More than one-third of adults in the United States are obese and more than two-thirds are overweight. Among the leading causes of preventable death are obesity-related conditions such as heart disease, stroke, type-2 diabetes and some cancers. Understanding the genetic architecture underlying the variation in body weight could lead to interventions that aid in effective weight management. Obesity has its highest prevalence in populations native to the islands of the Pacific Ocean, a prevalence that may be rooted in the unique population history of those peoples and evolutionary pressures they have survived under. My colleagues and I have conducted a population-based study of the genetics of obesity and related cardiometabolic traits in Samoans. We have uncovered a heretofore unknown major locus governing obesity, observed congruent biological effects in transfected cell lines and detected genetic signals consistent with positive selection acting on this locus.