SLITRK5, a protein that links striatal deficits to OCD-like behaviours in mice

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Slitrk5 deficiency impairs corticostriatal circuitry and leads to obsessive-compulsive-like behaviors in mice
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Obsessive–compulsive spectrum disorder (OCD) is one of the most prevalent psychiatric disorders. It is characterized by recurrent unwanted thoughts and/or repetitive behaviour. These manifestations vary both in range and severity. Therefore, questions have been raised as to whether OCD should be classified as a single or multiple conditions (1).
Because the very definition of the disorder is ambiguous, it is a challenge to study the condition as a whole. Fortunately, distinct behaviours within the OCD spectrum can be investigated individually. A behaviour that falls within the OCD spectrum, trichotillomania, is itself a common affliction affecting approximately 2% of the population (2). The characteristic repetitive self-hair-pulling of trichotillomania has been linked to serotonin (3) and dopamine signalling (4). In fact, some cases can be treated with selective serotonin reuptake inhibitors (SSRIs) and dopamine antagonists (4), which are used to block reward pathways in the brain. Interestingly, trichotillomania can be recaptured in mouse models, where affected mice persistently groom themselves, eventually leading to loss of hair patches and the development of ulcerous lesions.

Recently, mutations in Slitrk genes have been implicated in mental disorders (5, 6). For example, Slitrk1 is implicated in cases of Tourette’s syndrome (6), a disorder that falls within the OCD spectrum. Each of the six SLITRK proteins contains a single transmembrane domain along with domains resembling Slit signalling proteins and TRK neurotrophin receptors. The presence of these domains suggests that SLITRKs could have roles in extracellular signalling, cellular outgrowth, and differentiation. In a recent study, Shmelkov et al. describe that the loss of Slitrk5 leads to OCD-like behaviours in mice.

Although systemic loss of Slitrk5 in mice did not lead to obvious morphological defects, mutants displayed the OCD-like behaviour of persistent grooming. Animals carrying only one functional copy of Slitrk5 still developed the grooming phenotype, but exhibited delayed onset of the behaviour. Importantly, Slitrk5−/− mice displayed additional OCD-like symptoms, including an increased propensity to bury objects. Because the mutant mice had unaffected motor skills, the authors concluded that loss of Slitrk5 probably led to OCD-specific behaviours. Notably, treatment of Slitrk5−/− mice with the SSRI fluoxetine (FLX) alleviated the persistent grooming behaviour. Because the effects of FLX in Slitrk−/− mice were similar to the effects of SSRIs on human OCD patients, it is probably that the molecular mechanisms leading to compulsive behaviour are similar in both species.

Given that Slitrk5−/− mutants predominantly manifest behavioural deficits, Shmelkov et al. investigated changes in overall brain morphology and in neuronal structure. They found that Slitrk5−/− mice had smaller brain striatal volumes than their wild-type counterparts, agreeing with observations of decreased striatal volume in some OCD patients. In striatal medium spiny neurons (neurons that regulate body, limb, and eye movement) SLITRK5 localized to dendritic regions. In these neurons, Slitrk5 loss led to lower arborization of striatal dendrites, reflecting a decrease in synaptic connectivity. Shmelkov et al. also observed decreases in the amounts of glutamate receptor proteins. Probably because of these defects, corticostriatal neurotransmission was impaired, agreeing with the observation of altered corticostriatal transmission in OCD patients (7).

The grooming phenotype associated with Slitrk5 loss is similar to the phenotypes of Sapap3 and Hoxb8 mutants in mice (8, 9). These genes are all expressed in the striatum, suggesting that this brain region is critical for regulating the grooming behaviour (8, 9). Curiously, both Slitrk5 and Hoxb8 are also expressed in hematopoietic progenitors. Although it seems paradoxical that genes which regulate grooming behaviours are connected to tissues that govern immune function, it has been suggested that grooming could be coupled to immune responses as this behaviour could reduce organismal pathogenic load (9).

Overall, Shmelkov et al. establish a monogenic Slitrk5-based mouse model of trichotillomania. Because the SLITRK5 extracellular domain resembles neurotrophin receptors, it is plausible that these proteins could have similar ligands. This would be interesting as neurotrophic signalling is associated with neurological diseases (10), and because neurotrophins can be regulated by existing drugs such as FLX (11). However, the precise role of serotonin signalling in the context of Slitrk5 loss is still obscure; moreover, whether SLITRK5 plays a role in human OCD remains to be determined. Future studies that investigate the disease relevance of the human gene are essential for Slitrk5 to emerge as an important therapeutic target and/or biomarker for OCD.

References