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Letter to the Editor

LETTER TO THE EDITOR

UMOD genetic variations and myeloma cast nephropathy

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Myeloma cast nephropathy (MCN) is the leading mechanism of acute kidney injury (AKI) in patients with multiple myeloma (MM). It negatively impacts overall survival, and biomarkers that could predict individuals at risk for MCN are expected. MCN results from the co-precipitation of monoclonal free light chains and uromodulin. Although the light chain binding domain of uromodulin has been well characterized [1, 2], the question of whether the intrinsic physicochemical characteristics of this protein could have protective functions or indeed exacerbate MCN have as yet not been addressed. Encoded by the *UMOD* gene, uromodulin is secreted and passively excreted in the urine. Common *UMOD* promoter variants are known to influence urinary uromodulin levels [3], and genome-wide association studies have shown strong associations between these variants and chronic conditions including hypertension and chronic kidney disease [4, 5]. So far, neither the distribution of *UMOD* promoter variants nor the genomic-coding sequence of *UMOD* has been evaluated in patients with MM and MCN. We therefore set out to test the hypothesis that a genetic variant of *UMOD* could predispose to the development of MCN.

In this study, after collection of the written informed consent and full approval by the Institutional Review Board of the University Hospital of Toulouse, France (Comité Protection Personnes Sud-Ouest II; No. DC-2011-138), molecular analysis of *UMOD* was performed in 38 patients.

We initially performed direct sequencing of the 11 exons and intron–exon boundary regions of *UMOD* (chr 16p12.3) in 22 patients with MM, including 6 with MCN, 8 with MM and AKI but no MCN (biopsy findings), and 8 with MM but no AKI. No pathogenic mutations or rare variants were identified in the *UMOD* gene-coding regions of MCN patients.

We subsequently analysed two single-nucleotide polymorphisms (SNPs) mapping to the *UMOD* promoter: *rs 12917707* in position −3403 bp relative to the *UMOD* transcription start site and *rs4293393* in position −300 bp, which are in perfect linkage disequilibrium [6]. This analysis was performed on 38 patients: 14 with MCN (biopsy-proven $n = 11$), 11 with MM and AKI but no MCN on renal biopsy, and 13 with MM but no AKI. As depicted in Figure 1, the distribution of the risk alleles was not affected by renal phenotype (MCN or not). Moreover, neither estimated glomerular filtration rate (eGFR) nor proteinuria was influenced by these SNP *UMOD* variants (data not shown).

Thus, the distribution of *UMOD* risk alleles was irrespective of MCN status. Several parameters should be considered to explain the absence of effects of *UMOD* variants on eGFR. First, there is high genetic heterogeneity between populations. The effects of *UMOD* variants are dependent on genetic background and, thus, results may differ between Mediterranean and North European cohorts [7]. Secondly, SNPs seem to exert very small effects on eGFR, with only an estimated magnitude of <1%

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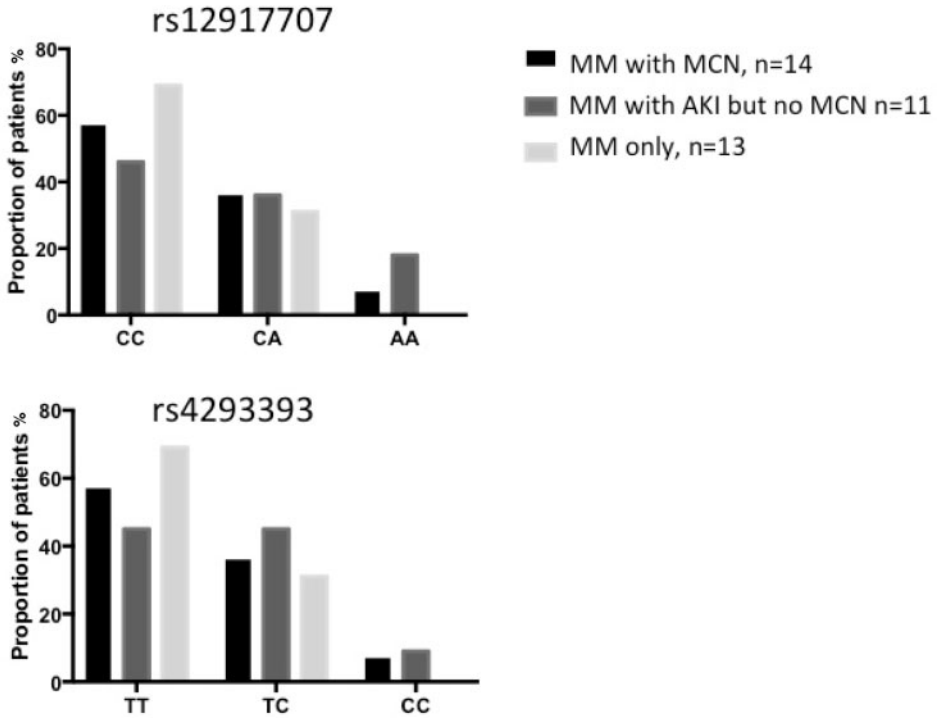

FIGURE 1: Distribution of *UMOD* promoter risk alleles in MM patients, and MM patients with MCN or non-MCN AKI.

detected in patients with long-term chronic kidney disease [8]. Even though a larger study may detect the predisposition towards a risk for MCN-related AKI, the SNP variants would not allow MM individuals prone to MCN to be identified at the individual level. In addition, exon-sequencing data were available from 22 MM patients and showed no specific mutations associated with the MCN phenotype. Recently, polymorphisms of exons 4 and 5 in *UMOD* have been studied in 24 patients with MM ± MCN. Consistent with our findings, whatever the severity of kidney injury, the frequency of polymorphisms was similar [9].

In conclusion, notwithstanding the small size of our cohort and the lack of biochemical analyses of the urinary uromodulin in our patients (i.e. glycosylation, sialylation, etc.), *UMOD* genetic variations do not appear to be major risk factors for developing MCN.

CONFLICT OF INTEREST STATEMENT

None declared.

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