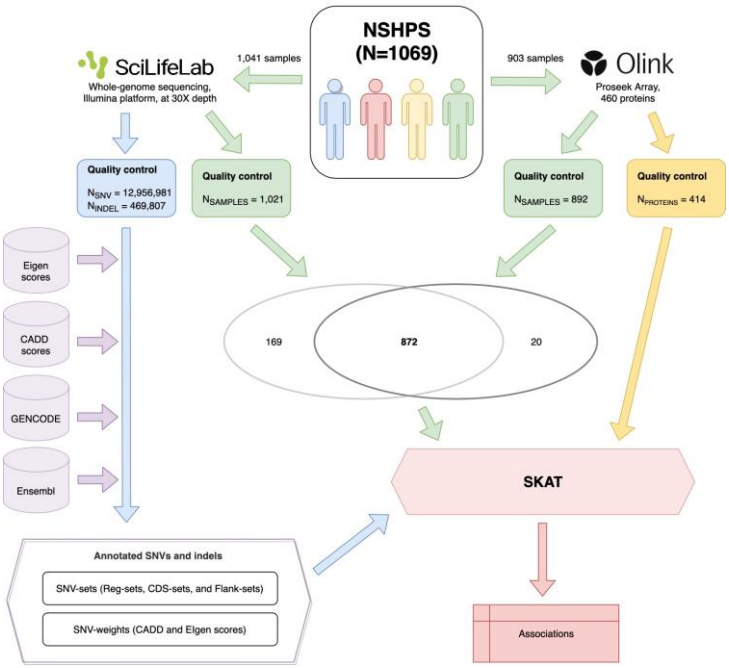
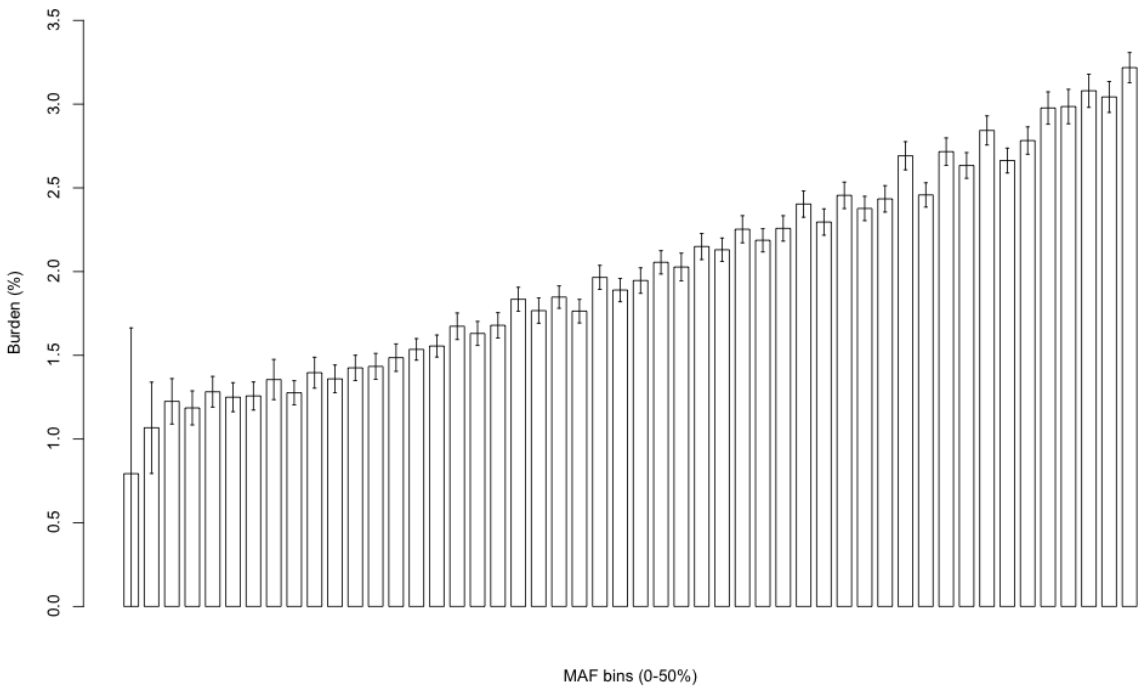
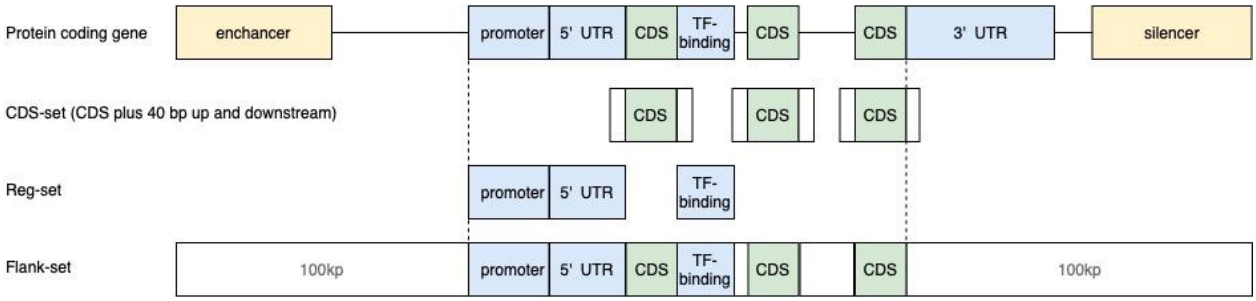


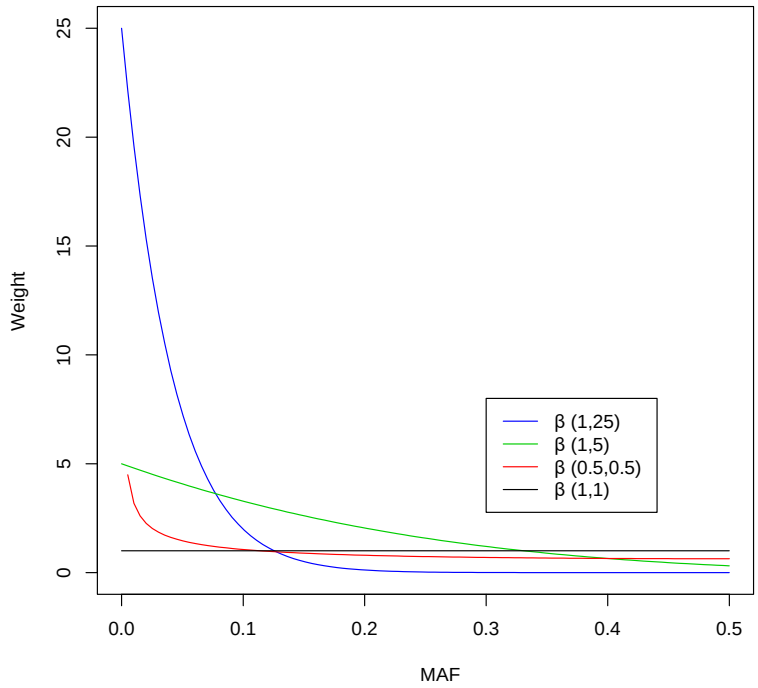
Supplementary Figure S1 *Flow chart of the study design*



Supplementary Figure S2*. The burden of damaging variants, as predicted by Eigen, per individual. Averages across all individuals are show and the error bars represent the 95% width of the distribution in the cohort.*



Supplementary Figure S3. Diagram of the SNV-sets (B). *CDS - Coding sequence, UTR - untranslated region, TF - transcription factor. The CDS-sets contain coding sequenced +-40 bp into the intronic regions to also capture splice sited. Reg-sets contains regions that have been annotated as regulatory and are located in direct proximity to the gene. Flank-sets includes the whole gene-region +-100kb up and downstream of each gene, aiming to also capture more distantly located regulatory regions.*



Supplementary Figure S4 *– MAF-weights for the variants depending on which parameters are used for the β-distribution. β (1,1) is without any weights (unweighted). The default weights in the SKAT model are β (1,25), and in CommonRare model, the default (that we also used in our study) is for rare: β (1,25) and common: β (0.5,0.5).*