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CORRESPONDENCE

Genetics and Epigenetics

GWAS for BMI: a treasure trove of fundamental insights into the genetic basis of obesity

J. R. Speakman[1,2] · R. J. F. Loos[3] · S. O'Rahilly[4] · J. N. Hirschhorn[5,6] · D. B. Allison[7]

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Summary

Muller et al. [1] have provided a strong critique of the Genome-Wide Association Studies (GWAS) of body-mass index (BMI), arguing that the GWAS approach for the study of BMI is flawed, and has provided us with few biological insights. They suggest that what is needed instead is a new start, involving GWAS for more complex energy balance related traits. In this invited counter-point, we highlight the substantial advances that have occurred in the obesity field, directly stimulated by the GWAS of BMI. We agree that GWAS for BMI is not perfect, but consider that the best route forward for additional discoveries will likely be to expand the search for common and rare variants linked to BMI and other easily obtained measures of obesity, rather than attempting to perform new, much smaller GWAS for energy balance traits that are complex and expensive to measure. For GWAS in general, we emphasise that the power from increasing the sample size of a crude but easily measured phenotype outweighs the benefits of better phenotyping.

In 2006, just before the first study that used GWAS for identification of BMI related variants was published, many researchers in the obesity field believed that we knew much about how body weight was regulated [2], and its genetic basis [3]. This confidence was born from the tremendous advances that had followed the discovery of leptin over a decade earlier [4]. In leptin, we had a candidate molecule that had all the required characteristics of a signal from body fat to the brain, consistent with a lipostatic control system [5, 6] as originally envisaged by Kennedy in the 1950's [7]. The pace of development of the field following the discovery of leptin was remarkable, and in short order, it was shown that leptin interacts with known neuropeptides in the hypothalamus that regulate food intake, such as NPY [8, 9] and the melanocortin system [10–12]. Further discoveries of novel peptides secreted by the alimentary tract [13, 14] seemed to make the picture complete. These gut derived hormones appeared principally to interact with centres in the brainstem to regulate short-term intake, while the longer term regulation in relation to body weight was orchestrated by the hypothalamus, and incoming signals reflecting adiposity, such as leptin and insulin [2, 15–17]. It was shown that there were humans with loss-of-function mutations in the leptin gene [18] and the leptin receptor gene [19] that had massively enhanced appetite and extreme obesity, from an early age. The proof of principle that these mutations were causal came from leptin repletion experiments, where the obesity caused by the loss-of-function mutations in the leptin gene could be completely reversed [20, 21]. Additional discoveries of genes underlying rare syndromes of monogenic obesity followed [22–26] and these genes were generally all located among the known elements of the standard model [27, 28]. Papers in special issues of Nature in 2000 and 2006 describing this lipostatic

✉ J. R. Speakman
J.Speakman@abdn.ac.uk

1 Institute of Genetics and Developmental Biology, Chinese Academy of Sciences, Beijing, China

2 Institute of Biological and Environmental Sciences, University of Aberdeen, Aberdeen, Scotland, UK

3 The Charles Bronfman Insititute for Personalized Medicine at Mount Sinai, Icahn School of Medicine at Mount Sinai, New York, NY, USA

4 Wellcome Trust-MRC Institute of Metabolic Science, Addenbrookes Treatment, Centre University of Cambridge, Cambridge CB2 OQQ, UK

5 Division of Endocrinology and Center for Basic and Translational Research, Boston Children's Hospital, Boston, MA, USA

6 Broad institute, Cambridge, MA, USA

7 School of Public Health, University of Indiana Bloomington, Bloomington, IN, USA

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model, and how the human genetic discoveries mapped into the pathway, have become classics in the field, some cited well over 3000 times [2, 3, 16, 29]. Hence, it seemed eminantly plausible that polygenic obesity—the type of obesity that underpins the genetic basis of obesity in the general population, would be due to subtler variants in the genome affecting the key players in the standard model.

Then came the first gene discovery from GWAS in 2007, and the bubble was burst. Frayling et al. [30] described a genetic variant in the first intron of a gene that virtually nobody in the obesity field had ever heard of, that had a major association with fat storage and the risk of obesity. The gene was *FTO*. In fact when it was discovered, FTO stood for 'Fused toes' from the gene's supposed phenotypic impact in mice, but the acronym was rapidly re-engineered to become the '**F**a**T**-mass and **O**besity-related' gene (for more details of the naming history, which is slightly more complex, see [31]). The FTO paper by Frayling et al. [30] has now been cited over 2000 times. The authors had found a common variant in the first intron of *FTO* by searching for genetic variants associated with diabetes using the GWAS approach, but showed that *FTO* had a significant association with the risk of diabetes only via its association with BMI. It is no exaggeration that this discovery is a prime example of one of Donald Rumsfeld's famous quotations. This was certainly one of the unknowns that we did not even know was unknown. The *FTO* gene variants are associated with differences in food intake [32–35] but not energy expenditure, and the gene encodes a 2-oxoglutarate dependent nucleic acid demethylase [36]. Work in mice confirmed the *Fto* gene may have functions related to energy balance [27, 37] and it may be an amino acid sensor linked to protein intake [38–40]. However, recent work suggests that the genetic variants, while located in the first intron of the *FTO* gene, may exert their effects via adjacent genes at the locus, such as IRX3 [41].

By 2010, we had 32 known genetic variants, close to, but seldom actually in the coding regions of genes, that were discovered by GWAS for BMI [42]. Some of these variants were located near to genes that would be anticipated to be important from the classic model—such as in *MC4R*, *POMC* and *BDNF*. However, many more of the variants were associated with genes that were not part of the standard model that had engrossed everyone in the early 2000s. Instead, they provided a diverse array of insights into how weight regulation is so much more complex than we had imagined it to be 10 years earlier. Several reviews have been published summarising the likely functional nature of FTO and the other main GWAS targets [31, 43] and the success of the GWAS approach to obesity genetics [44].

A couple of examples will suffice to demonstrate that GWAS has led us to completely novel genes, with unanticipated functions, that would likely remain undiscovered today without the GWAS approach. For instance, one of the genes identified in early GWAS of BMI was neuronal growth regulator 1 (NEGR1). This gene is highly expressed in the brain, particularly the hippocampus—a region not traditionally linked to food intake or energy balance regulation. Subsequently, however, it was shown to have high expression in arginine vasopressin and oxytocin expressing neurons in the hypothalamus. Knocking out the gene in mice resulted in an effect on the amount of lean tissue, with consequent impacts on energy expenditure [45]. Prior to GWAS for BMI we had no notion of the involvement of NEGR1 in regulation of energy expenditure. A second gene identified by GWAS linked to BMI was the neuronal cell adhesion molecule 2 (CADM2). Subsequent molecular work in mice has confirmed an important role for this gene in body-weight regulation [46, 47], which again would not have been anticipated without the GWAS for BMI. Finally, a more recent GWAS identified locus was the gene adenylate cyclase 3 (ADCY3). Subsequent association studies have identified functional variants in this gene in humans that lead to increased risk of both obesity and type 2 diabetes [48, 49]. This gene is localised in expression to the primary neuronal cilia [50] where it co-localises with the melanocortin 4 receptor (MC4R). Some of the MC4R mutations that lead to obesity impair the localisation of MC4R to the cilia, while impairment of ADCY3 signalling in the cilia also leads to increased body weight. This involvement of cilia in weight control has derived from our identification of targets from GWAS studies. These discoveries stemming from GWAS identification of NEGR1, CADM2 and ADCY3 provide a window into how GWAS for BMI can facilitate novel discoveries in both previously known, and unknown, pathways linked to obesity.

By 2016, the number of obesity genes discovered by GWAS had expanded to 112 [51] and last year by performing GWAS for BMI in different populations this expanded to more than 200 [52]. So, what is the basis for alleging that GWAS has not been useful? Muller et al. [1] make some quite valid points, but others that we feel are less cogent, and appear to have largely misconstrued the goals of GWAS, and the factors that determine the success of this approach. Before we address their argument, it is worthwhile briefly summarising the GWAS approach, some of its goals, and the factors that determine the success in achieving these goals. For a more detailed consideration of these topics, we refer readers to recent excellent reviews [53, 54].

First, a key goal of GWAS is to provide an unbiased and comprehensive search for causal biology. GWAS is not an end point, but the start of a process. The associated variants identify loci, but often do not point directly to the causal variant or gene at the locus (as illustrated by the *FTO* example mentioned above), nor do they explain the biology

of the genes in the locus—all of which requires additional work. GWAS provides the initial clues that would not otherwise be available. One way to think about it is that GWAS identifies flags along the genome that indicate something nearby may be important.

Second, much of the heritable contribution to polygenic traits such as measures of obesity are due to common variation [55, 56]. Because common variation has avoided negative selection through evolutionary pressure (as evidenced by the fact that it is common), the variants discovered by GWAS almost certainly represent small tweaks to biological pathways, and the effects of stronger perturbations to the pathway (either genetic or pharmacological) could easily have much larger and clinically significant effects. This is exemplified by common variation at *HMGCR* that has quite small effects on LDL-cholesterol levels but nonetheless points to a useful drug target for statins (which have much bigger effects than the common variation). Similarly, rare and common variants can coexist at the same gene (such as *MC4R*) and can have very different effect sizes, so the fact that a common variant has a modest effect size does not speak to the biological importance of the gene where it resides. Rare variants, especially rare coding variants, can be valuable discoveries to complement GWAS. This value comes not from variance explained (which, in most populations is small because of the low allele frequency), but rather from the large impact on biological pathways, making them useful experimental tools, and the fact that coding variants can point specifically to the correct gene.

Third, most quantitative traits and common diseases appear to be highly polygenic, meaning that, with occasional exceptions, no individual locus will explain a large fraction of heritable variation. The power for discovery depends on the underlying genetic architecture, but the field's collective experience with hundreds of diseases and traits suggests that sample sizes of tens of thousands are nearly always required to make even a handful of discoveries but that, after these initial discoveries, the number of new loci tends to increase linearly or even more rapidly with increasing sample size [57]. The key point that we shall return to later is that sample size is the main determinant to making discoveries in GWAS.

Returning to the arguments of Muller et al. [1], they highlight the small amount of variation explained by GWAS of BMI that have been completed to date. It is true that despite these spectacular advances in discovery of novel associated genes to BMI, and new insights into biology, the genes identified by GWAS together explain only 3–4% of the total variation in adiposity. Yet, we know that the variation in BMI explained by genetics is around 50–75%, averaging around 65% [58, 59]. So, one might argue (as they do) that the advance is actually rather modest. Locke et al. [51] modelled the likely expansion in the explained variation as more and more genes are added to the list, and concluded that maximally 30% of the variation might be tracked down to common variants.

Ultimately, with enough samples, we will end up with thousands of common variants associated with obesity (likely concentrated in many fewer loci, as many loci will have multiple signals of association) [53, 54]. Each variant will explain just a few grams difference in body weight. This is actually how the great geneticist Fisher envisaged polygenic traits being influenced by genetics in his 'infinitesimal model'. Although these variants, in aggregate, may have some predictive power that could be clinically important at some future time, it is important to reiterate that the goal of GWAS is not solely to provide predictive power, but mainly to provide a comprehensive, unbiased approach to point out relevant, targetable biology. Moreover, it is worth remembering that low explained variance may not necessarily imply an absence of clinical utility. There are scenarios where despite low variance explained there may be sufficient predictability to more effectively schedule patients into costly procedures. For example, theoretical simulations have shown that using whole genome sequencing to predict weight loss following bariatric surgery could be useful in targetting surgery where it will be most effective, even if the explained variance in the trait is only modest [60].

Perhaps then one of the greatest insights from GWAS is not the individual genes but the overall picture of where these genes act. In the context of BMI, for example, it is clear that the bulk of discovered genes thus far are mostly centrally (in the brain) rather than peripherally acting e.g. [61].

Why has GWAS seemed to be so slow, then, at discovering the variants that cause the majority of the variation in body fatness (2% discovered vs 30% that should be discoverable by GWAS)? Muller et al. [1] present what they consider is the main reason, and advance what they suggest is the way to get over this issue. We disagree with that interpretation, and suggest here an alternative explanation and way forwards. Despite the fact that GWAS of BMI have yielded more associations (c. 200) than for most other human polygenic traits and diseases, Muller et al. [1] suggest the main reason why GWAS for BMI has provided so little insight into the obesity problem is principally because BMI is an extremely poor measure of obesity. Not only that, but obesity—they suggest—is itself a complex outcome of energy imbalance, which is dominated by the complex traits of food intake and the multiple components of energy expenditure, plus their interactions. We cannot possibly hope they argue to capture this complexity by measuring someone's weight and height, and dividing one by the other squared. Therefore, the whole GWAS for BMI approach

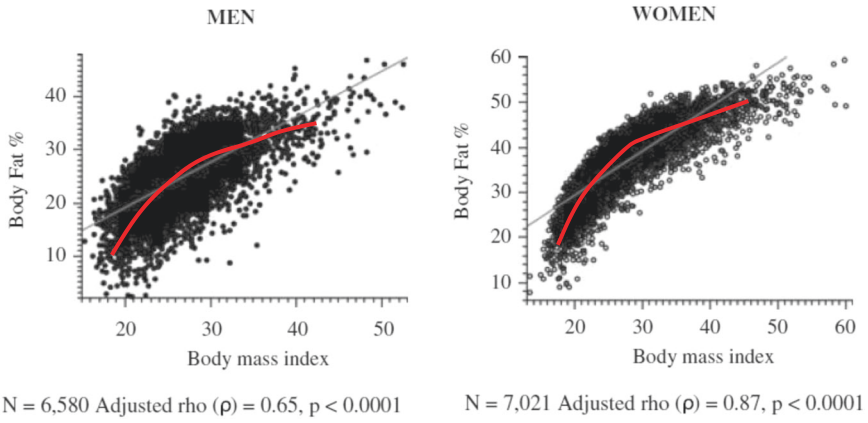

Fig. 1 Body-mass index in relation to the level of body fat measured by DXA. Data generated in NHANES and published by Romero-Corral et al. (2008). Two things are clear form this picture. **a** at any given level of BMI the level of body fatness varies enormously. Yet (**b**) the average population level of body fatness (in red) tracks the level of BMI closely (if not via a linear model)

has led us down a garden path to almost nowhere. If this is the case, then why not just replace BMI with a more accurate measure of adiposity? Instead, they argue, what we need are actually GWAS studies of the complex energy balance traits themselves. Their viewpoint is that only by dramatically enhancing the phenotype that we are trying to explain, do we stand any chance of understanding the genetic basis of obesity. It is an articulate and well made argument that, nevertheless, we think has flaws.

Nobody will argue with the suggestion that BMI can be a poor measure of adiposity at the individual level. There are countless individual examples that show the fallacy of using BMI to indicate how fat someone is. In particular, individuals with very high muscularity may have very low body fat, yet their BMIs place them among the obese category. An Internet favourite is the actor Arnold Schwartznegger, who when he was a competing Mr Universe entrant, had a BMI above 30, but less than 10% body fat. Single examples are interesting anecdotes, but do not make a good scientific case, because most people in a typical cohort are not Mr. Universe competitors: the vast majority of people with a high BMI actually have obesity. It is true that comparison of adiposity measured by dual-energy x-ray absorptiometry (DXA) and BMI (Fig. 1) in over 13,000 individuals involved in NHANES showed that for example a man with a BMI of 25 might have a body fatness anywhere between 10 and 35% [62]. It is a mistake, however, to equate these individual discrepancies with the use of BMI in GWAS. In GWAS, we are attempting to link genetic polymorphisms to adiposity at the population level–not the individual level. So, the issue is not how poor BMI might be as a measure of adiposity for any given individual, but how good it is on average–and the answer is pretty good. The average levels of body fatness rise consistently with the BMI (red lines in Fig. 1), hence at the population level BMI gives a fair reflection of adiposity. With large enough samples, the noise added by poor individual correspondence of BMI to actual adiposity is more than overcome by increased power.

The problem with their suggestion is that the success of GWAS for any polygenic trait, including BMI, or other measure of adiposity, depends on the number of variants contributing to the trait, the heritability explained by common variation and, most critically, the sample size. Thus, even if we could measure adiposity accurately or engage in complex phenotyping of weight loss/gain phenotypes, that would not be enough to achieve more discoveries relevant to obesity unless we could achieve sample sizes comparable to those readily available for BMI (currently in the millions). In fact, their proposed approach has been tried with many alternative measures of obesity, and most of the discoveries emerging from these refined phenotypes were also discoverable by the much larger studies of BMI [63, 64].

We suggest that this is why, when people follow up SNPs derived from GWAS from BMI in smaller populations, but using more accurate methods such as DXA or CT scanning, they generally find evidence that these SNPs do play a role in adiposity. If the individual discrepancies of BMI to adiposity were important, this might not happen. Validation studies using more accurate methods would show the BMI derived genes from GWAS to have no effect. They seldom do. Most critically, BMI has a major advantage for such association studies, where power is the limiting factor for discovery, and that is it is cheap to measure (and hence, routinely measured). It is easily possible to measure the BMI of a hundred subjects in a single day with the cost only of paying a technician who has had a few hours of training, and a room for them to do it. Even traits where the measurement lasts less than an hour (e.g. resting metabolic rate), but depends on sophisticated equipment, accumulating sufficient samples to perform GWAS involves a mammoth effort and yet routinely achieves relatively modest sample sizes compared with the sample for BMI. We may contrast this with the more sophisticated measures proposed by Muller et al. [1] as phenotypes that should be adopted for future GWAS studies. In particular, they focus on weight change phenotypes, that may be separated into weight loss and weight gain components that would not

necessarily be symmetrical. Hence, subjects would need to be exposed to carefully controlled dietary manipulations, which are generally only possible in a residential setting, linked to sophisticated quantification of changes in their body composition (both lean and fat compartments) over the time course of the intervention. A single measurement might take weeks to complete. The costs and impositions of such phenotyping mean that it will only be possible to maximally accumulate a few thousand suitably characterised individuals. Such a small sample is highly unlikely to provide any positive hits in a GWAS protocol because the power obtained by increased complexity and accuracy of phenotyping is much less than the power afforded by increased sample size. When it comes to GWAS, sample size is the limiting factor on discovery. Since phenotypic complexity limits attainable sample size, the traits envisaged by Muller et al. [1] are unlikely to yield many (if any) useful hits.

There are two additional issues. The first is that decomposing 'obesity' into components of energy balance may not necessarily throw up hits that have useful functionality with respect to obesity. This is because variations in the components of energy balance do not necessarily feed directly into variation in susceptibility to obesity, as they interact in complex ways [65]. For example, there have been many studies that have aimed to diagnose the genetic basis of physical activity (reviewed in [66]). Physical activity is obviously a component of energy balance that is potentially linked to energy expenditure and thereby obesity. Yet, very few of the genetic variants that are linked to physical activity are also linked to BMI. Hence, the insights from these studies into the aetiology of obesity is relatively small. Moreover, a fundamental assumption of GWAS is that the traits in question have a genetic basis to start with. This is a reasonable assumption because almost all traits that have been examined do have some heritability, including traits that one might not immediately imagine would have a genetic contribution, such as political conservatism [67] and religiosity [68]. A salient question, however, is how much do genetic factors contribute to the observed variability in a given trait. For most of the traits proposed by Muller et al. [1], we do not know if they are highly heritable or not (but see Bouchard et al. [69] for an exception). This is a serious problem because we may embark down a path of GWAS discovery for an expensive phenotypic trait that has only a very small genetic contribution to be discovered. Another major advantage then of BMI is that all the heritability estimates for ‚obesity‘ were actually originally performed using BMI as the trait [58, 70–72]. We know it is heritable, we know that the genetic variation in the trait is relatively high, and hence we also know there are lots of things to be discovered. For the traits proposed by Muller et al. [1] this knowledge of the magnitude of heritability is lacking. Hence, when the first GWAS rolls in with no hits, we will not know if that is because there is an insufficient sample of characterised individuals to deliver the required power, and simply more effort is needed—or if this is a trait for which there is only low heritability and few genetic variants to be found at any sample size.

We do not wish to underplay the enormous task that GWAS throws up in trying to understand the biological basis of the identified polymorphisms. Understanding how these individual variants translate into biology is likely a decades long task. This is particularly so when the variants are non-coding. This appears to be the case even when the SNP is intronic and one would imagine it has an effect in the gene where it is located e.g. *FTO* [41]. Progress is likely to be much more rapid when analysis focuses on coding variants via exome sequencing, and loss-of-function mutations, than when the SNP is located in a non-coding region [73]. Recent effort has therefore tended to focus much more into such coding variants (e.g. sequencing by the UK Biobank of more than 100,000 individuals). However, that is not a problem unique to GWAS for BMI. It will be a problem also for GWAS of the more complex traits proposed by Muller et al. [1].

How should we advance? A key issue highlighted by Muller et al. [1] is to understand why the common variants likely explain a limited percentage of the total genetic variance evaluated from classical heritability studies. This problem may be overstated [56], since the amount of unexplained variation is likely small for many polygenic traits. However, BMI is somewhat an outlier in this respect. We suggest this is not due to the poor BMI phenotype. Instead, the reason may be that as human populations fragmented after leaving Africa, local populations became isolated, and important mutations happened in relatively small groups. These might have been maintained by selection or possibly by drift [33, 74]. What this means is that what remaining unexplained variation there is may actually reside in variants that are rare, when examined at the global population level, and hence never rise to significance at in a GWAS, but are more common in small populations (for general arguments on relative contributions of rare and common variants see 55). An example is a recent study of the Samoan population [75]. This work showed that a genetic variant adjacent to the the CREB/RF gene, which is rare in the general global population occurs in 45% of Samoans can explain alone about 2% of the variation in obesity in this population. A single 'rare variant' mutation that explains as much as each of the common variants thus identified combined.

This potential role of rare variants filling the gap between known heritability and the variance explained by common variants identified by GWAS is supported by a recent

association study using exome sequencing, which showed that 14 rare variants have large effects on adiposity, including one rare variant, which had a 7 kg impact on body weight [73]. These variants were identified using an exome genotyping chip. Unfortunately, to reliably detect non-coding rare variants requires sequencing to about 30-fold depth, which is currently prohibitively expensive, and hence why the approach at the moment has been to use exome genotyping. Of course, one might argue that if 30-fold sequencing depth costs as much as complex phenotyping, then why is this any better an approach. The answer is that while the costs of sequencing follow Moore's law, the costs of complex phenotyping follow the retail price index. Hence, what we dream to do in genomics today, is tomorrow's reality. In contrast, complex phenotyping is always an expensive dream. Interestingly the rare variant explaining 7 kg differences in body weight from exome sequencing is in *MC4R* [73], and 2 other variants from the same study were in *GIPR* both of which were important players in the original standard model [3]. So things may eventually come full circle, and it may be that these rare variants reside predominantly in the standard model components, as most people originally expected them to 10 years ago.

In conclusion, GWAS for BMI is not a broken paradigm, but a treasure trove of biological discovery that has served us well. It is not perfect, but has many advantages over alternative suggested approaches. We demur from the suggestion that it needs a 'reboot'.

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