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Forward genetic ENU mutagenesis screen in mice identifies SrGAP3 as a regulator of cocaine responses

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We conducted an ENU mutagenesis screen in mice and isolated a mouse line with low acute response to cocaine responses. We mapped and cloned the causative variant responsible for the lowered response to cocaine. A mutation in Slit-Robo GTPase activating protein 3 (srGAP3) is responsible for this lowered locomotor activation phenotype. We confirmed this by recreating the mutation in C57BL/6J using CRISPR/Cas9 based precise engineering and observed the lowered cocaine response phenotype. Mechanistically, the mutation leads to a highly destabilized protein. SrGAP3 is a negative regulator of Rac1 signaling and interacts with WAVE regulatory complex. It has been implicated in regulation of dendritic spine and lammelapodia formation. In humans, SrGAP3 has been implicated in cognitive function. To the best of our knowledge, this is the first report of SrGAP3 as a regulator of cocaine responses. We are currently investigating its function in the reward circuit.