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Obesity related phenotypes in families selected for extreme obesity and leanness

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BACKGROUND: Obesity is a multigenic trait, and special methods and sampling designs are needed for gene identification.
OBJECTIVE: To describe characteristics of families selected to increase information for genetic linkage studies of obesity.
DESIGN: Families having extremely obese siblings with a lean parent and sibling.
SUBJECTS: 594 members of 94 Caucasian families.
MEASUREMENTS: Measured height and weight, bioelectric impedance, skinfolds, circumferences and questionnaires.
RESULTS: Families have an extreme range of obesity phenotypes, which are bimodally distributed. The obese individuals are predominantly women with an onset of obesity early in life. Obesity onset age was negatively correlated with level of obesity, and onset ages were correlated among family members. Individual obesity measures were highly correlated. The extreme range of phenotypes within families increases family variability and presumably gene segregation.
CONCLUSION: Sampling families through extremely obese sibling pairs with a lean parent and sibling results in families with an extreme range of obesity and leanness. The large within-family variance and early age of onset should make these families highly informative for gene mapping and gene identification studies.

Keywords: obesity; leanness; body mass index; percent fat; skinfolds; linkage; association; genetic; gene mapping; age at onset; childhood obesity

Introduction

Obesity is a complex trait influenced by multiple genes and non-family environment. A number of family, twin and adoption studies have established that obesity is heritable in humans,[1–4] and adoption studies consistently show that family environment has minimal influence on adult obesity.[1,4–6] Studies in humans and animals have demonstrated that this heritable pattern is due to multiple genes.[7]

Identifying genes for complex traits requires special analytic methods and sampling procedures.[8] In general, these methods focus on estimating linkage between a phenotype and genetic loci by evaluating identity (by state or by descent) of marker alleles shared by pairs of relatives. Preferential transmission of particular marker alleles from heterozygous parents to affected offspring indicates a genetic association. At present, linkage studies are used to localize susceptibility genes, and association studies are used for fine mapping and for tests of candidate genes. Future studies may use association methods for large scale genome scans as well.[9]

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The ability to identify genes for complex traits depends on the genetic heritability of the trait, the population and familial risk, and the proportion of variance accounted for by each specific gene. Risch[10] has shown that the ratio of familial to population risk is an indicator of whether a gene is likely to be identifiable. Generally, a risk ratio of at least two is thought to be needed for detection, but higher values are probably needed to assure gene identification. For example, Risch and Merikangas[9] recently argued that it may be difficult to identify genes with risk ratios below four. Allison *et al*[11] demonstrated that risk ratios for normal levels of body fat are very low and suggested that it will be necessary to sample more extreme phenotypes. Recently, our group demonstrated that families selected through individuals with a body mass index (BMI, kg/m^2) ≥ 40 give risk ratios of at least five.[12] Therefore, sampling families with extreme obesity should provide substantial power for identifying genes for human obesity.

Below we report on the nature of obesity and leanness in a new cohort of families selected through extremely obese individuals (BMI ≥ 40). In addition, we discuss issues related to the restrictive eligibility criteria we have imposed on our study design. This sampling design meets many of the requirements for mapping and identifying genes for a complex trait such as obesity.

Materials and methods

Rationale

We established several criteria for family ascertainment to optimize the probability of gene segregation within families. We selected families having two obese siblings, one lean sibling and one lean parent. Selecting families through an extremely obese person increases the probability that obesity predisposing genes are present in a family.[13] Requiring an additional extremely obese sibling increases the likelihood of the obesity being familial. Gene segregation (obesity predisposing genes and obesity protective genes within the same family) is increased by requiring that at least one parent and one sibling were never obese. Analyses focusing only on the obese siblings within such families will avoid problems associated with reduced gene penetrance and should minimize the influences of genetic background and environmental conditions. Moreover, concordant sibling pairs with an extreme phenotype and discordant sibling pairs have been shown to have high statistical power for mapping genes with small effects.[14] Therefore, this family sampling design should be useful for identifying genes with a range of effect sizes.

Sampling design

We selected families having at least one individual with current BMI/(weight (kg)/height (m^2)) ≥ 40, one or more siblings with current BMI ≥ 30, one or more siblings with maximum BMI < 27, and one parent with maximum lifetime BMI < 27. We required that a minimum of two obese siblings and one parent give blood for DNA extraction and genotyping. We expect to collect a total of 300 families using these criteria, including Caucasian and African-American families. This report focuses on the characteristics of the first 94 Caucasian families.

Source of ascertainment

We advertised nationally and locally for nuclear families having at least two members who were at least 50 pounds overweight. Based on self and informant reports of height and current and maximum weight, we computed BMI for all family members. We then selected families having two obese siblings, one lean sibling and one lean parent. These stringent criteria excluded most families which initially contacted us. The first 94 Caucasian families were ascertained from screening approximately 2169 family histories, resulting in an ascertainment proportion of 4.3%. Of those families ascertained, only 3% came from obesity treatment clinics, 14% came from national organizations, 36% came from newspaper advertisements, and 48% came from advertisements in national magazines. Most people who originally contacted us were female (94%).

Geographic distribution

This is a national sample, representing a total of 40 states and with many families having first-degree relatives who resided in two or more states. However, 11 states contributed three quarters of the sample (75%). The largest number of individuals came from Pennsylvania (20%) and from three surrounding states (New York, New Jersey, Maryland, 16%). Several other states contributed 15 or more individuals, California (11%) Minnesota (7%), Washington (6%), Texas (4%), Kentucky (4%), Michigan (3%), and Florida (3%).

Occupation and education

The sample appears to represent Caucasian families in the United States. However, this group had somewhat lower education and occupational levels than the national average, perhaps reflecting the well established negative correlation between obesity and socioeconomic status[15–17]: 2% of subjects were unemployed or received welfare, 74% were engaged in skilled or unskilled labor, 18% of subjects were in white collar and business positions and 6% of subjects were in professional careers. Education level roughly matched professional status: 10% of subjects did not finish high school, 29% of subjects were high school graduates, 32% of subjects completed some college or technical school, 20% of subjects completed college and 9% of subjects had post-baccalaureate degrees.

Obesity assessment

Obesity measures were selected which assessed total body fat and body fat distribution. We used two measures to assess overall obesity, BMI, and total fat mass (kg) and percent body fat as estimated from bioelectrical impedance (BIA). Subjects were measured for height and weight without shoes, wearing hospital gowns. BIA, which is used to estimate amount and percentage of body fat, was measured with the subject lying down using a Valhalla Bio-Resistance Body Composition Analyzer (Vallhalla Scientific, San Diego, CA, USA). We also assessed regional fat by measurement of skinfolds and circumferences. Three replicate skinfold measurements were taken at the mid-biceps, triceps, subscapular and suprailiac (level with the umbilicus) locations for all subjects using Lange calipers. Circumferences were measured at the upper arm, waist, abdomen, buttocks, calf, chest (males) and neck and shoulders (females) (all at widest part), and hips (just below iliac crest) and thigh (just below gluteal fold). Bone breadth was measured at the elbow, ankle and wrist to give an estimate of frame size.

We obtained weight and height values in three different ways. Subjects who were directly assessed were measured by the research interviewers as described above (direct assessment). Other subjects provided their weight and height, and a subset of these subjects also measured their own waist and hip

circumferences, using the same type of tape measure used by the interviewers, and with detailed instructions (self-measure). Self-measured heights and weights and self-measured body circumferences have been shown to be accurate.[18–23] Finally, when family members had died or the family member refused to participate, their age, height and weight were estimated by the median values reported for the missing family member by their first degree relatives. The estimation of the heights and weights of subjects by their first degree family members appears to be valid, although subject to the same bias of self-reported height and weight.[24–26]

Standardization of data collection

All research interviewers were trained to assess body composition and other phenotypic measures by attending at least two training sessions at the Obesity Research Center at St Luke's Hospital/Columbia University. New interviewers received further training at the University of Pennsylvania by performing dual measurements (experienced interviewer and new interviewer) for at least two families. The BIA measurement devices at the Obesity Research Center at St Luke's Hospital/Columbia University and at the Behavioral Genetics Laboratory at the University of Pennsylvania were calibrated by the makers (Vallhalla Scientific) to the same standard. Finally, we have validated BIA (total percent body fat) as a measure of body composition in a subset of our sample using hydrodensitometry ($r = 0.88$, $P < 0.001$, $n = 55$; standard error of estimate = 4.7, mean for percent body fat measured by BIA = 40.5%, by hydrodensitometry = 40.2%). Therefore, we used BIA derived estimates of body composition in all subsequent analyses.

Questionnaire information

Family members completed detailed questionnaires about their dietary and weight history (including type of diet, binging, purging, recent weight loss, age at onset of obesity) and exercise habits. In addition, they provided information on their physical and mental health, and hospitalizations (questionnaire available upon request).

Data analysis

Descriptive statistics and between trait interclass-correlations were calculated in SPSS 6.1. Family correlations were computed using the FCOR routines in SAGE.[27] Correlation coefficients were tested to determine whether they were statistically different than zero. Waist-to-hip ratio (WHR) was calculated by dividing the circumference of the waist (cm) by the circumference of the hips (cm). A combined measure of skinfold thickness was created by averaging the three replicate measurements for each skinfold site and summing the four average values for each skinfold site. This value was truncated at the upper tail, as some of the obese subjects had skinfolds in excess of the capacity of the calipers. When this occurred, the value of the maximum extension of the calipers was used. The ratio of subcutaneous fat in the trunk to that in the extremities is obtained by dividing the sum of average skinfold value for the biceps and triceps by the sum of the average skinfold value for the subscapular and suprailiac areas (extremities/trunk).

Results

Age and vital status

Parents were generally in their mid-sixties (mothers = 65 ± 9 y, range = 46–82 y, $n = 84$; fathers = 66 ± 10 y, range = 50–84 y, $n = 56$) and siblings were in their late thirties (sisters = 39 ± 8 y, range = 17–59 y, $n = 240$; brothers = 38 ± 8 y, range = 22–55 y, $n = 107$). From the 94 families, 37 fathers, 10 mothers and 40 brothers and 19 sisters died prior to their family's induction into the study. However, all families had at least one living parent at the time of assessment. Parental age was computed using living parents and does not include the age at death for deceased parents. The total number of siblings was 406, yielding an average sibship size of 4.3, with a range of 2–13. Siblings who were determined to be half-siblings based on genotyping were not included in the total.

Direct assessment, self-report, self-measure and informant report

Of 594 subjects, 383 (64%) were directly measured by our research interviewers (70 mothers, 32 fathers, 196 sisters, 85 brothers); 84 (14.1%) were self-measured (12 mothers, 12 fathers, 44 sisters and 16 brothers; and 127 (21.7%) were based on informant reports (12 mothers, 50 fathers, 19 sisters and 46 brothers). DNA samples were obtained on 467 family members (79%).

Obesity and leanness

Because of the multiple selection criteria, there was no single proband in these families. A few families recruited early in the study did not meet current study criteria. In 86 of 94 families at least one sibling had a BMI ≥ 40 (91%). Whereas all but the first few families met full eligibility criteria based on a telephone screen of family members, only approximately half (44 families, 47%) met all criteria following direct assessment. The most common reason for not meeting full criteria was the initial under-reporting of weight by the non-obese relatives. Even with this systematic under-reporting, the range of obesity phenotypes in these families is very large, 59 BMI units (kg/m^2) between the leanest and heaviest person in the study, and 27 BMI units, on average, within families.

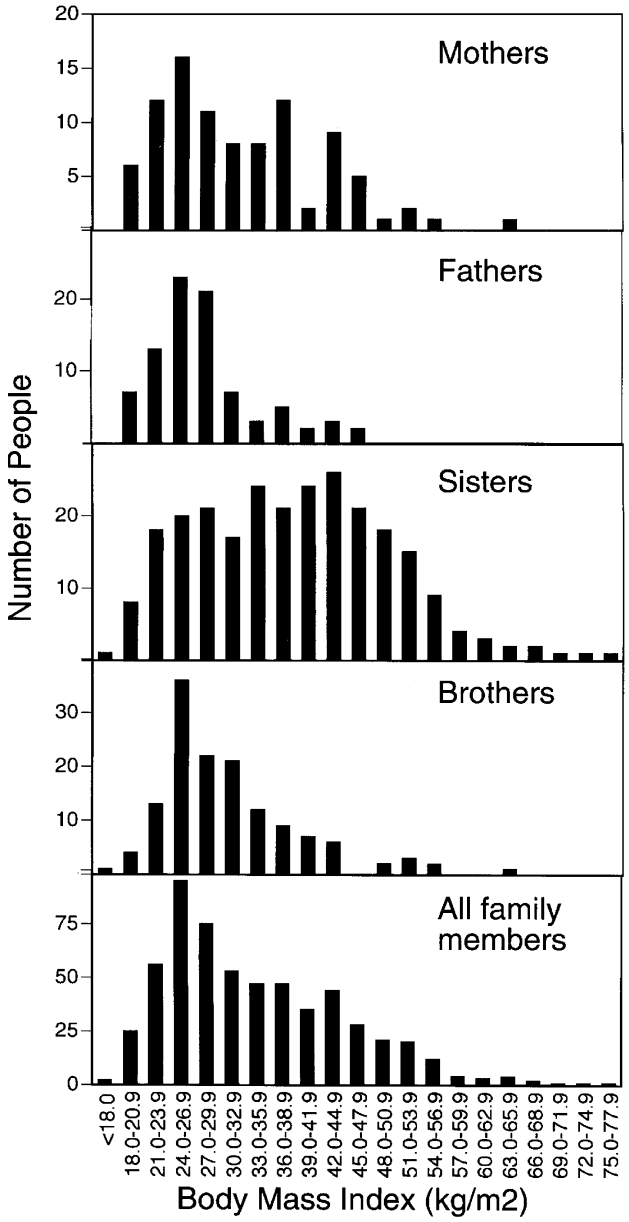

Figure 1 Distribution of body mass index (BMI, kg/m^2) for family members.

The distributions of BMI, arranged by gender and generation in Figure 1, clearly show several trends. The most severely obese individuals are usually women in the sibling generation. The sampling requirements, that families must have both obese and lean family members, produced a bimodal distribution of BMI, with high overall mean values and a marked skewing toward extreme obesity. The means and ranges of the measures related to body size, fatness and fat patterning, arranged by gender and generation, are presented in Table 1. The means, variances and ranges of the measures are consistent with the distributions of BMI. The families include many extremely obese individuals of both genders and generations, and there is a wide range of obesity from very lean to very obese.

Correlations among phenotypes are presented in Table 2. There were moderate to high correlations among all individual measures and indices of body fat. BMI, percent fat, sum of skinfolds and body circumference measures were all highly correlated for women and somewhat less so for men. In general, height was uncorrelated with obesity measures in both women and men. Waist to hip ratios (Whr) and the proportion of fat on the extremities *vs* the trunk (Ext/Trnk) were not correlated with overall obesity, particularly for women.

The correlations among family members for measures of obesity, stature, and fat patterning are given in Table 3. Because of the complex ascertainment scheme requiring that some relatives within each family must be lean and other relatives must be obese (based on BMI), family correlations for BMI are not reported. For several other obesity measures, within family variance was high relative to differences among families. Therefore, there were no significant correlations between parents and offspring or among siblings for obesity measures closely related to the ascertainment (i.e., BIA, fat mass (FM), and sum of skin folds, and waist and hip circumferences). However, there were significant family correlations for measures of regional fat and fat distribution (i.e., WHR and biceps, triceps, subscapular and suprailiac skinfold thickness, and the ratio of extremity fatness relative to trunk fatness). We also examined family correlations, restricting analyses to family members with BMI ≥ 30 (analyses not shown). There were significant correlations between parents and offspring for sum of skin folds and waist circumference and among siblings for BIA, sum of skin folds and waist, hip, and abdomen circumferences. The strongest correlations were between mothers and daughters.

Age at onset

Extreme obesity of subjects in this sample usually began early in life. Forty-two percent of individuals with BMI ≥ 40 reported onset of obesity during childhood (by age 10), 22% in adolescence (ages 11–19), and 36% in adulthood (age ≥ 20). For individuals with BMI between 30 and 40, the percentages were 31%, 16% and 53%, respectively. Mildly obese individuals ($27 < \text{BMI} < 30$) reported much later onsets, with 11%, 14% and 74%, respectively, in childhood, adolescence and adulthood (Figure 2). This negative association between severity of obesity and age of onset was highly significant ($X^2_{(4)} = 18.73$, $P = 0.0009$, Mantel-Hansel Test of linear association $(1) = 17.29$, $P = 0.00003$; Pearson correlation $(n = 255) = -0.39$, $P < 0.00001$). Among obese family members, self-reported age at onset of obesity was significantly correlated (parent offspring, $\boldsymbol{r} = 0.16$, $n = 126$, $P < 0.05$; sibling, $\boldsymbol{r} = 0.22$, $n = 140$, $P < 0.01$).

Discussion

We ascertained families having multiple extremely obese and lean individuals. Selecting families in this

Table 1 Measures of obesity, stature, and body fat distribution in human families selected for linkage studies

	Mothers					*Fathers*				
Measure	*Mean*	*s.d.*	*Min*	*Max*	*n*	*Mean*	*s.d.*	*Min*	*Max*	*n*
Weight	85.2	24.5	47.0	165.4	94	87.2	20.0	54.5	159.1	92
BMI	32.7	9.4	19.8	65.8	94	28.1	6.3	19.6	47.6	92
%fat	45.0	8.4	22.1	60.6	70	31.3	7.7	16.9	52.1	31
Skinfold thickness										
Bicep	30.3	14.6	2.5	67.0	70	18.4	10.6	5.0	39.3	33
Tricep	33.2	11.7	9.5	67.0	70	21.1	9.4	6.0	44.3	33
Sub-scapular	36.4	14.2	5.0	67.0	70	29.0	13.0	7.0	66.0	33
Suprailiac	33.0	14.4	5.0	67.0	70	32.7	13.3	9.0	67.0	33
Sum skinfold	133.0	49.6	25.5	242.0	70	101.3	40.2	28.0	208.3	33
Circumferences										
Waist	103.2	18.9	67.5	154.0	75	102.8	12.9	81.0	128.5	33
Hip	119.9	19.8	84.5	174.0	75	109.8	14.2	91.9	141.0	33
Abdomen	114.8	20.5	80.0	173.5	75	107.2	15.6	84.8	138.8	33
Height	161.6	6.6	141.5	175.3	94	176.3	7.6	156.0	198.1	92
Body fat distribution										
Waist/Hip	0.9	0.1	0.7	1.1	75	0.9	0.1	0.9	1.1	33
Trunk/Extremity	1.0	0.2	0.5	1.5	70	0.7	0.2	0.3	1.1	33
	Sisters					*Brothers*				
Weight	106.8	32.5	49.2	207.7	259	99.6	28.3	52.3	206.5	145
BMI	38.9	11.6	16.8	76.2	259	31.2	8.1	18.0	64.8	145
%fat	45.8	8.5	15.1	62.4	190	30.0	9.1	10.2	46.4	82
Skinfold thickness										
Bicep	37.3	13.6	5.3	67.0	197	22.1	11.5	4.2	56.3	83
Tricep	41.0	12.2	2.7	67.0	196	24.2	10.6	6.7	62.5	83
Sub-scapular	46.0	14.7	6.3	67.0	196	35.0	14.5	10.3	70.0	83
Suprailiac	42.8	13.8	6.3	67.0	196	45.2	14.6	11.7	67.0	82
Sum skinfold	167.3	48.5	32.3	254.0	194	126.8	43.5	37.3	248.5	82
Circumferences										
Waist	111.8	22.8	64.0	224.8	205	108.6	20.3	73.1	167.5	87
Hip	132.3	23.8	75.0	217.0	204	113.4	19.6	80.9	175.0	87
Abdomen	123.8	25.5	65.0	209.0	205	112.8	21.5	76.5	177.0	85
Height	165.9	7.8	148.0	195.6	259	178.4	8.0	152.4	197.6	146
Body fat distribution										
Waist/Hip	0.84	0.08	0.63	1.21	204	0.96	0.08	0.78	1.35	87
Trunk/Extremity	0.90	0.19	0.41	1.69	194	0.59	0.18	0.17	1.09	82

BMI = body mass index, weight (kg), BMI (kg/m^2), bicep (mm), tricep (mm), subscapular (mm), suprailiac (mm), waist (cm), hip (cm), abdomen (cm), height (cm), waist/hip = ratio HR of waist circumference divided by hip circumference, extremity/trunk = the sum of the skinfold thickness from the extremities (bicep and tricep) divided by the sum of skinfold measurements taken on the trunk (subscapular and suprailiac).

Table 2 Correlations between obesity, stature and body fat patterns in female (upper) and male (lower) family members

Measure	*Weight*	*BMI*	*% fat*	*FM*	*FFM*	*Bic*	*Tric*	*Sub*	*Il*	*Sum*	*Waist*	*Hips*	*Abdo*	*Height*	*WHR*	*Ext/Trnk*
Weight		0.95	0.81	0.98	0.90	0.73	0.75	0.77	0.64	0.80	0.84	0.93	0.87	0.23	**0.03**	**− 0.01**
BMI	0.94		0.83	0.96	0.84	0.77	0.78	0.78	0.64	0.82	0.85	0.94	0.89	**− 0.06**	**0.05**	**0.03**
% fat	0.77	0.78		0.89	0.53	0.69	0.72	0.77	0.61	0.77	0.77	0.83	0.81	**0.05**	**0.07**	**− 0.05**
FM	0.96	0.94	0.90		0.80	0.72	0.74	0.77	0.64	0.79	0.83	0.94	0.88	0.22	**0.01**	**− 0.03**
FFM	0.90	0.81	0.48	0.77		0.64	0.63	0.66	0.58	0.69	0.70	0.80	0.73	0.36	**− 0.03**	**− 0.06**
Biceps	0.63	0.68	0.59	0.65	0.48		0.83	0.77	0.69	0.91	0.65	0.72	0.66	**0.01**	**0.03**	0.23
Triceps	0.59	0.62	0.59	0.62	0.43	0.70		0.78	0.69	0.91	0.69	0.76	0.70	**0.01**	**0.05**	0.22
Subscap	0.74	0.77	0.71	0.77	0.58	0.65	0.66		0.77	0.92	0.76	0.79	0.77	**0.11**	0.13	− 0.24
Suprail	0.66	0.60	0.64	0.67	0.56	0.58	0.52	0.74		0.87	0.61	0.66	0.62	**0.10**	**0.05**	− 0.38
Sum skin	0.78	0.78	0.74	0.80	0.61	0.84	0.81	0.91	0.86		0.75	0.81	0.76	**0.06**	**0.07**	**− 0.06**
Waist	0.92	0.94	0.81	0.92	0.76	0.64	0.57	0.74	0.62	0.76		0.88	0.90	**0.08**	0.46	**− 0.09**
Hips	0.92	0.93	0.80	0.94	0.76	0.64	0.60	0.73	0.59	0.75	0.91		0.94	**0.10**	**− 0.01**	**− 0.05**
Abdomen	0.95	0.95	0.84	0.96	0.78	0.66	0.61	0.77	0.65	0.79	0.95	0.95		**0.08**	0.16	**− 0.09**
Height	0.37	**0.05**	0.19	0.31	0.52	**0.03**	**0.06**	**0.14**	0.38	0.20	0.20	0.22	0.23		**− 0.03**	− 0.14
WHR	0.18	0.20	0.19	**0.13**	**0.12**	**0.12**	**0.06**	**0.16**	0.18	**0.16**	0.40	**− 0.02**	0.20	**− 0.02**		**− 0.07**
Ext/Trnk	**0.00**	**0.08**	**0.03**	**0.01**	**− 0.06**	0.44	0.51	**− 0.08**	− 0.28	**0.11**	**0.03**	**0.06**	**0.02**	− 0.23	**− 0.04**	

Correlations between obesity, stature, bone breadth and body fat patterns in female (upper, above the identity line) and male (lower, below the identity line) family members. The number of observations used to compute the correlations for women ranged from 253–353, and for men ranged from 105–238. Because of the large sample size, most correlations were greater than zero ($P < 0.05$) and are given in regular text. Correlations not significantly greater than zero are given in **bold**. BMI = body mass index; % fat = percentage fat; FM = fat mass; FFM = fat-free mass; Subscap = subscapular skinfold thickness; Suprail = suprailiac skinfold thickness; Sum skin = summed value of all four skinfold thickness (bicep (Bic), tricep (Tric), subscapular (Sub) and suprailiac (Il)); WHR = waist to hip ratio; Ext/Trnk = the sum of the skinfold thickness from the extremities (bicep and tricep) divided by the sum of skinfold measurements taken on the trunk (subscapular and suprailiac).

Table 3 Inter- and intra-class correlations among family members for obesity measures, stature, and body fat distribution

Type	*Weight*	*% fat*	*FM*	*FFM*	*Bic*	*Tric*	*Sub*	*Il*	*Sum*	*Waist*	*Hips*	*Abdo*	*Height*	*WHR*	*E/T*
Par	−0.32	−0.10	−0.15	0.25	0.18	0.18	0.29	0.32	0.20	0.00	−0.14	−0.12	0.11	0.03	0.55
P-O	0.09	0.03	0.00	0.09	0.23	0.29	0.05	0.21	0.16	0.08	−0.01	0.00	0.28	0.24	0.31
Sib	0.02	0.01	−0.02	0.07	0.10	0.13	0.08	0.18	0.07	0.03	−0.03	0.00	0.15	0.23	0.26
M-Da	0.05	−0.08	−0.06	0.04	0.31	0.26	0.03	0.14	0.16	0.06	−0.09	−0.07	0.40	0.37	0.32
M-Son	0.01	0.10	0.03	0.18	0.07	0.36	0.06	0.32	0.18	0.15	0.00	0.04	0.23	0.20	0.22
F-Da	0.20	0.17	0.21	0.08	0.29	0.33	0.07	0.11	0.16	0.08	0.16	0.09	0.25	−0.05	0.36
F-Son	0.10	0.19	0.03	0.13	−0.07	0.14	0.03	0.49	0.12	0.04	0.13	0.06	0.21	0.04	0.33
S-S	−0.03	−0.04	−0.06	0.01	0.15	0.07	0.15	0.12	0.06	0.03	−0.05	0.00	0.16	0.27	0.31
S-B	0.06	0.01	−0.01	0.10	0.06	0.16	−0.07	0.20	0.03	0.00	−0.03	−0.02	0.17	0.15	0.26
B-B	0.05	0.15	0.08	0.09	0.05	0.30	0.33	0.36	0.27	0.12	0.09	−0.02	0.08	0.28	0.08

Par = parent-parent; P-O = parent-offspring; Sib = sibling; M-Da = mother-daughter; M-Son = mother-son; F-Da = father-daughter; F-Son = father-son; S-S = sister-sister; S-B = sister-brother; B-B = brother-brother. Significant deviations from 0.0 are underlined. The number of observations used to calculate the inter- and intra-class correlations for the parent-parent ranged from 24-92; parent-offspring, 299-803; sibling, 323-814; mother-daughter, 65-259; mother-son, 61-146; father-daughter, 61-255; father-son 30-143; sister-sister, 144-292; sister-brother 144-399; brother-brother, 33-123. %fat = percent body fat; FM = fat mass (kg); FFM = fat-free mass; Bic = bicep skinfold; Tric = tricep skinfold; Sub = subscapular skinfold; Il = suprailiac skinfold; Sum = sum of skinfolds; Waist = circumference; Abdo = abdomen; WHR = waist to hip ratio; E/T = extremities to trunk ratio.

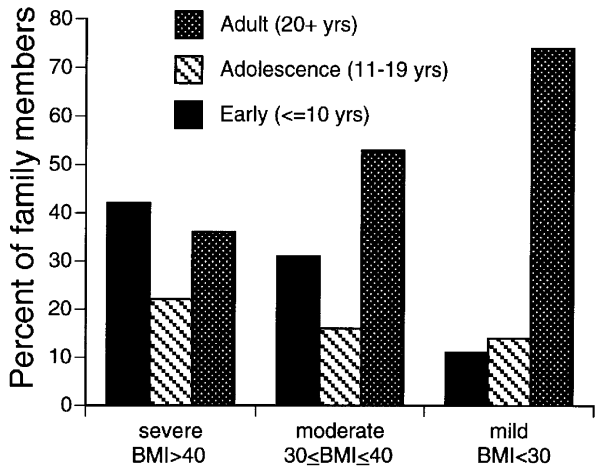

Figure 2 Age of obesity onset and body mass index (BMI, kg/m^2) of family members.

manner resulted in a wide range and bimodal distribution of obesity phenotypes and a large number of sibling pairs who were concordant and discordant for extreme obesity and leanness. The use of sibling pairs concordant and discordant for extreme phenotypes has been proposed as a powerful method for mapping genes for complex traits.[14,28] For example, it has been shown that study designs which sample sibling pairs from the upper and lower deciles require 10–40 times fewer sibling pairs to attain the same statistical power as unselected sibling pairs.[14,29] The theoretical advantages and practical difficulties of recruitment of sibling pairs extremely discordant for weight have recently been discussed by Allison,[30] who noted that extremely discordant sibling pairs are rare and have an increased frequency of covert non-paternity. Concordant sibling pairs with extreme and therefore rare phenotypes are also labor-intensive to recruit. These difficulties have been addressed in the current study design. By sampling nationally, we were able to screen over 2000 families, and locate 94 which provided both concordant and discordant pairs with extreme phenotypes. These concordant and discordant sibling pairs should provide substantial power for linkage and association studies.

Several linkage studies are underway; however, most studies were not specifically designed to maximize power for identifying genes for obesity. Some utilized samples recruited for studies of other disorders[31–35] or were unselected for obesity measures.[36,37] One study sampled a single large pedigree having multiple, extremely obese individuals.[38] That large family design has some of the characteristics of the current study, including an extreme range and bimodality of obese phenotypes. To our knowledge, only one group of investigators has selected sibling pairs based on extreme obesity measures.[39] That study ascertained affected sibling pairs, but in about 40% of cases, the sibling pairs had no parental DNA available. As a result, that study design does not take full advantage of the strengths of discordant sibling pairs or of identity-by-descent allele sharing, and thus should be statistically less powerful.

We only selected families having some members who were extremely dissimilar in BMI, and these selection criteria resulted in high within-family variability for BMI and closely related measures. This sampling design should maximize gene segregation within families but also suppresses family correlations, which are based on variation among families.

Previous studies have suggested that patterns of body fat distribution are influenced by different genes from those which influence overall adiposity,[40–47] and the current data are consistent with that hypothesis. We have a highly selected group of families whose familial correlation for overall adiposity is near zero, but the familial correlations for body fat distribution are highly significant. For example, we observed substantial family correlations for body shape as measured by WHR, the relative thickness of skinfold measures for each body site, and the proportion of fat on the arms *vs* the amount of fat on the trunk. Genes for these phenotypes may segregate independently of obesity within these families.

The pattern of phenotype correlations (for example), the correlation between BMI and percent body fat or body circumferences) observed in this sample is similar to patterns reported previously for obesity measures.[48–51] The range of phenotypes may in part account for the high correlations relative to other studies. There were few individuals in the normal range, where the correlation between BMI and percent fat tends to be lower than for subjects with mild or moderate obesity.[52] Consistent with earlier reports, the correlation between BMI and percent body fat was low in extremely obese subjects.[53–55]

A common characteristic of genetically influenced diseases is that they often being early in life. Early onset may also be an indicator of high genetic loading.[56] Almost half of the extremely obese individuals in the current study had a very early age at onset (onset age < 10 y). In a different study which ascertained families through a single extremely obese proband, rates of early-onset obesity were much lower than the rates in this study (12% compared with 42% in the current report[57]). The high rates of early-onset obesity seen in these family members may reflect the increased influence of genes in determining the phenotypes of these multiplex families. The age of obesity onset also appears to be familial, with early or late-onset obesity clustering within families. The early-onset portion of our sample may be particularly useful for linkage and association studies.

In summary, obesity is a multigenic trait, and special methods and sampling designs are needed for gene identification. Few family collections have been selected exclusively for linkage studies of obesity, and our collection utilizes a sampling strategy designed to optimize the likelihood that obesity genes are segregating within families. Families with extremely obese siblings with a lean parent and at least one lean sibling are highly informative for genetic linkage studies as these families should provide a large number of sibling pairs concordant and discordant for extreme obesity. In addition, a high proportion of early onset obesity in this study may increase the genetic loading.

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