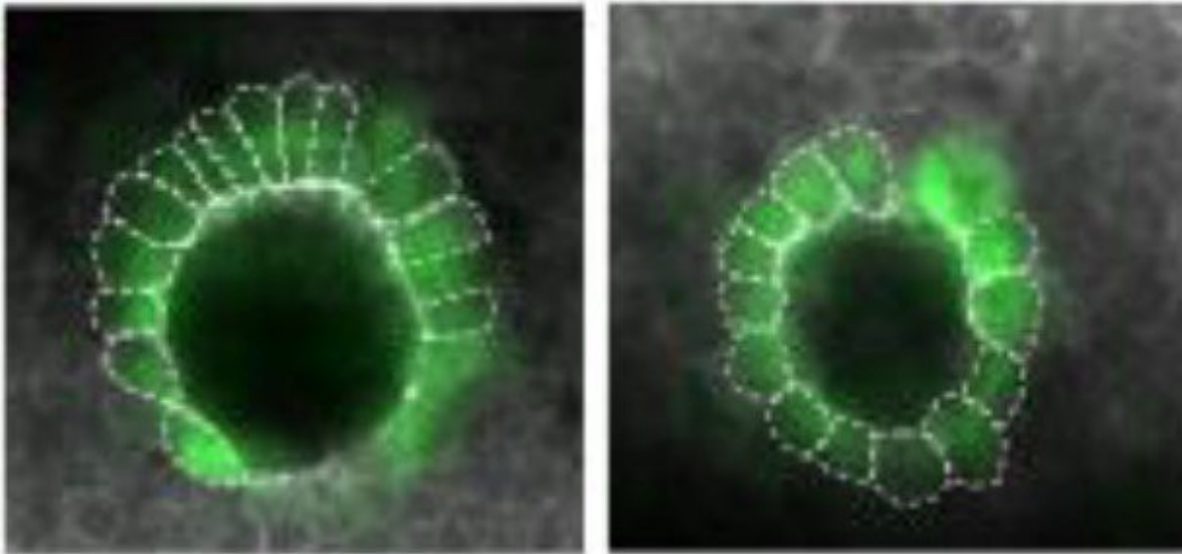


Genetic instructions from mom set the pattern for embryonic development

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An organ called Kupffer's vesicle, which helps specify the left and right sides of the developing fish, is shaped asymmetrically in a wild-type embryo (left), but is more symmetric in the absence of maternally inherited *gdf3* (right). Credit: Pelliccia et al., 2017

A new study indicates an essential role for a maternally inherited gene in embryonic development. The study found that zebrafish that failed to inherit specific genetic instructions from mom developed fatal defects earlier in development, even if the fish could make their own version of the gene. The study by researchers at Princeton University was published

Nov. 15 in the journal *eLife*.

When female animals form egg cells inside their ovaries, they deposit messenger RNAs (mRNAs) - a sort of genetic instruction set - in the egg cell cytoplasm. After fertilization, these maternally supplied mRNAs can be translated into proteins required for the early stages of [embryonic development](#), before the embryo is able to produce mRNAs and proteins of its own.

More than thirty years ago, researchers discovered that mRNAs encoding a [protein](#) called Vg1 are deposited in the cytoplasm of frog eggs. "vg1 is famous for being one of the first recognized maternal mRNAs," said Rebecca Burdine, associate professor of [molecular biology](#) at Princeton. "A wealth of papers have been written on how this RNA is localized and regulated, but it was never clear what the Vg1 protein actually does in the developing embryo."

In the study, Burdine and two graduate students Jose Pelliccia and Granton Jindal used CRISPR/Cas9 gene editing to remove Vg1, known as Gdf3 in zebrafish. Embryos that couldn't produce any Gdf3 of their own—but received a healthy portion of the *gdf3* mRNA from their mothers—developed perfectly normally. But embryos that didn't receive maternal *gdf3* mRNA showed major defects early on in their development, dying just three days after fertilization.

"If *gdf3* is not supplied to the egg by the mother, the fertilized egg cannot produce two of the three major types of cells required for development," Burdine said. "The embryos lack all [cell types known as] mesoderm and endoderm and are left with skin and some neural tissue, [which derive from the third major cell type, the ectoderm]."

Vg1/Gdf3 is a member of the TGF-beta family of cell-signaling molecules. Two other members of this family, Ndr1 and Ndr2, are

required to form the mesoderm and endoderm early in zebrafish development. Embryos lacking maternally supplied *gdf3* look very similar to embryos lacking both of these proteins, which are analogous to the Nodal 1 and 2 proteins in mammals.



Compared to a normal zebrafish embryo (right), an embryo lacking *gdf3* (left) inherited from mom shows major defects resulting from its inability to form mesoderm and endoderm cells early in development. Credit: Pelliccia et al., 2017.

The researchers found that maternal *gdf3* is required for *Ndr1* and *Ndr2*

to signal at the levels necessary to properly induce the formation of mesoderm and endoderm cells in early zebrafish embryos. In the absence of *gdf3*, *Ndr1* and *Ndr2* signaling is dramatically reduced and embryonic development goes awry.

Nodal signaling is also required later in zebrafish development when it helps to establish differences between the left and right sides of the developing embryo. It does this, in part, by directing the formation of an organ known as Kupffer's vesicle, whose asymmetric shape helps determine the embryo's left and right sides. Subsequently, Nodal signaling induces the expression of a third Nodal protein, called southpaw, in a group of mesoderm cells on the left-hand side of the embryo.

To investigate whether maternally supplied *gdf3* mRNA also plays a role in left-right patterning, the researchers used a series of experimental tricks to supply embryos with enough Gdf3 protein to form the mesoderm and endoderm and survive until the later stages of embryonic development.

As predicted, these [embryos](#) showed defects in left-right patterning. Their Kupffer's vesicles were abnormally symmetric in shape, and southpaw expression was greatly reduced, suggesting that *gdf3* is also required for optimal Nodal signaling during later stages of embryonic development. At this stage, however, embryonic *gdf3* seems to be capable of doing the job if maternally supplied *gdf3* is absent.

Nodal and Vg1 proteins are known to bind to each other in other species. "Thus, we hypothesize that Gdf3 combines with *Ndr1* and *Ndr2* to facilitate Nodal signaling during zebrafish development, acting as an essential factor in embryonic patterning," said Pelliccia, a graduate student in molecular biology. Co-author Jindal earned his Ph.D. in chemical and biological engineering in 2017.

At the same time as Burdine and colleagues, two other research groups, led by Joe Yost at the University of Utah and Alex Schier at Harvard University, made similar findings on the role of *gdf3* during zebrafish [development](#). "All three groups worked together to co-submit and co-publish in *eLife*, allowing the students involved to all get credit for their hard work," Burdine said. "It's a great example of how science should be done."

More information: Jose L Pelliccia et al, Gdf3 is required for robust Nodal signaling during germ layer formation and left-right patterning, *eLife* (2017). [DOI: 10.7554/eLife.28635](https://doi.org/10.7554/eLife.28635)

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