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Heritability of crystal related arthropathies

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ABSTRACT

The most common types of crystal arthropathies are gout and calcium pyrophosphate deposition (CPPD) disease. Serum urate levels are influenced by a combination of genetic factors and the environment. There are studies estimating the heritability of urate ranging from 45% to 73%. Approximately 3% of the variance in serum urate level is explained by the locus SLC2A9. Among the Caucasian population, 10% of all gout cases may be largely attributable to locus ABCG2. Loss or reduction function of ABCG2 halves the kidney's ability to secrete uric acid. Gain-of-function mutations in ENPP1 gene may be involved in the development of CPPD disease. Loss-of-function mutations in ANKH leads to excess calcium hydroxyapatite formation.

Conclusions: There is reason to believe that studying susceptibility genes for the crystal arthropathies will contribute to our understanding of the complexity of inheritance of these disorders. At present many other genes involved in crystal arthropathies are being investigated, and we hope that soon, novel therapeutic targets will be found.

Keywords: genetics, uric acid, gout, CPPD, chondrocalcinosis

INTRODUCTION

Crystal-related arthropathies are a group of joint disorders caused by deposits of crystals (monosodium urate, calcium pyrophosphate dihydrate, calcium hydroxyapatite, and calcium oxalate) in joints and the soft tissue. Once in the joint, the crystals activate phagocytic cells that release pro-inflammatory cytokines, and cause mononuclear and leukocyte cell migration (1). The most common types of crystal arthropathies are gout and calcium pyrophosphate deposition (CPPD) disease.

der of purine metabolism and/or uric acid excretion. The consequence of these disorders leads to hyperuricemia, in which the serum urate concentration exceeds physiologic plasmatic saturation of 6.8 mg/dL, followed by the deposition of urate crystals into the joints and soft tissue (2). The monosodium urate crystals incite an immune response clinically manifested by the classic signs of inflammation (redness, heat, pain, tumor) during gouty arthritis to the loss of joint function seen in chronic gout (Figure 1).

FIGURE 1. The three steps of gout pathogenesis

GENETICS OF HYPERURICEMIA AND GOUT

Gout is a crystalline arthritis caused by monosodium urate crystals. It is recognized as a disor-

Serum urate levels are influenced by a combination of genetic factors and the environment. Heritability estimates the degree of variation in a popula-

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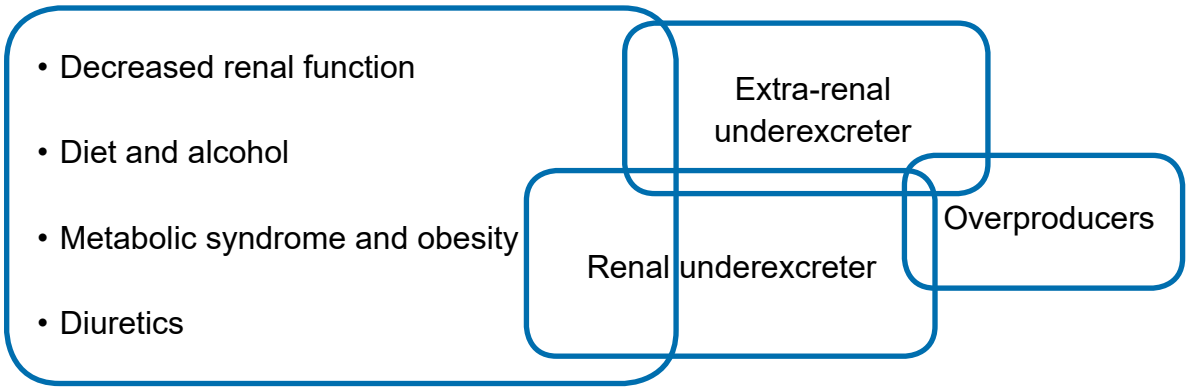

FIGURE 2. The pathophysiology model of gout - adapted from George RL and Keenan RT (2)

tion that is due to genetic variation between individuals as opposed to variation of environmental factors (3). There are studies estimating the heritability of urate ranging from 45% to 73% (4,5)

Genome-wide association studies have permitted the identification of several new and common genetic factors that contribute to hyperuricemia and gout. A study of more than 140000 European individuals, found significant associations of 28 separate genetic loci with serum urate levels (6). The twenty-four loci (out of 28) identified in Genome-wide association studies have been associated with gout in several populations (7). These loci are SLC2A9/GLUT9, ABCG2, SLC22A12/URAT1, SLC22A11/OAT4, SLC17A1/NPT1 (5). Most of them are involved with the renal urate transport system, generally considered the most influential regulator of serum urate homeostasis.

Approximately 3% of the variance in serum urate level is explained by the locus SLC2A9, which encodes the GLUT9 protein. This is considered a large effect when compared to other complex diseases, like obesity. The SLC2A9 isoforms are expressed on the renal tubular collecting duct, which either increases the reuptake of secreted uric acid or it is the main exit route of uric acid into the blood (5,8). Polymorphisms in SCL2A9 were found to be associated with hyperuricemia and gout in European population studies (9). Two independent studies suggested an association between SLC2A9 and the serum urate level above 0.4 mMol/L (2,10).

Gender influences are present, with SLC2A9 having a stronger effect in women (6). Almost eight percent of the variance in seric uric acid levels in women are explained by SLC2A9, compared to 1.7 % in men (2).

ABCG2 is a transporter of purine nucleoside analogs, having a similar structure to uric acid. There is a strong correlation between ABCG2 and gout in both whites and blacks. Among the Caucasian population, ten percent of all gout cases may be largely attributable to locus ABCG2 (2,11). Loss or reduction function of ABCG2 halves the kidney's ability to secrete uric acid (12).

Genome-wide association studies results show that hyperuricemia is more strongly associated with the SLC2A9 variants while gout is more strongly associated with ABCG2 variants (5,6).

The association between ABCG2 and gout is proved by studies that involved hyperuricemia asymptomatic subjects as controls (13). It is speculated that ABCG2 variants, aside from their influence on serum urate, may increase the formation of uric crystal and/or activation of the inflammatory system (5).

The gastrointestinal tract accounts for 30% of uric acid elimination and the transportation of uric acid to the gut may be susceptible to genetic polymorphisms. Studies demonstrated that the ABCG2 has a high expression in the gut, being an extra-renal mediator of excretion (14,15).

Lifestyle and dietary choices may influence the development of hyperuricemia and gout. Many dietary choices are advocated: meat and seafood, beer, sugar-sweetened drinks, cherries and coffee etc. This may be partially justified, but several studies suggested that genes that encode renal urate excretion may also be involved (2).

Heritability of gout should be seen as a part of the complex pathophysiology system that involves renal function, diet and comorbidities (Figure 2).

There is evidence that genes interact with the environment, influencing serum urate levels and the risk of gout. The interaction of sugar-sweetened beverage intake with a variant of SLC2A9 increases the risk of gout (16). An additive composite score developed by Tu HP and collaborators shows that high-risk alleles of SLC2A9 and ABCG2 associated with alcohol intake are modulating gout risk (17).

Aside from the loci involved in the urate transport system, the influence of other loci remains largely speculative. The genes encoding the glucokinase regulatory protein may influence urate production. Köttgen et al identified 18 loci connected to

glucose metabolism pathways, such as INHBB and ACVR2A. Another locus identified by the same research team is PRPSAP1, which is involved in purine synthesis (6).

As a clinically important consequence, in the future, genetic testing may be used for individualization of treatment with urate-lowering therapy. At present, the most widely used urate-lowering therapy is allopurinol. Lack of response to allopurinol has been associated with variants of ABCG2 (18). Febuxostat is a urate-lowering drug that inhibits ABCG2 but the role of ABCG2 on the efficacy of febuxostat in reducing seric uric acid is not clear (19).

GENETICS OF CPPD

Calcium pyrophosphate crystals are related to a variety of articular manifestations known as calcium pyrophosphate deposition (CPPD) arthritis. Although most cases of CPPD chondrocalcinosis are nonfamilial, familial cases of CPPD arthritis appeared to be inherited in an autosomal dominant manner (20).

The mechanisms responsible for the deposition of the CPPD crystals are not fully understood, although some studies have reported that structural changes in the articular cartilage extracellular matrix might promote this process (21). In addition to extracellular matrix proteins as potential candidates for CPPD disease, other studies have suggested that the biochemical pathway involved in the generation of inorganic pyrophosphate may play a role in crystal deposition. In vitro studies showed increased levels of intracellular inorganic pyrophosphate in synovial fluids and cultured fibroblasts and lymphoblasts of patients with familial CPPD disease (20,22).

The transportation of inorganic pyrophosphate across the cellular membrane to the interstitial tissue is influenced by the ANKH gene. An increase of intracellular inorganic pyrophosphate concentration and a decrease in extracellular concentration leads to excess calcium hydroxyapatite formation. These processes are largely influenced by loss-of-function mutations in ANKH (23).

Ectopic calcification disorders and arterial calcification may be linked to enzyme ectonucleotide pyrophosphatase 1 (ENPP1) (24,25). The location of ENPP1 is on chromosome 6 and its normal activity inhibits pyrophosphate-related calcification. Mutations in ENPP1 cause arterial calcification and low inorganic pyrophosphate level. Thus gain-of-function mutations in this gene may be involved in the development of CPPD disease (23,25).

The isozyme tissue-nonspecific alkaline phosphatase, encoded by the gene TNAP, is present in the osteoblast matrix vesicles and can hydrolyze inorganic pyrophosphate. Hypophosphatasia is caused by mutations in the TNAP gene and leads to low mineralization of bones and fractures, elevated concentrations of inorganic pyrophosphate, chondrocalcinosis, and CPPD (23). Zhang Y and collaborators suggested that in Caucasian populations, TNAP and ENPP1 are not major genetic determinants of CPPD susceptibility (26).

An important aspect of CPPD arthritis is its association with metabolic and endocrine disorders like hemochromatosis, hyperparathyroidism and hypomagnesemia, but the pathogenic mechanisms are not fully elucidated. One of the most common disease associations of CPPD chondrocalcinosis is hemochromatosis. Some studies have shown that iron may inhibit pyrophosphatases while other studies suggested antagonistic effects of Ferrous (Fe++) but not ferric (Fe) ions on CPPD crystal formation (23,27).

Hypophosphatemic rickets is a condition characterized by phosphaturia and their consequences: growth retardation, rickets and deficiency of Vitamin D. Hypophosphatemic rickets are caused by the mutations in the PHEX gene. This mutation leads to the occurrence of either ectopic hydroxyapatite or CPPD crystal deposition, causing widespread calcific enthesitis (23).

CONCLUSIONS

There is reason to believe that studying susceptibility genes for the crystal arthropathies will contribute to our understanding of the complexity of inheritance of these disorders. At present many other genes involved in crystal arthropathies are being investigated, and we hope that soon, novel therapeutic targets will be found.

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