Race-specific association analysis of genetic variants and flanking haplotypes in the surfactant protein B gene with neonatal respiratory distress syndrome: a case-control study from a Missouri cohort

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Abstract

Genetic contribution to the pathogenesis of neonatal respiratory distress syndrome (RDS) has been suggested by studies of gender, race, family clusters, and genetically modified murine lineages. The surfactant-associated protein B gene (SFTPB) (OMIM number: 178640; GenBank number: AF400074) is a candidate gene for association with neonatal RDS due to the unequivocal respiratory distress phenotype observed in both human infants and murine lineages with disrupted gene expression. The purpose of the present study was to examine the association of genetic polymorphisms and flanking haplotypes in SFTPB with RDS in Black and White newborns with estimated gestational age (EGA) ≥ 34 weeks. We sampled a total of 84 cases identified in the Neonatal Intensive Care Unit of St. Louis Children’s Hospital and 1,003 controls identified through the Missouri State Department of Health Newborn Screening Program. Fisher’s exact test and multiple logistic regression analysis were used to detect association of individual polymorphic sites with RDS phenotype within each racial group. The programs HAPLOVIEW and PHASE were used to identify race-specific blocks of linkage disequilibrium (LD) (Pairwise D’), and to test for association of haplotypes within LD blocks with RDS status. We identified 57 genetic variants among Whites (52 SNPs and 5 insertion/deletion sites) and 59 among Blacks (54 SNPs and 5 insertion/deletion sites) in 8.8 kb of SFTPB sequence, including 1.8 kb of the promoter region, 1.1 kb of exonic sequence, and 5.9 kb of intervening intronic sequence. Among Blacks, marker rs3024797 (genomic position 750) was significantly associated with RDS (Fisher’s P-value = 0.0032, Regression P-value = 0.0014). No significant associations were detected among Whites. Two LD blocks were identified among the Black population and one in the White. No haplotypes in any block were significantly associated with RDS status, although the haplotype 3744_G/4057_G/4521_C showed a nominal significance (P = 0.0816) in the Black population using HAPLOVIEW. The biologic mechanism by which the insertion/deletion site at genomic position 750 may lead to disease is unknown. We suggest that this site may be an intronic enhancer or other transcription regulatory region - a deletion of which could significantly lower transcription rates.