7-31-2007

The Etiology of Multiple Sclerosis and Correlation of the Distribution of the Disease with Migration and Settlement History of Northern Europeans

Kristin M. Gunderson

The Etiology of Multiple Sclerosis and Correlation of the Distribution of the Disease with Migration and Settlement History of Northern Europeans

by

KRISTIN M. GUNDERSON

B.S., UNIVERSITY OF GEORGIA

A Thesis Submitted to the Graduate Faculty
of Georgia State University in Partial Fulfillment
of the
Requirements for the Degree

MASTER OF PUBLIC HEALTH

ATLANTA, GEORGIA

The Etiology of Multiple Sclerosis and Correlation of the Distribution of the Disease with Migration and Settlement History of Northern Europeans

by

Kristin M. Gunderson

Approved:

Ike S. Okosun

Committee Chair

John Steward

Committee Member

Ruoxiang Wang

Committee Member

July 27, 2007

Date

AUTHOR'S STATEMENT

In presenting this thesis as a partial fulfillment of the requirements for an advanced degree from Georgia State University, I agree that the Library of the University shall make it available for inspection and circulation in accordance with its regulations governing materials of this type. I agree that permission to quote from, to copy from, or to publish this thesis may be granted by the author or, in his/her absence, by the professor under whose direction it was written, or in his/her absence, by the Associate Dean, College of Health and Human Sciences. Such quoting, copying, or publishing must be solely for scholarly purposes and will not involve potential financial gain. It is understood that any copying from or publication of this dissertation which involves potential financial gain will not be allowed without written permission of the author.

Kristin Gunderson

Signature of Author

KRISTIN M. GUNDERSON
The Etiology of Multiple Sclerosis and Correlation of the Distribution of the Disease with Migration and Settlement History of Northern Europeans
(Under the direction of Dr. Ike S. Okosun)

ABSTRACT

The geographic disparity of multiple sclerosis has been noted in the literature for well over a century. The frequency of the disease varies significantly both within countries and in different parts of the world. The goal of this project is to give new insight regarding the etiology of multiple sclerosis. Several theories regarding the etiology of the disease have been reviewed, including a geographic theory, a nutritional theory, and a genetic theory. Although the geographic and nutritional theories have been thoroughly investigated by researchers, neither of them provides a conclusive explanation for the etiology of the disease, and there are discrepancies with respect to both theories. The purpose of this study is to reveal the discrepancies in the epigenetic theories regarding the etiology of multiple sclerosis and to demonstrate the correlation of multiple sclerosis prevalence and the migration and settlement history of Northern Europeans, thus conferring the passage of a genetic susceptibility to the disease.

INDEX WORDS: multiple sclerosis, epidemiology, incidence, prevalence

NOTICE TO BORROWERS

All theses deposited in the Georgia State University Library must be used in accordance with the stipulations prescribed by the author in the preceding statement.

The author of this thesis is:

Student's Name: Kristin M. Gunderson

Street Address: 5953 Jim Crow Road

City, State, and Zip Code: Flowery Branch, GA 30542

The Chair of the committee for this thesis is:

Professor's Name: Ike S. Okosun, Ph.D.

Department: Institute of Public Health

College: College of Health and Human Sciences

Georgia State University
P.O. Box 4018
Atlanta, Georgia 30302-4018

Users of this thesis who not regularly enrolled as students at Georgia State University are required to attest acceptance of the preceding stipulation by signing below. Libraries borrowing this thesis for the use of their patrons are required to see that each user records here the information requested.

NAME OF USER	ADDRESS	DATE	TYPE OF USE (EXAMINATION ONLY OR COPYING)

Curriculum Vitae

KRISTIN MARIE GUNDERSON
5953 Jim Crow Rd., Flowery Branch, GA 30542
706.254.1806
kgunder@emory.edu

EDUCATION

January 2006-Present **Georgia State University** Atlanta, GA
Pursuing Master's of Public Health degree
- Expected graduation date: August 2007

2001-2003 **University of Georgia** Athens, GA
B.S. Psychology with emphasis in Premedical Studies

1999-2000 **SUNY at Stony Brook** Stony Brook, NY

WORK EXPERIENCE

January 2007-Present **Emory University Winship Cancer Institute** Atlanta, GA

Practicum Student

- Utilize public health skills gained in M.P.H. program to work directly with Dr. Ruoxiang Wang on a project entitled "Superimposition of global prostate cancer incidence with migratory and settlement of the Northern Europeans"
- Collect secondary data for interpretation based on background knowledge of migration of Northern Europeans.
- Review recent publications to gather new genetic and epidemiological information on prostate cancer and other diseases.

February 2005-Present **Emory University School of Medicine** Atlanta, GA

Research Project Coordinator, Sr.

- Prepare NIH and Foundation grant applications, progress reports, closeouts, renewals, and re-submissions; coordinate grant and manuscript preparation and submissions; type and proofread manuscripts, reports, and correspondence.
- Prepare and route IACUC animal compliance protocols. Work with Environmental Health and Safety officials to ensure biosafety and radiation safety compliance.
- Prepare and route IRB protocols for research conducted using human subjects or tissue specimens.
- Maintain and manage expenditures and budgets of over 15 research grant awards.
- Create and update websites for the Molecular Urology and Therapeutics Program (www.urology.emory.edu), the Emory University Winship Cancer Institute Prostate Cancer Program (http://cancer.emory.edu/research/teamdetails.php?id=108) and Dr. Leland Chung's NIH Program Project (P01) grant (password protected due to confidential research findings).
- Prepare budgets for grant applications; prepare internal budgets for each fiscal year; process laboratory financial transactions; prepare travel and expense reports and reimbursements.
- Process appointments and promotions of lab personnel.

TABLE OF CONTENTS

ACKNOWLEDGEMENTS

I would like to sincerely thank the members of my thesis committee, Dr. Ike Okosun, Dr. Ruoxiang Wang, and Professor John Steward, for their encouragement and constructive feedback. I would also like to thank my family and friends, especially my parents, Robert and MaryAnn Gunderson, for providing constant inspiration and motivation, and my husband Jarret for his continued love, support and never ending friendship.

CHAPTER I

INTRODUCTION

Multiple sclerosis is a chronic inflammatory disease that affects the central nervous system (CNS). In patients with multiple sclerosis, myelin, the fatty tissue which protects nerve fibers in the CNS, deteriorates leading to neurological problems and disorders of the CNS. Patients with multiple sclerosis suffer from a variety of symptoms, including visual problems, muscle weakness, difficulties with coordination and speech, fatigue, cognitive impairment, problems with balance, and pain. Multiple sclerosis is a debilitating disease which leads to impaired mobility and disability in most cases.

Currently, there are approximately 400,000 patients suffering from multiple sclerosis in North America, and approximately 1.1 million people suffer from the disease worldwide. The average age of onset is between 20 and 30 years. The disease rarely occurs prior to age 10 or after 60 years of age. However, patients as young as 3 and as old as 67 years of age have been diagnosed with the disease. Females are diagnosed 1.4 to 3.1 times more frequently than males (National Multiple Sclerosis Society 2007).

It appears that multiple sclerosis is a modern day disease, but there has been mention of symptoms associated with the disease as far back as the 14th century. In 1947, the skeleton of St. Lidwina of Schiedam, which is a suburb of Rotterdam, Holland, was discovered during a reconstruction project. It appeared that Lidwina, who lived from 1380 to 1433 had a case of MS. The skeleton showed signs of muscular atrophy and

paralysis of both legs. It was recorded that Lidwina suffered from difficulty walking and a "hanging lip" which could possibly be indicative of facial paralysis. It was also recorded that in the last 15 years of her life, Lidwina had large wounds on her body, difficulty swallowing, blindness, and other pains (Murray 2005).

In 1979, Flemish neurologist Medaer analyzed Lidwina's case and stated that it is likely she suffered from MS, although MS is not the only explanation for her symptoms. Other physicians have analyzed the case and believe that Lidwina's case could also be attributable to Lupus Erythematosus, which is another autoimmune disease associated with skin lesions and disorders of CNS, including blindness. Although Lidwina's case cannot conclusively be described as MS, there are some other cases throughout history that have also been ascribed as MS. It is interesting to note that all of the cases mentioned herein have been located in northern Europe, where it is believed the disease originated (Murray 2005 and Swiderski 1998).

The case of Sir Augustus Frederic D'Este, son of King George III of England, has also been described as a likely case of MS. As a child he suffered from common childhood infections and infestations. In 1827, D'Este exhibited the first serious health malady indicative of MS. Then, at age 33, D'Este stated that he was experiencing difficulty with vision, and he later experienced numbness of the lower back and thighs, difficulties walking and incontinence. D'Este died at the age of 35, and at the age of his death, he was losing his sense of hearing and was experiencing spasms so severe that he could only walk with the help of a servant (Murray 2005 and Swiderski 1998).

Robert Carswell was a Scottish medical student in the 1830s. Carswell was a medical artist who created a collection of drawings for his "Pathological Anatomy:

Illustrations of the Elementary Forms of Disease" (1834-1838). Within the collection of drawings, Carswell described lesions typical of MS based on two cases from Hospital of La Pitie and the Hospital of La Charite. Both patients suffered from paralysis. Furthermore, Jean Cruveilhier, a Parisian artist of the same time period as Carswell created another collection of pathological illustrations which were published in "Anatomie pathologique". Along with his drawings, Cruveilhier provided a case history and detailed clinical notes of patients including La Charite, Josephine Paget. The patient died at the age of 38 on March 20, 1840. Cruveilhier performed an autopsy and described what were likely to be MS lesions as "sclerose en plaques" (Swiderski 1998).

A French neurologist and student of Jean Cruveilhier, Jean-Martin Charcot, established the infamous Charcot Clinic at the Salpêtrière Hospital for investigating mental and neurological disorders. In 1862, Charcot and Edme Vulpian wrote a literature review on "sclerose en plaques" citing mostly German sources. Charcot studied multiple sclerosis intensely and gave lectures on the disease, which he continued to describe as "sclerose en plaque" between 1868 and 1871. In 1892, Charcot published the most comprehensive account of MS and it included accounts of mainly patients of northern European descent (Swiderski 1998).

Multiple sclerosis is characterized by its epidemiological disparity in that it is most frequently diagnosed in northern European nations and is rarely documented in non-Caucasian races. There are multiple theories on the etiology of multiple sclerosis, including geographic, cultural and behavioral, and genetic suppositions, but to date, none of these theories has been able to conclusively identify the etiology of the disease. Approximately 15 to 20% of affected individuals have a family history of the disease;

however, population studies have shown that there is no clear mode of inheritance of the disease (Compston and Coles 2002, Sadovnick 1988). Thus, the etiology of multiple sclerosis remains unknown. Studies have consistently shown that familial clustering results from shared genetic factors rather than epigenetic factors, leading to the idea that development of multiple sclerosis is primarily due to genetic predisposition.

The geographic disparity of multiple sclerosis has been noted in the literature for well over a century (Charcot 1877). Although the prevalence can be difficult to reliably assess from one geographical region to another (Poser 1994), it has become clear that the frequency of the disease varies significantly both within countries and in different parts of the world. The first epidemiological study by Davenport (1922) revealed how multiple sclerosis seemed to affect individuals of Scandinavian and Finnish descent more than individuals in other ethnic groups. Later, propositions that multiple sclerosis prevalence was related to global latitude sparked a nature versus nurture controversy that still exists today (Annegers 1991 and Betemps 1993).

When visually documented on a world map, the prevalence of multiple sclerosis demonstrates striking features, such as the fact that according to lack of data from Africa and physicians' claims, the disease is almost non-existent in African nations and other regions close to the equator, and the prevalence is much greater in nations of European descent. For the purposes of this research project, Caucasian will be defined as white individuals of northern European descent, and African Americans can be categorized as black individuals whose ancestors originated in Africa but are currently living in America. Furthermore, Asian Americans will be defined as people currently living in America whose ancestors originated in Asia, including China, Japan, Taiwan, India, and Vietnam.

Interestingly, the occurrence of multiple sclerosis is lower in African Americans and Asian Americans than it is in Caucasian Americans, and it has been shown that there is a higher percentage of African and Asian descendents who have developed multiple sclerosis than the percentage of native Africans and Asians who have developed the disease (Alter 1962, Oh 1969, and Rosati 2001). Thus, I hypothesize that since multiple sclerosis occurs frequently in certain racial groups in certain geographic areas, a comparison of global multiple sclerosis prevalence rates among nations and among racial groups within the nations would help to determine whether the disease coincides with the migration, settlement history, and admixture of the Scandinavians, who may carry a susceptibility allele to the disease. Furthermore, it is through genetic admixture from the Europeans to Africans throughout history, and specifically during the Slave Trade, that the genetic susceptibility to multiple sclerosis has been passed to the African genome.

Remarkably, similar studies have been conducted to link susceptibility to cystic fibrosis, hemochromatosis, and prostate cancer with the migration of northern Europeans. It has been found that the genetic epidemiology of cystic fibrosis, hemochromatosis, and prostate cancer has shown that inter-group breeding may lead to spreading of the susceptibility alleles to other racial and ethnic groups (Sandblom et al. 2003, Higgins et al. 2005, Gilbert et al. 1995, and Acton et al. 2001). It appears then that the geographic distribution of the varied frequencies of a disease reflects the history of migration, settlement, and admixture of the population carrying the susceptibility, and that it is possible for a genetic susceptibility to have been passed from one group to another over several generations. Genetic epidemiology has been used in tracing the history of cystic fibrosis, hemochromatosis, and prostate cancer to show that these diseases originated in

northern Europe and have been passed to other races and ethnicities through genetic admixture following inter-group breeding (Sandblom et al. 2003, Higgins et al. 2005, Gilbert et al. 1995, and Acton et al. 2001).

A genetics-based etiology of multiple sclerosis is challenged by several seemingly contradicting facts. First, the apparently random occurrence of multiple sclerosis in a population may be due to low penetrance of the etiologic alleles. However, the distribution within populations could also be explained by epigenetic mechanisms or by gene-environment interaction. Second, although African Americans, or individuals who have migrated to the United States from continental Africa, are susceptible to multiple sclerosis, generally, there is a much lower prevalence of the disease in their nations of origin in Africa, seemingly making it impossible for African Americans to have inherited the susceptibility from their African ancestors. Third, multiple sclerosis incidence has been continuously rising in recent years in nations that once exhibited extremely low incidence, and there currently seems to be a surge in incidence. Given that the cause of the trend is not clear, socioeconomic, dietary, and behavioral changes have been pondered as contributing factors. Each of these concepts favor an epigenetic, rather than a genetic etiology for multiple sclerosis.

Several epigenetic theories exist regarding the etiology of multiple sclerosis. The primary epigenetic theories, or theories that do not imply that genetic inheritance is the determining factor for developing multiple sclerosis, include a geographic theory and a nutritional theory. The geographic theory entails that geographic location with respect to proximity to the equator largely determines incidence of multiple sclerosis, while the nutritional theory indicates that diet and vitamin D intake influence development of the

disease. These epigenetic hypotheses for the etiology of multiple sclerosis have been studied at length, yet neither of these theories can fully explain the etiology of the disease.

It is of utmost importance to determine the etiology of this debilitating disease, especially for African Americans, who have proven to suffer from higher incidence of cerebellar dysfunction and more rapid accumulation of disabilities due to the progression of the disease (Marrie et al. 2006). Identification of genetic susceptibility to the disease could lead to the establishment of a genomic marker for prediction and prevention of multiple sclerosis, which would, in turn, be beneficial to public health. The purpose of this study is to reveal the discrepancies in the epigenetic theories regarding the etiology of multiple sclerosis and to demonstrate the association of multiple sclerosis prevalence rates with the migration and settlement history of Northern Europeans, thus conferring the passage of a genetic susceptibility to the disease.

CHAPTER II

REVIEW OF THE LITERATURE

There is an evident worldwide geographic distribution of multiple sclerosis which can be observed when the occurrence of the disease is plotted on a world map. It appears that the highest prevalence of the disease is found in the northernmost latitudes of the northern hemisphere and the southernmost latitudes of the southern hemisphere (Kurtzke 1977). This observation is based on the prevalence of the disease in Scandinavia, the northern United States and Canada, as well as Australia and New Zealand (Kurtzke 1977). There are currently several theories describing the epidemiology of multiple sclerosis, including a nutritional theory, a geographic theory, and a genetic theory, all of which are analyzed herein. Following the review of literature, Table 1 identifies some of the key literature reviewed in this research.

Geography and nutrition in relation to development of multiple sclerosis

Epidemiological data indicates quite clearly that multiple sclerosis is a geographically-related disease. The highest frequency of multiple sclerosis in the world is exhibited in Europe between 65 degrees and 45 degrees north latitude, the northern United States and southern Canada, and between 35 and 40 degrees south latitude in New Zealand, and southern Australia (Figure 1).

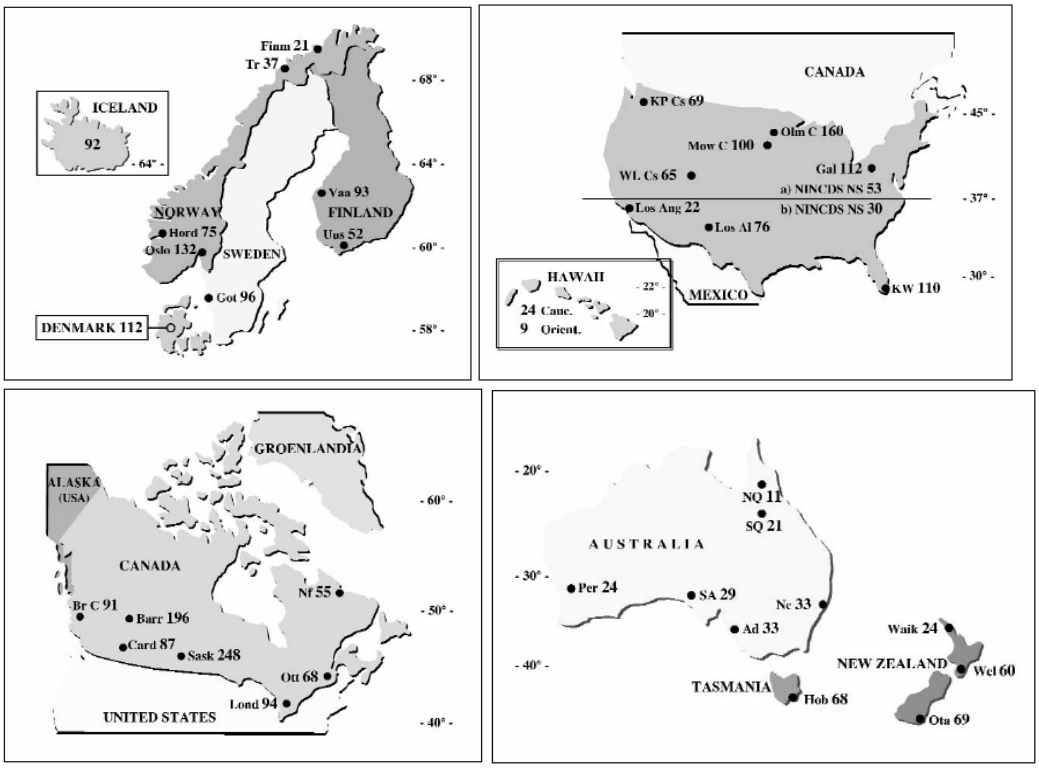


Figure 1. Nationwide prevalence rates in northern Europe, the U.S., Canada, and Australia and New Zealand, along with detailed latitudinal proximity to the equator

According to Kurtzke (1977), these regions are surrounded by regions exhibiting medium prevalence rates of multiple sclerosis in Europe to the north, east, and south; in the southern United States; and in the northern and inland Australia. Latin America, Asia and Africa exhibit fairly low prevalence of the disease. Kurtzke noted early on that latitude is not a sufficient criterion for determining multiple sclerosis risk considering that at 40 degrees north latitude, multiple sclerosis is high in America, medium in Europe, and low in Asia. Kurtzke (1977) did, however, note that high and medium risk areas appeared only in Europe or European colonies. Within the United States, multiple sclerosis appears to be more common in Caucasians of northern European descent than in African Americans, Asian Americans, and Native Americans.

One of the hallmarks of multiple sclerosis remains its unequal distribution across the globe. As previously noted, it is most common in populations of northern European descent, and is diagnosed most often in Scandinavian nations, the United Kingdom, and the northern United States and southern Canada (Compston 1997). Regions of high incidence have been found in northwestern Sardinia (Sotgiu 2002 and Marrosu 2002) and Sicily (Grimaldi 2001 and Nicoletti 2005). Several areas of abnormally high incidence of multiple sclerosis have been found in Finland, as well. In these regions, there is an approximately two-fold increased prevalence than the national average. Seinajoki in southern Ostrobothnia, Finland, recently demonstrated an incidence of 12 cases per 10,000 people, which is the highest rate of multiple sclerosis reported anywhere in the world (Sumelahti 2001).

Data from migration studies show that if the exposure to a higher risk environment occurs during adolescence (before 15 years of age,) the migrant assumes the higher risk of the environment. This concept is nicely illustrated in studies of native-born South African Caucasian population with low incidence of the disease versus high incidence of multiple sclerosis among Caucasian immigrants from Great Britain, where the disease is much more prevalent (Kurtzke 1977). Epidemics of multiple sclerosis have been reported and these provide further evidence of importance of environmental factors in multiple sclerosis. The most notable “epidemic” was described on the Faroe Islands after they were occupied by British troops in W.W.II. Similar increases in incidence of the disease were seen on Shetland and Orkney Islands, in Iceland, and in Sardinia. A specific point agent for these epidemics was never identified (Kurtzke 1977).

Rosati et al. (1996) conducted a study in northern Sardinia, an island off the coast of Italy, to investigate the incidence of multiple sclerosis in the Sardinian province of Sassari. Results of previous studies in the area had indicated that multiple sclerosis prevalence had increased more than two or three times than that of the standard increase in prevalence in continental Italy during the time between 1980 and 1996. The purpose of this study was to investigate the temporal trend of multiple sclerosis prevalence, which is that as distance from the equator increases, so does prevalence of the disease. Rosati et al. (1996) focused on the province of Sassari, which is located between latitudes 40º30' N and 41º N. The population of Sassari consists mostly of natives of Sardinia, and the count of foreign inhabitants with regards to the study was negligible. Thus, the researchers concluded that generalizations regarding the study population and the island of Sardinia were warranted. The differences between human genomes in Italy and Europe and Sardinia are 10 times higher than between non-Sardinian Italians and Europeans, yielding a genetically homogenous population (Pugliatti 2001).

The crude overall prevalence rate in Sassari in 1997 was 144.4 per 100,000. There were 686 total cases of multiple sclerosis, 492 women and 194 men. The incidence rate was studied for the period between January 1, 1968 and December 31, 1997. The average annual incidence was found to be 4.9 per 100,000. The total incidence rate had increased since the period of 1968-1972 from 2.0 per 100,000 to 6.8 per 100,000 from 1993-1997 population (Pugliatti 2001). Researchers concluded that the observed multiple sclerosis prevalence rates were markedly higher than expected rates would be in relation to the latitude of Sardinia. An increase in disease rate due to increase in life expectancy was ruled out, as was an increase in immigration of people in

high-risk age groups, and immigration of genetically high-risk individuals. Furthermore, comparison to survey data collected by Granieri et al. (1996) from Ferrara, a province in northern Italy revealed that prevalence of multiple sclerosis in Sassari was nearly three times higher and that better diagnostic accuracy and improved epidemiological methods could not fully account for the increased prevalence rates (Pugliatti 2001). Results from this study indicated that the prevalence of multiple sclerosis in Sassari is among the highest in the world (Kurtzke 1997). The high rate of multiple sclerosis in Sassari seems to contradict the latitude gradient-based theory of multiple sclerosis, which suggests that prevalence of multiple sclerosis is directly related to geographical latitudes, since multiple sclerosis rates increased considerably in Sassari over the 30 year period of the noted investigation, while they remained substantially unchanged in the similar latitudinal region of Ferrara (Pugliatti 2001 and Granieri 1996). Instead, this research indicates that multiple sclerosis is more prevalent in genetically susceptible populations.

Research also suggests that nutrition and diet, particularly those high in consumption of animal fat and with low intake of fish products, may play a role in the etiology of multiple sclerosis. Furthermore, it has also been suggested that vitamin D intake has a protective effect on the risk of multiple sclerosis (Munger et al. 2000).

The theory regarding the protective effect of vitamin D intake on risk of developing multiple sclerosis is directly related to the geographic theory of the disease, which is that as distance from the equator decreases, so does prevalence of multiple sclerosis. Exposure to sunlight, which increases as the distance from the equator decreases, results in greater intake of vitamin D (Goldberg 1974, Acheson 1960, Sutherland 1962, and Lebowitz 1967), and during the winter, high latitudinal regions

experience low levels of ultraviolet (UV) sunlight, thus producing inadequate amounts of vitamin D in individuals at latitudes greater than or equal to 42º (Webb 1988 and Ladizesky 1995).

It has been shown that vitamin D dietary supplements given to mice have prevented development of experimental autoimmune encephalomyelitis (EAE), which is an animal model of multiple sclerosis (Cantorna 1996). Vitamin D is known to have strong immunoregulatory effects (Provvedini 1983, Bhalla 1983, and Deluca 2001), and studies have found that multiple sclerosis patients often exhibit insufficient Vitamin D levels (Cosman 1994 and Nieves 1994). Researchers have also found that periods of low vitamin D expression are accompanied by the occurrence of high lesion activity, meaning that more demyelinization occurs simultaneously and after periods in which low levels of vitamin D are recorded (Auer 2000 and Embry 2000).

Low vitamin D status has been implicated in the etiology of multiple sclerosis, as well as other autoimmune diseases including rheumatoid arthritis, insulin-dependent diabetes mellitus, and inflammatory bowel disease. The level of vitamin D intake required to support optimal immune function remains unknown, but is likely to be at least the same as that required for healthy bones. The vitamin D hormone (1,25-dihydroxy vitamin D(3)) regulates T helper cell (Th1) and dendritic cell function while inducing regulatory T-cell function. Cantorna and Mahon (2004) concluded that the result is a decrease in the Th1-driven autoimmune response and decreased severity of symptoms of autoimmune diseases such as multiple sclerosis. It has been noted that the diet is an unreliable source of vitamin D; exposure to sunlight appears to be the most cost-effective approach to obtaining adequate levels of vitamin D. It is believed that one reason

prevalence rates of multiple sclerosis are so high in the northern hemisphere and in regions far from the equator is that exposure to sunlight and thus, intake of vitamin D, is considerably lower in these regions, especially during the winter time. Interestingly, researchers have noted that symptoms of multiple sclerosis fluctuate in severity seasonally (Goodkin 1989, Wuthrich 1970, Bamford 1983, Auer 2000).

In addition, it was determined in a German population that vitamin D status was strongly correlated with multiple sclerosis lesion frequency (Embry et al 2000). Additionally, Munger et al. (2000) studied vitamin D intake in more than 187,000 women from two separate cohorts, one of which was followed for 10 years and the other followed for 20 years. Overall, the risk of multiple sclerosis was 40% lower in women who ingested more vitamin D (Munger et al. 2000), although sunlight was not accounted for since the women in the study were ingesting vitamin D supplements. The researchers did conclude, however, that vitamin D ingested as a part of regular diet did not affect risk of developing multiple sclerosis (Munger et al. 2000). This research suggests that high vitamin D intake, regardless of sunlight exposure, is associated with the reduced risk of developing multiple sclerosis.

The nutritional aspect of multiple sclerosis was studied in relation to the latitudinal theory of the disease in an epidemiologic investigation conducted by Esparza et al. (1995). Researchers set out to determine the relationship between multiple sclerosis mortality rates during the period 1983-1989 obtained for 36 countries and dietary fat and latitude. The researchers conducted multiple regression analysis to determine the relation ship between saturated fatty acids, animal fat, and animal minus fish fat. They found that latitude was positively associated with multiple sclerosis mortality. The ratio of

polyunsaturated fatty acids to saturated fatty acids and the ratio of unsaturated fatty acids to saturated fatty acids were negatively correlated with multiple sclerosis mortality. These results suggest that dietary fat intake and latitude are positively associated with multiple sclerosis mortality (Esparza 1995).

Furthermore, recent epidemiological studies imply that unsaturated fatty acids may have a positive effect on the course of the multiple sclerosis. Schwarz and Lewleing (2005) conducted a meta-analysis of three clinical trials and found that there seemed to be a nutritional benefit from linoleic acid associated with development of multiple sclerosis. They also found that high intake of vitamin D is associated with lower prevalence rates of multiple sclerosis. However, from their studies, the role of minerals, trace elements, antioxidants, vitamins and fish oil remained unclear (Schwarz and Leweling 2005).

Furthermore, Ghadirian et al. (1998) studied the relationship between nutritional factors and incidence of multiple sclerosis in Montreal, Canada from 1992 to 1995. Researchers collected dietary information using a survey which was completed by 197 individuals. Dietary information was collected by employing a 164-item food frequency questionnaire in a face-to-face interview. It was found that there was an inverse association between high body mass index (BMI) and the risk of developing multiple sclerosis. As BMI increased, risk for developing multiple sclerosis decreased, suggesting that a fatty diet would be a protective factor against the disease. Furthermore, a positive association was observed for animal fat intake and risk for developing multiple sclerosis, and a significant protective effect was observed with other nutrients, including vegetable protein, dietary fiber, cereal fiber, vitamin C, thiamin, riboflavin, calcium, and potassium. These trends were similar in both males and females when examined separately. With

respect to specific foods (as opposed to nutrients), a higher intake of fruit juices was inversely associated with risk, suggesting that as ingestion of fruit juices increased, multiple sclerosis incidences decreased. Finally, a protective effect was also observed with cereal/breads intake for all cases combined, but for fish among women only, and pork/hot dogs and sweets were positively associated with risk for developing the disease.

Overall, Ghiardian et al. concluded that their study did support the hypothesis that a diet high in natural fruits, vegetables, and grains would have a protective effect on risk for developing multiple sclerosis, while the evidence also suggested an increased risk of the disease was associated with high intake levels of animal fat.

Yet another study to determine the relationship between nutrition and multiple sclerosis was conducted by Tola et al. (1999). The results of this case-control study, conducted in Italy, suggested that high intakes of bread, pasta, butter and lards, legume soup, horse flesh, and caffeine-containing beverages before the age of 15 would result in higher risk of developing multiple sclerosis. However, there was no association between intakes of these items and development of the disease after puberty.

The possible relationship between diet and multiple sclerosis has not been subjected to adequate study, and the protective role of nutrients with respect to the disease need to undergo further analysis. However, the epidemiological data suggest an association between multiple sclerosis and nutrition. It seems that populations that take in a higher quantity of foods of animal origin (i.e., meat and dairy products) seem to be the most affected by the disease. The role of saturated fatty acids in the progress of myelinic damage has been implicated, and some case control studies indicate a time-cause relationship between the intake of total calories and saturated fats and the incidence

of multiple sclerosis. Meanwhile, other prospective studies failed to confirm this hypothesis, yielding results that contradict the protective effect of a diet rich in anti-oxidant vitamins and polyunsaturated fatty acids. In patients with a progressive chronic form of the disease, polyunsaturated fatty acids did not demonstrate any effect on the progression of the invalidating lesions.

Nutritional interventions have been conducted in patients suffering from an acute and remittent form of multiple sclerosis; these interventions have pointed to the significant effect of treatment with polyunsaturated fatty acids in slowing down the progression of myelinated lesions only in cases with a slight initial degree of disability or no disability at all. However, the interventions seem to confirm the hypothesis of an association between the magnitude of the disease and consumption of saturated fats and show an improvement trend in patients treated with polyunsaturated fatty acids, although the data are not statistically significant. It appears that the data regarding the nutritional theory with respect to development of multiple sclerosis is inconclusive and ambiguous.

Genetics and the development of multiple sclerosis.

There are two types of evidence that suggest multiple sclerosis is a genetic disease. The first type of evidence is derived from population studies. Multiple sclerosis is a disease that affects primarily people of northern European heritage, and other ethnic groups tend to be less likely to develop it. Secondly, evidence from family studies indicates that individuals who have cases of multiple sclerosis in family members are more likely to develop the disease themselves (Carton 1997). For instance, the average person in the United States has an approximate chance of 1 in 750 of developing the

disease; however, people who have relatives with multiple sclerosis have a higher risk of developing the disease, ranging from 1 in 100 to 1 in 40 (Carton 1997). Furthermore, researchers have shown that the identical twin of a patient with multiple sclerosis has a 1 in 3 chance of developing the disease (Mumford 1994, Willer 2003, Hansen 2005, and Ristori 2006). Researchers have concluded from these twin and family studies that genetic make-up is important for determining who may develop multiple sclerosis.

One of the hallmarks of multiple sclerosis is its unequal distribution across the globe. It is most common in populations of northern European descent, and is diagnosed most often in Scandinavian nations, the United Kingdom, and the northern United States and southern Canada (Compston 1997). Regions of high prevalence have been found in northwestern Sardinia (Sotgiu 2002 and Marrosu 2002) and Sicily (Grimaldi 2001 and Nicoletti 2005). Several areas of abnormally high prevalence of multiple sclerosis have been found in Finland, as well. In these regions, there is an approximately two-fold increased prevalence than the national average (Panelius 1969, Wikstrom 1975, Kinnunen 1983, and Sumelahti 2000). Seinajoki, in southern Ostrobothnia, Finland, recently demonstrated an incidence of 12 cases per 10,000 people, which is the highest rate of multiple sclerosis reported anywhere in the world (Sumelahti 2001). It has been demonstrated that these areas are considered high-risk regions for multiple sclerosis. Recently, haplotypes associated with multiple sclerosis have been identified. Tienari et al. (2006) have suggested that such haplotypes could be used as molecular tools for tracing common ancestry between patients in separate locations, thus providing clues to historical origin of the disease. Furthermore, researchers have proposed that this archealogical genetic approach would help to narrow the size of the haplotype shared

between groups allowing for the identification of etiological variants of multiple sclerosis patients.

The evidence from family studies supporting a genetic susceptibility for multiple sclerosis is compelling. Studies have been conducted on twin, half-sibling, and adoptee populations of northern European descent, and the results of the studies suggest that increased susceptibility to the disease is genetic (Ebers 1995, Willer 2003). In monozygotic twins, there is a 20-30% increased risk for developing the disease, while the risk is only 3-5% in dizygotic twins. Interestingly, in twin studies conducted in France and Italy, the concordance rates for both monozygotic and dizygotic twins are reportedly 6-11% (French Research Group on MS 1992). The differing results from these two sets of studies suggest that the role of genetics in inheriting multiple sclerosis is more prominent in populations of northern European descent than in France and Italy. A recent Canadian twin study revealed concordance rates of 34% versus 3.8% in monozygotic versus dizygotic female-female pairs and 6.5% versus 11.4% in male-male pairs (Willer 2003). The results in the Canadian twin study suggest that the role of genetic factors is more powerful in women than in men.

The fact that the rate for identical twins both developing multiple sclerosis is significantly less than 100 percent suggests that the disease is not entirely genetically controlled. However, this could be due to the fact that some people with multiple sclerosis lesions remain asymptomatic throughout their lives. This could also be due to low penetrance of the susceptibility allele of multiple sclerosis.

Multiple sclerosis is considered to be a polygenic disease, meaning that multiple genes contribute to the development of the disease. Thus far, no mutation leading to the

disease has been identified. An association with the HLA-DRB1*1501-DQB1*0602-DQA1*0102 haplotype is the most common finding in universal molecular genetics studies on multiple sclerosis thus far. The association with HLA is not a new one. Although this association has been known for over 30 years, it is still largely unknown which of the three associations is the responsible variation, or if it is a combination of several of the three variations that leads to the disease. Few non-HLA loci have been found over the years, but the most common ones found in the literature are found on chromosome 5p (Ebers 1996 and Kuokkanen 1996), 17q (Sawcer 1996, Saarela 2002, and Barton 2004), and 19q13 (Barcellos 1997, D'Alfonso 2000, Pericak-Vance 2004, and Reunanen 2002). The predisposing genes in these regions have yet to be identified. Tienari et al. (2004) suggest that some of these genetic data are defined geographically, and certain allelic associations appear restricted to southern Ostrobothnia. In a sub-region analysis of Ostrobothnia, it was observed that the population area at high risk for developing multiple sclerosis was relatively small, the Kyronjoki river region with a population of approximately 100,000. The prevalence for multiple sclerosis in this region was 210 per 100,000 in 1993 (Tienari 2004). Research indicates that the proportion of patients with multiple sclerosis is higher in southern Ostrobothnia than in neighboring regions or in southern Finland (Figure 2) (Sumelahti 2003 and Tienari 2004).

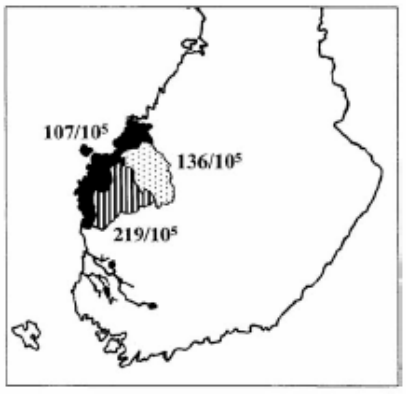


Figure 2. Prevalence of multiple sclerosis in Ostrobothnia compared to surrounding regions (Figure adapted from Tienari 2004).

Although Finland was not conquered by the Vikings, there is archaeological evidence for a Viking

influence in the southwestern high-risk area of Ostrobothnia (Lehtosalo-Hilander 1982); this evidence shows a connection with the Kyronjoki river region,
and these observations demonstrate the Scandinavian influence in this region, which may have been significant in leading to the high rate of occurrence in Finland today (Tienari et al. 2004).

Myelin Basic Protein (MBP) and other haplotype signatures can be used as DNA fingerprints to trace common ancestry between patients in different geographic locations. It is assumed that MBP can provide clues to the historical origin of multiple sclerosis, as well as be an approach to define a "superfamily" of multiple sclerosis patients with common ancestry and common pathogenetic mechanisms (Tienari 2006). MBP would help narrow the size of the shared haploytype identical-by-descent, and it would thus make it easier to define etiological variants in patients with multiple sclerosis (Tienari 2006). Since the stretches of DNA identical-by-descent become smaller as the genetic distance of patients increased, more focused high-density single nucleotide polymorphism (SNP) and haplotype analyses as well as functional experiments at smaller number of candidate sites are allowed. In other words, as the similarities between genomes become greater between groups, it becomes easier to identify portions of the genomes that may have mutations which could lead to inheritance of a certain disease. In the case of multiple sclerosis, if a genetic "superfamily" could be identified by comparing genomes of northern Europeans and African Americans, for instance, then this would indicate that northern Europeans may have passed a genetic susceptibility to African Americans if the same similarities between these two groups are not found in Africans

alone. This type of analysis would also facilitate the search for the specific genes that determine the etiology and risk for developing the disease.

Furthermore, genealogical evidence for a founder effect in multiple sclerosis has also been reported in Overkalix in northern Sweden (Binzer 1994), in Lysvik parish in western Sweden (Callander 2004), and in Sardinia (Marrosu 2002). A founder effect is described as the effect of establishing a new population by a small number of individuals who carry only a small portion of the original population's genetic variation. The resulting population could exhibith different genetic and phenotypic characteristics from the original population from which it was derived, and this is what appears to have happened in northern Sweden, Sardinia, and Ostrobothnia, Finland. Additionally, there are clusters, or areas of increased incidence or prevalence of a disease which are surrounded by regions where risk is not considered to be out of the ordinary, of multiple sclerosis in continental Europe, in northern Croatia and western Hungary. In these areas, some rural regions have reported prevalence rates approaching 200 cases per 100,000 population at risk (Guseo 2004). Inferences drawn from this data include probable genetic isolation and possible Germanic ancestry, which is interesting since many Scandinavians have Germanic ancestors (Tienari 2006).

The tools for SNP have advanced greatly with the Human Genome and HapMa Projects. Thus far, more than a million SNPs have been analyzed through the HapMap Project. Predisposing variants to multiple sclerosis will most reliably be caught by such grand scale associations studies as the HapMap Project (Tienari 2006).

Genetic research on the inheritance of multiple sclerosis has determined that if a person has multiple sclerosis, that person's first-degree relatives (i.e., parents, children

and siblings) have a 1-3 percent risk of inheriting the disease (Carton 1997). Although no specific gene for multiple sclerosis has been identified, several researchers have concluded that people with multiple sclerosis inherit certain regions on individual chromosomes more often than people without multiple sclerosis. Researchers are investigating the human leukocyte antigen (HLA) on chromosome 6, since the HLA patterns of multiple sclerosis patients appear to be different from those who do not have multiple sclerosis. Development of multiple sclerosis is likely to be influenced by the interactions of a number of genes, making it a polygenic disease. It is believed that each of the genes ultimately "responsible" for the development of multiple sclerosis has only a modest effect. Researchers continue to conduct studies to pinpoint specific genes that are involved in the disease, to determine the function of those genes, and to learn how each gene's interactions with other genes make an individual susceptible to multiple sclerosis. In addition to leading to better ways to diagnose multiple sclerosis, such studies should yield clues to the underlying causes of multiple sclerosis and, eventually, to better treatments or a way to prevent the disease.

Researchers have noted that genes contributing to susceptibility to multiple sclerosis are difficult to identify because they exert a relatively modest effect on disease risk (Giovananni and Ebers 2007). The only unambiguous genetic association and linkages identified thus far are with alleles of the human leukocyte antigen (HLA) class II region, which is a part of the major histocompatibility complex (MHC). A large linkage study conducted on 2692 individuals from 730 multiplex families of northern European descent confirmed linkage to the MHC on chromosome 6p21 and suggested possible linkage on chromosomes 17q23 and 5q33 (Sawcer 2005). Another large study of

Canadian and Finnish families with multiple sclerosis genotyped 4203 individuals with a high-density SNP panel spanning the genes encoding he MHC and flanking genomic regions. These two studies indicate that MHC-associated susceptibility to multiple sclerosis is determined by HLA class II alleles, their interactions, and possibly closely neighboring variants, and that other regions in the genome are unlikely to contribute much to disease susceptibility (Sawcer 2005, Lincoln 2005, Giovannani and Ebers 2007).

Multiple sclerosis is currently defined using a set of polythetic criteria, which by definition cannot be 100% specific. Thus, even low rates of misdiagnosis could drastically reduce the power of genomic studies to detect loci associated or linked with the disease (Cardon 2003).

Family history remains to be the strongest indicator in multiple sclerosis diagnosis. Segregation studies revealed that males with a history of multiple sclerosis in relatives of the first and second orders are much more vulnerable to the same disease (Carton 1997). In addition, histories of both paternal and maternal relatives have similar predicting power, indicating an autosomal transmission of susceptibility (Carton 1997). Multiple sclerosis exhibits a strong racial propensity. The disease is prevalent among Europeans and African Americans, whereas it appears to be rare, sporadic, and random in Asia and Africa. Normally, racial disparity is best explained by inheritance.

Recently, a whole-genome admixture scan found a candidate locus for multiple sclerosis susceptibility. Admixture mapping is the process of scanning the human genome for gene variants that affect risk for developing a disease. Studying genetic markers whose frequencies differ between Europeans and Africans allows for the genome of African or European ancestors to be more easily examined so that regions can be

identified where individuals with specific diseases, such as multiple sclerosis, have an abnormally high concentration of European or African genes (Rife 1954, Chakraborty 1988, Stephens 1994, Briscoe 1994, McKeigue 1997, and McKeigue 1998).

According to Smith et al (2004), there are two advantages to admixture scanning. First, since African and European immigrants came into contact in North America, there has been an average of only six generations of offspring from the two groups. Smith et al. (2004) note that due to the few generations of populations since these groups were first introduced in North America, there has been little recombination between chromosomes of African and European ancestry in the history of African American populations (Smith 2004). Thus, a genome scan tagging all of either the African or the European chromosomal segments in a group of African Americans requires only 1,000-3,000 markers, which is far fewer than the 300,000-1,000,000 markers required for a whole-genome haplotype scan (Carlson 2003). The second advantage of admixture mapping is that it is much more effective at detecting disease risk variants that are of very low or high frequency in Africans or Europeans but are highly differentiated in frequency across populations, thus making it a perfect candidate for use in diseases with large racial disparities. Multiple sclerosis is an excellent candidate for admixture mapping due to its evident racial disparity between European Americans and African Americans (Kurtzke 1979). Therefore, a whole-genome admixture scan was conducted in African American multiple sclerosis patients and compared with admixture scans for a group of cases and controls. It was hypothesized that if genetic risk factors for multiple sclerosis explain its epidemiology, they would be evident from the admixture scan as identifiable regions of high European ancestry in African Americans with multiple sclerosis compared to the

control group (Reich et 2005). As previously mentioned, genetic linkage scans have only identified one risk haplotype for multiple sclerosis, which is at HLA on chromosome 6. However, according to Reich et al. (2005), admixture mapping, which is considered to be an association scan, is much more likely to identify the weak factors that explain the disease risk. By estimating the extent of European ancestry in 605 African Americans with multiple sclerosis and comparing their genome scans with those of the genome-wide average for cases and controls, Reich et al. (2005) found that the strongest deviation from the genome-wide average was on chromosome 1 near the centromere. Admixture association was not detected anywhere else in the genome, and the researchers concluded that an immediate priority of multiple sclerosis research should be placed on fine-mapping the chromosome 1 peak identified in this study to further investigate the association between this locus and the risk of developing multiple sclerosis (Reich 2005).

Table 1. Key literature reviewed in Chapter II of the present study.

First author	Year	Study Hypothesis / Subject	Outcomes	Strengths / Weaknesses
Kurtzke	1977	Geography in MS – MS is an environmental, exogenous illness	High frequency of MS is found between 65 and 45º north latitude and southern Australia; Latin America, Asia, and Africa have low risk. All areas with high risk are in Europe or European colonies, thus it appears MS spread from western Europe. MS is less common in African Americans, Japanese Americans, and Amerindians than in Caucasians in the US	Study is still used as basis for geography and MS information. Study is old, published in 1997. Findings contradict the geographic theory of MS because at 40º latitude, MS was found to be high in America, medium in Europe, and low in Asia
Rosati	1996	Epidemiological studies from Sardinia since 1975 indicate 2 fold increased prevalence of MS than in surrounding areas. Previous populations too small to draw conclusions.	Frequency of MS was studied in northwestern Sardinia in a population of 270,000 and compared to other Italian populations. Confirmed higher frequency of MS among Sardinians and attributed rates to environmental and genetic factors.	Confirmed high rate of MS in an otherwise low frequency area close in proximity to the equator. Findings contradict the geographic theory of MS.

First author	Year	Study Hypothesis / Subject	Outcomes	Strengths / Weaknesses
Munger	2000	Study of the protective effect of vitamin D on risk of MS.	Dietary vitamin D intake was examined in 2 large cohorts (the Nurses' Health Study 1980-2000 and 1991-2001). Intake of vitamin D supplements was inversely associated with MS risk. No association was found between vitamin D from food and MS incidence.	Results support a protective effect of vitamin D intake on risk of developing MS.
Esparza	1995	Ecologic study of relation between MS mortality rates from 1983-1989 of 36 countries and dietary fat and latitude.	Stepwise multiple regression analysis determined that saturated fatty acids, animal fat, animal minus fish fat, and latitude correlated independently and positively with MS mortality.	Findings support hypothesis liking dietary fat intake and latitude to MS mortality. Inuit diet of mainly animal meat was not taken into consideration.
Ghadirian	1998	Nutrition and food patterns, specifically high intake of animal fat and low intake of fish play a role in etiology of MS.	Nutritional factors and MS studied in 197 incident cases and 202 controls in Montreal between 1992-1995. Dietary information was collected by 164-item food questionnaire and interview. Inverse association was observed between BMI and risk of MS. Tall women showed greater risk for MS. Protective effect observed with vegetable protein, dietary fiber, vitamin C, thiamin, riboflavin, calcium, and potassium. High intake of fruit juice inversely associated with risk.	Results support protective role for some components commonly found in fruits, vegetables, and grains, and increased risk was associated with high animal food intake. Native diets were not taken into consideration.
Sumelahti	2001	Investigation of prevalence trends in western and southern Finland from 1983-1993.	Age-adjusted and age-specific MS prevalence rates were calculated. A 1.7-fold increase was found in 1993 when compared to 1983 prevalence rates in Seinajoki, Finland. Prevalence and incidence in this region among the highest reported in the world.	Seinajoki, Finland region linked with Scandinavian migration. Highest reported incidence and prevalence indicates that MS may have originated in the area.
Willer	2003	Longitudinal study of MS concordance rates in twins and siblings.	Concordance rates of 25.3% for monozygotic and 5.4% for dizygotic twins. 2-fold increase in risk to DZ twins of non-twin siblings of twins.	Demonstrates genetic and familial facets of MS.
Tienari	2006	Geographic and genetic summary of MS.	Genetic studies identified haplotypes associated with MS patients in Finland suggesting a founder effect. Haplotypes can be used to trace common ancestry and geographic origin of MS.	Demonstrates genetic archeological approach to define a "superfamily" could implicate etiology of MS.
Reich	2005	Whole genome admixture scan to find a candidate locus for MS susceptibility.	Admixture scan focused on 605 African American cases and 1,043 African American controls and reported a locus on chromosome 1 significantly associated with MS.	Demonstrates ability to find susceptibility allele by examining "new" populations with only partial European ancestry.

CHAPTER III

METHODS AND PROCEDURES

In this study, published data from public records and multiple sclerosis prevalence estimates from governmental and institutional sources were collected. In addition to extracting data from the literature, related information on multiple sclerosis prevalence was obtained from various web publications, including those of the World Health Organization (WHO), the Centers for Disease Control and Prevention of the U.S. Department of Health and Human Services (CDC), and the Multiple Sclerosis International Federation (MSIF). From these databases, only the statistical information covering the last 10 years was extracted for this analysis. The National Institutes of Health website, PubMed, as well as internet search pages were used to collect data, and searches were conducted using phrases including, but not limited to *multiple sclerosis and genetic etiology, multiple sclerosis and environment, multiple sclerosis and nutrition, multiple sclerosis epidemiology, and distribution of multiple sclerosis.*

Incidence is defined as the proportion of new cases in a population at risk for developing multiple sclerosis divided by the size of the population at risk. Prevalence is defined as a measure of the total number of cases in a population, rather than the rate of occurrence of new cases, divided by the population at risk. In this project, primarily prevalence data were collected and used for analysis; however, in some cases incidence data was used. For instance, in First Nations Canadians, only incidence rates were found

in the literature. In these cases, the incidence rates were described in lieu of prevalence rates. When incidence data was used in this report, this fact is clearly stated so that prevalence is not to be confused with incidence. Additionally, some of the data sources reviewed in this project had differing incidence or prevalence rates for the same country. In such cases, registry data obtained from MSIF were used in the analysis in lieu of sample data. Registry information from MSIF was selected over sampling information because in some cases, sampling measures are not necessarily indicative of the prevalence of multiple sclerosis for an entire region. It appeared in all cases reviewed in this project that registry data were more comprehensive than sample data.

An investigation was performed by collecting and reviewing relevant literature on worldwide multiple sclerosis prevalence. Literature citing different explanations for the etiology of multiple sclerosis, including geographic, nutritional, and genetic theories for the etiology of the disease, were examined and summarized for this project. Some of the literature reviewed that listed key findings and implications related to this project was tabulated, and the table was inserted in Chapter II of this project.

The 2006 edition of the U.S. Central Intelligence Agency World Factbook was used to obtain racial and ethnic information for this analysis. For the purposes of this study, Caucasians are defined as white individuals with northern European ancestry; African Americans are defined as black individuals living in America whose ancestors originated in Africa; Asian Americans are defined as Americans whose ancestors originated in China, India, Japan, Taiwan, and Vietnam. In addition to history textbooks and archeological and anthropological literature, information on the migration, settlement, and admixture history of different racial and ethnic groups was obtained from the World

Factbook, from the free-content encyclopedia Wikipedia, from historical textbooks as referenced, and from many other websites dealing with historical aspects of nations.

Prevalence rates obtained from the MSIF database and Rosati's 2001 article from *Neurological Science* entitled "The prevalence of multiple sclerosis in the world: an update" were gathered for 77 nations, and the information was tabulated in order from greatest prevalence to least prevalence (Table 2). Asterisks note that the prevalence rate for the corresponding country was not obtained from MSIF, but rather from a literature source, and that source is duly noted. Three charts were derived from the data listed in Table 2. Data were separated into geographic areas as follows: Europe and Eastern Europe, including Russia; the Middle East, the Far East, New Zealand, and Australia; and North America, South America, and the Caribbean, and Figures 4, 5, and 6 demonstrate these findings. Following tabulation of the data, prevalence of multiple sclerosis for each nation was mapped manually on an editable outline map. Each nation was identified on a world map (Figure 7) and on a European map (Figure 8), found on the editable map, and then filled with a color corresponding to the prevalence rate as listed in the figure legend. Editable outline maps in Mercator projection in the Powerpoint format were obtained from Dr. Ruoxiang Wang, Assistant Professor of Urology at the Emory University School of Medicine. The Red-Green-Blue (RGB) color scheme was used to construct a continuous color spectrum to represent multiple sclerosis prevalence from $\leq 19 \times 10^5$ (green color: red, 0; green, 255; and blue, 0) to $\geq 150 \times 10^5$ (black color: red, 0; green, 0; and blue, 0). The outline of each nation was filled with the color that represented the prevalence of multiple sclerosis in that nation. Furthermore, in Figure 7, blue arrows depict the Northern European migration routes, orange arrows depict Iberian, or Spanish

and Portuguese, migration routes, and green arrows depict African migration routes. In Figure 8, arrows were drawn depicting the Germanic Migration and Expansion from 750 BC to 600 AD (pink arrows), the Norsemen, or Viking, migration from 790 AD to 1090 AD (green arrows), and the Crusades from 1095 AD to 1272 AD (black arrows). Arrows were drawn based on historical data found in textbooks and on Wikipedia.com (Christiansen 2006, Encyclopedia Britannica 2007, Hoerder 2002, Wikipedia 2007a, b, c, and d).

Data obtained from the Multiple Sclerosis International Federation

Results regarding the global occurrence of multiple sclerosis obtained from MSIF and additional publications indicate that although incidence of multiple sclerosis fluctuates on a yearly basis, the rate and trend for each nation remains relatively constant when compared to international data. The MSIF was especially useful in providing detailed international surveillance on multiple sclerosis prevalence rates. Specifically, the European Map of Multiple Sclerosis Database provided multiple sclerosis prevalence in 64 nations in the year 2006, a set of simplified but comprehensive statistical data informative of multiple sclerosis prevalence on a global scale. To date, the database consists of prevalence reports for 64 countries worldwide, but it is reported that another 32 will be added soon. Data from another 13 countries were added to this analysis using information collected from the literature.

The information and data contained in the MSIF Atlas of Multiple Sclerosis web application were collected using a questionnaire developed by MSIF, the WHO, and a number of multiple sclerosis professionals. The data were chosen because the

methodologies for obtaining the data were clearly outlined, well researched, and appeared to be reliable based on the collection methods and follow-up conducted by researchers.

MSIF expresses the prevalence of multiple sclerosis in each nation as a rate of cases per 100,000 population at risk. Upon collection of the MSIF questionnaires, which were sent to 98 countries worldwide, the responsive data from 64 countries were standardized and organized. MSIF compiled the responses, and took population data from the WHO's World Health Report 2000 to create an electronic database of global prevalence rates of multiple sclerosis, which is now accessible by the public as the European Map of Multiple Sclerosis Database at http://www.europeanmapofms.org/emsp.aspx. Other sources for prevalence figures used in this analysis are directly referenced herein.

CHAPTER IV

RESULTS

The hypothesis of the current proposal is that since multiple sclerosis occurs frequently in certain racial and ethnic groups, and since most nations of the world consist of a single racial group as the predominant racial group, a comparison of multiple sclerosis prevalence rates among nations would help to determine whether the disease coincides with migration, settlement, and admixture of an ethnic group that may carry certain susceptibility alleles.

After conducting a comprehensive review of the literature related to the different theories on the etiology of multiple sclerosis and compiling a table of global occurrence of the disease, the results indicate that multiple sclerosis prevalence does indeed correspond with the migration and settlement history of northern Europeans. The migration and settlement history of the Scandinavians, along with information regarding current global incidence or prevalence rates, depending on the information found for each country, is detailed below.

European multiple sclerosis prevalence and migration history of the Scandinavians.

Due to the global disparity in multiple sclerosis distribution, the present research project set out to investigate the existing multiple sclerosis prevalence data using a geographic epidemiological approach. The overarching hypothesis of the present study is that multiple sclerosis prevalence reflects a susceptibility genotype in individual

populations, and the susceptibility allele originated in the population of the highest prevalence and was distributed to other racial and ethnic groups through admixture. The genetic epidemiology of cystic fibrosis, hemochromatosis, and prostate cancer has shown that inter-group breeding may lead to spreading of the susceptibility alleles to other racial and ethnic groups (Sandblom et al. 2003, Higgins et al. 2005, Gilbert et al. 1995, and Acton et al. 2001). If this is truly the case, then the geographic distribution of the varied frequencies of a disease reflects the history of migration, settlement, and admixture of the population carrying the susceptibility.

In the present analysis, it was found that nations with the highest prevalence of multiple sclerosis are located in northern Europe. Table 2 and Figures 7 and 8 illustrate that other nations with comparable prevalence rates of multiple sclerosis are Canada (100 cases per 100,000 at risk), the United States of America (135 cases per 100,000 at risk), Scotland (187 cases per 100,000 at risk), Australia (78 cases per 100,000 at risk), and New Zealand (85 cases per 100,000 at risk), The residents of these nations share a common origin; most of these nations' residents are immigrants from northern Europe. However, it should be noted that the indigenous Native Americans of North America, the Aboriginals of Australia, and the Maoris of New Zealand, who inhabit similar geographical environments as the descendents of northern Europe, are rarely diagnosed with multiple sclerosis (Warren et al. 2007, Miller et al. 1986, Alter et al. 1971, Fawcett and Skegg 1988, and Hornabrook 1971, National Multiple Sclerosis Society 2007). This observation suggests that, at least in the U.S., Australia, and New Zealand, the high prevalence of multiple sclerosis accompanied the northern European immigrants during their migration, and this co-migration suggests that multiple sclerosis is almost certainly

an inherited disease which originated in northern Europe. To demonstrate how this co-migration may have occurred, it is important to map out the migration of the northern Europeans and to investigate the potential relationship between their migration and the current prevalence of multiple sclerosis.

Multiple sclerosis prevalence data for 77 European nations are available from MSIF and other sources in the literature. A gradient distribution of multiple sclerosis prevalence is a salient geographic epidemiological feature in Europe. With the highest prevalence in northern Europe appearing in Norway, high rates of multiple sclerosis prevalence spread along the coast of the northern Atlantic Ocean to all of the Western European nations (Figure 7). Prevalence of multiple sclerosis declines gradually in nations as they become more distant from Norway.

In addition to Norway, the other Scandinavian neighbors, Finland, Denmark, and Sweden, each have high prevalence rates. In general, with Norway as the apex, high multiple sclerosis prevalence radiates to the south and west to nations bordering the North Atlantic Ocean. This radiation covers the west half of northern Europe, countries including Sweden, Finland, Norway, Iceland, United Kingdom, and Ireland, all of western Europe (*i.e.*, Germany, the Netherlands, Belgium, Lithuania, France, Austria, and Switzerland), and the west part of southern Europe (*i.e.*, Italy, Spain, and Portugal). Following this pattern, multiple sclerosis prevalence appears inversely proportional to the respective country's distance from Norway (Figure 8). On the other hand, the inland portion of Europe, central and eastern European nations, as well as those in southeast Europe, shows markedly reduced multiple sclerosis prevalence, even though the distance

from Norway is essentially the same as the Western Europe nations (Figure 8), and the geographic latitude of these nations is similar, as well.

This gradient of multiple sclerosis prevalence rates in northern and western European nations is well recognized, and the relatively reduced multiple sclerosis prevalence in the rest of Europe is also well known. To date, however, there has been no satisfactory explanation for this phenomenon. Interestingly, European nations cohabit in a relatively similar geographic environment with similar levels of exposure to sunlight, similar climate, etc. Meanwhile northern and western Europeans enjoy the highest standard of living together with affordable medical care. Yet, cause for the high multiple sclerosis prevalence among these nations remains unknown.

As noted in the literature review, there are a number of theories regarding the reasons for the gradient of multiple sclerosis prevalence rates. None of the theories mentioned above can fully or conclusively explain the global distribution of multiple sclerosis. The geographic, or latitudinal theory, was discounted with the examination of multiple sclerosis incidence in Sassari, Sardinia. The latitudinal theory stated that as the distance from the equator increased, so did prevalence of multiple sclerosis, presumably due to the decrease in vitamin D intake. After investigating the incidence of multiple sclerosis in Sassari as well as in other parts of Europe and Italy, researchers concluded that the incidence of multiple sclerosis in Sassari was much higher than it would be expected to be if the latitudinal theory fully explained the distribution of the disease (Pugliatti 2001). Furthermore, Marrosu et al. (2002) examined the presence of familial aggregation in Sardinian patients with multiple sclerosis by investigating the recurrence risk in siblings of individuals affected with the disease. They evaluated factors

influencing risk, such as patient and sibling sex, patient age at onset, sibling birth cohort, and the presence of affected relatives other than siblings. To establish the contribution of genetic factors to familial multiple sclerosis aggregation, the researchers verified the presence of distant familial relationships among patients, tracing the extended pedigrees of all multiple sclerosis patients born in the Sardinian village described by researchers as "L.", which, according to Marrosu et al. (2002) could be considered a "genetic drift" on a microgeographic level. L.'s population showed little variation from the first census at the end of 1600 to 2001 when the study was conducted, in the absence of substantial admixture from nearby villages as reported from precise historical sources. Marrosu et al. (2002) showed that the ratio between lifetime risk for a sibling of a patient with multiple sclerosis divided by risk in the general population in Sardinians is similar to that reported in populations of Scandinavian descent. Furthermore, it was found that that recurrence risk in siblings of patients with multiple sclerosis varies widely according to the age at onset of the disease and whether there are other affected family members. According to the researchers, this finding suggests some degree of heterogeneity in the genetic mechanisms underlying familial aggregation. However, pedigrees of patients from the village of L., demonstrating that all affected subjects descended from three pairs of ancestors, substantiated a "founder effect" as responsible for the disease in the village and confirmed that Sardinian familial aggregation of the disease is genetic in nature (Marrosu et al. 2002). It is important to note that these findings support a genetic etiology of the disease.

Furthermore, the latitudinal theory is discounted with evidence showing that Native Americans who currently live in the same latitudinal geographic area as other

racial groups in the northwestern United States, do not exhibit the same high prevalence of multiple sclerosis as the latter group (Warren 2007). Although most native populations in North America have historically been nomadic, moving from one geographic latitude region to another, and probably originated in Eurasia, to date, there is no evidence in the literature that these groups have ever experienced moderate or high levels of multiple sclerosis. This trend of natives exhibiting lower prevalence and incidence rates of multiple sclerosis than migrants living in the same country can be seen in almost any nation where northern Europeans have traveled and settled among natives of the respective region (Kurtzke 1977).

Judging from Figure 7 it has become evident that elevated levels of multiple sclerosis prevalence are found mostly in coastal nations, and since northern Europeans conducted much of their exploratory traveling through maritime routes, it is not surprising that rates of multiple sclerosis are higher near the coasts where explorers would have migrated and settled. By examining the geographic distribution of multiple sclerosis prevalence rates in Europe, data from the present study indicate that susceptibility to multiple sclerosis is closely associated with the migration and settlement history of northern Europeans and that the prevalence gradient in Europe results from admixture of the Scandinavians with racial and ethnic groups in other parts of Europe. Subsequently, the susceptibility allele for developing the disease was transmitted to other races and ethnic groups throughout the migration and settlement history of the Europeans by interracial admixture. This investigation indicates that there is indeed a genetic susceptibility to multiple sclerosis, that the susceptibility originated in Scandinavia, and that the alleles have been transmitted by gene flow to other races.

The southward migration of the northern Europeans is well documented (Wikipedia 2007a, b, c, d and MSN Encarta 2007). Three successive waves of southward migration have been chronicled; the earliest of which was the Germanic Migration and Expansion from 750 BC to 600 AD (Encyclopedia Britannica, Wikipedia 2007d). During the Migration and Expansion, Germanic tribes in southern Scandinavia settled in continental Europe and the British Isles located in the North Atlantic Ocean (Encyclopedia Britannica 2007, Wikipedia 2007d). This wave of migration was followed by the Norsemen Migration from 790 AD to 1090 AD (MSN Encarta 2007). Since the Vikings had such advanced technology and navigational skills, it was natural for them to have traveled using maritime routes. They traveled mainly along the coast of the North Atlantic Ocean, through the Straits of Gibraltar to the Mediterranean Sea (Figure 8). In comparison, far fewer Scandinavians traveled into the inland area using other means of transportation (Christiansen 2006, MSN Encarta 2007).

The third wave of migration, known as the Crusades from 1095 AD to 1272 AD, consisted of large numbers of northwestern European men traveling to the Middle East (Hoerder 2002, Wikipedia 2007b). It is possible that at the end of the two thousand years of southward migration, settlement, and admixture, the original Scandinavian genetic attributes had been transmitted along maritime routes to the British Isles and the northwestern regions of continental Europe. Subsequently, genetic attributes were further transmitted to other parts of Europe to form the northern European genetic gradient of multiple sclerosis currently demonstrated. It is important to note that this gradient is congruous with the current gradient in geographic distribution of multiple sclerosis prevalence, suggesting that the susceptibility to multiple sclerosis is one of the genetic

attributes that originated in southern Scandinavia, and was transmitted to other European ethnic groups by admixture.

The geographic distribution of multiple sclerosis prevalence coincides with the migration routes of the Scandinavians, and the gradient of the prevalence also reflects the extent of Scandinavian settlements. Scotland and the United Kingdom, for example, are populated mainly with Scandinavians and the prevalence rates of multiple sclerosis there are reportedly among the highest in the world, making the prevalence rates in these two regions comparable to the levels of multiple sclerosis in Scandinavia. Furthermore, it is also known that Iceland was a frequent migration and settlement place for the Scandinavians, and currently, the country exhibits substantial prevalence rates of multiple sclerosis (Wikipedia 2007b and d).

Global multiple sclerosis and European migration, settlement, and admixture.

Due to the consideration that the gradient of multiple sclerosis prevalence in Europe may be a result of genetic admixture of the northern Europeans with other races and ethnicities, further analysis was performed in order to trace a potential link between the Europeans and high multiple sclerosis prevalence rates in other parts of the world.

The high prevalence rates of multiple sclerosis in Canada, the United States of America, Australia, and New Zealand could be due to migration and settlement by northern Europeans and their descendents. These nations were once again settled by northern Europeans in relatively recent historical times. Thus, it is possible that people migrating from Europe may have carried the multiple sclerosis susceptibility allele to Australia, New Zealand, and North America

Europeans began to migrate to the New World, or the United States, on a large scale in the 15th century, 700 years after the Scandinavians settled in different parts of Europe (The Library of Congress 2007). Currently, most of the residents in the U.S. are European migrants, their descendents, and the offspring of admixture between Europeans and Native Indians. Furthermore, emigrants from European countries often settle in regions where earlier emigrants from their native land have settled.

According to the data listed in Table 2, the national multiple sclerosis prevalence rates in the United States and Canada parallel those in the European countries where European Americans originated. Most of the European Americans in North America originated in northwestern Europe where the prevalence of multiple sclerosis is high. It is evident that both Canada and the United States of America have rates of multiple sclerosis comparable to the rates in northwestern Europe (Table 2, Figure 7). On the other hand, Central and South American countries, where the population majorities are descendants of the admixture between native Indians and Spanish or Portuguese colonists, exhibit much lower rates of the disease. Throughout history, the Spanish and Portuguese settlers of Central and South America divided the region into two separate territories. It is interesting to note that the South American countries (i.e., Peru, Mexico, Brazil, and Argentina) settled by the Spanish and Portuguese have relatively low prevalence rates of multiple sclerosis, as do Spain and Portugal when compared to their bordering nations.

The Caribbean countries have a complex history of colonization by several different European powers. Both the Scandinavians and the western Europeans colonized parts of the Caribbean at one point or another. In addition, European colonists brought Africans into this area by participating in the Slave Trade. During the Slave Trade,

admixture between the Europeans and the Africans was extensive and complete, meaning that much of the time, Africans were not permitted to mate with people of their own race. Furthermore, admixture was unidirectional in that it was the Caucasian men who were mating with African women, rather than African men breeding with Caucasian women. Thus, any genetic mixture between Africans and Caucasians would have been passed from African mothers to their offspring. Many of the Caribbean countries now exhibit relatively high multiple sclerosis prevalence rates, even though most of their current inhabitants originated in Africa where multiple sclerosis is considered a rare disease. For instance, Barbados reported prevalence of 26.3 cases per 100,000 at risk; Cuba reported 10 cases per 100,000; and Martinique reported 14 cases per 100,000.

Furthermore, the relatively high incidence of multiple sclerosis in African Americans is an important issue affecting multiple sclerosis research. Since the rate of multiple sclerosis in Africans is considerably lower than in African Americans, it is evident that Africans are much less susceptible to the disease. Family history is a strong risk factor for developing multiple sclerosis in African American populations indicating that the disease may also be an inherited disease in this population (Multiple Sclerosis Genetics Group 1998). Since African Americans could not have inherited multiple sclerosis from their African ancestors who show low rates of the disease, it seems that African Americans must have contracted the susceptibility allele from another source. To identify that source, the epidemiology of multiple sclerosis in Africa was examined.

Unfortunately, nations in Africa have a limited life expectancy and the healthcare systems in Africa are less advanced than in the rest of the world. Few African nations reported multiple sclerosis prevalence rates to MSIF. Generally, researchers contend that

Africa exhibits much lower levels of multiple sclerosis than Europe and the Americas (Kurtzke 1977, Kurtzke 2000, Rosati 2000, Oksenberg 2004, Elian and Dean 1987, and Modi 2001).

It is interesting to note that in addition to the much lower rate of multiple sclerosis afflicting people in Africa, the distribution of the disease is greatly scattered. South Africa exhibits a higher multiple sclerosis prevalence than Tunisia and Libya, which are farther from the equator, but were settled by northern Europeans later than South Africa (Wikipedia 2007c). It appears that multiple sclerosis prevalence rates reported in Africa are not distributed uniformly; however, there have been few reported prevalence rates on the continent. It is unknown whether this is because there are no cases to report, or if the less than mediocre healthcare system is not capable of diagnosing the disease. The highest prevalence of the disease in Africa has been reported in South Africa, where the British influence is highest and where there are many English-speaking inhabitants; meanwhile, no prevalence has been reported in inland Africa (Figure 7). In Libya, it appears that the highest prevalence is demonstrated in the coastal region, whereas lower prevalence has been reported from inland Libya. This could be indicative of the longer settlement history along the coast since the area was settled through maritime travel. Tunisia reported an prevalence rate of 10 cases per 100,000; Libya reported 9 cases per 100,000 in Kelibia, which borders the Mediterranean Sea, while Benghazi, further inland reported prevalence of 6 per 100,000 (Attia Romdhane 1993, and Radhakrisnan 1985). Additionally, 15 cases per 100,000 people at risk were reported in the Canary Islands (Ben Hamida 1977). For many years, physicians working in the region claimed that there were no cases of multiple sclerosis in sub-Saharan African nations (Poser 1996).

However, Poser (1996) reported that there was evidence of several cases of multiple sclerosis in black Africans in Senegal, although there were only 4 cases with autopsy evidence; still, it appears that the prevalence was incredibly rare. South Africa, on the other hand, has reported a relatively high prevalence of the disease (13 cases per 100,000 in English Speaking Caucasian south Africans, 4 cases per 100,000 in Afrikaans-speaking Caucasian Africans, and 3 cases per 100,000 in back South Africans), given that its neighboring countries have reported that multiple sclerosis is virtually non-existent within their borders (Dean 1967, Dean et al. 1994, and Kies 1989). Moreover, MSIF (2006) reported that the prevalence rate was 32 per 100,000 at risk in South Africa. The fact that multiple sclerosis appears to be more common in coastal regions in Africa, such as Tunisia, the Canary Islands, and South Africa and less common in inland Africa based on the lack of data coming out of the region and the observations by physicians that the disease is virtually non-existent there, supports the premise that genetic admixture led to the susceptibility of some, but not all Africans, given that admixture with Northern Europeans was more likely to have occurred in the coastal nations due to their maritime trade and migration routes (Poser 1996 and Rosati 2001).

The current research suggests that multiple sclerosis prevalence in these regions of Africa is associated with the history of European colonization. The history of European trade, migration, and settlement in Africa is well documented (Wikipedia 2007c). Five hundred years ago, Portuguese ships began exploring the Atlantic Coast. The Dutch and the British began to settle in Africa, after the Portuguese journeys, in the early 17th century along the same maritime route as the Portuguese (Wikipedia 2007c). The Dutch and the British first settled in the coastal regions of western and southern

Africa, and then moved inland. By the early 20th century most of Africa had become colonies of western European nations. Historically, Europeans traveled along the coast of the Indian Ocean much less frequently than they traveled along the Atlantic coast (Wikipedia 2007c).

There appears to be an association between the migration and settlement history of the Europeans and the geographic distribution of the elevated prevalence rates of multiple sclerosis on the continent of Africa (Figure 7). This observation suggests that Scandinavian admixture with other Europeans may have relayed a transmission of genetic susceptibility to multiple sclerosis to northern and South Africans over time. However, it is impossible to draw any conclusions about the incident rates in the interior of Africa since no prevalence has been reported in this region.

While European admixture with Africans in Africa is regional and historically transient, the European admixture with Africans in the Americas is historically thorough and permanent. In the past in the Americas, gene flow between northern Europeans and the Africans was mostly unidirectional from the former to the latter (Cavalli-Sforza et al. 1994 and Abe-Sandes 2004), and present day African Americans carry a substantial amount of the European genome (Sans et al. 2002, Sans et al. 2000, and Chakraborty 1992). Thus it seems possible that the genetic susceptibility to multiple sclerosis could have been transmitted from the Europeans to the African Americans.

According to the Mendelian theory of transmission of susceptibility alleles by admixture, it would be possible to increase the susceptibility to a disease in the recipient population, but the prevalence in the recipient population would not surpass that of the donor population unless additional additive or synergistic factors existed. If African

Americans inherited the susceptibility to multiple sclerosis from northern Europeans, then they should have an elevated multiple sclerosis prevalence with respect to that of native Africans. However, the prevalence of the disease in the African American population would still be lower than, or at most equal to, the northern Europeans. With this rationale, multiple sclerosis prevalence in African Americans was compared with that of European Americans. It was found that African Americans develop multiple sclerosis less frequently than European Americans (Bailey 1922, Alter 1962, Oh 1969, and Kurtzke 1979). A recent study indicated that African Americans had a relative risk of 0.64 for developing the disease compared to their European American counterparts (Wallin 2004). This observation suggests that African ancestry may indeed act as a protective effect against multiple sclerosis, but it appears that the increased prevalence of multiple sclerosis in African Americans compared to native Africans could be due to admixture of the resistant African population with the susceptible European American population.

Travelers from Scandinavia first explored the Western Hemisphere more than a thousand years ago (The Library of Congress 2007). However, true settlement of North America by Scandinavians began in the 17th and 18th centuries when wealthy Scandinavians sought religious and political freedom in North America. By the 19th century, the great migration of Scandinavians to the U.S. took place. Once in America, most of the immigrants from Sweden, Norway, Denmark, and Finland chose to settle primarily in the Midwest. They were drawn to the Midwest by the promise of open land, and many of the emigrants were recruited by railroad companies and local governments to settle remote parts of the country (The Library of Congress 2007). If the current

theory of transmission of a susceptibility allele for multiple sclerosis is true, it would be likely that the Midwest regions of America would have some of the highest rates of multiple sclerosis today.

According to Wynn et al. (1990), Olmstead County, Minnesota currently exhibits the highest prevalence of multiple sclerosis in the United States at 160 cases per 100,000. Additionally, Galion city, Ohio, and Mower County, Minnesota have reported very high prevalence rates at 112 and 100 cases per 100,000 population at risk, respectively (Hopkins 1991 and Kranz 1983). These rates are considerably higher than rates reported by other parts of the country. For instance, Los Angeles, California reported a prevalence of 22 per 100,000 population at risk (Visscher 1977); King-Pierce Counties, Washington reported 69 cases per 100,000 at risk (Visshcher 1977); 65 cases per 100,000 were reported for Weld-Larimer Counties, Colorado (Nelson 1986); and 76 cases per 100,000 reported in Los Alamos County, New Mexico (Hoffman 1981). Interestingly, Key West, Florida reported a prevalence rate of 110 cases per 100,000 population at risk in 1983 (Sheremata 1985). It should be noted that this area of Florida was primarily settled by the Spanish, who exhibit elevated levels of multiple sclerosis, but not as elevated as the Scandinavians.

It appears that the geographic distribution of multiple sclerosis in the United States is definitely influenced by the varying genetic susceptibility to the disease between racial and ethnic groups. In 1976, a national survey of multiple sclerosis reported prevalence rates among Caucasians to be 49, while the same survey revealed that prevalence among non-Caucasians was 26 (Baum 1986). In addition, a study of U.S. Army veterans demonstrated that the risk of African Americans developing the disease

was half that of Caucasian Americans, and the risk was even lower in Asians and American Indians (Kurtzke 1979). Furthermore, a study conducted in Hawaii indicated that the prevalence rate for multiple sclerosis in Caucasians was 26 per 100,000 at risk, while the prevalence for Asians was 9 (Alter 1971).

Multiple sclerosis prevalence in the Middle East and migration history of the northern Europeans.

Data from the Middle East regarding multiple sclerosis prevalence indicate that the disease is high in some parts, and very low in others. Israel reported the highest levels of the disease, but the data were difficult to interpret. In the northern region of Israel, reports ranged from 29 to 38 cases per 100,000. Meanwhile in southern Israel, near Jerusalem, rates ranged from 51 to 68 per 100,000. Kahana et al. (1994) examined multiple sclerosis prevalence among native-born Israelis. It was found that the rate of multiple sclerosis in native-born Israelis whose father had been born in Europe or America was found to be as high or higher than that found in immigrants from Europe or America. Furthermore, the incidence of multiple sclerosis in native-born Israelis of European or American descent was significantly higher than the rate in native-born Israelis of African or Asian descent. Once again, these data stress the genetic facets of the disease and suggest that being of African or Asian descent may present a preventative effect against developing multiple sclerosis (Kahana et al. 1994).

Other prevalence rates in the Middle East are fairly low. Iraq exhibited a prevalence of 4, Saudi Arabia reported 10 cases per 100,000 at risk, Jordan reported 7 cases, and Kuwait reported 24 cases per 100,000 (Rosati 2001). The prevalence data

reported to MSIF by these countries were 6, 25, 7, and 10, respectively. One possible explanation for the increased prevalence rates in Saudi Arabia and Kuwait could be that since these are two of the largest oil exporters in the world, they have been influenced by European and American migrants who have passed a genetic susceptibility to multiple sclerosis to the original inhabitants in these regions.

Russian, Indian, and Asian multiple sclerosis prevalence and migration history of the northern Europeans.

As previously mentioned, Scandinavian migration primarily followed a south and westward route. Scandinavians did not travel inland toward Russia and Asia where multiple sclerosis prevalence and incidence rates are relatively low (Wikipedia 2007b). European Russia and nations bordering Russia on the western side have reported multiple sclerosis prevalence rates ranging from 16 in Armenia to 50 in Latvia (MSIF 2006). Interestingly, in each of the nations in this region reported in Rosati's review (2001), the multiple sclerosis prevalence recorded for

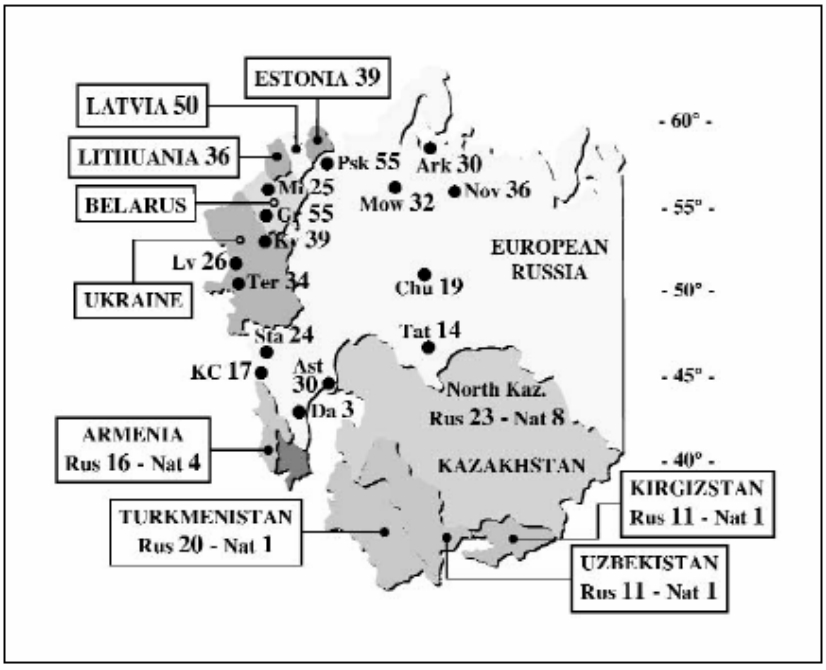


Figure 3. Frequency of multiple sclerosis in European Russia. Nat = prevalence in regional Natives (Rosati 2001).

natives was much lower than for Russians in the respective country (Figure 3). Rosati (2001) explained that the differences in these data imply that genetic factors related to development of the disease are very important. It was also pointed out that the risk of multiple sclerosis among Russians born or living in the south portion of the former Soviet Union was lower than that among Russians in the mother-country. This observation, Rosati (2001) explained, confirms a complementary role of environmental factors determining the geographic distribution of the disease.

Multiple sclerosis is considered to be a rare disease in India, China, Taiwan, and Japan. Most of India did not report high levels multiple sclerosis prevalence. It has been reported that although cases of multiple sclerosis have been recorded throughout India, the northern region of India suffers from higher prevalence of the disease than the southern portion. Moreover, northern India was settled by Indo-Europeans, while the south part was settled by Tamil and Dravidian populations (Jain 1985). To date, Poona and Bombay are the only regions of India with firmly reported incidence and prevalence rates. Rosati (2001) reported that prevalence rates in Poona and Bombay were 58 and 28 per 100,000 population at risk, respectively. However, Singhal and Wadia (Bharucha 1988) reported that multiple sclerosis prevalence was only 1 per 100,000 among native Indians in Bombay. The Parsi ethnic group in Bombay and Poona was the population that exhibited the greater prevalence levels of the disease. According to (Wadia 1990), the Parsis are of Persian origin and migrated to India in the 17th century. It is possible that before their migration, Scandinavians had migrated to Persian regions and passed their susceptibility to multiple sclerosis to the Parsis.

In China, the prevalence of multiple sclerosis is very low. There are few studies from China and Taiwan on the epidemiology of multiple sclerosis, but of the ones that do exist, the disease appears to be very rare. In 1986, a door-to-door study was conducted in Lang Cang Lu Hu Zu county of the Chinese Yunnan province, and it was estimated that the prevalence of the disease was 2 cases per 100,000 population at risk (Hung 1982). In Taiwan and Hong Kong, studies indicate that the rate is 1 per 100,000 (Hung 1982, Yu 1989, and Hou 1992).

Furthermore, multiple studies in Japan have indicated that the risk of developing multiple sclerosis in native Japanese is between 2 and 4 cases per 100,000 population at risk. However, it should be noted that there is a higher prevalence of the disease in Japanese Americans. Japanese Americans in Hawaii exhibited an elevated prevalence of 9 cases per 100,000 population at risk (Alter 1971).

As previously noted, the Scandinavians did not travel inland to Russia, China, or India as frequently as they traveled by sea (Wikipedia 2007b and d). Interestingly, the highest prevalence of multiple sclerosis in these regions has been reported in the western European nations bordering Russia as well as the northern and western regions of Italy bordering the Indian Ocean where Scandinavians did travel, albeit infrequently. Again, these observations support the idea that a genetic susceptibility was passed from Scandinavians to other ethnic groups via genetic admixture between the groups at some point throughout history.

Native American, First Nations Canadian, Aboriginal Australian, and New Zealand Maori multiple sclerosis prevalence rates and migration history of the northern Europeans.

Current explanations for the apparent ethnic disparity in multiple sclerosis and prevalence among native and aboriginal groups in Australia, North America and New Zealand include differences in socioeconomic factors and differences in environmental factors. For instance, the Alaskan Inuit and New Zealand Maori are less likely to present with multiple sclerosis symptoms to medical practitioners since they often do not seek professional medical attention (Chan 1977, Miller 1986, and Acers 1994). Also, these groups of people might be less likely to live in areas with exposure to environmental triggers of multiple sclerosis. Australian aboriginals, for example, live close to the equator, and according to the environmental geographic theory regarding development of multiple sclerosis, would be unlikely to develop the disease. However, yet another plausible explanation is that differential susceptibility to multiple sclerosis between these native groups and European groups is partially conferred by variation in genetic inheritance (Miller 1986).

Multiple sclerosis prevalence is relatively low in Australia compared to northern European nations. Rates from 11 in Northern Queensland, which is close to the equator, to 33 in Adelaide, which is in southern Australia, have been reported (Compston 1998). Interestingly, the British Royal Navy settled Australia's eastern coast in the late 1700s (Wikipedia 2007a). Moreover, they settled in the southern Australia region, which is now the capital, Sydney, and this is the region of Australia which currently exhibits the highest prevalence and incidence of multiple sclerosis. Additionally, New Zealand was

first visited by British Captain James Cook in 1779, and the island, along with Tasmania, was settled in the 18th century by people from Great Britain, who had Scandinavian ancestry (Wikipedia 2007a). New Zealand currently exhibits a multiple sclerosis prevalence of 69 cases per 100,000 population at risk (Compston 1998, Skegg 1987). Furthermore, there appears to be a gradient of distribution of multiple sclerosis in New Zealand, with higher prevalence rates exhibited in the south, and lower prevalence rates in the north. This gradient has previously been correlated to the higher proportion of people of Scottish ancestry in the south (Skegg 1987), thus implicating that genetic susceptibility to the disease has been passed to inhabitants in southern New Zealand throughout history.

Despite the relatively high prevalence rates exhibited by people of northern European ancestry in Australia, New Zealand, and North America, multiple sclerosis is considered to be a rare disease in aboriginal Australians, the Maoris in New Zealand, and the Native Americans in North America. Warren et al. (2007) analyzed data from government health databases and described the incidence of multiple sclerosis among First Nations aboriginal people in the province of Alberta, Canada. The researchers then compared the incidence in this group to the general population from 1994 to 2002. It was found that the general population rates were consistently higher than First Nations rates, and prevalence was essentially stable over the same period of time. First Nations people exhibited an incidence of 7.6 per 100,000, while the incidence of multiple sclerosis was 20.6 per 100,000 for Canadians of northern European descent in 2002. From 2000-2002 for First Nations the incidence was 12.7 for females and 7.6 for males, with a female-to-male ratio of 1.7:1. In addition, during the same time period, the incidence of multiple

sclerosis in the general population of Alberta, Canada was 32.2 for females and 12.7 for males, with a female-to-male ratio of 2.5:1. The high incidence rates are consistent with high prevalence rates reported for both groups in 2002: 99.9 per 100,000 for First Nations and 335.0 per 100,000 for the general population (Warren 2007). Warren et al. (2007) found that the incidence of multiple sclerosis was, indeed, significantly lower in First Nations people than in the general population of Alberta; however, it was also found that the incidence rates in First Nations people would not be considered "rare" by worldwide standards (Warren et al. 2007).

Furthermore, according to previous research studies, the incidence and prevalence of multiple sclerosis in the New Zealand Maori, a group of aboriginal people in New Zealand, have been reported to be substantially lower than in the European population. (Chancellor et al. 2003; Fawcett and Skegg 1988; Hornabrook 1971; and Miller et al. 1986). Remarkably, it has also been found that Caucasian individuals living in New Zealand who have Maori ancestry, appear to exhibit lower susceptibility to the disease (Skegg 1987).

Finally, according to the National Multiple Sclerosis Society, multiple sclerosis is virtually nonexistent in Inuits (Chan 1977, Acers 1994, Poser 1994, and National Multiple Sclerosis Society 2007). It has previously been hypothesized that these groups do not develop multiple sclerosis due to their diet of primarily animal meat and fish (Chan 1977). However, this idea completely contradicts the popular belief that diets low in saturated fat with no red meat and no high fat dairy products are the diets that prevent development of multiple sclerosis as reported previously in the review of

literature (Esparza 1995, Ghadirian 1998, Munger 2000, and Schwarz and Leweling 2005).

Table 2. Global occurrence of multiple sclerosis listed from greatest to least prevalence (Data obtained from MSIF 2006 unless noted with an asterisk.)

Country	Occurrence of MS per 100,000		Country	Occurrence of MS per 100,000
**Scotland	187		Turkey	34
Germany	149		Georgia	33
United States of America	135		Yugoslavia	32
Norway	132		South Africa	32
Czech Republic	130		Romania	31
Denmark	122		Barbados	26.3
Poland	120		United Arab Emirates	26
**Sweden	112		Malta	25
Switzerland	110		**Saudi Arabia	25
United Kingdom	110		Uruguay	22
Iceland	110		Turkmenistan	20
Finland	100		Brazil	18
Netherlands	100		Argentina	18
Ireland	100		Slovakia	17.5
Luxembourg	100		**Macedonia	16
Austria	100		Armenia	16
Canada	100		Tunisia	15
Italy	90		**Martinique	14
Belgium	88		Bahrain	13
Croatia	87.5		Chile	11.7
New Zealand	85		**Kyrgyzstan	11
**Slovenia	83		**Uzbekistan	11
France	80		**Albania	10
Bosnia and Herzegovina	80		Cuba	10
Hungary	79		**Kuwait	10
Greece	78		Mexico	9
Australia	78		Libyan Arab Jamahiriya	9
**Tasmania	68		Japan	8
Spain	59		**Jordan	7
Latvia	50		Iraq	6
Portugal	50		Paraguay	5.7
Serbia & Montenegro	50		Colombia	5
**Israel	50		Costa Rica	4.25
Belarus	47		Peru	4
Bulgaria	44.5		India	3
Cyprus	43		Guatemala	2.5
Russian Federation	40		China	2
Estonia	39		Viet Nam	2
Lithuania	36		Hong Kong	0.77

** Data obtained from Rosati et al. 2001

Figure 4. Occurrence of multiple sclerosis in Europe and Eastern Europe, including Russia

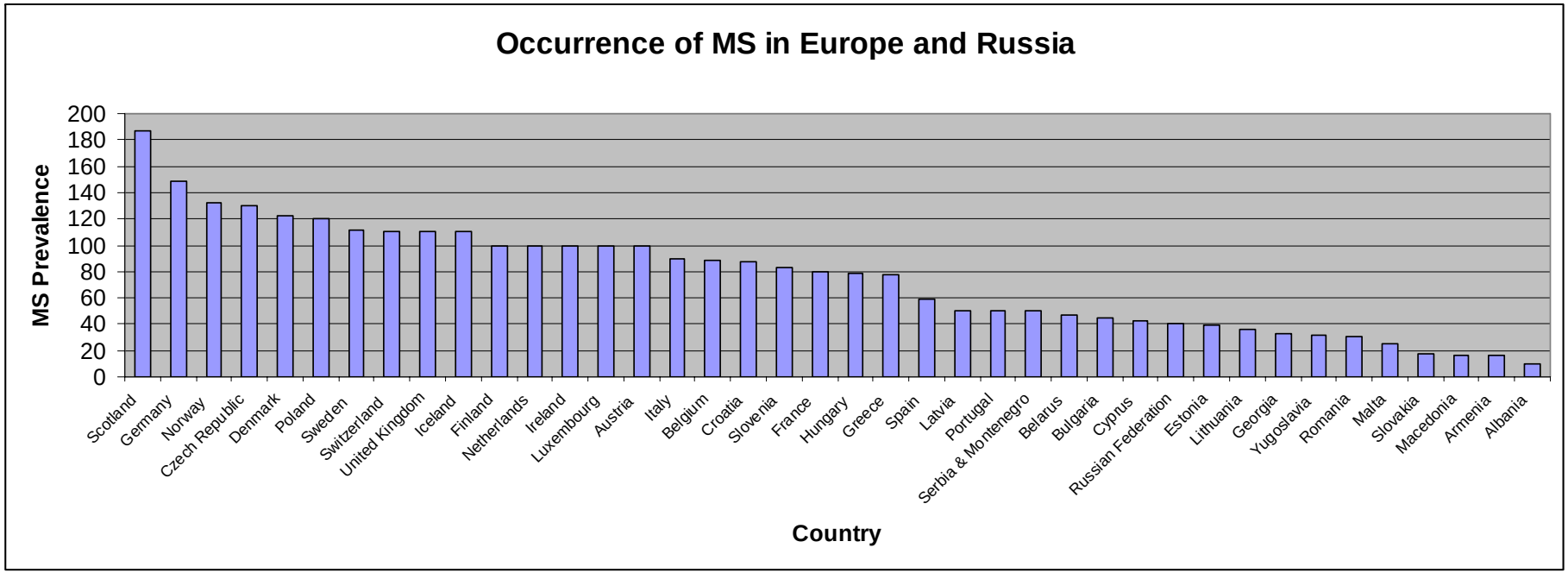


Figure 5. Occurrence of multiple sclerosis in the Middle East, the Far East, New Zealand, and Australia

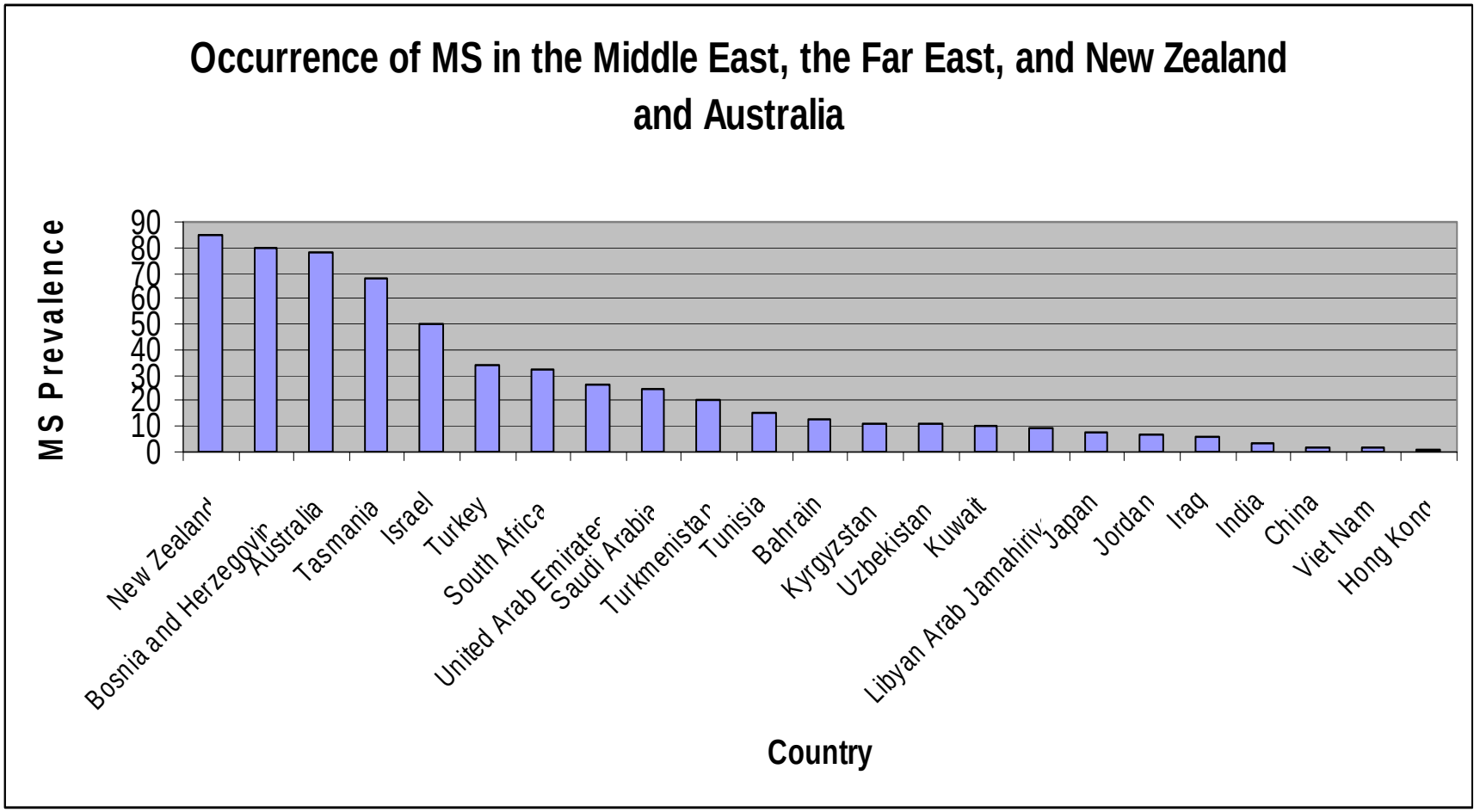


Figure 6. Occurrence of multiple sclerosis in North America, South America, and the Caribbean

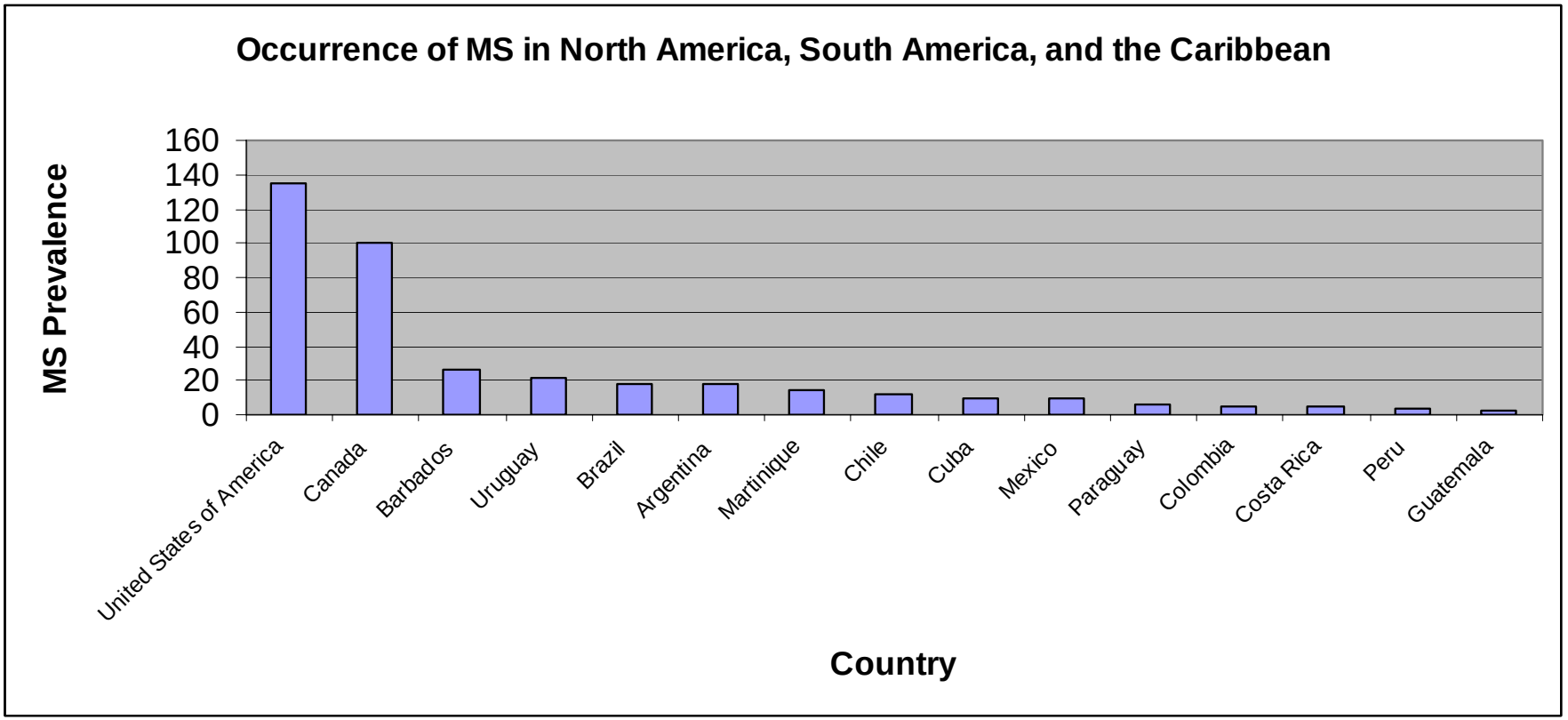


Figure 7. Global occurrence of multiple sclerosis and migration routes of Northern Europeans, Iberians, and Africans

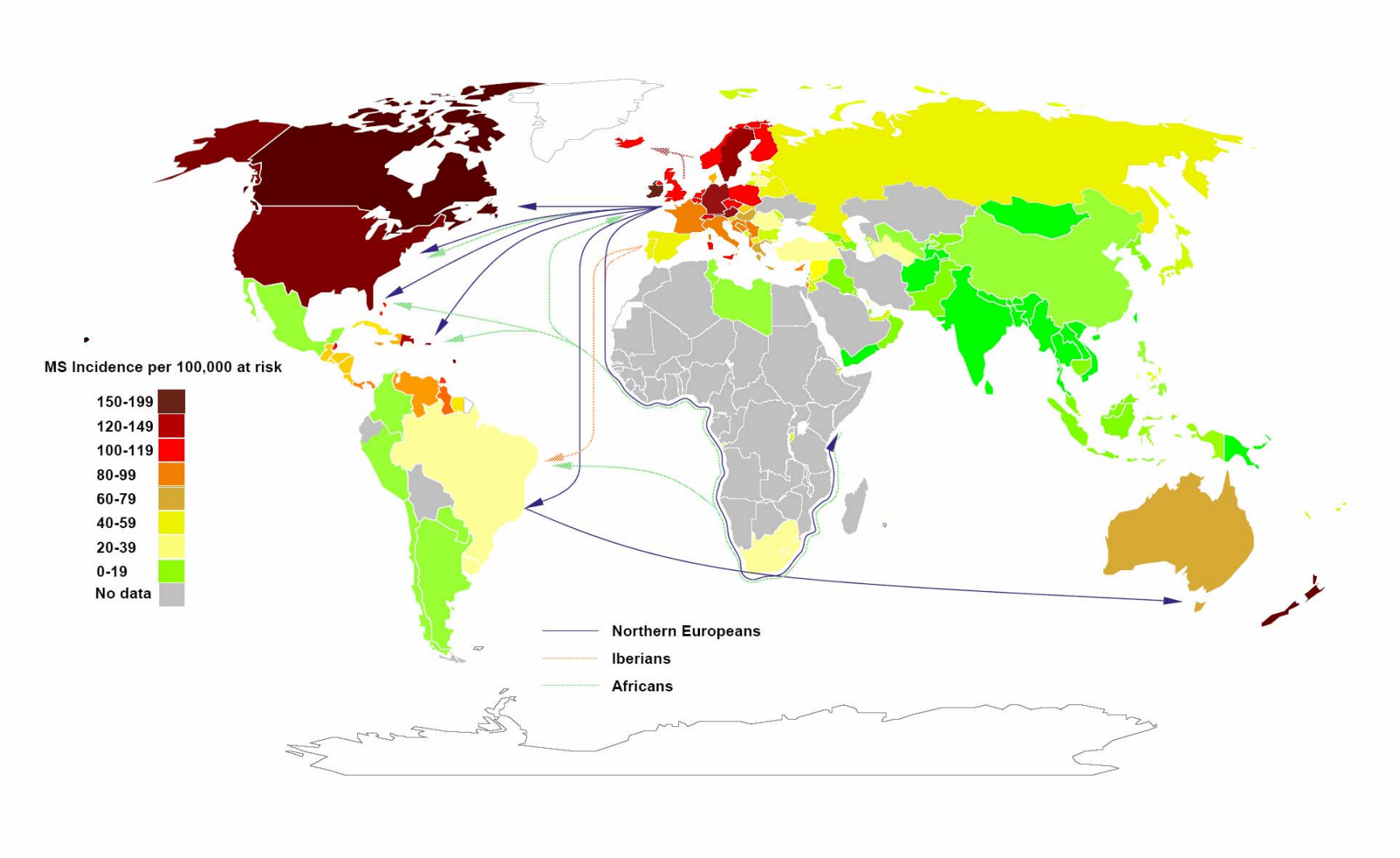
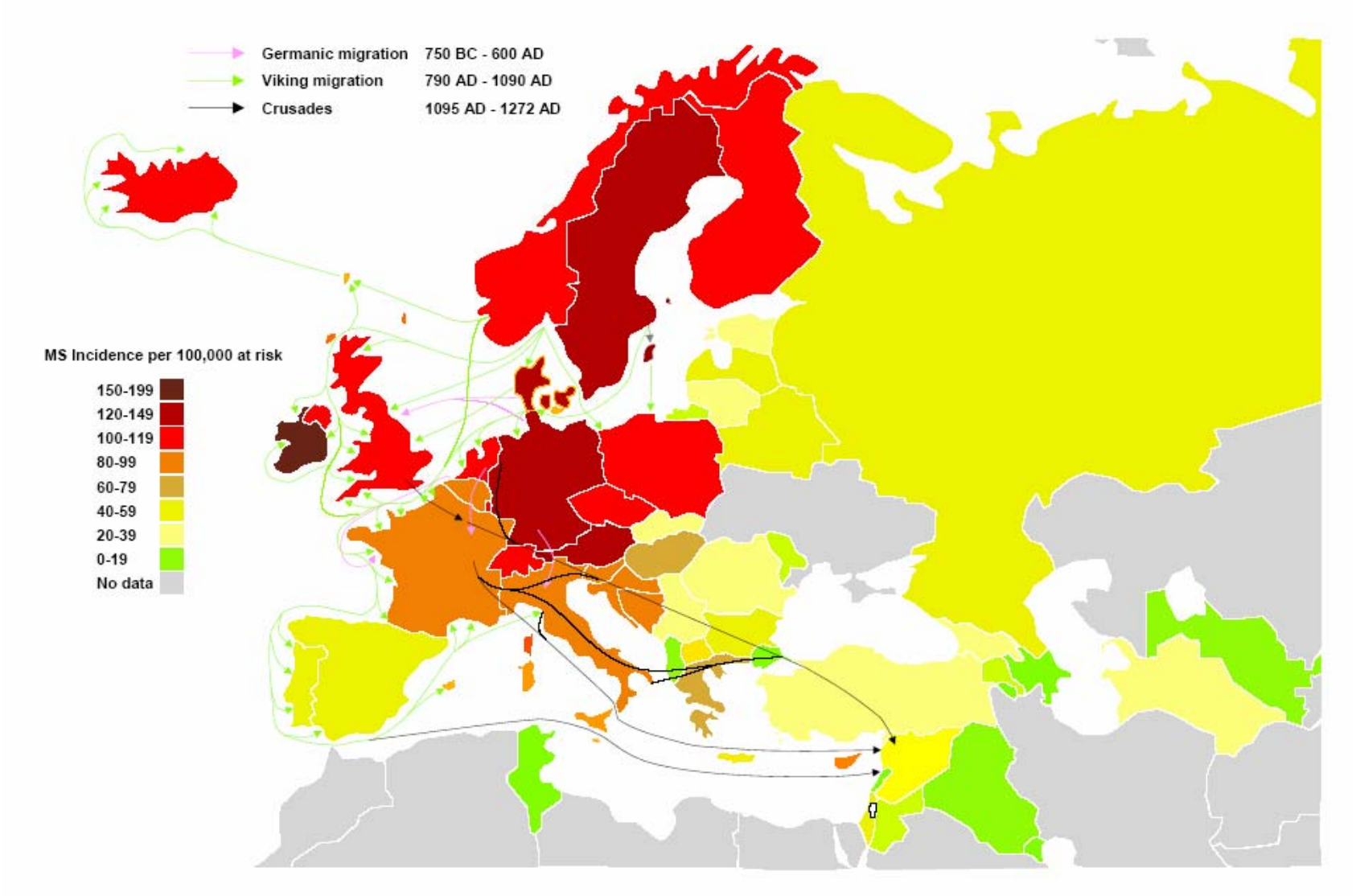


Figure 8. Occurrence of multiple sclerosis in Europe and Germanic, Viking, and Crusade migration route



CHAPTER V

DISCUSSION AND CONCLUSION

The goal of this project was to give new insight regarding the etiology of multiple sclerosis. Several theories regarding the etiology of the disease have been reviewed, including a geographic theory, a nutritional theory, and a genetic theory. Although the geographic and nutritional theories have been thoroughly investigated by researchers, neither of them provides a conclusive explanation for the etiology of the disease, and there are discrepancies with respect to both theories.

It has been suggested that nutrition and diet, particularly high consumption of animal fat and low intake of fish products, may play a role in the etiology of multiple sclerosis. Judging from the literature review, this theory regarding the etiology of the disease is ambiguous and inconclusive. There are contradictory findings regarding this theory. Results suggesting that diets high in fat intake and consisting of red meat increase the risk of developing multiple sclerosis are easily contradicted when we look at the distribution of the disease. For instance, the Inuits' diet of almost entirely red meat and few vegetables does not coincide with evidence suggesting this is a risky diet considering that multiple sclerosis is virtually non-existent within this population (Chan 1977 and Poser 1994).

Furthermore, the geographic, or latitudinal theory, which states that as the distance from the equator increases, so does the incidence and prevalence of multiple

sclerosis, was discounted with the examination of multiple sclerosis incidence in Sassari, Sardinia. Researchers found that the incidence of multiple sclerosis in Sassari was much higher to be expected if the latitudinal theory fully explained the distribution of the disease when they compared local data with surrounding incidence levels in Europe and Italy (Rosati 2001).

Additionally, the latitudinal theory is contradicted by evidence showing that Native Americans, who live in the same latitudinal geographic area as northwestern United States residents, do not exhibit the same high prevalence of multiple sclerosis as the latter group (Multiple Sclerosis Research Group 1998, Warren et al. 2006). This trend can be seen in almost any nation where northern Europeans have traveled and settled among natives of the respective region. Furthermore, Kurtzke (1977) demonstrated that latitude is not a sufficient criterion for determining multiple sclerosis risk. It was shown that at 40 degrees north latitude, multiple sclerosis is high in America, medium in Europe, and low in Asia. This observation is completely inconsistent with the theory that multiple sclerosis incidence and prevalence increase as does distance from the equator increase. It was, however, noted that high and medium risk areas appeared only in Europe or European colonies.

Since multiple sclerosis occurs frequently in certain racial and ethnic groups, and since most nations of the world consist of a single ethnic group as population majority, a comparison of multiple sclerosis prevalence rates among nations should help to determine whether high prevalence of the disease concurs with migration, settlement, and admixture of an ethnic group that may carry certain susceptibility alleles. Under this premise, the current project examined the geographic distribution of prevalence of

multiple sclerosis and found that susceptibility to the disease is closely associated with the migration and settlement history of northern Europeans. The gradient of disease prevalence which is demonstrated in Figure 2 results from the admixture of Scandinavian genes with ethnic groups in other parts of Europe throughout history. Following admixture of the Scandinavian genome, susceptibility to multiple sclerosis was transmitted to other races and ethnic groups throughout the migration and settlement history of the Europeans by interracial admixture. The current thesis research indicates that there is, indeed, a genetic susceptibility to multiple sclerosis which originated in Scandinavia, and the susceptibility alleles have been transmitted to other races by gene flow.

Mendelian diseases exhibit distinct inheritance patterns when passed from one generation to another. They are usually easily identified by a specific gene that segregates cleanly with the disease in affected families. Multiple sclerosis has not been identified as a disease with clean Mendelian pedigree, and to date, no one gene has been determined to be the cause of multiple sclerosis. Since multiple sclerosis cannot be fully described by a Mendelian genetic inheritance, a variety of genetic studies have been conducted to determine the genetic factors associated with the disease. To date, more than 55 full and partial genome screens and follow-up studies have been conducted for multiple sclerosis, and hundreds of genetic markers have been examined in these studies producing a number of interesting loci related to the disease. However, none of these loci have been shown to exhibit a particularly strong effect.

These data suggest that although there is not a particular Mendelian effect as far as genetics are concerned, it is likely that multiple sclerosis is a multi-gene disease and

that it is a disease with etiologic alleles of low penetrance. The low penetrance of a genotype would lead to an age-dependent and rare presentation of the corresponding trait, making it difficult to distinguish the genotype from external influences. Conversely, Mendelian inheritance makes the trait unique in certain ethnic groups, which may be transmitted to other groups by admixture. Since the genotype may have not yet been equally spread among different races and ethnic groups, the corresponding trait should be traceable, based on the migration, settlement, and admixture history of the original carrier.

In addition, histories of both paternal and maternal relatives have similar. predicting power, indicating an autosomal transmission of susceptibility (Schaid et al. 1998 and Valeri et al. 2003). Multiple sclerosis is prevalent among Europeans, Americans of northern European descent, and African Americans, whereas it appears to be a rare occurrence in Asia and Africa (Rosati 2001). The racial disparity is best explained by inheritance. Lastly, a candidate locus for multiple sclerosis susceptibility has recently been found in patients in the European, European American, and African American populations (Reich et al. 2005). In this case, it is clear that these unique genetic markers were transmitted by admixture between the two archeologically and anthropologically distinctive racial groups. Theoretically, these facts demonstrate that multiple sclerosis is an inherited disease.

Presently, there is minimal research regarding the significance of interracial admixture as it relates to passing susceptibility alleles from one racial group to another. However, it is well understood that genetic susceptibility to a specific disease will be transmitted among groups when the groups in question are geographically adjacent to one another. Susceptibility to cystic fibrosis, prostate cancer, and hemochromatosis are all

diseases that have been linked to northern European origination (Higgins et al. 2005, Gilbert et al. 1995, and Sandblom et al. 2003). It has been found that the susceptibility alleles of each of these diseases exist in racial and ethnic groups other than Caucasian northern Europeans. The transmission of these alleles was due to inter-group admixture (Higgins et al. 2005, Gilbert et al. 1995, and Sandblom et al. 2003).

Although the association between multiple sclerosis susceptibility and the migration history of the Europeans has been previously reported, the key conclusion of this study is that the high susceptibility in other racial and ethnic groups is due to admixture with Europeans. There are few studies on the significance of interracial admixture with respect to the spreading of genetic susceptibilities, but previous research supports the idea that a genetic susceptibility will be transmitted from one group to another as long as these groups are geographically adjacent to one another. For instance, northern Europeans are uniquely predisposed to diseases such as cystic fibrosis and idiopathic hemochromatosis. The respective northern European alleles are found in other racial and ethnic groups due to inter-group admixture (Higgins et al. 2005, Gilbert et al. 1995, Sandblom et al. 2003, Parra et al. 1998, Rybicki et al. 2002, Cabello et al. 1999, and Acton 2001).

The geographic distribution of the ΔF508 cystic fibrosis allele is a typical example of the results of European admixture. The mutation for cystic fibrosis originated in northwestern Europe, and it has been observed that the gradient distribution of its frequency in Europe is similar to that of multiple sclerosis prevalence. Furthermore, the ΔF508 allele has been transmitted to African Americans and Latin Americans through admixture in other parts of the world. The similarity in their geographic distributions

strongly suggests that, similar to cystic fibrosis, multiple sclerosis is transmitted by susceptibility alleles.

Additionally, in the case of insulin-dependent diabetes mellitus (IDDM), genetic epidemiology has indicated that gene flow from Europeans is responsible for the increased frequency and the early onset of IDDM among young African Americans (Pereira et al. 2001 and Vizzi et al. 2005). In addition, a recent genome linkage scan investigation defined two alleles at chromosome 8q24 that are associated with an increased prostate cancer incidence both in Northern Europeans and in African Americans, and the alleles seem to be of European ancestry (Pakkanen et al. 2007, Freedman et al. 2006, and Amundadottir et al. 2006). These alleles are not frequently found in native Africans and other racial and ethnic groups. It appears that these alleles are located in the chromosomes of northern Europeans, and that African American prostate cancer patients have inherited them through admixture with Europeans.

The results of this project demonstrate an alternative approach to the identification of the susceptibility alleles. Considering that admixture may transmit chromosomes from one race to another, probably in a random fashion, multiple sclerosis patients of non-European origin should share common European chromosomal components that harbor the susceptibility alleles (Reich et al. 2005). These same components should be found in multiple sclerosis patients in Africa and Asia, and the indigenous peoples in America, Australia, and New Zealand. Reich and colleagues (2005) noted that the tendency for multiple sclerosis to affect Europeans more frequently than Africans provided the opportunity to search for susceptibility genes by conducting an admixture linkage analysis. They hypothesized that African-American individuals

with multiple sclerosis would be expected to have a disproportionately greater degree of European ancestry in those regions of the genome encoding multiple sclerosis susceptibility genes, and they were able to implicate a novel susceptibility locus on chromosome 1. The fact that linkage in this region among European families is nonexistent suggests that the responsible variant is likely to have a very high background frequency in Europeans. This novel finding appears to explain the long-established excess risk seen in the European population and urgently requires replication and refinement (Reich et al. 2005).

Defining the minimal European chromosomal components shared among multiple sclerosis patients could be an effective approach to a comprehensive isolation of the susceptibility alleles for the disease. Determining and detecting the minimal European chromosomal components may be an accurate and reliable method for predicting the risk for developing multiple sclerosis at birth or early in life. It is possible that with early detection of these chromosome components, multiple sclerosis could be prevented, since the susceptibility alleles may have low penetrance, and because the onset of the disease occurs primarily in later life.

The results of this analysis may help to study other diseases that display substantial racial and ethnic differences in incidence. It is known that, compared to other races and ethnicities, Europeans are more susceptible to multiple forms of malignancies (Weinstein et al. 2002). Some of these malignancies, including breast cancer, lung cancer, and brain tumors, are known to be associated with genetic factors (Ahlbom et al. 1997). A study similar to the current one has been conducted with respect to prostate

cancer. Likewise, studies investigating the correlation between Scandinavian migration and settlement history and cancer incidence could be conducted.

Currently, the etiology of multiple sclerosis is unknown. Although inheritance primarily plays the determining role of whether an individual will develop the disease, other risk factors may have an immense effect on development. The current project adapted a reductionistic approach to address the importance of inheritance, in isolation from other contributing factors. The congruous geographic distribution between the European migration and settlement history and global multiple sclerosis prevalence is unlikely to be a coincidence. Identification of the minimal European chromosome components shared in multiple sclerosis patients in other racial and ethnic groups should confirm the results of this analysis.

A novel strategy to identify the etiology of multiple sclerosis was used in this study. The international prevalence data for multiple sclerosis in respect to racial and ethnic constituents of nations worldwide, together with the global migratory history of racial and ethnical groups was examined, and this study revealed a previously unrecognized aspect of multiple sclerosis epidemiology: high prevalence of multiple sclerosis in certain regions is associated with migration and settlement history of certain human races. This finding suggests that there is an inherited susceptibility to multiple sclerosis, which has been transmitted by admixture to different racial and ethnic groups.

Limitations of this analysis

There were several major limitations to this research project. First, the tabulated data from MSIF and literature sources were incomplete. Data were collected from a

variety of sources, but none of these sources had data from each country and some of the data were outdated, meaning the data were greater than 10 years old. The most common reason for missing data is that it simply did not exist within the countries in question, specifically in African nations. Second, the data used in this project were obtained from secondary sources. All data were obtained from publications and websites dedicated to researching the epidemiology and etiology of diseases such as multiple sclerosis. Some of these data sources had differing incidence and prevalence rates for the same country. In such cases, registry data were used over sample data, or the more reliable of the two rates was used (see Methods and Procedures). Third, much of the data used in the current project were obtained from the Multiple Sclerosis International Federation, which collected data primarily from voluntary sector sources. The Federation stated that a limitation to its own data collection methodology was that information regarding the public and private sectors may have been incomplete and may not have been completely generalizable or representative of the actual figures for the country in question.

Furthermore, both incidence and prevalence data were used in this analysis since prevalence data were not available for every country. Out of the 77 countries examined, prevalence data were used in 64 of them, with few prevalence rates accordingly noted. Using both incidence and prevalence data could have possibly skewed the results of this analysis. In future studies, it would be best to use only incidence or only prevalence data for each nation so that a baseline rate can be established.

To resolve some of these limitations, it would be helpful for just one foundation, perhaps the MSIF or National Multiple Sclerosis Society to take responsibility for keeping an updated, cohesive record of global multiple sclerosis incidence and

prevalence rates. If one foundation could take responsibility for keeping the record up to date and accurate, it would resolve the issues of figure differences between groups and outdated information. It would also be helpful to establish a registry of multiple sclerosis cases in Africa, where there currently is no such registry and thus prevalence data for the disease are difficult to find.

REFERENCES

Abe-Sandes K, Silva WA, Jr., Zago MA. (2004). Heterogeneity of the Y chromosome in Afro-Brazilian populations. *Human biology: an international record of research* 76(1):77-86.

Acers TE, Acers-Warn A. (1994). Incidence patterns of immunogenetic diseases in the North American Indians. *J Okla State Med Assoc.* 87(7):309-14.

Acheson ED, Bachrach CA, and Wright FM. (1960). Some comments on the relationship of the distribution of multiple sclerosis to latitude, solar radiation, and other variables. *Acta Psychiatry Scand*. 147(suppl):132-147.

Acton RT, Barton JC, Bell DS, Go RC, Roseman JM. (2001). HFE mutations in African-American women with non-insulin-dependent diabetes mellitus. Ethnicity & disease 11(4):578-84.

Ahlbom A, Lichtenstein P, Malmstrom H, Feychting M, Hemminki K, Pedersen NL. (1997). Cancer in twins: genetic and nongenetic familial risk factors. *Journal of the National Cancer Institute* 89(4):287-93.

Alter M, Okihiro M, Rowley W, Morris T. (1971). Multiple sclerosis among Orientals and Caucasians in Hawaii. *Neurology* 2:66-72.

Alter M. (1962). Multiple sclerosis in the Negro. *Arch Nuerol.* 7:83-91.

Amundadottir LT, Sulem P, Gudmundsson J, Helgason A, Baker A, Agnarsson BA, Sigurdsson A, Benediktsdottir KR, Cazier JB, Sainz J, Jakobsdottir M, Kostic J, Magnusdottir DN, Ghosh S, Agnarsson K, Birgisdottir B, Le Roux L, Olafsdottir A, Blondal T, Andresdottir M, Gretarsdottir OS, Bergthorsson JT, Gudbjartsson D,

Gylfason A, Thorleifsson G, Manolescu A, Kristjansson K, Geirsson G, Isaksson H, Douglas J, Johansson JE, Balter K, Wiklund F, Montie JE, Yu X, Suarez BK, Ober C, Cooney KA, Gronberg H, Catalona WJ, Einarsson GV, Barkardottir RB, Gulcher JR, Kong A, Thorsteinsdottir U, and Stefansson K. (2006). A common variant associated with prostate cancer in European and African populations. *Nature Genetics* 38(6):652-8.

Annegers JF, Appel S, Lee JR, Perkins P. (1991). Incidence and prevalence of amyotrophic lateral sclerosis in Harris County, Texas, 1985–1988. *Arch Neurol.* 48:589–593.

Attia Romdhane N, Ben Hamida M, Mrabet A et al. (1989). Prevalence study of neurologic disorders in Kelibia, Tunisia. *Neuroepidemiology* 12:285-299.

Auer DP, Schumann EM, Kumpfel T, Gossl C, and Trenkwalder C. (2000). Seasonal fluctuations of gadolinium-enhancing magnetic resonance imaging lesions in multiple sclerosis. *Ann. Neurol.* 47:276-277.

Auer DP, Schumann EM, Kumpfel T, Gossl C, Trenkwalder C. (2000). Seasonal fluctuations of gadolinium-enhancing magnetic resonance imaging lesions in multiple sclerosis. *Ann. Neurol.* 47:276–277.

Bailey P. (1922). Incidence of multiple sclerosis in United states troops. *Arch. Neurol. Psychiatry* 7:582-583.

Bamford CR, Sibley WA, Thies C. (1983). Seasonal variation of multiple sclerosis exacerbations in Arizona. *Neurology* 33:697–701.

Baum HM and Rothschild BB (1981). The incidence and prevalence of reported multiple sclerosis. *Ann. Neurol.* 10:420-428.

Ben Hamida M (1977). La sclerose en plaques en Tunisie. Etude clinique de 100 observations. *Rev. Neurol.* 133:109-117.

Betemps EJ, Buncher CR. (1993). Birthplace as a risk factor in motor neuron disease and Parkinson's disease. *Int J Epidemiol.* 22:898–904.

Bhalla AK, Amento EP, Clemens TL, Holick MF, and Krane SM. (1983). Specific high-affinity receptors for 1,25-dihydroxyvitamin D3 in human peripheral blood mononuclear cells: presence in monocytes and induction in T lymphocytes following activation. *J. Clin. Endocrinol. Metab.* 57:1308-1310.

Bharucha NE, Bharucha EP, Wadia NH, Singhal BS, Bharucha AE, Bhise AV, Kurtzke JF, and Schoenberg BS. (1988). Prevalence of multiple sclerosis in the Parsis of Bombay. *Neurology* 38:727-729.

Briscoe D, Stephens JC, and O'Briend SJ. (1994). Linkage disequilibrium in admixed populations: Applications in gene mapping. *J. Hered.* 85:59-63.

Cabello GM, Moreira AF, Horovitz D, Correia P, Santa Rosa A, Llerena J, Greg J, Grody WW, Degrave WM, Fernandes O, and Cabello PH.. (1999). Cystic fibrosis: low frequency of DF508 mutation in 2 population samples from Rio de Janeiro, Brazil. *Human biology; an international record of research* 71(2):189-96.

Cantorna MT, Hayes CE, and DeLuca HF. (1996). 1,25-Dihydroxyvitamin D3 reversibly blocks the progression of relapsing e3ncephalomyelitis, a model of multiple sclerosis. *Proc. Natl. Acad. Sci. USA* 93:7861-7864.

Carlson CS. (2003). Will admixture mapping work to find disease genes? *Nat. Genet.* 33:518-521.

Carton H, Vlietinck R, Debruyne J, et al. (1997). Risks of multiple scerlosis in relatives of patients in Flanders, Belgium. *J. Neurol. Neurosurg. Psychiatry* 62:329-333.

Cavalli-Sforza LL, Menozzi, P., and Piazza, A. (1994). *The history and geography of human genes.* Princeton, NJ: Princeton University Press.

Chakraborty R and Weiss KM. (1968). Admixture as a tool for finding inked genes and detecting that difference from allelic association between loci. *Proc. Natl. Acad. Sci. USA* 85:9119-9123.

Chakraborty R, Kamboh MI, Nwankwo M, Ferrell RE. (1992). Caucasian genes in American blacks: new data. *American Journal of Human Genetics* 50(1):145-55.

Chan WW. (1977). Eskimos and multiple sclerosis. *Lancet* 1(8026):1370.

Chancellor AM, Addidle M, Dawson K. (2003). Multiple sclerosis is more prevalent in northern New Zealand than previously reported. *Intern Med J.* 33:79–83.

Charcot J. Lectures on the diseases of the nervous system. (1877). *The New Sydenham Society.* 1:157–222

Christiansen E. (2006). *The Norsemen in the Viking Age (The Peoples of Europe).* Blackwell Publishing: Oxford.

Compston A. (1998). Distribution of multiple sclerosis. In: Compston A, Ebers G, Lassmann H, McDonald I, Matthews B, Wekerle H (eds). *McAlpine's multiple sclerosis, 3rd Ed.* Churchill Livingstone, London, pp. 63-100.

Compston A. and Coles A. (2002). Multiple Sclerosis. *Lancet* 359:1221-1231.

Compston D. (1997). Genetic epidemiology of multiple sclerosis. *J. Neurol. Neurosurg. Psychiatry* 62:553-561.

Cosman F, Nieves J, Herbert J, Shen V, and Lindsay R. (1994). High-dose glucocorticoids in multiple sclerosis patients exert direct effects on the kidney and skeleton. *J. Bone Miner. Res.* 9:1097-1105.

Davenport CB. (1922). Multiple sclerosis from the standpoint of geographic distribution and race. *Proc. Assoc. Res. Nerv. Ment. Dis.* 2:8-19.

Dean G, Bhigjee A, Bill PLA. (1994). Multiple sclerosis in black South Africans and Zimbabweans. *J. Neurol. Neurosurg. Psychiatry* 57:1064-1069.

Dean G. (1967). Annual incidence, prevalence, and mortality of multiple sclerosis in white South African-born and in white immigrants to South Africa. *Br. Med. J.* 2:724-730.

Deluca HF and Cantorna MT. (2001). Vitamin D: its role and uses in immunology. *FASEB J.* 15:2579-2585.

Embry AF, Snowdon LR, and Vieth R. (2000). Vitamin D and seasonal fluctuations of gadolinium enhancing magnetic resonance imaging lesions in multiple sclerosis. *Ann. Neurol.* 48:271-272.

Embry AF, Snowdon LR, Vieth R. (200). Vitamin D and seasonal fluctuations of gadolinium-enhancing magnetic resonance imaging lesions in multiple sclerosis. *Ann. Neurol.* 48:271–272.

Encyclopedia Britannica. (2007). Germany: The Migration Period. Accessed on July 17, 2007 at *Encyclopædia Britannica Online*: http://www.britannica.com/eb/article-58084.

Esparza ML, Sasaki S, and Kesteloot H. (1995). Nutrition, latitude and multiple sclerosis mortality: an ecologic study. *Am. J. Epidemiol.* 142(7):733-7.

Fawcett J, Skegg DC. (1988). Geographic distribution of multiple sclerosis in New Zealand: evidence from hospital admissions and deaths. *Neurology* 38:416–8.

Freedman ML, Haiman CA, Patterson N, McDonald GJ, Tandon A, Waliszewska A, Penney K, Steen RG, Ardlie K, John EM, Oakley-Girvan I, Whittemore AS, Cooney KA, Ingles SA, Altshuler D, Henderson BE, and Reich D. (2006). Admixture mapping identifies 8q24 as a prostate cancer risk locus in African-American men. *PNAS USA* 103(38):14068-73.

Gilbert F, Schoelkopf J, Li Z, Arzimanoglou II, Shaham M, Udey J, and Arzimanoglou I. (1995). Ethnic intermarriage and its consequences for cystic fibrosis carrier screening. *American Journal of Preventive Medicine* 11(4):251-5.

Goldberg P. (1974). Multiple sclerosis: vitamin D and calcium as environmental determinants of prevalence (a viewpoint). Part 1: sunlight, dietary factors and epidemiology. *Int. J. Environ. Studies* 6:19-27.

Goodkin DE, Hertsgaard D. (1989). Seasonal variation of multiple sclerosis exacerbations in *North Dakota. Arch Neurol* 46:1015–1018.

Granieri E, Malagu S, Casetta I, Tola MR, Govoni V, Paolino E, and Monetti VC. (1996). Multiple sclerosis in Italy: a reappraisal of incidence and prevalence in Ferrara. *Arch. Neurol.* 53:793-798.

Grimaldi L, Salemi G, Grimaldi G, Rizzo A, Marziolo R, Lo Presti C, Maimone D, and Savettieri G. (2001). High incidence and increasing prevalence of MS in Enna (Sicily), southern Italy. *Neurology* 57-1891-1893.

Hansen T, Skytthe A, Stenager E, Petersen HC, Bronnum-Hansen H, and Kyvik KO. (2005). Concordance for multiple sclerosis in Danish twins: an update of a nationwide study. *Mult. Scler.* 11:504-510.

Higgins PB, Fernandez JR, Goran MI, Gower BA. (2005). Early ethnic difference in insulin-like growth factor-1 is associated with African genetic admixture. Pediatric Research 58(5):850-4.

Hoerder D. (2002). *Cultures in Contact: World Migrations in the Second Millennium (Comparative and International Working-Class History)*. Duke University Press.

Hoffman RE, Zach MM, Davis LE, and Burchfiel CM. (1981). Increased incidence and prevalence of multiple sclerosis in Los Alamos County, New Mexico. *Neurology* 31:1489-1492.

Hopkins RS, Indian RW, Pinnow E, and Conomy J. (1991). Multiple sclerosis in Galion, Ohio: prevalence and results of a case-control study. *Neuroepidemiolgy* 10:192-199.

Hornabrook RW. (1971). The prevalence of multiple sclerosis in New Zealand. *Acta Neurol Scand.* 47:426–38.

Hou JB, Zang ZX (1992). Prevalence of multiple sclerosis: a door to door survey in Lan Cang La Hu Zu autonomous county, Yunnan Province of China. *Neuroepidemiology* 11:52.

Hung TP (1982). Multiple sclerosis in Taiwan. A reappraisal. In: Kuroiwa Y, Kurland LT (eds) *Multiple sclerosis: east and west.* Kyuhu University, Fukuoka, pp. 83-96.

Hung TP, Landsborough D, His MS. (1976). Multiple sclerosis amongst Chinese in Taiwan. *J Neurol Sci.* 27:459–484.

Jain S and Maheshwari M (1985). Multiple sclerosis: Indian experience in the last thirty years. *Neuroepidemiology*. 4:96-107.

Kies B. (1989). An epidemiological study of multiple sclerosis in Cape Town, South Africa. *Neurology India* 37:279 (Special Issue: XIV World Congress of Neurology, New Delhi).

Kinnunen E, Wikstrom J, Porras J, and Palo J. (1983). The epidemiology of multiple sclerosis in Finland: increase of prevalence and stability of foci in high-risk areas. *Acta Neurol. Scand.* 67:255-262.

Kranz JMS, Kurland LT, Schuman LM, and Layton D. (1983). Multiple sclerosis in Olmsted and Mower Counties, Minnesota. *Neuroepidemiology* 2:206-218.

Kurtkze JF, Beebe GW, and Norman JE Jr. (1979). Epidemiology of multiple sclerosis in U.S. veterans: 1. Race, sex, and geographic distribution. *Neurology* 29:1228-1235.

Kurtzke J. (1997). The epidemiology of multiple sclerosis. In: Raine C, McFarland H, Tourtellotte W (eds.). *Multiple sclerosis, clinical and pathogenetic basis.* Chapman and Hall medical, London, pp 91-139.

Kurtzke JF. Geography in multiple sclerosis. (1977). *J Neurol.* 215(1):1-26.

Kurtzke JF. (1993). Epidemiologic evidence for multiple sclerosis as an infection. *Clin Microbiol Rev.* 6:382–427.

Ladizesky M, Lu Z, Olveri B, San Roman N, Diaz S, Holick MF, Mautalen C. (1995). Solar ultraviolet B radiation and photoproduction of vitamin D3 in central and southern areas of Argentina. *J. Bone Minera. Res.* 10:545-549.

Leibowitz U., Sharon D, and Alter M. (1967). Geographical considerations in multiple sclerosis. *Brain* 90:871-886.

Marrie RA, Cutter G, Tyry T, Vollmer T, and Campagnolo D. (2006). Does multiple sclerosis-associated disability differ between races? *Neurology.* 66(8):1235-40.

Marrosu M, Lai M, Cocco E., Loi V, Spinicci G, Pischedda MP, Massole S, Marrosu G, and Contu P. (2002). Genetic factors and the founder effect explain familial MS in Sardinia. *Neurology* 58:283-288.

McKeigue PM. (1997). Mapping genes underlying ethnic differences in disease risk by linkage disequilibrium in recently admixed populations. *Am. J. Hum. Genet.* 60:188-196.

Miller DH, Hornabrook RW, Dagger J, Fong R. (1986). Ethnic and HLA patterns related to multiple sclerosis in Wellington, New Zealand. *J Neurol Neurosurg Psychiatry* 49:43–6.

MSN Encarta. (2007). Vikings. Accessed on June 2, 2007 at *MSN Encarta Online* http://encarta.msn.com/encyclopedia_761561500/Vikings.html.

Multiple Sclerosis Genetics Group. (1998). Linkage of the MHC to familial multiple sclerosis suggests genetic heterogeneity. *Hum Molec Genet.* 7:1229–1234

Mumford CJ, Wood NW, Kellar-wood H, Thorpe JW, Miller DH, and Compston DA. (1994). The British Isles survey of multiple sclerosis in twins. *Neurology* 44:11-15.

Munger KL, Zhang SM, O'Reilly E, Hernan MA, Olek MJ, Willett WC, and Ascherio A. Vitamin D intake and incidence of multiple sclerosis. *Neurology* 62:60–65, 2004.

Murray T.J. (2005). Multiple Sclerosis: The History of a Disease. *JAMA* 294: 376-377.

National Multiple Sclerosis Society (2007). About MS: Who Gets MS? Accessed on July 13, 2007 at *National Multiple Sclerosis Society Online*

http://www.nationalmssociety.org/site/PageServer?pagename=HOM_ABOUT_who_gets_ms.

National Multiple Sclerosis Society. (2007). Accessed on June 26, 2007 at *National Multiple Sclerosis Society Online* http://www.nationalmssociety.org/site/PageServer?pagename=HOM_LIB_sourcebook_epidemiology.

Nelson LM, Hamman RF, Thomson DS, Baum HM, Boteler DL, Burks JS, and Franklin GM. (1986). Higher than expecte4d prevalence of multiple sclerosis in northern Colorado: dependence on methodologic issues. *Neuroepidemiology* 5:17-28.

Nicoletti A, LoFermo S, Reggio E, Tarantello R, Liberto A, Le Pira F, Patti F, and Reggio A. (2005). A possible spatial and temporal cluster of multiple sclerosis in the town of Linugaglossa, Sicily. *J. Neurol.* 252(8):921-5

Nieves J, Cosman F, Herbert J, Shen V, and Lindsay R. (1994). High prevalence of vitamin D deficiency and reduced bone mass in multiple sclerosis. *Neurology* 44:1687-1692.

Oh SJ and Calhoun CL. (1969). Multiple sclerosis in the Negro. *J. Natl. Med. Assoc.* 61:388-392.

Pakkanen S, Baffoe-Bonnie AB, Matikainen MP, Koivisto PA, Tammela TL, Deshmukh S, Ou L, Bailey-Wilson JE, and Schleutker J. (2007). Segregation analysis of 1,546 prostate cancer families in Finland shows recessive inheritance. *Human Genetics* 121(2):257-67.

Panelius M. (1969). Studies on epidemiological, clinical and etiological aspects of multiple sclerosis. *Acta Neurol. Scand.* 39(suppl):1-82.

Parra EJ, Marcini A, Akey J, Martinson J, Batzer MA, Cooper R, Forrester T, Allison DB, Deka R, Ferrell RE, and Shriver MD. (1998). Estimating African American admixture proportions by use of population-specific alleles. *American Journal of Human Genetics* 63(6):1839-51.

Pereira AC, Mota GF, and Krieger JE. (2001). Hemochromatosis gene variants in three different ethnic populations: effects of admixture for screening programs. *Human biology; an international record of research* 73(1):145-51.

Poser CM. (1996). Multiple sclerosis. In: Shakir RA, Newman PK, Poser CM (eds) *Tropical neurology.* Saunders, London, pp. 437-455.

Poser CM. (1994). The dissemination of multiple sclerosis: a Viking saga? A historical essay. *Ann Neurol.* 36:S231–243.

Poser CM. (1994). The epidemiology of multiple sclerosis: a general overview. *Ann Neurol.* 36:S180–189.

Provvedini DM, Tsoukas CD, Deftos LJ, and Manolagas SC. (1983). 1,25-Dihydroxyvitamin D3 receptors in human leukocytes. *Science* 221:1181-1183.

Pugliatti M, Sotgiu S, Solinas G, Castiglia P, and Rosati G. (2001). Multiple sclerosis prevalence among Sardinians: further evidence against the latitude gradient theory. *Neurol. Sci.* 22:163-165.

Radhakrishnan K, Ashok PP, Sridharan R, Mousa ME (1985). Prevalence and pattern of multiple sclerosis in Benghazi, north-eastern Libya. *J. Neurol. Sci.* 70:39-46.

Reich D, atterson N, DeJager PL, McDonald G, Waliszewska A. Tandon A, Lincoln RR, DeLoa C, Fruhan SA, Cabre P, Bera O, Semana G., Kelly MA, Francis DA, Ardlie K, Khan O, Cree BAC, Hauser SL, Oksenberg JR, and Hafler DA. (2005). A whole-

genome admixture scan finds a candidate locus for multiple sclerosis susceptibility. *Nat. Genet.* 37:1113-1118.

Rife DC. (1954). Populations of hybrid origin as source material for the detection of linkage. *Am. J. Hum. Genet.* 6:26-33.

Ristori G, Cannoni S, Stazi MA, Vanacore N, Cotichini R, Alfo M, Pugliatti M, Sotgiu S, Solaro C, Bomprezzi R, Di Giovanni S, Figa Talamanca L, Nistico L, Fagnani C, Neale MC, Cascino I, Giorgi G, Battaglia MA, Buttinelli C, Tosi R, and Salvetti M. (2006). Multiple sclerosis in twins from continental Italy and Sardinia: a nationwide study. *Ann. Neurol* 59:27-34.

Rosati G, Aiello I, Pirastru MI, Mannu L, Sanna G, Sau GF, and Sotgiu S. (1996). Epidemiology of multiple sclerosis in Northwestern Sardinia: further evidence for higher frequency in Sardinians compared to other Italians. *Neuroepidemiology* 15:10-19.

Rosati G. (2001). The prevalence of multiple sclerosis in the world: an update. *Neurol Sci.* 22:117–139.

Rybicki BA, Iyengar SK, Harris T, Liptak R, Elston RC, Sheffer R, Chen KM, Major M, Maliarik MJ, and Iannuzzi MC. (2002). The distribution of long range admixture linkage disequilibrium in an African-American population. *Human Heredity* 53(4):187-96.

Sadovnick AD, Baird PA, and Ward RH. (1988). Multiple sclerosis: updated risks for relatives. *Am. J. Med. Genet.* 29:533-541.

Sandblom G, Dufmats M, Olsson M, and Varenhorst E. (2003). Validity of a population-based cancer register in Sweden--an assessment of data reproducibility in the South-

East Region Prostate Cancer Register. *Scandinavian Journal of Urology and Nephrology* 37(2):112-9.

Sans M, Weimer TA, Franco MH, Salzano FM, Bentancor N, Alvarez I, Bianchi NO, and Chakraborty R. (2002). Unequal contributions of male and female gene pools from parental populations in the African descendants of the city of Melo, Uruguay. *American Journal of Physical Anthropology* 118(1):33-44.

Sans M. (2000). Admixture studies in Latin America: from the 20th to the 21st century. *Human biology; an international record of research* 72(1):155-77.

Schaid DJ, McDonnell SK, Blute ML, Thibodeau SN. (1998). Evidence for autosomal dominant inheritance of prostate cancer. *American Journal of Human Genetics* 62(6):1425-38.

Scheremata WA, Poskanzer DC, Withum DG, MacLeod CL, and Whiteside ME. (1985). Unusual occurrence on a tropical island of multiple sclerosis. *Lancet* 2:618.

Schwarz S and Leweling H. (2005). Multiple sclerosis and nutrition. *Multiple Sclerosis* 11(1):24-32.

Skegg DCG, Corwin PA, and Raven RS. (1987). Occurrence of multiple sclerosis in the north and south of New Zealand. *J. Neurol. Neurosurg. Psychiatry* 50:134-139.

Smith MW, Patterson N, Lautenberger JA, Truelove AL, McDonald GJ, Waliszewska A, Kessing BD, Malasky MJ, Scafe C, Le E, De Jager PL, Mignault AA, Yi Z, De The G, Essex M, Sankale JL, Moore JH, Poku K, Phair JP, Goedert JJ, Vlahov D, Williams SM, Tishkoff SA, Winkler CA, De La Vega FM, Woodage T, Sninsky JJ, Hafler DA, Altshuler D, Gilbert DA, O'Brien SJ, and Reich D. (2004). A high-density admixture

map for disease gene discovery in African Americans . *Am. J. Hum. Genet.* 74:1001-1013.

Sotgiu S, Pugliatti M, Sanna A, Sotgiu A, Castiglia P, Solinas G, Dolei A, Serra C, Bonetti B, and Rosati G. (2002). Multiple sclerosis complexity in selected populations: the challenge of Sardinia, insular Italy. *Euro. J. Neurol.* 9:329-341.

Stephens JC, Briscoe D, and O'Brien SJ. (1994). Mapping by admixture linkage disequilibrium in human populations: Limits and guidelines. *Am. J. Hum. Genet.* 55:809-824.

Sumelahti M, Tienari P, Palo J, et al. (2001). Increasing prevalence of multiple sclerosis in Finland. *Acta Neurol. Scand.* 103:153-158.

Sumelahti M, Tienari P, Wikstrom J, Palo J, and Hakama M. (2000). Regional and temporal variation in multiple sclerosis incidence in Finland during 1979-1993. *Neuroepidemiology* 19:67-75.

Sutherland JM, Tryer JH, and Eadie MJ. (1962). The prevalence of multiple sclerosis in Australia. *Brain* 85:146-164.

Swiderski R.M. (1998). *Multiple Sclerosis Through History and Human Life*. McFarland & Comp. Inc., North Carolina.

Talat Islam, W. James Gauderman, Wendy Cozen, Ann S. Hamilton, Margaret E. Burnett and Thomas M. Mack. (2006). Differential Twin Concordance for Multiple Sclerosis by Latitude of Birthplace. *Annals of Neurology* 60(1):56-64.

Tienari P, Bonetti A, Pihlaja H, Saastamoinen KP, and Rantamaki T. (2006). Multiple sclerosis in G: Genes and geography. *Clinical Neurology and Neurosurgery* 108:223-226.

Tola MA, Yugueros MI, Fernandez-Buey N, and Fernandez-Herranz R. (1999). Prevalence of multiple sclerosis in Valladolid, northern Spain. *J Neurol.* 246(3):170-4.

Valeri A, Briollais L, Azzouzi R, Fournier G, Mangin P, Berthon P, Cussenot O, and Demenais F. (2003). Segregation analysis of prostate cancer in France: evidence for autosomal dominant inheritance and residual brother-brother dependence. *Annals of Human Genetics* 67(Pt 2):125-37.

Visscher BR, Detels R, Coulson AH, Malmgren RM, and Dudley JP. (1977). Latitude, migration, and the prevalence of multiple sclerosis. *Am. J. Epidemiol.* 106:470-475.

Vizzi E, Loureiro CL, Gerder M, de las Nieves Garcia-Casal M, Rodríguez-Larralde A, Gerace L, Ludert JE, Liprandi F, and Pujol FH. (2005). Mutation analysis of the HFE gene associated with hereditary hemochromatosis in a Venezuelan sample. *Annals of Hematology* 84(12):802-6.

Wallin MT, Page WF, and Kurtzke JF. (2004). Multiple sclerosis in US veterans of the Vietnam era and later military service: race, sex, and geography. *Ann. Neurol.* 55:65-71.

Warren S, Svenson LW, Warren KG, Metz LM, Patten SB, and Schopflocher DP. (2007). Incidence of Multiple Sclerosis among First Nations People in Alberta, Canada. *Neuroepidemiology* 28:21-27.

Webb AR, Kline L, and Holick MF. (1988). Influence of season and latitude on the cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. *J. Clin. Endocrinol. Metab.* 67:373-378.

Weinstein BS and Ciszek D. (2002). The reserve-capacity hypothesis: evolutionary origins and modern implications of the trade-off between tumor-suppression and tissue-repair. *Experimental Gerontology* 37(5):615-27.

Wikipedia. (2007a). British Empire. Accessed on June 2, 2007 at *Wikipedia Online* http://en.wikipedia.org/wiki/British_Empire.

Wikipedia. (2007b). Crusades. Accessed on June 2, 2007 at *Wikipedia Online* http://en.wikipedia.org/wiki/Crusades.

Wikipedia. (2007c). History of Africa. Accessed on June 2, 2007 at *Wikipedia Online* http://en.wikipedia.org/wiki/History_of_Africa.

Wikipedia. (2007d). Migration Period. Accessed on June 2, 2007 at *Wikipedia Online* http://en.wikipedia.org/wiki/Migration_Period.

Wikstrom J and Palo J. (1975). Studies on the clustering of multiple sclerosis in Finland I: comparison between the domiciles and places of birth in selected subpopulations. *Acta Neurol. Scand.* 51:85-98.

Willer CJ, Dyment DA, Risch NJ, Sadovnick AD, Ebers GC; Canadian Collaborative Study Group. (2003). Twin concordance and sibling recurrence rates in multiple sclerosis. *Proc Natl Acad Sci USA* 100:12877-12882.

Wuthrich R and Rieder HP. (1970). The seasonal incidence of multiple sclerosis in Switzerland. *Eur Neurol* 3:257–264.

Wynn DR, Rodriguez M, O'Fallon WM, and Kurland LT. (1990). A reappraisal of the epidemiology of multiple sclerosis in Olmstead County, Minnesota. *Neurology* 40:780-786.

Yu YL, Woo E, Hawkins BR et al. (1989). Multiple sclerosis among Chinese in Hong Kong. *Brain* 112:1445-1467.