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Association and linkage between an insulin-like growth factor-1 gene polymorphism and fat free mass in the HERITAGE Family Study

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OBJECTIVE: To investigate the relationship between a DNA microsatellite marker in the insulin-like growth factor-1 (IGF-1) gene and body composition phenotypes before and following exposure to 20 weeks of aerobic exercise training in the HERITAGE Family Study.
DESIGN: A controlled intervention study: fat mass (FM), percentage body fat (%FAT), fat free mass (FFM), body mass index (BMI) and abdominal visceral fat (AVF) at baseline (B) and in response to training (Δ = post minus pre-training value) were measured. Association and sib-pair linkage studies were undertaken.
SUBJECTS: A maximum of 502 Caucasian individuals (99 families; 190 parents and 312 adult offspring).
MEASUREMENTS: The polymorphism was typed by polymerase chain reaction and DNA sequencer. The body composition phenotypes were determined from the underwater weighing method, and AVF was assessed by computerized tomography scan.
RESULTS: 11 alleles were found: the lengths ranged from 189 to 209 base pairs (bp), and the frequency of the most common allele, 189 bp, reached 0.71. In association studies, significant differences for B-FM, B-FFM and B-%FAT among the three genotypes (189 bp homozygotes, heterozygotes and non-carriers) were detected. The B-FM for 189 bp homozygotes was 19.7 ± 0.6 kg, but 21.6 ± 0.7 and 21.3 ± 1.5 kg for the 189 bp heterozygotes and the non-189 bp carriers respectively ($P = 0.03$ after adjustment for age, sex and generation). Differences among the three genotypes were also observed for B-%FAT (25.9 ± 0.5 versus 27.4 ± 0.6 and 26.6 ± 1.2 kg; $P < 0.05$) and B-FFM (53.7 ± 0.4 versus 54.9 ± 0.5 kg and 54.4 ± 1.0 kg; $P < 0.05$). No significant difference for B-AVF was found among the three genotypes. Following 20 weeks of endurance exercise, the 189 bp homozygotes gained only about half the amount of FFM compared with the other two *IGF-1* genotypes (0.3 ± 0.1 vs 0.7 ± 0.1 and 0.5 ± 0.2 kg; $P = 0.005$). A strong linkage was observed between the *IGF-1* marker and the changes in FFM (308 pairs of full sibs, $P = 0.0002$) but only a suggestive linkage with B-AVF (352 pairs of full sibs, $P < 0.02$)
CONCLUSION: Associations were detected between the IGF-1 gene marker and FM, %FAT and FFM at baseline, and a strong association with the changes in FFM in response to training. Moreover, the IGF-1 gene marker was found to be strongly linked to the changes in FFM in response to 20 weeks of endurance exercise and weakly linked to abdominal visceral fat in the sedentary state.

Keywords: fat mass; fat free mass; abdominal visceral fat; allelic variation; endurance training; family study

Introduction

The two-compartment model of body composition is the most widely used. It partitions body mass into its fat and lean components, *i.e.* fat mass (FM) and fat free mass (FFM).[1] Abdominal visceral fat (AVF) refers to the fat tissue located within the abdominal cavity around the abdominal viscera, and it is commonly thought to be associated with cardiovascular diseases and type 2 diabetes mellitus.[2]

Aerobic exercise training can alter FM, FFM and AVF in humans,[3,4] and large individual differences in response have been reported.[5,6] Sex, age and pre-training level may explain some of these differences. That FM and FFM levels are partly under genetic control was shown in the Québec Family Study with twins, adopted siblings and nuclear families.[7] Consistent results from Mexican–American subjects and a twin study were also reported.[8,9] FM and FFM are also known to change with nutritionally induced changes in body weight, and these changes are to some extent genetically determined.[10] Familial aggregation for AVF was observed in both the Québec Family

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Study and HERITAGE Family Study.[11,12] Significant intrapair resemblance was observed for both the AVF reductions with negative energy balance and the AVF increases with overfeeding in identical twin studies.[6,10]

Although genetic factors explain a fraction of interindividual variations in body composition, little is known about the specific genes involved. Insulin-like growth factor-1 (IGF-1) is known for having strong anabolic effects both *in vitro* and *in vivo*.[13] IGF-1 can significantly increase fat oxidation and decrease protein oxidation without altering energy expenditure in rats.[14] IGF-1 blood level is positively correlated with the FFM/FM ratio and inversely correlated with AVF determined by computerized tomography (CT).[15,16] Treated for one month by recombinant human IGF-1 (rhIGF-1), whole body and muscle protein syntheses were significantly increased in 14 women, aged 66–82 y.[17] FM was decreased and FFM was significantly increased in 11 elderly women (mean age ± s.e.m. 71.9 ± 1.3 y) treated by rhIGF-1.[18]

The interindividual variation in circulating level of IGF-1 is also partly under genetic control. The proportion of variance attributable to genetic effects in blood level of IGF-1 was 38% in a twin study.[19] The gene coding for IGF-1 is located on the long arm of chromosome 12 at q23,[20] and a dinucleotide $(CT)_n$ repeat polymorphism in the 5′ region of the gene has been described.[21] The purpose of this study was to investigate the relationship between baseline level and changes in body composition following a 20-week aerobic exercise training program and this IGF-1 gene polymorphism in the HERITAGE Family Study.

Methods

Subjects

A total of 502 Caucasian subjects (99 families; 190 parents and 312 offspring) from the HERITAGE Family Study was studied. The study and its protocol have been previously described.[22] The subjects came from families that included the natural mother and father (aged 65 or less) and offspring (17 years of age or older). This paper describes the results of 502 Caucasian subjects studied at four Clinical Centers (Arizona State University [Indiana University since January, 1996], Laval University, University of Minnesota and the University of Texas at Austin). To be enrolled into the study, subjects had to be healthy and sedentary, meet a set of inclusion criteria,[22] pass a physical examination, including a 12-lead electrocardiogram (ECG) at rest and perform a maximal exercise test.[22] The study was approved by the Human Subjects Committee at each participating institution. Informed written consent was obtained from each subject.

Exercise training program

Following the pre-training testing periods, subjects participated in a 20-week exercise training program using standardized cycle ergometers. Details of the training program have been reported elsewhere.[22] The training program was conducted on cycle ergometers (Universal Aerobicycle, Cedar Rapids, IO) interfaced with a Mednet computer system (Universal Gym Mednet, Cedar Rapids, IO) to control the power output of the ergometers so that constant training heart rates could be maintained. Subjects started training at the heart rate associated with 55% of their initial $\dot{V}O_{2\ max}$ for 30 min per day and gradually progressed to the heart rate associated with 75% of their initial $\dot{V}O_{2\ max}$ for 50 min/d at the end of 14 weeks. They maintained this intensity and duration throughout the remaining six weeks. Frequency was maintained at three sessions per week throughout the 20-week training program.[22] The power output of the cycle ergometer was adjusted automatically to the heart rate response of the subject at all times during all training sessions. All training sessions were supervised on site.

Measurement of body composition

Body mass and stature were measured to the nearest 0.1 kg and 0.1 cm, respectively, using a balance beam scale and a stadiometer. The hydrostatic weighing method was used to assess body density according to the method of Behnke and Wilmore.[23] The subjects were instructed to exhale completely to the point of residual volume, at which point a load cell interfaced with a computer was used to obtain the underwater measurement of body mass. Ten trials were obtained and the three highest values were averaged. Residual lung volume was assessed at the Indiana, Minnesota and Texas Clinical Centres using the oxygen-dilution principle.[24,25] At the Laval University Clinical Centre, residual volume was measured using the helium-dilution technique.[26,27] Relative body fat was estimated from body density using the equations of Siri[28] for Caucasian men, and of Lohman[29] for Caucasian women. FFM was calculated by subtracting FM from body mass. The reproducibility of anthropometric and body composition measures was investigated and the intraclass correlations for repeated measures ranged from 0.95 to 0.99 for the anthropometric measures, and from 0.97 to 1.00 for the body composition measures.[30] More detail about the body composition assessment methods can be found in a previous publication.[30]

Measurement of abdominal visceral fat

AVF was quantified before and after training by the method of Sjöström *et al.*[31] This technique involves computed axial tomography (CT scan). Subjects were examined in the supine position with their arms stretched above the head, and the abdominal scan was obtained between 4th and 5th lumbar vertebrae using

the same protocol at all centres. The attenuation interval used in the quantification of the areas of adipose tissue was from −190 to −30 Hounsfield units. The AVF area was defined by drawing a line within the muscle wall surrounding the abdominal cavity.

Genetic analysis

Blood samples were collected in EDTA and lymphoblastoid cell lines were established by transformation of B-lymphocytes with Epstein-Barr Virus. Cells were then cultured until their freezing in liquid nitrogen. Such cell lines have an infinite life span and exhibit chromosomal stability over years.[32] Genomic DNA was prepared from these lymphoblastoid cell lines.[32] Amplification was done in 96 Thermowell PCR plates (Corning Costar Corp., Cambridge, MA) using 250 ng genomic DNA, 50 pmol of each primer, 300 µM dNTPs and 0.4 U TAQ polymerase (Perkin Elmer, Roche Molecular Systems, Branchburg, NJ) in polymerase chain reaction (PCR) buffer (100 mM Tris-HCl pH 8.3, 15 mM $MgCl_2$, 0.5 M KCl, 0.01% gelatin) for a final volume of 15 µl. Primers used for the $(CT)_n$ polymorphism of the IGF-1 gene were as follows: 5′ TTGTGTCAACTGCTGATATG 3′ and 5′ AACCAAAACATCATTCCCTA 3′.[21] PCR cycles consisted of one cycle at 95°C for 2 min, 55°C for 1 min, followed by 35 cycles at 95°C for 30 s, 55°C for 30 s, and one cycle at 72°C for 2 min (Easycycler, Ericomp, San Diego, CA). 10 µl of the PCR products were precipitated with ethanol and resuspended in 10 µl loading buffer (95% formamide, 0.01% bromophenol blue, and 0.01% cyanol blue). 4 µl were applied to a sequencing gel and after electrophoresis, DNA was transferred by capillarity to a nylon membrane (Amersham, N+, Arlington Heights, IL) and probed with IGF-1 primer labelled using chemiluminescent Kit (DIG, Boehringer-Manheim, Indianapolis, IN). Genotyping was done from the autoradiograms assisted by computer (ONE-Dscan, Scanalytics, Billirica, MA) after the autoradiograms had been scanned (Scanmaker II, Microtek, Redondo Beach, CA). Mendelian inheritance was confirmed on all subjects involved in the study. Alternatively 217 subjects were analysed using automatic DNA sequencer (LI-COR, model 4000, Lincoln, NE). Amplification was done in 96 Thermowell PCR plates using 50 ng genomic DNA, 0.1 pmol of IRD40 labelled primer, 0.4 pmol of non-labelled primer, 125 µM dNTPs and 0.3 U Taq polymerase (Perkin Elmer, Roche Molecular Systems, Branchburg, NJ) in buffer for a final volume of 10 µl. PCR cycles consisted of one cycle at 93°C for 2 min, 10 cycles at 94°C for 20 s, 57°C for 1 min, 24 cycles at 95°C for 20 s, 52°C for 1 min. 5 µl of loading buffer was added to the 10 µl PCR solution. 4µl were applied to the sequencer gel. Genotyping was done directly on the gel image as previously described. Both methods gave the same results in 50 samples.

Statistical analysis

A chi-square test (χ^2) was used to test whether the genotype frequencies were in Hardy-Weinberg equilibrium. An analysis of variance (ANOVA) was used to test for association with the IGF-1 marker. Altogether, 27 different genotypes were found. The frequency of 189/189 bp homozygotes reached 53.7%, that of the 189 heterozygotes 36.8%, while the frequency of all other 25 genotypes (non-189 bp carriers) reached 9.5%. There would not be enough subjects for effective analysis if the non-189 bp carriers were further divided among several genotypes. Therefore, all 25 genotypes were pooled together as non-189 bp carriers in association studies. Comparisons between genotypes were thus performed among the 189/189 bp homozygotes, 189 bp heterozygotes and non-189 bp carriers using ANOVA.

Recent simulation studies indicated that a family design can provide greater power in association studies with no bias in the type I error rate if the trait is not strongly heritable (Province *et al,* unpublished observation). These simulations showed that the relatedness of subjects in families does not cause problems in association analyses performed with ANOVA. Therefore, all subjects were included as independent observations in the present study. Age, sex and generation were used as covariates. AVF was also further adjusted for FM. The residuals derived from the regressions were used as phenotypes in the analysis. Changes (post-training minus pre-training) following the 20-week exercise training program were adjusted using the same procedure, but also further adjusted for the pre-training value. Genotype by age, genotype by sex and genotype by generation interactions were also verified for FM, %FAT, BMI, FFM and AVF at baseline and in response to 20 weeks of exercise.

The Haseman-Elston sib-pair linkage procedure was used to study possible linkages between FM, %FAT, BMI, FFM and AVF and the IGF-1 marker.[33] This is a nonparametric approach, which requires no assumption about the mode of inheritance of a trait. In the presence of linkage between the marker locus and a trait locus, an inverse relationship is expected between the proportion of alleles identical by descent at the marker locus and the sib-pair phenotypic difference. The squared sib-pair trait difference is regressed on the estimated proportion of marker alleles identical by descent at the marker locus. A one-sided *t* test is then used to test whether the regression coefficient is significantly different from zero. The linkage analysis was performed using the SIBPAL software program of the SAGE Statistical Package, release 3.1.[34]

Results

The physical characteristics of the subjects at baseline are shown in Table 1, while the changes following

Table 1 Physical characteristics of subjects at baseline

Variables	Male parents ($n=91-97$) (mean ± s.d.)	Female parents ($n=84-93$) (mean ± s.d.)	Male offspring ($n=139-148$) (mean ± s.d.)	Female offspring ($n=161-164$) (mean ± s.d.)
Age (y)	53.6 ± 5.3	52.1 ± 5.0	25.4 ± 6.1	25.4 ± 6.4
Body weight (kg)	87.8 ± 15.2	72.3 ± 13.3	82.5 ± 16.7	64.3 ± 13.1
BMI (kg/m^2)	28.3 ± 4.5[b]	27.5 ± 4.8[a,b]	25.7 ± 4.9[b,c]	23.7 ± 4.4[b,c]
FM (kg)	24.6 ± 9.1[b]	26.8 ± 10.4	17.3 ± 11.0[b]	18.2 ± 9.9[b]
FFM (kg)	62.3 ± 7.5[a,b]	44.4 ± 4.9[a,b]	64.4 ± 7.8[b,c]	46.0 ± 5.2[b,c]
%FAT	27.6 ± 6.4[a,b]	36.6 ± 7.9[a,b]	19.8 ± 9.2[b,c]	26.8 ± 9.0[b,c]
AVF (cm^2)	158.7 ± 61.9[a,b]	119.7 ± 59.2[a,b]	78.6 ± 43.9[b,c]	52.6 ± 29.2[b,c]

BMI = body mass index; FM = fat mass; FFM = fat free mass; %FAT = percentage body fat; AVF = abdominal visceral fat.
[a]Difference between male and female parents, $P<0.05$; [b]difference between parents and offspring, $P<0.05$; [c]difference between male and female offspring, $P<0.05$.

Table 2 The changes in physical characteristics with training

Variables	Male parents ($n=85-92$)	Female parents ($n=82-91$)	Male offspring ($n=131-140$)	Female offspring ($n=154-160$)
Body weight (kg)	−0.4 ± 1.8*	−0.4 ± 2.0	−0.3 ± 2.3	−0.1 ± 2.2
BMI (kg/m^2)	−0.1 ± 0.6*	−0.1 ± 0.8	−0.1 ± 0.7*	0.0 ± 0.8
FM (kg)	−0.7 ± 1.7**	−0.7 ± 1.7**	−1.0 ± 2.0**	−0.6 ± 1.9*
FFM (kg)	0.3 ± 1.0**	0.3 ± 1.1*	0.7 ± 1.4**	0.5 ± 1.2**
%FAT	−0.7 ± 1.6**	−0.7 ± 1.6**	−1.1 ± 1.8**	−0.8 ± 2.1**
AVF (cm^2)	−9 ± 21**	−6 ± 18**	−6 ± 15**	−2 ± 10**

BMI = body mass index; FM = fat mass; FFM = fat free mass; %FAT = percentage body fat, AVF = abdominal visceral fat.
Mean ± s.d. Paired t test: *$P<0.05$. **$P<0.01$.

exposure to the endurance exercise training program are described in Table 2. In male parents, body weight, BMI, FM, %FAT and AVF significantly decreased, and FFM significantly increased in response to the exercise program. In female parents, FM, %FAT and AVF decreased, and FFM significantly increased, but body weight and BMI did not change significantly. In male and female offspring, significant decreases in FM, %FAT and AVF, and a significant increase in FFM were observed following endurance training. Male offspring also had a small but significant drop in BMI.

Polymorphism of dinucleotide $(CT)_n$ repeats in IGF-1 gene

The polymorphism exhibited 11 alleles with the length of the alleles ranging from 189 bp to 209 bp. The 189 bp was the common allele with a frequency of 0.71 (Table 3). The estimate of heterozygosity was 0.485. Twenty-seven different genotypes were observed. The genotype frequency of the homozygotes for the 189 allele reached 0.54, 189 bp heterozygous 0.37 and all others 0.09. The genotype distribution was in Hardy-Weinberg equilibrium.

Table 3 Allelic frequencies for the dinucleotide $(CT)_n$ repeat polymorphism at IGF-1 in unrelated adults from the parental generation

Allele (bp)	Frequency	Allele (bp)	Frequency
189	0.71 ± 0.03	201	0.06 ± 0.01
191	0.06 ± 0.01	203	0.03 ± 0.01
193	0.02 ± 0.01	205	0.02 ± 0.01
195	0.03 ± 0.01	207	0.02 ± 0.01
197	0.02 ± 0.01	209	0.02 ± 0.01
199	0.01 ± 0.01		

Frequency ± s.e. Allelic frequencies were assessed from 190 unrelated subjects from the parental generation.

Association studies

Table 4 shows the results for the association analyses. The 189 bp homozygotes had a lower B-FM (19.7 ± 0.6 vs 21.6 ± 0.7 and 21.3 ± 1.5 kg; $P=0.03$ after adjustment for age, sex and generation). The 189 bp homozygotes also showed lower B-%FAT 25.9 ± 0.5 versus 27.4 ± 0.6 and 26.6 ± 1.2 kg; $P<0.05$ after adjustment for age, sex and generation). A significantly lower B-FFM (53.7 ± 0.4 versus 54.9 ± 0.4 and 54.4 kg; $P<0.05$ after adjustment for age, sex and generation) was also observed in 189 bp homozygous subjects. No significant difference for B-AVF was found among the three genotypes. For the responses to 20 weeks of endurance exercise, however, the 189 bp homozygous subjects gained less FFM, only about half of the amount compared with the other IGF-1 genotypes (0.3 ± 0.1 versus 0.7 ± 0.1 and 0.5 ± 0.2 kg; $P<0.005$ after adjustment for age, sex, generation and baseline value). No significant association for other phenotypes to training response was observed. When the association studies were performed in males and females separately, the FFM changes with training exhibited the same pattern in each sex with the 189 bp homozygotes gaining only half the amount of FFM as the other subjects (P values from 0.04 to 0.07).

Table 4 Comparison of body composition phenotypes by genotype at the IGF-1 gene locus

Variables	*189/189 bp homozygotes*	*189 bp heterozygotes*	*189 bp non carriers*	*P value*
B-BMI (kg/m^2)	25.4 ± 0.3	26.2 ± 0.3	26.7 ± 0.7	0.07
Δ BMI (kg/m^2)	−0.14 ± 0.05	−0.06 ± 0.05	−0.00 ± 0.12	0.29
B-FM (kg)	19.7 ± 0.6	21.6 ± 0.7	21.3 ± 1.5	**0.03**
Δ FM (kg)	−0.7 ± 0.1	−0.8 ± 0.1	−0.4 ± 0.3	0.57
B-FFM (kg)	53.7 ± 0.4	54.9 ± 0.5	54.4 ± 1.0	**0.046**
Δ FFM[a](kg)	0.3 ± 0.1	0.7 ± 0.1	0.5 ± 0.2	**0.005**
B-%FAT	25.9 ± 0.5	27.4 ± 0.6	26.6 ± 1.2	**0.049**
Δ%FAT	−0.9 ± 0.1	−1.0 ± 0.1	−0.6 ± 0.3	0.56
B-AVF[b] (cm^2)	91.4 ± 2.8	95.8 ± 3.2	92.5 ± 6.7	0.30
Δ AVF	−5.1 ± 0.9	−5.6 ± 1.1	−4.6 ± 2.3	0.72

B = baseline. Δ = change with training. BMI = body mass index; FM = fat mass; FFM = fat free mass; %FAT = Percentage body fat; AVF = abdominal visceral fat. Δ values were adjusted for age, sex, generation and baseline value. Δ AVF was also adjusted for FM at baseline. The number of subjects for the three genotypes varies as follows: 232–260, 184–197 and 40–44.

Linkage studies

The results of the sib-pair linkage analysis are shown in Table 5. A strong significant inverse relationship was observed between the proportion of alleles identical by descent in sib pairs and the within sib-pair differences for the changes in FFM adjusted for age, gender and baseline level (308 pairs; $P = 0.0002$), and a weak linkage was detected between the IGF-1 marker and AVF at baseline (352 pairs; $P<0.02$ after adjustment for age, gender, and baseline FM). No other significant linkage was found.

Discussion

The present study considered the relationships between body composition phenotypes in the sedentary state and their changes following a 20-week aerobic exercise-training program with an IGF-1 gene polymorphism. There were two important findings. First, significant associations were observed between the IGF-1 gene dinucleotide repeat polymorphism and BMI, FM, %FAT and FFM level at baseline. Suggestive evidence of linkage was also observed between the IGF-1 gene marker and AVF level at baseline. Second, the IGF-1 gene marker was found to be strongly linked and significantly associated with the changes in FFM in response to training.

Table 5 Sib-pair linkage analysis results with the IGF-1 marker

Variables	*n pairs*	*t-value*	*P value*
B-BMI	358	−1.48	0.07
Δ BMI	331	−1.16	0.12
B-FM	340	−0.74	0.23
Δ FM	308	−0.51	0.31
B-FFM	340	−0.78	0.22
Δ FFM[a]	308	−3.77	**0.0002**
B-%FAT	340	0.39	0.65
Δ%FAT	308	0.32	0.62
B-AVF[b]	352	−2.17	**0.02**
Δ AVF	311	0.64	0.74

B = baseline; Δ = change after training; BMI = body mass index; FM = fat mass; FFM = fat free mass; %FAT = percentage body fat; AVF = abdominal visceral fat.
[a]Adjusted by regression for age, sex and baseline value.
[b]Adjusted by regression for age, sex, baseline level and FM at baseline.

Several studies have shown that FM, FFM and AVF in sedentary people are partly under genetic control.[7–9] Moreover, identical twin intervention studies showed that the intrapair variation in responsiveness was significantly smaller than the interpair variation,[6,10] suggesting that the changes in FFM, FM, %FAT and AVF are also partly determined by genetic factors.

The main physiological function of IGF-1 is anabolic.[13] It promotes the synthesis of protein,[14] increases FFM,[15,17,18] increases fat oxidation,[14] and decreases FM.[18] Blood level of IGF-1 is inversely associated with visceral fat[16] and with the abdominal sagittal diameter.[35] In addition, the circulating level of IGF-1 is partly under genetic control.[19] Therefore, IGF-1 is a reasonable candidate gene for the study of the genetic determinants of body composition and, potentially, its responsiveness to endurance exercise training. Our results from both association and linkage studies provide significant evidence in support of this notion.

Linkage and association studies supply different types of information.[36] Linkage analysis tests the tendency of genes or DNA markers at specific loci to be inherited together as a consequence of their physical proximity on a single chromosome. Association analysis assesses the relationship between particular alleles at locus and trait variability.[37] In general, associations can arise from several sources: the DNA polymorphism may directly affect the trait aetiology, *i.e.* represent a functional variant or the polymorphism may be in linkage disequilibrium with the true functional variant or an association can arise on account of population stratification.[36]

The strong evidence for linkage between the IGF-1 gene and the changes in FFM in response to 20 weeks of endurance training ($P = 0.0002$) provides important support for the notion that variability in or near the IGF-1 gene indexed by the $(CT)_n$ repeat polymorphism is influencing fat free mass variation, presumably skeletal muscle mass in response to regular exercise. The IGF-1 polymorphism used here is located at base pair 140 of the IGF-1 gene at the 5′ end on chromosome 12q23.[21] While it is possible that gene expression could be altered owing to the presence of a $(CT)_n$ repeat of varying length, the data from this study do not allow us to distinguish among these possibilities. Although the possibility that the results are false positive cannot be ruled out until the findings are confirmed in other experiments, the probability is low in view of the strong biological justification for IGF-1 as a candidate gene, the relatively large number of subjects and the detection of positive results in both association and linkage studies.

Conclusion

Data from the HERITAGE Family Study show both association and linkage between a polymorphism at the IGF-1 gene and body composition phenotypes. The 189/189 bp homozygotes have less FM, %FAT and FFM. The 189/189 bp homozygotes gained less FFM compared with other genotypes when exposed to regular endurance exercise. A weak linkage was also found between AVF at baseline and the IGF-1 gene marker. A strong linkage was found between the changes in FFM and the IGF-1 gene marker. These results suggest that the IGF-1 gene is of importance in determining body composition in the sedentary state, particularly FFM level, and the response of FFM to regular exercise.

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