

Association of Morbid Obesity With *FTO* and *INSIG2* Allelic Variants

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Objective: To determine whether 2 single nucleotide polymorphisms (SNPs) in the obesity genes the fat mass and obesity associated gene (*FTO*) and the insulin induced gene 2 (*INSIG2*) are associated with class III, or morbid, obesity in patients undergoing bariatric weight loss operations.

Design: Retrospective analysis of genotype and clinical data.

Setting: Large rural tertiary care health system.

Patients: A total of 707 adult patients with a body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) of at least 40 undergoing open or laparoscopic Roux-en-Y gastric bypass operations for morbid obesity or its comorbid medical

problems at Geisinger Medical Center, Danville, Pennsylvania.

Results: The mean BMI in the predominantly white female cohort was 51.2. Approximately 21% of patients were homozygous for the *FTO* obesity SNP variant, 13% were homozygous for the *INSIG2* obesity SNP variant, and 3.4% were homozygous for both. Mean BMIs in the groups homozygous for each of these genes were not significantly different from nonhomozygotes. However, *FTO/INSIG2* double homozygotes and homozygote/heterozygote pairs had significantly higher BMIs than the other groups.

Conclusion: Increased BMI in morbid obesity is associated with a combination of *FTO* and *INSIG2* SNPs.

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BARIATRIC SURGERY IS A highly effective and therapeutic modality for many patients with morbid, or class III, obesity (body mass index [BMI; calculated as weight in kilograms divided by height in meters squared], ≥ 40) and its comorbid medical problems.¹ Substantial weight loss is achieved in most patients in the first 6 to 12 postoperative months. Although the long-term effectiveness of bariatric surgery is not surpassed by any other modality, a subgroup of patients remain resistant to weight loss.² Identification of variables that determine the success of bariatric surgery have shown little consistency, and long-term success may depend on not yet identified factors.³

See Invited Critique at end of article

One factor that may influence a patient's risk for obesity, and therefore the potential long-term success of bariatric surgery, is genetic susceptibility. Twin and adoption studies support an important role for genetic factors influencing the develop-

ment of obesity.⁴ However, most cases of adult obesity are not caused by single genetic defects.⁵ Efforts have therefore focused on the identification of genetic variants that predispose carriers to common, polygenic obesity. A large number of common genetic variants have been reported to be related to BMI, but few of the associations have been reproduced across multiple populations.⁶ Most studies have also been performed in individuals with normal weight, overweight, and class I obesity and have not included morbidly obese patients.

Two common genetic variants have recently been linked to obesity and this association has been replicated in several studies. One obesity variant, rs7566605, a single nucleotide polymorphism (SNP) near the insulin induced gene 2 (*INSIG2*), was found to be associated with BMI in a genome-wide association study from the offspring cohort of the Framingham Heart Study.⁷ The SNP has no known function and the closest gene (*INSIG2*) is involved with lipid and cholesterol metabolism⁸ and has been linked to obesity in rodents.⁹ The association of BMI with homozygosity for the minor allele of this SNP has been re-

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produced in a variety of populations, whereas this association has not been found in others.¹⁰

A second SNP associated with BMI, rs9939609, is found within the fat mass and obesity associated gene (*FTO*). The *FTO* SNP was first identified in a genome-wide association study of patients with type 2 diabetes.¹¹ However, subsequent analysis indicated that the *FTO* variant was actually associated with increased BMI, suggesting that the original relationship found between the *FTO* SNP and type 2 diabetes risk was mediated through BMI. Independent data reported for other SNPs within *FTO* in patients with morbid obesity and pediatric obesity corroborated the link to BMI.¹²

As an initial step in understanding potential genetic influences in patients undergoing bariatric surgery, the association of *FTO* and *INSIG2* SNPs with BMI was determined in a large cohort of morbidly obese patients enrolled in a bariatric surgery program. Because of the role of *INSIG2* in lipid and cholesterol metabolism, the effect of the 2 obesity genes on blood-lipid parameters was also analyzed.

METHODS

PATIENTS

Patients undergoing open or laparoscopic Roux-en-Y gastric bypass operations or laparoscopic adjustable gastric banding procedures for morbid obesity or its comorbid medical problems at Geisinger Medical Center, Danville, Pennsylvania, were enrolled in a clinical research program on obesity and metabolic syndrome. All patients undergoing bariatric operations at Geisinger Medical Center are required to participate in a standardized multidisciplinary preoperative program, which includes obtaining standardized clinical and laboratory data at designated times. An accurately measured BMI is obtained at the first visit at the weight management clinic. Blood samples for DNA and lipid measures were obtained approximately 3 weeks before the date of operation. Total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol (calculated), triglyceride levels, and the cholesterol to high-density lipoprotein ratio were also measured using standard clinical laboratory techniques. The institutional review board at the Geisinger Medical Clinic approved the research protocol and all participants provided written informed consent.

DATA ACQUISITION

Demographic, BMI, and laboratory data were obtained through an electronic search of EpicCare electronic medical records (Epic Systems, Verona, Wisconsin). The electronic medical record data were imported into SAS/STAT software (SAS Institute Inc, Cary, North Carolina) and were mapped to predefined fields. The resulting data were available for statistical analysis in SAS or for export into other software applications.

DNA ISOLATION

DNA was extracted from 0.35 mL of EDTA-anticoagulated whole blood using the Qiagen MagAttract DNA Blood Midi M48 Kit and Qiagen BioRobot M48 Workstation (Qiagen, Valencia, California) according to the manufacturer's directions. The final elution volume was 200 μ L. For a few patients, blood was not available, so DNA was extracted from fixed liver tissue. Livers

were first treated with proteinase K (1 μ g/ μ L) in 350 μ L of Qiagen Tissue Lysis Buffer (Qiagen) and incubated at 55°C overnight. Following digestion, samples were loaded onto the Qiagen BioRobot M48 Workstation and DNA was extracted, as described for blood samples. Quantification of extracted DNA was performed using a NanoDrop ND-1000 spectrophotometer (NanoDrop Technologies, Wilmington, Delaware).

GENOTYPE ANALYSIS

Single nucleotide polymorphism genotyping was performed on an Applied Biosystems 7500 Real-Time Polymerase Chain Reaction System (Applied Biosystems, Foster City, California). Assay reagents for each SNP were obtained from Applied Biosystems (*FTO* rs9939609, assay C__30090620_10; *INSIG2* rs7566605, assay C__29404113_20). DNA was genotyped according to the manufacturer's protocol. Briefly, the components for each genotyping reaction were as follows: 10 ng of DNA, 5 μ L of TaqMan Genotyping Master Mix (Applied Biosystems), 0.25 μ L of assay mix (40 \times), and water up to a total volume of 10 μ L. The thermocycler conditions were as follows: 50°C for 2 minutes, 95°C for 10 minutes, and 40 cycles at 95°C for 15 seconds and at 60°C for 60 seconds. The reaction was then analyzed using Applied Biosystems Sequence Detection Software.

STATISTICAL ANALYSIS

Deviation from Hardy-Weinberg equilibrium was tested with the HelixTree software package (Golden Helix, Bozeman, Montana). The HelixTree application was used to determine differences in genotype and allele frequencies to examine the association of SNPs with BMI and laboratory results. Multiple testing corrections were performed using simulations and the Bonferroni method. Significant association was considered likely for a Bonferroni-corrected $P < .05$.

RESULTS

PATIENT CHARACTERISTICS

The mean age of the patient cohort was 45.9 years, with a mean BMI of 51.2 (**Table 1**). More than 97% of the patients had white European ancestry, representative of the geographic area, and 81% were women. Mean lipid measurements were as follows: triglyceride level, 177.6 mg/dL (2.01 mmol/L); total cholesterol, 188.8 mg/dL (4.89 mmol/L); high-density lipoprotein cholesterol, 48.1 mg/dL (1.25 mmol/L); total cholesterol to HDL cholesterol ratio, 4.1; and calculated low-density lipoprotein, 106.2 mg/dL (2.75 mmol/L). The distribution of BMI measurements is shown in the **Figure**. Almost 4% of the population had BMIs higher than 70.

GENOTYPES

A total of 707 DNA samples were genotyped for the *FTO* (rs9939609) and *INSIG2* (rs7566605) SNPs (**Table 2**). Genotyping consisted of analyzing the DNA from each patient to determine whether he or she carried the A and/or T sequences in *FTO* and the G and/or C sequences near *INSIG2*. The *FTO* A SNP and the *INSIG2* C SNP are considered the obesity SNPs. The frequencies of the *INSIG2* and *FTO* SNPs in

Table 1. Characteristics of Patients Undergoing Roux-en-Y Gastric Bypass

Characteristic	Value
Body mass index ^{a,b}	
Mean (SD)	51.2 (8.5)
Median (range)	49.5 (40-88.4)
Triglycerides, mg/dL ^c	
Mean (SD)	177.6 (105.3)
Median (range)	153 (36-908)
Total cholesterol, mg/dL ^c	
Mean (SD)	188.8 (38.7)
Median (range)	184 (70-309)
HDL cholesterol, mg/dL ^c	
Mean (SD)	48.1 (11.3)
Median (range)	47 (22-103)
Total cholesterol to HDL cholesterol ratio ^c	
Mean (SD)	4.1 (1.1)
Median (range)	4 (1.5-7.8)
LDL cholesterol, mg/dL ^d	
Mean (SD)	106.2 (34)
Median	102 (5-226)
Age, y ^b	
Mean (SD)	45.9 (11.2)
Median (range)	46.6 (18.6-72.2)

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein. SI conversion factors: To convert HDL, LDL, and total cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113.

^aCalculated as weight in kilograms divided by height in meters squared.

^bN = 707.

^cn = 679.

^dn = 661.

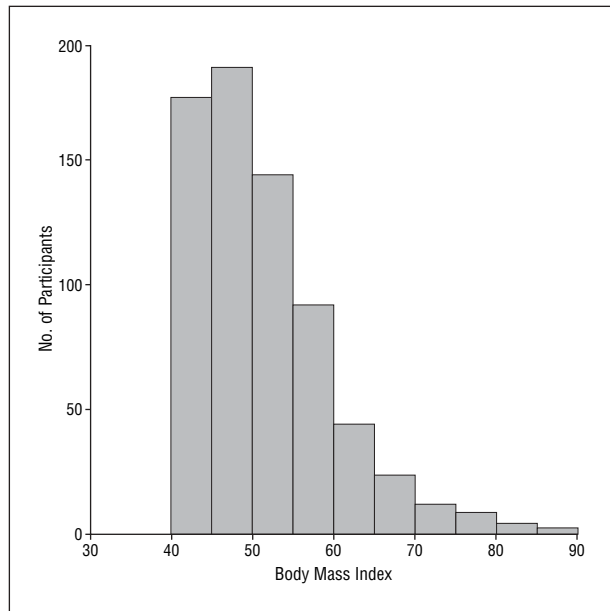


Figure. Histogram of body mass index (calculated as weight in kilograms divided by height in meters squared) in morbidly obese patients.

this population are presented in Table 2 and concur with previous studies.^{12,13}

To determine whether the population was genetically skewed through inbreeding or strong founder effects, a statistical test for Hardy-Weinberg equilibrium

Table 2. Frequencies of *FTO* and *INSIG2* Alleles in Morbidly Obese Patients

Allele	No. of Alleles	Allele Frequency
<i>FTO</i>		
A	638	0.45
T	776	0.55
<i>INSIG2</i>		
C	495	0.35
G	919	0.65

Abbreviations: *FTO*, fat mass and obesity associated gene; *INSIG2*, insulin induced gene 2.

Table 3. Frequencies of *FTO* and *INSIG2* Genotypes in Morbidly Obese Patients

Genotype	No. of Genotypes	Genotype Frequency
<i>FTO</i>		
AA	149	0.21
AT	340	0.48
TT	218	0.31
<i>INSIG2</i>		
CC	93	0.13
CG	309	0.44
GG	305	0.43

Abbreviations: *FTO*, fat mass and obesity associated gene; *INSIG2*, insulin induced gene 2.

was performed. Both SNPs were found to be well within Hardy-Weinberg equilibrium (*FTO*, $P > .44$; *INSIG2*, $P > .29$). Our frequency of SNP sequences is thus consistent with an out-bred, mixed, white European population.

The diploid SNP sequences, or genotypes (ie, AA, AT, and TT for *FTO* and CC, GC, and GG for *INSIG2*), of each patient for each gene were also analyzed (**Table 3**). The homozygous genotype AA in *FTO* was present in approximately 21% of the population and the homozygous genotype CC in *INSIG2* was present in approximately 13%, consistent with previous studies.^{12,13} These 2 homozygous genotypes are considered the high-obesity risk genotypes. The heterozygous AT and GC genotypes were found in 48% and 44% of the study population, respectively. The homozygous low-obesity risk genotype for *FTO* (TT) was found in 31% of the population and the low-obesity risk genotype (GG) for *INSIG2* was present in 43%.

ASSOCIATION OF BMI WITH SNPs

The relationship of BMI with the *INSIG2* and *FTO* obesity SNP genotypes was analyzed using the HelixTree Genetics Analysis Software (Golden Helix). With this program, data are analyzed by minimizing the sum of squared deviations of each group mean from the remainder of the observations. An *F* test was used to generate an unadjusted *P* value; an adjusted *P* value was calculated by curve-fitting thousands of simulations; and a Bonferroni correction for multiple comparisons of the adjusted *P* value

Table 4. Mean BMIs by *FTO* and *INSIG2* Genotypes in Patients Undergoing Roux-en-Y Gastric Bypass

Genotype Class	<i>FTO</i>		<i>INSIG2</i>	
	Genotype	BMI, Mean (SD)	Genotype	BMI, Mean (SD)
Homozygous for normal weight	TT	50.4 (7.7)	GG	50.7 (8.2)
Heterozygous	AT	51.1 (8.8)	GC	51.3 (8.4)
Homozygous for obesity	AA	52.5 (8.7)	CC	52.5 (9.3)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); *FTO*, fat mass and obesity associated gene; *INSIG2*, insulin induced gene 2.

Table 5. Significance of Association of Body Mass Index With *FTO*, *INSIG2*, and Combined Genotypes in Morbidly Obese Patients

Genotype	P Value		
	Unadjusted	Adjusted	Bonferroni Corrected
<i>FTO</i>	.026	.026	.051
<i>INSIG2</i>	.106	.274	.824
<i>FTO</i> and <i>INSIG2</i>	< .001	.003	.010

Abbreviations: *FTO*, fat mass and obesity associated gene; *INSIG2*, insulin induced gene 2.

was also calculated. A conservative threshold of < .05 was used for this Bonferroni-corrected P value.

The initial analysis was performed using BMI and the individual *FTO* and *INSIG2* SNP genotypes. Although the mean BMIs increased by approximately 2 kg/m² in *FTO* and *INSIG2* obesity genotypes (**Table 4**), they were not statistically different (**Table 5**). With a less stringent statistical threshold (not Bonferroni corrected), the BMIs of the 3 *FTO* genotypes were found to be significantly different ($P = .03$). No significant association was found between the *FTO* or *INSIG2* genotypes and any of the lipid parameters ($P > .10$).

When both the *FTO* and the *INSIG2* genotypes of each patient were considered together as a compound genotype (ie, AA/CC, AA/GC, AA/GG, AT/CC, AT/GC, AT/GG, AA/CC, AA/GC, and AA/GG), patients who were double homozygotes for the obesity-risk alleles (AA/CC) were found to have significantly higher BMIs ($P < .01$, Bonferroni corrected). Those who were *FTO* homozygous and *INSIG2* heterozygous (AA/GC) or *FTO* heterozygous and *INSIG2* homozygous (AT/CC) for obesity also had significantly higher BMIs. No significant association was found between the compound *FTO/INSIG2* genotypes and any of the lipid parameters ($P > .10$).

An interesting pattern in mean BMI was found in the compound groups (**Table 6**). The mean BMI was about 4 kg/m² higher in the group homozygous for the obesity-risk genotypes (AA/CC) and was about 3 kg/m² higher in the homozygous/heterozygous (AA/GC) and the heterozygous/homozygous (AT/CC) groups compared with the other compound genotype groups. This is consistent with the contribution of an approximately 1 kg/m² increase in BMI for each copy of the *FTO* A and *INSIG2* C obesity sequences in these groups. The association of

Table 6. Mean BMIs of *FTO/INSIG2* Compound Groups

Genotype Class	<i>FTO/INSIG2</i> Genotype	BMI (SD)
Normal weight/obesity	TT/CC	48.6 (5.6)
Normal weight/normal weight	TT/GG	50.6 (7.7)
Heterozygous/normal weight	TA/GG	50.6 (8.4)
Normal weight/heterozygous	TT/GC	50.7 (8.2)
Heterozygous/heterozygous	TA/GC	50.8 (8.6)
Obesity/normal weight	AA/GG	50.9 (8.4)
Obesity/Heterozygous	AA/GC	53.0 (8.3)
Heterozygous/Obesity	AT/CC	53.5 (10.0)
Obesity/obesity	AA/CC	54.4 (10.3)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); *FTO*, fat mass and obesity associated gene; *INSIG2*, insulin induced gene 2.

at least 2 copies of 1 obesity SNP and at least 1 copy of the other with increased BMI also suggests some degree of interaction between *FTO* and *INSIG2*. However, biological factors appear to influence the observed data, because the group homozygous for normal weight/obesity (TT/CC, respectively) was approximately 2 kg/m² lower than the group homozygous for obesity/normal weight (AA/GG, respectively) and about 6 kg/m² lower than the group homozygous for obesity (AA/CC).

COMMENT

Obesity is a multifactorial condition, with substantial evidence supporting a strong genetic component.⁴ Such genetic factors may influence therapies, including bariatric surgery; thus, their identification may be important in guiding treatment. Mutations in several genes have been found to be responsible for rare familial monogenic forms of obesity, and a large number of genes have been analyzed in common sporadic multigenic obesity.⁶ However, many studies of genes in common obesity have not been replicated across different populations.¹⁴

The 2 obesity gene variants studied here, rs9939609 (*FTO*) and rs7566605 (*INSIG2*), have previously been replicated in multiple, but not all, studies. For example, the *INSIG2* variant was first replicated in 4 separate cohorts composed of individuals with Western European ancestry, African American individuals, and children,⁷ but later, it was found to have both negative^{13,15-19} and positive¹⁰ associations in genetic analyses of several thousand in-

dividuals. There have been fewer studies of the *FTO* variant, though the data have been largely supportive of its association with BMI.^{11,20,21} These inconsistent results may be because the effect each SNP variant has on BMI is relatively small and could be influenced by slight differences in population characteristics and gene-gene and gene-environment interactions. Our results support the possibility that gene-gene interactions are important, because the strongest association with BMI occurred when both genes were analyzed together. No previous studies have examined the combined effects of the *FTO* and *INSIG2* SNPs in obesity.

Despite the large number of participants analyzed in studies examining the association of BMI with either the *INSIG2* or *FTO* SNPs, the populations have largely comprised individuals with normal weight, overweight, and class I obesity (BMI > 30 and < 35). The range of BMIs in most of the previous studies was less than 20 (~20-40) compared with a range of more than 45 in our population (~40-88). However, the studies showing an association between obesity and the *INSIG2* SNP have tended to have populations with higher BMIs.¹³ Similarly, an SNP in *FTO*, near but different than the SNP analyzed here, has been associated with BMI in a population of morbidly obese adults.¹²

The homozygous/homozygous, homozygous/heterozygous, and heterozygous/homozygous compound *FTO/INSIG2* SNP genotypes that were associated with higher BMIs were present in less than 20% of the cohort, indicating that a potentially large number of other genes that influence BMI in the morbidly obese are not yet identified. Candidate genes include those previously associated with obesity in rare monogenic forms of the condition and those involved in obesity based on cell biological or animal model studies.²² However, few new sequence variants were found in previously identified obesity candidate genes using a morbidly obese population similar to that studied here.⁵ These results indicate that sporadic morbid obesity is likely to be influenced by other, unidentified genes, not candidate genes selected by biological inference.²³⁻²⁶

Other factors that may also affect the influence of genetic variants on morbid obesity include sex and race, which were not addressed in the predominantly white female population studied here. The prevalence of morbid obesity is higher in women than in men and in individuals of African ancestry compared with white or Hispanic individuals,²⁷ with the lowest prevalence in Asian persons.²⁸ Two of the studies that found no association of BMI with the *INSIG2* genotype were conducted in patients with primarily African ancestry.^{10,15} Data from the International HapMap Project indicate that the high-obesity risk *INSIG2* CC genotype was present at a higher frequency in the Japanese and Han Chinese populations analyzed than in the European and African groups.²⁹ In contrast, the high-obesity risk *FTO* AA genotype was present at a lower frequency in the 2 Asian populations compared with the European and African groups. These data suggest that the effects of the 2 obesity SNPs may not be similar in all racial groups and that further studies will be needed to address other populations.

A limitation of association studies is that potential causative mechanisms cannot be identified, thus the poten-

tial pathophysiological role(s) of the *FTO* and *INSIG2* genes in morbid obesity are not known; *INSIG2* codes for an endoplasmic reticulum protein that regulates the movement of sterol regulatory element, binding proteins to the Golgi apparatus and regulating the synthesis of fatty acid and cholesterol.^{8,30} Overexpression of *Insig2* in the liver of rats reduced plasma triglyceride levels.⁹ Despite this clear involvement in lipid metabolism, no association between common lipid parameters and the *INSIG2* (or *FTO*) SNPs was found here. However, medication use was not accounted for in the analysis, thus the effects of lipid-lowering agents may have affected the phenotypes of those genetically predisposed to dyslipidemia. The function of the protein product of *FTO* has not yet been elucidated. Mice with the *Fto* syntenic fused toes mutation manifest developmental defects.^{31,32}

How the SNPs in *INSIG2* and *FTO* alter the function of their respective RNAs and/or proteins, increasing the risk for higher BMI in the morbidly obese, is not yet known. The *INSIG2* SNP is located about 10 000 base pairs upstream from the coding region, so it is likely involved in regulating the level of RNA and therefore the amount of protein produced. The *FTO* SNP is located in the first intron of the gene and also presumably affects levels of its RNA and protein. Future studies will be required to determine the molecular mechanism through which the specific DNA sequences, ie, A and T for *FTO* and G and C for *INSIG2*, affect the genes' functions. Our results indicate that the 2 genes may interact, suggesting that the physiological pathways in which each is involved may be linked in some way.

The effect of these genetic variants on bariatric surgery and its expected outcomes has yet to be determined. Surgical treatment for morbidly obese patients results in greater weight loss than medical treatment does.¹ Bariatric surgery has also been associated with increased life expectancy compared with the risk of surgical mortality and potential length of effectiveness.³³ Recent data on the long-term effectiveness of bariatric surgery on BMI³ suggest that, for most patients, BMI will be maintained substantially below preoperative levels, though some patients regain weight and relapse toward morbid obesity. We hypothesize that this subgroup carries genetic susceptibility alleles that overcome the results of the Roux-en-Y gastric bypass surgery, as has been investigated for several candidate genes in laparoscopic adjustable-band therapy and laparoscopic mini-gastric bypass.^{34,35} The identification of such susceptibility genes may therefore be important in identifying patients at high risk for postoperative weight gain. These studies may also represent some of the first specific examples of "surgicogenomics," paralleling the well-developed field of pharmacogenomics.³⁶

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