

Population-specific Interaction of the *TRIM46* / *MUC1* Locus With Cigarette Smoking May Influence the Risk of Gout

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Abstract

Background: Epidemiological and prospective studies suggest that current-smoking may be protective against developing gout and that smoking cessation may increase risk. The aim of this study was to identify interactions between smoking, genetic risk variants and the risk of gout.

Methods: A cohort of 520 New Zealand (NZ) East and West Polynesian participants with and 629 without gout were included in our discovery analysis. A cohort of European participants (7576 with and 364,445 without) and South Asian participants (156 with and 7504 without gout) of the UK Biobank were used for replication. Five loci with previous evidence of smoking-influenced associations with serum urate levels were tested for their interaction with smoking status (current-smoker or ex-smoker vs. never-smoker as the reference group) in determining gout risk. The 5 loci were in genes, *SLC2A9*, *ABCG2*, *GCKR*, *TRIM46*, and *HNF4G*.

Results: A non-additive interaction between genotype and smoking on gout risk was observed between ex-smoker status and *TRIM46* (rs11264341) in NZ East and West Polynesian people [interaction $OR_{meta} = 0.58$ (0.37-0.92), $p = 0.021$], but not in European ($OR = 0.94$ (0.88-1.01), $p = 0.10$) or South Asian (0.96 (0.55-1.66), $p = 0.88$) participants of the UK Biobank. *TRIM46* (rs11264341) interacted with current-smoker status in the Asian UK Biobank cohort [interaction $OR = 2.68$ (1.26-5.68), $p = 0.010$]. In smoking status subgroups the C-allele of *rs11264341* increased risk of gout specifically in never-smokers ($OR = 1.41$ (1.04-1.92), $p = 0.029$) of the NZ Polynesian sample set and in current-smokers (2.39 (1.13-5.05), $p = 0.022$) of the South Asian sample set. There was no evidence of interaction between smoking-status and the 4 remaining loci in 2 or more of the ancestral populations analysed in this study.

Conclusion: We provide evidence for a non-additive interaction between *TRIM46* (rs11264341) and smoking behaviour associated with gout risk in a NZ Polynesian sample set and a South Asian sample set, but not in a European sample set. *MUC1*, that encodes a transmembrane mucin in the lungs whose expression and function is affected by cigarette smoke, is a possible candidate gene at the *TRIM46* locus.

Background

Gout is a common form of inflammatory arthritis that is characterised by a recurring innate immune response to monosodium urate crystals within joint structures [1]. Monosodium urate crystallisation occurs when serum urate is elevated above the point of saturation (hyperuricaemia).

Gout and hyperuricaemia are complex traits that arise from an interplay between inherited genetic variants and the environment [2]. Genome-wide association studies have identified dozens of genomic loci that are associated with serum urate, which collectively explain 7.7% of phenotypic variance in serum urate concentrations [3, 4]. Among the loci with greatest effect are those containing genes that encode renal and gut urate transport-related proteins, particularly those involved in urate excretion, such as *SLC2A9* and *ABCG2*. The majority of the urate-associated loci have been associated with gout in various

ancestral groups, including European, New Zealand (NZ) Polynesian (Māori and Pacific Island), Japanese, and Chinese people [5–11].

In NZ, the prevalence of gout is two to three times greater in people of Eastern Polynesian (Aotearoa NZ Māori and Cook Island Māori) and Western Polynesian (Samoan, Tongan, Niuean, Tokelauan) ethnicity compared with NZ European [12]. Genetic risk factors are likely to contribute to the increased prevalence associated with ancestry [13].

Smoking is one of the most important modifiable risks to health and mortality. Multiple studies have provided evidence for an association of current smoking with reduced risk of gout independent of other measured confounders [14–19] (reviewed in [20]). However, the evidence is equivocal, with some studies providing evidence of association of current smoking with increased risk of gout [21, 22]. There is also evidence that the prevalence of gout is higher in ex- compared to never- and current-smokers [15, 18]. Additionally, smoking cessation has been associated with an increase in serum urate levels [23].

The impact of some environmental factors on hyperuricaemia and gout can include a component of interaction with genetic variants. Examples of gene-environment interactions influencing gout risk have been documented for alcohol and sugar-sweetened beverage consumption [24–27]. Moreover, the effects of several urate-associated loci have been shown to depend on smoking status, for example, in the Chinese population, the *GCKR* (rs1260326) and *TRIM46* (rs11264341) loci were associated with serum urate in current-smokers only, while the *HNF4G* (rs2941481) locus was specifically associated with serum urate in ex-smokers [11]. An interaction was observed between the haplotype of *SLC2A9* (rs3733591), *ABCG2* (rs2231142) and *PKD2* (rs2725220) with current smoking to influence risk of hyperuricaemia [28].

The aim of this study was to identify interactions between smoking and genetic variants with previous evidence of an interaction with smoking to influence serum urate [*GCKR* (rs1260326), *TRIM46* (rs11264341), and *HNF4G* (rs2941481)], and/or variants with very strong effects on serum urate and gout [*SLC2A9* (rs11942223) and *ABCG2* (rs2231142)].

Methods

Participants

For the purpose of this study we sought to analyse multiple ancestral groups and selected the largest dataset available to us for each ancestral group. Demographic and clinical data of study participants (who provided samples) are summarised in Additional file 1: Tables S1 and S2. People with gout and non-gout controls were recruited in NZ between 2010 and 2016. In the NZ sample set participants were categorised into East Polynesian (EP; Cook Island and NZ Māori; 381 non-gout controls and 352 people with gout) and West Polynesian (WP; Samoa, Tonga, Niue, Tuvalu and Tokelau; 248 non-gout controls and 168 people with gout) groups based on the self-reported ancestry of their grandparents. The NZ sample set included a separate Māori subset (44 with gout and 33 controls) from the rohe (area) of the Ngati Porou iwi (tribe) from the Tairāwhiti region on the East Coast of the NZ North Island. This sample

subset was recruited as part of a separate study in collaboration with Ngati Porou Hauora (health service). Publicly-available data of people with self-reported European ancestry (“British”, “Irish”, “White” or “Any other white background”; including 364,445 non-gout controls and 7,576 people with gout) and South Asian ancestry (“Indian”, “Pakistani”, “Bangladeshi”, “any other Asian background”, “Asian or Asian British” and “white and Asian”; including 8746 non-gout and 205 people with gout) from the UK Biobank Resource (approval number 12611) were also analysed [29] (Additional file 1: Table S3). Principal component vectors were used to confirm that each genetic sample matched the participant’s self-reported ancestry in the NZ Polynesian populations and the UK Biobank South Asian population. Principal component vectors for the NZ Polynesian populations were calculated from a set of 2,858 ancestry-informative markers [30]. Principal component vectors for the UK Biobank populations were supplied by the UK Biobank (Data Field 22009) and had been computed using the algorithm fastPCA38 [31, 32]. Gout was defined by American Rheumatism Association classification criteria (NZ) or, for the UK Biobank, by self-report and urate lowering therapy (ULT) use [33]. All controls self-reported no previous diagnosis of gout. The Northern Y Region Health Research Ethics Committee granted ethical approval for the Ngati Porou Hauora study cohort (NTY07/07/074), while the NZ Multi-Region Ethics Committee (MEC/105/10/130) granted ethical approval for the remaining NZ-based cohort. The UK Biobank was granted ethical approval by the North West Multi-Centre Research Ethics Committee (11/NW/0382). All participants gave written informed consent.

Data collection

NZ participants were asked to self-report if they were a current smoker (Yes/No) or an ex-smoker. UK Biobank participants were asked if they currently smoke: those who answered yes or occasionally were classified as current-smokers, while those who answered no were further sub-divided into ex-smoker or never-smoker based on smoking history. Those who self-reported never smoking or trying smoking < 3 times previously were classified as never-smokers. Participants who self-reported occasional or regular past smoking were classified as ex-smokers. Alcohol intake was determined in the NZ Polynesian cohort by asking participants how many servings (standard drinks) of beer, wine, spirits, and other alcohol they had consumed in the past week. These responses were used to calculate grams of alcohol consumed per week as described elsewhere [24]. Participants who reported no alcohol servings (0 grams/week) were categorised as non-drinkers and those who reported any alcohol consumption (> 0 grams/week) were categorised as drinkers. In the UK Biobank study, participants were asked “About how often do you drink alcohol?”, those who self-reported consuming alcohol on special occasions or more regularly were classified as current-drinkers, and those who answered never were classified as non-drinkers. Participants with missing data for smoking status, BMI and drinking status were excluded from the study.

Genotyping

Genotypes of rs7442295 (surrogate marker for rs11942223), rs11264341, rs1260326, rs2231142, and rs2941481) in the NZ sample sets were determined using the Infinium Human CoreExome-v24 single nucleotide polymorphism (SNP) array (Illumina, Inc., San Diego, CA, USA) [30]. The measure of linkage disequilibrium between rs7442295 and rs11942223 is $R^2 = 0.98$ in East Asian and South Asian samples

of the HapMap project [34]. Most European participant samples (331,513) and all Asian participant samples of the UK Biobank were genotyped using an Applied Biosystems Axiom™ array (820,967 markers; Affymetrix, Santa Clara, CA, USA, now part of Thermo Fisher Scientific) [29, 31]. Approximately 10% (40,508) of UK Biobank European population samples were part of the UK Biobank Lung Exome Variant Evaluation (BiLEVE) subset, and had been genotyped using the UK BiLEVE Applied Biosystems Axiom Array that shares 95% of marker content with the UK Biobank Axiom array and includes 807K markers [35]. Samples from both arrays were combined and imputed to approximately 73.3 million SNPs using SHAPEIT3 and IMPUTE2 with a combined UK10K and 1000 Genomes Phase 3 reference panel [31]. rs11264341, rs1260326, and rs2231142, were directly genotyped on the Axiom arrays, while genotypes of rs11942223 and rs2941481 were imputed.

Statistical analysis

All analyses were performed using R statistical software version 3.5.2 or 3.6.2. (R Core Team 2018) within the R studio integrated development environment version 1.1.463 (RStudio Team 2016) [36, 37]. Allele frequencies and results of the Hardy-Weinberg Equilibrium exact test were calculated for individual SNPs according to smoking and gout categories using the R package SNPAssoc (version 1.9.2) (results are presented in Additional file 1: Table S4 and S5) [38]. Two binary smoking variables were analysed - current-smoker compared to never-smoker (excluding ex-smokers) and ex-smoker compared to never-smoker (excluding current-smokers). Multivariable logistic regression was used for association analyses of smoking and gout, and to estimate interaction between individual SNP genotypes (additive model, using effect allele count) and smoking variables in gout risk. Association analyses of smoking and gout were carried out in male and female cohorts, as well as the overall cohort of the UK Biobank. Sex-stratified association analyses were not carried out for the NZ Polynesian and the UK Biobank South Asian populations because of the small number of participants in these cohort. Multivariable logistic regression for an association of the *TRIM46* (rs11264341) locus (C allele additive model) with gout prevalence was also performed within subgroups of never-smokers, current-smokers, and ex-smokers. All logistic regression models were adjusted for age (continuous), sex (dichotomous), BMI (continuous) and alcohol intake (dichotomous). Regression models were also adjusted for the first 10 principal components to adjust for genetic admixture or population substructure. Additional adjustment was carried out for genotyping array (UK Biobank Axiom™ or UK Biobank BiLEVE) for the UK Biobank European population to account for potentially confounding effects of this sample being enriched for non-smoking individuals [35]. Adjusted odds ratios (ORs) for gout and their 95% confidence intervals (CIs) were calculated. Meta-analysis of logistic regression interaction estimates was performed using meta package (version 4.9-2 and 4.10.0) in R [39]. Heterogeneity (P_{Het}) was calculated using the Q (chi squared, χ^2) test. Given our inclusion of replication sample sets we did not include Bonferroni correction in our analysis. Individual SNP vs gout association analyses for NZ East and West Polynesian populations and the UK Biobank populations are shown in Additional file 1: Table S6.

Results

Association analyses of smoking categories with gout.

People with gout were significantly more likely to be ex-smokers in the NZ East Polynesian subset [OR (95% CI); 2.60 (1.73–3.92), $p = 4.4 \times 10^{-6}$; Additional File 2: Figure S1 A]. An effect size in the same direction was observed in the NZ West Polynesian subset, but this was not statistically significant [OR (95% CI); 1.27 (0.70–2.31), $p = 0.43$]. No statistically significant association with ex-smoker status was observed in meta-analysis of regression estimates for NZ East and West Polynesian groups using the random effects model [OR of meta-analysis (OR_{Meta}): 1.88 (95% CI: 0.94–3.79), $p = 0.08$]. Similar to the NZ East Polynesian cohort, ex-smoker status associated with increased prevalence of gout in the UK Biobank European cohort [OR_{Meta} (95% CI): 1.23 (1.16–1.30), $p = 4.7 \times 10^{-15}$], as well as in stratified analysis of men [1.22 (1.16–1.29), $p = 4.8 \times 10^{-14}$] and women [1.31 (1.10–1.56), $p = 2.2 \times 10^{-34}$] (Additional File 2: Figure S1 C). Current-smoker status was associated with lower prevalence of gout in men [OR (95% CI): 0.90 (0.82–0.98), $p = 0.020$] and higher prevalence of gout in women [1.59 (1.18–2.13), $p = 2.2 \times 10^{-3}$] in the UK Biobank European cohort (Additional File 2: Figure S1 D). No association was detected between current-smoker status and gout, and odds ratios were in opposite directions, in the NZ East Polynesian [OR (95% CI); 1.32 (0.80–2.19), $p = 0.28$] and West Polynesian [0.48 (0.20–1.12), $p = 0.09$] sample sets [Additional File 2: Figure S1 B]. No association was observed for ex-smoker [OR (95% CI); 0.96 (0.64–1.45), $p = 0.86$] or current-smoker (1.10 (0.66–1.82), $p = 0.73$) categories with gout in the UK Biobank South Asian replication cohort (Additional File 2: Figure S1 A and B).

Smoking and SNP interaction in Polynesian

We carried out logistic regression analysis to identify any interactions between the 5 loci of interest and smoker status that effect the risk of gout risk in the NZ Polynesian and UK Biobank sample sets. An interaction was observed between the *TRIM46* (rs11264341) C allele and ex-smoker status to influence gout risk in the combined NZ East and West Polynesian subset [OR_{Meta} (95% CI) for interaction effect = 0.58 (0.37–0.92), $p = 0.021$, Table 1]. No interaction was observed between *TRIM46* (rs11264341) and ex-smoker status in the UK Biobank European [interaction OR (95% CI) = 0.94 (0.88–1.01), $p = 0.10$] or South Asian [OR = 0.96 (0.55–1.66), $p = 0.88$] sample sets [Table 1]. However, an interaction was observed between current-smoker status and *TRIM46* (rs11264341) to influence gout in the South Asian sample set [OR = 2.68 (1.26–5.68), $p = 0.010$, Table 2]. No interaction was observed for the *TRIM46* (rs11264341) locus with current-smoker status to influence gout in the NZ Polynesian [OR_{Meta} = 0.77 (0.43–1.40), $p = 0.40$] or UK Biobank European [OR = 0.98 (0.86–1.10), $p = 0.70$] datasets (Table 2). Main effects for *TRIM46* (rs11264341) were in the direction of higher risk of gout in NZ Polynesian [OR_{Meta} (95% CI) = 1.48 (1.08–2.02), $p = 0.015$] and UK Biobank European [1.16 (1.10–1.22), $p = 7.9 \times 10^{-8}$] sample sets, but in the direction of lower risk in the South Asian sample set although this was not significant [0.88 (0.66–1.17), $p = 0.377$] (Additional File 2: Figure S2 A).

Table 1
Genetic interaction effects for ex-smokers compared to never-smokers to gout risk

SNP	Gene	Effect allele	Polynesian		UK Biobank European		UK Biobank South Asian	
			OR_{Meta} (95% CI)	<i>P</i>	<i>OR</i> (95% CI)	<i>P</i>	<i>OR</i> (95% CI)	<i>P</i>
rs11942223	<i>SLC2A9</i>	T	0.61 (0.16– 2.28)	0.462	0.99 (0.9–1.1)	0.903	1.96 (0.8– 4.83)	0.143
rs2231142	<i>ABCG2</i>	T	0.94 (0.47– 1.89)	0.868	0.96 (0.88– 1.05)	0.347	1.45 (0.68– 3.06)	0.334
rs2941481	<i>HFN4G</i>	A	0.93 (0.58–1.5)	0.762	0.98 (0.92– 1.05)	0.639	0.85 (0.48– 1.5)	0.574
rs11264341	<i>TRIM46</i>	C	0.58 (0.37– 0.92)	0.021	0.94 (0.88– 1.01)	0.097	0.96 (0.55– 1.66)	0.879
rs1260326	<i>GCKR</i>	T	1.1 (0.66– 1.84)	0.721	0.99 (0.93– 1.07)	0.861	1.44 (0.79– 2.6)	0.231

Shown are odds ratios of the interaction effect model: SNP*ex-smoker status vs gout (response variable). Additive genetic model was assumed. Polynesian column from meta-analysis of East and West Polynesian populations. Fixed effects meta-analysis is shown. Heterogeneity was not detected ($P_{Heterogeneity} > 0.25$ for all markers). Odds ratios are adjusted for age, sex, drinker status and BMI and PC1 to PC10. Additional adjustment for genotyping array platform (AxiomTM/BiLEVE) was done for the UK Biobank European population. Current-smokers excluded from models comparing ex- to never-smokers. BMI, body mass index; CI, confidence interval; NZ, New Zealand; OR, odds ratio; PC, principal component; SNP, single nucleotide polymorphism.

Table 2
Genetic interaction effects for current-smokers compared to never-smokers on gout risk

SNP	Gene	Effect allele	NZ Polynesian		UK Biobank European		UK Biobank South Asian	
			OR_{Meta} (95% CI)	<i>P</i>	<i>OR</i> (95% CI)	<i>P</i>	<i>OR</i> (95% CI)	<i>P</i>
rs11942223	<i>SLC2A9</i>	T	0.48 (0.11–2.19)	0.344	0.88 (0.74–1.04)	0.125	0.67 (0.29–1.53)	0.338
rs2231142	<i>ABCG2</i>	T	0.77 (0.31–1.87)	0.557	1.17 (1.01–1.35)	0.040	0.83 (0.28–2.4)	0.725
rs2941481	<i>HFN4G</i>	A	0.87 (0.45–1.67)	0.677	1.06 (0.94–1.2)	0.337	1.22 (0.6–2.5)	0.583
rs11264341	<i>TRIM46</i>	C	0.77 (0.43–1.40)	0.395	0.98 (0.86–1.10)	0.703	2.68 (1.26–5.68)	0.010
rs1260326	<i>GCKR</i>	T	0.82 (0.43–1.56)	0.543	1.06 (0.94–1.2)	0.340	1.17 (0.54–2.56)	0.691

Shown are odds ratios of the interaction effect model: SNP*current-smoker status vs gout (response variable). Additive genetic model was assumed. Fixed effects meta-analysis is shown. Heterogeneity was detected for *GCKR* (rs1260326) ($P_{Heterogeneity} = 0.225$, random effects model OR (95% CI): 0.76 (0.33–1.78), $p = 0.53$) and *HFN4G* (rs2941481) ($P_{Heterogeneity} = 0.159$, random effects model OR (95% CI): 0.75 (0.26–2.16), $p = 0.59$), $P_{Heterogeneity} > 0.25$ for other markers. Odds ratios are adjusted for age, sex, drinker status, BMI and PC1 to PC10. Additional adjustment for genotyping array platform (AxiomTM/BiLEVE) was done for the UK Biobank European population. Ex-smokers excluded from models comparing current to never-smokers. BMI, body mass index; CI, confidence interval; NZ, New Zealand; OR, odds ratio; PC, principal component; SNP, single nucleotide polymorphism.

Smoking and SNP interaction in European

An interaction was also observed for *ABCG2* (rs2231142) [OR (95% CI) = 1.17 (1.01–1.35), $p = 0.04$] with current-smoker status in the UK Biobank European population [Table 2].

The TRIM46 interaction

Because the *TRIM46* (rs11264341) locus was found to interact with smoking behaviour in both NZ Polynesian and UK Biobank South Asian populations we further explored the potential nature of interactions involving this locus. We assessed the relationship of the *TRIM46* C allele (additive model) with gout in smoking status subgroups of the NZ Polynesian and UK Biobank Asian study populations (results are shown in Fig. 1). In the NZ Polynesian population an association was observed in the never-smoker subgroup where the C allele was associated with increased risk of gout [OR (95% CI) = 1.41 (1.04–1.92), $p = 0.029$; Fig. 1A]. No association was observed between *TRIM46* and gout in ex-smokers of

the NZ Polynesian sample set [OR (95% CI) = 0.88 (0.63–1.23), $p = 0.46$], despite the interaction observed between *TRIM46* and ex-smoker status (Fig. 1B). Additionally, no association was observed between *TRIM46* and gout in the NZ Polynesian current-smoker subgroup (Fig. 1C). The *TRIM46* C allele was associated with higher risk of gout specifically in current-smokers of the South Asian population [OR (95% CI) = 2.39 (1.32–5.05), $p = 0.022$, Fig. 1C]. No association was observed for the C allele with gout in the South Asian never-smoker [OR (95% CI) = 0.88 (0.67–1.18), $p = 0.40$] or ex-smoker [0.81 (0.50–1.32), $p = 0.40$] subgroups (Fig. 1A and B), nor in any meta-analysis of NZ Polynesian and South Asian smoker subgroup populations (Fig. 1A, B and C).

Discussion

Being an ex-smoker was associated with increased risk of gout in NZ East Polynesian and UK Biobank European subsets. This is consistent with previous evidence of increased risk of gout in ex-smokers [18, 19, 21, 40, 41], although reduced prevalence of gout in ex-smokers has also been reported [22, 42]. It is also consistent with evidence that ex-smokers have higher serum urate than never-smokers (reviewed in [20]) and that serum urate increases following smoking cessation [23, 43]. In our analysis of NZ Polynesian people and the large UK Biobank European cohort, no association was observed between self-reported current smoking and prevalence of gout in the overall cohorts. However, current smoking status was associated with increased risk of gout in women and decreased risk of gout in men of the UK Biobank European cohort. These opposing associations of current smoking with gout in men and women are also consistent with sex-specific differences reported previously where current smoking was found to be protective against developing gout in men, but not in women [14, 15]. Current smoking has been found to be associated with reduced incidence and prevalence of gout in multiple studies [14–16, 18, 19, 41, 44], although there have also been conflicting studies reporting increased risk of gout [21, 22] (reviewed in [20]). No association was observed between current- or ex-smoker status and gout in the UK Biobank South Asian population.

This study focused on identifying potential interactions of 5 loci with smoking that influence the risk of gout in a NZ study population of East and West Polynesian ancestry and in study populations of South Asian and European ancestry from the UK Biobank. One locus, *TRIM46* (rs11264341), was found to interact with ex-smoker status and with current-smoker status to influence gout in the NZ Polynesian and UK Biobank South Asian sample sets, respectively. There was no interaction of *TRIM46* (rs11264341) with smoking behaviour in the UK Biobank European population. We considered the potential nature of the interactions observed in the NZ Polynesian and UK Biobank Asian study populations by examining the effect of the *TRIM46* (rs11264341) locus on prevalence of gout in smoking status subgroups. The *TRIM46* (rs11264341) C allele was associated with higher prevalence of gout specifically in never-smokers, but not in ex-smoker or current-smoker status subgroups of the NZ Polynesian population. This suggests that the risk effect of *TRIM46* is only evident in the absence of current- or past-smoking behaviours. Perhaps the risk effect of past-smoking overrides the effect of the *TRIM46*. In the UK Biobank South Asian sample set *TRIM46* was specifically associated with gout in current-smokers, indicating that current-smokers of this ancestry may be specifically susceptible to the risk effect of the C-allele. This is

consistent with a study of 4,332 individuals of Chinese ancestry where the *TRIM46* locus C-allele was associated with higher serum urate in current-smokers [β coefficient for change in serum urate (β) = 7.541, false discovery rate corrected p value (p_{FDR}) = 0.040], but not in ex-smokers (β = 0.240, p_{FDR} = 0.975) or never-smokers (β = 18.860, p_{FDR} = 0.053) [11]. However, no formal test of interaction (e.g. using a *TRIM46**smoking-status interaction term versus serum urate) was done by Dong *et al.* [11].

Whether the differing interactions of *TRIM46* with smoking behaviour and gout seen in the NZ Polynesian and South Asian populations is explainable through the same biological pathway remains unknown. It is possible that inter-population variation in linkage disequilibrium pattern of rs11264341, involving a nearby causal variant, is responsible for differences in interaction effects. This could also explain why the main effects of *TRIM46* on gout risk are in opposing directions in the Polynesian and South Asian populations. Thus, subject to replication in other sample sets of Asian and Polynesian ancestry, we conclude evidence for a population-specific interaction of *TRIM46* (rs11264341) with risk of gout, with opposing effects on gout in current- and ex-smokers.

Causal candidate genes have been identified at the *TRIM46* (rs11264341) locus by colocalising the GWAS signal with *cis* expression quantitative trait locus (eQTL) analysis [45]. These include *SHE*, *MUC1*, *GBAP1*, and *FAM189B*, but not *TRIM46* itself or *PKLR* which were previously suggested to be causal candidates by the less accurate Gene Relationships Across Implicated Loci (GRAIL) tool [3, 46]. Based on current knowledge of these candidate causal genes, *MUC1* appears to be the most likely to interact with smoking behaviour to influence gout. *MUC1* encodes a transmembrane mucin expressed on the apical surface of epithelial cells lining the mucosa of the lungs, and in haematopoietic cells (reviewed in [47]). In the lung it has a pivotal anti-inflammatory function at later stages of the inflammatory response to bacterial infections, which it mediates by inhibiting Toll-like receptor signalling. There is evidence that chronic exposure to cigarette smoke in mice leads to increased expression of Muc1 in lung epithelial cells and macrophages, and increased numbers of Muc1-expressing macrophages in the lungs [48]. The same study also found that treating human macrophage cell lines with cigarette smoke extract induced MUC1 protein expression. There is also evidence that cigarette smoke provokes aberrant glycosylation and subcellular redistribution of MUC1, causing loss of E-cadherin and basolateral adherens junction integrity, which in turn leads to initiation of epithelial–mesenchymal transition and lung cancer development [49, 50].

Limitations of this study include the relatively small number of participants and people with gout in the NZ Polynesian and South Asian sample sets, which means potential interactions affecting these ancestral population may go undetected. Additionally, we did not have data of when current- or ex-smokers commenced or ceased smoking to test how this related to onset of gout, therefore we could not exclude ex-smokers who quit smoking after gout onset or current-smokers who took up smoking after gout onset. Furthermore, we did not have information on pack year history or serum cotinine levels to assess how duration and dose of cigarette smoking may interact with genetic factors to impact gout risk. It is possible that the higher prevalence of gout in ex-smokers may be influenced by increased access to smoking-cessation support in participants receiving care for gout, compared to those without gout.

Conclusions

In this study of NZ Polynesian people and South Asian and European people of the UK Biobank we identified ancestral-specific interactions of the *TRIM46* (rs1126434) locus and smoking behaviour that influence the risk of gout in NZ people of Polynesian ancestry and people of South Asian ancestry in the UK Biobank, where the C-allele (the urate-raising allele) specifically confers risk to gout in never-smokers and current-smokers of NZ Polynesian and South Asian descent, respectively. No replicated interactions were observed for the remaining 4 loci assessed in this study.

Abbreviations

ABCG2

Adenosine triphosphate-binding cassette G2 gene; BMI:body mass index; CI:confidence interval; eGFR:estimated glomerular filtration rate; GRAIL:Gene Relationships Across Implicated Loci; *GCKR*:Glucokinase regulatory protein gene; *HNF4G*:Hepatocyte Nuclear Factor 4 Gamma gene; Inf:infinity; NZ:New Zealand; OR:odds ratio; PC:principal component; *SLC2A9*:Solute carrier family 2, member 9 gene; SD:standard deviation; SNP:single nucleotide polymorphism; *TRIM46*:tripartite motif containing 46 gene; ULT:urate-lowering therapy; UK:United Kingdom.

Declarations

Ethical approval and consent to participate

Ethical approval was granted by the Northern Y Region Health Research Ethics Committee (NTY07/07/074) and the New Zealand Multi-Region Ethics Committee (MEC/105/10/130). The UK Biobank was granted ethical approval by the North West Multi-Centre Research Ethics Committee (11/NW/0382) and the approval number from the UK Biobank for this study was 12611. All participants gave informed written consent.

Consent for publication

Not applicable

Availability of data and materials

The individual-level data of the NZ dataset cannot be made publicly available due to consent restrictions, but data may be available from the corresponding author on reasonable request. UK Biobank data (www.ukbiobank.ac.uk) are owned by a third party. Legal constraints do not permit direct public access to the UK Biobank, but it is open to all bona fide researchers worldwide. Applications to access data must be made through UK Biobank Access Management System (www.ukbiobank.ac.uk/register-apply).

Competing interests

TRM has received consulting fees or grants from Ardea Biosciences and AstraZeneca. ND reports grants and personal fees from AstraZeneca, grants from Amgen, personal fees from Dyve, personal fees from Hengrui, personal fees from Horizon, personal fees from Kowa, personal fees from Abbvie, personal fees from Pfizer, personal fees from Janssen, outside the submitted work. LS declares speaker fees from Amgen. DW received speaker fees from Abbvie. The remaining authors declare that they have no competing interests.

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Authors' contributions

NCF, APG, RT, MC, JP, LKS, ND and TRM were involved in study design, analysis and interpretation of data, and writing of the manuscript. NCF drafted the manuscript. APG obtained and manipulated the NZ dataset. RT and MC obtained and manipulated the dataset from the UK Biobank. TJM carried out genotyping of the New Zealand dataset. JP oversaw the statistical analysis. DHW was involved in data collection and data checking for the NZ dataset. All authors read and approved the final manuscript. All authors are accountable for all aspects of the work.

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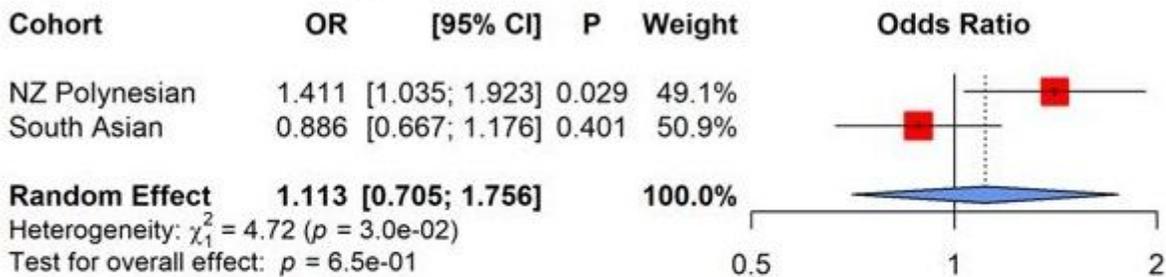
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Figures

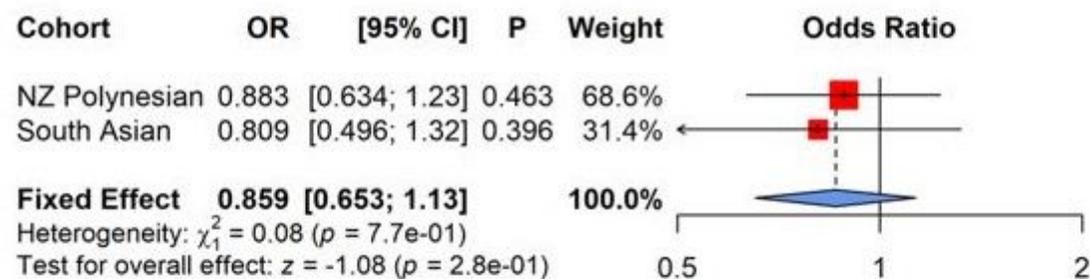
A

Never-smoker subgroup



B

Ex-smoker subgroup



C

Current-smoker subgroup

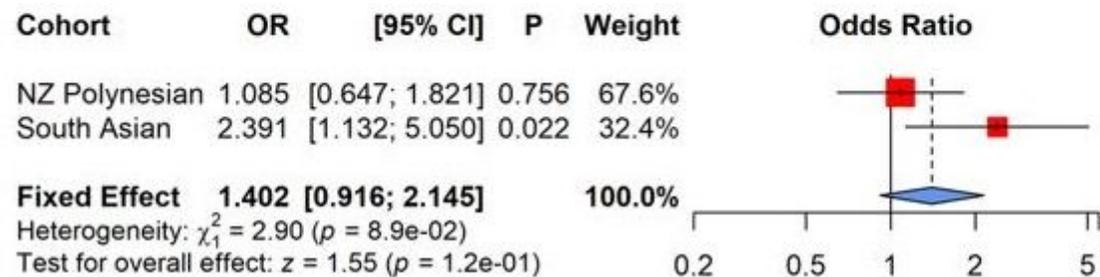


Figure 1

Meta-analysis of NZ Polynesian and UK Biobank South Asian population regression estimates for TRIM46 (rs11264341) C allele vs gout in subgroups of never-smokers (A), ex-smokers (B) and current-smokers (C).

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