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Title: Molecular analysis of genes BMPR2 and KCNA5 in Spanish patients with pulmonary arterial hypertension

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Body: Pulmonary arterial hypertension (PAH; OMIM 178600) is a rare and progressive vascular disorder characterized by obstruction of precapillary pulmonary arteries. PAH results from extensive remodelling of the pulmonary vasculature caused by an increased musculation of small arteries and the fibrosis of the intima that leads to obliteration of small pulmonary arteries. Without treatment, progression of pulmonary hypertension leads to right ventricular failure and death in three years from diagnosis. Approximately 75% of patients with the familiar form of PAH have a mutation in the gene encoding bone morphogenetic protein receptor type II (BMPR2). However, some other candidate genes have been advocated, including potassium voltage-gated channel, shakerrelated subfamily, member 5 (KCNA5). We included 30 PAH patients and 50 controls. The DNA extraction was performed with Qiagen FlexiGene DNA kit. BMPR2 and KCNA5 genes were amplified by PCR and sequenced. A total of 20 BMPR2 nucleotide changes were identified in 22 of 30 patients with PAH. Only 3 changes were identify with the Polyphen software as pathogenic (p.C84F, p.Q92L and p.W298Stop). These mutations were found in 4 patients. For KCNA5 gene 10 nucleotide changes were detected in 11 patients. Three were classified as pathogenic (p.P169R, p.R184P and p.E208X) we have found these mutations in 4 patients. None of the pathogenic mutations identified here were detected in a panel of 100 chromosomes from control individuals. In conclusion, mutations in genes BMPR2 and KCNA5 have been detected in the 28,5% of our pool of patients indicating that these genes are the most important genes implicated in the development of PAH.