Study illuminates mechanism that annotates genetic information passed from fathers to offspring

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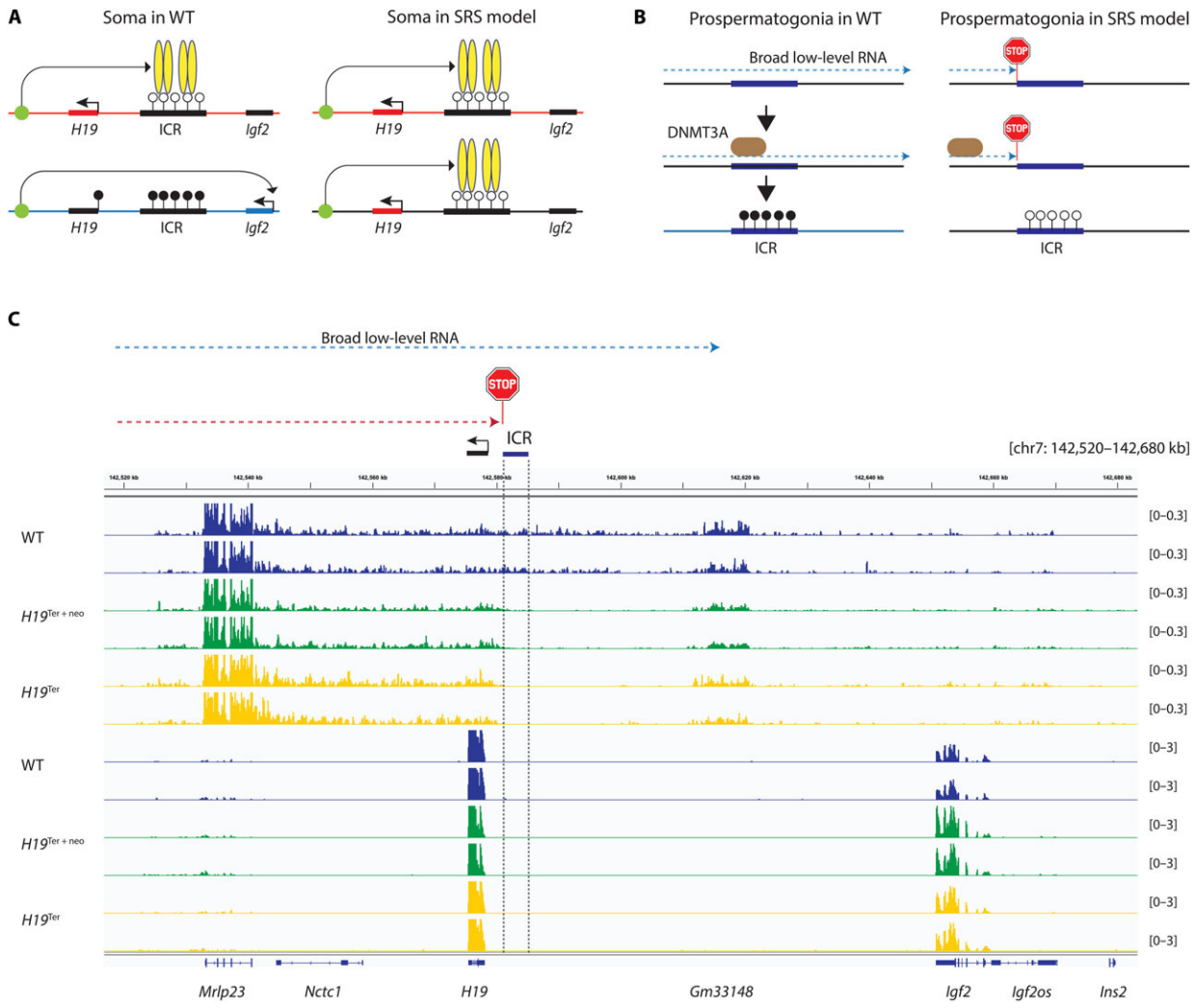

Testing the function of broad low-level transcription at the H19/Igf2 ICR. Credit: *Science Advances* (2023). DOI: 10.1126/sciadv.adi2050

Van Andel Institute scientists and collaborators have identified a key part of a mechanism that annotates genetic information before it is passed from fathers to their offspring.

The findings, published today in the journal *Science Advances*, shed new light on genomic imprinting, a fundamental, biological process in which a gene from one parent is switched off while the copy from the other parent remains active. Errors in imprinting are linked to a host of diseases, such as the rare disease Silver-Russell syndrome along with certain cancers and diabetes.

"Proper imprinting is crucial for lifelong health but, despite its importance, we still lack a full understanding of the factors that regulate this vital process," said VAI Associate Professor Piroska Szabó, Ph.D., the study's corresponding author. "Our findings reveal an RNA mechanism that governs establishment of imprinting and illuminates why it differs between fathers and mothers."

Our genetic information is encoded in DNA, a long, winding molecule that is tightly packed to form 23 pairs of chromosomes, half of which come from one's father and half from one's mother. Sperm and eggs only contain 23 single chromosomes—half of the genetic material required for life. During fertilization, they each contribute their half, resulting in a zygote with a full set of 23 pairs of chromosomes.

But not all instructions in DNA are needed at the same time or in the same places. That's where epigenetics come in. Epigenetic mechanisms annotate DNA with special chemical tags called methyl groups, which tell certain genes when to be active and when to be silent—all without changing the sequence of DNA itself.

Imprinting occurs when methyl groups are added to certain genes during either sperm or egg formation. This, in turn, is important for determining which parental copy of that gene is expressed in the offspring.

To better understand the processes that govern imprinting, Szabó and colleagues focused on an imprinting control region in the DNA that regulates the Igf2 gene. Igf2 plays key roles in fetal growth and only is active in the chromosome inherited from the father. Too little methylation in the IGF2 control region in humans can result in Silver-Russell syndrome, which is marked by reduced growth and increased risk of metabolic disease.

"If the IGF2 gene's imprinting control region from one's father is not methylated, it can result in disease," Szabó said.

Using genetic models and in-depth genetic sequencing, the team found that the methylation of the Igf2 control region in paternally inherited DNA is governed by an underlying RNA-based process in the male germline.

"We found earlier that RNA similarly runs through other paternally marked imprinted domains in the male germ cells, suggesting that this same process is generally true for paternal imprinting," Szabó said. "These results suggest a more broadly applicable process, which is exciting and will need to be confirmed in subsequent studies."

Other authors include Ji Liao, Ph.D., Zhen Fu, Ph.D., Ivan VanderKolk, Brianna M. Busscher and Kin H. Lau, Ph.D., of VAI; Sangmin Song of City of Hope Cancer Center; and Samuel Gusscott, Ph.D., and Julie Brind'Amour, Ph.D., of Université de Montréal.

More information: Ji Liao et al, Establishment of paternal

methylation imprint at the H19/Igf2 imprinting control region, *Science Advances* (2023). DOI: 10.1126/sciadv.adi2050