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Introduction

Chronic kidney disease (CKD) is a major global health problem with an increasing prevalence, especially in older populations (1–3). Diabetes and hypertension are common risk factors for kidney damage (4) and major contributors to the increased CKD prevalence (3). Higher levels of albuminuria are associated with diabetic kidney disease (DKD) (5), increased risk of end-stage renal disease, cardiovascular disease and premature mortality (6–9).

Several genome-wide association studies have identified numerous single nucleotide polymorphisms (SNPs) associated with microalbuminuria (mAlb), urine albumin-to-creatinine ratio (UACR) or albumin excretion rate (AER) in CKD and/or DKD, with the most consistent findings related to rs1801239, a T/C-missense substitution in the *CUBN* gene(10,11). *CUBN* encodes the protein cubilin, involved in renal tubular albumin reabsorption (12).

The aim of this study was to confirm the influence of 90 SNPs previously associated with albuminuria (mAlb, UACR, or AER) (11,13–18) on the development of mAlb in patients from the UK Biobank cohort.

Methods

Multivariate logistic regression was used to evaluate mAlb with/without stratification by diabetes (threshold for association: p-value <0.05). The definition of mAlb was UACR>25 mg/g in women and >17 mg/g in men (19,20). Covariates included in the analysis were age, body-mass index, blood pressure medication, cholesterol medication, diabetes (comprising the categories Diabetes Diagnosed by a Doctor or Insulin), smoking and insulin. Ninety SNPs, considered as allelic dosage, were investigated. SNPs with minor allele frequency (MAF) <1% or not fulfilling Hardy-Weinberg Equilibrium (HWE) in controls were removed from the analysis (p<0.05). Individuals were excluded if they withdrew consent; inferred gender did not match reported gender; excessive heterozygosity or missingness; relatedness; non-European ancestry (based on centralised sample quality control performed by UK Biobank) (21,22).

Results

A total of 396,812 patients fulfilled inclusion criteria (Total Cohort). Among them, 19,787 had diabetes (Diabetic Cohort); the remaining 377,025 comprised the Non-Diabetic Cohort. Twenty SNPs were not considered for association analysis due to noncompliance with HWE (13) or MAF <1% (7).

Ten SNPs were independently associated with mAlb in the Total Cohort (*CELF2*-rs1109861 (A/C), *CUBN*-rs1801239 (C/T), *MYOM1*-rs4528660 (C/T), *CNTN4*-rs13079877 (G/A), *OSMR-AS1*-rs13160548 (C/T), *GSTA5/A3*-rs13215455 (C/T), *SHROOM3*-rs17319721 (A/G), *THSD7B*-rs17346504 (T/C), *COL4A3*-rs55703767 (T/G), *DDR1*-rs116772905 (T/C)). All but *CELF2*-rs1109861 (A/C) and *THSD7B*-rs17346504 (T/C) were also associated with mAlb in the Non-Diabetic Cohort, along with *CD48*-rs3795324 (C/A) and *ALLC/COLEC11*-rs12615970 (G/A). Eleven SNPs were independently associated with mAlb in the Diabetic Cohort (*THBS3*-rs914615 (G/A), *CUBN*-rs1801239 (CT), *GABRG3*-rs2192224 (T/G), *MUC1*-rs4072037 (T/C), *KIRREL3*-rs4935985 (A/C), *PTPRT*- rs6513791 (C/T), *ABHD4*-rs7145202 (T/C), *GABRR1*-rs9942471 (C/A), *ALLC/COLEC11*-rs12615970 (G/A), *PCBD1*-rs12764441 (T/C), *SHROOM3*-rs17319721 (A/G).

Two SNPs were consistently associated with mAlb in all three cohorts, CUBN-rs1801239 (C/T) and *SHROOM3*-rs17319721 (A/G). Carriers of *CUBN*-rs1801239-C (OR:1.26;$CI_{95\%}$:1.17-1.36;p=1.1E-09) and *SHROOM3*-rs17319721-G alleles (OR:0.94;$CI_{95\%}$:0.90-0.99;p=1.5E-02) showed a lower risk of mAlb.

Discussion

The *CUBN*-rs1801239-C and *SHROOM3*-rs17319721-G alleles were associated with a protective effect against mAlb, regardless of the presence of diabetes, confirming previous results for UACR and mAlb respectively (11,15). The *CUBN*-rs1801239 variant has been associated with UACR and mAlb in different ethnicities (11,15). The *SHROOM3*-rs17319721 variant, leading to shroom3 overexpression, has been associated with increased allograft fibrosis in renal transplant patients (23) and with eGFR, serum creatinine and mAlb in Europeans (24–28). These results emphasise the importance of *CUBN* and *SHROOM3* genes in CKD.