Chapter 2
The Contribution of Heredity to Clinical Obesity

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2.1 Introduction

In order to discuss the contribution of heredity to clinical obesity, we first need to define our terms of reference to give us the common ground that is needed to explore the relationship between heredity, the environment, and clinical obesity. This will also serve to introduce these subjects for later chapters of this volume covering other aspects of the relative contributions of heredity and environment to the final clinical outcome of obesity. The importance of understanding the mechanisms underlying obesity cannot be overstated. Global rates of obesity are rising fast in most countries and the economic implications for maintaining the health care systems of those countries under the increasing burden of comorbidities and ill health are enormous [1].

2.2 Defining Heredity

Heredity can simply be defined as the transmission of characteristic traits from parent to offspring. In the mid-nineteenth century, Mendel took this idea and by painstaking experimentation was able to formalize it as his two laws of heredity: the law of segregation and the law of independent assortment. The study of the science of heredity is genetics. In the twenty-first century, we now know the molecular basis of the principles of heredity and though our understanding of human genetics is by no means complete, the information that we have on DNA, the human genome sequence, epigenetics, and the environment all inform our understanding of heredity. We should be clear from the outset that using the term heredity does not imply that there is a purely genetic mechanism underlying the transmission of a trait. For many common traits, and for common obesity in particular, the influence of the environment is clearly strong.

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2.3 Clinical Obesity

As with heredity, a definition of clinical obesity is needed and for the purposes of this chapter, obesity is defined using the World Health Organization criteria (see http://www.who.int/mediacentre/factsheets/fs311/en/index.html). This defines adult obesity as a body mass index (BMI) greater than 30 kg/m^2, overweight as a BMI between 25 and 30 kg/m^2, and leanness as a BMI less than 25 kg/m^2. BMI has become widely accepted as a measure of obesity because of the simplicity and reproducibility of obtaining this measure in large numbers of people. It should not be used uncritically however, as BMI is affected by the proportion of heavier muscle tissue to lighter fat tissue, e.g., bodybuilders could be classed as clinically obese using the BMI definition alone. Equally, the specific presence of excess abdominal fat tissue, and not just excess fat tissue in general, is very important for determining health outcomes in obesity [2, 3] and the metabolic syndrome [4]. This has led to other simple measures such as waist–hip ratio (WHR) and skinfold thickness, and recently more sophisticated measures of body composition such as air displacement plethysmography and dual energy X-ray absorptiometry (DEXA) (see references [5, 6] for discussion of obesity-related phenotypes).

2.4 The Environment

The third basic term that we need to define is environment. In biological terms, the environment is the surroundings that an organism exists within and interacts with. Within this definition, and with respect to obesity, the environment can cover anything from food availability to infectious disease prevalence to provision of treatment. It is clear that the rapid rise in obesity seen over the last few decades cannot be due to genetic changes; therefore, environmental effects are extremely important to delineate. However, this does not rule out the possibility that the changing environment has revealed in our genome the presence of variants that are very predisposing factors for obesity.

2.5 The Obesogenic Environment and the Rise in Obesity

The rapid rise in obesity cannot be due to the slow changes in the human genome that occur over thousands of years in response to strong evolutionary pressures. This leaves us with two possibilities: either the rise in obesity is purely due to nongenetic changes or the environment has changed enough that positive genetic adaptations to the old environment are now having a negative effect in the new environment, resulting in obesity. This is why the phrase “obesogenic environment” was coined (first PubMed reference in 1999 [7]), as a way of referring to the current environment, which differs in many ways from the environment that existed prior to the mid-1950s, i.e., before the end of food rationing in the Allied countries after World

War II. Our current environment is considered obesogenic because of the ready availability of cheap, calorie-rich foods, the increasing trend toward office working due to automation and computerization of manual jobs, the rise of leisure pastimes such as video games that require little or no physical effort, and the ubiquity of the Internet allowing activities that previously required some physical effort, such as shopping or social interaction, to occur through a computer.

2.6 Why Aren't We All Obese?

It has been generally accepted, both within the medical profession and in the wider community, that obesity is simply the consequence of eating too much and exercising too little. However, despite many years of expensive public health campaigns and clear evidence that large numbers of people diet regularly, the rise in obesity continues. In a heavily regulated environment, anyone can be made to lose weight by forcing a reduction in their caloric intake. However, in the real world, exposed to the obesogenic environment every day, it is virtually impossible to sustain diet-induced weight loss over many years. While the environment is a fundamental factor in the rise of obesity, this raises the important question of why it is that not everyone is obese. Historically, obesity has always existed, though at much lower frequency, and there is no doubt that heredity has a role to play in the determination of our body size within a particular environment.

2.7 Is Obesity Heritable?

It is one thing to observe anecdotally that obesity seems to run in families and another to try and formally measure its heritability. Heritability is the proportion of the variation of a trait that is genetic in origin. As we have seen above, there are good reasons why we might think that obesity is wholly environmental. This probably explains why even though the evidence has been there since the 1960s [8], it has only been with the discovery of rare, monogenic, extreme obesity disorders (see Chapter 3) [9], syndromic forms of obesity (see Chapter 4) [10], and genome-wide association scans (see Chapter 5) that the academic community became open to the idea that common obesity could have a strong genetic basis. Many study designs exist that can give information on the heritability of a trait, and the ones used in the field of obesity research will be explored here, purely from the angle of what information they have provided about heredity and obesity. We will cover twin studies, adoption studies and studies of families. Case–control studies can provide additional information about the role of specific genes in heredity, and they will be discussed in this context. Finally, a short description of two specific confounding factors when investigating heredity and obesity will be mentioned. A detailed discussion of statistical approaches to calculating heritability statistics in these studies is beyond the scope of this chapter and the reader is referred to a recent review [11].

2.8 Twin Studies

Some of the first twin studies ever reported were conducted by Sir Francis Galton (1822–1911). In the 1870s he published a series of seminal articles arguing that heredity was a stronger factor than environment in determining the characteristics of twins [12]. The first systematic comparison of twins was reported by Siemens in 1924 [13]. He determined that any heritable disease will be more concordant in identical twins than in nonidentical twins, and concordance will be even lower in nonsiblings. In his experiments, he compared the numbers of pigmented skin lesions ("moles") in twins, and then correlated the mole counts between identical and nonidentical twins. The correlation was higher in identical twins (0.4) than in nonidentical twins (0.2), suggesting the importance of genetic factors in mole count.

Since then, twin studies have been widely used to help disentangle environmental and genetic effects. Several different study designs have been developed: the classical twin study, the extended twin study, which includes family members (parents, siblings, spouses) and in some cases virtual twins (same-age biological and nonbiological siblings reared together since birth), and studies of identical twins discordant for a trait of interest. Furthermore, obesity-related traits can be measured at a single time point (cross-sectional study) or multiple measurements can be taken at different time points (longitudinal study). An overview of twin study designs is given in Table 2.1.

Table 2.1 Overview of twin study designs

Twin study design	Key characteristics	Application
Classical	Comparison of phenotypes in MZ and DZ twins	Estimate the contribution of genetic and environmental effects
Extended	Family members (parents, siblings, spouses, offspring) included	Estimate G × E covariance, imprinting, parent-of-origin effects
Extended with virtual twins	Virtual twin, i.e., same-age nonbiological sibling (adoptee), included	Estimate common environmental effects that cannot be separated from nonadditive genetic effects using biological siblings only
Co-twin control	Twins answer questionnaires about themselves and their co-twin	Reduce the risk of misreporting often seen in self-reported data
Discordant MZ twins	Case–control study with perfectly matched control	Estimate environmental and epigenetic effects

Table of published twin study designs used in the investigation of heritability of obesity-related traits, including key characteristics and applications. Key: G × E = gene–environment interaction

2.8.1 Types of Twin Studies

2.8.1.1 The Classical Twin Study

The classical twin study compares the phenotypic resemblance of monozygotic (MZ; identical) and dizygotic (DZ; nonidentical) twin pairs. MZ twins are virtually 100% genetically identical whereas DZ twins share on average 50%. Comparison of MZ and DZ twins offers the first estimate of the extent to which genetic variation determines the phenotypic variation of the trait.

If MZ twins show a higher degree of similarity than DZ twins, this indicates that the trait is under some level of genetic control. The heritability (h^2) of a trait can be estimated from twice the difference between the correlation in MZ (r_{MZ}) and the correlation in DZ twins (r_{DZ}), i.e. ($h^2 = 2(r_{MZ}–r_{DZ})$. For example, a correlation of 0.4 in MZ twins and 0.2 in DZ twins gives a heritability estimate of 2(0.4–0.2), which equals 0.40 or 40%.

The proportion of the variance that is due to shared environment is the difference between the observed twin correlation and the heritability. In MZ twins, the proportion is $r_{MZ}–h^2$, and in DZ twins $r_{DZ}–h^2/2$, where r is the correlation between twins.

Traditionally, most twin studies have used analysis of variance (ANOVA) and intraclass correlations for analysis, but now most studies use structural equation modeling (SEM). In SEM, genotypic and environmental effects are modeled as the contribution of unmeasured variables to the potentially multivariate phenotypic differences between individuals. The contributions of the unmeasured variables are estimated as regression coefficients in the linear regression of the observed variables on the unmeasured variables. This means that SEM can accommodate the analysis of many covariates, including, e.g., gender differences in heritability.

2.8.1.2 The Extended Twin Study

The effects of cultural transmission, gene × environment covariance, and parent-of-origin can be determined by extending the classical twin study to include parents, siblings, spouses, and offspring. It can also be extended to include virtual twins. A virtual twin is a same-age nonbiological sibling, i.e., an adoptee who shares the same family environment but not the genetic background. Inclusion of virtual twins provides an opportunity to estimate common environmental effects on phenotypes that cannot be separated from the nonadditive genetic component using only biological siblings. In a relatively small study (929 individuals) using virtual twins [14], 64% of the variance in BMI was explained by nonadditive genetic effects with some contribution from common environmental factors. The study concluded that both genetic components and common environmental factors such as diet or exercise play an essential role in BMI.

2.8.1.3 The Co-twin Control Study

A study of 713 MZ and 698 same-sex DZ twin pairs aged 22–28 years were assessed for eating, dieting, and physical activity using structured questionnaires. Each twin was asked to describe their own eating and exercise habits as well as compare them to those of their co-twin. For all twin pairs, the co-twin for whom both twin pair members concordantly answered that this twin eats more, snacks more, eats more fatty foods, eats faster, and exercises less had significantly higher BMI and waist circumference. Multivariate regression analysis revealed co-twin differences in the amount of food consumed as the strongest independent predictor of intrapair differences in BMI and WC. This type of study design, while rarely used, improves the risk of misreporting that is often seen in subjective self-reports [15].

2.8.1.4 The Discordant MZ Twin Study

As might be expected in genetically identical individuals, phenotypic discordance is rare among MZ twins, but where these pairs can be identified, they can be viewed as perfectly genetically matched case–controls. This then allows the examination of either epigenetic or nongenetic environmental causes of obesity.

In a small study of seven MZ and nine DZ middle-aged twin pairs with long-term discordance for physical activity, but with very long follow-up, the effects of physically inactive versus active lifestyle were studied in relation to presence of fat tissue (visceral, liver, and intramuscular) assessed by magnetic resonance imaging [16]. The more active co-twin at the beginning of the study remained more active throughout the follow-up period of 32 years. Within-pair analyses carried out at the end of follow-up showed that the physically inactive twin had 50% greater visceral fat, 170% higher liver fat, and 54% higher intramuscular fat as compared with the active co-twin. All trends were similar for MZ and DZ twins. The use of discordant twins allowed the authors to conclude that regular physical activity is an important factor in preventing accumulation of high-risk fat over time, even after controlling for genetic liability and childhood environment.

Weight discordance is very rare among MZ twin pairs, but a study of 14 discordant MZ twin pairs from the FinnTwin16 study ($n = 658$ twin pairs) provides additional support for the utility of this approach. Discordance was defined as a difference in BMI equal to or greater than 4 kg/m^2. Ten concordant pairs were included as controls. The weight differences in the discordant pairs emerged at 18 years of age leading to an average discordance of 16.4 kg (5.6 kg/m^2) at 25.7 years of age. The heavier co-twin weighed more at birth (221 g, 1 kg/m^2), but the difference was gone by 6 months of age and only reappeared at 18 years of age. Although this twin sample was very small, it identified that young adulthood represents a critical period for weight gain irrespective of genetic background [17].

2.8.1.5 Twins Reared Apart

In rare cases, twins are reared apart and this offers the possibility of examining the correlation of traits between genetically identical sibling pairs that have been

exposed to different environments. In a relatively small study of 53 MZ twin pairs from Finland, Japan, and America, estimates of heritability of BMI ranged between 0.5 and 0.7, consistent with other twin studies [18].

2.8.1.6 Twin Studies to Distinguish Between Genetic and Environmental Effects

Genetic effects can be divided into additive (A) and dominant (D) genetic effects. Environmental effects are typically divided into the common or shared environment (C) and the unique or nonshared environment (E).

Numerous twin studies in adults have demonstrated that BMI is influenced by additive genetic and unique environmental effects only [19]. On the other hand, most studies of children and young adolescents show a significant effect of common environment on children younger than 12 years [20–23]. The effect of the common environment then disappears during adolescence [24]. It is believed that this is due to greater parental influence over food choice and physical activity early in life as compared to adolescence.

2.8.2 Twin Studies and Obesity

Studies of MZ and DZ twins in the 1970s and 1980s resulted in identification of strong heritability for several obesity-related traits, such as skinfold thickness [25] and BMI [26]. Skinfold thickness was studied in children in 78 MZ and 144 DZ twin pairs. Significantly higher correlation coefficients were found in MZ twins compared to DZ twins. In the larger BMI study of 1,974 MZ and 2,097 DZ adolescent and adult twin pairs, the heritability estimate for BMI was reported to be between 0.77 and 0.84. The MZ twins also exhibited a markedly higher concordance rate for overweight than did DZ twins.

Further strong evidence of the heritability of BMI came from a study of identical twins separated at or near birth and brought up in different environments [27]. The study demonstrated that as adults, BMI was highly correlated between identical twins, but showed little correlation with that of their adoptive parents or siblings. Similar results have also been found in adoption studies not including identical twins (see below).

2.9 Genetic Linkage Studies Using DZ Twins

Variance due to early-life events is reduced in DZ twin pairs, making them highly valuable for linkage scans of complex traits, such as obesity. In one study, adult DZ female twin pairs from 1,094 pedigrees were studied for genome-wide linkage and positional candidate analysis, with the aim of identifying genes that play a role in regulating fat mass and distribution in women. Nonparametric multipoint

linkage analyses showed linkage of the trait of central fat mass to 12q24 with LOD = 2.2, and for BMI to 8q11 with LOD = 1.3. These findings supported previously established linkage data [28–30]. Novel areas of suggestive linkage identified were for total fat percentage to 6q12 (LOD = 2.4) and for total lean mass to 2q37 (LOD = 2.4). Follow-up fine mapping in an extended cohort of 1,243 twin pairs reinforced the linkage for central fat mass to 12q24 (LOD = 2.6). Forty-five single nucleotide polymorphisms (SNPs) were chosen from twenty-six positional candidate genes in the area. Significant associations were found for SNPs in two genes: PLA2G1B ($p = 0.0067$) and P2RX4 ($p = 0.017$). These results suggested that genes involved in phospholipase and purinoreceptor pathways may regulate fat accumulation and distribution [31].

In a large meta-analysis [32], genome-wide linkage scans were performed using a 10 cM microsatellite marker map in 4,401 families (10,535 individuals) from six data sets of European origin from Australia, Denmark, Finland, The Netherlands, Sweden, and the UK from the GenomEUtwin cohort. This study found suggestive evidence for QTLs for BMI on 3q29 and 7q36 in the total sample set, with MLOD values of 2.6 and 2.4, respectively. Two individual cohorts showed strong evidence for three additional loci: 16q23 (MLOD = 3.7) and 2p24 (MLOD = 3.4) in the Dutch cohort, and 20q13 (MLOD = 3.2) in the Finnish cohort. In summary, this large twin cohort study provided evidence for suggestive linkage to BMI at two previously identified loci and strong evidence of linkage to three new loci. The results also suggested a smaller environmental variance between DZ twins than full siblings, with a corresponding increase in heritability for BMI as well as an increase in linkage signal in well-replicated regions.

2.10 Twin Studies of Obesity-Related Traits

Some of the historically important twin studies in obesity have already been mentioned. The following discussion of different obesity-related phenotypes provides a flavor of the most current research in these areas.

2.10.1 BMI in Children

As has already been mentioned, the use of BMI as a phenotype in obesity studies is widespread and it is no different when twin studies are considered. Rather than attempting to detail all studies in this area, the results of some notable studies examining obesity in childhood, adolescence, and adulthood are discussed. BMI is normally distributed in the general population and twin study designs have been utilized to understand the overlap between the etiology of obesity and normal variation in BMI in children. In a recent study [33], height and weight data were available from 2,342 same-sex twin pairs aged 7 and from 3,526 same-sex pairs aged 10 all from the UK. Twin method and model-fitting techniques were used to estimate genetic and environmental contributions to BMI. DeFries–Fulker (DF) extremes

analysis was also used to investigate genetic and environmental influences on the mean difference between obese and normal-weight children. The results demonstrated a high heritability for BMI and obesity at both ages ($h^2 = 0.60$–0.74) and only a modest influence from shared environmental factors ($h^2 = 0.12$–0.22). The extremes analysis indicated that genetic and environmental influences on obesity are quantitatively and qualitatively similar across the whole range of BMI. The main conclusion was that obesity is simply one extreme result of the same genetic and environmental factors responsible for variation throughout the distribution of BMI.

A similar analysis [23] of more than 3,500 child twins with repeated assessments of BMI in a longitudinal sample indicated that the genetic influence on BMI becomes progressively stronger, with heritability increasing from 0.48 at age 4 to 0.78 at age 11. One suggested reason for the increasing heritability of the trait was the trend of children to increasingly select environments correlated with their genetic propensities.

While the heritability for height has been determined to be high [34], the other component of BMI, namely, weight has been less well explored. This was investigated using a longitudinal study of 231 MZ and 144 DZ male twin pairs born between 1973 and 1979 [35]. Anthropometric measurements of the subjects were obtained annually from birth to 18 years of age. The aim of the study was to determine the contribution of genetic and environmental factors to the development of relative weight during the growth period. The BMI at age 18 correlated with BMI at age 1 ($r = 0.32$) and this correlation increased steadily to age 17 ($r = 0.91$). The major part of these trait correlations (81–95%) was due to additive genetic factors, but unique environmental correlations were also present during the whole growth period. The results suggest persistent genetic regulation of BMI from age 1 to 18. In line with previous studies, this study showed a high heritability of obesity, as measured by BMI.

A very recent meta-analysis [36] of nine separate child twin studies identified a strong genetic effect on BMI variation at all ages. Heritability for BMI was moderate to high (0.55–0.93). Common environmental factors showed a strong effect in mid-childhood, but this effect disappeared in adolescence.

2.10.2 BMI in Adolescents

It is easy to see how the increasing independence that comes as children move into adolescence and young adulthood can result in reductions in shared environmental effects between twins. In order to investigate whether genetic effects are sex-limited, and whether nonadditive genetic effects contribute to BMI during these ages, a longitudinal study of BMI in 2,744 same-sex and 1,178 opposite-sex adolescents and young adult siblings was carried out [37]. Traits were measured at three separate time points: at baseline, after 1 year, and after 5 years. Models that included additive genetic, nonshared environment, and no sex-limited genetic effects gave the best fit with the data at all three measurement points. Heritable effects were large at all three measurements (0.75–0.86). The effects of nonshared environment

were highly correlated between baseline and the first time point but less correlated between baseline and the last time point (at 5 years), indicating that the effects of environment change with maturity from adolescence into young adulthood. The results underscore the importance of understanding early genetic influences on BMI and highlight the role that novel environmental experiences have at later ages.

A study using two time points (average of 7 years apart) examined genetic and environmental effects over time on BMI in 1,306 European-American (EA) and 404 African-American (AA) adolescent and young adult female twin pairs [38]. For EA women, the majority of the variance (82% for each time point) in BMI was due to additive genetic effects, with the rest due to nonshared environment. For AA women, the nonadditive genetic effects accounted for the majority of the variance (68% at the first time point and 73% at the second) with some variance also due to nonshared environment and additive genetic effects.

A study of 4,884 twins and 2,509 singletons from Finland (aged 16–17 years) gave results similar to those above [39], in that genetic factors played a significant role in the variation of BMI. However, in this case, modeling suggested that the set of genes that explain variation in BMI may differ between males and females. It was noted that at this age, twin boys but not twin girls were leaner than singletons.

A longitudinal study of 4,368 individuals has been carried out [40] to examine the role of shared household environment, additive genetic, and shared genetic effects in BMI, and BMI change over time, in adolescents and young adults using two measurements taken 6 years apart. The study reported a heritability of 0.43 for BMI change. Significant household effects were modest and only found during young adulthood. They reported a moderate-to-strong genetic correlation (0.61) for shared genetic effects between BMI and BMI change during adolescence and a weak-to-moderate genetic correlation (0.23) during young adulthood.

2.10.3 BMI in Adults

Recently, a large longitudinal study of 5,278 adult twin pairs with three measurements over 15 years follow-up was reported [41], which was designed to analyze the genetic factors influencing changes in BMI over time. A substantial genetic influence on BMI (80% in males and 82% in females) was reported, with a moderate-to-high genetic influence on rate of change of BMI (58% in males and 64% in females). This study shows that the genetic effects influencing rate of change in BMI are likely to be different from those affecting BMI itself.

One recent result from adult twin-pair studies is that the effect of common environment appears to be inconsistent across different European countries [42]. A comparison of adult female twin pairs from the Netherlands ($n = 222$ MZ, 103 DZ) and Spain ($n = 202$ MZ, 235 DZ) was carried out. Age-related weight gain was significantly stronger in the Spanish sample. For BMI, both the genetic and the environmental variance components were larger in the Spanish arm of the study as compared to the Dutch arm.

2.10.4 Other Anthropometric Measures

In addition to BMI, a range of other anthropometric measures have been used to investigate obesity. Weight, waist circumference (WC), hip circumference, and waist–hip ratio (WHR) are just as useful in characterizing obesity in the population as is BMI [43, 44]. A more complex anthropometric measure is skinfold thickness, typically measured using calipers at multiple points on the body. While this is relatively simple and cost effective, it is significantly more time consuming and user dependent, and it is unclear what the exact relationship is between skinfold thickness at specific points on the body and obesity.

A study [45] using 4,020 twin pairs and SEM analysis demonstrated that an additive genetic effects, dominant/nonadditive genetic effects, and unique environmental effects model provided the best fit and allowing for sex-specific effects significantly improved the fit. The heritability of that proportion of weight unrelated to height was high: 0.61 in males and 0.73 in females.

To study the effect of the obesogenic environment on BMI and WC in children, a large study was carried out aiming to quantify genetic and environmental influences on BMI and central adiposity in children growing up during the time of dramatic rises in pediatric obesity. BMI and WC were analyzed in a UK sample of 5,092 twin pairs of ages 8–11 years using quantitative genetic model fitting for the univariate analyses and bivariate quantitative genetic model fitting for the analysis of covariance between BMI and WC [22]. Both BMI and WC showed high heritability (77% for both). About 60% of the genetic influence on WC was common to that of BMI and there was also a significant independent genetic effect on WC (40%). There was a very modest effect of shared environment on both BMI and WC, with the remaining environmental variance being nonshared. This demonstrated that the genetic influences on BMI and abdominal adiposity remain high in children born since the onset of the pediatric obesity epidemic. Even though most of the genetic effects on WC are common to BMI, 40% is attributable to independent genetic influences.

In a cross-sectional study of the genetic and environmental contribution to the variance of anthropometric traits in 259 twin pairs, triceps, subscapular, and suprailiac skinfold thickness, as well as waist circumference, height, and weight were measured using a standardized protocol [46]. A parsimonious model that included only additive genetic effects and nonshared environmental factors provided an adequate explanation for the variation in anthropometric traits. In this largely preadolescent population, different magnitudes of genetic effects were seen in males and females for waist circumference, biiliac diameter, and suprailiac skinfold.

2.10.5 Body Composition

Body composition is a broad term encompassing both categorical phenotypes such as somatotype (body type) and highly accurate phenotypes such as fat mass, which can be measured very accurately. Somatotype is a different approach to that of BMI

as it is an attempt to categorize obesity based on relative fitness as well as adiposity. The three categories of somatotype are endomorph (substantial fat deposits, large waist), mesomorph (muscular, low adiposity, small waist, and large shoulders), and ectomorph (low adiposity, thin limbs, slim). The somatotype classification can be made more quantitative by using a sliding scale of all three features to classify a subject, e.g., individual scores for endomorphy, mesomorphy, and ectomorphy or a sum of all three.

In order to investigate the heritability of body fat distribution, a study of 108 MZ and 88 DZ Danish twins in two different age groups, 25–32 and 58–66, was carried out [47]. Body fat distribution was determined using DEXA. The intraclass correlations demonstrated higher correlations for MZ than DZ twins in both age groups. Modeling revealed a major genetic component of total and regional fat percentages in both age groups (h^2 estimates between 0.71 and 0.85). The study concluded that body fat distribution as determined by DEXA scans is under strong genetic control.

Genetic and environmental correlations between measures of obesity (BMI) and body fat distribution (WHR and subscapular/triceps skin thickness ratio (SSTR)) were examined in 133 MZ and 129 DZ adult elderly male twin pairs [48]. All measures were significantly correlated in twins, with BMI more closely related to WHR ($r = 0.52$) than SSTR ($r = 0.18$). Multivariate genetic analyses indicated a significant heritable component for each phenotype ($h^2 = 0.66$, 0.46, and 0.25 for BMI, WHR, and SSTR, respectively). The majority of the BMI–WHR correlation came from common genetic influences, suggesting that overall obesity and abdominal adiposity distribution are mediated, at least in part, by similar genetic influences. The results also indicated that the genetic influences on skinfold thickness distribution are independent of those on abdominal and overall body fat, supporting the hypothesis that WHR and SSTR indices do not assess the same aspects of body fat distribution.

Total body fat, central abdominal fat, and non-abdominal fat were measured using DEXA in 50 MZ and 36 DZ female adult twins [49]. A genetic influence was observed on total fat, central abdominal fat, and non-abdominal fat. The correlation among MZ twins for central abdominal fat was 0.66 compared to only 0.20 in DZ twins. After adjusting central abdominal fat for age and total body fat there was an independent genetic influence accounting for 70% of the population variance. This study concluded that the majority of interindividual variance in central abdominal fat in nonobese individuals is due to genetic factors. Since abdominal fat is associated with metabolic consequences, the inheritance of abdominal obesity may contribute to familial aggregation of insulin resistance, diabetes, and cardiovascular disease.

A more advanced look at the effects of genetics and environment on body composition was provided by a series of intervention studies in young adult male identical twins designed to determine if there was any evidence of interactions between genotype × overfeeding or genotype × negative energy balance, as measured by changes in body weight, body composition, fat distribution, and computerized tomography-assessed abdominal visceral fat [50]. Responses observed were more similar within twin pairs than between unrelated individuals. The intrapair resemblance in response

was particularly strong for changes in body mass, body composition, subcutaneous fat distribution, and abdominal visceral fat. This study concluded that there are individuals at risk of gaining weight and body fat or who are resistant to weight loss and that this can be largely explained by genetic factors.

Correlation between body composition (using DEXA) as an adult and birth weight has been investigated using 2,228 DZ and 842 MZ female twins [51]. Multivariate regression models were used to identify both individual-specific associations and those mediated through shared environment. Significant associations were found between birth weight and DEXA measures for individuals; an increased birth weight of 1 kg corresponded to an increase of 1.72 kg in lean mass, 0.25 kg in fat mass, and a 0.05 unit increase in lean:fat mass ratio. Within pairs, the analysis showed that associations between birth weight and absolute levels of lean and fat mass were mediated through individual-specific effects, whereas the relation between birth weight and the proportion of lean to fat mass was mediated purely through factors common in twin pairs. This study concluded that higher birth weight is associated with a higher proportion of lean to fat mass as adults and that this effect is mediated through factors in the shared common environment rather than by individual-specific factors in utero.

A study of twin resemblance for somatotype was carried out in 62 MZ and 40 DZ twin pairs (males and females) aged 9–23 years [52]. The mean somatotype did not differ between the sexes but males were significantly more mesomorphic than female twins. Analysis was performed in two ways. First, each somatotype was treated as independent from the other two, and second, as a composite by statistically controlling for the other two. Intraclass variations were significantly higher among MZ than DZ twins of both sexes. Within-pair variation was lower in MZ than DZ twins of both sexes. These results suggested that genetic variation affects physique in adolescents and young adults.

In a very small study of somatotype, with only 28 female individuals (5 MZ and 9 DZ pairs) of ages 7–19, significant differences between MZ and DZ twins were found for height and somatotype [53]. The heritability for these measures was high (0.88–0.97). No significant differences were found between MZ and DZ twins for weight and BMI and the heritability was lower for these traits (0.42 and 0.52). This study indicated that somatotype may be more sensitive to genetic effects than BMI in females.

In a study of 105 same-sex twin pairs from Belgium followed between 10 and 18 years of age, multivariate path analysis was used to take into account the covariation between somatotype components, gender heterogeneity, and common environmental influences distinguished from genetic effects [54]. The heritability for all three somatotypes ranged from moderate to high. In boys the heritability was 0.21–0.88, 0.46–0.76, and 0.16–0.73 for endomorphy, mesomorphy, and ectomorphy, respectively, and in girls 0.76–0.89, 0.36–0.57, and 0.57–0.76, respectively. Sex differences were present from the age of 14 years onward. More than half of the variance in all somatotypes could be explained by common factors. This study provided evidence of a substantial genetic influence on the variability of somatotype and it emphasized the need for sex-specific analyses.

A study of genetic and environmental determination of variation of somatotype in 803 individuals from 424 Flemish adult twin pairs using multivariate path analysis was subsequently reported [55]. The study again found significant sex differences and significant covariation between the three somatotypes. The variance in somatotype could be explained by additive genetic effects, shared environment, and unique environment. In both males and females, more than 70% of the total variation could be explained by sources of variation shared by all three components of somatotype. This study indicated that the high heritability for mesomorphy and ectomorphy in adolescence was maintained in adulthood.

2.10.6 Eating Behavior

Eating behavior is clearly an important aspect in the development of obesity. Many believe that obesity originates in the brain as a neurobehavioral disorder, which is consistent with the current finding that most obesity-associated genes appear to be expressed in the brain rather than adipose tissue (see reference [56] for review). The difficulty with assessing eating behavior as a phenotype is that its measurement using questionnaires is notoriously unreliable, due to underreporting, particularly in obese subjects (see reference [57] for a review of measures of the food environment).

2.10.6.1 Restraint, Emotional Eating, and External Eating

One of the most extensive studies of the heritability of eating behavior and body weight-related traits was carried out in a Korean sample set [58]. The study group consisted of 2,144 subjects: 443 MZ and 124 DZ adult same-sex twins and 1,010 family members. The Dutch Eating Behavior Questionnaire (DEBQ) [59] was used to assess three eating behavior subscales measuring restraint, emotional eating, and external eating. Heritability was estimated using a variance components approach. After consideration of shared environmental effects and adjustment for age and sex, the heritability estimates among twins and their family members were 0.31 for restraint, 0.25 for emotional eating, and 0.25 for external eating. Heritability was high for measured current and self-reported body weight at 20 years old (0.77 and 0.70, respectively). All three subscales were associated with all weight-related traits after adjustment for age and sex. The results of this study suggest that eating behaviors and weight-related traits have a genetic influence and eating behaviors are associated with measures of obesity. These results are similar to results obtained in Western populations.

In a second study, the effects of genetic and environmental factors on cognitive and emotional aspects of dieting behavior, BMI, and responsiveness to fatty foods were investigated [60]. One thousand three hundred and twenty-six adult twin individuals, mostly females, from the UK and Finland completed the revised version of the Three-Factor Eating Questionnaire [61] and genetic modeling was carried out using linear structural equations. Heritability estimates were calculated separately for each country and sex and were 26–63% for cognitive restraint, 45–69%

for uncontrolled eating, and 9–45% for emotional eating. Interindividual genetic differences were responsible for 25–54% for the variation in liking and use frequency of fatty foods. No significant correlations were found between BMI and fatty food use or liking, but BMI was positively correlated with all of the dieting behaviors. This correlation was mostly genetic ($r = 0.16$–0.51). Uncontrolled eating was both genetically and environmentally associated with liking for salty and fatty foods ($r = 0.16$) and emotional eating was genetically associated with liking for salty and fatty foods ($r = 0.31$). In conclusion, the relation between BMI and diet appears to be mediated through dieting behaviors.

2.10.6.2 Satiety and Food Responsiveness

Aspects of appetite that have been implicated in obesity include responsiveness to satiety and responsiveness to food cues. A recent study assessed the relative contribution of genes and environment using 5,435 twins aged between 8 and 11 years [62]. Quantitative genetic model fitting gave heritability estimates of 63% for satiety responsiveness and 75% for food cue responsiveness. Shared and nonshared environmental influences were 21 and 16%, respectively, for satiety responsiveness, and 10 and 15%, respectively, for food cue responsiveness. The study concluded a high heritability of appetite traits and suggests that genetic vulnerability to weight gain could operate through behavioral and metabolic pathways. It was suggested that intervention strategies aimed at improving satiety responsiveness and reducing food cue responsiveness in high-risk individuals could help in preventing the development of obesity, but if there is a high genetic effect this approach would not likely be successful.

A second study of satiety responsiveness and food cue responsiveness in children used twins from two age groups: 3–5 years ($n = 572$) and 8–10 years ($n = 10364$) [63]. BMI was measured in both age groups and waist circumference in the older group. In both sets, higher BMI was associated with lower satiety responsiveness ($r = –0.19$ in 3–5 year olds and $r = –0.22$ in 8–11 year olds) and higher food cue responsiveness ($r = 0.18$ in both groups). Waist circumference was also associated with satiety responsiveness ($r = –0.23$) and higher food cue responsiveness ($r = 0.20$). By analyzing the data using weight categories, children in higher weight and WC categories had lower satiety responsiveness and higher food cue responsiveness. This was true for both age groups but more pronounced in 8–11 year olds. Association between appetite and adiposity supports a behavioral susceptibility model of obesity. Assessing appetite in childhood could help identify children at high risk of developing obesity while they are still normal weight, enabling targeted interventions to prevent obesity.

2.10.6.3 Eating Rate and Eating Styles

In order to investigate the hypothesis that speed of eating is related to greater adiposity and that eating rate is a heritable trait, a study of 254 10–12-year-old twin children was carried out [64]. There was significant linear association across three

weight groups (obese/overweight, higher normal weight, and lower normal weight) for eating rate. Regression analysis demonstrated that eating rate correlated with BMI. In addition, the heritability of eating rate was high (0.62). This study showed that faster eating appears to be a heritable behavioral trait and is related to obesity.

In a prospective twin cohort study of 233 female and 2,060 male twins, the association of eating styles with overweight and obesity in young adults was investigated [65]. Twins were aged 16 at baseline (T1) and 22–27 at the time of nutritional assessment (T4). At T4, obesity was significantly cross-sectionally associated with restrictive eating, frequent snacks, eating in the evening, avoiding fatty foods, and failure to maintain healthy eating patterns ($p < 0.001$, 0.01, 0.01, and 0.05, respectively). These associations were independent of BMI at T1. After a multivariate analysis, only restrictive/overeating and health-conscious eating styles were significant correlates of obesity at T4, independent of gender and BMI at T1. The analysis was controlled for genetic background by restricting the analysis to MZ twin pairs discordant for obesity ($n = 39$ female pairs, 45 male pairs). Yet, restrictive/overeating eating style was still statistically significantly associated with excess weight. The study demonstrated that the eating styles of obese young adults differ from their normal-weight counterparts; and restrictive eating, overeating, and fewer healthy food choices are all associated with obesity.

2.10.7 Physical Activity

Physical activity is another aspect of behavior that is essential when considering the causes and treatment of obesity. Many studies support the role of physical activity in contributing to and especially maintaining weight loss [66]. One recent study has attempted to explore how physical activity and the proportion of energy as protein in the diet modify the genetic variation of BMI, WC, and percentage body fat (by bioelectrical impedance) in 756 Danish and 278 Finnish twin pairs aged 18–67 and 21–24, respectively [67]. High physical activity was associated with lower mean values for BMI, WC, and percentage body fat, and a high proportion of protein in the diet was associated with higher mean BMI, WC, and percentage body fat. This was statistically significant for WC in Danish men and Finnish women and for percentage body fat in Danish women. A meta-analysis of effects of physical activity on genetic variance of BMI, WC, and percentage body fat showed a significant modification by physical activity on BMI (–0.18; (95% CI –0.31 to 0.05) and WC (–0.14; 95% CI –0.22 to –0.05). The results suggest that in physically active individuals, the genetic variation in weight is reduced, possibly indicating that physical activity is able to modify the action of the genes responsible for predisposition to obesity.

Another recent study determined whether vigorous exercise shows evidence of a gene–environment correlation and gene × environment interaction with BMI among 2,710 MZ and 2,327 DZ male twin pairs [68]. The results show a significant modification of vigorous exercise on the additive genetic component of BMI, indicating a gene × environment interaction ($p < 0.001$). The genetic influence on BMI was

highest among those that did not report vigorous exercise. The results are consistent with existing reports that vigorous exercise may mitigate some of the genetic influences on obesity.

A third large study also investigated whether physical activity modifies the degree of genetic influence on BMI and WC in 4,343 subjects from the FinnTwin16 Study [69]. Data were obtained using questionnaires and self-measurement of WC. The analysis was done using linear structural equations and gene × environment interaction models. Overall heritability estimates for BMI were 79% in males versus 78% in females, 56% versus 71% for WC, and 55% versus 54% for physical activity, respectively. They found an inverse relationship between physical activity and WC in males and females ($r = –0.12$ and $r = –0.18$, respectively) and between physical activity and BMI in females ($r = –0.12$). The heritability of both BMI and WC was significantly modified by physical activity. High physical activity specifically decreased the additive genetic component in BMI and WC. In summary, these results suggest that the individuals at greatest genetic risk of obesity would benefit the most from physical activity.

A longitudinal study of 146 twin pairs from the Finnish Twin Cohort over 30 years has allowed the follow-up necessary to determine the effect of physical activity on obesity and the role of environmental effects. All pairs were discordant for intensity and volume of leisure physical activity at baseline in 1975 and in 1981 [70]. Eighty-nine pairs were alive and participated in a follow-up interview in 2005 where self-measured weight and WC as well as physical activity during the whole follow-up were assessed. In the 42 twin pairs that were discordant throughout the follow-up period, the mean weight gain over 30 years was 5.4 kg less and the WC in the year 2005 was 8.4 cm smaller in the more active twin. These trends did not differ significantly between MZ and DZ twins. No significant differences were detected in weight and WC between the twins of 47 twin pairs that were not consistently discordant for physical activity. Persistent physical activity over 30 years was associated with a decreased rate of weight gain and with a smaller WC, even when partially controlling for genetic liability and childhood environment by studying twins.

Another study evaluated the relative contribution of genetic and environmental factors to the variation and covariation in activity-induced energy expenditure (AEE) and physical activity (PA) [71]. This was a small study, consisting of 12 MZ and 8 same-sex twin pairs of ages 18–39, because measurement of AEE is difficult and time consuming. AEE was measured in a respiration chamber for 24 h and with doubly labeled water in daily life for 2 weeks. PA was measured at the same time using a triaxial accelerometer. Analyses were performed using SEM to separate the observed variance into sex-adjusted additive genetic and common and unique environmental contributions. The results from the respiration chamber showed that common and unique environmental factors explained all of the variance in AEE and PA, with no genetic contribution. On the other hand, in daily life genetic factors explained 72 and 78% of the variance in AEE and PA, respectively, with unique environmental factors explaining the remaining variance. The same genetic factors explained 67% of the covariance between AEE and PA in daily life. In conclusion, this small study used gold standard measurements for AEE and PA and

demonstrated that genetic factors explained a large part of the variation in AEE and PA in daily life, whereas environmental factors alone influenced variation in AEE and PA in the respiration chamber.

In summary, twin studies have provided good estimates of the heritability of obesity. Many different phenotypes can be used to assess obesity, each with different positive and negative aspects. Most studies have used BMI, with heritability estimates that are generally very high with a good concordance between studies, making it clear from twin studies that obesity has a genetic basis, whatever phenotype you consider.

2.11 Adoption Studies

The adoption study design is intended to clearly differentiate between the effects of genetics and environment. This is ideally achieved by contrasting the trait being measured between adoptive and biological siblings. If a trait is more similar between the adoptee and their biological rather than adoptive siblings then the trait is considered to have a stronger genetic basis and vice versa. However, this assumes that placement of the adopted child is random rather than selective, e.g., through an adoption agency rather than with other relatives, and it assumes that the prenatal environment, and any period of postnatal environment shared with biological parents, has no effect. Given that the average age at adoption from care in England for the year ending March 31, 2009 was 3 years and 9 months (figure from http://www.baaf.org.uk/info/stats/england.shtml), this is a significant length of time in the same environment as the biological parents. Given the inherent difficulties in recruiting and tracking both biological and adoptive families it is not surprising that few adoption studies have been carried out in obesity.

A recent systematic review [36] describes five adoption studies of childhood obesity [8, 72–75]. Of the four studies that included both natural and adopted families, the earliest, carried out in the UK, reported nonsignificant correlations between weight (adjusted for age and sex) of parents and adopted children and significant correlation between parents and biological children [8]. Two subsequent studies, one in the USA [72] and one in Canada [73], reported similar results. The US study also reported a correlation between mother and adoptive child (0.11, 95% CI 0.02–0.20) and the Canadian study reported that the correlation of weight/height in biological siblings was 0.37 ($p = 0.001$) compared to –0.03 ($p = 0.76$) for adopted siblings. A second US study, which utilized regular measures of BMI, was able to produce a heritability estimate of 0.09 at age 1, rising to 0.57 at age 9 [48]. The last report is a complete adoption study of 269 Danish adoptees involving both adoptive and biological families [75]. The average correlation between the adoptee and their biological siblings was 0.59 (95% CI 0.28–0.90) and with their adoptive siblings 0.14 (95% CI –0.13 to 0.41), demonstrating a strong influence of genetics on body mass index. A much lower correlation of 0.17 (0.03–0.31) with their biological mother and 0.17 (0.00–0.32) with their biological father was observed. No correlation was observed between the adoptee and their adoptive parents.

The contribution of the Danish group cannot be overstated as they are also responsible for the main adoption study of obesity in adults, initially reported in 1986 [76], and analyzed extensively in subsequent publications [77–79]. The initial study demonstrated that for a sample of 540 adult adoptees, there was a significant association between weight class (thin, median weight, overweight, or obese) of the adoptee and the BMI of their biological mother ($p < 0.0001$) and their biological father ($p < 0.02$). No significant association was observed with the adoptive parents [76]. Subsequent comparison of the adoptee weight class and full- and half-siblings' BMI demonstrated a highly significant trend of increasing BMI of full siblings with weight group for the adoptees ($p < 0.0001$) and a weaker trend for half-siblings ($p < 0.02$) [77]. Extension of the analysis to classify the adoptees using BMI and maximum BMI produced similar results, with correlation of BMI in the adoptee to biological mother, father, and full sibling being 0.15, 0.11, and 0.23, respectively ($p < 0.001$) [78]. Using a second measure of obesity, a silhouette score, similar correlations between adoptee obesity and their biological mother and full siblings were demonstrated. The correlation between adoptee and the biological father was nonsignificant [79]. Using a path analysis model, the heritability of obesity was subsequently estimated as 0.34 (± 0.03), with no evidence for effects due to the shared family environment. All familial resemblance in adults was attributed to genetic effects [80]. However, this clearly meant that over 50% of the interindividual differences in BMI were due to individual environmental influences that were not shared.

2.12 Family-Based Studies

While twin and adoption studies are family based, the primary aspect of each is the sibling relationship. These are special cases of the wider family-based study design. Typically, family-based studies are based on the identification of one or more probands within a family, and then recruitment of the whole or part of the family. For genetic studies, families are useful as the siblings share a common environment; thus, this is assumed to be a good basis on which to explore the genetic basis of a phenotype as the environment can be controlled for. Family-based studies are typically used to investigate genetic linkage of a trait with markers on the human genome, so regions (and ideally genes) that are linked to the trait can be identified. Classically, nuclear families recruited on the basis of sibpairs discordant for the trait of interest have been used to maximize the potential to detect genetic influences on a trait in the presence of a shared environmental effect. However, concordant sibpairs can also be used, as well as recruiting large, multigenerational or consanguineous families, each of which has advantages. Discussion of the details and merits of family-based study designs is outside the remit of this chapter, so the reader is referred to two recent reviews of the subject [81, 82].

As heredity is the main concern of this chapter, what follows is not a comprehensive summary of the results of genetic linkage studies in obesity but an illustration of

the evidence for heredity in obesity from family-based studies. Segregation analysis, the comparison of the observed proportion of affected subjects with the expected proportion given a specified mode of inheritance, has been the main method for trying to determine the genetic model that best fits the observed heredity patterns in obesity. In rare, monogenic forms of obesity, inheritance is autosomal recessive, though in the case of variants in the melanocortin-4 receptor gene, the frequency of mutation is sufficient that it is responsible for a small percentage of cases sampled from the general population [83], thus contributing to the more complex pattern of inheritance described for common obesity. Overall, the view of the field has been that the inheritance of common obesity is polygenic, with a possible role for one or two major genes [84–90]. Interestingly, analysis of the National Heart, Lung and Blood Institute Family Heart Study data gave a heritability value of 0.41–0.59, similar to the values obtained from twin studies [88]. Further complicating the picture of the heredity of common obesity, segregation analysis of the Swedish Obese Subjects study data suggested that below 20 years of age, a major gene effect was observed, while above the age of 20 a multifactorial mode of inheritance predominated [89].

In a genome-wide linkage study of BMI in the Amish [91], the heritability of obesity was estimated as 0.16–0.31 and for BMI percentile 0.40–0.52. Equally, in a genome-wide scan of Nigerian families for BMI, the heritability estimate was 0.46 ± 0.07. However, it should be noted that a study of intrafamilial correlation of BMI concluded that nonrandom mating and regional clustering may be inflating heritability estimates of BMI [92].

Analysis of the heritability of other obesity-related phenotypes has also demonstrated significant heritability values. For the trait of abdominal fatness (adjusted for total adiposity, age, and sex), a heritability of over 0.90 has been reported in a study of 300 South Indian families [93]. Eating behavior has a clear influence on obesity and in the Amish, heritabilities of 0.28 ± 0.09, 0.40 ± 0.10, and 0.23 ± 0.09 have been reported for the behavioral categories of restraint, disinhibition, and hunger, respectively [94]. Waist circumference is a commonly used obesity-related phenotype and in a recent study of the metabolic syndrome, waist circumference was reported to have a heritability of 0.38 ($p < 0.0001$) [95].

2.13 Case–Control Studies and the "Missing" Heritability Problem

As we have seen above, there have been many studies that have estimated heritability of common obesity and values obtained have been typically in the range of 0.5–0.7 for twin studies and 0.3–0.4 for adoption and family studies. Estimates of the contribution of individual genes to the total heritability of complex traits have emerged from genome-wide association (GWA) studies; see Chapter 5) [96] and this has revealed the so-called missing heritability problem [97]. For many complex traits, such as height or type 2 diabetes, large numbers of trait-associated loci have been identified (>20), but the proportion of the heritability that is explained by them

is still low (<6%). The reasons for this are not clear at the moment, but there is little evidence that it is the overall heritability measure that is incorrect (see reference [97] for discussion). Although there are a few exceptions, such as age-related macular degeneration, where a few gene variants are responsible for most of the heritability, the current evidence suggests that common obesity has the same missing heritability problem as other common diseases.

There are two main issues with the design of the current generation of GWAS that could explain the failure to explain a substantial part of the heritability. The first is that the SNP markers that are used have a minor allele frequency of 5% or above. This was based on the original hypothesis of "common disease, common variant" [98], which suggested that any trait common in a population would most likely be associated with common variants. However, there is evidence that rare variants can have strong genetic effects in obesity [99] and the sum of the rare variants within a population could explain the missing heritability.

The second issue is that GWAS currently only addresses single nucleotide variation in the genome, while other types of variation may be associated with obesity. While GWAS arrays typically include markers that provide information on copy number variant (CNV) regions, the analysis of these data has proved problematic and initial conclusions have been that common CNVs cannot account for the missing heritability [100, 101]. However, by analogy to the situation with SNPs, the contribution of rare CNVs should not be underestimated, and in fact, there has been very recent evidence of the contribution of a rare CNV to obesity [102, 103]. Further sources of genomic variation include DNA methylation, telomere length, and histone modification, all of which could contribute to missing heritability in common obesity.

2.14 Heredity and Nongenetic Traits in Obesity

The problem with heredity is that it can sometimes be difficult to distinguish between genetic, environmental, or epigenetic mechanisms that may underlie the transmission of traits between parents and offspring. In obesity, at least two situations have been described where, for nongenetic reasons, traits predisposing offspring to obesity appear to be transmitted from the parents.

The first is the influence of the same-sex parent on body shape. Recently, it was reported that the body shape of a child was strongly correlated with that of its same-sex parent and not with the opposite-sex parent [104]. It is difficult to come up with a genetic explanation for this phenomenon and families share more or less the same environment for most of the time. The authors concluded that the best explanation was that the psychological predisposition of a child was to learn behaviors from its same-sex parent and this could include eating behavior. A child observing a parent eating large amounts of food quickly might be expected to follow their lead and overeat as well. Most published genetic studies of obesity successfully control for this effect by including sex as a covariate.

The second situation is the relationship between gut flora and obesity. Several publications examining the metagenome, the sum total of the bacterial and viral genomes that we are host to, have demonstrated that the gut flora is significantly different between obese and nonobese subjects (see reference [105] for review). As yet, there is insufficient evidence to decide whether this association is cause or effect. The heredity effect here is that the newborn continually shares the environment with its mother, and to a lesser extent its father, over the first few months of life as the child is slowly weaned onto solid food. This has the effect of the offspring "inheriting" a significantly biased proportion of its gut flora from its parents and a possible predisposition toward obesity as a consequence.

2.15 Conclusions

From all the evidence presented in this chapter, it should be clear to the reader that the majority of cases of obesity have a genetic basis. The contribution of the environment, both shared and individual, is variable, ranging from nothing for rare monogenic obesity to the majority of the effect in common obesity. Every case of obesity can be considered to be on a continuum, with a specific balance of genetic and environmental effects in each case (see Fig. 2.1). Monogenic obesity is almost purely genetic, with only drastic calorie restriction exerting an effect.

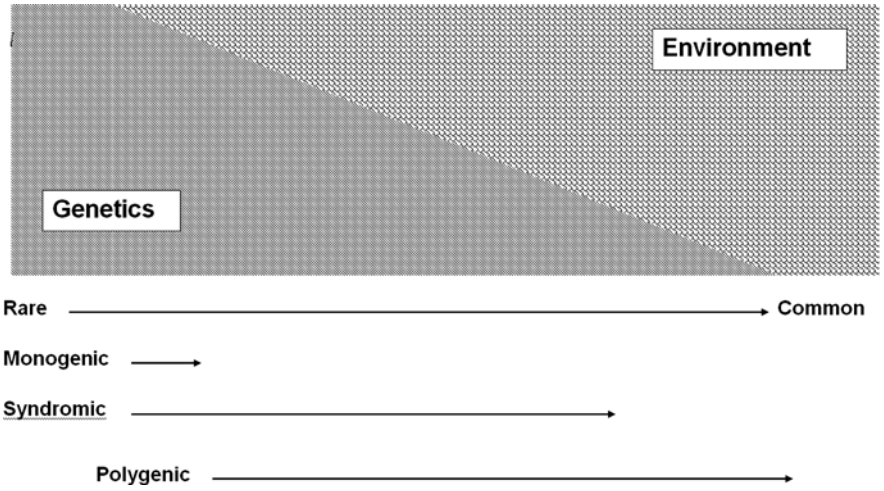

Fig. 2.1 The balance of genetic and environmental factors affecting obesity. Genetics and environment are shown as a balance of effects across the bulk of the spectrum, with regions of 100% genetics or environment at either end to emphasize the possibility of cases of clinical obesity being purely genetic (e.g., monogenic) or purely environmental (e.g., via learned behavior rather than genetics). The parts of the spectrum that the various forms of obesity occupy are shown below the figure, with monogenic disease being predominantly rare and genetic and common polygenic disease being caused by a balance of genes and environment

However, it should be remembered that even monogenic disease occurs in the context of a specific individual's genetic background, which may modify their outcome, e.g., BMI, in a specific environment. Syndromic obesity is more complex, as it may be monogenic or oligogenic, and obesity may not have to be present for diagnosis of the syndrome, e.g., in Bardet–Biedl syndrome. Both monogenic and syndromic subtypes of obesity are rare, presumably as a consequence of being severe disorders with consequent morbidity and mortality. Polygenic or complex obesity is common and had previously been suspected to be due to common variation in the genome. It is unlikely that common single nucleotide variations account for most of the heritability of obesity; whether it is rare variants of strong effect, other forms of genomic variation, or a combination of both remains an open question. It is already clear that copy number variation can contribute to obesity and there is every reason to believe that epigenetic mechanisms, such as DNA methylation or histone modification, could account for a significant part of the heritability of obesity.

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