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Genetic and Developmental Analysis of Zebrafish Reveals Candidate Genes Linked to Nicotine Addiction Vulnerability and Impulsivity

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We performed genetic and developmental analyses in zebrafish to identify genes and cellular processes underlying behaviors predictive of addiction vulnerability: nicotine reward and impulsivity. Forward genetic screens identified 19 families exhibiting heritable impulsivity or increased sensitivity to nicotine reward. Co-segregation analysis of known candidate mutations within these families led to the identification of candidate risk genes (znf804a, hdac1, yif1a, col25a1, prkcb). We generated lines carrying loss of function (LoF) mutations in these genes and in candidate genes previously associated with nicotine preference in humans (ANKK1, RBFOX1) or in analysis conducted by other researchers in the NAGC (TNIK, FEZ1) using CRISPR-Cas9 gene editing. yif1a, fez1, tnika and rbfox1 LoF larvae showed hyperactivity, reduced rate of habituation to acoustic startle and increased impulsivity. yif1a and fez1 LoF larvae showed altered sensitivity to dopaminergic drugs (apomorphine and amisulpride) and changes in the expression of key dopaminergic pathway components consistent with the observed behavioural alterations. tnika LoF larvae showed reduced sensitivity to clozapine (an antipsychotic drug known to reduce substance use among patients with schizophrenic disorders) on habituation. This study identifies critical genes, including yif1a, associated with addiction vulnerability and impulsivity, demonstrating the potential of zebrafish as a model for studying drug abuse-related phenotypes.