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Genetic predisposition to bronchopulmonary dysplasia

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ABSTRACT

The objective of this study is to review the candidate gene and genome-wide association studies relevant to bronchopulmonary dysplasia, and to discuss the emerging understanding of the complexities involved in genetic predisposition to bronchopulmonary dysplasia and its outcomes. Genetic factors contribute much of the variance in risk for BPD. Studies to date evaluating single or a few candidate genes have not been successful in yielding results that are replicated in GWAS, perhaps due to more stringent *p*-value thresholds. GWAS studies have identified only a single gene (*SPOCK2*) at genome-wide significance in a European White and African cohort, which was not replicated in two North American studies. Pathway gene-set analysis in a North American cohort confirmed involvement of known pathways of lung development and repair (e.g., CD44 and phosphorus oxygen lyase activity) and indicated novel molecules and pathways (e.g., adenosine deaminase and targets of miR-219) involved in genetic predisposition to BPD. The genetic basis of severe BPD is different from that of mild/moderate BPD, and the variants/pathways associated with BPD vary by race/ethnicity. A pilot study of whole exome sequencing identified hundreds of genes of interest, and indicated the overall feasibility as well as complexity of this approach. Better phenotyping of BPD by severity and pathophysiology, and careful analysis of race/ethnicity is required to gain a better understanding of the genetic basis of BPD. Future translational studies are required for the identification of potential genetic predispositions (rare variants and dysregulated pathways) by next-generation sequencing methods in individual infants (personalized genomics).

Introduction

Extremely preterm infants are at high risk of mortality and morbidity. One of the most common morbidities is bronchopulmonary dysplasia (BPD), affecting more than two-thirds of a recent cohort of extremely preterm infants in the United States.[1] BPD also accounts for much of the late (>60 days) mortality in extremely preterm infants.[2] Even after controlling for birth weight, gestational age, and sociodemographic characteristics, a diagnosis of BPD is associated with a large increase in direct costs for the initial neonatal intensive care unit hospitalization.[3] In a recent large cohort, 28% of extremely preterm infants were discharged home on oxygen,[4] suggesting that the morbidity and costs of BPD therapy extend for many infants well beyond the initial hospital stay. The genetics of BPD has been reviewed in *Seminars in Perinatology* by Bhandari

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and Gruen[5] in 2006 and subsequently by Shaw and O'Brodovich[6] in 2013. This review is therefore an update on recent advances in the field, with a brief overview of the evidence already covered in the previous reviews.

The search for genetic origins of BPD has been complicated by several factors. One issue is that the diagnostic criteria for BPD have changed many times since Northway et al.[7] first described BPD in 1967 as a pulmonary disease following mechanical ventilation of infants with respiratory distress syndrome, characterized by airway injury, inflammation, and lung fibrosis. In 1979, William Tooley defined BPD as when an infant at 30 days of age has any radiologic abnormality of the lung parenchyma plus at least one of the following: (1) an O_2 tension in arterial blood breathing room air of 60 Torr or less, (2) CO_2 tension in arterial blood of more than 45 Torr, and/or/ (3) O_2 dependence (i.e., requires an FiO_2 of more than 0.21).[8] In 1988, Shennan et al.[9] observed that the need for oxygen at 28 days became increasingly less useful as gestational age decreased, but irrespective of gestational age at birth, the requirement for additional oxygen at 36 weeks' corrected postnatal gestational age was a better predictor of abnormal outcome. A major limitation of these definitions is the wide-ranging criteria for oxygen "requirement" used by different clinicians. A workshop on BPD organized by the National Institute of Child Health and Human Development (NICHD), the NHLBI, and the Office of Rare Diseases (ORD) developed diagnostic criteria for BPD based on gestational age (<32 weeks vs. >32 weeks) and severity (Mild, Moderate, or Severe BPD, based on oxygen supplementation at 28 days of age and 36 weeks postmenstrual age).[10] Subsequently, Walsh et al.[11] described a "physiologic definition" of BPD by a standardized oxygen saturation monitoring at 36 weeks corrected age that was highly reliable and improved the precision of diagnosis of BPD. Currently, the NIH workshop definition and the physiologic definition are the most used. As these multiple definitions have evolved over time, and considering the fact that the infants who develop BPD in the current era (mostly 22–26 weeks gestational age at birth) are much more immature than the infants at highest risk of BPD in the 1970s (30–34-week infants) and 1990s (26–30-week infants), it is safe to state that the infants defined as having "BPD" in the 1970s or 1980s were very different from those with BPD in recent years. The pathology of BPD has also changed over the years, with the lungs in "old" BPD being characterized by alternating areas of atelectasis and overinflation, marked airway epithelial hyperplasia and squamous metaplasia, airway smooth muscle hyperplasia, extensive fibrosis and pulmonary hypertension, and decreased internal surface area and alveoli, whereas the histology of the current "new" BPD having fewer and larger simplified alveoli, less airway lesions, variable airway smooth muscle hyperplasia and interstitial fibrosis, fewer and dysmorphic capillaries, and less severe arterial remodeling.[12,13]

Another issue is that the definition of BPD (oxygen requirement) being an operational definition does not indicate the diverse underlying pulmonary pathology or the variable magnitude of pathology between different preterm infants. The magnitude of inhibition of alveolar development,[12] the extent of lung fibrosis (and resulting changes in lung compliance),[7] the severity of lung vascular remodeling (and resulting pulmonary hypertension),[14,15] and the degree of trachea-bronchomalacia[16] vary from one infant to another, and perhaps even in the same infant over time, as BPD is a disorder superimposed on normal lung development. Yet another issue, that we will discuss subsequently, is that severe BPD is different from mild or moderate BPD in its genetic basis, and that biologic pathways associated with BPD risk are very different in infants of different race/ethnicity.[17] Therefore, the single diagnosis "BPD" has been applied using varying criteria to infants of varying gestational age and illness severity, varying lung airway/vascular/parenchymal pathology, and of varying genetic background. It is likely that "BPD" is not a single entity, nor even a spectrum of disease resulting from a single pathophysiologic process, but the is the result of multiple pathophysiologic processes leading to varying magnitudes of inhibited alveolar septation, lung fibrosis, and abnormal vascular development and remodeling in preterm infants at the saccular or early alveolar stage of lung development. As may be expected, the genetic basis of each of these sub-phenotypes of BPD is likely to vary, depending upon the underlying clinical variables and pathophysiology.

Identification of the genetic basis of BPD

Familial and genetic susceptibility to BPD (defined as oxygen requirement at 36 weeks PMA with compatible radiographic findings) was evaluated in a multicenter retrospective study of twin pairs born at <32 weeks of gestation by Bhandari et al.[18] After controlling for the effects of covariates, the twin data showed that 65.2% (95% CI: 53–79% and $p < 0.001$) of the variance in liability for BPD could be accounted for by genetic and shared environmental factors. The genetic component was estimated from the correlation between monozygotic twins beyond that of dizygotic twins, and the observed concordance in monozygotic twins was significantly higher than the expected concordance. After controlling for covariates, genetic factors were considered to account for as much as 53% (95% CI: 16–89% and $p = 0.004$) of the variance in liability for BPD.[18] Lavoie et al.[19] evaluated the heritability of BPD defined according to the NIH consensus definition using clinical data from 318 twin pairs of known zygosity <30 weeks of gestation. Model-fitting analyses indicated that genetic effects accounted for 79% of the observed variance in moderate to severe BPD susceptibility.[19] The genetic factors that contribute to BPD susceptibility (or conversely, to the resistance to development of BPD in an otherwise susceptible extremely preterm infant) have been the subject of much investigation in recent years, when the technology has progressed sufficiently to (1) permit the survival of preterm infants despite severe lung disease and progress to BPD, (2) allow evaluation of single nucleotide polymorphisms (SNPs) in genes at sufficiently low cost and with rapid throughput.

Targeted evaluation of SNPs (candidate gene studies)

Several investigators have attempted to identify associations with BPD of molecules or pathways that are known to be