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A genetic marker of hyperuricemia predicts cardiovascular events in a meta-analysis of three cohort studies in high risk patients

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Abstract *Introduction:* The strongest genetic marker of uric acid levels, the rs734553 SNP in the GLUT9 urate transporter gene, predicts progression to kidney failure in CKD patients and associates with systolic BP and carotid intima media thickness in family-based studies.
Methods: Since genes are transmitted randomly (Mendelian randomization) we used this gene polymorphism as an unconfounded research instrument to further explore the link between uric acid and cardiovascular disease (cardiovascular death, and non-fatal myocardial infarction and stroke) in a meta-analysis of three cohort studies formed by high risk patients (MAURO: 755 CKD patients; GHS: 353 type 2 diabetics and coronary artery disease and the TVAS: 119 patients with myocardial infarction).
Results: In separate analyses of the three cohorts, the incidence rate of CV events was higher in patients with the rs734553 risk (T) allele (TT/GT) than in those without (GG patients) and the HR in TT/GT patients in the three cohorts (range 1.72–2.14) coherently signaled an excessive cardiovascular risk with no heterogeneity (I2 = 0.01). The meta-analytical estimate (total number of patients, n = 1227; total CV events, n = 222) of the HR for the combined end-point in TT/GT patients was twice higher (pooled HR: 2.04, 95% CI: 1.11–3.75, P = 0.02) than in GG homozygotes.
Conclusions: The T allele of the rs734553 polymorphism in the GLUT9 gene predicts a doubling in the risk for incident cardiovascular events in patients at high cardiovascular risk. Findings in this study are compatible with the hypothesis of a causal role of hyperuricemia in cardiovascular disease in high risk conditions.
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Introduction

Whether hyperuricemia is causally implicated in atherosclerotic complications is perhaps one of the most vexed questions in cardiovascular medicine [1]. A meta-analysis of observational studies supports the contention that uric acid is a relevant cardiovascular risk factor [2]. However other meta-analyses show that the same biomarker has just a modest, if any, independent predictive power for coronary heart disease events [3] and it is prevailing view that the association between hyperuricemia and coronary heart disease and other atherosclerotic events depends on the confounding effect of coexisting comorbidities like

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obesity, type-2 diabetes, dyslipidemia and hypertension [4]. On the other hand, the variability of serum uric acid levels attributable to environmental factors like nutrient intake, volume status, acid–base balance, renal function and the use of drugs, particularly allopurinol and diuretics, is considered as a major confounding factor for detecting the relationship between uric acid and cardiovascular events in observational studies [5].

The serum concentration of uric acid has an important genetic control. Because genes are transmitted randomly (Mendelian randomization) [6], polymorphisms in genes that regulate serum uric acid may allow further investigation of the link between uric acid and cardiovascular events minimizing confounding by environmental factors. Indeed genotype precedes life events and is therefore unaffected by lifestyle factors. The Mendelian randomization approach has already been applied in large meta-analyses of case-control studies across various populations and ethnicities and this approach failed to show a link between genes that regulate uric acid levels and cardiovascular disease events [7–9]. However, due to population admixture and population stratification large meta-analyses across various populations tend to dilute any underlying link between gene polymorphisms and clinical outcomes.

Studies based on homogeneous populations may provide important information about genetic associations. Indeed these populations are also more homogeneous for exposure to environmental factors. A polymorphism in the GLUT9 urate transporter gene was strongly associated with blood pressure in a study in the Amish community [10]. Furthermore we have recently shown that the risk allele (T allele) of the strongest genetic marker of uric acid levels in a meta-analysis including 28.000 individuals, the intronic SNP rs734553 in the GLUT9 gene [11], predicted chronic kidney disease (CKD) progression in a cohort of patients with chronic renal disease (CKD) in Southern Italy [12] and associated with systolic pressure [13] and carotid intima media thickness [14] in family-based studies in the same geographical area.

Uric acid has been repeatedly related with the incidence of cardiovascular events in cohort studies in patients at high cardiovascular risk including studies in patients with CKD [15] or with type-2 diabetes [16]. A least eight cohort studies in patients with myocardial infarction [summarized in a meta-analysis in 2012 [17]] cogently showed that hyperuricemia predicts new cardiovascular events in these patients. Therefore, to further explore the potential role of the T allele of rs734553 polymorphism in the GLUT9 gene in cardiovascular risk we have now tested the association between this polymorphism and incident cardiovascular events in three high risk cohorts, namely in the same cohort of CKD patients where we observed a strong link between rs734553 and CKD progression and in two additional cohorts composed by patients with type-2 diabetes and with recent myocardial infarction respectively. These cohorts were formed by patients of Italian descent and totaled 1227 patients in three communities with shared genetic background [18] and nutritional habits [19].

Methods

Study participants

Prospective studies

Sample 1 – the MAURO Study The study cohort included 826 stages 2–5 CKD patients, consecutively recruited from 22 Nephrology Units in Southern Italy. Patient enrollment was performed between October 18th, 2005 and October 2nd, 2008. All patients were in stable clinical condition and none had intercurrent infections or acute inflammatory processes. Inclusion criteria were: non acute or rapidly evolving renal diseases; age ranging from 18 to 75 years; non-transplanted; non-pregnant, not affected by cancer or diseases in the terminal phase. Patients were followed up until August 2011 [median follow-up time of 36 months (range: 1.4–48 months)]. Among these, 34 patients were lost to observation after the baseline visit, 33 were erroneously enrolled (i.e. had a GFR >60 ml/min/1.73 m^2) and in 4 patients no DNA samples were available; thus, 755 patients were included in this study.

Sample 2 – the Gargano Heart Study The study included 363 whites from Italy with type 2 diabetes (according to American Diabetes Association 2003 criteria) and coronary artery disease (CAD), as indicated by previous myocardial infarction (MI) or >50% stenosis of at least one major vessel at coronary angiography, or both. These individuals were cases of the cross-sectional case-control Gargano Heart Study (GHS) and were consecutively recruited at the Scientific Institute "Casa Sollievo della Sofferenza" from 2001 to 2008 and monitored until the end of 2009. The only exclusion criterion was the presence of poor life expectancy due to malignancies. Ten patients became untraceable before the first follow-up visit; therefore, data were available for 353 patients.

Sample 3 – the Tor Vergata Atherosclerosis Study A total of 143 whites from Italy were consecutively recruited from 2005 at "Tor Vergata" University Hospital (Rome). They all had been diagnosed with an acute MI according to the European Society of Cardiology and American Heart Consensus Guidelines. Exclusion criteria were the presence of malignancies and a medical record of diabetes, although 22 study participants (15.6%) were found to have subclinical diabetes after an oral glucose tolerance test. Because recruitment is still in progress, only patients who were recruited up to 2007, and as such underwent at least one follow-up visit, were included in this study. Two patients became untraceable before the first follow-up; in 22 patients the genetic analysis was not performed because DNA was not available; therefore, data were available for 119 patients.

Study end point The end point considered in all three samples was a major cardiovascular event, defined as nonfatal stroke, nonfatal MI, or cardiovascular death. Information on the occurrence of nonfatal events was sought yearly from study participants and confirmed by a review of hospital records if cardiovascular events were reported. If patients did not report to a scheduled visit, information on the occurrence of cardiovascular events was obtained

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