Genetic determinants of regional fat distribution

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Upper body fat and abdominal visceral fat are two obesity-related phenotypes of interest because of their relationships with a variety of metabolic complications. The heritability of the amount of upper body fat or the level of upper body fat relative to lower body fat ranges from ~30–50% of the phenotype's age, sex and total body fat adjusted variance. On the other hand, familial studies of abdominal visceral fat reveal that the familial transmission reaches >50% of the age, sex and total body fat adjusted variance. Complex segregation analysis undertaken with a panel of nuclear families indicates that major genes may account for a significant fraction of the variance in upper body fat and abdominal visceral fat. Two intervention studies conducted with pairs of male identical twins have shown that changes in upper body fat and visceral fat are more similar within pairs than between pairs, either in phenotype increments when challenged by chronic overfeeding, or in adipose tissue losses after exposure to long-term negative energy balance conditions. The evidence accumulated to date is sufficient to justify undertaking a search for the specific genes and molecular markers involved in the heterogeneity commonly observed in human fat topography.

Key words: fat distribution/gene environment interaction/genetics/upper body fat/visceral fat

Phenotypes

Interest in the genetics of human obesity has increased considerably during the last decade partly because of the realization that some forms of obesity are associated with high risks for various morbid conditions and mortality rate. Obesity cannot be seen any more as a homogeneous phenotype. We have proposed that four different types of human obesity can be recognized. We are not here referring to the heterogeneity of the clinical manifestations of obesity or their determinants but only to the phenotype of body fat. The first is characterized by excess total body fat without any particular concentration of fat in a given area of the body. The second type 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. The third is characterized by an excessive amount of fat in the abdominal visceral area and can be labelled abdominal visceral obesity. The last type is defined as gluteo-femoral obesity and is observed primarily in women (gynoid obesity). Thus, excess fat can be stored primarily in the truncal-abdominal area or in the gluteal and femoral area. This implies that a given body fat content, say 30% or 50 kg, may exhibit different anatomical distribution characteristics.

It is important to recognize that these types of obesity are not fully independent of one another as shown by the data of Figure 1. The level of covariation among the various body fat phenotypes ranges from ~30–50% (Bouchard, 1994). One implication of the above is that studies designed to investigate the causes of the individual differences in the various body fat phenotypes, including genetic causes, should control for these levels of covariation.

An important issue is that of the relationship among fat distribution phenotypes. Contrary to the

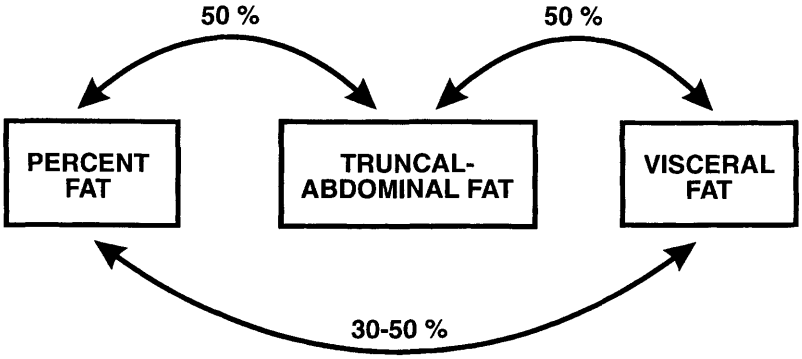

Figure 1. Common variance between three body fat phenotypes. Fat mass estimated from underwater weighing; truncal–abdominal fat assessed from skinfolds or computerized tomography (CT) scans; abdominal visceral fat estimated by CT scan at the L4/L5 vertebrae (from Bouchard, 1994).

general belief, these relationships are not very close. Thus the correlation between the waist-to-hip circumference ratio (WHR) and abdominal visceral fat (AVF) is positive and generally significant in various populations, but the association is characterized by a wide scatter of scores. For instance, in a study of 51 adult obese women, the correlation between WHR and computerized tomography (CT)-assessed AVF reached 0.55 (Ferland *et al.*, 1989). For a WHR of about 0.8, visceral fat area at the L4–L5 level ranged from a low of about 50 cm^2 to a high of ~200 cm^2. Even though the covariation between total body fat and AVF is statistically significant, the relationship is also characterized by a high degree of heterogeneity. As shown in Table I, when body mass index (BMI) and percentage body fat are constrained to narrow ranges, one generally finds a three-fold range for the amount of CT-assessed AVF in adult males. Thus in 16 men with BMI values of 30 or 31 and body fat of 30–33%, mean abdominal visceral fat was 153 cm^2 with a range of 77–261 cm^2. The same lack of coupling between BMI, percentage body fat and AVF was observed in adult women (Bouchard, 1994).

The above data suggest that even though it may be useful to use a prediction of AVF in clinical settings, in field work or large population surveys, the practice should not be recommended in the context of scientific and clinical research designed to understand the causes and metabolic consequences of variation in body fat content or in fat topography.

Genetic epidemiology of fat topography

We have reviewed more extensively elsewhere the topic of the genetics of fat topography phenotypes (Bouchard *et al.*, 1991, 1993), and the interested reader should consult these publications for a more extensive treatment of the subject matter.

Truncal–abdominal subcutaneous fat

Upper body obesity is more prevalent in males than in females and it increases in frequency with age in males and after menopause in females. It is moderately correlated with total body fat and appears to be more prevalent in individuals habitually exposed to stress. It is also associated in females with the elevated concentrations of plasma androgens and cortisol. In addition, the activity of abdominal adipose tissue lipoprotein lipase is elevated with higher levels of truncal–abdominal fat (Bouchard *et al.*, 1991).

Evidence for familial resemblance in body fat distribution has been reported (Donahue *et al.*, 1992). Based on skinfold measurements obtained in 173 monozygotic and 178 dizygotic pairs of male twins, Selby *et al.* (1989) concluded that there was a significant genetic influence on central deposition of body fat. Using data from the Canada Fitness Survey and the strategy of path analysis, we have shown that the transmissible effect across generation reached ~40% for trunk skinfolds (sum of subscapular and suprailiac skinfolds), limb skinfolds (sum of biceps, triceps and medial calf skinfolds), the trunk to limb skinfolds ratio and 28% for the WHR (Pérusse *et al.*, 1988).

Table I. Variation in amount of abdominal visceral fat measured by computerized tomography scan at L4–L5 for given body mass index (BMI) and percentage body fat classes in adult males[a]

n	BMI	Percentage fat (range)	Visceral fat (cm^2)		
			Mean	Min	Max
15	21–22	14–18	58	31	84
19	24–25	19–24	89	50	140
18	27–28	25–29	133	63	199
16	30–31	30–33	153	77	261

[a]Percentage fat derived from underwater weighing (Bouchard *et al.*, 1993).

The biological and cultural components of transmission in regional fat distribution were further assessed with data from the Québec Family Study (Bouchard *et al.*, 1988). Two indicators of regional fat distribution were considered. The trunk-to-limb skinfold ratio and the subcutaneous fat to fat mass ratio were obtained by dividing the sum of the six skinfolds by fat mass derived from body density measurements. Genetic effects of 25–30% were obtained. When the influence of total body fat was taken into account, the profile of subcutaneous fat deposition was found to be characterized by higher heritability estimates reaching ~40–50% of the residual variance (Bouchard, 1988, 1990). These results imply that for a given level of fatness, some individuals store more fat on the trunk or abdominal area than others.

Results from two studies suggest the influence of major genes for regional fat distribution phenotypes. In one study, Hasstedt *et al.* (1989) reported a major gene effect explaining 42% of the variance in a relative fat pattern index, defined as the ratio of the subscapular skinfold to the sum of the subscapular and suprailiac skinfold thicknesses. Recent results from the Québec Family Study suggest major gene effects for the trunk to extremity skinfold ratio, adjusted for total fat mass, accounting for ~35% of the phenotypic variance (Borecki *et al.*, 1995).

Abdominal visceral fat

We know less about the causes of individual differences in abdominal visceral fat level than for the other body fat depots. Visceral fat increases with age, in both genders, in lean as well as obese individuals (Enzi *et al.*, 1986). Males have, on average, more visceral fat than females and obese have more than lean persons. However, the level of visceral fat is only moderately correlated with total body fat, with a common variance level ranging from ~30–50%. In women, high plasma androgen and cortisol concentrations are commonly seen with augmented amounts of visceral fat. In addition, high lipoprotein lipase and lipolytic activities in the visceral adipose depot are observed, but we do not know if these characteristics are causes or effects of visceral obesity. Data from the Québec Family Study indicate that significant familial aggregation is observed for the level of abdominal visceral fat beyond that seen for total body fat. The study suggests that the heritability of abdominal visceral fat with proper control over total body fat reaches ~56% of the phenotype variance (Pérusse *et al.*, 1996).

Experimental overfeeding and negative energy balance

It is generally recognized that 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 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 or lose fat, more specifically upper body fat and AVF, when chronically exposed to positive energy balance or negative energy balance, and whether such differences were dependent or independent of the genotype. If the answer to these questions was affirmative then one

would have to conclude that there was a significant genotype–energy balance interaction effect. The results from two experiments suggested that such an effect was likely to exist for body weight, body fat, and fat distribution phenotypes.

In all, 12 pairs of male monozygotic twins ate a 1000 kcal per day caloric surplus, 6 days a week, during a period of 100 days (Bouchard *et al.*, 1990). Significant increases in body weight and fat mass were observed after the period of overfeeding. Data showed that there were considerable inter-individual 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 was at least three times more variance in response between pairs than within pairs for the gains in body weight, fat mass and fat free mass. These data, and those of the response to short-term overfeeding, 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 to be influenced by the genotype. When the changes in specific fat depots were considered, it was observed that there was about six times more variance in response between identical twin pairs than within pairs. Thus a strong within pair resemblance was observed for the increase in trunk subcutaneous fat and AVF in response to overfeeding.

Seven pairs of young adult male identical twins completed a negative energy balance protocol during which they exercised on cycle ergometers twice a day, 9 out of 10 days, over a period of 93 days while being kept on a constant daily energy and nutrient intake (Bouchard *et al.*, 1994). The mean total energy deficit caused by exercise above the estimated energy cost of body weight maintenance reached 244 MJ. Baseline energy intake was estimated over a period of 17 days preceding the negative energy balance protocol. Mean body weight loss was 5.0 kg and it was entirely accounted for by the loss of fat mass. Fat-free mass was unchanged. Body energy losses reached 191 MJ which represented ~78% of the estimated energy deficit. Subcutaneous fat loss was slightly more pronounced on the trunk than on the limbs as estimated from skinfolds, circumferences and computed tomography. The reduction in abdominal visceral fat area was quite striking, from 81 to 52 cm^2. Again, the within pair resemblance in the fat loss at specific trunk sites and in AVF was striking.

Strong support for the notion that the genotype is an important determinant of subcutaneous fat distribution and AVF phenotypes comes from these overfeeding and negative energy balance studies with identical twins. Indeed, with about six times more variance between pairs than within pairs for the increases in upper body subcutaneous fat level, and in computerized tomography assessed AVF with overfeeding, after controlling for the gains in total fat, and with a similar intra-pair resemblance for the loss of abdominal visceral fat in the negative energy balance experiment, it is quite apparent that the genes are playing a major role in fat deposition or fat mobilization of specific fat depots, particularly AVF.

Conclusions

It is now commonly recognized that the genetic heritability of fat distribution phenotypes is highly significant and could even be higher than the genetic effect observed for total body fat content. The major task has now become that of the identification of the genes and the specific sites of genetic individuality responsible for human variation in fat topography.

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