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Obesity Triggers: Sequencing the Genome vs Sequencing the Environment

Clifton Bogardus[1] and **Boyd Swinburn**[2,3]

[1]Phoenix Epidemiology and Clinical Research Branch, National Institute and Diabetes and Digestive and Kidney Diseases, National Institutes of Health [2]School of Population Health, University of Auckland, Auckland, New Zealand [3]Global Obesity Centre, Deakin University, Victoria, Australia

Sequencing the Genome

Many syndromic and non-syndromic forms of obesity are the consequence of single (monogenic) rare genetic variants. There are currently about 79 known[1] and 11 forms of non-syndromic obesity[2]. Most non-syndromic 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 severely obese children and 1% of the obese population across all ages are heterozygous for a functional missense variant in the melanocortin 4 receptor (MC4R)[3,4,5]. 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 proopriomelanocortin gene were successful 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 counties, 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 obese dogs of obese compared to lean owners[9].

But family studies have also shown that within any cultural environment, body mass index(BMI), as an estimate of adiposity, is significantly and highly heritable. Early, now classical and seminal studies, indicated significantly greater similarity of BMI between offspring and their biologic as compared to adopted parents[10]. Many investigators of twins and families have reported heritabilities of BMI between ~40–75%[2]. The heritability estimates are usually higher in twin studies for many reasons but these estimates may be more reliable since 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 GWASs have been associated with obesity in many different, but predominantly, European populations. However, only about 3% of the heritability can explained by SNPs currently known to associate with BMI[12]. In contrast, all ~17million 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 the heritability estimates may be somewhat inflated[12]. As recently reviewed 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 parents/family obesity status. Therefore, the utility and clinical impact of previous and future larger BMI GWAS studies is not for prediction but for identification of biologic 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 body mass index (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 reducing 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 (GxE 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 (ie GxE 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 GxE interactions. While this research is uncovering fascinating biological mechanisms, they 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 – those factors which are external to humans but which 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 to 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 (International Network For Food and Obesity/non-communicable disease Research, Monitoring and Action Support[19]) was launched in 2013 and, to date, 22 countries[20] are using its protocols for measuring various aspects of the 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 labelling, 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 the mechanisms were understood and Sudden Infant Death Syndrome has been reduced simply by converting the epidemiological relationships with sleeping position and bed-sharing into public health actions, while the mechanisms of action remain 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 has on 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. Single interventions on complex problems are destined to have relatively small, and often temporary, impacts. A third assumption relates to genotyping people to achieve a more accurate risk profile for predicting the development of obesity or tailoring treatment options. This assumes that telling someone that they have 20% greater genetic susceptibility to becoming obese will galvanize them into healthier lifestyles or that they are 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.

While 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 sub-national level, which has its own data on its own obesogenic environments and which 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.

Conclusions

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 their 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.

References

1. Kaur Y, de Souza RJ, Gibson WT, Meyre D. A systematic review of genetic syndromes with obesity. Obes Rev. 2017 Jun; 18(6):603–634. [PubMed: 28346723]
2. Pigeyre M, Yazdi FT, Kaur Y, Keyre D. Recent progress in genetics, epigenetics and metagenomics unveils the pathophysiology of human obesity. Clin Sci (Lond). 2016 Jun 1; 130(12):943–86. [PubMed: 27154742]
3. Faroogi IS, Keogh JM, Yeo GS, Lank EJ, Cheetham T, O'Rahilly S. Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. N Engl J Med. 2003 Mar 20; 348(12):1085–95. [PubMed: 12646665]
4. Alharbi KK, Spanakis E, Tan K, Smith MJ, Aldahmesh MA, O'Dell SD, Sayer AA, Lawlor DA, Ebrahim S, Davey Smith G, O'Rahilly S, Faroogi S, Cooper C, Phillips DI, Day IN. Prevalence and functionality of paucimorphic and private MC4R mutations in a large, unselected European British population, scanned by meltMADGE. Hum Mutat. 2007 Mar; 28(3):294–302. [PubMed: 17072869]
5. Lubrano-Berthelier C, Cavazos M, Dubern B, Shapiro A, Stunff CL, Zhang S, Picart F, Govaerts C, Froguel P, Bougneres P, Clement K, Vaisse C. Molecular genetics of human obesity-associated MC4R mutations. Ann N Y Acad Sci. 2003 Jun.994:49–57. [PubMed: 12851297]
6. Kuhnen P, Clement K, Weigand S, Blankenstein O, Gottesdiener K, Martini LL, Mai K, Blume-Peylavi U, Gruters Am Krude H. N Engl J Med. 2016 Jul 21; 375(3):240–246. [PubMed: 27468060]
7. The GBD Obesity Collaborators. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. NEJM. Jun 12.2017 doi: 10.1056/NEJMoa1614362
8. Bates LM, Acevedo-Garcia D, Alegria M, Krieger N. Immigration and generational trends in body mass index and obesity in the United States: results of the National Latino and Asian American Survey, 2002–2003. Am J Public Health. 2008 Jan; 98(1):70–7. [PubMed: 18048787]

9. Mason E. Obesity in pet dogs. Vet Rec. 1970 May 23; 86(21):612–6. [PubMed: 5465678]

10. Stunkard AJ, Sorenson TI, Hanis C, Teasdale TW, Chakraborty R, Schull WJ, Schulsinger F. An adoption study of human obesity. N Engl J Med. 1986 Jan 23; 314(4):193–8. [PubMed: 3941707]

11. Elks CE, den Hoed M, Zhao JH, Sharp SJ, Wareham NJ, Loos RJ, Ong KK. Variability in the heritability of body mass index: a systematic review and meta-regression. Front Endocrinol (Lausanne). 2012 Feb 28.3:29. [PubMed: 22645519]

12. Locke AE, Speliotes EK, et al. Genetic studies of body mass index yield new insights for obesity biology. Nature. 2015 Feb 12; 518(7538):197–206. [PubMed: 25673413]

13. Yang J, Bakshi A, Zhu Z, Hemani G, Vinkhuyzen AA, Lee SH, Robinson MR, Perry JR, Nolte IM, van Vliet-Ostaptchouk JV, Snieder H, Esko T, Milani L, Mägi R, Metspalu A, Hamsten A, Magnusson PK, Pedersen NL, Imgelsson E, Soranzo N, Keller MC, Wray NR, Goddard ME, Visscher PM. LifeLines Cohort Study. Genetic variance estimation with imputed variants finds negligible missing heritability for human height and body mass index. Nat Genet. 2015

14. Loos RJ, Janssens AC. Predicting Polygenic Obesity Using Genetic Information. Cell Metab. 2017 Mar 7; 25(3):535–543. [PubMed: 28273476]

15. Egger G, Swinburn B. An “ecological” approach to the obesity pandemic. Brit Med J. 1997; 315:477–480. [PubMed: 9284671]

16. Swinburn BA, Sacks G, Hall KD, McPherson K, Finegood DT, Moodie ML, Gortmaker S. The global obesity pandemic: shaped by global drivers and local environments. The Lancet. 2011; 378:804–814.

17. Visscher PM, Hill WG, Wray NR. Heritability in the genomics era – concepts and misconceptions. Nature Rev Genetics. 2009; 9:255–266.

18. NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. Lancet. 2016; 387:1377–96. [PubMed: 27115820]

19. Swinburn B, Sacks G, Vandevijvere S, Kumanyika S, Lobstein T, Neal B, Barquera S, Friel S, Hawkes C, Kelly B, L’Abbé M, Lee A, Ma J, Macmullan J, Mohan S, Monteiro C, Rayner M, Sanders D, Snowdon W, Walker C. for INFORMAS. INFORMAS (International Network for Food and Obesity/non-communicable diseases Research, Monitoring and Action support): overview and key principles. Obes Rev. 2013; 14(S1):1–12.

20. INFORMAS. International Network for Food and Obesity/non-communicable diseases Research, Monitoring and Action support. www.informas.org