IDENTIFICATION OF NEW AND RARE VARIANTS IN ABCG2, SLC22A1 AND ALDH16A1 GENES IN CRYSTAL-PROVEN EARLY-ONSET GOUT

C. Collet1, H. Moret1, M. Ricquebourg1, M. Cohen-Solal2, J.-L. Laplanche1, T. Pastacq1, T. Bardin2, F. Lioté2, P. Richette3, H.K. Ee4, 5Biochemistry, Hôpital Lanboisier; 2BioSarc, Inserm UMR 1312, Paris; 3Rheumatology, Groupement des Hôpitaux de l’Institut Catholique de Lille, Lille; 4rheumatology, Hôpital Lanboisier, Paris, France

Background: Early-onset or juvenile gout (EOG) without hypoxanthine-guanine phosphoribosyltransferase enzyme deficiency (HPRT1, OMIM 300323) and not related to familial juvenile hyperuricemic nephropathy (UMOD, OMIM 300323) is a rare gout phenotype characterised by a first flare in adolescence or in young adulthood. While numerous genome wide association studies (GWAS) have been done on classical late-onset gout, very few studies have been performed in EOG patients. Moreover, until now most genetic studies only assess association between pre-defined single nucleotide polymorphisms (SNP) and gout.

Objectives: Our aim was to identify the genetic variants of clinically confirmed EOG by screening all exons of gout-associated genes with targeted Next-Generation Sequencing (NGS) approach.

Methods: Twenty-six urate crystal-proven gout patients with first flare occurring before the age of 30 years were included. Gout history, comorbidities and patient characteristics were recorded. All participants provided written informed consent to genetic analysis. After DNA extraction from total blood samples, the NGS libraries were prepared with sureselect QXT (Agilent) and sequencing was performed with miseq (Illumina).

The multigene panel included 80 genes described in GWAS and genes involved in rare diseases such as HPRT1 and UMOD.

Results: Twenty-six patients (24 men, 20 Caucasians, 5 Asians and 1 African) with crystal-proven gout had experienced their first flare at a mean age of 22.8 years [14–29] (Gout duration was 11.5 years [1–46] and clinical tophi observed in 9 patients. Mean age was 37.5 [24–69] years and mean body mass index 27.6 kg/m2 [20.1–40.7]. Ten patients were overweight, 5 had obesity, 1 hypertension, 0 diabetes mellitus, 7 dyslipidemia and 10 chronic kidney disease stages 2–4. Mean serum urate level was 527 μmol/L [270–803]. Amongst 26 affected patients, 7 had a molecular anomaly (26.9%). Six patients harboured one rare or novel variant in ABCG2 (three Caucasian patients), ALDH16A1 (two Caucasian patients) and SLC22A1 (one African patient). Two other patients (one Caucasian and one Asian) carried an association of variants in both ABCG2 and ALDH16A1. All variants had a Minor Allele Frequency (MAF) below 0.3% or were never described in public databases. All variant were considered as probably pathogenic according to in silico predictive algorithms. Interestingly, the well-known p.Gln141Lys SNP of ABCG2 was identified in 3 Asian patients (11.5%) at homozygous level.

Conclusions: Our findings of very rare and novel pathogenic variants in ABCG2, ALDH16A1 and SLC22A1 genes provides better insights of the molecular pathogenesis in early-onset juvenile gout. However, our results also highlight the involvement of yet undetermined genes in this population.

Disclosure of Interest: None declared


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Treatments: friend or foe?

THE ROLE OF NSAIDS IN THE ASSOCIATION BETWEEN OSTEARTHRITIS AND CARDIOVASCULAR DISEASES: A POPULATION-BASED COHORT STUDY

M. Alqazzaman1, J. Kopcek2, M.E. Kalim3, H. Wong2, A. Anis2, 1Faculty of Pharmaceutical Sciences; 2School of Population and Public Health, University of British Columbia, Vancouver, Canada

Background: Worldwide, osteoarthritis (OA) is a major musculoskeletal disorder. Recent research suggests that OA is an independent risk factor for cardiovascular disease (CVD). The relationship is complicated because non-steroidal anti-inflammatory drugs (NSAIDs), a proven risk factor for CVD, are frequently used for the treatment of OA. Researchers have hypothesised that NSAID use in the causal pathway between OA and CVD is what may ultimately impact these relations models to estimate the risk of developing incident CVD (primary outcome) as well as ischaemic heart disease (IHD), congestive heart failure (CHF) and stroke (secondary outcomes). To estimate the mediating effect of NSAIDs, defined as current use of NSAID using linked prescription dispensing records, in the OA-CVD relationship, we implemented a marginal structural model.

Results: People with OA had 23% higher risk of developing CVD compared to people without OA after adjusting for SES, BMI, hypertension, diabetes, hyperlipidemia, COPD, and Romano comorbidity score. Adjusted HR (95% CI) was 1.23 (1.17, 1.29). Adjusted HR (95% CI) was 1.42 (1.33, 1.52), 1.17 (1.10, 1.27), 1.14 (1.08, 1.24) for CHF, IHD and stroke, respectively. Approximately 67.51% of the total effects on IHD and stroke was mediated through the current NSAID use. Among the secondary outcomes, approximately 44.77% of increased CHF risk was mediated through current NSAID use. More than 90% of the total effects on IHD and stroke was mediated through the current NSAID use.

Conclusions: Our study is the first to evaluate the mediating role of NSAID use in the OA-CVD relationship based on population-based health administrative data. The results of this study also indicate that OA is an independent risk factor for CVD. Our findings suggest that the mediating role of NSAID use substantially contributes to the OA-CVD association.

REFERENCES:


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