タイトル

Leucyl/cystinyl aminopeptidase 遺伝子多型と敗血症性ショック

Leucyl/cystinyl aminopeptidase (LNPEP) gene variants in septic shock

所属・氏名

千葉大学医学部付属病院 集中治療部　　中田孝明

Chiba University Graduate School of Medicine, Department of Emergency and Critical Care Medicine　　Taka-aki NAKADA

派遣期間　　2008 年 4 月 1 日- 2011 年 9 月 30 日

April 1, 2008- September 30, 2011

研究機関　　University of British Columbia, Critical Care Research Laboratories, Heart + Lung Institute, St. Paul's Hospital, 1081 Burrard Street, Vancouver, BC, Canada V6Z 1Y6

研究指導者　Prof. Keith R. Walley

Summary

The genetic variation in *LNPEP* (vasopressinase) is associated with 28-day mortality in septic shock and is associated with biological effects on vasopressin clearance and serum sodium regulation.

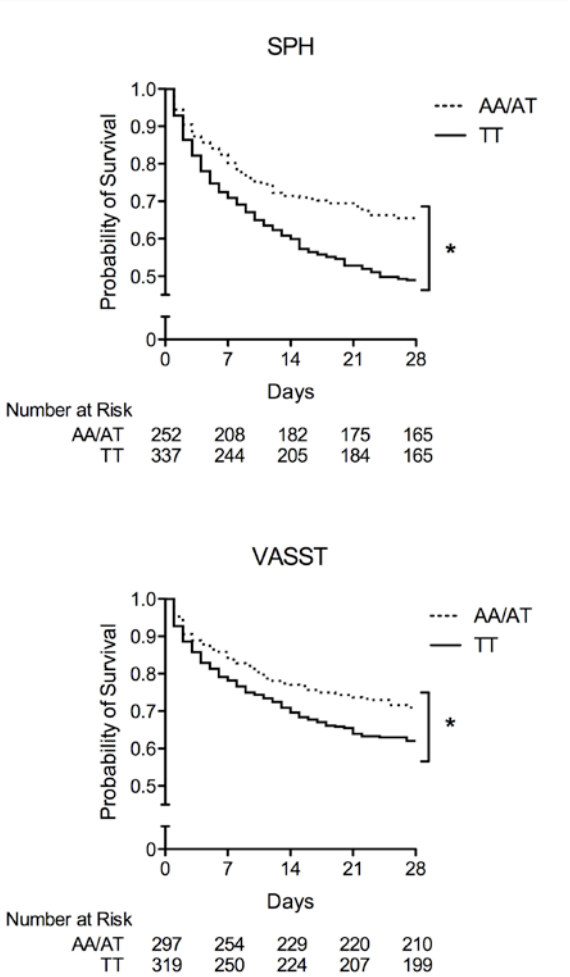
Background: Vasopressin is an essential peptide hormone regulating cardiovascular homeostasis and an adjunctive vasopressor therapy for septic shock.

Methods: We tested for association between single nucleotide polymorphisms (SNPs) in vasopressin pathway genes and altered outcome in derivation (n=589) and replication (n=616) cohorts of septic shock patients. The primary outcome was 28-day mortality and the secondary outcome was vasopressin clearance. In a third cardiac surgical cohort (n=977) we tested for locus-specific heritability of serum sodium concentrations.

Results: Of 17 tested tag SNPs in 5 vasopressin pathway genes (*AVP, AVPR1A, AVPR1B, LNPEP, OXTR*), rs18059 in *LNPEP* (also known as vasopressinase) was associated with 28-day mortality in the derivation cohort (*P*=0.037). Therefore, we re-sequenced the 160kb haplotype block encompassing the *LNPEP* gene including rs18059 and genotyped the 230 identified SNPs in the derivation cohort. The strongest signal was found for *LNPEP* rs4869317 (adjusted *P*=0.044). The rs4869317 TT genotype was associated with increased 28-day mortality in the derivation cohort (51.0% [TT] vs. 34.5% [AA/AT], adjusted hazard ratio [HR] 1.58, 95% CI 1.21-2.06, *P*=0.00073) and the replication cohort (38.6% vs. 29.6%, HR 1.36, 95% CI 1.03-1.80, *P*=0.030). We found that the TT genotype was associated with increased plasma vasopressin clearance (*P*=0.028) and rs4869317 genotype accounted for 80% of the

variance of serum sodium concentrations (locus-specific heritability) in cardiac surgical patients.

Conclusions: The genetic variation in *LNPEP* (vasopressinase) is associated with 28-day mortality in septic shock and is associated with biological effects on vasopressin clearance and serum sodium regulation. Further confirmation in additional cohorts is required.



Survival curves of patients with septic shock in two cohorts according to genotype of *LNPEP* rs4869317. Patients with the TT genotype of the *LNPEP* rs4869317 SNP had significantly decreased 28-day survival in the SPH and VASST cohort compared to patients with the AT/AA genotype (TT vs. AT/AA genotype, SPH, adjusted hazard ratio 1.58, 95% CI 1.21-2.06, *P*=0.00073; VASST, adjusted

hazard ratio 1.36, 95% CI 1.03-1.80, *P*=0.030). *P* values were calculated using Cox-regression analysis corrected for age, gender, surgical versus medical diagnosis, ancestry and with vasopressin versus without vasopressin infusion.