The placenta is the master regulator of the intrauterine environment1 and has lifelong impacts on health by altering developmental programming and influencing risk of common health conditions2. Large consortia studies of tissue-specific gene regulation underrepresent the placenta, especially in minority populations3–6. It is imperative to curate datasets with the unique goal of studying biological mechanisms within the placenta and integrate them with phenotypic data to interrogate effects of genomic dysregulation of the placenta on complex traits across the life course: perinatally, in childhood and adolescence, and later on in life. For example, changes in placental genomics are strongly associated with disparities in gestational course and outcomes7,8, and disentangling genetic and environmental effects on placental genomics can fill intractable gaps in understanding interrelated phenotypes, like metabolic traits and neurodevelopment.

Through integration of transcriptomic and genome-wide association studies (GWAS), it has been shown that genetic dysregulation of certain genes in the placenta may underlie genetic associations with both early- and later-in-life phenotypes, primarily with metabolic and anthropomorphic traits6,9. However, it is unclear if these genetic effects mediated by the placental transcriptome carry over across the life course or are localized to early childhood or generalize to populations not from European ancestry. Past studies are limited by poor diversity of ancestries and socioeconomic environments of the study populations, which hinders the ability to employ more sophisticated statistical methods to discover causal mechanisms linking placental genomics and phenotypes. **In this proposal, we will produce and analyze the first multi-ancestry placental genomic dataset, enabling us to uniquely study (1) the interplay between genetics, the environment, and placental genomics and (2) how phenotypes are driven by placental genomics and if these effects persist across the life course.**

We have organized a collaboration between three multi-ancestry cohorts (the Extremely Low Gestational Age Newborn Study, the Rhode Island Child Health Study, and the Growing Up in Singapore Towards healthy Outcomes Cohort) of fetal genetics and fetal -side placental genomics. In total, this study sample comprises of nearly 800 samples across individuals of European, African, Hispanic/Latin American, and East Asian ancestry with varied socioeconomic environments. We aim to catalogue the genetic effects on the placental transcriptome across multiple genetically-determined ancestries and across the various component cell-types that comprise the placenta and release these results to the scientific community as a resource. We will also develop methods to estimate the causal effects of genetic dysregulation of placental transcriptomics on related childhood and adult phenotypes, examining if the effects of these genetic loci are localized to one point of the life course.

*Aim 1: to detect genetic effects on the placental transcriptome, both on bulk tissue and deconvoluted cell-type levels.* Through mega-analysis across our multi-ancestry cohort, we will estimate the genetic effects on bulk placental gene and isoform expression10,11 and alternative splicing patterns12 using linear regression and conditional permutation testing to identify independent signals. Next, as the placenta is a heterogenous tissue, comprising of multiple cell-types (trophoblasts, myeloid cells, stromal cells), we will use single-cell RNA-seq expression profiles to reconstruct cell-type-specific gene expression for each sample13. By jointly modeling the shared and unique components of these cell-type-specific gene expression profiles, we will estimate cell-type-shared and -specific genetic effects on the placental transcriptome14.

*Aim 2: to detect ancestry-specific and environmentally-influenced genetic effects on placental transcriptomics.* We will use local ancestry inference and multivariable regression to estimate ancestry-specific allelic effects on the placental transcriptome. This analysis will reveal genetic variants with potentially different effects on gene expression across ancestry groups. Next, we will explore if ancestry-specific genetic effects attenuate when the multivariable regression models are adjusted with interactions with clinical and demographic variables. This analysis will study whether these genetic effects on the transcriptome are modified by differences in the environment, which may have key influences on placental genomics.

*Aim 3: to detect susceptibility genes for anthropomorphic and metabolic trait with differing effects across the life course.* Using traditional methods to integrate GWAS and transcriptomic data15,16, we will first detect any genes whose placental expression may underlie genetic associations with childhood and later-in-life metabolic traits. We will also develop methods that leverage instrumental variable analysis and mediation analysis to estimate whether the effects of genetic dysregulation of placental transcriptomics are localized to childhood traits, or if they have carry-over effects later-in-life.

The proposed work aims to provide in two major contributions to the field. First, we will provide a valuable catalogue of the genetic effects on placental transcriptomics: on both the gene- and isoform-level, across a variety of previously understudied ancestries, and across the various component cell-types that comprise the placenta. Second, we will develop and apply a novel methodology to study longitudinal genetic effects, mediated by genomic features, across related metabolic and anthropomorphic phenotypes across the life course. These contributions will enable the developmental genetic and molecular epidemiology community with valuable tools to further study the effects of the placenta and, more generally, other developmental tissues on complex traits, particularly from a life-course perspective.

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