Apple or Pear: Size and Shape Matter

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Obesity-related morbidity and mortality are related to fat accumulation and fat distribution in humans. Two large-scale meta-analyses recently published in *Nature* by Shungin et al. (2015) and Locke et al. (2015) report novel genetic associations for central and overall obesity; these greatly advance our understanding of the biology of obesity.

Obesity poses a major burden on health and is associated with a higher prevalence of chronic disorders. Obesity is characterized by excessive fat accumulation and intra-abdominal fat deposition (central obesity) in humans (Figure 1A). Body mass index (BMI) is used to assess the extent of general obesity, while waist-to-hip ratio (WHR), especially after adjusting for BMI, is used as a parameter for central obesity (apple-shaped or pear-shaped obesity). Both obesity traits have been shown to be highly heritable. Previous genome-wide associated studies (GWAS) identified 41 genetic loci associated with BMI and 16 with WHR (Heid et al., 2010; Speliotes et al., 2010). Two new meta-analyses (Locke et al., 2015; Shungin et al., 2015), with sample sizes of 339,224 and 244,459 human subjects, respectively, pinpoint to a much longer list of obesity-associated loci (97 BMI and 49 WHR loci).

Despite the large number of loci now discovered, they collectively explain less than 3% of the phenotypic variation observed. One important question is, where is the remaining heritability found? It has been suggested that a large number of common DNA variants contribute to the differences in phenotypic variation but that individually they have very modest effects, which makes them difficult to detect (Robinson et al., 2014). The two meta-studies have estimated that additional common variants can account for more than 20% of BMI variation and 12.1% of WHR variation. Another question is, how can we translate this knowledge into disease mechanisms or even clinical applications?

Over the past 5 years, tremendous efforts have helped identify causal variants and causal genes from GWAS as a first step toward understanding the underlying disease mechanism. This has proved challenging for three reasons. First, the lead GWAS SNP is not necessarily a causal one: the true causal variant can be identified by more detailed genetic mapping, by taking advantage of multi-ethnic groups, and/or by employing high-density SNP chips (Metabochip). Nevertheless, genuine proof that a causal variant has been identified requires additional mechanistic evidence.

Second, fine mapping is often used to refine the region of association to a single gene, which is then marked as disease-causing. This can be misleading, particularly when the causal SNP does not reside in the coding region of a gene but maps to a regulatory region. An example is the identification of a long-range effect from the associated SNP at the *FTO* locus on the expression of the *IRX3* gene, which lies at a distance of 1.2 Mb from the SNP (Smemo et al., 2014). *FTO* was implicated as an obesity gene in 2007 due to the strong association of an intronic SNP with BMI (Dina et al., 2007). Recently, new evidence for a causal role of *IRX3* has emerged from information on the functional and regulatory elements in the human genome generated by the ENCODE consortium (Bernstein et al., 2012). Prioritizing an incorrect gene may jeopardize the downstream analysis into pathways linked to obesity.

A particularly strong point of these two new meta-studies (Locke et al., 2015; Shungin et al., 2015) is that they provide a list of putative candidate genes by leveraging multiple lines of evidence, including the functional annotation of genetic variants, gene expression data, and expression quantitative trait loci (eQTL) in multiple tissue types, molecular pathways, functional predictions, and the literature. Even then, their results are complicated. Prioritization tools can only be based on current knowledge, and for 41% (23/56) of the new BMI loci discovered, no putative candidate genes could be prioritized based on the functional information available. Furthermore, different prediction tools lead to different predictions. For example, the eQTL data suggested putative candidate genes for 28%–36% of the new loci (16 BMI loci and 12 WHR loci). Most of the eQTL genes are not the genes nearest to the lead SNPs or genes from functional predictions or the literature.

The third reason is that most of the prioritization tools focus on the coding potential of the genome but completely ignore the many more non-coding transcripts that encode for different classes of regulatory RNA molecules (Lau, 2014).

The genes at different loci do not work in isolation but are likely to interact with each other and converge on certain pathways and networks. Pathway analyses on both BMI and WHR loci have yielded interesting findings, and different biological processes have been suggested to be associated with obesity and central obesity (Figure 1B). Obesity is a complex trait, driven by the interaction between genetic and environmental factors. In epidemiological studies, lifestyle is often treated as an environmental factor, independent of genetic factors. However, one striking observation is that BMI-associated loci are enriched for genes highly expressed in the central nervous system, suggesting there is a genetic component in lifestyle. These genes are thought to affect appetite, emotion, cognition, and

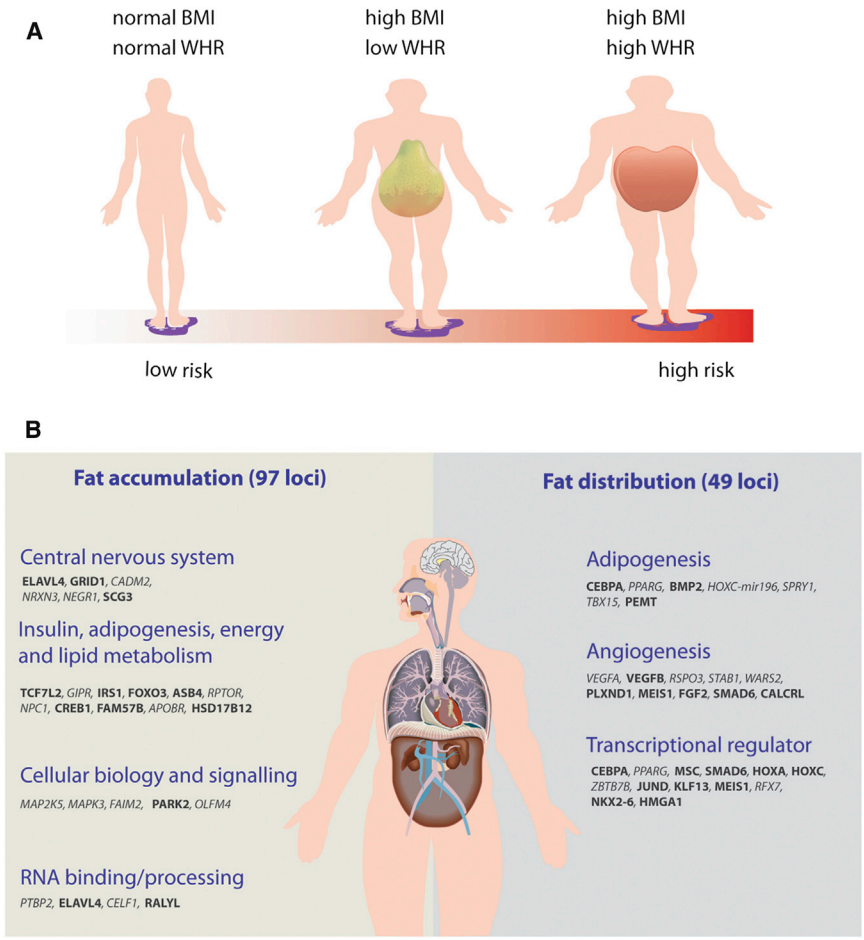

Figure 1. Genetic Analysis Suggests Different Pathways Are Active in Fat Accumulation and Its Distribution

(A) The risk of obesity in chronic disorders. This risk is not only determined by excessive fat accumulation but also by intra-abdominal fat deposition (central obesity) in humans. Epidemiologic evidence shows that central obesity (apple-shape, high waist-to-hip ratio, WHR) contributes a higher risk than general obesity (high BMI) to many chronic diseases, including cardiovascular diseases and type 2 diabetes.

(B) Biological processes involved in fat accumulation and fat distribution, summarized from the findings of Shungin et al. and Locke et al. Some of the newly identified genes are listed in bold: the evidence for them is derived from two independent sources, providing a more compelling reason that these are indeed causal genes.

self-control, thereby influencing an individual's energy intake and expenditure. Some people can be characterized as "natural-born eaters." In contrast, genes implicated in adipogenesis, angiogenesis, and insulin resistance seem to play key roles in determining an individual's fat distribution. For a long time, the field has been searching for the missing genetic link between obesity and type 2 diabetes; this has long been suspected from epidemiological studies.

We now have convincing evidence for a genetic link between central obesity and insulin resistance (Shungin et al., 2015); some of the WHR-associated genes act in the processes of insulin secretion and signaling (Figure 1B). Hence, these findings argue for a reciprocal relationship between central obesity and metabolism, together culminating in cardiovascular complications and other comorbidities.

The recent work by Shungin et al. and Locke et al. assessed the association of obesity-related loci with multiple anthropometric and non-anthropometric traits, and with metabolic disorders and traits, thereby providing more mechanistic insight into obesity and obesity-related morbidity. However, we still don't know whether some of these findings reflect a causal relationship or a pleiotropic association (Li et al., 2014). Answers to this question will help us better understand the biology of obesity and obesity-associated diseases and also offer strategies for obesity prevention and treatment.

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