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The Genetic Basis of Hyperuricaemia and Gout

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***Abstract*:** *Gout results from elevated urate concentrations in the blood (hyperuricaemia). When super-saturation of urate is reached, monosodium urate crystals form within the joint. In some individuals, these crystals elicit a painful self-limiting inflammatory response that is characteristic of acute gouty arthritis. The most important cause of hyperuricaemia is reduced excretion of uric acid in the urine. Uric acid excretion is coordinated by a suite of urate transport molecules expressed in the renal collecting tubules, and is a key physiological checkpoint in gout. Other checkpoints in gout are hepatic production of urate, monosodium urate crystal formation, and initiation of the acute inflammatory response. Genome-wide association scans for genes regulating serum urate concentrations have identified two major regulators of hyperuricaemia– the renal urate transporters SLC2A9 and ABCG2. The risk variants at each gene approximately double the risk for gout in people of Caucasian ancestry, with SLC2A9 also resulting in higher risk for gout in people of Polynesian ancestry, a diverse population characterized by a high prevalence of gout. Ongoing genetic association studies are identifying and confirming other genes controlling serum urate concentrations; although genome-wide association studies in gout per se await recruitment of suitable case sample sets.*

Key words: *gout, gouty nephropathy, gene, hyperuricemia.*

Gout is the most common form of inflammatory arthritis affecting men, occurring in 1-2% of Caucasian men in Westernized countries. The central biochemical cause of gout is excess urate. In most mammals urate is degraded by uricase to allantoin, which is highly soluble and readily excreted in the urine. During the Miocene period, two parallel mutations occurred in early hominids that disabled the uricase gene, resulting in higher serum urate concentrations. The parallel mutations suggest that inactivating the uricase gene was selectively advantageous to early hominids, possibly due to one, or a combination, of: the anti-oxidant activity of uric acid compensating for vitamin C deficiency; the ability of uric acid to maintain blood pressure under low-salt dietary conditions; the adjuvant activity of uric acid. Hyperuricaemia is the key predictor for development of gout – elevated

urate above super-saturation concentrations [6.8 mg/dL at physiological pH and temperature] leads to the formation of monosodium urate (MSU) crystals within joints and subcutaneous tissues with the development of very painful attacks of gouty arthritis. Early gouty arthritis is characterized by recurrent episodes of self-limiting acute inflammatory attacks of monoarthritis. Subsequently, gout progresses with more frequent attacks that involve multiple joints. In some patients, chronic tophaceous disease may develop with progressive joint destruction and disability.

Key checkpoints in gout pathogenesis (Fig. 1) 2.1. Urate production Urate is a product of hepatic purine metabolism, produced through metabolism of ingested purines (de novo synthesis) and endogenous metabolism of purines (salvage pathways). Hyperuricaemia may occur as a result of urate over-production, due to acquired causes such as high purine diet, fructose ingestion, alcohol intake, and myeloproliferative disorders, and also rare genetic causes such as hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency and PRPP synthetase (PRS) superactivity. Fructose ingestion increases urate production by increasing hepatic ATP degradation to AMP, a urate precursor. Recent studies have demonstrated a strong relationship between ingestion of fructosecontaining beverages and both hyperuricaemia and gout. Uric acid excretion The major regulator of serum urate is renal excretion of uric acid. In humans, net reabsorption of uric acid into the blood predominates owing to less excretion of uric acid than is filtered at the glomerulus. This renal exchange is mediated by specialised molecules expressed in renal proximal tubule cells. Identified molecules include the fructose transporter SLC2A9 (GLUT9), urate transporter 1 (URAT1;), organic anion transporters 1,3,4 (OAT1, OAT3, OAT4), multi-drug resistance protein 4 (MRP4), sodium-coupled monocarboxyl transporters SMCT1,2, and human ATP-binding cassette, subfamily G, 2 (ABCG2). Variants of SLC2A9 exchange uric acid with fructose and glucose from the proxFig. 2. The uric acid transportasome. Current understanding of uric acid transport in the proximal renal tubule. Monocarboxylates accumulate in the tubular cell through sodium-dependent monocarboxylate transporters SLC5A8 and SLC5A12, and dicarboxylates through SLC13A3. Uric acid enters the cell in exchange for monocarboxylate via apical URAT1 and for dicarboxylate via apical OAT4. Apical SLC2A9v2 plays a significant role in uric acid reabsorption, the reabsorbed uric acid exiting the cell through basolateral SLC2A9v1. For efflux of uric acid into the lumen, MRP4 and a voltage-driven organic anion transporter (vOAT1/NPT1) are candidates. OAT1 and OAT3 are known to transport uric acid, although the direction of transport is not clear. ABCG2 is a unidirectional transporter expressed on the apical membrane. PDZK1 is a scaffolding protein involved in assembly of a transporter complex in the apical membrane. Genetic variation in SLC2A9, ABCG2, URAT1, NPT1, OAT4 and PDZK1 is associated with serum urate levels and gout. imal tubule lumen across the apical and basolateral membranes, leading to net reabsorption of uric acid. SLC2A9 is inhibited by the uricosuric agent benzbromarone, but not by the commonly used uricosuric probenecid. URAT1 is substrate specific (compared to the multispecific OAT1 and OAT3) and is also inhibited by uricosuric drugs such as benzbromarone and probenecid. OAT4 is a low-affinity assymetric urate transporter that facilitates diureticassociated hyperuricaemia, also inhibited by benzbromarone and probenecid. MRP4 is an ATP-dependent efflux pump for urate. ABCG2 is a secretory urate transporter in the proximal tubule, currently there are no published data on effects of uricosuric drugs on ABCG2 activity. As described later, genetic variants in these genes have been associated with serum urate levels and gout.

Genetic factors associated with MSU crystal deposition and inflammatory response

The recent genetic findings confirm that renal excretion of uric acid is a major determinant of gout. However, there are other checkpoints in gout pathogenesis in which inherited genes may play a role in determining risk; hepatic production of urate, formation of MSU crystals, initiation and resolution of

the inflammatory response to MSU crystals. To date, no genetic factors have been convincingly implicated in any of these processes, with strong statistical support and replication in multiple sample sets. The recent leap in understanding of the major renal urate transport genes that control serum urate concentrations largely resulted from the use of extant population-based cohorts in which serum urate concentrations had been measured, a straightforward phenotype to ascertain. The best approach for identification of risk factors for gout, outside from those that control serum urate concentrations, is genomewide association studies in large cohorts of gout patients and controls. When such studies are done, it will be important to ascertain phenotype on the basis of American College of Rheumatology criteria or, ideally, by aspirate-proven disease. Ascertainment criteria that rely on administrative data leads to misclassification of gout, and self-reported diagnoses are likely to be unreliable. Close attention to classification of gout in GWAS will be essential for the detection of weaker genetic effects. Use of a hyperuricaemic non-gout control group would increase the power of any such study in detecting genes involved in MSU crystal deposition and/or MSU inflammatory response

Gout in Polynesia Although the prevalence of gout is increasing worldwide, certain populations have higher rates of gout. Possible gouty erosions in skeletons from the 3000-year old Polynesian Lapita culture in Vanuatu have been reported. Lesions consistent with gout were present in seven out of 20 skeletons (all male). The incidence of gout is 2% in men living on Tokelau, rising to 5% upon migration to New Zealand. Both Tokelau cohorts had mean urate concentrations in the hyperuricaemic range. On Pukapuka in the Cook Islands, alcohol is rarely consumed, yet gout incidence is 5.3% in men and 2.4% on Rarotonga. More than 40 years ago, it was recognised that “the people of the Pacific belong to one large gouty family” (Kellgren, 1964; quoted in). The prevalence of gout in the New Zealand Maori and Pacific Island populations is the high- ¯ est worldwide, 15% in men. However, the one Pacific outlier is the early (pre-Westernised) New Zealand Maori population, in ¯ which gout was not described in 1882; “Gout, a rare disease; one which will probably be almost or quite unknown to young New Zealanders, who in appearance and build show scant tendency to the gouty diathesis, and in habits and mode of life do little to promote the spread of this most unnecessary malady. When gout does appear, it is always in the person of an immigrant.” The varying incidences of Pacific gout, moderate in traditional island populations, low in pre-European NZ Maori, and high in ¯ modern New Zealand Maori and Pacific Island populations, can be ¯ understood using a scenario of a strong genetic tendency modulated by the environment. A diet containing increased fructose is known to increase the risk of hyperuricaemia and gout in the modern North American population. It is reasonable to speculate that a fructose-rich diet also promoted gout in ancient and traditional Pacific Island populations, owing to the ready availability of fructose-rich foods, such as fruit and coconuts. Gout may have been rare in pre-European Maori owing to a diet consist- ¯ ing largely of kaimoana (seafood), birds and tuberous vegetables. The modern diet rich in processed sugar (and fructose) may impact severely on New Zealand Maori and Pacific Island people, who are ¯ genetically vulnerable to developing gout. The same variants in the fructose and uric acid transporter SLC2A9 (also known as GLUT9) that confer risk in Caucasian (rs11942223, for example) also confer an extremely high risk for gout in NZ Maori and Pacific Island sam- ¯ ple sets, with a 500 percent increased risk (odds ratio = 5) conferred by the risk allele (compared with OR = 2 for Caucasian). Inheritance of dominantly protective variants at SLC2A9 appears to be very important in New Zealand Maori and Pacific Island people. In contrast, the Caucasian risk variants do not alter risk in Solomon Islander people, this population is monomorphic for the risk allele. However, there is an independent non-synonymous variant in SLC2A9 (Arg265His) that confers about a 2-fold increased risk for gout in Solomon Islander people. Collectively, the genetic results emphasize previous biochemical data that demonstrate the importance of renal urate transport in hyperuricaemia and gout, more so in people of

Polynesian ancestry. Strong association of the ABCG2 Q141K variant with gout has been reported in people of Western Pacific (Samoa, Tonga) ancestry (OR > 2.5) but not in people of Eastern Pacific ancestry (Cook Island and New Zealand Maori) (OR < 1.4). This is notable in the context of the high incidence of gout in both populations and the shared Polynesian ancestry and is likely to be caused by the founder events that occurred during Polynesian settlement of the Pacific (Fig. 3). These data emphasize the need to account for subpopulation differences when undertaking biomedical research in a group defined by a geographical region and shared ancestry but characterized bymigratory events that create bottlenecks and altered genetic diversity in the founder populations. 4.1. Genetic causes of familial gout Several genes with rare mutant alleles cause clinically distinct forms of familial gout. Mutations in the uromodulin gene cause familial juvenile hyperuricaemic nephropathy, a disease characterized by juvenile onset of hyperuricaemia, gout and progressive renal failure. Uromodulin (Tamm-Horsfall glycoprotein) is the most abundant protein in urine, and plays a role in prevention of urinary tract infecton. Mutations in the signal sequence of the renin gene result in early-onset hyperuricaemia and progressive renal failure by altering the intrarenal angiotensin system and kidney structure. The relatively common A150P (rs1800546) mutation in the aldolase B gene (ALDOB) causes the recessive disease hereditary fructose intolerance (HFI) in approximately twothirds of European cases – many HFI patients also present with hyperuricaemia and gout. A deficiency in hypoxanthine guanine phosphoribosyltransferase (HPRT) activity leads to overproduction of urate, mutations in this enzyme result in gout and neurological symptoms (Lesch-Nyhan syndrome). Mutations in the Xchromosome gene phosphoribosylpyrophosphate synthetase can lead to superactivity, uric acid overproduction, gout and neurodevelopmental impairment in some cases. Studying a possible role for these familial hyperuricaemia- and gout-causing genes in common gout is justified

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