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Original Article

# Study of the BMPR2 Gene in Patients with Pulmonary Arterial Hypertension

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ABSTRACT

*Introduction:* Mutations of the gene that code bone morphogenic protein type 2 receptor *(BMPR2)* are involved in the pathogenesis of pulmonary arterial hypertension (PAH), both in its familial (FPAH) and its idiopathic (IPAH) forms.
*Method:* With the aim of increasing the knowledge of these genetic factors in our area, the *BMPR2* gene was studied in 17 patients with PAH, 8 with FPAH and 9 with sporadic IPAH. Additionally, a study was made to see whether the presence of *BMPR2* mutations was associated with changes in the CO diffusing CO ($DL_{CO}$) with the aim of evaluating the interest in this measurement in the pre-clinical diagnosis.
*Results:* R491Q y R211X mutations were detected in 2 patients with FPAH (prevalence, 25%), and the R332X mutation in one case of IPAH (prevalence, 11%). The familial study of the patient with the R491Q mutation, 14 of the 28 subjects studied had the mutation, and 4 had the diseases (penetration, 36%). A decrease in the $DL_{CO}$/alveolar volume ($K_{CO}$) ratio was observed in asymptomatic family members who expressed the mutation, compared to those who did not express it (88±5% and 104±9% of the reference value, respectively; $P<.01$).
*Conclusion:* We conclude that the frequency of mutations in the *BMPR2* gene in the patients studied with FPAH is lower than was previously described. The decrease in the $K_{CO}$ observed in asymptomatic carriers of the mutation suggests a certain level of pulmonary vascular changes, therefore its measurement could be useful in the familial study of FPAH.



## Estudio del gen *BMPR2* en pacientes con hipertensión arterial pulmonar

*Palabras clave:*
Hipertensión arterial pulmonar
Receptor tipo 2 de las proteínas morfogénicas del hueso
Mutaciones
Cribaje genético
Capacidad de difusión del monóxido de carbono

RESUMEN

*Introducción:* Las mutaciones del gen que codifica el receptor 2 de las proteínas morfogénicas del hueso *(BMPR2)* contribuyen a la patogénesis de la hipertensión arterial pulmonar en sus formas familiar (HAPF) e idiopática.
*Método:* Con el objetivo de profundizar en el conocimiento de dichos factores genéticos en nuestro medio, se estudió el gen *BMPR2* en 17 pacientes con hipertensión arterial pulmonar, 8 con HAPF y 9 con hipertensión arterial idiopática esporádica. Adicionalmente, se analizó si la presencia de mutaciones del gen *BMPR2* se asociaba a cambios en la capacidad de difusión del CO a fin de evaluar el interés de esta medición en el diagnóstico preclínico.

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*Resultados:* Se detectaron las mutaciones R491Q y R211X en 2 pacientes con HAPF (prevalencia 25%), y la mutación R332X en un caso de hipertensión arterial idiopática (prevalencia 11%). El estudio familiar del paciente con la mutación R491Q demostró la presencia de la misma en 14 de los 28 sujetos estudiados, de los cuales 5 presentaban la enfermedad (penetrancia 36%). En dicha familia se observó un descenso de la relación en la capacidad de difusión del CO/volumen alveolar en los familiares asintomáticos que expresaban la mutación, comparado con los que no la expresaban (88 ± 5% y 104 ± 9% del valor de referencia, respectivamente; p < 0,01).
*Conclusión:* Concluimos que la frecuencia de mutaciones del gen *BMPR2* en los pacientes con HAPF estudiados es inferior a la descrita previamente. El descenso del volumen alveolar observado en portadores de la mutación asintomáticos sugiere cierto grado de alteración vascular pulmonar, por lo que su medición podría ser útil en el estudio familiar de la HAPF.


## Introduction

Pulmonary arterial hypertension (PAH) is a disease of unknown aetiology, characterised by an increase in pulmonary artery pressure.[1] Since PAH was well characterised in the 1980s, it has been known that a high percentage of cases have a family history of the disease;[2] this is known as hereditary or familial PAH (FPAH). This led to the search for genetic factors which could explain its origin. In 2000, Deng et al[3] used genetic linkage to identify the 2q33 region as a candidate region, and subsequently, mutations of the BMPR2 gene were reported to be the cause of the disease (International Primary Pulmonary Hypertension Consortium).[4] The BMPR2 gene encodes the bone morphogenic protein type 2 receptor, which is a member of the transforming growth factor β superfamily. Around 70% of FPAH patients have mutations in this gene, of which 300 different ones have been identified to date,[5] there being no recurrent mutations. Mutations of the BMPR2 gene have also been described in patients with sporadic idiopathic PAH (IPAH),[6,7] although less frequently than in FPAH, PAH associated with anorexigen consumption,[8] and PAH associated with congenital cardiopathies.[9] It is not known if the prevalence of these mutations varies in relation to geographical origin or ethnic group. The disease is inherited following a pattern of autosomal dominant inheritance with reduced penetrance. Only 10% to 20% of mutation carriers express the disease phenotypically.

To date, no studies have been published about the BMPR2 gene in FPAH patients in Spain. There is just one study into the Spanish population, performed on 8 patients with sporadic IPAH.[10]

At present no biomarker or functional measure exists which enables the early detection of the risk of asymptomatic carriers of the BMPR2 gene mutation developing PAH. However, it is suspected that healthy carriers of the mutation have abnormalities in the pulmonary vascular bed, since these subjects develop pulmonary hypertension during exercise.[11] Patients with PAH show a characteristic reduction in their Diffusion Lung Capacity for Carbon Monoxide (DLCO). As this parameter can be altered by the reduction in the pulmonary vascular bed, we have hypothesised that $DL_{CO}$ might also be reduced in healthy carriers of the BMPR2 gene mutation.

In order to improve our knowledge of the genetic factors associated with developing PAH in our area, we studied the BMPR2 gene of 17 patients, 8 with familial PAH and 9 with sporadic IPAH. Furthermore, an analysis was performed to see if the presence of BMPR2 mutations was associated with changes in $DL_{CO}$, in order to evaluate if this was of interest for the preclinical diagnosis of the disease.

## Method

### *Study Subjects*

The study included 17 consecutive and independent cases of patients diagnosed with PAH; 8 with FPAH and 9 cases of sporadic IPAH (Table 1).

We also evaluated 3 independent cases of healthy relatives of patients who had died of suspected FPAH who were referred for a genetic study. Furthermore, 50 healthy subjects with no relationship

**Table 1**
Demographic and haemodynamic characteristics of patients and results of the study of the BMPR2 gene

| Case | Sex (M/ F) | Age (years) | PAPm (mmHg) | CO ($lmin^{-1}$) | RVP ($dinscm^{-5}$) | PAH type | BMPR2 gene study | Exon | Nucleotide change | Aminoacid change |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 39 | 41 | 4.63 | 604 | Sporadic | No alteration | | | |
| 2 | F | 17 | 56 | 3.55 | 1.227 | Sporadic | Mutation | 8 | c.994C>T | R332X |
| 3 | F | 54 | 53 | 2.84 | 1.408 | Sporadic | No alteration | | | |
| 4 | F | 31 | 57 | 4.15 | 962 | Sporadic | Polymorphism | 12 | c.2324G>A | S775N |
| 5 | F | 32 | 40 | 3.48 | 873 | Familial | No alteration | | | |
| 6 | F | 40 | 58 | 4.5 | 880 | Sporadic | Polymorphism | 12 | c.2811G4A | R937R |
| 7 | M | 14 | 58 | 3.67 | 1.065 | Familial | Mutation | 11 | c.1472G>A | R491Q |
| | | | | | | | | | c.23224G>A | S775N |
| | | | | | | | | | c.600A>c | L200L |
| 8 | F | 18 | 36 | 3.93 | 711 | Sporadic | No alteration | | | |
| 9 | F | 17 | 50 | 2.21 | 1.690 | Sporadic | No alteration | | | |
| 10 | F | 20 | 50 | 2.41 | 1.359 | Sporadic | Polymorphism | 12 | c.2811G4A | R937R |
| 11 | M | 15 | NA | NA | NA | Familial | Polymorphism | 12 | c.2811G4A | R937R |
| 12 | M | 50 | NA | NA | NA | Familial | Polymorphism | 12 | c.2811G4A | R937R |
| 13 | F | 54 | NA | NA | NA | Familial | No alteration | | | |
| 14 | F | 60 | NA | NA | NA | Familial | No alteration | | | |
| 15 | F | 50 | NA | NA | NA | Sporadic | No alteration | | | |
| 16 | F | 25 | NA | NA | NA | Familial | No alteration | | | |
| 17 | F | 41 | 56 | 2.66 | 1.526 | Familial | Mutation | 6 | c.633C>T | R211X |

BMPR2: bone morphogenic protein type 2 receptor; CO: cardiac output; PAH: pulmonary arterial hypertension; NA: not available: PAPm: mean pulmonary arterial hypertension; PVR: pulmonary vascular resistance.

with the disease formed a control group in order to study the S775N polymorphism.

The diagnosis of PAH was performed by studying the pulmonary haemodynamics of all the subjects, and it was defined as the patients having a mean pulmonary artery pressure ≥ 25mmHg at rest and pulmonary artery occlusion pressure ≤ 15mmHg, with no evidence of associated causes.[1] To establish the diagnosis for FPAH, the following criteria were considered: 1) patients with relatives diagnosed with PAH after a study of pulmonary haemodynamics, or 2) a family history of isolated right-sided heart failure or sudden death of unknown origin. The patients' haemodynamic data were obtained from their clinical history and were provided by the doctor who referred the patients to our hospital.

*Molecular Study of the BMPR2 Gene*

We performed PCR amplification of the 13 exons with modified versions of the primers described by Deng et al[3] and Single Strand Conformation Polymorphism (SSCP) analysis of the abnormal migration bands, followed by sequencing with an ABI3100 sequencer.

Only the coding area and 50 base-pairs from the intron-exon boundary were studied. Changes in other regions were not analysed.

*Clinical and Functional Characterization of Families with Cases of Familial Pulmonary Arterial Hypertension*

Besides the genetic analysis, the relatives of 2 patients with familial PAH underwent a clinical study, a test of respiratory function and Doppler echocardiography. The two families were from Spain. Twenty-eight members of subject 7's family, and 5 of subject 5's, were evaluated. All the subjects gave their written consent after being informed of the nature and aims of the study. The clinical study consisted of a detailed anamnesis in which subjects were asked specifically about heart and breathing symptoms, a physical examination, chest x-ray, an electrocardiogram and echocardiogram. The study of respiratory function included forced spirometry and $DL_{CO}$ measurement.

The forced spirometry test and measurement of $DL_{CO}$ (Master Screen; Jaeger, Wüerzburg, Germany) were carried out following the recommendations of the Spanish Society of Pneumology and Chest Surgery.[12] The echocardiography study was performed with a transthoracic echocardiogram (Sonos 5500, Phillips, Holland) with 2.5–3.5MHz transducers. M-mode echocardiography was used to measure the cavities, and ventricular volumes were recorded by 2D echocardiography; the Doppler test was used to test transvalvular flow rates, and the tricuspid regurgitation velocity was measured from different planes.

Subsequently, a periodic clinical follow-up has been performed with the mutation-positive subjects.

*Statistical Analysis*

Data are expressed as mean ± SD for the quantitative variables and as a percentage of absolute values for the qualitative variables. The means of the groups were compared with the Student T test for independent measures. $P<.05$ was considered to be statistically significant in the contrast study.

## Results

The results of the haemodynamic and genetic studies are shown in Table 1.

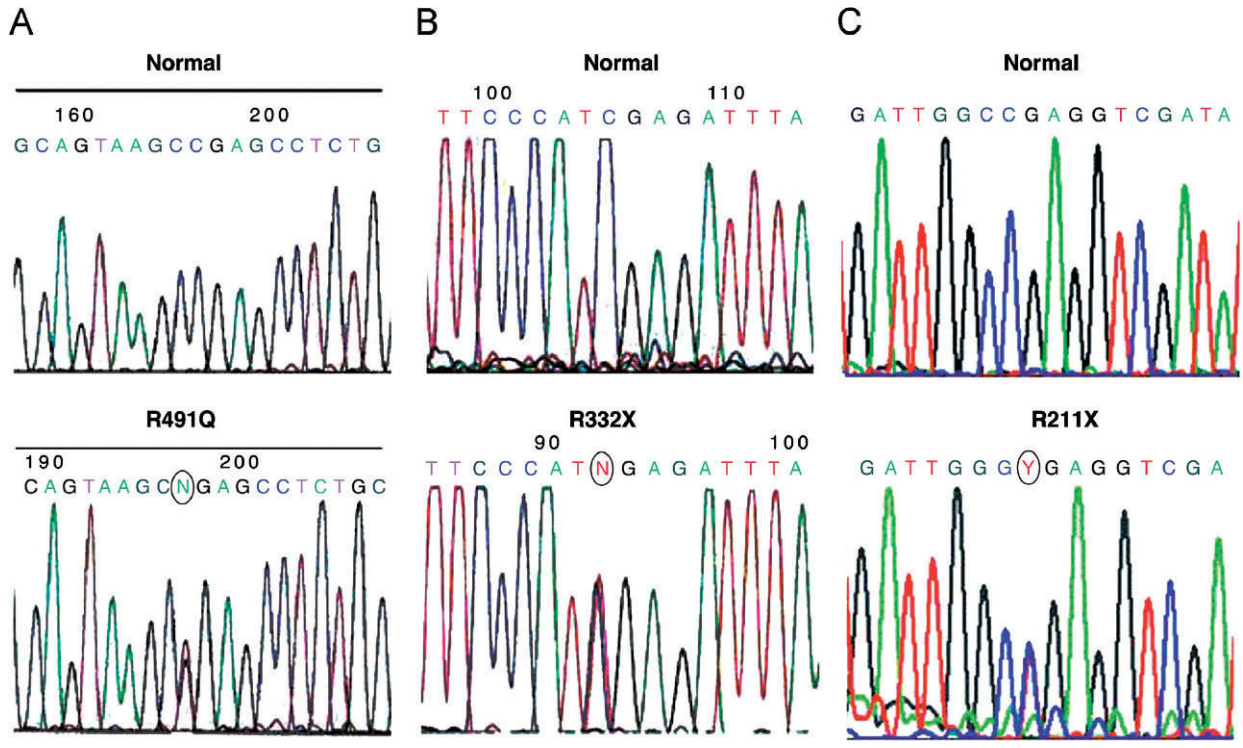


**Figure 1.** Partial sequences of the BMPR2 gene. At the top, the normal sequence, and at the bottom, the partial sequence corresponding to the exon with the mutation. The circle indicates the change.
A) Case 7, exon 11c.1472G4A, p. R491Q.
B) Case 2, exon 7c.994C4T; p. R332X.
C) Case 17, exon 6c.633C4T; p. R211X.

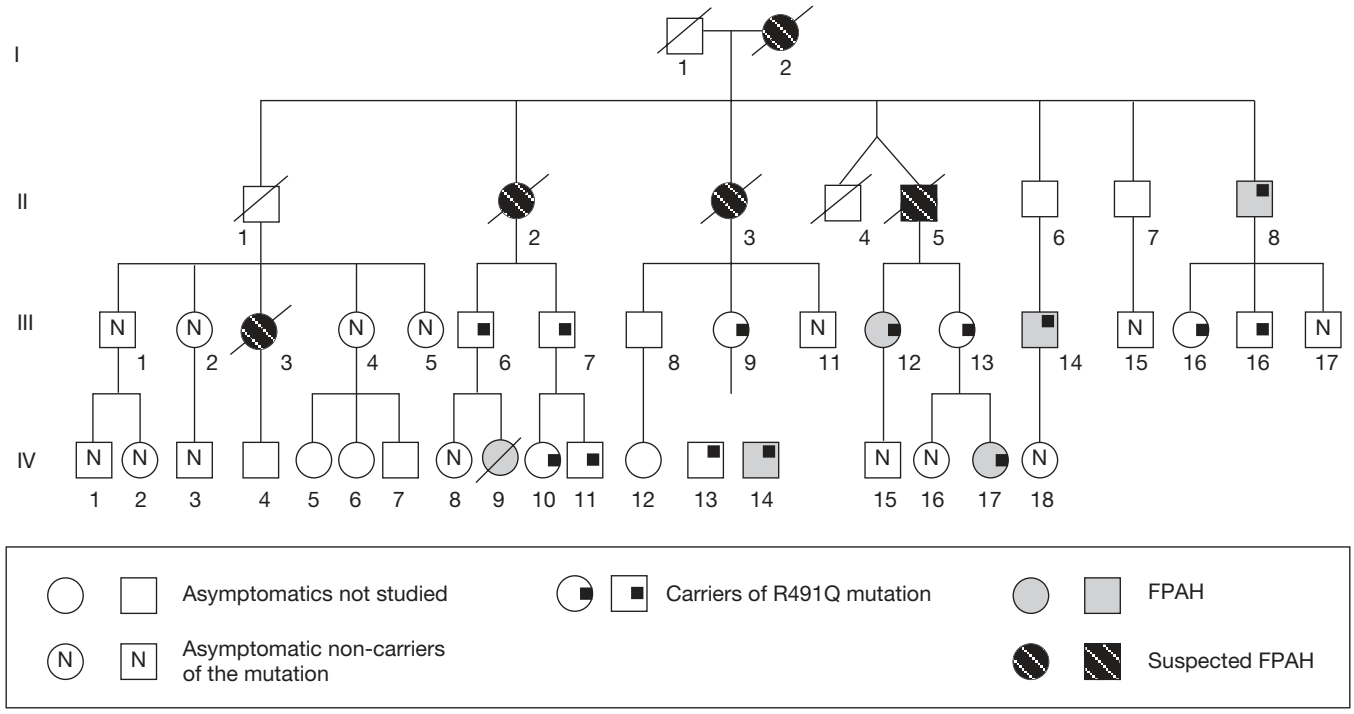


**Figure 2.** Family tree of the family with the R491Q mutation (case 7).

*Genetic Study of the BMPR2 Gene*

Ten sequence variants were detected in the BMPR2 gene, although only 3 correspond with mutations which have previously been described as causing the disease. The first (R332X) is a mutation that creates a stop codon and is therefore, a truncated protein (Figure 1). It was described by Thomson et al[6] in 2000 as the cause of the disease. It was detected in our series in one of the subjects in the sporadic IPAH cohort (subject 2), which gives a mutation frequency of 11.1% in this group.

The second mutation (R491Q), detected in subject 7 (FPAH group), is a missense mutation described by Deng et al[3] in 2000 (Figure 1). Finally, the third mutation (R211X), which like the first one gives rise to a stop codon and is thus a truncated protein, was detected in subject 17 (FPAH group) (fig. 1).[13] Since 2 mutations were identified in a total of 8 cases with FPAH, the mutation frequency in these cases is 25%.

It was possible to study a total of 28 family members for the R491Q mutation, 14 of whom where found to have the mutation. Of these 14, 5 had the disease, so the penetrance in this family is 35.7%.

On the other hand, in the FPAH subjects and also those patients with sporadic IPAH, various polymorphisms were detected which have not been proven to be responsible for the disease. One of these is the S775N polymorphism[14] detected in one subject with sporadic IPAH and in another with FPAH. Although this polymorphism causes an aminoacid change, it is not responsible for the disease and is found in 3.4% of the general population (50 controls studied).

No mutation was found in the 3 healthy subjects studied or in the relatives of patients diagnosed with PAH who had died.

*Phenotype Characterization of Families with Familial Pulmonary Arterial Hypertension*

We studied subject 7's family. The index case, a carrier of the R491Q mutation, was diagnosed with PAH at 14 years of age. The subject's family history included a cousin diagnosed with PAH who died aged 19, and 4 close relatives, including the maternal grandmother, who died of sudden death or unspecified heart disease (Figure 2). A familial study of the BMPR2 gene was carried out, totalling 28 cases from 3 generations, beginning with a brother of the maternal grandmother (2nd generation) (Figure 2). The mutation was detected in this subject at the age of 65, at which time he had a normal echocardiogram. Subsequently, after 9 years of follow-up, an abnormal increase in PAP was detected in the echocardiogram, and PAH was later diagnosed following a haemodynamic study.

Fifteen members of the 3rd generation were studied, 8 of whom were mutation carriers. Of these, two were also diagnosed with PAH after a study of haemodynamics after 5 and 7 years respectively. In the last generation analysed (4$^{th}$), 5 of the 12 subjects studied were mutation-positive, and the index case was diagnosed with PAH (described above), as well as another family member at 3 years of age. The mean age for disease onset was 75 years in the 2$^{nd}$ generation, 49 in the 3$^{rd}$, and 9 in the 4$^{th}$, thus confirming the genetic anticipation phenomenon.

In total, the R491Q mutation was detected in 14 of the 28 members of the family under study (50%). Among the mutation carriers, 5 (including the index case) were diagnosed with PAH after a haemodynamic study, so there is a penetrance of the disease in this family of 35.7%.

Table 2 shows the demographic and functional data of the subjects in this family, grouped in relation to the expression of the mutation.

Given the large number of subjects in the study, the family was investigated to see if the $DL_{CO}$ differed between the asymptomatic carriers of the mutation and non-carriers. Overall, there were no significant differences between the two groups. However, an analysis of variance taking generation as a cofactor, revealed an interaction between the value of the $DL_{CO}/K_{CO}$ ratio and generation. Next, the $K_{CO}$ values were compared between members of the same generation. The $K_{CO}$ value was observed to be lower in the asymptomatic mutation-positive subjects in the 3rd generation (n=7) when compared with the mutation-negative group (n=7) (88 ± 5% and 104 ± 9% of the reference value, respectively ($P$<.01) (Figure 3).

**Table 2**
Demographic and functional data of the family with the R491Q mutation

| | Mutation carriers n = 14[a] | Non-mutation carriers n = 14 |
|---|---|---|
| Age | 35 ± 9 | 29 ± 14 |
| Sex, male/female | 7/7 | 8/6 |
| Echocardiogram alterations[b], n, % | 2 (14) | 1 (7%) |
| FVC, % ref | 99 ± 22 | 103 ± 15 |
| FEV1, % ref | 103 ± 22 | 107 ± 17 |
| FEV1/FVC, % | 83 ± 8 | 86 ± 5 |
| DLCO, % ref | 94 ± 24 | 100 ± 20 |
| DLCO/AV, % ref | 87 ± 13 | 97 ± 14 |

$DL_{CO}$: diffusion capacity for carbon monoxide; $FEV_1$: forced expiratory volume in first second; FVC: forced vital capacity; % ref: percentage of reference value; AV: alveolar volume.

[a] Including patients with haemodynamic diagnosis of pulmonary hypertension.

[b] Increase in systolic pressure in pulmonary artery and/or changes in the right ventricle.

[c] $P<.05$.

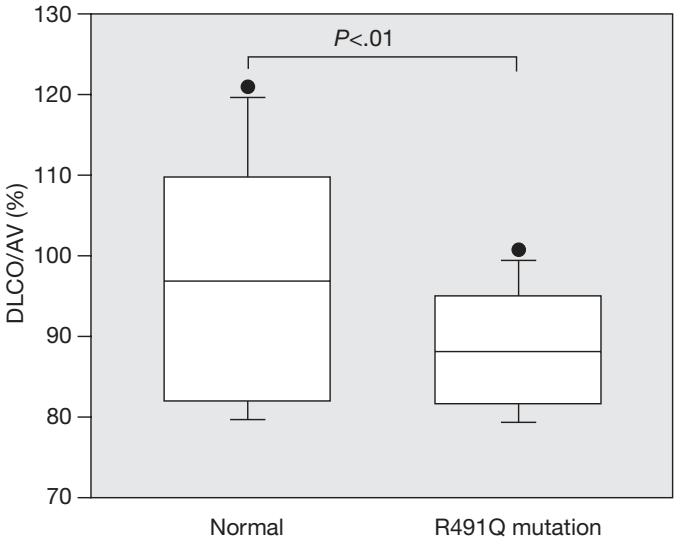


**Figure 3.** Value of the $DL_{CO}$/AV ratio in subjects who were carriers and non-carriers of the R491Q mutation, belonging to the 3rd generation of case 7's family.

Five relatives of case 5 were also studied simultaneously, without knowing the results of the genetic study of the index case. Mutations in the BMPR2 gene were not detected in the index case, and as expected, the relatives were also mutation-negative.

## Discussion

This is the first study to analyse the presence of mutations of the BMPR2 gene in FPAH patients in a Spanish population. Only 2 mutations were detected from 8 cases of FPAH, indicating a penetrance of 25% in this group. This percentage is low when compared with other published data, which indicates that up to 70% of patients with FPAH have BMPR2 gene mutations.[15] One possible explanation for this difference could be the high genetic heterogeneity of our population, which could mean that other unstudied genes participate in the pathogenesis of PAH. Another point to highlight is the technical limitations of the SSCP, since this technique has a detection efficiency of 80% when compared with direct sequence analysis, so using it would reduce the percentage of mutations detected.[16] Also, we should not rule out the presence of mutations in unstudied intronic regions, or even large deletions or duplications.

Being able to study 28 members of the same family has made it possible to evidence the genetic anticipation phenomenon (onset of the disease at earlier ages and/or greater clinical severity in subsequent generations). The R491Q mutation was identified in 14 individuals, corresponding to 50% of all those analysed in this family. PAH was diagnosed in 5 (35.7%) of the carriers studied, including the index case, giving a somewhat higher penetrance than that reported in other studies.[15] In any case, in general terms the penetrance can be considered low, meaning that not all the individuals who are mutation carriers will develop the disease. This suggests that the mutation of the gene is necessary but not enough on its own to express the disease.[17] Other factors might contribute to the pathogenesis of the disease, such as inflammatory or environmental mediators, which could behave as modifiers of the disease in the presence of a permissive genotype.[18,19]

In the IPAH cohort, the prevalence of BMPR2 gene mutations was 11%. This is in agreement with previous studies, although the studies in the literature show different results, with prevalence ranging between 11% and 40%.[7,13] In the first study, Thomson et al[6] observed BMPR2 gene mutations in 13 out of 50 patients diagnosed with IPAH (26%). In the study performed in the Spanish population cited earlier,[10] 2 of the 8 IPAH patients studied showed mutations, and a third showed a change which has not been proven to be responsible for PAH. Thus, the frequency of mutations in the other study in the Spanish population with sporadic IPAH patients (25%) is similar to that obtained in our study with cases of familial PAH, and higher than in the cases of sporadic IPAH. In any case, as these are series with a small number of subjects, it is not possible to draw conclusions with regard to these differences.

No mutations were detected, either in the healthy individuals with a family history of PAH who were referred to us for possible genetic advice, or in the relatives of case 5, who were studied before knowing if the index case was a carrier of the mutation or not. These data confirm that to perform correct family screening for PAH it is necessary to have an accurate genetic diagnosis of the index case.[15]

Undoubtedly, the most interesting clinical finding of this study was the difference in the carbon monoxide diffusion capacity observed between carriers and non-carriers of the mutation. This is an original observation, which has not been described previously. Although it is not possible to affirm that this alteration corresponds with an early manifestation of the disease, it is conceivable that the mutation makes subjects more susceptible to functional abnormalities in their pulmonary circulation (physiopathological disadvantage),[20] something which few studies have investigated. Studies with animal models show that BMPR2 gene mutation results in an impaired pulmonary vascular remodelling response when faced with an external stimulus such as prolonged hypoxia.[21] A significant increase in PAP was also observed during physical activity in asymptomatic carriers of the mutation, a change which was not evidenced in non-mutation carriers from the same family.[11] Sztrymf et al[22] analysed the influence of the BMPR2 gene mutation in the clinical course and prognosis of 223 patients diagnosed with familial PAH or sporadic IPAH, comparing mutation carriers (n=68) with non-carriers (n=155). Mutation carriers had a more severe form of the disease, with an earlier onset and their haemodynamic responses were more affected at the time of diagnosis. Furthermore, they were less likely to respond to acute vasodilator testing and were more prone to requiring intravenous prostanoid treatment or lung transplants.[22]

At present, no biomarker or measure of respiratory function exists which enables the early detection of alterations to the blood vessels in the lungs in BMPR2 gene mutation carriers. It has been suggested that reduced end-tidal partial $CO_2$ pressure during exercise could be used for early detection of this change, as it reveals relative hypoperfusion compared to ventilation.[23] The results of our study are consistent with this concept, as significant differences were observed with regard to $K_{CO}$ and not $DL_{CO}$, despite remaining within the

reference limits. More studies involving a greater number of BMPR2 gene mutation carriers are necessary in order to reach a better understanding of the significance of this finding.

In summary, this study shows a low prevalence of BMPR2 gene mutations in the patients with FPAH from our area who were studied. The prevalence of mutations is also low in the patients with sporadic IPAH, but this is in agreement with what has been reported in other geographical areas. Furthermore, our study reveals that a relationship exists between the $K_{CO}$ value and the presence of BMPR2 gene mutations in asymptomatic carriers, suggesting possible changes in the pulmonary vascular bed of these individuals. Studies with a wider sample of patients would make it possible to assess the complimentary role of this measure during screening and follow-up of cases of familial PAH.

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## Conflict of interest

The authors affirm that they have no conflicts of interest.

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