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Gene variant explains racial disparities in adverse reactions to urate-lowering drug

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A multi-institutional study led by a Massachusetts General Hospital (MGH) investigator finds significant racial disparities in the risk that patients being treated for gout will develop a serious, sometimes life-threatening adverse reaction to the most commonly prescribed medication. The increased risk closely correlates with the frequency of a gene variant previously associated with that adverse reaction, supporting recommendations to screen for that variant in patients from those populations.

"We found that Asian and black patients have a substantially higher risk of severe cutaneous adverse reactions to urate-lowering drugs than do white or Hispanic patients, which correlates with the frequency of the HLA-B*5801 gene in their U.S. populations," says Hyon K. Choi, MD, DrPH, of the MGH Division of Rheumatology, Allergy and Immunology, senior author of the report that has been published online in *Seminars in Arthritis and Rheumatism*. "This risk is almost certainly due to allopurinol, the dominant urate-lowering drug in the U.S., and screening gout patients from those populations for the HLA-B*5801 variant could help increase treatment safety."

Caused by excessive levels of uric acid in the body, gout involves the deposition of uric acid crystals in the joints, leading to inflammation and significant pain. Treatment can involve dietary changes - including reduced protein intake and alcohol consumption - anti-inflammatory and pain-relieving drugs, as well as urate-lowering medications. More than 95 percent of U.S. prescriptions for such drugs are for allopurinol.

Severe cutaneous reactions to allopurinol - which are called toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) - are rare, but can be extremely serious. In TEN, overwhelming inflammation causes the outer layer of skin to separate from the underlying layers, leaving the body open to severe infections. SJS/TEN can be fatal more than 30 percent of the time and may involve other major organs, potentially leaving survivors with long-term damage to the kidneys or eyes.

Studies have associated the HLA-B*5801 variant with the risk of these reactions in particular Asian populations - Koreans, Japanese, Thai and Han Chinese - and in some Europeans; and the current study was designed to investigate whether the frequency of the HLA-B*5801 variant across races leads to significant racial disparities in the risk of severe cutaneous reactions to urate-lowering drugs in a representative U.S. population. The researchers examined data covering 2009 to 2013 from the Nationwide Inpatient Sample of the Agency for Healthcare Research and Quality.

From that database of between 5 and 8 million hospitalizations each year, they identified 606 with a principal diagnosis of SJS/TEN related to an adverse reaction to urate-lowering drugs. While the database does not include information on specific medications, the frequency with which allopurinol is prescribed implies that most, if not all, of those reactions involved that drug, the authors note.

Among patients with that diagnosis, there was a significant over-representation of Asian and black patients compared with whites. For example, while another database indicates that Asian patients represented only 2 percent of U.S. allopurinol users in 2011-12, they represented 27 percent of those hospitalized for SJS/TEN related to urate-lowering drugs. Black patients represented 13 percent of allopurinol users and 26 percent of hospitalizations, while white patients

represented 81 percent of allopurinol users but only 29 percent of hospitalizations. The number of Hispanic patients in the hospitalization database with this diagnosis was extremely small.

Overall the risk of these dangerous reactions was 12 times higher for Asian patients and 5 times higher for black patients compared with white patients. Those differences are closely aligned with the frequency of the HLA-B*5801 variant in those populations - a 7.4 percent frequency in Asians, 4 percent in blacks, and 1 percent in both whites and Hispanics.

"Since no other urate-lowering drug is an established cause for these severe adverse reactions, our findings support the use of vigilance when considering allopurinol for Asian and black patients with gout," says Choi, who is a professor of Medicine at Harvard Medical School. "Right now, we recommend testing for the HLA-B*5801 variant among those patients, and further research may help to identify additional factors that can improve risk management. It should also be noted that our findings apply almost exclusively to patients who are starting allopurinol, since nearly all of these severe adverse events occur during the first three to six months of treatment. Patients who have been tolerating allopurinol after the initial few months almost certainly do not have to worry about these reactions."

More information: Na Lu et al. Racial Disparities in the Risk of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis as Urate-Lowering Drug Adverse Events in the US, *Seminars in Arthritis and Rheumatism* (2016). DOI: 10.1016/j.semarthrit.2016.03.014

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