Title: Gene-environment interactions and risk for obesity in Samoa

Dates of foreign study period: June-August 2010 (10 weeks)

Location: rural ‘Upolu and Savai’i of the independent nation of Samoa

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I am a first year PhD student in the Epidemiology program, and I am applying to conduct research on gene-environment interactions and obesity among Samoans. This includes travel to Samoa in summer 2010 to participate in the collection of data that will serve as the basis of my PhD research. After the fieldwork I will conduct basic and advanced data analyses under the mentorship of Dr. Stephen McGarvey and Dr. Eric Loucks, on the contribution of gene-environment interactions towards obesity in Samoans and American Samoans. Collection and analysis of data in the proposed study will be used as a part of my PhD dissertation, as well as for publishing in scholarly journals.

OBJECTIVE AND SPECIFIC AIMS

The prevalence of obesity has been dramatically increasing around the world in the last two decades (1,2) and contributes to several risks for mortality, CVD, type II diabetes, and certain cancers (3, 4). Obesity is a complex disease, determined by the interaction of multiple genes and environmental factors. An increasing trend towards a built and ‘obesogenic’ global environment has led way to major social and behavioral changes, and factors such as a sedentary lifestyle, consumption of large food portions, high-fat diet, and low socioeconomic position have been recognized as significant contributors to the growing obesity epidemic (5-7). Furthermore, the genetic components of obesity are rapidly being uncovered today due to more sophisticated and powerful methods such as those of genome-wide association studies (GWAS). Focus is now increasingly shifting towards understanding the interplay between genetic and environmental factors involved in the development of obesity.

Adult Samoans in the independent nation of Samoa and the US territory of American Samoa are characterized by a high prevalence of obesity. Rapid economic development has led to health, lifestyle, and dietary transitions in American Samoa, where 89% of men and 92% of women had a BMI > 26 kg/m² in 2002. In Samoa, where economic development is occurring at a slower pace, a lower prevalence of obesity is observed (68% of men and 84% of women had a BMI > 26 kg/m² in 2003) although still alarming (2, 8). Professor McGarvey has been conducting research on adiposity, CVD risk factors, and modernization in the Samoan islands since 1976. Furthermore, genetic influences on adiposity and associated risk factors have been the recent focus of his research in the Samoan Islands. The latest research project led by Dr. McGarvey focuses on using the more novel and powerful genome-wide association methods to better elucidate the genetic basis adiposity-related phenotypes. Furthermore, these new research plans will allow for collection of more detailed data on important environmental factors such as diet and physical activity. Previous study in Samoans and American Samoans revealed the importance of these factors in relation to obesity, diabetes, and metabolic syndrome, and additionally pointed to the potentially important role of such factors as modifiers of association between genetic susceptibility and adiposity-related phenotypes.

Therefore, I seek to commence my research efforts on gene-environment interactions and risk for obesity by carrying out the following specific aims

Specific Aim 1: To travel to the nation of Samoa from June through August 2010, in order to participate in collection of genetic, environmental, and adiposity phenotype data in 3000 participants recruited from throughout the nation of Samoa. DNA will be extracted from collected blood samples, for the purpose of a first-stage GWAS to discover genetic variants associated with obesity and adiposity-related phenotypes. Environmental factors of interest include diet, physical activity, and socioeconomic position (SEP) and data on these variables will be obtained with questionnaires and formal interviews. Height, weight, circumferences,
skinfolds and body composition data for the measurement of obesity will be obtained, as well as several serum biomarkers such as leptin and adiponectin.

Specific Aim 2: To conduct analyses on the contribution of gene-environment interactions towards risk for obesity. After identification of genetic variants associated with obesity in the final stage of the large GWAS project, I plan to carry out analyses on gene-environment interactions and risk for obesity. Of particular interest is the interaction of diet, physical activity, and SEP with genotype, in determining risk for obesity. Separate gene-environment analyses will be carried out for each of these 3 environment variables.

BACKGROUND AND SIGNIFICANCE

Gene-environment interactions and obesity

The concept of gene-environment interaction refers to a situation where the response to an environmental factor is conditional on the genotype of an individual. The epidemiology of obesity suggests that, for the majority of individuals, the disease arises from the complex interplay between multiple genes and environmental factors (9). In the context of the etiology of obesity, the environmental component can include any structural, lifestyle, or behavioural factor that has a bearing on energy intake and energy expenditure (5). An understanding of genetic contributions to obesity has recently been advanced due to the more powerful and comprehensive methods of GWAS. As evidence emerges from GWAS of genetic variants that are definitely associated with obesity, there is now greater potential for unravelling gene-environment interactions involved (9).

There is particular interest in understanding the role played by genotype-nutrition and genotype-physical activity interactions in the etiology of obesity. Although research in this area is still in its infancy, there is preliminary evidence of gene-environment interactions affecting BMI. A gene-physical activity interaction was observed in a recent study of the FTO gene (10), which plays a direct role in energy homeostasis by regulating energy expenditure (11). In a population-based sample of 6,514 Danes, BMI was 1.95 Kg/m2 higher among sedentary homozygous carriers of the risk A-allele than sedentary homozygous carriers of the T-allele. A similar gene-physical activity interaction was observed for another genetic variant in the FTO gene in a population-based cohort of 4,762 Finnish adolescents (12). In a study of gene-nutrition interaction influencing BMI, a significant interaction was observed between a genetic polymorphism in the APOA2 gene and saturated fat in 3,462 individuals from 3 independent study populations (13).

Finally, there is considerable recent interest in better understanding the effects of gene-social environment interactions on health, and this may be particularly relevant to the etiology of obesity. A significant body of research suggests that SEP is a risk factor for obesity (7, 14, 15), and the effects of SEP may even be greater for the large proportion of the population revealed to have a genetic predisposition to obesity (16). Gene-social environment interactions may be a crucial part of the mechanisms by which SEP influences obesity. Genetic polymorphisms may moderate the association of SEP with obesity. Likewise, the effect of risk or protective alleles for obesity may be moderated by SEP or the lifestyle and behavioural factors that are strongly patterned by SEP.

Exploring gene-environment interactions will allow a better understanding of the routes through which genetic susceptibility for obesity manifests. For example, it can unmask the effect of genetic variants that may have a small effect but are common in the population, thus having a significant public health impact (10). In a Danish study no association was observed between a genetic variant in the INSIG2 gene and obesity, however when taking the level of physical activity into account, physically inactive homozygous carriers of the risk allele had significantly increased BMI, thus revealing that an impact of this genetic variant exists at least in this subset of the population (10). Uncovering gene-environment interactions involved may also provide opportunities for developing strategies to intervene, as the interaction between genotype and environment is potentially modifiable if the environment is changed (17).

Gene-environment interactions: evidence from preliminary studies in Samoa and American Samoa

Previous work in Samoa and American Samoa has given insight into gene-environment interactions, which calls to be built upon. In a genetic association study, a genetic polymorphism in the INSIG2 gene did not show an association with BMI and abdominal circumference in the American Samoa Sample, however it showed a strong association with both traits in Samoan females (18). These preliminary observations show gender and
location effects on genetic association with obesity, and indicate the need to consider key effect modifiers such as sex, dietary pattern, and physical activity in further study of genetic predisposition to obesity in Samoa. In another study, a significant interaction was observed between a “Modern” dietary pattern (consisting of foods high in glycemic index and some fast-food items) and another genetic polymorphism in the INSIG2 gene, in relation to triglyceride levels (study to be published by the American Heart Association).

**PhD research goals and relevant previous experience**

My educational experience to date has taught me about the etiology of chronic disease from various different perspectives, and one of my overall research goals is to investigate how factors such as genetics, diet, lifestyle, and socioeconomic position independently and interactively shape the onset, progression, and outcome of chronic non-communicable diseases. In addition, I am always interested in understanding the upstream global forces that have downstream effects on chronic health, and thus pursuing global health research is an important goal for me. There is no doubt that macro-level factors such as globalization, trade, and industrialization play a role in increasing global trends for chronic diseases. This is precisely why exploration of genetic and environmental components of obesity in the context of global health research in Samoa would be a perfect fit for me. Upon initially applying to Brown for my PhD last year, I was in contact with Dr. McGarvey and Dr. Eric Loucks, and expressed my interest in working with them in this area of research. This was the main reason for my decision to begin a PhD in Epidemiology at Brown University. I believe it is integral to my PhD experience to participate in collection of original data to be used for my PhD research. Travelling to Samoa to accomplish this task will allow me to become familiar with the date on a more comprehensive level, perhaps leading me to generate new and interesting research hypotheses as well.

My academic experience to date is very relevant to my PhD and overall research goals. My undergraduate background consists of a Specialist in Genes and Genetics, which focused extensively on molecular genetics and genetic susceptibility for complex disease such as cancer, diabetes, obesity, and atherosclerosis. I also completed a Genetic Epidemiology courses during my Master’s training in Epidemiology at McGill University. As a result, I gained considerable understanding of methods involved in the design, analysis, and interpretation of Gene-environment studies. In addition, my previous educational training has also taught me about health from a global perspective, and this is why I am particularly interested in carrying out my PhD objectives in the context of global health research. I completed a Minor in Critical Medical Anthropology during my undergraduate years, where I learned about important global health issues and the environmental determinants of increasing chronic disease worldwide. Furthermore, during my Master’s training I took a Seminar course in Global Health Research Methods, which focused intensely on understanding, critiquing, and applying research methodology within a global health framework.

**METHODS and ANALYSES**

**Overview of recruitment and data collection**

A total of 3,000 adults 25-64 years of age will be sampled randomly from two census regions of the nation of Samoa, rural ‘Upolu and Savai’i. After selection of participants and informed consent, individuals will be recruited in central places of villages. Briefly, the examination of participants will consist of: anthropometrics and bioelectrical impedance (BIA) measures for body composition; blood draw; and interviews obtaining data on socio-demographic characteristics, dietary intake, physical activity, cigarette smoking, alcohol consumption, income, and education. This study sample represents the first stage ‘discovery’ sample of Dr. McGarvey’s multi-stage GWAS study. Upon completion of the GWAS study, risk alleles for obesity will be identified, which will then allow me to begin assessment of the contribution of gene-diet, gene-physical activity, and gene-SEP interactions towards risk for obesity.

**Diet**

Dietary intake will be assessed with a Samoan food frequency questionnaire (FFQ). In a random sample of 100 Samoan and women from the overall sample, this FFQ will be validated against three 24 hour recalls and biomarkers of fatty acid intake obtained through plasma samples. The data will be used for macro- and micro-nutrient analysis, as well as for the development and assessment of dietary patterns. These dietary patterns will
reflect the frequency of local Samoan foods, high quality food, and low quality foods including ‘junk’ foods. Based on previous dietary analyses in Samoa, 3 dietary patterns were identified: “Traditional pattern” consisting of local Samoan food, “Transition pattern” which is a traditional pattern but consists of some foreign food items as well, and a “Modern pattern” reflecting substantial departure from the traditional diet (19). Similar assessment of dietary patterns in the new study will allow for gene-environment interaction between genetic susceptibility and a specific dietary pattern, in relation to obesity. Previous study also revealed significant differences in dietary pattern between Samoan vs. American Samoan populations. A much higher consumption of non-native food items and significantly lower consumption of vegetables were observed in American Samoa relative to Samoa (20). Dietary differences will be explored in the proposed research, and gene-diet interactions based on such dietary differences will be explored. Analyses will also explore gene-nutrient interactions, as well as the potential interaction between specific fatty acids and certain genotypes.

**Physical Activity**
Work and leisure activity patterns will be assessed by structured interview, and specific questions about traditional activities such as farming will be included. A physical activity index will also be created based on patterns of physical exertion at work, and recreational exercise. Interactions between genetic variants and physical activity levels will be investigated accordingly.

**Socioeconomic position (SEP)**
SEP will be measured by education and occupation, which will be obtained through structured interviews. An SEP index was previously developed and used in analyses of CVD risk factor prevalence in Samoa and American Samoa. In the proposed work similar SEP indices will be created in order to investigate the interaction between genetic susceptibility and SEP level and its contribution to obesity.

**Obesity phenotype**
Standard anthropometric techniques from the 2005 National Health and Nutrition Examination Survey (NHANES) will be used to measure stature, weight, skin-fold thicknesses, and circumferences. Body weight will be taken with the participant without shoes and dressed in light clothing to the nearest 0.1 kg with an electronic scale. Stature will be measured with a portable anthropometer without shoes and the head held in the Frankfort plane to the nearest 0.1 cm. Categorical definitions of BMI will be used to define obesity as BMI >32 kg/m², similar to previous research (8).

**PLANS FOR DISSEMINATION**
Upon completion of data collection this summer, I will partake in the cleaning and management of data from anthropometric assessments and Dietary interviews. I will also conduct preliminary descriptive analyses on the distribution of weight, % body fat, dietary patterns, and other factors by sex, SEP, and physical activity. All analyses will be performed in SAS version 9.1. I previously completed my master’s thesis in SAS, and thus am well-equipped to carry out the above tasks.

As mentioned previously, after identification of genetic variants associated with obesity in the GWAS study (this will be done by statistical geneticists in the research team), I will begin analysis on gene-environment interaction in the study sample, as explained in sections above. As a research assistant for another similar project with Dr. Eric Loucks, I am currently conducting a literature review on statistical methods involved in gene-environment studies. This will allow me to determine what the best analytical approach is for investigating gene-environment interactions, and what analytical design will be most suitable (e.g. Case-only design vs. a prospective study design). This, among other preparations, will prepare me well for undertaking the research efforts outlined in this application throughout my PhD in the next 4 years. This work will serve as the basis of my PhD dissertation, and I also plan to publish the results of the study in scholarly journals. Results from this data will also go towards future grants for larger and more comprehensive studies on gene-environment interactions.

**DETAILED BUDGET**
Travel costs (flight to and from Samoa): approximately $2000
Transportation costs on site: approximately $500
Housing rent (8 weeks): approximately $700
Cost of meals (8 weeks): approximately $300

REFERENCES