Published in final edited form as:

J Hum Genet. 2011 July ; 56(7): 491–495. doi:10.1038/jhg.2011.46.

Pleiotropy of Type 2 Diabetes with Obesity

Sandra J Hasstedt[1], **Craig L Hanis**[2], **Swapan K Das**[3], **Steven C Elbein**[3,4], and **the American Diabetes Association GENNID Study Group**[*]

[1] Department of Human Genetics, University of Utah, Salt Lake City, Utah

[2] Human Genetics Center, School of Public Health, University of Texas Health Science Center, Houston, Texas

[3] Section on Endocrinology and Metabolism, Wake Forest University School of Medicine, Winston-Salem, North Carolina

Summary

The risk of type 2 diabetes (T2D) increases with obesity. One possible explanation is that pleiotropic genes affect risk of both T2D and obesity. To identify pleiotropic genes, we performed bivariate analysis of T2D with waist-hip ratio (WHR) and with body mass index (BMI) in the African American subset of the Genetics of NIDDM (GENNID) sample. Of 12 T2D loci identified through suggestive or higher univariate lod scores, we inferred pleiotropy with obesity for six (chromosomes 1 at 17–19 MB, 2 at 237–240 MB, 7 at 54–73 MB, 13 at 26–30 MB, 16 at 26–47 MB, and 20 at 56–59 MB). These findings provide evidence that at least some of the co-occurrence of obesity with T2D is due to pleiotropic genes. We also inferred four obesity loci through suggestive or higher lod scores for WHR (chromosomes 1 at 24–32 MB, 2 at 79–88 MB, 2 at 234–238 MB, and 3 at 148–159 MB).

Introduction

Obesity, especially abdominal obesity, increases the risk of type 2 diabetes (T2D), by more than twofold by some estimates[1]. Abdominal fat, more specifically visceral adipose tissue,

Correspondence: Sandra J. Hasstedt, sandy@genetics.utah.edu, (801) 581-4565.

[*]Genetic material collected by, and families characterized by, the American Diabetes Association GENNID Study Group, which includes Eric Boerwinkle, PhD, University of Texas Health Science Center; John Buse, MD, PhD, University of North Carolina; Ralph DeFronzo, MD, University of Texas Health Science Center; David Ehrmann, MD, University of Chicago; Steven C. Elbein, MD, University of Utah/University of Arkansas; Wilfred Fujimoto, MD, and Steven E. Kahn, MB, ChB, University of Washington; Craig L. Hanis, PhD, University of Texas Health Science Center; Richard A. Mulivor, PhD, and Jeanne C. Beck, PhD, Coriell Cell Repositories; Jill Norris, PhD, University of Colorado School of Medicine; M. Alan Permutt, MD, and Philip Behn, MD, Washington University School of Medicine; Leslie Raffel, MD, Cedars-Sinai Medical Center; and David C. Robbins, MD, Medlantic Research Institute.

[4]Steven C. Elbein passed away suddenly in June, 2010 during the preparation of this manuscript

Web Resources

jPAP http://hasstedt.genetics.utah.edu/
Eclipse2 http://www.stat.washington.edu/thompson/Genepi/Eclipse.shtml
MERLIN http://www.sph.umich.edu/csg/abecasis/Merlin
PedCheck http://watson.hgen.pitt.edu/register/docs/pedcheck.html
CIDR http://www.cidr.jhmi.edu/
GENNID http://professional.diabetes.org/Diabetes_Research.aspx?typ=18&cid=64380

secretes factors such as adiponectin and resistin that affect glucose metabolism[2]. As a measure of central obesity, waist-hip ratio (WHR) is expected to and in some studies[3], but not others[4] correlates more strongly with visceral fat than does body mass index (BMI). Regardless, WHR and BMI show similar associations with T2D risk[5–7].

Pleiotropic genes partially explain the co-occurrence of T2D and obesity. At least one T2D-obesity gene is known: *FTO* was identified through a genome-wide association (GWA) study of T2D then found to affect BMI[8]. Candidate T2D-obesity genes are supported by mouse studies (*PCK1* and *PCK2*[9]) or computational methods (*LPL* and *BCKDHA*[10]). On the other hand, some instances of the co-occurrence of T2D and obesity undoubtedly result from the interaction of independent genes and/or environmental factors, producing a mixture of pleiotropic and independent T2D and obesity genes underlying T2D in any population.

African Americans have less visceral fat than Caucasians with the same BMI[11], yet a higher risk of T2D at low BMI, although an equivalent risk at high BMI[12]. The relationship between T2D and obesity could differ between African Americans and Caucasians because different genes harbor T2D risk variants. Alternatively, the same genes, but with different variant frequencies, could alter the proportion of T2D in African Americans that reflects pleiotropic genes, thereby altering the relationship between T2D and obesity in the overall population. Consequently, T2D genes missed by Caucasian studies may be identified when studying African Americans, or other non-Caucasian samples[13], whether because of their limitation to or higher frequency in African Americans.

The American Diabetes Association established the Genetics of NIDDM (GENNID) study as a resource for the discovery of genes related to T2D and its complications. From 1993 to 2003 the GENNID study ascertained families through T2D-diagnosed siblings at multiple sites. In the African American subset of the GENNID sample, linkage scans using microsatellite markers identified one suggestive linkage peak for T2D on chromosome 10[14] and no evidence of linkage for the obesity factor of metabolic syndrome[15]. Following expansion of the sample and using SNP markers, we obtained a number of significant and suggestive linkages for T2D, BMI, and age of diagnosis (AOD)[16]. Herein, we repeat the T2D linkage analysis, not accounting for the effect of BMI on T2D risk as previously, and use bivariate linkage analysis to test for pleiotropy between T2D and obesity.

Subjects and Methods

The GENNID study ascertained families through a sibling pair each with a T2D diagnosis[17]. During Phase 1, extended family members were also studied; one site ascertained African Americans. During Phase 2, data collection beyond the sibling pair was limited to parents, or, if parents were unavailable, unaffected siblings; five sites ascertained African Americans. During Phase 3, sites were added which collected only affected sibling pairs and trios. In total, 1,496 African Americans members of 580 pedigrees were studied at 10 sites. See Elbein et al[16] for more detail. This study was approved by the Institutional Review Board at each participating institution.

T2D was diagnosed using National Diabetes Data Group criteria (fasting plasma glucose concentration >140 mg/dl on more than one occasion or 2-h and one other occasion during an OGTT that was >200 mg/dl)[17,18]. AOD was reported on a standardized questionnaire. Height, weight, and waist and hip circumference were obtained from physical examination, from which WHR and BMI were computed.

BMI and WHR were transformed, separately in males and females, using the inverse normal distribution, for which a quantile was assigned to each trait value and the corresponding inverse normal deviate assigned as the trait. Skew (−0.11 and 0.04) and kurtosis (−0.04 and −0.02) of transformed BMI and WHR, respectively, remained minimal after adjustment for gender and age.

The Center for Inherited Disease Research (CIDR) genotyped 5,958 autosomal SNPs on 1473 individuals using Illumina Linkage Panel IVb. Pedigree errors were identified using Eclipse2[19] and genotype errors were identified using Pedcheck[20] and MERLIN[21]. Multi-point identity by descent (IBD) probabilities were computed at each centimorgan (cM) using MERLIN[21], treating as haplotypes SNP sets with pairwise linkage disequilibrium $r^2 > 0.70$. See Elbein et al[16] for more details.

Likelihood analysis, as implemented in jPAP[22], was used for univariate linkage analysis of T2D, BMI, and WHR and for bivariate analysis of T2D paired with BMI and WHR. Transformed BMI and WHR were each modeled as a normal density with mean μ and standard deviation σ. Gender and age were included as covariates in all analyses; BMI and/or SNP genotypes were included as a covariate when indicated. T2D risk was modeled to account for AOD in affected pedigree members, while allowing for censored observations, through a modification of the age-of-onset regressive logistic model[23], also known as the age at diagnosis regressive model, and described as Method 2 in Cui et al[24]. Let W represent AOD or age last examined if unaffected, and X=0/1 for male/female. The logit of the probability of T2D equals

$$\text{logit}\,[p(w,x)]=\alpha+\beta w+\gamma x$$

where p(w, x)=Pr(T=1|W=w, X=x) denotes the probability of T2D, p=ln(α/1−α)) represents male lifetime penetrance, exp(β represents the annual odds ratio (OR) due to age, and exp(γ) represents the female/male OR. In addition, each univariate model included a polygenic effect (h^2 or heritability) and a quantitative trait locus (QTL) effect (q^2). Each bivariate model included h^2_i and q^2_i for trait i=1,2, as well as the correlations between the traits: ρ_q or pleiotropy, between QTL effects, ρ_g or the genetic correlation between polygenic effects, and ρ_e, the residual environmental correlation. Parameters were estimated as the values that maximized the likelihood.

In the univariate T2D and bivariate T2D-BMI and T2D-WHR analyses, we corrected the likelihood for the ascertainment of each pedigree through an affected sib pair. To perform autosome-wide variance components linkage analysis, we used the univariate and bivariate models in conjunction with the IBD probabilities. All the parameters of the models were

estimated every cM except for p, β and γ in the univariate T2D and bivariate analyses. In those analyses, p, β and γ were fixed at estimates obtained upon maximizing the likelihood of the linkage analysis model with $q^2 = 0$ or $q^2_1 = q^2_2 = \rho_q = 0$ while correcting the likelihood for the ascertainment of each pedigree through an affected sib pair. Ascertainment correction was not made in any linkage analyses.

Hypotheses were tested through comparison of the maximized likelihoods of general and nested models. Asymptotically, and under certain regularity conditions, twice the natural logarithm of the likelihood ratio distributes as a χ^2, or as a mixture of χ^2 for a 1-tailed test when the nested model constrains a parameter at its boundary[25]. Alternatively, we computed the lod score as the common logarithm of the likelihood ratio. Univariate linkage tested $q^2 = 0$ and distributed as a 1/2:1/2 mixture of a χ^2 with 1 degree of freedom and a point mass at zero. The test of a single QTL effect, that $q^2_2 = \rho_q = 0$, used the bivariate model and distributed as a 1/2:1/2 mixture of a χ^2 with 2 degree of freedom and a point mass at zero. The test of significant pleiotropy or QTL correlation, that $\rho_q = 0$, used the bivariate model and distributed as a χ^2 with 1 degree of freedom. The effect of a SNP was evaluated by including as a covariate genotypes coded as 0/1/2 when computing the lod score.

To account for multiple testing, autosome-wide statistics were considered significant (0.05 false positives expected per scan) if $P < 0.00005$, near-significant (0.1 false positives expected per scan) if $P < 0.0001$ and suggestive (one false positive expected per scan) if $P < 0.001$. Since SNP panels require higher thresholds than microsatellites[26], these probabilities are intermediate between those for 400 markers and a continuous map[27]. The corresponding significant, near-significant, and suggestive univariate lod scores were 3.29, 3.00 and 2.07. At each inferred T2D locus, QTL effects were tested for two traits (BMI, and WHR); therefore, $P < 0.05/2 = 0.025$ and $P < 0.1/2 = 0.05$ were considered significant and near-significant, respectively. At each inferred WHR locus, QTL effects were tested for one trait (T2D); therefore, $P < 0.05$ and $P < 0.1$ were considered significant and near-significant, respectively. For pleiotropy, tested only for significant QTL effects, $P < 0.05$ and $P < 0.1$ were considered significant and near-significant, respectively.

Results

The sample comprised 81% T2D cases and 65% women (Table 1). T2D cases were older with higher BMI and WHR. The near-significance of an effect of BMI on T2D risk (P=0.0574) was lost upon also accounting for WHR (P=0.336). In contrast, the effect of WHR on T2D risk remained highly significant after accounting for BMI (P=0.0000000172).

Twelve T2D loci were identified through autosome-wide univariate linkage analysis; five attained significance, two were near-significant, and five provided suggestive evidence of linkage (Table 2); differences from lod scores reported in Elbein et al[16] result from accounting for BMI therein. Two significant or near-significant loci showed evidence of pleiotropy with obesity: on chromosome 13 at 26–30 MB, pleiotropy attained significance for both BMI and WHR; on chromosome 2 at 237–240 MB, pleiotropy attained significance only for WHR. QTL effects for, but not pleiotropy with, WHR attained significance for the significant loci on chromosome 2 at 77–102 MB and at 113–117 MB, suggesting that these

locations harbor independent T2D and WHR loci. In addition, pleiotropy with obesity attained significance for four suggestive loci: on chromosome 20 at 56–59 MB with BMI and on chromosomes 1 at 17–19 MB, 16 at 26–47 MB, and 22 at 27–40 MB with WHR.

Two SNPs identified in GWA studies of T2D, rs10490072 near *BCL11A* and rs864745 near *JAZF1*[28], fall within our linkage regions on chromosomes 2 at 61–65 MB and 7 at 14–29 MB, respectively. Although both SNPs showed nominally significant associations with T2D in this sample[29], accounting for the SNP genotype decreased the lod score in the respective region only minimally (<0.2).

Despite evidence of pleiotropic effects on obesity risk for six of our inferred T2D loci, univariate linkage analysis produced no significant lod scores for either BMI or WHR. Nevertheless, suggestive lod scores supported three WHR loci, and adjustment of WHR for BMI added a fourth suggestive locus and strengthened the evidence for two of the suggestive loci: one to significance and the other to near-significance (Table 3). The support region of the significant locus overlapped our T2D-WHR locus on chromosome 2 at 237–240 MB and supported pleiotropy with T2D. The near-significant locus, located within the support region of our T2D locus on chromosome 2 at 77–102 MB, produced evidence of an effect on T2D, but no evidence of pleiotropy with T2D, in agreement with our previous conclusion that this region harbors independent T2D and obesity loci. For the remaining five T2D-obesity loci, univariate linkage analysis of BMI and WHR failed to produce genome-wide significance, although four of the five loci (except chromosome 22 at 27–40 MB) produced nominal significance (lod > 0.84) for either BMI or WHR.

Discussion

We identified 12 T2D loci through suggestive or higher lod scores. Although these loci include 9 that we reported previously[16], this analysis revealed three T2D loci that were previously obscured by accounting for the effect of BMI on T2D risk (chromosomes 2 at 237–240 MB, 7 at 14–29 MB, 20 at 56–59 MB), strengthened to significance the evidence for two previously suggestive loci (chromosomes 2 at 61–65 MB and 13 at 26–30 MB), and inferred pleiotropy with obesity for six T2D loci (chromosomes 1 at 17–19 MB, 2 at 237–240 MB, 7 at 54–73 MB, 13 at 26–30 MB, 16 at 26–47 MB, and 20 at 56–59 MB). In addition, we inferred four obesity loci through suggestive or higher lod scores for either WHR or WHR adjusted for BMI (chromosomes 1 at 24–32 MB, 2 at 79–88 MB, 2 at 234–238 MB, and 3 at 148–159 MB).

If obesity increases T2D risk solely because visceral adipose tissue produces diabetogenic substances[2], then WHR, a measure of central obesity, should be a stronger risk factor for T2D than BMI. In agreement, we found the effects on T2D risk to be highly significant for WHR, but non-significant for BMI, especially when also accounting for WHR. However, despite the non-significance of BMI in the absence of linkage information, accounting for BMI in linkage analysis lowered the lod scores by ≥0.5 for seven T2D loci[16], and we inferred pleiotropy with BMI for two T2D loci (chromosomes 13 at 26–30 MB, and 20 at 56–59 MB), suggesting that factors other than visceral adipose tissue affect T2D risk. One of the T2D-BMI pleiotropic loci (chromosome 13 at 26–30 MB) also showed pleiotropy

with WHR, as did four other T2D loci (chromosomes 1 at 17–19 MB, 2 at 237–240 MB, 16 at 26–47 MB, and 22 at 27–40 MB). The inference of pleiotropy with obesity may provide clues to the genes underlying these T2D loci. For example, while most T2D variants identified through genome wide association studies affect insulin secretion, the pleiotropic T2D-obesity gene *FTO* alters insulin resistance[30]. Whether this characteristic will distinguish other pleiotropic T2D-obesity genes awaits their discovery.

Visceral adipose tissue also correlates with lipid levels[31]. In fact, the considerable heterogeneity of plasma lipid profile in overweight and obese people depends partially on the degree of visceral adiposity and insulin resistance[32]. Six of the 12 T2D loci reported herein showed suggestive or stronger evidence of pleiotropy with a lipid level[33], five with triglyceride (2 at 77–102 MB, 2 at 237–240 MB, 7 at 54–73 MB, 13 at 26–30 MB, and 16 at 26–47 MB) and one with low density lipoprotein cholesterol (1 at 17–19 MB). All but two of these loci (chromosomes 2 at 77–102 MB and 7 at 54–73 MB) showed evidence of pleiotropy with WHR as well, consistent with visceral adiposity affecting both lipid levels and T2D.

Seven of the 12 T2D loci reported herein fall in replicated linkage regions[34]: three in the most highly replicated regions (2 at 237–240 MB, 20 at 56–59 MB, 22 at 27–40 MB) and four in regions reported in fewer, but still multiple studies (1 at 17–19 MB, 2 at 61–65 MB, 7 at 14–29 MB, 7 at 54–73 MB). However, the T2D linkage regions reported by Lillioja & Wilton[34] cover 1,139 MB, nearly 40% of the autosomal total, making the overlap of 54% of our loci less unexpected. The regions containing our loci were replicated in multiple ethnic groups, including samples with African ancestry. Possibly the 6 loci in non-replicated regions (2 at 77–102 MB, 2 at 113–117 MB, 11 at 119–122 MB, 13 at 26–30 MB, 16 at 26–47 MB, 22 at 27–40 MB) harbor African-specific T2D loci. However, none of these 6 regions was identified in T2D linkage scans of samples of African descent: three in African Americans[14,35,36] and one in African families from Ghana and Nigeria[37]. Instead, overlap occurred only in replicated regions: on chromosomes 7 at 14–29 MB[35,36], 7 at 54–73 MB[36] and 20 at 56–59 MB[37]. Further support for chromosome 7 at 54–73 MB comes from a linkage scan of insulin sensitivity index in obese African American families[38]. It should be noted that the samples used in the three African American T2D analyses included subsets of our sample.

In addition to overlap with linkage studies, two of our 12 T2D loci (chromosomes 2 at 61–65 MB and 7 at 14–29 MB) harbor SNPs identified in Caucasian GWA studies (rs10490072 near *BCL11A* and rs864745 in *JAZF1*[28]). Nevertheless, rs864745 was among 19 T2D-associated SNPs found to have consistent association in 5 racial/ethnic groups despite initial identification in Caucasians[39]; the study did not include rs10490072. While both SNPs showed nominally significant associations with T2D in this sample[29], neither explained much of the linkage in their respective regions. Nevertheless, these SNPs may be poor proxies for nearby causal variant(s) with larger effect sizes.

Also, three of our six T2D-obesity loci (chromosomes 13 at 26–30 MB, 16 at 26–47 MB, and 22 at 27–40 MB) harbor SNPs identified in GWA studies of BMI[40] or WHR[41] (rs4771122 in MTIF3, rs7359397 in SH2B1, and rs4823006 in ZNRF3). Deletion of the

SH2B1 gene in mice resulted in insulin resistance and glucose intolerance;[42] less is known about the other genes.

In summary, variance components linkage analysis provided suggestive or stronger evidence for 12 T2D loci, six of them pleiotropic with obesity, as well as for four obesity loci. Identification of the underlying genes should both increase understanding of the pathogenesis of obesity and T2D and aid in the dissection of the genetic heterogeneity of T2D.

Acknowledgments

This project was funded by NIH grants DK071100 and HD17463. This study was supported by the American Diabetes Association. Genotyping services were provided by the Center for Inherited Disease Research (CIDR). CIDR is fully funded through a federal contract from the National Institutes of Health to The Johns Hopkins University, contract number HHSN268200782096C.

References

1. Freemantle N, Holmes J, Hockey A, Kumar S. How strong is the association between abdominal obesity and the incidence of type 2 diabetes? Int J Clin Pract. 2008; 62:1391–1396. [PubMed: 18557792]
2. Hajer GR, van Haeften TW, Visseren FL. Adipose tissue dysfunction in obesity, diabetes, and vascular diseases. Eur Heart J. 2008; 29:2959–2971. [PubMed: 18775919]
3. Seidell JC, Björntorp P, Sjöström L, Sannerstedt R, Krotkiewski M, Kvist H. Regional distribution of muscle and fat mass in men--new insight into the risk of abdominal obesity using computed tomography. Int J Obes. 1989; 13:289–303. [PubMed: 2767882]
4. Weerarathna TP, Lekamwasam S, Rodrigo M. Prediction of total and visceral fat contents using anthropometric measures of adiposity in women. Ceylon Med J. 2008; 53:128–132. [PubMed: 19189790]
5. Wang Y, Rimm EB, Stampfer MJ, Willett WC, Hu FB. Comparison of abdominal adiposity and overall obesity in predicting risk of type 2 diabetes among men. Am J Clin Nutr. 2005; 81:555–563. [PubMed: 15755822]
6. Vazquez G, Duval S, Jacobs DR Jr, Silventoinen K. Comparison of body mass index, waist circumference, and waist/hip ratio in predicting incident diabetes: a meta-analysis. Epidemiol Rev. 2007; 29:115–128. [PubMed: 17494056]
7. Qiao Q, Nyamdorj R. Is the association of type II diabetes with waist circumference or waist-to-hip ration stronger than that with body mass index? Eur J Clin Nutr. 2010; 64:30–34. [PubMed: 19724291]
8. Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, et al. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science. 2007; 316:889–894. [PubMed: 17434869]
9. Beale EG, Harvey BJ, Forest C. PCK1 and PCK2 as candidate diabetes and obesity genes. Cell Biochem Biophys. 2007; 48:89–95. [PubMed: 17709878]
10. Tiffin N, Adie E, Turner F, Brunner HG, van Driel MA, Oti M, et al. Computational disease gene identification: a concert of methods prioritizes type 2 diabetes and obesity candidate genes. Nucleic Acids Res. 2006; 34:3067–3081. [PubMed: 16757574]
11. Stanforth PR, Jackson AS, Green JS, Gagnon J, Rankinen T, Després JP, et al. Generalized abdominal visceral fat prediction models for black and white adults aged 17–65 y: the HERITAGE Family Study. Int J Obes Relat Metab Disord. 2004; 28:925–932. [PubMed: 15148505]
12. Resnick HE, Valsania P, Halter JB, Lin X. Differential effects of BMI on diabetes risk among black and white Americans. Diabetes Care. 1998; 21:1828–1835. [PubMed: 9802729]
13. McCarthy MI. Casting a wider net for diabetes susceptibility genes. Nat Genet. 2008; 40 :1039–1040. [PubMed: 19165915]

14. Ehm MG, Karnoub MC, Sakul H, Gottschalk K, Holt DC, Weber JL, et al. Genetics of NIDDM. Genomewide search for type 2 diabetes susceptibility genes in four American populations. Am J Hum Genet. 2000; 66:1871–1881. [PubMed: 10793009]
15. Edwards KL, Hutter CM, Wan JY, Kim H, Monks SA. Genome-wide linkage scan for the metabolic syndrome: the GENNID study. Obesity. 2008; 16:1596–1601. [PubMed: 18421265]
16. Elbein SC, Das SK, Hallman DM, Hanis CL, Hasstedt SJ. Genome-wide linkage and admixture mapping of type 2 diabetes in African American families from the American Diabetes Association GENNID (Genetics of NIDDM) Study Cohort. Diabetes. 2009; 58:268–274. [PubMed: 18840782]
17. Raffel LJ, Robbins DC, Norris JM, Boerwinkle E, DeFronzo RA, Elbein SC, et al. The GENNID Study. A resource for mapping the genes that cause NIDDM. Diabetes Care. 1996; 19:864–872. [PubMed: 8842605]
18. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes. 1979; 28:1039–1057. [PubMed: 510803]
19. Sieberts SK, Wijsman EM, Thompson EA. Relationship inference from trios of individuals, in the presence of typing error. Am J Hum Genet. 2002; 70:170–180. [PubMed: 11727198]
20. O'Connell JR, Weeks DE. PedCheck: a program for identification of genotype incompatibilities in linkage analysis. Am J Hum Genet. 1998; 63:259–266. [PubMed: 9634505]
21. Abecasis GR, Cherny SS, Cookson WO, Cardon LR. Merlin--rapid analysis of dense genetic maps using sparse gene flow trees. Nat Genet. 2002; 30:97–101. [PubMed: 11731797]
22. Hasstedt SJ. jPAP: Document-driven software for genetic analysis. Genet Epidemiol. 2005; 29:255.
23. Elston RC, George VT. Age of onset, age at examination, and other covariates in the analysis of family data. Genet Epidemiol. 1989; 6:217–220. [PubMed: 2731708]
24. Cui JS, Spurdle AB, Southey MC, Dite GS, Venter DJ, McCredie MR, et al. Regressive logistic and proportional hazards disease models for within-family analyses of measured genotypes, with application to a CYP17 polymorphism and breast cancer. Genet Epidemiol. 2003; 24:161–172. [PubMed: 12652520]
25. Self SG, Liang KY. Asymptotic properties of maximum likelihood estimators and likelihood ratio tests under nonstandard conditions. J Am Stat Assoc. 1987; 82:605–610.
26. Wilcox MA, Pugh EW, Zhang H, Zhong X, Levinson DF, Kennedy GC, et al. Comparison of single-nucleotide polymorphisms and microsatellite markers for linkage analysis in the COGA and simulated data sets for Genetic Analysis Workshop 14: Presentation Groups 1, 2, and 3. Genet Epidemiol. 2005; 29 (Suppl 1):S7–28. [PubMed: 16342186]
27. Rao DC, Gu C. False positives and false negatives in genome scans. Adv Genet. 2001; 42:487–498. [PubMed: 11037337]
28. Zeggini E, Scott LJ, Saxena R, Voight BF, Marchini JL, Hu T, de Bakker PI, et al. Meta-analysis of genome-wide association data and large-scale replication identifies additional susceptibility loci for type 2 diabetes. Nat Genet. 2008; 40:638–645. [PubMed: 18372903]
29. Langberg KA, Hasstedt SJ, Hanis CL, Das SK, Elbein SC. Evaluation of type 2 diabetes (T2D) associated single nucleotide polymorphisms (SNP) in African American families from the American Diabetes Association GENNID study. American Diabetes Association. 2010 abstract number: 1263-P.
30. De Silva NM, Frayling TM. Novel biological insights emerging from genetic studies of type 2 diabetes and related metabolic traits. Curr Opin Lipidol. 2010; 21:44–50. [PubMed: 19956073]
31. Bulcão C, Ferreira SR, Giuffrida FM, Ribeiro-Filho FF. The new adipose tissue and adipocytokines. Curr Diabetes Rev. 2006; 2:19–28. [PubMed: 18220614]
32. Mooradian AD, Haas MJ, Wehmeier KR, Wong NC. Obesity-related changes in high-density lipoprotein metabolism. Obesity. 2008; 16:1152–1160. [PubMed: 18388903]
33. Hasstedt SJ, Hanis CL, Elbein SC. Univariate and bivariate linkage analysis identifies pleiotropic loci underlying lipid levels and type 2 diabetes risk. Ann Hum Genet. 2010; 74:308–315. [PubMed: 20597901]
34. Lillioja S, Wilton A. Agreement among type 2 diabetes linkage studies but a poor correlation with results from genome-wide association studies. Diabetologia. 2009; 52 :1061–1074. [PubMed: 19296077]

35. Sale MM, Freedman BI, Langefeld CD, Williams AH, Hicks PJ, Colicigno CJ, et al. A genome-wide scan for type 2 diabetes in African-American families reveals evidence for a locus on chromosome 6q. Diabetes. 2004; 53:830–837. [PubMed: 14988270]

36. Sale MM, Lu L, Spruill IJ, Fernandes JK, Lok KH, Divers J, et al. Genome-wide linkage scan in Gullah-speaking African American families with type 2 diabetes: the Sea Islands Genetic African American Registry (Project SuGAR). Diabetes. 2009; 58:260–267. [PubMed: 18835935]

37. Rotimi CN, Chen G, Adeyemo AA, Furbert-Harris P, Parish-Gause D, Zhou J, et al. Africa America Diabetes Mellitus (AADM) Study. A genome-wide search for type 2 diabetes susceptibility genes in West Africans: the Africa America Diabetes Mellitus (AADM) Study. Diabetes. 2004; 53:838–841. [PubMed: 14988271]

38. An P, Freedman BI, Rich SS, Mandel SA, Arnett DK, Myers RH, et al. Quantitative trait loci on chromosome 8q24 for pancreatic beta-cell function and 7q11 for insulin sensitivity in obese nondiabetic white and black families: evidence from genome-wide linkage scans in the NHLBI Hypertension Genetic Epidemiology Network (HyperGEN) study. Diabetes. 2006; 55:551–558. [PubMed: 16443794]

39. Waters KM, Stram DO, Hassanein MT, Le Marchand L, Wilkens LR, Maskarinec G, et al. Consistent association of type 2 diabetes risk variants found in Europeans in diverse racial and ethnic groups. PLoS Genet. 2010; 6:e1001078. [PubMed: 20865176]

40. Speliotes EK, Willer CJ, Berndt SI, Monda KL, Thorleifsson G, Jackson AU, et al. Association analysis of 249,796 individuals reveal 18 new loci associated with body mass index. Nat Genet. 2010; 42:937–948. [PubMed: 20935630]

41. Heid IM, Jackson AU, Randall JC, Winkler TW, Qi L, Steinthorsdottir V, et al. Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. Nat Genet. 2010; 42:949–960. [PubMed: 20935629]

42. Ren D, Zhou Y, Morris D, Li M, Li Z, Rui L. Neuronal SH2B1 is essential for controlling energy and glucose homeostasis. J Clin Invest. 2007; 117:397–406. [PubMed: 17235396]

Table 1

Characteristics of the sample by gender and T2D status.

Variable	Gender	T2D Status	N	Mean	SD	Minimum	Median	Maximum
Age (yrs)	Male	Affected	388	54.12	11.90	19	54	92
		Unaffected	109	50.33	16.35	18	49	90
	Female	Affected	778	54.48	12.10	20	55	96
		Unaffected	166	51.06	15.60	20	51	95
BMI(kg/m^2)	Male	Affected	378	30.58	6.01	16.75	29.89	55.27
		Unaffected	109	28.31	6.21	17.86	27.77	55.90
	Female	Affected	753	34.43	7.97	16.84	33.30	64.51
		Unaffected	155	33.03	7.91	17.28	32.65	55.93
WHR	Male	Affected	319	0.9745	0.0778	0.7899	0.9682	1.3833
		Unaffected	89	0.9199	0.0730	0.7714	0.9148	1.2595
	Female	Affected	701	0.9346	0.1014	0.5437	0.9261	1.3731
		Unaffected	136	0.8785	0.0936	0.6647	0.8725	1.2738

Table 2

Univariate lod scores > 2.07 (suggestive) for T2D and, at the same location, nominal P-valuestesting QTL effects (q^2_2) and pleiotropy with T2D (ρ_q) for BMI and WHR.

Chromosome	Position[1] (Mb)	Nearest SNP	Lod Score[2]	BMI[3]		WHR[3]	
				q^2_2	ρ_q	q^2_2	ρ_q
1	18 (17–19)	rs477558	2.37	0.0737	0.791	**0.000343**	**0.0106**
2	62 (61–65)	rs1919481	**3.58**	0.0708	0.142	0.0588	0.764
2	84 (77–102)	rs981525	**3.57**	0.160	0.548	**0.00221**	0.410
2	115 (113–117)	rs400960	**4.73**	0.120	0.921	**0.0166**	0.308
2	238 (237–240)	rs1198823	*3.04*	0.0463	0.0925	**0.0000257**	**0.000191**
7	24 (14–29)	rs1469000	2.61	0.103	0.206	0.105	0.210
7	67 (54–73)	rs956523	**3.77**	0.0955	0.202	0.0569	0.114
11	120 (119–122)	rs1073636	*3.00*	0.085	0.423	0.159	0.322
13	28 (26–30)	rs535534	**4.99**	**0.000375**	**0.00269**	**0.00639**	**0.0128**
16	30 (26–47)	rs11901	2.94	0.0638	0.466	**0.000722**	**0.00443**
20	57 (56–59)	rs2208087	2.96	**0.00766**	**0.0153**	0.0647	0.151
22	37 (27–40)	rs760519	2.27	0.0396	0.0793	**0.0103**	**0.0206**

[1] Megabases from Build 37.1 (1-lod drop support interval).

[2] Significant (>3.29, bold) and near-significant (>3.00, italics) univariate lod scores.

[3] For q^2_2, significant (<0.025, bold) and near-significant (<0.05, italics) P-values. For ρ_q, significant (<0.05, bold) and near-significant (<0.1, italics) P-values.

Table 3

Univariate lod scores > 2.07 (suggestive) for either WHR or WHR adjusted for BMI (WHRBMI) and, at the same location, nominal P-values testing QTL effects (q^2_2) for and pleiotropy (ρ_q) with T2D.

Chromosome	Position[1] (MB)	Nearest SNP	Lod Score[2]		T2D[3]	
			WHR	WHRBMI	q^2_2	ρ_q
1	29 (24–32)	rs8559	2.16	1.44	*0.0829*	0.176
2	81 (79–88)	rs1457342	2.15	*3.04*	**0.000600**	0.359
2	235 (234–238)	rs869214	2.90	**3.60**	**0.000185**	**0.00136**
3	152 (148–159)	rs325762	1.49	2.73	0.283	0.663

[1] Position of the higher lod score for either WHR or WHRBMI in megabases from Build 37.1 (1-lod drop support interval).

[2] Significant (>3.29, bold) and near-significant (>3.00, italics) univariate lod scores.

[3] For WHR or WHRBMI whichever had the higher lod score. For q^2_2 and ρ_q, significant (<0.05, bold) and near-significant (<0.1, italics) P-values.

J Hum Genet. Author manuscript; available in PMC 2012 January 01.