

Thrifty Genes: From Cold and Prolonged Starvation Adaptation to Obesity and Type 2 Diabetes in Polynesians

Simote Foliaki, foliaki@hawaii.edu
Biology 466, UH Hilo

Polynesians have been undefeated on the global ranks of obesity and Type 2 diabetes (T2D). The World Health Organization reported that in Tonga, about six in every ten people are obese, and most of these obese people have T2D. Researchers have studied the factors that possibly contribute to the prevalence of these devastating diseases in Polynesians. Some studies concluded that this huge obesity and T2D level could be associated with the long distance migration of the Polynesian ancestors (Zimmet 2001). These ancestors came through prolonged starvation, cold, and stress during their long journeys. As a result, those individuals with genes that saved energy in the form of fat had become naturally selected to survive throughout these tensions. The genetic materials or genes responsible for saving fats are believed to be the most associated factor with the enormous level of obesity and T2D in Polynesians.

Ancestors of Polynesians are thought to be originated from Taiwan about 5500 years ago and migrated through the Philippines, Indonesia, Papua New Guinea, Vanuatu, Fiji, and then settled in Samoa, Tonga and other Polynesian islands about 1800 to 3200 years before present (Moodley 2009 and Gray 2009). Another theorist, Thor Heyerdahl, stated Polynesians must have originated from South America by the aid of the trade wind, which was blown from East to West. However, further studies have concluded that Polynesian voyages were first driven from Southeast Asia to South America by a trade wind that gusted from West to East. This trade wind was then reversed and gusted from East to West, which allowed Polynesians to sail back and eventually settle on Polynesian Islands (Holton 2004). The duration of all these voyages were months to years before landing. Those long journeys illustrated pictures of prolonged starvation and cold, which allowed fat storage genes to be naturally selected. These fat storage genes consist of multiple interacted genes, which were first discovered by James V. Neel associated with intermittent starvation, obesity, and T2D. He called these genes "thrifty genes" (Neel 1999).

Figure 1 (top right): Natural selection of thrifty genes in Polynesians. How frequency of these genes becomes elevated in all Polynesian populations. (A) It Shows that those Polynesian ancestors who did not have thrifty genes died during their long journeys from Southeast Asia and South America due to the cold and prolonged starvation. (B) Survivors of these long voyages are those with thrifty genes. (C) Inter-marriages within an island or small population of survivors increase the frequency of thrifty genes. (D) Migrations between islands elevate the frequency of thrifty genes in all Polynesian islands.

Habermas	Lev	Lewins	Ekins	Rachlin
1. Symbiotic (Lack of Identity)	Awareness	Anxiety		Distress and Confusion
2. Egocentric (Natural Identity)	Seeking Information	Discovery	Beginning Male Femaling, Fantasying Male Femaling	Self Definition, Identifying Options
3. Sociocentric (Role Identity)	Disclosure Exploration: Identity and Self Labeling	Purging and Delay, Acceptance	Doing Male Femaling, Constituting Male Femaling	Acting to Make Changes Coping With Consequences of Transition
4. Universalistic (Ego Identity)	Exploration: Transition Integration	Surgical Reassignment Invisibility	Consolidating Male Femaling	Removing Gender Identity as a Central Issue

Survivors of Polynesians voyages who initially settled the Polynesian Islands had been naturally selected for the thrifty genes (Figure 1 A, B). Because population of these survivors per island was very small, it most likely got favored by genetic drift or founder effect in particular (Figure 1 C). In fact, after years of intermarriages within each small population, frequency of thrifty genes became elevated. Additionally, migrations of these Polynesian ancestors in the past and their descendants on these days favor the genetic flow of thrifty genes throughout the Polynesian islands (Myles 2007) (Figure 1 D). As a result, Polynesians have become highly burdened with fat storage genes believed to be thrifty genes, thus boosting their susceptibility to obesity and T2D (Neel 1999). However, do all fat storage genes belong to thrifty genes?

Among all fat storage genes found in Polynesians, only some of them can be classified as candidates of thrifty genes. Since thrifty genes have been reported to be highly related with obesity and T2D in Polynesians, all candidates of thrifty genes should be directly or indirectly associated with obesity and T2D. Those fat storage genes, which are highly expressed in Polynesians include CNTN4 and GRM7, PPARG and ADIPOQ, PPARGC1A and LEP/LEPR genes (Cauchi 2009). This review will discuss the association between these genes leading to obesity and T2D. These genes will be closely examined to determine whether these groups of genes are mostly related with obesity and T2D in Polynesians. The genes that are associated with obesity and T2D in Polynesians should be candidates of the thrifty genes.

CNTN4 (Contactin-4) and GRM7 (Metabotropic glutamate receptor 7)

Both CNTN4 and GRM7 genes are candidates of central nervous system genes located on 3p26-25 region of chromosome 3. The variants between CNTN4, GRM7, and its neighboring genes have been found to be highly related with obesity. These genes are highly expressed in the brain and they could cause changes to the body through connecting with gene-by-environment

interactions. Stresses become common environmental factors that can strongly induce psychological changes on the brain through interacting with CNTN4 and GRM7 to cause obesity (Kraja 2012). One study reported that individuals who were promoting healthy behavior went through restricted diets and resulted in regaining of weight. This regaining of weight was due to the increase in stresses caused by restricted diets (Pankevich 2010). Therefore, CNTN4 and GRM7 genes are highly expressed in the brain and can be psychologically induced by stresses causing obesity. These genes are mostly associated with obesity in Polynesians.

PPARG (Peroxisome proliferator-activated receptor gamma) and ADIPOQ (Adiponectin)

Both PPARG and ADIPOQ genes are related with the susceptibility to obesity and T2D (Johnson 2008). PPARG is located on chromosome 3p24. This gene is divided into two types, PPARG1 and PPARG2. PPARG1 is highly expressed in adipose tissues, skeletal muscles, heart, liver, and large intestine. PPARG2 is highly expressed in adipose tissues only (Cauchi 2009). Both types of PPARG are responsible for the increasing or decreasing the transcription rate of adipose target genes like ADIPOQ. ADIPOQ is one of the adipose tissues receptors that participate in pathogenesis of insulin resistance (Vimalaswaran 2008). Thus obesity and high insulin resistance could be indicators of the overexpression of PPARG. A study from India reported a correlation between expression of PPARG2/Pro12Ala gene and the onset of obesity and T2D (Sanghera 2010). Therefore, since T2D in Polynesians is mostly mediated through obesity, the PPARGs and ADIPOQ can be the highly associated genes (Sukala 2012)

PPARGC1A (Peroxisome proliferator-activated receptor gamma coactivator 1-alpha)

PPARGC1A is a transcriptional co-activator located on chromosome 4p151. It is responsible for the regulation of genes transcription involved in adaptive thermogenesis, adipogenesis, and oxidative metabolism. The susceptibility of PPARGC1A to obesity and T2D is due to a substitution mutation occurring in its Gly482Ser region. In this region, glycine is substituted by serine at codon 482, which affects the PPARGC1A co-activator activities and leads to changes in mitochondrial functions and insulin resistance (Choi 2006). A study from China found that Gly482Ser gene is highly linked with obesity and T2D. This gene is also believed to be associated with obesity and T2D in Polynesians. A study from Australia compared obesity and T2D in Polynesian, Chinese, and Papua New Guinean people. It was reported that the frequency of obesity in Polynesians is higher than the others. This result was due to the high expression of PPARGC1A gene with frequency of 0.7 in Polynesian. Therefore, the same study concluded that PPARGC1A gene could be a candidate gene for obesity and T2D in Polynesian (Myles 2007).

Leptin / Leptin receptor gene

Leptin gene is located on chromosome 7q32.1 and it is responsible for the production of leptin hormone. This hormone is an adipocyte-derived hormone that suppresses food intake by binding and activating its receptors in the hypothalamus. There are two main leptin receptor polymorphisms involved in this mechanism: K109R and Q223R. These receptors can be resistant to leptin hormones, which leads to obesity and T2D. A study of the distribution of LEP genes and LEP receptor genes on all Pacific Islands showed a wide spread of these genes over these islands. Interestingly, the same study stated that carriers of Q223R alleles have higher body weight and BMI (BMI \geq 30) than non-carriers. This study concluded that high obesity and T2D in all Pacific islanders must be associated with the presence of Q223R polymorphism (Furusawa 2009).

Discussion/Conclusion:

Both PPARGC1A and PPARG are directly related with fat storage in adipose tissues by expressing genes to store fats. These genes are closely related with each other, highly linked with obesity and T2D in Polynesians, and most likely candidates of thrifty genes. A study in New Zealand on Polynesian obesity and T2D genes reported that PPARGC1A was one of the known thrifty genes associated with obesity and T2D in Polynesians (Myles 2011). This result was supported by a study in Australia showing that Polynesians were more susceptible to obesity and T2D due to the heavy expression of PPARGC1A and PPARG (Myles 2007).

CNTN4 and GRM7, and LEP/LEPR genes are indirectly related with adipose tissues fat storage. This means that these genes can be classified as candidates of thrifty genes, but they have environmental factors associated with obesity and T2D in Polynesians. Both CNTN4/GRM7 and LEP/LEPR genes are expressed in the brain and passed through many pathways before affecting the adipose tissues activities. Some studies have recently reported that CNTN4/GRM7 can be linked with obesity and T2D in Polynesians due to the increase of modern life stresses (Kraja 2012). For instance, diet stresses, workplace stresses, and health stresses. LEP/LEPR genes on the other hand remain related with obesity and T2D in Polynesians through food consumption (Furusawa 2009). These genes become induced by the abundance of food intake as a result of the increased industrial foods imported into the Polynesian islands. The relationships between these genes and obesity, and T2D through environmental stresses indicate that they are most likely members of the thrifty genes

The high percentage of obesity and T2D in Polynesians is believed to be highly associated with thrifty genes. Since T2D in Polynesians is mostly mediated through obesity, candidates of thrifty genes should be directly or indirectly involved in adipose tissues fat storage. Therefore, since all these genes, CNTN4/GRM7, PPARG/ ADIPOQ, PPARGC1A, and LEP/LEPR found

directly and indirectly related with obesity, they should be members of thrifty genes. The PPARG/ADIPOQ and PPARGC1A are directly related with thrifty genes, while CNTN4/GRM7 and LEP/LEPR genes are indirectly associated with thrifty genes.

Thrifty genes in Polynesians have been hypothesized to be associated with obesity, which leads to T2D. In other words, thrifty genes cause T2D mediated through increasing of fats in adipose tissues (obesity). In fact, all candidates of thrifty genes should be directly or indirectly related with adipose tissues. Therefore, Polynesians should be one of the top carriers of thrifty genes which have been strongly associated with their elevated level of obesity and T2D.

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