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Re: “Widespread prevalence of a CREBRF variant among M ori and Pacific children is associated with weight and height in early childhood”

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Dear Editor

Your journal recently published the article “Widespread prevalence of a CREBRF variant amongst M ori and Pacific children is associated with weight and height in early childhood” [1]. The minor A-allele of the *CREBRF* rs373863828 variant (p.Arg457Gln) was analyzed in a pooled sample of New Zealand (NZ) children of maternally self-reported M ori, Pacific, European, or Asian ethnicity. Berry et al. [1] reported A-allele frequencies of 1.5% (European) and 1.1% (Asian). Other studies report that the A-allele has a prevalence of 26% in Samoa and American Samoa [2] and 15% in Tonga [3], but is extremely rare in other genotyped populations. In the Genome Aggregation Database [4], it was observed in 5/76,104 European (0.0033%) and 2/24,773 Asian individuals (0.0040%) (Table 1), and in TOPMed (www.nhlbiwgs.org) in 3/62,787 individuals (0.0024%). (In the original TOPMed release, a Samoan data set was included, thus an A-allele prevalence of 0.007 is recorded for TOPMed on Ensembl (as of 10 October 2017). However, in the latest Bravo Freeze 5 release

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Compliance with ethical standards

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(used here) that Samoan data set was not included.). Therefore, the frequencies reported by Berry et al. [1] are considerably greater than those observed in the Genome Aggregation Database and are extremely unlikely to have occurred by chance (European $P_{\text{Fisher}} = 4 \times 10^{-80}$; Asian 9×10^{-19}). They are also inconsistent with our own findings. We genotyped *rs373863828* in two NZ European sample sets and observed A-allele frequencies of 0.15% in the Screening for Pregnancy Endpoints (SCOPE) study and 0.19% in the Gout Genetics study (Table 1). These frequencies were considerably higher than observed in the Genome Aggregation Database ($P_{\text{Fisher}} = 1 \times 10^{-4}$ and 4×10^{-7} , respectively), consistent with the introduction of the A-allele into the NZ European population by admixture with the M ori and Pacific populations. However, the frequencies in our sample sets were tenfold lower than those reported by Berry et al. [1] and differed significantly ($P_{\text{Fisher}} < 3 \times 10^{-7}$), with non-overlapping 99% confidence intervals. We also genotyped two NZ Asian sample sets derived from the same studies, observing no A-allele-positive individuals in either sample set (Table 1).

The SCOPE European and Asian data are drawn from a similar population to that of Berry et al. [1]—the former from children born 2005–2008 in Auckland and the latter from children born in 2009 and 2010 in Auckland and the neighboring Waikato region. Non-reporting of M ori and/or Pacific ethnicity by European or Asian mothers cannot explain the observed A-allele prevalence in the European and Asian children (Table 2). Using New Zealand inter-ethnic partnership data [5] from the 2001 census, we estimate that if 10%, for example, of European or Asian mothers did not report M ori and/or Pacific ethnicity the A-allele prevalence would be 5.4×10^{-4} and 2.0×10^{-4} , respectively—considerably lower than the prevalences of 0.015 and 0.011, respectively, reported by Berry et al. [1].

We also note that the Gout Genetics and SCOPE NZ European genotypes exhibited Hardy–Weinberg equilibrium ($P = 0.96$ and 0.95 , respectively), whereas the Berry et al. [1] European data set did not ($P = 0.01$). Deviation from Hardy–Weinberg equilibrium can be caused by genotyping errors [6] or, in a multi-ethnic cohort, misalignment of genotype to individuals. These possibilities require further investigation by Berry et al., which could involve the use of ancestry informative markers, before accepting their results on the biologically important *CREBRF rs373863828* variant are correct or generalizable to the NZ population of children.

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Table 1
Comparison of *rs373863828* A-allele frequencies observed in four European and four Asian sample sets

Sample set	N	rs373863828				P_{Compare}^c	P_{HWE}
		GG	AG	AA	A-allele Freq. (99% CI)		
European							
Berry et al. [1]	1744	–	–	–	0.0150 (0.0097; 0.0203)	–	0.01
Genome Aggregation Database	76,104	76,099	5	0	0.000033 (0; 0.000071)	4×10^{-80}	0.99
SCOPE study ^a	969	966	3	0	0.0015 (0; 0.0038)	2×10^{-7}	0.96
Gout Genetics study ^b	1328	1323	5	0	0.0019 (0; 0.0041)	9×10^{-9}	0.95
Asian							
Berry et al. [1]	548	–	–	–	0.011 (0.003; 0.019)	–	0.06
Genome Aggregation Database	24,733	24,731	2	0	0.00004 (0; 0.00011)	9×10^{-19}	0.99
SCOPE ^a	81	81	0	0	0 (–; –)	0.38	–
Gout Genetics study ^b	208	208	0	0	0 (–; –)	0.04	–

^aThe SCOPE study [7] comprises six-year-old children from Auckland, New Zealand. Self-reported ethnicity data were collected from parents of the children. Referring to Table 1 of ref 7, Asian individuals included here comprise those of “Asian” ($n = 17$ here), “Indian” ($n = 29$ here) ethnicity and 35 “Admixed” individuals self-reporting Asian (defined here as East, South East, and South Asian) ethnicity

^bThe Gout Genetics study [8] comprises adult gout cases and controls recruited from throughout New Zealand. Participants were asked the ancestry of their grandparents

^cComparison to Berry et al. by Fisher’s exact test

Table 2

Estimated *rs373863828* A-allele frequency with maternal non-declaration of M ori and/or Pacific ancestry in children from partnerships [1] between Asian or European individuals and M ori or Pacific individuals

Proportion not declared ^a	Estimated <i>rs373863828</i> A-Allele Frequency ^b	
	European and M ori/Pacific	Asian and M ori/Pacific
1.0	0.0054 [2]	0.0020
0.8	0.0043	0.0016
0.6	0.0032	0.0012
0.4	0.0022	0.00079
0.2	0.0011	0.00040
0.1	0.00054	0.00020
0.05	0.00027	0.00010

^a The proportion of opposite-sex inter-ethnic partnerships was calculated from the number of individuals reporting such partnerships in the 2001 New Zealand Census (Tables 7 and 8 of ref. [5]); European = 10.3%, Asian = 3.8%

^b Calculated by multiplying the A-allele frequency in the combined Maori and Pacific sample sets of Berry et al. (0.104) by the proportion of European or Asian inter-ethnic partnerships, then dividing by two (to account for the Asian or European partner)