Abstract

Canine genome-wide association study identifies *DENND1B* as an obesity gene in dogs and humans

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Editor's summary

Obesity is frequently seen not only in humans, but also in dogs, and some breeds are particularly at risk. Owner behaviors such as limiting food access and providing physical activity can help mitigate the dogs' risks, but genetic variants are also thought to play a role. Wallis *et al*. performed a genome-wide association study in hundreds of pet Labrador retrievers and identified the gene *DENND1B* as a major culprit in these dogs' obesity. The authors demonstrated that DENND1B regulates the activity of the melanocortin 4 receptor, which plays a major role in energy homeostasis. They also identified a human patient with a mutation in *DENND1B* and other humans with additional mutations found in the dogs, demonstrating the connection to human physiology. —Yevgeniya Nusinovich

Structured Abstract

INTRODUCTION

Obesity is a heritable disease, but its genetic basis is incompletely understood, and moving from common genetic associations to mechanistic insight has proven challenging. Hypothalamic leptin-melanocortin signaling is a critical nexus of the central control of energy balance that integrates peripheral signals of energy status, translating them into alterations in energy expenditure and eating behavior to maintain energy homeostasis.

RATIONALE

Dogs are a compelling model of obesity because they develop obesity subject to environmental influences similar to those that influence obesity in humans and because population bottlenecks at breed formation render trait mapping highly tractable. We studied an obesity-prone dog breed, the Labrador retriever, and tested whether variants associated with canine adiposity highlight genes that are also relevant to human obesity.

RESULTS

In 241 adult pet Labrador retrievers, we performed a genome-wide association study (GWAS) for body condition score (BCS), a measure of canine adiposity. The top association was intronic within the gene DENN domain containing 1B (*DENND1B*). Each allele of the lead variant in dogs conferred ~7.5% higher body fat. At the syntenic region of the human genome, there was also a highly significant association with body mass index (BMI), although with small effect size (0.011 kg/m^2 increase per copy of the risk allele; $P = 9.42 \times 10^{-9}$). Multiple lines of evidence implicated that *DENND1B* is the most likely causal gene at this locus. Rare, damaging variants in *DENND1B* were also nominally associated with BMI in the UK Biobank study [$P = 0.0087$; effect size (β) = 0.35 kg/m^2], and a homozygous, damaging variant was implicated as the cause

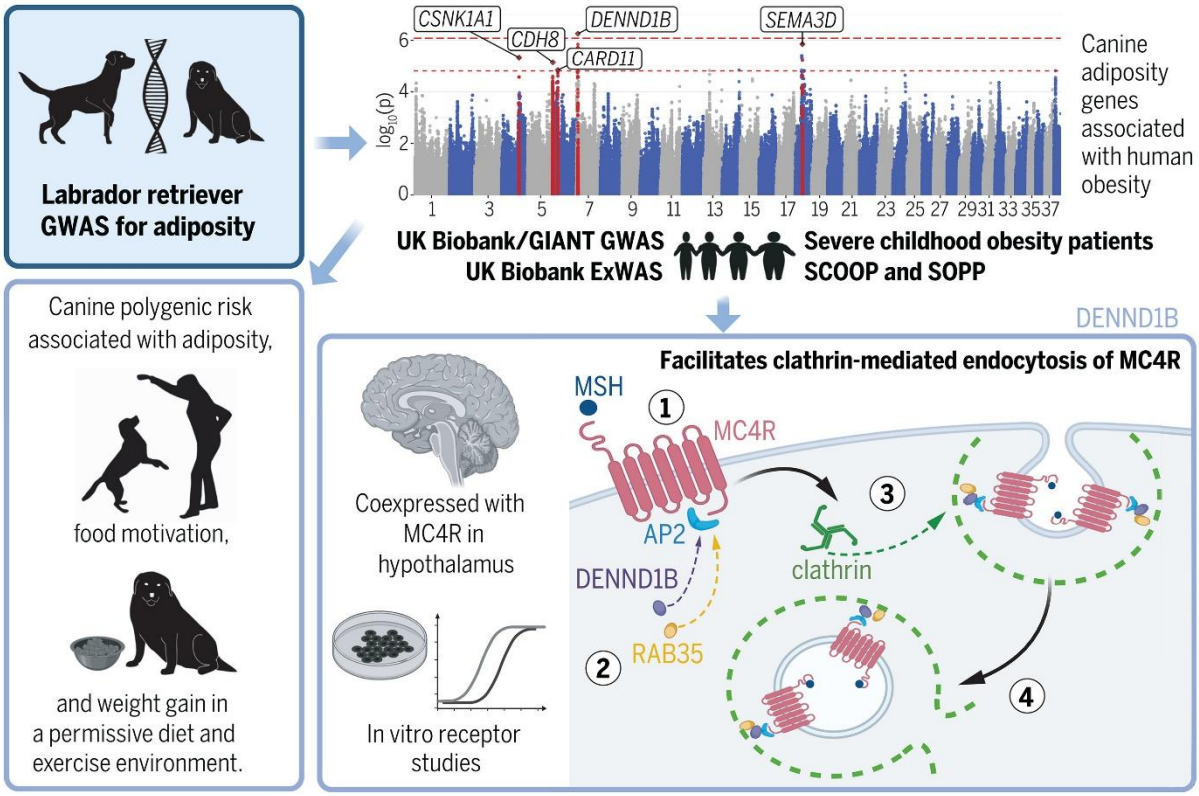
of severe childhood obesity in a single proband. At each of the four additional canine loci that met a less stringent significance threshold, positional candidate genes were also associated with human BMI.

DENND1B has a known role in clathrin-mediated endocytosis that underlies its association with human asthma through the regulation of T cell receptor function. We hypothesized that it would affect the activity of receptors involved in energy homeostasis, particularly melanocortin 4 receptor (MC4R). We showed that *DENND1B* is coexpressed with *MC4R* and other relevant receptors in single-cell expression data from both the murine and human hypothalamus. In cell models, overexpression of *DENND1B* increased MC4R internalization after ligand activation and reduced cyclic adenosine 3',5'-monophosphate (cAMP) signaling, with the converse effect on *DENND1B* knockdown. By contrast, there was no such effect on the orexigenic receptor, growth hormone secretagogue receptor (GHSR).

A canine polygenic risk score (PRS) improved prediction of BCS and body weight in an independent set of Labrador retrievers but had little or no predictive value in other breeds. Association of PRS with food motivation indicated that genetic risk is in part mediated by greater appetite in dogs. That relationship may underlie the higher PRS observed in Labradors selected to be assistance dogs because high food drive could improve their responsiveness to food used to positively reinforce desirable behaviors during training. We also observed that strict owner control of diet and exercise was influential in preventing obesity in dogs with high polygenic risk but not in dogs with low polygenic risk, which were relatively resistant to becoming overweight.

CONCLUSION

We identified obesity-related genes in humans by studying the canine model, with findings relevant to preventative and therapeutic interventions in both species. The discovery of DENND1B as a regulator of MC4R activity informs our understanding of melanocortin signaling—a critical pathway in hypothalamic regulation of energy homeostasis. Notably, our findings show that even high polygenic risk can be mitigated. These findings demonstrate the benefits of studying complex disease in nontraditional animal models, such as the dog, and have practical implications for improved management of canine obesity.



***DENND1B* and other canine obesity genes were also associated with obesity in humans.**

After (1) ligand activation of the hypothalamic melanocortin receptor (MC4R), DENND1B (2) binds adaptor protein 2 (AP2) and RAB35 to initiate (3) clathrin-mediated endocytosis, a process that leads to (4) deactivation of the receptor, providing a mechanistic link between DENND1B expression and regulation of energy homeostasis. ExWAS, exome-wide association study; SCOOP, Severe Childhood Onset Obesity Project; SOPP, Severe Obesity in Pakistani Population; MSH, melanocyte-stimulating hormone.