Genomic map implicates broad immune cell involvement in multiple sclerosis

26 September 2019

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The International Multiple Sclerosis Genetic Consortium (IMSGC) reports the results of its latest study, "Multiple sclerosis genomic map implicates peripheral immune cells and microglia in susceptibility", in the journal *Science* today: the highly productive collaborative group presents a new milestone in its efforts to understand the genetic basis of multiple sclerosis (MS). In a study of 115,803 individuals, the authors have identified 233 sites or loci in the human genome that contribute to the onset of MS. This is the largest study to date in MS and is based on the generous contribution of genetic material from 47,429 MS patients and 68,374 healthy individuals. The study's results confirm earlier results and offer a rich new perspective on the molecular events that lead some individuals to develop MS: it appears that dysfunction of many different immune cell types, both in the peripheral blood and the brain, contribute to triggering a cascade of events that ultimately leads to brain inflammation and neurodegeneration.

Dr. Philip De Jager, who directs the Multiple Sclerosis Center and the Center for Translational & Computational Neuroimmunology at Columbia University Irving Medical Center in New York City, and the principal investigator of the study says that "the study has created a detailed genetic map of MS, identifying over two hundred regions of the human genome that influence a large number of different immune cells, highlighting the fact that this disease is not caused by a single immune cell type but rather by a broad dysfunction of the immune system." MS has an initial inflammatory component and a secondary neurodegenerative component, so the investigative team looked closely at available data from human brain to assess whether changes in brain cells contribute to the onset of MS. Until now, it appeared that immune cells found in blood that come from the bone marrow played a critical role; the new study confirms this but also implicates microglia, the immune cells that live in the human brain. However, there is little evidence that other brain cells such as neurons that carry electrical signals in the brain are implicated in triggering MS.

Dr. Nikolaos Patsopoulos, Director of Systems Biology and Computational Science Program at the Ann Romney Center for Neurologic Diseases of Brigham & Women's Hospital and Harvard Medical School in Boston, says that "our study explains approximately half of the heritability of MS, establishing MS as one of the well-characterized common diseases in terms of their genetic architecture". He adds that "this study highlights the complexity of the genetic contribution to MS susceptibility by identifying several regions of the genome with multiple genetic variants that play a small role. Further, we report the first ever association of genetic variant in chromosome X with MS, a disease that affects mainly young women. This study more than doubled our knowledge of MS genetics, however our findings

suggest that there is more work to be done to fully understand how the human genome is involved in MS."

Dr. Tomas Olson, an author on the study from the Karolinska Institute in Stockholm, Sweden says that "this collaborative effort integrated multiple streams of North American and European funding to establish an important foundation for future projects that will uncover the sequence of events leading from health to MS. These genetic variants are not sufficient to cause MS; they interact with a host of environmental factors, making it more likely that a viral infection or other exposure triggers an autoimmune reaction against the brain and spinal cord."

Dr. Adrian Ivinson, Chief Operating Officer of the UK Dementia Research Institute who is also an author of this study adds that "this study reflects the combined, collaborative efforts of the international MS Genetics community to advance our understanding of MS disease mechanisms and the continuing support of the National MS Society in the completion of this project, the development of young investigators and support for basic research in MS. It is an excellent example for the success of collaborative team-oriented science in medicine."

This study is an important milestone in identifying which genetic variants play a role in triggering MS, but it unfortunately does not clarify why some MS patients have a more severe course than others. The IMSGC is pursuing that question in other projects. The results of this project will impact most the development of clinical algorithms to manage individuals at risk of developing MS and the development of treatments for preventing MS. All current treatments aim to stop the inflammation after it has already started, so the study of MS genetics has opened a unique perspective on the earliest events that lead to the disease and that can now be targeted by drug-development efforts.

The Columbia University Multiple Sclerosis Center provides compassionate care for MS patients, and we engage with our our patients to perform both basic research that brings new insights into our understanding of the disease and clinical research that brings the latest technologies and medications with which to improve our management of each patient. This is study is an example of Columbia's leadership of international collaborations in the field of MS and of the emerging foundation for Precision Medicine in MS.

More information: "Multiple sclerosis genomic map implicates peripheral immune cells and microglia in susceptibility" *Science* (2019). science.sciencemag.org/cgi/doi … 1126/science.aav7188

Provided by Columbia University Irving Medical Center