Disease, CCR5-Δ32 and the European spread of agriculture? A hypothesis

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From its origins in the Starčevo-Körös culture of the Hungarian Plain around 5700 BC the Neolithic archaeological assemblage of the Linearbandkeramik (LBK) spread within two centuries to reach Alsace and the middle Rhine by 5500 BC, though the rapidity of the spread makes it difficult to measure using available radiocarbon evidence (Dolukhanov *et al*. 2005). In this same time period, during the Terminal Mesolithic, *c*. 5800 to 5500 BC, there is evidence for forager-herder-horticulturists in Central and Western Europe prior to the appearance of the LBK (Gronenborn 1999, 2009). The Cardial Neolithic complex spread round the shores of the northern Mediterranean from southern Italy to Portugal in the period 5700–5400 BC.

Unfavourable climate change may have facilitated the rapid LBK spread, but seems insufficient to explain the magnitude and speed of this transition (Gronenborn 2009). Population density of Mesolithic groups would have been crucial, and the earliest LBK settlements were in areas of deciduous forests and loess soils considered scarcely visited by Mesolithic foragers, as evidenced by the paucity of Terminal Mesolithic sites in Central Europe (Lüning *et al*. 1989). By contrast, areas where LBK did not spread readily tend to correspond with demonstrable Mesolithic occupation, including north-west France, the North European Plain and southern Scandinavia. The speed of LBK spread thus appears correlated with low density Late Mesolithic population. In the Mediterranean, the Cardial similarly bypassed areas of Mesolithic settlement and often occupied areas with little Mesolithic habitation.

A hypothesis for low Terminal Mesolithic populations is the introduction of new diseases such as smallpox, measles, brucellosis and influenza into Europe with incoming Neolithic populations (Wolfe *et al*. 2007; Barnes *et al*. 2010). Those diseases known as 'zoonoses' may have been derived through domestic livestock living in close and regular proximity with humans in substantial populations (Weiss 2001; Armelagos & Harper 2005; Wolfe *et al*. 2007). Such conditions arose during the eighth or seventh millennium BC at settlements such as Çatalhöyük in southern Turkey, which probably housed several thousand inhabitants (Cessford 2005). Spreading Neolithic farming populations may then have carried these diseases across Europe.

Mediterranean Europe may also have been affected by zoonoses spreading through hunter-gatherer populations in advance of the spread of farming. In the Adriatic, the number of

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ANTIQUITY 86 (2012): 207–210 http://antiquity.ac.uk/ant/086/ant0860207.htm

sites declined sharply in the Late Mesolithic (Biagi & Spataro 2002), and along the northern shore of the western Mediterranean there is usually a stratigraphic gap of several centuries or more between Mesolithic and Neolithic (Perrin 2005; Forenbaher & Miracle 2006; Guilaine & Manen 2007).

Following on from the Mesolithic–Neolithic transition in the Near East or Anatolia, an Early Neolithic population would subsequently have undergone expansion and, in association with increased population density, seen the development of outbreaks of communicable diseases (Diamond & Bellwood 2003). Some resistance would have been likely to have evolved through increased allelic variation of the major histocompatibility complex in members of this population in response to the pathogens concerned (Gluckman *et al.* 2009). If previously unexposed, the European Mesolithic population would have no such protection. Though the differences in susceptibility were probably not as great as for the North American colonisation (Dobyns 1966; Diamond & Bellwood 2003; Wolfe *et al.* 2007), such diseases might still have devastated Terminal Mesolithic populations.

Though some diseases, such as tuberculosis, are observable from archaeological skeletal remains (Roberts & Buikstra 2003), most zoonoses are not so detectable, even by ancient DNA analysis (Barnes & Thomas 2006). There is, nevertheless, evidence of rapid selection for genetic resistance to one or more of these diseases during the last 7000 years or so (Wolfe *et al.* 2007).

We suggest that a prime genetic candidate for this resistance is CCR5-Δ32, a mutant allele of the CCR5 gene. Normally, this gene encodes the lymphocyte transmembrane co-receptor to which HIV can bind (Dean *et al.* 1996; Liu *et al.* 1996), enabling the virus to infect CD4 lymphocytes. In people homozygous for the CCR5-Δ32 allele, however, the truncated CCR5 does not reach the cell surface, thus preventing access to HIV.

The CCR5-Δ32 allele is found in 10–15% of people of Northern European descent and is rare or absent in those of Asian or African descent (O'Brien *et al.* 2008). Within Europe there is a north to south gradient in its distribution with highest frequencies being found in Finnish and adjacent Russian populations, suggesting that the original mutation producing this allele took place in north-east Europe (Libert *et al.* 1998).

Mesolithic DNA from southern Sweden dates the allele to around 7000 years ago, suggesting it originated in Mesolithic populations, and yet achieved a frequency of 17% in Swedish Neolithic populations (Liden *et al.* 2006). To increase in frequency so rapidly implies considerable selection pressure. The Early Neolithic was a time of unique new selection pressure; the gene-culture co-evolution of Neolithic subsistence farmers with persistent lactase production enabling lactose tolerance occurred through strong selection for the T-13910 allele that exists among most modern Europeans, but which was negligible amongst the earliest Neolithic Europeans (Burger *et al.* 2007; Itan *et al.* 2010).

Among the diseases CCR5-Δ32 allele may originally have conferred resistance against, HIV-1 is an unlikely candidate because it is thought to have originated in early twentieth-century Central Africa (Korber *et al.* 2000; Vidal *et al.* 2000). However, CCR5-Δ32 may also protect against pox viruses that, like HIV, gain entry to leucocytes by using chemokine receptors (Lalani *et al.* 1999). Galvani and Slatkin (2003) suggested that children, being immunologically naïve, were more likely to be killed by smallpox, which selected

against those without the protective CCR5-Δ32 allele, thus increasing its frequency in populations.

If diseases such as smallpox had been brought to Europe via Neolithic spread, it would be ironic if LBK populations gained CCR5-Δ32 frequency through intermarriage with certain north European Mesolithic groups, who were already carriers of the CCR5-Δ32 allele (Liden *et al*. 2006). This could explain the relative survival of some Mesolithic groups while others, lacking both CCR5-Δ32 and the more general resistance of Neolithic groups, perished.

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