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Epigenetics, and Human Biology and Health Responses to Modernization in the Samoan Archipelago

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A B S T R A C T

Epigenetic mechanisms offer explanations for how environmental exposures at critical life periods may affect human biological and disease phenotypes. Incorporation of epigenetic approaches into research on health consequences of societal transitions may increase understanding of the complex biobehavioral factors influencing changing populations. Description of present and planned genetic epidemiology research, including epigenetic studies, among Samoans experiencing economic modernization and globalization offer examples for progress in knowledge of population health transitions.

Key words: *epigenetics, Samoans, cardiometabolic phenotypes, gene by environment interaction*

Introduction

Understanding human biological and disease risk responses to the changing environmental conditions from economic modernization and globalization has been a key area for biological anthropology and human biology research for the last thirty years[1,2]. These more recent studies are built on the long-standing concern for how biological and behavioral phenotypes are a product of the combined actions of genetic factors and environmental exposures through the lifespan. As molecular biology, genetics of development, genetic epidemiology and population genetics have made progress our more simple models have had to integrate the increased knowledge of how genetic and environment factors work together to form the range of phenotypes and health conditions of interest to human population biologists[3].

The impact of structural genetic variation, i.e., the usually understood coding region or exon, on human phenotypes and health has been less easy to decode, although there are key successes including 1) sickle cell and other hemoglobin variants and malaria[4], 2) lactase persistence in relation to dairy products consumption[5] and 3) the start of unraveling the genetics of the variety of human adaptations to high altitude hypoxia[6]. The rapid changes in contemporary ways of life, especially dietary intake, physical activity patterns, changes in natural selection from infectious disease mortality and the psychosocial stressors present unique challenges for research on the interplay of genetic factors and environmental exposures.

The essence of gene by environment interaction, as Ellen Demerath discusses in this issue, lies in the alterations in the way the structural genetic variants express their amino acids, protein products and ultimately, measurable phenotypes, in response to variation in environmental exposures, conditioned on the complexities of development stage, age and sex. The observation of phenotypes changing in different environments is a classic one in human biology and biological anthropology including century-old studies growth and development changes in migrants to higher resource societies[7], regardless of the current understanding of the biological mechanisms. More recently and currently, studies continue to find gene-by-environment interactions in the rising context of non-communicable diseases (NCDs), such as obesity, diabetes and hypertension in relation to the excess energy balance stemming from the global nutrition transitions[8,9]. The new challenge for molecular biologists is to document how the environment embodies its effects on gene transcription and translation, on the level and rate of amino acids produced and then on phenotypes[10,11].

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The principles of epigenetic processes and how these are regulated has become crucially important because of the limited success provided by the last ten years of genome-wide association studies (GWAS)[12,13]. The first generation of GWAS proceeded on the common disease and common genetic variant assumption, i.e. that the common diseases of public health interest, NCDs such as obesity and diabetes, non-rare cancers, and neuropsychiatric conditions such as depression, would be influenced by non-rare, or common, risk alleles at SNPs generally defined as $q>0.05$ in frequency. Although GWAS have identified hundreds of common variants associated with complex traits, they explain only a small fraction of phenotypic variance[14]. Thus the contribution of allelic variants at the exon or exons, i.e., the structural genes, to phenotypic variation or disease risk is much smaller than optimistically hoped at the start of the genomic era.

The key insight of the epigenetic perspective is that the regulation of gene expression at structural genes or exons, happens in other adjacent or distant genomic regions. The greatest degree of progress in unraveling epigenetic process has been made in DNA methylation: the addition of a methyl group to the five position of the cytosine pyrimidine ring or the number six nitrogen of the adenine purine ring. DNA methylation, particularly in CG-rich promoter sequences (CpG islands) has been shown to modify gene expression in a heritable manner[8,12]. As one of the most accessible biomarkers of epigenetic modification, DNA methylation has been widely studied in cancer and other human diseases but only recently has research begun to characterize epigenetic variation in normal tissues and at critical developmental time points, such as fetal development where major epigenetic reprogramming occurs. The level of DNA methylation at specific gene regulatory sites, as well as throughout the whole genome, is currently under study by many groups, as excitement builds about the ability to disentangle how well-measured environmental exposures lead to increased or decreased DNA methylation and contribute to transcription and translation processes of specific exons[15].

For us the questions are, »what is the importance of these new research areas and findings for our focus on the biology and health profiles of societies in transition?«, and »what are the policy consequences of such anthropological, biological and epidemiologic research for societies experiencing diverse forms of political and economic change?« A related set of epigenetic questions applied to health and biology of ethnic and minority groups in high income nations has been presented and discussed by Kuzawa and Sweet (2009)[16]. They emphasized in a very creative manner how health disparities stemming from poverty and discrimination are embodied in biology and disease risk through epigenetic mechanisms. Influenced by all these innovations this paper presents some preliminary results on gene by environment interaction and epigenetics from my 35-year long research on modernizing Samoans. Lastly, I offer some brief ideas about how societies may intellectually contextualize public health prevention and medical treatment efforts given this perspective.

Samoan Modernization and Genetics Research

Samoans are characterized by high levels of adiposity and noncommunicable diseases (NCDs) such as type 2 diabetes mellitus and cardiovascular disease[17–20].The prevalence of these conditions increased markedly in the last 30 years with economic development and shifts in lifestyle toward increased caloric intake and more sedentary behavior. Samoans from the independent nation of Samoa and the US territory of American Samoa are identical from a population genetic perspective[21,22]. Global increases in obesity suggest that the Samoan pattern of obesity is becoming more common globally, making this genetically homogeneous, relatively isolated and rapidly modernizing population an excellent model for genetic and environmental forces driving global obesity trends, as well as for the proposed epigenetic questions. For example, societies in transition such as the Samoas, may be ideal populations to determine if epigenetics helps us understand now different environmental exposures influence DNA methylation at specific regulatory regions and thus influence the initiating and/or promoting roles of exons on cardiometabolic phenoptypes.

Our ongoing bioanthropological and epidemiologic research in Samoa has provided understanding of the lifestyle factors associated with obesity in adults for more than 30 years[1,9,20,23–26]. We have shown that obesity and its associated conditions aggregate within Samoan families and are associated with genetic variation in specific genomic regions, many of which have also been identified in other population groups[27,28]. The summary of these findings is that we were able to detect important genomic regions associated with obesity and related phenotypes such as blood pressure and serum lipids, but there was little evidence of any specific Polynesian genetic influences. Rather we found regions that had been previously identified for these traits.

We are now conducting statistical analyses from our recently completed GWAS research with over 3,100 adults from Samoa focusing on obesity and associated cardiometabolic phenotypes or conditions. We are hopeful of detecting significant genomic regions for further intensive fine-mapping to find genetic variants related to phenotypes of interest, followed by biological studies to identify functional variants.

Epigenetic studies among Samoans are at their beginning. We used LINE-1 or global DNA methylation results from 366 members of our 2002–03 family pedigrees from Samoa and American Samoa or Samoans[29]. LINE-1 methylation uses information on the amount of DNA methylation from known repeat sequences throughout the genome and is thus termed global methylation[30]. Lower levels of LINE-1 methylation in peripheral blood have been previously associated with risk of developing non-communicable conditions[31], the most well-explored of

these being cancer[32]. Studies examining LINE-1 methylation in association with metabolic and cardiovascular chronic conditions are lacking, despite evidence suggesting that these associations are important. Men had significantly higher LINE-1 levels than women, and lower levels of LINE-1 methylation were found in men with lower levels of HDL cholesterol, adjusting for age, insulin, cigarette smoking, and alcohol consumption. In women only, LINE-1 was associated with insulin and testosterone when levels were adjusted for age, HDL, and cigarette smoking. The findings suggest that specific hormone levels are associated with LINE-1 DNA methylation differences between men and women and argue for further research to understand the relationships between LINE-1 DNA methylation and metabolic and cardiovascular disease.

There are several next steps we will take to use the new epigenetic concepts and methods. First, we will explore our ongoing work on gene by environment interactions and ask questions about DNA methylation of genomic regions that may partially contribute to the differences we observe in the effect of differing environmental exposures on the association of allelic variants with measured traits or phenotypes. For example, in our study of INSIG2 gene variants, on chromosome 2q14.2, and obesity we did not find that the rs7566605 variant was associated with obesity in Samoans[33]. This had not been confirmed in other studies so we explored the potential for gene by environment interaction by nutritional patterns, thinking that differences in environmental factors across populations may mask genetic associations. Using a longitudinal approach with a dietary pattern measure in more than 700 Samoan adults, we found a significant interaction on serum triglycerides between the modern dietary pattern and the rs9308762 polymorphism in the INSIG2 gene. Those from Samoa consuming the modern pattern have higher triglycerides if they are homozygous for the rs9308762 C allele. We concluded that one of the INSIG2 alleles was associated with poorer metabolic control and a greater sensitivity of triglycerides to a modern dietary pattern. It is clear that environmental factors need to be taken into account when assessing genetic associations across and within populations. Our next epigenetic step will be to search for modifications of the specific regulatory regions of the INSIG2 gene, with an initial focus on DNA methylation.

In related work on the FTO gene we found that the common risk variant was not associated with obesity in Samoans[34]. Ongoing work appears to indicate that levels of dietary intake of saturated fat modify the effect of specific FTO gene variants on BMI levels in Samoans (unpublished data). If this is confirmed we will explore potential epigenetic influences on this dietary interaction with FTO genetic variants.

As we identify genomic regions from our current GWAS research on cardiometabolic phenotypes, we will target those specific genomic regions and their regulatory regions for studies of DNA methylation and other epigenetic modifications. In addition we will use the GWAS materials to conduct an epigenome-wide association study (EWAS), alongside of the GWAS research, as advocated by a recent influential review[15].

Finally, we are turning our attention to the period of the human lifespan when developmental changes occur so rapidly which may affect later biology, function and health: fetal and early life stages[35,36]. We are now designing a study of the developmental origins of Samoan cardiometabolic conditions focusing on both epigenome-wide and targeted epigenetic studies of maternal characteristics, pregnancy exposures, patterns of fetal and infant growth, and later childhood metabolic phenotypes.

We are optimistic that these epigenetic studies will provide additional insights for understanding how the nutritional, health and societal transitions underway among Samoan populations influence human biology and health.

In closing I offer some speculations about how epigenetic approaches can address some of our meeting themes: »How can traditional values that underpin society be maintained in a situation of a rapidly changing physical and social milieu?« And, »Is it important to maintain traditional values when social changes require perhaps a new paradigm of social organization and interaction?«

Epigenetic perspectives support and represent a partial shift from assigning responsibilities for biological changes and disease risks *largely to individuals* and their behaviors and choices, to a wider view of the importance of social and political economic conditions that structure the environmental exposures of communities and their members. The production of individuals' phenotypes and health status are a product of strong and prevalent environmental conditions modifying the effects of family-based individual genetic endowments. These contemporary environments of societies in transition include: 1) the modern work place and its pace of production, degree of autonomy and degrees of stability and predictability given the global economic system and global and national governmental practices; 2) the industrial food enterprise and its role in increasing lower food prices for low quality nutritional foods, while also being responsive to high food prices in resource limited societies; 3) the mismatch between *Homo sapiens* energetic balance over many thousands of years of evolutionary history, and the current obesogenic way of life; 4) the reduction in some nation states of central financial support of health systems for best practices in primary prevention and comparative effectiveness.

An additional meeting theme was: »In the face of epidemiological transition how can society address the treatment of emerging chronic diseases using both traditional and transitional approaches?« Although the following recommendation has little to do with epigenetics it is clear that health systems should emphasize local community strengths and weaknesses and then develop and train cadre of traditional healers and biomedical community health workers to engage in household level education, primary prevention and non-physician clinical care[37,38]. We need to make sure the combination of

central government investment and insurance schemes incentivize primary care prevention at the household and local institutional level including schools and workplaces.

Lastly, the theme, »What are the societal consequences of understanding epigenetic modes of inheritance and the implications for the health and wellbeing of future generations?« Since strong evidence is gathering and further detailed hypotheses are being generated that early life exposures to toxins, excess calories, psychosocial stressors and economic inequality may predetermine biology and disease risk through epigenetic mechanisms, it is clear that unequal distribution of resources and social goods can contribute to health disparities and inequalities[35]. Epigenetic perspectives suggest that biological mechanisms exist to explain how social inequalities appear later as poor health or function[16]. Therefore, the health and well-being of future generations may be improved by integrating an epigenetically-informed model of the longer temporal trajectory of a wide variety of environmental risk exposures and the short- and long--term-effects on health. This more genetically-based etiology can be seen as complementary to the scholarly considerations of the human right to health and its gradual impact on political and economic reforms to improve population biology and health.

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EPIGENETIKA I REAKCIJE HUMANE BIOLOGIJE I ZDRAVLJA NA MODERNIZACIJU U SAMOANSKOM ARHIPELAGU

S A Ž E T A K

Epigenetički mehanizmi objašnjavaju način na koji okolišni čimbenici mogu utjecati na ljudski fenotip općenito i osobito fenotip bolesnika u kritičnim životnim periodima. Uključivanjem epigenetičkog pristupa u istraživanja zdravstvenih posljedica tranzicija može se doprinijeti boljem razumijevanju kompleksnih biobihevioralnih faktora koji utječu na populaciju koja se mijenja. Opis trenutnog i planiranog genetičko-epidemiološkog istraživanja (uključujući i epigenetički aspekt) na Samoancima koji prolaze kroz proces ekonomske modernizacije i globalizacije nudi korisne primjere za napredak u poimanju i razumijevanju zdravstvenih tranzicija u populaciji.