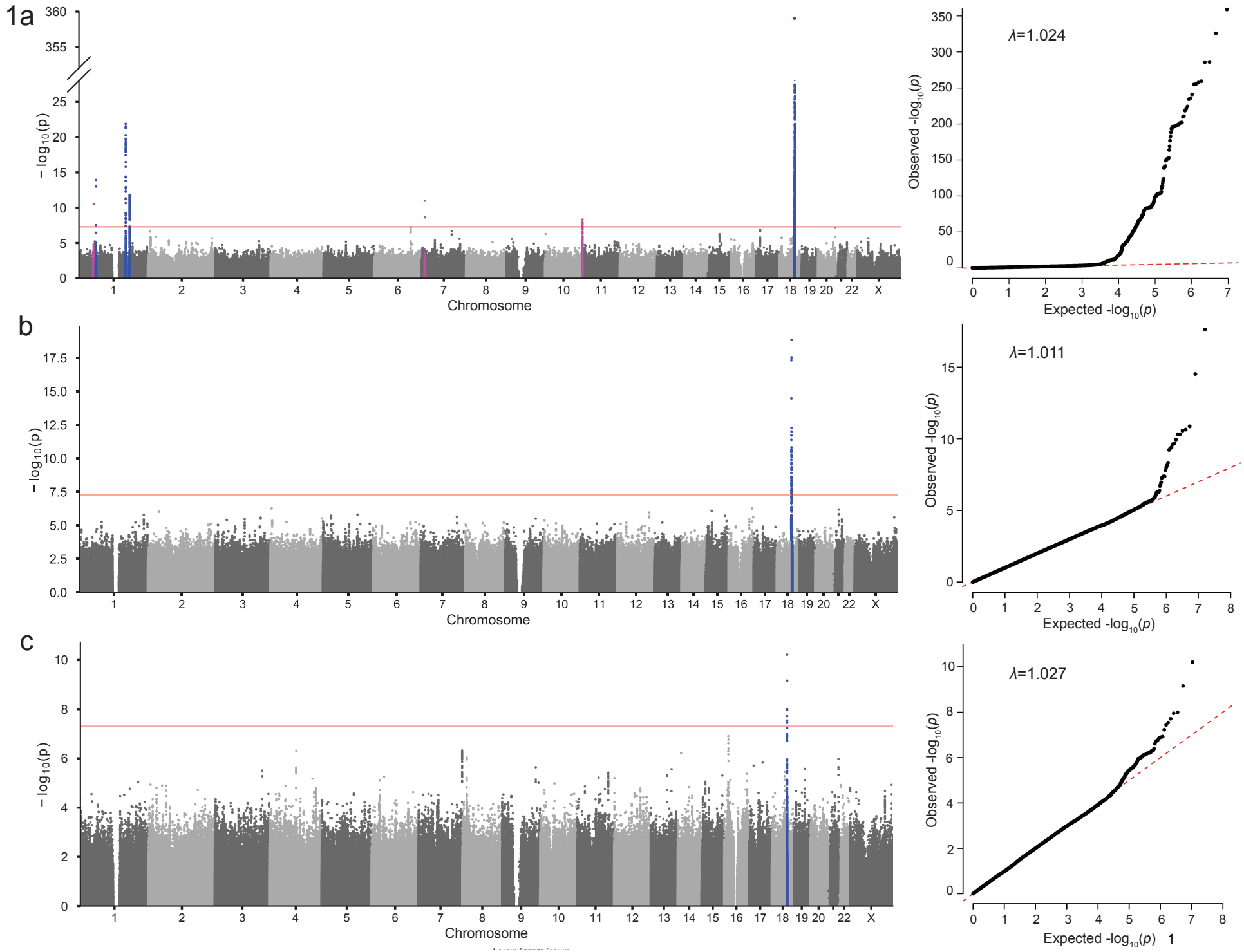
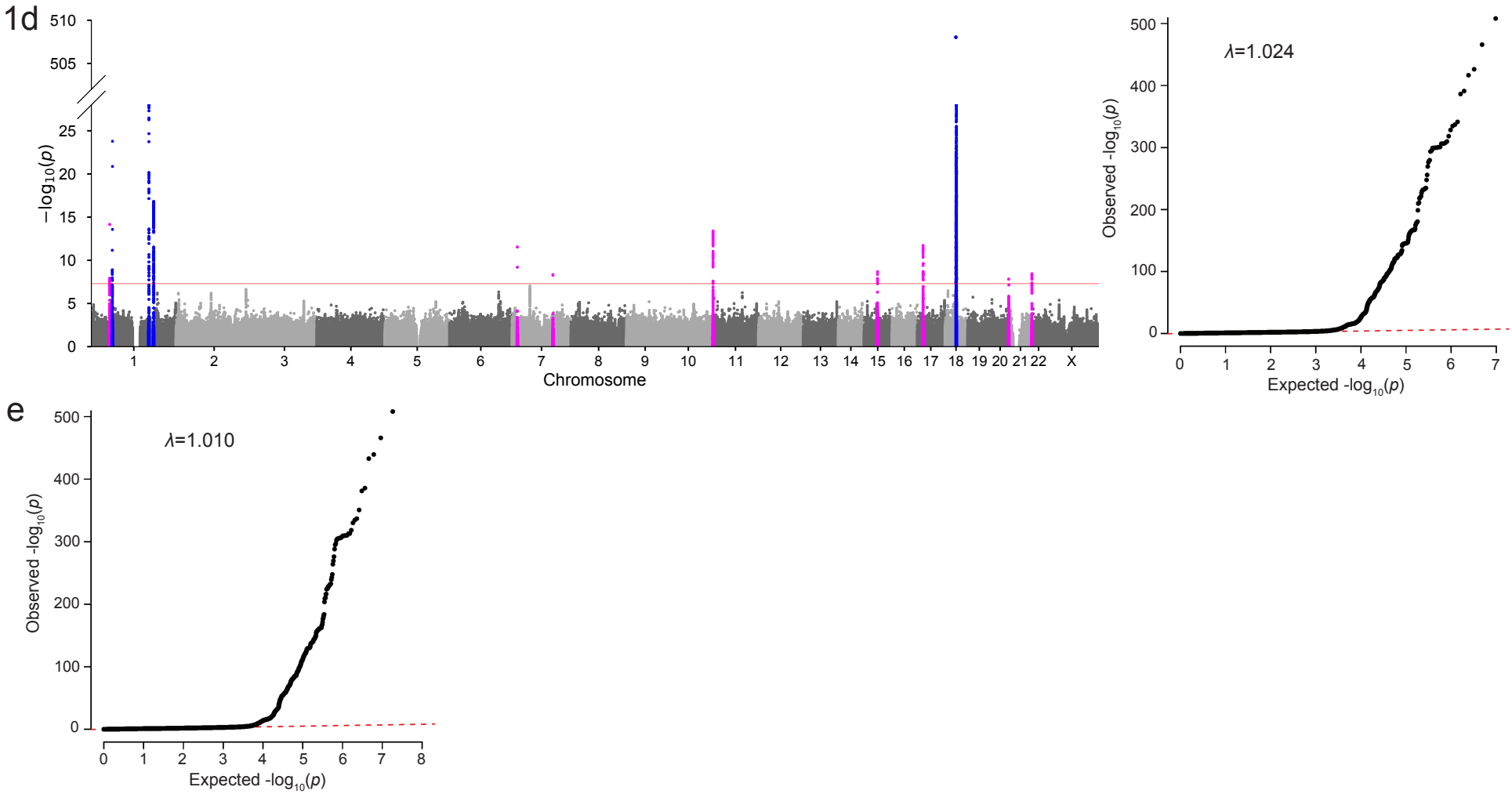
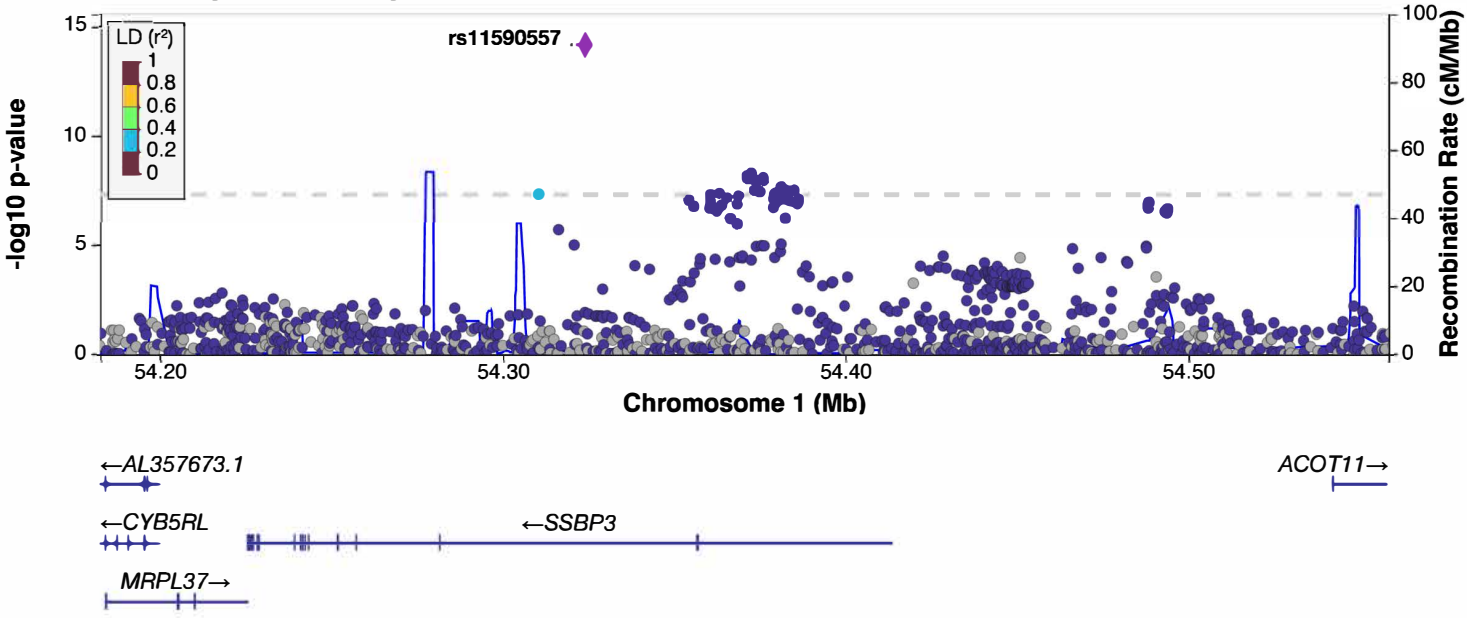

1a
b
c
− log10(p)
Chromosome
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 22 X
λ=1.024
λ=1.011
λ=1.027
Observed -log10(p)
Expected -log10(p)



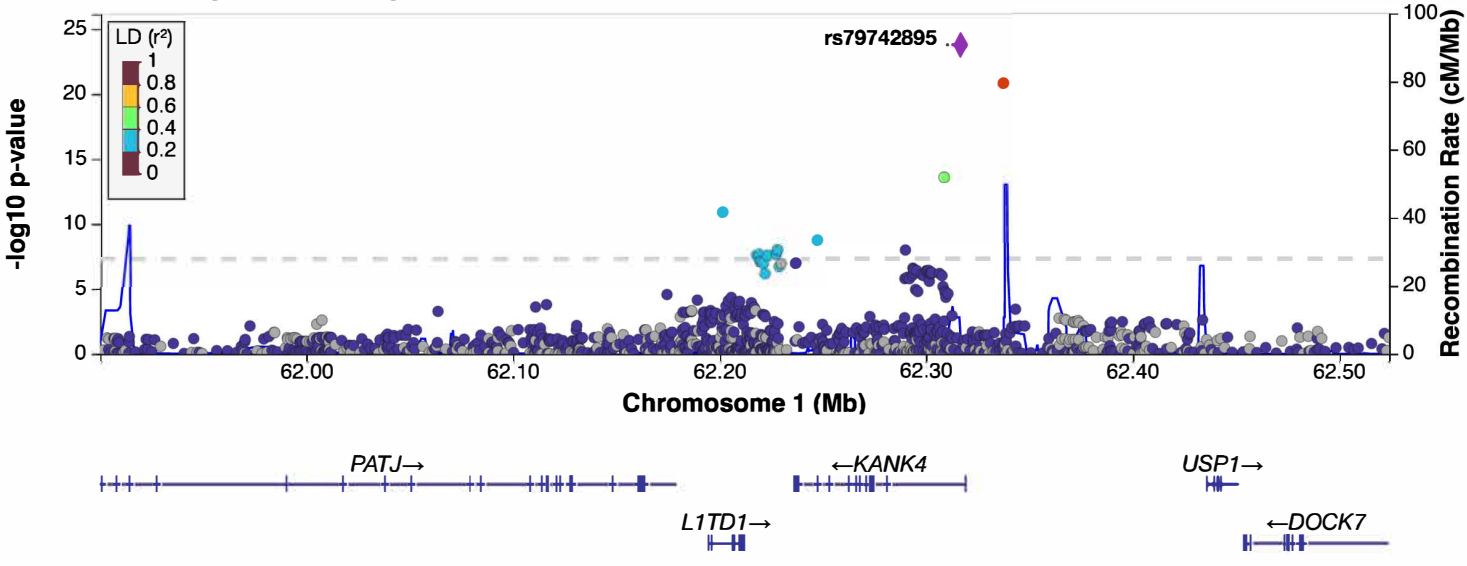
S1 Figure. Manhattan and QQ plots. Left: Manhattan plots showing -log10(P) for associations of genetic variants with FECD across 22 autosomal chromosomes, plus chromosome X, for **(a)** European, **(b)**, admixed African, and **(c)** Hispanic/Latino MVP cohorts; and **(d)** European meta-analysis. Right: Quantile-quantile (QQ) plots showing observed versus expected distributions of association P-values for a-d plus **(e)** multi-ancestry meta-analysis (multi-ancestry Manhattan plot in Figure 2).

2

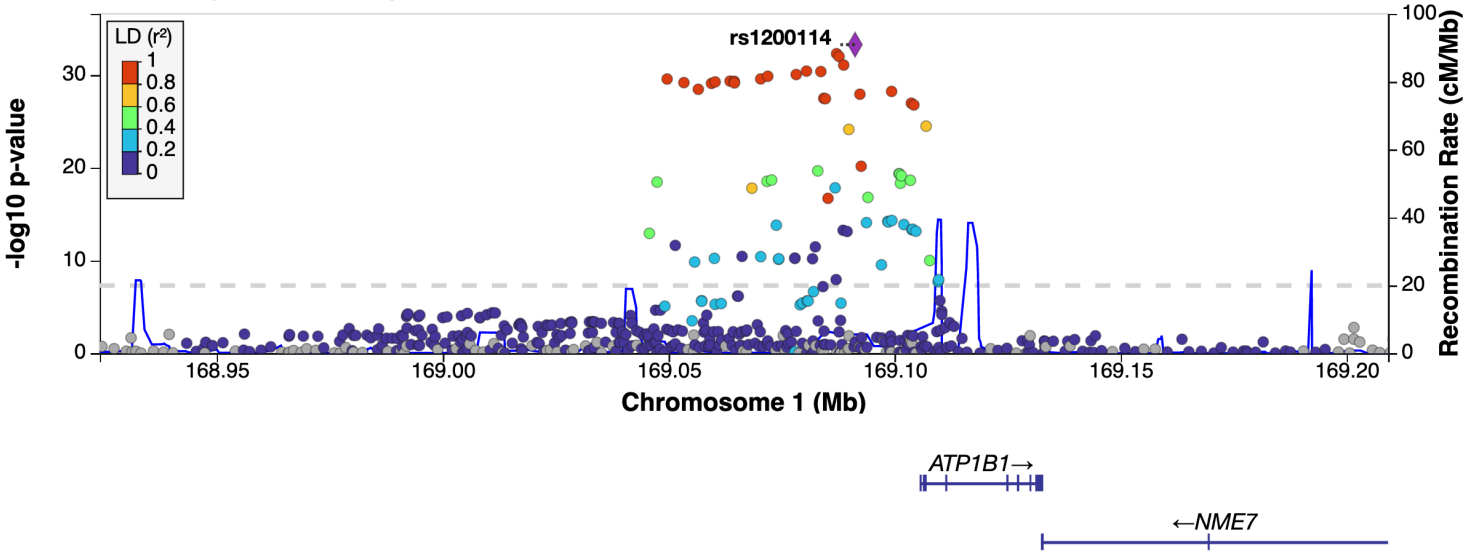
Multi-ancestry meta-analysis



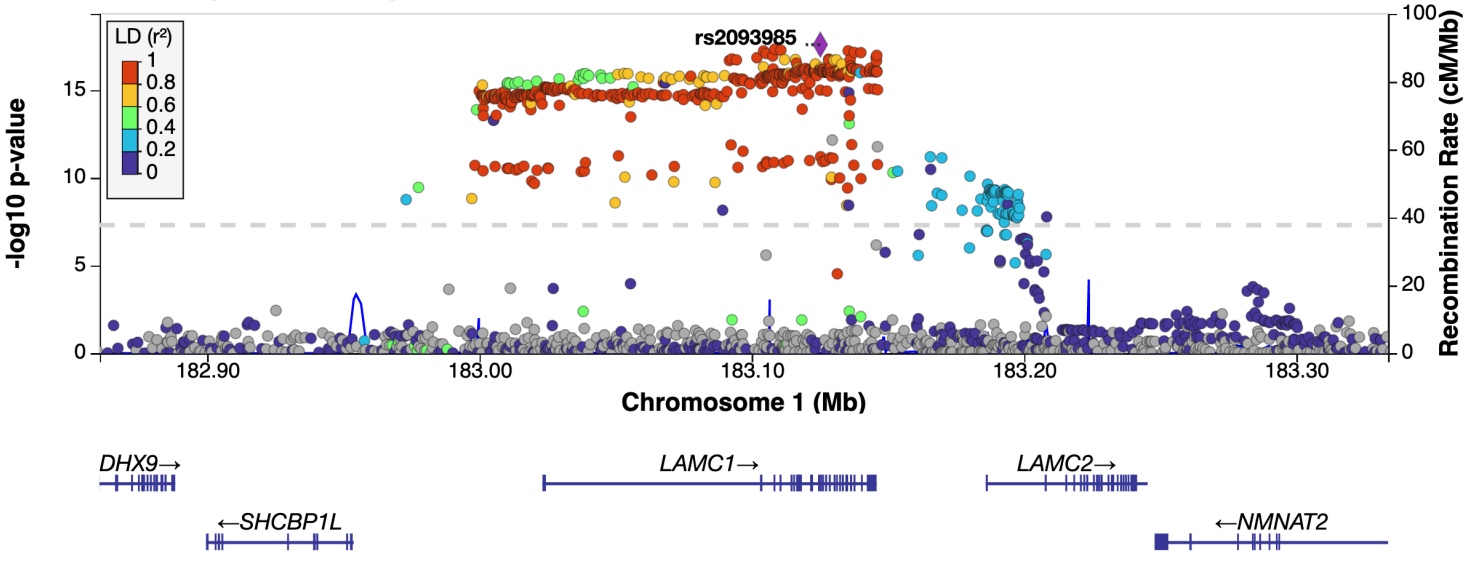
Multi-ancestry meta-analysis

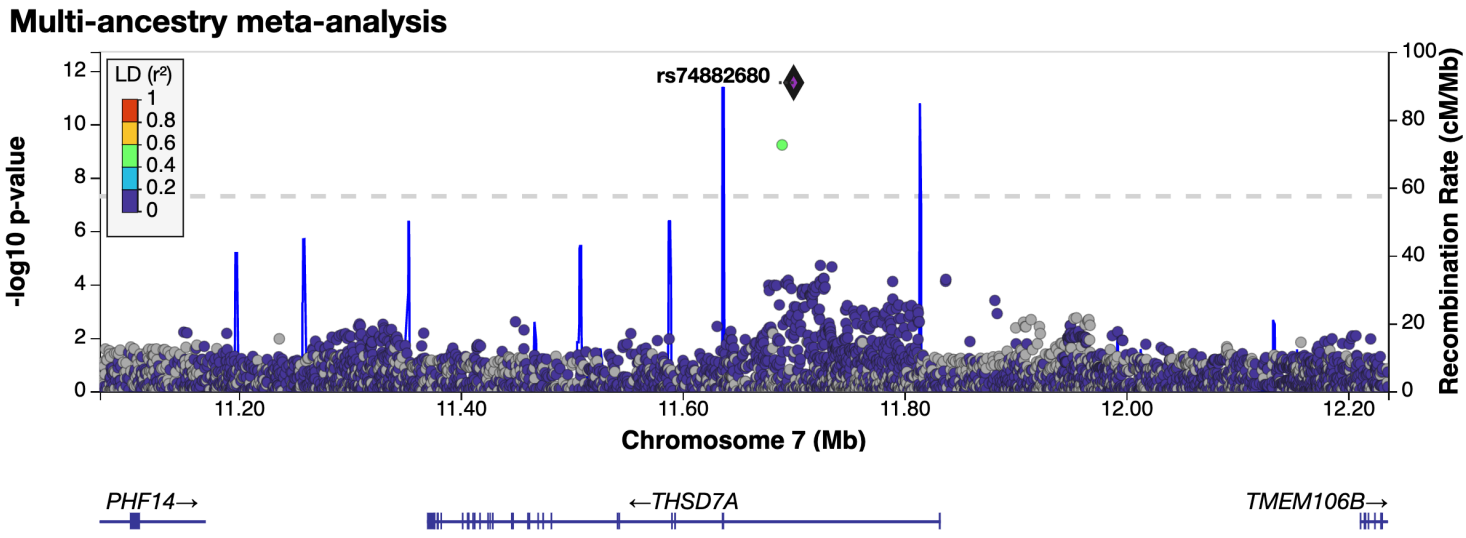


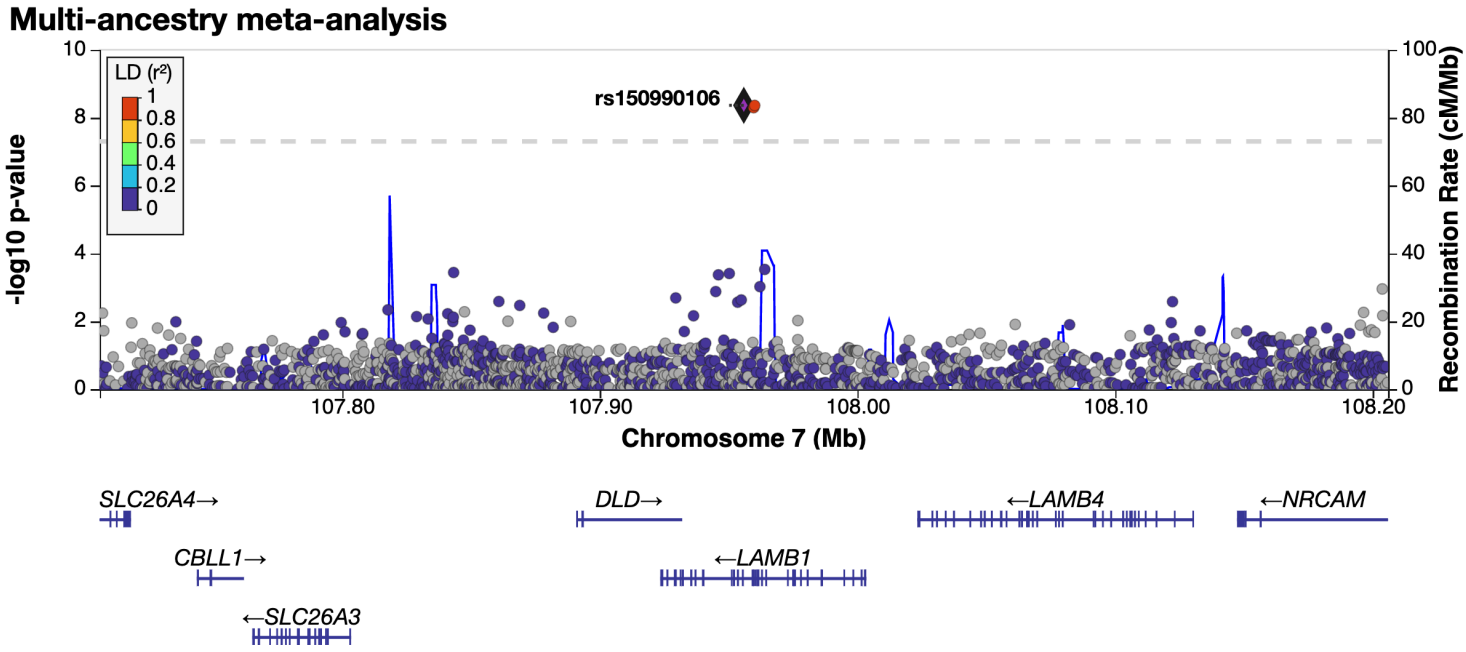
Multi-ancestry meta-analysis



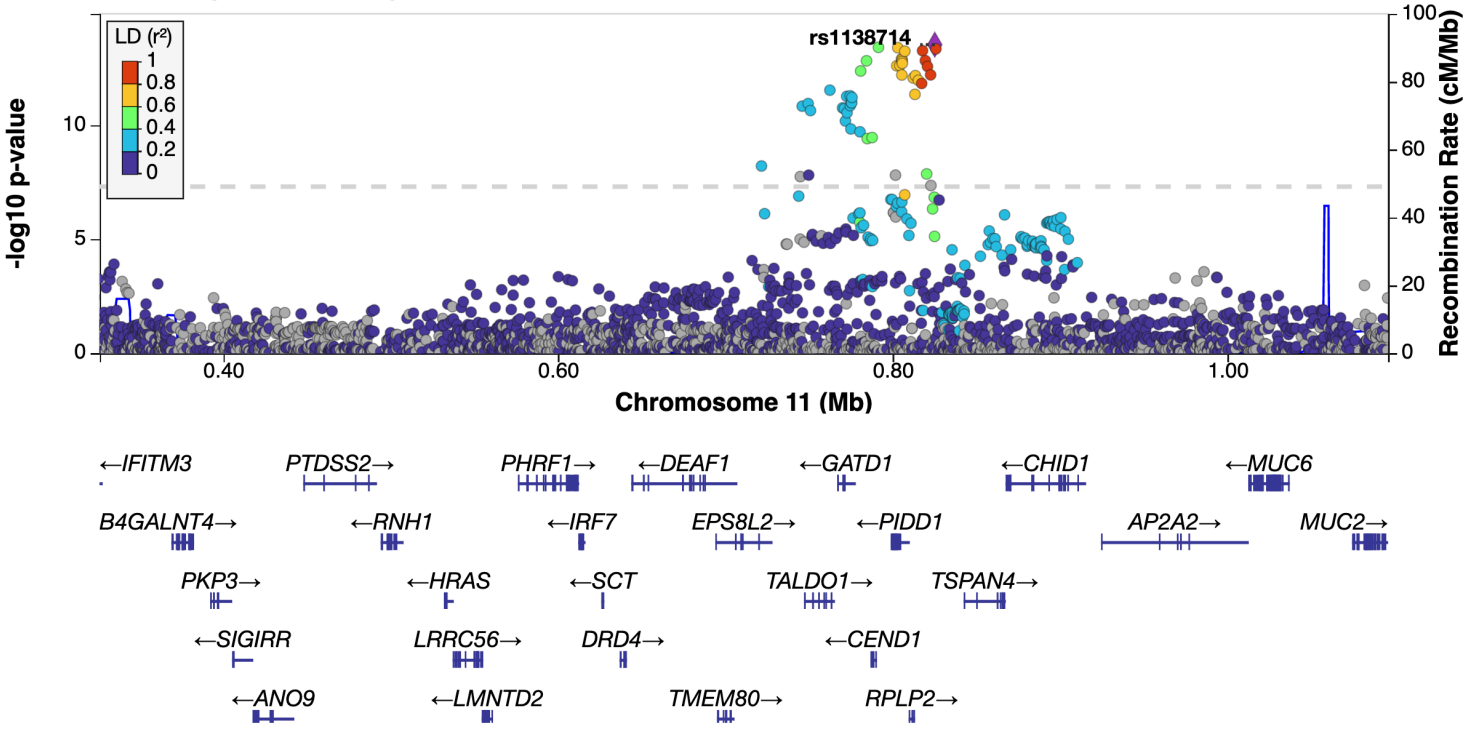
Multi-ancestry meta-analysis



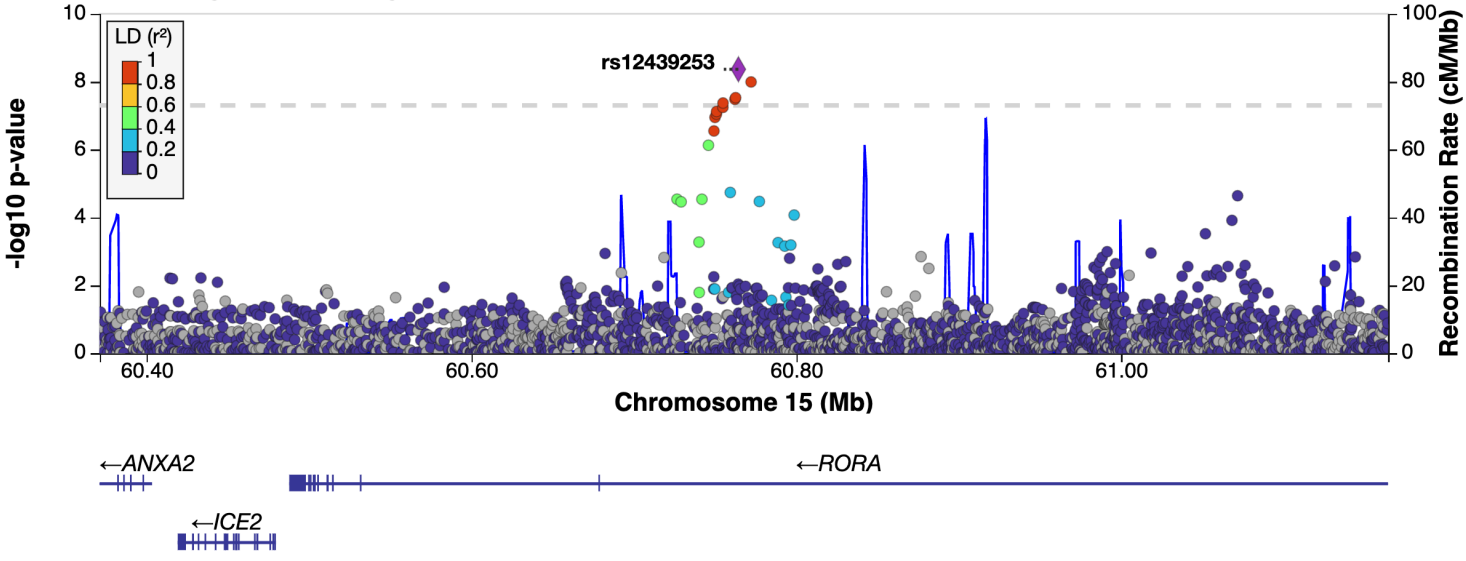

Multi-ancestry meta-analysis
LD (r²)
1
0.8
0.6
0.4
0.2
0
rs74882680
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 7 (Mb)
11.20
11.40
11.60
11.80
12.00
12.20
PHF14→
←THSD7A
TMEM106B→


Multi-ancestry meta-analysis
LD (r²)
1
0.8
0.6
0.4
0.2
0
rs150990106
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 7 (Mb)
107.80
107.90
108.00
108.10
108.20
SLC26A4→
DLD→
←LAMB4
←NRCAM
CBLL1→
←LAMB1
←SLC26A3

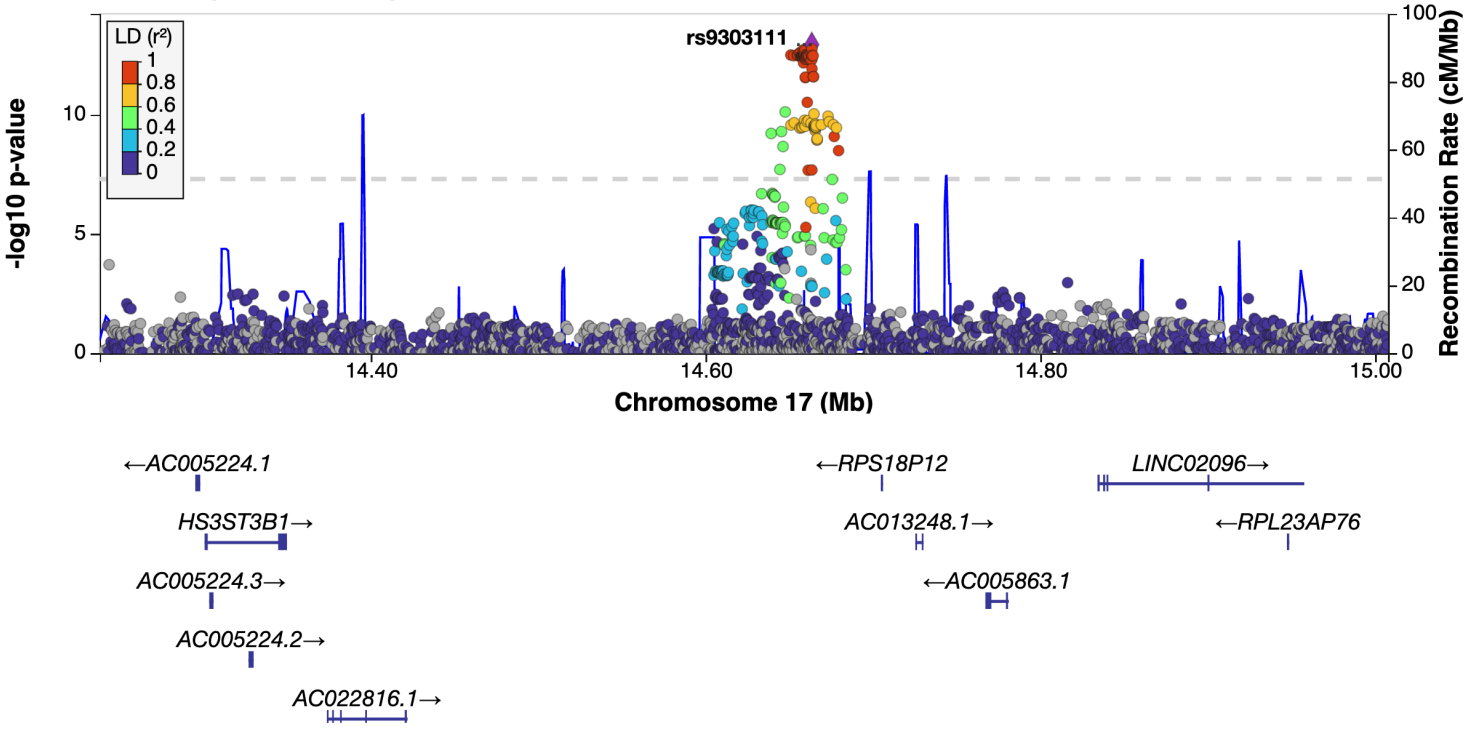
Multi-ancestry meta-analysis



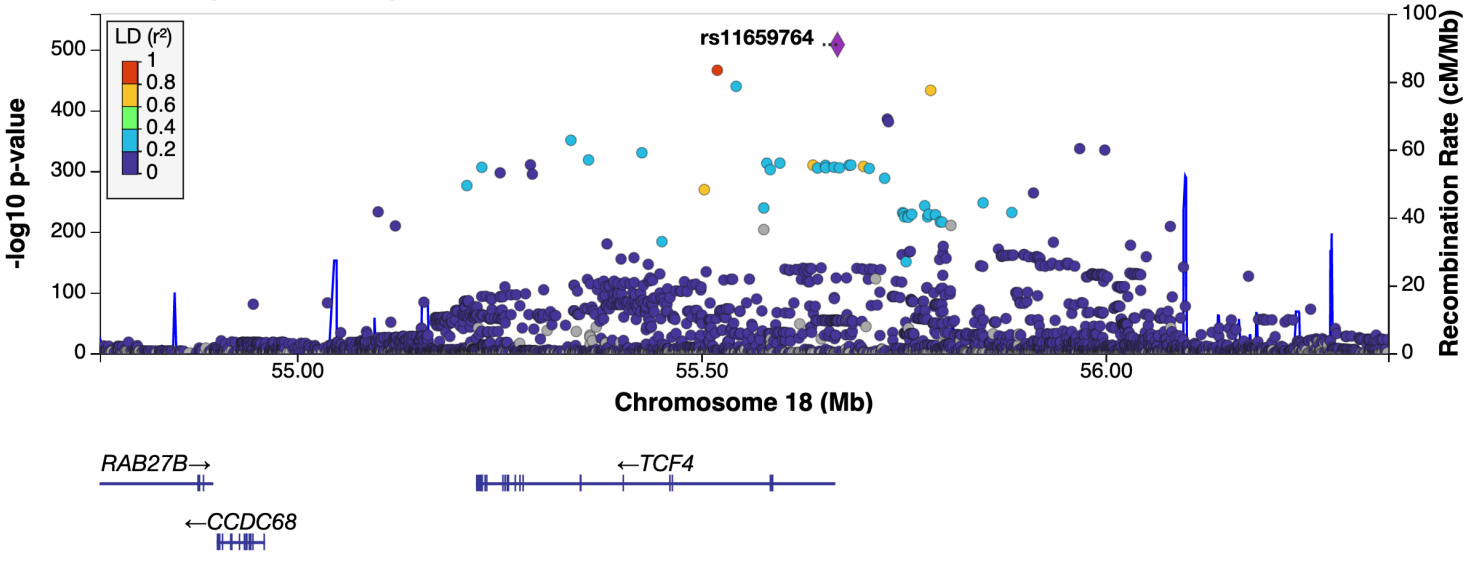
Multi-ancestry meta-analysis



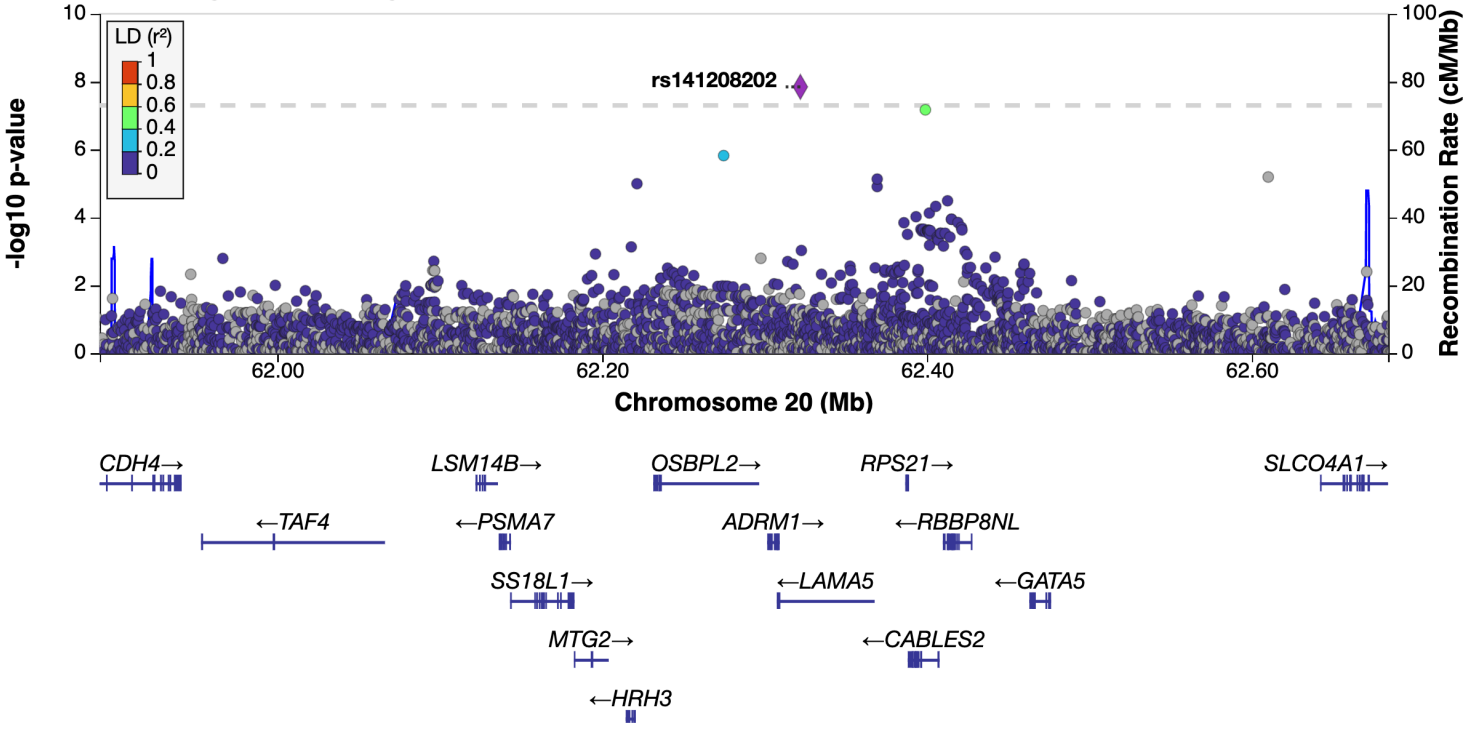
Multi-ancestry meta-analysis



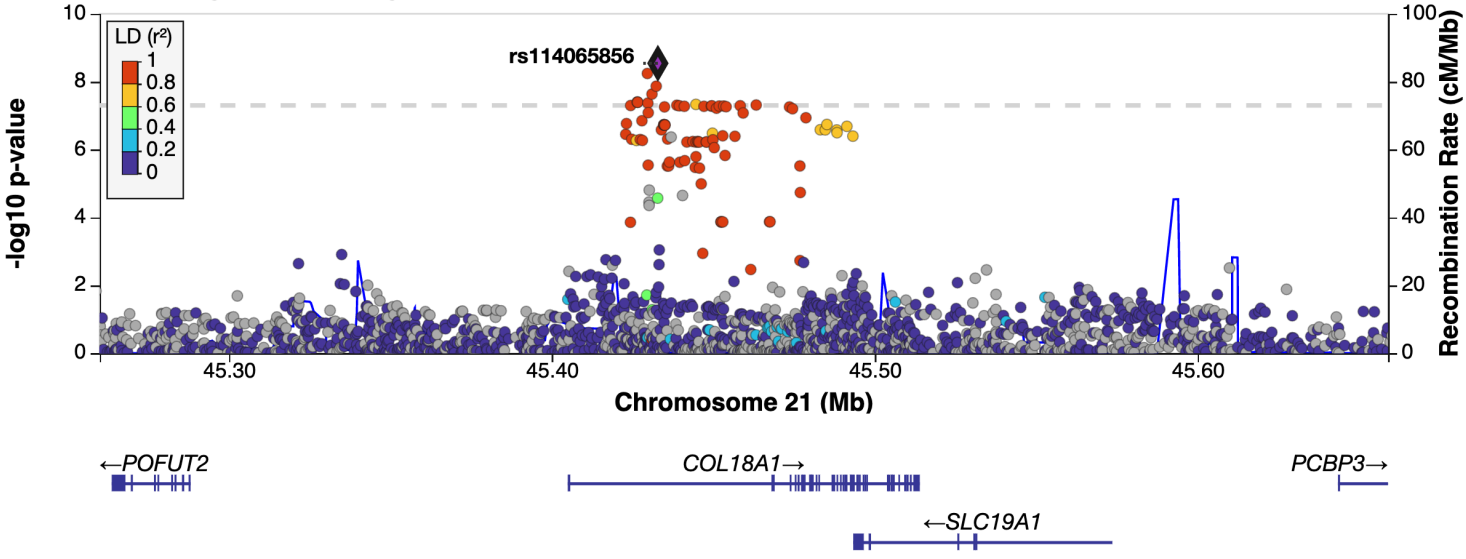
Multi-ancestry meta-analysis



Multi-ancestry meta-analysis

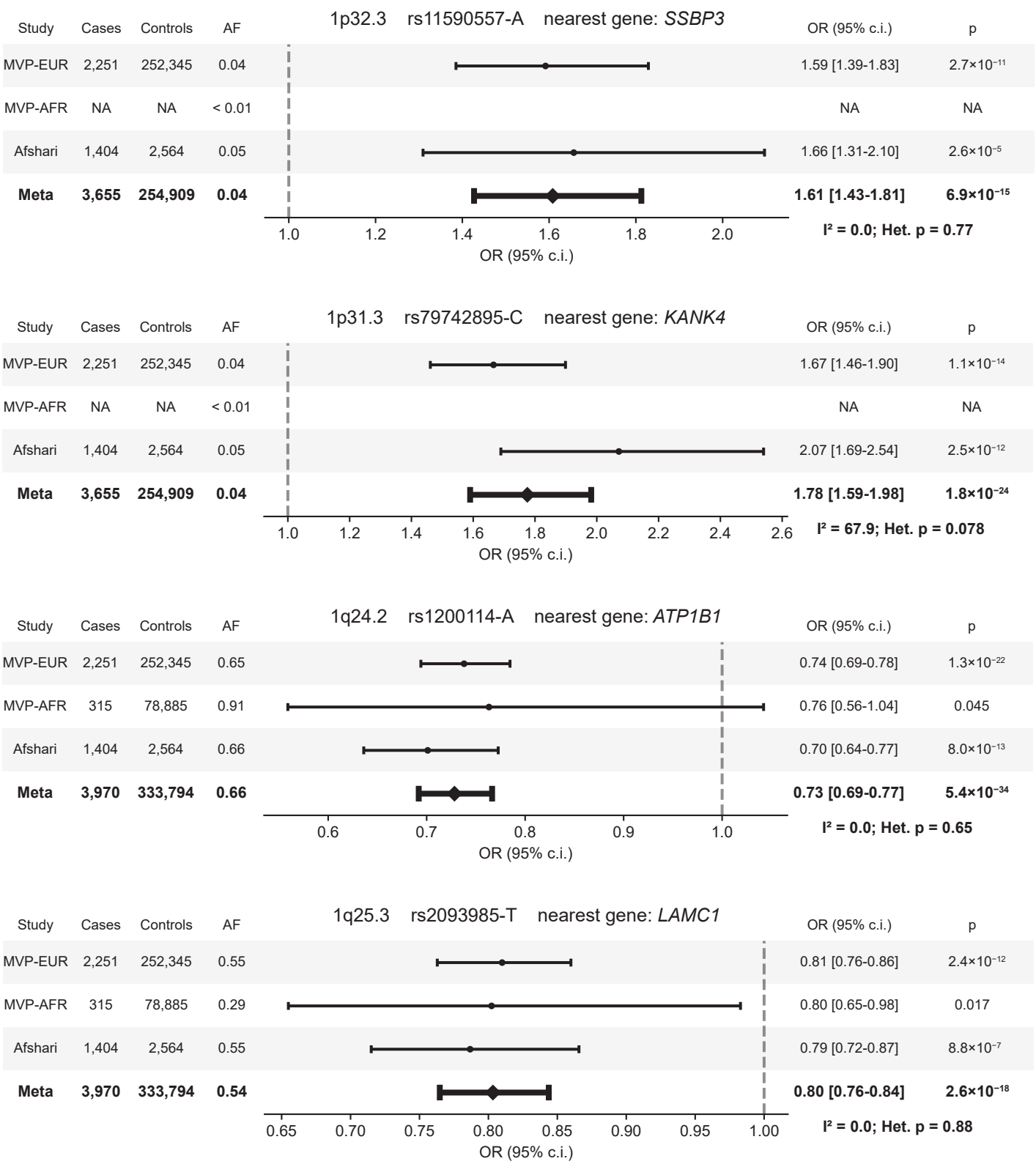


Multi-ancestry meta-analysis



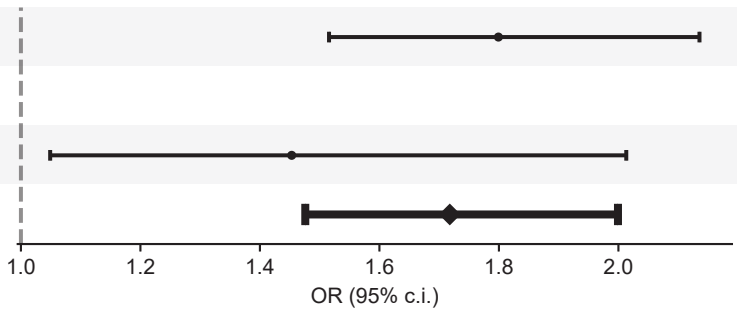
S2 Figure. Local Manhattan plots for significant loci. LocusZoom regional Manhattan plots showing variant-level associations and local linkage disequilibrium structure of twelve significant multi-ancestry meta-analysis loci, arranged by genomic coordinates.

3


1p32.3 rs11590557-A nearest gene: SSBP3
Study Cases Controls AF OR (95% c.i.) p
MVP-EUR 2,251 252,345 0.04 1.59 [1.39-1.83] 2.7×10−11
MVP-AFR NA NA < 0.01 NA NA
Afshari 1,404 2,564 0.05 1.66 [1.31-2.10] 2.6×10−5
Meta 3,655 254,909 0.04 1.61 [1.43-1.81] 6.9×10−15
I² = 0.0; Het. p = 0.77
1.0 1.2 1.4 1.6 1.8 2.0
OR (95% c.i.)
1p31.3 rs79742895-C nearest gene: KANK4
Study Cases Controls AF OR (95% c.i.) p
MVP-EUR 2,251 252,345 0.04 1.67 [1.46-1.90] 1.1×10−14
MVP-AFR NA NA < 0.01 NA NA
Afshari 1,404 2,564 0.05 2.07 [1.69-2.54] 2.5×10−12
Meta 3,655 254,909 0.04 1.78 [1.59-1.98] 1.8×10−24
I² = 67.9; Het. p = 0.078
1.0 1.2 1.4 1.6 1.8 2.0 2.2 2.4 2.6
OR (95% c.i.)
1q24.2 rs1200114-A nearest gene: ATP1B1
Study Cases Controls AF OR (95% c.i.) p
MVP-EUR 2,251 252,345 0.65 0.74 [0.69-0.78] 1.3×10−22
MVP-AFR 315 78,885 0.91 0.76 [0.56-1.04] 0.045
Afshari 1,404 2,564 0.66 0.70 [0.64-0.77] 8.0×10−13
Meta 3,970 333,794 0.66 0.73 [0.69-0.77] 5.4×10−34
I² = 0.0; Het. p = 0.65
0.6 0.7 0.8 0.9 1.0
OR (95% c.i.)
1q25.3 rs2093985-T nearest gene: LAMC1
Study Cases Controls AF OR (95% c.i.) p
MVP-EUR 2,251 252,345 0.55 0.81 [0.76-0.86] 2.4×10−12
MVP-AFR 315 78,885 0.29 0.80 [0.65-0.98] 0.017
Afshari 1,404 2,564 0.55 0.79 [0.72-0.87] 8.8×10−7
Meta 3,970 333,794 0.54 0.80 [0.76-0.84] 2.6×10−18
I² = 0.0; Het. p = 0.88
0.65 0.70 0.75 0.80 0.85 0.90 0.95 1.00
OR (95% c.i.)

7p21.3 rs74882680-G nearest gene: *THSD7A*

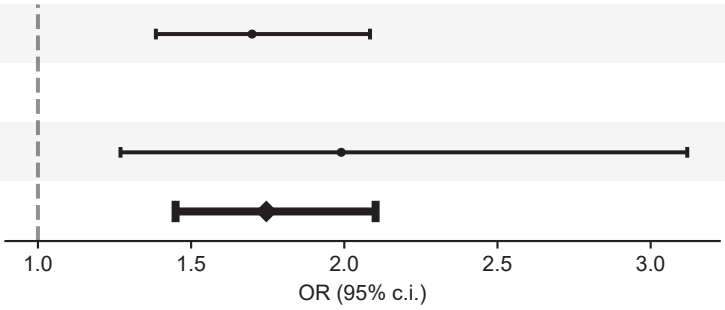
Study	Cases	Controls	AF	OR (95% c.i.)	p
MVP-EUR	2,251	252,345	0.02	1.80 [1.52-2.14]	9.5×10^{-12}
MVP-AFR	NA	NA	< 0.01	NA	NA
Afshari	1,404	2,564	0.02	1.45 [1.05-2.01]	0.025
Meta	**3,655**	**254,909**	**0.02**	**1.72 [1.48-2.00]**	**2.8×10^{-12}**



I^2 = 22.6; Het. p = 0.26

7q31.1 rs150990106-A nearest gene: *LAMB1*

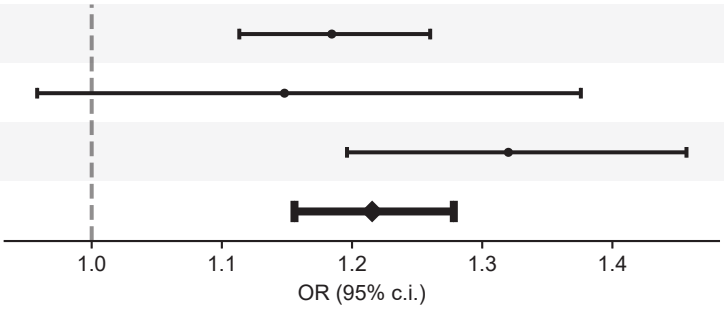
Study	Cases	Controls	AF	OR (95% c.i.)	p
MVP-EUR	2,251	252,345	0.02	1.70 [1.39-2.08]	1.8×10^{-7}
MVP-AFR	NA	NA	< 0.01	NA	NA
Afshari	1,404	2,564	0.01	1.99 [1.27-3.12]	0.0027
Meta	**3,655**	**254,909**	**0.02**	**1.75 [1.45-2.10]**	**4.3×10^{-9}**



I^2 = 0.0; Het. p = 0.53

11p15.5 rs1138714-G nearest gene: *PNPLA2*

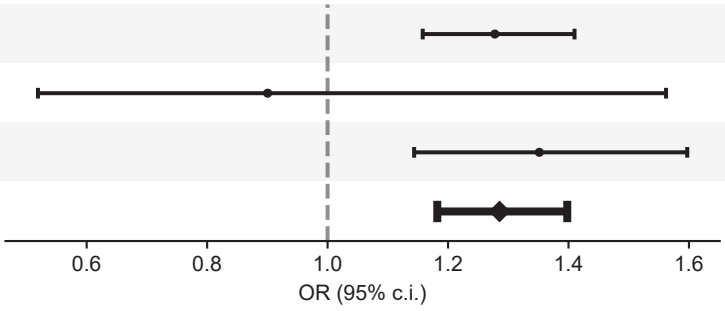
Study	Cases	Controls	AF	OR (95% c.i.)	p
MVP-EUR	2,251	252,345	0.56	1.18 [1.11-1.26]	4.1×10^{-8}
MVP-AFR	315	78,885	0.26	1.15 [0.96-1.38]	0.13
Afshari	1,404	2,564	0.54	1.32 [1.20-1.46]	3.4×10^{-8}
Meta	**3,970**	**333,794**	**0.53**	**1.22 [1.16-1.28]**	**3.0×10^{-14}**



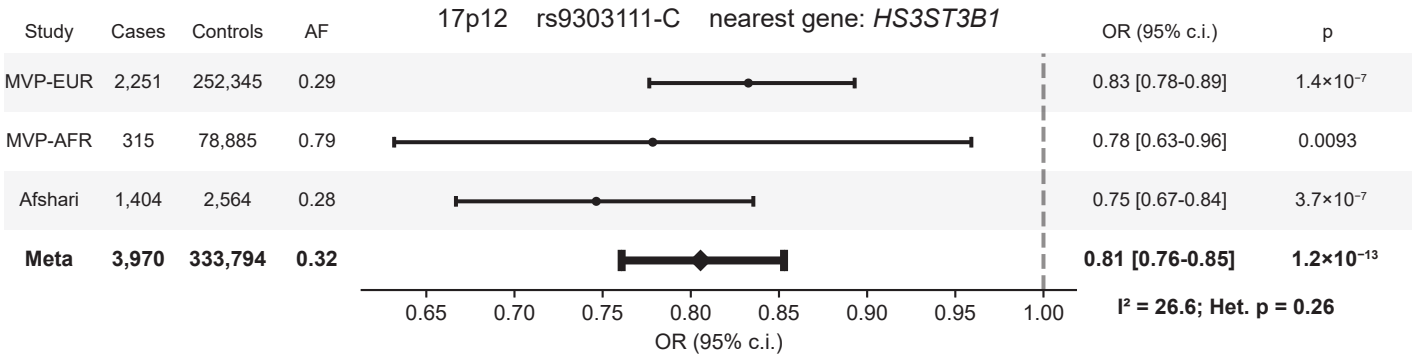
I^2 = 46.6; Het. p = 0.15

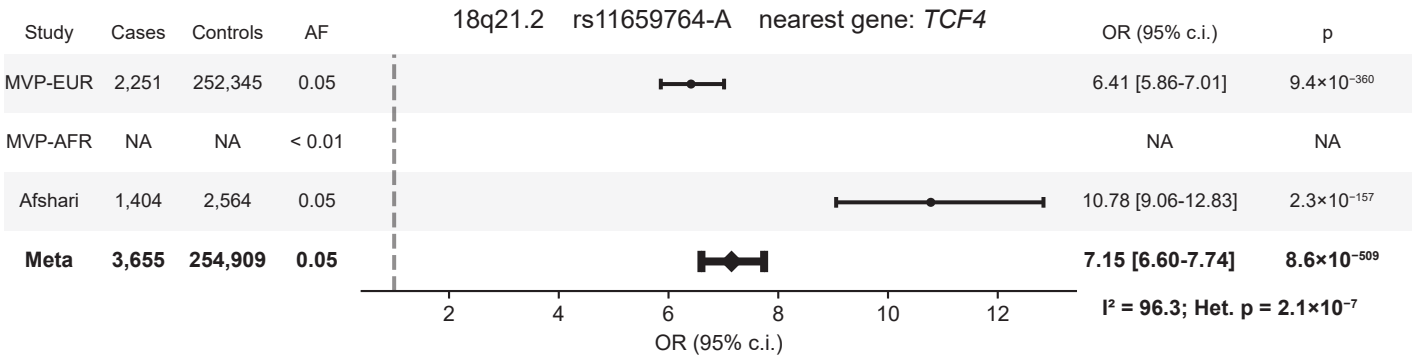
15q22.2 rs12439253-T nearest gene: *RORA*

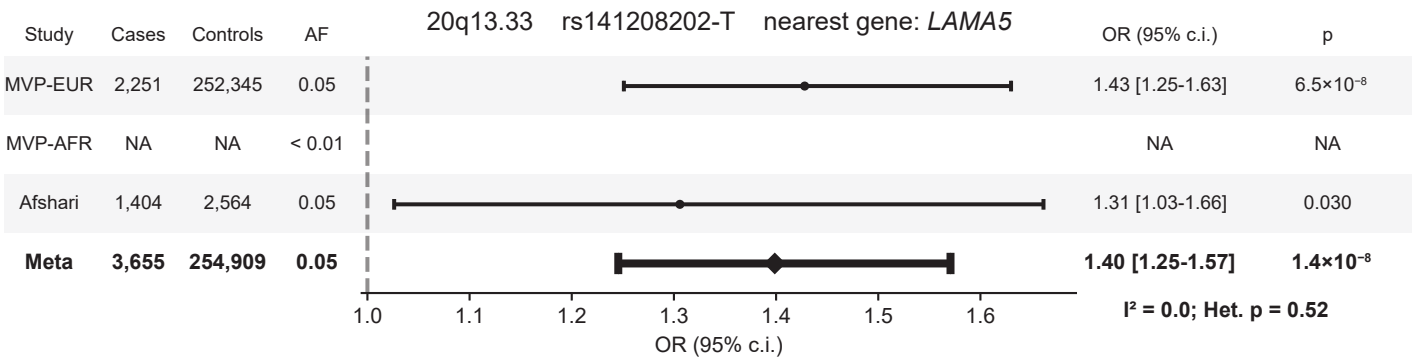
Study	Cases	Controls	AF	OR (95% c.i.)	p
MVP-EUR	2,251	252,345	0.09	1.28 [1.16-1.41]	5.3×10^{-7}
MVP-AFR	315	78,885	0.02	0.90 [0.52-1.56]	0.71
Afshari	1,404	2,564	0.08	1.35 [1.14-1.60]	0.00041
Meta	**3,970**	**333,794**	**0.08**	**1.29 [1.18-1.40]**	**4.3×10^{-9}**

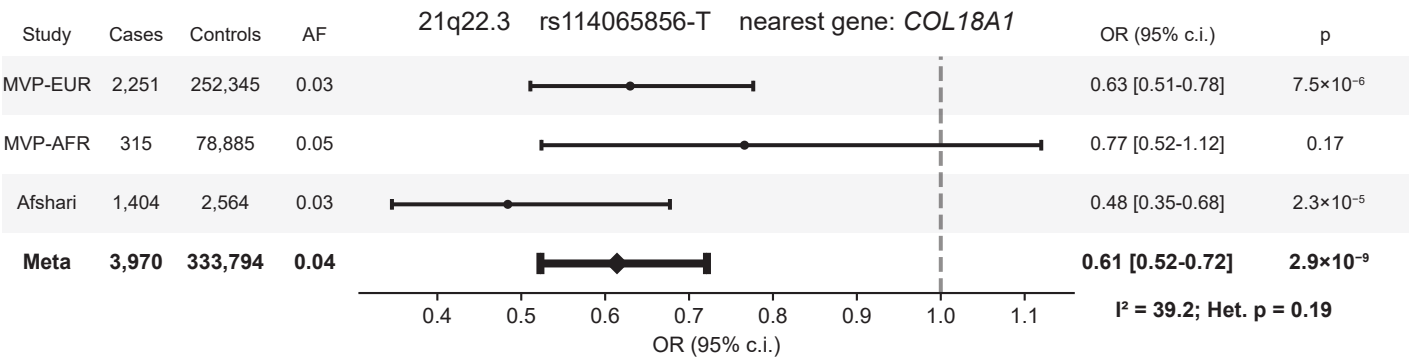


I^2 = 0.0; Het. p = 0.37

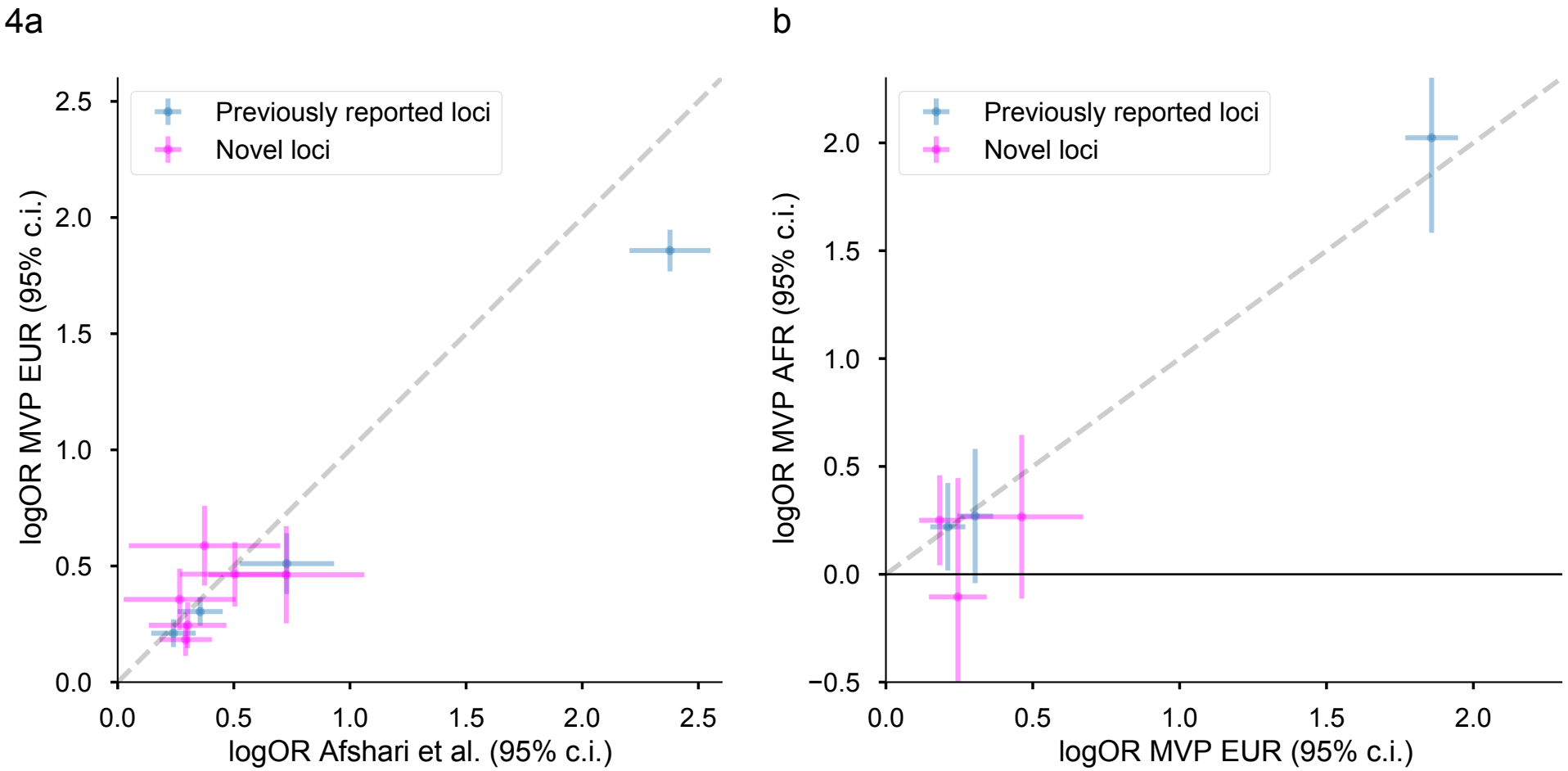

17p12 rs9303111-C nearest gene: HS3ST3B1
Study Cases Controls AF OR (95% c.i.) p
MVP-EUR 2,251 252,345 0.29 0.83 [0.78-0.89] 1.4×10⁻⁷
MVP-AFR 315 78,885 0.79 0.78 [0.63-0.96] 0.0093
Afshari 1,404 2,564 0.28 0.75 [0.67-0.84] 3.7×10⁻⁷
Meta 3,970 333,794 0.32 0.81 [0.76-0.85] 1.2×10⁻¹³
I² = 26.6; Het. p = 0.26
0.65 0.70 0.75 0.80 0.85 0.90 0.95 1.00
OR (95% c.i.)


18q21.2 rs11659764-A nearest gene: TCF4
Study Cases Controls AF OR (95% c.i.) p
MVP-EUR 2,251 252,345 0.05 6.41 [5.86-7.01] 9.4×10⁻³⁶⁰
MVP-AFR NA NA < 0.01 NA NA
Afshari 1,404 2,564 0.05 10.78 [9.06-12.83] 2.3×10⁻¹⁵⁷
Meta 3,655 254,909 0.05 7.15 [6.60-7.74] 8.6×10⁻⁵⁰⁹
I² = 96.3; Het. p = 2.1×10⁻⁷
2 4 6 8 10 12
OR (95% c.i.)


20q13.33 rs141208202-T nearest gene: LAMA5
Study Cases Controls AF OR (95% c.i.) p
MVP-EUR 2,251 252,345 0.05 1.43 [1.25-1.63] 6.5×10⁻⁸
MVP-AFR NA NA < 0.01 NA NA
Afshari 1,404 2,564 0.05 1.31 [1.03-1.66] 0.030
Meta 3,655 254,909 0.05 1.40 [1.25-1.57] 1.4×10⁻⁸
I² = 0.0; Het. p = 0.52
1.0 1.1 1.2 1.3 1.4 1.5 1.6
OR (95% c.i.)

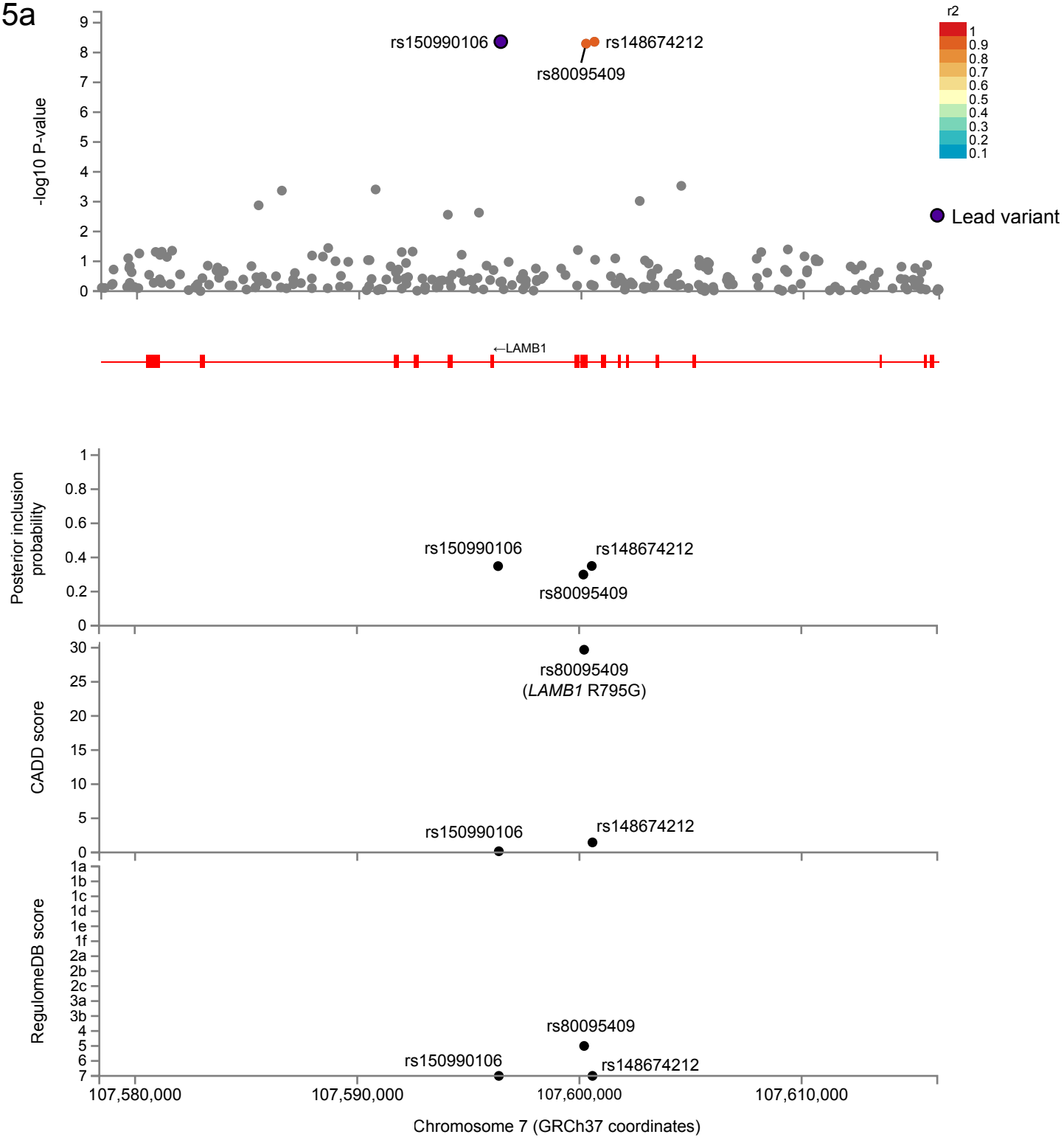

21q22.3 rs114065856-T nearest gene: COL18A1
Study Cases Controls AF OR (95% c.i.) p
MVP-EUR 2,251 252,345 0.03 0.63 [0.51-0.78] 7.5×10⁻⁶
MVP-AFR 315 78,885 0.05 0.77 [0.52-1.12] 0.17
Afshari 1,404 2,564 0.03 0.48 [0.35-0.68] 2.3×10⁻⁵
Meta 3,970 333,794 0.04 0.61 [0.52-0.72] 2.9×10⁻⁹
I² = 39.2; Het. p = 0.19
0.4 0.5 0.6 0.7 0.8 0.9 1.0 1.1
OR (95% c.i.)

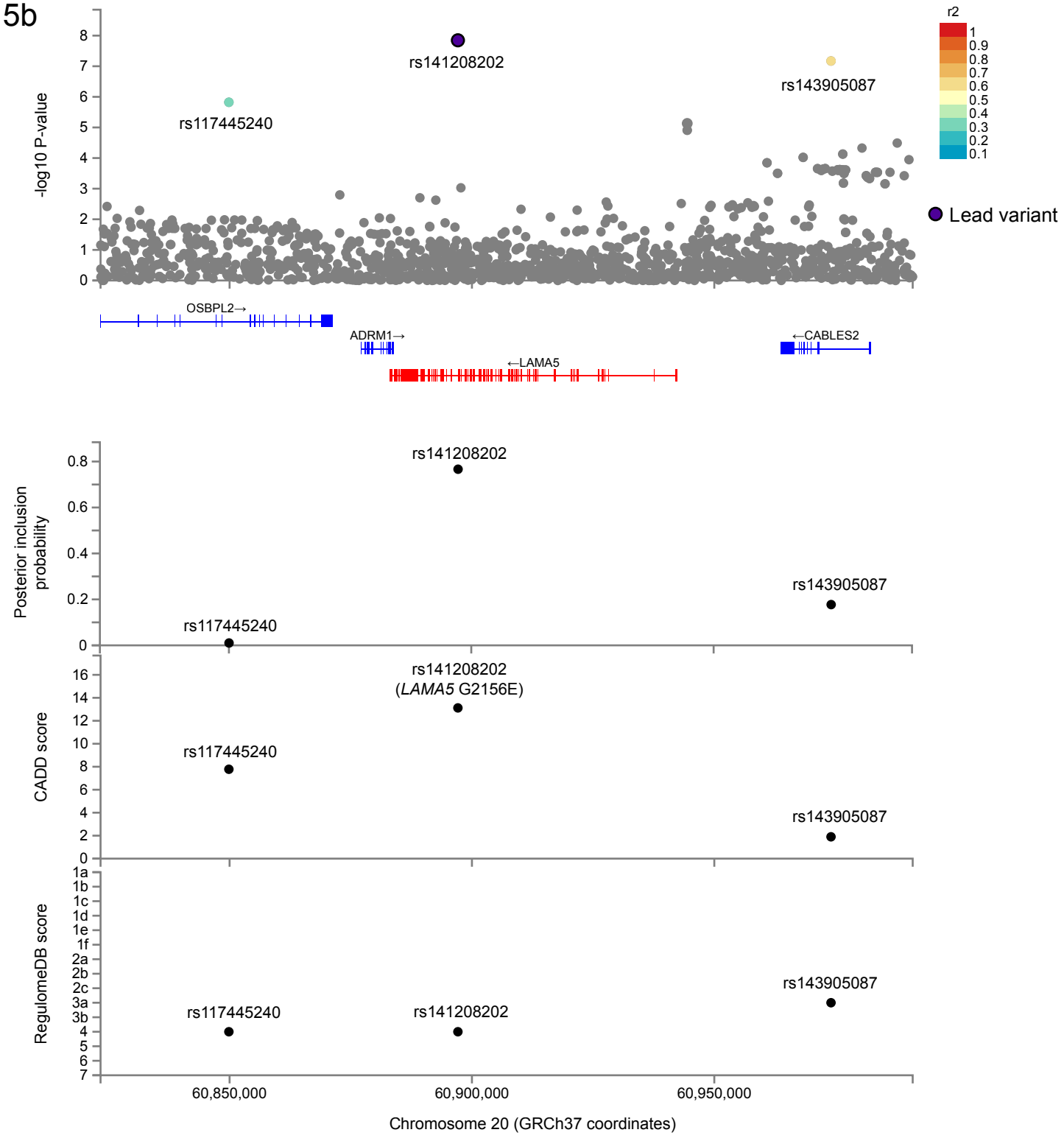
S3 Figure. Forest plots of lead SNPs. Odds ratios (OR) and 95% confidence intervals for FECD at twelve significant lead SNPs in MVP European (EUR), admixed African (AFR), and Afshari (Afshari et al., 2017) cohorts, and combined multi-ancestry meta-analysis (Meta). OR is not shown for six of twelve AFR index variants which did not meet the meta-analysis MAF cutoff of ≥1%.



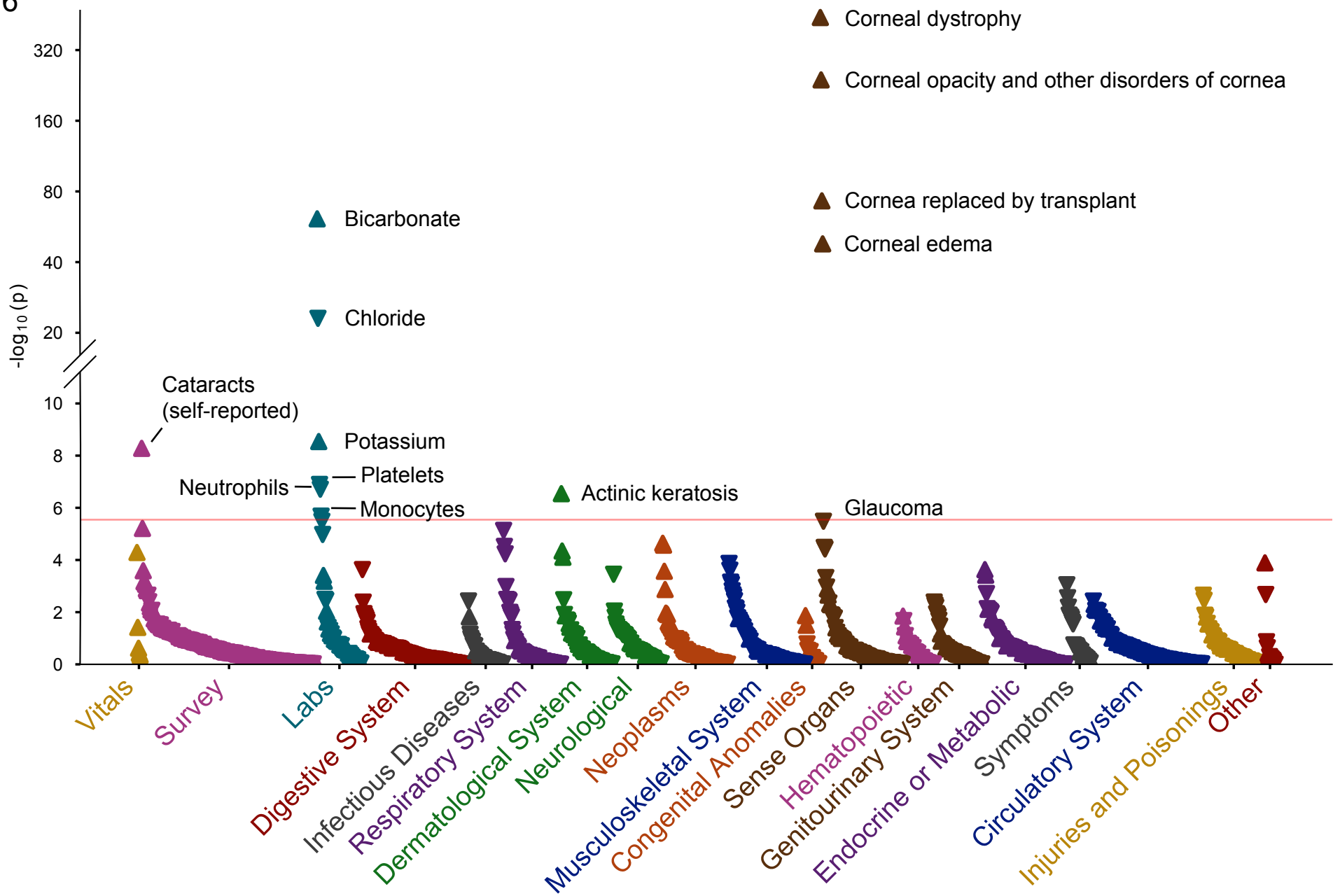
S4 Figure. Comparison of allele effect sizes. Scatterplots comparing effect sizes (logarithm of odds ratios and 95% confidence interval) of previously reported (blue) and novel (pink) lead SNPs between **(a)** MVP European (EUR) vs the most recent FECD GWAS (Afshari et al., 2017) and **(b)** MVP admixed African (AFR) vs MVP EUR. Directions of effects estimates between cohorts were consistent for all lead SNPs except one, rs12439253 (RORA), which was not significant in AFR.

5a


r2
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
Lead variant
-log10 P-value
rs150990106
rs148674212
rs80095409
←LAMB1
Posterior inclusion probability
CADD score
rs80095409
(LAMB1 R795G)
RegulomeDB score
107,580,000
107,590,000
107,600,000
107,610,000
Chromosome 7 (GRCh37 coordinates)

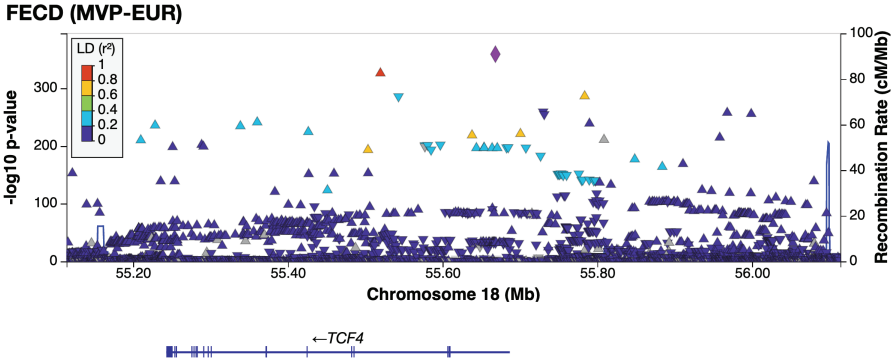


S5 Figure. Novel laminin gene causal variant prediction. Local Manhattan plots, fine-mapping posterior inclusion probabilities, Combined Annotation Dependent Depletion (CADD) scores, and RegulomeDB scores for significant FECD associations at (A) rs80095409 (LAMB1) and (B) rs141208202 (LAMA5).

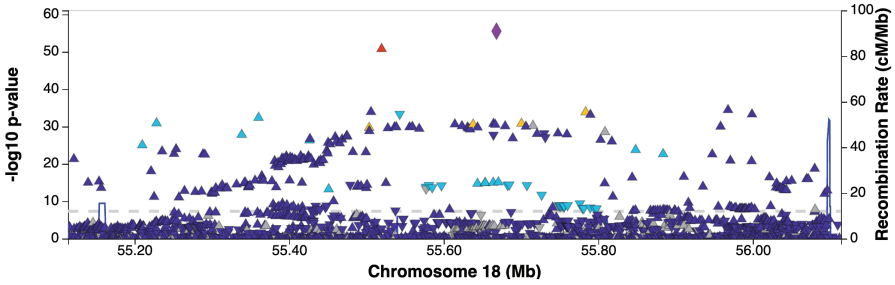


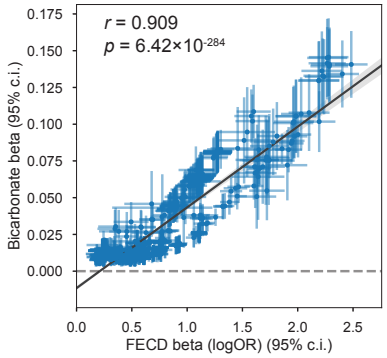
S6 Figure. rs11659764 variant-level PheWAS. Phenome-wide associations with rs11659764, the lead FECD variant at *TCF4*. Phenotypes are grouped by category and those reaching multiple testing corrected significance ($P < 2.9 \times 10^{-6}$; red line) are labeled. Point direction indicates positive or negative effect. Y-axis break indicates change to logarithmic scale. FECD (not shown) had the most significant trait effect at rs11659764 ($P = 5.01 \times 10^{-658}$). All lab measures are rank inverse normal transformed.

FECD (MVP-EUR)

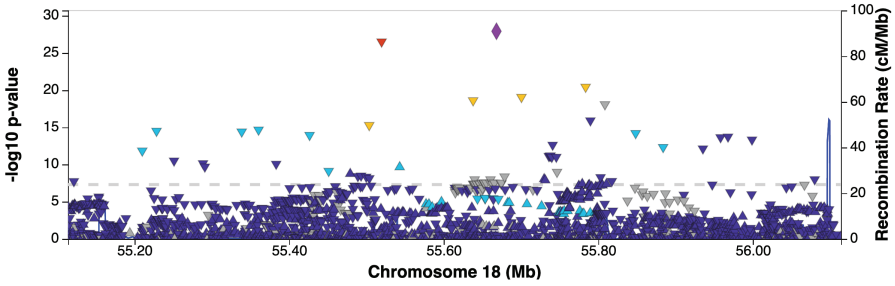


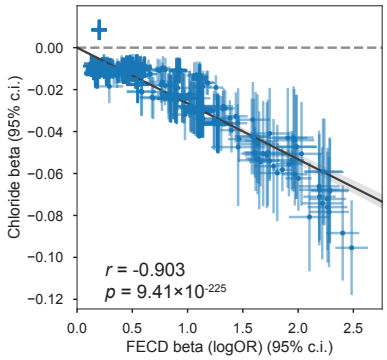
Serum bicarbonate



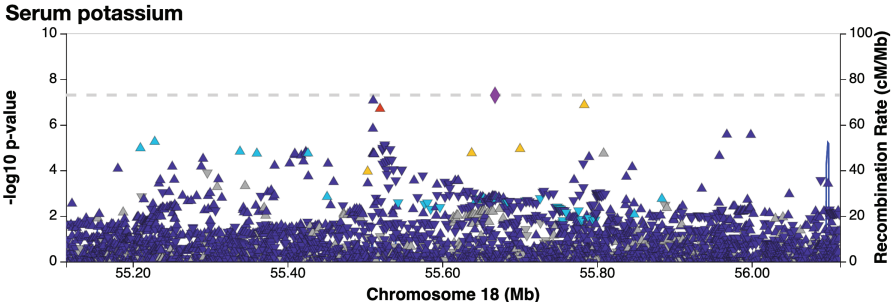


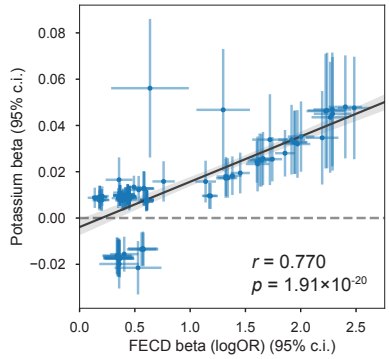
Serum chloride



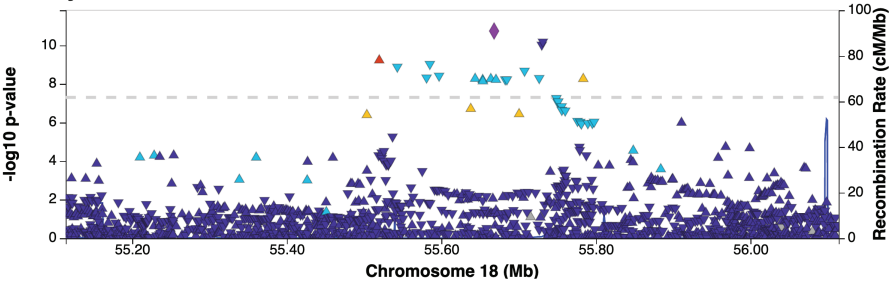


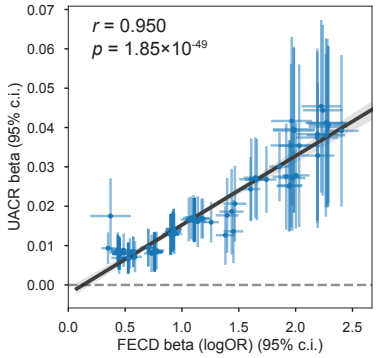
Serum potassium





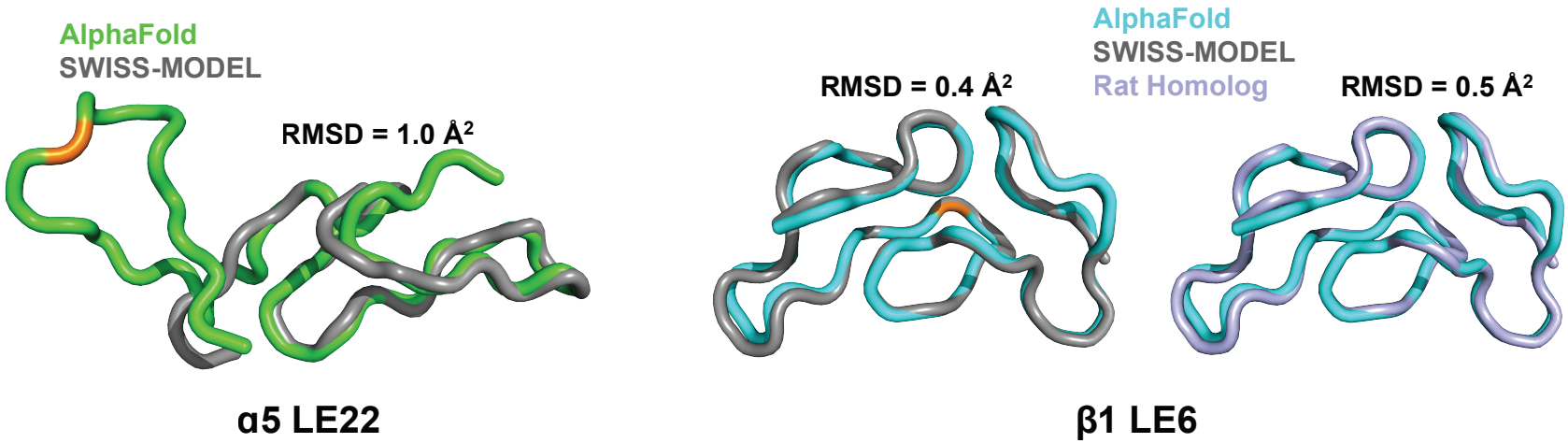
Urinary albumin to creatinine ratio



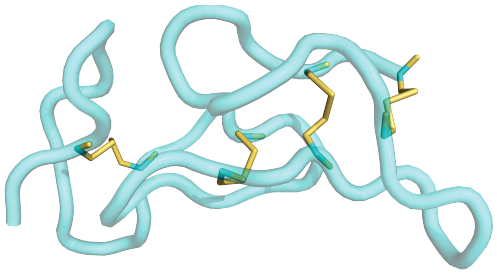


S7 Figure. Colocalization at TCF4. For associations at FECD, serum bicarbonate, serum chloride, serum potassium, and urinary albumin-to-creatinine ratio, regional Manhattan plots (left) and effects comparison scatterplots with 95% confidence intervals (right). FECD effects are shown as logarithm of odds ratios.

8a



b



Mutation	H-BOND(count)	Predicted G (kcal/mol)
α5-LE22 G2156E	0	-0.266
β1 LE6 R795G	-3	-1.226

S8 Figure. Predicted impact of mutation on LE domain structure. (a) Human β1 LE6 target sequence and its rat homolog have a 67% sequence identity. The AlphaFold prediction for β1 LE6 has excellent agreement with the crystallized rat homolog as well as the SWISS-MODEL homology model. (b) The homolog template for α5 does not cover the entire target sequence, hence the predicted homology model does not include a portion of the domain. However, given the excellent agreement between the AlphaFold prediction and the homology model for the existing portion of the domain of α5 LE22 and for β1 LE6, it is likely that AlphaFold is providing a feasible conformation of the α5 LE22 loop missing in the template structure. (c) Shown on the left is the AlphaFold prediction of β1 LE6 with the 4 disulfide links that fortify the tertiary structure of the domain displayed as yellow sticks. (d) Change in hydrogen bond content and Gibbs free energy introduced by the mutations. The substitution of a glycine with glutamic acid in A5 LE22 does not result in loss or gain of hydrogen bonds within the domain. Meanwhile, the replacement of the arginine by a glycine in β1 LE6 results in a loss of 3 hydrogen bonds.