

GENETICS

Metabolic pathways newly implicated in gout epidemiology

By combining genome-wide association study (GWAS) data with network analyses, a major international collaboration now provides genetic insights into the control of urate levels and the epidemiology of gout. Describing their *Nature Genetics* paper on behalf of her co-authors, Murielle Bochud notes that it “more than doubles the number of loci robustly associated with serum urate levels.” Besides these sites, the study also implicates novel pathways in gout pathogenesis.

Hyperuricaemia causes gout, and serum urate levels are highly heritable, but much of the genetic basis for this familiarity remains uncharacterized. Investigators of the Global Urate Genetics Consortium conducted meta-analyses of data from GWAS of serum urate levels (total of 110,347 participants) and in gout (2,115 patients and 67,259 controls), with subsequent pathway analysis. “Whereas the GWAS approach is hypothesis-free,

the network approach incorporates prior biological knowledge in a systematic way and facilitates biological interpretation of the findings,” explains Bochud.

The presence of variants at 11 loci previously linked to urate concentration were confirmed; 6 mapped to genes involved in urate transport. Of 18 newly identified loci, many were associated with carbohydrate metabolism. Novel among implicated pathways was the inhibins–activins pathway—a pleiotropic growth factor system involved in diverse functions, including energy balance.

Identification of such pathways is “very interesting, in view of the epidemiological data showing the strong relationship between obesity, metabolic syndrome and fructose intake with hyperuricaemia and gout,” says gout expert Nicola Dalbeth (University of Auckland, New Zealand), who was not involved in the study. Michael Becker (University of Chicago), also an

independent expert, predicts that the study will renew interest in how glucose and fructose metabolism influence urate levels. New therapeutic targets might well emerge, he notes, “but the major thrust should be identifying the roles of associations shown but not yet understood.”

“Important tasks will be to identify causal variants,” concurs Bochud. Also, as only 7% of variance in serum urate levels has been explained, “a key next step will be to examine interactions between genetic variants and environmental risk factors in the risk of gout,” concludes Dalbeth.

Emma Leah

Original article Köttgen, A. *et al.* Genome-wide association analyses identify 18 new loci associated with serum urate concentrations. *Nat. Genet.* doi:10.1038/ng.2500

Further reading Reginato, A. M. *et al.* The genetics of hyperuricaemia and gout. *Nat. Rev. Rheumatol.* **8**, 610–621 (2012)