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HEREDITY AND BODY FAT

Claude Bouchard and Louis Pérusse

Physical Activity Sciences Laboratory, Laval University, Ste-Foy, Québec, Canada G1K 7P4

CONTENTS

INTRODUCTION

The role of biological inheritance in human obesity (15, 46) and body fat in individuals of normal weight (39) has been considered in recent reviews. These reviews dealt primarily with body weight, relative body weight, body mass index (body weight in kilograms divided by height in meters squared) (BMI), and skinfold thickness at a few sites, which reflected the data then available in the literature.

This review focuses on the genetics of body fat, fat distribution, and relative fat patterning. It does not deal with the affectors of body fat such as energy intake, the various components of energy expenditure, adipose tissue metabolism, and substrate cycling. Rather, the emphasis is on fat mass and fat topography. The additive genetic effect and the genotype-environment interaction phenomenon are emphasized.

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Mendelian disorders and chromosomal aneuploidies affecting body fat are reviewed first. Second, the evidence for the presence or the absence of a significant additive genetic effect is summarized for several phenotypes, including BMI, amount of subcutaneous fat (skinfold thickness), percentage fat and fat mass, fat distribution, and relative subcutaneous fat patterning. The review relies heavily on the literature of the last three years or so, but occasionally uses older studies if they are useful in developing a concept or if they support a trend in the data. Third, the genotype-overfeeding interaction, as a special case of the genotype-environment interaction, is described in terms of its relevance for individual differences in fat mass. Finally, a comment is offered on the limitations of the studies dealing with the phenotype of body fat as opposed to research on the affectors of the phenotype. Current and future lines of research on the role of the genotype in obesities and normal variation in body fat and fat distribution are briefly outlined.

MENDELIAN INHERITANCE

Body fat is a continuously distributed phenotype and, for most individuals, the excessive accumulation of body fat can probably be explained by the obvious determinants of a positive energy balance. However, there is evidence, particularly from animal studies (16, 54), that obesity and the susceptibility to its development may be genetically transmitted, sometimes by a single gene. In humans, there are only rare cases in which obesity follows a clear Mendelian mode of inheritance (14, 15, 28). These genetic syndromes and their postulated mode of inheritance are listed in Table 1. For each syndrome, except the Edwards (25) and the Vasquez (56) syndromes, the McKusick's catalog number (37) is given in parentheses. Classification of these syndromes as separate genetic entities is sometimes a difficult task because many of them share several common clinical features. Hypogonadism is one of these features and it has already been used as a basis for classification (15). Similarity in phenotypes has led some authors to classify the Bardet-Biedl syndrome as the Laurence-Moon-Biedl-Bardet syndrome, while the Laurence-Moon syndrome was seen as a different entity without obesity as a clinical feature (37). Another problem is that some of these syndromes could represent different stages of the same genetic defect. For example, the Pickwickian syndrome, also known as the obesity hypoventilation syndrome, may represent an extreme case of the Prader-Willi syndrome in which obesity reaches such a proportion that cardiorespiratory problems may develop (5).

For most of these syndromes, the genetic defect is not known and there are no obvious chromosomal anomalies, except for the Prader-Willi syndrome in which an abnormality of chromosome 15 is detectable in about 50% of the

cases (17). This syndrome is the most common of those listed in Table 1, with an estimated incidence of 1 in 25,000 live births (17). A particular characteristic of this syndrome is that patients, early in infancy, develop an uncontrollable hyperphagia; this led to the suggestion that a hypothalamic dysfunction may be involved. However, no lesions have been detected thus far from postmortem examinations. It has been reported that fat synthesis from acetate during fasting was 10 times greater in patients with the Prader-Willi syndrome than in unaffected sibs, and that hormone-stimulated lipolysis was depressed (37). This could perhaps explain why these subjects depend on a continuous supply of exogenous calories to survive.

In addition, excess body weight or body fat is regularly found in some chromosomal aneuploidies. Among these, the Down's syndrome (mongolism or trisomy 21) and the Turner's syndrome (females with only one X chromosome) are probably the most frequent. Finally, there are some cases of genetic defects in which the accumulation of body fat is localized in specific parts of the body. These patients suffer from tumors of adipose tissue (lipomas) that are thought to be associated with autosomal dominant mechanisms (14).

No dietary or exercise treatment is expected to prevent the development of obesity in the cases listed here, although the restriction of caloric intake in patients with the Prader-Willi syndrome may delay somewhat the development of obesity. Fortunately, these genetic disorders represent only a very small fraction of the obese population.

Table 1 Genetic disorders including obesity as a clinical feature

Syndrome	Proposed mode of transmission[a]	Chromosomal anomalies
Alstrom (20380)[b]	Autosomal recessive	No
Bardet-Biedl (20990)	Autosomal recessive	No
Biemond II (21035)	Autosomal recessive	No
Borjeson (30190)	X-linked	No
Carpenter (20100)	Autosomal recessive	No
Cohen (21655)	Autosomal recessive	No
Edwards (25)[c]	Autosomal recessive	No
Morgagni-Stewart-Morel (14480)	Autosomal dominant	No
Macrosomia Adiposa Congenita (24810)	Autosomal recessive	No
Prader-Willi (17627)	Autosomal dominant	Yes
Pickwickian (25750)	Autosomal recessive	No
Triglyceride Storage II (19043)	Autosomal dominant	No
Vasquez (56)[c]	X-linked	No

[a] According to McKusick (37).
[b] Refers to the McKusick catalog number (37).
[c] Syndromes not listed in McKusick catalog; the number given in parentheses refers to the bibliographic reference.

MULTIFACTORIAL INHERITANCE AND BODY FAT

The Model

Measurements of body fat in humans are obtained on a continuous scale. Moreover, body fat can be influenced in both sexes and at all ages by persistent negative or positive energy balance, i.e. nongenetic factors. Such quantitative phenotypes that are determined by a variety of genetic and environmental or lifestyle factors are defined as multifactorial traits. Variation in multifactorial phenotypes are best studied by the methods of quantitative genetics or from the emerging field of genetic epidemiology. In the context of a simple paradigm, variation in a phenotype (P), like body fat, can be described in terms of the following equation (8):

$$P = G + E + G \times E + e,$$

in which, G represents the additive genetic effect, E the environmental and lifestyle influences, $G \times E$ the genotype-environment or lifestyle interaction effect, and e the sources of error. In this review, we are concerned with both the G and $G \times E$ effects on body fat. More is said about these variance components in the following sections.

Genetics of Body Fatness Indicators

Three types of study designs have generally been used to assess the role of heredity in body fat: family studies, twin studies, and adoption studies. We first consider the studies pertaining to the additive genetic effect in various indicators of body fat. For each fatness indicator, familial correlations in first-degree relatives (parent-child, siblings, dizygotic or monozygotic twins) and heritability estimates derived from twin studies and from studies using the path analysis methodology are reviewed. Only correlations and heritability estimates derived from the studies published since 1983 are presented. The reader is referred to the review of Mueller (39) for studies published before 1983.

BODY MASS INDEX The body mass index is an indicator commonly used to assess obesity, and several studies have used it as the phenotype in an attempt to determine the role of heredity in obesity. It should be kept in mind, however, that the BMI is an indicator of "heaviness" rather than "fatness" and, as pointed out recently (8, 30), a genetic effect in BMI may reflect the contribution of genes in body build, proportions, and lean body mass as well as in body fat.

Correlations among selected kinds of relatives are summarized in Table 2. Parent-child correlations for the BMI are typically in the 0.2 to 0.3 range and

Table 2 Familial correlations (r) in first-degree relatives for body mass index[a]

Source	Type of relatives	Number of pairs	r
Khoury et al, 1983 (35)	Mother-child	186	.23
	Father-child	150	.29
	Siblings	77	.35
Annest et al, 1983 (1)	Father-child	127	.02
	Mother-child	127	.18
	Siblings	47	.40
Heller et al, 1984 (33)	Father-son	1057	.27
	Father-daughter	954	.23
	Mother-son	1063	.23
	Mother-daughter	1133	.21
	Brother-brother	331	.27
	Sister-sister	361	.25
Longini et al, 1984 (36)	Father-child	842	.27
	Mother-child	842	.25
	Siblings	445	.36
Mueller, 1986 (40)	Siblings	111	.36
Stunkard et al, 1986 (51)	Dizygotic twins	2097	.42
	Monozygotic twins	1974	.81
Zonta et al, 1987 (57)	Father-child	317	.31
	Mother-child	317	.37
Pérusse et al, 1988 (43)	Parent-child	7102	.20
	Siblings	3372	.31
Bouchard et al, 1988 (11)	Parent-child	1239	.23
	Siblings	370	.26
	Dizygotic twins	69	.34
	Monozygotic twins	87	.88

[a] Includes only studies since 1983. For studies published before 1983, the reader should refer to the review of Mueller (39). Age and gender effects are statistically controlled or kept to a minimum by design.

they are generally slightly lower than the coefficients reported among siblings. Two large sets of data should be particularly highlighted here. The BMI was obtained in more than 4000 parent-offspring pairs from the Framingham Heart Study (33). Correlations in sex-specific parent-child pairs were found to range from 0.21 to 0.27. From the data obtained in a nationwide survey (Canada Fitness Survey), we reported parent-child (N = 7102 pairs) and sibling (N = 3372 pairs) correlations of 0.20 and 0.31, respectively, for BMI (43). Sibling correlations are generally lower than correlations between dizygotic twins who have the same degree of genetic relationship as regular siblings. Monozygotic twin correlations are consistently the highest.

This pattern of familial resemblance in BMI may be associated with similarities in lifestyle and environmental conditions among the relatives, in addition to the genes they share by descent. In order to untangle these effects,

some authors have compared correlations among siblings living together and siblings living apart (35, 36). Correlations around 0.35 were reported for siblings living together, compared to correlations around 0.15 for siblings living apart. These results suggest that shared lifestyle and environmental conditions are important in determining some of the familial resemblance in BMI. A similar conclusion can be reached from data that we recently reported (7) based on midparent (mean value of both parents)-child data. We found no difference in midparent–natural child (N = 622 pairs) and foster midparent–adopted child (N = 154 pairs) correlations for BMI, with values of 0.30 and 0.29, respectively. All these data suggest a low genetic effect in BMI.

Two recent adoption studies (47, 52), which were among the first to include data on the biological parents of the adoptees, reached different conclusions about the role of heredity in BMI. These studies examined the relationship between BMI of adult adoptees (adopted early in life) and those of their biological and adoptive parents, respectively. In both studies the authors concluded that the BMI of the adoptees was more closely related to the BMI of their biological parents than to their adoptive parents, which suggests that there was a strong genetic component in obesity, as measured by the BMI. Quantitatively, however, these results do not support a strong genetic effect in obesity because the proportion of the variance in the BMI of the adoptees accounted for by the BMI of biological or adoptive parents was found to be quite small (31). Furthermore, it has been claimed that methodological limitations (31, 32, 38), intrauterine factors (6), and the resemblance between the BMI of the lean adoptees and that of their biological parents (23) could explain the results obtained by Stunkard et al (52) in one of these studies.

Results from the twin studies generally support the notion of a strong contribution of heredity in BMI. Thus, in one study (51), BMI measurements were available in 2097 dizygotic and 1974 monozygotic male twin pairs and correlations of 0.42 and 0.81, respectively, were obtained. By taking twice the difference between mono- and dizygotic twin correlations (26), the authors reported a heritability estimate of 0.77 for BMI. In another recent study, Austin et al (3) obtained BMI measurements in 411 pairs (171 dizygotic and 240 monozygotic pairs) of female twins. After adjustment for age and sex they found a heritability of 0.89 for BMI, but after further statistical adjustment for shared environmental and behavioral effects, the heritability was reduced to 0.73. Comparisons of dizygotic twin and regular brother or sister correlations (Table 2) suggest, however, that the dizygotic twin resemblance is enhanced by nongenetic factors, and there are reasons to believe that the monozygotic correlation is increased by nongenetic influences to even a larger extent (13). This, of course, sets the stage for spuriously high estimates of heritability.

Using the "structured exploratory data analysis" strategy, Karlin et al (34) found that familial aggregation of BMI was mostly associated with nongenetic environmental influences, with a possible secondary weak effect of a major gene. Data from a recent study also support the presence of a major gene with a small effect in obesity defined in a complex manner from a discriminant analysis using log-transformed weight, subscapular skinfold thickness, and chest depth corrected for stature, age, and sex (57).

The technique of path analysis (21, 48) has been used in some recent studies to determine the contribution of genetic factors in BMI (1, 11, 36, 43). This technique has been described as a powerful method for separating genetic and nongenetic effects in multifactorial phenotypes (20). Results from these studies suggest a low to moderate effect of heredity in BMI. Using an approach that partitions the covariance among family members into genetic and environmental components, heritability estimates of 0.17 (1) and 0.35 (36) have been reported for BMI. In a recent study undertaken with data from the Canada Fitness Survey, we found that the joint transmission of biological and cultural factors from one generation to another accounted for 36% of the phenotypic variation in BMI (43). On the other hand, using a model of path analysis (the BETA model) that allows the separation of biological and cultural components of inheritance, we reported a transmissible variance of 35% for BMI, but a biological inheritance of about 5% (Figure 1), which suggest that BMI may be influenced by environmental factors such as nutritional or physical activity habits that could be transmitted (cultural inheritance) from parents to offspring (11).

When extensive data sets are used, including several kinds of biological and nonbiological relatives, one finds a total transmission effect across generations accounting for about one third of the phenotypic variance, but a smaller additive genetic component when the BMI is adjusted for age and gender differences.

AMOUNT OF SUBCUTANEOUS FAT Skinfold measurements at various sites of the body can be used to estimate the amount of subcutaneous fat. From the review of Mueller (39) and from some recent studies (13, 40, 49), it seems that parent-child correlations ranging from 0.15 to 0.25 and sibling correlations ranging from 0.20 to 0.40 are typical for individual skinfold measurements. On the other hand, results from twin data alone (13, 50) suggest heritability estimates around 0.80 for individual skinfolds. However, a better indicator of the amount of subcutaneous fat can be obtained from the sum of several skinfold thicknesses. This has been used in some recent studies (11, 43, 53); the correlations obtained are presented in Table 3. Parent-child correlations around 0.20 and sibling correlations around 0.25 have been reported. We reported, from twin data alone (13), a heritability estimate of

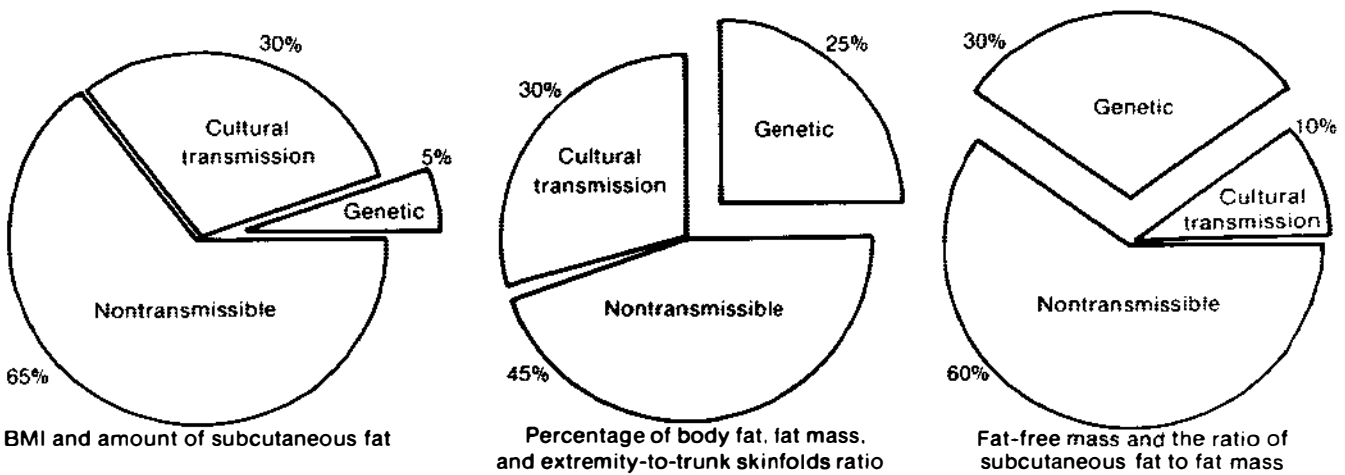

Figure 1 Total transmissible variance and its genetic component for indicators of body fat and fat distribution. From Bouchard et al (11). (Reproduced with permission from John Libbey & Company Ltd.)

0.88 for subcutaneous fat measured as the sum of six skinfolds. These studies suggest a substantial contribution from heredity to the amount of subcutaneous fat. Another indication about the role of heredity can be obtained by comparing midparent–natural child and midparent–adopted child correlations. We computed these for the sum of six skinfolds and found correlations of 0.31 and 0.36, respectively (7). The similarity between these two correlations (0.31 vs 0.36) suggests a weak contribution of genetic factors in the absolute amount of subcutaneous fat. This is in contrast with the results from the twin study and emphasizes the need to rely on other kinds of relatives to quantify the additive genetic effect (13).

Recently, we have used the BETA path analysis procedure to determine the additive genetic effect in individual skinfolds measured in the Quebec families. Results demonstrated a transmissible effect (joint transmission of both

Table 3 Familial correlations (r) in first-degree relatives for amount of subcutaneous fat, total body fat, regional fat distribution, and fat patterning[a]

Fatness indicator (Source)	Parent-child		Siblings		Dizygotic twins		Monozygotic twins	
	N pairs	r	N pairs	r	N pairs	r	N pairs	r
Subcutaneous fat								
Sum of 3 skinfolds (53)	431	.20						
Sum of 5 skinfolds (43)	6773	.21	3319	.27				
Sum of 6 skinfolds (11)	1239	.22	370	.26	69	.39	87	.83
Total body fat								
Percent body fat (11)	531	.21	152	.17	58	.21	76	.73
Fat mass (11)	531	.22	152	.16	58	.31	76	.76
Fat distribution								
Trunk/extremity skinfolds (11)	1239	.31	370	.36	69	.40	87	.80
(43)	6773	.20	3319	.34				
Waist-hip ratio (43)	6929	.16	3313	.23				
Subcutaneous fat/mass (11)	1239	.20	370	.26	69	.15	87	.61
Fat patterning[b]								
Trunk vs extremity fat component								
(41)	289	.09[c]	207	.23				
	318	.17[d]						
(9)	622	.31[e]						
Upper body vs lower body fat component								
(41)	289	−.08[c]	207	.03				
	318	.08[d]						

[a] Includes only studies since 1983. For studies published before 1983, the reader should refer to the review of Mueller (39). Age and gender effects are statistically controlled or kept to a minimum by design.
[b] Obtained by principal component analysis (see text for details).
[c] Father-child correlation.
[d] Mother-child correlation.
[e] Midparent-child correlation.

biological and cultural inheritance) ranging from 0.28 to 0.55, but an additive genetic effect ranging from 0.01 to 0.18 for skinfold measurements (8). Path analysis has also been used by other investigators (18, 22), who have estimated total transmissibility to be from 0.40 to 0.55 for individual skinfold measurements. These estimates are therefore quite coherent in suggesting a reasonably high transmission effect across generations for individual skinfolds, but with little evidence of a strong genetic effect. Two recent studies also used the path analysis procedure to assess the additive genetic effect in the amount of subcutaneous fat defined as the sum of several skinfolds (11, 43). In one study, we reported a total transmissible effect of 37% for subcutaneous fat as measured by the sum of five skinfolds obtained in 13,328 subjects who took part in the Canada Fitness Survey (43). In the Quebec family study, we found a joint transmission effect of 35% for the sum of six skinfolds with an additive genetic component of only about 5% (see Figure 1). Taken together, these data suggest a rather low genetic effect for the absolute amount of subcutaneous fat as assessed by the sum of several skinfolds.

PERCENTAGE BODY FAT AND FAT MASS Despite the number of studies dealing with the genetics of obesity, few of them have used direct measurements of total body fat. To the best of our knowledge, the only familial correlations reported were those from the Quebec study (11, 13, 44, 49). Correlations for total body fat presented in Table 3 are from a recent study (11) in which body density measurements were obtained in 531 pairs of parent-child, 152 pairs of regular siblings, 58 pairs of dizygotic twins, and 76 pairs of monozygotic twins. When these data and those from other types of relatives [spouses, unrelated siblings, foster parent–adopted child, first-degree cousins, and uncle(aunt)-nephew(niece)] were analyzed by the strategy of path analysis, a genetic effect of about 25% was found for percentage body fat and fat mass (see Figure 1). These results, combined with the lack of a significant genetic effect in amount of subcutaneous fat, suggest that deep fat (or visceral fat) is probably the fat component more under genetic control (11).

REGIONAL FAT DISTRIBUTION Obesity has long been recognized as a risk factor for coronary heart disease, and it is now well documented that fat distribution is also an independent risk factor, as emphasized by three recent symposia on that topic (10, 42, 55). Fat distribution refers to the amount of fat in various compartments or regions of the body and can be characterized by a variety of indicators relating, for example, upper body fat to lower body fat, trunk fat to extremity fat, subcutaneous fat to total fat mass, and many others (10). In contrast to the absolute amount of fat, regional fat distribution appears to be little affected by nutritional interventions. We recently studied

the role of heredity in fat distribution using the Quebec cohort of families and the Canada Fitness Survey data (7–9, 11, 13, 43). A combination of the following indicators have been used to assess regional fat distribution: the ratio of trunk to extremity skinfolds, the ratio of subcutaneous fat (sum of the skinfolds) to fat mass, and the waist-to-hip ratio (i.e. the ratio of waist to hip circumferences). Parent-child correlations of about 0.20 and sibling correlations of about 0.30 were found for these indicators (Table 3). Estimates of heritability derived from twin data alone suggested a strong genetic effect (about 80 to 90%) in fat distribution (13). However, when the method of path analysis was used to assess the degree of biological inheritance, results revealed a total transmission effect ranging from about 30 to 55% for the various indicators of fat distribution (11, 43), with an additive genetic effect of about 25 to 30% (11) for the proportion of fat in the trunk versus that in the extremities and the ratio of subcutaneous fat to total fat mass (see Figure 1).

SUBCUTANEOUS FAT PATTERNING Fat patterning is the notion used to describe the relative anatomical distribution of subcutaneous fat. Subcutaneous fat patterns are generally derived from a principal component analysis that yields unrelated components from a set of correlated variables. Using this technique, Mueller & Reid (41) identified three components of body fat from four skinfold measurements (triceps, subscapular, suprailiac, and medial calf). The first component correlated with all skinfolds and was identified as a general fat component, while the second and third components described a trunk to extremity fat pattern and an upper body to lower body fat pattern, respectively. The parent-child and sibling correlations for the second and third components are shown in Table 3. From these correlations and from the absence of spouse resemblance for the trunk to extremity ($r = 0.05$) and the upper to lower ($r = 0.07$) body fat components compared to the general subcutaneous fat component ($r = 0.26$), Mueller & Reid (41) concluded there is a stronger genetic effect in fat patterning than in fatness.

In a more recent study (9), the same procedure was applied to six skinfold measurements (triceps, biceps, suprailiac, subscapular, abdomen, and medial calf) adjusted for age and gender; the first two components were similar to those identified by Mueller & Reid (41). Midparent–natural child and midparent–adoptive child correlations were computed for these components and the results were suggestive of a higher genetic effect in the trunk to extremity subcutaneous fat component compared to the general subcutaneous fat component, even after adjustment of the component score for BMI. These data were also analyzed with the BETA model of path analysis (C. Bouchard et al, unpublished results), and a total transmission effect of about 40% was observed for the trunk vs extremity fat component, with an additive genetic effect of 18%, increasing to 30%, before and after adjustment for BMI, respectively.

Genotype-Environment Interaction in Body Fat

The low to moderate additive genetic effect reported thus far in human body fat does not necessarily imply that genetic factors have nothing to do with the development of obesity or fat topography anomalies. It is generally recognized that there are some individuals prone to excessive accumulation of fat for whom losing weight represents a continuous battle and others who seem relatively well protected against such a menace. We recently tried to test whether such differences could be accounted for by genetic factors. In other words, we asked whether there were differences in the sensitivity of individuals to gain fat when chronically exposed to a positive energy balance and whether such differences were dependent or independent of the genotype. If the answer to both of these questions was affirmative, then one would have to consider that there was a kind of genotype-environment interaction ($G \times E$) effect. The results from one experiment suggest that such a $G \times E$ effect exists for body fat.

To test for the presence of a $G \times E$ effect, we subjected both members of monozygotic twin pairs to a similar experimental treatment and compared intrapair (within genotype) and interpair (between genotypes) resemblances in the response. Six pairs of male monozygotic twins were subjected to a 1000-kcal/day caloric surplus during 22 consecutive days (45). Significant increases in body weight, sum of 9 skinfolds, trunk skinfolds, extremity skinfolds, and fat mass were observed after the period of overfeeding (Table 4). It is interesting to note that the largest changes were observed in absolute skinfold thicknesses ($30.5 \leq F$ ratios ≤ 46.1), which suggests that subcutaneous fat is indeed quite labile under environmental pressure. Data suggest that there were considerable interindividual differences in the adaptation to excess of calories and that the variation observed was not randomly distributed, as indicated by the generally significant genotype-overfeeding interaction component.

The intrapair resemblance in the response to overfeeding was quite high, as revealed by intraclass correlations ranging from 0.64 to 0.90. For instance, the intraclass correlation of 0.88 for fat mass indicates that almost 90% of the variance in the response of fat mass to overfeeding is found between genotypes (between pairs) while only about 10% is found within pairs (Figure 2). These data demonstrate that some individuals are at greater risk of gaining fat than others. In other words, the amount of fat stored in response to a caloric surplus is largely determined by the genotype of the individual. These are exciting findings that need to be confirmed with more prolonged studies.

Summary of the Role of Heredity

Several points need to be emphasized in summarizing the role of biological inheritance in human body fat variation. First, at least two kind of genetic

Table 4 Analysis of variance and intraclass correlations for body fat following short-term overfeeding[a]

Variable	Effect of overfeeding (F ratio)[b]	Genotype-overfeeding interaction (F ratio)[b]	Intrapair resemblance in response
Body weight (kg)	49.4[c]	4.6[d]	0.64
Sum of 9 skinfolds (mm)	46.1[c]	7.7[d]	0.77
Trunk skinfolds (mm)	40.7[c]	5.6[d]	0.70
Extremity skinfolds (mm)	30.5[c]	6.9[d]	0.75
Body fat (%)	3.8	18.4[c]	0.90
Fat mass (kg)	6.2[d]	16.3[c]	0.88

[a] An extra 1000 kcal/day for 22 consecutive days in 6 pairs of male monozygotic twins. Adapted from Poehlman et al (45)

[b] The effects of overfeeding and the genotype-overfeeding interaction were assessed by a two-way analysis of variance for repeated measures on one factor. Intraclass correlations were computed with changes induced by overfeeding.

[c] $P \leq 0.01$.

[d] $P \leq 0.05$.

effects must be considered: the additive genetic effect and the genotype-environment interaction effect. One should keep in mind that the presence of an additive genetic effect or some other kind of genetic variation is a requirement for a $G \times E$ effect to exist. Second, from the data reviewed here, we proposed that the additive genetic effect (h^2) in amount of subcutaneous fat is quite low ($h^2 \leq 10\%$) and that it is higher (~25–30%) for percentage body fat, fat mass, and regional fat distribution. These results suggest that visceral fat is perhaps more influenced by the genotype than subcutaneous fat. Third, it appears that a genotype-overfeeding interaction component exists for body fat, which suggests that sensitivity of individuals to changes in body fat following overfeeding are genotype dependent.

LIMITATIONS OF THESE STUDIES

The use of more sophisticated designs from the field of genetic epidemiology and the distinction between the additive genetic effect and the genotype-environment interaction effect represent improvements in the effort to understand the genetics of obesity. However, there are still major limitations in the approaches currently used that preclude any definitive conclusions about the contribution of the genes to human obesity (8). First, except for the rare genetic disorders described earlier, obesity is not a clear-cut Mendelian trait but rather a multifactorial phenotype. Thus, the effects of the genes are not readily observed at the phenotypic level because they are attenuated or amplified by nongenetic factors such as nutritional habits or other lifestyle factors. Because of that limitation, one has had to rely solely thus far on

familial data and the methods of genetic epidemiology to try to understand the connection between the genes and human body fat variation.

Second, obesity is not a homogeneous phenotype stemming from a unique gene or set of genes. The heterogeneity of the obesity phenotype represents probably one of the most important current issues. Obesity can be viewed as a diagnostic term used to define all types of excessive accumulation of fat. This is of course an oversimplification, as shown by the useful distinction made recently between abdominal obesity and peripheral obesity types. It would therefore be useful to intensify the efforts to characterize the different forms of obesity in order to have a better-defined phenotype for genetic and clinical studies. In that context, a recent workshop on the characterization of human obesity (19) has provided valuable information.

Third, one should recognize that excess body fat or a given type of obesity can be generated by different combinations of a variety of causes associated with the energy balance equation. In some cases, the energy intake may be more or less incriminated while in other individuals one or more of the energy expenditure components may be the determining cause. Genetic studies designed to analyze body fat as the phenotype endpoint will not distinguish among the various affectors and will, therefore, have little chance of improving our understanding of the role of the genes in body fat or as a determinant of obesity.

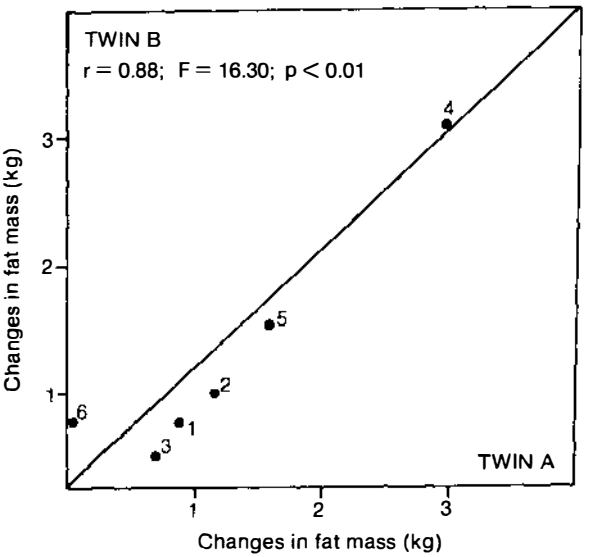

Figure 2 Intrapair resemblance (intraclass coefficient) in magnitude of changes in total fat mass following 22 days of a 1000-kcal/day caloric surplus. Constructed from the data of Poehlman et al (45).

Fourth, body fat is seldom measured by direct methods. When body fat is defined on the basis of weight, relative weight, BMI, one or two skinfolds, or other indirect approaches, we are essentially increasing the error in the assessment of the phenotype and thus making genetic studies potentially less precise. The use of more direct techniques (underwater weighing, potassium-40, computerized axial tomography, etc) to assess body fat and its distribution should be encouraged.

RESEARCH TRENDS

The heterogeneity of the obesity phenotype represents a major difficulty that must be overcome before meaningful progress can be achieved in this area. In the meantime, the emphasis is shifting from the study of the genetics of body fat or obesity to the genetics of the causes or presumptive causes of obesity because these causes are generally more clearly defined and often less heterogeneous than the phenotype itself. Another line of research that may be quite profitable is to look for protein or DNA markers of obesity or of the abdominal and peripheral subtypes.

To be more specific, in studying the genetics of the causes of obesity one may want to consider each behavioral and biological affector of body fat and their complex interactions. A simple paradigm of the major affectors of body fat and their interactions is described in Figure 3. Each affector includes several components, and the complete picture is indeed a complicated one. For instance, in the subset of energy expenditure, one could find components such as basal metabolic rate, resting metabolic rate, diet-induced thermogenesis, energy expenditure related to exercise and work, stress-induced thermogenesis, and perhaps others. Some of these components of energy expenditure are presumably more important than others. Nevertheless, in all cases it would be appropriate to undertake studies in order to quantify the additive

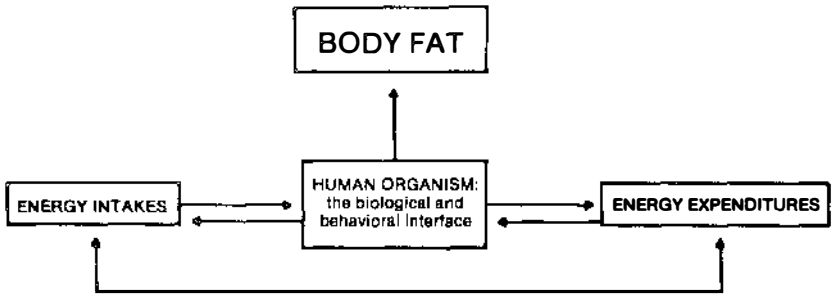

Figure 3 A paradigm of the major affectors of body fat. From Bouchard (8). (Reproduced with the permission from John Libbey & Company Ltd.)

genetic effect and determine whether there is a genotype–energy intake or a genotype–energy expenditure interaction effect.

The search for protein or DNA markers of obesity becomes increasingly important because they will provide an opportunity to detect individuals more at risk than others of developing excess body fat. Attempts to find such genetic markers of obesity (2, 4, 24, 29) or body fat (12) have not been very successful in the past, but more recent approaches look promising (27). Genetic markers may be protein variants of the adipose tissue or other relevant tissues detected by electrophoretic or electrofocusing techniques. On the other hand, with the progress in DNA technology, it is possible to study genetic variation at the DNA level. This may prove to be an important line of research as a very high proportion of the genetic variation is not expressed at the protein level because the variation is found in the noncoding regions of the human genome. Thus, one should look for restriction fragment length polymorphisms that could be useful as genetic markers of body fat variation, abdominal obesity, and other phenotypes. In addition to their use in the screening of individuals at risk, genetic markers could also be used in linkage analysis with other markers to bring us closer to some of the genes of interest in obesity. Future developments in the genetics of obesity will undoubtedly have to rely increasingly on the tools of biochemical genetics and DNA technology.

SUMMARY

The genetics of human obesity was reviewed here in terms of studies dealing with body fat and fat distribution. The role of heredity was examined by reviewing genetic disorders in which obesity is a clinical feature. Two kinds of genetic effects were discussed: the additive genetic effect and the genotype-environment interaction effect. Several indicators of body fat exist, including body mass index, amount of subcutaneous fat, percentage body fat, fat mass, regional fat distribution, and subcutaneous fat pattern. A low additive genetic effect of less than 10% of human phénotypic variation is found in body mass index and amount of subcutaneous fat, while percentage body fat, fat mass, fat distribution, and fat patterning are characterized by heritability estimates of about 25%. On the other hand, a recent study demonstrates that there is an important genotype-environment interaction effect in human body fat variation induced by overfeeding. Limitations of current approaches to the study of the genetics of human body fat and obesity are considered and comments are offered concerning promising areas of future research.

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