Rare VEXAS disease affecting only men is found to be more common than first thought

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A rare disease first identified in 2020 is much more common than first thought, say researchers at the University of Leeds investigating its origins.

VEXAS syndrome is a serious inflammatory condition which develops in men over 50, causing them to become very sick and fatigued, and can be fatal. It was originally thought to be rare, but a new study has identified genetic mutations which indicate that the disease is actually much more common.

The researchers developed a genetic test to identify patients who may have the disease, and now want to screen more people showing symptoms to understand exactly how common it is.

VEXAS syndrome causes unexplained fevers, painful skin rashes and affects the bone marrow resulting in a reduced number of red and white blood cells. The disease affects only men because it is caused by genetic mutations on the X chromosome, and men carry only one X chromosome. The mutations are not present at birth, instead they develop during the patient's lifetime.

The disease was identified in 2020 by a team of researchers which included Dr. Sinisa Savic, Clinical Associate Professor at the University of Leeds' School of Medicine and Honorary Consultant immunologist at Leeds Teaching Hospitals NHS Trust. Now, further research led at Leeds by Dr. Savic and Dr. James Poulter, Academic Fellow in Molecular Neuroscience in the School of Medicine, has identified additional genetic mutations which show new ways in which the disease can develop.

The team, which included 13 academics and clinicians from Leeds, Hull, York and the US, examined DNA samples to establish the prevalence of the genetic mutations identified when the disease was first discovered.

Dr. Poulter said: "In our new study, we screened a cohort of 18 local patients who matched the symptoms and found mutations in 10 of them. Eight had the known variant previously associated with the disease, but two patients had completely different variants. This identified a new way in which the mutations can cause VEXAS, meaning it is likely to be much more common than we currently think.

"We want to screen more people with these symptoms to really understand how common VEXAS is and to better understand the disorder.

"Most patients have had lots of tests, tried lots of treatments and have not been able to get an answer to what they have. Now, by sequencing their DNA for mutations in the VEXAS gene, we can identify those patients who do have VEXAS and get them on the best treatment that is available. This could be a bone marrow transplant or switching to a different drug."

Dr. Savic runs a specialist Allergy and Clinical Immunology service at the Leeds Teaching Hospitals NHS Trust. It is one of four centers in the UK to be part of the European Reference Network for rare immunodeficiencies, autoinflammatory and autoimmune disorders.

He said: "I have been looking after a number of patients with what we now know is VEXAS syndrome for several years. Their care has been complicated by the fact that we did not have a diagnosis which made choosing their treatment and advising them about the prognosis very difficult.

"Having established the cause of VEXAS we now have a real opportunity to transform the care of these patients. We know there are still many patients who have a VEXAS-like condition, but in whom we do not know the cause. We plan to continue our research in the hope of discovering other genetic causes of these disorders."

More information: James A Poulter et al, Novel somatic mutations in UBA1 as a cause of VEXAS syndrome, *Blood* (2021). DOI: 10.1182/blood.2020010286

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