



Evidence of the Ancestries of COVID-19 Virus in East Asia, More Than 20,000 Years Ago

**Dariush D. Farhud^{1,2,3}, Moslem Bahadori^{2,4}, Marjan Zarif-Yeganeh³*

1. School of Public Health, Tebran University of Medical Sciences, Tebran, Iran

2. Department of Basic Sciences, Academy of Medical Sciences, Tebran, Iran

3. Farhud Genetic Clinic, Tebran, Iran

4. School of Medicine, Tebran University of Medical Sciences, Tebran, Iran

***Corresponding Author:** Email: farhud@tums.ac.ir

(Received 15 Jul 2021; accepted 22 Jul 2021)

According to the paleo DNA studies, ancient viral epidemics can be identified through adaptation mechanisms in the host genome. Paleo virologists' studies using genetic methods and DNA testing have shown evidence that the coronaviruses dates back to more than 20,000 years ago originated from East Asia (1,2).

Studying the human genome from more than 2,500 modern humans from 26 worldwide populations of 1000 genome project, researchers deciphered the genetic "footprint" of an ancient coronavirus epidemic in the East Asia region, more than 20,000 years ago (Fig. 1). Such studies

could help identify the distant past and future viruses' outbreak. "It is like finding fossilized dinosaur footprints instead of finding fossilized bones directly," said David Enard, a professor of Ecology and Evolutionary Biology, University of Arizona, USA. "We did not find the ancient virus directly – instead we found signatures of the natural selection that it imposed on human genomes at the time of an ancient epidemic (3)." This study showed the better understanding how humans have adapted to historical coronavirus outbreaks.

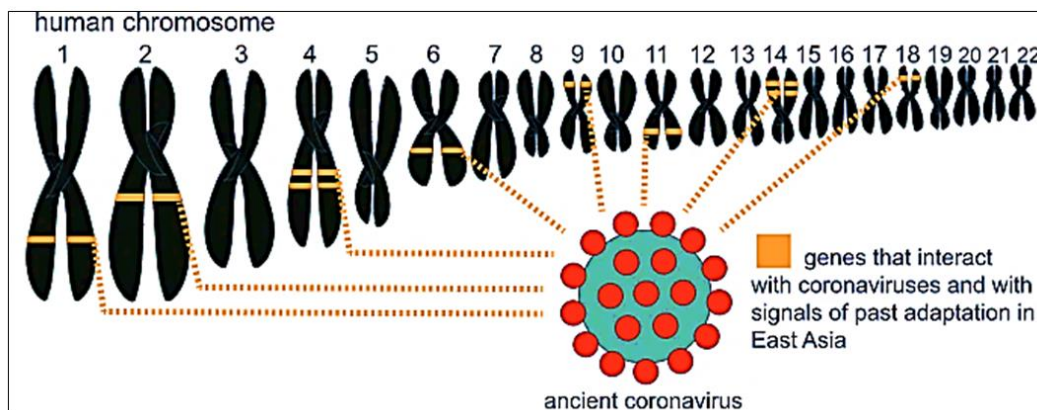


Fig.1: Ancient viral epidemics can be identified through adaptation in host genomes and human Genomes in East Asia bear the signature of about 25,000-year-old viral epidemic (3)



Copyright © 2021 Farhud et al. Published by Tehran University of Medical Sciences.

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International license

(<https://creativecommons.org/licenses/by-nc/4.0/>). Non-commercial uses of the work are permitted, provided the original work is properly cited.

The virus can rule the region for many years, unless it is managed and controlled as soon as possible through effective vaccination or treatment, can affect future human generations around the world (3).

Modern human genomes contain evolutionary information tracing back hundreds of thousands of years, including physiological and immunological adaptations that have enabled humans to survive new threats, including viruses (4,5).

Coronaviruses are a large family of viruses that usually cause mild to moderate upper-respiratory tract illnesses, like the common cold. However, some new coronaviruses have emerged from animal reservoirs over the past two decades to cause serious and widespread illness and death in the world (6).

There are hundreds of coronaviruses, most of which circulate among such animals as pigs, camels, bats and cats. Sometimes those viruses jump to humans—called a spillover event—and can cause disease. Four of the seven known coronaviruses that sicken people cause only mild to moderate disease. Three can cause more serious, even fatal, disease. SARS coronavirus (SARS-CoV) emerged in November 2002 and caused severe acute respiratory syndrome (SARS) (7). That virus disappeared by 2004. Middle East respiratory syndrome (MERS) is caused by the MERS coronavirus (MERS-CoV). Transmitted from an animal reservoir in camels. MERS was identified in September 2012 and continues to cause sporadic and localized outbreaks (8). The third novel coronavirus to emerge in this century is called SARS-CoV-2. It causes coronavirus disease 2019 (COVID-19), which emerged from China in December 2019 and was declared a global pandemic by the World Health Organization on March 11, 2020 (6).

The Coronaviruses have had perhaps a hundred different mutations so far, the most important and dangerous of which are the British, African, especially Indian (Delta), and South American (Lambda) variants. The lambda variant was first identified in Peru in August 2020, according to the WHO (9). It had been predicted the emer-

gence of these mutations, including the Delta mutation, in my previous remarks, given the genetics of the population and ecosystem of the Indian subcontinent. Older versions of the virus also appeared about 800 years ago.

The effects of this virus in humans, can lead to the activation of genes which cause resistance to this virus in humans (10).

Throughout the history of human evolution, natural selection has largely led to the preservation of proteins that physically interact with viruses, like proteins that are involved in the immune system. Million years ago, micro mutations and micro selection led to the establishment of genetic variants encoding proteins interacting viruses (VIPs) (11). Strong selection has also continued to retain VIPs in human populations over the past 100,000 years (3).

In a project on the human genome (3), 420 VIPs who could respond to the corona virus were studied in 26 populations of the 1000 genome project population (Table1).

The results of this study showed that an epidemic of coronavirus or similar viruses that used similar VIPs, existed in the ancestors of East Asia, and it was possible to identify 42 VIPs about 900 generations (25,000 years ago). The genes encoding these Cov-VIPs also have multiviral effects. In general, viruses have had a strong selective power over modern humans (3). This study is a clear indication of the adaptability of East Asian humans more than 20,000 years ago to the virus' ancestors. This compromise is limited to the same region and has not been seen in other parts of the world (3). Other independent studies have shown that mutations in VIP genes may mediate coronavirus susceptibility and also the severity of COVID-19 symptoms (Markers Associated with COVID-19 Susceptibility, Resistance, and Severity) (3-5). Several VIPs are either currently being used in drug treatments for COVID-19 or are part of clinical trials for further drug development. Researches can help identify viruses that have caused epidemics in the distant past and may do so in the future.

Table 1: Asian East population of 1000 genome project (3)

	<i>Population description</i>	<i>Superpopulation name</i>
1	Daur in China (HGDP)	East Asia (HGDP)
2	Tu in China (HGDP)	East Asia (HGDP)
3	Tujia in China (HGDP)	East Asia (HGDP)
4	Xibo in China (HGDP)	East Asia (HGDP)
5	Yakut in Siberia (HGDP)	East Asia (HGDP)
6	Oroqen in China (HGDP)	East Asia (HGDP)
7	Lahu in China (HGDP)	East Asia (HGDP)
8	Naxi in China (HGDP)	East Asia (HGDP)
9	Miao in China (HGDP)	East Asia (HGDP)
10	Han in China (HGDP)	East Asia (HGDP)
11	Northern Han in China (HGDP)	East Asia (HGDP)
12	Japanese in Japan (HGDP)	East Asia (HGDP)
13	She in China (HGDP)	East Asia (HGDP)
14	Cambodian in Cambodia (HGDP)	East Asia (HGDP)
15	Dai in China (HGDP)	East Asia (HGDP)
16	Hezhen in China (HGDP)	East Asia (HGDP)
17	Mongolian in China (HGDP)	East Asia (HGDP)
18	Yi in China (HGDP)	East Asia (HGDP)
19	Burmese in Myanmar (SGDP)	East Asia (SGDP)
20	Dai in China (SGDP)	East Asia (SGDP)
21	Thai in Thailand (SGDP)	East Asia (SGDP)
22	Cambodian in Cambodia (SGDP)	East Asia (SGDP)
23	Miao in China (SGDP)	East Asia (SGDP)
24	Yi in China (SGDP)	East Asia (SGDP)
25	Uyгур in China (SGDP)	East Asia (SGDP)
26	Japanese in Japan (SGDP)	East Asia (SGDP)
27	Han in China (SGDP)	East Asia (SGDP)
28	Ami in Taiwan (SGDP)	East Asia (SGDP)
29	Hezhen in China (SGDP)	East Asia (SGDP)
30	Korean in Korea (SGDP)	East Asia (SGDP)
31	Kinh in Vietnam (SGDP)	East Asia (SGDP)
32	Xibo in China (SGDP)	East Asia (SGDP)
33	Tujia in China (SGDP)	East Asia (SGDP)
34	She in China (SGDP)	East Asia (SGDP)
35	Tu in China (SGDP)	East Asia (SGDP)
36	Daur in China (SGDP)	East Asia (SGDP)
37	Oroqen in China (SGDP)	East Asia (SGDP)
38	Lahu in China (SGDP)	East Asia (SGDP)
39	Atayal in Taiwan (SGDP)	East Asia (SGDP)
40	Naxi in China (SGDP)	East Asia (SGDP)
41	Han Chinese South	East Asian Ancestry
42	Kinh in Ho Chi Minh City, Vietnam	East Asian Ancestry
43	Japanese in Tokyo, Japan	East Asian Ancestry
44	Han Chinese in Beijing, China	East Asian Ancestry
45	Chinese Dai in Xishuangbanna, China	East Asian Ancestry

Studies like Enard et al, help researchers to compile a list of potentially dangerous viruses and to develop diagnostics, vaccines and drugs for the event of their return (12). Due to the emergence of different mutations in this virus and adaptation of human genes on the other hand, we may see the circulation of this virus for two generations or more. On the other hand, according to some evolutionary geneticists, such predictions about the age of this gene are not easy and cannot be easily accepted (13, 14).

Years ago, in a German magazine, it was written a very detailed article about the replay of a dormant virus by a group of cavers while visiting an abandoned cave that is several hundred years old. They carried a latent out with them that caused severe human infections.

There is ample experience with many virus strains that spread every few years from around the world, especially in Asia. Also, limited viral and bacterial epidemics are usually observed with different intensity every year after religious ceremonies and pilgrimages due to the presence of pilgrims from different countries and the crowded population.

There are a lot to be said about the history of AIDS, which has spread terribly around the world in the last 3-4 decades. In 1999, researchers identified a species of chimpanzee SIV (simian immunodeficiency virus) called SIVcp2, which was almost identical to HIV, transmitted from monkeys to chimpanzees and from chimpanzees to humans through rhesus monkeys. They believe that the first human-to-human transmission of SIV to HIV, which led to a global epidemic, occurred in 1920 in Kinshasa, the capital and largest city of the Democratic Republic of the Congo, the virus appears to have been brought to the city by an infected person who had traveled to the Congo via the Cameron River (15).

Also, in the history of sexually transmitted diseases (such as syphilis), the disease was first very prevalent in South America and entered Europe in 1492 when Christopher Columbus's crew returned from the Americas. The first examples of the spread of syphilis in Europe date back to 1494 and 1495 in Naples, Italy, during the French

invasion of Italy, and then gradually spread from there to other parts of the world (16, 17).

In one of our writings (about 46 years ago) we emphasized that the greatest enemy of humanity are these viral diseases that cannot even be treated with antibiotics. The governments, instead of massive factories and staggering arms and weapons of mass destruction, must devote all their energy and resources to the fight against diseases, whether viral, bacterial or genetic, as well as four groups of cardiovascular, Cancers, metabolic and eventually mental spectrum disorders (18).

Conflict of interest

The authors declare that there is no conflict of interests.

References

1. Emerman M, Malik HS (2010). Modern Consequences of Ancient Viruses. *PLoS Biol*, 8(2): e1000301.
2. Al-Osail AM, Al-Wazzah MJ (2017). The history and epidemiology of Middle East respiratory syndrome corona virus. *Multidiscip Respir Med*, 7; 12:20.
3. Souilmi Y, Lauterbur ME, Tobler R, et al (2021). An ancient viral epidemic involving host coronavirus interacting genes more than 20,000 years ago in East Asia. *Curr Biol*, 31(16):3704.
4. Enard D, Petrov DA (2020). Ancient RNA virus epidemics through the lens of recent adaptation in human genomes. *Philos Trans R Soc Lond B Biol Sci*, 375(1812):20190575.
5. Enard D, Petrov DA (2018). Evidence that RNA Viruses Drove Adaptive Introgression between Neanderthals and Modern Humans. *Cel*, 175(2):360-371.e13.
6. NIH (2021). <https://www.niaid.nih.gov/diseases-conditions/coronaviruses>
7. Malik YA (2020). Properties of Coronavirus and SARS-CoV-2. *Malays J Pathol*, 42(1):3-11.
8. Azhar EI, Hui DSC, Memish ZA, et al (2019). The Middle East Respiratory Syndrome (MERS). *Infect Dis Clin North Am*, 33(4):891-905.

9. Aleem A, Samad ABA, Slenker AK (2021). Emerging Variants of SARS-CoV-2 And Novel Therapeutics Against Coronavirus (COVID-19). In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; Jan. Jul 18.
10. Fakhroo AD, Thani AA, Yassine HM (2021). Markers Associated with COVID-19 Susceptibility, Resistance, and Severity. *Viruses*, 13(1), 45.
11. Uricchio LH, Petrov DA, Enard D (2019). Exploiting selection at linked sites to infer the rate and strength of adaptation. *Nat Ecol Evol*, 3(6):977-984.
12. Kong HE, Stoff BK (2020). Approach to VIPs during the COVID-19 pandemic and beyond. *J Am Acad Dermatol*, 83(4):1231-1232.
13. Farhud DD, Zokaei SH (2020). Fight against Viruses (COVID-19): Peace among Nations. *Iran J Public Health*, 49(Suppl 1):1-3.
14. Farhud DD (2020). Social Health and COVID-19 Pandemic. *Iran J Public Health*, 49(10):i.
15. Wise J (2014). HIV pandemic originated in Kinshasa around 1920, say scientists. *BMJ*, 349: g5967.
16. Burg G (2012). History of sexually transmitted infections (STI). *G Ital Dermatol Venereol*, 147(4):329-40.
17. Tampa M, Sarbu I, Matei C, et al (2014). Brief history of syphilis. *J Med Life*, 7(1):4-10. Epub 2014 Mar 25.
18. Farhud DD, Zokaei SH. (2021). A Brief Overview of COVID-19 Vaccines. *Iran J Public Health*, 50 (7):i-vi.