Obesity Triggers: Sequencing the Genome Versus Sequencing the Environment

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Sequencing the Genome

Many syndromic and nonsyndromic forms of obesity are the consequence of single (monogenic) rare genetic variants. There are currently about 79 syndromic (1) and 11 nonsyndromic forms of obesity (2). Most nonsyndromic obesity is a result of monogenetic variation in genes of the melanocortin pathway, and the most commonly affected gene is the melanocortin 4 receptor (MC4R). About 5% of children with severe obesity and 1% of the population with obesity across all ages are heterozygous for a functional missense variant in MC4R (3-5). The effect size of a disease-causing monogenic variant is generally large, and the affected pathway is typically well defined, making these forms of obesity more amenable to drug therapy. As a recent example, two individuals with loss-of-function variants in the proopiomelanocortin gene were successfully treated with a new MC4R agonist (6).

In contrast to monogenic obesity, common forms of overweight or obesity are unquestionably affected by environmental/cultural/lifestyle determinants. The population-based prevalence of obesity varies between countries and has increased worldwide in recent decades (7), and migrants tend to match the new cultural environment in succeeding generations (8). Perhaps the most convincing evidence that an obesogenic environment can be created is the higher prevalence of obesity in dogs with owners who have obesity, compared with dogs with lean owners (9).

But family studies have also shown that, within any cultural environment, BMI as an estimate of adiposity is significantly and highly heritable. Early, now classical and seminal studies have indicated a significantly greater similarity of BMI between offspring and their biological parents, as compared with their adopted parents (10). Many investigators of twins and families have reported heritabilities of BMI that were between ~40% and 75% (2). The heritability estimates are usually higher in twin studies for many reasons, but these estimates may be more reliable because the possible genetic factors are more carefully controlled for than in family-based studies. The heritability estimates are also higher at younger ages and for more extreme obesity (11).

Many common (>5%) and uncommon/rare single-nucleotide polymorphisms (SNPs) are significantly associated with BMI, based on targeted candidate gene analyses or hypothesis-free genome-wide association studies (GWAS) (2). As many as 200 SNPs in various GWAS have been associated with obesity in many different but predominantly European populations. However, only about 3% of the heritability can be explained by SNPs currently known to associate with BMI (12). In contrast, all ~17 million imputed SNPs based on whole-genome sequences in a largely unrelated European population sample can account for ~30% of BMI heritability (13). This indicates that most, if not all, of the heritability of BMI can be explained by a large number of variants across the genome, especially assuming that the heritability estimates may be somewhat inflated (12). As recently posited by Loos and Janssens (14), these findings indicate that although obesity is generally a polygenic disorder, currently identified BMI SNPs are poor predictors of obesity. A better predictor than SNP genotype is knowledge of an individual's parental/family obesity status. Therefore, the utility and clinical impact of previous and future larger BMI GWAS are not from prediction but rather from the identification of the biological pathways that affect body weight, which may serve as potential therapeutic targets for obesity.

Sequencing the Environment

It has long been recognized that obesity is a normal physiological response to an abnormal pathological (obesogenic) environment (15). Getting to a BMI of 30 is very easy when the food environment is full of cheap, highly palatable, processed foods and the built environment favors cars over active transport. If our goal is to reduce obesity, then the environment should be the predominant focus for research and action because that is where the pathology lies.

Part of the reason for the discordance, noted above, between high heritability estimates for obesity and the low explanatory power of SNPs may be that heritability studies do not include the breadth of environmental exposure (16). Heritability is the proportion of genetic variance divided by the total phenotypic variance, and it is often not understood that the estimate is for a specific population, in a specific (or narrow) environment, at a specific point in time, and it assumes that there are no interactions between genes and environments (G×E interactions) (17). Wide variance across environments and over time will increase the denominator, thus reducing the heritability estimates.
Differential gene expressions in the same environment (i.e., G×E interactions) are likely to be common in obesity. Research is exploring new aspects of biology, such as epigenetic, neuroendocrine, or gut biota pathways, to explain G×E interactions. Although this research is uncovering fascinating biological mechanisms, these are best thought of as mediators by which the environment influences the organism, rather than being the drivers of the obesity epidemic (16).

The research endeavor to sequence the human genome cost about $3 billion. Imagine if even a fraction of that cost could be invested in “sequencing” human environments, or those factors that are external to humans but that powerfully influence human behaviors and health. This would give us powerful comparative data on these key drivers, such as food composition, food prices, food marketing, urban walkability, school food, school physical education, and so on. Such data across multiple geographies and over time could be used to explain the wide variance and changing rates of obesity prevalence (16,18), identify which drivers to prioritize for intervention, identify which countries have best practice policies, and evaluate the impact of interventions. Measuring progress on government and private sector actions is also of high importance.

This vision of sequencing the human environment has been taken up for food environments by an international network of food researchers. INFORMAS (the International Network for Food and Obesity/Non-communicable Diseases Research, Monitoring and Action Support (19)) was launched in 2013 and, to date, 22 countries (20) are using INFORMAS protocols for measuring various aspects of their food environments and food policies. The first set of international comparisons, due in 2018, will be on government progress on food policies, the composition of processed foods, marketing of unhealthy foods to children, food labeling, and food industry actions. In some countries, such as Chile and Mexico, where major food policies are being implemented, the INFORMAS data will help to evaluate the impact of the policies on food environments.

Genetic research is advancing our understanding of biology, but for it to translate into advances in obesity treatment or prevention, certain assumptions need to hold. The first assumption is that we really need to know the biological mechanisms to guide our actions. Knowing the mediating pathways of problems and solutions is helpful, but often not essential. Digitalis and aspirin were used for centuries before their mechanisms of action were understood, and sudden infant death syndrome has been reduced simply by converting the epidemiological relationships of sleeping position and bed-sharing into public health actions, despite the mechanisms of action remaining unknown. A second assumption is that understanding mechanisms will allow the identification of potential therapeutic targets for pharmacological therapy. To date, drugs have been about as effective in reducing obesity as blocking one road into a city would be in reducing downtown traffic. Energy balance and road networks have many interconnecting pathways as an intrinsic feature of their prime purposes, which are to maintain energy stores and get people in and out of the city, respectively. Singular interventions for complex problems are destined to have relatively small, and often temporary, impacts. A third assumption is that genotyping people will achieve a more accurate risk profile for predicting the development of obesity or tailoring treatment options. This assumes that telling someone that he or she has a 20% greater genetic susceptibility to developing obesity will galvanize him or her into adopting a healthier lifestyle or assumes that telling someone that he or she is genetically 20% more likely to respond to a particular diet will improve long-term adherence to that diet. Even a small amount of personal or clinical experience with obesity will uncover the fallacy of this personalized medicine assumption.

Although obesogenic environments are manifold and differ by population, standardized protocols for measuring these environmental factors, at least for food (19), are available and are being applied, even in low-income countries (20). A population, at the national or subnational level, that has its own data on its own obesogenic environments that are benchmarked against environments in other countries is well armed for better prevention. It can diagnose the problem in terms of priority environments for action, it can use international benchmarks as a catalyst and target for outcomes, and it can readily measure the impact of policies or actions on food environments. Healthier food and activity environments are not only the mainstay of prevention but also help those with obesity to maintain healthier diets and regular physical activity.

**Conclusion**

Major advances in research in recent years are rapidly increasing our understanding of the genetic, epigenetic, and metabolic pathways to obesity. This is expected to lead to innovative treatment and prevention strategies, including new and better pharmaceuticals. Research on measuring, understanding, and influencing environmental determinants of obesity is much more nascent, but it will form the basis for catalyzing public health policy action in the coming decades.

For now, we consider that two clear conclusions can be drawn from our current understandings on the interrelationships between genes and environments. The first is that both genetic and environmental influences are powerful and can readily overwhelm the personal willpower needed to maintain a healthy weight throughout life in an obesogenic environment, especially for those people already struggling on low incomes. Also, for those people who have obesity, there are vigorous metabolic responses that counteract weight loss attempts. Exhorting people to be more responsible with diet and physical activity is, therefore, an unfair and unrealistic approach to reducing obesity. This leads to the second conclusion, which is that the best way to reduce the prevalence of obesity is to prevent it, particularly in children, and there are signs in several high-income countries that childhood obesity is plateauing or declining.

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