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SHORT COMMUNICATION

FTO polymorphisms in oceanic populations

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Abstract It has been suggested that Neel's "thrifty genotype" model may account for high body weights in some Oceanic populations, which presumably arose in modern times. In European populations, common variants (rs1421085-C, rs17817449-G, and rs9939609-A) in the fat mass and obesity (*FTO* associated) were recently found to be associated with body mass index (BMI) or obesity. In this study, we investigated the population frequencies of these variants in six Oceanic populations (Melanesians, Micronesians, and Polynesians) and tested for an association with BMI. Unlike European populations, the Oceanic populations displayed no significant association between the *FTO* polymorphisms and BMI. These variants were in strong linkage disequilibrium. The population frequencies ranged between 4.2 and 30.3% in the six Oceanic populations, and were similar to those in southeast and east Asian populations. Our study of the *FTO* polymorphisms has generated no evidence to support the thrifty genotype hypothesis for Oceanic populations.

Keywords *FTO* · Body mass index · Polynesian · Melanesian · Micronesian

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Introduction

The overall prevalence of obesity, defined as a body mass index (BMI) >30 kg m^{-2}, is increasing in Oceanic populations. In Tonga, more than 60% of adults (>15 years old) were reported to be obese (Duarte et al. 2003). It has been suggested that a high predisposition to obesity in Polynesians such as Tongans reflects an evolutionary development in energy-storage metabolism, allowing the individual to conserve energy in times of famine and store fat to excess in times of food abundance. The genotype associated with high metabolic efficiency may have been under positive selection in ancestors of Polynesian populations during their voyaging to the Polynesian Islands. This "thrifty genotype", originally hypothesized by Neel (1962), may be currently involved in obesity or type 2 diabetes under conditions of modernization.

Recently, common variants (rs1421085-C, rs17817449-G, and rs9939609-A) in the fat mass and obesity associated gene (*FTO*; MIM 610966) on chromosome 16 were found to be significantly associated with BMI or obesity in European populations (Dina et al. 2007; Frayling et al. 2007). The significant association has been replicated in several European populations in studies with large sample size (Dina et al. 2007; Frayling et al. 2007), confirming that the variants in the *FTO* gene region are involved in BMI in Europeans.

The obesity risk alleles of *FTO* are observed not only in Europeans (including the HapMap populations of Utah residents with ancestry from northern and western Europe), but also in other populations studied in the HapMap project: Africans (Yoruba in Ibadan, Nigeria) and East Asians (Japanese in Tokyo, Japan, and Han Chinese in Beijing, China) (The International HapMap Consortium 2003). The Austronesian (AN)-speaking groups or Polynesian ancestors are believed to have come from Asia/Taiwan and to have admixed with indigenous Melanesians before their dispersal to Polynesian Islands (Ohashi et al. 2006c). If Neel's "thrifty genotype" model is the appropriate explanation for a high predisposition to obesity in Polynesians, these obesity-associated alleles are expected to be at higher frequency in Polynesian than in Asian populations. In this paper, we investigate the geographic distribution of these alleles in six Oceanic populations (one Polynesian, one Micronesian, and four Melanesian), one Southeast Asian population, and two East Asian populations. Furthermore, we examine whether these variants are associated with BMI in Oceanic populations.

Materials and methods

Subjects

Oceanic subjects were drawn from three AN-speaking Melanesian populations (Munda, Paradise, and Balopa), one AN-speaking Micronesian population (Rawaki), one AN-speaking Polynesian population (Tonga), and one non-AN-speaking Melanesian population (Gidra); the locations are shown in Fig. 1. The subjects consisted of 39 individuals living in Munda town, 96 in Paradise village, 96 in Rawaki village, 39 Balopa islanders, 48 Gidra, and 198 Tongans. Munda is the main town In New Georgia Island, in the western Solomon Islands. Paradise is a coastal village 32 km north of Munda. The Paradise villagers are thought to have originally lived in a mountainous area and to have moved to the northern coast of New Georgia Island. Rawaki village is located on New Georgia Islands, but Rawaki villagers are AN-speaking Micronesians who migrated from the Gilbert Islands, Kiribati, to the New

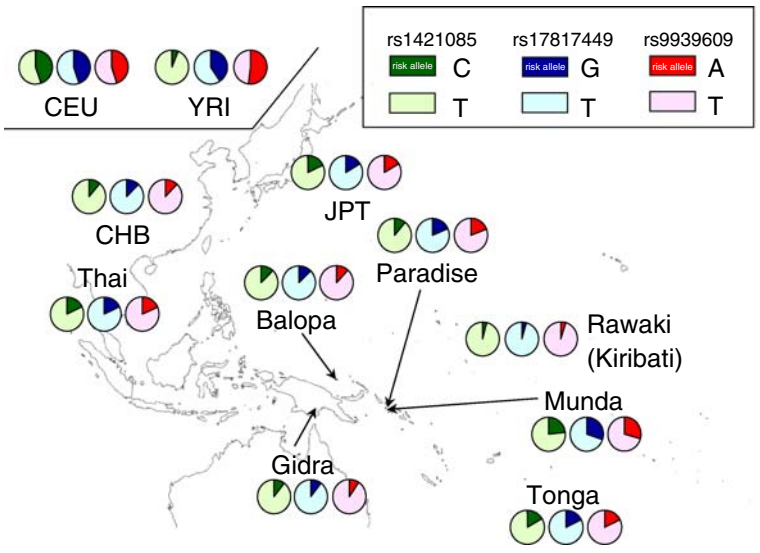

Fig. 1 Map of the populations studied and the allele frequencies of the *FTO* polymorphisms

Georgia Islands about 30 years ago. Thus, in this paper, Rawaki villagers are regarded as Micronesians. The Balopa Islands consist of three inhabited Islands (Lou, Pam, and Baluan) in Manus province of Papua New Guinea. The Gidra-speaking population, included in the non-AN-speaking group, is located in the southwestern lowlands of Papua New Guinea. Our previous studies have shown that the Gidra are genetically distant from the AN-speaking populations and have been isolated (Ohashi et al. 2000, 2004, 2006a, b, c; Yoshida et al. 1995). The Tongans were recruited from residents of Ha'ano and Fakakakai villages of Ha'apai Island and Nuku'alofa of Kingdom of Tonga.

To assess a southeast Asian population, 48 individuals living in Thailand were also investigated. In addition, the study included DNA samples and genotyping results from 60 Utah residents with ancestry from northern and western Europe (CEU), 60 Yoruba in Ibadan, Nigeria (YRI), 44 Japanese in Tokyo, Japan (JPT), and 45 Han Chinese in Beijing, China (CHB). The CEU, YRI, JPT, and CHB were HapMap panel subjects (The International HapMap Consortium 2003).

Blood sampling was conducted after obtaining informed consent from each participant. This study was approved by the Health Ethics Committee, Ministry of Health, Solomon Islands; the Ministry of Education and Training, Solomon Islands; the Medical Research Advisory Committee of Papua New Guinea; the institutional review board of the Faculty of Tropical Medicine, Mahidol University; and the Research Ethics Committee of the Faculty of Medicine, University of Tokyo.

Genotyping

Genomic DNA was extracted from peripheral blood using a QIAamp Blood Kit (Qiagen, Hilden, Germany). Three SNPs in the *FTO* gene, rs1421085, rs17817449, and rs9939609, were genotyped by using TaqMan assays.

Statistical analysis

Allele frequencies of the *FTO* polymorphisms were estimated by direct counting. The haplotype frequencies and linkage disequilibrium (LD) parameters were estimated by SNPAlyze software (Dynacom, Tokyo, Japan) based on the expectation–maximization algorithm. To assess the association of rs9939609 with BMI or weight, we performed a multiple regression analysis adjusted for age and sex. Only subjects at least 20 years old were analyzed in the regression analysis. The genotypes of rs9939609-AA, rs9939609-AT, and rs9939609-TT were coded as 2, 1, and 0, respectively. One-sided *P*-values were calculated because the associated allele (i.e., rs9939609-A) had been established.

To examine whether the *FTO* gene has been subjected to natural selection, the number of synonymous substitutions per synonymous site (d_S) and the number of nonsynonymous substitutions per nonsynonymous site (d_N) between coding sequences from two different species were estimated using the Jukes–Cantor model (Jukes and Cantor 1969), in which the numbers of synonymous and nonsynonymous substitutions and the numbers of potentially synonymous and potentially nonsynonymous sites were calculated using the Nei–Gojobori method (Nei and Gojobori 1986). The following coding sequences were used for the calculation: human (XM_941142), chimpanzee (XM_510968), and mouse (NM_011936). The nucleotide sequence alignment was based on the amino acid sequence. Because three amino acids were found to be inserted in human and chimpanzee sequences, these codons were excluded from the analysis for comparison of human with mouse. For testing whether the observed difference $D = d_N - d_S$ is different from 0, a codon-based Z test was performed by using Mega version 3.1 (Kumar et al. 2004).

P-values of less than 0.05 were regarded as statistically significant in this study.

Results and discussion

The population frequencies of the obesity-associated *FTO* variants ranged between 4.2 and 30.3% in six Oceanic populations (Table 1). Interestingly, the allele frequencies in Oceanic populations, except for Munda, were less than those in Thailand and JPT. Since genetic studies have shown that AN-speaking Polynesian ancestors came from Asia/Taiwan to the Bismarck Archipelago in Near Oceania,

Table 1 Allele frequencies of *FTO* polymorphisms

Population	rs1421085-C (no. of subjects)	rs17817449-G (no. of subjects)	rs9939609-A (no. of subjects)
Munda	0.237 (38)	0.303 (38)	0.295 (39)
Paradise	0.111 (95)	0.189 (95)	0.193 (96)
Rawaki	0.042 (95)	0.047 (95)	0.047 (96)
Balopa	0.125 (36)	0.128 (39)	0.118 (38)
Gidra	0.106 (47)	0.104 (48)	0.096 (47)
Tongan	0.167 (177)	0.177 (184)	0.176 (187)
Thai	0.181 (47)	0.181 (47)	0.188 (48)
JPT	0.182 (44)	0.167[a] (42)	0.167 [a] (45)
CHB	0.114 (44)	0.125[a] (40)	0.122 [a] (45)
CEU	0.448[a] (58)	0.447[a] (57)	0.450 [a] (60)
YRI	0.060 (58)	0.405[a] (58)	0.517 [a] (60)

[a] Data were obtained from the HapMap database

and then expanded into Remote Oceania, the thrifty genotype model would predict that the population frequencies of the obesity risk alleles would be increased from Asians to Polynesians. However, such a geographic cline was not observed in the populations studied (Fig. 1). Thus, we may conclude that the *FTO* polymorphisms do not support Neel's thrifty genotype model for Oceanic populations.

The three SNPs were in strong LD ($D' = 1$) with each other, and only two haplotypes (H1: rs1421085-T, rs17817449-T, rs9939609-T; H2: rs1421085-C, rs17817449-G, rs9939609-A) were observed at population frequencies >1% in CEU, Asian, and most of the Oceanic populations. In Munda and Paradise, however, a third haplotype (H3: rs1421085-T, rs17817449-G, rs9939609-A) was found at population frequencies of 6.6 and 7.9%, respectively. Because Munda and Paradise populations are closely located on New Georgia Island, the H3 haplotype might be specific to this area. Interestingly, a fourth haplotype (H4: rs1421085-T, rs17817449-T, rs9939609-A) was observed at a population frequency of 12.5% in YRI. In short, four haplotypes with population frequency >1% were detected in YRI, three in Munda and Paradise, and two in the other populations.

The association between the rs9939609-A allele and obesity was examined in four of the Oceanic populations. The mean values of BMI and weight were very different among these populations (Table 2). As Duarte and colleagues reported (Duarte et al. 2003), the mean BMI was very high in the present Tongan subjects; in our study, 73.3% of these were obese. In all four populations, rs9939609-A was not significantly associated with either BMI or weight (Table 3). In addition, the significant association was not detected even when all the subjects ($n = 320$) were analyzed together (data not shown). Due to strong LD between the three SNPs, rs1421085-C and rs17817449-G were not examined in this study. The sample sizes of this study were much smaller than those of previous studies for European populations (Dina et al. 2007; Frayling et al. 2007). This may be a reason why no significant association was detected. However, our results suggest that the contribution of the *FTO* polymorphisms to a high predisposition to obesity is small or absent in Oceanic populations. There may be other common variants more strongly associated with BMI in Oceanic populations.

To examine whether the *FTO* gene has been subjected to natural selection, the human sequence was compared to mouse and chimpanzee sequences for the numbers of synonymous (d_S) and nonsynonymous (d_N) substitutions. For the human-to-mouse comparison, the $D = d_N - d_S$ was significantly lower than 0 ($P < 10^{-4}$ by Z test), suggesting that purifying selection or negative selection has operated on the *FTO* gene since the divergence of mouse and human lineages. The same result was obtained between human and chimpanzee ($P = 0.016$). This highly selective constraint is consistent with the observation that only one nonsynonymous SNP (rs16952624) has been detected in human populations (NCBI dbSNP build 127). Thus, it would be

Table 2 Age, height, weight, and BMI in Oceanic subjects for association studies

Population	No. of subjects (male/female)	Age (years)	Height (cm)	Weight (kg)	BMI (kg m^{-2})
Munda	23/16	51.2 ± 12.9	160.4 ± 7.9	70.7 ± 13.9	27.4 ± 4.6
Paradise	46/44	41.6 ± 14.0	158.7 ± 7.5	61.3 ± 6.7	24.4 ± 2.3
Rawaki	43/32	38.0 ± 13.6	166.2 ± 7.8	80.6 ± 16.9	29.2 ± 6.0
Tongans	36/80	46.9 ± 11.9	167.2 ± 7.0	104.4 ± 16.0	37.3 ± 4.9

Data are mean ± SD. The analysis included only those subjects whose age was at least 20 years

Table 3 Association of rs9939609-A with BMI or weight in Oceanic populations

Population	BMI		Weight	
	Partial regression coefficient	*P*-value (one-sided)	Partial regression coefficient	*P* value (one-sided)
Munda ($n = 39$)	0.01553	0.4951	0.41258	0.4519
Paradise ($n = 90$)	–0.41766	0.8240	–1.27518	0.8458
Rawaki ($n = 75$)	2.34434	0.1655	6.93293	0.1740
Tongans ($n = 116$)	0.28210	0.3711	–0.81090	0.6156

Subjects whose age was at least 20 years were analyzed in the multiple regression analysis with independent variables of age, sex, and rs9939609 genotype. Partial regression coefficients estimated for age and sex are not shown

interesting to elucidate the biological function of FTO not only in mice but also in humans.

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