

 GENETICS

## Evolving risks of *UMOD* variants

Common variants in *UMOD*, which encodes uromodulin, are associated with an increased risk of chronic kidney disease (CKD) and hypertension in the general population. Now, Olivier Devuyst and colleagues suggest that the high frequency of the top *UMOD* risk variant, rs4293393, might be the result of pathogen-driven natural selection.

The researchers report that the T allele of rs4293393, which is associated with CKD, hypertension, salt retention and increased urinary levels of uromodulin, is present in primates and in most anatomically modern human populations, whereas two archaic hominids — the Denisova and the Neanderthal — were homozygous for the rs4293393 C allele. They demonstrate that the T allele is the ancestral allele and the C allele likely arose in the human lineage after separation of the primate lineages but before separation of the lineage leading to the Denisovans and Neanderthals.

The ancestral susceptibility model for salt-sensitive hypertension suggests that variants that increase salt retention were

advantageous in ancient populations in hot, humid climates, but increase the risk of hypertension in modern populations in temperate climates.

Devuyst and colleagues found that the global distribution of the rs4293393 T allele does not fit this model, but does correlate with pathogen diversity and the prevalence of antibiotic-resistant, uropathogenic strains of *Escherichia coli*, suggesting that this variant is present at an increased frequency in areas with a high prevalence of urinary tract infections (UTIs).

Finally, the researchers showed an inverse correlation between urinary levels of uromodulin — which has antimicrobial properties — and markers of UTIs in a large population-based cohort. “These results substantiate the potential link between common, biologically active *UMOD* variants and protection against UTIs,” says Devuyst. The researchers conclude that the rs4293393 T allele has likely been conserved throughout human evolution because of its protective effect against UTIs.



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