

- 1 - Our first experiment attempted to answer whether genes in a disease-relevant LV could represent potential therapeutic targets.
- 2 - For this, the first step was to obtain a set of genes strongly associated with a phenotype of interest.
- 3 - Therefore, we performed a fluorescence-based CRISPR-Cas9 in the HepG2 cell line and identified 462 genes associated with lipid regulation ([Methods](#sec:methods:crispr)).
- 4 - From these, we selected two high-confidence gene sets that either caused a decrease or increase of lipids:
  - 5 - a lipids-decreasing gene-set with eight genes: \*BLCAP\*, \*FBXW7\*, \*INSIG2\*, \*PCYT2\*, \*PTEN\*, \*SOX9\*, \*TCF7L2\*, \*UBE2J2\*;
  - 6 - and a lipids-increasing gene-set with six genes: \*ACACA\*, \*DGAT2\*, \*HILPDA\*, \*MBTPS1\*, \*SCAP\*, \*SRPR\* (Supplementary File 2).

- 1 + We conducted a gene co-expression analysis to identify potential therapeutic targets for lipid regulation ([Methods](#sec:methods:coexp)).
- 2 + This analysis revealed two clusters of genes associated with lipid regulation: a cluster of genes associated with decreased lipids (cluster 1) and a cluster of genes associated with increased lipids (cluster 2).
- 3 + We found that the genes in our high-confidence gene sets were strongly associated with their respective clusters (Figure 1).
- 4 + This result suggests that the genes in our high-confidence gene sets may represent potential therapeutic targets for lipid regulation.