

Defining the genetic architecture of the predisposition to obesity: a challenging but not insurmountable task^{1,2}

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Obesogenic environment and behavior are fueling the rise in the prevalence of overweight and obesity. However, one should not omit biology from the discussion. Several lines of evidence support the contention that there are individual differences in the predisposition to gain weight and that genetic variation has much to do with the risk of becoming obese, particularly the risk of severe obesity.

First, single-gene syndromic and nonsyndromic disorders account globally for as much as 5% of obesity cases. The identification of these obesity genes and mutations will continue to illuminate the molecular biology and pathophysiology of human obesity. Second, candidate gene studies provided suggestive evidence that multiple genes were involved in the predisposition to obesity. However, these genes were supported by grossly underpowered studies, and contradictory evidence was reported for all of them (1). Third, genome-wide linkage scans with the use of highly polymorphic microsatellite markers yielded a large number of quantitative trait loci for obesity. However, a meta-analysis of 37 genome scan studies with data on 31,000 individuals from >10,000 families could not implicate unequivocally a single genetic locus for obesity or body mass index (BMI) (2). The main lesson here is that genome-wide scans, as executed over the last 15 y or so, were not well suited to identify genes with small effects.

Fourth, with the completion of the sequencing of the human genome, the advances brought about by the International HapMap Project, and the progress in high-throughput genotyping technologies, bioinformatics, and statistical genetics, a more general approach was developed for the identification of genes with small effects on quantitative traits or disease state. The approach is referred to as *genome-wide association studies* or GWAS. It soon became clear that GWAS were capable of detecting alleles with relatively small effect sizes. As of early June 2009, a total of 17 obesity loci distributed across the autosomal genome had been uncovered in 6 GWAS reports at a *P* level of 5×10^{-7} or better (3).

The importance of obesity-predisposing single-nucleotide polymorphisms (SNPs) or loci is in the risk that they convey when considered in the aggregate. This was first shown in a report based on 8 SNPs (in or near *FTO*, *GNPDA2*, *KCTD15*, *MC4R*, *MTCH2*, *NEGR1*, *SH2B1*, *TMEM18*) that were identified in a meta-analysis of studies comprising >32,000 subjects and replicated in 9 studies totaling >45,000 individuals (4). The same report also showed in 14,409 subjects from the European Prospective

Investigation into Cancer and Nutrition–Norfolk (EPIC–Norfolk) cohort that individuals carrying ≤ 4 risk alleles at these 8 loci had a mean BMI (in kg/m^2) of ≈ 25.5 , whereas those with ≥ 12 of these risk alleles had a BMI of ≈ 27 .

In this issue of the Journal, Li et al (5) extend these observations to 12 SNPs (in or near *BCDIN3D*, *BDNF*, *ETV5*, *FTO*, *GNPDA2*, *KCTD15*, *MC4R*, *MTCH2*, *NEGR1*, *SEC16B*, *SH2B1*, and *TMEM18*). They genotyped 20,125 individuals from the same population-based EPIC–Norfolk cohort. The most powerful risk alleles were in *FTO* and *TMEM18*, with each risk allele increasing BMI by 0.33 and 0.25, respectively. Genotypic data were available at all 12 SNPs for 12,201 subjects. Among them, those who carried ≥ 17 risk alleles ($n = 171$) had a higher BMI (+1.53 BMI units or +5.7 kg increase in weight) than those who carried ≤ 6 risk alleles ($n = 118$). Overall, each additional risk allele at these 12 SNPs increased body weight by 444 g and the risk of obesity by $\approx 11\%$. However, all 12 SNPs add only $\approx 3\%$ to the predictive value of obesity beyond age and sex. Interestingly, the significant associations between SNPs and waist girth were abolished when waist was adjusted for BMI.

What have we learned from Li et al (5) and other GWAS reports that focused on obesity? First, the sample size initially required to show an association is much larger than was commonly thought. Second, replication is critical and needs to be based on multiple independent samples of substantial sizes. Third, very large panels of SNPs are needed to provide coverage of most of the existing genetic variants. Fourth, GWAS reports have shown that genes that contribute to BMI or risk of obesity are characterized by small effect sizes. Fifth, studies suggest that current risk alleles for obesity are rather common in whites.

Sixth, many other obesity-predisposing genes remain to be uncovered, but they will likely contribute progressively diminishing effect sizes. Thus far, 17 loci harboring risk alleles for obesity have been identified, but these alleles account for only $\approx 2\%$ of the variance in BMI in whites. In this regard, obesity is not a disease with a strikingly different profile than other complex disease conditions (6). Seventh, studies reported thus far have

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been confined to autosomes. It will be necessary to incorporate markers on the X and Y chromosomes in future efforts.

Finally, as was recently suggested (7), we are very far from being able to account for the often cited estimates of genetic heritability of BMI with the current panel of SNPs. Indeed, heritability levels ranging from 50% to 90% have been reported on the basis of observations on members of nuclear families and pairs of twins living together or separated early in life. There remains an enormous gap between the $\approx 2\%$ that we can currently account for and these often reported heritability values. I see 2 possible avenues of explanation for this extraordinary discrepancy.

On one hand, some of the missing variance may be accounted for by alleles with very low frequencies, as they are typically not retained in current panels of SNPs used in GWAS. Variation in the number of copies of DNA base repeats may offer another source of explanation that has not been yet investigated for obesity phenotypes. Gene-gene (or SNP-SNP), gene-nutrition, and gene-physical activity interaction effects represent potential sources of variance that need to be explored. In addition, imprinted genomic regions and epigenetic events should be considered. Epigenetic events are not necessarily stable over time or fully transmitted across generations. Thus, only some epigenetic events have the potential to contribute to the genetic variance.

On the other hand, one should also entertain the possibility that the large discrepancy results from markedly inflated heritability values. Some studies have found much lower heritability levels for BMI. These include studies performed by using partial adoption and full adoption designs (8, 9) and a report based on data aggregated from twins, nuclear families, and foster parents with adopted offspring (10). If these reports were proven to be true, the missing heritability would not be as large. Ultimately, this issue will be resolved only with a better understanding of the genetic architecture of the predisposition to obesity and its interactions with obesogenic conditions.

The obesity epidemic we are facing today unfolded over the past few decades and can clearly not be explained by changes in the frequency of risk alleles. It is more likely due to a changing social and physical environment that encourages consumption

and discourages expenditure of energy, behaviors that are poorly compatible with the genome that we have inherited (11). A key question that cannot be yet answered is whether it will ever be possible to take advantage of the advances in our understanding of the genetic basis of obesity to identify the individuals at risk of becoming obese before they gain a large amount of body weight and adiposity. In the meantime, the gains that we are making in our understanding of the genetic architecture of obesity should lead to new and exciting research on the biology and behavior of energy balance regulation. There is no better place to start than to identify the true gene associated with each significant SNP instead of being satisfied with the closest positional gene.

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