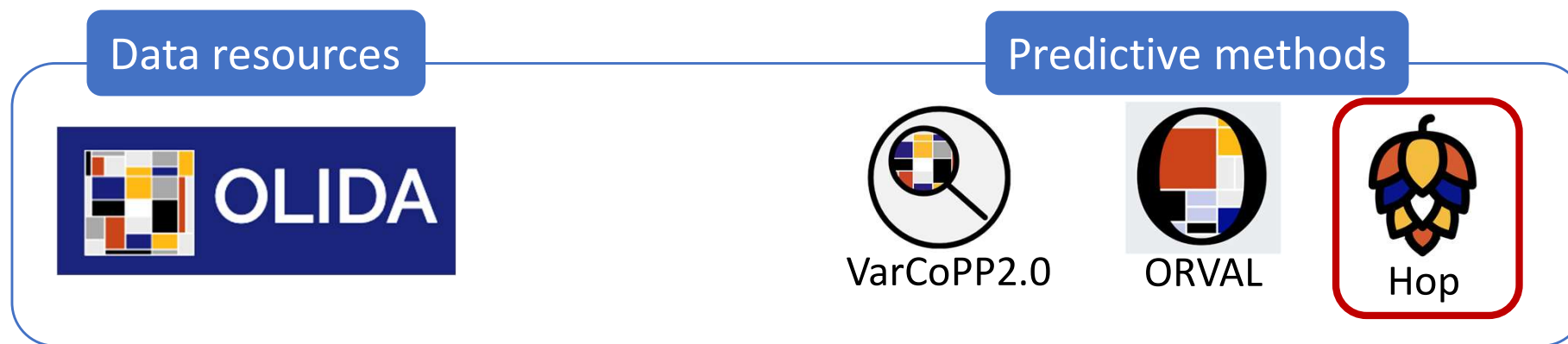


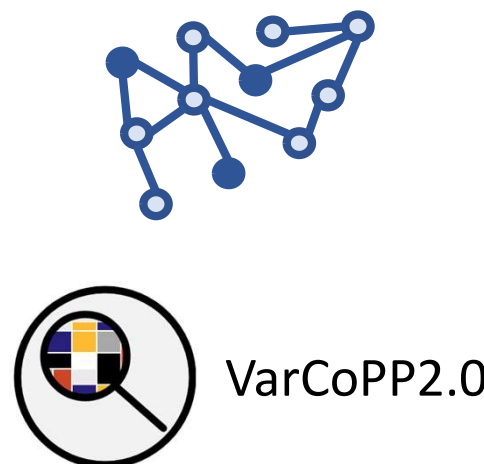


Hop: High-throughput oligogenic prioritizer

Patient variants and
disease data



Knowledge propagation and
pathogenicity prediction



Ranking of variant
combinations

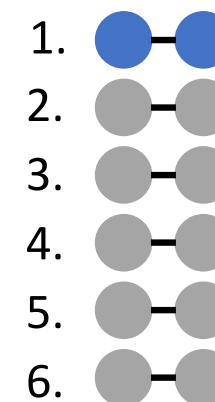


Figure S1. Oligogenic toolbox. Data resources and predictive methods used for oligogenic analysis. OLIDA is a repository containing published genetic data on known digenic diseases. VarCoPP2.0 is a pathogenicity predictor for variant combinations in gene pairs that is based on data available in OLIDA and on neutral variant combinations from the 1000 Genomes project. ORVAL is a platform combining VarCoPP predictions to identify variant combinations in more than two genes. Hop is a prioritization tool for digenic variant combinations. It uses variant information, information about the patient's disease and the predictions from the VarCoPP2.0 tool to rank all possible variant combination in the exome based on how likely they are to cause the patient disease.

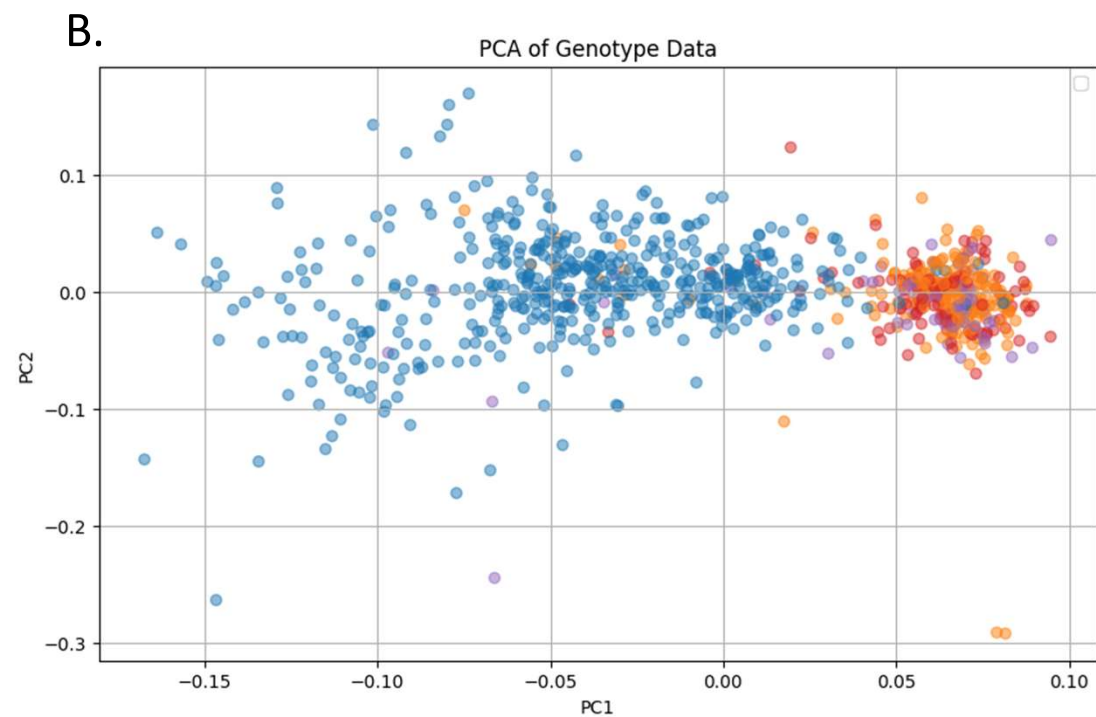
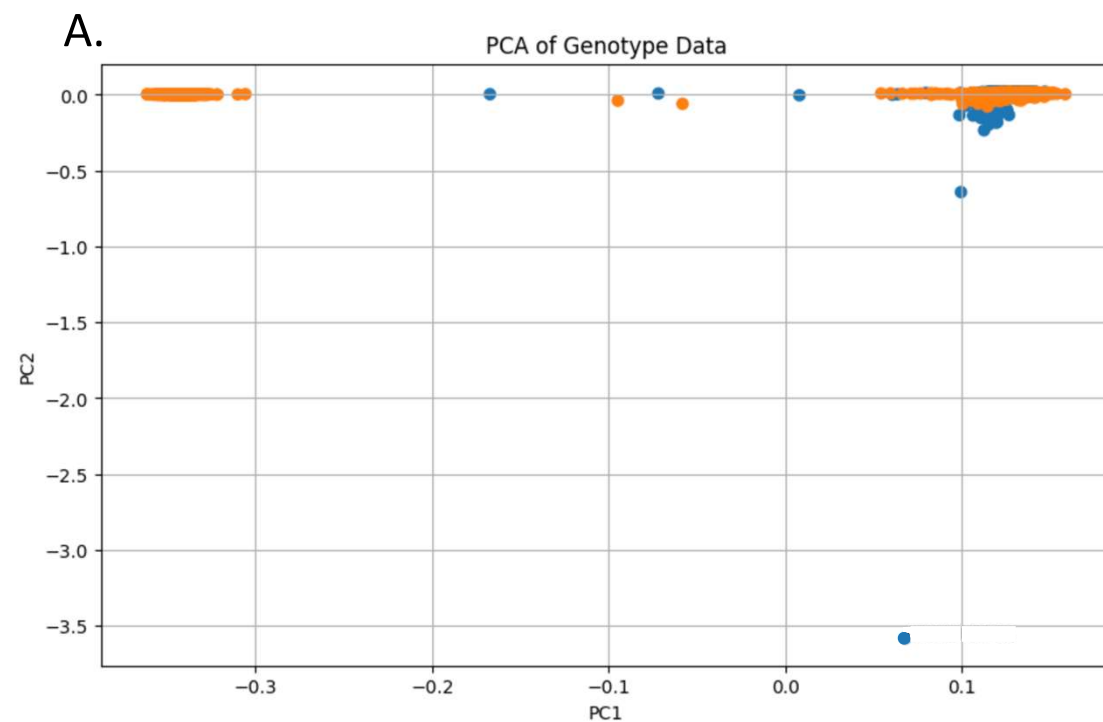


Figure S2. Principal Component analysis (PCA). A PCA was performed using genotypic data from cases and controls and the outliers were removed. **A.** Initial PCA plot. Orange dots are controls, blue dots are cases. **B.** Final PCA plot. In the final PCA plot, 474 controls and 352 cases remain, among which 240 non-lesional cases. Blue dots are controls. Orange, red and purple dots represent different types of epilepsies.

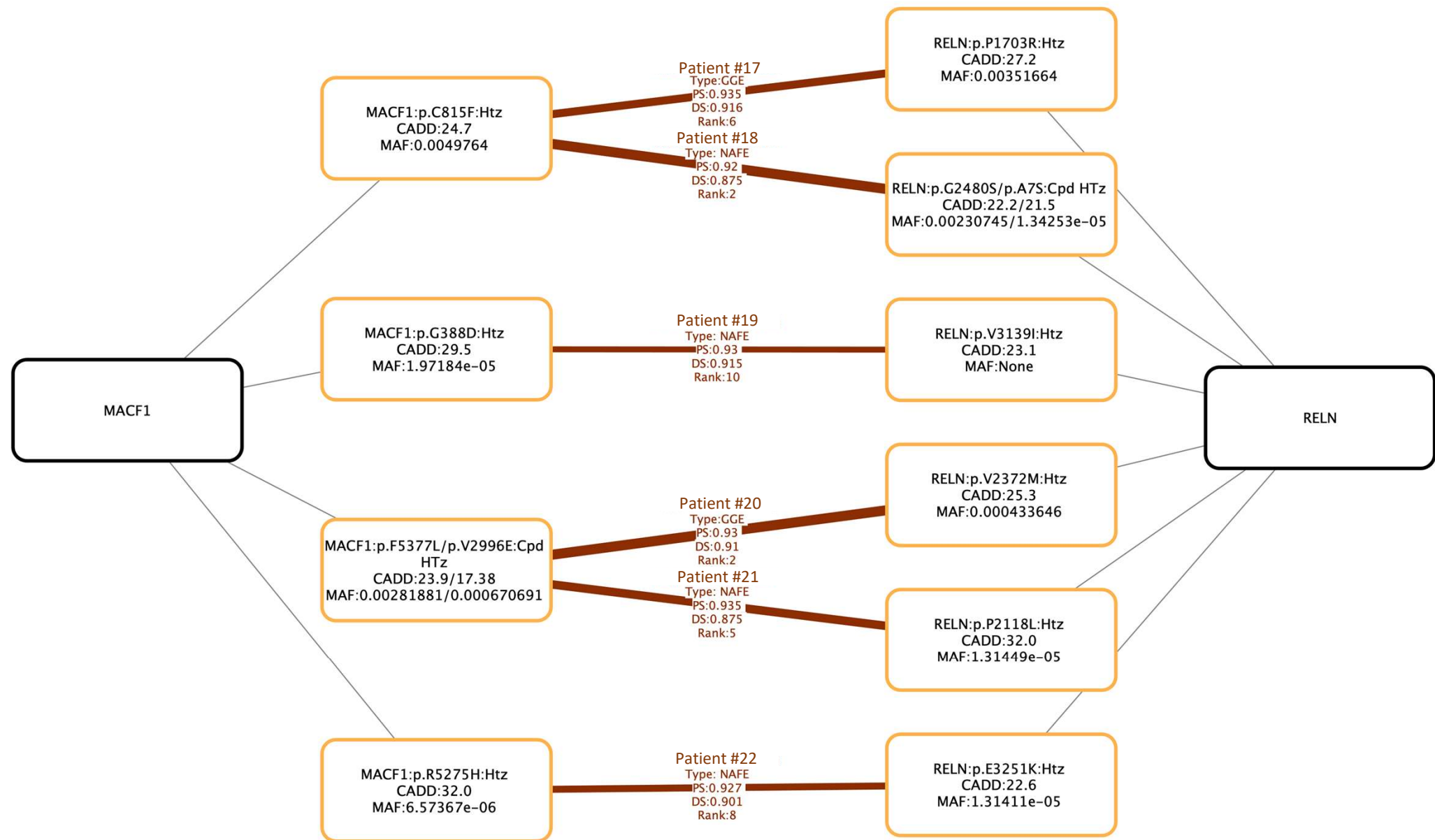


Figure S3. An example of oligogenic analysis – cohort approach. Representation of the variant combinations involving the genes *MACF1* and *RELN*. The variants are described inside the frames, along with their CADD score and minor allele frequency (MAF) from GnomAD. Htz, heterozygous. Cpd, compound. The lines between the frames represent the patients harbouring the variant combinations, along with patient code, epilepsy type, digenic prediction scores from Hop and ranking among the top 50 variant combinations of the patient. Thicker lines indicate higher scores. PS, pathogenicity score. DS, disease relevance score.

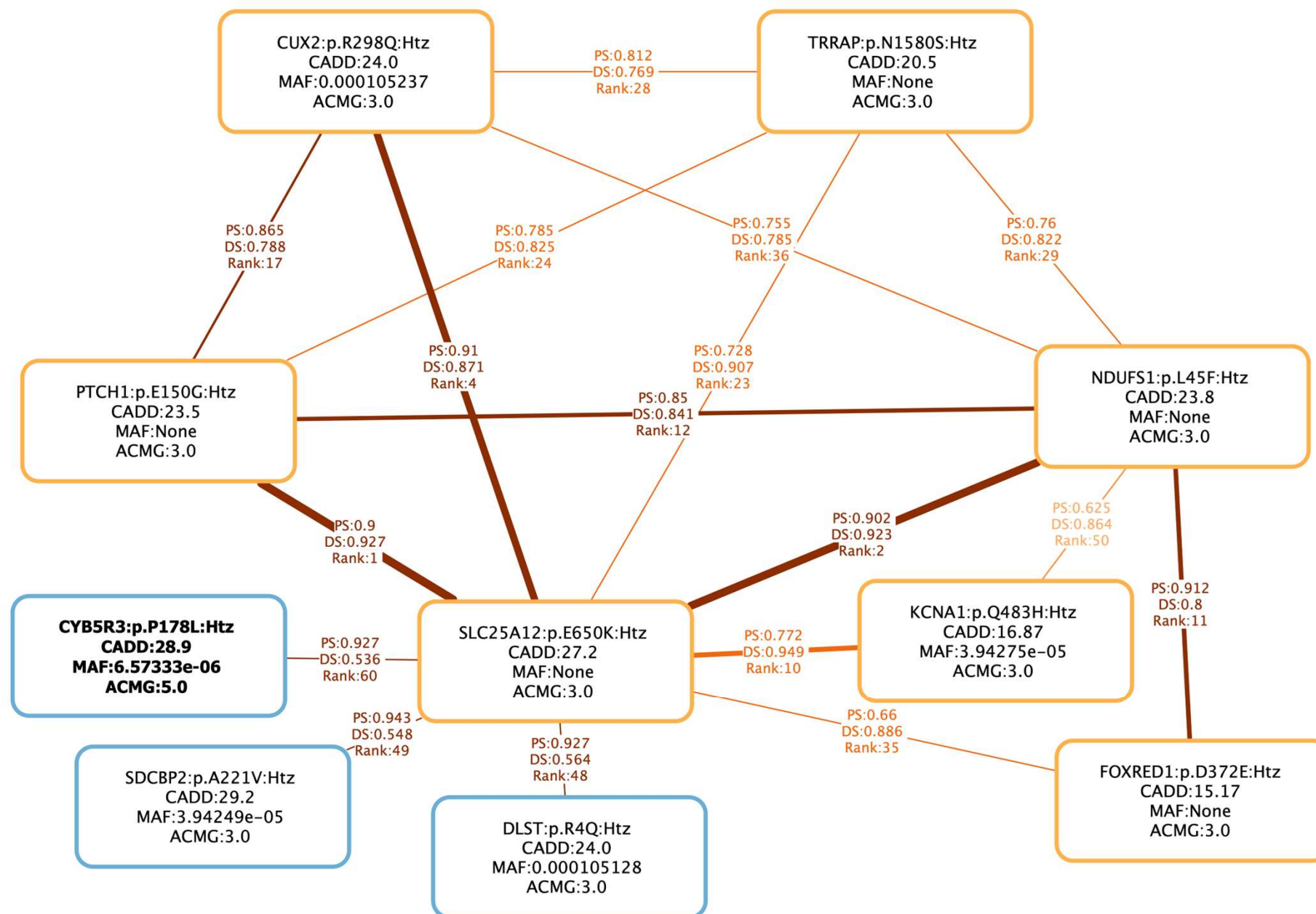


Figure S4. An example of oligogenic analysis – individual approach. Representation of the variant combinations in one selected patient. The variants are described inside the frames, along with their CADD score, minor allele frequency (MAF) from GnomAD and ACMG automated classification from Franklin. Blue frames indicate variants in genes not included in the 555 gene panel. Htz, heterozygous. The lines between the frames represent the variant combinations, with digenic prediction scores from Hop and ranking among the patient’s top 50 variant combinations. Thicker lines indicate higher scores. PS, pathogenicity score. DS, disease relevance score.