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Review

Genetics and epigenetics of obesity

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ABSTRACT

Obesity results from interactions between environmental and genetic factors. Despite a relatively high heritability of common, non-syndromic obesity (40–70%), the search for genetic variants contributing to susceptibility has been a challenging task. Genome wide association (GWA) studies have dramatically changed the pace of detection of common genetic susceptibility variants. To date, more than 40 genetic variants have been associated with obesity and fat distribution. However, since these variants do not fully explain the heritability of obesity, other forms of variation, such as epigenetics marks, must be considered.

Epigenetic marks, or "imprinting", affect gene expression without actually changing the DNA sequence. Failures in imprinting are known to cause extreme forms of obesity (e.g. Prader–Willi syndrome), but have also been convincingly associated with susceptibility to obesity. Furthermore, environmental exposures during critical developmental periods can affect the profile of epigenetic marks and result in obesity.

We review the most recent evidence for genetic and epigenetic mechanisms involved in the susceptibility and development of obesity. Only a comprehensive understanding of the underlying genetic and epigenetic mechanisms, and the metabolic processes they govern, will allow us to manage, and eventually prevent, obesity.

Contents

Abbreviations: BMI, body mass index; WC, waist circumference; WHR, waist:hip ratio; T2D, type-2-diabetes; LD, linkage disequilibrium; CNV, copy number variants; PWS, Prader–Willi syndrome; QTL, quantitative trait loci; SNP, single nucleotide polymorphism.

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1. Introduction

Overweight and obesity are becoming more widespread with global projections of more than 2.16 billion overweight and 1.12 billion obese individuals by 2030 [1]. This clearly presents a worldwide clinical and public health burden, associated with social and personal criticism. It is also correlated with an increased risk of type-2-diabetes (T2D), cardiovascular disease, cancer and mortality [2,3]. Despite intensive research, current efforts to reduce obesity by diet, exercise, education, surgery and drug therapies are failing to provide effective long-term solutions to this epidemic.

At an individual level, obesity occurs when abnormal amounts of triglycerides are stored in adipose tissue and released from adipose tissue as free fatty acids (FFA) with detrimental effects [4]. Excess fat accumulation occurs when energy intake exceeds energy expenditure, although individuals respond differently to this imbalance owing to genetic predisposition. Twin studies estimate heritability of body mass index (BMI) to be 40–70% in children and adults [5–7], and other anthropometric measures of obesity and regional fat distribution [skinfold thickness, waist circumference (WC) and waist:hip ratio (WHR)] show similar heritability [5–12]. Furthermore, there are ethnic differences in obesity; admixture mapping studies demonstrate that obesity correlates closely with the percentage of ancestry derived from ethnic groups with elevated prevalence [13,14]. The goal of obesity research is to elucidate pathways and mechanisms that control obesity and to improve prevention, management and therapy.

Here we review recent advances in identifying factors contributing to obesity susceptibility. We focus on:

(a) recent successes in identification of genetic variation affecting obesity trait susceptibility;
(b) emerging evidence connecting epigenetic (heritable changes which affect gene function but do not modify DNA sequence) events with obesity.

We discuss the impact of recent findings in these two areas and their joint potential to enhance understanding of obesity susceptibility mechanisms and aetiology.

2. The identification of susceptibility loci for obesity

Until 2006, the main approaches used to track down common variants influencing obesity, involved either hypothesis-free genome-wide linkage mapping in families with multiple obese subjects or association studies within 'candidate' genes using case–control samples or parent–offspring trios. The former suffered from being underpowered for any sensible susceptibility models, as linkage is best placed to detect variants with high penetrance. As far as we can tell, common variants with high penetrance do not contribute substantially to risk of common forms of obesity and few, if any, robust signals have emerged from such efforts [15,16]. The latter candidate-gene association approach has historically been compromised by difficulties in selecting credible candidates. Selection was typically based on hypotheses about biological mechanisms putatively involved in obesity pathogenesis but, as the function of much of the genome is poorly characterized, it remains almost impossible to make fully informed decisions. In addition, all too often these candidate-gene studies were conducted in sample sets far too small to offer confident detection of variants with the range of effect sizes that are now known to be realistic. With hindsight, it is easy to appreciate why these approaches yielded few examples of genuine obesity–susceptibility variants.

Consequently, over the last two decades, efforts in identifying and replicating genetic variants predisposing individuals to common forms of obesity were largely characterized by slow progress and limited success, in sharp contrast to the successful gene identification in monogenic and syndromic forms of obesity [15]. The most recent edition of the "Human Obesity Gene Map" gives an excellent overview of this; it lists 11 single gene mutations, 50 loci related to Mendelian syndromes relevant to human obesity, 244 knockout or transgenic animal models and 127 candidate genes, of which slightly less than 20% are replicated by 5 or more studies [15]. A total of 253 quantitative trait loci (QTL), for different obesity-related phenotypes, have been reported from 61 genome-wide linkage scans and of these, only ~20% are supported by more than one study [15].

Over the past three years it has become possible, from technical and economic perspectives, to undertake hypothesis-free GWA testing in samples of sufficient size to generate convincing association results. The advent of the GWA approach was the result of three components. The first was the human genome sequence which subsequently enabled cataloguing genome-sequence variation. Secondly, the International HapMap Consortium (http://www.hapmap.org) [17] taught us that, in non-African-descent populations, extensive correlations (linkage disequilibrium, LD) between neighbouring single nucleotide polymorphisms (SNPs) constrain the number of independent genetic tests required to survey the genome, such that ~80% of all common variation can be sampled using ~500 000 carefully selected SNPs [18,19]. Lastly, novel genotyping methods address the challenges of massively parallel SNP-typing at high accuracy and low cost [20]. The GWA approach has been hugely successful in identifying loci harbouring common forms of obesity (as defined by anthropometric measures: BMI, WC and/or WHR) susceptibility genes and hereto results from a total of 15 'high-density' GWAs (i.e. ≥300 000 SNPs, offering genome-wide coverage >65%) have been published (Table 1). These studies combined, have yielded over 50 loci associated with obesity (p-values $<5 \times 10^{-8}$ in genotyped and imputed data sets, or $<5 \times 10^{-7}$ in directly genotyped data only) (Table 2).

The first gene unequivocally associated to common, non-syndromic obesity, *FTO* (fat mass and obesity associated) [21], was initially identified as a result of a GWA of T2D [22]. While it was the second strongest associated locus, the association was completely abolished when adjusting for T2D. The association of the *FTO* region to obesity explains ~1% of BMI heritability, such that adults homozygous for the risk allele, have a 2–3 kg higher weight compared to non-risk allele homozygous [21]. Interestingly, *FTO* is reported to operate on fat mass and was suggested to encode a 2-oxoglutarate-dependent nucleic acid demethylase involved in regulation of food intake [23]. In parallel, it was reported to be involved in decreased lipolytic effect in adipocytes [24]. It is unclear whether the association effect acts through *FTO* or the adjacent *FTM* gene and the precise role of the *FTO* locus in obesity needs further investigation.

With reports of the first, robust dichotomous trait associations [25] and the discovery of *FTO* [21,26,27], came the realization that the effect sizes detected would be smaller than anticipated and that successful analysed would require larger sample sizes than previ-