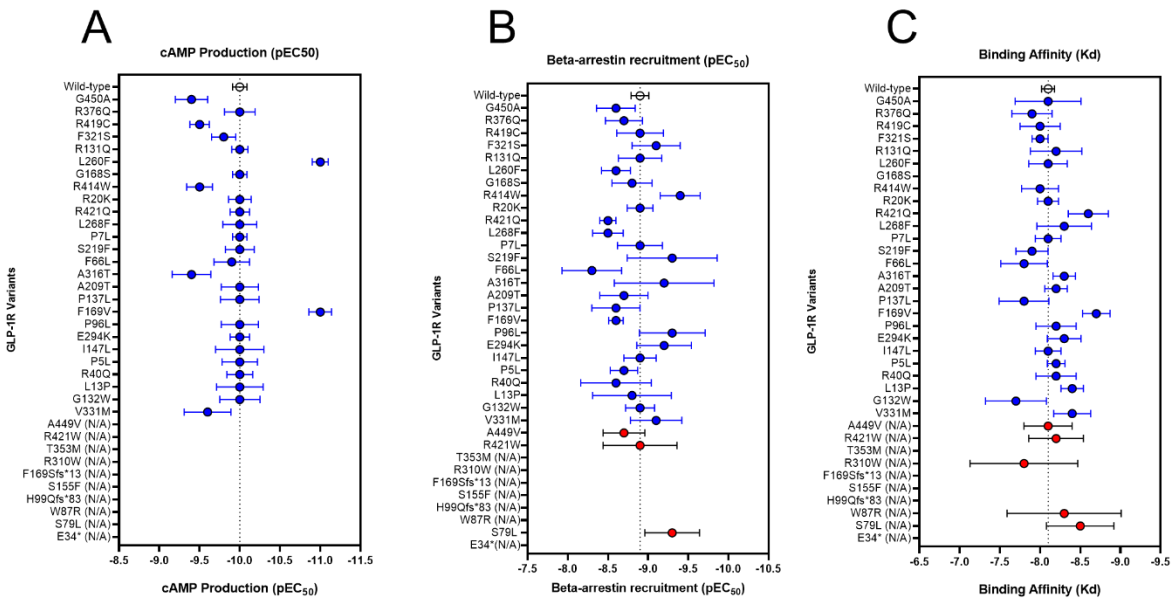
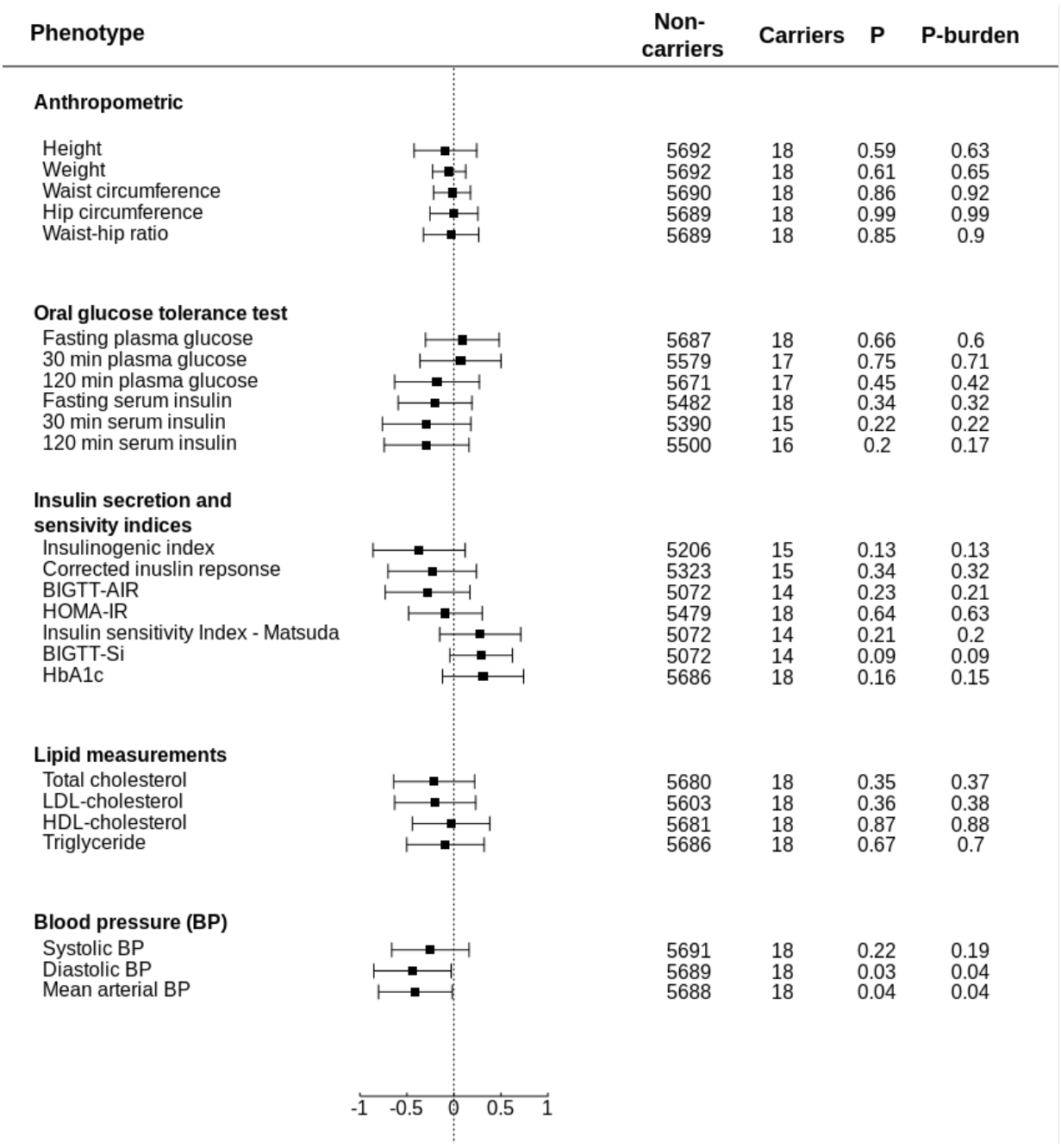
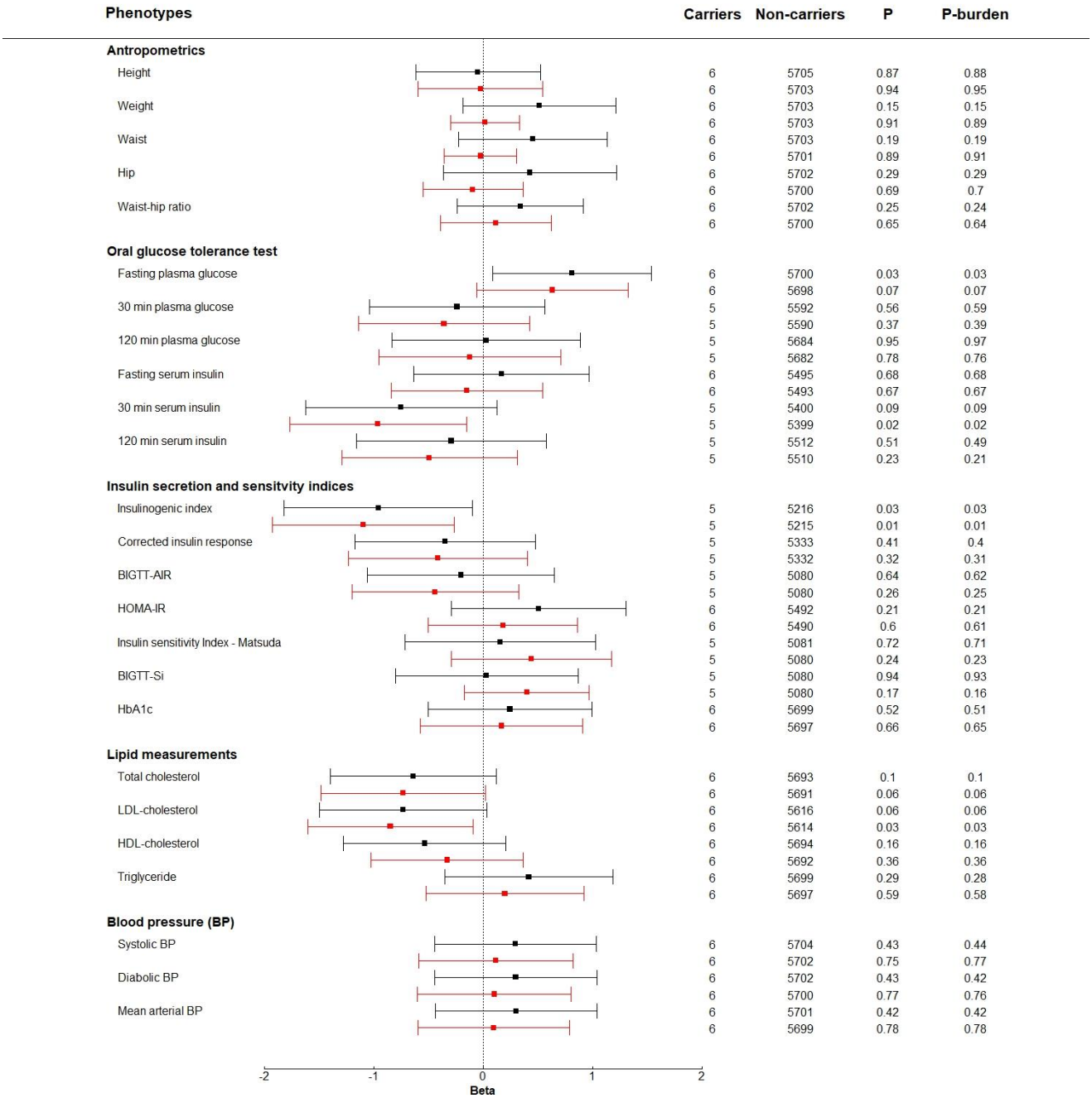


Supplementary Figure 1. Potencies in cAMP and arrestin recruitment as well as GLP-1 affinity of 36 GLP-1R variants. pEC_{50} represents the negative logarithm of agonist concentration in molar that produces half the maximal response. K_d represents affinity (pLog values). Blue: WT like; red, loss of function. NA, no activation observed. A: cAMP pEC_{50} values B: beta-arrestin recruitment pEC_{50} values; C: binding K_d values.

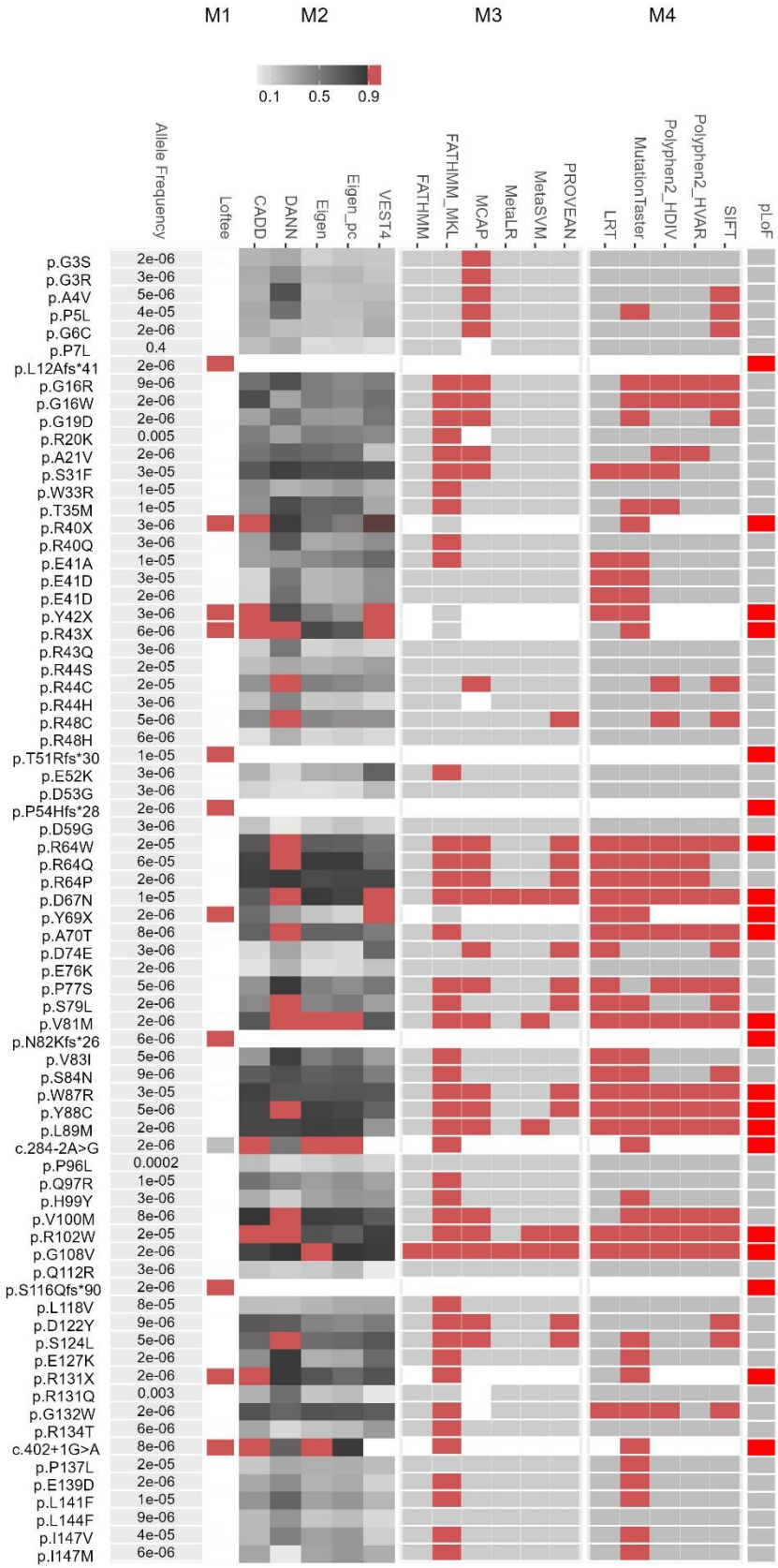


Supplementary Figure 2. Quantitative trait analyses of loss-of-signalling *GLP1R* variants in the Inter99 cohort with adjustment for body mass index. Non-carriers = number of individuals with phenotype information who do not carry any of the variants; Carriers = number of individuals with the phenotype who carry a LoS variant; P, p-value of the linear regression model; Abbreviations: P-burden, *p*-value of burden test; BP, blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, hemoglobin A1c; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; BIGTT-AIR, beta-cell function, insulin sensitivity, and glucose tolerance test – acute insulin response.; BIGTT-Si, beta-cell function, insulin sensitivity, and glucose tolerance test – sensitivity index.



Supplementary Figure 3. Quantitative trait analyses of LoS *GLP1R* variants predicted as pLoF variants in the Inter99 cohort. Non-carriers = number of individuals with phenotype information who do not carry any of the variants; Carriers = number of individuals with the phenotype who carry a LoS variant predicted as pLoF; P, p-value of the linear regression model; Abbreviations: P-burden, *p*-value of burden test; BP, blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, hemoglobin A1c; HOMA-IR, Homeostatic

Model Assessment for Insulin Resistance; BIGTT-AIR, beta-cell function, insulin sensitivity, and glucose tolerance test – acute insulin response.; BIGTT-Si, beta-cell function, insulin sensitivity, and glucose tolerance test – sensitivity index. Black lines represent analyses without BMI adjustment, whereas red lines represent analyses adjusted for BMI.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M4
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FATHMM_MKL
MCAP
MetaLR
MetaSVM
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LRT
MutationTaster
Polyphen2_HDIV
Polyphen2_HVAR
SIFT
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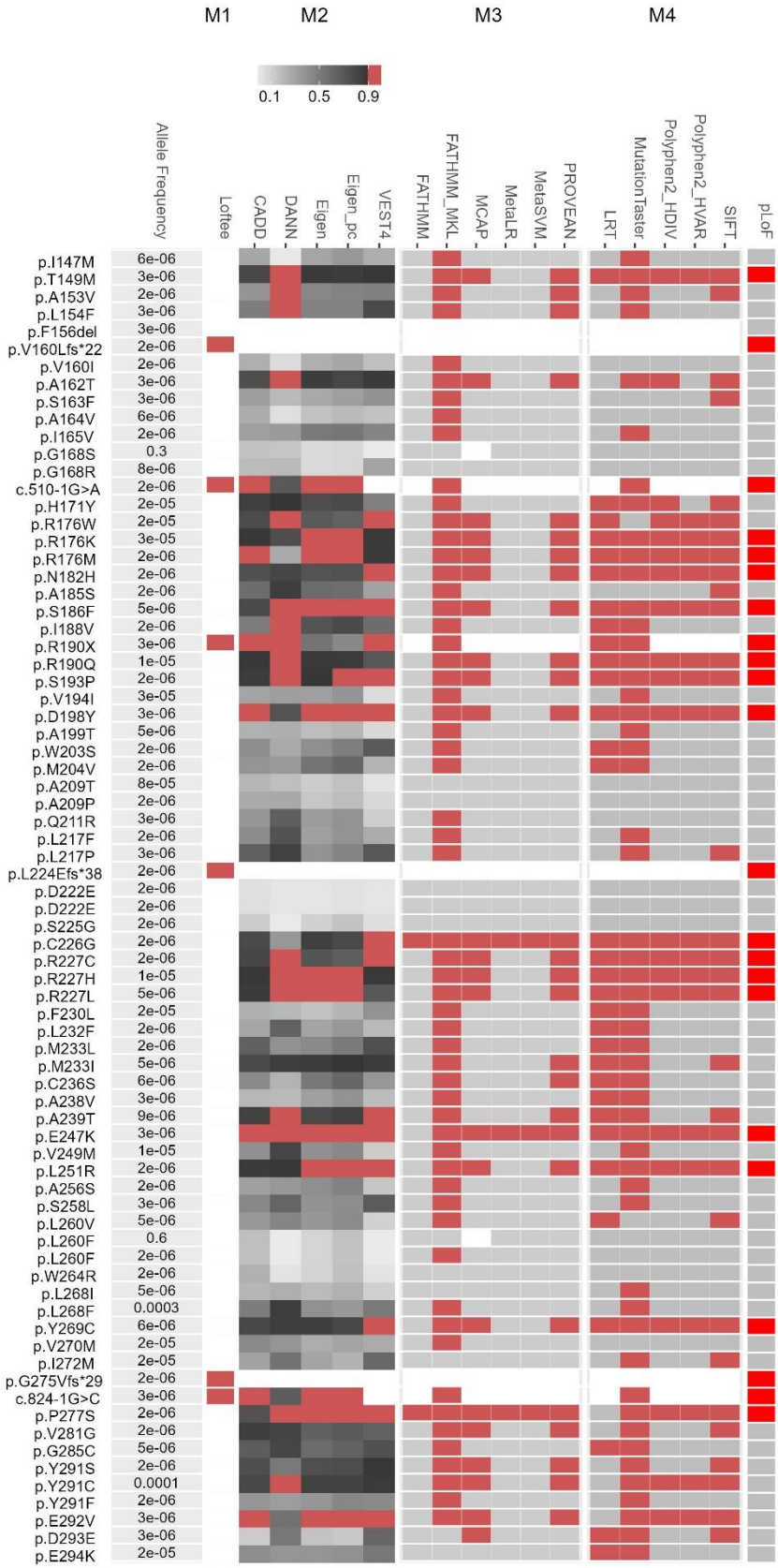
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M2
M3
M4
0.1
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DANN
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Eigen_pc
VEST4
FATHMM
FATHMM_MKL
MCAP
MetaLR
MetaSVM
PROVEAN
LRT
MutationTaster
Polyphen2_HDIV
Polyphen2_HVAR
SIFT
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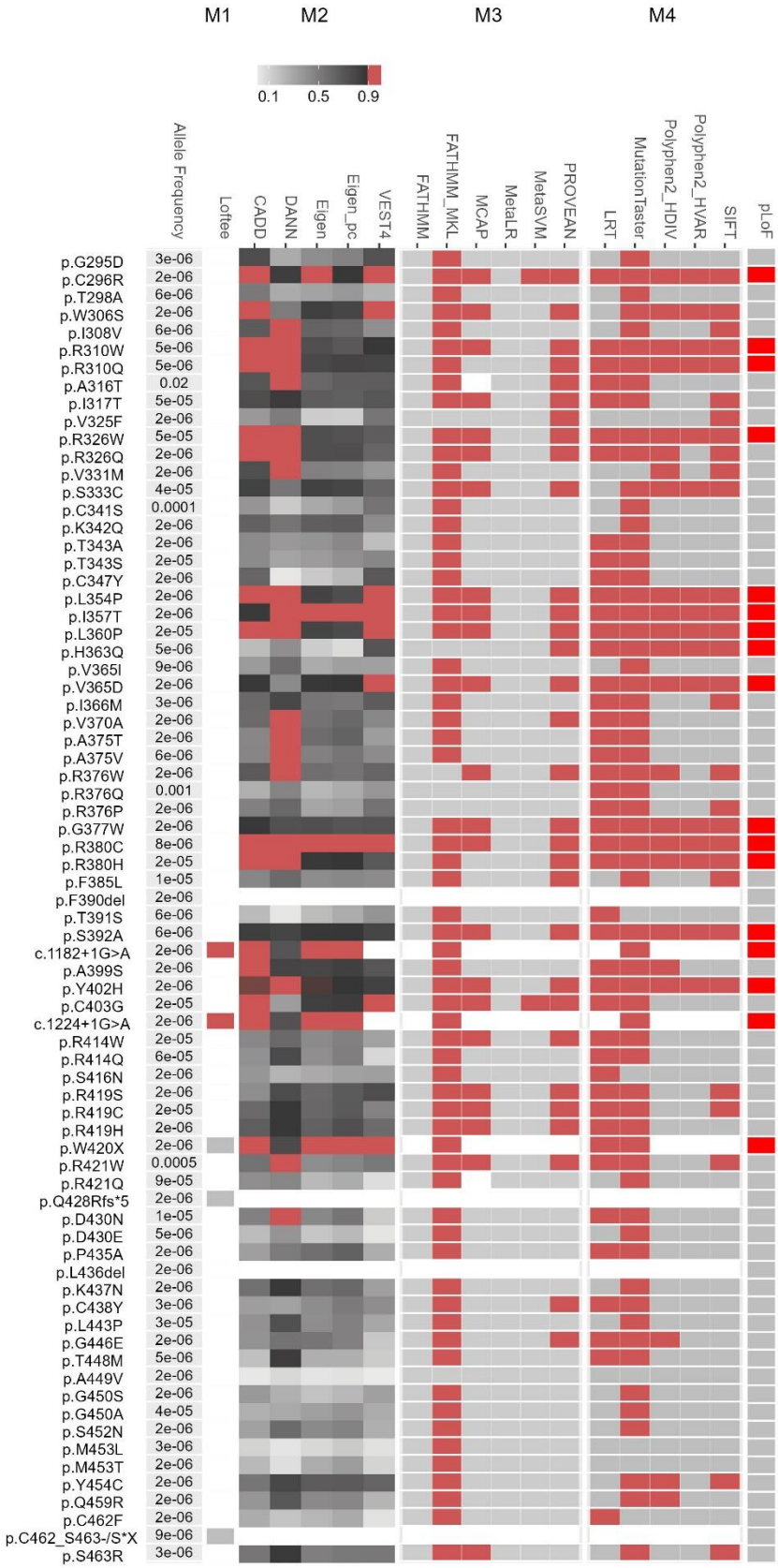
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M2
M3
M4
0.1
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VEST4
FATHMM
FATHMM_MKL
MCAP
MetaLR
MetaSVM
PROVEAN
LRT
MutationTaster
Polyphen2_HDIV
Polyphen2_HVAR
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Supplementary Figure 4. Binary heatmap showing variant severity prediction of *GLP1R* variants in the UK Biobank. The **left panel** shows the minor allele frequency (MAF) of each *GLP1R* variant. **Panel M1** shows if the variant is a predicted loss-of-function (pLoF, red) variant by the Loss-of-Function Transcript Effect Estimator (Loftee) high-confidence (HC) mask. **Panel M2-M4** shows the predicted deleteriousness of each variant for prediction algorithms grouped in masks. A red box indicates variants passing the specific algorithm as LoF. White colour indicates no information (NA). **Panel pLoF**; predicted LoF variants (bright red).

The masks consist of the following algorithms:

M2: VEST4, CADD, DANN, Eigen-raw, and Eigen-PC-raw.

M3: FATHMM, FATHMM-MKL, PROVEAN, MetaSVM, MetaLR, and MCAP.

M4: PolyPhen2 HDIV, PolyPhen HVAR, SIFT, LRT, and MutationTaster.