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A QTL for genotype by sex interaction for anthropometric measurements in Alaskan Eskimos (GOCADAN study) on chromosome 19q12-13

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Abstract

Variation in anthropometric measurements due to sexual dimorphism can be the result of genotype by sex interactions (G×S). The purpose of this study was to examine the sex-specific genetic architecture in anthropometric measurements in Alaskan Eskimos from the Genetics of Coronary Artery Disease in Alaska Natives (GOCADAN) study. Maximum likelihood based variance components decomposition methods, implemented in SOLAR, were used for GxS analyses. Anthropometric measurements included BMI, waist circumference (WC), waist/height ratio, percent body fat (%BF) and subscapular and triceps skinfolds. Except for WC, mean values of all phenotypes were significantly different in men and women ($p < 0.05$). All anthropometric measures were significantly heritable ($p< 0.001$). In a preliminary analysis not allowing for G×S interaction, evidence of linkage was detected between markers D19S414 and D19S220 on chromosome 19 for WC (LOD = 3.5), %BF (LOD = 1.7), BMI (LOD = 2.4), WHtR (LOD = 2.5), subscapular (LOD = 2.1) and triceps skinfolds (LOD = 1.9). In subsequent analyses which allowed for G×S interaction, linkage was again found between these traits and the same two markers on chromosome 19 with significantly improved LOD scores for: WC (LOD = 4.5), %BF (LOD = 3.8), BMI (LOD = 3.5), waist/height ratio (LOD = 3.2), subscapular (LOD = 3.0) and triceps skinfolds (LOD = 2.9). These results support evidence of a G×S interaction in the expression of genetic effects resulting in sexual dimorphism in anthropometric phenotypes and identify the chromosome 19q12-13 region as important for adiposity-related traits in Alaskan Eskimos.

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Author contributions:
VSV and AGC performed or supervised all aspects of the statistical analyses and were helped by HHHG, SL, VPD, JB and SAC. KH and SAC were responsible for the 10cM STR genotyping. JGU, SL, and CRW helped with the recruitment, data entry and preparation of the manuscript. SOE, RBD, RRF, JWM, BVH and AGC are responsible for the execution of the study and contributed to the preparation of the manuscript.

Disclosure statement:
Authors have no conflict of interest

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Keywords

Abdominal obesity; Adiposity; Body composition; Linkage

Introduction

Alaskan Eskimos have been a genetically isolated population who until recent years followed a traditional lifestyle and diet, and had low rates of coronary artery disease. As late as 1965, mortality rates due to cardiovascular disease (CVD) were lower in Eskimos than in Whites in the United States (1). Since then, however, there have been many changes in diet and lifestyle of this population accompanied by a slowly increasing CVD mortality rate. This recent increase in CVD may, in large part, be attributed to the increasing availability of westernized diets along with a reduction in physical activity (2,3).

A key risk factor for CVD is abdominal obesity (4). Abdominal obesity is a major indicator of upper body fat accumulation. Increased waist circumference (WC), an important measure of abdominal obesity, is associated with several metabolic abnormalities (5). Greater visceral fat was associated with increased coronary lesions in two studies conducted in male adolescents and women < 50 years of age (6,7). In another study, WC and waist-hip ratio were independently associated with the risk of coronary heart disease in women (8). Increase in upper body fat is also associated with increased turnover of free fatty acids (9) which in turn contributes to defects in glucose metabolism leading to type 2 diabetes, dyslipidemia, hypertension, and gall bladder disease in addition to CVD.

The pattern of body fat distribution is greatly influenced by sexual dimorphism. Men tend to have more of an abdominal pattern of fat deposition, in contrast to women who tend to accumulate less fat in the abdominal region; even though the total amount of fat is greater in women than men (10). This disparity can be attributed, to a great extent, to the differences in reproductive biology (11). Given the differences in body fat distribution and the relative risk associated with related-metabolic disorders among the sexes (12,13), it is important to investigate the influence of sexual differences on genetic patterns of anthropometric measurements.

To understand the difference in sex-specific genetic architecture of anthropometric measurements we used a genotype by environment (GxE) interaction model. The GxE model can result in the same genotype giving rise to two different phenotypes in two different environments. The hormonal differences between men and women can be considered as two different environments. Genotype by sex (GxS) interaction can result in differential effects on the variation in the same trait in men and women. Thus our aim was to investigate the sex-specific genetic differences in anthropometric measurements in Alaskan Eskimos using a GxS interaction model.

Methods

Study design

The GOCADAN study recruited 1,214 individuals (over 18 years of age) from villages in the Norton Sound region of Alaska (14,15). The study population were members of multigenerational families, primarily Inupiat Eskimos. The average participation was 82.6 % in seven of the nine villages participating in the study. Of the total participants, 1,151 belong to the same extended pedigree. They are linked by marriage/matings within and between villages. All participants had a baseline examination. Diet, physical activity and medical history were recorded using a standardized interview protocol. Participants attended clinics

for a blood draw following an overnight 12-hour fast. Blood was drawn by venipuncture and samples were stored in aliquots at −80 C for phenotypic analysis and DNA extraction. Physical examinations were performed along with electrocardiogram and carotid artery scans. Details of the study design, recruitment and methods have been reported previously by Howard et al (14) and Ebbesson et al (15). This study was approved by the Institutional Review Boards from all participating institutions and informed consent was obtained from all participants.

Demographic and phenotypic data

Standard demographic and genealogical data were collected during the surveys and included names, genders, dates, and places of birth, current home of the participant and his/her spouse and first degree relatives of all household members. Anthropometric measurements included height, weight, skinfolds and WC. Height was measured to the nearest quarter inch while the participant was standing, using a vertical mounted ruler; weight was determined to the nearest tenth of a pound, using a scale (Detecto, model 683-P, Cardinal Scale Mfg. Webb City, MO). Skinfolds (subscapular and triceps) were measured to the nearest millimeter with a Lange caliper. The subscapular measurement was taken 1 cm inferior to the angle of the right scapula while the participant was standing with shoulders relaxed and arms hanging loosely at his/her sides. The triceps measurement was taken directly over the right triceps muscle, halfway between the acromial and olecranon processes, with the arms hanging comfortably at the participant's side. WC was measured at the level of the umbilicus with the subject in a supine position. Body mass index (BMI) was computed by dividing weight in kilograms by height (meters) squared. Waist-height ratio was calculated by dividing WC (cm) by height (cm).

Genotypic data

mean were removed and the remaining traits were transformed by inverse normalization prior to analysis, to meet assumptions of normality.

Bivariate genetic analysis—Phenotypic, genetic and environmental correlations were calculated between plasma FAs and other adiposity-related traits as summarized by the following model:

where h_1^2 andh_2^2 are heritabilities of the two phenotypes being studied, and rho_G and rho_E are the additive genetic and environmental correlations between the traits, respectively(21).

To test whether the genetic correlation is significantly different from zero, a model in which all parameters were estimated was compared with a model in which the genetic correlation was constrained to zero. The LRT in this case is distributed as a χ^2 with 1 d.f. To test for complete pleiotropy between the two traits, a model in which the genetic correlation was constrained to one was compared with a model in which all parameters were estimated. Since the null in this case lies at a boundary, the LRT is distributed as a 50:50 mixture of a point-mass at 0 and a χ^2 with 1 d.f. Evidence of pleiotropy (a commonset of genes influencing more than one trait) was indicated bya genetic correlation significantly different from 0.

Genotype by sex interaction—To examine the sex-specific genetic architecture in anthropometric measurements, we first tested the GxS interaction in a basic polygenic model (not including linkage component). A variance components decomposition method was used to estimate the heritability. This method is implemented in the software package SOLAR, which has been described in detail previously (19). The approach for GxS interaction is an

effects at a quantitative trait locus (QTL). In this case, the LRT is distributed as a χ^2 with 1 d.f. We term this type of interaction QTL GxS interaction. All logarithm of odds (LOD) scores estimated under this model were corrected for increased degrees of freedom relative to the standard model. To verify our linkage results, we determined empirical LOD scores which are computed by multiplying the observed LOD score by a correction constant. In SOLAR, a correction constant was estimated by regressing the expected LOD scores on the observed simulated LOD scores (22,23)

RESULTS

Descriptive statistics

A total of 1,214 individuals (men = 537, women = 677) were included in these analyses. Women had higher BMI, waist-height ratio, percent body fat and skinfold measurements as compared to men ($p < 0.001$). WC was not significantly different between the sexes (Table 1).

Heritabilities of anthropometric measurements

The pedigrees included in the analyses for these anthropometric traits ranged between 315 and 325. All anthropometric measurements were significantly heritable and their heritabilities ranged from 0.48 to 0.58. The highest heritability was obtained for subscapular

Sex-specific linkage analysis

Because we detected polygenic GxS interaction effects, we tested whether there were any QTL GxS interaction effects on anthropometric traits. We found that QTL effects, all clustering around the same location on chromosome 19, were significantly different between the two sexes (variances due to QTLs) for all measured anthropometric traits (Table 4). Due

were obtained for these traits in a study conducted in non-Hispanic Whites and African-Americans from the HyperGEN study (10). They also found significant GxS interaction as well as separate QTLs for adiposity measures in men and women. We replicated this in the sense that we found separate QTLs for men and women. The significant GxS interactions complement our sex-specific findings.

We conducted a genome-wide scan for detecting QTLs that regulate sex-specific architecture for these traits. We found a region on chromosome 19q12-p13 which harbored QTLs for all these anthropometric traits in both standard and QTL GxS interaction models. Important and relevant candidate genes in this region are transforming growth factor-beta 1 (*TGFB1*), glycogen synthase 1-muscle (*GYS1*), hormone sensitive lipase (*LIPE*), apolipoprotein E (*APOE*), gastric inhibitory polypeptide receptor (*GIPR*) and lipolysis-sensitive lipoprotein receptor (*LSR*). The peptides expressed by these genes are generally associated with growth and differentiation (32) or clearance of very low density lipoproteins and chylomicron remnants (33), insulin and glucocorticoid metabolism (34), mobilization of free fatty acids from adipose tissue (35) and lipid transporter activity and clearance of dietary triglycerides (36).

Association of polymorphisms in the above mentioned genes with obesity-related anthropometric traits has been reported. Variants in *TGFB1* have been associated with abdominal obesity and BMI (37). Similarly, variants in *APOE* gene have been associated with percent fat mass, BMI and waist circumference (37). To check whether the *APOE* gene variants in this region might be responsible for the linkage signal, we analyzed the phenotypes using *APOE* alleles, e2, e3, e4 as covariates. These alleles were not significant therefore could not be used in the final model, therefore indicating that the strength of the linkage signal is not explained by theses alleles. Body composition measures have been consistently associated with polymorphisms in the hormone sensitive lipase gene (*LIPE)* (38). Knockout animal studies for *LIPE* have shown reduced abdominal fat mass and resistance to diet-induced obesity (39). In addition, this region has been associated with obesity-related traits in genome-wide linkage studies (40). Bell et al (41) found a QTL in this region that was associated with severe obesity (BMI > 35) in French Caucasians.

Other QTLs that were found in this region are for triglycerides and adiposity (42), development of type 2 diabetes in Dutch population (43) and blood pressure in a Nigerian population (44).

In summary, this study provides strong evidence of GxS interaction on anthropometric measurements in Alaskan Eskimos. In addition to the formal demonstration of GxS interaction effects, we also found a QTL on chromosome 19q12-q13.3 that may have strong differential effects on the anthropometric measurements in men and women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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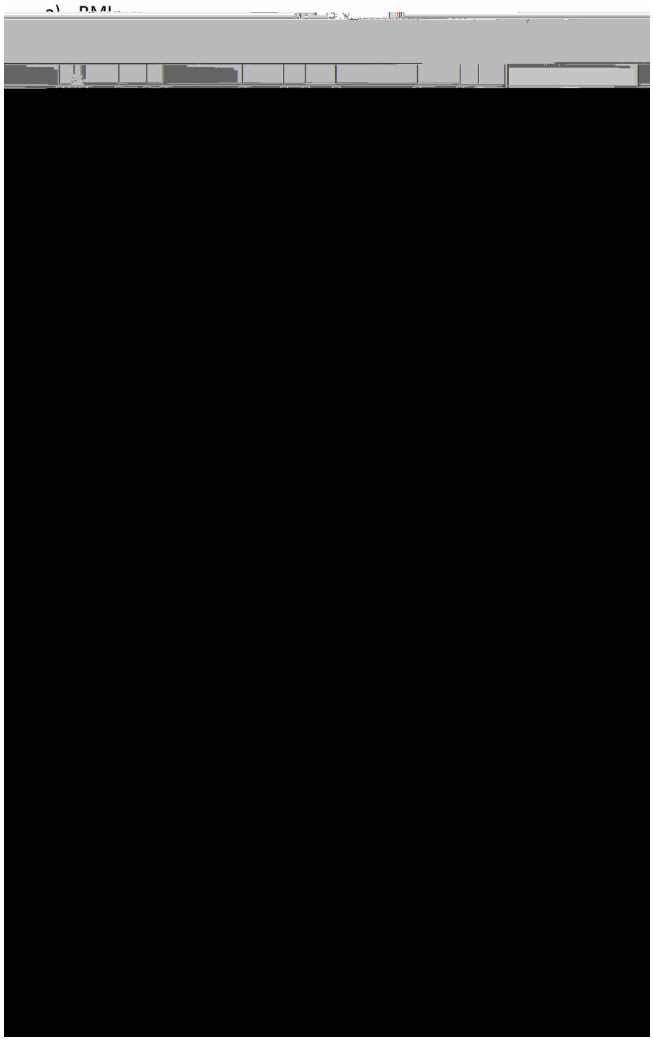

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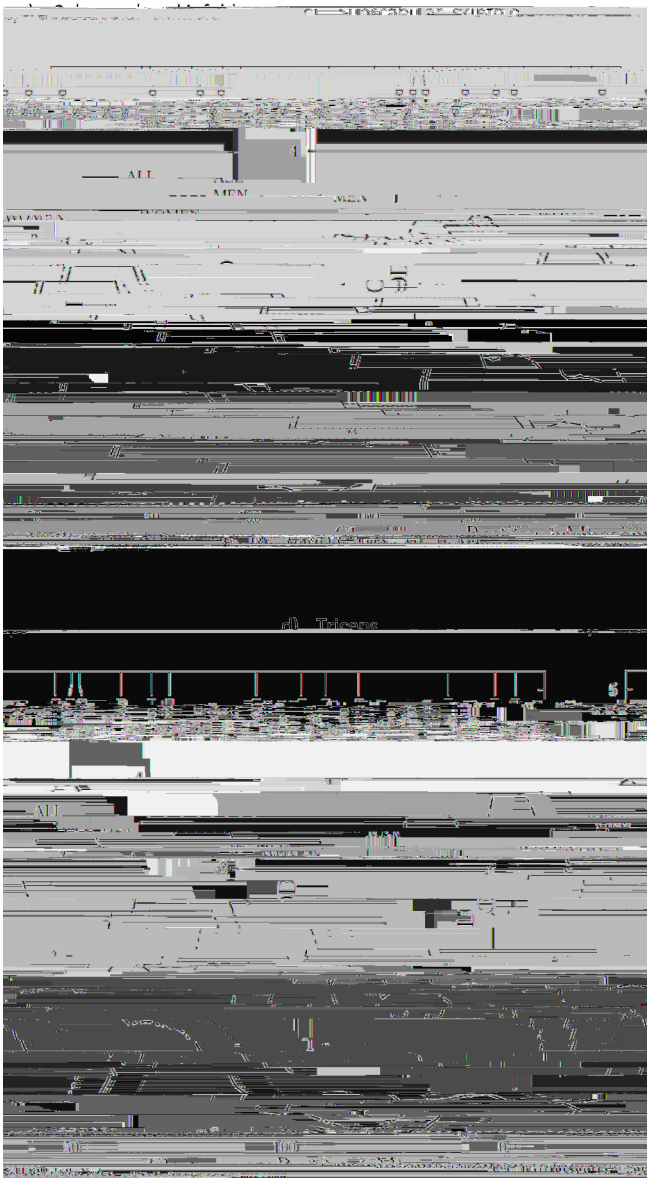

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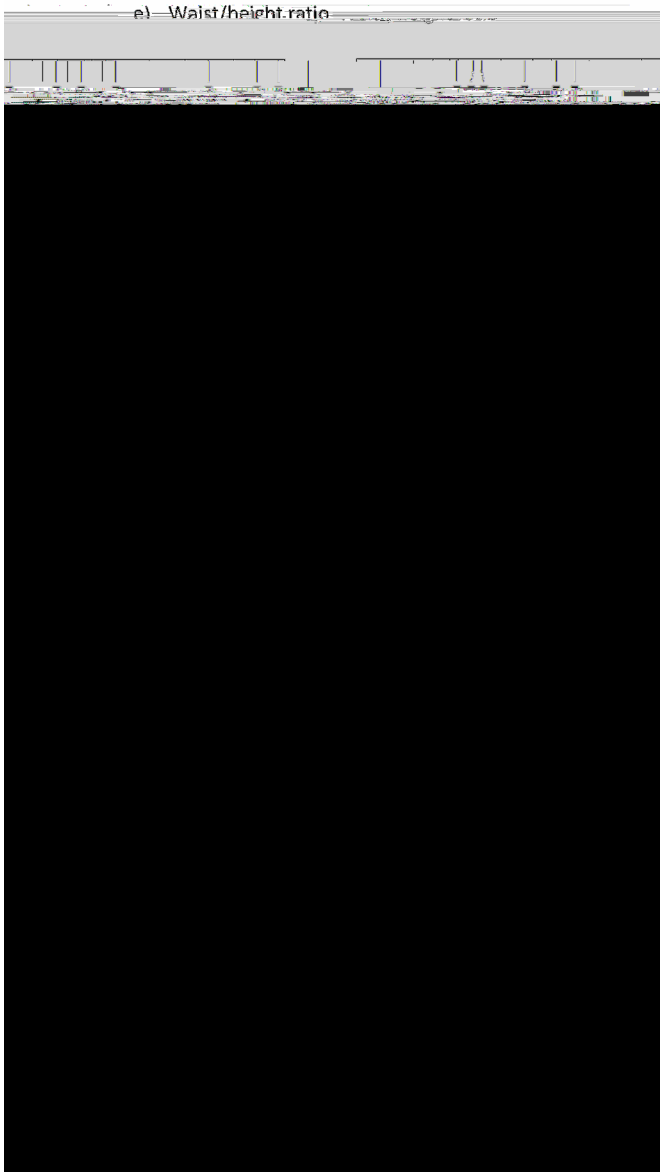

Figure 1.
Multipoint linkage analysis of anthropometric measurements (stratified by sex) on chromosome 19*. X axis represents chromosomal position in cM and Y axis represents strength of the signal via LOD score

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Table 2

Heritabilities of anthropometric traits

	All		Men		Women	
Trait	**h^2 (SE)**	**p value**	**h^2 (SE)**	**p value**	**h^2 (SE)**	**p value**
BMI (kg/m2)	0.55 (0.07)	1.9×10^{-17}	0.49 (0.15)	3.7×10^{-4}	0.69 (0.12)	1.1×10^{-9}
Waist circumference (inches)	0.55 (0.07)	2.3×10^{-16}	0.67 (0.16)	3.9×10^{-5}	0.56 (0.12)	1.0×10^{-7}
Waist/height ratio	0.53 (0.08)	4.2×10^{-15}	0.62 (0.16)	1.1×10^{-4}	0.56 (0.12)	5.0×10^{-7}
Body fat (%)	0.56 (0.07)	3.4×10^{-17}	0.54 (0.16)	2.6×10^{-4}	0.66 (0.12)	2.4×10^{-9}
Subscapular skinfold	0.58 (0.07)	1.7×10^{-19}	0.51 (0.17)	1.5×10^{-3}	0.70 (0.11)	1.4×10^{-12}
Triceps skinfold	0.48 (0.07)	3.7×10^{-14}	0.36 (0.16)	0.010	0.50 (0.11)	2.0×10^{-7}

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Table 3

Genetic and phenotypic correlations between the anthropometric measurements

Phenotype1	Phenotype2	rhog (SE)	p value	rhop (SE)	p value
BMI	Waist circumference	0.95 (0.02)	4.9×10^{-16}	0.91 (0.06)	1.0×10^{-30}
	Waist/height ratio	0.96 (0.01)	1.6×10^{-15}	0.92 (0.06)	1.0×10^{-30}
	Percent body fat	0.91 (0.02)	2.2×10^{-15}	0.89 (0.03)	1.0×10^{-30}
	Subscapular skinfold	0.87 (0.03)	1.3×10^{-15}	0.81 (0.04)	7.4×10^{-21}
	Triceps	0.80 (0.05)	5.9×10^{-12}	0.71 (0.05)	1.8×10^{-14}
Waist circumference	Waist/height ratio	0.95 (0.10)	3.3×10^{-14}	0.96 (0.05)	1.0×10^{-30}
	Percent body fat	0.95 (0.02)	4.7×10^{-16}	0.89 (0.03)	1.0×10^{-30}
	Subscapular skinfold	0.88 (0.04)	1.9×10^{-15}	0.80 (0.02)	4.7×10

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Table 4

Summary of the GxS interaction for anthropometric traits

	GxS Interaction		QTL specific effects
Trait	**σgM = σgW p value**	**ρ*G*(M,W) = 1 p value**	**σqM = σqW p value**
BMI	0.004	0.26	0.000175
Waist circumference	0.30	0.29	0.000273
Waist/height ratio	0.076	0.37	0.000257
Percent fat	0.30	0.39	0.008207
Subscapular skinfold	0.01	0.12	0.d000567
Triceps	0.035	0.5	0.000883

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Table 5

Sex-specific linkage results for anthropometric measurements used in this study

	Peak LOD score/Chromosome (location in cM)		
Phenotype	**Men**	**Women**	**All**
BMI	1.5/9 (121)	4.5/19 (61)	2.4/19 (66)
Waist circumference	1.9/8 (109)	4.8/19 (63)	3.5/19 (66)
Waist/height ratio	1.9/8 (108)	3.8/19 (65)	2.5/19 (66)
Percent body fat	1.8/7 (25)	5.0/19 (61)	1.7/19 (69)
Subscapular skinfold	1.8/9 (101)	3.3/19 (61)	2.1/19 (69)
Triceps	2.3/9 (99)	4.0/19 (61)	1.9/19 (62)