Genetic susceptibility to the 'obesogenic' environment: the role of eating behaviour in obesity and an appetite for change

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Short running head

Appetite, genetic risk and obesity

The sudden onset of the obesity epidemic in high income countries at the end of the last century coincided with major changes to the food supply, resulting in larger portion sizes, greater availability and affordability of energy dense foods, and increased marketing (1). Notwithstanding diminished physical activity levels the modern food environment is deemed largely responsible for increases in obesity. However, despite the ubiquity of the 'obesogenic' environment, we have not uniformly developed obesity. On the contrary, there is large population variation in adiposity. In fact, it is not uncommon for siblings living in the same household to be discordant for weight status, highlighting the considerable variability in susceptibility to obesity even among those exposed to similar environments. Obesity is about far more than the environment we live in.

Genetic variation helps to explain why some are susceptible, and others resistant, to the modern obesogenic world. Decades of twin and family studies have established that human body weight is highly heritable (47-90%) (2) – and it is as heritable now as it was prior to the obesity epidemic. Genome-wide meta-analyses have made major progress in identifying many common genetic variants (single nucleotide polymorphisms, SNPs) involved, which collectively explain approximately 3% of variation in body mass index (BMI) (3). The question of interest is; *how* do genes confer differential obesity risk? Identifying gene mechanisms may reveal novel targets for pharmacological, behavioural or psychological intervention, paving the way for much-needed progress in the development of effective prevention and management strategies.

Recently, researchers from behavioural science, epidemiology and genetics joined forces to propose that genetic risk of obesity likely operates via the neurobiology controlling appetite regulation. The working hypothesis is that genetic susceptibility to obesity manifests itself as the tendency to overeat when prompted by environmental

food cues and the opportunity to eat. This aetiological model appeals on several grounds: it makes sense of the seeming paradox of dual determination of obesity by genes and environment by proposing that obesity develops from a combination of genetic susceptibility to overeating and exposure to an obesogenic environment; more than fifty years of research suggests that an aberrant appetite predisposes to obesity; and the SNPs discovered so far are predominantly expressed in areas of the central nervous system consistent with appetitive mechanisms.

A few studies have reported associations between 'obesity genes' and characteristics of an avid appetite, such as blunted satiety sensitivity (4), but a limited number of eating behaviors have been examined. In this issue of AJCN Jacob and colleagues (5) describe the most detailed study to date of the link between genetic susceptibility to obesity and a large number of appetite-related eating behaviors, among 768 French Canadian men and women from the Quebec Family Study. Participants were genotyped for 97 SNPs identified in the most recent genome wide meta-analysis of BMI, which were combined into a genetic risk score (GRS) for obesity. Researchers examined associations between the GRS, BMI and waist circumference, and the eating behaviors enshrined in the full Three-Factor Eating Questionnaire: 'disinhibition', the tendency to overeat in response to negative emotion, situational food cues, or habit; 'hunger', driven by internal and external cues; and 'cognitive restraint', intentional restriction of food intake to control weight, characterized as five sub-types. Adults at greater genetic risk of obesity reported more habitual and situational disinhibited eating, and a more pronounced tendency to feel hungry both internally and in response to external cues. Notably too, each of these traits partially mediated the associations between genetic risk and measures of adiposity, adding to the burgeoning evidence base that appetite-related behaviors may be one of the mechanisms through which genes determine adiposity level.

Yet important questions remain. Correlation does not equal causation. It is possible that genes influence adiposity via other processes, and adiposity causes subsequent changes in appetite. However, gene expression studies show enrichment in the hypothalamus and pituitary gland pointing towards an appetitive pathway, and involvement of the hippocampus and limbic system also implicate other psychological processes governing eating behavior such as emotion, memory, cognition and learning (3). Another question is *when* genetic effects occur. Genetic influence on BMI varies by age; effects increase during childhood and adolescence, peak in early adulthood and decline towards midlife (6,7). The cross-sectional association among adults may well reflect genetic influence on appetite (and adiposity) that occurred earlier in life. Longitudinal studies of appetite and weight gain are rare but, in infancy, prospective associations from appetite to weight gain are stronger than the reverse (8), while in childhood, fat mass prospectively predicts increasing food cue responsiveness (9), suggesting developmental change in direction of influence. We also know little about stability and change in appetite over the lifespan. Longitudinal studies of genetic risk, adiposity and appetite are needed to establish directions of association and timing of expression; but to date there have been none. Research to establish generalizability to non-European populations is needed too, as well as replication among those exposed to very different food environments such as transitional countries.

An appetite model of obesity has important implications for policy and practice. When it comes to obesity risk and our desire to eat, we are not born equal. Those who have inherited a predisposition to feel hungry in response to external food cues are particularly vulnerable to the modern food environment in which palatable food is accessible, on show, cheap, and promoted aggressively. In this context some individuals are ‘battling their biology’; and for many it is virtually impossible to maintain a healthy weight, however strong-willed or well intentioned they might be.

Radically changing the environment to reduce exposure to food cues seems a more fruitful public health endeavour than encouraging individuals to make more judicious food choices, but there are several obstacles to action. Policymakers worldwide largely attribute obesity to personal responsibility (10) – a view challenged firmly by this research – which impedes intervention. Government regulation of the food supply is rarely supported by the public who defend their free will to make food choices of their own, and would oppose moves to make food less palatable, less accessible, and more expensive. It makes commercial sense to exploit appetitive vulnerabilities because excess consumption means profit, so this will continue unless regulated. The UK government's new plans to limit advertising of foods high in sugar and fat, and remove them from supermarket checkouts are a move in the right direction, but legislation of industry rather than reliance on good will is likely have a greater impact.

A key translational question for clinical practice is; if eating behavior has a genetic basis, is it amenable to change? There is a dearth of research into the modifiability of appetite and eating behaviour, but this is important work going forward. However, research suggests that expression of genetic susceptibility to obesity depends partly on environmental prompts to eat and the opportunity to do so. Somewhat ironically, research into the genetic basis of obesity has revealed more than anything the urgent need for environmental modification.

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