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Rasd2 Modulates Psychotomimetic Drug Effects in Mice and Schizophrenia-related Phenotypes in Humans

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Background: Rasd2 is a striatal GTP-binding protein that modulates Akt and mTOR signaling cascades, well known to be highly vulnerable pathways in psychiatric disorders.

Aims: We investigated the association of Rasd2 and its genetic variation with a series of prefronto-striatal phenotypes related to psychosis in rodents and humans.

Objectives: We want to provide evidence that Rasd2 controls the vulnerability to schizophrenia-related behavior induced by psychothomimetic drugs in mice. Moreover, we aim to find genetic variations within the *Rasd2* gene that influence a series of brain schizophrenia-related phenotypes in human.

Methods:*Rasd2* knockout mice were employed to evaluate schizophrenia-like behaviors induced by psychotomimetic drugs like amphetamine and phencyclidine. Furthermore, we investigated if *RASD2* genetic variations in humans are associated with mRNA expression in *post-mortem* prefrontal cortex, as well as prefrontal and striatal grey matter volume and physiology during working memory as measured with MRI in healthy subjects. Finally, we assessed *RASD2* mRNA expression levels in *post-mortem* brains of patients with schizophrenia and bipolar disorder.

Results: We found that both psychotomimetics triggered greater vulnerability to motor stimulation and to prepulse inhibition deficits in *Rasd2* mutants. In humans, we found that a genetic variation (rs6518956) within *RASD2* predicts prefrontal mRNA expression as well as prefrontal grey matter volume and prefronto-striatal activity during working memory. Finally, we reported that *RASD2* mRNA expression is slightly reduced in post-mortem prefrontal cortex of patients with schizophrenia.

Conclusions: Collectively, our data suggests that *RASD2* represents a gene of potential interest in psychiatric disorders for its ability to modulate prefronto-striatal phenotypes related to schizophrenia.

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