***In silico* common pathways analysis**

**Methods**

In order to understand the common genetic pathways underlying ALS and other common heath diseases (i.e., coronary artery disease, cardiomyopathy, arrhythmia, heart failure, respiratory failure, pneumonia, metabolic syndrome, dystrophy) we adopted an *in silico* approach similar to the one used by Sukarov et al. (https://pubmed.ncbi.nlm.nih.gov/32299060/) . Briefly, we used *PubTator* (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3692066/>)*,* a freely available text mining tool to automatically annotate publications present in the National Library of Medicine (Pubmed) with the corresponding genes with high accuracy (93%). We used standardized search queries (see Supplementary Materials) for ALS and cardiac diseases. Then we used the {RISmed} R package to retrieve the pubmed ids (PMID) of the retrieved records. Finally, retrieved PMID were compared to the *PubTator* database to retrieve, for each publication, the corresponding associated genes. The Jaccard index was used to test the similarity between the gene sets.

A gene set enrichment analysis for each disease was conducted in the *Reactome* database through the {ReactomePA} R package. Top overlapping pathways were retrieved setting the filters to adjusted p-value < 0.01 and occurrences > 150. Analysis and plotting were conducted with R v.4.3.0.

**Results**

Mean percentage Jaccard index between ALS genes and the other heart disease was 5.6 (sd = 0.8) % showing an overlap of about 5% in the genes. The most overlapping disease was cardiomyopathy with 6.8%, and the least one was heart failure with 4.5% overlapping genes.

We found 1440 Rectome pathways in common among the diseases. Top common pathways involved inflammation and second messengers’ pathways, with SARS -CoV infections pathways present but likely to be “contaminant” pathways. Top pathways are reported in Figure XXX.

Figure caption:

**Top common pathways among ALS and heart diseases.** Pathways in common among ALS and heart diseases from the *in silico* analysis. Pathways were selected using adjusted (false discovery rate) p-values <0.01 and occurrences >150.