The Role of ASB3 Gene Single Nucleotide Polymorphism in the Progression to Bronchopulmonary Dysplasia in Extremely Low Birth Weight Infants

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Background

Bronchopulmonary dysplasia (BPD) is a major cause of neonatal morbidity in Extremely Low Birth Weight (ELBW) infants. The pathogenesis of BPD is very complex and has a number of mechanisms: it is associated with smooth muscle proliferation; there is airway epithelial and vascular endothelial cell dysregulation; these changes occur under the influence of hypoxia, barotrauma and inflammation; and, there is a strong genetic foundation.

Mechanical stress (i.e. mechanical ventilation) and hyperoxia (i.e. free radicals) may promote bronchial myogenes, causing both hypertrophy and hyperplasia of the myocytes. The changes in the muscular layer of the airways place many former preterm infants at higher risk for subsequent wheezing disorders in infancy, childhood and adulthood.

Among the candidate genes that may influence smooth muscle cell changes is the ASB3 gene, located on chromosome 2. It is a member of the ankyrin repeat and SOCS box-containing family of proteins. A recent study reported that genetic variations of the ASB3 gene are associated with asthma and bronchodilator responsiveness to inhaled β2-agonists. ASB proteins may also play an important role at various levels of myogenesis (figure 1).

Hypothesis

ASB3 gene variants are associated with the progression to bronchopulmonary dysplasia in ELBW infants.

Methods

Design:
- Ongoing cohort study of infants <1kg born without congenital or chromosomal anomalies.
- Informed written parental consent obtained.

Methods:
- DNA was isolated from buccal mucosa and subjected to allelic discrimination using RT-PCR and specific probes for 5 ASB3 related SNPs (single nucleotide polymorphism): rs350729, rs1840321, rs1384918, rs1319797 and rs1020566.
- BPD was defined as oxygen dependence at 36 weeks PMA.

Statistics:
- x² test, Fisher exact test, t-test, z-test, logistic regression and haplotype analyses were performed as appropriate.
- A p value of <0.05 was considered statistically significant.

Results

Demographics of Enrolled ELBW Infants

<table>
<thead>
<tr>
<th>Variable</th>
<th>No BPD (N = 95)</th>
<th>BPD (N = 105)</th>
<th>P- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BW (grams: median; IQR)</td>
<td>850 (750, 930)</td>
<td>710 (625, 850)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>GA (weeks: median; IQR)</td>
<td>26 (23,27)</td>
<td>25 (24,26)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Male</td>
<td>34 (36%)</td>
<td>52 (50%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td>0.8</td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>31 (33%)</td>
<td>30 (29%)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>27 (28%)</td>
<td>33 (31%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>33 (35%)</td>
<td>35 (33%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4 (4%)</td>
<td>7 (7%)</td>
<td></td>
</tr>
</tbody>
</table>

Patients with BPD were born earlier (p<0.001) and weighed less (p<0.001) when compared to infants without BPD.

The Presence of Minor Allele for ASB3-related SNPs

<table>
<thead>
<tr>
<th>SNP</th>
<th>rs1384918 P = 0.036</th>
<th>rs1840321 P = 0.040</th>
<th>rs350729 P = 0.049</th>
<th>rs1319797 P = 0.078</th>
<th>rs1020566 P = 0.030</th>
</tr>
</thead>
<tbody>
<tr>
<td>No BPD</td>
<td>63 (65%)</td>
<td>44 (40%)</td>
<td>39 (42%)</td>
<td>45 (47%)</td>
<td>25 (24%)</td>
</tr>
<tr>
<td>BPD</td>
<td>47 (52%)</td>
<td>40 (36%)</td>
<td>30 (36%)</td>
<td>22 (25%)</td>
<td>7 (22%)</td>
</tr>
</tbody>
</table>

Any minor allele

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>OR</th>
<th>5% CI</th>
<th>95% CI</th>
<th>P- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA</td>
<td>-0.569</td>
<td>0.556</td>
<td>0.457</td>
<td>0.702</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>rs1384918</td>
<td>0.676</td>
<td>1.965</td>
<td>1.061</td>
<td>3.638</td>
<td>0.032</td>
</tr>
</tbody>
</table>

Outcome

Conclusions

Genetic variations of ASB3 are associated with the development of BPD in ELBW infants, independently of gestational age.

Speculations

We speculate that these genetic variants influence smooth muscle cell differentiation, hypertrophy, and the responsiveness to bronchodilators and, that they increase the susceptibility to BPD in ELBW infants.

References