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Diseases and Human Evolution: Understanding the Relation Through Endogenous Retroelements’ Impact on Evolution and Sickle-Cell Trait Prevalence in Malaria Endemic Regions as Proof of Human Evolution and Natural Selection

ABSTRACT

Diseases were and still are fundamental to evolution. From proving it happened to actually contributing to it, they have shaped the course of evolution by natural selection. In this review, two examples of the impact of illnesses on evolution, sickle-cell trait prevalence in malaria endemic regions and Endogenous Retroviruses (ERVs) in human and non-human ape genomes, were explored in order to establish this connection. Literature reviews were performed on a number of articles pertaining to these topics and the data was compiled in order to write this review, which encompasses several different topics that are relevant to this theme.

Keywords: human evolution; natural selection; sickle-cell trait; malaria; human endogenous retroviruses; evolutionary biology

INTRODUCTION

It is well known that human evolution was and still is heavily impacted by diseases [14], but understanding exactly how is one of the current big questions being asked by the scientific community. Pandemics and epidemics--past and present-- have not only influenced the course of humanity by directly impacting human evolution, but also prove Darwin’s theory of evolution by turning the human genome into a living archive of inactive viruses that once plagued humankind. In fact, 5-8% of the human genome is composed of endogenous retroviruses with viral sequences similar to those of infectious retroviruses [10].

The malaria epidemic that has been overtaking the African continent for more than 5000 years and its connections to the rising number of sickle-cell disease diagnoses is certainly a more current example of the impact that diseases can have on natural selection. Malaria endemic regions coincide with the regions of most notable prevalence of the sickle-cell trait, a mutation in the gene responsible for beta-globin production [1].

In this article, the relation between diseases and human evolution will be explored from two different points of view: the malaria epidemic and its relation to the sickle-cell trait and HERVs in the human genome, both of these being explored as proof and contributing factors to human evolution and natural selection.

METHODS

To understand the impact of diseases on evolution by natural selection, I performed a search for a variety of articles pertaining to the themes explored and performed literature reviews. The sourced information was then compacted into this article for the sake of easy access and creation of an overview of a series of related topics.

To perform the search, these filters were used:

* malaria AND sickle-cell trait
* epidemics AND natural selection AND evolution
* human endogenous retrovirus AND disease AND evolutionary biology AND human genome

Only unrefuted articles were used. In order to check the reliability of the information, the impact factor of the journals, where the articles were published and the number of accesses and citations were taken into consideration.

RESULTS

**Sickle-cell trait prevalence in malaria endemic regions as proof of evolution by natural selection:**

Sickle-cell anemia and the sickle-cell trait:

Sickle-cell disease is a disorder caused by a mutation in the HBB gene, responsible for the production of hemoglobin beta. There are several types of possible mutations responsible for the defect, all of which cause the red blood cells to become rigid, sticky and sickle shaped because of the mutated beta-globin. The hemoglobin is made up of two alpha-globins and two beta-globins, meaning that a person diagnosed with sickle cell disease will have defectuous hemoglobin (hemoglobin S) because of the mutated beta-globins. Hemoglobin S clumps when there is not enough oxygen in the red blood cells, which is what causes the red blood cells of these individuals to become rigid and sickle shaped in venous blood. This impedes them from carrying oxygen properly.

Individuals diagnosed with sickle cell disease are homozygous and are at disadvantage, since the severity of the symptoms often cause premature deaths. 80% of homozygous carriers pass away before being able to reproduce [2].

Homozygous sicklers present serious symptoms such as [3]:

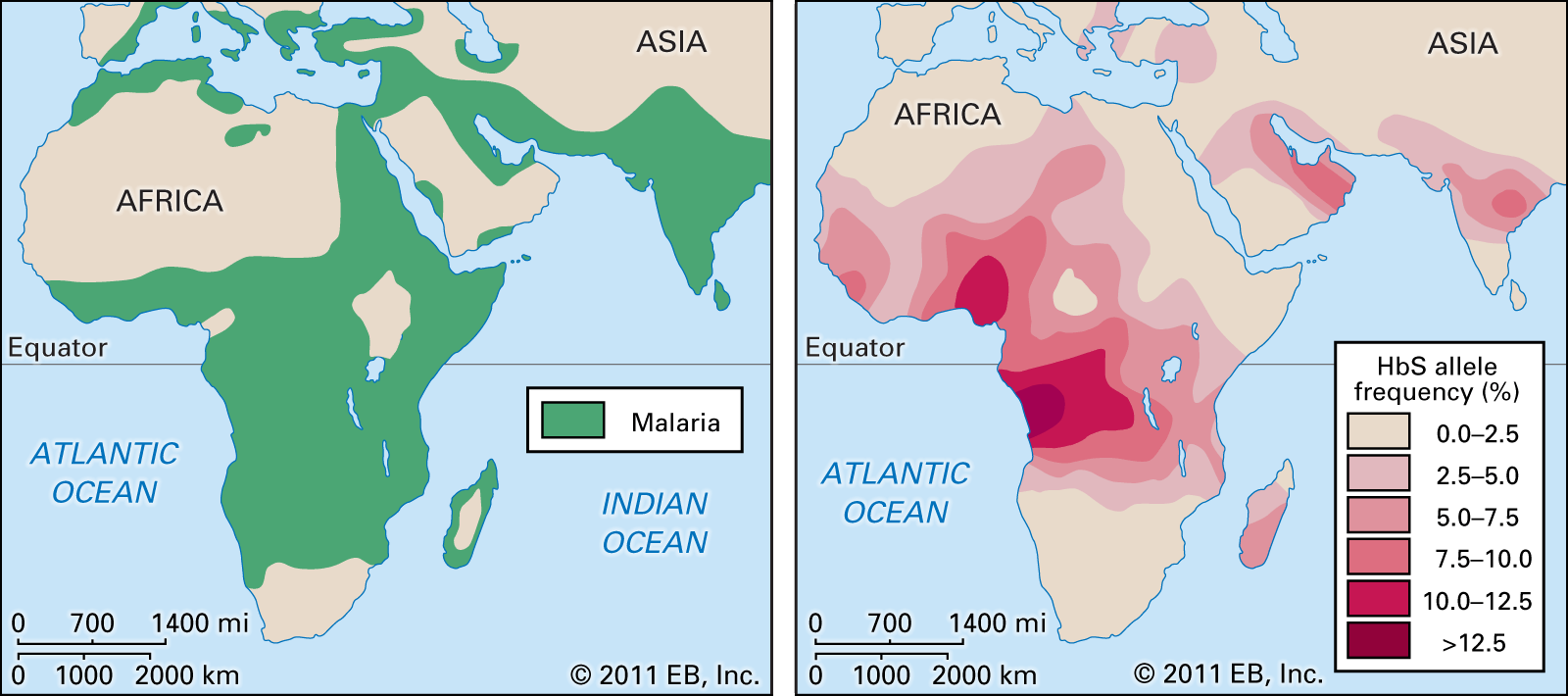
* Anemia: Lack of red blood cells because of the much shorter life span of hemoglobin S (10 to 20 days) when compared to normal adult hemoglobin A (120 days).
* Pain episodes: Occur when sickle cells block blood flow in small veins.
* Organ damage: Occurs over time because not enough oxygen gets to the individual’s organs because of the misshapen cells.

Heterozygous sickle-cell trait carriers--it is worth noticing that carrying the sickle-cell trait isn’t the same as having sickle-cell anemia, which is a recessive homozygous disease--, on the other hand, do not present severe symptoms since they inherited the unmutated, dominant allele from one parent [2]. This means that these individuals tend to have equal quantities of hemoglobin S and normal adult hemoglobin A [2]. These SA individuals do not have sickle-cell anemia and are healthy.

The statistical relations between the sickle-cell trait and malaria:

Because of the seriousness of the consequences of sickle cell anemia, nothing could truly explain why the disease is still so prevalent. In 1949, though, Anthony C. Allison noticed that malaria endemic regions have a very high number of sickle-cell trait carriers and hypothesized that heterozygotes have a selective advantage because they are relatively resistant to malaria. They then pass on the trait, explaining why a normally disadvantageous characteristic would still be so prevalent [5].

In 1953, after conducting his first experiments with adults and determining that the results would be tainted because of the effects of acquired immunity, Anthony C. Allison conducted experiments using blood samples from 6 month old to 4 year old children from Buganda. The samples showed: “Children heterozygous for HbS were found to have lower parasite counts than children with HbA. In particular, the high parasite counts shown previously by Field to be correlated with mortality were significantly less frequent in the AS group. I postulated that AS children are more likely to survive through early childhood in a highly malarious environment than AA children.” [1] [5]

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Source: <https://www.britannica.com/science/sickle-cell-anemia>

The sickle-cell trait has been proven to protect carriers from the malaria parasites-- how does that work?

*Malaria causative agent Plasmodium sp. and its life cycle in the human host:*

The *Plasmodium sp.* is the causative agent of malaria. It is a protozoan and only five species can cause the disease, *falciparum* being the most serious type. *P. falciparum, P. malariae, P. vivax, P. ovale* and *P. knowlesi* are the five different pathogenic *Plasmodium* species that cause malaria [11].

A female *Anopheles* mosquito infected by *Plasmodium sp.* feeds off an individual and injects sporozoites into the human host. These infect liver cells, mature into schizonts and ultimately burst, releasing merozoites and asexually multiplying in red blood cells. This is the stage responsible for the clinical manifestation of malaria. The blood stage is also the most relevant one to this paper, since this is the reason for the malaria resistance in sicklers. Some parasites will then go on to a sexual stage, generating gametocytes which will infect the *Anopheles* mosquito when it feeds off the human host [4].

*Heterozygous sickle-cell trait carriers are at selective advantage--why?*

As previously discussed, SS homozygotes are at disadvantage when compared to heterozygotes and non-sicklers (AA homozygotes), since the severity of their symptoms leads them to premature deaths [2]. Heterozygotes, though, are at advantage when in malaria-endemic regions.

Heterozygous sickle-cell trait carriers, differently than individuals with sickle-cell anemia, produce both healthy and defective beta-globin. Since the malaria parasite *Plasmodium* is an obligate microaerophile [7], it cannot survive in sickle shaped cells because the defective beta-globin impedes the red blood cells from carrying oxygen [1] [5].

Because heterozygotes have both S and A hemoglobin, they will end up having a significantly lower parasitic load but will still present healthy red blood cells to carry out their proper function, putting them at selective advantage [1] [5].

Conclusion:

The relation between malaria and the sickle-cell trait is of extreme importance to evolutionary biology because it quite literally proves Darwin’s theory of evolution to be true. This is a trait that, if not for malaria, would have probably been eliminated long ago because of its selective disadvantages in non-endemic regions. This process--heterozygote has selective advantage and passes on the sickle-cell trait--has been going on for such a long time (~5000 years), that African-Americans are much more likely to be born with sickle-cell anemia than Americans of Hispanic descent, por example [15].

**Human endogenous retroviruses and human evolution:**

Introduction:

When searching for proof of human evolution, the genome is the first thing that comes to mind. Currently, about 8% of our genome is made up of endogenous retroviruses, a type of LTR retroelement that was integrated into the genome through the infection of germline cells [10]. When a comparative analysis of two different genomes is performed, endogenous retroviruses are incredibly useful when it comes to proving those two species are related. This is because the probability of a retrovirus infecting the same site in two different species is so incredibly miniscule, that if they share the same ERV originated gene sequence, in the same site, common descent is certain [8]. Retroviruses with open reading frames (ORFs) have been found in the human genome and proven to encode proteins, directly influencing human evolution and physiology.

Retroviruses:

Retroviruses are viruses that have single-stranded RNA for genetic material and use the reverse transcriptase enzyme to transform the RNA into cDNA. They infect the host by injecting the cDNA created during reverse transcription into the host’s cells. After this happens, the viral cDNA is integrated into the cell’s genome and is expressed using the host cell’s machinery, generating new components which, after assembled, will create new viruses [10] [9].

Endogenization:

Most of the times an organism is infected by retroviruses, the DNA insertion occurs in somatic cells, meaning that the viral DNA will die out with the host. Sometimes, though, the insertion occurs in germline cells, being transmitted from generation to generation and ultimately being inserted into the host species genome. The endogenization of retroviruses implies a number of effects regarding the host, such as: ERV-Derived proteins, alteration of gene expression and presentation of alternative splicing sites [10] [9].

Endogenous retroviruses in humans and non-human apes as proof of evolution and existence of a common ancestor/origin:

The integration of many HERV-K (human endogenous retrovirus K) into the human genome occurred before the separation of the human lineage from gorilla and chimpanzee lineages, and many others occurred after this separation, and can be found at orthologous positions in chimpanzee, gorilla, human and bonobo genomes [8]. This indicates that the HERV-K group has been around before and after the separation of these lineages. It also indicates that all of these species are related and share a common ancestor, since the probability of the same retrovirus infecting the exact same site in two different species at random is close to non-existent [8].

In a study performed in 2001, a retrovirus from the HERV-K group was found in chimpanzees, bonobos and gorillas, but not in humans. This suggests that at some point in history, these three species were evolutionarily closer to each other than they were to us humans. This finding directly contradicts the hypothesis that chimpanzees and humans are closer to each other than chimpanzees are to bonobos and gorillas [8].

A study investigating comparative genomics of chimpanzee endogenous retroviruses performed in 2006, showed the existence of at least 42 families of endogenous retroviruses in chimpanzees. Of the 42 families, only two did not have orthologs in humans (CERV1/PtERV1 and CERV2). PCR amplification of the CERV2 ERV group found in chimpanzees showed that this family is present in chimpanzee, bonobo, gorilla and old-world monkeys but absent in human, orangutan and new-world monkeys genomes. The study’s results showed that a significant portion of INDEL variation between chimpanzees and humans can be attributed to endogenous retroviruses, proving the evolutionary significance of these LTR retroelements present in the human genome [16].

Endogenous retroviruses contribute to evolution:

Studying endogenous retroviruses may be a way of figuring evolution out and proving it is real, but their impact on evolutionary biology is by no means limited to that. Recent evidence has brought up ways endogenous retroviruses have contributed to human evolution. Several human specific LTRs are found in promoter or enhancer regions. They are also found in introns of known genes, meaning these LTR sequences could end up impacting gene expression. It is hypothesized that endogenous retroviruses influenced gene expression during the period of human and chimpanzee divergence, directly impacting the course of human evolution [9].

Of the many impacts that HERVs have on physiological function, the role it played in mammalian placental formation is certainly notable. The *env* gene of the HERV-W provirus codes for the protein syncytin-1, which is expressed in trophoblasts, cells that form the outer layer of the placenta [10]. After screening for other possible *env* genes, protein syncytin-2, which has the same properties as syncytin-1, was found. [10] According to the study [Effects of Retroviruses on Host Genome Function](https://demystifyingmedicine.od.nih.gov/dm16/m02d02/reading01.pdf) [10], “Phylogenetic analysis of the env genes encoding both syncytin-1 and -2 shows that both have been subjected to strong purifying selection during primate evolution consistent with the proposed role in placentation”. The uniqueness of placental mammalians can be largely credited to endogenization of retroviral elements.

The leptin receptor (OBR) is involved in energy expenditure, production of sex hormones, hunger, body temperature and other important biological processes. Two alternatively spliced forms of the leptin receptor, short (OBRa) and long (OBRb), exist. Studies show that the short form (OBRa) is associated with endogenous retroelements, being a result of alternative splicing within a HERV-K (HML-2) LTR. Additionally, HERV-K (HML-2) LTR encodes 67 different amino acids in OBRa [9].

Other examples of HERV LTRs being expressed in human tissues are embryonic tissues, several tumors, liver and kidneys, among others [9].

Conclusion:

ERVs are significant to evolution. Analysis of more ancient ERVs, integrated into the genome before human ancestors diverged from those of other primates, can prove the relation and common ancestry of these species. Studying both more recent and much older endogenous retroelements has brought up significant discoveries pertaining to human evolution and relevant factors that set humans aside from many other species.

CONCLUSIONS

Human evolution and diseases are thoroughly connected. Through the analysis of the number of sickle-cell diagnoses in malaria endemic regions, it is possible to draw the relation between malaria, the sickle-cell trait and natural selection.

Human Endogenous Retroviruses (HERVs) are yet another way to establish a connection between diseases and evolution. Not only has the article confirmed that HERVs are proof of evolution and common ancestry between humans and non-human primates, but HERVs have also influenced evolution and traits in humans over time.

When it comes to the study of evolutionary biology, diseases are extremely important. From directly influencing our physiology, to proving our origins and impacting natural selection, pathology will always walk hand in hand with evolutionary biology.

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