Online Box 16-1 ***A Human Angle*** **Genetics in Local Populations**

The American politician and former Speaker of the House of Representatives, Thomas O'Neill, once famously said that 'all politics is local', meaning that debates about large national policies usually were less important to the average citizen than the issues in his own town or neighborhood. Whether this is true or not for politics, it is true for human genetics: most people are somewhat interested in the broad principles of human genetics, but they particularly want to understand their own heritage. Many of us are the outcomes of diverse and migrating ancestral populations, and our genomes exhibit variation that reflects that history.

But for some human populations, their genetic history is very local. The founding populations for these groups were unusually small or especially isolated from their neighbors. Thus, as the population grew, it had a distinctly local genetic heritage that has been preserved, alleles that are common in this location but rare elsewhere, and traits that are distinctly different from the surrounding groups. Many of these populations have embraced their distinct heritage and geneticists have been able to study them in detail for many decades – in some cases, well before genome analysis was common.

Genetics has been combined with cultural ancestry, linguistics, archeology, and physical anthropology to produce detailed and subtle portraits of various human populations. The classic book in this complex and fascinating field is *The History and Geography of Human Genes*, by Cavalli-Sforza, Menozzi, and Piazza, published in 1994. Genomic analysis of specific populations has greatly expanded our knowledge since that publication.

Chapter 16 and its associated study questions introduce you to some of these local and distinct populations, such as Icelanders, French Canadians, and Pacific Islanders. But these are far from the only populations with distinct genetic structures. Genome analysis has also been applied to dozens of other populations and cultures, and much additional data about the history and geography of human genes has been gained in the past 20 years. Sub-populations like Icelanders and Pacific Islanders were often geographically isolated from the larger population. In other cases, the reproductive isolation occurred because of language, culture, and religion, as with French Canadians or Ashkenazi Jews.

For example, the Basques who live in the Pyrenees Mountains on the border between Spain and France were both linguistically and geographically isolated from the rest of Europe. This shows up in some of their genetic traits: about 35% of Basques are Rh negative, compared to about 16% elsewhere in Europe, and the I^B allele of the ABO blood group is almost completely absent among the Basques, so nearly all of them have type A or O blood. The historical origins of the Basque people are uncertain and somewhat controversial. Both their mitochondrial and Y chromosome DNA are similar to genotypes found in the rest of Europe, although with some rare variants, particularly among ancient specimens. These features suggest that, while they are certainly distinct, the Basques have not always been so reproductively separate from the rest of Europe as once believed.

Two other European populations have also been extensively studied by geneticists. The Finnish Disease Heritage database (http://www.findis.org) is a compilation of 36 single gene diseases that are found much more commonly among the Finns than among the rest of Europeans. For these genetic diseases, both the gene and the underlying molecular alteration have been identified. For most of these diseases, a single allele that is unique to or common among the Finns accounts for nearly all of the cases, and OMIM often lists a "Finnish variant". Some of these genetic diseases show a distinct regional distribution within Finland as well, being particularly prevalent in some geographical regions of Finland and not common in others. These are not only disease variants. Note in Figure 16.22 that there is a specific Finnish variant associated with lactase persistence as well.

Both the heritage of these diseases and their regional distribution arise from the settlement history of Finland, in some of the most northern regions of Europe. (The Sami or Saami people in the Arctic Circle region of Finland, Norway, Sweden, and part of Russia, are also genetically, linguistically, and culturally distinct from the Finns and other groups.) Finland has an extensive coastline and the inland regions are heavily forested, so the original permanent settlements occurred along the coast. These settlements were apparently quite small, with only a few hundred residents, and each population lived at a very low density for most of its history, with considerable distances between settlements. The language is distinct from other Indo-European languages, related only to Hungarian, Estonian, and Saame among extant languages, which led to further reproductive separation from the rest of Europe. This history, followed by a recent rapid expansion of the population, accounts for the distinct distribution of genetic diseases among Finns – the Finnish Disease Heritage.

So what of this recent expansion? The Finnish census in 1760 found a population of 457,000 people, mostly living in villages along the coast. During the next 250 years, the population grew very rapidly, to more than 4 million people in 1950, and more than 5 million today. Following the Second World War, the population also moved from their coastal villages into the towns and cities. The rapid growth and recent internal migration are the classic ingredients of Founder Effects. The Finns also show a very low diversity of Y chromosome polymorphisms, consistent with their original low population density, which probably began with a few families in each location. They have more mitochondrial diversity, however, which may indicate that wives came from other settlements to reduce local consanguinity.

While the Finns were isolated by language and geographical location, people on the island of Sardinia were primarily isolated by geography, although the language is also distinct and not comprehensible to speakers of Italian. Sardinia, located 200 kilometers west of Italy, is the second largest island in the Mediterranean Sea and comprises an autonomous region of Italy. The island has never been densely populated, in part because of its very rocky and steep coastline, and immigration to and from the island has traditionally been very low. Molecular genetic analysis has indicated that Sardinia is the most genetically distinct population in Europe.

Two genetic diseases are common among Sardinians: β-thalassemia and glucose-6-phosphate dehydrogenase (G-6-PD) deficiency or favism. The β-globin mutation giving rise to thalassemia among Sardinians is distinctive: a stop codon at position 39, which is very rare in other parts of Europe. Similarly, the most common mutation in G-6-PD among Sardinians is a missense mutation that changes a serine to a phenylalanine at position 188; this mutation is not prevalent elsewhere in the world. In both of these cases, it is reciprocally true that the most common mutations for these genes elsewhere in the world are rare in Sardinia.

Mitochondrial and Y chromosome DNA analysis also show the distinct origins of the people of Sardinia. While the same haplogroups present in other parts of Europe are also found in Sardinia, the frequencies are much different. Mitochondrial haplogroups J, U, V, and X are more than twice as common in Europe as a whole than in Sardinia, while haplogroups H and I are more common in some regions of Sardinia than in the rest of Europe. Similarly, one Y chromosome haplogroup that has a frequency of 0.16 among Sardinian men is virtually unknown in the rest of Europe, and some of the Y chromosome haplogroups common in the rest of Europe are rare in Sardinia.