



The Path to a Cure **Interview with MS geneticist Jorge Oksenberg**

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Someday there will be a cure for MS. That's a comforting statement, but people with MS and their loved ones want to know more. How far along are we on this path to a cure? What still remains to be done? What are the main obstacles to reaching this goal, and what new technologies, resources, efforts, or collaborations will help us get past them?

To address these important questions, the Boston Cure Project is launching a series of interviews with the creative, determined people working to cure MS. In this first interview, MS geneticist Jorge Oksenberg talks with BCP's Hollie Schmidt about what has been accomplished so far in the search for the genes that cause MS, what needs to be done next, and why finding MS genes is so essential. Jorge is Associate Professor in the Department of Neurology at the University of California, San Francisco. He has been involved in MS research since his post-doctoral work at Stanford University, and his research involves the analysis of genomic and post-genomic factors affecting MS susceptibility and disease course.

You've developed an impressive body of work on the genetics of MS. Can you tell me how you came to choose this field of study?

Early in my scientific training as an immunologist, I was very intrigued by experimental observations suggesting that genetic factors control the strength of the immune response to pathogens. Years later, a Nobel prize was awarded for these discoveries. As my involvement in MS research evolved into a commitment, these early pioneering experiments provided a spark. Could it be that genetic factors alter the "fine tuning" of the immune response resulting in a misguided response against the brain? Indeed, we have overwhelming evidence that MS is a disease with strong immunologic and genetic components. So, I decided then that this is the fundamental MS problem I wanted to study. The timing for focusing on heredity and MS was right. The Human Genome Project was maturing at full speed providing the scientific community with advanced tools for meaningful genetic explorations in diseases like MS. In addition, Stephen Hauser had just moved to San Francisco to lead the Department of Neurology at UCSF, and was developing an extraordinary infrastructure (material and intellectual) that would allow us for the first time to fully address in a rigorous fashion the role of genetic factors in MS. He invited me to join the effort. I gladly accepted because we

share the vision that knowledge of the genetic events leading to MS will create new opportunities – unimaginable today – to prevent, treat and cure this terrible disease.

What are the biggest potential benefits to MS patients from identifying the genes that increase the risk of MS?

Using the analogy of MS pathogenesis as a very complex jigsaw puzzle, genetic research will provide us with the key pieces in the margins and center that will allow us to complete the puzzle. We are certain that genes, the fundamental hereditary units, play a key role in determining who is at risk for developing MS. We also believe that the genes (please note the plural) associated with MS are not themselves abnormal. Rather, they include some subtle but specific structural variations. In fact, some of these variations are common in the population at large and may be advantageous to have. However, in some combinations these normal genes appear to predispose some individuals to develop MS following exposure to an undefined environmental factor or factors. Solving the puzzle will open a wide window into the intricacies of this disease leading to opportunities for developing new therapies or, possibly, a cure.

In addition, our results demonstrate that genes not only influence who is at risk for MS, but also affect clinical features such as age of symptom onset, severity, progression and response to drugs. Our research seeks to identify the genetic variations that explain differences in disease progression or heterogeneity in individual responses to drug therapy. We foresee important implications for this type of investigation. For example, in the future genetic profiling may help the neurologist to match individual patients with tailored therapies and disease management strategies.

Let's review where we currently stand in identifying those genes that increase the risk of someone developing MS. One approach has been to choose a particular gene (a "candidate gene") and see whether that gene differs between people who have MS and those who don't. Another approach is the genome-wide screen approach, where scientists examine markers scattered through the genome to see which regions tend to be different in people with MS. Several genome screens and hundreds of candidate gene studies have been conducted in MS to date. What have we learned from them? Have we ruled any genes definitely "in" or "out?"

First, let me clarify that both types of study designs are not necessarily exclusive or conflicting. The human genome contains approximately 35,000 genes, and from my point of view, every one is a suspect. Given our partial knowledge of disease mechanisms, choosing the right disease gene from so many candidates may not be a promising strategy. The goal of genome scans or screens is to develop a genomic road map to help us determine

where the candidate MS genes are (roughly) located. With this spatial information on hand we can compile a manageable list (in the hundreds rather than in the thousands) of candidate genes and study if and how they work in MS. My good friend and colleague Larry Steinman likes to remind me that we should not continue looking under the same lamp post for the lost keys. The screens aim to illuminate in the genome as many lamp-posts as possible. Either way, these studies are laborious enterprises that require substantial resources, and a very large number of motivated study participants.

What have we learned so far? As I mentioned before we know today that genes not only influence who is at risk or susceptible for MS, but also affect clinical features such as age of symptom onset, severity, progression, and response to drugs. Several of these “disease modifiers” have been already identified, most notably the ApoE gene, which is also a risk factor for Alzheimer’s disease. As for disease susceptibility genes, we do have an extended list in the “definitely out” group, but we may have only one in the “definitely in” group. This is the HLA-DRB1 gene, a master switch of the immune response located in the short arm of chromosome number 6. Many other chromosomal regions harbor disease genes. Each gene contributes only modestly to the overall risk, making them more difficult to find. Fortunately, the genetic trail is getting clear, and we are in hot pursuit.

How do you think this pursuit will play out? What new strategies, technologies and techniques should scientists adopt to speed up the hunt for MS genes?

We need to cover a lot of real estate with respect to the genomic landscape. Therefore, it will be necessary to adopt some of the high-throughput methods invented by the pharmaceutical and high-tech industries in order to reduce costs and increase speed. We also need to develop partnerships between research groups and achieve a critical mass of multi-disciplinary expertise in different fields such as genetics, statistics, mathematics, genealogy, epidemiology, molecular biology, neuropathology, and informatics.

If you could design the ideal experiment to once and for all identify the genes that influence the risk of MS, what would it involve?

I can only design an experiment based on what I know today. This knowledge is incomplete, so the experiment will not be ideal. Nevertheless, I will first try to recruit to the study 5,000 typical MS patients and their parents, I will also ask them to bring a friend, preferably healthy and from the same sex and ethnicity to serve as controls. I will extend recruitment to patients at the tails of the distribution, with mild and rapidly aggressive disease for example,

perhaps 1,000 in each group, and patients with ethnic backgrounds with low prevalence of MS (African-, Asian-, and Latino-Americans). Finally, to complete this extraordinary genetic library, I will send explorers all over the world to find the very rare families in which MS occurred in more than 2 generations. In addition to DNA, I will collect from each patient a wealth of information about their clinical and demographic history. The challenge in the lab will be then to interrogate this genomic collection for MS cues at the highest possible level of resolution with the available technology.

With current technology, this is a multi-million dollars experiment! The extraordinary thing is that a variation of this experiment, not as ambitious, but possibly more practical, may come to fruition soon through an up-and-coming multi-center collaboration. A multi-national consortium has been recently established, representing the US MS Genetics Group (UCSF/Duke/Vanderbilt), the Cambridge, Massachusetts group (Whitehead/MIT/Harvard) and the United Kingdom MS Genetics group (Cambridge, UK), who have come together in order to improve the understanding of MS pathogenesis and to utilize genetic information to realize progress in diagnostic, management and preventative strategies for individuals affected by MS. We hope soon to extend the consortium to other research groups in the world with demonstrated commitment to MS genetics.

What specific projects is this consortium proposing to undertake?

Briefly, we will develop a very large DNA bank (~5,000 patients and their parents), and use a novel research approach called "haplotype mapping" to crack the genetic code of MS. Haplotypes are modules of genetic information that remain together through generations as units or blocks (Most of the genetic material breaks and reorganizes across generations, this is the way to create diversity). This modularization simplifies genetic variation, so rather than having to examine the millions of individual genetic variants found in humans, it may be only necessary to study the common patterns in which these variants are packaged. A separate multinational effort similar to the Human Genome Project is developing haplotype maps for all chromosomes in human populations. As this data is generated, we will apply it (in real-time) to MS. This project may take a few years to complete and will require several million dollars in funding, but represents an exciting opportunity to dramatically expand our understanding of MS.

Overall, what do you expect will be accomplished in the search for MS genes in the next few years?

In the short term, we will have a very good grasp of the genes affecting disease progression. In the mid term we will know most of, if not all, the genes affecting susceptibility. Finally, with the partnership of the pharmaceutical and biotech industries, within a few years we want to see direct diagnostic and prognostic applications of genetic information. Hopefully, we will also see then in the pipeline therapeutic applications derived directly or indirectly from genetic research.

Once scientists find a gene that affects progression or susceptibility, what is involved in turning this knowledge into a new treatment? For example, you mentioned the MS susceptibility gene HLA-DRB1. What are scientists doing (or what could they do) with this particular gene that might lead to a therapy?

Understanding the genetics roots of MS has the potential to uncover the basic mechanisms of the disease, and this knowledge undoubtedly will lead to new and more effective ways to treat the disease. Translating genetic information from the laboratory bench to the bed-side may not be straightforward. 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 then to manipulate or target it because we may be doing more harm than good. On the other hand, if the gene codes for a product that it is less essential for normal physiological function, then we could screen for chemicals or natural molecules that interact with and block or neutralize such a product. We could also develop therapeutic antibodies for example, that upon injection will neutralize the offending product.

The example that you bring (HLA-DRB1) is quite illustrative. We already know for several years that using antibodies engineered to recognize and block these molecules have remarkable therapeutic effects in laboratory models of MS. However, we are hesitant to try them in humans since these HLA molecules are so important in immunological responses. Blocking them may result in impaired defensive responses against infections. On the other hand, the in-depth study of the biology of HLA-DRB1 led to the suggestion of using statins, the cholesterol-reducing drugs, in MS. Clinical trials are underway!

Another potential application of genetic information lies in the development of diagnostic and prognostic kits that will help the neurologist with early diagnosis and to tailor therapies to certain genetic profiles associated with a rapid or slow progression, good or bad response to interferon, etc. I truly believe that we are a few years away from individualized medicine. I just hope our health care system will be "healthy" enough to allow this promise to become a reality.

Q. Is there anything else you'd like our readers to know about current MS genetic research?

Yes, I would like them to know that our short-, medium- and long-term objective is to reduce the impact of multiple sclerosis – to apply the fundamental knowledge we acquire to improve our capacity to prevent, diagnose, treat and cure MS. We understand that the urgency of developing successful interventions is paramount; progress may look slow at times, but it is steady and promising.

I also want to let your readers know that without the participation of hundreds of patients and their relatives, this undertaking would not be possible. Their willingness to participate has been remarkable and we are grateful for their commitment. The Human Genome Project has heightened public awareness of the potential benefits of genetic research along with concerns about access to personal genetic information and how it will be used. We are very sensitive to such concerns and have always maintained strict research guidelines to protect privacy. At all times, records and other information that is shared with investigators are handled in a confidential manner. Blood samples are coded with a number and any data obtained from the study never has names or any identifiable characteristics attached. Databases with clinical and demographic information are password protected, with only authorized and trained personnel having access to this information. Our research is regulated and reviewed once a year by an Institutional Review Board, which was established to protect the rights of study participants. It is very important to us to maintain the trust that study participants have placed in our research.