Human Genetic Variant OtpQ153R/+ Causes Excessive Weight Gain and Glucose Intolerance in Mice

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Obesity has reached epidemic proportions, becoming a preventable leading cause of death worldwide. A multitude of approaches and animal models have been employed to investigate the pathophysiology of obesity. Among them, genome-wide association studies have led to the discovery of several “obesity genes” that build the foundation of the current understanding of the genetics behind obesity. However, of the hundreds of obesity-associated loci identified, only a few have been studied functionally. This lack of understanding of the mechanistic function of the genes limits the transformation of genomic data towards insights into the pathogenesis of obesity. One of these obesity genes is a rare heterozygous variant OtpQ153R/+ that has been recently discovered in a large cohort of individuals with severe, early-onset obesity. Otp is a developmental gene that encodes a homeodomain transcription factor that is expressed in multiple groups of hypothalamic neurons. The substitution of glutamine (Q153) with arginine (R153) in Otp results in a loss of function mutation, OtpQ153R/+. Hence, it was hypothesized that the human genetic variant OtpQ153R/+ can cause weight gain and glucose intolerance. In this study, a new mouse model carrying the human OtpQ153R/+was generated and tested. The results suggest that the human genetic variant OtpQ153R/+ indeed leads to weight gain and the development of glucose intolerance in mice, suggesting a possible mechanism of obesity in humans. Understanding the genetic causes of obesity can provide a better comprehension of a serious medical condition and open doors to identifying potential targets for the treatment of early-onset obesity.

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