Our history, our genes

Population genetics lets researchers look back in time at human migrations

Greek mythology tells us that Crete was the cradle of Western civilization. The ancient legends relate how Zeus seduced Europa, the daughter of a Phoenician king, by turning himself into a bull and hiding in the king's herd. While gathering flowers, Europa stroked the bull and ended up on his back. Zeus went to the ocean and swam to Crete. The Greek historian Herodotus (circa 484–425 BC) also relates the tale of Europa, but with a different twist: as an act of revenge, the Minoans, who had been living on Crete, kidnapped Europa and took her to their island. Either way, Europa ended up on Crete to become the 'mother' of Western civilization.

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Modern archaeologists, who have been researching the original human settlement of Crete since the latter half of the nineteenth century, offer a third, less fantastical version, which leaves no space for a mythological Europa. Finds of pottery and ancient remnants of agriculture support the theory that the island's first permanent inhabitants arrived around 7,000 BC, possibly from Anatolia. Neolithic farmers settled in the lowlands and became part of the Minoan civilization 4,000 years later. Throughout the centuries, Greeks, Romans, Byzantines and Turks also migrated to Crete until the island became unified with mainland Greece in the early twentieth century.

Now, researchers in population, molecular and evolutionary genetics are contributing to the investigation of the origins of Crete's population. Given that the Cretans

might have been the first modern humans in Europe, it is a fascinating story. "What you have [is] this empty space sitting out in the Mediterranean, and there's no pre-existing genetic substrate there from a human perspective. Then you have a group of people [arriving] by boat from someplace about 9,000 years ago," said Peter Underhill, a population geneticist at Stanford University (Stanford, CA, USA). "Crete has some of the earliest farming found outside of the Fertile Crescent. So these are pioneer agriculturalists, and they create the first genetic substrate there."

Among the biologists who are interested in Crete's history is Rene Herrera, Professor of Biology at Florida International University (Miami, FL, USA). Herrera went to the island with his students and collected fresh DNA samples from Cretans, from readily accessible areas and from the Lasithi Plateau—an isolated area in eastern Crete that is thought to have acted as a refuge for the Minoans. In January 2007, Herrera's team reported in the *European Journal of Human Genetics* that the diversity of Y-chromosome haplogroups, "reflects the genetic legacy of multiple migrations over the last 9,000 years" (Martinez *et al*, 2007).

Their analysis found that R1a1 chromosomes from the Lasithi plateau had a close affinity to chromosomes from the Balkans, but not to those found in the Cretan lowlands. In addition, Cretan R1b microsatellite-defined haplotypes resembled those from northeast Italy rather than from Turkey or the Balkans (Fig 1). The researchers suggest that the isolation of the Lasithi population either resulted in genetic drift, or that more recent migration created the genetic differences between the plateau and other areas on Crete. But there is more to come from the analysis of mitochondrial DNA, which represents the maternal line. Herrera, who is preparing another publication, said mitochondrial DNA from eastern Crete shows that "the female component is heavily influenced by Asia and the Middle East as opposed to Europe" (Fig 1). Could it have been a certain Phoenician princess after all?

During the past two decades, population geneticists have used non-recombining DNA from the Y chromosome, mitochondrial DNA and other markers to probe, refine and redefine the prehistorical and historical record of migratory patterns in human history. Mark Stoneking, an evolutionary geneticist at the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, who was a member of the team that proposed the African Eve hypothesis that modern humans originated in eastern Africa, said that population genetics has been gathering steam in recent years because, "[i]t's gotten a lot cheaper and technically a lot easier to gather genetic variation in human populations. We have huge amounts of data available now that we didn't have a few years ago."

"We're able to address different questions than we used to be able to address. For example, we can ask about effective selection on the genomic scale. Whereas before, if you wanted to deal with selection in human populations, you had to think about looking at maybe one particular gene," Stoneking explained. "Now we can search across the entire genome and use statistical methods and look for genomic regions that statistically show an indication that there has been selection even though we have no idea what those genes might be doing or why they are in the selection."

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Stoneking's recent work has focused on the origins of the Polynesian people in the Southern Pacific. Sixty years ago, the Norwegian explorer and writer Thor Heyerdahl (1914–2002) argued that the Polynesians had come from South America. He and his team built a balsa-wood raft, the

Fig 1 | Chromosomal, microsatellite and mitochondrial DNA evidence hints at diverse ethnic origins for the modern Cretan Lasithi population.

Kon-Tiki, on which they travelled from Peru to the Tuamotu Islands in 101 days to prove the point. Stoneking said Heyerdahl's experiment, "was a way of demonstrating it's possible [to get from South America to Polynesia on a raft], but it appears to be wrong. There is no genetic evidence of direct contact between South America and Polynesia."

On the basis of archaeological, linguistic and now genetic information, the ancestors of the Polynesians were probably from East Asia, most likely Taiwan. "Probably 5,000 years ago, people started spreading out of Taiwan down through the Philippines, through Indonesia, along the coast of New Guinea and then on out to Polynesia," Stoneking explained. Polynesian mitochondrial DNA contains mutations that can be traced from Indonesia to Taiwan.

However, as with the Lasithi Plateau, the mitochondrial DNA and the Y-chromosome DNA each tell a different story (Kayser *et al*, 2006). "In general, when we do this work in other parts of the world, we see a reasonably good correlation between what the Y-DNA and the mitochondrial DNA tells us about the population origins in history," Stoneking said. However, "[t]he majority of Y-chromosomes [in Polynesians] came from New Guinea. You don't see them anywhere else in the world. It was surprising to us that you would have such a large discrepancy between the mitochondrial DNA and the Y-chromosome evidence of this population of Polynesians."

The researchers therefore looked at autosomal markers, which can shed light on the blend of human origins. Their most recent paper, scheduled for publication in the *American Journal of Human Genetics*, reports that 80% of the genes in Polynesians come from Asia and 20% from New Guinea. "It's a bit unusual, but it fits with some other evidence," Stoneking said.

Some anthropologists subscribe to a 'fast train' theory in which the ancestral Polynesians sped through New Guinea. But the genetic research, combined with research from archaeology and linguistics, is now suggesting what Stoneking calls, "a slow-boat model," in which the ancestors lingered, admixed and spent some time with the local New Guinean populations. "They did so in what would appear to be a rather peculiar fashion. Normally, when you have this new population moving in and admixture going on, usually what you have are males from the incoming population mating and having access to females from the resident population, but not the other way around. Here it would appear to be the other way around," he said. The Polynesians appear to have started out from East Asia about 5,000 years ago, spreading along the coast of New Guinea, where extensive intermixing occurred with preferential mating with males from the local group.

This work helps to shed light on ancient human history and it is not surprising that there is a genuine interest in the results. For example, Chris

Tyler-Smith, an evolutionary geneticist at The Wellcome Trust Sanger Institute (Hinxton, UK), received much public attention for his population genetics work in 2003 after a high-profile study of Genghis Khan's descendants. However, as he said, the research was not originally driven by an interest in Khan. "We didn't set out to investigate the impact of Genghis Khan. It was rather a population study to understand the Y-chromosomal variation in Central Asian populations and expanded from there to other geographical areas as it became more interesting." Tyler-Smith eventually found that 8% of men living in the former Mongol empire have Y chromosomes that seem to be characteristic of the Mongol ruling house.

More recently, Tyler-Smith has been checking claims that Pathan tribesmen from Pakistan descended from Alexander the Great's army, as claimed in oral traditions. "The crude initial studies did not find any evidence of a contribution from Greece. But they would have only detected a very large contribution. The final study looked more closely at individual, rare haplotypes," he said. The results of this work, published in 2007 in the *European Journal of Human Genetics*, seem to support the oral tradition as they describe two Pathans with E3b1 lineages, which are otherwise specifically associated with Macedonia and Greece (Firasat *et al*, 2007). However, Tyler-Smith also cautioned that population genetics does not provide full certainty; rather, it contributes to archaeological and

linguistic findings to refine the story of human migrations.

Yet, population genetics not only provides a riveting glimpse into ancient human history, but also has the potential to collide with political and religious issues, as Stoneking and Herrera related. In 2007, Herrera published an article about the mitochondrial DNA composition of Sunni and Shia Muslim sects in Uttar Pradesh in northern India (Terreros *et al*, 2007). The research found that the two groups are more similar to each other and other Indian groups than to human populations from the Middle East, central Asia or northeast Africa. Combined with earlier Y-chromosome DNA research, Herrera commented that, “a scenario [emerges] of Hindu to Islamic conversion in these two populations.”

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Following the publication, Herrera came under fire, even though the research confirmed the historical record. “For all kinds of wrong reasons, people were outraged. They said we were trying to create subdivisions among the Indian people,” he said. Herrera, who is now studying the impact of the Muslim invasion of Spain to determine if the invaders came from Saudi Arabia, added, “[h]istory can get contaminated over time. But DNA does not lie.”

Similarly, Stoneking faced charges from an Indian academic that he was practicing “Nazi science” after publishing a 2004 study in *Current Biology* that showed how migration from central Asia contributed to the Indian caste system and gene pool (Cordaux *et al*, 2004). Archaeological and linguistic evidence had supported an immigration theory for the origins of the Hindu caste system, whereas some genetic evidence argued that the caste system was derived from local tribal groups. By analysing Y-chromosomal DNA, Stoneking and his colleagues found that the paternal origins of Indian caste groups primarily descended from Indo-European speakers who migrated from central Asia approximately 3,500

years ago, whereas tribal groups originated indigenously.

As Stoneking said, his critic, “is someone who essentially believes that humans originated in India, that all further development in India after the original migration was indigenous, and any proposed subsequent invasion he promptly labels as ‘Aryan invasion theories.’” Stoneking, an American, added that charges of Nazism are taken quite seriously in Germany where he works and that, “I took it seriously enough to ask the director of our institute to conduct a formal investigation and clear me of any charges of Nazi science.”

Disputes and criticism notwithstanding, the use of population genetics continues to yield new insights into the history of human migrations and immigrations. Tyler-Smith expects that a torrent of genetic data will become available for population genetics and related fields as soon as the US\$1,000 genome becomes a reality. He contrasts today’s tools with those he used on his Y-chromosome work back in 1997. “There were barely a handful of microsatellites and a handful of SNPs [single-nucleotide polymorphisms]. In fact, in a landmark paper that we published then, we used just two Y-SNPs and one of them was typed by Southern blotting. And that’s kind of inconceivable now,” he said. “There are now hundreds of well-characterized Y-SNPs. For the rest of the genome, there are millions. The numbers used are going to explode in the very near future as individual genomes are sequenced and released.”

Tyler-Smith also foresees more practical applications as population genetics will contribute to identifying genes associated with human disease and response to pharmaceuticals. “Some studies like to concentrate on the anthropology and genetic anthropology aspects and distance themselves from any medical relevance,” he said. “But clearly understanding population structures and population history and relatedness is highly relevant for understanding disease complex disorders. [...] We’re very interested in regions of the human genome that have been selected recently. If someone has been selected, then that means that other people have died in order for that selection to happen. That’s something related to health and survival.”

Similarly, Herrera, who frequently gives expert forensic testimony, commented that

his research has an impact on public health, medicine and forensics because it can help to determine whether people from certain populations are susceptible or resistant to certain chemicals or drugs. Yet, he is personally interested in primarily, “finding our origins, finding where we’re from. That is the basic scientific issue.”

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Stoneking is even more blunt about what he sees as the possible medical or public health benefits. “If you want practical value [from this research], there is none whatsoever,” he said. However, he commented that it is nevertheless fascinating because it helps to satisfy human curiosity. “We want to know about our origins. Where am I from? Where am I going?” he said. “Some people will say what we learn about genetic diversity will also give insights into human diseases. Yeah, there’s an element of truth in this. But that’s not why most of us do this work. I am not doing this because by studying the origins of Polynesians I am going to learn how to cure some human disease. It’s because I am curious about where Polynesians came from and how they got there and how it happened.”

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doi:10.1038/sj.embor.7401164