3-23-2017

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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 β2-agonists. ASB proteins may also play an important role at various levels of myogenesis (figure 1.)

Mechanisms

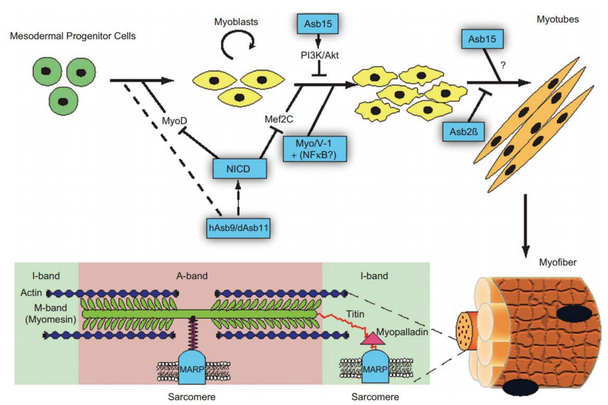

Fig. 1 used from Tee and Peppelenbosch.

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:

- X^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.

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