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**Genetic Polymorphisms Associated With Susceptibility and Outcome in ARDS**

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**Abbreviations:** ACE = angiotensin-converting enzyme; IL = interleukin

ARDS remains an important cause of mortality on the ICU for which there are no specific therapies. Factors predicting the onset or severity of this syndrome are poorly understood, but the low incidence of ARDS in the relatively large group of patients at risk of having this syndrome develop suggests the involvement of genetic factors. No specific genes have been identified to date. We have examined genotype/allele frequencies for common polymorphisms in two candidate genes: angiotensin converting enzyme (ACE) and interleukin (IL)-6.

Activation of a local renin-angiotensin system within the pulmonary circulation and lung parenchyma could influence the pathogenesis of ARDS via a number of mechanisms pertinent to the onset and severity of lung injury. The human ACE gene contains a polymorphism in which the presence of a C allele is associated with reduced gene function.3 We therefore hypothesized that the C allele would be associated with both the onset and progression of ARDS.

The elevation and persistence of circulating IL-6 has been associated with increased mortality in critically ill patients with ARDS, sepsis, and trauma. We have previously described a functional polymorphism in the promoter region of the IL-6 gene (-174GC), whereby the presence of a C allele is associated with reduced gene promoter activity and lower circulating IL-6 concentrations.3 We therefore hypothesized that the C allele would be associated with both the onset and progression of ARDS.

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be associated with a lower mortality rate in patients with acute respiratory failure admitted to the ICU. Genotyping was performed as previously reported in 96 white patients fulfilling the American European Consensus Committee criteria for ARDS (ARDS group), 88 patients admitted to the ICU for non-ARDS respiratory failure (ICU group), 174 non-ICU patients at risk of ARDS admitted to the ICU for non-ARDS respiratory failure (ICU group), and 1,906 healthy UK men (UK group).

**RESULTS AND DISCUSSIONS**

The frequency of the DD ACE genotype (associated with higher tissue and circulating ACE) was increased in the ARDS group compared to the ICU group (p < 0.005), CABG group (p < 0.005), or UK group (p < 0.01). D allele frequency was also increased in the ARDS group (p < 0.0005 vs CABG group/ICU group, and p < 0.005 vs UK group) and was significantly associated with mortality (Fig 1; p < 0.02). The strength of this association suggests a major role for renin-angiotensin system in the development and progression of this syndrome.

In relation to IL-6 genotypes, there was no difference in genotype or allele frequencies between the ARDS, ICU, and UK (control male United Kingdom population) groups (C allele frequency of 0.4 for both). However, the C allele and CC genotype frequencies were significantly reduced in both the ARDS group and ICU group nonsurvivors compared to survivors (p = 0.023 and p = 0.035 respectively for both groups). Serum IL-6 levels within 24 h of admission to the ICU were also significantly lower in survivors (median, 17.8 pg/mL; range, 10 to 610 pg/mL) compared to nonsurvivors (median, 1,067 pg/mL; range, 5 to 2,071 pg/mL; p < 0.001) and correlated with IL-6 genotype (p < 0.001). These data suggests that the enhanced IL-6 response observed in nonsurvivors of critical illness is, at least in part, genetically determined, and that the C allele is an important prognostic factor in the critically ill.

In conclusion, we provide the first report of genetic factors associated with the onset and severity of ARDS. Confirmation of these results in other ICU populations and the identification of additional polymorphisms could aid both our understanding of pathogenic mechanisms in ARDS, the identification of susceptible individuals, and the targeting of therapies.

**REFERENCES**


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**Microarray Analysis Indicates That Pulmonary Edema Fluid From Patients With Acute Lung Injury Mediates Inflammation, Mitogen Gene Expression, and Fibroblast Proliferation Through Bioactive Interleukin-1**

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**Abbreviations:** ALI = acute lung injury; IL = interleukin.

Although the fibroproliferative response to lung injury occurs with a high frequency in patients with acute lung injury (ALI), the mechanisms of this response are largely unknown. This study was undertaken...