A meta-analysis of genome-wide data from five European isolates reveals an association of COL22A1, SYT1, and GABRR2 with serum creatinine level.

Abstract:
Serum creatinine (S CR) is the most important biomarker for a quick and non-invasive assessment of kidney function in population-based surveys. A substantial proportion of the inter-individual variability in S CR level is explicable by genetic factors. We performed a meta-analysis of genome-wide association studies of S CR undertaken in five population isolates (‘discovery cohorts’), all of which are part of the European Special Population Network (EUROSPAN) project. Genes showing the strongest evidence for an association with SCR (candidate loci) were replicated in two additional population-based samples (‘replication cohorts’). After the discovery meta-analysis, 29 loci were selected for replication. Association between SCR level and polymorphisms in the collagen type XXII alpha 1 (COL22A1) gene, on chromosome 8, and in the synaptotagmin-1 (SYT1) gene, on chromosome 12, were successfully replicated in the replication cohorts (p value = 1.0 x 10(-6) and 1.7 x 10(-4), respectively). Evidence of association
was also found for polymorphisms in a locus including the gamma-aminobutyric acid receptor rho-2 (GABRR2) gene and the ubiquitin-conjugating enzyme E2-J1 (UBE2J1) gene (replication p value = 3.6 $\times$ 10^{-3}). Previously reported findings, associating glomerular filtration rate with SNPs in the uromodulin (UMOD) gene and in the schroom family member 3 (SCHROOM3) gene were also replicated. While confirming earlier results, our study provides new insights in the understanding of the genetic basis of serum creatinine regulatory processes. In particular, the association with the genes SYT1 and GABRR2 corroborate previous findings that highlighted a possible role of the neurotransmitters GABA receptors in the regulation of the glomerular basement membrane and a possible interaction between GABA receptors and synaptotagmin-I at the podocyte level.