International team of scientists discover link between genes and penicillin allergy using

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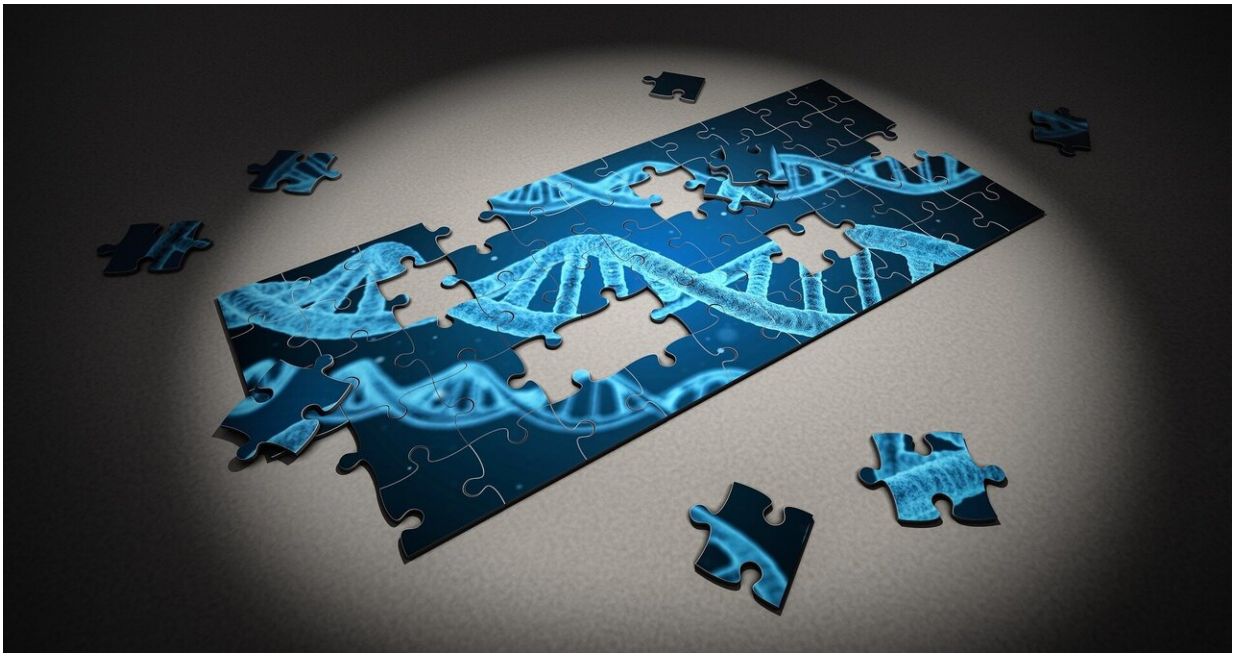

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Penicillin, a life-saving medicine, is the most common cause of drug allergy, with clinical manifestations ranging from temporary skin reactions to life-threatening systemic syndromes. Thus far, genetic factors have only been found for rare severe allergic reactions to penicillin. However, less is known about the genetics behind milder forms of penicillin hypersensitivity reactions that occur in a larger

proportion of the population.

A collaborative effort by scientists from the Estonian Genome Center, University of Tartu, Statens Serum Institut, University of Oxford, Vanderbilt University Medical Center, Harvard Medical School, Broad Institute of MIT and Harvard, and 23andMe sought to identify genetic risk factors underlying penicillin-induced hypersensitivity reactions by harnessing self-reported data and the electronic health records of more than 600,000 participants of European ancestry from the UK Biobank, Estonian Biobank and Vanderbilt University Medical Center's biobank (BioVU).

The genome-wide association study (GWAS) of self-reported penicillin allergy in the different biobanks revealed a locus located in the major histocompatibility complex (MHC) I gene HLA-B. Fine-mapping of the association narrowed the signal down to the HLA-B*55:01 allele, which was further confirmed by independent replication in 23andMe's research cohort. Overall, carriers of the allele were found to have a 33% higher relative odds of penicillin allergy. The study also detected a genome-wide significant missense variant in the PTPN22 gene. This variant has been associated with several autoimmune diseases and more recently with drug-induced liver injury.

Dr. Kristi Krebs, first author of the study, said, "When examining other conditions associated with the HLA-B*55:01 allele, we found a significant association with lower white blood cell counts. Further, the top hit overlapped with regions found to have regulatory function in T-cells and correlated with the expression levels of PSORS1C3, which has previously been associated with hypersensitivity reactions to several medications. These findings together raise the possibility that the variant may predispose to a T-cell-mediated process leading to a delayed penicillin reaction."

Dr. João Fadista, one of the lead authors of the paper, further shared that "a genome-wide genetic correlation analysis of the self-reported penicillin allergy results revealed overlap with the autoimmune diseases rheumatoid arthritis and psoriasis. This, together with the finding in the PTPN22 gene, indicates a possible underlying autoimmune factor in the development of penicillin allergy investigated in our study."

Prof. Lili Milani, one of the lead authors of the paper, emphasized the power of biobanks. "We have leveraged data from four large-scale cohorts, including more than 100,000 cases, to provide insights into the genetic architecture associated with self-reported penicillin allergy, and provide robust evidence implicating the HLA-B*55:01 allele and autoimmune factors in this condition. Further studies are necessary to determine the precise underlying immune processes and how these change over time, as several studies have reported that a large proportion of patients labeled as allergic to penicillin develop tolerance over time."

More information: Kristi Krebs et al, Genome-wide Study Identifies Association between HLA-B∗55:01 and Self-Reported Penicillin Allergy, *The American Journal of Human Genetics* (2020). DOI: 10.1016/j.ajhg.2020.08.008

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