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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 hyperoxia, 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 myogenesis, 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 variants of the ASB-3 gene are associated with asthma and bronchodilator responsiveness to inhaled β 2-agonists. ASB proteins may also play an important role at various levels of myogenesis (figure 1.)

Mechanisms

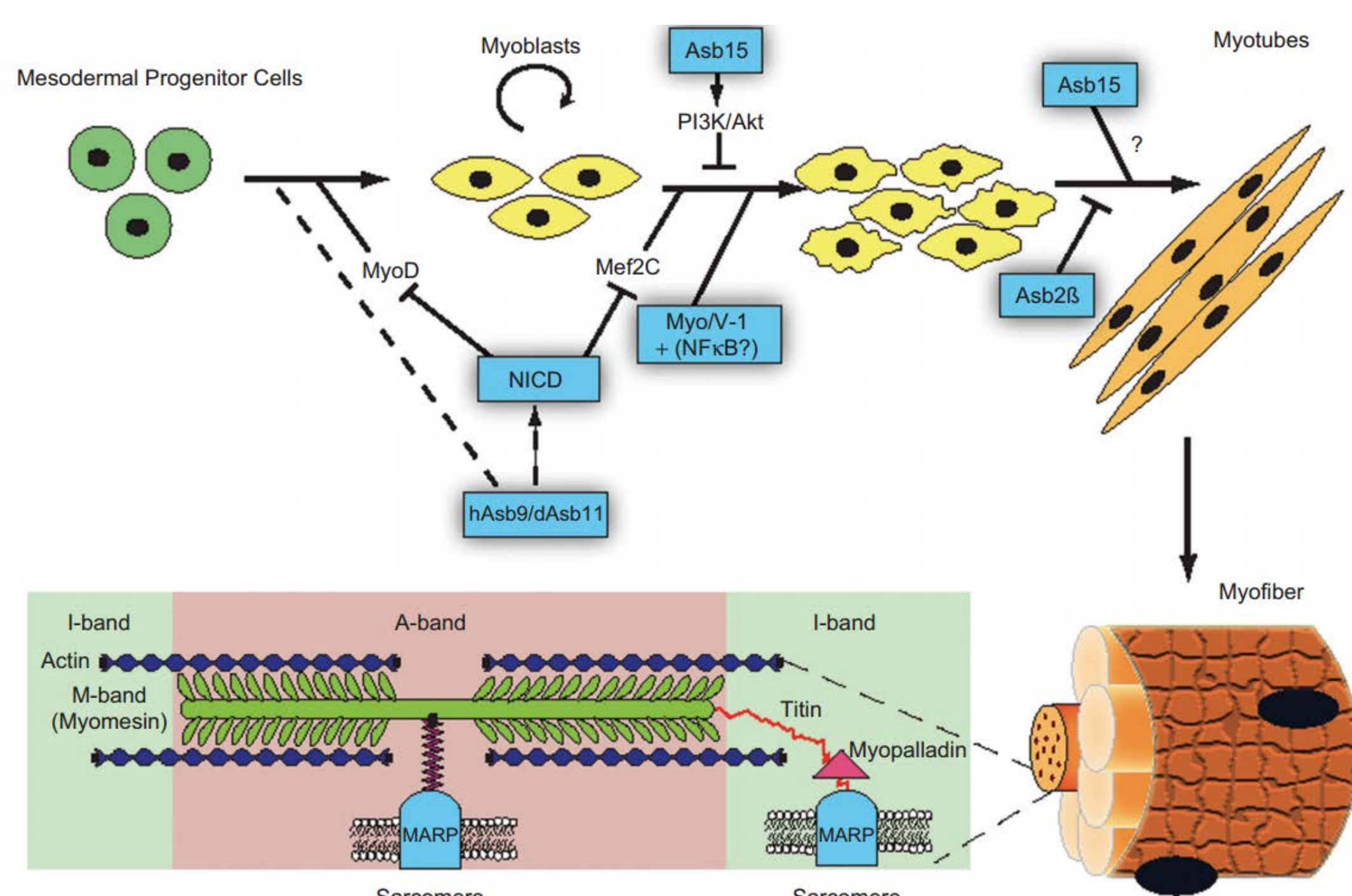


Fig. 1 used from Tee and Peppelenbosch.

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 rs10205606.
- BPD was defined as oxygen dependence at 36 weeks PMA.

Statistics:

- χ^2 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

| Demographics of Enrolled ELBW Infants | | | |
|---------------------------------------|-----------------|----------------|----------|
| | No BPD (N = 95) | BPD (N = 105) | P- value |
| BW (grams: median; IQR) | 850 (750, 930) | 710 (625, 850) | < 0.001 |
| GA (weeks: median; IQR) | 26 (25,27) | 25 (24,26) | < 0.001 |
| Male | 34 (36%) | 52 (50%) | 0.07 |
| Race | | | |
| Non-Hispanic White | 31 (33%) | 30 (29%) | 0.8 |
| Non-Hispanic Black | 27 (28%) | 33 (31%) | |
| Hispanic | 33 (35%) | 35 (33%) | |
| Other | 4 (4%) | 7 (7%) | |

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

Outcome

| The Presence of Minor Allele for ASB3- related SNPs | | | | | | | | | | |
|---|------------------------|----------|------------------------|----------|-----------------------|----------|------------------------|----------|-------------------------|----------|
| | rs1384918 P = 0.036 | | rs1840321 P = 0.040 | | rs350729 P = 0.849 | | rs1319797 P = 0.078 | | rs10205606 P = 0.630 | |
| | No BPD | BPD | No BPD | BPD | No BPD | BPD | No BPD | BPD | No BPD | BPD |
| Wild type | 53 (55%) | 42 (40%) | 47 (52%) | 30 (36%) | 38 (42%) | 29 (40%) | 44 (47%) | 25 (34%) | 7 (29%) | 14 (35%) |
| Any minor allele | 43 (45%) | 62 (60%) | 44 (48%) | 53 (64%) | 53 (58%) | 44 (60%) | 49 (53%) | 49 (66%) | 17 (71%) | 26 (65%) |

Logistic regression

| Variable | Coefficient | OR | 5% CI | 95% CI | P- value |
|-----------|-------------|-------|-------|--------|----------|
| GA | -0.569 | 0.556 | 0.457 | 0.702 | <0.001 |
| rs1384918 | 0.676 | 1.965 | 1.061 | 3.638 | 0.032 |

Summary

- Two SNPs (rs1384918 and rs1840321) out of five analyzed for ASB3 showed differences in the genotype distributions for the BPD and no BPD groups.
- A logistic regression analysis confirmed that this association is independent of gestational age.
- A haplotype analysis revealed that two specific haplotypes from these SNPs were associated with the progression to BPD.

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

- Jobe AH. The New Bronchopulmonary Dysplasia. *Curr Opin Pediatr.* 2011 April; 23(2): 167–172.
- Tee JM et al. Anchoring skeletal muscle development and disease: the role of Ankyrin repeat domain containing proteins in muscle physiology. *Crit Rev Biochem Mol Biol.* 2010 Aug;45(4):318-30; figure 1.
- Israel E et al. Genome-Wide Association Study of Short-Acting beta2 Agonists: A Novel Genome-Wide Significant Locus on Chromosome 2 near ASB3. *Am J Respir Crit Care Med.* 2015 Mar 1; 191(5): 530–537.
- Zhou L, Hershenson MB. Mitogenic signaling pathways in airway smooth muscle. *Respir Physiol Neurobiol* 2003;137:295-308
- Wang H et al. Severity of neonatal hyperoxia determines structural and functional changes in developing mouse airway. *Am J Physiol Lung Cell Mol Physiol* 2014 Aug 15;307(4):L295-301.
- McDaniel TG et al. Ankyrin repeat and SOCS box protein 15 Regulates Protein Synthesis in skeletal muscles. *Physiol Regul Integr Comp Physiol.* 2006 Jun;290(6):R1672-82
- Chung AS et al. Ankyrin Repeat and SOCS Box 3 (ASB3) Mediates Ubiquitination and Degradation of TNF α Receptor II. *Mol Cell Biol.* 2005 Jun; 25(11): 4716–4726.