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SHORT COMMUNICATION

A missense variant, rs373863828-A (p.Arg457Gln), of *CREBRF* and body mass index in Oceanic populations

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It has been suggested that a 'thrifty' genotype hypothesis can account for high prevalence of obesity in the island populations of Oceania. A recent genome-wide association study revealed that a missense variant, rs373863828-A (p.Arg457Gln), of the *CREBRF* gene (encoding CREB3 regulatory factor) was associated with an excessive increase in body mass index (BMI) in Samoans. In the present study, the association of rs373863828-A with an increase in BMI was examined in four Austronesian (AN)-speaking populations in Oceania. We found that rs373863828-A was frequently observed (frequency of 0.15) in Tongans (Polynesians), and was strongly associated with higher BMI ($P = 6.1 \times 10^{-4}$). A single copy of the rs373863828-A allele increased BMI by 3.09 kg m^{-2} after adjustment of age and sex. No significant association was detected in the other three AN-speaking populations (Melanesians and Micronesians) living in Solomon Islands. This was probably due to the low allele frequency (0.02–0.06) of rs373863828-A as well as small sample size. The rs373863828-A allele was not found in both AN-speaking and non-AN-speaking Melanesians living in Papua New Guinea. Our results suggest that rs373863828-A of *CREBRF*, a promising thrifty variant, arose in recent ancestors of AN-speaking Polynesians.
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Prevalence rates of obesity are increasing in the island populations of Oceania. A 'thrifty' genotype hypothesis, originally hypothesized by Neel,[1] may account for a high predisposition to obesity in Oceanic populations. The genotype associated with high metabolic efficiency or obesity at the present day seems to have been selectively advantageous when Oceanian ancestors spread out across the Pacific to Polynesia. A recent genome-wide association study (GWAS) revealed that a missense variant, rs373863828-A (p.Arg457Gln), of the *CREBRF* gene (OMIM *617109) encoding CREB3 regulatory factor is strongly associated with an increase in body mass index (BMI) in Samoans.[2] Although rs373863828-A is certainly associated with BMI in Samoans, it is unclear whether this variant is also associated with BMI in other Oceanic populations. The aims of this paper are as follows: (1) to investigate the geographical distribution of rs373863828-A in Oceania and (2) to examine the association with an increase in BMI in Oceanic populations other than Samoans.

Two single nucleotide polymorphisms (SNPs) in *CREBRF*, rs373863828 and rs12513649, were genotyped by using TaqMan assays (Applied Biosystems, Foster City, CA, USA) for six Oceanic populations: Munda, Kusaghe, Balopa, Rawaki, Tonga and Gidra. They are classified into four groups in terms of linguistics and geography (Figure 1): two Austronesian (AN)-speaking Melanesians in Solomon Islands (Munda and Kusaghe) and one in the northwestern end of the Bismarck Archipelago of Papua New Guinea (PNG) (Balopa), one AN-speaking Micronesians in Solomon Islands (Rawaki), one AN-speaking Polynesians in Tonga (Tonga), and one non-Austronesian (NAN)-speaking Melanesians in southwestern lowlands of PNG (Gidra). Genomic DNA was extracted from peripheral blood using a QIAamp Blood Kit (Qiagen, Hilden, Germany). The blood sampling was conducted after obtaining informed consent from each subject.

The population frequencies of rs373863828-A and rs12513649-G, a variant firstly identified in discovery sample of 3072 Samoans in a previous GWAS,[2] in six Oceanic populations were shown in Figure 1 and Table 1. The genotype frequencies were not significantly deviated from Hardy–Weinberg equilibrium except for rs12513649 in Munda (P-value = 0.022). These alleles were found in AN-speaking Melanesians and Micronesians as well as Polynesians, and the frequencies were much higher in Polynesians (that is, Samoans and Tongans) than those in the other Oceanic populations. Interestingly, neither rs373863828-A nor rs12513649-G was detected in Gidra, who are NAN-speaking Melanesians, implying that these variants are not derived from indigenous Melanesians.

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Our previous studies suggested that ancestors of Polynesians were likely to mix with indigenous Melanesians in the Bismarck Archipelago (that is, ancestors of Balopa islanders).[3,4] Although the sample size is too small to conclude, lack of rs373863828-A in Balopa islanders might reflect the recent origin of rs373863828-A. This expectation is consistent with the observation that rs373863828-A exhibited remarkable extended haplotype homozygosity in Samoans.[2] Taken together, we speculate that a missense variant, rs373863828-A (p.Arg457Gln), of *CREBRF* arose in recent ancestors of AN-speaking Polynesians after they had left the Bismarck Archipelago for Polynesia. To clarify the origin of rs373863828-A, more Oceanic populations need to be studied.

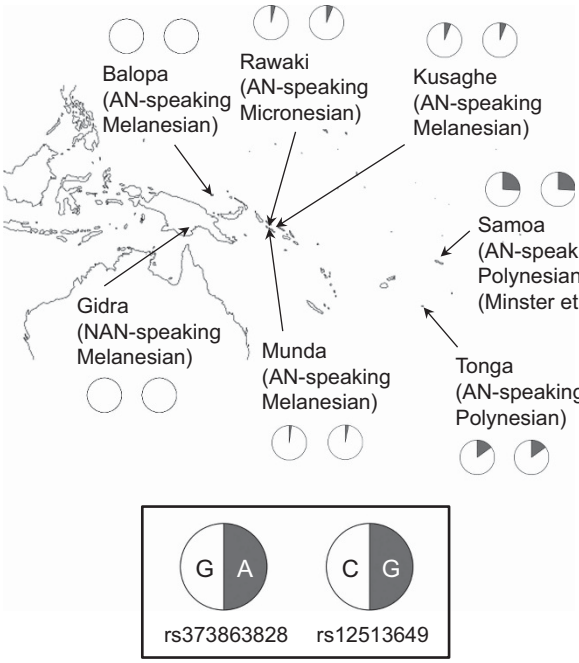

Figure 1 Allele frequencies of rs373863828 (pie chart on the left side) and rs12513649 (pie chart on the right side) in Oceanian populations. Two SNPs in *CREBRF*, rs373863828 and rs12513649 were investigated in six Oceanian populations: Munda, Kusaghe, Rawaki, Balopa, Gidra and Tonga. Munda is the main town on New Georgia Island in the western Solomon Islands. Kusaghe is a coastal village, which is 32 km North of Munda. Rawaki village is located on New Georgia Islands, but Rawaki people are Austronesian (AN)-speaking Micronesians who migrated from the Gilbert Islands, Kiribati to the New Georgia Islands about 50 years ago. Rawaki villagers are therefore regarded as Micronesians in this paper. The Balopa Islands, which consist of three inhabited Islands (Lou, Pam and Baluan) in Manus province of Papua New Guinea (PNG). The Gidra people, non-Austronesian (NAN)-speaking Melanesians live in the southwestern lowlands of PNG. Tongans are people living in Ha'ano and Fakakakai villages of Ha'apai Island and in Nuku'alofa of Kingdom of Tonga.

A multiple regression analysis adjusted for age and sex revealed the significant associations of rs373863828-A (P-value $= 6.1 \times 10^{-4}$) and rs12513649-G (P-value $= 5.2 \times 10^{-4}$) with an increase in BMI in Tongans (Table 1). A single copy of the rs373863828-A allele increased BMI by 3.09 kg m^{-2}, although the 95% confidence interval was wide. Considering that the regression coefficient for rs9939609-A, a *FTO* (OMIM *612460) variant strongly associated with BMI in Europeans,[5,6] was 0.28 kg m^{-2} in the same sample of Tongans,[7] a missense variant, rs373863828-A (p.Arg457Gln), of *CREBRF* seems to be a major genetic determinant of BMI in Tongans. The rs373863828-A variant was also significantly associated with increases in waist (P-value $= 0.0058$) and hip circumferences (P-value $= 0.0010$) in Tongans. A single copy of rs373863828-A increased waist by 5.73 cm and hip by 5.69 cm. No significant association with BMI was found in the other populations living in Solomon Islands; however, the lack of association would have come from the low allele frequency as well as small sample size. The regression coefficients, β, were positive in all the populations tested (Table 1), and more significant association was detected (P-value $= 1.1 \times 10^{-4}$; $\beta = 1.96$ kg m^{-2}) when four populations were combined in a multiple regression analysis adjusted for age, sex and population. Therefore, we may say that rs373863828-A is a promising thrifty variant in Oceanic populations.

The Lapita people, common ancestors of AN-speaking Melanesians, Micronesians and Polynesians appeared in the Bismarck Archipelago in Near Oceania, and then expanded into Remote Oceania. The rs373863828-A variant may have helped the ancestors of AN-speaking Polynesians to survive the long sea voyages across open ocean and/or to store energy (fat) from limited food resources at the time of the first settlement of each island.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

Table 1 Association of CREBRF polymorphisms with BMI in Oceanic populations

				BMI (kg m^{-2})			*rs373863828-A*			*rs12513649-G*		
Population	*Region*	*Languege*	n	*Mean*	*Median*	*s.d.*	*Frequency*	β *(s.e.)*	P-*value*	*Frequency*	β *(s.e.)*	P-*value*
Tonga	Polyneisa	AN	171	34.3	33.6	6.4	0.15	3.09 (0.89)	6.1×10^{-4}	0.15	3.08 (0.87)	5.2×10^{-4}
Rawaki	Micronesia	AN	150	28.0	26.9	5.3	0.04	1.07 (1.58)	0.50	0.06	0.64 (1.29)	0.62
Munda	Melanesia	AN	169	26.0	25.8	4.9	0.02	2.18 (2.01)	0.28	0.03	0.75 (1.44)	0.60
Kusaghe	Melanesia	AN	202	24.1	23.8	2.5	0.06	0.59 (0.51)	0.25	0.06	0.59 (0.51)	0.25
Balopa	Melanesia	AN	32	N/A	N/A	N/A	0	N/A	N/A	0	N/A	N/A
Gidra	Melanesia	NAN	95	N/A	N/A	N/A	0	N/A	N/A	0	N/A	N/A

Abbreviations: AN, Austronesian; *n*, sample size; NAN, non-Austronesian; N/A, not applicable; β, unstandardized coefficient.
Only subjects aged 18 years and older were analyzed in the association analyses.
The genotypes of rs373863828 and rs12513649 were coded as 2, 1 and 0, reflecting the number of copies of variant allele at each SNP.
A linear regression analysis adjusted for age and sex was performed to examine the association of each variant allele with BMI.
Two-sided *P*-values were calculated.

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Informed consent

Informed consent was obtained from the patient for publication of this paper.

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