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Titel des Beitrags: Genome-wide association study of survival from sepsis due to pneumonia: an observational cohort study.

Abstract: Sepsis continues to be a major cause of death, disability, and health-care expenditure worldwide. Despite evidence suggesting that host genetics can influence sepsis outcomes, no specific loci have yet been convincingly replicated. The aim of this study was to identify genetic variants that influence sepsis survival. We did a genome-wide association study in three independent cohorts of white adult patients admitted to intensive care units with sepsis, severe sepsis, or septic shock (as defined by the International Consensus Criteria) due to pneumonia or intra-abdominal infection (cohorts 1-3, n=2534 patients). The primary outcome was 28 day survival. Results for the cohort of patients with sepsis due to pneumonia were combined in a
meta-analysis of 1553 patients from all three cohorts, of whom 359 died within 28 days of admission to the intensive-care unit. The most significantly associated single nucleotide polymorphisms (SNPs) were genotyped in a further 538 white patients with sepsis due to pneumonia (cohort 4), of whom 106 died. In the genome-wide meta-analysis of three independent pneumonia cohorts (cohorts 1-3), common variants in the FER gene were strongly associated with survival ($p=9.7 \times 10^{-8}$). Further genotyping of the top associated SNP (rs4957796) in the additional cohort (cohort 4) resulted in a combined $p$ value of $5.6 \times 10^{-8}$ (odds ratio 0.56, 95% CI 0.45-0.69). In a time-to-event analysis, each allele reduced the mortality over 28 days by 44% (hazard ratio for death 0.56, 95% CI 0.45-0.69; likelihood ratio test $p=3.4 \times 10^{-9}$, after adjustment for age and stratification by cohort). Mortality was 9.5% in patients carrying the CC genotype, 15.2% in those carrying the TC genotype, and 25.3% in those carrying the TT genotype. No significant genetic associations were identified when patients with sepsis due to pneumonia and intra-abdominal infection were combined. We have identified common variants in the FER gene that associate with a reduced risk of death from sepsis due to pneumonia. The FER gene and associated molecular pathways are potential novel targets for therapy or prevention and candidates for the development of biomarkers for risk stratification. European Commission and the Wellcome Trust.