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LETTER TO THE EDITOR

CLINICAL GENETICS WILEY

Indigenous Arabs have an intermediate frequency of a Neanderthal-derived COVID-19 risk haplotype compared with other world populations

To the Editor,

SARS-CoV-2 has been identified as the cause of an ongoing pandemic (COVID-19) that has infected more than 25 m individuals and caused more than 1 m deaths worldwide (WHO). The highly variable clinical course despite a relatively stable viral genome strongly implicates host factors, including genetics. Mendelian large effect variants have recently been identified although these likely account for a very small number of cases.[1] On the other hand, the contribution of several common variants has been demonstrated,[2] particularly one locus on chr3 which was identified in the first major GWAS on genetic predisposition to severe COVID19.[3] Interestingly, a very recent study has convincingly shown that the risk haplotype in the chr3 locus was introgressed into modern humans from Neanderthal.[4] The distribution of this risk haplotype was estimated for a wide range of human populations although Middle Eastern Arabs were missing.[4] Here, we calculate the distribution of the risk haplotype in Arabia and discuss that in the context of the overall Neanderthal ancestry in the local population. Representative samples from the major indigenous tribes in Arabia were chosen for analysis with informed consent and genotyped as described in detail elsewhere (Mineta et al, 2020).[5] We first confirmed by Haploview that the 13 SNPs that constitute the risk haplotype are in complete LD in indigenous Arabs using previously published WGS data. We then tested the frequency of rs13078854 in 953 samples representing the 28 major indigenous tribes in Arabia. The overall risk allele frequency was 8.6% with 135 heterozygotes and 14 homozygotes (of note, homozygotes had only been documented among South Asians [~10%] and 1 individual in Colombia). As shown in Figure 1, the distribution was largely similar between the different regions.

The very recent revelation that the best-known risk haplotype for COVID-19 severity is derived from Neanderthal has important evolutionary and clinical implications.[4] Most surprisingly, the distribution of this haplotype in the world major populations did not fully correlate with the known distribution of Neanderthal ancestry. While Africans predictably lacked the risk haplotype since they are known to have no significant Neanderthal ancestry, the dramatic enrichment among South Asians and near elimination among East Asians are at odds with published estimates of Neanderthal contribution to these populations. This suggests that this risk allele may have gone through strong selection pressure in opposing directionality in different populations.[4] Native inhabitants of Arabia, or indigenous Arabs, have been hypothesized to represent a very ancient split of the early wave of out-of-Africa human migration, which is consistent with the rather low Neanderthal contribution of 2.6%.[6] It remains unclear at this point if the higher frequency of the risk haplotype (8.6%) represents positive selection since this has not been confirmed even in populations with a much higher frequency, for example, 37.8% in Bangladesh. Clinically, it is worth highlighting that despite the compelling effect of the risk haplotype on the severity of COVID-19 (OR 2.14),[2] the fact that its world distribution has only very recently been established makes it hard to conclude if this correlates with ethnic variation in disease severity. It has been noted, for example, that Bangladeshi patients in the UK are twice as likely to have severe COVID-19 (Public Health England). However, case fatality rate in Bangladesh remains relatively low at 1.5% (WHO), which is identical to Saudi Arabia (WHO) despite the dramatic difference in the risk haplotype distribution. Clearly, the risk haplotype is but one of many factors that influence the outcome of SARS-CoV-2 infection. Nonetheless, it will be helpful to track patient outcome by this haplotype in ethnically diverse cohorts to establish a more general estimate of its clinical impact.

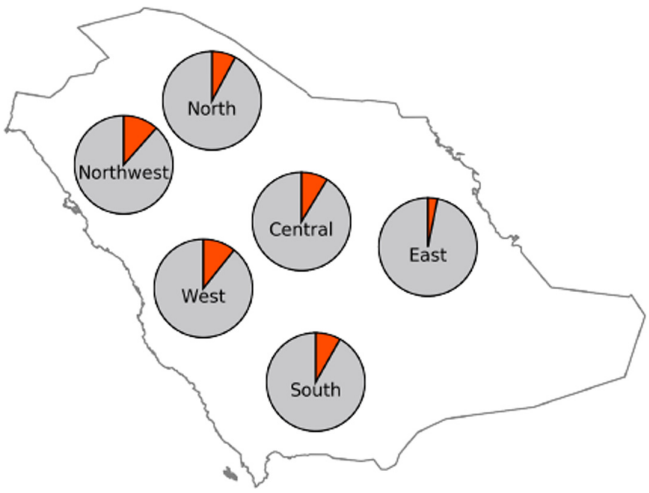

FIGURE 1 Distribution of risk allele of rs13078854 in the different regions of Saudi Arabia

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Zhang Q, Bastard P, Liu Z, et al. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. *Science*. 2020;370:eabd4570.
2. Pairo-Castineira E, Clohisey S, Klaric L et al. Genetic mechanisms of critical illness in Covid-19. *medRxiv* 2020.
3. Genomewide Association Study of Severe Covid-19 with Respiratory Failure. *New England Journal of Medicine*. 2020;383(16):1522-1534. http://dx.doi.org/10.1056/nejmoa2020283.
4. Zeberg H, Paabo S. The major genetic risk factor for severe COVID-19 is inherited from Neandertals. *BioRxiv* 2020.
5. Mineta K, Goto K, Gojobori T, Alkuraya FS. Population Structure of Indigenous Inhabitants of Arabia. *PLOS Genet*. 2020. https://doi.org/10.1371/journal.pgen.1009210 [in press].
6. Rodriguez-Flores JL, Fakhro K, Agosto-Perez F, et al. Indigenous Arabs are descendants of the earliest split from ancient Eurasian populations. *Genome Res*. 2016;26:151-162.