

# Correlation between Human Origin and the Severity of COVID19

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**KEYWORDS:** CAVID-19, Neanderthal, Severity, Homo sapiens



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## Abstract

It has been reported that the severity of coronavirus infectious disease (COVID-19) is due to several factors such as age and the presence or absence of chronic disease. Furthermore, it has been reported that genetic factors affect the severity of COVID-19. A recently published study of the COVID-19 Host Genetics Initiative suggests that genetic manifolds in the region located on chromosome 3 may increase the risk of the severity of COVID-19.

It is known that humans have crossed with Neanderthals, who are said to have become extinct 20,000 to 40,000 years ago and inherited their DNA. In about 50,000 years ago, risk factors of the severity of COVID-19 <sup>note1</sup> is, may have been brought from the gene of Neanderthal <sup>note2</sup>. Professor Svante Pääbo's research group in Okinawa Institute of Science and Technology Graduate University published the research results of human genetics related to the severity of COVID-19 in the English scientific journal Nature [1,2].

In COVID-19, people with chronic diseases such as hypertension and diabetes and the elderly are more likely to become severely ill with COVID-19 [3]. In addition, in the symptoms of COVID-19, genetic factors are also considered to be related to the severity of COVID-19. So far, an international project specializing in human genetics research of COVID-19, the COVID-19 Host Genetics Initiative, has reported on the existence of genes associated with the severity of COVID-19.

Genome analysis was performed in a population of approximately 3,200 in patients with COVID-19 and approximately 900,000 estimated to be uninfected with SARS-CoV-2 [1,2]. Previous studies have suggested that differences in the genetic information of "chromosome 3" out of 23 pairs of chromosomes are associated with respiratory failure associated with the need for hospitalization [1,2]. A research team led by Professor Pääbo, who is also the director of the Department of Evolutionary Genetics at the Max Planck Institute for Evolutionary Anthropology in Germany, noted that this difference is located in a small part (about 0.02%) of chromosome 3 [1,2]. It was reported that similar differences were found in the Neanderthals found in Southern Europe about 50,000 years ago.

The Neanderthals became extinct about 40,000 years ago. The Neanderthals are the closest archaic humans to the present Homo sapiens, and are like "cousins" who are said to have branched off from a common ancestor with the present Homo sapiens about 550,000 years ago [4] (Figure 1). According to a study by Professor Pääbo and others so far, crosses between the two species occurred about 40,000 to 60,000 years ago. From the results of previous studies, it has been reported that 1 to 4% of the current genetic information of Homo sapiens, excluding Africans, comes from Neanderthals. In other words, the gene associated with the severe risk of respiratory failure in COVID-19 was found to be a gene inherited from the ancient archaic Neanderthals. It is believed that if people carry this gene, they are about three times more likely to become severely ill with COVID-19. In other words, the areas where races carrying genes associated with the severity of COVID-19 live often overlap with the areas where there are many people with the severity of COVID-19 [1,2] (Figure 2).

Currently, about 50% of the people of South Asian population, such as India and Pakistan, has this gene. Then, about 16% people of the total population of Europeans, have this gene. East Asians and Africans, including the Japanese people, do not have this gene.

In previous studies, 8.5 million or more single nucleotide polymorphism (SNP) from the entire genome derived from the 1,610 people critically ill patients in the COVID-19, which have been admitted to seven hospitals in Italy and Spain and a healthy person 2,205 people is examined, and then genes associated with the severity of COVID-19 were searched [5]. As results from the outcome, the two gene region and related the severity of COVID-19 were identified (Figure 3).

An SNP in a region of chromosome 3 was identified as a gene region associated with the severity of COVID-19. In the SNP, two types of "A" and "GA" was observed. The frequency of GA in the critically ill patient group with COVID-19 was 14% in Italy and 9% in Spain (Figure 4) [5]. On the other hand, the frequency of GA in the group of healthy people was 9% in Italy and 5% in Spain, and it was found that the frequency of GA was high in the group of critically ill patients with COVID-19 (Figure 4) [5]. Other factors such as age, gender, and other

factors that contribute to the severity of COVID-19 were statistically adjusted to calculate a more certain risk. As a result, it was clarified that the risk of the severity of COVID-19 was about twice as high in GA type as compared with A type (Figure 4).

The study found that the risks associated with Neanderthal gene fragments were not evenly distributed around the world. The frequency of GA type was confirmed in various countries around the world (Figure 4). In East Asia (China, Mongolia, Taiwan, South Korea, Japan, *etc.*), the frequency of GA type has been shown to be close to zero. In Europe, the frequency of GA type is about 5-10 % (Figure 4). Data from South Asia such as India and Bangladesh show that the frequency of GA type is 25% or more (Figure 4). In addition, GA types are rarely recognized in Africa, on the other hand, the GA type in Bangladesh is most frequently recognized.

### Conclusion

The relationship between the virus and humankind revealed this time can be regarded as a historical story that led to hundreds of thousands of years ago. Unlike Asian countries, there are countries with many young patients with COVID-19 critically ill. In addition to age and chronic illness, innate genes may also be closely associated with the severity of COVID-19. It remains to be seen why this Neanderthal gene region leads to a risk of the severity of COVID-19. Further research is still being conducted to elucidate this problem.

### Annotation:

#### Note 1: Severity of COVID-19

The definition of severe is respiratory failure.

#### Note 2: Neanderthals

The male fossil human skeleton found in the Felthofer cave in the Neanderthal valley on the outskirts of Düsseldorf, Germany, in 1856 is called the Neanderthal. In other words, the Neanderthals, is a popular name of *Homo Neanderthalensis*, which is a kind of old people. About 250,000 to 30,000 years ago, Neanderthals lived in Europe and West Asia. Neanderthal brain skull long in the form of collapsed low, supraorbital ridge bulges, slope forehead and back of the head projects, leaving a characteristic of hominids. On the other hand, the brain volume is also 1,300 to 1,600 cubic centimeters, no different from *Homo sapiens*. The Neanderthal's face protrudes forward near the center. A Neanderthal man is about 165 cm tall, but is estimated to weigh more than 80 kg. Neanderthals are said to have adapted to the cold climate of Europe.

### Author contributions

TH performed most of the clinical medicine and coordinated the project. TH performed diagnostic pathological studies.

TH created the study and wrote the manuscript. IK carefully reviewed this manuscript and commented on aspects of medical science. IK shared information on clinical medicine and oversaw the entirety of the study.

### Footnote

The material (manuscript and figure) is original research, has not been previously published and has not been submitted for publication elsewhere while under consideration.

### Disclosure of potential conflicts of interest

The authors declare no potential conflicts of interest.

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Hayashi Figure 1

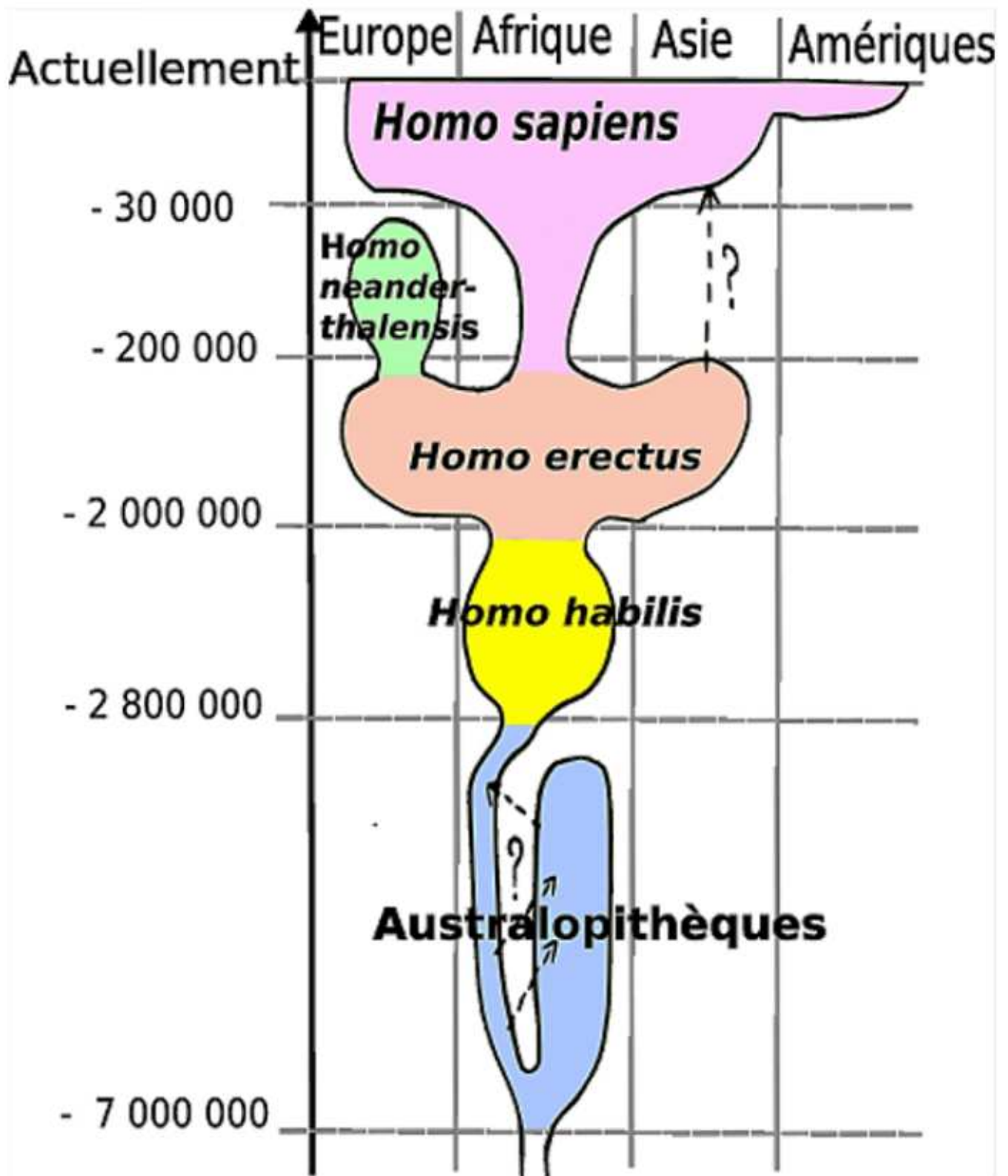


Figure 1 The Neanderthals are said to have Heidelberg ancestry, but the Heidelbergs are a type or subspecies of Homo erectus. (However, the exact difference between species and variants has not been revealed). Neanderthals are not the ancestors of Homo sapiens. Homo sapiens evolved separately from Homo erectus. The dotted lines in the figure represent the Flores and Denisovans described below.

Hayashi Figure 2

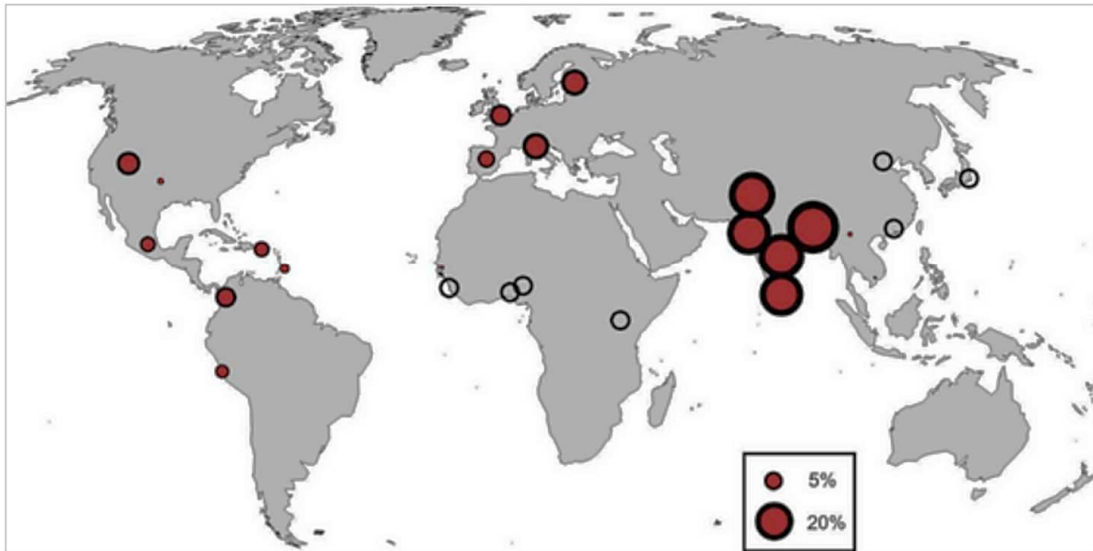


Figure 2 Areas where people live that hold DNA from Neanderthal to improve the severe risk of COVID-19 is shown in a red circle. In addition, the transparent circles shown in East Asia, including Africa and Japan, mean that the DNA was not found in this area. Figure is adapted from Ref.1 and Ref.2.

Hayashi Figure 3

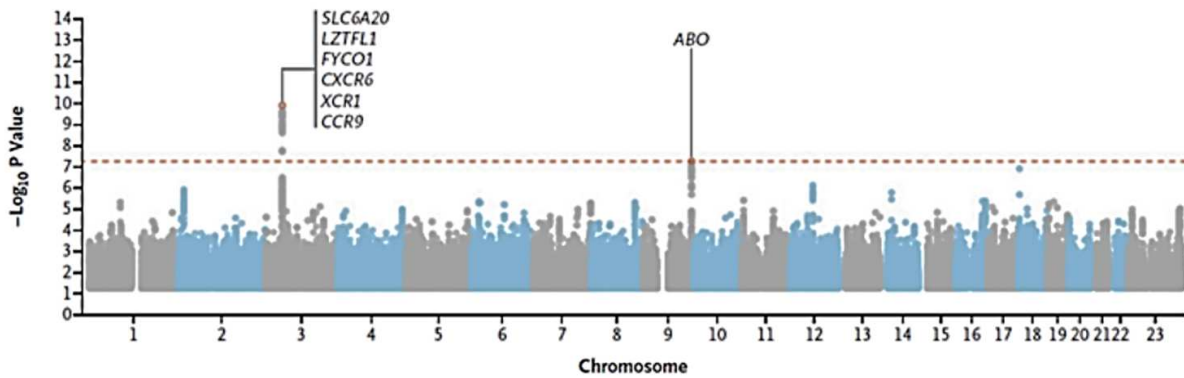


Figure 3 Genome analysis identifies genetic regions associated with the severity of COVID-19. The results of examining more than 8.5 million SNPs are shown. Beyond the orange dotted line, SNPs that are statistically associated with the severity of COVID-19 are shown. Figure is adapted from Ref.5.

Hayashi Figure 4



Figure 4 The population ratio of people with variants (A type, or AG type) that contribute to the risk of the severity of COVID-19 in each country is shown in the world map. Figure is adapted from Ref.1 and Ref.2.