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Study identifies pathway required for normal reproductive development

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Massachusetts General Hospital (MGH) clinical researchers, in collaboration with basic scientists from the University of California, Irvine (UC Irvine) have identified a new molecular pathway required for normal development of the reproductive, olfactory and circadian systems in both humans and mice.

In their report to appear in the Proceedings of the National Academy of Sciences, the team describes defects in a gene called PROK2 (prokineticin 2) in human siblings with two different forms of infertility. The UC Irvine team had previously reported that mice lacking PROK2 had abnormal olfactory structures and disrupted circadian rhythm. The paper is receiving early online release.

“We have demonstrated that PROK2 signaling is a novel pathway that is critical to the development of neurons that control the reproductive system, findings that should enable better understanding of human reproduction,” says lead author Nelly Pitteloud, MD, of the Reproductive Endocrine Unit in the MGH Department of Medicine.

The current study is the latest in a series of investigations by the MGH group into the genetic basis of idiopathic hypogonadotropic hypogonadism (IHH), a rare condition in which puberty does not take place naturally. IHH occurs when a structure in the brain called the hypothalamus fails to develop neurons that secrete gonadotropin-releasing hormone (GnRH), a major controller of the reproductive system. Several genes involved in IHH have been discovered by the

MGH investigators and others throughout the world; however, only 30 percent of IHH cases can currently be attributed to a known gene defect.

The investigation focused on PROK2, a protein known to regulate the development of the olfactory bulbs, the portion of the brain involved in the sense of smell, and to have a critical role in circadian rhythm in the mice. . A form of IHH called Kallmann syndrome involves lack of both reproductive development and a sense of smell. PROK2's involvement in these systems led the researchers to investigate the protein's potential role in GnRH deficiency in human and mice.

The MGH team analyzed the PROK2 genes of 100 study participants: 50 with Kallmann syndrome and 50 with IHH and a normal sense of smell. Three members from the same family in Portugal – two brothers and a sister – had identical defects in both copies of the PROK2 gene. Further study of this family revealed another brother with the mutation in only one PROK2 copy and a normal reproductive history. Five siblings of these individuals – now in their 70s – had died in infancy; similar early deaths have been seen in the PROK2-deficient mice. Interestingly, while the two affected brothers both had Kallmann syndrome, their affected sister had a normal sense of smell but did not experience normal puberty.

"Until recently, IHH with a normal sense of smell and Kallmann syndrome with no sense of smell had been considered two distinct clinical entities," says Pitteloud, an assistant professor of Medicine at Harvard Medical School. "We now have described several kindreds in which different family members exhibit both syndromes yet harbor the identical mutation. So, it looks like additional gene defects or environmental cues modify how these syndromes develop in affected families."

The collaborative UC Irvine team was led by Qun-Yong Zhou, PhD, a professor of Pharmacology in its School of Medicine. His group has

made fundamental contributions to the understanding of the neurobiological functions of prokineticin and its receptors. Their analysis of the reproductive status of mice lacking functional copies of Prok2 gene revealed that the animals' reproductive defect is due to the abnormal migration of neurons that secrete GnRH.

"Many recessive human genetic disorders, particularly the ones that have associated infertility symptom, are very difficult or almost infeasible to investigate using genetic analysis. The current study provides an elegant example how mouse studies can pinpoint the underlying genetic cause for human IHH disorders." says Zhou.

Source: Massachusetts General Hospital