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Association between functional polymorphisms in the nitric oxide synthase 3 gene and pediatric acute respiratory distress syndrome

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ABSTRACT. Nitric oxide mediates multiple physiological functions, including neurotransmission, immune regulation, angiogenesis, antiplatelet activity, and surfactant maturation or secretion. Mice deficient in the nitric oxide synthase 3 (*NOS3*) gene displayed defective lung vascular development and fatal respiratory distress. Polymorphisms in *NOS3* have been reported to be associated with respiratory distress syndrome (RDS). The role of *NOS3* polymorphisms as a risk factor for pediatric acute respiratory distress syndrome (PARDS) was evaluated by analyzing the possible functional single nucleotide polymorphisms (SNPs) in the regulatory and coding regions of *NOS3*. Samples from 216 PARDS patients and 225 healthy control subjects were genotyped

at 4 SNP loci (rs11771443 and rs3918188 in the promoter region, rs1799983 in exon 7, and rs7830 at the intron24-exon23 boundary). Statistically significant differences were observed in the allelic or genotypic frequencies of the rs1799983 and rs11771443 polymorphisms in *NOS3*. The T and G alleles of rs1799983 and rs11771443 were associated with a significantly higher risk of PARDS compared to the C allele ($P = 0.030$) and the T allele ($P = 0.004$), respectively. Strong linkage disequilibrium was observed in one block ($D' > 0.9$). Subjects with PARDS displayed significantly fewer T-C haplotypes ($P = 0.013$) in block 1 (rs1799983-rs11771443). These findings indicate that *NOS3* polymorphisms play a definitive role in PARDS, and therefore may be useful for future genetic or neurobiological studies on RDS.

Key words: Pediatric acute respiratory distress syndrome; Nitric oxide synthase 3; Single nucleotide polymorphisms