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The genetic basis for bronchopulmonary dysplasia

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1. ABSTRACT

While the 'original' bronchopulmonary dysplasia (BPD) was attributed to the iatrogenic effects of oxygen and barotrauma on the preterm lung, analyses of the 'new' BPD suggests that these environmental effects may contribute to arrested pulmonary development, and that there may also be genetic foundations for the susceptibility to BPD. Twinning, family and population studies implicate heritable factors in the evolution of BPD. The candidate genes examined for their potential role in BPD include surfactant apoprotein and inflammatory genes. With the identification and mapping of single nucleotide polymorphisms (SNPs), an explosion of testing for these genetic components that may contribute to a number of complex, multigenic disease conditions-including BPD-have been initiated. Sophisticated multiplex analyses are now available to link candidate SNPs to conditions such as BPD. However, there continues to be wide variation in the expression of BPD throughout neonatal units. Differentiating the effects caused by environmental and environmental-genetic interactions from isolated genetic etiologies is still problematic and will require carefully designed genetic analyses of preterm infant groups and their families.

2. INTRODUCTION

Bronchopulmonary Dysplasia (BPD) is the most common chronic lung disease of infancy (CLDI), which is manifested in the preterm infant following surfactant-deficient respiratory distress syndrome (RDS). The evolution of BPD is manifested by biochemical, histological, physiological, radiological and developmental pulmonary changes (Figure 1).

BPD has arisen during an era when life-saving mechanical ventilation and oxygen administration played major roles in the progression of pulmonary manifestations (1). The "New BPD" typically (but not always) begins *in utero* with an inflammatory insult, and progresses post-natally to involve both the respiratory epithelium and vascular endothelium and to result in arrested lung development and alveolar hypoplasia, with diminished -- but not insignificant -- contributions from ventilator-induced lung injury (VILI) [for a more detailed discussion, please see (2)].

There are other pulmonary and non-pulmonary origins that may lead to chronic airflow obstruction, increased work of breathing, and airway hyperreactivity of

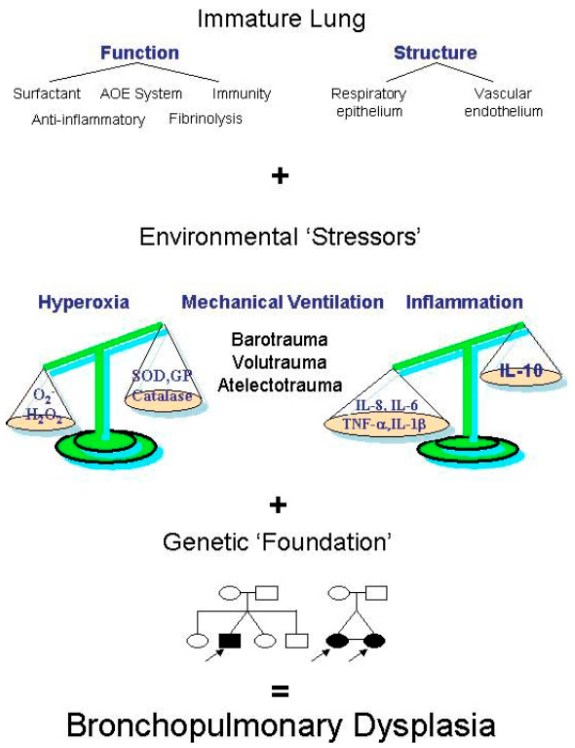

Figure 1. Proposed paradigm for the evolution of BPD. Abbreviations: AOE-anti-oxidant enzyme system; SOD-superoxide dismutase; GP-glutathione peroxidase; IL-interleukin; TNF-α-tumor necrosis factor alpha. Affected offspring are denoted by darkened circles (monozygotic twins) or a darkened square (male of dizygotic twin).

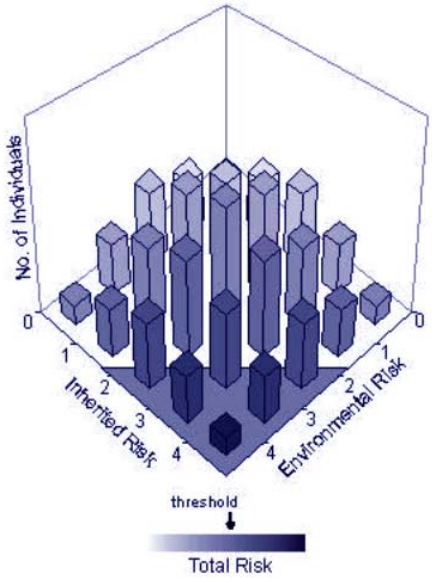

Figure 2. Inherited risk and Environmental Risk are plotted on X and Y axes, with individuals shown on the Z axis. The threshold for this condition is surpassed for individuals within the shaded region of the XY plane, when various combinations of genetic and environmental risks combine to manifest this disease condition.

CLDI such as pneumonia/sepsis, meconium aspiration pneumonia, pulmonary hypoplasia, persistent pulmonary hypertension, apnea, tracheoesophageal fistula, congenital diaphragmatic hernia, congenital heart disease, and congenital neuromuscular disorders (3, 4) -- but they will not be specifically addressed by this review. This diversity of conditions, however, suggests that there may be confounding pathways leading to CLDI.

The definition of BPD has also evolved over time, and the "New BPD" definition stratifies by post-natal oxygen and pressure requirements (5). This review examines the evidence supporting a genetic foundation for this "New BPD."

3. DISEASE AS A CONSEQUENCE OF GENETIC-ENVIRONMENTAL INTERACTIONS

In contrast to earlier models of human disease that follow the one gene-one disease paradigm, it is now recognized that many human diseases result from a combination of genetic and environmental factors (6) that interact to create a personal risk for disease (7) (as exemplified in Figure 2).

If this paradigm is applied to BPD, a number of putative environmental exposures can be identified including inflammation, hyperoxia, volutrauma, and atelectotrauma. The timing of these exposures to the very premature infant may be critical, and may impact alveologenesis through a number of key growth factors (8). In addition, polymorphisms effecting pathways of oxidative stress and detoxification of reactive oxygen species would be candidate genes to place preterm infants at increased risk for BPD (9). Putative inherited risks have also been implicated, particularly for surfactant apoproteins (10) and pro-inflammatory mediators (11). The focus of this review will be to examine the evidence that genetic factors form a foundation for the evolution of BPD in the preterm infant.

4. TWINNING STUDIES IMPLICATE A GENETIC FOUNDATION FOR BPD

A positive family history of asthma has long been associated with the susceptibility to develop BPD (12). However, since asthma is also likely to be the consequence of multiple environmental and genetic interactions, it has been difficult to identify a common genetic thread linking asthma and BPD. One way to incriminate genetic factors-without specifically identifying them-is through twin studies, since either identical [monozygotic (MZ)] or fraternal [dizygotic (DZ)] twins share genetic information.

When risk factors for BPD were analyzed in 108 twin pairs of infants with birth weights ≤ 1.5 kg, the BPD status of the firstborn twin was found to be a highly significant predictor of BPD in the second twin (adjusted odds ratio 12.3, $p<0.001$) (13). When 418 twin sets ≤ 32 weeks from 5 centers were analyzed for the development of BPD -- as defined by oxygen need at 36 weeks postmenstrual age -- logistic regression analysis identified several independent covariates including birth weight, RDS

and BPD in the second twin as being highly predictive for BPD in the subject ($p<0.001$) (14). The observed concordance rate for BPD in MZ twins was almost 4-fold, while that of DZ twins was 1.4-fold over the expected concordance rate ($p<0.001$), suggesting a genetic susceptibility for the development of BPD. This investigation also highlights the importance of covariate analysis for interpreting the etiology of BPD -- BPD occurs in the presence of prematurity and RDS, each of which in turn, is likely to have genetic foundations that may or may not contribute to the heritability of BPD.

5. PREMATURITY HAS GENETIC FOUNDATIONS

Identifying genetic factors responsible for preterm birth (PTB) is problematic due to contributions from environmental risk factors such as poverty, cigarette smoking, and infection. It is likely that the paradigm for PTB mimics other disease conditions (as described in Figure 2). In spite of these difficulties, a genetic foundation in the etiology for PTB is emerging from a number of lines of evidence [for a more extensive review, see this issue, Nesin M, *et al*, and (15)].

Indirect evidence from repeat spontaneous PTB in individual women, families and certain ethnic groups implicates a genetic etiology for PTB. Mothers, who were themselves products of PTB, are also at increased risk of bearing a PTB (16). Recurrent PTB was studied in 27 677 Norwegian women (17), in Danish (18) and Scottish (19) cohorts, and they all conclude that a prior PTB remains one of the most consistent risk factors for subsequent PTB. A Scottish cohort (20) found that sisters were more likely to have a preterm delivery than were sisters-in-law (16% and 9%, respectively). Paternal inheritance may also contribute to the risk for PTB, but to a much lesser degree. Changing partners after a PTB resulted in a 33% reduction in the risk for a subsequent PTB, while changing partners after a full term delivery resulted in a 16% increase in the risk for PTB (21).

Disparities in rates of PTB are also found in racial groups -- most notably an approximately two-fold increased risk of PTB for black women in the U.S.A. compared with white U.S. women. Environmental risk factors for these studies are carefully controlled, suggesting either a distinct environmental risk factor common to U.S. blacks, or genetic determinants that are race-specific (22). The prevalence of PTB was 16.7% in black women and 8.0% in white women of a 19 554 cohort of PTBs in North Carolina (23). This was similar to the odds ratio of 1.79 (95% CI 1.55-2.08) for blacks (compared to whites, normalized to 1.00) in a cohort of 28 330 women from California (24).

Since these familial aggregation and racial patterns offer increasing evidence for a genetic foundation in PTB, identification of specific candidate genes and gene polymorphisms has been sought. One candidate single nucleotide polymorphism (SNP) is the (-308) TNF-α polymorphism -- TNF2, which results in augmented expression when this less common allele is present (25). Homozygous genotyping for 1048 children in Western Kenya found that TNF2 homozygosity was highly associated with PTB when compared with TNF1 homozygosity [relative risk 7.3 (95% CI 2.85-18.9, $p=0.002$)] (26). When an association was sought between TNF2 (hetero- or homozygotes) and PTB in U.S. blacks, it was not significant (27). However, a subgroup analysis of those with both PTB and preterm premature rupture of membranes (PPROM) found a significant association ($p=0.008$) with TNF2. Identifying additional genes or SNPs of genes associated with PTB will likely require extensive population studies. In addition, identifying whether genetic foundations for PTB and BPD are shared or unique will require familial transmission disequilibrium test (TDT) analysis.

6. RESPIRATORY DISTRESS SYNDROME HAS GENETIC FOUNDATIONS

Genetic evidence has been sought from preterm infants with RDS, since it is a critical covariate for the evolution of BPD [for a more extensive review, see Hallman *et al*, in this issue, and (28)].

6.1. Surfactant Apoprotein Genes May Be Associated with BPD

Surfactant deficiency is implicit in the preterm infant who develops RDS, who may or may not progress to BPD. Candidate gene(s) that may influence the progression to BPD have been sought from the four surfactant apoproteins-SP-A, SP-B, SP-C, and SP-D, which have important roles in surfactant structure, function, and metabolism (28-30). Twenty-three infants with BPD (as defined by oxygen dependency at 28 days of life) were matched by gestational age with 23 non-BPD infants (10). A significantly increased frequency of the SP-A1 polymorphism 6A6 was identified in those with BPD. When 365 preterm Finnish infants $\leq$ 32 weeks were genotyped for SP genes, only the SP-B intron 4 deletion variant allele was increased in BPD (SP-A1 polymorphism 6A6 was not analyzed) versus controls ($P = 0.008$, OR = 2.0, 95% CI 1.2-3.4) -- and this allele was not increased in RDS (31). There may be additional modifier genes that influence the transcription, expression, or stabilization of these surfactant apoproteins. As additional SP gene variations are identified, further associations may be linked to the evolution of BPD.

7. INFLAMMATORY GENES ARE ASSOCIATED WITH THE EVOLUTION OF BPD

In utero inflammatory conditions have been associated with PTB, RDS and the evolution of BPD (32, 33). Early neonatal measurements of fluids present in the airways of preterm infants have also demonstrated the predominance of pro-inflammatory mediators in those who progress to BPD (34-36). While initiating factors for an inflammatory cascade may not always be identified, the fetus and preterm infant are at a disadvantage because of their inability to induce an anti-inflammatory counter-response (36). SNPs for genes that participate in this inflammatory response may offer the preterm infant protection -- if they result in lower levels of expression of

pro-inflammatory mediators; or may result in increased susceptibility -- if pro-inflammatory mediators are expressed at amplified levels.

The substitution of an adenine for a guanine in the -238 polymorphism of the early pro-inflammatory mediator-TNF-α-is associated with decreased expression of TNF-α (37) as well as decreased severity of non-pulmonary diseases and improved outcomes among adults (38-41). Fifty-one preterm infants who developed BPD were compared with 69 infants who did not develop BPD (11). The BPD group was significantly younger (mean±SD:27±4 versus 29±2 weeks) and had lower birthweights (853±184 versus 997±193 g) than the Non-BPD group. Surprisingly, the adenine allele was absent among infants with severe BPD and occurred significantly less often among infants with moderate or severe BPD, compared to infants with mild BPD, which was contrary to expectations. This study population consisted primarily of African Americans (80% of No BPD group; 75% of BPD group). Since SNP frequencies may vary significantly between racial groups, sampling such a racial distribution may provide specific insights for the majority population -- but may not be applicable to other populations.

In another study, additional SNPs of TNF-α were analyzed (42, 43), including ones located at: –1031, -863, -857, -308, and –238. Haplotype frequencies were compared for combinations of these SNPs for preterm infants stratified by the "New BPD" (5): No BPD (N=18), Mild BPD (N=27), Moderate BPD (N=32), and Severe BPD (N=28). Linkage disequilibrium between all pairs of loci indicated 2 SNP blocks at loci (-1031, -863, -857) and (-308, -238), which were consistent with the distances between these SNPs. Haplotype-specific analysis revealed no significant association between BPD severity and any of the 5-marker common haplotypes with 10 or more copies in study population. As with the previous study, the birthweights and gestational ages were significantly different between the No, Mild, Moderate, and Severe BPD groups (mean±SEM: birthweights-892±23; 804±27; 771±19; and 707±18 g; gestational ages-28±0.4; 26±0.3; 25±0.2; and 25±0.2 weeks; respectively), thus confounding the evolution of BPD with prematurity.

The latter study used PHASE software (version 2.1.1) to infer haplotypes from genotype data in this population sample of unrelated individuals (44, 45). This software takes advantage of a statistical model for patterns of linkage disequilibrium among multiple SNPs in a population sample. Among other features, this model may have advantages over existing approaches since all loci are considered simultaneously, rather than pair wise; and since it avoids the assumption that LD necessarily has a "block-like" structure. Comparison with existing expectation-maximization (EM) algorithms have been made (46), and PHASE provides more accurate haplotype estimates than does EM and other existing methods, particularly when there is "clustering" in the true haplotype configuration-often seen with real data sets (47).

Isolated SNPs for TNF-α (-308), monocyte chemoattractant protein-1 (MCP-1) (-2518) and transforming growth factor-β (TGF-β) (+915) were investigated in a retrospective, case-controlled study that utilized archival tracheal aspirate pellets from earlier studies of cytokine concentrations as the source of genomic DNA in a largely African-American population (48). One hundred seventy eight patients with birth weights < 1500 g, who received mechanical ventilation during the first week of life were analyzed. No effect of any of these SNPs were seen on the development of BPD, suggesting that these SNPs did not play a significant role in determining the risk for BPD in preterm infants, although roles for these SNPs in other neonatal co-morbidities could not be excluded. The potential weaknesses of this study are that it was a retrospective study that focused on isolated SNPs in a relatively small sample.

A SNP for the anti-inflammatory cytokine IL-10 was tested for its association with the risk of death or BPD in 294 ventilated very low birth weight infants (49). This SNP results in a lower expression of IL-10, and hence should offer less protection from BPD. Infants who manifested this SNP allele were larger and more mature at birth (940±22 vs. 882±18 g, $P < 0.05$; 26.9±0.2 vs. 26.30.2 weeks, $P < 0.05$, respectively), perhaps confounding this analysis. Isolated SNP analysis failed to show any effect of this SNP on mortality or the development of BPD.

IL-4 stimulates and amplifies the inflammatory response, stimulates collagen synthesis in fibroblasts, promotes the progression to fibrosis and has been shown to inhibit the production of several inflammatory cytokines in the development of BPD and airway hyperreactivity. A case-control study of 224 Taiwanese preterm infants (< 30 weeks gestation) with RDS and needing mechanical ventilation were genotyped for IL-4 intron 3 and IL-4 promoter SNP (-590) (50). No significant association of these genotypes was found for the preterm infants who developed BPD (oxygen-dependent at 36 weeks post conceptional age) and those who did not.

8. IDENTIFYING GENETIC FOUNDATIONS OF BPD RESULTING FROM SNPs

While 99.9% of DNA sequences are identical between individuals, 80% of the 0.l% differences consist of SNPs, which are single base substitutions that are seen at frequencies greater than 1% in the general population. Precise estimates of SNP frequencies often vary with population and genomic region. To date, approximately 1.8 million human SNPs have been identified out of an estimated 10-30 million (51). These SNPs are displayed across the human genome-it has been estimated that there are about 15 SNPs for gene loci of average size.

This single nucleotide change may amplify or diminish the expression of that gene many-fold. For example, the -308 SNP for TNFα has been well studied for its potential influence on a number of human conditions. This SNP has been shown to result in a 5-fold increase in transcription of the pro-inflammatory TNFα gene because of its strategic location in the promoter region of this gene (25). In fact, TNF-α measured from tracheal aspirates of preterm infants has been associated with the progression to

BPD (52), suggesting that this SNP would be an ideal candidate for investigation. In contrast, the –238 SNP of TNF-α abrogates the expression of this pro-inflammatory mediator (38-41), thus potentially offering protection.

But how can one identify the SNP(s) responsible for disease conditions from the possible 10-30 million total in the human genome, particularly in conditions such as BPD that result from multifactorial inheritance in combination with environmental pressures? Approximately 10 million human SNPs are not inherited independently, but create SNP haplotype block patterns, which may be transmitted through many generations without recombination. One need only 'tag' one of the SNPs in this block to identify each haplotype. Therefore, by studying SNP haplotype profiles associated with a disease condition, disease-associated genes may be identified. In addition, population history can be probed by analyzing ancestral SNP haplotype modifications.

Another powerful tool to identify alleles that contribute to multifactorial inheritance is transmission disequilibrium test analysis (TDT). TDT measures the transmission of marker alleles of heterozygous parents to the affected offspring. The non-transmitted parental marker alleles serve as internal controls to the transmitted alleles. This method is more powerful than the standard case-control studies since it avoids associations due to admixture, heterogeneity, or stratification of the population (53). This analysis was employed to look for the association of SP-A alleles and RDS (54). Thirty-two families, consisting of 64 parents and 58 offspring, were subjected to TDT. Linkage was demonstrated between SP-A and RDS, with certain SP-A alleles/haplotypes demonstrating increased susceptibility to RDS-$1A^0$, $6A^2$, $1A^0/6A^2$, while others were associated with protection from RDS-$1A^5$, $6A^4$, $1A^5/6A^4$. Some racial and sex differences were also appreciated in this analysis.

This strategy may also be productive when searching for genetic foundations of BPD. Alleles and haplotypes already associated with PTB and RDS can also be subjected to TDT analysis to search for protection or increased susceptibility to BPD.

More powerful, automated, high-throughput SNP genotyping offers the ability to perform genome-wide association studies to detect genetic variations that may predispose to complex disorders (55). The International Haplotype Mapping Project (56) and recent data from Perlegen Sciences (57) have contributed data for more than 2 million SNP markers with verified allele frequencies. Highly multiplexed microarray systems for SNP genotyping have recently been developed, which offer the potential for performing genome-wide SNP mapping of genes involved in complex diseases (58). Successful association studies for identification of alleles associated with disease susceptibility however may require the analysis of thousands of DNA samples in parallel utilizing these multiplexed systems (59). These complex analyses will generate data sets requiring novel approaches to interpretation and analysis, and will have limitations [for a comprehensive discussion, please see (55)]. Additional strategies designed to identify candidate genes for BPD may analyze expression patterns utilizing DNA microarrays following environmental stressors such as prolonged oxygen exposure at critical stages of lung development (9).

9. PERSPECTIVE

In conclusion, rudimentary genetic foundations for the complex condition – BPD -- are beginning to be realized during an era that has witnessed an explosion in sophisticated multiplex analyses, which are now available to determine allelic and haplotype frequencies for thousands of candidate genes simultaneously. Selection of populations subjected to analyses will be critical in identifying associations of these genotypes specifically to BPD, particularly since there is a wide variation in the expression of this phenotype between neonatal intensive care units (60, 61). This variation may reflect complex interactions between treatment strategies-environmental pressures, and racial population distributions-genetic pressures.

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