Genetic Score Could ID Patients With Gout Risk

BY KERRI WACHTER
Senior Writer

A new genetic risk score for gout, based on three recently identified genes believed to be involved in renal urate transportation, could help physicians identify patients with asymptomatic hyperuricemia and guide therapy, according to a study reported online in the Lancet on the Oct. 1.

"Our genetic risk score was associated with up to 40-fold increased risk of developing gout, which is substantially higher than for environmental risk factors, suggesting that knowledge of genotype could help identify individuals at risk of developing gout long before the onset of clinical features of the disease," wrote Dr. Abbas Dehghan of the Erasmus Medical Center in Rotterdam, the Netherlands, and coauthors from both the United States and the Netherlands (Lancet 2008 Oct. 1[doi:10.1016/S0140-6736(08)613-4]).

The researchers used phenotype and genotype results from a cohort of the Framingham Heart Study and a Rotterdam cohort to identify genetic loci associated with uric acid concentration and then replicated the findings in a third population-based study, the Atherosclerosis Risk in Communities (ARIC) study. The single nucleotide polymorphisms (SNPs) they identified as being associated with uric acid concentration were tested next for association with gout. These results were then replicated using genetic samples from the ARIC study. Finally, they developed the additive gout risk score of high-risk alleles at the three loci identified.

The researchers identified two new loci, ABCG2 and SLC17A3, that show an association with uric acid concentration and risk of gout. In addition, they confirmed the previously reported association of SLC2A9 with uric acid and gout in white individuals and extended the findings to black individuals.

The Framingham cohort study involved three generations of participants, who underwent examinations every 2 years to identify cardiovascular diseases and their risk factors. Almost all were self-identified as white. The Rotterdam cohort study is a prospective, population-based study of determinants of several chronic diseases in individuals older than 5 years. All participants were residents of the Ommoord district of Rotterdam and underwent periodic examination. ARIC is an ongoing population-based study in four U.S. communities. White and black participants aged 45-64 years were recruited and underwent examination roughly every 3 years.

'Our genetic risk score was associated with up to 40-fold increased risk of developing gout, which is substantially higher than for environmental risk factors.'

In the Framingham cohort, uric acid concentration was measured at the first examination cycle. Gout was self-reported in the offspring and third-generation cohorts. In the Rotterdam cohort, uric acid concentration was measured at baseline. Individuals treated with drugs exclusively prescribed for gout were regarded as gout patients, based on pharmacy records. In the ARIC study, uric acid concentration was measured at visit one. Gout was identified by self-report at visit 4.

Genotyping of the Framingham cohort was performed for 9,274 participants, and the final sample size was 7,699. Genotyping for the Rotterdam cohort was done for 6,680 participants, with a final sample size was 5,974.

In the ARIC study, the central DNA laboratory genotyped SNPs rs16890979, rs2231142, and rs1165205 individually for 11,024 white participants and 3,843 black participants.

SNPs in SLC2A9 have previously been identified as having an association with uric acid concentration and were connected with low renal fractional excretion of uric acid (the most common cause of hyperuricemia). Three loci had SNPs that reached genome-wide significance in the Framingham cohort. For each locus, the most significant SNPs were rs16890979 (a missense SNP in SLC2A9), rs2231142 (a missense SNP in ABCG2), and rs1165205 (intron 1 of SLC17A3). Similarly, two loci showed genome-wide significance in the Rotterdam cohort: rs6449213 (intron 4 of SLC2A9) and rs2231142.

Both rs6449213 and rs2231142 were strongly associated with uric acid concentration in white and black participants; rs1165205 was strongly associated with uric acid in white participants only. The missense SNP rs16890979 in SLC2A9 has the strongest association with uric acid concentration and gout. In addition, rs16890979 explained the largest variation in uric acid concentration, ranging from 2.8% to 5.3% in white participants across studies; rs16890979 was associated with gout in white individuals from all three studies. Results showing significance were also seen for rs2231142, rs1165205, and rs6449213. In black individuals, only rs2231142 showed a marginal association with gout.

In the Framingham cohort, only rs2231142 remained associated with gout after adjusting for uric acid (odds ratio 1.57, $P = .0053$). No SNPs in the Rotterdam cohort were significant after adjustment for uric acid. Substantial attenuation of the genotypic effect for all three loci on gout risk was seen after adjustment for uric acid in the ARIC group.

A genetic risk score was generated for every individual by counting the number of alleles associated with high uric acid concentration (rs16890979 C, rs2231142 T, and rs1165205 A; range 0-6). Mean uric acid concentration increased linearly with the number of risk alleles. For individuals with no risk alleles, the crude prevalence of gout was 1%-2% across studies and increased to 8%-18% with six risk alleles. "Although individual common genetic variants confer a modest risk of gout, their combination resulted in a large association with uric acid and gout," they wrote.

The study was funded by the Netherlands Organisation for Scientific Research and the National Heart, Lung, and Blood Institute. The authors reported that they had no conflicts of interest. ■

Don't Neglect Foot Pain and Deformity in Psoriatic Arthritis

BY BRUCE JANCIN
Denver Bureau

PARIS — When it comes to psoriatic arthritis, don't forget the feet.

The foot is a neglected area of the body in patients with psoriatic arthritis. The burden of foot pain and deformity is high and the level of foot care provision is low, Deborah E. Turner, Ph.D., reported at the annual European Congress of Rheumatology.

A big part of the reason the feet of psoriatic arthritis patients are underassessed clinically is that the disease activity measures widely used in both clinical practice and research ignore the foot, according to Dr. Turner of Glasgow (Scotland) Caledonian University.

She reported on an unselected series of 88 consecutive psoriatic arthritis patients at Glasgow Royal Infirmary who underwent a clinical foot examination by a podiatrist. Two-thirds of the patients reported chronic foot pain; in most cases, the medical team was unaware of the problem because nobody had ever asked.

"Patients generally don't tend to offer this information. They'll mention other areas—the hand, the spine—but not the feet," Dr. Turner observed.

On clinical examination, 30% of the cohort had plantar fasciitis and 24% had Achilles tendonitis. These are probably marked underestimates of the true prevalence of pathology at these sites, as ultrasound studies have shown that roughly three-quarters of psoriatic arthritis patients are affected.

A novel finding reported for the first time in this study was that 40% of the psoriatic arthritis patients had inflammatory involvement of the posterior tibial tendon.

Of 88 consecutive psoriatic arthritis patients who underwent a foot examination by a podiatrist, two-thirds reported chronic foot pain.

"While it's not a classical enthesis, it is categorized as a functional enthesis because it has an element of fibrocartilage under the tendon at the point at which it goes over the malleolus," she continued.

Joint tenderness was detected in one or more of the metatarsophalangeal joints of nearly half of subjects, while the interphalangeal joints were affected in one-third.

A striking finding in the study was the very high prevalence of flat feet in the patients with significant foot pain. Why should psoriatic arthritis be strongly associated with a low arch profile? The working hypothesis is that a combination of inflammation of tendons and in the joints around the ankle and rear foot leads to weakened foot ligaments, which then stretch under the stress of weight bearing, resulting in flattening of the arch. This theory requires confirmation in planned follow-up imaging studies utilizing MRI and ultrasound, Dr. Turner said.

She added that foot problems are often one of the earliest features of psoriatic arthritis. A common scenario in young patients participating in sports is that months before they receive the diagnosis of psoriatic arthritis, they develop Achilles tendonitis and/or plantar fasciitis, which are misinterpreted solely as chronic overuse athletic injuries.

Mean scores on the Leeds Foot Impact Scale impairment and activity limitation subscales in the Glasgow psoriatic arthritis cohort were similar to those typically associated with rheumatoid arthritis.

"A lot of attention is given to foot problems in rheumatoid arthritis, but we found the overall burden of foot problems in terms of how much they contribute to the patients' disability was as high for patients with psoriatic arthritis as for those with rheumatoid arthritis," Dr. Turner said in an interview.

Nevertheless, only one-quarter of study participants had received conservative foot care.

The standard podiatric treatment for painful flat foot deformities is the use of a rigid arch support. As part of Dr. Turner's ongoing research project funded by the Arthritis Research Campaign, she plans to see whether correcting the abnormal foot mechanics in psoriatic arthritis patients improves their inflamed lower extremity joints and tendons.

She stressed that detecting foot problems in psoriatic arthritis patients is a straightforward matter for physicians regardless of whether they are rheumatologists, dermatologists, or primary care physicians. All they have to do is look for them.

"It's a matter of assessing the key structures for tenderness and swelling, as is part of the routine assessment procedures they do elsewhere on the body. If they note that the patient has a low arch profile and the heel is not vertical and is collapsed, they can send the patient off to a podiatrist for treatment," Dr. Turner said. ■