

Absence of *SLC22A12/URAT1* Gene Mutations in Patients with Primary Gout

To the Editor:

In most patients with primary gout, hyperuricemia has been related to a decreased urinary uric acid excretion, but the specific gene abnormalities that may cause an impaired tubular transport of urate are unknown. The first urate transporter described was *SLC22A12/URAT1*¹. Mutations in the *SLC22A12/URAT1* gene have been associated to primary renal hypouricemia type I (OMIM 220150) in several populations^{1,2,3,4,5}, although some ethnic differences may explain the lack of association between this gene and primary renal hypouricemia in other populations such as Greek whites⁶. Because this transporter reabsorbs urate from the renal tubule, loss of function mutations may cause renal urate wasting and hypouricemia. However, it has been reported that among 69 Mexican patients with primary gout, 16 (23%) showed 6 different *SLC22A12/URAT1* mutations⁷. Could these mutations explain hyperuricemia due to impaired renal uric acid excretion? Although none of these mutations was segregated in the 240 chromosomes of healthy individuals⁷, no study has confirmed or refuted *SLC22A12/URAT1* mutations in patients with gout, and it is uncertain whether an enhanced tubular reabsorption of urate may cause hyperuricemia. Notably, one of these mutations has also been associated with primary renal hypouricemia type I⁷.

In an extensive series of white patients with primary gout, we have determined whether the previously reported *SLC22A12/URAT1* gene mutations in Mexican patients with gout, or other mutations in this gene, could explain their increased serum urate concentrations.

Seventy-seven patients with primary gout according to Wallace, *et al*⁸ criteria and who had had at least 2 acute gouty arthritis episodes were studied at the metabolic and vascular unit of La Paz University Hospital, Madrid, Spain. All studies were conducted according to the Declaration of Helsinki, and were approved by the Institutional Research and Ethics Review Committees of La Paz University Hospital. Among the 77 patients with gout, 73 were men (95%). Their mean age (\pm SD) was 59.8 ± 9.1 years. Mean serum urate concentration was 8.2 ± 1.5 mg/dl and 24-h uric acid excretion was 455 ± 111 mg/24 h/1.73 m². All patients exhibited a decreased urinary uric acid excretion rate, according to their increased serum urate levels⁹.

RNA-free genomic DNA samples from patients with gout were isolated from whole blood, and the 10 exons of the human *SLC22A12/URAT1* gene were amplified by polymerase chain reaction with the gene's flanking intron sequences. Strands (forward and reverse) of the amplified DNA fragments were sequenced in an ABI Prism 377 DNA Sequencer (Applied Biosystems, Foster City, CA, USA).

Both forward and reverse sequences were successful and consistent. Genetic analysis detected no mutations in the *SLC22A12/URAT1* gene, except for the previously reported silent polymorphisms rs 3825016, 11231825, 1630320, 7932775, and the intronic polymorphism rs 79866595. In this regard, in recent years serum uric acid has been associated with several single-nucleotide polymorphisms (SNP) of different genes, mainly by genome-wide association studies (GWAS). SNP in *SLC22A12/URAT1* were first associated with hyperuricemia in white, Japanese, and Italian cohorts. Association was replicated in other GWAS in population-based cohorts¹⁰, although this contributes only modestly to explaining variability in serum urate.

The absence of *SLC22A12/URAT1* coding sequence mutations in our Spanish patients with gout can best be interpreted to mean that their decreased uricosuria and hyperuricemia cannot be attributed to an abnormality in this transporter. However, a mutation in the noncoding sequence

of this gene, or in other different genes, that may lead to increased amounts of URAT1 protein cannot be ruled out. A disturbance in other tubular urate transporters, such as ABCG2, which secretes urate into the tubular lumen, may contribute to reduce uric acid excretion and increase serum urate concentrations. We wonder whether the previously reported base substitutions in Mexican patients⁷ could be related to silent polymorphisms instead of gain-of-function mutations.

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