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Ankk1 regulates the dopaminergic response mediated by dopamine receptor D2 in zebrafish brain

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ANKK1 is suggested to be involved in vulnerability to addictions. The mechanism by which *ANKK1* may impact addiction vulnerability is poorly understood but has been suggested to involve effects on development and/or functioning of dopaminergic pathways. To test this hypothesis, we generated a CRISPR-Cas9 loss of function *ankk1* zebrafish line. We assessed *ankk1* mutants and wild-type siblings for behavioural phenotypes at 5 days post fertilization (dpf). *Ankk1*$^{-/-}$ show decreased locomotor activity and recovered slowly in forced light/dark test. To test impact of *ankk1* loss of function on dopamine regulated behaviour associated with addiction vulnerability, we examined the effects of amisulpride on habituation to acoustic startle. We observed a gene x dose interaction such that homozygous mutants were less sensitive to inhibition of habituation to acoustic startle than wild-type fish consistent with disruption of dopaminergic signalling. As chronic alteration in dopamine signalling is predicted to affect brain dopamine receptor expression, we examined the expression of components of the dopamine pathway by qPCR, and of dopamine D2 receptor by immunohistochemistry. At 5dpf, we found a significant up-regulation of drd2b mRNA expression levels. In adult zebrafish brain, drd2 protein was detected in cerebral cortex, cerebellum, hippocampus and caudate homologue regions, resembling the pattern in humans. In contrast, in *ankk1* mutants drd2 expression was reduced in cortical regions and being predominantly found in the hindbrain. Our findings support a role for *ANKK1* in the development of the dopaminergic pathway.