
See related articles, “Competing-Risk Analysis of ESRD and Death among Patients with Type 1 Diabetes and Macroalbuminuria,” on pages 537–544 and “Risk for ESRD in Type 1 Diabetes Remains High Despite Renoprotection,” on pages 545–553.

Are Cubilin (CUBN) Variants at the Heart of Urinary Albumin Excretion?

John F. O’Toole* and John R. Sedor†

*Department of Medicine and the Rammelkamp Center for Education and Research, MetroHealth System Campus, Cleveland, Ohio; and †Department of Physiology and Biophysics, Case Western Reserve University School of Medicine, Cleveland, Ohio

doi: 10.1681/ASN.2011010097

In this issue of JASN, Böger et al.1 report the results of a meta-analysis from approximately 63,000 individuals of European ancestry with genotype information identifying a susceptibility locus for the quantitative trait known as urinary albumin-to-creatinine ratio (UACR) and the clinical diagnosis microalbuminuria. A single variant within a protein-coding exon of CUBN, which encodes the proximal tubular epithelial cell apical protein, cubilin, reached genome-wide significance. The association of a cubilin variant with UACR and microalbuminuria resonates with existing knowledge about cubilin function from genetic, experimental animal, and in vitro studies.

CUBN mutations have been identified in patients with Imerslund-Grasbeck syndrome (IGS).2 This rare autosomal recessive disease is characterized by megaloblastic anemia and a variable degree of proteinuria. Cubilin was first identified as the intrinsic factor-cobalamin (IF-Cbl) receptor in the ileal mucosa and kidney of the rat,3 and the IGS mutations linked to CUBN disrupt the cubilin binding of IF-Cbl.4 Subsequent genetic studies of patients with IGS and without CUBN mutations have identified mutations in AMN5 that encodes a protein, amnionless, which is required for the localization of cubilin to the apical surface of epithelial cells.6 Taken together, these studies identify a molecular pathway to explain the IGS phenotype. Megaloblastic anemia in patients with IGS results from defects in the intestinal absorption of IF-Cbl. The variable degree of proteinuria, averaging 750 mg/d, in these patients is related to cubilin’s role in the proximal tubular reabsorption of albumin.7

Filtered albumin binds to an amino terminal domain of cubilin. Megalin directly interacts with two noncontiguous sites of the cubilin protein,12 and the megalin-cubilin-albumin complex is endocytosed by the cell. Megalin and cubilin are recycled to the apical membrane, and albumin is delivered to the lysosomal compartment.13 These data demonstrate that CUBN mutations do result in impairments of proximal tubular albumin reabsorption but not nephrotic-range proteinuria and are consistent with the study by Böger et al.,1 in which the degree of albuminuria is very modest. The variant identified in this report1 results in the conservative, nonsynonymous amino acid substitution I2984V. This residue falls within a protein domain previously reported to participate in the megalin–cubilin protein interaction.11 The identification of a coding variant within a functional protein domain suggests that the associated variant is causing increased albumin excretion. The cubilin protein, encoded by the variant gene, may be unable to bind megalin, a required event for normal endocytosis of albumin. However, the conservative nature of the substitution and the fact that bioinformatic algorithms predict the change to be benign with respect to function require this hypothesis to be experimentally proved. Further work will be needed to determine whether a variant cubilin with an I2984V substitution increases albuminuria.

The CUBN single-nucleotide polymorphism reported by Böger et al.1 accounts for only 0.15% of the variance in UACR, but because this variant is common, it would account for a large population-attributable risk for albuminuria. Regardless of whether the associated variant contributes to abnormal albumin excretion, its identification points to some interesting possibilities from a genetic perspective. First, if it is causal but has only a minor contribution to the variance in albuminuria, then CUBN should be scanned for rare variants not genotyped on current platforms that may have larger effects. Second, if it is not causal, then it must be viewed as a positional marker of a genomic region harboring the causal variant. The true causal variant may not have been identified because it was not genotyped in this study but lies in close proximity to the sentinel
single-nucleotide polymorphism responsible for the association signal. The causal variant could be located in the CUBN gene itself or reside in a nearby gene or regulatory region and may possibly have a more substantial effect size. As whole-genome sequencing accelerates and rare variants are more densely mapped, the data generated may clarify these possibilities.

Although successful gene mapping studies are provocative, the greatest challenge remains determining the clinical importance of associated variants. In this particular case, the identification of genetic variants regulating albumin excretion is of interest because of the epidemiologic association of albuminuria with renal failure and cardiovascular events. The authors note that they did not find this variant to be associated with estimated GFR, suggesting that cubilin-mediated mechanisms of abnormal albuminuria do not have a direct impact on glomerular function. The association of a CUBN variant with UACR does not discount the importance of glomerular mechanisms of albuminuria, which is clearly a complex phenotype with contributions from multiple genetic and environmental factors. Unfortunately, the authors do not comment on whether this CUBN variant is associated with an increased cardiovascular disease risk, although many of the cohorts used in their analysis were used to establish the association of UACR with cardiovascular events and mortality.15,16

The findings presented in this issue of JASN reinforce the previously established role of cubilin in proximal tubular albumin reabsorption and suggest that CUBN variants may modify the degree of albuminuria in the general population. Experimental work will define whether the CUBN mutation associated with UACR is causal or is a positional marker pointing to the true variant. Its relation with cardiovascular risk remains an open question. The association between the amount of albumin in the urine and renal progression or heart disease has been repeatedly and robustly demonstrated. The mechanism for this epidemiologic connection remains speculative. Measuring the association of CUBN variants with cardiovascular disease risk phenotypes and studying their effects on cubilin function may unravel this mystery and move the statistical association of CUBN with UACR toward clinical utility.

DISCLOSURES
None.

REFERENCES
Radiation Exposure in Dialysis Patients

David R. Pickens and Martin P. Sandler
Department of Radiology and Radiological Sciences, Vanderbilt School of Medicine, Nashville, Tennessee

doi: 10.1681/ASN.2011010105

Doses of radiation from medical imaging procedures including fluoroscopy, computed tomography (CT), and nuclear medicine procedures can be substantial in certain groups of patients for whom the likelihood of repetitive studies is high. Today, there is increasing concern that multiple imaging procedures leading to cumulative radiation exposure may increase the likelihood of developing cancer in the future, particularly when radiation exposure starts at an earlier age. Among these specialized groups of patients are those undergoing dialysis while awaiting kidney transplantation.

In a study reported in this issue of JASN, De Mauri et al.1 observed that patients who received renal replacement therapy (hemodialysis and/or renal transplantation) during a 3-year period had, in addition to the inherent risk for cancer, increased radiation exposure, placing them at a risk for cancer four times greater than the general population; cancer risk was 1.0 to 1.5 times greater during dialysis and 2.5 to 5.0 times greater after kidney transplantation. Adjusting for 23 patient deaths and six transplants, the study covered a total of 281 patient-years and measured cumulative effective dose (CED), which allows for comparisons or summation of radiation exposure generated from different kinds of images.

Patients ranged from 18 to >70 years, with 63% being in the 50- to 70-year group; 63 were male. Eighty-two patients were prevalent with a median dialysis period of 4 years; the remainder initiated dialysis during the study period. Younger patients and those on the transplant waiting list had higher radiation exposure and annual CED. Study patients received a total of 1303 examinations: 848 conventional diagnostic radiologic images, 248 CT scans, 108 nuclear medicine studies, and 99 interventional procedures. CT examinations accounted for 19% of studies and 76% of total CED; within that group, abdominal/pelvic examinations accounted for 43.1% of the procedures, 73.2% of the CT radiation exposure, and 55.6% of total CED. A total of 7.6% interventional procedures generated 8.1% CED, and 8.2% nuclear medicine procedures resulted in 7.6% CED.

Assumed risk factors for this study were derived from analyses of mortality data based on Japanese atomic bomb survivors exposed to radiation doses typical of two or three CT scans in adults, using a linear no-threshold model (LNT), which is not adjusted for factors such as rate of exposure or genetic repair. Although leading international scientific bodies believe that the use of the LNT model for estimating low-dose radiation risk is appropriate, many scientists contend that it is not supported by data at doses less than approximately 100 millisievert or at long-term dose rate up to at least 200 millisievert per year.2–5 However, the LNT model is still considered the most appropriate and conservative for the purposes of radiation protection.6

The authors cite studies by various authors to support their thesis that dialysis patients receive higher radiation doses than other chronically ill patients, further referencing the American College of Radiology white paper on radiation dose favoring more explicit tracking of CT-related exposures, including identifying exposures for specific populations, such as hemodialysis patients. The authors conclude that a significant number of non-notable findings or negative results present an imperative to rethink justification for repetitive CT examinations. Huda recommended that nonionizing alternatives should be considered and that the benefits should clearly exceed the risks of radiation exposure before CT examinations are performed. Furthermore, as diagnostic facilities implement measures to reduce radiation exposure, a reduction in the number of CT examinations should be accompanied by reduced exposures per examination when possible.

This study is an example of what is often seen in patient care settings where individuals of varying clinical experience order diagnostic imaging procedures. De Mauri et al.1 do not specify whether attending physicians, fellows, or residents ordered the studies; whether there were consultations with imaging specialists; or how benefits versus radiation risks for the imaging procedures were defined. In general, certain types of procedures are often overused because they are relatively easy to perform and a large amount of information is provided very quickly. The particular example described here, that of CT scans, can produce substantial cumulative doses of radiation when used multiple times.

The conservative approach to addressing the issue of cumulative radiation dose necessitates defining groups of patients who would be considered high risk for exposure to ionizing radiation. This group would likely include children because the potential for radiation-induced cancer is more likely over their lifetimes than in older patients. In circumstances in which clinical management appropriately requires multiple imaging procedures, careful monitoring of the cumulative radiation dose should be done and should be part of the patient’s record so that careful consider-