Founder Mutations

A special class of genetic mutations that often cause human disease is enabling scientists to trace the migration and growth of specific human populations over thousands of years

By **Dennis Drayna**

Two middle-aged men who live thousands of miles apart In the U.S. and have never met each other may have a common trait: a propensity to absorb iron so well that this seeming benefit can actually become unhealthy, potentially causing multiple-organ damage and even death. Someone with this condition, called hereditary hemochromatosis, often has it because each of his parents passed on to him the same mutation in a specific gene, an error that originated long ago in a single individual in Europe. The mutation was then carried through time and space in that European's descendants, who now include some 22 million Americans possessing at least one copy of the gene—including the two men, who might be surprised to learn that they are related. The long-gone ancestor is known as the founder of the population, and his or her genetic legacy is called a founder mutation.

Geneticists have discovered thousands of mutations responsible for diseases in humans, but founder mutations stand apart. The victims of many genetic diseases die before reproducing, stopping the mutant genes from reaching future generations. But founder mutations often spare their carriers and therefore can spread from the original founder to his or her descendants. And some of the disorders resulting from these mutations are common, such as the hereditary hemochromatosis caused by the mutation mentioned above, as well as sickle cell anemia and cystic fibrosis. (Why does evolution preserve rather than weed out such seemingly detrimental mutations? Nature's logic will be illustrated presently.)

Medical researchers study disease mutations in the hope of finding simple ways to identify at-risk groups of people, as well as coming up with new ideas for preventing and treating the conditions related to these mutations [see box Yesterday's Genes, Tomorrow's Medicine]. But in a remarkable byproduct of such efforts, investigators have discovered that founder mutations can serve as the footprints humanity has left on the trail of time—these mutations provide a powerful way for anthropologists to trace the history of human populations and their migrations around the globe.

The Uniqueness of Founder Mutations

AN APPRECIATION of the unusual status of founder mutations and why they can provide so much information requires a brief examination of mutations in general. Mutations arise by random changes to our DNA. Most of this damage gets repaired or eliminated at birth and thus does not get passed down to subsequent generations. But some mutations, called germ-line mutations, are passed down, often with serious medical consequences to the offspring who inherit them—more than 1,000 different diseases arise from mutations in different human genes.

Founder mutations fit in the germ-line category but are atypical. Inherited diseases ordinarily follow two general rules. First, different mutations in the same gene generally cause the same disease. As a consequence, different families affected by the same disease usually have different mutations responsible for that disease. For example, the bleeding disorder hemophilia is caused by mutations in the gene encoding factor VIII, a component of the blood-clotting system. In general, each new case of hemophilia carries a discrete, single mutation in the

"Founder Mutations," Dennis Drayna. *Scientific American*. October 2005, pp. 78–85.

Noteworthy Founder Mutations

Affected gene	Condition	Mutation origin	Migration	Possible advantage of one copy
HFE	Iron overload	Far northwestern Europe	South and East across Europe	Protection from anemia
CFTR	Cystic fibrosis	Southeast Europe/Middle East	West and north across Europe	Protection from diarrhea
HbS	Sickle cell disease	Africa-Middle East	To New World	Protection from malaria
FV Leiden	Blood clots	Western Europe	Worldwide	Protection from sepsis
ALDH2	Alcohol toxicity	Far East Asia	North and west across Asia	Protection from alcoholism, possibly hepatitis B
LCT	Lactose tolerance	Asia	West and north across Eurasia	Allows consumption of milk from domesticated animals
GJB2	Deafness	Middle East	West and north across Europe	Unknown

factor VIII gene—researchers have spotted mutations at hundreds of locations in the gene.

In a few disorders, however, the same mutation is observed over and over. And there are two ways this identical mutation can arise—as a hot-spot mutation or a founder mutation. A hot spot is a DNA base pair (the individual units of DNA) that is especially prone to mutation. For example, achondroplasia, a common form of dwarfism, usually occurs as a result of a mutation at base pair 1138 in a gene called *FGFR3* on the short arm of human chromosome 4. Individuals who harbor hot-spot mutations are usually not related to one another, and thus the rest of their DNA will vary, as is typical of unrelated people. Founder mutations, which get passed down intact over the generations, are quite distinct from spontaneous hot-spot mutations.

In everyone with a founder mutation, the damaged DNA is embedded in a larger stretch of DNA identical to that of the founder. (Scientists refer to this phenomenon as "identical by descent.") This entire shared region of DNA—a whole cassette of genetic information— is called a haplotype. Share a haplotype, and you share an ancestor, the founder. Furthermore, study of these haplotypes makes it possible to trace the origins of and to track human populations.

The age of a founder mutation can be estimated by determining the length of the haplotype—they get shorter over time. The original founder haplotype is actually the entire chromosome that includes the mutation. The founder passes on that chromosome to offspring, with the founder's mate contributing a clean chromosome. These two chromosomes, one from each parent, randomly exchange sections of DNA, like two sets of cards being crudely cut and mixed.

The mutation will still be embedded in a very long section of the founder's version of DNA after only one recombination, just as a marked card would still be accompanied by many of the same cards that were around it in its original deck after only one rough cut-and-mix. But a marked card will have fewer of its original companions after each new cut-and-mix. And the haplotype that includes the mutated gene will likewise get whittled down with each subsequent recombination.

A young founder mutation—say, only a few hundred years old—should thus be found in the midst of a long haplotype in people who have it today. An ancient founder mutation, perhaps tens of thousands of years old, rests in a short haplotype in current carriers.

The hemochromatosis gene aberration is just one of a rogue's gallery of founder mutations. A number of others are known and well studied in Europeans, and a few are now recognized in Native American, Asian and African populations [*see box*

Noteworthy Founder Mutations]. A striking fact is how common these mutations can be—hundreds or even thousands of times more frequent than typical mutations that cause disease. Most disease mutations exist at a frequency of one in a few thousand to one in a few million. But founder mutations can occur in as much as a few percent of the population.

This anomaly—shouldn't evolution get rid of these harmful genes rather than select for them?—offers an important clue as to why founder mutations persist and spread, over land and sea and across time.

The answer, perhaps not surprisingly, is that under some circumstances founder mutations prove beneficial. Most founder mutations are recessive: only a person with two copies of the affected gene, one from each parent, will suffer from the disease. The much larger percentage of people with only one copy are called carriers. They can pass on the gene to their children and have no symptoms of disease themselves, and the single copy of the founder mutation gives the carrier an advantage in the struggle for survival.

For example, carriers of the hereditary hemochromatosis mutation are thought to be protected from iron-deficiency anemia (a life-threatening condition in the past), because the protein encoded by that mutated gene makes the person absorb iron more effectively than can those who carry two normal copies of the gene. Carriers thus had an edge when dietary iron was scarce.

Perhaps the best-known example of a double-edged genetic mutation is the one responsible for sickle cell disease. The sickle cell mutation apparently arose repeatedly in regions riddled with malaria in Africa and the Middle East. A single copy of a sickle cell gene helps the carrier survive malarial infection. But two copies doom the bearer to pain and a shortened life span. The sickle cell mutation

Yesterday's Genes, Tomorrow's Medicine

The ability to identify founder mutations has profound implications for the practice of medicine. Knowledge of such mutations can, for instance, help physicians identify patients who should be tested for certain diseases. Currently physicians may rely on an individual's ethnicity to assign some disease risks and perform further tests. For example, most sickle cell disease occurs in those of African ancestry. But as the world's peoples become more genetically mixed, it will become increasingly difficult to assign an ancestral geographic origin or specific ethnicity to any person. With ethnic background disappearing as a diagnostic clue, physicians will therefore rely on testing individuals' DNA more as they try to identify disease risks or the cause of patients' symptoms. And finding founder mutations now, while human populations remain genetically distinct, will help identify the specific genes responsible for numerous conditions.

In fact, known founder mutations may be viewed as special cases of a much larger group of disease-causing variants in our DNA. Although we do not yet know what many of these are, such variants are most likely to be ancient in origin. As the accompanying article notes, such disease-related variants were probably beneficial to humans in their ancestral homes and therefore became common in the population. But the meeting of our old genes from far-flung places with modern environments and behaviors can lead to illnesses, which have become major disorders.

Genetic evaluation will be important in the broad practice of medicine because these numerous variants probably predispose us to many common disorders, not just to rare inherited diseases. Examples of such genetic variants might be those that help us make cholesterol but now contribute to high cholesterol or those that help conserve salt but now lead to salt-sensitive high blood pressure. The recognition of specific genetic profiles tied to common deleterious conditions will mean that genetics will go from being a subspecialty of medicine, concerned with rare and obscure ailments, to center stage in the prevention, diagnosis and management of human disease.

—**D.D.**

today can be found in five different haplotypes, leading to the conclusion that the mutation appeared independently five times in five different founders. (Although sickle cell disease usually results from a founder mutation, some cases do arise from other mutations.)

The frequency of a founder mutation in the population is governed by two competing forces—someone who has two copies will probably die before reproducing, but those who have only one copy will survive preferentially over those with no copies. This produces so-called balancing selection, in which the beneficial effects drive the frequency of the mutant gene up while the harmful effects damp down the frequency. Evolution giveth and evolution taketh away, so that over time the gene maintains a relatively steady level in the population.

Researchers still have not found the advantage conferred by some disease-related founder mutations, although a gene's continuing presence does point to such a benefit. For example, a recent discovery may explain the persistence of factor V Leiden, a mutation in the factor V gene, which is responsible for another blood-clotting component. This founder mutation, present in 4 percent of Europeans, leads to thrombosis, a condition of pathological blood clots. In 2003 Bryce A. Kerlin and his colleagues at the Blood Center of Southeast Wisconsin and the Medical College of Wisconsin demonstrated that carriers of this mutation are resistant to the lethal effects of bacterial infections in the bloodstream, a huge threat to survival in the preantibiotics past and still a cause of death today.

A Gene Spread Round the World

LONG BEFORE modern transportation, founder mutations migrated great distances, journeys that in many cases took dozens or even hundreds of generations. The sickle cell trait migrated from Africa west to America on slave ships and north to Europe. A common founder mutation in a gene called *GJB2* causes deafness; this mutation has been traced from its ancient origins in the Middle East along two routes, one along the Mediterranean coast to Italy and Spain and the other along the Rhine and Danube River valleys to northern Europe. A founder mutation in a gene called *ABCA4* that causes blindness appears to have arisen in Sweden about 2,700 years ago and spread to the south and west across Europe.

The most extreme example of migration, however, is probably provided by a genetic variability in our sense of taste. About 75 percent of everyone on earth perceives a substance called phenylthiocarbamide (PTC) as very bitter. The remaining 25 percent do not experience PTC as bitter at all. My colleagues and I at the National Institutes of Health and other institutions recently discovered that the combination of three different changes brings about the form of the gene that codes for the nontaster PTC receptor. Virtually all nontasters worldwide are descended from a founder individual who had these specific alterations in this gene. (Our sense of bitter taste exists to protect us from ingesting toxic substances in plants, but what might be the advantage of the nontaster variant of the gene? We suspect that the nontaster form codes for a version of the PTC detector that has switched to sensing some other toxic substance not yet identified.)

The nontaster mutation is embedded in an exceedingly short stretch of ancestral DNA, only 30,000 base pairs in some carriers, which tells us that the founder mutation is extremely ancient—probably more than 100,000 years old. In the past year, worldwide studies have shown that seven different forms of the PTC gene exist in sub-Saharan Africa. But only the major taster and the major nontaster forms have been found at significant frequency outside of African populations. Of the five remaining forms, one is found only occasionally in non-African populations (and never in New World natives), whereas the other four are exclusively African.

The PTC nontaster mutation provides a remarkable amount of information about early human migration. Its current distribution and frequency confirms anthropological and archaeological evidence that the original population of modern humans lived in Africa and that a small subgroup of those Africans emerged about 75,000 years ago and spread across five other continents—the Out of Africa hypothesis. All existing non-African populations descend from them. But in addition to confirming previous findings, the nontaster form helps to answer one of modern anthropology's most controversial questions: As our *Homo sapiens* ancestors spread across the world, did they interbreed with the

more archaic hominids they met in Europe and Asia?

These archaic hominids would almost certainly have had their own forms of the PTC gene, selected for as a response to natural toxins in the local flora. If other hominids produced offspring with *H. sapiens* partners, we would then expect to find different forms of the PTC gene in European, East Asian or Southeast Asian populations. But there is a conspicuous absence of such variation. We therefore believe that the examination of founder mutations in humans alive today shows that no successful interbreeding between *H. sapiens* and other human groups took place during this great outmigration tens of thousands of years ago.

Finding a Founder

A CLOSER LOOK at the haplotype at the root of hereditary hemochromatosis shows how the conjunction of historical records and genetic analysis of current populations can provide new insights into the causes and history of a particular condition. In the 1980s, before the gene for this disease was identified, medical geneticists found that almost everyone with the condition had a virtually identical stretch of DNA on one part of chromosome 6. This finding was stunning because most of these patients were apparently unrelated to one another and would thus have been expected to have random differences at any place in the sequence. Because of this unique stretch of DNA, researchers realized that patients with hereditary hemochromatosis most likely were all descendants of a common, long-lost ancestor and that the gene responsible for the condition probably sat within the shared area.

Operating on this hypothesis, our research group in the 1990s performed a detailed analysis in 101 patients of the genes we could find in the relevant region of chromosome 6. We also looked at the DNA of 64 control subjects who did not have hemochromatosis. Most patients shared a long region of several million base pairs. A few, however, matched in only a smaller fraction of this region. When we compared the part of chromosome 6 that matched in *all* the patients, we found that this region contained 16 genes. Thirteen of the genes coded for proteins known as histones, which bind to and wind up DNA into sausage-shaped structures visible under the microscope during cell divisions. Histones, and the genes for them, are virtually identical throughout living things, so we thought it was unlikely that they were involved in hemochromatosis. That left three genes of interest.

Two of the genes were the same in the hemochromatosis patients and the healthy control subjects. But in one of those genes, now designated *HFE*, we discovered a mutation that was present in people who had the disease but conspicuously absent from those who did not have an iron problem. This gene thus had to be the one containing the founder mutation that causes hereditary hemochromatosis.

Our discovery of the hemochromatosis founder mutation immediately led to several questions, including, Who was this founder? When and where did this person live?

Chasing the answer to these questions led medical geneticists to join forces with anthropologists and historians, producing answers that have only recently become clear. Surveys showed that hereditary hemochromatosis occurs all across Europe but is somewhat more common in northern Europe. In addition, the founder mutation was present in virtually all patients in the north but appeared in less than two thirds of the eastern and southern European patients. That result meant that the other third had some other mutation in the *HFE* gene or perhaps actually had a different iron disorder altogether.

Focusing in on northwestern Europe, more detailed genetic surveys revealed that the highest frequency of the founder mutation occurs in Ireland, western Great Britain and across the English Channel in the French province of Brittany. This pattern almost perfectly overlaps the current distribution of a particular group of people: the Celts.

The Celts rose to power in central Europe more than 2,000 years ago. Some were displaced northward and westward by the expanding Roman Empire, whereas others intermixed with southern Europeans and remained in their original location. Did the hemochromatosis founder mutation arise in central Europe and move north with its migrating carriers? Or did it originate in the north? Additional studies of the surrounding DNA on chromosome 6 led to the probable answer.

The extensive length of the modern haplotype indicates that the founder mutation is quite young,

having come into being probably only between 60 and 70 generations ago, around A.D. 800. An earlier date might have led us to the conclusion that the founder lived in central Europe and that the mutation spread north and west as his descendants were driven out by an expansionist Rome. But the Roman Empire had fallen by 800, so our founder mutation most likely originated in northwestern Europe. It was then spread to the south and east by the founder's descendants.

Anthropologists, notably Luigi Cavalli-Sforza, have previously studied other types of DNA variants to trace populations. Founder mutations now add a new dimension to DNA studies: calibrating the haplotype length dates the mutation, and calculating the frequency of the haplotype in the population measures the geographic spread of the founder's descendants.

Each of us bears biochemical witness to the fact that all humans are indeed members of a single family, bound together by the shared inheritance of our genome. In addition to confirming the Out of Africa hypothesis, analyses of founder mutations have revealed the common ancestry of various other seemingly unrelated groups—recent research by David B. Goldstein of Duke University, for instance, has revealed an unexpected genetic connection between the Celts and the Basques. Further investigations of founder mutations and their haplotypes will no doubt reveal more of the genetic relationships that give us new insights into where we came from and how we arrived at our modern locations. Such study also reveals surprising kinships that may inspire a deeper appreciation for the shared roots of humanity's family tree.

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