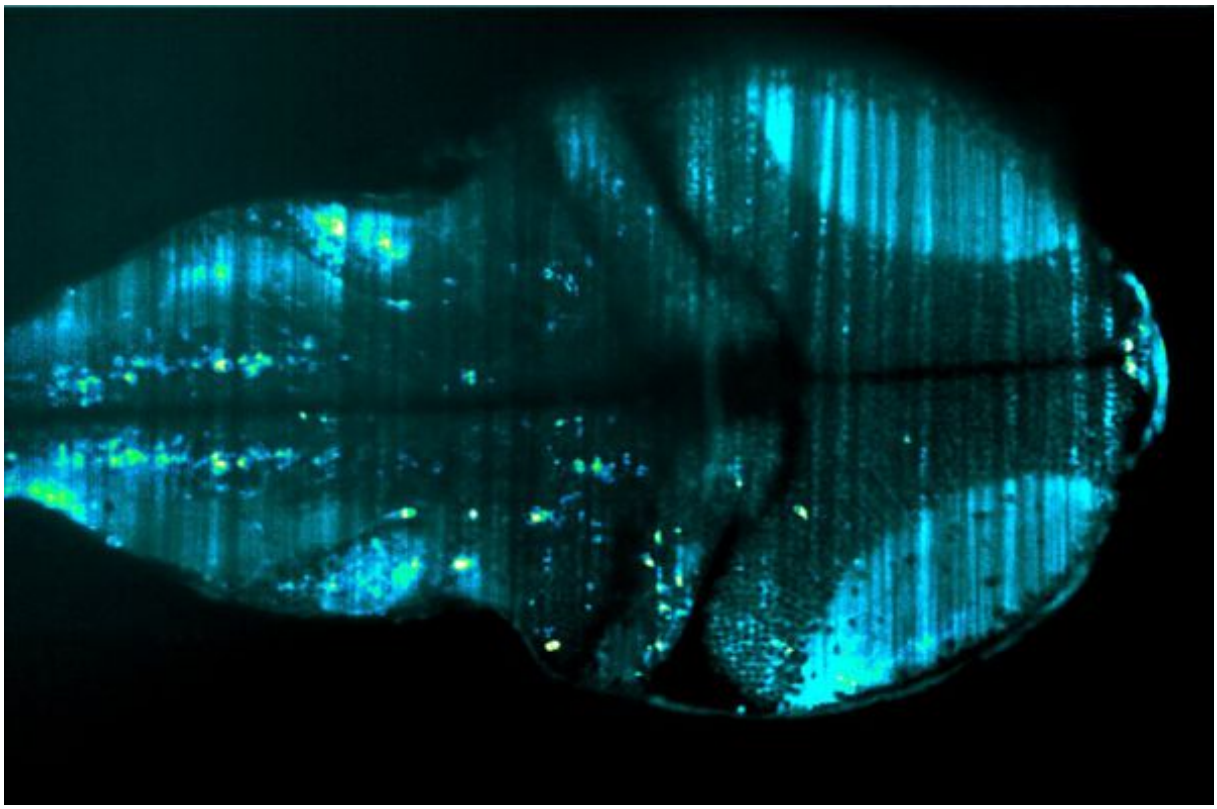


Studying the role of the ywhaz gene in the brain activity and behavior

Researchers report in Molecular Psychiatry that the deficiency in the ywhaz gene alters the brain activity and behavior of the zebrafish, shedding some light on the role of this gene in neurodevelopmental disorders. It also highlights the importance of whole-brain imaging techniques.

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The genetic information stored in our DNA determines, in part, all our observable traits and characteristics, from how we are to how we move or behave. Genes are the smallest units of functional information in our bodies, regions of DNA that encode a specific function. When the information in a gene is used - or expressed, it produces other molecules, either RNA or proteins, that ultimately guide the functions of our cells.

When our genes suffer alterations, our functions might be altered too. Neurodevelopmental disorders arise when the development of the central nervous system is somehow impaired, deviating from the typical development course.?

Researchers found that alterations in a gene named ywhaz, which encodes for a protein

responsible for neuron formation and migration, modify the neurodevelopment in humans and mice. These alterations contribute to certain psychiatric disorders such as schizophrenia and autism spectrum disorder. But the biological mechanisms underlying this damage are still unclear.

Studying the brain of the zebrafish

Now, researchers Gustavo Castro, Emilio J. Gualda, and Pablo Loza, from the SLN group at ICFO, have given more details about the function of that gene in the development of neurons and behavior using whole-brain imaging techniques. In a study published in Molecular Psychiatry, they have collaborated with research groups from the University of Barcelona, the Institute of Biomedicine and the Institute of Neurosciences of the University of Barcelona, the University of Leicester, the RIKEN Center for Brain Science, and the CIBER of Rare Diseases.

The team studied the role of the ywhaz gene in the neurodevelopment of zebrafish. Small, with well-defined behaviors and with a lot of genes similar to humans, these fishes are often used as a model organism for biological sciences, specifically to study brain development or psychiatric disorders. They are also ideal for imaging studies because the embryo is transparent, and eggs-to-larvae phase happens in just three days.

The researchers studied two groups of zebrafish larvae and adults. One of the groups was healthy individuals, while the other group was genetically modified to express the ywhaz gene less.

Altered brain activity and behavior

First, the team measured the gene expression of the animals. They found that, although the ywhaz gene was expressed in all the neurons during the early stages of the larvae, in adults it was expressed only in a specific group of neurons in the cerebellum. Then, the SLN team performed whole-brain imaging experiments using a light-sheet microscope on the fish with a calcium-fluorescent marker. This allowed them to see, in real-time, the neuronal activity and connectivity, as the neurons illuminated after activity - synapsis - occurred. Moreover, this imaging technique provided spatial and temporal resolution, giving information about where and when neurons activate.

Finally, they conducted a set of behavioral tests on the adults. When the adult individuals with the altered gene were exposed to new stimuli, they froze, and their activity and connectivity of the lower back part of the brain were altered. They also saw that these fish had lower levels of certain neurotransmitters such as the dopamine and serotonin, and problems to synthesize them. The team tested a treatment by proceeding to give two types of medicines - fluoxetine and quinpirol - that were able to revert these behavioral alterations.

The findings show the relevance of the ywhaz gene in neurodevelopment, clarifying the mechanisms of its role in the disorders. It also highlights the potential of the 3D imaging techniques in such studies, adding spatial and temporal resolution currently unavailable with other techniques. Moreover, it outlines the use of specific treatments to revert various symptoms associated with psychiatric diseases.

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Cited article: Anton-Galindo, E., Dalla Vecchia, E., Orlandi, J.G. et al. Deficiency of the ywhaz gene, involved in neurodevelopmental disorders, alters brain activity and behaviour i zebrafish Mol Psychiatry (2022). https://doi.org/10.1038/s41380-022-01577-9