Beyond Single-Nucleotide Polymorphisms

Genetics, Genomics, and Other 'Omic Approaches to Acute Respiratory Distress Syndrome

Nuala J. Meyer, MD, MS

KEYWORDS

• Acute respiratory distress syndrome • Genomic • Proteomic • Metabolomic • Gene expression • Complex trait

KEY POINTS

- Numerous candidate gene-association studies and protein investigations have been used in acute respiratory distress syndrome (ARDS) to moderate success, but large-scale genomic, proteomic, or metabolomic studies have not yet been undertaken. There exists significant opportunity to apply 'omic platforms to advance the understanding of ARDS pathophysiology.
- Although small proteomic and metabolomics investigations into ARDS have proven feasibility, to date there has been limited mechanistic follow-up of compelling candidates and questions remain regarding the optimal target tissue and the best analytical strategy for ARDS.
- Future studies could leverage 'omic experience gained evaluating other non-ARDS complex traits, and could explore unbiased analytical strategies for class distinction or network analysis.
- The success of high-throughput discovery 'omic investigations derives from tracing observations in human populations back to their mechanistic underpinnings.

Acute respiratory distress syndrome (ARDS) inflicts considerable morbidity and mortality among critically ill patients and lacks any specific pharmacologic therapy.[1,2] Because clinical factors alone fail to explain which patients with ARDS risk factors will develop the syndrome, or to accurately predict which patients will die as a result of ARDS, there is great interest to understand whether one could leverage new biologic techniques to better characterize risk and prognosis. With major advances in the fields of genomics, mass spectroscopy, and bioinformatics, there are numerous approaches that can now be applied to a complex trait like ARDS, yet the benefit of these is uncertain (**Table 1**). This article reviews the state of knowledge of genetic contributions to ARDS risk and mortality, reviews broader applications of genomics to ARDS pathogenesis, and considers examples from non-ARDS fields whereby genomic approaches have yielded major advances. Applying similar approaches to ARDS may deepen our understanding and offer new therapeutic paradigms for patients with ARDS.

SHIFTING THE PARADIGM: WHAT CAN GENOMICS TEACH ABOUT A TRAIT LIKE ACUTE RESPIRATORY DISTRESS SYNDROME?

Many investigators associate the word "genomic" with inherited conditions that obviously cluster among families. Because there are no reported families in whom ARDS has affected multiple

The author has no disclosures relevant to this publication.
Pulmonary, Allergy, and Critical Care Medicine, University of Pennsylvania, Perelman School of Medicine, 3600 Spruce Street, 5039 Maloney Building, Philadelphia, PA 19104, USA
E-mail address: nuala.meyer@uphs.upenn.edu

Clin Chest Med 35 (2014) 673–684
http://dx.doi.org/10.1016/j.ccm.2014.08.006

Table 1
Potential applications of different 'omic technologies to a complex trait like ARDS

Analyte *Field*	Infer Mechanism	Candidate Marker Validation	Candidate Marker Discovery	Identify Subclasses	Risk Stratify	Improve Diagnosis	Identify Therapeutic Targets
DNA *Genomics*	x	x	x		x		x
DNA methylation or acetylation *Epigenomics*	x	x			x		x
mRNA miRNA ncRNA *Transcriptomics*	x	x	x	x	x		x
Proteins *Proteomics*	x	x	x	x	x	x	x
Metabolites *Metabolomics*	x	x	x	x	x	x	x
Systems *Interactome*	x			x	x		x
Microbiota *Microbiome*	x	x	x	x	x	x	x

Abbreviations: mRNA, messenger RNA; miRNA, micro RNA; ncRNA, noncoding RNA.
For each application, the tested analyte is named and the most likely potential applications are highlighted with an X.

members, one might conclude that genomics would offer little to the understanding of ARDS. However, an alternative perspective is to consider ARDS as a pattern of response to injury, be it pneumonia, sepsis, or trauma. As a trait, the response to injury has significant heritability.[3–7] In fact, death from infection was the most heritable condition when studied in a large Danish registry of adoptees, with a much stronger heritability than vascular disease or cancer.[8] Rather than acting as monogenetic, or Mendelian, traits, whereby a single genetic variation explains the bulk of the observed phenotype, ARDS risk and severity are likely influenced by multiple genetic variants that each contribute to a modest degree. Small effect sizes of each contributing gene variant mandate large study populations for detection. In addition, ARDS is ripe for the use of intermediate traits and the identification of endotypes, or subtypes, which may demonstrate a more homogeneous genetic background.

SURVEYING THE LANDSCAPE OF ACUTE RESPIRATORY DISTRESS SYNDROME GENOMICS

Numerous candidate gene-association studies have been reported in ARDS, and several reproducible associations have emerged. Although a complete review of the genetic associations with ARDS risk or ARDS mortality is beyond the scope of this article, comprehensive reviews recently have been published.[9–11] The best replicated genetic variants for ARDS risk represent the present understanding of ARDS pathophysiology; proinflammatory and anti-inflammatory cytokine gene polymorphisms are well represented (*IL6*, *IL10*, *IL1RN*, *MBL2*),[12–18] as are vascular injury markers (*VEGFA*, *ANGPT2*, *ACE*, *MYLK*),[19–24] innate immunity pathway members (*IRAK3*, *TLR1*, *NFKB1*, *NFKBIA*, *FAS*, *PI3*),[5,25–28] and markers of respiratory epithelial injury (*SFTPB*).[29,30] Although each of these associations has been associated with ARDS risk or outcome in at least two populations, none influences ARDS risk or severity to a degree that warrants genetic testing of at-risk populations. Instead, the main contribution of ARDS genetic associations to date has been to focus attention on molecular pathways at play in causing or perpetuating the syndrome.

Furthermore, it is tempting to speculate that genetic associations may highlight potential therapeutic targets to either prevent ARDS or to improve outcomes once it has developed. For example, the association of variants in the angiopoietin-2 gene (*ANGPT2*) with ARDS risk in mixed intensive care unit population and trauma populations,[22,23] coupled with strong animal