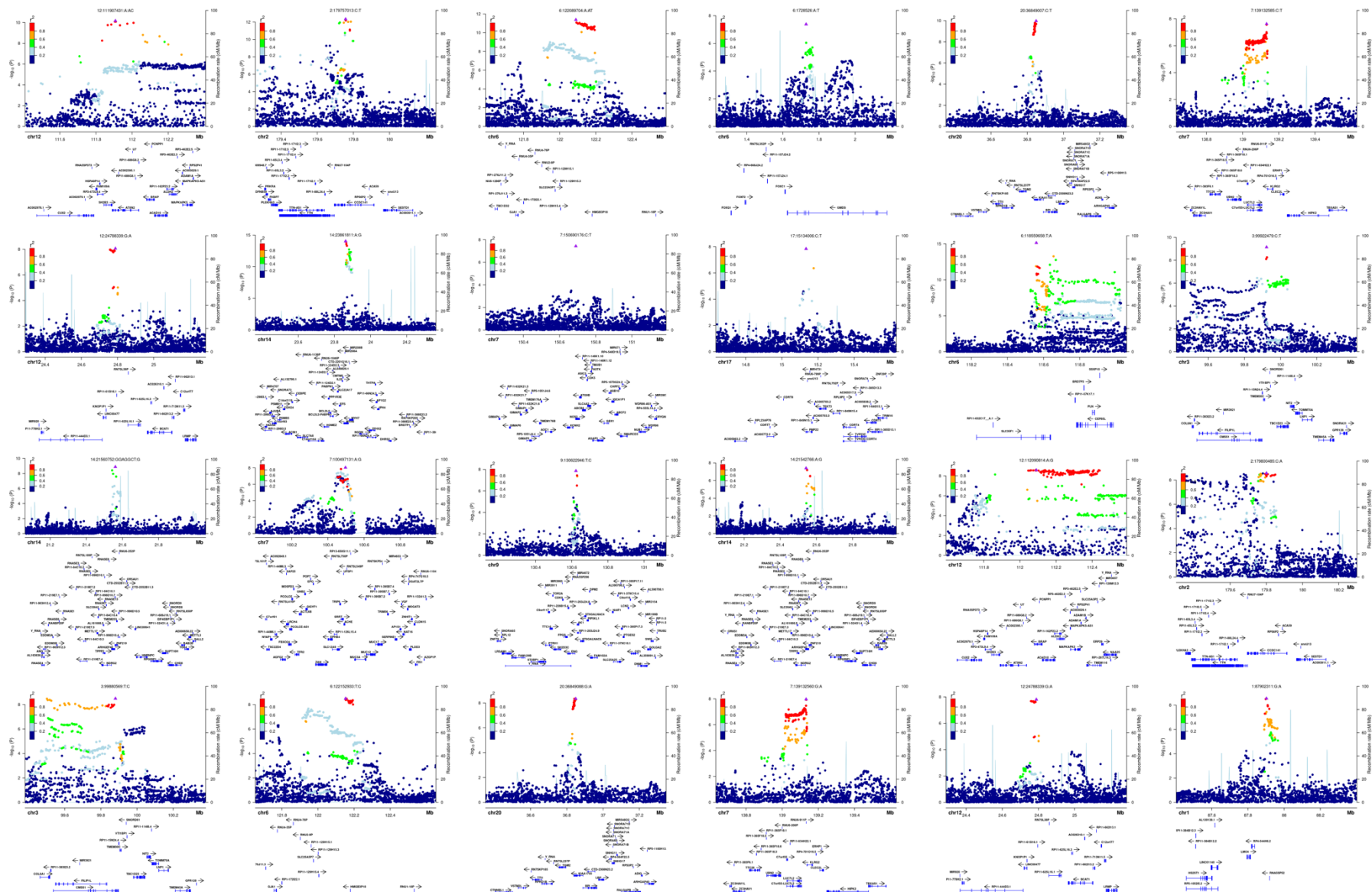
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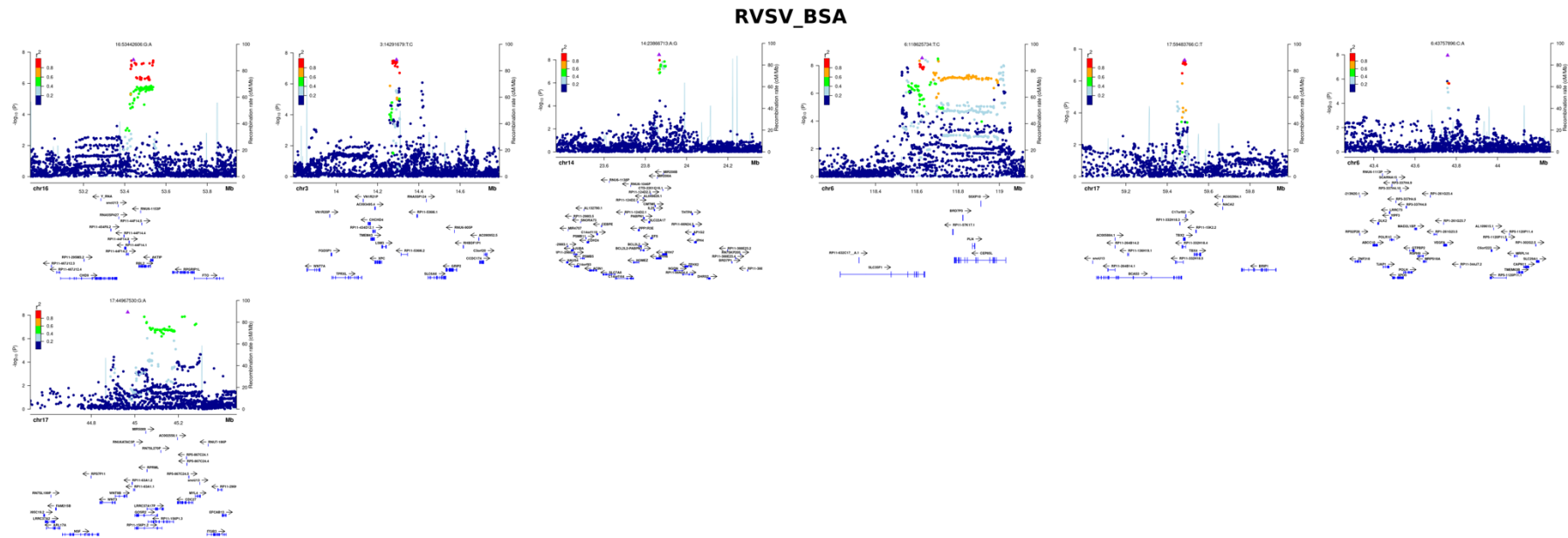


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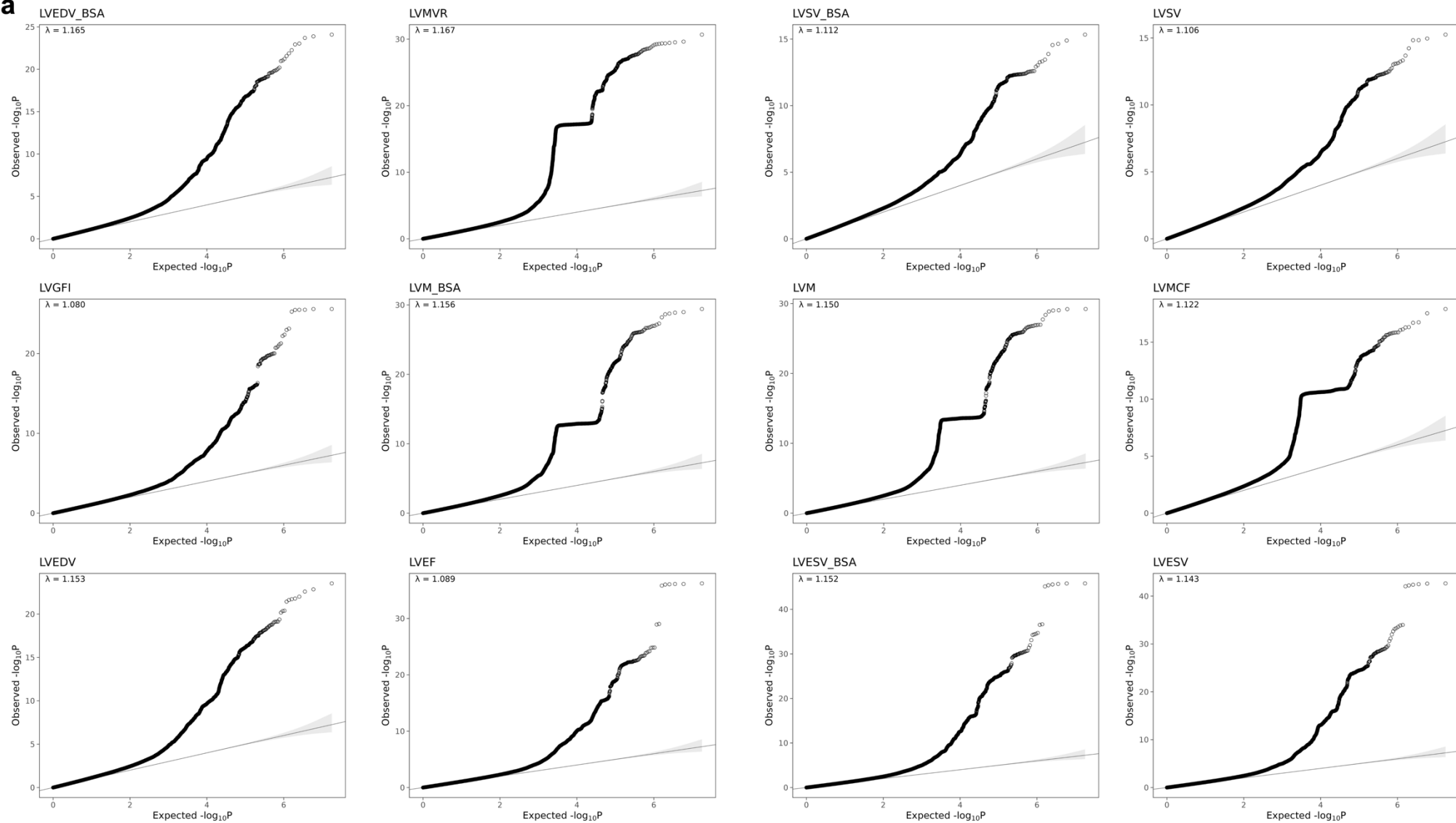


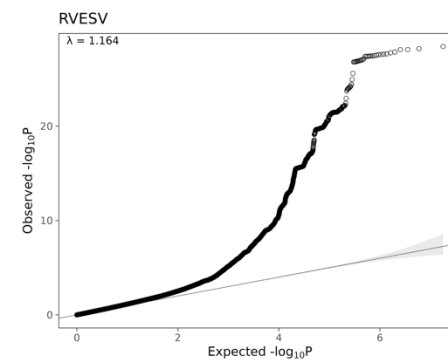
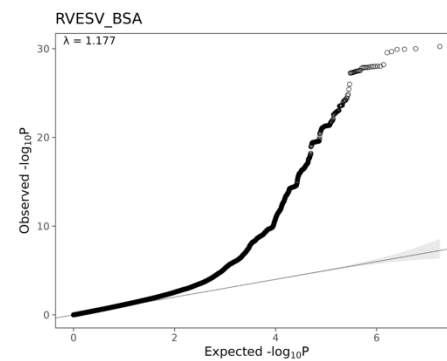
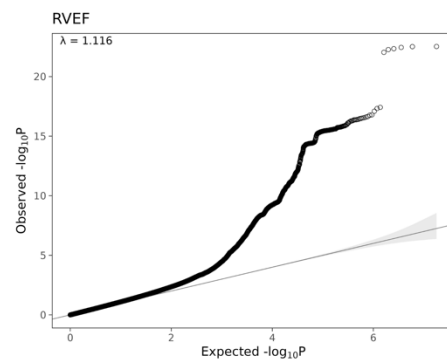
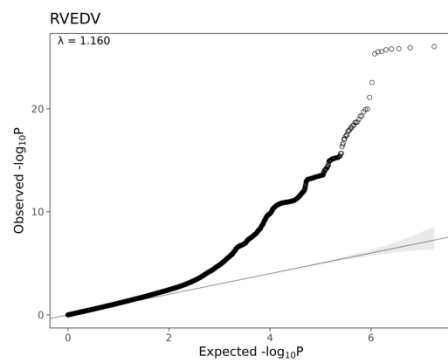
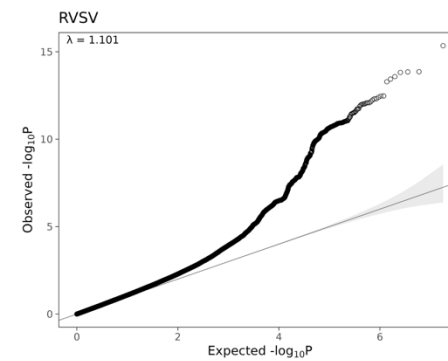
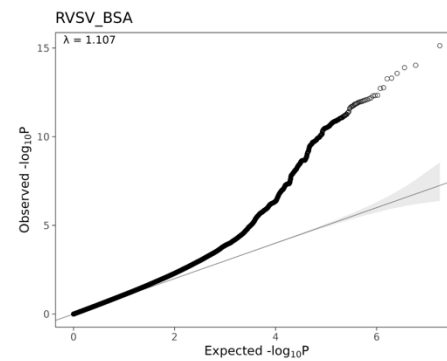
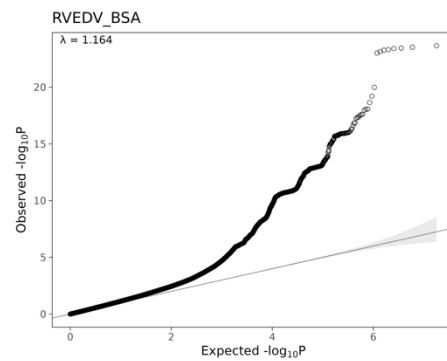
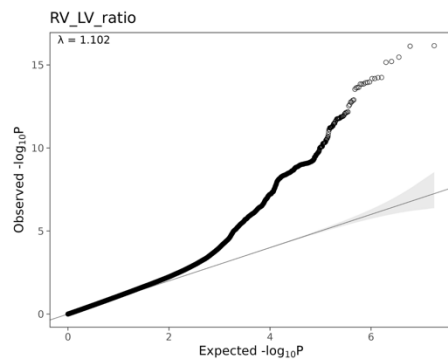
RVSV_BSA

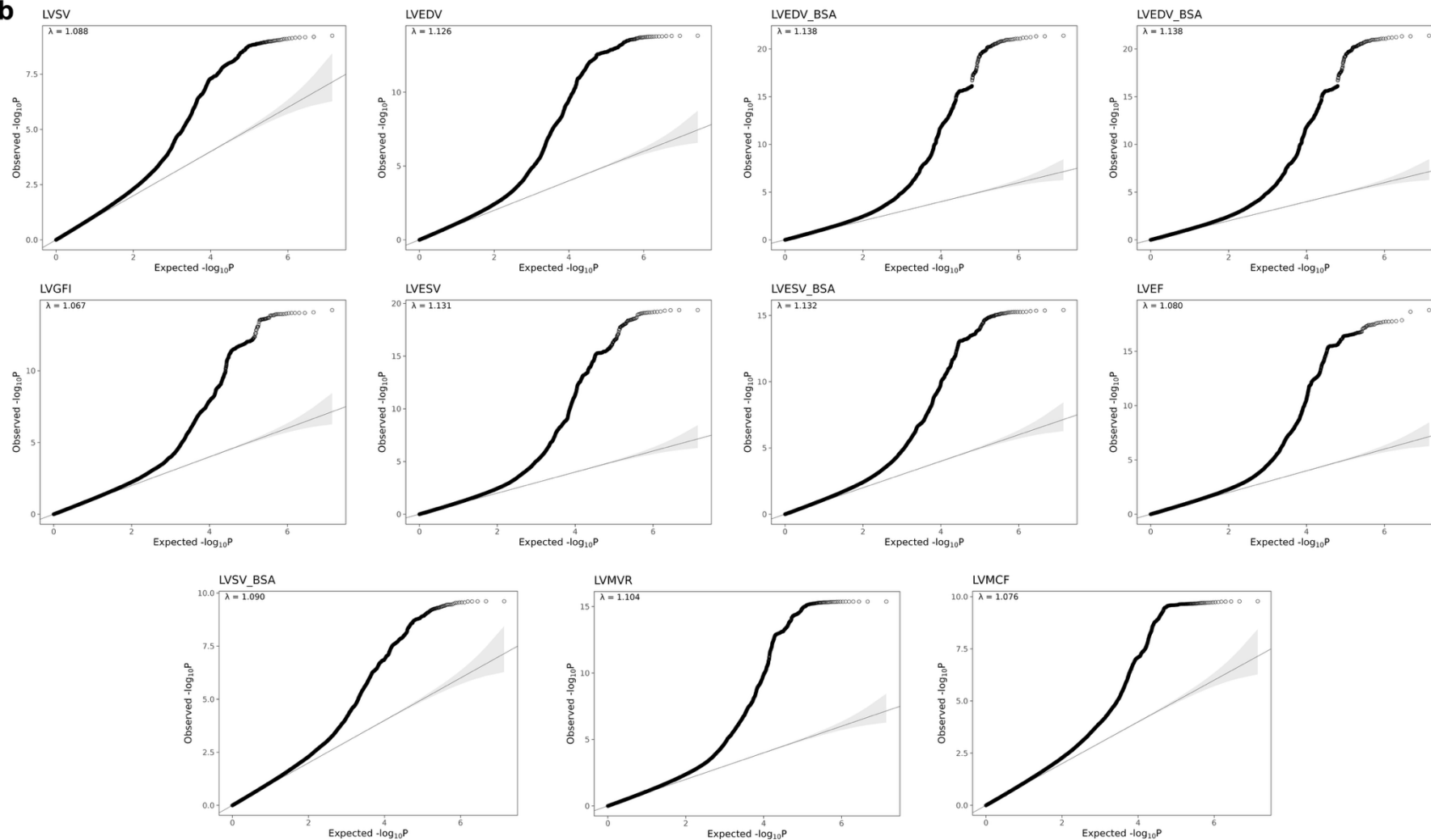


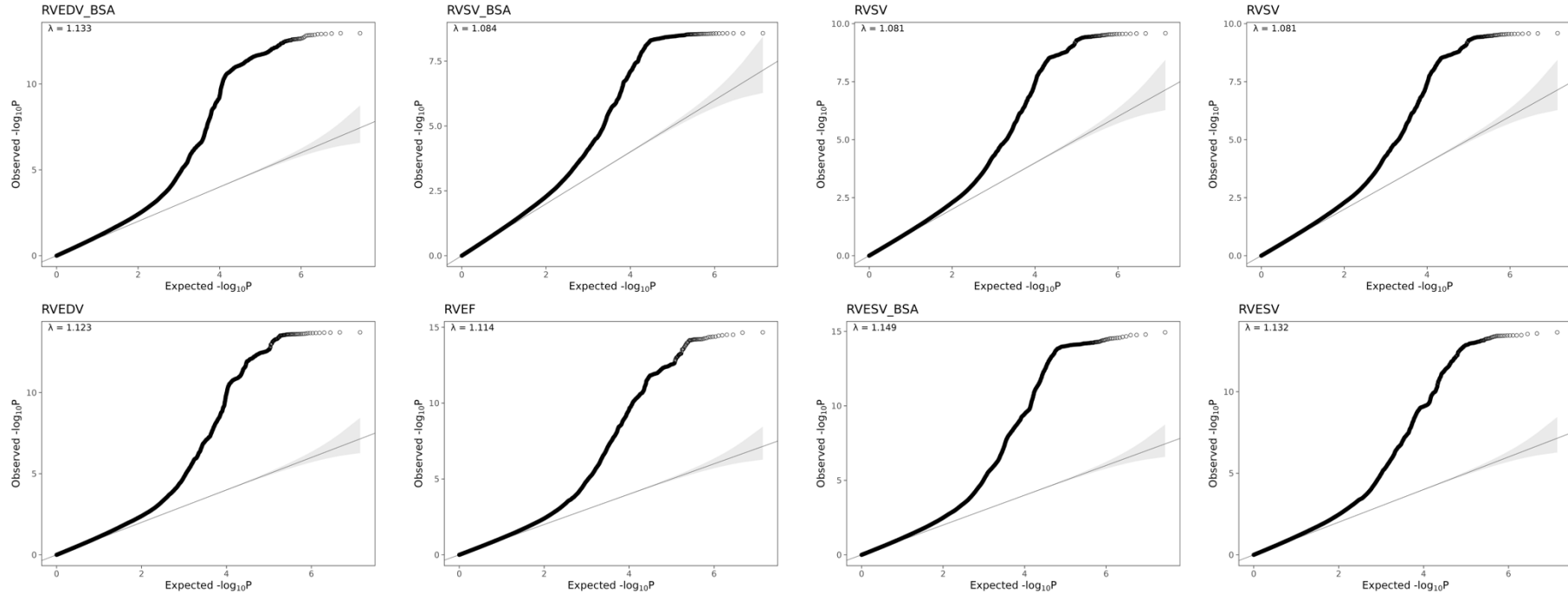


Supplementary Fig 3. LocusZoom plots of all left and right ventricular traits. Regional association plots of significant loci for left and right ventricular traits. P-values were calculated using a two-sided Wald test within the REGENIE linear regression framework. The additive genetic model was used to test for single-variant associations. The y-axis denotes the $\log_{10}(\text{p-value})$ and the x-axis denotes the genomic region. Linkage disequilibrium (r^2) for the lead variant (indicated by a purple triangle) was calculated based on the UK Biobank reference panel. The full summary statistics underlying these plots are publicly available via the GWAS Catalog (Accession codes: GCST90797570-GCST90797613). LVEDV, Left Ventricular End-Diastolic Volume; LVESV, Left Ventricular End-Systolic Volume; LVSV, Left Ventricular Stroke Volume; LVEF, Left Ventricular Ejection Fraction; LVGFI, Left Ventricular Global Function Index; LVMCF, Left Ventricular Myocardial Contraction Fraction; LVM, Left Ventricular Mass; LVMVR, Left Ventricular Mass-to-Volume Ratio; LVEDV BSA, Left Ventricular End-Diastolic Volume Indexed to Body Surface Area; LVESV BSA, Left Ventricular End-Systolic Volume Indexed to Body Surface Area; LVSV BSA, Left Ventricular Stroke Volume Indexed to Body Surface Area; LVM BSA, Left Ventricular Mass Indexed to Body Surface Area; RVEDV, Right Ventricular End-Diastolic Volume; RVESV, Right Ventricular End-Systolic Volume; RVSV, Right Ventricular Stroke Volume; RVEF, Right Ventricular Ejection Fraction; RV LV ratio, Right Ventricular to Left Ventricular Ratio; RVEDV BSA, Right Ventricular End-Diastolic Volume Indexed to Body Surface Area; RVESV BSA, Right Ventricular End-Systolic Volume Indexed to Body Surface Area; RVSV BSA, Right Ventricular Stroke Volume Indexed to Body Surface Area.

a

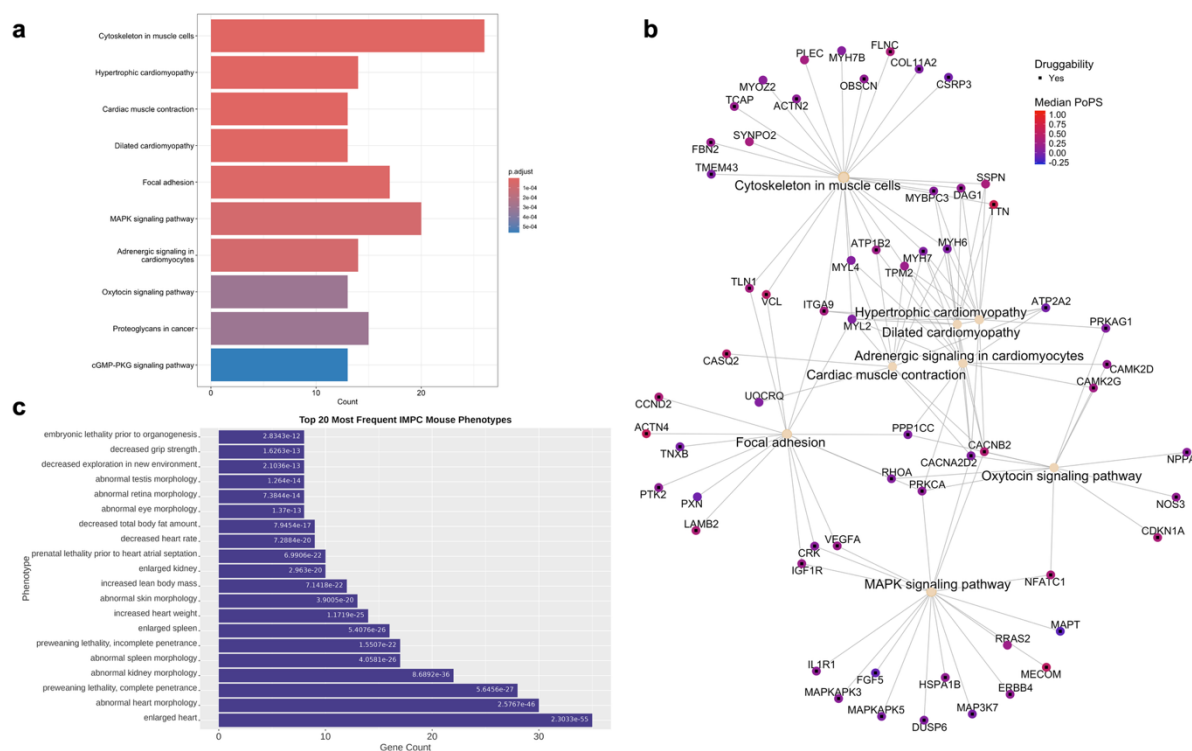


b



Supplementary Fig 4. QQ plots of all left and right ventricular traits. Single-trait quantile-quantile (QQ) plots (a) and multi-trait genome-wide association analysis QQ plots (b). P-values were derived from two-sided Wald tests using a linear regression model within the REGENIE framework. λ is the genomic inflation factor. The y-axis denotes the observed $\log_{10}(p\text{-value})$ and the x-axis denotes the expected $\log_{10}(p\text{-value})$. The full summary statistics underlying these plots are publicly available via the GWAS Catalog (Accession codes: GCST90797570-GCST90797613). LVEDV, Left Ventricular End-Diastolic Volume; LVESV, Left Ventricular End-Systolic Volume; LVSV, Left Ventricular Stroke Volume; LVEF, Left Ventricular Ejection Fraction; LVGFI, Left Ventricular Global Function Index; LVMCF, Left Ventricular Myocardial Contraction Fraction; LVM, Left Ventricular Mass; LVMVR, Left Ventricular Mass-to-Volume Ratio; LVEDV BSA, Left Ventricular End-Diastolic Volume Indexed to Body Surface Area; LVESV BSA, Left Ventricular End-Systolic Volume Indexed to Body Surface Area; LVSV BSA, Left Ventricular Stroke Volume Indexed to Body Surface Area; LVM BSA, Left Ventricular Mass Indexed to Body Surface Area; RVEDV, Right Ventricular End-Diastolic Volume; RVESV, Right Ventricular End-Systolic Volume; RVSV, Right Ventricular Stroke Volume; RVEF, Right Ventricular Ejection Fraction; RV LV ratio, Right Ventricular to Left Ventricular Ratio; RVEDV BSA, Right Ventricular End-Diastolic Volume Indexed to Body Surface Area; RVESV BSA, Right

Ventricular End-Systolic Volume Indexed to Body Surface Area; RVSV BSA, Right Ventricular Stroke Volume Indexed to Body Surface Area.



Supplementary Fig 5. Gene enrichment analysis. (a) shows the most significantly enriched KEGG (Kyoto Encyclopedia of Genes and Genomes) pathways for the 488 prioritised genes. Statistical significance was determined using a two-sided Fisher's Exact Test with p-values adjusted for multiple comparisons using the Benjamini-Hochberg False Discovery Rate (FDR) method. (b) visualises the gene network interaction between the top eight most significantly enriched KEGG pathways. In panel b, genes that have a "druggable" annotation in the drug-gene interaction database are denoted by a black square. The median PoPS (polygenic priority score) is identified per each gene node, using a red to blue colour gradient identifying highest (red) to lowest (blue) PoP scores. (c) shows a bar chart of the top 20 most significantly enriched knockout mouse model phenotypes and the counts of all their prioritised genes per phenotype. Statistical significance was assessed using a two-sided Fisher's Exact Test, with p-values adjusted for multiple comparisons using the FDR method. Source data are provided as a Source Data file.

a

