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Identification of a QTL for adipocyte volume and of shared genetic effects between adipocyte volume with aspartate aminotransferase

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Abstract

Plasma levels of Aspartate aminotransferase (AST), a liver enzyme, are elevated in patients with visceral obesity. The purpose of this study was to examine if adipocyte volume is under the influence of genetic factors and to evaluate its genetic correlations with AST. Fasting plasma of 374 pedigreed baboons from the Southwest National Primate Research Center at the Southwest Foundation for Biomedical Research, San Antonio, TX were assayed for AST. Adipocyte volume was measured using biopsies of omental adipose tissue. Adipocyte volume, body weight and plasma AST were heritable. Genetic correlations between the measured adiposity - related phenotypes and AST were significant. A QTL (LOD score of 3.2) for adipocyte volume was identified on the baboon homologue of human chromosome 6 near marker *D6S1028*. These results suggest that omental adipocyte volume is under genetic regulation and that shared genetic factors influence adiposity associated traits and AST.

Keywords

non-alcoholic fatty liver disease; obesity; adipocyte size; genome scan; QTL; aspartate aminotransferase

Introduction

In obesity, white adipose tissue enlarges due to increased adipocyte size (hypertrophy) and/or number (hyperplasia) (Hausman *et al.*, 2001). Adipocyte size is a function of the balance between lipogenesis and lipolysis (Schling *et al.*, 2002). However, fat cell number is controlled by the equilibrium between proliferation (or differentiation) and apoptosis (Avram *et al.*, 2005). It is postulated that failure of preadipocytes to differentiate into mature lipid storage

cells expands the existing adipocytes during periods of surplus energy intake (Heilbronn *et al.*, 2004). The resultant hypertrophic cells are known to have dysfunctional lipid and glucose metabolism (Smith *et al.*, 2006), leading to insulin resistance (McGarry and Dobbins, 1999) and ectopic fat accumulation in tissues other than adipose depots (Danforth, 2000).

Most obesity related diseases are associated with hypertrophic adipocytes (Greenberg and Obin, 2006). The large fat cells are highly susceptible to apoptosis because of stress and consequently they attract mononuclear cells (Chen *et al.*, 2005). The recruited macrophages secrete cytokines that impair insulin sensitivity of the surrounding fat cells within the tissue (Shi *et al.*, 2006). The insulin resistance augments lipolysis, resulting in elevated concentrations of unesterified fatty acids in the circulation. Consequently, high plasma levels of insulin and free fatty acids may induce hepatic steatosis by the up regulation of the synthesis and accumulation of triglycerides in the liver (Mendez-Sanchez *et al.*, 2006).

It is hypothesized that omental adiposity is directly related to non-alcoholic fatty liver disease (NAFLD) (Adams and Angulo, 2005) because blood supply from visceral adipose tissue drains directly into the liver via the portal vein. Donnelly *et al.* (2005) have shown that 60% of the triglycerides accumulated in the liver are derived from the visceral adipocytes. One of the features of NAFLD is elevated levels of liver enzymes. Aspartate aminotransferase (AST), a liver enzyme is the key focus of this paper as it is elevated in patients with visceral obesity and fatty liver disease (Cancello *et al.*, 2006). The variation in the circulating levels of this enzyme is under genetic influence in humans (Bathum *et al.*, 2001). Also, it is well established that genetic factors contribute to obesity related phenotypes. Therefore, the goal of this study is to identify specific chromosomal regions containing genes that might affect adipocyte size and to determine whether genes contributing to variation in these adiposity-related traits also influence variation in AST in baboons.

The pedigreed baboons from the colony maintained by the Southwest National Primate Research Center are an excellent model for this study. Gene and protein sequence identity is conserved between baboons and humans and both are physiologically and developmentally similar (Rogers and Hixson, 1997). Although all the baboons share similar diet and housing conditions, approximately 10% become obese spontaneously and approximately 4% become hyperglycemic (Comuzzie *et al.*, 2003). Furthermore, during weight gain fat is deposited primarily in the abdominal area of baboons (Comuzzie *et al.*, 2003) and these animals exhibit the whole spectrum of histological changes associated with NAFLD (Bose *et al.*, 2006). It is more feasible to obtain omental adipose tissue biopsies from a large number of pedigreed baboons than it is in humans. Thus, baboons serve as an advantageous model for studying the genetic factors associated with obesity-related diseases.

Materials and methods

Animals

This study included 374 (254 females, 96 males) pedigreed baboons (*Papio hamadrayas*) from the colony maintained at the Southwest National Primate Research Center located at the Southwest Foundation for Biomedical Research (SFBR) in San Antonio, TX, USA. These animals consist primarily of olive baboons, but also include yellow baboons and olive-yellow hybrids. These animals are gang-housed and fed a low fat standard monkey chow diet *ad libitum* (Harlan Teklad 15% monkey diet, 8715, Indianapolis, IN).

Sampling and Phenotypic analyses

The Institutional Animal Care and Use Committee of the SFBR approved all procedures. Animals were fasted overnight (12 hours) and sedated with ketamine prior to collection of

blood samples. Body weight was measured on a calibrated electronic scale (GSE, Chicago, IL). A total of 10 ml of blood was drawn from the antecubital vein in heparin tubes for analysis of AST. Plasma was obtained by centrifugation at $2000 \times g$ for 10 minutes and was stored in aliquots at -80°C for future analysis. Assay of AST was conducted by standard laboratory techniques using Alfa Wasserman ACE clinical chemistry instrument (West Cladwell, NJ). Omental adipose tissue biopsies were collected as previously described by Cole *et al.* (2003). Adipocyte volume was analyzed by the method of Lewis (1986). All samples whose replicates had $>5\%$ variations were reanalyzed.

Genotyping

The animals in this study had previously been genotyped at more than 400 highly polymorphic microsatellite marker loci for the construction of a whole genome linkage map with an average marker density of 10cM (Cox *et al.*, 2006). We made use of these maps and identity-by-descent coefficients estimated from the genotype data in our analyses.

Statistical genetic methods

The maximum likelihood variance decomposition method implemented in the software program SOLAR (Almasy and Blangero, 1998) was used to perform the statistical genetic analyses presented in this paper. We used this method to partition the phenotypic variance of the quantitative traits studied into additive genetic and non-genetic (environmental) components. From this decomposition, we estimated the proportion of the variance due to the additive effects of genes – i.e., the heritability (h^2).

We further decomposed the additive genetic variance for each trait into a component for individual loci and a residual (polygenic) component and performed multipoint whole genome linkage screens to identify quantitative loci (QTLs) that influence adipocyte volume. Essentially, these tests consisted of comparing the likelihood of a restricted model for the trait in which the variance due to a QTL is constrained to zero (no linkage, null hypothesis) to an unrestricted model in which the QTL-specific variance is freely estimated. Twice the difference of the log likelihoods was asymptotically distributed as $\frac{1}{2} : \frac{1}{2}$ mixture of chi-square variable, with one degree of freedom and a point mass at zero (Self and Liang, 1987). The difference between the two $\log_{10}$ likelihoods yields a LOD score, which measures the support for the hypothesis of linkage over that of “no linkage” at a given chromosomal location. Our threshold for significant evidence of linkage was $\text{LOD} = 2.69$, and for suggestive evidence of linkage was $\text{LOD} = 1.46$. We obtained these genome-wide significance thresholds using a modification of an approach suggested by Feingold *et al.* (1993) to control for the overall false positive rate in our whole genome linkage screens of a single phenotype. Our approach takes into account the finite marker density in the linkage map utilized in the multipoint QTL screens and the mean recombination rate for these pedigreed baboons.

An extension of the univariate model was used for bivariate genetic analyses. The bivariate phenotype is a result of the phenotypic values, population means, the additive genetic estimates and environmental effects. This model was used to calculate the genetic and environmental variance-covariance matrices, in addition to genetic and environmental correlations. Both univariate and bivariate genetic analyses were conducted using the Sequential Oligogenic Linkage Analysis Routines (SOLAR) computer program (Almasy and Blangero, 1998). Age, sex, age squared and their interactions were included as covariates for the analyses. All the traits were inverse normalised for the analyses. According to this step, observations are ranked and replaced by expected value for that rank from a standard normal distribution. Software program PEDSYS computed the group means and ranges of male and female baboons.

Results

The number of relative pairs represented in the genetic analyses are shown in Table 1. Table 2 provides the descriptive statistics by sex. There were twice as many females as males, and the female baboons were older and had lower body weights. However, males had a higher concentration of plasma AST and smaller adipocyte volume.

The heritabilities for body weight, plasma AST, and adipocyte volume are given in Table 3. All of these heritabilities were significant with body weight having the highest heritability of all the traits studied. Table 4 shows the genetic correlations between plasma concentration of AST and markers of adiposity. Circulating concentrations of AST had a positive genetic correlation with body weight and adipocyte volume.

The genome wide scan for adipocyte volume is shown in Figure 1. The strongest signal obtained was detected on the baboon homologue of human chromosome 6, with a maximum LOD score of 3.2 at 73 cM near marker *D6S1028* (Figure 2). A genome wide scan for AST was conducted but a significant linkage signal was not obtained.

Discussion

This is the first study to identify a significant QTL for adipocyte volume and also report significant genetic correlations between AST and omental adipocyte volume and body weight. Aspartate aminotransferase (AST) also called glutamate oxaloacetate transaminase, is a pyridoxal phosphate-dependent enzyme that participates in amino acid metabolism as well as the urea and tricarboxylic acid cycles in the liver (Panteghini, 1990). The levels of this enzyme are elevated in obese subjects, (Marchesini *et al.*, 2005) presumably due to the NAFLD, which is highly prevalent in these individuals (Gholam *et al.*, 2007). In these patients, visceral adiposity, coupled with the presence of insulin resistance, may link obesity to fatty liver disease (Angelico *et al.*, 2005).

Adipocytes comprise about 0.5 to 1 % of the total body cells. The weight of the adipocytes accounts for approximately 2–3 % of the body weight in a healthy person, as opposed to 30–40% in the obese (Prins and O’Rahilly, 1997). In obesity, hyperplasia and hypertrophy cause expansion of the adipose tissue mass. It is believed that during weight gain adipocytes increase in size to accommodate the newly synthesized triglycerides (Spiegelman and Flier, 1996).

However, it is hypothesized that fat cells have a limited capacity to expand (Kawada *et al.*, 2001). Once the enlarged cells reach a critical mean volume they are liable to rupture due to stress (Monteiro *et al.*, 2006). It is plausible that the inability of hypertrophied adipocytes to expand further and the inability of preadipocytes to proliferate and differentiate into mature fat cells might lead to obesity related diseases (Bakker *et al.*, 2006).

The dead adipocytes activate inflammatory signaling pathways. These pathways could compromise the insulin sensitivity of the remaining fat cells (Cinti *et al.*, 2005). In addition, dead cells attract macrophages into the adipose tissue to clear cellular debris (Weisberg *et al.*, 2003). These immune cells release cytokines into the milieu, which further exacerbates insulin resistance within the adipose tissue (Xu *et al.*, 2003). The impairment of insulin signaling, in turn, stimulates lipolysis and increases the circulating concentrations of unesterified fatty acids (Permana *et al.*, 2006). These free fatty acids that are released, particularly from the visceral fat depots, are transported to the nearby organs such as the liver and may cause organ damage by initiating hepatic triglyceride accumulation (Eguchi *et al.*, 2006).

In this study we found a significant genetic relationship between plasma levels of AST, body weight and adipocyte volume. These results imply that the common genetic factors may influence these adiposity-related traits and levels of AST.

The identification of a QTL for omental adipocyte volume is the other significant finding of this study. Larger adipocytes have been implicated in the development of type II diabetes (Weyer *et al.*, 2000) and high plasma levels of non-esterified fatty acids (Paolisso *et al.*, 1995). It has been shown that bigger fat cells have higher mRNA concentrations of enzymes involved in lipid synthesis and hydrolysis than do those of a smaller size (Farnier *et al.*, 2002). Moreover, the hypertrophic adipocytes appear to be metabolically dysregulated.

Adipocyte size also affects the secretion of cytokines. Hypertrophy induces the release of pro-inflammatory adipokines which might be responsible for the chronic state of inflammation in obesity (Skurk *et al.*, 2007). Fat cells with a larger volume produce significantly more chemoattractants which attract monocytes into the adipose tissue. The cytokines released by these immune cells further promote apoptosis of the existing cells (Lin *et al.*, 2004). Therefore, in addition to total fat mass, both the size of cells that constitutes the adipose tissue play a major role in the pathology of obesity related co-morbidities.

Two potential positional candidate genes present within the one LOD support interval of the signal for adipocyte volume on chromosome 6 are fatty acid binding protein (*FABP7*) (OMIM 602965) (Shimizu *et al.*, 1997) and forkhead transcription factor (*FOXO3A*) (OMIM 602681) (Anderson *et al.*, 1998). Fatty acid-binding proteins (FABPs) are small proteins that increase the transfer of fatty acids into the cell and enhance the catalytic action of enzymes involved in fatty acid metabolism. It is believed that FABP helps to maintain the systemic energy homeostasis by providing a critical link between lipid metabolism and cellular functions in adipose tissue and other organs (Maeda *et al.*, 2005). The other candidate gene, forkhead transcription factor is stimulated due to stress and induces the expression of genes related to cell death. Its expression was upregulated in rats fed a high fat diet suggesting that apoptotic pathways might be activated in obesity (Relling *et al.*, 2006).

In conclusion, this study establishes that the volume adipocytes are heritable. The bivariate genetic analyses demonstrate that AST levels, fat cell volume and body weight are influenced by common set of genes. Future work should identify polymorphisms in the chromosomal region of the QTL for adipocyte cell volume that might influence obesity related co-morbidities.

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FIG. 1.

Genome-wide scan of adipocyte volume. The y-axis denotes the chromosomal location and the x-axis represents the LOD score

FIG. 2.
Map depicting LOD scores (X axis) and marker distances (Y axis) for adipocyte volume on chromosome 6

TABLE 1

Descriptive statistics of baboons *

Phenotype	Males/Females	Range
Number	119/225	
Age (yrs)	12.17 (3.9)/15.93 (4.9)	6.9–31
Body weight (kg)	31.50 (4.5)/19.53 (4.0)	12.1–48.2
Aspartate aminotransferase (IU/L)	31.43 (9.3)/26.78 (8.4)	3 – 75
Adipocyte		
Volume (nl)	0.386 (0.41)/0.579 (0.42)	.0037 – 2.16

* Mean (SE)

TABLE 2

Heritabilities of body weight, aspartate aminotransferase and adipocyte volume

Phenotype	Heritability $\pm$ SE	p value
Body weight	0.70 ± 0.10	< 0.0001
Aspartate aminotransferase	0.37 ± 0.11	< 0.0001
Adipocyte		
Volume	0.30 ± 0.11	< 0.0001

TABLE 3

Genetic (ρ_G) correlations between plasma concentration of aspartate aminotransferase and body weight, adipocyte volume

Phenotype	ρ Genetic	p value
Body weight	0.40	0.04
Adipocyte Volume	0.80	0.03

TABLE 4

Relative pairs in the analyzed sample

Relationship	Number
Parent-offspring	122
Siblings	260
Grandparent-grandchild	2
Avuncular	60
Half-siblings	2851
Half avuncular	616
1st cousins	1
Half 1st cousins	15
Half siblings & 1st cousins	2
Half siblings & half 1st cousins	62
Half siblings & half avuncular	8