

# The Genetic Architecture of Cervical Length and Risk of Spontaneous Preterm Birth

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## Introduction

Sonographic cervical length is a powerful predictor of spontaneous preterm birth (sPTB) and is used as part of clinical care to prevent preterm birth. Twin and family studies have established a maternal genetic heritability for sPTB ranging from 13 to 20%. Yet, there are no corresponding estimates of heritability for mid-trimester cervical length or an understanding of how genetic factors contribute to changes in the cervix across pregnancy.

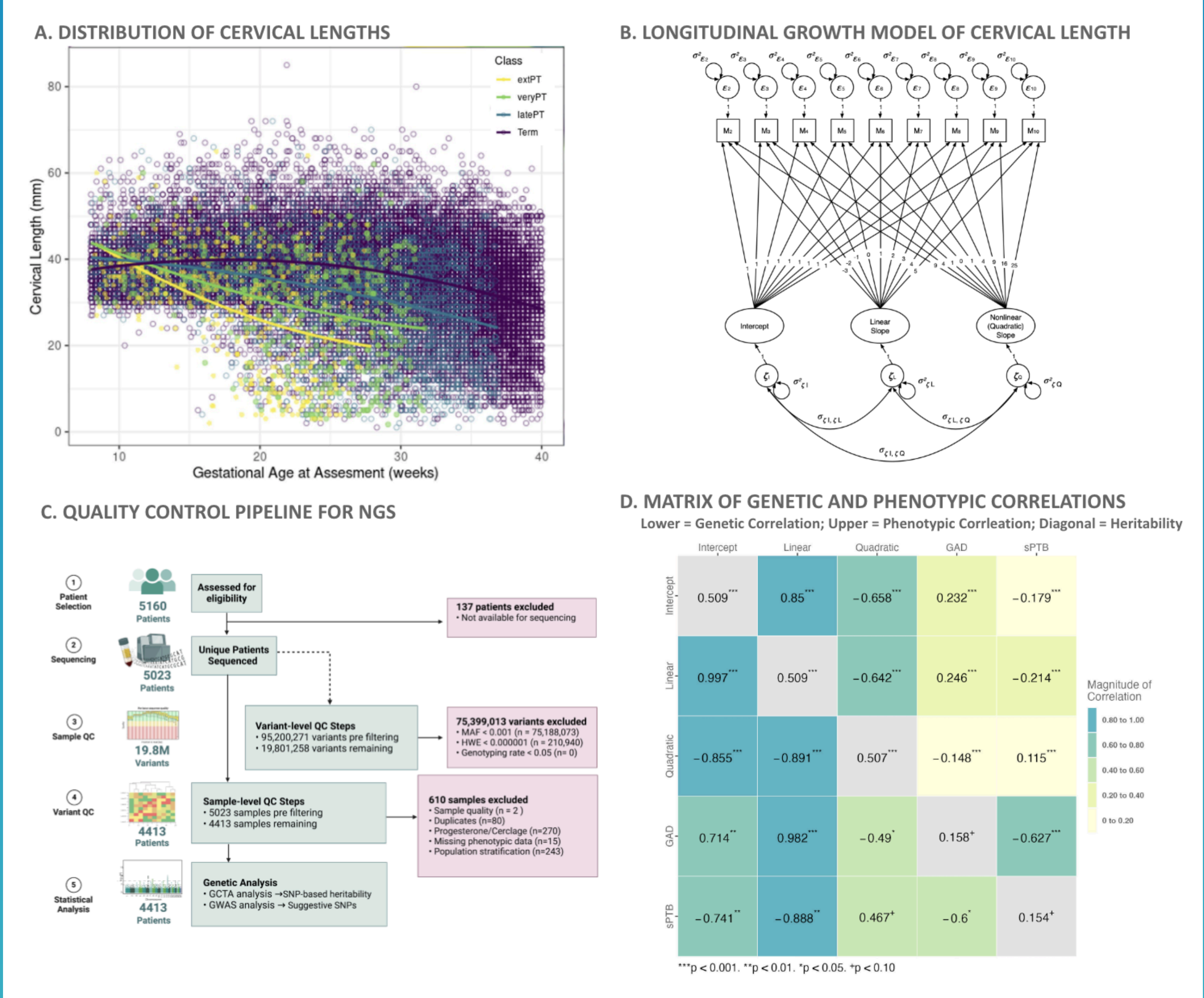
## Objectives

1. Provide the first heribility estimate for cervical length change in pregnancy.
2. Estimate the extent to which genetic factors contributing to cervical length also influence pregnancy duration. (*i.e.*, genetic correlation).

## Methods

- Next-generation 1x sequencing was performed on maternal blood DNA from **5023** patients resulting in **19.8M** variants and **4413** samples after quality control.
- The cervix was imaged via **transvaginal ultrasound** between **8 and 40 weeks** of gestation, with a median of 5 (IQR: 3-8) serial CL measurements recorded per pregnancy.
- Gestational age at assessment (GAA) and gesational age at delivery (GAD) were measured from the last menstrual period and confirmed by ultrasound.
- Pregnancy-specific change in CL during pregnancy was modeled as a non-linear **longitudinal growth curve**, described by an intercept (I), linear slope (L), and quadratic slope (Q).
- Heritability and genetic correlations were estimated using Genome-wide Complex Trait Analysis (GCTA, Yang 2011).

# Shared Genetic Etiology between Cervical Length and Preterm Birth



## Results

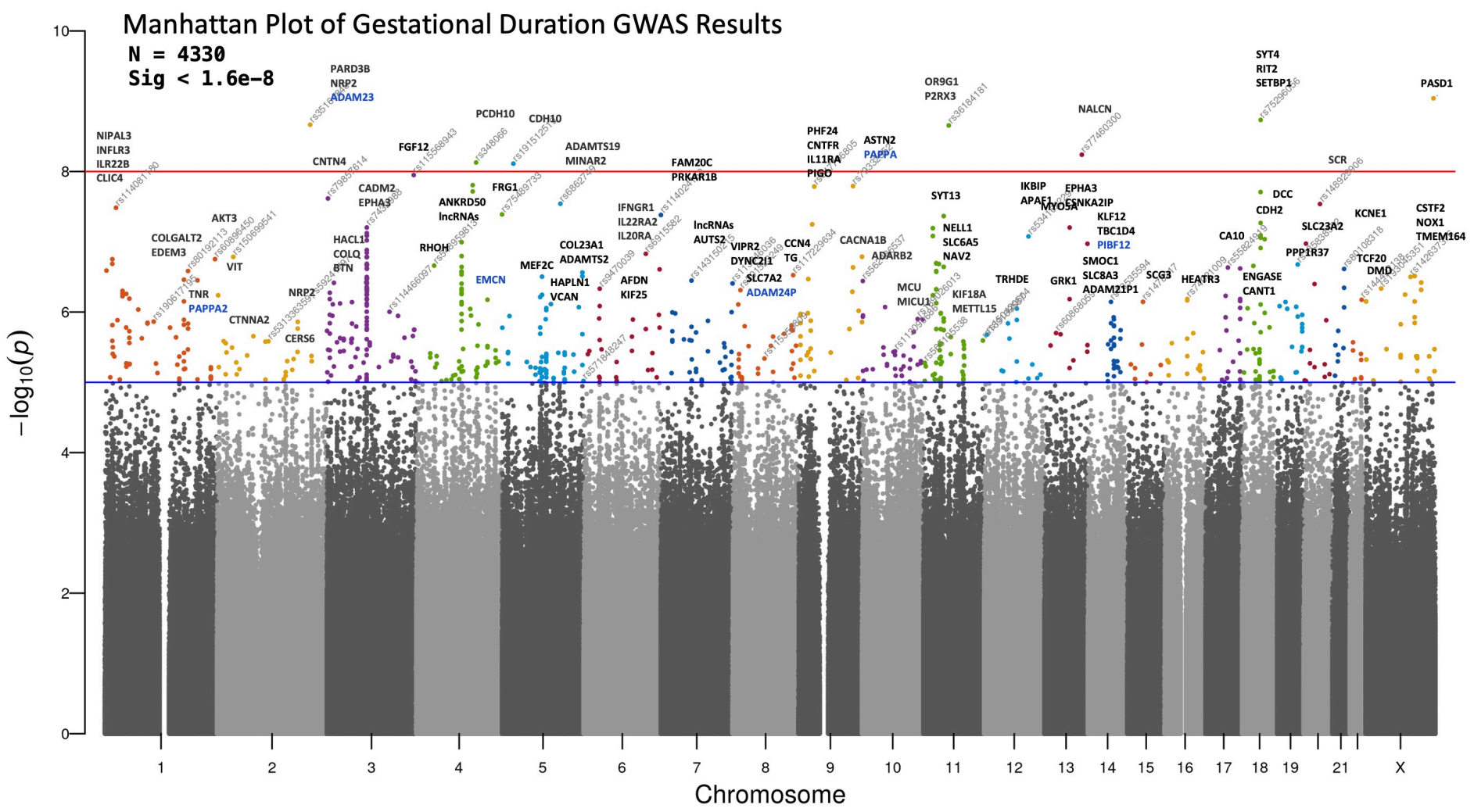


Figure 1: Cervical Length Gestational Duration GWAS Results.

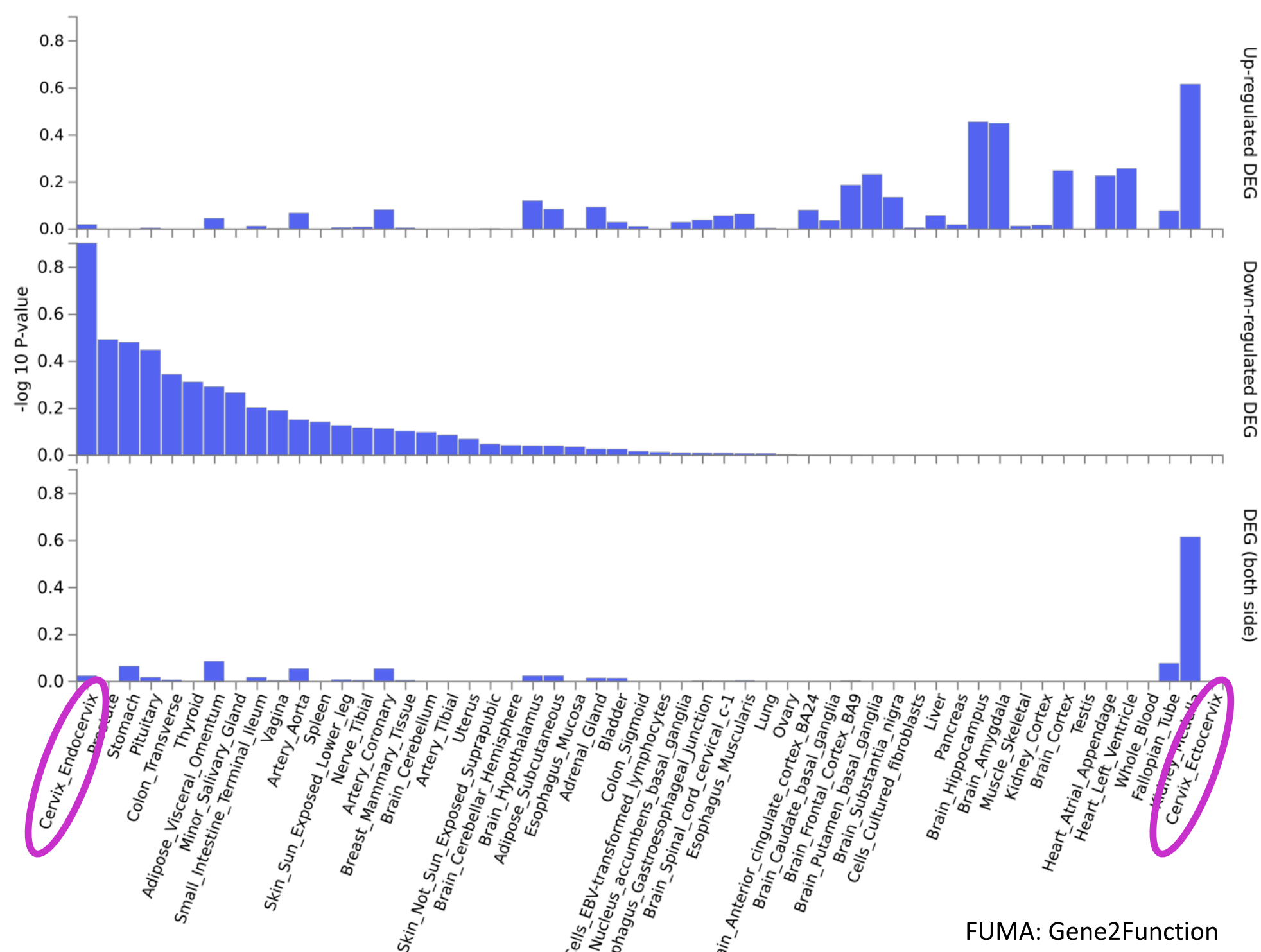


Figure 2: GTEx Tissue Gene Expression Enrichment across CL GWAS.

SNP	Chr	Trait	P-value	Symbol	Gene Name	Expression	Description
rs6548907	2	Intercept; Linear	3.46e-07	LOXL3	Lysyl Oxidase Like 3	Cervix; placenta; endometrium	Formation of crosslinks in collagens and elastin
rs11056394	12	Intercept	7.45e-07	RERG	RAS like estrogen regulated growth inhibitor	Cervix; endometrium	Hydrolase; estrogen-regulated inhibitor in endometriosis
rs147395300	11	Intercept; GAD	7.73e-07	PGR	Progesterone receptor	Endometrium; ovary; cervix	Pregnancy maintenance and cervical ripening
rs7865534	9	Intercept	7.14e-06	PAPPA	Pregnancy-Associated Plasma Protein A	Cervix; ovary; placenta	Metalloproteinase activates the IGF pathway
rs35460272	9	Intercept Linear	1.10e-06 1.06e-07	RLN2	Relaxin 2	Cervix; placenta	Induces ripening/dilation of the cervix during pregnancy
rs7584162	2	Linear	3.33e-06	Col3A1 Col5A2	Collagen type 3 alpha chain	Cervix; uterus; placenta; vagina; endometrium;ovary	Mutations associated with Ehlers-Danlos Syndrome
rs13431344	2	Intercept Linear	3.63e-06	GREB1	Growth regulating estrogen receptor binding 1	Cervix; ovary; uterus; vagina; endometrium	Atypical development of female reproductive tract
rs7584162	2	Linear	3.33e-06		Alpha chain of fibrillar collagens	Cervix	Antimicrobial activity; Phagocyte mediated host defense

Figure 3: SNPs of Interest across Cervical Length GWAS.

## Conclusions

- **Cervical Length** change was influenced by **genetic** factors (heritability = 51%)
- Genetic risk for **GAD/sPTB** was highly shared with genetic risk for **Cervical Length** change.
- Suggests that a large proportion of genes for pregnancy duration exert their influence through cervical length change.

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