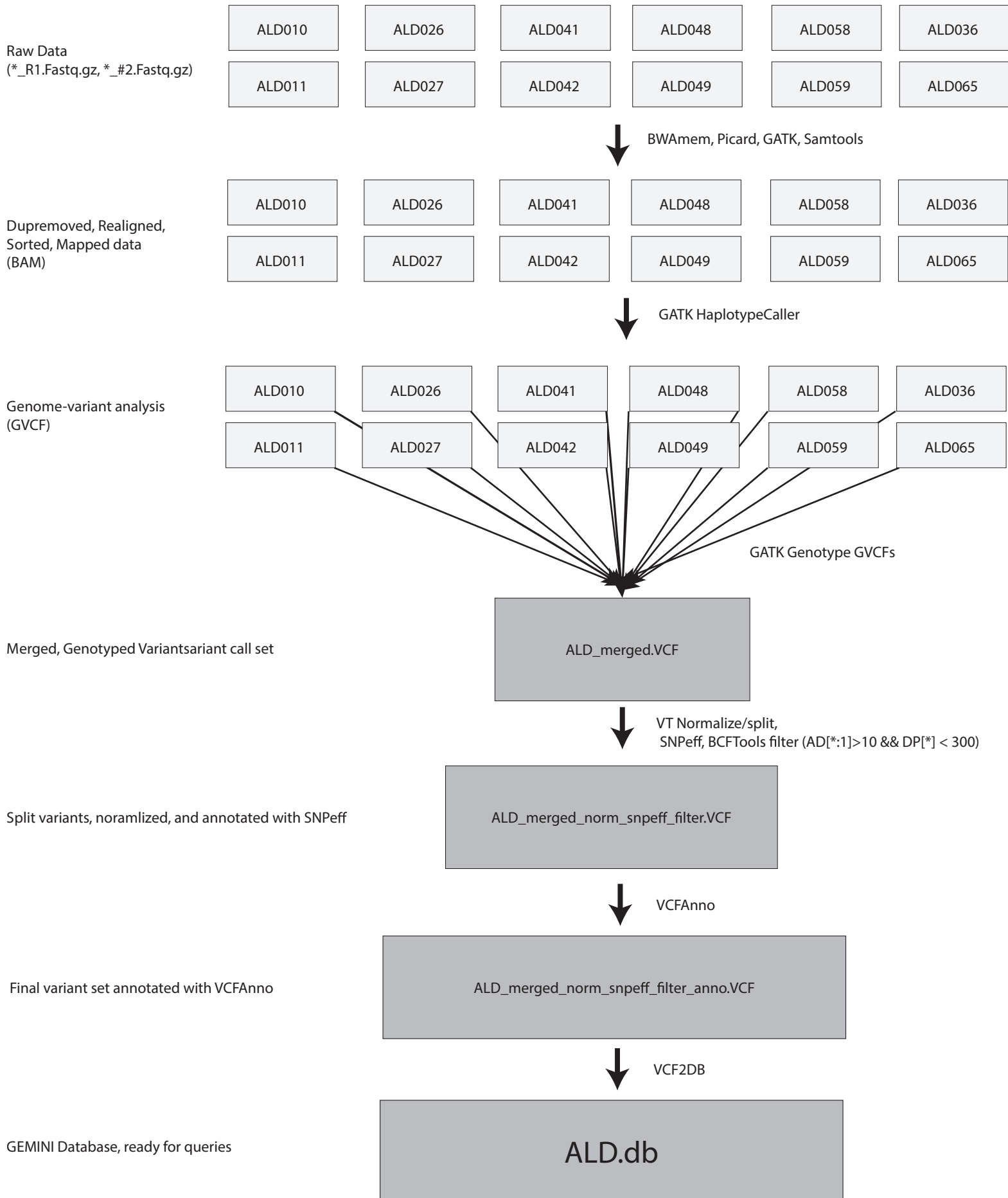


# SNV/Indel Workflow



Supplemental Figure 2

**DOMINANT DAMAGING** - A heterozygous (or homozygous) variant within a CALD sibling, where the AMN sibling is homozygous reference.

Allele Representation:  
(CALD Heterozygous Alternate || Homozygous Alternate) && (AMN Homozygous Reference)

**RECESSIVE DAMAGING** - A homozygous variant within a CALD sibling, where the AMN sibling is heterozygous or homozygous reference

Allele Representation:  
(CALD Homozygous Alternate) && (AMN Heterozygous || Homozygous Reference)

**DOMINANT PROTECTIVE**- A heterozygous (or homozygous) variant within a CALD sibling, where the AMN sibling is homozygous reference.

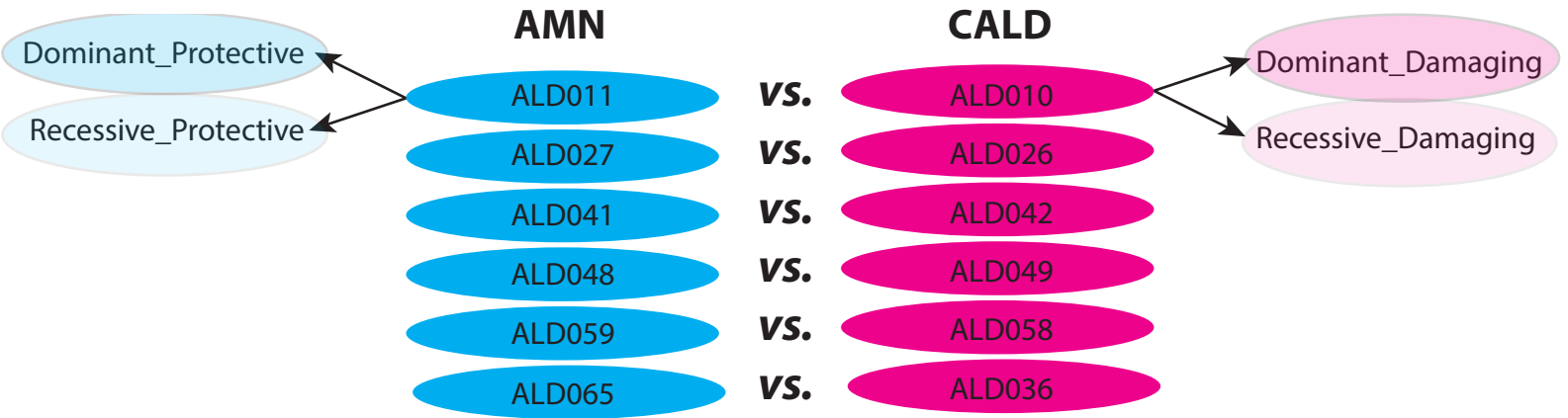
Allele Representation:  
(AMN Heterozygous Alternate || Homozygous Alternate) && (CALD Homozygous Reference)

**RECESSIVE PROTECTIVE**- A homozygous variant within a AMN sibling, where the CALD sibling is heterozygous or homozygous reference

Allele Representation:  
(AMN Homozygous Alternate) && (CALD Heterozygous || Homozygous Reference)

## Approach

Pairwise comparisons between siblings to extract the individual categories (Dominant Damaging, Recessive Damaging, Dominant Protective, Recessive protective).

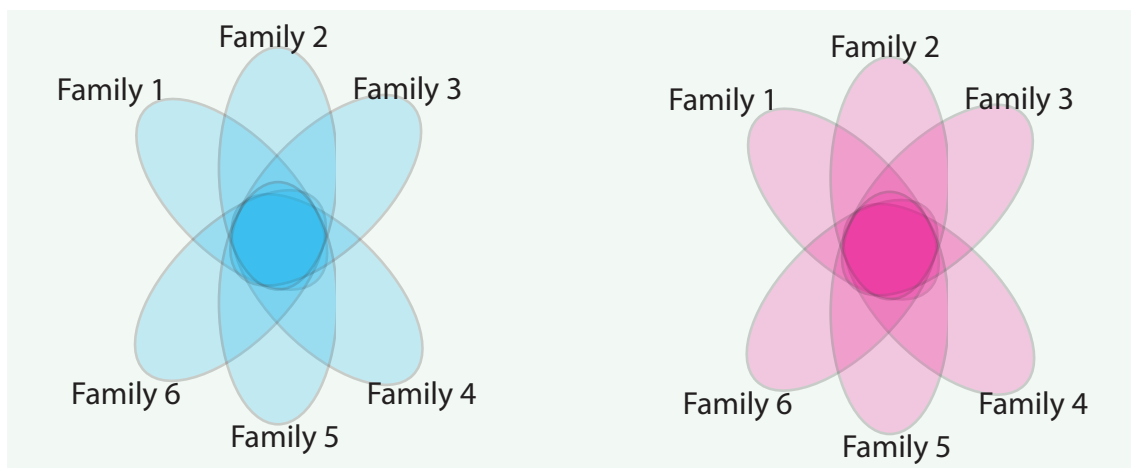


Summary of these intra-family comparisons can be found in Table 1

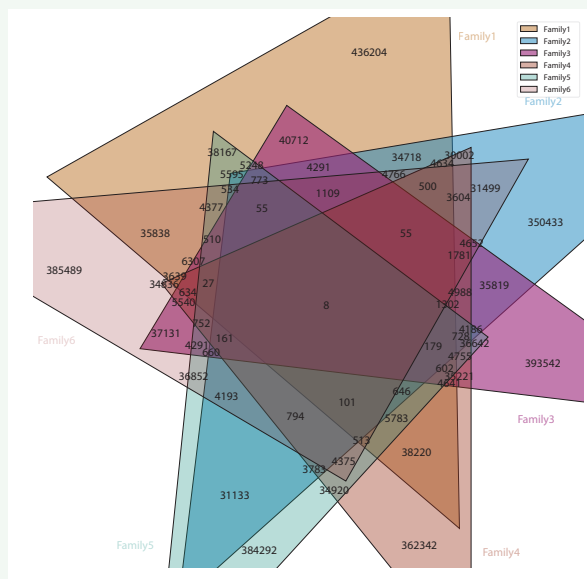
# Variant Level Analysis

Next, we will run intersections across families, using the categories from the intra-family comparisons.

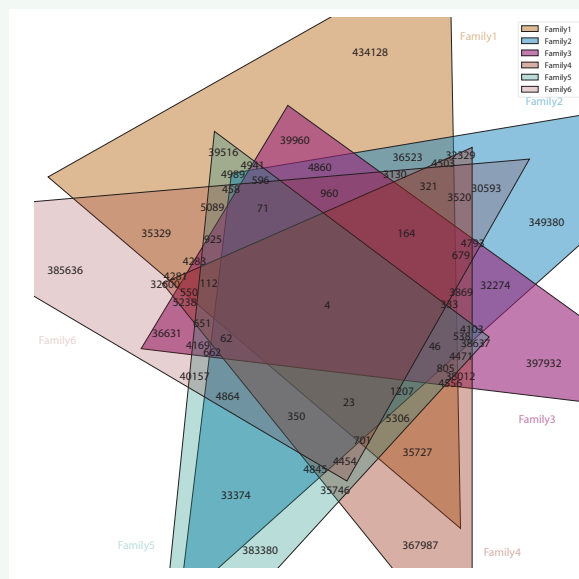
Genehancer



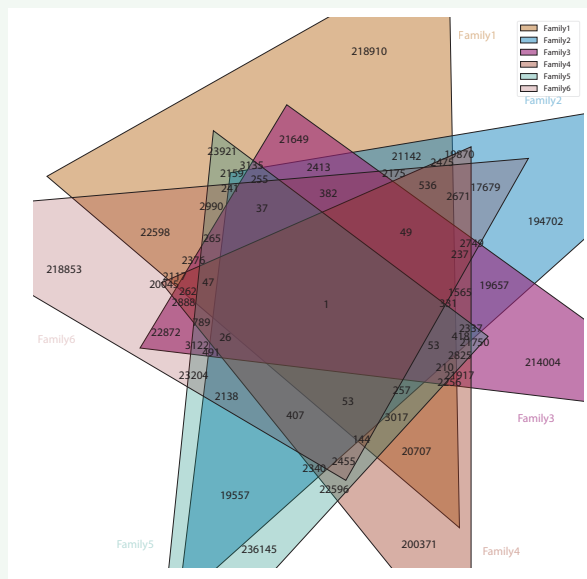
## Dominant Protective



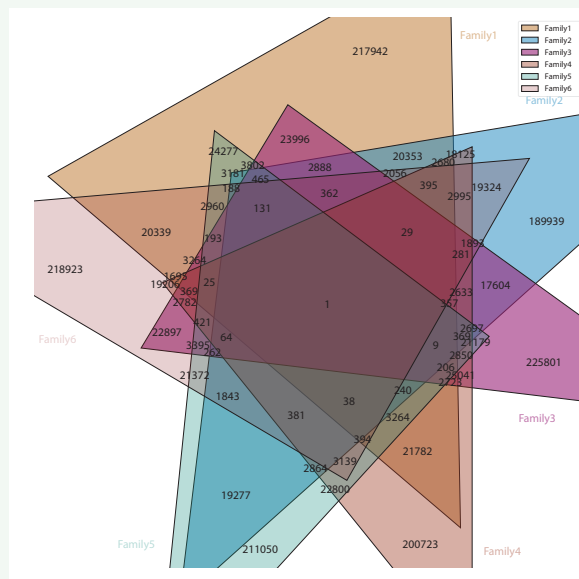
## Dominant Damaging



## Recessive Protective



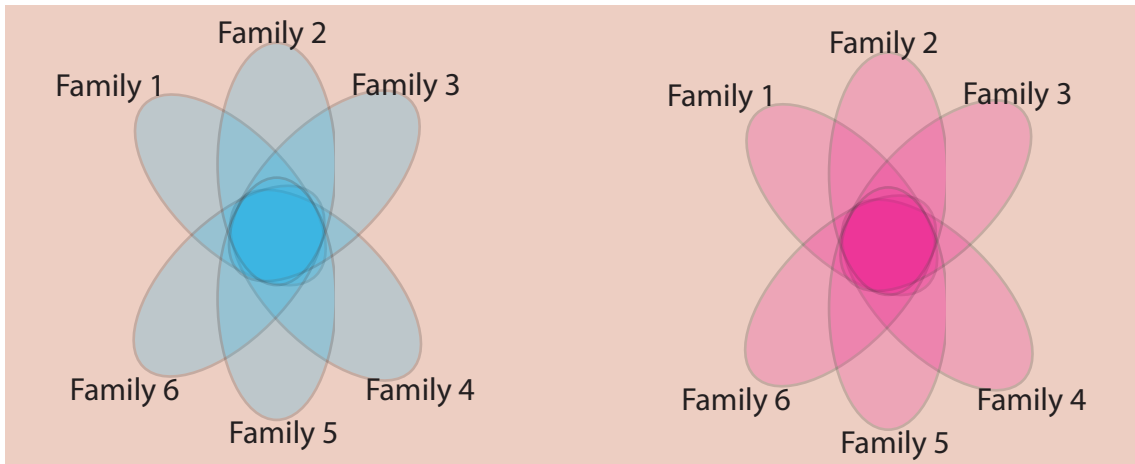
## Recessive Damaging



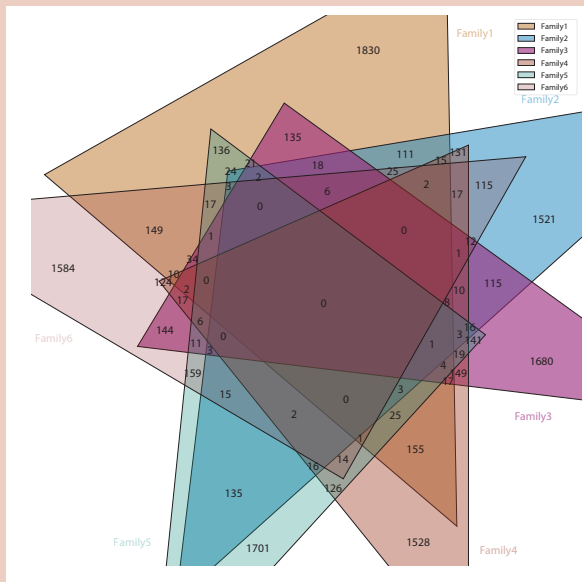
# Variant Level Analysis

Next, we will run intersections across families, using the categories from the intra-family comparisons.

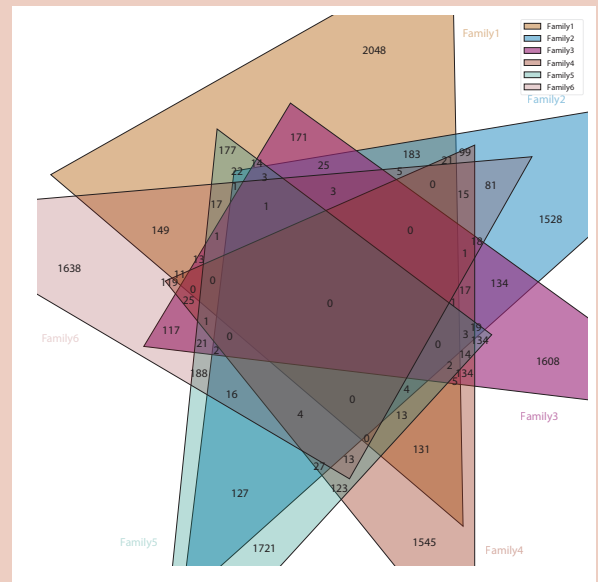
HIGH/MED



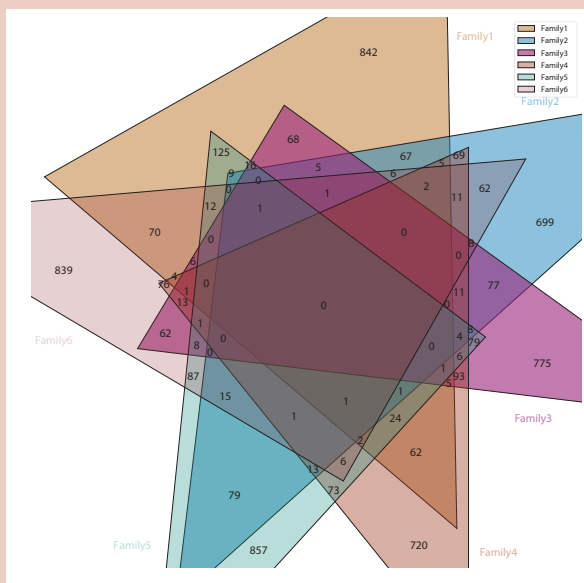
## Dominant Protective



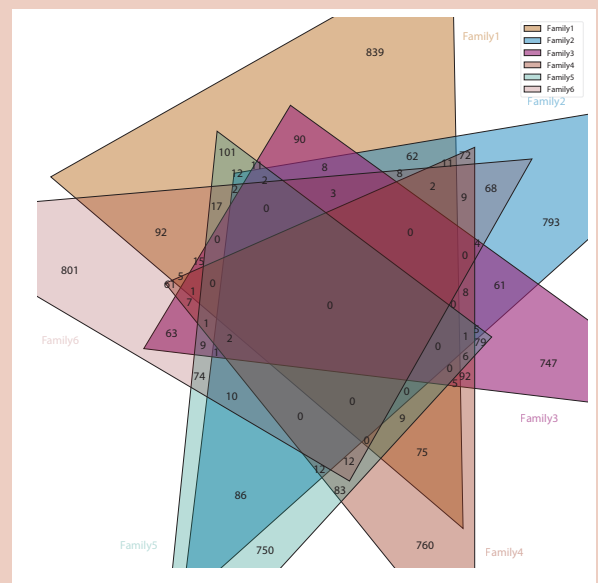
## Dominant Damaging



## Recessive Protective



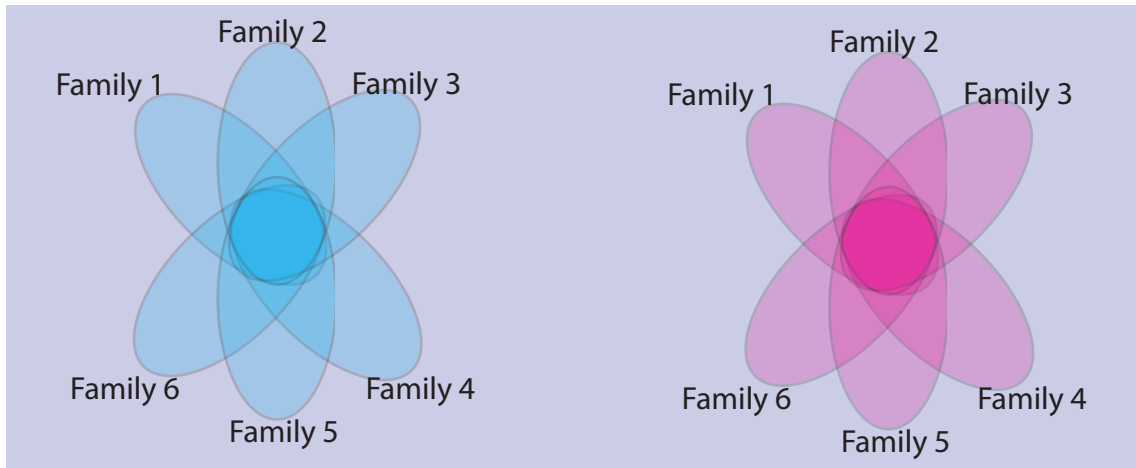
## Recessive Damaging



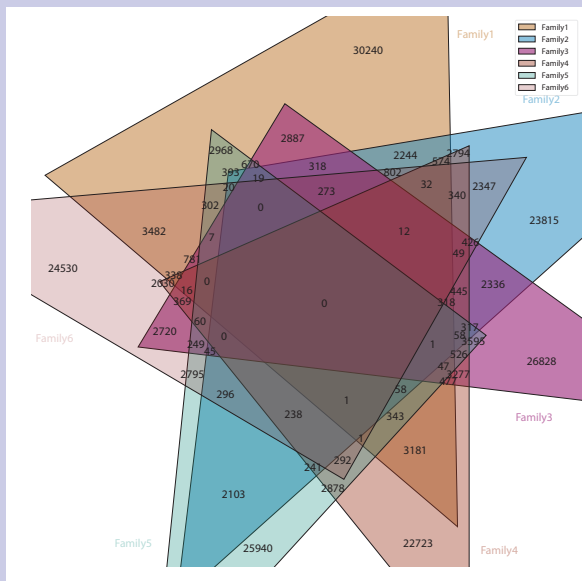
# Variant Level Analysis

Next, we will run intersections across families, using the categories from the intra-family comparisons.

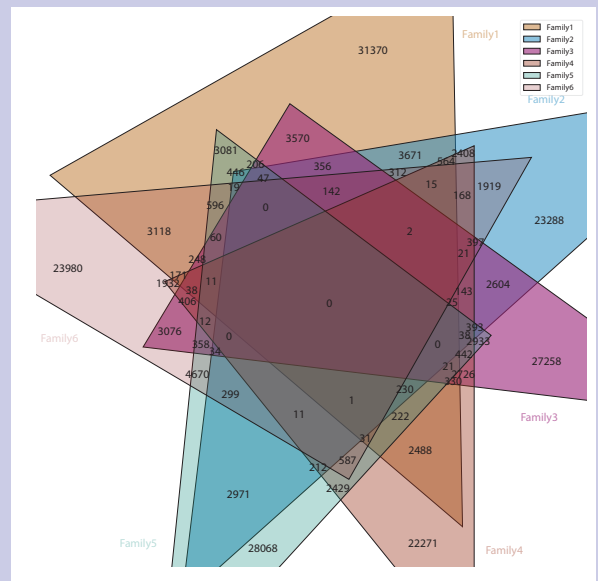
eQTL



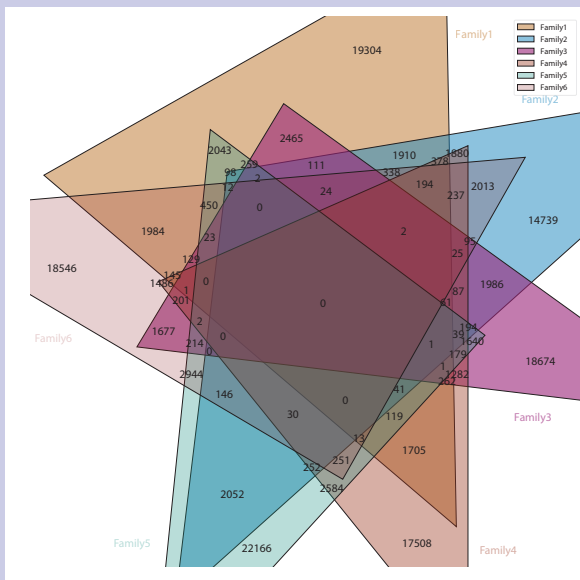
## Dominant Protective



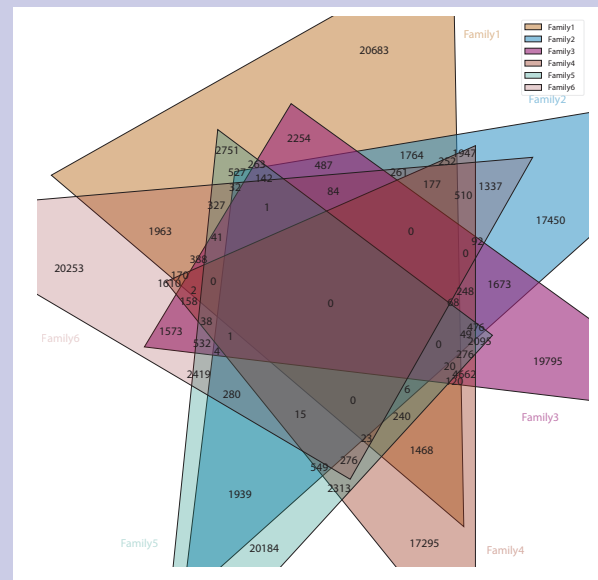
## Dominant Damaging



## Recessive Protective



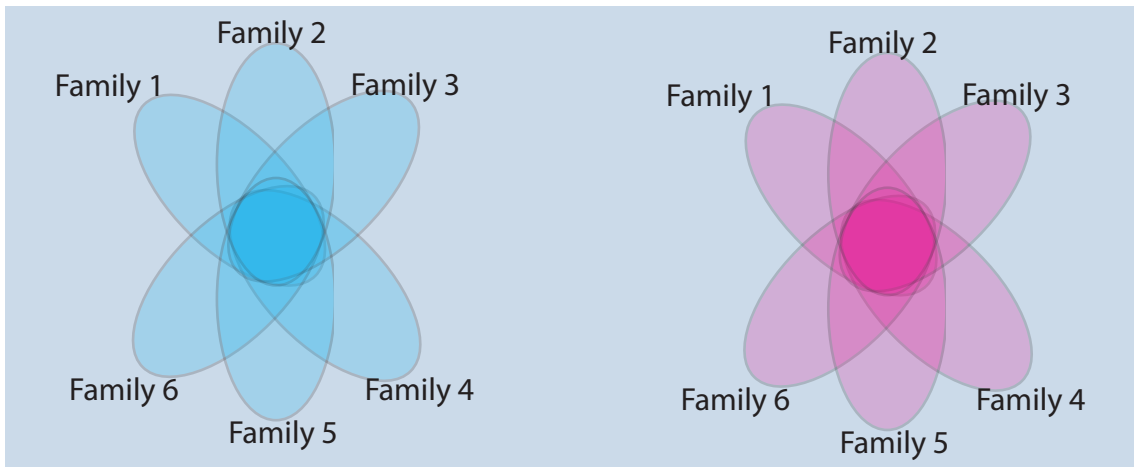
## Recessive Damaging



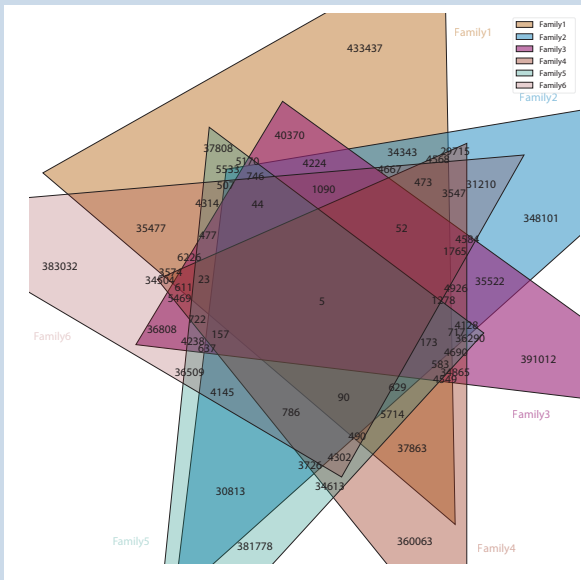
# Variant Level Analysis

Next, we will run intersections across families, using the categories from the intra-family comparisons.

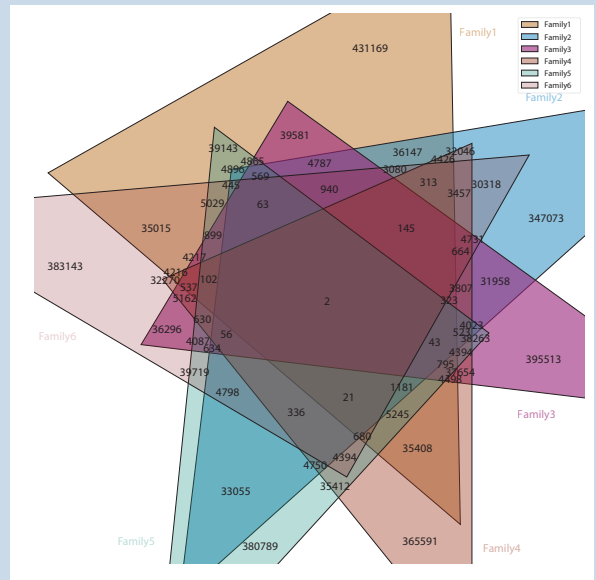
LOW



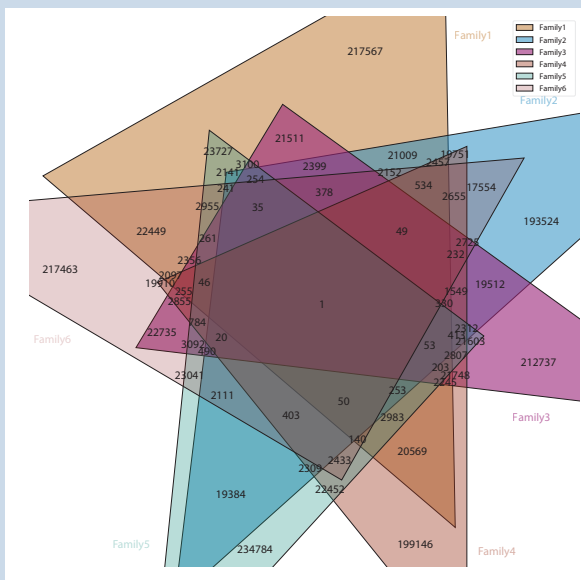
## Dominant Protective



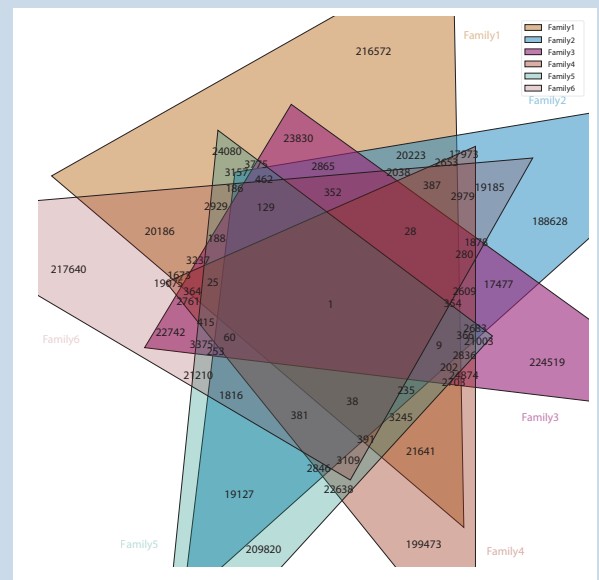
## Dominant Damaging



## Recessive Protective



## Recessive Damaging



# Gene Level Analysis

For this analysis, we are going to abstract the variants out to the gene level per family, and then run intersections. It only makes sense to perform this at the HIGH/MED level, not cis-regulatory

Variant Level

Dominant\_Protective

Recessive\_Protective

Dominant\_Damaging

Recessive\_Damaging

Gene Level

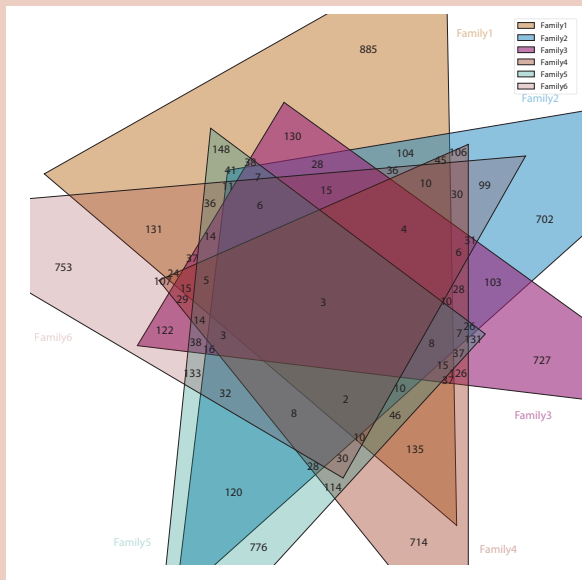
Dominant\_Protective Genes

Recessive\_Protective Genes

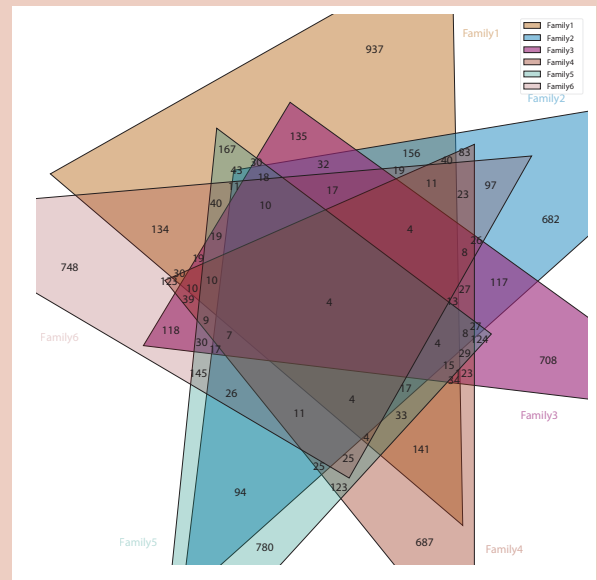
Dominant\_Damaging Genes

Recessive\_Damaging Genes

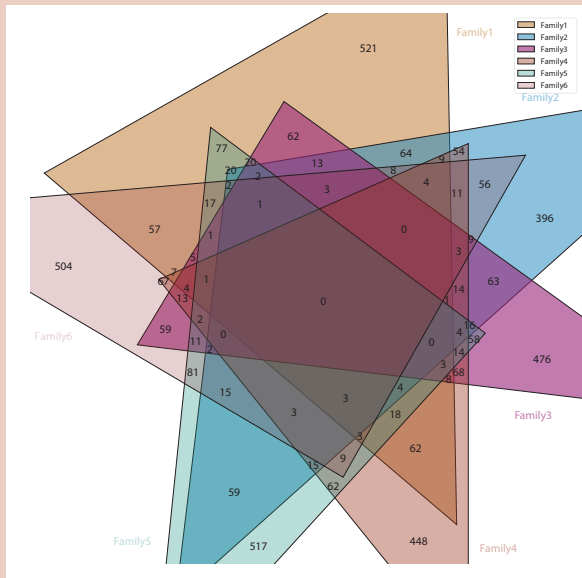
## Dominant Protective



## Dominant Damaging



## Recessive Protective



## Recessive Damaging

