

Exploring Genetic Cues to Solve the Gout Mystery

What strikes most of us when someone says 'crystal' is probably a pleasant adjective like beautiful, pure or exquisite. Unfortunately, a gout patient is more likely to perceive it as painful, sore, tender or aching! Gout, referred to as the urate crystal deposition disease, is a painful inflammatory arthritis that can drop the quality of life of affected individuals and restrict them to a wheelchair if not treated on time. In fact, gout was described as "the unwalkable disease" way back in the fifth century BC.¹

Acute gouty arthritis is characterized by severe pain, redness, tenderness, heat and swelling of the affected joint(s), causing restricted joint mobility. Formation of large crystal deposits called "tophi", observed in chronic gout, can cause irreparable damage to the joints and lead to joint disability. Joints at the extremities of the body (fingers and toes) are commonly affected.

The basic pathophysiological feature of gout is the deposition of monosodium urate crystals in the synovial fluid of the joints following longstanding hyperuricemia. Hyperuricemia is described as the presence of higher than normal level of serum urate. It results from a compromise in the delicate balance between the production and excretion of uric acid in the body, primarily in the liver and the kidneys, respectively. Hyperuricemia is an essential although not sufficient parameter for gout.²

Hyperuricemia and gout are complex traits. A number of genetic loci and gene-environment interactions together confer risk to develop these traits. The key environmental risk factors that can trigger gout flares include alcohol consumption and a high intake of purine-rich foods (meat and sea-foods).³

On the other hand, at least 28 genomic loci that potentially contain variants affecting serum urate concentration have been identified by genome-wide association studies.⁴ One such critically important region that has been identified is the *SLC2A9* locus located on chromosome 4 of the human genome. It turns out to be a major locus that strongly influences serum urate concentration in the body, which is not surprising given that the *SLC2A9* gene encodes a uric acid transporter protein.⁵

Population-specific genetic effects are evident in the case of hyperuricemia and gout. It is interesting and obvious to us that the population we belong to does influence our appearance. But, what is more interesting and less obvious is that it also dictates whether or not we are

susceptible to certain diseases. The presence/absence of certain genetic variants (single nucleotide polymorphisms) in a population predisposes the population to hyperuricemia, and hence gout.

Gout is highly prevalent in the New Zealand Māori and Pacific (Polynesian) peoples, and my research attempts to understand the reason for this increased prevalence. My research therefore focuses on the identification of population-specific genetic variants within the *SLC2A9* locus that are associated with hyperuricemia specifically in the Polynesian people.

This research will of course provide a greater insight into the genetic causes of gout but, more importantly, the identification of penetrant variants could be applied in precision medicine and public health genomics to improve health outcomes for the target population.

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