DISPATCH

Human Genetics: Lactase Persistence in a Battlefield

Lactase persistence is a common genetic trait in Europeans and other pastoralists. New ancient DNA evidence from a Bronze Age battlefield indicates that selection for lactase persistence was strong and on-going in the last 3,000 years. [OK?]

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Around 3,300 years ago, a massive battle was raging in the Tollense valley in North-Eastern Germany. Although archaeological finds have been unearthed there since the 1980's, systematic excavations did not start before 1996 when amateur archaeologist Ronald Borgwardt recovered human bones. These included a humerus with a flint arrowhead lodged in the shoulder joint, giving first indications of interpersonal violence [1]. Starting from 2008, the area has been subject to thorough archaeological and anthropological research led by Detlef Jantzen and Thomas Terberger [2]. The site has been dated to the Bronze Age around 1,300–1,250 BCE [3] and has revealed skeletal material from more than 140 individuals [4]. The remains mostly belong to young adult males, several with signs of trauma – likely warriors who died in battle [4]. It has been estimated that the number of combatants could have surpassed 2,000 [3]. In this issue of *Current Biology*, Joachim Burger and colleagues [5] present ancient DNA data from Tollense valley individuals, revealing the genetic structure and ancestry of the combatants and investigating positive selection on lactase persistence.

Genetic Structure and Ancestry

It has previously been established based on strontium and carbon isotope ratios that both local and non-local warriors (possibly from Bohemia) took part in the battle [6]. Now, Burger and colleagues [5] performed genetic analyses on individuals from both groups and show that they likely belonged to a single population that was genetically quite homogenous and lacks

substructure. Even though some of the individuals were not from the Tollense valley, genetically they were part of the same population or they were genetically too similar to be distinguishable using the data available.

By and large, the genomes of modern European populations are a mixture of three past migration waves [7,8]. Anatomically modern humans arrived in Europe around 45,000 years ago [9] and survived the Last Glacial Period, retaining their hunter-gatherer lifestyle. Around 8,000 years ago, early farmers from the Near East arrived [10], bringing about major social and cultural changes connected to the transition to agriculture. The third main wave of migrating people were East European steppe pastoralists associated with the Yamnaya culture around 5,000 years ago [11]. The proportions of these ancestries vary between modern European populations: the highest degree of hunter-gatherer ancestry is found in the genomes of the Eastern Baltic, whereas Southern Europeans have the highest amount of early farmer ancestry and Northern European populations have the most steppe ancestry [8].

Burger and colleagues [5] show that the Bronze Age individuals from Tollense valley are genetically most similar to modern Central and Northern European populations. This suggests that there has been no big genetic influx to the area since the Bronze Age. The same can be said about two other Bronze Age sites that have undergone focused local-scale studies – the Lech valley in Bavaria, southern Germany (4,750–3,300 years old) [12] and the Mokrin necropolis in northern Serbia (4,100–3,800 years old) [13]. The Lech valley individuals are most similar to modern Central Europeans and the Mokrin population to Central and Southern Europeans, corresponding with their geographic location.

Interestingly, several close familial relationships and kin groups were found in both the Lech valley and Mokrin [12,13], but no close relatives were reported in the Tollense valley [5]. This is in accordance with the Lech valley sites and the Mokrin necropolis being burial grounds associated with settlements and therefore representing local populations while the Tollense valley remains are connected to a battle with combatants recruited from a broader area.

Lactase Persistence

In addition to population history, Burger and colleagues [5] were also interested in another phenomenon: the high frequency of lactose tolerance in modern European populations. Lactase is the mammalian enzyme that hydrolyzes the milk sugar lactose into glucose and galactose which can then be used as sources of energy [14]. Lactase is essential for infants to be able to live on mother's milk, but its expression decreases after weaning in most

mammals and also in the majority of humans, leading to lactose intolerance in adults [14]. However, in some humans, lactase expression continues throughout their life, known as lactase persistence [14]. In Europe, the frequency of lactase persistence decreases from North-West to South-East: over 80% in the British Isles and Scandinavia to 10–20% in Southern Europe [15].

The trait is driven by mutations in the lactase (*LCT*) gene regulatory regions in the *MCM6* gene [16]. The main mutation underlying lactase persistence in Europeans is 13,910*T or rs4988235A [16]. It has been shown using both modern [17] and ancient data [18] that not only was the trait recently under positive natural selection, but it produces the strongest selection signal in the human genome. Selection studies on ancient samples have shown that the frequency of the main lactase persistence allele in Europe was still low during the Late Neolithic and at the beginning of the Bronze Age but started to increase rapidly around 3,000 years ago [18,19]. It has been suggested that lactase persistence originated in the East European steppe and spread into Europe with the steppe migration [7]. The hypothesis is based on the frequency for the rs4988235A allele of over 25% in five Yamnaya culture-associated individuals [7].

Burger and colleagues [5] set out to test this hypothesis on the Tollense individuals, as well as a more extensive set of published and new data. They estimate the rs4988235A allele frequency for the Tollense valley and Mokrin necropolis [13] individuals at <10%. This suggests that around 3,200 years ago, more than 80% of individuals were still lactose intolerant. Furthermore, they determined that the frequency of the lactase persistence allele was already higher than 50% by around 2,700 years ago in Kivutkalns, Latvia [20]. When comparing allele frequencies between the Bronze Age Tollense valley samples and modern Central Europeans, the authors see signs of strong positive selection within the last 3,000 years. The estimated selection coefficient is around 6%, while it has been estimated at 1.8% for the same allele and only around 0.5% for two other positively selected alleles *SLC22A4*/rs1050152 and *FADS1*/rs174546 in Europe over the last 6,500 years [19].

In addition, Burger and colleagues [5] present PCR genotyping results for 37 individuals from Copper and Bronze Age Eastern Europe and East European steppe (Bulgaria, Ukraine, Russia). They do not detect the rs4988235A allele in any of these individuals. Moreover, they reanalyze the published data of an additional 37 East European steppe individuals and see no signs of lactase persistence. Although these results do not provide information on the

origin of the lactase persistence allele, they contradict the notion that the allele frequency increase seen in Europe was facilitated by the steppe migration.

Surprisingly, the only other allele, for which selection was detected after the Bronze Age, is rs5743810 in the *TLR6* gene. This locus is associated with innate immune response and pathogen pattern recognition. A question raised, but not yet answered, in this study is whether the selection on this locus could be related to epidemic disease resistance or which other factors might be driving the selection, for example, factors related to increases in population and settlement density.

Overall, the study of Burger and colleagues [5] shows that while large-scale ancient DNA studies have revealed a lot about the past, important questions can also be answered through well-designed and focused local-scale studies.

References

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Figure 1. Lactase persistence in a battlefield.
Burger and colleagues studied positive selection on lactase persistence using ancient DNA from the remains of combatants of a Bronze Age battle in the Tollense valley in Germany(photo: Stefan Sauer/Tollensetal project).

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