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Urate Genetic Assessment in Asian and Pacific Islander Subgroups of Pregnant Women: Implications for Personalized Medicine and Means to Reduce Health Disparities

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Urate Genetic Assessment in Asian and Pacific Islander Subgroups of Pregnant Women: Implications for Personalized Medicine and Means to Reduce Health Disparities

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science, Pharmacotherapy and Outcomes Science at Virginia Commonwealth University

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DEDICATION

I dedicate this work to my primary mentor Dr. Roman for his help, mentorship and patience; without him, I would not have reached this point. I also dedicate this work to my family: my father, my mother, my brothers, my sisters, my dear wife, and my son, Battal, for their support. Moreover, I dedicate this work to my colleague in the lab, Khalifa Alrajeh, and my friends in the Pharmacotherapy and Outcomes Departments. I also dedicate it to my country and its people. I hope the day comes when I can serve them and apply everything I have learned from this program to improve their lives.

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Abstract

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Background

Gout is one of the most common rheumatological conditions and appears to have a higher prevalence in certain populations Risk factors for gout and its precursor, hyperuricemia, are also significant risk factors for preeclampsia, a major pregnancy-related morbidity. We hypothesized that uric acid (UA) allele frequencies are associated with certain populations and the development of preeclampsia. This project aimed to assess UA risk allele frequencies across a diverse cohort of pregnant individuals and to determine if UA risk allele are associated with risk factors for preeclampsia.

Methods

A retrospective cross-sectional study was conducted on pregnant women from different ethnicities who 100% reported their ethnicities from the Asian Pacific Islander population. Numerous UA genes and clinical conditions were addressed, and all study details were reviewed and exempted by the University of Hawaii human Studies Program (Protocol Number: 2018-00225). The biospecimens repository at the University of Hawaii provided DNA samples, medical information, and demographic data on study participants. These samples were collected after receiving written consent. DNA was extracted from cord blood samples, and genotyping was performed at the Cancer Center's Genomics and Bioinformatics Shared Resource (Honolulu, HI).

Our primary outcome was to assess the frequencies of the eight UA risk alleles provided by the biospecimens repository across the Asian, Native Hawaiian, and Pacific Islander populations compared to European (EUR) ancestry. All UA risk alleles and genotypes for EUR were estimated from the Ensembl genome browser. Our secondary outcome was to assess the role of both UA risk alleles and other factors involving age/BMI contributing to CMDs in Filipino and Samoan subgroups. We estimated the proportion of UA genotype in the presence and absence of the CMDs. Moreover, we tested for association between CMDs and both age and BMI. Finally, we compared mean BMI among different UA genotypes across the Filipino and Samoan populations.

Results

In this study, 1059 pregnant women aged 18 or older self-reported their race and ethnicity, including Asian, Native Hawaiian, and Pacific Islander populations. The UA risk alleles frequencies amongst our participants differed from EUR. Compared to EUR, 8/8 UA risk alleles were found in Japanese, 6/8 in Korean, 6/8 in Filipino, 8/8 in Samoan, 6/8 in Hawaiian, and 6/8 in Marshallese. The HU/gout risk alleles indices were 8, 5, 6, 5, 4, and 4 in Japanese, Koreans, Filipinos, Samoans, Marshallese, and Hawaiians, respectively. Out of the eight SNPs, the risk alleles associated with HU/gout in Japanese and Filipino were 100%, followed by 83.5% in Korean. In addition, we found alleles at the *ABCG2* gene to be associated with increased risk of diabetes mellitus in the Filipino population under both additive and recessive genetic models, $p < 0.05$. Under the recessive genetic model, we found that *SLC22A11* alleles were trending towards a significant association with the development of chronic hypertension ($p=0.085$) and gestational diabetes mellitus ($p=0.063$) in the Samoan subgroup. Using logistic regression analysis. we found both age and BMI were associated with increased risk of chronic hypertension across the Filipino subgroup (OR= 1.06, 95%

CI= 0.99- 1.13, p= 0.06 (BMI), and (OR= 1.11, 95% CI= 1.02- 1.22, p=0.013 (Age)). Moreover, age factor was associated with gestational diabetes mellitus development across the Samoan population (OR=1.15, 95% CI 1.06- 1.25, p=0.0006). Finally, ANOVA test showed lower mean BMI in both Filipino and Samoan subjects carrying risk genotypes compared to wild-type genotype.

Conclusion

Our study found that Asian pregnant women had a higher prevalence of UA risk alleles compared to the EUR population. The Asian population is at high risk of cardiometabolic disorder prevalence, and we found UA risk alleles may be associated with developing CMDs across the Asian population. This is the first study of its type to look at the genetics of uric acid in ethnicities who are underrepresented in studies. This research is considered the first report to estimate the UA risk allele and nongenetic factors (age and BMI) and their role in CMDs across different ethnicities. We recommend that further studies be conducted on large sample sizes and in different locations to validate our findings.

Keywords: Gout, Hyperuricemia, Uric acid, Cardiometabolic diseases, Single nucleotide polymorphisms, European ancestry, Asian, Native Hawaiian, Pacific Islander, Pregnancy

Chapter 1: Introduction of hyperuricemia and gout disease

Hyperuricemia and Gout definitions

Gout is an inflammatory arthritic condition characterized by precipitation of monosodium urate (MSU) crystals in or around joints due to chronic elevation of serum urate (SU), exceeding saturation point.[1] Several factors could lead to gout, including both genetic and non-genetic risk factors.[2] Hyperuricemia (HU) resulted due to excessive production or under excretion of uric acid.[3] Genetic, comorbidities and environmental factors are major contributors to HU [4], which is defined as serum uric acid levels of more than 7 mg/dl in men and 6 mg/dl in women (Table 1.1).[1]

Epidemiology of hyperuricemia and gout

Gout is one of the most frequent inflammatory arthritis. It is critical to evaluate its prevalence patterns in order to prepare for adequate health care resources. Unfortunately, epidemiologic data is limited, variable, and without a standard approach to diagnosis. A systematic review that aimed to collect data from different regions around the world to estimate the differentiation in gout prevalence and incidence reported that the data indicating gout distribution globally is unclear due to the lack of standardized methods used to diagnose gout in developed and developing countries.[5]

The prevalence and incidence of gout and hyperuricemia are more common in developed rather than developing countries. The prevalence of gout has remained high since ancient times, but it has more than doubled over the last 20 years.[6,7] Globally, reports indicate that the prevalence of gout ranges from 0.1% to about 10%, with an incidence rate ranging from 0.3 to 6 cases per 1,000 person-years.[5]

On the one hand, the prevalence of gout in developed countries estimated >1% in countries like North America and Europe. Furthermore, Europe, Greece has the highest gout prevalence of about 4.75% among the adult community[8], whereas in Portugal (about 0.3%) among adults.[9] A previously published survey reported that the Japanese and South Korean

populations had the lowest incidence of gout, which is 0.51% (2003) and 0.4% (2008), respectively, using the health insurance database. Moreover, Taiwan, Hong Kong, and Singapore reported a much higher prevalence of gout. The Hong Kong population aged 45–59 was shown to have a 5.1% prevalence, while those older than 60 years had a gout prevalence of 6.1%. In Singapore and Taiwan, the prevalence was reported as 4.1% and 4.92%, respectively, in 2004.[5] Other study has reported that gout incidence in South Korea increased by 25% between 2009 and 2015.[10]

In the USA, the National Health and Nutrition Examination Survey (NHANES) from 2015 to 2016, combined with data from 5467 subjects consisting of both men and women in the United States (US), has reported that the gout prevalence is approximately 3.9% among the US adult population, affecting roughly 9.2 million persons, with men having a higher gout prevalence rate than women [5.2% (5.9 million) versus 2.7% (3.3 million)].[11] In addition, the means that serum urate levels were 6.0 mg/dl in men and 4.8 mg/dl in women. Hence, the prevalence of hyperuricemia was 20.2% and 20.0% in men and women, respectively (Table 1.2).[11]

On the other hand, a community-oriented program for the control of rheumatic diseases (COPCORD) survey was conducted among 15 developing countries to estimate the prevalence of gout. The prevalence of gout in Central and South America was low, with a rate of 0.3% to 0.4% in Mexico, Cuba, and Venezuela [12,13], compared with Asian countries such as Indonesia, which had a gout prevalence of 1.7%, and Kuwait, which had a gout prevalence of 0.8%, while other Asian countries reported gout prevalence of less than 0.5%.[5]

A limited diagnosis tool or absence of gout flare symptoms impact the gout disease reports. For instance, asymptomatic hyperuricemia is common in some countries but goes undiagnosed. Aside from this, a study conducted in Saudi Arabia which interviewed 487 Saudi participants in 14 primary care clinics in Riyadh over seven months from September

1998 to March 1999 indicated that up to 8.2% of people (males and females) had high SU, but none of them had symptoms of gout.[14] Thus, it is clear that the prevalence of gout is highest in developed countries, whereas data is lacking for some parts of the developing world, particularly Africa and South America.[15]

In summary, gout prevalence varies globally, with the highest prevalence reported in Oceanic countries, particularly in indigenous and South Pacific Island populations, and the lowest prevalence in the developing world. In addition to the previously reported increasing prevalence of gout in Europe and the USA, there is evidence of increasing prevalence in Australia (self-reported), Canada, China, and South Korea.[15]

Pathophysiology of Gout

Physiologically, HU occurs via increased catabolism of purine substances or under excretion of UA from the body. These mechanisms could result from different circumstances, as motioned before[16] Purine production could occur through endogenous or exogenous pathways. Nucleic acid degradation, known as the endogenous process, HU could also occur by exogenous due to numerous factors, which eventually convert to uric acid.[17] Physiologically, enzymes dysfunction, mainly those responsible for the balance of endogenous purine production, could cause increased activity of 5'-ribosyl-1'-pyrophosphate (PRPP) synthetase and a decrease in hypoxanthine phosphor-ribosyltransferase enzyme (HPRT). Hence, these enzyme defects may result in excessive purine production.[18] In addition, several clinical conditions, including rhabdomyolysis, hemolysis, and tumor lysis syndrome, are prime examples of cell turnover and significant purine sources, which eventually lead to increased urate production.[3]

Once purine is converted to UA and exceeds the normal range, that leads to the formation of monosodium urate (MSU) crystals that precipitate in the synovial fluid and soft

tissues, causing signs and symptoms of acute gout flares.[11] MSU deposits trigger the inflammatory pathways through the activation of macrophages, which have a role in releasing inflammatory cytokines, such as interleukin (IL-1β). This chemical release leads to the onset of acute gout flare that is characterized by erythema, swelling, and severe pain, in addition to neutrophil-activated proinflammatory mediators, such as arachidonic acid, prostaglandins (PGE), leukotriene (LTB), and NLRR3 inflammasome. NLRR3 is an innate immune system component that may trigger a range of cellular damage and the release of proinflammatory cytokines such as IL-1B/IL-18.[19] (Figure 1.1)[20]

The renal system eliminates two-thirds of uric acid generated in the body and the gut excretes the remaining one-third. Thus, changes in renal function may impact uric acid removal from the body through increased absorption or decreased excretion.[3] On the other hand, impairment of kidney function is not always the main reason for uric acid under excretion. Uric acid under excretion may be due to genetic defects or variations in renal uric acid transporter genes, such as the ATP binding cassette subfamily G (*ABCG2*), glucose transporter 9 (*SLC2A9*), and others.[21]

Genetics of hyperuricemia and gout

The interaction between genetic variants and environmental factors can explain the development of hyperuricemia and its progression to gout. Urate heritability has been estimated to be between 45% and 73%.[22] One of the largest genome-wide association studies (GWAS) conducted in over 110,000 people of European and other ancestries discovered 28 loci associated with urate.[23] These loci are dominated by genes encoding the uric acid transporters in the kidney and the gastrointestinal system (*SLC2A9/GLUT9*, *ABCG2, SLC22A11/OAT4, SLC22A12/*URAT1*, SLC17A1/*NPT1, and the scaffolding protein gene *PDZK1*).[22] (Figure 1.2)[24]

Several genes were reported to influence the excretion or reabsorption of uric acid.[25] For example, the ATP-binding cassette transporter is located in the apical membrane in the renal proximal tubule and is responsible for urate excretion. *ABCG2* is a gene transporter for UA in the proximal tubular cells of the kidney and the gastrointestinal (GI) tract. The *ABCG2* gene encodes an ATP transporter, so the presence of polymorphisms may cause clinical consequences, either a higher or lower risk of HU/gout. The *ABCG2* gene possesses a high capacity and affinity for uric acid excretion and is expressed in different tissues, including the kidneys, intestines, and liver. Therefore, this gene's polymorphism could lead to decreased urate excretion [26] and an inadequate response to medication, such as the urate-lowering therapy allopurinol.[27]

A meta-analysis conducted in Aotearoa, New Zealand, demonstrated that a particular *ABCG2* gene, rs2231142 polymorphism, is associated with the adequate response levels of allopurinol. The missenses variant of *ABCG2* 141K could increase allopurinol concentration in the kidney tubules and decrease concentration in the tubular fluid. This can result in reduced or inhibited SU excretion from the kidneys, causing inadequate allopurinol response. [27] Another example is the *SLC2A9* (*GLUT9*) gene, which has a high-affinity urate transporter. It has a role in SU re-absorption and might lead to renal hypouricemia due to loss of function.[28,29] Meanwhile, genetic polymorphisms of some genes, such as inhibin beta C (*INHBC*), a transforming growth factor (TGF)-β gene product in the super-family of proteins, could lead to an increase in the risk for gout flares through numerous cellular processes.[30]

SLC17A1 and *SLC17A3* transportome genes are involved in the urate transporter and located in the apical side of the kidneys. Other genes involved in regulating SU include the *SLC22A11*, *GCKR*, *LRRC16A*, and *PDZK1* genes.[31,32] The prevalence of hyperuricemia and gout across a given population is also associated with race and ethnicity. These differences may make some ethnicities more susceptible to the diseases, gout in particular, than others.

For example, African-American (AA) groups have more gout risk compared to their European counterparts (EUR).[33] Asian populations, including Japanese and Han-Chinese, are also at high risk of gout relative to EUR ancestry.[34] This research confirms that the prevalence of hyperuricemia and gout among people varies across different populations.

Moreover, several risk factors could be both genetic and non-genetic in regard to an individual's susceptibility to HU/gout development as previously mentioned. Genetically many single nucleotide polymorphisms (SNPs) in genes involved in uric acid regulation play an important role in distinguishing the frequency and incidence of gout amongst ethnic groups. According to a study conducted in 2014 by Sakiyama et al. in which the ethnic differences of polymorphism of the *ABCG2* gene among three populations were examined, it was shown that differences with respect to *ABCG2* rs2231142 polymorphism, which causes variations in uric acid regulation and drug response, do exist among three ethnicities, namely Japanese, Caucasian, and African-American.[35]

Risk factors of hyperuricemia and gout

Several risk factors are associated with developing HU/gout, and these factors are classified into modifiable and non-modifiable factors.[36] Non-modifiable risk factors include age, sex, race, and genetic polymorphisms in the UA transportome. In contrast, lifestyle and some dietary habits involve alcohol consumption, purine-rich foods, fructose/sugar-sweetened beverages, and other dietary aspects, which contribute to an increase in the risk of HU/gout. These factors can be avoided to reduce the risk of HU/ gout development. Depending on gender, men are generally at a higher risk of gout than women of all ages. The main reason for the difference in uric acid levels between men and women is the uricosuric action of the estrogen hormone, which helps enhance uric acid excretion in females. However, the risk of gout increases in postmenopausal women, which could be mitigated by

using hormone replacement therapy.[37,38] The biological function of organs such as kidneys declines with increased age, suggesting that age could be a risk factor in the development of HU/gout since two-thirds of SU is eliminated by the renal system.[39]

Genetic risk factors constitute a large part of developing hyperuricemia and gout either through rare monogenic disorders or urate transporter polymorphisms. Lesch-Nyhan Syndrome is an example of a monogenic disease caused by the deficiency of HPRT, which may result in HU with hyperuricosuria.[18] So far, genome-wide association studies (GWAS) have reported many UA genes related to HU/gout development. These studies were performed amongst different populations, and specifically targeted UA genes such as *ABCG2*, *SLC2A9*, and *SLC22A12*. The loss of function of these genes may lead to a higher or lower risk of gout. For example, among multiple populations, including White, African, and Asian groups, a significant association was found between rs2231142 SNP and increased SU (due to a 53% reduction in *ABCG2* function), resulting in a decrease in uric acid efflux.[4]

Other types of risk factors that have been identified as having the potential to induce HU/gout include alcohol consumption, protein/purine-rich food, and beverages containing fructose/sugar, as well as other lifestyle choices. Consuming a high amount of alcohol is associated with an increased risk of HU/gout due to the ethanol catabolism mechanism. Ethanol catabolism leads to purine degradation, resulting in the formation of lactic acidosis, which affects renal UA excretion.[40] Diets including a high amount of purine, such as seafood, red meat, and foods with high carbohydrate levels have also been linked with the increased incidences of HU/gout.[41]

Additionally, current studies have found a strong relationship between fructose intake and ongoing hyperuricemia and gout. In a study conducted by Martin Underwood in 2008, it was shown that “consuming two servings a day of any sugar-sweetened soft drink will increase the risk of developing gout by 85%” (relative risk 1.85, 95% confidence interval [CI]

1.08–3.16).[42] Consumption of high-fructose corn syrup could increase the risk of gout through elevated uric acid production by a prompted breakdown of ATP.[43] Additionally, obesity, in which the body mass index registers 30 kg/m^2 or more, could interact with other factors, causing an increase in the possibility of the incidence of gout[44], whereas consuming low-fat dairy products, coffee, and vitamin C supplements might be beneficial for minimizing the risk of gout.[45,44]

Comorbidities diseases and gout

The relationship between gout and comorbidities, such as cardiovascular conditions, renal impairment, and metabolic syndrome, may be exacerbated by high uric acid levels.[46] Since the late 19th century, cardiovascular disease (CVD) has been recognized as one of the several chronic disorders that may appear as part of diseases associated with HU. However, this relationship is still the subject of debate, although the risk of CVD development has been shown to increase among patients with serum uric acid levels of more than 6 mg/dl.[47,48] Physiologically, HU could increase the production of reactive oxygen species (ROS), which then leads to a decrease in nitric oxide (NO) bioavailability. Decreasing the NO may lead to endothelial dysfunction, causing vasoconstriction and cardiac dysfunction. Likewise, decreasing NO activates the renin-angiotensin system (RAS), which may increase the possibility of cardiovascular damage.[49] Moreover, gout was shown to be strongly correlated with a risk of chronic kidney disease (CKD) up to three-fold in older people aged 65–74 years with a hazard ratio (HR) of 3.05 (95% CI 2.99–3.10).[50] HU may contribute to decreasing kidney function by activation of the nucleotide-binding domain, leucine-rich repeat (NALP3) inflammasome, which leads to stimulation of interleukin (IL)-1β and IL-18 and other pro-inflammatory cytokines and contributes to CKD progression.[49]

High uric acid levels contribute to hyperinsulinemia and insulin resistance (IR) via stimulation of mitochondrial oxidative stress, which plays an essential role in causing a

decrease in insulin signaling. Moreover, HU inhibits signaling enzymes, such as protein kinase B (AKT) and adenosine monophosphate (AMP), activated protein kinase (AMPK) phosphorylation that influences the glucose metabolic pathway. The inhibition phosphorylation of these enzymes might result in decreased hepatic glucose production, ultimately causing IR.[52] IR can lead to other complications, such as type 2 diabetes (T2DM), which is recognized as one of the most common clinical syndromes due to the development of impaired insulin-mediated glucose transport 4 (GLUT4).[53] Other metabolic syndrome subsets, such as dyslipidemia and hypertension, could occur, causing an increased risk of cardiovascular disease risks.[54] (Figure 1.3)[55]

These biological observations beg the question of whether urate-lowering therapy (ULT) in patients that have hyperuricemia could assist in improving metabolic syndrome and increasing insulin sensitivity. A few studies reported that ULT could support a reduction in IR, hence patients who have already used benzbromarone have a significantly lower risk of developing diabetes than other hyperuricemia patients, as shown by data from the Taiwan National Health Insurance Program (HR = 0.86; 95% CI 0.79–0.94).[56] A more recent analysis of a US cohort heavily enriched for stroke found that hyperuricemia was associated with stroke (HR 1.42, 95% CI 1.12-1.80), but this association seemed primarily mediated by the effect of treatment-resistant hypertension (full adjustment HR 1.17, 95% CI 0.87-1.56).[57] Other reported gout associations with co-morbidities, including macular degeneration[58], erectile dysfunction[59], atrial fibrillation[60], and thrombo-embolism[61], are an attestation to the complexities that rheumatologists and other providers caring for gout have to consider when making treatment decisions (Table 1.3)[62]

Medication-induced hyperuricemia

HU could occur as a result of a particular medication's side effects. Many pharmacological classes have been reported as being associated with inducing HU. For instance, diuretics, anti-tubercular drugs, immunosuppressant agents, nicotinic acid, low-dose aspirin, cytotoxic chemotherapy, non-glucose carbohydrate, lactate infusion, and testosterone can all promote uric acid production or inhibit uric acid excretion.[63]

Diuretics are commonly prescribed medications that improve outcomes in patients with cardiovascular diseases.[64] Diuretic pharmacotherapy increases the risk of HU by approximately 6% to 21%.[63] Loop and thiazide-diuretic, for example, may induce HU due to the inhibition of SU excretion in the proximal renal tubule through causing alterations in such transporters, like organic anion transporters (OAT)1 and 3 and human sodium phosphate transporter (NPT)-4.[63,65] Furthermore, loop diuretics such as furosemide induced a high level of lactic acidemia that interacts with urate elimination.[66]

Anti-tubercular drugs, such as pyrazinamide and ethambutol, have been associated with an increase in SU, which could lead to HU and acute gout flares. Studies have proposed a strong relationship between the use of pyrazinamide and developing gout. Pyrazinamide inhibits urate excretion up to 80% due to extensive urate retention in a therapeutic dose of 300 mg/day.[67] Ethambutol also alters SU by reducing the fractional excretion of uric acid. Hence, 43% to 100% of patients who receive ethambutol may develop HU.[63,65]

Calcineurin inhibitors are a group of medications that inactivate immune cells; they are used after an organ transplant to reduce tissue rejection.[68] Certain immunosuppressant agents should be used after tissue transplant, including cyclosporine, tacrolimus, and mizoribine, all of which may increase uric acid levels.[69] Cyclosporine is extensively used post-transplant of organs, including kidney, heart, and liver. Cyclosporine induces HU and acute gout flare due to an increase in urate reabsorption, mainly when administered with diuretics due to arteriolar

vasoconstriction that leads to a decrease in glomerular function.[63] Cyclosporine has been found to produce a more significant effect regarding inducing HU compared to other immune suppression agents, such as azathioprine (84% versus 30%, respectively, p-value < 0.0001).[70]

Tacrolimus immune suppressive agent is similarly causing an increased incidence of HU, but a recent study demonstrated that Tacrolimus has fewer effects on SU levels than cyclosporine with a mean (+/- standard deviation) level of uric acid (303±75 μmol/L versus 344 ± 62 μmol/L; *P*= 0.006.[71] Nevertheless, some studies have concluded that there is an insignificant difference between either agent in inducing hyperuricemia.[72]

Mizoribine is another type of immunosuppressant agent used with transplant patients, mainly in the Asian population. Also, other clinical uses of mizoribine are in patients who suffer from lupus nephritis, rheumatoid arthritis, and nephrotic syndrome.[73] Mizoribine-induced HU is primarily due to the inhibition of guanine nucleotides synthesis.[63]

Nicotinic acid, identified as niacin or vitamin B3, has been used since 1955 to improve neurological function.[74] HU could result at therapeutic doses of 3 to 6 g of nicotinic acid.[63] This effect is most likely due to uric acid elimination reduction, since nicotinic acid increases urate reabsorption by the kidneys in addition to OAT10 transporter exchange with nicotinic acid, thus leading to HU. Moreover, niacin may simulate the uricase enzyme that leads to elevated SU levels.[63,75]

In patients with stroke, atherosclerosis, and angina, aspirin is often given as secondary prevention. Consequently, aspirin users have lower ischemic stroke numbers than non-aspirin users (OR: 0.83, 95% CI: 0.74–0.93; *P* = 0.45).[76,77] Aspirin has a unique biphasic mechanism that acts on uric acid levels. A low dose of salicylate (1-2 g/day) competes for SU excretion, causing urate retention resulting in increased uric acid levels. Conversely, a high dose of salicylates (>3g/day) hinders urate reabsorption, resulting in decreased SU, an indication that a high dose has a uricosuric effect.[78]

Cytotoxic chemotherapy is associated with tumor lysis syndrome (TLS). TLS results in the formation of excessive nucleic acids due to cell breakdown. The nucleic acids are then converted into hypoxanthine and xanthine to form uric acid, resulting in HU.[79] As a result, HU is one of the most common complexities associated with cancer medications and might pose a serious threat to acute uric acid nephropathy. Different types of tumors such as Non-Hodgkin's lymphoma, solid tumors, acute myeloid leukemia, and acute lymphocytic leukemia are the most well-known malignancies associated with increased TLS and hospital mortality about 21%.[80]

Fructose metabolism could lead to elevated uric acid levels and gout risk due to purine nucleotide degradation or *denovo* purine synthesis. Also, fructose at a high concentration leads to lactic acid formation, causing blockages in urate elimination, resulting in HU. Thus there is an overt indication that the severity of HU-related fructose is dose-related.[36,81] Genetically, the variants in GLUT9, which is responsible for fructose transport, could increase the risk of gout flare in different multi-ethnicities.[82]

Sodium lactate infusion is administered to critically ill patients and yields benefits resulting in organ function improvement, specifically heart and brain, in ischemic situations.[83] Nonetheless, lactate infusion could cause HU at high doses due to decreases in urinary fractional excretion of uric acid.[84]

Testosterone replacement therapy (TRT) is used for treating men who have gender identity disorder (GID) due to hypogonadism. TRT has shown several beneficial anabolic impacts on biological functions, including metabolism, cardio-protection, and enhanced bone and muscle cells synthesis.[85,86] A recent study reported that dose-dependent TRT increases SU after three months of treatment (intramuscular injection of testosterone enanthate), with a 29% to 43.4% increase after using 125 and 250 mg every two weeks.[87] In addition, numerous studies have found that TRT induces gout disease [88]. Hormonal replacement therapy could

affect gene expression. Hence, the therapy changes the level of urate transporters, causing HU due to a reduction in renal uric acid elimination. Additionally, because muscle is the major source of purine, increasing muscle mass during the early phases of therapy is linked to HU.[63]

There are also a variety of miscellaneous agents that could contribute to high uric acid levels, inducing HU and gout flare. Examples of these agents include acitretin, didanosine, ritonavir, filgrastim, L-dopa, omeprazole, peg-interferon, ribavirin sildenafil, teriparatide, ticagrelor, and topiramate. These agents have different mechanisms inducing HU, either through increasing uric acid production or decreasing urate elimination. Meanwhile, other agents such as teriparatide could lead to HU by creating an imbalance in endocrine function and thereby increasing serum parathyroid hormone levels, which are significantly associated with hyperuricemia (OR: 1.045; 95%CI: 1.017–1.075; $P = 0.002$).[63,89]

In short, several medications are associated with HU and gout flares due to different mechanisms of action. Additional studies are required to classify these pharmacological classes according to their severity in increasing uric acid levels from baseline to mild, moderate, and severe.

Management of hyperuricemia and gout

It is usually accepted to define hyperuricemia when the uric acid level is above 7.0 mg/dl. Meanwhile, the presence of HU without signs or symptoms of MSU crystal deposition is called asymptomatic hyperuricemia, linked to metabolic syndromes developments. [90] The goal of gout management is to prevent acute flare and prevent the complications that HU could cause. There are numerous pharmacological agents used in gout management, either in acute gout flare or in long-term management. These agents include nonsteroidal inflammatory drugs (NSAIDs), steroids, colchicine, and urate-lowering therapy (ULT).

Moreover, diet and social lifestyle changes could contribute to mitigating hyperuricemia complications and gout flare.[91]

Management of acute gout flare

Acute gout flare is characterized by severe pain due to the deposition of MSU crystals in the joints.[20] The primary purpose of treating acute gout is to reduce and resolve the pain associated with the flare. The drug choices used in clinical practice to manage gout flares consist of anti-inflammatory drugs, including non-steroid anti-inflammatory drugs (NSAIDs), colchicine, glucocorticoids (intra-articular, intramuscular, intravenous), as well as the incorporation of local ice therapy to decrease flare severity.[92] Ibuprofen, indomethacin, and naproxen, classified as NSAIDs used to help relieve gout flare symptoms by inhibiting cyclo-oxygenase enzyme (COX). Therefore, until the flare resolves, these drugs should be taken at the FDA-approved doses. Moreover, some NSAIDs, such as indomethacin, can also reduce SU due to uricosuric effects.[93] Using NSAIDs in the long term may cause gastrointestinal bleeding in some patients; proton pump inhibitors could help minimize these side effects.[94] Colchicine is one of the effective medications used for an acute gout flare. Initiation of colchicine should be with a loading dose at 1.2 mg, followed by a 0.6 mg single dose after one hour, then continuous use of prophylactic doses of 0.6 mg once or twice a day, but not exceeding 1.6 mg/day to avoid toxicity.[95] Colchicine is a cytochrome P450 and P-glycoprotein substrate. As a result, it can interact with various drugs, including antineoplastic, macrolide antibiotics, and calcium channel blockers, potentially increasing colchicine toxicity (Table 1.4).[96]

Other options that could be used to treat an acute flare and decrease pain severity are steroids, either via intravenous or intra-articular administration. These options should be given with caution so as to avoid any complications related to steroid usage.[97] Steroids such as oral prednisone, at a daily dose of 30 mg/d for 7 days, have been shown to be effective[98]

and are recommended by the ACR and EULAR panels as potential first-line therapy in the management of gout flares.[99] Steroids are best administered in patients contra-indicated for NSAIDs or colchicine (i.e. CKD patients). When not contraindicated, co-prescription a low dose (0.5–1 mg/d) of colchicine may help prevent uncommon inflammation relapses after steroid discontinuation.[20]

Open-label studies also suggest that adrenocorticotropic hormone (ACTH) can relieve gout inflammation.[100] Intra-articular steroid injections appear to be very effective and are recommended by both the ACR and the EULAR in the management of mono or poly-articular flares, despite the lack of randomized clinical trials (RCT). Open-label studies of the IL-1 receptor antagonist anakinra support its off-label use in patients who are resistant or have a contraindication to NSAIDs, colchicine, and steroids. [101,102]

Canakinumab agent is a long-acting antibody to IL-1 beta that is approved by the European Medical Agency following two RCT trials against intramuscular triamcinolone acetonide.[103] The EULAR recommends considering IL-1 blockers for the management of gout flares in patients with frequent flares contraindicated to NSAIDs, colchicine, and steroids (oral or injectable).[20]

Long-term management of gout

Urate lowering therapy (ULT) agents are used in long-term gout management to reach target uric acid levels within the normal range. The American College of Rheumatology (ACR) strongly recommends administering ULTs such as allopurinol for all patients with the presence of frequent acute flare at least once per year, chronic kidney disease stage 3 or higher, or history of nephrolithiasis in patients diagnosed with gout arthritis. Furthermore, it has been recommended that following a restricted diet and social life habits could help in gout management.[104]

Allopurinol and its active metabolite, oxypurinol, are xanthine oxidase enzyme inhibitors that reduce uric acid production. The half-life of both allopurinol and oxypurinol are 1-2 and 15 hours, respectively, and both are excreted renally.[105] When initiating ULT, it is important to provide gout prophylaxis to prevent ULT-induced gout flares. When the uric acid levels start to fall, the crystallization in the joints could shift, and this shift in the crystals may cause an acute gout flare. Thus, it is essential to continue gout prophylaxis for three to six months to avoid gout flares during UTL treatment. [106,107] Allopurinol dosage is determined on kidney function; thus, patients with normal kidney function should start at 100 mg daily (but not more than 300 mg), with dose titration up to 50 mg every two to four weeks until the target uric acid level is achieved.[105] Patients who suffer from renal function decline should be started on allopurinol 50 mg, followed by a titration up to 50 mg every two to five weeks until the uric acid levels reach the normal range.[96]

Although allopurinol hypersensitivity syndrome is uncommon, it could occur in some patients, notably in the elderly with renal impairment, patients using a thiazide diuretic, and some Asian groups with HLA-B* 5801 genotypes. Thus, ACR recommends using alternative ULTs in the Asian ethnic population who have tested positive for the HLA-B* genotype so as to avoid allopurinol hypersensitivity syndrome, leading to Stevens-Johnson syndrome or toxic epidermal necrolysis. These major adverse effects are characterized by vasculitis, hepatocellular and acute kidney injury, fever, leukocytosis, and eosinophilia. Therefore, the initial dose in normal and decreasing renal function patients should be less than 100 mg and 50 mg, respectively, to reduce the risk of allopurinol hypersensitivity. [105,108]

The FDA approved Febuxostat in February 2009 for the treatment of chronic gout patients. Febuxostat is a non-purine selective xanthine oxidase inhibitor. The half-life of febuxostat is about five to eight hours, and it is metabolized mainly by the liver and eliminated by renal and hepatic routes.[109] Compared to allopurinol, with respect to its safety

profile, febuxostat is associated with increased cardiovascular-related mortality; therefore, the FDA recommends minimizing its use only in patients who do not derive any benefits from allopurinol or who have serious side effects from allopurinol use. Therefore, before switching from allopurinol to other xanthine oxidase inhibitor agents, allopurinol should be titrated to the maximum tolerable dose possible.[110]

Febuxostat is a once-daily pill available in multiple doses, available in 40 and 80 mg doses in the USA and 80 and 120 mg doses in Europe. Febuxostat is a more effective ULT than allopurinol at dosages of 80 and 120 mg/d (maximum levels authorized in the United States and Europe, respectively). [111] Febuxostat is contraindicated in patients diagnosed with CVD, including ischemic heart disease and congestive heart failure. In addition, febuxostat is more costly than allopurinol.[96] Moreover, febuxostat is associated with elevated liver enzymes compared with allopurinol, and it can cause adverse drug reactions such as nausea, arthralgia, and rashes.[109]

Uricosuric medications such as probenecid and benzbromarone are pharmacological agents used to facilitate uric acid excretion in order to achieve the target urate levels. Probenecid is an appropriate adjunctive or second-line therapy for preventing acute flare by inhibiting the renal excretion of organic anions in the proximal renal tubule and reducing tubular urate reabsorption.[96] The use of probenecid is recommended as a ULT in gout if allopurinol is ineffective or contraindicated. Using probenecid as a ULT monotherapy is rare. However, the use of probenecid in combination with allopurinol results in a significant reduction in uric acid levels.[112] Benzbromarone is more effective than probenecid uricosuric agent, but it is infrequently used due to hepatotoxicity. Thus, it is restricted only to patients who cannot tolerate other ULT agents.[113] Furthermore, patients who suffer from kidney stones, renal impairment, or who indicate the presence of uricosuria (higher than 700 to 800

mg/24 hours) must avoid these uricosuric agents.[92] Other pharmacological agents including losartan and fenofibrate show a uricosuric effect, but it is not a class-wide effect.[114]

Pegloticase is another option that could be used for the treatment of chronic tophaceous gout cases. It can be used if the patient cannot take the available conventional urate-lowering drugs such as allopurinol, febuxostat, or probenecid. Pegloticase is a potent ULT and could improve the quality of life in patients with tophaceous gout by reducing the size and severity of urate tophi.[115] From a pharmacological perspective, pegloticase is a human recombinant enzyme that helps to convert uric acid into allantoin, which is more soluble and easier to excrete.[116] However, pegloticase has several adverse drug reactions, including anaphylactic symptoms related to infusion administration.[117] Moreover, pegloticase is contraindicated in special ancestral groups such as Africans and Middle Easterners with glucose-6 phosphate dehydrogenase (G6PD) deficiency.[118]

In summary, in this chapter, we have discussed the whole prospective of HU/gout prevalence. Published reports afford us multiple opportunities to investigate other reasons for HU/gout prevalence between different races. Therefore, we decided to assess the urate transportome genetic polymorphism across the different societies in the US. The main goal is to take the first step into personalized medicine in order to minimize health inequalities between population groups.

Table 1.1: Uric acid normal range[1]	
Gender	**mg/dl**
Males, postmenopausal women	3.5 – 7.2
Premenopausal women	2.6 – 6.0

Table 1.2: Prevalence of hyperuricemia (HU)/ Gout in USA, NHANES 2015-2016[11]			
Category	**Gout Prevalence % (95% CI)**	**Hyperuricemia Prevalence % (95% CI)**	**Persons with gout (N)**
All	3.9 (3.2, 4.7)	20.1 (17.8, 22.4)	9.2 million
Male	5.2 (4.4, 6.2)	20.2 (16.6,24.3)	5.9 million
Female	2.7 (2.0, 3.8)	20.0 (17.8, 22.4)	3.3 million
Caucasian	4.0 (3.1, 5.3)	21.4 (18.1, 25.1)	6.13 million
African American	4.8 (3.8, 6.0)	22.6 (20.9, 24.3)	1.3 million
Hispanic	2.1 (1.4, 2.9)	14.9 (12.6, 17.5)	0.73 million

Table 1.3:Gout Comorbidities [62]	
Organ system	Clinical condition
Cardiovascular	Hypertension Coronary heart disease Atherosclerosis Stroke Heart failure Peripheral vascular disease Atrial fibrillation Thromboembolism
Renal/genitourinary	Chronic kidney disease Nephrolithiasis Erectile dysfunction
Metabolic	Diabetes Metabolic syndrome Osteoporosis
Neurological	Alzheimer's disease Vascular dementia Parkinson's disease
Ophthalmological	Macular degeneration
Rheumatological	Osteoarthritis

Table 1.4: Common drugs that interact with colchicine [96]		
Strong CYP3A4 inhibitors	Moderate CYP3A4 inhibitors	P-glycoprotein inhibitors
Clarithromycin	Cimetidine	Amiodarone
Cobicistat	Ciprofloxacin	Carvedilol
Diltiazem	Cyclosporine	Clarithromycin
Itraconazole	Erythromycin	Itraconazole
Ketoconazole	Fluconazole	Quinidine
Ritonavir	Fluvoxamine	Ranolazine
Telithromycin	Imatinib	Ritonavir
Voriconazole	Verapamil	Verapamil

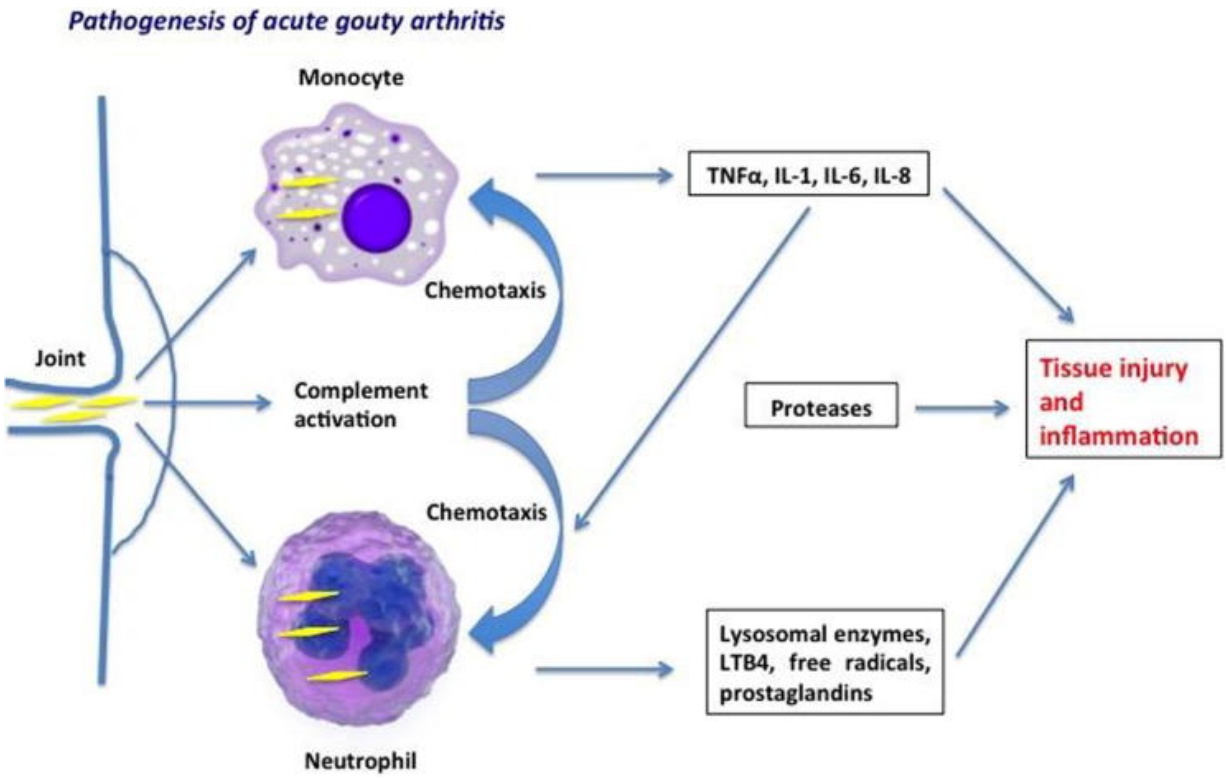

Figure 1.1: Pathogenesis of Acute Gouty Inflammation[20]

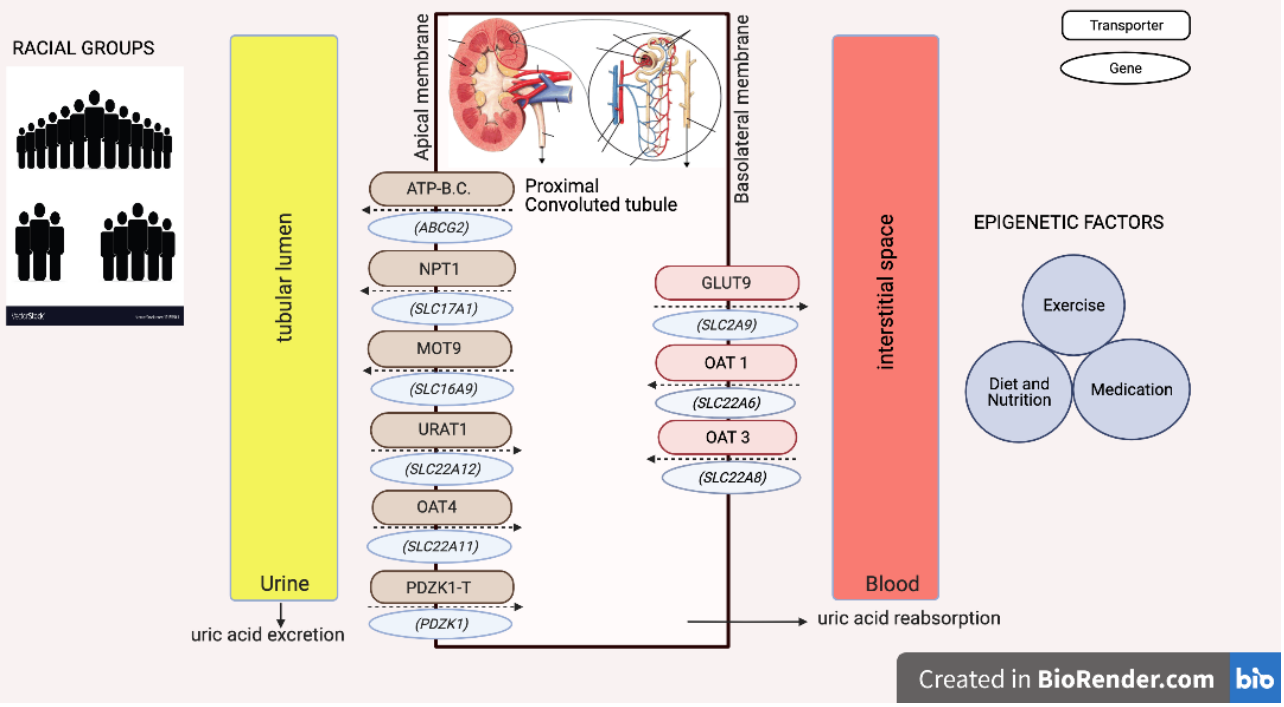

Figure 1.2: Uric Acid Transportome Genetics[24]

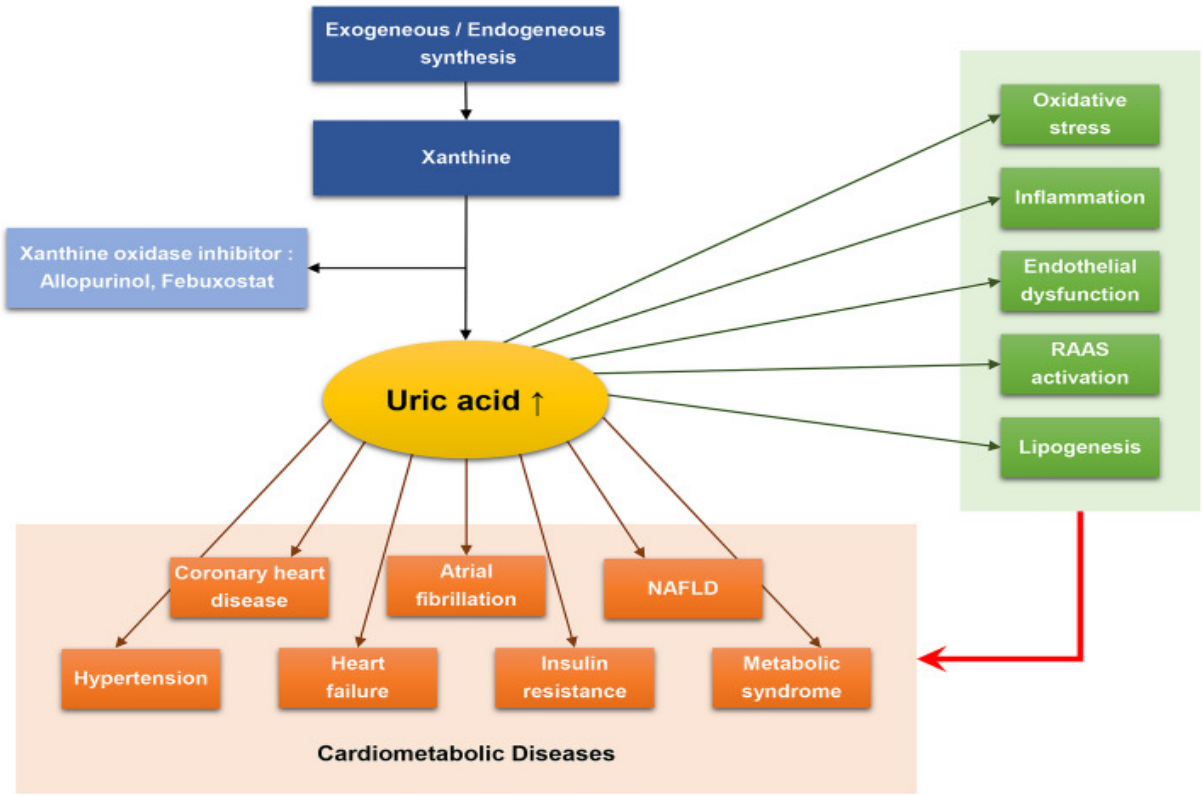

Figure 1.3: Uric acid and cardio metabolic diseases[55]

(NAFLD): Non-alcoholic fatty liver disease, (RAAS): Renin-Angiotensin-Aldosterone system

Chapter 2: 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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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 regulating urate levels within the human body, rendering some racial and ethnic groups more 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. Urate allele frequencies in Japanese, Korean, Filipino, Native Hawaiian, Samoan, and Marshallese were then compared with Europeans (EUR).

Methods:

The biospecimens repository center at the University of Hawaii provided DNA samples of consented post-partum women. The DNA was 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 (HWE) for genotype frequencies was assessed using the Chi-Square test with $p<0.05$ for statistical significance. Allele frequencies in our study were compared to EUR from the 1000 Genomes Project Phase 3 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. The total count of HU and gout risk alleles between our participants and EUR 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% in Japanese and Filipino followed by 83.5% in Korean.

Conclusions:

Compared to EUR, Asian subgroups, particularly Japanese, Filipinos had the highest percentage of UA risk alleles at 100%, followed by Koreans at 83.5%. These results could partly explain that some individuals of Asian descent are at an increased risk of developing HU or gout.

Keywords: Gout, Hyperuricemia, Health Disparities, Genetics, Asian Ancestry, Native Hawaiians, Pacific Islanders, Single nucleotide polymorphisms, Pregnancy

Introduction

Gout is an inflammatory arthritic condition 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 flares affect monoarticular joints (e.g., knees, ankles, and metatarsophalangeals), causing severe inflammation marked with excruciating pain, swelling, erythema, and reduced mobility.[20] The prevalence of gout in developed countries is higher than the developing ones. In the United States (U.S.), gout prevalence is up to 3.9%, affecting about 9.2 million people.[11] Gout and hyperuricemia prevalence varies by sex and age groups. Also, specific racial and ethnic subgroups have distinct HU and gout prevalence, ushering the notion of population-specific risk and suggesting distinct HU and gout risk allele frequencies across different racial and ethnic groups.[36]

Many factors play significant roles in regulating SU levels and might lead to HU and gout.[119] Genetic polymorphisms in uric acid transporters, 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 estimate the heritability of urate is up to 73%.[22] 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.[23] These loci are predominately in genes encoding urate transporters, including *SLC2A9, ABCG2, SLC22A11, SLC22A12, SLC17A1,* and the scaffolding protein-encoding gene *PDZK1*.[22] Indeed, the prevalence of and HU 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 may increase prevalence.[120]

Studies published in 2015 and thereafter showed substantial increase in gout incidence over recent decades in the U.S., 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.[116,121–125] Gout incidence in South Korea increased by 25% between 2009 and 2015.[10] A recent study reported that the Maori and Pacific Islanders groups in New Zealand have a gout prevalence of 7.6%.[126] 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 Oceanic countries having one of the highest prevalence worldwide, 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 U.S. Census Bureau, Chinese and Filipino communities are considered the largest Asian subgroups. Similarly, Native Hawaiians and Samoans are the largest Pacific Islander subgroups.[127] Amongst all the ethnic subgroups in the U.S., populations with Asian ancestry are approximately three times more likely to develop gout than Europeans (EUR).[128] Despite the correlation between genetic polymorphisms in urate disposition and incidence of gout amongst different ethnic groups, the frequencies of HU and gout risk alleles in a low admixed subgroups remain unknown. Therefore, the purpose of this study is to estimate the frequencies of selected SNPs in essential urate genes across diverse populations rarely represented in genetic or clinical research (Filipino, Japanese,

Korean, Samoan, Marshallese, and Native Hawaiian) compared with EUR. 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. Furthermore, to establish the genetic basis between ethnicity and gout prevalence. We hypothesized that the risk allele frequencies of HU and gout significantly differ between the Asian, Native Hawaiian, and Pacific Islander subgroups compared to European (EUR) population.

Methods

Study participant and urate genes

Participants included in this study were pregnant women who are 18-year-old or older. All participants self-reported 100 % of their respective race/ethnicity, indicated by both biological parents and four grandparents being of the same race/ethnicity. We excluded any participants age <18 years old, with a history of cancer or organ transplant, and poor DNA quality in the final analysis. The uric acid gene/SNPs were: *SLC17A1* (rs1183201), *PDZK1* (rs12129861), *SLC22A11* (rs17300741), *ABCG2* (rs2231142), *SLC16A9* (rs2242206), *SLC22A12* (rs505802), *SLC2A9* (rs734553), *LRRC16A* (rs742132), *GCKR* (rs780094).

Sample procurement and genotyping

DNA samples along with medical and demographics information of study participants were provided by the University of Hawaii biospecimens repository. Historically, these samples were collected after obtaining the written consent. The placenta and umbilical cord of the participants were collected as part of the routine care. DNA extraction was from cord blood samples and genotyping was carried out at the Genomics and Bioinformatics Shared Resource, Cancer Center (Honolulu, HI). A customized TaqMan genotyping assay panel was run on the Quant Studio 12K Flex

Real-Time PCR system (Applied Biosystems). All study details were previously published.[129] All study material were reviewed and exempted by the University of Hawaii Human Studies Program (protocol Number: 2018-00225).

Statistical analysis

The data analysis was conducted utilizing SPSS Statistics for Windows, version 23 (IBM SPSS, IBM Corp., Armonk, N.Y., USA). Shapiro – Wilk test was used to evaluate normal distribution for continuous variables. Demographic characteristics were expressed as means (+/- standard deviation and minimum-maximum) for parametric data and number (%) for categorized data. Allele frequencies in our data were compared with EUR, using Chi-square or Fisher's exact test, when appropriate. Bonferroni correction was used for multiple comparisons with $p < 0.006$ for statistical significance. Deviation from Hardy-Weinberg Equilibrium in our selected genetic polymorphisms was assessed using Chi-square test with $P<0.05$ for statistical significance. Ensemble genome browser was used to estimate the allele and genotype frequencies of EUR population (Reference). In our study, the risk allele was defined as the allele associated with the baseline or higher risks of developing HU and/or gout.

Results

Study participants characteristics and demographics in this study, 1059 participants were included. Demographic characteristics of all participants are shown in Table 2.1. 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. It is worth mentioning that Asian and Asian Americans are at high risk of obesity at lower BMI than in whites.[130] 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 2.6). 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 2.7).

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 Table 2.3 & Table 2.4. 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 2.5). 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 2.5). 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 2.5). All these six SNPs in Filipino were more prevalent (100%) than EUR. These genes/SNPs included: rs1183201 **T**> A in *SLC17A1*, rs2231142 G>T in *ABCG2*, rs2242206 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 2.5). 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 population, eight out of the eight urate SNPs were significantly different from EUR **(**Table 2.5**)**. 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 2.5**).** 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 indices 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 subgroups were 66.5% in Native Hawaiians and Marshallese, followed by 62.5% in Samoan **(**Table 2.5**).**

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.[131] 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.[131] 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.[132]

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, 27.8% in Koreans, and 25.6% in Japanese **(**Table 2.3**)**. In our Korean cohort, however, the rs2231142 (G>T) deviated from the HWE (p=0.0407) (Table 2.6). 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.[34,133,134] 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).[135] 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).[136] 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).[137] 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.[138] 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.[139] 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.[140] 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. It is known to be strongly associated with urate regulation in the human body.[141] It is mainly expressed in the kidneys and liver, but it is also expressed in human articular cartilage.[142] 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.[143] 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.[144]

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, 98.8% in Filipinos, and 98.3% in Koreans compared to 75.5% in EUR ($p<0.0001$). 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 2.3**)**. 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. Therefore, 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. 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.[137]

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=0.002). 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%, 17.1%, and 20.9% for Koreans, Japanese, and Filipinos respectively vs. 46.1% p<0.00001) **(**Table 2.3**)**. 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.[145] 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.[146] 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.[147] 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 ($p<0.00001$). Our results found that the prevalence of T-alleles was 3-4-folds lower in both Asian and NHPI populations **(**Table 2.3**)**, 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%, $p<0.00001$). 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.[148] The intronic variant rs17300741 (A>G) in the *SLC22A11* gene was associated with renal urate under excretion type gout in the Japanese population ($p=0.049$).[149] 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 ($p = 6.7\times10-14$).[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 (89.6%, 85.3%, and 84.7%, respectively vs. 46.2% in EUR ($p<0.00001$). Furthermore, the A allele frequency was higher in Samoan, Native Hawaiian, and Marshallese compared with EUR (78.5%, 72.3%, and 70%, respectively, vs. 46.2% in EUR ($p<0.00001$). 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.[150] 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 2.3**)**. 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. 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.[151] Our cohort analysis showed that the frequency of T allele across minority subgroups was significantly higher than that of EUR ancestry **(**Table 2.3**)**.

Remarkably, the Asian subgroup (Koreans, Japanese, and Filipinos) had the highest prevalence of T allele, which is approximately two times higher vs. EUR (59.2%, 55.5%, and 45%, respectively, vs.26.6%, $p<0.00001$). 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%) ($p<0.00001$). However, the polymorphism rs2242206 (G>T) in the *SLC16A9* was not in HWE in Samoans and Hawaiians **(**Table 2.6**)**. 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.[152,153] 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.[154] 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).[137]

In our analysis, the frequency of T-allele was higher in the Japanese subgroup than EUR (58% vs. 41.1%, $p<0.00001$) and lower in Samoans than EUR (30.6 vs. 41.1%, $p=0.0005$) **(**Table 2.3**)**. 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.[155] 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).[155] Kolz et al. have identified the role of scaffolding *PDZK1* protein in SU baseline regulation.[32] 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 2.6**)**. 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. In genetic science, the Hardy Weinberg equilibrium principle applies to estimate if the allele and genotype frequencies remain constant from generation to the next. Several factors may influence HWE, and the technical issues in the genotyping sequencing consider one of them.[156] In our dataset, the PDZK1 across the whole population deviated from HWE, and we assume a lab error happened during genotyping.

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.[32,157] 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.[158]

The genetic polymorphism rs742132 in *LRRC16A* is associated with increased SU in EUR ancestry.[32] Notably, a GWAS study conducted on East Asian groups, including Koreans, showed that the rs742132 in *LRRC16A* is associated with elevated urate levels.[159] Our analysis showed that Japanese had a higher frequency of the A-allele compared to EUR (78.2%, vs. 69%, p=0.0009). However, the frequency of the A-allele in the Filipinos was indifferent compared with EUR (69.7% vs. 69, p=0.836). In addition, Koreans had an insignificantly different A-allele frequency compared with EUR (78%, vs. 69, p=0.017). On the other hand, in NHPI groups, there was a deviation from Hardy-Weinberg equilibrium in the Native Hawaiians p<0.05 **(**Table 2.6**)**. Also, although the prevalence of A-allele in Marshallese was higher than EUR, it was not statistically significant (70%, vs. 69%, p=0.819) **(**Table 2.3**)**. Moreover, Samoans had a lower frequency of the A-allele compared with EUR (51.7%, vs. 69%, p<0.00001) **(**Table 2.3**)**. 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.[160] Our findings suggest that the genetic polymorphism in rs742132 of *LRRC16A* may explain the differential prevalence of HU/gout across different population's subgroups.

Collectively, our results have 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 (reference). 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.[34,161,162]

Limitations

We have several limitations in this study. First, this study was retrospective, and the participants were selected from one location. Hence the sample size may not be representative of all populations. In addition, in retrospective studies, the medical records system provides information, and those datasets are obtained in a pre-designed form that may not match the study's purposes. Therefore, some data would constantly be missing. Furthermore, certain variables that can influence the result may have gone unseen.

Hence a more representative sample of the population is needed in future studies to validate our findings. Hyperuricemia and gout are polygenic conditions, so other genes/SNPs are also involved in urate disposition. 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.

Other factors that may also influence urate levels, including older age, smoking, diuretic use, dietary and social lifestyle factors. Nonetheless, 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 because genetic and epigenetic factors vary across the population, which could influence disease prevalence.

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. 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 a deviation from HWE.

Conclusions

Our analysis suggested that HU and gout risk alleles were significantly more frequent in the Asian subgroup, Korean, Japanese, and Filipino, than EURs. These findings are consistent with previous reports suggesting that Japanese and Han-Chinese populations having the highest prevalence of gout/HU risk alleles than EUR. Hence, our findings may partially explain the three-time higher risk of gout diagnosis in Asian subgroups living in the US than EUR. Meanwhile, consistent with the epidemiology of gout, child-bearing age women are unlikely to develop gout, despite having the genetic risk. This the first report of its kind to investigate the genetics of uric acid in populations that are minimally and rarely represented in research.

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 assess in the clinical practice 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. Furthermore, this investigation could help future research assess the role of HU and gout-risk-alleles in pregnant women to identify patients at higher risk of

maternal comorbidities such as gestation diabetes and gestation hypertension, which are associated with preeclampsia.

Table 2.1: Demographic Characteristics across populations							
Characteristics	Total sample population (n=1059)	Filipino (n= 229)	Japanese (n= 210)	Samoan (n= 200)	Marshallese (n= 160)	N. 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 (80.63%)	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	25.18±6.2	28.19±7.3	24.51±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 (Ibs)	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

Table 2.2: 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 by 50%, urate under-excretion, and hyperuricemia is caused by Glu 141 Lys amino acid substitution.	[32]
SLC2A9 (GLUT9)	*SLC2A9* is a 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. Beta effect= 0.315	[32,163]
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 ROL gout ($p = 0.012$), with an odds ratio (OR) of 1.28.	[151]

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)	*SLC22A11* is expressed in the kidney and encodes the organic anion transporter 4 (OAT4), responsible for urate reabsorption regulation.	rs17300741(**A**>G) (Intronic variant)	It is linked to renal under-excretion of UA in EUR descent. Beta effect= 0.062	[32,149]
SLC22A12 (URAT1)	*SLC22A12* is Protein encodes for urate transporter (URAT1), located on the apical side of proximal tubules and responsible for reabsorption of UA.	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	[32,152,153]

PDZK1 (PDZ)	Known as 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	[32,164]
LRRC16A (CARMIL1)	*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 UA reabsorption.	rs742132 (**A**>G) (Intronic genetic variation)	A risk allele related to increased risk of gout in Europe. Beta effect= 0.054	[32,157]

Table 2.3: Uric acid risk allele frequencies comparisons Asian and Native Hawaiian and Pacific Islanders										
Gene (SNP)	SNP 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)* **27.8 (51)**	74.4 (278) * **25.6 (96)**	87.3 (253) **12.7(37)**	82.4 (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) **53.9 (542)**	20.9 (73) * **79.1 (277)**	14.6 (26)* **85.4 (152)**	17.1 (63)* **82.9 (305)**	34.0 (98)* **66.0 (190)**	57.2 (135)* **42.8 (101)**	28.4 (103)* **71.6 (259)**	↓
SLC16A9 (s2242206 G>**T**)	Intronic	G **T**	73.4 (738) **26.6 (268)**	55.0 (197) * **45.0 (161)**	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)	Intronic	**A** G	**46.2 (465)** 53.8 (541)	**85.3 (297)*** 14.7 (51)	**89.6 (163)*** 10.4 (19)	**84.7 (305)*** 15.3 (55)	**72.3 (201)*** 27.7 (77)	**70.0 (167) *** 30.0 (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)**	2.1 (5) * **97.9 (230)**	31.5(116)* **68.5 (252)**	↓
LRRC16A (rs742132 **A**>G)	Intronic	**A** G	**69.0 (694)** 31.0 (312)	**69.7 (251)** 30.3 (109)	**78.0 (142)** 22.0 (40)	**78.2 (291)*** 21.8 (81)	**58.6 (171)*** 41.4 (121)	**70.0 (168)** 30.0 (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)	**56.8 (92)** 43.2 (70)	**48.9 (178)** 51.1 (186)	**39.3 (106)*** 60.7 (164)	**39.5 (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 2.4: Uric acid Genotype frequencies comparisons Asian, Native Hawaiian, and Pacific Islanders								
Gene (SNP)	Genotype	EUR % (n)	Filipino % (n)	Korean % (n)	Japanese % (n)	Native Hawaiian % (n)	Marshallese % (n)	Samoan % (n)
ABCG2 (rs2231142 G>**T**)	GG GT TT	82.3 (414) 16.5 (83) 1.2 (6)	28.5 (51) 51.4 (92) 20.1 (36)	56.5 (52) 31.5 (29) 12.0 (11)	56.7 (106) 35.3 (66) 8.0 (15)	75.5 (110) 23.1 (33) 1.4 (2)	68.0 (83) 28.7 (35) 3.3 (4)	48.9 (89) 40.1 (73) 11.0 (20)
SLC2A9 (rs734553 G>**T**)	GG GT TT	5.6 (28) 37.8 (190) 56.6 (285)	- 2.3 (4) 97.7 (172)	- 3.2 (3) 96.8 (90)	- 1.1 (2) 98.9 (183)	1.4 (2) 15.4 (22) 83.2 (119)	- - 100 (121)	- 3.3 (6) 96.7 (176)
SLC17A1 (rs1183201 **T**>A)	AA AT TT	23.1 (116) 46.1 (232) 30.8 (155)	4.0 (7) 33.7 (59) 62.3 (109)	1.1 (1) 27.0 (24) 71.9 (64)	3.8 (7) 26.6 (49) 69.6 (128)	11.8 (17) 44.4 (64) 43.8 (63)	29.7 (35) 55.0 (65) 15.3 (18)	6.6 (12) 43.7 (79) 49.7 (90)
SLC16A9 (rs2242206 G>**T**)	GG CT TT	54.9 (276) 37.0 (186) 8.1 (41)	32.9 (59) 44.1 (79) 23.0 (41)	15.2 (14) 51.1 (47) 33.7 (31)	16.9 (31) 55.2 (101) 27.9 (51)	34.7 (50) 40.3 (58) 25.0 (36)	31.9 (38) 47.1 (56) 21.0 (25)	33.0 (60) 55.5 (101) 11.5 (21)
GCKR (rs780094 C>**T**)	CC CT TT	33.6 (169) 50.7 (255) 15.7 (79)	31.8 (57) 46.4 (83) 21.8 (39)	35.9 (33) 44.6 (41) 19.5 (18)	18.8 (35) 46.3 (86) 34.9 (65)	41.7 (60) 48.6 (70) 9.7 (14)	41.3 (50) 46.3 (56) 12.4 (15)	48.1 (88) 42.6 (78) 9.3 (17)
SLC22A11 (rs17300741**A**>G)	AA AG GG	23.5 (118) 45.5 (229) 31.0 (156)	73.6 (128) 23.5 (41) 2.9 (5)	80.2 (73) 18.7 (17) 1.1 (1)	71.7 (129) 26.1 (47) 2.2 (4)	54.0 (75) 36.7 (51) 9.3 (13)	53.3 (64) 32.5 (39) 14.2 (17)	62.6 (112) 31.8 (57) 5.6 (10)
SLC22A12 (rs505802 **C**>T)	CC CT	9.9 (50) 38.8 (195)	61.2 (112) 34.4 (63)	63.4 (59) 32.3 (30)	67.7 (126) 28.0 (52)	35.8 (52) 53.1 (77)	90.9 (110) 8.3 (10)	48.9 (90) 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	AA	48.3 (243)	48.9 (88)	60.4 (55)	62.4 (116)	30.2 (44)	51.7 (62)	25.2 (46)
(rs742132 **A**>G)	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)	9.4 (17)	4.4 (4)	5.9 (11)	13.0 (19)	11.6 (14)	22.0 (40)
PDZK1	CC	30.4 (153)	42 (71)	54.3 (44)	47.8 (87)	36.3 (49)	37.7 (43)	42.2 (72)
(rs12129861 **C**>T)	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)	40.8 (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 2.5: Summary of Total Risk Alleles across Asian, Native Hawaiian, and Pacific Islanders							
Alleles significantly different from EUR	EUR	Japanese	Korean	Filipino	Marshallese	Hawaiian	Samoan
	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 2.6: 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 2.7: SNPs Call Rate (%)									
	SLC22A12 (rs505802)	*SLC17A1* (rs1183201)	*SLC16A9* (rs2242206)	*ABCG2 (rs*2231142)	*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
Native 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

Table 2.8: 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	Preeclampsia
MAF	Minor Allele Frequency
HWE	Hardy-Weinberg Equilibrium

Chapter 3: Assessment of Cardiometabolic Risk Factors among selected Pregnant Asian-Pacific Islander groups.

Abstract

Background

Preeclampsia (PE), known as severe new onset of the hypertensive disorder occurring after 20 weeks of gestation, can lead to maternal and fetal defects. Several risk factors are associated with developing PE. The most common risk factors include the history of comorbid conditions, advanced/younger age, high body mass index (BMI), or history of chronic kidney disease (CKD). Hyperuricemia (HU) was found to be an independent risk factor for developing cardiovascular diseases. Biologically, dysfunctional urate transporters due to genetic polymorphisms could lead to clinical consequences associated with increased or decreased serum urate (SU) levels. HU has been reported as a significant risk predictor of developing cardiometabolic diseases (CMDs). Examples of CMDs include chronic hypertension (CHTN), gestational hypertension (GHTN), diabetes mellitus (DM), and gestational diabetes mellitus (GDM). CMDs are considered major risk factors associated with developing PE. Therefore, this study focuses on assessing the genetics of uric acid disposition and other non-genetic factors in developing CMDs across selected pregnant Asian-Pacific Islander groups.

Methods

The biospecimens repository at the University of Hawaii provided DNA samples of consenting post-partum women. The DNA was extracted from the cord blood and genotyped at the Genomics and Bioinformatics Shared Resource, Cancer (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. Age and BMI were selected as non-genetic risk factors associated with developing CMDs.

The Hardy-Weinberg Equilibrium (HWE) for genotype frequencies was assessed using the Chi-Square test with $p<0.05$ for statistical significance.
The association between genotype and CMDs phenotypes (CHTN, GHTN, DM, and GDM) were assessed using chi-square or Fisher exact test as appropriate at $p<0.05$ in different genetic assumption models (Additive, Dominant, and Recessive). Then a logistic regression analysis test was used after conducting a global hypothesis test to determine the association between age, BMI, and CMDs phenotype. Finally, the univariate statistical analysis (ANOVA) was used to ascertain the association between BMI and different UA genotypes.

Results

This study involved 429 post-partum pregnant women aged 18 years or older who self-reported their respective race and ethnicity. Specifically, we chose the Filipino group as the Asian subgroup and the Samoan population as the Pacific Islander subgroup. No one of the participants reported a history of gout disease. Based on the HWE results, we excluded some UA gene/SNPs in Filipino and Samoan sample populations. All UA risk alleles were consistent with HWE ($p>0.05$), except *PDZK1* (rs12129861 C>T) in both groups, and *SLC16A9* (rs2242206 G>T) in the Samoan group ($p =0.0275$). Using a chi-square test, we found a significant association between UA genotype and diabetes mellitus in the Filipino group. These genotypes were *ABCG2* (rs2231142 G>T) in both additive and recessive models 75% vs. 18.9% ($p=0.016$, 0.026, respectively).

Meanwhile, in the Samoan group, we found trending toward significant differences between the recessive genetic model of UA genotype of *SLC22A11*

(rs17300741 A>G) in the CHTN and GDM. The proportion of UA AA genotypes trended significantly higher in the presence of CHTN (100%) versus (61.2%) in participants without (p=0.085). The proportion of the UA genotype AA of *SLC22A11* in the presence of GDM was trending toward a significantly higher, around (80.9%) vs. (60.2%) in the Samoan population without GDM (p=0. 063). In performing a logistic regression analysis, we found age associated with developing CHTN (OR=1.11, 1.026-1.225 95% CI, p=0.0139) in the Filipino population. Moreover, we found a trending toward a significant association between BMI and CHTN in the Filipino cohort (OR=1.08, 0.99- 1.13 95% CI, p= 0.06). Furthermore, age also associated with developing GDM in the Samoan population (OR=1.15, 1.063- 1.254 95% CI, p= 0.0006).

In a univariate analysis test in the Filipino sample population, our results found a significant difference in the mean BMI among *ABCG2* (rs2231142 G>T) within the dominant model (mean of GT+ TT= 24.14 relative to GG (reference)= 26.88, (p= 0.04). In the Samoan population, we found a trending toward significant under the additive model of *GCKR* (rs780094 C>T) (mean of TT= 26.56 compared to 29.72 of CC (reference), (p = 0.08). Moreover, significant differences in mean BMI have been shown in the Samoan population under the additive and recessive model of *LRRC16A* (rs742132 A>G). Under the additive model, the mean BMI of AA (genotype risk) was lower, 27.47 relative to 28.65 of GG (reference) p=0.03. Moreover, under the recessive model, the mean BMI of AA (genotype risk) was lower, 27.47 compared to 30.3 of AG+GG (reference) p=0.031).

Conclusion

The UA risk alleles were associated with the development of diabetes mellitus among the Filipino group. In contrast, they were trending toward an association

between UA risk alleles and gestational diabetes and chronic hypertension in Samoan ancestry. Age risk factors have shown an association with CMDs developments in both Filipinos and Samoans. Moreover, BMI has shown an association with CHTN in the Filipino population. Our statistical analysis results are consistent with a previous study that confirms the Asian population had the highest prevalence of UA risk alleles relative to the Pacific Islander population. In addition, these results are consistent with current studies showing that the Asian population has the highest prevalence of CMDs compared to the Pacific Islander population.

Key Words: Asian-Pacific Islanders, Gestational Diabetes, Chronic Hypertension, Gestational Hypertension, Preeclampsia, Filipinos, Samoans, Uric acid, Single Nucleotide Polymorphisms

Introduction

Preeclampsia (PE) is a new onset of the hypertensive disorder occurring after 20 weeks of gestation, potentially leading to maternal and fetal defects. This condition affects up to 8% of pregnant women in the world. Additionally, in the US, severe PE risk increased up to six-fold between 1980 and 2003, which increased the burden and costs on the health care system.[165] Several risk factors are related to developing PE, including family history, multiple pregnancies, maternal comorbidities such as diabetes, CVD, CKD, genetic predisposition, and in some population such as African and African-American ancestry (odds ratio [OR]: 3.70, 95% CI: 2.19–6.24) compared to white women.[166–168] Nakagawa et al. found the prevalence of PE in the under-represented population of Hawaii to be higher among the Asian and Pacific Islander populations.[169] Several studies have suggested the association between UA during pregnancy and PE causing severe maternal and fetus complications.[170]

Chemically, uric acid (UA) is the final product of purine metabolism.[171] Placental ischemia enhances xanthine oxidase (XO) activation, further activating uric acid formation.[172] The first discovered association between high serum uric acid (SU) and PE in pregnant women was in 1934.[173] In 2008, a large-scale prospective multi-center study was conducted by Paula et al., wherein it was pointed out that SU level correlated with the perinatal prognosis of patients with hypertensive disorders of pregnancy (HDP).[174]

Hyperuricemia (HU) potentiates PE by stimulating inflammation, endothelial dysfunction, and oxidative stress.[175] Multiple studies reported the association between SU and adverse maternal outcomes. Maternal gout, for instance, was found to be associated with an increased risk of low birth weight, preterm birth, Cesarean delivery,

and PE pathology.[176,177] A recent study reported a correlation between hypertension and UA levels, as well as the predictive capability of UA levels in severe PE.[178]

Additionally, some studies suggest that HU could be an essential indicator for pregnancy-related disorders, including HDP development, PE, and preterm birth.[177] Hyperuricemia could lead to hypertension and proteinuria, which are clinical markers commonly used to diagnose PE.[179] Women with PE have elevated SU, representing an equally effective marker to proteinuria in detecting perinatal risk in gestational hypertensive women.[180,181] Relative to women with PE and normal SU, women with PE and hyperuricemia have a higher risk of adverse perinatal outcomes.[180,181] Nonetheless, a correlation between hyperuricemia and maternal and fetal morbidity pointing to its diagnostic value in predicting PE development has been reported.[182]

Hyperuricemia could be utilized as a predictor of fetal outcome in women with PE. Studies have found that women with hyperuricemia occurring before 35 weeks of gestation often have deliveries with adverse consequences, such as intrauterine growth restriction (IUGR) and intrauterine death (IUD).[183] A recent study reported that 72% of newborns of mothers with hyperuricemia had low birth weights. In comparison, 62% of newborns from women with normal uric acid levels had average birth weights.[184]

Despite these promising findings, it is unclear whether UA could be used as a marker for PE or adverse maternal outcomes.[182] Opposing studies have suggested that high SU was not related to negative maternal effects. Moreover, SU may not be involved in PE development, and thereby might not be a reliable marker for predicting the incidence of adverse pregnancy outcomes.[185] Studies investigating the effects of SU on pregnancy and its potential as a marker for various maternal outcomes were inconsistent.

HU has the potential to inhibit trophoblast invasion of the placenta, resulting in reduced blood supply and oxygen for the fetus.[186] Biologically, HU could also reduce nitric oxide (NO) production in endothelial cells, contributing to poor trophoblast invasion[187]. This mechanism could imply the role of HU in PE pathogenesis.[175]

PE can happen due to several risk factors involving coexisting comorbidities, most of which could be associated with HU/gout. Furthermore, several risk factors may increase the risk of PE, such as diet and social factors, socioeconomic status, and psychological disorders. Additionally, some ethnic groups—for instance, African Americans—have a significantly higher risk of PE.[188,189]

Genetic polymorphism of the urate transportome may lead to clinical disorders such as hyperuricemia. An example of the UA genes is *SLC22A12* (URAT1), *ABCG2*, which showed a strong association with chronic renal injury. [190,139] Interestingly, reports showed significant association between various UA risk alleles, single nucleotide polymorphisms (SNPs), and PE among pregnant South African women. A case-control study demonstrated a strong association between the human urate transporter *SCL22A12/* rs502802 (URAT 1) and PE, specifically late-onset PE versus a control group of pregnant women (OR=1.73, 95% CI=1.258- 2.442, p=0.028).[191]

The results of that previous study may highlight a possible role of UA risk alleles in the development of chronic metabolic diseases. The link between HU/gout and chronic complications, such as cardiovascular diseases (CVD), renal impairment, and metabolic syndromes, may be exacerbated by HU. HU is implicated in the progress of many metabolic diseases, as previously mentioned.[192] Clinically, several risk factors have been associated with the development of PE disease. According to the National Institute for Health and Care Excellence (NICE) guidelines, these risk factors are classified into high and moderate levels. If the pregnant women had a history of

hypertension in their last pregnancy or suffered from gestational diabetes, kidney disorders, or autoimmune diseases, they were classified at a high risk of PE. Additionally, some other clinical factors like the woman's age (≥ 40-years) or body mass index (BMI) ≥ 35 kg/m^2, as well as other risks, were classified as moderate clinical determinants.[193] Pregnant women diagnosed with diabetes mellitus as well as those who develop gestational diabetes are at a two- to four-fold risk of being diagnosed with preeclampsia.[194]

In this study, we hypothesized that UA genetic polymorphisms and non-genetic factors including age and BMI may contribute to metabolic disorder development, which are major risk factors for maternal outcomes in the Asian and Pacific Islander subgroups. This study proposed to look at the impact of several UA gene/SNP pair variations among selected pregnant women, variations that had been shown to cause cardiometabolic syndromes such as diabetes mellitus (DM), gestational diabetes mellitus (GDM), chronic hypertension (HTN), and gestational hypertension (GHTN). Finally, this analysis aimed to assess the association between genetic/non-genetic risk factors contributing to cardiometabolic disorders, which a major risk factors of PE disease.

Methods

Preliminary Statistical analysis

Previously, we aimed to test an association between cardiometabolic diseases and UA risk alleles using simple and multiple logistic regression analysis, adjusting for other covariates, including age and body mass index (BMI), across the entire sample population of the Asian and native Hawaiian-Pacific Islander populations. Unfortunately, the results were uninterpretable because they were biologically and directionally inconsistent with some UA genes associated with cardiometabolic

diseases. We postulated that inconsistency might partly be due to the low frequency of the outcomes and population heterogeneity. All previous statistical analyses appear in the appendix section.

As a follow-up, we decided to focus our analysis only on Filipino and Samoan groups using logistic regression analysis. Although the logistic regression results were uninterpretable with some genes, it pointed to the possibility of specific non-genetic risk factors associated with developing CMDs. We describe the process in the appendix section.

Frist, we used chi-square and Fisher exact tests at $p<0.05$ to compare the prevalence of comorbidities in the Asian population versus native Hawaiians and Pacific Islanders. We summarize all the results in Table 3.3. Figure 3.1

In addition, we compared the same comorbidities conditions among Filipino relative to the Samoan population, as well we compare the prevalence of each ethnicity to the overall population. We summarized all findings in the Table 3.2., Figure 3.2.

To minimize the heterogeneity within the population, while considering the sample size and the frequency of the outcome of interest, we decided to focus our analysis only on Filipino and Samoan populations to run genetic and non-genetic factors models. We assessed the association between CMDs and the prevalence of HU genotypes, using chi-square or Fisher exact test $p<0.05$. In addition, we used multiple logistic regression models to test the association between non-genetic risk factors (age/BMI) and cardiometabolic diseases. Moreover, a univariate analysis test (ANOVA) was used to analyze the differences among mean BMI between different genotypes of UA genes. We reported the results of the exploratory analysis of the entire cohort combined in the appendix section.

Study participant and urate genes

Participants in this study were pregnant women ≥18 years old. All of them self-reported as having Asian or Pacific Islander subgroups ancestry (Filipino and Samoan). Age, gestational age, BMI, and other demographic information were provided. In Table 3.1, we summarize all demographic characteristics. Blood samples were collected from participants for DNA extraction. The uric acid genes addressed in this study include *SLC17A1* (rs1183201), *PDZK1* (rs12129861), *SLC22A11* (rs17300741), *ABCG2* (rs231142), *SLC2A9 (*rs734553) G>T, *SLC164A9* rs2242206, SLC22A12 (rs505802), *CARMIL1*, *LRRC16A* rs742132, and *GCKR* (rs780094). It should be noted that the University of Hawaii provided all data we mentioned.

Following HWE analysis results and other quality assessments across the selected population groups, we excluded *PDZK1, SLC2A9* in both groups*,* and *SLC16A9* genes in the Samoan population. Social risk factors such as a history of smoking and alcohol use were reported in the demographic information (Table 3.2). Maternal medical conditions, including gestational hypertension, chronic hypertension, gestational diabetes, diabetic mellitus, Preeclampsia, and premature labor, were also reported and appear in Table 3.2. Participants' younger than18 years of age or having a history of cancer and/or organ transplants were excluded.

Sample procurement and genotyping

Genotype, medical, and demographical information were provided by the University of Hawaii biospecimens repository. Post-partum women gave consent to donate their placentas and umbilical cords. The DNA was extracted from the blood and genotyped at the genomics and Bioinformatics Shared Resource, Cancer center (Honolulu, HI). A customized TaqMan genotyping assay panel was run on the Quant Studio 12K Flex Real-Time PCR system (Applied Bio systems). All study details were previously

published.[129] All study materials were reviewed and exempted by the University of Hawaii Human Studies Program (protocol Number: 2018-00225).

Statistical analysis

Data obtained during the study were analyzed utilizing R software Version 1.3.1073. We assessed our data with Hardy-Weinberg Equilibrium at P <0.05 across our selected population (Table 3.6). Chi-square statistical analysis and Fisher exact tests were used to estimate the associations between gene variations and cardiometabolic phenotypes across all three genetic models (additive, dominant, and recessive) at p<0.05. The phenotypes of interest were presence and absence of gestational hypertension, gestational diabetes, chronic hypertension, and diabetic mellitus. Other risk factors, including age and BMI, were assessed in relationship to cardiometabolic diseases using multiple logistic regression analysis tests and reported odds ratios (OR), 95% CI and p-value <0.05 for statistical significance. The association of BMI amongst the different genotypes of UA genes was determined using one-way ANOVA.

Results

Our previous study concluded that the Asian population had the highest prevalence of UA risk alleles as compared to native Hawaiians and Pacific Islanders (Table 2.5). Moreover, our results show that the Asian population had a significantly higher prevalence of cardiometabolic disorders as compared to native Hawaiian and Pacific Islanders (Table 3.3) (Figure 3.1). Consistently, the current study has shown that Filipinos have the highest prevalence of cardiometabolic diseases relative to the Samoans (Table 3.2, Figure 3.2). The demographic, clinical, and social characteristics across selected population ancestry is summarized in Table 3.1. Among all uric acid

gene/SNPs, some deviated from HWE, and those deviations are summarized in Table 3.6.

Hardy-Weinberg Equilibrium and quality control

We used a chi-square statistical test analysis to perform HWE principle in order to check all genes/ SNPs for deviation or consistency in regard to HWE across selected populations. In both Filipino and Samoan populations, all UA risk alleles were consistent with HWE, except *PDZK1* (rs12129861 C>T) in both subgroups, and *SLC16A9* (rs2242206 G>T) in the Samoan population p =0.0275 (Table 3.6). In addition, we excluded *SLC2A9* (rs734553 G>T) in both groups due to a lack of GG frequency.

Association of UA Genotypes (Additive, Dominant, and Recessive models) and Cardiometabolic Diseases amongst Filipino and Samoan Subgroups

Based on the overall dataset, the prevalence of comorbid diseases, and the largest sample size across Asian, native Hawaiians, and Pacific Islanders, we selected the Filipino and Samoan population groups to determine the association between genotypes and phenotypes. All UA genotype risk alleles were included in the Filipino population except *PDZK1*, due to its deviation from HWE (Table 3.6). In the Samoan population, we excluded *PDZK1* and *SLC16A9* out of a total of nine UA genes, also due to their deviation from HWE (Table 3.6).

In the Filipino cohort, we found a trending toward significant differences between *SLC16A9* (rs2242206 G>T) and CHTN. The proportion of the TT risk allele of *SLC16A* (rs2242206 G>T) was lower (0%) in the presence of CHTN, relative to (24.4%) in participants without CHTN in both additive (TT vs. GT vs. GG (reference)) and recessive (TT vs. GT+TT (reference)) models (p=0.09, 0.07), respectively.

Moreover, our analysis has not shown any statistical significance among the rest of UA genes and chronic hypertension in Filipinos (Table 3.5). Meanwhile, in the Samoan group, there was trending toward a significant relationship between *SLC22A11* (rs17300741 A>G) and CHTN. Under the recessive model (AA vs. AG+GG (reference)), the proportion of AA risk alleles were higher (100%) in participants who were diagnosed with CHTN compared to (61.2%) in participants without. (p=0.08). **(**Table 3.4**).**

Across the Filipino population, for those with diabetes mellitus (DM), there was a significantly higher prevalence of genotype risk alleles of *ABCG2* (rs2231142 G>T) and diabetes mellitus in both additive and recessive genetic models. (Table 3.5). The proportion of TT risk allele of *ABCG2* (rs2231142 G>T) in the additive model (TT vs. GT vs. GG (reference)) and recessive model (TT vs. GT+TT (reference)) was significantly higher in the presence of DM (75%) as compared to the absence of DM (18.9%) (P=0.016, 0.026), respectively. (Table 3.5).

In contrast, within the Samoan group, our analysis found a significantly lower proportion of TT risk genotype of *SLC17A1* (rs1183201 T>A) in the presence of DM than in its absence ($p<0.05$) (Table 3.4). Our statistical analysis results have not shown any significant differences between UA genotypes and gestational hypertension phenotype in both Filipino and Samoan groups (Table 3.4 & Table 3.5).

In gestational diabetes mellitus (GDM), our analysis did not show any statistical differences in the proportion of UA genotype and phenotype across the Filipino population. However, in the Samoan population, we saw a trending toward a significant association between *SLC22A11* (rs17300741 A>G) and GDM. Under the recessive model (AA vs. AG+GG (reference)) of *SLC22A11* (rs17300741 A>G), the proportion of

AA genotype was higher (80.9%) in participants who had been diagnosed with GDM compared to (60.2%) in Samoan participants without (p=0.06). (Table 3.4).

Association of Cardiometabolic Diseases (CHTN, DM, GHTN, and GDM) and non-genetic risk factors (BMI and age) amongst Filipino and Samoan population

We used multiple logistic regression analysis models for both global and secondary hypothesis to estimate age and BMI, which are considered non-genetic risk factors associated with the development of cardiometabolic diseases. We found what we determined to be an odd ratio, 95% CI, and p-value of multiple logistic regression analysis, which has been summarized in Table 3.7.

Results of the analysis show higher odds significantly associated between CHTN and age in the Filipino subgroup [(OR=1.11, 95% CI= 1.026- 1.225, p= 0.0139)], as well as a trending toward significant in BMI [(OR=1.06, 95% CI= 0.991- 1.135, p= 0.06)] (Table 3.7). No significant association was found to exist between age, BMI, and diseases such as DM, GDM, and GHTN in the Filipino population. (Table 3.7). In contrast, for the Samoan population, the statistical analysis showed a significant association between age and GDM [(OR=1.15, 95% CI= 1.06-1.25, p= 0.0006)]. (Table 3.7).

The differences in the mean BMI amongst UA genotypes in Filipino and Samoan population

In this part of the analysis, we tested the differences in the mean BMI across the different genotypes of UA genes in all three genetic models (additive, dominant, and recessive). I started to test the assumption of variance using Bartlett's test to decide on using equal/unequal ANOVA. The statistical analysis showed a significant difference in the mean BMI of *ABCG2* (rs2231142 G>T) under the dominant model (GT+TT vs. GG (reference)) across the Filipino population. Thus, the mean BMI of GT+TT of the

dominant model was lower relative to the mean of the GG (reference) genotype (mean= 24.14 vs. 26.88, p=0.04), respectively. (Table 3.8) (Figure 3.3)

However, in the Samoan subpopulation, a trending toward significant was found between mean of BMI and TT genotype of the additive model (TT compared to CC) of *GCKR* (rs780094 C>T) (mean BMI of TT genotype was 26.56 relative 29.72 of CC (reference) genotype (p=0.08). (Table 3.9) (Figure 3.4). Moreover, in the Samoan population, significantly lower differences were found under additive (GG (reference) vs. AG+GG) and recessive (AG+GG (reference) vs. AA) genetic models of *LRRC16A* (rs742132 A>G). The mean BMI of AA was 27.47 is in contrast to the reference GG= 28.65, (p=0.03) in the additive model (Figure 3.5), while in the recessive genetic model, the mean BMI of AA= 27.47 was lower than the reference AG+GG= 30.31 at (p=0.03) (Figure 3.6). Furthermore, no significant differences were found in the remaining genes and BMI across both populations (Table 3.9).

Discussion

Hypertension is considered one of the most common diseases in the Asian/Pacific Islander populations.[195] Pregnant women with a history of CHTN are considered more susceptible to a higher risk of PE.[193] Among many risk factors, UA is associated with the development of cardiovascular diseases. Genetic polymorphisms of urate transporters could cause an imbalance between urate excretion and reabsorption, which could lead to metabolic disorders. Therefore, a high UA level could be an independent predictor of several complications, such as hypertension.[22] In our Filipino cohort, the proportion of most UA genotypes were higher in participants that had CHTN versus participants without CHTN, but there was not enough evidence to suggest a statistically significant association (P>0.05). (Table 3.5). An example of UA risk alleles associated with CVD is *GCKR* (rs780094 C>T) gene polymorphism, which is related to

triglyceride and other cardiovascular risks.[196] Our data analysis shows an insignificantly higher proportion of T risk allele of the *GCKR* (rs780094 C>T) in the presence of CHTN in all three genetic models (additive, dominant, and recessive) (36.4% vs. 20.7%, and 72.8% vs 67.4% vs. 36.4, and 20.7%, respectively, ($p>0.05$) (Table 3.5). At this point, our results are inconsistent with available literature; therefore, further studies should be conducted on a large enough sample size in order to validate the existing results.

On the other hand, in the same Filipino group, the proportion of T risk allele of *SLC16A9* (rs2242206 G>T) trended significantly lower in women who had CHTN compared to those without CHTN (0% vs. 24.4% $p=0.090$ in additive model (GT+TT vs. GG (reference) and 0% vs. 24.4% $p=0.069$ in the recessive model (TT vs. GT+GG (reference)) (Table 3.5). The results we found conflict with the physiological function of *SLC16A9* and its metabolic trait association. *SLC16A9* codes for a monocarboxylic acid protein (MCT9), which has a role in carnitine transportation and UA excretion from the intestine. Carnitine is mostly excreted through the glomerular tubules of the kidney. Based on kidney function, carnitine is a competitive substrate in regard to UA. If it is not excreted well, carnitine could cause renal overload gout due to high UA, causing cardiovascular dysfunctions and other metabolic traits.[197]

By contrast, in the Samoan subgroup, the study analysis results show a trend toward a significantly higher proportion of AA genotype of *SLC22A11* (rs17300741 A>G) under a recessive genetic model (AG+GG (reference) vs. AA) in regard to the presence of CHTN relative to non-CHTN. The proportion of AA genotype (100%) relative to AG+GG (61.2%) $p=0.0851$). (Table 3.4). Flynn et al. have found that the *SLC22A11* (OAT4) is strongly associated with UA and gout in the Pacific Islander population.[198] Apart from this, we found that in our cohort, the prevalence of the A risk allele is

significantly higher in both the Asian and native Hawaiian and Pacific Islander populations than EUR.

Additionally, *ABCG2* (rs2231142G>T), *LRRC16A* (rs742132 A>G), and *GCKR* (rs780094 C>T) genotypes were insignificantly associated with increased risk of CHTN in the Samoan population. Conversely, *SLC22A12* (rs505802 C>T) and *SLC17A1* (rs1183201 T>A) UA risk alleles were insignificantly lower in CHTN risk development p >0.05 across the Samoan population. (Table 3.4).

Gestational hypertension (GHTN) can occur during pregnancy, causing an elevation in blood pressure. During the first quarter of pregnancy, if the UA levels are about 3.15 mg/dl it can be indicative of GHTN, which is classified as a decisive risk factor of PE development. Hence, UA level is one of the predictive factors for cardiometabolic diseases.[199] Our analysis showed that Filipino-American population groups in Hawaii had an insignificant association between UA gene polymorphisms and GHTN. In the Filipino subgroup, UA genotypes of *SLC22A11* (rs17300741 A>G), *SLC17A1* (rs1183201 T>A), *ABCG2* (rs2231142 G>T), SLC16A9 (rs2242206 G>T), and *LRRC16A* (rs742132 A>G) were insignificantly higher in the proportion of the risk allele in the presence of GHTN (Table 3.4). It should be noted that Filipino-Americans tend to have a higher risk of developing cardiometabolic conditions due to numerous risk factors.[200] Further studies are needed to explore the role of genetic factors associated with heart-related diseases in the Filipino-American group.

On the other hand, our results have not shown any significant association between UA gene polymorphisms and GHTN development in the Samoan subgroup. Most UA genotypes had an insignificantly higher proportion in the presence of GHTN relative to absence status p>0.05 in the Samoan population. These alleles include *SLC22A12* (rs505802 C>T), *SLC17A1* (rs1183201 T>A), *SLC22A11* (rs17300741

A>G), and *GCKR* (rs780094 C>T) in all three genetic models, while *ABCG2* (rs2231142 G>T) only appeared in dominant genetic model (Table 3.4). Although our results may not be statistically significant, they are consistent with the biological function of the association between UA gene polymorphisms and CMDs development.[197] The T risk allele of *GCKR* (rs780094 C>T) is an example of a polymorphism that is biologically associated with the cardiometabolic trait.[201] However, the AA genotype of *LRRC16A* (rs742132 A>G) was insignificantly lower in proportion in regard to the presence of GHTN as compared to Samoan pregnant women without GHTN in both dominant and recessive models $p>0.05$ (Table 3.4). What's more, *LRRC16A* genes have a biological role in metabolic traits, and our cohort results show the opposite physiological direction in the Samoan population. We can hence conclude that not only genetic factors contribute to metabolic diseases across the different populations; indeed, there may be many other factors. This explanation leads us to focus on other risk factors such as BMI and study their relationship to metabolic traits. Lee et al. have reported that BMI over 21 kg/m^2 and obesity are associated with coronary heart disease at a level of approximately 58% in Samoan-Americans.[202] Conversely, In the Filipino cohort, our analysis showed that the prevalence of AA genotype of *LRRC16A* (rs742132 A>G) was higher in proportion in the presence of GHTN relative to pregnant women without GHTN, but there was no evidence to fully support that association ($P>0.05$) (Table 3.5).

Diabetes mellitus (DM) is a metabolic disorder resulting in reduced insulin secretion, causing an elevation of the blood glucose level, leading to hyperglycemia.[203] A history of DM, either type 1 or 2, among pregnant women increases the risk of PE as well as gestational diabetes.[194] Biologically, there is a potential association between urate transporters' heritability and metabolic disorder development.[197] Hence, we

conducted our analysis toward detecting an association between diabetes, gestational diabetes, and UA genetic polymorphisms across Filipino and Samoan subgroups. *SLC22A12* (rs505802 C>T) is encoded for urate transporter 1 (URAT1), a major transporter responsible for urate reabsorption. In addition, *SLC22A12* has a role in phosphorylation enzyme called phosphokinase-c (PKC), which contributes to activating phosphoinositide inositol-3 kinase (PI3K), which is associated with insulin secretion and glucose uptake. Reduced function in this protein reduces insulin secretion from the beta cell, causing insulin resistance and DM. [197] Although the prevalence of the CC genotype of *SLC22A12* (rs505802 C>T) has been shown to be higher in the presence of DM than in non-DM Filipino pregnant women in an additive model (TT (reference) vs. CC)) 75% vs. 60.9%, respectively, our analysis did not show any significant association (p=0.10) (Table 3.5). In addition, another genetic model had also found a non-significantly higher proportion of the C risk allele *SLC22A12* (rs505802 C>T) in participants with DM as compared to the non-DM p>0.05 across the Filipino cohort (Table 3.5).

In the same Filipino cohort, the proportion of TT genotype of *ABCG2* (rs2231142 G>T) shows a significantly higher association that contributed to DM relative to women without DM in both additive and recessive genetic models (75% vs. 18.9% p 0.01627 and 75% vs. 18.9 p= 0.02611, respectively) (Table 3.5). It is well established that *ABCG2* is highly associated with hyperuricemia and gout across different populations, and that it possibly contributes to cardiometabolic illnesses such as diabetic mellitus.[204]

As previously mentioned, *SLC16A9* codes for a protein monocarboxylic acid transporter 9 (MCT9), which has a role in carnitine transporter that assists in insulin secretion improvement; thus, lack of *SLC16A9* function is associated with many

conditions such as type 2 DM and cardiovascular disorders.[197] Our analysis has found a non-significantly higher proportion of the TT genotype of *SLC16A9* (rs2242206 G>T) under a dominant model (GT+TT vs. GG (reference)) across Filipino participants that had DM relative to participants without (75% vs.66.8%, respectively, p=1). Other genetic models also resulted in higher proportions but were not considered statistically significant (Table 3.5). Furthermore, the analysis has found a higher proportion in both genotypes of *SLC22A11* (rs17300741 A>G) and *GCKR* (rs780094 C>T) in regard to those with DM within the Filipino cohort, but these proportions were statistically insignificant (p>0.05) (Table 3.5). Our final analysis showed an association between UA genotypes and developing DM across Filipino pregnant women, supporting that hyperuricemia may be considered a predictor of the risk factor for CMD.

In the Samoan subgroup, our analysis found a non-significantly higher proportion of the AA risk genotype of *SLC22A11* (rs17300741 A>G) across pregnant women who had DM (75%) as compared to those without DM (62.3%), P>0.05. The remainder of the genes—including *SLC22A12* (rs505802 C>T), *ABCG2* (rs2231142 G>T), *SLC16A9* (rs2242206 G>T), *LRRC16A* (rs742132 A>G), *GCKR* (rs780094 C>T)—have zero prevalence of UA risk genotypes, which has an effect on the results (Table 3.4). These results lead us to look for other risk factors related to DM, such as obesity and age of the pregnant woman, as well as other demographic characteristics.

Gestational diabetes mellitus (GDM) is a subtype of DM, and it occurs most often in the mid-phase of pregnancy. Relating to PE, GDM increases the risk of PE by about 30%; it can also have negative effects on both the mother and her fetus.[205] The analysis shows trending toward a significant association between the AA genotype of *SLC22A11* (rs17300741 A>G) and GDM across the Samoan population. Under the recessive model (AG+GG (reference) vs. AA), the proportion of AA was higher

(80.9%) of the pregnant Samoan with GDM compared to (60.2%) in those without GDM (p=0.06) (Table 3.4). This indicates that the prevalence of GDM amongst the Pacific Islander population was very high, particularly in the Samoan subgroup.[206]

In both subgroups, our results did not find any significant association between remaining UA SNPs risk alleles and GDM (p>0.05) (Table 3.4 & Table 3.5). In fact, along with UA genetic risk factors, GDM might occur through different causes, and maternal obesity is considered a major one of those causes.[207]

In summary, this cohort analysis aimed to detect a genetic association between UA genotypes and CMDs among the Asian/Pacific Islander population, specifically those in the Filipino and Samoan subgroups. Genetically, the Samoan population is at risk of developing CHTN and GDM due to UA risk alleles of *SLC22A11*. Meanwhile, the Filipino subgroup has shown a high risk of CMDs, mainly DM, due to genetic polymorphism in *ABCG2*. Overall, from a genetic perspective of urate heritability, we would argue that both Filipino and Samoan populations are at a higher risk of developing cardiometabolic disorders. These findings are partially consistent with our previous results that found Asian subgroups and the Filipino population to have the highest prevalence of UA risk alleles and cardiometabolic disorders relative to the population cohort and its subgroups of native Hawaiian and Pacific Islanders (Table 2.5& Table 3.4).

Non-genetic risk factors (Age, BMI) and development of comorbid Diseases (CMDs)

The logistic regression analysis test was used amongst Filipino and Samoan subgroups to determine nongenetic risk factors involving the mother age and BMI associated with CMDs progression. All associations between nongenetic risk factors and CMDs were summarized in the Table 3.7. Across the Asian-Pacific community, obesity is associated with an increased risk of comorbid diseases.[208] Along with the

relationship between CMDs and PE, obesity and advanced maternal age could be classified as moderate risk factors associated with PE.[193]

Our analysis has shown an association between age and CHTN in Filipino pregnant women (OR = 1.11, 95% CI = 1.026- 1.225, p = 0.0139 *). In addition, BMI has been shown to be associated with CHTN in the Filipino population (OR=1.06, 95% CI= 0.99-1.13, p=0.06). (Table 3.7). This result is consistent with other data published in 2018 that reported that those Filipinos of an older age and those with a BMI greater than 23kg/m^2 were considered to be at risk for developing hypertension.[209]

Whereas Linhart et al. have reported that obesity and an increased BMI rate are strongly associated with hypertension across the Samoan population[210], the global hypothesis test results of age/BMI covariates related to CHTN was insignificant (p>0.05), which did not show an association between BMI and GHTN in the Samoan population (Table 3.7).

Sugiyama et al. have reported that Pacific Islander pregnant women who are 30 years or older and have a BMI ≥ 30 kg/m2 are at a higher risk of GDM and maternal consequences such as high weight infants and fetal death as compared to women without GDM.[211] Moreover, the severity of perinatal outcomes due to GDM vary across ethnicities. The multiple logistic results show that age is considered a significant high-risk factor for development of GDM in the Samoan population (OR= 1.15, 95% CI = 1.06- 1.25, p = 0.0006 ***). Although the odds of BMI were positive in GDM in the Samoan cohort, there was no evidence to suggest that association p>0.05 (Table 3.7). This analysis shows that age and BMI could be contribute to cardiometabolic disorders, which may negatively impact both mothers and fetuses. A previous study reported that infants of Filipino mothers had twice the risk of developing macrosomia than other Pacific Islander subgroups in the US.[212]

The mean body mass index (BMI) between different genotypes of UA genes

Hyperuricemia has been reported to be associated with obesity metabolic traits such as dyslipidemia.[213] Urate genetic polymorphism could contribute to that association. A recent study has found an association between *GCKR* (rs780094 C>T) and multiple types of lipids, which may cause obesity and several other metabolic complications.[152] We utilized a univariate analysis ANOVA test to assess the differences of mean BMI across the UA genes in different genetic models (additive, dominant, and recessive). In the Filipino cohort, the analysis showed carriers risk of TT genotype had a higher mean BMI relative to CC genotype (reference) of *GCKR* (780094 C>T), but these results were not statistically significant. (P>0.05). (Table 3.8). Conversely, in the same Filipino cohort, we found a significant difference in mean BMI under the dominant model (GG (reference) vs. GT+TT) of *ABCG2* (rs2231142 G>T). The participant carriers GT+TT had a lower mean BMI of 24.14 relative to GG (reference) 26.88. (p=0.04). (Table 3.8). These results were in conflict with the published literature, as previous studies have found a loss of function in *ABCG2* (rs2231142 G>T) variant associated with gout in obese male compared to nonobese females in a subset of Taiwanese patients.[214] On the other hand, in the Samoan population cohort, our analysis found a trend toward significant in the mean BMI of *GCKR* (780094 C>T) genotypes. The mean BMI under the additive model CC (reference) vs. TT (risk genotype) of *GCKR* (780094 C>T) was significantly lower in the TT genotype, around 26.56 compared to 29.72 in CC (reference) genotype of GCKR (p=0.082) (Table 3.9). In addition, in the same Samoan cohort, a significant difference of mean BMI and *LRRC16A* (rs742132 A>G) genotypes were found under additive and recessive models. The mean BMI of the AA genotype of the *LRRC16A* additive model was about 27.47 lower compared to the GG genotype of 28.65 (reference) (p=0.033).

Also, the mean BMI of the AA genotype of the *LRRC16A* recessive model was lower, around 27.47, compared to AG+GG (reference), about 30.31 (p=0.031). (Table 3.9).

Numerous risk factors, both genetic and non-genetic, contribute to the increased risk of cardiometabolic disorders. From a genetic perspective, women of Asian ancestry, mainly Filipino pregnant women, had a higher frequency of HU risk alleles that could partially match their risk of developing metabolic disorders. On the other hand, apart from non-genetic risk factors, both Samoan and Filipino pregnant women show significant non-genetic risk factors, including age and BMI, associated with metabolic disorders.

Limitations

This study is retrospective, so we were limited to a certain number of genetic and nongenetic risk factors. We conducted our investigation between genotypes and phenotypes only on limited UA genetic polymorphisms from the genetic side. Meanwhile, on the nongenetic side, we only assessed age and BMI as predictors associated with developments of CMDs. We believe that other factors associated with CMDs are lifestyle, diet, physical activity, smoking, and alcohol use. The average age of pregnant women in this study was 28 years old, and at this age, the proportion of comorbid disorders is lower than in older age. In addition, the frequency of some UA risk alleles in the presence of diseases was very low, which may have affected the exact results and the exact association between genetic/nongenetic risk factors and cardiometabolic disorders. Finally, the data was convenient, selected from one geographical location and one hospital on the same average age. Further studies should be conducted on a more representative and larger sample size to validate our results.

Conclusion

Our analysis found that HU/gout risk alleles and other factors such as age and BMI are associated with the development of CMDs in the selected Asian-Pacific Islander populations. These study findings are consistent with already published studies that explain the biological function of UA gene heritability and other demographic factors in CMDs development. Genetically, our results have found both Filipinos and Samoans may be at a higher risk of CMDs due to HU risk alleles in *ABCG2* (rs2231142 G>T) and *SLC22A11* (rs17300741 A>G).

Other factors, including age and BMI, are reported as high-risk factors associated with the development of CMDs across both Samoan and Filipino populations. We believe that further studies across different populations will support our hypothesis. Finally, we would say that the difference in the prevalence of comorbid diseases across populations could partially be explained by different genetic backgrounds. Hence, this study suggests that the Asian population in the Filipino subgroup is at a higher risk of CMDs due to numerous risk factors, including both genetic and nongenetic, resulting in potentially serious outcomes in pregnant women.

Table 3.1: Demographic Characteristics across Filipino and Samoan populations				
Characteristics	Total population cohort (n= 1059)	Filipino (n= 229)	Samoan (n= 200)	p-value (Filipino vs Samoans)
Mother's age (years)	28.8±6.3	29.8±6.1*	26.3±5.7*	$1.391e^{-09}$
Gestational age (weeks)	38.0±2.27	37.82±2.27**	38.4±2.0*	0.004
Preterm (<37 weeks)	182 (17.3%)	44 (19.4%)**	27 (13.5%)**	0.17
Full term (≥37 weeks)	871 (82.2%)	183 (80.63%)**	173 (86.5%)**	0.58
Body mass index (kg/m^2)	26.3±6.9	25.0±6.0*	30.1±7.5*	$4.758e^{-}12$
Pre- gravida weight (Ibs)	151.2±46.5	132.7±28.4*	203.7±44.7*	$<2.2e^{-16}$

Table 3.2: Clinical and Social Characteristic among Filipino and Samoan Ethnicities				
Characteristics	Total population cohort (n=1059)	Filipino (n= 229)	Samoan (n= 200)	p-value (Filipino vs Samoans)
Premature labor	169 (15.9%)	36 (15.7%)**	27 (13.5%)**	0.00001
Gestational diabetes mellitus	137 (12.9%)	48 (20.9%)*	23 (11.0%)**	0.0255
Diabetes mellitus	19 (1.8%)	4 (1.7%)**	6 (3.0%)**	0.401
Gestational hypertension	38 (3.6%)	6 (2.6%)**	9 (4.5%)**	0.307
Chronic hypertension	50 (4.7%)	21 (9.1%)*	7 (3.5%)**	0.0259
Mild preeclampsia	41 (3.9%)	10 (4.3%)**	14 (7.0%)**	<0.00001
Severe preeclampsia	15 (1.4)	8 (3.5%)*	4 (2.0%)**	0.1574
Eclampsia	1 (0.1)	1 (0.4%)**	-	-
History of alcohol intake	27 (2.5%)	4 (1.7%)**	4 (2.0%)**	0.01833
History of smoking	162 (15.3%)	17 (7.4%)*	56 (28.0%)**	<0.00001
*Indicates significant value at p <0.05 of Chi-square analysis relative to the total population **Indicate non-significant value at p<0.05 of Chi-square analysis relative to the total population				

Table 3.3: Clinical and Social Characteristic among Asian and Non-Asian population (NHPIs)				
Characteristics	Total population cohort (n=1059)	Asian (n= 543)	NHPIs (n= 516)	p-value (Asian vs NHPIs)
Premature labor	169 (15.9%)	95 (17.5%)**	74 (14.3)**	0.2327
Gestational diabetes mellitus	137 (12.9%)	90 (16.6%)**	47 (9.1%)*	0.0014
Diabetes mellitus	19 (1.8%)	7 (1.3%)**	11 (2.3%)**	0.2972
Gestational hypertension	38 (3.6%)	17 (3.1%)**	21 (4.1%)**	0.4282
Chronic hypertension	50 (4.7%)	36 (6.6%)**	14 (2.7%)**	0.0041
Mild preeclampsia	41 (3.9%)	20 (3.6%)**	21 (4.1%)**	0.7538
Severe preeclampsia	15 (1.4)	10 (1.9%)**	5 (0.9%)**	0.2362
Eclampsia	1 (0.1)	1 (0.18)**	0	-
History of alcohol intake	27 (2.5%)	14 (2.6%)**	13 (2.5%)**	0.9527
History of smoking	162 (15.3%)	39 (7.2%)*	23.8%)*	0.0748
*Indicates significant value at p <0.05 **Indicate non-significant value at p<0.05				

Table 3.4: Association of UA Risk Alleles and CMDs Across the Samoan Subgroup- continue												
Gene (SNP)	**Chronic Hypertension**			**Gestational Hypertension**			**Diabetes Mellitus**			**Gestational Diabetes Mellitus**		
SLC22A12 (rs505802 **C**>T)	**Yes % (N)**	**No % (N)**	**p-value**	**Yes % (N)**	**No % (N)**	**p-value**	**Yes % (N)**	**No % (N)**	**p-value**	**Yes % (N)**	**No % (N)**	**p-value**
Additive												
CC CT TT (Ref.)	33.3 (2) 50 (3) 16.7 (1)	49.4 (88) 38.8 (69) 11.8 (21)	0.59	57.1 (4) 42.9 (3) 0 (0)	48.6 (86) 39.0 (69) 12.4 (22)	0.877	40.0 (2) 20.0 (1) 40.0 (2)	49.2 (88) 39.7 (71) 11.1(20)	0.191	47.6 (10) 38.1 (8) 14.3 (3)	49.0 (80) 39.2 (64) 11.8 (19)	0.895
Dominant												
TT (Ref.) **CT+CC**	16.7 (1) 83.3 (5)	11.8 (21) 88.2 (157)	0.539	0 (0) 100 (7)	12.4 (22) 87.6 (155)	1	40.0 (2) 60.0 (3)	11.2 (20) 88.8 (159)	0.109	14.2 (3) 85.8 (18)	11.6 (19) 88.4 (144)	0.721
Recessive												
CT+TT (Ref.) **CC**	66.7 (4) 33.3 (2)	50.5 (90) 49.5 (88)	0.682	42.9 (3) 57.1 (4)	51.4 (91) 48.6 (86)	0.716	60.0 (3) 40.0 (2)	50.9 (91) 49.1 (88)	1	52.4 (11) 47.6 (10)	51.0 (83) 49.0 (80)	0.899
SLC17A1 (rs1183201 **T**>A)												
Additive												
AA (Ref.) AT **TT**	16.7 (1) 66.6 (4) 16.7 (1)	6.3 (11) 42.9 (75) 50.8 (89)	0.126	(0) 42.8 (3) 57.2 (4)	6.9 (12) 43.7 (76) 49.4 (86)	1	60.0 (3) 40.0 (2) 0 (0)	5.1(9) 43.7 (77) 51.2 (90)	0.0004	10.0 (2) 30.0 (6) 60.0 (12)	6.2 (10) 45.4 (73) 48.4 (78)	0.350
Dominant												
AA (Ref.) **AT+TT**	16.7 (1) 83.3 (5)	6.3 (11) 93.7 (164)	0.341	0 (0) 100 (7)	6.9 (12) 93.1 (162)	1	60.0 (3) 40.0 (2)	5.1 (9) 94.9 (167)	0.002	10.0 (2) 90.0 (18)	6.2 (10) 93.8 (151)	0.625
Recessive												
AA+AT (Ref.) **TT**	83.3 (5) 16.7 (1)	49.2 (86) 50.8 (89)	0.210	42.8 (3) 57.2 (4)	50.6 (88) 49.4 (86)	0.720	100 (5) 0 (0)	48.8 (86) 51.2 (90)	0.059	40.0 (8) 60.0 (12)	51.6 (83) 48.4 (78)	0.329

Table 3.4: Association of UA Risk Alleles and CMDs Across the Samoan Subgroup- continue												
Gene (SNP)	**Chronic Hypertension**			**Gestational Hypertension**			**Diabetes Mellitus**			**Gestational Diabetes Mellitus**		
SLC22A11 (rs17300741 **A**>G)	**Yes % (N)**	**No % (N)**	**p-value**	**Yes % (N)**	**No % (N)**	**p-value**	**Yes % (N)**	**No % (N)**	**p-value**	**Yes % (N)**	**No % (N)**	**p-value**
Additive												
AA AG GG (Ref)	100 (6) (0) (0)	61.2 (106) 32.9 (57) 5.9 (10)	0.193	85.7 (6) 14.3 (1) (0)	61.6 (106) 32.6 (56) 5.8 (10)	0.618	75.0 (3) 25.0 (1) (0)	62.3 (109) 32.0 (56) 5.7 (10)	0.822	80.9 (17) 19.1 (4) 0 (0)	60.1 (95) 33.6 (53) 6.3 (10)	0.196
Dominant												
GG (Ref.) **AG+AA**	(0) 100 (6)	5.8 (10) 94.2 (163)	0.511	0 (0) 100 (7)	5.8 (10) 94.2 (162)	0.511	(0) 100 (4)	5.7 (10) 94.3 (165)	0.622	(0) 100 (21)	6.3 (10) 93.7 (148)	0.609
Recessive												
AG+GG (Ref.) **AA**	(0) **100** (6)	38.8 (67) **61.2** (106)	**0.085**	14.3 (1) 85.7 (6)	38.4 (66) 61.6 (106)	0.258	25.0 (1) 75.0 (3)	37.7 (66) 62.3 (109)	0.603	19.1 (4) **80.9** (17)	39.8 (63) **60.2** (95)	**0.063**
ABCG2 (rs2231142 G>**T**)												
Additive												
GG (Ref.) GT **TT**	66.8 (4) 16.6 (1) 16.6 (1)	48.3 (85) 41.0 (72) 10.7 (19)	0.384	28.6 (2) 71.4 (5) 0 (0)	49.7 (87) 38.8 (68) 11.5 (20)	0.314	40.0 (2) 60.0 (3) 0 (0)	49.2(87) 39.6 (70) 11.2 (20)	0.810	45.0 (9) 45.0 (9) 10.0 (2)	49.4 (80) 39.5 (64) 11.1 (18)	0.941
Dominant												
GG (Ref.) **GT+TT**	66.7 (4) 33.3 (2)	48.3 (85) 51.7 (91)	0.436	28.5 (2) 71.5 (5)	49.7 (87) 50.3 (88)	0.444	40.0 (2) 60.0 (3)	49.1(87) 50.9 (90)	0.686	45.0 (9) 55.0 (11)	49.3 (80) 50.7 (82)	0.711
Recessive												
GG+GT (Ref.) **TT**	83.4 (5) 16.6 (1)	89.2 (157) 10.8 (19)	0.507	100 (7) 0 (0)	88.5 (155) 11.5 (20)	0.343	100 (5) 0 (0)	88.8 (157) 11.2 (20)	0.425	90.0 (18) 10.0 (2)	88.9 (144) 11.1 (18)	0.880

Table 3.4: Association of UA Risk Alleles and CMDs Across the Samoan Subgroup- continue												
Gene (SNP)	**Chronic Hypertension**			**Gestational Hypertension**			**Diabetes Mellitus**			**Gestational Diabetes Mellitus**		
SLC16A9 (rs2242206 G>**T**)	**Yes % (N)**	**No % (N)**	**p-value**	**Yes % (N)**	**No % (N)**	**p-value**	**Yes % (N)**	**No % (N)**	**p-value**	**Yes % (N)**	**No % (N)**	**p-value**
Additive												
GG (Ref.) GT **TT**	33.3 (2) 66.7 (4) 0 (0)	33.0 (58) 55.1 (97) 11.9 (21)	0.651	71.4 (5) 28.6 (2) 0 (0)	31.4 (55) 56.6 (99) 12.0 (21)	0.135	40 (2) 60 (3) (0)	32.8 (58) 55.4 (98) 11.8 (21)	0.708	47.6 (10) 47.6 (10) 4.8 (1)	31.0 (50) 56.6 (91) 12.4 (20)	0.273
Dominant												
GG (Ref.) **GT+TT**	33.3 (2) 66.7 (4)	33.0 (58) 67.0 (118)	0.984	71.4 (5) 28.6 (2)	31.4 (55) 68.6 (120)	0.0400	40.0 (2) 60.0 (3)	32.7 (58) 67.3 (119)	0.665	47.6 (10) 52.4 (11)	31(50) 69 (111)	0.128
Recessive												
GT+GG (Ref.) **TT**	100 (6) 0 (0)	88.1 (155) 11.9 (21)	0.368	100 (7) 0 (0)	88.0 (154) 12.0 (21)	0.329	100 (5) (0)	88.2 (156) 11.8 (21)	0.412	95.2 (20) 4.8 (1)	87.6 (141) 12.4 (20)	0.475
LRRC16A (rs742132 **A**>G)												
Additive												
AA AG GG (Ref.)	16.7 (1) 66.6 (4) 16.7 (1)	25.6 (45) 52.3 (92) 22.1 (39)	0.782	14.2 (1) 42.8 (3) 42.8 (3)	25.7 (45) 53.2 (93) 21.1 (37)	0.510	(0) 60.0 (3) 40.0 (2)	26.0 (46) 52.6 (93) 21.4 (38)	0.333	33.3 (7) 47.6 (10) 19 (4)	24.2 (39) 53.4 (86) 22.4 (36)	0.646
Dominant												
GG (Ref.) **AG+AA**	16.7 (1) 83.3 (5)	22.1 (39) 77.9 (137)	0.749	42.8 (3) 57.2 (4)	21.1 (37) 78.9 (138)	0.18	40.0 (2) 60.0 (3)	21.4 (38) 78.6 (139)	0.302	19.0 (4) 81.0 (17)	22.3 (36) 77.7 (125)	0.730
Recessive												
AG+GG (Ref.) **AA**	83.3 (5) 16.7 (1)	74.4 (131) 25.6 (45)	0.621	85.7 (6) 14.3 (1)	74.3 (130) 25.7 (45)	0.772	100 (5) (0)	74.1 (131) 25.9 (46)	0.332	66.7 (14) 33.3 (7)	75.8 (122) 24.2 (39)	0.366

Table 3.4: Association of UA Risk Alleles and CMDs Across the Samoan Subgroup- continue												
Gene (SNP)	**Chronic Hypertension**			**Gestational Hypertension**			**Diabetes Mellitus**			**Gestational Diabetes Mellitus**		
GCKR (rs780094 C>**T**)	**Yes % (N)**	**No % (N)**	**p-value**	**Yes % (N)**	**No % (N)**	**p-value**	**Yes % (N)**	**No % (N)**	**p-value**	**Yes % (N)**	**No % (N)**	**p-value**
Additive												
CC (Ref.) CT **TT**	33.3 (2) 66.7 (4) 0 (0)	48.6 (86) 41.8 (74) 9.6 (17)	0.563	28.6 (2) 57.1 (4) 14.3 (1)	48.9 (86) 42.0 (74) 9.1 (16)	0.413	60.0 (3) 40.0 (2) (0)	47.8 (85) 42.7 (76) 9.5 (17)	0.727	57.2 (12) 38.1 (8) 4.7 (1)	47.0 (76) 43.2 (70) 9.8 (16)	0.736
Dominant												
CC (Ref.) **CT+TT**	33.3 (2) 66.7 (4)	48.6 (86) 51.4 (91)	0.683	28.5 (2) 71.5 (5)	48.8 (86) 51.2 (90)	0.446	60.0 (3) 40.0 (2)	47.7 (85) 52.3 (93)	0.672	57.1 (12) 42.9 (9)	46.9 (76) 53.1 (86)	0.377
Recessive												
CT+CC (Ref.) **TT**	100 (6) 0 (0)	90.4 (160) 9.6 (17)	0.425	85.7 (6) 14.3(1)	90.9 (160) 9.1 (16)	0.500	100 (5) (0)	90.5 (161) 9.5 (17)	1	95.3 (20) 4.7 (1)	90.2 (146) 9.8 (16)	0.697
The bold letter indicates the UA risk allele (Ref.) Reference												

Table 3.5: Association of UA Risk Alleles and CMDs Across the Filipino Subgroup												
Gene (SNP)	**Chronic Hypertension**			**Gestational Hypertension**			**Diabetes Mellitus**			**Gestational diabetes Mellitus**		
SLC22A12 (rs505802 **C**>T)	**Yes % (N)**	**No % (N)**	**p-value**	**Yes % (N)**	**No % (N)**	**p-value**	**Yes % (N)**	**No % (N)**	**p-value**	**Yes % (N)**	**No % (N)**	**p-value**
Additive												
TT (Ref.) CT **CC**	0 (0) 27.2 (3) 72.8 (8)	4.7 (8) 34.8 (60) 60.5 (104)	0.848	20.0 (1) 20.0 (1) 60.0 (3)	3.9 (7) 34.8 (62) 61.3 (109)	0.247	25.0(1) (0) 75.0 (3)	3.9 (7) 35.2 (63) 60.9 (109)	0.108	0 (0) 45.7 (16) 54.3 (19)	5.4 (8) 31.8 (47) 62.8 (93)	0.162
Dominant												
TT (Ref.) **CT+CC**	0 (0) 100 (11)	4.6 (8) 95.4 (164)	0.464	20.0 (1) 80.0 (4)	3.9 (7) 96.1 (171)	0.202	25.0 (1) 75.0 (3)	3.9 (7) 96.1 (172)	0.165	0 (0) 100 (35)	5.4 (8) 94.6 (140)	0.356
Recessive												
CT+TT (Ref.) **CC**	27.2 (3) 72.8 (8)	39.5 (68) 60.5 (104)	0.533	40.0 (2) 60.0 (3)	38.7 (69) 61.3 (109)	0.955	25.0 (1) 75.0 (3)	39.1 (70) 60.9 (109)	0.947	45.7 (16) 54.3 (19)	37.2 (55) 62.8 (93)	0.440
SLC17A1 (rs1183201 **T**>A)												
Additive												
AA (Ref.) AT **TT**	0 (0) 36.4 (4) 63.6 (7)	4.4 (7) 33.5 (55) 62.1 (102)	1	(0) 60.0 (3) 40.0 (2)	4.1 (7) 33.0 (56) 62.9 (107)	0.467	(0) 75.0 (3) 25.0 (1)	4.1 (7) 32.7 (56) 63.2 (108)	0.257	(0) 35.3 (12) 64.7 (22)	5.0 (7) 33.3 (47) 61.7 (87)	0.579
Dominant												
AA (Ref.) **AT+TT**	(0) 100 (11)	4.3 (7) 95.7 (157)	1	(0) 100 (5)	4.1 (7) 95.9	1	(0) 100 (4)	4.1 (7) 95.9 (164)	1	(0) 100 (34)	4.9 (7) 95.1	0.348

					(163)						(134)	
Recessive												
AA+AT (Ref.) **TT**	63.4 (4) 63.6 (7)	37.8 (62) 62.2 (102)	1	60.0 (3) 40.0 (2)	37.1 (63) 62.9 (107)	0.366	75.0(3) 25.0 (1)	36.8 (63) 63.2 (108)	0.151	35.2 (12) 64.8 (22)	38.3 (54) 61.7 (87)	0.844

Table 3.5: Association of UA Risk Alleles and CMDs Across the Filipino Subgroup- continue

Gene (SNP)	**Chronic Hypertension**			**Gestational Hypertension**			**Diabetes Mellitus**			**Gestational diabetes Mellitus**		
SLC22A11 (rs17300741 **A**>G)	**Yes % (N)**	**No % (N)**	**p-value**	**Yes % (N)**	**No % (N)**	**p-value**	**Yes % (N)**	**No % (N)**	**p-value**	**Yes % (N)**	**No % (N)**	**p-value**
Additive												
AA AG GG (Ref.)	81.8 (9) 18.2 (2) (0)	73.0 (119) 23.9 (39) 3.1 (5)	0.744	75.0 (3) 25.0 (1) (0)	73.5 (125) 23.5 (40) 3.0 (5)	0.940	75.0 (3) 25.0 (1) 0 (0)	73.5 (125) 23.5 (40) 3(5)	0.940	70.5 (24) 29.5 (10) 0 (0)	74.3 (104) 22.2 (31) 3.5 (5)	0.525
Dominant												
GG (Ref.) **AG+AA**	(0) 100 (11)	3.0 (5) 97.0 (158)	1	(0) 100 (4)	2.9 (5) 97.1 (165)	1	(0) 100 (4)	3.0 (5) 97.0 (165)	0.727	(0) 100 (34)	3.5 (5) 96.5 (135)	0.584
Recessive												
AG+GG (Ref.) **AA**	18.2 (2) 81.8 (9)	27.0 (44) 73.0 (119)	0.729	25.0 (1) 75.0 (3)	26.4 (45) 73.6 (125)	0.947	25.0 (1) 75.0 (3)	26.5 (45) 73.5 (125)	0.947	29.5 (10) 70.5 (24)	25.8 (36) 74.2 (104)	0.661
ABCG2 (rs2231142 G>**T**)												
Additive												
GG (Ref.) GT **TT**	18.2 (2) 54.5 (6) 27.3 (3)	29.2 (49) 51.2 (86) 19.6 (33)	0.656	(0) 60.0 (3) 40.0 (2)	29.3 (51) 51.2 (89) 19.5 (34)	0.279	25.0 (1) (0) **75.0** (3)	28.5 (50) 52.6 (92) **18.9** (33)	**0.016**	32.4 (11) 50.0 (17) 17.6 (6)	27.6 (40) 51.7 (75) 20.7 (30)	0.834
Dominant												

GG (Ref.) **GT+TT**	18.2 (2) 81.8 (9)	29.2 (49) 70.8 (119)	0.731	0) 100 (5)	29.3 (51) 70.7 (123)	0.323	25.0 (1) 75.0 (3)	28.5 (50) 71.5 (125)	0.8757	32.3 (11) 67.7 (23)	27.5 (40) 72.5 (105)	0.579
Recessive												
GG+GT (Ref.) **TT**	72.7 (8) 27.3 (3)	80.4 (135) 19.6 (33)	0.464	60.0 (3) 40.0 (2)	80.4 (140) 19.6 (34)	0.263	25.0 (1) **75.0** (3)	81.1 (142) 18.9 (33)	**0.026**	82.4 (28) 17.6 (6)	79.4 (115) 20.6 (30)	0.6904

Table 3.5: The Association of UA Risk Alleles and CMDs Across the Filipino Subgroup- continue												
Gene (SNP)	**Chronic Hypertension**			**Gestational Hypertension**			**Diabetes Mellitus**			**Gestational diabetes Mellitus**		
SLC16A9 (rs2242206 G>**T**)	**Yes % (N)**	**No % (N)**	**p-value**	**Yes % (N)**	**No % (N)**	**p-value**	**Yes % (N)**	**No % (N)**	**p-value**	**Yes % (N)**	**No % (N)**	**p-value**
Additive												
GG (Ref.) GT **TT**	54.5 (6) 45.5 (5) 0 (0)	31.6 (53) 44.0 (74) 24.4 (41)	**0.090**	20.0 (1) 40.0 (2) 40.0 (2)	33.3 (58) 44.3 (77) 22.4 (39)	0.718	25.0 (1) 50.0 (2) 25.0 (1)	33.2 (58) 44.0 (77) 22.8 (40)	0.942	44.1 (15) 29.4 (10) 26.5 (9)	30.4 (44) 47.6 (69) 22 (32)	0.143
Dominant												
GG (Ref.) **GT+TT**	54.5 (6) 45.5 (5)	31.6 (53) 68.4 (115)	0.181	20.0 (1) 80.0 (4)	33.3 (58) 66.7 (116)	0.531	25.0 (1) 75.0 (3)	33.2 (58) 66.8 (117)	1	44.1 (15) 55.9 (19)	30.4 (44) 69.6 (101)	0.124
Recessive												
GT+GG (Ref.) **TT**	100 (11) **0** (0)	75.6 (127) **24.4** (41)	**0.071**	60.0 (3) 40.0 (2)	77.6 (135) 22.4 (39)	0.3226	75.0 (3) 25.0 (1)	77.2 (135) 22.8 (40)	0.919	73.5 (25) 26.5 (9)	78.0 (113) 22.0 (32)	0.582
LRRC16A (rs742132 **A**>G)												
Additive												
GG (Ref.) AG **AA**	9.1 (1) 36.4 (4) 54.5 (6)	9.5 (16) 42.0 (71) 48.5 (82)	0.902	(0) 20.0 (1) 80.0 (4)	9.7 (17) 42.3 (74) 48.0 (84)	0.500	25.0 (1) 50.0 (2) 25.0 (1)	9.1 (16) 41.5 (73) 49.4 (87)	0.298	5.9 (2) 41.2 (14) 52.9 (18)	10.3 (15) 41.8 (61) 47.9 (70)	0.755
Dominant												
GG (Ref.) **AG+AA**	9.1 (1) 90.9 (10)	9.5 (16) 90.5 (153)	1	(0) 100 (5)	9.7 (17) 90.3 (158)	1	25.0 (1) 75.0 (3)	9.1 (16) 90.9 (160)	0.329	5.9 (2) 94.1 (32)	10.3 (15) 89.7 (131)	0.744
Recessive												

AG+GG (Ref.) AA	45.5(5) 54.5 (6)	51.5 (87) 48.5 (82)	0.698	20.0 (1) 80.0 (4)	52.0 (91) 48.0 (84)	0.203	75.0 (3) 25.0 (1)	50.6 (89) 49.4(87)	0.621	47.1 (16) 52.9 (18)	52.1 (76) 47.9 (70)	0.599

Table 3.5: Association of UA Risk Alleles and CMDs Across the Filipino Subgroup- continue												
Gene (SNP)	**Chronic Hypertension**			**Gestational Hypertension**			**Diabetes Mellitus**			**Gestational diabetes Mellitus**		
GCKR (rs780094 C>**T**)	**Yes % (N)**	**No % (N)**	**p-value**	**Yes % (N)**	**No % (N)**	**p-value**	**Yes % (N)**	**No % (N)**	**p-value**	**Yes % (N)**	**No % (N)**	**p-value**
Additive												
CC (Ref.) CT **TT**	27.2 (3) 36.4 (4) 36.4 (4)	32.6 (55) 46.7 (79) 20.7 (35)	0.435	60.0 (3) 20.0 (1) 20.0 (1)	31.4 (55) 46.9 (82) 21.7 (38)	0.368	25.0 (1) 50.0 (2) 25.0 (1)	32.4 (57) 46.0 (81) 21.6 (38)	0.950	29.4 (10) 58.8 (20) 11.8 (4)	32.9 (48) 43.2 (63) 23.9 (35)	0.176
Dominant												
CC (Ref.) **CT+TT**	27.2 (3) 72.8 (8)	32.6 (55) 67.4 (114)	1	60.0 (3) 40.0 (2)	31.4 (55) 68.6 (120)	0.33	25.0 (1) 75.0 (3)	32.4 (57) 67.6 (119)	0.754	29.4 (10) 70.6 (24)	32.8 (48) 67.1 (98)	0.697
Recessive												
CT+CC (Ref.) **TT**	63.6 (7) 36.4 (4)	79.3 (134) 20.7 (35)	0.256	80.0 (4) 20.0 (1)	78.3 (137) 21.7 (38)	0.926	75.0 (3) 25.0 (1)	78.4 (138) 21.6 (38)	0.87	88.2 (30) 11.8 (4)	76.1 (111) 23.9 (35)	0.119
The Bold letter Indicates the UA risk allele (Ref.) Reference												

Table 3.6: Hardy Weinberg Equilibrium (HWE) Assessment of Targeted SNPs		
Gene/SNP	Filipino	Samoan
SLC17A1 (rs1183201)	0.7789	0.3326
PDZK1(rs12129861)	0.0000**	0.0000**
SLC22A11(rs17300741)	0.4439	0.4465
ABCG2 (rs2231142)	0.6376	0.3942
SLC16A9 (rs2242206)	0.1473	0.0275**
SLC22A12 (rs505802)	0.8183	0.2042
SLC2A9 (rs734553)	0.8788	0.8211
LRRC16A (rs742132)	0.8602	0.4492
GCKR (rs780094)	0.3981	0.9620

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

Table 3.7: Association of BMI & Age (non-genetic factors) with Cardiometabolic Diseases (CMDs) in Filipino and Samoan								
	Chronic Hypertension		Gestational Hypertension		Diabetes Mellitus		Gestational diabetes mellitus	
	Filipino (OR CI 95% P-value)	Samoan (OR CI 95% P-value)	Filipino (OR CI 95% P-value)	Samoan (OR CI 95% P-value)	Filipino (OR CI 95% P-value)	Samoan (OR CI 95% P-value)	Filipino (OR CI 95% P-value)	Samoan (OR CI 95% P-value)
Global hypothesis test (p-value)	**0.008**	0.11	0.51	0.07	0.35	0.10	8.03^{-04}	**9.48^{-04}**
BMI	(**1.06** 0.99- 1.13 **0.06**)	(1.08 0.98-1.20 0.10)	(1.07 0.93-1.19 0.19)	(1.10 1.01-1.22 0.031)	(0.98 0.77- 1.16 0.88)	(1.05 0.98- 1.28 0.32)	(1.01 0.96- 1.07 0.512)	(1.03 1.063- 1.254 0.380)
Age	(1.11 1.02- 1.22 **0.013**)	(1.06 0.93- 1.21 0.30)	(1.01 0.85- 1.20 0.86)	(0.93 0.79- 1.06 0.34)	(1.16 0.949- 1.53 0.190)	(1.12 0.98- 1.28 0.07)	(1.11 1.05- 1.19 0.45)	(**1.15** 1.06- 1.25 **0.0006)**
R^2	7.0%	7.0%	3.0%	7.0%	6.0%	8.0%	6.0%	11.0%

Table 3.8: Association between Uric Acid Risk Alleles and BMI across the Filipino Population.						
Gene/SNP	Bartlett test p-value	Sum	Mean	SD	95% CI	ANOVA-p-value
SLC22A11(rs17300741A>G) (Additive)						
AA	0.247	109	25.34	6.74	24.06-26.62	0.371
AG		37	24.26	5.97	22.27-26.25	
GG (Ref.)		5	23.06	3.47	18.74-27.37	
SLC22A11 (Dominant)						
GG (Ref.)	0.157	5	25.34	6.74	24.06-26.62	0.496
AG+AA		146	25.06	6.55	28.33-30.76	
SLC22A11(Recessive)						
AG+GG (Ref.)	0.217	42	24.11	5.71	21.71-35.13	0.299
AA		109	25.34	6.74	24.06-26.62	
SLC22A12 (rs505802 C>T)						
CC	0.1704	94	25.16	6.12	22.71-25.85	0.388
CT		58	25.03	6.91	23.62-26.45	
TT (Ref.)		6	22.95	3.46	22.80-28.72	
SLC22A12 (Dominant)						
TT (Ref.)	0.119	6	25.16	6.12	22.71-25.85	0.413
CT+CC		152	25.11	6.41	24.08-26.14	
SLC22A12 (Recessive)						
CT+TT (Ref.)	0.450	64	24.83	6.67	19.31-26.58	0.754
CC		94	25.16	6.12	22.71-25.85	

Table 3.8: Association between Uric Acid Risk Alleles and BMI across the Filipino Population - continue						
Gene/SNP	Bartlett test p-value	Sum	Mean	SD	95% CI	ANOVA-p-value
ABCG2 (rs2231142 G>T) (Additive)						
GG (Ref.)	0.00243	45	26.88	8.12	24.44-29.32	0.1204
GT		79	24.17	5.64	22.91-25.44	
TT		31	24.04	4.82	22.27-25.81	
ABCG2 (Dominant)						
GG (Ref.)	0.00075	45	26.88	8.12	24.44-29.32	**0.041**
GT+TT		110	24.14	5.40	23.12-25.16	
ABCG2 (Recessive)						
GG+GT (Ref.)	0.030	124	25.16	6.74	19.31-26.58	0.295
TT		31	24.04	4.82	22.27-25.81	
SLC16A9 (rs2242206 G>T) (Additive)						
GG (Ref.)	0.448	56	30.18	7.78	23.28-26.87	0.982
GT		85	29.47	6.82	23.34-26.47	
TT		16	27.7	8.20	22.63-27.04	
SLC16A9 (Dominant)						
GG (Ref.)	0.403	56	30.18	7.78	23.28-26.87	0.416
GT+TT		101	29.19	7.04	27.80-30.58	
SLC16A9 (Recessive)						
GG+GT (Ref.)	0.486	141	29.75	7.20	28.55-30.95	0.287
TT		16	27.7	8.20	22.63-27.04	
GCKR (rs780094) (Additive)						
CC (Ref.)	0.04043	53	24.28	5.69	22.71-25.85	0.614
CT		71	25.04	5.98	23.62-26.45	
TT		32	25.76	8.20	22.80-28.72	
GCKR (Dominant)						
CC (Ref.)	0.180	53	24.28	5.69	22.71-25.85	0.365
CT+TT		103	25.26	6.72	23.95-26.58	
GCKR (Recessive)						
CT+CC (Ref.)	0.011	124	24.71	5.85	23.67-25.75	0.500
TT		32	25.76	8.20	22.80-28.72	

Table 3.8: Association between Uric Acid Risk Alleles and BMI across the Filipino Population- continue						
Gene/SNP	Bartlett test p-value	SUM	Mean	SD	95% CI	ANOVA-p-value
LRRC16A (rs742132 A>G) (Additive)						
AA	0.04307	78	25.78	7.22	24.15-27.41	0.2523
AG		62	24.23	5.38	22.86-25.60	
GG (Ref.)		15	23.54	5.43	20.53-26.55	
LRRC16A (Dominant)						
GG (Ref.)	0.393	15	23.54	5.43	20.53-26.55	0.374
AG+AA		140	25.1	6.50	24.01-26.18	
LRRC16A (Recessive)						
AG+GG (Ref.)	0.0100	77	24.10	5.36	22.88-25.32	0.101
AA		78	25.78	7.22	24.15-27.41	
SLC17A1 (rs1183201 A>T) (Additive)						
AA (Ref.)	0.003144	6	23.71	3.39	20.15-27.27	0.469
AT		47	25.95	8.05	23.58-28.31	
TT		98	24.61	5.56	23.50- 25.73	
SLC17A1 (Dominant)						
AA (Ref.)	0.105	6	23.71	3.39	20.15-27.27	0.618
AT+TT		145	25.04	6.47	23.98-26.11	
SLC17A1 (Recessive)						
AA+AT (Ref.)	0.006	53	25.69	7.68	23.57-27.81	0.368
TT		98	24.61	5.56	23.50- 25.73	

Table 3.9: Association between Uric Acid Risk Alleles and BMI across the Samoan Population.						
Gene/SNP	Bartlett test p-value	Sum	Mean	SD	95% CI	ANOVA-p-value
SLC22A11 (rs17300741 A>G) (Additive)						
AA	0.877	97	29.61	7.53	24.06-26.62	0.921
AG		48	29.42	7.13	22.27-26.25	
GG (Ref.)		8	28.42	8.02	18.74-27.37	
SLC22A11 (Dominant)						
GG (Ref.)	0.759	8	28.42	8.02	18.74-27.37	0.676
AG+AA		145	29.55	7.38	28.33-30.76	
SLc22A11 (Recessive)						
AG+GG (Ref.)	0.711	56	29.28	7.20	28.09-31.12	0.792
AA		97	29.61	7.53	24.06-26.62	
SLC22A12 (rs505802 C>T) (Additive)						
CC	0.7864	79	28.88	7.38	23.91-26.41	0.471
CT		61	30.38	7.48	23.21-26.84	
TT (Ref.)		18	30.14	6.52	19.31-26.58	
SLC22A12 (Dominant)						
TT (Ref.)	0.490	18	30.14	6.52	19.31-26.58	0.718
CT+CC		140	29.53	7.43	28.29-30.78	
SLC22A12 (Recessive)						
CT+TT (Ref.)	0.859	79	30.33	7.23	26.90-33.38	0.214
CC		79	28.88	7.38	23.91-26.41	
ABCG2 (rs2231142 G>T) (Additive)						
GG (Ref.)	0.1618	75	29.22	7.04	24.44-29.32	0.760
GT		64	30.11	6.90	22.91-25.44	
TT		17	29.57	9.69	22.27-25.81	
ABCG2 (Dominant)						
GG (Ref.)	0.574	75	29.22	7.04	24.44-29.32	0.508
GT+TT		81	30	7.51	28.33- 31.66	
ABCG2 (Recessive)						
GG+GT (Ref.)	0.05	139	29.63	6.97	26.90-33.38	0.981
TT		17	29.57	9.69	22.27-25.81	

Table 3.9: Association between Uric Acid Risk Alleles and BMI across the Samoan Population- continue						
Gene/SNP	Bartlett test p-value	SUM	Mean	SD	95% CI	ANOVA-p-value
GCKR (rs780094 C>T) (Additive)						
CC (Ref.)	0.171	77	29.72	7.83	22.71-25.85	**0.082**
CT		66	30.28	6.92	23.62-26.45	
TT		14	26.56	5.19	22.80-28.72	
GCKR (Dominant)						
CC (Ref.)	0.201	77	29.72	7.83	22.71-25.85	0.936
CT+TT		80	29.63	6.77	28.12-31.13	
GCKR (Recessive)						
CT+CC (Ref.)	0.119	143	29.98	7.40	28.75-31.20	0.094
TT		14	26.56	5.19	22.80-28.72	
LRRC16A (rs742132 A>G) (Additive)						
AA	0.414	41	27.47	7.21	24.15-27.41	**0.033**
AG		84	30.92	6.73	24.15-27.41	
GG (Ref.)		31	28.65	8.18	22.86-25.60	
LRRC16A (Dominant)						
GG (Ref.)	0.291	31	28.65	8.18	22.86-25.60	0.437
AG+AA		125	29.79	7.05	28.54-31.04	
LRRC16A9 (Recessive)						
AG+GG (Ref.)	0.976	115	30.31	7.18	28.98-31.64	**0.031**
AA		41	27.47	7.21	24.15-27.41	

Table 3.9: Association between Uric Acid Risk Alleles and BMI across the Samoan Population- continue						
Gene/SNP	Bartlett test p-value	SUM	Mean	SD	95% CI	ANOVA-p-value
SLC17A1 (rs1183201 A>T) (Additive)						
AA (Ref.)	11	29.79	8.76	20.15-27.27		0.393
AT	64	30.46	7.49	23.58-28.31		
TT	81	28.75	7.00	23.50-25.73		
SLC17A1 (Dominant)						
AA (Ref.)	11	29.79	8.76	20.15-27.27		0.902
AT+TT	145	29.50	7.24	28.31-30.69		
SLC17A1 (Recessive)						
AA+AT (Ref.)	75	30.36	7.63	28.60-32.12		0.172
TT	81	28.75	7.00	23.50-25.73		

Table 3.10: Abbreviations	
NHPI	Native Hawaiian and Pacific Islander population
CMDs	Cardiometabolic diseases
DM	Diabetes Mellitus
GDM	Gestational Diabetes Mellitus
CHTN	Chronic hypertension
GHTN	Gestational hypertension
SU	Serum uric acid
PE	Preeclampsia
IR	Insulin resistance
NO	Nitric oxide
PKC	Phosphokinase-c
PI3K	Phospho inositol-3 kinase
BMI	Body Mass Index
IUGR	Intrauterine growth restriction
IUD	Intrauterine death

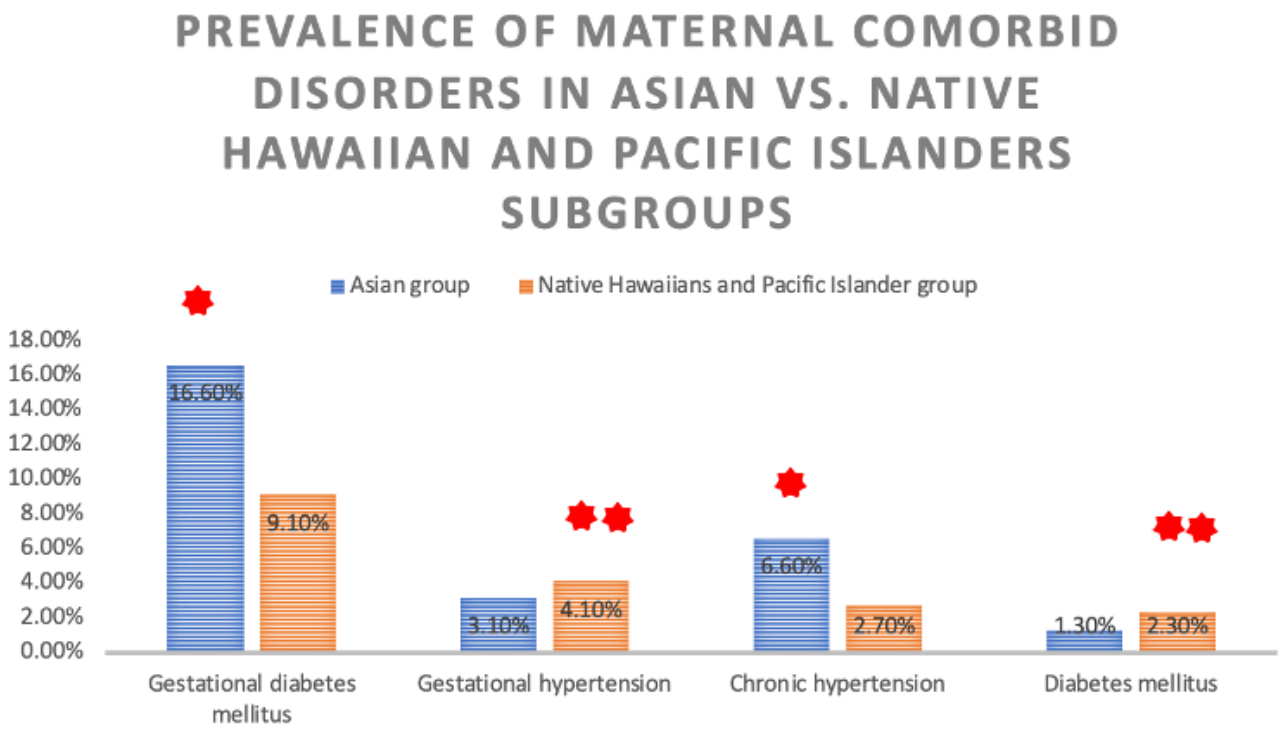


Figure 3.1: The prevalence of comorbid diseases across Asian and native Hawaiian-Pacific Islanders population

The prevalence of GDM and CHTN were significantly higher in Asian versus non-Asian groups (NHPIs) (16.6% versus 9.1%, **P=0.001** and 6.6% versus 2.7%, **P=0.004**, respectively)

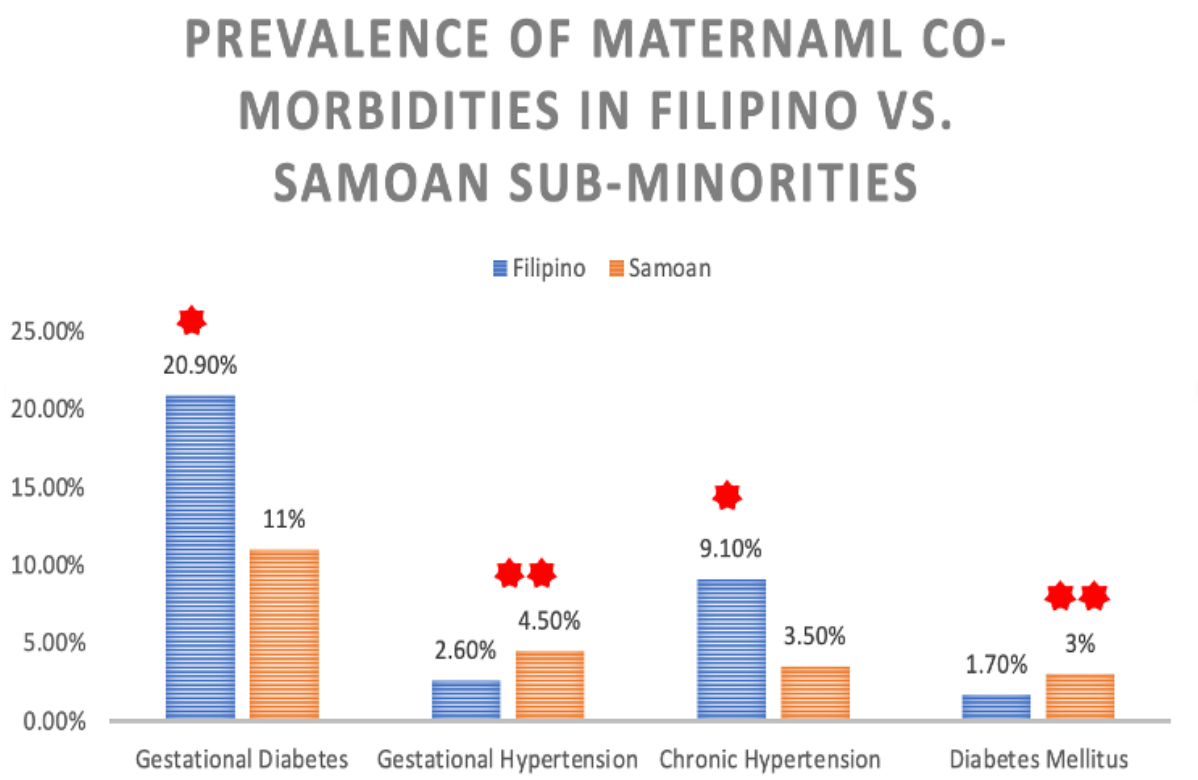
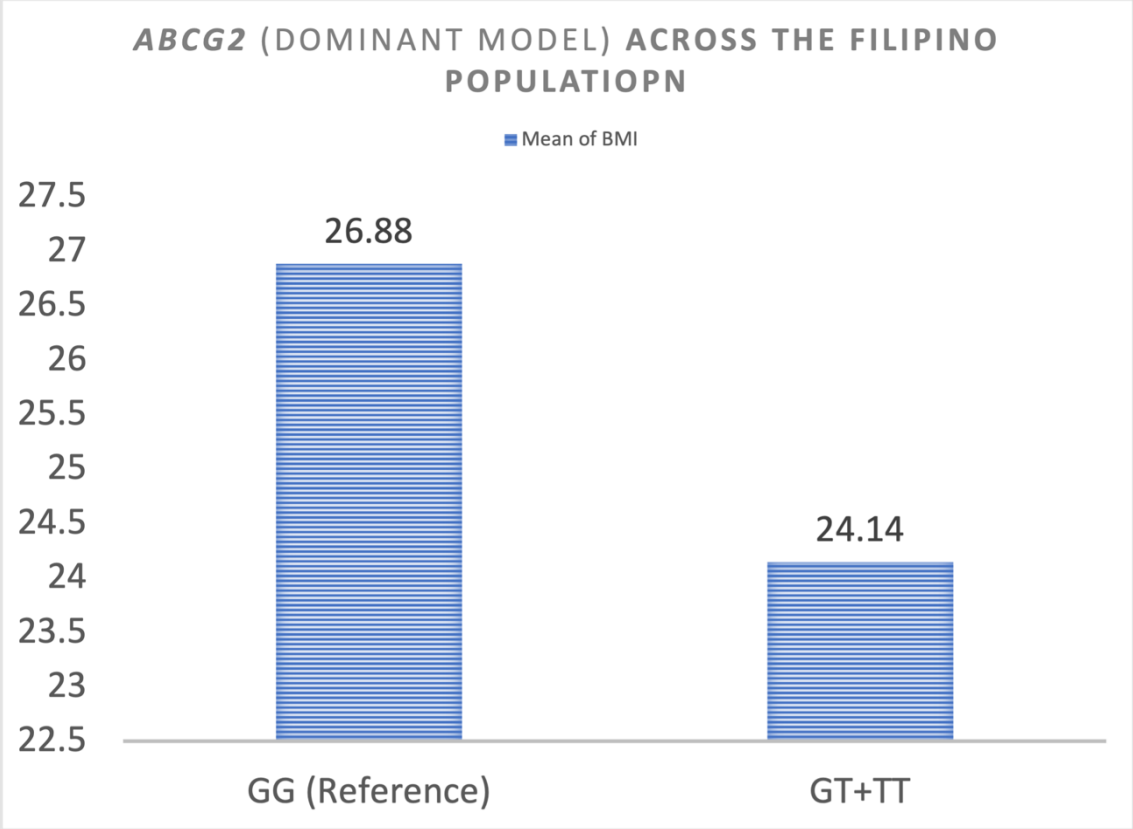


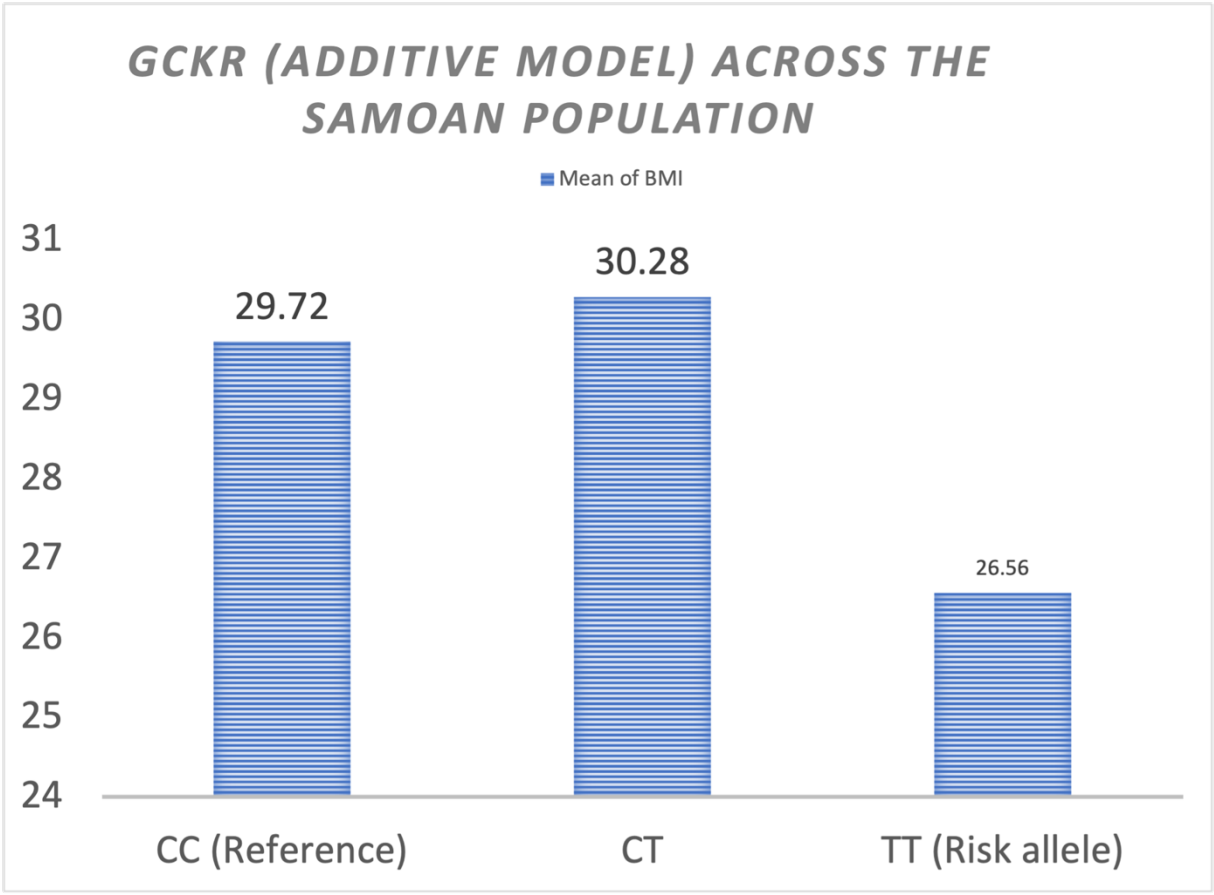
Figure 3.2: The prevalence of comorbid diseases across Filipino and Samoan populations

The prevalence of GDM and CHTN were significantly higher in Filipino versus Samoan (20.9% versus 11%, **P=<0.025** and 9.1% versus 3.5%, **P=0.025**, respectively)



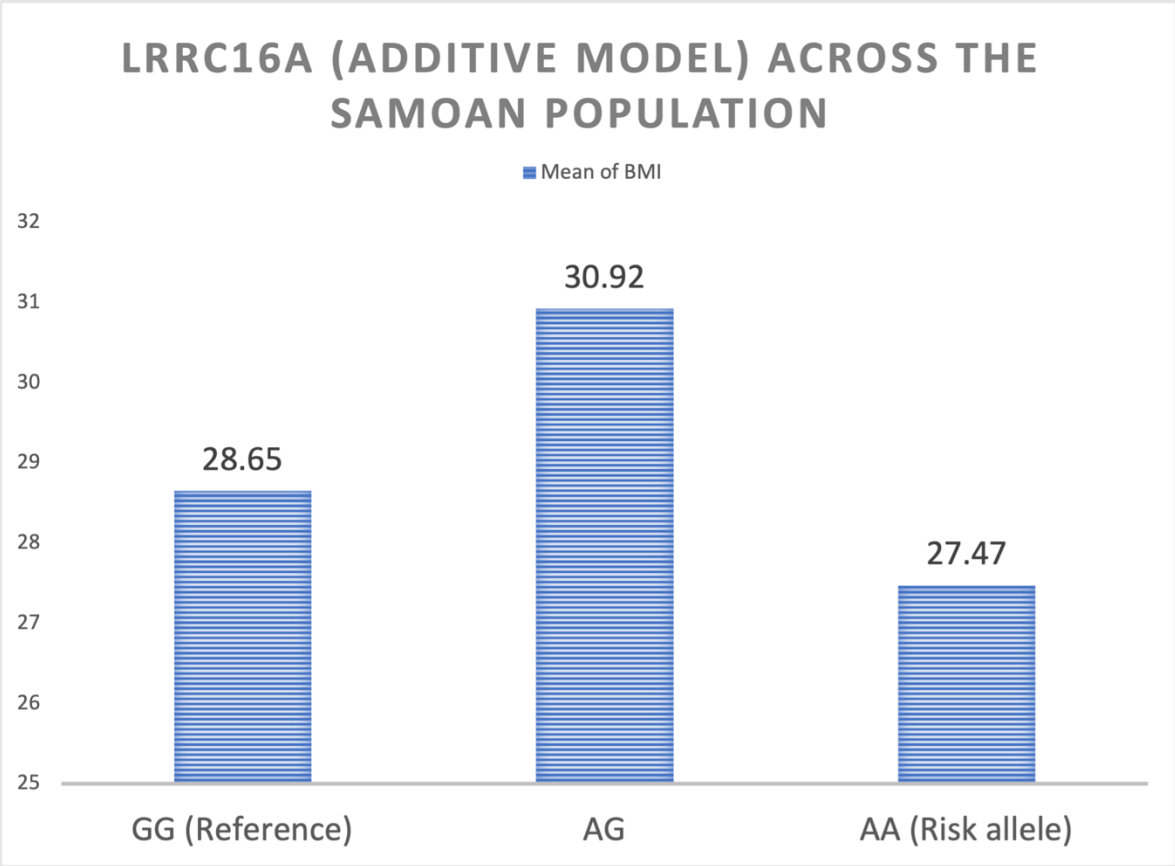
P-value= 0.04

Figure 3.3: Mean of BMI in the dominant model of *ABCG2*/rs2231142 among the Filipino population



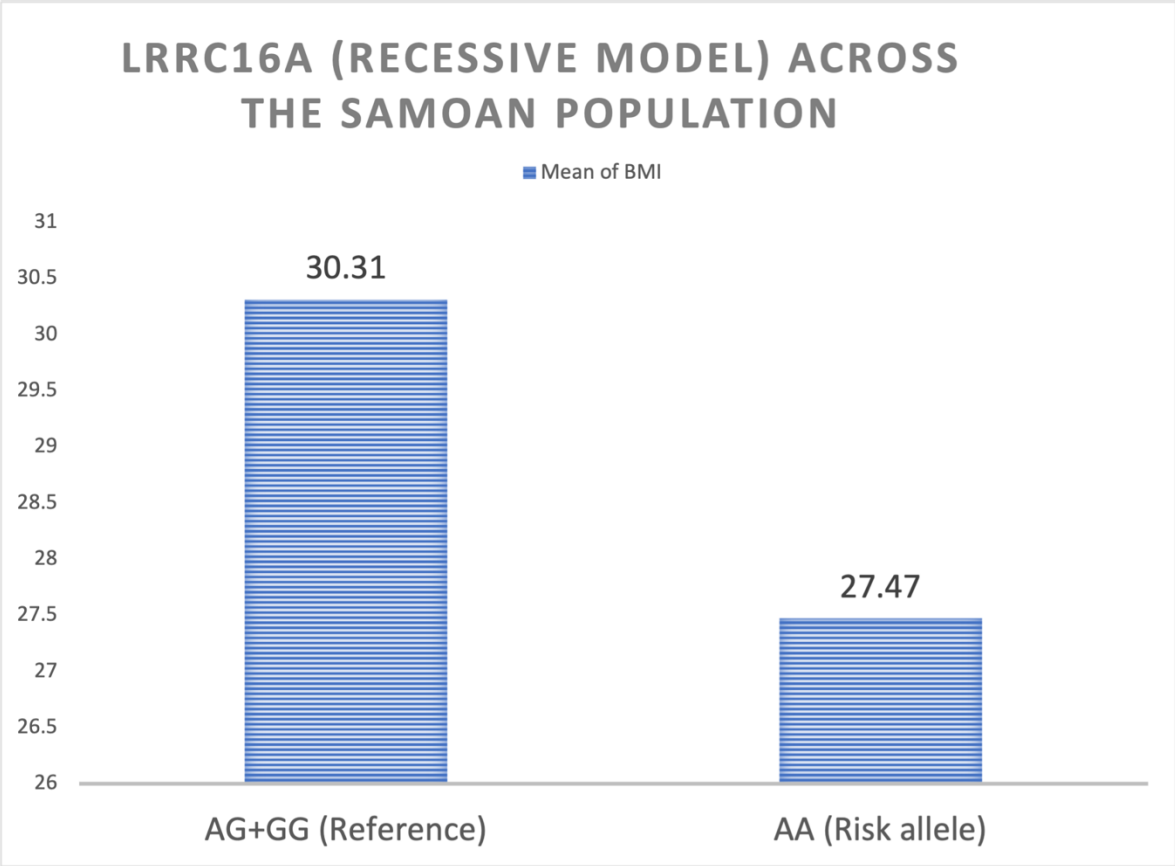
P-value=0.082

Figure 3.4: Mean of BMI in the additive model of *GCKR*/rs2780094 among the Samoan population



P-value=0.033

Figure 3.5: Mean of BMI in the additive model of *LRRC16A*/rs742132 among the Samoan population



P-value=0.031

Figure 3.6: Mean of BMI in the recessive model of *LRRC16A*/rs742132 among the Samoan population

Chapter 4: Overall conclusion

The prevalence of hyperuricemia and gout disease among the US population varies due to differences in genetic backgrounds. Many studies conducted on several racial groups reported that individuals of those racial groups experience a higher rate of hyperuricemia (HU)/gout conditions when compared with Europeans. Participants in this study were selected from the Hawaii area and were of diverse races, confirming that the prevalence of disease variability was not similar between subgroups. The Asian and Pacific Islander groups are two of the largest minorities living in the US; the Filipino minority group is the second largest Asian sub-population after the Chinese sub-group, and the Samoan sub-group is the largest minority group across Pacific Islanders.

This study found that the Asian subgroups, including Filipinos, Koreans, and Japanese, had the highest UA risk alleles relative to other minorities. Moreover, they also had a high prevalence of comorbidities, such as hypertension and diabetes mellitus. Our cross-sectional study was retrospective, and we were limited to specific uric acid (UA) gene/SNPs pairs associated with the development of HU/gout. That limitation provides potential direction in terms of further research opportunities across several UA genes. After analyzing our preliminary findings, we can partially confirm that the Asian population living in the US is at higher risk of rheumatological diseases, particularly HU/gout.

Genetic investigations among different populations could assess and aid knowledge as to why some diseases present higher in some ethnicities when compared to others. These differences detected might provide insights to allow clinicians and clinical researchers to think about the best ways of diagnosing and treating patients. Hence, our results may improve patient and health care outcomes by investigating diseases and selecting the proper drug at the proper dose for individual patients. Also,

genetic testing could enhance both the health care system and patients' treatment options through decreased healthcare costs associated with incorrect prescribing.

Physiologically, the UA transportome genes show a role in metabolic diseases through specific pathological mechanisms. These mechanisms might explain the relationship between UA genes loss of function or polymorphism, and why they can result in some disorders like insulin resistance or elevated blood pressure. Mendelian randomization, for example, suggests that not all patients who have a high UA level would have gout disease, though a high percentage of them might develop cardiometabolic-related complications. UA risk alleles should be considered a predictive diagnostic parameter in metabolic diseases together with other risk factors.

Consistent with the epidemiology of gout, women of child-bearing age are unlikely to develop gout, despite their having the genetic risk factors for HU/gout. The presence of hormones like estrogen plays an essential role in UA excretion in females, particularly premenopausal women. Estrogen is a nuclear hormone and has a role in urate efflux through the increased expression of the *ABCG2* gene, which is responsible for urate excretion. Additionally, the estrogen hormone suppresses the URAT1 genes like *SLC22A12*, causing changes in urate reabsorption activity. Therefore, further studies involving women and men of different ages are needed to compare UA levels more accurately.

In summary, this study's findings add clarity to the prevalence of UA risk alleles among the different populations. The difference in the genetic background across populations could explain a part of HU/gout risk factors and why a prevalence of these conditions vary among different ethnicities. Several investigational studies are essential to validate these results.

Genetic polymorphisms, particularly UA risk alleles, have a role in the development of cardiometabolic syndromes. In the final chapter, we reported on genetic polymorphisms associated with developing different metabolic disorders like diabetes mellitus, gestational diabetes mellitus, and chronic hypertension. The forementioned comorbidities are considered significant risk factors for the maternal preeclampsia (PE), affecting both the mother and fetus. The pathophysiology of PE could partially happen indirectly through metabolic syndromes, and there is a role played by the UA transporter in the progression of metabolic traits. That, in turn, leads to an investigation of the association between UA risk alleles and the development of cardiometabolic diseases (CMDs). Several studies have reported the prevalence of PE in some ethnic groups such as African Americans. On the other hand, limited studies have reported risk factors or causes of PE on different ethnicities. Our study findings add feasibility and clarify information on the diverse populations that have a high risk of developing PE. These results assess and provide more knowledge on health inequalities between different racial groups.

The risk of PE has been reported to have increased up to six-fold between 1980 and 2003 in the US population. Specifically, the Asian-Pacific Islander population living in Hawaii has a higher prevalence of PE. Filipino and Samoan American subgroups have the highest prevalence of comorbidities like gestational diabetes mellitus, which ultimately leads to an increased risk of PE by around 30%. Moreover, PE disease increases the risk of maternal and fetus defects, significantly increasing the associated cost of health care by about $2.18 billion.

These results have shown that Filipinos living in Hawaii are at a higher risk of developing metabolic diseases, particularly diabetes mellitus, due to UA genetic polymorphisms as compared to the Samoan subgroup. This study finding is to be

partially consistent with other studies that reported that Filipino American women in the US had the highest incidence of PE when compared to Chinese and Samoan Pacific Islander women. More studies investigating the relationship between UA genetic defect and prevalence of metabolic disorders will help validate and generalize our results, contributing to personalized medicine in diagnostic and treatment disease approaches.

From a non-genetic perspective, there are many risk factors associated with the development of PE. Examples of these factors include younger/advanced age and body mass index above the normal range. Our findings have shown that the Asian/Pacific Islander population is at a higher risk of cardiometabolic disorders, and that could be partially due to age and BMI, in addition to other risk factors. Besides these risk factors, we believe that other factors associated with PE development include lifestyle, socioeconomic status, and psychological disorders.

These preliminary findings have shown both genetic and non-genetic risk factors associated with developing cardiometabolic disorders. The Asian population, for instance, had significantly higher UA risk alleles and cardiometabolic diseases relative to the native Hawaiian and Pacific Islander populations. Furthermore, the Filipino sub-Asian population had the highest prevalence of both UA risk alleles and cardiometabolic syndromes such as gestational diabetes and chronic hypertension as compared to the Samoan population. Future prospective cross-sectional studies should be conducted on different ages and ethnicities, and large representative sample sizes should be included to validate our results findings.

Future prospective

The risk factors contributing to HU/gout diseases vary across different ethnicities and between males and females. Investigational tools, particularly from a genetic perspective, greatly help detect possible genetic differences between minorities. This

study was retrospectively conducted on only pregnant women. A prospective investigational study on different racial and age groups is necessary to more fully develop our findings. Moreover, the current study was limited to specific UA gene/SNPs from Genome-Wide Association Studies performed on EUR ancestry. Additionally, the sample size was drawn from a limited location with a younger age average.

We believe that these findings could achieve in the creation of personalized treatment options under individual genetic profiles. Detecting genetic polymorphisms that have physiological and pathological roles in diseases could minimize the health disparities between minorities. Conducting community-based research will help engage different populations at higher risks of certain diseases, particularly gout. To our knowledge, this research project is the first study performed on pregnant women from different genetic backgrounds. This study is also the first study that reported the genetic association between UA risk alleles and cardiometabolic complications in pregnant women across different races. These findings could expand the clinical research paradigm to determine ethnicity/race-specific risk factors in regard to patients developing preeclampsia.

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Chapter 6

Appendix

In this section, we would mention how we got these results after doing different statistical analyses. First, we tried to build the logistic regression model to detect an association between phenotypes and UA risk alleles in the different genetic models, adjusting for other covariates, including age and body mass index across the whole sample size. In this test findings, we did not get an exact result because if we aggregated the population into one group, we assume that the variability around whatever covariate, such as SNPs or genotype, is similar across all subgroups. Nevertheless, this is not true because the variability is different around the UA-genotype. Furthermore, we reported that in the appendix **(Section 6.A)** as an example.

Then we decided to focus our hypothesis test on the Filipino population as one group of Asian minorities and Samoan population as one group of Pacific Islander population. Our selection depended on the several factors involved in those ethnicities known as major minorities in the US. It is also they have the largest sample size of participants amongst other populations in the data. In addition, they reported the highest prevalence of both metabolic and maternal conditions in our dataset. (Table 3.2). We started to test our hypothesis that aimed to detect an association between cardiometabolic diseases (CMDs) and both genetic (uric acid (UA) risk alleles) and non-genetic (age/BMI) using logistic regression analysis. In the first step, we conduct a simple logistic model to detect an association between metabolic diseases and BMI covariate, then we add to the model age/BMI. In this analysis, we decided to select both age/BMI as covariates associated with phenotypes **(Section 6.B)**. The selection was based on the global hypothesis test and R^2 results, which explain how close the data are to the fitted regression in both models. (Table 3.7).

Then we were built a model adding other covariates involve UA genotypes besides age/BMI using multiple logistic regression analysis. Unfortunately, the results were uninterpretable because they were biologically and directionally inconsistent with some UA genes toward cardiometabolic diseases **(Section 6.C).** We assumed that might partly be due to the low frequency of the outcomes. Although the multiple logistic regression results were uninterpretable with some genes, it gave us a signal about non-genetic risk factors associated with CMDs developments. These findings led us to think about doing other statistical analyses to figure out the association between cardiometabolic phenotypes and UA genotypes.

We moved to use chi-square or Fisher exact test as appropriate. We found an interesting significant result in several UA genes that are biologically associated with cardiometabolic diseases developments across both Filipino and Samoan populations. It should be noted that these results consistent with the previous study that we found Asians overall and Filipino, in particular, had the highest prevalence of UA risk alleles compared to Pacific Islanders population. (Table 2.5) Moreover, in characteristic clinical information, our results have shown Asian population had a significantly higher metabolic diseases relative to Native Hawaiian and Pacific Islanders. The same analysis has found Filipino population had a significant prevalence of metabolic diseases.
In the final analysis, we conducted univariate (ANOVA) to assess the mean of BMI across the different UA genes. First, we selected equal or unequal ANOVA depend on the Bartlett's test results, which assess the homogeneity of variance (Table 3.8 & Table 3.9). We found mean BMI in some genes consistent with biology and literature amongst the Filipino subgroup, but there was insufficient evidence to support that association. On the other hand, we found a significantly lower mean of BMI in some UA genes in both Filipino and Samoan.

Overall, this study discussed both genetic and genetic risk factors associated with metabolic syndromes in Filipino and Samoan populations using different statistical analyses. These findings were found Asian overall, and Filipino subgroup in particular at high risk of metabolic syndromes due to both UA risk alleles and age/BMI compares to Pacific Islanders population generally and Samoan.

Section 6.A: The logistic regression analysis results across the whole population

Table1. Association between chronic hypertension and UA risk alleles across the whole population sample (Simple Logistic regression)				
Gene/SNP	**Test model**	**Odds Ratio**	**95% CI**	**p-value**
SLC17A1(rs1183201 **T**>A)	Additive			
	AA (Reference) AT TT	0.87	0.541- 1.475	0.614
	Dominant			
	AA (Reference) Vs. AT+TT	**1.68**	0.500- 10.532	0.477
	Recessive			
	AA+AT (Reference) Vs. TT	0.69	0.350- 1.356	0.287
SLC22A12(rs505802 **C**>T**)**	Additive			
	TT (Reference) CT CC	0.73	0.449-1.236	0.225
	Dominant			
	TT (Reference) Vs. CT+CC	0.53	0.204-1.853	0.258
	Recessive			
	CT+TT(Reference) Vs. CC	0.72	0.370-1.424	0.342
GCKR (rs780094 C>**T**)	Additive			
	CC (Reference) CT TT	**1.40**	0.885-2.228	0.147
	Dominant			
	CC (Reference) Vs. CT+TT	**1.27**	0.632-2.723	0.515

	Recessive			
	CT+CC (Reference) Vs. TT	**1.98**	0.9228-4.032	**0.0647**
SLC16A9 (rs2242206 G>**T**)	Additive			
	GG (Reference) GT TT	0.74	0.455-1.189	0.22
	Dominant			
	GG (Reference) Vs. GT+TT	0.87	0.436-1.888	0.729
	Recessive			
	GT+GG (Reference) Vs. TT	0.40	0.120-1.048	0.096
LRRC16A (rs742132 G>**A**)	Additive			
	GG (Reference) AG AA	0.99	0.613-1.655	0.984
	Dominant			
	GG (Reference) Vs. AG+AA	**1.05**	0.409-3.610	0.916
	Recessive			
	AG+GG (Reference) Vs. AA	0.96	0.488-1.888	0.924

Table 1.A. CHTN vs. dominant models of UA genotypes + BMI+ age across the whole population			
Measurements	OR	95% CI	p-value
BMI	1.07	1.027-1.118	0.000984 ***
Mother age	1.13	1.070-1.213	5.37e-05 ***
SLC17A1 (rs1183201 T>A)	1.48	0.382-10.106	0.619781
GCKR (rs780094 C>T)	1.20	0.563-2.730	0.641019

SLC22A12 (rs505802 C>T)	0.48	0.165-1.769	0.215692
SLC16A9 (rs2242206 G>T)	0.80	0.382-1.787	0.578133
LRRC16A (rs742132 G>A)	0.80	0.277-3.023	0.722494

Table 1.B. CHTN vs. recessive models of UA genotypes + BMI+ age across the whole population			
Measurements	OR	95% CI	p-value
BMI	1.07	1.028-1.120	0.000893 ***
Mother age	1.15	1.081-1.229	1.74e-05 ***
SLC17A1 (rs1183201 T>A)	0.38	0.166-0.865	0.023208 *
GCKR (rs780094 C>T)	1.74	0.726-3.880	0.189174
SLC22A12 (rs505802 C>T)	0.63	0.302-1.320	0.220837
SLC16A9 (rs2242206 G>T)	0.34	8.190963e-02 - 1.024	0.091488
LRRC16A (rs742132 G>A)	1.17	0.516-2.650	0.697015

Table2. Association between GHTN and UA risk alleles across the whole population (Logistic regression)				
Gene/SNP	**Test model**	**Odds**	**95% CI**	**p-value**

		Ratio		
SLC17A1(rs1183201 **T**>A)	Additive			
	AA (Reference) AT TT	**1.77**	0.967-3.580	**0.0825**
	Dominant			
	AA (Reference) Vs. AT+TT	**3.00**	0.630- 53.855	0.283
	Recessive			
	AA+AT (Reference) Vs. TT	**1.89**	0.901- 4.236	0.103
*SLC22A1*2 (rs505802 **C**>T**)**	Additive			
	TT (Reference) CT CC	0.68	0.408- 1.193	0.165
	Dominant			
	TT (Reference) Vs. CT+CC	0.34	0.135- 1.038	**0.0341 ***
	Recessive			
	CT+TT(Reference) Vs. CC	0.78	0.384- 1.647	0.521
GCKR (rs780094 C>**T**)	Additive			
	CC (Reference) CT TT	**1.08**	0.655- 1.781	0.743
	Dominant			
	CC (Reference) Vs. CT+TT	**1.17**	0.557- 2.623	0.688
	Recessive			
	CT+CC (Reference) Vs. TT	**1.05**	0.385- 2.445	0.913
SLC16A9 (rs2242206 G>**T**)	Additive			
	GG (Reference) GT TT	0.96	0.577- 1.617	0.904
	Dominant			
	GG (Reference) Vs. GT+TT	0.90	0.421- 2.106	0.805
	Recessive			
	GT+GG	**1.02**	0.402- 2.312	0.952

	(Reference) Vs. TT			
LRRC16A (rs742132 G>**A**)	Additive			
	GG (Reference) AG AA	0.99	0.587- 1.738	0.985
	Dominant			
	GG (Reference) Vs. AG+AA	0.85	0.324- 2.936	0.773
	Recessive			
	AG+GG (Reference) Vs. AA	0.85	0.324- 2.936	0.773

Table 2.A. GHTN vs. dominant models of UA genotypes +BMI+ mother age across the whole population

Measurements	OR	95% CI	p-value
BMI	1.07	1.025-1.121	0.001431 **
Mother age	1.03	0.968-1.105	0.307908
SLC17A1 (rs1183201 T>A)	2.82	0.530-52.824	0.329488
GCKR (rs780094 C>T)	1.36	0.576-3.498	0.497834
SLC22A12 (rs505802 C>T)	0.49	0.152-2.205	0.280605
SLC16A9 (rs2242206 G>T)	0.70	0.307-1.700	0.411459
LRRC16A (rs742132 G>A)	0.55	0.193-2.004	0.307878

Table 2.B. GHTN vs. recessive models of UA genotype +BMI+ mother age across the whole population			
Measurements	OR	95% CI	p-value
BMI	1.07	1.025-1.121	0.00151 **
Mother age	1.03	0.965-1.103	0.35517
SLC17A1 (rs1183201 T>A)	1.89	0.780-4.924	0.16884
GCKR (rs780094 C>T)	0.85	0.240-2.381	0.78913
SLC22A12 (rs505802 C>T)	0.92	0.411-2.150	0.85971
SLC16A9 (rs2242206 G>T)	0.89	0.291-2.292	0.83196
LRRC16A (rs742132 G>A)	0.80	0.335-1.917	0.63180

Table3. Association between DM and UA risk alleles across the whole population sample (Logistic regression)				
Gene/SNP	**Test model**	**Odds Ratio**	**95% CI**	**p-value**
SLC17A1 (rs1183201 **T**>A)	Additive			
	AA (Reference) AT TT	0.35	0.175-0.702	**0.00299 ** **
	Dominant			
	AA (Reference) Vs. AT+TT	0.28	0.095-1.029	**0.032 * **
	Recessive			
	AA+AT (Reference) Vs. TT	0.19	0.045-0.620	**0.012 * **
SLC22A12 (rs505802 **C**>T**)**	Additive			
	TT (Reference) CT CC	0.77	0.378-1.738	0.507
	Dominant			
	TT (Reference) Vs.	0.19	0.066-0.722	**0.00621 ** **

	CT+CC			
	Recessive			
	CT+TT(Reference) Vs. CC	**1.45**	0.523- 4.639	0.493
GCKR (rs780094 C>**T**)	Additive			
	CC (Reference) CT TT	0.56	0.249- 1.162	0.139
	Dominant			
	CC (Reference) Vs. CT+TT	0.42	0.150- 1.149	0.091
	Recessive			
	CT+CC (Reference) Vs. TT	0.62	0.096- 2.248	0.53
SLC16A9(rs2242206 G>**T**)	Additive			
	GG (Reference) GT TT	0.75	0.364- 1.522	0.441
	Dominant			
	GG (Reference) Vs. GT+TT	0.85	0.307- 2.732	0.771
	Recessive			
	GT+GG (Reference) Vs. TT	0.47	0.074- 1.723	0.329
LRRC16A (rs742132 G>**A**)	Additive			
	GG (Reference) AG AA	0.50	0.248- 1.005	**0.0498 ***
	Dominant			
	GG (Reference) Vs. AG+AA	0.56	0.178- 2.495	0.379
	Recessive			
	AG+GG (Reference) Vs. AA	0.27	0.062- 0.857	**0.0445 ***

Table 3.A. DM vs. dominant models of UA genotypes +BMI+ mother age across the whole population

Measurements	OR	95% CI	p-value
BMI	1.07	1.000-1.151	0.035402 *
Mother age	1.21	1.099-1.367	0.000362 ***
SLC17A1 (rs1183201 T>A)	0.18	4.334797e-02-0.911	0.025620 *
GCKR (rs780094 C>T)	0.47	0.142-1.533	0.208353
SLC22A12 (rs505802 C>T)	0.24	6.489311e-02-1.137	0.050988
SLC16A9 (rs2242206 G>T)	0.91	0.279-3.551	0.887322
LRRC16A (rs742132 G>A)	1.00	0.218-6.625	0.992782

Table 3.B. DM vs. recessive models of UA genotypes+ BMI+ mother age across the whole population sample			
Measurements	OR	95% CI	p-value
BMI	1.07	0.998- 1.148	0.041939 *
Mother age	1.21	1.105-1.360	0.000162 ***
SLC17A1 (rs1183201 T>A)	0.20	4.008983e-02-0.749	0.027274 *
GCKR (rs780094 C>T)	0.79	0.118-3.190	0.773659
SLC22A12 (rs505802 C>T)	1.54	0.497-5.422	0.463180
SLC16A9 (rs2242206 G>T)	0.29	0.155-1.585	0.247074
LRRC16A (rs742132 G>A)	0.49	9.984576e-02-1.897	0.336590

Table4. Association between GDM and UA risk alleles across the whole population sample (Logistic regression)				
Gene/SNP	**Test model**	**Odds Ratio**	**95% CI**	**p-value**

SLC17A1 (rs1183201 **T**>A)	Additive			
	AA (Reference) AT TT	**1.42**	1.029-2.000	**0.0374 ***
	Dominant			
	AA (Reference) Vs. AT+TT	**1.28**	0.634- 2.958	0.521
	Recessive			
	AA+AT (Reference) Vs. TT	**1.64**	1.090- 2.498	**0.0188 ***
SLC22A12(rs505802 **C**>T**)**	Additive			
	TT (Reference) CT CC	**1.04**	0.756- 1.453	0.813
	Dominant			
	TT (Reference) Vs. CT+CC	**1.96**	0.785- 6.584	0.201
	Recessive			
	CT+TT(Reference) Vs. CC	0.92	0.623- 1.396	0.723
GCKR (rs780094 C>**T**)	Additive			
	CC (Reference) CT TT	0.90	0.680- 1.192	0.476
	Dominant			
	CC (Reference) Vs. CT+TT	0.861	0.574- 1.304	0.476
	Recessive			
	CT+CC (Reference) Vs. TT	0.88	0.512- 1.473	0.663
SLC16A9 (rs2242206 G>**T**)	Additive			
	GG (Reference) GT TT	0.84	0.635- 1.117	0.238
	Dominant			
	GG (Reference) Vs. GT+TT	0.65	0.432- 0.999	**0.0464 ***
	Recessive			
	GT+GG (Reference)	**1.03**	0.635- 1.632	0.89

	Vs. TT			
LRRC16A (rs742132 G>**A**)	Additive			
	GG (Reference) AG AA	**1.25**	0.931- 1.717	0.141
	Dominant			
	GG (Reference) Vs. AG+AA	**1.57**	0.810- 3.436	0.214
	Recessive			
	AG+GG (Reference) Vs. AA	**1.27**	0.855- 1.898	0.232

Table 4.A. GDM vs. dominant models of UA genotype + BMI+ age across the whole population			
Measurements	OR	95% CI	p-value
BMI	1.04	1.011-1.070	0.00588 **
Mother age	1.10	1.064-1.144	9.12e-08 ***
SLC17A1 (rs1183201 T>A)	1.20	0.526-3.271	0.68266
GCKR (rs780094 C>T)	0.75	0.481-1.185	0.21606
SLC22A12 (rs505802 C>T)	2.00	0.756-6.957	0.20840
SLC16A9 (rs2242206 G>T)	0.62	0.395-0.982	0.03914 *
LRRC16A (rs742132 G>A)	1.95	0.862-5.268	0.14114

Table 4.B. GDM vs. Recessive models of UA genotype + BMI+ age across the whole population

Measurements	OR	95% CI	p-value
BMI	1.03	1.008-1.068	0.00894 **
Mother age	1.10	1.062-1.142	2.02e-07 ***
SLC17A1 (rs1183201 T>A)	1.35	0.842-2.189	0.21441
GCKR (rs780094 C>T)	0.69	0.373-1.219	0.22306
SLC22A12 (rs505802 C>T)	1.04	0.675-1.633	0.84342
SLC16A9 (rs2242206 G>T)	1.16	0.692-1.906	0.55293
LRRC16A (rs742132 G>A)	1.04	0.656-1.649	0.86408

Section 6.B: The simple model between phenotype versus BM and phenotype versus both age/BMI

Association of BMI + Age (non-genetic factors) with Cardiometabolic diseases (CMD) in Filipino and Samoan (Simple model)

A. Filipino subgroup

Chronic hypertension

Filipino, CHTN, (Global test)			
CHTN vs. BMI			
Adjusted R-square	Global statistic	DF	P-value
0.0214	2.797	1	**0.094**

	Filipino, CHTN, (second hypothesis test)			
BMI	OR	SE	95% CI	p-value
	1.05	0.032	0.98- 1.12	**0.081**

Filipino, CHTN, (Global test)			
CHTN vs. BMI + mother age			
Adjusted R-square	Global statistic	DF	P-value
0.07	9.602	2	0.008

	Filipino, CHTN, (second hypothesis test)			
	OR	SE	95% CI	p-value
BMI	1.06	0.033	0.99- 1.13	**0.06**
Age	1.11	0.044	1.02- 1.22	**0.01 ***

Gestational hypertension

Filipino, GHTN, (Global test)			
GHTN vs. BMI			
Adjusted R-square	Global test	DF	P-value
0.0334	1.311	1	0.252

	Filipino, GHTN, (second hypothesis test)			
BMI	OR	SE	95% CI	p-value
	1.07	0.055	0.93- 1.18	0.193

Filipino, GHTN, (Global test)			
GHTN vs. BMI + mother age			
Adjusted R-square	Global test	DF	P-value
0.034	1.34	2	0.511

GHTN, (second hypothesis test)				
	OR	SE	95% CI	p-value
BMI	1.07	0.056	0.93-1.19	0.193
Mothers Age	1.01	0.084	0.85- 1.20	0.860

Diabetes Mellitus

Filipino, DM, (Global test)			
DM vs. BMI			
Adjusted R-square	Global test	DF	P-value
0.0008	1.34	1	0.246

	Filipino, DM, (second hypothesis test)			
BMI	OR	SE	95% CI	p-value
	0.98	0.103	0.76- 1.14	0.877

Filipino, DM, (Global test)			
DM vs. BMI + mother age			
Adjusted R-square	Global Test	DF	P-value
0.067	2.09	2	0.351

Filipino, DM, (second hypothesis test)				
	OR	SE	95% CI	p-value
BMI	0.98	0.101	0.77- 1.16	0.880
Mothers Age	1.16	0.118	0.94- 1.53	0.190

Gestational diabetes mellitus (GDM)

Filipino, GDM, (Global test)			
GDM vs. BMI only			
Adjusted R-square	Global test	DF	P-value
0.0017	0.381	1	0.536

	Filipino, GDM, (second hypothesis test)			
BMI	OR	SE	95% CI	p-value
	1.01	0.026	0.96- 1.07	0.532

Filipino, GDM, (Global test)			
GDM vs. BMI + mother age			
Adjusted R-square	Global test	DF	P-value
0.86	14.25	2	8.03e-04

	Filipino, GDM, (second hypothesis test)			
	OR	SE	95% CI	p-value
BMI	1.01	0.027	0.96- 1.07	0.512
Mothers Age	1.11	0.031	1.05- 1.19	0.457

B. Samoan sub-group

Chronic hypertension

CHTN, (Global test)			
CHTN vs. BMI only			
Adjusted R-square	Global statistic	DF	P-value
0.055	3.243	1	0.071

	Samoan, CHTN, (second hypothesis test)			
BMI	OR	SE	95% CI	p-value
	1.09	0.051	0.99- 1.21	0.075

Samoan, CHTN, (Global test)			
CHTN vs. BMI + mother age			
Adjusted R-square	Global statistic	DF	P-value
0.07	4.25	2	0.119

	Samoan, CHTN, (second hypothesis test)			
	OR	SE	95% CI	p-value
BMI	1.08	0.051	0.98-1.20	0.103
Age	1.06	0.064	0.93- 1.21	0.304

Gestational hypertension

Samoan, GHTN, (Global test)			
GHTN vs. BMI only			
Adjusted R-square	Global statistic	DF	P-value
0.0598	4.241	1	0.039

	Samoan, GHTN, (second hypothesis test)			
BMI	OR	SE	95% CI	p-value
	1.09	0.045	1.004- 1.205	0.042 *

Samoan, GHTN, (Global test)			
GHTN vs. BMI + mother age			
Adjusted R-square	Global statistic	DF	P-value
0.073	5.242	2	**0.072**

	Samoan, GHTN, (second hypothesis test)			
	OR	SE	95% CI	p-value
BMI	**1.10**	0.048	1.01- 1.22	**0.031 ***
Age	0.93	0.071	0.79- 1.06	0.341

Diabetes mellitus

Samoan, DM, (Global test)			
DM vs. BMI only			
Adjusted R-square	Global statistic	DF	P-value
0.026	1.39	1	0.237

Samoan, DM, (second hypothesis test)				
BMI	OR	SE	95% CI	p-value
	1.06	0.053	0.95- 1.18	0.236

Samoan, DM, (Global test)			
DM vs. BMI + mother age			
Adjusted R-square	Global statistic	DF	P-value
0.086	4.49	2	0.105

Samoan, DM, (second hypothesis test)				
	OR	SE	95% CI	p-value
BMI	1.05	0.054	0.94- 1.17	0.328
Age	**1.12**	0.066	0.98- 1.28	**0.074**

Gestational diabetes mellitus

Samoan, GDM, (Global test)			
GDM vs. BMI only			
Adjusted R-square	Global statistic	DF	P-value
0.014	1.71	1	0.189

Samoan, GDM, (second hypothesis test)				
BMI	OR	SE	95% CI	p-value
	1.04	0.031	0.97- 1.11	0.189

Samoan, GDM, (Global test)			
GDM vs. BMI + mother age			
Adjusted R-square	Global statistic	DF	P-value
0.116	13.92	2	**9.48e-04**

Samoan, GDM, (second hypothesis test)				
	OR	SE	95% CI	p-value
BMI	1.03	0.033	0.96- 1.10	0.380
Age	1.15	0.041	1.06- 1.25	**0.0006** ***

Table1. A. Shows the global hypothesis test results of multiple logistic regression (additive model) of chronic hypertension (CHTN) vs. BMI + Mother's age + uric acid (UA) genes across the Filipino population			
Adjusted R-square	Test statistic	DF	p-value
0.17	12.69	9	0.177

Section 6.C. multiple logistic regression analyses conducting on the separate groups

Table 1.A.1 Shows the secondary hypothesis results of multiple logistic regression of CHTN vs. BMI+ mother age+ Additive model of UA genes across the Filipino population			
Measurements	OR	95% CI	p-value
BMI	1.03	0.92-1.14	0.490
Mother age	1.14	1.01-1.31	**0.047***
SLC17A1 (rs1183201 **T**>A)	0.87	0.24-3.88	0.848
GCKR (rs780094 C>**T**)	0.94	0.35-2.48	0.913
SLC22A12 (rs505802 **C**>T)	1.31	0.39-6.75	0.713
SLC16A9 (rs2242206 G>**T**)	0.33	0.08-0.99	**0.070**
LRRC16A (rs742132 G>**A**)	1.21	0.40-4.30	0.741
SLC22A11(rs17300741	2.05	0.50-15.04	0.385
ABCG2(rs2231142 G>**T**)	1.27	0.44-3.66	0.648

Table 1.B. Shows the global hypothesis test results of multiple logistic regression (dominant model) of CHTN vs. BMI + Mother's age + UA genes across the Filipino population			
Adjusted R-square	Test statistic	DF	p-value
0.16	12.23	9	0.200

Table 1.B.1. Shows the secondary hypothesis results of multiple logistic regression of CHTN vs. BMI+ mother age+ Dominant models of UA genes across the Filipino population			
Measurements	OR	95% CI	p-value
BMI	1.03	0.93- 1.13	0.489
Mother age	1.15	1.02- 1.32	0.032 *
SLC17A1 (rs1183201 **T**>A)	1.06e+07	2.86e-90-NA	0.995
GCKR (rs780094 C>**T**)	7.84e-01	018- 4.08	0.751
SLC22A12 (rs505802 **C**>T)	7.10e+06	5.81e-81-NA	0.995
SLC16A9 (rs2242206 G>**T**)	0.36	8.28e-02- 1.49	0.162
LRRC16A (rs742132 G>**A**)	0.70	9.01e-02- 1.51e+01	0.769
SLC22A11(rs17300741 **A**>G)	8.35e+06	4.899638e-64- NA	0.995
ABCG2(rs2231142 G>**T**)	1.82	0.36-14.23	0.500

Table 1.C. Shows the global hypothesis test results of multiple logistic regression of CHTN vs. BMI + Mother's age + UA genes across the Filipino population			
Adjusted R-square	Test statistic	DF	p-value
0.19	12.36	9	0.193

Table 1.C.1 Shows the secondary hypothesis results of multiple logistic regression of CHTN vs. BMI+ mother age+ Recessive models of UA genes across the Filipino population

Measurements	OR	95% CI	p-value
BMI	1.06	0.95- 1.16	0.233
Mother age	1.15	1.01- 1.36	0.049*
SLC17A1 (rs1183201 **T**>A)	0.68	0.14- 3.59	0.641
GCKR (rs780094 C>T)	2.06	0.25- 1.32	0.449
SLC22A12 (rs505802 **C**>T)	1.58	0.35- 8.60	0.562
SLC16A9 (rs2242206 G>**T**)	2.90e-08	NA - 7.40e+49	0.99
LRRC16A (rs742132 G>**A**)	1.21	0.24- 6.33	0.810
SLC22A11(rs17300741 **A**>G)	2.30	0.43-18. 82	0.367
ABCG2(rs2231142 G>**T**)	1.12	0.14- 6.18	0.896

Table 2.A. Shows the global hypothesis test results of multiple logistic regression of diabetes mellitus (DM) vs. BMI + Mother's age + UA genes across the Filipino population			
Adjusted R-square	Test statistic	DF	p-value
0.17	5.19	9	0.816

Table 2.A.1 Shows the secondary hypothesis results of DM vs. BMI+ mother age+ Additive models of UA genes across the Filipino population			
Measurements	OR	95% CI	p-value
BMI	0.99	0.78- 1.21	0.970
Mother age	1.16	0.92-1.64	0.260
SLC17A1 (rs1183201 **T**>A)	0.74	8.51e-02 - 7.51	0.778
GCKR (rs780094 C>**T**)	1.04	0.19- 5.57	0.958
SLC22A12 (rs505802 **C**>T)	0.48	5.74e-02 - 4.40	0.482
SLC16A9 (rs2242206 G>**T**)	0.56	6.05e-02 - 3.98	0.574
LRRC16A (rs742132 G>**A**)	0.37	4.35e-02 - 2.38	0.306
SLC22A11 (17300741 **A**>G)	1.00	0.10 - 27.68	0.995
ABCG2(rs2231142 G>**T**)	2.39	0.38 - 20.50	0.362

Table 2.B. Shows the global hypothesis test results of multiple logistic regression

of DM vs. BMI + Mother's age + UA genes across Filipino population			
Adjusted R-square	Test statistic	DF	p-value
0.36	10.59	9	0.304

Table 2.B.1 Shows the secondary hypothesis results of logistic regression of DM vs. BMI+ mother age+ Dominant models of UA genes across the Filipino population			
Measurements	OR	95% CI	p-value
BMI	0.97	0.74 - 1.21	0.858
Mother age	1.32	1.01- 2.06	0.091
SLC17A1 (rs1183201 **T**>A)	1.154e+08	5.24e-192 – NA	0.996
GCKR (rs780094 C>**T**)	2.00	0.10 - 78.61	0.659
SLC22A12 (rs505802 **C**>T)	3.98e-03	1.46e-06 - 0.34	0.038 *
SLC16A9 (rs2242206 G>**T**)	0.67	4.11e-02 - 17.83	0.775
LRRC16A (rs742132 G>**A**)	9.95e-03	1.72e-06 - 0.86	0.097
SLC22A11 (17300741 **A**>G)	4.51e+06	3.13e-234 – NA	0.997
ABCG2(rs2231142 G>**T**)	0.10	1.19e-04 - 5.31	0.314

Table 2.C. Shows the global hypothesis test results of multiple logistic regression of DM vs. BMI + Mother's age + *UA* genes across the Filipino population			
Adjusted R-square	Test statistic	DF	p-value
0.26	7.64	9	0.570

Table 2.C.1 Shows the secondary hypothesis results of DM vs. BMI+ mother age+ Recessive models of UA genes across the Filipino population			
Measurements	OR	95% CI	p-value
BMI	0.90	0.71- 1.18	0.708
Mother age	1.15	0.91- 1.61	0.279
SLC17A1 (rs1183201 **T**>A)	0.23	8.14e-03 - 3.47	0.303
GCKR (rs780094 C>**T**)	1.63	6.53e-02 – 24.40	0.717
SLC22A12 (rs505802	1.97	0.14 – 54.02	0.624

C>T)			
SLC16A9 (rs2242206 G>**T**)	7.92e-08	NA - 1.08e+160	0.995
LRRC16A (rs742132 G>**A**)	0.57	2.27e-02 - 7.83	0.685
SLC22A11(17300741 **A**>G)	0.62	3.56e-02 – 15.79	0.731
ABCG2(rs2231142 G>**T**)	6.97	0.581 - 1.73e+02	0.139

Table 3.A. Shows the global hypothesis test results of multiple logistic regression of gestational hypertension (GHTN) vs. BMI + Mother's age + UA genes across Filipino population

Adjusted R-square	Test statistic	DF	p-value
0.71	15.00	9	0.090

Table 3.A.1 Shows the secondary hypothesis results of GHTN vs. BMI+ mother age+ Additive models of UA genes across Filipino population

Measurements	OR	95% CI	p-value
BMI	0.69	0.21 - 1.60	0.518
Mother age	013	1.55e-03 – 0.52	0.358
SLC17A1 (rs1183201 **T**>A)	7.59e+13	0.00 - NA	0.998
GCKR (rs780094 C>**T**)	4.60e-02	4.95e-12 - 5.08e+03	0.654
SLC22A12 (rs505802 **C**>T)	2.09e-07	2.03e-24 - 2.15e-02	0.411
SLC16A9 (rs2242206 G>**T**)	1.73e-02	1.03e-05 - 1.34	0.261
LRRC16A (rs742132 G>**A**)	5.52e+20	0.0000 – NA	0.996
SLC22A11 (17300741 **A**>G)	2.82e+12	0.0000 - NA	0.998
ABCG2(rs2231142 G>**T**)	1.81e+10	1.64e+03 - 5.07e+33	0.368

Table 3.B. Shows the global hypothesis test results of multiple logistic regression of GHTN vs. BMI + Mother's age + UA genes across the Filipino population			
Adjusted R-square	Test statistic	DF	p-value
0.33	6.97	9	0.639

Table 3.B.1 Shows the secondary hypothesis results of GHTN vs. BMI+ mother age+ Dominant model of UA genes across Filipino population			
Measurements	OR	95% CI	p-value
BMI	1.23	0.97 - 1.686	0.098
Mother age	0.82	0.54 - 1.142	0.264
SLC17A1 (rs1183201 **T**>A)	4.65e+06	0.0000 – NA	0.999
GCKR (rs780094 C>**T**)	0.28	0.007 - 9.126	0.425
SLC22A12 (rs505802 **C**>T)	1.96e+07	0.0000 - NA	0.999
SLC16A9 (rs2242206 G>**T**)	0.37	0.009 - 19.681	0.573
LRRC16A (rs742132 G>**A**)	4.22e+07	0.000 - NA	0.998
SLC22A11(17300741 **A**>G)	1.26e+08	0.000 - NA	0.999
ABCG2(rs2231142 G>**T**)	3.18e+09	0.000 - NA	0.996

Table 3.C. Shows the global hypothesis test results of multiple logistic regression of GHTN vs. BMI + Mother's age + UA genes across the Filipino population			
Adjusted R-square	Test statistic	DF	p-value
0.64	13.66	9	0.134

Table 3.C.1 Shows the secondary hypothesis results of multiple logistic regression of GHTN vs. BMI+ mother age+ Recessive model of UA genes across the Filipino population			
Measurements	OR	95% CI	p-value
BMI	1.09	0.52-2.16	0.760

Mother age	0.57	7.85e-02 - 1.10	0.326
SLC17A1 (rs1183201 **T**>A)	9.68e+08	0.0000 – NA	0.998
GCKR (rs780094 C>**T**)	3.05e-06	NA - INF	0.999
SLC22A12 (rs505802 **C**>T)	3.37e-02	8.782e- 07 - 6.06	0.356
SLC16A9 (rs2242206 G>**T**)	2.38e-10	NA – INF	0.999
LRRC16A (rs742132 G>**A**)	3.29e+10	0.000 – NA	0.998
SLC22A11(17300741 **A**>G)	2.54e+11	0.000 – NA	0.998
ABCG2(rs2231142 G>**T**)	8.52e+02	0.17 - 3.69e+14	0.371

Table 4.A. Shows the global hypothesis test results of multiple logistic regression of gestational diabetes (GDM) vs. BMI + Mother's age + UA genes additive model across the Filipino population

Adjusted R-square	Test statistic	DF	p-value
0.06	9.72	9.0	0.37

Table 4.A.1 Shows the secondary hypothesis results of multiple logistic regression of GDM vs. BMI+ mother age+ dominant models of UA genes across the Filipino population

Measurements	OR	95% CI	p-value
BMI	1.00	-0.05-0.07	0.799
Mother age	1.09	.027-0.16	0.007
SLC17A1 (rs1183201 **T**>A)	1.11	-0.67-0.95	0.787
GCKR (rs780094 C>**T**)	0.71	-0.91-0.23	0.254
SLC22A12 (rs505802 **C**>T)	0.98	-0.73-0.75	0.978
SLC16A9 (rs2242206 G>**T**)	0.82	-0.76-0.38	0.521
LRRC16A (rs742132 G>**A**)	1.02	-0.63-0.70	0.936
ABCG2(rs2231142 G>**T**)	0.80	-0.79-0.38	0.508
SLC22A11 (17300741 **A**>G)	1.22	-0.54-1.04	0.607

Table 4.B. Shows the global hypothesis test results of multiple logistic regression of GDM vs. BMI + Mother's age + UA genes in dominant model across the Filipino population			
Adjusted R-square	Test statistic	DF	p-value
0.12	19.38	9.0	0.022

Table 4.B.1 Shows the secondary hypothesis results of multiple logistic regression of GDM vs. BMI+ mother age+ dominant model of UA genes across the Filipino population			
Measurements	OR	95% CI	p-value
BMI	9.9^{-01}	-0.07-0.05	0.985
Mother age	1.09	0.02-0.16	0.009
SLC17A1 (rs1183201 **T**>A)	1.70^{+07}	-147.13-NA	0.992
GCKR (rs780094 C>**T**)	8.67^{-01}	-1.03-0.78	0.758
SLC22A12 (rs505802 **C**>T)	1.52^{+07}	-161.88-NA	0.992
SLC16A9 (rs2242206 G>**T**)	5.49^{-01}	-1.44-0.26	0.168
LRRC16A (rs742132 G>**A**)	1.47	-1.10-2.34	0.643
ABCG2(rs2231142 G>**T**)	7.77^{-01}	-160-0.68	0.589
SLC22A11 (17300741 **A**>G)	1.58^{+07}	3.12-	0.992

Table 4.C. Shows the global hypothesis test results of multiple logistic regression of GDM vs. BMI + Mother's age + uric acid genes across Filipino population (recessive)			
Adjusted R-square	Test statistic	DF	p-value
0.08	12.7	9.0	0.173

Table 4.C.1 Shows the secondary hypothesis results of GDM vs. BMI+ mother age+ Recessive models of UA genes across the Filipino population			
Measurements	OR	95% CI	p-value

BMI	1.01	-0.05-0.07	0.699
Mother age	1.10	0.03-0.17	0.004
SLC17A1 (rs1183201 **T**>A)	1.00	-0.91-0.96	0.994
GCKR (rs780094 C>**T**)	0.31	-2.46—0.08	0.051
SLC22A12 (rs505802 **C**>T)	0.97	-0.86-0.84	0.957
SLC16A9 (rs2242206 G>**T**)	1.42	-0.65-1.30	0.478
LRRC16A (rs742132 G>**A**)	0.91	-0.96-0.80	0.851
ABCG2(rs2231142 G>**T**)	0.74	-1.41-0.70	0.582
SLC22A11 (17300741 **A**>G)	0.90	-0.98-0.83	0.829