Mechanics of HTLV - 1 Driven ATL

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Abstract

HTLV - 1 (Human T - lymphotropic Virus -1) is a retrovirus that can cause a non-Hodgkin's ATL (Adult T - Leukemia/ Lymphoma). This virus can develop into ATL after a latency period of 30+ years after initial infection and integration of the viral genome into the host genome. (International Agency for Research on Cancer, 2012) This disease can be hard to treat in its ``Aggressive" forms as stated by the Lymphoma Research Foundation. This virus can be spread through bodily fluids such as semen or breast milk from an infected person as described by the WHO. Although less than 5% of people who have HTLV - 1 develop ATL, most patients with ATL pass away with a median survival rate of 8 months and a 4-year survival rate of 12%. Kensai Tobinai(2009). ATL is currently known to have 4 subtypes; Smoldering, Chronic, Acute, and Lymphomatous. Shimoyama M. (1991). They vary by their location and progression within the body. Currently, there is no vaccine against the virus, and ATL has no set treatment, guaranteeing life. David I. Marks, Clare Rowntree(2017). The virus-driven ATL is known to have low genetic diversity across the endemic regions of southern Japan, South America, The Caribbean, and tropical Africa. Gessain and Cassar, (2012) This is interesting since ATL has been previously thought to be driven by viral proteins rather than host genetics. Bangham, C. R., & Ratner, L. (2015); Toshiki Watanabi(2017).

This evidence has shown that this virus can develop based on the host's genes. Furthermore, the studies of the blood samples from patients infected with HTLV - 1 also show that the samples have low genetic diversity.Nobre, A., Almeida, et al(2018). This suggests host-driven genetic factors that drive the development of ATL. In addition, the integration sites of the viral genome are near host cancer genetic markers.Rosewick, N., Durkin, K., Artesi, M. et al (2017) . In this review, we present the evidence gathered to date that demonstrates the correlation between patient genetics and HTLV - 1 driven ATL.

HTLV-1 Background

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 infection of T-Cells. Durer C, Babiker HM. Adult T Cell Leukemia. (2022).

A more known example of a retrovirus is HIV - 1 (Human Immunodeficiency Virus), which was discovered in 1983 by Luc Montagnier's team at the Pasteur Institute of Paris. Gallo R. C. (2005). Similarly to HTLV - 1, HIV causes AIDS (Acquired Immunodeficiency Syndrome), which is an autoimmune disease. HIV transmits through sexual contact between people. If you get HIV you will have it for life, as there is no vaccine for it. WHO

Similarly to HTLV - 1, HIV like other retroviruses uses reverse transcription, to insert its RNA genome and produces a double-stranded DNA copy. There are no vaccines against HIV - 1 infections.

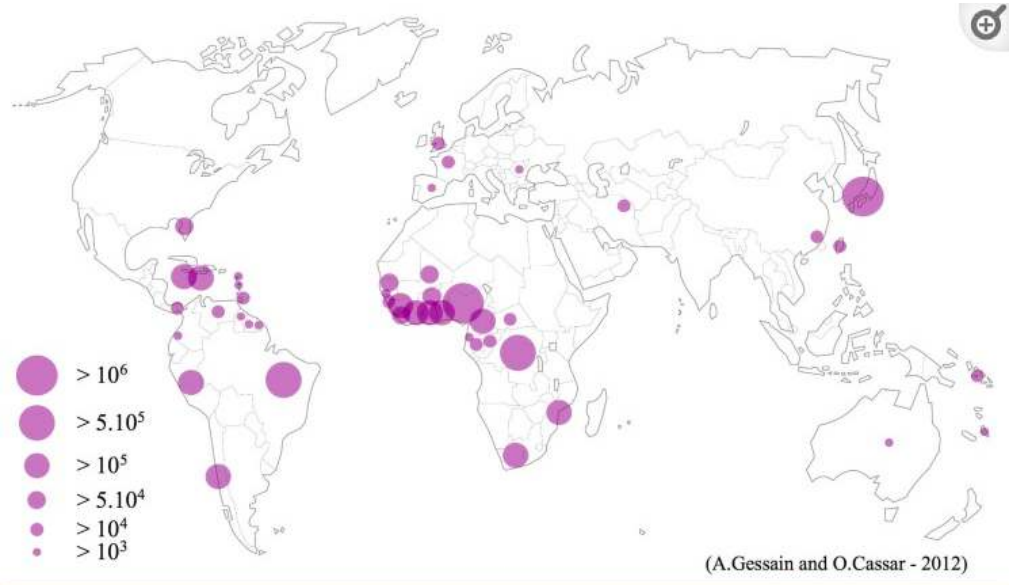

Figure 1: Geographical Distribution of HTLV - 1 cases (Gessain and Cassar, 2012)

The map in Figure 1 above shows us the distribution of HTLV - 1 cases in the world. This map can help us visualize the endemic locations and possibly aid us in the donation of vaccines when further knowledge is known.

The map in Figure 2 shows the transmission paths of HTLV - 1 from humans to humans. We can clearly see that the virus is more prevalent in Japan, Africa, and Southern America.

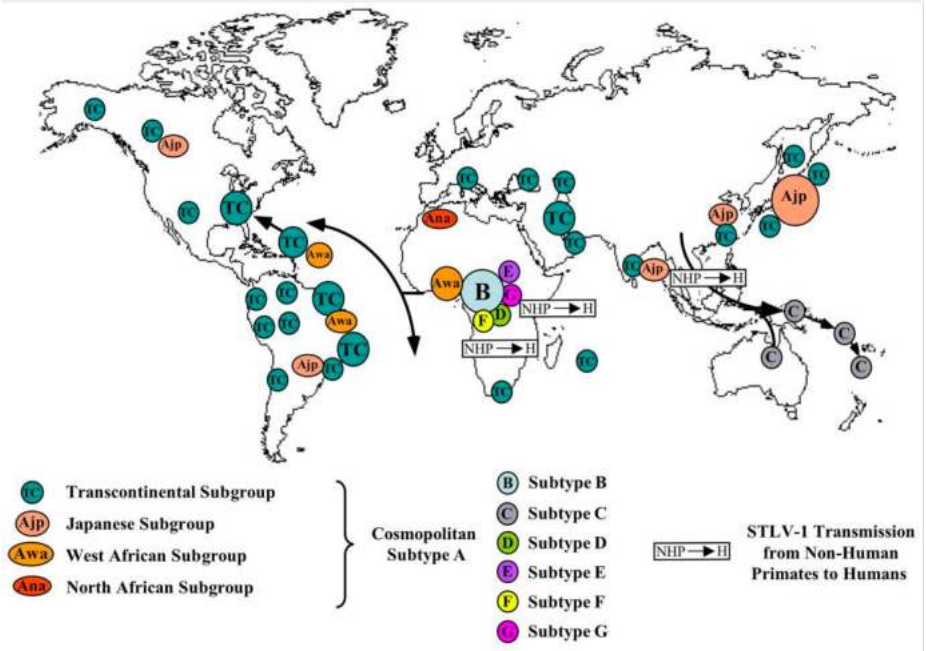

Figure 2: Known Routes of HTLV -1 spread by humans(Gessain and Cassar, 2012)

We can see in Figure 2 that the Japanese subgroup spread to eastern China and Korea. The African subgroup can be seen mutating as there are multiple subtypes in one region. HTLV - 1 may be more common in Africa may be due to the fact that men in Africa may have more than one wife. This is important due to the fact that the men-to-woman transmission rate is 60.8%, while the woman-to-men rate is only 0.4% shown in recent studies by Nunes, D., Boad Sorte et al. The South American subgroup can be seen traveling up to North America. These different routes show us how the different landscapes and cultures affect how HTLV - 1 travels through different regions of the world. We can also determine how different races are prominent to having HTLV - 1 via genetics.

Slightly after the discovery of HTLV - 1, a primate counterpart was soon discovered. 1.Jégado, B., Kashanchi, F., Dutartre, H. et al. (2019). It can be believed that STLV - 1 was transmitted to humans after contact with a primate which makes sense because in the southern region of Japan the elevation level is higher than much of the rest of the country as shown in Figure 3 below.

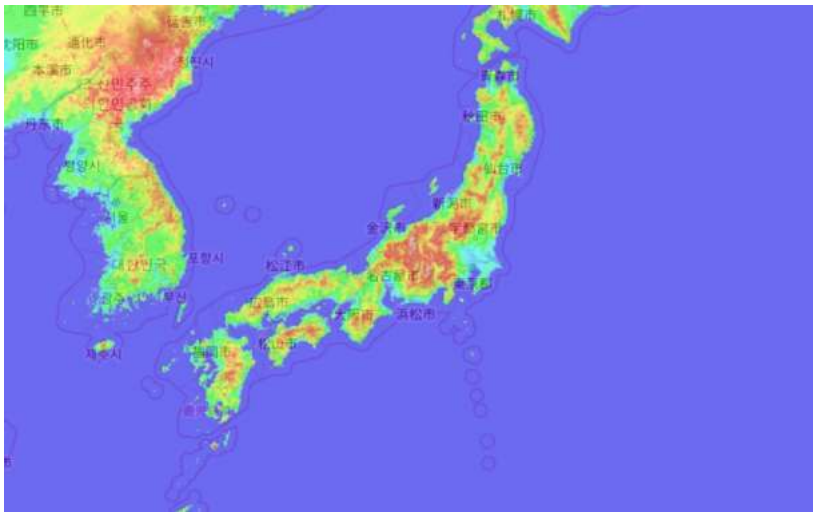

Figure 3: Elevation Heat Map of Japan (https://en-gb.topographic-map.com/)

Japanese macaques are a species that live in the mountainous regions of Japan. It would make sense that a farmer or hunter would come in contact with one of these monkeys. It was common that monkeys would terrorize villagers, so they would fight back killing the monkeys. This can be said for the African subtype as well. African hunters would hunt a species of primates called “red colobuses.”Red colobuses are also prevalent in East Africa, where HTLV - 1 cases are at a high. Red Colobuses are also known for carrying STLV - 1 as studied by Leendertz SA, Junglen S, Hedemann C, Goffe A, Calvignac S, et al. It would be logical if one spread STLV - 1 through food preparation like COVID-19. We can connect our knowledge of these two viruses. Based on genetic sequences scientists have inferred that SARS-CoV-2 originated from horseshoe bats. Smriti Mallapty (2020)

Strongyloides stercoralis is a parasite that is also prominent in central Africa that can speed up the development of ATL with HTLV-1. When co-infected studies show that ATL development may be faster. The parasite can attack the immune system, disabling it which

helps the virus attack the body easier, which is also noted by Schär, F., Trostdorf, et al and Yoshiya Sato, Yoshiyuki Shiroma et al.

HTLV - 1 infects a cell and then makes DNA from the infected cell RNA blueprint using an enzyme called reverse transcriptase. This DNA then acts as the blueprint to make more RNA and then viral proteins. The DNA form integrates at a random site within the host genome. When studying samples often a peripheral blood smear happens. As defined by the NIH, a peripheral blood smear is ”a procedure in which a sample of blood is viewed under a microscope to count different circulating blood cells (red blood cells, white blood cells, platelets, etc.)”. When a peripheral blood smear is conducted on an HTLV-1 sample special cells called “flower cells” can be found. These cells are shown in the image below. These infected T- cells indicate that the patient from which the sample was drawn is positive for HTLV - 1. These are leukemic cells that have an indented nucleus and usually are only found in HTLV - 1 positive samples.

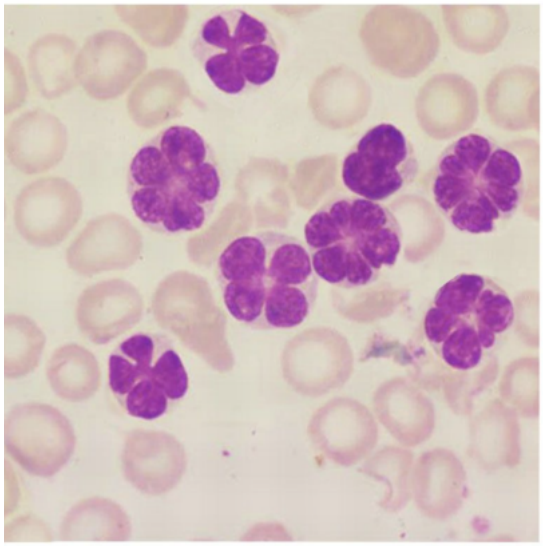

Figure 4: HTLV - 1 Positive Sample
(https://imagebank.hematology.org/image/12563/flower-cells-of-leukemia)

ATL Has four different subtypes; Smoldering, Chronic, Acute, and Lymphomatous. Smoldering and Chronic subtypes grow slowly, while Acute and Lymphomatous grow rapidly, while the Lymphomatous subtype starts in the immune system, unlike the others. This Leukemia/ Lymphoma has no direct treatment, but can be treated by stem transplant surgery. Since Leukemia attacks the bone marrow STS(Stem Transplant Surgery) can be helpful. STS can help patients with ATL because it takes the unhealthy cells produced by the bone marrow, and replaces them with healthy ones. These healthy stem cells can start producing blood cells again, which was paused when leukemia attacked the bone marrow. When conducting STS we also get rid of the genetic mutations while replacing cancerous cells with healthy ones. *Shimoyama M. (1991).*

Discussion

In central Africa, there are a lot of diseases such as Malaria, Yellow fever, Dengue, and Ebola. At this high of a number, genetics has to play a certain 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 of these countries, so a gene could be passed on that could leave this vulnerability in the genes of the people that originate from them. Recently a study has been found that states that integration sites of HTLV - 1 are near genetic cancer markers.*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 is also prevalent. Maybe these diseases can be associated with HTLV - 1 and also help us study the possibility of genetics influencing disease rates. It is known that parasites like *Strongyloids Stercoralis* can be infecting 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.

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. We can see the life cycle of the parasite in the figure below. This parasite can be found in areas where agricultural activities are done. *Strongyloids Steracoralis* can be transmitted through birds, reptiles, amphibians, primates, dogs, and cats.

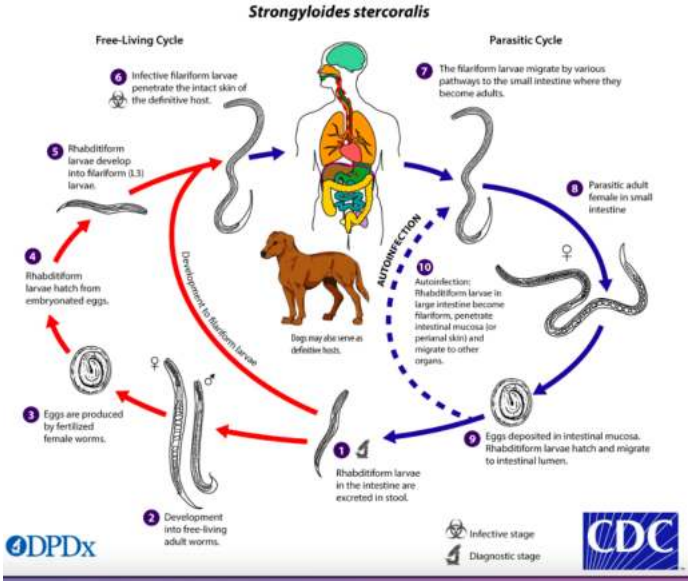

Figure 5: Strongyloids Stercoralis life cycle (https://www.cdc.gov/dpdx/strongyloidiasis/modules/Strongyloides_LifeCycle_lg.jpg)

When Co-infected with HTLV - 1 the growth rate of Adult T-Cell Leukemia can be 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 6 and 7.

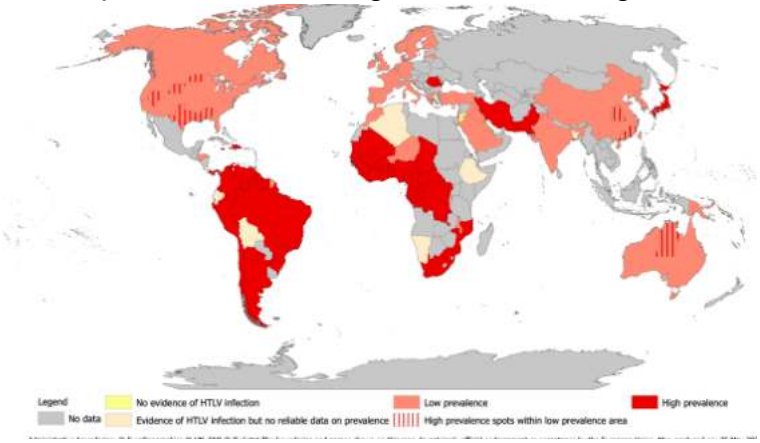

Figure 6: HTLV - 1 Distribution Map. (Josh King-Robson,1 Timothy Hampton,2 Carolina Rosadas,3 Graham P Taylor,3 Biba Stanton) (2021)

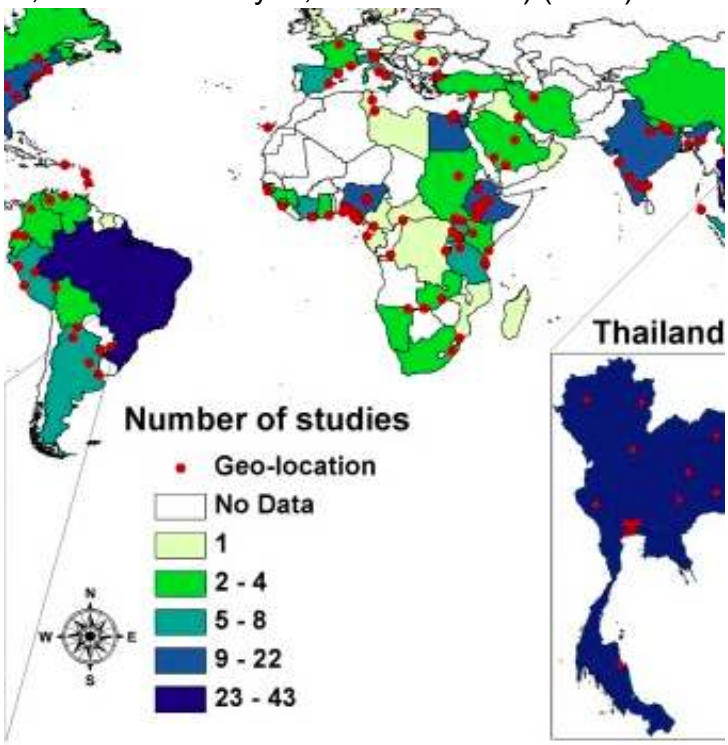

Figure 7: *Strongyloids Stercoralis distribution map (Schär, F., Trostdorf, U., Giardina, F., Khieu, V., Muth, S., Marti, H., Vounatsou, P., & Odermatt, P.) (2013).*

It can be seen in figures 6 and 7 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.

Conclusion

HTLV - 1 and ATL are not as known as many other viruses and diseases in the world. We should spread awareness so more people can learn about it and more research can be done. The virus also does not have a vaccine yet. More knowledge about this virus will help us make a vaccine for it and distribute it in endemic areas in the world. There are also multiple factors of ATL we should keep in consideration; such as *Strongyloids Stercoralis,* genetics, and cancer markers. Genetics helps us determine why some places are more endemic than others, such as Southern Japan and Africa. We can predict the chances of developing ATL by seeing what ancestry a patient might have. It is clearly apparent to us that HTLV-1 and ATL is a big problems in our world and we should work to fix it. The sooner we learn more knowledge we can help the hundreds of thousands of people worldwide.

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