Cell Genomics, Volume *2*

# Supplemental information

# Systematic single-variant and gene-based association testing of thousands of phenotypes in 394,841 UK Biobank exomes

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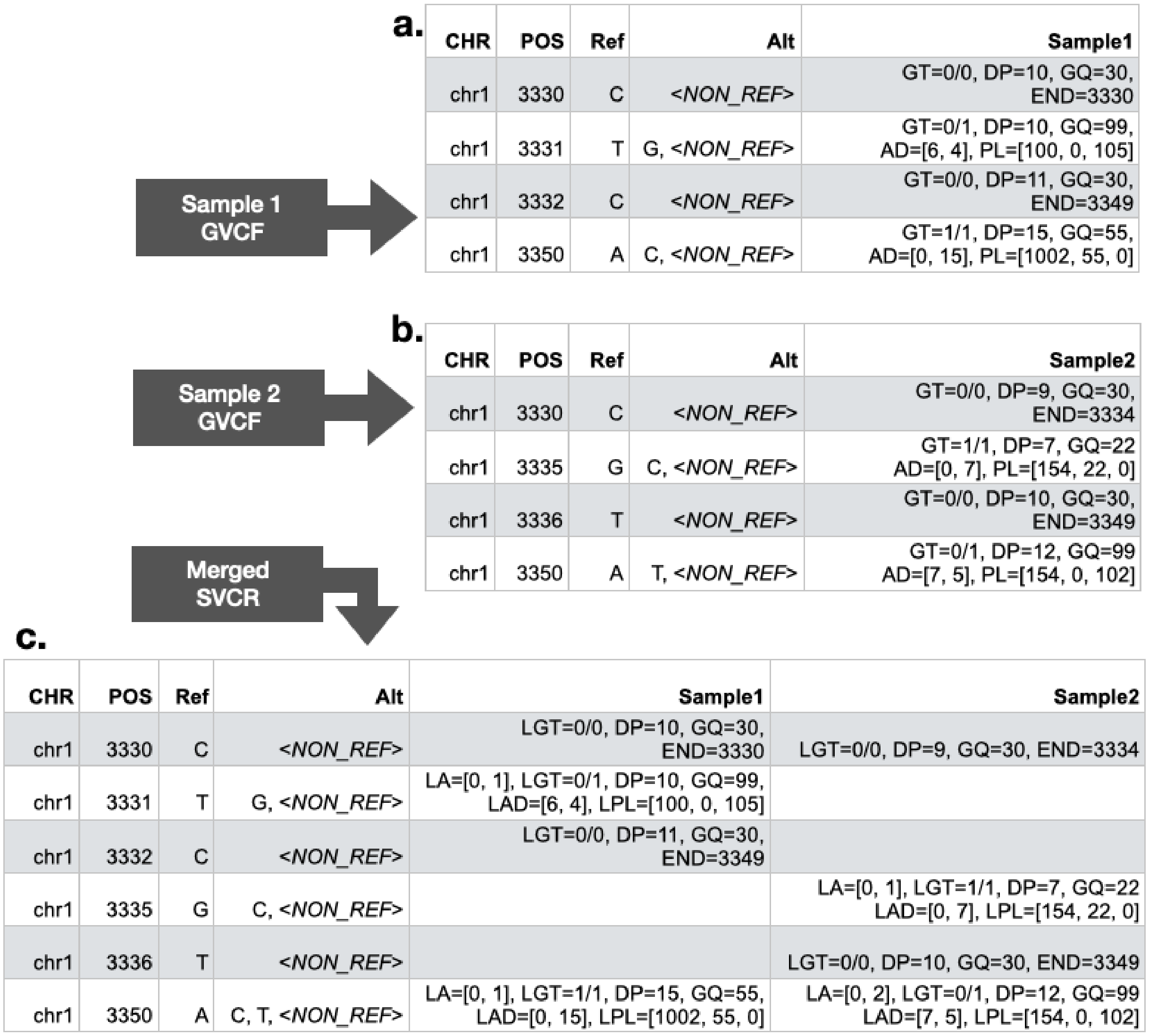


| CHR | POS | Ref | Alt | Sample1 |
|---|---|---|---|---|
| chr1 | 3330 | C | *<NON_REF>* | GT=0/0, DP=10, GQ=30, END=3330 |
| chr1 | 3331 | T | G, *<NON_REF>* | GT=0/1, DP=10, GQ=99, AD=[6, 4], PL=[100, 0, 105] |
| chr1 | 3332 | C | *<NON_REF>* | GT=0/0, DP=11, GQ=30, END=3349 |
| chr1 | 3350 | A | C, *<NON_REF>* | GT=1/1, DP=15, GQ=55, AD=[0, 15], PL=[1002, 55, 0] |

| CHR | POS | Ref | Alt | Sample2 |
|---|---|---|---|---|
| chr1 | 3330 | C | *<NON_REF>* | GT=0/0, DP=9, GQ=30, END=3334 |
| chr1 | 3335 | G | C, *<NON_REF>* | GT=1/1, DP=7, GQ=22 AD=[0, 7], PL=[154, 22, 0] |
| chr1 | 3336 | T | *<NON_REF>* | GT=0/0, DP=10, GQ=30, END=3349 |
| chr1 | 3350 | A | T, *<NON_REF>* | GT=0/1, DP=12, GQ=99 AD=[7, 5], PL=[154, 0, 102] |

| CHR | POS | Ref | Alt | Sample1 | Sample2 |
|---|---|---|---|---|---|
| chr1 | 3330 | C | *<NON_REF>* | LGT=0/0, DP=10, GQ=30, END=3330 | LGT=0/0, DP=9, GQ=30, END=3334 |
| chr1 | 3331 | T | G, *<NON_REF>* | LA=[0, 1], LGT=0/1, DP=10, GQ=99, LAD=[6, 4], LPL=[100, 0, 105] | |
| chr1 | 3332 | C | *<NON_REF>* | LGT=0/0, DP=11, GQ=30, END=3349 | |
| chr1 | 3335 | G | C, *<NON_REF>* | | LA=[0, 1], LGT=1/1, DP=7, GQ=22 LAD=[0, 7], LPL=[154, 22, 0] |
| chr1 | 3336 | T | *<NON_REF>* | | LGT=0/0, DP=10, GQ=30, END=3349 |
| chr1 | 3350 | A | C, T, *<NON_REF>* | LA=[0, 1], LGT=1/1, DP=15, GQ=55, LAD=[0, 15], LPL=[1002, 55, 0] | LA=[0, 2], LGT=0/1, DP=12, GQ=99 LAD=[7, 5], LPL=[154, 0, 102] |

Fig. S1 | Scalable Variant Call Representation (SVCR) created from two gVCF inputs. Panels a and b display information contained in gVCFs for two distinct samples in a small genomic window. Panel c represents the merged SVCR, which contains all loci present in either a or b. There is no entry for Sample2 at chr1:3331 because Sample2's gVCF does not contain the locus chr1:3331. The GT field has been renamed to LGT (local GT), and the LA (local alleles) field has been added to record the original alleles in each gVCF, which is important at chr1:3350, a locus where both input samples have a variant call. Related to STAR Methods.

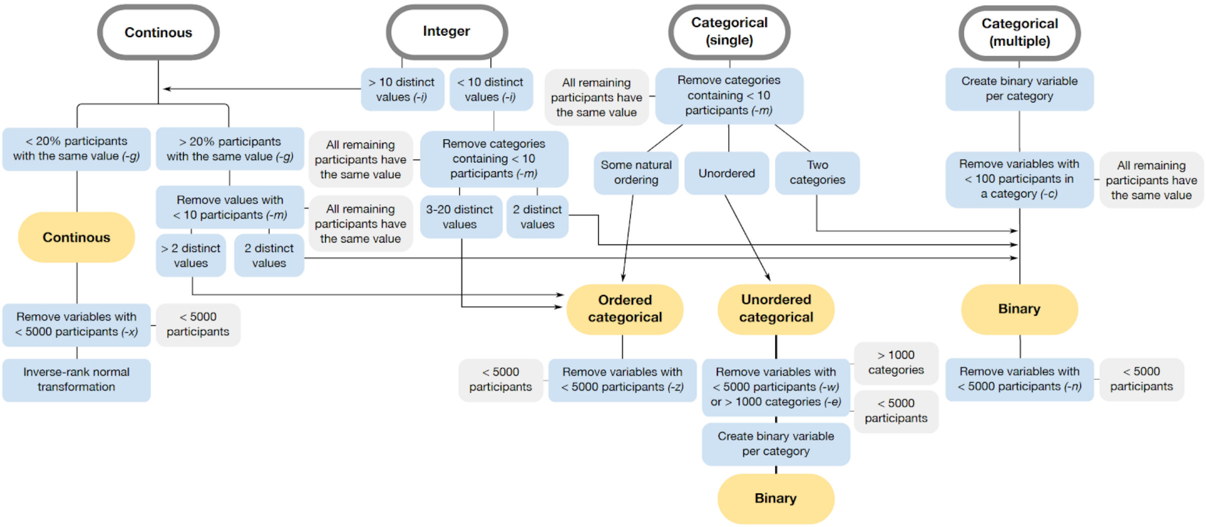

Continous
Integer
Categorical (single)
Categorical (multiple)
> 10 distinct values (-i)
< 10 distinct values (-i)
All remaining participants have the same value
Remove categories containing < 10 participants (-m)
Create binary variable per category
< 20% participants with the same value (-g)
> 20% participants with the same value (-g)
All remaining participants have the same value
Remove categories containing < 10 participants (-m)
Some natural ordering
Unordered
Two categories
Remove variables with < 100 participants in a category (-c)
All remaining participants have the same value
Continous
Remove values with < 10 participants (-m)
All remaining participants have the same value
3-20 distinct values
2 distinct values
> 2 distinct values
2 distinct values
Ordered categorical
Unordered categorical
Binary
Remove variables with < 5000 participants (-x)
< 5000 participants
Inverse-rank normal transformation
< 5000 participants
Remove variables with < 5000 participants (-z)
Remove variables with < 5000 participants (-w) or > 1000 categories (-e)
> 1000 categories
< 5000 participants
Remove variables with < 5000 participants (-n)
< 5000 participants
Create binary variable per category
Binary

Fig. S2 | Phenotype curation pipeline. Raw phenotype data (gray outlined boxes) are passed to PHESANT, and a collection of filters (blue boxes) are applied. The thresholds shown here are the defaults in our modified version of PHESANT that can be altered in our code as desired using the flags displayed in parentheses. Grey filled boxes display the criteria for removal, and yellow filled boxes show the category of the variable after the rules in the blue boxes have been enforced. Related to STAR Methods.

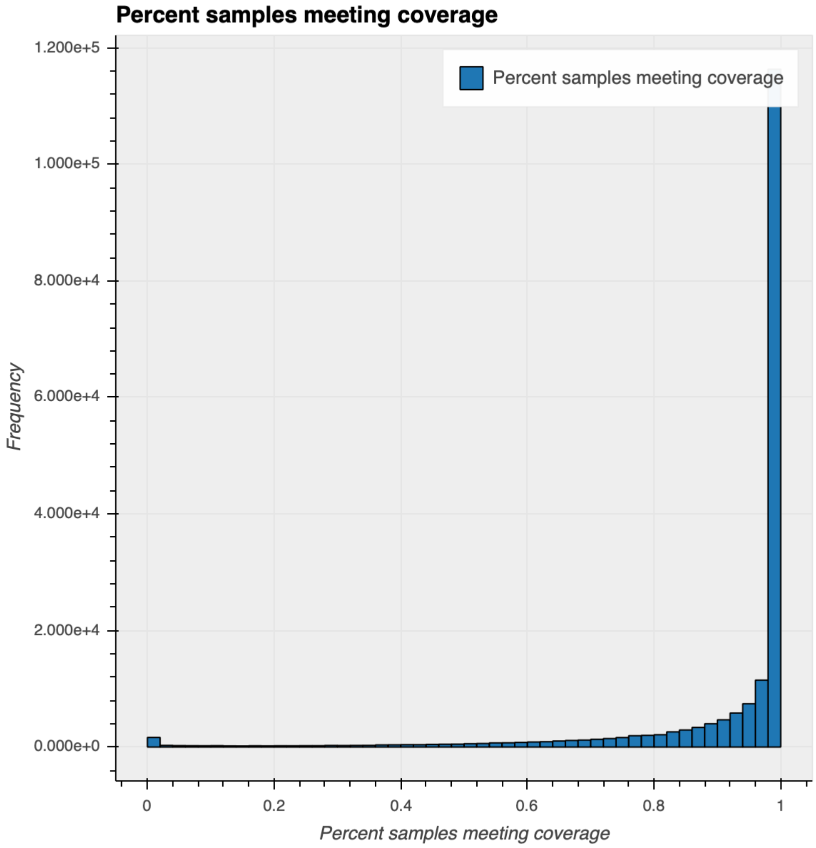


Fig. S3 | Histogram showing the percentage of samples meeting 20X mean coverage for each exome capture interval. Related to STAR Methods.

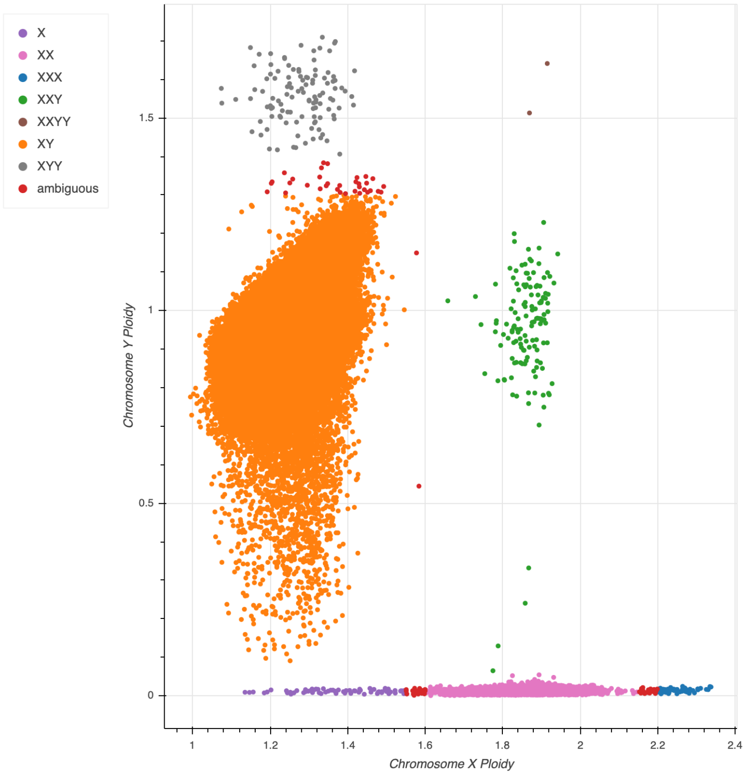


Fig. S4 | Normalized chromosome X ploidy plotted against normalized chromosome Y ploidy and colored by sex karyotype. XY samples are spread out in terms of their normalized chromosome Y coverage. This long tail of samples is likely due to mosaic loss of chromosome Y. Related to STAR Methods.

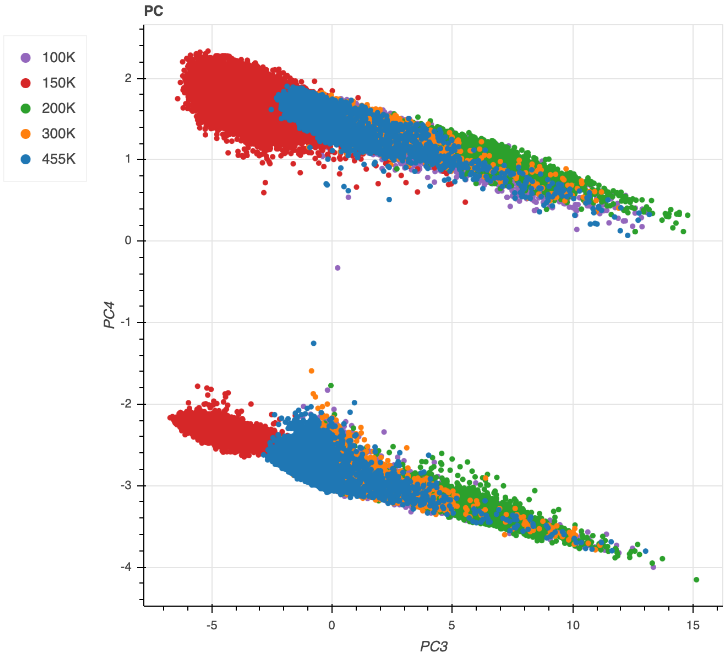


Fig. S5 | Platform inference using missingness PCA. PC3 vs PC4 colored by batch. Note that the batch names indicate the additional samples added from that batch. Thus, ‘100K’ refers to data tranche 1, ‘150K’ refers to samples added in tranche 1.5 (the first 50K samples released to the public), ‘200K’ refers to samples added in tranche 2, ‘300K’ refers to samples added in tranche 3, and '455K' refers to samples added in tranche 4. The separation in PC4 is driven by a common copy number variant. Related to STAR Methods.

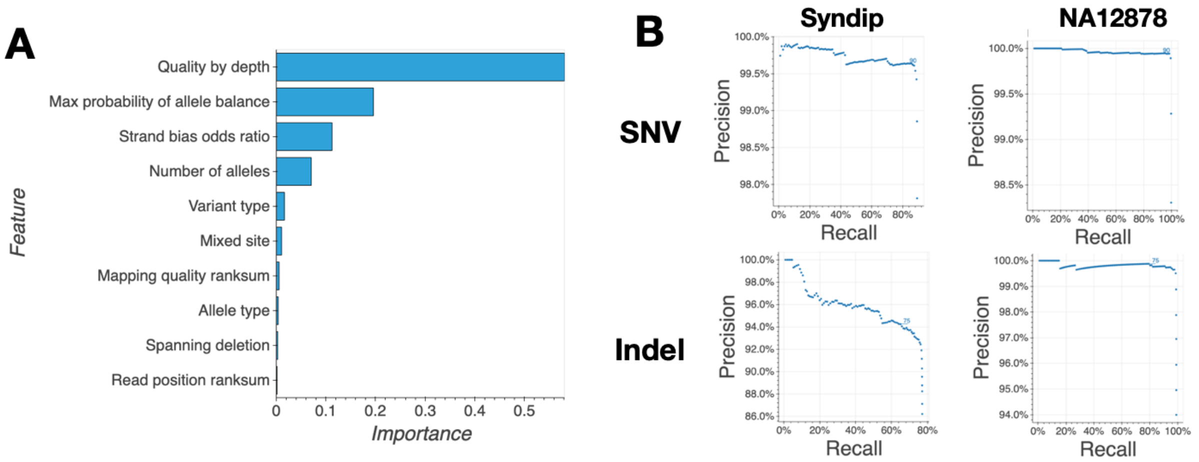


Fig. S6 | Variant QC (**A**): A summary of the features used in the random forests model and their relative importance in the model generated. (**B**): Precision and recall curves for the random forest classifier using two truth samples present in our data (NA12878 and syndip). The highlighted points at 90 for SNVs and 75 for indels indicate the cutoffs used for variant filtering. Related to STAR Methods.

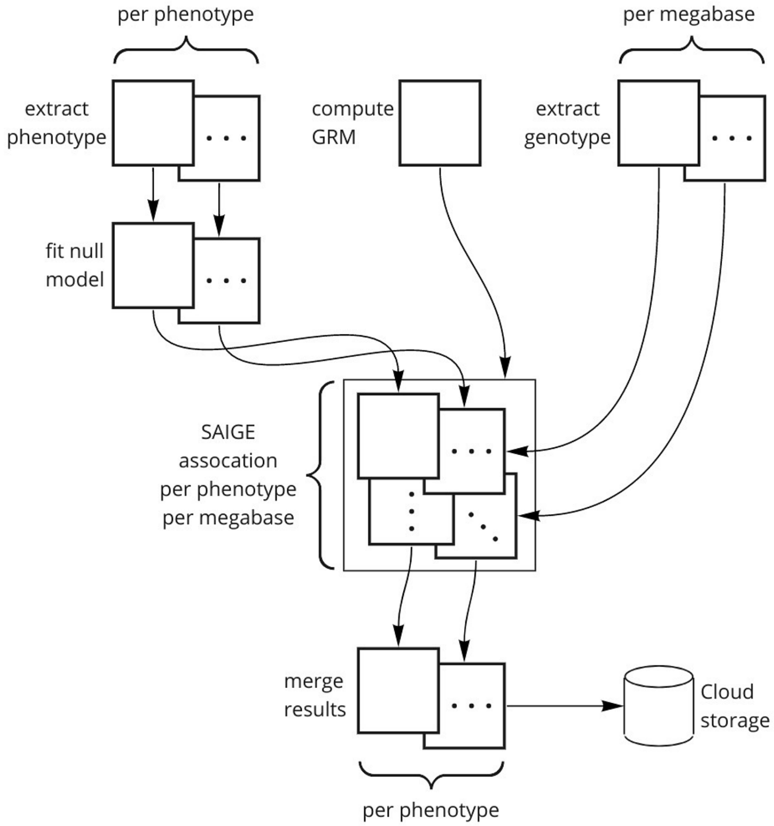


Fig. S7 | Hail Batch schematic for SAIGE association analysis. An example batch (the SAIGE pipeline used in this manuscript) is shown here. Related to STAR Methods.

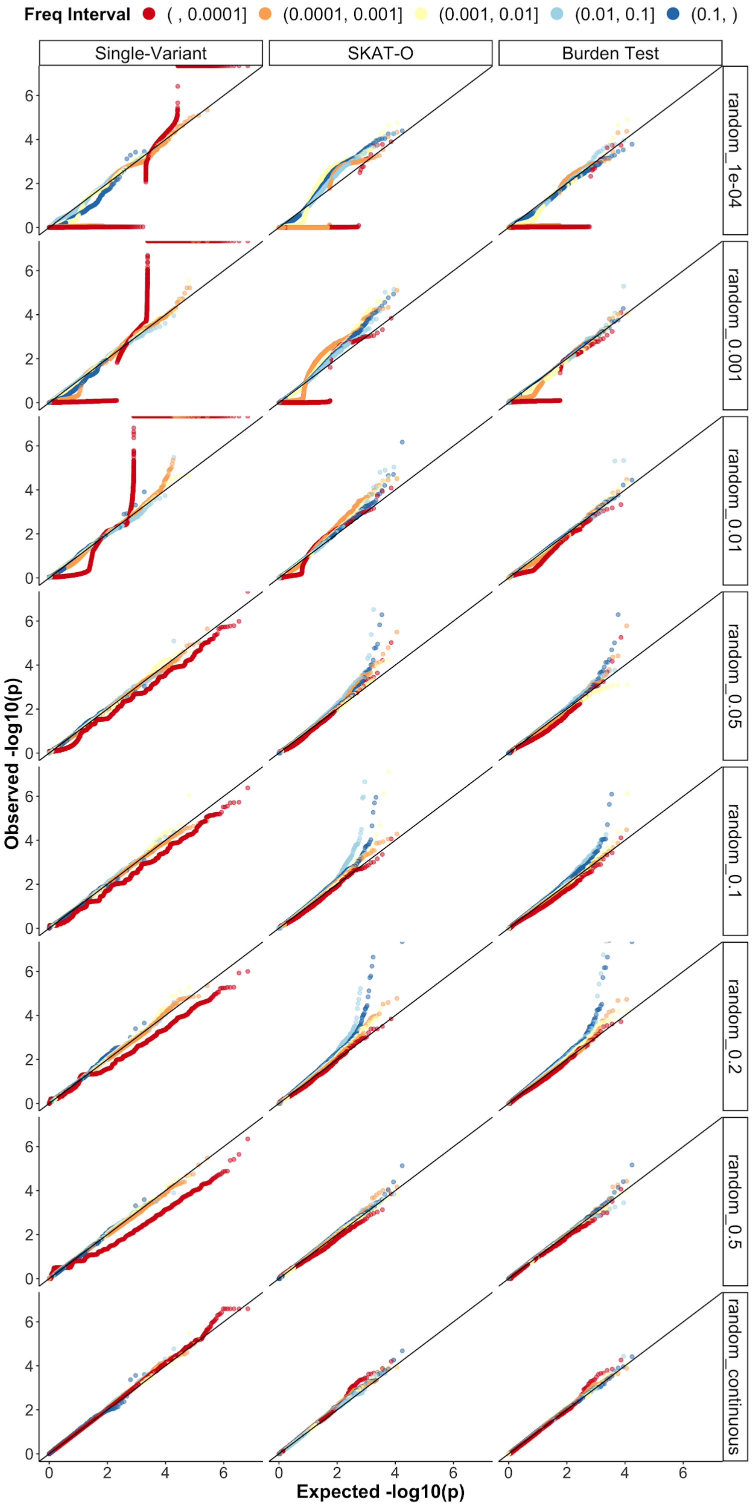


Fig. S8 | QQ-plots of randomly generated heritable (heritability = 100%) phenotypes for single-variant tests (left) and for group tests (SKAT-O, middle; and burden tests, right). The increasing prevalence of each binary phenotype is indicated by the label on the right (1e-4 to 0.5), followed by continuous traits. Related to STAR Methods.

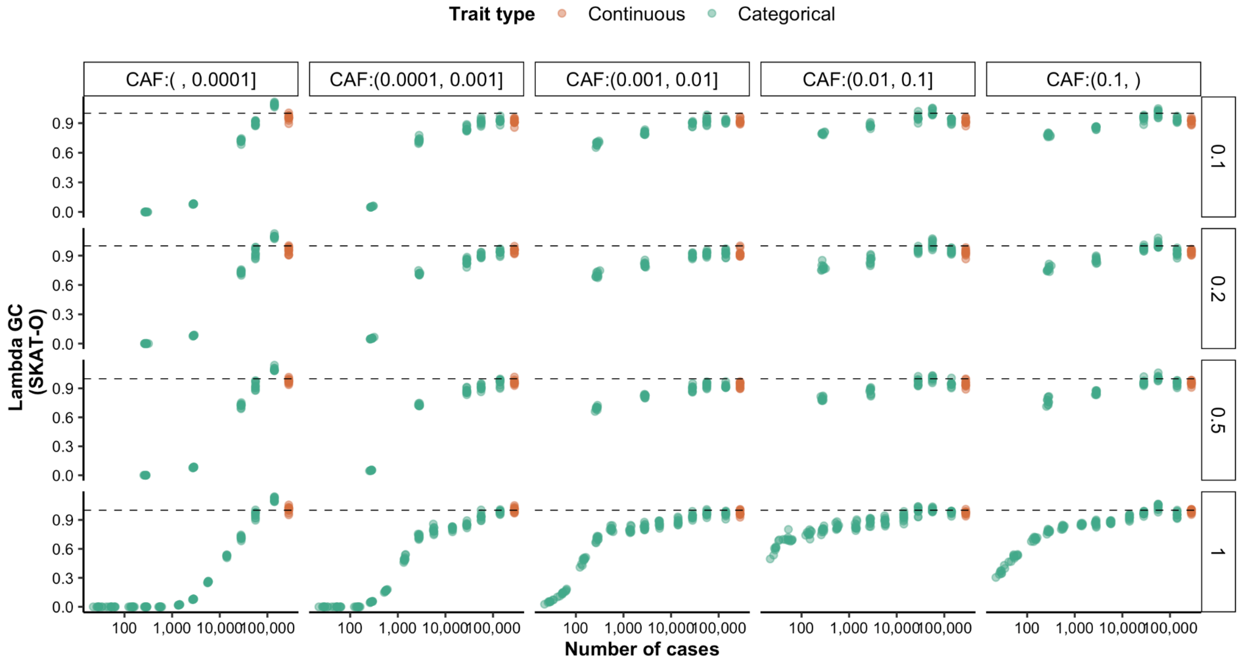


Fig. S9 | Lambda GC by cumulative allele frequency (CAF) by heritability. The heritability of the phenotypes are shown by the label on the right. Related to STAR Methods.

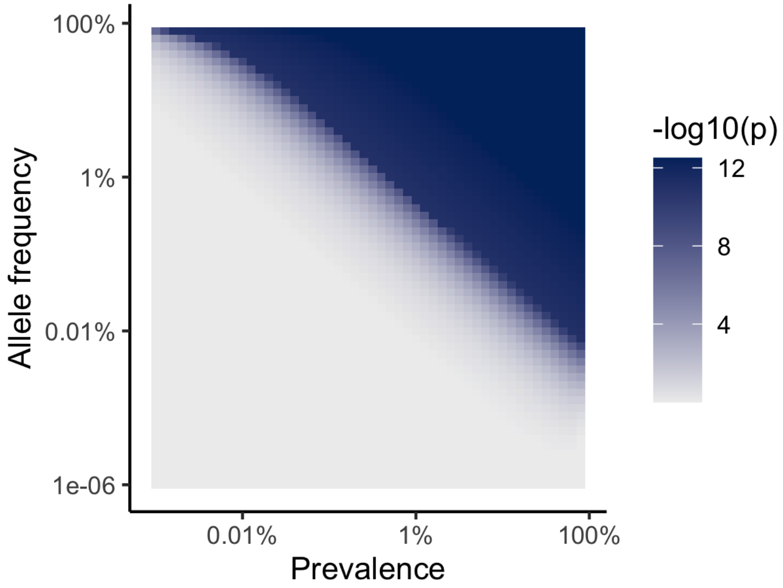


Fig. S10 | Power for rare variant associations. The minimum p-value possible from a protective mechanism with an odds ratio = 0: here, we compute the p-value of a chi-squared test of the case where the variant is absent from cases, while controls have a frequency as plotted. For the color-scale, a second logarithm is applied to p values below $10^{-10}$. Related to STAR Methods.

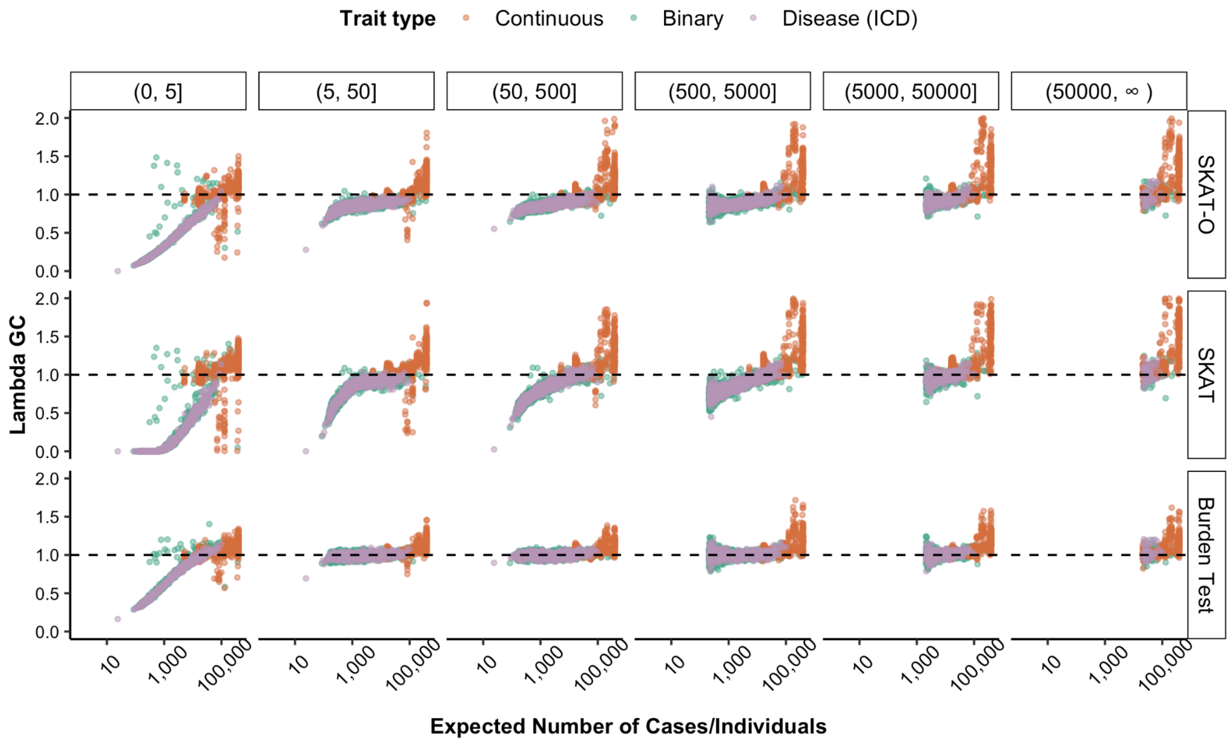


Fig. S11 | Lambda GC for each phenotype vs case count, split by expected AC interval for SKAT-O, SKAT and burden tests. Related to STAR Methods.

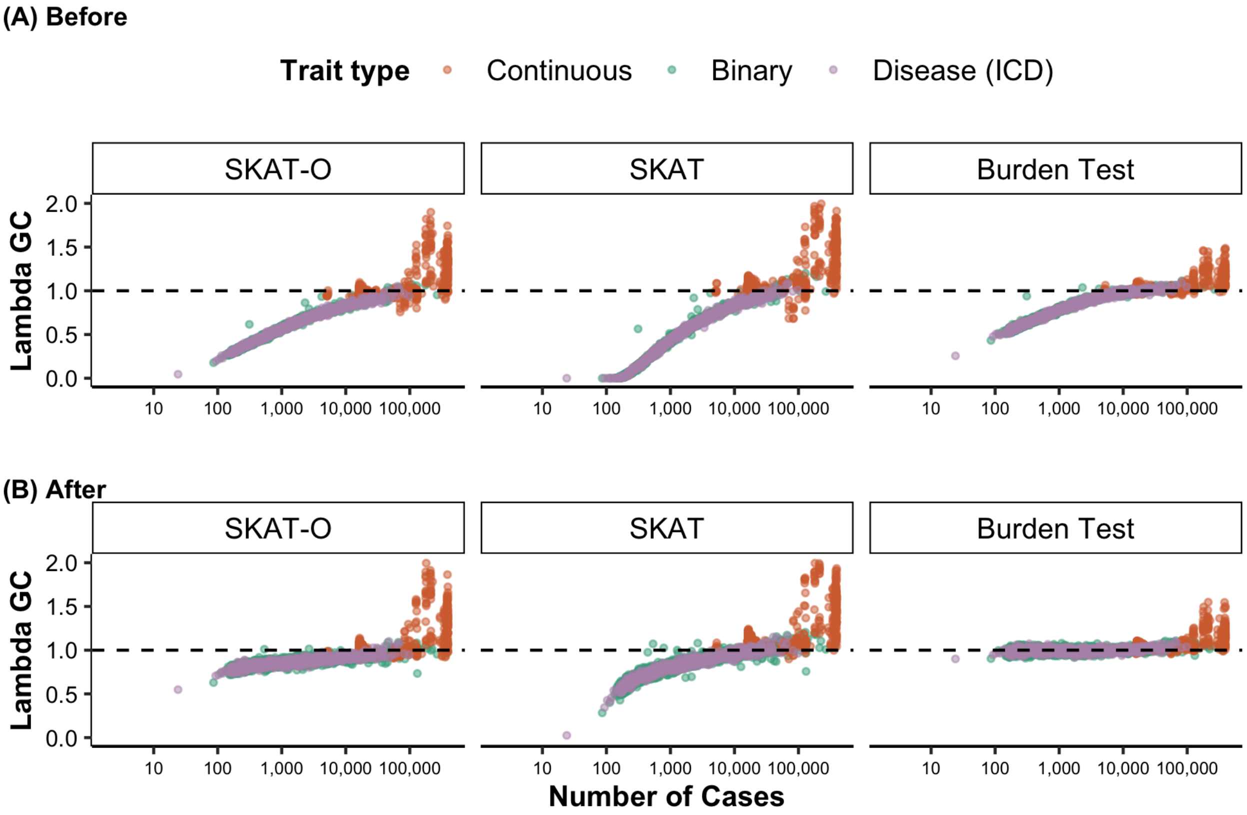


Fig. S12 | Lambda GC for each phenotype vs case count for SKAT-O, SKAT and burden tests, before and after filtering out summary statistics with expected AC < 50, number of variants tested < 2, and coverage < 20. Related to STAR Methods.

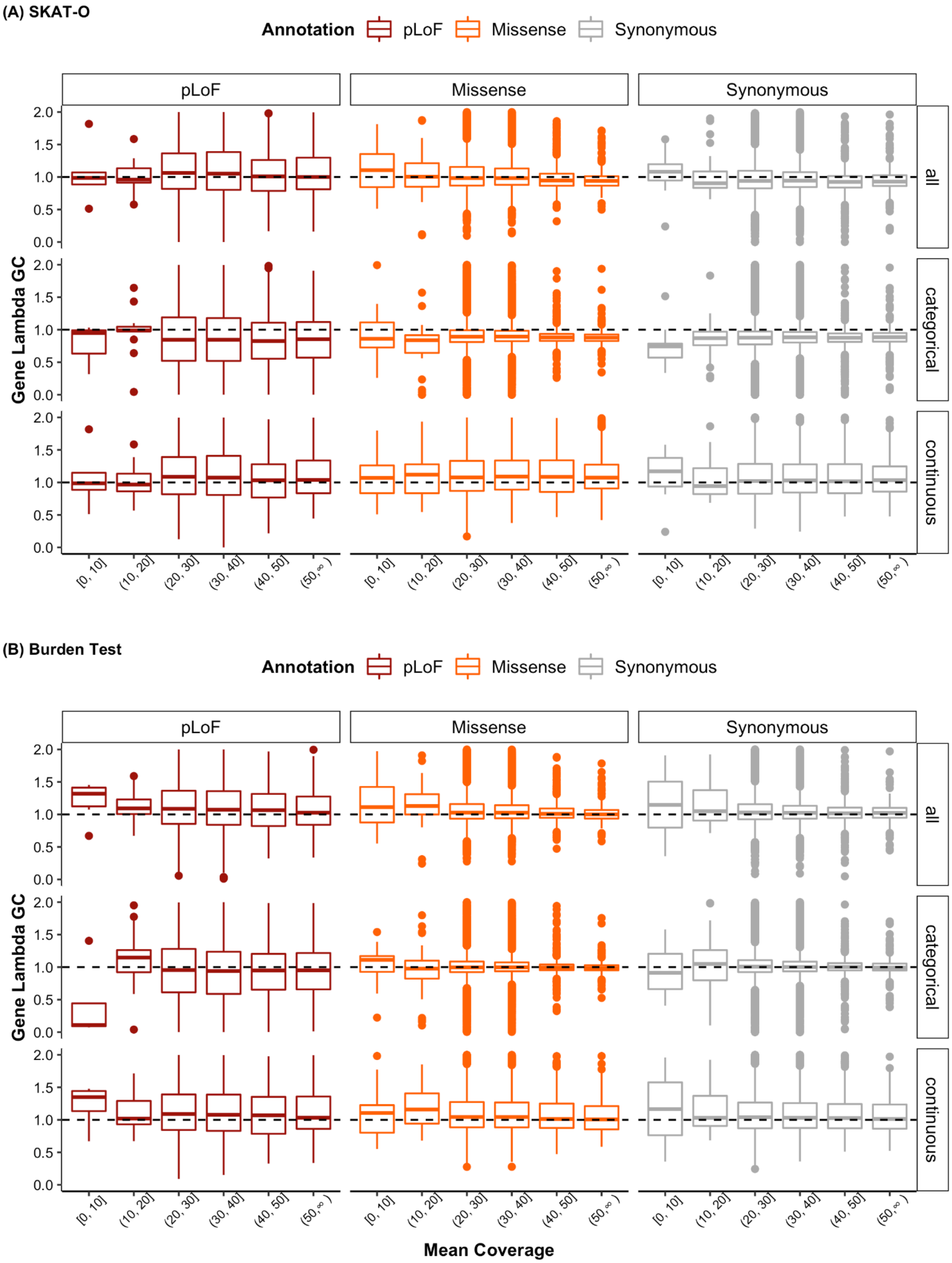


Fig. S13 | Coverage vs gene-based lambda GC, for SKAT-O (**A**) and burden tests (**B**). Related to STAR Methods.

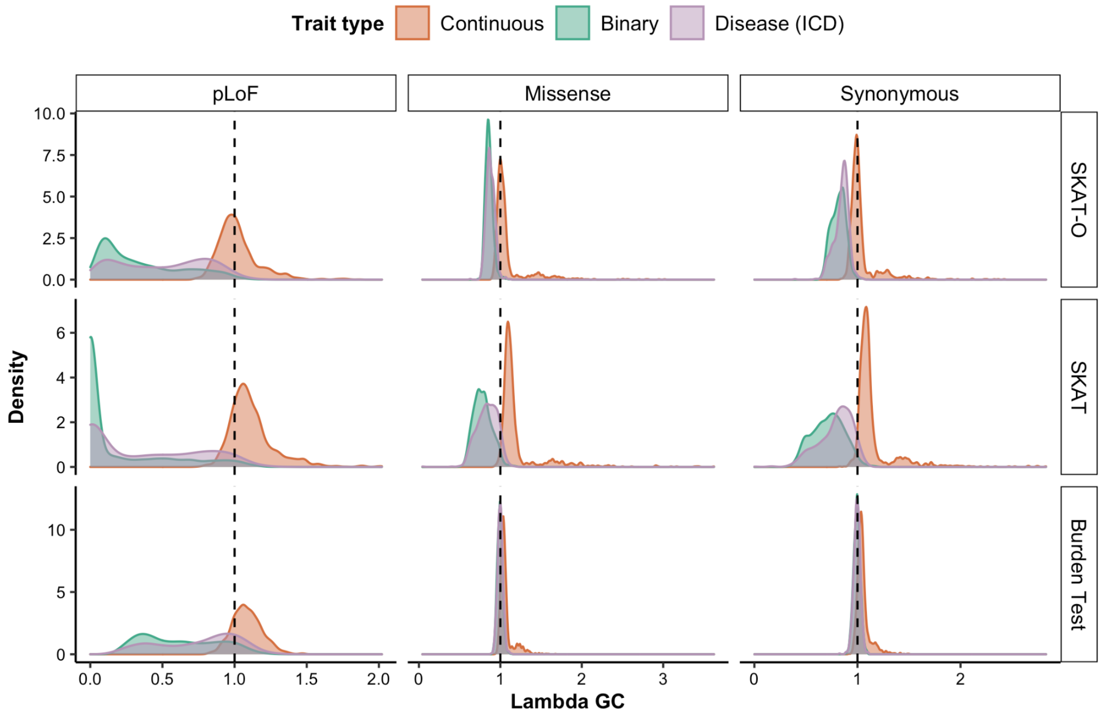


Fig. S14 | Lambda GC for each phenotype. A density plot of the distribution of lambda GC values for each phenotype is shown, broken down by trait type, test type, and set of variants used in the lambda calculation. Related to STAR Methods.

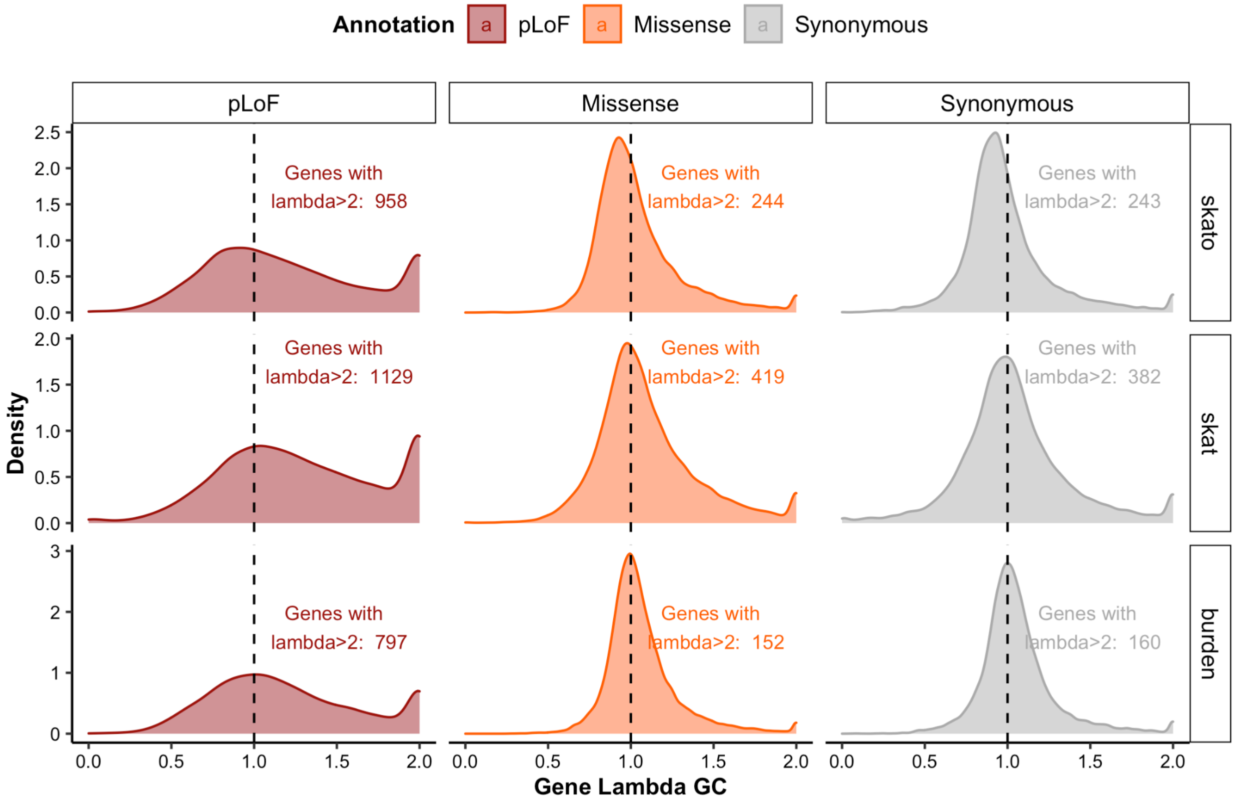


Fig. S15 | Lambda GC for each gene. A density plot of the distribution of lambda GC values for each gene is shown, broken down by test type and set of variants used in the lambda calculation. Related to STAR Methods.

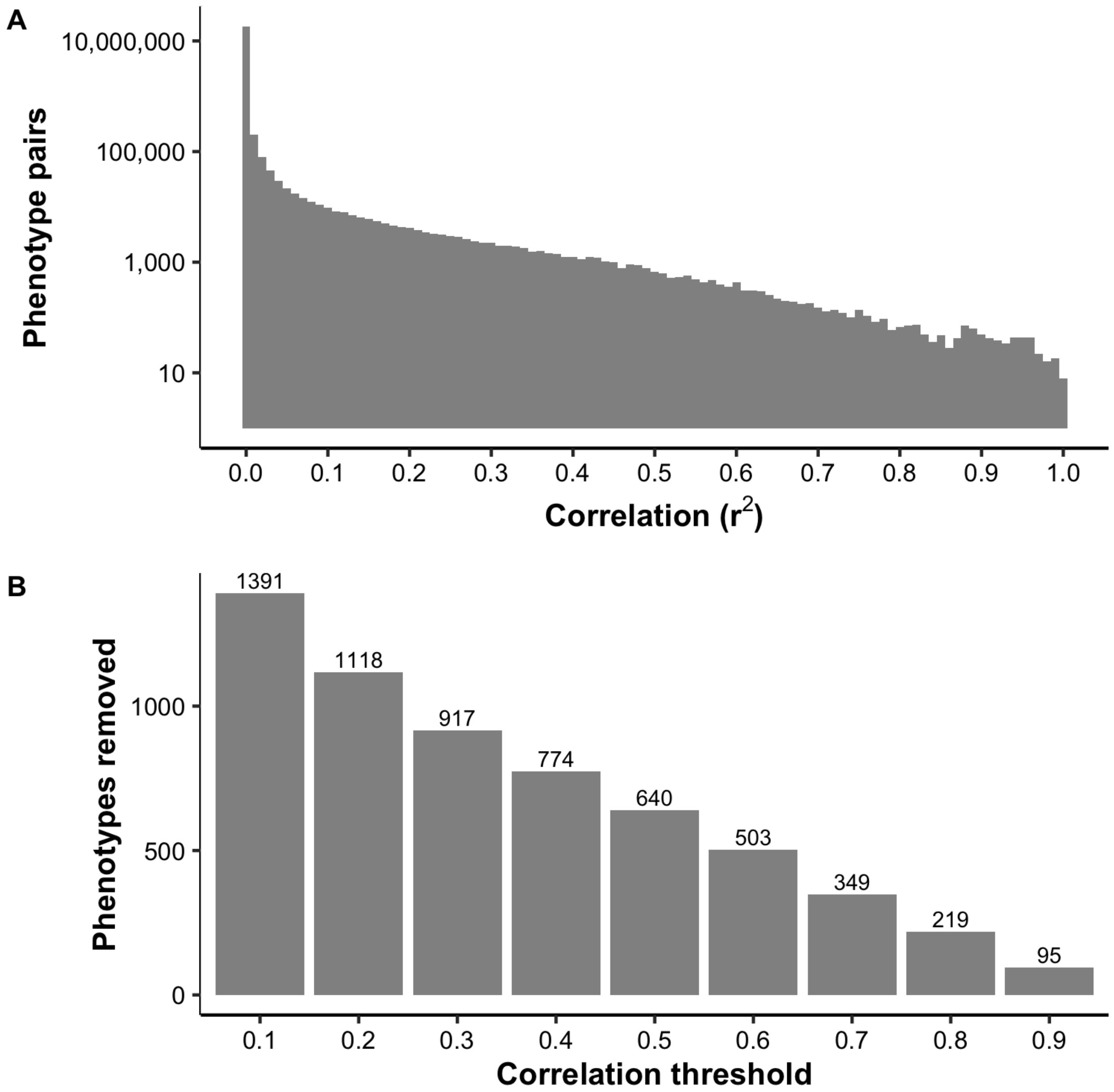


Fig. S16 | Independence of phenotypes. (**A**): A histogram of the number of phenotype pairs by correlation ($r^2$). (**B**): The number of phenotypes that would be removed by the maximum independent set method, by $r^2$ threshold. Related to STAR Methods.

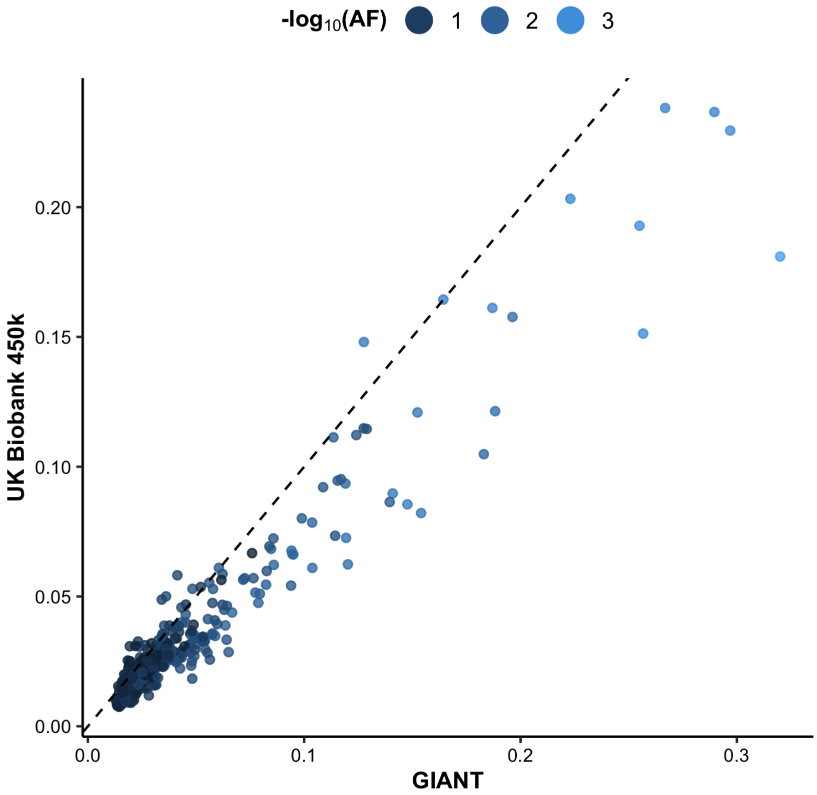


Fig. S17 | Comparison of effect sizes between UK Biobank and GIANT for height. The y = x line is shown for reference. Related to STAR Methods.

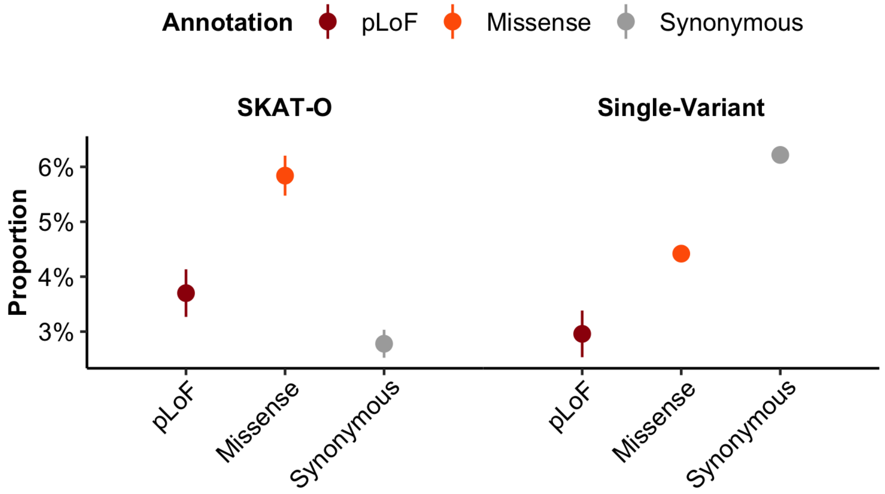


Fig. S18 | The proportion of genes (**A**) and variants (**B**) associated with at least one trait, broken down by functional class. Related to Figure 3 and STAR Methods.

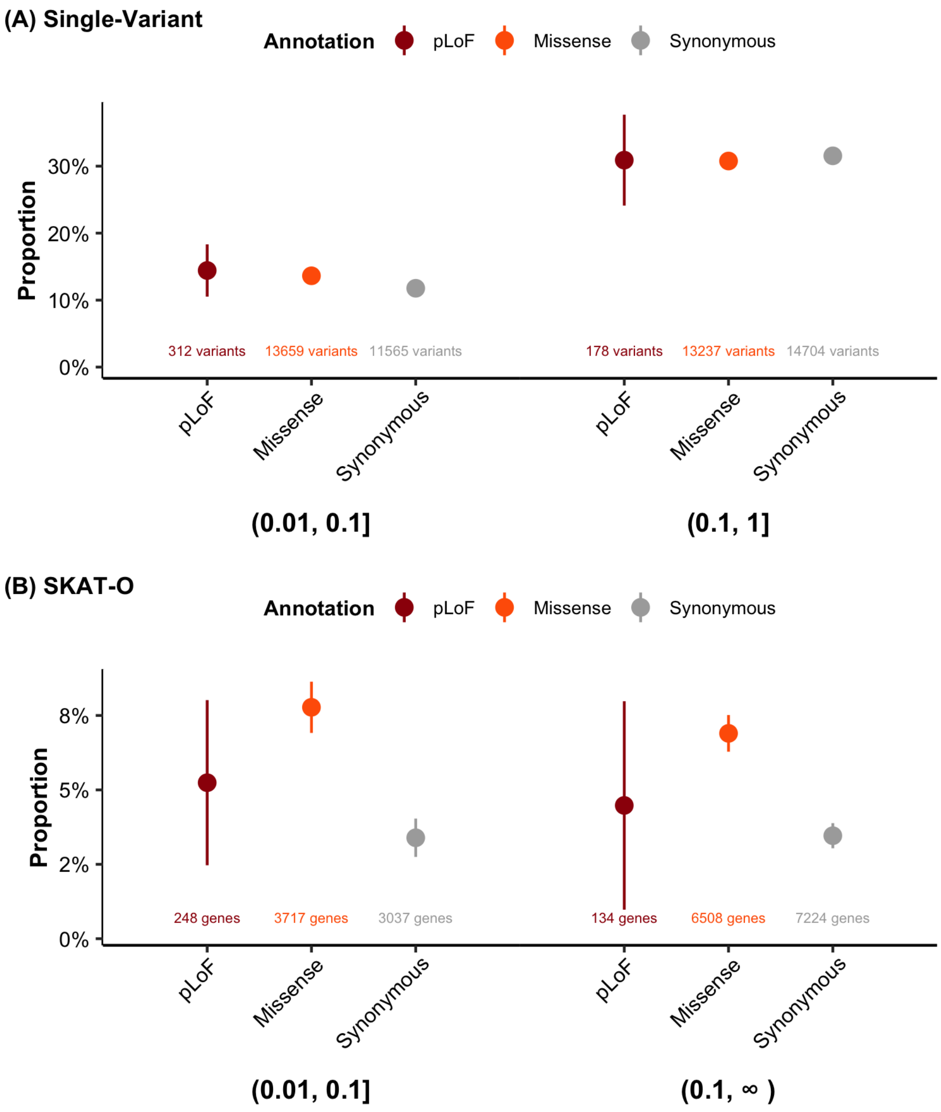


Fig. S19 | The proportion of variants (**A**) and genes (**B**) with at least one phenotype reaching our p-value threshold is shown broken down by allele frequency category (**A**) or cumulative allele frequency category (**B**) and by functional category. For common variants, missense variants show a higher proportion of associations than synonymous variants, but pLoF variants do not show a higher proportion as might be expected, likely due to artifacts at common pLoF variants. Related to Figure 3 and STAR Methods.

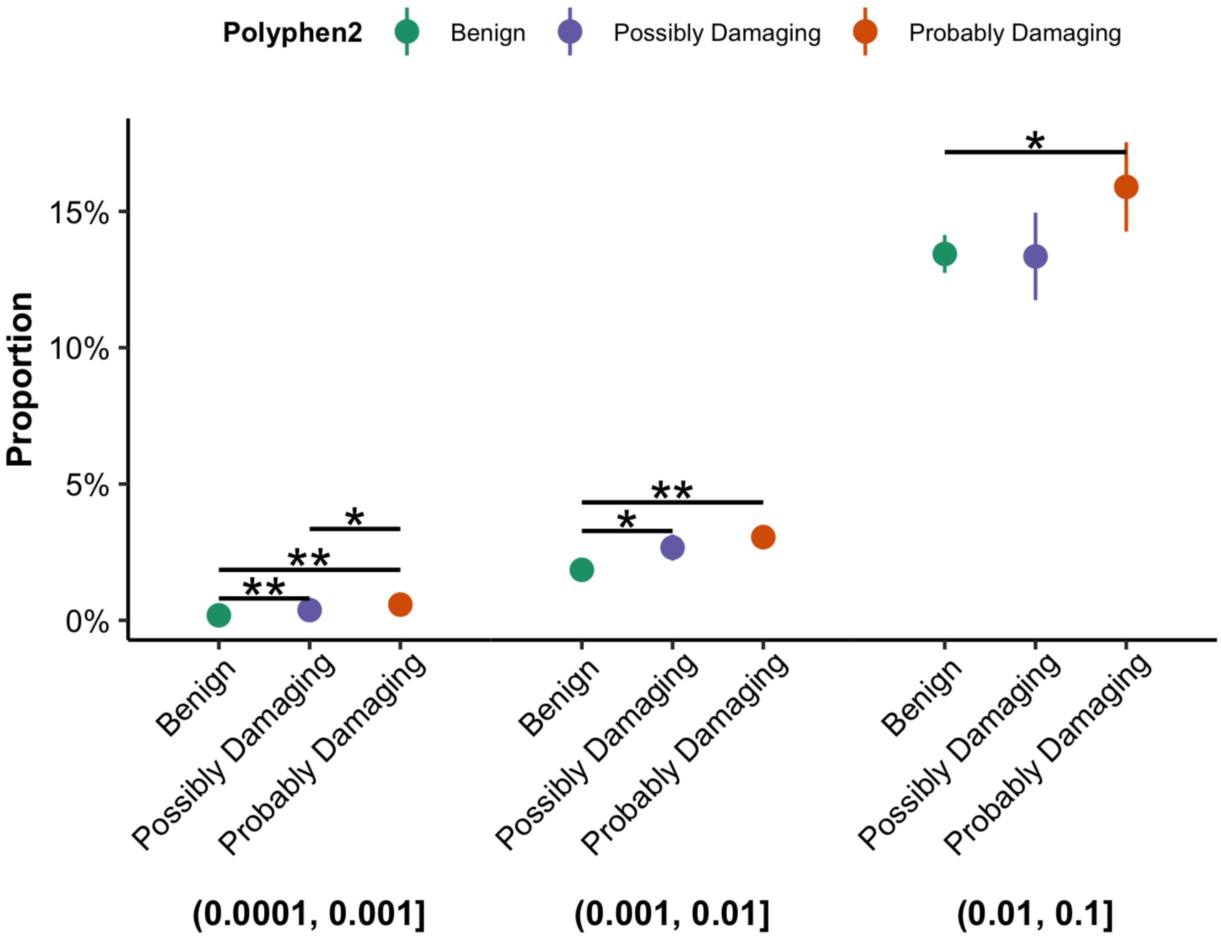
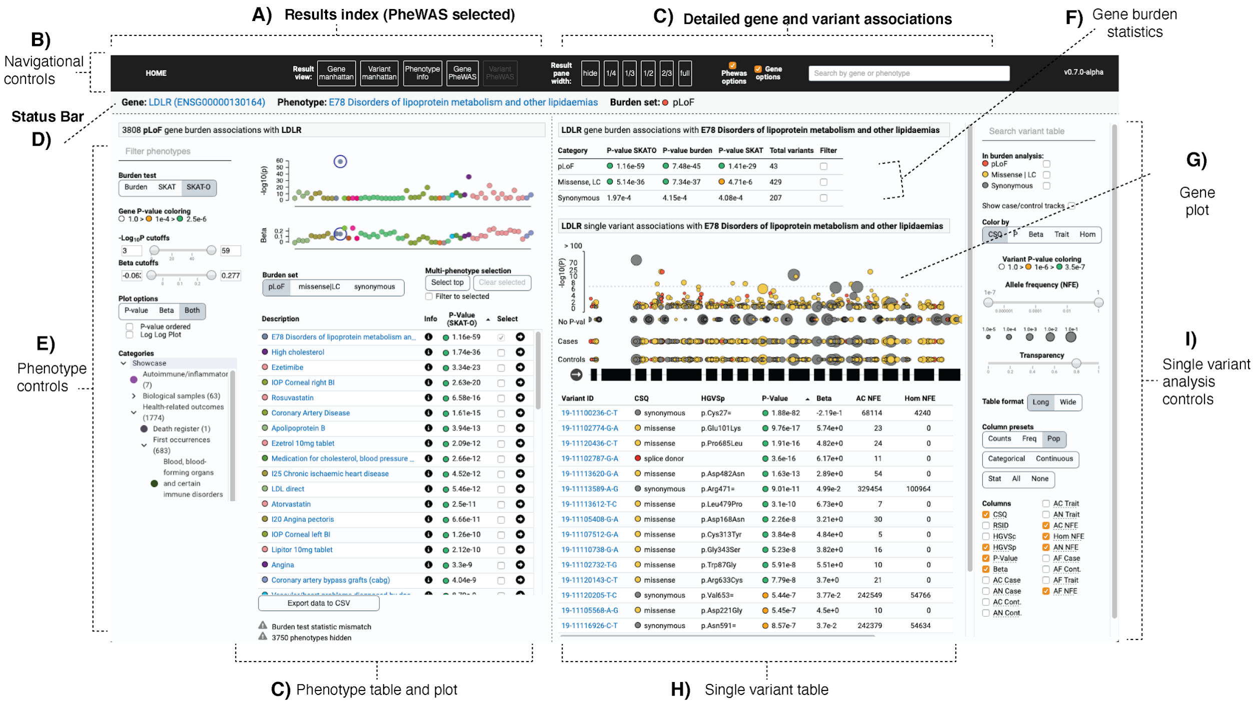


Fig. S20 | The proportion of variants with at least one association is shown broken down by PolyPhen2 annotation group and allele frequency category. * and ** indicate a significant group difference by chi-square test at $p < 0.05$ and $p < 0.001$, respectively. No significant difference is observed for allele frequencies above 10%. Related to Figure 3 and STAR Methods.



**Gene:** LDLR (ENSG00000130164) **Phenotype:** E78 Disorders of lipoprotein metabolism and other lipidaemias **Burden set:** ● pLoF

3808 **pLoF** gene burden associations with **LDLR**

Filter phenotypes

Burden test: Burden SKAT [✓ SKAT-O]

Gene P-value coloring: ○ 1.0 > ● 1e-4 > ● 2.5e-6

-Log₁₀P cutoffs: 3 – 59

Beta cutoffs: -0.06: – 0.277

Plot options: P-value Beta [✓ Both]

□ P-value ordered
□ Log Log Plot

Categories
- Showcase
  - ● Autoimmune/inflammator (7)
  - Biological samples (63)
  - Health-related outcomes (1774)
    - ● Death register (1)
    - First occurrences (683)
      - ● Blood, blood-forming organs and certain immune disorders

Burden set: [✓ pLoF] missense|LC synonymous

Multi-phenotype selection: Select top Clear selected
□ Filter to selected

| Description | Info | P-Value (SKAT-O) | Select |
|---|---|---|---|
| ● E78 Disorders of lipoprotein metabolism an... | ℹ | ● 1.16e-59 | ☑ |
| ● High cholesterol | ℹ | ● 1.74e-36 | □ |
| ● Ezetimibe | ℹ | ● 3.34e-23 | □ |
| ● IOP Corneal right BI | ℹ | ● 2.63e-20 | □ |
| ● Rosuvastatin | ℹ | ● 6.58e-16 | □ |
| ● Coronary Artery Disease | ℹ | ● 1.61e-15 | □ |
| ● Apolipoprotein B | ℹ | ● 3.94e-13 | □ |
| ● Ezetrol 10mg tablet | ℹ | ● 2.09e-12 | □ |
| ● Medication for cholesterol, blood pressure ... | ℹ | ● 2.66e-12 | □ |
| ● I25 Chronic ischaemic heart disease | ℹ | ● 4.52e-12 | □ |
| ● LDL direct | ℹ | ● 5.46e-12 | □ |
| ● Atorvastatin | ℹ | ● 2.5e-11 | □ |
| ● I20 Angina pectoris | ℹ | ● 6.66e-11 | □ |
| ● IOP Corneal left BI | ℹ | ● 1.26e-10 | □ |
| ● Lipitor 10mg tablet | ℹ | ● 2.12e-10 | □ |
| ● Angina | ℹ | ● 3.3e-9 | □ |
| ● Coronary artery bypass grafts (cabg) | ℹ | ● 4.04e-9 | □ |

⚠ Burden test statistic mismatch
⚠ 3750 phenotypes hidden

**LDLR** gene burden associations with **E78 Disorders of lipoprotein metabolism and other lipidaemias**

| Category | P-value SKATO | P-value burden | P-value SKAT | Total variants | Filter |
|---|---|---|---|---|---|
| pLoF | ● 1.16e-59 | ● 7.48e-45 | ● 1.41e-29 | 43 | □ |
| Missense, LC | ● 5.14e-36 | ● 7.34e-37 | ● 4.71e-6 | 429 | □ |
| Synonymous | 1.97e-4 | 4.15e-4 | 4.08e-4 | 207 | □ |

**LDLR** single variant associations with **E78 Disorders of lipoprotein metabolism and other lipidaemias**

| Variant ID | CSQ | HGVSp | P-Value | Beta | AC NFE | Hom NFE |
|---|---|---|---|---|---|---|
| 19-11100236-C-T | ● synonymous | p.Cys27= | ● 1.88e-82 | -2.19e-1 | 68114 | 4240 |
| 19-11102774-G-A | ● missense | p.Glu101Lys | ● 9.76e-17 | 5.74e+0 | 23 | 0 |
| 19-11120436-C-T | ● missense | p.Pro685Leu | ● 1.91e-16 | 4.82e+0 | 24 | 0 |
| 19-11102787-G-A | ● splice donor | | ● 3.6e-16 | 6.17e+0 | 11 | 0 |
| 19-11113620-G-A | ● missense | p.Asp482Asn | ● 1.63e-13 | 2.89e+0 | 54 | 0 |
| 19-11113589-A-G | ● synonymous | p.Arg471= | ● 9.01e-11 | 4.99e-2 | 329454 | 100964 |
| 19-11113612-T-C | ● missense | p.Leu479Pro | ● 3.1e-10 | 6.73e+0 | 7 | 0 |
| 19-11105408-G-A | ● missense | p.Asp168Asn | ● 2.26e-8 | 3.21e+0 | 30 | 0 |
| 19-11107512-G-A | ● missense | p.Cys313Tyr | ● 3.84e-8 | 4.84e+0 | 5 | 0 |
| 19-11110738-G-A | ● missense | p.Gly343Ser | ● 5.23e-8 | 3.82e+0 | 16 | 0 |
| 19-11102732-T-G | ● missense | p.Trp87Gly | ● 5.91e-8 | 5.51e+0 | 10 | 0 |
| 19-11120143-C-T | ● missense | p.Arg633Cys | ● 7.79e-8 | 3.7e+0 | 21 | 0 |
| 19-11120205-T-C | ● synonymous | p.Val653= | ● 5.44e-7 | 3.77e-2 | 242549 | 54766 |
| 19-11105568-A-G | ● missense | p.Asp221Gly | ● 5.45e-7 | 4.5e+0 | 10 | 0 |
| 19-11116926-C-T | ● synonymous | p.Asn591= | ● 8.57e-7 | 3.7e-2 | 242379 | 54634 |

Search variant table

In burden analysis:
● pLoF □
● Missense | LC □
● Synonymous □

Show case/control tracks □

Color by: [✓ CSQ] P Beta Trait Hom

Variant P-value coloring: ○ 1.0 > ● 1e-6 > ● 3.5e-7

Allele frequency (NFE): 1e-7 – 1

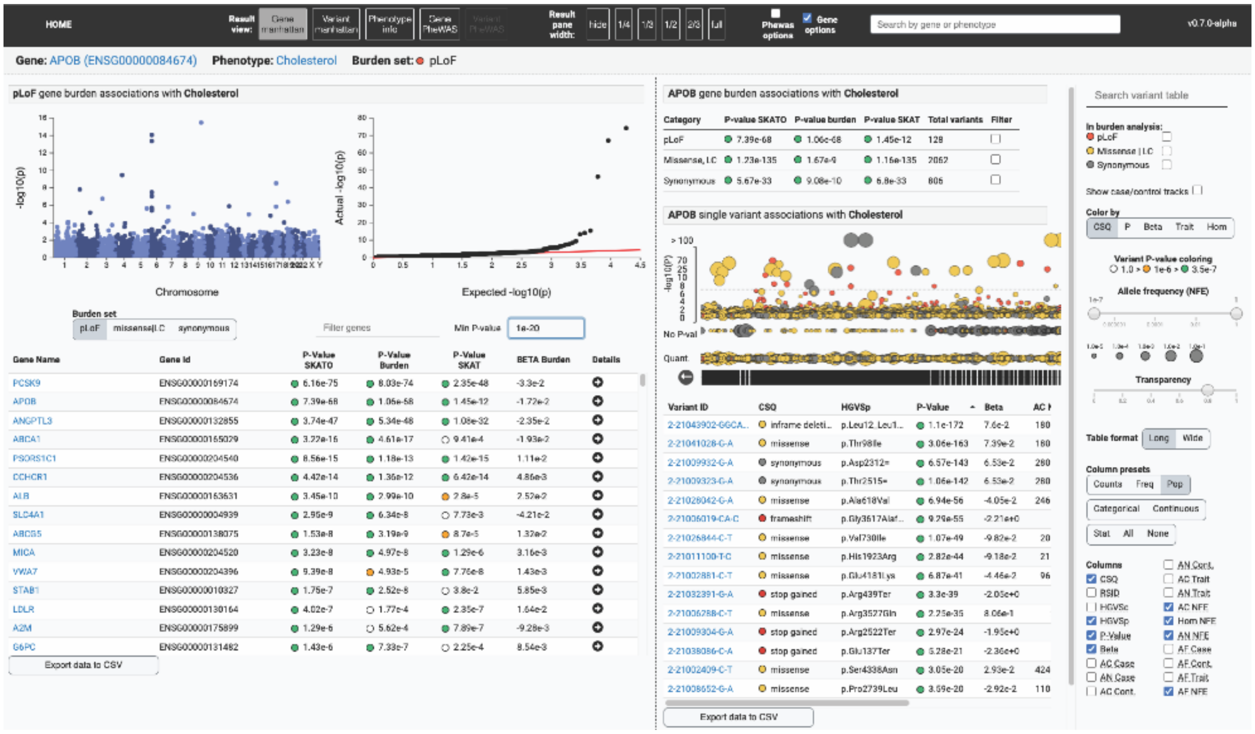
Transparency

Table format: [✓ Long] Wide

Column presets: Counts Freq [✓ Pop]
Categorical Continuous
Stat All None

Columns
☑ CSQ
□ RSID
□ HGVSc
☑ HGVSp
☑ P-Value
☑ Beta
□ AC Case
□ AN Case
□ AC Cont.
□ AN Cont.
□ AC Trait
□ AN Trait
☑ AC NFE
☑ Hom NFE
☑ AN NFE
□ AF Case
□ AF Cont.
□ AF Trait
☑ AF NFE

Fig. S21 | Overview of the UKBB exome gene browser interface. The left hand side of the page provides access to all associations with a given gene, variant, or phenotype. The right hand side is for exploring detailed gene test associations (burden, SKAT-O, SKAT) across annotation groups (pLoF, missense and low confidence pLoF, synonymous) in addition to single variants that were included in the burden tests. Related to STAR Methods.



**Gene:** APOB (ENSG00000084674) **Phenotype:** Cholesterol **Burden set:** ● pLoF

**pLoF** gene burden associations with **Cholesterol**

Burden set: [✓ pLoF] missense|LC synonymous

Filter genes

Min P-value: 1e-20

| Gene Name | Gene Id | P-Value SKATO | P-Value Burden | P-Value SKAT | BETA Burden | Details |
|---|---|---|---|---|---|---|
| PCSK9 | ENSG00000169174 | ● 6.16e-75 | ● 8.03e-74 | ● 2.35e-48 | -3.3e-2 | ⊕ |
| APOB | ENSG00000084674 | ● 7.39e-68 | ● 1.06e-68 | ● 1.45e-12 | -1.72e-2 | ⊕ |
| ANGPTL3 | ENSG00000132855 | ● 3.74e-47 | ● 5.34e-48 | ● 1.08e-32 | -2.35e-2 | ⊕ |
| ABCA1 | ENSG00000165029 | ● 3.22e-16 | ● 4.61e-17 | ○ 9.41e-4 | -1.93e-2 | ⊕ |
| PSORS1C1 | ENSG00000204540 | ● 8.56e-15 | ● 1.18e-13 | ● 1.42e-15 | 1.11e-2 | ⊕ |
| CCHCR1 | ENSG00000204536 | ● 4.42e-14 | ● 1.36e-12 | ● 6.42e-14 | 4.86e-3 | ⊕ |
| ALB | ENSG00000163631 | ● 3.45e-10 | ● 2.99e-10 | ● 2.8e-5 | 2.52e-2 | ⊕ |
| SLC4A1 | ENSG00000004939 | ● 2.95e-9 | ● 6.34e-8 | ○ 7.73e-3 | -4.21e-2 | ⊕ |
| ABCG5 | ENSG00000138075 | ● 1.53e-8 | ● 3.19e-9 | ● 8.7e-5 | 1.32e-2 | ⊕ |
| MICA | ENSG00000204520 | ● 3.23e-8 | ● 4.97e-8 | ● 1.29e-6 | 3.16e-3 | ⊕ |
| VWA7 | ENSG00000204396 | ● 9.39e-8 | ● 4.93e-5 | ● 7.76e-8 | 1.43e-3 | ⊕ |
| STAB1 | ENSG00000010327 | ● 1.75e-7 | ● 2.52e-8 | ○ 3.8e-2 | 5.85e-3 | ⊕ |
| LDLR | ENSG00000130164 | ● 4.02e-7 | ○ 1.77e-4 | ● 2.35e-7 | 1.64e-2 | ⊕ |
| A2M | ENSG00000175899 | ● 1.29e-6 | ○ 5.62e-4 | ● 7.89e-7 | -9.28e-3 | ⊕ |
| G6PC | ENSG00000131482 | ● 1.43e-6 | ● 7.33e-7 | ○ 2.25e-4 | 8.54e-3 | ⊕ |

Export data to CSV

**APOB** gene burden associations with **Cholesterol**

| Category | P-value SKATO | P-value burden | P-value SKAT | Total variants | Filter |
|---|---|---|---|---|---|
| pLoF | ● 7.39e-68 | ● 1.06e-68 | ● 1.45e-12 | 128 | □ |
| Missense, LC | ● 1.23e-135 | ● 1.67e-9 | ● 1.16e-135 | 2062 | □ |
| Synonymous | ● 5.67e-33 | ● 9.08e-10 | ● 6.8e-33 | 806 | □ |

**APOB** single variant associations with **Cholesterol**

| Variant ID | CSQ | HGVSp | P-Value | Beta | AC I |
|---|---|---|---|---|---|
| 2-21043902-GGCA... | ● inframe deleti... | p.Leu12_Leu1... | ● 1.1e-172 | 7.6e-2 | 180 |
| 2-21041028-G-A | ● missense | p.Thr98Ile | ● 3.06e-163 | 7.39e-2 | 180 |
| 2-21009932-G-A | ● synonymous | p.Asp2312= | ● 6.57e-143 | 6.53e-2 | 280 |
| 2-21009323-G-A | ● synonymous | p.Thr2515= | ● 1.06e-142 | 6.53e-2 | 280 |
| 2-21028042-G-A | ● missense | p.Ala618Val | ● 6.94e-56 | -4.05e-2 | 246 |
| 2-21006019-CA-C | ● frameshift | p.Gly3617Alaf... | ● 9.29e-55 | -2.21e+0 | |
| 2-21026844-C-T | ● missense | p.Val730Ile | ● 1.07e-49 | -9.82e-2 | 20 |
| 2-21011100-T-C | ● missense | p.His1923Arg | ● 2.82e-44 | -9.18e-2 | 21 |
| 2-21002881-C-T | ● missense | p.Glu4181Lys | ● 6.87e-41 | -4.46e-2 | 96 |
| 2-21032391-G-A | ● stop gained | p.Arg439Ter | ● 3.3e-39 | -2.05e+0 | |
| 2-21006288-C-T | ● missense | p.Arg3527Gln | ● 2.25e-35 | 8.06e-1 | |
| 2-21009304-G-A | ● stop gained | p.Arg2522Ter | ● 2.97e-24 | -1.95e+0 | |
| 2-21038086-C-A | ● stop gained | p.Glu137Ter | ● 5.28e-21 | -2.36e+0 | |
| 2-21002409-C-T | ● missense | p.Ser4338Asn | ● 3.05e-20 | 2.93e-2 | 424 |
| 2-21008652-G-A | ● missense | p.Pro2739Leu | ● 3.59e-20 | -2.92e-2 | 110 |

Export data to CSV

In burden analysis:
● pLoF □
● Missense | LC □
● Synonymous □

Show case/control tracks □

Color by: [✓ CSQ] P Beta Trait Hom

Variant P-value coloring
○ 1.0 > ● 1e-6 > ● 3.5e-7

Allele frequency (NFE)

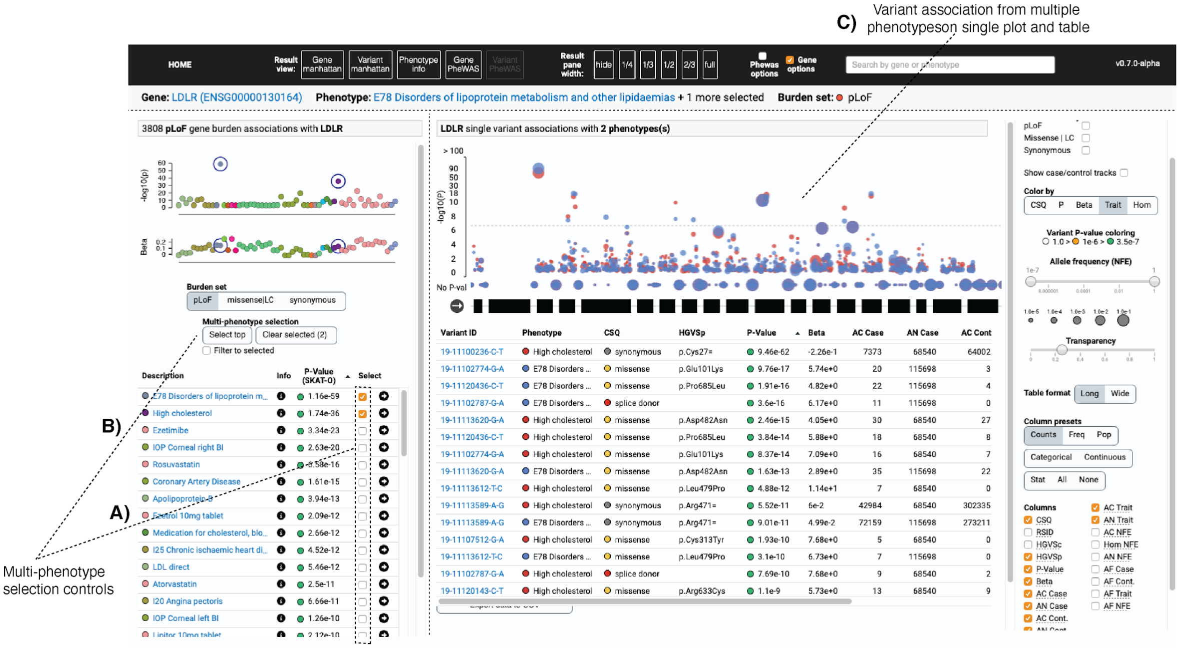
Transparency

Table format: [✓ Long] Wide

Column presets: Counts Freq [✓ Pop]
Categorical Continuous
Stat All None

Columns
☑ CSQ
□ RSID
□ HGVSc
☑ HGVSp
☑ P-Value
☑ Beta
□ AC Case
□ AN Case
□ AC Cont.
□ AN Cont.
□ AC Trait
□ AN Trait
☑ AC NFE
☑ Hom NFE
☑ AN NFE
□ AF Case
□ AF Cont.
□ AF Trait
☑ AF NFE

Fig. S22 | Results by phenotype. For a given phenotype, gene or variant association results are displayed in Manhattan plot formats in addition to an exportable table. Detailed gene results can be quickly previewed using the arrow button located in each row of the table. Related to STAR Methods.



**Gene:** LDLR (ENSG00000130164) **Phenotype:** E78 Disorders of lipoprotein metabolism and other lipidaemias + 1 more selected **Burden set:** ● pLoF

3808 **pLoF** gene burden associations with **LDLR**

**Burden set**
[✓ pLoF] missense|LC synonymous

**Multi-phenotype selection**
Select top | Clear selected (2)
□ Filter to selected

| Description | Info | P-Value (SKAT-O) ▲ | Select | |
|---|---|---|---|---|
| ● E78 Disorders of lipoprotein m... | ℹ | ● 1.16e-59 | ☑ | ➔ |
| ● High cholesterol | ℹ | ● 1.74e-36 | ☑ | ➔ |
| ● Ezetimibe | ℹ | ● 3.34e-23 | □ | ➔ |
| ● IOP Corneal right BI | ℹ | ● 2.63e-20 | □ | ➔ |
| ● Rosuvastatin | ℹ | ● 6.58e-16 | □ | ➔ |
| ● Coronary Artery Disease | ℹ | ● 1.61e-15 | □ | ➔ |
| ● Apolipoprotein-B | ℹ | ● 3.94e-13 | □ | ➔ |
| ● Ezetrol 10mg tablet | ℹ | ● 2.09e-12 | □ | ➔ |
| ● Medication for cholesterol, blo... | ℹ | ● 2.66e-12 | □ | ➔ |
| ● I25 Chronic ischaemic heart di... | ℹ | ● 4.52e-12 | □ | ➔ |
| ● LDL direct | ℹ | ● 5.46e-12 | □ | ➔ |
| ● Atorvastatin | ℹ | ● 2.5e-11 | □ | ➔ |
| ● I20 Angina pectoris | ℹ | ● 6.66e-11 | □ | ➔ |
| ● IOP Corneal left BI | ℹ | ● 1.26e-10 | □ | ➔ |
| ● Lipitor 10mg tablet | ℹ | ● 2.12e-10 | □ | ➔ |

**LDLR** single variant associations with **2 phenotypes(s)**

| Variant ID | Phenotype | CSQ | HGVSp | P-Value ▲ | Beta | AC Case | AN Case | AC Cont |
|---|---|---|---|---|---|---|---|---|
| 19-11100236-C-T | ● High cholesterol | ● synonymous | p.Cys27= | ● 9.46e-62 | -2.26e-1 | 7373 | 68540 | 64002 |
| 19-11102774-G-A | ● E78 Disorders ... | ● missense | p.Glu101Lys | ● 9.76e-17 | 5.74e+0 | 20 | 115698 | 3 |
| 19-11120436-C-T | ● E78 Disorders ... | ● missense | p.Pro685Leu | ● 1.91e-16 | 4.82e+0 | 22 | 115698 | 4 |
| 19-11102787-G-A | ● E78 Disorders ... | ● splice donor | | ● 3.6e-16 | 6.17e+0 | 11 | 115698 | 0 |
| 19-11113620-G-A | ● High cholesterol | ● missense | p.Asp482Asn | ● 2.46e-15 | 4.05e+0 | 30 | 68540 | 27 |
| 19-11120436-C-T | ● High cholesterol | ● missense | p.Pro685Leu | ● 3.84e-14 | 5.88e+0 | 18 | 68540 | 8 |
| 19-11102774-G-A | ● High cholesterol | ● missense | p.Glu101Lys | ● 8.37e-14 | 7.09e+0 | 16 | 68540 | 7 |
| 19-11113620-G-A | ● E78 Disorders ... | ● missense | p.Asp482Asn | ● 1.63e-13 | 2.89e+0 | 35 | 115698 | 22 |
| 19-11113612-T-C | ● High cholesterol | ● missense | p.Leu479Pro | ● 4.88e-12 | 1.14e+1 | 7 | 68540 | 0 |
| 19-11113589-A-G | ● High cholesterol | ● synonymous | p.Arg471= | ● 5.52e-11 | 6e-2 | 42984 | 68540 | 302335 |
| 19-11113589-A-G | ● E78 Disorders ... | ● synonymous | p.Arg471= | ● 9.01e-11 | 4.99e-2 | 72159 | 115698 | 273211 |
| 19-11107512-G-A | ● High cholesterol | ● missense | p.Cys313Tyr | ● 1.93e-10 | 7.68e+0 | 5 | 68540 | 0 |
| 19-11113612-T-C | ● E78 Disorders ... | ● missense | p.Leu479Pro | ● 3.1e-10 | 6.73e+0 | 7 | 115698 | 0 |
| 19-11102787-G-A | ● High cholesterol | ● splice donor | | ● 7.69e-10 | 7.68e+0 | 9 | 68540 | 2 |
| 19-11120143-C-T | ● High cholesterol | ● missense | p.Arg633Cys | ● 1.1e-9 | 5.73e+0 | 13 | 68540 | 9 |

pLoF □
Missense | LC □
Synonymous □

Show case/control tracks □

**Color by**
CSQ P Beta [✓ Trait] Hom

**Variant P-value coloring**
○ 1.0 > ● 1e-6 > ● 3.5e-7

**Allele frequency (NFE)**
1e-7 — 1
0.000001 0.0001 0.01 1
1.0e-5 1.0e-4 1.0e-3 1.0e-2 1.0e-1

**Transparency**
0 0.2 0.4 0.6 0.8 1

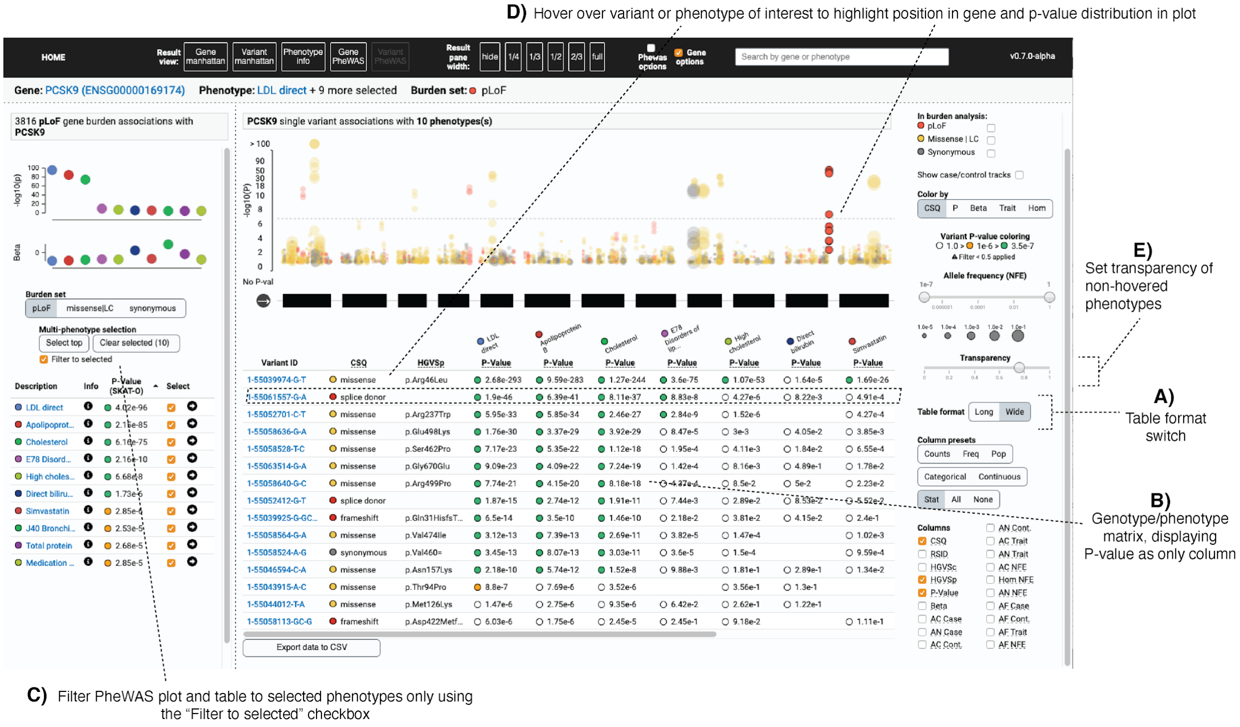
**Table format** [✓ Long] Wide

**Column presets**
[✓ Counts] Freq Pop
Categorical Continuous
Stat All None

**Columns**

| | |
|---|---|
| ☑ CSQ | ☑ AC Trait |
| □ RSID | ☑ AN Trait |
| □ HGVSc | □ AC NFE |
| ☑ HGVSp | □ Hom NFE |
| ☑ P-Value | □ AN NFE |
| ☑ Beta | □ AF Case |
| ☑ AC Case | □ AF Cont. |
| ☑ AN Case | □ AF Trait |
| ☑ AC Cont. | □ AF NFE |
| ☑ AN Cont. | |

Fig. S23 | Multi-phenotype plotting. Many phenotypes can be selected simultaneously to be overlaid for comparison of single variant analysis associations. Related to STAR Methods.



D) Hover over variant or phenotype of interest to highlight position in gene and p-value distribution in plot
E) Set transparency of non-hovered phenotypes
A) Table format switch
B) Genotype/phenotype matrix, displaying P-value as only column
C) Filter PheWAS plot and table to selected phenotypes only using the “Filter to selected” checkbox
HOME
Result view:
Gene manhattan
Variant manhattan
Phenotype info
Gene PheWAS
Variant PheWAS
Result pane width:
hide
1/4
1/3
1/2
2/3
full
Phewas options
Gene options
Search by gene or phenotype
v0.7.0-alpha
-log10(p)
Beta
-log10(P)
No P-val

**Gene:** PCSK9 (ENSG00000169174) **Phenotype:** LDL direct + 9 more selected **Burden set:** ● pLoF

3816 **pLoF** gene burden associations with **PCSK9**

Burden set: [✓ pLoF] missense|LC synonymous

Multi-phenotype selection: Select top | Clear selected (10)

☑ Filter to selected

| Description | Info | P-Value (SKAT-O) ▲ | Select |
|---|---|---|---|
| ● LDL direct | ℹ | ● 4.02e-96 | ☑ ➔ |
| ● Apolipoprot... | ℹ | ● 2.15e-85 | ☑ ➔ |
| ● Cholesterol | ℹ | ● 6.16e-75 | ☑ ➔ |
| ● E78 Disord... | ℹ | ● 2.16e-10 | ☑ ➔ |
| ● High choles... | ℹ | ● 6.68e-8 | ☑ ➔ |
| ● Direct biliru... | ℹ | ● 1.73e-6 | ☑ ➔ |
| ● Simvastatin | ℹ | ● 2.85e-6 | ☑ ➔ |
| ● J40 Bronchi... | ℹ | ● 2.53e-5 | ☑ ➔ |
| ● Total protein | ℹ | ● 2.68e-5 | ☑ ➔ |
| ● Medication ... | ℹ | ● 2.85e-5 | ☑ ➔ |

**PCSK9** single variant associations with **10 phenotypes(s)**

| Variant ID | CSQ | HGVSp | ● LDL direct<br>P-Value | ● Apolipoprotein B<br>P-Value | ● Cholesterol<br>P-Value | ● E78 Disorders of lip...<br>P-Value | ● High cholesterol<br>P-Value | ● Direct bilirubin<br>P-Value | ● Simvastatin<br>P-Value |
|---|---|---|---|---|---|---|---|---|---|
| 1-55039974-G-T | ● missense | p.Arg46Leu | ● 2.68e-293 | ● 9.59e-283 | ● 1.27e-244 | ● 3.6e-75 | ● 1.07e-53 | ○ 1.64e-5 | ● 1.69e-26 |
| 1-55061557-G-A | ● splice donor | | ● 1.9e-46 | ● 6.39e-41 | ● 8.11e-37 | ● 8.83e-8 | ○ 4.27e-6 | ○ 8.22e-3 | ○ 4.91e-4 |
| 1-55052701-C-T | ● missense | p.Arg237Trp | ● 5.95e-33 | ● 5.85e-34 | ● 2.46e-27 | ● 2.84e-9 | ○ 1.52e-6 | | ○ 4.27e-4 |
| 1-55058636-G-A | ● missense | p.Glu498Lys | ● 1.76e-30 | ● 3.37e-29 | ● 3.92e-29 | ○ 8.47e-5 | ○ 3e-3 | ○ 4.05e-2 | ○ 3.85e-3 |
| 1-55058528-T-C | ● missense | p.Ser462Pro | ● 7.17e-23 | ● 5.35e-22 | ● 1.12e-18 | ○ 1.95e-4 | ○ 4.11e-3 | ○ 1.84e-2 | ○ 6.55e-4 |
| 1-55063514-G-A | ● missense | p.Gly670Glu | ● 9.09e-23 | ● 4.09e-22 | ● 7.24e-19 | ○ 1.42e-4 | ○ 8.16e-3 | ○ 4.89e-1 | ○ 1.78e-2 |
| 1-55058640-G-C | ● missense | p.Arg499Pro | ● 7.74e-21 | ● 4.15e-20 | ● 8.18e-18 | ○ 4.37e-4 | ○ 8.5e-2 | ○ 5e-2 | ○ 2.23e-2 |
| 1-55052412-G-T | ● splice donor | | ● 1.87e-15 | ● 2.74e-12 | ● 1.91e-11 | ○ 7.44e-3 | ○ 2.89e-2 | ○ 8.53e-2 | ○ 5.52e-2 |
| 1-55039925-G-GC... | ● frameshift | p.Gln31HisfsT... | ● 6.5e-14 | ● 3.5e-10 | ● 1.46e-10 | ○ 2.18e-2 | ○ 3.81e-2 | ○ 4.15e-2 | ○ 2.4e-1 |
| 1-55058564-G-A | ● missense | p.Val474Ile | ● 3.12e-13 | ● 7.39e-13 | ● 2.69e-11 | ○ 3.82e-5 | ○ 1.47e-4 | | ○ 1.02e-3 |
| 1-55058524-A-G | ● synonymous | p.Val460= | ● 3.45e-13 | ● 8.07e-13 | ● 3.03e-11 | ○ 3.6e-5 | ○ 1.5e-4 | | ○ 9.59e-4 |
| 1-55046594-C-A | ● missense | p.Asn157Lys | ● 2.18e-10 | ● 5.74e-12 | ● 1.52e-8 | ○ 9.88e-3 | ○ 1.81e-1 | ○ 2.89e-1 | ○ 1.34e-2 |
| 1-55043915-A-C | ● missense | p.Thr94Pro | ● 8.8e-7 | ○ 7.69e-6 | ○ 3.52e-6 | | ○ 3.56e-1 | ○ 1.3e-1 | |
| 1-55044012-T-A | ● missense | p.Met126Lys | ○ 1.47e-6 | ○ 2.75e-6 | ○ 9.35e-6 | ○ 6.42e-2 | ○ 2.62e-1 | ○ 1.22e-1 | |
| 1-55058113-GC-G | ● frameshift | p.Asp422Metf... | ○ 6.03e-6 | ○ 1.75e-6 | ○ 2.45e-5 | ○ 2.45e-1 | ○ 9.18e-2 | | ○ 1.11e-1 |

Export data to CSV

In burden analysis:
● pLoF □
● Missense | LC □
● Synonymous □

Show case/control tracks □

Color by: [✓ CSQ] P Beta Trait Hom

Variant P-value coloring: ○ 1.0 > ● 1e-6 > ● 3.5e-7
▲ Filter < 0.5 applied

Allele frequency (NFE): 1e-7 – 1

Transparency

Table format: Long [✓ Wide]

Column presets: Counts Freq Pop | Categorical Continuous | [✓ Stat] All None

Columns:
☑ CSQ
□ RSID
□ HGVSc
☑ HGVSp
☑ P-Value
□ Beta
□ AC Case
□ AN Case
□ AC Cont.
□ AN Cont.
□ AC Trait
□ AN Trait
□ AC NFE
□ Hom NFE
□ AN NFE
□ AF Case
□ AF Cont.
□ AF Trait
□ AF NFE

D) Hover over variant or phenotype of interest to highlight position in gene and p-value distribution in plot

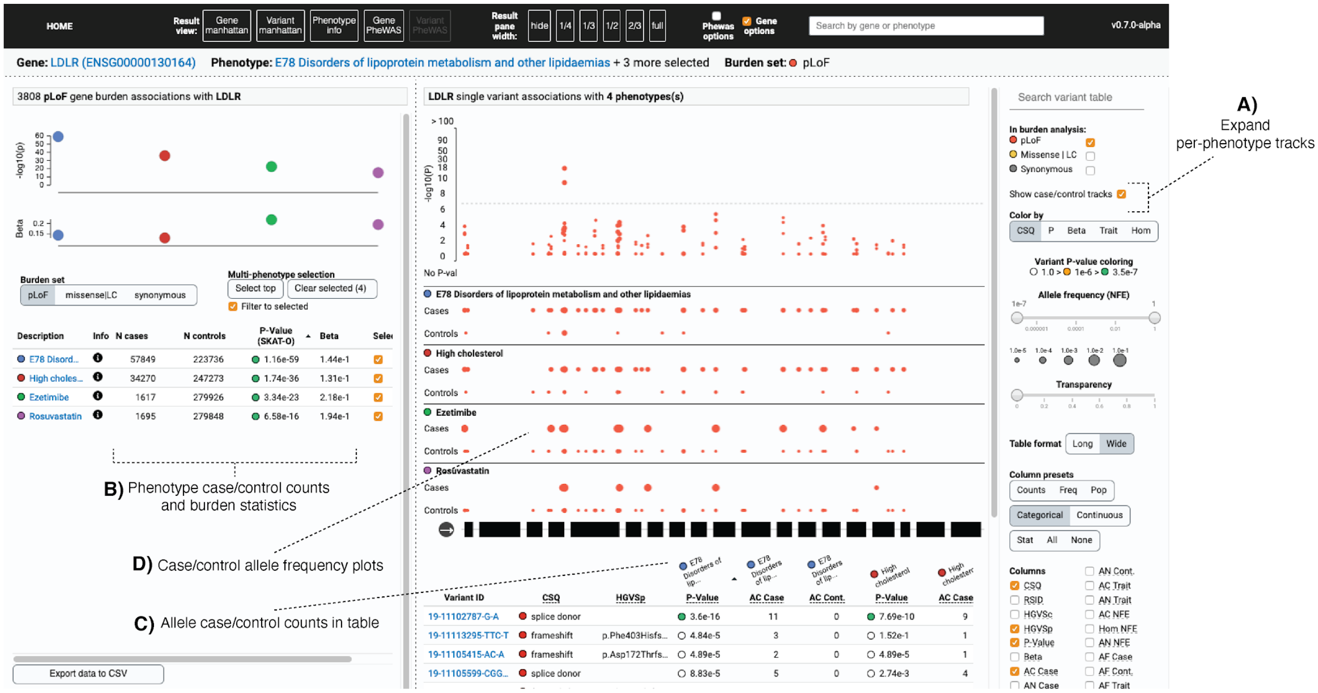
E) Set transparency of non-hovered phenotypes

A) Table format switch

B) Genotype/phenotype matrix, displaying P-value as only column

C) Filter PheWAS plot and table to selected phenotypes only using the “Filter to selected” checkbox

Fig. S24 | Using hover interactions with the multi-phenotype pivot table. Here 10 LDLR associations are compared simultaneously and one splice donor of interest is hovered in the variant table to highlight the plot. Related to STAR Methods.



**Gene:** LDLR (ENSG00000130164) **Phenotype:** E78 Disorders of lipoprotein metabolism and other lipidaemias + 3 more selected **Burden set:** ● pLoF

3808 **pLoF** gene burden associations with **LDLR**

**Burden set** [✓ pLoF] missense|LC synonymous

**Multi-phenotype selection** Select top | Clear selected (4)

☑ Filter to selected

| Description | Info | N cases | N controls | P-Value (SKAT-O) ▲ | Beta | Sele |
|---|---|---|---|---|---|---|
| ● E78 Disord... | ℹ | 57849 | 223736 | ● 1.16e-59 | 1.44e-1 | ☑ |
| ● High choles... | ℹ | 34270 | 247273 | ● 1.74e-36 | 1.31e-1 | ☑ |
| ● Ezetimibe | ℹ | 1617 | 279926 | ● 3.34e-23 | 2.18e-1 | ☑ |
| ● Rosuvastatin | ℹ | 1695 | 279848 | ● 6.58e-16 | 1.94e-1 | ☑ |

Export data to CSV

**LDLR** single variant associations with **4 phenotypes(s)**

● **E78 Disorders of lipoprotein metabolism and other lipidaemias**

● **High cholesterol**

● **Ezetimibe**

● **Rosuvastatin**

| Variant ID | CSQ | HGVSp | ● E78 Disorders of lip...<br>P-Value ▲ | ● E78 Disorders of lip...<br>AC Case | ● E78 Disorders of lip...<br>AC Cont. | ● High cholesterol<br>P-Value | ● High cholester<br>AC Case |
|---|---|---|---|---|---|---|---|
| 19-11102787-G-A | ● splice donor | | ● 3.6e-16 | 11 | 0 | ● 7.69e-10 | 9 |
| 19-11113295-TTC-T | ● frameshift | p.Phe403Hisfs... | ○ 4.84e-5 | 3 | 0 | ○ 1.52e-1 | 1 |
| 19-11105415-AC-A | ● frameshift | p.Asp172Thrfs... | ○ 4.89e-5 | 2 | 0 | ○ 4.89e-5 | 1 |
| 19-11105599-CGG... | ● splice donor | | ○ 8.83e-5 | 5 | 0 | ○ 2.74e-3 | 4 |

**In burden analysis:**
● pLoF ☑
● Missense | LC □
● Synonymous □

Show case/control tracks ☑

**Color by** [✓ CSQ] P Beta Trait Hom

**Variant P-value coloring**
○ 1.0 > ● 1e-6 > ● 3.5e-7

**Allele frequency (NFE)**

**Transparency**

**Table format** Long [✓ Wide]

**Column presets**
Counts Freq Pop
[✓ Categorical] Continuous
Stat All None

**Columns**

| | |
|---|---|
| ☑ CSQ | □ AN Cont. |
| □ RSID | □ AC Trait |
| □ HGVSc | □ AN Trait |
| ☑ HGVSp | □ AC NFE |
| ☑ P-Value | □ Hom NFE |
| □ Beta | □ AN NFE |
| ☑ AC Case | □ AF Case |
| □ AN Case | □ AF Cont. |
| | □ AF Trait |

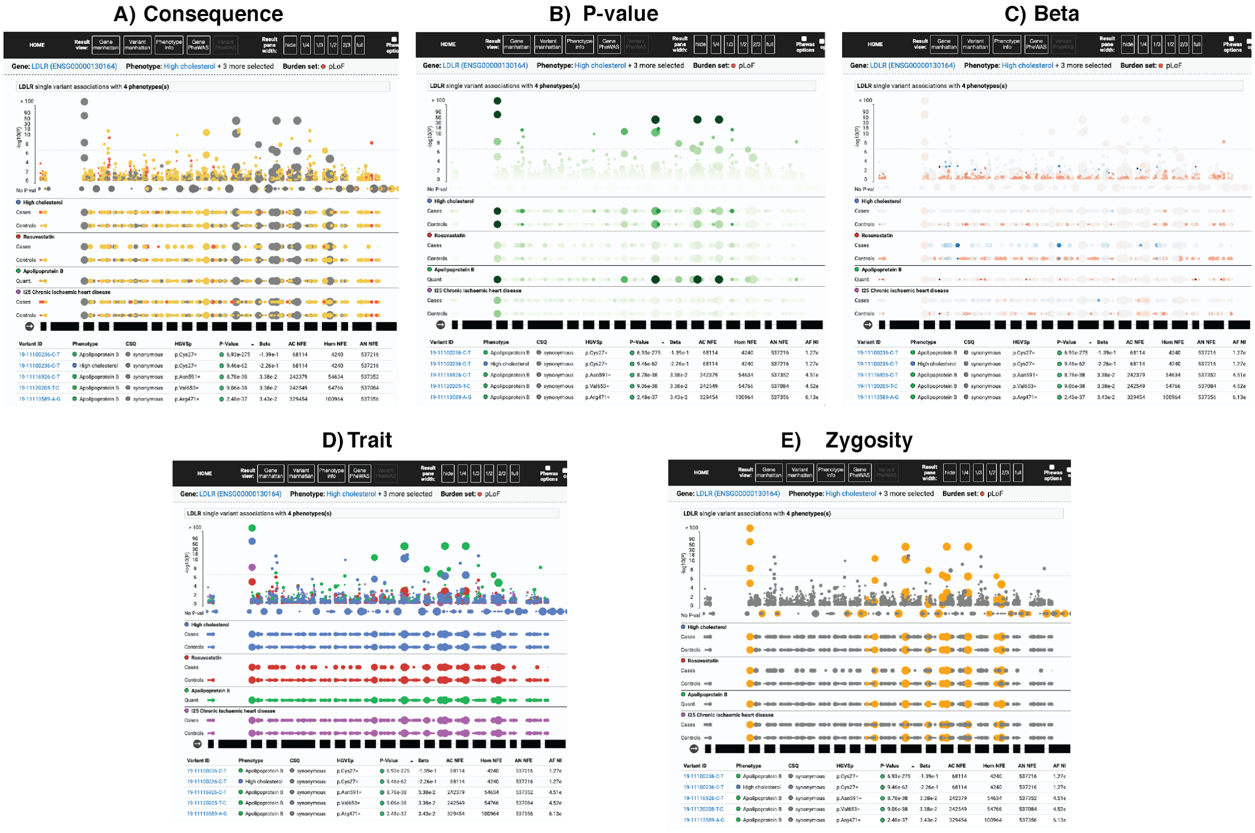
**A)** Expand per-phenotype tracks

**B)** Phenotype case/control counts and burden statistics

**D)** Case/control allele frequency plots

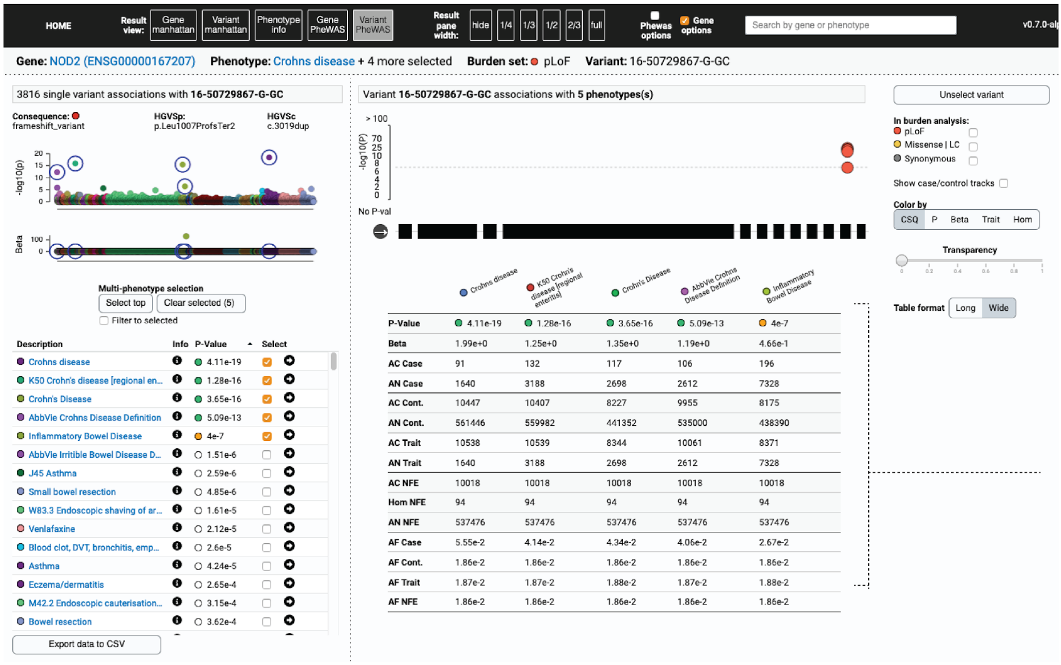
**C)** Allele case/control counts in table

Fig. S25 | Viewing case-control counts and allele frequencies for pLoF variants across traits in a gene. Related to STAR Methods.



| Variant ID | Phenotype | CSQ | HGVSp | P-Value | Beta | AC NFE | Hom NFE | AN NFE |
|---|---|---|---|---|---|---|---|---|
| 19-11100236-C-T | Apolipoprotein B | synonymous | p.Cys27= | 6.93e-275 | -1.39e-1 | 68114 | 4240 | 537216 |
| 19-11100236-C-T | High cholesterol | synonymous | p.Cys27= | 9.46e-62 | -2.26e-1 | 68114 | 4240 | 537216 |
| 19-11116926-C-T | Apolipoprotein B | synonymous | p.Asn591= | 8.78e-38 | 3.38e-2 | 242379 | 54634 | 537352 |
| 19-11120205-T-C | Apolipoprotein B | synonymous | p.Val653= | 9.06e-38 | 3.38e-2 | 242549 | 54766 | 537084 |
| 19-11113589-A-G | Apolipoprotein B | synonymous | p.Arg471= | 2.48e-37 | 3.43e-2 | 329454 | 100964 | 537356 |

Fig. S26 | Color variants by attribute to uncover patterns in A) consequence, B) p-value, C) beta, D) trait, or E) zygosity. Related to STAR Methods.



**Gene:** NOD2 (ENSG00000167207) **Phenotype:** Crohns disease + 4 more selected **Burden set:** ● pLoF **Variant:** 16-50729867-G-GC

3816 single variant associations with **16-50729867-G-GC**

**Consequence:** ● frameshift_variant **HGVSp:** p.Leu1007ProfsTer2 **HGVSc** c.3019dup

□ Filter to selected

| Description | Info | P-Value ▲ | Select | |
|---|---|---|---|---|
| ● Crohns disease | ℹ | ● 4.11e-19 | ☑ | ➡ |
| ● K50 Crohn's disease [regional en... | ℹ | ● 1.28e-16 | ☑ | ➡ |
| ● Crohn's Disease | ℹ | ● 3.65e-16 | ☑ | ➡ |
| ● AbbVie Crohns Disease Definition | ℹ | ● 5.09e-13 | ☑ | ➡ |
| ● Inflammatory Bowel Disease | ℹ | ● 4e-7 | ☑ | ➡ |
| ● AbbVie Irritible Bowel Disease D... | ℹ | ○ 1.51e-6 | □ | ➡ |
| ● J45 Asthma | ℹ | ○ 2.59e-6 | □ | ➡ |
| ● Small bowel resection | ℹ | ○ 4.85e-6 | □ | ➡ |
| ● W83.3 Endoscopic shaving of ar... | ℹ | ○ 1.61e-5 | □ | ➡ |
| ● Venlafaxine | ℹ | ○ 2.12e-5 | □ | ➡ |
| ● Blood clot, DVT, bronchitis, emp... | ℹ | ○ 2.6e-5 | □ | ➡ |
| ● Asthma | ℹ | ○ 4.24e-5 | □ | ➡ |
| ● Eczema/dermatitis | ℹ | ○ 2.65e-4 | □ | ➡ |
| ● M42.2 Endoscopic cauterisation... | ℹ | ○ 3.15e-4 | □ | ➡ |
| ● Bowel resection | ℹ | ○ 3.62e-4 | □ | ➡ |

Variant **16-50729867-G-GC** associations with **5 phenotypes(s)**

| | ● Crohns disease | ● K50 Crohn's disease [regional enteritis] | ● Crohn's Disease | ● AbbVie Crohns Disease Definition | ● Inflammatory Bowel Disease |
|---|---|---|---|---|---|
| **P-Value** | ● 4.11e-19 | ● 1.28e-16 | ● 3.65e-16 | ● 5.09e-13 | ● 4e-7 |
| **Beta** | 1.99e+0 | 1.25e+0 | 1.35e+0 | 1.19e+0 | 4.66e-1 |
| **AC Case** | 91 | 132 | 117 | 106 | 196 |
| **AN Case** | 1640 | 3188 | 2698 | 2612 | 7328 |
| **AC Cont.** | 10447 | 10407 | 8227 | 9955 | 8175 |
| **AN Cont.** | 561446 | 559982 | 441352 | 535000 | 438390 |
| **AC Trait** | 10538 | 10539 | 8344 | 10061 | 8371 |
| **AN Trait** | 1640 | 3188 | 2698 | 2612 | 7328 |
| **AC NFE** | 10018 | 10018 | 10018 | 10018 | 10018 |
| **Hom NFE** | 94 | 94 | 94 | 94 | 94 |
| **AN NFE** | 537476 | 537476 | 537476 | 537476 | 537476 |
| **AF Case** | 5.55e-2 | 4.14e-2 | 4.34e-2 | 4.06e-2 | 2.67e-2 |
| **AF Cont.** | 1.86e-2 | 1.86e-2 | 1.86e-2 | 1.86e-2 | 1.86e-2 |
| **AF Trait** | 1.87e-2 | 1.87e-2 | 1.88e-2 | 1.87e-2 | 1.88e-2 |
| **AF NFE** | 1.86e-2 | 1.86e-2 | 1.86e-2 | 1.86e-2 | 1.86e-2 |

**In burden analysis:**
● pLoF □
● Missense | LC □
● Synonymous □

Show case/control tracks □

**Color by** [✓ CSQ] P Beta Trait Hom

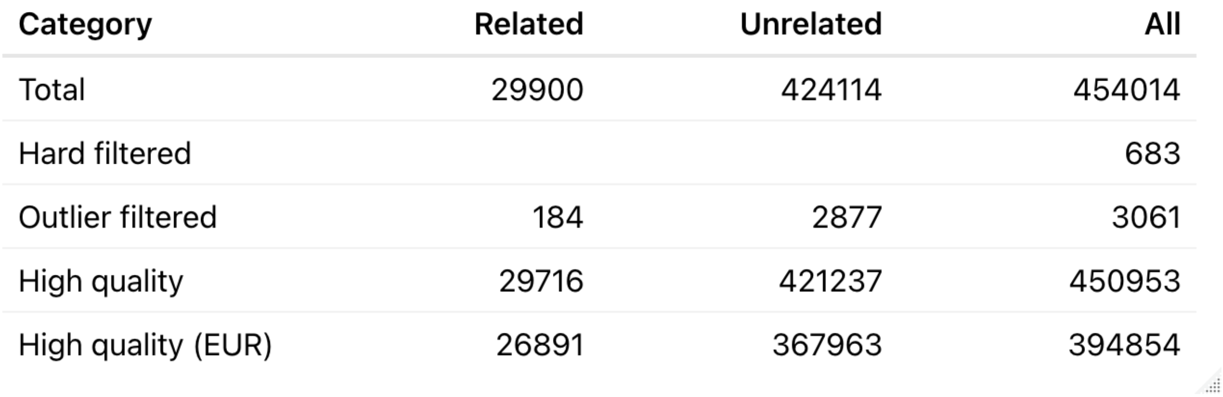
**Table format** Long [✓ Wide]

Press unselect to go back to gene

Compare variant results across selected traits

Fig. S27 | Single variant page. Related to STAR Methods.

Table S1 | Final sample counts passing QC. "nfe" refers to samples inferred as having non-Finnish European ancestry. Note that relatedness was run after hard filtering, so the total number of related and unrelated individuals is equal to the total number of samples less 683. Related to STAR Methods.



| Category | Related | Unrelated | All |
|---|---:|---:|---:|
| Total | 29900 | 424114 | 454014 |
| Hard filtered | | | 683 |
| Outlier filtered | 184 | 2877 | 3061 |
| High quality | 29716 | 421237 | 450953 |
| High quality (EUR) | 26891 | 367963 | 394854 |

Table S2 | QC of summary statistics. All filters are applied sequentially. Related to STAR Methods.

| | Description | Count<br>(% Percentage Remaining) | | | |
|---|---|---|---|---|---|
| | | **pLoF** | **Missense** | **Synonymous** | **Total** |
| **Group<br>(SKAT-O)** | Before filtering | 18,358 | 19,403 | 19,372 | 75,767<br>(Oth:18,634) |
| | Number of variants >= 2 | 17,876<br>(97.4%) | 19,392<br>(99.9%) | 19,355<br>(99.9%) | 75,251<br>(99.3%)<br>(Oth:18,628) |
| | Mean coverage >= 20 | 17,370<br>(94.6%) | 18,791<br>(96.8%) | 18,768<br>(96.9%) | 72,999<br>(96.3%)<br>(Oth:18,070) |
| | At least 1 phenotype with expected AC (CAF*n_cases) >= 50 | 8,044<br>(43.8%) | 18,461<br>(95.1%) | 18,068<br>(93.3%) | 62,350<br>(82.3%)<br>(Oth:17,777) |
| | Lambda of the synonymous group > 0.75 | 7,296<br>(39.7%) | 15,943<br>(82.2%) | 16,014<br>(82.7%) | 54,647<br>(72.1%)<br>(Oth:15,394) |
| **Variant** | Before filtering | 515,246 | 5,279,243 | 2,274,565 | 8,074,878<br>(NA: 5,824) |
| | Annotation defined | 515,246 | 5,279,243 | 2,274,565 | 8,069,054<br>(99.9%) |
| | At least 1 phenotype with expected AC (AF*n_cases) >= 50 | 6,117<br>(1.2%) | 155,705<br>(2.9%) | 101,874<br>(4.5%) | 263,696<br>(3.3%) |
| | | **Continuous** | **Categorical** | **Disease (ICD)** | **Total** |
| **Phenotype<br>(SKAT-O)** | Before filtering | 1,233 | 2,571 | 725 | 4,529 |
| | Lambda > 0.75 | 1,233<br>(100%) | 2,514<br>(97.8%) | 710<br>(97.9%) | 4,457<br>(98.4%) |
| | Correlation < 0.5 | 677<br>(54.9%) | 2,434<br>(94.7%) | 708<br>(97.7%) | 3,819<br>(84.3%) |

Table S3 | Comparison to 32 rare (MAF < 1%) variants associated with adult height in GIANT; in UK Biobank, 21 of these variants are found to be associated with height at $p < 8 \times 10^{-9}$ (blue), and 29 are associated with height at $p < 0.05$ (light blue). Related to STAR Methods.

| Locus | Allele (Ref) | Allele (Alt) | Annotation | Gene | P-value | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | UK Biobank | GIANT | | |
| | | | | | | Discovery | Validation | Combined |
| 1:32673514 | G | C | missense | IQCC | 1.11E-10 | 7.92E-08 | 3.83E-06 | 1.34E-12 |
| 1:41540902 | G | A | missense | SCMH1 | 1.34E-27 | 1.58E-25 | 9.42E-13 | 1.35E-36 |
| 1:41618297 | G | A | missense | SCMH1 | 6.88E-24 | 1.92E-15 | 1.32E-08 | 1.80E-22 |
| 1:149902342 | C | T | missense | MTMR11 | 1.82E-14 | 4.16E-06 | 7.11E-06 | 3.03E-10 |
| 1:183495812 | A | G | missense | SMG7 | 5.47E-14 | 4.97E-11 | 8.94E-05 | 1.61E-14 |
| 1:223178026 | T | C | missense | DISP1 | NA | 1.11E-09 | 1.22E-06 | 1.27E-14 |
| 2:219920461 | T | A | missense | IHH | 1.17E-06 | 1.09E-15 | 1.48E-09 | 1.85E-23 |
| 2:220078652 | C | T | missense | ABCB6 | 3.13E-16 | 3.43E-13 | 4.40E-04 | 2.47E-15 |
| 3:46939587 | C | T | missense | PTH1R | 9.93E-09 | 1.30E-11 | 5.48E-10 | 1.14E-19 |
| 4:73179445 | C | T | missense | ADAMTS3 | 5.40E-10 | 1.82E-08 | 1.32E-04 | 1.30E-11 |
| 4:120422407 | T | G | missense | PDE5A | 1.04E-10 | 7.50E-17 | 1.28E-08 | 2.65E-23 |
| 5:32784907 | G | A | missense | NPR3 | 3.93E-22 | 1.05E-08 | 1.78E-06 | 7.91E-14 |
| 5:64766798 | G | A | missense | ADAMTS6 | 9.39E-17 | 7.82E-09 | 1.37E-08 | 4.80E-16 |
| 5:127668685 | G | T | missense | FBN2 | 1.04E-30 | 2.47E-33 | 5.06E-20 | 1.47E-52 |
| 5:172755066 | C | A | missense | STC2 | 2.25E-34 | 5.69E-15 | 1.32E-17 | 1.15E-30 |
| 6:155450779 | A | G | missense | TIAM2 | NA | 1.45E-08 | 8.50E-01 | 3.96E-08 |
| 7:73482987 | G | A | missense | ELN | 1.48E-13 | 2.63E-06 | 1.51E-03 | 2.31E-08 |
| 8:135614553 | G | C | missense | ZFAT | 2.66E-45 | 4.42E-26 | 1.20E-14 | 6.12E-38 |
| 8:135622851 | G | A | missense | ZFAT | 4.76E-14 | 1.54E-12 | 5.94E-18 | 2.05E-28 |
| 11:27016360 | G | A | missense | FIBIN | 3.70E-08 | 5.79E-12 | 1.56E-03 | 3.26E-14 |
| 11:94533444 | G | A | missense | AMOTL1 | 1.96E-06 | 9.01E-16 | 3.84E-07 | 2.84E-21 |
| 12:58138971 | G | A | missense | TSPAN31 | 4.63E-01 | 8.26E-08 | 2.85E-03 | 5.50E-09 |
| 12:121756084 | G | A | missense | ANAPC5 | 4.32E-15 | 1.09E-11 | 1.44E-11 | 1.45E-21 |
| 15:44153571 | C | T | missense | WDR76 | 1.05E-04 | 1.56E-06 | 3.42E-04 | 2.32E-09 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 15:89424870 | G | T | missense | HAPLN3 | 1.51E-33 | 2.84E-13 | 2.43E-11 | 1.02E-22 |
| 16:31474091 | A | G | missense / splice acceptor | ARMC5 | 5.76E-10 | 5.88E-12 | 1.16E-03 | 1.62E-13 |
| 16:47684830 | C | A | missense | PHKB | 1.39E-06 | 3.96E-14 | 1.04E-01 | 3.43E-12 |
| 16:67470505 | G | A | missense | HSD11B2 | 4.15E-08 | 1.27E-07 | 3.38E-04 | 1.97E-10 |
| 16:84900645 | G | A | missense | CRISPLD2 | 5.32E-14 | 9.13E-12 | 4.34E-09 | 2.92E-19 |
| 16:84902472 | G | A | missense | CRISPLD2 | 2.66E-22 | 7.75E-14 | 3.49E-08 | 2.36E-20 |
| 16:88798919 | G | T | missense | PIEZO1 | 4.38E-17 | 5.27E-12 | 1.99E-08 | 8.68E-19 |
| X:66941751 | C | G | missense | AR | 1.06E-08 | 7.05E-07 | 7.12E-09 | 2.67E-14 |

Table S4 | Comparison to 59 low-frequency (MAF between 1% and 5%) variants associated with adult height in GIANT; in UK Biobank, 10 of the variants were not tested, 30 of these variants are found to be associated with height at $p < 8 \times 10^{-9}$ (blue), and 49 are associated with height at $p < 0.05$ (light blue). Related to STAR Methods.

| Locus | Allele (Ref) | Allele (Alt) | Annotation | Gene | P-value | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | UK Biobank | GIANT | | |
| | | | | | | Discovery | Validation | Combined |
| 1:51873967 | G | A | missense | EPS15 | 3.84E-18 | 5.07E-08 | 7.60E-11 | 2.56E-17 |
| 1:119427467 | A | C | missense | TBX15 | 6.10E-31 | 1.61E-24 | 4.19E-15 | 2.79E-36 |
| 1:150551327 | G | A | missense | MCL1 | 1.33E-25 | 2.16E-09 | 7.86E-12 | 1.55E-19 |
| 1:154987704 | C | T | missense | ZBTB7B | 1.82E-12 | 7.30E-17 | 4.46E-10 | 3.46E-25 |
| 1:180886140 | C | T | missense | KIAA1614 | 1.50E-05 | 1.41E-06 | 4.51E-04 | 2.63E-09 |
| 2:20205541 | C | T | missense | MATN3 | NA | 2.67E-23 | 6.60E-19 | 3.74E-41 |
| 2:219949184 | C | T | intron | NHEJ1 | NA | 5.96E-21 | 1.12E-15 | 8.20E-37 |
| 2:179474668 | G | A | missense | TTN | NA | 1.35E-07 | 2.15E-01 | 3.44E-07 |
| 2:233077064 | A | G | intron | DIS3L2 | NA | 2.35E-16 | 2.58E-15 | 6.46E-31 |
| 3:14214524 | G | A | missense | XPC | 1.22E-09 | 1.22E-08 | 1.68E-02 | 1.29E-08 |
| 3:47162886 | C | T | missense | SETD2 | 1.30E-08 | 2.24E-08 | 2.22E-07 | 1.65E-13 |
| 3:49162583 | C | T | missense | LAMB2 | 2.72E-37 | 3.28E-12 | 1.33E-16 | 3.49E-27 |
| 3:98600385 | T | C | missense | DCBLD2 | 4.69E-04 | 1.23E-07 | 5.62E-05 | 1.68E-12 |
| 4:5016883 | G | A | missense | CYTL1 | 8.93E-18 | 2.01E-17 | 6.68E-11 | 1.86E-25 |
| 4:87730980 | C | T | missense | PTPN13 | 6.71E-36 | 1.94E-19 | 1.38E-15 | 9.43E-32 |
| 4:135121721 | T | C | missense | PABPC4L | 4.83E-07 | 1.39E-13 | 1.33E-04 | 7.54E-16 |
| 4:144359490 | C | T | missense | GAB1 | 8.42E-07 | 1.04E-08 | 3.24E-04 | 4.29E-12 |
| 4:154557616 | C | T | missense | TMEM131L | 4.32E-08 | 7.75E-08 | 5.75E-06 | 2.18E-12 |
| 5:102338811 | A | G | missense | PAM | NA | 3.76E-06 | 8.47E-06 | 1.63E-10 |
| 5:126250812 | C | T | missense | MARCH3 | 5.87E-05 | 4.25E-08 | 2.45E-03 | 1.67E-10 |
| 5:135288632 | A | G | missense | LECT2 | 7.90E-06 | 1.02E-07 | 4.77E-04 | 1.36E-09 |
| 5:172196752 | A | G | missense | DUSP1 | 6.30E-14 | 4.00E-14 | 1.26E-06 | 1.93E-20 |
| 5:176637471 | G | A | missense | NSD1 | 3.58E-23 | 2.38E-17 | 2.62E-12 | 4.27E-30 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 5:176722005 | G | A | missense | NSD1 | 1.01E-37 | 1.86E-26 | 8.42E-18 | 2.32E-41 |
| 6:30851933 | G | A | intron | DDRI | NA | 1.11E-08 | 1.24E-05 | 4.64E-13 |
| 6:34730395 | C | T | synonymous | SNRPC | 5.24E-52 | 9.21E-33 | 9.59E-31 | 3.45E-60 |
| 6:41903798 | C | A | missense | CCND3 | 1.74E-41 | 5.51E-17 | 3.41E-08 | 1.28E-22 |
| 7:99489571 | G | A | 3'UTR | TRIM4 | NA | 3.28E-10 | 2.26E-07 | 1.40E-17 |
| 7:100490077 | G | A | synonymous | ACHE | 3.34E-06 | 8.59E-10 | 2.92E-02 | 2.98E-10 |
| 7:135123060 | G | C | missense | CNOT4 | 4.59E-20 | 2.31E-17 | 5.04E-10 | 3.90E-26 |
| 8:42226805 | C | G | missense | POLB | 8.53E-05 | 1.95E-06 | 1.30E-02 | 1.88E-07 |
| 9:34660864 | C | T | missense | IL11RA | 7.28E-11 | 5.20E-13 | 4.42E-03 | 4.01E-13 |
| 9:95063947 | C | T | missense | NOL8 | 3.67E-04 | 2.56E-06 | 3.45E-02 | 3.33E-06 |
| 10:79580976 | G | A | missense | DLG5 | 1.68E-21 | 2.72E-11 | 5.15E-11 | 7.66E-20 |
| 10:97919011 | A | G | missense | ZNF518A | 1.29E-05 | 9.94E-08 | 3.05E-03 | 3.91E-09 |
| 11:65715204 | G | A | missense | TSGA10IP | 2.23E-41 | 1.82E-21 | 1.41E-23 | 1.52E-43 |
| 12:7548996 | C | G | missense | CD163L1 | 1.05E-03 | 4.11E-08 | 6.68E-02 | 1.87E-08 |
| 12:69140339 | G | C | missense | SLC35E3 | 1.87E-10 | 1.13E-09 | 5.UE-04 | 1.29E-11 |
| 12:104408832 | T | C | missense | GLT8D2 | NA | 8.72E-10 | 5.82E-10 | 1.60E-17 |
| 13:50842259 | G | A | intron | DLEU1 | NA | 2.33E-37 | 7.02E-25 | 5.66E-57 |
| 14:23313633 | G | A | missense | MMP14 | 5.63E-08 | 1.72E-08 | 7.81E-09 | 3.27E-16 |
| 14:24707479 | G | A | missense | GMPR2 | 1.38E-16 | 3.67E-16 | 1.34E-11 | 2.13E-29 |
| 14:45403699 | C | A | missense | KLHL28 | 1.53E-07 | 1.55E-06 | 4.13E-04 | 3.05E-09 |
| 14:70633411 | C | T | missense | SLC8A3 | 4.05E-11 | 2.49E-11 | 2.02E-06 | 2.03E-16 |
| 14:94844947 | C | T | missense | SERPINA1 | 1.53E-100 | 1.39E-45 | 2.50E-34 | 1.72E-75 |
| 14:101349454 | G | T | missense | RTL1 | 7.09E-12 | 1.17E-11 | 2.12E-04 | 2.50E-15 |
| 15:34520687 | T | C | missense | EMC4 | 6.45E-02 | 1.16E-06 | 2.19E-02 | 1.60E-07 |
| 15:72462255 | C | T | missense | GRAMD2A | 2.04E-27 | 8.72E-17 | 3.66E-13 | 1.28E-27 |
| 15:89388905 | C | T | synonymous | ACAN | 1.61E-150 | 4.30E-72 | 1.08E-56 | 3.79E-130 |
| 16:4812705 | A | G | missense | ZNF500 | 4.21E-10 | 8.61E-17 | 2.34E-07 | 2.89E-21 |
| 16:24804954 | A | T | missense | TNRC6A | 3.87E-13 | 1.08E-09 | 1.65E-07 | 1.90E-15 |
| 16:67409180 | G | A | missense | LRRC36 | 2.22E-19 | 1.08E-18 | 3.91E-13 | 6.40E-31 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 17:67081278 | A | G | missense | ABCA6 | 5.70E-14 | 2.17E-06 | 5.58E-07 | 5.57E-12 |
| 18:74980601 | A | T | missense | GALR1 | 6.28E-07 | 3.60E-18 | 3.64E-05 | 5.11E-19 |
| 19:45296806 | C | T | missense | CBLC | 5.91E-03 | 1.48E-07 | 1.19E-02 | 2.96E-08 |
| 19:55879672 | C | T | missense | IL11 | 5.24E-47 | 1.02E-57 | 2.28E-23 | 5.32E-81 |
| 19:55993436 | G | T | missense | ZNF628 | 9.38E-47 | 2.28E-18 | 1.17E-18 | 6.33E-34 |
| 22:28501414 | C | T | missense | TTC28 | NA | 9.47E-11 | 3.24E-09 | 3.93E-19 |
| 22:42095658 | T | G | missense | MEI1 | 4.63E-04 | 2.25E-08 | 6.59E-03 | 3.70E-10 |

Table S5 | Comparison to 10 genes associated with adult height in GIANT. In UK Biobank, FLNB (pLoF, missense|LC), NOX4 (missense|LC), OSGIN1 (missense|LC), and UGGT2 (pLoF) reach our genome-wide significance threshold (SKAT-O p < 2.5 x $10^{-7}$ ; Burden p < 6.7 x $10^{-7}$) (blue), but all are found nominally significant for either pLoF or missense variants (light blue). Related to STAR Methods.

| **Gene** | **UK Biobank** | | | **GIANT P-value** | | | |
|---|---|---|---|---|---|---|---|
| | **Annotation** | **Burden Test** | **SKAT-O** | **SKAT-Broad** | **VT-Broad** | **SKAT-Strict** | **VT-Strict** |
| B4GALNT3 | missense\|LC | 5.49E-03 | 6.64E-03 | 2.40E-05 | 1.90E-05 | 1.80E-05 | **3.10E-07** |
| | pLoF | 3.25E-06 | 4.76E-06 | | | | |
| | synonymous | 6.46E-01 | 2.33E-01 | | | | |
| CCDC3 | missense\|LC | 3.80E-02 | 9.03E-03 | 6.30E-04 | 6.30E-06 | 3.00E-07 | **5.40E-09** |
| | pLoF | 7.55E-01 | 6.25E-01 | | | | |
| | synonymous | 4.00E-01 | 5.62E-01 | | | | |
| CRISPLD1 | missense\|LC | 8.61E-02 | 1.37E-01 | 2.20E-07 | **6.70E-11** | 8.50E-06 | 8.90E-07 |
| | pLoF | 5.00E-03 | 6.84E-03 | | | | |
| | synonymous | 3.81E-02 | 6.55E-02 | | | | |
| CSAD | missense\|LC | 3.57E-03 | 6.54E-03 | 2.30E-08 | **2.40E-09** | 0.83 | 0.59 |
| | pLoF | 3.33E-01 | 4.63E-01 | | | | |
| | synonymous | 8.84E-02 | 6.97E-04 | | | | |
| FLNB | missense\|LC | 2.99E-08 | 2.12E-08 | 2.20E-06 | 5.10E-04 | **2.40E-09** | 3.20E-06 |
| | pLoF | 5.51E-11 | 9.35E-11 | | | | |
| | synonymous | 7.37E-01 | 3.00E-02 | | | | |
| G6PC | missense\|LC | 5.77E-01 | 6.64E-02 | 1.30E-05 | **3.60E-08** | 5.50E-06 | 1.30E-06 |
| | pLoF | 3.03E-03 | 5.28E-03 | | | | |
| | synonymous | 4.82E-01 | 4.06E-01 | | | | |
| NOX4 | missense\|LC | 1.47E-10 | 5.27E-14 | 5.10E-06 | **1.40E-07** | NA | NA |
| | pLoF | 3.01E-04 | 5.04E-04 | | | | |
| | synonymous | 8.31E-01 | 2.39E-01 | | | | |
| OSGIN1 | missense\|LC | 8.14E-04 | 9.28E-11 | **4.30E-11** | 4.50E-05 | 0.19 | 0.18 |
| | pLoF | 7.40E-01 | 7.76E-02 | | | | |
| | synonymous | 4.65E-01 | 6.53E-01 | | | | |
| SNED1 | missense\|LC | 3.67E-02 | 6.24E-02 | 1.90E-05 | **4.30E-09** | NA | NA |
| | pLoF | NA | 3.69E-01 | | | | |
| | synonymous | 1.32E-01 | 2.16E-01 | | | | |
| UGGT2 | missense\|LC | 4.47E-05 | 1.09E-04 | 3.00E-05 | **2.60E-07** | 2.30E-05 | 4.80E-07 |
| | pLoF | 7.84E-09 | 6.51E-09 | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | synonymous | 8.76E-02 | 1.48E-01 | | | | |

Table S6 | Comparison of 20 associations between missense variants and 7 major red blood cell phenotypes discovered at the genome-wide significant loci of the marginal tests in TOPMed; in UK Biobank, 9 of these associations are significant at $p < 8 \times 10^{-9}$ (blue), and 19 are found significant at $p < 0.05$ (light blue). Related to STAR Methods.

| Phenotype | UKB phenocode | Locus | Allele (Ref) | Allele (Alt) | Gene | Annotation | P-value | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | TOPMed | UK Biobank |
| hematocrit (HCT) | 30030: hematocrit percentage | chr6:26092913 | G | A | HFE | missense | 6.40E-17 | 5.05E-174 |
| | | chr22:37066896 | A | G | TMPRSS6 | missense | 1.03E-26 | 3.28E-182 |
| | | chrX:154536002 | C | T | G6PD | missense | 3.36E-22 | 1.61E-03 |
| hemoglobin (HGB) | 30020: hemoglobin concentration | chr6:26092913 | G | A | HFE | missense | 2.16E-30 | 1.00E-300 |
| | | chr22:37066896 | A | G | TMPRSS6 | missense | 3.16E-51 | 1.00E-300 |
| | | chrX:154536002 | C | T | G6PD | missense | 1.47E-28 | 2.02E-02 |
| mean corpuscular hemoglobin (MCH) | 30050: Mean corpuscular hemoglobin | chr11:5227003 | C | T | HBB | missense | 1.24E-23 | 2.06E-02 |
| | | chrX:154536002 | C | T | G6PD | missense | 2.12E-48 | 7.91E-03 |
| mean corpuscular hemoglobin concentration (MCHC) | 30060: Mean corpuscular hemoglobin concentration | chr6:26092913 | G | A | HFE | missense | 9.52E-17 | 3.59E-246 |
| | | chr11:5227003 | C | T | HBB | missense | 4.29E-43 | 2.37E-02 |
| | | chr22:37066896 | A | G | TMPRSS6 | missense | 3.25E-26 | 5.70E-189 |
| mean corpuscular volume (MCV) | 30040: mean corpuscular volume | chr1:247876149 | C | T | TRIM58 | missense | 1.77E-16 | 1.33E-118 |
| | | chr11:5227003 | C | T | HBB | missense | 1.36E-64 | 2.87E-04 |
| | | chr16:67184472 | T | C | EXOC3L1 | missense / synonymous | 2.13E-09 | 7.48E-29 |
| | | chrX:154536002 | C | T | G6PD | missense | 3.96E-82 | 5.87E-02 |
| red blood cell count (RBC) | 30010: red blood cell (erythrocyte) count | chr11:5227003 | C | T | HBB | missense | 2.44E-22 | 1.49E-02 |
| | | chrX:154536002 | C | T | G6PD | missense | 3.72E-82 | 1.27E-04 |
| red blood cell width (RDW) | 30070: red blood cell (erythrocyte) distribution width | chr6:26092913 | G | A | HFE | missense | 5.80E-15 | 1.00E-300 |
| | | chr11:5227003 | C | T | HBB | missense | 1.59E-10 | 1.51E-02 |
| | | chrX:154536002 | C | T | G6PD | missense | 8.27E-106 | 1.87E-04 |