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An evolutionary medicine perspective on Neandertal extinction

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ABSTRACT

The Eurasian sympatry of Neandertals and anatomically modern humans – beginning at least 45,000 years ago and possibly lasting for more than 5000 years – has sparked immense anthropological interest into the factors that potentially contributed to Neandertal extinction. Among many different hypotheses, the "differential pathogen resistance" extinction model posits that Neandertals were disproportionately affected by exposure to novel infectious diseases that were transmitted during the period of spatiotemporal sympatry with modern humans. Comparisons of new archaic hominin paleogenome sequences with modern human genomes have confirmed a history of genetic admixture – and thus direct contact – between humans and Neandertals. Analyses of these data have also shown that Neandertal nuclear genome genetic diversity was likely considerably lower than that of the Eurasian anatomically modern humans with whom they came into contact, perhaps leaving Neandertal innate immune systems relatively more susceptible to novel pathogens. In this study, we compared levels of genetic diversity in genes for which genetic variation is hypothesized to benefit pathogen defense among Neandertals and African, European, and Asian modern humans, using available exome sequencing data (three individuals, or six chromosomes, per population). We observed that Neandertals had only 31–39% as many nonsynonymous (amino acid changing) polymorphisms across 73 innate immune system genes compared to modern human populations. We also found that Neandertal genetic diversity was relatively low in an unbiased set of balancing selection candidate genes for primates, those genes with the highest 1% genetic diversity genome-wide in non-human hominoids (apes). In contrast, Neandertals had similar or higher levels of genetic diversity than humans in 12 major histocompatibility complex (*MHC*) genes. Thus, while Neandertals may have been relatively more susceptible to some novel pathogens and differential pathogen resistance could be considered as one potential contributing factor in their extinction, the expectations of this model are not universally met.

1. Introduction

Neandertals went extinct ~41–39 ka, following spatiotemporal overlap with anatomically modern humans in Europe for 2600 to 5400 years (Higham et al., 2014), with possibly longer overlap in the Middle East (Barker et al., 2007; Demeter et al., 2012). Numerous hypotheses to explain Neandertal extinction have been proposed. Although it has been suggested that climatic fluctuations ~40 ka played a key role in the Neandertal extinction process (Tzedakis et al., 2007; Golovanova et al., 2010; Valet and Valladas, 2010), this scenario seems unlikely given the environmental resilience demonstrated by Neandertals during previous periods of intense climate change (Lowe et al., 2012). Most other extinction hypotheses focus on Neandertal–modern human competition (Horan et al., 2005; Banks et al., 2008; Raichlen et al., 2011; Sandgathe et al., 2011; Gilpin et al., 2016). For example, potentially shorter inter-birth intervals for modern humans could have allowed more rapid population growth compared to Neandertals, facilitating eventual replacement (Trinkaus, 1984; Ponce de Leon et al., 2008). Alternatively, anthropologists have speculated that the intelligence and language capabilities of anatomically modern humans were greater than those of Neandertals (Chase and Dibble, 1987; Davidson and Noble, 1989; Marwick, 2003; Maricic et al.,

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2013), perhaps facilitating competitive hunting and other subsistence strategy advantages through the development of more efficient tool technologies (Benazzi et al., 2015; El Zaatari et al., 2016). A recent proposal is that modern humans benefitted from the early domestication of dogs, which may have aided large animal hunts to increase caloric yields for the modern humans and fuel their rapid population growth and ultimately larger population sizes (Shipman, 2015).

Given the important role of disease in population dynamics, it has also been hypothesized that viral disease transmission from modern humans could have contributed to the ultimate disappearance of the Neandertals (Wolff and Greenwood, 2010). This notion has recently been echoed and expanded upon by Houldcroft and Underdown (2016). Such a "differential pathogen resistance" model would require an anatomically modern human pathogen (or pathogens) of limited virulence for out-of-Africa migrating human populations, but one that would have strongly affected immunologically naïve Neandertal populations upon contact and transmission. Moreover, the viability of this scenario also requires i) relatively fewer Neandertal pathogens/disease strains at the time of contact, ii) some mechanism by which modern humans might not have been as negatively affected as Neandertals upon novel pathogen exposure, or iii) both of these factors to be present. Otherwise, post-contact modern human populations would have been equally adversely affected by exposure to novel Neandertal pathogens. In this paper we assess the plausibility of the differential pathogen resistance model by comparing levels of genetic diversity between Neandertal and modern human populations in genes for which genetic variation is hypothesized to benefit pathogen defense.

Recent advances in genomic sequencing technologies and ancient DNA methods have facilitated the generation of a high-quality Altai Neandertal nuclear genome sequence from Siberia (dated to ~50 ka; Green et al., 2010). When analyzed in combination with modern human genomic data, this genome has provided convincing evidence that anatomically modern humans and Neandertals interbred, with some introgressed Neandertal haplotypes preserved in non-African modern human populations (Green et al., 2010; Sankararaman et al., 2012; Prüfer et al., 2014; Vernot and Akey, 2015; Sams et al., 2016; Simonti et al., 2016; Nielsen et al., 2017). The requisite intercourse demonstrates at least some level of direct contact between these populations, and thus opportunities for the transfer of infectious diseases. Moreover, analyses of both the high-coverage diploid nuclear genome sequence from the Altai Neandertal and mitochondrial DNA sequence data that are available for multiple Neandertal individuals suggest that Neandertal genetic diversity was substantially lower than that observed within modern human populations (Briggs et al., 2009; Green et al., 2010; Dalen et al., 2012; Prüfer et al., 2014). Recently, Castellano et al. (2014) used a DNA capture method to sequence the exomes (protein-coding regions of the nuclear genome) of two additional Neandertals, individuals who lived ~49 ka (Wood et al., 2013) and ~44 ka (Krings et al., 2000; Green et al., 2010) in Spain and Croatia, respectively. Observed levels of heterozygosity for these two Neandertals are also relatively low, suggesting that low nuclear genome genetic diversity was a general Neandertal characteristic rather than restricted to an Altai Neandertal population isolate (Castellano et al., 2014). Specifically, considering only sites with sequence coverage sufficient for single nucleotide polymorphism (SNP) identification for each of the three Neandertals, only 30.3%, 44.9%, and 45.3% synonymous SNPs (i.e., those that do not change amino acids) were observed in Neandertals compared to equal-sized population samples of modern human Africans, Europeans, and Asians, respectively (Castellano et al., 2014).

Within genes directly related to immune function, greater functional genetic diversity increases the potential responsiveness of the immune system to foreign pathogens (Markert et al., 2004; Wolff and Greenwood, 2010). Balancing selection is thought to maintain advantageous functional diversity (i.e., nonsynonymous, or amino acid-changing, SNPs) within these genes (Andres et al., 2009; Qutob et al., 2012), and individuals with more genetic diversity across the genome tend to have higher fitness (Markert et al., 2004). Based on population genetic theory, genetic drift is a relatively stronger force, while natural selection is relatively less effective, in smaller populations (Gravel, 2016; Henn et al., 2016). Thus, compared to a larger population, a population with a historically small effective population size may have lower genetic diversity in general across the genome, and different patterns of diversity at loci affecting individual health and fitness. Indeed, along with relatively reduced overall genetic diversity, Castellano et al. (2014) observed a higher proportion of predicted damaging nonsynonymous SNPs than benign nonsynonymous SNPs in Neandertals compared to modern humans, consistent with the reduced effectiveness of purifying selection to remove or reduce the frequencies of strongly deleterious variants in Neandertals (Hughes et al., 2003; Zhao et al., 2003; Do et al., 2015; Harris and Nielsen, 2016; Juric et al., 2016).

In addition to purifying selection, other types of natural selection, including balancing selection, are also expected to be less effective in smaller populations. Thus, the generally low genetic diversity of Neandertals relative to humans may even be exacerbated at functional sites in genes related to immune function that would otherwise be preserved via balancing selection. Theoretically, such a difference could have facilitated the differential morbidity following contact and infectious disease transfer between Neandertals and modern humans potentially required under the Pleistocene epidemiological scenarios (the differential pathogen resistance model) detailed by Wolff and Greenwood (2010) and Houldcroft and Underdown (2016).

In this study we compared the levels and patterns of genetic variation between Neandertal and modern human populations at i) 73 genes associated with innate immune functions, ii) 164 virus-interacting protein genes, iii) 12 major histocompatibility complex (*MHC*) genes, and iv) the 1% of genes across the genome with the consistently highest levels of genetic diversity among four ape species. Our analysis represents an evaluation of the plausibility of the differential pathogen resistance model as a factor potentially contributing to Neandertal extinction. Specifically, relatively lower genetic variation in Neandertal populations among genes in these four categories would be consistent with the idea of greater susceptibility to novel pathogens in Neandertals compared to the modern human populations with which they interacted. In contrast, similar levels of Neandertal and modern human genetic diversity would raise major questions about the plausibility of this epidemiological extinction hypothesis.

2. Materials and methods

We downloaded the Neandertal exome DNA capture data published by Castellano et al. (2014) (http://cdna.eva.mpg.de/neandertal/exomes/VCF). Specifically, we considered the SNP genotype data for autosomal chromosomes from the "combined" VCF files from this dataset, in which SNP genotypes for each of the 13 individuals in the dataset (three modern humans of African descent, three modern humans of European descent, three modern humans of Asian descent, three Neandertal individuals, and one individual from the archaic hominin Denisovan population) were provided for only the individuals with a minimum of six independent sequencing reads at that position. The nine modern human individuals and three Neandertal individuals included in the Castellano et al. (2014) dataset are listed in Table 1. Ancient DNA