Genetic factors affecting pregnancy duration in humans

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska Akademin, Göteborgs Universitet kommer att offentligen försvaras i hörsal Järneken, Östra Sjukhuset, Diagnosvägen 15, torsdagen den 22 november 2018, klockan 13.00

av

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Avhandlingen baseras på följande delarbeten:


Genetic factors affecting pregnancy duration in humans

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Abstract
This thesis investigates the mechanisms behind human pregnancy duration. Too short gestation is a direct cause of perinatal, neonatal, and infant mortality. Deviation from normal pregnancy length is also associated with a child's morbidity, even in the adulthood. The mechanisms determining pregnancy duration are not understood well enough to design an effective preterm birth prevention method, nor a method that would prevent preterm birth sequelae. The three included studies use genomic and epidemiological methods to contribute to our understanding of causal factors triggering birth.

Study I is a hypothesis-free genome-wide search for genetic variants affecting gestational age at birth. The study uses genotyped mothers (n=1921) and children (n=1199) from a Norwegian cohort MoBa. While finding no statistically significant associations, the study empirically shows that the top implicated loci are enriched in genes biologically relevant to the field of obstetrics and gynecology, and that the enrichment is mainly caused by infection/inflammation-related genes.

Study II explores whether a well-known association between maternal height and duration of pregnancy could be causally linked. It utilizes a novel version of Mendelian randomization, which is based on the non-transmitted maternal haplotype and its polygenic risk score for human height. With the help of genomic data from 3485 mother-child pairs from Nordic countries, the study confirms the causal relationship.

Study III follows up on the findings from the Mendelian randomization study, this time using non-genetic epidemiological data to explain the mechanism behind the causal relationship. A uterine distention hypothesis is formulated and tested by comparing the expected and observed patterns of interaction between fetal growth rate, maternal height and the child's gestational age at birth. The twin (n=2846) and singleton (n=527 868) data is obtained from the Swedish Medical Birth Register. Since the observed and expected interaction patterns agree with each other, the study concludes that uterine distention is likely to be one of the causal mechanisms regulating pregnancy duration.

Keywords
Gestational age at birth, preterm delivery, preterm birth, genome-wide association study, GWAS, enrichment, Mendelian randomization, causality, uterine distention, interaction.