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Phenylethanolamine N-Methyltransferase Gene Polymorphisms and Adverse Outcomes in Acute Kidney Injury

Ahsan Alam[a] Daniel T. O'Connor[c] Mary C. Perianayagam[b] Alexey Y. Kolyada[b] Yuqing Chen[c] Fangwen Rao[c] Manjula Mahata[c] Sushil Mahata[c] Orfeas Liangos[b] Bertrand L. Jaber[b]

[a]Division of Nephrology, Tufts Medical Center and [b]Division of Nephrology, Kidney and Dialysis Research Laboratory, St. Elizabeth's Medical Center, Boston, Mass., and [c]Department of Medicine and Center for Human Genetics and Genomics, University of California at San Diego, La Jolla, Calif., USA

Key Words
Acute kidney injury · Phenylethanolamine N-methyltransferase · Single nucleotide polymorphisms · Mortality

Abstract
Background/Aims: The catecholaminergic pathway is important in the physical stress response; however, its role is not well understood in acute kidney injury (AKI). We studied single nucleotide polymorphisms (SNPs) of phenylethanolamine N-methyltransferase *(PNMT)*, the terminal enzyme of the catecholaminergic pathway, and their association with adverse outcomes in AKI. ***Methods:*** We performed a case-control study of 961 Caucasian subjects (194 with AKI and 767 controls). The *PNMT* promoter G–161A (rs876493) and coding A+1543G (rs5638) SNPs were genotyped and haplotypes generated. The outcomes of interest were the development of AKI, in-hospital mortality, dialysis requirement, oliguria, and hemodynamic shock. Urine catecholamines were measured in cases to explore genotype-phenotype correlations. ***Results:*** The *PNMT* +1543 G allele was associated with AKI [odds ratio (OR) 2.19, 95% confidence interval (CI): 1.04–4.60]. For AKI cases, each *PNMT* –161 A allele was associated with lower mortality (OR 0.58, 95% CI: 0.35–0.99) and hemodynamic shock (OR 0.63, 95% CI: 0.40–1.00). The *PNMT* +1543 G allele was associated with oliguria (OR 3.35, 95% CI: 1.13–9.95). Urine adrenaline was associated with increased hemodynamic shock and mortality, but was lowest in *PNMT* –161 A/A carriers. ***Conclusion:*** In Caucasians, *PNMT* SNPs are associated with the development of AKI, disease severity, and in-hospital mortality. The adrenergic pathway provides another area of focus in the study of AKI.

Introduction

Acute kidney injury (AKI) is an important and complex disorder associated with significant morbidity and mortality. The incidence of AKI in hospitalized patients is estimated to be 5–10%, and is much higher in the critically ill [1–3]. AKI, like any other acute physiologic stress,

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Bertrand L. Jaber, MD, MS
Department of Medicine, St. Elizabeth's Medical Center
736 Cambridge Street
Boston, MA 02135 (USA)
Tel. +1 617 562 7832, Fax +1 617 562 7797, E-Mail bertrand.jaber@caritaschristi.org

may evoke the biosynthesis and release of various adrenergic hormones [4]. Stress-regulated control of catecholamines, with epinephrine as the major stress hormone, may play an important role in the development, evolution, propagation, or resolution of AKI.

Physical stress results in epinephrine and norepinephrine release and the stimulation of the catecholamine biosynthetic enzymes, tyrosine hydroxylase, dopamine β-hydroxylase, and phenylethanolamine N-methyltransferase *(PNMT)* [5]. The biosynthetic activity of *PNMT*, the terminal enzyme of the catecholaminergic pathway, converts epinephrine from norepinephrine by N-methylation, thereby replenishing depleted stores [4, 6]. Genetic single nucleotide polymorphism (SNP) analyses have commonly been employed in the study of complex disease traits. Adrenergic pathway gene SNPs may result in an altered homeostatic response during periods of acute illness. Little is known of their role in the context of patients with AKI.

Using a case-control design and a candidate gene approach, we first examined the association of 2 *PNMT* gene SNPs with the development of hospital-acquired AKI in an adult Caucasian population. Among those hospitalized with AKI, we prospectively explored the association of each SNP and their common haplotypes with the outcomes of in-hospital mortality, dialysis requirement, oliguria, and hemodynamic shock. Finally, the SNPs and AKI-related outcomes were related to the intermediate phenotype of urine adrenaline and noradrenaline levels.

Subjects and Methods

Study Design and Population

Hospitalized patients with AKI were recruited from 2 tertiary care hospitals in Boston, Mass., USA. Subjects were recruited from November 2003 to January 2007. All eligible patients were ≥18 years of age and received in-hospital nephrology consultation for AKI. Subjects were excluded if they were pregnant, required chronic dialysis, had an organ transplant in the past 1 year, or any evidence of acute obstructive uropathy. Informed consent was obtained for each subject, and the Institutional Review Board at both hospitals approved the protocol.

In addition, we obtained data for a control group of 767 non-hospitalized adult Caucasian subjects who had been genotyped for the same 2 *PNMT* gene SNPs, but had no diagnosis of AKI. The mean (±standard deviation) age of the control group was 45 ± 17 years. Fifty-four percent were men and 19% had a diagnosis of hypertension.

Data Collection

Medical records were reviewed prospectively to retrieve data on the hospitalized patients with AKI including demographic characteristics, coexisting conditions, hospitalization course, and outcomes. AKI was defined at enrollment according to an increase in serum creatinine by 44, 89 or 133 μmol/l (0.5, 1.0 or 1.5 mg/dl) from a baseline level of ≤176, 177–434 or ≥435 μmol/l (≤1.9, 2.0–4.9 and ≥5.0 mg/dl), respectively [7]. Stages of AKI were later classified according to the staging system proposed by the AKI Network [8]. Sepsis was ascertained using the systemic inflammatory response syndrome criteria [9]. For subjects with multiple biogeographic ancestries, self-identified ethnicity was used, and our analysis was restricted only to Caucasian study participants to account for population stratification.

Genotyping Analyses

DNA was prepared from blood leukocytes with an automated device (X-tractor Gene, Corbett Robotics, Brisbane, Qld., Australia), and samples were genotyped using a Pyrosequencing™ I96A (Pyrosequencing AB, Uppsala, Sweden) instrument according to standardized protocol [10]. Resulting sequences were analyzed by visual inspection and automatically by SNP software. The *PNMT* local genomic region was 'tagged' with 2 SNPs: proximal promoter G–161A (rs876493) and coding region (exon 3) A+1543G (synonymous Lys152Lys, rs5638). Base positions are numbered with respect to the cap (exon 1 start) site, in National Center for Biotechnology Information genomic (phage lambda vector) source clone X52730 [11]. These 2 SNPs were selected since they spanned both the promoter and the 2,210-bp coding region, and were non-redundant in that their pair-wise correlations were relatively low ($r^2 = 0.02$ in 23 control white subjects). Given the low degree of linkage disequilibrium between these 2 SNPs by SNP spectral decomposition, the effective number of SNPs tested was ~1.98. We maintained a $p < 0.05$ as the threshold for significance due to the exploratory nature of our analysis.

Haplotypes were generated from the 2 *PNMT* gene SNPs using a previously described statistical algorithm (Haplotype Resolution, Version 3.0) [12]. The 2 most common haplotype distributions were haplotype 1 (–161G/+1543A) and haplotype 2 (–161A/+1543A), and these were expressed as the number of chromosomal copies of the haplotype for each patient. The –161G/+1543G haplotype did not exist in our cohort. We also created a diploid haplotype representing the number of copies of haplotypes 1 and 2 (haplotype 1/haplotype 1 homozygotes, haplotype 1/haplotype 2 heterozygotes, or haplotype 2/haplotype 2 homozygotes).

Urine Catecholamine Measurements

Urine adrenaline and noradrenaline were measured in patients with AKI using a competitive ELISA (Labor Diagnostika Nord, Nordhorn, Germany). Adrenaline and noradrenaline were extracted from urine samples using a *cis*-diol-specific affinity gel, acylated and then derivatized enzymatically for quantification. The limit of detection for adrenaline and noradrenaline in urine are 0.33 and 1.33 ng/ml, respectively. The intra-assay and inter-assay coefficients of variation were 11.0 and 14.3% for adrenaline, and 13.0 and 11.8% for noradrenaline. Catecholamine levels were normalized to creatinine excretion (mg/dl) from the same urine collection. A ratio of adrenaline to noradrenaline was also calculated. Due to markedly skewed distributions, catecholamine levels were log transformed for analysis.

Outcome Measures

The primary outcomes were all-cause in-hospital mortality, dialysis requirement during hospitalization, as well as the development of oliguria or hemodynamic shock. Dialysis requirement

Table 1. Observed and expected distribution for each *PNMT* gene polymorphism in cases and controls

Locus	SNP	Ref SNP No. (dbSNP)	Domain	Group	Variant allele	HWE p value
PNMT	–161 G to A	rs876493	promoter	cases controls	A (50%) A (45%)	0.14 0.13
PNMT	+1543 A to G	rs5638	exon 3 (Lys152Lys)	cases controls	G (4%) G (3%)	0.55 0.38

HWE = Hardy-Weinberg equilibrium.

was defined as the initiation of any intermittent or continuous dialysis therapy. Urine output was measured for a 24-hour period at study enrolment, and oliguria was defined as a urine volume <400 ml/day. Hemodynamic shock was defined by a systolic blood pressure <100 mm Hg and a heart rate >100 beats/min, or the use of vasopressor agents.

Statistical Analysis

Genotype frequencies for each *PNMT* gene polymorphism were examined for deviation from Hardy-Weinberg equilibrium using the χ^2 test. Comparisons across genotypes were performed for each covariate of interest. Data are presented as proportions, means and standard deviations, or as medians with interquartile ranges, as appropriate. The Student t or analysis of variance tests were used for normally distributed continuous measures, while the Wilcoxon rank sum or Kruskal-Wallis tests were used for non-parametric variables. We used χ^2 or Fisher exact tests for categorical variables.

We used an additive genetic model (i.e. copies of the minor allele or haplotype) for all logistic and linear regression analyses. All models were adjusted for age, sex, race, and treatment center. We also explored SNP-by-SNP interactions in all regression models.

Logistic regression analysis was used to examine the association of each *PNMT* gene polymorphism and haplotype, as well as urine catecholamine levels, with the outcomes of in-hospital death, dialysis requirement, and the presence of oliguria or hemodynamic shock. Urine output was log transformed due to a skewed distribution.

All statistical tests were performed with the use of SAS software, version 9.1 (SAS Institute, Cary, N.C., USA). A $p \leq 0.05$ was considered significant for all outcomes.

Results

Characteristics of the AKI (Case) and Control Cohort

A total of 961 Caucasian patients were included in the case-control study, of whom 194 were enrolled for a diagnosis of AKI. Of those with AKI, 82 (42%) of patients required dialysis and 49 (25%) died over a median follow-up of 16 days (interquartile range 9–26 days). The majority of subjects enrolled had severe AKI as defined by the AKIN criteria. There were 64 (33%) classified with stage 1, 32 (16%) with stage 2, and 93 (48%) with stage 3 AKI. Genotype analyses were performed on 194 subjects for the *PNMT* G–161A promoter SNP and 184 for the *PNMT* A+1543G coding SNP. The minor allele frequency of the *PNMT* promoter –161 A allele was 54%, but was only 3% for the coding +1543 G allele. Tests for Hardy-Weinberg equilibrium showed no deviation from expected frequencies (table 1).

Patients with AKI, on average, were 20 years older than the control subjects, and had a significantly higher prevalence of hypertension (78 vs. 19%; $p < 0.001$). The genotype frequency of the *PNMT* G–161A SNP did not vary between patients with AKI and control subjects. The *PNMT* +1543 G allele, however, was significantly associated with AKI, with an odds ratio (OR) of 2.19 [95% confidence interval (CI) 1.04–4.60], when adjusted for differences in age, sex, and presence of hypertension (table 2).

The characteristics of the AKI cohort stratified by *PNMT* genotype are shown in table 3. Patient demographics and disease severity measures did not significantly differ across genotypes, except at position –161, where the heterozygous (G/A) genotype was associated with a lower baseline serum creatinine compared to both homozygous genotypes ($p = 0.02$). Urine adrenaline was significantly lower among patients with the *PNMT* –161A/A genotype ($p = 0.04$). The *PNMT* +1543 A/A genotype was only associated with a higher prevalence of hypertension (80 vs. 56%, $p = 0.03$).

PNMT Genotypes and AKI-Related Outcomes

Each copy of the *PNMT* promoter –161 A allele was associated with 41% lower odds for in-hospital mortality, and this protective benefit persisted after multivariate adjustment (table 4). Similarly, there was a lower odds for hemodynamic shock in those carrying copies of the A allele (adjusted OR 0.63, 95% CI: 0.40–1.00). Although the effect

Table 2. Association of *PNMT* genotypes with the development of AKI

PNMT SNP	OR (95% CI)
–161 A allele (vs. G/G genotype) (n = 951)	
Unadjusted	0.81 (0.65–1.03)
Adjusted for age, sex, and presence of hypertension	0.81 (0.61–1.07)
+1543 G allele (vs. A/A genotype) (n = 961)	
Unadjusted	1.38 (0.76–2.49)
Adjusted for age, sex, and presence of hypertension	2.19 (1.04–4.60)*

* $p \leq 0.05$.

estimate was in the same direction towards a protective effect, there was no significant association with dialysis requirement or the development of oliguria (table 4).

The *PNMT* +1543 G/A genotype was associated with a 3.3-fold increased odds for oliguria, before and after adjusting for age, sex and treatment center. This SNP, however, was not associated with in-hospital death, dialysis requirement, or presence of hemodynamic shock.

PNMT Haplotypes and AKI-Related Outcomes

The most common haplotype was –161G/+1543A (haplotype 1) estimated on 231 chromosomes, while –161A/+1543A (haplotype 2) was detected on 199 chromosomes. The haplotype analyses revealed that haplotype 1 (increasing copies of –161G/+1543A) was associated with a higher prevalence of hemodynamic shock (adjusted OR 1.56, 95% CI: 1.00–2.44). Table 4 also shows that increasing copies of –161A/+1543A (haplotype 2) was associated with decreased in-hospital mortality (adjusted OR 0.60, 95% CI: 0.37–0.99) and less hemodynamic shock (adjusted OR 0.65, 95% CI: 0.42–1.00). Haplotype 2 also trended towards an association with less oliguria (adjusted OR 0.63, 95% CI: 0.37–1.08, p = 0.09).

We tested for SNP-by-SNP interactions, but found no significant associations with any of our outcomes (data not shown).

Urine Catecholamine Levels and AKI-Related Outcomes

We examined the association of urine adrenaline, noradrenaline, and their ratio with adverse outcomes (table 5). On multivariate analysis, each log increase in urine adrenaline was significantly associated with an adjusted 1.5-fold increased odds for in-hospital mortality, and a 1.36-fold increased odds for the presence of hemodynamic shock. Similarly, on multivariate analysis, each log increase in urine noradrenaline was associated with 1.23-fold increased odds for in-hospital mortality, and 1.32-fold increased odds for the presence of hemodynamic shock. There was no association between urine catecholamine levels and dialysis requirement or the presence of oliguria. We also found no interactions between vasopressor use and urine catecholamine excretion with any of the outcomes (data not shown).

Discussion

In the present study, we examined the association of a promoter and synonymous coding SNP of the *PNMT* gene with the development of AKI in a Caucasian population. The *PNMT* coding +1543 G allele was associated with more than a 2-fold increase in the development of AKI. In those with AKI, we studied the association of *PNMT* SNPs with disease severity and in-hospital mortality. The *PNMT* promoter –161 A allele was strongly associated with lower odds for in-hospital mortality and hemodynamic shock, while the *PNMT* +1543 G/A genotype was associated with oliguria.

The *PNMT* polymorphisms that we examined included a promoter and a coding (albeit synonymous, Lys-152Lys) SNP, both of which might influence gene expression. The *PNMT* promoter –161 A/A genotype was also associated with lower urine adrenaline levels. We also noted that higher urine adrenaline levels were associated with higher odds for in-hospital mortality. This relationship between genotype and intermediate phenotype supports the possibility of a functional role of the *PNMT* –161 promoter SNP.

We also conducted haplotype analyses to further refine our findings. Due to the low minor allele frequency of the *PNMT* +1543 SNP, the common haplotypes generated did not provide any additional information compared to the individual SNPs alone. This could also suggest that our candidate SNPs represent the functional polymorphism(s), and are not simply in the same haplotype block, i.e. close linkage disequilibrium, to another 'culprit' SNP. However, this clinical study does not establish a precise mechanistic link between *PNMT* gene expression and outcomes.

The adrenergic pathway has been studied in kidney disease, but there are limited genetic studies of these pathways in AKI. The catechol-O-methyltransferase (COMT) gene polymorphism (nonsynonymous G-to-A

Table 3. Characteristics of patients with AKI stratified by *PNMT* genotypes

Characteristic	*PNMT* promoter –161 G/A genotypes (n = 184)				*PNMT* coding +1543 A/G genotypes (n = 194)		
	GG (n = 41)	GA (n = 102)	AA (n = 41)	p value	AA (n = 178)	AG (n = 16)	p value
Age, years	67 ± 15	66 ± 15	62 ± 16	0.28	65 ± 15	68 ± 13	0.40
Male sex, n	22 (54)	49 (48)	29 (71)	0.05	97 (54)	8 (50)	0.73
BMI	33.4 ± 17.5	31.1 ± 8.6	30.9 ± 8.3	0.51	31.7 ± 11.3	32.5 ± 9.4	0.81
Contributing causes to AKI, n				0.27			0.22
Ischemic	11 (27)	36 (35)	7 (17)		50 (28)	6 (38)	
Nephrotoxic	8 (20)	15 (15)	6 (15)		30 (17)	0 (0)	
Septic	6 (15)	7 (7)	5 (12)		17 (10)	3 (19)	
Multifactorial/other	16 (39)	44 (43)	23 (56)		81 (46)	7 (44)	
Comorbid conditions, n							
Diabetes mellitus	17 (41)	42 (41)	21 (51)	0.53	80 (45)	6 (38)	0.57
Cardiovascular disease	33 (80)	67 (66)	28 (68)	0.22	124 (70)	11 (69)	0.94
Hypertension	32 (78)	78 (76)	34 (83)	0.70	142 (80)	9 (56)	0.03
Liver cirrhosis	3 (7)	12 (12)	2 (5)	0.39	14 (8)	3 (19)	0.14
Chronic lung disease	9 (22)	17 (17)	5 (12)	0.50	29 (16)	4 (25)	0.37
Chronic kidney disease	26 (63)	65 (64)	27 (66)	0.97	114 (64)	10 (63)	0.90
Medical (vs. surgical) admission, n	27 (66)	70 (69)	28 (68)	0.95	121 (68)	11 (69)	0.95
ICU admission, n	34 (83)	81 (79)	28 (68)	0.23	137 (77)	11 (69)	0.46
Presence of SIRS, n	24 (59)	43 (42)	19 (46)	0.21	84 (47)	5 (31)	0.22
Enrollment MAP, mm Hg	74.6 ± 16.6	74.2 ± 19.0	79.4 ± 14.5	0.26	75.9 ± 17.5	71.9 ± 17.8	0.39
Median serum creatinine, μmol/l							
Baseline	133 (98–168)	115 (89–168)	142 (115–213)	0.02	124 (98–168)	106 (89–151)	0.29
Enrollment	257 (204–346)	284 (195–390)	284 (195–470)	0.46	275 (204–399)	337 (222–426)	0.36
Peak	337 (248–434)	337 (239–443)	364 (231–550)	0.78	346 (231–479)	319 (248–443)	0.96
Discharge	177 (115–222)	168 (115–266)	204 (133–372)	0.23	177 (124–275)	177 (106–257)	0.79
AKI stage at enrollment, n				0.66			0.28
Stage 1	13 (32)	33 (32)	18 (44)		61 (34)	3 (19)	
Stage 2	6 (15)	20 (20)	4 (10)		27 (15)	5 (31)	
Stage 3	20 (49)	47 (46)	18 (44)		85 (48)	8 (50)	
Hospital length of stay, days	20 (11–32)	17 (9–25)	12 (10–21)	0.13	16 (9–26)	19 (14–27)	0.40
Median urine catecholamine level							
Adrenaline, ng/mg creatinine	6.8 (3.4–10.7)	6.7 (3.1–13.4)	3.5 (1.7–7.7)	0.04	5.9 (2.7–11.7)	7.1 (3.9–10.7)	0.59
Noradrenaline, ng/mg creatinine	11.8 (6.2–61.6)	16.7 (5.5–71.9)	29.1 (6.3–71.5)	0.94	17.4 (5.5–70.1)	31.0 (9.6–92.1)	0.40
Adrenaline-noradrenaline ratio	3.6 (0.8–10.8)	2.5 (0.9–11.0)	5.9 (1.4–23.5)	0.22	3.6 (0.9–12.4)	4.0 (1.8–26.7)	0.47

Figures in parentheses represent percentage. BMI = Body mass index; ICU = intensive care unit; SIRS = systemic inflammatory response syndrome; MAP = mean arterial pressure.

Table 4. Association of *PNMT* genotypes and haplotype with adverse clinical outcomes in patients with AKI

PNMT SNP	OR (95% CI)			
	in-hospital death	dialysis requirement	oliguria	hemodynamic shock
–161 A allele (vs. G/G genotype)				
Unadjusted	0.59 (0.35–0.99)*	0.82 (0.53–1.27)	0.68 (0.39–1.18)	0.65 (0.41–1.03)
Adjusted for age, sex and treatment center	0.58 (0.35–0.99)*	0.80 (0.51–1.25)	0.67 (0.38–1.20)	0.63 (0.40–1.00)*
+1543 G/A genotype (vs. A/A genotype)				
Unadjusted	1.88 (0.65–5.49)	1.41 (0.51–3.91)	3.23 (1.15–9.57)*	1.02 (0.35–2.93)
Adjusted for age, sex, and treatment center	1.85 (0.63–5.43)	1.48 (0.53–4.16)	3.35 (1.13–9.95)*	1.04 (0.36–3.04)
–161 A/+1543 A haplotype				
Unadjusted	0.61 (0.37–0.99)*	0.81 (0.53–1.23)	0.63 (0.37–1.06)	0.67 (0.44–1.04)
Adjusted for age, sex, and treatment center	0.60 (0.37–0.99)*	0.78 (0.51–1.19)	0.63 (0.37–1.08)	0.65 (0.42–1.00)*

* $p \leq 0.05$.

Table 5. Association of urine catecholamine levels with adverse clinical outcomes in patients with AKI

Urine catecholamine	OR (95% CI)			
	in-hospital death	dialysis requirement	oliguria	hemodynamic shock[1]
Adrenaline (per ng/mg log increase)				
Unadjusted	1.48 (1.07–2.04)*	1.17 (0.89–1.54)	1.00 (0.70–1.42)	1.33 (1.00–1.77)*
Adjusted for age, sex, treatment center, and vasopressor use	1.50 (1.06–2.13)*	1.14 (0.85–1.52)	0.89 (0.60–1.31)	1.36 (1.01–1.83)*
Noradrenaline (per ng/mg log increase)				
Unadjusted	1.27 (1.04–1.55)*	1.11 (0.93–1.32)	1.14 (0.92–1.42)	1.32 (1.09–1.58)*
Adjusted for age, sex, treatment center, and vasopressor use	1.23 (1.00–1.53)*	1.10 (0.92–1.32)	1.03 (0.81–1.31)	1.32 (1.10–1.59)*

* $p \leq 0.05$. [1] Model not adjusted for vasopressor use, as it is included in the definition of hemodynamic shock.

polymorphism in exon 4) was studied in 260 patients undergoing cardiac surgery. The COMT enzyme is essential for catecholamine degradation. Homozygosity for the minor allele, reflecting low COMT enzymatic activity, was found to be associated with a higher prevalence and longer duration of hemodynamic shock, incidence of AKI, and prolonged hospital stay [13]. A previous study by one of the coauthors examined adrenergic gene polymorphisms in patients with chronic kidney disease. These authors explored the gene variants in chromogranin A, an enzyme that regulates catecholamine storage and release and plays a role in influencing sympathetic tone, and showed an association with the risk of hypertensive kidney failure in black patients [14], while variants at several sites in the adrenergic pathway influenced urine albumin excretion [15]. We have also previously explored oxidative stress-related genes in AKI, and found that polymorphism in the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase p22phox was associated with dialysis requirement or in-hospital death [16]. The adrenergic pathway has been proposed to be important in critical illness, but this had not previously been extended to AKI. Exploration of additional candidate genes associated with catecholamine biosynthesis, catabolism, exocytosis, catecholamine receptors, and postreceptor signal transduction would be appropriate.

Limitations of our study include the sample size, which, even with 194 subjects with AKI, may be less than optimal for a gene association study and which is a vexing issue in genetic analyses of complex diseases. Also, the *PNMT* A+1543G polymorphism had a low minor allele frequency (~3%), enhancing the likelihood of a type II error for some of our associations. We included a spectrum of phenotypes likely to be influenced by adrenergic homeostasis, namely dialysis requirement, oliguria and hemodynamic shock, and considered these to be intermediate markers of mortality. We acknowledge that dialysis initiation and management of oliguria is subjective, and is influenced by patient as well as physician factors. Furthermore, we enrolled subjects with AKI at the time of nephrology consultation rather than at its onset. Finally, our findings are restricted to Caucasian subjects and cannot be generalized to other ethnic groups.

The strengths of our study include a substantial number of control subjects without AKI, which allowed us to examine whether the *PNMT* SNPs are associated with the development of AKI. For patients with AKI, we were able to prospectively and comprehensively capture in-hospital outcomes, without attrition or loss to follow-up. Our AKI population was seen and managed in 2 academic medical centers and we believe it is representative and generalizable to most tertiary care settings.

In conclusion, in the present study, we provide support for the hypothesis that *PNMT* gene polymorphisms play a role in characterizing the development of AKI as well as predicting clinical outcomes in patients with AKI. Specifically, *PNMT* SNPs are associated with in-hospital mortality, hemodynamic compromise, and adverse renal outcomes such as oliguria. We also found some correlation between the *PNMT* promoter G–161A SNP and urine adrenaline levels, suggesting a possible functional role for this polymorphism. This relationship should be further explored, and externally validated in other more diverse populations. Adrenergic gene pathways may provide valuable genomic biomarkers for the development of AKI, risk stratification, prognosis, and possibly response to therapeutic interventions.

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