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Multi-ancestry fine mapping implicates OAS1 splicing in risk of severe COVID-19

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Previous studies on mainly people of European ancestry have found that individuals carrying a particular segment of DNA have a 20 percent lower risk of developing a critical COVID-19 infection. This DNA segment encodes genes in the immune system and is inherited from Neanderthals in about half of all people outside Africa. Since the Neanderthal inheritance occurred after the ancient migration out of Africa, we saw a potential in focusing on individuals with African ancestry who lack heritage from the Neanderthals and therefore also the majority of this DNA segment.

We found that individuals of predominantly African ancestry had the same protection as those of European ancestry, allowing us to identify the OAS1/2/3 cluster as a risk locus for severe COVID-19 among individuals of European ancestry, with a protective haplotype of approximately 75 kilobases (kb) derived from Neanderthals in the chromosomal region 12q24.13. This haplotype contains a splice variant of OAS1, which occurs in people of African ancestry independently of gene flow from Neanderthals. Using trans-ancestry fine-mapping approaches in 20,779 hospitalized cases, we demonstrate that this splice variant is likely to be the single nucleotide polymorphism (SNP) responsible for the association at this locus, thus strongly implicating OAS1 as an effector gene influencing COVID-19 severity. In effect, the protective gene variant (rs10774671-G) determines the length of the protein encoded by the gene OAS1, with a longer variant being more effective at breaking down SARS-CoV-2.

Our study highlights the importance of conducting clinical trials and studying genetic risk factors in a wider diversity of individuals to increase our understanding and develop new drugs against COVID-19.

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