Fetal genome involved in triggering premature birth

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Mutations in the gene that codes for SLIT2, a protein expressed in fetal cells in placentas and involved in directing the growth of the fetal nervous system, may contribute to premature births, possibly by

activating the mother's immune system. Mika Rämet of the University of Oulu and colleagues report these findings in a new study published 13th June in *PLOS Genetics*.

More than 10 percent of babies worldwide are born prematurely, which is the leading cause of newborn death and a source of lifelong complications. Preterm birth can run in families, suggesting that there are underlying genetic factors in the mother and the fetus that contribute to the problem. To identify the fetal genetic factors, Rämet and his colleagues performed a genome-wide association study on a Finnish population that included 247 premature infants born before 36 weeks and 419 babies carried to term.

The analysis pinpointed a variation in gene for a protein called SLIT2 that helps guide the growth of neurons during development and binds to a receptor protein called ROBO1. Using placentas, which are partly fetal tissue, the researchers showed that SLIT2 and ROBO1 were expressed at higher levels in placentas from premature babies, compared to placentas from babies that were carried to term. Furthermore, in experiments using cell cultures of placental tissue, the researchers found that ROBO1 plays a role in regulating several pregnancy-associated genes related to infection, inflammation and immune response.

The researchers propose that SLIT2 and its receptor, ROBO1, are part of the signalling network that causes spontaneous preterm birth, potentially by triggering inflammation and activating the maternal immune system. The findings dovetail with previous findings that the SLIT2-ROBO1 signalling pathway is associated with multiple pregnancy complications, including preeclampsia and ectopic pregnancy. Author Mika Rämet stated that "our results are important as more detailed understanding about the fetal—as well as maternal—determinants triggering preterm birth will help us to identify those who are at the highest risk. This will allow targeted therapeutic interventions." In the future, the researchers

hope to validate these findings using a larger population. Such an analysis might also identify additional genetic factors that contribute to early birth.

More information: Tiensuu H, Haapalainen AM, Karjalainen MK, Pasanen A, Huusko JM, Marttila R, et al. (2019) Risk of spontaneous preterm birth and fetal growth associates with fetal SLIT2. *PLoS Genet* 15(6): e1008107. doi.org/10.1371/journal.pgen.1008107