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NARRATIVE REVIEW

I blame my parents for my waistline. But is this genetic alibi valid?

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Abstract

Purpose: The objectives of this narrative review are to consider the contribution of inherited factors to the development of obesity and its response to treatment, and the extent to which an adverse inheritance provides a "genetic alibi" to those who are obese. **Methods**: Information obtained from Ovid/Medline and Google Scholar through to December 2018 was supplemented by a search of the author's extensive personal files. **Results**: Animal models demonstrate that specific single genetic mutations can cause severe obesity, as in ob/ob and db/db mice and in the Zucker fatty rat. In humans, also, traditional genetic studies of adopted children, twins and entire families point to a substantial contribution of inheritance to such measures of obesity as BMI. However, perhaps because of a lesser impact of a shared family environment, estimates of heritability coefficients are substantially smaller for family studies (a 50th percentile coefficient of 0.46) than for twin studies (a 50th percentile coefficient of 0.75). Estimates of heritability vary widely for both approaches, with populations that are faced by an obesogenic environment tending to show higher values for coefficients derived from either type of data set. Attempts to link such heritability estimates to specific genetic sites have as yet been able to account for less than 5% of the total inter-individual variation in BMI. The main probable factors limiting the discovery of relevant chromosomal sites are a polygenic rather than monogenic basis for obesity and a strong modification of gene expression by epigenetic influences. **Conclusion:** Inherited factors appear to make a substantial contribution to the accumulation of body fat. Nevertheless, the validity of the "genetic alibi" is weakened in that dietary moderation and regular physical activity can greatly limit the phenotypic expression of obesity-inducing genetic characteristics. **Health & Fitness Journal of Canada 2019;12(1):34-79**.
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Introduction

People who have become obese frequently look for a "genetic alibi;" they blame their excess of body fat upon some quirk of ancestry, pointing to parents who may be as fat or fatter than them. A number of early clinical texts supported the view that obesity was an inherited problem. Thus Bauer (1945) noted that 73% of 1000 obese patients had obese parents, and Rony (1940) reported that in 173 of 250 obese patients one or both parents were also obese. However, such observations do not point inexorably to an effect of heredity; they could simply reflect a family environment where over-eating and a lack of adequate physical activity are the norm.

Any build-up of body fat necessarily implies an intake of food that exceeds an

individual's current energy expenditures in terms of basal metabolism and the added costs of normal daily physical activity. Have some people inherited genes skewing the balance between these two processes, and does this provide a "genetic alibi" for those who have become obese? There is certainly some evidence for the existence of "thrifty" genes that encourage the storage of body fat when food is in plentiful supply (Speakman, 2006), and these genes seem to be expressed more actively in some people than in others. Such an inheritance could conceivably influence not only a person's propensity to accumulate body fat in the face of over-eating and a sedentary lifestyle, but might also lead to an excessive accumulation of fat despite what seems a perfectly normal food consumption (Bouchard, 1994; 2010). It remains much less clear if the obesity epidemic of the past few decades (Shephard, 2018) can be blamed simply upon inherited abnormalities in a person's handling of fat. Why would the action of "thrifty genes" have increased suddenly during the second half of the last century? The epidemic can be explained without resorting to genetic explanations; it is often evident that families where everyone is obese are characterized by over-eating and/or a lack of adequate daily physical activity. Nevertheless, estimates for the heritability of fatness are to date quite large, ranging widely from 30 to 80%. But as we shall see, the interpretation of findings has been complicated by the fact that the most observers have used body mass index (BMI) as a convenient surrogate of fatness, rather than measuring body fat more directly; high BMI values could reflect not only an excessive accumulation of fat, but also well-developed muscles.

The present review explores how much truth there is in the "genetic alibi," and it also examines possible mechanisms underlying the genetic transmission of obesity. After a brief consideration of the "thrifty gene" hypothesis, the article looks at animal models of extreme obesity and it then lays out the various techniques used to estimate the strength of genetic influences in humans, noting the extent to which genetic factors contribute to both the development of obesity and its response to treatment. Thought is given to the information yielded by both genetic markers and animal models. The text also recognizes that the volume and intensity of habitual physical activity are important factors in the achievement of an overall energy balance, and that an individual's patterns of habitual physical activity are also strongly influenced by constitution (Bouchard and Tremblay, 1990; Pérusse, Tremblay, and Leblanc, 1989). A part of the inter-individual differences in body fat content that analysts have commonly attributed to issues in the regulation of fat metabolism and storage could in fact reflect inherited differences in patterns of habitual physical activity. This review thus attempts to disentangle problems in the interpretation of obesity that are introduced by both genetically and environmentally determined inter-individual differences in habitual physical activity.

In addition to the obesity that is currently widely widespread in the general population of developed societies, a number of relatively rare congenital pathologies can give rise to extreme obesity. These conditions require specialist treatment, and will not be discussed here. The interested reader is referred to sources such as the review by Farooqi (2005).

The "thrifty gene" hypothesis

After a brief description of the "thrifty gene" hypothesis, we will explore whether humans have been exposed to a sufficient number of famines over the course of history to modify their genotype, and we will look at other evolutionary factors potentially modifying fat metabolism and storage.

The hypothesis

The "thrifty gene" hypothesis was first advanced quite briefly by Neel, more than 50 years ago (Neel, 1962); he was seeking explanations for the large children that were born to diabetic mothers, and reasons for the evolutionary persistence of what were apparently disadvantageous genes underlying an increased susceptibility to diabetes mellitus. In essence, the "thrifty gene" hypothesis suggests that over the course of evolution, some humans developed a gene that increased efficiency in the intake and/or utilization of food; this allowed conservation of excess energy as fat when food supplies were abundant, with the release and use of this energy in a subsequent famine. It is postulated that in the early history of humankind, this characteristic had evolutionary survival value, particularly during the "lean'" periods of winter. Indeed, such a characteristic may also have survival value for many animal species. Pressures exerted by extended famines could have led to the progressive emergence and widespread propagation of the "thrifty gene."

Neel (1962) suggested that in "thrifty" individuals the post-prandial insulin secretion from the pancreatic islets of Langerhans persisted longer than in an ordinary person, pushing down blood sugar levels and encouraging further eating. It was also possible that in such people a continued pancreatic secretion of insulin kept blood glucose levels at a low average level, thus minimizing the post-prandial urinary excretion of glucose.

The history of famines

Some scientists have argued that humans first faced periods of major starvation with the transition from hunting and gathering to a settled, agricultural lifestyle, some 5000 years ago. Problems were likely to have been particularly acute in communities where one segment of society claimed for itself more than an equitable proportion of the food available to a community (Sen, 1981).

Hunter-gatherers could also have faced a lack of food during the colder months of winter, but nevertheless they were somewhat less vulnerable to episodic starvation than primitive agriculturalists, because they relied on a much wider range of food resources; in the event of that there was an acute shortage of one type of game, their mobility allowed them to move their camp to an alternative habitat. Speakman (2006) argued that since some of the small populations still following a traditional hunter-gatherer lifestyle have not become obese despite the modern availability of abundant food supplies (Alemu & Lindtjorn, 1995; Kirchengast, 1998; Shephard & Rode, 1996), hunter-gatherers have never developed "thrifty genes." But against this view, there are former hunter-gatherer Inuit and Indian communities in North America where the traditional physically active lifestyle has now been abandoned, with an associated substantial increase in body fat content (Shephard & Rode, 1996).

Theoretical calculations suggested to Speakman (2006) that one would need a total of 950 severe famine events over the

course of human history in order to replace an "unthrifty" gene by a new, randomly occurring "thrifty" one, given a world population averaging around 5 million people. If his calculation is correct, then the number of famines that have actually occurred may be too few to have influenced the course of natural selection. Prentice (2005) documented periodic famines that have troubled the world for around 5000 years, and Keys et al. (1950) presented data showing that in Britain over the past two millennia, severe famines tended to recur every 10 years or so. Food shortages during some of the worst famines were sufficient to cause the death of 25-50% of the population (Juttikkala, 1955; Watkins & Menken, 1985), with the survival prospects being greater among those who were initially obese. However, a 10% increase of mortality rate was a more likely outcome in a "typical" famine (as exemplified by the Irish potato famine of the 1840s (Speakman, 2006). Some investigators have indeed argued that food shortages of sufficient severity to increase the annual mortality rate substantially have occurred only about once every 100 years (Dupaquier, 1979).

Another important issue is the age of those affected by severe episodes of famine. The resulting deaths occur predominantly in those aged <5 years or >60 years, and an increased mortality among the elderly necessarily cannot have an impact upon genetic selection (Menken & Campbell, 1992). The total number of famines experienced by world populations over the course of history, their severity, and their resulting impact upon mortality and human genetic selection thus remains debatable. Certainly, a "thrifty gene" no longer has survival value in today's society. It is also unclear how far the persistence of a maladaptive gene could have contributed to the recent obesity epidemic. It is unlikely that major population changes in genetic characteristics have emerged over the mere two or three decades coinciding with the obesity epidemic, but it remains possible that some feature of the "thrifty gene" is particularly susceptible to aspects of our modern environment, be it commercial pressures to over-eat or the progressive reduction of habitual physical activity among much of today's population.

Other factors modifying genotype

Another evolutionary mechanism pushing the human species towards a more obese phenotype during early history may have been a greater fecundity among those who were obese, particularly if they were able to maintain adequate stores of fat to conceive when food was scarce. In more recent years, such a phenomenon was very obvious in birth-rate statistics for the Netherlands during the final winter of German occupation (1945) (Stein, 1975) and it was also seen in China during the famine associated with the "Great Leap Forward" (St. Clair, Xu, & Wang, 2003).

On the other hand, there is also a need to consider adverse effects of obesity upon survival prospects; a person with an above average body fat content is usually slower than average in their movement patterns, and thus (in a primitive hunter-gatherer society) they would have been more vulnerable to predators, with this danger could have set an upper limit to the evolutionary development of such a trait (Speakman, 2018).

Irrespective of how they first became prevalent in the human genome, the "thrifty" alleles (variant forms of a gene)

that favour food conservation have now become unfavourable adaptations, predisposing to the development of a body phenotype with negative consequences for health (Neel, 1962). Food supplies for most people are now copious, there are strong commercial pressures encouraging over-eating (Shephard, 2018), and the resulting obesity has many substantial negative consequences for the affected individual (physiological, biomechanical, psycho-social and medical) (Shephard, 2019a; 2019b; 2019c).

Animal models of gross obesity

Abnormal genetic configurations certainly can cause the development of extreme forms of obesity in some animal models. Investigators have chosen to exploit single-gene mutations in small mammals, whether these have occurred spontaneously, or have resulted from exposure to radiation or mutagenic chemicals. The latter approach is necessarily untargeted, with the potential for mutagenesis spread across the entire genome (Russell & Russell, 1992). Alternatively, current advances in genetic engineering now allow a specific locus to be targeted for enhancement or disruption; such techniques can cause the development of an unusually lean or obese phenotype, but conclusions may be hampered because the mutation has caused the animal to die before reaching maturity, or compensatory changes have occurred in other body systems over the course of development (Speakman, Hambly, & Mitchell, 2008). A final option is to study animals with an above average level of fatness, developed by selective breeding.

A number of specific examples can be cited, where an abnormality of function in a single gene involved in leptin production or leptin response has caused an uncontrollable food intake, type 2 diabetes, insulin resistance, and massive obesity in the animal's progeny. The best known of these genetic anomalies are the ob/ob mouse (Zhang, Proenca, & Maffei, 1994), the db/db mouse and the Zucker fatty rat (Zucker & Zucker, 1961).

Ob/ob mouse

The first ob/ob mouse (Figure 1) was noticed as a mutation that developed spontaneously in a colony of mice bred at the Roscoe B. Jackson research laboratory in Bar Harbor, Maine, in 1949 (Ingalls, Dickie, & Snell, 1950). The variant animals had a single recessive base-pair deletion at the gene involved in leptin production, a hormone that plays a major role in the regulation of appetite (Friedman & Halaas, 1998). The affected mice thus developed a syndrome comprising uncontrollable appetite, type 2 diabetes mellitus, insulin resistance and a gross increase in their body fat content. Homozygous animals were sterile, but heterozygotes bred normally. When born, the ob/ob members of a litter looked as though they would become normal adult animals, but by 4-6 weeks of age they could be distinguished from their peers by their greater size, and as they grew further, they became grossly obese. As adults, their body mass was as much as three times that of their litter mates, and blood sugar levels remained high despite enlargement of the pancreatic islets and an increased secretion of insulin (Lindström, 2007).

db/db mouse

The db/db mouse also has a recessive mutation; this affects chromosome 4, leaving the animal with an excessive appetite, increased metabolic efficiency, and insulin resistance (Bahary, Leibel, & Joseph, 1990).

Zucker fatty rat

The Zucker fatty rat was first named by Louis M and Theodore F. Zucker, pioneers in the genetics of rat obesity. The fatty rat, in contrast to its thinner peers, has a double recessive miss-sense mutation on chromosome 5, with malfunction of the gene controlling development of the leptin receptor. This leads to insulin resistance, but with a relatively normal blood sugar. Obesity can develop without diabetes mellitus, and animals typically reach a weight of around 1 kg (Figure 2), double that of a normal rat. Diabetic strains of the Zucker fatty rat have been bred, and some double recessives have been able to reproduce (Yokoi, Hoshino, & Hidaka, 2013).

Polygenic animal models

Similar monogenic mutations can occur occasionally in humans, but as with most single gene anomalies they are found in only a small proportion of the total population, and any substantial contribution to the current obesity epidemic is correspondingly unlikely. In most cases, human obesity seems to have a polygenic rather than a monogenic basis.

Some animal models of polygenic obesity are available. For example, if Sprague-Dawley rats are exposed to a high energy diet, some members of the litter become obese, but other animals prove resistant to such diets (Levin and Dunn-Meynell, 2000). The 2 variants (resistant and non-resistant animals) each seem to persist through several generations of off-spring.

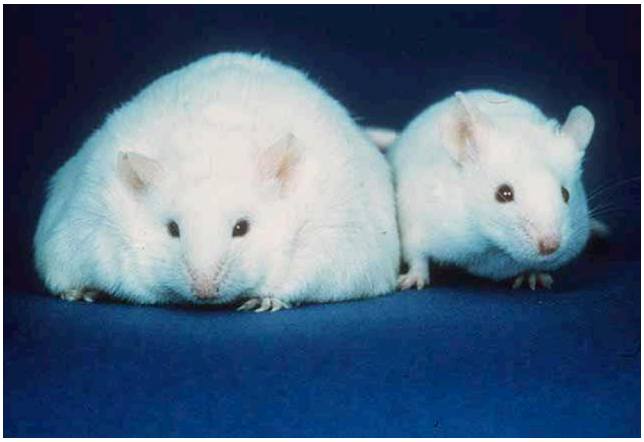

Figure 1. The Ob/ob mouse (left) is obese because of an inability to secrete leptin; a normal mouse is shown on the right. Source: https://en.wikipedia.org/wiki/Ob/ob_mouse.

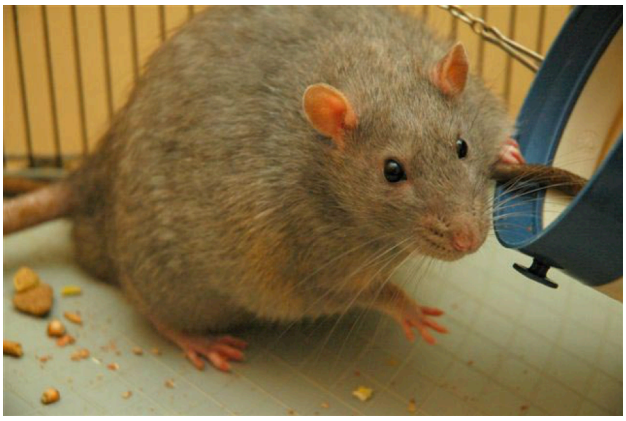

Figure 2. The Zucker fatty rat. A mis-sense mutation of the gene on chromosome 5 that controls the function of the leptin receptor causes gross obesity in this animal. Source: https://fr.wikipedia.org/wiki/Rat_Zucker

Conclusions

Ob/ob and db/db mice and the Zucker fatty rat demonstrate that monogenetic abnormalities can give rise to extreme obesity in animal models. However, such manifestations have greater relevance to rare congenital human abnormalities such as those discussed by Farooqi (2005) than to the widespread obesity found in developed societies today. Some practical

applications of animal models to our understanding of the present obesity epidemic are discussed further below.

Traditional methods of assessing the contribution of heredity to human obesity

Advocates of a "genetic alibi" assume that most of inter-individual differences in body fat content is due to heredity, and that very little is due to a person's environment and lifestyle. The experimental methods used when examining the magnitude of the genetic component Vg of the total variance in any body characteristic, relative to its environmental counterpart Ve, include classical adoption, twin and family studies, supplemented by the matching of body characteristics against specific genetic markers. Empirical estimates of the heritability of obesity vary quite widely over the range 30-80%, reflecting the many conceptual and practical difficulties in current methods of analysis.

In the simplest approach it is assumed that in the inheritance of a body phenotype such as obesity, the observed variance of this characteristic (Vp) reflects the combined effects of a genetically determined variance (Vg), an environmentally determined variance (Ve), variance due to an interaction of genes with environment conditions (Vgxe), and an experimental error (VE) that is assumed to be randomly distributed and unrelated to the other elements in the model:

$$Vp = Vg + Ve + Vgxe + VE$$

Further, (and not always wisely), the interaction term [Vpxe] and the experimental error term [VE] are commonly assumed to be sufficiently small that they can be neglected; thus, the genetic component is expressed as a simple percentage of the total variance:

$$Vg\% = 100\ Vg\ /\ (Vg + Ve)$$

Unlike animal models such as the ob/ob mouse, human obesity usually reflects the synthesis of small effects mediated at numerous genes (a polygenic response) which may (or may not) be additive. This substantially complicates the analysis and interpretation if findings.

Adoption studies

Theoretical basis

When children are adopted, comparisons may be drawn between the characteristics of the child and the adopting parents, or one may look at the relative similarities of adopted and natural children to their parents (a partial adoption study). More rarely, information is available on both the biological and the adoptive parents (a complete adoption study). Such analyses have the potential to allow qualitative inferences about the inheritance of traits such as obesity. If adopted children show a similar degree of obesity as their genetic parents, this is considered evidence of a strong genetic influence, whereas a resemblance of the child to the adopting parents suggests that the main influence is the environment in which the child is reared.

Pre-requisites of effective analyses (not all of which are usually satisfied) include the use of a representative population sample (rather than a selection of the low socio-economic status infants who predominate among adoptees), early and complete separation of the adopted children from their biological parents, avoiding instances of selective adoption (for instance, by a close relative), correct

assignment of paternity, an absence of assortative mating (Sørensen & Stunkard, 1994) and a lack of significant maternal or other environmental influences. The last issue is usually the most contentious, since undertaking regular vigorous physical activity at an early age can minimize the influence of an adverse genetic profile upon BMI and waist circumference (Andreasen, Syender-Petersen, & Morgensen, 2008; Mustelin, Silventoinen, & Pietilainen, 2008; Rampersaud, Mitchell, & Pollin, 2008). In partial adoption studies, one must also assume that environmental effects are equal for adoptees and natural families. In a partial adoption study, correlation coefficients relating the body fat content of adopted and natural children (from the same family, or even in other families) are compared, with a significant difference in the 2 coefficients implying a genetic influence. And in a full adoption study, coefficients relate the obesity of the child to that of both biological and adoptive parents.

Empirical data

There have been at least 9 adoption studies of the inheritance of obesity (Table 1). Shenker et al. (1974) noted that the obesity of 66 infants (53 of whom were "black") was greater if the foster mothers weighted >160 pounds (68 kg) than if it was in the normal range, but no formal estimate of inheritance was made. Other reports of this same question include both partial and complete adoption studies.

Partial adoption analyses. Withers (1964) conducted an early study in London, England. He questioned 300 parents of adoptees aged 8-13 years, comparing data on their heights and weights with findings for two groups of natural families. The percentages of parents and adoptees that were overweight was calculated relative to the average for the British population. The resulting correlation coefficients were 0.11 for adoptive fathers, 0.16 for adoptive mothers, and 0.14-0.42 (median 0.19) for natural parents. It is unclear whether these small inter-group differences were statistically significant, but Withers suggested that clearer conclusions might be obtained if the study was repeated using a better indicator of obesity.

Stanley Garn and his colleagues (Garn et al., 1977) published several papers on issues of inheritance as a part of the large Tecumseh study of children and adolescents. One sample of 13,659 participants included children aged 0-18 years who were adoptees and step children as well as members of natural families. Measurements of triceps and sub-scapular skin-folds showed correlations with parental data that appeared to be lower for adoptees (0.11 and 0.09, respectively) than for natural children (0.21 and 0.19), but again these apparent differences were not tested statistically.

Hartz et al. (1977) examined 23 mothers who were attending the TOPS weight-control programme, along with 45 unrelated children aged 4-11 years (39 of the latter were adoptees, mostly placed with the women before they reached the age of 6 months). Excess weights were calculated both for adoptees and the parents' natural children, and correlations appeared to be somewhat weaker for the adoptees (0.03 for fathers, 0.09 for mothers) than for the natural offspring (0.11 and 0.10). The authors estimated that family environment accounted for 32% of the variance in fatness, and that heritability was responsible for only11% of the variance.

Table 1. Adoption studies looking at the inheritance of obesity.

Authors	Type of study	Subjects	Obesity criterion	Conclusion
Amnest et al. (1983)	Partial adoption	553 children aged 1-10 yr	Weight adjusted for age and height	Family resemblance mainly reflects shared genes
Bouchard et al. (1985)	Partial adoption	Children aged 8-26 yr	Weights, skin-folds, hydrometry	Correlations similar for natural and adoptive children
Cardon (1991)	Complete adoption	245 adoptive, 245 non-adoptive families	BMI	Genetic effects large at birth, but diminish by age 9 yr
Garn et al. (1977)	Partial adoption	13,659 children aged 0-18 yr	Skin-folds	Correlations with parental data lower for adoptees than for natural children
Hartz et al. (1977)	Partial adoption	23 mothers in TOPS programme, 39 adopted children aged 4-11 yr	Excess weights	Correlations somewhat weaker for adoptees than for natural children
Price et al. (1987)	Complete adoption	357 adoptees aged 18-38 years	BMI	Positive correlations for biological parents, near zero for adoptive parents
Shenker et al. (1974)		66 infants (53 "black") entering foster care at 2 months; Mothers of normal weight and weight > 150 pounds (68 kg)	BMI of infants and foster mothers	Obesity ratios higher where foster mothers were overweight
Stunkard et al. (1988)	Complete adoption	540 adoptees on Danish register followed to age 13 yr	4-level classification of weights	Genetic factors important, family environment little effect
Withers (1964)	Partial adoption	300 adoptees aged 8-13 yr	Weight as percent of population average	Larger correlations for natural than for adoptive parents

Annest et al. (1983) based their reports on children aged 1-10 years, drawn from 553 families who were living in Montreal. Adopted children had typically been placed in their new homes by the age of 3 months. Correlation coefficients in this study were -0.03 (fathers) and 0.10 (mothers) for adoptees, and 0.11 and 0.24 for natural children. It was concluded from this analysis that the family resemblance in weight adjusted for age and height was due mainly to shared genes, although the family environment

also contributed to resemblances of weight adjusted only for age and sex.

Claude Bouchard and his colleagues (1985) included an analysis of data for adopted and biological children as a part of their extensive Quebec City family study. Data were obtained for height, weight, skin-fold thicknesses and body fat content as determined by underwater weighing in children aged 8-26 years. Here, correlations were similar for adoptive (0.22) and natural (0.23) children, with rather similar coefficients for the various estimates of body fat content. It was also noted in this study that comparisons of monozygous and dizygous twins gave high and probably unrealistic estimates of heritability, perhaps because of the differential effects of the shared environment in monozygous and dizygous twin pairs.

Complete adoption studies. Stunkard et al. (1988) examined information on children identified from the Danish adoption register. Among 540 adoptees studied to an age of 13 years they noted that the adult body build showed small but statistically significant correlations with data for their genetic parents, whom they had usually not met (with their mothers, $r = 0.15$, $p < 0.0001$, with their fathers, $r = 0.11$, $p < 0.02$), whereas their adult builds showed no significant relationships with figures for their adoptive parents.

The Iowa study of Price, Cadoret, and Stunkard (1987) located 357 adoptees when they had reached an age of 18-38 years. Interpretation of the data was complicated by the fact that a half of the biological families concerned had some type of psychopathology. Correlations of BMI with data for the biological parents were all positive (mother/daughter 0.40, mother/son, 0.15, father/daughter 0.18, father/son 0.08), whereas correlations for adoptive parents were all close to zero (0.09 to -0.09).

The study of Cardon (1991) was based on 245 adoptive and 245 matched non-adoptive families living in Colorado. This analysis found strong genetic influences upon the BMI at birth, but the effects became progressively smaller by the age 9 of years.

Overall assessment of adoption studies. Sib-sib correlations are commonly larger than those found for parent-sib relationships. This may reflect those environmental influences that are shared between siblings, but not between siblings and their parents. It is sometimes possible to disentangle environmental effects if the data-base includes information on the biological parents and the biological siblings of the adoptee. Some investigators have also endeavoured to discern possible gene-environmental interactions, but to date findings have been inconclusive.

One argument advanced in favour of adoption studies as a means of investigating inheritance is that unlike most analyses that are based on twin and family groupings, in adoptees genetic effects are separated relatively completely from environmental factors, at least from shortly after birth. Nevertheless, interpretation can still be complicated by periods that a child has spent with foster-parents prior to formal adoption, and often, children have been exposed to the domestic environment of a combination of genetic, foster and adoptive parents. Moreover, even if a child has been adopted at an early age, it was necessarily exposed to the maternal environment while *in utero.*

Reports based on adoptions to date show a fairly consistent effect of genes,

and little impact of the family environment upon levels of obesity. However, the data do not allow a convincing quantitative calculation of the contribution of heritability to the child's phenotype. Future adoption studies are limited by the growing rarity of domestic adoptions in Europe and North America.

Twin studies

Theoretical basis

The use of twins in the study of inheritance dates back to the work of Francis Galton (1876), as he wrote on "*the relative powers of nature and nurture*," although interestingly he seems to have drawn no clear distinction between monozygotic and dizygotic twins. Early quantitative studies of the heritability of cutaneous moles and of fingerprints (Mayo, 2009; Poll,1914; Siemens, 1924) led to subsequent analyses of the inheritance of various anthropometric characteristics among twins, pointing the way to studies of obesity in monozygous and dizygous twin pairs. The process was greatly facilitated by the establishment of twin registries in many countries, beginning with Denmark in 1954.

One early technique looked at the relative concordance rates for obesity among monozygous and dizygous twin pairs, using a Chi^2 test to test the statistical significance of any observed differences. A second simple approach compared intra-pair correlation coefficients for monozygous and dizygous twins. If fatness were entirely genetic, it was assumed that the correlation would be 1.0 for monozygotic twin pairs (where genetic effects were necessarily equal) and 0.5 in dizygotic twin pairs (where only a half of the genes were shared). Thus, if r_{mz} is the correlation coefficient for monozygous and r_{dz} the coefficient for dizygous twin pairs, then the heritability (G) of obesity should be indicated by each of three equations:

$$G = r_{mz}$$

$$G = 2\, r_{dz}$$

$$\text{and } G = 2[r_{mz} - r_{dz}]$$

The third equation has the merit of largely eliminating the spurious component of correlation arising from the common environmental factors to which both categories of twin children were exposed by subtracting the observed correlation coefficient for dizygous twins from that for monozygous twins. Nevertheless, such a manipulation of the data assumes that environmental effects are equivalent for monozygous and dizygous twins. Moreover, as with any correlation-based calculations, the respective magnitudes of the correlations are vulnerable to any differences in the overall variance of data between the monozygous and dizygous groups.

Since a part of the similarity between twin pairs reflects a common living environment, a distinction is drawn between broad estimates of heredity (which include this familial environmental factor), and narrow estimates (that exclude it). The common living environment component V_c is sometimes estimated as:

$$V_c = r_{dz} - 1/2G$$

since 1/2 G is the extent to which dizygotes share common genes.

A related method of determining heritability has been to compare the respective variances of data s_{mz}^2 and s_{dz}^2

for monozygous and dizygous twin pairs. In its simplest form,

$$G\% = (s_{dz}^2 - s_{mz}^2)/s_{dz}^2$$

A more precise calculation assumes that any variance seen in data for the monozygous twin pairs is attributable to a combination of methodological and environmental factors ($_{m}s_{mz}^2$), whereas that of the dizygotic twin pairs ($_{m}s_{dz}^2$) is further boosted by a genetic contribution. Heritability is then calculated as:

$$G\ (\%) = [(s_{dz}^2 - {}_{m}s_{dz}^2) - (s_{mz}^2 - {}_{m}s_{mz}^2)]/\ [s_{dz}^2 - {}_{m}s_{dz}^2] \times 100$$

Many of the limitations in these estimates are similar to those already discussed for adoption studies. One critical assumption is that environmental influences make a similar contribution to variance for the monozygotic and dizygotic twin pairs, although in practice monozygotic twins usually share a more closely similar living environment than dizygotic twins. It is also assumed that there is no (gene x environment) interaction; however, such an interaction might arise if (for example) a greater number of obesity-prone individuals were raised in a familial environment where over-eating or a lack of adequate physical activity was the norm. Such problems are largely overcome if the analysis can be based on the characteristics of twins who have been reared apart from one another because of adoption. As a further unavoidable complication, the twin phenotype is inevitably influenced by the common environmental factors arising from a shared pre-natal environment. Moreover, assortative mating may lead to both partners in a marriage being either thin or fat; this artificially boosts the genetic similarity of dizygous twins, but cannot influence the similarity of monozygous twins, since they are already genetically identical.

Empirical data

Empirical data on the obesity of twins are available for both childhood and adult life. Available findings include observations on both patterns of fat deposition and response to dietary constraints.

Children. A comparison of subcutaneous fat deposition (summed triceps, sub-scapular and abdominal skin-fold data) between 40 monozygotic and 61 dizygotic twin pairs aged 7 years convinced Börjeson (1976) that genetic factors played a decisive role in the genesis of obesity. Indeed, he calculated a heritability index of 0.88 using the formula $G\% = (s_{dz}^2 - s_{mz}^2)/s_{dz}^2$, although he cautioned that this figure could be an over-estimate of the true value due to the intervention of environmental influences.

Another analysis in 78 monozygotic and 144 dizygotic twin pairs aged 3-15 years used the sum of triceps and sub-scapular skin-folds as a measure of fat accumulation (Brook et al., 1975). Unfortunately, this sample included relatively few obese children, but

Table 2. Heritability of subcutaneous fat (the sum of triceps and subscapular skin-folds) in children, as calculated from the 3 possible methods of analyzing intra-class correlation coefficients. Based on the data of Brook et al. (1975) for monozygous and dizygous twin pairs.

Method	Heritability estimate
$G = r_{mz}$,	0.77
$G = 2\ r_{dz}$	0.80
$G = 2[r_{mz} - r_{dz}]$	0.74

nevertheless estimates of heritability using each of the 3 possible methods of manipulating intra-pair correlation coefficients yielded quite high values, similar to those obtained by other investigators (Table 2). When the sample was sub-divided by the age of participants, the estimate of genetic effects was much more obvious in those aged > 10 years (G = 0.98) than in younger children (G = 0.52). The authors of this report suggested that environmental factors (particularly intra-uterine effects and early parental control of feeding) had a much stronger effect relative to inheritance in the younger members of their sample. In the boys, coefficients of correlation for the monozygous twins were also systematically higher for the sub-scapular than for the triceps skin-folds, but in the girls no such difference was seen. Over all twin pairs, the heritability index was 0.98 for the sub-scapular data, but only 0.46 for the triceps folds.

Medlund et al. (1976) used an extensive registry of some 10,000 child twin-pairs to examine the heritability of a simple surrogate measure of obesity. The individual's relative weight was calculated as Weight (kg)/ [Height (cm) - 100] x 0.9, and participants with a relative weight >1.2 were classed as obese. Concordance of this index was twice as great in monozygotic as in dizygotic twin pairs (Medlund et al., 1976).

In line with the observations of Brook et al. (1975), Lajunen et al. (2009) found an apparent increase in the heritability index with age. In a sample of 2413 monozygous and dizygous Finnish twin pairs, the heritability of BMI was estimated at 0.58-0.69 for those aged 11 years, but it had risen to 0.83 in boys and 0.74 in girls by the age 17 of years.

Comparisons of Caucasian and East Asian twins aged 13-15 years found that the former showed a greater inter-individual variance in BMI. Moreover, genetic factors contributed to the difference in variability between the 2 ethnic groups (Hur, Kaprio and Iacono, 2008).

Adults. In an early study of adult twins drawn from U.S. veterans aged 42-56 years, Feinleib et al. (1977) compared the weights of 250 monozygotic and 266 dizygotic twin pairs relative to Metropolitan Life Insurance table predictions of ideal weights. Their analysis of within and between pair variances ($G = 2[r_{mz} - r_{dz}]$) and of intra-class correlation coefficients ($G = 2[r_{mz} - r_{dz}]$) yielded heritability indices of 0.47 and 0.64, respectively. A further analysis on 514 members of this same subject group looked at changes in BMI from induction into the Armed Forces at the age of 17-24 years to the values seen some 23 years later, at an age of 42-56 years. The heritability index ($G = 2[r_{mz} - r_{dz}]$) at induction was 0.80, falling to 0.67 at age 25, and 0.57 at the final examination, with a heritability of 0.60 for the change from induction to the final examination (Fabsitz, Feinleib, & Hrubec, 1980).

Table 3. Similarities in excess body mass between twin pairs at recruitment and after a 25-year follow-up. Based on the data of Stunkard et al.(1986).

Excess body mass (%)	Initial concordance (%)		Concordance at follow-up (%)	
	Monozygous	Dizygous	Monozygous	Dizygous
15	61	31	68	49
20	57	27	60	40
25	48	24	54	26
30	51	19	47	16
35	44	12	43	9
40	44	0	36	6

Analysis of data for a much larger sample of 1974 monozygotic and 2097 dizygotic twin pairs (Stunkard et al., 1986) showed that in general the concordance of body build (as assessed by a chi^2 comparison of the distribution of BMI and of excess body mass relative to "ideal" values for the two types of twin) was approximately twice as great for monozygotic as for dizygotic twins (Table 3), both when the subjects were first recruited at age 20 years and after a 25-year follow-up. However, this ratio was no longer conserved in the most obese individuals as they became older. The average heritability of BMI (estimated from the difference in intra-class correlation coefficient $\{G = 2[r_{mz} - r_{dz}]\}$ was 0.77 at age 20, and 0.84 at age 45 years. BMI values were highly correlated with each other over time, and a path analysis suggested that much of this co-variation was genetically determined.

Patterns of fat deposition. Carey et al. (1996) demonstrated a distinct heritability of factors leading to the central deposition of body fat. Their dual energy x-ray absorptiometry study was based on 50 monozygotic and 36 dizygotic non-obese middle-aged (~45 year old) female twin pairs. After adjusting their data for age and total body fat content, the genetic influence on central adiposity was set at 70% of the population variance ($G = 2[r_{mz} - r_{dz}] = 0.42$).

Growth, diet and other influences. Hainer et al. (2001) studied the response to a dietary regimen (a limitation of food intake to 1.6 MJ/day for 28 days) in premenopausal women (14 monozygous female twin pairs with an average age of 39 years). Although there were substantial inter-pair differences, Hainer et al. (2001) also noted a strong intra-pair correlation in losses of body mass ($r = 0.85$) and hydrostatic estimates of fat loss ($r = 0.88$) over the 28 days of dietary restriction, suggesting that genetic factors have a marked influence upon the response to dieting. This could imply that there are inherited differences of metabolic efficiency between twin pairs (for instance, there may be inter-individual differences in the relative proportions of white and brown fat). But as the authors of this report acknowledge, such findings could also reflect inter-pair differences in patterns of habitual physical activity or in non-exercise thermogenesis (such as fidgeting).

Bouchard et al. (1994) made similar observations on the response of 7 young adult male monozygotic twin pairs to a negative energy balance; 93 days of exercise and a cumulative dietary deficit of 244 MJ led to changes in both total and abdominal fat, with respective correlation coefficients of 0.62 and 0.84. Using monozygotic and dizygotic twins, Bouchard and his colleagues further reported that genetic factors had a marked

influence upon changes in body composition during periods of either deliberate over-feeding or dietary restriction, with some 40% of the variance in the resting metabolic rate, the thermic effect of food and the energy cost of low to moderate physical activity seemingly being dependent upon inheritance (Bouchard & Tremblay, 1990).

A review by Min et al. (2013) confirmed the view noted above that the heritability of obesity was modified by age (effects peaking at an age of ~ 20 years). Other factors modifying the influence of heredity were the time period of observation, the average BMI of the sample, the gross domestic product and any periods of rapid economic growth; the effects of inheritance increased with a larger average BMI and a greater GDP, probably because these variables were linked to an obesogenic environment leads and a more aggressive expression of obesity-producing genes. This idea was supported by Rokholm et al. (2011); they reviewed Danish twin studies from 1994 and 2002, finding that the size of additive genetic variation was positively correlated with the prevalence of obesity and the mean of the BMI distribution. Dubois et al. (2012) again noted that the heritability of height, body mass and BMI increased from a figure of around 7% at birth to ~ 50% at 5 months of age.

A further meta-analysis of 88 studies (140,525 twin pairs) found the heritability of BMI peaking in late adolescence at values ranging quite widely from 0.47-0.90, with a 50th percentile of 0.75 (Elks et al., 2012). A study of 37,0000 adult twin pairs across 8 countries showed that the variation of BMI was greater for women than for men, and that this variation was attributable primarily to additive genetic influences (Schousboe, Willemsen, & Kyvik, 2003). Other reported influences of age and sex upon heritability, as deduced from twin studies, are summarized in Table 4. Age effects do not seem to be very consistent, but apparently peak at an age of around 18 years. In disagreement with Schousboe et al. (2003), heritability also seems rather similar in males (0.73) and females (0.75) when averaged across the various studies. Heritability coefficients were 0.05 lower for self-reported BMI versus BMI determinations based upon carefully

Table 4. Overview of the heritability of BMI based on twin studies collected by Elks et al. (2012). See original paper for details of references, and note that several of the large studies contain overlapping samples.

Author	Sample	BMI measure	Heritability estimate
Austin et al. (1997)	630 twins aged 18-85 yr	Clinical BMI	0.83 (f)
Baird et al. (2001)	396 twins aged ~44 yr	Clinical BMI	0.77
Carmichael & McGue (1995)	1,475 twins aged ~32 yr	Self-reported BMI	0.82
Comes et al. (2007)	1812 twins aged ~12 yr	Clinical BMI	0.77 (m) 0.76 (f)
Faith et al. (1999)	132 twins aged ~11 yr	Clinical BMI	0.88
Forbes et al. (1995)	174 twins aged 7-68 yr	Clinical BMI	0.75
Harris et al. (1995)	4,508 twins aged 18-25 yr	Self-reported BMI	0.72 (m) 0.83 (f)
Hewitt et al. (1991)	160 twins aged ~19 yr	Clinical BMI	0.84 (m)

measured data, and they were also 0.05 lower if reliance was placed upon self reports of zygosity rather than DNA based reports.

Family studies

As can be seen above, some investigators have been successful in obtaining large groups of twin-pairs, thanks to modern twin registries, and others have carried out extensive meta-analyses of twin-based studies. Nevertheless, one advantage that has commonly been claimed for family studies is the availability of a much larger subject sample than when the analysis of inheritance has been restricted to twin-pairs. We will look at the theoretical basis of family studies and will then examine some empirical findings for obesity, noting that this approach generally points to a substantially smaller heritability index [a value of around 0.46, (Elks et al., 2012)] than that derived from twin-based studies. As noted above, a part of the high values usually found through twin studies has been attributed to subjective methods of estimating both zygosity and BMI (Elks et al., 2012), but a more important consideration has probably been the difficulty in allowing for shared environmental factors.

Theoretical basis

Analyses of heritability based on family studies have manipulated the correlation coefficients seen in several potential familial relationships, making the assumptions summarized in Table 5. Sometimes, sophisticated path analyses have been applied (Cloninger, Rao, & Rice, 1983), but the simplest approach assumes that the variance in any given trait such as obesity has 4 main components (Cavalli-Sforza and Bodmer, 1971): additive (V_a), dominant (V_d), genetic (V_g),and environmental (V_e), together with epistatic effects arising from interactions between adjacent gene loci.

Table 5. Commonly accepted distribution of additive and dominant components of variance as seen in various family relationships. Based on the concepts of Bouchard and Malina (1983).

Relationship	Variance component
First cousins	$1/8\ V_a$
Uncle/nephew	$1/4\ V_a$
Half-sibs	$1/4\ V_a$
Parent-offspring	$1/2\ V_a + V_f$
Sib-sib	$1/2\ V_a + 1/4\ V_d + V_f$
Diygotic twins	$1/2\ V_a + 1/4\ V_d + V_f$
Monozygotic twins	$V_a + V_d + V_f$

Where V_f is the environmental component attributable to cohabitation as a family.

The additive fraction of variance reflects the observed differences between homozygotes, summed over genes, and it is calculated from the correlation ($r_{p\text{-}o}$) of values for a trait between parent and offspring:

$$V_a/V_p = 2\ (r_{p\text{-}o})$$

The dominant fraction of variance is due to any deviation of values for heterozygotes from a value intermediate between 2 contrasting homozygotes. If ($r_{s\text{-}s}$) is the sib-sib correlation, then:

$$V_d/V_p = 4\ [(r_{s\text{-}s}) - (r_{p\text{-}o})]$$

The genetic component of variance is given by the sum of additive and dominant components:

$$V_g/V_p = V_a/V_p + V_d/V_p$$

The phenotypic value is then the sum of all components ($V_p = 1$) and the environmental component is the phenotypic value minus the genetic component:

Table 6. Family studies of the inheritance of obesity, based in part on studies accumulated by Elks et al. (2010). For details of studies not listed in the bibliography below, see Elks et al. (2010).

Author	Sample	Heritability of BMI
Abney et al. (2001)	666 South Dakota Hutterites	0.54
Arya et al. (2002)	1903 Indians (nutritional study)	0.25
Bastarrachea et al. (2007)	375 Mexicans (metabolic study)	0.36
Bayoumi et al. (2007)	1,198 Omani (family study)	0.68
Bijkerk et al. (1999)	1,583 Rotterdam residents	0.53
Bogaert et al. (2008)	674 semi-rural Belgian communities	0.81
Bouchard et al. (1985)	841 people living in Quebec City	0.58
Butte et al. (2006)	1,030 U.S. Hispanic population	0.39
Coady et al. (2002)	1,051 citizens of Framingham, U.S.A.	0.37
Deng et al. (2006)	1,031 of Shanghai population	0.49
de Oliveira et al. (2008)	1,666 Brazilians (heart study)	0.51
Friedlander et al. (2009)	476 Israeli Kibbutz inhabitants	0.64
Henkin et al. (2003)	1,032 Americans (insulin resistance study)	0.54
Hunt et al. (1989)	1,102 Utahans (pedigree study)	0.24
Hunt et al. (2002)	1,315 Canadians (fitness survey)	0.39
Jee et al. (2002)	7,589 Koreans (insurance study)	0.26
Li et al. (2006)	478 Mexican Americans (coronary study)	0.59
Longini et al. (1984)	5,174 Tecumseh (U.S.) population	0.35
Luke et al. (2001)	1,815 Nigerians, 614 Jamaicans, 2,097 Americans (hypertension study)	0.49, 0.53, 0.57
Moll et al. (1991)	1,580 U.S. (ponderosity study)	0.58
Patel et al. (2008)	1,802 Cleveland (U.S.) family study	0.65
Sale et al. (2005)	580 African Americans	0.64
Treuth et al. (2001)	303 Americans, Houston	0.35
Vogler et al. (1995)	2,476 Danes (adoption registry)	0.34
Wu et al. (2003)	1,724 Taiwan4se (mental health screening)	0.39
Zabaneh et al. (2009)	1,634 Asian Indian families in UK	0.30

$$V_e = 1 - [V_a/V_p + V_d/V_p]$$

The generally accepted distribution of additive and dominant components of variance among the various members of a family is summarized in Table 5. However, family calculations based on the assumption of equal maternal and paternal inheritance may be incorrect if characteristics are determined by genes located on the Y chromosome.

Empirical estimates of heritability

Elks et al. (2010) documented many of the family studies of BMI (Table 6), although they omitted from their consideration the data obtained from the Quebec family study, one of the first and perhaps the most widely documented analyses of the effects of family

relationships upon body composition and habitual physical activity patterns. The Quebec study examined relationships among adopted, unrelated individuals, cousins, siblings, dizygotic and monozygotic twins. After looking at details of this study, we will review some of the other large family investigations that have been completed over the past 30 years, separating data for well-nourished populations in developed countries from figures for developing societies where many members of the population sample have likely been less well nourished.

Quebec Family Study. The Quebec family study was based on 871 people living in and around Quebec City. Inter-individual differences in body fatness were 2-3 times greater between families than within families (Bouchard et al., 1985; Savard, Bouchard, & Leblanc, 1983). Moreover, correlations of body fatness within families were much stronger where there were common genes and a common environment than when only the family environment was shared (Table 7). Indeed, intra-pair correlations were not statistically significant for adopted or unrelated siblings.

The heritability values that were calculated represent the combined effects of genetics and a shared family environment (a "broad heritability" figure). As with other analyses, a substantial component of the total variance in the various measures of obesity was attributed to heredity (Table 8). Habitual physical activity was also examined, and this also was also influenced by heredity, at least to a small extent (a heritability coefficient of 0.27). Further, the correlations used in the calculation of the heritability of obesity were not greatly changed by controlling data for either the total energy intake (as derived from a 3-day dietary record) or habitual physical activity (as estimated from crude 3-day diary estimate of energy expenditures) (Savard et al., 1983).

The various potential estimates of the heritability of obesity all yielded rather similar coefficients, at around 0.60, substantially less than those obtained by

Table 7. Data from the Quebec family study showing within-pair correlations of body composition data for various categories of family member. Based on the data of Bouchard et al. (1985).

Variable	Adopted	Unrelated	Cousins	Siblings	Dizygotes	Monozygotes
Sum of 6 skin-folds	-0.01	0.11	0.28	0.27	0.39	0.83
Body density	-0.14	-0.04	0.18	0.20	0.22	0.73
Subcutaneous/total fat	-0.01	0.12	0.32	0.29	0.15	0.61

Table 8. Data from the Quebec family study estimating the multi-factorial heritability of various indices of obesity (representing the combined effects of genetics and a shared family environment, V_f). Present author's values, based on the published parent-sib and sib-sib correlations of Bouchard et al. (1985).

Variable	Parent-offspring correlations	Sib-sib correlations	Multifactorial heritability*
BMI	0.23	0.26	0.58
Sum of 6 skin-folds	0.22	0.26	0.60
Hydrostatic percent body fat	0.23	0.17	0.70
Visceral fat	0.28	0.28	0.56

* Calculated from parent/offspring and sib/sib correlations, as $Va/V_p + V_d/V_p$

the twin-pairs approach.

Estimates for developed societies.

***U.S. Hispanic children study*.** Butte and associates (2006) examined data for 1030 U.S. Hispanic children between the ages of 4 and 19 years; subjects were drawn from 319 families, and 51% were overweight. Body fat was assessed in terms of BMI, waist circumference, and dual x-ray estimates of body fat content, and habitual physical activity was also assessed by accelerometry. Coefficients for the narrow heritability of body composition were estimated at 018 to 0.35, and those for habitual physical activity ranged from 0.32 to 0.60.

***Framingham study*.** Coady et al. (2002) followed the BMI of 1051 participants in the Framingham study from the age of 35 to 55 years. Their BMI values showed a moderate broad heritability index (0.38). However, genetic factors apparently had little influence on fluctuations of BMI over the 20 years of observation. Cross-sectional analysis using data from the original Framingham cohort and their offspring yielded somewhat larger heritability estimates of 0.46 to 0.52 (Heller, Garrison, and Havklik, 1984).

Tecumseh Study. Longini et al. (1984) examined familial data for body mass index on a broad sample of 5,174 participants in the Tecumseh study, ranging in age from 6 to 74 years. Heritability data were co-varied for age, sex and socio-economic status, and coefficients of 0.35, 0.31 and 0.37 were determined, based on the three possible assumptions of no assortative mating, indirect and direct assortative mating, respectively.

Muscatine Ponderosity Study. Moll et al. (1991) looked at differences in the estimates of heritability for 1,302 family relatives in Iowa, depending on the assumptions that were made about the type of control of obesity (monogenic or polygenic). On average, the parents were aged ~45 years, and the children were ~20 years old. BMI values were adjusted for age, sex, and the type of family relationship. The conclusion was drawn that the data were best satisfied by a model with a single recessive locus plus polygenic effects and shared environmental effects; a heritability coefficient of 0.58 was cited.

***Utah Pedigrees Stud*y.** Hunt et al. (1989) estimated the heritability of cardiac risk factors in 1,102 adults aged ~36 years. Their sample was drawn from 67 Utah family pedigrees. After adjusting data for age and sex, heritability estimates were 0.24 for BMI (as compared with 0.54 in a twin study that had been conducted on the same population).

IRAS Family Study. The IRAS Family Study (Henkin, Bergman, & Bowden, 2003) was concerned mainly with genetic influences upon diabetes mellitus and insulin resistance. In order to obtain a population with a high prevalence of problems in glucose regulation, it recruited a sample of 1,379 African- and Hispanic Americans living in New York City. The mean age of the group was 45 years. BMI was measured, and a heritability index of 0.54 was determined; age, sex and ethnicity made only small contributions to this number (~2.3%).

British Insulin Resistance Study. In Britain, another study of Insulin resistance recruited 1634 individuals of Asian Indian

descent (86% Sikh and 14% Hindu families, with an average of 12 people per household). Metabolic disturbances were very common in these two populations (Zabaneh, Chanbers, & Elliott, 2009). Narrow-sense heritability coefficients for those not receiving medications for their diabetes were 0.31 for BMI and 0.27 for the waist-hip ratio.

Sleep Apnoea Study. Patel et al. (2008) measured BMI and waist circumferences as a part of a sleep apnoea study of 1,802 individuals from 310 families who were living in Cleveland, Ohio. Their average age of the subjects was ~35 years. Heritability indices were 0.55 for BMI, and 0.50 for waist circumference measurements.

Canadian Fitness Survey data. Katzmarzyk et al. (1999) obtained data on from the Canada Fitness Survey of 1981 and Campbell's Fitness Survey of Canadians, conducted in 1988. Their article looked at 7-year changes in obesity-related phenotypes in 376 pairs of spouses aged 20-69 years. For BMI, spousal correlations were ~ 0.18 in 1981, and 1988, and for the sum of 5 skin-folds correlations were ~0.20 for both surveys. Hunt et al. (2002) expanded this analysis, drawing on data from 655 women and 660 men. At baseline in 1981, heritability coefficients were 0.39 for BMI, 0.41 for the sum of 5 skin-folds, and 0.39 for waist circumferences, with much smaller but still significant coefficients for the change in these variables over the 7 years of observation (0.14, 0.12, and 0.45, respectively). It was concluded that age-related genetic effects may contribute to adiposity.

Danish Adoption Registry Study. Vogler et al. (1995) applied the family analysis methodology to 2,476 Danish adult adoptees. The model incorporated effects from the assortative mating of biological and of adoptive parents, from shared pre-adoptive environmental influences between the biological mother and the adoptee, and from a possible selective placement of the adoptee. The estimated heritability coefficient was 0.34, with no evidence of significant influence from a shared family environment either before or after adoption.

Radiologic Osteoarthritis Study. The primary objective of Bijkerk et al. (1989) was to study radiographic osteoarthritis, but data were also obtained on heights and weights. Subjects were a random sample of 1,583 older individuals (aged ~63 years) living in a suburb of Rotterdam, in the Netherlands. The estimate of heritability for BMI was 0.53, after adjusting data for age and sex.

Developing societies.

Visakhapatnam Study, India. This analysis involved 342 nuclear Indian families from several different castes (Arya, Duggirala, & Comuzzie, 2002). The sample of 1,912 individuals ranged in age from 6 to 72 years. A substantial amount of anthropometric data included body mass index and the sum of triceps and sub-scapular skin-folds. Heritability indices for these two measures were 0.25 and 0.31, respectively, after adjusting data for sex, age and caste. Substantial caste effects were thought to reflect a poor standard of living in some groups other than the Brahmins.

Oman Family Study. Bayoumi et al. (2007) investigated the metabolic

syndrome in a sample of 1,198 Omani Arabs aged 16-80 years. The older members of this group continued traditional farming, but the younger members of families had experienced a rapid change of lifestyle with the oil boom, and had moved into more sedentary occupations. The overall prevalence of the metabolic syndrome was 23%. Relatively high coefficients of heritability were calculated for BMI (0.68), percentage body fat (0.53) and waist circumference (0.40), with respective contributions of 0.16, 0.43 and 0.31 from co-variance effects.

***Baspendi Heart Study*.** In rural Brazil, de Oliveira et al. (2008) conducted a cardiac risk factors study on 1,666 members of 81 families aged >18 years. After adjusting for several co-variates (age, age^2, sex and age x sex interaction), broad heritability coefficients were substantially increased, to 0.40 for waist circumference, 0.41 for truncal obesity and 0.51 for BMI. Sedentary habits were measured, but heritability of this characteristic was not calculated.

Chinese Han sample. In a study focused primarily upon bone density, Deng et al. (2006) examined 217 complete nuclear families (585 parents and 446 children) of Chinese Han ancestry living in Changsha, China. Parents were aged ~60 years, and offspring ~31 years. The broad heritability of BMI was ~0.50, with the common environment shared by family members (the household effect, G_f) having a significant influence on this coefficient (indeed, if allowance was made for household effects, the heritability of BMI became statistically non-significant).

Korean Medical Insurance Study. The Korean Medical Insurance Study (Jee, Suh, and Won, 2002) was based on 7,589 individuals, drawn from1,891 families. BMI was included among the various cardiac risk factors that were measured. After adjusting data for age, sex, smoking and alcohol consumption, heritability was estimated from the slope of the line relating offspring to mid-parental values. For BMI, this coefficient was 0.26.

Taiwan Health-Screening Study. Wu et al. (2003) examined data for BMI, waist-to-hip ratio and the estimated percentage of body fat in 1,724 members of 431 families who were participating in a health-screening initiative in Taiwan. Age ranges for parents and for children were 35-81 and 9-49 years, respectively, and hypertensive and hyperlipidaemic subjects were excluded from the analysis. After age-adjustments, respective heritability coefficients for the 3 obesity markers were 0.39, 0.30 and 0.35, with family environmental factors having less impact on waist-hip ratio than on the other two surrogates of obesity.

Conclusion from family studies. A meta-analysis of the family studies yielded a 50th percentile heritability index of 0.46, with quite a broad range, from 0.25 to 0.68 (Elks et al., 2010). Most of the studies included in this average measured broad heritability (a value that included shared familial influences). Given the influence of age upon heritability, most studies were also complicated by differences of age between parents and their siblings, and by era effects (such as an amplification of the obesogenic genotype by the effects of the obesity-favouring environment now encountered in much of Western society) (Andreasen et al., 2008).

The genetic component was commonly calculated using the SOLAR

software package. The substantial difference in findings between twin and family analyses has generally been attributed to a differing impact of V_f, the shared environmental influence, when using these two options. This relative influence of environment is much smaller in family than in twin studies, and for family-based analyses it is sometimes not statistically significant. There also seem to be regional differences in heritability coefficients for BMI, with genetics having a much stronger influence in countries and population groups where there is access to an over-abundance of food. Similar gradations of genetic influence are found within nations, for instance in India, between high-caste, well-nourished Brahmins and lower caste groups who even in recent times have often remained undernourished (Arya et al., 2002).

Genetic markers of obesity

The body's chromosomes comprise a complex of DNA, RNA and protein. The original search for genetic markers of obesity looked for abnormalities of single genes, but technology that has been perfected over the last 2 decades now allows investigators to make a genome-wide search of an individual's chromosomes for loci that are correlated with overall adiposity, patterns of fat distribution, and levels of habitual physical activity (Lindgren, Heid, & Randall, 2009). It is now possible to determine the influence of both individual genes and their combinations upon phenotypic characteristics, and also to explore the influence of age, sex environment and a variety of epigenetic factors upon the expression of any given genotype.

The first single gene defect associated with human obesity was described by Montague, Farooqi, and Whitehead (1997). They discovered that a congenitally determined deficiency of leptin secretion led to early and severe obesity. Other monogenetic defects are associated with a variety of relatively rare obesity syndromes, such as the Prader-Willi syndrome. But many genes are potentially involved in metabolic regulation, and it is now recognized that obesity most commonly has a polygenic basis (that is, it depends on the combined response to small effects at a multiplicity of genetic loci, rather than on one aberration at a particular chromosomal site) (Hinney & Hebebrand, 2008). One report suggested that although a few of the mutations associated with obesity were monogenic, some 43% were inter-genic and 45% were intronic (that is, a situation where a nucleotide sequence within a gene has been removed by RNA splicing during maturation of the final RNA product) (Hindorff, Sethupthy, & Junkins, 2009). The location of genetic anomalies and their exploitation in treatment (San-Cristobal, Milagro, &Martinez, 2013) is complicated by this polygenic basis. Polymorphisms at sites regulating adiponectin (ADIPOQ), interleukin 1-b, IL-6, and tumour necrosis factor-α may all be involved in an excessive accumulation of body fat (Yu, Han, & Cao, 2011). An already complex situation is further complicated in that epigenetic factors can amplify or suppress the phenotypic expression of either a specific gene or a combination of genes regulating the accumulation of body fat.

The discovery of correlations between a given phenotype and specific chromosomal sites can confirm that inheritance influences a given characteristic, but it cannot measure the strength of this influence other than in

terms of the magnitude of the correlation coefficient for a given allele. More importantly, the discovery of a particular association may offer a clue as to the underlying physiological and biochemical mechanisms predisposing to fat accumulation in that person, and thus a potential pathway for treatment.

Observed associations.

There are two main approaches to unraveling the genetics of obesity- the study of single candidate genes and genome wide analyses. The first type of analysis begins from a hypothesis, such as the involvement of leptin or proprio-melatonocortin in metabolic regulation, and it then looks for anomalies in the genetic regions known to regulate the production of these substances (Bell, Walley, & Frougel, 2005). Because multiple genes are usually involved in the genesis of obesity, the impact of any single variant is usually small, and this methodology has had a correspondingly limited success. The first significant finding was a specific anomaly of the melanocortin-receptor gene that was negatively associated with obesity (Geller, Reichwald, & Dempfle, 2005).

The second approach makes an arbitrary genome wide analysis, looking through as many as 2,000,000 genetic variants in a search for any markers with a greater than expected frequency in individuals who are overweight or obese. Early studies of this type contrasted genome-wide analyses in individuals with a large BMI relative to people with a BMI in the normal range. Despite some positive findings, it was quickly appreciated that all of the genetic variants thus identified accounted for less than 5% of the observed inter-individual differences in BMI (Hebebrand, Volckmar, & Knoll, 2010; Locke, Kahali, & Berndt, 2015; McCarthy, 2010). This was a somewhat surprising finding, given the high levels of heritability inferred from twin and family studies. It might seem to imply that many loci remain to be discovered, the so-called "missing heritability" (Manolio, Collins, and Cox, 2009). One group of investigators thus suggested that only a limited association was being seen because too few rare genetic variants had been studied (Jenkins, Batterham, & Samocha-Bonet, 2013). Others have attributed problems in identifying significant variants to environmental and other epigenetic effects limiting gene expression (Fraga, Ballestar, & Paaz, 2005), to the polygenic aetiology of obesity, to the use of poor markers of obesity and to inadequate statistical techniques (Symonds, Budge, & Frazier-Wood, 2013).

Speliotes, Willer, and Berndt (2010) and Hruby and Hu (2015) pointed to more than 60 relatively *common* genetic markers that were now known to be associated in some degree with an increased susceptibility to obesity. Many of these sites affected susceptibility to obesity in children, as well as in adults (Zhao, Bradfield, & Zhang, 2011), although this was not always the case (Hollensted, Sahluwalia, & Have, 2015). But despite an increasingly broad analysis, the 32 most common genetic variants obstinately still account for less than 1.5% of inter-individual variation in BMI (Speliotes et al., 2010). People with the highest genetic risk (carriers of over 38 risk alleles on a genome-wide analysis) have a BMI that is on average only 2.7 kg/m^2 greater than that of individuals with a low genetic risk; in other words, the body mass is on average only 7.5 kg greater in a genetically vulnerable individual than in a normal person. A study of 191,161

European adults looked at copy number variants (those portions of the genome where sequences were repeated a differing number of times in different individuals); again it set the differential effect of two copy number variants at an increase in BMI of only ~ 3.5 kg/m^2 (Macé, Tuke, & Deelen, 2017). Thus, the study of genetic markers to date confirms that these play a statistically significant role in the genesis of obesity, but their level of influence is by no means sufficient to account for the dramatic rise in obesity of the population that has occurred over the last half century. It remains to be determined whether the study of epigenetic effects can explain this anomaly.

Mechanisms of operation

Chromosomal abnormalities associated with obesity include not only the monogenic and the polygenic, as discussed above, but also the oligogenic (where a small number of genes have quite a large impact upon an individual's susceptibility to obesity). We will look in detail at the first (and still an important determinant) of obesity, the FTO gene, and will examine other recognized loci more briefly.

FTO obesity gene. One of the first genome-wide studies of metabolic disorders compared 1924 individuals with type 2 diabetes mellitus against 2938 population controls (Frayling, 2007). Those with diabetes appeared to have at least 11 regions with specific genomic abnormalities, but one with a particularly strong linkage to fat accumulation involved the FTO obesity gene. This gene is located on chromosome 16; it encodes the fat mass and obesity-associated protein (FTO), also known as alpha-ketoglutarate-dependent dioxygenase.

FTO abnormalities modify feeding behaviour, leading to increased feelings of hunger and decreased satiety, but do not seem to change resting energy expenditure or physical activity significantly (Fawcett and Barroso, 2010; Speakman, 2015). Those individuals who have an anomaly of the FTO gene develop a greater than average BMI, a finding consistently confirmed by investigators (Loos, 2008; Scuteri, 2007; Speakman, 2015). An over-expression of the FTO gene in mice has similar obesogenic effects to those seen in humans, but If the FTO gene is "knocked out," the adiposity of the affected animal is reduced and energy expenditure seems to be increased (Speakman, 2015).

IRX3 is one locus of particular interest to those concerned with the genetic regulation of obesity by the FTO gene. Although IRX3 is situated at a distance of some 500 kB from the FTO gene, it interacts with this site and shows a strong association with obesity (Srivastnava, Srivastava, and Mittal, 2016). Among other functions, this locus mediates a browning of white fat (Claussnitzer, Dankel, and Kim, 2015; Pigeyre, Yazdi,and Kaur, 2016), thus modulating the body content of a tissue where any surplus energy intake can be quickly disbursed in heat production. The occurrence of a genetic variant at the IRX3 site reduces the capacity of adipose tissue for thermogenesis by a factor of 5, with a corresponding increase in fat storage.

Although a single variant in *FTO* (rs9939609) increases the odds of obesity in risk allele carriers by an estimated 23% per allele, this risk is readily moderated by an increase of physical activity. Thus, this mutation does not provide a good alibi for a person who has accumulated an excess of body fat. The

adverse effects of an IRX3 mutation can also be countered quite readily by dieting and an increase of habitual physical activity (Kilpeläinen, Qi, & Brage, 2011; Rankinen, Rice, and Teran-Garcia, 2010).

A meta-analysis of 10 studies confirms the important finding that that although those with the obesity-predisposing FTO allele accumulate fat more readily than their peers, they also lose fat more easily than those without this anomaly if they decide to participate in appropriate lifestyle interventions (Xiang, Wu, & Pan, 2016).

Other specific obesity-linked genes. Early reports identified at least 11 monogenic obesity-linked genes, including the FTO site (Table 9). Their role in modifying energy balance seems mediated, among other routes, through the leptin–melanocortin pathway (Farooqi, 2005; Pigeyre et al., 2016), with actions stemming from the leptin, leptin receptor, pro-opiomelanocortin (POMC), and melanocortin 4 receptor MC4R genes (Chambers, Elliott, & Zabaneh, 2008; Srivastnava et al., 2016).

One of the relevant genes (RGS7) is located near to the chromosomal region associated with G-protein 7 signaling (Aissani et al., 2006). Abnormalities at this site show association with both BMI and the percentage of body fat that are statistically highly significant. RGS7 is a GTPase activating protein; thus, it causes a fast inactivation of GTP, and an inhibition of GPCR signaling, thereby altering the reward behaviour that is normally associated with feeding (Anderson, Psosokhova, & Martem, 2009).

Another site of interest is 12q24.3; in one survey of 521 adults, it showed a strong genetic linkage to the amount of abdominal subcutaneous fat (as assessed by computed tomography after adjustment for a hydrostatic estimate of total body fat content) (Pérusse et al., 2001).

Three other loci showing significant linkages to central fat accumulation are located close to genes that regulate the level of sex steroids (Pérusse et al., 2001).

Four loci demonstrated an association with susceptibility to hunger (Bouchard et al., 2004), the most significant being with a locus (q24-q25) on chromosome 15, in the region of the neuromedin-b gene. A mis-sense mutation within this gene strongly increases the desire to eat, with resultant obesity.

In a study of 163 adults, Jacobson et al. (2006) further reported that the resting metabolic rate was linked to 3 chromosomes. Of these, the 3q26.1 location was linked to the secretion of ghrelin, the appetite increasing hormone.

At least 3 loci other than FTO are now

Table 9. Some specific individual genes identified as relevant to obesity, abdominal fat distribution, hunger and resting metabolic rate.

Affected variable	Gene	Marker	Location	Reference
Hunger and satiety	FTO	rs9939609	Chromosome 16 ?1RX3	Fawcett et al. (2010)
BMI and body fat %	RGS7	D1S184	Chromosome 1 1q43	Aissani et al. (2006)
Abdominal subcutaneous fat adjusted for total fat mass	HNF1	D12S2078	Chromosome 12 12q24.3	Pérusse et al. (2001)
Hunger	NMB	D15S206	Chromosome 15 15q24-q25	Bouchard et al. (2004)
Resting metabolic rate	GLUT2	D3S1763	Chromosome 3 3q26.1	Jacobson et al. (J2006)

Table 10. Increase of BMI (kg/m²) per risk allele as seen in genome-wide association studies (Frayling, 2007; Loos and Bouchard, 2008; Scuteri et al., 2007).

Chromosomal loci	Increase of BMI associated with allele (kg/m²)
FTO	0.39
Near TMEM18	0.31
Near M4CR	0.23
Near SEC16B	0.22

known to increase the BMI by more than 0.2 kg/m² per risk allele (Table 10), although in the case of these anomalies it is not immediately certain which specific gene or genes are involved (Frayling, 2007; Loos & Bouchard, 2008; Scuteri, Sanna, & Chen, 2007).

More recent reports have now identified at least 32 loci that are known to be associated with obesity, and 97 loci that could possibly impinge upon fat accumulation (Speliotes et al., 2010). One of these genetic variants is near the *GPRC5B* gene. The functions of the protein thus encoded are as yet unknown. However, some of the pin-pointed loci (*MC4R, POMC, SH2B1, BDNF*) are near to key hypothalamic regulators of energy balance, and one is near *GIPR*, an incretin receptor; incretins are hormones released after eating, and they increase the pancreatic secretion of insulin. Other quite widely scattered locations where mutations can give rise to obesity include *TMEM18, GNPDA2, NEGR1, ETV5, MTCH2, OLFM4 on13q14, HOXB5 on 17q21, and KCTD15* (Bradfield, Taal, & Timpson, 2012; Frayling, Timpson, & Weedon, 2007; Thorleifson, Walters, & Stefansson, 2009)(Table 11).

Many of the mutations that are linked to obesity seem similar in children and in adults, but a review of data from 20 studies covering 35,658 children found a few loci (rs13253111, near ELP3; rs8092503, near RAB27B, and rs13387838, near ADAM23) that seemed unique to children (Felix, Bradfield, & Monnereau, 2016).

Possible mechanisms underlying the heritability of obesity

The association between certain genetic anomalies and obesity provides clues as to the mechanisms that underlie the inheritance of obesity. Energy homeostasis depends upon a balancing of short-term signals coming from the gut that stimulate appetite (ghrelin secretion) or inhibit feeding (the secretion of peptide YY, glucagon-like peptide, and cholecystokinin), with longer-term effects from changes in the secretion of and sensitivity to insulin and leptin (the latter decreasing appetite and stimulating thermogenesis) (Farooqi, 2005).

Other possible mechanisms include an increased secretion of thyroid-stimulating hormone, altered sleep duration, altered energy expenditure when sleeping, altered total energy expenditures (Comuzzie, Col, & Laston, 2012), and an altered response to the inclusion of a physical activity programme in a weight-reduction programme. According to Rankinen et al. (2010), the A/A allele of FTO increases the risk of obesity in white subjects by a factor of 1.67, and after adjusting data for age, sex and baseline status, CC homozygotes showed 3 times larger fat losses than AA homozygotes when participating in similar exercise programmes (Table 12). However, this differential effect was not seen in the "black" members of their sample.

There is a frank absence of leptin in ob/ob mice, but in most humans changes in the activity of various regulatory mechanisms are more subtle; modifications are seen at sites associated with cellular development, weight,

Table 11. Genetic locations where variants have been associated with obesity.

Gene	Full name	Function	Author
GPRC5B (16p and 16q)	G-protein coupled C group 5 member B	May mediate cellular effects of retinoic acid on G protein signaling cascade	Loftus, Kim, & Sneddon (1999)
MC4R (18q21.32)	Melanocortin 4 receptor	Modifies feeding behaviour	Fan, Boston & Kesterson (1999)
POMC (2p23.3)	Propriomelanocortin	Regulates appetite and satiety	Varela & Horvath (2012)
SH2B1 (16p2.11)	SHB2 adaptor protein 1	Associated with obesity	Nelms, O'Neill & Li (2000)
BDNF (11p14.1)	Brain-derived neurotrophic factor	Regulation of food intake	Rosas-Vargas, Martinez-Ezquerro & Bienvenu (2011)
GIPR (19q.13.3)	Gastric inhibitory polypeptide receptor	Glucose and insulin regulation	Saxena & Hivert (2010)
TMEM18 (2p25.3)	Trans-membrane protein 18	Insulin and glucagon signaling	Wiemerslage, Gohel, & Maestri (2016)
GNPDA2 (4p12)	Glucosamine-6-phosphate deaminase 2	Variants associated with obesity	Zhao, Bradfield & Li (2009)
NEGR1 (1p31.1)	Neuronal growth regulator 1	Variants associated with obesity	Thorleifson et al., (2009)
ETV5 (3q27.2)	Transcription fraction Etv5	Orthologue linked to obesity	Williams, Klockars, & Eriksson (2016)
MTCH2 (11p.11.2)	Mitochondrial carrier 2	Variants associated with obesity	Renström, Payne & Nordström (2009)
OLFM4 (13q14.3)	Olfactomedin 4	Variants associated with obesity	Albuqueque, Nóbrega & Rodriguez-López, 2014 ; Bradfield et al., 2012)
HOXB5 (17q21.32)	Homebox protein HOXB5	Variants associated with obesity	Bradfield et al. (2012)
KCTD15 (19q13.11)	Potassium channel tetramerization domain 5	Variants associated with obesity	Thorleifson et al. (2009)

hormonal regulation and biological functions such as synaptic signaling, glutamate signaling, insulin secretion and response, lipid biology and adipogenesis (Elks et al., 2010; Locke, Kahali, & Berndt, 2015). One genetic variant (ADCY-POMC) seems to predispose to reduced pubertal growth, early puberty, and adult obesity (Cousminer, Berry, & Timpson, 2013). Variants associated with polygenic obesity (Pigeyre et al., 2016) act upon a multiplicity of systems, including pathways in the central nervous system, mechanisms of food sensing and digestion, adipocyte differentiation, insulin signaling, lipid metabolism, muscle and liver biology, and gut microbiota. A number of the relevant loci influence the production of substances that are highly expressed in the central nervous system, particularly in the arcuate nucleus of the hypothalamus. These brain regions influence appetite, satiety, energy expenditures and behavioural patterns (Willer, Speliotes, & Loos, 2009). Notably, the fat mass and obesity associated protein FTO is found in

Table 12. Association between alleles of the FTO rs8050136 genotype and the response of "white" individuals to a standard exercise programme, after adjustment for age, sex and baseline characteristics (based on data of Rankinen et al., 2010).

Variable	A/A allele	A/C allele	C/C allele
D BMI (kg/m^2)	0.3	-0.4	-0.2
D Fat mass (kg)	-0.2	-0.8	-0.8
D Fat (%)	-0.3	-0.9	-1.0

parts of the brain that govern energy balance (Gerken, Girard, & Tung, 2007) and feeding behaviour (Fredriksson, Hagglund, and Olszewski, 2008). Its presence in the hypothalamus is up-regulated following food deprivation, and this is known to modify lipolytic activity in adipose tissue (Wahlen, Sjolin, and Hoffstedt, 2008).

Disruption of the melanocortin receptor MC4R gene causes hyperphagia, hyperinsulinaemia and hyperglycaemia (Huszar, Lynch, & Fairchild-Huntress, 1997). SH2B1 is an adaptor protein involved in various signaling pathways. It increases serum levels of leptin (Li, et al., 2007), and disruption of the SH2B1 gene predisposes to hunger and insulin resistance. Other genes act peripherally, mainly in adipose tissue. The gene encoding transcription factor AP2B (TFAP2B), for example, influences glucose transport, lipid accumulation, and adiponectin expression (Huszar et al., 1997), the gene encoding transcription factor cMAF is involved in adipogenesis (Meyre, Delplânque, and Chevre, 2009), and the gene for natural cytotoxicity-triggering receptor 3 (NCR3) probably mediates its effects by causing a low-grade inflammation of adipose tissue (Virtueand Vidal-Puig, 2008).

Epigenetic effects and other modifiers of gene expression

Epigenetics involves the study of heritable changes in gene expression (particularly the change from active to inactive genes) that occurs without alterations in the underlying DNA sequence. The term epigenetics was first introduced in 1942 by the developmental biologist Conrad Hal Waddington (Choudhuri, 2011). Translation of an obesity-favouring genetic profile into an obese phenotype depends to a large extent upon epigenetic mechanisms that control expression of the relevant gene sequence (Cordero, Li, & Oben, 2015); in effect, these epigenetic mechanisms act as very effective ON/OFF switches (Dalgaard, Landgraf, & Heyne, 2016; Quarta, Schneider, & Tschöp, 2016).

The epigenome is highly variable, being modified by nutritional status, habitual physical activity, aging, and other factors (Franks & Ling, 2010). Evidence of epigenetic actions can potentially be detected through changes in DNA methylation, covalent reactions in the structure of histone-amino acid chains, and microRNA-mediated regulation around sites such as the FTO gene (Bell, Finer, & Lindgren, 2010; Cordero et al., 2015; Wang, Zhu, & Sneider, 2010).

Epigenetics may eventually explain much of the surprisingly large "missing" component in the heritability of obesity (McCarthy & Hinchhorn, 2008; Pigeyre et al., 2016), but as yet studies have been blighted by contradictory reports and the potential of this approach has still to be realized (Symonds et al., 2013; Waterland, 2014). Indeed, a meta-analysis conducted in 2015 concluded that there was still no consistent evidence of a relationship

between global methylation and obesity (van Dijk, Molloy, & Varinli, 2015), possibly because the data were confounded by effects from diet, alcohol, tobacco, age, sex and ethnic background that were not always included as co-variates in the analysis. Nevertheless, some epigenetic associations have been demonstrated for gene locations of metabolic importance (van Dijk et al., 2015), with evidence of the methylation of DNA at sites such as FTO (Bell et al., 2010). The situation may be clarified through a further exploration of epigenetic effects and nutrient-gene interactions (Moleres, Martinez, & Marti, 2013), coupled with the use of more precise measures of obesity than self-reported BMI.

Methylation of the DNA prevents the binding of transcription factors, inhibiting transcription and RNA production, and it may also recruit transcription co-repressors, thus effectively silencing the gene concerned (Herrera, Keildson, & Lindgren, 2011). Such effects are exacerbated by changes in the shape of the histone chains that restrict access to DNA. Both methylation and histone chain modification seem to be age- and tissue-specific processes, and methylation is also modified by dietary levels of folic acid, dieting, weight loss and regular exercising (van Dijk et al., 2015).

Many epigenetic effects are probably induced early during foetal development and by the familial environment immediately following birth (Soubry, Hoyo, & Jirtle, 2014). Indeed, some epigenetic changes can be detected in sperm chromatin even prior to conception (Houfflyn, Matthys, & Soubry, 2017). Thus, early life over-nutrition leads to DNA methylation of the hypothalamically expressed proprio-melanocortin promoter, which has a powerful influence upon feelings of hunger and satiation (Plagemann, Harder, & Brunn, 2009). Over the course of the life cycle, environmentally induced epigenetic influences can cause a substantial divergence even in the phenotype of monozygous twins (Fraga et al., 2005).

Advances in our understanding of obligatory and facilitated epigenetic variation obtained from genome-wide and epigenome-wide association studies are now beginning to offer a better understanding of gene–environmental interactions}, as well as offering potential new pathways for the treatment of obesity (Bouchard, Rabasa-Lhoret, & Faraj, 2010; Milagro, Miranda, & Portillo, 2013). However, there remains a need to elucidate the impact of dietary and environmental factors, age, habitual physical activity and sex, all of which can modify epigenetic effects (Cordero et al., 2015).

Dietary influences. Campión et al. (2009) documented some of the many potential dietary influences that can have epigenetic effects (Table 13). Another area of nutrition with a substantial impact upon the expression of obesity-favouring genes is the intestinal flora (Bäckhed, Ding, & Wang, 2004; Turnbaugh & Gordon, 2009). Studies in knock-out mice have demonstrated that a suppression of fasting-induced adipose factor (Fiaf) is essential for the microbial-induced deposition of triglycerides in adipocytes (Bäckhed et al., 2004), and variations of the core gut microbiome are associated with disturbances of energy balance and obesity (Turnbaugh & Gordon, 2009).

Physical activity. After a series of reports had spoken both for and against an effect of habitual physical activity upon the impact of FTO variants, a meta-analysis of

Table 13. Some dietary factors modifying epigenetic effects upon the development of obesity. Ssee Campión, Milagro, and Martinez (2009) and Wu and Suzuki (2006) for references.

- Maternal dietary restriction
- Reduction of uterine blood flow
- Protein restriction during pregnancy
- Restriction of methyl donors (e,g. vitamin B complex, methionine)
- Hypomethylating compounds (e.g. bisphenol A)
- High fat diet
- alcohol
- vitamin A
- selenium deprivation
- vegetarian vs. omniverous diet
- tocopherols
- tea phenols
- garlic
- genistein

45 studies on 218.166 adults and 9 studies on 19,268 children (Kilpeläinen et al., 2011) demonstrated that the influence of variants in intron1 of the FTO gene upon the risk of developing obesity was attenuated by regular habitual physical activity. This association was established despite a relatively weak categorization of study participants (a binary classification of active vs. inactive individuals, with the inactive subjects having a sedentary job and undertaking less than 1 hour per week of moderate to vigorous leisure-time or commuting activity). Specifically, it was found that the minor FTO allele rs9939609 increased the risk of obesity by 30% in inactive adults, but by only 22% in those who engaged in regular physical activity. This differential effect was greater in North American than in European studies, possibly because the average population level of physical activity was lower and/or dietary challenges were greater in North America. However, physical activity did not modify the risk significantly in children (possibly simply because of a smaller sample size), and even in adults the apparent impact was only a small change in what was initially a relatively small impact upon the risk of obesity. Nevertheless, the full impact of physical activity may have been obscured because only a simple binary measure of this variable was used in the analysis.

Interestingly, a 6-month physical activity programme for previously sedentary men induced significant genome-wide changes in the methylation of adipose tissue (Ronn, Volkov, & Davegardh, 2013).

Effects of an individual's sex. The influence of genetic variants upon an obese phenotype can be strongly modified by an individual's sex. A study of waist-hip ratios identified 7 loci where variants had a greater impact upon obesity in women than in men (Lindgren et al., 2009)(Table 14). Interestingly, these locations were different from those associated with BMI, and indeed effects persisted after controlling data for BMI; possibly, this set of genes control local fat deposition rather than the hypothalamic regulation of food intake and habitual physical activity.

A part of the sexual differentiation reflected a gender-related impact of the genetic anomaly on hip vs. waist dimensions. The primary functions of these loci are quite varied: HOXc13 controls embryonic development, RSP03 and VEGFA angiogenesis and adipogenesis, ADAMT59 and GRB14 insulin signaling and resistance, LYPOLAL1 lipase signaling, and ITPR2 intracellular calcium signaling. Several of the gene sites that were identified differed in their impact upon gluteal and

Table 14. Single nucleotide polymorphisms (SNPs) and nearby genes with sex-specific impact on waist-hip ratios. Based on data of (Lindgren et al., 2009)

SNP	Nearby gene	Male beta-weight	Female beta-weight
rs9491696	RSP03	0.026	0.047
rs6905288	VEGFA	0.013	0.052
rs10195352	GRB14	0.009	0.053
rs4846567	STAB1)LYPOLAL1	0.010	0.064
rs718314	ITPR2-SSPN	0.010	0.047
rs1443512	HOXC13	0.011	0.048
rs6795735	ADAMT59	0.017	0.033

abdominal deposition of fat (RSPO3, TBX15, ITPR2, WARS2 and STAB1).

A further meta-analysis, based on 270,775 individuals participating in 94 studies (Randall, Winkler, & Kutalik, 2013), confirmed that some genetic traits influenced the waist/hip ratio but not the BMI. This analysis also identified 3 further markers that exerted effects in women but not in men (near MAP3K1, HSD1784 and PPARG respectively). However, there was no evidence that opposite types of effect occurred in men than in women; rather the obesogenic effects were more pronounced in women. Underlying mechanisms included differences in insulin sensitivity, lipid-related states and triglyceride concentrations.

Complications arising from genetically-mediated differences in habitual physical activity

In addition to the impact of habitual physical activity upon obesogenic genotypes, there are significant linkages between genotype and commitment to habitual physical activity. Some of the similarities in body build between close relatives descr9bed above thus reflects genetically-mediated similarities in habitual physical activity rather than inherited differences in the genes that control fat accumulation more directly. However, until recently little attention has been paid to genetic and epigenetic influences modifying habitual physical activity and thus influencing a person's body fat content. This remains an important area to explore more completely, since data from the Framingham study suggests that the genetic influence upon obesity is much smaller in active than in sedentary individuals, with the influence of the FTO gene being attenuated by as much as 40% (Guo, Liu, & Wang, 2015).

Animal studies

Animal studies underline the importance of activity patterns. Studies of wild mice born to obese mothers found that they were not hyperphagic, but rather they had low levels of habitual physical activity and daily energy expenditure (Baker, Li, & Kohorst, 2013). Likewise, obesity in the SL (lymphoma susceptible) mouse was associated not with a high intake of food, but rather with a persistently low level of habitual physical activity (Li et al., 2013).

Twin studies

Twin studies in humans have suggested that the heritability coefficient for physical activity lies in the range 0.3-0.8. Thus, a study of 411 Portuguese twin pairs used the Baecke questionnaire to assess physical activity. It found a heritability of 68% in the men, but only 40% in the women (Maia, Thomis, & Beunen, 2002). Likewise, a seven-country analysis of leisure-time exercise behaviour in 37,051

twin pairs set heritability coefficients in the range 48-71% in most countries except Norway, where it was only 27% (Stubbe, Boomsma, & Vink, 2006).

Another study based on 1432 twins and sibling pairs found a heritability of exercise participation of 68.5% in males and 46.3% in females (De Moor, Liu, & Bomsma, 2009). The genetic overlap between the 2 sexes was 0.32, suggesting that some of the exercise behaviours were regulated by different genes in men and women.

Mustelin et al. (2012) further noted that in 1274 Finnish twins, heritability was greater for sports participation (64%) than for other types of leisure activity (41%).

Family studies

Pérusse and associates (1989) examined physical activity patterns in 1610 members of 375 Quebec families. A 3-day physical activity record was kept, and a path analysis divided the variance of this score into genetic, cultural (related to family lifestyle) and other environmental components, neglecting the complications of dominance, epistasis and gene-environment interactions. Heritability of a person's average level of habitual physical activity was estimated at 27%, and cultural factors within the family contributed a further 12% to the variance of daily exercise at an intensity > 5 METs. Bouchard and Tremblay (1990) estimated that about 40 percent of the variance in resting metabolic rate, the thermic effect of food and the energy expended during low to moderate intensity exercise was also explained by inherited factors. In another family study based on 1693 Brazilians, the heritability of physical activity in non-sedentary individuals was 35%, but figures were much lower for sedentarism, weekly activity and intensity of activity (9-14%) (Horimoto, Giolo, and Oliveira, 2011).

Longitudinal studies

Several longitudinal studies have suggested that inherited differences in habitual physical activity diminish as a person ages (Aaltonen, et al., 2013; Eriksson, Rasmussen, and Tynelius, 2006; van der Aa, De Geus, & van Beijsterveldt, 2010).

Genetic markers

Positive findings from genome-wide studies of physical activity are presently limited. An analysis of 432 markers on 767 subjects from the Quebec family study (Simonen, Rankinen, & Perusse, 2003) found a significant linkage with physical activity at one chromosome site (2p22-p16) and four others showed suggestive linkages with inactivity, total activity, moderate to strenuous physical activity, and total time devoted to physical activity. Graff et al. (2017) confirmed the association between the FTO locus and habitual physical activity, as previously described by Kilpeläinen et al. (2011). A study from Japan linked another novel SNP located in the inter-genic region between NPSR1 and DPY19L1 to questionnaire estimates of habitual physical activity in an adult population (Hara, Hachiya, & Sutoh, 2018).

Other genome-wide analyses have as yet shown few associations with exercise participation have been identified, perhaps because of a limited sample size and rather crude assessments of habitual physical activity. In an analysis of genome-wide data for 8,842 adults, Kim et al. (2014) did not find any one SNP with a significant impact, but they identified 76 sites with some contribution to the

prediction of habitual physical activity. The 19p13.3-13.2 region has, however, shown suggestive linkages to muscle performance and blood flow, which might in turn influence exercise behaviour (De Moor et al., 2009; De Moor, Posthuma, & Hottenga, 2007). Moreover, 37 novel single nucleotide polymorphisms in the PAPSS2 gene and 2 inter-genic regions at chromosome sites 2q33.1 and 18p11.32 have been associated with questionnaire estimates of exercise participation (De Moor et al., 2009). Hara, Hachiya, Sutoh et al. (2018) identified another specific STP linked to physical activity; this was located in the intergenic region betweenNPSR1 and DPY19L1. However, the total heritability (~3.3%) was very low in this sample of middle-aged adults.

Bauman et al. (2012) posited that genetic influences could have both positive and aversive consequences for habitual physical activity. Further, they noted that there were associations with many of the same genetic loci that have been associated with obesity including sites controlling dopaminergic and melanocortinergic pathways, the MC4R receptor (Loos, Rankinen, & Tremblay, 2004), the leptin receptor (Stefan, Vozarova, & Del Parigi, 2002), and the dopamine receptor (Simonen, Rankinen, & Perusse, 2003).

Plainly, there is a need for further careful analysis, applying objective techniques such as accelerometry rather than simple questionnaires to large subject samples in order to distinguish the impact of genetically determined differences in physical activity and other co-variates upon the fraction of heritability that is presently attributed to obesity-related genes.

Lessons learned from animal studies

There are a number of important practical advantages to the use of experimental animals rather than human volunteers when studying the inheritance of obesity. The food intake of a batch of animals can be carefully controlled in terms of energy content and type, and if desired a high fat or a high carbohydrate diet can be provided. Further, habitual physical activity and resulting energy expenditures can be closely regulated, using such well-established methods of daily exercise as an activity wheel, enforced swimming with weighted tails, or running on a treadmill in response to repeated electrical shocks.

Genetic analyses are also facilitated in small mammals because they breed large families over relatively short periods of time. Further, it is possible to explore whether there are epigenetic effects caused by over-feeding or underfeeding, both while the animals are *in utero* and subsequent to birth. Finally, investigators are free to test the efficacy of a wide range of pharmaceuticals that could potentially help in the treatment of obesity. On the other hand, the artificial generation of random mutations by radiation or chemical agents and their reproduction in a sufficient number of offspring for a research study is a costly undertaking.

It is not always easy to transfer the findings obtained on small laboratory mammals to human situations, given a differing body size, lifespan and overall substantial evolutionary divergence. Further, it must be admitted that both the enforced physical activity of experimental animals and the enforced inactivity of controls are rather abnormal situations, as is the standardized diet of the animal laboratory. Another particular weakness of animal models is that they have often focused upon a relatively rapid onset of

obesity, as contrasted with the slow development typical of human experience (Symonds et al., 2013).

Nevertheless, an enormous number of transgenic and knock-out mouse models have been created by genetic engineering since a mapping of the human genome identified appropriate loci which, if mutated or expressed as trans-genes, led to unusual leanness or obesity (Rankinen, Zuberi, & Chagnon, 2006). Studies of such genetically modified animals have added substantially to our knowledge of the mechanisms governing biological energy balance, although if an animal is followed over a long period, care has to be taken that the body has not found some method of adapting to the missing or modified gene. One can see the effects of mutations of certain genes upon the propensity for obesity, and can also determine whether the animals that have become obese have any particular difficulties in reducing excess fat stores by a combination of greater physical activity and dietary restriction.

Discussion and conclusions

Given the data reviewed in this article, can individuals who are obese legitimately plead a genetic alibi, blaming their obesity upon an unfortunate inheritance of obesogenic genes? Despite a substantial volume of research, the answer to this question remains far from clear. There is no doubt that rare genetic abnormalities can cause gross obesity, both in animals and in humans. Twin and family studies also point to substantial heritability coefficients for obesity. However, formal genome-wide analyses account for only a small part of the variance in BMI and other surrogates of fat accumulation. It remains to be clarified whether the "missing variance" reflects an inflation of coefficients by genetically mediated differences in habitual physical activity, a poor choice of markers of obesity, an inadequate search of genetic variants, or a suppression of genetic response by epigenetic influences.

A reasonable conclusion from the data currently available is that genetic factors do predispose some people to accumulate fat more readily than others, by modifying regulatory functions in both the hypothalamus and adipose tissue. However, there are also substantial effects from genetically controlled inter-individual differences in habitual physical activity and from environmental influences (including personal choices in regard to habitual physical activity and dietary patterns). Moreover, although certain genetic abnormalities predispose to the accumulation of body fat, this susceptibility to obesity can be greatly minimized by avoiding over-eating and taking an adequate daily dose of physical activity. Further, some of the obesogenic genes make it easy for a person to shed excess fat when participating in an appropriate weight-loss programme. The weakness of the "genetic alibi" has been underlined by studies of the FTO genotype; a meta-analysis of 10 recent studies has shown that this genotype not only favours fat accumulation, but also facilitates the response to a weight-loss programme relative to that of non-carriers (Xiang et al., 2016). Thus, a supposed genetic predisposition to obesity should not serve as a reason for allowing a person to remain excessively fat.

A number of topics merit further research. It remains unclear whether "thrifty genes" had evolutionary value for primitive hunter-gatherers and/or agriculturalists. How frequent were the severe famines when a gross

accumulation of fat would have helped survival? And would this same accumulation of fat have had a negative impact upon marriage prospects or survival during intervening periods of plenty?

Twin and family studies seemingly point to a substantial heritability of obesity. But how much of this is due to inter-individual differences in habitual physical activity? Some studies have not included physical activity as a co-variate, and others have used only a very weak indicator of this variable. It thus remains important to determine how much of the apparent heritability of obesity really reflects the heritability of habitual physical activity.

The relatively rapid development of the obesity epidemic makes it most unlikely that this phenomenon can be explained by any change in the typical population genotype. This leaves the question as to how far a rapid change of epigenetic influences could explain either the "missing heritability" or the obesity epidemic. Better data are needed to assess the quantitative impact of epigenetic and environmental factors upon expression of an individual's genotype. Finally, there is need for a closer examination of the role of gut microbiota in modifying an individual's susceptibility to obesity.

Future genome mapping seems likely to identify more obesity-predisposing genotypes, and it may point more clearly to underlying mechanisms, thus may facilitating and focusing future preventive efforts. However, such discoveries should not be allowed to strengthen the "alibi" of those who seek an excuse for not participating in well-designed physical activity and diet-based fat reduction programmes.

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Authors' Qualifications

The author's qualifications are as follows: Roy J. Shephard, C.M., Ph.D., M.B.B.S., M.D. [Lond.], D.P.E., LL.D., D.Sc., FACSM, FCSEP, FFIMS.

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