Journal of Research High School

Vol. 2023 (1) 36 – 39
ISSN 2688-3651 [online]

Mechanics of HTLV - 1 Driven ATL

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Received November 21, 2022; Revised May 15, 2023; Accepted, June 8, 2023

Abstract

HTLV-1 (Human T-lymphotropic virus 1) is a retrovirus that can lead to the development of Adult T-cell leukemia/lymphoma (ATL), a non-Hodgkin's lymphoma, after a long latency period. Despite its low incidence rate, ATL is difficult to treat and has a poor prognosis with a median survival rate of 8 months and a 4-year survival rate of 12%. Recent research has suggested that ATL is host-driven, with low genetic diversity across endemic regions, challenging the previous assumption that ATL is solely caused by viral proteins. Blood sample studies from infected patients have revealed low genetic diversity, indicating the involvement of host genetic factors in ATL development. Host cancer genetic markers have also been found near the integration sites of the viral genome. This review highlights the correlation between patient genetics and HTLV-1 driven ATL, and how understanding the role of genetic markers and genes can lead to the development of new treatments or vaccines to improve patient outcomes.

Keywords: HTLV-1, Leukemia, ATL, Cancer, Viral Genome

1. Introduction

HTLV-1(Human T-Lymphotropic virus) is a non-Hodgkins retrovirus. Discovered in 1980 by Robert C. Gallo, HTLV-1 was the first retrovirus to have been discovered as described by Vahlne. ATL (Adult T-Cell Leukemia) is cancer that develops from HTLV-1's infection of T-Cells.

One of the most well-known retroviruses is HIV-1 (Human Immunodeficiency Virus), which was first identified in 1983 by LUC Montagnier's team at the Pasteur Institute of Paris. Similar to HTLV-1, HIV is responsible for causing AIDS (Acquired Immunodefiency Syndrome) an autoimmune disease. HIV is most transmitted through sexual contact between individuals. As of right now, there is no vaccine available for either HTLV-1, or HIV. This means that individuals infected with either virus will remain infected for life. As with other retroviruses, HIV uses reverse transcription to insert its RNA genome.

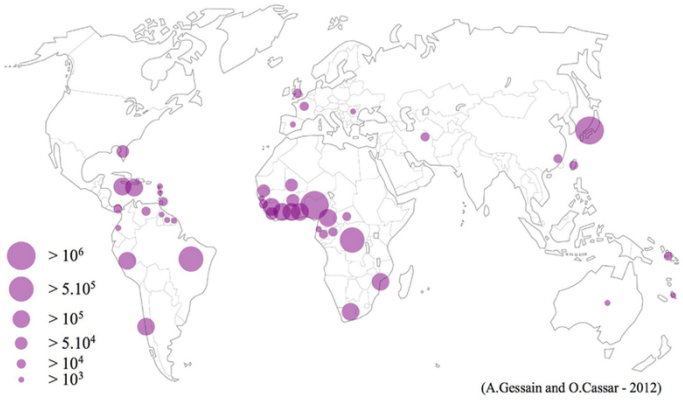

Figure 1: Geographical Distribution of HTLV - 1 cases (Gessain and Casser, 2012)

The global distribution of HTLV-1 subtypes can provide insight into the spread of this retrovirus across distinct regions of the world. As illustrated in Figure 1, the Japanese subgroup of HTLV-1 has spread to eastern China and Korea, while the African subgroup has been observed to mutate and diversify within specific regions of Africa. The higher prevalence of HTLV-1 in Africa, especially among men with multiple wives, suggests that cultural practices may contribute to the spread of the virus. This is important considering that the male-to-female transmission rate is 60.8%, while the female-to-male transmission rate is merely 0.4% shown in recent studies by Nunes et al. (2019).

Similarly, the South American subgroup has been observed to travel to North America, showcasing the influence

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ISSN 2688-3651 [online]

of physical geography on HTLV-1.

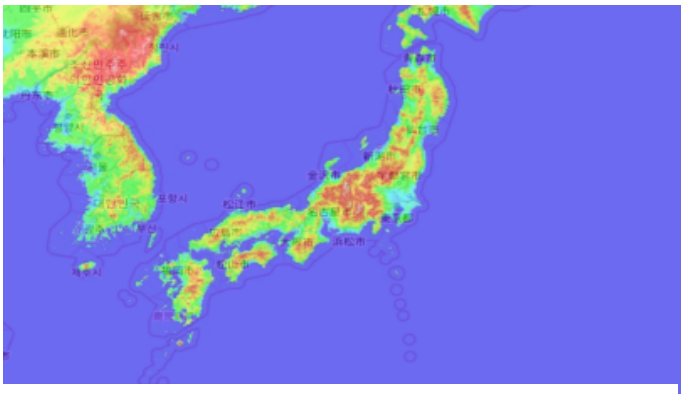

Figure 2: Elevation Heat Map of Japan; Japanese macaques are known to inhabit the mountainous regions of Japan (Yoshikawa et al., 2014).

Furthermore, the discovery of a primate counterpart to HTLV-1, known as STLV-1 (Simian T-Cell Leukemia Virus), has led researchers to hypothesize that the virus may have been transmitted to humans through contact with infected primates according to Jègado et al. (2019). This theory is supported by evidence that the southern region of Japan, where HTLV-1 is prevalent, has a higher elevation level as shown in Figure 2 below. This makes it a potential habitat for primates.

Similar to African hunters who hunt red colobuses in East Africa, which are known to carry STLV-1 (Leendertz et al., 2004), it is common for farmers or hunters in Japan to come into contact with these primates. Monkeys were known to terrorize villagers, leading to retaliation and the killing of the monkeys (Ohkuma & Tsuji, 2009). The African subtype of HTLV-1 is prevalent in central and East Asia, where red colobuses are found (Gessain et al., 2013). It is possible that the virus was spread through food preparation, like SARS-CoV-2, which is believed to have originated from horseshoe bats (Mallapaty, 2020).

Alongside STLV-1, a parasite known as *Strongyloids steracoralis* can contribute to a higher risk of developing ATL compared to only having HTLV-1 (Carvalho et al., 2015; Gotuzzo et al 2015). The mechanism by which *Strongyloids steracoralis* accelerates the development of ATL is not fully understood, but it is thought to involve the parasite's ability to suppress the host's immune system and increase HTLV-1 proviral load (Ito et al., 2014; Koga et al., 2005). Therefore, it can be hypothesized that the parasite plays an important role and should not be overlooked when considering the prevention and management of ATL in endemic areas.

In this review, we will explore the significance of HTLV-1 and ATL, which have a considerable impact on public health worldwide. Even though less than 5% of individuals infected with HTLV-1 develop ATL, the disease is highly aggressive and has a low survival rate. Additionally, there is currently no established treatment or vaccine available, making the development of effective interventions a pressing concern. By highlighting the correlation between patient genetics and HTLV-1 driven ATL, this review aims to emphasize the importance of understanding the role of genetic markers and genes in the development of ATL. By doing so, we can identify potential therapeutic targets and develop new treatments or vaccines to improve patient outcomes.

2. Discussion

In central Africa, there are many diseases such as Malaria, Yellow fever, Dengue, and Ebola. This high prevalence indicates that genetics must play an important role in developing ATL. A lot of these other diseases are rampant in this region due to many factors, but genetics plays a big role. It could be that the genetics of many people in Central Africa and Japan could be suffering from a malignancy in genetics. This would make sense because HTLV-1 originates from both countries, A gene could be passed on from a previous generation that may cause vulnerability in the genes of their descendants. Recently, a study has been found that states that integration sites of HTLV-1 are near genetic cancer markers.

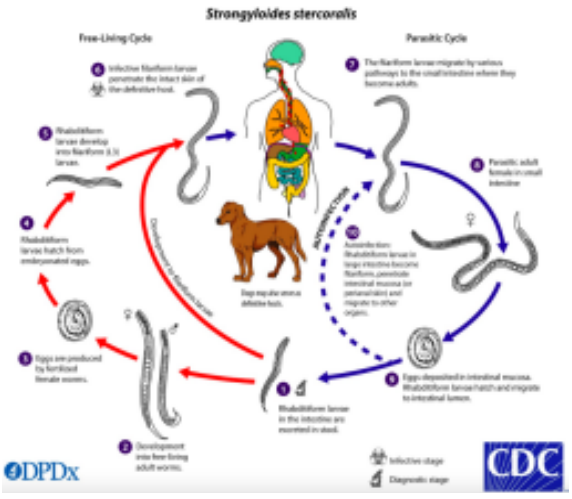

Figure 3: Strongyloids Stercoralis life cycle (https://www.cdc.gov/dpdx/strongyloidiasis/modules/Strongyloides_LifeCycle_lg.jpg)

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ISSN 2688-3651 [online]

(Rosewick, N., Durkin, K., Artesi, M. et al., 2017). The people of these endemic regions could also have these genetic markers from which they could be getting infected. In Southern Japan, Ebola, and Dengue are also prevalent. These diseases may be associated with HTLV-1 and also support the possibility that genetics influences disease rates. It is known that parasites like *Strongyloids Stercoralis* can infect the host that may also have HTLV-1. So, it is reasonable to infer that other viruses or diseases can help increase the chances of developing ATL. Testing the samples of other diseases in these endemic regions can majorly impact the knowledge of HTLV-1 and ATL.

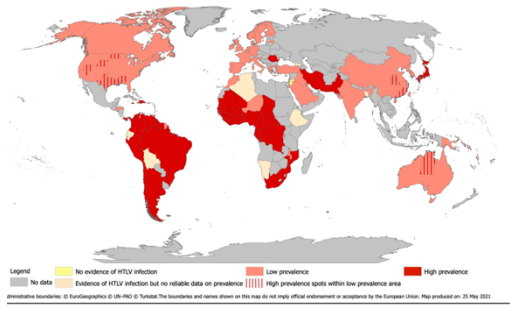

Figure 4: HTLV - 1 Distribution Map. Josh King-Robson,1 Timothy Hampton,2 Carolina Rosadas,3 Graham P Taylor, 3 Biba Stanton (2021)

In the central region of Africa alongside HTLV-1, some carriers have a parasite called *Strongyloids steracoralis*. This parasite would enter the body through soldiers' wounds during wartime. The life cycle of the parasite can be viewed in the figure below. This parasite can be found in areas where agricultural activities are performed. *Strongyloids steracoralis* can be transmitted through birds, reptiles, amphibians, primates, dogs, and cats.

When Co-infected with HTLV- 1 the growth rate of Adult T-Cell Leukemia is increased. This is due to the parasite's attack mechanism on the host's immune system which can increase the speed of leukemia. In the maps below, the prevalence of *strongyloids* and HTLV-1 is presented in the regions shown in Figures 4 and 5.

It can be seen in figures 4 and 5 Africa the regions of the high prevalence of *Strongyloids* and HTLV-1 are similar. It can be considered that in these regions HTLV-1 and *Strongyloids* can coexist in a person's body and cause ATL.

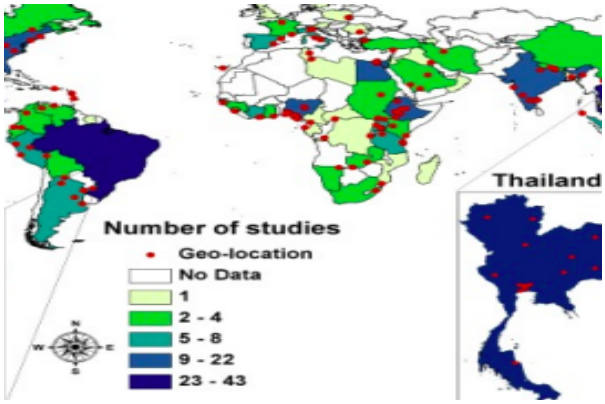

Figure 5: Strongyloids Stercoralis distribution map (Schär, et al., 2013).

3. Conclusion

HTLV-1 and ATL are not as widely recognized as many other viruses and diseases, and increasing awareness about them is crucial. Without adequate awareness, funding for research and the development of vaccines will be insufficient, hindering the ability to combat the spread of the virus. It is essential to understand the various factors contributing to ATL, such as *Strongyloids steracoralis*, genetics, and cancer markers. Genetics plays a significant role in determining the prevalence of ATL in certain regions, such as Southern Japan and Africa, and ancestry can be a predictor of one's likelihood of developing the disease.

Given the seriousness of this disease and its prevalence in endemic areas, it is critical to develop a vaccine for HTLV-1 and distribute it to affected zones. With more research, we can better understand the virus and develop effective prevention and treatment strategies. The fact that hundreds of thousands of people worldwide are affected by HTLV-1 and ATL cannot be ignored. Thus, we must prioritize finding ways to address the problem and work towards a solution.

Acknowledgments

I appreciate my parents for supporting me throughout my research. I also thank my research advisor Natalia for helping me throughout my research essay.

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ISSN 2688-3651 [online]

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