Tacrolimus (Tac) is an immune suppressant used in >90% of organ transplant recipients. Tac has a narrow therapeutic index and troughs, routinely monitored, are associated with efficacy and toxicity. Tac troughs are highly variable partly due to genetics. To address this variability, we performed next generation sequencing and extreme phenotype sampling (EPS) to identify novel genetic variants associated with tacrolimus metabolism in kidney transplant recipients.

**Methods**

We performed targeted sequencing of gDNA from a cohort of 1,443 transplant recipients using next generation sequencing (NGS) and extreme phenotype sampling (EPS). Subject DNA was genotyped. Linear mixed-effects models were used to test for associations between ln–transformed Tac troughs from the EA or AA cohorts, after accounting for clinical factors (Table 2). By both logistic regression case-control test and linear regression continuous trait test.

**Results**

- **15 Variants in POR, ADIPOR1, OVCH2 and CYB5R2 were associated with AA group (p<0.005)**
- **9 Variants in ABC1C1, ANAPC10, NR3C1 and OTUD4 were associated with EA group (p<0.005)**
- **Gene based test identified the association of CYB5R2 with Tac and AAs (SKAT, p=0.0007)**
- **In CYB5R2, rs61733057 (elevated allele frequency in AAs) was predicted to disrupt protein function by SIFT & PolyPhen2**

**Conclusions**

The identified variants in CYB5R2 and other genes merit further validation and investigation relevant to Tac metabolism.

---

**Acknowledgements:** This study was supported in part by NIH/NIAID grants 5U19-AI070119, 5U01-AI058013 and K01AI130409.