Genetic Factors of the Disease Course after Sepsis: A Genome-Wide Study for 28Day Mortality.

Scherag A, Schöneweck F, Kesselmeier M, Taudien S, Platzer M, Felder M, Sponholz C, Rautanen A, Hill AV, Hinds CJ, Hossain H, Suttorp N, Kurzai O, Slevogt H, Giamarellos-Bourboulis EJ, Armaganidis A, Trips E, Scholz M, Brunkhorst FM (2016) Genetic Factors of the Disease Course after Sepsis: A Genome-Wide Study for 28Day Mortality. *EBioMedicine* 12, 239-246.

Abstract

Sepsis is the dysregulated host response to an infection which leads to life-threatening organ dysfunction that varies by host genomic factors. We conducted a genome-wide association study (GWAS) in 740 adult septic patients and focused on 28day mortality as outcome. Variants with suggestive evidence for an association (p≤10(-5)) were validated in two additional GWA studies (n=3470) and gene coding regions related to the variants were assessed in an independent exome sequencing study (n=74). In the discovery GWAS, we identified 243 autosomal variants which clustered in 14 loci (p≤10(-5)). The best association signal (rs117983287; p=8.16×10(-8)) was observed for a missense variant located at chromosome 9q21.2 in the VPS13A gene. VPS13A was further supported by additional GWAS (p=0.03) and sequencing data (p=0.04). Furthermore, CRISPLD2 (p=5.99×10(-6)) and a region on chromosome 13q21.33 (p=3.34×10(-7)) were supported by both our data and external biological evidence. We found 14 loci with suggestive

evidence for an association with 28day mortality and found supportive, converging evidence for three of them in independent data sets. Elucidating the underlying biological mechanisms of VPS13A, CRISPLD2, and the chromosome 13 locus should be a focus of future research activities.

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