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ROCK2 Gene Single Nucleotide Polymorphisms and Association with Bronchopulmonary Dysplasia in Extremely Low Birth Weight Infants

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Background

Bronchopulmonary dysplasia (BPD) leads to significant morbidity in ELBW infants.

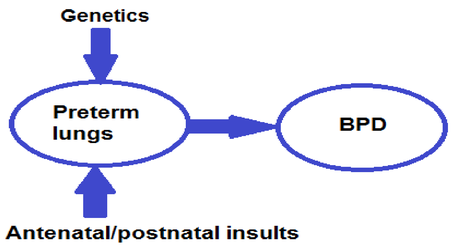
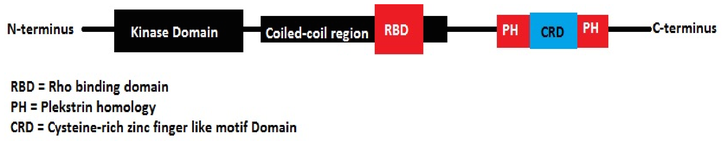


Fig 1. Pathogenesis of BPD

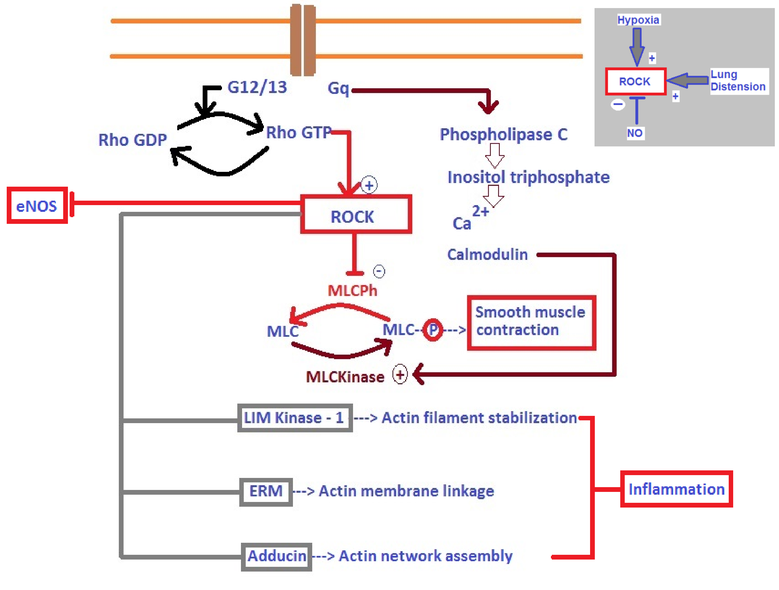
Rho associated coiled-coil containing protein kinase 2 (ROCK-2) gene

- On chromosome 2p24
- ROCK: Serine/threonine protein kinase



RBD = Rho binding domain
PH = Plekstrin homology
CRD = Cysteine-rich zinc finger like motif Domain

Fig 2. ROCK-2 functional domains



*ROCK inhibitor decreases pulmonary edema, microvascular permeability and lung injury

Fig 3. ROCK pathways (eNOS, endothelial Nitric Oxide Synthase; ERM, ezrin/radixin/moesin; MLCPh, Myosin Light Chain Phosphatase)

ROCK-2 SNP rs2290156

- In intron; MAF (Minor Allele Frequency), C= 0.30
- G allele and GC genotype more in RDS

ROCK-2 SNP rs726843

- In intron; MAF, A = 0.35
- TC genotype more in RDS compared to controls

ROCK-2 SNP rs978906

- In 3' UTR; MAF, C = 0.39
- Affects ROCK2 expression by interfering with microRNA-1183 binding
- Association with stiffer arteries and with high altitude essential hypertension

Hypothesis

We hypothesize that ROCK2 gene SNP variants rs2290156, rs726843 and rs978906 are associated with development of BPD in ELBW infants.

Methods

Inclusion criteria

- ELBW infants (birth weight < 1kg)
- Informed parental consent

SNP Analysis

DNA was isolated from buccal swabs of 137 ELBW infants and analyzed via real-time PCR using Taqman probes for ROCK2 gene SNP variants rs2290156, rs726843 and rs978906.

BPD was defined by the need for Oxygen supplementation at 36 weeks postmenstrual age.

Statistics

Chi-square test, Fisher's exact test, Mann-Whitney Rank Sum test and t-test were performed for statistical analysis; p <0.05 was considered significant.

Results

Demographic Characteristics

		No BPD (n = 57)	BPD (n = 80)	p value
Gestational age, wks, median (IQR)		26 (24, 27)	25 (24, 26)	0.22
Birth weight, g, mean (SD)		792.9 (123.8)	752.0 (147.3)	0.09
Female Gender, n (%)		32 (56)	48 (60)	0.78
Race, n (%)	Non Hispanic White	18 (33)	29 (38)	0.89
	Non Hispanic Black	16 (29)	20 (26)	
	Hispanic	16 (29)	23 (30)	
	Other	5 (9)	5 (6)	
Antenatal steroids, n (%)		43 (81)	68 (91)	0.18

Genotype Distributions

Genotype		No BPD n (%)	BPD n (%)	P value
rs2290156	Wild allele	25 (64)	32 (71)	0.13
	Heterozygous	7 (18)	11 (24)	
	Minor allele	7 (18)	2 (4)	
	GG	25 (64)	32 (71)	0.64
	Any c	14 (36)	13 (28)	
rs726843	Wild allele	21 (55)	24 (42)	0.42
	Heterozygous	12 (32)	25 (44)	
	Minor allele	5 (13)	8 (14)	
	GG	21 (55)	24 (42)	0.22
	Any a	17 (45)	33 (58)	
rs978906	Wild allele	22 (52)	20 (33)	0.09
	Heterozygous	11 (26)	28 (47)	
	Minor allele	9 (21)	12 (20)	
	TT	22 (52)	20 (33)	0.04*
	Any c	20 (47)	40 (67)	

Conclusions

- ROCK2 gene SNP rs978906 shows association with BPD
- We speculate that this variant may play a role in the development of BPD by influencing smooth muscle tone in the pulmonary vasculature

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