We hypothesized that accounting for epistatic interactions within GSEA will improve the identification of relevant biological themes or pathways and lead to novel hypotheses.

> GSEA uses gene-level univariate associations to identify gene set-phenotype associations for hypothesis generation and interpretation.

> Relief-based algorithms (RBAs) are feature importance scoring and selection methods that uniquely capture both main effects and epistatic interactions with computational efficiency.

> CHD is a genetically heterogeneous disease and the most common birth defect in infants.

**RESULTS**

While only a few of the GO terms from the univariate GSEA met FDR sig. (adj. p < 0.05), top pathways highlighted the epithelial to mesenchymal transition during OFT development.

> Significant (FDR adj p > 0.05) GO terms from the RBA analysis emphasize a number of shared factors that control the patterning of both the nervous and vascular systems.

> Twenty-six genes (Fig. 2) replicated across all four RBA analyses, many of which have been implicated in cardiac development and CHD.

**CONCLUSIONS**

> RBAs offer a computationally efficient approach to ranking features involved with underlying epistatic interactions.

> Using CTD GWAS data, we saw similar themes of cell signaling, cell adhesion, and axon/neuron development and extension replicate across analyses. These GO terms highlight the common factors that guide neural and vascular patterning.

> Leading edge analyses further confirmed the enrichment of genes related to the SHF and CNCC migration in OFT development.

> We speculate that the significant terms related to CNCC migration and progenitor behavior in the SHF captured by the Relief-based analyses reflect interactions between key signaling genes (Fig. 3).

**REFERENCES**