CLINICAL IMPLICATIONS OF BASIC RESEARCH

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Obesity — On or Off?

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Obesity imposes major health risks on the individual patient, and its prevalence is rapidly increasing. The heterogeneous and complex causes of this disorder, including interactions between genetic predisposition and environmental factors (almost all of which are unknown), are challenging to treat and to prevent.

A recent study by Dalgaard and colleagues[1] forces us to rethink aspects of the heritable component of obesity. Dalgaard et al. characterized mice carrying a mutation in the gene encoding tripartite motif–containing 28 (*Trim28*). Trim28 is a zinc-finger transcription factor that enhances transcriptional repression — in other words, a mutation in one copy of *Trim28* causes an unexpected heritable bimodal (on–off) obesity distribution that seems to depend on certain environmental factors to "flip the switch." The average weight gain (approximately 7 g) in the obese ("on") mouse with the *Trim28* mutation was largely due to an increased mass of adipose tissue distributed uniformly across all adipose depots and a very slight increase in length (1 to 2%), whereas the weight in the "off" phenotype did not differ from that in wild-type animals. The approximate doubling of the adipose-tissue mass in the "on" phenotype was accompanied by a doubling in the number of adipocytes in the tissue.

However, the mechanism for the accumulation of adipose tissue in the obese *Trim28* mice was difficult to understand. The characterization of energy homeostasis was puzzling because of the observed behavioral effects (anxiety, stress sensitivity, and nightly hypoactivity), which implicate the central nervous system in driving the "on" form of obesity in these animals. Their primary metabolic profiles and secondary metabolic complications were not substantially different from those of their nonobese *Trim28* littermates.

To find the causal mechanisms of obesity in the *Trim28* mice, the investigators compared differences in gene-expression profiles of the epididymal adipose tissue in the obese mice and those in the lean mice with such differences in wild-type mice that were fed a high-fat diet and those that were fed regular chow. They observed a low correlation between the differences in these two data sets, which suggests that the obesity caused by overeating in the wild-type mice and obesity caused by a deficiency in Trim28 have biologically different mechanisms. Because the *Trim28* mutation was previously shown to have a silencing effect,[2] the authors chose to focus on genes that were down-regulated in adipose tissue in *Trim28* mice but that showed an opposite transcriptional pattern (i.e., one that was unaltered or up-regulated) in wild-type obese mice that were fed a high-fat diet. The investigators identified a set of nine imprinted genes and an imprinted gene network (which they called IGN1) that showed substantial differences in expression between these groups of mice, genes that were down-regulated in obese *Trim28* mice. Some of these genes have been implicated in body size and weight control.[3] However, the authors could find no differences in DNA methylation of these genes among the different groups of mice.

To test whether down-regulation of the IGN1 gene cluster could cause the bimodal (on–off) obesity distribution, the investigators knocked out some of the genes in the cluster in a subgroup of mice. The loss of at least two of the genes in the IGN1 cluster (*Nnat* and *Peg3*) reproduced the "on" *Trim28* phenotype (Fig. 1). Mice that were deficient in either gene have a more pronounced phenotype than the *Trim28* haploinsufficient mice. Thus, with strong circumstantial evidence for an epigenetic regulation of the on–off heritable pattern, the investigators con-

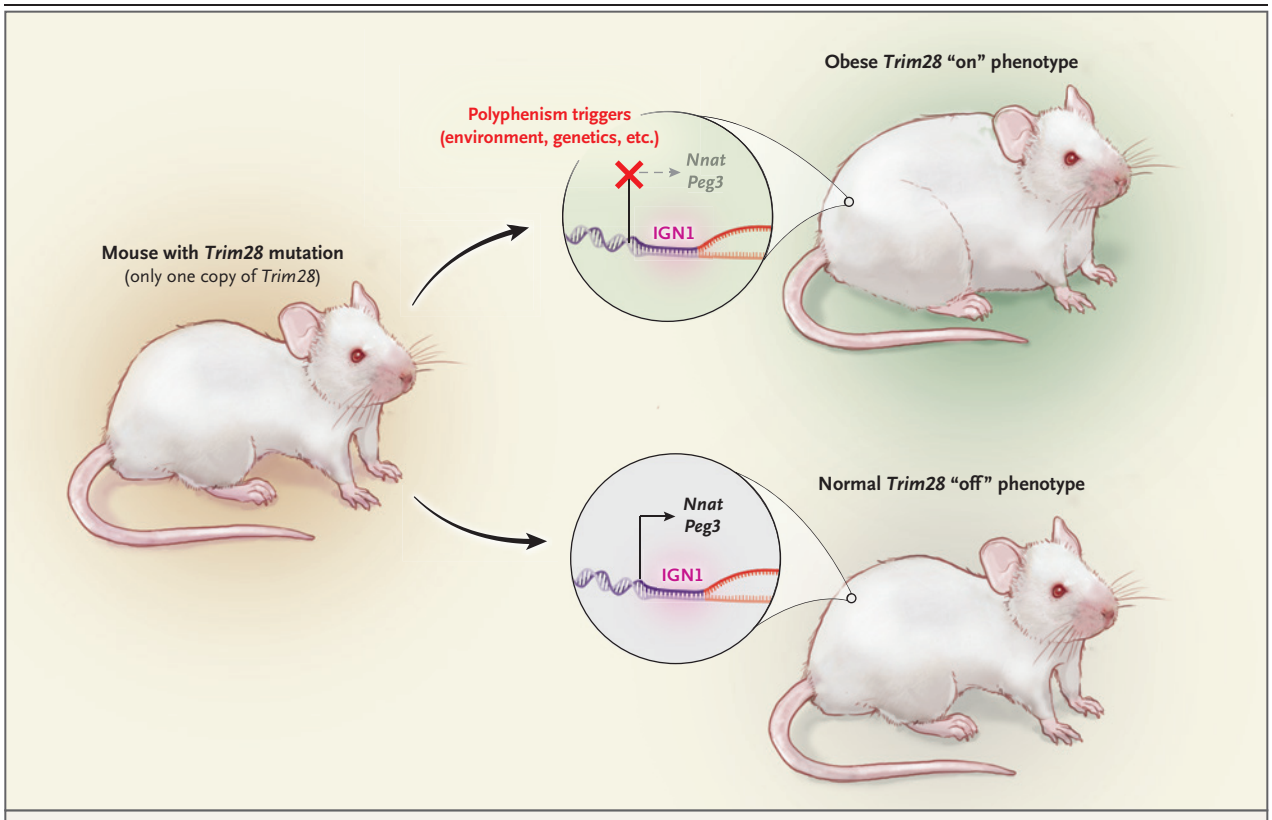

Figure 1. Trim, Not So Trim, and *Trim28*.

A stable complex involving tripartite motif–containing 28 and the ZFP57 zinc-finger protein (TRIM28–ZFP57) is required for chromatin stability during embryonic development. Mutations in *Trim28* appear to have downstream epigenetic consequences that are linked to a concerted down-regulation of a network of imprinted genes (IGN1), as described by Dalgaard et al.[1] The down-regulation of genes in this network, in particular *Nnat* and *Peg3*, appear to cause an obese ("on") phenotype in mice with a *Trim28* mutation in which a single copy of *Trim28* is inactivated. This polyphenism, a random phenotypic switch in the genetically identical mice carrying the *Trim28* mutation, shows a bimodal distribution ("on" or "off") of obesity with no intermediate phenotype. Since these mice are genetically identical, environmental signals (e.g., temperature, hormones, and diet) could be influencing the phenotype switch and polyphenism.

cluded that dysregulation of imprinted genes caused the *Trim28*-dependent bimodal obesity. Further work will be needed to identify the precise epigenetic mechanism by which the expression of these genes is down-regulated.

Are these findings relevant to obesity in humans? The bimodal obesity phenotype was obvious in the inbred *Trim28* mice, and the authors obtained suggestive data that polyphenism is also manifested in human populations. They observed that *TRIM28* expression levels in human adipose tissue sorts samples into one of two subsets. Persons with low levels of *TRIM28* expression have IGN1 dysregulation and are more likely to be obese than are persons with high levels of *TRIM28* expression, a finding that is in line with the observations in mice. In addition, they report that the distributions of body-mass index within a homogeneous pediatric cohort (4000 children of European ancestry) as well as within a heterogeneous cohort (persons of black American, Mexican-American, and Han Chinese ancestries) fit two distinct gaussian distributions rather than a single gaussian distribution. However, we note that there could be other explanations (e.g., skewed social and environmental stratification) for a bimodal distribution. The regulation of *TRIM28* expression in humans remains unknown.

Does the study by Dalgaard and colleagues point to a new approach to the treatment of obesity? Although 40 to 70% of the variability in obesity among individuals is commonly attributed to genetic factors, less than 20% of the

variability is explained by known common genetic variants.[4] The authors propose the existence of a mechanism that links the environment to gene expression (e.g., of *TRIM28*) and thereby modulates the prevalence of obesity in the population. The authors speculate that environmental cues, such as ambient temperature, could be a modulator of the on–off obesity phenotype. Genetic contribution to polyphenism per se would be difficult to detect with the use of existing analysis strategies. Although genomewide association studies have yielded obesity-related loci, the study design assumes that the phenotype under scrutiny is normally distributed. The authors propose that mechanisms that cause a bimodal nonmendelian distribution of obesity exist in humans and that there may be signals of these mechanisms in current data sets.

Much research is needed before any conclusions on whether polyphenism contributes to the human obesity epidemic can be made. If it can be shown that environmental regulators cause obesity as a polyphenism, then modifying these environmental triggers would be an obvious opportunity to manipulate obesity.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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