Editorial

Molecular Genetic Diagnosis of Pulmonary Arterial Hypertension: An Increased Complexity

Diagnóstico genético molecular de la hipertensión arterial pulmonar: una complejidad creciente

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In this issue of the Revista Española de Cardiología, Navas et al. present an important series of pulmonary arterial hypertension (PAH) patients who were studied for their genetic status concerning the major PAH genes, BMPR2, KCNK3 and TBX4, and for the possible influence of the mutations detected on their clinical status. BMPR2 was recognized in 2000 by the international PAH consortium as the major predisposing gene for PAH and more than 300 mutations have been identified and collected through large collaborative studies. The present study reports novel BMPR2 mutations, which is not surprising because, until now, few investigations have been conducted in Spain on this gene. Furthermore, previously described mutations are dispersed throughout the coding sequence of the gene, with some particular features described for mutations localized in the cytoplasmic tail of the receptor. Interestingly, the rate of BMPR2 deleterious mutation found in the familial forms of PAH is lower than that found in reported European studies (50% vs 84%). Indeed, mutations were detected by the same methods as those used in other European centers. This series of patients includes both adult and pediatric forms of PAH (although no details are given about the distribution of the ages in the article). Pediatric forms of PAH can be also linked to ACVR1 mutations responsible for hereditary hemorrhagic telangiectasia, and the disease may be unapparent at the time of PAH occurrence in childhood; some authors have identified families with an unrecognized hereditary hemorrhagic telangiectasia causing PAH in childhood. This difference might also be due to the criteria used for defining familial forms.

Some authors have also explored genes more recently identified as involved in PAH. KCNK3 (alias Task-1) was found to be mutated after initial exome sequencing in an unresolved case of familial PAH and subsequent investigations of familial and idiopathic PAH. This was the first gene involved in PAH not belonging to the bone morphogenetic proteins signaling pathway, since KCNK3 is a 2-pore, pH-dependent potassium channel. All missense mutations initially described were either in the extracellular loop or in the intracellular N-terminal domain of the channel. The early mean age of onset of PAH in the patients carrying the KCNK3 variants of the present series, at 17.5 ± 10 years, suggests a childhood onset at least for 1 of the 3 carrier patients. The 2 missense variants are likely to affect the function of the gene based on in silico analysis, but even more surprisingly, 1 of the carriers is homozygous for the missense mutation and his form of the disease is severe, even though the age at onset is not indicated. This observation is really unique and should spur extensive clinical and pharmacological investigation of the patient in order to better understand the role of the channel in PAH. In mice, biallelic disruption of the Task-1 gene is not lethal because Task-3 subunits compensate for the absence of the Task-1 subunit. The study by Navas et al. is the first to report missense variants in PAH since the description of the KCNK3 mutations in 2013.

Interestingly, 3 variants of TBX4 were also found in this large series of PAH patients. TBX4 variants identified are missense variants or an in-frame insertion of a single amino acid that cannot be considered as disease-causing mutations until functional studies have been performed, allowing the function of the mutated transcription factor to be tested at least in vitro. The 2 missense variants are not likely to have a functional effect according to in silico analysis by various algorithms. TBX4 mutations are most often found in pediatric pulmonary hypertension according to results reported by Kerstjens-Frederikse et al. Indeed, TBX4 loss-of-function mutations, which are responsible for small patella syndrome, are found at a far lower frequency in adult PAH than in the pediatric form and the cause of this difference is not known. The PAH patients carrying the TBX4 variants in this study showed no clinical or radiological signs of small patella syndrome, which does not indicate a functional deleterious effect of these variants.

The baseline clinical and hemodynamic status and the survival rate of the PAH patients included in this study were carefully collected and analyzed in relation to the genotypes of the patients and the type of PAH, idiopathic PAH (IPAH) vs hereditary PAH. This study confirms the younger age at onset in hereditary PAH, in particular in individuals who are BMPR2 mutation carriers. Unfortunately, the clinical and hemodynamic parameters were not available during the follow-up period.

Hemodynamic parameters in BMPR2 mutation carriers have a tendency to be more severe than in noncarriers, as observed by...
Evans et al.\textsuperscript{10} in a recent large meta-analysis but, due to the size of the patient sample in this series, the differences were not significant, likely due to a lack of power.

The proportion of acute responders in iPAH patients in this study, 39\% in the iPAH population, is in striking contrast with the proportion of around 12\% reported in the literature.\textsuperscript{13} This difference might be due to criteria used for defining acute response, which should be clarified to determine whether there is another reason for this difference. However, a lower rate of acute responders was observed in this study among the BMPR2 mutation carriers, which is in accordance with published data.\textsuperscript{12}

Due to the limited number of patients in each gene mutation category, it is difficult to draw any strong conclusions about the genotype/phenotype correlation, because a lack of difference can be due to weak statistical power. Moreover, the uncertainty about the pathological significance of the variants in TBX4 and KCNK3 hampers any robust interpretation.

Some lessons can be drawn from this article, and from other recently published studies.

To identify the causative gene, it is important to perform, when possible, a complete genetic investigation in PAH patients, including BMPR2, KCNK3, TBX4, and ACVRL1 genes, the 2 last genes being more important in pediatric PAH, as already mentioned. Moreover, wide mutation screening can be achieved by the design of large panels for sequencing covering all the genes involved in PAH, including those rarely involved, such as caveolin-1, and Smad9.\textsuperscript{13} It is also important to systematically test the EIF2AK4 gene, at least in pediatric forms of pulmonary hypertension, because the signs of pulmonary veno-occlusive disease can be missed, in order to make the correct diagnosis and to avoid the complications of inappropriate treatment.\textsuperscript{14} It is also important for the genetic counselling of the parents because hereditary pulmonary veno-occlusive disease is a recessive disease.

Finding a deleterious mutation should encourage physicians to select efficient and carefully monitored treatment in view of the increased severity of the clinical course in mutation carriers.

These results also reveal the need for large international collaborations to gather mutations and the cognate clinical annotations in order to improve knowledge of the disease and the genotype-phenotype correlations.

CONFLICTS OF INTEREST

None declared.

REFERENCES


