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Common Variants in *FTO* Are Not Significantly Associated with Obesity-Related Phenotypes among Samoans of Polynesia

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Summary

The association between obesity and the fat mass and obesity-associated (*FTO*) gene has been widely replicated among Caucasian populations. The limited number of studies assessing its significance in Asian populations has been somewhat conflicting. We performed a genetic association study of 51 tagging, genome-wide association studies, and imputed single nucleotide polymorphisms with 12 measures of adiposity and skeletal robustness in two Samoan populations of Polynesia. We included 465 and 624 unrelated American Samoan and Samoan individuals, respectively; these populations derive from a single genetic background traced to Southeast Asia and represent one sociocultural unit, although they are economically disparate with distinct environmental exposures. American Samoans were significantly larger than Samoans in all measures of obesity and most measures of skeletal robustness. In separate analyses of American Samoa and Samoa, we found a total of 36 nominal associations between *FTO* variants and skeletal and obesity measures. The preponderance of these nominal associations (32 of 36) was observed in the Samoan population, and predominantly with skeletal rather than fat mass measures (28 of 36). All significance disappeared, however, following corrections for multiple testing. Based on these findings, it could be surmised that *FTO* is not likely a major obesity locus in Polynesian populations.

Keywords: Obesity, *FTO*, association analysis, Samoa

Introduction

Genome-wide association studies (GWAS) have provided new insights into obesity genetics with the identification of sequence variants in several genes including *INSIG2*, *FTO*, *MC4R*, *BDNF*, and *SH2B1* (Herbert et al., 2006; Frayling et al., 2007; Dina et al., 2007; Loos et al., 2008; Chambers et al., 2008; Thorleifsson et al., 2009). Among these genes, *FTO* has emerged as the strongest candidate conferring risk of obesity, with replication of common variants across populations of European and Hispanic descent (Dina et al., 2007; Frayling et al., 2007; Scuteri et al., 2007; Grant et al., 2008; Thorleifsson et al., 2009). Less certain and inconclusive, however, are the associations of *FTO* variants with body fatness measures in Asian populations (Cha et al., 2008; Ng et al., 2008; Tan et al., 2008; Li et al., 2008; Yajnik et al., 2009; Fang et al., 2010; Li et al., 2010). In comparison to most worldwide populations, levels of obesity are considerably higher in Oceanic populations (Collins et al., 1990) and associations of GWAS obesity-related loci among these populations are yet to be thoroughly explored. Based on a relatively smaller number of subjects, Ohashi et al. (2007) reported that *FTO* variants are not associated with obesity in six Oceanic populations, including one Polynesian group from Tonga. We conducted an association study of common *FTO* variants with obesity-related traits among Samoans of Polynesia who

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have a remarkably high prevalence of overweight and obesity (McGarvey, 1991; Keighley et al., 2006).

Samoans of Polynesia are distributed in two polities: the independent nation of Samoa and the U.S. territory of American Samoa. Both groups share a common evolutionary history, form a single sociocultural unit with frequent exchange of mates, and genetically represent a single homogenous population without evidence of substructure (McGarvey, 2001; Tsai et al., 2004). There is, however, substantial economic disparity between the two locales, which reflects the patterns of distribution of adiposity in the two groups. Based on the Polynesian body mass index (BMI) standards of 26–32 kg/m^2 and >32 kg/m^2 defining overweight and obesity, respectively (Swinburn et al., 1999), 59% of men and 71% of women are obese in American Samoa compared to 29% of men and 53% women in the less developed nation of Samoa (Keighley et al., 2006). To determine the significance of *FTO* variants in this population, we conducted a comprehensive association analysis of *FTO* tagging variants, supplemented with previously identified GWAS single nucleotide polymorphisms (SNPs) and SNPs imputed from the Phase III HapMap database with measures of obesity in adults residing in the Samoan islands. We expanded the phenotypic traits beyond those typically included in GWAS (classical measures including weight and BMI) to 12 anthropometric measures of body fatness and skeletal robustness. In all, we tested association of 51 *FTO* variants in a sample of 1089 unrelated individuals.

Materials and Methods

Subjects

A total of 1089 adult individuals (465 American Samoan and 624 Samoan) were included in this study. The sample from American Samoa included 260 males and 205 females; the Samoan sample included 300 males and 324 females. These subjects were recruited in a previous longitudinal study of adiposity and cardiovascular disease risk factors performed from 1990 to 1995 (Galanis et al., 1999; McGarvey, 2001). They were between the ages of 25 and 59 years with all four grandparents of Samoan ancestry. Anthropometric measurements of height (Ht), weight (Wt), waist circumference (WC), and hip circumference (HC) were obtained following standard protocols. Body mass index (BMI = Wt in kg/Ht in m^2) and waist–hip ratio (WHR = WC/HC) were calculated. A set of body fat measures including thigh circumference (THICIR), upper arm circumference (UAC), and calf circumference (CLFCIR) was obtained. In addition, three measures of skeletal mass and frame size were obtained according to Lohman et al. (1998), including the elbow breadth (distance between the epicondyles of the humerus), wrist breadth (distance between the medial aspect of ulna styloid and lateral aspect of radial styloid), and knee breadth (the distance between the most medial and lateral aspects of the femoral condyles). All data were collected at baseline, 1990–1991.

SNP Selection and Genotyping

A total of 32 SNPs, including 24 tagging SNPs within 30 kb upstream and 30 kb downstream of the original and potentially most significant *FTO* SNP (rs9939609) reported by Frayling et al. (2007) and seven additional significant SNPs from previous GWAS (rs9939973, rs1421085, rs1121980, rs17817449, rs8050136, rs3751812, rs7190492), were genotyped. Tagging SNPs were selected based on pairwise r^2 ($\geq$0.8) among all common SNPs with minor allele frequency (MAF $\geq$ 0.05) using the approach of Carlson et al. (2004). These SNPs fall within introns 1 and 2 of the *FTO* gene. In addition, we imputed SNPs to increase the coverage of *FTO* variants within a 70 kb region containing the original SNPs. Imputation was performed using all available populations in HapMapIII as reference, since the inclusion of multiple reference haplotypes increases the performance and quality of the imputation in novel populations (Marchini & Howie, 2010). The final set of SNPs included in the study was 60, with 24 tagging, 8 GWAS, and 28 imputed SNPs. The SNPlex protocol (Applied Biosystems, Foster City, CA, USA) was used for SNP genotyping, which is a multiple oligonucleotide ligation/polymerase chain reaction assay with universal ZipChute probe detection. Six internal replicates and negative controls were included to assure genotypic quality control, and the consistency rate was 100%. The overall genotype call rate of the 32 genotyped SNPs was >99.5%.

Statistical Analysis

Descriptive statistics of the study sample were computed using SAS v.9.2 (SAS Institute, Inc., Carey, NC, USA). All phenotypic traits were normalised using the Box-Cox method and adjusted for age and gender. Linkage disequilibrium (LD; r^2) between markers was estimated in Haploview (v.4.1) (Barrett et al., 2005). Genotype imputation was performed in Mach1, a Markov-chain-based haplotyper for unrelated populations (Li et al., 2009), and imputed SNPs were compiled with original SNPs prior to association testing. All genetic association analyses were performed using PLINK v1.07 (Purcell et al., 2007), using a 1 df linear model to assess the additive effects of the SNPs. A permutation test with 10,000 replications was used to assess significance after accounting for the presence of multiple markers. Association results were combined through fixed-effects meta-analyses using PLINK v1.07. Genotype

Table 1 Descriptive statistics of the phenotypic measures.

Trait	American Samoa (N = 465) Mean ± S.D.	Samoa (N = 624) Mean ± S.D.	*P*
Age (years)	38.58 ± 7.83	38.09 ± 8.82	0.34
Height* (cm)	166.86 ± 8.02	164.97 ± 8.03	0.0001
Body mass index* (kg/m^2)	34.71 ± 6.16	29.90 ± 5.22	<0.0001
Weight* (kg)	97.24 ± 19.72	81.43 ± 15.22	<0.0001
Waist circumference* (cm)	108.04 ± 15.01	95.10 ± 13.37	<0.0001
Hip circumference* (cm)	114.74 ± 12.71	103.48 ± 10.20	<0.0001
Waist–hip ratio*	0.94 ± .06	0.92 ± .07	<0.0001
Calf circumference (cm)	42.59 ± 4.47	39.47 ± 3.80	<0.0001
Thigh circumference* (cm)	48.38 ± 6.08	44.54 ± 5.37	<0.0001
Upper arm circumference* (cm)	37.65 ± 4.85	34.03 ± 4.11	<0.0001
Elbow (cm)	6.88 ± .76	6.94 ± 0.66	0.16
Wrist* (cm)	5.68 ± .58	5.57 ± .44	0.0004
Knee* (cm)	10.41 ± 1.21	10.05 ± 1.08	<0.0001

*American Samoa mean values are significantly greater than Samoa mean values.

frequencies and their conformity to Hardy–Weinberg equilibrium (HWE) were also assessed in PLINK, using an exact test (Wiggington et al., 2005). SNPs that showed significant deviations from HWE with a *P*-value of <0.01 and/or had an MAF of <0.05 were excluded from analysis.

Results

Descriptive statistics of the 12 anthropometric measures from both polities are presented in Table 1. As previously stated, all measures were adjusted for the effects of age and gender due to their correlation with body fat. The American Samoans had significantly higher fat-related measures, were taller, and had significantly larger skeletal measurements except elbow breadth in comparison to the Samoans.

Two genotyped SNPs and seven imputed SNPs were excluded from the analysis due to low MAF (<0.05) and deviations from HWE ($P < 0.01$). The pairwise LD plot of the remaining 51 SNPs was identical for American Samoa and Samoa (data not shown). There were no significant differences in allele frequencies between American Samoa and Samoa; compiled SNP statistics with comparative minor allele frequencies from Asian (CHB) and Caucasian (CEU) HapMaps are presented in Table 2. In general, Samoan allele frequencies were relatively closer to those of the Asian population than those of the Caucasian population. Of note, MAFs of the previously reported eight GWAS SNPs were significantly lower in both Samoan groups (0.161–0.239) than the CEU (0.292–0.478).

We tested associations of 51 SNPs with the anthropometric traits adjusted for age and gender. The analysis was performed separately for American Samoan and Samoan samples due to significant differences in phenotypic traits between the two polities (see Table 1). Thirty-six out of 1224 *P*-values were nominally significant, though none were previous GWAS SNPs (Table 3; all data with the nominal *P*-values are presented in Supplementary Tables S1 and S2). Thirty-two of the 36 nominal associations were observed in the Samoan sample. Of these, 26 were associated with measures of skeletal robustness (height and knee, wrist, and elbow breadth). No significant association, however, was found with any SNP after correction for multiple testing. A combined analysis and gender-specific analysis of the *FTO* SNPs in the American Samoan and Samoan samples did not uncover any further associations (data not shown). Finally, a meta-analysis was performed to uncover any consistent signals of association observed in both polities, but the results did not change (Supplementary Table S3). A second meta-analysis was performed to combine the association signals of rs9939609 in both Samoan polities and the Tongan population reported by Ohashi et al. (2007), but the signal remained insignificant ($P = 0.424$).

Since the majority of previous FTO reports have included BMI as the principal phenotype, we have estimated the effect sizes of nominally significant SNPs on BMI in the American Samoan and Samoan samples. There was no commonly associated SNP with BMI between the two polities; the effect size estimates for the two SNPs in Samoa (rs1861869, $\beta = -0.347$; rs7186521, $\beta = -0.586$) were lower than the SNP effect size estimate in American Samoa (rs1164281, $\beta = -0.931$). The confidence intervals of these estimates (Table 3) overlapped with reported point estimates in previous GWAS.

Table 2 SNP ID, origin, genomic position, and minor allele frequencies.

SNP information				Minor allele frequencies			
rs Number	Origin	Position	Minor allele	Am Samoa	Samoa	CHB*	CEU*
rs7186637	Imputed	52337603	T	0.466	0.464	0.177	0.256
rs1861869	Tagging	52347682	C	0.268	0.250	0.533	0.284
rs1077128	Tagging	52349154	T	0.417	0.405	0.207	0.389
rs7186521	Tagging	52350423	G	0.243	0.216	0.5	0.159
rs13334933	Imputed	52353137	G	0.467	0.466	0.155	0.389
rs16952517	Imputed	52354558	A	0.238	0.244	0.067	0.289
rs4784323	Imputed	52355066	A	0.257	0.241	0.292	0.244
rs7206790	Tagging	52355409	A	0.188	0.173	0.509	0.167
rs9930333	Imputed	52357478	G	0.209	0.197	0.482	0.182
rs12446228	Imputed	52357888	A	0.242	0.240	0.345	0.302
rs9939973	GWAS	52358069	A	0.187	0.173	0.482	0.186
rs9940128	Imputed	52358255	A	0.187	0.173	0.475	0.189
rs1421085	GWAS	52358455	C	0.182	0.168	0.448	0.114
rs16952520	Tagging	52360539	G	0.356	0.384	0.059	0.433
rs10852521	Tagging	52362466	T	0.440	0.434	0.417	0.356
rs12447107	Tagging	52362593	C	0.005	0.002	0.025	0.067
rs11075986	Tagging	52362845	G	0.373	0.397	0.102	0.477
rs9922047	Imputed	52363781	C	0.436	0.432	0.415	0.356
rs16952522	Imputed	52364999	G	0.070	0.067	0.022	0.058
rs17817288	Tagging	52365265	A	0.441	0.434	0.441	0.422
rs1477196	Imputed	52365759	A	0.238	0.235	0.341	0.302
rs1121980	GWAS	52366748	A	0.193	0.172	0.475	0.189
rs7193144	Imputed	52368187	C	0.188	0.170	0.442	0.122
rs16945088	Tagging	52370025	G	0.068	0.060	0.084	0.111
rs8057044	Imputed	52370115	A	0.256	0.230	0.542	0.233
rs17817449	GWAS	52370868	G	0.189	0.170	0.447	0.125
rs8063946	Tagging	52370999	T	0.373	0.397	0.049	0.512
rs8050136	GWAS	52373776	A	0.188	0.169	0.45	0.122
rs4783820	Imputed	52374285	A	0.306	0.323	0.017	0.411
rs9935401	Imputed	52374339	A	0.182	0.168	0.45	0.122
rs3751812	GWAS	52375961	T	0.188	0.168	0.45	0.122
rs3751813	Imputed	52376209	T	0.389	0.364	0.617	0.265
rs9939609	GWAS	52378028	A	0.191	0.172	0.45	0.122
rs12597786	Imputed	52378808	T	0.305	0.339	0.014	0.317
rs7202116	Imputed	52379116	G	0.189	0.169	0.448	0.122
rs7201850	Imputed	52379363	T	0.193	0.172	0.462	0.212
rs9931164	Imputed	52382739	G	0.003	0.002	0.018	0.07
rs9941349	Imputed	52382989	T	0.190	0.171	0.467	0.189
rs7190492	GWAS	52386253	A	0.242	0.239	0.351	0.298
rs9930501	Tagging	52387953	G	0.190	0.173	0.483	0.202
rs9930506	Imputed	52387966	G	0.190	0.171	0.475	0.256
rs2111650	Imputed	52390317	C	0.307	0.340	0.017	0.409
rs7204609	Imputed	52391106	C	0.307	0.340	0.018	0.422
rs8044769	Imputed	52396636	T	0.438	0.433	0.425	0.344
rs6499646	Imputed	52401034	C	0.372	0.398	0.11	0.465
rs17218700	Tagging	52402080	A	0.198	0.194	0.142	0.067
rs11642841	Tagging	52402988	A	0.118	0.104	0.45	0.056
rs9935403	Imputed	52404427	A	0.052	0.044	0.042	0.022
rs1861867	Tagging	52406062	A	0.217	0.209	0.357	0.278
rs11075994	Tagging	52407580	A	0.080	0.085	0.358	0.178
rs1421090	Tagging	52407671	G	0.489	0.484	0.729	0.467

*CHB = HapMap Chinese; CEU = HapMap Caucasian.

Table 3 SNPs showing nominally significant associations ($P \leq 0.05$) with anthropometric traits in American Samoa and Samoa samples.

SNP	Trait[#]	Allele	Effect size	Lower CI	Upper CI	*P*	Population
rs11075986*	Height	G	−0.192	−0.322	−0.062	0.027	Samoa
rs16945088*	Height	G	−0.559	−0.890	−0.228	0.014	Samoa
rs8063946*	Height	T	−0.131	−0.261	−0.001	0.026	Samoa
rs3751813*	Height	T	0.222	0.093	0.351	0.013	Samoa
rs6499646*	Height	C	−0.165	−0.296	−0.034	0.045	Samoa
rs1861869	Body mass index	C	−0.347	−0.693	−0.001	0.050	Samoa
rs7186521*	Body mass index	G	−0.586	−1.069	−0.102	0.018	Samoa
rs1421090	Hip circumference	G	−0.722	−1.360	−0.084	0.027	Samoa
rs17218700*	Waist–hip ratio	A	0.043	0.026	0.057	0.034	Samoa
rs7186521*	Thigh circumference	G	−0.635	−1.123	−0.148	0.011	Samoa
rs9930333	Thigh circumference	G	−0.724	−1.397	−0.051	0.038	Samoa
rs16952520	Elbow breadth	G	−0.056	−0.102	−0.011	0.015	Samoa
rs10852521*	Elbow breadth	T	0.048	0.006	0.090	0.025	Samoa
rs11075986*	Elbow breadth	G	−0.063	−0.108	−0.018	0.006	Samoa
rs9922047*	Elbow breadth	C	0.048	0.007	0.089	0.021	Samoa
rs17817288*	Elbow breadth	A	0.052	0.013	0.092	0.020	Samoa
rs8063946*	Elbow breadth	T	−0.056	−0.097	−0.015	0.008	Samoa
rs4783820	Elbow breadth	A	−0.062	−0.112	−0.012	0.016	Samoa
rs12597786	Elbow breadth	T	−0.055	−0.104	−0.006	0.029	Samoa
rs2111650	Elbow breadth	C	−0.054	−0.103	−0.004	0.034	Samoa
rs7204609	Elbow breadth	C	−0.054	−0.103	−0.004	0.034	Samoa
rs8044769*	Elbow breadth	T	0.049	0.007	0.091	0.023	Samoa
rs6499646*	Elbow breadth	C	−0.061	−0.105	−0.017	0.007	Samoa
rs11075986	Wrist breadth	G	−0.060	−0.116	−0.004	0.037	Samoa
rs16945088*	Wrist breadth	G	−0.101	−0.200	−0.001	0.047	Samoa
rs3751813*	Wrist breadth	T	−0.068	−0.124	−0.013	0.017	Samoa
rs6499646*	Wrist breadth	C	−0.063	−0.123	−0.003	0.040	Samoa
rs10852521*	Knee breadth	T	0.068	0.004	0.132	0.038	Samoa
rs9922047*	Knee breadth	C	0.060	0.001	0.120	0.050	Samoa
rs17817288*	Knee breadth	A	0.067	0.003	0.131	0.040	Samoa
rs8044769*	Knee breadth	T	0.069	0.005	0.133	0.036	Samoa
rs17218700*	Knee breadth	A	0.082	0.002	0.162	0.045	Samoa
rs11642841*	Body mass index	A	−0.931	−1.774	−0.088	0.031	Am. Samoa
rs11642841*	Calf circumference	A	−0.904	−1.764	−0.044	0.040	Am. Samoa
rs17218700*	Elbow breadth	A	−0.069	−0.137	−0.001	0.050	Am. Samoa
rs17218700*	Wrist breadth	A	−0.101	−0.198	−0.017	0.042	Am. Samoa

*Indicates SNPs with multiple nominally significant signals.
[#]Height was measured in cm, body mass index in kg/m^2, hip circumference in cm, thigh circumference in cm, elbow breadth in cm, wrist breadth in cm, knee breadth in cm, and calf circumference in cm.

Discussion

We investigated the association of 51 tagging, GWAS, and imputed SNPs with an expanded set of obesity-related anthropometric measures among Samoans and American Samoans. With respect to the phenotypic traits, there were significant differences in all measures of fatness and skeletal robustness (except elbow breadth) between the two Samoan groups, with the American Samoans showing significantly higher mean values of these traits. This likely reflects the effect of differential exposure to modernization with relatively higher affluence in American Samoa and a more neo-traditional life in Samoa (Keighley et al., 2006; McGarvey, 1991, 1994). There was, however, no difference in allele frequency distributions and LD patterns between the two groups reaffirming that the American Samoans and Samoans share a common genetic background as reported previously (Deka et al., 1994; Tsai et al., 2004).

Although *FTO* has emerged as a major gene influencing obesity particularly in populations of European descent, results from Asian populations have been less conclusive. Our study does not provide replication among the Samoans, which

can be attributed to several reasons. First, our sample size (465 American Samoans and 624 Samoans) may not have adequate power to capture the effect of the variants. For example, we have 80% power to detect a BMI effect size of 1.01 kg/m^2 in the American Samoan sample, 0.88 kg/m^2 in the Samoan sample, and 0.664 kg/m^2 in the combined sample, based on the allele frequency in our study populations of the widely replicated obesity-related *FTO* SNP (rs9939609) at alpha equal to 0.05. We have the power to detect only effect sizes that are somewhat larger than those reported in previous studies of FTO in Asian and Oceanic populations (Ohashi et al., 2007); therefore, we cannot conclusively rule out the involvement of *FTO* with obesity. Although we have greater power to detect smaller effect sizes in the combined sample, there were significant differences in phenotypic measurements between the two groups, and as noted above, a meta-analysis combining the two samples did not reveal significant associations after correcting for multiple testing. Effect size confidence intervals of SNPs nominally associated with BMI in our study population include the point estimates of previous GWAS reports, which might indicate inadequate power to maintain significance following adjustment for multiple testing. The effect size of *FTO* SNPs on BMI was stronger in the American Samoa sample than the Samoan sample, which may reflect the decreased power to detect smaller effects due to lower sample size, or the environmental component of excess caloric intake and sedentary lifestyles may obscure the direct genetic impact. Second, Samoan allele frequencies are significantly different from those in the reported GWAS and replication studies, particularly the European populations. Corollary to this is the evolutionary history of the Polynesians, who migrated from Southeast Asia about 4000–5000 years ago (Kirch, 2000; Soares et al., 2011). This together with a likely founder effect followed by genetic drift resulting in allele frequency changes could have masked the contribution of the *FTO* variants on obesity-related phenotypes among the Polynesians. Third, body compositions of contemporary Samoans are different from the Europeans with higher body and subcutaneous fat mass, bone mineral density as well as a higher proportion of fat-free soft tissue (Swinburn et al., 1999). This may suggest that mechanisms underlying energy balance in Polynesians are different. This could implicate instead other genetic loci with stronger influence on obesity-related traits that may be influenced by physiological and anthropometric differences between Asian and Caucasian populations. In addition, the high BMI of the population per se may contribute to the nonreplication, which could account in part for the limited signal detection in the American Samoan sample. A study among six Oceanic populations that included 116 Tongans from Polynesia also did not replicate the association of FTO variants with BMI (Ohashi et al., 2007); though this study was somewhat underpowered, these and the combined results from our second meta-analysis substantiate our nonreplication. Based on inconclusive studies, it could be surmised that *FTO* is not likely a major obesity locus in populations of Asian descent.

Authors' Contributions

The Samoan obesity study was conceived and designed by STM. The genetic study was designed by STM, DEW, and RD. Field work, data collection, and analysis of phenotypic traits were conducted under the supervision of STM. SV and JT provided guidance in the conduct of field work in Samoa and American Samoa, respectively. DEW provided supervision in statistical analysis. RK carried out the primary statistical analysis; RK and RD wrote much of the manuscript in consultation with STM and DEW. SG and HC performed genotyping under the supervision of RD. All the authors read and approved the final manuscript.

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Supporting Information

Additional supporting information may be found in the online version of this article:

Table S1 American Samoa nominal *P*-values.
Table S2 Samoan nominal *P*-values.
Table S3 Meta-analysis nominal *P*-values.

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