Associations between a UMOD gene variant, uromodulin excretion and renal function in a large Canadian survey: the CARTaGENE study.

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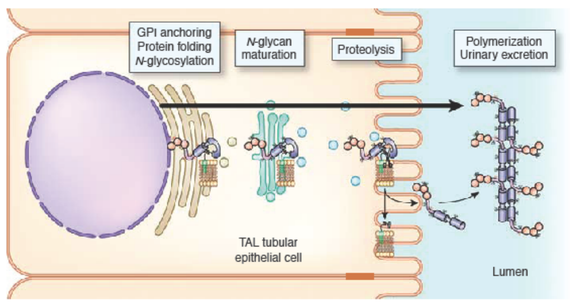
BACKGROUND and OBJECTIVES

Uromodulin is expressed exclusively in the thick ascending limb and is the most abundant protein excreted in normal urine (1)



Recent studies have suggested that uromodulin plays a role in CKD. GWAS have identified associations between SNPs near the UMOD gene and GFR. A small nested case-control study from the Framingham Heart Study has linked the C allele at rs4293393, in the UMOD promoter, to a reduced excretion of uromodulin and a lower risk of CKD at 10 years (2).

Evidence also supports that uromodulin regulates the activity of the sodium-potassium-chloride transporter and the renal outer medullary potassium channel. The Global BPGen Consortium associated rs13333226 (near rs4293393) with hypertension. The G allele predicted a lower risk of hypertension and lower excretion of uromodulin (3).

However, while GWAS studies on SNPs near UMOD, CKD and blood pressure are numerous, few studies detail the relations between the product of the gene, (uromodulin) and CKD and blood pressure.

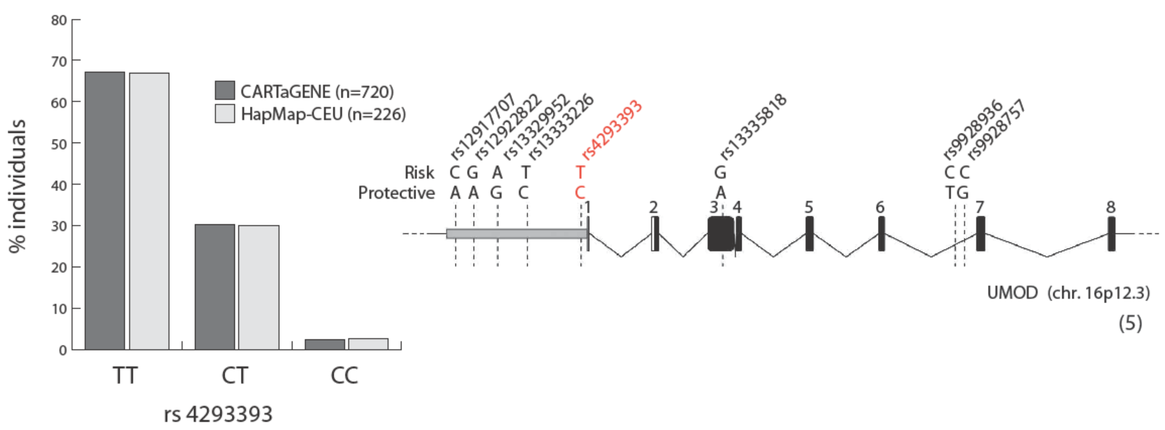
We investigated the association between the UMOD variant rs4293393, the product of the gene, uromodulin, GFR and blood pressure.

METHODS

Study design:
Cross-sectional analysis of the CARTaGENE survey performed between July of 2009 and October of 2010 (4).

CARTaGENE database
CaG is a databank and biobank initiated as an infrastructure for population genomics research and created to develop better diagnosis, treatment, and disease prevention programs (http://www.cartagene.qc.ca/). It includes 20,004 participants or 1% of the Quebec population ages 40–69 years. Participants were recruited randomly from the general population from 4 metropolitan regions of Quebec. The survey included a medical questionnaire, a physical examination and sample gathering including urine and DNA. GFR was estimated using the CKD-EPI equation. A sample of 946 subjects from the CARTaGENE survey was genotyped for rs4293393.

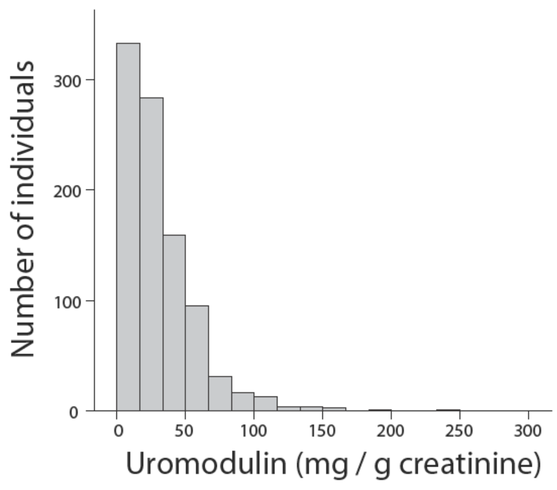
Genotyping and uromodulin measurement
The SNPs have been determined using the HumanOmni2.5 chip from illumina. The distribution of the rs4293393 SNP in the population was similar to a European population. Uromodulin was measured at the Zurich university institute of physiology. This laboratory has considerable experience in the measurement of uromodulin and uses a validated and robust ELISA method with high sensitivity (2.8 ng/ml) and CV of <8% for intra-assay precision in urine samples.



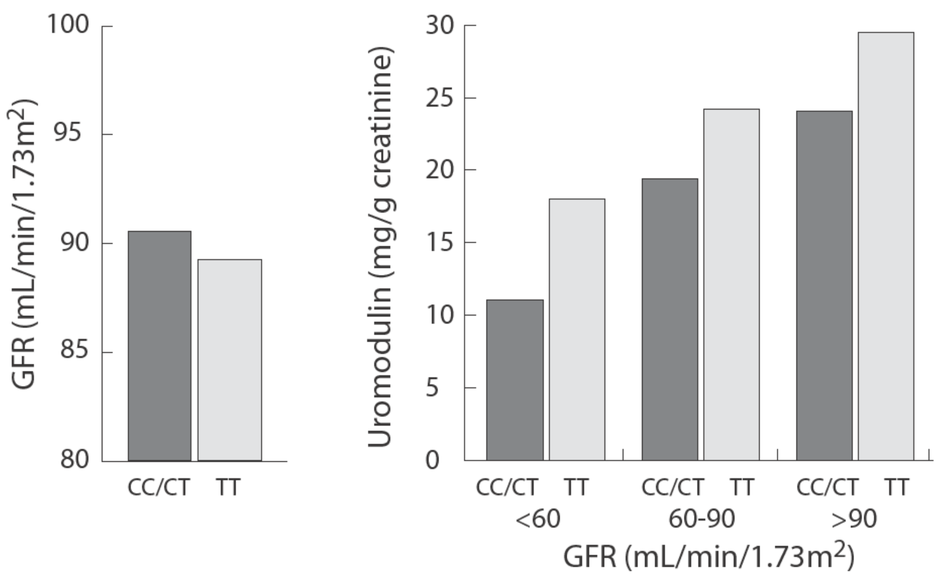
RESULTS

The population studied was 946 with available genotyping. 83% reported ethnicity as Caucasian.

Age:	54 ± 9 years	Systolic (mmHg)	124 ± 18
Female	51 %	Diastolic (mmHg)	73 ± 11
GFR (CKD-EPI)	90±14 ml/min	History of hypertension	17 %
Diabetes	8.4 %	History of CAD/stroke	25 %



The CC/CT genotypes were associated with higher eGFR (CT/CC: 91±13 vs. TT: 89±14 ml/min/1.73m2, p=0.056) and lower urine uromodulin levels (CT/CC: 21, IQR 10-34 vs. TT: 27 (12-44) mg/g creatinine, p<0.001. We found no relation between genotype and blood pressure or use of antihypertensive medication (data not shown)



In addition, uromodulin excretion strongly decreased as eGFR declined (p>0.001), regardless of rs4294493 status.

Using multivariate analysis, both the UMOD variant and uromodulin excretion were independent predictors of GFR (adjusted for age, sex, blood pressure, history of hypertension, diabetes or CAD/stroke.

	GFR (mL/min/1.73m²)	p
rs4294493 (CC/CT)	+ 2.7 ± 0.9	0.002
uromodulin (log mg/g creatinine)	+1.6 ± 0.4	<0.001

CONCLUSIONS

Uromodulin excretion decreases as the GFR declines. At the same time, the CC/CT variants of rs4293393 in the promoter region of UMOD are associated with a lower uromodulin excretion but a better renal function. We found no association between rs4293393 and blood pressure

Further studies are needed to elucidate the mechanisms underlining these findings.

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