Genome-wide rare variant analysis for thousands of phenotypes in over 70,000 exomes from two cohorts

Cirulli et al.

Supplementary note

Additional analysis methods

Gene-based collapsing analysis utilizing CADD scores

In addition to our LoF and coding models, we also tried two different collapsing models, both of which restricted to rare (MAF<0.1%) variants with a CADD score above the 95% mutation significance cutoff (MSC) for its gene[1–3]. The inclusive CADD model collapsed all such variants that were within 5kb of a gene, and the restrictive CADD model only collapsed coding variants (stop_lost, missense_variant, start_lost, splice_donor_variant, inframe_deletion, frameshift_variant, splice_acceptor_variant, stop_gained, or inframe_insertion) that met these criteria.

In our initial analysis performing BOLT-LMM analysis on European ancestry individuals in the UKB cohort, we identified 17 significant associations ($p<3.4x10^{-10}$) in the inclusive CADD model and 26 in the restrictive CADD model. All of these associations were also statistically significant in the European ancestry BOLT-LMM meta-analysis coding or LoF models used in the main paper. In contrast, nearly half of the significant results from the main UKB European ancestry BOLT-LMM coding and LoF models were not found among the significant CADD model associations. Because these additional models did not provide new insights, we did not include these analysis results in the main manuscript.

SKAT analysis

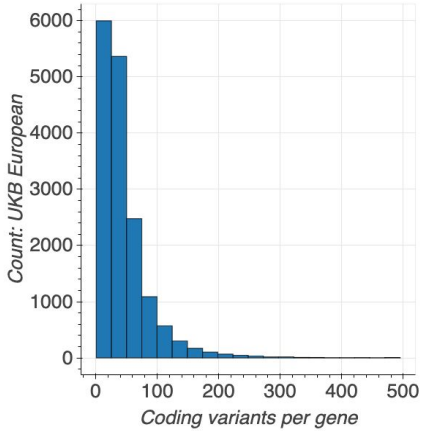
We also performed a gene-based SKAT analysis of the unrelated European ancestry individuals [4]. We performed this analysis in Hail, with accuracy set at $1x10^{-11}$ and $1x10^{9}$ iterations and using age, sex, and 10 European-specific principal components as covariates [5]. We used two models: a basic SKAT model with weights based on beta (1,25) of the MAF and using the same set of coding variants from our main gene-based collapsing analysis (MAF model); and a SKAT model with weights of beta (1,25) x Phred-scaled CADD score that used all coding variants with MAF<0.1% (MAF-CADD model). The MAF-CADD model included 2,000,908 variants for the UKB cohort and 1,427,500 for the HNP, approximately twice as many as the MAF model.

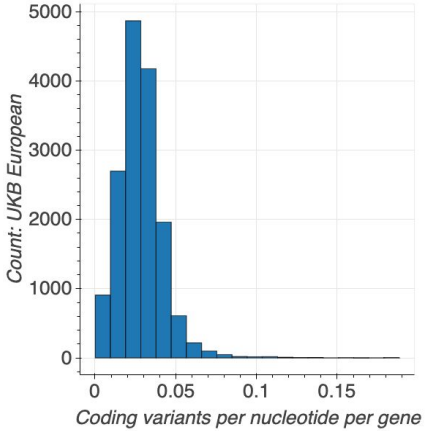
We started with the set of unrelated European ancestry individuals from the UKB cohort as a discovery set. We ran the full set of 4,264 phenotypes and restricted to results where at least five individuals were variant carriers for quantitative traits, or five expected case carriers based on the overall prevalence for binary traits. We ran linear regression for quantitative traits and logistic regression for binary traits. We identified 464 statistically significant results ($p<3.4x10^{-10}$) for the MAF model and 1,331 for the MAF-CADD model. Of these, 235 and 778 respectively had data available for replication in the HNP cohort. When we attempted to replicate the findings, we found that respectively only 8.1% of the 8.6% associations generated a statistically significant result ($p<0.0002$, Bonferroni correction for 235 tests, and $p<6.4x10^{-5}$, correction for 788 tests). This is in contrast to 46% formal replication in our main gene-based collapsing

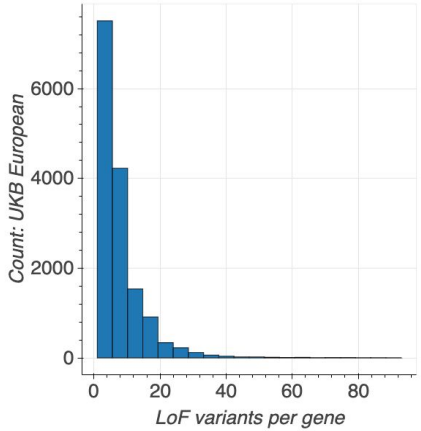
analysis, as described in the main text. Furthermore, if we chose a more lenient replication p-value cutoff that would confirm at least the suggestion of replication ($p<0.05$), we found that respectively only 24.2% and 24.4% of associations replicated, compared to 82% in our main gene-based collapsing analysis as described in the main manuscript. In our main gene-based collapsing analysis, 100% of signals showed at least the same direction of effect in the replication cohort, but this statistic cannot be analyzed in the context of a SKAT analysis as there is no main direction of effect provided.

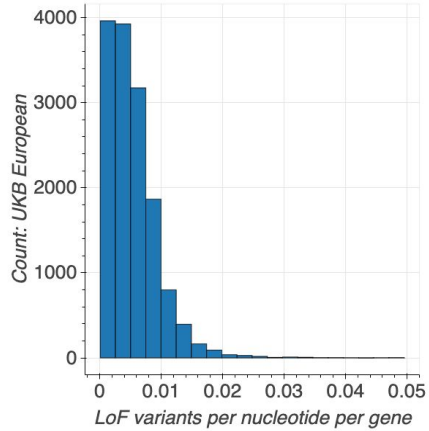
Even when we were more stringent about which SKAT analyses to include as significant, the replication rate was very low. For example, when we required the significant binary associations to have at least 10 expected case carriers based on the overall frequency, for the MAF model, only 25% of the 32 eligible associations replicated ($p<0.0015$, correction for 32 tests), and only 34% had uncorrected $p<0.05$. For the MAF-CADD model, only 7.3% of the 82 eligible associations replicated ($p<0.0006$, correction for 82 tests), and only 24.4% had uncorrected $p<0.05$.

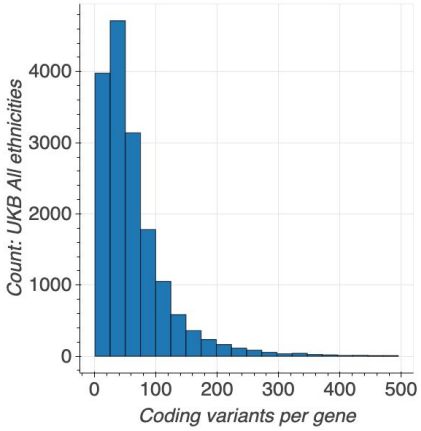
Our results coincide with a number of previous studies documenting that the results of SKAT analyses in real-world datasets can often be noisy and difficult to interpret[6,7]. Given these difficulties, we did not include these analysis results in our main manuscript.

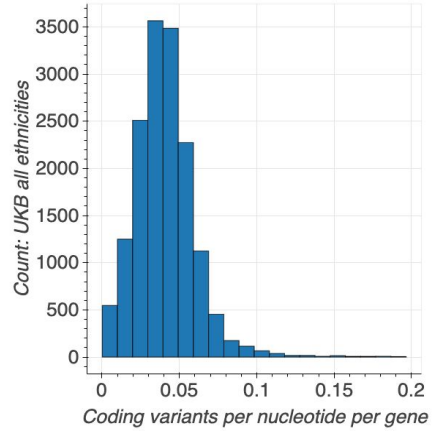

Count: UKB European
6000
5000
4000
3000
2000
1000
0
0
100
200
300
400
500
Coding variants per gene

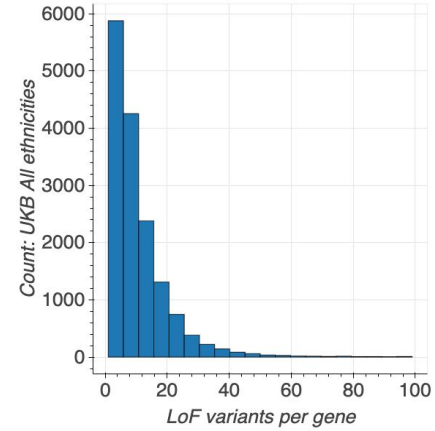

Count: UKB European
5000
4000
3000
2000
1000
0
0
0.05
0.1
0.15
Coding variants per nucleotide per gene

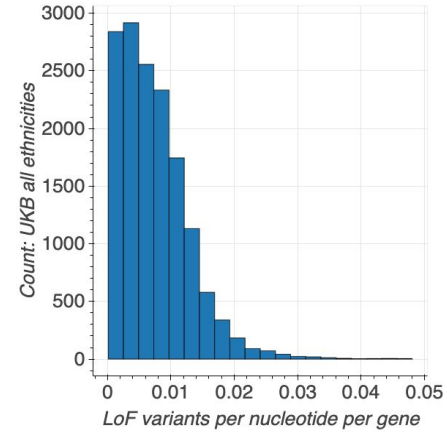

Count: UKB European
6000
4000
2000
0
0
20
40
60
80
LoF variants per gene

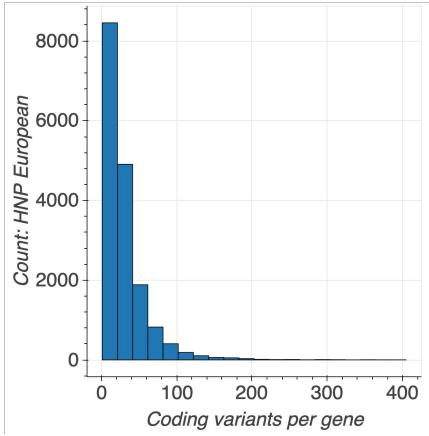

Count: UKB European
4000
3000
2000
1000
0
0
0.01
0.02
0.03
0.04
0.05
LoF variants per nucleotide per gene

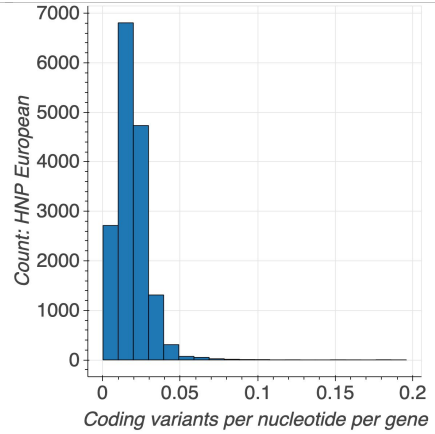

Count: UKB All ethnicities
4000
3000
2000
1000
0
0
100
200
300
400
500
Coding variants per gene

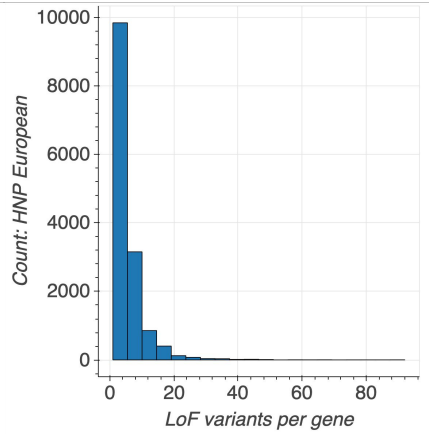

Count: UKB all ethnicities
3500
3000
2500
2000
1500
1000
500
0
0
0.05
0.1
0.15
0.2
Coding variants per nucleotide per gene

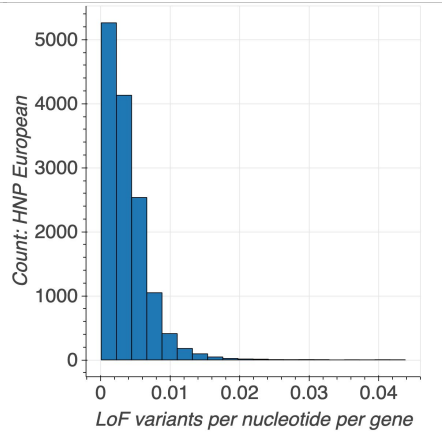

Count: UKB All ethnicities
6000
5000
4000
3000
2000
1000
0
0
20
40
60
80
100
LoF variants per gene

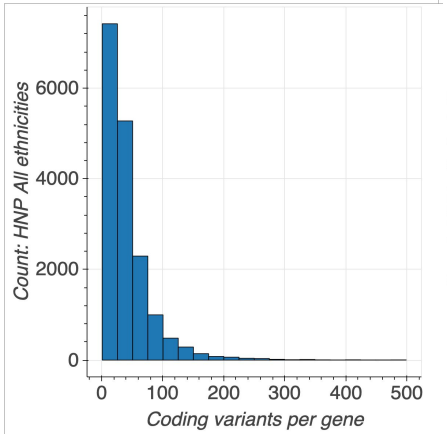

Count: UKB all ethnicities
3000
2500
2000
1500
1000
500
0
0
0.01
0.02
0.03
0.04
0.05
LoF variants per nucleotide per gene

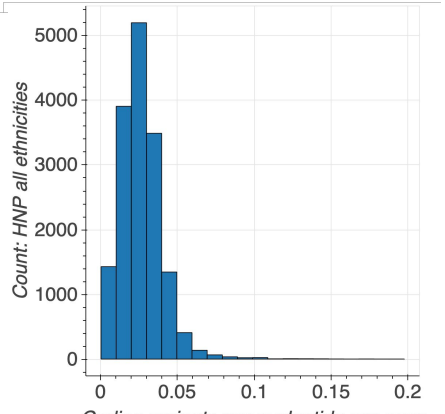

Count: HNP European
Coding variants per gene

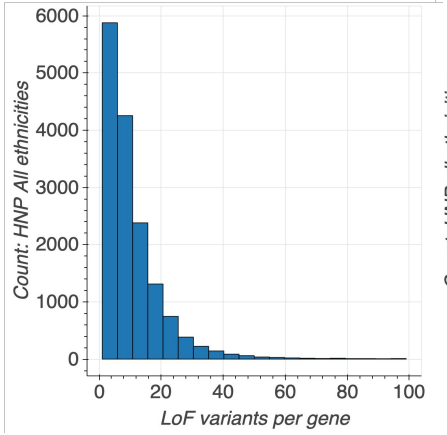

Count: HNP European
Coding variants per nucleotide per gene

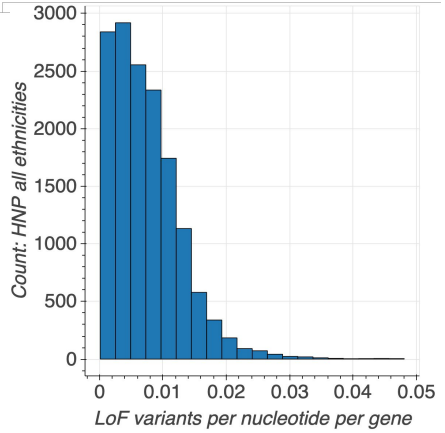

Count: HNP European
LoF variants per gene


Count: HNP European
LoF variants per nucleotide per gene

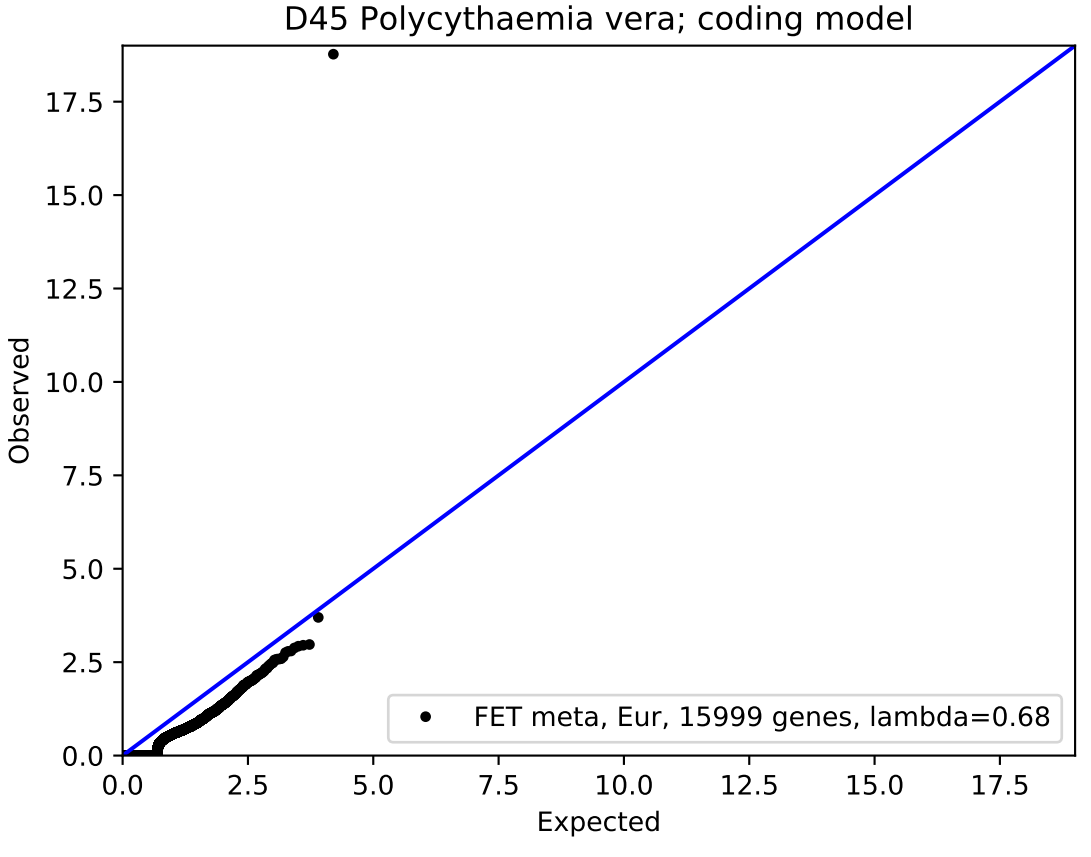

Count: HNP All ethnicities
Coding variants per gene

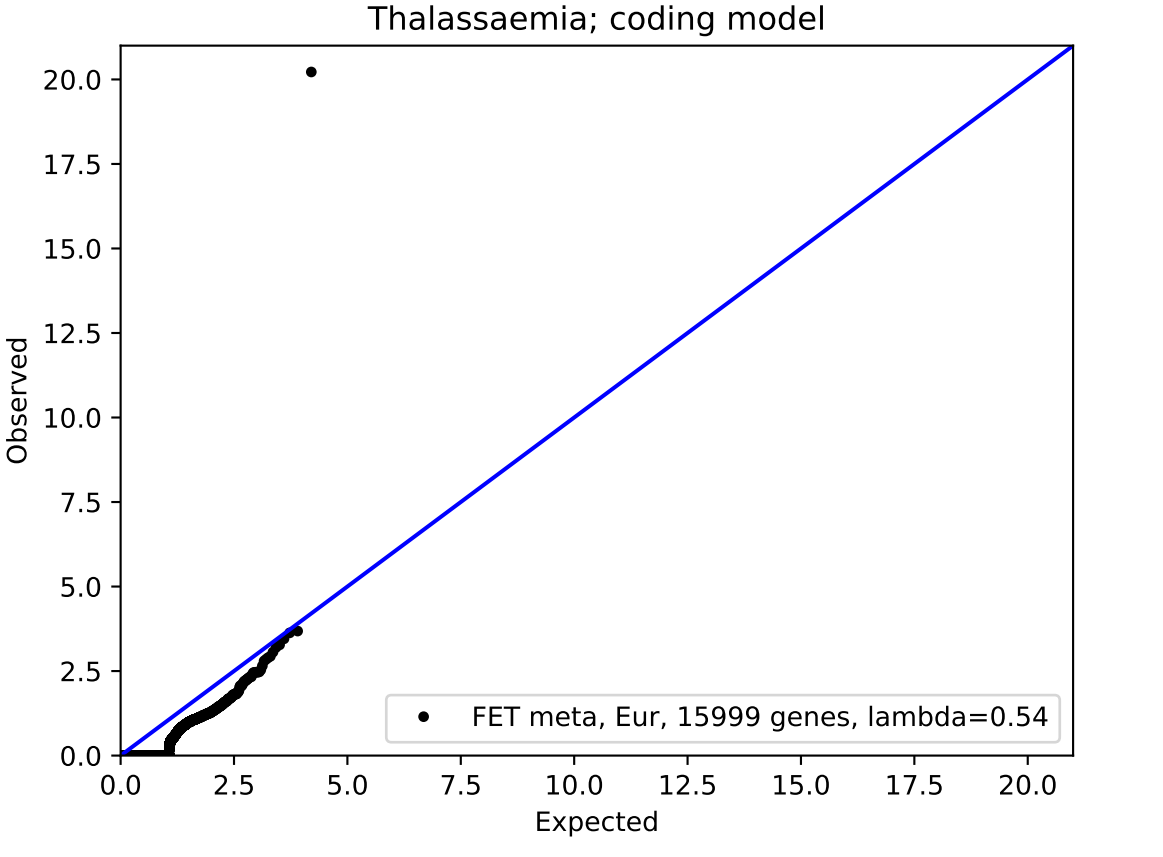

Count: HNP all ethnicities
Coding variants per nucleotide per gene

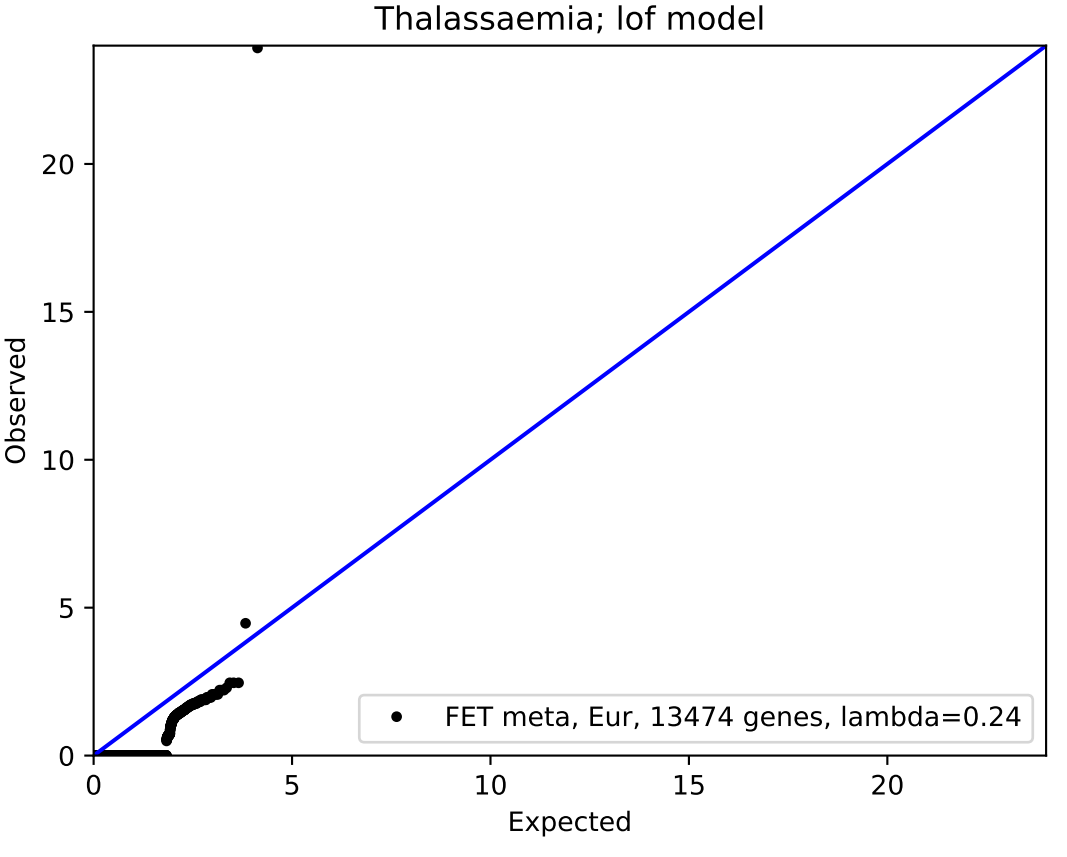

Count: HNP All ethnicities
LoF variants per gene

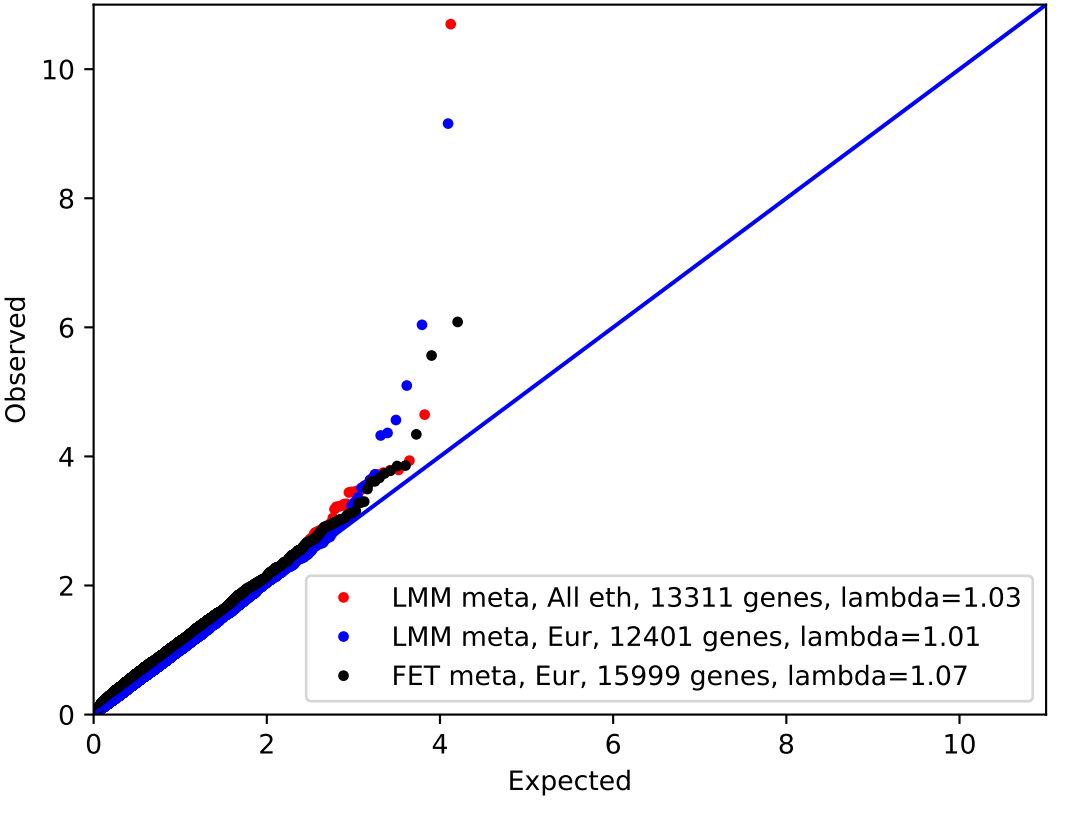

Count: HNP all ethnicities
LoF variants per nucleotide per gene

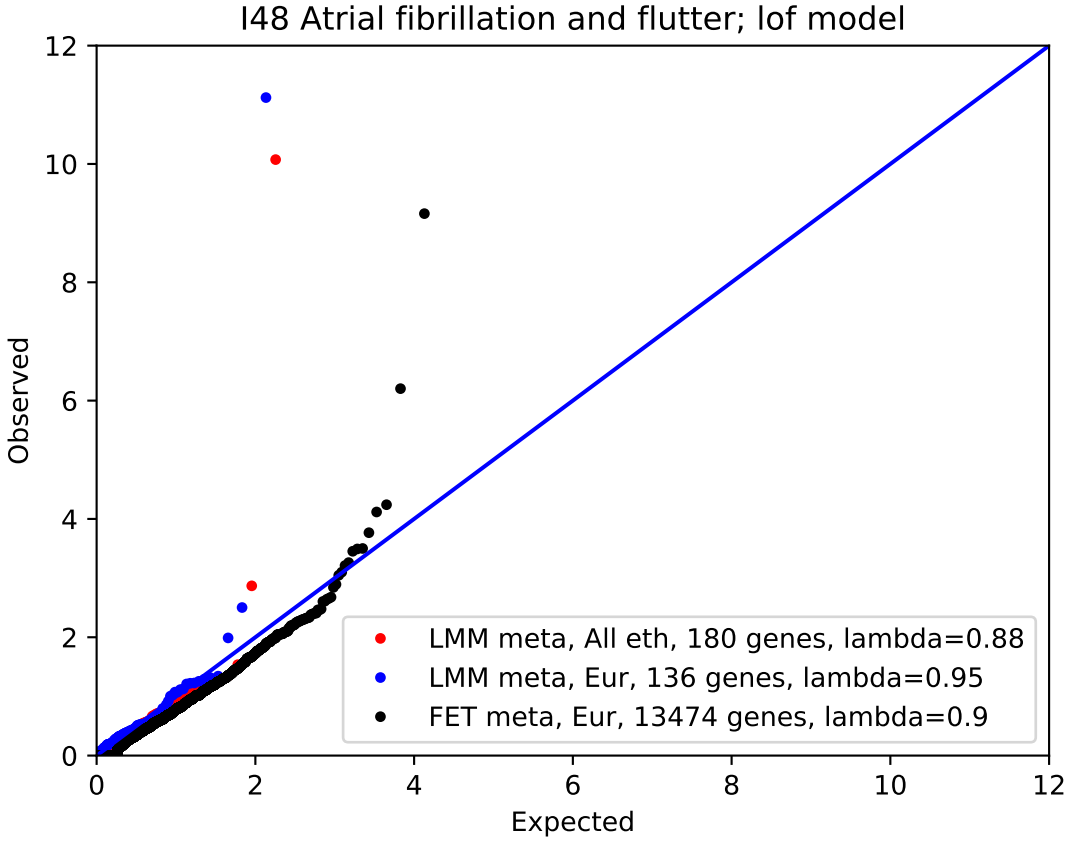
Supplementary Figure 1. Histograms of number of qualifying variants per gene. Each histogram is labeled to indicate whether it is UKB or HNP cohort, European ancestry only or all ancestries, coding or LoF model, and number of qualifying variants per gene or number of qualifying variants per coding nucleotide of each gene. Between 1 and 42 genes were excluded from each plot as they were out of range.

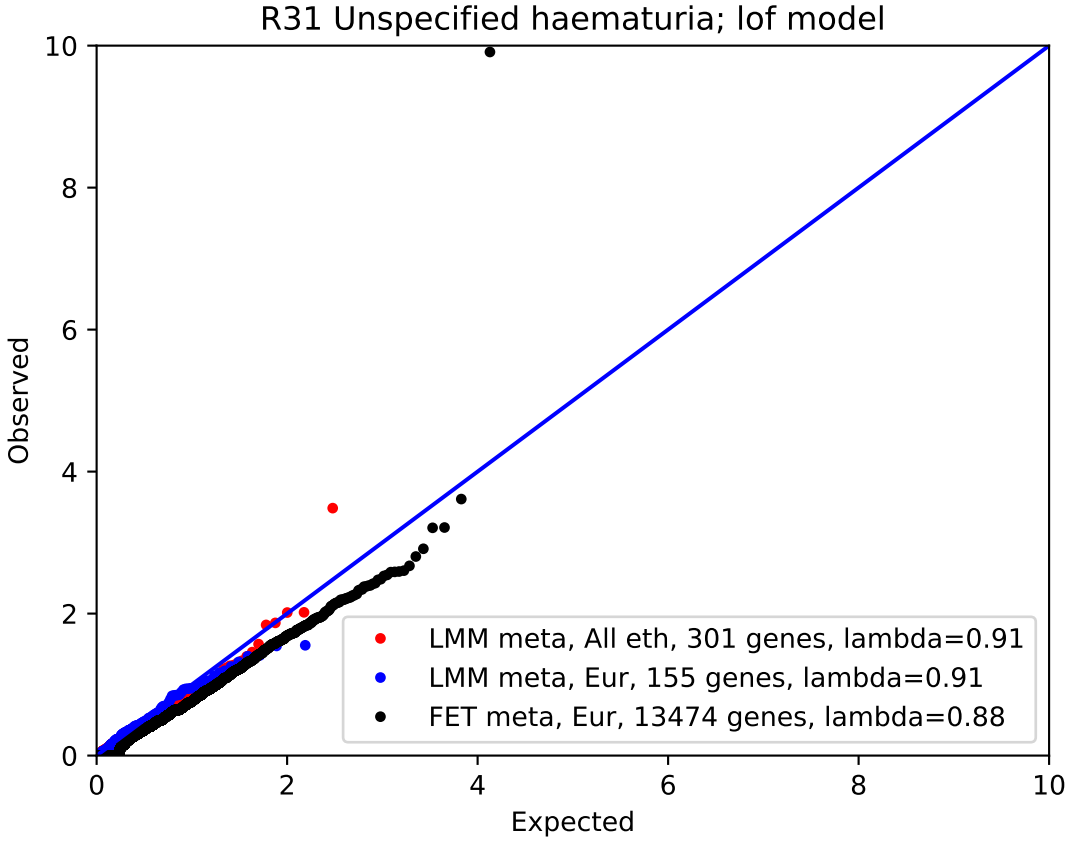

D45 Polycythaemia vera; coding model
Observed
Expected
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
FET meta, Eur, 15999 genes, lambda=0.68

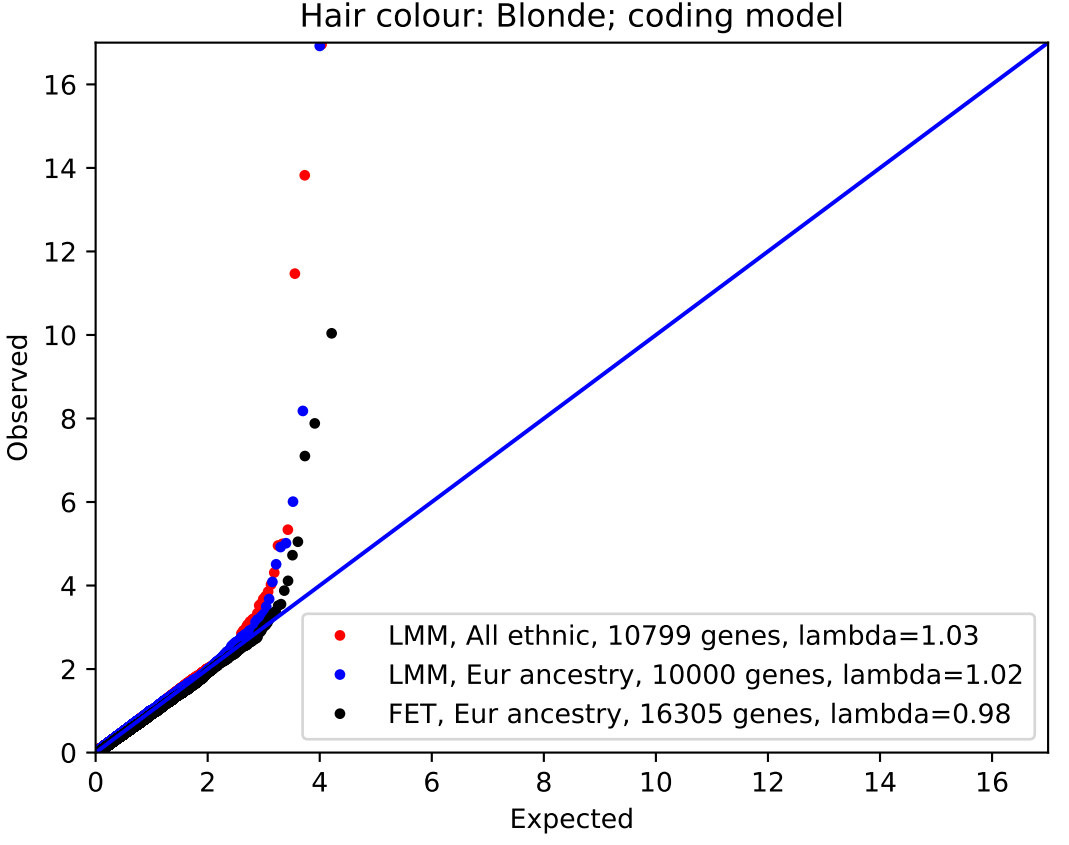

Thalassaemia; coding model
Observed
Expected
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0
FET meta, Eur, 15999 genes, lambda=0.54

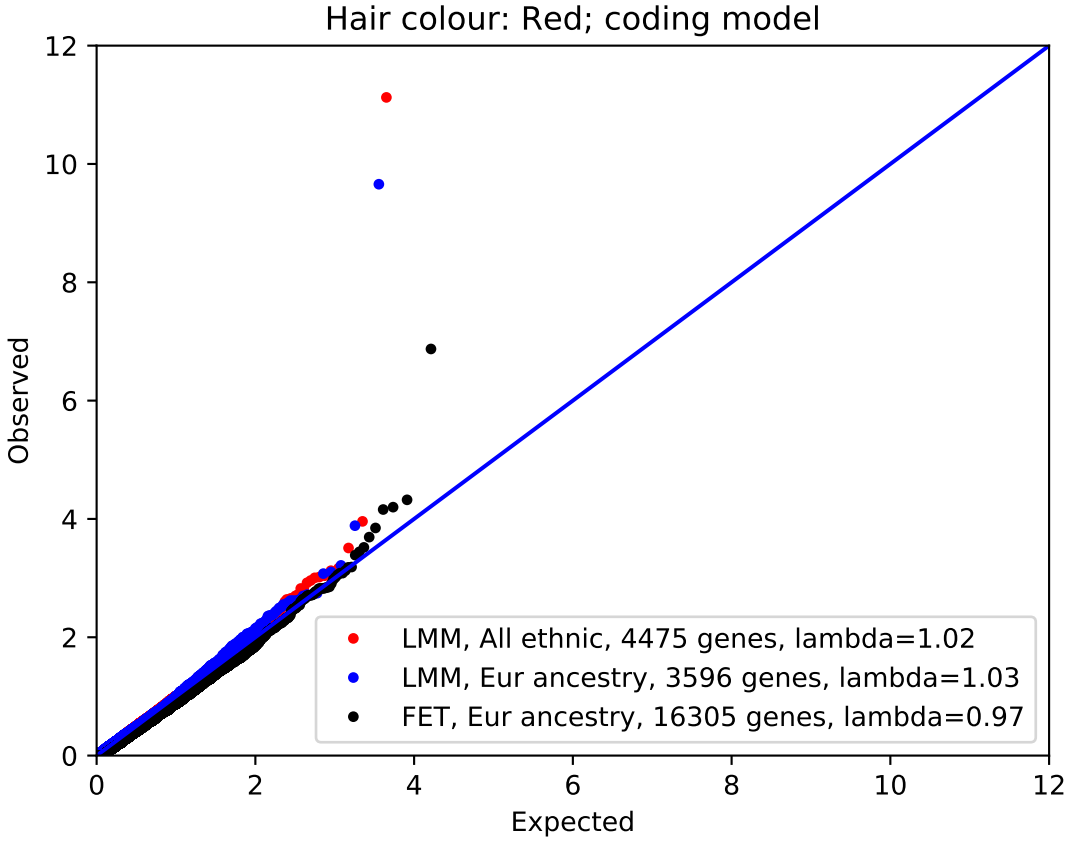

Thalassaemia; lof model
Observed
Expected
0
5
10
15
20
FET meta, Eur, 13474 genes, lambda=0.24

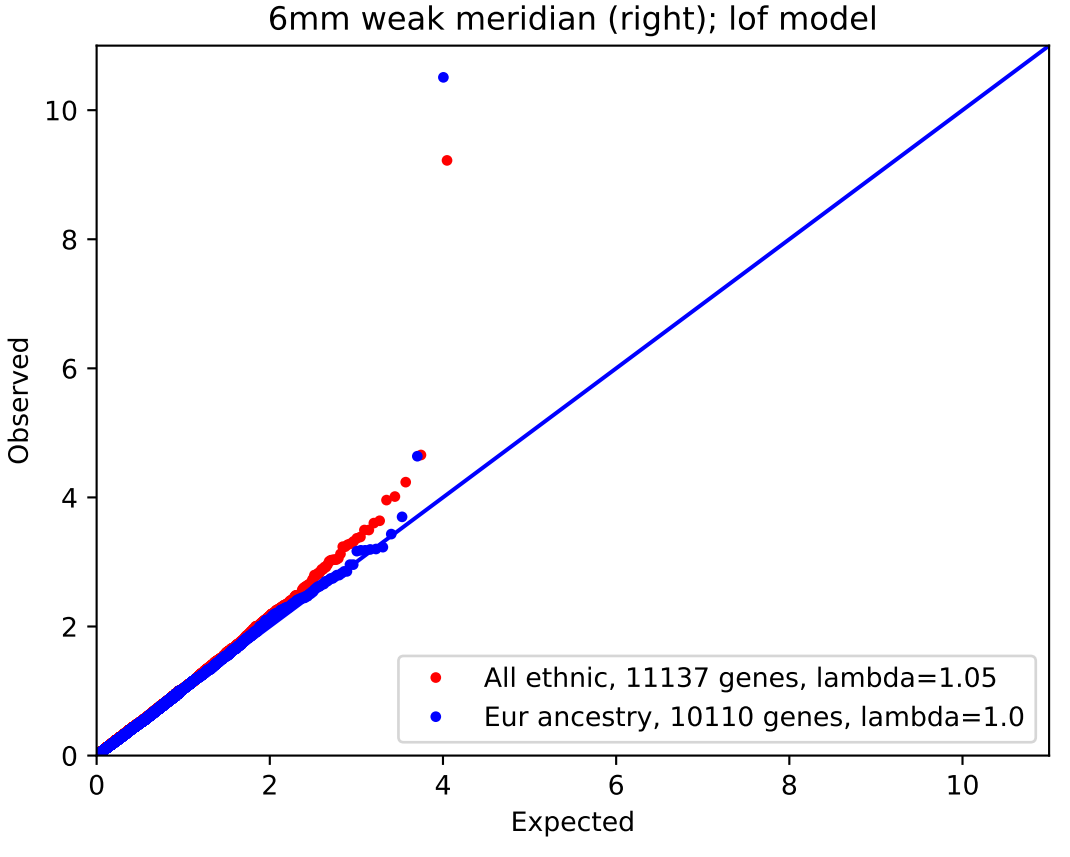

E78.0 Pure hypercholesterolaemia; coding model
Observed
Expected
0
2
4
6
8
10
LMM meta, All eth, 13311 genes, lambda=1.03
LMM meta, Eur, 12401 genes, lambda=1.01
FET meta, Eur, 15999 genes, lambda=1.07

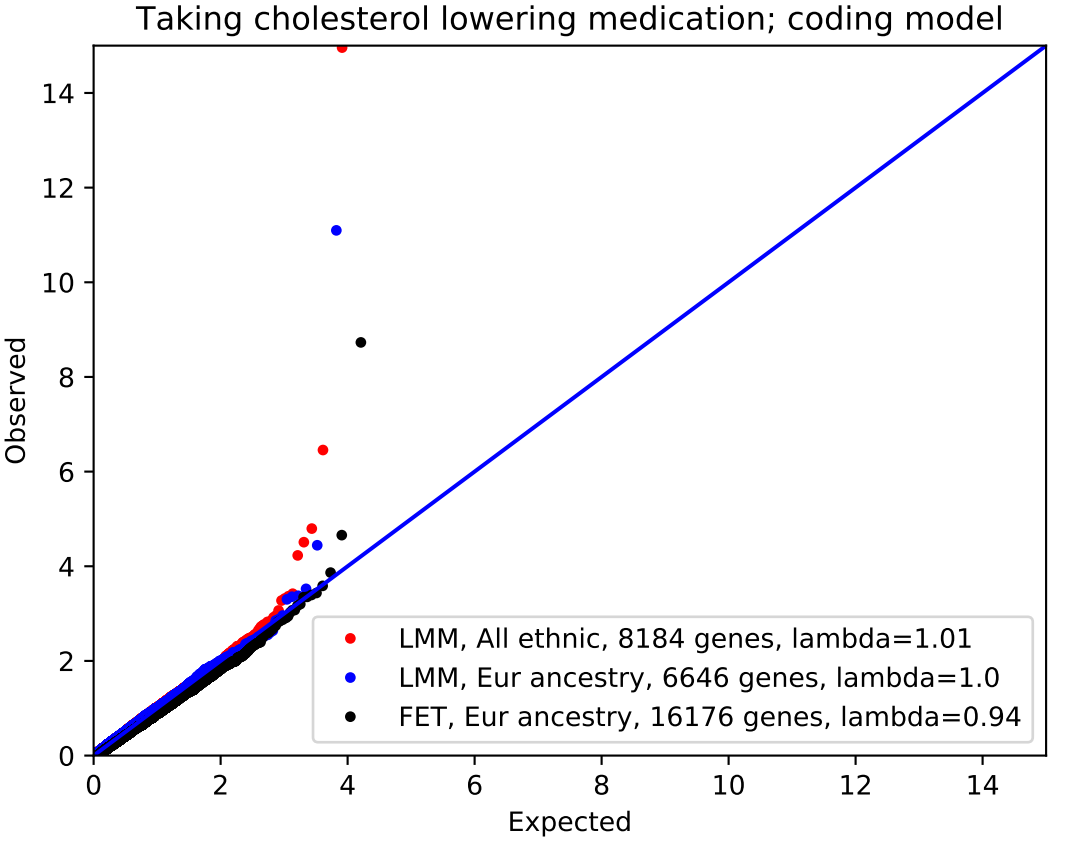

I48 Atrial fibrillation and flutter; lof model
Observed
Expected
0
2
4
6
8
10
12
LMM meta, All eth, 180 genes, lambda=0.88
LMM meta, Eur, 136 genes, lambda=0.95
FET meta, Eur, 13474 genes, lambda=0.9

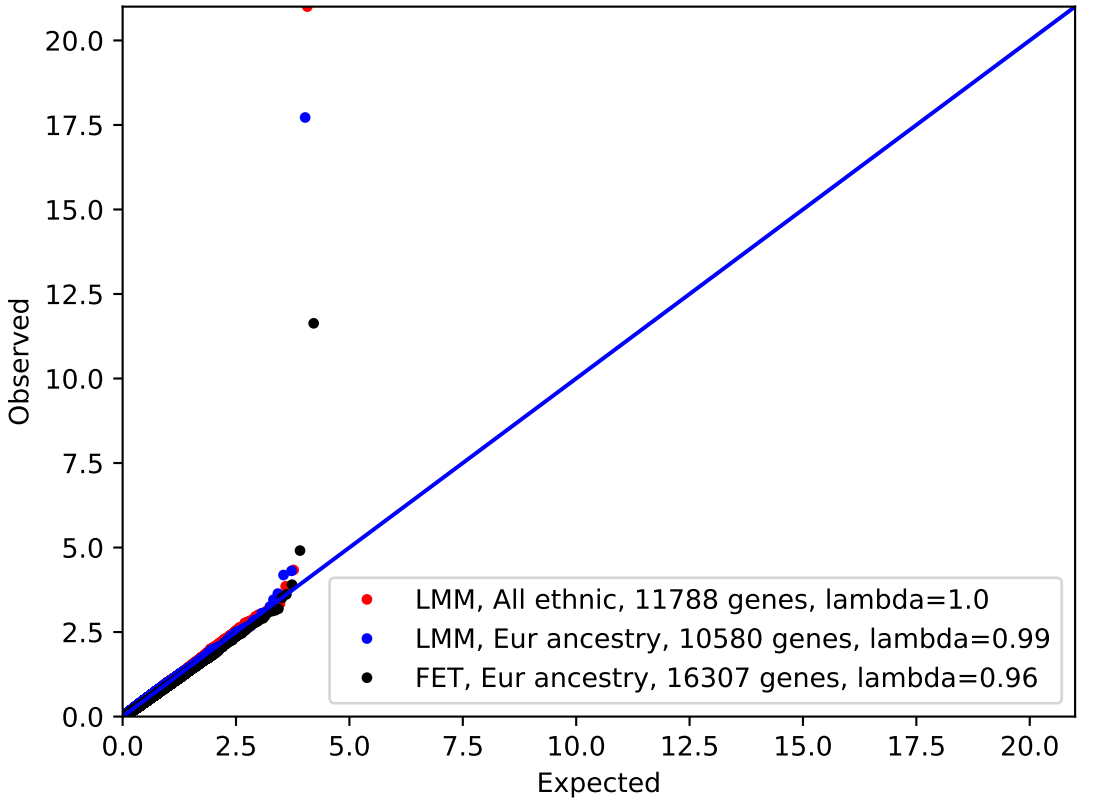

R31 Unspecified haematuria; lof model
Observed
Expected
0
2
4
6
8
10
LMM meta, All eth, 301 genes, lambda=0.91
LMM meta, Eur, 155 genes, lambda=0.91
FET meta, Eur, 13474 genes, lambda=0.88

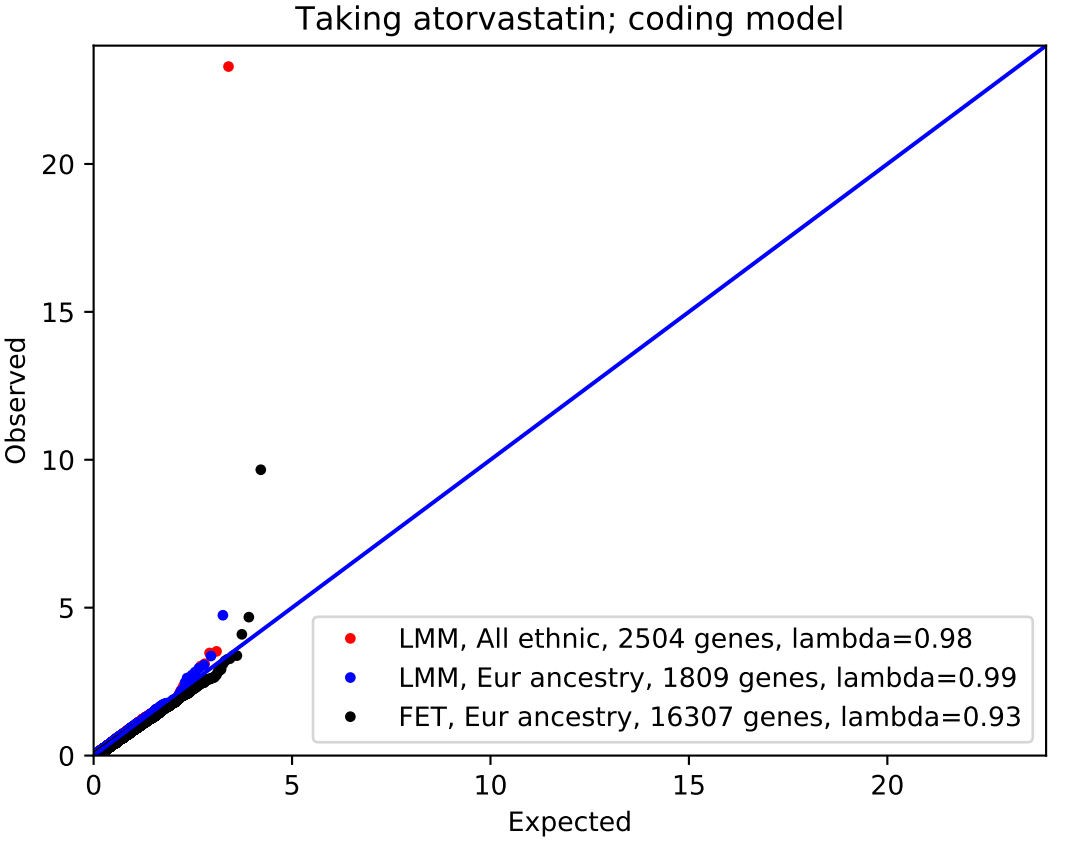

Hair colour: Blonde; coding model
Observed
Expected
0
2
4
6
8
10
12
14
16
LMM, All ethnic, 10799 genes, lambda=1.03
LMM, Eur ancestry, 10000 genes, lambda=1.02
FET, Eur ancestry, 16305 genes, lambda=0.98

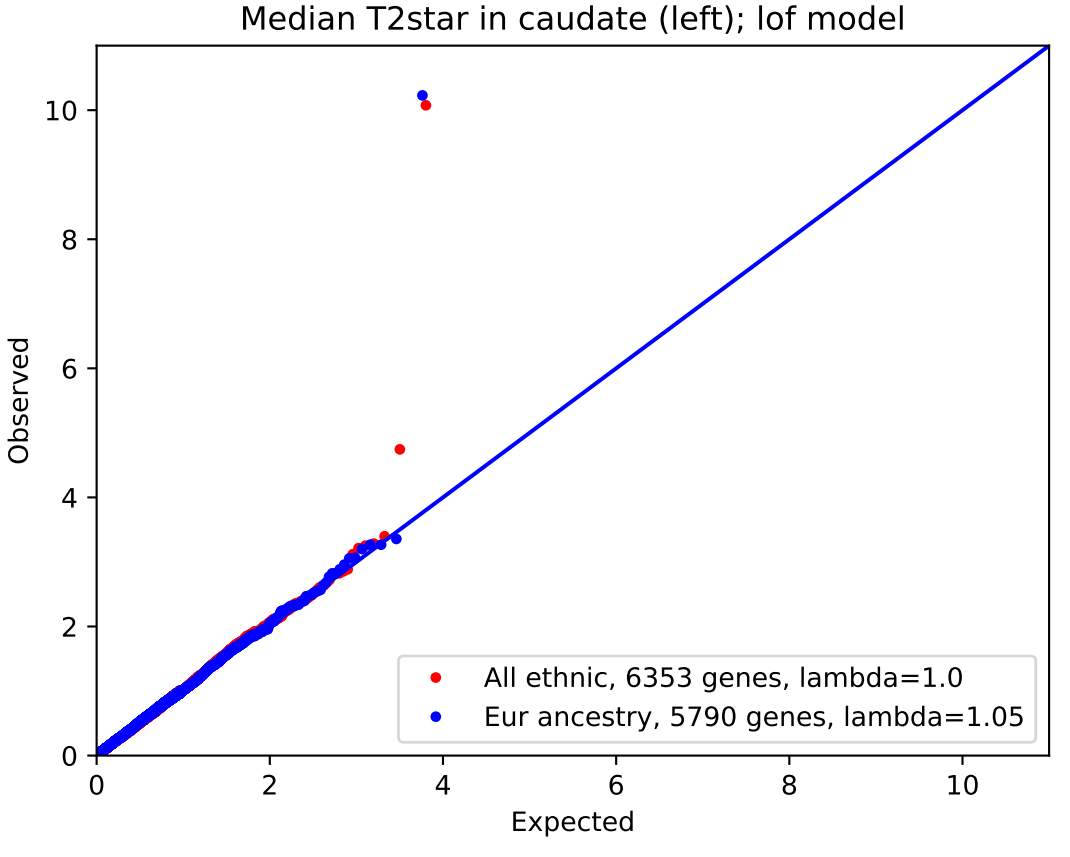

Hair colour: Red; coding model
Observed
Expected
0
2
4
6
8
10
12
LMM, All ethnic, 4475 genes, lambda=1.02
LMM, Eur ancestry, 3596 genes, lambda=1.03
FET, Eur ancestry, 16305 genes, lambda=0.97

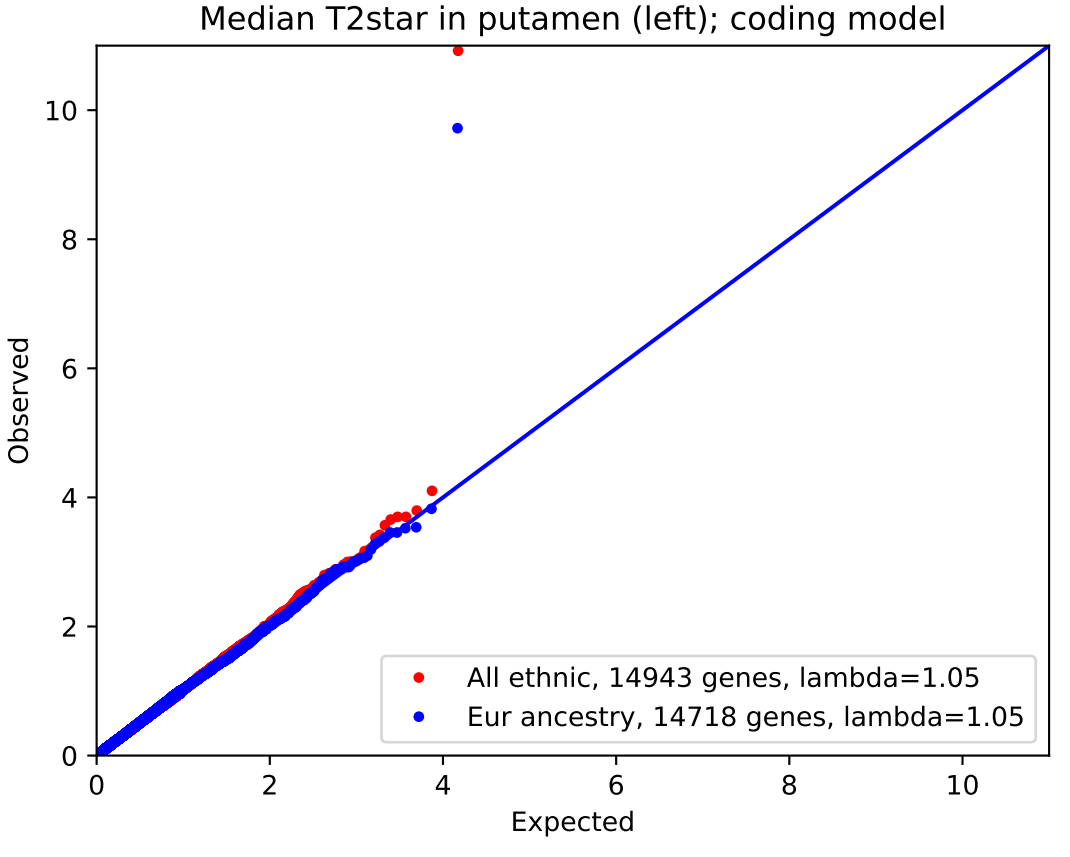

6mm weak meridian (right); lof model
Observed
Expected
0
2
4
6
8
10
All ethnic, 11137 genes, lambda=1.05
Eur ancestry, 10110 genes, lambda=1.0

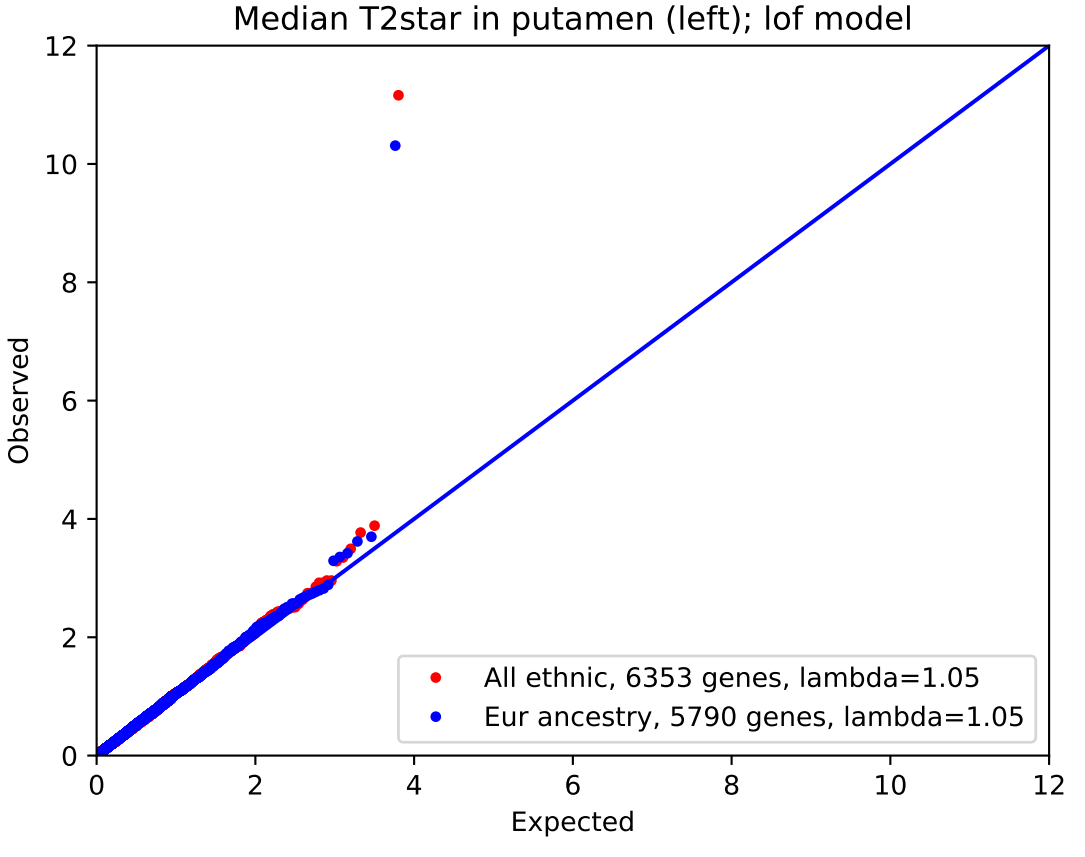

Taking cholesterol lowering medication; coding model
Observed
Expected
0
2
4
6
8
10
12
14
LMM, All ethnic, 8184 genes, lambda=1.01
LMM, Eur ancestry, 6646 genes, lambda=1.0
FET, Eur ancestry, 16176 genes, lambda=0.94

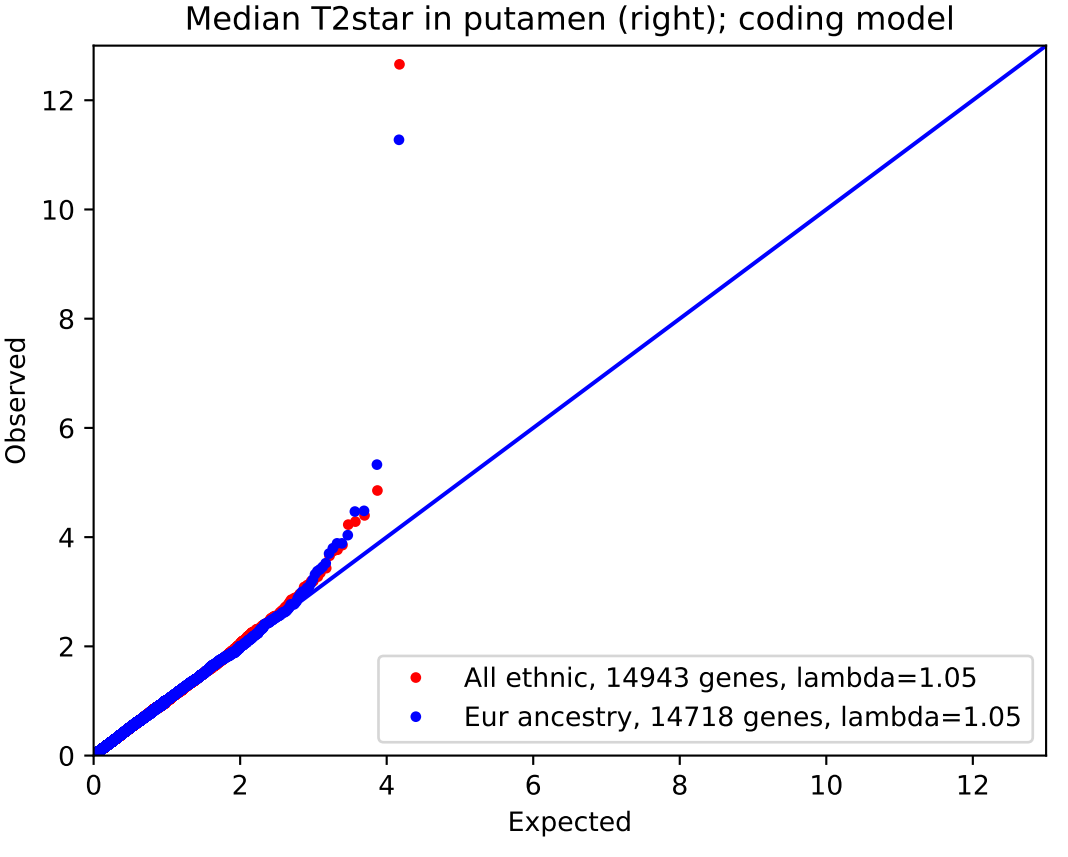

Self-reported high cholesterol; coding model
Observed
Expected
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0
LMM, All ethnic, 11788 genes, lambda=1.0
LMM, Eur ancestry, 10580 genes, lambda=0.99
FET, Eur ancestry, 16307 genes, lambda=0.96

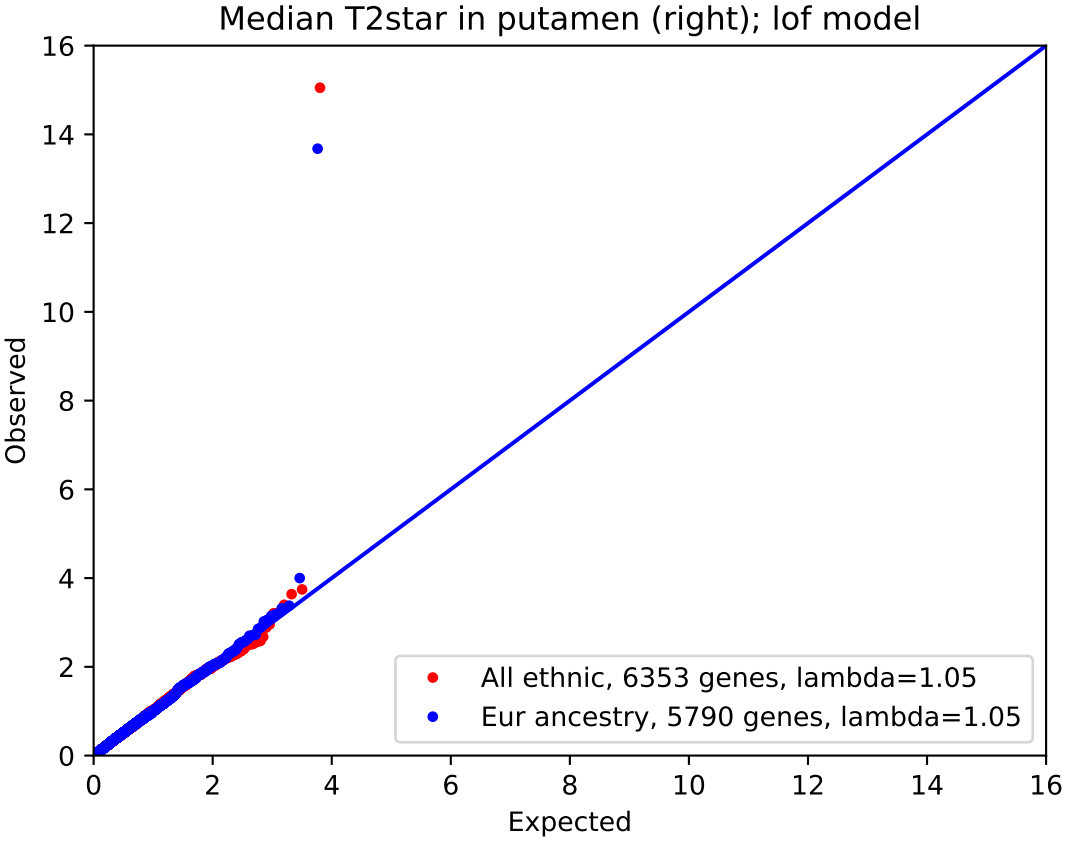

Taking atorvastatin; coding model
Observed
Expected
0
5
10
15
20
LMM, All ethnic, 2504 genes, lambda=0.98
LMM, Eur ancestry, 1809 genes, lambda=0.99
FET, Eur ancestry, 16307 genes, lambda=0.93

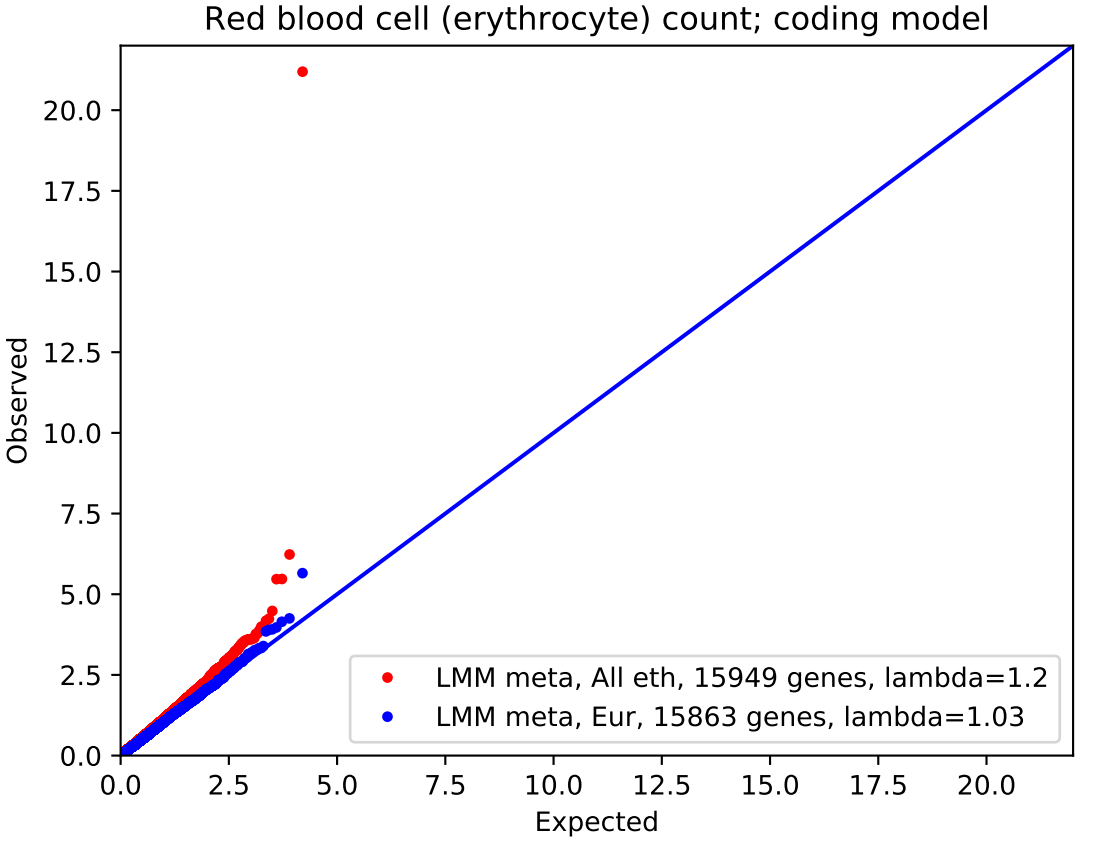

Median T2star in caudate (left); lof model
Observed
Expected
0
2
4
6
8
10
All ethnic, 6353 genes, lambda=1.0
Eur ancestry, 5790 genes, lambda=1.05

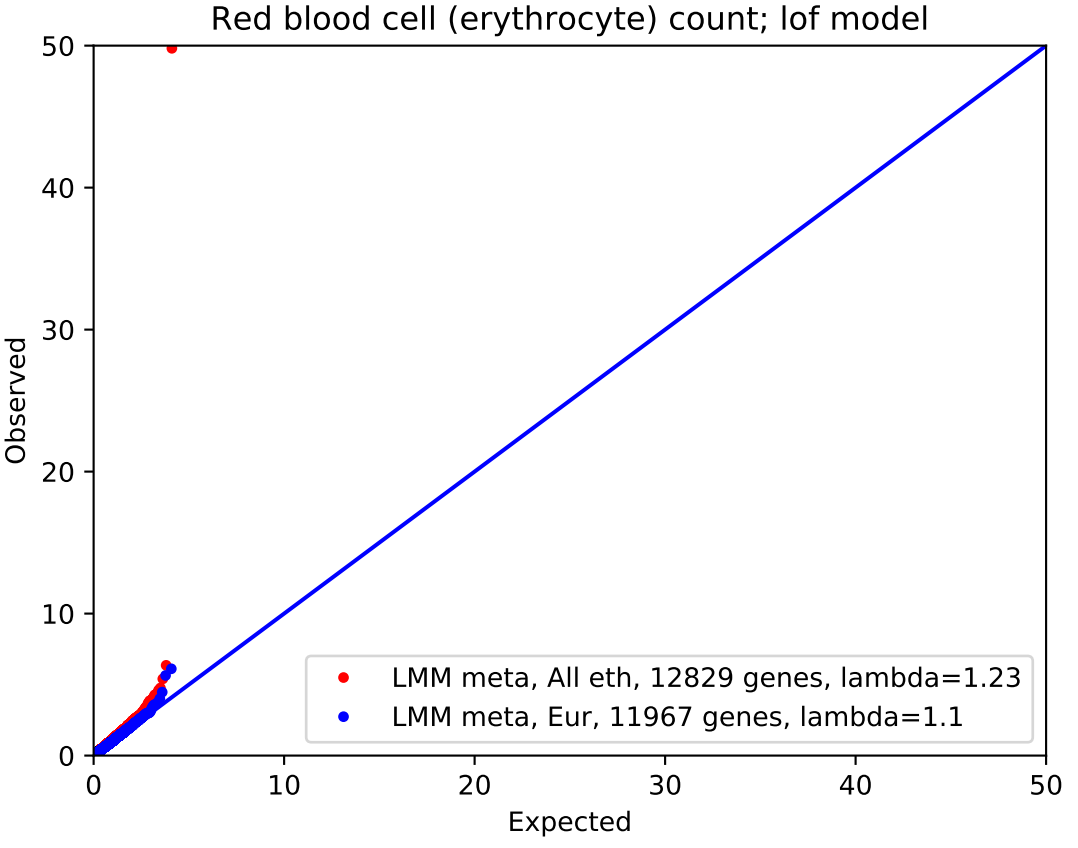

Median T2star in putamen (left); coding model
Observed
Expected
0
2
4
6
8
10
All ethnic, 14943 genes, lambda=1.05
Eur ancestry, 14718 genes, lambda=1.05

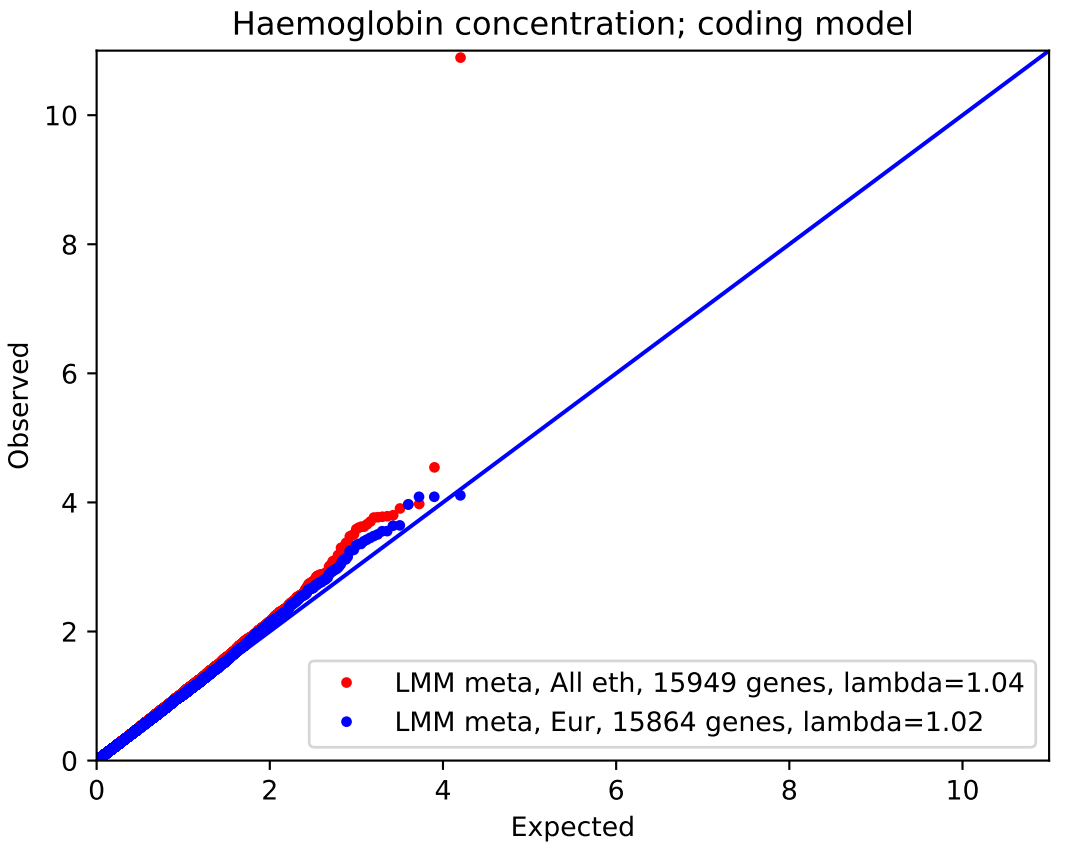

Median T2star in putamen (left); lof model
Observed
Expected
0
2
4
6
8
10
12
All ethnic, 6353 genes, lambda=1.05
Eur ancestry, 5790 genes, lambda=1.05

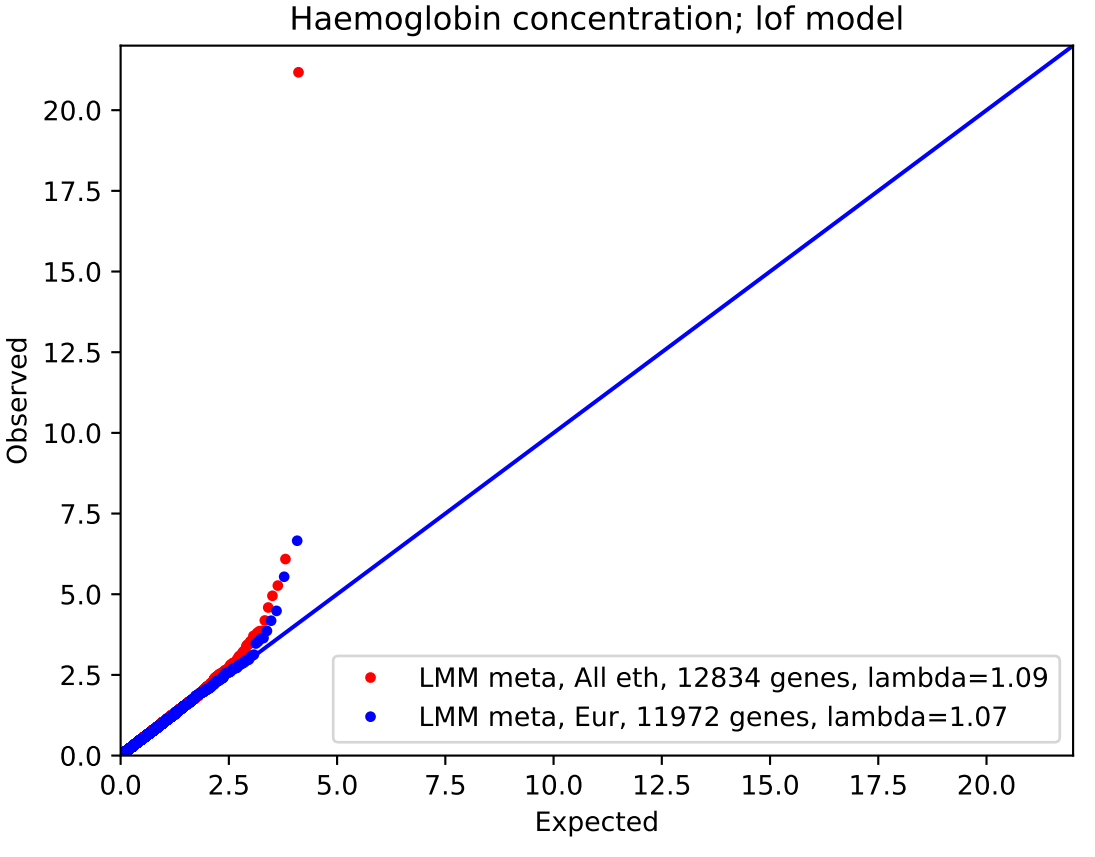

Median T2star in putamen (right); coding model
Observed
Expected
0
2
4
6
8
10
12
All ethnic, 14943 genes, lambda=1.05
Eur ancestry, 14718 genes, lambda=1.05

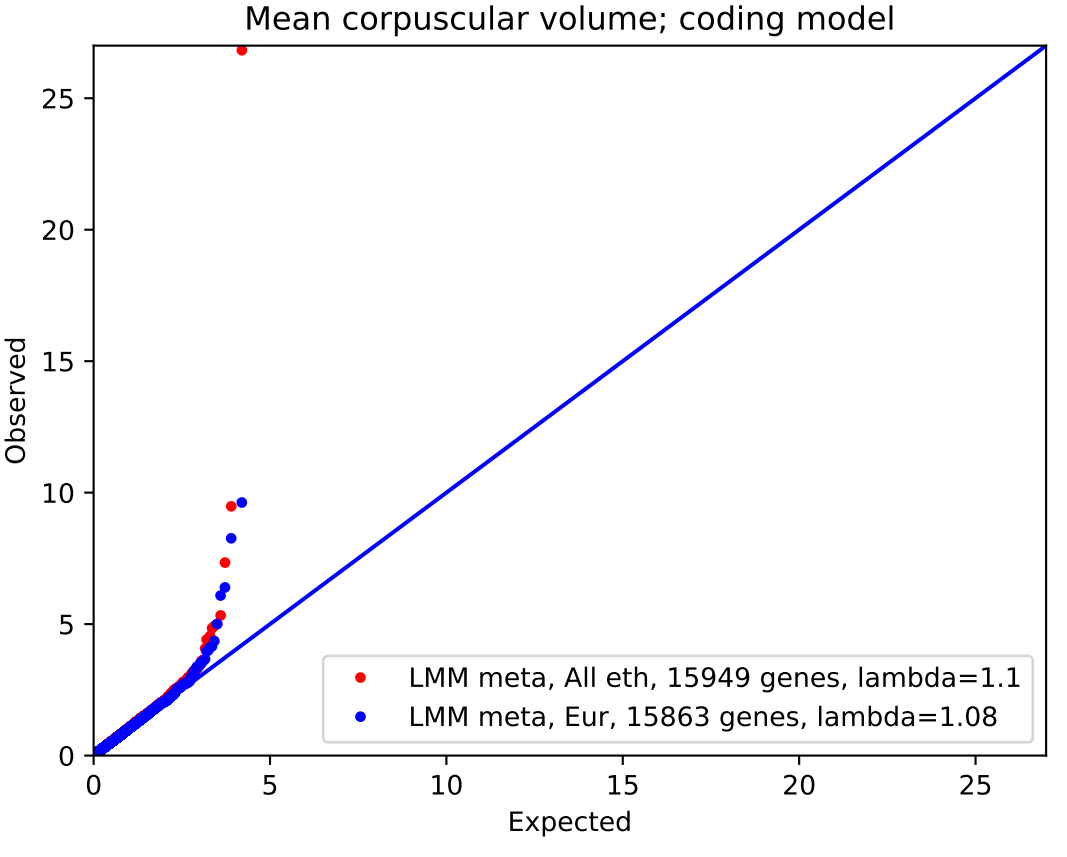

Median T2star in putamen (right); lof model
Observed
Expected
0
2
4
6
8
10
12
14
16
All ethnic, 6353 genes, lambda=1.05
Eur ancestry, 5790 genes, lambda=1.05

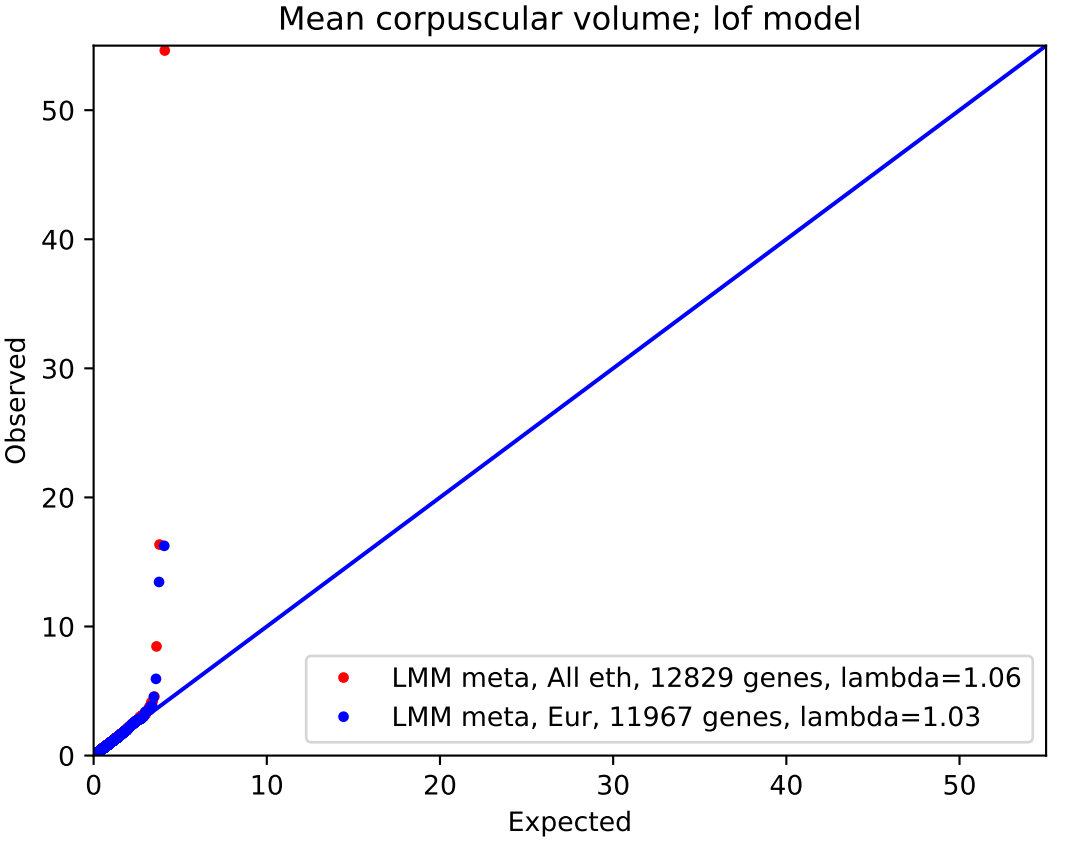

Red blood cell (erythrocyte) count; coding model
Observed
Expected
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0
LMM meta, All eth, 15949 genes, lambda=1.2
LMM meta, Eur, 15863 genes, lambda=1.03

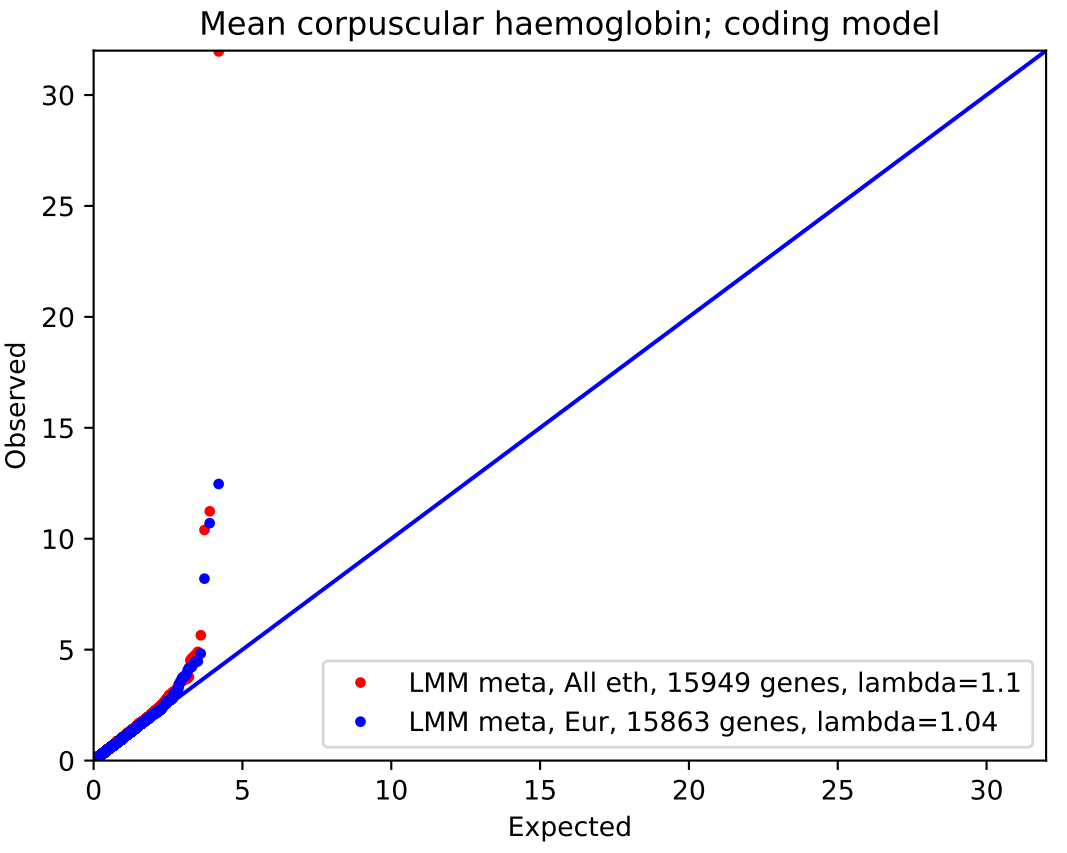

Red blood cell (erythrocyte) count; lof model
Observed
Expected
0
10
20
30
40
50
LMM meta, All eth, 12829 genes, lambda=1.23
LMM meta, Eur, 11967 genes, lambda=1.1

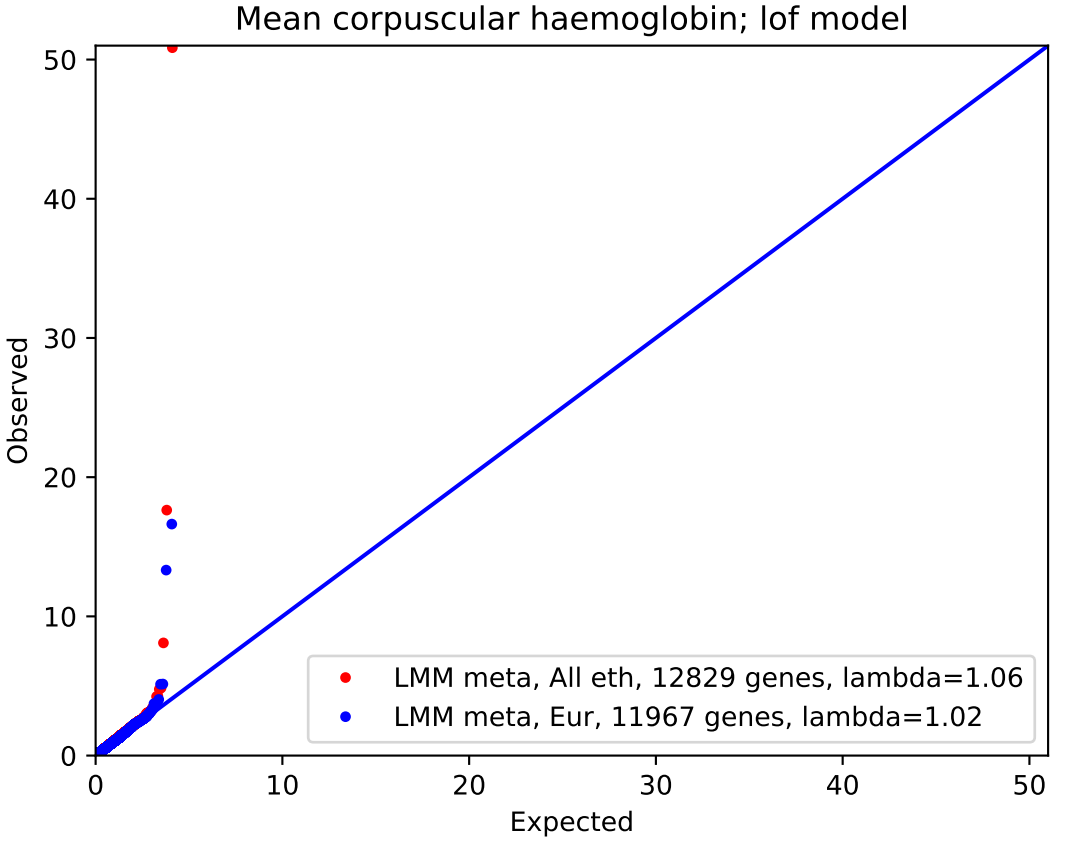

Haemoglobin concentration; coding model
Observed
Expected
0
2
4
6
8
10
LMM meta, All eth, 15949 genes, lambda=1.04
LMM meta, Eur, 15864 genes, lambda=1.02

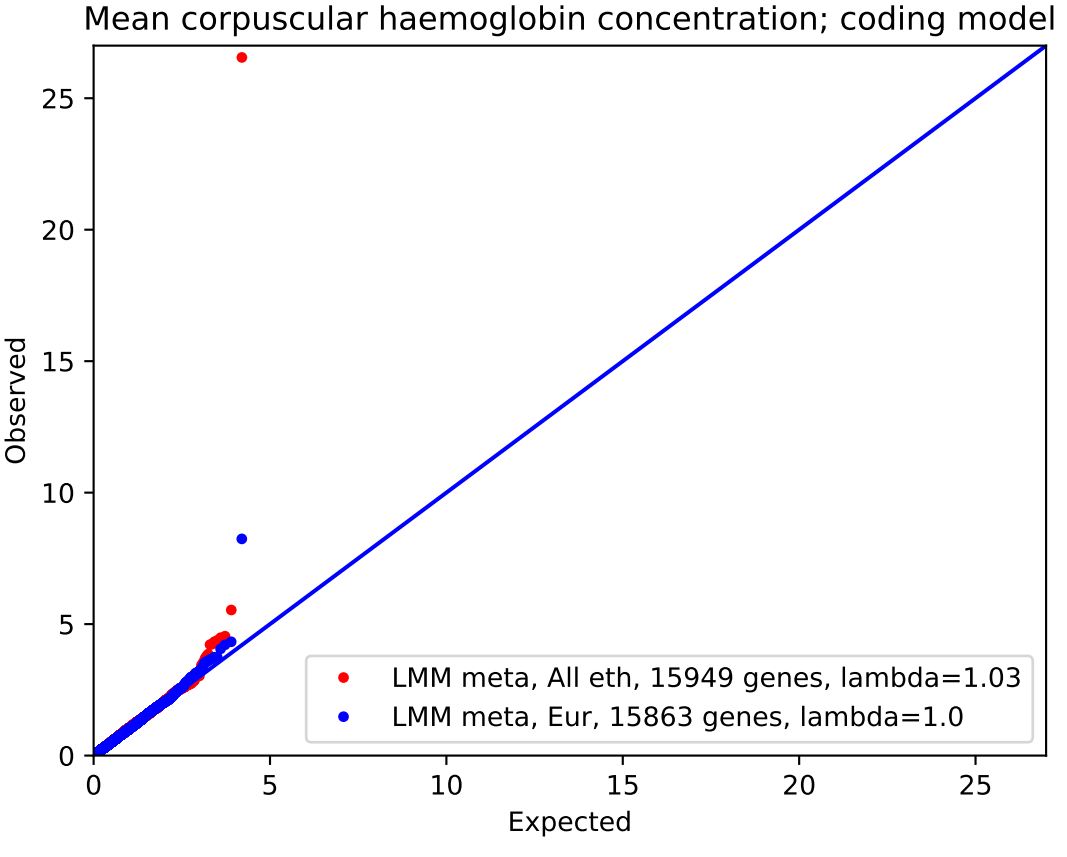

Haemoglobin concentration; lof model
Observed
Expected
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0
LMM meta, All eth, 12834 genes, lambda=1.09
LMM meta, Eur, 11972 genes, lambda=1.07

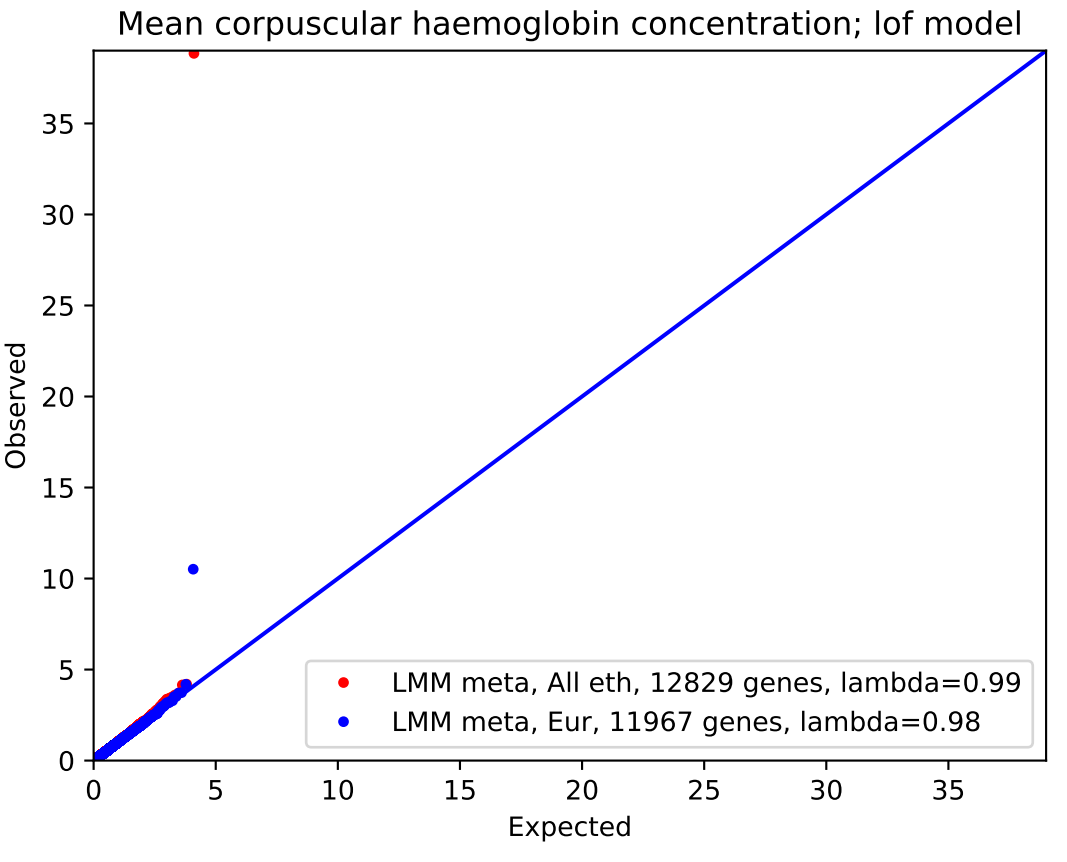

Mean corpuscular volume; coding model
Observed
Expected
0
5
10
15
20
25
LMM meta, All eth, 15949 genes, lambda=1.1
LMM meta, Eur, 15863 genes, lambda=1.08

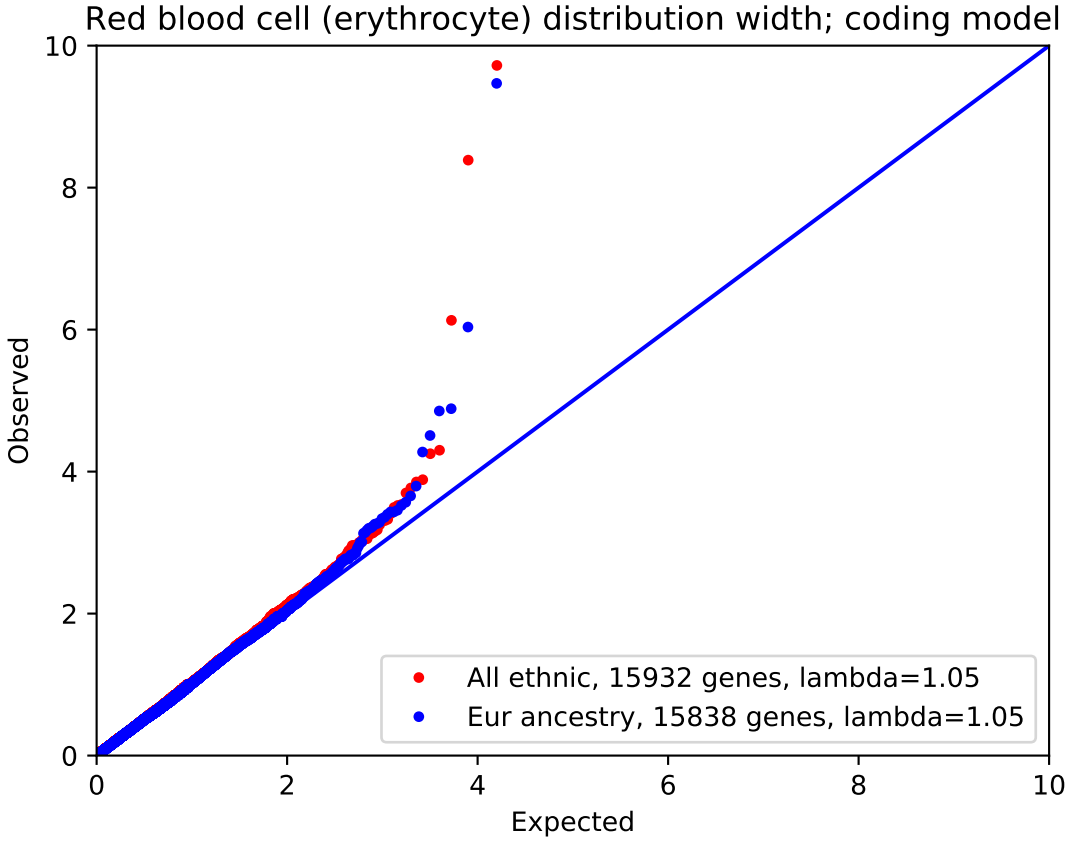

Mean corpuscular volume; lof model
Observed
Expected
0
10
20
30
40
50
LMM meta, All eth, 12829 genes, lambda=1.06
LMM meta, Eur, 11967 genes, lambda=1.03

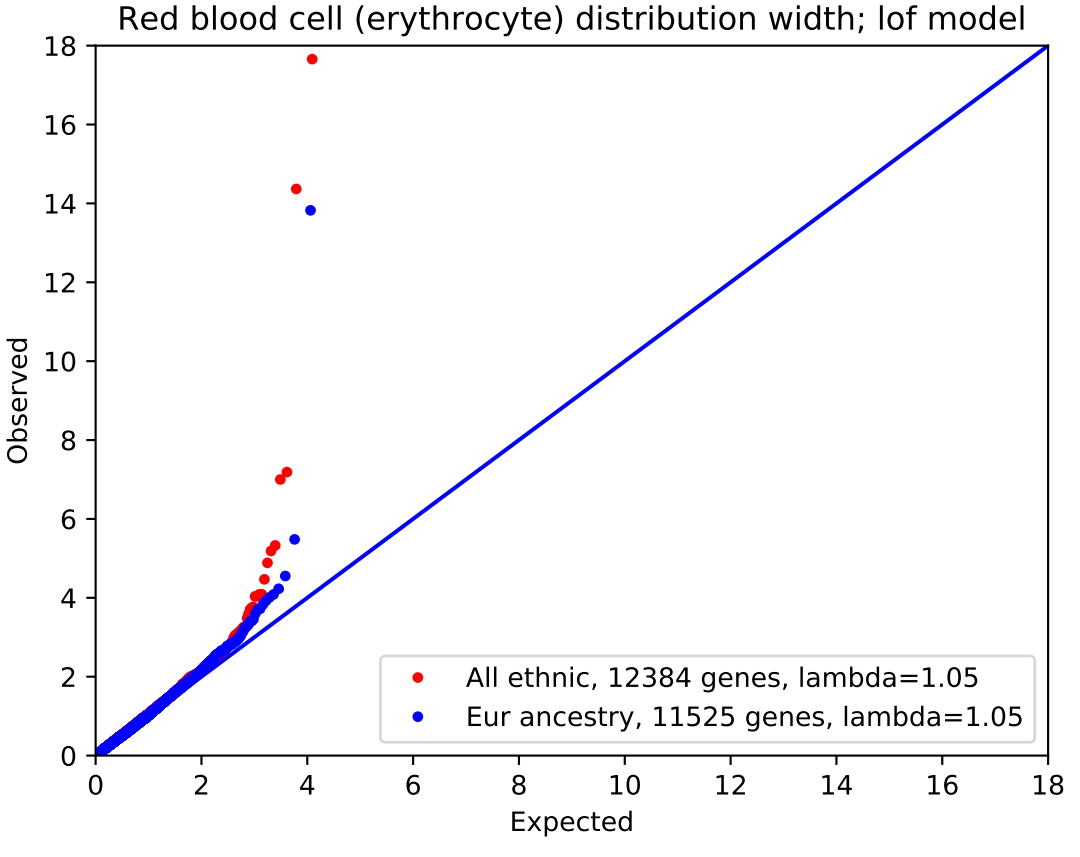

Mean corpuscular haemoglobin; coding model
Observed
Expected
0
5
10
15
20
25
30
LMM meta, All eth, 15949 genes, lambda=1.1
LMM meta, Eur, 15863 genes, lambda=1.04

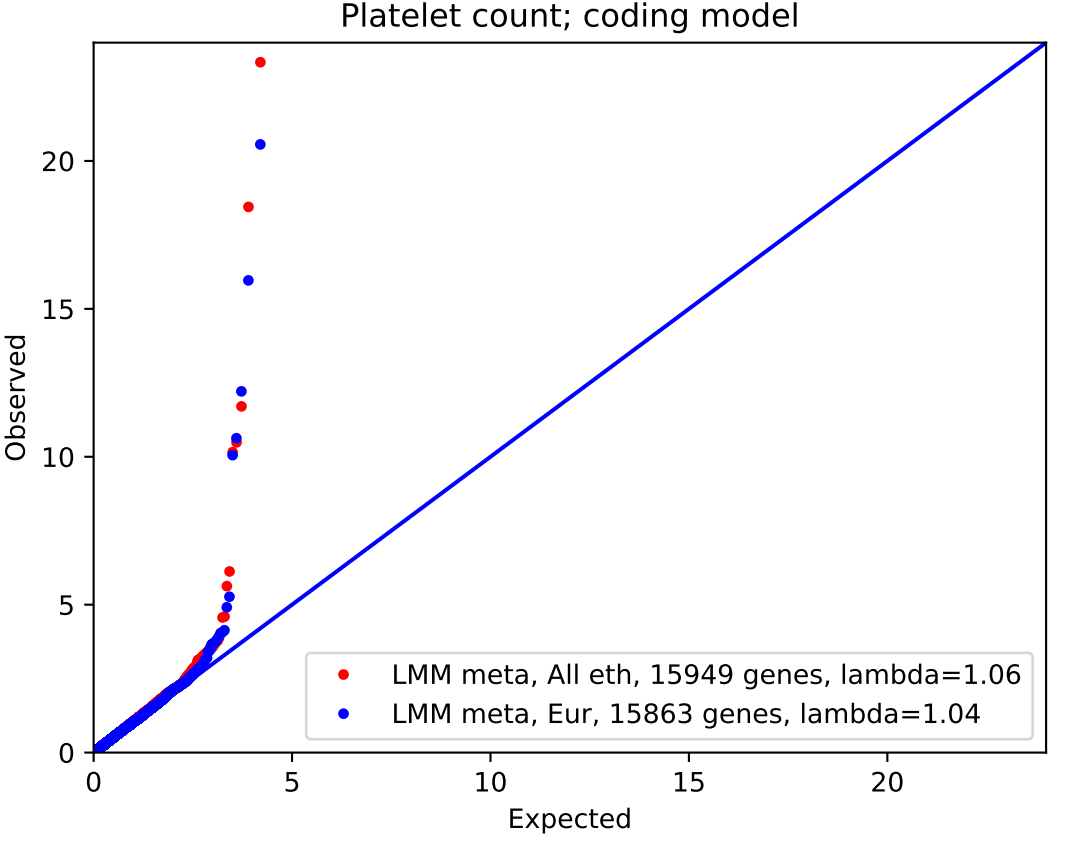

Mean corpuscular haemoglobin; lof model
Observed
Expected
0
10
20
30
40
50
LMM meta, All eth, 12829 genes, lambda=1.06
LMM meta, Eur, 11967 genes, lambda=1.02

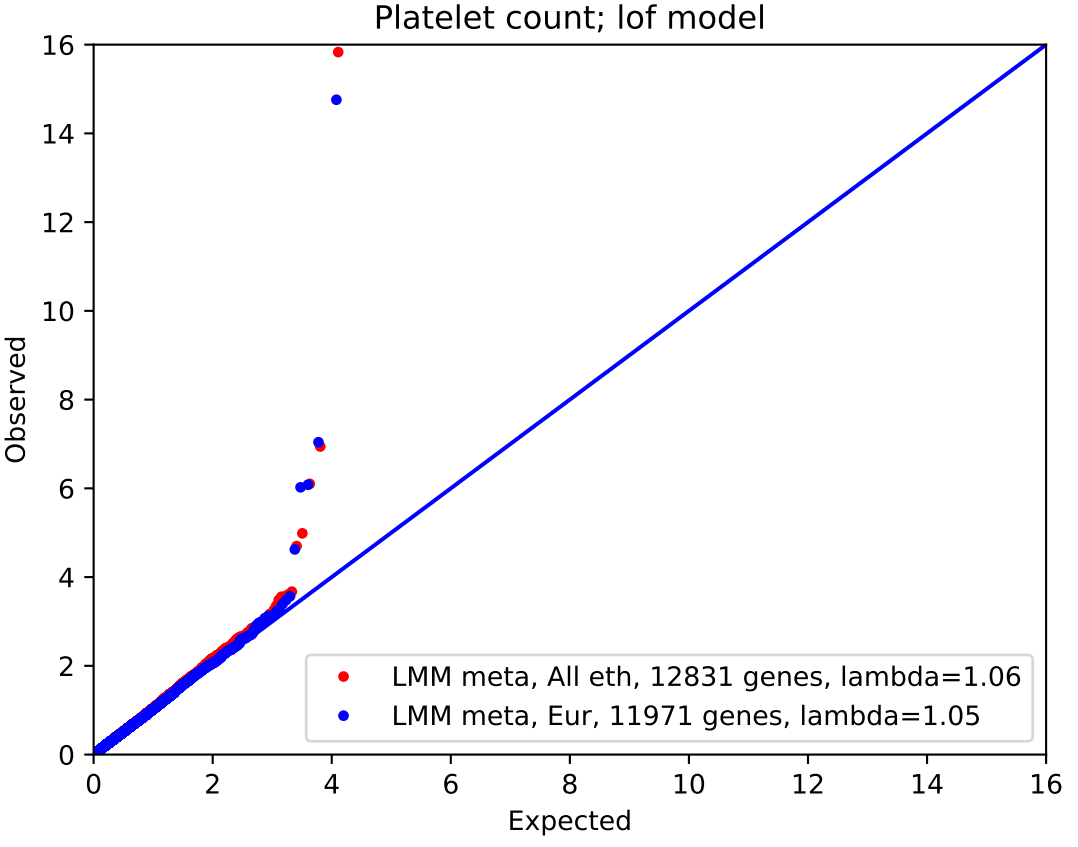

Mean corpuscular haemoglobin concentration; coding model
Observed
Expected
0
5
10
15
20
25
LMM meta, All eth, 15949 genes, lambda=1.03
LMM meta, Eur, 15863 genes, lambda=1.0

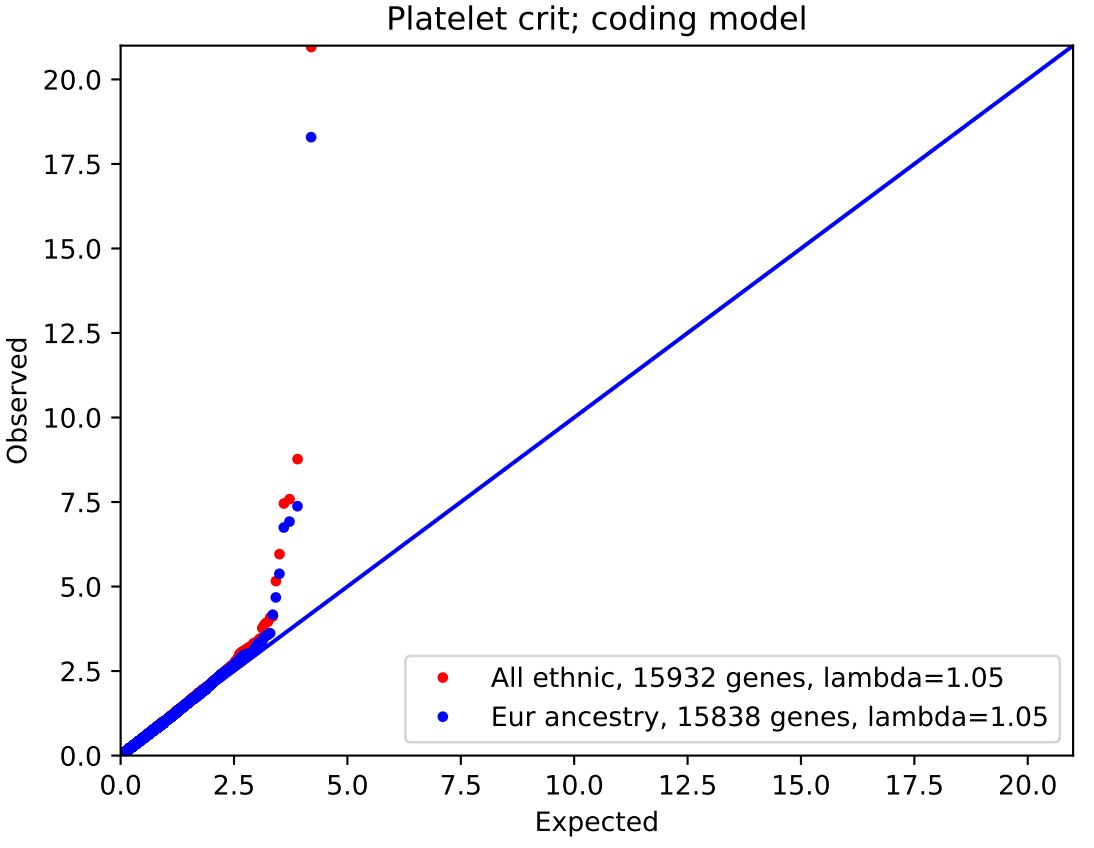

Mean corpuscular haemoglobin concentration; lof model
Observed
Expected
0
5
10
15
20
25
30
35
LMM meta, All eth, 12829 genes, lambda=0.99
LMM meta, Eur, 11967 genes, lambda=0.98

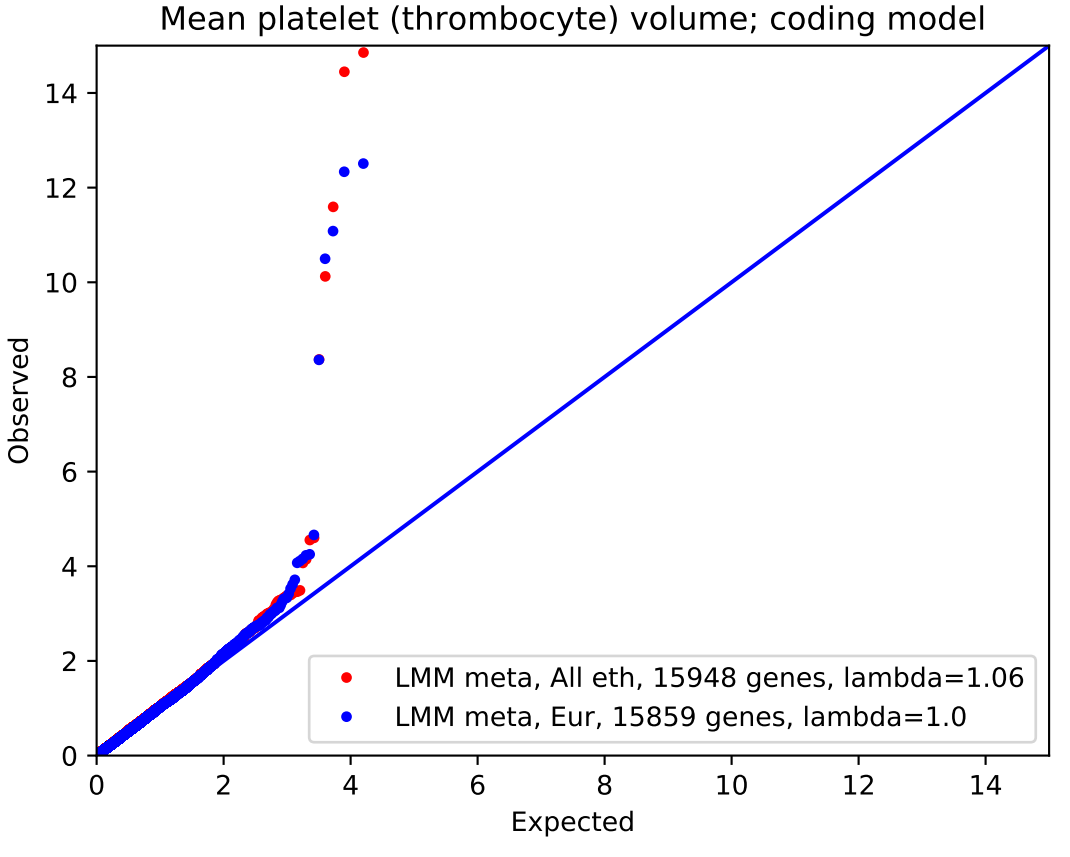

Red blood cell (erythrocyte) distribution width; coding model
Observed
Expected
0
2
4
6
8
10
All ethnic, 15932 genes, lambda=1.05
Eur ancestry, 15838 genes, lambda=1.05

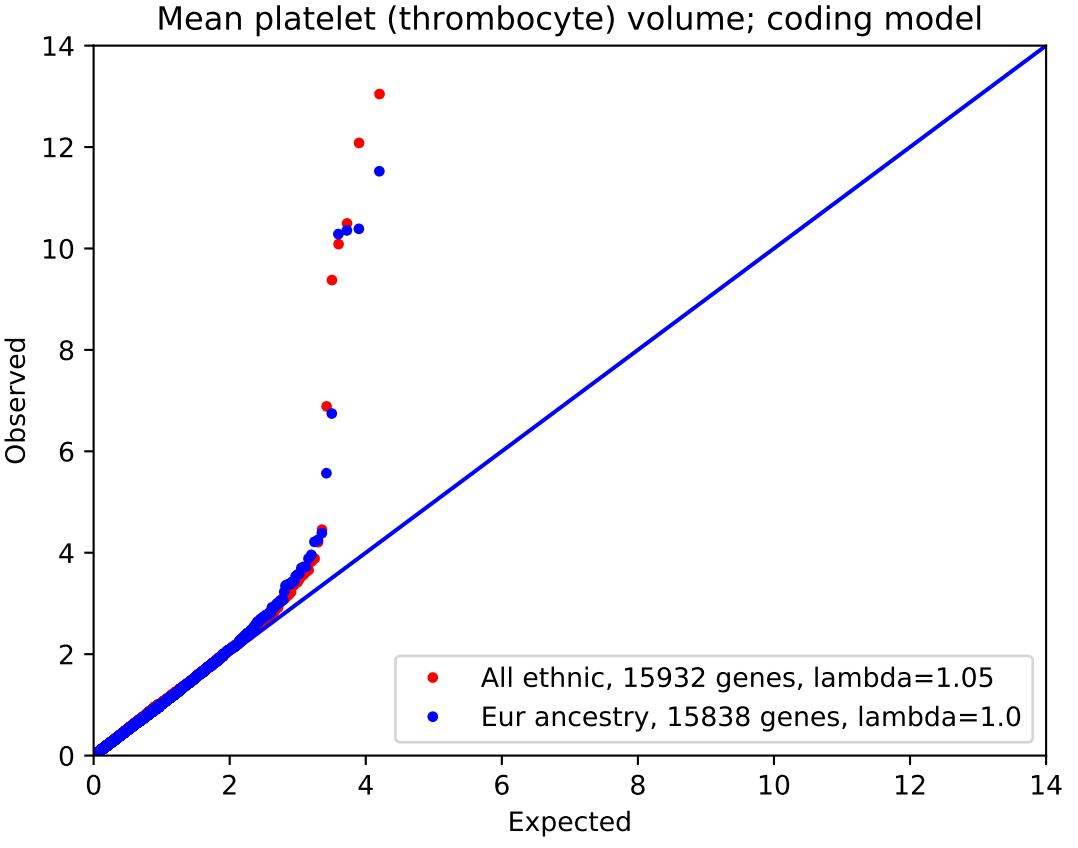

Red blood cell (erythrocyte) distribution width; lof model
Observed
Expected
0
2
4
6
8
10
12
14
16
18
All ethnic, 12384 genes, lambda=1.05
Eur ancestry, 11525 genes, lambda=1.05

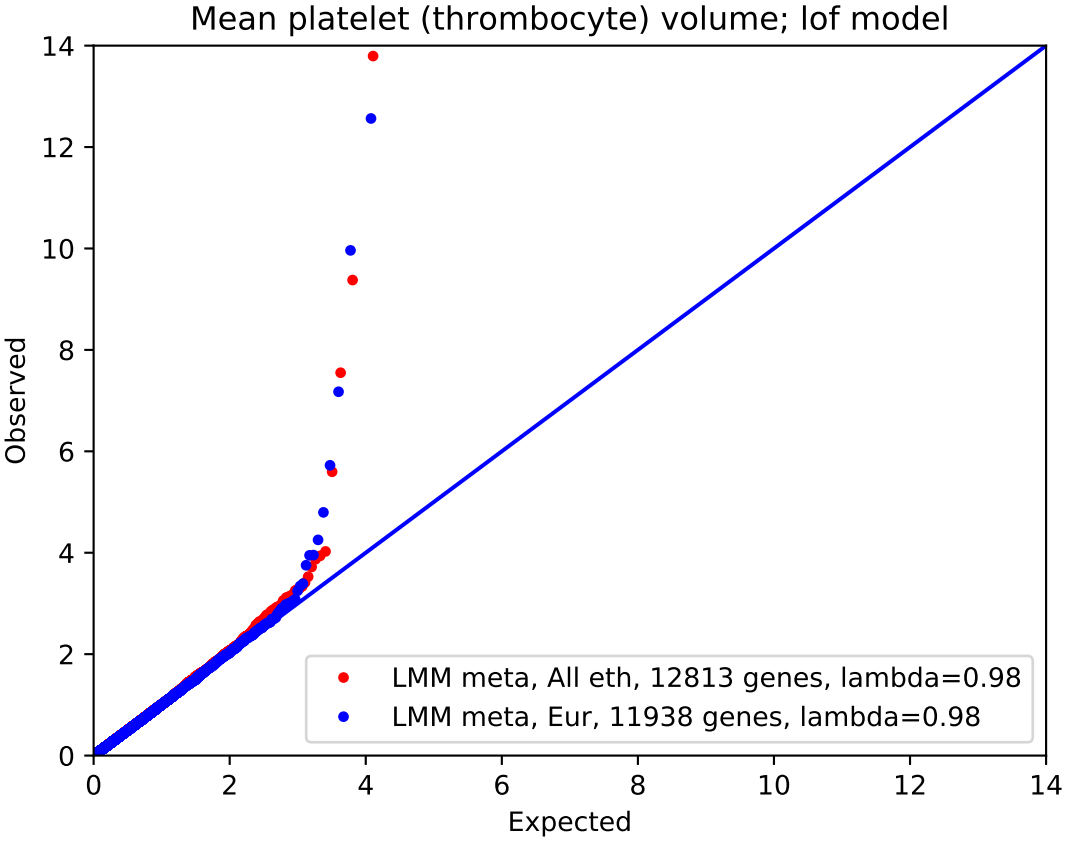

Platelet count; coding model
Observed
Expected
0
5
10
15
20
LMM meta, All eth, 15949 genes, lambda=1.06
LMM meta, Eur, 15863 genes, lambda=1.04

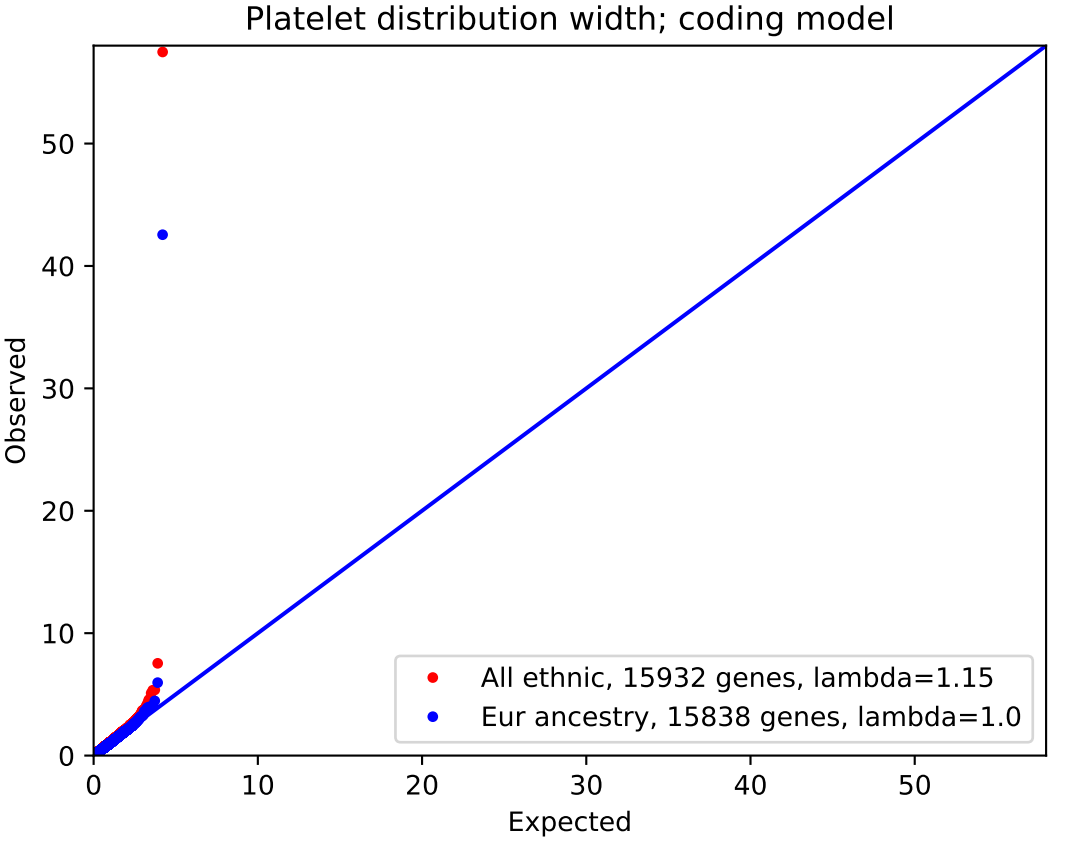

Platelet count; lof model
Observed
Expected
0
2
4
6
8
10
12
14
16
LMM meta, All eth, 12831 genes, lambda=1.06
LMM meta, Eur, 11971 genes, lambda=1.05

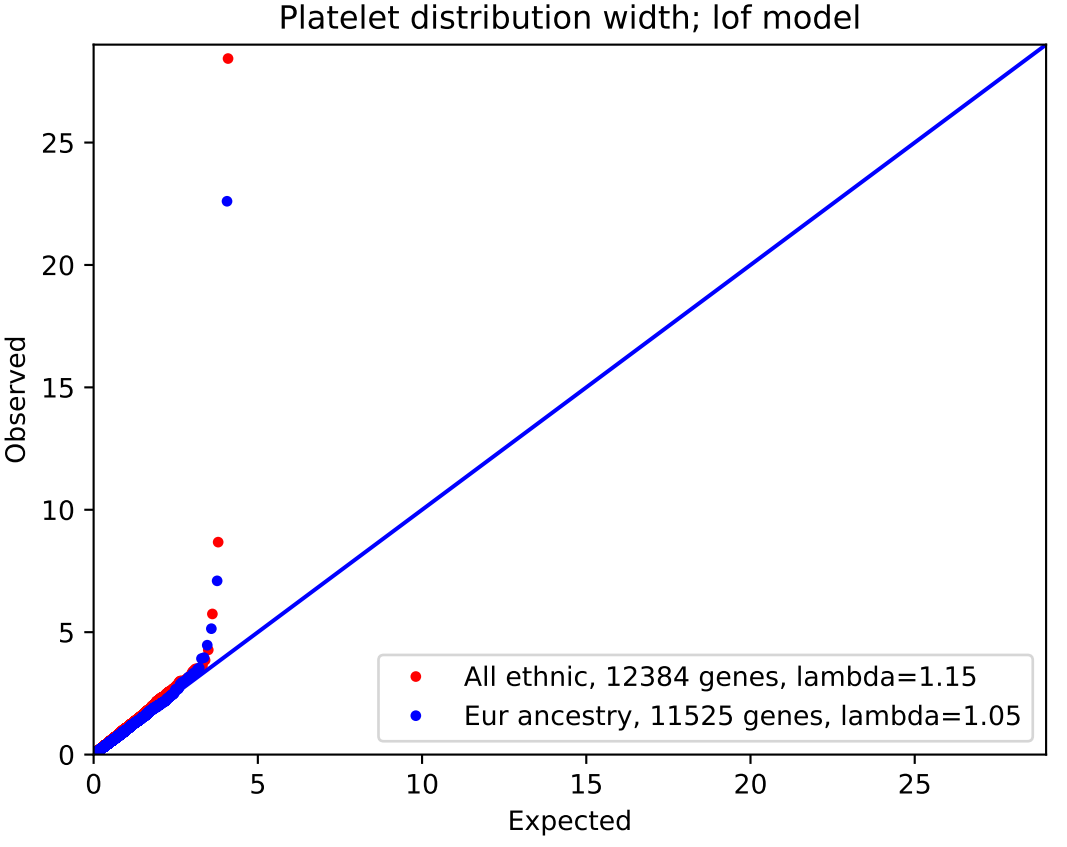

Platelet crit; coding model
Observed
Expected
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0
All ethnic, 15932 genes, lambda=1.05
Eur ancestry, 15838 genes, lambda=1.05

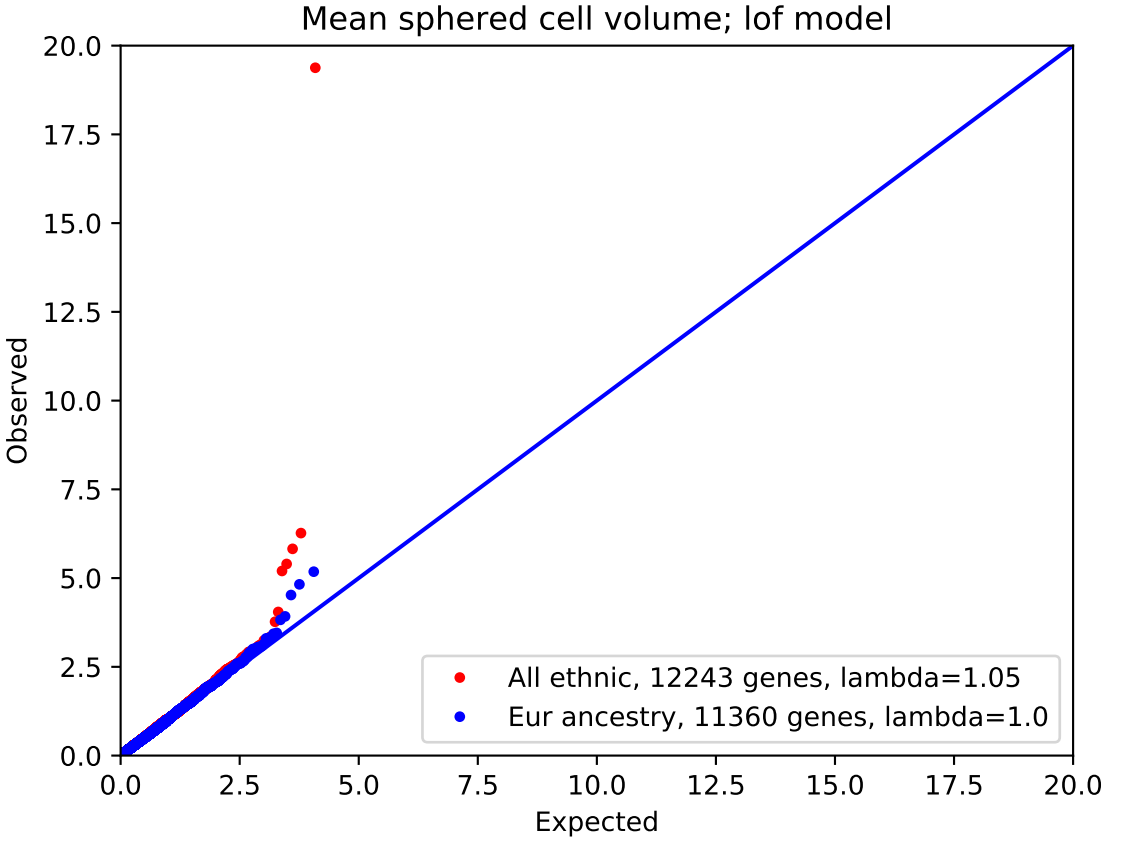

Mean platelet (thrombocyte) volume; coding model
Observed
Expected
0
2
4
6
8
10
12
14
LMM meta, All eth, 15948 genes, lambda=1.06
LMM meta, Eur, 15859 genes, lambda=1.0

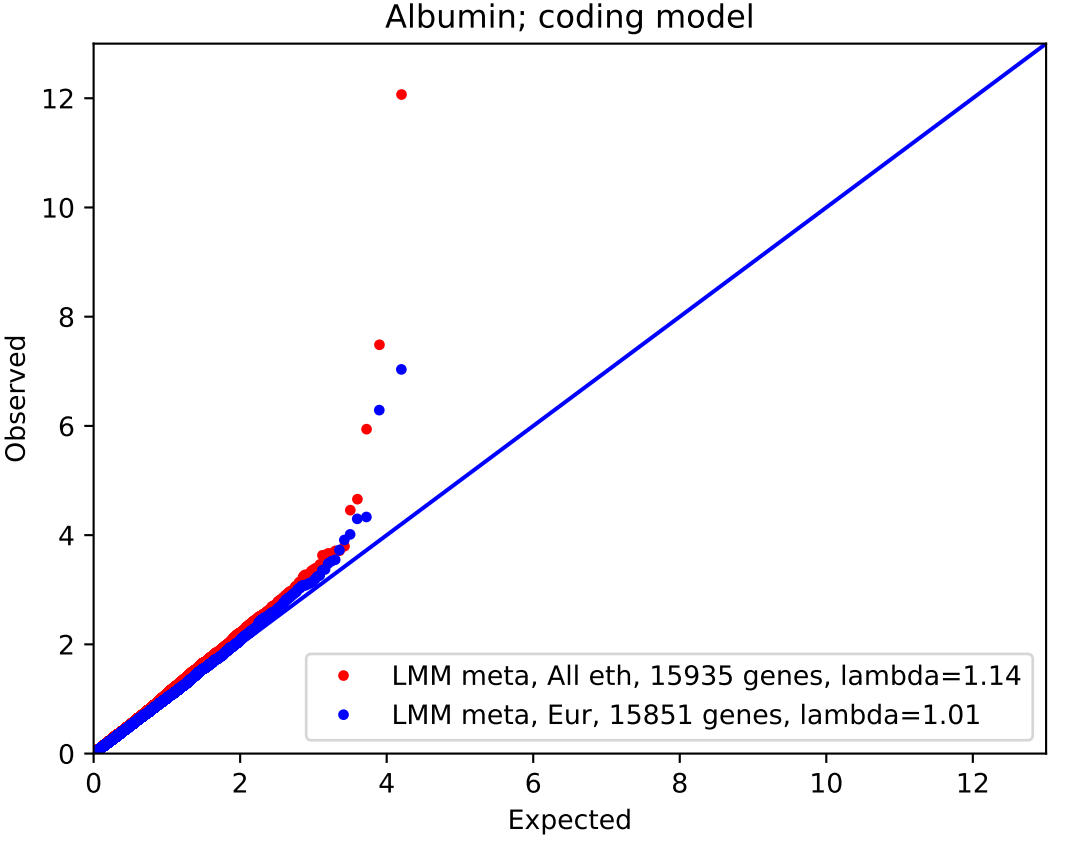

Mean platelet (thrombocyte) volume; coding model
Observed
Expected
0
2
4
6
8
10
12
14
All ethnic, 15932 genes, lambda=1.05
Eur ancestry, 15838 genes, lambda=1.0

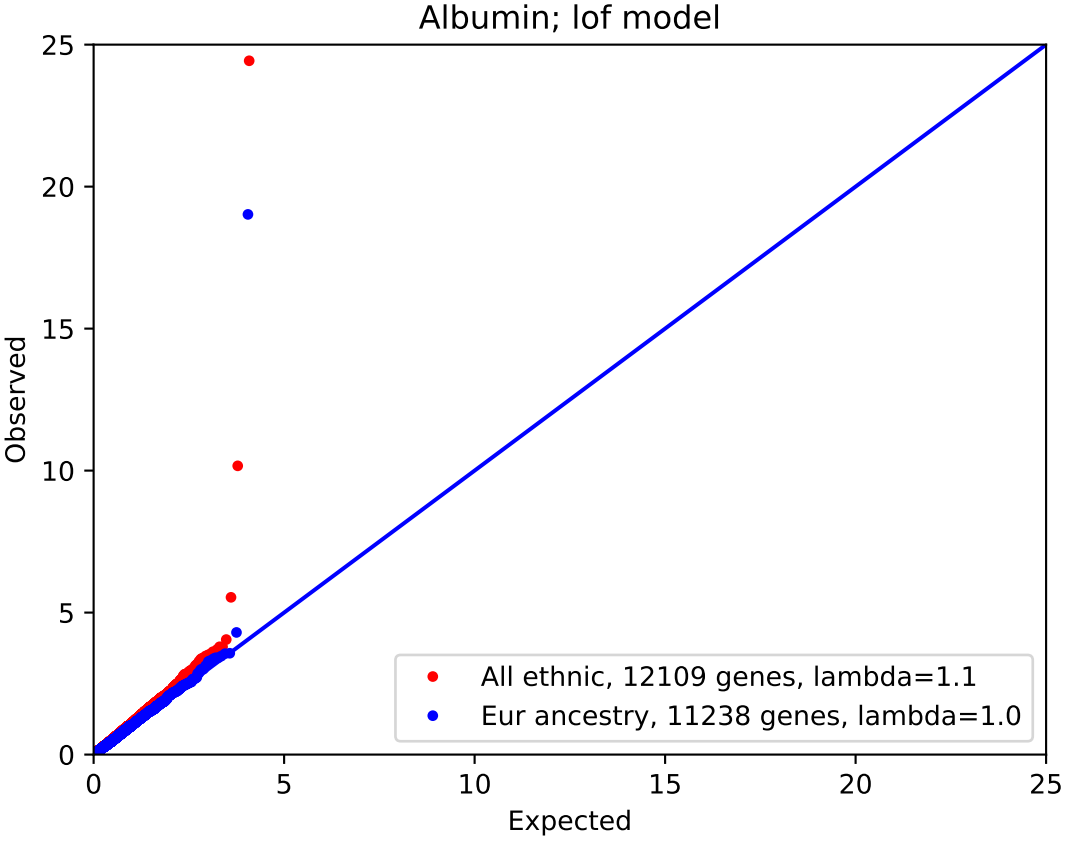

Mean platelet (thrombocyte) volume; lof model
Observed
Expected
0
2
4
6
8
10
12
14
LMM meta, All eth, 12813 genes, lambda=0.98
LMM meta, Eur, 11938 genes, lambda=0.98

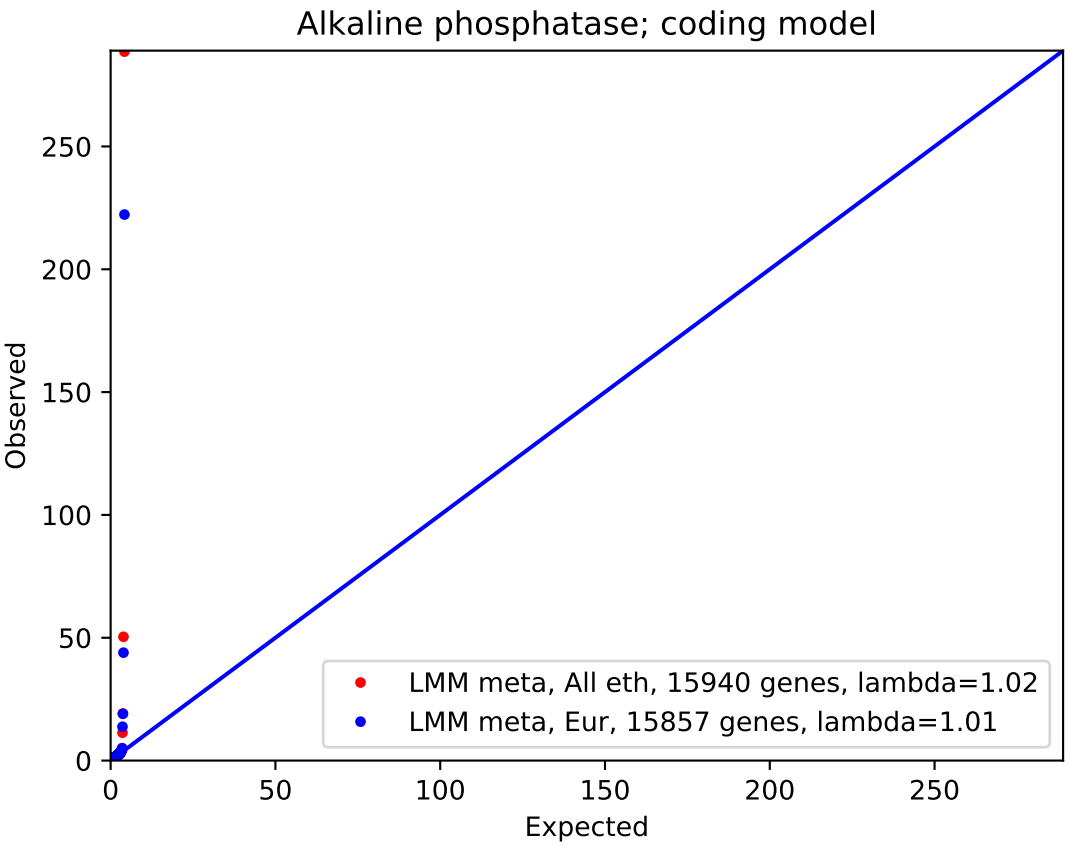

Platelet distribution width; coding model
Observed
Expected
0
10
20
30
40
50
All ethnic, 15932 genes, lambda=1.15
Eur ancestry, 15838 genes, lambda=1.0

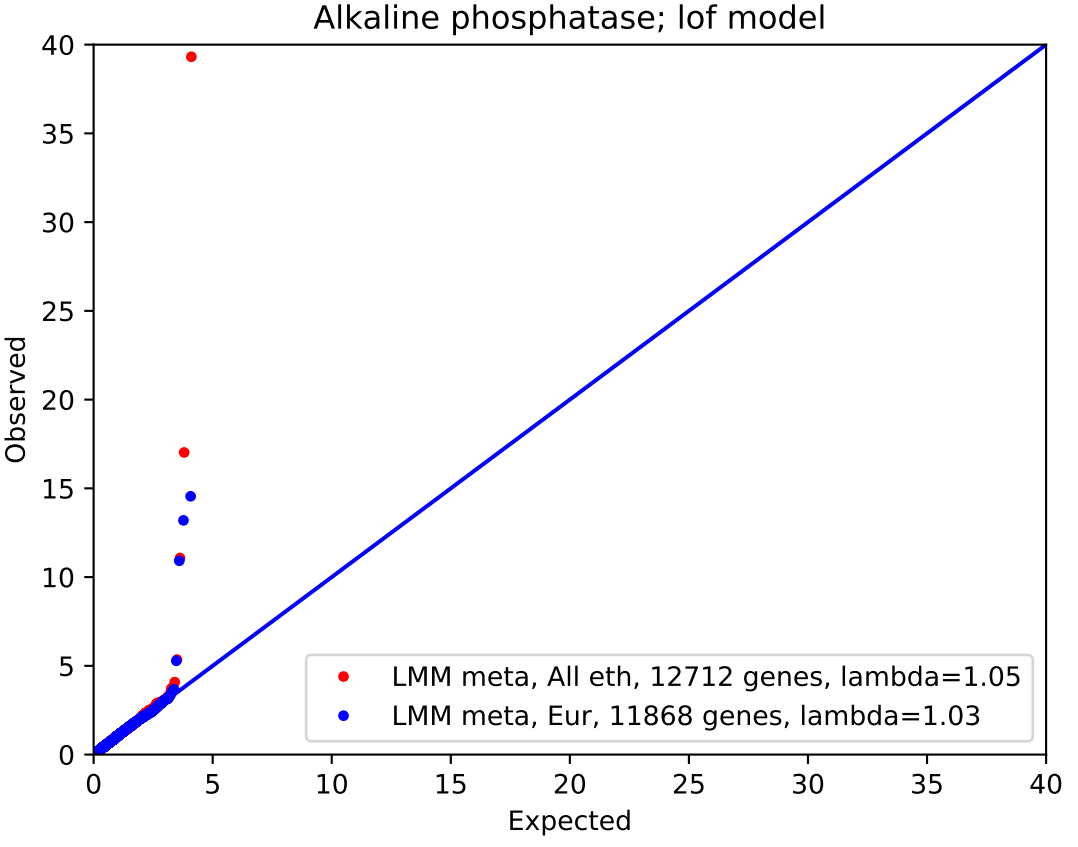

Platelet distribution width; lof model
Observed
Expected
0
5
10
15
20
25
All ethnic, 12384 genes, lambda=1.15
Eur ancestry, 11525 genes, lambda=1.05

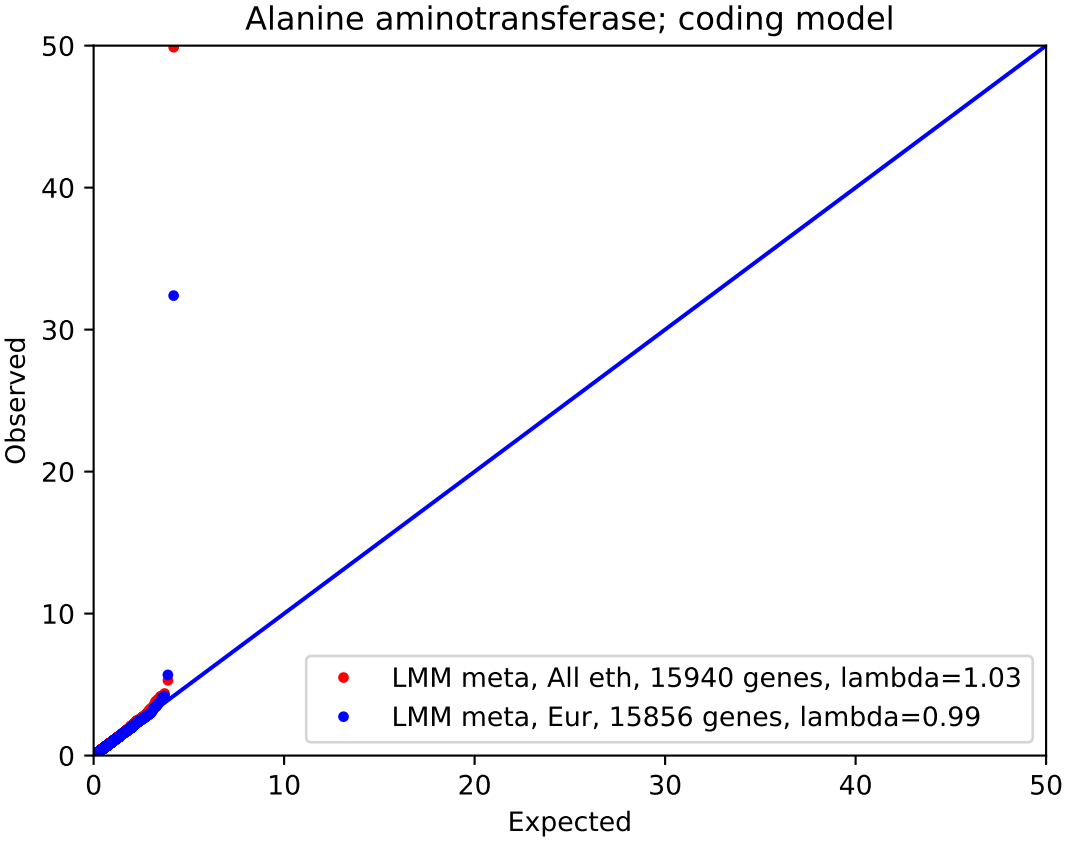

Mean sphered cell volume; lof model
Observed
Expected
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0
All ethnic, 12243 genes, lambda=1.05
Eur ancestry, 11360 genes, lambda=1.0

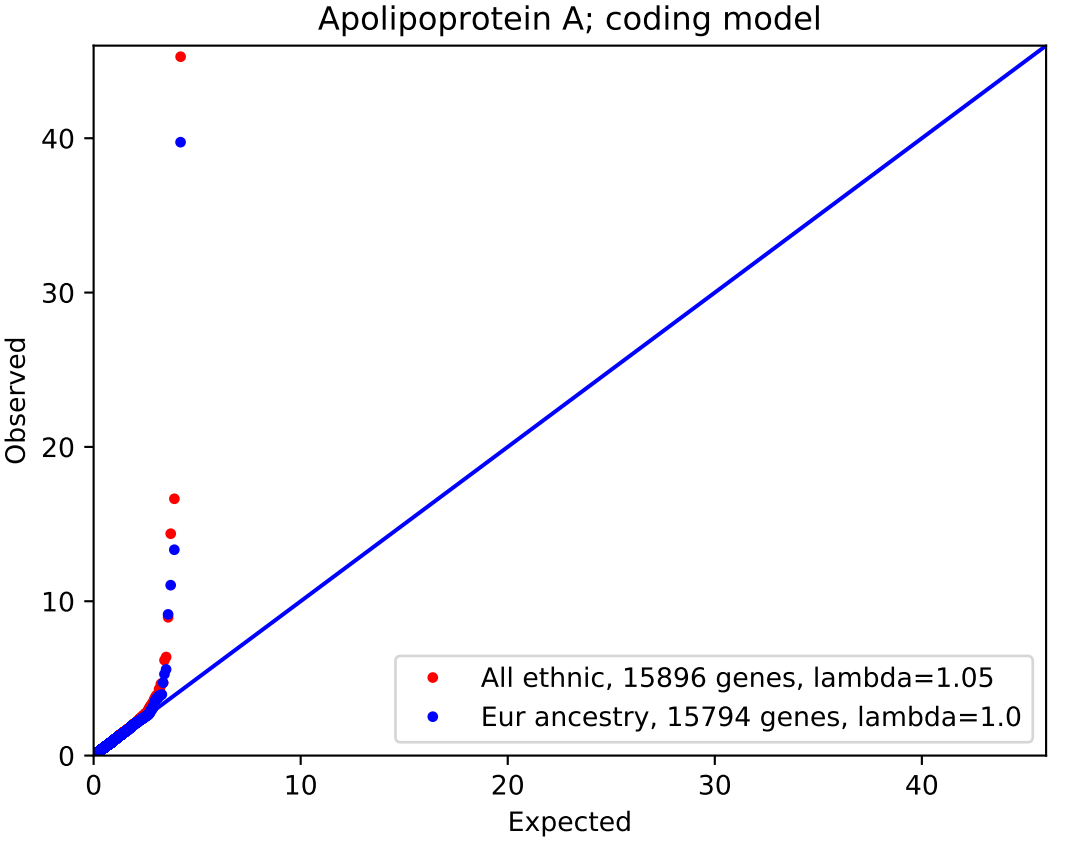

Albumin; coding model
Observed
Expected
0
2
4
6
8
10
12
LMM meta, All eth, 15935 genes, lambda=1.14
LMM meta, Eur, 15851 genes, lambda=1.01

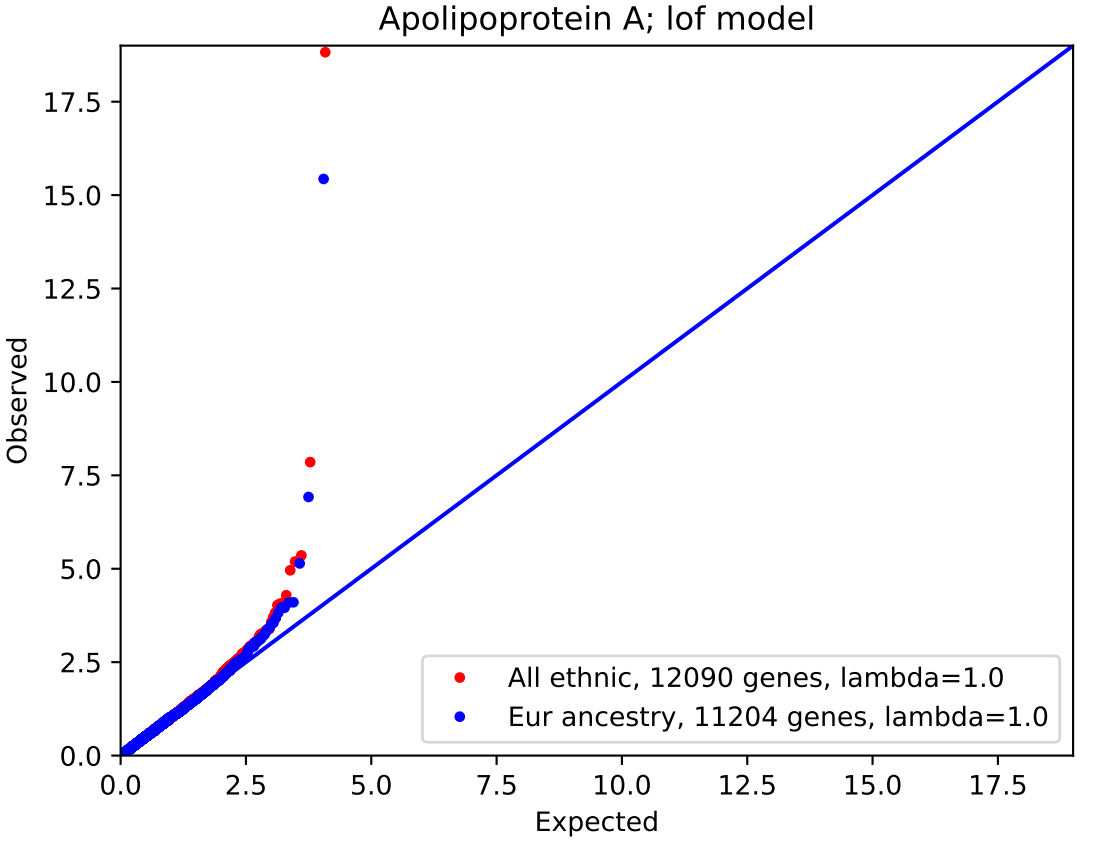

Albumin; lof model
Observed
Expected
0
5
10
15
20
25
All ethnic, 12109 genes, lambda=1.1
Eur ancestry, 11238 genes, lambda=1.0

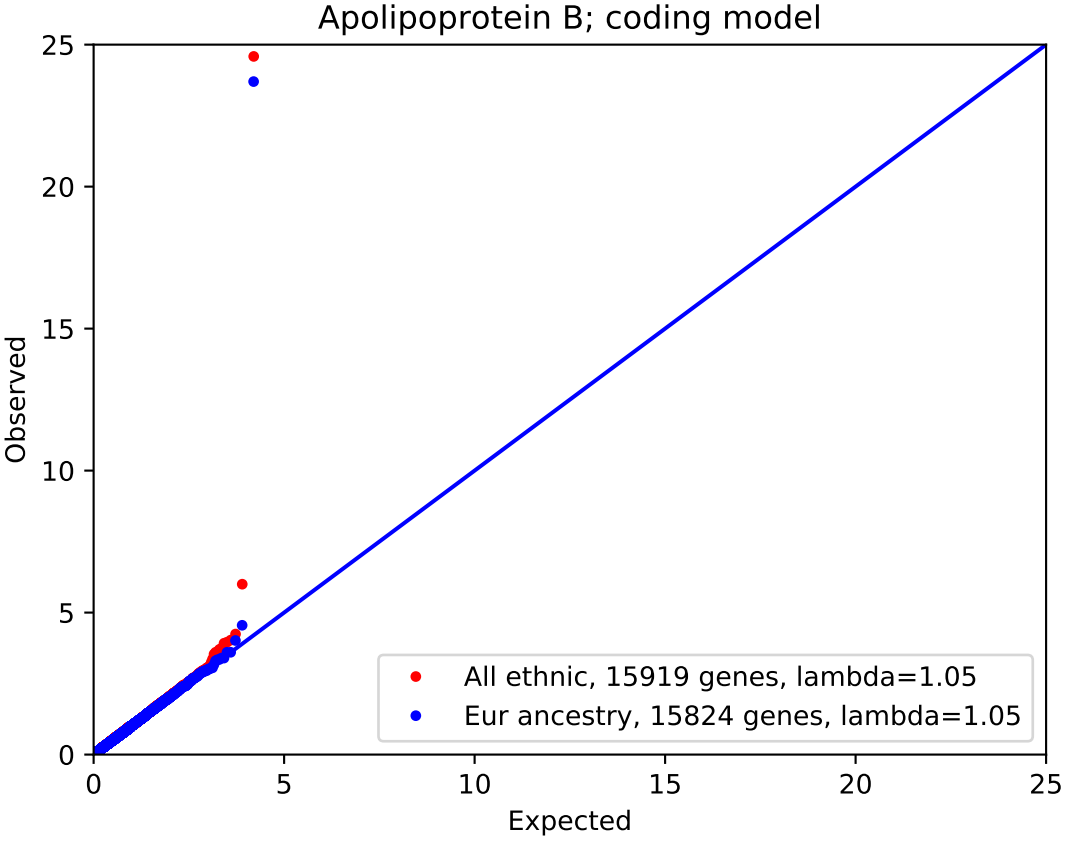

Alkaline phosphatase; coding model
Observed
Expected
0
50
100
150
200
250
LMM meta, All eth, 15940 genes, lambda=1.02
LMM meta, Eur, 15857 genes, lambda=1.01

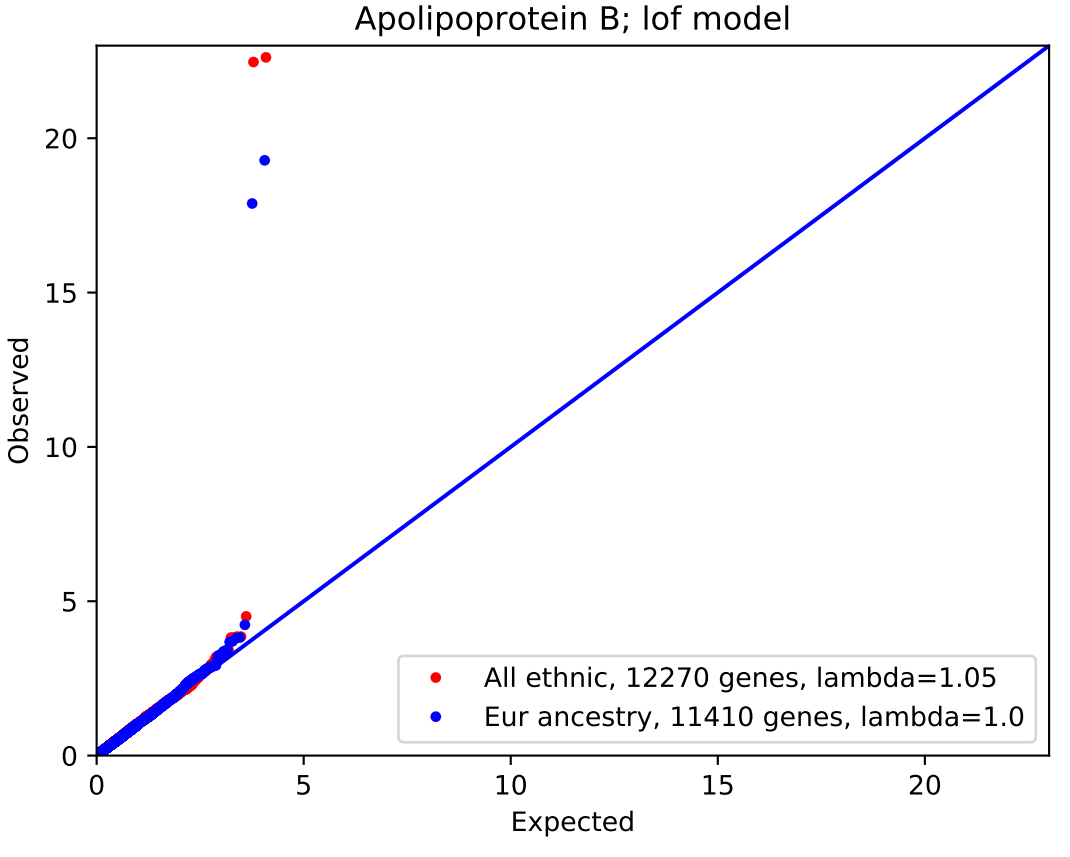

Alkaline phosphatase; lof model
Observed
Expected
0
5
10
15
20
25
30
35
40
LMM meta, All eth, 12712 genes, lambda=1.05
LMM meta, Eur, 11868 genes, lambda=1.03

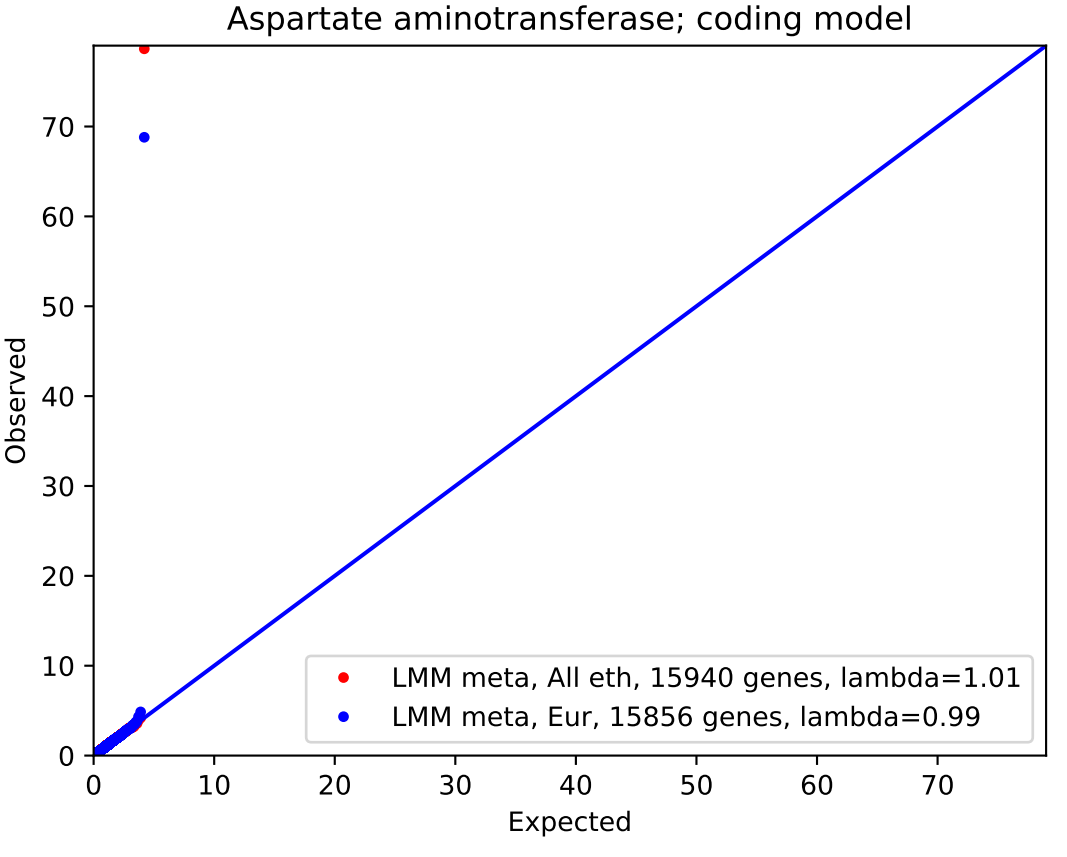

Alanine aminotransferase; coding model
Observed
Expected
0
10
20
30
40
50
LMM meta, All eth, 15940 genes, lambda=1.03
LMM meta, Eur, 15856 genes, lambda=0.99

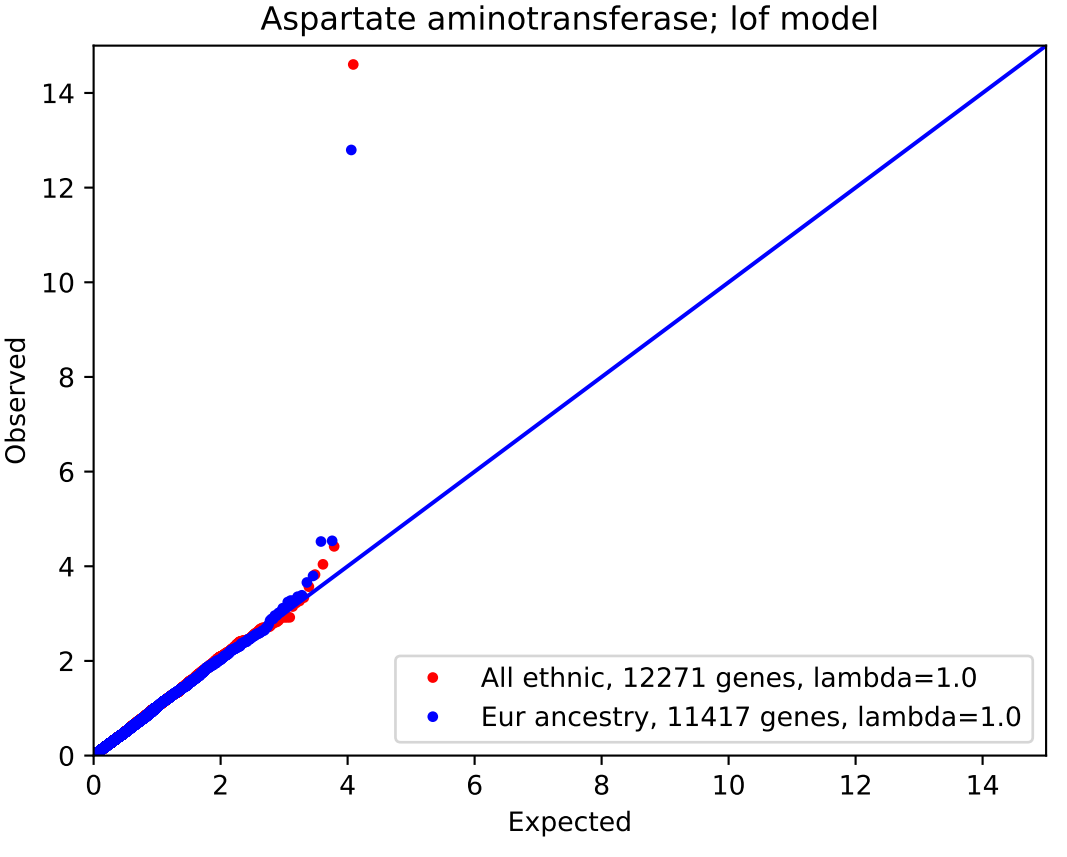

Apolipoprotein A; coding model
Observed
Expected
0
10
20
30
40
All ethnic, 15896 genes, lambda=1.05
Eur ancestry, 15794 genes, lambda=1.0

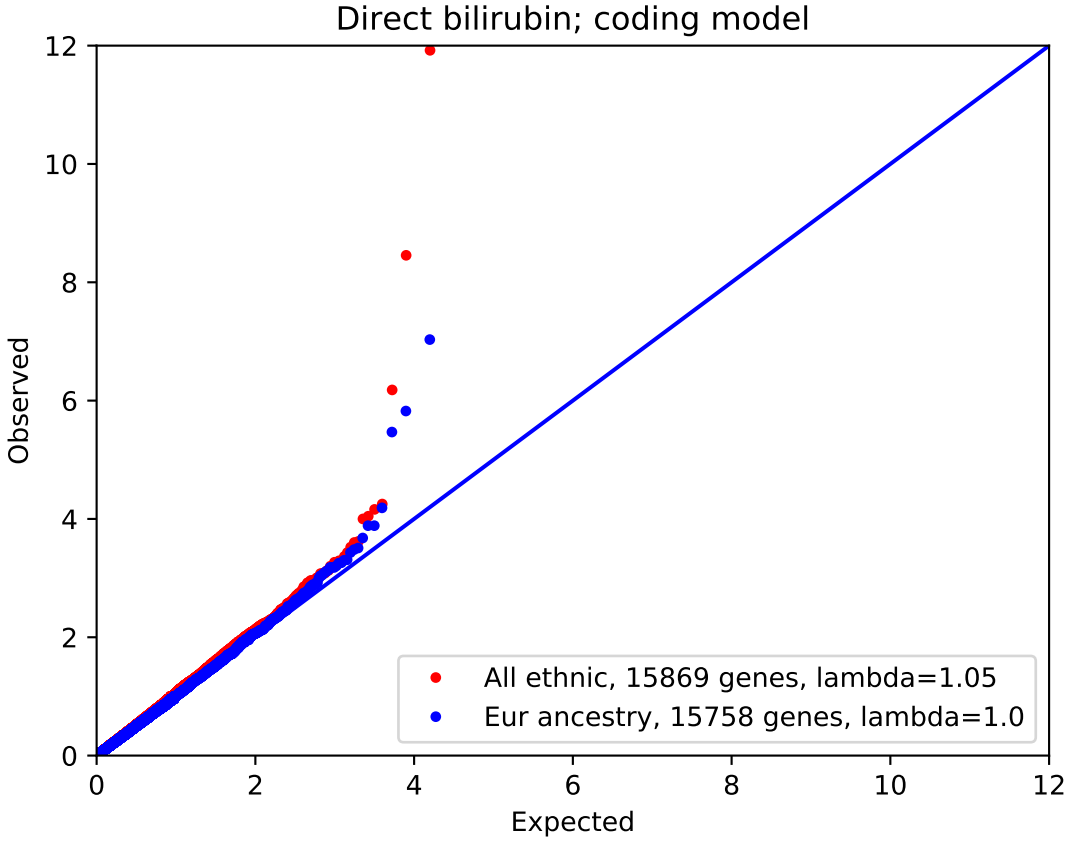

Apolipoprotein A; lof model
Observed
Expected
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
All ethnic, 12090 genes, lambda=1.0
Eur ancestry, 11204 genes, lambda=1.0

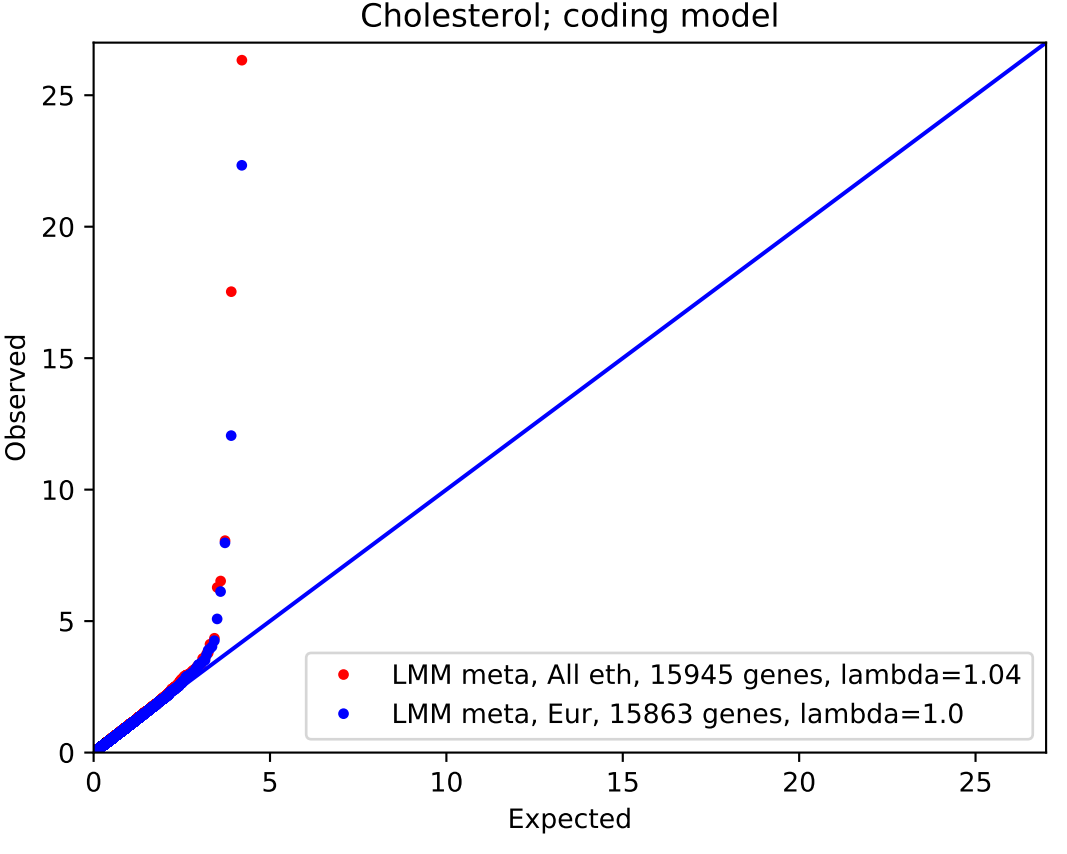

Apolipoprotein B; coding model
Observed
Expected
0
5
10
15
20
25
All ethnic, 15919 genes, lambda=1.05
Eur ancestry, 15824 genes, lambda=1.05

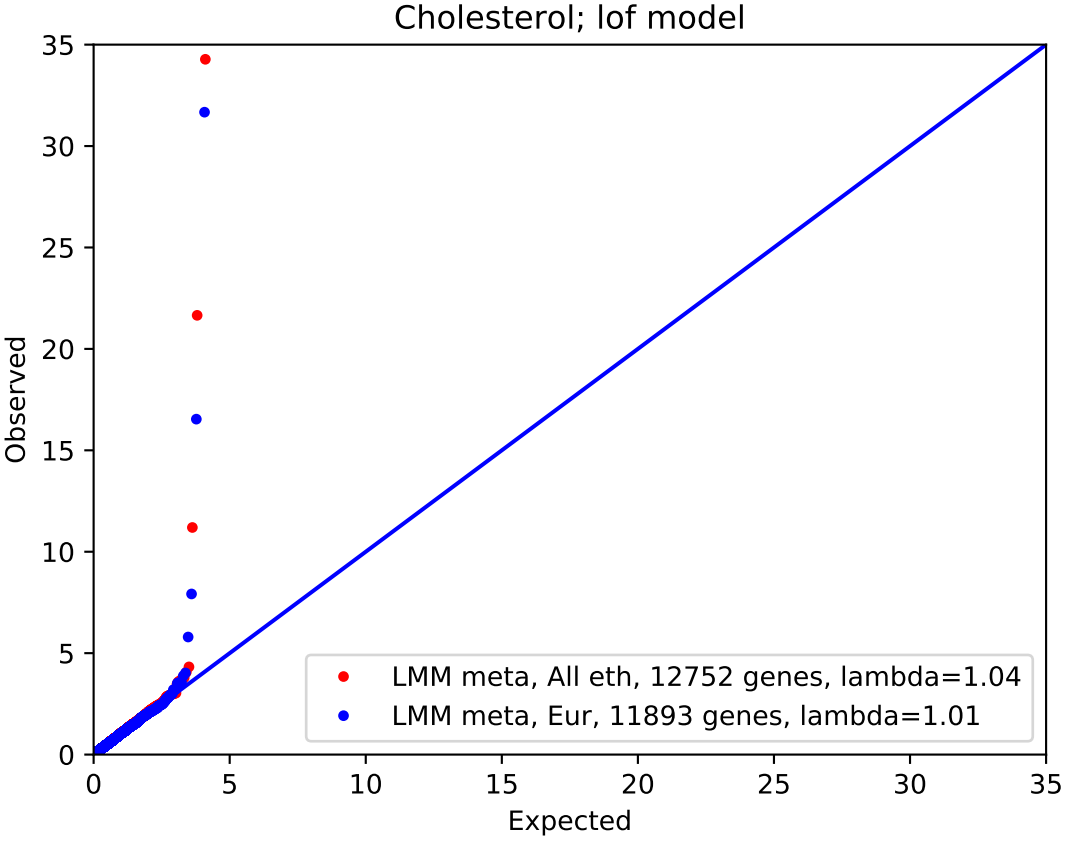

Apolipoprotein B; lof model
Observed
Expected
0
5
10
15
20
All ethnic, 12270 genes, lambda=1.05
Eur ancestry, 11410 genes, lambda=1.0

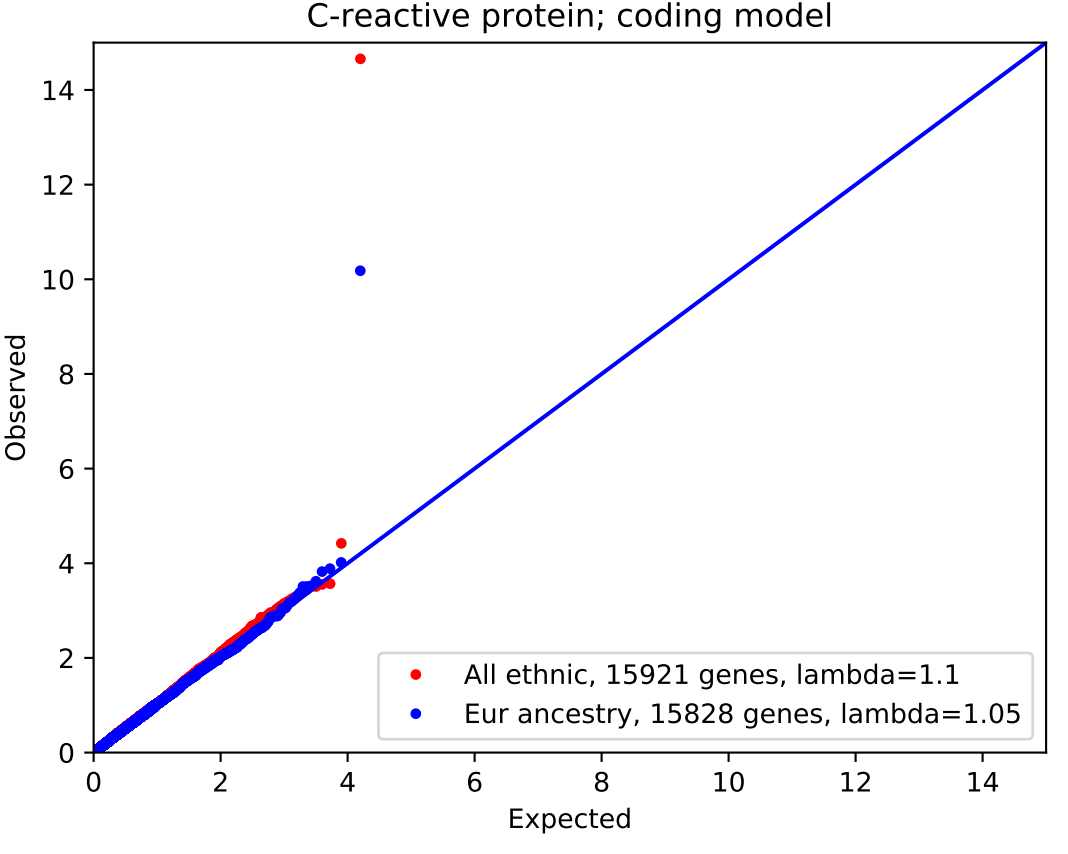

Aspartate aminotransferase; coding model
Observed
Expected
0
10
20
30
40
50
60
70
LMM meta, All eth, 15940 genes, lambda=1.01
LMM meta, Eur, 15856 genes, lambda=0.99

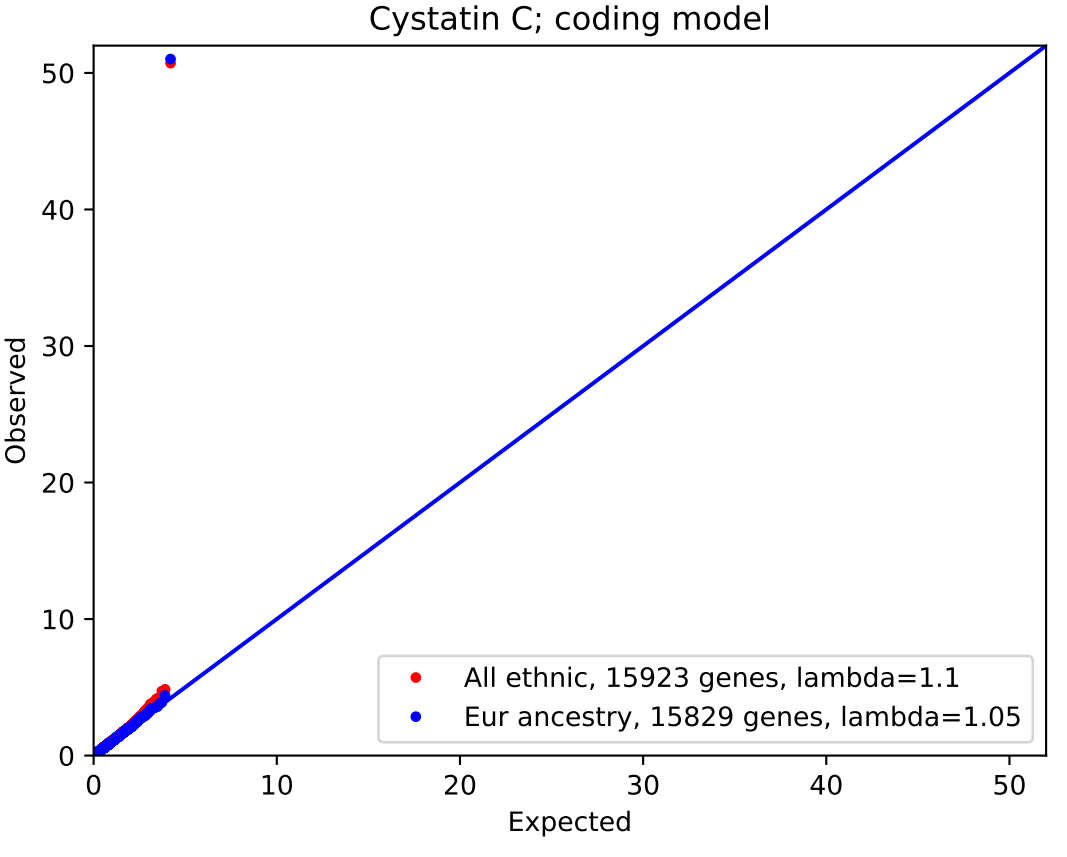

Aspartate aminotransferase; lof model
Observed
Expected
0
2
4
6
8
10
12
14
All ethnic, 12271 genes, lambda=1.0
Eur ancestry, 11417 genes, lambda=1.0

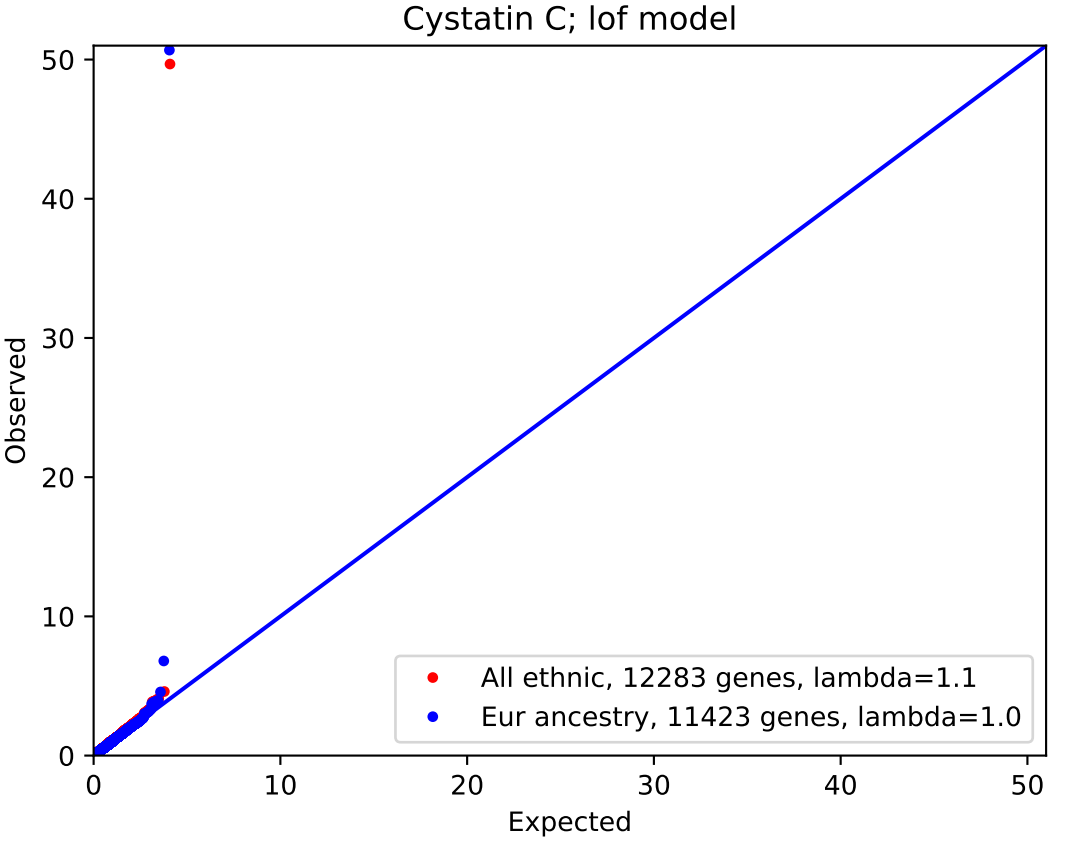

Direct bilirubin; coding model
Observed
Expected
0
2
4
6
8
10
12
All ethnic, 15869 genes, lambda=1.05
Eur ancestry, 15758 genes, lambda=1.0

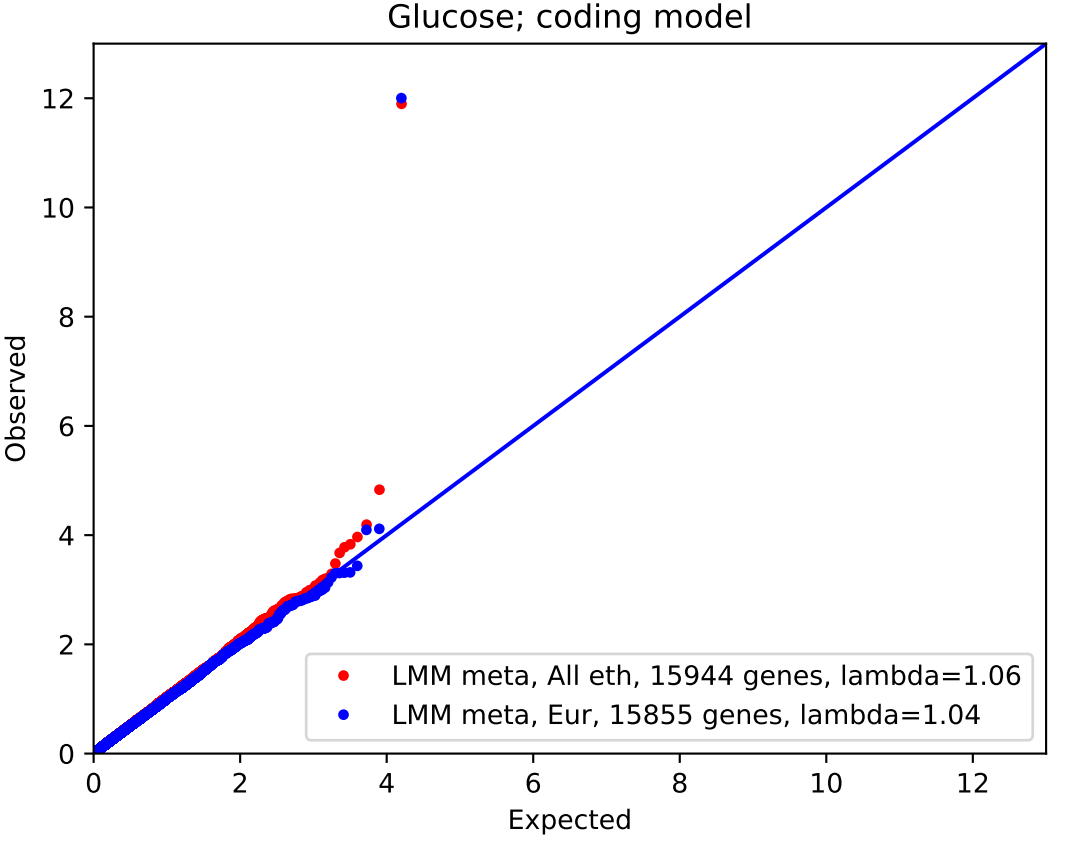

Cholesterol; coding model
Observed
Expected
0
5
10
15
20
25
LMM meta, All eth, 15945 genes, lambda=1.04
LMM meta, Eur, 15863 genes, lambda=1.0

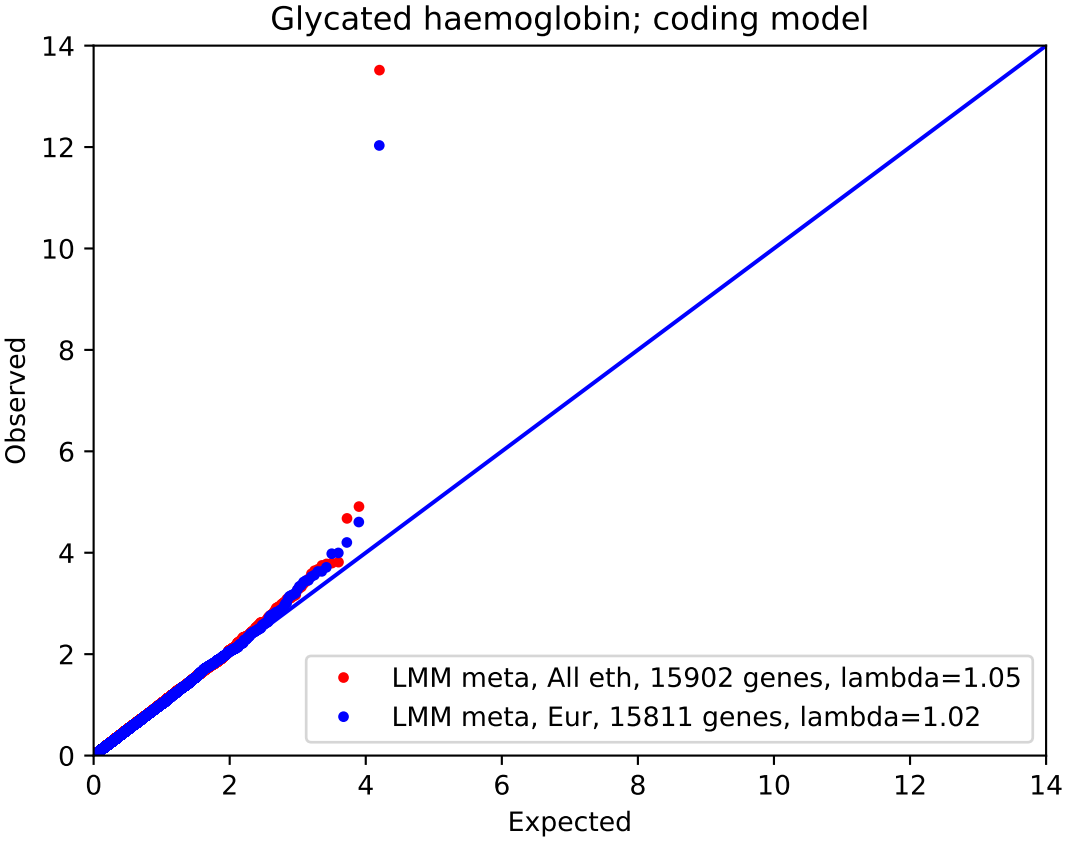

Cholesterol; lof model
Observed
Expected
0
5
10
15
20
25
30
35
LMM meta, All eth, 12752 genes, lambda=1.04
LMM meta, Eur, 11893 genes, lambda=1.01

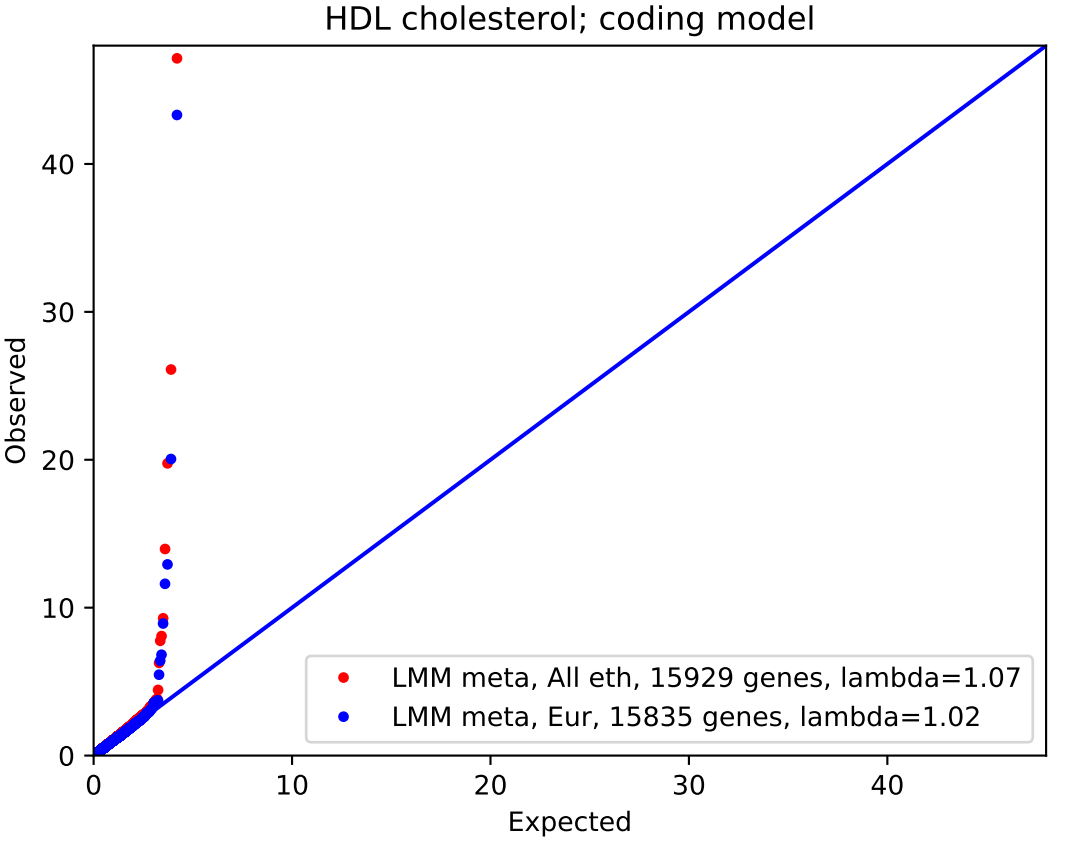

C-reactive protein; coding model
Observed
Expected
0
2
4
6
8
10
12
14
All ethnic, 15921 genes, lambda=1.1
Eur ancestry, 15828 genes, lambda=1.05

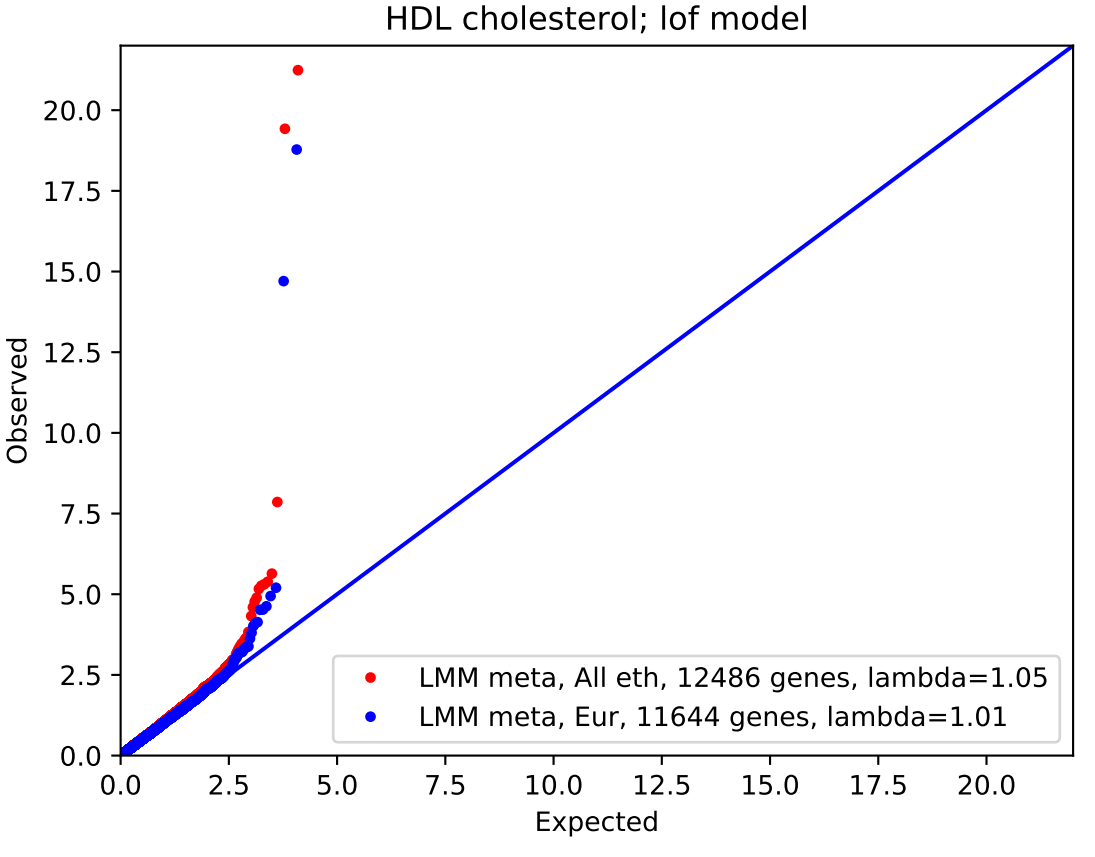

Cystatin C; coding model
Observed
Expected
0
10
20
30
40
50
All ethnic, 15923 genes, lambda=1.1
Eur ancestry, 15829 genes, lambda=1.05

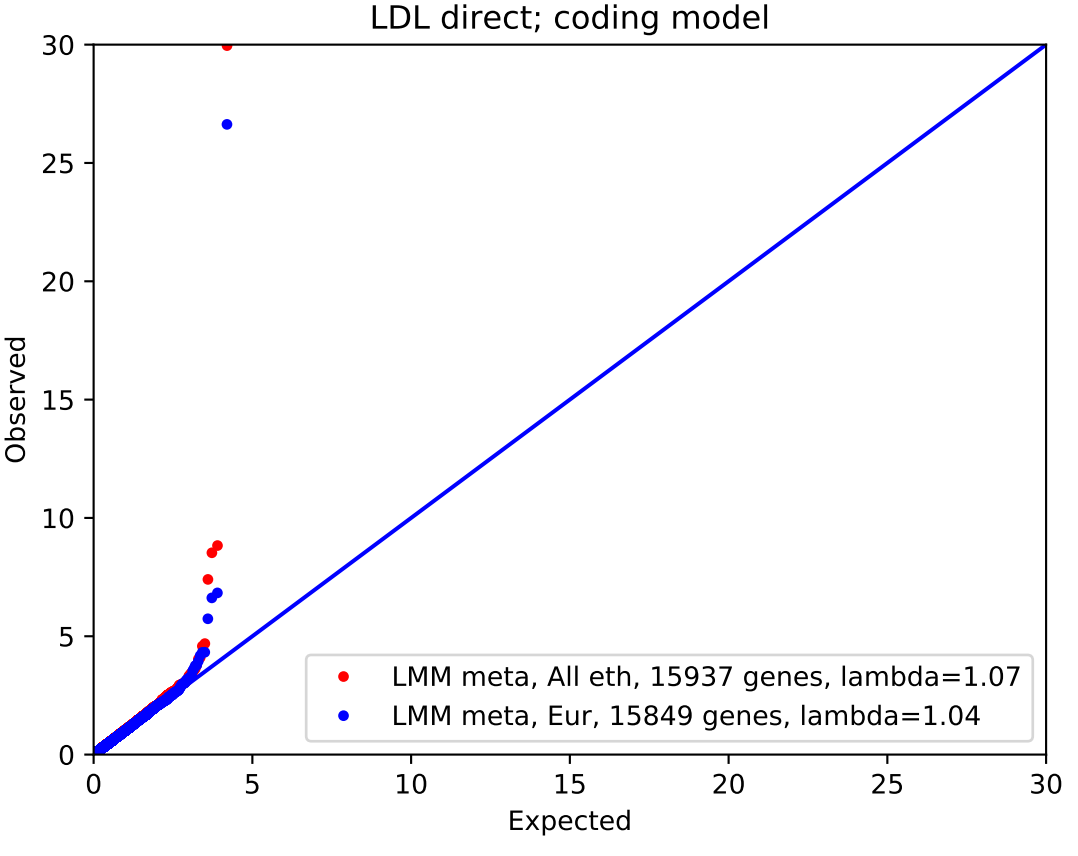

Cystatin C; lof model
Observed
Expected
0
10
20
30
40
50
All ethnic, 12283 genes, lambda=1.1
Eur ancestry, 11423 genes, lambda=1.0

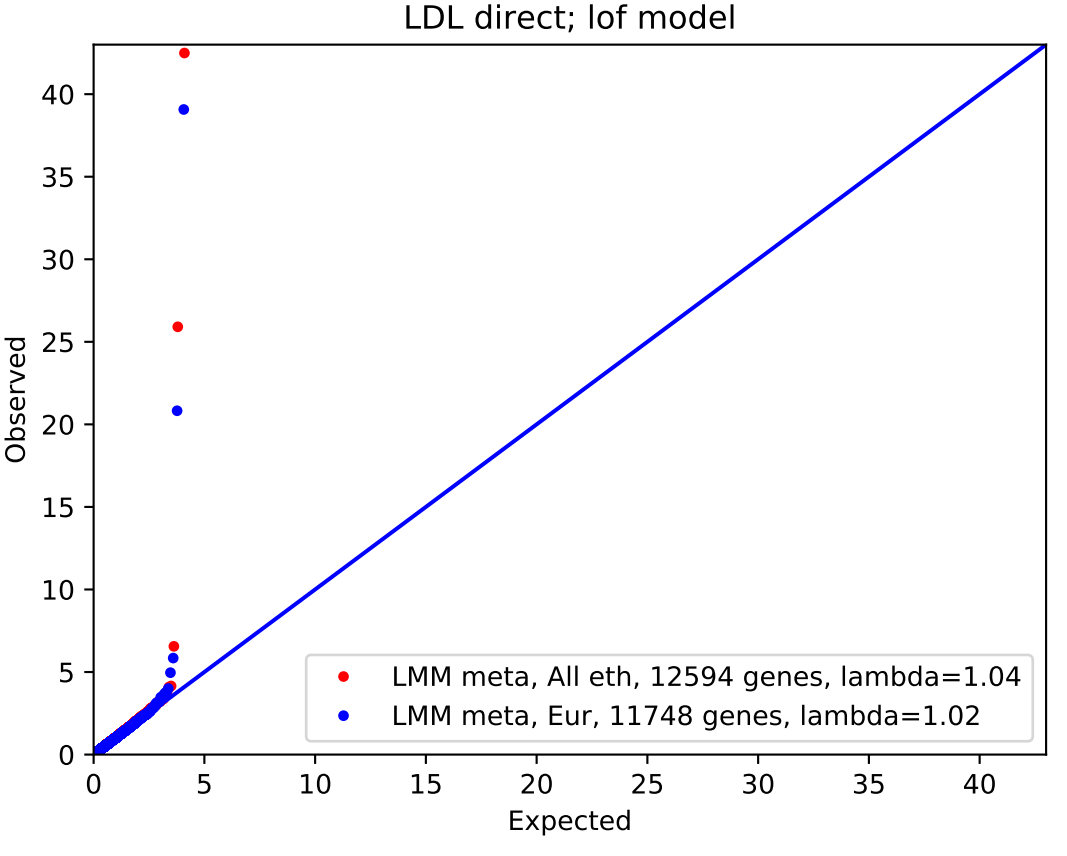

Glucose; coding model
Observed
Expected
0
2
4
6
8
10
12
LMM meta, All eth, 15944 genes, lambda=1.06
LMM meta, Eur, 15855 genes, lambda=1.04

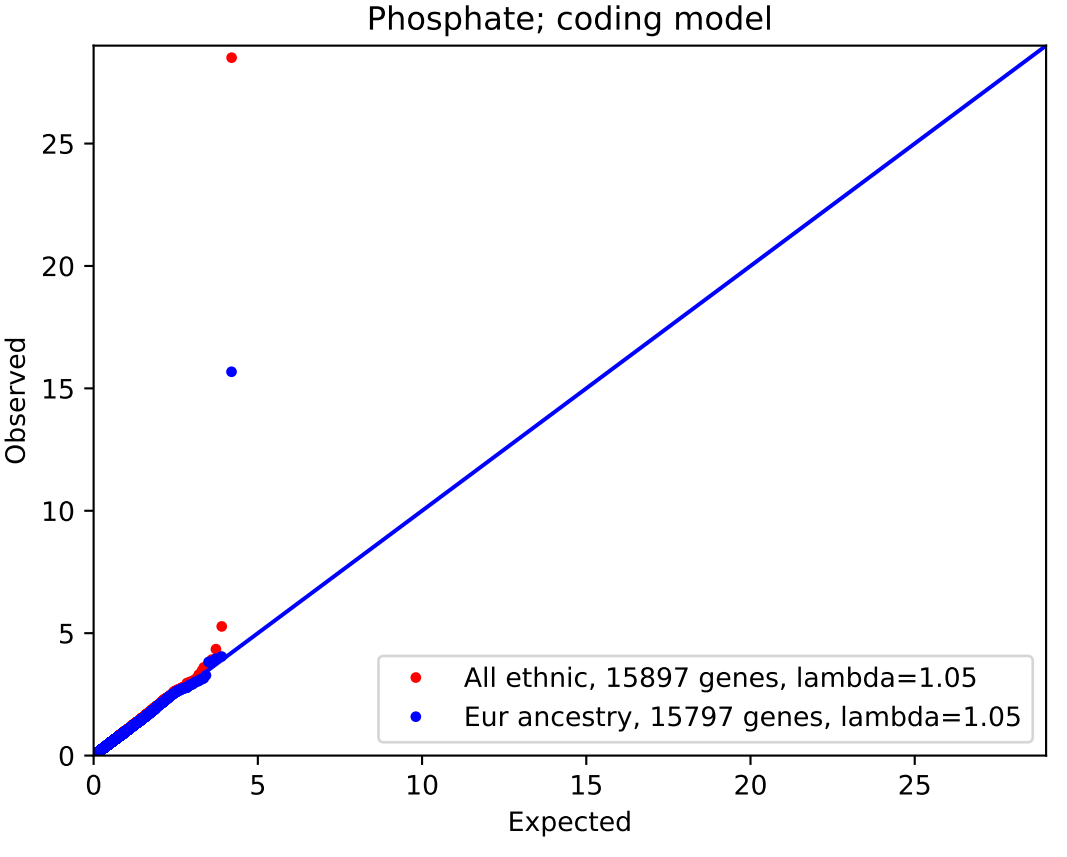

Glycated haemoglobin; coding model
Observed
Expected
0
2
4
6
8
10
12
14
LMM meta, All eth, 15902 genes, lambda=1.05
LMM meta, Eur, 15811 genes, lambda=1.02

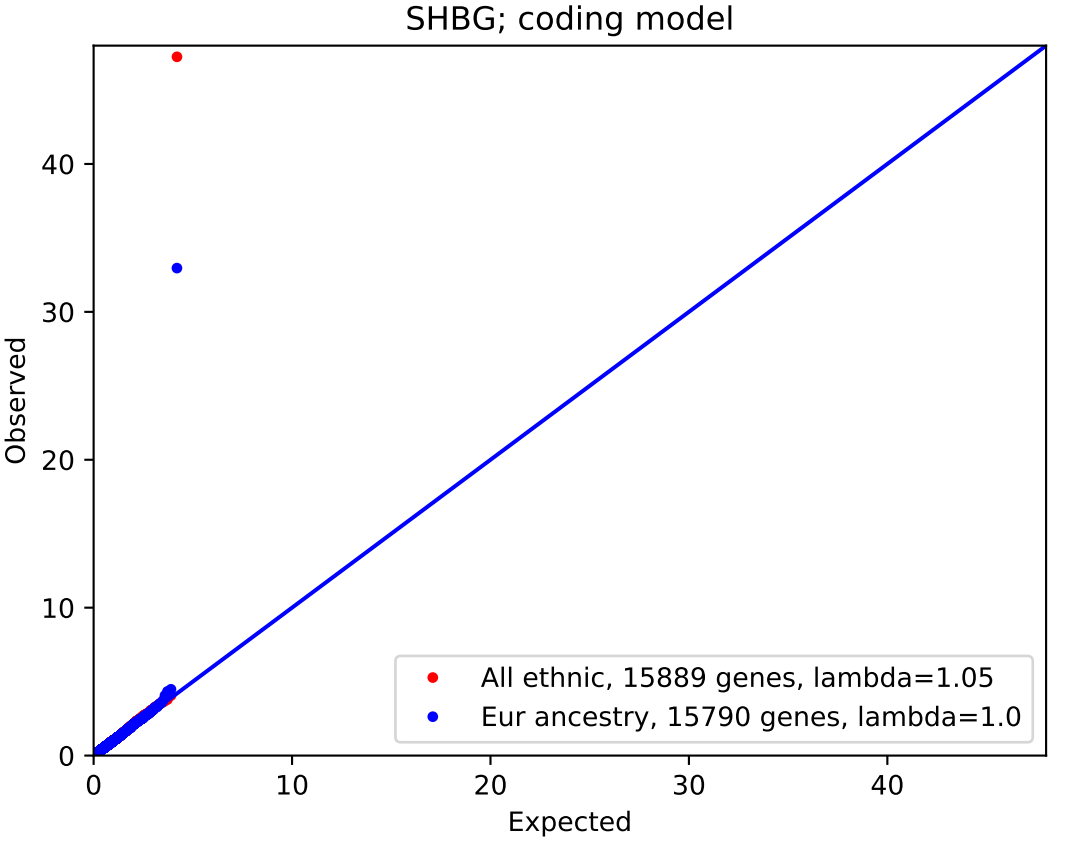

HDL cholesterol; coding model
Observed
Expected
0
10
20
30
40
LMM meta, All eth, 15929 genes, lambda=1.07
LMM meta, Eur, 15835 genes, lambda=1.02

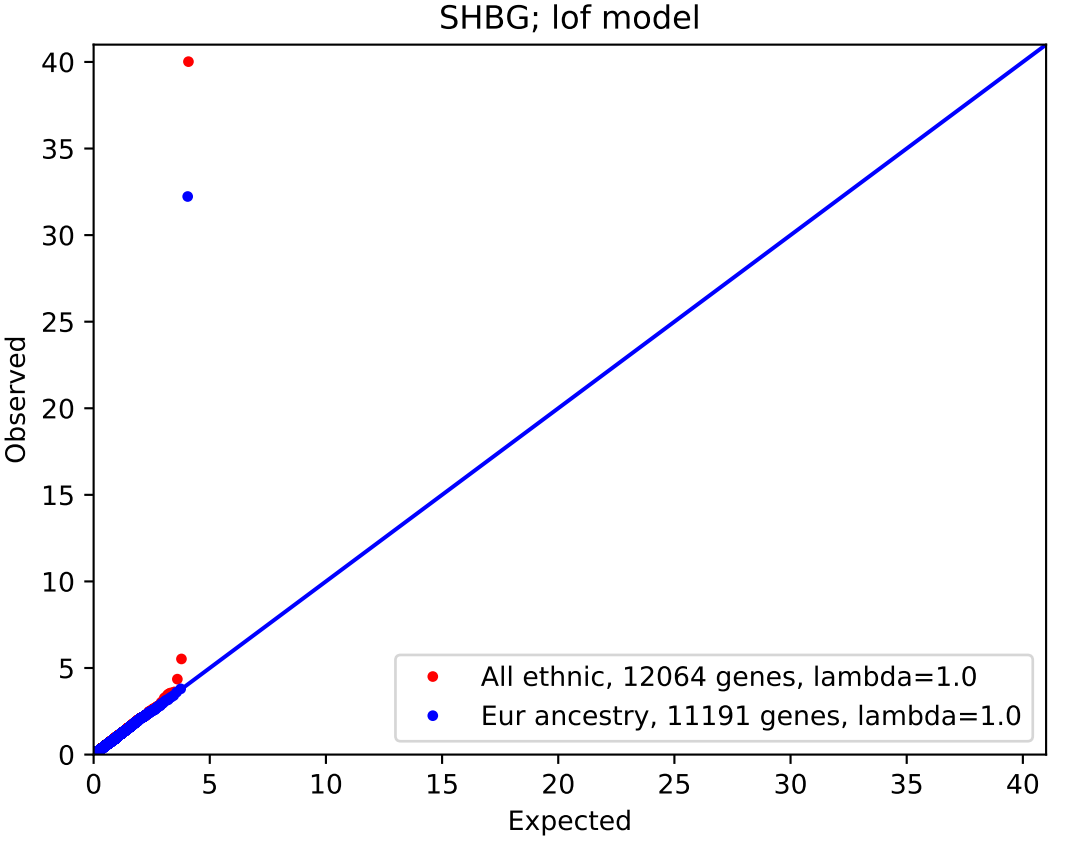

HDL cholesterol; lof model
Observed
Expected
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0
LMM meta, All eth, 12486 genes, lambda=1.05
LMM meta, Eur, 11644 genes, lambda=1.01

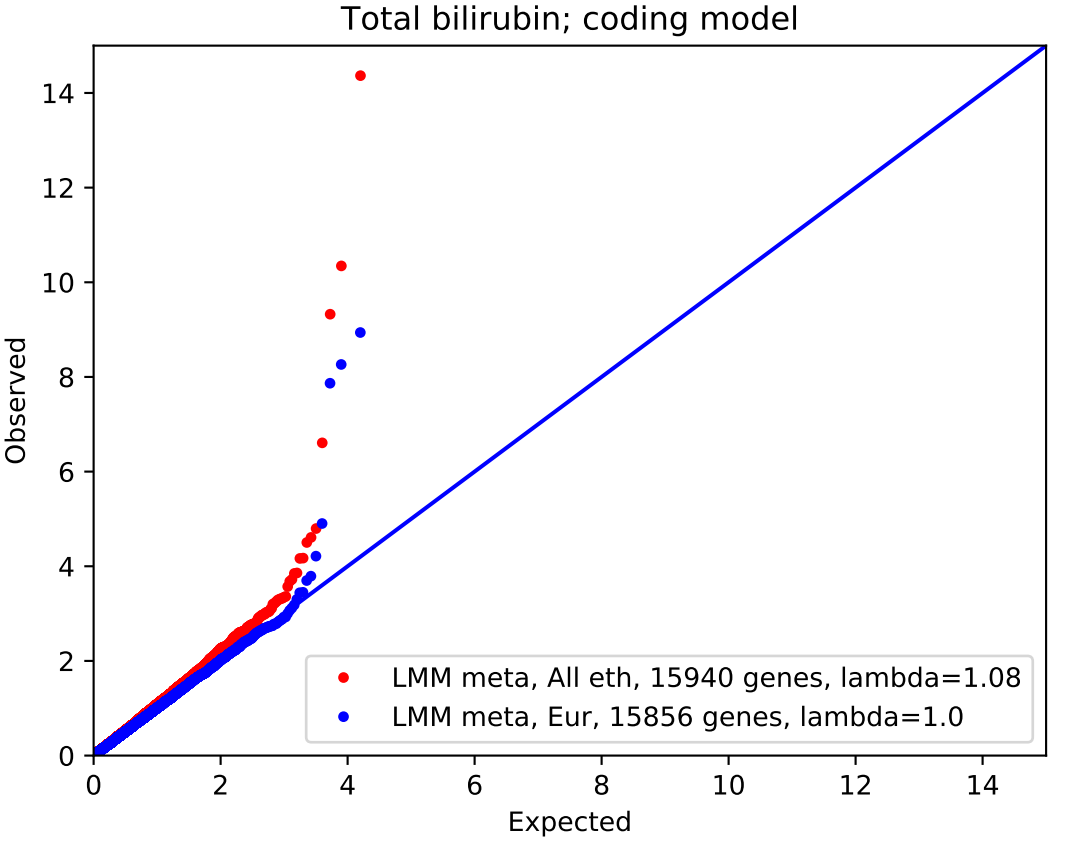

LDL direct; coding model
Observed
Expected
0
5
10
15
20
25
30
LMM meta, All eth, 15937 genes, lambda=1.07
LMM meta, Eur, 15849 genes, lambda=1.04

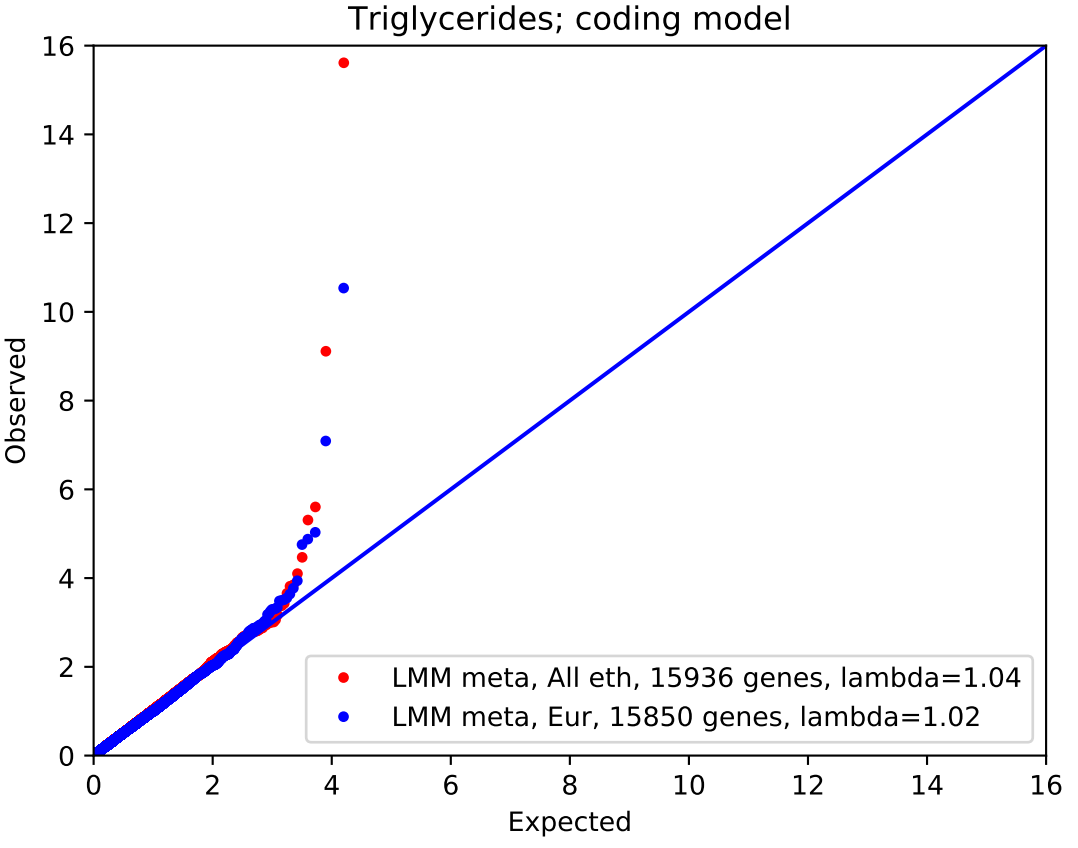

LDL direct; lof model
Observed
Expected
0
5
10
15
20
25
30
35
40
LMM meta, All eth, 12594 genes, lambda=1.04
LMM meta, Eur, 11748 genes, lambda=1.02

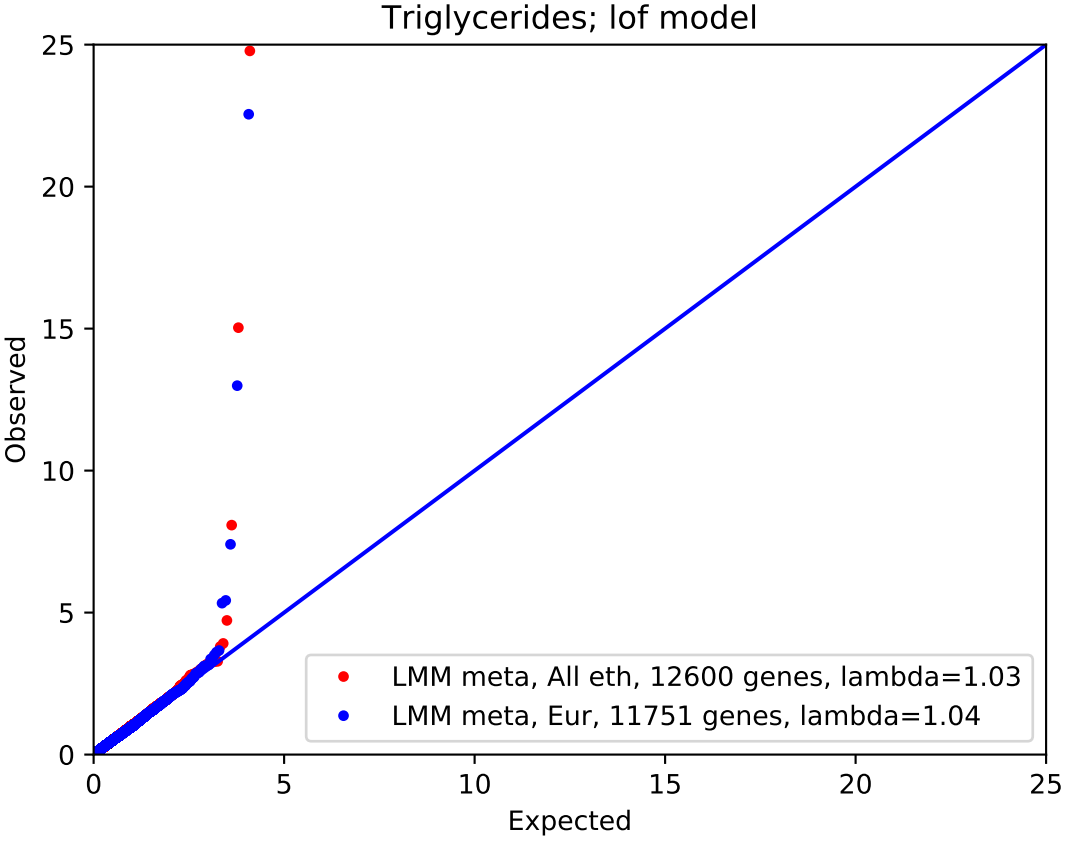

Phosphate; coding model
Observed
Expected
0
5
10
15
20
25
All ethnic, 15897 genes, lambda=1.05
Eur ancestry, 15797 genes, lambda=1.05

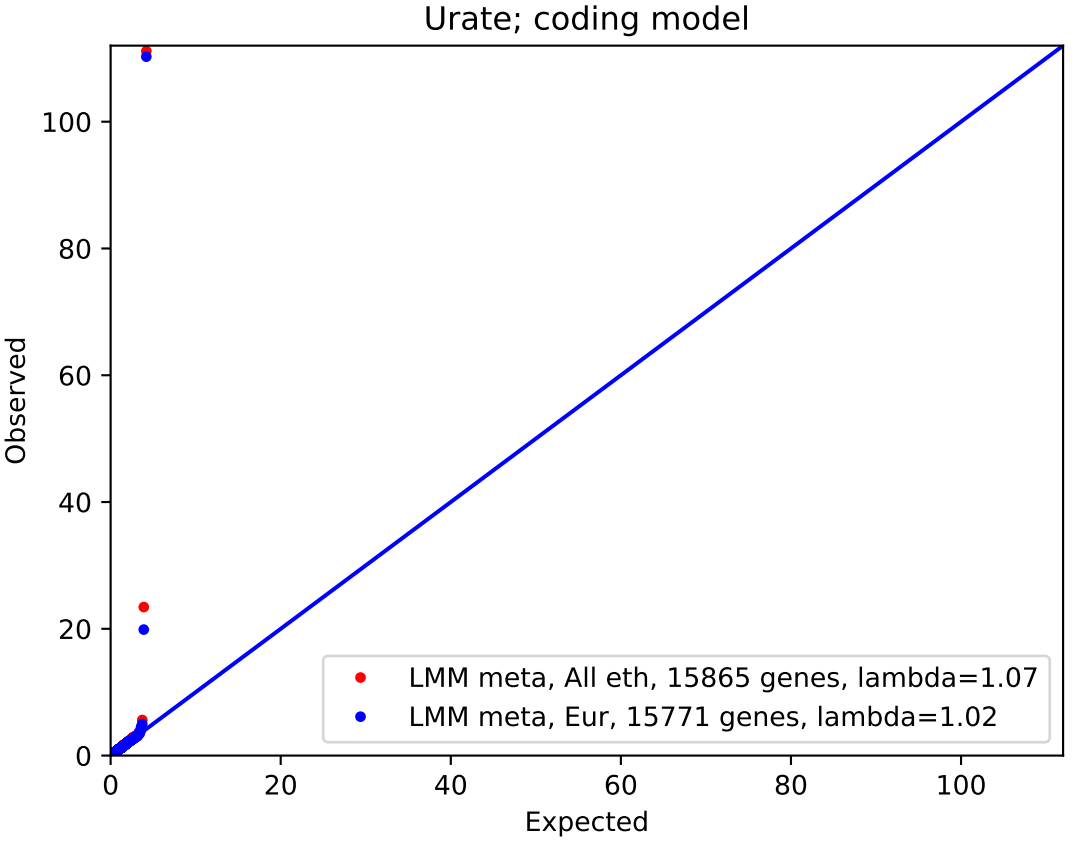

SHBG; coding model
Observed
Expected
0
10
20
30
40
All ethnic, 15889 genes, lambda=1.05
Eur ancestry, 15790 genes, lambda=1.0

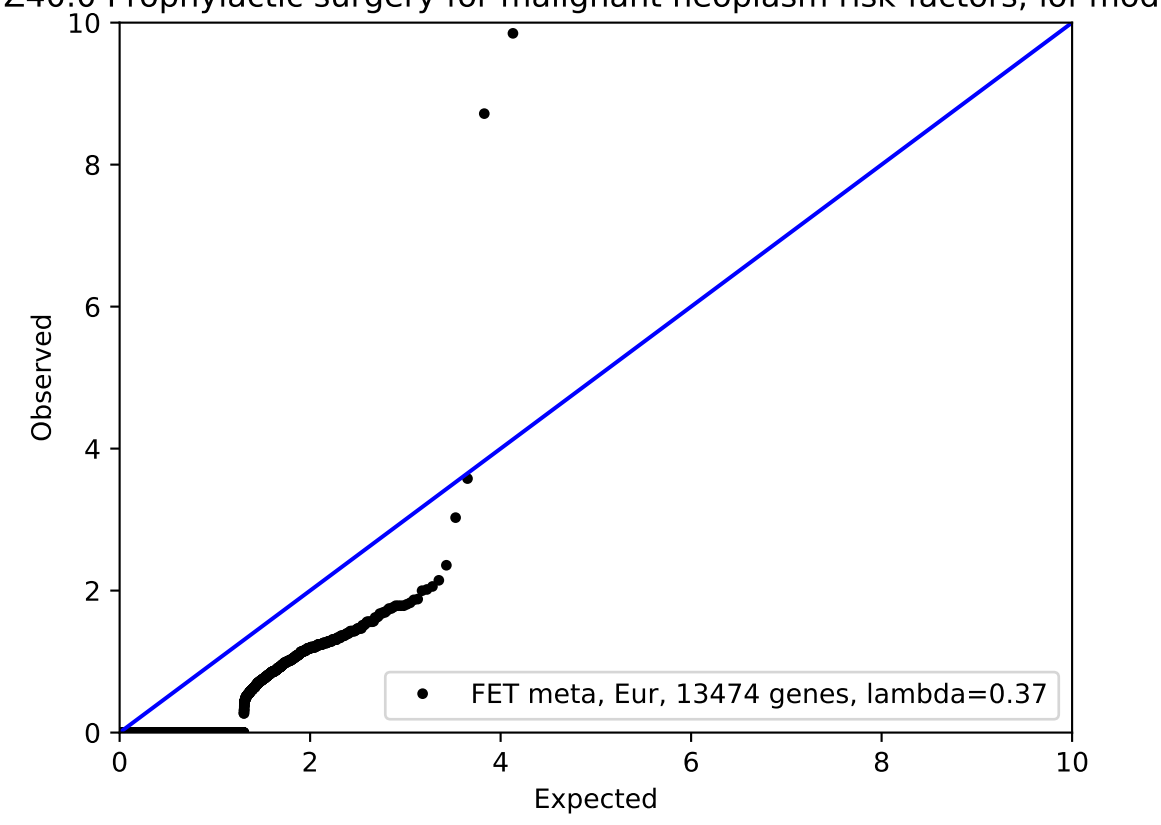

SHBG; lof model
Observed
Expected
0
5
10
15
20
25
30
35
40
All ethnic, 12064 genes, lambda=1.0
Eur ancestry, 11191 genes, lambda=1.0


Total bilirubin; coding model
Observed
Expected
0
2
4
6
8
10
12
14
LMM meta, All eth, 15940 genes, lambda=1.08
LMM meta, Eur, 15856 genes, lambda=1.0

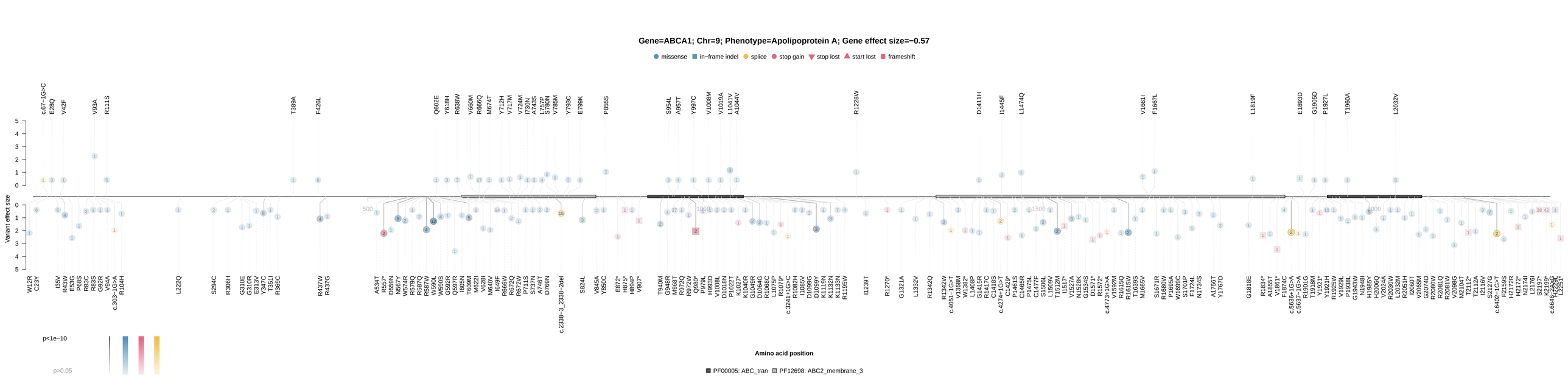

Triglycerides; coding model
Observed
Expected
0
2
4
6
8
10
12
14
16
LMM meta, All eth, 15936 genes, lambda=1.04
LMM meta, Eur, 15850 genes, lambda=1.02


Triglycerides; lof model
Observed
Expected
0
5
10
15
20
25
LMM meta, All eth, 12600 genes, lambda=1.03
LMM meta, Eur, 11751 genes, lambda=1.04


Urate; coding model
Observed
Expected
0
20
40
60
80
100
LMM meta, All eth, 15865 genes, lambda=1.07
LMM meta, Eur, 15771 genes, lambda=1.02


Z40.0 Prophylactic surgery for malignant neoplasm risk-factors; lof model
Observed
Expected
0
2
4
6
8
10
FET meta, Eur, 13474 genes, lambda=0.37

Supplementary Figure 2. Overlaid QQ plots for each each phenotype that produced a statistically significant association. Shown is the number of genes analyzed and resulting lambda (genomic inflation factor) for each analysis.


Gene=ABCA1; Chr=9; Phenotype=Apolipoprotein A; Gene effect size=−0.57
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
Variant effect size
Amino acid position
p<1e−10
p>0.05
PF00005: ABC_tran
PF12698: ABC2_membrane_3

Gene=ABCA1; Chr=9; Phenotype=Apolipoprotein A; Gene effect size=−0.82

splice stop gain stop lost start lost frameshift

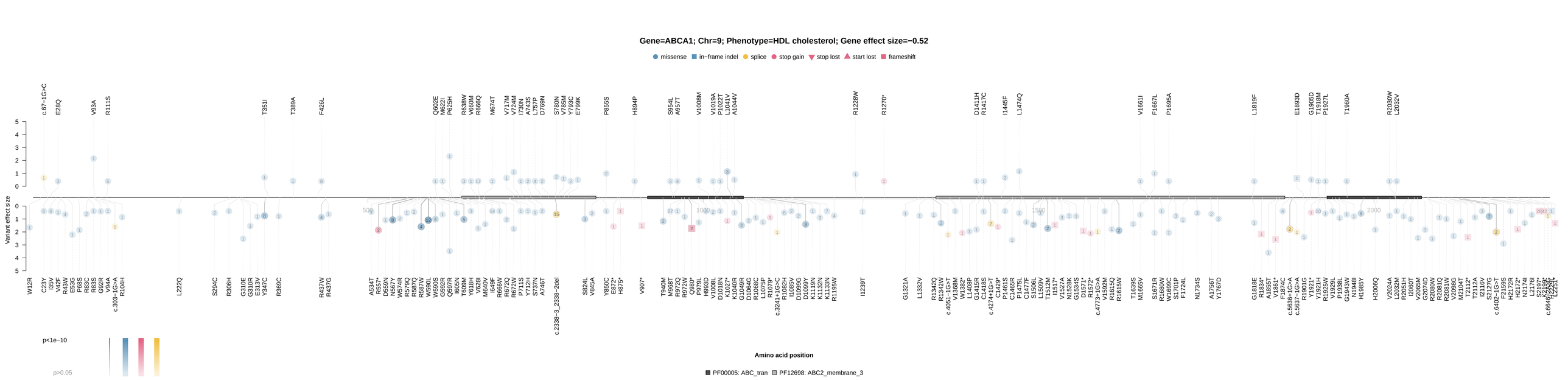
Variant effect size

Amino acid position

PF00005: ABC_tran PF12698: ABC2_membrane_3

p<1e−10

p>0.05


Gene=ABCA1; Chr=9; Phenotype=HDL cholesterol; Gene effect size=−0.52
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
Variant effect size
Amino acid position
PF00005: ABC_tran
PF12698: ABC2_membrane_3
p<1e−10
p>0.05

Gene=ABCA1; Chr=9; Phenotype=HDL cholesterol; Gene effect size=−0.71

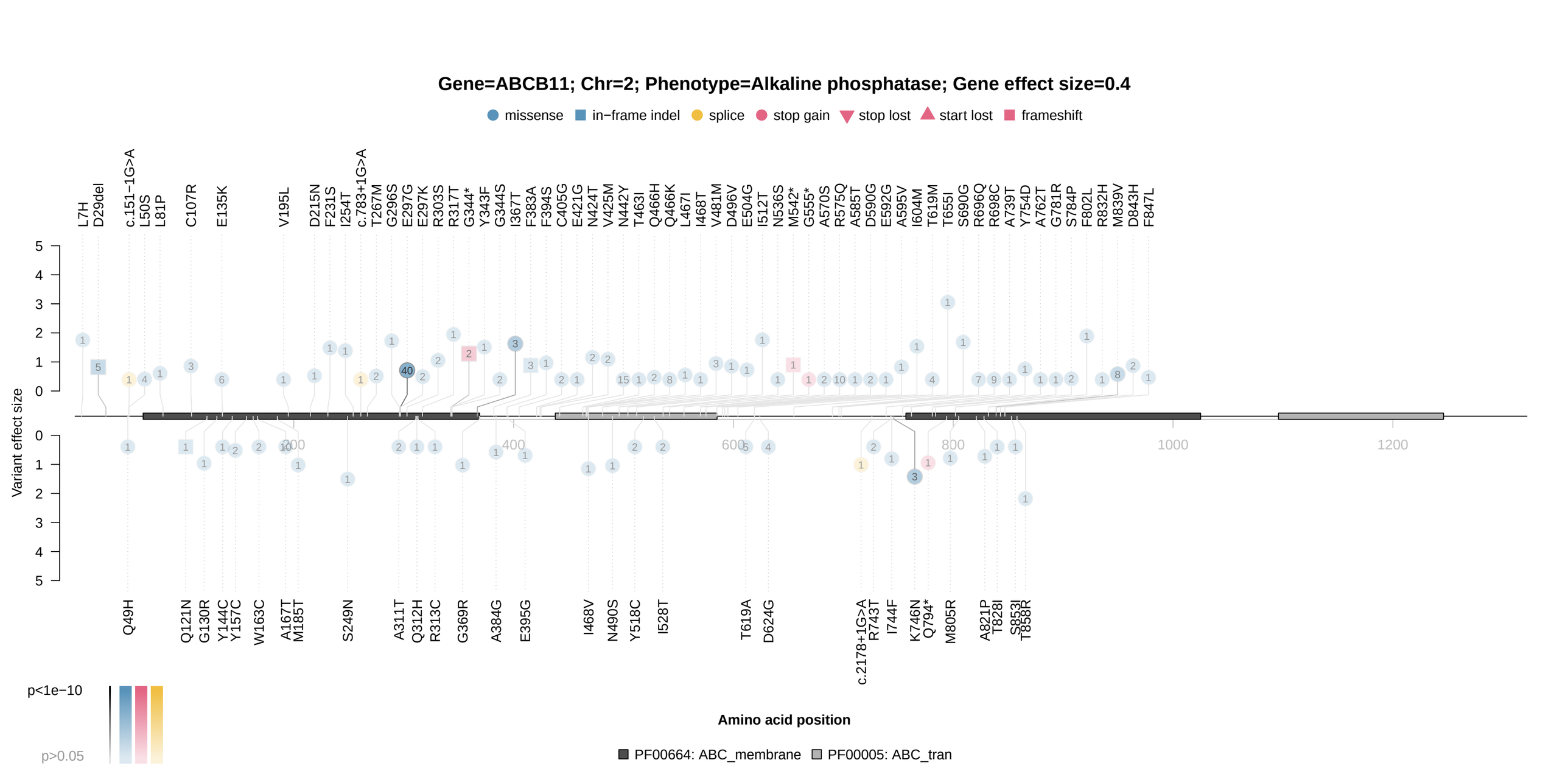
splice · stop gain · stop lost · start lost · frameshift

Variant effect size

Amino acid position

PF00005: ABC_tran · PF12698: ABC2_membrane_3

p<1e−10 … p>0.05


Gene=ABCB11; Chr=2; Phenotype=Alkaline phosphatase; Gene effect size=0.4
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
Variant effect size
Amino acid position
p<1e−10
p>0.05
PF00664: ABC_membrane
PF00005: ABC_tran

Gene=ALPL; Chr=1; Phenotype=Alkaline phosphatase; Gene effect size=−2.08

missense · in−frame indel · splice · stop gain · stop lost · start lost · frameshift

L43F · A179T · P280T · V304M

Variant effect size

Amino acid position

PF00245: Alk_phosphatase

p<1e−10 … p>0.05

Gene=ALPL; Chr=1; Phenotype=Phosphate; Gene effect size=0.72

missense · in−frame indel · splice · stop gain · stop lost · start lost · frameshift

R30* A33V A40D A40V L43F Q44* G59E R71P I72T Q76R T100M A116T Y117C N124S V128M A132T T134P T134N G162S H171R T173I A176T A179T D189N c.648+1G>A G221* G220R R223Q R223L G249A V253L P261L R272* R272C R272P P280T D294Y D294A Y297* R321W F328del F327C c.997+2T>A L349A I359M S368del R391C G392A c.1189+2T>C G397V N417S A443V E452K V459L V461A A468V G473S V474I Y479C H482N A492* G491R

Variant effect size

T36P Y39C Y101* C119R R138W T141I D156Y V217A I218M M219I Y225H H267F E298K V304M E311K E476K

p<1e−10

p>0.05

Amino acid position

PF00245: Alk_phosphatase

Gene=ANGPTL3; Chr=1; Phenotype=Apolipoprotein A; Gene effect size=−0.52

missense | in−frame indel | splice | stop gain | stop lost | start lost | frameshift

Variant effect size

Amino acid position

p<1e−10 … p>0.05

PF00147: Fibrinogen_C

Gene=ANGPTL3; Chr=1; Phenotype=Cholesterol; Gene effect size=−0.5

missense | in−frame indel | splice | stop gain | stop lost | start lost | frameshift

Variant effect size

Amino acid position

PF00147: Fibrinogen_C

p<1e−10

p>0.05

Gene=ANGPTL3; Chr=1; Phenotype=Cholesterol; Gene effect size=−0.66

splice stop gain stop lost start lost frameshift

Variant effect size

Amino acid position

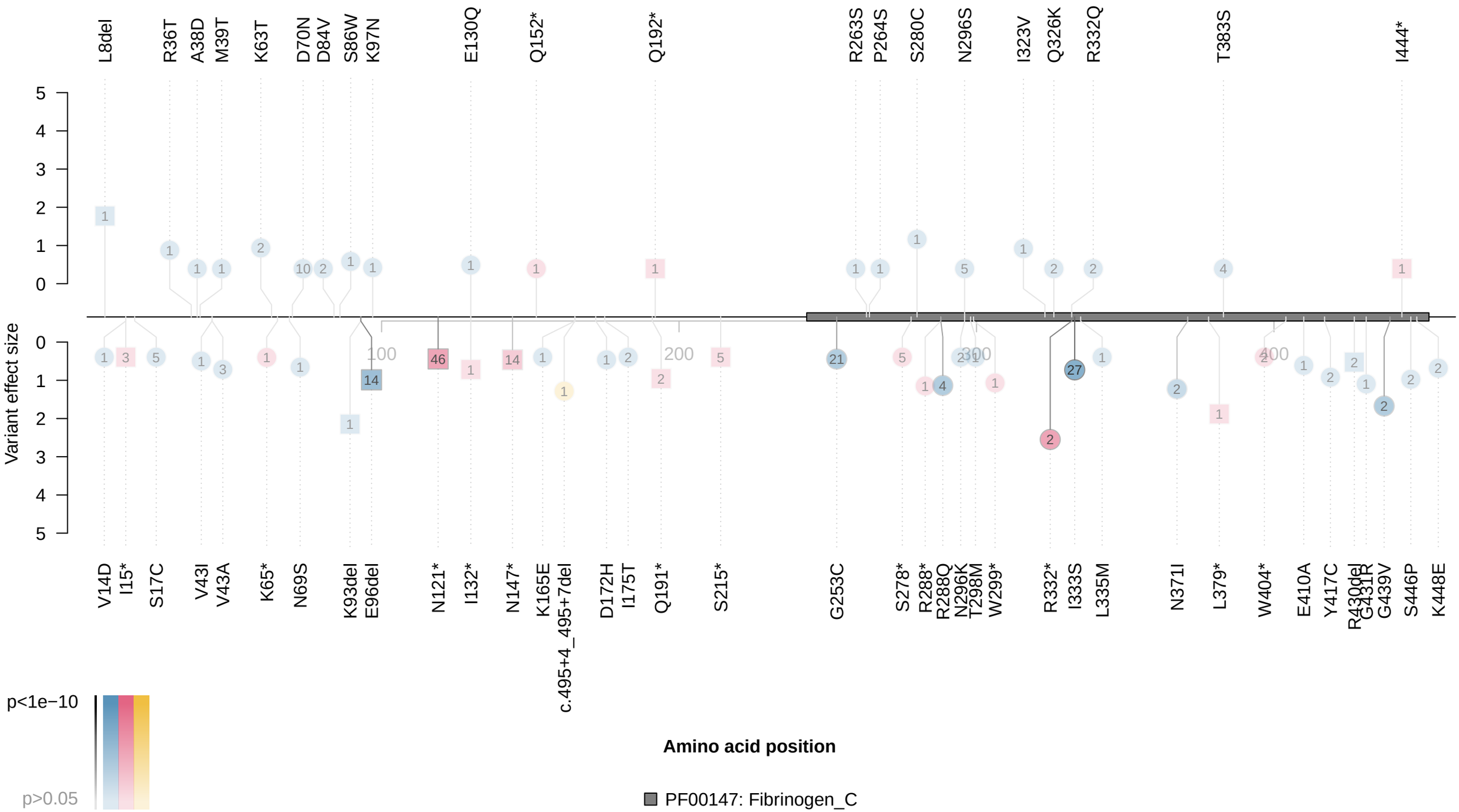
PF00147: Fibrinogen_C

p<1e−10

p>0.05

Gene=ANGPTL3; Chr=1; Phenotype=Triglycerides; Gene effect size=−0.49

missense | in−frame indel | splice | stop gain | stop lost | start lost | frameshift



Gene=APOA5; Chr=1; Phenotype=Triglycerides; Gene effect size=1

splice stop gain stop lost start lost frameshift

Q95* Q97* R143* H182* Q252* Q275* Q295* D332* S361*

Variant effect size

5 4 3 2 1 0 0 1 2 3 4 5

2 28 2 1 1 11 1 1 1 3

50 100 150 200 250 300 350

c.−32−2A>G

p<1e−10

p>0.05

Amino acid position

PF01442: Apolipoprotein

Gene=APOB; Chr=2; Phenotype=Apolipoprotein B; Gene effect size=−1.07

splice · stop gain · stop lost · start lost · frameshift

Variant effect size

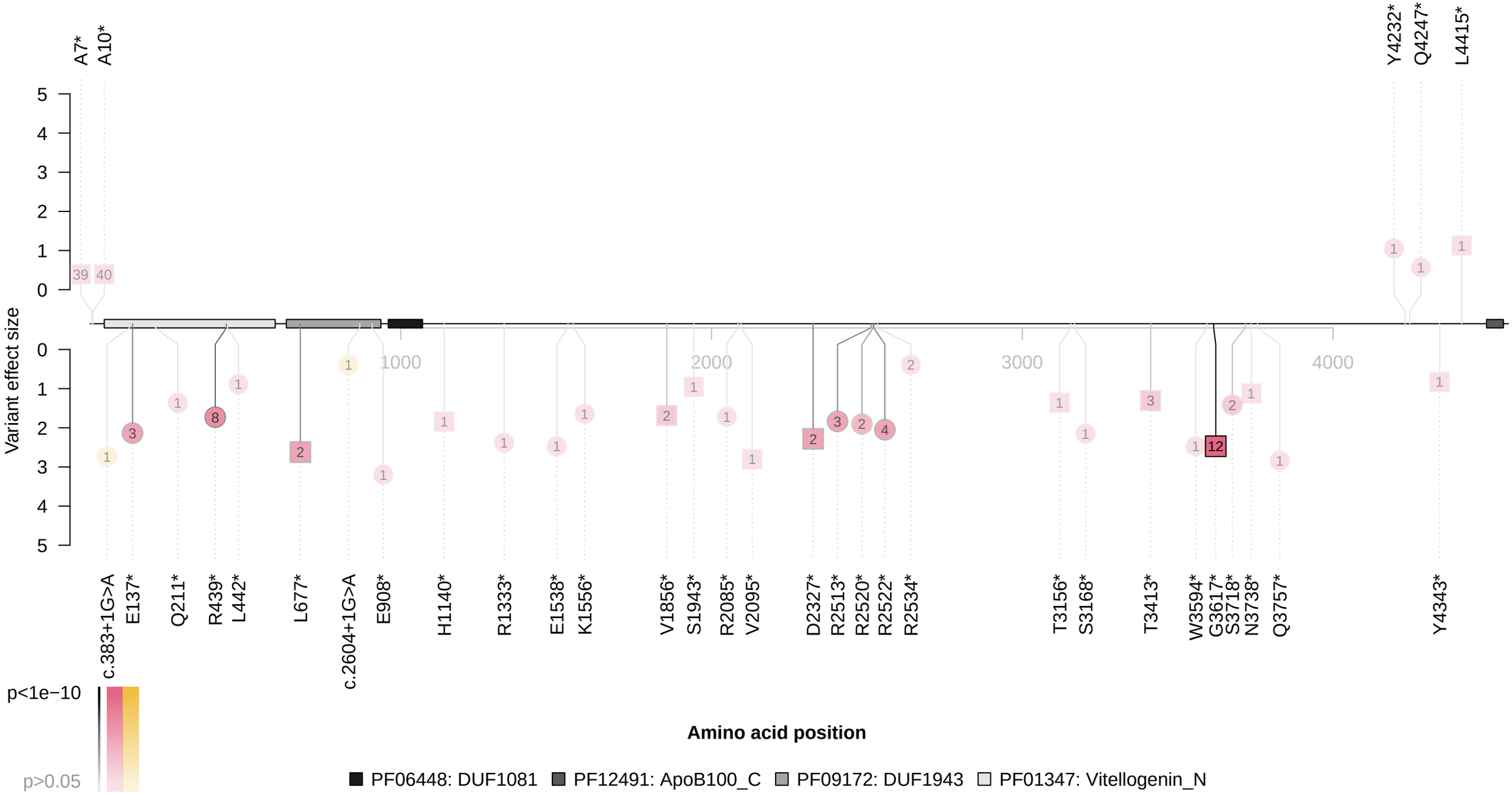
Amino acid position

p<1e−10 … p>0.05

PF06448: DUF1081 · PF12491: ApoB100_C · PF09172: DUF1943 · PF01347: Vitellogenin_N

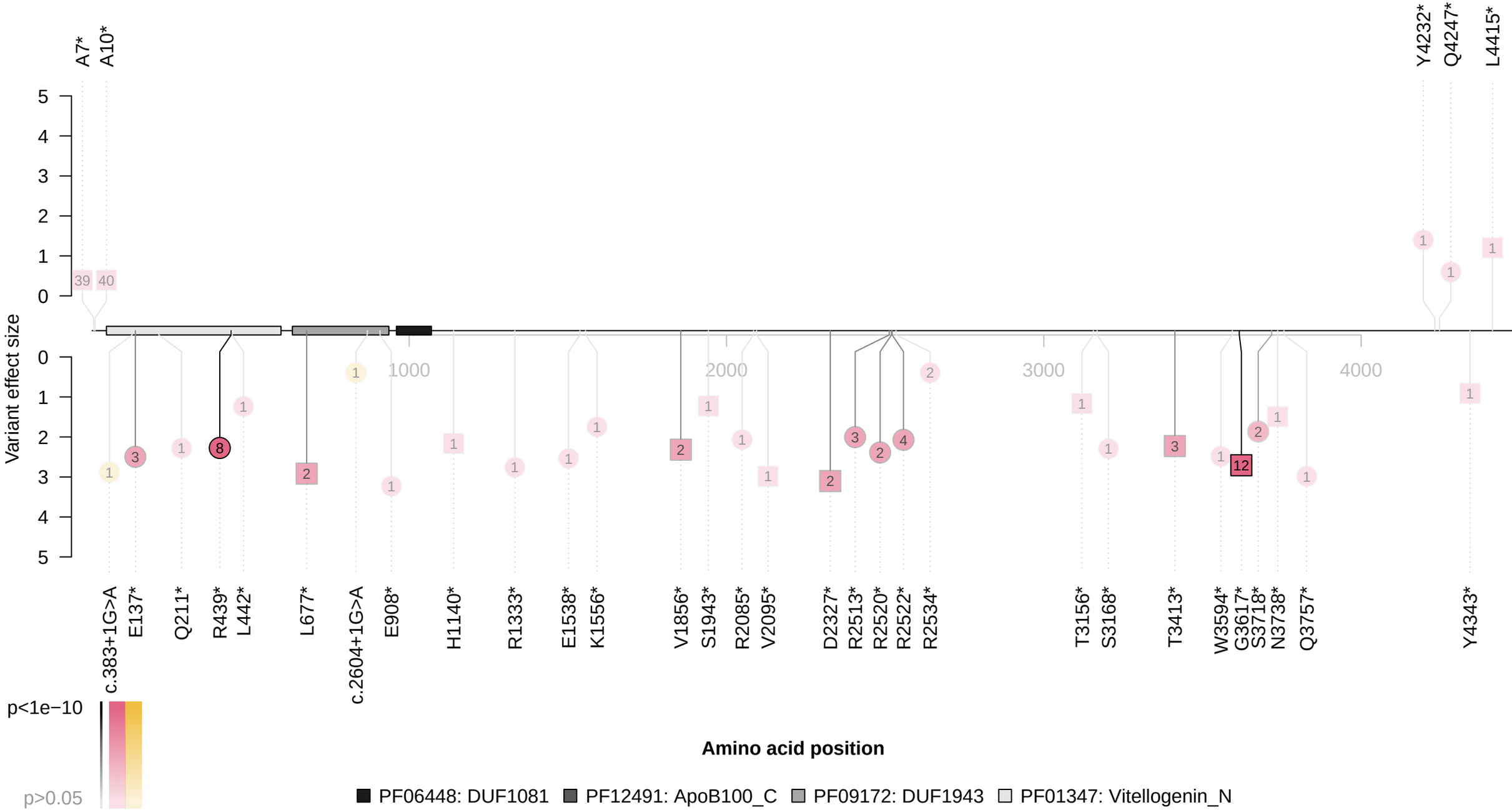
Gene=APOB; Chr=2; Phenotype=Cholesterol; Gene effect size=−1.06

splice · stop gain · stop lost · start lost · frameshift



Gene=APOB; Chr=2; Phenotype=LDL direct; Gene effect size=−1.22

splice stop gain stop lost start lost frameshift



Gene=APOB; Chr=2; Phenotype=Triglycerides; Gene effect size=−0.81

splice · stop gain · stop lost · start lost · frameshift

Variant effect size

Amino acid position

p<1e−10 … p>0.05

PF06448: DUF1081 · PF12491: ApoB100_C · PF09172: DUF1943 · PF01347: Vitellogenin_N

Gene=ASGR1; Chr=1; Phenotype=Alkaline phosphatase; Gene effect size=0.64

missense | in−frame indel | splice | stop gain | stop lost | start lost | frameshift

E14K L21* c.187+2T>C T81P G95* K101N c.356−2A>G E118* H126Q L134M S138R C139G C153G P155L V159* S164C R183G Q198H D216N G226R T227R K234T D242G W244* W244* G246S H247G E253K D261E R263C W264S C269R W275C W275R E278D

Variant effect size

0 1 2 3 4 5

50 100 150 200 250

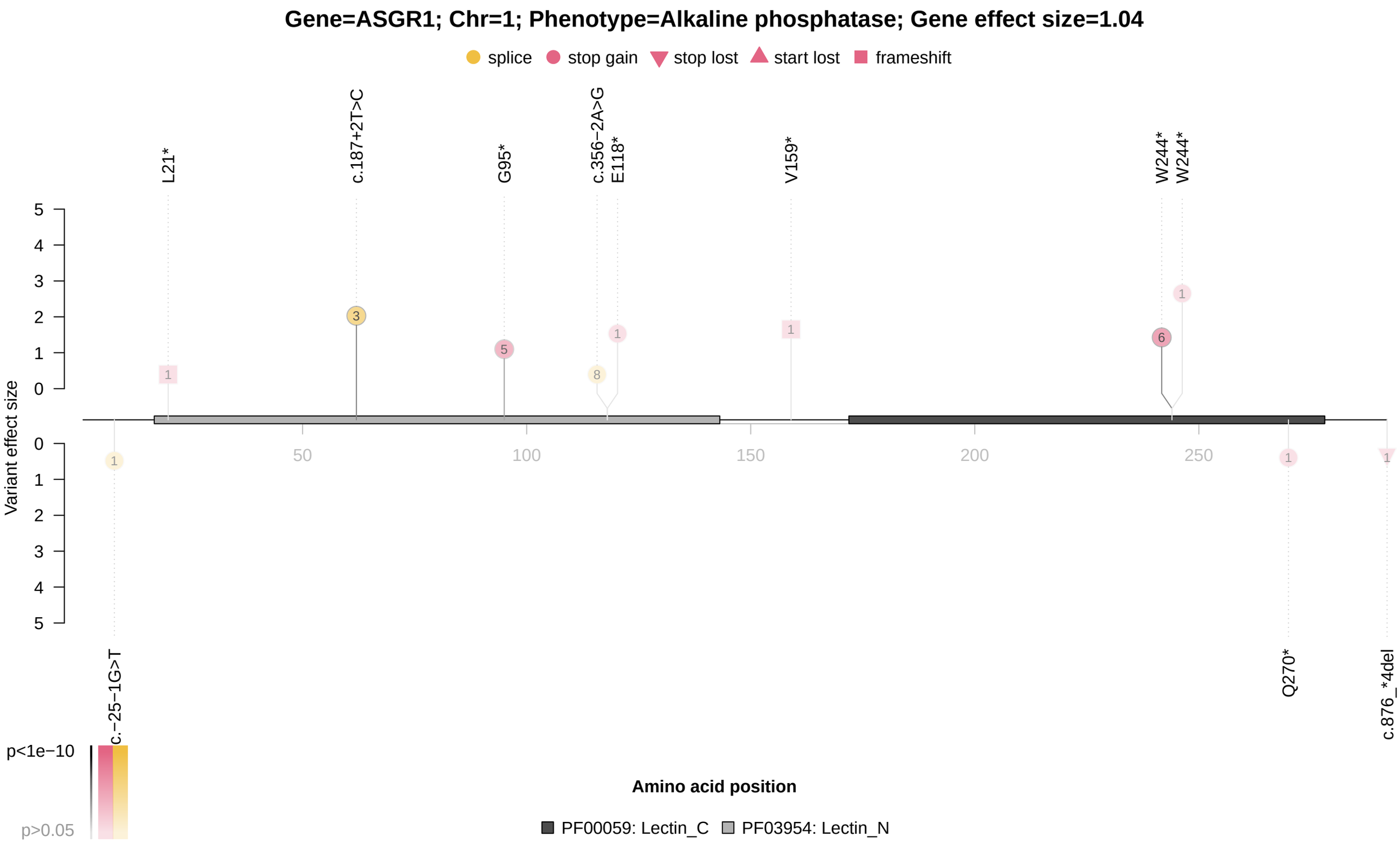
c.−25−1G>T Q9E L50H V54M C57S T84M H126Q V127L V156F H161N V191A D254N Q270* R274L L281M c.876_*4del

p<1e−10

p>0.05

Amino acid position

PF00059: Lectin_C PF03954: Lectin_N


Gene=ASGR1; Chr=1; Phenotype=Alkaline phosphatase; Gene effect size=1.04
splice
stop gain
stop lost
start lost
frameshift
L21*
c.187+2T>C
G95*
c.356−2A>G
E118*
V159*
W244*
W244*
Variant effect size
0
1
2
3
4
5
50
100
150
200
250
c.−25−1G>T
Q270*
c.876_*4del
p<1e−10
p>0.05
Amino acid position
PF00059: Lectin_C
PF03954: Lectin_N

Gene=CETP; Chr=1; Phenotype=HDL cholesterol; Gene effect size=0.46

missense | in−frame indel | splice | stop gain | stop lost | start lost | frameshift

T5* V29M R31H c.118+4_118+7del c.119−2A>G D59H E63K L84F S89G Q104* K115M D131N E133K c.439+1G>A C148Y E176K I180F Q182* Q199L c.598−1G>C L223* L223R Y244* L264* S275P R276C F280I F280S R285* L290P R299C F318* G354E P368* S375* K395E L397H c.1215−1_1224del Q405H T410* V411* S421F V433G I435T c.1321+1G>A c.1321+1G>T E443K R468* H483D *494*

Variant effect size

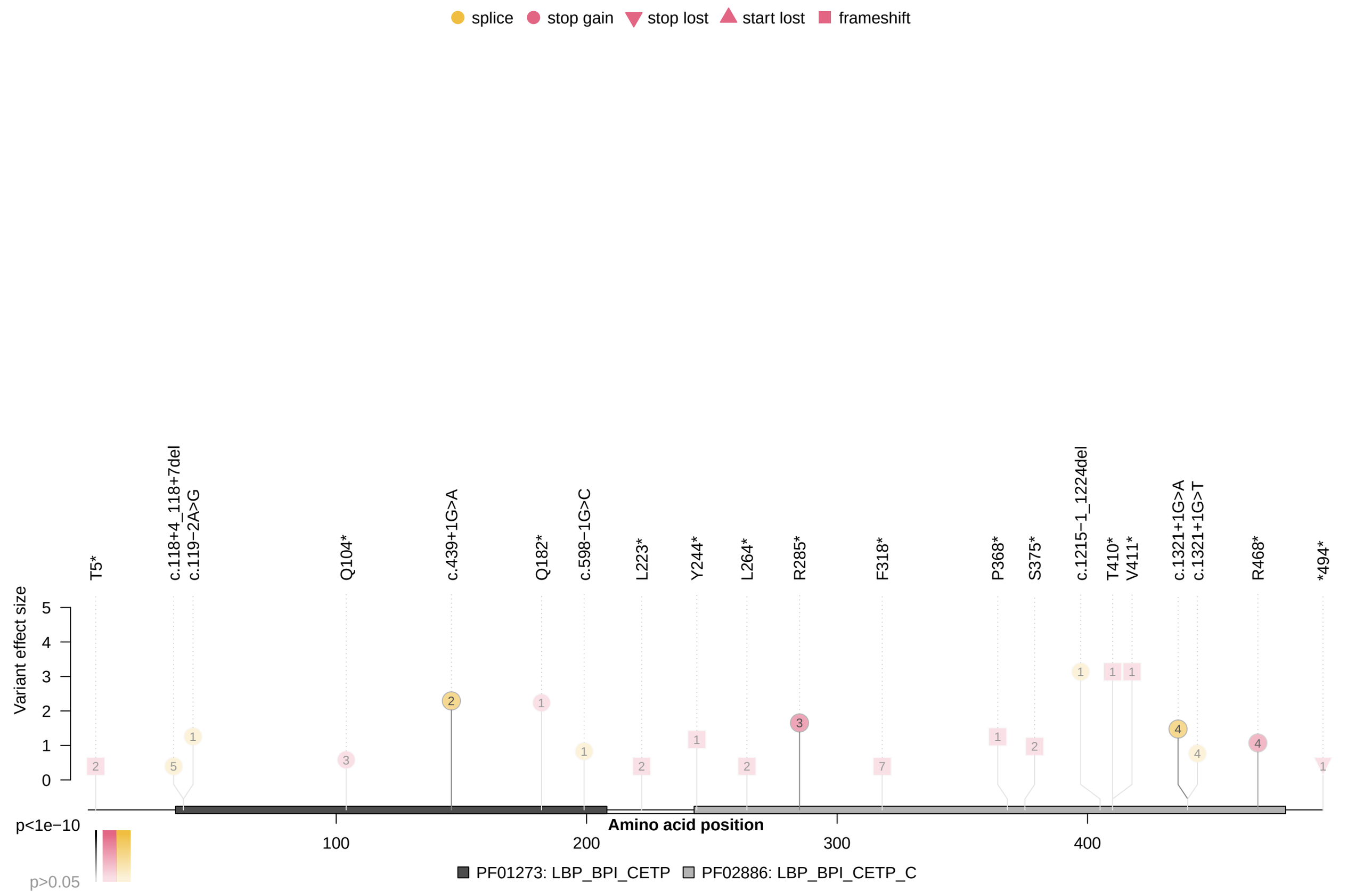
T61M A65P V108M T113S V153L D156V L171F L183R A212D I228T V230A T235S G251D G251V Q389E S456R

Amino acid position

p<1e−10 … p>0.05

PF01273: LBP_BPI_CETP | PF02886: LBP_BPI_CETP_C

Gene=CETP; Chr=1; Phenotype=HDL cholesterol; Gene effect size=1.01



Gene=COL4A4; Chr=2; Phenotype=R31 Unspecified haematuria; Gene effect size=0.17

splice stop gain stop lost start lost frameshift

c.1099+1G>A Y378* G388* S969* R1377* A1573* *1691*

Variant effect size

1 0.8 0.6 0.4 0.2 0

0 0.2 0.4 0.6 0.8 1

1 1 1 1 1 1 1 1 1 64 1 1 1 3 1 1 1 1 1 1 1 1

500 1000 1500

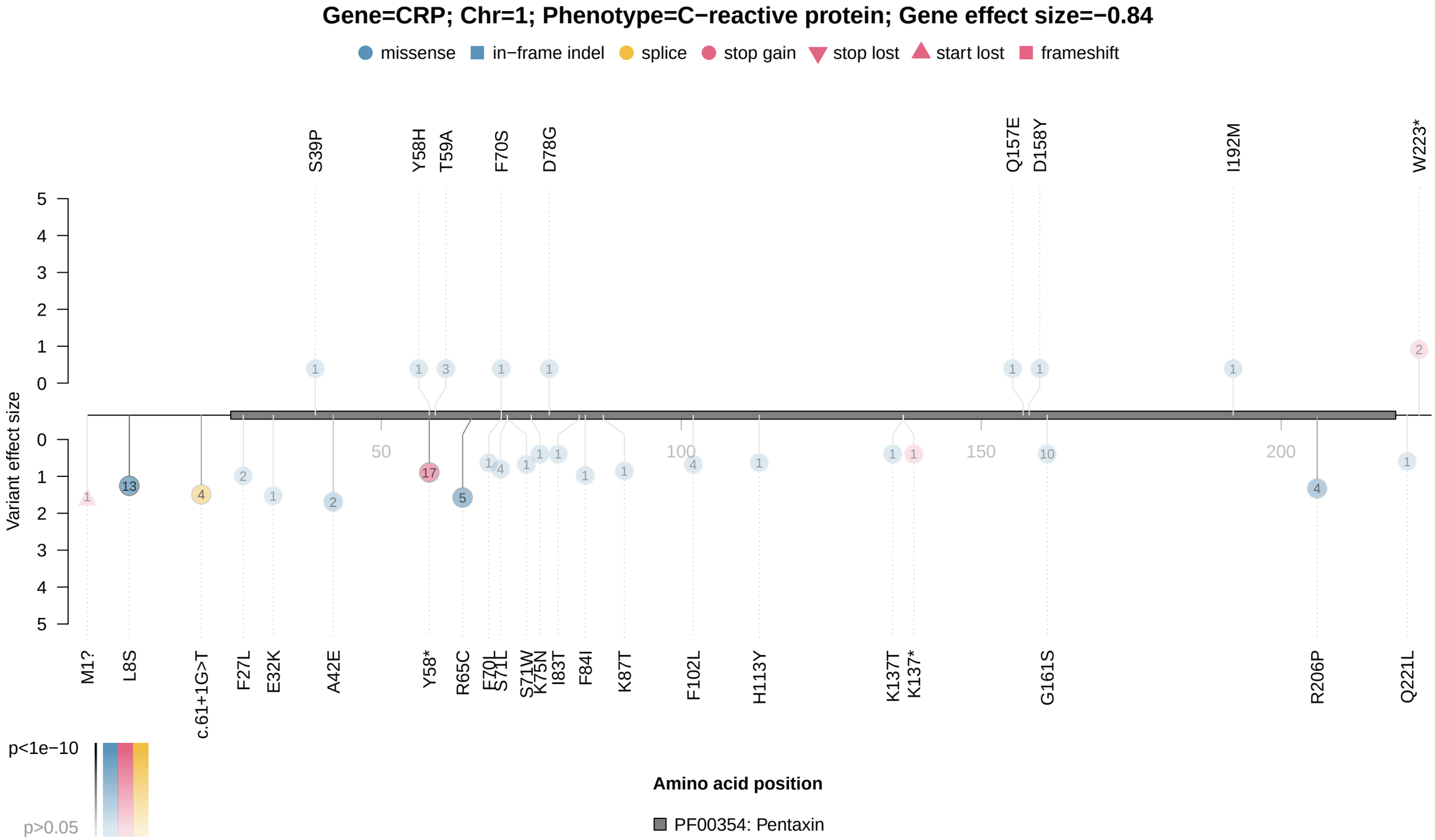
W24* Y43* c.192+1G>T c.327+1G>A G223* c.871−1G>C G509* A880* G915* P1059* G1227* G1273* G1310* Y1311* G1389* L1470* D1668*

p<1e−10

p>0.05

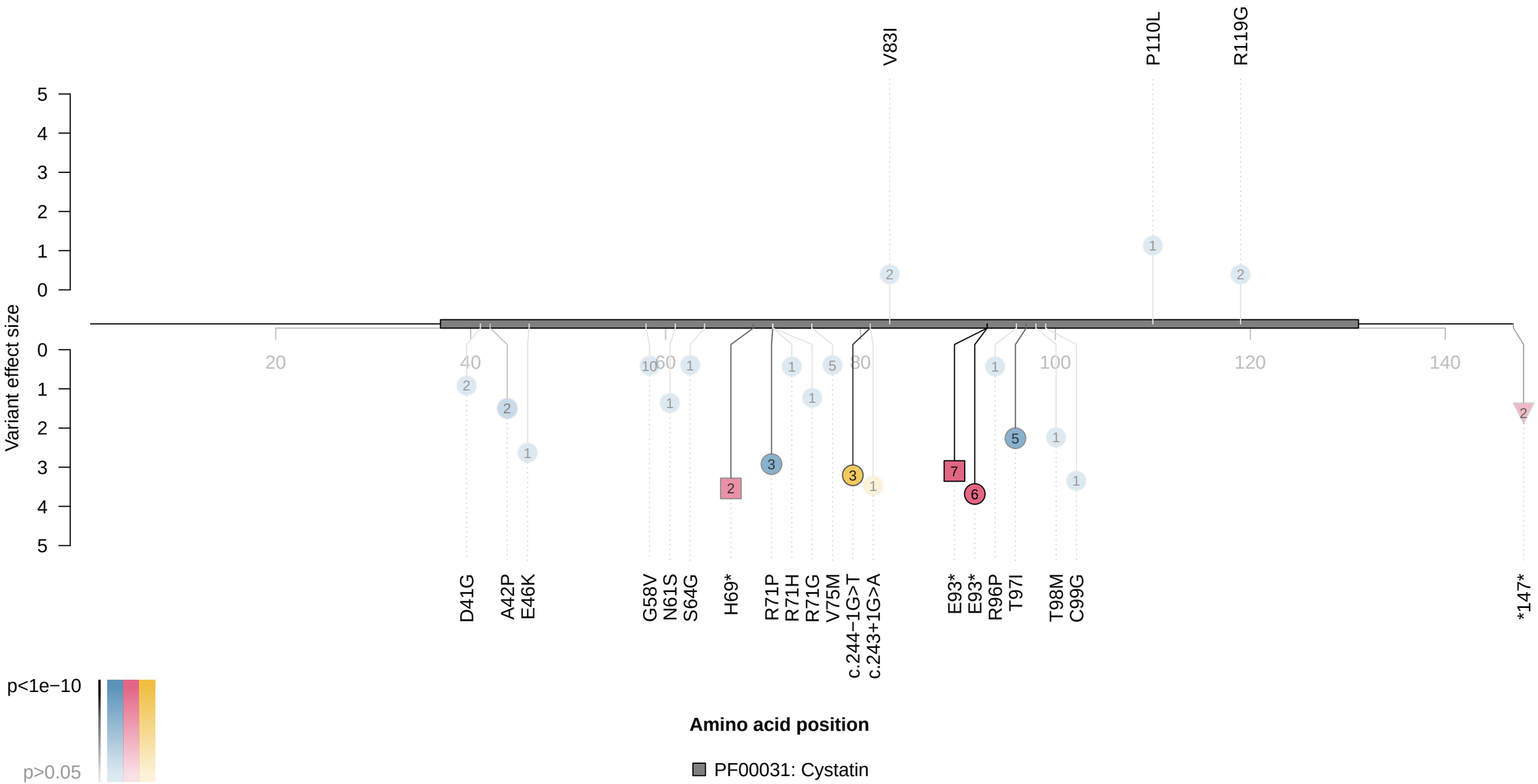
Amino acid position

PF01413: C4 PF01391: Collagen


Gene=CRP; Chr=1; Phenotype=C−reactive protein; Gene effect size=−0.84
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
Variant effect size
S39P
Y58H
T59A
F70S
D78G
Q157E
D158Y
I192M
W223*
M1?
L8S
c.61+1G>T
F27L
E32K
A42E
Y58*
R65C
E70L
S71L
S71W
K75N
I83T
F84I
K87T
F102L
H113Y
K137T
K137*
G161S
R206P
Q221L
p<1e−10
p>0.05
Amino acid position
PF00354: Pentaxin

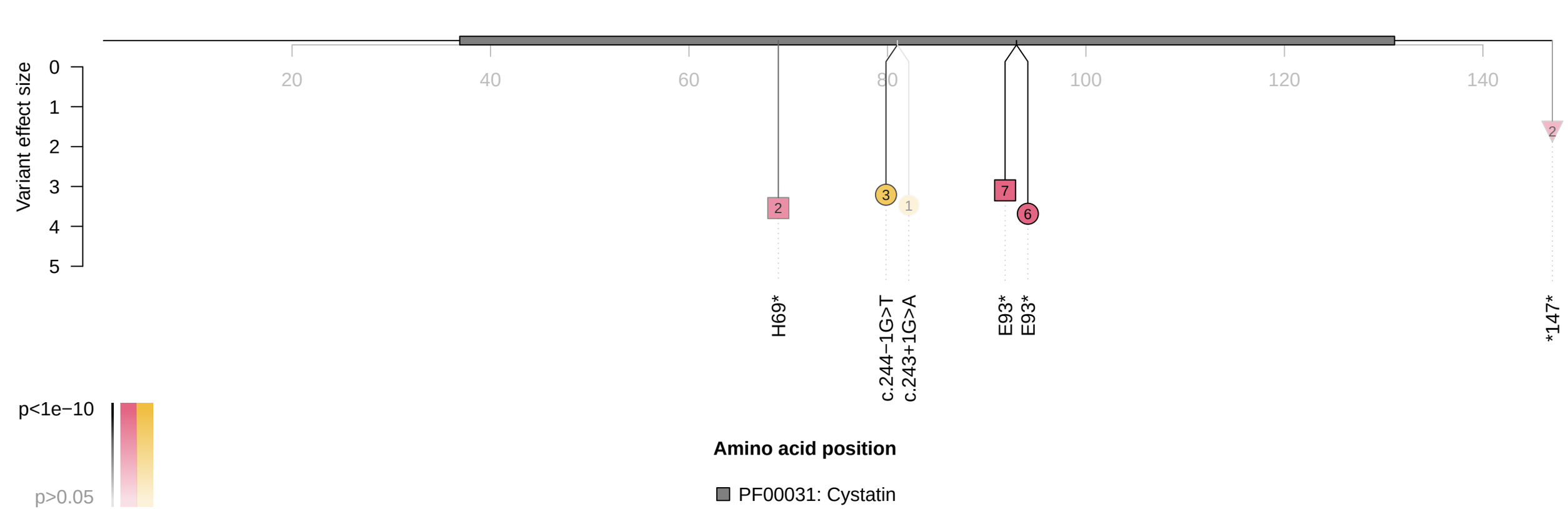
Gene=CST3; Chr=2; Phenotype=Cystatin C; Gene effect size=−1.66

missense | in−frame indel | splice | stop gain | stop lost | start lost | frameshift



Gene=CST3; Chr=2; Phenotype=Cystatin C; Gene effect size=−2.69

splice stop gain stop lost start lost frameshift



Gene=FCGRT; Chr=1; Phenotype=Albumin; Gene effect size=−0.84

missense | in−frame indel | splice | stop gain | stop lost | start lost | frameshift

Variant effect size

Amino acid position

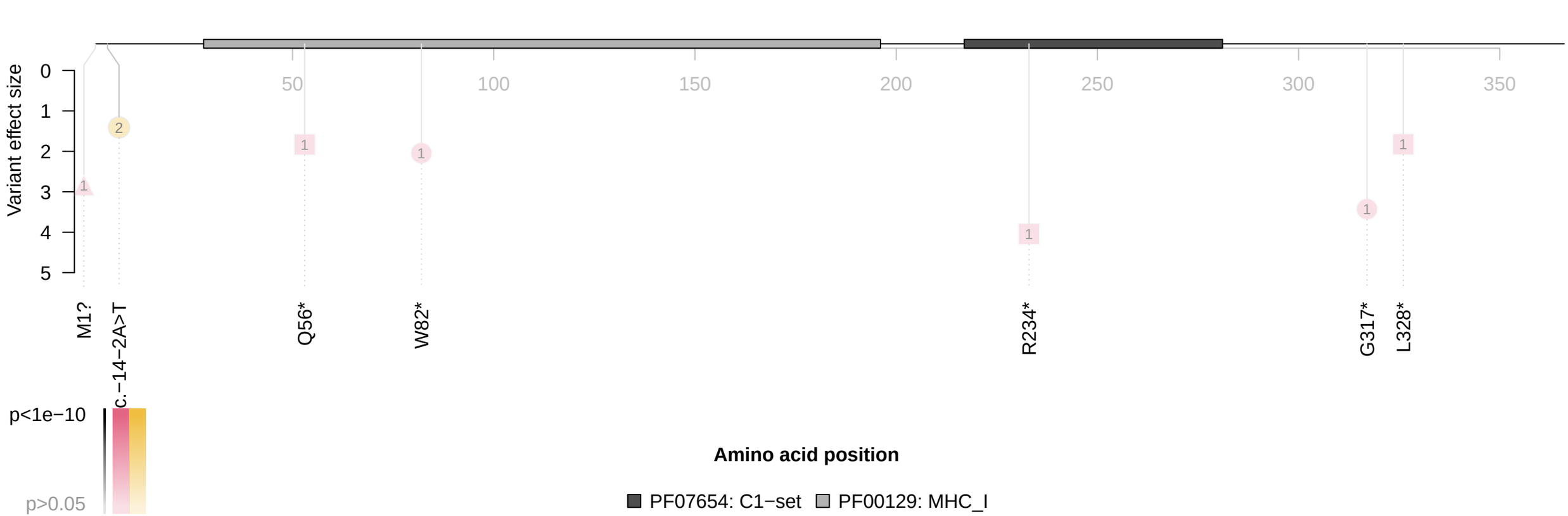
PF00129: MHC_I | PF07654: C1−set

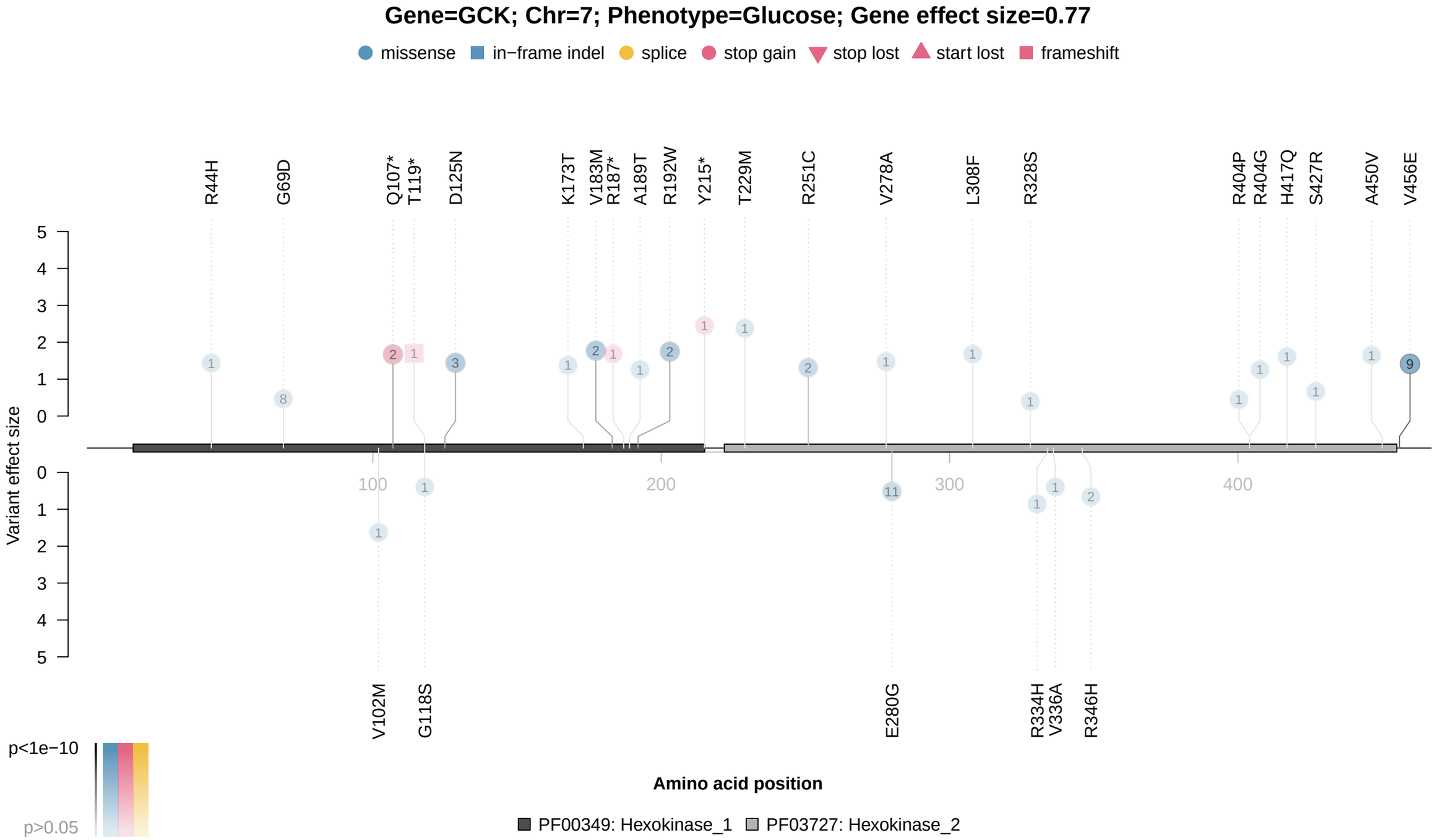
p<1e−10

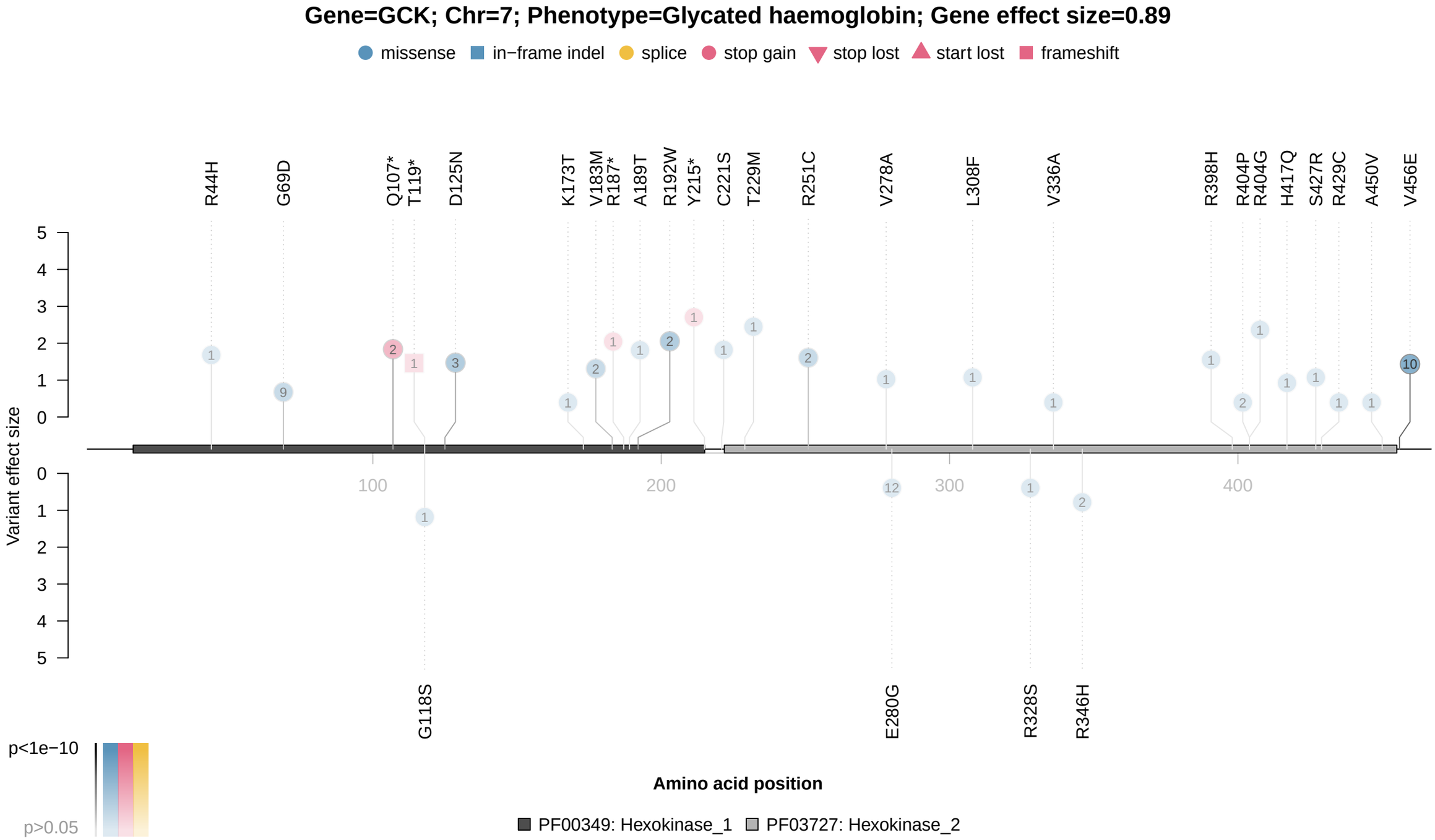
p>0.05

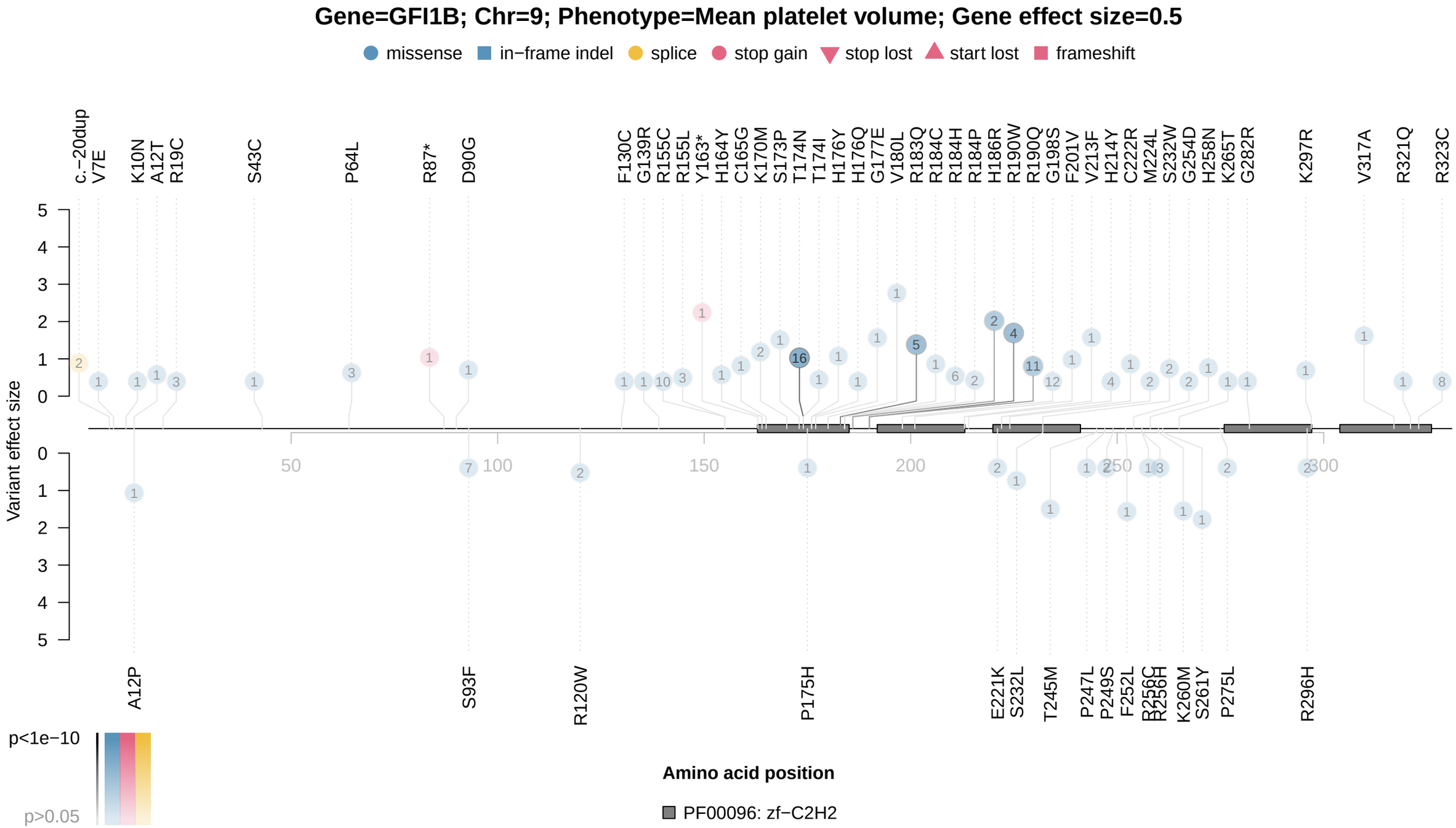
Gene=FCGRT; Chr=1; Phenotype=Albumin; Gene effect size=−2.37

splice stop gain stop lost start lost frameshift




Gene=GCK; Chr=7; Phenotype=Glucose; Gene effect size=0.77
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
R44H
G69D
Q107*
T119*
D125N
K173T
V183M
R187*
A189T
R192W
Y215*
T229M
R251C
V278A
L308F
R328S
R404P
R404G
H417Q
S427R
A450V
V456E
Variant effect size
V102M
G118S
E280G
R334H
V336A
R346H
Amino acid position
p<1e−10
p>0.05
PF00349: Hexokinase_1
PF03727: Hexokinase_2


Gene=GCK; Chr=7; Phenotype=Glycated haemoglobin; Gene effect size=0.89
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
R44H
G69D
Q107*
T119*
D125N
K173T
V183M
R187*
A189T
R192W
Y215*
C221S
T229M
R251C
V278A
L308F
V336A
R398H
R404P
R404G
H417Q
S427R
R429C
A450V
V456E
G118S
E280G
R328S
R346H
Variant effect size
100
200
300
400
Amino acid position
p<1e−10
p>0.05
PF00349: Hexokinase_1
PF03727: Hexokinase_2


Gene=GFI1B; Chr=9; Phenotype=Mean platelet volume; Gene effect size=0.5
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
c.−20dup
V7E
K10N
A12T
R19C
S43C
P64L
R87*
D90G
F130C
G139R
R155C
R155L
Y163*
H164Y
C165G
K170M
S173P
T174N
T174I
H176Y
H176Q
G177E
V180L
R183Q
R184C
R184H
R184P
H186R
R190W
R190Q
G198S
F201V
V213F
H214Y
C222R
M224L
S232W
G254D
H258N
K265T
G282R
K297R
V317A
R321Q
R323C
Variant effect size
A12P
S93F
R120W
P175H
E221K
S232L
T245M
P247L
P249S
F252L
R256C
R256H
K260M
S261Y
P275L
R296H
p<1e−10
p>0.05
Amino acid position
PF00096: zf−C2H2

Gene=GOT1; Chr=1; Phenotype=Aspartate aminotransferase; Gene effect size=−1.45

missense | in−frame indel | splice | stop gain | stop lost | start lost | frameshift

Variant effect size

Amino acid position

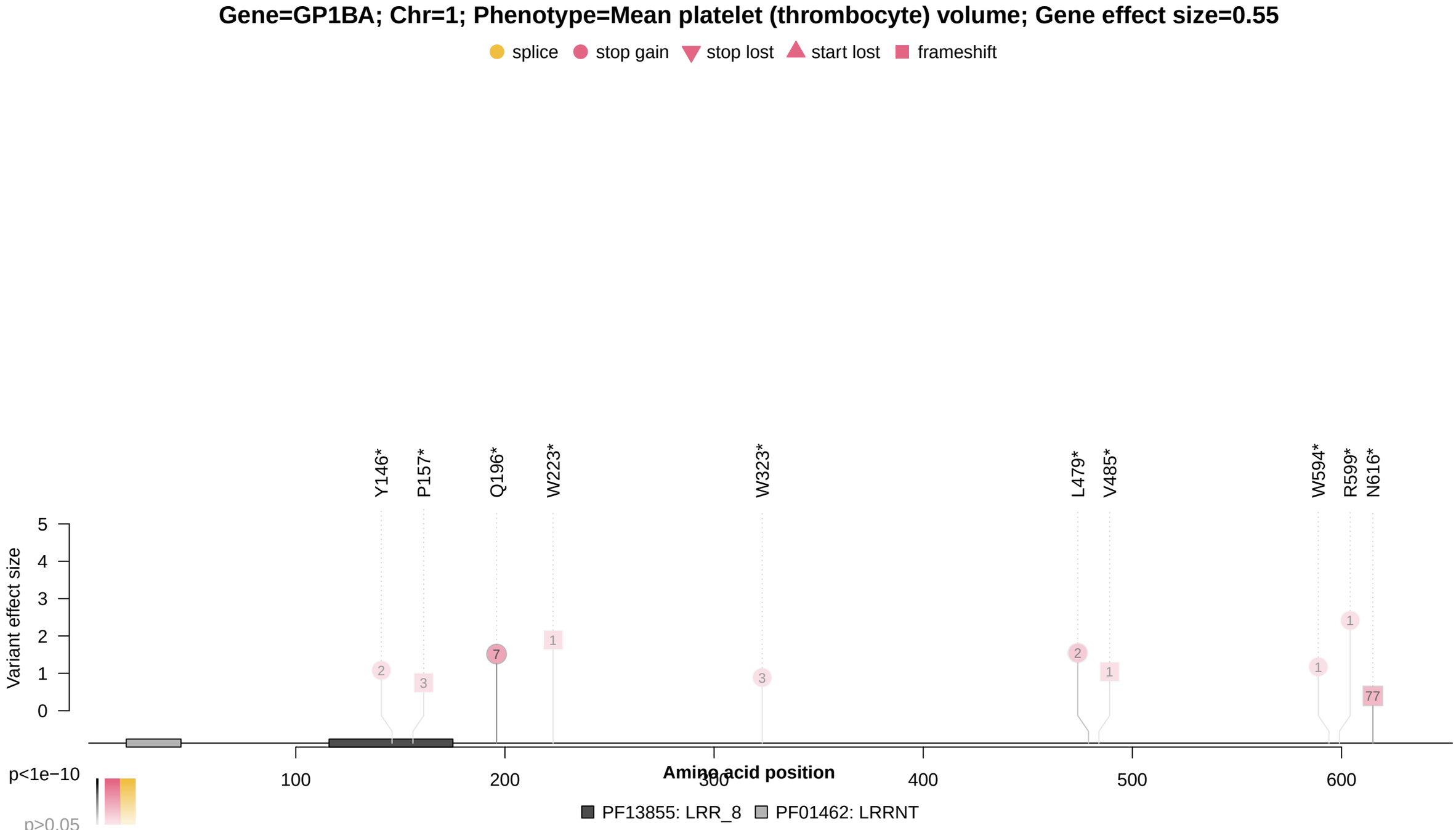
PF00155: Aminotran_1_2

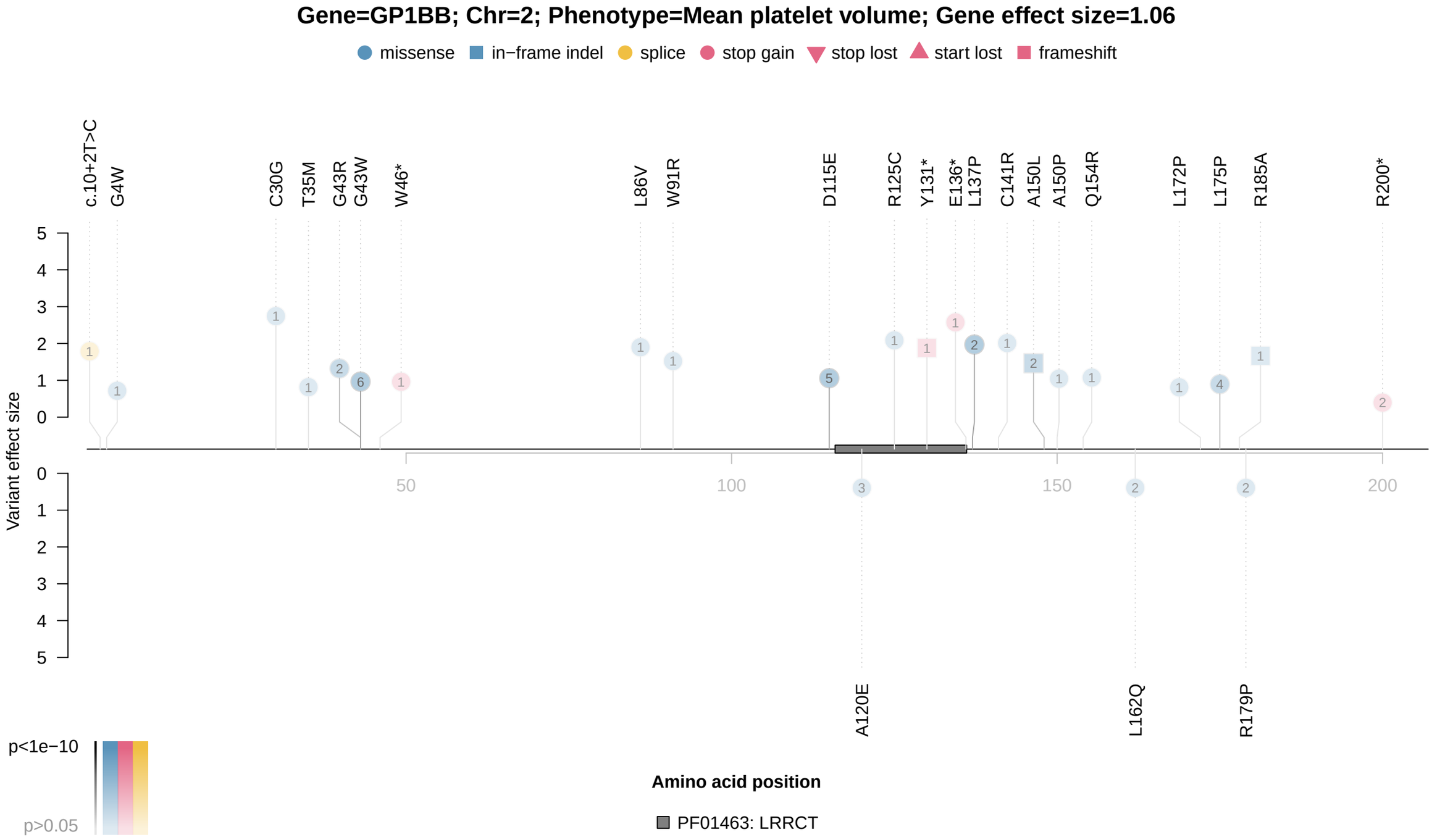
p<1e−10

p>0.05

Gene=GOT1; Chr=1; Phenotype=Aspartate aminotransferase; Gene effect size=−2.15

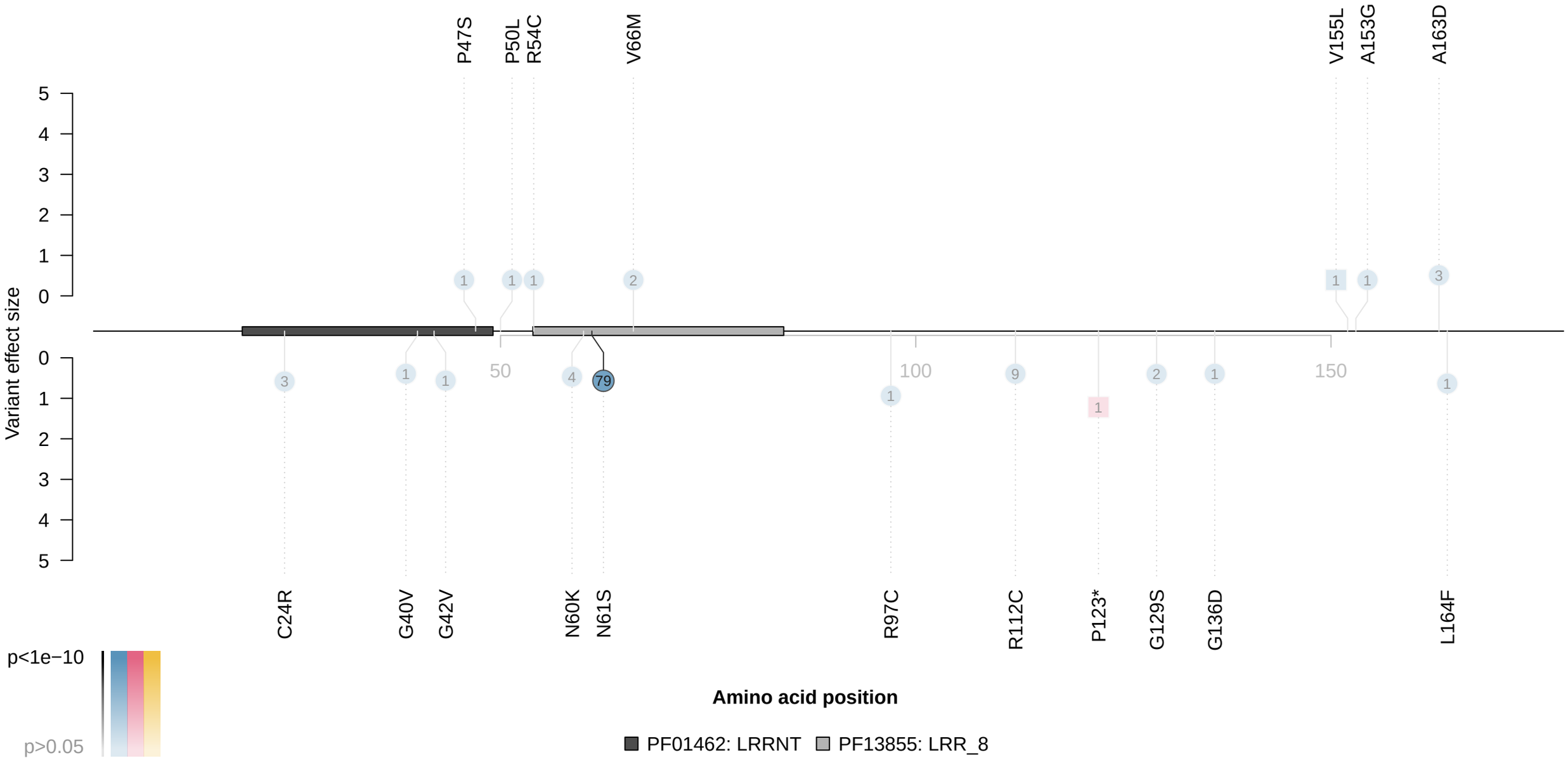
splice stop gain stop lost start lost frameshift


Gene=GP1BA; Chr=1; Phenotype=Mean platelet (thrombocyte) volume; Gene effect size=0.55
splice
stop gain
stop lost
start lost
frameshift
Y146*
P157*
Q196*
W223*
W323*
L479*
V485*
W594*
R599*
N616*
Variant effect size
0
1
2
3
4
5
2
3
7
1
3
2
1
1
1
77
100
200
300
400
500
600
Amino acid position
p<1e−10
p>0.05
PF13855: LRR_8
PF01462: LRRNT


Gene=GP1BB; Chr=2; Phenotype=Mean platelet volume; Gene effect size=1.06
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
c.10+2T>C
G4W
C30G
T35M
G43R
G43W
W46*
L86V
W91R
D115E
R125C
Y131*
E136*
L137P
C141R
A150L
A150P
Q154R
L172P
L175P
R185A
R200*
Variant effect size
0
1
2
3
4
5
50
100
150
200
A120E
L162Q
R179P
p<1e−10
p>0.05
Amino acid position
PF01463: LRRCT

Gene=GP9; Chr=3; Phenotype=Platelet count; Gene effect size=−0.55

missense | in−frame indel | splice | stop gain | stop lost | start lost | frameshift



Gene=GP9; Chr=3; Phenotype=Mean platelet volume; Gene effect size=0.59

missense | in−frame indel | splice | stop gain | stop lost | start lost | frameshift

C24R G42V R54C N60K N61S R112C P123* G136D L164F

Variant effect size

5 4 3 2 1 0 0 1 2 3 4 5

3 1 1 4 79 9 1 1 1

1 1 50 2 1 100 2 150 1 1 3

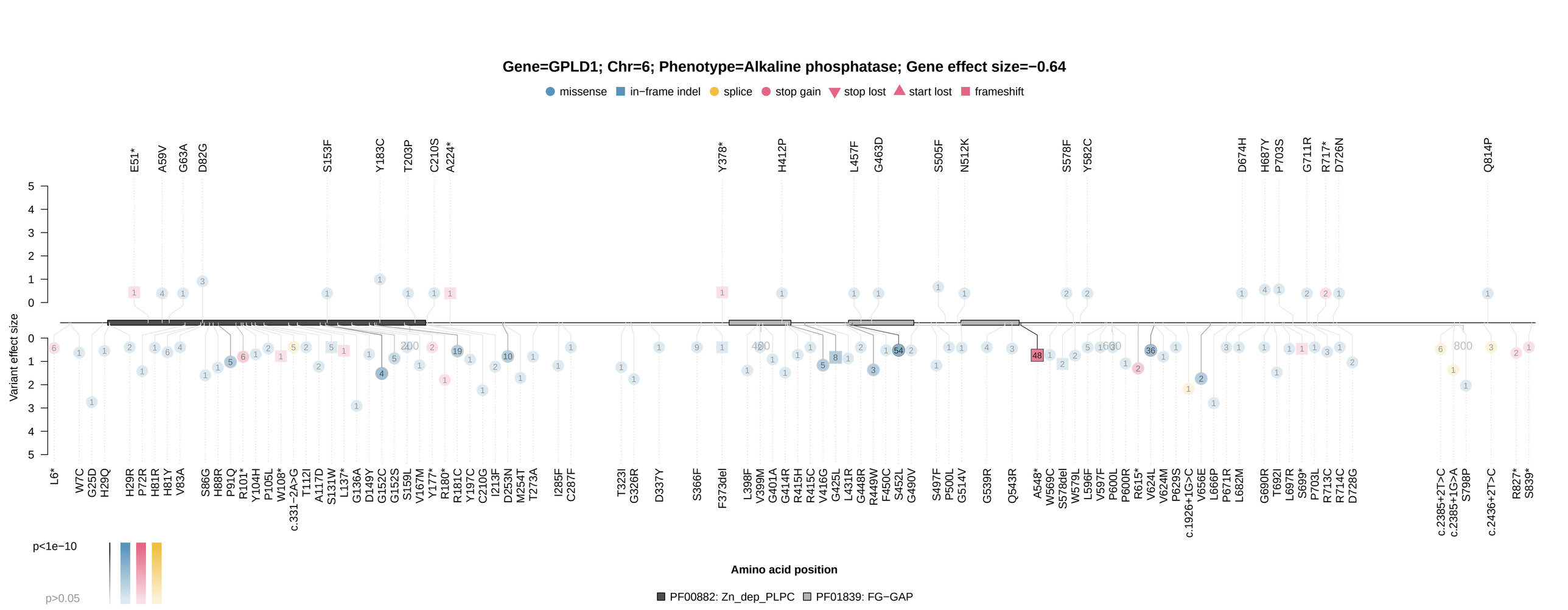
G40V P47S V66M R97C G129S V155L A153G A163D

p<1e−10

p>0.05

Amino acid position

PF01462: LRRNT PF13855: LRR_8


Gene=GPLD1; Chr=6; Phenotype=Alkaline phosphatase; Gene effect size=−0.64
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
Variant effect size
E51*
A59V
G63A
D82G
S153F
Y183C
T203P
C210S
A224*
Y378*
H412P
L457F
G463D
S505F
N512K
S578F
Y582C
D674H
H687Y
P703S
G711R
R717*
D726N
Q814P
L6*
W7C
G25D
H29Q
H29R
P72R
H81R
H81Y
V83A
S86G
H88R
P91Q
R101*
Y104H
P105L
W108*
c.331−2A>G
T112I
A117D
S131W
L137*
G136A
D149Y
G152C
G152S
S159L
V167M
Y177*
R180*
R181C
Y197C
C210G
I213F
D253N
M254T
T273A
I285F
C287F
T323I
G326R
D337Y
S366F
F373del
L398F
V399M
G401A
G414R
R415H
R415C
V416G
G425L
L431R
G448R
R449W
F450C
S452L
G490V
S497F
P500L
G514V
G539R
Q543R
A548*
W569C
S578del
W579L
L596F
V597F
P600L
P600R
R615*
V624L
V624M
P629S
c.1926+1G>C
V656E
L666P
P671R
L682M
G690R
T692I
L697R
S699*
P703L
R713C
R714C
D728G
c.2385+2T>C
c.2385+1G>A
S798P
c.2436+2T>C
R827*
S839*
p<1e−10
p>0.05
Amino acid position
PF00882: Zn_dep_PLPC
PF01839: FG−GAP

Gene=GPLD1; Chr=6; Phenotype=Alkaline phosphatase; Gene effect size=−0.71

splice · stop gain · stop lost · start lost · frameshift

E51* · A224* · Y378* · R717*

Variant effect size

L6* · R101* · W108* · c.331−2A>G · L137* · Y177* · R180* · A548* · R615* · c.1926+1G>C · S699* · c.2385+2T>C · c.2385+1G>A · c.2436+2T>C · R827* · S839*

p<1e−10 … p>0.05

Amino acid position

PF00882: Zn_dep_PLPC · PF01839: FG−GAP

Gene=GPT; Chr=8; Phenotype=Alanine aminotransferase; Gene effect size=−1.01

missense | in−frame indel | splice | stop gain | stop lost | start lost | frameshift

Variant effect size

0 1 2 3 4 5

100 200 300 400

R53C

T22M R31G R32* R38C R38H R38L R44* A45D L52R R53H c.162+2T>C P59L R65H A73T Q76H

C450W V451M R467W I470V E475* P472S R478W

p<1e−10

p>0.05

Amino acid position

PF00155: Aminotran_1_2

Gene=HBB; Chr=1; Phenotype=Red blood cell count; Gene effect size=0.68

missense | in−frame indel | splice | stop gain | stop lost | start lost | frameshift

Variant effect size

Amino acid position

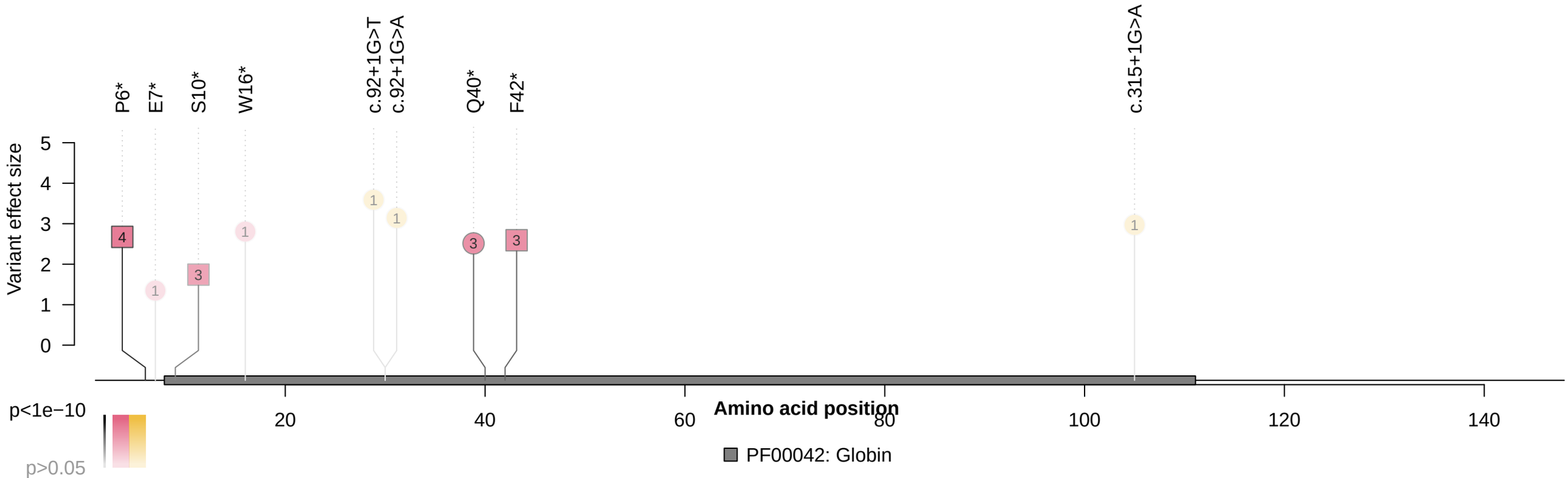
PF00042: Globin

p<1e−10

p>0.05

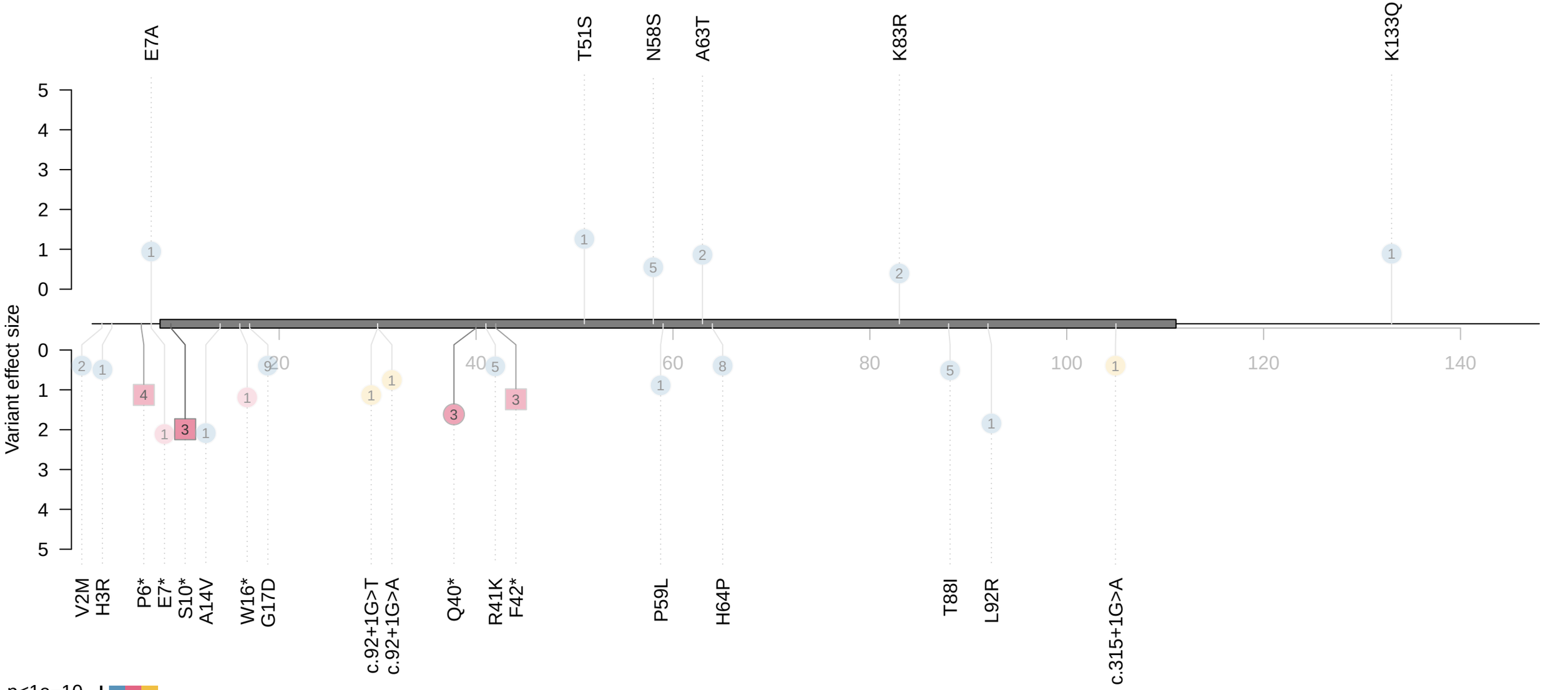
Gene=HBB; Chr=1; Phenotype=Red blood cell count; Gene effect size=2.51

splice stop gain stop lost start lost frameshift



Gene=HBB; Chr=1; Phenotype=Haemoglobin concentration; Gene effect size=−0.54

missense · in−frame indel · splice · stop gain · stop lost · start lost · frameshift



p<1e−10

p>0.05

Amino acid position

PF00042: Globin

Gene=HBB; Chr=1; Phenotype=Haemoglobin concentration; Gene effect size=−1.42

splice stop gain stop lost start lost frameshift

Gene=HBB; Chr=1; Phenotype=Mean corpuscular volume; Gene effect size=−0.78

missense | in−frame indel | splice | stop gain | stop lost | start lost | frameshift

H3R G17D T51S P59L A63T K83R L92R

Variant effect size

0 1 2 3 4 5

1 9 1 1 2 2 1

0 20 40 60 80 100 120 140

2 1 4 1 3 1 1 1 1 3 5 5 8 5 1 1

V2M P6* E7A E7* S10* A14V W16* c.92+1G>T c.92+1G>A Q40* R41K F42* N58S H64P T88I c.315+1G>A K133Q

p<1e−10

p>0.05

Amino acid position

PF00042: Globin

Gene=HBB; Chr=1; Phenotype=Mean corpuscular volume; Gene effect size=−2.51

splice stop gain stop lost start lost frameshift

Gene=HBB; Chr=1; Phenotype=Mean corpuscular haemoglobin; Gene effect size=−0.94

missense | in−frame indel | splice | stop gain | stop lost | start lost | frameshift

Variant effect size

H3R G17D T51S A63T L92R

V2M P6* E7A E7* S10* A14V W16* c.92+1G>T c.92+1G>A Q40* R41K F42* N58S P59L H64P K83R T88I c.315+1G>A K133Q

p<1e−10

p>0.05

Amino acid position

PF00042: Globin

Gene=HBB; Chr=1; Phenotype=Mean corpuscular haemoglobin; Gene effect size=−2.49

splice stop gain stop lost start lost frameshift

Gene=HBB; Chr=1; Phenotype=Mean corpuscular haemoglobin concentration; Gene effect size=−0.9

missense | in−frame indel | splice | stop gain | stop lost | start lost | frameshift

Variant effect size

T51S A63T K133Q

V2M H3R P6* E7A E7* S10* A14V W16* G17D c.92+1G>T c.92+1G>A Q40* R41K F42* N58S P59L H64P K83R T88I L92R c.315+1G>A

p<1e−10

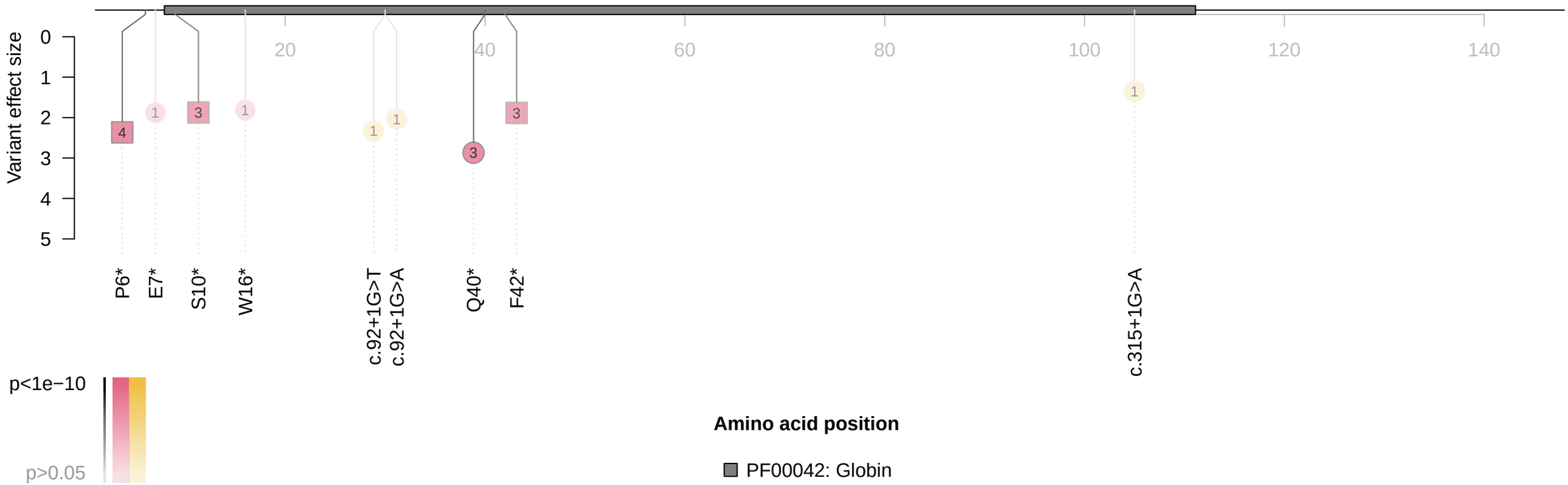
p>0.05

Amino acid position

PF00042: Globin

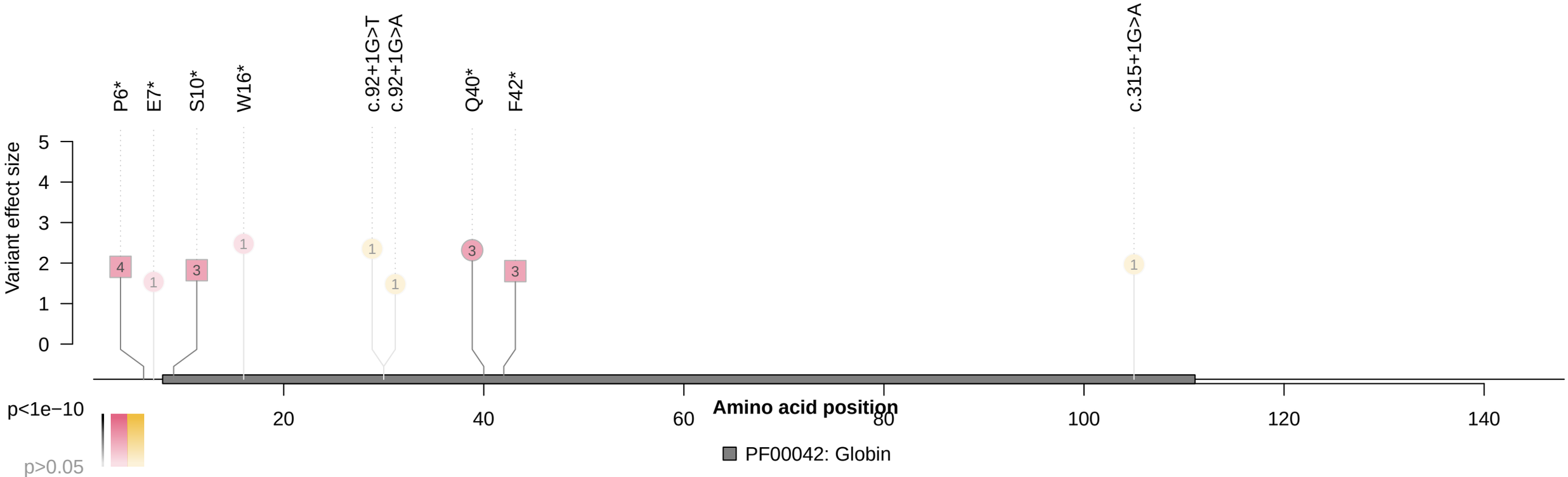
Gene=HBB; Chr=1; Phenotype=Mean corpuscular haemoglobin concentration; Gene effect size=−2.18

splice stop gain stop lost start lost frameshift



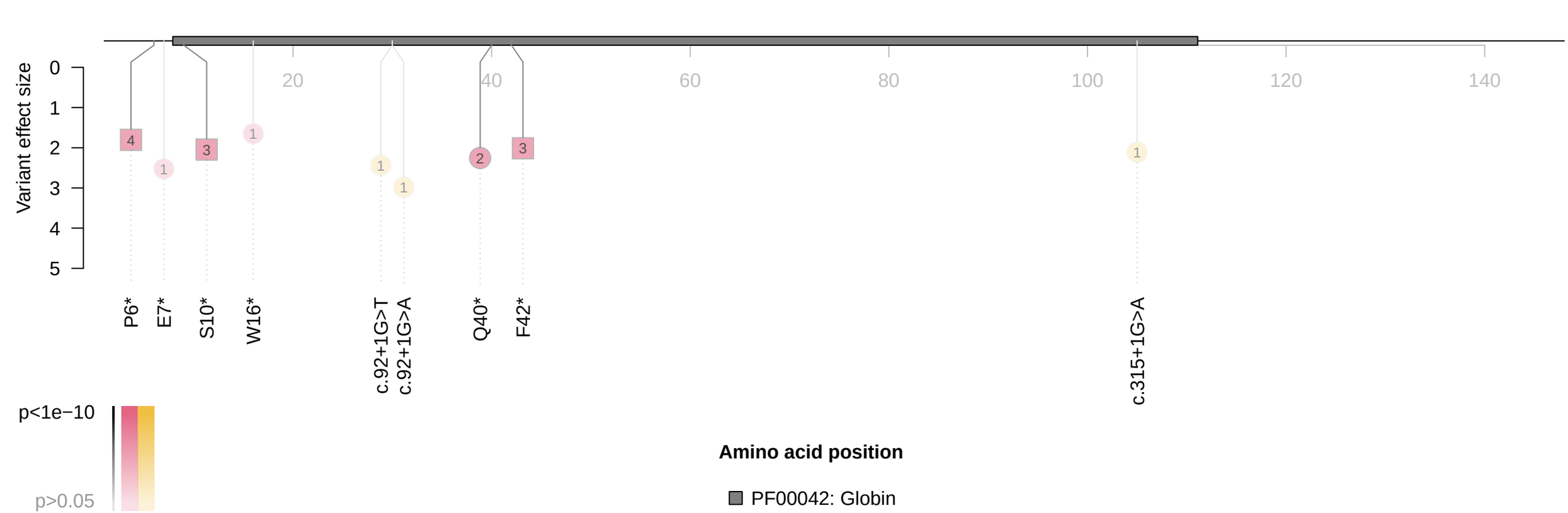
Gene=HBB; Chr=1; Phenotype=Red blood cell distribution width; Gene effect size=2

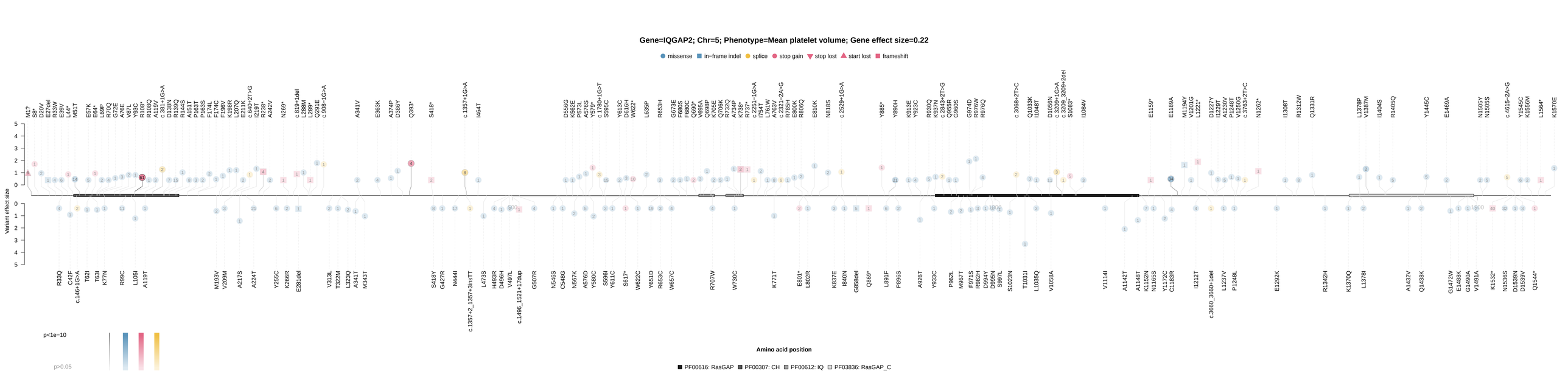
splice stop gain stop lost start lost frameshift

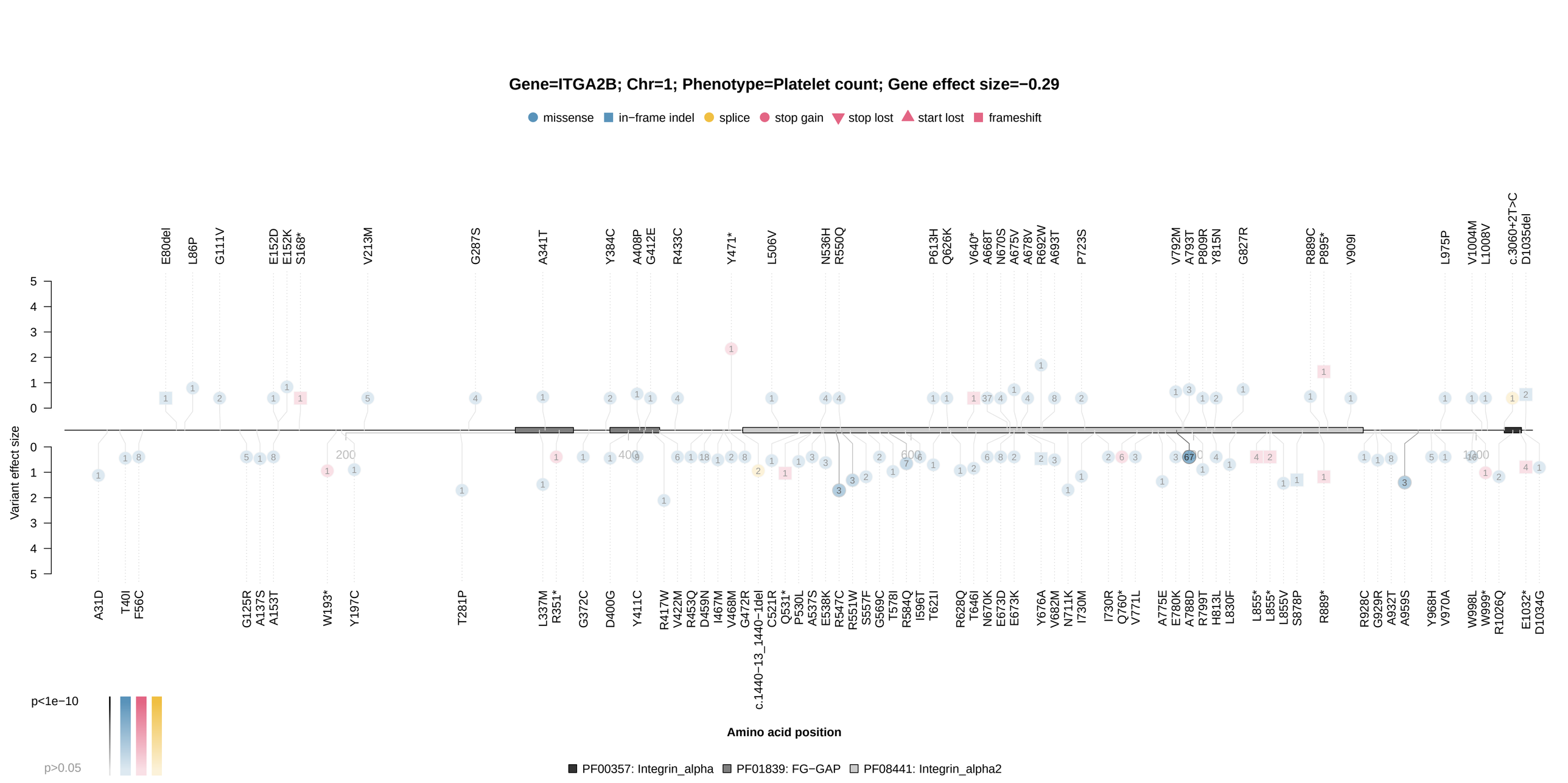


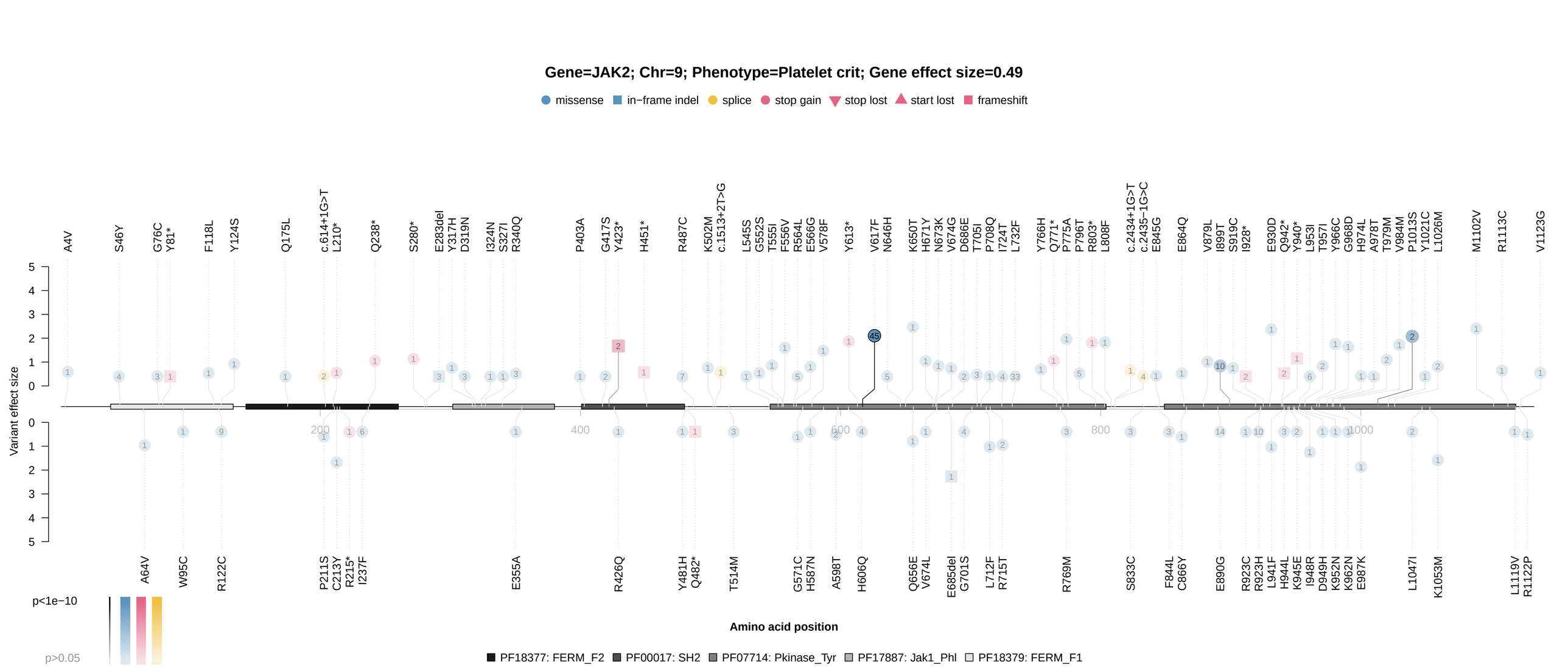
Gene=HBB; Chr=1; Phenotype=Mean sphered cell volume; Gene effect size=−2.11

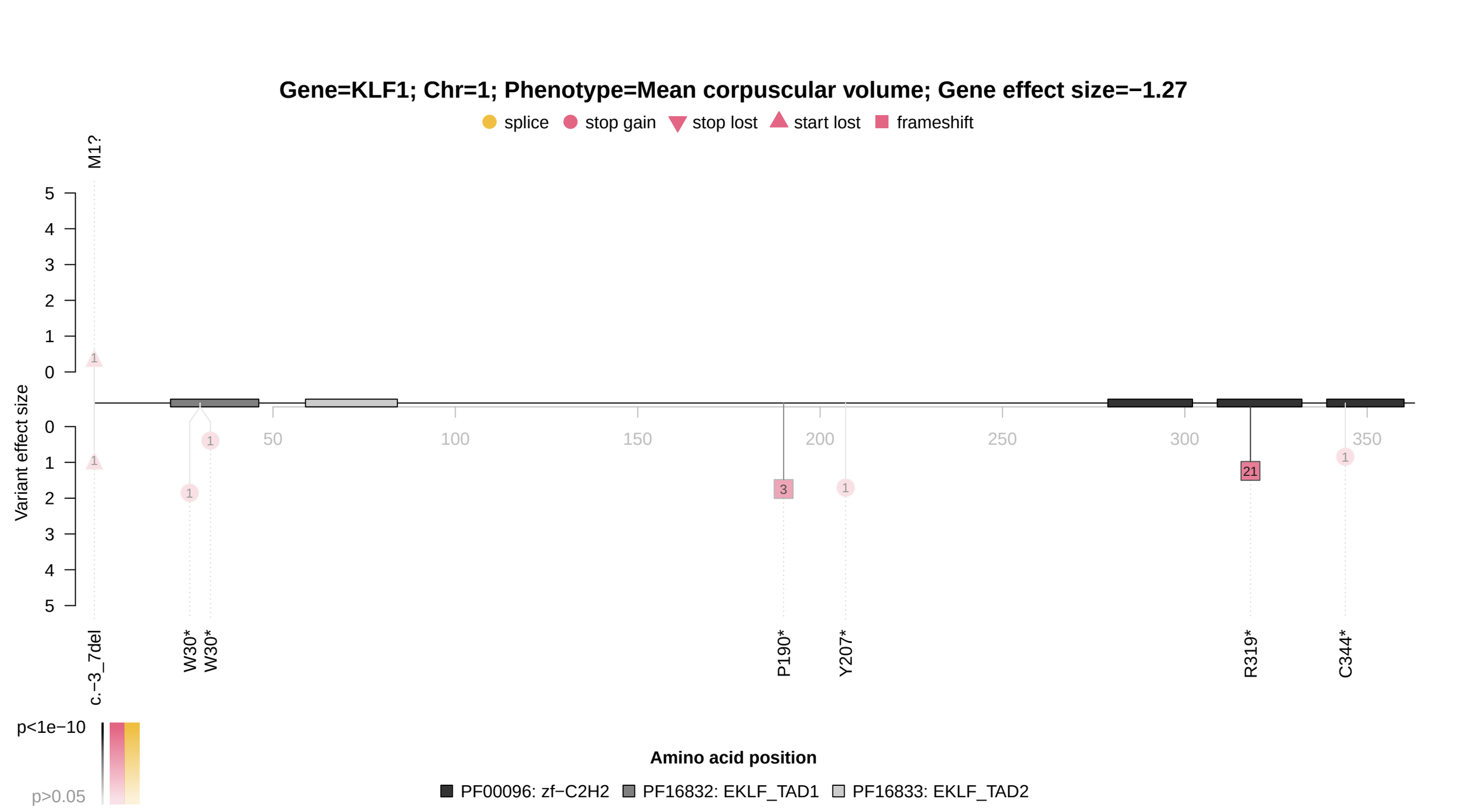
splice stop gain stop lost start lost frameshift

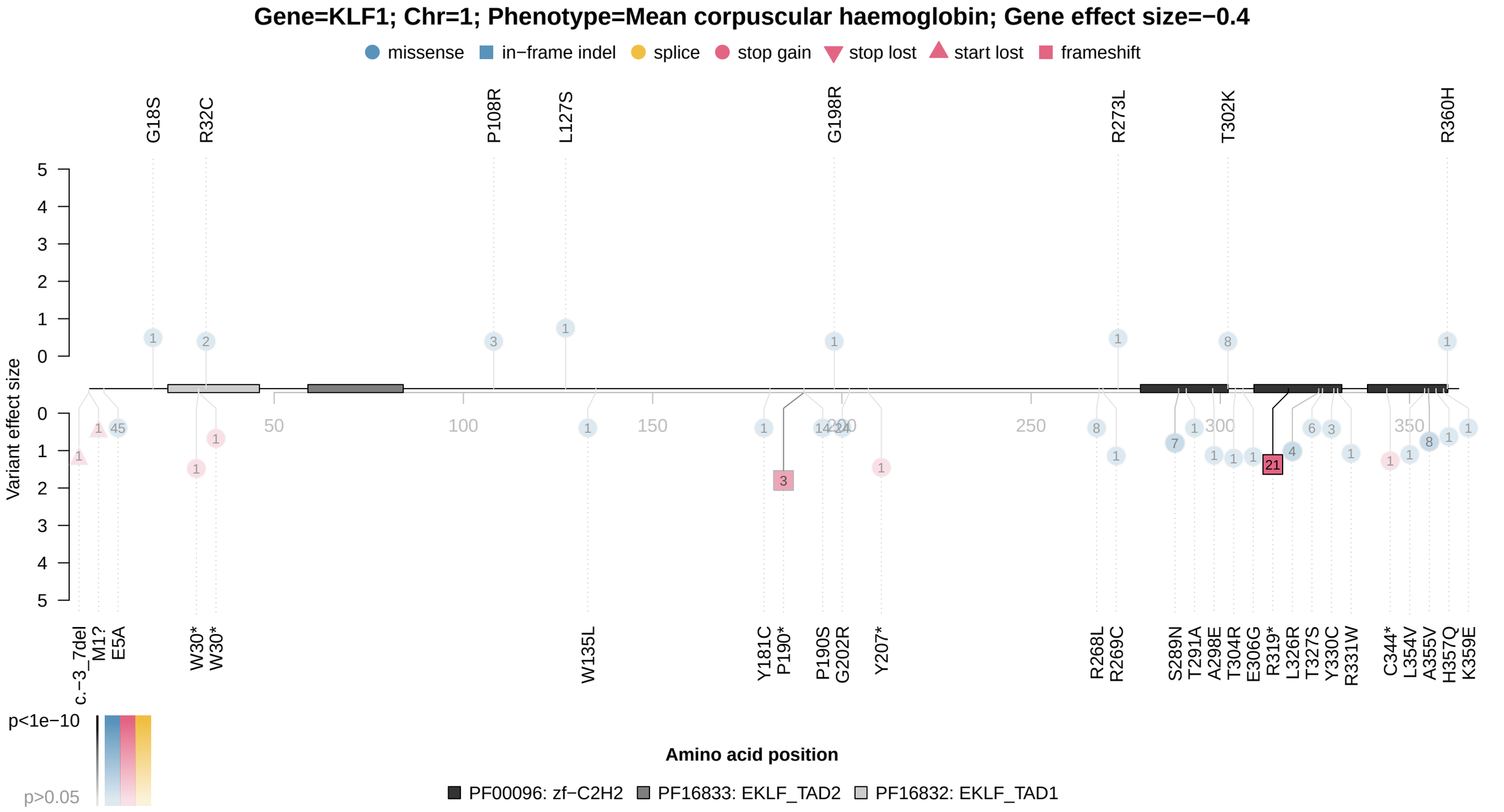


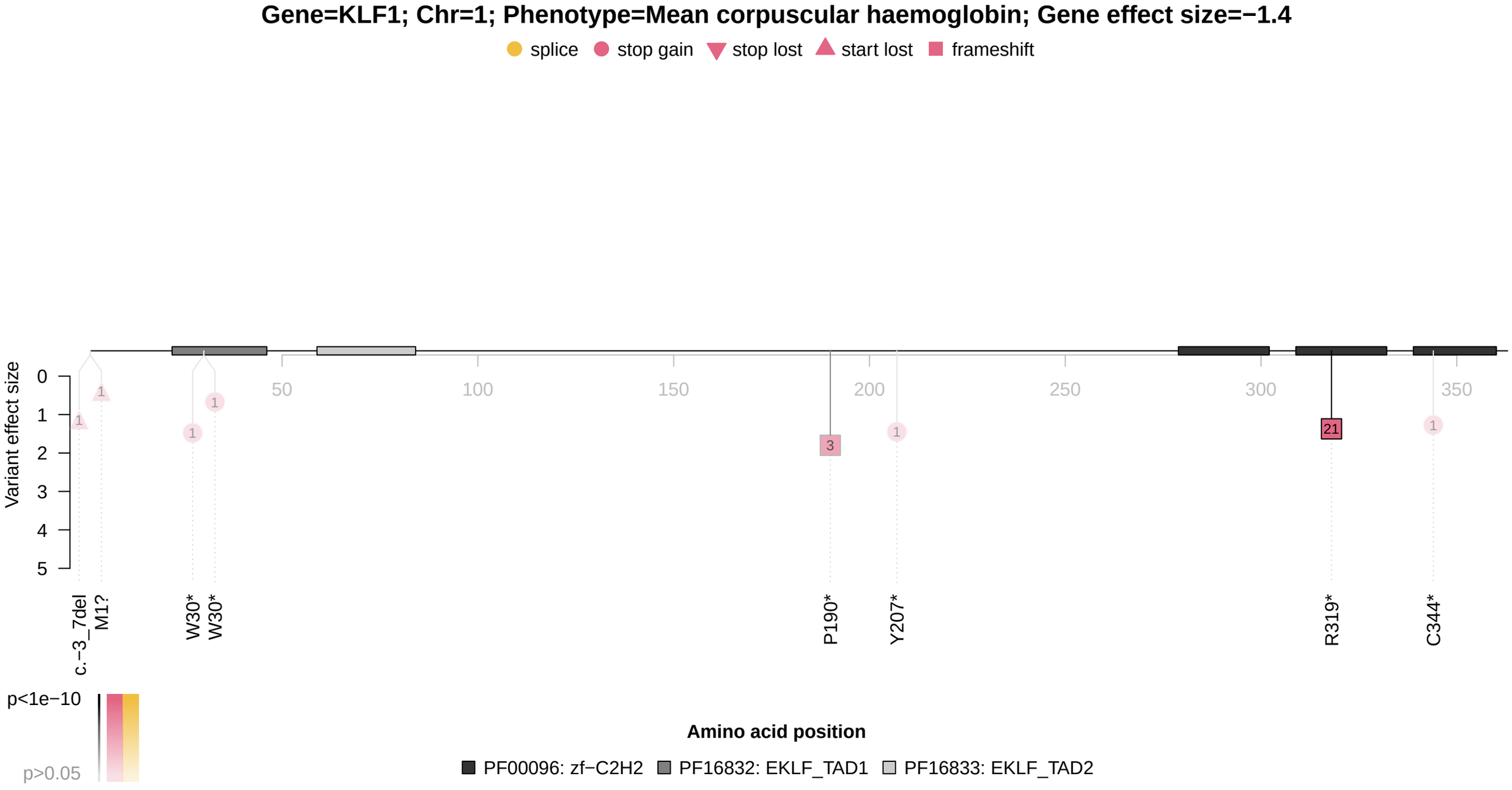

Gene=IQGAP2; Chr=5; Phenotype=Mean platelet volume; Gene effect size=0.22
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
Variant effect size
Amino acid position
p<1e−10
p>0.05
PF00616: RasGAP
PF00307: CH
PF00612: IQ
PF03836: RasGAP_C

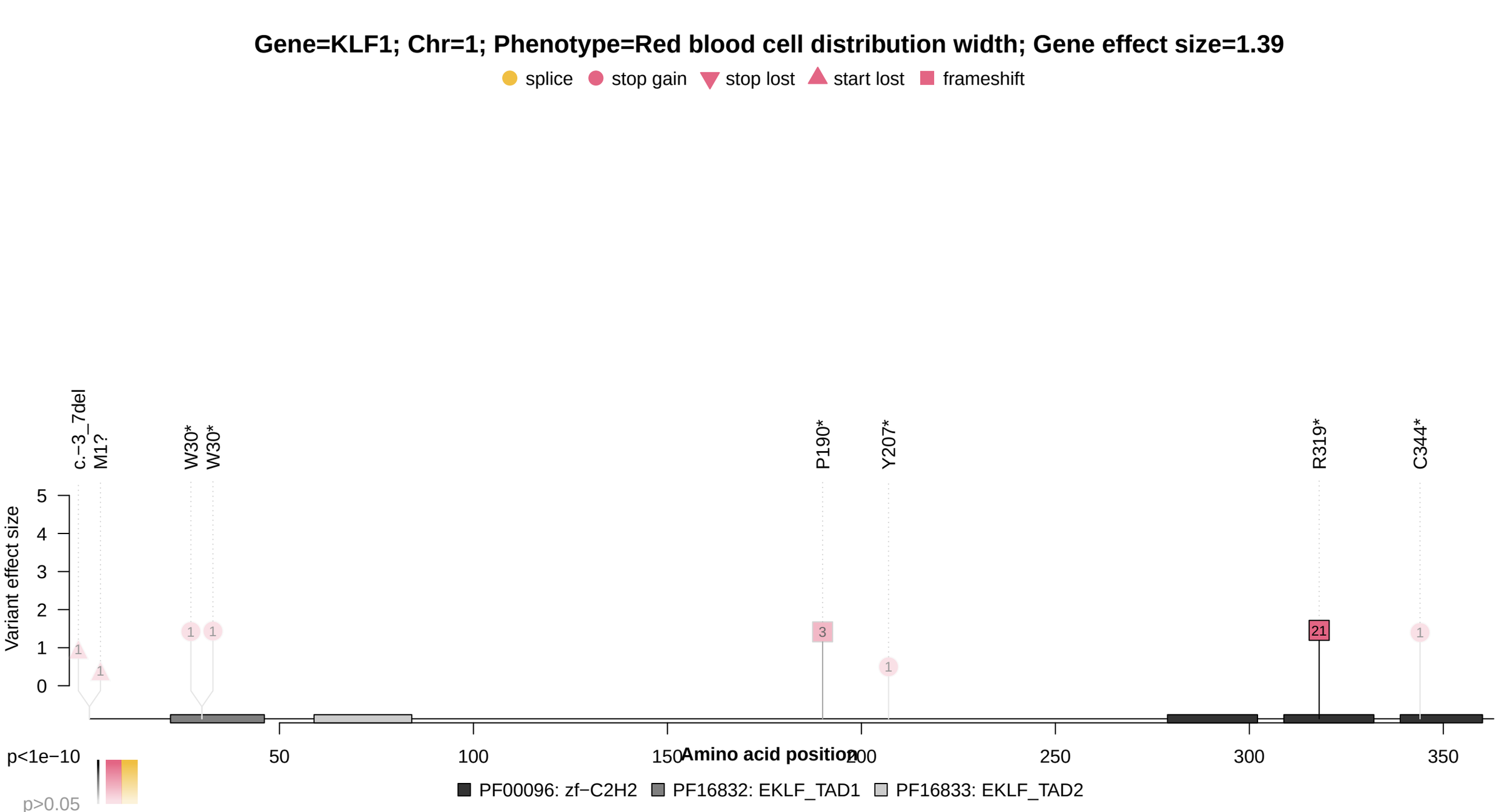

Gene=ITGA2B; Chr=1; Phenotype=Platelet count; Gene effect size=−0.29
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
Variant effect size
Amino acid position
p<1e−10
p>0.05
PF00357: Integrin_alpha
PF01839: FG−GAP
PF08441: Integrin_alpha2

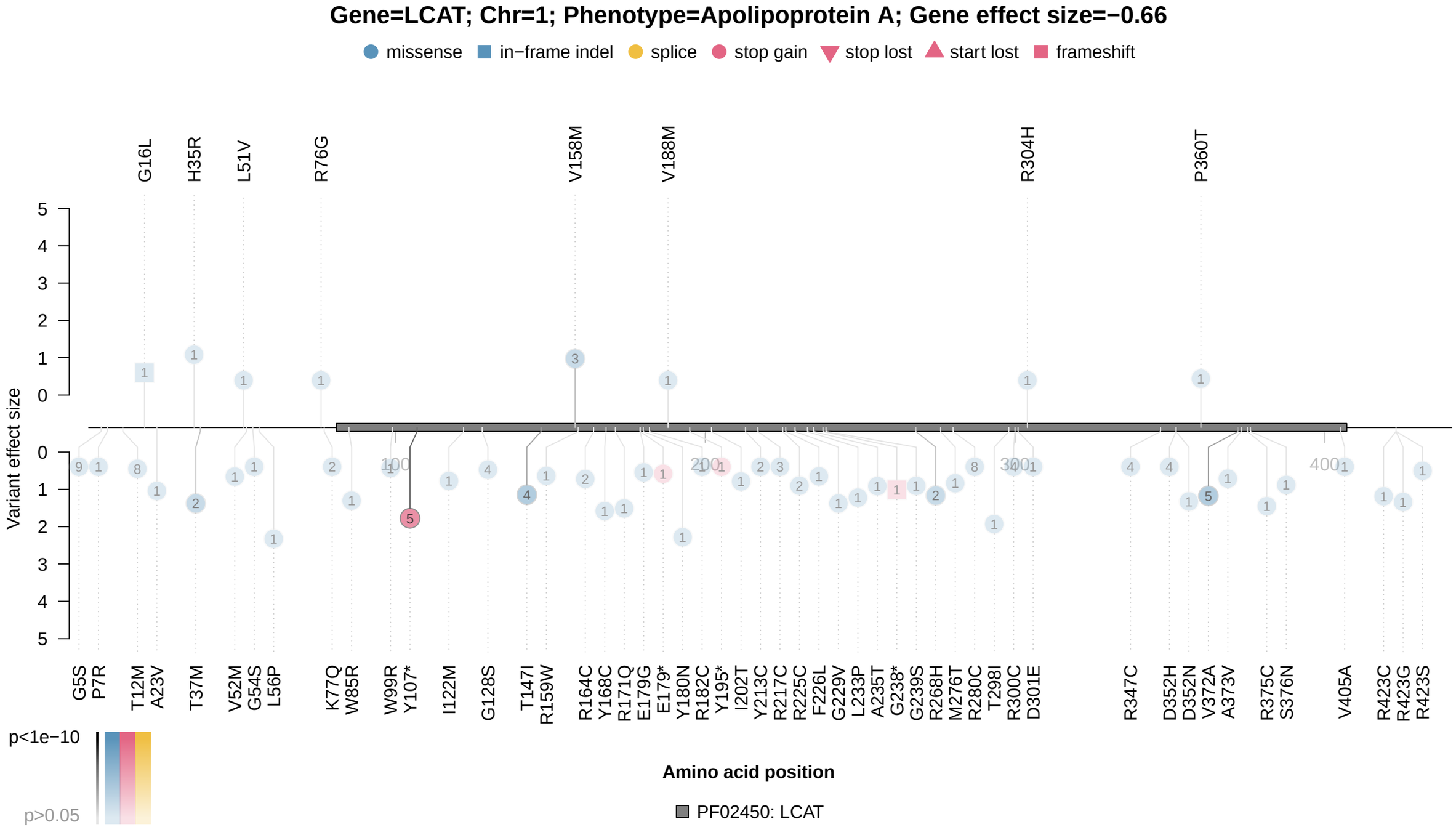

Gene=JAK2; Chr=9; Phenotype=Platelet crit; Gene effect size=0.49
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
A4V
S46Y
G76C
Y81*
F118L
Y124S
Q175L
c.614+1G>T
L210*
Q238*
S280*
E283del
Y317H
D319N
I324N
S327I
R340Q
P403A
G417S
Y423*
H451*
R487C
K502M
c.1513+2T>G
L545S
G552S
T555I
F556V
R564L
E566G
V578F
Y613*
V617F
N646H
K650T
H671Y
N673K
V674G
D686E
T705I
P708Q
I724T
L732F
Y766H
Q771*
P775A
P796T
R803*
L808F
c.2434+1G>T
c.2435−1G>C
E845G
E864Q
V879L
I899T
S919C
I928*
E930D
Q942*
Y940*
L953I
T957I
Y966C
G968D
H974L
A978T
T979M
V984M
P1013S
Y1021C
L1026M
M1102V
R1113C
V1123G
Variant effect size
Amino acid position
A64V
W95C
R122C
P211S
C213Y
R215*
I237F
E355A
R426Q
Y481H
Q482*
T514M
G571C
H587N
A598T
H606Q
Q656E
V674L
E685del
G701S
L712F
R715T
R769M
S833C
F844L
C866Y
E890G
R923C
R923H
L941F
H944L
K945E
I948R
D949H
K952N
K962N
E987K
L1047I
K1053M
L1119V
R1122P
p<1e−10
p>0.05
PF18377: FERM_F2
PF00017: SH2
PF07714: Pkinase_Tyr
PF17887: Jak1_Phl
PF18379: FERM_F1

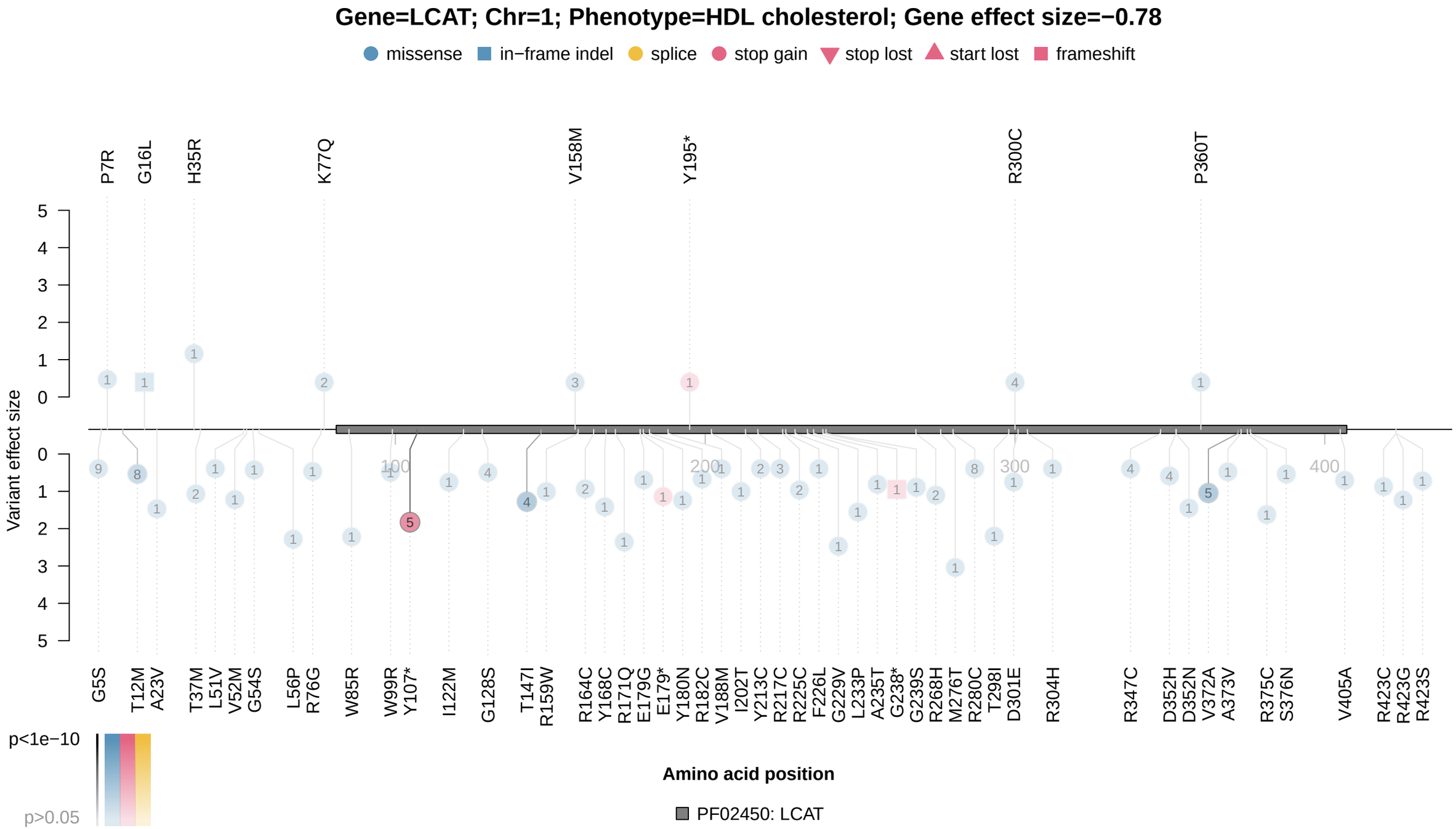

Gene=KLF1; Chr=1; Phenotype=Mean corpuscular volume; Gene effect size=−1.27
splice
stop gain
stop lost
start lost
frameshift
M1?
Variant effect size
5
4
3
2
1
0
0
1
2
3
4
5
1
1
1
1
3
1
21
1
50
100
150
200
250
300
350
c.−3_7del
W30*
W30*
P190*
Y207*
R319*
C344*
p<1e−10
p>0.05
Amino acid position
PF00096: zf−C2H2
PF16832: EKLF_TAD1
PF16833: EKLF_TAD2

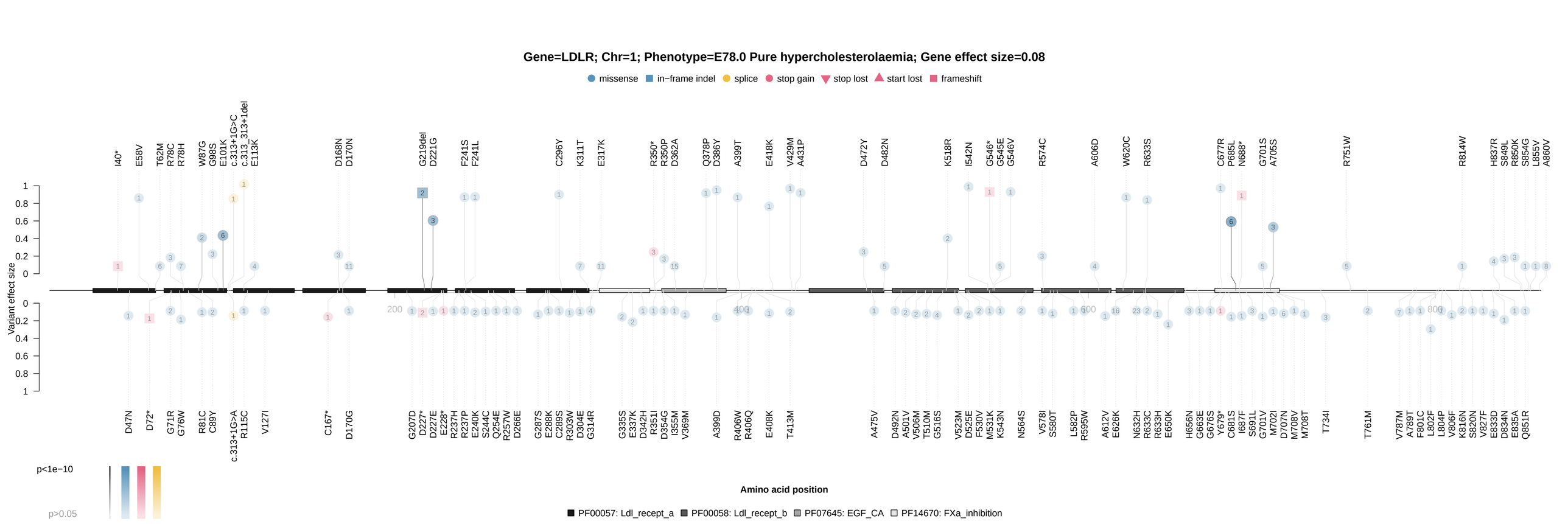

Gene=KLF1; Chr=1; Phenotype=Mean corpuscular haemoglobin; Gene effect size=−0.4
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
G18S
R32C
P108R
L127S
G198R
R273L
T302K
R360H
Variant effect size
Amino acid position
c.−3_7del
M1?
E5A
W30*
W30*
W135L
Y181C
P190*
P190S
G202R
Y207*
R268L
R269C
S289N
T291A
A298E
T304R
E306G
R319*
L326R
T327S
Y330C
R331W
C344*
L354V
A355V
H357Q
K359E
p<1e−10
p>0.05
PF00096: zf−C2H2
PF16833: EKLF_TAD2
PF16832: EKLF_TAD1


Gene=KLF1; Chr=1; Phenotype=Mean corpuscular haemoglobin; Gene effect size=−1.4
splice
stop gain
stop lost
start lost
frameshift
Variant effect size
0
1
2
3
4
5
50
100
150
200
250
300
350
1
1
1
1
3
1
21
1
c.−3_7del
M1?
W30*
W30*
P190*
Y207*
R319*
C344*
p<1e−10
p>0.05
Amino acid position
PF00096: zf−C2H2
PF16832: EKLF_TAD1
PF16833: EKLF_TAD2


Gene=KLF1; Chr=1; Phenotype=Red blood cell distribution width; Gene effect size=1.39
splice
stop gain
stop lost
start lost
frameshift
c.−3_7del
M1?
W30*
W30*
P190*
Y207*
R319*
C344*
Variant effect size
0
1
2
3
4
5
1
1
1
1
3
1
21
1
50
100
150
200
250
300
350
Amino acid position
p<1e−10
p>0.05
PF00096: zf−C2H2
PF16832: EKLF_TAD1
PF16833: EKLF_TAD2


Gene=LCAT; Chr=1; Phenotype=Apolipoprotein A; Gene effect size=−0.66
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
G16L
H35R
L51V
R76G
V158M
V188M
R304H
P360T
Variant effect size
Amino acid position
PF02450: LCAT
p<1e−10
p>0.05
G5S
P7R
T12M
A23V
T37M
V52M
G54S
L56P
K77Q
W85R
W99R
Y107*
I122M
G128S
T147I
R159W
R164C
Y168C
R171Q
E179G
E179*
Y180N
R182C
Y195*
I202T
Y213C
R217C
R225C
F226L
G229V
L233P
A235T
G238*
G239S
R268H
M276T
R280C
T298I
R300C
D301E
R347C
D352H
D352N
V372A
A373V
R375C
S376N
V405A
R423C
R423G
R423S


Gene=LCAT; Chr=1; Phenotype=HDL cholesterol; Gene effect size=−0.78
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
P7R
G16L
H35R
K77Q
V158M
Y195*
R300C
P360T
Variant effect size
G5S
T12M
A23V
T37M
L51V
V52M
G54S
L56P
R76G
W85R
W99R
Y107*
I122M
G128S
T147I
R159W
R164C
Y168C
R171Q
E179G
E179*
Y180N
R182C
V188M
I202T
Y213C
R217C
R225C
F226L
G229V
L233P
A235T
G238*
G239S
R268H
M276T
R280C
T298I
D301E
R304H
R347C
D352H
D352N
V372A
A373V
R375C
S376N
V405A
R423C
R423G
R423S
p<1e−10
p>0.05
Amino acid position
PF02450: LCAT


Gene=LDLR; Chr=1; Phenotype=E78.0 Pure hypercholesterolaemia; Gene effect size=0.08
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
Variant effect size
Amino acid position
PF00057: Ldl_recept_a
PF00058: Ldl_recept_b
PF07645: EGF_CA
PF14670: FXa_inhibition
p<1e−10
p>0.05
I40*
E58V
T62M
R78C
R78H
W87G
G98S
E101K
c.313+1G>C
c.313_313+1del
E113K
D168N
D170N
G219del
D221G
F241S
F241L
C296Y
K311T
E317K
R350*
R350P
D362A
Q378P
D386Y
A399T
E418K
V429M
A431P
D472Y
D482N
K518R
I542N
G546*
G545E
G546V
R574C
A606D
W620C
R633S
C677R
P685L
N688*
G701S
A705S
R751W
R814W
H837R
S849L
R850K
S854G
L855V
A860V
D47N
D72*
G71R
G76W
R81C
C89Y
c.313+1G>A
R115C
V127I
C167*
D170G
G207D
D227*
D227E
E228*
R237H
R237P
E240K
S244C
Q254E
R257W
D266E
G287S
E288K
C289S
R303W
D304E
G314R
G335S
E337K
D342H
R351I
D354G
I355M
V369M
A399D
R406W
R406Q
E408K
T413M
A475V
D492N
A501V
V506M
T510M
G516S
V523M
D525E
F530V
M531K
K543N
N564S
V578I
S580T
L582P
R595W
A612V
E626K
N632H
R633C
R633H
E650K
H656N
G663E
G676S
Y679*
C681S
I687F
S691L
G701V
M702I
D707N
M708V
M708T
T734I
T761M
V787M
A789T
F801C
L802F
L804P
V806F
K816N
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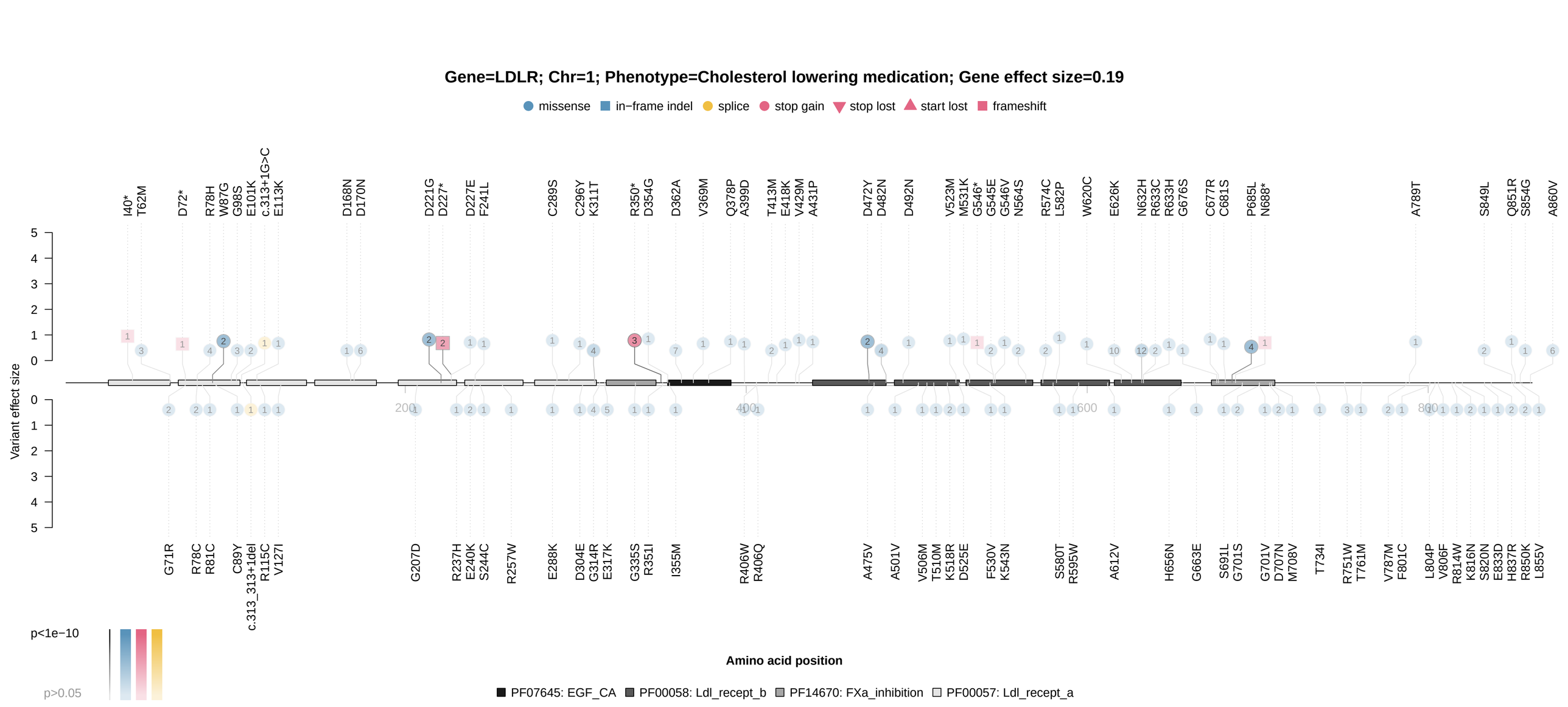
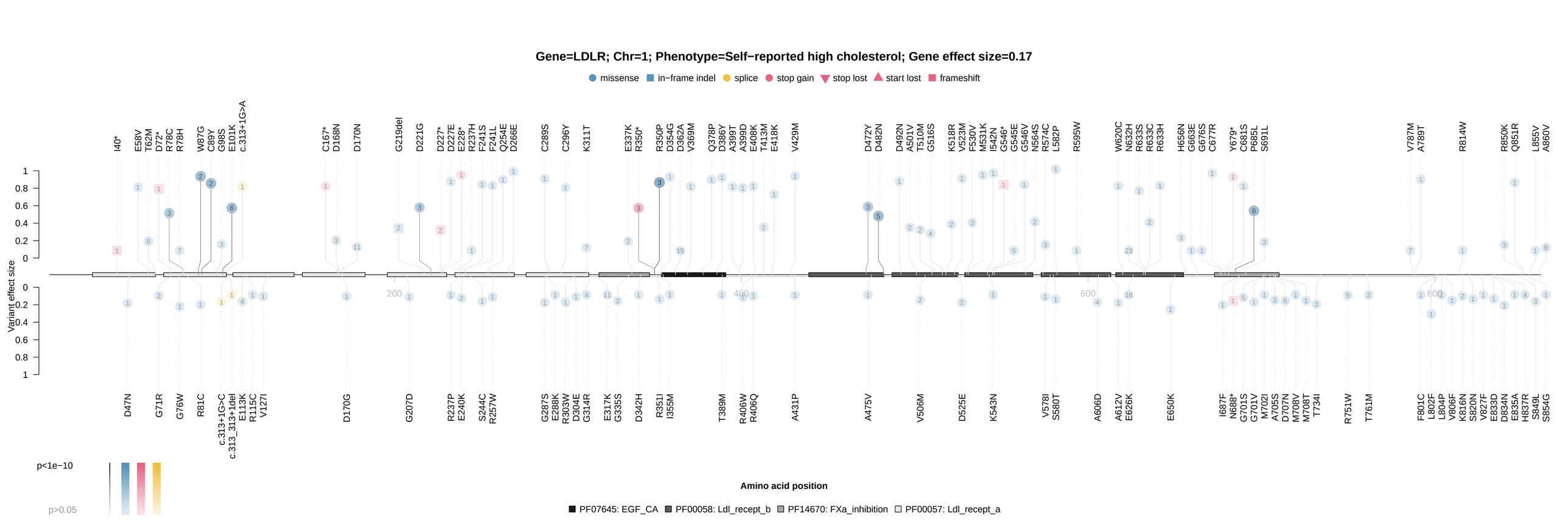
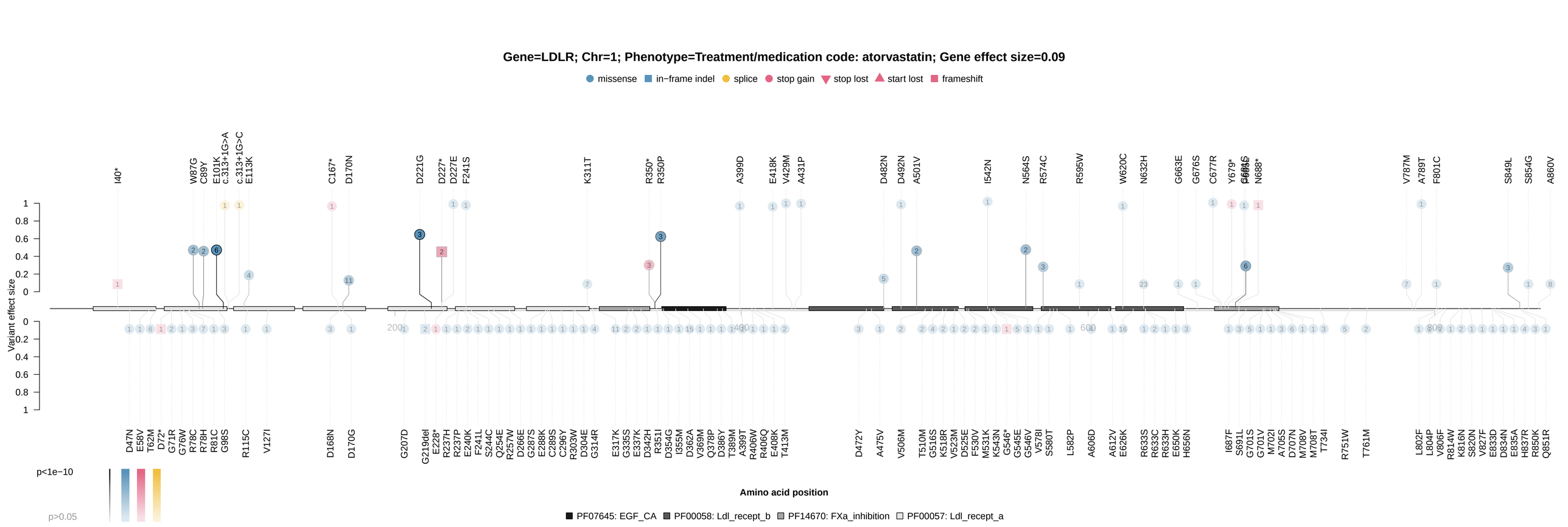
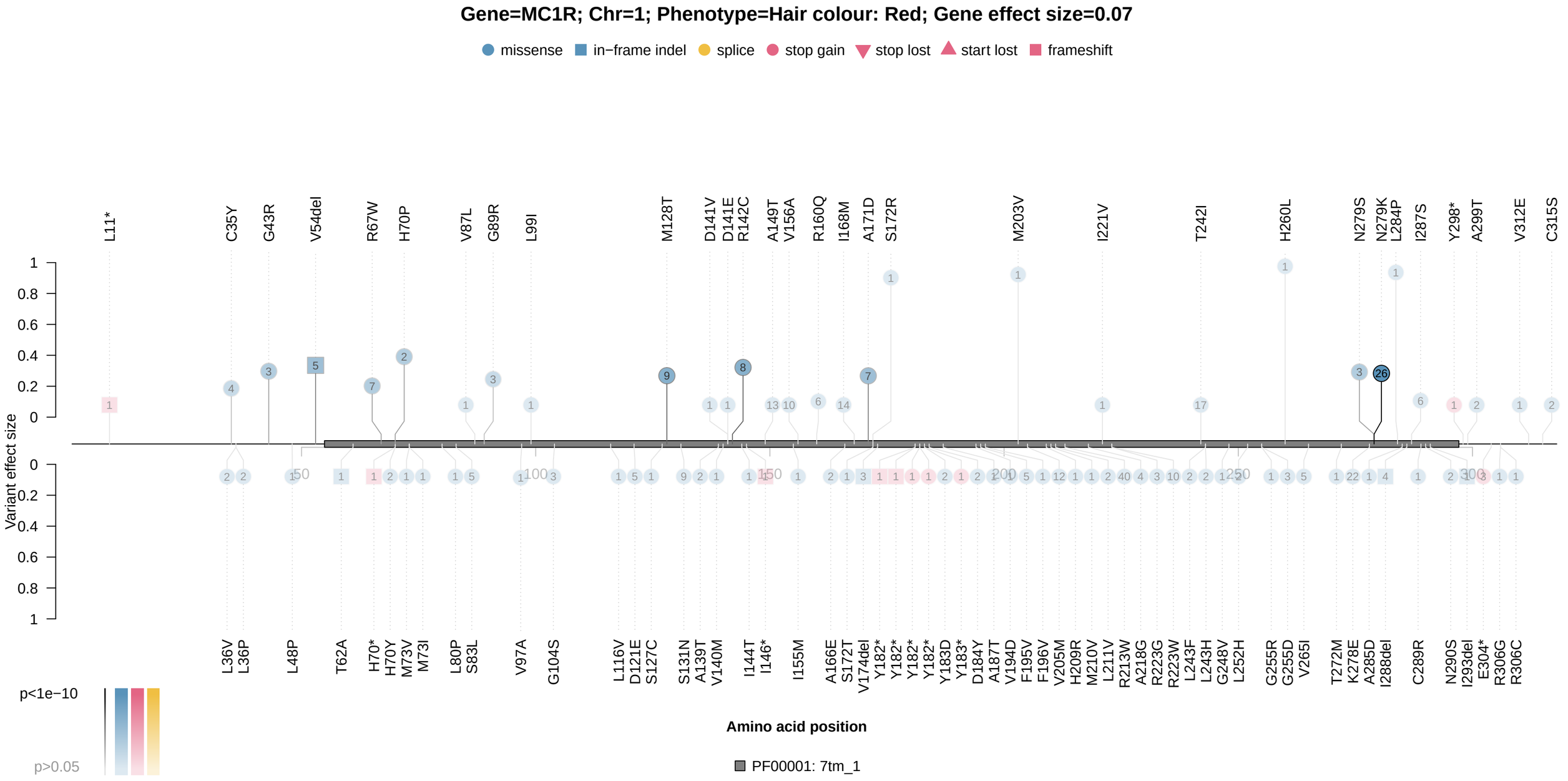
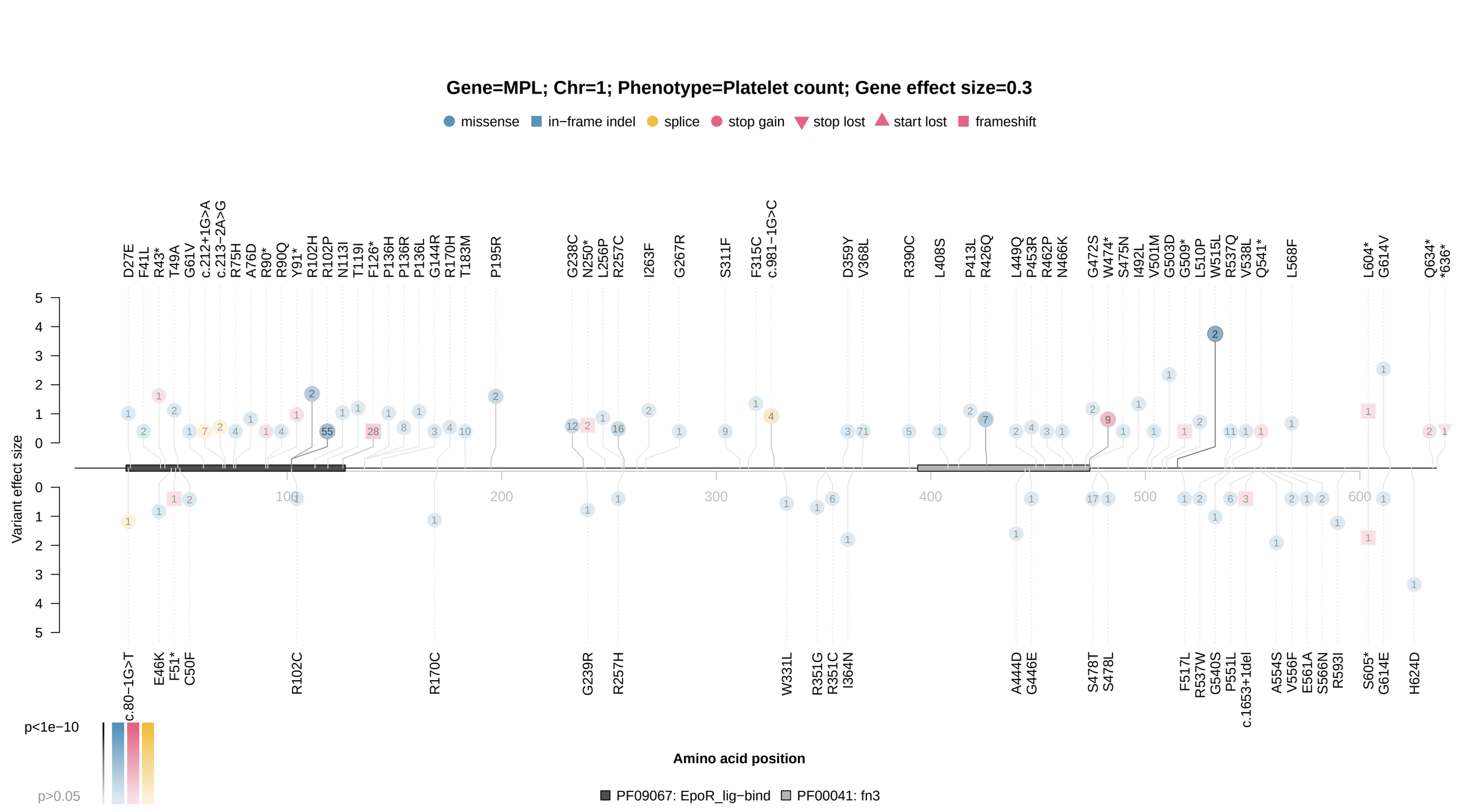
V827F
E833D
D834N
E835A
Q851R

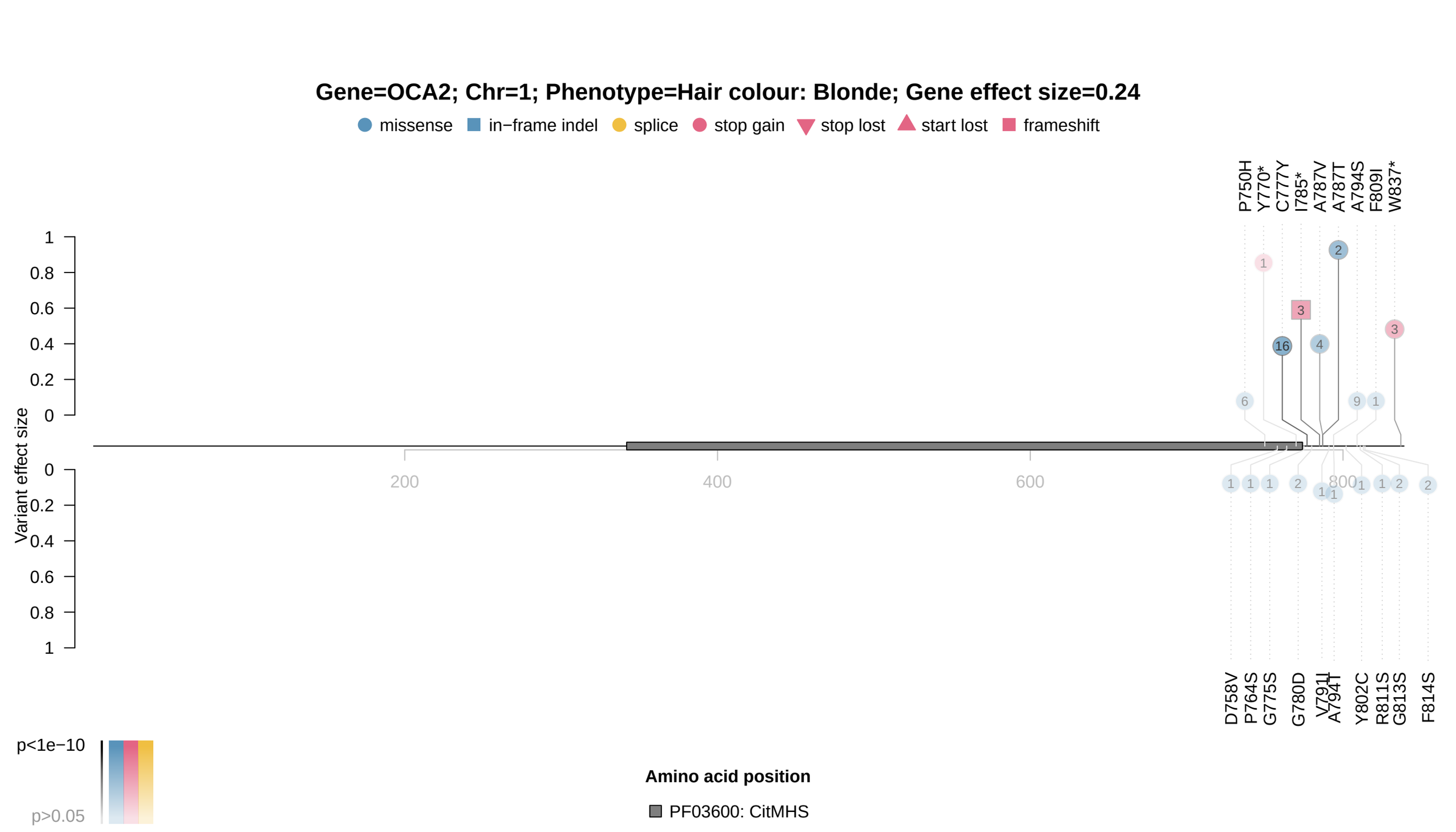

Gene=LDLR; Chr=1; Phenotype=Cholesterol lowering medication; Gene effect size=0.19
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
I40*
T62M
D72*
R78H
W87G
G98S
E101K
c.313+1G>C
E113K
D168N
D170N
D221G
D227*
D227E
F241L
C289S
C296Y
K311T
R350*
D354G
D362A
V369M
Q378P
A399D
T413M
E418K
V429M
A431P
D472Y
D482N
D492N
V523M
M531K
G546*
G545E
G546V
N564S
R574C
L582P
W620C
E626K
N632H
R633C
R633H
G676S
C677R
C681S
P685L
N688*
A789T
S849L
Q851R
S854G
A860V
Variant effect size
5
4
3
2
1
0
0
1
2
3
4
5
200
400
600
800
G71R
R78C
R81C
C89Y
c.313_313+1del
R115C
V127I
G207D
R237H
E240K
S244C
R257W
E288K
D304E
G314R
E317K
G335S
R351I
I355M
R406W
R406Q
A475V
A501V
V506M
T510M
K518R
D525E
F530V
K543N
S580T
R595W
A612V
H656N
G663E
S691L
G701S
G701V
D707N
M708V
T734I
R751W
T761M
V787M
F801C
L804P
V806F
R814W
K816N
S820N
E833D
H837R
R850K
L855V
p<1e−10
p>0.05
Amino acid position
PF07645: EGF_CA
PF00058: Ldl_recept_b
PF14670: FXa_inhibition
PF00057: Ldl_recept_a

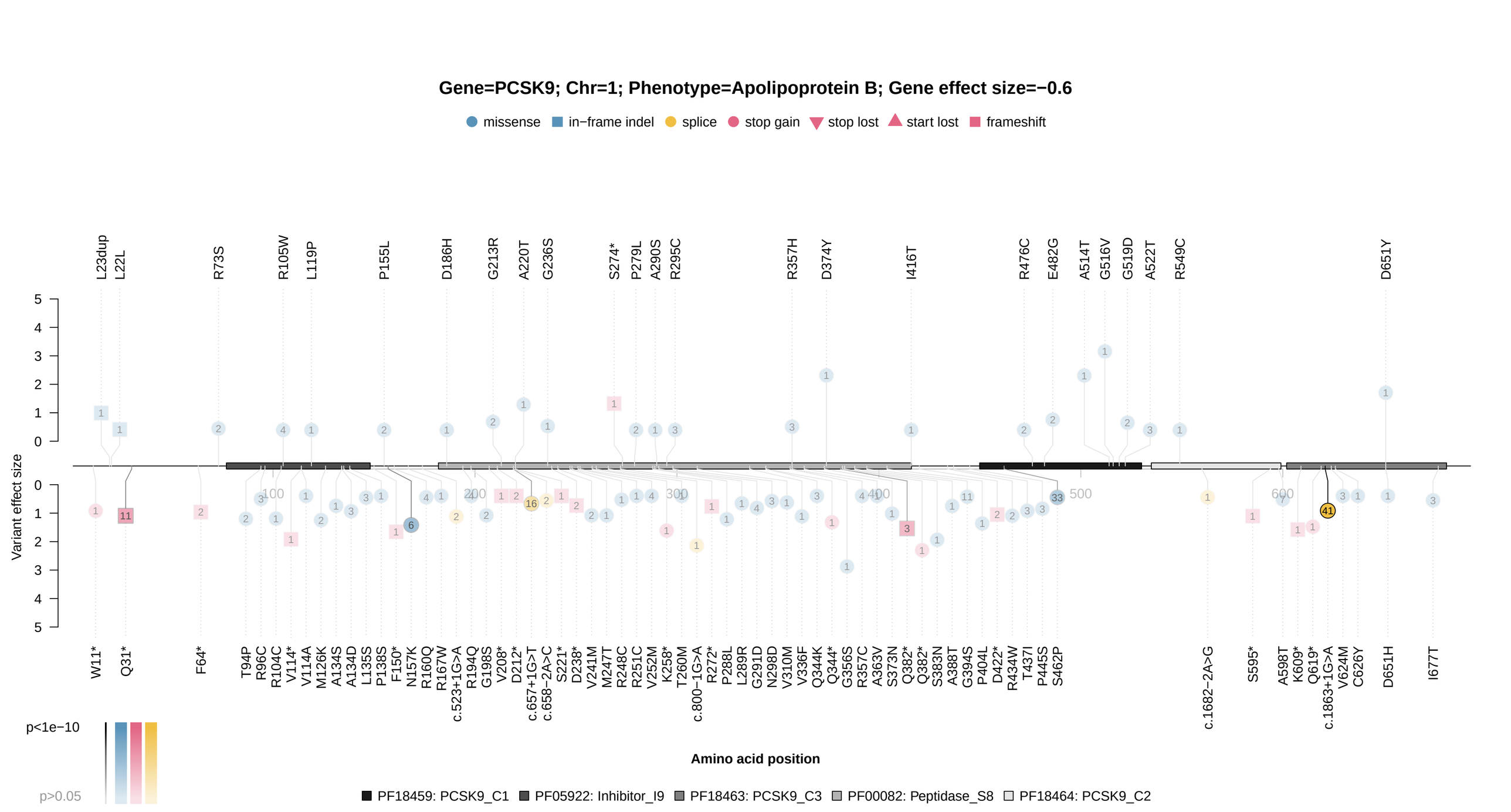

Gene=LDLR; Chr=1; Phenotype=Self−reported high cholesterol; Gene effect size=0.17
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
Variant effect size
Amino acid position
p<1e−10
p>0.05
PF07645: EGF_CA
PF00058: Ldl_recept_b
PF14670: FXa_inhibition
PF00057: Ldl_recept_a


Gene=LDLR; Chr=1; Phenotype=Treatment/medication code: atorvastatin; Gene effect size=0.09
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
Variant effect size
Amino acid position
p<1e−10
p>0.05
PF07645: EGF_CA
PF00058: Ldl_recept_b
PF14670: FXa_inhibition
PF00057: Ldl_recept_a


Gene=MC1R; Chr=1; Phenotype=Hair colour: Red; Gene effect size=0.07
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
L11*
C35Y
G43R
V54del
R67W
H70P
V87L
G89R
L99I
M128T
D141V
D141E
R142C
A149T
V156A
R160Q
I168M
A171D
S172R
M203V
I221V
T242I
H260L
N279S
N279K
L284P
I287S
Y298*
A299T
V312E
C315S
Variant effect size
1
0.8
0.6
0.4
0.2
0
L36V
L36P
L48P
T62A
H70*
H70Y
M73V
M73I
L80P
S83L
V97A
G104S
L116V
D121E
S127C
S131N
A139T
V140M
I144T
I146*
I155M
A166E
S172T
V174del
Y182*
Y182*
Y182*
Y182*
Y183D
Y183*
D184Y
A187T
V194D
F195V
F196V
V205M
H209R
M210V
L211V
R213W
A218G
R223G
R223W
L243F
L243H
G248V
L252H
G255R
G255D
V265I
T272M
K278E
A285D
I288del
C289R
N290S
I293del
E304*
R306G
R306C
p<1e−10
p>0.05
Amino acid position
PF00001: 7tm_1


Gene=MPL; Chr=1; Phenotype=Platelet count; Gene effect size=0.3
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
Variant effect size
Amino acid position
p<1e−10
p>0.05
PF09067: EpoR_lig−bind
PF00041: fn3


Gene=OCA2; Chr=1; Phenotype=Hair colour: Blonde; Gene effect size=0.24
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
Variant effect size
1
0.8
0.6
0.4
0.2
0
200
400
600
800
P750H
Y770*
C777Y
I785*
A787V
A787T
A794S
F809I
W837*
D758V
P764S
G775S
G780D
V791I
A794T
Y802C
R811S
G813S
F814S
p<1e−10
p>0.05
Amino acid position
PF03600: CitMHS


Gene=PCSK9; Chr=1; Phenotype=Apolipoprotein B; Gene effect size=−0.6
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
Variant effect size
Amino acid position
p<1e−10
p>0.05
PF18459: PCSK9_C1
PF05922: Inhibitor_I9
PF18463: PCSK9_C3
PF00082: Peptidase_S8
PF18464: PCSK9_C2

Gene=PCSK9; Chr=1; Phenotype=Apolipoprotein B; Gene effect size=−0.99

splice · stop gain · stop lost · start lost · frameshift

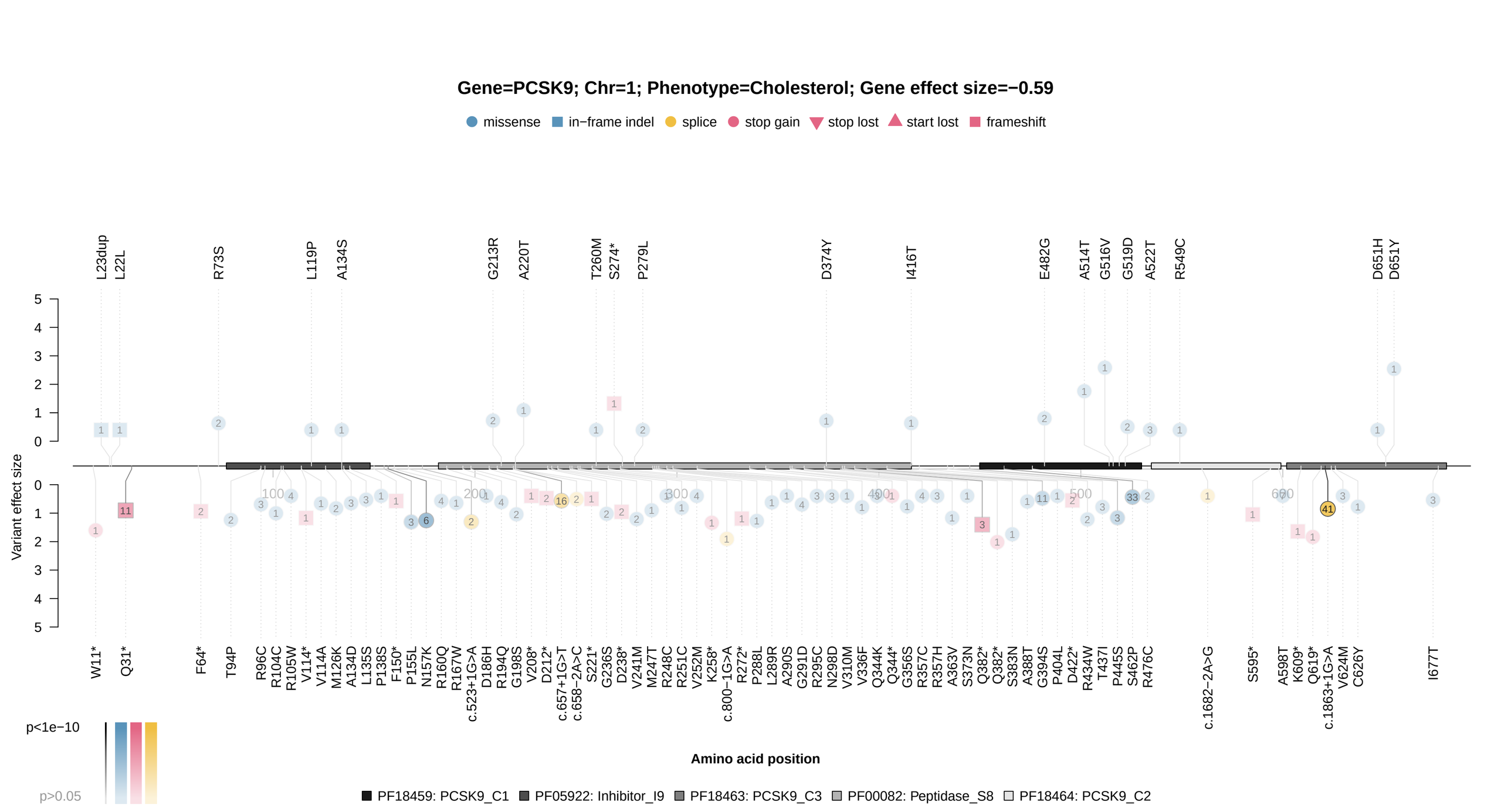
Variant effect size

Amino acid position

p<1e−10 … p>0.05

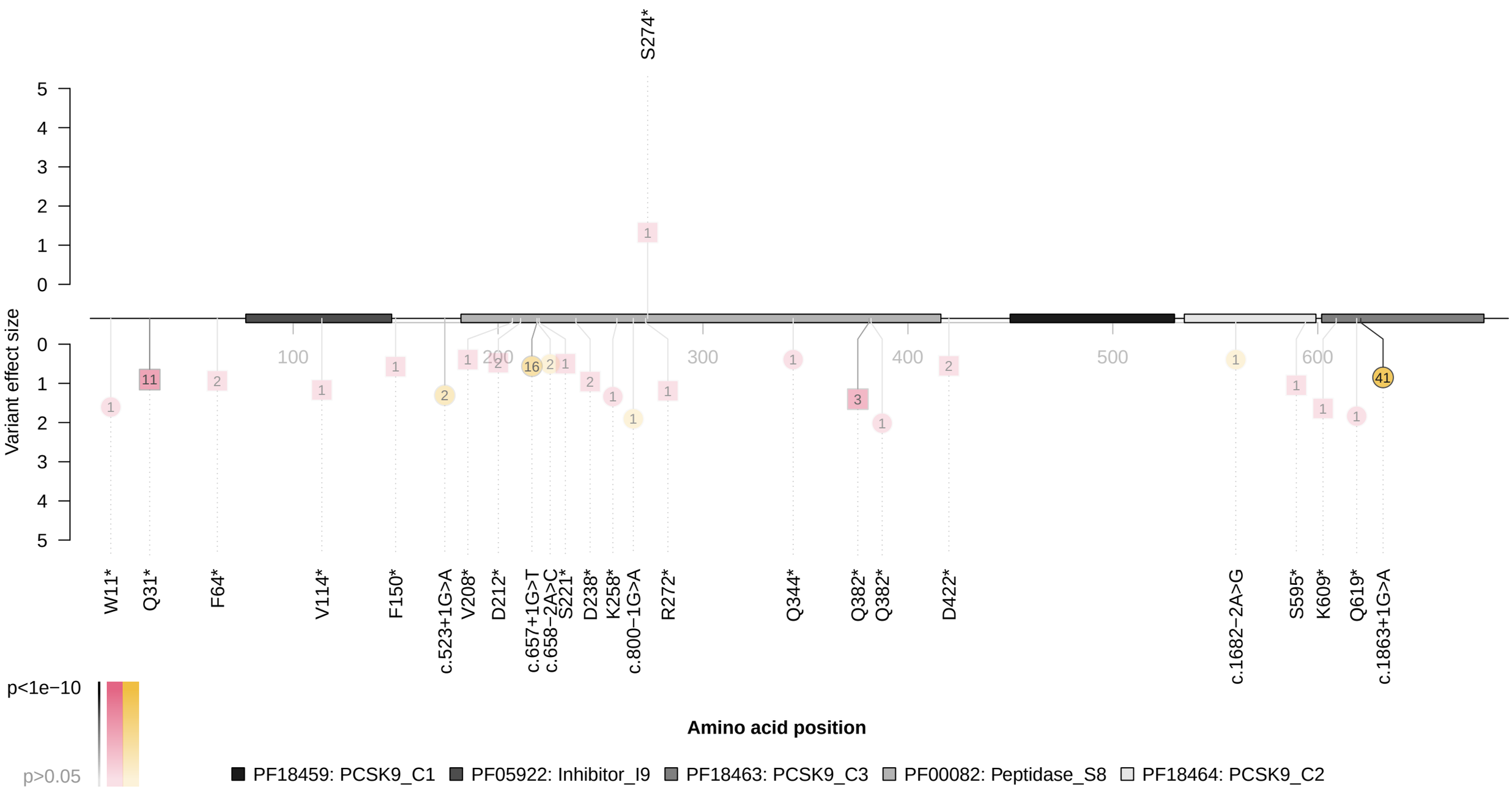
PF18459: PCSK9_C1 · PF05922: Inhibitor_I9 · PF18463: PCSK9_C3 · PF00082: Peptidase_S8 · PF18464: PCSK9_C2

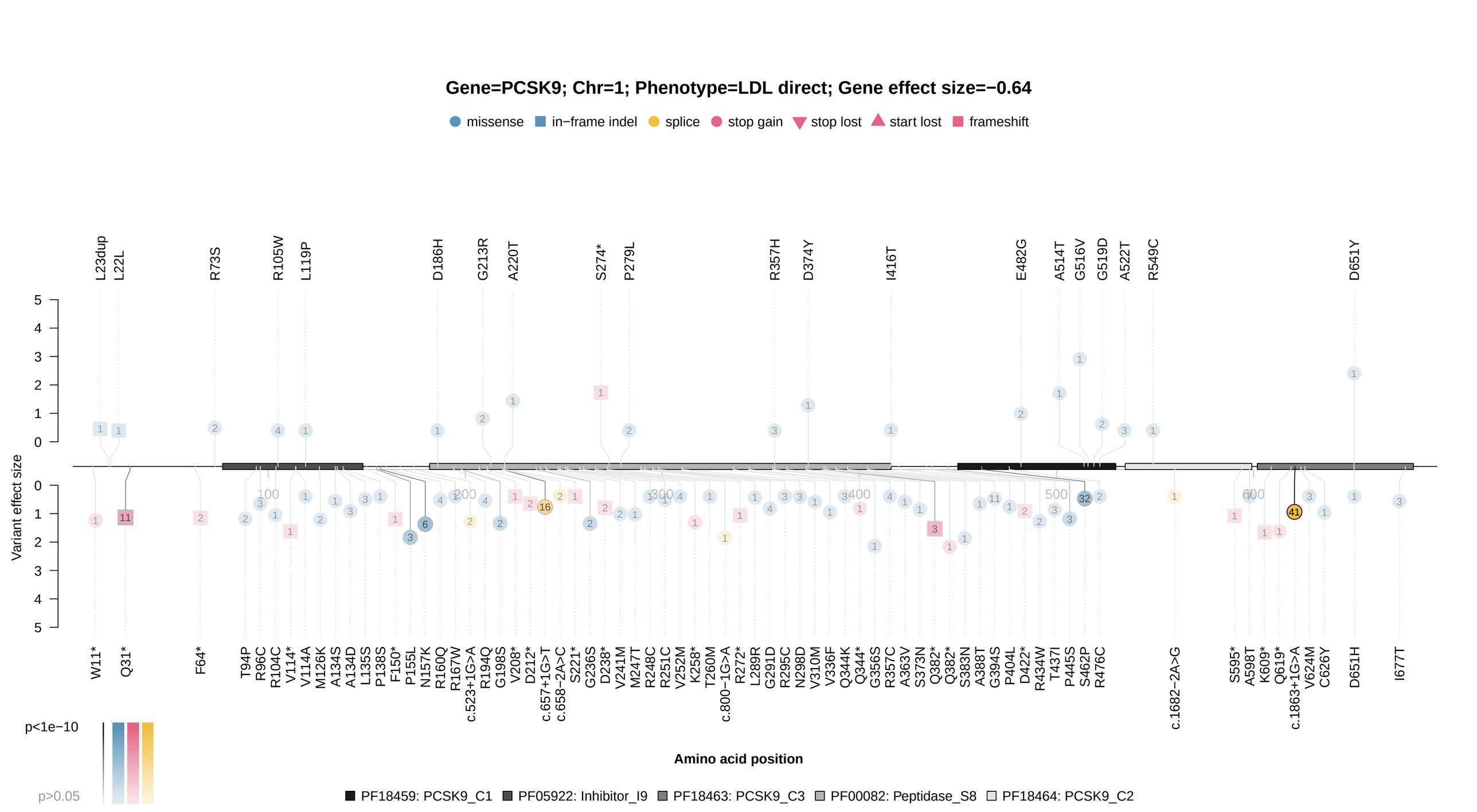
S274*
W11*
Q31*
F64*
V114*
F150*
c.523+1G>A
V208*
D212*
c.657+1G>T
c.658−2A>C
S221*
D238*
K258*
c.800−1G>A
R272*
Q344*
Q382*
Q382*
D422*
c.1682−2A>G
S595*
K609*
Q619*
c.1863+1G>A


Gene=PCSK9; Chr=1; Phenotype=Cholesterol; Gene effect size=−0.59
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
Variant effect size
Amino acid position
p<1e−10
p>0.05
PF18459: PCSK9_C1
PF05922: Inhibitor_I9
PF18463: PCSK9_C3
PF00082: Peptidase_S8
PF18464: PCSK9_C2
L23dup
L22L
R73S
L119P
A134S
G213R
A220T
T260M
S274*
P279L
D374Y
I416T
E482G
A514T
G516V
G519D
A522T
R549C
D651H
D651Y
W11*
Q31*
F64*
T94P
R96C
R104C
R105W
V114*
V114A
M126K
A134D
L135S
P138S
F150*
P155L
N157K
R160Q
R167W
c.523+1G>A
D186H
R194Q
G198S
V208*
D212*
c.657+1G>T
c.658−2A>C
S221*
G236S
D238*
V241M
M247T
R248C
R251C
V252M
K258*
c.800−1G>A
R272*
P288L
L289R
A290S
G291D
R295C
N298D
V310M
V336F
Q344K
Q344*
G356S
R357C
R357H
A363V
S373N
Q382*
Q382*
S383N
A388T
G394S
P404L
D422*
R434W
T437I
P445S
S462P
R476C
c.1682−2A>G
S595*
A598T
K609*
Q619*
c.1863+1G>A
V624M
C626Y
I677T

Gene=PCSK9; Chr=1; Phenotype=Cholesterol; Gene effect size=−0.9

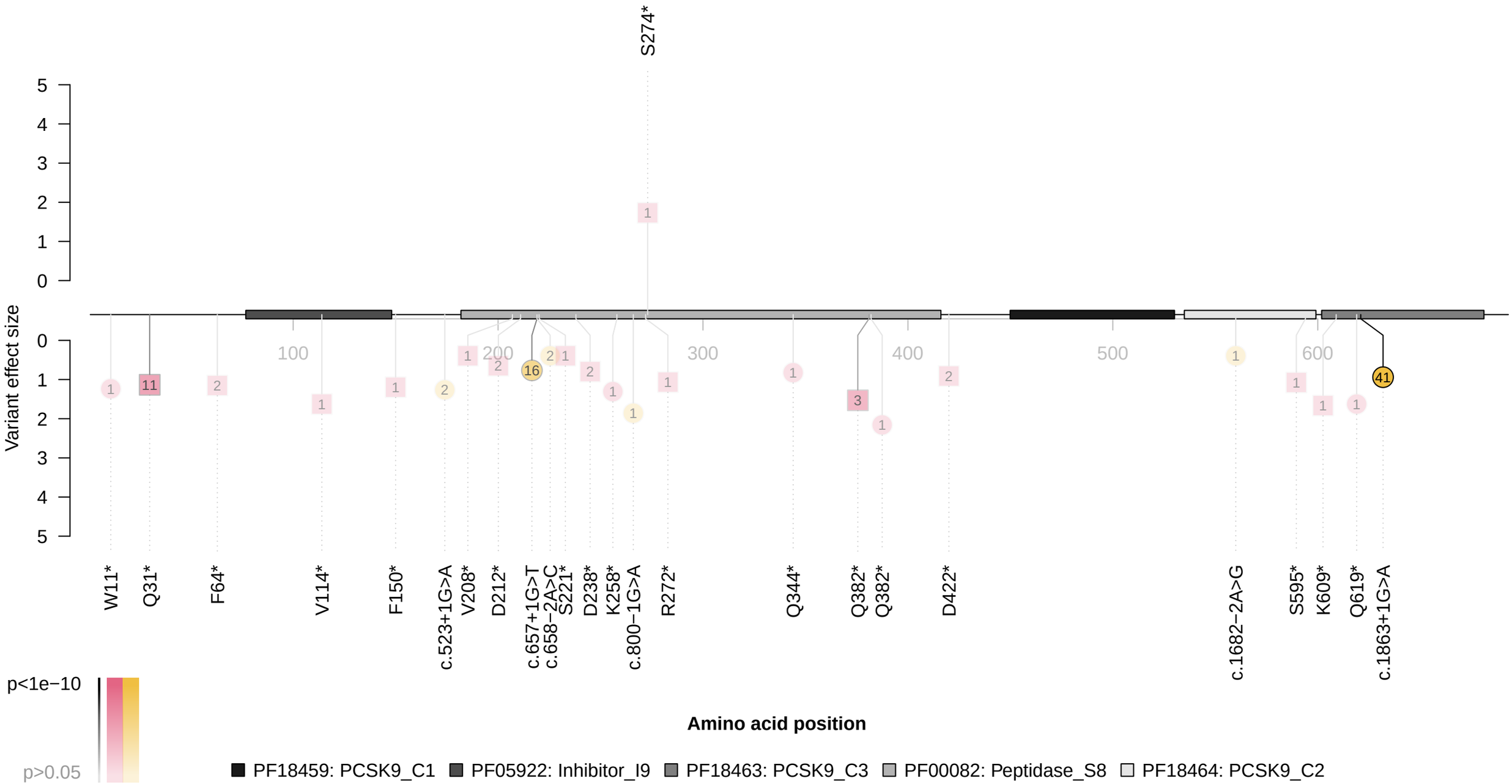
splice · stop gain · stop lost · start lost · frameshift




Gene=PCSK9; Chr=1; Phenotype=LDL direct; Gene effect size=−0.64
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
Variant effect size
Amino acid position
p<1e−10
p>0.05
PF18459: PCSK9_C1
PF05922: Inhibitor_I9
PF18463: PCSK9_C3
PF00082: Peptidase_S8
PF18464: PCSK9_C2
L23dup
L22L
R73S
R105W
L119P
D186H
G213R
A220T
S274*
P279L
R357H
D374Y
I416T
E482G
A514T
G516V
G519D
A522T
R549C
D651Y
W11*
Q31*
F64*
T94P
R96C
R104C
V114*
V114A
M126K
A134S
A134D
L135S
P138S
F150*
P155L
N157K
R160Q
R167W
c.523+1G>A
R194Q
G198S
V208*
D212*
c.657+1G>T
c.658−2A>C
S221*
G236S
D238*
V241M
M247T
R248C
R251C
V252M
K258*
T260M
c.800−1G>A
R272*
L289R
G291D
R295C
N298D
V310M
V336F
Q344K
Q344*
G356S
R357C
A363V
S373N
Q382*
Q382*
S383N
A388T
G394S
P404L
D422*
R434W
T437I
P445S
S462P
R476C
c.1682−2A>G
S595*
A598T
K609*
Q619*
c.1863+1G>A
V624M
C626Y
D651H
I677T

Gene=PCSK9; Chr=1; Phenotype=LDL direct; Gene effect size=−1.02

splice · stop gain · stop lost · start lost · frameshift



Gene=SCARB1; Chr=1; Phenotype=HDL cholesterol; Gene effect size=0.5

missense | in−frame indel | splice | stop gain | stop lost | start lost | frameshift

P48A P84L G90R V93M K100I F121I G128S P137S A145V P152L A162E R174C T175A E178V W181R S216C V221M V234* V234M G239R c.727−2A>G D249Y P263L P277L

Variant effect size

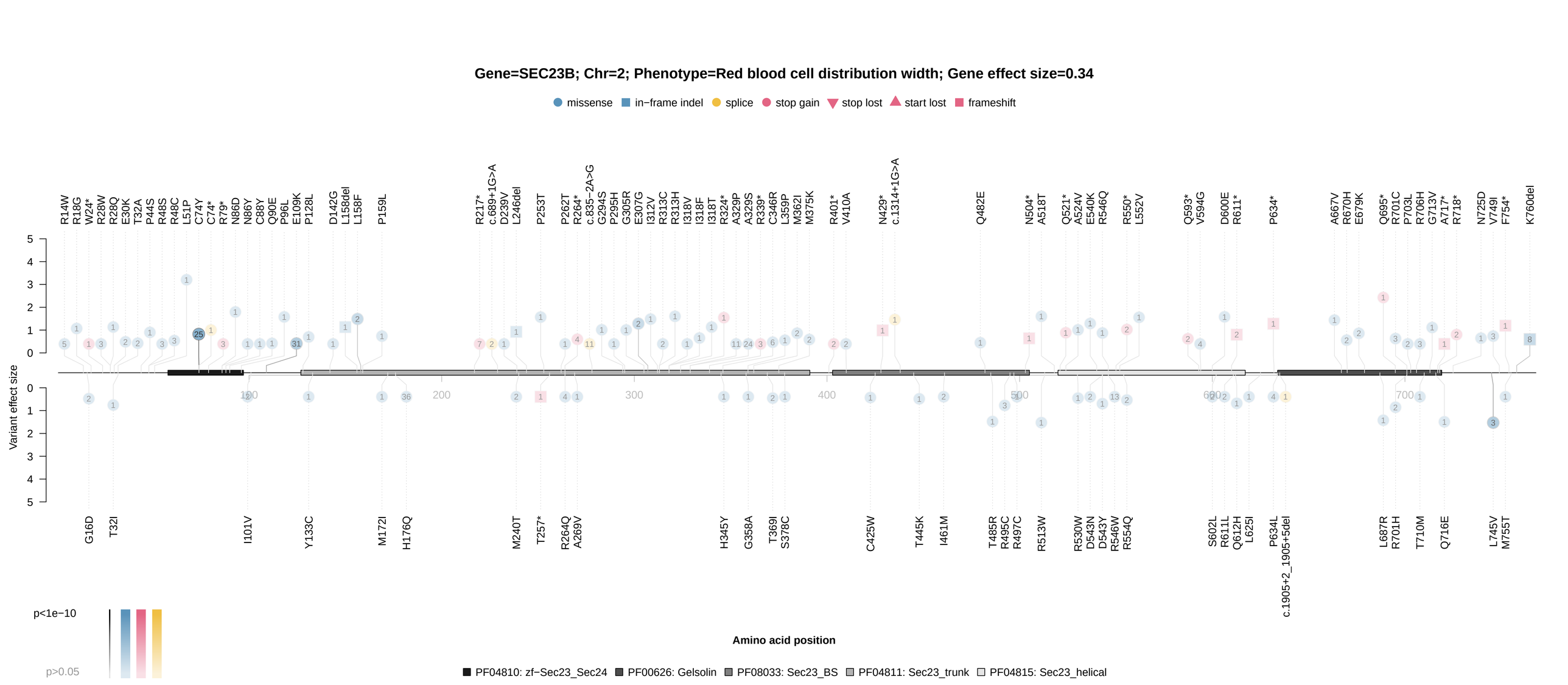
L19P V44M W56* E96G P123H L157P E168K N213T T223M

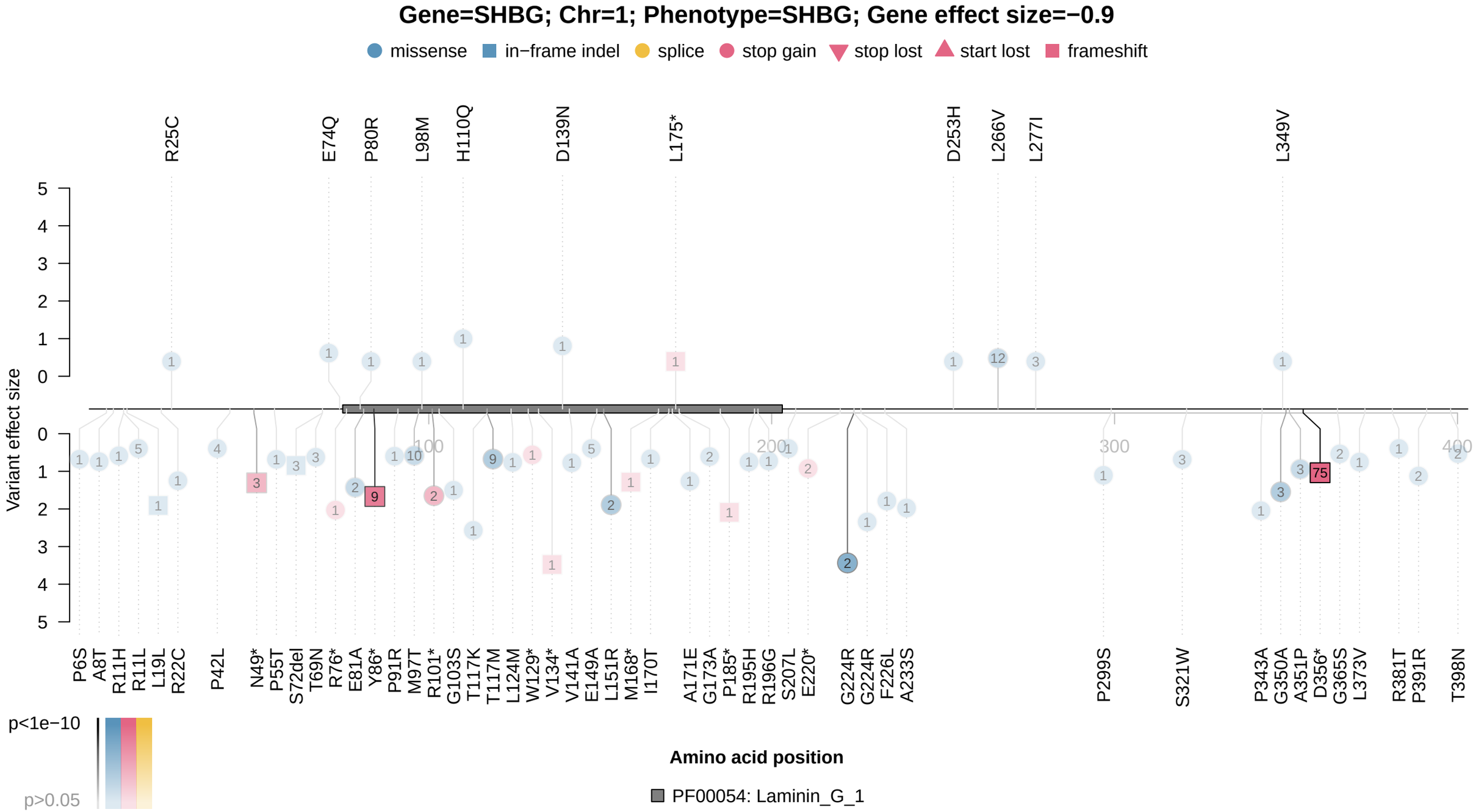
p<1e−10

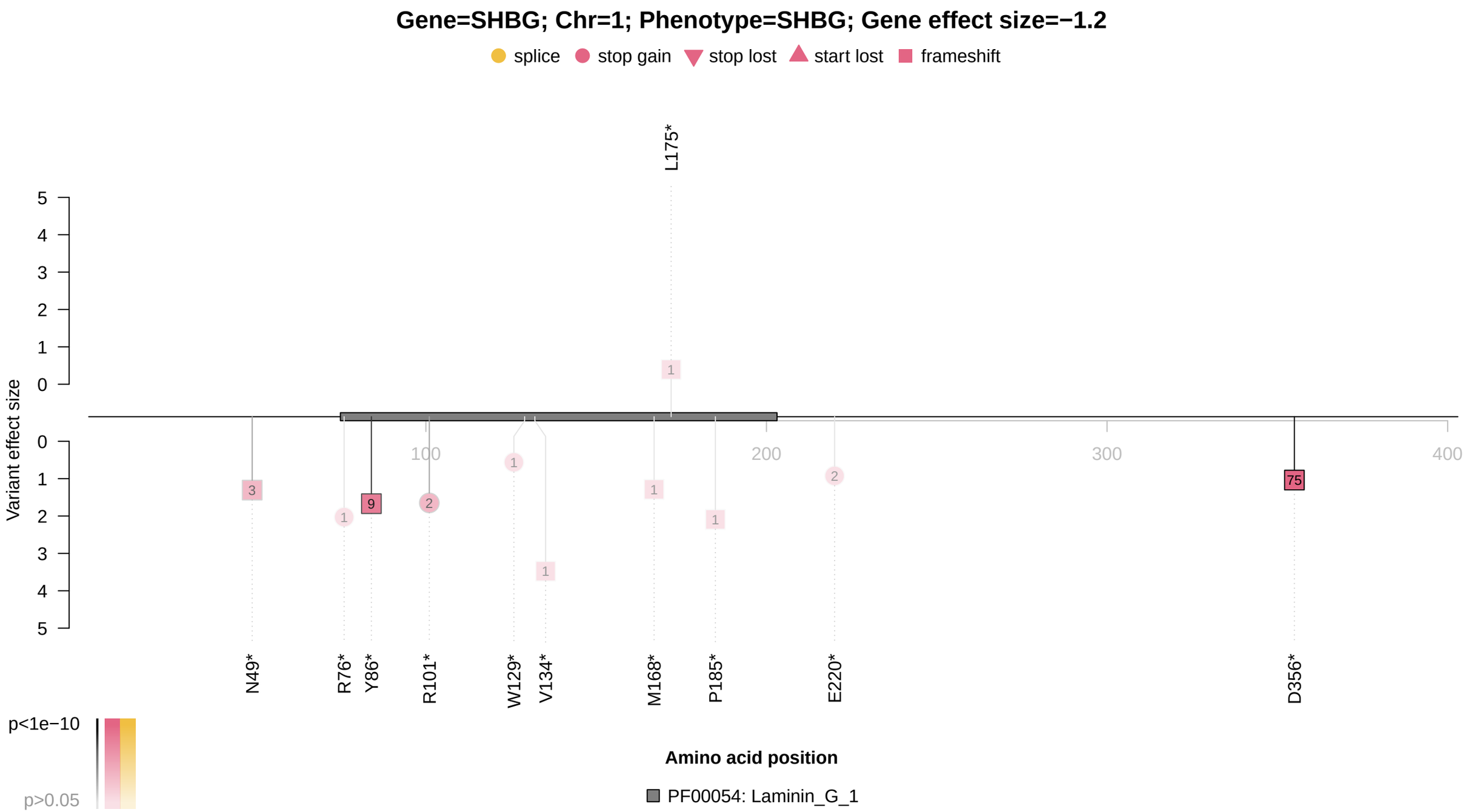
p>0.05

Amino acid position

PF01130: CD36

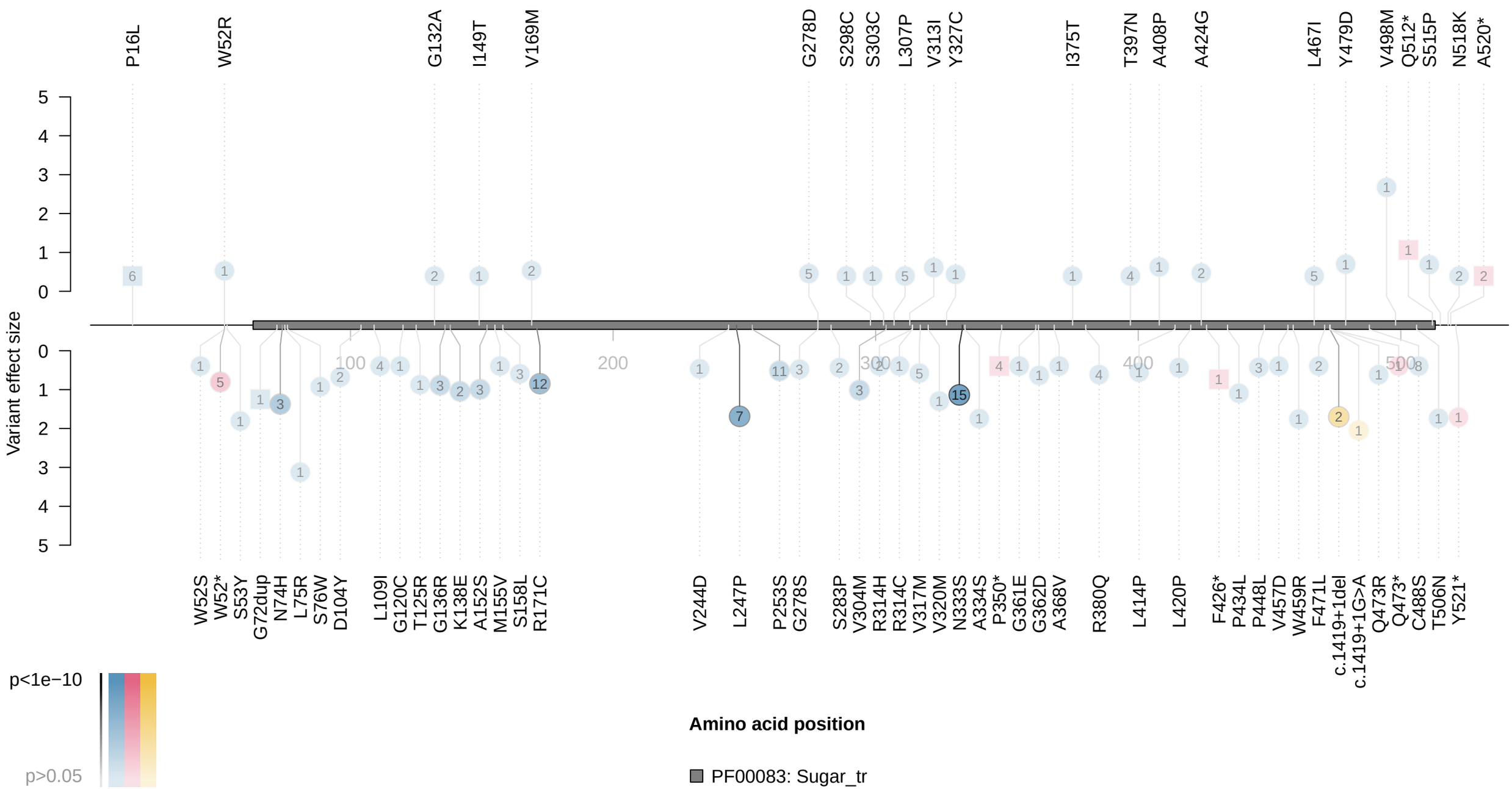

Gene=SEC23B; Chr=2; Phenotype=Red blood cell distribution width; Gene effect size=0.34
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
Variant effect size
Amino acid position
p<1e−10
p>0.05
PF04810: zf−Sec23_Sec24
PF00626: Gelsolin
PF08033: Sec23_BS
PF04811: Sec23_trunk
PF04815: Sec23_helical


Gene=SHBG; Chr=1; Phenotype=SHBG; Gene effect size=−0.9
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
R25C
E74Q
P80R
L98M
H110Q
D139N
L175*
D253H
L266V
L277I
L349V
Variant effect size
P6S
A8T
R11H
R11L
L19L
R22C
P42L
N49*
P55T
S72del
T69N
R76*
E81A
Y86*
P91R
M97T
R101*
G103S
T117K
T117M
L124M
W129*
V134*
V141A
E149A
L151R
M168*
I170T
A171E
G173A
P185*
R195H
R196G
S207L
E220*
G224R
G224R
F226L
A233S
P299S
S321W
P343A
G350A
A351P
D356*
G365S
L373V
R381T
P391R
T398N
Amino acid position
p<1e−10
p>0.05
PF00054: Laminin_G_1


Gene=SHBG; Chr=1; Phenotype=SHBG; Gene effect size=−1.2
splice
stop gain
stop lost
start lost
frameshift
Variant effect size
5
4
3
2
1
0
0
1
2
3
4
5
100
200
300
400
L175*
N49*
R76*
Y86*
R101*
W129*
V134*
M168*
P185*
E220*
D356*
3
1
9
2
1
1
1
1
2
75
p<1e−10
p>0.05
Amino acid position
PF00054: Laminin_G_1

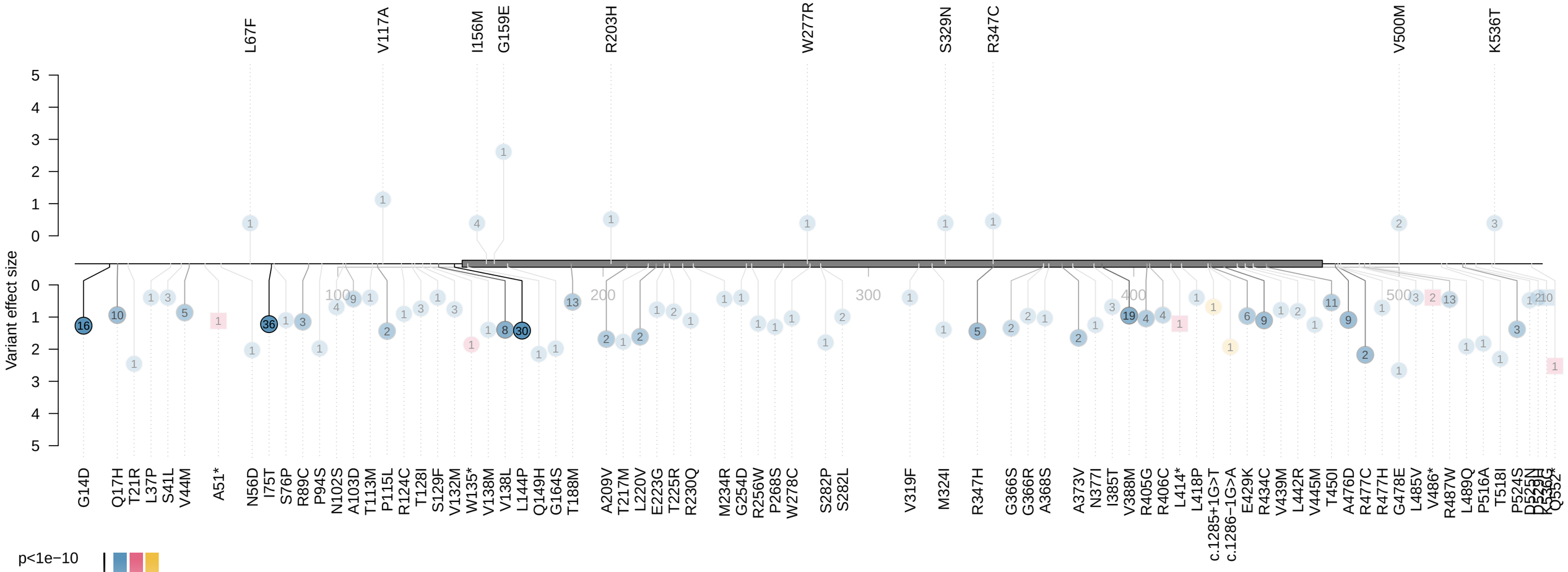
Gene=SLC2A9; Chr=4; Phenotype=Urate; Gene effect size=−0.6

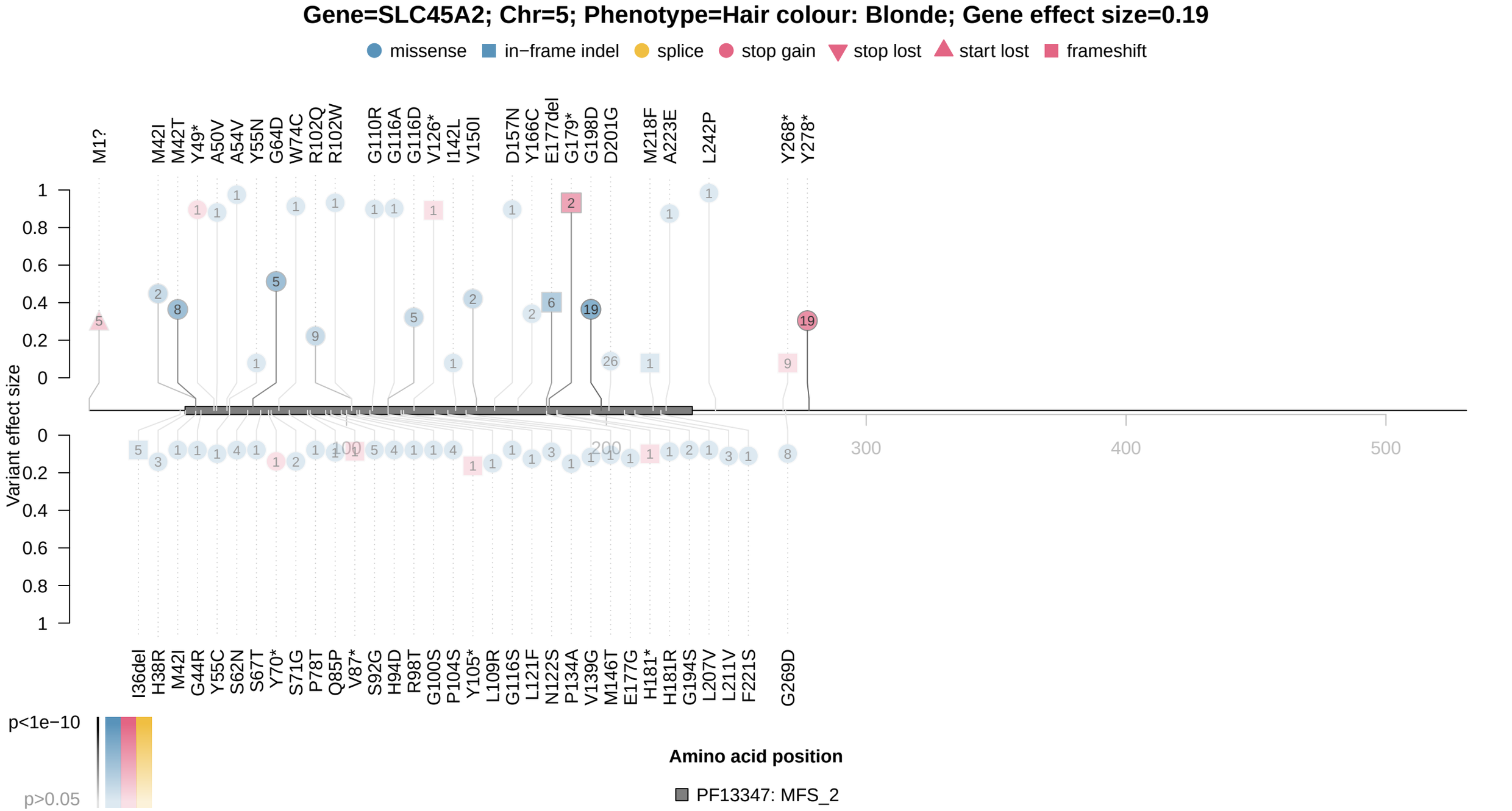
missense | in−frame indel | splice | stop gain | stop lost | start lost | frameshift

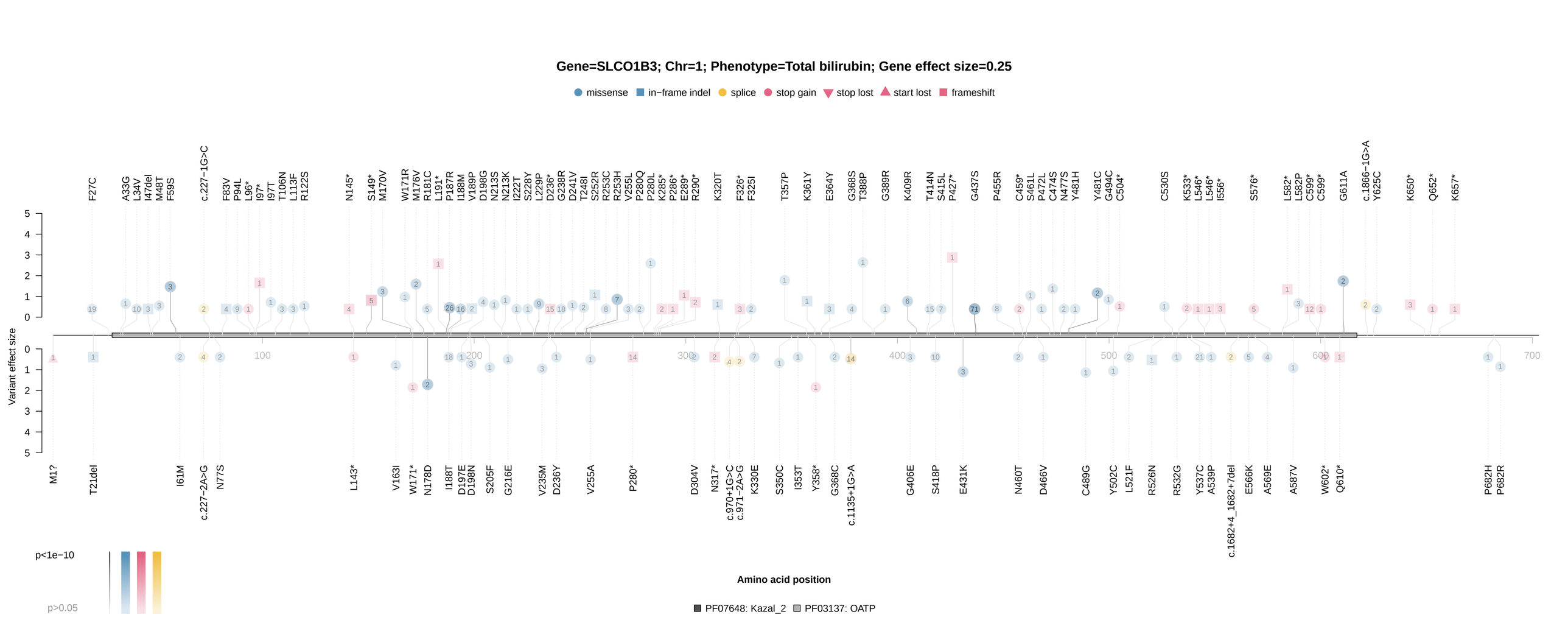


Gene=SLC22A12; Chr=1; Phenotype=Urate; Gene effect size=−1.02

missense | in−frame indel | splice | stop gain | stop lost | start lost | frameshift




Gene=SLC45A2; Chr=5; Phenotype=Hair colour: Blonde; Gene effect size=0.19
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
M1?
M42I
M42T
Y49*
A50V
A54V
Y55N
G64D
W74C
R102Q
R102W
G110R
G116A
G116D
V126*
I142L
V150I
D157N
Y166C
E177del
G179*
G198D
D201G
M218F
A223E
L242P
Y268*
Y278*
Variant effect size
100
200
300
400
500
I36del
H38R
M42I
G44R
Y55C
S62N
S67T
Y70*
S71G
P78T
Q85P
V87*
S92G
H94D
R98T
G100S
P104S
Y105*
L109R
G116S
L121F
N122S
P134A
V139G
M146T
E177G
H181*
H181R
G194S
L207V
L211V
F221S
G269D
p<1e−10
p>0.05
Amino acid position
PF13347: MFS_2


Gene=SLCO1B3; Chr=1; Phenotype=Total bilirubin; Gene effect size=0.25
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
Variant effect size
Amino acid position
p<1e−10
p>0.05
PF07648: Kazal_2
PF03137: OATP
M1?
T21del
I61M
c.227−2A>G
N77S
L143*
V163I
W171*
N178D
I188T
D197E
D198N
S205F
G216E
V235M
D236Y
V255A
P280*
D304V
N317*
c.970+1G>C
c.971−2A>G
K330E
S350C
I353T
Y358*
G368C
c.1135+1G>A
G406E
S418P
E431K
N460T
D466V
C489G
Y502C
L521F
R526N
R532G
Y537C
A539P
c.1682+4_1682+7del
E566K
A569E
A587V
W602*
Q610*
P682H
P682R

Gene=SMAD6; Chr=1; Phenotype=6mm weak meridian (right); Gene effect size=0.93

splice stop gain stop lost start lost frameshift

M1? R3* Q74* R75* G114* W115* C126* D120* C126* S130* S158* Y177* V201* P209* L207* F230* W232* Q236* C247* c.818−2del Y300* c.952+2T>C Y350* F389* G433* E442*

Variant effect size

R91* A153* T190* Q223* E396* Y434* K437* D440*

p<1e−10

p>0.05

Amino acid position

PF03166: MH2 PF03165: MH1

Gene=STAB1; Chr=3; Phenotype=Median T2star in caudate (left); Gene effect size=0.93

splice stop gain stop lost start lost frameshift

G31*
Q76*
E117*
R231*
Q375*
K460*
c.1831−2A>C
N680*
C908*
R931*
R1122*
c.4638+1G>T
S1559*
R1584*
Q1661*
V1689*
E1712*
F1826*
Q1847*
c.5908+1G>C
Q1994*
Q2242*
Q2350*
H2410*
A2477*
A2482*
R2502*
E2516*
F2523*
E2528*

Variant effect size

0 1 2 3 4 5

0 1 2 3 4 5

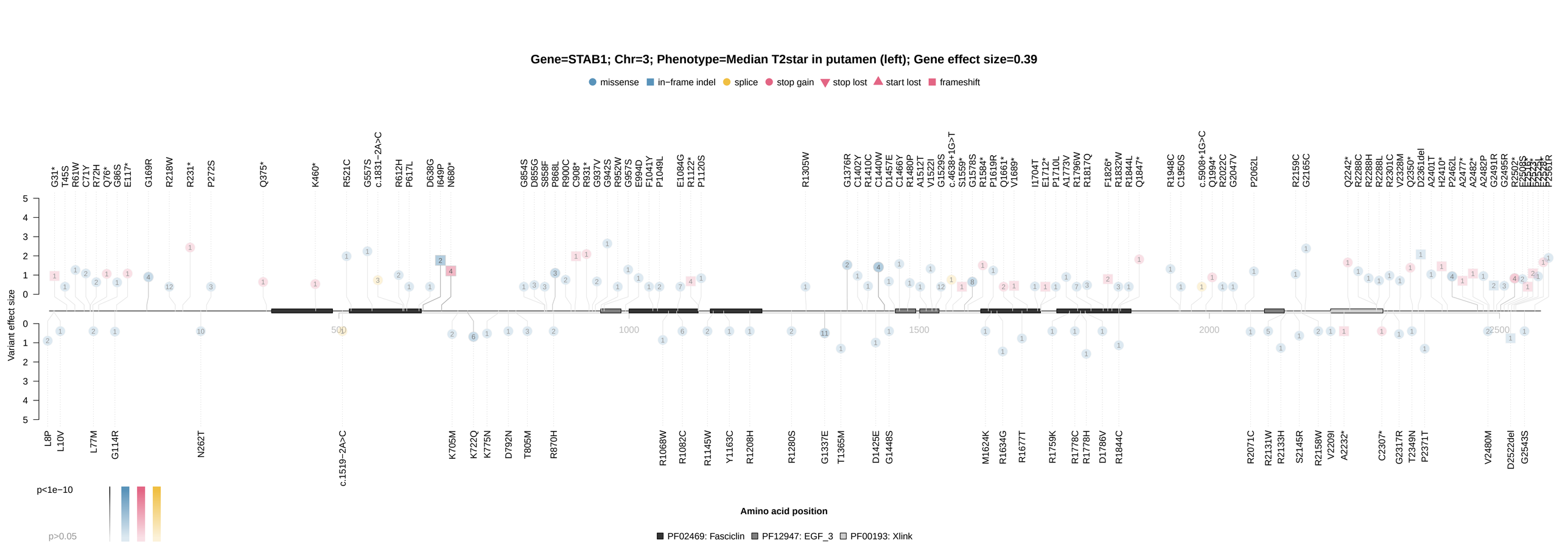
500 1000 1500 2000 2500

c.1519−2A>C
A2232*
C2307*

p<1e−10
p>0.05

Amino acid position

PF00193: Xlink PF12947: EGF_3 PF02469: Fasciclin


Gene=STAB1; Chr=3; Phenotype=Median T2star in putamen (left); Gene effect size=0.39
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
Variant effect size
Amino acid position
p<1e−10
p>0.05
PF02469: Fasciclin
PF12947: EGF_3
PF00193: Xlink

Gene=STAB1; Chr=3; Phenotype=Median T2star in putamen (left); Gene effect size=0.94

splice stop gain stop lost start lost frameshift

G31* Q76* E117* R231* Q375* K460* c.1831−2A>C N680* C908* R931* R1122* c.4638+1G>T S1559* R1584* Q1661* V1689* E1712* F1826* Q1847* c.5908+1G>C Q1994* Q2242* Q2350* H2410* A2477* A2482* R2502* E2516* F2523* E2528*

Variant effect size

5 4 3 2 1 0 0 1 2 3 4 5

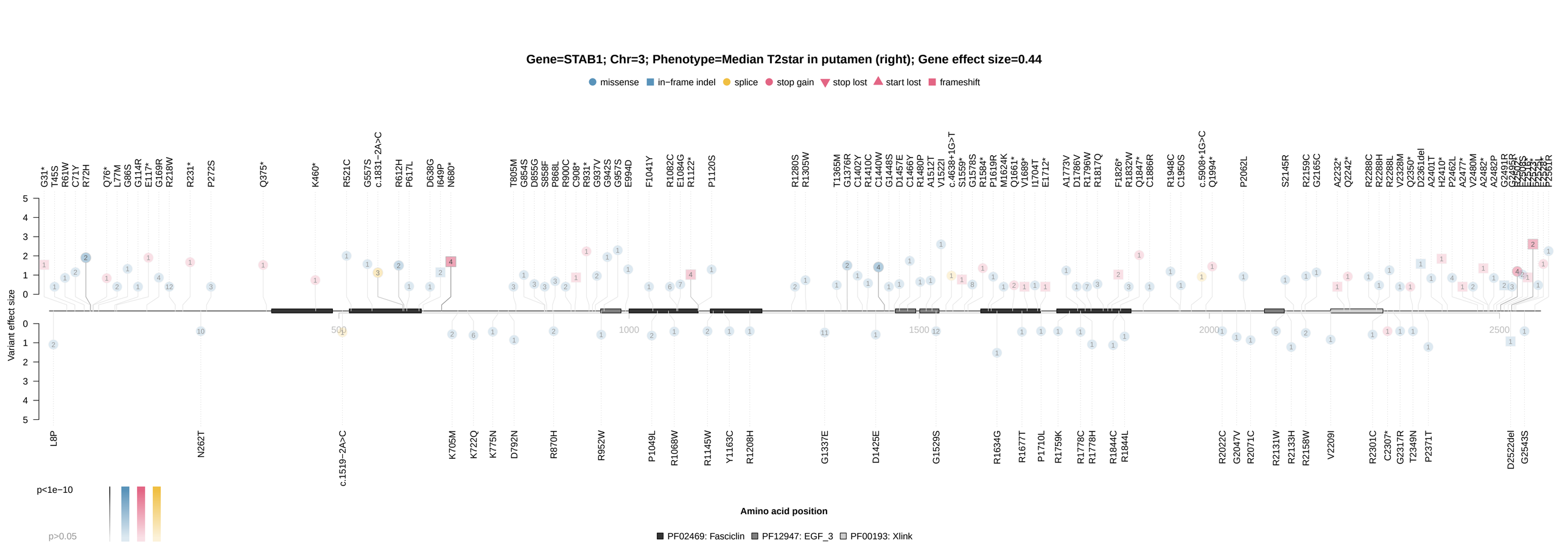
500 1000 1500 2000 2500

c.1519−2A>C A2232* C2307*

p<1e−10 p>0.05

Amino acid position

PF00193: Xlink PF12947: EGF_3 PF02469: Fasciclin


Gene=STAB1; Chr=3; Phenotype=Median T2star in putamen (right); Gene effect size=0.44
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
Variant effect size
Amino acid position
p<1e−10
p>0.05
PF02469: Fasciclin
PF12947: EGF_3
PF00193: Xlink

Gene=STAB1; Chr=3; Phenotype=Median T2star in putamen (right); Gene effect size=1.16

splice stop gain stop lost start lost frameshift

G31* Q76* E117* R231* Q375* K460* c.1831−2A>C N680* C908* R931* R1122* c.4638+1G>T S1559* R1584* Q1661* V1689* E1712* F1826* Q1847* c.5908+1G>C Q1994* A2232* Q2242* Q2350* H2410* A2477* A2482* R2502* E2516* F2523* E2528*

Variant effect size

5 4 3 2 1 0 0 1 2 3 4 5

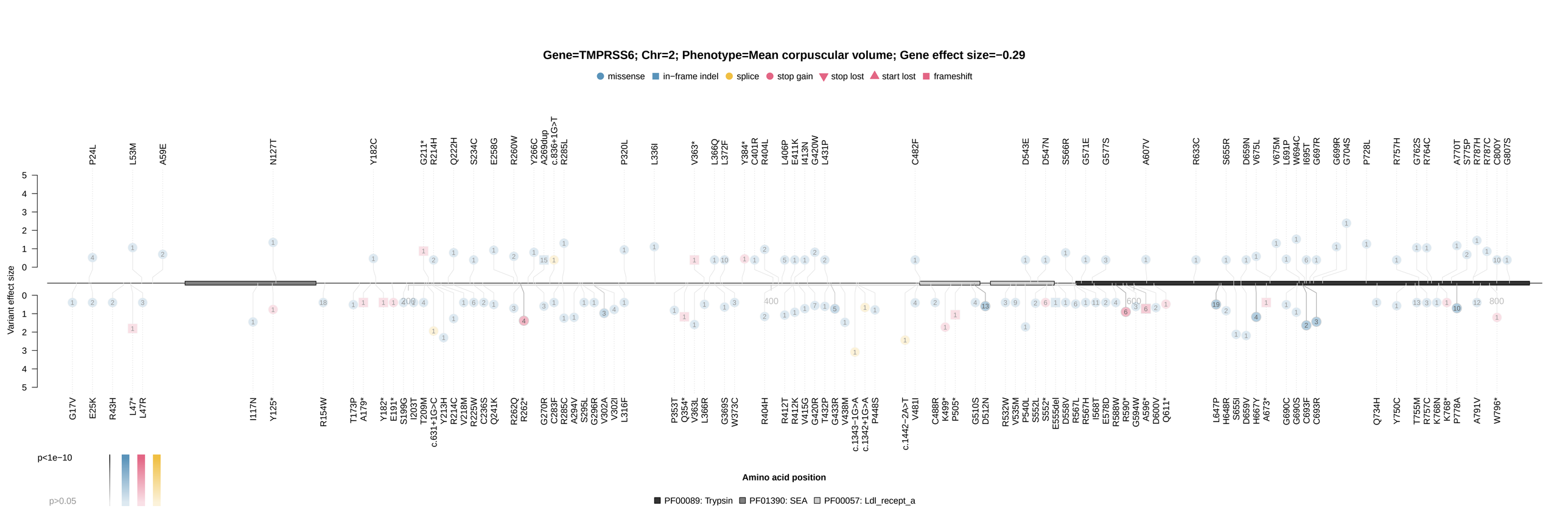
500 1000 1500 2000 2500

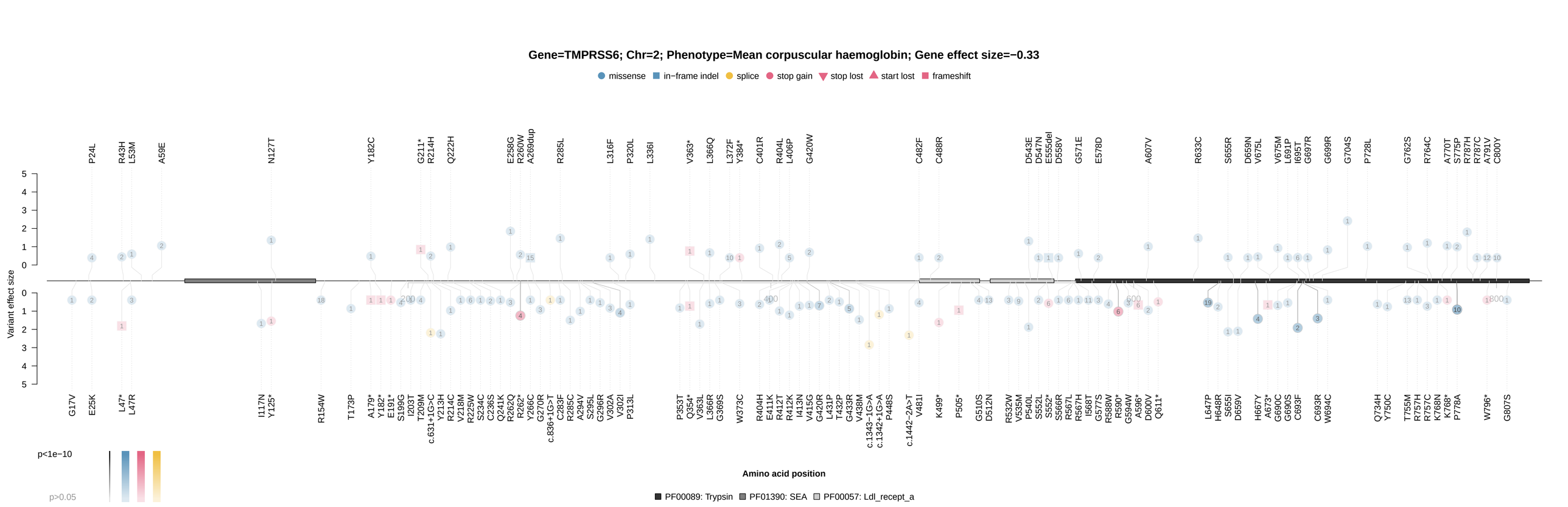
c.1519−2A>C C2307*

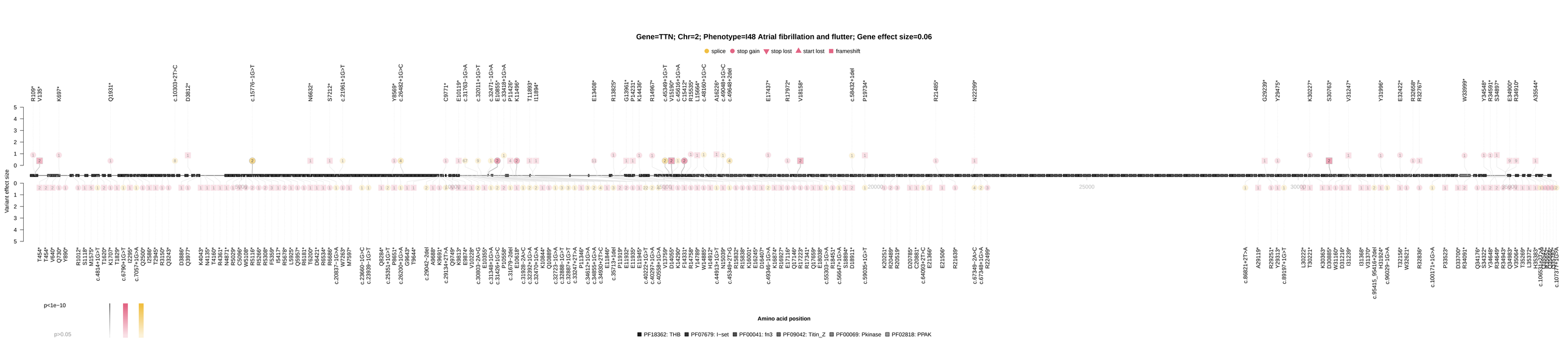
p<1e−10 p>0.05

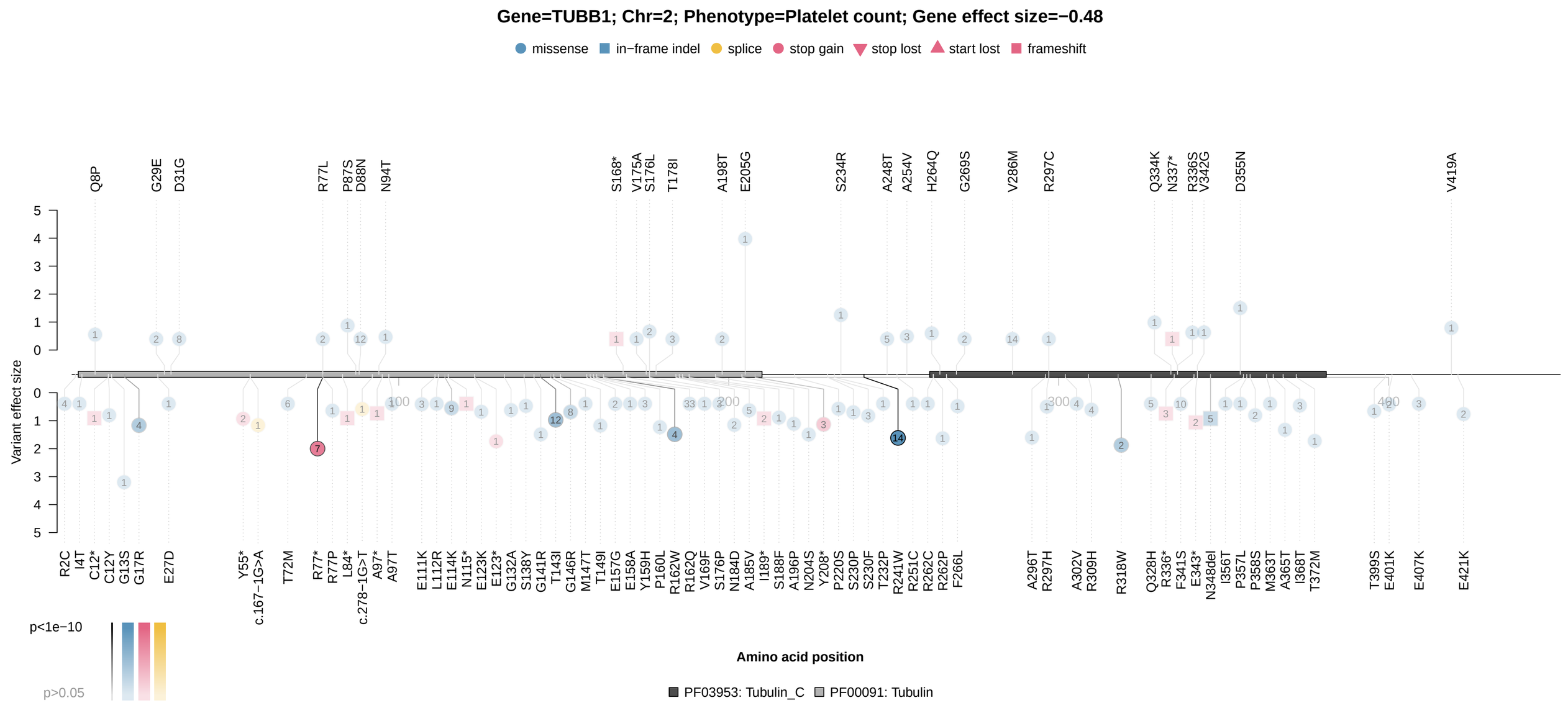
Amino acid position

PF00193: Xlink PF12947: EGF_3 PF02469: Fasciclin


Gene=TMPRSS6; Chr=2; Phenotype=Mean corpuscular volume; Gene effect size=−0.29
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
Variant effect size
Amino acid position
p<1e−10
p>0.05
PF00089: Trypsin
PF01390: SEA
PF00057: Ldl_recept_a


Gene=TMPRSS6; Chr=2; Phenotype=Mean corpuscular haemoglobin; Gene effect size=−0.33
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
Variant effect size
Amino acid position
PF00089: Trypsin
PF01390: SEA
PF00057: Ldl_recept_a
p<1e−10
p>0.05


Gene=TTN; Chr=2; Phenotype=I48 Atrial fibrillation and flutter; Gene effect size=0.06
splice
stop gain
stop lost
start lost
frameshift
Variant effect size
Amino acid position
PF18362: THB
PF07679: I−set
PF00041: fn3
PF09042: Titin_Z
PF00069: Pkinase
PF02818: PPAK
p<1e−10
p>0.05


Gene=TUBB1; Chr=2; Phenotype=Platelet count; Gene effect size=−0.48
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
Variant effect size
Amino acid position
p<1e−10
p>0.05
PF03953: Tubulin_C
PF00091: Tubulin
Q8P
G29E
D31G
R77L
P87S
D88N
N94T
S168*
V175A
S176L
T178I
A198T
E205G
S234R
A248T
A254V
H264Q
G269S
V286M
R297C
Q334K
N337*
R336S
V342G
D355N
V419A
R2C
I4T
C12*
C12Y
G13S
G17R
E27D
Y55*
c.167−1G>A
T72M
R77*
R77P
L84*
c.278−1G>T
A97*
A97T
E111K
L112R
E114K
N115*
E123K
E123*
G132A
S138Y
G141R
T143I
G146R
M147T
T149I
E157G
E158A
Y159H
P160L
R162W
R162Q
V169F
S176P
N184D
A185V
I189*
S188F
A196P
N204S
Y208*
P220S
S230P
S230F
T232P
R241W
R251C
R262C
R262P
F266L
A296T
R297H
A302V
R309H
R318W
Q328H
R336*
F341S
E343*
N348del
I356T
P357L
P358S
M363T
A365T
I368T
T372M
T399S
E401K
E407K
E421K

Gene=TUBB1; Chr=2; Phenotype=Platelet count; Gene effect size=−1.14

splice · stop gain · stop lost · start lost · frameshift

Variant effect size

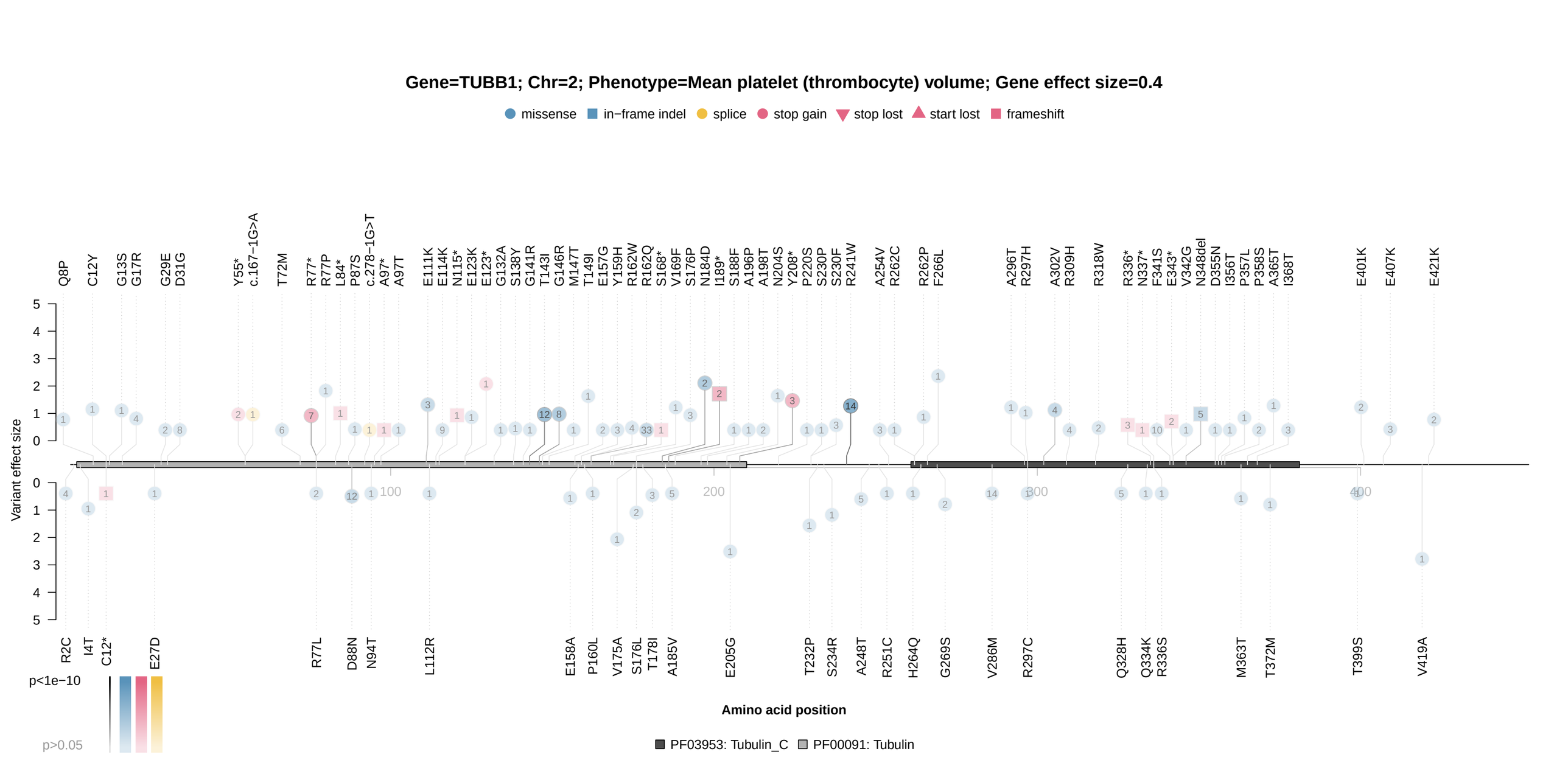
S168* N337*

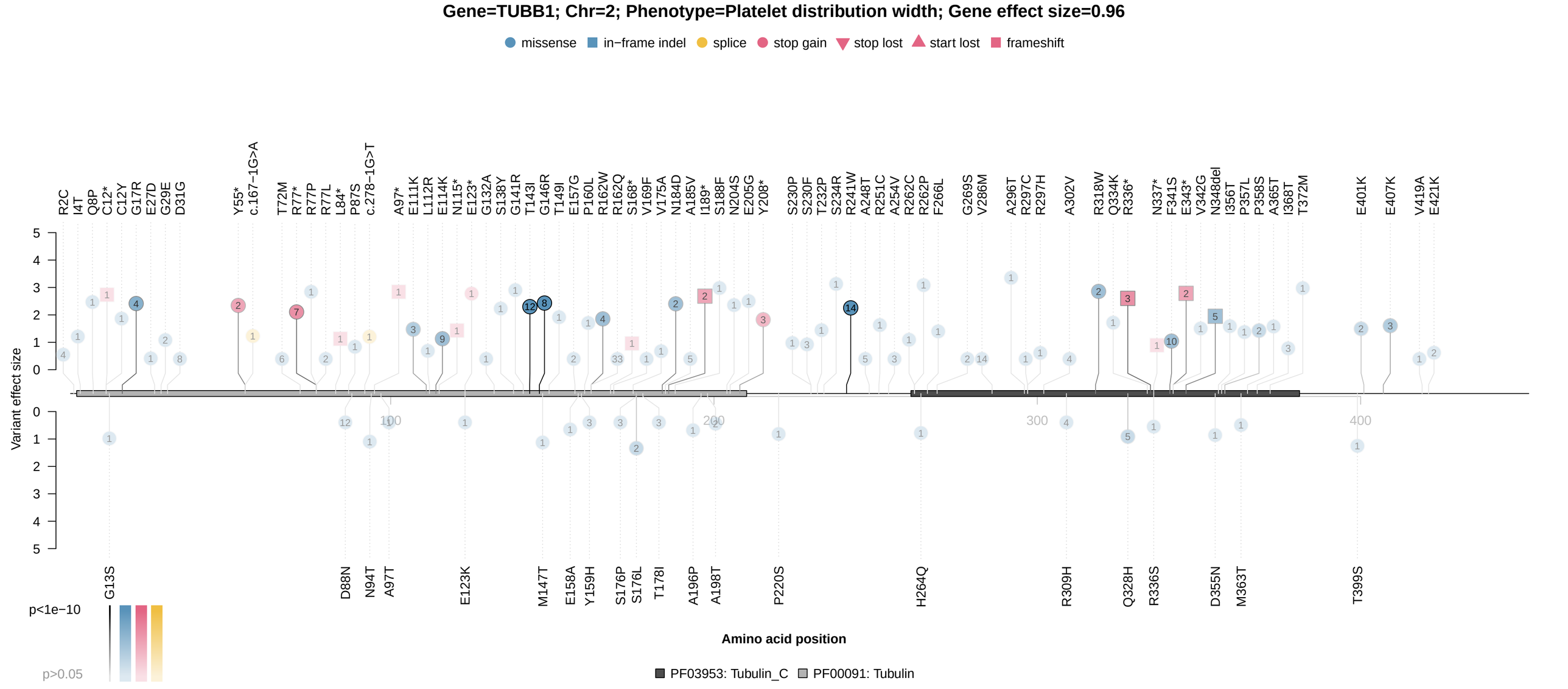
C12* Y55* c.167−1G>A R77* L84* c.278−1G>T A97* N115* E123* I189* Y208* R336* E343*

p<1e−10 p>0.05

Amino acid position

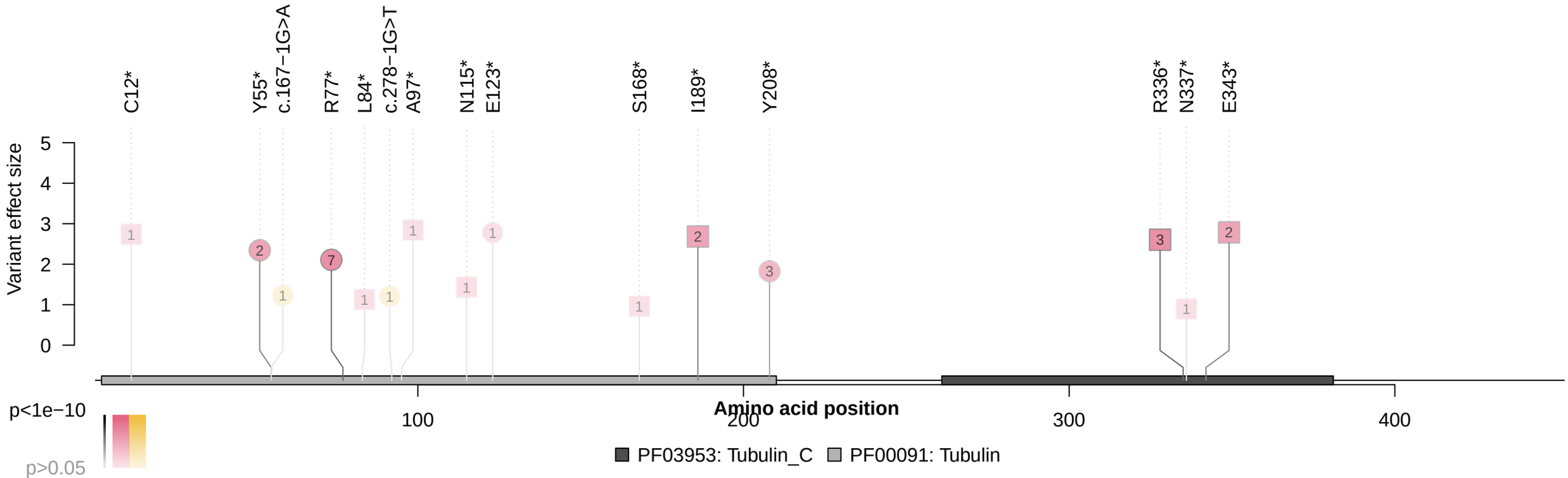
PF03953: Tubulin_C PF00091: Tubulin

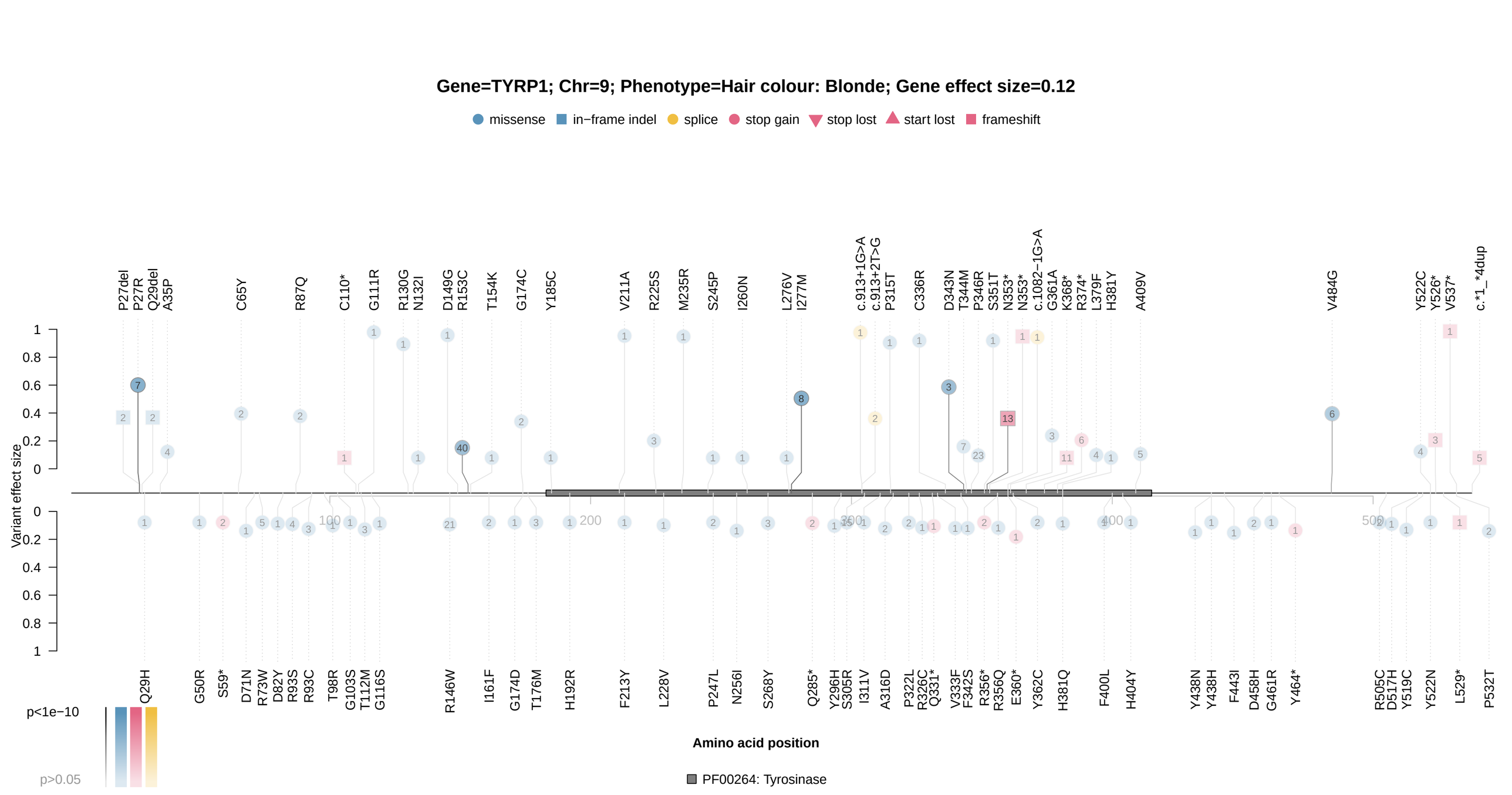

Gene=TUBB1; Chr=2; Phenotype=Mean platelet (thrombocyte) volume; Gene effect size=0.4
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
Variant effect size
Amino acid position
PF03953: Tubulin_C
PF00091: Tubulin
p<1e−10
p>0.05
Q8P C12Y G13S G17R G29E D31G Y55* c.167−1G>A T72M R77* R77P L84* P87S c.278−1G>T A97* A97T E111K E114K N115* E123K E123* G132A S138Y G141R T143I G146R M147T T149I E157G Y159H R162W R162Q S168* V169F S176P N184D I189* S188F A196P A198T N204S Y208* P220S S230P S230F R241W A254V R262C R262P F266L A296T R297H A302V R309H R318W R336* N337* F341S E343* V342G N348del D355N I356T P357L P358S A365T I368T E401K E407K E421K
R2C I4T C12* E27D R77L D88N N94T L112R E158A P160L V175A S176L T178I A185V E205G T232P S234R A248T R251C H264Q G269S V286M R297C Q328H Q334K R336S M363T T372M T399S V419A

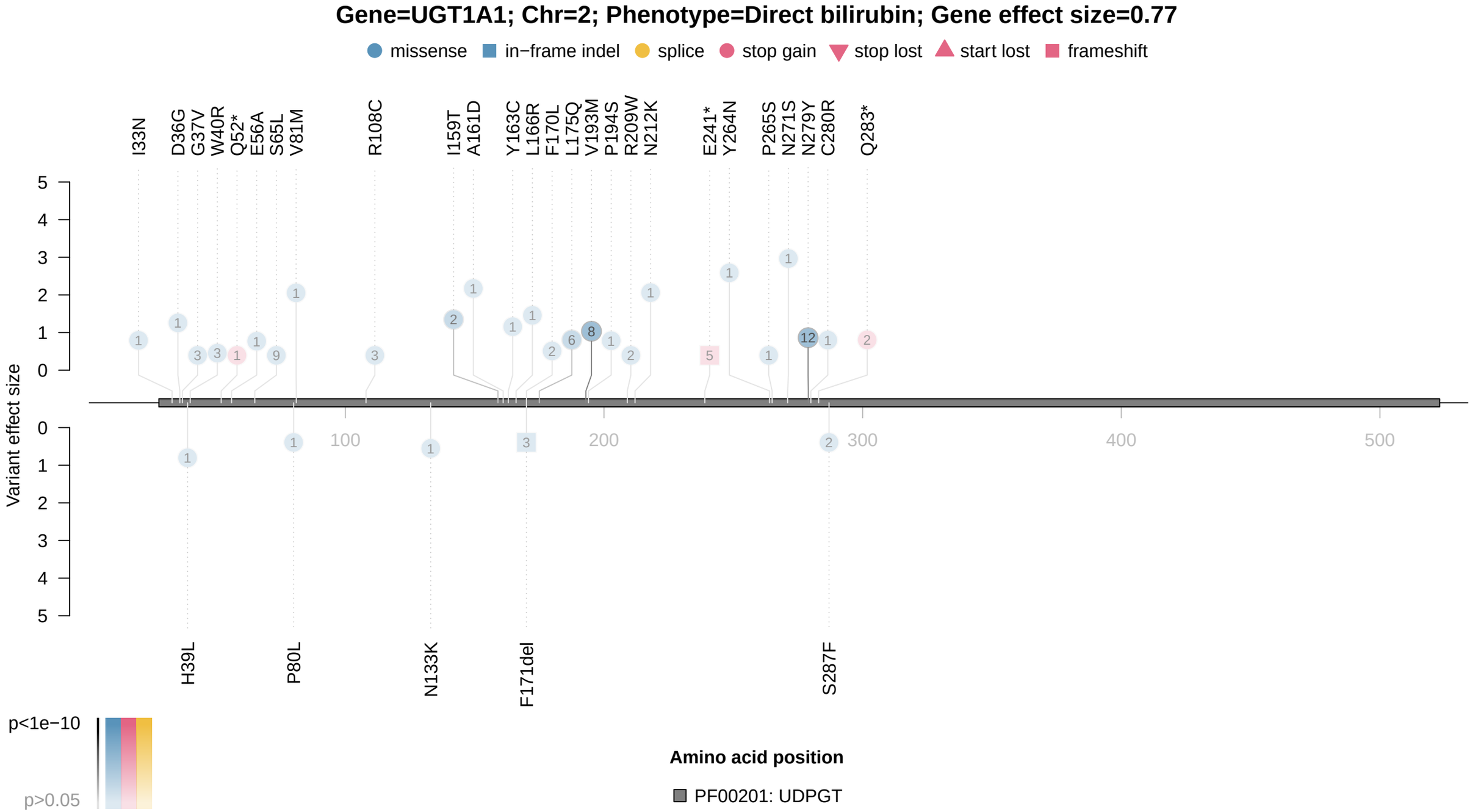

Gene=TUBB1; Chr=2; Phenotype=Platelet distribution width; Gene effect size=0.96
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
R2C
I4T
Q8P
C12*
C12Y
G17R
E27D
G29E
D31G
Y55*
c.167−1G>A
T72M
R77*
R77P
R77L
L84*
P87S
c.278−1G>T
A97*
E111K
L112R
E114K
N115*
E123*
G132A
S138Y
G141R
T143I
G146R
T149I
E157G
P160L
R162W
R162Q
S168*
V169F
V175A
N184D
A185V
I189*
S188F
N204S
E205G
Y208*
S230P
S230F
T232P
S234R
R241W
A248T
R251C
A254V
R262C
R262P
F266L
G269S
V286M
A296T
R297C
R297H
A302V
R318W
Q334K
R336*
N337*
F341S
E343*
V342G
N348del
I356T
P357L
P358S
A365T
I368T
T372M
E401K
E407K
V419A
E421K
Variant effect size
Amino acid position
G13S
D88N
N94T
A97T
E123K
M147T
E158A
Y159H
S176P
S176L
T178I
A196P
A198T
P220S
H264Q
R309H
Q328H
R336S
D355N
M363T
T399S
p<1e−10
p>0.05
PF03953: Tubulin_C
PF00091: Tubulin

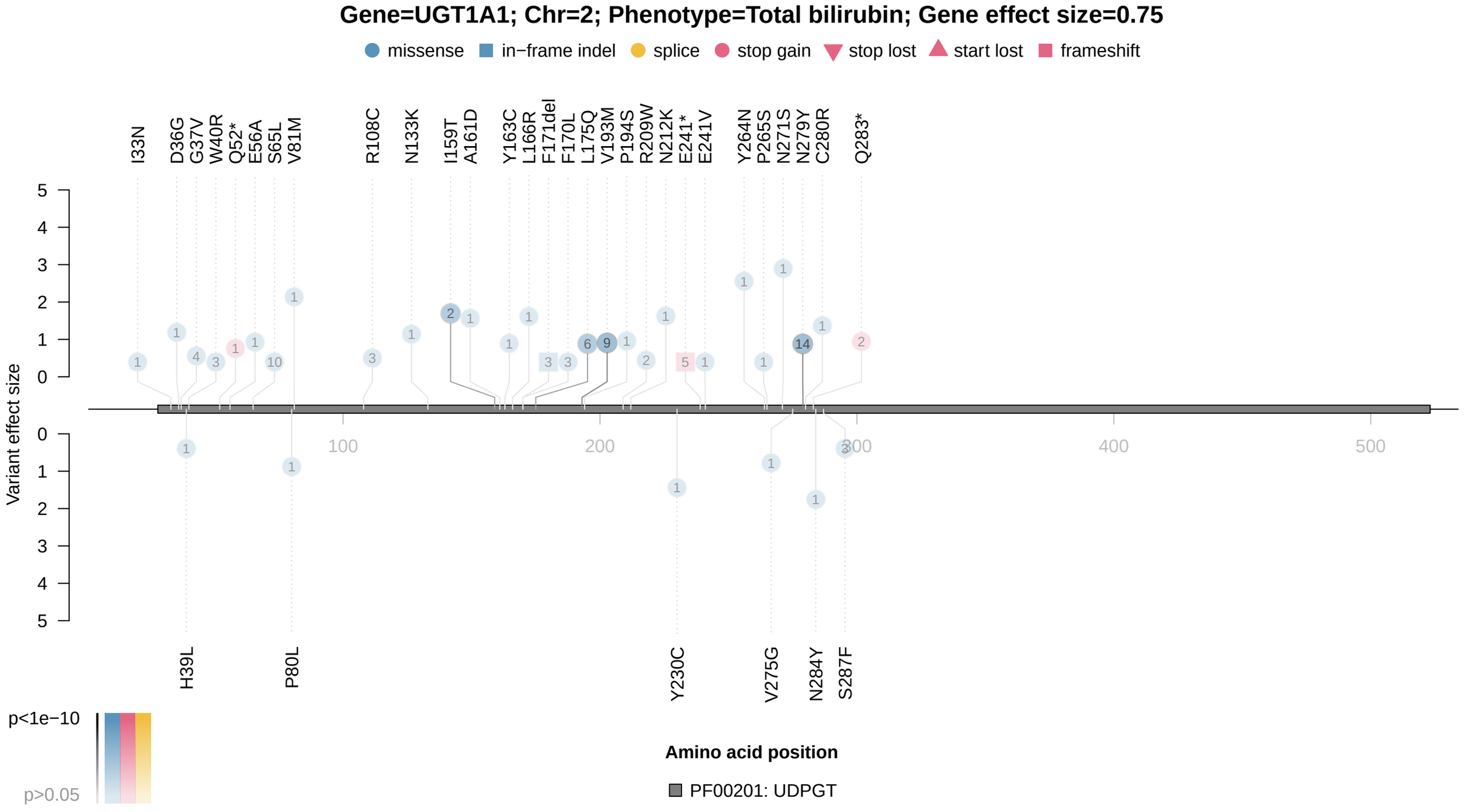
Gene=TUBB1; Chr=2; Phenotype=Platelet distribution width; Gene effect size=2.13

splice stop gain stop lost start lost frameshift




Gene=TYRP1; Chr=9; Phenotype=Hair colour: Blonde; Gene effect size=0.12
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
P27del
P27R
Q29del
A35P
C65Y
R87Q
C110*
G111R
R130G
N132I
D149G
R153C
T154K
G174C
Y185C
V211A
R225S
M235R
S245P
I260N
L276V
I277M
c.913+1G>A
c.913+2T>G
P315T
C336R
D343N
T344M
P346R
S351T
N353*
N353*
c.1082−1G>A
G361A
K368*
R374*
L379F
H381Y
A409V
V484G
Y522C
Y526*
V537*
c.*1_*4dup
Variant effect size
Q29H
G50R
S59*
D71N
R73W
D82Y
R93S
R93C
T98R
G103S
T112M
G116S
R146W
I161F
G174D
T176M
H192R
F213Y
L228V
P247L
N256I
S268Y
Q285*
Y296H
S305R
I311V
A316D
P322L
R326C
Q331*
V333F
F342S
R356*
R356Q
E360*
Y362C
H381Q
F400L
H404Y
Y438N
Y438H
F443I
D458H
G461R
Y464*
R505C
D517H
Y519C
Y522N
L529*
P532T
Amino acid position
p<1e−10
p>0.05
PF00264: Tyrosinase


Gene=UGT1A1; Chr=2; Phenotype=Direct bilirubin; Gene effect size=0.77
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
I33N
D36G
G37V
W40R
Q52*
E56A
S65L
V81M
R108C
I159T
A161D
Y163C
L166R
F170L
L175Q
V193M
P194S
R209W
N212K
E241*
Y264N
P265S
N271S
N279Y
C280R
Q283*
Variant effect size
100
200
300
400
500
H39L
P80L
N133K
F171del
S287F
p<1e−10
p>0.05
Amino acid position
PF00201: UDPGT


Gene=UGT1A1; Chr=2; Phenotype=Total bilirubin; Gene effect size=0.75
missense
in−frame indel
splice
stop gain
stop lost
start lost
frameshift
I33N
D36G
G37V
W40R
Q52*
E56A
S65L
V81M
R108C
N133K
I159T
A161D
Y163C
L166R
F171del
F170L
L175Q
V193M
P194S
R209W
N212K
E241*
E241V
Y264N
P265S
N271S
N279Y
C280R
Q283*
Variant effect size
100
200
300
400
500
H39L
P80L
Y230C
V275G
N284Y
S287F
p<1e−10
p>0.05
Amino acid position
PF00201: UDPGT

Supplementary Figure 3. Distribution of effects of rare variants on phenotypes in genes with statistically significant associations. Plots show the effect sizes of rare damaging variants on the phenotypes. The legend shows the gene, its associated phenotype, and the Effect Size (β). The effect size is computed from the gene-based collapsing model, in which individuals were coded as either having or not having a qualifying variant. A positive value indicates that variant carriers have, on average, higher values for the phenotype, while a negative value indicates that variant carriers have lower values. The amino acid positions are shown on the x-axis, with the PFAM domain highlighted. The y-axis displays the beta of each individual variant, with negative values shown below and positive values above the horizontal axis. Variants are indicated according to their consequence as shown and labeled according to their amino acid change or splice site variation. The number inside the circle is the number of people carrying that variant. Darker lines connecting the variants to the gene and darker-filled shapes indicate more significant p-values for the association. The cohort used is the UKB all ethnicities cohort.

Supplementary Table 1. Van Hout et al. comparison.

Gene	Phenotype	Van Hout p	Our p	N carriers	N expected case carriers	FET p	Replication?	Reason not replicated
TUBB1	Platelet distribution width	2.50E-23	2.50E-23	25			Yes	N/A
KALRN	Mean platelet thrombocyte volume	2.70E-23	3.90E-01	1			No	Lead Van Hout SNP MAF>0.1%
IQGAP2	Mean platelet thrombocyte volume	1.10E-19	7.80E-15	167			Yes	N/A
KLF1	Mean corpuscular haemoglobin	1.70E-16	5.00E-15	27			Yes	N/A
KLF1	Mean corpuscular volume	4.00E-14	6.90E-14	27			Yes	N/A
KLF1	Red blood cell erythrocyte distribution width	1.50E-13	1.50E-14	27			Yes	N/A
IL33	Eosinophill percentage	5.40E-12	7.90E-01	85			No	Lead Van Hout SNP MAF>0.1%
ASXL1	Red blood cell erythrocyte distribution width	2.40E-11	3.30E-06	126			No	Unclear, appears due to difference in variant calls used for indels
MLH1	Z85.0, Personal history of malignant neoplasm of digestive organs	3.50E-11	5.30E-26	6	0	3.64E-07	No	Too few expected carriers for regression, and Fisher's exact not significant
PKD1	N18, Chronic kidney disease (CKD)	2.90E-10	N/A	N/A	N/A	N/A	No	Outside of GIAB high confidence regions
IL33	Eosinophill count	3.30E-10	5.30E-01	85			No	Lead Van Hout SNP MAF>0.1%
COL6A1	Corneal resistance factor mean	3.60E-10	1.30E-05	10			No	Some variants outside of GIAB high confidence regions
HBB	Red blood cell erythrocyte count	1.70E-09	1.20E-01	1			No	Too few carriers in this population subset
TUBB1	Platelet count	2.10E-09	5.60E-10	25			No	Difference in p-value cutoff
ASXL1	Platelet distribution width	4.70E-09	8.00E-08	126			No	Unclear, appears due to difference in variant calls used for indels
GMPR	Mean corpuscular haemoglobin	1.10E-08	1.60E-02	7			No	Lead Van Hout SNP MAF>0.1%
TTN	I42, Cardiomyopathy	1.40E-08	3.90E-15	9	1	2.96E-06	No	Too few expected carriers for regression, and Fisher's exact not significant

MEPE	Heel bone mineral density	1.40E-08	3.30E-05	106			No	Unclear, appears due to difference in variant calls used for indels
COL6A1	Corneal hysteresis mean	2.10E-08	7.00E-05	10			No	Some variants outside of GIAB high confidence regions
TUBB1	Mean platelet thrombocyte volume	2.40E-08	2.10E-07	25			No	Small difference in p-value
PIEZO1	I83.9, Asymptomatic varicose veins of lower extremities	2.70E-08	2.30E-15	19	4	7.16E-06	No	Too few expected carriers for regression, and Fisher's exact not significant
CALR	D47, Other neoplasms of uncertain behavior of lymphoid, hematopoietic and related tissue	4.10E-08	7.60E-122	2	0	2.06E-05	No	Too few expected carriers for regression, and Fisher's exact not significant
HBB	Red blood cell erythrocyte distribution width	5.80E-08	1.80E-02	1			No	Too few carriers in this population subset
GP1BA	Mean platelet thrombocyte volume	6.40E-08	8.40E-09	88			No	Difference in p-value cutoff
CHEK2	Platelet crit	7.90E-08	7.60E-01	55			No	Lead Van Hout SNP MAF>0.1%

The p-values from Van Hout et al. are from an analysis of unrelated European ancestry individuals from the UKB cohort with a MAF cutoff of 1%. The p-values shown for our analysis are from the linear mixed model (LMM) analysis of the European UKB cohort, including relatives, with a 0.1% MAF cutoff and a restriction to Genome in a Bottle (GIAB) high-confidence regions. The number of carriers in our analysis is shown for quantitative traits, and for binary traits the number of case carriers and expected number of case carriers (given overall prevalence) is shown separately. Fisher’s exact test (FET) is performed for binary traits as well.

Supplementary References

1. Rentzsch, P., Witten, D., Cooper, G. M., Shendure, J. & Kircher, M. CADD: predicting the deleteriousness of variants throughout the human genome. *Nucleic Acids Res.* **47**, D886–D894 (2019).
2. Kircher, M. *et al.* A general framework for estimating the relative pathogenicity of human genetic variants. *Nat. Genet.* **46**, 310–315 (2014).
3. Itan, Y. *et al.* The mutation significance cutoff: gene-level thresholds for variant predictions. *Nat. Methods* **13**, 109–110 (2016).
4. Lee, S. *et al.* Optimal unified approach for rare-variant association testing with application to small-sample case-control whole-exome sequencing studies. *Am. J. Hum. Genet.* **91**, 224–237 (2012).
5. Hail Team. Hail 0.2.21-f16fd64e0d77. https://github.com/hail-is/hail/releases/tag/0.2.21
6. Long, T. *et al.* Whole-genome sequencing identifies common-to-rare variants associated with human blood metabolites. *Nat. Genet.* **49**, 568–578 (2017).
7. Girard, S. L. *et al.* Mutation burden of rare variants in schizophrenia candidate genes. *PLoS One* **10**, e0128988 (2015).