Modern genetics answers age-old question on Garrod's fourth inborn error of metabolism

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Fifty years after participating in studies of pentosuria, an inherited disorder once mistaken for diabetes, 15 families again welcomed medical geneticists into their lives. Their willingness to have their DNA analyzed with advanced genomics technologies has solved a mystery more than a hundred years old.

Researchers from the University of Washington, Israel, and Switzerland reported the solution in the Oct. 31 Early Edition of the Proceedings of the National Academy of Sciences.

Their findings may help elucidate historical and geographical patterns of genetic mutations -- when and how human mutations appear and are carried over generations and with migration of human populations.

Pentosuria occurs almost exclusively in Ashkenazi Jews, whose ancestors trace back to the Middle Ages in Central or Eastern Europe. Traditionally, Ashkenazi Jews have married within their religious and ethnic group.

Dr. Arno Motulsky, professor emeritus of medicine, Division of Medical Genetics, and of genome sciences at the UW, and one of the founders of the discipline of medical genetics, was the senior author of the study. He was among the geneticist sleuths who tracked down the families and the genetic mutations responsible for the metabolic condition that ran in their families.

In the early and mid 20th century, clinical testing methods did not distinguish between pentosuria and diabetes mellitus. The confusion resulted in potentially dangerous treatment errors.

Diabetic patients have problems with increased levels of glucose, a six-carbon sugar, whereas pentosuria causes high levels of a five-carbon sugar, xylulose, in urine and blood. Pentosuria itself is completely harmless. But when pentosuria patients were misdiagnosed with diabetes and received insulin, their blood glucose levels plummeted and they suffered insulin reactions.

The diagnostic errors motivated New York City biochemist Margaret Lasker to devise an accurate urine test for the five-carbon sugar that is characteristic of pentosuria. This test, and accurate tests for glucose in the urine, resolved the issue.

"People with pentosuria, which needs no treatment, no longer came to clinical attention," Motulsky said.

Lasker also conducted extensive family pedigree and survival studies of people with pentosuria. She concluded that pentosuria, which has no effect on lifespan and no clinical symptoms, was inherited as an autosomal recessive condition: a person had to inherit a causative gene sequence from both parents to have the disorder.

Pentosuria remained the last of Garrod's four inborn errors of metabolism for which the responsible DNA mutations were unknown. In 1904 Dr. Archibald Garrod of the Royal College of London had introduced the idea that certain inherited metabolic conditions were caused by a disease-specific genetic error.

Garrod surmised that the mutation disrupted a specific chemical reaction. He gave as examples albinism, cystinuria, alkaptonuria, and

pentosuria. The underlying mutations for three of these traits have since been discovered.

By 2002, researchers had identified the gene that codes for the enzyme that normally rids the body of excess xylulose. Still no mutations were identified in pentosuria.

However, in the course of sequencing DNA, the UW genomics laboratory of Dr. Mary-Claire King serendipitously discovered a deletion in this gene in an individual of Ashkenazi Jewish background. King is a professor of medicine, Division of Medical Genetics, and of genome sciences at the UW.

King and Motulsky hypothesized that, because the mutated gene led to a protein missing about 50 amino acids, it couldn't produce the right sugar-busting enzyme.

King, Motulsky, their team, and colleagues from Israel and Switzerland set about to determine whether this mutation caused pentosuria. Other UW researchers involved in the study were Sarah Pierce, Cailyn Spurrell, Ming Lee, and Sunday Stray of the Department of Genome Sciences and the Division of Medical Genetics, Department of Medicine; Jessica Mandell of the Division of Medical Genetics, and Michael MacCoss and Michael Bereman of the Department of Genome Sciences.

The problem in connecting the mutation to pentosuria was that people with the condition were no longer identified in their doctors' offices. Current urine tests do not check for this trait.

Fortuitously, before her death in 1976, Lasker had entrusted Motulsky with her extensive research archives on the disorder. She had hoped that in the future Motulsky or his colleagues might be able to carry out new

studies to determine the genetic cause of pentosuria.

Motulsky called and wrote to the families named in the Lasker records. Participants with pentosuria from the original studies or the children of deceased individuals with pentosuria agreed to the new study. Fifteen families enrolled.

Genetic analysis of DNA samples from the families led to the discovery of two different DCXR mutations linked to loss of function of the xylulose-breaking enzyme. In nine unrelated people with pentosuria, six had one type of mutation, one had the other, and two had both. None had the active enzyme in question in their blood cells, and all had high levels of xylulose in their blood. This confirmed the relationship between the mutations and the metabolic error.

Studies of the frequency of the two mutations in 1,067 Ashkenazi Jews showed that one mutation is more common than the other and suggested that pentosuria occurs in about 1 in 3,330 people of this ancestry. Pentosuria has also been found in a large Lebanese family, a Japanese family, and an Athabascan Canadian Indian in British Columbia, but the mutations in these individuals are not known.

The frequency of the two DCXR mutations causing pentosuria in Ashkenazi Jews follows a pattern of other rare recessive mutations in this population. The Israeli National Genetic Database shows that for most of the "Jewish genetic diseases", including Tay Sachs disease, Canavan syndrome, maple syrup urine disease and Gaucher disease, two or more mutations in the same gene have been found, with one mutation more common than the other, according to the researchers.

For conditions like cystic fibrosis and a certain inherited hearing loss that are common in Jews and other groups, two or more mutations in the same gene have been discovered, with the more common mutation found

throughout Europe and the less common one specific to the European Jewish population.

Other studies have suggested that many of the "founder" mutations for Ashkenazi Jewish genetic diseases date back to three time periods: the expansion of the Jewish population in the Middle East about 100 generations ago, the entry of the Jewish population into Central Europe about 50 generations ago, and their movement into Lithuania and the Pale of the Settlement about 12 generations ago. (A human generation is about 30 years).

"It will be interesting to determine the ages of the newly identified pentosuric mutations relative to Jewish history in Europe," the researchers on the current PNAS paper noted.

Although previous studies of pentosuria indicate that it is entirely benign, animal studies on the DCXR enzyme suggest that mutations that result in a loss of enzyme function could play a role in kidney damage. If so, patients with both pentosuria and diabetes could be more susceptible to diabetic kidney disease.

More information: "Garrod's fourth inborn error of metabolism solved by the identification of mutations causing pentosuria," *Proceedings of the National Academy of Sciences.*

Provided by University of Washington