PrgmNr 2459 - Mitochondrial and sex chromosome genetically regulated gene expression implicates new genes in complex traits across multiple human populations

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The majority of GWAS are conducted in European ancestry populations and are limited to autosomal chromosomes, ignoring the genetic content of the mitochondria and sex chromosomes. Alongside GWAS, transcriptome-wide association studies (TWAS) can provide useful information about the direction of gene regulation underlying complex traits. Given the genetic diversity among individuals, we sought to build mitochondrial and sex chromosome transcriptome prediction models for use in TWAS in diverse populations, including those underrepresented in GWAS and TWAS.

We used transcriptome data from the Multi-Ethnic Study of Atherosclerosis (MESA) comprised of up to 1004 individuals of African, Chinese, European and Hispanic/Latino ancestries. For each of 3 blood cell types, peripheral blood mononuclear cells (PBMC), CD16+ monocytes, and CD4+ T cells, we built models in each population and also a model including all individuals. We used cross-validated elastic net to estimate gene expression from local SNPs within 1Mb of each gene through an additive linear model. Depending on population, our modeling resulted in 24-57 genes with Spearman correlation Ï>0.1. Smaller sample sizes were available for monocytes and T cells, resulting in 3-16 and 4-13 genes with Ï>0.1, respectively. Most predicted genes were on the X chromosome, while few Y chromosome and mitochondrial genes had Ï>0.1.

With these prediction models, we applied S-PrediXcan to X chromosome GWAS summary statistics from two different multi-ancestry studies, the Population Architecture using Genomics and Epidemiology (PAGE) study (n=49,839) and Pan UK Biobank (PanUKB, n=488,377). We identified 5 gene-trait pairs that were significant in both studies (PGRIPAP1 associated with diastolic blood pressure, *STARD8* with platelet count, *PLXNA3* with triglyceride levels, and both *TSC22D3* and *SPIN2B* with height. Of these 5 gene-trait pairs, only *STARD8* - platelet count association had been reported previously; thus, the remaining 4 correlations may be novel. For the mitochondrial genes, GWAS summary statistics were only available from the UK Biobank. We identified statistically significant correlations between *MT-ND3* and mean corpuscular hemoglobin, mean corpuscular volume, mean platelet volume, plateletcrit, red blood cell count and red blood cell width distribution (P-7). We expect that conducting more integrative omics studies that include mitochondria and sex chromosomes in multi-ethnic cohorts will identify new gene-trait associations and promote diversity in biomedical research.