Minireview

Narrowing down the role of common variants in the genetic predisposition to obesity

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Abstract

The extent to which common variants contribute to common phenotypes and disease in humans has important consequences for the future of medical genomics. Two reports have recently clarified this issue for one of the most pressing public health concerns, obesity. These large and comprehensive genome-wide association studies find that common variants within at least 11 genes are associated with obesity. Interestingly, most of these genes are highly expressed in the central nervous system, further highlighting its role in the pathogenesis of obesity. However, the individual and combined effects of these variants explain only a small fraction of the inherited variability in obesity, suggesting that rare variants may contribute significantly to the genetic predisposition for this condition.

Genetic factors in human obesity

Obesity has become a major public health concern, as it increases mortality and the risk of morbidity from hypertension, dyslipidemia, diabetes mellitus and cardiovascular disease [1,2]. Body mass index (BMI; weight divided by the square of the height) is the most commonly used clinical measure of adiposity, and individuals with a BMI above 30 kg/m^2 are classified as obese. The most recent National Health and Nutrition Examination Survey shows that the prevalence of obesity among US adult men and women was 33.3% and 35.3%, respectively [3].

Both environmental and genetic factors are involved in the onset and progression of weight gain [4]. Excess caloric intake and the tendency towards a more sedentary lifestyle are certainly to blame for the increased prevalence of obesity, but individuals exposed to the same environmental pressures have different levels of vulnerability. Indeed, genetic epidemiologic studies, such as twin studies [5] and adoption studies [6], have implicated genetic factors in the susceptibility to obesity. These studies have shown that genetic factors account for 40-70% of the population variation in BMI and that the heritability of obesity increases with its severity [7]. Emphasis has therefore now shifted from the question of whether human obesity has a genetic component to how many and which genetic variants underlie this susceptibility [8,9].

In theory, genetic susceptibility to obesity in humans could result from the additive effects of common genetic variants (minor allele frequency >5%), from different rare mutations in a large set of genes, or from a combination of both [8,9]. Several genes in which rare mutations cause severe monogenic or syndromic forms of obesity have been described, and these have furthered our knowledge of the molecular pathways involved in food intake regulation and the control of body weight [10]. The genes implicated in these rare human monogenic forms of obesity encode proteins that have a role in the central regulation of energy homeostasis, in particular at the level of the hypothalamus.

The common variant piece of the obesity pie

Hundreds of studies in the past 15 years have suggested a positive association of common variants in a large number of candidate genes with obesity or obesity-related phenotypes. As for several other common diseases, most of these studies failed to be replicated, being limited by their insufficient sample size and by stratification and multiple testing issues [9].

In 2008, reports of the first genome-wide association studies (GWASs) for obesity revealed previously unreported associations with common variants near the fat mass and obesity-associated gene *FTO* [11], a gene with a yet unknown function, and near the melanocortin 4 receptor (*MC4R*) gene [12], in which multiple rare variants had previously been shown to cause, in aggregate, 2-4% of severe obesity (BMI ≥40 kg/m²) cases in humans [13,14]. These findings were replicated across several populations, but the common alleles at these two loci had only a modest effect on BMI (0.2-0.4 kg/m²), suggesting that additional common variants could account for a significant fraction of the inherited BMI population variation.

By combining extremely large samples of GWASs, recent reports now provide us with a more comprehensive view of the extent to which common variants are associated with obesity [15,16]. Investigators of the Genetic Investigation of Anthropometric Traits (GIANT) consortium conducted a meta-analysis of GWASs from a total of 32,387 subjects of European ancestry in 15 cohorts for association with BMI [16]. The strongest signals from 35 variants were used for follow-up in 14 additional cohorts with over 59,000 subjects of European ancestry. In parallel, a group at deCODE Genetics performed a GWAS with single nucleotide polymorphisms (SNPs) typed in over 30,000 individuals of mixed descent (predominantly Icelandic, but also Dutch, European American, African American and Scandinavian) in search of polymorphic variants that affect variation in two common measures of obesity, weight and BMI [15]. The strongest signals from 43 variants were then tested for association in 5,586 Danish individuals and compared *in silico* with the results of the GIANT consortium [15].

Both studies confirmed the association of BMI with variants at the *FTO* and *MC4R* genes and identified six and nine novel loci, respectively, at which variants were associated with BMI and/or weight, four of which (*NEGR1*, *TMEM18*, *SH2B1* and *KCTD15*) were common to both studies (Table 1).

Many of the new loci, in particular those found by the GIANT consortium, are located near genes that are highly expressed in the central nervous system, several in the hypothalamus, possibly emphasizing, as in rare monogenic forms of obesity, the role of the hypothalamus in the predisposition to obesity. Of course, this conclusion is preliminary, as the actual causative variants, which remain to be identified by fine mapping at each of these loci, may affect other genes in these regions.

In both studies, the allelic odds ratio for being obese (BMI >30 kg/m²) remained greatest with the *FTO* variant (Table 1), with odds ratios of 1.03-1.25 [16] and 1.07-1.27 [15]. All of the variants identified are relatively common, and their combined effect explains only a small percentage of the variation in weight and BMI. The GIANT consortium examined the combined impact of the associated variants on BMI. They weighted the number of BMI-increasing alleles by their relative effect size and calculated a genotype score for each individual. They found that individuals that have 13 or more BMI-increasing alleles (representing 1.2% of the sample) are only 0.59 kg/m² heavier than the average individual in their study. In addition, when the GIANT consortium removed the associated loci from the analysis, they no longer identified an excess of *p*-values smaller than what is expected by chance [16]. The authors rightly argue that common variants with even smaller effects may not have been detected and could still be found with even larger sample sizes. However, as these effects will be small, the data from both studies suggest that most of the heritability of BMI captured by common variants has been accounted for.

The future of obesity genetics: a common disease but many rare variants?

What then is the basis for the largest portion of BMI heritability? One possibility, not yet explored extensively for obesity, is a role for copy number variations. Such variations have recently been implicated in the genetic predisposition to common neurological diseases such as autism and schizophrenia [17,18]. The GIANT consortium looked at the contribution of copy number polymorphisms on BMI and found that the SNP that was most strongly associated with one of six loci, around the gene *NEGR1*, was linked to a 45-kb deletion polymorphism [16]. This suggests that this copy number polymorphism could be a candidate causal variant, and further copy number variant studies may be deemed fruitful.

Both the GIANT and deCODE studies also acknowledge that their results lend credence to the hypothesis that rare or unique alleles with strong or intermediate effects could account for the majority of one individual's predisposition to obesity. Testing this hypothesis, and finding genes for which this is the case, will require comparative sequencing to search for an increase in the aggregate number of rare variants at each locus in cases versus controls. The largest pioneering study yet to test this hypothesis sequenced the entire coding region of 58 candidate genes in 379 extremely obese and 378 extremely lean adults [19]. The authors found an increase in unique non-synonymous variations in severely obese individuals, specifically in a subset of genes expressed in the central nervous system and for which the corresponding mouse phenotype was suggestive of a role in obesity. Searching for such loci systematically at a genome-wide level will require extremely large-scale sequencing, for which the technology is currently being developed and which

Table 1

Summary of loci associated with variation in adult BMI in two large GWASs

		Odds ratio (95% CI) of obesity in adults		
Chromosome	Genes	GIANT	deCODE	Relevant tissue expression and/or function
1p31	*NEGR1*	1.05 (1.01-1.11)	1.07 (1.02-1.12)	Adipose
1q25	*SEC16B*, *RASAL2*		1.11 (1.05-1.18)	Liver
2	*TMEM18*	1.19 (1.11-1.26)	1.20 (1.13-1.27)	
3	*ETV5*, *SFRS10*, *DGKG*		1.11 (1.05-1.17)	
4	*GNPDA2*	1.12 (1.07-1.17)		Adipose
6p21	*NCR3*, *AIF1*, *BAT2*		1.07 (1.02-1.12)	Hypothalamus; NCR3 also adipose
11p14	*BDNF*, *LGR4*, *LIN7C*		1.12 (1.06-1.19) 1.11 (1.05-1.16)	*BDNF*: hypothalamus; humans with *BDNF* deletion are obese, and knockdown in mouse hypothalamus leads to obesity
11p11	*MTCH2*	1.03 (0.98-1.08)		Adipose, hypothalamus and liver
12	*FAIM2*, *BCDIN3D*		1.14 (1.09-1.19)	Adipose, hypothalamus and liver
16p11	*SH2B1*, *ATP2A1*	1.11 (1.06-1.17)	1.08 (1.03-1.13)	*SH2B1*: adipose and hypothalamus; null mice are obese
16q12	*FTO*, *RPGRIP1L*	1.25 (1.19-1.31)	1.27 (1.21-1.32) 1.16 (1.10-1.21)	*FTO*: adipose and hypothalamus
18q21	*MC4R*	1.15 (1.08-1.21)	1.12 (1.06-1.17)	Hypothalamus; associated with obesity in humans, and *MC4R* deficient mice are obese
19	*KCTD15*, *CHST8*	1.04 (0.98-1.10)	1.10 (1.04-1.15)	Adipose and hypothalamus

Gene name abbreviations: *AIF1*, allograft inflammatory factor 1; *ATP2A1*, ATPase, Ca++ transporting, cardiac muscle, fast twitch 1; *BAT2*, HLA-B associated transcript 2; *BCDIN3D*, BCDIN3 domain containing; *BDNF*, brain-derived neurotrophic factor; *CHST8*, carbohydrate (N-acetylgalactosamine 4-0) sulfotransferase 8; *DGKG*, diacylglycerol kinase, gamma 90kDa; *ETV5*, ets variant 5; *FAIM2*, Fas apoptotic inhibitory molecule 2; *FTO*, fat mass and obesity associated; *GNPDA2*, glucosamine-6-phosphate deaminase 2; *KCTD15*, potassium channel tetramerisation domain containing 15; *LGR4*, leucine-rich repeat-containing G protein-coupled receptor 4; *LIN7C*, in-7 homolog C; *MC4R*, melanocortin 4 receptor; *MTCH2*, mitochondrial carrier homolog 2; *NCR3*, natural cytotoxicity triggering receptor 3; *NEGR1*, neuronal growth regulator 1; *RASAL2*, RAS protein activator like 2; *RPGRIP1L*, RPGR-interacting protein 1-like protein; *SEC16B*, SEC16 homolog B (*Saccharomyces cerevisiae*); *SFRS10*, splicing factor, arginine/serine-rich 10; *SH2B1*, SH2B adaptor protein 2; *TMEM18*, transmembrane protein 18. CI, confidence interval.

will present us with new statistical challenges and methodological difficulties pertaining, for example, to the functional study and classification of identified variants.

Ultimately, the success of these approaches will depend on the number of genes in which variations can predispose to obesity and the effect size of both the individual variants and their combined effect at each locus. We should now have learned not to be too optimistic and expect the possibility that the heritability of obesity may be accounted for by rare or unique variations at hundreds of different genes.

Abbreviations

BMI, body mass index; GIANT, Genetic Investigation of Anthropometric Traits consortium; GWAS, genome-wide association studies; SNP, single nucleotide polymorphism.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Both authors contributed to the writing of the manuscript and have approved the final version.

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