Cytoplasmic FMR1-interacting protein 2 is a major genetic factor underlying binge eating

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Background: Eating disorders are lethal and heritable; however, the underlying genetic factors are unknown. Binge eating is a highly heritable trait associated with eating disorders that is comorbid with mood and substance use disorders. Therefore, understanding its genetic basis will inform therapeutic development that could improve several comorbid neuropsychiatric conditions.

Methods: We assessed binge eating in closely related C57BL/6 mouse substrains and in an F_2 cross to identify quantitative trait loci (QTL) associated with binge eating. We used gene targeting to validated candidate genetic factors. Finally, we used transcriptome analysis of the striatum via mRNA sequencing (RNA-seq) to identify the premorbid transcriptome and the binge-induced transcriptome to inform molecular mechanisms mediating binge eating susceptibility and establishment.

Results: C57BL/6NJ but not C57BL/6J mice showed rapid and robust escalation in palatable food consumption. We mapped a single genome-wide significant QTL on chromosome 11 (LOD=7.4) to a missense mutation in cytoplasmic FMR1-interacting protein 2 (*Cyfip2*). We validated *Cyfip2* as a major genetic factor underlying binge eating in heterozygous knockout mice on a C57BL/6N background that showed reduced binge eating toward a wild-type C57BL/6J-like level. Transcriptome analysis of premorbid genetic risk identified the enrichment terms “morphine addiction” and “retrograde

endocannabinoid signaling” whereas binge eating resulted in the downregulation of a gene set enriched for decreased myelination, oligodendrocyte differentiation, and expression.
Conclusions: We identified *Cyfip2* as a major significant genetic factor underlying binge eating and provide a behavioral paradigm for future genome-wide association studies in populations with increased genetic complexity.

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