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A forward genetic screen of ENU-mutagenised zebrafish identifies lines showing deficits in impulse control

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Impulsivity is defined as acting on a momentary basis without consideration of outcomes. Two forms of impulsivity are impulsive action involving difficulty inhibiting a pre-potent response and impulsive choice referring to difficulty delaying gratification. Both forms of impulsivity are reported in many disorders such as addiction, ADHD and bipolar disorder. While Impulse control disorders show moderate to high degrees of heritability, the genetics of impulsivity is not widely studied. We aimed to identify genes and pathways underlying impulsivity using a forward genetic screen of ENU-mutagenised zebrafish. We screened 64 families estimated to cover 5072 dominant and 1327 recessive alleles. We also screened Rbfox1 loss of function line predicted to show high impulsivity. Impulsive action was assessed using a zebrafish version of 5-choice serial reaction time task. In this task, after the animal learns the association between a stimulus and a reward, a pre-stimulus interval is introduced during which a premature response is recorded as a measure of impulsive action. Rbfox1 line showed increased premature responding. We identified six candidate lines showing increased premature responding of which one has been further analysed revealing a heritable deficit in impulse control. The exome sequencing of founders of the line identified 29 candidate mutations of which three are associated with ADHD including one associated with four other psychiatric disorders as well. Future work should identify genes and pathways underlying this phenotype. We demonstrated for the first time that a forward genetic screen of zebrafish for impulsivity could identify lines with translational relevance to human.