NEWS

Dopamine transmission may influence neurofibromatosis type 1

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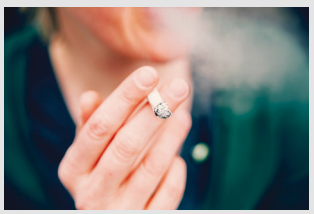
Skin lesions, skeletal abnormalities, neoplasia, and learning disabilities characterize neurofibromatosis type 1 (NF1), an autosomal dominant disorder caused by pathogenic variants in the *NF1* gene. Many people with NF1, which affects 1 in 3500 individuals worldwide, also exhibit impaired executive functioning, speech and language delays, attention deficits, hyperactivity, and/or impulsivity. Scientists generally consider weak neurotransmission of dopamine in mesolimbic and nigrostriatal circuits to underlie the attentional, learning, and motivational deficiencies seen in mouse models of the disease, as these circuits help to translate relevant stimuli into motivated behaviors and have been implicated in the pathophysiology of ADHD and other impulsivity disorders. Until now, however, no one has tested dopaminergic transmission in these circuits in NF1 models in vivo. In a study recently published in *eLife* (https://elifesciences.org/articles/48983), Robinson and colleagues found that NF1 mice displayed perturbed dopamine neurotransmission and exhibited more robust dopaminergic and behavioral responses to stimuli compared with wild-type mice. Together, the findings uncover new pathophysiological mechanisms behind NF1, according to the authors. To observe dopaminergic neurotransmission in wild-type and heterozygous *NF1* knockout mice, the researchers used a genetically encoded, fluorescent dopamine sensor called dLight1.2. Baseline dLight1.2 recordings showed that dopaminergic neurons in NF1 mice displayed reduced transient frequency compared with wild-type littermates. Spontaneous firing rates of dopaminergic neurons from the ventral tegmental area (VTA) of NF1 mice were also lower due to increased inhibition from GABAergic neurons, a mechanism that has been hypothesized to modulate cognitive deficits associated with NF1. Subsequent experiments revealed that inhibiting GABAergic neurons in the VTA restored dopaminergic neurotransmission. Compared with wild-type mice, NF1 rodents exhibited more robust behaviors in response to visual stimuli. For example, when the researchers exposed the mice to an overhead disc meant to mimic an approaching predator, the NF1 mice were more likely to escape to a shelter than their wild-type counterparts were. Optogenetic inhibition of GABAergic neurons in the VTA prevented the NF1 mice from overreacting to the looming disc. The findings implicate VTA GABAergic neurons in the visual-response phenotypes caused by *NF1* haploinsufficiency, the researchers write. They conclude that the findings may provide new insights for people since patients with NF1 display visual-processing deficits.
—V. L. Dengler, News Editor

Smoker face: genetic variant affects smoking heaviness and facial aging



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Smoking cigarettes or using tobacco has detrimental health impacts such as lung cancer development. Research has shown that genetic variants such as those found in the *CHRNA5* gene that affect nicotine receptor function are robustly associated with how much a person smokes. A challenge in research, however, is to figure out whether the effects of a genetic variant associated with heavier smoking come from using more tobacco products or are a result of carrying the risk variant but unrelated to tobacco use. In a study published recently in *PLOS Genetics* (https://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1008353), Millard and colleagues present a novel method to identify and separate these two kinds of effects. The approach combines Mendelian randomization phenome-wide association studies (MR-PheWAS) to search for the effects of an exposure with a gene-by-environment (GxE) study design to determine whether a genetic variable affects an outcome via pathways other than the exposure of interest. In the proof-of-principle study, the researchers tested causal effects of smoking heaviness. Using the variant rs16969968 as an instrument for smoking heaviness, the authors drew on data from more than 330,000 people registered in the UK Biobank, nearly 183,000 of whom reported never smoking and about 151,000 of whom reported being previous or current smokers. The number of cigarettes smoked per day determined a previous or current smoker's smoking heaviness. The team then performed an MR-PheWAS analysis using a software package they developed called PHEASANT that systematically tested the association of smoking heaviness across more than 18,000 traits in the UK Biobank. The analysis replicated established effects of smoking heaviness on lung function and identified eight results where greater rs16969968 allele dosage was associated with phenotypes such as higher risk of chronic obstructive pulmonary disease, emphysema, and cancer. The analysis also uncovered novel associations such as an unfavorable impact of heavier smoking on facial aging. The GxE MR-PheWAS revealed that a higher genetic predisposition to heavier smoking associated with an increased risk of appearing to others as older than one's true age. The researchers conclude that the GxE MR-PheWAS approach can be used to identify potential causal effects of an exposure of interest such as alcohol consumption that occurs in recognizable subsets of a population.
—V. L. Dengler, News Editor

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