

Supplementary Information

Supplementary Methods

Comorbidities were curated from the national databases using the International Classification of Diseases (ICD)-10 and ICD-9 codes. The codes used to extract each comorbidity are listed below (% sign indicates that any code with the preceding number was utilized).

Atrial Fibrillation:

ICD-9: 427.31%

ICD-10: I48.2%, I48.0%, I48.91%, I48.1%

Coronary Artery Disease:

ICD-9: 410%, 411%, 412%, 413%, 414%

ICD-10: I20%, I21%, I22%, I23%, I24%, I25%

Chronic Kidney Disease:

ICD-9: 403.01%, 404.02%, 404.10%, 585.00%, 403.11%, 404.03%, 404.90%, 586.00%, 403.91%, 404.10%, 584.00%, 792.50%

ICD-10: V42.0%, V56.0%, V56.3%, N18%, V45.1%, V56.1%, V56.8%, V56.2%

Diabetes Mellitus:

ICD-9: 250%

ICD-10: E08%, E09%, E10%, E11%, E12%, E13%

Hyperlipidemia:

ICD-9: 272%

ICD-10: E78.0, E75.249, E78.01, E77.0, E78.1, E77.1, E78.2, E78.81, E78.3, E78.89, E78.4, E78.9, E78.5, E88.1, E78.6, E88.89, E75.21, E75.22

Hypertension:

ICD-9: 401%, 402%, 403%, 404%, 405%

ICD-10: I10%, I11%, I12%, I13%, I15%, I16%, I67.4%

Peripheral Vascular Disease:

ICD-9: 440%, 441%, 442%, 443%, 444%, 447%, 451%, 452%, 453%, 557%

ICD-10: E08.51, E08.52, E09.51, E09.52, E10.51, E10.52, E11.51, E11.52, E13.51, E13.52, I67.0, I70.0, I70%, I71%, I72%, I73.01, I73.1, I73.81, I73.89, I73.9, I74.01, I74.09, I74.10, I74.11, I74.19, I74.2, I74.3, I74.4, I74.5, I74.8, I74.9, I77%, I79.0, I79.1, I79.8, I80%, I81, I82%, K55%, K76.5, M31.8, M31.9

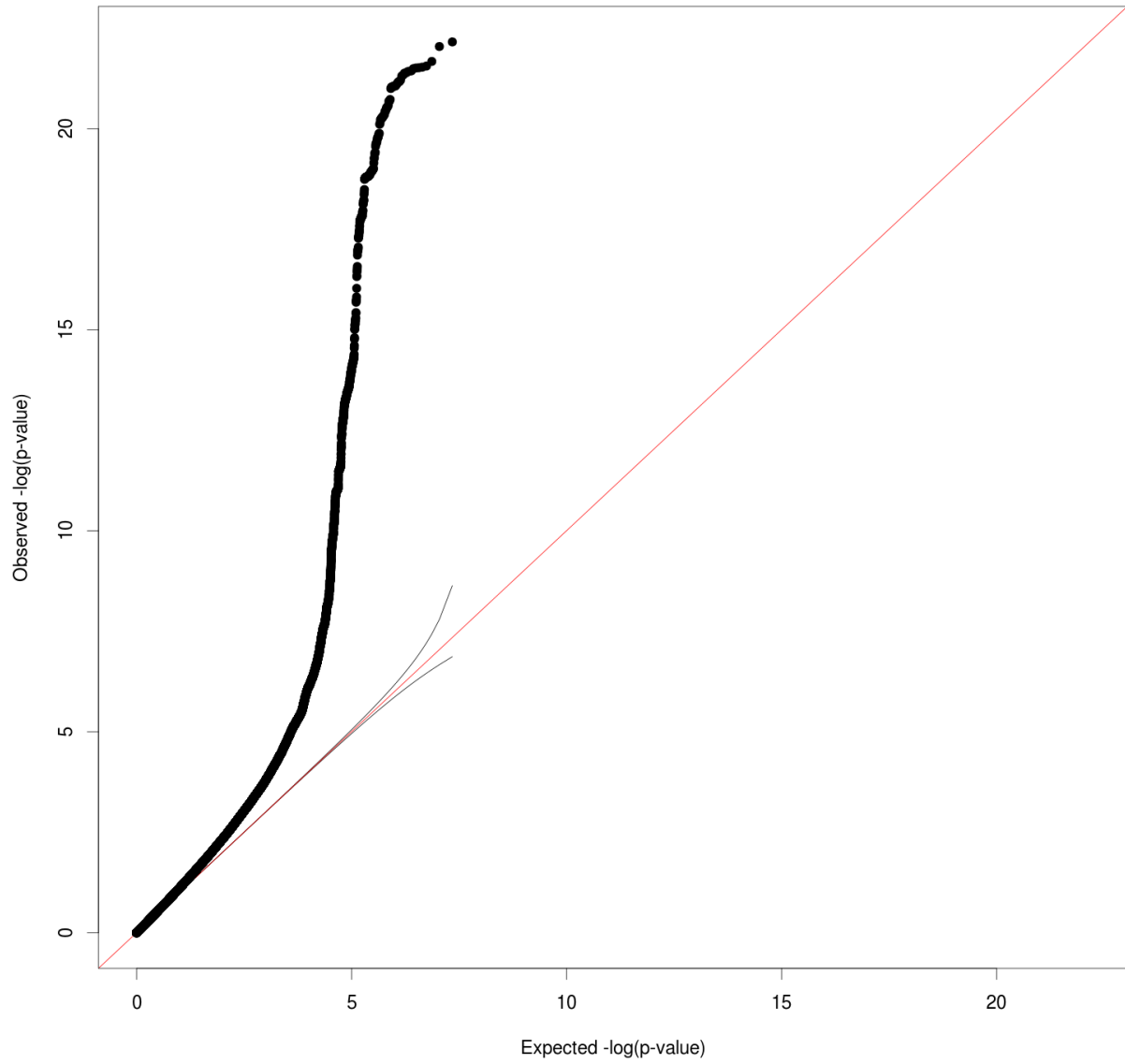
Stroke or Transient Ischemic Attack:

ICD-9: 430%, 431%, 433%, 434%, 436%, 437.0%, 437.6%

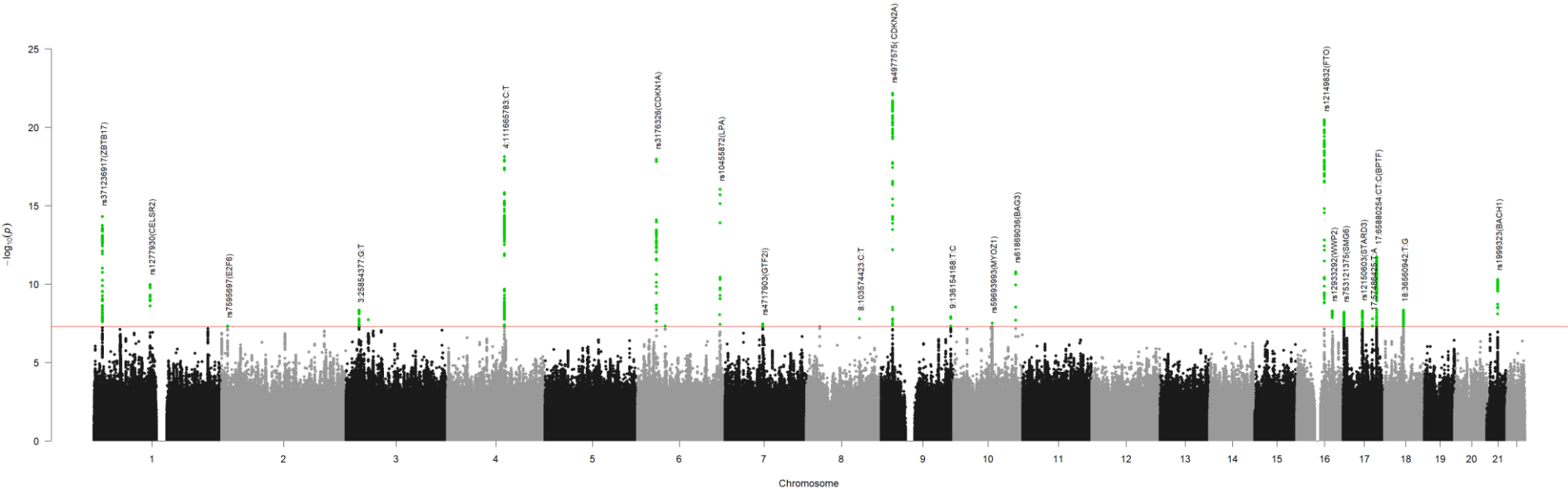
ICD-10: I63%, I65%, I66%, I67.2%, I67.8%, I67.6%, I60%, I61%, G45%

Supplementary Figures

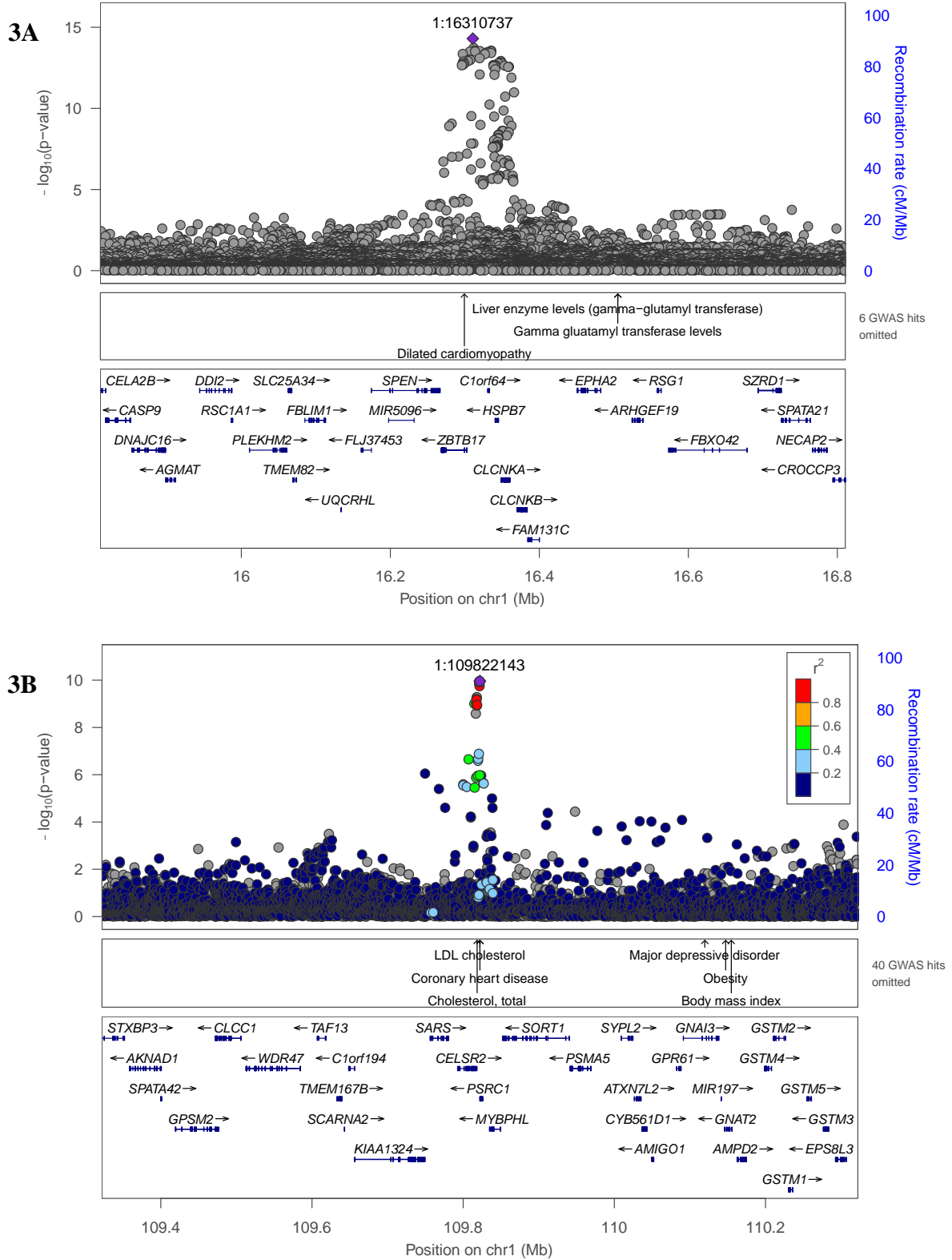
Supplementary Figure 1. Quantile-quantile plot of genome-wide meta-analysis of heart failure.

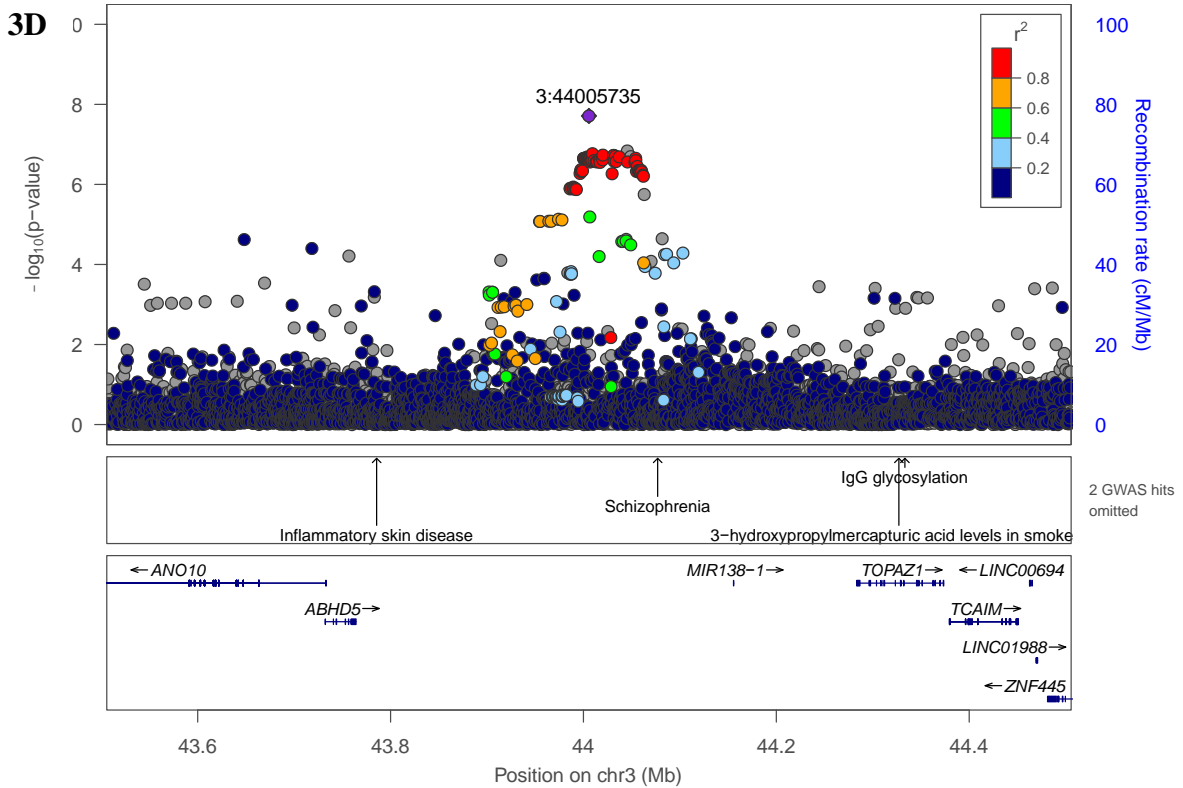
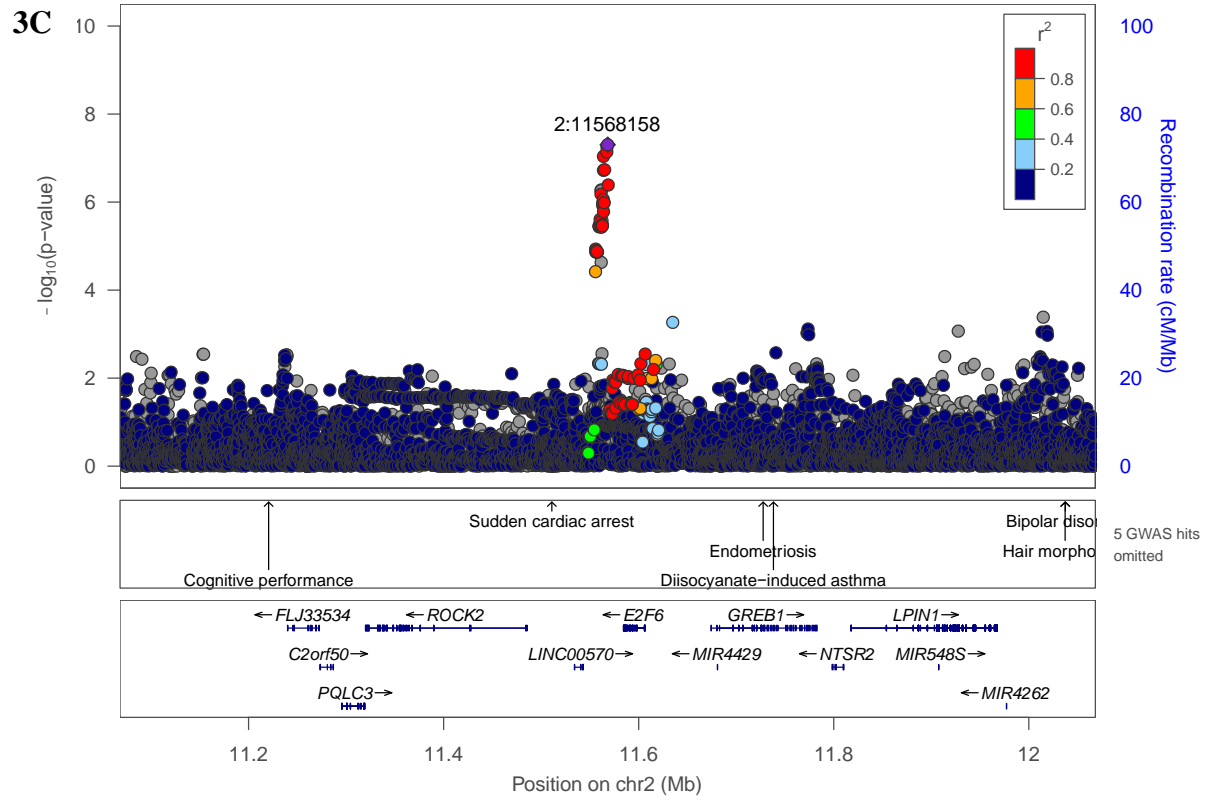


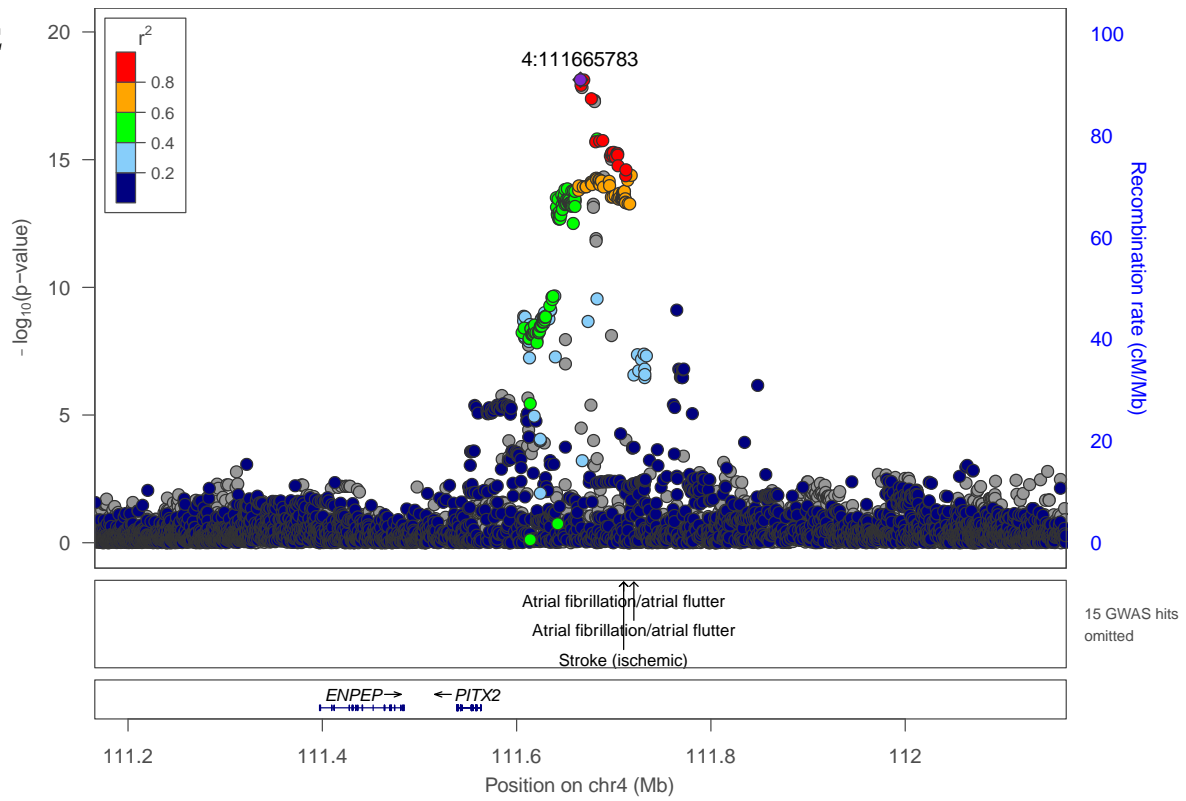
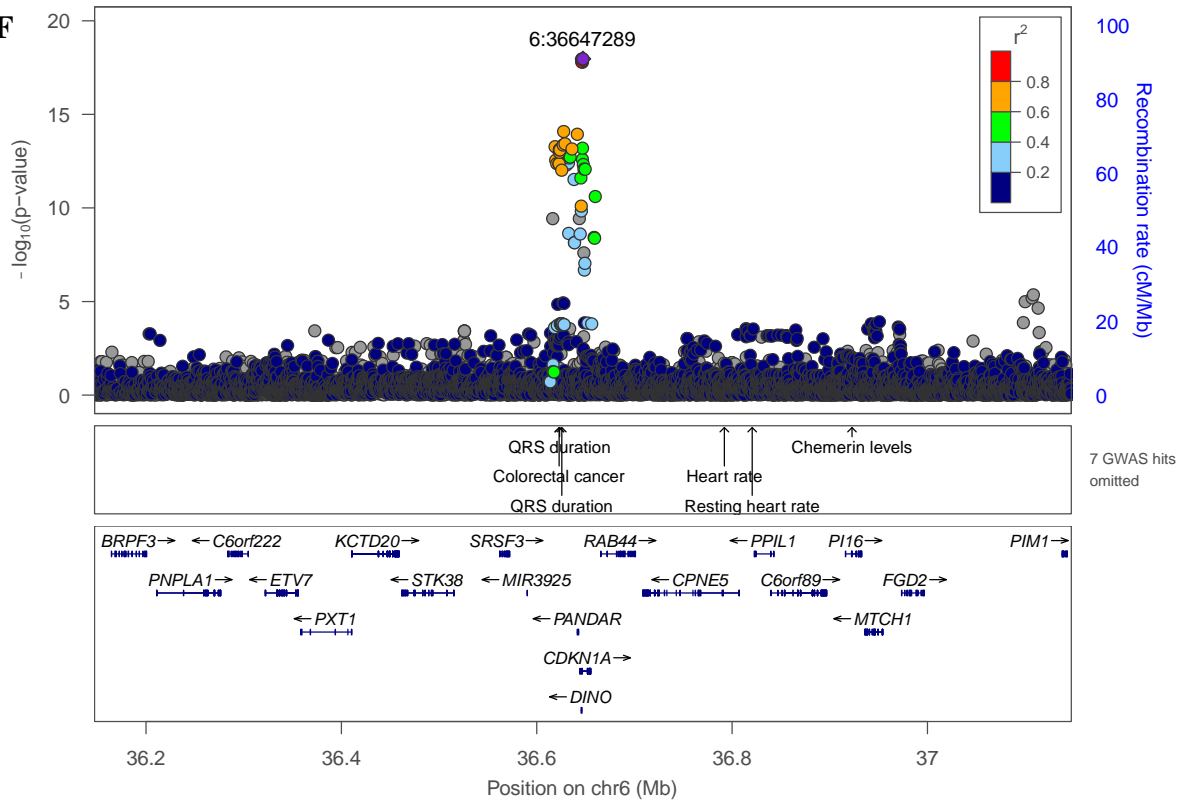
Supplementary Figure 2. Manhattan plot of genome-wide meta-analysis of unclassified heart failure.



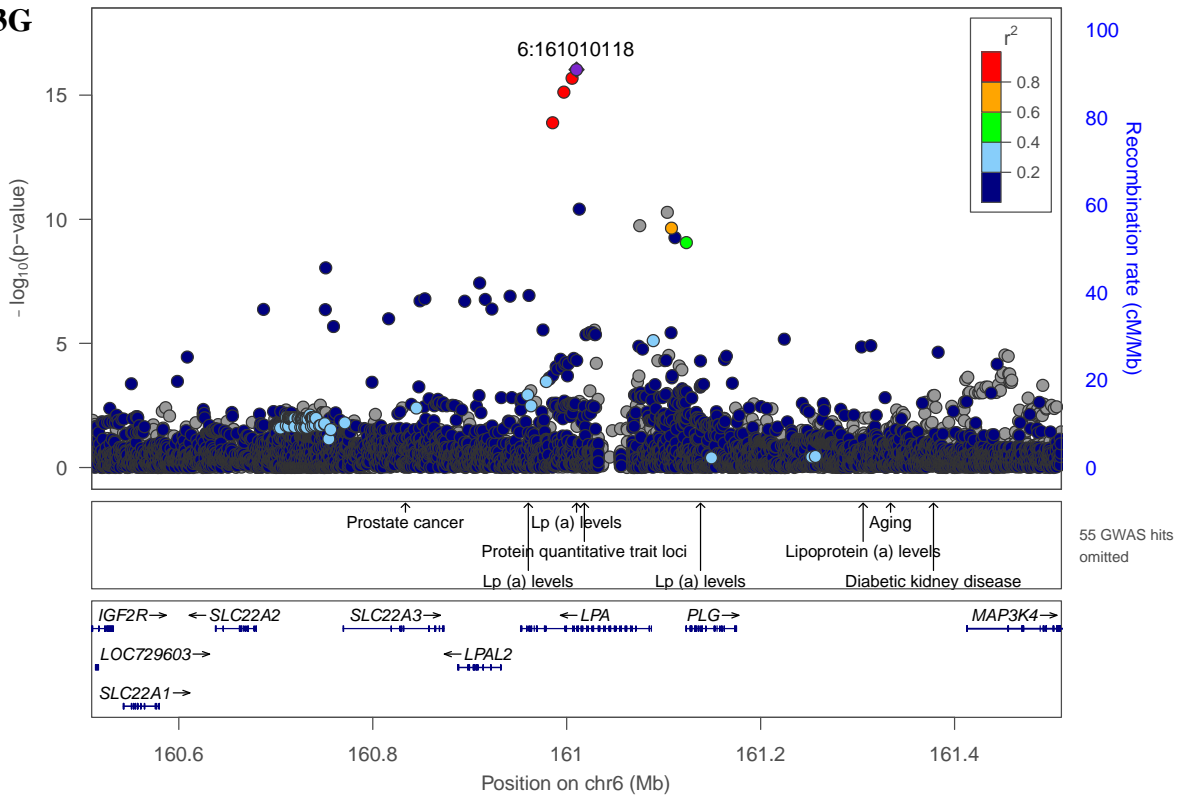
Supplementary Figure 3A-T. Genome-wide significant loci (n=20) associated with heart failure.



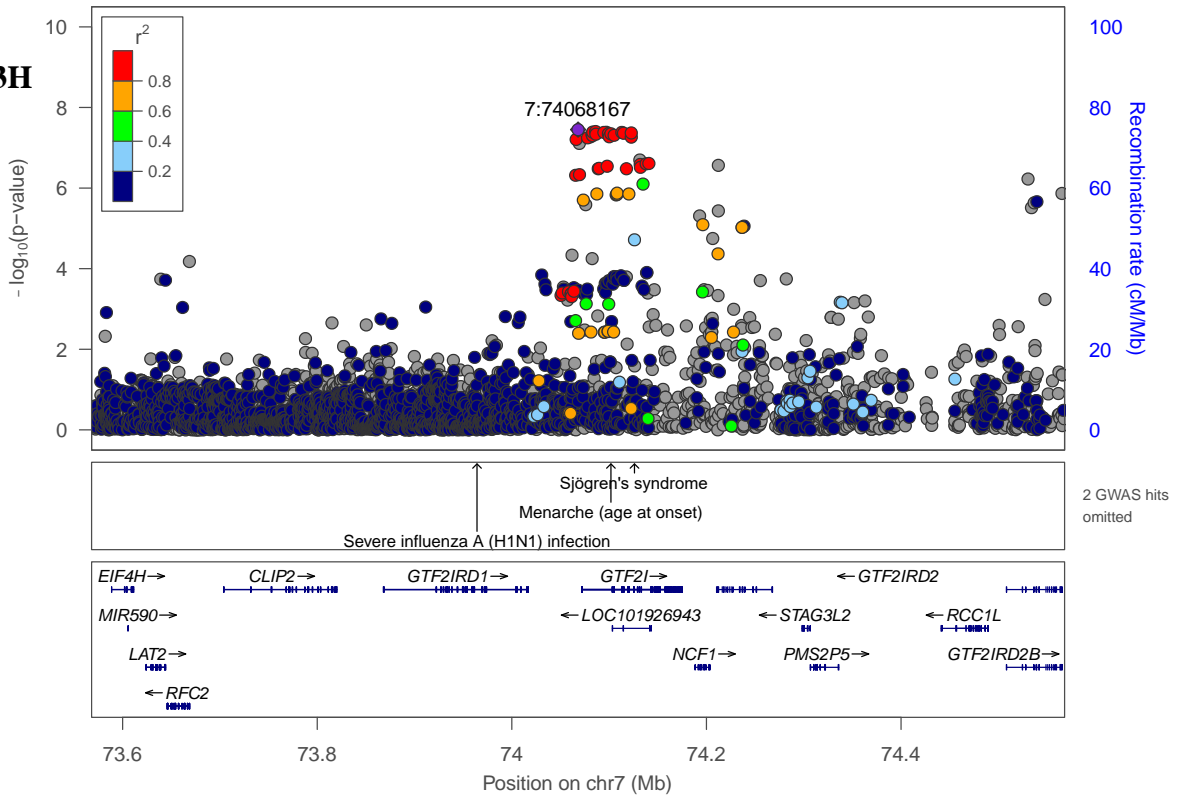


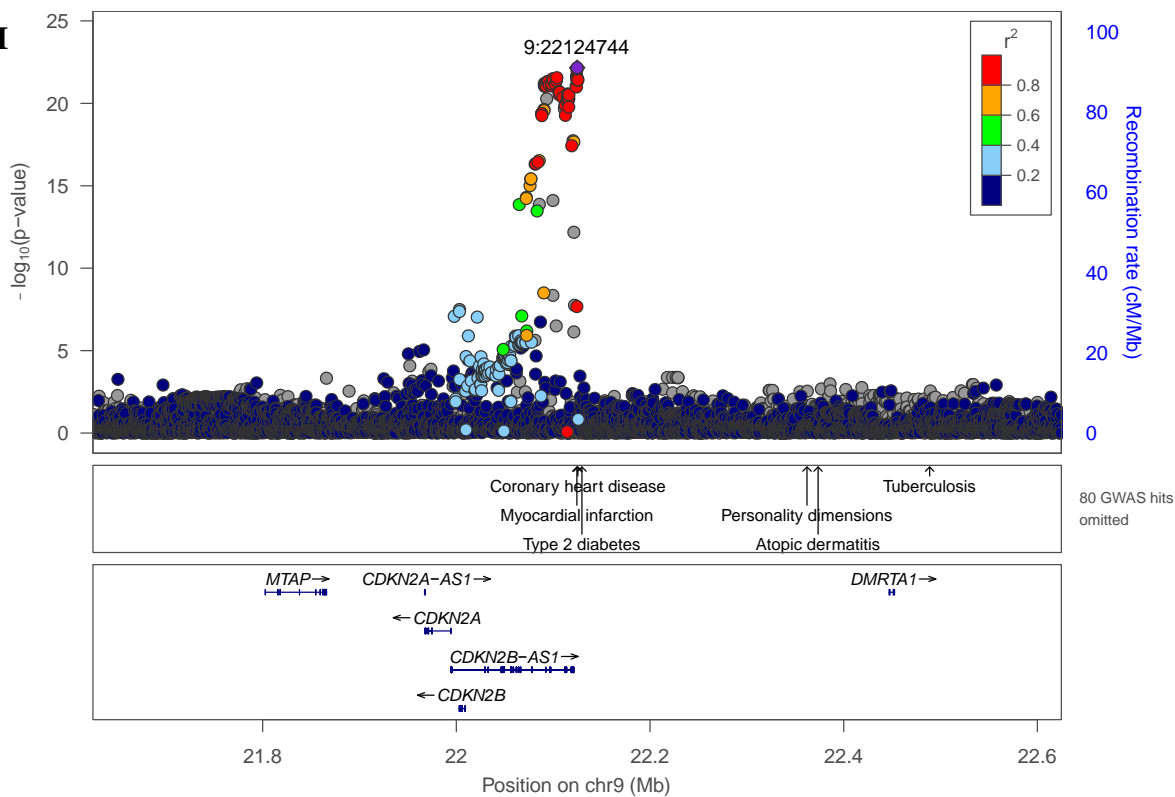
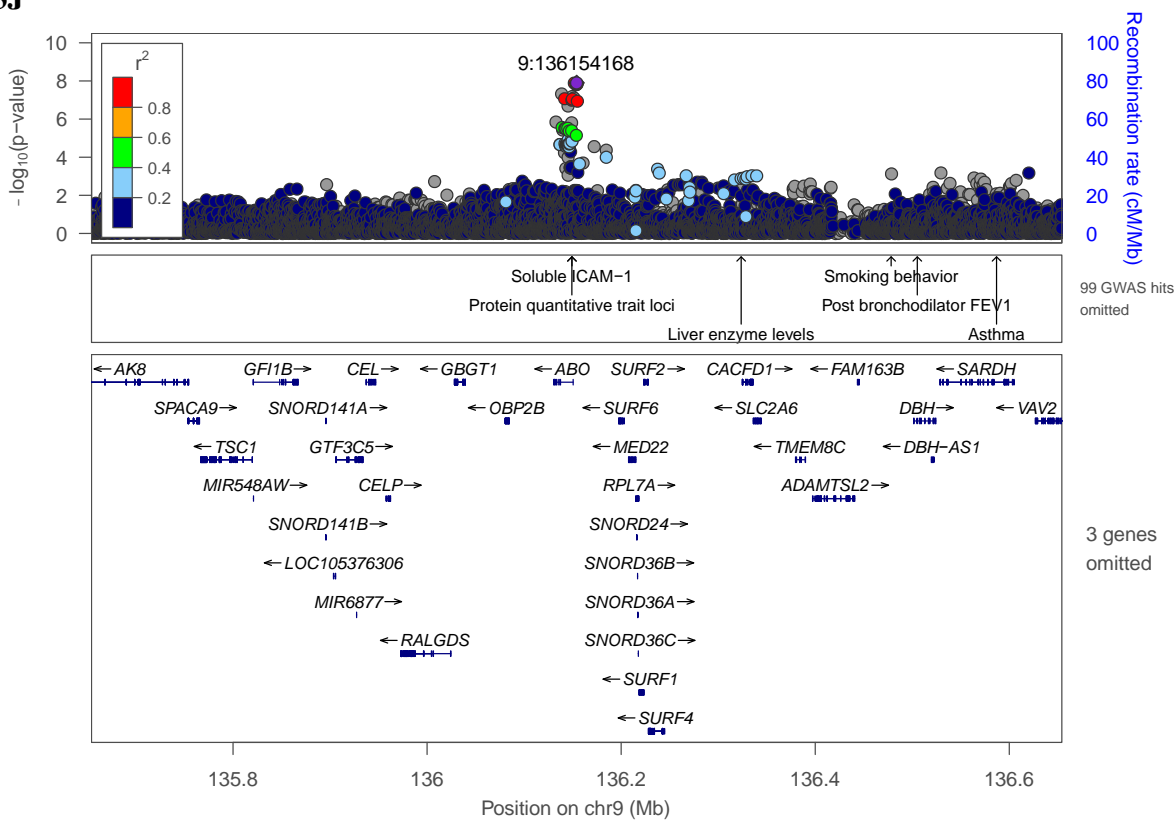
3E**3F**

3G

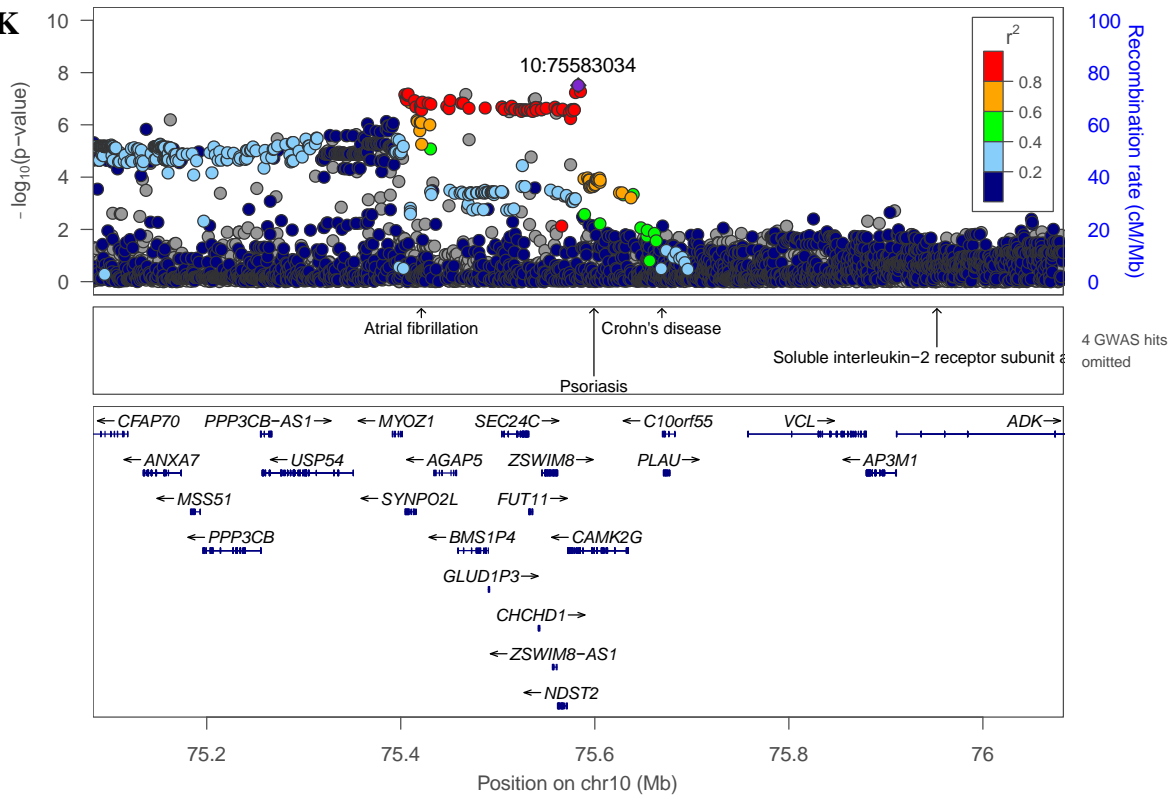


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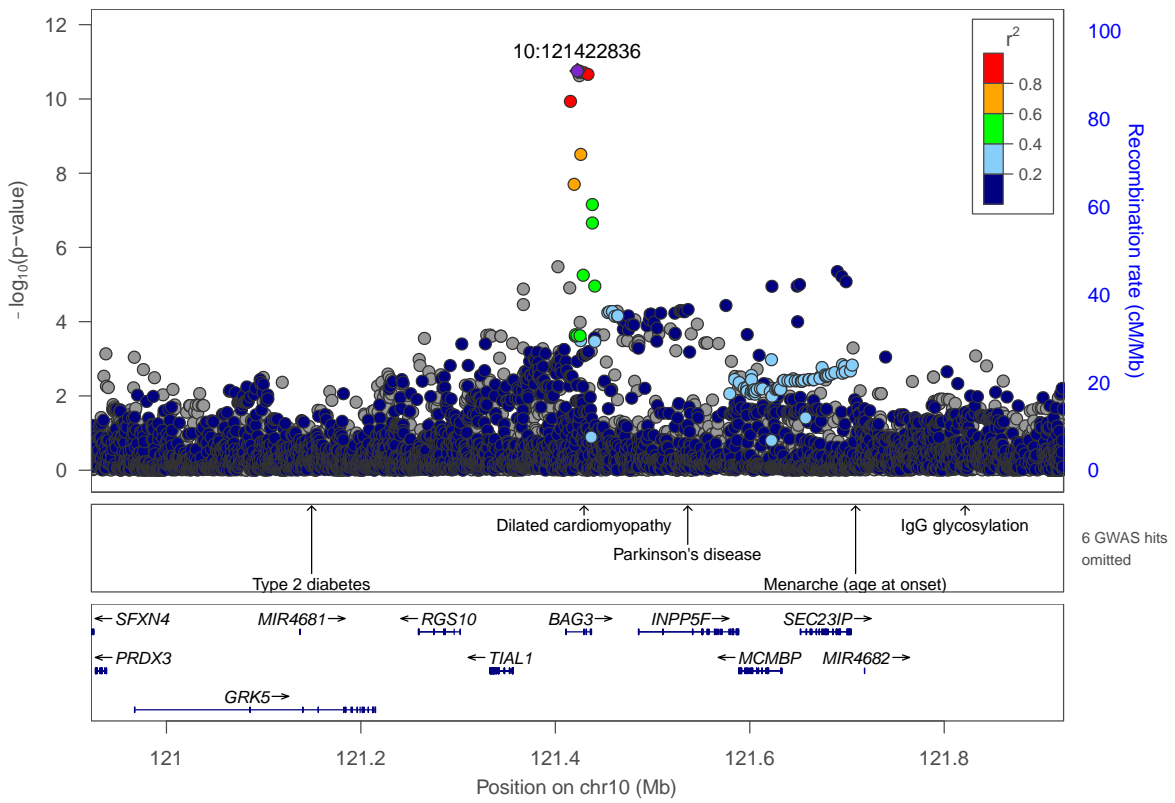


3I**3J**

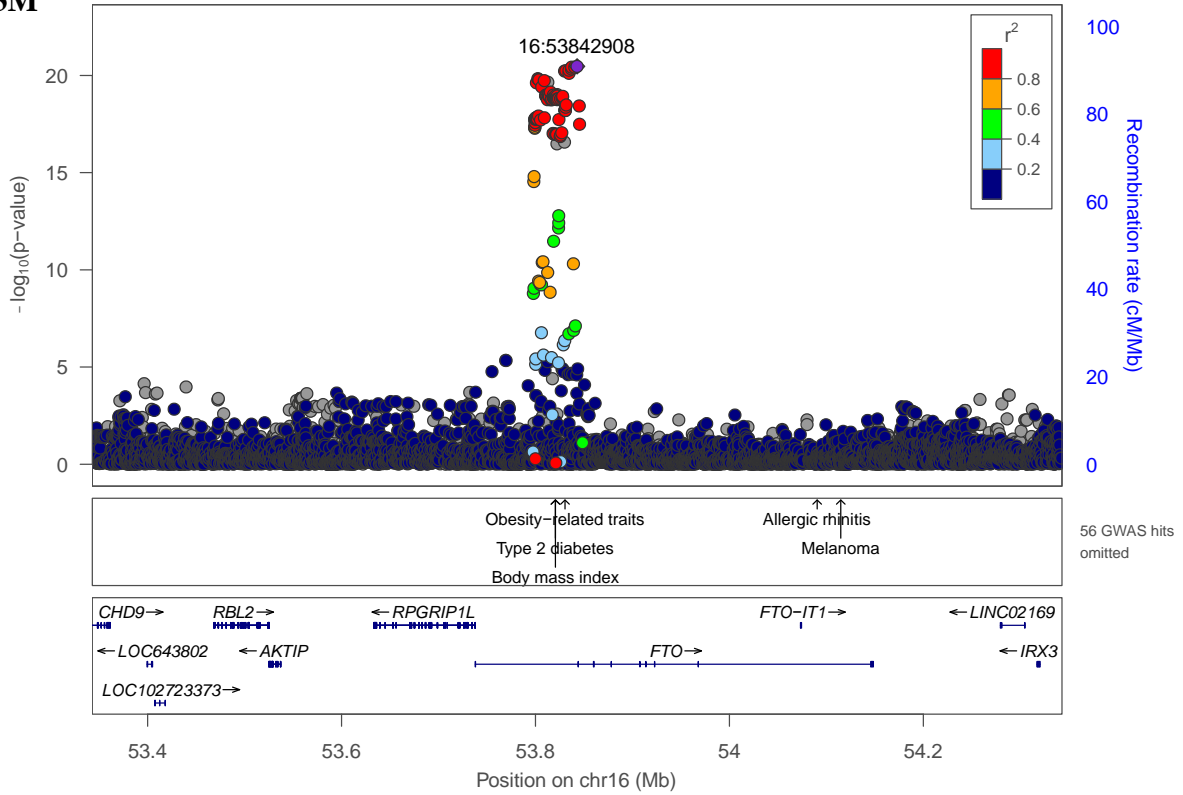
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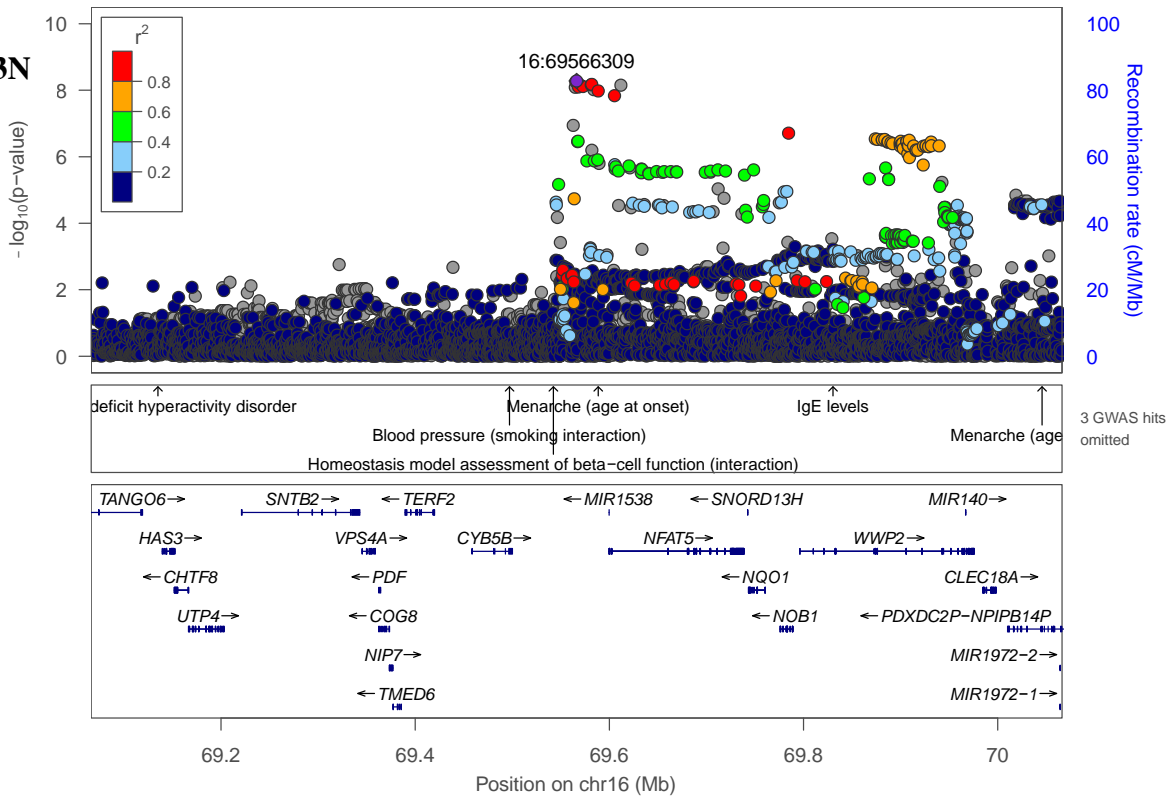
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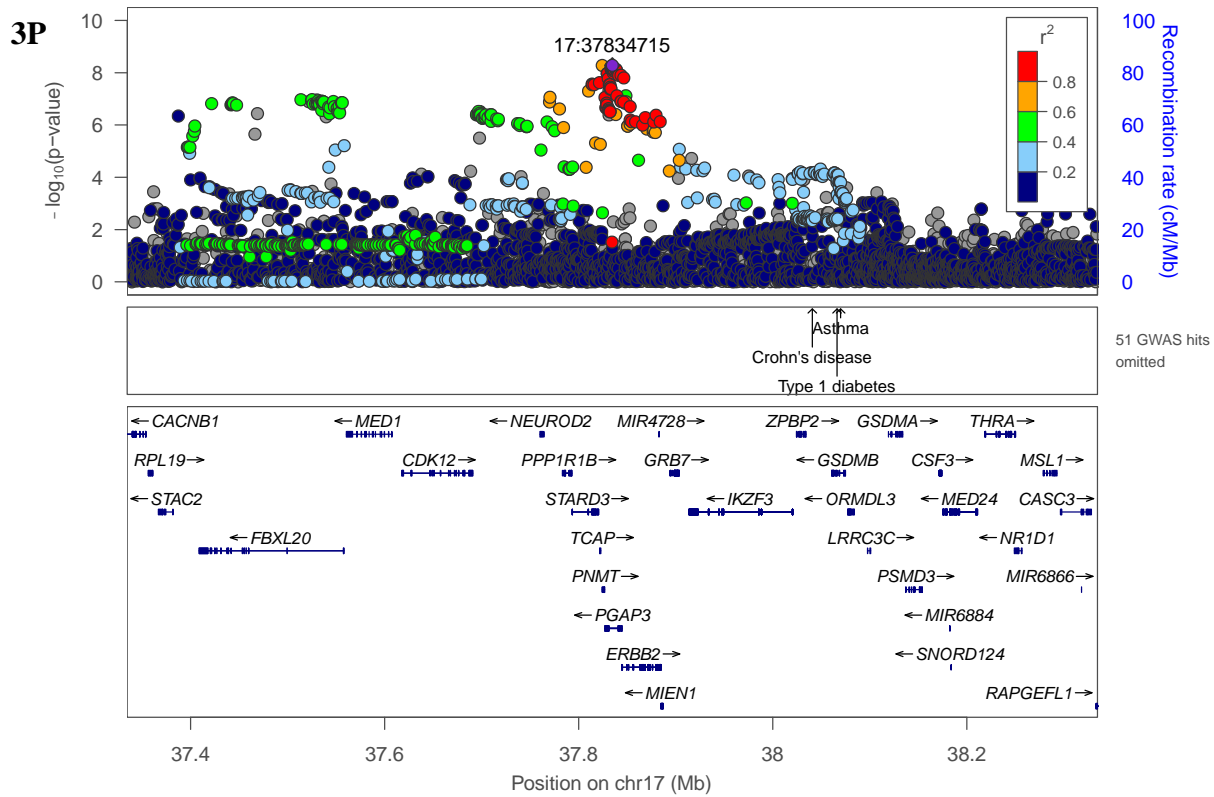
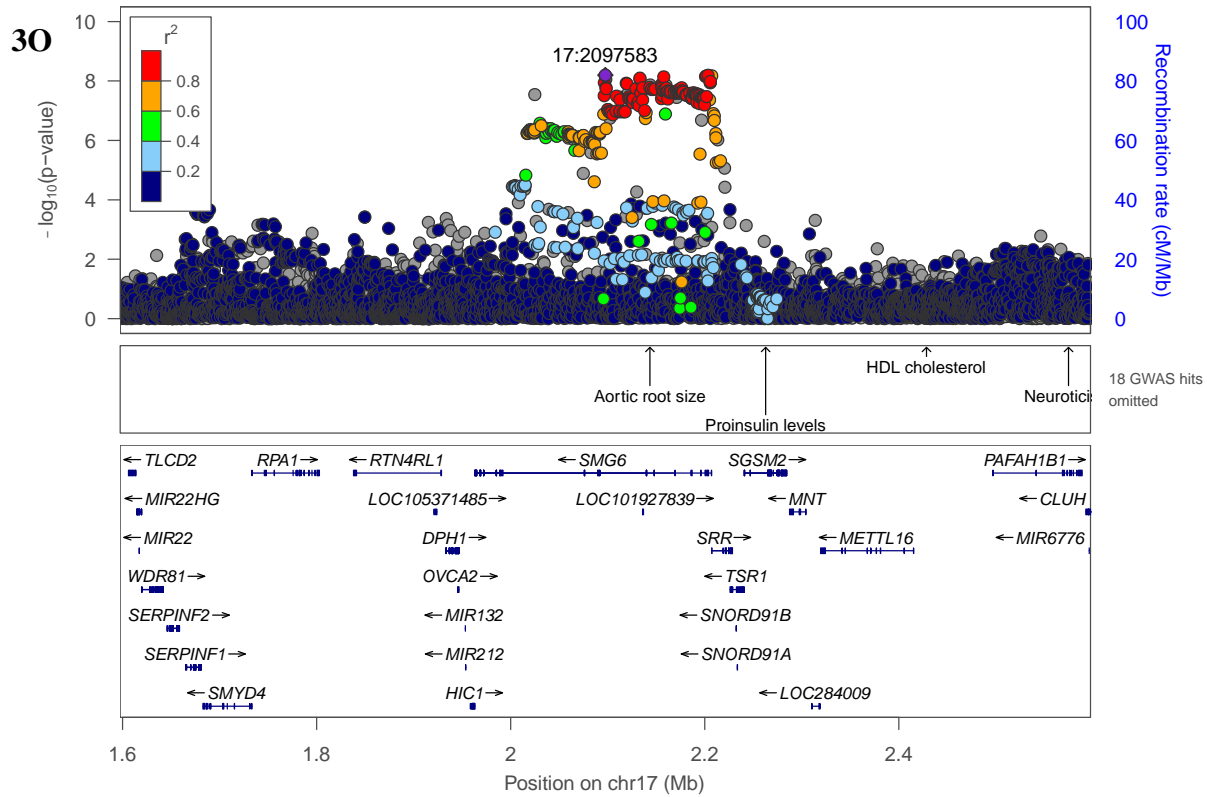


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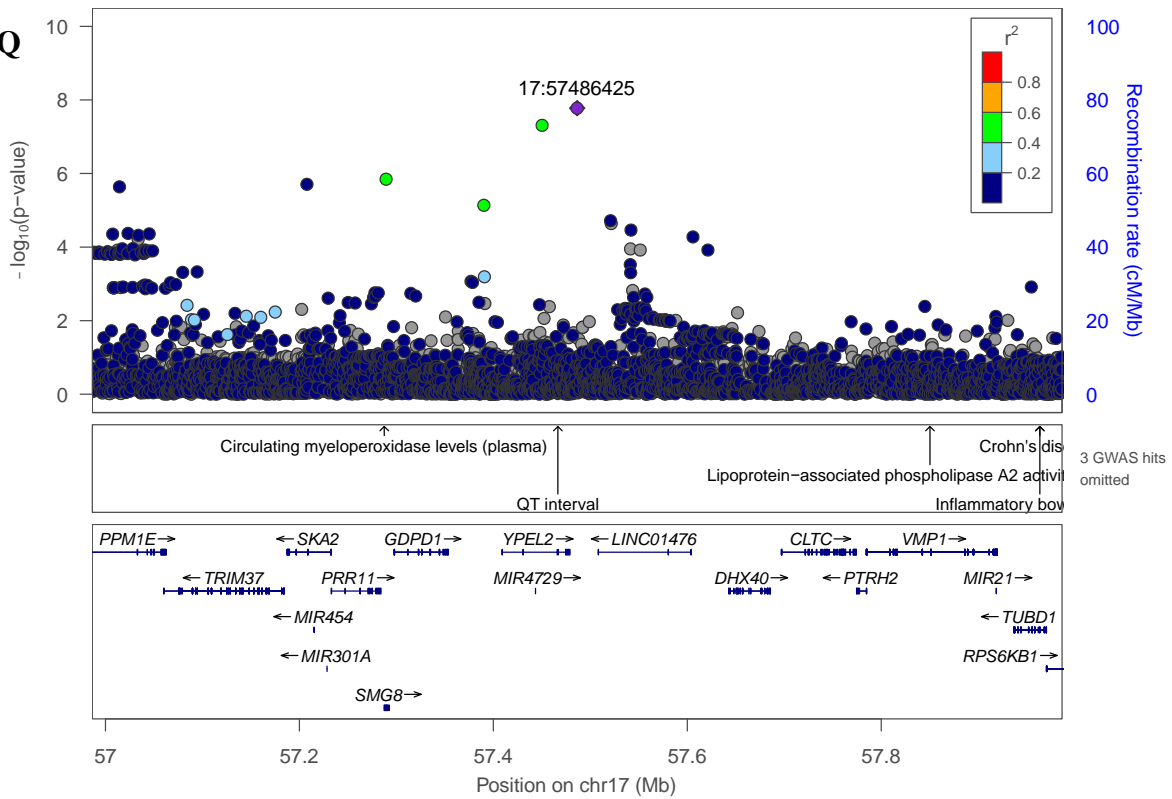


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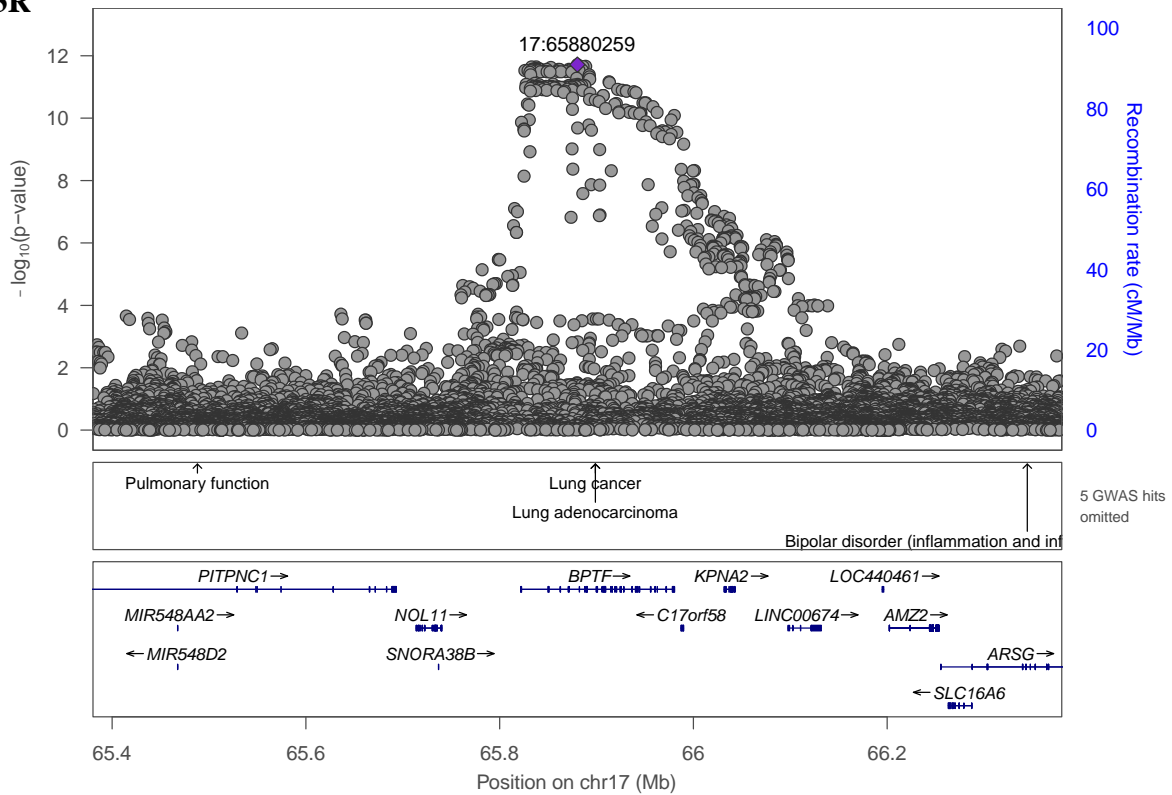




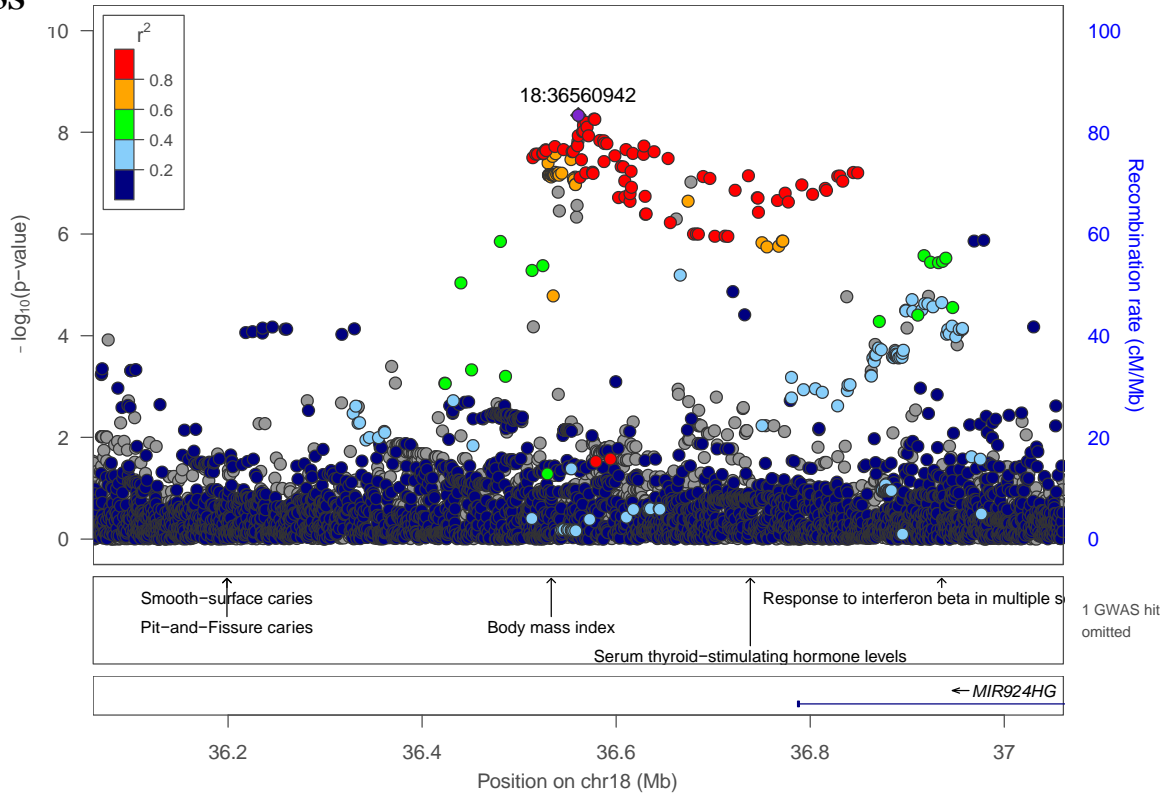
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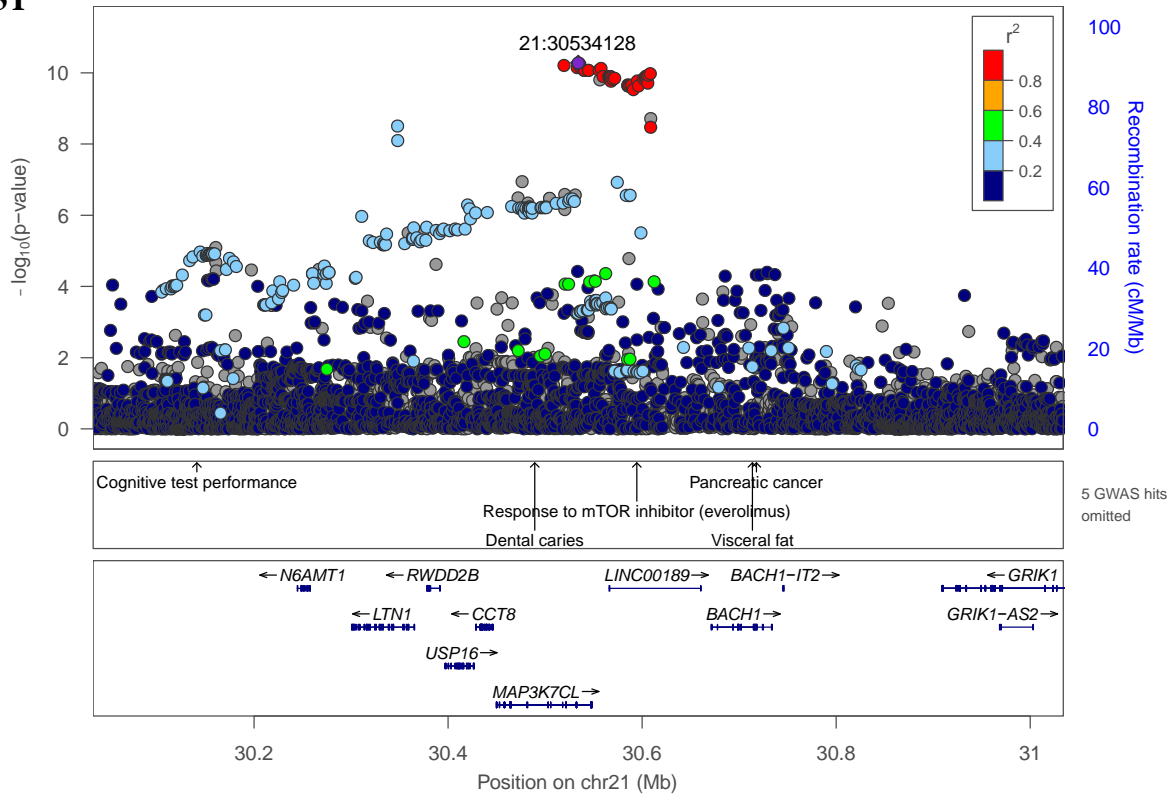
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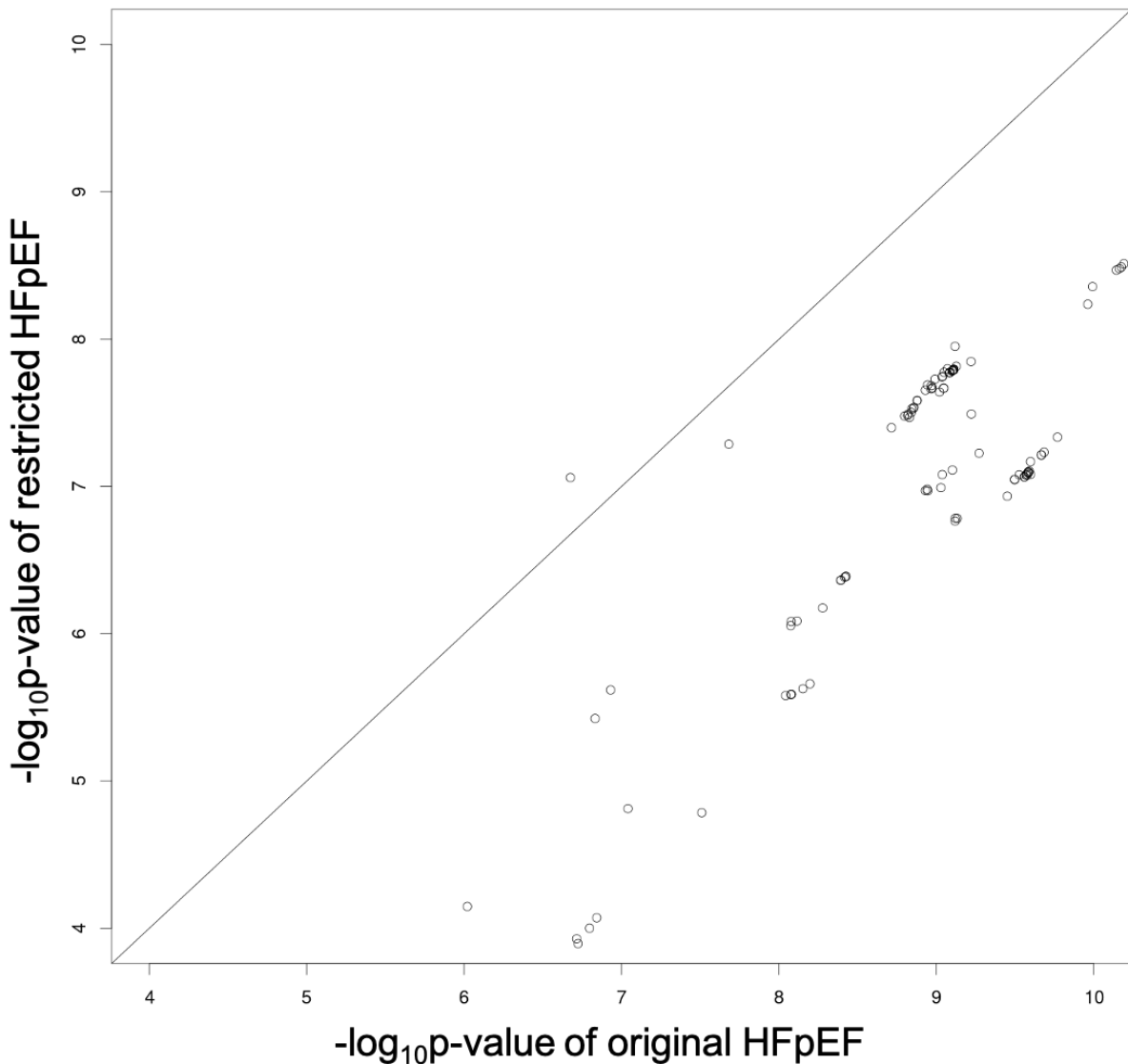


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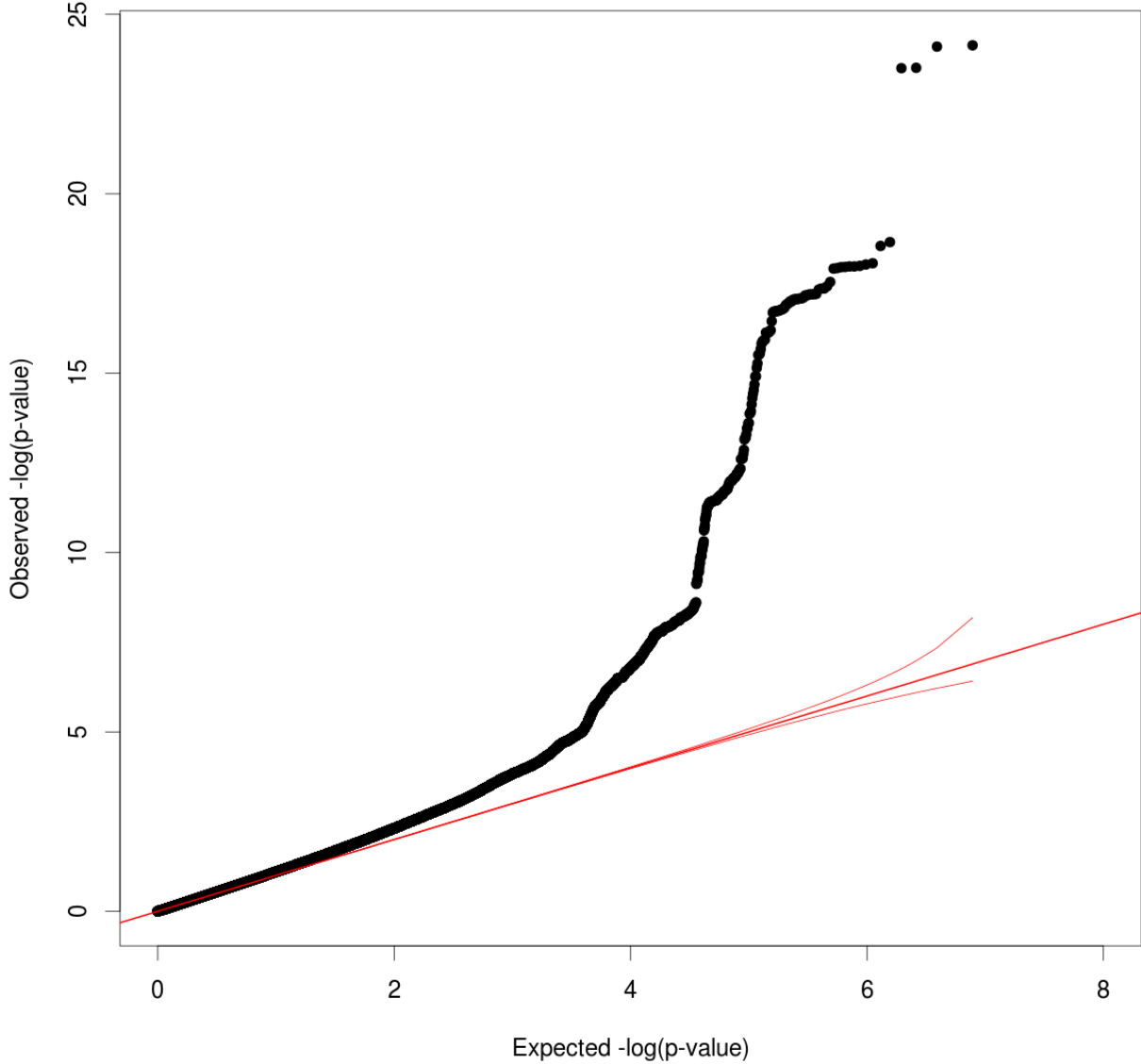


Supplementary Figure 4. Comparison of top HFpEF-associated between GWAS results from two HFpEF definitions - a more restrictive definition (n=12,119 cases) and the definition used for the primary HFpEF GWAS (n=19,598 cases).

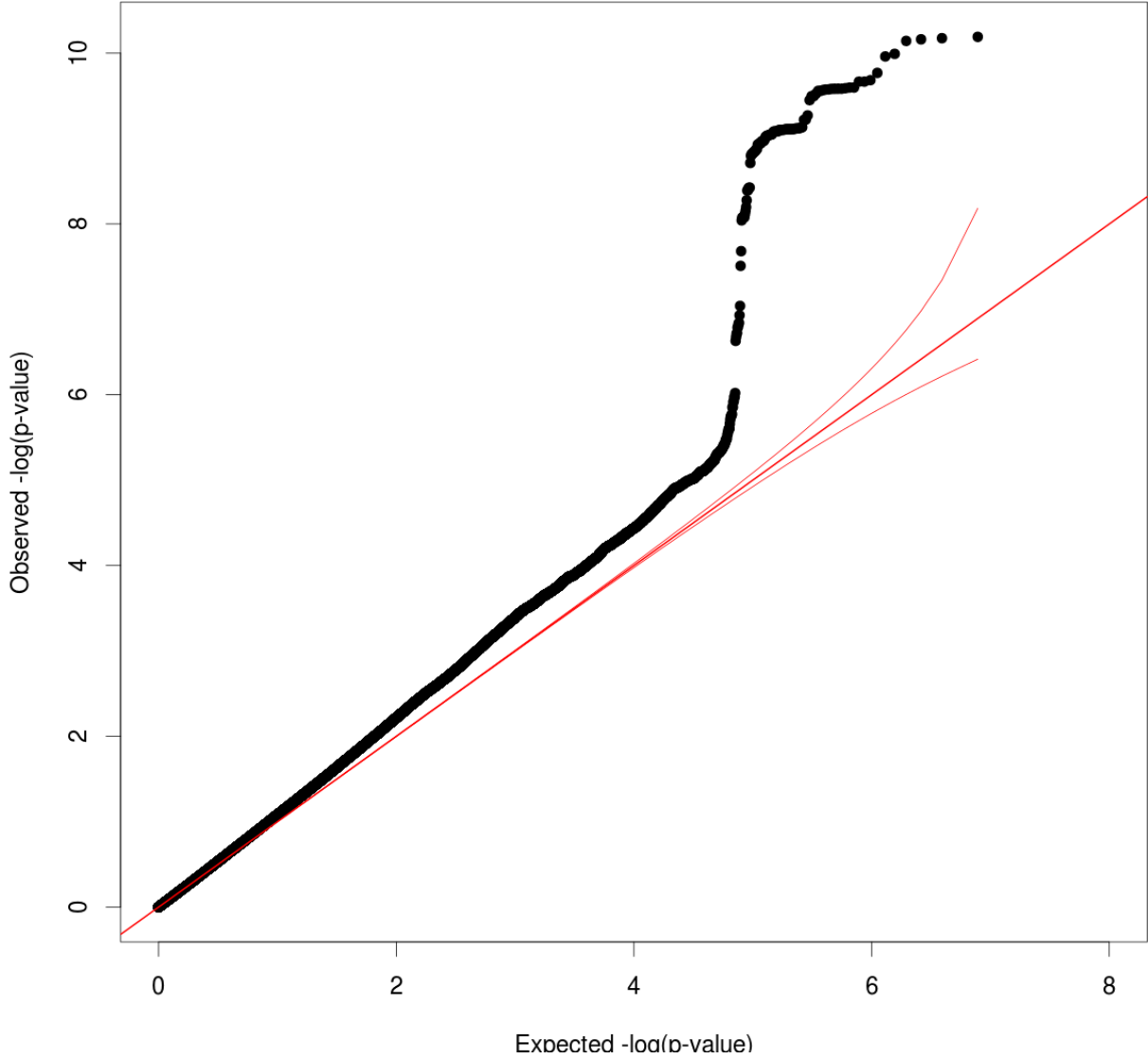
Similar to the primary HFpEF GWAS, only one genome-wide significant locus (*FTO*) was identified. Using LDSC and the GWAS summary statistics, we found that the genetic correlation between the two HFpEF definitions was very high ($r=0.981$, $p<2\times 10^{-16}$). Among top 110 HFpEF-associated common SNPs ($p<10^{-6}$, $MAF>1\%$), the genetic effects between the two HFpEF GWAS were highly correlated ($r=0.995$, $p<2\times 10^{-16}$). Mostly driven by a larger number of HFpEF cases in the original definition (19,598 vs. 12,119), the p-values of 109 out of 110 SNPs were lower in the original HFpEF GWAS conducted in the less restrictive cohort. All tests were two-sided without adjustment for multiple comparisons.



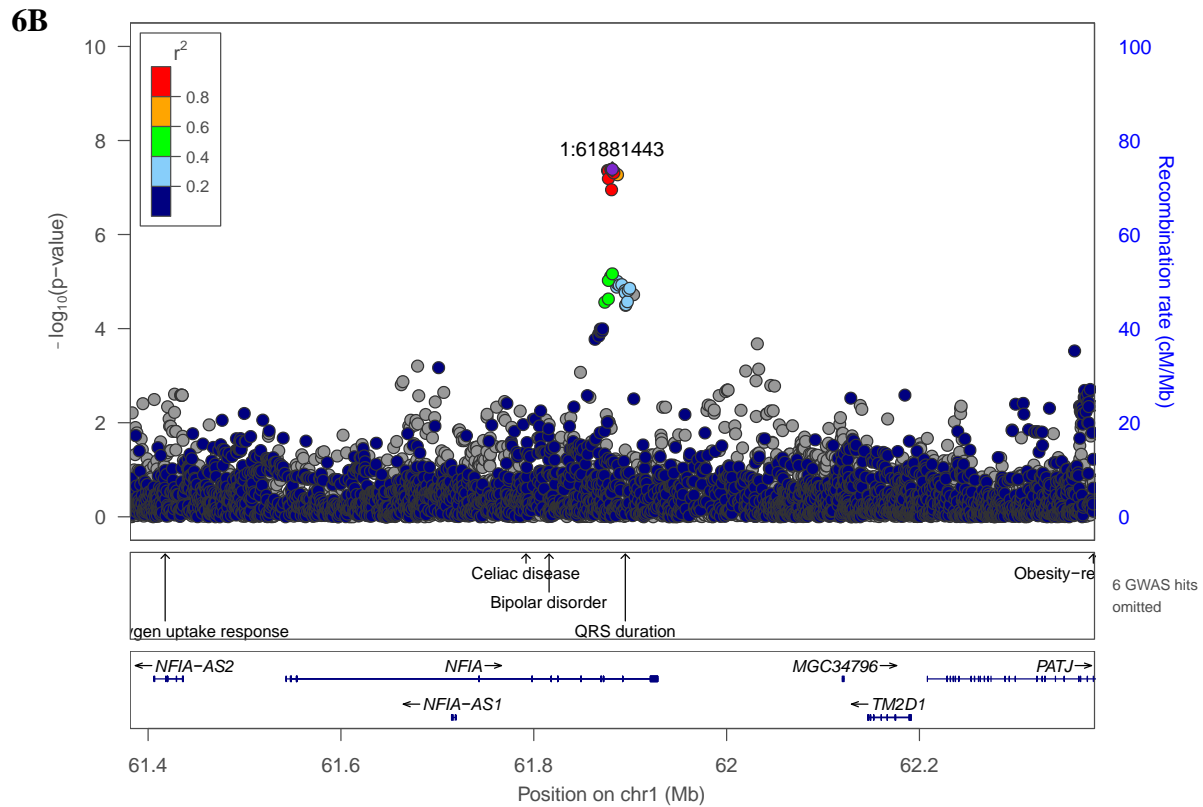
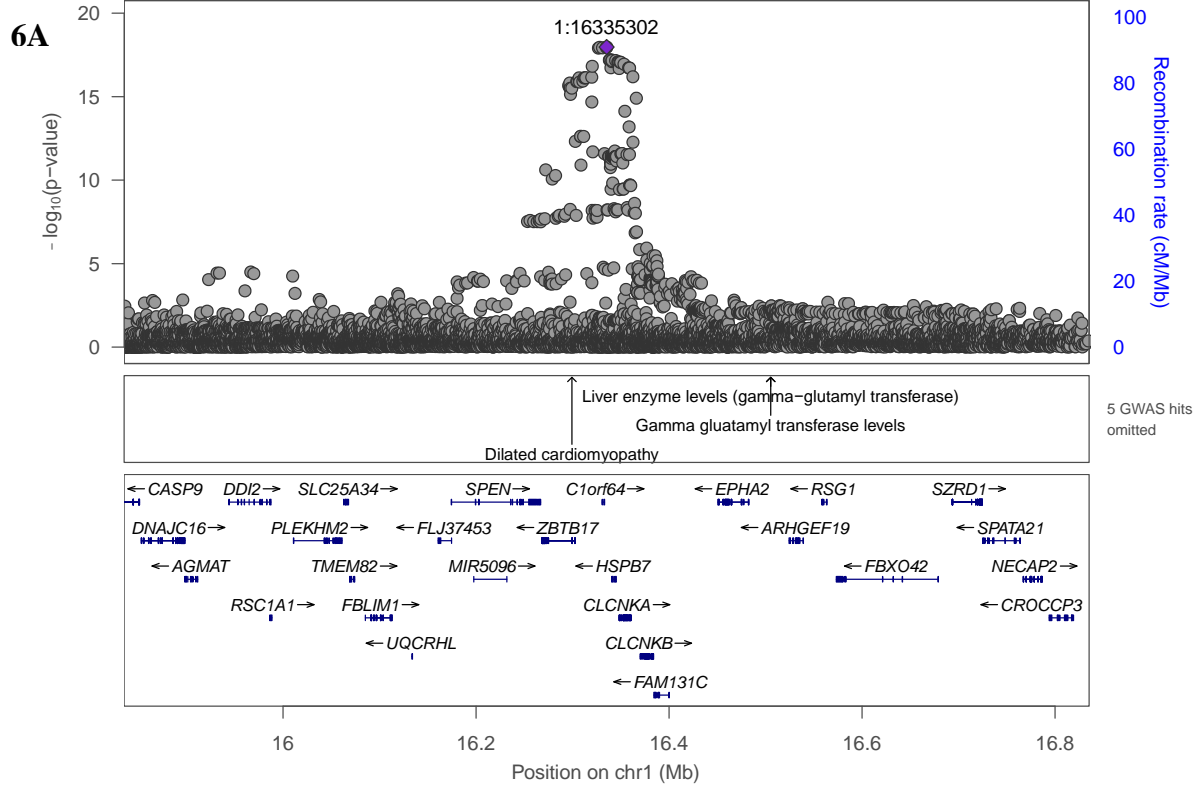
Supplementary Figure 5A. Quantile-quantile plot of genome-wide association study of heart failure with reduced ejection fraction (HFrEF).

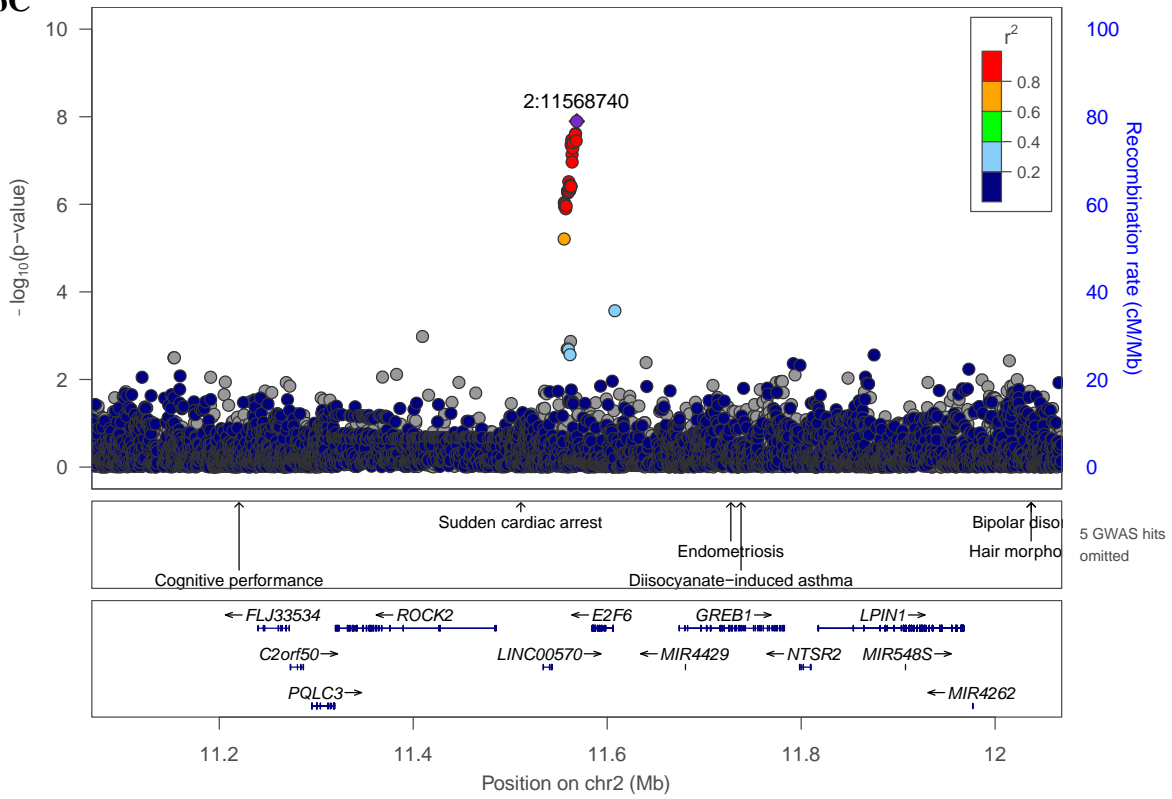
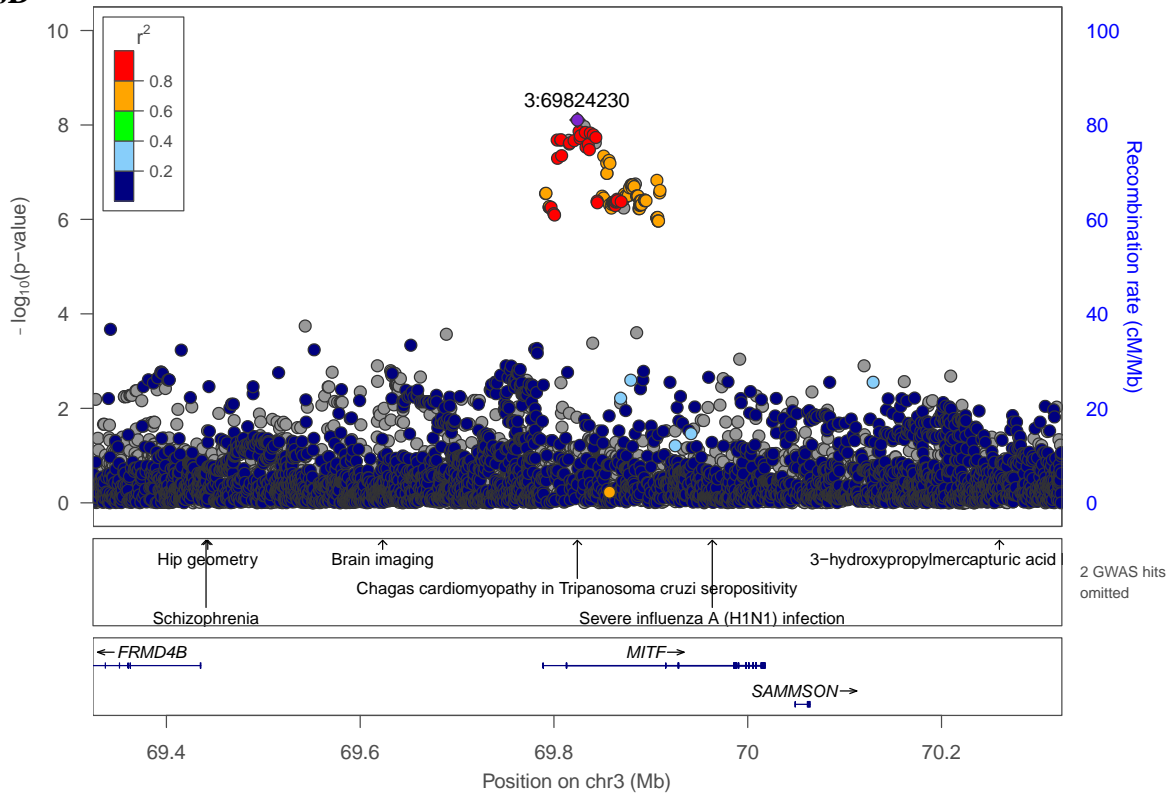


Supplementary Figure 5B. Quantile-quantile plot of genome-wide association study of heart failure with preserved ejection fraction (HFpEF).

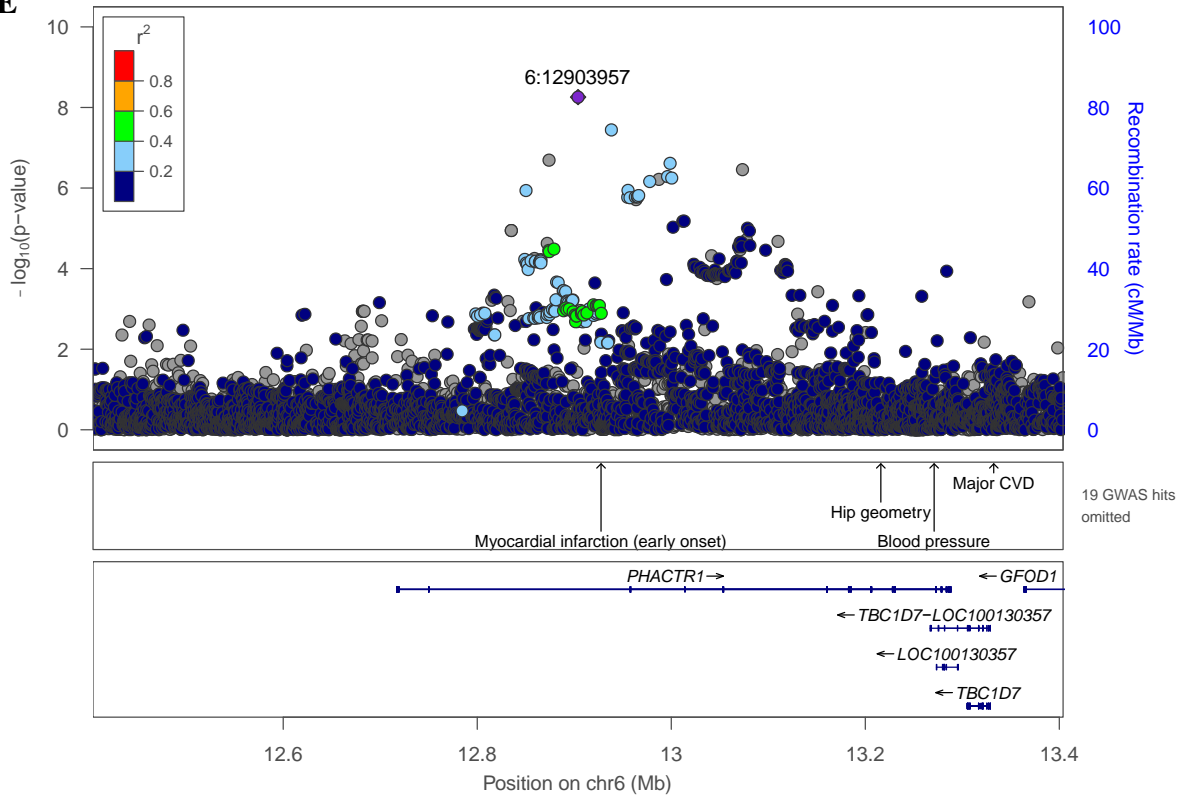


Supplementary Figure 6 A-M. Genome-wide significant loci associated with HFrEF/HFpEF

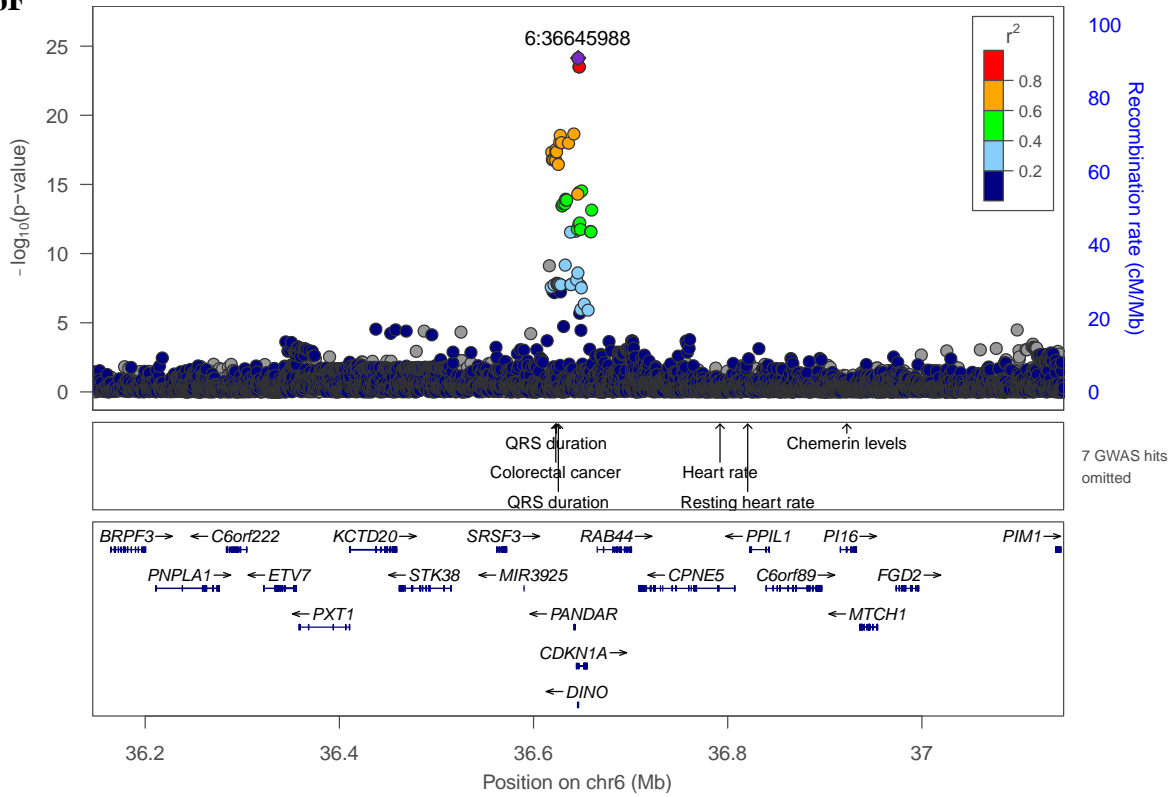


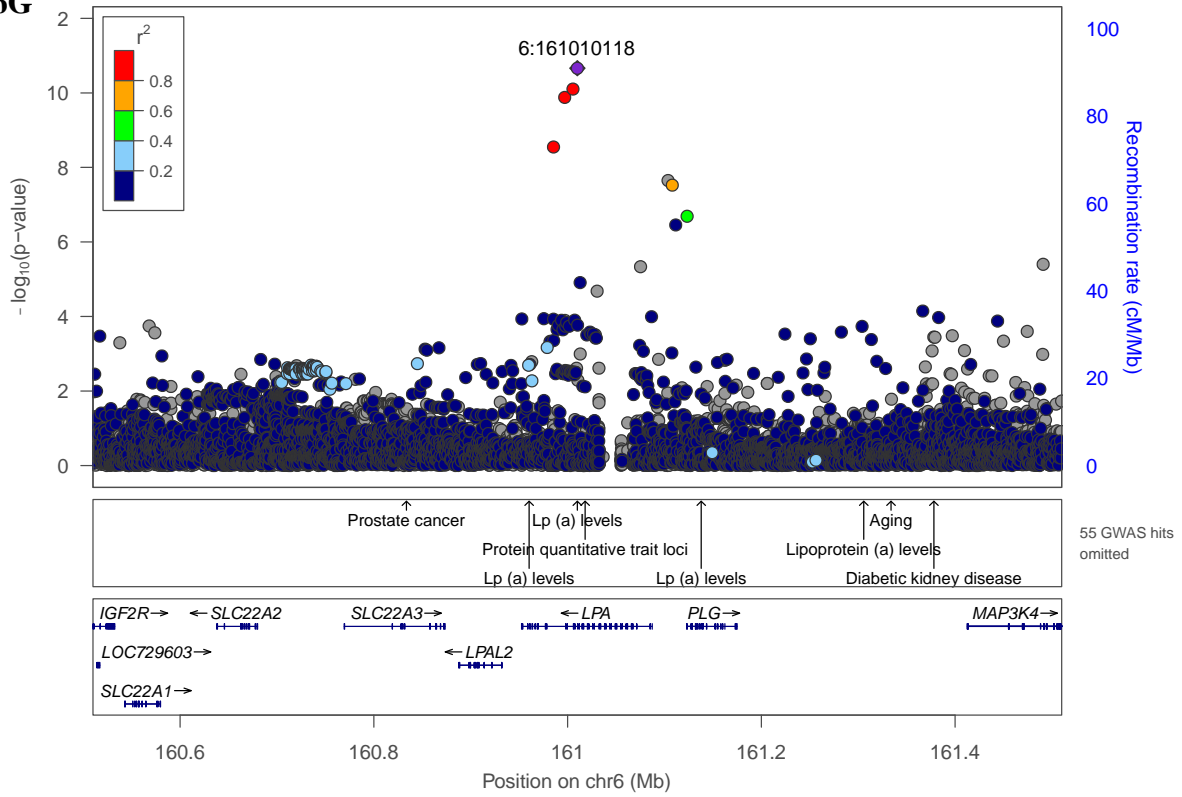
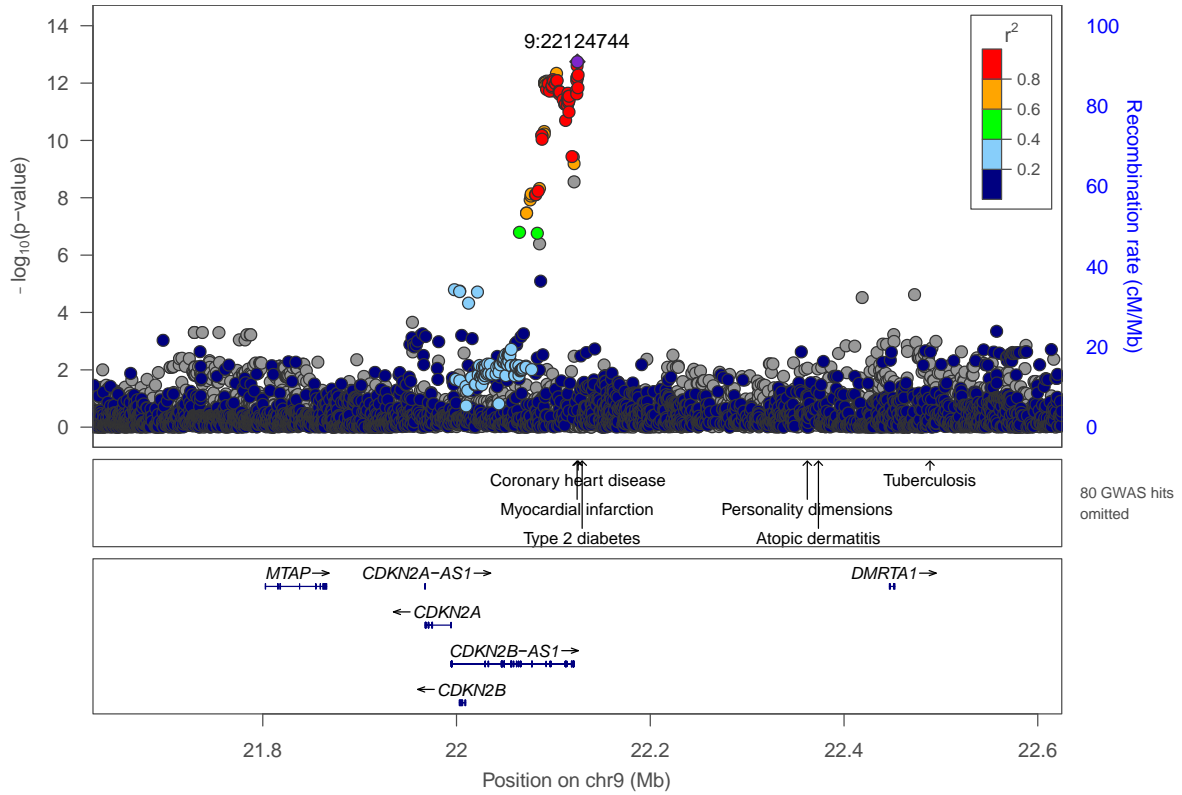
6C**6D**

6E

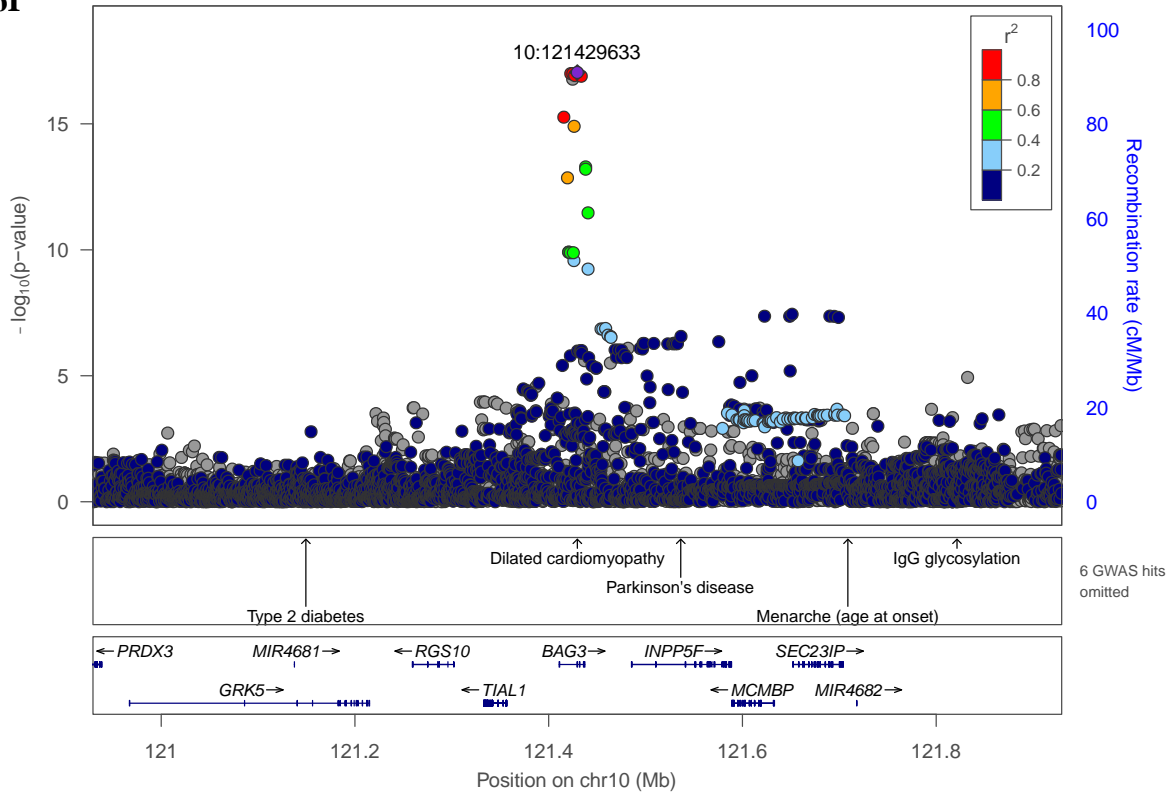


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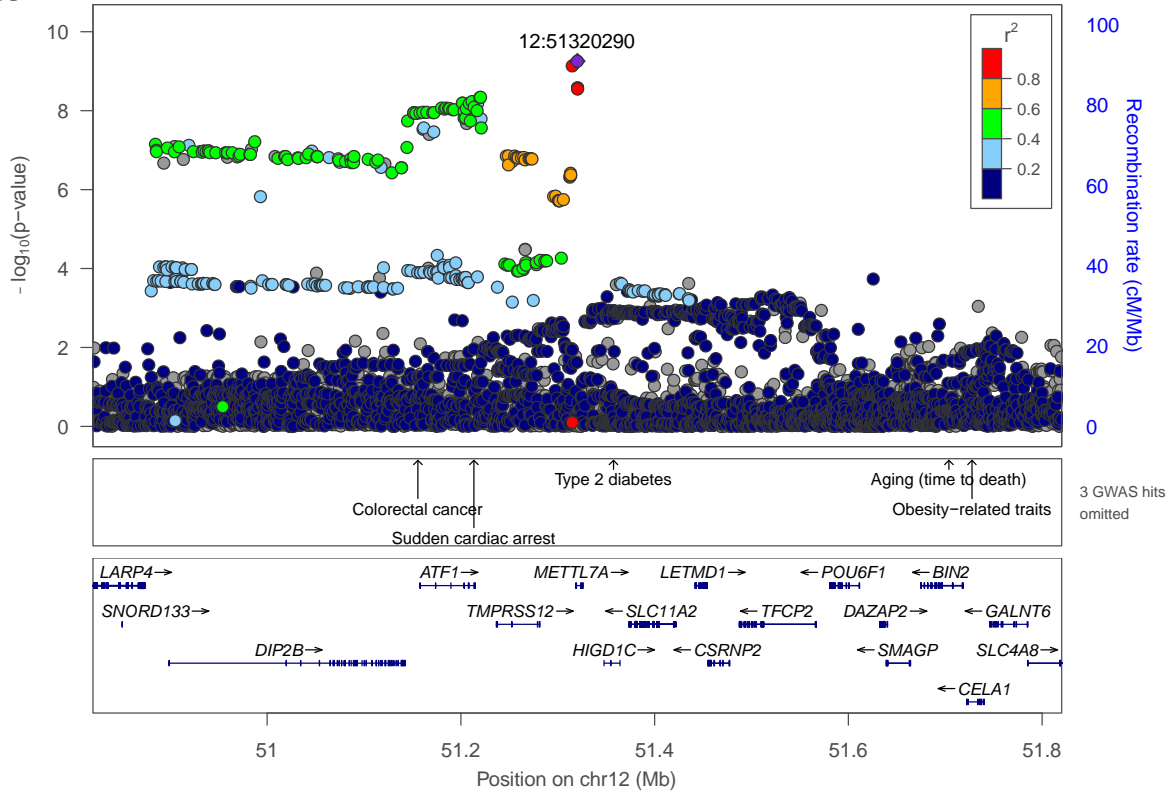


6G**6H**

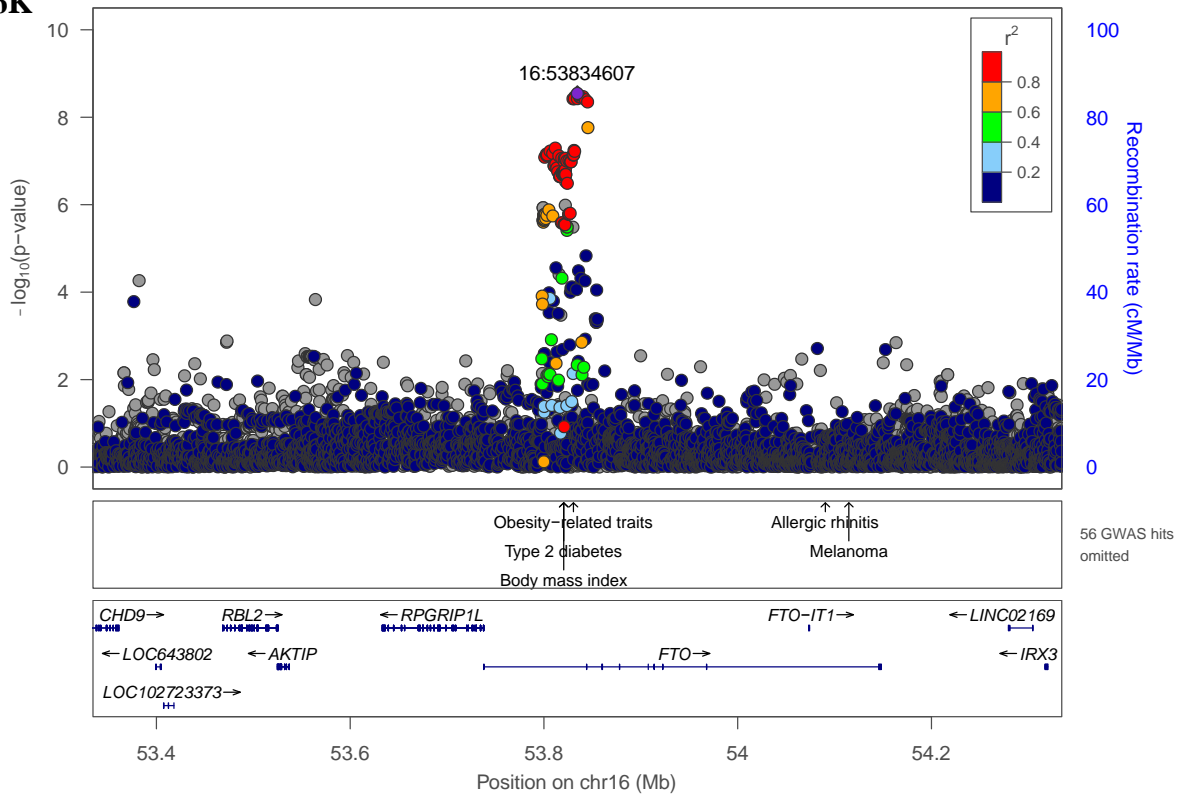
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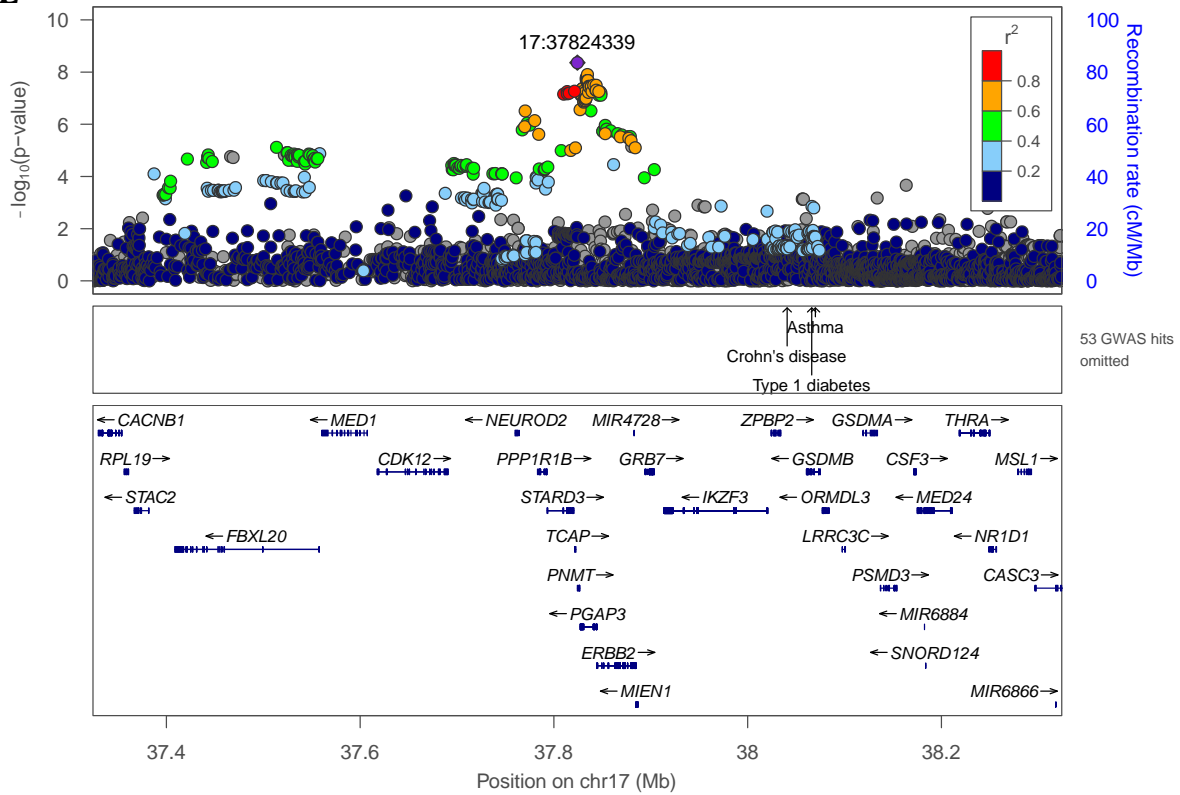
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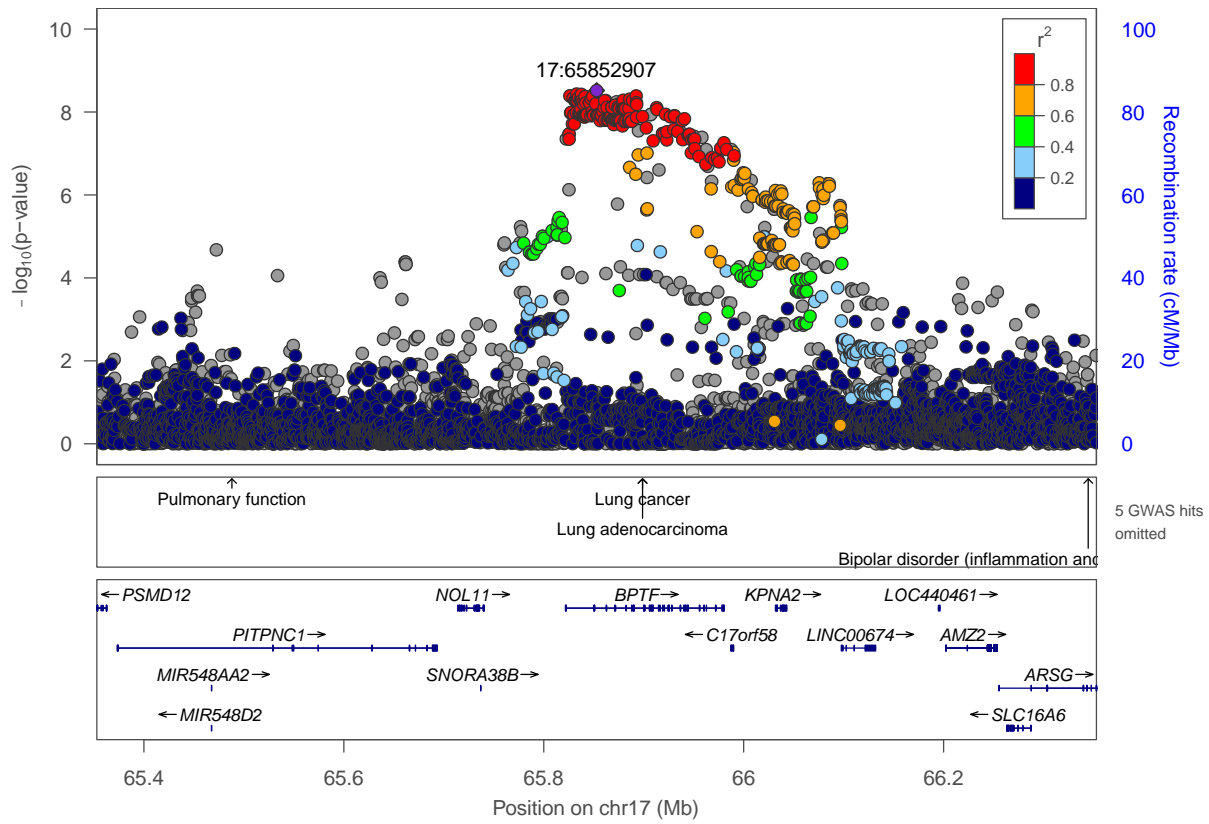
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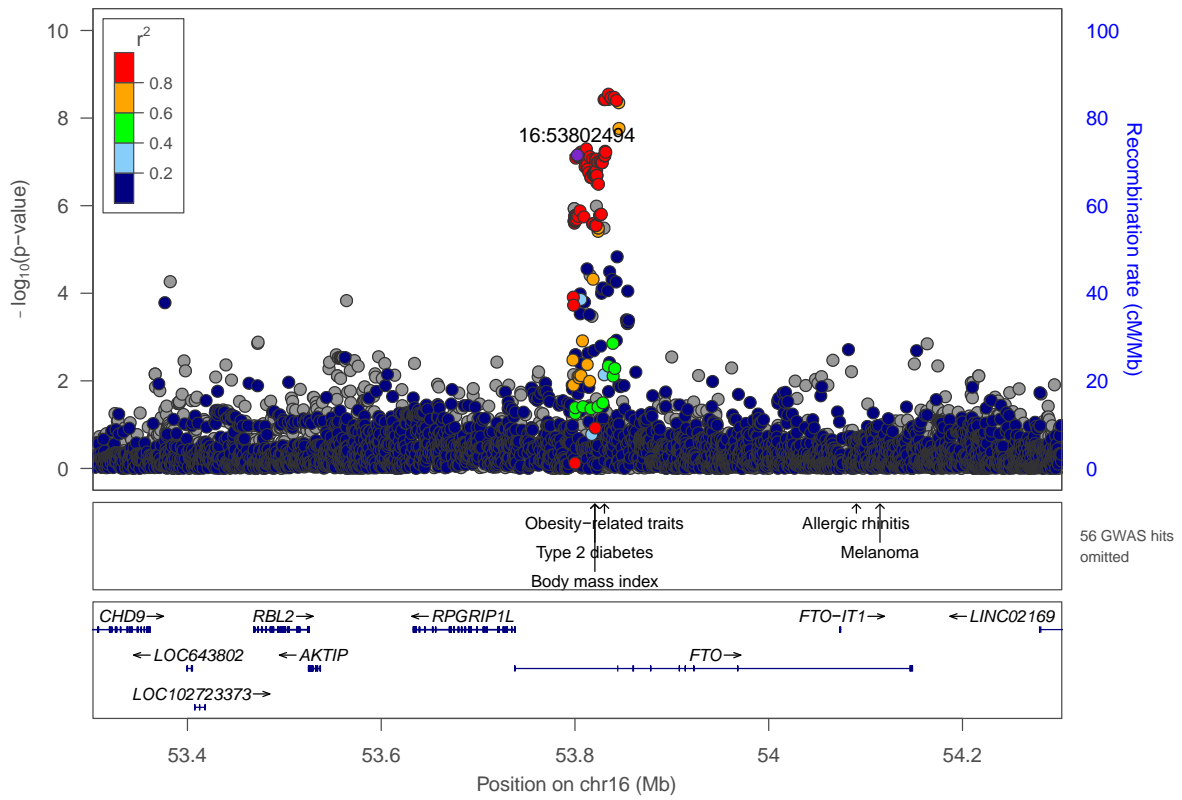
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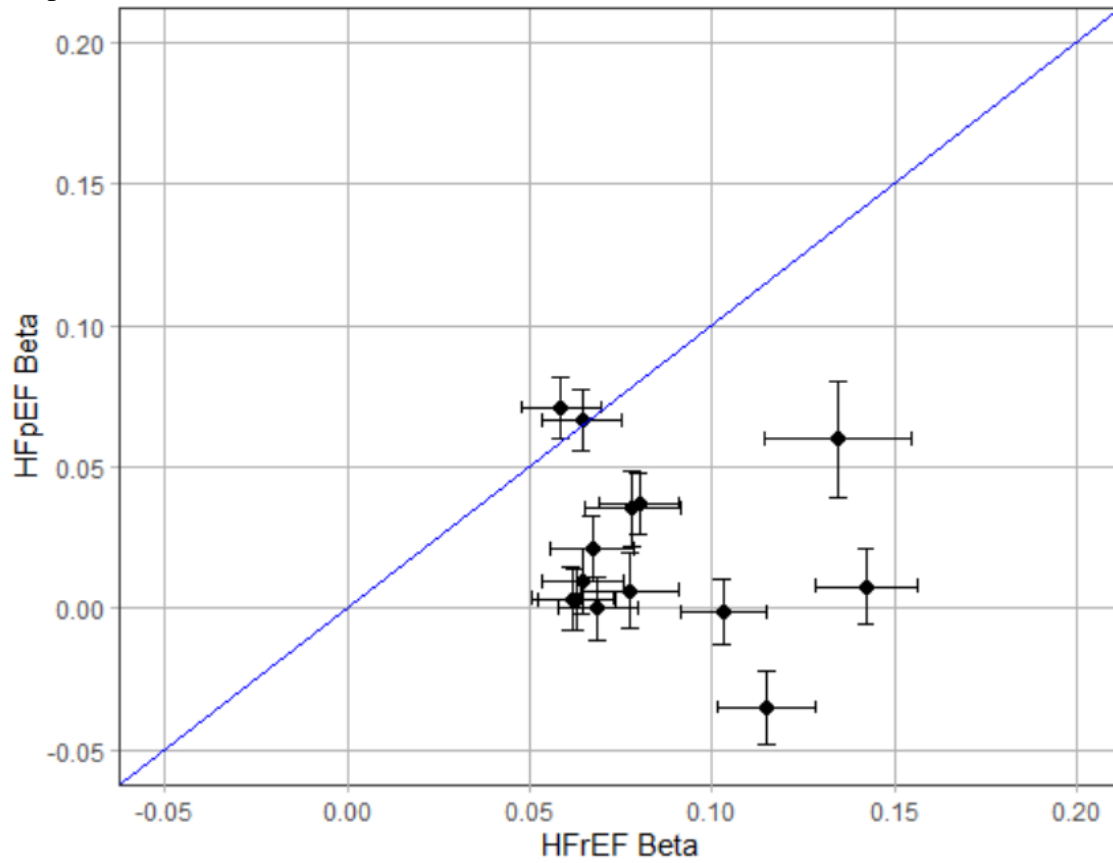
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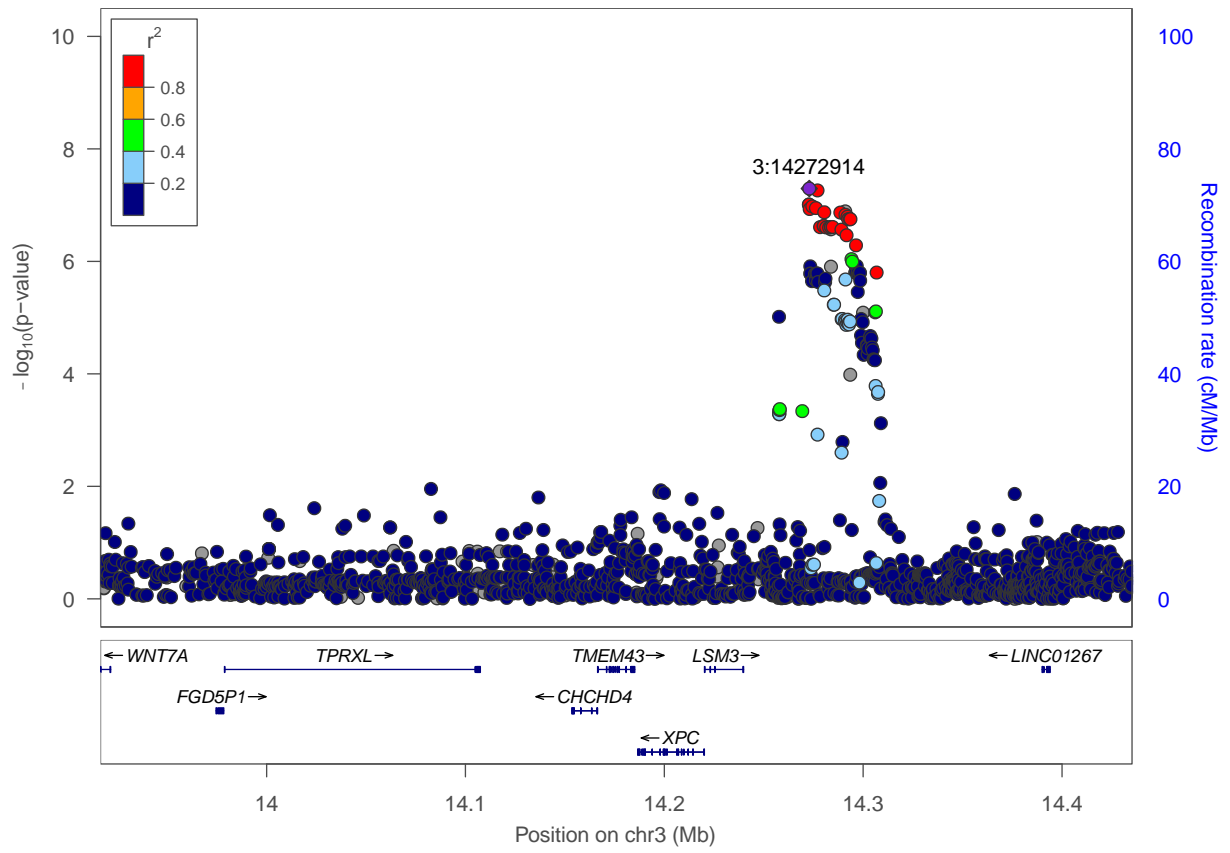
Supplementary Figure 6N. Genome-wide significant locus associated with HFpEF



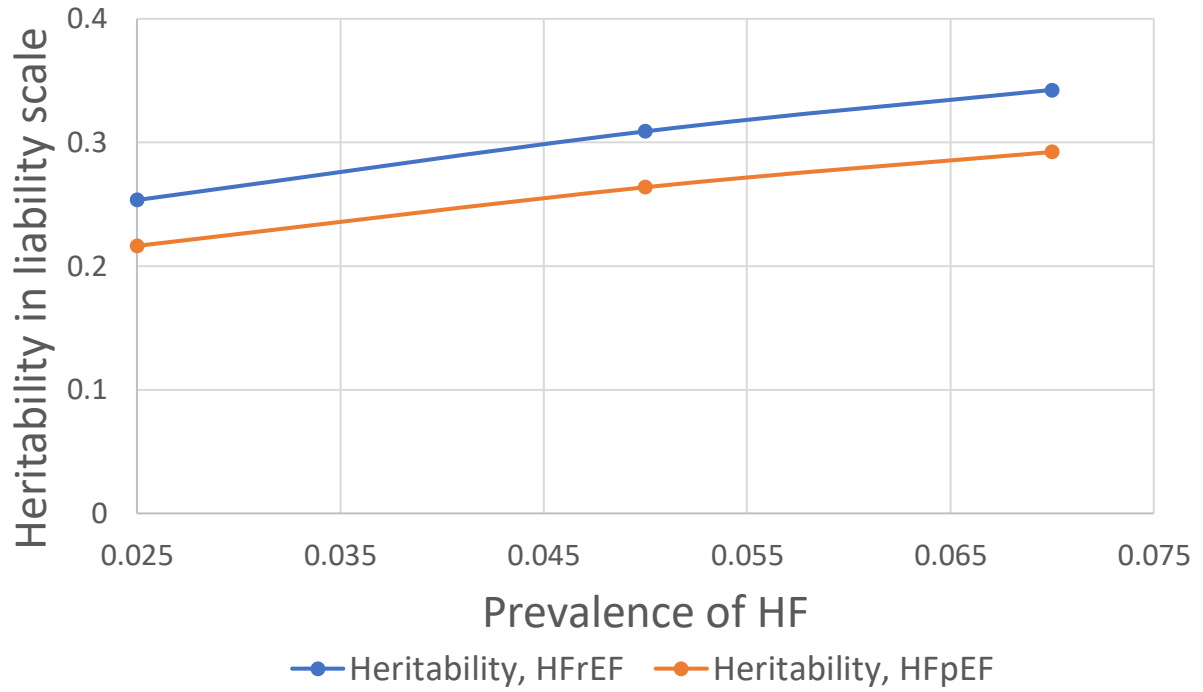
Supplementary Figure 7. Comparison in effect size for the genome-wide significant loci between HFrEF and HFpEF, with error bars for standard errors of HFrEF on the X axis and HFpEF on the Y axis.



Supplementary Figure 8. Genetic associations of HF_rEF in the *TMEM43* region.



Supplementary Figure 9. SNP-based heritability using GREML-LDMS-I in MVP non-Hispanic Whites.



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Updated May 26, 2020

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- VA Southern Nevada Healthcare System (Joseph Fayad, M.D.)
6900 North Pecos Road, North Las Vegas, NV 89086
- VA Tennessee Valley Healthcare System (Adriana Hung, M.D., M.P.H.)
1310 24th Avenue, South Nashville, TN 37212
- Washington DC VA Medical Center (Jack Lichy, M.D., Ph.D.)
50 Irving St, Washington, D. C. 20422
- W.G. (Bill) Hefner VA Medical Center (Robin Hurley, M.D.)
1601 Brenner Ave, Salisbury, NC 28144
- White River Junction VA Medical Center (Brooks Robey, M.D.)
163 Veterans Drive, White River Junction, VT 05009
- William S. Middleton Memorial Veterans Hospital (Robert Striker, M.D., Ph.D.)
2500 Overlook Terrace, Madison, WI 53705