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Minireview

Obesity genes: so close and yet so far...

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Abstract

Little is known about genetic variants that predispose individuals toward leanness or fatness. This minireview highlights recent advances in the study of human populations, animal models and synergistic efforts as described by De Luca and colleagues in *BMC Genetics*, which are beginning to harvest low-hanging fruit in the search for obesity genes.

Few research topics capture the public's imagination like the search for genes that predispose to obesity. Ever since the discovery that the *ob* mouse mutation was caused by a deficiency in the protein leptin [1], each new finding is hailed in the headlines with promises of pharmaceutical intervention to prevent weight gain. However, it is clear that complex diseases such as obesity are not caused by genes alone, but involve interplay between genetics, diet, infectious agents, environment, behavior and social structures [2]. This multifactorial nature, combined with the fact that complex traits are controlled by many genes, most with small effects (as has long been hypothesized by quantitative geneticists for height in humans, and recently confirmed [3]), has rendered the search for obesity genes exceedingly difficult.

Is there light at the end of the tunnel? In this minireview we first evaluate very recent attempts to find obesity genes using powerful association-mapping strategies in large human populations, and then discuss improved animal models and strategies for their use in obesity genetics. The synergy of these two approaches is illustrated by the work of Maria De Luca and colleagues recently reported in *BMC Genetics* [4].

Genome-wide association studies in humans

In humans, the newest approach for identifying DNA variants associated with obesity is the genome-wide association (GWA) study. In these studies, hundreds of thousands to millions of single nucleotide polymorphisms (SNPs) are tested for association with a quantitative trait such as body mass index (BMI), or categorical measures of obesity. GWA studies have recently become feasible because of the identification of increasing numbers of SNPs, development of high-throughput genotyping technologies, and construction of haplotype maps that reveal the patterns of SNPs inherited together in populations [5]. Over the past two years, GWA studies have been successful in identifying genomic loci for several common complex traits [5]. Compared with candidate gene approaches, which are by definition limited to small subsets of loci with known physiological roles in the regulation of a trait, GWA studies provide an unbiased approach through which candidate genes and novel genes or pathways may be linked to a trait.

Despite the intensive search for obesity genes using GWA studies, only a few genes have been found that were subsequently confirmed to explain a portion of inter-individual

variation in human BMI. An early GWA study reported that a SNP upstream of insulin-induced gene 2 (*INSIG2*) was associated with BMI; when this study was expanded to nine cohorts from eight populations across multiple ethnicities (to include around 17,000 people), the evidence of association was confirmed in both unrelated and family-based samples, but with a modest effect [6]. Two independent studies of more than 300,000 SNPs in thousands of individuals identified obesity-associated variants within the first intron of the fat mass and obesity associated gene (*FTO*), and this association has been repeatedly replicated in samples of adults and children from populations around the world [7]. Biological studies are beginning to determine the expression pattern and potential function of *FTO*, an excellent example of a novel obesity gene discovered by GWA. Most recently, a GWA study for BMI in 16,876 samples, with follow-up in more than 60,000 adults and almost 6,000 children, identified associated SNPs more than 100 kb downstream of the melanocortin-4 receptor gene (*MC4R*) [8], and an independent study of 2,684 individuals described similar associations with waist circumference and insulin resistance [9]. These new associations with common variants downstream of *MC4R* cannot be explained by the previously described uncommon MC4R amino acid substitutions Val103Ile and Ile251Leu [8].

Despite this evidence of success, GWA studies are no panacea. The current genotyping chips and analysis methods still do not capture all common SNPs, and study designs may miss the effects of rare variants and structural genomic variants with large effects on a trait. Given the large number of statistical tests of association performed in a typical GWA study, further analysis in additional samples is often needed to provide evidence that a signal is authentic.

The overall variation in BMI explained by the *FTO* and *MC4R* variants together is only around 1.17 BMI units in adults [8], a modest effect similar in magnitude to GWA results for other quantitative traits. Many common variants influencing obesity have not yet been identified, and large sample sizes will be required to detect reliable evidence of novel loci. Given the small number of genes identified so far in studies including thousands to tens of thousands of participants, larger datasets and expanded collaborations will be critical. As more studies of different populations and designs are analyzed together, however, heterogeneity of the studies may become a problem. Will there be a limit to the effectiveness of large sample sizes in detecting common variants? The answer depends on the value of identifying variants with smaller and smaller effects on obesity. Nonetheless, large sample sizes will continue to be important to identify less common variants.

Improved animal models and strategies for their use

Animal models, primarily mice, have been important tools in elucidating the genetic architecture of polygenic traits such as obesity, and the mouse 'obesity map' is now well populated with genes influencing body weight, fatness and components of energy balance [10]. However, robust identification of these quantitative trait loci (QTL) at the gene or nucleotide level has proved frustratingly elusive. Given the recent rise of GWA studies and their success, it might seem that the role of mouse models for complex trait analysis requires re-evaluation [10,11]. In fact, the success of GWA studies is likely to increase the importance of relevant animal models for several reasons. First, mouse models will now be important in pursuing the mechanisms of genes discovered in association studies [12]. Second, many important obesity-related phenotypes (for example, those requiring measures of energy intake and energy expenditure) are challenging for GWA studies because of the high cost of obtaining accurate measurements, and require informative animal models for initial evaluation of genetic predisposition (see, for example, [13]).

Useful animal models extend beyond the mouse, as illustrated by De Luca and colleagues in their paper in *BMC Genetics* [4]. They identified *LanA5* as a candidate gene for triacylglycerol storage in *Drosophila melanogaster*, which led to their subsequent finding of an association of SNPs in the closely related human gene *LAMA5* with body composition. Mechanisms for regulating energy balance are a relatively common thermodynamic inheritance of all organisms, and thus studies using *Drosophila*, *Caenorhabditis elegans* and zebrafish are showing that genetically tractable lower organisms can contribute to our understanding of obesity [14]. These non-mammalian animal models have several advantages over mice, including shorter generation times, ease of breeding very large populations, powerful tools for genetic mapping, and high-throughput methods for creation and screening of mutants and phenocopies and conducting quantitative complementation testing. The findings of De Luca *et al*. confirm that *D. melanogaster* is a good model to identify genes that have evolutionarily conserved effects on body composition and that may represent obesity-predisposition genes in humans. Nevertheless, the discovery of association in a relatively small study in a limited human population will require replication in other human cohorts.

The third, and perhaps the most important, reason for using animal models is the difficulty in implementing robustly powerful designs for human association studies that could test anything beyond relatively simple models of obesity. Appropriately designed animal models can uncover networks of functionally important relationships

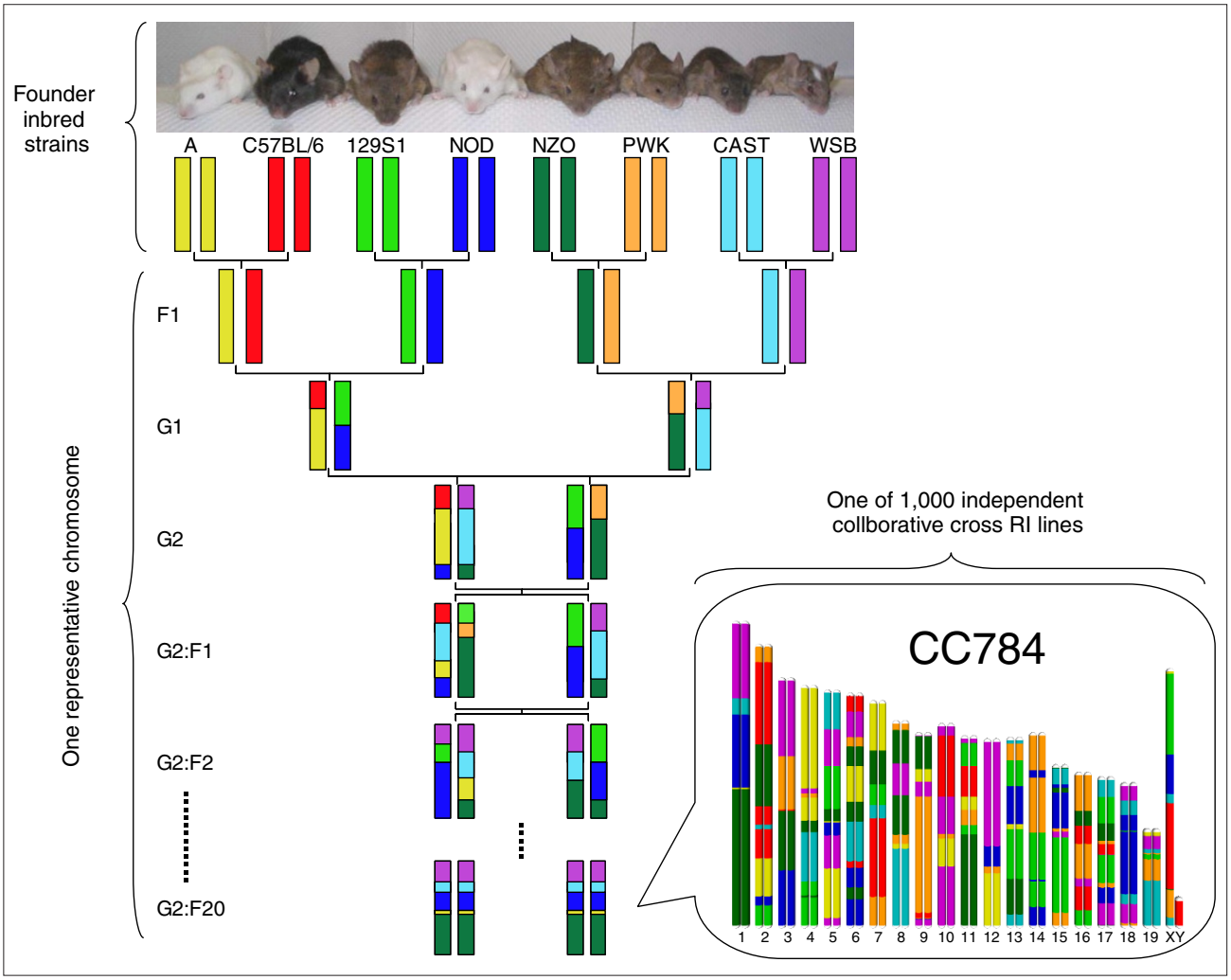

Figure 1
The Collaborative Cross for complex trait analysis. Starting with eight inbred mouse strains capturing 90% of all genetic variation in mice, a funnel breeding scheme is used to randomize variation. A single breeding funnel results in one immortal CC recombinant inbred line that is a mosaic combination of the eight founder genomes. The CC will consist of multiple independent lines (the target is 1,000), each of which will represent a different yet fixed capture of genetic variation. Figure courtesy of Fernando Pardo-Manuel de Villena and David Threadgill.

within and among diverse sets of biological and physiological phenotypes that can be altered by relevant external factors (for example, diet and exercise), and thus incorporate multiple genetic, environmental and developmental variables into comprehensive models describing susceptibility to obesity and its progression. Such a model is represented by a new paradigm for complex-trait analysis, the 'collaborative cross' (CC) [15].

The CC is a large panel of recombinant inbred mouse lines derived from a genetically diverse set of eight founder strains (Figure 1). It has a distribution of allele frequencies resembling that seen in human populations, in which many variants are found at low frequencies and only a minority of variants are common [16]. The eight parental inbred lines contributing to the CC are estimated to capture more than 90% of the known variation present in all mouse strains. Existing data on the founder strains and on many of the early generations in development of the CC demonstrate broad variability in many obesity phenotypes (F Pardo-Manuel de Villena, DW Threadgill, D Pomp, unpublished data), indicating that the CC will represent an excellent resource for identifying genes controlling predisposition to many traits relevant to obesity, and for understanding the pathways, networks and systems that control obesity.

Not only are new models of obesity being developed, but the approaches used to evaluate such models are rapidly evolving. For example, the blending of technologies to study genes, genomes, transcriptomes, proteomes and metabolomes in order to identify the molecular basis for common diseases such as obesity is on the increase [17]. This 'systems biology' approach incorporates the synergistic connections between 'omic' and environmental influences into a comprehensive framework.

What does the future hold?

Although tools for risk prediction can be created using combinations of predisposition genes [18] and lifestyle information, their impact may be limited because the individual effects of genes uncovered by GWA studies appear to be quite modest, and obesity may be caused by a multitude of rare, as opposed to common, variants. Novel obesity loci detected by either GWA studies or systems-biology approaches may be more likely to inform the development of therapeutic drugs. Additional analyses may detect variants that exhibit differences in effect between genders, between populations, at diverse ages, or have an impact on shifts in obesity over time or in response to environmental changes such as dietary intake and physical activity.

As if the dissection of genetic predisposition to obesity were not confusing enough, emerging complexities are sure to muddy the waters further. For example, there is evidence that it is not just a person's genome that helps determine their obesity phenotype, but also the genomes of the multitude of commensal bacteria that populate the digestive tract [19]. There are also studies suggesting that what a person eats (and potentially other experiences as well) not only affects their own body-weight phenotype, but can also (in the case of women) affect the body-weight phenotype of their offspring through epigenetic mechanisms [20]. While the evidence in humans is still contentious [21], it is possible that these epigenetic effects can persist across multiple generations, a process known as transgenerational epigenetic inheritance. Such a mode of inheritance, if established and shown to have effects on obesity, would represent a significant shift in the way we conceptualize, and research, the genetics of obesity both in animal models and in humans.

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