Supplementary Information for *"*The power of genetic diversity in genome-wide association studies of lipids*"*

Sarah Graham *et al.* for the Global Lipids Genetics Consortium 2021

Contents

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Africa America Diabetes Mellitus

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List of Supplementary Tables

Supplementary Table 2: Lambda GC values by minor allele frequency for ancestry-specific meta-analysis with RAREMETAL

Common: MAF ≥ 5%, Low: 1% ≤ MAF < 5%, Rare: MAF < 1%

Ancestry	Trait	All	Common	Low	Rare
AdmAFR	HDL-C	1.02	1.11	1.02	0.98
AdmAFR	LDL-C	1.02	1.11	1.02	0.98
AdmAFR	TG	1.01	1.13	1.01	0.96
AdmAFR	nonHDL-C	1.02	1.04	1.03	1.00
AdmAFR	TC	1.02	1.13	1.02	0.97
EAS	HDL-C	1.06	1.16	1.05	1.01
EAS	LDL-C	1.05	1.11	1.06	1.01
EAS	TG	1.05	1.13	1.07	1.01
EAS	nonHDL-C	1.05	1.16	1.05	1.01
EAS	TC	1.06	1.16	1.07	1.01
EUR	HDL-C	1.14	2.08	1.36	1.03
EUR	LDL-C	1.13	1.45	1.19	1.07
EUR	TG	1.10	1.80	1.28	1.01
EUR	nonHDL-C	1.16	1.51	1.23	1.10
EUR	TC	1.12	1.61	1.25	1.06
HIS	HDL-C	1.03	1.08	1.02	1.02
HIS	LDL-C	1.02	1.05	1.02	1.01
HIS	TG	0.99	1.09	1.02	0.95
HIS	nonHDL-C	1.02	1.00	1.01	1.03
HIS	TC	1.02	1.07	1.01	1.00
SAS	HDL-C	1.04	1.08	1.04	1.01
SAS	LDL-C	1.03	1.06	1.04	1.01
SAS	TG	1.04	1.08	1.05	1.02
SAS	nonHDL-C	1.03	1.06	1.04	1.02
SAS	TC	1.04	1.07	1.04	1.02

Supplementary Table 4: Lambda GC values by minor allele frequency for trans-ancestry meta-analysis (as performed in MR-MEGA)

Common: MAF ≥ 5%, Low: 1% ≤ MAF < 5%, Rare: MAF < 1%

	All	Common	Low	Rare
HDL-C	1.14	1.32	1.13	1.06
LDL-C	1.10	1.19	1.09	1.05
logTG	1.13	1.30	1.11	1.04
nonHDL-C	1.09	1.16	1.07	1.05
TC	1.10	1.22	1.10	1.05

Supplementary Table 8: Genetic correlation results calculated from bivariate GREML analysis in UK Biobank and the Million Veteran Program

	UK Biobank (AdmAFR and EUR)		MVP (AFRAMR and EUR)	
Trait	rG	p-value	rG	p-value
HDL-C	0.844	0.259	0.671	1.17E-04
LDL-C	0.520	0.003	0.473	4.14E-06
TG	0.596	0.022	0.685	4.80E-04
nonHDL-C	0.590	0.016	NA	NA
TC	0.540	0.003	0.537	2.59E-06

Supplementary Table 13: Number of individuals by ancestry group included in the GWAS used to generate each set of PRS weights

Score	AdmAFR	EAS	EUR	HIS	SAS	Total
SAS	0	0	0	0	33,658	33,658
HIS	0	0	0	46,040	0	46,040
EAS	0	82,587	0	0	0	82,587
AdmAFR	87,760	0	0	0	0	87,760
EUR_2010	0	0	95,454	0	0	95,454
EUR (100K)	0	0	99,952	0	0	99,952
EUR_2010_AdmAFR	87,760	0	95,454	0	0	183,214
EUR (200K)	0	0	200,026	0	0	200,026
EUR_2010_nonEUR	87,760	82,587	95,454	46,040	40,473	352,314
EUR (400K)	0	0	400,016	0	0	400,016
EUR	0	0	831,666	0	0	831,666
ALL	87,760	82,587	831,666	46,040	40,473	1,088,526
AdmAFR (MVP only)	62,033	0	0	0	0	62,033
ALL (100K, 20% each ancestry)	20,779	19,813	21,802	20,323	20,441	103,158
EUR (50K) + AdmAFR (MVP only)	62,033	0	50,754	0	0	112,787
ALL (100K, original proportions)	8,052	8,291	76,575	3,899	3,668	100,485

Supplementary Table 21: Correlation of trans-ancestry polygenic score with principal components in 1KGP3 individuals

PC	Pearson_R	Pvalue
1	-0.676	0
2	-0.009	0.670281
3	-0.080	6.59E-05
4	-0.003	0.900171
5	-0.049	0.014626
6	-0.033	0.100402
7	-0.059	0.003025
8	-0.003	0.893794
9	-0.017	0.388338
10	-0.045	0.025012
11	-0.008	0.694459
12	-0.009	0.652035
13	-0.023	0.240671
14	0.038	0.056858
15	-0.030	0.133212
16	-0.007	0.724553
17	0.005	0.810559
18	0.031	0.119962
19	0.013	0.504673
20	0.000	0.990678

Supplementary Table 22: Correlation of mean LDL-C value with PCs in European and African American MGI participants

	African American		European	
PC	Pearson_R	Pvalue	Pearson_R	Pvalue
1	-0.012	0.662	0.004	0.631
2	-0.013	0.628	-0.011	0.143
3	0.003	0.912	-0.004	0.589
4	-0.013	0.641	-0.012	0.103
5	-0.015	0.593	0.012	0.114
6	-0.010	0.708	-0.010	0.184
7	-0.005	0.859	-0.008	0.300
8	-0.005	0.862	-0.009	0.261
9	-0.014	0.601	0.009	0.214
10	-0.006	0.819	0.006	0.466
11	0.011	0.696	0.009	0.257
12	0.012	0.656	0.005	0.491
13	0.001	0.963	0.009	0.219
14	0.002	0.934	0.005	0.471
15	-0.006	0.837	-0.002	0.762
16	0.008	0.779	-0.001	0.895
17	-0.001	0.965	-0.009	0.251
18	-0.058	0.034	-0.005	0.519
19	-0.021	0.445	0.000	0.997
20	-0.013	0.645	0.004	0.580

Supplementary Table 23: Prediction of LDL-C in MGI individuals based on varying numbers of PCs included in the model

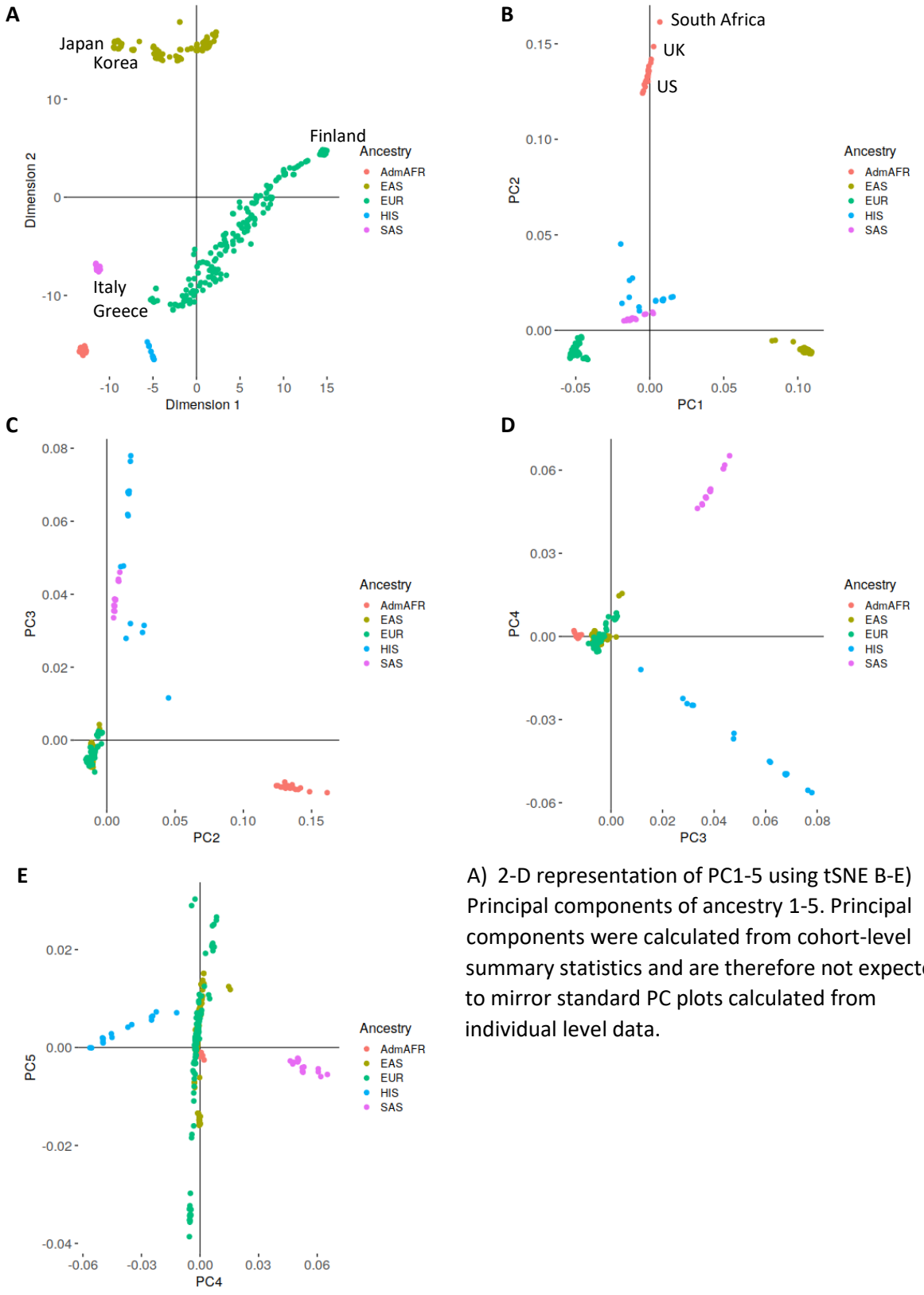
The polygenic score was normalized within each ancestry group separately

Model	adj_R2	Lower_95_CI	Upper_95_CI	Ancestry
gender+birth_year+BATCH	0.022	0.009	0.041	African American
gender+BATCH+birth_year+PC1-4	0.019	0.009	0.044	African American
gender+BATCH+birth_year+PC1-10	0.017	0.008	0.048	African American
gender+BATCH+birth_year+PC1-20	0.014	0.011	0.054	African American
gender+BATCH+birth_year+PC1-4+normalized trans-ancestry risk score	0.122	0.094	0.159	African American
gender+BATCH+birth_year+PC1-10+normalized trans-ancestry risk score	0.119	0.097	0.164	African American
gender+BATCH+birth_year+PC1-20+normalized trans-ancestry risk score	0.115	0.098	0.167	African American
normalized trans-ancestry risk score	0.092	0.065	0.124	African American
normalized AdmAFR risk score	0.084	0.060	0.114	African American
normalized EUR risk score	0.040	0.020	0.062	African American
gender+BATCH+birth_year+PC1-4+normalized AdmAFR risk score	0.115	0.089	0.155	African American
gender+BATCH+birth_year+PC1-10+normalized AdmAFR risk score	0.112	0.088	0.157	African American
gender+BATCH+birth_year+PC1-20+normalized AdmAFR risk score	0.108	0.092	0.159	African American
gender+BATCH+birth_year+PC1-4+normalized EUR risk score	0.062	0.044	0.095	African American
gender+BATCH+birth_year+PC1-10+normalized EUR risk score	0.059	0.044	0.099	African American
gender+BATCH+birth_year+PC1-20+normalized EUR risk score	0.055	0.046	0.099	African American
gender+birth_year+BATCH	0.013	0.010	0.017	European
gender+BATCH+birth_year+PC1-4	0.014	0.011	0.018	European
gender+BATCH+birth_year+PC1-10	0.014	0.011	0.018	European
gender+BATCH+birth_year+PC1-20	0.013	0.011	0.018	European
gender+BATCH+birth_year+PC1-4+normalized trans-ancestry risk score	0.130	0.122	0.140	European
gender+BATCH+birth_year+PC1-10+normalized trans-ancestry risk score	0.130	0.121	0.141	European
gender+BATCH+birth_year+PC1-20+normalized trans-ancestry risk score	0.130	0.121	0.140	European
normalized trans-ancestry risk score	0.117	0.109	0.127	European
normalized AdmAFR risk score	0.060	0.053	0.067	European
normalized EUR risk score	0.116	0.107	0.126	European

gender+BATCH+birth_year+PC1-4+normalized AdmAFR risk score	0.074	0.066	0.082	European
gender+BATCH+birth_year+PC1-10+normalized AdmAFR risk score	0.074	0.067	0.083	European
gender+BATCH+birth_year+PC1-20+normalized AdmAFR risk score	0.074	0.068	0.082	European
gender+BATCH+birth_year+PC1-4+normalized EUR risk score	0.129	0.120	0.140	European
gender+BATCH+birth_year+PC1-10+normalized EUR risk score	0.129	0.120	0.140	European
gender+BATCH+birth_year+PC1-20+normalized EUR risk score	0.129	0.121	0.140	European

List of Supplementary Figures

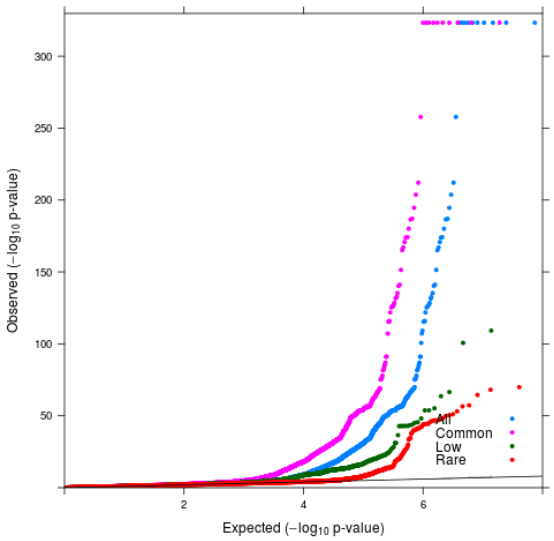
Supplementary Figure 1: Ancestral diversity of contributing cohorts



A) 2-D representation of PC1-5 using tSNE B-E) Principal components of ancestry 1-5. Principal components were calculated from cohort-level summary statistics and are therefore not expected to mirror standard PC plots calculated from individual level data.

Supplementary Figure 2: QQ Plots from each single-ancestry meta-analysis

AdmAFR HDL-C



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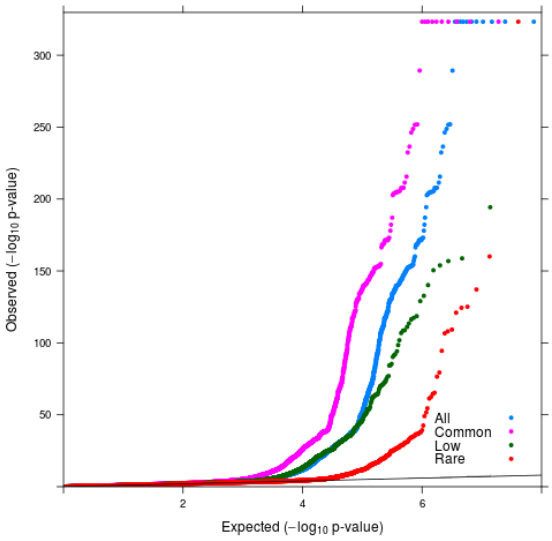

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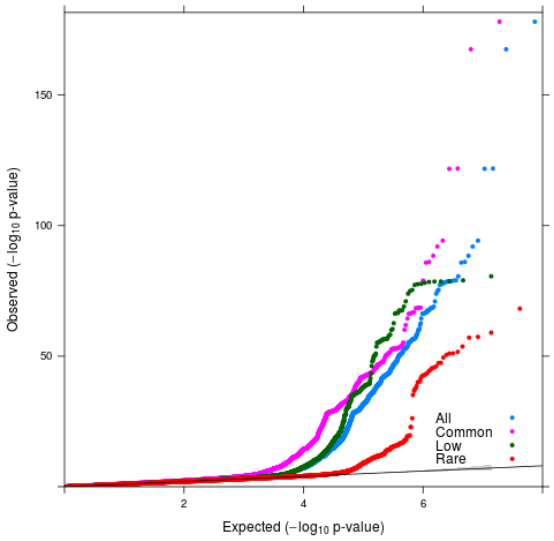
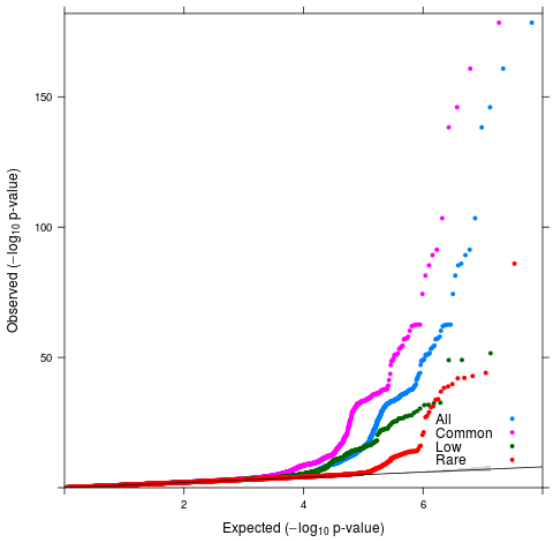
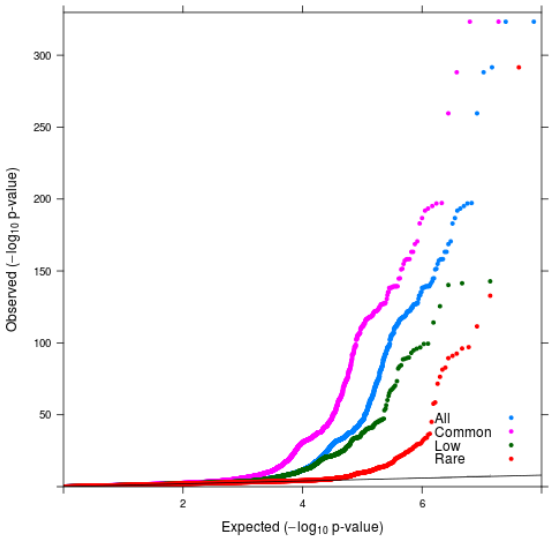


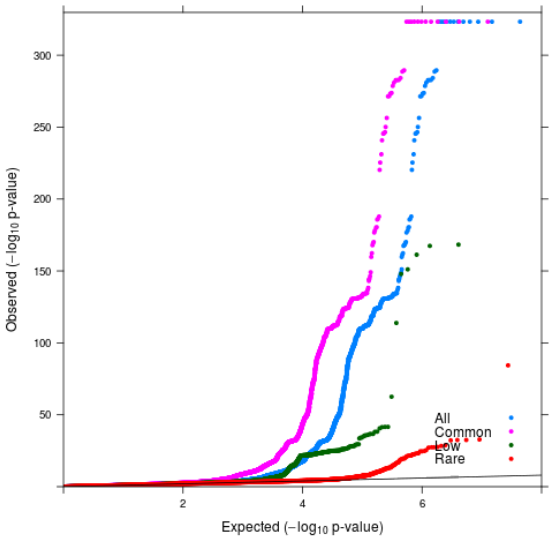
AdmAFR nonHDL-C



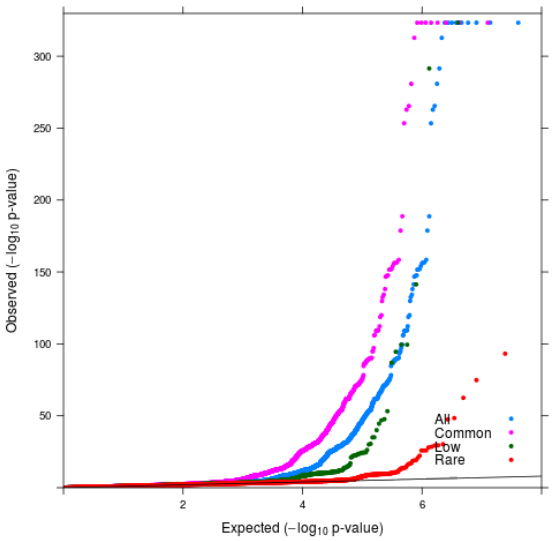
AdmAFR TC



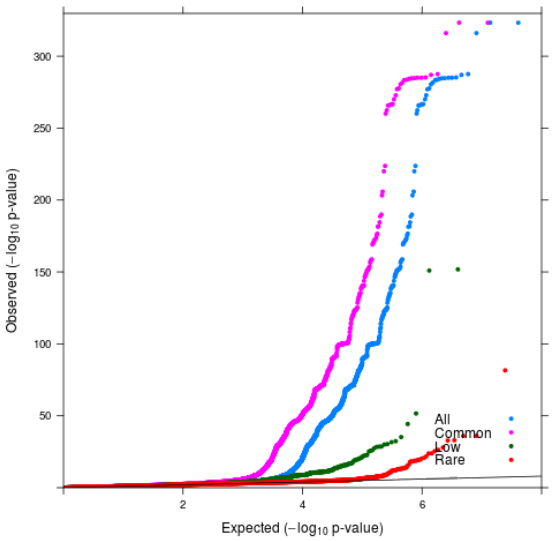
EAS HDL-C



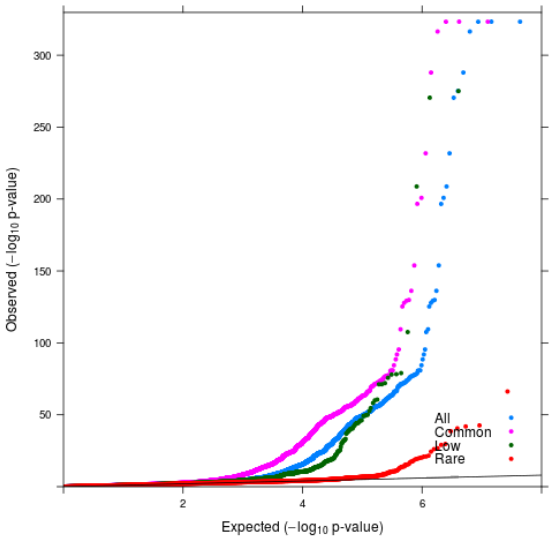
EAS LDL-C



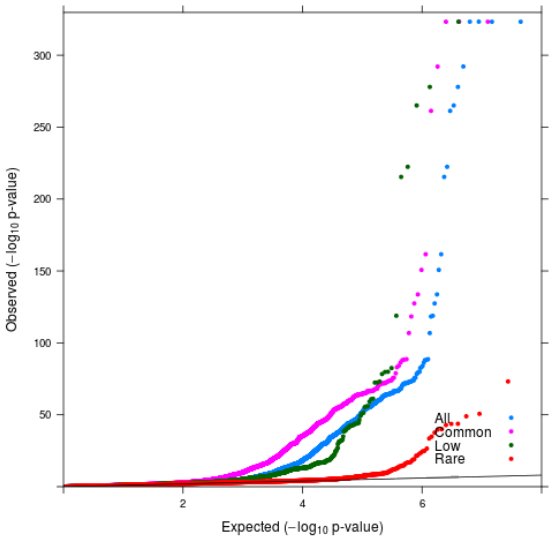
EAS TG



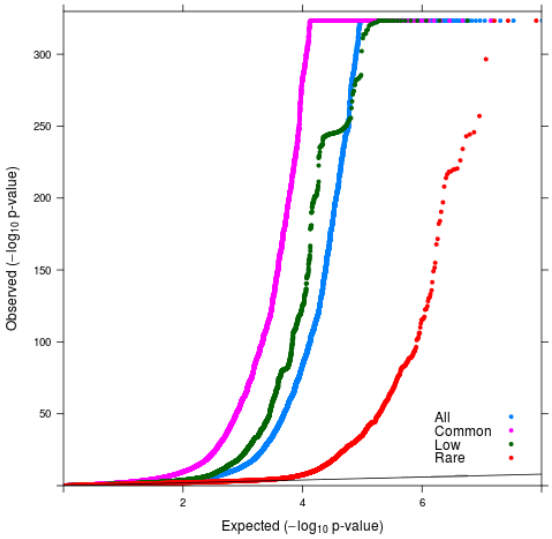
EAS nonHDL-C



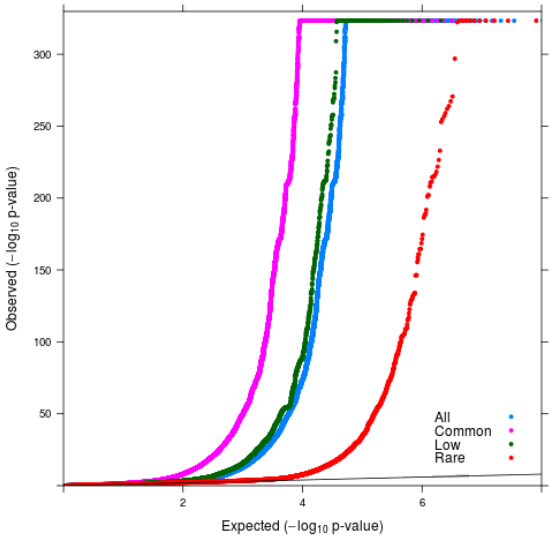
EAS TC



EUR HDL-C



EUR LDL-C



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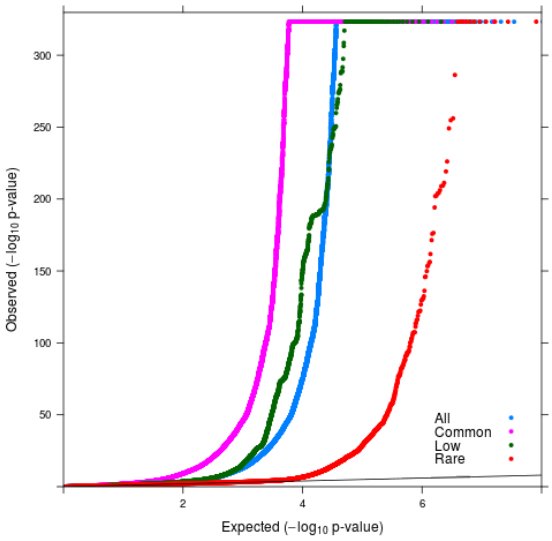

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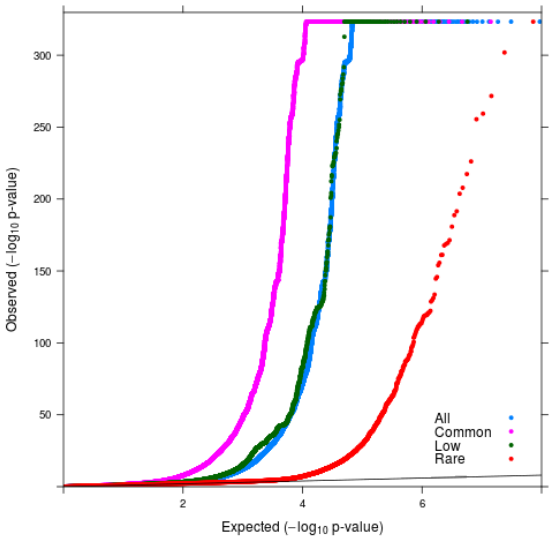

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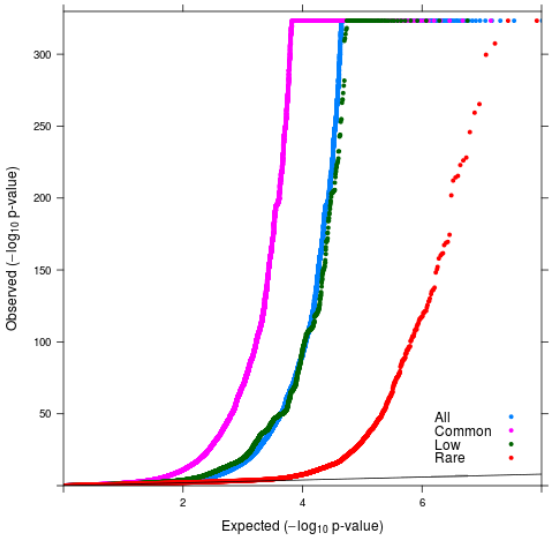
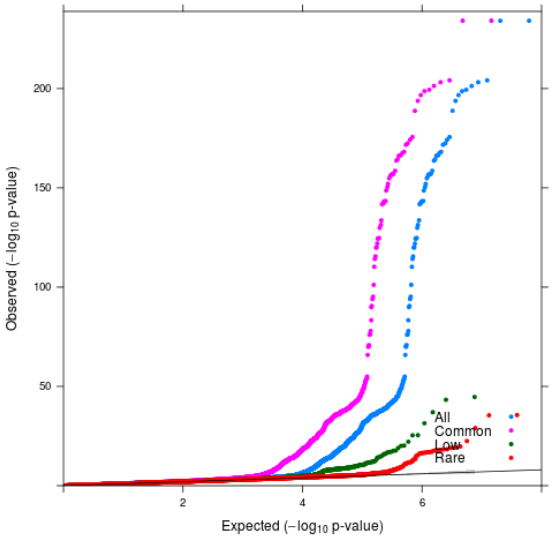


HIS HDL-C



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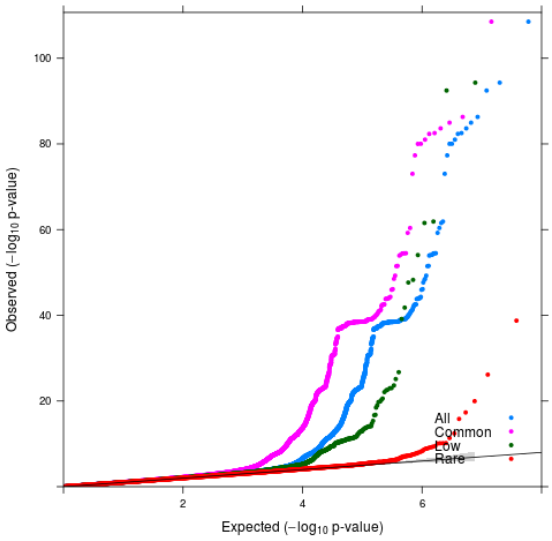

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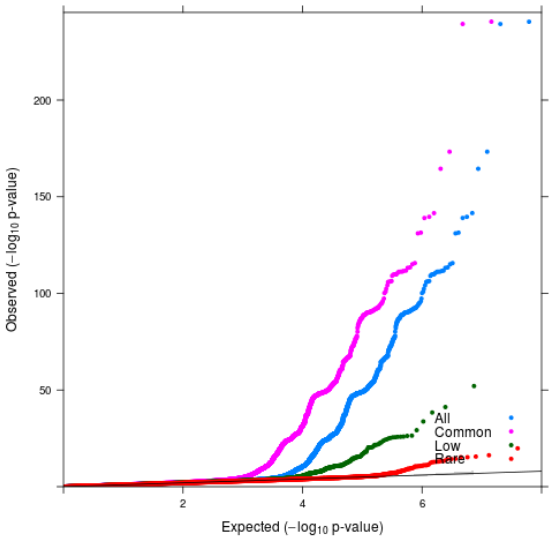

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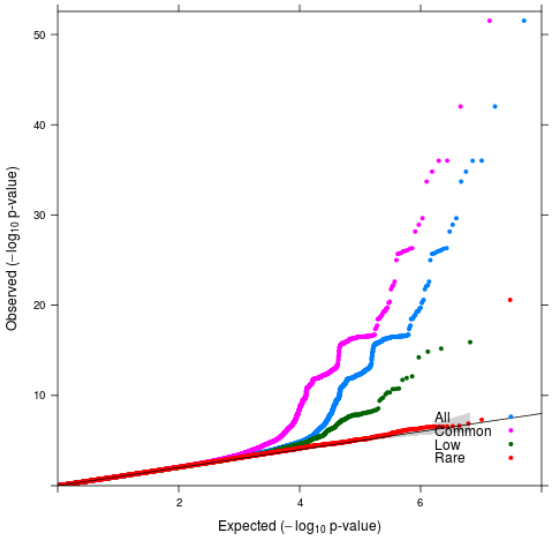

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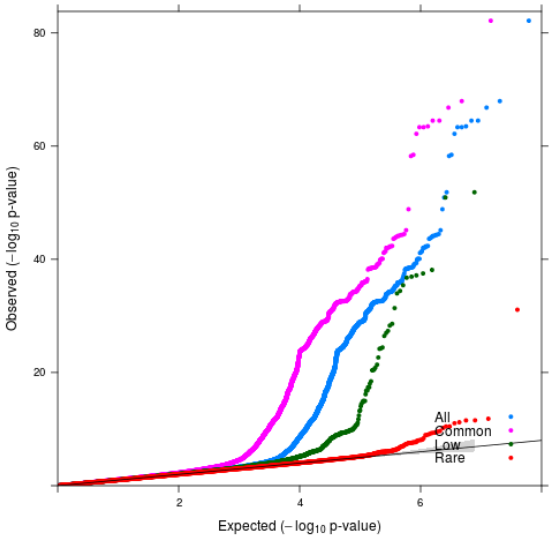
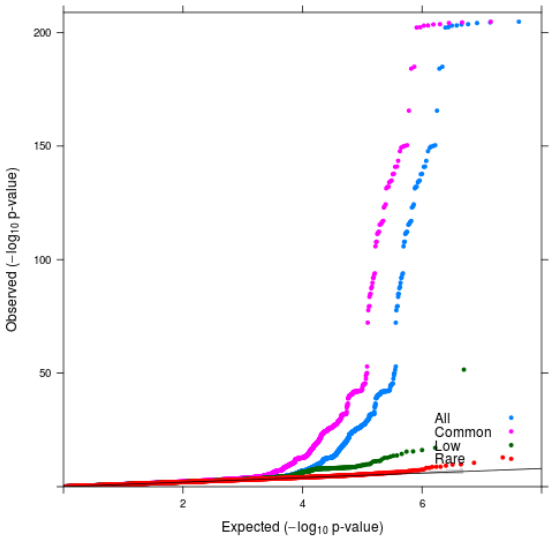


SAS HDL-C



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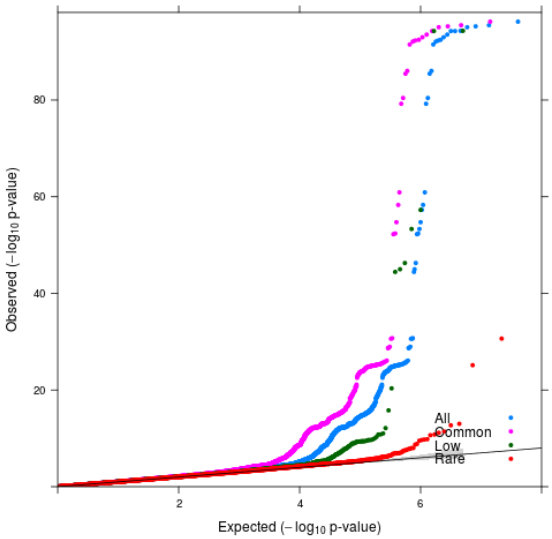

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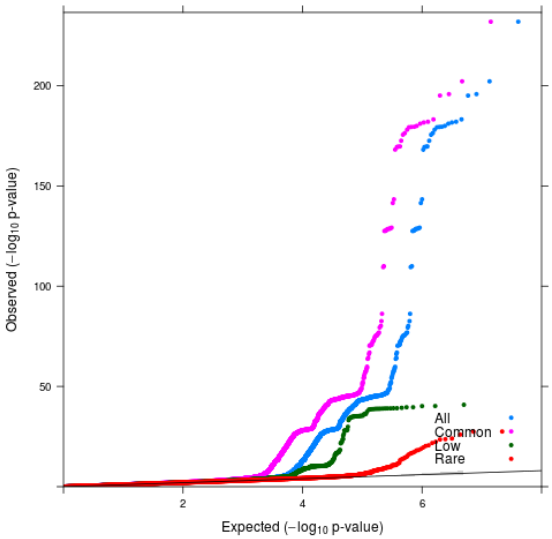
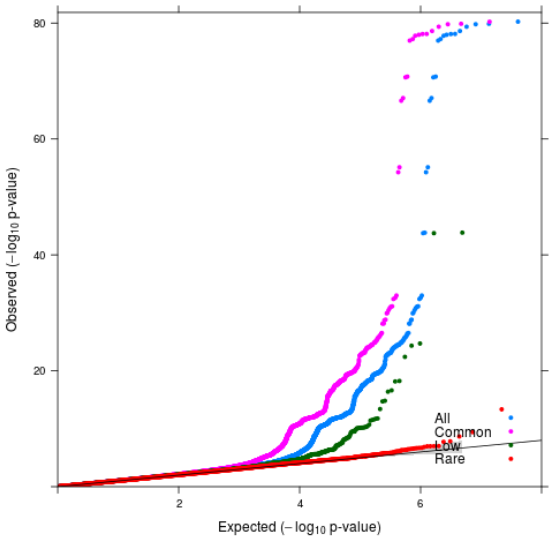
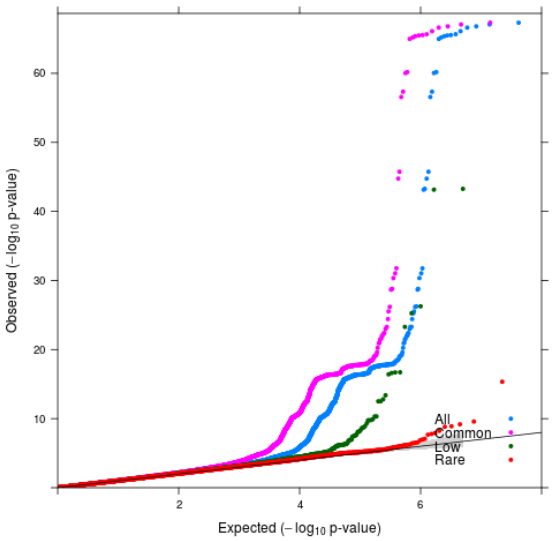


SAS nonHDL-C

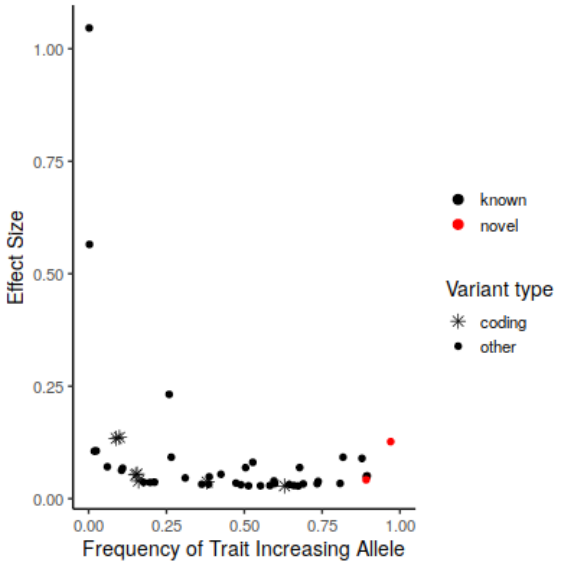


SAS TC

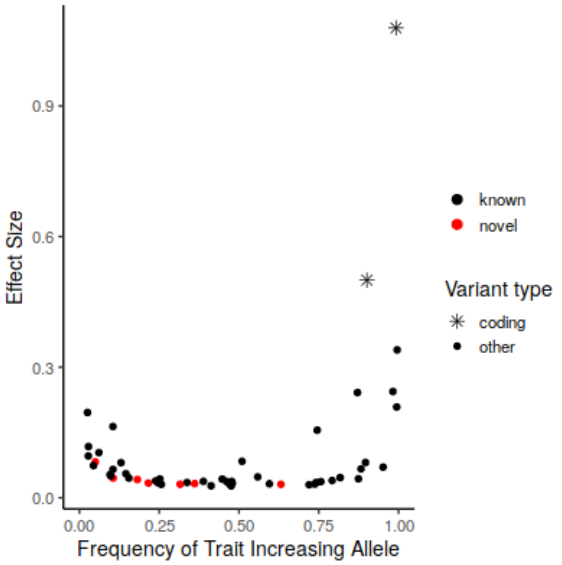

Observed (−log10 p-value)
Expected (−log10 p-value)
All
Common
Low
Rare

Supplementary Figure 3: Effect sizes and allele frequencies of identified index variants from ancestry-specific meta-analysis

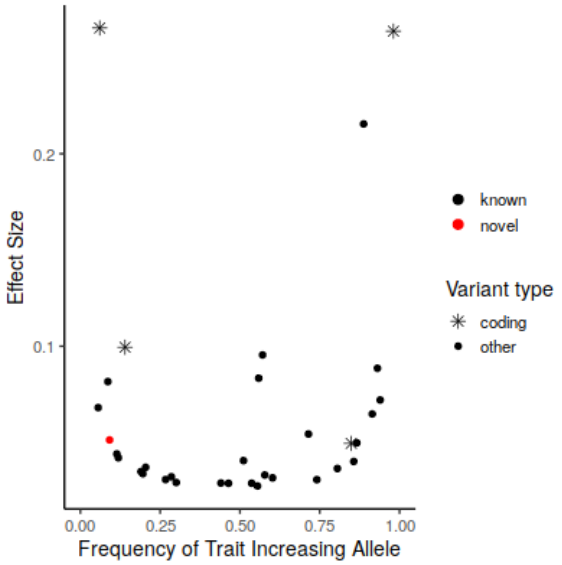
AdmAFR HDL-C



AdmAFR LDL-C



AdmAFR TG



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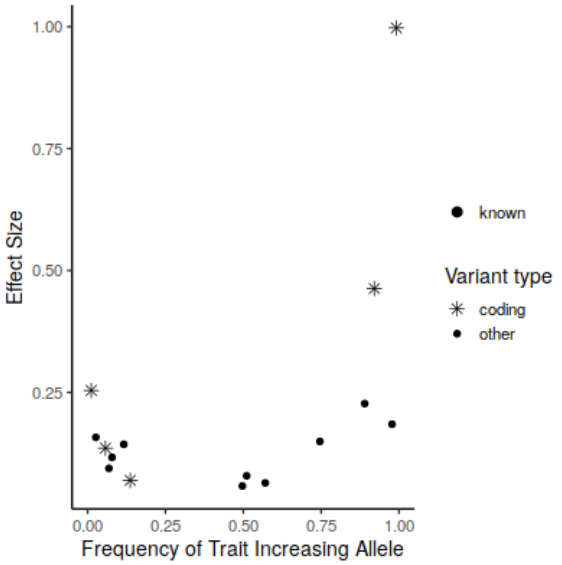
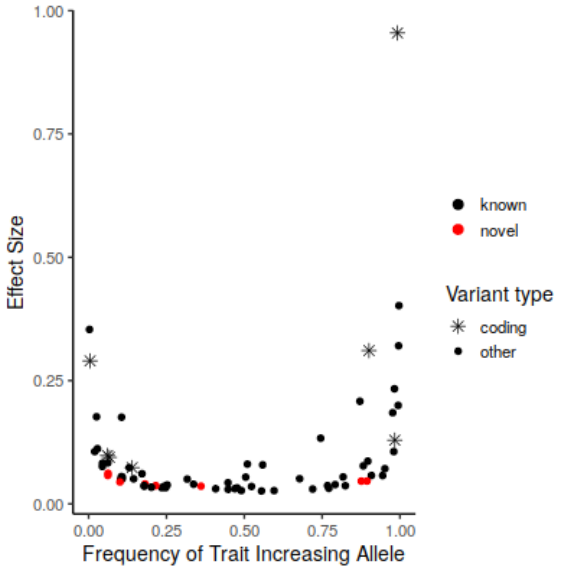
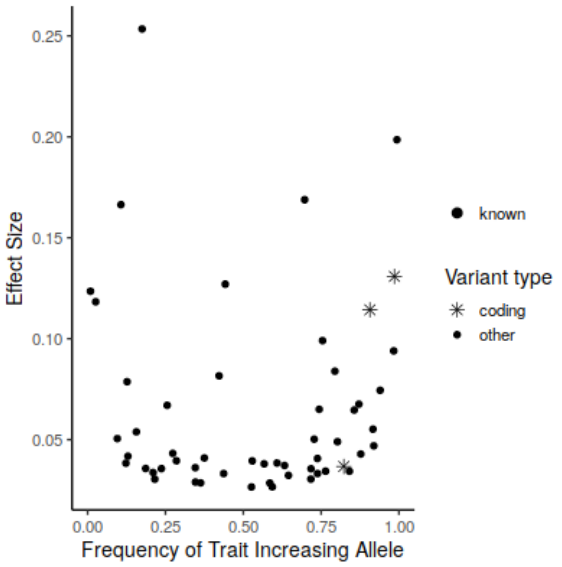


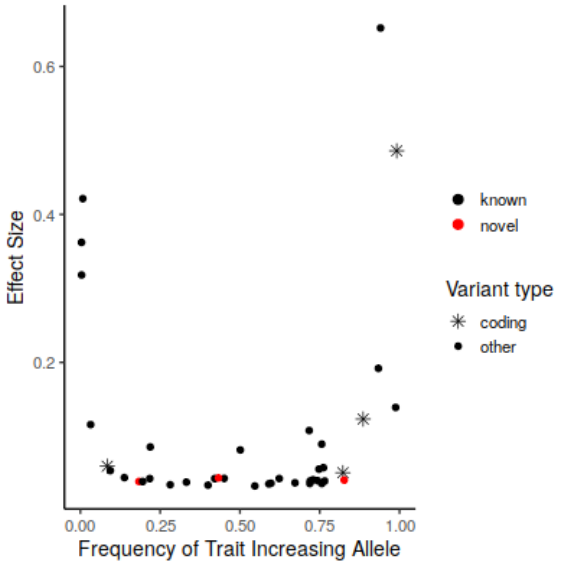
AdmAFR TC



EAS HDL-C



EAS LDL-C



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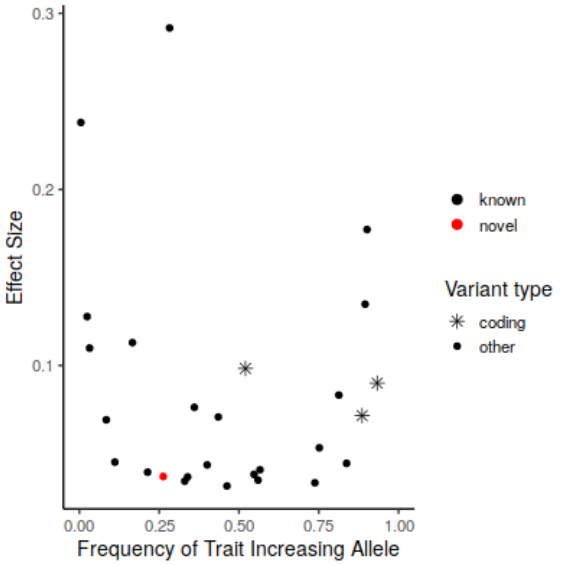

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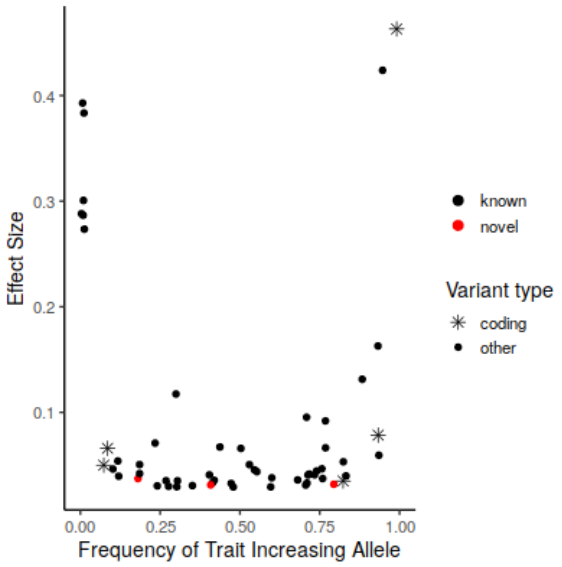

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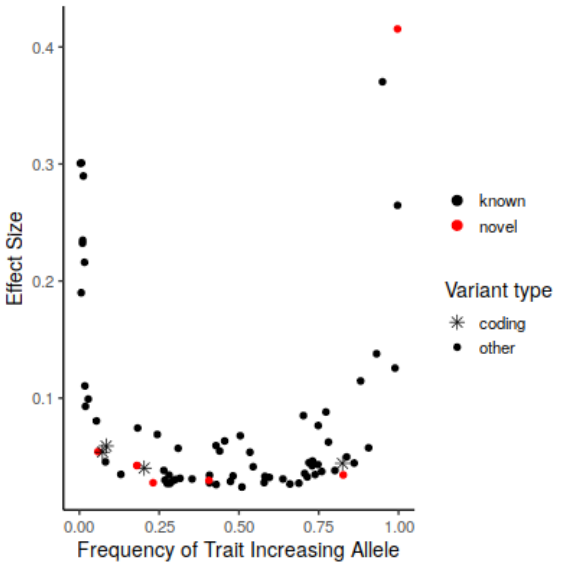
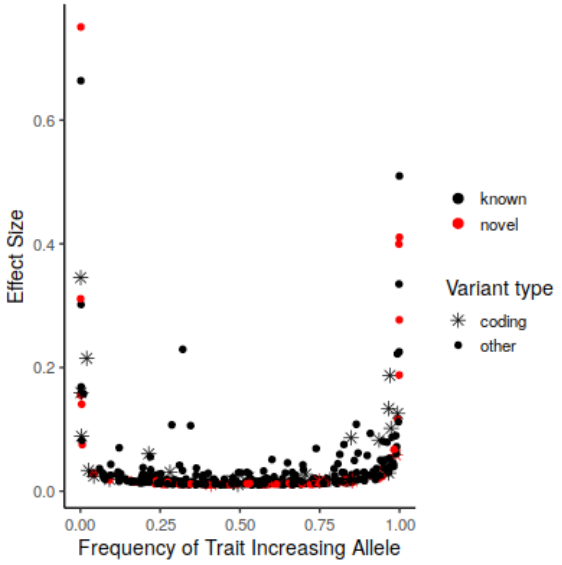
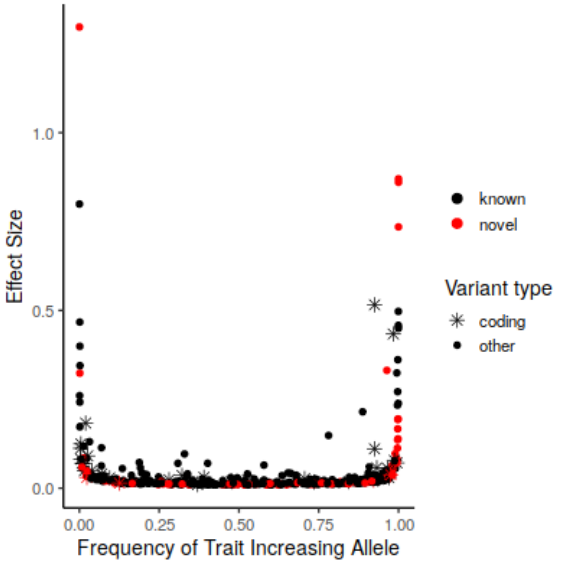


EUR HDL-C



EUR LDL-C



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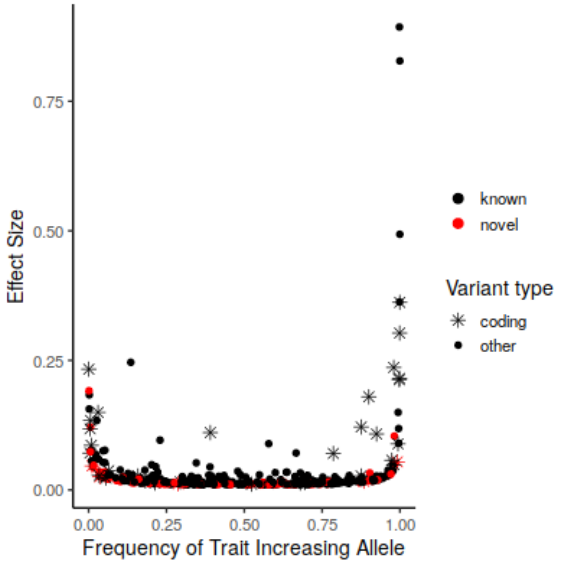
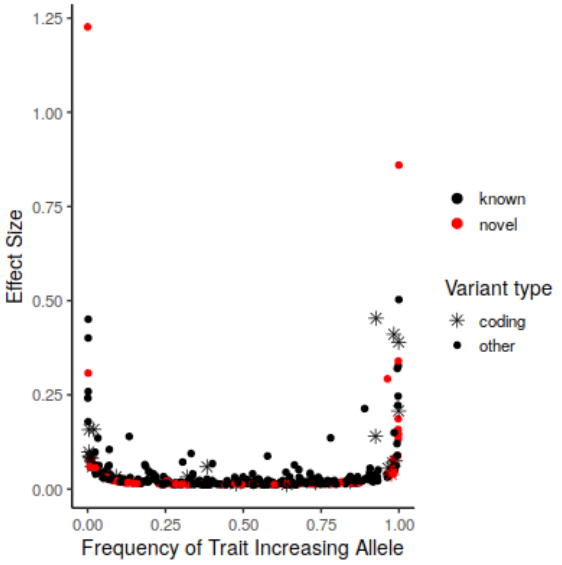
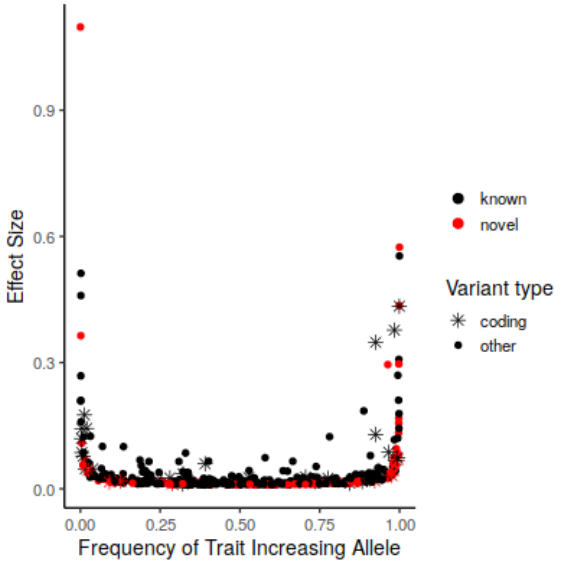


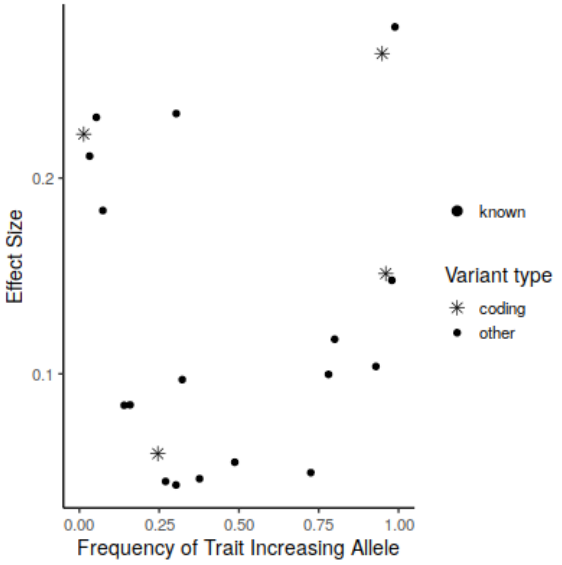
EUR nonHDL-C



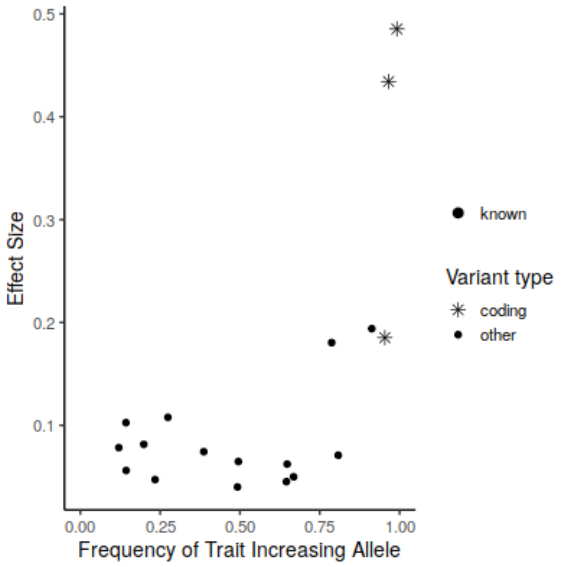
EUR TC



HIS HDL-C



HIS LDL-C



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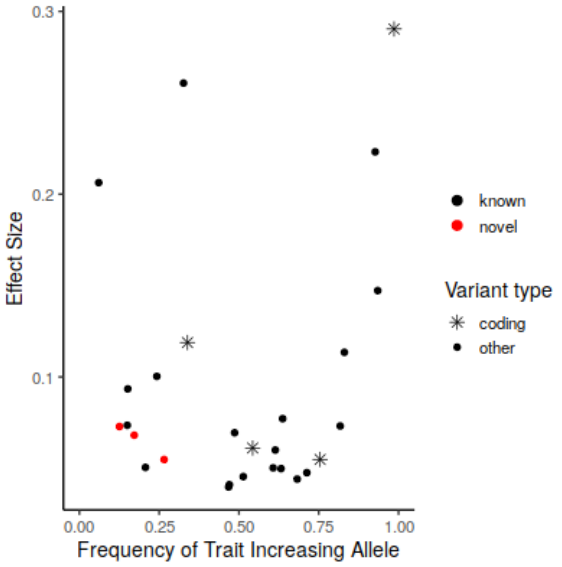

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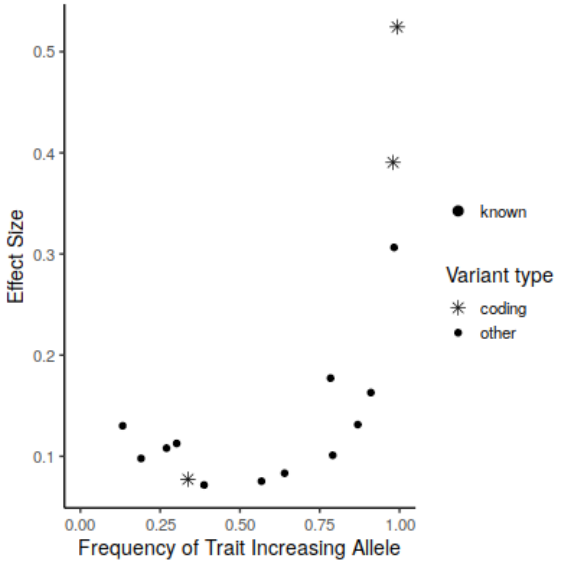

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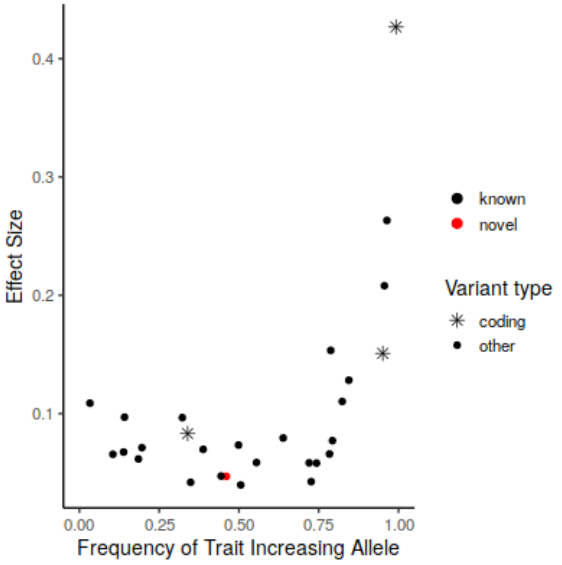
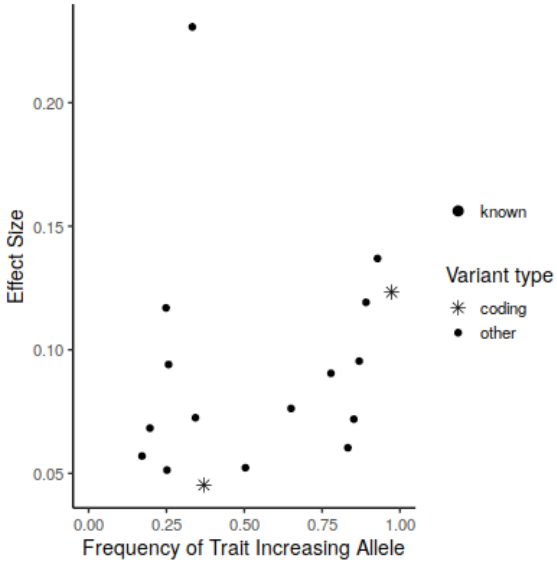
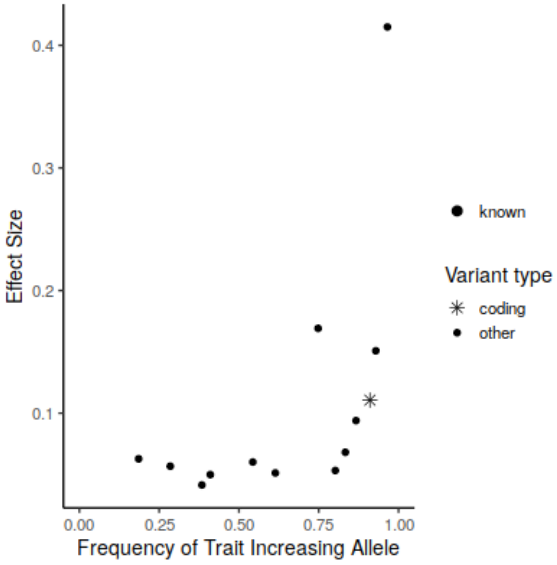


SAS HDL-C



SAS LDL-C



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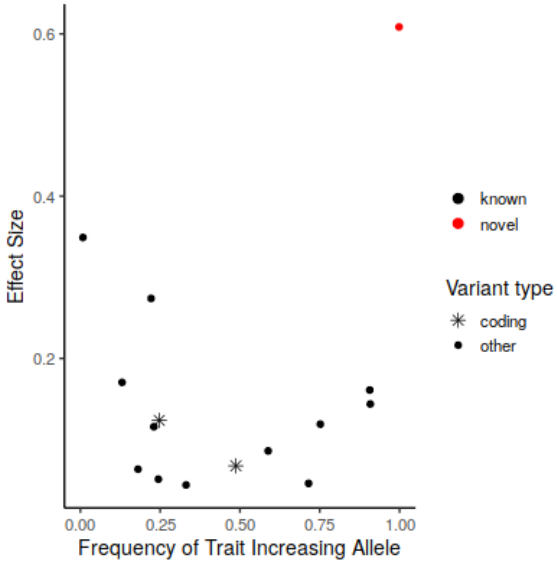
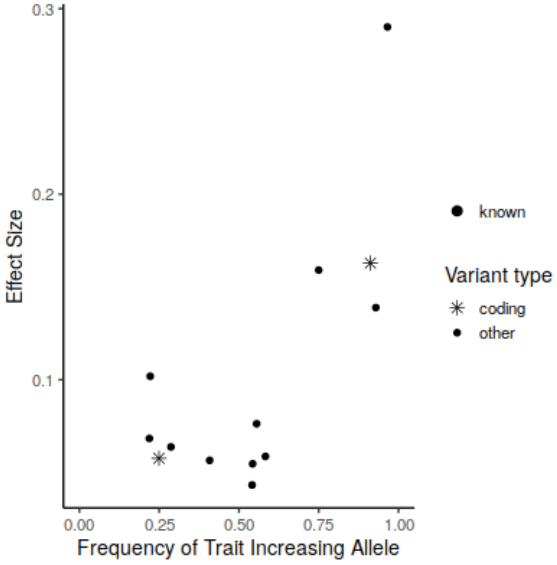


SAS nonHDL-C



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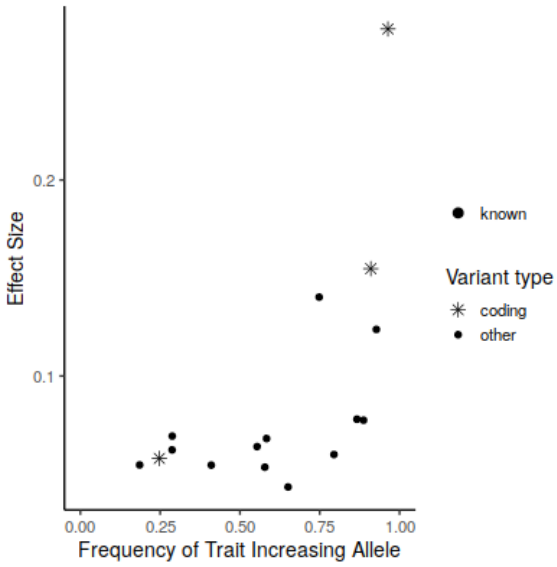
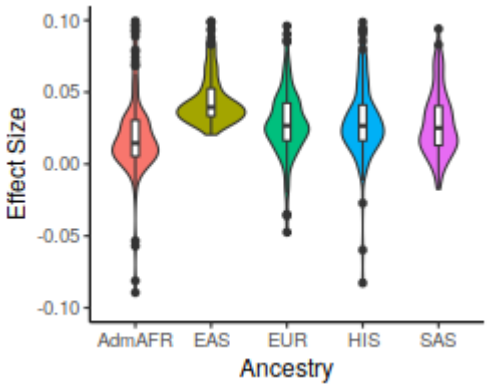
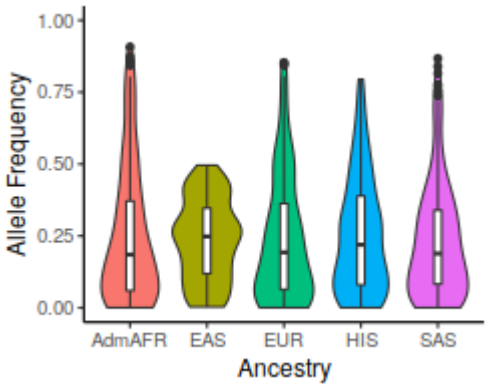


EAS index variants



EAS index variants



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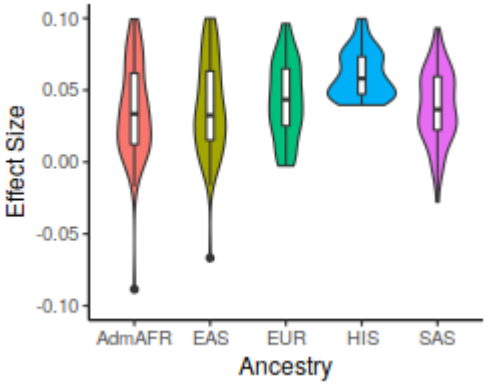
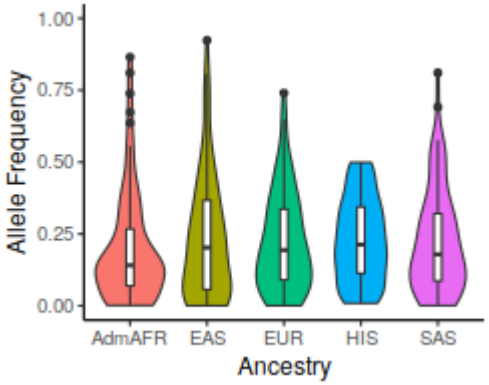


HIS index variants



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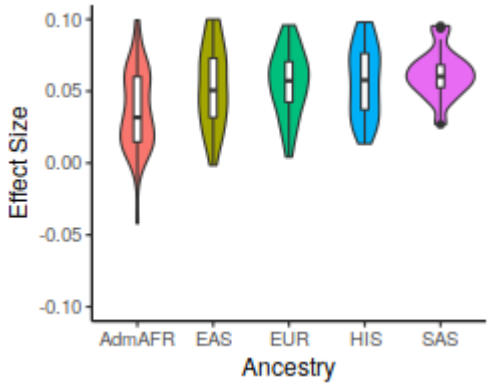

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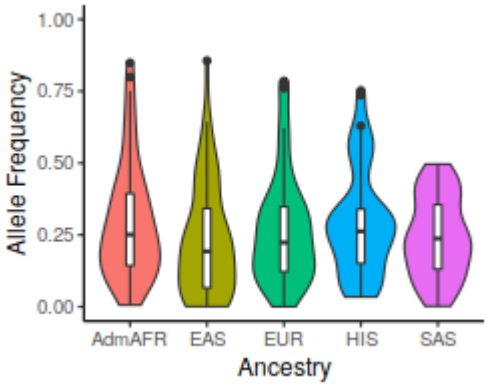
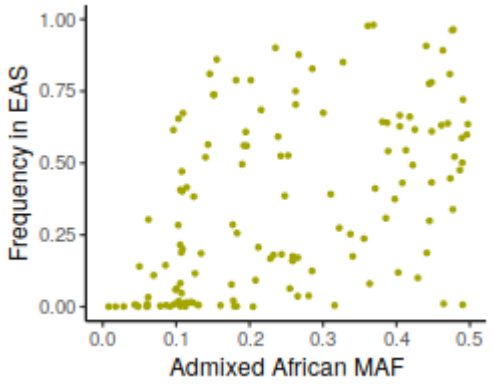
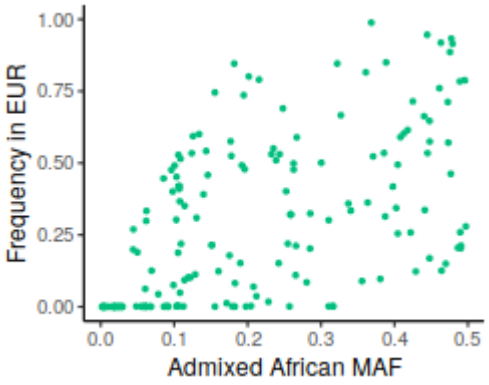


AdmAFR index variants



AdmAFR index variants



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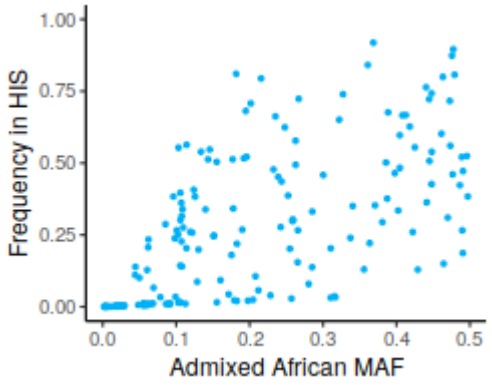
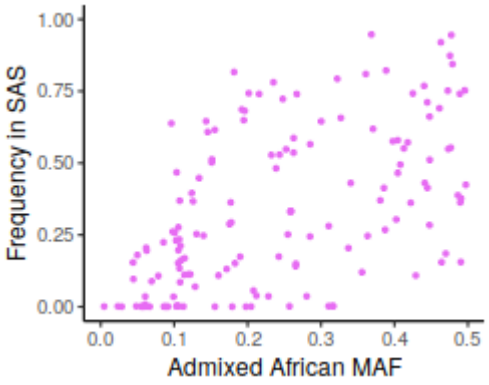
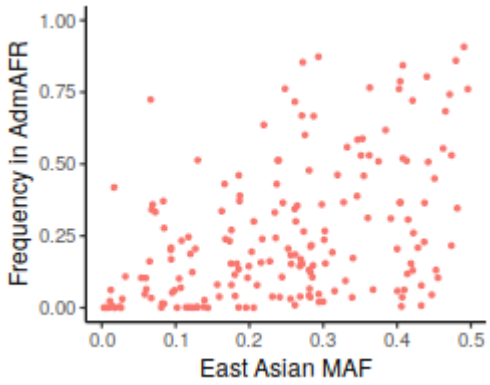


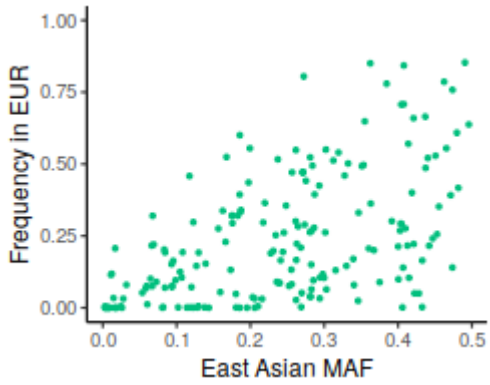
AdmAFR index variants



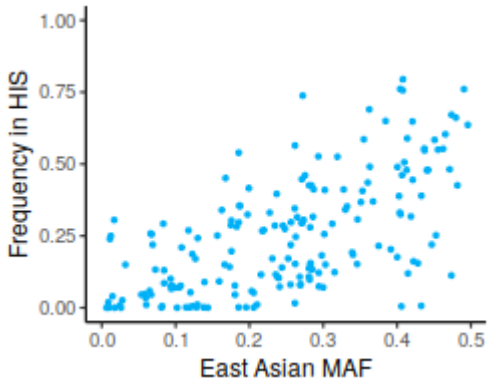
EAS index variants



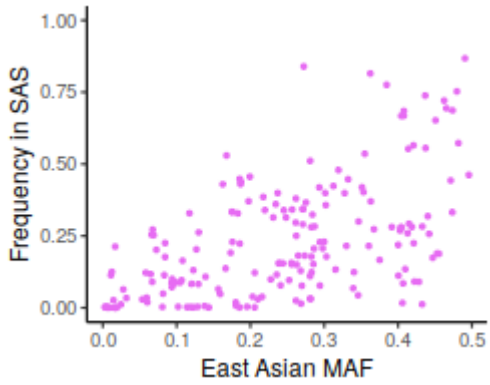
EAS index variants



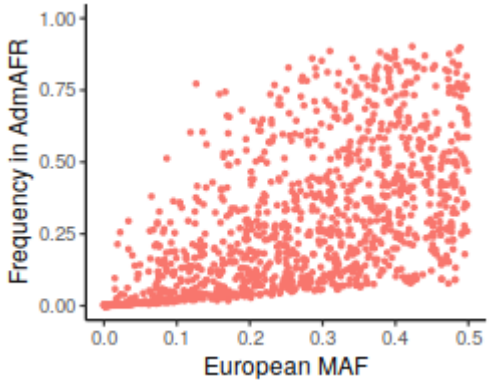
EAS index variants



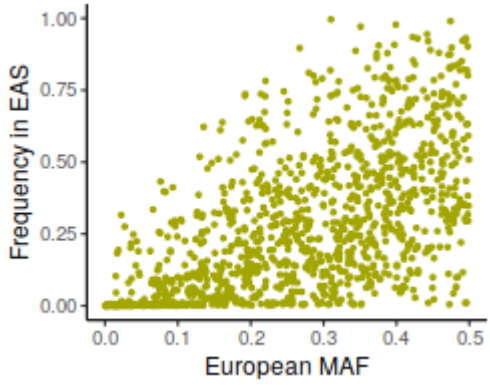
EAS index variants



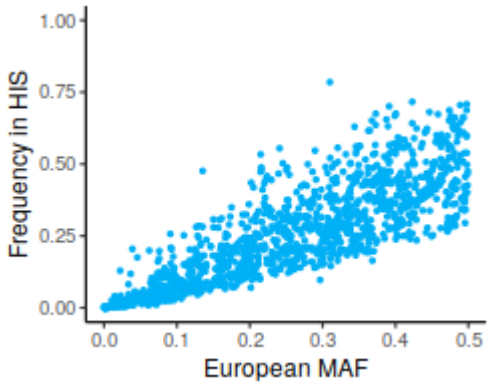
EUR index variants



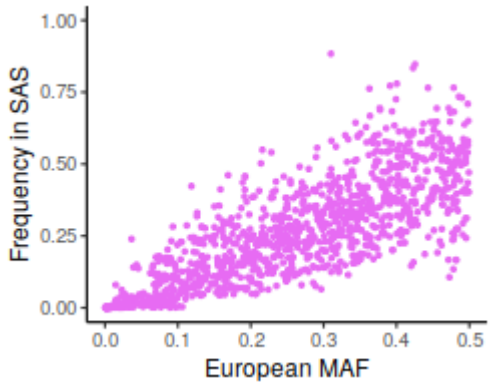
EUR index variants



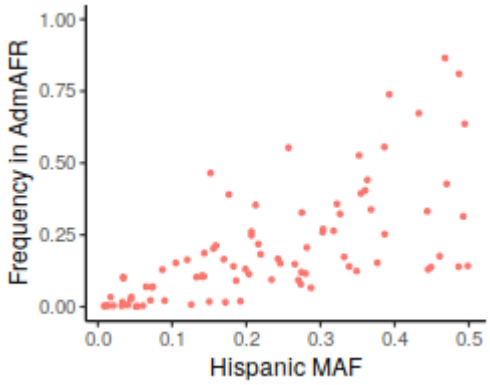
EUR index variants



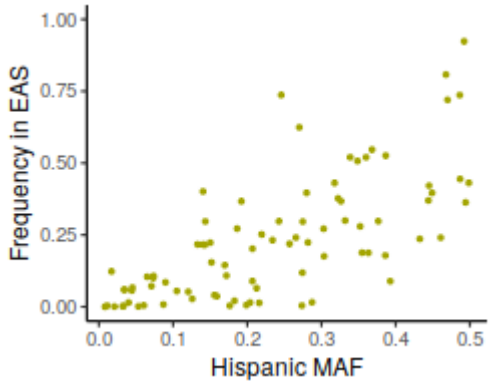
EUR index variants



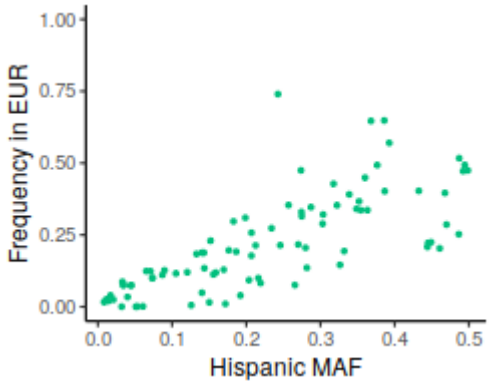
HIS index variants



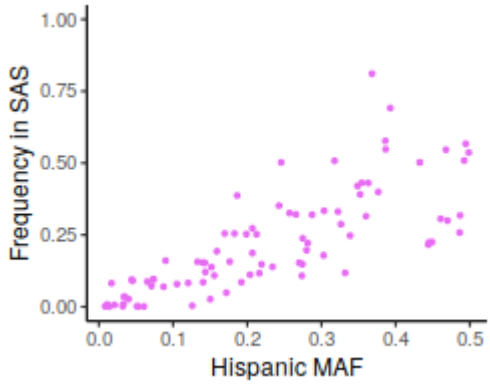
HIS index variants

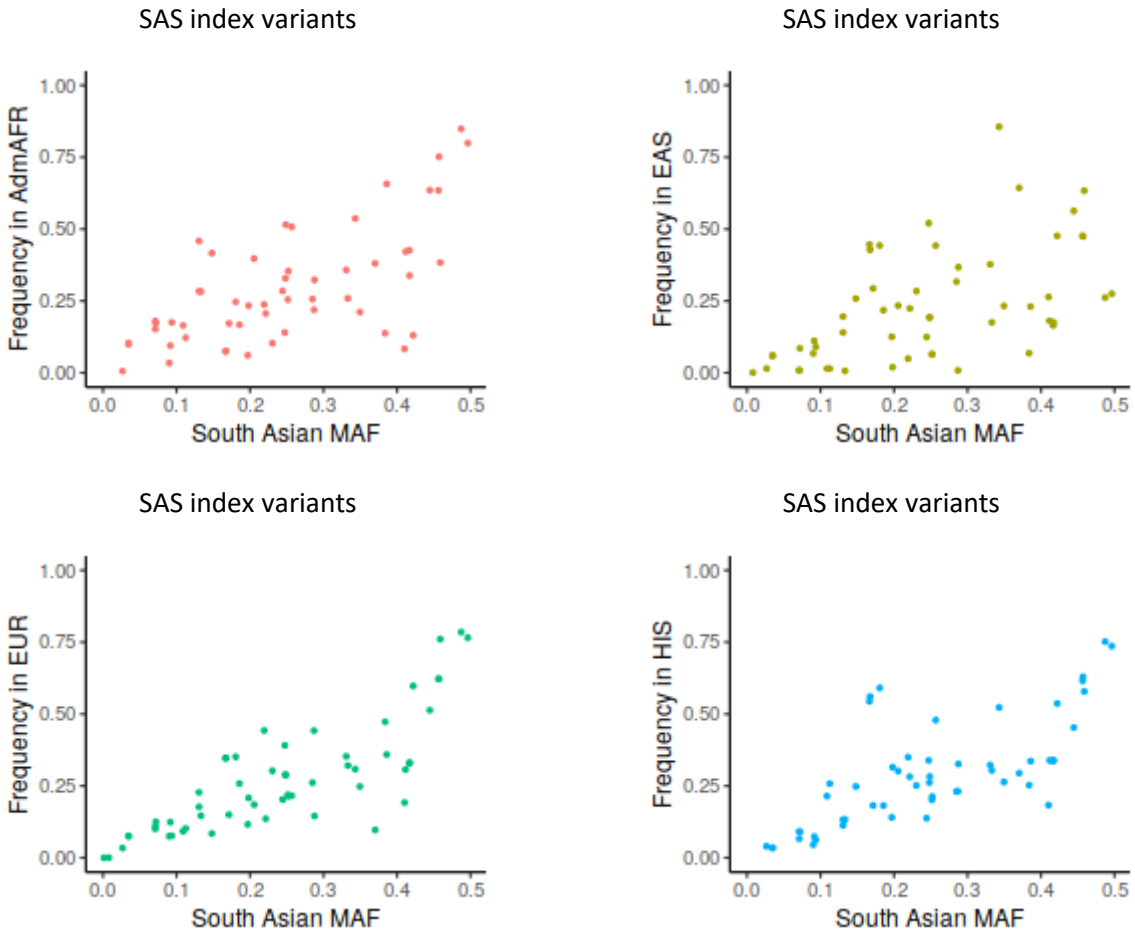


HIS index variants



HIS index variants

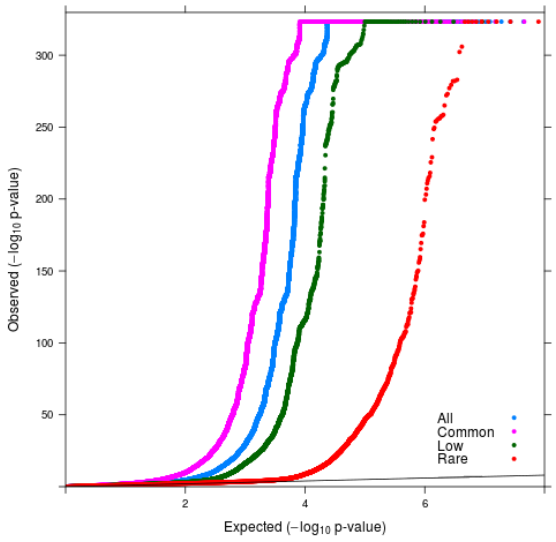




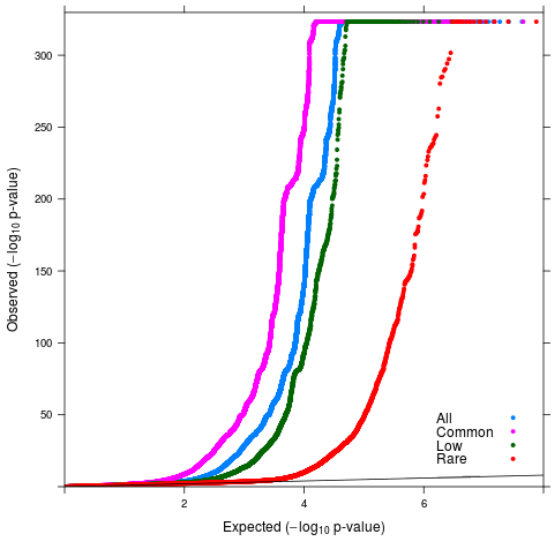
Sample sizes for each index variant are given in Supplementary Table 3 and for each ancestry overall in Table 1. Boxplots depict the median value as the center, first and third quartiles as box boundaries and whiskers extending 1.5 times the inter-quartile range, with points beyond this region shown individually.

Supplementary Figure 4: QQ plots from trans-ancestry meta-analysis

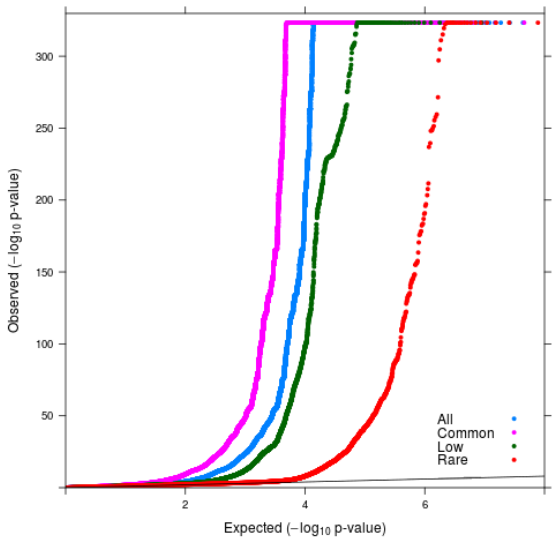
HDL-C



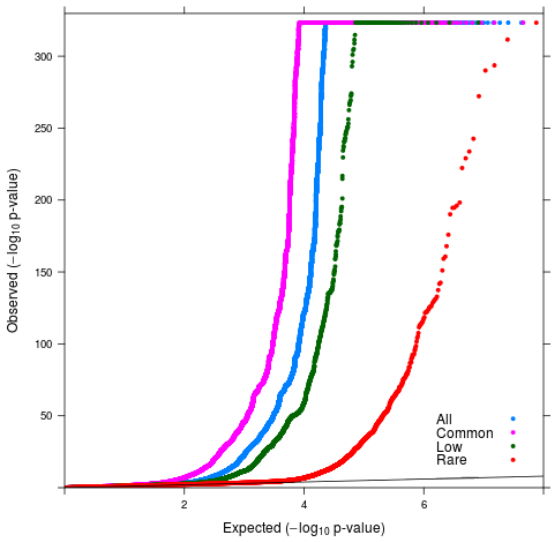
LDL-C



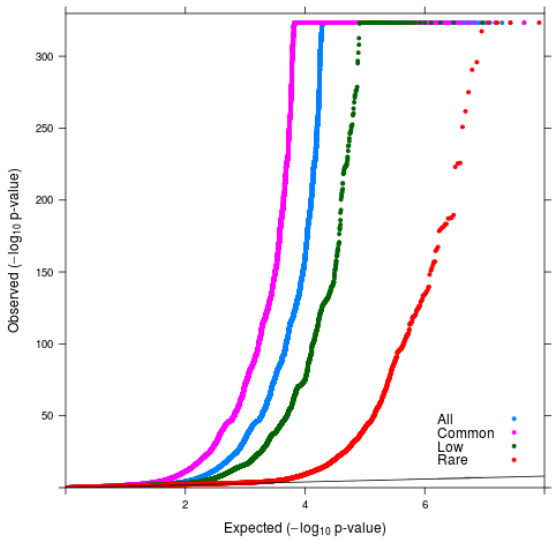
TG



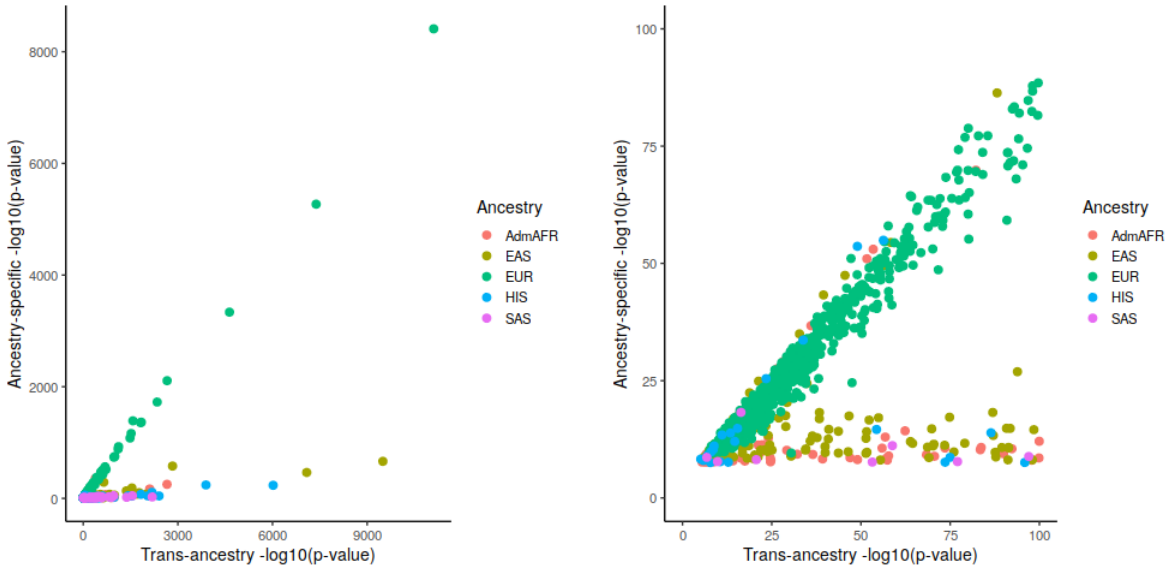
nonHDL-C



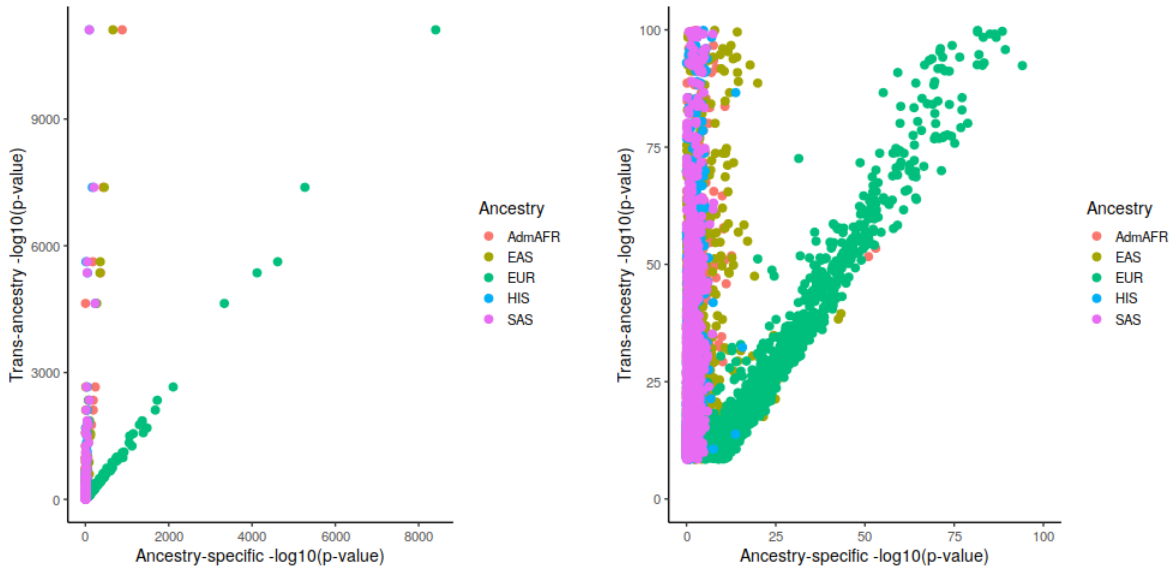
TC


Observed (−log10 p-value)
Expected (−log10 p-value)
All
Common
Low
Rare

Supplementary Figure 5: Comparison of association results for ancestry-specific and trans-ancestry analysis

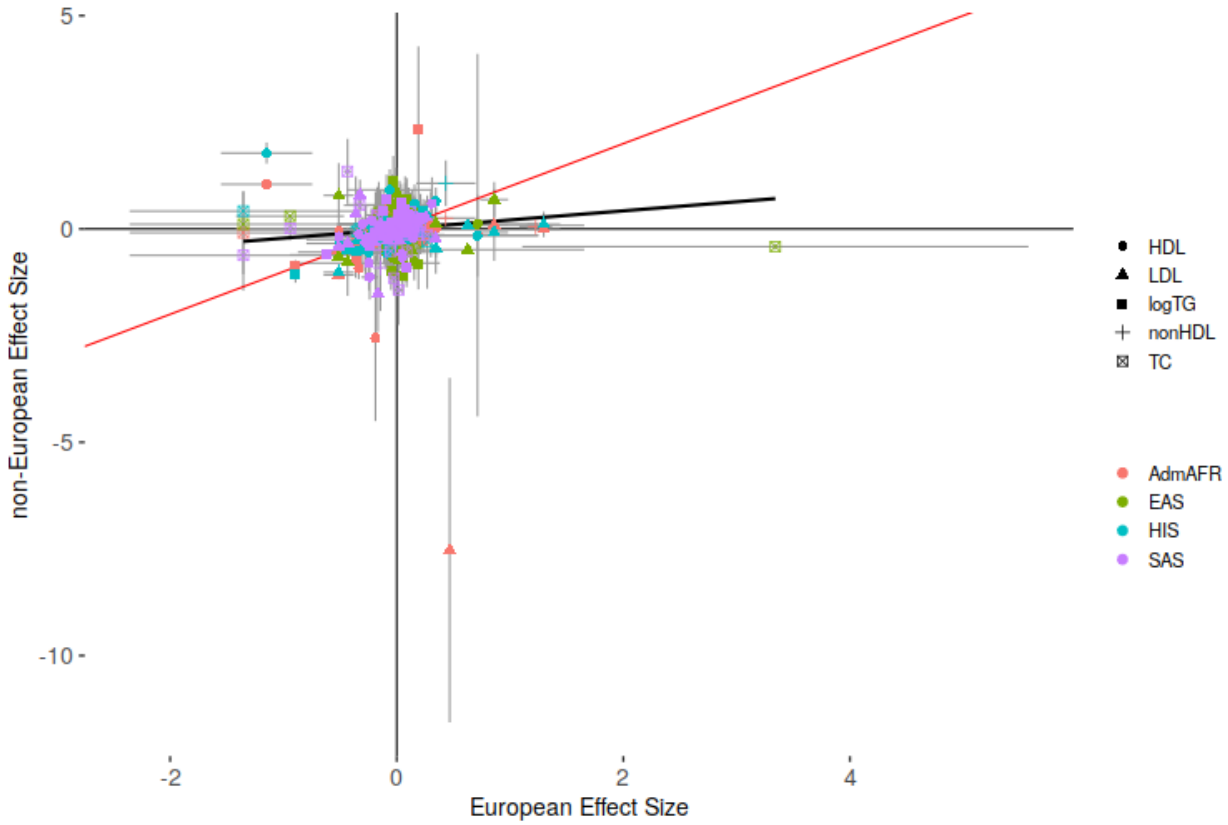


A) Trans-ancestry association results for variants identified in ancestry-specific analysis

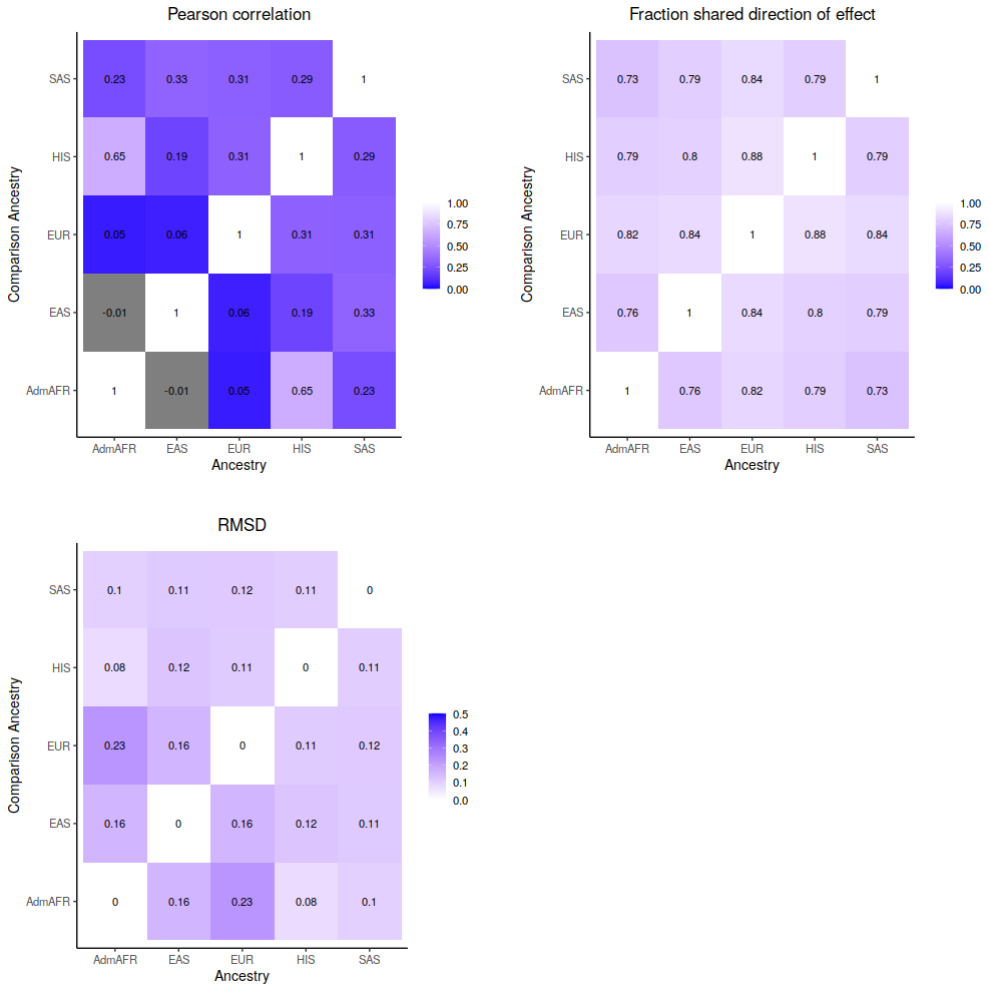


B) Ancestry-specific association results for variants identified in trans-ancestry analysis

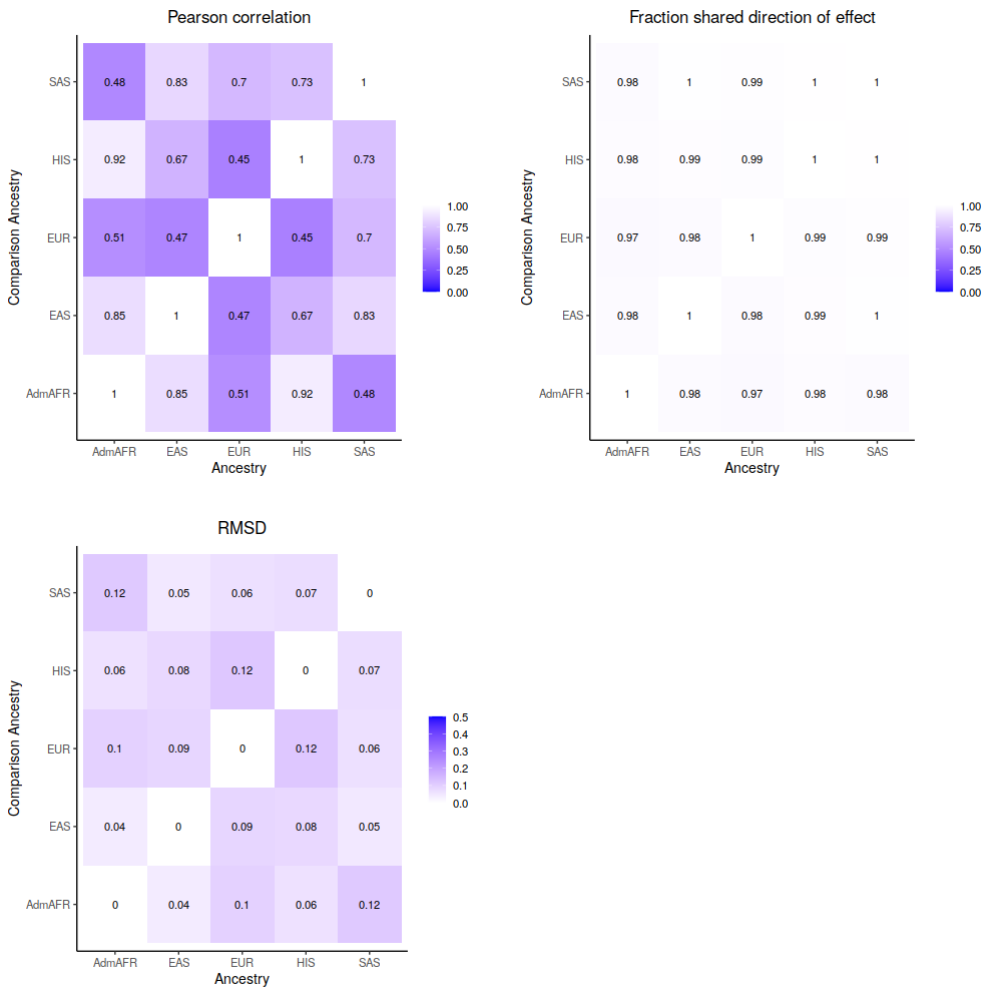
Supplementary Figure 6: Effect sizes by ancestry for unique index variants from ancestry-specific meta-analysis



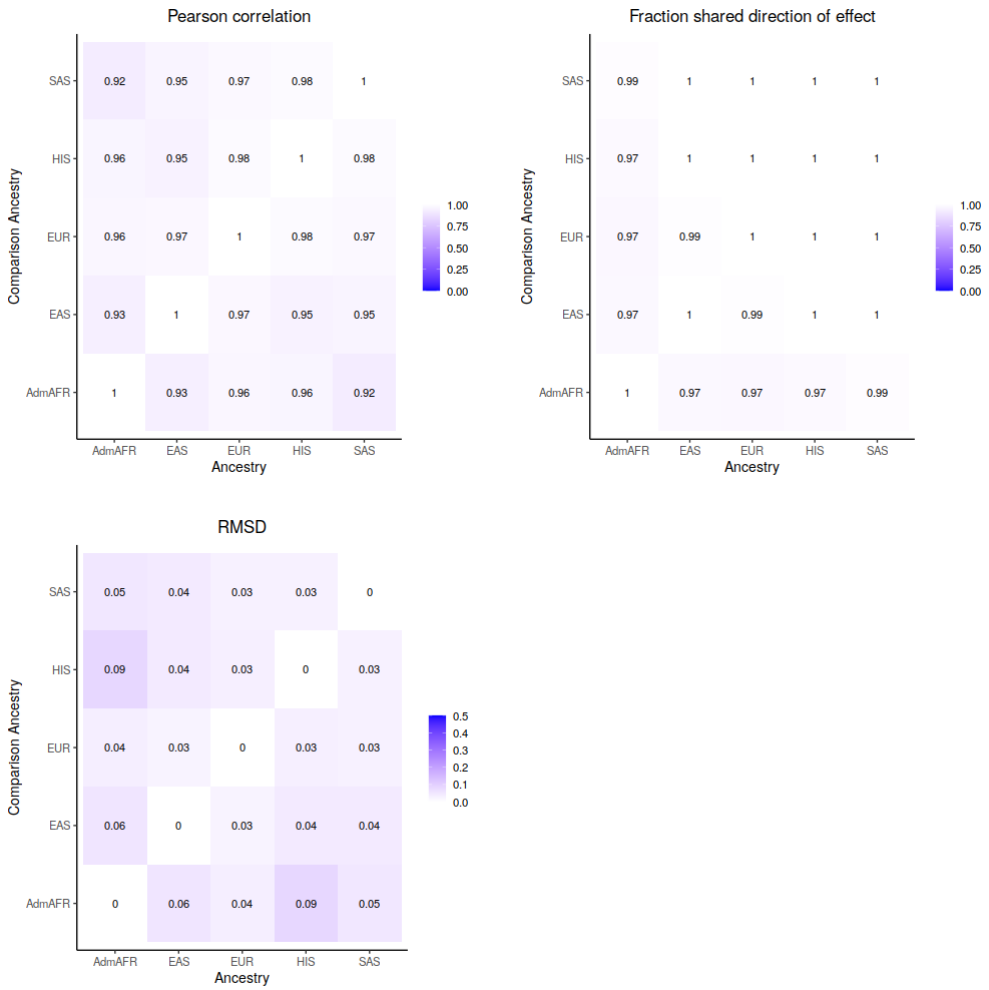
A) Comparison of effect sizes (with standard errors) for all variants, R^2=0.02. This plot includes all unique index variants (p-value < 5x10-8 in at least one ancestry as given by RAREMETAL) compared against the effect sizes in the other ancestries, without filtering of variants based on their significance in the compared ancestry group. Association results for all index variants are given in Supplementary Table 3. The corresponding effect size values are given in Supplementary Table 6. The European effect size = non-European effect size line is given in red while a linear regression line is given in black.



B) Pairwise correlation of effect sizes, fraction of shared direction of effect, and comparison of the magnitude of effect size differences (given as RMSD) between ancestries for all variants

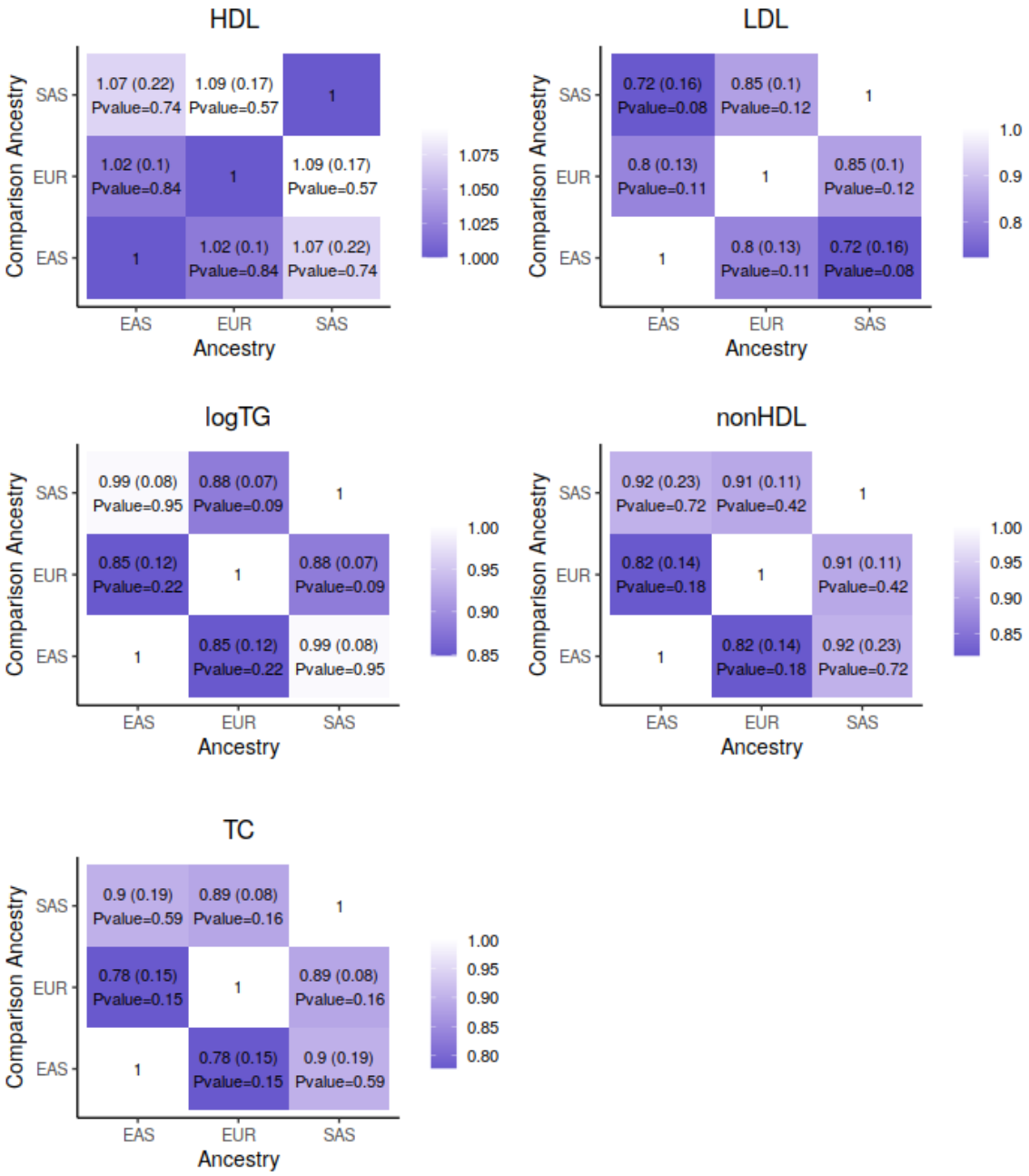


C) Pairwise correlation of effect sizes, fraction of shared direction of effect, and comparison of the magnitude of effect size differences between ancestries for variants reaching nominal significance (p-value < 0.05 as given by RAREMETAL) in both compared ancestries. Association results for all index variants are given in Supplementary Table 3.



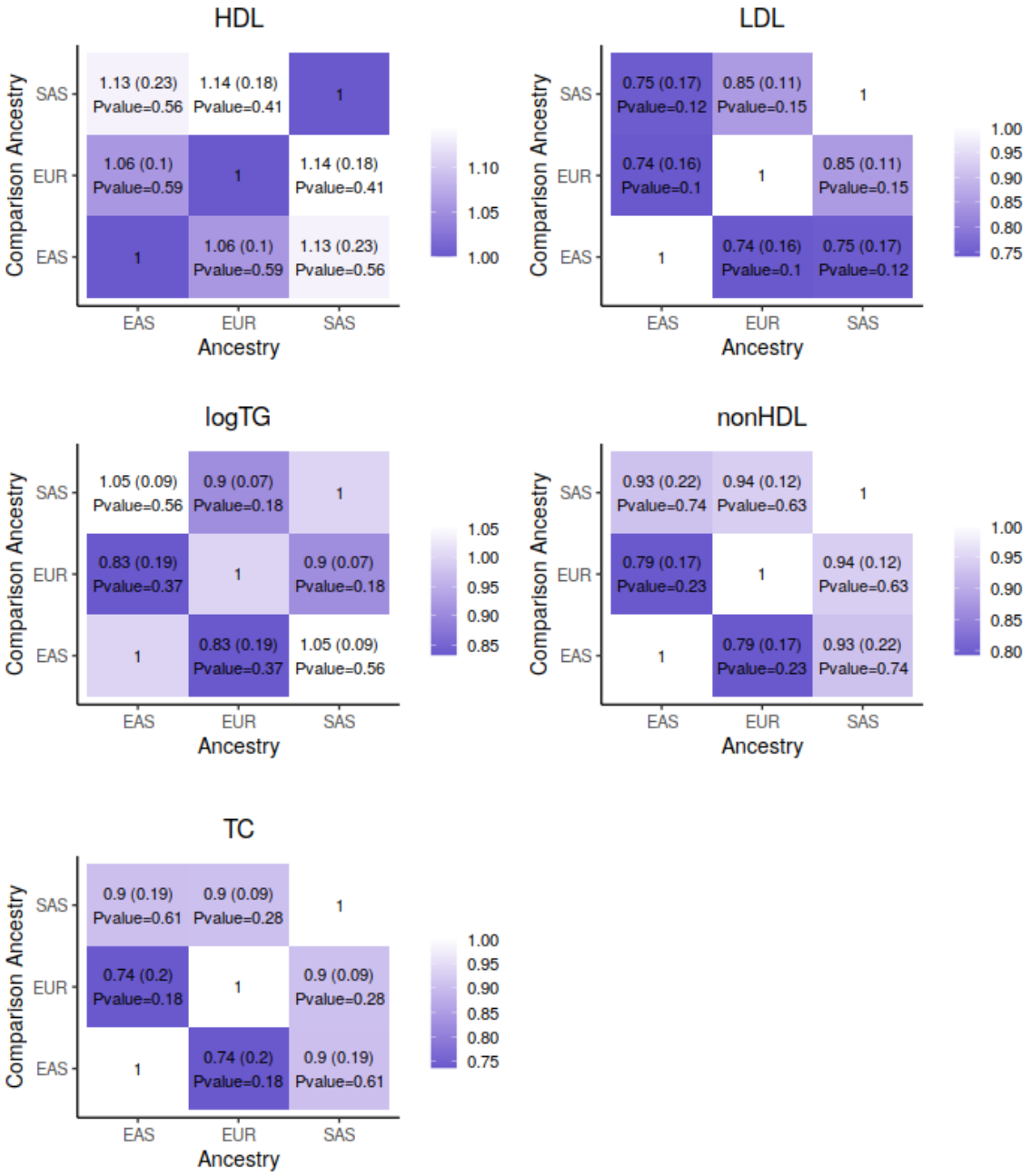
D) Pairwise correlation of effect sizes, fraction of shared direction of effect, and comparison of the magnitude of effect size differences between ancestries for variants reaching genome-wide significance (p-value < $5x10^{-8}$ as given by RAREMETAL) in both compared ancestries. Association results for all index variants are given in Supplementary Table 3.

Supplementary Figure 7: Genetic impact correlation estimates between ancestries for each trait analyzed



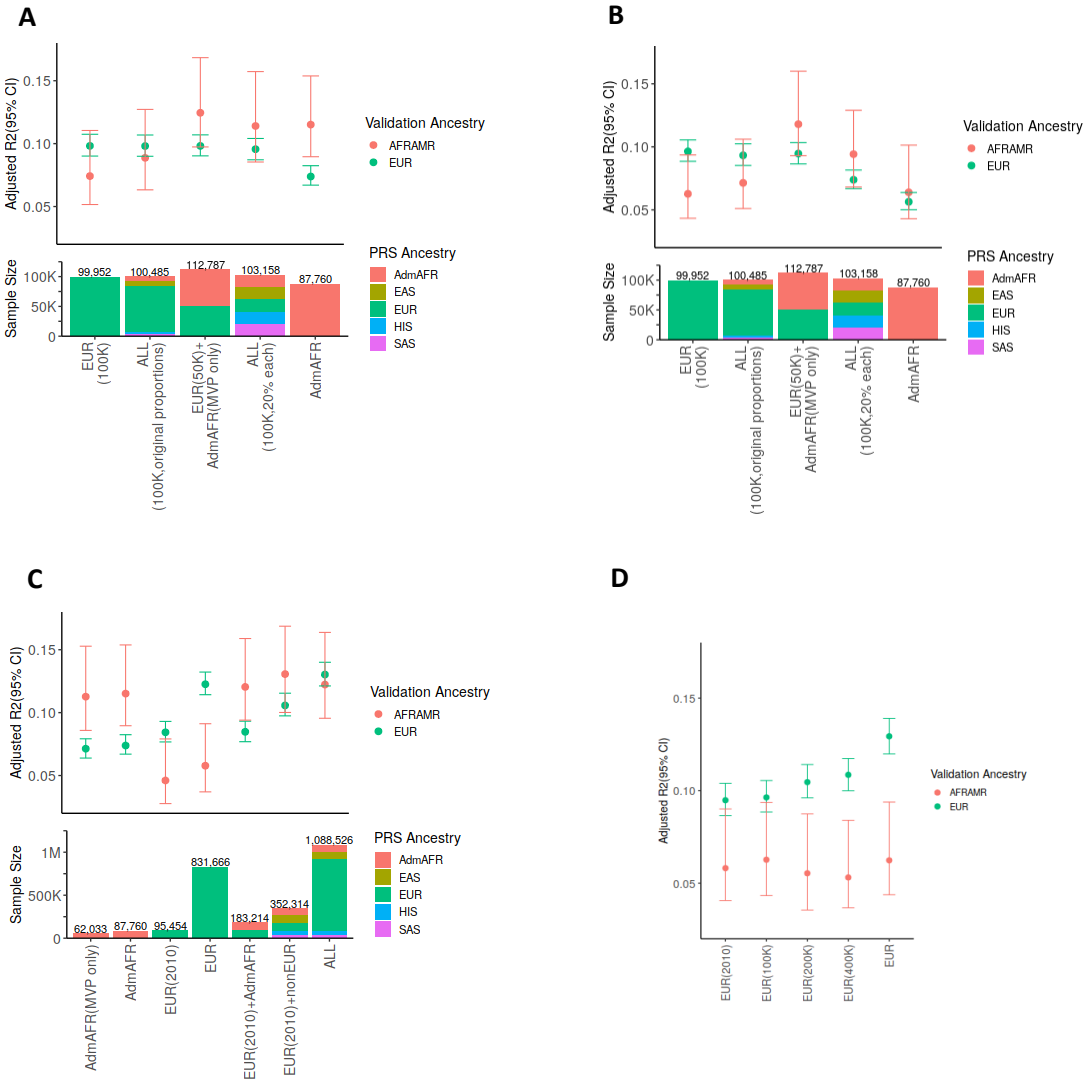
Correlation estimates were calculated with Popcorn and are given followed by the standard error in parentheses. Correlations were not significantly less than 1 (p-value > 0.05).

Supplementary Figure 8: Genetic effect correlation estimates between ancestries for each trait analyzed



Correlation estimates were calculated with Popcorn and are given followed by the standard error in parentheses. Correlations were not significantly less than 1 (p-value > 0.05).

Supplementary Figure 9: Comparison of PRS source ancestry and sample size with prediction in European and African-American individuals

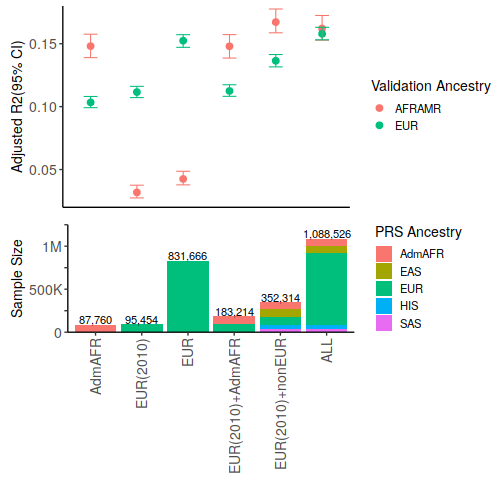


Error bars represent 95% confidence intervals. The Michigan Genomics Initiative includes 17,190 European-ancestry individuals and 1,341 African American individuals. The Million Veteran Program includes 68,381 European-ancestry individuals and 18,251 African American individuals.

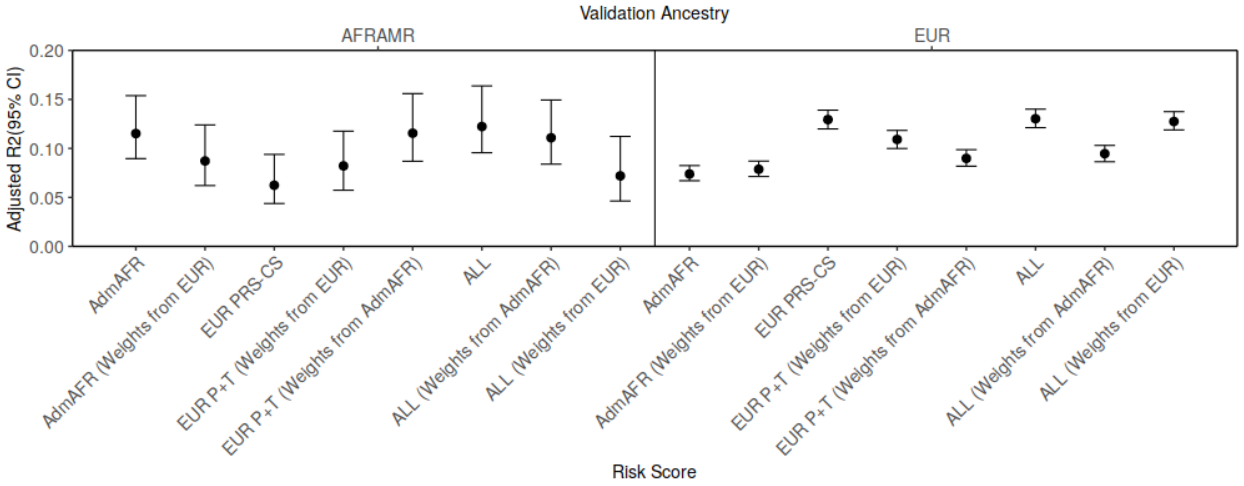
A) At constant sample size (~100,000) and using only pruning and thresholding to create risk scores used for prediction in the Michigan Genomics Initiative (MGI)
B) At constant sample size (~100,000) and using only PRS-CS to create risk scores used for prediction in the Michigan Genomics Initiative (MGI)

C) Using only pruning and thresholding to create risk scores with variable numbers of individuals from each ancestry group tested in the Michigan Genomics Initiative (MGI)
D) Using only PRS-CS with variable numbers of European individuals tested in the Michigan Genomics Initiative (MGI)

E



F

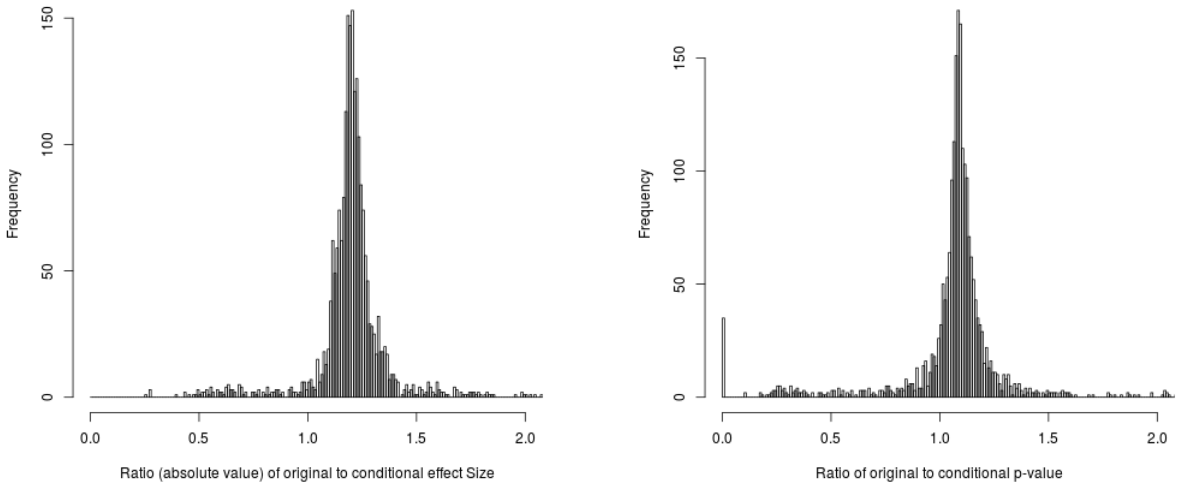


E) Using only pruning and thresholding to create risk scores with variable numbers of individuals from each ancestry group tested in the Million Veteran's Program (MVP)

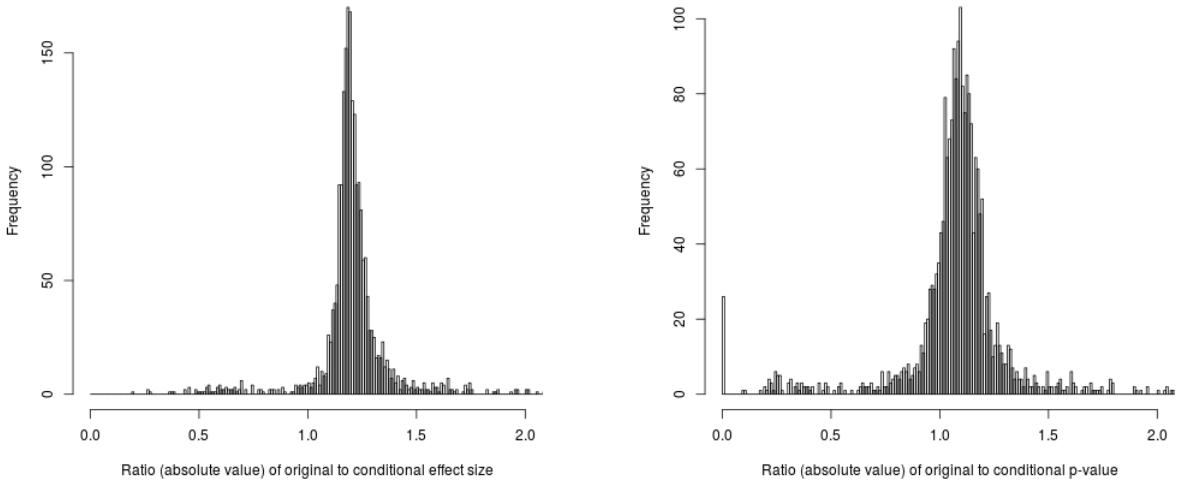
F) Comparison of effect size source ancestry with prediction in MGI

Supplementary Figure 10: Comparison of original and conditional effect sizes

A



B



A) From ancestry-specific meta-analysis

B) From trans-ancestry meta-analysis

The x-axis of each plot is truncated at a ratio of 2 to aid in visualization**.**

Supplementary Notes

Comparison of associated variants by ancestry group

We assessed whether the ancestry-specific variants were enriched by trait or ancestry. The six Hispanic-specific index variants were all associated with triglycerides and concentrated within a region in length of several megabases on chromosome 11 that has been previously identified to be associated with high TG levels among individuals with Indigenous American ancestry[29,30]. Other ancestry-specific associated variants were relatively evenly distributed among the different lipid traits (**Supplementary Table 3, Supplementary Figure 3**).

Approximately 0.5% of tested genome-wide variants reached significance ($P<5x10^{-8}$) for at least one trait. The associated regions encompass 13% of the genome across all traits based on the minimum and maximum positions of variants that reach genome-wide significance at each locus. By trait, 7%, 5%, 6%, 5%, and 6% of the genome was associated with HDL-C, LDL-C, TG, nonHDL-C, and TC, respectively. Overall, the novel trans-ancestry index variants reaching genome wide significance explained ~0.8% of the variance in each trait, with all variants explaining 12%, 13%, 9%, 13%, and 12% of the variance across all ancestries, for HDL-C, LDL-C, TG, nonHDL-C, and TC, respectively. Using population-specific effect size estimates and allele frequencies, we find that the proportion of variance explained by the trans-ancestry index variants within each ancestry on average is 28%, 11%, and 17% lower in Admixed Africans, East Asians, and South Asians and 1% and 6% higher in Europeans and Hispanics, respectively, relative to the trans-ancestry estimate (**Supplementary Table 19**). For variants successfully imputed into all ancestry groups, this corresponds to 8%, 9%, 11%, 11%, and 9% of the variance for Admixed African, East Asian, European, Hispanic, and South Asian individuals, respectively. However, it is important to note that genes involved in lipid levels can be effective therapeutic targets in all ancestry groups even if naturally occurring variation, for example in the non-coding region, has a small effect on the trait (e.g. HMGCR[29] and statins) or if genetic variants have a differential impact by ancestry.

Improvement in credible sets by ancestry group

In order to quantify the improvement in fine-mapping through trans-ancestry meta-analysis, we grouped the 2,286 index variants into 1,486 independent association signals based on an LD r^2 threshold of 0.7 between index variants. This was done to avoid double-counting overlapping association signals. Considering all independent association signals under the assumption of a single, shared causal variant, we found a median 40% reduction in credible set size for regions with improved fine-mapping in the trans-ancestry meta-analysis. We next aimed to determine whether differences in linkage disequilibrium patterns or allele frequency differences were driving this improvement. Starting with the independent association signals, we selected for further analysis the 151 signals that reached a significance threshold of p-value < $5x10^{-8}$ in both the Admixed African and European meta-analyses alone. For each of these regions, we manually inspected LocusZoom plots from the Admixed African and European ancestry-specific meta-analyses and from trans-ancestry meta-analysis to exclude any loci with apparent secondary signals within the region. Of the 69 association signals selected for further analysis (**Supplementary Table 20**), 36 (52%) had the smallest 99% credible set from the trans-ancestry meta-analysis, 6 (9%) from the Admixed African ancestry meta-analysis, 3 (4%) from the European ancestry

meta-analysis, and 24 (35%) had equivalent fine-mapping in two or more analyses. Among the 36 signals with improved fine-mapping, we observed a median 50% reduction in credible set size.

We next focused our comparisons on the 36 association signals with improved fine-mapping in the trans-ancestry meta-analysis. The trans-ancestry index variants at these signals were more common in Admixed Africans than Europeans 56% of the time (20/36), with a median 1.3-fold difference. We then identified all variants in 1000 Genomes that were in strong linkage disequilibrium (r^2>0.8) with the trans-ancestry index variant in Africans or Europeans. Nearly all loci (33/36, 92%) with improved fine-mapping had fewer variants in high LD among Africans compared to Europeans. For example, in 1000 Genomes Africans there was a median of 6 variants having r^2>0.8 with the trans-ancestry index variant compared to a median of 40 variants having r^2>0.8 in Europeans. Therefore, the improved fine-mapping observed in the trans-ancestry meta-analysis appears to be primarily due to the smaller number of variants in high LD with the lead index variant in Africans relative to Europeans rather than differences in allele frequency between populations.

Polygenic scores by ancestry group

Previous studies have suggested that population stratification may influence the predictive ability of polygenic scores across diverse populations[26]. We tested for correlation between the trans-ancestry polygenic score and principal components of ancestry (PCs) in 1000 Genomes individuals. Significant correlation was observed between the trans-ancestry polygenic score and PCs 1 and 3 only (p-value < 0.0025; 0.05/20 tested PCs; **Supplementary Table 21**). Within the MGI cohort, we found that median LDL-C values were not significantly correlated with any of the first twenty principal components (p-value > 0.0025) and prediction of LDL-C as measured by adjusted R^2 was similar when either PCs 1-4, 1-10, or 1-20 were included as covariates in the model with the ancestry-specific or trans-ancestry polygenic scores (**Supplementary Tables 22** and **23**). We note that normalization of LDL polygenic scores should be performed within each ancestry.

We next aimed to determine the underlying basis for the success of the LDL-C trans-ancestry score. Several factors may influence the predictive ability of a polygenic score, including the GWAS-related factors of sample size and ancestry makeup and factors related to PRS method such as variant selection and estimation of polygenic score weights. Polygenic scores developed from the GWAS with the largest sample sizes (European or trans-ancestry) were less sensitive to the optimizing approach (i.e. weights derived from PRS-CS or a variety of p-value thresholds performed similarly), whereas the other ancestry-specific scores showed much more variable performance of the PRS depending on the optimizing parameters (**Extended Data Figure 6b**). In order to identify which factors were most important, we created five different GWAS at fixed sample sizes of ~100k: EUR and AdmAFR single-ancestry GWAS, a half EUR, half AdmAFR bi-ancestry GWAS, and two trans-ancestry GWAS, one with equal numbers of the five ancestries and one where each ancestry matched the proportion in the full 1.65m meta-analysis. Using a pruning and thresholding approach, we created optimized polygenic score weights for each of these five different GWAS meta-analyses. As expected, LDL-C prediction in admixed African individuals was relatively poor from an entirely European ancestry GWAS, irrespective of the sample size (adjusted R^2 MVP = 0.03-0.04, **Supplementary Figure 10, Supplementary Table 17**). The ancestry matched single-ancestry scores were similar or slightly worse predictors of LDL-C compared to the trans-ancestry scores (**Supplementary Figure 10**). The trans-ancestry score with equal proportions of

each ancestry group predicted LDL-C better among African Americans, and both trans-ancestry scores predicted LDL-C similarly well among Europeans. Lastly, the ancestry-mismatched scores predicted LDL-C less well in African Americans (65% of trans-ancestry polygenic score) than the ancestry-mismatched score predicted LDL-C in European Americans (77% of trans-ancestry polygenic score).

We next examined the improvement in prediction of LDL-C with increasing sample size. We generated polygenic scores from MVP AdmAFR only, the full AdmAFR meta-analysis, the 2010 Global Lipids Genetics Consortium LDL-C meta-analysis[4] (EUR N=95,454, imputed with HapMap) and subsets of the European and trans-ancestry meta-analyses. Increasing the sample size of the discovery GWAS with ancestry-matched samples led to an increased prediction accuracy for both admixed African and European ancestry individuals. For example, we observed a 36% increase in the predictive accuracy of LDL-C polygenic scores (adjusted R^2 MVP = 0.11 and 0.15, respectively) with the nine-fold increase in sample size between the 2010 and present European-specific polygenic score.

Finally, we aimed to investigate the role of variant selection and weights in polygenic score performance. Poor performance of ancestry mismatched scores could be caused by either missing ancestry-specific variants in the score or by differing LD with the underlying causal variant between ancestry groups leading to imperfect variant weights. Starting with ancestry mismatched pruning and thresholding scores, we attempted to 'correct' the ancestry mismatch by first applying ancestry-matched weights. This helps with future study design questions – e.g. would a single pre-defined set of variants on an array be useful for all ancestries if we applied updated ancestry-specific weights? We used the predictive ability of the pruning and thresholding trans-ancestry score as the 'gold standard' because it achieved the highest R^2 for any polygenic score. In admixed African individuals, we recovered 87% of the gold standard polygenic score when we used the European variant list with admixed African weights compared to just 47% when using the European variant list with weights from Europeans (**Extended Data Figure 7**, **Supplementary Figures 10**, **Supplementary Table 17**).

We then examined the role of optimizing variants selected for polygenic scores. We found that European ancestry GWAS-derived score had improved prediction in individuals with admixed African ancestry when the variant selection parameters (such as p-value thresholds for pruning and threshold) were selected based on optimizing the score in admixed African ancestry rather than in Europeans. Using parameters optimized from only European individuals led to prediction in admixed African individuals that was just 47% of the gold standard while using parameters optimized in admixed African individuals (a more stringent p-value threshold of $5x10^{-10}$) resulted in prediction that was 67% of the gold standard (**Supplementary Table 17**), even with European weights. Finally, using the AFR ancestry-matched weights and ancestry-matched variant list from a single-ancestry AFR GWAS resulted in 94% of the gold standard (trans-ancestry) polygenic score performance. Taken together, our findings suggest that polygenic scores derived from ancestry-mismatched GWAS may be improved by substituting ancestry-specific weights for the selected variants when ancestry-matched GWAS of sufficient sample sizes are not available, and/or by optimizing the variant selection in ancestry-matched individuals.

We noted that the LDL-C polygenic score showed greater variability in prediction of LDL-C for cohorts within Africa than it did among African American cohorts. Mean lipid levels within each cohort also exhibited greater variation between the continental African cohorts compared to all other ancestry

groups. Additional studies are needed to better understand both the genetic and environmental factors influencing LDL-C levels.

Supplementary Methods: Derivation of approximate Bayes factors

Consider two models, M_0 and M_1. Let $\hat{\theta}_k$ denote the maximum likelihood estimates of model parameters under model M_k and let d_k denote the dimension of model M_k. The Schwarz Criterion is given by

$$S = \log f\left(y\middle|\hat{\theta}_1, M_1\right) - \log f\left(y\middle|\hat{\theta}_0, M_0\right) - \frac{(d_1 - d_0)}{2}\log(n)$$

where y are observed data and n is the sample size. The Bayes' factor in favour of model M_1 over M_0 is then approximated by $\exp(S)$.

In the context of our study, the null model M_0 corresponds to allelic effect sizes fixed at 0, whilst under the alternative model M_1 allelic effect sizes are unconstrained. The difference in log-likelihoods between the two models is given by $X^2/2$, where X^2 is the deviance between the two models, which is approximated by the observed chi-square statistic,

$$X^2 = \frac{\beta^2}{SE^2}$$

It then follows that

$$BF \approx \exp\left[\frac{X^2 - \log(n)}{2}\right]$$

References:

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