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**No Association between Genetic Loci near *IRF2* and *TBX1* and Acute Kidney Injury in the Critically Ill***To the Editor:*

Acute kidney injury (AKI) is common in critical care and is independently associated with increased morbidity and mortality (1). No clinical treatments exist, and risk factors such as sepsis or diabetes mellitus (2) cannot exclusively explain AKI. Genetic predisposition plausibly contributes to the occurrence and pathophysiology of AKI, although genetic association studies have reported conflicting findings (3).

Zhao recently suggested associations between four SNPs near the *IRF2* (transcription factor interferon regulatory factor 2) and *TBX1* (transcription factor T-box 1) genes and AKI development in critically ill patients (4). Nonetheless, larger studies and external replication cohorts are warranted to confirm or refute their findings (4). Accordingly, we aimed to replicate the previous findings by Zhao and colleagues (4).

We conducted a prospective, multicenter, observational cohort study in intensive care units in Finland. The outcome was development of AKI by the Kidney Disease: Improving Global Outcomes (KDIGO) criteria (5), and thus was based on both daily measured creatinine and hourly measured urine output data. We performed our primary analysis considering stage 2 and 3 to be severe AKI (6) compared with patients without AKI (KDIGO stage 0). We performed a secondary analysis with AKI stage 1–3, an analysis with AKI defined as a 0.3-mg/dl or 50% increase in serum creatinine from baseline for at least 2 consecutive days, and a sensitivity analysis with cardiac surgery patients only (4). We excluded patients with chronic kidney disease, defined as an estimated glomerular filtration rate <60 ml/min/1.73 m² for at least 3 months, to strengthen the AKI phenotype. The Ethics Committee of Helsinki University Hospital approved the study.

Human whole blood samples were stored at –80°C for subsequent DNA isolation from frozen blood in a chemagic DNA Blood10k Kit on a chemagic 360 instrument (Perkin Elmer). We genotyped the four SNPs with previous significant associations with AKI ($P < 0.05$) (4): rs62341639 and rs62341657 on chromosome 4 near *IRF2* and rs9617814 and rs10854554 on chromosome 22 near *TBX1*. Because of primer design limitations, we revealed rs1463998 ($r^2 = 0.65$; $D' = 1.0$) and rs1217965

($r^2 = 0.29$; $D' = 0.66$) to be best proxy SNPs for rs62341657. Finally, we genotyped the SNPs rs62341639, rs1463998, and rs1217965 on chromosome 4 and rs9617814 and rs10854554 on chromosome 22.

We performed our main analyses with the additive model, similar to the previous study, and second, extended our analyses using two different heritage models: dominant and recessive.

We performed the genotyping with iPLEX Gold chemistry (Agena) and genetic association analysis through logistic regression, using PLINK software (version 1.07). We examined the genotyping quality by a detailed quality control procedure consisting of success rate check, duplicated samples, water controls, and Hardy-Weinberg Equilibrium testing. All statistical analysis was performed with Statistical Package for the Social Sciences (version 22) (IBM Corp.). The level of statistical significance was set to 0.05 as a replication study. We performed power calculations with Quanto software (James Gauderman, University of Southern California). A 39% AKI incidence was used (1). We used minor allele frequencies (MAFs) from gnomAD database for European (Finnish) populations (7). We assumed odds ratios (ORs) from the replication cohort of the previous study (4). We assumed to perform 10 tests, and because of multiple testing, we adjusted the significant P value to 0.005. The power was 77% for rs62341639 (MAF, 0.12; OR, 0.71), 85% for rs9617814 (MAF, 0.29; OR, 0.77), and 95% for rs10854554 (MAF, 0.24; OR, 0.72).

Of 2,642 adult patients with DNA available and without chronic kidney disease, 1,065 (40% of 2,642) had AKI (KDIGO stage 1–3), of which 625 (24% of 2,642) had severe AKI (KDIGO stage 2–3). All the tested SNPs were in Hardy-Weinberg Equilibrium ($P > 0.05$). The success rates, indicating the percentage of the wells that scored above the success threshold for genotyping, varied between 99.0% and 99.9%.

None of the genotyped SNPs was associated with severe AKI (KDIGO stage 2 or 3), nor with AKI (KDIGO stage 1, 2, or 3; Table 1). Adjusting for age, sex, diabetes, hypertension, sepsis, and renal replacement therapy did not change the results (Table 1), regardless of the genetic model. Excluding sepsis and renal replacement therapy from adjustment did not change the results. Using the definition of AKI from the previous study (4), adjusting for age, sex, diabetes, and hypertension did not affect findings significantly. The sensitivity analysis with 227 cardiac surgery patients revealed no association between the SNPs and AKI development (Table 2). Minor alleles of rs1217965, rs1463998, and rs62341639 showed an OR point-estimate lower than 1, whereas the minor alleles of rs9617814 and rs10854554 showed an OR above 1 (not significant).

Notably, we could not replicate previously published associations between SNPs near *IRF2* and *TBX1* and AKI development (4) in a prospective cohort of critically ill patients. We were not able to confirm the minor alleles of rs9617814 and rs10854554 to be protective (4). We performed our analysis as recommended (8) by using the same analytic methods that were used in the previous study.

Some possible explanations for the failure in replication attempt need consideration. First, we defined AKI according to the most widely adapted KDIGO criteria. Nonetheless, our additional analysis (available on request) using the same AKI definition did not influence the results significantly. Second, we were unable to

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Table 1. Associations between the SNPs and Severe AKI* or AKI†, Using an Additive Genetic Model

SNP	Minor Allele	Severe AKI (KDIGO Stage 2 or 3)			AKI (KDIGO Stage 1, 2 or 3)		
		MAF	Multivariate OR (95% CI)‡	P Value	MAF	Multivariate OR (95% CI)‡	P Value
rs1217965	G	0.17/0.18	0.90 (0.72–1.14)	0.38	0.17/0.18	0.93 (0.79–1.1)	0.40
rs1463998	G	0.18/0.19	0.88 (0.71–1.10)	0.27	0.18/0.19	0.91 (0.77–1.07)	0.24
rs62341639	T	0.11/0.12	0.85 (0.65–1.12)	0.24	0.12/0.12	0.96 (0.79–1.17)	0.70
rs9617814	G	0.28/0.27	1.09 (0.90–1.33)	0.37	0.27/0.27	1.03 (0.89–1.19)	0.70
rs10854554	G	0.23/0.21	1.12 (0.91–1.38)	0.28	0.22/0.21	1.07 (0.92–1.25)	0.38

Definition of abbreviations: AKI = acute kidney injury; CI = confidence interval; KDIGO = Kidney Disease: Improving Global Outcomes; MAF = minor allele frequency, cases/controls; OR = odds ratio.

Bold emphasizes the nonsignificance of the findings.

*KDIGO Stage 2 or 3; $n = 2,202$.

†KDIGO Stage 1, 2, or 3; $n = 2,642$.

‡Adjustments were made for age, sex, diabetes, hypertension, sepsis, and renal replacement therapy.

Table 2. Sensitivity Analysis with a Cohort Containing Cardiac Surgery Patients Only*, Using an Additive Genetic Model

SNP	Minor Allele	Severe AKI (KDIGO Stage 2 or 3)			AKI (KDIGO Stage 1, 2 or 3)		
		MAF	Multivariate OR (95% CI)†	P Value	MAF	Multivariate OR (95% CI)†	P Value
rs1217965	G	0.2/0.19	0.84 (0.34–2.08)	0.70	0.2/0.19	0.98 (0.57–1.71)	0.95
rs1463998	G	0.24/0.18	1.32 (0.58–2.99)	0.51	0.21/0.18	1.08 (0.62–1.86)	0.80
rs62341639	T	0.14/0.12	0.98 (0.35–2.76)	0.98	0.14/0.12	1.13 (0.60–2.11)	0.71
rs9617814	G	0.27/0.32	0.98 (0.41–2.33)	0.96	0.26/0.32	0.79 (0.48–1.31)	0.36
rs10854554	G	0.23/0.27	1.30 (0.53–3.23)	0.57	0.23/0.27	0.96 (0.58–1.61)	0.89

For definition of abbreviations, see Table 1.

Bold emphasizes the nonsignificance of the findings.

* $n = 227$.

†Adjustments were made for age, sex, diabetes, hypertension, sepsis, and renal replacement therapy.

condition the study population on ethnicity. However, 99.9% of the Finnish-speaking inhabitants are white. The MAF for rs62341639 in our cohort was lower than the MAF reported by Zhao. Third, an overestimated effect of the suggested associations in the previous study might explain our inability to replicate. As a consequence, if the true genetic effect size is lower than reported in the previous study (4), our study might have been underpowered to detect this effect. Finally, the biological effect of the studied SNPs near *IRF2* and *TBX1* is unknown, and their role in AKI is still unclear (9). In the future, individual patient meta-analyses combining data from multiple cohorts and differentiating AKI subphenotypes (10) may detect smaller effects and overcome reporting false-positive effects. ■

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Perspectives on Burnout from Pulmonary, Critical Care, and Sleep Medicine Division Directors

Physician burnout is a major threat to the quality and safety of patient care (1). Physicians suffering from burnout have higher rates of depression, suicidal ideation, and substance abuse, and are more likely to turn over or retire early (2). Burnout rates vary across medical specialties, which may be related to distinct work-related characteristics (3). For example, critical care physicians tend to have higher burnout prevalence, possibly because of the work environment and organizational characteristics of the ICU (4).

Local leaders play a critical role in identifying and addressing these burnout drivers. Despite the importance of leadership in promoting physician well-being, limited evidence exists on directors' perspectives on burnout, especially in the fields of pulmonary, critical care, and sleep medicine. Understanding directors' perspectives on burnout could inform effective initiatives to promote well-being in physicians practicing in these fields and may provide guidance for other medical specialties.

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Methods

We conducted a qualitative study of free-text responses to a survey about drivers of and solutions to burnout, distributed in May 2018 to members of the American Thoracic Society's Association of Pulmonary, Critical Care, and Sleep Division Directors, an organization formed to foster best practices among leaders in clinical medicine, research, and education. The survey included three questions that addressed whether respondents perceived burnout as a problem in their division (yes/no), the biggest burnout drivers in their division, and effective interventions to combat burnout.

The survey was distributed on the association's listserv via email link to an anonymous online platform, with 74 (34.6%) of 214 directors responding. We used summary statistics to report results of the yes/no question and grounded theory analysis, a qualitative method that allows concepts to emerge inductively, to analyze free-text responses (5). Three researchers (S.T.R., E.A., and L.S.) independently read the responses, assigned codes to important concepts in the text, and selected exemplary quotes. Final code structure was agreed on with research team members.

Results

Most directors (79.7%) indicated that burnout was a problem in their division. Three overarching themes emerged from qualitative analysis of responses about drivers of burnout: individual characteristics, inherent work characteristics (i.e., inherent features of clinical work that would exist even under ideal working conditions), and existent work characteristics (work-related factors present under current working conditions; Table 1). We determined that "moral distress," defined as feeling constrained in the ability to provide appropriate and ethical care, was attributed to both inherent work characteristics (e.g., feeling constrained by patient and caregivers' wishes) and existent work characteristics (e.g., feeling constrained by hospital policy and regulations), and we included it in both themes.

Although some responses mentioned individual characteristics and/or inherent work characteristics as drivers of burnout, most focused on existent work characteristics, such as misalignment between clinicians and administrators, excessive workload, inadequate support, frustrations with the electronic health records, and poor workplace climate. These issues detract from optimal working conditions, often through external pressures that increase the burden of work. As one respondent summarized, "The demands placed on us far exceed the supports provided to us to meet those demands." Other exemplary quotes are included in Table 2.

Responses to the question about solutions to burnout fell under three categories: targeted solutions (focused on specific drivers of burnout), general solutions (broad solutions not focused on specific drivers), and absent solutions (responses that indicated a lack of burnout solutions). It is notable that none of the targeted solutions addressed inherent work characteristics, which may reflect the sense that these inherent characteristics are perceived as less modifiable.

Discussion

In this nationwide survey of pulmonary, critical care, and sleep division leaders, most directors acknowledged that burnout was a problem in their division, highlighting a growing awareness of the scope and effect of physician burnout. Individual and existent work characteristic themes from our qualitative analysis reinforce conceptual models from