Insulin-Like Growth Factor Pathway Polymorphisms Associated with Body Size in Hispanic and Non-Hispanic White Women

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Abstract

Polymorphisms affecting insulin-like growth factors (IGF), their binding proteins (IGFBP), insulin receptor substrates (IRS), and other IGF regulatory molecules may affect growth, obesity, and obesity-related diseases, including cancer. The objective of this study was to better describe the associations between several IGF pathway variants and body size. Hispanic (n = 462) and non-Hispanic White (n = 1,702) women were recruited as controls in collaborative population-based case-control studies in Arizona, New Mexico, Colorado, Utah, and California. Body size measurements were taken by trained interviewers; genotypes were determined for the *IGF1* CA repeat, the *IGFBP3* −202 C > A substitution, the *IRS1* G972R and *IRS2* G1057D substitutions, and the vitamin D receptor (*VDR*) *Bsm*I and *Fok*I polymorphisms. Two associations were observed that were consistent in both Hispanics and non-Hispanic Whites: IGF1 CA repeat alleles of length other than 19 were associated with higher mean waist-to-hip ratios (WHR), P = 0.01, and women who carried an *IGFBP3* A allele, compared with women with the CC genotype, more often reported high birthweight (odds ratio, 1.9; 95% confidence interval, 1.1-3.2). We observed trends for associations between *IGFBP3* A allele and taller height, *IRS1*R allele, and smaller WHR, and *VDR Fok*I ff genotype and larger WHR; each of these trends was present in only one ethnic group, and heterogeneity of effect by ethnicity was detected. These results provide evidence that IGF pathway polymorphisms have functional effects on growth and central obesity and indicate that genotype-phenotype relationships are ethnic specific. (Cancer Epidemiol Biomarkers Prev 2005;14(7):1802–9)

Introduction

Insulin-like growth factor I (IGF-I) is a regulatory molecule that responds to growth hormone signaling and affects cell proliferation and apoptosis (1). Circulating IGF-I influences growth, weight gain, body fat distribution, and risk of obesity-related diseases including cancer (2). Genetic polymorphisms that affect IGF-I and other molecules in IGF signaling pathways, including the binding protein IGFBP3, the insulin receptor substrates (IRS), and the vitamin D receptor (VDR), are hypothesized to influence cancer risk through a mechanism of altered IGF signaling. Whereas some studies have reported associations between these polymorphisms and growth or obesity, the functional consequences of common polymorphisms in IGF pathway genes are not yet well understood.

A dinucleotide (CA) tandem repeat polymorphism is present in the *IGF1* promoter region (3); the most common allele contains 19 repeats. The 19/19 genotype was reported to be associated with lower concentrations of circulating IGF-I (4). Other studies, however, have found no association or a reversed association between *IGF1* genotype and serum IGF-I levels (5-9). Based on studies in European and North American White populations, the CA repeat polymorphism has been reported to be associated with differences in body size at birth (10), percent body fat (11), abdominal visceral fat (11), and height (5, 8). Associations with and breast (12, 13) and prostate cancers (14-16) have been investigated, with inconsistent results.

IGFBP3 is the predominant binding protein of circulating IGF-I, and serum concentrations of IGFBP3 are predictive of risk of some cancers (2). IGFBP3 influences IGF-I signaling by modifying the amount of free IGF-I available to interact with receptor, and, in addition, seem to influence cell growth through other mechanisms. A single nucleotide polymorphism in the promoter region of the *IGFBP3* gene, −202 C > A, was reported to be associated with higher promoter activity *in vitro* (17). Presence of the A allele has consistently been associated with higher serum IGFBP3 levels (17-20) in studies in Caucasian and Asian populations. The distribution of *IGFBP3* C −202A genotypes was observed to differ according to height, with the AA genotype overrepresented in subjects with short stature (17). The *IGFBP3* −202 C > A single nucleotide polymorphism has been investigated as a candidate cancer susceptibility polymorphism (19-21).

Insulin receptor substrates 1 and 2 are important signaling molecules in tissues containing insulin or IGF receptors. Genetic variants in *IRS1* and *IRS2* have been examined in relation to obesity, birthweight, noninsulin-dependent diabetes mellitus, glucose tolerance, insulin sensitivity, and diabetes in populations of European and Native American heritage (22-33). A common *IRS1* variant is a single nucleotide polymorphism that introduces an amino acid substitution (glycine to arginine) at codon 972, affecting association with the insulin receptor *in vitro* (34). The *IRS2* gene contains a polymorphism encoding a glycine-to-asparagine change at codon 1057, and functional significance of this variant has been suggested due to its reported association with obesity (27, 30).

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Single studies have reported evidence for associations between the *IRS1* G972R and *IRS2* G1057D variants and colon (35) and prostate (36) cancer risk, whereas another found no association with familial breast cancer (37).

Vitamin D has a marked antiproliferative effect on cancer cells *in vitro* and is thought to be protective against cancer *in vivo* (38). One mechanism for vitamin D's effect on cell proliferation is modulation of IGF signaling via VDR-mediated stimulation of IGFBP synthesis (39-41). Therefore, inherited polymorphisms affecting the VDR can be hypothesized to affect IGF signaling, and in turn growth, obesity, and obesity-related disease. A group of polymorphisms in the 3′ untranslated region of the *VDR*, including one detected by the *Bsm*I restriction enzyme, exhibit close linkage disequilibrium (42). *In vitro* studies have not detected functional differences associated with presence of the *VDR* untranslated region polymorphisms (43). However, multiple studies are supportive of an association between the *VDR* variants and bone density (reviewed in ref. 44), providing evidence of a biological effect *in vivo*. A polymorphism detected by the *Fok*I restriction enzyme alters a translation initiation site (45). The *VDR* polymorphisms have been reported to influence growth and height in European and Australian Caucasian children (46, 47). Several studies have reported that the untranslated region and/or the *Fok*I polymorphisms are associated with cancer risk (48-54).

In summary, polymorphisms affecting IGF pathway genes have been the subject of a number of reports assessing associations between genotype and cancer. Other studies, appearing for the most part in the cardiovascular disease literature, have reported that the same polymorphisms affect growth and/or obesity. Understanding the functional effects of a polymorphism is critical for evaluating of the biological plausibility of association between genotype and cancer and for interpreting the role that the variant may play in disease pathways. The existing reports of associations between IGF pathway variants and body size have limitations. Some of these studies have been based on subjects with extreme phenotypes (e.g., small-for-gestational age birthweights or diabetic patients with severe obesity). In several studies, all study participants were White. Finally, certain associations have been reported in only one study and require replication. The goal of the present study is to better characterize the functional consequences of several polymorphisms in genes involved in IGF signaling by evaluating associations with anthropometric measures that describe *in utero* growth (birthweight), childhood growth (height), overweight as an adult (body mass index, BMI, and waist), and central distribution of body fat (waist circumference and WHR). We assessed these relationships in a study population that represents two ethnic groups, randomly sampled from women in five Southwestern U.S. states.

Patients and Methods

Study Population. We report on women ages 25 to 79 years who participated as controls in collaborative case-control studies of cancers of the colon (interviewed 1992-1995; ref. 55), rectum (interviewed 1997-2002; ref. 56), and breast (interviewed 1999-2004). Subjects ages ≤64 years were randomly selected from computerized drivers' license lists in New Mexico and Utah and from commercially available lists in Arizona and Colorado; subjects ages ≥65 years were selected from Center for Medicare Studies (formerly Health Care Finance Administration) lists in all of these states. Membership lists of the Kaiser Permanente Northern California health care system were used as a sampling frame in northern California. Details of the procedures for recruitment of participants have been described (55-57); recruitment and interviewing was conducted in accordance with human subjects' research protocols approved at each responsible institution. By design, control groups were frequency matched to the age distributions of incident cancer cases, and, in the breast cancer study, Hispanic women had a higher probability of being sampled. Hispanic ethnicity was initially identified by surname using the Generally Useful Ethnic Search System program (58), or from an ethnicity code in the Center for Medicare Studies database. Final classification of ethnicity was based on self-report at interview. Response rates among controls in the colon and rectal cancer studies were 64% and 65%, respectively, as reported elsewhere (56, 59). Final response rates for the breast cancer study can not be calculated because interviews are ongoing; response rates to date in Utah seem similar to the other studies (57).

Anthropometric and Interview Data. Anthropometric measurements were made by a study staff member. All three studies used the same measurement protocol, with the subject wearing light clothing and without shoes. Weight was measured using the TraveLite Portable Digital Scale, placed on a flat, uncarpeted surface, and recorded to the nearest 0.5 lb. Height was measured using the Road Rod Stadiometer, consisting of a vertical board with an attached metric rule and a horizontal headboard lowered to the most superior point on the head. Waist and hip circumference measurements were taken using a flexible tape, with the participant standing, and were recorded to the nearest 0.5 inch. Waist was measured at the smallest point between the 10th rib and the iliac crest over bare skin or minimal clothing. Hip circumference was measured at the maximum protrusion of the buttocks. Two measurements of weight, height, and waist and hip circumferences were made; if two measurements differed by >1 lb or 0.5 inch, a third measurement was obtained. The average was used for data analysis.

Each subject in the breast cancer study was asked to report her weight at birth; if a women was not able to report her birthweight in pounds or kilograms, she was asked whether she weighed ''less than 5.5 lbs or about 2.5 kilos'', or ''9 lbs or more or about 4 kilos'' at birth. The questionnaires for all three studies included a diet history questionnaire (adapted from the CARDIA dietary history; ref. 60). Each participant was asked to identify her race or ethnic background. Women whose response was Hispanic or Latina, White, Caucasian, or non-Hispanic White were included in the present analysis.

Genotyping. Participants were asked to provide a blood sample for DNA extraction; blood was obtained for 77% of interviewed colon cancer study controls and 85% of rectal cancer study controls (35). *IGF1* CA repeat genotypes were determined by PCR amplification using primers *IGF1*-F 5′-GCTAGCCAGCTGGTGTTATT-3′ and *IGF1*-R 5′-ACCACTCTGGGCGAAGGGTA-3′. PCR conditions consisted of a 2-minute denaturation at 94°C followed by 30 cycles at 94°C for 10 seconds, 57°C for 10 seconds, and 72°C for 15 seconds. The products were then sized using an ABI 3700. The most common allele, with a product length of 192 bp, represents 19 CA repeats. The *IGFBP3* −202 C > A substitution was detected by PCR and digestion with the *Alw*21I restriction enzyme (17); alleles containing the restriction site were scored as C, and those not cut by the restriction enzyme contain A. The G-to-A transition in the *IRS1* gene that results in an amino acid change, G972R, was assayed using PCR and digestion of the resulting product with *Bst*NI (22); the absence of the restriction site indicates the G allele, and its presence indicates the R allele. The *IRS2* G1057D polymorphism was detected using a Taqman assay (61) with modifications as described (35). The *VDR Bsm*I and *Fok*I polymorphisms were detected by published PCR and RFLP methods (62, 63) with modifications as described (50). Presence of the *Bsm*I restriction site is represented by ''b'' and absence as ''B''; presence of the *Fok*I restriction site if represented by ''f'' and its absence by ''F.''

Data Analysis. BMI was calculated from height and weight measured at interview using the formula of (weight in kg) / (height in m^2); WHR was calculated as the ratio of waist and hip circumferences.

IGF1 CA repeat alleles were classified according to the presence of the most frequent allele, containing 19 CA repeats, as homozygous 19/19, 19/other, or other/other. Each of the other polymorphisms examined in this study has two alleles, and genotypes were classified as homozygous for the common allele, heterozygous, or homozygous for the variant allele. If the number of subjects in the homozygous variant genotype category was small, it was combined with the heterozygous category for analysis. We compared the allele frequency of each variant allele by ethnicity using a test for difference in proportions.

We evaluated associations between genotypes and anthropometric measures by estimating least squared means of the anthropometric measure in each genotype category from a generalized linear model. Analyses were adjusted for age and study center. BMI was strongly inversely related to height; therefore, models with BMI as outcome were adjusted for height to estimate associations between genotype and BMI independent of height. Similarly, models with WHR as outcome were adjusted for BMI. Further adjustment for total energy intake and total hours of physical activity reported in the interview did not appreciably affect associations.

We assessed trend in anthropometric measures according to number of variant alleles for each genotype by including a variable representing number of variant alleles (0, 1, or 2) as a continuous variable in the linear model. We also transformed anthropometric variables to improve fit to a normal distribution; the results for transformed and untransformed variables were similar; therefore, results based on the original scale of measurement are reported. The linear models were run for Hispanic and non-Hispanic White women separately. Heterogeneity of the association by ethnicity was tested using an interaction term. ANOVA was used to assess the relative contribution of ethnicity and other variables to variability in anthropometrics. For birthweight, we also created categories according to commonly used cut points (birthweights <2.5 kg as low, those ≥4 kg as high) and used a polytomous regression model to calculate the odds ratio for being in the low or high birthweight category compared with normal. SAS 8.2 (SAS Institute, Inc., Cary, NC) was used for statistical analysis.

Results

Anthropometric measures and other characteristics of 462 Hispanic women and 1,702 non-Hispanic White women are described in Table 1. Forty-three percent of Hispanic women and 29% of non-Hispanic White women had BMI values of ≥30 kg/m^2, meeting the criteria for obesity. Hispanic women had lower birthweights and heights, higher BMIs, and larger waists and WHRs than non-Hispanic White women (Table 1), and these differences were significant when age differences between the two samples were taken into account. Because birthweight was included in the questionnaire for the breast cancer study but not the colon and rectal cancer studies, the number of subjects available for analysis of birthweight was smaller than for other analyses. Allele frequencies were significantly different between Hispanics and non-Hispanic Whites for the *IGFBP3* C −202 A, *IRS2* G1057D, and *VDR Bsm*I polymorphisms (Table 2).

Mean values of birthweight did not differ significantly according to genotype within either ethnic group (Table 3). Birthweights were nonsignificantly higher among women who had one or more A alleles at the *IGFBP3* −202 C > A polymorphism than those with the CC genotype. When the two ethnic groups were combined there was limited evidence of a trend (P = 0.07) in birthweight according to number *IGFBP3* A alleles. A categorical analysis of the birthweight data, calculating odds ratios for high and low birthweight categories, provided better statistical power because an additional 295 women who did not state a birthweight in pounds or kg but who reported birthweights of low, normal, or high, could be included. The categorical analysis detected a significant association between high birthweight and *IGFBP3* genotype, with an odds ratio of 1.9 (95% confidence interval, 1.1-3.2) for the AC and AA genotypes compared with CC. The odds ratio for low birthweight for women with AC or AA genotypes was 0.7 (95% confidence interval, 0.5-1.1).

Table 1. Characteristics of Hispanic and non-Hispanic White women participating as controls in three population-based studies; values are *n* (%) or mean ± SE

	Hispanic	Non-Hispanic White	*P**
Total	462	1,702	
Center			
Arizona	117 (25.3)	194 (11.4)	
California	99 (21.4)	182 (10.7)	
Colorado	50 (10.8)	525 (30.8)	
New Mexico	83 (18.0)	256 (15.0)	
Utah	113 (24.5)	545 (32.0)	
Age	56.0 ± 0.6	60.4 ± 0.3	<0.001
Birthweight†, kg	3.12 ± 0.04	3.23 ± 0.03	0.03
Height, m	1.56 ± 0.003	1.63 ± 0.002	<0.001
BMI, kg/m^2	30.0 ± 0.3	27.5 ± 0.2	<0.001
Waist, cm	92.4 ± 0.7	87.2 ± 0.4	<0.001
WHR	0.843 ± 0.004	0.813 ± 0.002	<0.001

*P values for differences in anthropometric variables by ethnicity are from generalized linear models, controlling for age.
†For birthweight, n = 254 for Hispanics and n = 626 for non-Hispanic Whites.

The *IGFBP3* A allele was associated with greater height (P = 0.003) among Hispanic women (Table 3) but not among non-Hispanic White women, and there was evidence of heterogeneity by ethnicity (P = 0.003) for the association with height. There was no evidence that the other polymorphisms were associated with height.

Mean BMI generally did not differ across genotype categories (Table 4). An exception was an association between the *VDR Bsm*I B allele and lower BMI among Hispanic women. Although there was no evidence of heterogeneity of effect by ethnicity, the mean BMIs among non-Hispanic White women did not show this trend. Waist circumference was highly correlated with BMI in this data set (r = 0.84), and presence of the *VDR Bsm*I B allele was weakly associated with smaller waist among Hispanic women, consistent with the finding for BMI. Overall, there were no significant associations between genotypes and waist circumference.

IGF1 CA repeat alleles of lengths other than 19 were significantly associated with larger WHR values among non-Hispanic White women (Table 4). A similar trend, although nonsignificant was observed in Hispanic women. The P value for trend in association between WHR and *IGF1* genotype in the combined study population, adjusted for ethnicity, was 0.01. The rare *IRS1* 972 R allele was associated with smaller WHR among Hispanic women but not among non-Hispanic White women, with evidence of heterogeneity of effect. Similarly, the *VDR Fok*I genotype was associated with WHR in Hispanic women only, with evidence of heterogeneity of effect.

The mean values of birthweight and height (Table 3) among Hispanic women are smaller than those of non-Hispanic White women with the same genotype, almost without exception. The mean values of BMI, waist, and WHR (Table 4) are higher for Hispanic than non-Hispanic White women in every genotype category. In an ANOVA, the variables with the most explanatory power for the variance in BMI were energy intake,

Table 2. Genotypes and allele frequencies for *IGF1*, *IGFBP3*, *IRS1*, *IRS2*, and *VDR* polymorphisms from population-based samples of Hispanic and non-Hispanic White women

	Hispanic, *n** (%)	Non-Hispanic White, *n** (%)	*P*†
IGF1 CA repeat			
19/19	196 (43.4)	708 (42.1)	0.38
19/other	181 (40.0)	770 (45.8)	
Other/other	75 (16.6)	205 (12.2)	
Other allele frequency	0.37	0.35	
IGFBP3 −202 C > A			
CC	190 (41.3)	494 (29.2)	<0.001
AC	207 (45.0)	833 (49.3)	
AA	63 (13.7)	362 (21.4)	
A allele frequency	0.36	0.46	
IRS1 G972R			
GG	411 (89.5)	1,481 (87.6)	0.21
GR	47 (10.2)	199 (11.8)	
RR	1 (0.2)	10 (0.6)	
R allele frequency	0.05	0.06	
IRS2 G1057D			
GG	160 (34.7)	689 (40.8)	0.007
GD	222 (48.2)	771 (45.7)	
DD	79 (17.1)	228 (13.5)	
D allele frequency	0.41	0.36	
*VDR Bsm*I			
bb	243 (53.3)	593 (35.3)	<0.001
bB	176 (38.6)	811 (48.2)	
BB	37 (8.1)	277 (16.5)	
B allele frequency	0.27	0.41	
*VDR Fok*I			
FF	165 (36.4)	617 (37.3)	0.08
Ff	204 (45.0)	824 (49.8)	
ff	84 (18.5)	214 (12.9)	
f allele frequency	0.41	0.38	

*Some genotype categories do not sum to the total due to missing data.
†*P* values for differences in allele frequencies by ethnicity, from a test for difference in proportions.

age, study center, and race; addition of genotypes to the model did not appreciably reduce the amount of variance attributable to race. For WHR, the most important variables were age, study center, and race; genotypes contributed a larger partial sum of squares for WHR than for BMI, but again, the explanatory value of race was not diminished when genotypes were introduced into the model. Thus, the genotypes investigated in this study do not account for the differences in anthropometric measures between Hispanic and non-Hispanic White women.

Discussion

Among six IGF pathway gene polymorphisms and five anthropometric measures investigated, we found only two associations that were consistent in both Hispanic and non-Hispanic White women: the *IGFI* non-19 CA repeat allele with high WHR, and the *IGFBP3* A allele with high birthweight. We observed trends for associations within one ethnic group for *IGFBP3* A allele and taller height, *IRS1* R allele and smaller WHR, *VDR Bsm*I B allele and lower BMI, and *VDR Fok*I ff genotype and larger WHR. Heterogeneity of effect by ethnicity was detected for three of these trends. Thus, our results provide some support for the interpretation that several IGF-pathway polymorphisms have functional consequences for growth and central obesity. Our analysis indicates that the biological effect of these polymorphisms differs by racial or ethnic group.

The *IGF1* promoter CA repeat polymorphism has previously been reported to be related to both growth and adult body composition. A study of French small-for-gestational age children reported that the longest allele detected in that study population was less likely to be transmitted from parents to small-for-gestational age children (10). Our study relied on adult women's recall of birthweight; therefore, we were not able to classify individuals for the end point of small-for-gestational age. Our data did not reveal any significant trend in birthweight associated with IGF1 genotype. Homozygous carriers of the *IGF1* 19 CA repeat allele have been reported to be taller than subjects with other genotypes (5, 8), but one study reported that the association was limited to men (8). Our results regarding height and *IGF1* genotype were null, in agreement with the previous data reporting no association among women (8). In the present study, there was no association between the *IGF1* CA repeat polymorphism and BMI, consistent with data from previous studies (5, 64). We found a significant trend in the association between presence of *IGF1* non-19 repeat alleles and higher WHR, and the trend was present in both ethnic groups. A study of the *IGF1* CA repeat polymorphism among participants in an exercise intervention reported linkage of the polymorphism with change in fat free mass, an end point that can not be considered in our cross-sectional study (64). The intervention study also found that participants with the *IGF1* 19/19 genotype had lower baseline abdominal visceral fat (11), a finding that is qualitatively similar to our observation of lower WHR in subjects with this genotype. Thus, our data and that from another study provide evidence that carrying an *IGF1* non-19 CA repeat allele affects *IGF1* signaling in a way that results in central distribution of body fat. These results support the biological plausibility of a role for this polymorphism in chronic disease etiology.

We found limited evidence of an association between the *IGFBP3* −202 A variant and higher birthweight. The association was significant in a categorical analysis but only suggestive in the analysis of means, which had less statistical power. To our knowledge, this is the first study to report such an association. An association was observed between the *IGFBP3* A allele and taller stature, but this association was detected in only one ethnic group and was in the reverse direction from the association reported in another study (17). Studies have consistently found that the *IGFBP3* −202 A allele affects concentrations of circulating IGFBP3 (17-20).[6] Our results add to the literature supporting functional effects of this polymorphism.

The *IRS1* variant was not associated with BMI, serum glucose, or insulin in a previous study of a Mexican population (26). A study of Caucasian subjects in Denmark found no association between *IRS1* G972R genotype and birthweight (28). In our population, there was no relationship between *IRS1* G972R genotype and birthweight, height, BMI, or waist. There was an association between the variant allele and WHR among Hispanic women. A previous report indicated linkage between abdominal visceral fat and the *IRS1* locus in a family-based study (29). However, the family study detected this association in White subjects, whereas in our data the association with WHR was present only in Hispanics.

Haplotypes containing the D variant of the *IRS2* G1057D polymorphism were associated with severe obesity among French subjects (27), whereas in our study, there was no indication of an association with BMI, waist, or WHR. Differences between the two studies might be explained by differences in study populations; some of the subjects from the study in France were selected because of the presence of severe obesity and comorbidities, whereas our control subjects represent the normal distribution of overweight and obesity in the general population.

In contrast to the findings of previous studies reporting that *VDR* genotype was related to height among children and

[6] Slattery, submitted for publication.

Table 3. Mean ± SE values of measures of growth among Hispanic and non-Hispanic White women, by *IGF1*, *IGFBP3*, *IRS1*, *IRS2*, and *VDR* genotypes

Genotype	Birthweight, kg		Height, m	
	Hispanic	Non-Hispanic White	Hispanic	Non-Hispanic White
IGF1 CA repeat				
19/19	3.07 ± 0.07	3.23 ± 0.04	1.563 ± 0.005	1.626 ± 0.003
19/other	3.10 ± 0.07	3.24 ± 0.04	1.566 ± 0.005	1.628 ± 0.003
Other/other	3.19 ± 0.12	3.14 ± 0.08	1.566 ± 0.007	1.625 ± 0.005
*P**	0.39	0.62	0.69	0.91
IGFBP3 −202 C > A				
CC	3.05 ± 0.07	3.19 ± 0.05	1.557 ± 0.005	1.628 ± 0.003
AC	3.14 ± 0.07	3.23 ± 0.04	1.568 ± 0.005	1.625 ± 0.003
AA	3.11 ± 0.12	3.29 ± 0.06	1.583 ± 0.008	1.627 ± 0.004
*P**	0.47	0.18	0.003†	0.79
IRS1 G972R				
GG	3.10 ± 0.05	3.23 ± 0.03	1.564 ± 0.004	1.626 ± 0.002
GR or RR	3.10 ± 0.14	3.24 ± 0.07	1.576 ± 0.009	1.630 ± 0.005
*P**	0.99	0.97	0.21	0.42
IRS2 G1057D				
GG	3.21 ± 0.08	3.19 ± 0.04	1.566 ± 0.005	1.628 ± 0.003
GD	3.05 ± 0.07	3.26 ± 0.04	1.563 ± 0.005	1.624 ± 0.003
DD	3.05 ± 0.10	3.27 ± 0.07	1.574 ± 0.007	1.632 ± 0.005
*P**	0.13	0.23	0.53	0.89
*VDR Bsm*I				
bb	3.09 ± 0.06	3.26 ± 0.04	1.563 ± 0.004	1.628 ± 0.003
bB	3.11 ± 0.07	3.19 ± 0.04	1.568 ± 0.005	1.629 ± 0.003
BB	3.19 ± 0.16	3.31 ± 0.07	1.564 ± 0.011	1.618 ± 0.004
*P**	0.55	0.97	0.61	0.06
*VDR Fok*I				
FF	3.07 ± 0.07	3.24 ± 0.04	1.566 ± 0.005	1.628 ± 0.003
Ff	3.05 ± 0.07	3.24 ± 0.04	1.566 ± 0.005	1.626 ± 0.003
ff	3.14 ± 0.09	3.17 ± 0.07	1.562 ± 0.007	1.623 ± 0.005
*P**	0.59	0.44	0.71	0.29

NOTE: Means are adjusted for age and study center. The numbers of subjects by genotype category are shown in Table 2.
*P value from test for trend in anthropometric variable according to number of variant alleles.
†Significant evidence of heterogeneity of genotype effect by race, $P = 0.003$.

adolescents (46, 47), we found no association between *VDR* genotype and height. In our study, there was a lower mean BMI associated with the *VDR Bsm*I B allele and an increased mean WHR among women with the *VDR Fok*I ff genotype but only for Hispanics. To our knowledge, there is no previous report that considered *VDR* genotype and overweight or central body fat.

We detected evidence of heterogeneity of effect by ethnicity for the associations between *IGFBP3* and height, *IRS1* genotype and WHR, and *VDR Fok*I genotype and WHR. In the present analysis, overall, we detected more instances of heterogeneity than situations in which a genotype affected anthropometrics in a consistent manner for the two ethnic groups. Linkage studies have reported that genetic determinants of obesity differ by race or ethnicity (29, 65, 66). Heterogeneity of effect of candidate polymorphisms may indicate that, within each ethnic group, linkage disequilibrium with other functional polymorphisms in the same chromosomal region influences the association. Other differences between ethnic groups in the IGF signaling genes, even genes located on different chromosomes, or differences in environmental factors, could modify the effect of the polymorphisms that we studied and result in heterogeneity of effect. Several studies have reported differences by race and ethnicity in circulating IGF-I and IGFBP3 concentrations (6, 67),[7] lending further support to the idea that genetic control of these pathways differs across racial and ethnic groups. Whereas our data do not suggest that differences in the frequencies of IGF pathway variants explain any of the differences in anthropometrics between Hispanic and non-Hispanic White women, the findings of heterogeneity of effect indicate that associations between IGF pathway allelic variants and disease may also be expected to be race or ethnicity specific. It follows that research results should be presented stratified by race.

For the *IGF-I, IRS1*, and *VDR Fok*I polymorphisms, our data indicate no association with overweight and obesity as measured by BMI but significant trends in association with WHR in at least one ethnic group. These trends were present in models that included BMI as a covariate, indicating that the polymorphisms contribute to the variability in WHR independent of BMI. Elevated WHR is indicative of central deposition of body fat and is more specifically associated with an adverse metabolic profile, and risk of certain chronic diseases, than general overweight as measured by BMI. It is plausible that BMI and WHR could be controlled by different genetic factors. Furthermore, BMI may be more strongly influenced by lifestyle and environment, whereas the tendency for body fat to have a central versus peripheral distribution at a given level of BMI may be more genetically controlled. Cancer epidemiology studies have more often used BMI than WHR as a measure of overweight and obesity. Our findings, that genetic variation in the IGF pathway influences central obesity independent of BMI, suggest the hypothesis that IGF pathway variants may act as effect modifiers of the association between elevated BMI and disease risk.

A strength of the present study is the large population-based sample of female subjects from two ethnic groups available for analysis. Sex hormones influence the insulin and IGF signaling pathways (1), and studies have reported differences between men and women in correlation between circulating IGF-I and anthropometric measures (68, 69), and differences by sex in the association between the *IGFI* CA repeat genotype and anthropometrics (8). In light of these gender differences, it is

[7] Slattery, unpublished data.

Table 4. Mean ± SE values of measures of adult obesity among Hispanic and non-Hispanic White women, by *IGF1*, *IGFBP3*, *IRS1*, *IRS2*, and *VDR* genotypes

Genotype	BMI, kg/m^2		Waist, cm		WHR	
	Hispanic	Non-Hispanic White	Hispanic	Non-Hispanic White	Hispanic	Non-Hispanic White
IGF1 CA repeat						
19/19	29.9 ± 0.5	27.7 ± 0.3	92.2 ± 1.1	86.6 ± 0.6	0.841 ± 0.005	0.802 ± 0.003
19/other	29.5 ± 0.5	27.5 ± 0.2	92.3 ± 1.2	87.0 ± 0.6	0.851 ± 0.005	0.813 ± 0.003
Other/other	29.3 ± 0.8	27.1 ± 0.4	91.8 ± 1.8	85.8 ± 1.1	0.852 ± 0.008	0.808 ± 0.005
*P**	0.48	0.15	0.87	0.82	0.13	0.03
IGFBP3 −202 C > A						
CC	29.6 ± 0.5	27.4 ± 0.3	91.8 ± 1.2	86.6 ± 0.7	0.846 ± 0.005	0.809 ± 0.004
AC	29.4 ± 0.5	27.8 ± 0.2	91.6 ± 1.1	87.3 ± 0.6	0.846 ± 0.005	0.809 ± 0.003
AA	30.7 ± 0.8	27.4 ± 0.3	94.2 ± 1.9	85.7 ± 0.8	0.852 ± 0.008	0.803 ± 0.004
*P**	0.41	0.90	0.41	0.54	0.19	0.17
IRS1 G972R						
GG	29.7 ± 0.4	27.5 ± 0.2	92.3 ± 0.8	86.6 ± 0.5	0.849 ± 0.004	0.808 ± 0.002
GR or RR	29.6 ± 0.9	28.0 ± 0.4	90.3 ± 2.2	88.1 ± 1.1	0.828 ± 0.010	0.807 ± 0.005
*P**	0.94	0.32	0.36	0.17	0.02†	0.92
IRS2 G1057D						
GG	29.4 ± 0.5	27.7 ± 0.3	90.8 ± 1.2	86.9 ± 0.6	0.843 ± 0.005	0.809 ± 0.003
GD	29.8 ± 0.5	27.7 ± 0.2	92.8 ± 1.1	86.7 ± 0.6	0.849 ± 0.005	0.806 ± 0.003
DD	29.7 ± 0.7	27.0 ± 0.4	92.5 ± 1.7	86.3 ± 1.0	0.845 ± 0.007	0.808 ± 0.005
*P**	0.68	0.24	0.31	0.59	0.60	0.63
*VDR Bsm*I						
bb	30.1 ± 0.4	27.6 ± 0.3	93.1 ± 1.0	86.6 ± 0.7	0.848 ± 0.004	0.806 ± 0.003
bB	29.4 ± 0.5	27.5 ± 0.2	91.4 ± 1.2	86.8 ± 0.6	0.845 ± 0.005	0.808 ± 0.003
BB	27.8 ± 1.1	27.5 ± 0.4	88.5 ± 2.5	86.8 ± 0.9	0.840 ± 0.011	0.810 ± 0.005
*P**	0.04	0.80	0.06	0.81	0.46	0.47
*VDR Fok*I						
FF	29.4 ± 0.6	27.4 ± 0.3	91.1 ± 1.3	86.1 ± 0.7	0.840 ± 0.006	0.806 ± 0.003
Ff	29.8 ± 0.5	27.6 ± 0.2	92.2 ± 1.1	87.1 ± 0.6	0.843 ± 0.005	0.811 ± 0.003
ff	29.3 ± 0.7	27.9 ± 0.4	92.5 ± 1.7	87.1 ± 1.1	0.864 ± 0.007	0.800 ± 0.005
*P**	0.99	0.35	0.42	0.23	0.01†	0.77

NOTE: Means are adjusted for age and study center, with BMI also adjusted for height, and WHR adjusted for BMI. The numbers of subjects by genotype are shown in Table 2.

*P value from test for trend in anthropometric variable according to number of variant alleles.

†Significant evidence of heterogeneity of genotype effect by race: IRS1 and WHR, $P = 0.05$; VDR *Fok*I and WHR, $P = 0.03$.

valid to conduct analysis of phenotype in relation to IGF pathway polymorphisms separately for women.

Although our study was population-based, nonparticipation by eligible subjects in randomly selected study samples is always a methodologic concern and can adversely affect representativeness. We believe that our study population is likely to be reasonably representative in terms of anthropometrics and genetic characteristics. The proportion of women who were overweight or obese was similar to the estimated population prevalences among Hispanic and non-Hispanic White women in the United States (70), and genetic polymorphisms such as those examined here are not expected to influence study participation. Thus, our results should not be biased by factors related to study participation and should be generalizable to Hispanic and non-Hispanic White women living in the U.S. Southwest.

The small number of variants examined, one per gene for each of four genes and two for *VDR*, is a potential limitation of our study. Studies of the genetics of obesity traits within families have examined linkage across the whole genome (29, 65, 66, 71). Our study was not intended to achieve the same goals as these family studies. Studies of candidate genes within populations of unrelated individuals can complement family studies by exploring potential high-prevalence, low-penetrance candidate gene variants affecting growth and obesity phenotypes. We focused on the IGF pathway, which is thought to play a role in development of obesity-related cancer. We selected candidate polymorphisms that are common and that had some prior evidence of association with growth or obesity. Recent reports have described multiple polymorphisms and complex haplotype patterns affecting these IGF pathway genes (20, 27, 72). Our results support the idea that genetic variation in IGF pathway molecules has functional consequences on growth and central obesity. Future research should consider additional single nucleotide polymorphisms and haplotypes in these genes in relation to anthropometrics to further define the role of IGF pathway genetic variants in growth and obesity.

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Insulin-Like Growth Factor Pathway Polymorphisms Associated with Body Size in Hispanic and Non-Hispanic White Women

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