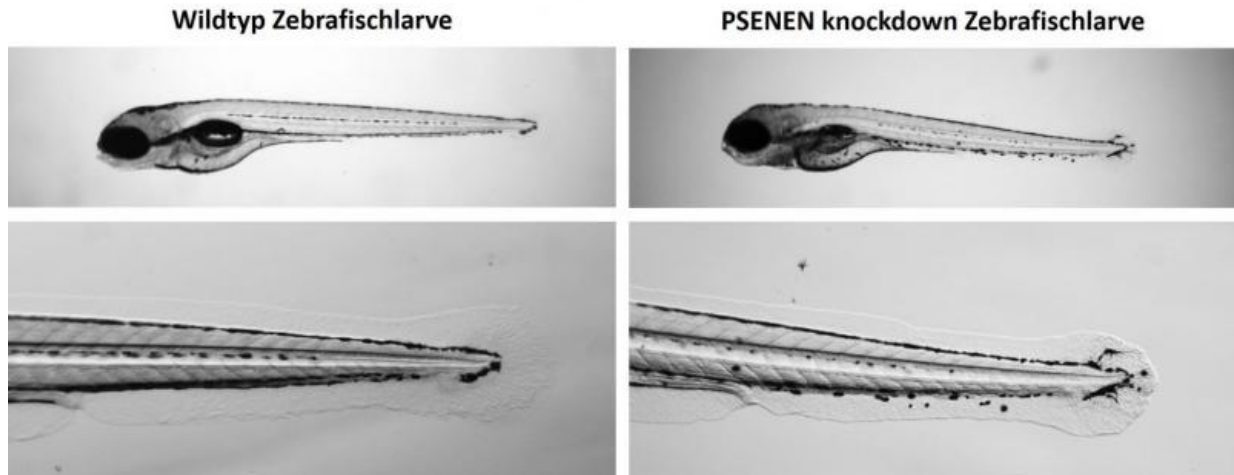


Zebrafish without stripes

March 14 2017



Microscopic image of zebrafish larvae: The distribution of the pigment cells (black) can be seen easily in the animals, which are only the size of an eyelash. If the function of the PSENEEN gene (right) was disrupted, these collected in unusual places to form clearly visible patches – similar to people with Dowling-Degos disease. Credit: AG Betz / Universität Bonn

Dowling-Degos disease is a hereditary pigmentation disorder that generally progresses harmlessly. However, some of those affected also develop severe skin inflammation. An international team of researchers under the leadership of the University of Bonn has now found a cause for this link. Their knowledge comes thanks to an animal that is known among aquarium owners for its characteristic pigmentation: the zebrafish. The results have now been published in the *Journal of Clinical*

Investigation.

People with Dowling-Degos disease have a noticeably large number of dark pigment spots. These are frequently found in certain areas of the body, such as the face, neck, torso, hands, and the bending folds of the arms and legs. The pigmentation disorder generally progresses harmlessly; however, it can have a negative aesthetic effect.

Occasionally, those affected also develop extremely unpleasant [skin inflammation](#), called [acne inversa](#). This is not only painful but is also associated with festering blisters that can leave scars when they burst. The colonization of microorganisms on the affected areas of skin also creates unpleasant body odor. Acne inversa has a chronic progression; a permanent solution is only provided by surgery.

"We have genetically examined 90 people with Dowling-Degos disease since 2005," explains Prof. Regina Betz from the Institute of Human Genetics at the University Hospital of Bonn. "Six of them also suffered from acne inversa." The scientists found a special characteristic in this subgroup: the patients displayed mutations in what is known as the PSENEN gene.

It has been known that PSENEN mutations can cause acne inversa. "However, we were able to show for the first time that changes in this gene primarily cause Dowling-Degos disease and around half of the mutation carriers develop acne inversa," emphasizes Damian Ralser, who is currently working on his doctorate at the Institute of Human Genetics.

To do this, the scientists used an animal that should be known to many aquarium enthusiasts due to its striking pigmentation: the zebrafish. However, the characteristic blueish black stripes, which give the fish its name, only form over time. The eyelash-sized zebrafish larvae are more or less transparent.

Fish as a model organism

Many processes in the body can thus be observed easily under an optical microscope. For this reason, the zebrafish is now used as a model organism by scientists around the globe. At the University of Bonn, Prof. Benjamin Odermatt from the Anatomical Institute is researching how zebrafish repair defective nerve tissue.

Zebrafish also have the PSENEN gene. "In order to be able to research more closely what effect PSENEN has, we, in collaboration with Prof. Odermatt, deactivated the gene in some zebrafish larvae and then compared these with normal larvae under the microscope," explains Damian Ralser.

The pigment cells – the melanocytes – usually wander in a certain direction in the zebrafish larvae. This ensures that the characteristic striped pattern develops over time. However, the pigment cells wandered back and forth aimlessly in animals in which the functioning of PSENEN was disrupted. They ultimately collected in unusual places to form clearly visible patches – similar to people with Dowling-Degos disease.

Only a small proportion of all Dowling-Degos patients carry a PSENEN mutation. "There are also other disease genes that lead to the pigmentation disorder," says Betz. She recommends that all those affected undergo testing. If a disrupted PSENEN gene is the actual cause, there is a significantly increased risk of also suffering from acne inversa. However, the scientist emphasizes that no one is exposed to this risk without protection: "This severe form of acne develops in particular in PSENEN mutation carriers who smoke a lot or who are overweight."

More information: Damian J. Ralser et al. Mutations in γ -secretase subunit–encoding PSENEN underlie Dowling-Degos disease associated

with acne inversa, *Journal of Clinical Investigation* (2017). DOI: [10.1172/JCI90667](https://doi.org/10.1172/JCI90667)

Provided by University of Bonn

Citation: Zebrafish without stripes (2017, March 14) retrieved 20 April 2024 from <https://medicalxpress.com/news/2017-03-zebrafish-stripes.html>

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