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The case of GWAS of obesity: does body weight control play by the rules?

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Abstract

As yet, genome-wide association studies (GWAS) have not added much to our understanding of the mechanisms of body weight control and of the etiology of obesity. This shortcoming is widely attributed to the complexity of the issues. The appeal of this explanation notwithstanding, we surmise that (i) an oversimplification of the phenotype (namely by the use of crude anthropometric traits) and (ii) a lack of sound concepts of body weight control and, thus, a lack of a clear research focus have impeded better insights most. The idea of searching for polygenetic mechanisms underlying common forms of obesity was born out of the impressive findings made for monogenetic forms of extreme obesity. In the case of common obesity, however, observational studies on normal weight and overweight subjects never provided any strong evidence for a tight internal control of body weight. In addition, empirical studies of weight changes in normal weight and overweight subjects revealed an intra-individual variance that was similar to inter-individual variance suggesting the absence of tight control of body weight. Not least, this lack of coerciveness is reflected by the present obesity epidemic. Finally, data on detailed body composition highlight that body weight is too heterogeneous a phenotype to be controlled as a single entity. In summary GWAS of obesity using crude anthropometric traits have likely been misled by popular heritability estimates that may have been inflated in the first place. To facilitate more robust and useful insights into the mechanisms of internal control of human body weight and, consequently, the genetic basis of obesity, we argue in favor of a broad discussion between scientists from the areas of integrative physiologic and of genomics. This discussion should aim at better conceived studies employing biologically more meaningful phenotypes based on *in depth* body composition analysis. To advance the scientific community—including the editors of our top journals—needs a re-launch of future GWAS of obesity.

Introduction

Genome-wide association studies (GWAS) of obesity have been undertaken with the goal to identify human obesity genes, that would in turn unravel the internal biological causes of obesity and its associated co-morbidities. Moreover it was hoped that variants in these genes would also allow an early identification of susceptible individuals, thereby facilitating personalized prevention and treatment of obesity. Until today GWAS have identified 115 genetic loci where sequence variation is statitistically associated with the body mass index (BMI) at the population level [1]. Taken together however these associations explain only 2–3% of the variation in adult BMI. Moreover, longitudinally no significant associations were found between any lead single nucleotide polymorphisms (SNPs) from the respective genome regions and weight changes suggesting that these SNPs were not involved in body weight control

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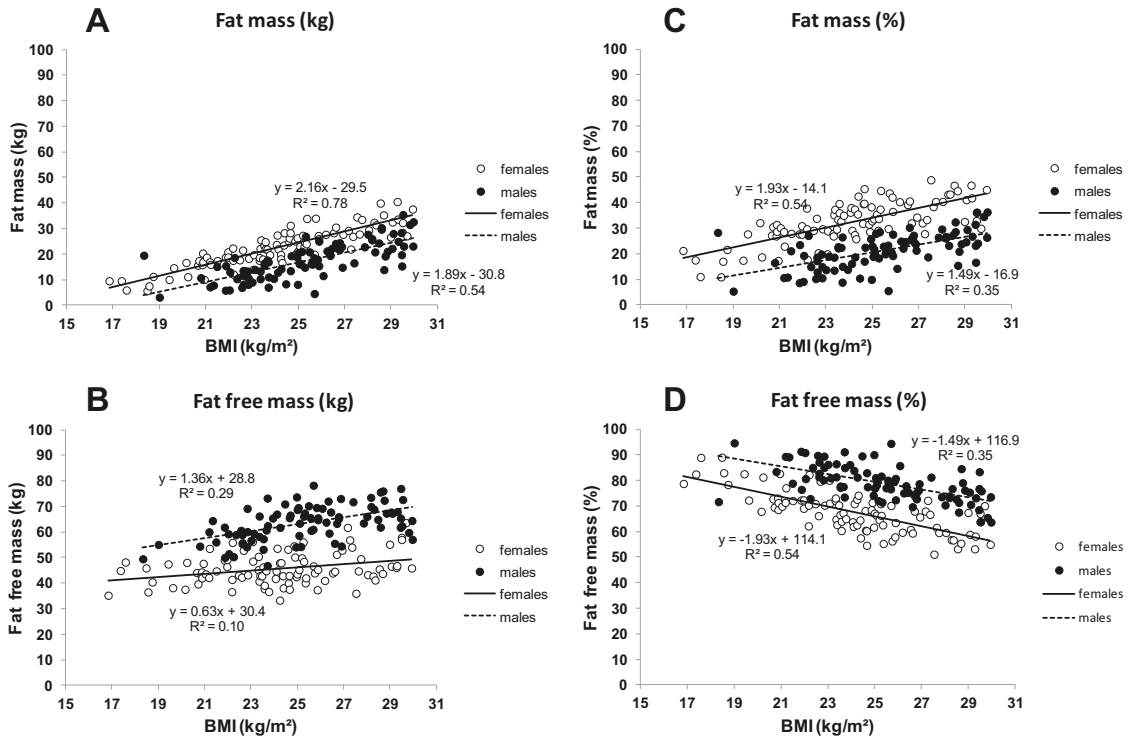

Fig. 1 Sex-differences in the associations between BMI and fat mass (**a** in kg, **c** in % body weight) and fat-free mass (**b** in kg, **d** in percentage body weight). Data are shown for 180 healthy adults at a mean age of 42.7 ± 15.5 years (93 females and 87 males) and a mean BMI of 24.8 ± 2.99 kg/m^2. Obese subjects were excluded from the analysis. Significant sex-differences in between the *r*-values were observed for all regeressions shown ($p < 0.05$). In addition the slope of regression lines for BMI and FFM were significantly different between males and females. For original data and more details of the protocol see ref. 17

[2]. These results and the low level of variance-explained clearly call into question the clinical relevance of GWAS-identified obesity genes.

GWAS of BMI alone are unlikely to provide much information because BMI is merely a crude surrogate measure of nutritional status. The concept of BMI dates back to a period of underdeveloped scientific methodologies and simplistic theories [3–5]. Some GWAS have tried to overcome this inadequacy of the BMI by including other commonly available anthropometric traits, such as waist circumference (WC), hip circumference (HC), waist-to-hip- (WC/HC-) ratio or height [6–8] and by analyzing these traits in both univariate and multivariate fashion. There are also some of the first genetic studies of body composition traits such as percentage FM, visceral adipose tissue (VAT) and lean body mass (LBM; [9–12]) that identified some novel genetic associations. However, the percent variance explained by SNPs was still low (e.g., 0.16% for LBM, [12]) and only few of the SNPs previously linked to BMI were also found to be associated with body fatness [11].

The vast majority of the gene variants related to BMI and obesity have neither established biological relevance nor have they shown clinical relevance for obesity treatment and prevention. They have also failed to explain genetic heritability of obesity. The many BMI-associated SNP alleles have relatively small effect size, both individually and in total [13]. The fat mass (FM) and obesity related (*FTO*) gene has the strongest genetic association with obesity but even for the lead SNP in this gene, the median per-allele effect on BMI is as low as 0.36 kg/m^2 (for a review see [14]). FTO was also found to associate both with FM and LBM [14]. Moreover, while the impact of the *FTO* gene seems to increase upon fat and protein intake, physical activity has been shown to have the opposite effect [15].

Contrary to prior expectations GWAS have not yet facilitated the identification of individuals at risk of becoming obese before they gained weight [13]. This realization suggests that genetic epidemiology may be inherently unlikely to help to prevent obesity. Along the same vein, because the functional link between BMI and associated SNPs is mostly unknown GWAS also did not unravel biological control mechanisms of energy balance. In response to this failing GWAS have been extended so as to draw upon next generation sequencing efforts (e.g., investigating extremely obese subjects) and alternative study designs (e.g., by involving other phenotypic traits like eating behavior, physical activity, and sedentary behavior) but to little effect.

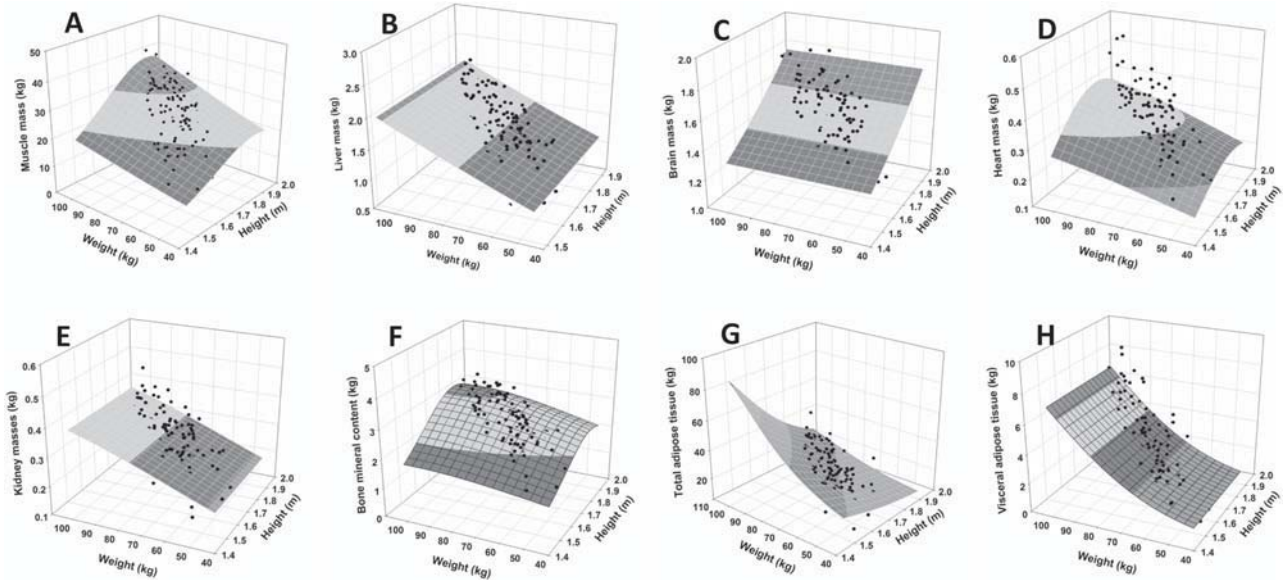

Fig. 2 Three dimensional data interpolation of masses of skeletal muscle (**a**), liver (**b**), brain (**c**), heart (**d**), kidneys (**e**), bone (**f**), whole body adipose tissue (**g**), and visceral adipose tissue (**h**) as a function of height and weight. For details of the calculations see ref. 16. Organ and tissue masses were measured by whole body magnetic resonance imaging (MRI) with a 1.5 T scanner (Magnetom Vision Siemens, Erlangen, Germany). Cross-sectional organ and tissue areas were determined manually using a segmentation software (SliceOmatic, version 4.3, TomoVision Inc. Montreal, Canada). For further details of the method and the study population see legend of Fig. 1

We surmise that the discouraging performance of GWAS of obesity in the past is not only due to the frequently invoked complexity of human body weight control. Instead, it seems likely that the limited outcome of GWAS resulted from an oversimplification of both, the investigated phenotype and the concepts of its biological basis. In 1995, a group of leading obesity experts recommended the use in genetic studies of phenotypes based upon body composition, metabolism, and ingestive behavior [16]. However, up to now none of this advice have been taken on board. Instead the powerful tools of modern molecular biology have been applied to crudes of measurements whereas modern concepts of body composition and its control were largely ignored. The following comments here are an attempt to stimulate a new debate about how GWAS of obesity can be improved—to the benefits of both, future scientific research and patient care.

Limitations of anthropometric traits as targets of GWAS

BMI and the likes are not biological phenotypes

Anthropometric measures such as BMI and WC have practical value in clinical settings where they are used for risk assessment and patient stratification [3–5]. Physicians must think and decide pragmatically and/or by convention (i.e., based on guidelines) which led them and not biology to define BMI, WC, HC, and WC/HC-ratio. Taking these anthropometric measures for biological entities has been misleading in the first place. The BMI for example is merely a numerical score that is calculated from two other numerical measurements, body weight and height, and therefore has no biological meaning per se [3–5]. The same holds true for WC, HC, and the WC/HC-ratio. Thus, GWAS for commonly available anthropometric traits have been investigating the genetic basis of a 'non-biological' phenotype. This is an odd practice; strictly speaking, none of these simple anthropometric traits can be used as quantitave outcomes in genomic research.

What is more, body weight and thus BMI are composites, they integrate body components such as FM, and fat-free mass (FFM) as well as individual organs, tissues and elements of differing masses and opposing course. Owing to the consequent inter-individual variance and sex-dependence of the associations between the BMI and different body components (e.g., FM and FFM, see Fig. 1), BMI, cannot be a measure of body composition. In summary, BMI and similar anthropometric traits are not 'biological' phenotypes and may therefore be of little value in genetic studies of obesity.

What is body shape?

In multivariate analyses of anthropometric traits one should be aware that BMI, WC, and HC are highly correlated [17]. Recently, a GWAS of obesity, tried to address these interdependencies by way of principal component analysis

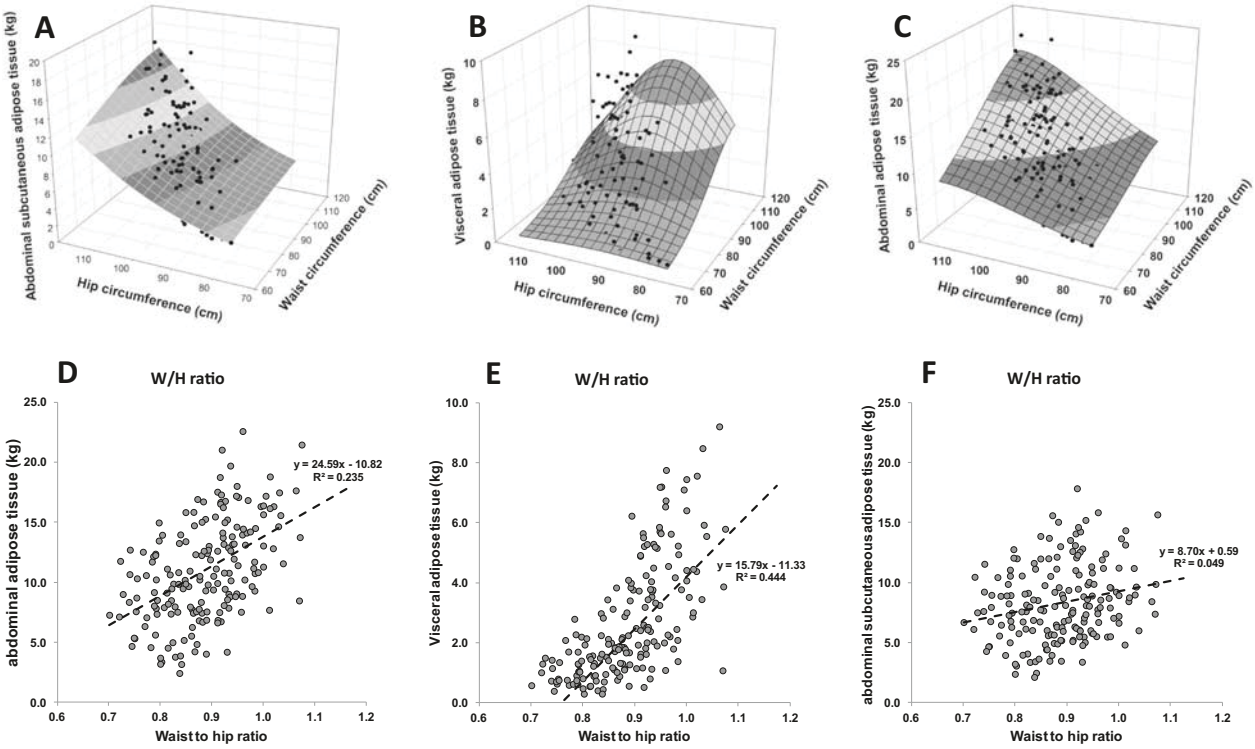

Fig. 3 Three (ABC) and two (DEF) dimensional data interpolation of masses of abdominal subcutaneous adipose tissue (**a**, **d**), visceral adipose tissue (**b**, **e**), and the sum of abdominal subcutaneous adipose tissue plus visceral adipose tissue (**c**, **f**) as a function of either waist and hip circumferences or the ratio between waist to hip circumferences = w/h-ratio. For further details of the method and the study population see legend of Figs. 1 and 2

(PCA) transforming multiple correlated traits into uncorrelated albeit abstract anthropometric parameters that were claimed to define body shape [6]. Such indices of body shape have been proposed before including BMI [18], body adiposity index [19], a body shape index [20], body roundness [21], waist/hip circumference [22, 23], height^3/waist circumference^3 [24], waist circumference/height, among others. These measures were not only found to be correlated and overlapping [21, 24] but varied widely in terms of their relationship to chronic diseases [23–27]. The utility of PCA-derived body shape parameters still remains to be determined, but it is evident that single numerical measures are rather crude substitutes of something as complex as body shape. We suspect that they will therefore be as ineffective in biomedical research as classical anthropometric traits and will be particularly inferior to the advanced imaging-based phenotyping systems that are currently being introduced in clinical and research settings [25].

Organ and tissue masses vs weight and height

Using three dimensional data interpolation of (i) weight, height, and masses of organ and tissues and (ii) WC, HC, and abdominal subcutaneous adipose tissue (aSAT) or VAT, revealed considerable variations in terms of the underlying statistical associations (Figs. 2 and 3; [17]). Different organ and tissue masses scale differently as body weight and height (e.g., VAT scales as body weight only whereas skeletal muscle scales as both height and weight; Fig. 2). The same applies to the relationship between aSAT and VAT on the one hand and WC and HC on the other (Fig. 3). These differences highlight further the very limited value of simple anthropometric traits as measures of body composition. Similarly body shape appears to be rather loosely associated with body composition too, in that it was found to improve predictions of percentage body fat and VAT only slightly, compared to BMI, WC, and HC [21].

In summary the use of anthropometric traits as surrogate phenotypes in GWAS of obesity can be justified only by the fact that these traits are easily available, inexpensive, and non-invasive. From a scientific point of view however such opportunistic arguments are not valid because of the 'non-biological' nature of the traits in question implies that their genetic analysis may have been inherently in vain.

What is body weight control about?

At present, GWAS are on genetics of the BMI or genetics of obesity, i.e., a BMI > 30 kg/m^2. This idea follows the

historical heritability estimates of BMI obtained in either twin or family or adoption studies (see below). From a physiological point of view the concept of genetics of BMI is not sound, because the genetic basis relates to control of body weight rather than a 'fixed' weight. From a physiological point of view it does not make much sense to look for GWAS of a static state unless one assumes that the subjects are at their *set point* at the time of assessment. Then, the random BMI may reflect the *set point*. However, in population studies this idea is speculative. In addition the concept of a *set point* is under debate (see below). However if we assume that a *set point* exists it is likely that random BMI data measured in population studies vary around the individual *set points* and are affected by recent weight changes. We feel that we should address the genetic basis of control of body weight rather than the genetics of the BMI.

The concept of body weight control

The concept of body weight control originated from experimental observation of changes in appetite and weight that resulted from hypothalamic lesions in rats (for overviews see [28, 29]). The concept has remained virtually unchanged until today. When it comes to understanding the genetic basis of obesity however, we think that a more sophisticated concept of body weight control is required. More specifically, it has to be agreed what is controlled and when this control occurs. Does body weight control mean control (i) of the static masses of individual organs and tissues (which add up to body weight) or (ii) of their interrelationships or (iii) of their concerted changes when body weight changes? Moreover distinct concepts apply to body weight control related to growth, puberty, pregnancy, and lactation.

A weight-change phenotype

A control of body weight can become apparent only in the context of weight changes whereas a stable body weight reflects adaptation say to lifestyle or environmental conditions but not control [28]. This implies that future GWAS of obesity should focus on what may called a 'weight change phenotype'. Moreover, if any, then body weight control is probably asymmetric [29, 30], so that it must be distinguished between a 'weight loss phenotype' and a 'weight gain phenotype' even though the current evidence suggests that the latter does not exist in humans [30]. As yet only one study [2] has addressed the associations between genetic variation and weight loss and subsequent regain. Although some gene-lifestyle interactions were found, the observed effect sizes were not considered clinically relevant.

A body composition phenotype

Body weight comprises many different organs and tissue masses. This underlying heterogeneity puts into question the general idea that body weight as a single entity is under stringent internal control. As far as GWAS are concerned it appears more appropriate to define and use a 'body composition phenotype'. However it would be too simplistic to replace anthropometric traits such as BMI by single body components such as FM or FFM or even specific organ and tissue masses (such as skeletal muscle, brain, liver or VAT). Although each component and its changes are related to specific metabolic functions (e.g., FFM is closely related to resting energy expenditure, REE; [17, 31]), no single body composition trait or its change will strongly reflect metabolic and physical functioning or the presence of cardio-metabolic risk factors. Thus notwithstanding individual body components are much more closely connected in biological processes. Therefore these relationships are likely more useful to address than anthropometric measures of obesity.

Correlation between different masses

Since the individual organs and tissue masses are strongly correlated with one another and again differently correlated with weight and height (except for brain;17), GWAS for single body components are still unlikely to unravel much of the genetic basis of obesity. Instead of assessing such individual masses, GWAS on obesity should therefore involve weight change-associated changes in body composition (i.e., the individual components and their relationships). This is because a change in one component of the body (such as FM) is usually accompanied by a change in other components (e.g., FFM). There is evidence that control is about the association between masses and volumes rather than about masses and volumes themselves [32–37].

What is a suitable phenotype to be studied in future GWAS for obesity?

Should we address changes in FM and FMM?

A high FM is not the cause of obesity but its consequence. Therefore FFM is just as important for understanding obesity (and its genetic basis) as FM. Moreover individual body components including FM and FFM not only change differently with weight changes but also impact differently upon body weight-related changes in neuro-endocrinology, metabolism, and cardio-metabolic risks [37].

Changes in FM and FFM with weight change impact upon and are both reflected by the 'p-ratio' a parameter

originally defined to address a classical issue in nutritional science [30] namely energy partitioning. The 'p-ratio' equals the fraction of energy mobilized during starvation or energy gained during re-feeding in the form of protein, it characterizes a 'body component unit' (i.e., body energy and protein are closely inter-related; [36, 37]). During starvation, both, initial FM and the protein compartment that can be used as energy reserve jointly determine the inter-individual variation in protein sparing and thus the 'p-ratio' [33]. As yet, the genetic factors underlying this variability and/or linking the two energy reserves together are unknown so that the 'p-ratio' would provide a phenotype worthwhile to study in future GWAS of obesity. Moreover, since body composition and its changes relate to many other outcomes like energy expenditure (EE), energy intake (EI), glucose tolerance, protein synthesis, physical performance, and disease risks unraveling the genetic basis of the 'p-ratio' would have far reaching consequences for a more general understanding of metabolism-related disease and health.

Energy partitioning with weight change is not only related to the major body components, FM and FFM. Functional 'body composition units' are also obvious for other organ-tissue masses-inter-relationships, for example with respect to associations between the liver mass and VAT and/or skeletal muscle and bone mass [36, 37]. Each body component has its own internal control. For example total body water is regulated by hormones including anti-diuretic hormone (ADH) and aldosterone and by kidney function; body fat is influenced by the appetite control system with leptin as a possible feedback control signal; bone mineral content is regulated by osteocalcin, parathormone, and vitamin D; muscle mass is controlled by anabolic factors such as insulin, insulin-like growth factor 1, and testosterone. Since organ and tissue masses are also interrelated by multiple cross-talks, the latter add to body weight control as well. All these different 'body component units' suggest that body weight is too heterogenous to be regulated as a single entity.

Is an adipocentric view sufficient?

During the last 20 years, research on body weight control focused mainly on the feedback loop between FM and the hypothalamic melanocortin neuronal system brought about by leptin [29]. However, since FM accounts for only 10–40% of body weight, regulation of FM can only represent a similarly sized part of the body weight control. Furthermore, a FM-related body weight control system could hardly explain overeating in overweight subjects; by contrast leptin is considered as a 'starvation hormone' counteracting a negative energy balance and weight loss only [38]. Finally the temporal complexity of weight changes (i.e., from minutes to hours dependent on acute changes in plasma hormones and metabolites; from hours to days dependent on hepatic glycogen stores; from days to weeks and probably months dependent on fat stores and body protein) argues in favor of the action of different control systems too. Obviously this multifacetness cannot be reflected appropriately by the 'genetics' of the BMI.

What is the evidence for a genetic control of human body weight?

As yet 19 syndromic monogenetic obesities have been elucidated [39]. These diseases have a beautiful simplicity about a genetic mispelling resulting in obesity: A single mutation results in obesity. The same data stimulated research also into the polygenetic mechanisms of common obesities by way of genomic screening of large population samples. However faced with the many years of limited success of GWAS of obesity it may be worthwhile reconsidering the underlying assumption that body weight is genetically controlled.

Observational studies

In humans, long-term observational data on body weight are frequently taken as indirect evidence that EI and EE are strongly controlled. Indeed, studies of energy balance over long periods of time (e.g., one year) suggest a tight control of body weight with a daily imbalance between EI and EE of only 10–20 kcal (see discussion in [40, 41]). However long-term balance data cannot be extrapolated to make inference about short-term control [42]. In fact, at the individual level there is no correlation between EE on a given day and EI of that day but a compensation may occur later [42]. Obviously, the short-term matching of EI and EE is poor.

Weight regain after weight loss (as is frequently seen during the dietary treatment of obese patients) has been taken as further evidence for the biological control (or a 'set point') of body weight. However weight regain after weight loss may be explained by physiological adaptation to restore FM and FFM according to their partitioning characteristics [35, 43–45] rather than by genetic signals. In particular, the drive to eat for the restoration of body weight is determined by feedback signaling of the losses in both, FM and FFM [44]. An 'active' role of FFM deficit in the control of EI [35, 45] is hence distinct from the 'passive' role of FFM in long-term control of EI whereby energy demand of FFM, which is the major determinant of REE, drives EI, hunger and self-selected meal size [35, 45–47].

During periods of diet-induced weight loss, the decrease in FM exceeds the decrease in FFM. Some 75% of weight

loss is explained by FM compared to 25% explained by FFM [48, 49]. After weight loss, the concomitant depletion of FFM (i.e., loss of FFM relatively to pre-weight loss values) contributes a strong drive to eat and hyperphagia, which again leads to a re-gain of both, FM and FFM. This has been described as 'collateral fattening' [45]. As a consequence FFM and thus REE increase until a new equilibrium between EI and EE and thus a stable body weight is reached again. This idea derives from the results of the classic Minnessota Starvation Study [32] and is also supported by the clinical observation, that the decrease of FFM in weight-reduced overweight and obese patients was significantly associated with the regain of FM [50]. Taken together, weight regain after weight loss is best explained by energy balance effects rather than by a distinctive genetic mechanism.

Heritability estimates

In humans, the idea of genetic control of body weight goes back to rather high heritability estimates as obtained in twin or other family studies (see [16, 51–53]). For example the familial correlation in BMI was between 0.20 and 0.23 in parent–offspring pairs, 0.20 to 0.34 in di-zygotic twins and reached 0.58 to 0.88 in mono-zygotic twins [16, 51]. However heritability is a statistical concept, that draws upon correlations between relatives to quantify how much of the overall variability of a phenotype at the population level is due to genetic variation. For example, a heritability of 0.5 for body weight would imply that half of the weight difference between two unrelated individuals is directly or indirectly attributable to genetic differences between them. This number puts research into the genetic basis of obesity into perspective. Moreover, heritability does not give evidence about the complexity of the genotype-phenotype relationship in question. In any case, in view of the limited outcome of past GWAS of BMI that cannot account for existing heritability estimates for body weight, it has been suggested that these heritability estimates were in fact inflated [54]. However, even if the heritability were accurate, they would still imply that GWAS have tried to explain a rather limited proportion of the variance in body weight only.

The use of weight changes and the associated changes in body composition as targets of genomic research would address yet another important aspect. Differences in the response to overfeeding had been studied for periods of 22 and 100 days in mono-zygotic twins [55, 56]. and the inter-pair variance in gains of either weight, FM and VAT was found to be three to six times higher than the intra-pair variance. This was taken as evidence for a 'genotype-overfeeding interaction' that determines weight and fat gain as well as fat distribution. The response to negative energy balance (i.e., with underfeeding and after an exercise program for periods of 22 and 100 days; [57, 58]) was also investigated and at least under the long-term protocol [57], the intra-pair variances in weight, FM and VAT reductions were lower than the inter-pair variances suggesting a 'genotype-underfeeding interaction' as well. However, these data have to be seen together with the intra-individual variances in body weight changes, which have not been taken into account in the studies cited [55–58].

Intra-individual and inter-individual variances in changes of body weight

Up to now the intra- or within individual variances of changes in body weight (and body composition) in response to controlled under-feeding and over-feeding have not been systematically studied. Variance is a mathematical property. If the intra-individual variance (intra-CV) in changes in body weight (or in masses of organs and tissues) is high, inter-personal variance (inter-CV) in these outcomes is difficult to relate to biological factors. In a series of controlled five week under-feeding and over-feeding studies of young healthy men [59] the observed between-one-week-run-differences in changes in body weight, FFM and FM were within the order of the inter-CV. Within each individual there were considerable day-to-day-variances in weight changes (and also changes in FFM and FM) varying between 26 and 88%. The high intra-individual day-to-day-variances in body weight, FFM and FM suggest that at least within short-term there is no tight biological control of body weight. Within individuals, the huge day-to-day-variance in body weight also questions a randomly measured body weight as a sufficiently stable phenotype for use in genetic epidemiological studies. Obviously, habitual body weight (which is addressed in GWAS) cannot be assessed with confidence.

Weighing the evidence

The idea of a biological control of body weight in normal weight and overweight humans originated mainly from observational data and heritability estimates. In view of (i) the variance in body weight changes observed in repeated measurements and (ii) the high intra-individual day-to-day-variances in weight loss and weight gain however a strict internal control of over-feeding and underfeeding-related changes in body weight and/or body composition seems elusive at least for short-term changes. Since carefully controlled long-term experiment (e.g., over one year) cannot be done in humans definite clarification of this issue will be difficult. It is possible that in 'modern' humans, living an abundant life, the biological control of body weight and the proposed metabolic susceptibility to weight gain are

obscured by strong environmental and societal driving forces. Instead, high energy supply and a sedentary lifestyle are the major drivers of body weight (e.g., in children and adolescents, see [60, 61]). This view suggests a passive adaptation rather than an active control of body weight [28] which varies according to individual partitioning characteristics (mainly due to FM and the FM-FFM-ratio at baseline; [43, 45]) explaining most of the inter-individual variance in weight changes (see above).

The 'set point' *paradigm* revisited

'Set' and/or 'settling'

Current research into the genetic basis of obesity follows the idea that human body weight itself is under strong internal control. This view is in line with the so-called *'set point'*-theory invoking a feedback system draws total body weight to a constant 'body-inherent' weight. To this end the system would actively adjust EI and/or EE in proportion to the difference between the current body weight and the 'set point' weight. The theory originated from animal studies but has been questioned repeatedly in humans and a passive feedback relationship has been alternatively proposed between EI and the body size needed to change EE such that a new energy balance is reached (i.e., the *'settling point'*; [28, 41, 62]).

EI and/or EE

Most of current research into the regulation of energy balance and body weight focuses on EI [63]. EI supposedly meets both energy and reward needs. Data from observational studies suggested that at least in humans living in highly developed countries the biological control of EI to meet energy needs is loose rather than tight [35, 64, 65]. Not least the obesity epidemic itself adds to the notion that environmental and social characteristics (e.g., high food supply, social inequalities in health) rather than biology per se are major drivers of EI (e.g., [60, 61]). Compared to EI, EE seems to be controlled within more narrow margins because it is a vital characteristic and oxygen consumption is a matter of survival [64]. Then control of body weight is more about control of EE.

A 'dual intervention point model' of EE

Any increase or a decrease in body weight suggests that EI has exceeded or fallen below some specific margin of EE. Accordingly the 'dual intervention point model' of body weight control [38, 41] can be replaced by a 'dual intervention point model' of control of EE [64]. Then, the 'upper intervention point' of EE reflects mitochondrial capacity (sum of mitochondria in the body and their functional state) whereas the 'lower intervention point' of EE reflects metabolic adaptation to minimize energy needs during caloric restriction [30, 59, 64]. The two intervention points of EE and/or the distance between the two points are suggested to be under biological control [64].

Teleologically, adaptation to energy deficit (i.e., the 'lower intervention point') is about sparing body energy and concomitantly meeting the basal energy needs of the brain [30, 64]. By contrast, the 'upper intervention point' may be related to the protection of mitochondria themselves (e.g., limiting the production of reactive oxygen species in response to overfeeding). Following this model the focus of GWAS of BMI (and obesity) is shifted to the two separate EE intervention points and/or the distance between the two boundaries. In practice, the body weight- (or FFM-) REE association and, thus, the residuals of the measured REE on FFM (taking age, sex, and FM as covariates) reflect the respective phenotype. From a physiological point of view, this metabolic phenotype is followed during controlled periods of over-feeding and underfeeding.

The case of epigenome-wide association studies

DNA methylation regulates the molecular phenotype in response to for example high fat intake, physical activity, and obesity [66]. Alterations in DNA methylation were seen for some candidate genes for obesity such as *FTO* in adipose tissue [67]. However epigenome-wide association studies revealed that these changes are a consequence rather than a cause of obesity: Levels of DNA methylation in blood were shown to be associated with metabolic disturbances and to modify the risk of type 2 diabetes mellitus which was independent of BMI and WC [67].

To put these data into a context it is worthwhile remembering that the association of BMI, WC, and/or FM with cardio-metabolic traits are at best moderate (e.g., see data in [68]). In cross-sectional studies, the respective correlation coefficients rarely exceeded 0.4, and the strongest associations were observed with a biomarker of insulin resistance (i.e., the HOMA index). A high correlation coefficient was observed when comparing liver fat and insulin resistance (up to $r = 0.80$; 68). This finding is in line with previous evidence showing that liver fat is closely linked to metabolic complications of obesity [68–70]. Since neither BMI nor WC nor FM nor VAT are correlated with liver fat [71], the data argue again in favor of a detailed and functional body composition analysis rather than involvement single anthropometric and/or body component traits.

Appreciation of a hypothesis-free approach

GWAS are hypothesis-free and, hence, represent a heuristic approach to scientific research. In principle, any positive GWAS result (i.e., even weak effects) may be biologically meaningful and, therefore, worthwhile publishing. However, studies of genotype-phenotype relationships merely reveal statistical associations that do not necessarily imply causality. Furthermore, GWAS are not primarily focused upon the meaning of results (which may only become apparent in years to come, if ever) but operationally confine themselves to adding to the "approximately true description of reality" [72]. This may be a reasonable justification for undertaking GWAS in the first place but, because obesity is a complex phenotype [73], collecting a virtually unlimited number of measurements just for the sake of technical feasibility is unlikely to add much to our understanding of its complexity.

Hypothesis-driven research may be a more suitable strategy to study obesity and, indeed, has been regarded superior to hypothesis-free GWAS in this regard before. As yet, however, the hypothetico-deductive strategies also have failed to disentangle the complexity of obesity. In the end, this is not surprising because complex problems rarely have single solutions. In our view, it is therefore advisable to accept and combine both research approaches. In so doing, however, we strongly advocate the use of other, more advanced phenotypes than, say BMI or body shape. The latter lack biological relevance and should therefore be replaced by more plausible phenotypes, based upon functional body composition.

Conclusions

GWAS published so far have not added much to our understanding of the proposed genetics of human obesity. This is mainly due to the facts that (i) obesity, when defined by BMI, is not a workable phenotype and (ii) GWAS of anthropometric traits lack a sound concept of body weight control. It is also possible that at least in normal weight and overweight humans tight control of body weight does not exist which is reflected by the high intra-individual variance in weight change raising doubt about a widely hold idea that "a genetic basis of obesity and body composition is well established" [65].

The unbroken optimism of genomics research sometimes leaves us with the feeling that all molecular biology problems have already been solved or will at least going to be solved soon. However, GWAS of obesity highlight the fact that this is far from the truth. We surmise that a comprehensive, systems-oriented approach will be required to advance obesity research that puts genetic variation into the wider biological context including metabolic pathways, protein–protein interactions and gene-regulatory networks. In any case, future GWAS undoubtedly must draw more heavily upon biologically-determined hypotheses about their target genotype-phenotype relationships. To do that a 'Phenome-Wide Association Study' (PheWAS or Reverse GWAS) using a 'weight change phenotype' as outcome is a promising strategy.

Solid scientific research into the genetic basis of obesity must no longer work in isolation from other disciplines. Instead, GWAS should look more closely at the achievements of physiological research on obesity which at least at present suggest a possibility that GWAS of obesity went wrong in the past. It is never too late to do the right thing even if, for the time being, the loaf has been hardly more than none. We recommend a re-launch of future well conceived GWAS of obesity.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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