Treating neurological symptoms of CHARGE syndrome

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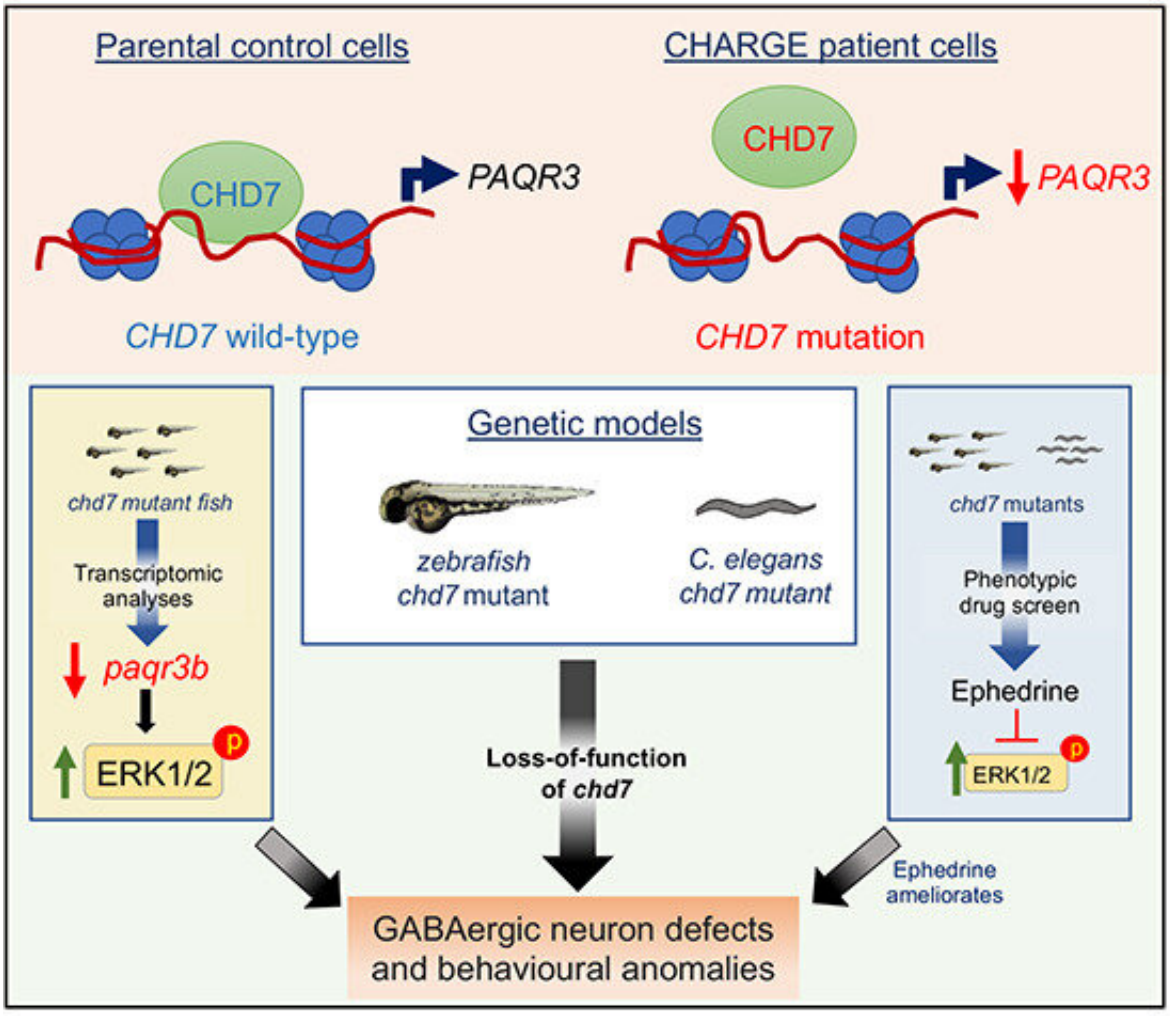

SYNOPSIS: Loss-of-function of chd7 causes defects in GABAergic neuron development and behavioural anomalies reminiscent of CHARGE syndrome, which are rescued by genetic and pharmacological interventions in zebrafish. Credit: *EMBO reports* (2021). DOI: 10.15252/embr.202050958

CHARGE syndrome is a rare genetic disorder affecting about 1 in 10,000 newborns. It can lead to neurological and behavioral disorders for which no treatment is currently available. Dr. Kessen Patten and his team from the Institut National de la Recherche Scientifique (INRS) have just discovered a compound that could alleviate these symptoms. The results of their research were published in the journal *EMBO Reports*.

Understanding Neurological Disorders

First described in 1979, CHARGE syndrome is caused by mutations in the CHD7 gene and is associated with neurodevelopmental disorders such as intellectual disability, attention deficit disorder with or without hyperactivity, seizures and autism spectrum disorder. Dr. Patten's research team studied the neurological symptoms of this syndrome, which are still poorly understood.

The team developed a genetic model of zebrafish with loss of function of the CHD7 gene similar to that observed in humans. They found that the CHD7 gene regulated the type of GABAergic neurons that are essential for proper brain function.

"The loss of function of CHD7 appears to cause developmental and functional abnormalities in GABAergic neurons in the zebrafish brain that are related to the observed neurological and behavioral disorders," explained Dr. Patten, who specializes in genetics and neurodegenerative diseases. The team also identified molecular events controlled by the CHD7 gene to explain these neurological symptoms in their genetic model. Similar findings were made using cells from patients with the disease.

Finding a Drug

The research team tested hundreds of compounds already approved for clinical use by the U.S. Food and Drug Administration. Drug screening was used to identify potential candidates for treatment—ephedrine was selected as the most therapeutic compound. "We observed therapeutic effects on both, the neurological and behavioral symptoms," said Ph.D. student Priyanka Jamadagni, lead author of the article. "It allowed the diseased zebrafish model to partially recover its normal functions."

This research opens the door to new avenues for the treatment of other neurological disorders with similar neuronal imbalances, such as autism spectrum disorder and hyperactivity.

More information: Priyanka Jamadagni et al, Chromatin remodeller CHD7 is required for GABAergic neuron development by promoting PAQR3 expression, *EMBO reports* (2021). DOI: 10.15252/embr.202050958

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