A Genomewide Linkage Scan for Abdominal Subcutaneous and Visceral Fat in Black and White Families

The HERITAGE Family Study

Treva Rice,1 Yvon C. Chagnon,4 Louis Pérusse,5 Ingrid B. Borecki,1,2 Olavi Ukkola,7,8 Tuomo Rankinen,8 Jacques Gagnon,6 Arthur S. Leon,9 James S. Skinner,10 Jack H. Wilmore,11 Claude Bouchard,7 and D.C. Rao1,2,3

Abdominal visceral fat (AVF), abdominal subcutaneous fat (ASF), and abdominal total fat (ATF) were measured using a computed tomography scan, both before (baseline) and after (post) a 20-week endurance exercise training protocol in the HERITAGE Family Study. Each of the baseline and response (post minus baseline) measures was adjusted for several covariates, including total fat mass, and responses to training were further adjusted for baseline levels. Multipoint variance components linkage analysis using a genomewide scan of 344 markers was conducted separately by race using race-specific allele frequencies. Several promising results ($P < 0.0023$) were obtained. For baseline AVF, the best evidence was on 2q22.1 and 2q33.2-q36.3 (including the IRS1 locus) in whites, with suggestive findings on 7q22.2-q31.3 (including the LEP locus) in blacks. Although several regions were indicated for baseline ASF, only 4q31.22-q32.2 and 11p15.4-p11.2 replicated the results of another study. For responses to training, promising results were limited to ASF and ATF primarily on 7q36.2 (including NOS3) in blacks, with suggestive results ($P < 0.01$) on 1q21.2-q24.1 (S100A, ATP1A2, and ATP1B1), 10q25.2 (ADRA2A), and 11p15.5 (IGF2). In summary, the 4q and 11p regions have now been implicated in two independent studies for ASF; further research is warranted to identify the genes and mutations in these regions that are responsible for fat accumulation in the abdominal depot. Additional work in an independent sample is needed to verify the linkages for baseline AVF as well as the response measures. 

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Excess upper-body adipose tissue is strongly associated with insulin resistance (1,2) and clinical conditions associated with cardiovascular risk, such as hypertension and dyslipidemia (3–5). Sex and growth hormones, glucocorticosteroids, and catecholamines all contribute to abdominal fat accumulation within this context (6,7). The relative importance of abdominal visceral fat (AVF) and abdominal subcutaneous fat (ASF) in insulin resistance is under debate, with some studies reporting better insulin and glucose homeostasis with AVF (8) and others favoring ASF (9,10).

Based on results from the Québec Family Study (QFS) and the HERITAGE Family Study (11,12), it is clear that abdominal fat depots are strongly influenced by genetic factors, with maximal heritabilities $>55\%$ for AVF and abdominal total fat (ATF) and $>40\%$ for ASF. Segregation analyses further suggest that the familial effect is primarily attributable to major recessive genes for AVF (13,14). Candidate gene studies have identified regions that may contribute to this variability (15). For example, there are reports of associations or linkages between AVF and the glucocorticoid receptor gene (16), the $\beta3$-adrenergic receptor gene (17,18), and the fatty acid binding protein–2 gene (19). The first genomewide scan for abdominal adiposity was from the QFS (20), in which linkage was found primarily for ASF. As expected for complex traits, multiple linked regions were found, the magnitude of the results was moderate, and replication was needed to strengthen the credibility of the findings.

Other lines of investigation have suggested that adiposity changes in response to intervention are attributable in part to genetic factors (21). For example, a segregation analysis of the AVF response to 20 weeks of exercise training in the HERITAGE Family Study suggested a heritability of nearly 20%, which was primarily due to a putative recessive locus (22). To date, candidate gene
studies of the abdominal fat response phenotypes have been primarily negative (23), although other dimensions of body composition training responses (fat and fat-free mass, BMI, and sum of skinfolds) have been linked to several genomic regions (24).

The objective of the current investigation was to conduct a genomewide search for linkage regions influencing AVF, ASF, and ATF, both in a sedentary state (baseline) and in response to endurance exercise training, using data on black and white families participating in the HERITAGE Family Study. A total of 344 markers spanning 22 autosomes were typed, including microsatellites as well as some candidates for adiposity and related cardiovascular risk factors. Baseline and response measures were adjusted for several covariates, including total fat mass, and analyses were conducted separately by race.

**RESEARCH DESIGN AND METHODS**

The HERITAGE Family Study was designed to investigate the role of familial factors underlying the cardiovascular, metabolic, and hormonal responses to a standardized aerobic exercise—training program. Several criteria were used to screen participants (25). In general, the goal was to obtain sedentary families consisting of two parents and at least three biological offspring, although family structure/size requirements were relaxed for black families. Sedentary was defined as not participating in any regular strenuous exercise, characterized as exercise lasting ≥30 min and involving energy expenditure of 7 (age ≥50 years) or 8 METS (age <50 years) for more than one week for the previous 6 months. Nonsedentary members in otherwise qualifying families discontinued exercise for at least 6 months before the family was reconsidered for enrollment in the study. All parents were required to be age ≥65 years and offspring to be ages 17–49 years. With a few exceptions approved by a physician, subjects had a BMI <40 kg/m² and a resting blood pressure ≤150/99 mmHg. Exclusionary criteria were based on ethical concerns regarding maximal exercise testing in previously sedentary subjects. For example, conditions or diseases that were life threatening or that could interfere with or be aggravated by cycle ergometric exercise were causes for exclusion. After consideration of missing data, there were 668 individuals with complete data, forming 99 white and 105 black families. The number of individuals in white families ranged from two to six, with 90% of the families consisting of two or more members (for a total of 288 sibling pairs). The black family size was generally smaller, with about 70% consisting of two or more members (for a total of 72 sibling pairs). Each institutional review board of the HERITAGE Family Study consortium approved the study protocol, and written informed consent was obtained from each participant.

Each subject was trained on a cycle ergometer three times per week for 20 weeks. Duration and intensity of training were automatically adjusted every 2 weeks. Duration progressively increased from 30 min at baseline to 50 min for the last 6 weeks of training, and intensity increased progressively from a heart rate associated with 55% of the baseline VO₂max to that associated with 75% of VO₂max for the final 8 weeks. The power output of the cycle ergometer was adjusted automatically to the heart rate response during exercise via a built-in computerized control. Each training session was supervised on site, and adherence to the protocol was strictly monitored (25).

A complete battery of tests was administered both before (baseline) and after training. Computed axial tomography (CT) measures were obtained as a 50:50 mixture of a x₁ and a point mass at zero (34), and the correct P value associated with the linkage test was 0.5 of that corresponding to the x₁. The logarithm of odds (LOD) score was computed as \( \log P \approx \sum r - 1 \) and in response to endurance exercise training, using data from the location database of Southampton, U.K. (http://cedar.genetics.soton.ac.uk) and the Marshfield map (http://www.marshfieldmed.edu/genetics).

**RESULTS**

A total of 344 markers (291 microsatellites and 53 restriction fragment—length polymorphisms) from 22 autosomes were genotyped. The mean heterozygosity was 0.69 (0.01–0.97), and the average spacing between markers was 9.7 cm (range <0.1 to 25 cm). In the sample, 1129 and 129% (black and white, respectively) of the parents were of normal weight (BMI <25); 50 and 40%, respectively, were overweight (BMI ≥25 and <30); and 28 and 31%, respectively, were obese (BMI ≥30). Means and SDs for age, BMI, FM, AVF, ASF, and ATF are given in Table 1 by sex, generation, and sample.

The data adjustments for the baseline variables suggested that FM is a significant predictor in each of the eight (sex by generation by race) groups for all three phenotypes, accounting for 35–54% of the variance. Age accounts for additional variance in offspring. For responses to training, the most consistent predictor is the baseline value, although baseline FM and age also are significant in some groups. Figure 1 shows the frequency distributions for the standardized residuals after data adjustments. Intra-individual correlations between AVF and ASF were 0.52 (P < 0.0001) for raw data, 0.67 (P < 0.0001) after age/sex adjustment, and −0.01 (P = 0.86) after age/sex/FM adjustment. Thus, the AVF and ASF variables analyzed in this study (age/sex/FM adjusted) were uncorrelated. In contrast, correlations between ASF and ATF were much larger (0.97 for raw and age adjusted and 0.82 for age/FM adjusted), suggesting they index a similar adiposity trait.
Data are means ± SD. *Significant mean differences across black and white groups (race within sex and generation); † significant mean differences across parent and offspring groups (generation within race and sex); ‡ significant mean differences across male and female groups (sex within race and generation).

Multipoint linkage results for a LOD score ≥ 1.75 (P ≤ 0.0023) are presented in Table 2. (Complete results are available from T.R.) Figure 2 shows a graph of the complete results for the baseline ATF and ASF results, Fig. 3 represents the complete results for baseline AVF, and Fig. 4 shows all response measures. For comparison purposes, Figs. 2 and 3 include results for the only other known screen of these abdominal measures (the QFS), as reported by Pérusse et al. (20).

Results were promising for baseline ASF and ATF (P < 0.0023) on chromosomes 2p, 5q, and 22q in whites and 3p, 3q, 4q, 7q, 11p, and 14q in blacks (Table 2 and Fig. 2). For baseline AVF (Table 2 and Fig. 3), promising linkages were seen in whites on 2q22.1 and 2q36.1-q36.3 and include the IRS1 gene. No other region reached this level of significance for AVF. However, it was interesting to note a nominal result (P < 0.01) with baseline AVF in blacks on 7q31.33 at the LEP locus (P < 0.009). For responses to training (Table 2 and Fig. 4), ATF appeared to be linked to 7q36.2 (including NOS3) in blacks. Nominal evidence was noted in the response of blacks for several candidates on 1q21.2-1q24.1 (S100A, ATP1B1, and ATP1A2), 10q25.2 (ADRA2A), and 11p15.5 (IGF2).

The most likely regions for further investigation (Table 3 and Fig. 5) were replicated across the HERITAGE black and QFS samples. These linkage regions with ASF on 4q

<p>| TABLE 2 |
| Multipoint linkage results |</p>
<table>
<thead>
<tr>
<th>Cytogenic location</th>
<th>Marker</th>
<th>Distance from P-ter (cm)</th>
<th>Trait Sample</th>
<th>LOD</th>
<th>P</th>
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</table>

Results are P ≤ 0.0023. In “Trait Sample” column, the prefix B is baseline, prefix R is response to training; the suffix B is black, and the suffix W is white.
DISCUSSION

Body composition is an oligogenic complex trait, and thus the effect size for any single gene is expected to be moderate. Although the HERITAGE samples have ~80% (white) and <60% (black) power to detect major gene effects, accounting for as much as 50% of the variance and affecting 10% of the sample as indicated for these baseline traits (13,14), it is likely that individual quantitative trait loci (QTLs) will have even smaller effect sizes. Accordingly, as recommended by Rao and Province (35), more liberal criteria ($P < 0.0023$) were used to identify interesting or promising regions, with an increased reliance on replication and other methods for pruning out false positives. However, only one previous genome screen of baseline abdominal fat has been reported (the QFS) (20), and none is available for the responses to training.

Replication was inferred when linkage results were similar across HERITAGE black or white samples or similar to the QFS sample within a 1-LOD interval. Although no signals ($P < 0.0023$) were replicated across all three samples for AVF or ASF, there was some similarity across two of the samples for ASF. Of the nine QTL regions for ASF reported in the QFS, three in HERITAGE whites and six in HERITAGE blacks, only two (4q and 11p) replicated across QFS and HERITAGE blacks.

There are several differences among these cohorts that could lead to differential evidence for linkage. For example, the QFS consists primarily of white Canadian families of French ancestry, as compared to the admixed white (primarily of Western European descent) and black HERITAGE samples. The QFS sample is larger, being approximately the same size as the combined HERITAGE cohorts, with family structures as large as those of the whites. There are also sample-specific differences in adiposity levels. For example, there are more obese subjects in the QFS, as about half of the families were required to have at least two members with a BMI $\geq 32$ as compared to the required BMI <40 in the HERITAGE study. Moreover, the HERITAGE black sample has significantly higher adiposity levels than HERITAGE whites for weight, BMI, FM, and ASF, although the reverse pattern is noted for AVF (26). However, one major point of similarity between the HERITAGE and QFS cohorts is in the genome screen data. Most of the same markers were collected in both studies (overlap of 61% of HERITAGE and 70% of QFS markers), all were assayed in the same core labs, and the maps used for multipoint linkage analysis were taken from the same published source. Thus, these two studies provide a relatively homogeneous marker background for comparison.
of results across samples with different characteristics, and replicated findings may be generalized to the North American population.

For baseline ASF, several regions showed promising results ($P < 0.0023$) on 2p, 5q, and 22q in whites and 3p, 3q, 4q, 7q, 11p, and 14q in blacks. However, replication within a 1-LOD interval was limited to 4q and 11p. In both regions, linkage was detected in HERITAGE blacks (smallest sample) and in the QFS cohort (largest sample), but was absent in HERITAGE whites. The most obvious similarity between HERITAGE blacks and the QFS cohort was that these two samples are more obese or overweight than the HERITAGE whites. This suggests that the unidentified QTLs may have modest effects that are dependent on adiposity levels.

The broadest replicated region for ASF spans 40 cM on 11p15.4-p11.2 (including the C11P15.3, SUR, GATA34E08, and D11S1392 markers). The linkage at GATA34E08 is a specific replication of that reported with ASF ($P = 0.01$) by Péрусse et al. (20). In this region, the linked candidate SUR ($P < 0.005$) is related to insulin secretion. Two other candidates in this 1-LOD interval are the CCKBR gene (11p15.4) and the human homolog of the TUB gene (11p15.4). Antagonists of cholecystokinin-B brain receptors may decrease the satiety effect (39), and the CCKBR gene has been linked to susceptibility of type 2 diabetes (40). The average intermarker distance in this region is about 3 cM (range 0.1–10). Given these suggestive results with replication across two samples, denser mapping, including typing of CCKBR and TUB genes is warranted to uncover the source of these signals.

In the 4q31.21-q32.2 region (D4S2431, D4S2417, D4S2951), there was good replication between the HERITAGE blacks and the QFS cohort (both results $P < 0.0023$). The CPE gene (4q31.1), which is the human homolog of the rodent Fat gene (41), is <9 cM upstream of D4S2431 and is located within the 10-cM gap to the next measured marker. Thus, the CPE gene is a possible candidate based on physiological function and cytogenic location and could be responsible for this signal, although denser mapping is needed to narrow the QTL region.

For baseline AVF, suggestive evidence ($P < 0.0023$) was limited to chromosome 2 in whites, at 2q22.1 (D2S1334 and D2S1399) and 2q36.1-q36.3 (D2S434 and IRS1). There was no replication for AVF with the HERITAGE blacks or the QFS samples in this or any other region (Fig. 3). IRS1 (LOD = 1.87, $P = 0.00168$), not included in the QFS marker panel, is involved in insulin action and has been associated with current and longitudinal change in BMI in African-Americans (36) and with plasma leptin levels in obese subjects (37). It is interesting to note that this 2q region also is syntenic to several rodent models of obesity, including the Fob1, Mob6, Mob7, Obq2, Obq3, Nidd5, and Pfat1 loci (38). These results imply that there may be one
or more QTLs for abdominal adiposity in this area. Because the map density is somewhat wide in this region (average intermarker distance of 13 cM, range 2.6–21.0), denser mapping is needed to better localize these QTLs.

Another region showed interesting results for baseline AVF in blacks: on 7q31.33, the human homolog of the ob gene (LEP) was nominal (LOD = 1.24, \(P = 0.00831\)). Leptin is involved in satiety and has been associated and linked with various body composition measures in the past (38). Although the marker density is quite good at the LEP locus (seven markers within 1 cM), there is a >15 cM gap both upstream and downstream; denser mapping is needed to narrow down these QTL regions as well.

For the response to training data, no results were noted in whites, and evidence was limited to ATF at 7q36.2 (D7S3070 and NOS3) in blacks. The NOS3 locus is a vasoactive molecule relating to cardiovascular function and thus is a biological candidate for training responses. Three other areas were nominal (\(P < 0.01\)) with biological candidates involved in thermogenesis (ATP1A2, ATP1B1) and muscle-specific action (S100A) on 1q21.2-q24.1, adipose tissue lipolysis on 10q25.2 (ADRA2A), and insulin secretion and growth factors on 11p15.5 (IGF2). Each of these candidates previously has been linked or associated with adiposity and/or fitness measures. For example, a marker within 10 cM of NOS3 (D7S2195) was linked to \(V_{O_{2\max}}\) (42); in addition, Norman et al. (43) reported linkage near S100A (D1S1679, D1S2125) with 24-h energy expenditure and respiratory quotient. ATP1B1 and ATP1A2 have been linked or associated with percentage of fat and respiratory quotient (44,45). Moreover, the ATP1A2 locus was recently shown to influence the \(V_{O_{2\max}}\) response (i.e., trainability) in these HERITAGE families (42,46), as was the D1S1677 microsatellite located within 2 cM of ATP1A2 (42). Moreover, fat mass and fat-free mass responses to

![FIG. 4. Linkage results for response variables for each of the 22 chromosomes (Ch). LOD scores are along each Y-axis, and chromosomal locations (in centimorgans from p-ter) are on each X-axis. Locations of typed markers are indicated in each graph.](image-url)

### TABLE 3
Replicated linkage regions (1-LOD interval) across HERITAGE and QFS samples

<table>
<thead>
<tr>
<th>Cytogenetic location</th>
<th>Marker Location</th>
<th>Distance from p-ter (cM)</th>
<th>Trait_</th>
<th>Sample</th>
<th>LOD</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>4q31.22</td>
<td>D4S2431</td>
<td>159.50</td>
<td>BASF_B</td>
<td>2.34</td>
<td>0.00052</td>
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<tr>
<td>4q32.1</td>
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<td>BASF_Q</td>
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<tr>
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<td>1.34</td>
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<td>BASF_B</td>
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<td>1.12</td>
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</tbody>
</table>

In "Trait_ Sample" column, prefix B is baseline, suffix B is black in HERITAGE sample, and Q is QFS sample.
exercise training were also linked to the S100A and ATP1A2 loci in these HERITAGE families (24). ADRA2A previously has been associated with the trunk-to-extremity skinfold ratio (47) and with ASF and ATF (but not AVF) in the QFS cohort (48). Given the relatively small inter-marker distances in these regions, these candidates warrant further investigation to determine the functional variants and possible interactions among them.

In summary, this investigation provided several interesting results for baseline abdominal fat and represents the first genomewide scan for the abdominal fat responses to exercise training. In particular, these results provided some evidence for at least one QTL affecting baseline AVF levels near 2q22.1–q36.3 (including the IRS1 candidate), although this finding was not replicated across samples. We detected multiple baseline ASF signals, but only two were replicated across samples near 4q31.21–q32.2 and 11p15.4–p11.2. Finally, for the responses to training, there was nominal evidence for candidates involved in vasoactive molecules related to cardiovascular function (7q), thermogenesis (1q), adipose tissue lipolysis (10q), and insulin secretion and growth factors (11p). It is important to note that the abdominal fat phenotypes used in the present study were adjusted for total adiposity. Thus, the QTLs identified here in the sedentary state or in response to regular exercise pertain to the propensity to accumulate or lose fat (responses) in the abdominal depot at any level of adiposity. Some of these findings for baseline ASF constitute replications and strongly warrant follow-up work to identify the genes and mutations responsible for fat accumulation in the abdominal depot. Results for baseline AVF (i.e., promising linkage with IRS1 and suggestive results for the leptin gene) are biologically consistent with reported phenotypic associations among abdominal visceral adiposity, insulin sensitivity, and leptin concentrations (49,50); replication of this result in an independent study is needed.

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REFERENCES


FIG. 5. The 1-LOD interval is indicated by vertical dotted lines for regions on 4q (A) and 11p (B) that were replicated across studies for baseline ASF. LOD scores are along each Y-axis, and chromosomal locations (in centimorgans from p-ter) are on each X-axis. Locations of typed markers are indicated in each graph. ♂, ASF black; ♀, ASF QFS; □, ASF white; ○, ATF black; □, ATF QFS; △, ATF white.

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