Göteborg, 2018

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

Jonas Bačelis

Fakultetsopponent:
Professor Rolv Terje Lie
Department of Global Public Health and Primary Care
University of Bergen, Norway

Avhandlingen baseras på följande delarbeten:

I. Bacelis J, Juodakis J, Sengpiel V, Zhang G, Myhre R, Muglia LJ, Nilsson S, Jacobsson B. **Literature-informed analysis of a genome-wide association study of gestational age in Norwegian women and children suggests involvement of inflammatory pathways**.
PLOS One, 2016. 11(8): e0160335. [doi:10.1371/journal.pone.0160335]

II. Zhang G, Bacelis J, Lengyel C, Teramo K, Hallman M, Helgeland Ø, Johansson S, Myhre R, Sengpiel V, Njølstad PR, Jacobsson B, Muglia L. **Assessing the causal relationship of maternal height on birth size and gestational age at birth: a Mendelian randomization analysis**.
PLOS Medicine, 2015. 12(8): e1001865. [doi:10.1371/journal.pmed.1001865]

III. Bacelis J, Juodakis J, Adams Waldorf KM, Sengpiel V, Muglia LJ, Zhang G, Jacobsson B. **Uterine distention as a factor in birth timing: retrospective nationwide cohort study in Sweden**.
BMJ Open, 2018. 0:e022929 [doi:10.1136/bmjopen-2018-022929]

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GOTHENBURG

Genetic factors affecting pregnancy duration in humans

Jonas Bačelis

Department of Obstetrics and Gynecology,
Institute of Clinical Sciences, Sahlgrenska Academy,
University of Gothenburg, Gothenburg, Sweden

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.

ISBN 978-91-7833-175-8 (PRINT) number of pages: [12+**65**+7] + [25+33+10] = 152
ISBN 978-91-7833-176-5 (PDF) number of pages: [12+**65**+7] = 84

http://hdl.handle.net/2077/57420