The role of Loss-of-Function mutations on development of rejection after heart transplantation

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Heart transplant donor/recipient (D-R) matching is suboptimal. Besides HLA, also other genetic factors play a role in graft rejection. Possible sources of genetic variation underpinning rejection are Loss-of-Function (LoF) variants ablating two copies of a given gene, resulting in incompatibility across the proteomes of donor and recipient. iGeneTRAiN (www.igenetrain.org) is a large-scale international consortium, which consist of over 12,000 solid organ transplant donor-recipient (D-R) pairs. We have developed a pipeline to identify human knockouts and aim to associate the detected knockout genes with acute rejection after heart transplantation. We have included almost 900 heart transplant donor-recipient (D-R) pairs. We ultimately aim to translate genetic data into clinical applications such as more optimal immune suppression therapy dosing based on genomic compatibility of D-R pairs.

From genotypes to Loss-of-Function variants

Donor and recipient genotypes (>12,000 pairs, of which 888 heart transplant) with extensive phenotype data

Quality control to keep only high quality samples and genetic variants

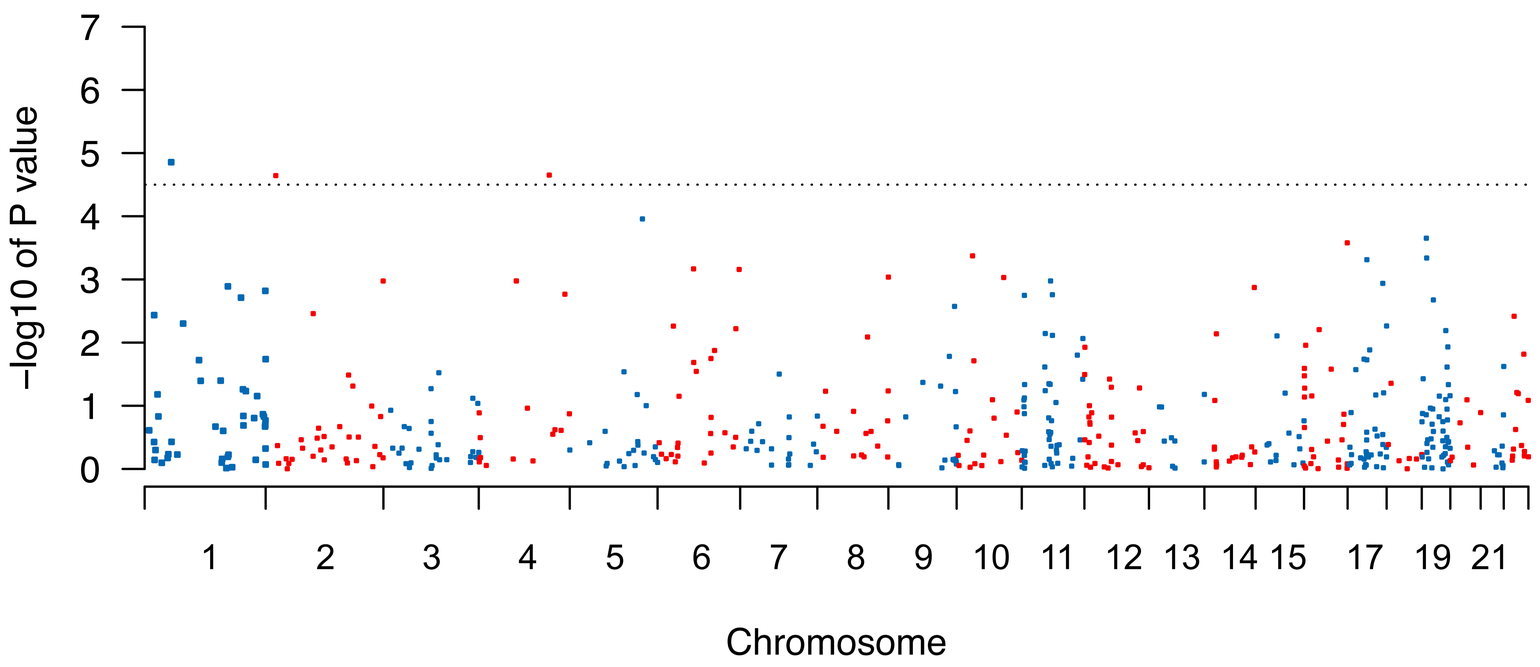
Imputation to increase the number of genetic variants from ~800,000 to 90 million

Quality control to keep only high quality variants (~20 million)

ENSEMBL's Variant Effect Predictor with LOFTEE plugin to extract high-confidence LoF variants, including frameshifts, splice donor and acceptor dinucleotide mutations, and nonsense mutations

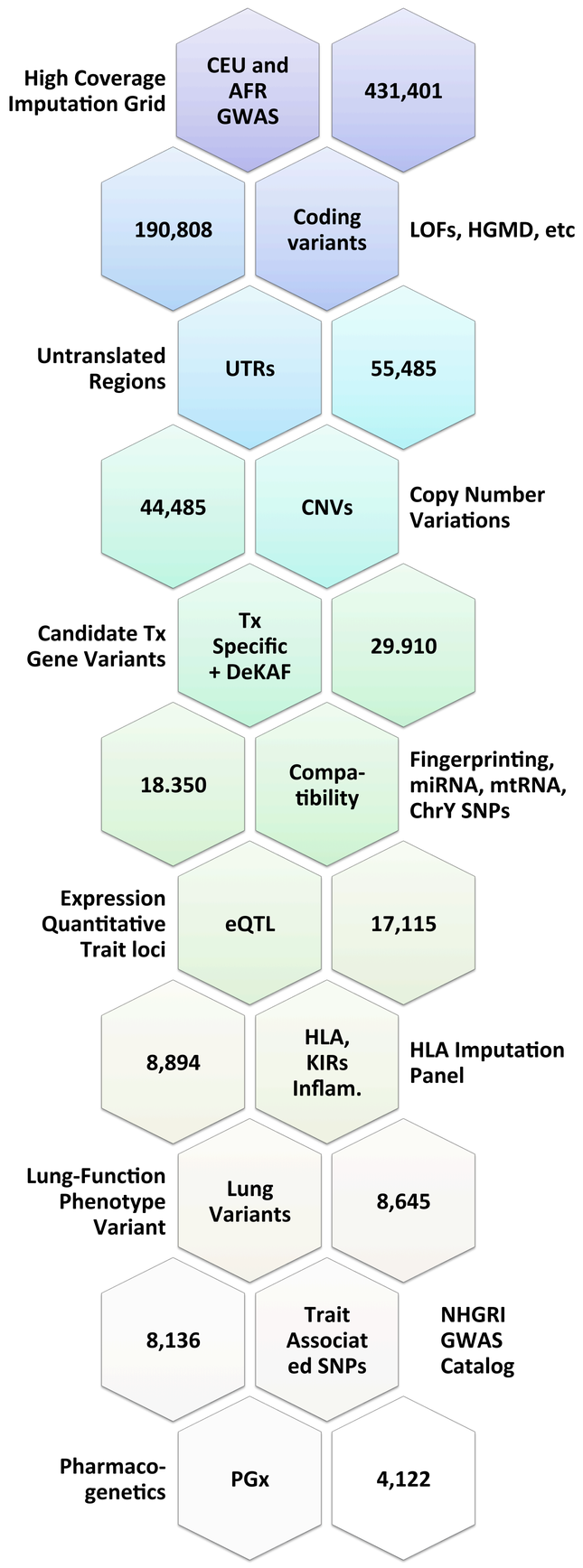
Identify genes that are inactive (two-copy loss) in the recipient but active in the donor

Mismatched genes associated with time to first biopsy proven rejection



We identified 695 genes that were inactive in the recipient but active in the donor in at least one D-R pair. These genes were tested for association with time to first biopsy proven rejection. For this study, we collected 888 D-R pairs from the Netherlands, Spain, and United States. Approximately 30% of patients developed rejection. Three genes were significantly associated with rejection. We aim to replicate our findings in a larger sample, followed by RNA sequencing and *in silico* analyses.

Transplantation-specific genotyping array



We designed a low-cost genome-wide SNP array specifically tailored for the transplantation community containing over 767,000 genetic variants.

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