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Title: Analysis of BMPR2 mutations, and endothelin-1 and nitric oxide synthase genes polymorphisms in pulmonary arterial hypertension

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Body: PAH may be heritable. Much of what is known about the genetic basis of PAH is related to bone morphogenetic protein receptor 2 (BMPR2). We studied variants in BMPR2, endothelin-1 (ET-1) and nitric oxide synthase 2 (NOS2). Patients with idiopathic and associated PAH were included. DNA was amplified for the 17 validated amplicons spanning the coding sequence of BMPR2 gene. For ET-1 gene the polymorphism K198N was selected because homozygous for Asn (T/T genotype) have higher levels of ET-1. NOS2 play a key role in endothelial dysfunction. CCTTT repeat polymorphism was studied. 30 PAH patients (14 idiopathic, 16 associated) and 50 controls were included. BMPR2: 21 mutations were identified in 22 patients. Six were missense, one nonsense, 3 deletions and 7 synonymous changes. According to PolyPhen software changes with involvement in the pathogenesis were present in 4 of the 30 patients (14%). Various missense polymorphisms were detected. Although these polymorphisms causes an amino-acid change, they don't reached pathologic value. Silent mutation p.R937R was present in 5 patients. ET-1: genotype GG was present in 43%, GT in 53% and TT in only 4%, the same pattern as in controls. NOS2: PAH patients have a lower number of repetitions for CCTTT polymorphism than controls (12 vs 13.5, $p = 0.001$). Conclusions. Frequency of pathogenic mutations in BMPR2 in non heritable PAH was 14%. It would be interesting to perform functional studies of non pathogenic mutations to test their effect on BMP proteins. CCTTT repeat polymorphism showed statistical differences between patients and controls. K198N (G/T) polymorphism in ET-1 gene showed similar distribution.