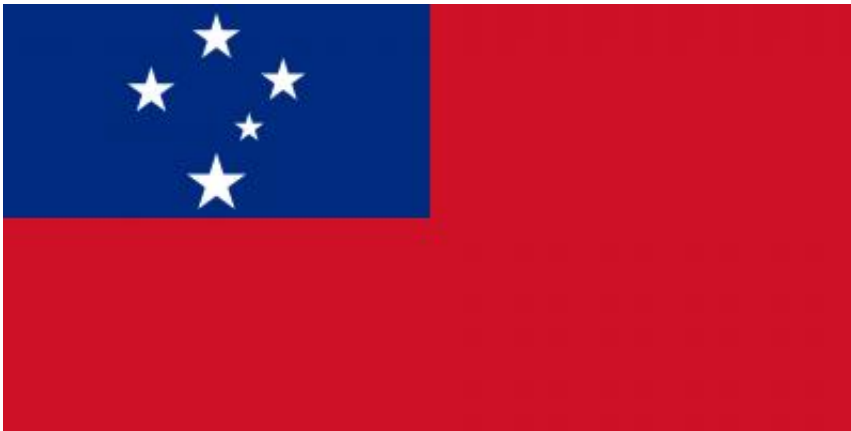


# Newly found, 'thrifty' genetic variant influences Samoan obesity

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The flag of the US territory. Credit: Public domain

The Samoas' world-leading rate of obesity is a recent phenomenon, heavily influenced by the globe's rapid shift to calorie-rich, processed foods and more sedentary lifestyles.

A new study, however, suggests nearly half of Samoans have a newly identified and significant genetic variant that contributes to obesity risk; a variant that had remained undiscovered until researchers focused on the islands' populations. In cell models in the lab, this "thrifty" variant promoted more efficient storage of more fat.

"A previously unknown genetic variant in an understudied gene is strongly associated with body-mass index (BMI) levels and other

adiposity measures in Samoan men and women we studied in 2010," said Stephen McGarvey, corresponding author of the paper in *Nature Genetics* and professor in the Brown University School of Public Health. While the variant helps to explain why 80 percent of Samoan men and 91 percent of Samoan women were overweight or obese in 2010, he said, it is by no means a dominant factor.

"Although we have found a genetic variant with a reasonable biological mechanism, this genetic variant is just one part of the many reasons for the high levels of BMI and obesity among Samoans," he said.

McGarvey with a team of colleagues at the University of Pittsburgh, the University of Cincinnati and Yale University, as well as Samoan government officials, conducted the study. The team pinpointed a single genetic variant on chromosome 5 that, according to the researchers' estimate, is associated with about 35 percent higher odds of being obese compared to not having the gene variant.

While this elevated risk is much greater than any other known common BMI risk variant, overall it explains only about 2 percent of the variation in BMI among Samoans. Other factors such as diet, physical activity and early life nutrition and growth are important, and their influences on obesity in the context of this gene variant will be investigated in future studies, McGarvey said.

In several independent samples of people from the islands, totaling more than 5,000 individuals studied since the 1990s, 7 percent of volunteers had two copies of the mutation and another 38 percent had one copy. The other 55 percent of Samoans in the study did not have the variant.

Those with it were more likely to have a higher BMI than those who didn't have it. At the same time, those with the variant were less likely to have developed Type 2 diabetes. Nevertheless, Samoans also have

among the world's highest rates of that condition.

Meanwhile, the variant is virtually nonexistent in African and European populations, McGarvey said, and is present at only very low frequency among East Asians.

## **Vetting a variant**

Body measurements, cardiovascular and metabolic health indicators from blood samples were collected from participants living in 33 villages throughout Samoa in 2010 by a field team led by Nicola Hawley, formerly of Brown and now an assistant professor at Yale University. Blood samples were processed in makeshift laboratories in villages and shipped to the University of Cincinnati where DNA was extracted. There, the DNA specimens were tested (also known as genotyped) for almost 1 million gene variants across the entire genome of each person for over 3,000 Samoan adults. Ranjan Deka, a long-time collaborator with McGarvey in genetic epidemiology studies in Samoans, and his colleague, Guangyun Sun, led the work.

Statistical geneticists Ryan Minster and Daniel Weeks at the University of Pittsburgh Graduate School of Public Health performed analyses using the genotype information to look for signals across the whole genome that genetic variants might be associated with BMI. They found that one region of chromosome 5 was strongly associated. The team drilled down in that region using more precise DNA sequencing, imputation (genotype prediction), and follow-up genotyping methods in the 2010 sample and replication samples from McGarvey's earlier Samoan studies. They pinpointed a "missense" mutation called "rs373863828" in the CREBRF gene as the variant associated with higher BMI. The effect of the mutation, the team found, was that it causes the gene's code to specify the amino acid glutamine in a protein when the unmutated gene would normally specify arginine.

But the team needed to identify the biological mechanisms that might be responsible for this genetic association with BMI.

They turned to University of Pittsburgh molecular geneticist Zsolt Urban and endocrinologist Erin Kershaw, who used a laboratory model of mouse fat cells to determine what happens when the novel missense mutation was introduced into the fat cells. Along with Chi-Ting Su, they found that the fat cells exposed to the missense mutation stored more fats and did so more efficiently, using less energy. Moreover, the variant protected the cells against death induced by starvation just as well as the common version of the gene did.

## **An evolutionary hypothesis**

The findings hint at an evolutionary story, McGarvey said, for which much more archaeological, anthropological and biological proof is needed. But the hypothesis goes like this:

The earliest Samoans may have faced considerable food insecurity when sailing to and settling the South Pacific islands. Those who had this gene variant might have been more efficiently able to extract and store energy from the available food. This may have led to natural selection favoring those who carried this "thrifty" gene variant, McGarvey said, and could account for the notable frequency of the variant in contemporary Samoans.

Once modern conveniences like motor vehicles and high-calorie foods became prevalent among Samoans, they, like many people around the world, became more prone to obesity. The rare genetic variant that long had helped them endure food scarcity, the hypothesis goes, now may somewhat exacerbate BMI in a very different lifestyle context.

"Samoans weren't obese 200 years ago," he noted. "The gene hasn't

changed that rapidly—it's the nutritional environment that changed that rapidly."

One of the findings, led by Weeks of the University of Pittsburgh, is that the pattern of genetic variant in the chromosomal region encompassing the discovered [gene variant](#) is consistent with it having been evolutionarily selected for among ancient Samoans.

Regardless of how it came to be, McGarvey cautioned strongly against taking the variant's discovery to mean that obesity is somehow inevitable for Samoans. At most it may account for a somewhat elevated risk when many other factors such as diet and physical activity come into play.

"Don't take this as 'You are Samoan, you are fated to be obese,'" McGarvey said. "We don't think that's true. We don't have any evidence that that's the case. A healthy diet and [physical activity](#) are still key to maintaining a healthy weight."

**More information:** A thrifty variant in CREBRF strongly influences body mass index in Samoans, *Nature Genetics*, [DOI: 10.1038/ng.3620](https://doi.org/10.1038/ng.3620)

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