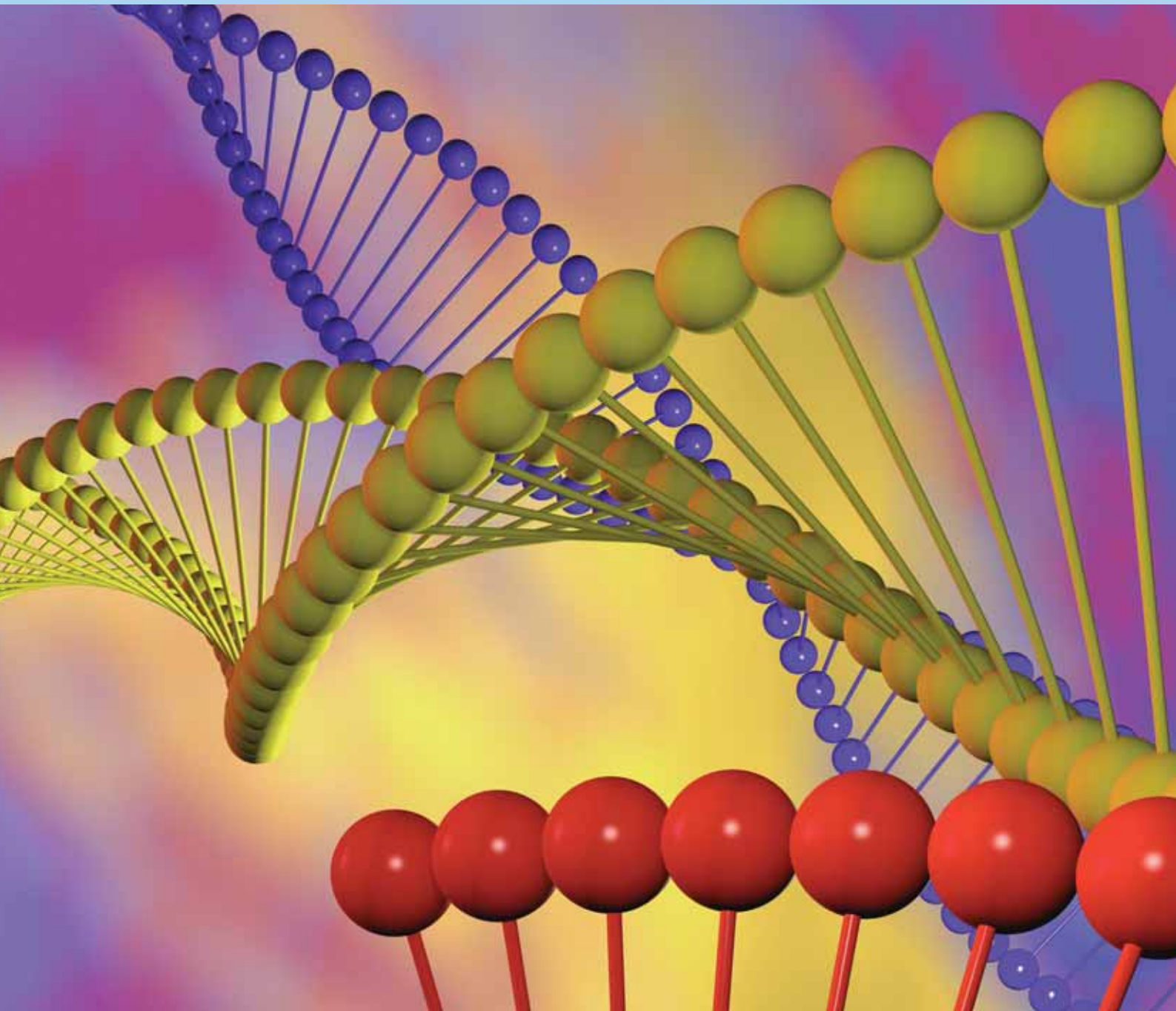


# MS *in focus*

Issue 8 • 2006

- Genetics and hereditary aspects of MS



multiple sclerosis  
international federation

## Editorial Board

### Multiple Sclerosis International Federation

MSIF leads the global MS movement by stimulating research into the understanding and treatment of MS and by improving the quality of life of people affected by MS. In undertaking this mission, MSIF utilises its unique collaboration with national MS societies, health professionals and the international scientific community.

Our objectives are to:

1. Support the development of effective national MS societies
2. Communicate knowledge, experience and information about MS
3. Advocate globally for the international MS community
4. Stimulate research into the understanding, treatment and cure of MS

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## Letter from the Editor



Last year the Editorial Board of *MS in focus* made an important decision to dedicate an issue of the magazine to genetics. Genes and MS is a complicated topic and is relevant for many people with MS and their families.

Although the complete story of the role of genetics in MS is still unfolding, researchers have made a great deal of progress over the last several years. That progress is presented here, in a format that should answer fundamental questions about MS, genes and genetic factors.

In compiling this issue, we have involved some of the world's most renowned MS genetic scientists. They have collaborated to provide a complete picture of what we know and where current knowledge is leading us in this field. Given this, we hope you will appreciate that it was no small feat to combine such expertise from major research groups worldwide. In fact, this is the first time that such a combination of expertise has been achieved!

Professor Alastair Compston, from the University of Cambridge, actively participated in helping us put together this issue of *MS in focus*, and we sincerely thank him for assisting us in clarifying the questions we wanted to answer, as well as in identifying the experts who we have invited to contribute. Without Professor Compston's collaboration, we would never have been able to take on such a complex task. Further, on behalf of the Editorial Board, I would like to thank the contributors, who, despite their many commitments, agreed to be part of this very important issue of the magazine.

Finally, we appreciate the topic of genes and MS is an extremely complex one, and thus, have provided a glossary on page 27, in order to assist readers to digest the information. We hope you find this helpful.

I look forward to receiving your comments.

**Michele Messmer Uccelli**, Editor

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The next issue of *MS in focus* will be on caregiving and MS. Send questions and letters to [michele@aism.it](mailto:michele@aism.it) or marked for the attention of Michele Messmer Uccelli at the Italian MS Society, Via Operai 40, Genoa, Italy 16149.

## Editorial statement

The content of *MS in focus* is based on professional knowledge and experience. The editor and authors endeavour to provide relevant and up-to-date information. Information provided through *MS in focus* is not intended to substitute for advice, prescription or recommendation from a physician or other healthcare professional. For specific, personalised information, consult your healthcare provider. MSIF does not approve, endorse or recommend specific products or services, but provides information to assist people in making their own decisions.

# Introduction to

Alastair Compston, Department of Clinical Neurosciences, University of Cambridge, UK

Why me? The person with MS must often wonder what factors, unseen and unheard, cause the illness to affect one person but not another, one group of people but not another, and one part of the world but not another. The answer lies in the genetic make-up of individuals and particular ethnic groups. But what are these genes, how do they work, and can they be fixed?

These and other questions are addressed in this issue of *MS in focus* in which representatives from the leading research teams internationally explain why understanding the genetic basis of susceptibility to MS matters, how this knowledge is being gathered in different parts of the world, what remains to be learned, and what this knowledge means to people who have the disease.

About one person in five (20 percent) with MS has someone else in their family also affected. Since roughly only one in five hundred of the population gets MS, this rate is higher than expected by chance. Everything points to the increased risk depending on being a close relative rather than living together during childhood. Fortunately, the actual risk to any particular relative is pretty low. So why bother to unravel the genetic story?

Knowing why some people are at higher risk of the disease than others does nothing immediately to help put right the problem, but the main reward should come from the clues provided by understanding what is happening to the brain and spinal cord of people with MS. Until recently, trying to identify susceptibility genes was extremely hard.



*Test tubes containing the entire human genome. As a whole, these tubes contain all the DNA found in a human cell, and can therefore be called a human gene bank. Gene banks were commonly used to inform the Human Genome Project.*

Now, thanks to advancing technology, the problem can be approached systematically, with good prospects of success in unravelling the story.

# genes and MS



Genes are codes or messages that determine all the features that make one person different from another. They work alone or in groups. Through a complex sequence of events these genetic codes are converted into the proteins from which all cells and tissues are made. Most of these genes show person-to-person variations. Some genes are actually faulty and make defective proteins, but that is

not thought to be the situation in MS: rather, the idea is that affected individuals happen to have slight variations, called polymorphisms, that are perfectly healthy genes but – by chance – fit together badly so that the normal workings of cells, especially those that make up the body's immune system and the brain and spinal cord, are subtly altered.

Once this assortment of badly-fitted genes has come together by chance in the genome (a complete set of DNA) of one individual, it stands to reason that some or all of these factors may be shared within families through the normal mechanisms of inheritance. Put another way, if a particular gene contributes to MS, and two people in the family both have the illness, then it is likely that those two individuals will have inherited the same risky part of the genome. Genetic effects can also be unravelled by making comparisons between people who have MS and unrelated individuals who do not.

This issue of *MS in focus* tells the story of how medical scientists have worked with people who have MS, especially those in whom there is a family history, trying to identify and map the genes that increase susceptibility. Progress has been slow for several reasons, and many questions have yet to be answered. Where should the search be directed and how should it be organised? Before the Human Genome Project, it made sense to pick sensible candidates from amongst the increasing list of genes that had already been identified. The guesswork was not so inspired, although this approach did identify the HLA (also referred to as the "major histocompatibility complex" or MHC), as containing one (probably the most

important) susceptibility gene for MS. HLA proteins are found on the surface of all body cells. They act as a signal to the immune system to confirm that the cell is part of the body and should not be attacked.

Now the Human Genome Project has provided a much improved opportunity for progress. The Project has identified and mapped each and every one of the 30,000 genes we all possess, and has started the process of characterising the differences which occur between individuals, so that a systematic search can be made. We might be overwhelmed by the amount of information coming from modern data analysis techniques, but methods for analysing these data and seeing the bigger picture are also being devised.

Who can help most with this research? Decisions have had to be made on whether the answers will come faster by working within families having several cases of MS, or by concentrating on people who have the illness whether or not there is a family history. Both can be useful, but in different ways.

Once identified, can the genes be fixed? There is no possibility for gene therapy designed to insert a brand new set of "better" polymorphisms. In any event, these are healthy genes and are presumably doing a very good job in many other respects.

Is it only risky genes that cause this disease? Clearly not: these are perfectly healthy structures and the susceptibility, or risk, is just that; something else has to happen that releases the effect of these genes. Triggers, presumably something environmental such as a virus, are what actually set off the disease process.

Sometimes the notion of genetic risk implies blame. Where did these genes come from? The origins of MS are obscure but it seems to



*James D Watson and Francis Crick, who discovered the structure of DNA in the 1950s, for which they were awarded the 1962 Nobel prize award. This work formed the basis for the Human Genome Project.*

be more common in northern Europeans than other populations, and especially in Nordic peoples. The Vikings have been blamed for distributing the genes that increase the risk. They might have done so, but presumably those genes belonged to their predecessors and did not just appear out of the Northern Mists.

So, here is a mystery that is ripe for solution. Over the next few years, several international research groups are expected to re-screen the human genome with high expectations of finding some, if not all, the genes that contribute to MS susceptibility. The new knowledge is expected to provide even more revelations about disease mechanisms and perhaps help us direct specific treatments to the most responsive individuals. The knowledge will fill in the puzzle and make the big picture on MS ever easier to read, understand, and solve.

# Understanding the genetics of MS

Graeme Stewart, Westmead Hospital, Sydney, and Trevor Kilpatrick, Royal Melbourne Hospital, Melbourne, Australia

Multiple sclerosis is a complex disease influenced by many factors rather than driven by a single cause. Genetic or inherited factors are important but environmental exposure also plays a part. This distinguishes MS from so called "simple" genetic conditions where disease is caused by a deficit in a single gene. The inherited risk of MS is likely to involve several genes (perhaps 5-10) interacting with each other and with environmental factors. Research into the genetics of MS therefore involves the search for genes that contribute to susceptibility and/or to the severity and other aspects of the disease. More recently, genetic research has extended into the study of inherited variations in response to treatment (pharmacogenetics).

## *How is it known that genes are important in MS?*

For many years it has been evident that close family members of a person with MS have a higher risk of having the disease, and the closer they are genetically, the higher the risk. Unrelated family members (such as husband or wife) show no increased risk but the children of marriages where both parents have MS have a particularly high risk. A large study of people with MS who were adopted under the age of one year clearly showed that risk is largely due to genetic factors rather than the environment.

In the 1970s, there was a breakthrough with the discovery of a very strong association between MS and genes that control immune cell function, known as HLA genes. For people of northern



Photo: courtesy of the Institute for Immunology & Allergy Research, Westmead Millennium Institute

European origin about 60 percent with MS have the same HLA gene type, a type found in only 20 percent of the general population. This relationship between MS and a genetic marker, and other associations, make up an important part of what we mean by the "genetics of MS". With the Human Genome Project leading to a complete map of the human chromosomes, and with advances in technologies for rapidly typing many genes, many research groups worldwide are actively involved in genetics research.

## *How is genetic influence achieved?*

Genes contain information that we inherit from our parents and this information is used to produce proteins. Proteins are components of all living cells: some provide essential building materials; some control the breakdown of energy sources and waste products; some act as important messengers; some recognise and destroy bacteria and viruses; others are master regulators that control the activity of genes and their ability to produce other proteins.

Susceptibility to some diseases, in particular those that can be directly transmitted from parent to child, occurs when abnormal genes are copied in either sperm or eggs, thereby leading to the perpetuation of expression of abnormally functioning proteins and hence, inherited disease. In the case of MS and other complex diseases, it is more likely that subtle changes in the structure and function of a combination of proteins, rather than a devastating mutation in a single protein, are relevant. These combinations act to increase the risk of disease but do not reflect the sole cause. Environmental factors also have a role to play.

Many of the proteins produced by genes exert their effects not in isolation but as part of pathways, akin to cogs in a production line. As in industry, it is possible to compensate for a single, minor problem but if there are several sequential deficits in a single pathway or alternatively, deficits in both primary and auxiliary pathways, then more overt susceptibilities emerge; essentially, there is a multiplier effect. In addition, if there are deficits in regulatory proteins, these are likely to exert their influence at either multiple points in a single pathway or in multiple pathways.

Variable susceptibility to complex diseases among individuals is a consequence of genetic diversity that is driven by two principal factors. Firstly, the genetic make-up of a child is a mix of that provided by each of its parents. Secondly, sections of the parents' DNA that were contributed by either of their parents can swap over, or 'recombine', at the time sperm or eggs form, potentially leading to yet further diversity. More than one minor variation in a gene coding for a given protein might produce increased susceptibility. In addition, different combinations of minor variations in different genes either in a single pathway or in interacting pathways could each increase susceptibility. These influences may also be exerted in a given cell type or between interacting cells. For example, variations could be at work in either immune cells or in the



*Scientists believe that low levels of sunlight exposure during childhood may have an influence on MS susceptibility.*

cells within the brain and spinal cord that they target. This would explain why no one genetic 'signature' confers susceptibility to MS. This also explains why complex diseases such as MS are not usually inherited directly from parent to child but are, instead, driven by the unique genetic 'mix' present in any given individual.

*Why is there so much research into the genetics of MS?*

The search for MS genes is important because their discovery will provide vital information on which biologic mechanisms influence the disease. This will lead to a better understanding of what causes MS and to the development of new approaches to treatment and prevention. There is a real hope that in the future, genetic tests may



predict the likelihood of benefit (or side effects) of a particular treatment and thereby assist with a more personalised choice of treatment for each person. This already occurs in other diseases although such work is still in its early days.

*Which are the best genes to study first in MS?*  
With perhaps 5-10 genes to find amongst the 30,000 known genes of the human genome, the search may seem impossible. Current knowledge of MS, however, helps researchers to focus in on certain groups of genes.

It is thought that MS is an example of autoimmune disease, a group of disorders that arise when the immune system – so important in protecting against bacteria and viruses – inappropriately targets the body's own tissues. In MS this attack is directed to the brain and spinal cord. It is therefore likely that genes which change the susceptibility to MS include those

which influence the immune cells that drive this attack. Genes that influence the level of nervous system damage and its capacity for repair are also likely to be involved.

*Are there examples of how genes and the environment might interact?*

A current hypothesis holds that low sunlight exposure in childhood could predispose individuals to MS. This predisposition may be exerted through reduced Vitamin D, which is normally produced in the skin by ultraviolet light exposure. Vitamin D is known to dampen immune responses. The genetic influence here could conceivably come through variants in the Vitamin D receptor protein or in other proteins that are activated when Vitamin D binds to this receptor. This would result in an individual variation in the degree of immune system modulation exerted by a given level of sunlight exposure and Vitamin D production. In this way, differences in genetic make-up could contribute to determining individual susceptibility when there is fairly uniform exposure to an environmental trigger, for example low sunlight, by a larger population.

*Future directions in the genetics of MS*

The genetics of MS is not a simple phenomenon that will be unravelled by the analysis of a few individuals. Given the likelihood that multiple genes are involved, each producing a small effect and with none causally involved in all affected individuals, it is clear that studies of many thousands of people with MS, as well as matched controls of similar ethnic background, will be needed in order to detect MS susceptibility genes. To undertake such studies requires an immense effort, which involves recruitment of participants, assessment of the genetic composition of each of the many thousands of recombined segments, or haplotypes, present in each individual followed by detailed statistical analysis. Despite these challenges, in order to achieve fundamental advances in our understanding of MS, this is a genetic puzzle that we must continue to strive to unravel. Research groups in many countries throughout the world are collaborating in this effort.

# The challenges of studying genes

Jorge R Oksenberg, PhD and Stephen L Hauser, MD, Department of Neurology, University of California, San Francisco, USA

Understanding the genetic roots of MS has the potential to uncover the basic mechanisms of the disease, and this knowledge will undoubtedly lead to new and more effective ways to treat, and perhaps prevent, the disease.

Research studies strongly suggest that genes not only influence who is at risk for MS, but also affect factors such as age of symptom onset, severity, progression and response to drugs. We foresee important implications for this type of investigation. For example, in the future genetic profiling may help the neurologist to match individuals with tailored therapies and disease management strategies.

The genetic aspect of MS was recognised prior to the end of the nineteenth century, but progress in understanding the role of genes in this disease has been slow and appears to be beyond the grasp of any single research team. Given the complexity of the biological mechanisms leading to MS, tackling this problem in a meaningful and decisive manner requires the development of close partnerships among research groups to achieve a critical mass of multi-disciplinary expertise in different fields including neuropathology, genetics, statistics, mathematics, genealogy, epidemiology, and molecular biology.



Photo: Stacy J. Caillier, UCSF MS Genetics Group

Although figuring out which genes are involved and what they do is an enormous task, recent methodological advances and an improved understanding of both MS pathology and the underlying structure of the human genome are likely to lead to answers in the very near future.

Translating genetic information from the laboratory to the clinical setting may also present challenges. For example, if the gene discovered to be involved in the

disease process happens to have multiple and different important functions in the organism, it may be difficult to manipulate or target it because we may be doing more harm than good. But if the gene is less essential for normal physiological function, then we could screen for chemicals or natural molecules that interact with and block or neutralise it. We could also develop therapeutic antibodies, for example, that would neutralise the offending product.

The short-, medium- and long-term objective of all genetic research is to reduce the impact of MS and to apply the fundamental knowledge we acquire to improve our capacity to prevent, diagnose, treat, and cure MS.

# Progress in genetics and MS

Stephen Sawcer, University of Cambridge Department of Clinical Neurosciences, Addenbrooke's Hospital, Cambridge, UK and Mark Daly, Massachusetts General Hospital, Boston, and The Broad Institute of Harvard and MIT, Cambridge, Massachusetts, USA

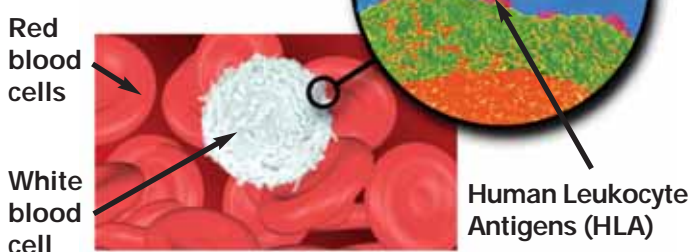
The observation that genetic factors influence susceptibility to MS has rightly prompted tremendous efforts to identify the responsible genes, as recognition of these genes will almost certainly implicate the mechanisms responsible for the disease. It is logical to expect that this knowledge will have profound and beneficial effects, eventually allowing us to curtail, cure or even prevent MS.

To date the most important discovery arising from these efforts has been the identification of the association between MS and the "Human Leukocyte Antigens" (HLA). These antigens are proteins which are found on the surface of cells and are important in the process which allows the immune system to distinguish healthy cells from those needing to be removed because, for

example, they are from a foreign organism, infected with viruses, or are developing cancer.

The six most important antigens are known as HLA-A, -B, -C, -DRB1, -DQA1 and -DQB1. Like all proteins these antigens are each encoded by a specific gene and interestingly, the genes for these six proteins all lie very close to each other on chromosome number 6. Each of these antigens comes in many different forms which correspond to slightly different underlying DNA sequences. For example there are more than 500 different forms of HLA-B (the most variable gene known). Scientists refer to different versions of the same gene as "alleles", and therefore would say that there are more than 500 different alleles known for the HLA-B gene, each one encoding for a slightly different form of the HLA-B protein.

*HLA, shown here on the surface of a human white blood cell, has been linked with MS*



For each of these six genes, an individual will have inherited one allele each from his or her mother and father. The particular set of 12 alleles (two for each gene) carried by one individual is unlikely to be the same as the set carried by a second individual, unless they are related. Doctors refer to this particular set of antigens, determined by the alleles inherited, as an individual's "tissue type". When someone needs a transplant doctors say they have to "match the tissue type", which means finding a donor with the same set of antigens. If

the tissue does not match, the recipient's immune system will spot the different set of antigens and reject the organ as foreign and destroy it.

It turns out that certain of these antigens are more common in people with MS than they are in the general population. The strongest association is seen with allele 15 of the HLA-DRB1 gene, a very common allele carried by 1 in 4 people in the UK (25 percent of the population). Thus in the UK, which has a population of approximately 60 million, some 15 million people carry this HLA allele. However, amongst the 60,000 people in the UK who have MS, roughly 60 percent carry the 15 allele. This illustrates some important characteristics of the sort of genetic effects likely to be relevant in MS. First, the vast majority of people who carry the risk allele will not develop the disease – 15 million people carry the 15 allele of HLA-DRB1 but only about 0.3 percent of them develop the disease. In other words, although carrying the 15 allele increases an individual's chance of developing the disease, the effect is small and more than 99 percent of 15 allele carriers will not develop MS. Second, the allele is not required to develop disease, as some 40 percent of people with MS do not carry this particular risk allele.

Although the association between MS and HLA was first recognised more than 30 years ago, the complexity of this region of the genome is so great that scientists are still trying to discover how it is that inheriting particular HLA alleles manages to influence the risk of developing MS. What is clear is that the HLA genes determine only a small part of the genetic susceptibility to MS. Scientists have long wanted to search the rest of the genome for other similar effects. Unfortunately the human genome is so large and so variable that there are literally millions of possible genetic factors that could be relevant. Moreover, since the effects exerted by relevant genes are individually modest, each potentially relevant factor needs to be studied in hundreds, perhaps thousands, of people with MS in order to be conclusively identified.



Testing hundreds of thousands, if not millions, of factors in many hundreds, if not thousands, of people has, until now, been a technical impossibility. Previously, scientists searching for the genetic factors influencing susceptibility to MS have only been able to consider a handful of factors from a few carefully selected genes. Sadly these efforts have not produced any consistent findings beyond HLA, but they have taught us much about the methods and problems to be overcome in identifying the genetic causes of MS.

It is now clear that the genetic analysis of MS stands poised to reap the benefits of several decades of academic effort, much of which has been supported by people with MS and MS societies. The requirements for well-powered systematic searches of DNA variation in the human genome are finally in place: large and carefully evaluated groups of people with MS have been engaged in genetic research projects; the Human Genome Project and subsequent projects have provided detailed knowledge about millions of DNA sequence variants in the human genome that might play a role in disease; and a cost effective technology for assessing these DNA variants is just becoming available. Prospects for success are so bright that profit-making organisations are now entering the field.

There is building enthusiasm that identifying the genes determining susceptibility to MS is within reach. As genes emerge from these studies it will be essential to confirm their relevance by studying more people with MS. Thus, support for continued enrolment of participants should not be forgotten.



# Genes, MS and families

George C Ebers, The Wellcome Trust Centre for Human Genetics and the Department of Clinical Neurology University of Oxford, UK, and A Dessa Sadovnick, Department of Medical Genetics and Faculty of Medicine, Division of Neurology, University of British Columbia, Vancouver, Canada, and Hospital Notre Dame, Montreal, Canada

Many people are familiar with the concept of single gene disease, in which the presence or absence of one form of the gene dictates, to a great extent, whether or not the disease will occur, for example Huntington's disease, muscular dystrophy, and sickle cell disease. It is only relatively recently that the most common diseases of adult life, including MS, have been shown to result from complex interactions between genes and the environment.

This concept has emerged over the last two decades largely because of longitudinal family studies (called genetic epidemiology), especially those from Canada. These studies of

twins, adoptees, half siblings, stepsiblings and the offspring of first cousin marriages have formed a uniform picture. MS susceptibility risk clearly is not due to the shared familial microenvironment. The environmental effects appear to exert their influence at a broad level, implicating climate and/or diet as important causative factors. Merely living in the household with someone who has MS or who is destined to develop MS does not increase the risk of developing the disease. This interpretation was made at the time the original Canadian twin study 20 years ago.

### *What do we know about the risks of inheriting MS?*

People with MS may be concerned about passing the disease on to their children. The recurrence risk (the chance that another family member will develop MS if one already has the disease) for first-degree relatives (parents, children, siblings) of persons with MS have been determined by observation over many years. Although this risk can vary in special circumstances, if one parent has MS, the risk for an offspring to eventually develop the disease is approximately 3-5 percent, depending on parent and offspring gender. It is very similar to the risk for brothers and sisters of the affected parent. This risk drops with the decrease in the proportion of genes shared by individuals. For example, while children share half their genes with each parent, first cousins only share one eighth of their genes and thus, their risk to develop MS is perhaps slightly more than half-a-percent.

The overall recurrence risks may seem low at 3-5 percent, but this is still a 50-fold increased risk compared to the general population. To illustrate, a person with MS with five children would have a one in five chance that one of the children will develop MS during his or her lifetime.

It is clear from the genetic epidemiological studies that the increase among biological



relatives as compared to the general population is genetically determined. A major influence comes from the major histocompatibility complex, a region located on chromosome 6 and known to be important in immune function. We have recently shown that the allele (form of the gene) inherited by the child from each parent interact to influence overall risk for MS. From this work, it is possible that in the near future, individuals will be given more precise information about the risk for their offspring to develop MS since it has been possible to identify certain alleles that appear to suppress the disease. More will be heard about this line of investigation in the near future.

Data from Canadian studies of half siblings, non-identical twins, and their non-twin siblings, and timing of birth, suggest that the risk to develop MS is significantly greater from a mother with MS than from a father with MS. It is possible that MS risk might even be



environmentally determined in gestation or very early in life. This could have important implications, not only for uncovering the source of MS risk, but also for defining the “critical period” for prevention. There are both genetic and environmental mechanisms that could explain these “parent of origin” observations and indeed a gene-environment interaction is possible.

*Additional risks to onset, attack, and outcome*

It is important to distinguish between factors determining susceptibility to MS and those influencing onset, the triggering of attacks, and long-term outcome. The Canadian longitudinal twin study shows that the age of onset and long-term outcome are probably genetically determined. In approximately 20-26 percent of identical twins (who share 100 percent of their genetic material), only one individual will have MS, but when identical twins are both affected with MS, the age of onset and long-term outcome tend to be similar.

It is quite possible that genes influencing MS susceptibility are largely distinct from those that dictate outcome or how a person is affected by having MS. It would be reasonable to expect that two biological relatives (for example, parent and child, or brother and sister) with MS share susceptibility genes. Yet, when we investigated families with two or more biologically related individuals with MS, we consistently found a striking variation in outcome. One important result from these family studies is the observation that families show the entire spectrum of MS outcomes. This can be reassuring, at least to some degree, since a severe case in a parent does not prevent the child from having a far milder form of the disease.

An important goal of the Canadian longitudinal study has been to identify the way in which genes and the environment interact in order to bring effective treatment to light and provide insights on how the disease might be prevented.



## Genetic studies in childhood MS

Brenda L Banwell, MD, FRCPC, Pediatric Multiple Sclerosis Clinic, Research Institute, The Hospital for Sick Children, University of Toronto, Canada

Although most people diagnosed with MS are aged between 20 and 50, children can also develop MS. This is very rare, and scientists are still trying to understand the causes and characteristics of childhood MS.

If the onset of MS in childhood reflects a heightened risk for MS, then it follows that these children and their families may have a greater genetic susceptibility to the disease. However, in our recent international study of MS in children, only 11 percent of the affected children reported a family history of MS. This may be because the family members of children with MS may develop the disease themselves in the future. Therefore long-term family studies are required before we can fully evaluate the risk of occurrence of MS in relatives of children with MS.

Little is known about the frequency of childhood-onset MS occurring in families in which a parent also has MS. Similarly, few studies have specifically explored the genetic aspects of childhood MS. In a Russian study, children with MS had an increased frequency of a specific

genetic feature (the HLA-DR2 (15) phenotype) as compared to their siblings, parents, and healthy peers. Other genetic studies have been performed in an attempt to find a specific gene defect in childhood MS, but studies looking for defects have failed to find any abnormalities. A study searching for mutations in the Leber's Hereditary Optic Neuropathy genes in children with MS that affects the optic nerves identified several common variations, but no actual disease-causing genetic errors.

Studies involving groups of more than 20,000 adults with MS have, to date, consistently identified only the HLA as a disease-susceptibility marker. Given the relative rarity of MS in children, it is unlikely that even collaborative studies will provide sufficient numbers of participants for similar studies to be done in childhood MS. More detailed genetic analysis of childhood MS will await identification of specific genes in adult MS which can then be extended to genetic studies in childhood-onset disease.

# Taking part in an MS genetics study

Robin Lincoln, BS, The Multiple Sclerosis Genetics Group, University of California, San Francisco, USA

A human genetics research study is a collaborative effort between the scientific research group and people volunteering to participate. Both sides invest considerable time in the project with the ultimate goal of preventing or curing MS.

## *Preparation*

Long before a potential volunteer becomes aware of a genetics study the research group will have prepared a plan stating the goals of the project, how the study will be run and a "human subjects' consent form", all of which must be reviewed and approved by their institution's internal review board. The purpose is to ensure protection for the volunteers. No research can begin without this approval and it must be reviewed on at least a yearly basis.

## *How do people find out about the study?*

People with MS often learn about a study on the Internet, at their MS centre, or from their neurologist. Pamphlets explaining the study and how to contact the research group are often made available in clinic waiting rooms. MS society publications may provide information, or the investigators may be invited to speak at MS support groups or MS society meetings. Other methods used to promote research studies include advertisements in newspapers and on radio.

## *Recruiting volunteers*

It can take many, many months to recruit, enrol and finally begin analysing individuals in the laboratory.

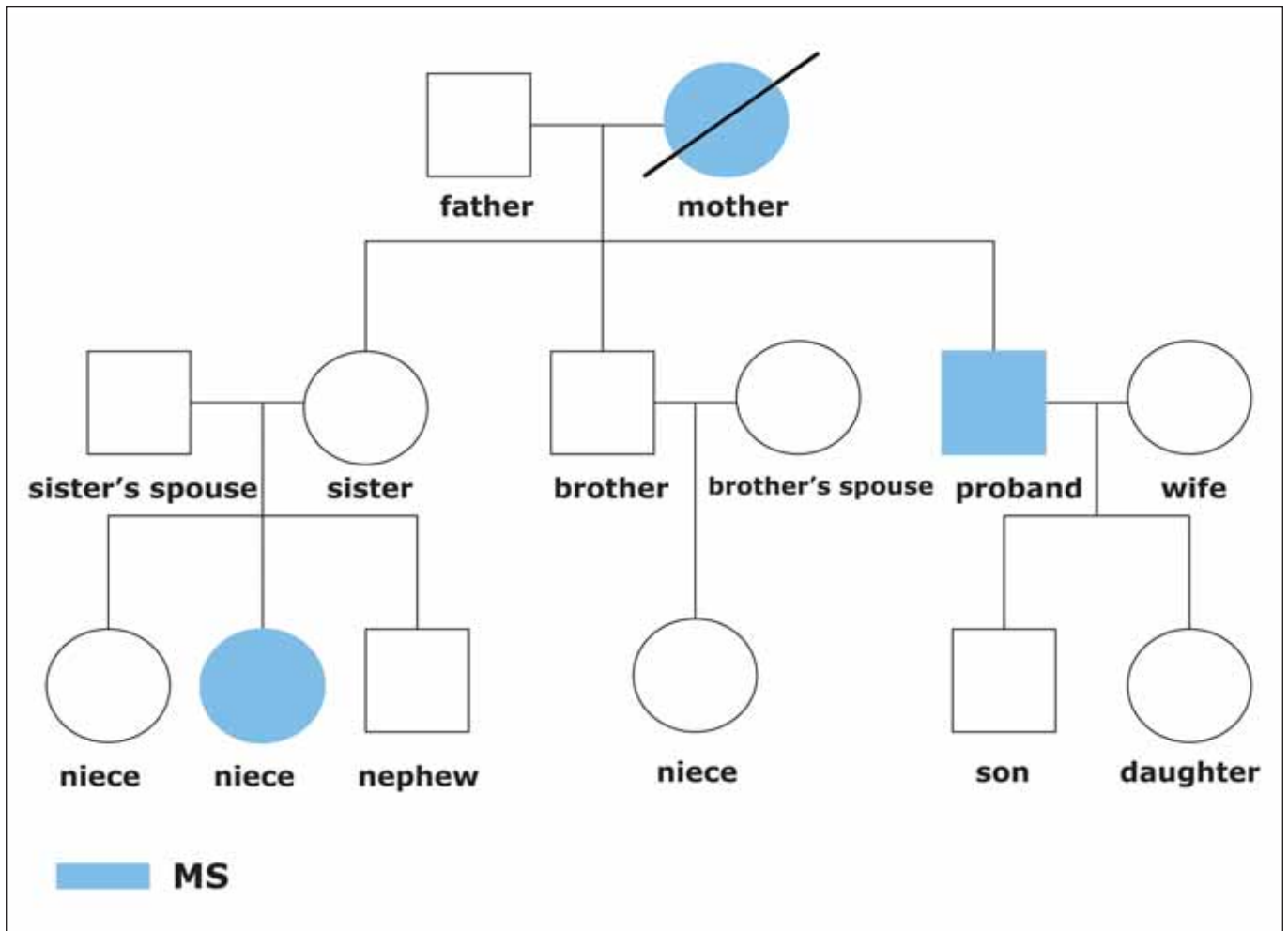
Recruitment typically begins with a telephone call. Since the scientists may be a thousand miles away, an initial phone conversation between the potential participant and a study coordinator will explain the study and give the coordinator an opportunity to become better acquainted with the volunteer.

Individuals will be asked to fill out a family history form providing information on themselves and the family members, spouses and friends that have agreed to participate. Contact will not be made with anyone who does not wish to participate.

A "pedigree" is generated for each family in the genetics study (see figure), based on information provided in the family history form. It can be used as a diagrammatic reference and also in conjunction with genetic data to check for inheritance patterns.

People diagnosed with MS will be asked to complete medical record release authorisations as obtaining medical records is crucial. Tracking down records is time consuming, especially for individuals who have seen multiple doctors.

Once sufficient medical records have been obtained, they are reviewed by the study coordinator and a neurologist to determine if entry criteria are met. At this point, the



**A pedigree for a family in an MS study**

*The proband is an individual or member of a family being studied in a genetic investigation, who is the point of reference in identifying the other family members. All of the other members are labelled according to their relationship with the proband. The blue circle or square signifies a person with MS. The strike across the circle represents a deceased family member.*

volunteers who meet the study criteria will be ready for the final step of enrolment: providing a blood sample.

*How is a blood sample given and what happens to it?*

To collect blood samples for our research, phlebotomy kits are sent to an individual's home to be taken to their physician or local clinic. Sometimes arrangements are made to have someone go to a participant's home to take their sample. In each case, the sample is then shipped immediately to be processed by the lab.

Each sample is processed and added to ongoing experiments in the lab. Sharing samples with collaborators is common. Some groups are also known to share samples with other scientists who request these important materials and who have a valid scientific need and purpose for them.

We usually ask the person with MS, their parents and perhaps their siblings, to donate a blood sample. In addition, samples from friends or spouses/significant others are routinely collected as controls.

# Geographical influence: MS genetics in Japan

Jun-ichi Kira, MD, PhD, Department of Neurology, Neurological Institute, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

MS in Asians is often characterised by selective and severe involvement of the optic nerve and spinal cord. Fifteen to forty percent of Japanese people with MS have this opticospinal type, while others have features similar to those of MS in Caucasians (conventional type).

Opticospinal MS is characterised by frequent relapses, severe disability, few brain lesions being visible on magnetic resonance imaging (MRI) and long extensive lesions on spinal cord MRI. Further, in approximately 90 percent of people with MS, there are a series of distinct bands found in the immunoglobulin of the cerebral spinal fluid, known as oligoclonal IgG bands. In the non-conventional type of MS there is an absence of these bands. Moreover, in Caucasians, familial clustering of MS is well known, but familial occurrence of MS in Japanese people is rare. A nationwide survey of MS in Japan, undertaken in 2004, found familial cases of MS constitute less than one percent. The

underlying mechanisms causing these differences are unknown but appear to be partly based on differences in immunogenetic backgrounds.

In people of European descent, susceptibility to MS is associated with a specific haplotype, or a set of closely linked alleles (genes or DNA polymorphisms) inherited as a unit (HLA-DRB1\*1501-DQA1\*0102-DQB1\*0602). One allele of this haplotype (HLA-DRB1\*1501) has also been recently identified in African-Americans as being associated with susceptibility to MS. Among groups who have higher proportions of opticospinal MS - such as Japanese, Chinese, Southeast Asians, and Gulf Arabs - the same haplotype has not been associated with MS susceptibility. However, when MS is clinically classified into conventional MS and opticospinal MS, conventional MS in Japanese is associated with the same allele identified in African-Americans, whereas opticospinal MS is associated with a different allele (HLA-DPB1\*0501).

Even in conventional MS, oligoclonal IgG band-positive MS is associated with that seen in African-Americans, while oligoclonal IgG band-negative MS is associated with an allele that has been identified in people with MS on the island of Sardinia, Italy and in Turkey (HLA-DRB1\*04). These observations suggest that differences in clinical features and immune responses in MS are in part related to polymorphisms, or a common variation or mutation in DNA, in HLA class II genes, a type of gene that codes for a protein.

Genome-wide studies on MS susceptibility genes have not been undertaken in Asians. However, such studies might help identify novel genes involved in certain forms of the disease including the opticospinal MS common in Japanese people.



# Results of the online survey on genetics and MS

Responses to an online survey on the MSIF website ([www.msif.org](http://www.msif.org)) have revealed what some of our readers have experienced in learning about genetics and MS and how this information has influenced them since being diagnosed. We also asked about where they go for information on genetics and MS and about their views toward research funding in this area. Two hundred and seventy-four people with MS responded to the survey.



Photo: Stacy J. Caillier, UCSF MS Genetics Group

## Diagnosis of MS and information about genetic susceptibility

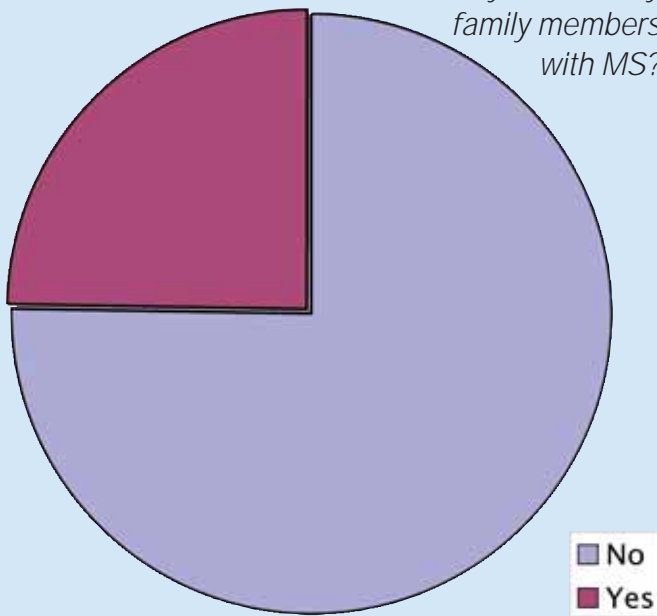
The vast majority of respondents (82 percent) did not receive information about genetic susceptibility at the time they were diagnosed with MS. Of those who did, nearly one-third (27 percent) felt that it was incomplete and unclear. Of the 48 respondents who had received genetic information at the time of diagnosis, one-third reported that this information influenced their choice to have children or not.

## Familial MS

Sixty-eight out of 274 respondents (25 percent) reported that more than one member of their family had MS. Table 1 provides a breakdown of the details.

In a minority of cases, having multiple family members with MS was a relevant factor in the

Do you have any family members with MS?

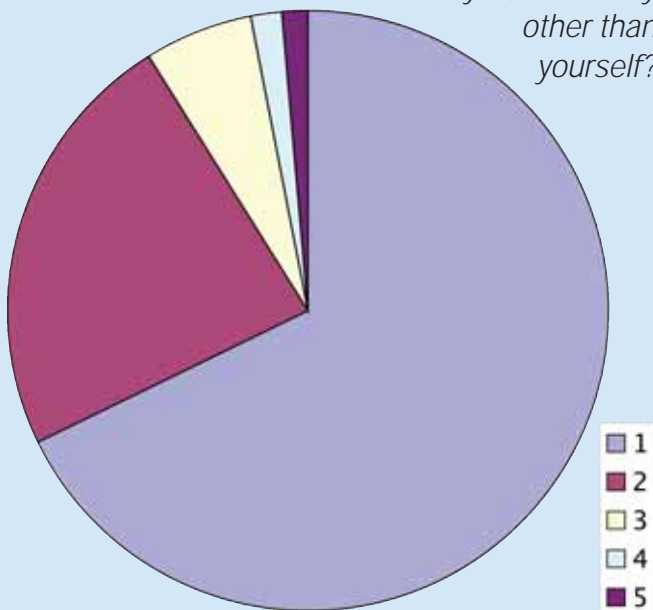


decision to have children or not (10 out of the 68 respondents with a family member with MS – 15 percent).

### Learning about genetics and MS

The large majority of subjects felt that they were not sufficiently informed about progress in MS genetic research (68 percent). The Internet was the most widely utilised resource for learning about genetics and MS and for keeping updated on related topics (70 percent). Other sources included MS society magazines, neurologists and medical and scientific journals.

If yes, how many other than yourself?



### Supporting research

Some respondents felt that MS societies and other funding sources do not dedicate a sufficient amount of money to genetics studies (24 percent) compared to 46 respondents (17 percent) who felt that enough money was currently being dedicated to these studies. The survey found that a large number of people with MS are apparently not well informed as to the amount of funding their MS society dedicates to genetics research (approximately 60 percent).

### Conclusion

The survey suggests that the topic of genetic susceptibility is often not discussed at the time of diagnosis. However, this result may be biased according to when people were diagnosed. Hopefully, since our understanding of genetics has increased over the past years, susceptibility to MS is becoming a more common topic of discussion at the time of communicating an MS diagnosis.

Fortunately, people interested in being informed and updated on progress in genetic research in MS have many sources of information to access. National MS societies are often able to assist people to sort through the often complicated, and sometimes inaccurate, information available on the Internet.

Number of family members with MS (including respondent)	Number of respondents:
2	46
3	16
4	4
5	1
6	1
more than 6	0



# Your questions answered

Readers of *MS in focus* ask questions to the Editor, Michele Messmer Uccelli

**Q.** My partner and I are thinking about starting a family, but I have MS and am worried about passing it on to our children. What things should we be taking into consideration?

**A.** The possibility that the child of a person with MS will develop the disease is estimated to be around 3-5 percent, depending on the gender of the parent and of the child. Please refer to the article "Genes, MS and Families" on pages 13-15 for a complete discussion of risk factors.

Other important issues to consider when thinking about a pregnancy include the possible impact of discontinuing any medications (such as a disease modifying treatment) during pregnancy and/or while breast feeding, the increased risk within the first three months after delivery of having a relapse, preparing for the potential worsening of some symptoms, such as bladder and bowel problems, during pregnancy, and organising additional help in the home if needed. Refer to *MS in focus*, Issue 3 on Families, page 17, for further advice.

**Q.** What is the Human Genome Project and how is it helping MS research?

**A.** The Human Genome Project is an international effort that began in October, 1990. The primary goal of the project was to identify all the genes in human DNA and to determine the

sequences of the three billion chemical base pairs that make up human DNA. Practically speaking, the purpose of learning more about the effects of differences in DNA among people should lead to new ways to diagnose, treat, and hopefully someday, prevent many diseases and disorders. More information can be found on a number of websites describing the project, by typing "human genome project" into an Internet search engine.

**Q.** I have rheumatoid arthritis and MS. My doctor told me that both are immune diseases. Do they have something in common genetically? Is it common for people with MS to have other immune diseases as well?

**A.** Autoimmune diseases include approximately 50 different diseases with varying symptoms. Though each disease is different, malfunctioning of the immune system occurs in all of them. A person with one autoimmune disease is more predisposed to having another. Also, in families where one member has an autoimmune disease, other family members are more likely to be diagnosed with other autoimmune diseases. So, for example, a person with MS may have one family member with rheumatoid arthritis, and another with diabetes mellitus. The MS genetics studies discussed in this issue of *MS in focus* do look at the presence of other autoimmune diseases in participating families in the hope of answering the questions of how and why this occurs.



## *MS in focus* interviews

# Professor Maria Giovanna Marrosu

Professor Maria Giovanna Marrosu is an MS scientist in Cagliari, on the island of Sardinia, Italy. She talks to *MS in focus* about MS clusters.

### **Professor Marrosu, can you tell our readers what an MS cluster is?**

The term “cluster” means different things. One is the familial cluster of MS, which means an aggregation of people with MS within a family. This kind of cluster may consist of siblings, a parent or child, and other more distant relatives affected with MS. Another type of MS cluster is the spatio-temporal cluster. In this case, we observe a high number of people with MS in a defined framework of time or in a defined geographic area.

### **How exactly is an MS cluster determined or verified?**

An MS cluster can be verified through epidemiologic studies. For example, researchers who decide to study a familial cluster obtain information from a large population of people with MS (generally from a population of people followed by one or more MS clinics), building pedigrees of all families of their patients. If there are other individuals with a diagnosis of MS within a person’s family, they are inserted as “affected” in the pedigree of the family. The total number of those affected is compared with the total number of this category of individuals (total number of siblings, or mothers, or fathers...), in order to obtain data about the prevalence of the disease in these families. This number, which is the percentage of people with MS observed in the families, is compared with the percentage of people with MS in the general population. In the case of a study of temporal clusters, researchers collect information about all people with MS in a defined country, registered in a given

time (generally 20 years or more). In this case, the goal of the study is to observe if there is any variation in the number of people with MS in a given time.

### **How could clusters help researchers improve their understanding of MS?**

Studies of familial clusters are very useful in understanding the genetic basis of the disease. Researchers have firmly established that a familial cluster of MS is determined by genetic factors and not by environmental factors. Consequently, it is important to understand how and how many genes are involved in the predisposition to MS.

Spatio-temporal clusters help us to understand if variation in the environment may be responsible for the disease, thus, promoting studies on the role of external factors in MS.

### **Why is the prevalence of MS so high on the island of Sardinia and do researchers know why it is so much higher than in the rest of Italy?**

The prevalence of MS in Sardinia is about three times more than in the rest of Italy. We have no definite explanation for this phenomenon, but we think that the population of Sardinia is particularly prone to MS because of its genetic make-up. Sardinian people carry different genetic variants from the rest of Italy and Europe, which are probably responsible for the high predisposition of MS and other autoimmune diseases (such as autoimmune diabetes). Moreover, studies demonstrate that



*Prof Marrosu (back row, 5 from left) and her research team in Sardinia*

there is a progressive increase of the disease on the island. This, combined with our demonstration that the onset of the disease in the last decades is progressively occurring earlier, suggests that other non-genetic factors may be responsible for this dramatic number of people with MS in Sardinia.

### **Do clusters follow a geographical pattern?**

MS is more common in populations of Scandinavian descent, a fact that may reflect genetic material carrying susceptibility genes in this population. In general, the prevalence of the disease in Europe follows a north-south gradient, being more frequent in the northern countries. Despite the fact that these studies are rather old, the general concept is still accepted. Spatial clusters of MS were described by Kurtzke many years ago in the Faroe Islands.

### **Does Sardinia have certain aspects in common with other sites of verified clusters in different parts of the world? Are all clusters on islands?**

There are no common aspects between Sardinia and sites of other clusters, such as the Faroe Islands. However, when reporting on the Faroe Islands, Kurtzke believed that viral agents

carried by English soldiers (an exogenous factor) were involved in the epidemic cluster of MS. Similar events may be hypothesised to explain the temporal increase and the lowering of age-at-onset of the disease that has been seen in Sardinia. However, it is unlikely that the Sardinia cluster involves specific viral agents, but rather a complex environmental variation occurring on the island in the last 30-40 years.

### **Is a specific type of MS more common in these clusters?**

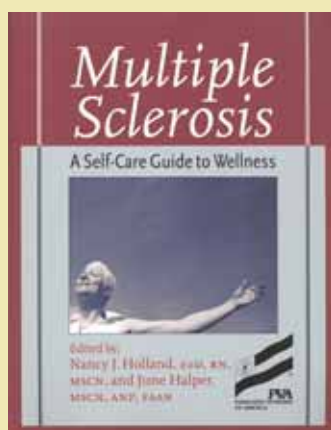
No, there are no specific types of MS in these clusters. The only definite type associated with a cluster is the so-called "Asian-type" of MS, a particular form of the disease involving the spinal cord and optic nerve, which is frequent in Japan (see page 19).

### **What have you learned from studying the particular situation of Sardinia?**

I think that the nature of MS is still obscure and elusive, and that we may not fully understand it during my lifetime. Despite this, Sardinia may be a very interesting natural experiment and may provide a framework for understanding the role of familial, particularly genetic determinants, and environmental factors in MS.



# Reviews



## **Multiple Sclerosis – a Self-Care Guide to Wellness**

*2nd edition 2005.*

*Edited by Nancy J. Holland and June Halper*

*Review by Elsa*

*Teilimo, Finnish MS Society*

When reading this book, I asked myself: 'Why was this book not published twenty years ago when I was younger', because the book is excellent. It explains everything worth knowing about MS and its management. Its language is simple, its illustrations clear, and even a person with limited English language ability could follow all of it.

Chapters like "An Overview of Multiple Sclerosis" or especially "Hope through Research" hit the mark by being not only informative, but also encouraging. This is what people with MS most need: information and encouragement. One writer says: "There has never been a more exciting time in the history of MS and never better prospects that a cure will be found."

The section "Medications Commonly Used in MS" gives very thorough and detailed information. I

found the chapter describing proper usage, precautions and possible side effects of all available medications in MS the best list of its kind I have seen.

This great book has been written by American experts and there is naturally advice on some matters for the US audience, but in general the book is absolutely suitable for everyone interested in self-care, whether they have MS or whether they are a friend or family member of someone with MS.

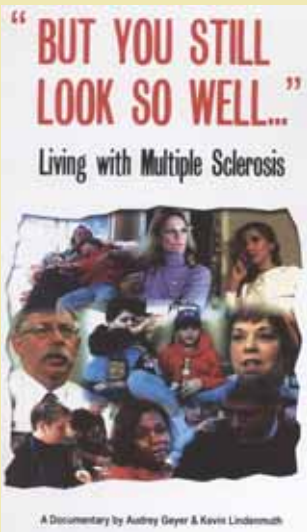
*Editor's note: The back cover of this book states "The book emphasizes the needs of readers who have been living with the disease for some time and may have developed neurologic deficits as a result".*

*Demos Medical Publishing  
386 Park Avenue South, Suite 201  
New York, N.Y. 10016  
www.demosmedpub.com  
Price \$19.95  
ISBN 1-932603-07-7*

## **"But You Look So Well"**

*Video produced by the Michigan Chapter of the National MS Society, USA  
Review by Brian Lee, Sydney, Australia*

The target audience is people with MS and their families. The aim is to help them understand what to expect following a diagnosis of MS.



The families selected were people that any viewer in a similar situation could identify with. The personal stories, especially by the children, were very well told and reflected a good cross-section of the concerns and thoughts, feelings and reactions, of people with MS and their families.

The film deals with depression and anxiety very gently and in a matter-of-fact way which is very pleasing to see. It is too easy to skirt around this issue so it was refreshing to see it confronted by these families and to hear their reactions.

I thought the positive aspects of a father having MS, as discussed by one of the children, was particularly good, especially for someone newly diagnosed.

It was very good to include footage of these families reacting together in their homes as well as attending sporting events and other family outings.

Unfortunately, the film was too long. I think it would be better if it were presented in three, half-

hour segments so the viewer could choose to watch them one after the other or break them up. Also, I really disliked the transitions between scenes - the use of so many was distracting.

Although the film mentioned fatigue quite a few times I felt it could have received more emphasis and been described in more detail, especially the typical feeling of the all-consuming fatigue that is common in MS.

The film did not touch on urinary problems at all, which, from my experience, is a problem that affects nearly every person with MS. As with depression, urinary problems can be handled delicately but needs to be discussed front on. I felt this was a significant omission.

On the whole the film is a very worthwhile resource for people with MS and their families, especially early on in their MS journey. With the exception of urinary problems it covers most of the issues people can expect to confront. Bravo to these brave families who opened their homes and their hearts to share their experiences.

*To order a copy, please email  
AudreyGeyer@aol.com or  
Infolindenmuth@aol.com, go online to  
www.geyerlindenmuth.com or call  
(+1) 810 225 7796  
Running time: 84 minutes*

**The International Organization of Multiple Sclerosis Nurses has produced a booklet called *Genetics in Multiple Sclerosis – A Guide for Nurses*. This clear and informative illustrated guide is available free (excluding postage) by writing to:**

International Organization of MS Nurses  
PO Box 450  
Teaneck  
NJ 07666  
USA  
or email [info@iomsn.org](mailto:info@iomsn.org)



# Glossary of terms used

**Allele** - any one of a number of viable DNA codings of the same gene occupying a given position on a chromosome. For example, a single gene may control hair colour, but the variations of this gene – alleles – give some people fair hair and others dark hair.

**Autoimmune disease** - a group of disorders that arise when the immune system inappropriately targets the body's own tissues.

**Chromosome** – one of the thread-like structures found in the cell nucleus that carry the genetic information in the form of genes.

**DNA** – the nucleic acid that forms the material of which the chromosomes and genes of almost all living organisms are composed. DNA contains coded instructions for the transmission of genetic information from one generation to the next and for the manufacture of all the proteins that are required for the growth and development of a whole new organism.

**Epidemiological study** - a statistical study on human populations, which attempt to link human health effects to a specified cause.

**Familial cluster** – an aggregation of people with a condition or disease within the same family.

**Genes** - characteristics passed from parents to offspring. Genes are encoded in genetic material, and control physical development and behaviour.

**Genome** – a complete set of DNA. It contains all the genetic instructions to build and maintain an organism.

**Familial aggregation** – grouping of characteristics of a family or its members.

**Haplotype** – a set of closely linked alleles inherited as a unit.

**HLA** - Human Leukocyte Antigens. Proteins found on the surface of cells which allow the immune system to distinguish healthy cells from those that need to be removed. Also referred to as major histocompatibility complex (MHC).

**Human Genome Project** - a map to identify all the genes present in the human genome.

**Immune cells** – cells which help protect the body against infection.

**Immunogenetic** - study of the interrelation between immunity to disease and genetic makeup.

**Immunoglobulin** - one of a group of proteins found in blood plasma that act as antibodies.

**Incidence (of a disease)** - the number of new cases of disease occurring in a population during a defined time interval. The number is useful to epidemiologists because it is a measure of the risk of disease.

**Longitudinal study** – a research study that involves observations of the same subjects over long periods of time, often many decades.

**Phenotype** - characteristics of an organism determined by the interaction between its genotype and environmental factors.

**Polymorphism** - having multiple alleles of a gene within a population.

**Spatio-temporal cluster** – a high number of people with a condition or disease within a defined timeframe or defined geographic area.

**Susceptibility** – the likelihood of an individual to develop a disease or condition.



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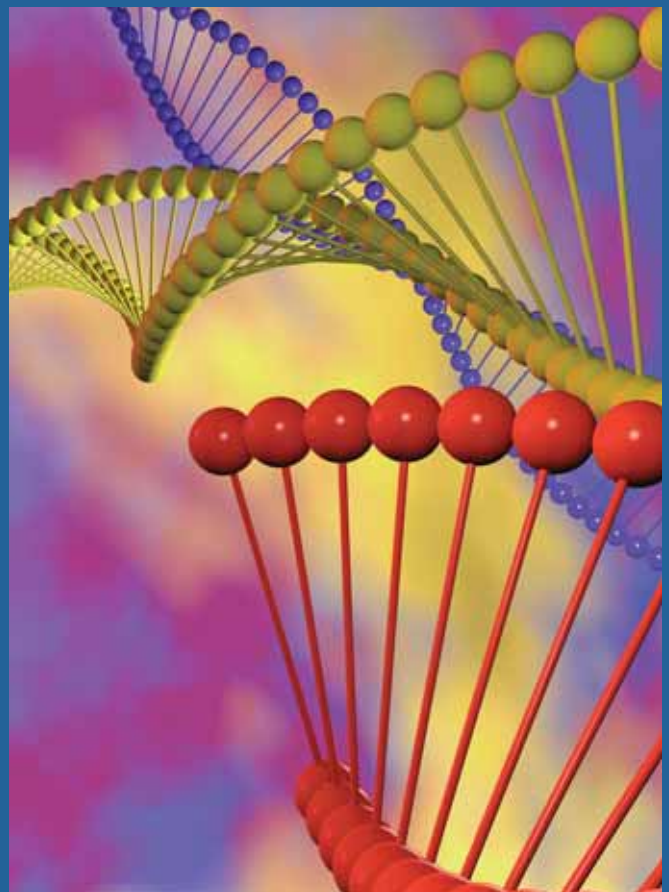
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towards understanding the genetic basis of MS. Serono has a long-term commitment to people with MS through constant research and discovery efforts as we look for new therapies and hopefully, one day, a cure.