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GENETICS OF OBESITY

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CONTENTS

INTRODUCTION

The field was reviewed by us five years ago in the 1988 issue of this publication (11). The emphasis was on genetic epidemiologic data concerning total body fat content, amount of subcutaneous fat, regional fat distribution, and subcutaneous fat patterning. Since then, much research that is relevant to the general topic of the genetics of obesity has been reported and a new review of the field is warranted.

The present review deals not only with the genetics of body fat content and regional fat distribution phenotypes but also with the genetics of some of the

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main affectors of these phenotypes such as energy intake, resting metabolic rate, level of habitual physical activity, and nutrient partitioning. Additive genetic effects, major gene and single gene effects, temporal trends, and genotype-environment interaction effects are considered.

A complex phenotype, obesity is not readily reduced to simple Mendelian segregation patterns primarily for two reasons. First, body fat content, and more specifically an excessive amount of body fat, results from an intricate network of additive and interactive causes that may be related to DNA sequence variation but may also be associated with behavioral and lifestyle characteristics. Second, obesity is a heterogeneous phenotype, and evidence is growing that each phenotypic entity is modulated by a different set of causal factors. Recently, we have proposed that it would be useful to distinguish a minimum of four obesity phenotypes for the study of the etiology and the causes of human obesities as well as for the investigation of their clinical implications (7–9). These four phenotypes were defined as an excessive total amount of body fat (Type I), an excessive amount of subcutaneous fat on the trunk and abdominal area (Type II), an excessive amount of abdominal visceral fat (Type III), and an excessive amount of gluteo-femoral fat (Type IV). Very few studies have dealt with the genetics of obesity-related phenotypes as defined in this scheme. Indeed, as was observed in our 1988 review, most recent studies have again relied on the body mass index (weight in kilograms divided by height in meter squared) as a surrogate measurement for total amount of body fat (Type I).

HUMAN GENETIC RESEARCH STRATEGIES

Geneticists rely on a large number of traditional and innovative research designs and procedures in the current massive effort to define the genetic and molecular basis of common complex and multifactorial diseases that bear a striking similarity to the case of human obesities. Ultimately, the goal is to identify DNA sequence variants that impact on the various obesity phenotypes and to understand the mechanisms by which they exert these influences on body fat content and fat topography. Four broad categories of research strategies are commonly used to define the genetic basis of such phenotypes. The division is somewhat arbitrary and hybrid approaches are becoming the rule rather than the exception.

The first class of methods is one in which inference about heritability, the quantitative nature of the genetic effects, segregation patterns, and single gene effects is obtained from nuclear family, extended pedigree, twin, or adoption data without any information on genetic polymorphism. These methods have been classified as a so-called "top-down" approach to the problem (65). Alternatively, one may begin from genetic variation at a given locus or at several genes and proceed in the opposite direction by a variety of procedures

that attempt to relate genetic polymorphisms to the variance in the phenotype of interest. Collectively, this second class of methods has been labelled as the "bottom-up" strategy (65). A more productive strategy that has evolved recently is to combine both methods in the same study design (3).

Progress can be anticipated also through a very different approach in which a great number of experimental and analytical techniques can be used to examine the positional cloning strategy. Positional cloning (the third class of methods) can be useful in a variety of circumstances, several of which are particularly relevant to human obesities. In broad terms, positional cloning will enable the precise localization of the chromosomal region that seems to include the gene(s) responsible for the undesirable phenotype characteristics. In some cases, the investigation may begin with an animal model of the human phenotype and evolve toward definition of the human chromosomal region homologous to the animal genome segment encoding the deficient gene (30). In other cases, the research may focus on a segment of a human chromosome known to segregate with some or all of the phenotype manifestations in an attempt to identify progressively the position of the gene by a combination of several techniques. Animal crosses and backcrosses from informative strains and transgenic animal models are very valuable resources in an elaborate positional cloning strategy. The recently developed "quantitative trait loci" (37, 45) approach is rapidly becoming an important technique in the efforts to identify genes or coding sequences relevant to a complex multifactorial phenotype and to assist in localizing them on the genomic map.

One of the most important goals of genetic research is to identify the relevant gene(s) and the DNA sequence variant(s) that are involved (the fourth class of methods). Many of the genes that have been implicated so far in complex multifactorial diseases or clinical conditions exhibit several different DNA mutations, which has led to the recognition that genetic heterogeneity may exist for many entities. Sequencing the gene or appropriate DNA fragments in informative individuals will ultimately provide the evidence that one or several DNA base pairs are implicated and will provide the molecular information to investigate the mechanisms relating DNA sequence alteration(s) to the gene product and to the phenotype of interest. Short of sequencing the whole DNA, techniques have also become available to identify DNA variation and provide information on the physical position of the variant in the DNA sequence [single-standed conformation polymorphism (SSCP), RNAse cleavage mismatch methods, heteroduplex analysis, etc].

Finally, it is important to recognize that major progress in understanding the genetics of obesity and other complex human disease phenotypes is likely to come about with the development of transgenic animals. Although research with transgenic animal models is not, strictly speaking, an investigative tool specific to human genetic issues, the power of the technology is such that it

will have a major influence on human genetics in the future. The development of transgenic animals has received a great deal of attention in the recent past, and a number of approaches can now be used in a variety of circumstances (41).

EXCESS BODY FAT

Although the familial nature of obesity is well established (11, 32, 44, 57), there is still some disagreement among researchers regarding the importance of genetic factors in this familiality. Most studies on the genetics of obesity used the body mass index (BMI) or the sum of skinfold thicknesses at only two or three sites as measures of excess body fat. Heritability estimates ranging from almost zero to values as high as 90% have been reported for BMI (1a, 11, 69). Given the use of different designs (twin, family, and adoption studies); a large variation in age of subjects; studies of only a few types of relatives; and, very often, a small sample size, such a wide variation in the reported heritabilities of type I obesity is not unexpected. With few exceptions, these studies could not separate the effects of genes from those of the environment shared by relatives living together in the same household. The comparison of monozygotic (MZ) twins reared apart with MZ twins reared together represents an interesting design to assess the role of heredity without the confounding influence of shared family environment. The results of three recent studies (39, 55, 70) using this design are summarized in Table 1. Except for the 24 female twin pairs from the study by MacDonald & Stunkard (39), the correlations of MZ twins reared apart are very similar to those of MZ twins reared together and suggest that shared familial environment did not

Table 1 Intraclass correlations between monozygotic twins reared apart or together for the body mass index

	Monozygotic twins			
	Reared apart		Reared together	
Reference	*N* pairs	*r*	*N* pairs	*r*
Stunkard et al (70)				
Males	49	0.70	66	0.74
Females	44	0.66	88	0.66
MacDonald & Stunkard (39)				
Males	14	0.64	14	0.68
Females	24	0.39	25	0.76
Price & Gottesman (55)[a]	34	0.61	38	0.75

[a]Data adjusted for the effects of age and gender.

contribute to the variation in BMI. The correlations of MZ twins reared apart provide a direct estimate of the genetic effect if we assume that these twins were not placed in similar environments and that intrauterine factors did not influence variation in BMI. According to these studies, the heritability of body mass index would be in the range of 40 to 70%.

Five recent adoption studies (54, 66–68, 71) in which BMI data were available from both the biologic as well as the adoptive relatives of the adoptees reported that the effect of shared family environment on BMI was negligible. In a recent review of behavior genetic studies relevant to obesity, Grilo & Pogue-Geile (33) also concluded that experiences shared among family members appear largely irrelevant in determining individual differences in weight and obesity. These findings are somewhat at odds with the strong familiality of the major affectors of excess body fat, i.e. energy intake (47) and energy expenditure (12), and should be interpreted with caution.

The role of genes in type I obesity has also been studied with the strategy of path analysis. Path analysis is a method used in genetic epidemiology to assess the relative contribution of genetic and environmental factors based on correlations computed among various pairs of relatives by descent or adoption. We used this strategy in two different population-based samples (the Quebec Family Study and the 1981 Canada Fitness Survey) to determine the contribution of heredity in BMI, subcutaneous fat (sum of 6 skinfold thicknesses), and percent body fat derived from underwater weighing (13, 49). The total transmission effect across generations reached 35% for BMI and amount of subcutaneous fat and 55% for percent body fat and total fat mass, but most of this transmission effect was cultural, as the genetic effect (heritability) reached only 5% for BMI and amount of subcutaneous fat and 25% for percent body fat and total fat mass.

More recently, BMI measurements obtained in a Norwegian sample of about 75,000 individuals were used to compute familial correlations in a large

Table 2 Familial correlations for body mass index in various types of relatives[a]

Relative	*N* pairs	*r*
Spouses	23,936	0.123
Father-offspring	19,632	0.193
Mother-offspring	23,954	0.202
Brothers	6,017	0.262
Sisters	3,858	0.258
Brother-sister	9,278	0.206
MZ twins	79	0.576

[a]Adapted from Tambs et al (72). Age- and gender-adjusted data.

number of first- and second-degree relatives (72). Correlations obtained in first-degree relatives are summarized in Table 2. As indicated in this table, correlations were about 0.12 for spouses, 0.20 for parent-offspring, opposite-sexed siblings, and dizygotic (DZ) twins, 0.26 for same-sexed siblings, and 0.58 for MZ twins. Correlations among second-degree relatives (not shown in table) were close to zero. By fitting a path model to these data, the authors found a heritability level of 40% for BMI plus a moderate, but significant effect of cultural transmission. These results, derived from path analysis and based on the largest number of relatives ever used in genetic studies of BMI, suggest that heritability accounts for a maximum of 40% of the variance in BMI.

REGIONAL FAT DISTRIBUTION

The increased interest in the genetics of human obesities observed in the last few years is in part attributable to the fact that regional fat distribution has been shown to be an important determinant of the relationship between obesity and health and an independent risk factor for various morbid conditions such as cardiovascular diseases or noninsulin-dependent diabetes.

Evidence for familial resemblance in body fat distribution has been reported (23). Using skinfold measurements obtained in 173 monozygotic and 178 dizygotic pairs of male twins, Selby et al (63) recently reported heritability estimates of 0.77 (p 0.0001) for subscapular skinfold, 0.29 (p 0.05) for the difference between subscapular and triceps skinfolds, and 0.17 (p 0.05) for the subscapular to triceps skinfolds ratio. After adjustment for body mass index, heritability levels were reduced and remained significant only for subscapular skinfold ($h^2 = 0.44$, $p = 0.002$). Thus, the authors 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 (49) that the transmissible effect across generation reached about 40% for trunk skinfolds (sum of subscapular and suprailiac skinfolds), extremity skinfolds (sum of biceps, triceps, and medial calf skinfolds), the trunk to extremity skinfolds ratio (TE ratio), and 28% for the waist to hip ratio (WHR). If we assume that all transmissible effects are genetic, these results suggest that heredity accounts for a maximum of 40% of the phenotypic variance for various indicators of type II obesity. The biological and cultural components of transmission in regional fat distribution were assessed with data from the Quebec Family Study (13). Two indicators of regional fat distribution were considered: the TE ratio and the subcutaneous fat to fat mass ratio obtained by dividing the sum of the 6 skinfolds by fat mass derived from body density measurements. A genetic effect of 25% was found for the TE

ratio with a slightly higher genetic effect of 30% for subcutaneous fat to fat mass ratio. These results suggest that the pattern of subcutaneous fat distribution is partly determined by the genotype. When the influence of total body fat was taken into account, the profile of subcutaneous fat deposition was characterized by higher heritability estimates reaching about 40 to 50% of the residual variance (6, 7). These results imply that for a given level of fatness some individuals store more fat on the trunk or abdominal area (type II) while others store primarily on the lower body (type IV). No heritability estimates have been reported so far for abdominal visceral fat or type III obesity.

ENERGY AND NUTRIENT INTAKE

Energy and nutrient intakes have long been shown to aggregate in families, with significant resemblance observed between spouses as well as between parents and their children (47). Several twin studies have been undertaken to assess the role of heredity in energy intake, and most studies have reported greater similarities in dietary intakes between MZ twins than between DZ twins, which suggests that genetic factors might contribute to interindividual differences. However, these findings must be interpreted with caution, as some authors (25, 35) observed that MZ twins tended to get together and eat together more regularly than DZ twins, which immediately suggests that the greater similarity in energy intake among MZ twin pairs could be partly explained by a greater degree of shared environment.

We studied the role of heredity in energy intake using familial correlations computed in several types of relatives by descent or adoption from the Quebec Family Study and the BETA model of path analysis (51). Energy intake measurements were derived from a 3-day dietary record filled out by each family member and checked by trained nutritionists during individual interviews to ensure completeness. Food intake was recorded during two weekdays and one weekend day. The transmission effect across generations was found to be almost entirely cultural, as no significant genetic effect was observed for total energy intake. If one considers the large intra-individual day-to-day variation in energy intake in subjects followed over a one-year period (73), the absence of genetic effect for energy intake is not surprising. However, when intakes of carbohydrate, fat, and protein were expressed in percent of total energy intake, the contribution of genetic factors increased, ranging from 11% for percent of energy derived from protein to 20% for percent of energy derived from carbohydrate (51). If we assume that the fraction of energy derived from macronutrients is an indicator of food selection, these results suggest that food selection may be partially under genetic control. If excess body fat is often associated with a lipid-rich diet, food selection may be one

of the factors determining the susceptibility of some individuals to be in positive energy balance over a long period of time. Several peptides reportedly stimulate or inhibit food intake and intake of specific macronutrients in animal models (20). Although their role in the regulation of human energy intake is unclear, these peptides represent promising candidate genes for studying the genetic basis of individual differences in energy and macronutrient intakes.

METABOLIC RATE AND ENERGY EXPENDITURE

Reduced energy expenditure for a given energy intake level causes positive energy balance and may eventually lead to excess body weight and obesity. The causes of interindividual differences in energy expenditure are important to consider in the study of the genetic basis of obesity. Several studies have reported that most obese subjects do not seem to have higher energy intake than their lean counterparts. Energy expenditure is a complex phenotype that includes various components: basal and resting metabolic rates, thermic effect of food, energy expenditure of activities, and energy cost for given activities. Little is known about the contribution of genetic factors to these various components of energy expenditure, although both total daily (24-hour) energy expenditure (61) and resting metabolic rate (2) were found to aggregate in families.

Resting Metabolic Rate

Resting metabolic rate (RMR) is the largest component of energy expenditure and accounts for about 70% of daily energy expenditure. We have published two studies regarding the heritability of RMR using parent-child and MZ and DZ twin data (19, 28). Results of these studies reveal that correlations are always higher in MZ twins than in DZ twins, whether RMR is expressed per kilogram of body weight or fat free mass. Heritability estimates derived from these results by doubling the difference between MZ and DZ twin correlations suggest that 40 to 80% of the variance in RMR, after adjustment for age, gender, body mass, and body composition, could be inherited. Heritability of 42% has recently been reported for casual metabolic rate measured at rest in 40 pairs of MZ and 40 pairs of DZ male twins (16 to 24 years), but this significant genetic effect was found to be entirely accounted for by body weight (36). However, when metabolic rate was measured under psychological stress, the authors found evidence for a significant genetic effect, independent of the genetic effect on body weight, accounting for 22% of the variance in the augmented energy expenditure measured during the stress. Metabolic rate was measured during a very short period of time (4 min) and in the late afternoon or evening. Even though the data cannot be considered as valid estimates of

RMR, the findings of Hewitt et al (36) support the notion of a genotype-dependent response of metabolic rate to environmental stimulus.

Thermic Effect of Food

The thermic effect of food (TEF) is the integrated increase of energy expenditure after food ingestion. To our knowledge, only one study (19) has considered the heritability of TEF. In that study, energy expenditure was measured during 4 consecutive hours after ingestion of a 1000 kcal carbohydrate meal in 31 parent-child pairs as well as in 21 pairs of DZ twins and 37 pairs of MZ twins. Correlations of 0.30, 0.35, and 0.52 in parent-child, DZ, and MZ pairs, respectively, were found, which suggest a heritability level of 40 to 60% for TEF.

Physical Activity Level

Studies on the genetic effect of energy expenditure associated with physical activity are also limited. Using data from the 1981 Canada Fitness Survey, we studied the importance of familial resemblance in leisure-time energy expenditure (48). A total of 18,073 individuals living in thousands of households across Canada completed a questionnaire on their physical activity habits. Detailed information on frequency, duration, and intensity of activities performed on a daily, weekly, monthly, and yearly basis was obtained and used to determine average daily energy expenditure (kJ/day/per kg body weight). Familial correlations of 0.28, 0.12, and 0.21 were obtained in spouses (N = 1024 pairs), parent-offspring (N = 1622 pairs), and siblings (N = 1036), respectively, suggesting a weak genetic contribution to interindividual differences in leisure-time energy expenditure (48).

More recently, the familial resemblance in the level of habitual physical activity was investigated with the Caltrac accelerometer in 100 children, 4 to 7 years of age, 99 mothers, and 92 fathers from the Framingham Children's Study (43). Data were obtained with the accelerometer for about 10 hours per day for an average of 9 days in children and 8 days in fathers and mothers. Active (accelerometer counts per hour above the median) fathers or active mothers were more likely to have active children than inactive fathers or mothers, with odds ratios of 3.5 and 2.0, respectively. When both parents were active, the children were 5.8 times more likely to be active than children of two inactive parents.

Results from a few twin studies suggest that physical activity level as behavior (person having an active temperament) and leisure-time physical activity could be partly inherited (12). With data from the Quebec Family Study and the strategy of path analysis we assessed the role of heredity in two different indicators of physical activity derived from a 3-day activity record filled out by 1610 individuals of 375 families encompassing 9 types of relatives

by descent or adoption (50). Two indictors were used: "habitual physical activity" included all activities of each day, while "exercise participation" included only sport activities, i.e. activities of a higher intensity. Most of the variance in these two indicators of physical activity level was explained by nontransmissible environmental factors with values of 71% for habitual physical activity and 88% for exercise participation. The transmission effect across generation was significant but entirely accounted for by genetic factors for habitual physical activity, with a value of 29%, and by cultural transmission (12%) for exercise participation with no genetic effect. These results were interpreted as an indication of inherited differences in the propensity towards being spontaneously active.

NUTRIENT PARTITIONING

Nutrient partitioning can be defined as the propensity to store the ingested energy in the form of fat or lean tissue. Only one report has dealt with the heritability of nutrient partitioning characteristics in humans and it is based on data from the Quebec Family Study (15). A total transmission effect of about 50%, with a genetic transmission of approximately 20% after adjustment for the proper concomitants, was reported.

MAJOR GENE EFFECTS

The results reviewed thus far indicate a wide range of heritability levels for the various body composition phenotypes and their affectors. This variability in the contribution of genetic factors is expected if one considers the very different nature of all the phenotypes involved, but what appears more surprising is the large variation observed in the heritability of some obesity phenotypes. Heritabilities ranging from about 5 to 90%, for example, are reported for BMI. In interpreting these findings, one must keep in mind that several factors could influence the heritability of a given phenotype. Different designs and methods will obviously give different estimates, but, within a given method, values could differ not only from one population to another but also within a given population, depending on the age of the subjects and on other circumstances. In that context, knowing the exact heritability value of an obesity phenotype is not the most important issue, as most researchers in the field will agree that genes are undoubtedly involved to some extent in the development of obesity. Other issues like the identification of major genes and the recognition that genes may influence not only the level of the phenotype but also its response to growth and aging (temporal trends) and to changes in the environment (G $\times$ E effect) are more important in the quest for understanding the genetic basis of obesity.

The genetic effect reported above for the various obesity phenotypes was assumed to be polygenic; that is, it resulted from the additive effects of a large number of genes with each having small effects on the phenotypes. Recent research reported over the last few years provided evidence that, in addition to a polygenic component, some obesity phenotypes are influenced by major gene effects. Most of the evidence for the contribution of major genes in measures of body fat comes from commingling and segregation analyses. Commingling analysis is used to obtain preliminary evidence of major gene effects by testing the hypothesis that the distribution of a variable is best fitted by a mixture of two or three distributions rather than one. Although evidence of commingling or mixture of distributions is compatible with a major gene effect on the phenotype, it is not sufficient to conclude that a major locus genotype exists, because commingling can also result from the influence of nongenetic factors. More direct evidence for a major gene effect can be obtained with segregation analysis, a method used by geneticists to evaluate alternative models of genetic transmission by analysis of pedigree data.

A summary of the current evidence for major gene effects in body fat phenotypes is presented in Table 3. Evidence of commingling has been reported for all indicators of body fat and fat distribution. Results from segregation analyses support the hypothesis that a major gene contributes to percent body fat, subcutaneous fat to fat mass, trunk to extremity skinfolds, and subscapular to sum of subscapular and suprailiac skinfolds ratios. Results for BMI are conflicting: Three studies provided support for a major gene effect (42, 56, 58), whereas another (T. Rice et al, submitted) did not. As for percent body fat, results from a recent study provided evidence for a major locus genotype accounting for 45% of the phenotypic variance with another 22 to 26% of the variance attributable to a multifactorial component (62). Results from two studies also suggest the influence of major genes on regional fat distribution phenotypes. In one study, Hasstedt et al (34) reported a major gene effect explaining 42% of the variance in a relative fat pattern index

Table 3 Evidence from commingling and segregation analyses for major gene effects in body composition phenotypes[a]

Phenotype	Commingling	Segregation
BMI	Yes	Yes/no
Percent body fat	Yes	Yes
Subcutaneous fat/fat mass	Yes	Yes
Trunk/extremity skinfolds	Yes	Yes
Subscapular/subscapular and suprailiac skinfolds	Yes	Yes

[a]Adapted from References (5, 21, 34, 42, 56, 58, 59, 61a, 62) and from I. B. Borecki et al (submitted) and T. Rice et al (submitted).

defined as the ratio of the subscapular skinfold to the sum of the subscapular and suprailiac skinfold thicknesses. Recent results from the Quebec Family Study suggest major gene effects for the amount of subcutaneous fat (sum of 6 skinfolds) as well as for the trunk to extremity skinfolds ratio, both adjusted for total fat mass and accounting for about 35% of the phenotypic variance (I. B. Borecki et al, submitted).

TEMPORAL TRENDS

Commingling analyses undertaken on body composition measurements obtained in individuals from the Quebec Family Study (5) revealed the presence of commingling for BMI and percent body fat, but only in the parental generation and not in offspring. This finding raises the possibility that the effects of some genes could be different in children and adults. This issue of temporal trends has received little attention from geneticists, but is increasingly recognized as an important component of the genetic basis of obesity (4). Using path analysis models that incorporate parameters defined as a function of time, investigators have observed significant temporal trends in the transmissibility of BMI (60). More recently, a longitudinal study performed on a cohort of 514 adult male twin pairs, who were examined 3 times over a 43-year period of time, concluded that changes in BMI across adulthood were largely genetic (24). These results suggest that genetic factors may be involved in determining the changes of body mass, and perhaps body fat, over time and, consequently, may put some individuals at increased risk of developing obesity as they progressively age.

GENETIC-ENVIRONMENT INTERACTION

We all know that some individuals are susceptible to excessive accumulation of fat and are always trying to lose these extra pounds while others seem relatively well protected against the extra calories they ingest. We recently tried to test whether such differences could be explained by genetic factors by comparing the intrapair (within genotype) and interpair (between genotypes) resemblances in the response of MZ twins to overfeeding and negative energy balance or, in other words, by testing for the presence of genotype-environment interaction effect.

Response to Overfeeding

Two experiments were undertaken to study individual differences when exposed to a positive energy balance protocol. In both experiments, subjects had to eat a caloric surplus of 4.2 MJ (1000 kcal) per day for a period of 22 days, in a short-term overfeeding experiment (17, 52), and 100 days in a

long-term overfeeding experiment (16). Both experiments resulted in significant changes in the various obesity phenotypes, but considerable interindividual differences in the adaptation to the extra calories were observed. In the long-term overfeeding experiment (16), the mean body mass gain of the 24 subjects (12 pairs of MZ twins) was 8.1 kg, but the range of weight gain was from 4 to 13 kg. However, the variation observed was not randomly distributed: Variance in response between pairs was about three times greater than within pairs for gains in body weight and fat mass, and was about six times greater between pairs than within pairs for changes in visceral fat (assessed by computerized tomography) after adjustment for gains in fat mass (16). These results suggest that the amount of fat stored in response to a caloric surplus is significantly influenced by the genotype of the individual. This genotype-overfeeding interaction effect appears to be more important for fat topography than for the amount of fat gained as indicated by higher F ratios for the amount of abdominal visceral fat gained. These findings suggest that genes may determine not only the gain in fat mass or body energy when subjected to positive energy balance but also the pattern of fat deposition among the various fat depots of the body. This has important implications for health because truncal-abdominal fat and, particularly, visceral fat are associated with greater health risks than total amount of body fat.

Response to Negative Energy Balance

In two other experiments, exercise was used to induce an energy deficit in MZ twins in order to test for the contribution of the genotype in the response to negative energy balance sustained for 22 days (53) or 100 days (18). In both experiments, the energy deficit was obtained by exercising twins on a cycle ergometer twice a day for about 50 min per session. The exercise prescription was designed to induce an extra energy expenditure of 4.2 MJ (1000 kcal) while maintaining energy intake at the baseline level throughout the study. Results from the long-term experiment revealed a significant within-pair resemblance for the reduction in body weight and fat mass as well as for the changes in regional fat distribution phenotypes, while results from the short-term study revealed that only fat-free mass changes were characterized by a significant MZ twin resemblance.

Thus, results from both overfeeding and negative energy balance experiments generally suggest that undetermined genetic characteristics specific to each individual are associated with the response to changes in energy balance. The use of the measured genotype approach could be helpful in the identification of some of the genes involved in determining variation in responsiveness. Genetic variation at some apolipoprotein gene loci has been used to study the role of genetic factors in the response of blood lipids and lipoproteins to changes in the diet (1) or the response of aerobic performance

and markers of aerobic metabolism to exercise training (10), but no study has been published yet for phenotypes associated with obesity.

CONTRIBUTION OF SINGLE GENES: A BEGINNING

The definition of the genetic architecture of excess body fat in humans has just begun. It is likely that the human obesity genotypes will be complex multigenic systems with networks of gene-gene and gene-environment interactions (9). Already, some promising data, primarily derived from animal models, are highly suggestive of significant contributions from single gene mutations.

Some studies had suggested that allelic variation at the class I loci of the HLA system (chromosomal assignment: 6p21.3) was associated with the BMI as a marker of obesity (22, 26, 31). However, a study with relatively large samples of males and females and more elaborate assessments of body fat has not confirmed these results (14).

Sib-pair linkage analysis data obtained in four large families have suggested significant associations between a subcutaneous fat pattern index and the adenylate kinase 1 locus (9q34) as well as the glutamic-pyruvate transaminase locus (8q24) (64). Erythrocyte acid phosphatase (locus 1) (2p25) phenotypes exhibiting low enzyme activity levels (ACP_1A and BA) were reported to be associated with excess body mass for age, height, and gender among 75 children, 3 to 14 years of age (38). On the other hand, mitochondrial DNA sequence variation was also found to be nonrandomly related to body fat content and fat topography in 42 women (J. Truchon et al, submitted). Thus, carriers of the EcoRV morph 2 in the D-loop region were leaner than noncarriers, whereas carriers of the morph 1 generated by the KpnI in the D-loop were markedly fatter than the noncarriers.

The augmented expression of adipocyte genes was studied in overfed primates and rats in an attempt to identify candidate genes that could be used in genetic studies of body weight regulation and obesity (76). A subtractive cDNA cloning strategy allowed investigators to identify a 5-kilobase message expressed preferentially in the adipose tissue of overfed macaques and rats. The 5-kb mRNA was also found in human subcutaneous fat. The precise nature of the protein encoded by this message and potential polymorphism of the gene have not yet been established to our knowledge.

The relationship between rodent obesity genes and human obesity is being considered by several investigators. Friedman et al (30) have reported that five mouse mutations that cause obesity in the animals are encoded on five different mouse chromosomes. However, these mouse obesity genes seem to be part of coding regions that have homologous counterparts on human chromosomes. These human homologous regions are also located on five different human

chromosomes (1p31-ter; 7q31; 11p15.1; 16q22-24; 20q13). Interestingly, the mouse *db* gene may be homologous to the rat *fa* obesity gene (74), and they both appear to have a human counterpart on chromosome 1p31 (29).

Two putative new loci for excessive body fat content have been identified in backcross mice by quantitative trait loci mapping with restriction fragment length polymorphism (75). Backcross progeny from crosses between mouse strains C57BL/6J and *Mus spretus* exhibit a body fat content ranging from almost zero to 50% (27). One locus on chromosome 1 and one on chromosome 10 were identified by these procedures (75).

A transgenic mouse with impaired corticosteroid receptor function was created by partially knocking out gene expression with type II glucocorticoid receptor (5q31-32) antisense RNA (46). The transgenic animals had increased fat deposition and a body mass that by about 6 months of age was twice as high as that of controls. An elevated body fat content was observed despite the fact that transgenic animals ate about 15% less than the normal mice.

The results reported thus far suggest that several genes have the potential to cause obesity in humans. It seems likely that the obesity genotype is a complex multigenic system; perhaps the more severe cases carry mutations at several loci and the less affected individuals carry one or only a few of the mutant genes. Each of the putative single gene effects reviewed here seems to be encoded on a different human chromosome region, including 1p31, 2p25, 5q31-32, 6p21.3, 7q31, 8q24, 9q34, 11p15.1, 16q22-24, 20q13. Moreover, we know that another putative obesity gene, causing the paternally imprinted Prader-Willi syndrome, is encoded on human chromosome 15q11-13 (40).

The growing number of obesity-related or obesity-causing genes does not bode well for the single gene hypothesis. It implies, however, that genetic heterogeneity is likely to become a major challenge in future genetic studies of this complex phenotype.

Literature Cited

1. Abbey, M. 1992. The influence of apolipoprotein polymorphism on the response to dietary fat and cholesterol. *Curr. Opin. Lipidol.* 3:12–16

1a. Bodurtha, J. N., Mosteller, M., Hewitt, J. K., Nance, W. E., Eaves, L. J., et al. 1990. Genetic analysis of anthropometric measures in 11-year-old twins: the Medical College of Virginia Twin Study. *Pediatr. Res.* 28:1–4

2. Bogardus, C., Lillioja, S., Ravussin, E., Abbott, W., Zawadkzi, J. K., et al. 1986. Familial dependence of the resting metabolic rate. *N. Engl. J. Med.* 315:96–100

3. Bonney, G. E., Lathrop, G. M., Lalouel, J. M. 1988. Combined linkage and segregation analysis using regressive models. *Am. J. Hum. Genet.* 43: 29–37

4. Borecki, I. B., Province, M. A., Bouchard, C., Rao, D. C. 1993. Genetics of obesity: etiologic heterogeneity and temporal trends. In *Genetics of Obesity*, ed. C. Bouchard. Boca Raton: CRC Press. In press

5. Borecki, I. B., Rice, T., Bouchard,

C., Rao, D. C. 1991. Commingling analysis of generalized body mass and composition measures: the Québec Family Study. *Int. J. Obes.* 15:763–73

6. Bouchard, C. 1988. Inheritance of human fat distribution. In *Fat Distribution During Growth and Later Health Outcomes*, ed. C. Bouchard, F. E. Johnson, 17:103–25. New York: Liss. 363 pp
7. Bouchard, C. 1990. Variation in human body fat: the contribution of the genotype. In *Obesity: Towards a Molecular Approach, UCLA Symp. Mol. Cell. Biol. New Ser.*, ed. G. A. Bray, D. Ricquier, B. M. Spiegelman, 132:17–28. New York: Wiley-Liss. 307 pp
8. Bouchard, C. 1991. Current understanding of the etiology of obesity: genetic and nongenetic factors. *Am. J. Clin. Nutr.* 53:1561S–65S
9. Bouchard, C. 1992. Human obesities: chaos or determinism? In *Obesity in Europe 91, Proc. 3rd Eur. Congr. Obes.*, ed. G. Ailhaud, B. Guy-Grand, M. Lafontan, D. Ricquier, pp. 7–14. Paris: Libbey
10. Bouchard, C., Dionne, F. T., Simoneau, J. A., Boulay, M. R. 1992. Genetics of aerobic and anaerobic performances. *Exerc. Sport Sci. Rev.* 20: 27–58
11. Bouchard, C., Pérusse, L. 1988. Heredity and body fat. *Annu. Rev. Nutr.* 8:259–77
12. Bouchard, C., Pérusse, L., Dériaz, O., Després, J. P., Tremblay, A. 1993. Genetic influences on energy expenditure in humans. In *Child and Adolescent Obesity: What, How and Who?*, ed. L. J. Filer. Washington, DC: Int. Life Sci. Inst. In press
13. Bouchard, C., Pérusse, L., Leblanc, C., Tremblay, A., Thériault, G. 1988. Inheritance of the amount and distribution of human body fat. *Int. J. Obes.* 12:205–15
14. Bouchard, C., Pérusse, L., Rivest, J., Morissette, J., Allard, C., et al. 1985. HLA system, body fat and fat distribution in children and adults. *Int. J. Obes.* 9:411–22
15. Bouchard, C., Tremblay, A., Després, J. P., Dériaz, O., Dionne, F. T. 1992. The genetics of body energy content and energy balance: an overview. See Ref. 20, pp. 3–21
16. Bouchard, C., Tremblay, A., Després, J. P., Nadeau, A., Lupien, P. J., et al. 1990. The response to long-term overfeeding in identical twins. *N. Engl. J. Med.* 302:1477–82
17. Bouchard, C., Tremblay, A., Després, J. P., Poehlman, E. T., Thériault, G., et al. 1988. Sensitivity to overfeeding: the Quebec experiment with identical twins. *Prog. Food Nutr. Sci.* 12:45–72
18. Bouchard, C., Tremblay, A., Després, J. P., Thériault, G., Nadeau, A., et al. 1992. The response to exercise with constant energy intake in identical twins. *FASEB J.* 6:A1647 (Abstr.)
19. Bouchard, C., Tremblay, A., Nadeau, A., Després, J. P., Thériault, G. 1989. Genetic effect in resting and exercise metabolic rates. *Metabolism* 38:364–70
20. Bray, G. A. 1992. The effect of peptides on nutrient intake and the sympathetic nervous system. In *The Science of Food Regulation: Food Intake, Nutrient Partitioning and Energy Expenditure*, ed. G. A. Bray, D. H. Ryan, pp. 257–76. Baton Rouge: Louisiana State Univ. Press. 408 pp
21. Byard, P. J., Siervogel, R. M., Roche, A. F. 1989. X-linked pattern of inheritance for serial measures of weight/stature. *Am. J. Hum. Biol.* 1:443–49
22. Digy, J. P., Raffoux, C., Pointel, J. P., Perrier, P., Drouin, P., et al. 1985. HLA and familial obesity: evidence for a genetic origin. In *Recent Advances on Obesity Research*, ed. J. Hirsch, T. Van Italie, pp. 171–75. London: Libbey. 402 pp.
23. Donahue, R. P., Prineas, R. J., Gomez, O., Hong, C. P. 1992. Familial resemblance of body fat distribution: the Minneapolis Children's blood pressure study. *Int. J. Obes.* 16:161–67
24. Fabsitz, R. R., Carmelli, D., Hewitt, J. K. 1992. Evidence for independent genetic influences on obesity in middle age. *Int. J. Obes.* 16:657–66
25. Fabsitz, R. R., Garrison, R. J., Feinleib, M., Hjortland, M. 1978. A twin analysis of dietary intake: evidence for a need to control for possible environmental influences in MZ and DZ twins. *Behav. Genet.* 8:15–25
26. Fabsitz, R. R., Nam, J. M., Gart, J., Stunkard, A., Price, A. R., et al. 1989. HLA associations with obesity. *Hum. Hered.* 39:156–64
27. Fisler, J. S., Pace, M. J., Warden, C. H., Lusis, A. J. 1991. Spretus/B6: A new mouse model of polygenic obesity. *Int. J. Obes.* 15(Suppl. 3):54 (Abstr.)
28. Fontaine, E., Savard, R., Tremblay, A., Després, J. P., Poehlman, E. T., et al. 1985. Resting metabolic rate in monozygotic and dizygotic twins. *Acta Genet. Med. Gemellol.* 34:41–47
29. Friedman, J. M., Leibel, R. L. 1992. Tackling a weighty problem. *Cell* 69: 217–20
30. Friedman, J. M., Leibel, R. L., Bahary,

N. 1991. Molecular mapping of obesity genes. *Mammalian Genome* 1:130–44
31. Fumeron, F., Apfelbaum, M. 1981. Association between HLA-B18 and the familial obesity syndrome. *N. Engl. J. Med.* 305:645
32. Garn, S. M., Sullivan, T. V., Hawthorne, V. M. 1989. Fatness and obesity of the parents of obese individuals. *Am. J. Clin. Nutr.* 50:1308–13
33. Grilo, C. M., Pogue-Geile, M. F. 1991. The nature of environmental influences on weight and obesity: a behavior genetic analysis. *Psychol. Bull.* 110:520–37
34. Hasstedt, S. J., Ramirez, M. E., Kuida, H., Williams, R. R. 1989. Recessive inheritance of a relative fat pattern. *Am. J. Hum. Genet.* 45:917–25
35. Heller, R. F., O'Connell, D. L., Roberts, D. C. K., Allen, J. C., Knapp, P. L., et al. 1988. Lifestyle factors in monozygotic and dizygotic twins. *Genet. Epidemiol.* 5:311–21
36. Hewitt, J. K., Stunkard, A. J., Carroll, D., Sims, J., Turner, J. R. 1991. A twin study approach towards understanding genetic contributions to body size and metabolic rate. *Acta Genet. Med. Gemellol.* 40:133–46
37. Lander, E. S., Botstein, D. 1989. Mapping mendelian factors underlying quantitative traits using RFLP linkage maps. *Genetics* 121:185–99
38. Lucarini, N., Finocchi, G., Gloria-Bottini, F., Macioce, M., Borgiani, P. 1990. A possible genetic component of obesity in childhood. Observations on acid phosphatase polymorphism. *Experientia* 46:90–91
39. MacDonald, A., Stunkard, A. J. 1990. Body mass indexes of British separated twins. *N. Engl. J. Med.* 322:1530
40. McKusick, V. A. 1992. *Mendelian Inheritance in Man. Catalogs of Autosomal Dominant, Autosomal Recessive, and X-linked phenotypes.* Baltimore: Johns Hopkins Univ. Press. 2320 pp. 10th ed
41. Merlino, G. T. 1991. Transgenic animals in biomedical research. *FASEB J.* 5:2996–3001
42. Moll, P. P., Burns, T. L., Lauer, R. M. 1991. The genetic and environmental sources of body mass index variability: The Muscatine Ponderosity Family Study. *Am. J. Hum. Genet.* 49:1243–55
43. Moore, L. L., Lombardi, D. A., White, M. J., Campbell, J. L., Oliveria, S. A., et al. 1991. Influence of parents' physical activity levels on activity levels of young children. *J. Pediatr.* 118: 215–19
44. Mueller, D. F. 1983. The genetics of human fatness. *Yearb. Phys. Anthropol.* 26:215–30
45. Paterson, A. H., Lander, E. S., Hewitt, J. D., Peterson, S., Lincoln, S. E. 1988. Resolution of quantitative traits into mendelian factors by using a complete linkage map of restriction fragment length polymorphisms. *Nature* 335:721–26
46. Pépin, M. C., Pothier, F., Barden, N. 1992. Impaired type II glucocorticoid-receptor function in mice bearing antisense RNA transgene. *Nature* 235: 725–28
47. Pérusse, L., Bouchard, C. 1993. Genetics of energy intake and food preferences. In *Genetics of Obesity*, ed. C. Bouchard. Boca Raton: CRC Press. In press
48. Pérusse, L., Leblanc, C., Bouchard, C. 1988. Familial resemblance in lifestyle components: results from the Canada Fitness Survey. *Can. J. Public Health* 79:201–5
49. Pérusse, L., Leblanc, C., Bouchard, C. 1988. Inter-generation transmission of physical fitness in the Canadian population. *Can. J. Sport Sci.* 13:8–14
50. Pérusse, L., Tremblay, A., Leblanc, C., Bouchard, C. 1989. Genetic and environmental influences on level of habitual physical activity and exercise participation. *Am. J. Epidemiol.* 129: 1012–22
51. Pérusse, L., Tremblay, A., Leblanc, C., Cloninger, C. R., Reich, T., et al. 1988. Familial resemblance in energy intake: contribution of genetic and environmental factors. *Am. J. Clin. Nutr.* 47:629–35
52. Poehlman, E. T., Tremblay, A., Després, J. P., Fontaine, E., Pérusse, L., et al. 1986. Genotype-controlled changes in body composition and fat morphology following overfeeding in twins. *Am. J. Clin. Nutr.* 43:723–31
53. Poehlman, E. T., Tremblay, A., Marcotte, M., Pérusse, L., Thériault, G., et al. 1987. Heredity and changes in body composition and adipose tissue metabolism after short-term exercise-training. *Eur. J. Appl. Physiol.* 56:398–402
54. Price, R. A., Cadoret, R. J., Stunkard, A. J., Troughton, E. 1987. Genetic contributions to human fatness: an adoption study. *Am. J. Psychiatry* 144:1003–8
55. Price, R. A., Gottesman, I. I. 1991. Body fat in identical twins reared apart: roles for genes and environment. *Behav. Genet.* 21:1–7
56. Price, R. A., Ness, R., Laskarzewski,

P. 1990. Common major gene inheritance of extreme overweight. *Hum. Biol.* 62:747–65

57. Price, R. A., Stunkard, A. J., Ness, R., Wadden, T., Heshka, S., et al. 1990. Childhood onset (age 10) obesity has high familial risk. *Int. J. Obes.* 14:185–95
58. Province, M. A., Arnqvist, P., Keller, J., Higgins, M., Rao, D. C. 1990. Strong evidence for a major gene for obesity in the large, unselected, total community health study of Tecumseh. *Am. J. Hum. Genet.* 47(Suppl.):A143 (Abstr.)
59. Province, M. A., Keller, M., Higgins, M., Rao, D. C. 1991. A commingling analysis of obesity in the Tecumseh Community Health Study. *Am. J. Hum. Biol.* 3:435–45
60. Province, M. A., Rao, D. C. 1985. Path analysis of family resemblance with temporal trends: application to height, weight and Quetelet index in Northeastern Brazil. *Am. J. Hum. Genet.* 37:178–92
61. Ravussin, E., Lillioja, S., Knowler, W. C., Christin, L., Freymond, D., et al. 1988. Reduced rate of energy expenditure as a risk factor for body weight gain. *N. Engl. J. Med.* 318:467–72

61a. Rice, T., Borecki, I. B., Bouchard, C., Rao, D. C. 1992. Commingling analysis of regional fat distribution measures: the Quebec Family Study. *Int. J. Obes.* 16:831–44

62. Rice, T., Borecki, I. B., Bouchard, C., Rao, D. C. 1993. Segregation analysis of fat mass and other body composition measures derived from underwater weighing *Am. J. Hum. Genet.* In press
63. Selby, J. V., Newman, B., Quesenberry, C. P. Jr., Fabsitz, R. R., King, M. C., et al. 1989. Evidence of genetic influence on central body fat in middle-aged twins. *Hum. Biol.* 61:179–93
64. Siervogel, R. M., Wilson, A. F., Baumgartner, R. N., Elston, R. C. 1991. Evidence of possible genetic linkage for a postulated fat patterning gene and marker genes using the robust sib-pair method. *Am. J. Hum. Biol.* 3:67
65. Sing, C. F., Boerwinkle, E. A., Moll, P. P., Templeton, A. R. 1988. Characterization of genes affecting quantitative traits in humans. In *Proceedings of the 2nd International Conference on Quantitative Genetics*, ed. B. S. Weir, E. J. Eisen, M. M. Goodman, G. Namkoong, pp. 250–69. Sunderland:Sinauer. 704 pp.
66. Sorensen, T. I. A., Holst, C., Stunkard, A. J. 1992. Childhood body mass index—genetic and familial environmental influences assessed in a longitudinal adoption study. *Int. J. Obes.* 16:705–14
67. Sorensen, T. I. A., Holst, C., Stunkard, A. J., Theil, L. 1992. Correlations of body mass index of adult adoptees and their biological relatives. *Int. J. Obes.* 16:227–36
68. Sorensen, T. I. A., Price, R. A., Stunkard, A. J., Schulsinger, F. 1989. Genetics of obesity in adult adoptees and their biological siblings. *Br. Med. J.* 298:87–90
69. Stunkard, A. J., Foch, T. T., Hrubec, Z. 1986. A twin study of human obesity. *J. Am. Med. Assoc.* 256:51–54
70. Stunkard, A. J., Harris, J. R., Pedersen, N. L., McClearn, G. E. 1990. The body mass index of twins who have been reared apart. *N. Engl. J. Med.* 322:1483–87
71. Stunkard, A. J., Sorensen, T. I. A., Hannis, C., Teasdale, T. W., Chakraborty, R., et al. 1986. An adoption study of human obesity. *N. Engl. J. Med.* 314:193–98
72. Tambs, K., Moum, T., Eaves, L., Neale, M., Midthjell, K., et al. 1991. Genetic and environmental contributions to the variance of the body mass index in a Norwegian sample of first- and second-degree relatives. *Am. J. Hum. Biol.* 3:257–67
73. Tarasuk, V., Beaton, G. H. 1991. The nature and individuality of within-subject variation in energy intake. *Am. J. Clin. Nutr.* 54:464–70
74. Truett, G. E., Bahary, N., Friedman, J. M., Leibel, R. L. 1991. Rat obesity gene fatty (fa) maps to chromosome 5: Evidence for homology with the mouse gene diabetes (db). *Proc. Natl. Acad. Sci. USA* 88:7806–9
75. Warden, C. H., Fisler, J. S., Pace, M. J., Diep, A., He, K. Y., et al. 1991. Identification of two loci underlying polygenic obesity in mice. *Int. J. Obes.* 15(Suppl. 3):54 (Abstr.)
76. Wilson, B. E., Meyer, G. E., Cleveland, J. C., Weigle, D. S. 1990. Identification of candidate genes for a factor regulating body weight in primates. *Am. J. Physiol.* 259:R1148–55