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Recent Findings on the Genetics of Obesity: Is there Public Health Relevance?

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Abstract Since initial studies investigating familial forms of obesity, genome-wide association studies (GWAS) have been tremendously successful at detecting replicable associations between common genetic variation and measures of fat mass and obesity. The contributory variants found by this approach are limited, as one might expect, in terms of effect size and appear to offer little in terms of direct clinical applicability. However, can these variants with established associations be of value? This review will revisit how common genetic variation reliably associated with measures of fat mass and obesity can inform etiological understanding, improve knowledge of genetic architecture, and enable applied epidemiological analyses. With the discovery of additional body mass index-associated loci and the further functional characterization of identified variants, attempts can be made to better understand and causally analyze the genetic, biological, and environmental pathways to effect involved in obesity and its related comorbidities.

Keywords Genetic · Obesity · BMI · Genome-wide · Variants · Genetic architecture · Translational · Epidemiology · Public health

Introduction

Considered in its purest form, obesity may be defined as abnormal body composition in terms of an excessive fat-to-lean mass ratio. Obesity status is well established as a clinical correlate of numerous health problems, including metabolic and vascular disease and certain cancers [1, 2] and is a leading risk factor for global mortality [3, 4]. It is predicted that between 573 million and 1.12 billion individuals will be obese by 2030 if secular trends continue [5]. The pandemic status of obesity has been attributed to the rise of an "obesogenic" environment that tips the balance between energy intake and energy expenditure [6], driving individuals toward increased adiposity along environmentally determined lines [7]. Despite this, it is important to realize that, within the obesogenic environment to which many of us are exposed, not all individuals become overweight or obese. In reality, a complex interplay of both genetic and environmental factors must be considered to better our understanding of the regulation of body weight.

A common objective of genetic studies has been to identify genetic variants that explain the heritability[1] of obesity and related intermediate phenotypes, such as body mass index (BMI) or fat mass/adiposity [8, 9]. Initial studies investigating familial forms of obesity were successful in identifying rare monogenic determinants [10–13]. However, we have now entered an era of genome-wide association studies (GWAS), which search for common genetic variants associated with BMI and obesity. GWAS provide an encompassing method of identifying variants with generally small but replicable effects [14]. These efforts have been tremendously successful in detecting common genotypic associations with complex phenotypes measured at the level of the population.

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[1] Quantitative trait genetics is concerned principally with the partitioning of phenotypic variance into genetic and non-genetic components. The proportion of total phenotypic variance explained by the complete genetic component (i.e. that containing additive and non-additive parts) may be considered broad sense heritability and is that often referred to in estimates of total heritability.

The characteristics of these approaches have been extensively reviewed [15, 16] and will not be revisited here. Rather, the focus of this review will be on the merits of GWAS for BMI and obesity in light of the considerable criticism they have received; criticism leveled at the relative cost of these studies given their apparently limited return due to the challenge of explaining heritability (identified variants currently accounting for <2 of the estimated 40–70 % of BMI variance though to be heritable) [17]. Despite the apparent limitations in the direct clinical applicability of findings coming from the study of common genetic correlation of BMI and obesity, we will attempt to illustrate how confirmed genetic loci inform etiological understanding, increase awareness of the genetic architecture of obesity, and have allowed the development of applied epidemiological analyses. We will aim to revisit the most recent advances in the analysis of common genetic variation and its relationship with obesity (and intermediate measures thereof) and explore the likely public health impact that current findings may have.

GWAS—Doing What They Were Designed To Do

Early work in genetics was largely focused on clearly segregating outcomes within familial studies. In the case of obesity, the identification of highly penetrant alleles causing severe early onset obesity [10–13] led to an understanding of their mechanism of action and in the case of congenital leptin deficiency, has allowed the development of a highly effective targeted therapy [18]. Over the past 5 years research has continued to uncover novel, highly penetrant, alleles responsible for rare genetically determined cases of childhood obesity [19, 20]. Functional analyses of these specific gene defects have continued alongside their discovery [21–24] and existing research has established the mechanisms of molecular dysfunction in several syndromic forms of this disorder [25–28]. However, therapeutic treatments for many severe, familial forms of obesity are lacking and such forms only explain about 5 % of all cases of obesity.

In contrast to this, common forms of obesity (which do not segregate in families) have a multifactorial basis, with obese individuals harboring any number of common genetic variants, most of which are thought to exert only small effects on realized adiposity. Consequently, to uncover the genetic etiology of obesity on a population level, a different approach is required. Initially, candidate gene studies, which attempted to find common variants based on prior knowledge of the location of genes with a supposed biological role, were undertaken in population-based collections. These studies often were hampered by low statistical power and a failure to adequately replicate findings (criteria now rigorously applied in most GWAS settings), as evidenced in the 2005 Human Obesity Gene Map where only 22 of 127 candidate genes could be reproduced in at least 5 studies [29].

GWAS, as opposed to candidate gene studies, employ a nonhypothesis-driven approach to identify variants consistently associated with disease. GWAS use genotyping chips with a dense array of several hundred thousand, or more, single nucleotide polymorphisms (SNPs) positioned across the entire genome to capture common variants most associated with complex traits [30]. In 2007, a genome-wide association study identified variation in the first intron of the fat mass and obesity association (*FTO*) gene on chromosome 16 initially through its association with type 2 diabetes (T2D)[31••]. This was the first locus found to harbor common variants reliably associated with BMI at the level of the population [31••, 32, 33]; the carriers of the minor homozygote at this locus being on average 3 kg heavier than the major allele carriers.

It now transpires that *FTO* was a "low hanging fruit" in genetic association studies for obesity-related traits, and other putative adiposity-associated variants in GWAS were not as consistently replicated [34]. It has since been acknowledged that a robust replication of initial genetic association findings in GWAS is fundamentally enabled by larger sample sizes, greater genomic coverage, more rigorous discovery and replication phases, appropriate corrections for multiple testing and population stratification, as well as the development of large meta-analyses [35, 36]. Indeed a meta-analysis of more than 16,000 individuals from seven European studies, involving the imputation of haplotypes from the International HapMap Project [37], produced the next locus of relatively large effect at the population level and was located within a supposed regulatory site 188 kb downstream of the *MC4R* gene [38]. *MC4R* is a tantalizing locus because of the rare mutations in the same gene which leads to monogenic obesity [13, 26]. However, common variation at this locus makes a smaller contribution to total variation in fat mass than *FTO*, explaining only approximately 0.14 % for adult BMI [38].

Subsequent GWAS have sequentially increased sample size and imputation/genotyping density, and collaborations have been achieved through the development of the Genomic Investigation of Anthropometric Traits (GIANT) consortium, to expand the list of confirmed BMI loci [39, 40•, 41•, 42••]. To date, the largest study successfully identified and replicated 32 BMI-associated loci in 249,796 individuals of European ancestry. In total, these variants are estimated to account for 1.45 % of the variation in BMI, compared with 0.34 % accounted for by *FTO* alone [42••]. Of the identified loci, some have been found to map near hypothalamic regulators, providing potentially new biologic insights into weight regulation and adiposity risk.

Further Developments in the Genetics of Obesity

Case-Control Versus Cohort Studies

GWAS for adiposity-related traits has made use of both case-control samples and population-based cohorts in the discovery and elucidation of common variants [43]. Whereas longitudinal cohorts may offer a number of quantitative measures of BMI or fat mass from which to draw associations, enriched sampling of individuals with extreme phenotypes can be an efficient alternative for identifying common variants. The finding that the pattern of common genetic variation associated with extreme overweight is similar to that found for general BMI is providing a valuable source of validation for identified variants and comment on the nature of the contribution of common variants to this trait [43, 44].

Alternative Phenotypes

Variants have been discovered that are associated with particular manifestations of adiposity, such as central obesity [45], waist circumference [46], and waist-hip ratio [47]. Identification of such variants that have a larger influence on fat distribution is important as the particular location of fat deposition may lead to more severe health problems [48]. In addition, the existence of strong gene-by-sex interactions has revealed sexual dimorphism in the genetic basis of fat distribution [47]. It also is possible to investigate whether variants are particularly influential at certain points of the life-course [49, 50]. Longitudinal work has been used to establish that some of the BMI-associated loci identified in GWAS meta-analysis also are found in the context of childhood adiposity alongside findings, suggesting that specific variants are associated with BMI at certain points of the life-course [49–51]; novel loci associated with obesity have been identified from the analysis of children specifically [52].

Searching for Variants in Non-European Populations

Because much of the work in GWAS has been focused on European populations, the exploration of common variants in non-Europeans may yield additional confirmed associates, whose biological function in the etiology of obesity may be further investigated. Large-scale GWAS in Asian populations have found adiposity hits, which have replicated findings from European-based studies [53, 54], and on further investigation, some of the novel hits in these non-western samples also show evidence for association with BMI in European populations, providing a further method of validation for GWAS hits [55, 56].

What Can we Learn from the Advances of Common Variant Genetics?

By continuing with the GWAS strategy for identifying common variants, according to Speliotes et al. [42••], "a sample size of 730,000 probands would be required to pick up an additional 250 loci, explaining 4.5 % of BMI variation." This draws the questions whether it is going to be both feasible and cost-effective to perform a continued search, and what can be learnt from those variants that have already been discovered?

It is clear that increasing knowledge of human genetics has already aided the understanding and etiology of obesity and, in the case of monogenic variants, has even been translated into treatment of the disease [18]. In addition, the partially overlapping continuum between monogenic and polygenic forms of obesity, such as the *MC4R*, *POMC*, and *BDNF* variants, may be utilized in the elucidation of biological candidacy whereby biological mechanisms involved in the more severe forms of disease may also influence the population at large [14]. However, many of the variants identified in GWAS are located in intronic and intergenic regions and so their precise role in the mechanisms leading to obesity are largely unknown as of yet.

Novel Biological Understanding (The Benefits of a Non-Hypothesis Driven Approach)

It should be emphasized that the importance of discoveries in genetic association studies is not just to explain an increasing amount of the heritability in a trait. A secondary analysis of the biological pathways in which the variants are implicated is an equal, if not more important goal for GWAS. The *FTO* variant started out as a largely unknown locus [57], yet secondary analysis has revealed much about this gene's pathways to effect and has in turn enabled the improved etiological understanding of obesity. *FTO* was first identified in a GWAS strongly associated with risk of type-2 diabetes [30, 58]. However, it was realized that this association between *FTO* and T2D was abolished when adjusted for BMI indicating that this was an adiposity specific locus and that adiposity was playing a mediating role between *FTO* and other metabolic traits [59]. Since then, mouse models have been used to better understand the biological function and metabolic effects of this common adiposity variant [60, 61, 62•]. In addition, epidemiological studies in humans have been used to improve knowledge about the role of *FTO* variants in feeding behavior and appetite [63, 64, 65•].

For other loci, associations with intermediate phenotypes such as appetite levels, dietary intake, and amounts of energy expenditure have started to be investigated. Some variants are thought to derive their associations from nutrient-specific food

preference, as well as hyperphagia [63, 64, 65•, 66, 67]. Whilst *FTO* and *MC4R* have been linked with higher intake of fats [63, 66] and it is thought that *FTO* may be expressed in the behavioral phenotype of food enjoyment and diminished satiety [64, 65•], it is necessary to explore more of the common variants identified in GWAS. For both biological and behavioral phenotypes, the use of animal models for the characterization of different obesity loci has so far been very successful [68], and the combination of functional annotation and in-depth phenotyping is now a recognized prerequisite for the functional characterization of established gene effects [69]. Obesity loci appear to lie within various biochemical and metabolic pathways involved in energy regulation and fat deposition, with genotypes influencing metabolic rate, hyperphagia, energy expenditure, lipid metabolism, and adipogenesis [70•] (Table 1). In particular, many of the loci implicated in GWAS are highly expressed in the central nervous system and suggest a key role for the hypothalamus, a region of the brain involved in the regulation of hunger, satiation, and taste preference [40•]. It is hoped that the further identification and biological categorization of variants will create a clearer image of the complex genetic architecture influencing obesity traits. In addition, the clarification of biological pathways using genetic data may enable them to become amenable to manipulation.

Applied Causal Analyses and the Application of Mendelian Randomization

One area of genetic epidemiology that is becoming particularly promising for utilizing GWAS hits in the elucidation of risk factors for disease is the technique of Mendelian randomization (MR) [71]. This uses genetic markers as instrumental variables to detect and assess the effect of modifiable risk factors and is used in ascertaining causal relationships. MR is not focused on asserting the genetic component of a disease but uses identified variants to proxy for phenotypic or environmental factors pertinent to biological understanding. The motivation for using genetic variation in this way is that independently segregating heritable units informative by their association with potentially modifiable risk factors of interest are allocated essentially at random with respect to environmental/confounding factors. Furthermore, given their allocation at conception, they also may be used to infer directionality in apparently causal epidemiological relationships.

As a natural extension of this paradigm, which is illustrated in the causal linking of BMI to T2D through the effect of *FTO* [31••, 59], other BMI-associated genotypes have been used in a MR framework to assess a causal relationship between greater adiposity and a number of phenotypes and diseases, including cardiovascular risk [72, 73, 74•, 75•, 76] (Fig. 1), cancer [77], mental health [78, 79], and fetal overnutrition [80]. With these simple investigations of the causal impact of BMI on health-related factors, more complex multidirectional assessments also have been undertaken. For example, exploring the relationship between the acute phase reactant C-reactive protein (CRP) and BMI, reciprocal MR has exploited variation at BMI associated variants (including *FTO* and *MC4R*) to evaluate whether BMI had a causal effect on CRP and simultaneously variation at *CRP* loci to assess whether CRP had a causal effect on BMI. This work provided evidence that adiposity causally influences circulating CRP and not vice versa, implicating BMI as a causal agent in inflammation and asserting directionality in an otherwise unclear network of complex phenotypes [74•, 75•].

As well as investigating BMI as a causal agent in respect to other phenotypes and outcomes, a potential future application of Mendelian randomization in the obesity field will be establishing environmental risk factors for obesity. A recent debate in the *Lancet* exemplifies the importance of establishing a causal link between dietary components and risk of obesity, where some assert that obesity develops because of the volume of food intake and dietary composition does not matter [81], whereas others contend that specific macronutrients, such as glycemic load, are important risk factors [82]. Identification of a genotypic variant directly and specifically related to macronutrient intake would make it available as a proxy measure to assess causality of particular macronutrients on adiposity levels.

Alongside the potential benefits MR studies offer for inferring causal association, there are limitations that have been previously described [83]. Of these limitations, power and population stratification may be overcome with rigorous sampling techniques, whereas the issues of pleiotropy and canalization of effects often are more difficult to quantify and tackle, although considerable advance has been made in the addressing of these [84].

Translation and Therapeutic Intervention

There is still a long way to go before the variants discovered in GWAS may be utilized for clinical advances and the development of therapeutic targets for obesity. Although it may be possible to obtain genetic risk scores for individuals based on the array of variants they possess, these variants currently identified have only a small effect on overall adiposity. For this reason, the development of personalized medicine, in the field of obesity appears unlikely as identified variants provide limited information for predicting individual disease risk, etiology, and treatment optimization. However, stratified medicine and recall by genotype [69, 85] offer potential for investigating the etiology of obesity specific biological pathways. Although variants are unlikely to be predictive of individuals who initially gain weight, the

Table 1 Known adiposity loci from recent meta-analyses and possible biological connections between nearby genes and adiposity phenotypes

Biological candidacy for top-hits from adiposity meta-analyses (all with genome-wide significance <5×10–8)			
Strongest SNP-risk allele	Region of the genome	Nearest gene	Biological candidacy of nearby loci[§]
Body mass index[42••]			
rs1558902-A	16q12.2	*FTO**	Hypothalamic control of appetite and food intake; regulation of global metabolic rate
rs2867125-C	2p25.3	*TMEM18**	Neuronal influence in energy homeostasis; leptin-melanocortin signaling pathway
rs571312-A	18q21.32	*MC4R*	Neuronal influence in energy homeostasis
rs10938397-G	4p12	*GNPDA2**	Neuronal influence in energy homeostasis
rs10767664-A	11p14.1	*BDNF*	Neuronal regulator of appetite or energy balance; leptin-melanocortin signalling pathway
rs543874-G	1q25.2	*SEC16B**	Involved in transport of protein and lipids
rs2815752-A	1p31.1	*NEGR1**	Neuronal outgrowth
rs713586-C	2p23.3	*RBJ**	?
		POMC	Leptin-melanocortin signaling pathway
rs12444979-C	16p12.3	*GPRC5B**	?
rs7359397-T	16p11.2	*SH2B1*	Neuronal regulator of appetite or energy balance; leptin signaling and leptin resistance
rs987237-G	6p12.3	*TFAP2B*	Adipocyte differentiation; insulin sensitivity and lipid accumulation
rs2241423-G	15q23	*MAP2K5**	Responds to growth factors
rs9816226-T	3q27.2	*ETV5**	?
rs7138803-A	12q13.12	*FAIM2**	Cellular apoptosis
rs2287019-C	19q13.32	*QPCTL**	?
		GIPR	Incretin hormone receptor mediating insulin secretion
rs1514175-A	1p31.1	*TNNI3K**	Cardiac physiology
rs13107325-T	4q24	*SLC39A8**	Pro-inflammatory
rs2112347-T	5q13.3	*FLJ35779**	?
		*HMGCR**	Cholesterol biosynthesis
rs10968576-G	9p21.1	*LRRN6C**	?
rs3817334-T	11p11.2	*MTCH2**	Mitochondrial carrier protein; evidence for expression in the brain
rs3810291-A	19q13.32	*TMEM160**	Adipocyte expression
rs887912-T	2p16.1	*FANCL**	?
rs10150332-C	14q31.1	*NRXN3**	Central nervous adhesion, waist circumference, addiction and reward behavior
rs13078807-G	3p12.1	*CADM2**	?
rs11847697-T	14q12	*PRKD1**	Cardiac hypertrophy, angiogenesis
rs2890652-C	2q22.2	*LRP1B*	Adipogenesis
rs1555543-C	1p21.3	*PTBP2**	Neuronal functioning
rs4771122-G	13q12.2	*MTIF3**	Nuclear-encoded mitochondrial gene
rs4836133-A	5q23.2	*ZNF608**	?
rs4929949-C	11p15.4	*RPL27A**	?
		TUB	Hypothalamic regulation of body weight
rs29941-G	19q13.11	*KCTD15**	Neuronal influence in energy homeostasis
rs206936-G	6p21.31	*NUDT3**	Adipocyte differentiation
Non-European BMI[53, 54]			
rs2206734-C, rs9356744-T	6p22.3	*CDKAL1*	Risk locus for T2D, insulin secretion
rs11142387-C	9q21.12	*KLF9*	Pro-adipogenic transcription factor
rs261967-C	5q15	*PCSK1*	POMC and insulin are substrates
rs12597579-C	16p12.3	*GP2**	Glycoprotein in pancreatic secretory granule membranes
Childhood/extreme obesity[50]			
rs9568856-?	13q14.3	*OLFM4**	Secreted glycoprotein, link to gut microbiome

Table 1 (continued)

rs9299-?	17q21.32	*HOXB5*	Regulation during gut development
Waist-hip ratio[46]			
rs10195252-T	2q24.3	*GRB14*	Insulin signaling
rs4846567-G	1q41	*LYPLAL1*	Lipase activity
rs9491696-G	6q22.33	*RSPO3**	Wnt and β-catenin signaling
rs6905288-A	6p21.1	*VEGFA*	Angiogenesis
rs984222-G	1p12	*TBX15*	Adipocyte development
		*WARS2**	Mitochondrial activity
rs1055144-T	7p15.2	*NFE2L3**	?
rs1011731-G	1q24.3	*DNM3**	?
		*PIGC**	Lipid biosynthesis
rs718314-G	12p12.1	*ITPR2*	Intracellular calcium signaling
		*SSPN**	?
rs1294421-G	6p25.1	*LY86**	Recognition of lipopolysaccharide
rs6795735-C	3p14.1	*ADAMTS9*	Insulin signaling
rs1443512-A	12q13.13	*HOXC13**	Embryonic development
rs9491696-G	6q22.33	*RSPO3**	Angiogenesis
rs4823006-A	22q12.1	*ZNRF3**	?
		*KREMEN1**	Wnt and β-catenin signaling
rs6784615-T	3p21.1	*NISCH*	Insulin signaling
		*STAB1**	Angiogenesis
rs6861681-A	5q35.2	*CPEB4**	?
Waist circumference[44]			
rs7826222-G	8p23.1	*TNKS – MSRA**	Insulin-regulated glucose disposal

§ Possible biological roles of variants obtained from the literature cited, as well as a search of GeneCards

*Novel loci not previously implicated in obesity before genome-wide association studies

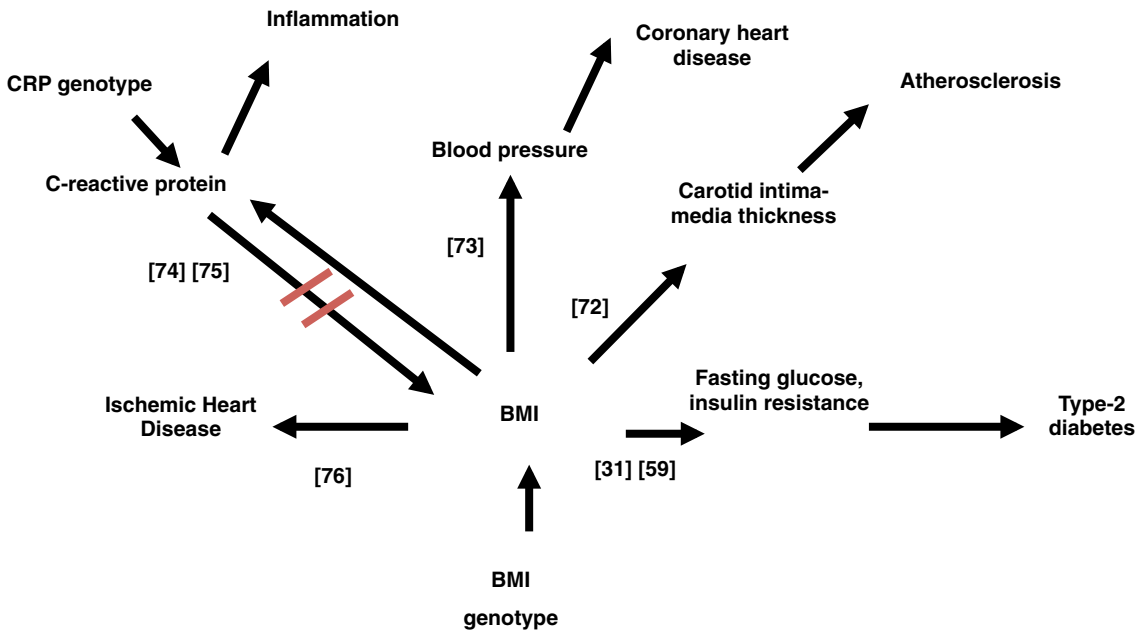

Fig. 1 BMI as a causal agent: using Mendelian Randomization to establish causal relationships between adiposity and metabolic/cardiovascular outcomes (Numbers in brackets refer to the articles in the references which investigate causal analyses between BMI and cardiovascular outcomes with the use of BMI genotypes)

verdict is still out as to whether particular genetic loci may be implicated in the ability to lose weight and the success of potential treatments [86, 87].

Rather than therapeutic intervention, the possibility for translating obesity genetics into the public health field is most likely to be realized by focusing on methods of obesity prevention. The use of Mendelian randomization and study designs, such as recall by genotype in highlighting causal pathways between obesity and its comorbidities, as well as between modifiable environmental factors disposing to adiposity traits, offers much to public health in terms of informing individuals of true obesity risk factors and the specific health implications of being overweight.

Missing Heritability

The formation of and work produced by the GIANT consortium represent great achievements from the field of GWAS at identifying the proportion of heritability that may be explained by common variants [88]. However, there remains a great disparity in the amount of variation currently explained and previous heritability estimates of BMI and adiposity or approximately 70–80 % [9]. The existence of this "missing heritability" is evident in not only studies examining obesity, but also for most complex diseases [15, 89, 90].

Development of Genetic Data Collection

Direct genotyping in GWAS and viable imputation using original HapMap reference panels only covers a limited number of SNPs and range of allele frequencies. The development of denser genotyping chips and imputation methods using data from the HapMap 3 [91] and 1,000 genomes project [92] will enable extension to a larger set of variants and will allow for targeted resequencing and systematic fine mapping to produce a complete portfolio of sequence variation. Such sequence variation is likely to consist of rare variants, present in less than 1 % of the population (the threshold for polymorphism in traditional GWAS), with potentially larger penetrance effects than previously identified common variants [93]. More than 100 different mutations have now been identified within the *MC4R* region and, although many of these variants are very rare, together they account for a higher proportion of total variation in adiposity [94].

It also has been proposed that particular structural variants in the genome might play a role in the predisposition to obesity. One kilobase repeats known as copy number variants (CNVs) are assumed to be involved in the regulation of neighboring genes [95]. For example, a CNV located in a region near to the neuronal growth regulator 1 (*NEGR1*) gene may be involved in regulation of this gene [40•]. In addition, the role of noncoding RNAs, including microRNAs that regulate posttranscriptional gene expression, is being increasingly researched in this field [96].

Gene-Gene and Gene-Environment interactions

Genetic analyses often are based assuming simple additive models, when in reality, alternative modes of contribution and gene-gene interactions are likely to be common in complex traits, which have a vast number of pathways to effect [97]. To date, very few genuine gene-gene interactions have been ascertained due to the computational and power-intensive requirements of such studies and the requirement for a priori knowledge of the specific genes involved [98]. Nonetheless, a potential benefit of identifying interacting loci is that it might aid in our understanding of the biological role of genetic variants, and their relative positions in the pathways to disease, and so value must be placed on this ongoing search.

It also is important to gain a better picture of both genetic and environmental pathways to effect in the field of obesity and to understand the interplay between environmental contributions and genetic predispositions. It is likely that the effects of different obesity loci are dependent on the environment in which they are expressed. Differences in the environment and heterogeneity in lifestyle offers a potential explanation for why different variants may be identified in GWAS of individuals from different regions and at differing points in the lifecourse. Therefore, as well as potential for gene-gene interactions in explaining some of the missing heritability, it also is necessary to consider gene-environment interactions to obtain a full understanding of the genetic architecture of obesity [99]. For example, it has been proposed that the effects of a high-fat diet may interact with risk alleles, including *FTO*, to accentuate the influence of these variants on BMI [100]. In addition, interactions also have been proposed between risk genotypes and physical activity levels [101, 102]. With the benefit of large sample sizes, a meta-analysis has recently provided evidence that a high physical activity level attenuates the effect of a risk *FTO* allele [102].

Conclusions

With the increasing size and resolution of genome-wide association studies, we are starting to establish a common variant genetic architecture for obesity to go with that known for more rare forms. The exploration of this architecture, in terms of the functional consequences of individual loci, as well as their positions and interactions along

biological pathways, may be used to better understand and dissect the web of obesity and identify important causal factors in its etiology. The primary value of genetic studies concentrated on common variation appears not in risk prediction but rather in the provision of novel insights into mechanisms of disease. In turn, bringing together all types of analysis on recently discovered genetic variants from life-course approaches, animal models, expression data, and genetic-environment interfaces may aid clinical advances for identifying therapeutic targets and the potential pharmacological manipulation of pathways to obesity.

A clear understanding of the role of genetic variants also may aid Mendelian randomization studies for the identification of causal environmental risks, providing insights for the prevention of obesity. Such discoveries should allow us to progress along the continuum of translational research in the obesity field in terms of health application, practice guidelines and population health impact.

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References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Kopelman PG. Obesity as a medical problem. Nature. 2000;404 (6778):635–43.
2. Kopelman PG. Health risks associated with overweight and obesity. Obes Rev. 2007;8:13–7.
3. Whitlock G, Lewington S, Sherliker P, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet. 2009;373:1083–96.
4. Global health risks: mortality and burden of disease attributable to selected major risks. Geneva, World Health Organization, 2009 (http://www.who.int/healthinfo/global_burden_disease/GlobalHealthRisks_report_full.pdf Accessed on 31/7/12).
5. Kelly T, Yang W, Chen CS, et al. Global burden of obesity in 2005 and projections to 2030. Int J Obes. 2008;32(9):1431–7.
6. Swinburn B, Egger G, Raza F. Dissecting obesogenic environments: the development and application of a framework for identifying and prioritizing environmental interventions for obesity. Prev Med. 1999;29(6):563–70.
7. Hill JO, Peters JC. Environmental contributions to the obesity epidemic. Science. 1998;280(5368):1371–4.
8. Ramachandrappa S, Farooqi IS. Genetic approaches to understanding human obesity. J Clin Invest. 2011;121(6):2080–6.
9. Wardle J, Carnell S, Haworth CM, Plomin R. Evidence for a strong genetic influence on childhood adiposity despite the force of the obesogenic environment. Am J Clin Nutr. 2008;87(2):398–404.
10. Schwartz MW, Woods SC, Porte Jr D, Seeley RJ, Baskin DG. Central nervous system control of food intake. Nature. 2000;404:661–71.
11. Montague CT, Farooqi IS, Whitehead JP, et al. Congenital leptin deficiency is associated with severe early-onset obesity in humans. Nature. 1997;387(6636):903–8.
12. Jackson RS, Creemers JW, Ohagi S, et al. Obesity and impaired prohormone processing associated with mutations in the human prohormone convertase 1 gene. Nat Genet. 1997;16(3):303–6.
13. Huszar D, Lynch CA, Fairchild-Huntress V, et al. Targeted disruption of the melanocortin-4 receptor results in obesity in mice. Cell. 1997;88(1):131–41.
14. Hinney A, Vogel CI, Hebebrand J. From monogenic to polygenic obesity: recent advances. Eur Child Adolesc Psychiatry. 2010;19 (3):297–310.
15. McCarthy MI, Abecasis GR, Cardon LR, et al. Genome-wide association studies for complex traits: consensus, uncertainty and challenges. Nat Rev Genet. 2008;9(5):356–69.
16. Hirschhorn JN, Daly MJ. Genome-wide association studies for common diseases and complex traits. Nat Rev Genet. 2005;6:95–108.
17. Goldstein DB. Common genetic variation and human traits. New Engl J Med. 2009;360:1696–8.
18. Farooqi IS, Jebb SA, Langmack G, et al. Effects of recombinant leptin therapy in a child with congenital leptin deficiency. N Engl J Med. 1999;341(12):879–84.
19. Bochukova EG, Huang N, Keogh J, et al. Large, rare chromosomal deletions associated with severe early-onset obesity. Nature. 2010;463:666–70.
20. Walters RG, Jacquemont S, Valsesia A, et al. A new highly penetrant form of obesity due to deletions on chromosome 16p11.2. Nature. 2010;463:671–5.
21. Farooqi IS, O'Rahilly S. Leptin: a pivotal regulator of human energy homeostasis. Am J Clin Nutr. 2009;89(3):980S–4S.
22. Frank S, Heni M, Moss A, et al. Leptin therapy in a congenital leptin-deficient patient leads to acute and long-term changes in homeostatic, reward, and food-related brain areas. J Clin Endocrinol Metab. 2011;96(8):E1283–7.
23. Martinelli CE, Keogh JM, Greenfield JR, et al. Obesity due to melanocortin 4 receptor (MC4R) deficiency is associated with increased linear growth and final height, fasting hyperinsulinemia, and incompletely suppressed growth hormone secretion. J Clin Endocrinol Metab. 2011;96:E181–8.
24. Nogueiras R, Wiedmer P, Perez-Tilve D, et al. The central melanocortin system directly controls peripheral lipid metabolism. J Clin invest. 2007;117:3475–88.
25. Kimber W, Peelman F, Prieur X, et al. Functional characterization of naturally occurring pathogenic mutations in the human leptin receptor. Endocrinology. 2008;149:6043–52.
26. Tan K, Pogozheva ID, Yeo GS, et al. Functional characterization and structural modeling of obesity associated mutations in the melanocortin 4 receptor. Endocrinology. 2009;150:114–25.
27. Creemers JW, Lee YS, Oliver RL, et al. Mutations in the amino-terminal region of proopiomelanocortin (POMC) in patients with early-onset obesity impair POMC sorting to the regulated secretory pathway. J Clin Endocrinol Metab. 2008;93:4494–9.
28. Farooqi IS, Volders K, Stanhope R, et al. Hyperphagia and early-onset obesity due to a novel homozygous missense mutation in prohormone convertase 1/3. J Clin Endocrinol Metab. 2007;92:3369–73.
29. Rankinen T, Zuberi A, Chagnon YC, et al. The human obesity gene map: the 2005 update. Obesity. 2006;14(4):529–644.
30. Burton PR, Clayton DG, Cardon LR, et al. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature. 2007;447:661–78.
31. •• Frayling TM, Timpson NJ, Weedon MN, et al. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science. 2007;316 (5826):889–94. *This paper reports the first reliable common variant association with BMI.*

32. Dina C, Meyre D, Gallina S, et al. Variation in FTO contributes to childhood obesity and severe adult obesity. Nat Genet. 2007;39 (6):724–6.
33. Scuteri A, Sanna S, Chen WM, et al. Genome-wide association scan shows genetic variants in the FTO gene are associated with obesity-related traits. PLoS Genet. 2007;3(7):e115.
34. Heid IM, Huth C, Loos RJF, et al. Meta-analysis of the INSIG2 association with obesity including 74,345 individuals: does heterogeneity of estimates relate to study design? PLoS Genet. 2009;5(10):e1000694.
35. Ioannidis JPA. Non-replication and inconsistency in the genome-wide association setting. Hum Hered. 2007;64:203–13.
36. Ioannidis JPA, Boffetta P, Little J, et al. Assessment of cumulative evidence on genetic associations: interim guidelines. Int J Epidemiol. 2008;37:120–32.
37. International HapMap Consortium. A haplotype map of the human genome. Nature. 2005;437(7063):1299–320.
38. Loos RJF, Lindgren CM, Li S, et al. Common variants near MC4R are associated with fat mass, weight and risk of obesity. Nat Genet. 2008;40(6):768–75.
39. Loos RJF, Speliotes EK, Willar CJ, et al. Genome-wide association meta-analysis of more than 32,000 individuals identifies several new genetic variants robustly associated with body mass index. Obesity. 2008;16:S69–9.
40. • Willer CJ, Speliotes EK, Loos RJF, et al. Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. Nat Genet. 2009;41(1):25–34. *This GWAS increased the number of common variants reproducibly associated with body mass index (BMI) from two loci (FTO and MC4R) to eight. Several of the likely causal genes are known to play a role in the cenral nervous system*.
41. • Thorleifsson G, Walters GB, Gudbjartsson DF, et al. Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity. Nat Genet. 2009;41(1):18–24. *This GWAS identified seven novel loci which reached a genome-wide threshold for their association with weight and body mass index. Five of these variants were also confirmed in the GWAS by Willer et al (2009)*.
42. •• Speliotes EK, Willer CJ, Berndt SI, et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. Nat Genet. 2010;42(11):937–U53. *This GWAS identified a further 18 BMI-associated loci, bringing the total number of robustly associated variants up to 32, explaining 1.45 % of variation in BMI*.
43. Paternoster L, Evans DM, Nohr EA, et al. Genome-wide population-based association study of extremely overweight young adults - the GOYA study. PLoS One. 2011;6:e24303.
44. Ingelsson E, Magi R, Gustafsson S, et al. Association analyses of up to 263,000 individuals provide new insights into the biology and genetic architecture of the extremes of anthropometric traits. Circulation. 2012;125:A048.
45. Lindgren CM, Heid IM, Randall JC, et al. Genome-wide association scan meta-analysis identifies three Loci influencing adiposity and fat distribution. PLoS Genet. 2009;5(6): e1000508.
46. Heard-Costa NL, Zillikens MC, Mondal KL, et al. NRXN3 is a novel locus for waist circumference: a genome-wide association study from the CHARGE Consortium. PLoS Genet. 2009;5(6): e1000539.
47. Heid IM, Jackson AU, Randall JC, et al. Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. Nat Genet. 2010;42(11):949–60.
48. Walley AJ, Blakemore AI, Froguel P. Genetics of obesity and the prediction of risk for health. Hum Mol Genet. 2006;Spec No 2: R124–30.
49. Hardy R, Wills AK, Wong A, et al. Life course variations in the associations between FTO and MC4R gene variants and body size. Hum Mol Genet. 2010;19:545–52.
50. Mei H, Chen W, Jiang F. Longitudinal replication studies of GWAS risk SNPs influencing body mass index over the course of childhood and adulthood. Plos One. 2012;7(2): e31470.
51. Sovio U, Mook-Kanamori D, Warrington N, et al. Association between common variation at the *FTO* locus and changes in body mass index from infancy to late childhood: the complex nature of genetic association through growth and development. PLoS Genetics. 2010;7(2):e1001307.
52. Bradfield JP, Taal HR, Timpson NJ, et al. A genome-wide association meta-analysis identifies new childhood obesity loci. Nat Genet. 2012;44:526–31.
53. Liu Y, Liu Z, Song YQ, et al. Meta-analysis added power to identify variants in FTO associated with type 2 diabetes and obesity in the Asian population. Obesity. 2010;18:1619–24.
54. Taylor AE, Sandeep MN, Janipalli CS, et al. Associations of FTO and MC4R variants with obesity traits in Indians and the role of rural/urban environment as a possible effect modifier. J Obes. 2011;2011:307542.
55. Wen WQ, Cho YS, Zheng W, et al. Meta-analysis identifies common variants associated with body mass index in east Asians. Nat Genet. 2012;44:307–U112.
56. Okada Y, Kubo M, Ohmiya H, et al. Common variants at CDKAL1 and KLF9 are associated with body mass index in east Asian populations. Nat Genet. 2012;44:302–U105.
57. Peters T, Ausmeier K, Dildrop R, Ruther U. The mouse Fused toes (Ft) mutation is the result of a 1.6-Mb deletion including the entire Iroquois B gene cluster. Mamm Genome: Official Journal of the International Mammalian Genome Society. 2002;13:186–8.
58. Zeggini E, Weedon MN, Lindgren CM, et al. Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. Science. 2007;316:1336–41.
59. Freathy RM, Timpson NJ, Lawlor DA, et al. Common variation in the FTO gene alters diabetes-related metabolic traits to the extent expected given its effect on BMI. Diabetes. 2008;57 (5):1419–26.
60. Gerken T, Girard CA, Tung YC, et al. The obesity-associated FTO gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase. Science. 2007;318(5855):1469–72.
61. Church C, Lee S, Bagg EA, et al. A mouse model for the metabolic effects of the human fat mass and obesity associated FTO gene. PLoS Genet. 2009;5(8):e1000599.
62. • Church C, Moir L, McMurray F, et al. Overexpression of Fto leads to increased food intake and results in obesity. Nat Genet. 2010;42(12):1086–92. *This study shows that ubiquitous overexpression of Fto leads to a dose-dependent increase in body and fat mass*.
63. Timpson NJ, Emmett PM, Frayling TM, et al. The fat mass- and obesity-associated locus and dietary intake in children. Am J Clin Nutr. 2008;88(4):971–8.
64. Cecil JE, Tavendale R, Watt P, et al. An obesity-associated FTO gene variant and increased energy intake in children. N Engl J Med. 2008;359(24):2558–66.
65. • Wardle J, Llewellyn C, Sanderson S, Plomin R. The FTO gene and measured food intake in children. Int J Obes (Lond). 2009;33 (1):42–5. *This study shows that children with two copies of the lower-risk FTO alleles ate less than those with one or two higher-risk alleles, irrespective of BMI*.
66. Qi L, Kraft P, Hunter DJ, Hu FB. The common obesity variant near MC4R gene is associated with higher intakes of total energy and dietary fat, weight change and diabetes risk in women. Hum Mol Genet. 2008;17(22):3502–8.

67. Bauer F, Elbers CC, Adan RA, et al. Obesity genes identified in genome-wide association studies are associated with adiposity measures and potentially with nutrient-specific food preference. Am J Clin Nutr. 2009;90(4):951–9.
68. Burgess DJ. Complex traits old meets new in obesity genetics. Nat Rev Genet. 2012;13(5):301.
69. McGuire SE, McGuire AL. Don't throw the baby out with the bathwater: enabling a bottom-up approach in genome-wide association studies. Genome Res. 2008;18:1683–5.
70. • O'Rahilly S. Human genetics illuminates the paths to metabolic disease. Nature. 2009;462(7271):307–14. *This article explores the extent to which human molecular genetic research has improve understanding of underlying pathophysiological mechanisms related to obesity and type 2 diabetes*.
71. Davey Smith G, Ebrahim S. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? Int J Epidemiol. 2003;32(1):1–22.
72. Kivimaki M, Davey Smith G, Timpson NJ, et al. Lifetime body mass index and later atherosclerosis risk in young adults: examining causal links using Mendelian randomization in the cardiovascular risk in young Finns study. Eur Heart J. 2008;29 (20):2552–60.
73. Timpson NJ, Harbord R, Davey Smith G, et al. Does greater adiposity increase blood pressure and hypertension risk? Mendelian randomization using the FTO/MC4R genotype. Hypertension. 2009;54(1):84–U131.
74. • Welsh P, Polisecki E, Robertson M, et al. Unraveling the directional link between adiposity and inflammation: a bidirectional Mendelian Randomization Approach. J Clin Endocrinol Metab. 2010;95(1):93–9. *This study, and the one by Timpson et al [75], explore the direction of causality between adiposity and inflammation using genetic variants in a Mendelian Randomization analysis. Both studies provide good evidence to suggest that higher adiposity is associated with increased inflammation, but not vice-versa*.
75. • Timpson NJ, Nordestgaard BG, Harbord RM, et al. C-reactive protein levels and body mass index: elucidating direction of causation through reciprocal Mendelian randomization. Int J Obes. 2011;35(2):300–8. *This study, and the one by Welsh et al [74], explore the direction of causality between adiposity and inflammation using genetic variants in a Mendelian Randomization analysis. Both studies provide good evidence to suggest that higher adiposity is associated with increased inflammation, but not vice-versa*.
76. Nordestgaard BG, Palmer TM, Benn M, et al. The effect of elevated body mass index on ischemic heart disease risk: causal estimates from a mendelian randomisation approach. PLoS Med. 2012;9(5):e1001212.
77. Brennan P, McKay J, Moore L, et al. Obesity and cancer: Mendelian randomization approach utilizing the FTO genotype. Int J Epidemiol. 2009;38(4):971–5.
78. Lawlor DA, Harbord RM, Tybjaerg-Hansen A, et al. Using genetic loci to understand the relationship between adiposity and psychological distress: a Mendelian Randomization study in the Copenhagen General Population Study of 53 221 adults. J Intern Med. 2011;269:525–37.
79. Kivimaki M, Jokela M, Hamer M, et al. Examining overweight and obesity as risk factors for common mental disorders using Fat Mass and Obesity-Associated (FTO) genotype-instrumented analysis. Am J Epidemiol. 2011;173:421–9.
80. Lawlor DA, Timpson NJ, Harbord RM, et al. Exploring the developmental overnutrition hypothesis using parental-offspring associations and FTO as an instrumental variable. PLoS Med. 2008;5:e33.
81. Swinburn BA, Sacks G, Hall KD, et al. The global obesity pandemic: shaped by global drivers and local environments. Lancet. 2011;378(9793):804–14.
82. Astrup A, Brand-Miller J. Diet composition and obesity. Lancet. 2012;379(9821):1100–0.
83. Davey Smith G, Ebrahim S. Mendelian randomization: prospects, potentials, and limitations. Int J Epidemiol. 2004; 33:30–42.
84. Palmer TM, Lawlor DA, Harbord RM, et al. Using multiple genetic variants as instrumental variables for modifiable risk factors. Stat Methods Med Res. 2012;21(3):223–42.
85. Beskow LM, Fullerton SM, Namey EE, et al. Recommendations for ethical approaches to genotype-driven research recruitment. Hum Genet. 2012;131(9):1423–31.
86. Hsiao DJ, Wu LS, Huang SY, Lin E. Weight loss and body fat reduction under sibutramine therapy in obesity with the C825T polymorphism in the GNB3 gene. Pharmacogenet Genomics. 2009;19(9):730–3.
87. Still CD, Wood GC, Chu X, et al. High allelic burden of four obesity SNPs is associated with poorer weight loss outcomes following gastric bypass surgery. Obesity (Silver Spring). 2011;19(8):1676–83.
88. Hebebrand J, Vockmar AL, Knoll N, Hinney A. Chipping away the 'missing heritability': GIANT steps forward in the molecular elucidation of obesity - but still lots to go. Obes Facts. 2010;3 (5):294–303.
89. Maher B. Personal genomes: the case of the missing heritability. Nature. 2008;456(7218):18–21.
90. Manolio TA, Collins FS, Cox NJ, et al. Finding the missing heritability of complex diseases. Nature. 2009;461(7265):747–53.
91. Altshuler DM, Gibbs RA, Peltonen L, et al. Integrating common and rare genetic variation in diverse human populations. Nature. 2010;467:52–8.
92. Buchanan CC, Torstenson ES, Bush WS, Ritchie MD. A comparison of cataloged variation between International HapMap Consortium and 1000 Genomes Project data. J Am Med Inform Assoc. 2012;19(2):289–94.
93. Dickson SP, Wang K, Krantz I, Hakonarson H, Goldtein DB. Rare variants create synthetic genome-wide associations. PLoS Biol. 2010;8(1):e1000294.
94. Fan ZC, Tao YX. Functional characterization and pharmacological rescue of melanocortin-4 receptor mutations identified from obese patients. J Cell Mol Med. 2009;13(9B):3268–82.
95. Conrad DF, Pinto D, Redon R, et al. Origins and functional impact of copy number variation in the human genome. Nature. 2010;464(7289):704–12.
96. Krutzfeldt J, Stoffel M. MicroRNAs: a new class of regulatory genes affecting metabolism. Cell Metab. 2006;4(1):9–12.
97. Zuk O, Hechter E, Sunyaev SR, Lander ES. The mystery of missing heritability: genetic interactions create phantom heritability. Proc Natl Acad Sci U S A. 2012;109(4):1193–8.
98. Wei WH, Hermani G, Gyenesei A et al. Genome-wide analysis of epistasis in body mass index using multiple human populations. Eur J Hum Genet, 2012.
99. Andreasen CH, Andersen G. Gene-environment interactions and obesity–further aspects of genomewide association studies. Nutrition. 2009;25(10):998–1003.
100. Corella D, Arnett DK, Tucker KL, et al. A high intake of saturated fatty acids strengthens the association between the fat mass and obesity-associated gene and BMI. J Nutr. 2011;141 (12):2219–25.
101. Andreasen CH, Stender-Petersen KL, Mogensen MS, et al. Low physical activity accentuates the effect of the FTO rs9939609 polymorphism on body fat accumulation. Diabetes. 2008;57 (1):95–101.
102. Kilpelainen TO, Qi L, Qi L, Brage S, et al. Physical activity attenuates the influence of FTO variants on obesity risk: a meta-analysis of 218,166 adults and 19,268 children. PLoS Med. 2011;8 (11):e1001116.