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Etiology of obesity: genetic factors

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The evidence for a role of inherited factors in the development and the maintenance of overweight and obesity is limited but highly suggestive at this time. In contrast, the evidence for the contribution of behavioral and lifestyle factors in the development and maintenance of obesity is abundant and generally strong (1). It is also increasingly recognized that there are inherited differences in the susceptibility to become overweight or obese under given behavioral and lifestyle conditions. The interest for the genetics of the overweight and obesity phenotypes has increased considerably during the last decade partly because of the realization that they were associated at times with high risks for various morbid conditions and for mortality rate. However, overweight or obesity cannot be seen anymore as a homogeneous phenotype. Based on the topography of the adipose tissue and its association with a variety of metabolic characteristics, we have proposed that four different types of human overweight or obesity can be recognized (1-3).

TABLE 1
THE TYPES OF OBESITY PHENOTYPES IN A HEALTH PERSPECTIVE

Type I Obesity:	excess body mass or percent fat
Type II Obesity:	excess subcutaneous truncal-abdominal fat (android)
Type III Obesity:	excess abdominal visceral fat
Type IV Obesity:	excess gluteo-femoral fat (gynoid)

These four types are briefly described here. Type I is characterized by excess total body mass for height or body fat without any particular concentration of fat in a given area of the body. The other types have to do with excessive accumulation of fat in some areas of the body. Type II is defined as excess subcutaneous fat on the trunk, particularly in the abdominal area, and is equivalent to the so-called android or male type of fat deposition. Type III is characterized by an excessive amount of fat in the abdominal visceral area and can be labelled abdominal visceral obesity. The last type (Type IV) is defined as gluteo-femoral obesity and is observed primarily in women (gynoid obesity). This implies that a given body fat content, say, 30% or 50 kg, may exhibit different anatomical distribution characteristics. Yet, individuals with quite different phenotypic characteristics are often lumped together and studied as if they all had the same trait.

HERATABILITY OF THESE PHENOTYPES

Many authors have reported that obese parents had higher risk of having overweight or obese children than lean parents (4). This does not constitute a clear demonstration that the obesity of the offspring is determined by their genes as both generations share not only genes but also the household milieu and many environmental conditions. Nonetheless, these studies suggest that having an obese mother or one obese parent meant a greater risk of becoming overweight or obese. The parents of obese probands are more often obese than expected with an odds ratio of about 1.5 over a wide range of age and for both

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genders (5). The relationship reaches its peak when the probands are teenagers. That weight status at or around puberty may be an important correlate of adult weight was also suggested by a recent report on a 40-year follow-up of overweight children (6).

The literature on the topic of the genetics of the body mass index (BMI) as a surrogate measure for type I obesity is confusing at times. There are dozens of reports that have dealt with one aspect or another of the problem and the additive genetic effect reported ranges from almost zero to values of about 90 percent of the age and gender adjusted phenotypic variance. In general, they have concluded on the basis of only two or a few types of relatives. With few exceptions, they could not truly distinguish between the effects of the genes shared by descent from the household and environmental conditions shared by relatives living together.

Three adoption studies of BMI have been reported in recent years (7-9). They unanimously concluded that BMIs in the range of overweight and obesity are strongly influenced by genetic factors. However, from our review of these studies, we find that the correlations between biological parents and offspring given for adoption is only about 0.2, while the correlation for foster parents and adopted children attains about 0.1. The difference between these two coefficients is of course compatible with a genetic effect but certainly not with a very high heritability level.

Recently, two studies have been reported on the BMI of various sets of DZ and MZ twins who had been reared together or apart (10-11). The estimates of heritability ranged from about 30% to 100%, with a significant non additive genetic component and, surprisingly, no shared childhood and familial environmental effects (10). In other words, having lived together in the same household did not influence the twin resemblance for the BMI. This finding is of course at odds with much of what we know about the familiality of body fat and about the effects of nutritional habits, habitual physical activity level and other lifestyle components on body weight and body composition. As it is derived from twin data alone, it should be interpreted with caution until we understand better the role of genetic similarity on behavioural traits that may impact on body mass.

Based on a stratified representative sample of the Canadian population, BMI, skinfolds and circumferences data were available on 18,073 subjects living in 11,884 different households (12). Correlations could be computed for 5 kinds of relatives, i.e. spouses, parent-child, siblings, uncle(aunt)-nephew(niece), and grandparent-grandchild. Coefficients were of the order of zero for the pairs of uncle(aunt)-nephew(niece) and grandparent-grandchild, slightly above 0.1 for spouses, and about 0.2 for parent-child and 0.3 for pairs of brothers and sisters. Such results are clearly not supportive of a very strong genetic effect. We were able to establish that the total transmission effect across generations for the age and gender adjusted BMI or sum of 5 skinfolds pheno-typic variance reached about 35 percent.

Using a model of path analysis, we have studied the relative importance of the genetic and the non-genetic (cultural) components of inheritance as well as the non-transmissible effect in the BMI pheno-type after control over variations in age and gender (13). The data were obtained in 1.698 members of 409 families which included 9 types of relatives by descent or adoption. We reported a total transmissible variance across generations of about 35%, but a genetic effect of only 5%. The importance of the non-transmissible variance (about 65%) may be partly caused by the fact that several tissues with their own pattern of transmission are contributing to the phenotype or because the BMI is indeed quite susceptible to lifestyle and environmental conditions. These data taken as a whole thus indicate that the BMI, an index of heaviness, is not characterized by a significant heritability component even though the transmissible component of the age and gender adjusted variance may be as high as 35 percent. In this research, we also had underwater weighing measurements of body density. About half of the variance, after adjustment for age and gender, in fat mass or percent body fat was associated with a transmissible effect and 25% of the variance was an additive genetic effect.

What do we know about the genetics of the other three types of obesity? Based on the stratified sample of the Canadian population, transmissibility across generations for trunk fatness (type II) expressed as a percent of the age and gender adjusted phenotypic variance ranged from about 30 to 40 percent and were identical for the maternal and the paternal transmission (12). The issue was further investigated with a cohort of families that included 9 kinds of relatives by descent or by adoption in order to distinguish between the genetic and the nongenetic transmission (13-15). When taking into account the influence of variation in total body fat on the heritability estimates of type II body fat, the amount of subcutaneous fat on the trunk relative to the limbs as well as the truncal-abdominal fat alone were both characterized by an additive genetic effect of about 30 percent. Principal component analysis of six individual skinfolds adjusted for age, gender and total fat yielded a first component with high loadings for trunk and abdominal skinfolds. A path analysis study of this component was undertaken and it resulted in heritability estimates ranging from 35 to 50% (16).

These results imply that for a given level of fatness, some individuals are storing more fat on the trunk or abdominal areas (type II) while others are storing primarily on the lower body (type IV) segments (16, 17). In this context, the recent observation that the relative distribution of subcutaneous fat on the trunk is influenced by a major locus (42 percent of the variance) and polygenic inheritance (10 percent) is quite interesting (18) and deserves further research. No data have yet been reported on the heritability of abdominal visceral fat (type III) levels and the population data needed to deal with this issue are difficult to generate with the present methodology.

THE RESPONSE TO OVERFEEDING IN IDENTICAL TWINS

There are some individuals prone to excessive accumulation of fat, for which losing weight represents a continuous battle, and others who seem relatively well protected against such a menace. We have attempted to test whether such differences could be accounted for by inherited differences. In other words, we asked whether there were differences in the sensitivity of individuals to gain fat when chronically exposed to positive energy balance and whether such differences were dependent or independent of the genotype. If the answer to both questions was affirmative then one would have to conclude that there was a significant genotype-environment interaction effect. The results from two experiments suggest that such an effect exists for the four phenotypes of total body fat and regional fat distribution (17, 19, 20).

In the most comprehensive of these studies (17), 12 pairs of male MZ twins ate a 1,000 kcal per day caloric surplus, 6 days a week, during a period of 100 days for a total overfeeding stimulus of 84,000 kcal. Significant increases in body weight and fat mass were observed. Data showed that there were considerable interindividual differences in the adaptation to excess calories and that the variation observed was not randomly distributed, as indicated by the significant within pair resemblance in response. For instance, there were at least 3 times more variance in response between pairs than within pairs for the gains in body weight, fat mass and fat free mass. These data demonstrate that some individuals are more at risk than others to gain fat when energy intake surplus is clamped at the same level for everyone and when all subjects are confined to a sedentary lifestyle. The within identical twin pair response to the standardized caloric surplus suggests that the amount of fat stored is likely influenced by the genotype. The genetic effect is, however, likely to be moderate and accounts for only a maximum of about 50 percent of the variation in the response of body weight and body composition to the protocol.

The long-term overfeeding study also revealed that there were 6 times more variance between pairs than within pairs for the changes in truncal-abdominal subcutaneous fat and in computerized tomography determined abdominal visceral fat when both were adjusted for the gain in total fat mass (17). These observations indicate that some individuals are storing fat predominantly in selected fat depots primarily as a result of undetermined genetic characteristics. It also suggests that variations in regional fat distribution are probably more closely related to the genotype of the individuals than variations in overall body composition.

NUTRIENT PARTITIONING: FAT MASS TO FAT FREE MASS RATIO

The mean body mass gain for the 24 subjects of the 100-day overfeeding experiment was 8.1 kg, of which 5.4 kg were fat mass and 2.7 kg were fat free mass increases (19). Assuming that the energy content of body fat is about 9,000 kcal per kg and that of fat free tissue is 1,021 kcal per kg, then a total of about 63 percent of the excess energy intake were recovered as body energy gain. There were, however, individual differences among the 24 subjects with respect to the amount of fat and fat free tissues gained. The changes in the ratio fat mass to fat free mass were correlated with the changes in body weight and the coefficient reached 0.61 ($p < 0.01$) (17). In other words, about 37 percent of the variation in weight gain as a result of exposure to long term overfeeding was associated with this dimension of nutrient partitioning. Those who gained more fat relative to fat free tissues were the high gainers for body mass while those who gained relatively more lean tissues were the low gainers. Chances are that a substantial proportion of those prone or resistant to obesity find themselves in this vulnerable or desirable position because of inherited or acquired differences in nutrient partitioning mechanisms.

Our previous research on the heritability of total body fat and fat free mass has revealed that the apparent level of genetic transmission across generations is quite moderate with values clustering around 25 percent for the various phenotypes after controls over age and gender differences (13). A similar level of heritablilty is also found for the ratio of fat mass in kg to fat free mass in kg or the ratio adjusted for stature (unpublished data). Such a level of heritability implies of course that most of the individual differences in body composition are independent from the genotype and result from individuality in nongenetic factors. Nonetheless, despite these low levels of heritability, genetic variation remains quite important in determining individual differences in the adjustement to positive energy balance as shown by the research summarized above. Clearly, some are more at risk of becoming overweight or type I, II, III or IV obese because of the fact that they store or mobilize fat more readily than others under identical energy intake, dietary composition and level of physical activity conditions.

In conclusions, the data suggest at this point that when energy intake is clamped at the same level above baseline, two main classes of factors appear to be involved for a given genotype in determining the changes in body mass.

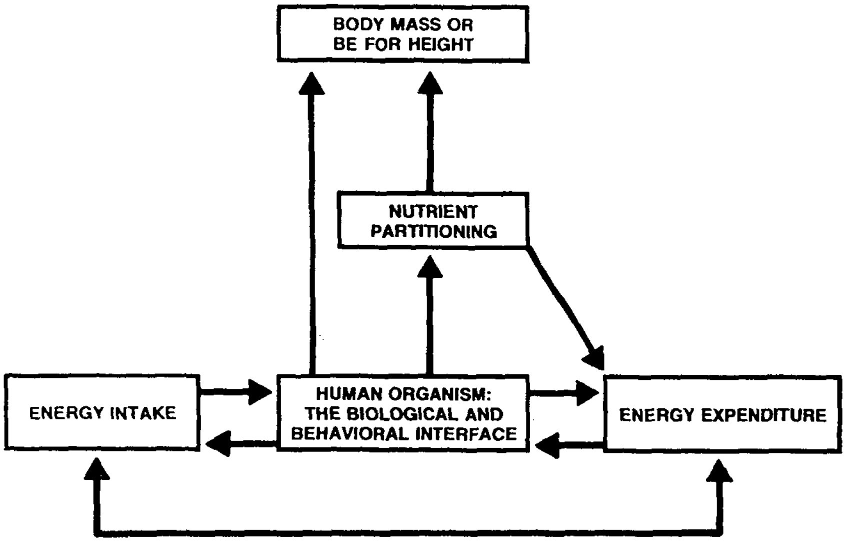

FIGURE 1

A model of the major affectors of body mass, body fat or body energy content. The model is a modification of the paradigm described in earlier publications (1-3).

These are schematically illustrated in Figure 1. It would seem from the overfeeding study summarized here that nutrient partitioning (gain in fat or fat free tissues) is an important factor to explain the individuality in body mass gain. Chances are that a substantial proportion of those prone or resistant to obesity find themselves in this vulnerable or desirable position because of inherited or acquired differences in nutrient partitioning mechanisms. This factor in addition to a low resting metabolic rate per unit of fat free mass and a low level of lipid oxidation relative to carbohydrate are emerging, at this time, as being the three most useful predictors of weight gain over time (1). More longitudinal data are clearly needed on these and other potential determinants of weight gain and obesity and on their genetic basis.

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