# The Effects of Risk Alleles for Gestational Diabetes Mellitus on Type 2 Diabetes Mellitus in Samoan Women

by

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## ABSTRACT

Gestational diabetes mellitus (GDM) is a type of diabetes diagnosed during pregnancy and is associated with increased risk of complications during pregnancy as well as long term health conditions for mother and child. Fifty percent of women affected with GDM will subsequently develop type two diabetes mellitus (T2DM). Because family history is a risk factor for GDM, previous research has explored the association of genetic risk factors and GDM. In general, Pacific Islanders have a high prevalence of GDM, and Samoans, specifically, have high rates of obesity, a risk factor for both T2DM and GDM. Thus, Samoans are at high-risk for development of T2DM and GDM, but the relationship of genetic variants and GDM in Samoans is unknown. Using data from a previous study, association between seven variants (reported to be associated with GDM in other populations) and T2DM status, as a surrogate for GDM. Because neither pregnancy nor GDM data were measured for females, males were used as the control group.

A variant in the CDKAL1 locus (rs7754840) was significantly associated with T2DM status ($p<0.006$). Compared to women who were homozygous for the G allele (GG), women who were heterozygous CG or homozygous CC had higher odds of developing T2DM (OR = 1.429, CI = 1.006–2.020, $p < 0.006$ and OR = 1.834, CI = 1.262–2.668, $p < 0.006$, respectively). The magnitude of the effect on diabetes status is comparable to previous reports. None of the SNVs were significantly associated with diabetes status in the men.

Additional studies should include pregnancy and GDM data to further investigate the effect of thee risk alleles and provide additional insights regarding genetic risk factors. This information

would subsequently be used to identify women at higher risk for GDM and T2DM, develop intervention to mitigate this increased risk, and reduce development of T2DM and improve public health.

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# PREFACE

We would like to thank the Samoan participants and local village authorities and research assistants over the years. We acknowledge the support of our research collaboration with the Samoa Ministry of Health; the Samoa Bureau of Statistics; and the Samoa Ministry of Women, Community and Social Development. The Samoan Obesity, Lifestyle, and Genetics Adaptations (OLaGA) Study Group investigators are Ranjan Deka, Jenna Carlson, Kima Fa‘asalele-Savusa, Nicola L. Hawley, Vaimoana Lupematisila, Stephen T. McGarvey, Ryan L. Minster, Leausa Toleafoa Take Naseri, Muagututi‘a Sefuiva Reupena, Melania Selu, John Tuitele, Asiata Satupa‘itea Viali and Daniel E. Weeks.

# 1.0 INTRODUCTION

## 1.1 PUBLIC HEALTH BURDEN OF GESTATIONAL DIABETES MELLITUS (GDM)

Gestational diabetes mellitus (GDM), a type of diabetes diagnosed during pregnancy, is associated with an increased risk of developing a myriad of health complications for both mother and child. GDM is estimated to affect 7%–10% of all pregnancies globally. Prevalence can vary by population given differing frequencies of risk factors (Behboudi-Gandevani, Amiri, Bidhendi Yarandi, & Ramezani Tehrani, 2019; Zhu & Zhang, 2016). Prevalence of GDM is highest in the Middle East and North Africa with a median estimate of 12.9%, followed by Southeast Asia and Western Pacific regions with an estimated prevalence of 11.2%–11.7%. Europe has the lowest prevalence of GDM, with a median of 5.8% (Zhu & Zhang, 2016).

Estimates of GDM prevalence across regions of the world are limited by a number of factors, such as population characteristics, screening practices, and diagnostic criteria. For example, the United States screens 87.5%–96.5% of all pregnant women for GDM. On the other hand, Sweden practices a risk-factor-based screening and only 30.7% of pregnant women meeting criteria are screened for GDM (Zhu & Zhang, 2016). Diagnostic criteria have changed over the past few decades, and when a country has adopted the new criteria this greatly affects the reported prevalence of GDM. For example, adopting a diagnosis of GDM using a lower threshold for glucose tolerance will result in higher prevalence of disease. A population study in Brazil revealed a 15.7% difference in prevalence when using the International Association of Diabetes and Pregnancy Study Groups (IADPSG) (18% prevalence) criteria versus using the 2010 American Diabetes Association criteria (2.7% prevalence) (Trujillo et al., 2015).

Risk factors for developing GDM include older maternal age, pre-pregnancy obesity, excessive gestational weight gain, and family history of GDM and/or type 2 diabetes mellitus (T2DM) (Price, Lock, Archer, & Ahmed, 2017). The prevalence of risk factors varies across populations and should be considered when comparing prevalence of GDM across regions and countries. For example, the prevalence of orbesity is high in the United States (38.2% of women), but low in Japan (3.9% of women) ("Obesity Prevalence, by country," 2016). Another risk factor is race/ethnicity. Countries that contain a multi-ethnic population, such as the United States, report differences in GDM prevalence across races/ethnicities. In addition, body mass index (BMI) thresholds for increased risk of GDM differ across races/ethnicities (Hedderson et al., 2012). For example, in the United States, Asian and Filipina women have a lower BMI threshold for increased GDM risk compared to non-Hispanic white and African American women. Based on a study of 123,040 women from Northern California, the prevalence of GDM in Asian and Filipina women is 10.2% and 10.9% respectively. This prevalence is over two times higher than that of non-Hispanic white women and African American Women (prevalences 4.5% and 4.4%, respectively) (Hedderson et al., 2012).

Obesity is strongly associated with risk of GDM and prevalence of obesity is increasing globally at a rapid rate (Johns, Denison, Norman, & Reynolds, 2018). A meta-analysis of data on 591,564 women among 20 studies from North America (United States and Canada), Europe (Italy, France, and Finland), United Kingdom, United Arab Emirites, Isreal, and Australia estimated that the risk of developing GDM is about two, four, and eight times higher among women who have overweight, obesity, or severe obesity, respectively, compared to women of normal weight (Chu et al., 2007).

GDM puts the mother at a high risk for complications during pregnancy and birth. Maternal outcomes of gestational diabetes include pregnancy-induced hypertension and pre-eclampsia, prolonged labor, obstructed labor, post-partum hemorrhage, and infection. All of these complications are leading global causes of maternal death (Veeraswamy, Vijayam, Gupta, & Kapur, 2012). A meta-analysis of 16 studies from Asian countries (India, Thailand, China, Pakistan and Bangladesh), five studies from African countries (South Africa, Sudan Uganda, and Nigeria), and studies from Iran, and Brazil reported a median incidence rate of 10.5% for hypertension and 5% median incidence rate of pre-eclampsia among GDM diagnosed mothers. In the United States, the median prevalence of hypertension is 17% among GDM diagnosed mothers across black, white Hispanic, Asian and other race/ethnicities. This prevalence is higher than the estimated prevalence in countries like the United Kingdon, Australia, and Italy (6.5%–6.9%) (Wang, Kanguru, Hussein, Fitzmaurice, & Ritchie, 2013). A study of 694 women in Northwest Ethiopia revealed a 13.2% prevalence of post-partum hemorrhage among women diagnosed with GDM compared to a 3.1% prevalence of post-partum hemorrhage in non-GDM diagnosed women (Muche, Olayemi, & Gete, 2020).

Not only does GDM increase the risk of problems during pregnancy, but it is associated with the development of chronic conditions after pregnancy for both the mother and child. According to the Centers for Disease Control and Prevention (CDC), 50% of women with GDM will subsequently develop T2DM. Additionally, the child is at greater risk for developing T2DM, obesity, cardiovascular disease, and other metabolic disorders (Price et al., 2017). A Canadian cohort study of 73,180 mother-offspring-father triads showed that incidence of pediatric diabetes is higher among offspring born to mothers with GDM (4.52 per 10,000) than offspring born to mothers without GDM (2.41 per 10,000). Maternal GDM was also associated with diabetes in

offspring from birth to age 22 (Blotsky, Rahme, Dahhou, Nakhla, & Dasgupta, 2019). As GDM rates increases globally, GDM may be contributing to the increasing prevalence of diabetes, obesity, and other related health issues (Veeraswamy et al., 2012). Public health interventions targeted toward prevention of GDM and awareness of associated risk factors may decrease prevalence of T2DM and morbidity in children of affected mothers.

### 1.1.1 GDM and T2DM

Gestational diabetes is defined as "carbohydrate intolerance resulting in hyperglycemia of variable severity with onset or first recognition during pregnancy" (Alberti & Zimmet, 1998). This definition includes individuals who return to normal glucose levels after delivery and who had diabetes mellitus (DM) that was undiagnosed before pregnancy or began at the time of pregnancy (Johns et al., 2018). Early pregnancy screening during the first trimester is recommended for high-risk women. For example, The American Diabetes Association (ADA) recommends that women with one or more risk factor for diabetes mellitus be screened during their first trimester. These risk factors include a first-degree relative with DM, a high-risk race/ethnicity such as black, Asian Indian, Filipina, Pacific Islanders, Chinese, and Mexican, hypertension, and obesity (Hederson, Darbinian & Ferrara, 2010; Johns et al. 2018) Screening for GDM later in pregnancy is performed between 24 and 28 weeks of pregnancy.

Screening procedures for GDM use an oral glucose tolerance test (OGTT), which is performed after 8 h–14 h of fasting by giving 75 g of anhydrous glucose in 250 ml–300 ml of water. Plasma glucose is measured after 8 h–14 h fasting and two hours after oral glucose (Alberti & Zimmet, 1998). Alternative methods involve a two-step method with a glucose challenge test, followed by an OGTT for individuals with a positive result (Johns et al., 2018). Diagnostic

thresholds for GDM using OGTT vary among different guideline committees. The World Health Organization (WHO) recommends that one or more of the following glucose measurements meet the following diagnostic thresholds after a 75 g OGTT: (1) fasting glucose = 92 mg/dl–125 mg/dl; or (2) one hour after OGTT, glucose ≥ 180 mg/dl; or (3) 2 hours after OGTT, glucose ≥ 153 mg/dl ("Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy: a World Health Organization Guideline," 2014).

T2DM, also called adult onset diabetes, is characterized by insulin resistance and high glucose levels in the blood. (American Diabetes, 2005). T2DM often goes undiagnosed for many years because the hyperglycemia increases overtime and in early stages is often not severe enough for a patient to notice any symptoms. The risk of developing T2DM increases with age, higher BMI, and lack of exercise. As previously stated, the risk of developing T2DM is greater if a patient had GDM during pregnancy (American Diabetes, 2005). The ADA's diagnostic criteria for T2DM are (1) a fasting plasma glucose level ≥ 126 mg/dL, (2) a two-hour plasma glucose level ≥ 100 mg/dL during 75 g oral glucose tolerance test, (3) a random plasma glucose ≥ 200 mg/dL in a patient with symptoms of hyperglycemia, or (4) a hemoglobin A1c level ≥ 6.5% (American Diabetes, 2014).

Global prevalence of T2DM is estimated to be about 6.28%. More than one million deaths were attributed to T2DM in 2017 (Khan et al., 2020). T2DM is ranked as the seventh leading disease in global burden by disability-adjusted life years, or DALYs (Khan et al., 2020). Prevalence of T2DM has been increasing globally for the past two decades. Regions such as the Pacific islands are sustaining a high level of prevalence with American Samoa's estimated prevalence at 18,312 per 100,000 in 2017 (Khan et al., 2020). The rate of increase in prevalence and incidence of T2DM does not seem to be slowing down. Researchers predict it is unlikely the

rate of increase will stabilize or decrease in projected models over the next 30 years unless new effective prevention strategies are introduced (Imperatore et al., 2012). The global increase in prevalence and incidence of T2DM is associated with increases in economic development, urbanization, calorie-dense western diets, and sedentary lifestyles (Khan et al., 2020). These observations may explain why we see a higher prevalence in socio-economically developed countries as in Western Europe, the United States, and China. For the Pacific island region, researchers hypothesize that a genetic predisposition and the effect of nutritional changes on indigenous populations could be contributing to the abnormally high incidence of T2DM (Khan et al., 2020).

As previously stated, almost 50% of women with GDM during pregnancy subsequently develop T2DM. A 23 year cohort study in Finland, one of the longest follow-up studies on women with GDM, concluded that the risk of developing T2DM remains for almost two decades after a GDM affected pregnancy (Auvinen et al., 2020). By the end of the follow-up period, 50.4% of the cohort developed T2DM and incidence of T2DM across time remained linear (Auvinen et al., 2020). This result supports the protocol that women with GDM affected pregnancies should be carefully monitored and life-long follow-up screening procedures for T2DM should be performed.

Both T2DM and GDM prevalence have been increasing globally the past two decades. Among women diagnosed with GDM, however, a few may have had undiagnosed T2DM pre-pregnancy (Zhu & Zhang, 2016). Therefore, determining if the increased prevalence of T2DM is contributing to the increase in prevalence of GDM is difficult. In contrast, an individual with GDM is at an increased risk of developing T2DM. Therefore, the increased prevalence of GDM may be a factor contributing to the increase in the prevalence of T2DM (Zhu & Zhang, 2016). In either

scenario, GDM and T2DM are closely related in the public health challenge they pose and should be further studied together.

#### 1.1.1.1 Genetics of GDM and T2DM

Family history of GDM and/or T2DM is a known risk factor for developing GDM, which implies that development of the disease may have a genetic component. Results from a case-control study of 506 women indicated that women with any parental history of diabetes experience over a two-fold greater risk of GDM compared to women without a parent with diabetes. And women with a sibling with diabetes have an 8.4-fold higher risk for GDM compared to women without a sibling with diabetes (Williams, Qiu, Dempsey, & Luthy, 2003). Many genetic studies have shown that T2DM is a multigenetic disease, and common genetic risk variants interact with the individual's environment to cause the disease. With pathology and risk factors similar to T2DM, GDM is likely to be a multigenic disease as well and may share similar risk variants (Robitaille & Grant, 2008).

A genome wide association study (GWAS) was conducted among 468 Korean women with GDM to test for associations with known T2DM risk variants. The investigators reported an association of genetic variants in the *CDKAL1* and *MTNR1B* loci with GDM (Kwak et al., 2012). To identify additional loci associated with GDM, researchers conducted a case-control study among 8,722 women in two independent samples from the Nurses' Health Study II and the Danish National Birth cohort. They investigated a total 112 genetic variants and confirmed associations with 3 loci reported in previous studies. They also reported significant associations between GDM and eight novel loci. The variants were in genes *HNF1A, GLIS3, SLC30A8, RREB1, TCF7L2, GPSM1,* and *GLIS3,* with multiple variants found in *MTNR1B* and *TCF7L2* (Ding et al., 2018). A meta-analysis of the relationship between GDM and common risk variants for T2DM confirmed

an association of 8 variants in the following genes: *TCF7L2, MTNR1B, IGF2BP2, KCNJ11, CDKAL1, KCNQ1* and *GCK* (Mao, Li, & Gao, 2012). This analysis encompassed many different populations, including Korean, American, Swede, Chinese, Danish, Turkish, Greek, French, and Euro-Brazilian (Mao et al., 2012). A full reference list of variants is in the Appendix (Table 1).

Identifying GDM susceptibility variants is critical to understanding the biological mechanisms and relationship between T2DM and GDM. The genes associated with GDM (Appendix Table 1) are involved with impaired beta-cell function, insulin resistance, and abnormal utilization of glucose. Knowledge of these biological pathways and the effects of genetic variants on these pathways may lead to development of new therapies and opportunities for disease prevention (Mao et al., 2012). Although GWAS can lead to a better understanding of the genetic predisposition to GDM, the environment-gene interaction should be studied further. Thus, studies in populations, such as Samoans, that have relatively high rates of T2DM and risk factors for T2DM (e.g., higher rates of obesity) may reveal insights in the relationship between GDM and T2DM. These insights may also lead to development of interventions to reduce the risk of GDM and T2DM in high-risk populations.

## 1.2 SAMOAN POPULATION

The Samoan Islands are located in the Polynesian region of the Pacific Ocean. The population of Samoa in 2010 was estimated to be 186,405 and a life expectancy at birth was 74.2 years. Samoa is classified as a lower-middle income country (Hawley et al., 2014). Non-communicable diseases are a top health priority for Samoa as the country continues to develop.

### 1.2.1 Non Communicable Disease Burden

Samoans generally have high levels of adiposity and a high prevalence of obesity in the population. Non-communicable diseases are increasing in prevalence globally and are a major concern for the Samoan population (Price et al., 2017). Over the last 30 years, Samoa has seen a documented rise in prevalence of noncommunicable diseases (NCDs), such as T2DM and cardiovascular disease related to urbanization, lifestyle changes like increased caloric intake and sedentary behavior (Hawley et al., 2014). According to a 2014 study, 64% of Samoan women in the study sample and 41.2% of Samoan men in the study sample had obesity according to Polynesian BMI cutoffs (Swinburn, Ley, Carmichael, & Plank, 1999). Additionally, 17.8% of Samoan women in the study sample and 16.4% of Samoan men in the study sample had diabetes (Hawley et al., 2014).

### 1.2.2 Gestational Diabetes Mellitus in Samoa

The prevalence of GDM in Pacific Islanders is estimated to be 9.9%–14.8% compared to the global prevalence of 7%–10% (Freeman et al., 2015). Although prevalence of GDM in the Pacific Islander population is high, awareness and overall knowledge among the Samoan population are mixed. A quantitative cross-sectional study of 141 pregnant women being seen at Tupua Tamasese Mea‘ole hospital in Apia, Samoa, assessed the awareness of GDM risk factors and general GDM knowledge. Among these women, with a median age of 26 years, 82 of 141 (58%) were aware that diabetes can occur during pregnancy for the first time. The remaining 42% either were unsure or did not think diabetes could occur during pregnancy for the first time (Price et al., 2017). Family history was the most recognized GDM risk factor, with 40 women identifying

it, followed by the second most recognized, obesity. Only one woman out of the entire study group could identify all four major risk factors (Price et al., 2017). Almost 80% of the women in this study identified healthy eating and exercise as preventive lifestyle changes. Women on the older end of the age spectrum of the study sample (age 33–37) had the least amount of awareness of GDM compared to the group with the most awareness, the younger age group (age 18–22) (Price et al., 2017).

Screening practices for the high-risk Samoan population have also been studied. According to a study performed in 2008-2009, out of 623 women, 86.5% received some form of GDM screening during their prenatal care visits. However, 60.4% of the women screened before 28 weeks gestation did not receive a follow-up screening (Freeman et al., 2015). In addition, 35.5% of the study participants were not screened or only screened after 28 weeks gestation. The majority of the women who received no GDM screening also received no prenatal care (8.3% of entire sample). For the women screened after 28 weeks gestation, almost none were enrolled in prenatal care (Freeman et al., 2015). The researchers concluded that only 16.1% of the study sample was receiving adequate GDM screening based on Samoa's local guidelines (Freeman et al., 2015). Their research revealed an association between prenatal care attendance and GDM screening and thus, provides insight on how local guidelines can be further improved.

A mixture of clinical screening protocols and genetic testing could potentially allow targeted resources to high risk individuals in the Pacific Island population. A prospective cohort study of 112 Māori and Pacific pregnant women explored the effect of an allele of CREBRF rs373863828, an allele previously associated with increased BMI and reduced risk of T2DM, to test association with GDM. The rs373863828 minor (A) allele was associated with a reduced likelihood of GDM in women with obesity (Krishnan et al., 2020). This variant is carried by 28%

of the Polynesian women in the study sample and women carrying this allele are eight times less likely to develop GDM (90% predictive value) (Krishnan et al., 2020). This study gives insight to the potential clinical utility of this genetic information in combination with clinical risk factors. Prevention, pharmacotherapy, and early diagnostic testing resources could be focused more on women at higher risk (absent minor allele) (Krishnan et al., 2020). This study also provides motivation for further investigation of the genetic factors associated with GDM in the Pacific Islander population.

## 2.0 SPECIFIC AIMS

Previous research indicated that T2DM and GDM are pathologically similar, share similar risk factors, and share some common genetic risk variants. In Samoa, high rates of obesity and other non-communicable diseases position Samoa as a high-risk population for the development of both GDM and T2DM. The goal of this essay is to further explore the biological and socio-demographic factors contributing to high prevalence of T2DM, and potentially GDM. Specifically, this essay investigates whether single nucleotide variants (SNVs) that had been associated with risk of developing GDM in other populations are associated with T2DM risk in Samoan women. Because diagnosis of GDM or pregnancy history was not collected in this sample, genetic variants associated with GDM in other populations were identified and tested for association with T2DM status among women and men. The results in men served as an imperfect control because if an association was found in women and men, the risk allele likely affected T2DM risk and not GDM risk, especially because several alleles associated with susceptibility for GDM also affect susceptibility for T2DM. However, if an association was found in women, but not in men, the risk allele may primarily influence susceptibility for T2DM via susceptibility for GDM.

The specific aims of this study are to:

1. Characterize the sample of Samoan women

   a. develop a consensus T2DM trait by combining information on T2DM diagnosis and blood glucose levels

   b. identify demographic risk factors associated with this T2DM trait
2. Identify genes and SNVs associated with gestational diabetes mellitus in other populations determine that are also present in Samoans

3. Test for association between SNVs and T2DM in Samoan women.

    a. Compare results to previous studies of GDM and T2DM in women

    b. Test for association between SNVs and T2DM in men

# 3.0 METHODS

## 3.1 STUDY SAMPLE AND DATA COLLECTION

Data were collected in 2010 from the independent nation of Samoa. The population of Samoa in 2010 was approximately 186,405 and life expectancy at birth was 74.2 years (Hawley et al., 2014). The original study had a target sample size of 3,500 participants aged 24.5 to 65 years of age. Samoa is classified as a lower-middle income country and ranked 94 of 182 according to Human Development Index 2009. The participants were recruited from all four census regions of Samoa: Apia Urban Area (AUA), Northwest ‘Upolu (NWU), Rest of ‘Upolu (ROU), and Savai‘i (SAV). Participants resided in 33 villages among the three regions: nine from AUA, eight from NWU, eight from ROU and eight from SAV (Hawley et al., 2014). Recruitment of participants was undertaken in collaboration with village leaders and completed using a study orator whose role was to explain the purpose and procedures of the study to gain interest. Recruitment took place from February to July 2010. The Samoan Bureau of Statistics spent two to three days in each village completing study activities. Participation in the study was completely voluntary (Hawley et al., 2014). All participants gave written informed consent via Samoan language consent forms. The research in Samoa was reviewed and approved by the institutional review boards of Miriam Hospital, Providence, RI; Brown University; University of Cincinnati; and University of Pittsburgh. Research in Samoa was also reviewed and approved by the Health Research Committee of the Samoan Ministry of Health.

## 3.2 DESCRIPTION OF DATA

The inclusion criteria for the original study were that participants had to be (1) between the ages 24.5 to 65 years, (2) were of Samoan ancestry (having four Samoan grandparents), and (3) willing and able to complete the survey. Individuals who were pregnant or had severe cognitive impairment were excluded (Hawley et al., 2014). A total of 3,504 participants were recruited and 3,475 were eligible. Data were collected through four main components: questionnaire, anthropometric measures, serum sampling, and DNA sampling. 99.4% of participants completed the questionnaire and anthropometry collection, 91.1% participated in DNA processing, and 84.6% of participants' serum sample was analyzed (Hawley et al., 2014).

The questionnaire included information on socio-demographics, detailed health history, alcohol and tobacco consumption, physical activity estimates, household assets inventory, and acculturation assessment. Anthropometric measures included height, weight, BMI, skinfold thickness, numerous body measurements, fat mass and body fat percentage, and blood pressure (Hawley et al., 2014). Blood samples were collected to measure fasting cholesterol, LDL, and HDL cholesterol and triglycerides, and fasting blood glucose levels. DNA samples were collected as whole blood samples for genotyping (Hawley et al., 2014). SNVs were genotyped as part of Genome-Wide Human SNP 6.0 arrays (Affymetrix). Extensive quality control was conducted on the basis of a pipeline developed by Laurie et al. (2010). Additional details of sample genotyping and genotype quality control are described in Minster et al. (2016).

## 3.3 DATA ANALYSIS

To develop a candidate gene list of SNVs associated with GDM, all SNVs reported to have a statistical association with GDM from any GWAS, case-control study, or meta-analysis were included. The dbSNP database ("Database of Single Nucleotide Polymorphisms (dbSNP),") was referenced for risk allele frequency in specific populations. A list of rs numbers for each SNV, along with allele frequencies from the Samoan dataset, was cross referenced with the list of SNVs reported in the literature.

Data analysis was performed using SAS University Edition and Microsoft Excel. For the first set of preliminary analysis, the demographic data were analyzed using the frequency procedure in SAS. A variable, “All diabetics” was created to distinguished participants with diabetes and those without diabetes. Individuals were classified as having diabetes if they reported that they were diagnosed with diabetes and/or had a glucose level equal to or greater than 125.99 mg/dL. Any individual who did not report a diabetes diagnosis and had a glucose level below 125.99 mg/dL was classified as not having diabetes. A binary logistic regression function of SAS was used to test the relationship between specific variables and diabetes. These variables were: BMI and current smoker status. The outcome of interest was diabetes status.

Seven SNVs were analyzed in men and women separately. The men in the sample were used as the control group because the information on pregnancy or GDM status had not been collected. Binary logistic regression was performed for each SNV to assess the relationship between SNV genotypes and diabetes. Bonferroni correction was applied to decrease false positive results. If a covariate had a significant relationship with diabetes in the study sample, it was included in the logistic regression model when analyzing the SNVs.

## 4.0 RESULTS

The study sample was mostly female (59%), between 30 and 50 years of age (78%), did not have a diabetes diagnosis (92%), had completed up to secondary school education (69%) and were non-smokers at time of data collection (66%) (Table 1). Fifteen percent of the sample had a blood glucose level of greater than or equal to 126 mg/dL, although only 8% of the total sample had a previous diagnosis of diabetes, and 55% of the study sample had a BMI of ≥ 32 kg/m$^2$. Women had a higher prevalence of high glucose level (16% over 126 mg/dL) and a higher prevalence of obesity (64%) compared to men (14% and 41%, respectively). The proportion of men and women who had previously been diagnosed with diabetes was similar for men and women.

**Table 1. Characteristics of Study Sample**

| **Characteristic n (%)** | | **Total** | **Women** | **Men** |
|---|---|---|---|---|
| | | 3483 | 2042 | 1441 |
| **Sex** | | | | |
| | Male | 1441 (41) | | |
| | Female | 2042 (59) | | |
| **Age Group** | | | | |
| | 20's | 430 (12) | 245 (12) | 185 (13) |
| | 30's | 824 (24) | 502 (25) | 322 (22) |
| | 40's | 937 (27) | 567 (28) | 370 (26) |
| | 50's | 931 (27) | 523 (26) | 408 (28) |
| | 60+ | 361 (10) | 206 (10) | 155 (11) |
| **Diabetes Diagnosis** | | | | |
| | Yes | 291 (8) | 179 (9) | 112 (8) |
| | No | 3168 (92) | 1852 (91) | 1316 (92) |
| **Diabetes Status (based on venous blood sample)** | | | | |
| | Without diabetes | 1978 (67) | 1198 (63) | 780 (66) |

| | | | | |
|---|---|---|---|---|
| | Pre-diabetes | 523 (18) | 280 (17) | 243(20) |
| | Diabetes | 443 (15) | 276 (16) | 167 (14) |
| **All Diabetics** | | | | |
| | Diabetes diagnosis and/or glucose ≥ 126 mg/dl | 518 (17) | 320 (18) | 198 (17) |
| **Glucose Levels (mg/dL)** | | | | |
| | Mean Glucose | 107.5 | 107.9 | 106.9 |
| **BMI (kg/m$^2$)** | | | | |
| | Mean BMI | 33.3 | 34.8 | 31.3 |
| | BMI 32 kg/m$^2$ and Over | 1898 (55) | 1311 (64) | 587 (41) |
| **Current Smoker** | | | | |
| | Yes | 1181 (34) | 446 (22) | 735 (51) |
| | No | 2295 (66) | 1594 (78) | 701 (49) |
| **Education completed** | | | | |
| | Less than primary | 12 (.3) | 4 (.2) | 8 (.6) |
| | Primary School | 810 (23) | 424 (22) | 386 (27) |
| | Secondary School | 2363 (69) | 1457 (77) | 906 (63) |
| | College/University | 238 (7) | | 109 (8) |
| | Postgraduate | 21 (0.6) | 9 (0.4) | 12 (0.8) |
| | No Formal Education | 16 (0.4) | 7 (0.3) | 9(0.6) |

1. **Diabetes is diagnosed at fasting blood sugar of ≥ 126 mg/dl (ADA 2020) 2. Insulin 25 and higher is an indicator of possible T2DM. 3. BMI 32 kg/m$^2$ and over is Polynesian criteria for obesity (Swinburn et al. 1999)**

In the current study, a composite "all diabetics" trait was created in which all individuals who had fasting blood glucose levels > 126 mg/dl or had previously been diagnosed with diabetes were designated at "1" and individuals who did not meet either criteria, that is, they did not have T2DM, were designated as "0." Of the total sample, 17.46% met the criteria for "all diabetics" (i.e, all diabetes = 1). Of the women in the sample, 18.09% met the criteria for "all diabetics." Of the men in the sample, 16.54% met the criteria for "all diabetics."

Logistic regression analyses were use to test for the effects of BMI and smoking on diabetes status in men and women separately. In women, higher BMI was significantly associated with greater odds of diabetes (OR = 1.02, $p = 0.021$), but smoking was not ($p = 0.68$) (Table 2). In men, greater odds of diabetes was significantly associated with higher BMI (OR = 1.8, $p < 0.0001$) and with smoking (OR = 1.36, $p = 0.049$) (Table 3).

**Table 2. Covariate Analysis of Samoan Women**

| Covariate | Odds Ratio (95% CI) | *p* value |
|---|---|---|
| **BMI** | 1.021 (1.003–1.039) | 0.021 |
| **Current Smoker** | 1.065 (0.790–1.435) | 0.680 |

**Table 3. Covariate Analysis of Samoan Men**

| Covariate | Odds Ratio (95% CI) | *p* value |
|---|---|---|
| **BMI** | 1.804 (1.057–1.111) | < 0.0001 |
| **Current Smoker** | 1.360 (1.001–1.848) | 0.049 |

Table 4 lists the frequencies of the SNVs in the Samoan sample, as well as the frequencies for the reference population in which the previous GWAS had been conducted. In general, the frequencies of SNVs in the Samoan sample were similar to those in the reference population, with a few exceptions. For example, the frequency of the rs1470579 C allele was 0.315 in Samoans and 0.293 in Koreans. The frequency of the SNV rs7754840 C allele was 0.445 in Koreans and is the minor (less frequent) allele, whereas in Samoans, it is the major (more frequent) allele, with a frequency of 0.532. Finally, rs4506565-T (in *TCFL7*) was less frequent in Samoa (0.050) than in Europeans (0.182).

**Table 4. SNV Frequency in Samoan Sample and Reference Population**

| Gene | SNV in Samoa | Samoan Allele Frequency | Reference Population | Risk Allele Frequency in Ref Pop. | Study |
|---|---|---|---|---|---|
| ***IGF2BP*** | rs1470579-C | 0.315 | East Asian (Korean) | 0.293 | Kwak SH (GWAS) |
| | rs4402960-T | 0.313 | East Asian (Korean) | 0.268 | |
| ***CDKAL1*** | rs7754840-C | 0.532 | East Asian (Korean) | 0.462 | |
| ***AP003171.1, SNRPGP16*** | rs10830962-G | 0.408 | East Asian (Korean) | 0.430 | |
| ***TCF7L2*** | rs4506565-T | 0.050 | European | 0.182 | Ding (Case-Control) |
| ***MTNR1B*** | rs10830963-G | 0.414 | East Asian | 0.500 | Mao (Meta-Analysis) |
| ***AL162373.1, SLITRK6*** | rs10220124-A | 0.005 | East Asian (Chinese) | 0.009 | Wu NN (GWAS) |

The results of the association analyses between diabetes status and genotype in women and men are shown in Table 5 and 6, respectively. Except for rs7754840, none of the SNVs was significantly associated with diabetes in women. For rs7754840, the CG heterozygotes were associated with higher odds of T2DM compared to GG homozygotes (OR = 1.429, 95% CI = 1.006–2.020, $p < 0.006$). The CC homozygotes were also associated with higher odds of T2DM compared to GG homozygotes (OR = 1.834, 95% CI = 1.262–2.668, $p < 0.006$). In the male sample, none of the SNVs was significantly associated with diabetes status.

**Table 5. Odds of Diabetes by Genotype in a Sample of Samoan Women**

| SNV | Comparison | Odds Ratio (95% CI) | *p* value |
|---|---|---|---|
| **rs1470579-C** | AA vs CC | 0.786 (0.516–1.197) | 0.186 |
| | AC vs CC | 0.997 (0.656–1.516) | |
| **rs4402960-T** | GG vs TT | 0.786 (0.514–1.201) | 0.136 |

| | | | |
|---|---|---|---|
| | GT vs TT | 1.022 (0.669–1.560) | |
| **rs7754840-G** | CC vs GG | 1.835 (1.262–2.668) | 0.006 |
| | CG vs GG | 1.429 (1.006–2.020) | |
| **rs10830962-G** | CC vs GG | 0.884 (0.613–1.274) | 0.752 |
| | CG vs GG | 0.880 (0.621–1.247) | |
| **rs4506565-T** | AA vs AT | 0.657 (0.451–0.955) | 0.028 |
| **rs10830963-G** | CC vs GG | 0.930 (0.642–1.347) | 0.878 |
| | CG vs GG | 0.913 (0.642–1.298) | |
| **rs10220124-A** | GG vs AG | 0.653 (0.236–1.802) | 0.410 |

**Confidence intervals are 95% Wald confidence limits.**

**Table 6. Odds of Diabetes by Genotype in a Sample of Samoan Men**

| SNV | Comparison | Odds Ratio (95% CI) | *p* value |
|---|---|---|---|
| **rs1470579-C** | AA vs CC | 0.927 (0.527–1.630) | 0.959 |
| | AC vs CC | 0.958 (0.543–1.691) | |
| **rs4402960-T** | GG vs TT | 0.928 (0.528–1.630) | 0.965 |
| | GT vs TT | 0.947 (0.537–1.671) | |
| **rs7754840-G** | CC vs GG | 0.760 (0.477–1.210) | 0.422 |
| | CG vs GG | 0.958 (0.640–1.434) | |
| **rs10830962-G** | CC vs GG | 0.854 (0.532–1.368) | 0.793 |
| | CG vs GG | 0.927 (0.593–1.449) | |
| **rs4506565-T** | AA vs AT | 0.859 (0.510–1.447) | 0.567 |
| **rs10830963-G** | CC vs GG | 0.725 (0.534–1.392) | 0.725 |
| | CG vs GG | 0.989 (0.632–1.548) | |
| **rs10220124-A** | GG vs AG | 0.348 (0.099–1.219) | 0.099 |

**Confidence intervals are 95% Wald confidence limits.**

# 5.0 DISCUSSION AND CONCLUSION

GDM is an important risk factor for T2DM and has lasting health effects on the mother and child. The prevalence of GDM and T2DM is high among Pacific Islanders, and may be associated with the high prevalence of obesity and non-communicable diseases, the varying awareness and overall knowledge of GDM and T2DM and their risk factors. In addition, differences in allele frequencies in genes that have been associated with susceptibility for GDM and T2DM, as well as and interactions between genes and environmental factors, may also contribute to the high prevalence of GDM and T2DM in these populations

Samoa has a high prevalence of obesity, which is a risk factor for developing GDM and T2DM. As shown in Table 1, (64%) of women in this study sample reported a BMI greater than the Polynesian cutoff for obesity. This high prevalence of obesity has contributed to the increased prevalence of noncommunicable diseases such as T2DM and cardiovascular disease in Samoa over the last 30 years. Recently, a novel locus, *CREBRF*, has been associated with higher BMI in Samoans (Minster et al., 2016). The allele in this locus that is associated with higher BMI is extremely rare in other populations, but common in Samoa. This example shows that differences in allele frequencies may influence differences in disease susceptibility.

The current study investigated whether alleles that have previously been reported to influence GDM also influenced GDM and T2DM in Samoan women. Because information on GDM was not available, analyses used T2DM status as a proxy for GDM. The analysis yielded only one SNV with a significant association to T2DM, rs7754840, in women. Previous reports indicate that the C allele for locus rs7754840 is associated with higher risk of gestational diabetes in Korean women. Women with one or two C alleles had significantly higher odds of GDM (OR

= 1.707, CI = 1.459-1.997, $p = 2.5 \times 10^{-11}$) (Kwak et al., 2012). In Samoan women, the C allele for locus rs7754840 had an additive effect on risk of T2DM. Women with one copy of the C allele had higher odds of T2DM = 1.49, whereas those with .two copies of the C allele (i.e., genotype = CC) had higher odds of T2DM = 1.83. Thus, the magnitude and direction of the effect of the SNV on T2DM in Samoan women is similar to the findings of the SNV on GDM in Korea. Both the C and G alleles are very common in the Samoan population (C = 0.53, G = 0.45). If this variant is having a large impact on GDM, then approximately half of Samoan women (those with CG genotypes) have a 42.9% higher risk for GDM, and one fourth of Samoan women (those with CC genotypes) have a 83.5% higher risk for GDM. Compared to Samoans, the frequency of the C allele is slightly lower in Koreans, although still high (C = 0.46). Korean women have a lower prevalence of GDM than Samoans, (5.7%–9.5% versus 9.9%–14.8%, respectively), perhaps due to a lower prevalence of obesity, a risk factor for GDM. The prevalence of obesity in Samoan women is 64%, whereas the prevalence in Korean women is 29.4% (Kim, Ahn, & Nam, 2005). Given the difference in the prevalence of GDM and the frequency of the CC homozygotes in these two populations, not everyone with the risk genotype will develop GDM or, subsequently, T2DM.

GDM prevalence in Koreans is twice that among non-Hispanic white women who have a higher prevalence of obesity (39.8% vs. 29.4%) (Hales, Carroll, Fryar, & Ogden, 2020; Koo, Lee, Kim, Jang, & Lee, 2016). In addition, although Korean women have a lower prevalence of obesity, the prevalence of T2DM in Koreans is 12.4%–13.5%, which is similar to the prevalence of diabetes among women in the current study (16%) (Choi, Jin, Kim, & Shin, 2020). These observations may indicate that genetic and environmental risk factors contribute to risk of GDM and T2DM.

The gene closest to variant rs7754840 is *CDKAL1*, and this variant is an intron variant ("Database of Single Nucleotide Polymorphisms (dbSNP)."). Multiple variants in *CDKAL1* are

known to be associated with greater risk of GDM in Koreans and T2DM in Asians, including Koreans (Kwak et al., 2012). *CDKAL1* is a protein coding gene that codes for cyclin-dependent kinase 5 regulator subunit-associated protein 1-like 1 (CDKAL1) (Kwak et al., 2012). The CDKAL1 protein inhibits cyclin dependent kinase 5 (CDK5), which promotes pancreatic β-cell survival (Kwak et al., 2012).; β-cells secrete insulin. During pregnancy, insulin resistance may increase and adversely affects β-cell survival (Buchanan, 2001). If variants in *CDKAL1* affect CDK5 function, β-cell compensation is compromised and a greater insulin resistance could result in GDM. Because multiple variants in this gene have been associated with T2DM and GDM, this region of the genome should be further explored in association with other metabolic disorders.

## 5.1 LIMITATIONS

The main limitation of this analysis is that the 2010 survey did not ask about gestational diabetes or number of children, and pregnancy at time of participation was an exclusion criterion. T2DM was the trait analyzed because of the relationship between GDM and T2DM. Approximately 50% of women with GDM subsequently develop T2DM. Analyzing T2DM instead of GDM reduces the power of the analysis because women who do not have GDM are also included in the analysis group, thus diluting the effect.

Questionnaires pose their own limitation. For this data set, many data points were missing for participants, thus the questionnaire was incomplete. Also, in general, questionnaires pose challenges such as differences in a participant's understanding or interpretation of questions, as well as failure to accurately recall information about medical history or family history.

## 5.2 CONCLUSION & FUTURE DIRECTIONS

In conclusion, this analysis gives insights regarding the potential genetic factors that are contributing to the high prevalence of GDM and T2DM in Samoa. For future studies, pregnancy data, such as number of pregnancies and gestational diabetes status should be collected for associations with risk alleles. The identification of these risk alleles could lead to identification of individuals at risk and interventions could take place, even before pregnancy, to reduce risk.

# APPENDIX

**Appendix Table 1. Risk Genes and SNVs from Literature**

| Gene | Variant and risk allele | Location | Risk allele frequency | Population | First author (Study) |
|---|---|---|---|---|---|
| ***IGF2BP*** | rs1470579-C | 3:185811292 | 0.293 | East Asian (Korean) | Kwak SH (GWAS) |
| | rs4402960-T | 3:185793899 | 0.2697 | East Asian | Mao (Meta-Analysis) |
| ***CDKAL1*** | rs7754840-C | 6:20661019 | 0.445 | East Asian (Korean) | Kwak SH (GWAS) |
| ***AP003171.1, SNRPGP16*** | rs10830962-G | 11:92965261 | 0.43 | East Asian (Korean) | Kwak SH (GWAS) |
| ***AL162373.1, SLITRK6*** | rs10220124-A | 13:85834386 | 0.008696 | East Asian (Chinese) | Wu NN (GWAS) |
| ***NUMBL, LTBP4*** | rs7254268-A | 19:40635529 | 0.213 | East Asian (Chinese) | Wu NN (GWAS) |
| ***TCF7L2*** | rs7903146-T | 10:112998590 | 0.031 | East Asian | Mao (Meta-Analysis) |
| | rs34872471-C | 10:112994312 | 0.27 | South Asian | Ding (Case-Control) |
| | rs4506565-T | 10:112996282 | 0.1819 | European | Ding (Case-Control) |
| ***MTNR1B*** | rs10830963-G | 11:92975544 | 0.5 | East Asian | Mao (Meta-Analysis) |
| | rs1387153-T | 11:92940662 | 0.371 | East Asian | Ding (Case-Control) |
| ***KCNJ11*** | rs5219-C | 11:17388025 | 0.6246 | South Asian | Mao (Meta-Analysis) |
| ***KCNQ1*** | rs2237892-T | 11:2818521 | 0.348 | East Asian | Mao (Meta-Analysis) |

| | | | | | |
|---|---|---|---|---|---|
| | rs2237895-C | 11:2835964 | 0.41 | South Asian | Mao (Meta-Analysis) |
| ***GCK*** | rs4607517-A | 7:44196069 | 0.17 | Other Asian | Mao (Meta-Analysis) |
| ***HNF1A*** | rs7957197-A | 12:121022883 | 0.2089 | European | Ding (Case-Control) |
| ***GLIS3*** | rs10814916-C | 9:4293150 | 0.5494 | South Asian | Ding (Case-Control) |
| | rs7041847-G | 9:4287466 | 0.5 | Asian | Ding (Case-Control) |
| ***SLC30A8*** | rs3802177-A | 8:117172786 | 0.403 | Asian | Ding (Case-Control) |
| ***RREB1*** | rs9379084-A | 6:7231610 | 0.237 | Asian | Ding (Case-Control) |
| ***GPSM1*** | rs11787792-A | 9:136357696 | 0.6631 | European | Ding (Case-Control) |

**Appendix Table 2.Comparison of Genotypes without BMI covariate in Samoan Women**

| SNV | Comparison | Odds Ratio (95% CI) | *p* value |
|---|---|---|---|
| **rs1470579-C** | AA vs CC | 0.767 (0.506–1.162) | 0.170 |
| | AC vs CC | 0.971 (0.643–1.469) | |
| **rs4402960-T** | GG vs TT | 0.766 (0.504–1.165) | 0.128 |
| | GT vs TT | 0.994 (0.655–1.509) | |
| **rs7754840-G** | CC vs GG | 1.720 (1.191–2.484) | 0.013 |
| | CG vs GG | 1.323 (0.937–1.868) | |
| **rs10830962-G** | CC vs GG | 0.934 (0.650–1.343) | 0.855 |
| | CG vs GG | 0.906 (0.640–1.281) | |
| **rs4506565-T** | AA vs AT | 0.671 (0.462–0.975) | 0.037 |
| **rs10830963-G** | CC vs GG | 0.982 (0.680–1.419) | 0.898 |
| | CG vs GG | 0.932 (0.657–1.323) | |
| **rs10220124-A** | GG vs AG | 0.665 (0.242–1.828) | 0.429 |

**Appendix Table 3.Comparison of Genotypes without BMI covariate in Samoan Males**

| SNV | Comparison | Odds Ratio (95% CI) | *p* value |
|---|---|---|---|
| **rs1470579-C** | AA vs CC | 0.864 (0.500–1.493) | 0.870 |
| | AC vs CC | 0.895 (0.516–1.552) | |
| **rs4402960-T** | GG vs TT | 0.870 (0.504–1.503) | 0.883 |
| | GT vs TT | 0.889 (0.513–1.542) | |
| **rs7754840-G** | CC vs GG | 0.723 (0.460–1.136) | 0.354 |
| | CG vs GG | 0.886 (0.599–1.312) | |
| **rs10830962-G** | CC vs GG | 0.849 (0.535–1.347) | 0.722 |
| | CG vs GG | 0.958 (0.619–1.483) | |
| **rs4506565-T** | AA vs AT | 0.875 (0.524–1.459) | 0.608 |
| **rs10830963-G** | CC vs GG | 0.870 (0.544–1.389) | 0.637 |
| | CG vs GG | 1.028 (0.663–1.595) | |
| **rs10220124-A** | GG vs AG | 0.336 (0.097–1.160) | 0.085 |

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