

Supplemental Figures

Supplemental Figure 1 : Sharing of deleterious variation relative to equivalent neutral variants.

Supplemental Figure 2 : PCA of married-in pedigree members with unrelated TS cases and controls

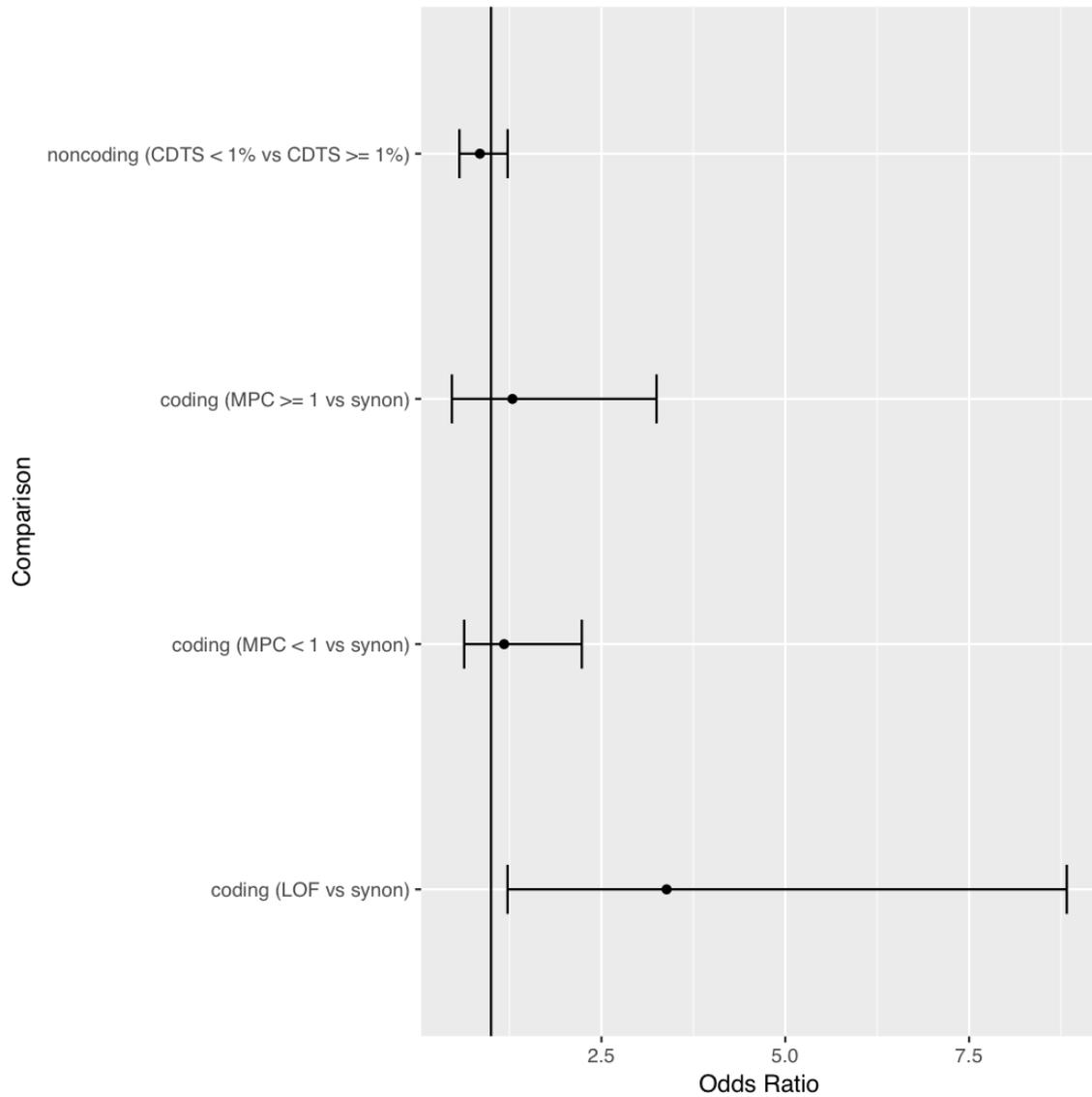
Supplemental Figure 3 : PCA of a key in-family individual with unrelated TS cases and controls.

Supplemental Figure 4 : Comparisons of OCD GRS to unrelated controls

Supplemental Figure 5 : Comparisons of ADHD GRS to unrelated controls

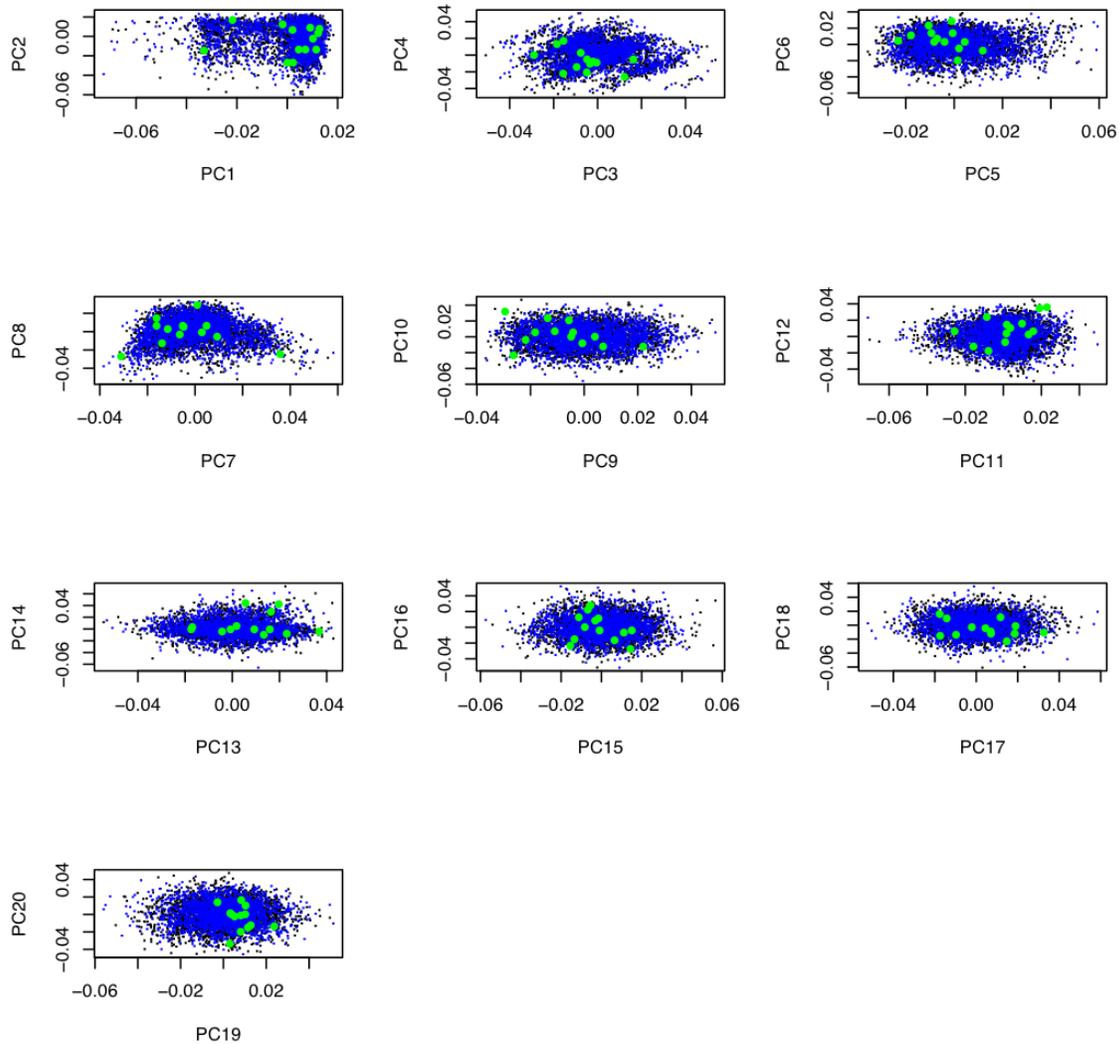
Supplemental Figure 6 : Relatedness-aware pairwise comparisons of GRS using a logistic mixed model

Supplemental Figure 1 : Sharing of deleterious variation relative to equivalent neutral variants.



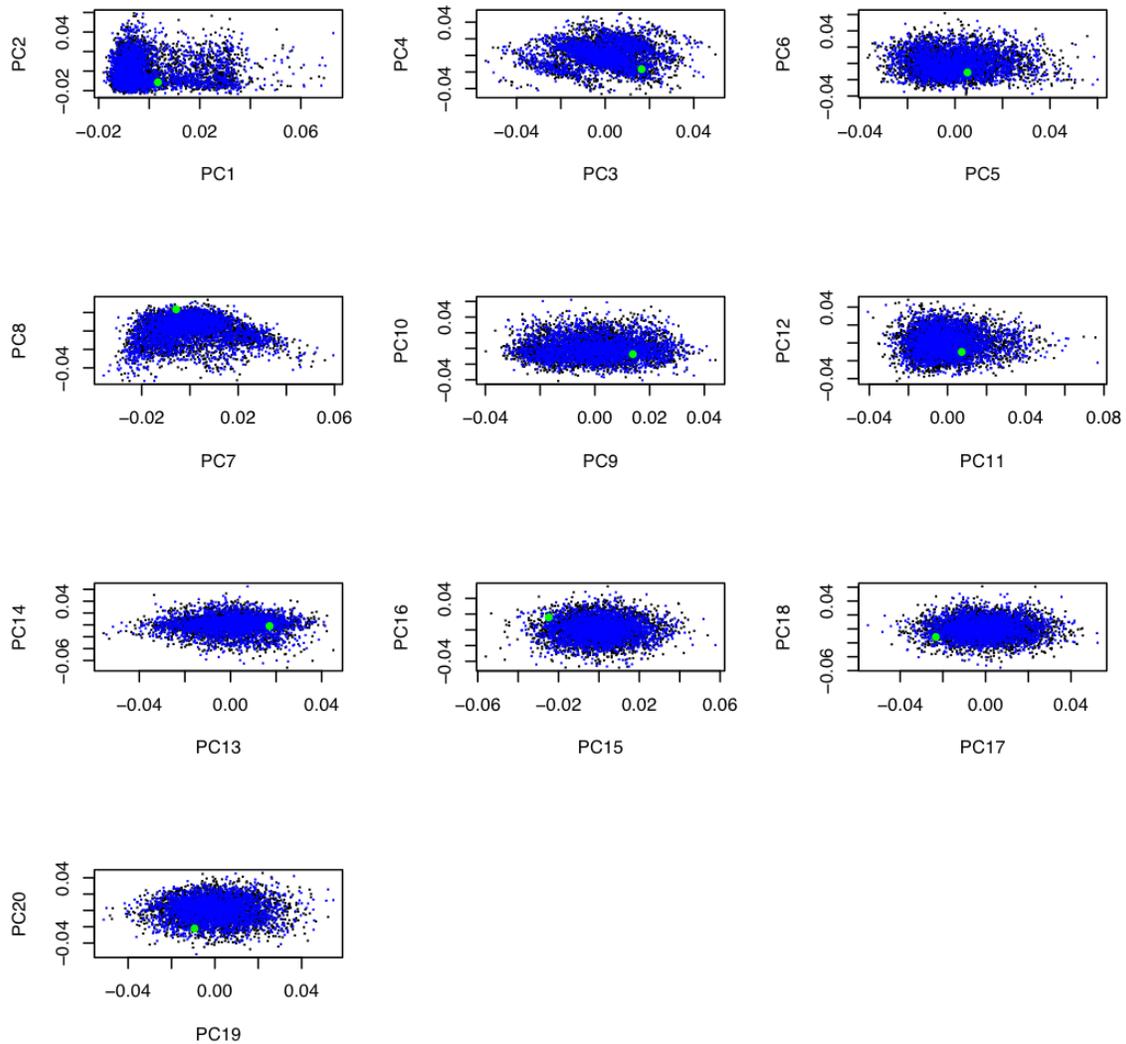
We compared the portion of deleterious SNVs and indels that were shared in two or more of the 8 index cases that were whole genome sequenced relative to those found in only one sample. We compared the patterns of sharing to variants that fit the same general annotation as the test group (coding, noncoding) but are considered neutral in comparison. For coding variation we used synonymous variation, whereas for noncoding variation we used variants in a region with CDTS $>$ 5%. The only class of variation where we found some evidence of oversharing was loss of function variation SNVs and indels, relative to synonymous variants.

Supplemental Figure 2 : PCA of married-in pedigree members with unrelated TS cases and controls



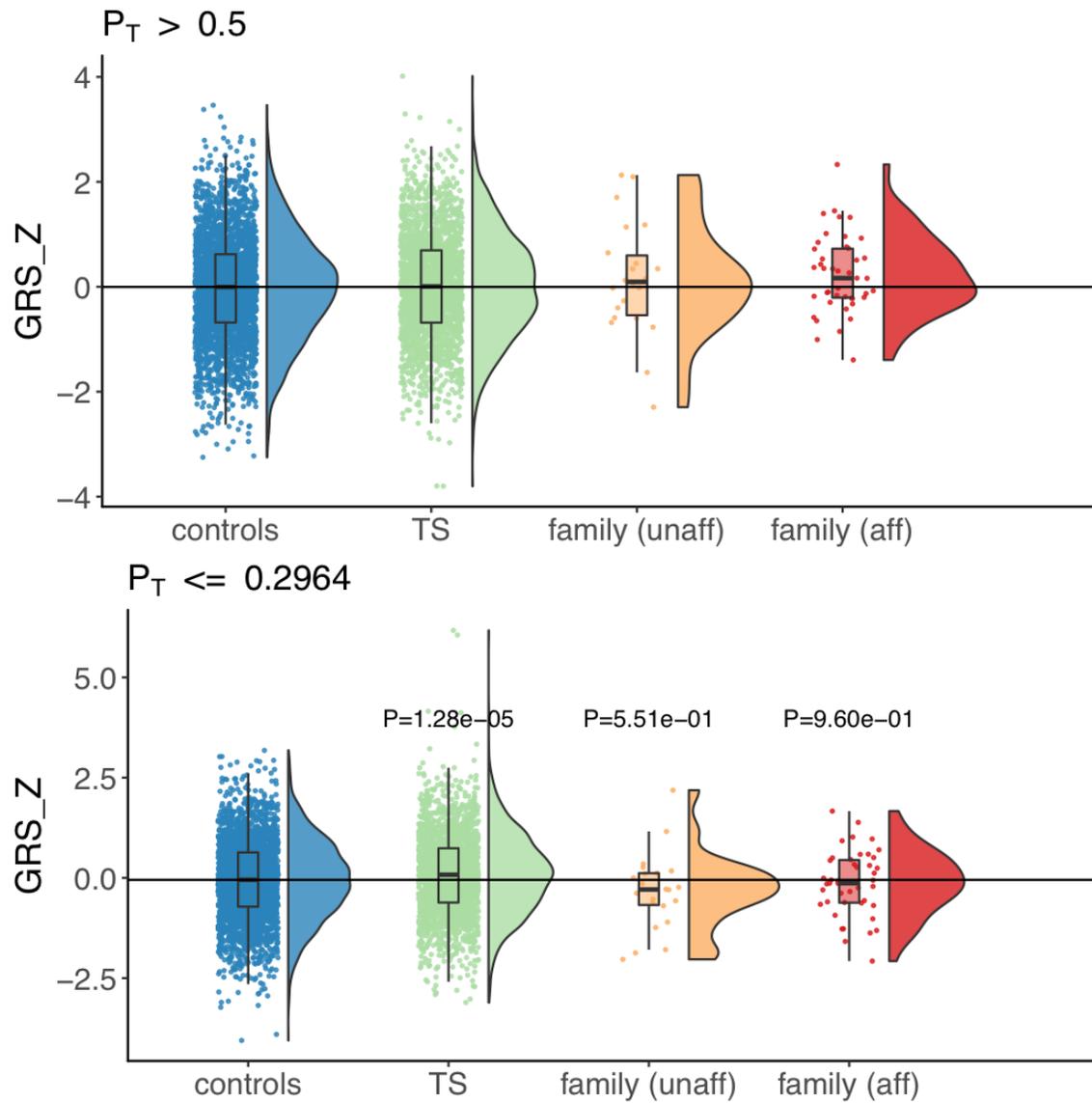
To determine if there was any evidence for systemic differences in genetic data from pedigree members and from unrelated TS cases and controls, we selected 13 members of the pedigree that were married into the family and have no relatedness to one another. We then performed PCA on the genetic data from these combined samples. We see that there is no clear separation of unrelated TS cases (blue) and unaffected controls (black), as expected. We also see that the married-in pedigree members (green) do not form a separate cluster in any PC, acting as strong evidence that the pedigree data do not have strong biases compared to additional unrelated samples based on ethnicity or other unknown factors.

Supplemental Figure 3 : PCA of a key in-family individual with unrelated TS cases and controls.



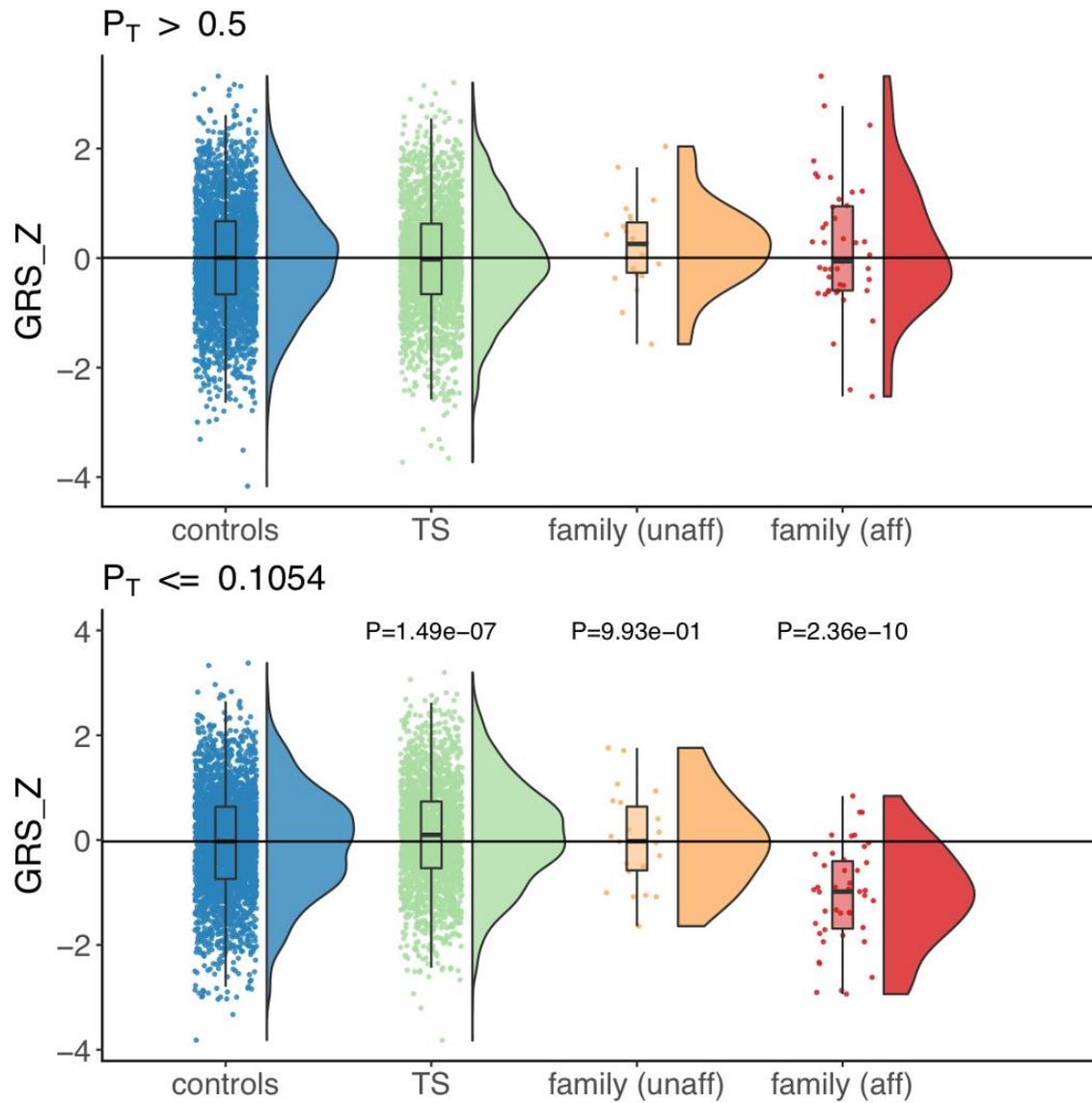
PCA of a single in-family individual selected based on their being the individuals with DNA that was available that among the closest in relationship to the founders in the pedigree. As in Supplemental Figure 2, We see that there is no clear separation of unrelated TS cases (blue) and unaffected controls (black). We also see the key family member (green) clusters well with unrelated TS cases and controls across all PCs.

Supplemental Figure 4 : Comparisons of OCD GRS to unrelated controls



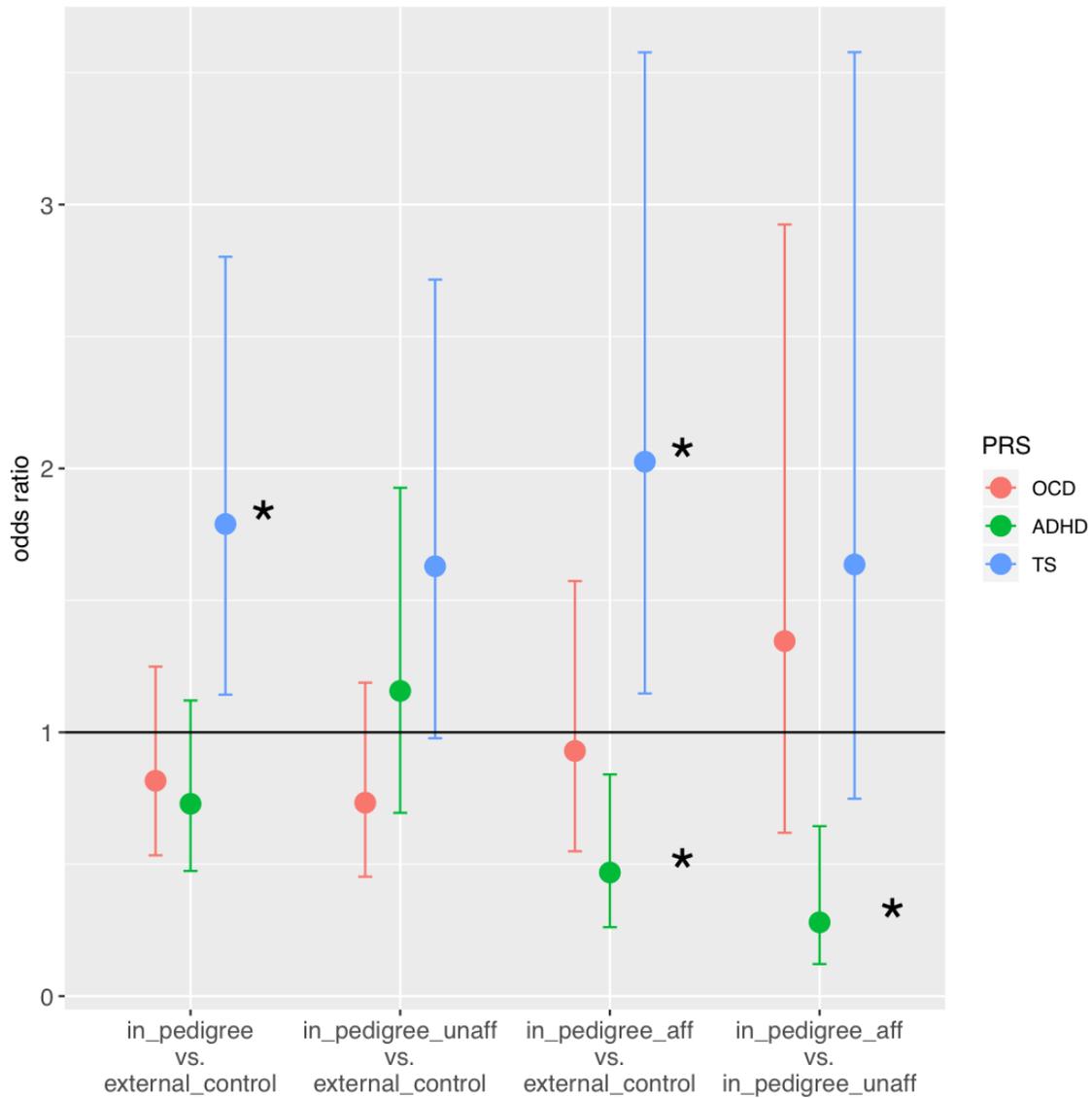
We performed the same GRS procedure as that focused on TS described in the main text, here instead focused on OCD GRS. As before, we show that GRS produced from lead SNPs with $P_T > 0.5$ do not segregate any group from controls (top). We do not observe any significant separation of pedigree members (both unaffected and affected) from controls (bottom).

Supplemental Figure 5 : Comparisons of ADHD GRS to unrelated controls



We repeat the GRS procedure, this time focused on ADHD GRS. Again, GRS produced from lead SNPs with $P_T > 0.5$ do not segregate any group from controls (top). Interestingly, we observe a significant drop in ADHD GRS in affected pedigree cases, but none in unaffected cases (bottom). As expected, unrelated TS cases display a higher GRS on average than controls.

Supplemental Figure 6 : Relatedness-aware pairwise comparisons of GRS using a logistic mixed model



Here, we show the results of pairwise comparisons between pedigree samples (n=65 total) with a randomly selected set of external controls (n=260). The control sample size was chosen to obtain a 1:4 pedigree/control sample ratio. Dots indicate the odds ratio point estimate, bars indicate the 95% confidence interval around the estimate, and stars indicate instances where the significance level of the result survives correction for a 10% false discovery rate. Relative to external controls, the only GRS that is elevated in the pedigree is for TS. This excess preferentially maps to affecteds within the pedigree.