



Polymorphisms in the SUFU gene are associated with organ injury protection and sepsis severity in patients with *Enterobacteriaceae* Bacteremia

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ABSTRACT

Background: Organ injury including acute kidney injury (AKI) and acute lung injury (ALI) are major contributors to mortality and morbidity in the setting of sepsis. Hedgehog pathway has been recognized as an important mediator in repair of organ injury. There are some clinical predictors associated with the development of organ injury in sepsis; however few host genetic risk factors have been identified and candidate genes for organ injury susceptibility and severity are largely unknown.

Methods: A prospective cohort study in a tertiary care hospital included 250 adult hospitalized patients with *Enterobacteriaceae* bacteremia. We selected a panel of 69 tagging SNPs for genes in the Hedgehog signaling pathway using the TagSNP functionality of the SNPInfo web server and designed a panel on the GoldenGate Veracode genotyping assay (Illumina). We confirmed Illumina data using Taqman allelic discrimination assays. We assessed SNPs in combination with clinical variables for associations with outcomes and organ injury.

Results: Significant associations were identified using logistic regression models, controlling for age, race and gender. From the 69 tagging SNPs, 5 SNPs were associated with renal function and 2 with APACHEII score after false discovery rate correction. After multivariate analysis SNPs rs10786691 ($p = 0.03$), rs12414407 ($p = 0.026$), rs10748825 ($p = 0.01$), and rs7078511 ($p = 0.006$), all in the suppressor of fused homolog (SUFU) gene, correlated with renal function. Likewise, SUFU SNPs rs7907760 ($p = 0.009$) and rs10748825 ($p = 0.029$) were associated with APACHEII score. SNPs rs12414407 and rs1078825 are in linkage disequilibrium (LD) with rs2296590, a SNP in the 5'-UTR region that is within a predicted transcription factor bind site for CCAAT-enhancer-binding proteins. In multivariate analyses functional SNP rs2296590 was correlated with renal function ($p = 0.004$) and APACHEII score ($p = 0.049$).

Conclusions: Host susceptibility factors play an important role in sepsis development and sepsis related organ injury. Polymorphisms in the SUFU gene (encoding for a negative regulator of the hedgehog signaling pathway) are associated with protection from *Enterobacteriaceae* bacteremia related organ injury and sepsis severity.

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1. Introduction

Sepsis is an important cause of mortality with increasing incidence rates heightening the need to identify new risk factors, interventions and treatments. An epidemiologic survey of sepsis in the US estimated that around 200,000 deaths each year result from sepsis (Angus et al., 2001). The incidence rate of sepsis-related

hospitalization doubled in the period from 2000 to 2008 (Hall et al., 2010). An increasing proportion of sepsis caused by gram negative bacilli compared to gram positive has been observed and higher mortality has been associated with sepsis resulting from gram negative bacilli, including *Enterobacteriaceae* (Feld, 2008; Martin et al., 2003).

Organ injury including acute kidney injury (AKI) and acute lung injury (ALI) are major contributors to mortality and morbidity in the setting of sepsis. AKI and ALI have been consistently linked to higher mortality rates in critically ill patients (Hudson et al., 1995; Uchino et al., 2005). Although several clinical risk factors associated with these organ injury outcomes have been identified,

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such as delay in initiation of adequate antibiotic therapy, obesity, or tobacco use; susceptibility related to host genetic factors also plays a role. For instance, some cytokine polymorphisms have been associated with sepsis related kidney injury. Using the known genetic risk factors and newly identified susceptibility genes it may be possible to stratify patients by genetic profiles and develop therapeutics that are individualized to patients specific genetic profiles.

Hedgehog signaling is one of the key regulators of animal development and has been extensively studied in the context of cancer. The conserved action of Hedgehog ligands is to switch the Gli transcription factors from being transcriptional repressors to activators. When receiving cells lack Hedgehog ligand, the Hedgehog ligand receptor, patched (PTCH), is bound and prevents membrane association of smoothened (SMO). Hedgehog binding to PTCH enables translocation of SMO to the primary cilium where its associated G protein activity inhibits suppressive kinase action on Gli, leaving Gli free to translocate to the nucleus and activate Hedgehog target genes. Two crucial negative regulators of this signaling process are suppressor of fused homolog (SUFU) and hedgehog interacting protein (HHIP). Hedgehog pathway also has an active role in immune activation and inflammation and its expression is increased while injured organs are being repaired (Watkins et al., 2003). Our group has demonstrated that Hedgehog signaling is differentially regulated in macrophage cell lines stimulated with lipopolysaccharide (LPS) (Yang et al., 2011b) and in mice treated systemically with LPS. (Yang et al., 2011a). The aim of this study was to identify host genetic related factors in the Hedgehog pathway associated with organ injury and sepsis severity in patients with *Enterobacteriaceae* bacteremia.

2. Materials and methods

2.1. Ethics statement

The present project is in compliance with the Helsinki Declaration (Ethical Principles for Medical Research Involving Human Subjects). Written informed consent from participants was obtained according to protocols approved by the Institutional Review Board (IRB) at Duke University Hospital. Analyses of clinical data have been performed under an approved protocol at the University of Colorado Denver.

2.2. Patients and data collection

A prospective cohort study in a tertiary care hospital that included adult patients hospitalized with *Enterobacteriaceae* sepsis and bacteremia was used for the study. The study participants consisted of subjects selected from the Sepsis Registry at the Duke University Medical Center, Durham, North Carolina. The data collection took place from 2002 to 2007. The number of patients enrolled was uniform throughout the study period, with the exception of 2005 in which fewer participants were enrolled. Inclusion criteria for the study were defined as adults (≥ 18 years) with culture-confirmed *Enterobacteriaceae* bacteremia since it was a designed adult based study only. Exclusion criteria were negative blood cultures, outpatient status and isolation of any other pathogen besides *Enterobacteriaceae* from blood culture. The study collected clinical data and microbiologic features from 250 patients.

2.2.1. Clinical variables

Clinical variables included: (1) demographics: age, sex and gender; (2) comorbidities and risk factors: presence or absence of diabetes mellitus (DM), neoplasm, use of corticosteroids at presentation, surgery in the previous 30 days, transplanted organ recipient status, exposure to antibiotics over the last 30 days, and

hemodialysis (HD); (3) symptoms: presence or absence of fever, temperature ≥ 38 °C, days of symptoms before presentation; (4) route of acquisition: community acquired vs. health care associated; (5) primary known sources of bacteremia: urinary, biliary, pneumonia or indwelling intravascular catheters related blood stream infection (CRBSI); (6) laboratory data: white blood cell count (WBC), platelet count, serum creatinine and albumin; (7) sepsis severity score (APACHE II); (8) complications: presence or absence of acute organ injury (AKI or ALI), septic shock, disseminated intravascular coagulation (DIC), mechanical ventilation (MV), death caused by bacteremia or all cause attributable mortality; (9) total days of effective antibiotic therapy; and (10) microbiology characteristics, in particular, the type of *Enterobacteriaceae* in the blood culture. Blood cultures were processed using the BACTEC 9240 automated culturing system. Antibiotic exposure was defined as any antibiotic therapy >24 h but <30 days prior to the time when the positive blood cultures were drawn. Total days of effective antibiotic therapy were defined as the time an effective antibiotic was started based on antibiogram susceptibility results of the isolate to the time were therapy was completed. Neoplasm included any type of cancer: hematologic or solid organ. Indwelling intravascular catheter included any peripheral, central, peripherally inserted, tunneled or arterial intravascular catheters. Infection of a catheter line was defined as having simultaneous positive blood cultures from the line and from a peripheral site with first positivity arising from the line. Analyses were performed excluding missing values.

2.3. Blood collection and DNA extraction

Blood samples and DNA was collected and extracted using Paxgene tubes and extraction kits (Qiagen).

2.4. Genotyping

The TagSNP functionality of the SNPInfo web server (Xu and Taylor, 2009) was used to select 69 tagging SNPs in the Hedgehog pathway and variation in both European and African American populations was captured. SNPs were scored in Illumina's Assay Design Tool (ADT) and those with acceptable scores (>0.6) were included in the Oligonucleotide Pool Assay (OPA) designed as a GoldenGate Veracode genotyping panel (Illumina). For SNPs with significant associations, we verified the Hardy–Weinberg equilibrium (HWE) and examined other SNPs in the linkage disequilibrium (LD) bin with predictions for functional consequence of the SNP using the National Institute of Environmental Health Sciences (NIEHS) SNPInfo website (Xu and Taylor, 2009). In addition, we genotyped the functional SNPs using a pre-designed Taqman allelic discrimination assay (Applied Biosystems).

2.5. Statistical analysis

Continuous variables were assessed for normal distribution using the Shapiro–Wilk test. Initial individual SNP analysis was performed under the additive genetic model with logistic or linear regression for the clinical variable outcome (e.g., ALI, AKI, APACHEII, etc.) as the dependent variable and the SNPs, age, race and gender as independent variables. The false discovery rate (FDR) method was used to correct p -values for multiple testing and generate new q -values. SNPs with q -values <0.05 or functional SNPs were considered for further study with a multivariate analysis. Bivariate analysis for the outcome of interest was conducted using a chi square test for dichotomous variables and t -test or linear regression for continuous variables. Variables were included in the analysis if the association with the outcome variable produced a p -value of ≤ 0.025 and each SNP that remained statistically

significant after FDR correction, in a forward, stepwise multivariate linear and logistic regression models. We considered a two-sided p -value <0.05 to be statistically significant. All analyses were performed using STATA software; version 12.0.

2.6. Transcription factor binding site analysis

Transcription factor binding site analysis was performed in MatInspector (Genomatix).

3. Results

3.1. Clinical characteristics of the Enterobacteriaceae Bacteremia cohort

Data from 250 selected patients with Enterobacteriaceae bacteremia were analyzed (Table 1). The mean age was 60.2 ± 14.6 ; 56.4% of patients were male, 72.4% were Caucasian and 27.6% were African-American. Fever was present in 89.8% of the patients and the mean duration of symptoms was 3.9 ± 6.2 days. We identified a total of 34.0% healthcare-associated bacteremias and 66.0% community acquired bacteremias. From the analyzed cohort, 40.9% of patients had previously received antibiotic therapy, 33.2% had a surgical procedure within the 30-day period preceding presentation and 48.6% had neoplasm. Evaluation of co-morbidities found that 30.0% of patients had a diagnosis of DM, 12.2% were transplant recipients and 15.0% received hemodialysis. The three most common known sources of bacteremia were genitourinary (23.5%),

catheter related blood stream infection (CRBSI) (17.2%), pneumonia (5.9%) and biliary tract (3.9%). The Enterobacteriaceae bacteremias were more commonly caused by *Escherichia coli* (34.0%) and *Klebsiella pneumoniae* (24.3%). Mean laboratory data was WBC: $10.6 \pm 9.3 \times 10^3/\mu\text{L}$, platelet count: $153.3 \pm 116.1 \times 10^9/\text{L}$, albumin: 2.7 ± 0.8 g/dl and creatinine: 2.5 ± 2.8 mg/dl. The mean APACHE II score was 16.2 ± 4.8 with a substantial proportion of patients developing septic shock (34.6%), acute lung injury (14.5%), acute kidney injury (7.5%), DIC (6.9%), death (12.3%) or requiring MV (9.4%).

3.2. Hedgehog pathway SNPs and association with clinical outcomes variables

69 Tagging SNPs were selected in six genes (PTCH1, PTCH2, GLI1, SMO, HHIP and SUFU) within the Hedgehog pathway. From the 69 tagging SNPs, 5 SNPs (rs10786691, rs12414407, rs10748825, rs10748827 and rs7078511) in the SUFU gene were associated with serum creatinine levels adjusted by age, race and gender after FDR correction. 2 SNPs (rs7907760, rs10748825) in the SUFU gene were associated with APACHEII score. No associations were present for ALI, death or septic shock after FDR correction. The selected SNPs were in HWE.

3.2.1. Organ injury and severity of sepsis

3.2.1.1. Renal function. Creatinine levels were associated with age, race, antibiotic exposure over the last 30 days, neoplasm, CRBSI,

Table 1
Cohort clinical and demographic characteristics with outcome bivariate analysis results. Creatinine (mg/dl). Mean: Mean \pm SD or Number of occurrences (%). * p -Value <0.025 ; AB: antibiotics; CRBSI: Catheter related blood stream infection; APACHE: Acute Physiology and Chronic Health Evaluation; DIC: Disseminated Intravascular coagulation.

Variable	N=	Mean	p-Value		
			ALI	Creatinine	APACHEII
Age	249	60.2 \pm 14.6	0.5	0.015*	0.001*
Race			0.34	0.01*	0.11
Caucasian	250	181 (72.4%)			
African-American	250	69 (27.6%)			
Gender (Male)	250	141 (56.4%)	0.18	0.56	0.95
Fever	244	219 (89.8%)	0.92	0.46	0.79
Days of Symptoms	241	3.9 \pm 6.2	0.86	0.45	0.61
Route					
Health care	250	85 (34%)	0.187	0.58	0.09
Community Acquired	250	165 (66%)	0.93	0.58	0.09
AB exposure last 30 days	242	99 (40.9%)	0.88	0.024*	0.72
Neoplasm	247	120 (48.6%)	0.15	0.00001*	0.38
Bacteremia					
<i>Escherichia coli</i>	247	84 (34.0%)	0.83	0.1	0.05
<i>Klebsiella pneumoniae</i>	247	60 (24.3%)	0.75	0.09	0.71
Source					
Urinary	234	55 (23.5%)	0.311	0.48	0.01*
CRBSI	239	41 (17.2%)	0.97	0.00001*	0.59
Biliary	234	9 (3.8%)	0.76	0.36	0.23
Pneumonia	239	14 (5.9%)	0.541	0.72	0.11
Surgery in last 30 days	244	81 (33.2%)	0.03	0.024*	0.18
Diabetes mellitus	247	74 (30.0%)	0.08	0.0001*	0.07
Transplant recipient	246	30 (12.2%)	0.1	0.079	0.013*
Corticosteroids	245	58 (23.7%)	0.966	0.69	0.06
Septic shock	159	55 (34.6%)	0.06	0.96	0.7
APACHE II (0-71)	250	16.2 \pm 4.8	0.24	0.0001*	NA
White blood count ($\times 10^3/\mu\text{L}$)	248	10.6 \pm 9.3	0.14	0.0001*	0.13
Platelets ($\times 10^9/\text{L}$)	246	153.3 \pm 116.1	0.09	0.73	0.03
Albumin (gr/dl)	108	2.7 \pm 0.8	0.07	0.038	0.72
Creatinine (mg/dl)	246	2.5 \pm 2.8	0.89	NA	0.0001*
Days of effective AB therapy	218	16.8 \pm 12.3	0.3	0.94	0.28
Acute lung injury	159	23 (14.5%)	NA	0.82	0.24
Acute kidney injury	159	12 (7.5%)	0.053	NA	0.004
DIC	159	11 (6.9%)	0.004*	0.78	0.36
Mechanical ventilation	244	23 (9.4%)	$<0.005^*$	0.49	0.002*
Hemodialysis	246	37 (15.0%)	0.06	0.00001*	0.005*
Death (all causes)	244	30 (12.3%)	0.002*	0.27	0.0007*

surgery over the last 30 days, DM, APACHE II score, WBC and HD in a bivariate analysis.

In a multivariate analysis, including the selected individual SNPs after FDR correction, rs10786691 ($p = 0.03$), rs12414407 ($p = 0.026$), rs10748825 ($p = 0.01$), and rs7078511 ($p = 0.006$) were correlated with renal function. In contrast, SNP rs10748827 was not statistically significant after adjustment ($p = 0.06$) (Table 2). Additionally, WBC, HD, DM, neoplasm and race were also independently associated with renal function.

3.2.1.2. APACHE II score. Severity of sepsis based on APACHEII score was associated with age, urinary source, transplant recipient, creatinine levels, MV, HD and death in a bivariate analysis (Table 1). In a multivariate analysis that included selected SNPs after FDR correction we determined that SUFU gene SNPs rs7907760 ($p = 0.009$) and rs10748825 ($p = 0.029$) remained statistically significantly associated with APACHEII score.

3.2.1.3. Acute lung injury. In a bivariate analysis acute lung injury was associated with DIC, MV and death. After FDR correction none of the SNPs were significantly associated with ALI. Although a low number of ALI cases; from SNPs associated with renal function or APACHEII score; SUFU SNPs rs12414407 (odds ratio (OR) 0.29; 95% confidence interval (CI) 0.13–0.66; $p = 0.003$) and rs10748827 (OR 0.37; 95% CI 0.16–0.84; $p = 0.018$) were significantly correlated with ALI in a multivariate analysis (Table 2).

3.2.1.4. Other potential outcome variables. Additional analyses were conducted to investigate other potential markers of sepsis severity, but no correlations with septic shock, DIC or bacteremia-related death were observed.

3.2.2. SUFU SNP consideration

SUFU SNPs rs12414407 and rs10748825 are in high linkage disequilibrium with rs2296590 (Fig. 1). rs2296590 (minor allele frequency = 0.325) is in the promoter (−1368 from the transcription start site [TSS]) and is in a predicted transcription factor (TF) binding site for CEBP (CCAAT-enhancer-binding proteins), among others (Supplemental Table S1). Additionally other predicted TFs included cAMP-responsive element binding proteins (CREB) and Nuclear respiratory factor 1 (NRF1). In a bivariate analysis rs2296590 was correlated with renal function ($p < 0.0001$) and APACHEII score ($p = 0.001$) but was not correlated with lung injury

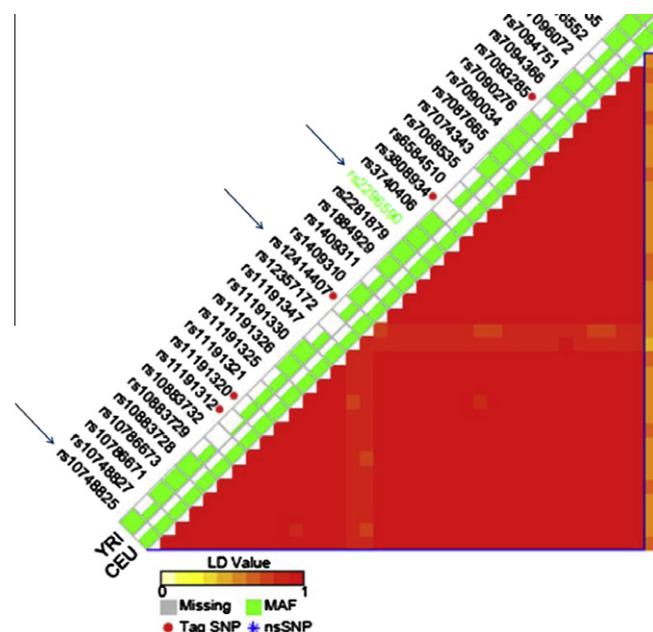


Fig. 1. Linkage disequilibrium map for the SUFU gene demonstrates high LD value between the selected SNPs (blue arrows). MAF: minor allele frequency. (For interpretation of color in this figure, the reader is referred to the web version of this article.)

($p = 0.2$). In a multivariate analysis the correlation with renal function and APACHEII score was still significant ($p = 0.004$ and $p = 0.049$, respectively) (Table 2).

4. Discussion

The SUFU gene is a negative regulator of the Hedgehog signaling pathway; and we found a subset of polymorphisms within the SUFU gene that are independently associated with improved renal function and less severe *Enterobacteriaceae* bacteremia related sepsis syndrome. Host genetic factors conferring distinctive prognostic indicators in sepsis are widely described in the literature (Namath and Patterson, 2009); however, contradictory findings have called these associations into question (Clark and Baudouin, 2006). Difficulties in precisely defining the sepsis phenotype and the marked heterogeneity in patient populations may explain some of the

Table 2
Multivariate analysis of outcome variables and selected SUFU gene SNPs.

	Creatinine (mg/dl)			Coefficient	95% CI	p-Value
	Genotype 0	Genotype 1	Genotype 2			
<i>Multivariable analysis of outcome variables with selected SNPs</i>						
rs10786691	3.25 ± 2.88 (47)	2.49 ± 2.69 (118)	2.25 ± 3.00 (72)	−0.16	(−0.30)–(−0.02)	0.03
rs12414407	3.64 ± 3.20 (27)	2.36 ± 2.22 (114)	2.46 ± 3.27 (99)	−0.18	(−0.33)–(−0.02)	0.026
rs10748825	3.53 ± 3.04 (36)	2.41 ± 2.41 (118)	2.15 ± 2.86 (85)	−0.19	(−0.34)–(−0.05)	0.01
rs10748827	3.43 ± 3.20 (22)	2.38 ± 2.25 (116)	2.55 ± 3.29 (102)	−0.14	(−0.30)–0.006	0.06
rs7078511	3.75 ± 3.75 (70)	2.26 ± 2.41 (111)	1.64 ± 1.57 (59)	−0.20	(−0.34)–(−0.06)	0.006
rs2296590	3.80 ± 3.18 (28)	2.51 ± 2.60 (114)	2.20 ± 2.88 (78)	−0.23	(−0.39)–(−0.76)	0.004
<i>APACHEII Score</i>						
rs10748825	18.72 ± 6.39 (36)	16.22 ± 4.62 (120)	15.13 ± 4.04 (87)	−1.00	(−1.90)–(−0.11)	0.029
rs7907760	18.29 ± 6.13 (49)	16.12 ± 4.47 (130)	14.94 ± 3.97 (69)	−1.15	(−2.00)–(−0.29)	0.009
rs2296590	18.61 ± 5.98 (28)	15.96 ± 4.32 (115)	15.28 ± 4.51 (80)	−0.95	(−1.90)–(−0.002)	0.049
<i>ALI (Acute Lung Injury)</i>						
	Genotype 0	Genotype 1	Genotype 2	OR	95% CI	p-Value
rs12414407	7 (30.4%)	10 (43.5%)	6 (26.1%)	0.29	0.13–0.66	0.003
rs10748827	6 (26.1%)	10 (43.5%)	7 (30.4%)	0.37	0.16–0.84	0.018
rs2296590*	6 (27.3%)	11 (50.0%)	5 (22.7%)	0.54	0.26–1.15	0.111

* rs2296590 was analyzed with 22 patients only since the genotype output of one of the patients was not interpretable.

discrepancies in these findings. The cohort described herein represents a more homogenous patient population since it was infected with a specific group of gram-negative organisms, *Enterobacteriaceae*, which may possess characteristic pathogenic factors. In addition, the organ injury observed in these patients was defined using physiologically-relevant measures such as creatinine levels and the APACHEII score. Other notable features of the cohort were the presence of a significant proportion of neoplasm and CRBSI within the cohort; these factors may correlate independently with greater severity of sepsis or increase predisposition to *Enterobacteriaceae* colonization.

Previous genetic associations with lung injury in sepsis have included polymorphisms in the surfactant protein B (Gong et al., 2004), angiotensin converting enzyme (ACE) (Marshall et al., 2002), duffy antigen/receptor for chemokines (Kangelaris et al., 2012) and myosin light chain kinase (MYLK) genes (Gao et al., 2006). Additionally, polymorphisms of TNF- α , IL-6, IL-10 and NADPH oxidase among others have been associated with AKI in sepsis (Haase-Fielitz et al., 2007).

The SUFU gene encodes a negative regulator of the sonic hedgehog (SHH) signaling pathway. This pathway was initially described as critical in embryonic development (Nusslein-Volhard and Wieschaus, 1980) and has since been associated with tumor genesis, particularly in medulloblastoma (Corcoran and Scott, 2006) and skin basal cell carcinoma (Xie et al., 1998). SHH has been implicated in immune activation processes as well. Alveolar macrophages, infiltrating lymphocytes and circulating T lymphocytes express PTCH, the Hedgehog ligand receptor (Stewart et al., 2003). SHH has been shown to be critical for T lymphocyte development, CD4 + T cell activation and myeloid cell maturation in the thymus (Crompton et al., 2007; Stewart et al., 2002; Varas et al., 2008). Additionally, commercial recombinant preparation of SHH up-regulates PTCH and leads to production of pro-inflammatory cytokines in human peripheral blood mononuclear cells (PBMC). PTCH expression in macrophages increased after stimulation with lipopolysaccharide (LPS) derived from *E. coli* (Wakelin et al., 2008). Our previous work demonstrated that mice heterozygous for PTCH were more responsive to systemic LPS (Yang et al., 2011a). Furthermore the SHH pathway has also been implicated in organ injury repair. Animal models have shown increased SHH expression in limb ischemia angiogenesis (Pola et al., 2001), lung injury (Pogach et al., 2007; Watkins et al., 2003) and kidney injury (Ding et al., 2012).

The association with protection from lung injury was not as strong possibly in part due to low number of observations with this variable and thus conclusive association with this particular organ injury are not possible to make. Potential functional follow up with polymorphisms within this gene were showed after rs2296590, a polymorphism in the promoter of SUFU within a prediction binding site for the transcription factor CEBP, also was independently associated with renal function and APACHEII score. CEBP has been implicated in inflammasome activation during endoplasmic reticulum stress (Murakami et al., 2012), and is associated with LPS-induced tubular damage (Glaros et al., 2012). In addition, CEBP is part of the mechanism of cellular stress response in kidney injury (van de Water et al., 2006). Furthermore, this SNP also predicted a binding site for CREB and NFR1 transcription factors which are important regulators in LPS-induced inflammation to mitochondrial biogenesis (Suliman et al., 2010).

Since renal failure and the severity of sepsis are well established prognostic factors in this setting, the associated SUFU polymorphisms may have a potential role as possible prognostic factors in *Enterobacteriaceae* related sepsis syndrome as well.

Unfortunately, different types of sepsis-related organ injury markers such as mental status changes or acute liver injury were not documented; therefore analysis for associations was not possible. Likewise, analysis of other potential outcomes or markers of

sepsis severity such a DIC or septic shock did not yield significant associations. The main limitation of our study is that the findings need to be validated in an independent cohort. Furthermore, these associations may be limited to *Enterobacteriaceae*, thus extension of our findings to gram-positive bacteria or other pathogens related sepsis syndrome would be inappropriate unless these pathogens were studied directly. This will be especially true if the underlying mechanisms are LPS mediated in humans. One additional limitation is that our racially heterogeneous cohort had insufficient size to investigate population stratification by race. Although adjustment for race was included in our analyses, differential genetic backgrounds related to race could alter susceptibility to infection as well.

5. Conclusions

Polymorphisms in the SUFU gene (encoding for a negative regulator of the hedgehog signaling pathway) are associated with protection from *Enterobacteriaceae* bacteremia related organ injury and sepsis severity based on serum creatinine levels and APACHEII score. This association may be explained in part due to the polymorphism changing binding of transcription factor CEBP. Further validation of this association through independent cohorts is warranted to establish potential tools for risk stratification or therapeutic options in patients with *Enterobacteriaceae* bacteremia.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.meegid.2013.03.025>.

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