CASE REPORT

What Kept Back on the Mirror of COVID-19-Related Acute Transverse Myelitis? A Genetic Background!

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Abstract

COVID-19-associated acute transverse myelitis (ATM) cases have been reported worldwide. Nevertheless, Iran, Italy, and the USA are the most affected countries, witnessing the possibility that genetic factors might be associated with this susceptibility. The genetic variants of the coronavirus-2 entry mechanisms and host innate immune response-related genes like interferons, interleukins, Toll-like receptors, human leukocyte antigens, blood groups, and some risk loci may be accountable. This study describes the compatibility of the geographical distribution between ATM and the Neanderthal core haplotype that confers risk for severe COVID-19 and some possible culprit genes.

Keywords: COVID-19; Transverse myelitis; Genetic
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Introduction

The neurotropism of the novel coronavirus has been well demonstrated. Acute transverse myelitis (ATM) is not uncommon as a neurological complication associated with COVID-19. The review by Roman et al. includes a pediatric patient and provides relevant insight regarding the world distribution of COVID-19-related ATMs, resulting in more attention to its unique geographical distribution (1). However, forty-three patients were reported from twenty-one countries worldwide as follows: Seven cases from Iran, six cases from Italy and US each, four cases from the United Kingdom, two cases from Brazil, Spain, and Turkey each, and finally, one case from Australia, Belgium, China, Denmark, Germany, India, Indonesia, Mexico, Moldova, Panama, Pakistan, Qatar, Switzerland, and Emirate each. While Europe and Asia are flagship continents with 17 and 15 cases, this report does not address African countries (Figure

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1). Iran, Italy, and the USA are the most affected countries, witnessing the possibility that genetic factors might be associated with susceptibility to the COVID-19-related ATM. (Figure 1)

Materials & Methods

All scientific articles regarding the geographical distribution of ATM and the Neanderthal core haplotype that confers risk for severe COVID-19, as well as some possible culprit genes related to neurological manifestations of COVID-19 until August 01, 2021, were included.

Discussion

Historically, humans gradually encouraged both host and pathogen genetic characteristics that could play critical roles in the progression of infectious diseases. Evidence shows that the susceptibility to Influenza is strongly heritable (3). There are considerable variations in disease severity and even death rates among COVID-19 patients, highlighting the probability of genetic differences. For example, peoples of Bangladeshi origin in the UK have about two times higher risk of dying from COVID-19 than the general population. New genome-wide significant associations from 2,244 critically ill COVID-19 patients compared to healthy controls were found on chromosomes 12q24.13 in a gene cluster that encodes antiviral restriction enzyme activators; 19p13.2 near the gene that encodes tyrosine kinase-2; 19p13.3 within the gene that encodes dipeptidyl peptidase; and 21q22.1 in the interferon receptor gene IFNAR1 (4).

Similarly, one risk locus (3p21.31) has been identified as a genetic susceptibility locus associated with respiratory failure and hospitalization in COVID-19 patients. At this locus, the association signal spanned the genes, one of which is SLC6A20, that encodes the proline transporter-1, which interacts with the Angiotensin Converting Enzyme-2 (ACE-2) cell surface receptor. The association signal at locus 9q34.2 coincided with this study's ABO blood group locus. However, a higher susceptibility to COVID-19 was shown in blood group A, and a protective effect was shown in blood group O (5). Zeberg et al. revealed that the risk is conferred by a nearly fifty kilobases genomic segment that is inherited from Neanderthals and is carried by nearly 50% of people in south Asia and around 16% of people in European countries (Figure 1) (2). In contrast, a Neanderthal haplotype on chromosome 12 is protective against severe COVID-19. It is present in populations in Eurasia and America at carrier frequencies that often reach and exceed 50% (6).

However, several studies revealed that the genetic variants of the coronavirus-2 entry mechanisms and host innate immune response-related genes like

interferons, interleukins, Toll-like receptors, human leukocyte antigen (HLA), ABO blood groups, and some risk loci (e.g., 12q24.13, 3p21.31, 9q32.2, 19p13.2, 19p13.3, 21q22.1, and so on) are the main determinants of the susceptibility. Epigenetic mechanisms could regulate the interferon signaling, ACE-2, and immunity-related genes that avoid X-chromosome inactivation (7). Recently, an initial whole-exome sequencing and analysis of the host genetic contribution to COVID-19 severity and susceptibility were conducted on 332 COVID-19 patients in China. The most significant gene locus associated with severity was located in TMEM189-UBE2V1, which was involved in the IL-1 signaling pathway. They concluded that HLA-B*51:01, HLA-A*11:01, and HLA-C*14:02 alleles significantly had the worst outcome (8).

Transverse myelitis (TM), a rare inflammatory condition, damages the thoracic spinal cord with varying degrees of weakness, sensory alteration, and autonomic dysfunction. This neurological complaint has been frequently reported in COVID-19 patients (1). The cause of this condition is generally unknown (idiopathic). However, it might be associated with various infections, immune system disorders, and other inflammatory conditions (9). Interestingly, a rare genetic mutation in VPS37A has been found among family members affected with ATM, emphasizing the genetic susceptibility aspect of COVID-19-related ATM (10). Similarly, a single nucleotide polymorphism (SNP) in the human HLA region (rs1964995) was associated with neuromyelitis optica spectrum disorders (NMOSD) susceptibility. HLA-DRB1*08:02 and HLA-DRB1*16:02 were risk alleles for NMOSD susceptibility. In addition, an SNP in potassium calcium-activated channel subfamily M alfa-1 (KCNMA1) gene was associated with disability score with genome-wide significance (re1516512, $P=2.33\times10^{-8}$) and ATM (OR=1.77, P=0.011). HLA-DPB1*05:01 and HLA-DPB1*03 were reported to confer NMOD susceptibility in Japanese and Europeans, respectively (11). Ligocki et al. found a unique expansion of CD27 high plasma blasts in cerebrospinal fluid and periphery of TM patients. This expansion utilizes VH4 and JH6 genes and increases extensive somatic hyper-mutation, resulting in disease severity and progression (12).

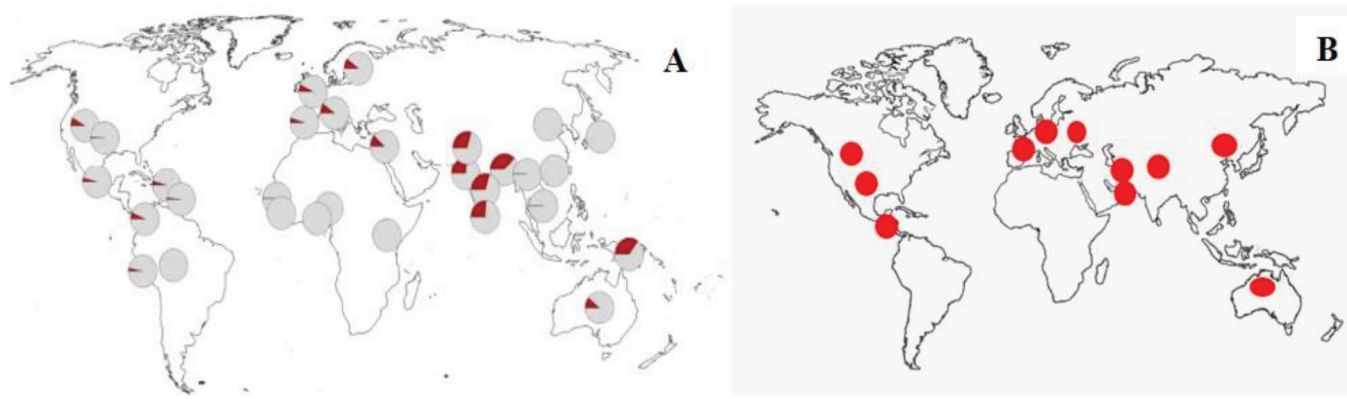

Figure 1. *Pie charts show the minor allele frequency at rs35044562 (A). A. Geographical distribution of the Neanderthal core haplotype that confers risk for severe COVID-19 [2]. B. Geographical distribution of COVID-19-related ATM.*

In Conclusion

Understanding who is at a more significant risk of severity and dangerous forms of the disease plays an essential role in ongoing studies. The genes involved in antiviral defense and the genes implicated in severe COVID-19 are increasingly being reported. The patchy geographical distribution of COVID-19-related ATMs in specific regions can be linked to the genetic background of COVID-19 and NMOSD (specifically TM) affected patients. Indeed, providing the genetic background of different phenotypes among patients affected by COVID-19 may guide targeting with more effective strategies.

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Author's Contribution

All the authors contributed to the design and implementation of the research, analysis of the results, and writing of the manuscript.

Conflict of Interest

The authors declared no conflict of interest.

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