Cyfip1 haploinsufficiency increases compulsive-like behavior and food consumption: Parent-of-origin effects and potential implications for Prader-Willi Syndrome

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Binge eating (BE) is a heritable trait associated with eating disorders that involves consumption of a large quantity of food in a short period of time. We recently identified cytoplasmic FMR-interacting protein 2 (*Cyfip2*) as a major genetic factor underlying BE and compulsive-like eating. *CYFIP2* is a closely related gene homolog of *CYFIP1* which is one of five additional, paternally deleted genes in patients with the more severe type Type I Prader-Willi Syndrome (PWS). PWS is a neurodevelopmental genetic disorder in which 70% of cases involve paternal deletion of 15q11-q13. PWS is defined in part by hyperphagia, obsessive and compulsive behaviors, and cognitive disability. Here, we tested the hypothesis that *Cyfip1* haploinsufficiency in mice on a C57BL/6NJ background would increase premorbid compulsive-like behavior and palatable food consumption in a parent-of-origin (paternal)-selective manner. Additionally, because we previously identified an association between a C57BL/6NJ-derived missense mutation in *Cyfip2* and a marked increase in palatable food consumption, we ran the same study in N3 mice generated via three generations of backcrossing to C57BL/6J mice to produce mice that were homozygous for the wild-type C57BL/6J (B6J) allele at the *Cyfip2* locus. *Cyfip1* haploinsufficiency increased compulsive-like behavior (marble burying) on both backgrounds as well as an increase in palatable food consumption that was more pronounced with paternal inheritance, in particular when assessed on the lower-consuming N3 background. These results provide the first evidence that paternal *CYFIP1* haploinsufficiency could contribute to compulsive behavior and hyperphagia in patients with Type I PWS and warrant future mechanistic and translational investigation that could inform patient-specific treatments.