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Evolution points to genes involved in birth timing

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Evolutionary changes that make us uniquely human – such as our large heads and narrow pelvises – may have "pushed" human birth timing earlier and can be used to identify genes associated with preterm birth, a new study suggests.

Investigators from Vanderbilt University, Washington University and the University of Helsinki report that variations in a gene with accelerated evolution in humans, the follicle stimulating hormone receptor (FSHR), may increase a woman's risk for delivering her infant prematurely. The findings in the April 14 open-access journal *PLoS Genetics* point to a novel biological pathway that may influence birth timing.

More than half a million babies per year in the United States – one in eight – are born prematurely (before 37 weeks of gestation). Premature babies face an increased risk of death and serious short-term and long-term medical complications, yet there are no adequate therapies to prevent preterm birth.

"Part of the problem is that we don't understand the fundamental biology of human pregnancy and birth timing," said Louis Muglia, M.D., Ph.D., professor and vice chair for Research Affairs in the Vanderbilt Department of Pediatrics. "We don't know if preterm birth in humans is the normal process gone awry, or if it's an entirely distinct process."

Attempts to use animal models to understand human pregnancy have been of limited success, Muglia said. "The signals that control pregnancy

and birth timing in animal models aren't able to be extended to humans; human pregnancy differs from pregnancy in other animal species."

Muglia and his colleagues proposed that our large heads and narrow pelvises have put pressure on human pregnancy "to adapt and shift the time of birth to the earliest time compatible with optimal survival for both the mom and the fetus."

To explore whether this idea of evolutionary pressure on birth timing had merit, the researchers compared the length of gestation in humans and non-human primates. They show in the current study that gestation length has decreased in the evolutionary lineage leading to modern humans.

They also compared body and brain sizes at birth in humans and non-human primates (a process called allometric scaling) and demonstrated that human gestation is shorter than would be predicted based on this comparison.

"We think there is good evidence that human gestation has been pushed to shorter times, which means there should be a 'signature' in the human genome – genes with accelerated evolution to accommodate this process," Muglia said.

Justin Fay, Ph.D., associate professor of Genetics at Washington University and co-leader of the study, developed comparative genomic methods to identify "human accelerated genes" – genes that are most altered in humans compared to six other animals. The researchers identified a set of 450 human accelerated genes and narrowed the list to 150 genes that were plausible candidates for having a role in human pregnancy.

They examined variations in these 150 genes in a cohort of Finnish

mothers and found that certain variations in the FSHR gene were more frequent in mothers who had experienced preterm birth. The same variations may also be associated with preterm birth in African-Americans, further analyses suggested. The FSHR gene has not previously been implicated in the timing for birth or preterm birth risk.

Studies in larger cohorts could point to additional accelerated genes with roles in birth timing and provide new targets for therapeutic or preventive measures, Muglia said.

"Ideally we'd like to predict which women are at greatest risk for having preterm birth and be able to prevent it. That would really have an impact on infant mortality and the long-term complications of being born prematurely."

Provided by Vanderbilt University Medical Center