This investigation explores the distribution of polygenic risk scores (PRS) for congenital heart disease (CHD) across six different endo-phenotypes. Previous work showed a significant relationship between case/pseudo-control status and polygenic risk scores (PRS) but the directionality of the effect was opposite from what was expected, with individuals having higher PRS scores having a lower risk of CHD. PRS scores only consider common variants, so perhaps rare variants may be behind this unexpected result. The cases analyzed are probands, which are the offspring of two parents per family, and pseudo controls that are made with one half of the un-transmitted genetic material from parent 1 and the other from parent 2. The purpose of making a pseudo-control instead of using the parents individually was to utilize individuals with the least possible overlap in common allele variants to compare the pseudo-controls and the probands with each other.

**Introduction**

To expand upon this study, the deciles of each endo-phenotype PRS were investigated to characterize finer resolution differences between probands and pseudo-controls. Although the previous paper showed that the heart valve PRS is significantly associated with the phenotype and demonstrates that the tenth decile is significantly different, a Wilcoxon test was conducted to determine the mean difference between the probands and pseudo-controls amongst all deciles and found that there is no significant difference between the two.

**PRS Data Analysis**

Box plots of individual deciles were made to see finer resolution of differences between the first and tenth decile specifically. Once this was determined it was suspected that these interesting but miniscule differences could account for de novo variants, so singletons were used to investigate this hypothesis. Singletons were identified using VCFtools in order to start investigating the distribution of specific probands with each other. By definition are variants that are found in one individual in the entire dataset. Since we have the probands parents’ genetic data, singletons are a good proxy for quantifying de novo variants, which are super-rare variants that are individual to a person and not inherited. The number of singletons for individuals in the top and bottom deciles for all heart valve SNVs PRS and all severity heart sounds SNVs PRS was calculated.

**Conclusion**

In brief, after closely looking at singleton analyses, heart valves for all SNVs PRS was found to have a nominally significant p-value. Thus, it was revealed that more rare variants was seen in the first decile over the tenth, but generally there is no significant difference between the two when examining probands only. To continue this investigation, more types of rare variants and even common variants can be determined in each decile to yield a more accurate understanding of the affected proband’s genetic architecture. Genetic architecture underlying the endo-phenotypes themselves is rather more complex than expected. Thus, different PRS’s might be better for different phenotypes.