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

Camron D. Bryant1*, Richard K. Babbs1, Qiu T. Ruan1,2, Julia C. Kelliher1, Stacey L. Kirkpatrick1, Fred A. Rodriguez1, Ashley X. Feng1, and Fabiola Benitez1

1Laboratory of Addiction Genetics, Department of Pharmacology and Experimental Therapeutics, Boston University School of Medicine (BUSM); 2T32 Graduate Training Program in Biomolecular Pharmacology, BUSM

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 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.