A Genome-Wide Scan for Childhood Obesity–Associated Traits in French Families Shows Significant Linkage on Chromosome 6q22.31-q23.2

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We conducted a genome-wide search for childhood obesity–associated traits, including BMI ≥95th percentile (PCT95), 97th percentile (PCT97), and 99th percentile (PCT99), as well as age of adiposity rebound (AAR), which corresponds to the beginning of the second rise in childhood adiposity. A set of 431 microsatellite markers was genotyped in 506 subjects from 115 multiplex French Caucasian families, with at least one child with a BMI ≥95th percentile. Among these 115 pedigrees, 97 had at least two sibs with a BMI ≥95th percentile. Fine-mapping was performed in the seven most positive loci. Nonparametric multipoint analyses revealed six regions of significant or suggestive linkage on chromosomes 2q33-2q36.3, 6q22-31-q23.2, and 17p13 for PCT95, PCT97, or PCT99 and 15q12-15q15.1, 16q22.1-q24.1, and 19p13.3-p13.11 for AAR. The strongest evidence of linkage was detected on chromosome 6q22.31 for PCT97 (maximum likelihood score: 4.06) at the marker D6S287. This logarithm of odds score meets genome-wide significance tested through simulation (empirical genome-wide P = 0.01 [0.0027–0.0254]). Six independent genome scans in adults have reported quantitative trait loci on 6q linked to energy or glucose homeostasis–associated phenotypes. Possible candidate genes in this region include SIM1, MCHR2, and PC-1. Diabetes 53: 803–811, 2004

The available prevalence data show that not only is pediatric obesity dramatically increasing in most developed and developing countries, but there is also an increasing degree of adiposity in youth, particularly in older children and adolescents (1). Young-onset obesity is directly associated with early-onset type 2 diabetes (2) and an increase in the mortality risk of coronary heart disease once an adult (3). In childhood, several important periods of life giving higher risk for persistent obesity were pointed out: the prenatal period and early infancy, the time of adiposity rebound, and adolescence (4). BMI increases during the first year of life, after which it subsequently decreases and then begins to increase again around ~6 years of age. This second rise in childhood adiposity has been defined as the adiposity rebound (5). Six independent studies have confirmed that early adiposity rebound is associated with an increased BMI in adulthood (6,7). Early adiposity rebound could represent an indicator of a genetically determined propensity to deposit fat readily (8).

If the current epidemic of obesity clearly has its underpinnings in the changes in culture during the past half-century, the role of susceptibility genetic factors is likely to be stronger in the extreme phenotypes such as very-early-onset and/or severe forms of obesity. The rare monogenic forms of obesity were almost all identified in children or adolescents with massive obesity (9). In addition, evidence for strong inheritance of young-onset obesity has been established through family studies, investigating either parent–offspring fatness relationships (10), twins (11), or adopted children (12). These studies reported heritability estimates of 30–80% for common childhood obesity phenotypes. In adults, the risk of being overweight in relatives proportionally increases with the degree of obesity of the proband, suggesting that genetic influences are stronger in extreme phenotypes (13). Focusing on pedigrees with extreme forms of familial obesity with early age of onset can maximize our ability to detect genetic linkage by reducing the underlying genetic heterogeneity of the trait. In addition, parental genotypes are mostly available in pedigrees with obese children, therefore increasing the proportion of genetic information extracted from the dataset with substantial effects both on the power of our study to detect true linkage and on the significance of any linkage finding (14).

About 30 genome-wide searches for “obesity” genes have been published (15). Surprisingly, only three studies focused on extreme phenotypes. The group of R.A. Price reported a linkage with obesity in 10p13 and in 20q12-q13 from the analysis of families with extreme obesity (one proband with BMI ≥40 kg/m2 and an additional obese sibling with BMI ≥30 kg/m2) (16). Stone et al. (17), after the analysis of pedigrees containing at least three members with BMI ≥40 kg/m2, revealed a major predisposition locus for severe obesity on chromosome 4p15-p14 and replicated the linkage with obesity in 20q12-q13. To our
TABLE 1
Family structures

<table>
<thead>
<tr>
<th>Phenotypes</th>
<th>Number of pedigrees</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of pedigrees</td>
<td>115</td>
</tr>
<tr>
<td>Pedigrees with one sib with BMI ≥95th percentile</td>
<td>18</td>
</tr>
<tr>
<td>Pedigrees with two sibs with BMI ≥95th percentile</td>
<td>74</td>
</tr>
<tr>
<td>Pedigrees with three sibs with BMI ≥95th percentile</td>
<td>21</td>
</tr>
<tr>
<td>Pedigrees with four sibs with BMI ≥95th percentile</td>
<td>2</td>
</tr>
<tr>
<td>Number of documented sibpairs</td>
<td>233</td>
</tr>
<tr>
<td>Number of sibpairs with BMI ≥95th percentile</td>
<td>149</td>
</tr>
<tr>
<td>Number of sibpairs with BMI ≥97th percentile</td>
<td>135</td>
</tr>
<tr>
<td>Number of sibpairs with BMI ≥99th percentile</td>
<td>109</td>
</tr>
</tbody>
</table>

knowledge, the only genome-wide search for adolescent obesity was performed in two sets of 89 and 76 German families, but no suggestive peak of linkage (logarithm of odds [LOD] >2.2) with obesity was observed (18). Here we present a genome-wide scan of childhood obesity and show evidence for linkage with obesity phenotypes or with the age of adiposity rebound at six chromosomal regions.

RESEARCH DESIGN AND METHODS
Our sample consisted of 97 Caucasian nuclear families collected through a multimedia campaign at the Institut Pasteur de Lille in France and in the Department of Pediatric Endocrinology of Jeanne de Flandres Hospital. Families with at least two minor probands with a BMI >95th percentile for age and sex before the age of 8 and two living parents were included in the study (Table 1). Moreover, 18 pedigrees with at least two minor sibs and only one proband with a BMI >95th percentile for age and sex were added for analysis of age of adiposity rebound. This pool of 115 families gave informed written consent, and family participants (sibs, parents, and grandparents) were then submitted to detailed personal and medical questionnaires and anthropometric measurements. This study was approved by the Ethics Committee of the Paris Hôtel-Dieu Hospital. The main phenotypic characteristics of children by affection status are given in Table 2.

Phenotyping. Children with a BMI >97th percentile for age and sex in the tables of a French reference population (19) were defined as obese by the European Childhood Obesity Group (20). The European Childhood Obesity Group recommendations use the 90th percentile threshold to define overweight status. From these data, the 95th, 97th, and 99th percentiles reported in the tables by Rolland-Cachera were chosen in this study to define a range of the three worst levels of childhood adiposity. Height and weight were measured with an empty bladder and without a requirement for fasting. BMI was calculated as weight (kilograms) divided by height (meters) squared. BMI curves were individually established from data obtained from the child’s health notebook when available. Age at which BMI exceeded the 97th percentile for age and sex in the tables of a French reference population (19) were defined as obese by the European Childhood Obesity Group (20). The European Childhood Obesity Group recommendations use the 90th percentile threshold to define overweight status. From these data, the 95th, 97th, and 99th percentiles reported in the tables by Rolland-Cachera were chosen in this study to define a range of the three worst levels of childhood adiposity. Height and weight were measured with an empty bladder and without a requirement for fasting. BMI was calculated as weight (kilograms) divided by height (meters) squared. BMI curves were individually established from data obtained from the child’s health notebook when available. Age at which BMI exceeded the 97th percentile for age and sex was defined as obesity onset. Age of obesity onset was evaluated graphically as the age of upward inflection of BMI curve (5). Figure 1 shows the distribution of the age of adiposity rebound in children below and above the 95th percentile of BMI.

Genotyping. Genomic DNA was extracted from peripheral blood cells by PURE-GENE D50K DNA isolation kits (Genta Systems). Genotyping was performed using a fluorescently labeled human linkage mapping set (PE-LMSV2) comprising 400 highly informative microsatellite markers, according to a procedure detailed elsewhere (21). Among 400 markers in PE-LMSV2, two markers were not included because of technical problems. In addition to PE-LMSV2, 33 additional markers were genotyped. Therefore, a final total of 431 markers were genotyped with an average heterozygosity equal to 0.78. The average spacing between markers was 8.58 cM. After the first-stage genome search, seven regions were saturated with 87 additional markers to support and more accurately localize the linkage results. Six markers were discarded because of technical problems. We subsequently saturated the region of chromosomes 2q24-q36, 6q16.1-q21.1, 7q34-q36, 15q11-q22, 16q12-q24, 17p13, and 19p13.2-q12 with 15, 13, 7, 17, 13, 12, and 4 additional microsatellite markers, respectively. The average spacing between markers in the fine-mapped regions was 2.89 cM. We used Genethon data to build our maps. When markers were missing, we referred to Marshfield data to complete the maps. To detect mendelian inconsistencies, we ran the PED-CHECK 1.1 program (22). Five individuals were discarded from the analysis because at least 10% of the markers showed recurrent mendelian incompatibilities. Using the program MERLIN (23), we detected suspected double recombination for 0.31% of the genotypes (n = 826). These genotypes were removed. We checked the departure from the Hardy-Weinberg equilibrium with the program HWE, and if necessary, markers were replaced or removed. Finally, we compared the position of a marker according to our data versus the one given by Genethon or Marshfield by using the program VITESS. A marker showing a difference higher than the double was replaced or removed. Eight markers were removed after the position was checked.

Statistical analysis. Obesity is a complex disease with no clear model of inheritance, therefore, we used model-free methods to detect linkage. Three childhood obesity traits were analyzed. Children were considered affected in PCT95, PCT97, and PCT99 traits when their BMI exceeded thresholds of the 95th, 97th, and 99th percentiles, respectively, for age and sex of a French reference population (19). Only the concordant affected sibpairs from the pool of 97 obese multiplex families were taken into account for the PCT95, PCT97, and PCT99 obesity threshold analyses. We used this binary status because our ascertainment scheme resulted in reduced variability of the quantitative traits BMI in our sample compared with its variability in the general population. We analyzed the age of adiposity rebound (AAR) trait in the whole set of 115 families, taking into account both lean and obese children. We created four categories according to the distribution of data (Fig. 1). The number of categories and their probabilities were determined after visual inspection of the traits’ distribution and prior epidemiological hypotheses. We used a very early age of rebound (<2 years) as the first category. We also included in this category obese individuals who failed to show a rebound. An absence of adiposity rebound or a rebound before the age of 2 years were never observed in our sample of children with a BMI <95th percentile. On the contrary, 99% of children without any rebound of adiposity or with a rebound before the age of 2 years harbored a BMI higher than the 99th percentile at the age of examination, suggesting that they both can be included in the same category of massively obese children with early onset of the disease. We put individuals whose rebound occurred between 2 and 3 years including these parameters in

TABLE 2
Phenotypic characteristics by affection status

<table>
<thead>
<tr>
<th>Phenotypes</th>
<th>Children with BMI &lt;95th percentile</th>
<th>Children with BMI &gt;95th percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>n$_{total}$</td>
<td>47 (boys: 51.1%)</td>
<td>237 (boys: 51.1%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>11.91 ± 7.23 (47)</td>
<td>11.89 ± 6.05 (237)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>18.30 ± 4.99 (47)</td>
<td>29.12 ± 13.56 (237)</td>
</tr>
<tr>
<td>Z score of BMI</td>
<td>0.379 ± 1.47 (47)</td>
<td>3.965 ± 2.57 (237)</td>
</tr>
<tr>
<td>Age of obesity onset (years)</td>
<td>—</td>
<td>4.05 ± 5.27 (219)</td>
</tr>
<tr>
<td>Age of rebound (years)</td>
<td>5.29 ± 2.86 (38)</td>
<td>2.49 ± 3.25 (207)</td>
</tr>
</tbody>
</table>

Data are means ± 95% CI (n).
the second category, and we put those with rebounds between 3 and 5 years including the upper parameter in the third category. In the final fourth category, we gathered individuals with a rebound after the age of 5 years. Age of adiposity rebound could not be analyzed as a classical quantitative trait because a subgroup of obese children in our sample was characterized by the absence of an adiposity rebound. Furthermore, the advantage of the categorized trait is its robustness when the quantitative trait does not follow a normal distribution or is an ordinal score.

We used two methods to assess linkage for (affected status) traits. The first method, called maximum likelihood score (MLS) (24), calculated the identical by descent (IBD) status probabilities \(P(\text{IBD} = 0), P(\text{IBD} = 1), \) and \(P(\text{IBD} = 2)\) (\(z_0, z_1, \) and \(z_2\) respectively) in affected pairs through maximum likelihood estimation. The obtained maximum log likelihood \((L_{\text{m}})\) was compared with likelihood \((L_{\text{n}})\) under null hypothesis of no linkage (\(z_0 = 0.25, z_1 = 0.5, \) and \(z_2 = 0.25\)). The difference followed a mixture of \(\chi^2\) with 1 and 2 degrees of freedom. The method was implemented in the Genehunter 2.1 package.

The maximum likelihood binomial (MLB) method (25), implemented in the MLBGH software, is based on the probability \((\alpha)\) that sibship members of the same phenotypic category (affected sibs, for example) had received the same allele from a heterozygous parent. In case of linkage, \(\alpha\) is higher than 0.5. The log-likelihood difference followed a mixture of \(0.5 \chi^2\) with 0 and 1 degree of freedom. The ASPEX program was used to test for linkage on chromosome X. MLB has been extended (26) to quantitative traits (Q). A latent binary variable was used to categorize traits. The second method, called maximum likelihood score (MLS) (24), calculated the maximum MLS reached (MLSmax) and analysis-specific maximum MLS (MLS-95, MLS-97, MLS-99, and LOD-AAR, respectively). This gave us two empirical genome-wide \(P\) values. The first one, \(P_{\text{UNCORR}}\), was the probability that MLSmax exceeded an observed MLS for one trait. This \(P_{\text{UNCORR}}\) value was therefore specific for each trait. The second one, \(P_{\text{CORR}}\), was the probability that MLSmax exceeded MLS in the entire experiment: how many times the MLSmax > observed MLS out of 400. These \(P\) values account for multiple testing at all positions of the genome, and the latter one, \(P_{\text{CORR}}\), also accounted for multiple testing of four correlated phenotypes according to the phenotype. This last \(P\) value can be considered the \(P\) value for the entire experiment.

RESULTS

The Pearson correlation coefficients between the traits PCT95, PCT97, PCT99, and AAR are shown in Table 3. Results of the MLS and MLB multipoint analysis of the initial genome scan for selected qualitative (PCT95, PCT97, and PCT99) and categorized traits (AAR) are summarized in Table 4. Only the regions with suggestive evidence for linkage (LOD MLS \(\geq 2.32, \) LOD MLB \(\geq 2.08, P < 0.001\)) are reported here. Figure 2 presents an overview of the linkage analysis results. Multipoint analyses in the initial genome scan revealed five regions with suggestive evidence of linkage on chromosomes 2q35, 6q23.3, 15q14, 16q23.1, and 19p13.12 (Table 4). No linkage to any binary trait was detected on chromosome X. Among these results, the 6q23.3 linkage is significant after controlling for multiple markers and phenotypes analyses (\(P_{\text{CORR}} = 0.01\) [0.0027–0.0254]).

The five regions of interest (2q24-q34, 6q16.1-q24.1, 15q11-q22, 16q12-q24, and 19p13.2-q12) were chosen after the first stage mapping (Table 4) for partial saturation with additional markers. In addition, two other loci were fine-mapped: the locus 7q34–36, harboring an MLS value of 2.18 for PCT97, which is close to the selected threshold, and the locus 17p13, showing only a weak evidence of linkage for PCT95 and previously described as a quantitative trait loci for the metabolic syndrome (28). Results of the multipoint analyses for the high resolution genetic mapping at chromosomes 2, 6, 7, 15, 16, 17, and 19 are reported in Fig. 3 and Table 5. After fine-mapping, presence of suggestive linkage was observed at six loci (2q33.2-q36.3, 6q22.31-q23.2, 15q12-q15.1, 16q22.1-q24.1, 17p13, and 19p13.3-p13.11), whereas the saturation with

### Table 3

Pearson correlation coefficients between the AAR and the child-hood obesity–associated traits PCT95, PCT97, and PCT99

<table>
<thead>
<tr>
<th>Traits</th>
<th>PCT95</th>
<th>PCT97</th>
<th>PCT99</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAR</td>
<td>-0.54</td>
<td>-0.53</td>
<td>-0.53</td>
</tr>
</tbody>
</table>

All correlations are significant with a \(P\) value < 0.001.

### Table 4

Markers with evidence for linkage \((P \leq 0.001)\) in the 10-cM genome scan

<table>
<thead>
<tr>
<th>Positive markers</th>
<th>Interval</th>
<th>Position</th>
<th>Traits</th>
<th>MLS LOD (P)</th>
<th>1-LOD unit (cM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(cM)</td>
<td>(cM)</td>
<td>(cM)</td>
<td>(P)</td>
<td>(cM)</td>
</tr>
</tbody>
</table>

*Chromosomes locations were determined from the map available in the Human Genome Browser. †Haldane’s distances were used to determine the locations of linkage peaks. ‡Single-test \(P\) value; §Empirical genome-wide \(P\) value when considering all the traits; **Empirical genome-wide \(P\) value when considering one trait only. NA, not available. A Genethon map was used.
additional markers at the locus 7q34-q36 shifted the LOD value from 2.18 to 1.66 for PCT97 (Fig. 3), under the threshold of suggestive linkage (MLS 2.32, $P = 0.001$). Increasing the number of markers led two linkage peaks to suggestive significance on chromosomes 2q33.2-q36.3 (PCT97) and 17p13 (PCT95), whereas one suggestive peak of linkage decreased under the threshold of suggestive linkage, for PCT99 on chromosome 6q16.1-q24.1 (Fig. 3). Saturation with additional markers led to an increase of the LOD score values in six peaks from eight among suggestive linkage peaks (Table 5). The saturation decreased the 1-LOD unit CI for six of the eight suggestive linkage peaks, and this decrease was of 38% in average (Table 5). On chromosome 6q22.31-q23.2, the increased density of microsatellite markers led to an LOD score MLS of 4.06 for linkage with PCT97. The saturation decreased the 1-LOD unit CI on chromosome 6q from 17.03 to 10.85 cM (Table 5). Strong evidence of linkage was supported on chromosome 2q33.2-q36.3 for PCT99. After fine-mapping, three loci harbored suggestive linkage for AAR on chromosomes 15q12-q15.1, 16q22.1-q24.1, and 19p13.3-p13.11, with simultaneous indication of linkage for PCT99 (Fig. 3).
DISCUSSION

Our results show indication for linkage with childhood obesity and obesity-related traits on six chromosomes. The locus on 6q22.31-q23.2 showed the most significant evidence of linkage for PCT97 (Fig. 3), according to the criteria proposed by Lander and Kruglyak (29) and according to the empirical $P$ values ($P = 0.01$). Another suggestive linkage peak (MLS 3.05) with massive obesity is located on chromosome 2q33.2-q36.3. In addition, three chromosomal regions on 15q12-q15.1, 16q22.1-q24.1, and 19p13.3-p13.11 contain quantitative trait loci modulating the age of the physiological adiposity rebound (Fig. 3). This trait was considered as a categorized trait rather than a quantitative one because it displayed clear cutoffs in the distribution. Moreover, there are individuals with no observable age of rebound who were not removed from the study but represented an additional category. Therefore, we could only use MLB method cat because other programs and especially those partitioning the variance were not well tailored for this case. Our study allows us to identify regions harboring genes with a heritability of 15%, with a power of 80%. Thus, we do not expect all these regions to harbor genes of obesity. The simulation conducted to determine empirical genome-wide $P$ values also showed that an MLS LOD score $>2$ would occur two times [0.24-7.16] per genome scan on average. This clearly means that most of these loci need further replication and that the chromosome 6q, which reaches a satisfactory genome-wide empirical $P$ value, is the major result of our study.

FIG. 2. Continued.
FIG. 3. Results of the MLS (PCT95, PCT97, and PCT99) and MLB (AAR) multipoint analyses after fine-mapping. The y-axis indicates the LOD score. Red, green, and blue curves correspond to PCT95, PCT97, and PCT99 traits, respectively. Black curves correspond to the AAR trait. A Genethon map was used.
A recent publication based on simulation data suggested that fine-mapping has little value to reduce the error in the estimated location of a locus linked to a quantitative trait with an LOD score $>3$ (30). In our study, the fine-mapping step enabled us to exclude one artificial locus on 7q34-q36 and to further support two peaks with suggestive evidence for linkage that were under the corresponding threshold (LOD MLS $=2.32$, LOD MLB $=2.08$, $P = 0.001$) in the initial genome scan and to reduce the 1-LOD CI by 38% on average, in six suggestive peaks from 8. For instance, the saturation of markers on 6q16.1-q24.1 led to a decrease from 17.03 to 10.85 cM of the 1-LOD CI of our highest peak of linkage with childhood obesity (Table 5). Therefore, we believe that, at least for small sample-sized genome scans, fine-mapping is of interest.

Our results show significant evidence for linkage with childhood obesity (PCT97) on the locus 6q22.31-q23.2. Interestingly, a strong linkage with BMI (LOD score 4.64) was found on the chromosome 6q23–25 region from the study of 1,764 individuals of the Framingham Heart Study (31). A peak of linkage (LOD score $=2.2$) for leptin concentrations was also reported at marker D6S1009 (141 cM on our map) in 579 nondiabetic Mexican Americans (32). The chromosome 6q16.1-q24.1 region shows additional evidence of linkage for insulin sensitivity, insulin secretion, and susceptibility to type 2 diabetes. In the same Mexican-American population (32), a strong linkage was reported with the variation of fasting insulin levels (LOD score 5.08) from analysis of 257 Chinese pedigrees with a history of type 2 diabetes (36). There is much evidence to believe that the genetic bases of childhood obesity and glucose intolerance/type 2 diabetes could be partially redundant. Insulin has potent anorectic actions in the central nervous system (37). However, insulin also promotes in peripheral tissues the induction of genes involved in lipogenesis and the repression of those involved in lipolysis. In insulin-resistant states, it was suggested that hepatic lipogenesis and lipid storage are driven in excess, whereas insulin effects related to glucose homeostasis are impaired (38). Hence, insulin’s antilipolytic effect is relatively preserved, resulting in maintenance or expansion of adipose stores. In Pima Indians, a population prone to obesity and type 2 diabetes, fasting hyperinsulinemia is a strong predictor for the development of obesity in young children (39). Consistent results were recently reported for a sample of Caucasian and African-American children, because a lower insulin sensitivity, a higher fasting insulin level, and a higher acute insulin response were significantly associated to higher increases in fat mass 3–6 years later (40). In addition, in a genetic study focusing on the variable number of tandem repeats (VNTR) of the INS gene, it was shown that French young obese patients homozygous for class I VNTR alleles secret more insulin and gain more weight than those with other genotypes (41). Within the 6q confidence interval for linkage map are the single minded 1 (SIM1) and melanocortin concentrating hormone receptor 2 (MCHHR2) and the plasma cell membrane glycoprotein (PC-1) genes, which are strong candidates for obesity. Mice homozygous for a null allele of SIM1 lack the paraventricular nucleus of the hypothalamus and die perinatally, and null heterozygous SIM1 mice are hyperphagic and develop early-onset obesity (42). In humans, deletion of SIM1 or disruption of the gene by translocation result in severe early-onset obesity (43,44). MCHHR2 is a putative receptor for MCH, a peptide involved in the regulation of feeding and energy homeostasis. The expression of MCHHR2 mRNA is restricted to several regions of the brain, including the arcuate nucleus and the ventral medial hypothalamus—areas implicated in regulation of body weight (45). MCHHR2 shares 38% amino acid identity with MCHR1 (45). MCHR1-deficient mice are lean, hyperphagic, and resistant to diet-induced obesity (46). The plasma cell membrane glycoprotein PC-1 gene, when overexpressed, has been shown to be an inhibitor of insulin receptor tyrosine kinase activity, and its levels are elevated in muscle, fat, and fibroblasts of subjects with insulin resistance (47,48). A polymorphism (K121Q) in exon 4 of the PC-1 gene was

### Table 5

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Fine-mapping interval (cM)</th>
<th>Average density</th>
<th>Trait</th>
<th>MLB LOD ($P$*)</th>
<th>MLS LOD ($P$*)</th>
<th>1-LOD unit (CI) (cM)</th>
<th>Location (cM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2q33.2-q36.3</td>
<td>D2S112-D2S396</td>
<td>3.84</td>
<td>PCT97</td>
<td>2.73 (0.0002)</td>
<td>3.05 (0.0002)</td>
<td>22.34 (214.96–237.30)</td>
<td>230.62</td>
</tr>
<tr>
<td>6q22.31-q23.2</td>
<td>D6S462-D6S441</td>
<td>3.01</td>
<td>PCT97</td>
<td>2.08 (0.001)</td>
<td>2.33 (0.001)</td>
<td>24.46 (214.00–238.46)</td>
<td>230.62</td>
</tr>
<tr>
<td>15q12-q15.1</td>
<td>D15S128-D15S153</td>
<td>2.22</td>
<td>AAR</td>
<td>2.53 (0.0003)</td>
<td>NA</td>
<td>13.67 (21.71–35.38)</td>
<td>32.69</td>
</tr>
<tr>
<td>16q22.1-q24.1</td>
<td>D16S415-D16S520</td>
<td>3.13</td>
<td>AAR</td>
<td>2.54 (0.0003)</td>
<td>NA</td>
<td>21.68 (95.63–117.31)</td>
<td>105.15</td>
</tr>
<tr>
<td>17p13.1</td>
<td>D17S849-D17S799</td>
<td>1.96</td>
<td>PCT95</td>
<td>2.25 (0.0007)</td>
<td>2.35 (0.001)</td>
<td>6.50 (16.59–23.60)</td>
<td>18.70</td>
</tr>
<tr>
<td>19p13.3-q13.11</td>
<td>D19S221-D19S414</td>
<td>2.58</td>
<td>AAR</td>
<td>2.13 (0.0009)</td>
<td>NA</td>
<td>22.62 (24.71–47.33)</td>
<td>44.60</td>
</tr>
</tbody>
</table>

*P* single-test *P* value. A Genethon map was used. Only the traits with suggestive evidence for linkage are reported here (LOD MLS $=2.32$, LOD MLB $=2.08$, $P = 0.001$).
associated with insulin resistance in Caucasian subjects from Sicily, Sweden, and Finland (48,49).

Previous studies also found suggestive linkage for concurrence-associated traits on chromosomes 2q33.2-q36.3, 6q22.31-q23.2, 1q42.1-q42.4, 17p13, and 19p13.3-p13.11 in general or obese-enriched samples (15). Surprisingly, no linkage with morbid obesity in adults was reported in these regions, whereas this phenotype can be considered a logical continuation in adulthood of the early-onset obesity. However, this lack of replication may be due to the scarcity of genome-wide scans with morbidly obese sibpairs. Alternatively, it may be possible that the molecular determinants of the severe forms of obesity in infancy (a phenotype that was very infrequent 20 years ago) are not the same that those associated with morbid obesity in adults.

An early adiposity rebound has been extensively related to higher BMI values or risk of obesity in adulthood (6,7). In this article, we show that individuals harboring a very early rebound (before age of 2 years) or an absence of BMI rebound systematically develop an overweight phenotype in childhood (Fig. 1). Indeed, a very early or absent rebound is present in 30% of children who become overweight, whereas no lean children harbor a rebound before the age of 2 years. The recognition of a very early age of adiposity rebound or the absence of BMI rebound by the age of 2 years is a simple mechanism to identify an “at high risk of childhood obesity” subpopulation for clinicians.

In summary, this report provides significant evidence of a linkage for childhood obesity on chromosome 6q22.31-q23.2. Further work will be required to confirm our linkage chromosomal regions for childhood obesity in new independent samples and to test associations of positional candidate genes with occurrence of early-onset obesity.

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