The renal urate transporter SLC17A1 locus: confirmation of association with gout

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Introduction: Two major gout-causing genes have been identified, the urate transport genes SLC2A9 and ABCG2. Variation within the SLC17A1 locus, which encodes sodium-dependent phosphate transporter 1, a renal transporter of uric acid, has also been associated with serum urate concentration. However, evidence for association with gout is equivocal. We investigated the association of the SLC17A1 locus with gout in New Zealand sample sets.

Methods: Five variants (rs1165196, rs1183201, rs9358890, rs3799344, rs12664474) were genotyped across a New Zealand sample set totaling 971 cases and 1,742 controls. Cases were ascertained according to American Rheumatism Association criteria. Two population groups were studied: Caucasian and Polynesian.

Results: At rs1183201 (SLC17A1), evidence for association with gout was observed in both the Caucasian (odds ratio (OR) = 0.67, \( P = 3.0 \times 10^{-6} \)) and Polynesian (OR = 0.74, \( P = 3.0 \times 10^{-3} \)) groups. Meta-analysis confirmed association of rs1183201 with gout at a genome-wide level of significance (OR = 0.70, \( P = 3.0 \times 10^{-8} \)). Haplotype analysis suggested the presence of a common protective haplotype.

Conclusion: We confirm the SLC17A1 locus as the third associated with gout at a genome-wide level of significance.

Introduction
Regulation of serum urate concentration is central to the development of gout, with renal uric acid excretion a critical checkpoint [1]. Genome-wide association scans examining the genetic control of serum urate concentrations have identified two renal urate transporters - SLC2A9 and ABCG2 - that have a strong effect on gout risk in multiple ethnic groups [2]. Whilst amongst other loci (SLC22A11, GCKR, INHBC, SLC17A1, RREB1, PDZK1, SLC16A9, LRRC16A) have been associated with serum urate concentrations at a genome-wide level of significance in genome-wide association scans [3,4], only some of them (SLC22A11, GCKR, INHBC, SLC17A1) were associated with gout at a nominal level of significance (\( P < 0.05 \)) in 1,100 cases nested within a large genome-wide association scan population-based cohort [4]. To understand why some loci do not associate with gout, and to assess the weakly associated loci in clinical gout, it will be necessary to minimize heterogeneity owing to the type of gout (primary or secondary to other causes such as diuretic use) and to test for association in clinically proven cases.

The solute carrier family 17 member 1 (encoded by SLC17A1), also known as sodium phosphate transport protein 1 (NPT1), is expressed on the apical membrane of renal tubular cells and mediates sodium and inorganic phosphate co-transport [5]. Sodium-dependent transporter 1 has also been identified as a urate transport protein [6,7], probably secretory [7] with the gout-protective allele of I269T [8] leading to increased sodium-dependent transporter 1 activity [6] and, presumably, increased secretion of uric acid. Genome-wide association scans have shown that genetic variants associate with serum urate concentration in a Caucasian sample [3,4]. SLC17A1 has been associated with gout in a Japanese sample set (I269T (rs1165196), odds ratio (OR) = 0.55, \( P = 0.005 \)) [8] but with conflicting results in Caucasian sample sets. Marker
rs1165205 in SLC17A3 was first associated with gout (OR = 0.85, P = 0.002) [9]. A later study incorporating the same clinical material with additional cases and controls, however, reported reduced combined evidence for association with gout using a strongly correlated marker within SLC17A1 (rs1165196, $r^2 = 0.96$; OR = 0.89, P = 0.013) [4] - in this study the markers most strongly associated with serum urate were within SLC17A1 (rs1165196 and other tightly correlated markers), suggesting that this gene was more likely than SLC17A3 to harbor an etiological variant. A separate study reported no evidence in Caucasian for association with gout (rs1183201, $r^2$ with rs1165196 = 0.87, OR = 0.97, P = 0.68) [10]. This equivocal evidence for association with gout in a Caucasian population is notable given the genome-wide evidence for association with serum urate concentration [4]. Both studies had adequate power to detect association of a moderate effect size, but neither study used clinical criteria to define gout. Here, we aimed to test the SLC17A1 locus for association with gout, in multiple ancestral groups, using cases defined as a diagnosis of gout by the 1977 American College of Rheumatology (ARA) clinical criteria. The variants tested were rs1183201, demonstrated to influence serum urate concentration in Caucasian populations [3], the maximally gout-associated SNP (rs1165196 (I269T)) in Japanese [8], and three other SNPs predicted to tag major variation in Polynesian populations.

Materials and methods
Study participants
There were a total of four New Zealand (NZ) case-control sample sets, one of Caucasian ancestry and three of different Polynesian ancestries (see Supplemental Table S1 in Additional file 1). The sample sets were Eastern Polynesian (EP; NZ Māori and Cook Islands, 284 cases and 349 controls), Western Polynesian (WP; Samoa, Tonga, Niue and Tokelau, 251 cases and 144 controls), combined Eastern and Western Polynesian (EP/WP; 15 cases and 21 controls) and Caucasian (421 cases and 1,228 controls; of the controls, 590 had been SNP typed genome wide [11,12]). The EP samples were further subdivided into two groups to remove effects of stratification, as described in more detail below, based on the estimated proportion of EP ancestry (EP/N, 236 cases and 192 controls; and EP/Z, 48 cases and 157 controls). All gout cases recruited had a diagnosis of gout confirmed according to the American College of Rheumatology (ACA) clinical criteria. The variants tested were rs1183201, demonstrated to influence serum urate concentration in Caucasian populations [3], the maximally gout-associated SNP (rs1165196 (I269T)) in Japanese [8], and three other SNPs predicted to tag major variation in Polynesian populations.

SNP selection and determination of genotypes
Using CHB HapMap data as the most closely related and available population to Polynesia, Haploview software (Broad Institute, Cambridge, MA, USA) was used to define four haplotype blocks using the Gabriel confidence interval method covering SLC17A1 (defined by rs4712972 (25.772 Mb) to rs12192635 (25.881 Mb)). Variants tagging major haplotypes were selected: rs9358890 in block 1, rs3799344 in block 2, rs1183201 in block 3 (previously associated with control of serum urate concentration) [3] and rs12664474 in block 4. The haplotype blocks extended into flanking genes (SLC17A4 and SLC17A3). In Centre d’Etude du Polymorphisme Humain (CEU) Caucasian population and the CHB population, rs1183201 and rs3799344 exhibited some intermarker linkage disequilibrium (LD) ($r^2 = 0.77$ and 0.50, respectively) and rs9358890 and rs12664474 also exhibited LD ($r^2 = 0.35$ and 0.62, respectively). SNP rs9358890 is in SLC17A4, and rs12664474 is in SLC17A3. SNP rs1165196 (SLC17A1) was also selected, in strong LD with rs1183201 ($r^2 = 0.87$ in CEU and 0.91 in CHB) (Figure 1).

Genotyping was done by TaqMan® SNP genotyping assays (Applied Biosystems, Foster City, CA, USA) using a Lightcycler® 480 Real-Time PCR System (Roche,
Indianapolis, IN, USA) for four SNPs: rs1183201 (assay ID: C_1911034_10), rs9358890 (assay ID: C_25595118_10), rs3799344 (assay ID: C_194536_10) and rs12664474 (assay ID: C_11189653_10). SNP rs1165196 was genotyped using Sequenom technology (Sequenom, Inc. San Diego, CA, USA). SNPs rs9358890 and rs12664474 had been genotyped over 590 of the Caucasian controls on the Affymetrix 6 SNP array (Affymetrix, Santa Clara, CA, USA) [12] - genotypes were imputed for rs3799344 and rs1183201 with IMPUTE2, using HapMap3 CEU (NCBI Build 36 (db126b)) as reference haplotypes.

Statistical analysis
ORs were calculated using PLINK software [17]. Because the case-control sample sets were not matched for sex, association analysis also included sex as a possible confounder. Analysis of association of haplotypes was also performed using PLINK. Meta-analysis was carried out using Rmeta software (within STATA 8.0, Stata, College Station, TX, USA) to calculate the combined Mantel-Haenszel OR. Thirty-seven biallelic genic control markers (see Supplemental Table 2 in Additional file 1) were genotyped in the EP sample set, and STRUCTURE software [19] was used to estimate the individual proportion of EP ancestry. This estimation was performed using the following parameters: number of populations assumed to be two, 30,000 burn-in period, and 100,000 Markov chain Monte Carlo replications after burn-in. Caucasian control individuals genotyped for the 67 markers were included as representative of the ancestral Caucasian population to aid in population clustering, although we were unable to include EP ancestral representatives. Plots of self-reported ancestry versus STRUCTURE estimated ancestry are shown in Supplemental Figure 1 in Additional file 1. For association analysis we created two datasets matched for EP ancestry - EP/N with estimated EP ancestry > 0.65 (the geometric mean; 236 cases and 192 controls), and EP/Z with estimated EP ancestry ≤ 0.65 (48 cases and 157 controls). The estimated average proportion of EP ancestry in the EP/N sample set was 0.90 in cases and 0.88 in controls, and for the EP/Z group was 0.41 in cases and 0.40 in controls.

Results
Association with gout was observed in the NZ Caucasian sample set for rs1165196, rs1183201, rs3799344 and rs12664474 (OR = 0.71 (95% confidence interval...
(CI) = 0.60 to 0.83), \( P = 5.5 \times 10^{-5}; \) OR = 0.67 (95% CI = 0.57 to 0.79), \( P = 3.0 \times 10^{-5}; \) OR = 0.69 (95% CI = 0.58 to 0.81), \( P = 2.8 \times 10^{-5}; \) and OR = 1.36 (95% CI = 1.12 to 1.66), \( P = 1.3 \times 10^{-5}; \) respectively), but not for \( rs9358890 \) (OR = 1.31 (95% CI = 0.93 to 1.85), \( P = 0.17 \) (Table 1). Given the low LD between \( rs12664474 \) and \( rs1183201 \) in CEU \( (r^2 = 0.16), \) suggesting the possibility of an independent effect at \( rs12664474 \), we tested for association of \( rs12664474 \) conditional on genotype at \( rs1183201 \) in the NZ Caucasian samples; there was no evidence for a separate genetic effect on gout risk at \( rs12664474 \) (\( P = 0.37 \)). We also tested for conditional associations at \( rs1183201 \) and \( rs1165196 \) \( (r^2 \text{ in controls} = 0.90) \) - there was association at \( rs1183201 \) conditional on genotype at \( rs1165196 \) (\( P = 0.007 \)), but not at \( rs1165196 \) when conditioned on genotype at \( rs1183201 \) (\( P = 0.14 \)).

The five variants were then tested for association in the Polynesian sample sets (Table 1), with the only evidence for association in individual sample sets coming from WP at \( rs1183201 \) (\( OR = 0.70, P = 0.03 \)) and \( rs3799344 \) (\( OR = 0.67, P = 0.02 \)). However, meta-analysis of the Polynesian sample sets - carried out to increase power - replicated the association observed in Caucasian at \( rs1165196 \) \( (OR = 0.67, P = 0.013, P_{\text{het}} = 0.33); \) \( rs1183201 \) \( (OR = 0.74 (95\% \text{ CI} = 0.61 to 0.91), P = 0.003, P_{\text{het}} = 0.57); \) and \( rs3799344 \) \( (OR = 0.74 (95\% \text{ CI} = 0.61 to 0.90), P = 0.003, P_{\text{het}} = 0.33); \) but not at \( rs9358890 \) \( (OR = 1.15 (95\% \text{ CI} = 0.95 to 1.40), P = 0.16, P_{\text{het}} = 0.28); \) or \( rs12664474 \) \( (OR = 1.16 (95\% \text{ CI} = 0.96 to 1.40), P = 0.13, P_{\text{het}} = 0.23). \)

The Caucasian and Polynesian sample sets were combined in meta-analysis for \( rs1165196 \) \( (OR = 0.72 (95\% \text{ CI} = 0.64 to 0.82), P = 5.7 \times 10^{-7};) \) \( rs1183201 \) \( (OR = 0.70 (95\% \text{ CI} = 0.62 to 0.79), P = 3.0 \times 10^{-8}, P_{\text{het}} = 0.64); \) \( rs9358890 \) \( (OR = 1.19 (95\% \text{ CI} = 1.00 to 1.41), P = 0.05, P_{\text{het}} = 0.37); \) \( rs3799344 \) \( (OR = 0.71 (95\% \text{ CI} = 0.62 to 0.80), P = 7.4 \times 10^{-8}, P_{\text{het}} = 0.43); \) and \( rs12664474 \) \( (OR = 1.25 (95\% \text{ CI} = 1.09 to 1.43), P = 2.0 \times 10^{-5}, P_{\text{het}} = 0.23). \)

Of the five SNPs, \( rs1183201 \) was the only one significant at a genome-wide level of significance \( (P < 5 \times 10^{-8}) \). None of the SNPs were significantly associated with serum urate levels in Caucasian \( (r^2 = 0.92 \text{ and } r^2 = 0.87, \text{ respectively}); \) Given that \( rs269T \) has been shown to affect the function of \( SLC17A1 \), with the protective variant \( (269T, \text{ minor allele of } \text{SLC17A1}) \), conferring significant protection in three out of the five sample sets (also with \( OR < 1 \) in both EP sample sets). There were no haplotypes consistently conferring risk. Combining the populations provided a genome-wide level of significance for association of \( rs1183201 \) with gout \( (OR = 0.70, P = 3.0 \times 10^{-8}); \) This confirms the \( SLC17A1 \) locus as the third associated with gout.

The role of \( SLC17A1 \) has been previously evaluated in gout in a Japanese sample set \( (8) \), with the nonsynonymous variant \( I269T (rs1165196) \) having the strongest evidence for association \( (OR = 0.55, P = 0.004, \text{ minor allele (269T) protective}); \) \( rs1165196 \) is in strong LD with \( rs1183201 \) - the maximally associated variant in our study - in Japanese (HapMap JPT) and Caucasian (HapMap CEU) samples \( (r^2 = 0.92 \text{ and } r^2 = 0.87, \text{ respectively}); \) Given that \( I269T \) has been shown to affect the function of \( SLC17A1 \), with the protective variant \( (269T, \text{ minor allele of } rs1165196) \) leading to increased activity in \( Xenopus \) oocytes and, presumably, increased renal elimination of urate \( (6) \), it is therefore possible that \( rs1165196 \) is an etiological variant. However, we found no evidence in the Caucasian sample set supporting association at \( rs1165196 \) when conditioned on genotype at \( rs1183201 \), and association was weaker at \( rs1165196 \) than \( rs1183201 \) in combined Caucasian and Polynesian meta-analysis \( (OR = 0.72, P = 5.7 \times 10^{-7} \text{ and } OR = 0.70, P = 3 \times 10^{-8}, \text{ respectively}) \) and in Polynesian alone \( (OR = 0.75, P = 0.013 \text{ and } OR = 0.74, P = 0.003, \text{ respectively}) \) (we did not conditionally analyze the small Polynesian sample sets). Ostensibly this observation argues that \( rs1183201 \) (or a variant in strong LD) is more likely than \( rs1165196 \) to be an etiological variant within \( SLC17A1 \). Given that \( rs1165196 \) has a stronger effect in serum urate levels in Caucasian \( ([4] \beta = 6.205 \text{ vs. } 6.050 \text{ for } rs1183201) \) populations, however, this interpretation
### Table 1 Association analysis in New Zealand case-control sample sets

| SNP   | Cases MAF | Controls MAF | P unadjusted | P adjusted | OR (95% CI) | HWE case | HWE control |
|-------|-----------|--------------|--------------|------------|-------------|----------|-------------|
| rs1165196 |            |              |              |            |             |          |             |
|        | TT (0.400) | 201 (0.482)  | 49 (0.118)   | 0.359      | 389 (0.318) | 590 (0.482) | 246 (0.200) | 0.442 | 5.5 × 10⁻⁶ | 0.71 (0.60 to 0.83) | 0.33 | 0.41 |
|        | CT (0.708) | 33 (0.071)   | 47 (0.113)   | 0.368      | 13 (0.035)  | 176 (0.139) | 94 (0.076)  | 0.282 | 0.26 | 0.81 (0.60 to 1.11) | 0.65 | 0.98 |
|        | CC (0.186) | 12 (0.031)   | 9 (0.021)    | 0.368      | 8 (0.035)   | 16 (0.126)  | 7 (0.057)   | 0.426 | 0.51 | 0.88 (0.55 to 1.38) | 0.72 | 0.16 |
|        |            |              |              |            |             |          |             |
|        |            |              |              |            |             |          |             |
|        |            |              |              |            |             |          |             |
|        |            |              |              |            |             |          |             |
| rs1183201 |            |              |              |            |             |          |             |
|        | TT (0.384) | 205 (0.499)  | 48 (0.117)   | 0.366      | 356 (0.291) | 608 (0.496) | 261 (0.213) | 0.461 | 2.0 × 10⁻⁶ | 0.67 (0.57 to 0.79) | 0.13 | 0.89 |
|        | CT (0.606) | 130 (0.496)  | 86 (0.377)   | 0.421      | 96 (0.505)  | 78 (0.411)  | 16 (0.084)  | 0.289 | 0.11 | 0.78 (0.57 to 1.06) | 0.65 | 0.98 |
|        | CC (0.010) | 15 (0.037)   | 21 (0.088)   | 0.407      | 52 (0.349)  | 61 (0.409)  | 36 (0.242)  | 0.446 | 0.49 | 0.85 (0.52 to 1.39) | 0.94 | 0.04 |
|        |            |              |              |            |             |          |             |
|        |            |              |              |            |             |          |             |
|        |            |              |              |            |             |          |             |
|        |            |              |              |            |             |          |             |
| rs9358890 |            |              |              |            |             |          |             |
|        | AA (0.384) | 47 (0.114)   | 1 (0.002)    | 0.059      | 1114 (0.291) | 608 (0.496) | 261 (0.213) | 0.470 | 0.30 | 1.20 (0.92 to 1.57) | 0.25 | 0.63 |
|        | AG (0.616) | 307 (0.706)  | 119 (0.377)  | 0.390      | 80 (0.411)  | 78 (0.411)  | 16 (0.084)  | 0.300 | 0.21 | 0.76 (0.54 to 1.06) | 0.30 | 0.57 |
|        | GG (0.010) | 17 (0.042)   | 14 (0.063)   | 0.407      | 52 (0.349)  | 61 (0.409)  | 36 (0.242)  | 0.446 | 0.49 | 0.85 (0.52 to 1.39) | 0.94 | 0.04 |
|        |            |              |              |            |             |          |             |
|        |            |              |              |            |             |          |             |
|        |            |              |              |            |             |          |             |
|        |            |              |              |            |             |          |             |
| rs3799344 |            |              |              |            |             |          |             |
|        | CC (0.404) | 193 (0.473)  | 50 (0.123)   | 0.359      | 379 (0.309) | 592 (0.483) | 255 (0.207) | 0.450 | 5.9 × 10⁻⁶ | 0.69 (0.58 to 0.81) | 0.58 | 0.38 |
|        | CT (0.596) | 88 (0.386)   | 12 (0.035)   | 0.426      | 97 (0.524)  | 73 (0.395)  | 15 (0.081)  | 0.278 | 0.46 | 0.37 (0.28 to 0.51) | 0.88 | 0.08 |
|        | TT (0.000) | 17 (0.037)   | 22 (0.089)   | 0.378      | 53 (0.353)  | 64 (0.427)  | 33 (0.220)  | 0.433 | 0.35 | 0.72 (0.49 to 1.29) | 0.79 | 0.49 |
|        |            |              |              |            |             |          |             |
|        |            |              |              |            |             |          |             |
|        |            |              |              |            |             |          |             |
|        |            |              |              |            |             |          |             |
| rs12664474 |           |              |              |            |             |          |             |
|        | AA (0.561) | 104 (0.434)  | 41 (0.174)   | 0.396      | 74 (0.392)  | 77 (0.407)  | 38 (0.201)  | 0.405 | 0.79 | 0.55 (0.40 to 0.76) | 0.25 | 0.03 |
|        | AG (0.439) | 75 (0.326)   | 20 (0.086)   | 0.426      | 107 (0.576) | 69 (0.427)  | 33 (0.220)  | 0.433 | 0.35 | 0.72 (0.49 to 1.29) | 0.79 | 0.49 |
|        | GG (0.000) | 7 (0.026)    | 3 (0.012)    | 0.378      | 53 (0.353)  | 64 (0.427)  | 33 (0.220)  | 0.433 | 0.35 | 0.72 (0.49 to 1.29) | 0.79 | 0.49 |
|        |            |              |              |            |             |          |             |
|        |            |              |              |            |             |          |             |
|        |            |              |              |            |             |          |             |
|        |            |              |              |            |             |          |             |

CI, confidence interval; HWE, [AU Query: Define]; MAF, [AU Query: Define]; OR, odds ratio. aGenotyping success rate: rs1165196 Caucasian, Eastern Polynesian (EP), Western Polynesian (WP) and EP/WP - cases 99.0%, 95.8%, 98.8% and 100%, respectively, controls 99.8%, 96.8%, 95.0% and 100%, respectively; rs1183201 Caucasian, EP, WP and EP/WP - cases 97.6%, 95.4%, 96.8% and 100%, respectively, controls 97.9%, 97.1%, 98.6% and 95.2%, respectively; rs9358890 Caucasian, EP, WP and EP/WP - cases 98.3%, 97.9%, 95.6% and 100%, respectively, controls 99.2%, 99.4%, 100% and 95.0%, respectively; rs3799344 Caucasian, EP, WP, EP/WP - cases 96.9%, 96.1%, 98.4% and 100%, respectively, controls 99.3%, 98.9%, 98.6% and 100%, respectively. bAdjusted for sex. cMeta-analysis by the Mantel-Haenszel method. Breslow-Day test for heterogeneity: rs1165196, P = 0.45; rs1183201, P = 0.75; rs9358890, P = 0.77; rs3799344, P = 0.58; rs12664474, P = 0.97. dPopulation attributable risk (the reduction in gout incidence if the risk variant was absent) for positivity of the risk (T) allele of rs1183201 is 38.2% for Caucasian, 21.4% for EP/N, 27.3% for EP/N and 41.3% for WP.
should await further testing in larger gout and serum urate sample sets.

In the Caucasian analysis, rs1183201 was strongly associated with gout (OR = 0.67 (95% CI = 0.57 to 0.79)). This SNP, or SNPs in strong LD, has been shown to be a transport substrate for sodium-dependent urate transporter 4 (encoded by SLC17A3), and functional polymorphic variants are likely to influence transport function of urate transporters encoded in the SLC17A1 locus. It is also conceivable that diuretics directly influence the function of urate transporters encoded in the locus. The loop diuretic bumetanide has recently been shown to be a transport substrate for sodium-dependent transporter 4 (encoded by SLC17A3), and functional polymorphic variants are likely to influence transport activity [26]. Given the likelihood that gene-diuretic interactions exist, one would be prudent to exclude gout cases taking diuretic medication as a potential confounding factor in order to evaluate the direct effect of genetic variation in the SLC17A1 locus on primary gout.

## Conclusion

We provide, for the first time, a genome-wide level of evidence supporting a role for genetic variation in the

### Table 2 Association of four-marker rs9358890-rs3799344-rs1183201-rs12664474 haplotypes with gout

| Haplotype* | Frequency | Case | Control | OR (95% CI) | P value |
|------------|-----------|------|---------|-------------|---------|
| Caucasian  |           |      |         |             |         |
| A-T-A-A    | 270 (0.339) | 1044 (0.428) | 0.66 (0.56 to 0.78) | 1.5 × 10^-6 |
| A-C-T-A    | 327 (0.410) | 876 (0.360) | 1.22 (1.03 to 1.44) | 0.014 |
| A-C-T-G    | 121 (0.152) | 284 (0.117) | 1.34 (1.06 to 1.69) | 0.015 |
| G-C-T-G    | 47 (0.059) | 104 (0.043) | 1.39 (0.98 to 1.98) | 0.067 |
| EP/N       |           |      |         |             |         |
| A-T-A-A    | 107 (0.273) | 101 (0.274) | 0.84 (0.61 to 1.15) | 0.27 |
| A-C-T-A    | 160 (0.356) | 109 (0.297) | 1.33 (0.99 to 1.78) | 0.06 |
| G-C-T-G    | 161 (0.360) | 140 (0.380) | 0.93 (0.70 to 1.23) | 0.60 |
| EP/Z       |           |      |         |             |         |
| A-T-A-A    | 32 (0.372) | 120 (0.414) | 0.84 (0.51 to 1.38) | 0.49 |
| A-C-T-A    | 32 (0.372) | 111 (0.384) | 0.95 (0.58 to 1.56) | 0.84 |
| G-C-T-G    | 9 (0.095) | 26 (0.090) | 1.19 (0.53 to 2.64) | 0.68 |
| A-C-T-G    | 10 (0.116) | 22 (0.075) | 1.63 (0.74 to 3.59) | 0.23 |
| WP         |           |      |         |             |         |
| A-C-T-A    | 171 (0.357) | 96 (0.343) | 1.07 (0.78 to 1.45) | 0.70 |
| A-T-A-A    | 116 (0.241) | 89 (0.318) | 0.68 (0.49 to 0.94) | 0.021 |
| G-C-T-G    | 171 (0.356) | 77 (0.275) | 1.46 (1.06 to 2.02) | 0.021 |
| A-C-T-G    | 12 (0.025) | 12 (0.043) | 0.57 (0.25 to 1.29) | 0.17 |
| EP/WP      |           |      |         |             |         |
| A-T-A-A    | 5 (0.167) | 16 (0.400) | 0.30 (0.10 to 0.95) | 0.035 |
| A-C-T-A    | 15 (0.500) | 13 (0.324) | 2.08 (0.78 to 5.50) | 0.14 |
| G-C-T-G    | 6 (0.200) | 11 (0.275) | 0.66 (0.21 to 2.05) | 0.47 |

CI, confidence interval; EP, Eastern Polynesian; OR, odds ratio; WP, Western Polynesian. *Haplotypes are listed in descending order of control frequency; those with frequency < 0.03 were excluded.
SLC17A1 locus in the etiology of gout. This is the third
urate transport locus associated with gout with this
robust level of evidence, and our results further empha-
size the importance of urate transport in gout.

Additional material

Additional file 1: Supplemental Table 1 presenting participant
demographic and clinical details, Supplemental Table 2 presenting
genomic control SNPs, and Supplemental Figure 1 showing the
correlation of self-reported number of EP grandparents with
estimated EP ancestry using 67 genomic control markers

Abbreviations
ABC: ATP-binding cassette; ARA: American Rheumatism Association; CEU:
Centre d'Etude du Polymorphisme Humain; CHB: Han Chinese Beijing; CI:
confidence interval; EP: Eastern Polynesian; LD: linkage disequilibrium; NZ:
New Zealand; OR: odds ratio; SLC: solute carrier family; SNP: single
nucleotide polymorphism; WP: Western Polynesian.

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JEHM, AJ-G and FRM helped to design the study, oversee its execution,
and prepare the manuscript. GTJ, AvR, PJG, AAH, JH, PB, LKS and ND helped
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helped to collect data and prepare the manuscript. All authors read and
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Competing interests
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