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Opinion

The Conjecture of Poser on the Origins of Multiple Sclerosis: New Theoretical Considerations and Proposal

Victor M. Rivera

Department of Neurology, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, USA; vrivera@bcm.edu

Abstract: The origins of multiple sclerosis (MS) have been a subject intriguing researchers and scholars for generations. The multifactorial etiological nature of the disease continues to be studied as a complex combination of genetic aspects and environmental or external risk elements contributing to the development of the disease. Descriptions of symptoms or clinical disorders suggestive of MS affecting historical figures or prominent individuals (i.e., Lidwina of Schiedam, Heinrich Heine, Augustus d'Este) did not provide clues on the origin of the disease, except for the observation that all these early possible cases were white European individuals. MS was initially framed as a neurological entity and named in the 19th century by the historical participation of the French masters Cruveilhier, Vulpian, and Charcot, among others, but the question of how the disease originated was not addressed until Charles Poser raised his conjecture on the origins of MS in two historical essays (1994 and 1995), raising the question if the Viking voyages and invasions from the 8th to the 11th century carried the Scandinavian MS genetic risk factor to Europe and the rest of the known world at that time. Poser did not have the benefit of access to ancient molecular DNA data and based his theoretical postulation on interesting historical and archeological observations. A series of studies and opinions published in 2024, utilizing sophisticated genetic analyses and genome identification, archeological DNA analysis, and other advanced techniques and biological computation, distinctly demonstrate the installation of HLA-DRB1*15:01 (class II allele) in Europe (with a higher prevalence in Scandinavia) following the massive Yamnaya pastoralists migration from the Pontic Steppe in Eurasia to western Europe (~5000 to 2500 BCE). The data suggest HLA-DRB1*15:01, the strongest genetic association with MS, underwent an evolutive switch ("thrifty drift") from immune protector against novel zoonotic diseases appearing among the early pastoralists of the Yamnaya civilization to an autoimmune deleterious reactor to molecular mimicry and self-antigens, enabled by lifestyle changes and reduction of pastoralism once communities settled in Europe after the migration from the Pontic Steppe. This writer offers a new perspective on the origins of MS through a phase 1, the ancient east to west migration in the late Bronze Age, consolidating the HLA-DRB1*15:01 haplotype in Europe, and phase 2, the additional dissemination of the genetic MS risk through the Viking invasions, reinforcing inheritability by enabling a homozygous dominant inheritance.

Keywords: multiple sclerosis; ancient genes; HLA; origin of MS

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1. Introduction

Multiple sclerosis (MS), an inflammatory, demyelinating, and neurodegenerative disease of the CNS, displays a global distribution affecting, with a few exceptions, practically all ethnicities [1]. The 2020 Atlas of MS of the World Health Organization and the MS International Federation [2] reports 2.8 million people living with MS globally. The prevalence of this disorder has collectively increased over the last decades. This epidemiologic phenomenon is probably the result of a combination of factors, among others, development and availability of diagnostic criteria, access to MR imaging, improved neurological education, and increased public awareness of a disease that is no longer confined exclusively to certain human groups residing in certain areas of the world [3].

The cause of MS is not known. A complex etiological setting is thus far identified, integrated by a host of factors where genetics represents practically one-half of the components and the rest is constituted by environmental and external risk factors, including smoking, low vitamin D levels, childhood and adolescence obesity, Epstein-Barr virus infection, and many more not yet identified [4]. Some of these risk factors contribute to accelerating the clinical onset of MS and its worsening (i.e., relapse development or progression of disease), and some have been adjudicated epigenetic effects [5].

How and when MS developed as a disease has been a perennial question, intriguing generations of researchers and scholars. The French masters from the second half of the 19th Century, Cruveilhier, Vulpian, and Charcot, framed the pathologic understanding of MS at the Salpêtrière and named the disease [6], but had little, or no reason at all, in expressing their views on the origins of this neurological disorder. Traditionally, the historical records point to the case of Lidwina of Schiedam (1380–1433), a young Dutch woman sanctified by the Catholic Church as "patroness of chronic pain and falling", as the first suspected case of MS [7]. Throughout the course of time, numerous prominent social or historically recognized individuals have been considered retrospectively to have had clinical presentations or symptoms suggestive of MS. Heinrich Heine (1797–1856), celebrated German political writer and poet, complained of visual symptoms intermittently and eight years before his death became paralyzed and bedridden [8]. Augustus d'Esté (1794–1848), illegitimate grandson of King George III of England and cousin of Queen Victoria, experienced a relapsing and eventually progressive neurological disease for 26 years. He kept a detailed diary and an almanac of his many symptoms, including severe intolerance to heat, blurred vision, numbness, tremor of the hands, urinary and erectile dysfunctions, and difficulty walking [9]. These possible early cases of MS are historically well-documented and have a commonality: all were White young individuals of Northern European origin.

The geographic distribution of MS appears to have a genetic influence. While individual susceptibility is increased by inheriting specific genetic signatures, this is further augmented by the interaction with certain external and environmental risk factors. The MS genetic set up involves, thus far, 233 commonly occurring variants, identified through several methods including Genome-Wide Association Studies (GWAS). At least 32 variants are located in the area of the MHC, chromosome 6p21.3, in the HLA region [10]. The association of the HLA system with MS was first demonstrated by Compston in 1976 [11]; however, more specifically, the gene HLA-DRB1, allele *15:01, the strongest MS gene risk, was initially identified in ancient populations of the western Eurasian steppe subsequently expanding to Western and Northern Europe and Asia during the Bronze Age (see below) [12]. Genetic risk dissemination through migration and other phenomena of human population movements eventually spread the risk to other areas of the world.

Charles Marcel Poser (1923–2010), an American neurologist and recognized academician and MS researcher, proposed, in 1994, the theory that a predisposition toward the disease could "*possibly have arisen among the Vikings (Scandinavia, Northern Europe) and spread by them to their descendants in many parts of the world?*" [13]. Poser's notion that through the Viking's raids in the first millennium and their subsequent commercial trade, their descendants established settlements in many areas of Europe and the Middle East and had participation in the Crusades (Norsemen in the Byzantine service) and exerted further impact in diverse areas of the world during the Middle Ages. All these historical events originating with the Viking invasions and voyages (eighth and tenth centuries) contributed to the dissemination of MS genetic material throughout the world. Poser's proposition was based on historical aspects without the benefit of molecular genetic technology; nevertheless, the Viking saga hypothesis continues to be the currently accepted version of the origins of MS.

In the present paper, utilizing data based on evidence, a new proposal is offered as to how the genetic risk initiating in Eurasia on ancient populations, solidified in Europe over time, and, through migration and other human population movements, including the Viking invasions, eventually spread beyond Europe to other areas of the world.

2. Methods

The present study is a review and personal viewpoint focusing on the scarcely published data and expert opinions addressing the origins of MS.

Poser presented his hypothesis on the Vikings voyages and sagas as the factors of dissemination of MS in two fundamental papers published in 1994 (Annals of Neurology) [13] and 1995 (Acta Neurological Scandinavica) [14]. The first paper contains 14 figures depicting ancient maps, artifacts, photographs and pictures, and 47 references. The second article is shorter, representing a modified version of the first paper, with 12 figures and 38 references. Poser and the author of the present writing had extensive personal discussions on the subject and both attended numerous international conferences addressing and debating this proposal and its implications in the actual MS distribution in the world (from early 1990s to the time he stopped his academic activities in 2005).

Considering the complexity and unusuality of the subject, a criterion for published material selection was applied using online search engines such as PubMed, Scopus, and Google Scholar. Keywords included multiple sclerosis, history of MS, epidemiology, linguistics in MS, and archeology in MS. A recent series of articles studying these subjects have been published in 2024, supporting the postulation that MS is rooted in European prehistory [15]. These data are referenced in the text.

3. Charles M. Poser

Poser was born in Antwerp, Belgium, in 1923, and, together with his family, moved to New York City where he completed his bachelor and medical degree studies and trained at the Neurological Institute of Columbia University—Presbyterian Medical Center, under Houston Merritt's mentorship in the early 1950s. He was awarded a Fullbright Scholarship to work with Ludo van Bogaert, another of his mentors, in neuropathology at the Bunge Institute in Antwerp in 1955. Upon his return to the USA, he was a member of the faculty and chair of the neurology departments at Kansas University and University of Vermont Medical College. From 1981, he served as Professor of Neurology lecturing at Harvard Medical School, Boston University, and Tufts University, in Boston, Massachusetts [16]. Poser had a remarkable career and acquired international recognition (Figure 1), particularly after he led the panel elaborating the first modern diagnostic criteria of MS in 1983 [17], known as the "Poser Criteria".

Poser addresses, in his two classic papers [13,14], the theoretical dissemination of MS from Scandinavia to the rest of the ancient world during the first millennium, originating by the Viking sagas and invasions. He thought that the transmission of this genetic MS risk had been perpetuated over many centuries by the Vikings lineage, including their "distant descendants mostly British". Both papers are profusely illustrated, with the second article, produced a year later in 1995, displaying some added material; however, the main concept is unaltered between papers. He also concluded it was not necessary to postulate that MS existed in the Vikings. As mentioned, Poser did not have access to molecular genetic studies but did acknowledge "these (eventually) may confirm this suggestion". These ideas were presented for the consideration of the MS international audience in a very attractive fashion and were reinforced during time with multiple magisterial conferences carried out by Poser. His conjecture is the currently accepted proposal on the origins of MS. There are more actual findings discussed here.

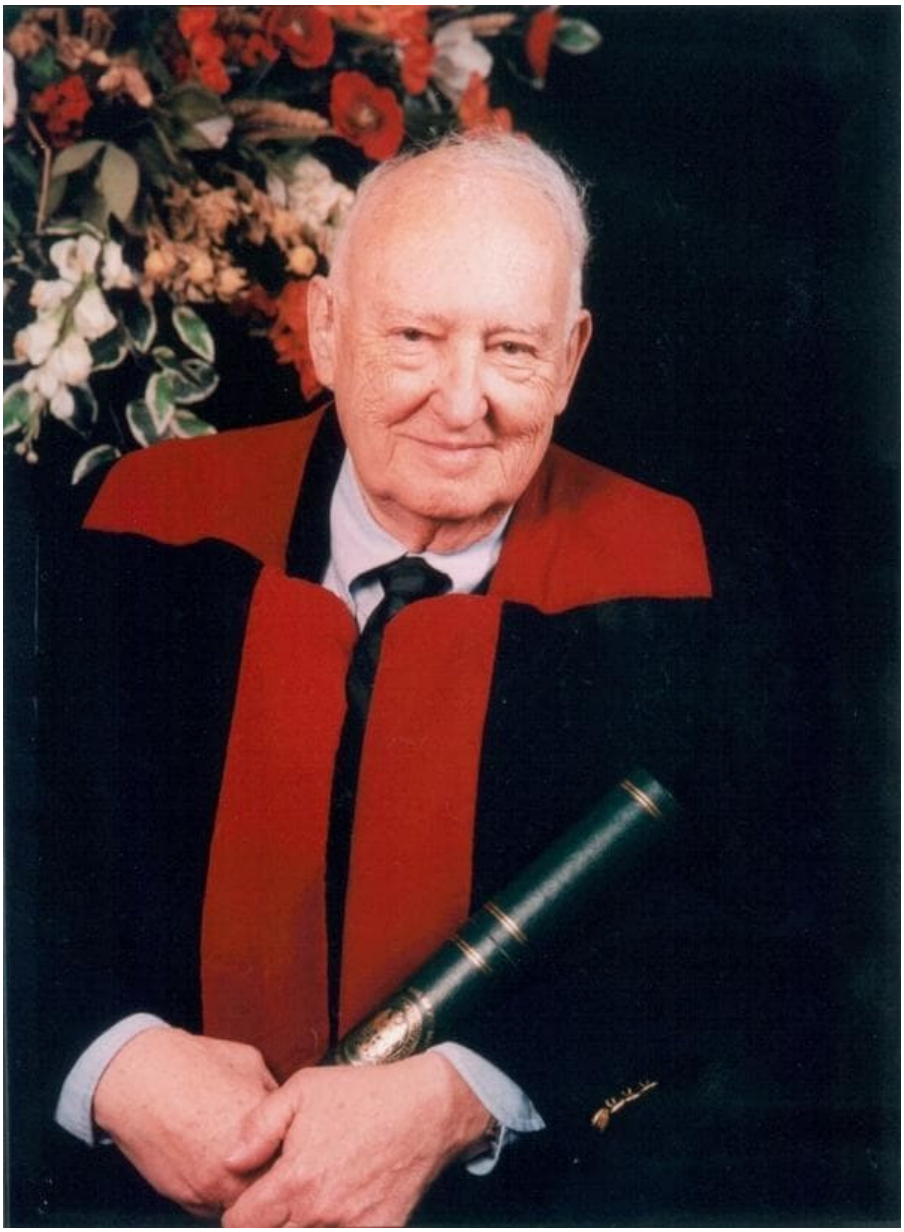


Figure 1. Charles Marcel Poser upon his induction into the Royal Society of Medicine in Edinburgh.

4. The Origin of the MS Genetic Risk Factor from European Prehistory

4.1. Ancestral Developments

While the precise appearance of modern humans in Europe is not known, it is estimated to have occurred more than 45,000 years ago [18] and was preceded by the presence of *homo heildelbergensis* by many millennia (Middle Pleistocene) [19]. During the Early Bronze Age (≥8000 years BCE), human populations were concentrated in a large area of Northern Eurasia, the Pontic Steppe, which includes parts of what are now Ukraine, Western Russia, and Kazakhstan. For several millennia, the survival of these groups depended on hunter-gathering activities, while concomitantly early societal and community development was taking place. Eventually, a pastoralist society evolved, introducing domesticated animals around 5000 years ago, including herding and the utilization of horse traction, permitting bulk wagon transport. Herding facilitated the gradual disappearance of the need for hunting and gathering while adding to the regular diet of meat, massive ingestion of milk, and the development of dairy products.

The earliest detection of HLA-DRB1*15:01 was obtained from ancient Balkan DNA from the Varna and Smyadovo sites, estimated to be ~6000–5000 years old [20]. Studies have shown this HLA was a sporadic occurrence until the introduction to Europe of domestic animals and herding by pastoralists between 5000 and 2500 BCE [15,21]. The frequency of this genetic variant identified in the genomes of ancient individuals, sampled from across Europe, increased notoriously after domestication and herding had evolved as a new human activity. (Figure 2).

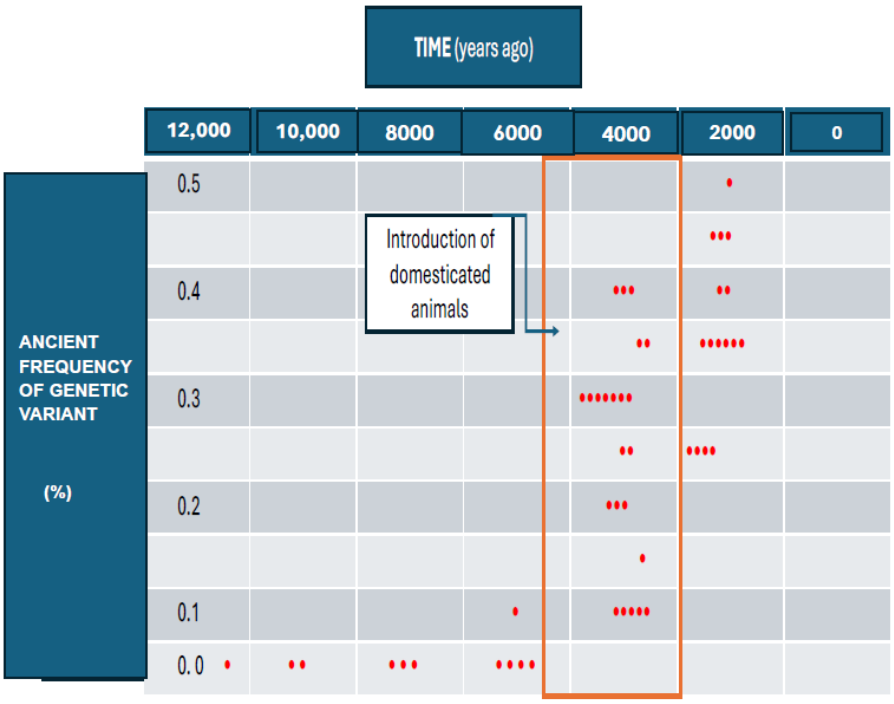


Figure 2. The frequency of HLA-DRB1*15:01 increased notoriously (shown for illustration purposes by the number of red dots) after the introduction to Europe of domesticated animals by pastoralists between 5000-2500 years ago (adapted from Asgari and Pouzas, *Nature* 2024, [15].

HLA-DRB1*15:01 modulates immune responses to peptides (antigens) presented to lymphocyte T-cell lymphocytes by a peripheral vigilant, macrophage, or neuritic cell. The cascade of the innate immune system reaction protecting against infection is initiated. Novel infections affecting humans previously naïve to such appeared among the pastoralists due to contagions from the animals they herded (zoonotic diseases) and once they had become an intimate part of the household. The outstanding and sophisticated study by Barrie et al. [21], published in 2024, addresses several significant aspects related to these ancient occurrences and how they impacted the origin of MS in Europe (and the world). HLA-DRB1*15:01 was produced by the human immune system as a protector against the new infections appearing due to animal domestication. The infections appearing in the new scenario, as expected, were predominantly bacterial (abscesses, ulcers, infected wounds), mycosis, tuberculosis, brucellosis, and viral with a larger manifestation of varicella-zoster species, more than Epstein-Barr virus (EBV), considering this is the modern main concern as infectious contributor to MS. This finding suggests EBV probably became a contributing element in later millennia (Figure 3). Rheumatoid Arthritis, another autoimmune mediated disease, apparently has similar ancestral DNA molecular roots to MS.

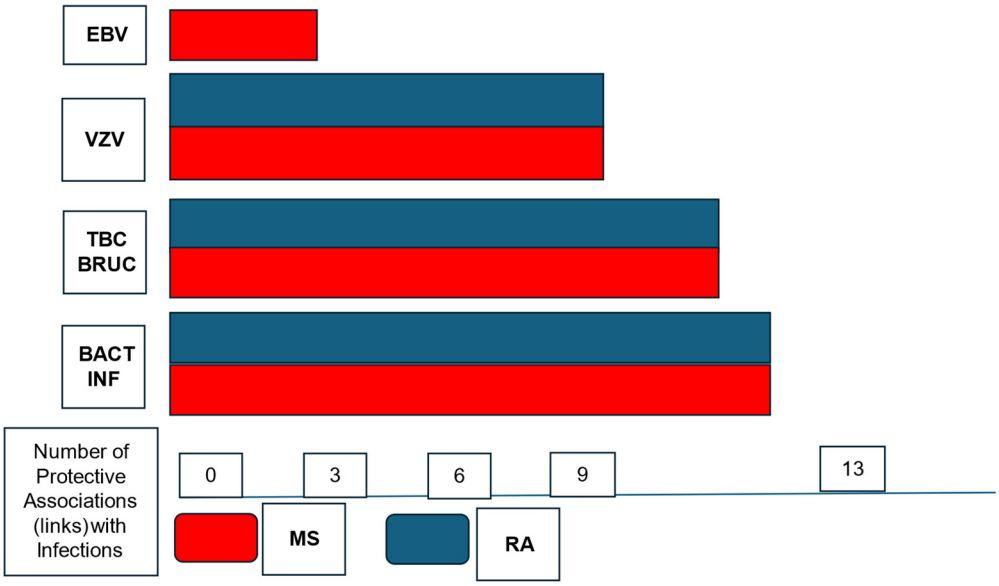


Figure 3. Genomes of selected infectious agents' associations (links) detected utilizing diverse SNP identification methods. The approximately protection levels are liberally depicted in the figure strictly for illustration purposes. Samples were obtained from pastoralist sites and from later migration trajectories towards west and northern Europe from the Eurasian Steppe. Abbrv., EBV = Epstein-Barr Virus; VZV = Varicella-Zoster Virus; TBC = Tuberculosis; BRUC = Brucellosis; BACT INF = Bacterial Infections. (Adapted from Barrie et al., *Nature*, 2024) [21].

4.2. Migration from West Eurasia to West and Northern Europe Carrying the MS Genetic Risk

In the Post-Glacial Mesolithic Period to the Bronze Age [22], pastoralist lifestyle and farming was already taking place in the large area of the Pontic Steppe, known as the Yamnaya Culture ("Pit Grave Culture"), and HLA-DRB1*1501 had strongly developed in response to the novel infections acquired from the animals they had domesticated (zoonotic diseases). The Yamnaya population was an admixture of Eastern Hunter-Gatherer, Caucasian, Anatolian, and Western Hunter-Gatherer. They spoke a Proto Indo-European language (originated in Western India and Persia), and there is evidence that the evolution from darker to lighter skin and brown/blonde hair was also taking place among the Yamnaya people, a slow genetic phenotypic process resulting over several millennia as an evolutionary response adapting to the new environment following the very early human diaspora from Africa.

It is not known what provoked a massive migration, from 5000 to 2500 years ago, from the steppe to the west (and even to the east to the Altai Mountains, although in a smaller proportion). It is speculated that farming and climatological aspects were or became not favorable for survival and the continuation of effective pastoralism. This migration resulted not only in genetic dissemination (particularly of the HLA-DRB1*15:01) through intermarriage but also allowed the formation of the Corded-Ware culture in Central Europe and Germany and brought the Indo-European language to Europe. The family of languages derived from the Indo-European roots constitute, at present, tongues spoken by 46% of the world population, some more globally extensive like English, French, Dutch, Portuguese, Spanish, and Russian [23]. Another effect of this migration was the introduction to Europe of horses and cartwheeled transportation and the initiation of trade. The migration reached an extensive geographic range and allowed the seeding of shared genetics throughout the continent. HLA-DRB1*15:01 became particularly prevalent in Scandinavia. Descendants from this conglomerate eventually replaced 90% of local genetics in all European areas. Sources of DNA have included archeological searches of tombs, skeletons, and other human remains like dental pieces as well as artifacts found in the burial sites. The age of the specimens is obtained by utilizing the common technology of dating radiometric with carbon-14. Findings from Medieval and post-Medieval genomes

from Denmark, obtained from sites such as ancient cemeteries and tombs in cathedrals and basilicas, confirmed the Yamnaya/pastoralist lineage. A modern current source utilized by Barrie et al. [21] is the dataset of the UK Biobank, comprising ~410,000 self-identified white British individuals [24]. The above data are extensively presented and reviewed in their main article and in additional commentaries published in 2024 in the same issue. The accompanying bibliographies enriched the segment of the present paper.

*4.3. The Evolutionary Conversion of HLA-DRB1*15:01*

The effect in the causality and epidemiology of MS exerted by HLA-DRB1*15:01 is inescapable. It is the genetic MS marker more commonly identified among white northern Europeans, while 1 in 4 people with MS in the world carry this allele. This haplotype is found in about 10% of white populations globally, and 30% of whites with MS [25]. The compelling data available indicate that this gene was introduced into northern European populations through the massive Yamnaya migration from Eurasia. The prevalence of MS is lower among populations with lower presence of this HLA [26], including southern Europeans [15], and the disease is either extremely rare or non-existent in non-mixed ethnic groups without the genetic exposure to outside high-risk groups, i.e., Amerindians in Latin America [27,28].

The theory explaining the transformation of HLA-DRB1*15:01 from a protective agent (beneficial positive selection) fighting the new appearance of zoonotic infections in early pastoralist societies, as discussed above, to a harmful genetic facilitator of MS as autoimmune disease, lies in the known and accepted phenomenon of evolutionary trade-off or "thrifty genetic drift" due to adaptive evolution switching the positive selection of the function of the gene ("selfish gene theory"). The molecular structure of the gene and allele remains unchanged even during prolonged periods of time, but its functionality may be modified as an evolutionary adaptation [29]. This phenomenon apparently occurred in the case of HLA-DRB1*15:01, and is associated with population expansion and density in Europe following the Yamnaya migration. Over the course of several centuries, new communities were settled in Europe, gradually changing the environment and lifestyle, reducing pastoralism and hence the exposure to some microorganisms. Hygiene and sanitation gradually developed, along with changes in diet and gut microbiome. The theoretical consideration is that all these evolutionary changes resulted in the modern immune sensitivity drift of HLA-DRB1*15:01 reacting to molecular mimicry and to responses to self-antigens conducing to autoimmunity damage.

5. A New Proposal on the Origins of MS

The objective data point to the idea that the genetic propensity to MS in Europe resulted from ancient human activities and group movements from east to west. This author considers this established phenomenon as "Phase 1" (Figure 4) of the origination of MS.

Inheriting at least one of two copies from the HLA-DRB1*15:01 allele (homozygous) increases the risk of developing MS in a 2–3-fold compared to not having the allele [30].

The conjuncture of Poser regarding the origin of MS is based on the historic Viking invasions from Scandinavia to the British Islands initially, then to the rest of continental Europe and beyond during the first millennium. It is an interesting concept even though his postulation did not come with the support of more modern molecular archeology and genetics. Nevertheless, it is reasonable to assume that this significant human activity taking place in the opposite direction (west to east) to the Yamnaya migration, initiating from the region with the highest prevalence of the MS allele risk factor, reinforced the genetic dissemination of the disease. This genetic enhancement possibly favored a dominant homozygous inheritance (inheriting two identical dominant copies) as well, increasing the rate of expression of MS by 4–6-fold. This author considers, as "Phase 2" of the origination of MS, this incremented genetic transmission of disease resulting from the Viking saga (Figure 5).



Figure 4. Phase 1: introduction of the MS genetic risk into Europe through massive migrations from the Pontic Steppe (5000–2500 BCE). The arrows indicate the proposed pathways of the migration from the East to West and Northern Europe.

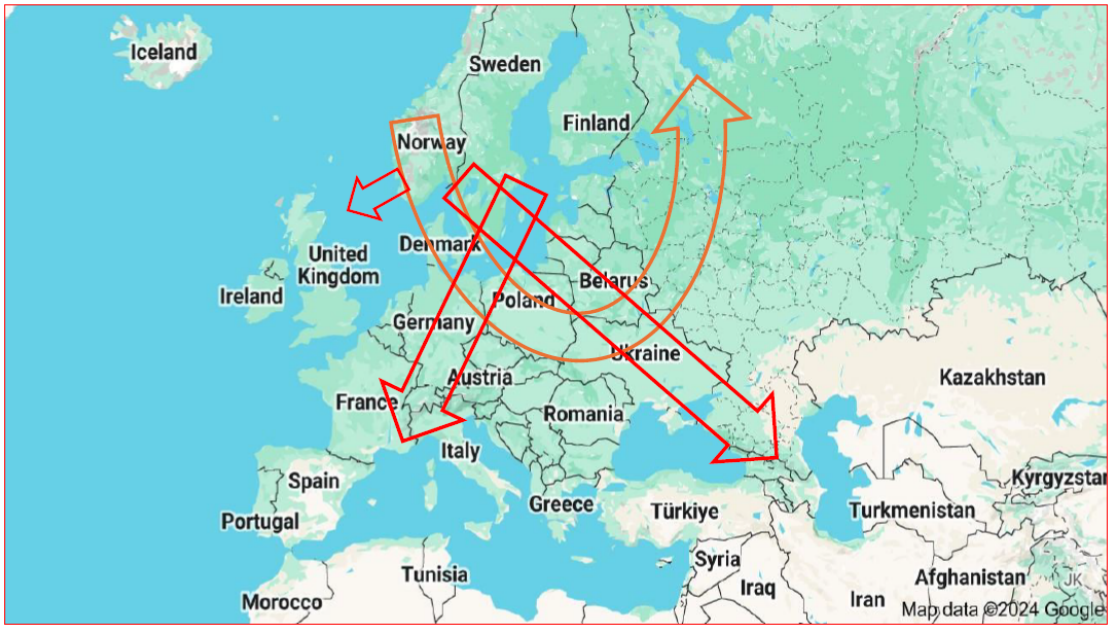


Figure 5. Phase 2: genetic reinforcement of the genetic MS risk from Scandinavia to continental Europe and beyond (8th century to 11th century). The arrows indicate the historical paths of the Viking sagas.

Historically, throughout diverse epochs, starting particularly in the 15th century, the European-originated genetic risk factor for MS spread to the rest of the world through migration, colonization, trade, and other human undertakings. Local genetic allele expressions not related to HLA-DRB1*15:01 have appeared in populations with MS (i.e., HLA-DRB1*04:05 in Japanese); however, the global distribution of the allele *15:01 is predominant, and includes other Asian people, Chinese, and Latin American populations [31]. The distribution of MS in the world at the present time shows a clear higher prevalence in the areas where white Europeans or their descendants live. This geographic distribution

does follow a north-south gradient, which most likely is driven by genetic influences, although associated environmental influences are undeniable, such as reduced solar (ultraviolet light) exposure resulting in 25-hydroxyvitamin D deficiency. The most updated information on geographic presence of MS and prevalence rates is provided by the MS International Federation (Figure 6) [2].

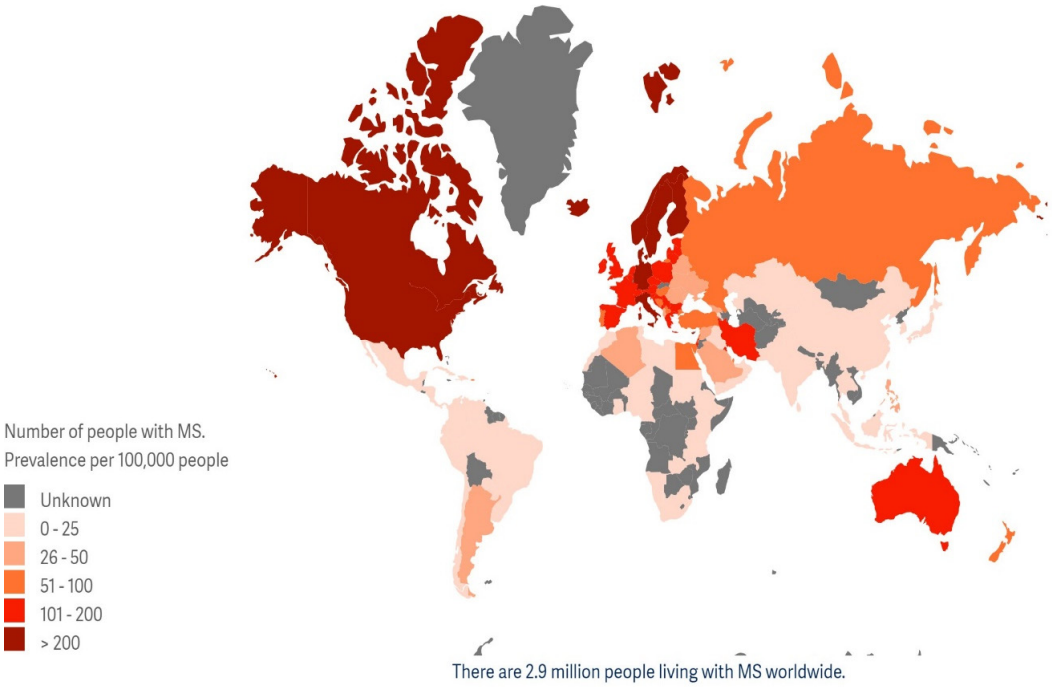


Figure 6. Atlas of MS, 2024. Source: Multiple Sclerosis International Federation [2].

6. Conclusions

A proposed theory explaining the origins of MS is presented here and is described in two phases. Based on historical facts and established archeology, including ancient genetic molecular data, genomes, and studies on the massive historical human migration from Eurasia (pastoralist civilization) to west Europe, the presence of the main risk factor, HLA-DRB1*:15:01, was particularly rooted in Scandinavia (Phase 1). This gene underwent an evolutive adaptation ("thrifty drift") from immune protection against new appearing zoonotic diseases among the pastoralist population to harmful facilitator of autoimmune mechanisms in MS once lifestyle changed and population density increased in settled European communities. The Poser postulation adjudicated the origins of MS to the Viking invasions (from Scandinavia to the British Islands, continental Europe, and beyond), although access to molecular genetics was not available at the time of his conjecture. Nevertheless, the Viking saga probably increased the genetic dissemination and propensity to MS (Phase 2) by enhancing the possibilities of dominant homozygous inheritance.

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