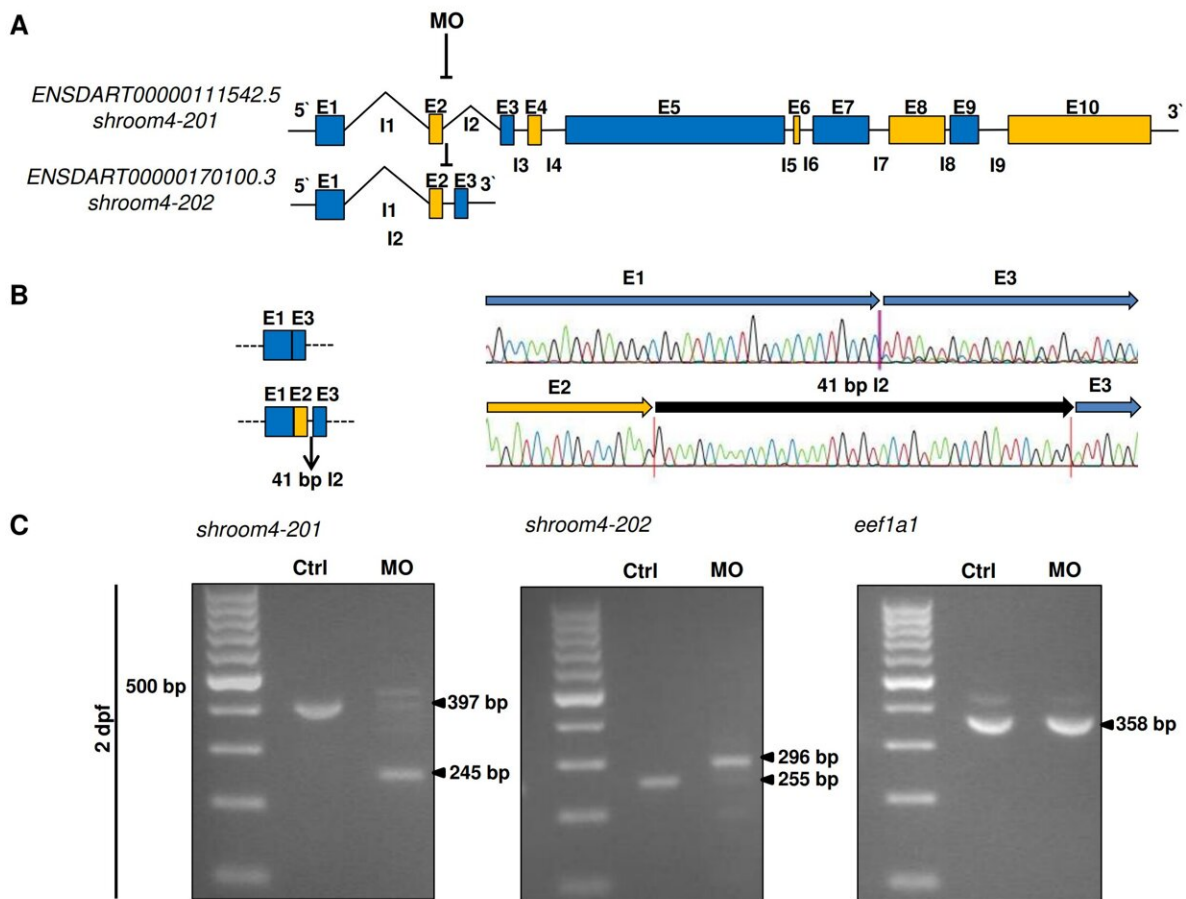


Study identifies gene that plays important role in embryonic development

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An international study led by the medical Faculty of the University of

Bonn has identified a gene that plays an important role in the development of the human embryo. If it is altered, malformations of various organ systems can result. The gene emerged very early in evolution. It also exists in zebrafish, for example, and performs a similar function there. The results have now been published in the *Journal of Medical Genetics*.

The researchers tracked down the gene when they studied two individuals with congenital malformations. "It was a man and his niece," explains Dr. Gabriel Dworschak. "Both had malformed kidneys, [urinary tract](#) and esophagus, and the man also had a malformed right arm and heart."

The physician at the University Children's Hospital in Bonn conducts research on [rare genetic diseases](#) at the Institutes of Anatomy and Human Genetics. When the team looked at the genetic makeup of the family members, they came across an anomaly: A gene called SHROOM4 was altered in affected individuals compared to healthy individuals.

SHROOM4 was already familiar from another context: It was known to play a key role in brain function. Mutations can result in intellectual impairment, epileptic seizures and behavioral abnormalities. "Our findings indicated though, that it may play a broader role in embryonic organ development," Dworschak explains.

The team from Bonn searched internationally for other cases in which abnormalities in the SHROOM4 gene had also been found—and succeeded: "Together with our cooperation partners, this led us to four more affected individuals from three families," says Prof. Dr. Heiko Reutter, who has since moved from the University Hospital Bonn to the University of Erlangen-Nuremberg. "All of them had the SHROOM4 gene altered, but not always in the same way."

Zebrafish also needs SHROOM4

However, this did not necessarily clarify whether SHROOM4 variants were actually responsible for the malformations. But there is an animal that has a very similar gene: the zebrafish. It serves as a [model organism](#) in many genetic studies today—and not only because it is easy to keep in a species-appropriate manner and able to reproduce quickly: The skin of its larvae is almost transparent. This makes it easy to observe the animals' embryonic development under the light microscope.

"Here at the University Hospital, we have the advantage that the research group led by Prof. Dr. Benjamin Odermatt from the Institute of Neuroanatomy works a lot with zebrafish," says Dr. Caroline Kolvenbach, who was also involved in the study of SHROOM4. "This expertise came in handy in our study."

The researchers almost completely inactivated SHROOM4 in the larvae. The animals then showed malformations similar to those seen in the patients. If, on the other hand, larvae with SHROOM4 switched off were injected with the intact human genetic material, they developed almost normally. "This shows first that they absolutely need a functional SHROOM4 for healthy development; and second, that the [human gene](#) can still take over the function of the fish gene," Dworschak says.

The team now wants to find out which part the gene plays in embryonic development. "We assume that it is needed for very basic processes in the cell," says Dworschak. "It's hard to explain otherwise why changes in the same gene cause such a variety of symptoms."

Small piece in the mosaic of an extremely complex picture

How a mouse, a dog or a human being develops from a fertilized ovum is still not fully understood. This is because the ovum has the ability to form any type of tissue in the organism, whether it is bone, skin, muscle or the brain. Its [daughter cells](#) are genetically identical to it; so in principle they should be able to do the same. But at a very early stage, certain programs are activated in their cells that irrevocably determine their developmental fate.

This process must be coordinated down to the finest detail. Because only then it is ensured that the eyes form in the appropriate spot on the face, while other cells very close by differentiate into the nasal cartilage. Surprisingly, however, there is no conductor wielding the baton. It is as if a Lego spaceship were assembling itself—only infinitely more complicated. "Our study is a small piece of the mosaic to this picture, which is still largely incomplete," Dworschak says.

More information: Caroline M Kolvenbach et al, X-linked variations inSHROOM4are implicated in congenital anomalies of the urinary tract and the anorectal, cardiovascular and central nervous systems, *Journal of Medical Genetics* (2022). [DOI: 10.1136/jmg-2022-108738](https://doi.org/10.1136/jmg-2022-108738)

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