Genetic marker for drug risk in multiple sclerosis offers path toward precision medicine

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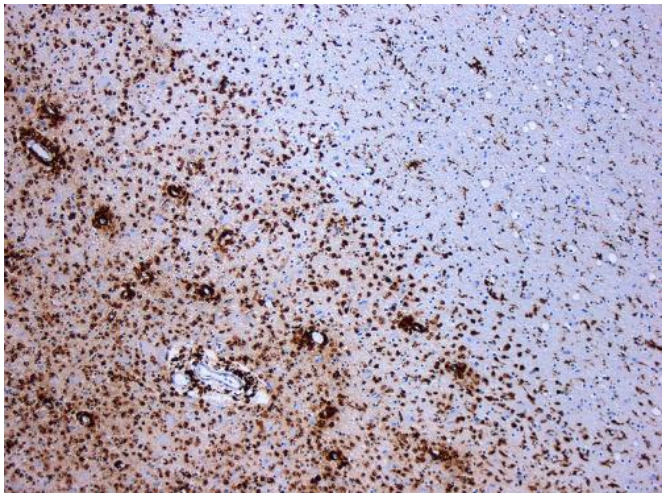

Demyelination by MS. The CD68 colored tissue shows several macrophages in the area of the lesion. Original scale 1:100. Credit: CC BY-SA 3.0 Marvin 101/Wikipedia

A team of researchers has uncovered a specific gene variant associated with an adverse drug reaction resulting in liver injury in a people with multiple sclerosis (MS). It is the first time researchers have been able to establish a validated genetic marker for a drug-induced harm in people with MS.

Published July 16 in the journal *Nature Genetics*, the findings inform a broader understanding of genetic risk of drug reactions in MS and may lead to clinically useful tests for more individualized approaches to MS treatment and care.

MS rates in Canada are the highest in the world, and the disease affects an estimated 100,000 Canadians. Most people diagnosed with MS are young adults between the ages of 15 and 40 but the disease can also be diagnosed in young children and older adults. MS results from the body's immune system attacking myelin, the fatty material that insulates neurons and enables rapid transmission of electrical signals. When myelin is damaged, communication between the brain and other parts of the body is disrupted, leading to vision problems, muscle weakness, difficulty with balance and coordination, and cognitive impairments.

"One in 50 people with MS who are treated with interferon-beta, one of the most commonly prescribed MS therapies, will develop abnormally high levels of liver enzymes," said Dr. Kaarina Kowalec, a Marie Curie postdoctoral fellow at Sweden's Karolinska Institute and co-lead author of the new study.

Liver injury is a common side effect of many drugs, but this is the first time researchers have connected a genetic marker with a biologic drug and elevated risk of liver injury. Currently people with MS have their blood monitored for increased liver enzymes, which can indicate potential injury.

Dr. Kowalec conducted her Ph.D. research at the University of British Columbia under the supervision of Dr. Helen Tremlett at the Djavad Mowafaghian Centre for Brain Health and Dr. Bruce Carleton at BC Children's Hospital.

"Risk of liver injury increases eight fold with this marker. It's important that we be able to understand who might be most at risk so that we can intervene with an altered treatment plan or increased monitoring to prevent liver damage," said Dr. Carleton.

Interferon-beta is a first-generation MS drug that is prescribed to treat the relapse-remitting form of the disease. The biologic drug works with an

individual's own interferons—naturally occurring molecules—that exist in the body to reduce inflammation.

"There's a lot of talk about precision medicine, and whether it can work as well as we hope," said Dr. Kowalec. "Pharmacogenomic testing is a big part of that and we're showing that it is possible. It's something that's been done outside for cancer therapies but now we've shown that there's potential for precision medicine in MS as well."

"We often can't determine a person's individual risk for a future adverse drug event very well; that was the case for liver injury in MS, until now," said Dr. Tremlett. "We achieved this by looking for genetic markers. Many were skeptical we would find anything, but we did, and part of what we've done here is set out the methods for other researchers to pursue a similar line of work with the other drugs for MS."

"With more therapeutic options for multiple sclerosis becoming available, identifying predictive biomarkers for drug safety is of increasing importance," said Dr. Galen Wright, co-first author and postdoctoral researcher in Dr. Michael Hayden's lab at the Centre for Molecular Medicine & Therapeutics at UBC. "As highlighted by the findings of our study, genomics can play a leading role in this regard."

The genetic marker was identified with the help of 150 patients from five Canadian clinics and then validated in 120 patients from three sites in the U.S. and one in Sweden.

"This is the kind of research that makes drugs safer," said Dr. Kowalec. "We are now looking at newer MS drugs and taking a similar approach so that one day, genetic risk may factor into how we diagnose, treat and monitor people with MS in Canada and around the world."

More information: Kaarina Kowalec et al, Common variation near IRF6 is associated with IFN-?-induced liver injury in multiple sclerosis, *Nature Genetics* (2018). DOI: 10.1038/s41588-018-0168-y

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