Genetic Assessment of Hyperuricemia and Gout in Asian, Native Hawaiian, and Pacific Islander Subgroups of Pregnant Women: Biospecimens Repository Cross-Sectional Study

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Research Article

Abstract

Background

Gout, an inflammatory condition, is characterized by the precipitation of monosodium urate crystals (MSU) in or around joints. The latter is caused by chronic hyperuricemia (HU) - high urate levels in the blood. Genetic variations in urate transporters play a significant role in determining urate levels within the human body, rendering some racial and ethnic groups more or less susceptible to developing HU or gout. This study aims to estimate the frequencies of HU and gout risk alleles in Asian, Native Hawaiian, and Pacific Islander subgroups, using biorepository DNA samples.

Methods

The biospecimens repository center at the University of Hawaii provided DNA samples of consented post-partum women of Japanese, Korean, Filipino, Native Hawaiian, Samoan, and Marshallese descent. The DNA was previously extracted from the cord blood and genotyped at the Genomics and Bioinformatics Shared Resource, Cancer Center (Honolulu, HI). Nine urate genes: *ABCG2, SLC2A9, SLC16A9, GCKR, SLC22A11, SLC22A12, LRR16A, PDZK1,* and *SLC17A1*, were selected due to their significant association with HU and gout risk. Hardy-Weinberg equilibrium for genotype frequencies was assessed, using the Chi-Square test with p<0.05 for statistical significance. Allele frequencies in our study were then compared to EUR from the 1000 Genomes Project Database, using the Chi-square or Fisher exact test as appropriate. Bonferroni correction for multiple comparisons was used, with p<0.006 for statistical significance.

Results

Our study involved 1095 post-partum women 18-year-old or older who self-reported their respective race and ethnicity, including Asian and Pacific Islander ancestry. Asian groups involved Korean, Japanese, and Filipino. Besides, the Pacific Islander group includes Native Hawaiian, Marshallese, and Samoan. None of the study participants had a history of gout. We excluded the *PDZK1* gene from the final analysis due to its deviation from HWE (p<0.05) across all the populations. Compared to EUR, the genetic polymorphism frequencies were significantly different-8/8 in Japanese, 6/8 in Korean, 6/8 in Filipino,8/8 in Samoan, 6/8 in Hawaiian, and 6/8 in Marshallese. HU and gout risk alleles indices were 8, 5, 6, 5, 4, and 4 in Japanese, Korean, Filipinos, Samoans, Marshallese, and Hawaiians, respectively. The percentage of cumulative risk alleles was 100 percent in Japanese and Filipino followed by 83.5% in Korean.

Conclusions

Compared to EUR, Asian subgroups, particularly Filipinos, Japanese, and Korean, had the highest risk of allele index. These results could partly explain that Asian people have an increased risk of developing HU or gout.

Introduction

Gout is one of the most common inflammatory arthritic conditions characterized by the precipitation of monosodium urate crystals (MSU) in or around distal joints.[1] Chronically elevated serum urate (SU), a condition known as hyperuricemia (HU), is the culprit of developing gout. Acute gout flare affects monoarticular joints (e.g., knees, ankles, and metatarsophalangeals), causing severe inflammation with excruciating pain, swelling, erythema, and reduced mobility.[2] The prevalence of gout in developed countries is higher than the developing ones. In the United States (US), gout prevalence is up to 3.9% affecting about 9.2 million people. Gout and hyperuricemia prevalence varies by sex and age groups. Also, specific racial and ethnic subgroups tend to have distinct HU and gout prevalence, ushering the notion of population-specific risk and suggesting distinct HU and gout allele frequencies across different racial and ethnic groups.

Many factors play different roles in regulating SU levels and might lead to HU and gout.[3] Uric acid transporter genetic polymorphisms, mainly single nucleotide polymorphisms (SNPs), have been implicated in developing HU or gout. Numerous studies have ascertained the role of the genetic variation of urate transporters, and it estimated the heritability of urate by up to 73%.[4] One of the largest genome-wide association studies (GWAS) metanalysis, involving more than 110,000 participants from different racial backgrounds, discovered 28 loci associated with SU levels.[5] These loci are predominately in genes encoding urate transporters, including *SLC2A9, ABCG2, SLC22A11, SLC22A12, SLC17A1*, and the scaffolding protein-encoding gene *PDZK1*.[4]

Indeed, the prevalence of HU and gout varies among people and countries. Along with differences in the genetic background, several demographic and environmental characteristics such as diet and lifestyle, smoking, alcohol consumption, or beverages containing high amounts of fructose corn syrup may increase HU and gout prevalence.[6] Studies published in 2015 and thereafter showed a substantial increase in gout incidence over recent decades in the US, Canada, Denmark, Sweden, and South Korea, confirming greater incidence in men relative to women, and increased incidence in later life decades. Besides, recent studies in North America and Scandinavia found a 1.5–2-fold increase in gout incidence over the past two to three decades.[7–12] Gout incidence in South Korea increased by 25% between 2009 and 2015.[13] A recent study reported that the sub-populations Maori and Pacific Islanders in New Zealand have a gout prevalence of 7.63%.[14] These trends indicate that gout incidence increased in many countries over recent decades and that the aging population in these countries may drive this increased gout incidence. Gout prevalence varies globally, with one of the highest prevalence in Oceanic countries, particularly in indigenous and South Pacific Island populations. Along with the earlier reported increasing prevalence of gout in Europe and the US, there is evidence of increasing prevalence in Australia (self-reported), Canada, China, and South Korea as well.[15] According to the US Census Bureau,

Chinese and Filipino communities are considered the largest Asian subgroups. Similarly, Native Hawaiians and Samoans are the largest Pacific Islander subgroups.[16] Amongst all the ethnic subgroups in the US, populations with Asian ancestry are approximately three times more likely to develop gout than Europeans (EUR).[17]

There is a correlation between genetic polymorphisms in urate disposition and incidence of gout amongst different ethnic groups. Therefore, the purpose of this study is to estimate the frequencies of selected SNPs in key urate genes across diverse populations (Filipino, Japanese, Korean, Samoan, Marshallese, and native Hawaiian) compared with the EUR population. With the growing need for racial diversity in genomic research, this study will further our understanding of the genetics of HU and gout in underrepresented minorities. We hypothesized that the risk allele frequencies of HU and gout are significantly higher in the Asian, Native Hawaiian, and Pacific Islander subgroups compared to the EUR population.

Results:

Study participants characteristics and demographics

In this study, 1059 participants were included. Demographic characteristics of all participants are shown in Table 1. The participant's age ranged from 18 to 47 years with a means of 29 years. The gestational age ranged from 24 to 41 weeks with a means of 38 weeks, of which 82.2% (n = 871) were full term and 17.3% (n = 182) were pre-term. Using the pregravida weight, the body mass index (BMI) ranged from 24.5 to 30.1 kg/m^{2,} with mean of 26.3 kg/m^2, of which 43.4% (n = 400) were classified as having normal weight, 26.9% (n = 248) were classified as obese, 22.9% (n = 211) were classified as overweight, and 6.8% (n = 63) were classified as underweight. Our study consisted of 21.5%. (n = 229) Filipinos, 19.8% (n = 210) Japanese, 18.9% (n = 200) Samoans, 15.1% (n = 160) Marshallese, 14.7% (n = 156) Hawaiian, and 9.8% (n = 104) were Koreans. No subjects reported a history of gout.

Genetic Analysis and Quality Control

As a measure of quality control, genetic results were assessed for Hardy-Weinberg Equilibrium (HWE), using chi-square with p < 0.05 for significance (Table 6). SNPs call rates were evaluated and reported for each ethnic group and for the overall study cohort (n = 1059 participants). Overall SNPs call rate were 97.4% in *SLC22A12*, 95.1% in *SLC17A1*, 96% in *SLC16A9*, 96.9% in *ABCG2*, 94.3 in *SLC22A11*, 91% in *PDZK1*, 96.1% in *SLC2A9*, 96.4 % in *LRRC16A*, and 96.7% in *GCKR (*Table 7).

Hyperuricemia and Gout Risk Alleles Frequencies

Risk alleles and genotype frequencies of all nine uric acid genes/SNPs in all ethnic subgroups are summarized in Tables 3 and 4. Due to deviation from the HWE, we excluded the rs12129861 C > T in *PDZK1* from the final analysis. In the Japanese group, eight out of the eight uric acid SNPs were significantly different from EUR (Table 5). All these eight alleles (100%) were prevalent in the Japanese population from EUR and were considered risk alleles. These risk alleles included: rs1183201 T > A in *SLC17A1*, rs2231142 G > T in *ABCG2*, rs2242206 G > T in *SLC16A9*, rs505802 C > T in *SLC22A12*, rs734553 G > T in *SLC2A9*, rs17300741 A > G in *SLC22A11*, rs742132 A > G in *LRRC16A*, and rs780094 C > T in *GCKR*.

In the Korean group, six out of the eight uric acid SNPs were significantly different from EUR (Table 5). Five out of the six alleles (83.5%) were more prevalence in Koreans than EUR and were considered risk alleles. These risk alleles genes/SNPs included: rs1183201 T > A in *SLC17A1*, rs2242206 G > T in *SLC16A9*, rs505802 C > T in *SLC22A12*, rs734553 G > T in *SLC2A9*, rs17300741 A > G in *SLC22A11*.

In the Filipino group, six out of the eight uric acid SNPs were significantly different than those of EUR (Table 5). All these six SNPs in Filipino were more prevalent (100%) than EUR. These genes/SNPs included: rs1183201 T > A in *SLC17A1*, *rs*2231142 G > T in *ABCG2*, rs2242206 G > T in *SLC16A9*, rs505802 C > T in *SLC22A12*, rs734553 G > T in *SLC2A9*, and rs17300741 A > G in *SLC22A11*.

In the Marshallese group, six out of the eight uric acid SNPs were significantly different in the Marshallese population than those of EUR (Table 5). Among those six SNPs, the Marshallese population had four uric acid alleles significantly more prevalent (66.5%) than EUR. These genes/SNPs included: rs2231142 G > T in *ABCG2*, rs2242206 G > T in *SLC16A9*, rs505802 C > T in *SLC22A12*, and rs734553 G > T in *SLC2A9*.

In the Samoan group, eight out of the eight urate SNPs were significantly different from EUR (Table 5). Among those eight SNPs, five uric acid alleles (62.5%) had a higher prevalence in the Samoan population than EUR. These genes/SNPs included: rs2231142 G > T in *ABCG2*, rs505802 C > T in *SLC22A12*, rs734553 G > T in *SLC2A9*, rs17300741 A > G in *SLC22A11*, rs1183201 T > A in *SLC17A1*.

In the Native Hawaiian group, six out of the eight uric acid SNPs were significantly different from EUR (Table 5). Four out of six alleles (66.5%) were more prevalence in Native Hawaiian population than EUR and were considered risk alleles. These genes/SNPs include: rs505802 C > T in *SLC22A12*, rs734553 G > T in *SLC2A9*, rs17300741 A > G in *SLC22A11*, and rs1183201 T > A in *SLC17A*.

Among all our studied population subgroups, Asian subgroups of Japanese, Koreans, and Filipinos had the highest HU and gout risk allele indexes of 8, 5, and 6, respectively. The percentages of risk alleles were 100% in Japanese and Filipino, followed by 83.5% in the Korean subgroup. Pacific Islander sub-groups were 66.5% in Native Hawaiians and Marshallese, followed by 62.5% in Samoan (Table 5).

Discussion

Our study found that the population of Asian ancestry had a higher prevalence of HU and/or gout risk alleles compared with the EUR population. Uric acid associated alleles found in the Asian subgroup were significantly different from the EUR population and were all considered HU and/or gout risk allele. These results could partially explain the differential prevalence of hyperuricemia and gout across different ethnic and racial groups based on their genetic makeup. Therefore, a discussion on the role of these various genes/alleles in developing HU and/gout is warranted.

ABCG2 gene encodes the ATP-Binding Cassette G-protein transporter located in the apical membrane in the proximal renal tubule, and it is also expressed in the gastrointestinal tract and liver. ABCG2 is a major urate excretion transporter.[18] Genetic polymorphisms in the *ABCG2* gene were reported to contribute to elevated urate levels leading to hyperuricemia and gout. The SNP rs2231142 G > T (Q131K) in *ABCG2* is associated with increased urate levels in the presence of the T-allele. Therefore, individuals with the TT genotype are at high risk of HU and gout than GG counterparts. A recent study reported that T-allele presence is 3- times higher in East Asians than EUR. This suggests that East Asian populations are at higher risk for developing HU and gout.[19]

Similarly, our findings showed that the prevalence of the T allele of the rs2231142 (G > T) was 9.4% in EUR, 45.8% in Filipinos, 27.7% in Koreans, and 25.6% in Japanese (Table 5). In our Korean cohort, however, the rs2231142 (G > T) deviated from the HWE (p = 0.0407) (Table 6). In the Native Hawaiian and Pacific Islander (NHPI) subgroups, the frequencies of the T allele of the rs2231142 (G > T) were 31.1%, 17.6%, and 12.7% in Samoan, Marshallese, and Native Hawaiian subgroups, respectively. The genetic polymorphism rs22131142 (G > T) in *ABCG2* is significantly associated with urate levels and increased risk for HU and gout among different populations.[20–22] A study conducted in the Korean population showed that the rs22131142 G > T is strongly associated with gout risk (Odds ratio [OR] 3.32; 95% confidence interval [CI]: 2.11 to 5.20).[23]Also, in a study of 6881 Koreans identified that the genetic polymorphism rs2231142 (G > T) was associated with increased SU levels (Effect size = 0.220, p = 2.06E-29).[24] Consistent with our results, a previous study reported that the minor allele frequency (MAF) of the T risk allele of the genetic variant rs2231142 in *ABCG2* was high in Japanese and Koreans compared to Caucasians (0.29, 0.28, vs. 0.11).[25] Additionally, a meta-analysis conducted on a multi-ethnic cohort reported that the T allele of rs22131142 G > T in *ABCG2* was strongly associated with HU and gout across populations, and the severity is affected by gender and ethnicity.[26]

Overall, the genetic polymorphism rs2231142 (G > T) of the *ABCG2* gene is considered the most significant gene polymorphism related to the increased risk of HU and/or gout in selected minorities compared with other risk alleles. Sun *et al.* studied the association between 11 genetic loci of which *ABCG2* rs2231142 (G > T) was one of the genes associated with serum urate concentrations in the Chinese population.[27] Also, Zhang et al. reported that the SNP rs2231142 of the *ABCG2* gene was associated with hyperuricemia in the American population consisting of EUR Americans, African Americans, Mexican Americans, and Indian Americans.[28] Our finding provides that the genetic variants in *ABCG2* rs2231142 (G > T) may increase urate levels and gout risk in Asian, Native Hawaiian, and Pacific Islander subgroups compared to EUR.

SLC2A9 encodes the GLUT9 transporter, which has a high-capacity transporter for urate, fructose, and glucose. *SLC2A9* is known to be strongly associated with urate regulation in the human body.[29] It is mainly expressed in the kidneys and liver, but it is also expressed in human articular cartilage.[30] The intronic polymorphism rs734553 (G > T) in *SLC2A9* is associated with increased HU risk and gout resulting from a change in transporter affinity for urate. [31] This genetic variation strongly affects SU levels in EUR ancestry and could significantly affect SU in women (Effect size = 0.315, p = 5.22x10-201).[32] Reginato Am et al. have identified that polymorphism rs734553 of the *SLC2A9* gene is linked to SU levels and gout in the Islandic Polynesian population. [33] Our analysis has shown that the T-allele's prevalence in Asian and Pacific Islander populations was higher than in the EUR population. Specifically, the frequency of rs734553 (G > T) was 99.5% in Japanese, 98.9% in Filipinos, and 98.3% in Koreans compared to 75.5% in EUR (p < 00.006). Additionally, the frequency of rs734553 (G > T) was 100% in Marshallese, 98.3% in Samoans, and 90.9% in Hawaiians compared to 75.5% in EUR (p < 0.006) (Table 3). Our results suggest that carrying the T -allele will likely increase the risk of elevated SU in both the Asian and NHPI subgroups.

SLC17A1 encodes the voltage-gated human sodium-dependent phosphate co-transporter type 1 protein (NPT1), located in the proximal tubule's apical side in the kidney and works as renal urate efflux transporter. Decreased SU Levels were found to be associated with the genetic polymorphism rs1183201 (T > A) in *SLC17A1* (Effect size = -0.062, 95% CI: -0.078; -0.459) with the effect of allele A as the protective allele of EUR descent. In the intronic SNP rs1183201 (T > A) of *SLC17A1*, the A allele was associated with decreased SU level with a prevalence of 48.2% in EUR descent.[32] The polymorphism rs1165205 of *SLC17A3* has strong linkage disequilibrium r2 = 0.966 with rs1183201of *SLC17A1* and has shown an association with gout and SU in Korean population with a MAF of T allele of 0.137.[25]

Our analysis found that the prevalence of A allele in both Asian and Pacific Islander populations was lower than EUR descent except in Marshallese, where it was 57.2% vs. 46.1% (p < 0.006). Amongst the Asian population, the frequency of A allele for rs1183201 (T > A) was 2-3-folds lower than that observed in EUR (14.6%, 16.1%, and 20,7% for Koreans, Japanese, and Filipinos respectively vs. 46.1% p < 0.006)) (Table 3). The significant differences in A allele frequency across minorities covered in our study suggest that some ethnicities could be genetically predisposed to high urate levels.

SLC22A12 encodes for URAT1, a protein found on the kidney's apical side of the proximal tubules. This transporter is responsible for the majority of the urate reabsorption from the kidneys and a primary target for urate-lowering therapies.[34] A previous study reported that the loss of activity in URAT1 had been found to cause hypouricemia in Japanese populations, suggesting that URAT1 plays an essential role in regulating the renal tubular reabsorption of urate.[35] The intergenic polymorphism rs505802 (C > T) in *SLC22A12* was observed to reduce urate levels in EUR ancestry. Specifically, the T- allele correlates with lower SU levels in women and men (Beta effect – 0.073, -0.047, respectively) in EURs.[32] Jang et al. reported that the T6092C genetic variant of *SLC22A12* was also significantly associated with SU concentration amongst the male Korean population.[36] The T6092C at rs1529909 of *SLC22A12* was found in linkage disequilibrium (LD = 1, r^2 = 1) with rs505802 of *SLC22A12*. However, the prevalence of the T-allele in our population subgroups was lower than EUR population (p < 0.006). Our results found that the prevalence of T-alleles was 3-4-folds lower in both Asian and NHPI populations (Table 3), which suggests a higher baseline line urate levels in the Asian and NHPI population subgroups compared with EURs. Furthermore, our findings showed that the C-allele frequency was higher in both subgroups of targeted populations compared with EUR. Particularly, the frequency of the

C allele in Marshallese was more than three times than EUR (95% vs. 29.3%, p < 0.006). These results propose a higher risk for HU and/or gout in our studied populations and suggest a possible implication in the response to treatments targeting URAT1 transporter in Asian and NHPI subgroups.

SLC22A11 is predominantly expressed in the proximal tubule's apical side in the kidney and encodes the organic anion transporter 4 (OAT4). The Organic anion transporter 4 (OAT4) is associated with regulating UA reabsorption, like URAT1, and a target for urate-lowering therapy.[37] The intronic variant rs17300741 (A > G) in the *SLC22A11* gene was associated with renal urate underexcretion type gout in the Japanese population (p = 0.049).[38] Kolz et al. have reported a significant association between the polymorphism in OAT4/SLC22A11 rs17300741 A > G and UA levels in individuals of Caucasian descent (p = 6.7×10 − 14).[32] Our analysis found that the A-allele prevalence was higher across selected minorities than EUR. The A allele frequency in the Asian subgroups of Koreans, Filipinos, and Japanese, was about 2-fold higher than EUR (89.5%, 85.3%, and 84.7%, respectively vs. 46.2% in EUR (p < 0.006). Furthermore, the A allele frequency was higher in Samoan, Native Hawaiian, and Marshallese compared with EUR (78.7%, 72.3%, and 70%, respectively, vs. 46.2% in EUR (p < 0.006). Our analysis of the rs17300741 A > G in *SLC22A11* suggests a higher genetic risk for higher baseline urate levels or gout in Asian and NHPI compared with EUR. Hence, our results are consistent with the previous literature confirming the association of rs17300741 A > G with the prevalence of gout, which is two-fold higher in non-EURs relative to EURs.[39] Collectively, our study shows that the frequencies of risk alleles C and A in both loci-*SLC22A12* and *SLC22A11*, respectively, were significantly higher in Filipino, Korean, Japanese, Samoan, Marshallese, and Native Hawaiian relative to EUR (Table 3). Notably, the prevalence of risk alleles rs505802 (C > T) of *SLC22A12* and rs17300741 (A > G) of *SLC22A11* genes were highest in Asian subgroups compared with the NHPI population.

SLC16A9 encodes for monocarboxylic acid transporter protein across the cell membrane (MCT9). It is located on the proximal tubule's apical side of the kidney and responsible for urate excretion. A missense variant rs2242206 (G > T) in the *SLC16A9* has been reported to dysregulate urate level. The exact function of the MCT9 transporter is still unclear. Nonetheless, Nakayama et al. have found a significant relationship between the rs2242206 G > T (K258T) in *SLC16A9*, and gout (*p* = 0.012), with an odds ratio (OR) of 1.28 in a Japanese population.[40] Our cohort analysis showed that the frequency of T allele across minority subgroups was significantly higher than that of EUR ancestry (Table 3). Remarkably, the Asian subgroup (Koreans, Japanese, and Filipinos) had the highest prevalence of T allele, which is approximately two times higher vs. EUR (59.5%, 55.5%, and 54%, respectively, vs.26.6%, p < 0.006). Additionally, the prevalence of risk allele T in Native Hawaiians (45.1%), Marshallese (44.5%), and Samoans (39.3%) were significantly higher compared with EUR (26.6%) (p < 0.006). However, the polymorphism rs2242206 (G > T) in the *SLC16A9* was not in HWE in Samoans and Hawaiians (Table 6). These findings suggest that individuals of Asian descent, carrying the polymorphism in rs2242206 (G > T) in *SLC16A9* could be at higher risk for and an increase the susceptibility to gout, especially in individuals of Japanese, Korean, and Filipino descent.

GCKR is a protein that encodes glucokinase regulatory protein (*GCKR*), which has a role in developing the metabolic syndrome, involving triglyceride regulation and glucose metabolism.[41, 42] Several studies have shown the relationship between urate levels and metabolic syndrome-related traits such as insulin resistance and hypertension through oxidative stress and inflammatory pathway.[32] The intronic variant rs780094 (C > T) of the *GCKR* gene has shown a strong association with gout in the male Han-Chinese population.[43] Furthermore, the T- allele of Intronic polymorphism of rs780094 C > T has been associated with UA concentration regulation in EUR ancestry.[32] Meanwhile, the MAF of the C allele was higher in the Korean group compared with Caucasian ancestry (0.47, vs. 0.42).[25] In our analysis, the frequency of T-allele was higher in the Japanese subgroup than EUR (58% vs. 41.1%, p < 0.006) and lower in Samoans than EUR (30.6 vs. 41.1%, p < 0.006) (Table 3). This signifies that allele is associated with less risk for HU and/or gout. There was no significant difference between Filipinos and Koreans compared to EUR, although the T-allele frequency was higher in Asian subgroup ancestry. Overall, these results found that the Japanese subgroup could be predisposed to developing HU and gout compared with other subgroups in the study. Noteworthy, *GCKR* protein is associated with modulating the metabolic activities; hence, this finding might partially suggest a biological mechanism between genetic variations and the development of cardiometabolic disorders, including HU and gout, which may contribute to the health disparities seen in gestational diabetes and hypertension in pregnant women.

PDZK1 has been identified in the kidney and acts as a scaffolding protein for different transporter proteins associated with SU levels baseline.[44] The Intergenic variants rs12129861 (C > T) of *PDZK1* protein have shown an association with reducing the risk of gout in the male Han-Chinese population (OR = 0.727, *P* = 0.015) [40]. Kolz et al. have identified the role of scaffolding *PDZK1* protein in SU baseline regulation.[32] Our analysis pointed that only the Korean minority had a higher frequency of the C- allele than EUR but was not statistically significant (56.7% vs. 54.1%, p > 0.006). In addition, other Asian subgroups, Filipinos and Japanese, had a lower prevalence of C-allele than EUR and were not statistically significant, with Japanese (48.9% vs. 54.1%, p > 0.006). Only the Filipino population in Asian minorities had a significant difference compared with EUR but had a lower prevalence of the C- allele (44.7% vs. 46.4% p < 0.006). In contrast, Pacific Islander sub-groups- Native Hawaiians, Marshallese, and Samoans had a significantly lower prevalence of the C-allele relative to European (39.3%, 39.4%, 46.4% vs. 54.1%, p < 0.006). It should be noted that we found a deviation when we conducted the Hardy-Weinberg equilibrium investigation *PDZK1* rs12129861 (C > T) genotypes across all minorities addressed in the study (p < 0.05) (Table 6). In this case, further studies having a larger sample size and different ethnic backgrounds are needed to investigate the prevalence of risk alleles to validate our results. Hence, we excluded this protein from the results of this study to avoid any conflicts in our findings.

LRR16A is expressed in the apical side of proximal tubules in the kidneys, which encodes a protein called capping protein ARP2/3 and myosin-I linker (CARMIL). This protein has a role in urate transportome formation, which mediates urate reabsorption.[32, 45] Hiraka Ogata et al. have found a significant association between intergenic variant homozygote AA in rs742132 A > G of *LRRC16A* and risk of gout disease among Japanese males.[46] Moreover, a genetic variant rs742132 in *LRRC16A* is associated with increased SU in EUR ancestry.[32] Notably, a GWAS study conducted on East Asian minorities, including Koreans, showed that rs742132 in *LRRC16A* is associated with elevated urate levels.[47] Our analysis shows that the Asian subgroup (Japanese) had a significant difference and the highest frequency of the A-allele compared to EUR (78.2%, vs. 69%, p < 0.006). However, the frequency of the A-allele in the Filipino subgroup was indifferent compared with EUR (69.7% vs. 69, p > 0.006). In addition, the Korean sub-minority had an insignificant A-allele prevalence than EUR (78%, vs. 69, p > 0.006). On the other hand, in NHPI minorities, there was a deviation from Hardy-Weinberg equilibrium in the Hawaiian

population p < 0.05 (Table 6). Also, although the prevalence of A-allele in Marshallese was higher than EUR, no significant difference was found (70%, vs. 69%, p > 0.006) (Table 3). Moreover, the Samoan subgroup had a lower frequency of A-allele compared with EUR (51.7%, vs. 69%, p < 0.006) (Table 3). Asian subgroups of Japanese and Koreans had the highest A-allele frequency as compared to the other subgroups in this study, and this is consistent with other results in the literature.[48] Our findings suggest that the genetic polymorphism in rs742132 of *LRRC16A* may explain the differential prevalence of HU/gout across different populations subgroups.

Our results have collectively shown that the frequency of HU and/or gout risk alleles in several population subgroups significantly differs from EUR (p < 0.006). We found out that the Asian subgroups had the highest prevalence of HU and/or gout risk alleles as compared to the NHPI populations. These results are consistent with the patient claims data in the ambulatory care clinics that gout diagnosis in the Asian population living in the U.S. is about three times more than EUR. Consistent with the previously published reports, our results provide more evidence that populations of Asian descent have a higher risk of developing HU and/or gout than EUR.[21, 49, 50] We believe that other genes/SNPs are also involved in urate disposition and other factors that may influence urate levels (i.e., older age, smoking, diuretic use, and dietary habits). However, we provide primary knowledge that could help clinical practitioners understand the pathophysiology of diseases in some understudied population subgroups. Further replication in different ethnic subgroups with larger population samples is needed.

Limitations

The first limitation of the study is that it was only conducted on pregnant women; hence more representative samples of the population are needed in future studies to validate our findings. We believe that some other factors such as dietary habits, older age, and male sex contribute to HU and gout. Our results might partially be associated with gout pathophysiology besides other factors. We believe that multiple genes/SNPs are associated with the development of HU and gout. Nevertheless, our study had a limited number of genes/SNPs selected from GWAS conducted in EUR. While the lack of gout diagnosis in our analysis may not have changed the outcomes, it is important to replicate these results in a more representative sample. Furthermore, study participants did not have levels of SU measured to conduct association analysis between genotype and phenotype. Also, in some subgroups, the sample size was not enough to estimate the exact prevalence of risk alleles, leading to deviation from HWE. Finally, gout risk is markedly lower in pregnant women which explains no cases of gout, but our genetic findings remain consistent with the documented high risk of gout in Asian subgroups.

Future Perspective

Personalized medicine based on individual genetic profiles could play a crucial role in predicting and addressing some health inequalities across different racial and ethnic groups. Our research proposes that genetic data may improve patients' outcomes by predicting disease risk, selecting an appropriate drug, and reducing the risk of new disease onset. This study is the first genetic investigation focusing on several urate genes/SNPs pairs and multiple underserved populations involving Asian and NHPI pregnant women population. Furthermore, this investigation could help future research assess HU's and/or gout-risk-alleles roles in pregnant women to identify patients at higher risk of maternal comorbidities such as gestation diabetes, gestation hypertension, and pre-eclampsia (PE).

Table 1
Demographic characteristics across populations

Characteristics	Total population (n = 1059)	Filipino (n = 229)	Japanese (n = 210)	Samoan (n = 200)	Marshallese (n = 160)	Hawaiian (n = 156)	Korean (n = 104)
Mother's age (years)	28.8 ± 6.3	29.8 ± 6.1	33.4 ± 5.2	26.3 ± 5.7	25.1 ± 4.6	26.2 ± 5.5	31.3 ± 5.2
Gestational age (weeks)	38.0 ± 2.2	37.8 ± 2.2	2.6 ± 37.6	2.0 ± 38.4	38.0 ± 2.0	38.2 ± 2.0	38.3 ± 2.4
Gestational age category							
Preterm (< 37 weeks)	182 (17.3%)	44 (19.4%)	50 (23.8%)	27 (13.5%)	29 (18.4%)	21 (13.5%)	11 (10.8%)
Full term (≥ 37 weeks)	871 (82.2%)	183 (80.6%)	160 (76.2%)	173 (86.5%)	129 (81.6%)	135 (86.5%)	91 (89.2%)
Body mass index (kg/m^2)	26.3 ± 6.9	25.0 ± 6.0	24.4 ± 5.6	30.1 ± 7.5	25.1 ± 6.2	28.1 ± 7.3	24.5 ± 7.2
Body mass index categories							
Underweight (< 18.5 kg/m^2)	63 (6.8%)	18 (9.0%)	20 (10.4%)	5 (2.9%)	10 (7.8%)	-	10 (11.5%)
Normal weight (18.5–24.9 kg/m^2)	400 (43.4%)	94 (46.8%)	93 (48.4%)	44 (25.3%)	68 (53.1%)	58 (41.4%)	43 (49.4%)
Overweight (25–29.9 kg/m^2)	211 (22.9%)	56 (27.9%)	46 (24.0%)	38 (21.8%)	18 (14.1%)	30 (21.4%)	23 (26.4%)
Obese (≥ 30 kg/m^2)	248 (26.9%)	33 (16.4%)	33 (17.2%)	87 (50.0%)	32 (25.0%)	52 (37.1%)	11 (12.6%)
Pre- gravida weight (lbs)	151.2 ± 46.5	132.7 ± 28.4	127.2 ± 26.0	203.7 ± 44.7	142.5 ± 41.9	166.9 ± 47.9	133.6 ± 34.5
Data are expressed as number (%) or mean +/- standard deviation (minimum-maximum).							

Table 2
Gene (SNP) and Function Summary

Gene (Protein)	Protein Function	SNP (Class)	SNP Effect	References
ABCG2 (ABCG2)	Protein coding gene for ATP-binding cassette transporter responsible for urate excretion.	rs2231142 (G > T) (Missense variant)	Reduction in ABCG2-mediated urate transport, urate under-excretion, and hyperuricemia is caused by Glu 141 Lys amino acid substitution.	[32]
SLC2A9 (GLUT9)	High-capacity urate, fructose, and glucose transporter located on both sides of the kidney's apical and basolateral membrane. This protein is expressed in liver, kidney, and chondrocytes tissues. Also strongly associated with increase serum UA.	rs734553 (G > T) (Intronic variant)	Increases risk for gout through altering urate transporter affinity.	[51]
SLC16A9 (MCT9)	Monocarboxylic acid transporter protein located in the apical side of kidneys, responsible for urate excretion	rs2242206 (G > T) (Missense variant)	Reported to substantially increase the risk of renal overload gout ($p = 0.012$), with an odds ratio (OR) of 1.28.	[40]
SLC17A1 (NPT1)	Uric acid transport protein localized at the apical membrane of the renal proximal tubule which contributes to urate efflux	rs1183201(T > A) (Intronic variant)	Known to be associated with decreased urate levels and the A allele seems to be the protective allele in the EUR population (Effect size= -0.062).	[32]
SLC22A11 (OAT4)	Organic anion transporter 4 (OAT4), responsible for urate reabsorption regulation in the kidney	rs17300741(A > G) (Intronic variant)	It is linked to renal under-excretion of UA in EUR descent (Beta effect = 0.062).	[32, 38]
SLC22A12 (URAT1)	Urate 1 transporter (URAT1), located on the apical side of proximal tubules and responsible for UA reabsorption	rs505802 (C > T) (Intergenic variant)	It is associated to decrease SU levels in the EUR population. Effect size= -0.056	[32]
GCKR (GCKR)	Glucokinase regulator protein has a role in metabolic syndromes that may be associated with urate concentrations	rs780094 (C > T) (Intronic variant)	It is associated with glucose metabolism, lipid regulation, SU levels, and gout disease risk (Beta effect = 0.052).	[32],[41], [42]
PDZK1 (PDZ)	It is scaffolding protein located in the apical side of the proximal tubule in the kidneys, which has a role in maintaining the balance of urate levels through the formation of urate transportome.	rs12129861(C > T) (Intergenic variant)	It is associated with lower serum urate levels among people of EUR ancestry (Effect size= -0.06)	[32, 52]
LRRC16A (CARMIL1)	Protein expressed on the apical side of proximal tubules in the kidneys, which is known as capping protein ARP2/3 and myosin-I linker (CARMIL). This protein has a role in urate transportome formation, which mediates UA reabsorption.	rs742132 (A > G) (Intronic variant)	A risk allele related to increased risk of gout in EUR (Beta effect = 0.054).	[32, 45]

Table 3
Uric acid risk allele frequencies comparisons Asian and Native Hawaiian and Pacific Islanders

Gene (SNP)	Variant Type	Allele	EUR % (n)	Filipino % (n)	Korean % (n)	Japanese % (n)	Hawaiian % (n)	Marshallese % (n)	Samoan % (n)	Gout/ Urate Effect (↑↓)
ABCG2 (rs2231142 G > T)	missense	G T	90.6 (911) 9.4 (95)	54.2(194)* 45.8 (164)	72.2(133)* 27.7 (51)	74.3(278)** 25.6 (96)	87.3 (253) 12.7(37)	82.3(201)* 17.6 (43)	68.9(251)* 31.1 (113)	↑
SLC2A9 (rs734553 G > T)	intronic	G T	24.5 (246) 75.5 (760)	1.2 (4)* 98.8 (348)	1.7 (3)* 98.3 (183)	0.5 (2)* 99.5 (368)	9.1 (26)* 90.9 (260)	0 (0)* 100 (242)	1.7 (6)* 98.3 (358)	↑
SLC17A1 (rs1183201 T > A)	intronic	A T	46.1 (464) 53.8 (542)	20.7 (73) * 79.2 (277)	14.6 (26)* 85.3 (152)	17.1 (63)* 82.9 (305)	34 (98)* 66 (190)	57.2 (135)* 42.8 (101)	28.4(103)* 71.6 (259)	↓
SLC16A9 (s2242206 G > T)				55 (197) * 45 (161)						
	Intronic	G T	73.4 (738) 26.6 (268)		40.8 (75) * 59.2 (109)	44.5(163)* 55.5 (203)	54.9(158)* 45.1 (130)	55.5 (132)* 44.5 (238)	60.7(221)* 39.3 (143)	↓
GCKR (rs780094 C > T)	missense	C T	58.9 (593) 41.1 (413)	55.1 (197) 44.9 (161)	58.2 (107) 41.8 (77)	42 (156) * 58 (216)	65.9(190) 34.1 (98)	64.5 (156) 35.5 (86)	69.4(254)* 30.6 (112)	↑
SLC22A11 (rs17300741 A > G)	intron variant	A G	46.2 (465) 53.8 (541)	85.3 (297)* 14.7 (51)	89.5 (163)* 10.4 (19)	84.7(305)* 15.2 (55)	72.3(201)* 27.7 (77)	70 (167) * 30 (73)	78.5(281)* 21.5 (77)	↑
SLC22A12 (rs505802 C > T)	intergenic	T C	70.7 (711) 29.3 (295)	21.6 (79)* 78.4 (287)	20.4 (38)* 79.6 (148)	18.3 (68)* 81.7 (304)	37.6(109)* 62.4 (181)	12 (5) * 95 (230)	31.5(116)* 68.5 (252)	↓
LRRC16A (rs742132 A > G)	intron variant	A G	69 (694) 31 (312)	69.7 (251) 30.3 (109)	78 (142) 22 (40)	78.2(291)* 21.8 (81)	58.6(171)* 41.4(121)	70 (168) 30 (72)	51.7(188)* 48.3 (176)	↑
PDZK1 (rs12129861 C > T)	intergenic	C T	54.1 (544) 45.9 (462)	44.7 (151)* 55.3 (187)	56.7(92) 43.2 (70)	48.9 (178) 51 (186)	39.3(106)* 60.7 (164)	39.4 (90)* 60.5 (138)	46.5(159)* 53.5 (183)	↓

The **bolded** letter refers to the risk allele linked to HU/gout

* Indicates statistical significance p < 0.006 between minorities and comparator group (EUR)

Table 4
Uric acid Genotype frequencies comparisons Asian, Native Hawaiian, and Pacific Islanders

Gene (SNP)	Genotype	EUR % (n)	Filipino % (n)	Korean % (n)	Japanese % (n)	Hawaiian % (n)	Marshallese % (n)	Samoan % (n)
ABCG2 (rs2231142 G > **T**)	GG	82.3 (414)	28.4 (51)	56.5 (52)	56.7 (106)	75.5 (110)	68.0 (83)	48.6 (89)
	GT	16.5 (83)	51.4 (92)	31.5 (29)	35.3 (66)	23.1 (33)	28.7 (35)	40.4 (73)
	TT	1.2 (6)	20.1 (36)	12.0 (11)	8.0 (15)	1.4 (2)	3.3 (4)	10.9 (20)
SLC2A9 (rs734553 G > **T**)	GG	5.6 (28)	-	-	-	1.4 (2)	-	-
	GT	37.8 (190)	2.3 (4)	3.2 (3)	1.1 (2)	15.4 (22)	-	3.3 (6)
	TT	56.7 (285)	97.7 (172)	96.8 (90)	98.9 (183)	83.3 (119)	100 (121)	96.7 (176)
SLC17A1 (rs1183201 **T** > A)	AA	23.1 (116)	4.0 (7)	1.1 (1)	3.8 (7)	11.8 (17)	29.7 (35)	6.6 (12)
	AT	46.1 (232)	33.5 (59)	27.0 (24)	26.6 (49)	44.4 (64)	55.1 (65)	43.6 (79)
	TT	30.8 (155)	62.3 (109)	71.9 (64)	9.6 (128)	43.8 (63)	15.3 (18)	49.5 (90)
SLC16A9 (rs2242206 G > **T**)	GG	54.9 (276)	32.9 (59)	15.2 (14)	16.9 (31)	34.7 (50)	31.9 (38)	33.0 (60)
	CT	37.0 (186)	44.1 (79)	51.1 (47)	55.2 (101)	40.3 (58)	47.1 (56)	55.5 (101)
	TT	8.2 (41)	23.0 (41)	33.7 (31)	27.9 (51)	25.0 (36)	21.0 (25)	11.5 (21)
GCKR (rs780094 C > **T**)	CC	33.6 (169)	31.8 (57)	35.9 (33)	18.8 (35)	41.7 (60)	41.3 (50)	48.1 (88)
	CT	50.7 (255)	46.4 (83)	44.6 (41)	46.2 (86)	48.6 (70)	46.3 (56)	42.6 (78)
	TT	15.7 (79)	21.8 (39)	19.6 (18)	34.9 (65)	9.7 (14)	12.4 (15)	9.3 (17)
SLC22A11 (rs17300741 **A** > G)	**AA**	23.5 (118)	73.5 (128)	80.2 (73)	71.7 (129)	54.0 (75)	53.3 (64)	62.6 (112)
	AG	45.5 (229)	23.5 (41)	18.7 (17)	26.1 (47)	36.7 (51)	32.5 (39)	31.8 (57)
	GG	31.0 (156)	2.9 (5)	1.1 (1)	2.2 (4)	9.3 (13)	14.2 (17)	5.6 (10)
SLC22A12 (rs505802 **C** > T)	**CC**	9.9 (50)	61.2 (112)	63.4 (59)	67.7 (126)	35.8 (52)	90.9 (110)	48.9 (90)
	CT	38.8 (195)	34.5 (63)	32.3 (30)	28.0 (52)	53.1 (77)	8.3 (10)	39.1 (72)
	TT	51.3 (258)	4.4 (8)	4.3 (4)	4.3 (8)	11.1 (16)	0.8 (1)	12.0 (22)
LRRC16A (rs742132 **A** > G)	**AA**	48.3 (243)	48.9 (88)	60.4 (55)	62.4 (116)	30.1 (44)	51.7 (62)	25.2 (46)
	AG	41.4 (208)	41.7 (75)	35.2 (32)	31.7 (59)	56.8 (83)	36.7 (44)	52.8 (96)
	GG	10.3 (52)	9.5 (17)	4.4 (4)	5.9 (11)	13.0 (19)	11.7 (14)	22.0 (40)
PDZK1 (rs12129861 **C** > T)	**CC**	30.4 (153)	42 (71)	54.3 (44)	47.8 (87)	36.3 (49)	37.7 (43)	42.2 (72)
	CT	47.3 (238)	5.4 (9)	4.9 (4)	2.2 (4)	5.9 (8)	3.5 (4)	8.7 (15)
	TT	22.3 (112)	52.6 (89)	40.7 (33)	50.0 (91)	57.8 (78)	58.8 (67)	49.1 (84)

The **bolded** letter refers to the risk allele linked to HU/gout

Table 5
Summary of Total Risk Alleles across Asian, Native Hawaiian, and Pacific Islanders

	EUR	Japanese	Korean	Filipino	Marshallese	Hawaiian	Samoan
Total alleles significantly different from EUR	Reference (8 SNPs)	100% (8/8)	75% (6/8)	75% (6/8)	75% (6/8)	75% (6/8)	100% (8/8)
HU or/gout risk allele index*		8	5	6	4	4	5
Percentage of risk allele*		100% (8/8)	83.5% (5/6)	100% (6/6)	66.5% (4/6)	66.5% (4/6)	62.5% (5/8)

*Indicates the risk allele that contributes to hyperuricemia or gout.

EUR: European

Table 6
Hardy Weinberg Equilibrium (HWE) Assessment of Targeted SNPs

Gene/SNP	Filipino	Japanese	Samoan	Marshallese	Hawaiian	Korean
SLC17A1 (rs1183201)	0.7789	0.4036	0.3326	0.1743	0.9035	0.4449
PDZK1 (rs12129861)	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
SLC22A11 (rs17300741)	0.4439	0.9076	0.4465	0.0109**	0.3224	0.9926
ABCG2 (rs2231142)	0.6376	0.3044	0.3942	0.8952	0.7880	0.0407**
SLC16A9 (rs2242206)	0.1473	0.1129	0.0275**	0.6046	0.0250**	0.5789
SLC22A12 (rs505802)	0.8183	0.3809	0.2042	0.1753	0.1123	0.9398
SLC2A9 (rs734553)	0.8788	0.9410	0.8211	0.0000	0.4077	0.8743
LRRC16A (rs742132)	0.8602	0.3476	0.4492	0.1642	0.0384**	0.8089
GCKR (rs780094)	0.3981	0.4903	0.9620	0.9112	0.3209	0.4184

** Indicates for deviated from HWE $p < 0.05$

Table 7
SNPs Call Rate (%)

	SLC22A12 (rs505802)	*SLC17A1* (rs1183201)	*SLC16A9* (rs2242206)	*ABCG2* (rs2231142)	*SLC22A11* (rs17300741)	*PDZK1* (rs12129861)	*SLC2A9* (rs734553)	*LRRC16A* (rs742132)	*GCKR* (rs780094)
Filipino	96.3	92.1	94.2	94.2	91.5	88.9	92.6	94.7	94.7
Japanese	98.4	97.3	96.8	98.9	95.2	96.2	97.8	98.4	98.4
Korean	97.9	93.6	95.9	96.8	95.7	85.2	97.8	95.7	96.8
Hawaiian	99.3	98.6	98..6	99.3	95.2	92.4	97.9	98.6	98.6
Marshallese	93.8	91.4	92.2	94.6	93	88.3	93.7	93	93.7
Samoans	98.4	96.7	97.3	97.3	97.3	91.4	97.3	97.3	97.8
Overall	97.4	95.1	96	96.9	94.3	91	96.1	96.4	96.7

Abbreviations

Abbreviations	
SU	Serum urate
HU	Hyperuricemia
SNP	Single nucleotide polymorphism
NHANES	National Health and Nutrition Examination Survey
GWAS	Genome-Wide Association Studies
EUR	European
NHPI	Native Hawaiian and Pacific Islander
HD	Health Disparities
CVD	Cardiovascular Disease
IR	Insulin Resistance
CKD	Chronic Kidney Disease
PE	Pre-eclampsia
MAF	Minor Allele Frequency
HWE	Hardy-Weinberg Equilibrium

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