Screening of zebrafish identifies gene involved in human nicotine addiction

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Researchers at Queen Mary University of London have shown that zebrafish can provide genetic clues to smoking, a complex human behaviour.

By studying genetically-altered zebrafish they were able to pinpoint a human gene, Slit3, involved in nicotine addiction and also discover the ways in which it may act.

While zebrafish have been used extensively in genetic research, they've been used only in developmental models, such as identifying genes

associated with disease, rather than to predict genes involved in a complex cognitive behaviour such as smoking.

Although smoking has long been known to have a genetic element, relatively little has been known about the genes involved since it has been difficult to identify them from human studies alone.

In a study published in *eLife* journal, the researchers tested families of genetically altered zebrafish for nicotine preference. When one family showed a much stronger nicotine preference compared to the others, the researchers identified all the mutations in the family, eventually narrowing down to a mutation in the Slit3 gene linked to the behaviour.

To see if the same gene affected nicotine preference in people, the researchers looked for association between variants in the human Slit3 gene and smoking behaviour, such as decreased or increased desire to smoke and how easy it was to quit, in groups of people in the UK and Finland. They found 3 variants in the human Slit3 gene that were significantly linked to smoking activity.

To then learn more about how the Slit3 gene might be working, the researchers tested both mutant and wild type fish for sensitivity to a dopaminergic drug. In humans this drug affects the startle reflex—our physical reaction to a sudden loud noise—that is linked to addictions, including nicotine addiction. When tested with the startle reaction, the mutant fish showed decreased sensitivity to the drug. After testing various different receptors that might be involved in the reduced drug sensitivity, the researchers found that only one receptor was implicated—the serotonin receptor 5HT 1AA.

Caroline Brennan, Professor of Molecular Genetics at Queen Mary University of London, led the research. She explained: "This gives us a hypothesis for how the Slit3 gene works in humans. It is somehow

altering the level of serotonin receptors present; and the differences in the levels are presumably then influencing sensitivity to nicotine addiction."

Professor Brennan added: "As well as finding out more about the genes involved in nicotine addiction, most importantly, we've found an easier way of finding these genes in the future. Although zebrafish are a 'lower' organism, they have a similar genetic structure to humans and share 70% of genes with us. 84% of genes known to be associated with human disease have a zebrafish counterpart; and while there has been scepticism regarding their usefulness in terms of human cognition, we have shown that they can give insight into the genetics of that as well."

More information: Judit García-González et al, Identification of slit3 as a locus affecting nicotine preference in zebrafish and human smoking behaviour, *eLife* (2020). DOI: 10.7554/eLife.51295

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