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The genetic underpinnings of obesity

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Obesity has now reached pandemic levels, with a quarter of the world's population being overweight or obese and thus at a greater risk of developing type 2 diabetes (T2D) and cardiovascular disease (CVD) [1•]. Largescale biobanks, combined with genome-wide discovery efforts, have identified thousands of loci associated with obesity traits including body composition, fat distribution and their causal relationships with disease risk. These findings have begun to shed light on some of the biological mechanisms driving human adiposity. In conjunction with comprehensive functional annotation efforts, such as cell-level transcriptome maps and phenotypic analyses of model organisms, we are poised to reveal fundamental biology and disease risk mechanisms at an unparalleled resolution. Integration of genetic and experimental approaches will be pivotal in the translation of genomic signals into the causal and functional mechanisms behind obesity, with the potential of delivering precision medicine strategies in the near future.

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Introduction

Obesity is the fifth leading cause of death worldwide and affects more than 600 million people [1•]. It is commonly defined as a body mass index (BMI) over 30 kg/m^2 and it is estimated that high BMI (>25 kg/m^2) accounts for up to 4 million deaths annually [1•]. Most of these deaths are due to CVD, one of the major comorbidities of obesity, alongside T2D and various cancers [2].

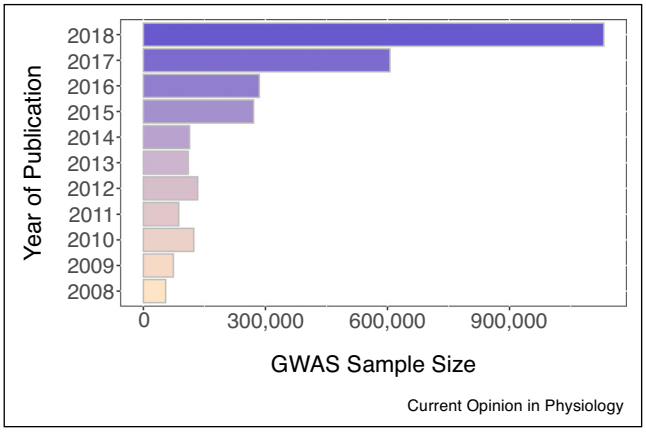
The rapid inflation of obesity prevalence to pandemic levels is a result of the interaction between intrinsic genetic susceptibility and certain modern obesogenic environments, such as increased availability of highly energy dense foods, consequent excessive caloric intake, decreased physical activity and socioeconomic factors, among others [3]. Over and above total fat mass, detrimental anatomical distribution of body fat further exacerbates health risks. Most prominently, visceral adipose tissue (VAT), which surrounds the intra-abdominal organs, increases the risk of T2D and CVD, whereas subcutaneous adipose tissue (SAT) is cardio-metabolically protective [4]. Thus, it is worthwhile disentangling the distinct biology of adipose tissue expansion within these different depots and specifically the genetic underpinnings for any divergence.

Heritability estimates for obesity traits can vary depending on the measures used, but range from 50 to 60% [5]. Identifying the genetic drivers of obesity is of interest due to the aforementioned public health burden. However, lifestyle-altering health campaigns have been largely unsuccessful and a subset of severe obesity would, in any case, remain refractory to such therapy, as it is caused by particularly damaging mutations. To gain insight into therapeutically tractable, but common genetic mechanisms of obesity, genome-wide association studies (GWAS), which link common DNA variants to adiposity and metabolic disease traits, have been employed with ever-increasing power. GWAS of anthropometric (e.g. BMI) and other adiposity traits have now identified more than a thousand candidate genomic loci [6•,7•]. Work on these loci is beginning to provide insight into the functional and mechanistic profile of GWAS candidate genes, with the ultimate goal being the translation of such insights into actionable targets to treat obesity, as reviewed below.

Gene drivers of obesity

The first insights into the genetics of obesity came from screening studies of severe, early-onset human obesity, which revealed mutations in the leptin hormone pathway, which is central for appetite control [8,9]. Such studies used methods like linkage analysis in affected pedigrees and were suited to detect rare variants of large, mostly monogenic, effects.

Figure 1



Ever-increasing GWAS sample sizes.
Maximum sample size of GWAS studies on the GWAS Catalog [11], per year since the publication of the Wellcome Trust Case Control Consortium (WTCCC) [10]. From 2008–2014 large studies comprised of consortium GWAMAs and rarely included more than 100 000 participants. In 2015, with the first release of UK Biobank [13], larger studies were possible. GWAMAs of UK Biobank and consortia followed and culminated in the first few GWAMAs with over a million participants in 2018 [14,15]. Data accessed and downloaded in March 2019.

The focus later shifted towards interrogating the common variation of quantitative traits at the population level. Since the first major GWAS meta-analysis (GWAMA) was published in 2007 [10], efforts have focused on increasing sample size and modelling easily accessible and measurable traits (Figure 1). Now, with the advent of large-scale biobanks, the number of obesity candidate genes has reached an unparalleled high. Namely, there are currently over 2000 loci associated with different measures of obesity in the GWAS catalog [11]. Nevertheless, even for simple traits such as BMI, no more than 4% of the observed variance has been genetically explained [12]. Strikingly, experimental follow-up and biological insight into the identified loci is lagging behind technological advancements in the field.

Assessing obesity

Obesity is caused by an energy imbalance, where energy intake exceeds expenditure, causing supplemental energy to be stored in adipocytes in the form of lipids. The anatomical distribution of adipose tissue confers added health risks. Central or abdominal adiposity, characterised by VAT that surrounds the intra-abdominal organs, is associated with increased CVD risk, whereas lower-body SAT has been linked to a reduced risk [4,16]. Since identifying high risk individuals for targeted pharmaceutical or lifestyle interventions is of obvious epidemiological significance, disentangling the genetic determinants that favour VAT accretion over SAT expansion could help inform tailored prevention or treatment strategies.

GWAS are a powerful tool for discovering such genetic signals. However, so far, they have mostly focused on using anthropometric surrogate indicators of obesity (i.e. BMI, waist-hip ratio (WHR), etc.), rather than direct measures of the risk-conferring depots. BMI is the suggested proxy measurement for obesity, as increased BMI amplifies the risk of CVD [17]. However, the discriminative capacities of BMI are far from optimal, as it does not differentiate between adipose and lean tissue or between different body shapes [18]. Waist-hip ratio (WHR) has a closer correlation with myocardial infarction risk than BMI [19], but still does not accurately capture peripheral fat stored in the upper limbs or the distribution of fat between VAT and SAT.

To delineate the biological mechanisms of adipose tissue expansion (hyperplasia and/or hypertrophy) and their relations to disease aetiology, direct measurements of individual fat depots are needed. Fat distribution is heritable (heritability of around 40% for SAT and VAT [20]) and can be studied at a population scale. Indeed, some large cohorts now prioritise whole-body imaging to assess fat distribution. However, imaging at such a scale is very costly, both in terms of resources and manpower. Computerised tomography (CT), dual emission X-ray absorptiometry (DEXA) and magnetic resonance imaging (MRI) scans are the most regularly used imaging platforms and the most precise direct measurements of body composition. Bioelectrical impedance analysis (BIA), albeit much less precise, is often preferred when factoring in the challenges of large studies. GWAS using each of these platforms have provided some interesting novel genetic insights into the biology of obesity, including a predominance of brain versus peripheral signalling pathways related to fat mass and distribution, respectively.

GWAS of anthropometry

The GIANT consortium has dominated the field of anthropometric GWAS for the past several years. Earlier efforts consisted of GWAMAs of around 250 000 participants of European ancestry [12,21] and collectively identified around 150 loci that associated with BMI and WHR. The latest iterations included data from the 500 000 UK Biobank participants [13], bringing the overall cohort size to 700 000 individuals and effectively sky-rocketing the number of associations. More specifically, Yengo *et al.* [7•], identified 941 genetic signals for BMI, 751 of which were novel. WHR adjusted for BMI (WHRadjBMI) was also pursued as a GWAS phenotype due to its reported pleiotropy with total body fat percentage (BF%) [21]. As an anthropometric phenotype, WHRadjBMI was described as an "unexpected fat distribution given the BMI" [22•]. Indeed, in the largest WHRadjBMI GWAMA to date, Pulit *et al.* [6•] showed that out of 346 WHRadjBMI loci, around a seventh also associated with BF%.

An important factor to consider is the inherent sexual dimorphism in adipose patterns in humans. Women are

biologically predisposed to accumulate fat around their lower halves, whereas men do so in their upper body. Thus, phenotypes like WHR can be highly predictive of body composition in women, while inferior to measures such as BF% in men [6•]. Commonly, around a third of the identified loci exhibit sex-specific effects on the queried phenotypes, with most of those being female-specific [6•,23].

Enforcing earlier findings [12,21], BMI candidate loci were enriched for genes involved in neurogenesis and the general development of the central nervous system, consistently with monogenic forms of obesity [24•]. While, WHR signals were involved in more peripheral pathways of metabolism, such as adipocyte regulation and insulin resistance [23] (Figure 2).

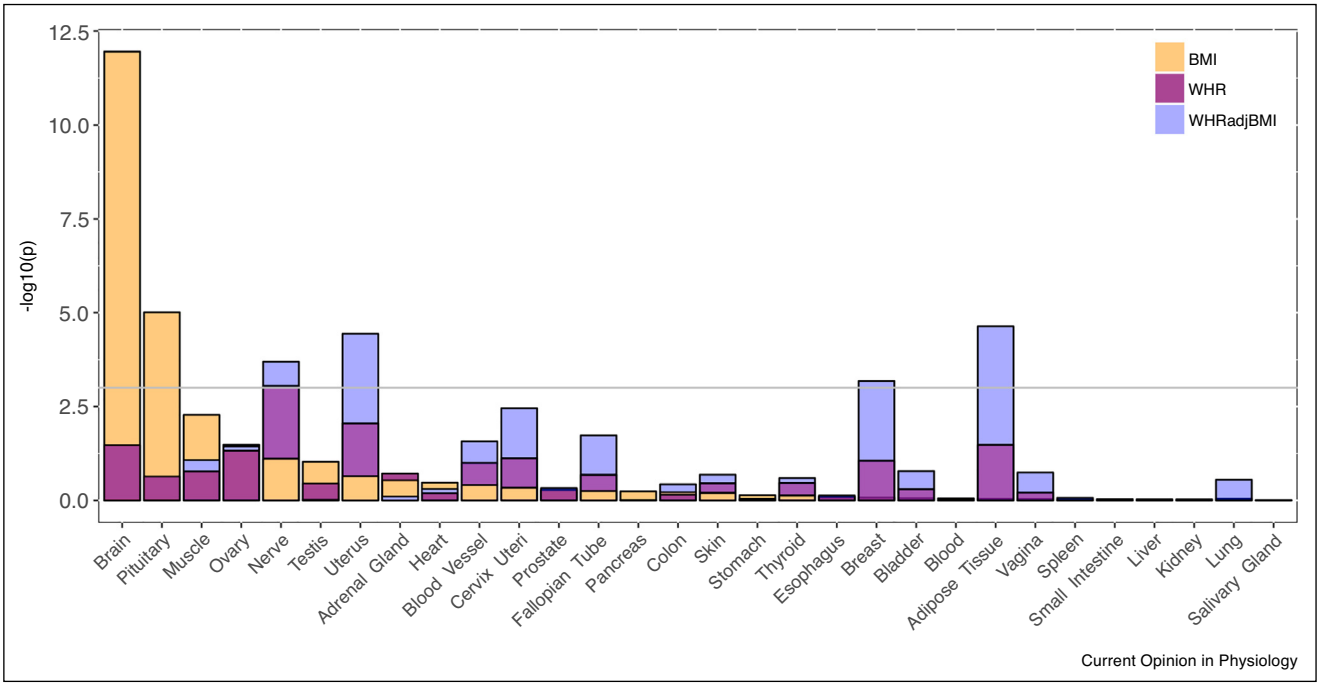
Notably, of the hundreds of loci associated with various measures of central obesity, most were intronic or intergenic variants and exerted relatively small effects over the phenotypes in question. A strategy for discovering more immediately functional variants was to look at common and rare exonic variants, based on the assumption that their effects would more closely link to the biological basis of obesity [23–25]. Indeed, such rare exonic variants had much greater effect sizes, compared to their common counterparts (up to tenfold) [23,25]. A striking example was a nonsense mutation in *MC4R* (p.Tyr35Ter), which had a frequency of one in a thousand, and caused a bodyweight increase of ~7 kg per copy of the effect allele [25]. Such studies led to the identification of numerous novel and potentially causative candidate genes, several of which had previously been implicated in monogenic forms of obesity, but not with BMI variation in the general population [25].

GWAS of imaging

Early studies using various imaging platforms had modest successes. A 2012 CT-scan based GWAS effort focused on the VAT and SAT components of around 10 000 participants and found some novel loci, which highlighted the extreme sex dimorphism of body fat distribution [20]. They also replicated known loci for BMI and waist circumference, as proxies for central adiposity, in their VAT analysis.

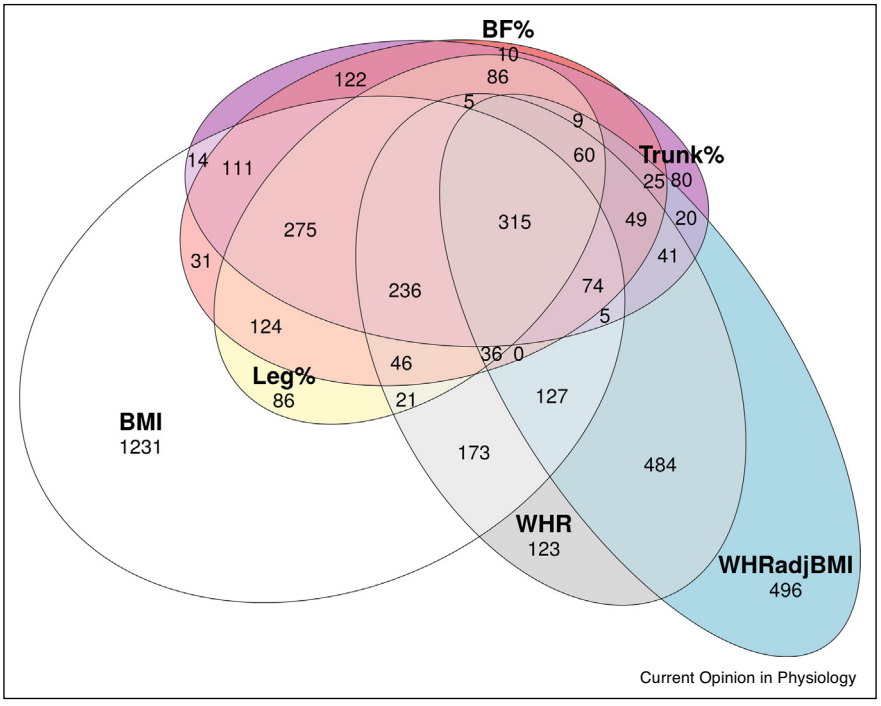
More recently, the largest imaging GWAMA analysed VAT, SAT and pericardial fat, of 18 000 people and identified a few novel loci [26•]. Testing for the

Figure 2



Tissue type enrichment for anthropometric candidate loci of obesity and central adiposity.
BMI loci are predominantly enriched for brain expression. WHRadjBMI hints at novel biological mechanisms, beyond that related to WHR alone. Many gene drivers for monogenic obesity also act through the brain, primarily affecting eating behaviours [9]. WHR and WHRadjBMI loci are enriched for expression in peripheral obesity-relevant tissues, such as adipose and female-specific tissues, highlighting the sex-specificity of some of these loci. GWAMA summary statistics are from GIANT and UK Biobank (as presented in Ref. [6•], are available via https://zenodo.org/record/1251813#.XKMVaxNKiiB) and were analysed using MAGMA.

Figure 3



Gene candidate overlap among phenotypic measures of obesity.
Obesity is commonly defined as BMI>30 kg/m^2. However, BMI is agnostic for body shape. WHR is a suggested proxy for central adiposity and WHRadjBMI highlights regional adiposity that cannot be explained given the BMI. The genetic overlap between these three phenotypes and the measures of adiposity they are meant to represent is imperfect. This has often been attributed to differences in discovery power, due to the unavailability of true adiposity measures. Now with BIA in UK Biobank, segmental body fat phenotypes (BF% - body fat percentage, Leg% - leg fat percentage, Trunk% - trunk fat percentage) are available for more than 350,000 individuals, making the sample size comparable to the largest anthropometric GWAMAs (BMI, WHR, and WHRadjBMI conducted within the GIANT consortium), which currently include 700 000 individuals. Depicted, are the numbers of genes to which the associated loci map for each of the phenotypes. It is apparent that anthropometric phenotypes and BIA cluster separately. There is also a large number of BMI genes that do not overlap with any other phenotype. Anthropometric phenotype summary statistics are from the meta-analysis GIANT and UK Biobank (as presented in Ref. [6•], available via https://zenodo.org/record/1251813#.XKMVaxNKiiB). BIA summary statistics from UK Biobank were acquired via http://www.nealelab.is/uk-biobank. The mapping of variants to genes was done via http://fuma.ctglab.nl/ and does not represent individual loci.

association of these depot-specific fat signals with BMI and WHR, revealed no overt overlap, whereas most BMI or WHR loci appeared directionally consistent in their adiposity analyses. The lack of overlapping association signals across the distinct depots could reflect their unique biology or simply power limitations in the analysis (concept further explored in Figure 3). Chu *et al.* [26•] then followed up the four most promising novel loci by modelling the effects of their candidate gene deletion in mice, thereby, establishing a role for two of the genes in adipocyte differentiation [27].

Early this year the first GWAMA of DEXA derived phenotypes was published [24•], with a collective cohort size of 17 000 individuals, targetting discrete fat depots and assessing the effect of protein-coding variants on them. Neville *et al.* identified visceral fat gene-enriched variants that did not affect abdominal subcutaneous fat and that exerted an opposing effect on leg fat mass. They also identified variants that affect peripheral fat mass, without exhibiting any other effects on whole-body adiposity. This demonstrated the distinct genetic signatures of different depots.

In a recent study, Rask-Andersen *et al.* [27] conducted GWAS of segmental BIA on the participants of UK Biobank, focusing on the proportions of fat mass distributed between the general trunk, arm or leg areas. In doing so, they identified 98 independent loci, a third of which are novel. Rask-Andersen *et al.*, also observed strong sexual dimorphism among their signals, with most being more pronounced in females. The identified candidates were enriched for expression in mesenchymal and female reproductive tissues, highlighting a potential role for adipogenesis and sex hormones.

Such emerging more accurate fat distribution studies exhibit how using specific phenotypes leads to novel discoveries and mechanistic insights and pave the way for translatable findings.

Molecular mechanisms of obesity

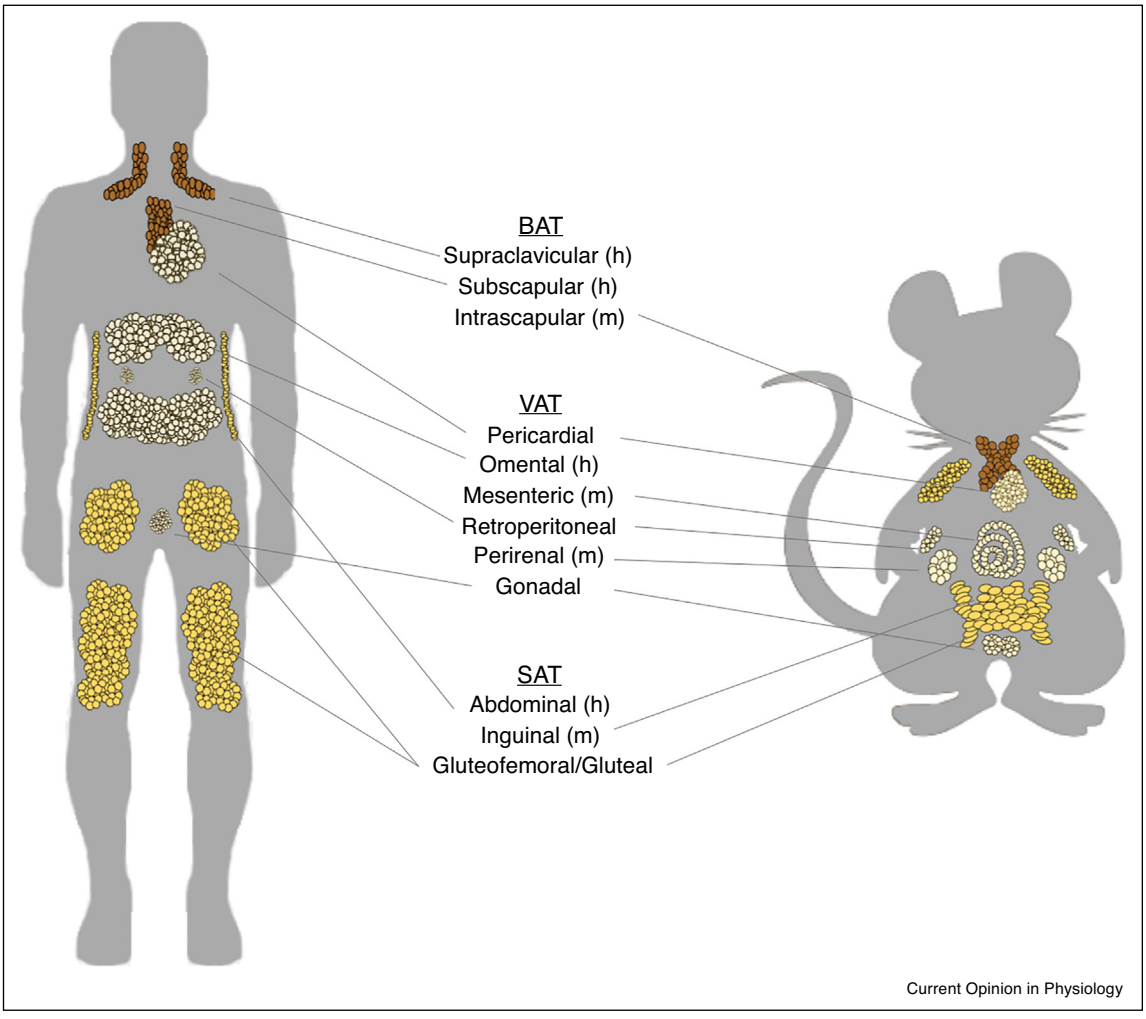
Fine mapping of GWAS candidates & *FTO*

More than 90% of GWAS signals are non-coding and fall within intronic and intergenic regions of the genome [28]. Thus, it has been difficult to ascertain their functional significance, in terms of gene regulation. Traditionally, GWAS candidate genes were assigned based on proximity to the signal. However, the most proximal gene is often not causal. An archetypal example of that is *FTO*, a BMI and fat mass candidate locus with the strongest association in GWAMAs [29].

The strongest *FTO* BMI signal lies within an intron of the *FTO* gene and early studies pursued the functional characterisation of this gene as the causal candidate [30]. Although supported by some *in vivo* evidence [31], humans with inactivating mutations in *FTO* exhibited no weight-related phenotype [32]. After many years and a battery of computational and functional approaches, there is now evidence that certain variants within the *FTO* interval of association with BMI affect the binding of distal enhancers of *IRX3* and *IRX5*, specifically in adipocytes [33••], while other variants are associated with changes in the expression of *RPGRIP1L*, specifically in neurons [34].

This example demonstrates the need for extensive fine–mapping of GWAS candidate loci, which has not yet happened for most association signals. Clearly, GWAS are only the first step to unravelling the mechanisms of

Figure 4



Rodents are a tractable mammalian model for human adipose anatomy.
Humans and mice are both multi fat-depot animals. They also exhibit strikingly similar anatomical distributions of brown adipose tissue (BAT; a thermogenic, calorie-burning, metabolically protective fat subtype activated by cold exposure), VAT and SAT. Both species have BAT depots around the scapular area, however rodent BAT mass is proportionally greater and more active, which must be carefully accounted for when extrapolating rodent studies to the human context. VAT depots are mostly located around and between the intra-abdominal organs. SAT is localised mainly on the lower halves of the body. Human and mouse outlines designed by Freepik (www.freepik.com) and modified for this work.

obesity. Following the identification of a robust signal, other approaches are needed to determine the candidate gene at the locus. One option is to use transethnic cohorts, as was the case for Chu *et al.* [26•], which simplified the genomic structures observed in the study and helped narrow down the region of interest. Further to that, chromatin conformation data (i.e. Hi-C) was used to determine whether the interval of association interacted with distal genomic elements (i.e. enhancers, promoters, etc.), therefore implicating the regulation of distinct genes [33••]. Expression quantitative trait loci (eQTL) data can also indicate regulatory effect of a variant on neighbouring genes and several tools have been developed to use such data in a GWAS-complimentary framework [35–38]. The next steps include gene manipulations of the fine-mapped candidates in model systems to test biological hypotheses on their causality for obesity or fat distribution.

Mouse models of obesity

Rodents have been invaluable *in vivo* models of many human diseases and are by far the most commonly used in terms of metabolic disease and the translation of scientific findings [39]. Translationally, rodents are an important model due to the anatomical similarities between mouse fat pads and human fat depots [40] (Figure 4). In general, human VAT loosely equates to the mesenteric, retroperitoneal, gonadal and perirenal pads, while SAT exists in two major mouse depots, one anterior and one posterior [41]. As understanding the genetic underpinnings of VAT and SAT distributions is pivotal, the use of a mammalian multi–depot organism is essential to increase relevance to human biology.

The *FTO* paradigm has shown that it is vital to build models that interrogate the effect of regulatory variants that can exert differential effects at different times and tissues during development. Doing so in cell lines would be impossible; model organisms are needed to observe holo-organismal and spatiotemporally restricted effects. However, functional conservation is a vital issue in translating non-coding mutations from one species to another. The ENCODE project has found approximately 70% of mouse regulatory elements (i.e. enhancers, promoters, transcription factor binding sites, and DNaseI hypersensitivity sites) have human homologues with at least 10% sequence similarity [42]. Importantly, regions occupied by transcription factors orthologous between the mouse and human genome are enriched for GWAS signals [43], suggesting regulatory domains near genes are highly conserved.

Altogether, a high level of conservation of biology between rodents and humans support their utility for modelling regulatory variants. The availability of readily validated and recently finessed cell-type specific and drug-inducible conditional transgenic approaches allow tissue and temporal specific hypothesis testing and permit highly relevant investigative tools for testing human candidate obesity genes.

Causal relationships between obesity and health

With the ever-increasing number of GWAS candidate loci, there has been a rise in efforts to disentangle the direct effects between obesity and its comorbidities. More specifically, Mendelian randomisation (MR) exploits the inherent properties of human genomic variation to make causal inferences between an exposure (i.e. obesity) and an outcome (i.e. CVD, T2D) and has been widely applied to test causality in the face of 'chicken or egg' confounders. Such approaches have recently shown that the observational effect of obesity on heart disease and metabolic disease in general, is, in fact, causal [44–46].

MR studies of GWAMAs of BMI and WHRadjBMI showed that the latter has a selective influence on the development of stroke, while both confer higher risk of CVD, T2D, and blood lipid and glycaemic traits [46]. Moreover, MR showed that the causal relationship between BMI and T2D is stronger in women and that WHR in men confers a higher risk of renal and also lung dysfunction, although the latter is potentially mediated via increased propensity to smoking [47].

Another recent study [22•] interrogated the genetic overlap between BMI, WHR, and WHRadjBMI, to better classify the associations into metabolically favourable or unfavourable adiposity and implicating relevant biological pathways that have never been highlighted in similarly-powered work. Expanding on favourable adiposity, genetic signals that seem to increase BF% and BMI, whilst lowering T2D or CVD risk, highlight the importance of SAT over VAT expansion [48].

Approaching this effect from a slightly different perspective, Lotta *et al.* [49••] reinforced the argument that excess VAT drives insulin resistance of the intra-abdominal organs, while also noting that the failure to preferentially expand gluteofemoral SAT also directly increases disease risk. They also noted that gluteofemoral SAT expansion inability is exhibited in patients with extreme lipodystrophies [50], drawing genetic links between common variation in body composition and monogenic disease [51].

Developing such efforts to include more cardiometabolically relevant phenotypes could potentially lead to promising preventative measures and treatments.

Concluding remarks

The past decade has seen an unparalleled bloom in genome-wide discovery efforts, including progressively bigger sample sizes, more detailed phenotyping and a wide variety of tools to computationally analyse these ever-increasing datasets. GWAS candidate obesity loci

have gone from tens [52] to over a thousand [6•,7•] in just a few years. Significant advances have been made in disentangling the anatomical components of obesity from its disease sequelae. Pinpointing causal genes within these candidate loci and explaining their effect on molecular metabolism is still lagging. With the upscaling of tools for functional assessment of variants will come further insights into causal mechanisms and pathways behind obesity. The next few years will see vast returns on the promise of human genetics, the unravelling of obesity biology and the identification of novel pharmacotherapeutic interventions.

Conflict of interest statement

Nothing declared.

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