this study shows the power of combined drosophila and mammalian genetics in uncovering novel regulators of metabolism.

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Adipose Tissue, Appetite, & Obesity

LBSUN99

Combination Of Drosophila And Mammalian Genetics Identifies Lcorl As A Novel Regulator Of Metabolism

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Obesity and adult-onset diabetes result from a complex interaction of multiple genetic, environmental, and behavioral factors. The hypothalamus contains multiple nuclei required for the regulation of metabolic homeostasis. One nucleus, termed the ventromedial hypothalamus (VMH), facilitates glucose homeostasis and metabolic adaptations to challenges such as high fat diet (HFD) and exercise. Using a combination of Drosophila and mouse genetics, we uncovered a novel gene network whose function is required for VMH-regulated whole body metabolism. Using Drosophila to rapidly screen orthologs of genes enriched in the mouse VMH, we identified the gene encoding the Ecdysone Induced Protein 93F (E93; human ortholog, Ligand dependent corepressor-like, Lcorl). Adult flies with neural knockdown of E93 are obese and hyperphagic, with increased energy stores, reduced exercise endurance, and dampened circadian amplitude. These findings reveal a novel role of E93 in metabolism. We found that the knockdown of E93 specifically in myoinhibitory peptide (MIP) and GABAergic neurons are sufficient to recapitulate the phenotype seen in a pan-neuronal E93 knockdown. | In mice, we found that Lcorl, the mammalian orthologue of E93, is highly expressed throughout the entire VMH. We used CRISPR/Cas9 to generate mice harboring both a Lcorl KO and a floxed allele to investigate its function in the whole-body and in a tissue specific manner. Lcorl KO mice are viable and fertile. However, they have disruptions in growth, lipid metabolism, and circadian rhythm. Taken together these data reveal that Lcorl is as a novel regulator of energy metabolism and circadian rhythm. Additionally,