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## Genetic variants of the BMPR2 gene and their contribution to the development of pulmonary arterial hypertension.

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### Abstract

Pulmonary arterial hypertension (PAH) is a devastating disease characterized by a progressive increase in pressure in the pulmonary arteries. This leads to vascular remodeling and, eventually, right heart failure. Variants in the BMPR2 gene, which encodes the bone morphogenetic protein receptor type 2, are the most common genetic cause of hereditary and idiopathic PAH. These variants disrupt the transforming growth factor-beta (TGF- $\beta$ ) signaling pathway, triggering abnormal proliferation of pulmonary artery smooth muscle cells and apoptosis of endothelial cells. This results in complex vascular remodeling, characterized by thickening of the vascular walls, formation of plexiform lesions, and in situ thrombosis. Endothelial dysfunction also contributes to an imbalance between vasoconstrictors and vasodilators, exacerbating pulmonary hypertension. While current therapies aim to restore this balance, they have a limited impact on the underlying vascular remodeling.

Emerging strategies seek to restore the functionality of BMPR2 variants or enhance their signaling through agonists and read-through molecules. Additionally, a higher penetrance of the disease has been observed in women carrying BMPR2 variants, suggesting an interaction with sex hormone metabolism.

The research aims to understand the role of BMPR2 gene variants in the development of PAH and to explore emerging strategies to restore the functionality of these variants or enhance their signaling.

**Keywords:** BMPR2 gene; Genetic variants; Pulmonary arterial hypertension; Pulmonary vascular remodeling.

### 1. Introduction

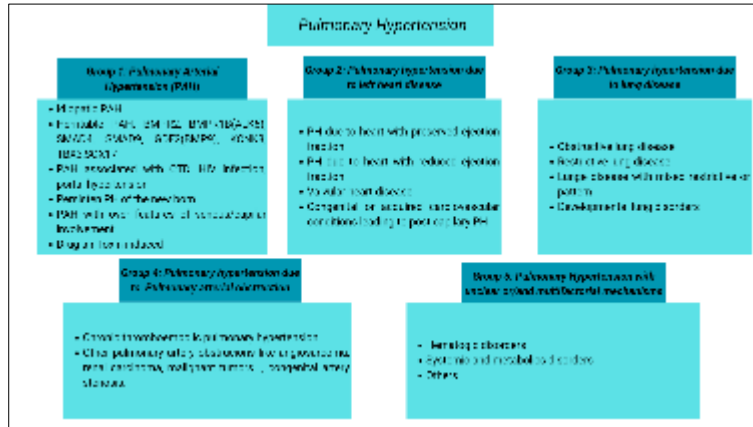
PAH is characterized by significant changes in the pulmonary blood vessels and a progressive increase in pressure within these vessels, leading to hypertrophy and remodeling of the right ventricle of the heart. Without treatment, it can result in right ventricular failure and death. Hemodynamically, it is defined as a mean pulmonary arterial pressure greater than 20 mm Hg at rest, measured by right heart catheterization [1,2].

PAH is classified into two main types: precapillary pulmonary hypertension, characterized by a significant increase in pulmonary vascular resistance, and isolated postcapillary pulmonary hypertension, where increased pulmonary arterial pressure is due to elevated filling pressures on the left side of the heart. Additionally, PAH is categorized based on its underlying mechanism of production: group 1 includes PAH, group 2 is related to left heart disease, group 3 involves chronic respiratory diseases and hypoxia, group 4 is due to chronic thromboembolic pulmonary vascular

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obstruction, and group 5 encompasses cases with uncertain or multifactorial mechanisms. All types involve the loss or abnormal remodeling of the pulmonary vascular bed.

The underlying molecular pathogenesis of PAH is complex and multifactorial, involving various aspects such as inflammation, metabolic alterations, genetic and epigenetic abnormalities, the influence of sex and hormones, and right ventricular abnormalities [3].



**Figure 1** Group classification according to the mechanism of PH production based on Bousseau et.al and Simonneau et. al [3,4]

A meta-analysis including 1,550 patients with idiopathic, hereditary, and anorexigen-associated PAH from 8 cohorts in 6 countries revealed that the presence of a BMPR2 gene variation is associated with an earlier and more severe presentation of the disease, as well as a higher risk of death or need for lung transplantation. Overall, 29% of patients carried a BMPR2 variation. These patients were diagnosed at an average age of 35, compared to 42 years in patients without the variation. Additionally, at the time of diagnosis, variation carriers exhibited significantly more compromised hemodynamic parameters, including higher mean pulmonary arterial pressure, greater pulmonary vascular resistance, and lower cardiac index. Notably, only 3% of BMPR2 variation carriers responded to acute vasodilator testing, compared to 16% of non-carriers. After adjusting for age and sex, the presence of a BMPR2 variation conferred a 42% higher risk of death or lung transplantation and a 27% higher risk of all-cause mortality. This increased risk was even more pronounced in younger patients at the time of diagnosis. Collectively, these findings underscore the adverse clinical impact of BMPR2 variants on the presentation and progression of PAH. [2]

The pathogenesis of pulmonary arterial hypertension involves the interaction among various types of cells in the lung, such as vascular, immune, and circulating cells. Endothelial cells, smooth muscle cells, and fibroblasts of the pulmonary artery are crucial in this process. Endothelial dysfunction, caused by factors like shear stress and injuries, leads to a reduction in the production of vasodilators and an increase in pro-contractile mediators. Moreover, there is observed stimulation of cell proliferation and remodeling of the extracellular matrix due to the increased production of growth factors and pro-inflammatory cytokines. [3]

Abnormalities in the signaling pathways of transforming growth factor  $\beta$  and bone morphogenetic protein receptor 2 are crucial in the development of pulmonary arterial hypertension. BMPR2 gene variants cause hereditary PAH by promoting abnormal proliferation of endothelial and smooth muscle cells in the pulmonary artery. Additionally, heightened activity in the TGF- $\beta$  pathway exacerbates cellular dysfunction in PAH. Although there are other relevant molecular abnormalities, they are discussed in other studies. [3]

### 1.1. Pulmonary vascular remodeling.

Vascular remodeling arises from abnormal proliferation and survival of vascular smooth muscle cells and myofibroblasts, leading to thickening of the vessel walls. Additionally, altered proliferation and survival of endothelial cells contribute to the formation of complex lesions known as plexiform lesions. [5]

At the center of these processes is the BMPR2 receptor, expressed in pulmonary artery endothelial cells (PAECs), pulmonary artery smooth muscle cells (PASMCs) and adventitial fibroblasts. [6]

Variants in *BMPR2* cause an imbalance in various signaling pathways leading to vascular remodeling. This process mainly involves excessive apoptosis of PAECs, as well as proliferation and hypertrophy of PSMCs. Endothelial cells play a crucial role in regulating normal vascular functions, maintaining a balance between the production of vasoconstrictor and vasodilator mediators, activators and inhibitors, as well as between the growth and migration of vascular smooth muscle cells and pro-inflammatory signaling and anti-inflammatory. [7]

Importantly, PAECs expressing mutant *BMPR2* are more susceptible to apoptosis, which triggers the secretion of large amounts of TGF- $\beta$ 1 and fibroblast growth factor 2 (FGF2), stimulating the proliferation of PSMCs. This vascular remodeling affects all three layers of the arterial wall: the adventitia, the media, and the intima. Activated fibroblasts migrate from the adventitia into the media and intima, where they differentiate into similar smooth muscle cells and generate matrix proteins that are deposited along the arterial walls.[7]

In carriers of BMP variants or other forms of hereditary PAH, this process is presumed to trigger hypertrophy of the arterial walls, followed by the development of neointima and the accumulation of myofibroblasts and extracellular matrix between the endothelium and the internal elastic lamina as well as neovascularization. Furthermore, overexpression of matrix metalloproteinases (MMP-1 and MMP-9) promotes the migration of adventitial fibroblasts, further contributing to the vascular remodeling observed in PAH.[7]

In the vascular remodeling process associated with PAH, the most advanced form known as arteriolar remodeling vasculopathy (ARV) presents plexiform lesions. These lesions consist of glomeruloid-like structures with hyperproliferative endothelial cells (ECs) and smooth muscle cells (SMCs), as well as matrix proteins, which eventually lead to vascular occlusion. In patients with idiopathic PAH (IPAH), somatic frameshift variants resulting in a premature stop codon of transforming growth factor beta receptors beta (*TGF $\beta$ 2*) have been identified in approximately 30% of plexiform lesions. Moreover, unlike normal ECs, 90% of the ECs found within plexiform lesions do not express *TGF $\beta$ 2*. Inflammation is presumed to play an important role in the vascular remodeling process, as evidenced in PAH, particularly in systemic inflammatory conditions like systemic lupus erythematosus, where treatment with immunosuppressive therapy has been shown to improve clinical outcomes. In fact, it is estimated that up to 30-40% of patients with PAH of various etiologies have elevated plasma levels of circulating autoantibodies, proinflammatory cytokines such as interleukin-1 (IL-1) and interleukin-6 (IL-6), as well as chemokines like fractalkine and MCP-1, indicating an inflammatory state. Furthermore, inflammatory cells such as B/T lymphocytes, dendritic cells, mast cells, and macrophages have been found in the plexiform lesions of patients with severe PAH, and the pulmonary vascular endothelium of patients with PAH expressed high levels of chemokines such as RANTES and fractalkine.[7,8]

Aside from inflammation, abnormal potassium channel function, with decreased expression of vasodilators such as nitric oxide (NO) and prostacyclin, and overexpression of vasoconstrictors such as endothelin-1 (ET-1), is thought to contribute to dynamic vasoconstriction and further modulate vascular tone, resulting in vascular remodeling. In fact, the basis for current PAH therapy includes the oral prostacyclin receptor (PI) agonist selexipag and prostaglandin analogues such as iloprost, treprostenil, and epoprostenil, which act on the prostacyclin pathway to promote vasodilation through the production of cyclic adenosine monophosphate (cAMP). Additionally, the soluble guanylate cyclase stimulator riociguat and phosphodiesterase type V inhibitors such as sildenafil, which act on the nitric oxide signaling pathway, are also used to raise cyclic guanosine monophosphate (cGMP) levels, thereby which leads to vasodilation. This, in turn, will modify the action of endothelin-1 receptor antagonists such as bosentan, which act on the endothelin receptor to eventually cause vasoconstriction. Although these therapies in combination have been able to improve life expectancy, they have not contributed to changing the course of the pathogenesis of the disease. [7, 9]

## 1.2. Increased vascular resistance

When small peripheral pulmonary arteries become blocked, it results in a continual increase in pulmonary vascular resistance, elevated pulmonary arterial pressure, and eventually, right heart failure leading to death.

Additionally, endothelial dysfunction disrupts the delicate balance between vasoconstrictors and vasodilators in the pulmonary circulation. Variants that deactivate *BMPR2* are the most common genetic alteration in hereditary forms of PAH, underscoring the fundamental importance of the *BMPR2* pathway in its pathogenesis. Approaches to restore *BMPR2* signaling are currently under investigation, either by increasing receptor expression or downstream signaling targets, as innovative strategies to prevent and improve experimental pulmonary hypertension (PH) and PAH in patients. [10]

variants in the *BMPR2* gene destabilize the balance between vasoconstrictor and vasodilator agents, as well as between endothelium-derived mitogenic and antimitogenic factors.[6]

## 2. Genetics of Pulmonary Arterial Hypertension

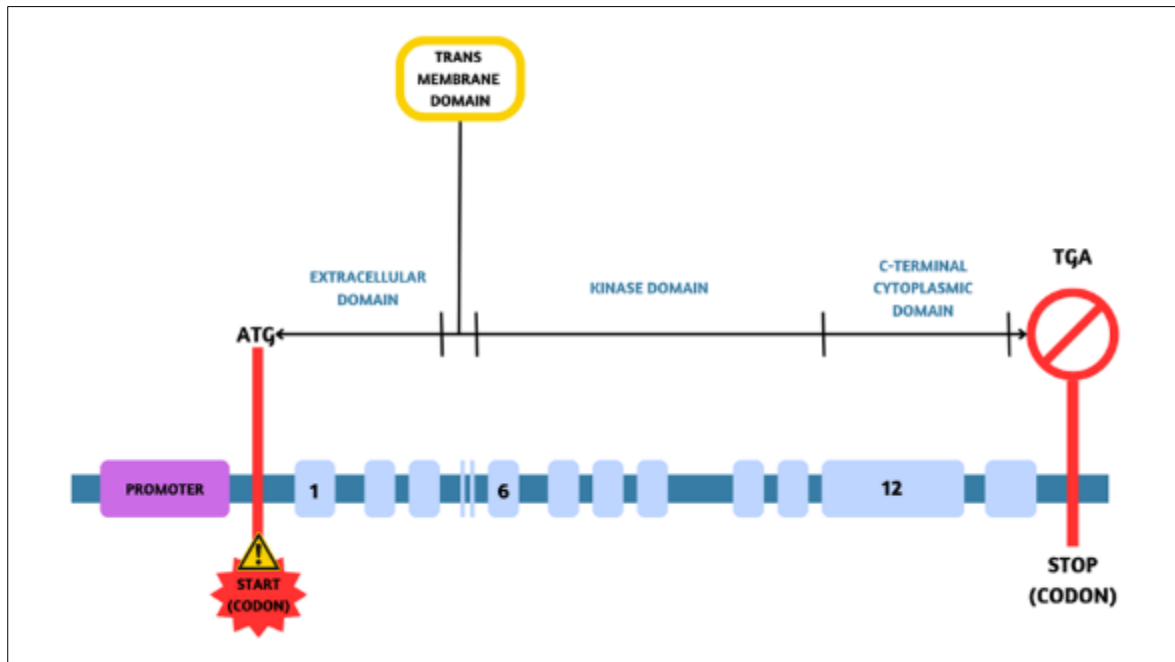
### 2.1. Associated Genetic Factors

The BMPR2 gene is considered the primary genetic determinant of pulmonary arterial hypertension (PAH). However, there are other genes involved in the pathogenesis of PAH, such as ACVRL1, CAV1, KCNK3, ENDG, SMAD9, and BMPR1B, although these are less common (1-3%). Recently, the genes SMAD9 and BMPR18 have also been identified as possible causes of PAH [11]

### 2.2. The BMPR2 gene

In 2000, the BMPR2 gene was identified as the main cause of familial pulmonary arterial hypertension (FPAH). This discovery was achieved by sequencing candidate genes and determining their association with the disease. The anomaly that gives rise to the disease is located in a gene on chromosome 2q33, which encodes the type 2 receptor of bone morphogenetic proteins. BMPR2 gene variants were found to be present in both patients with FPAH and in apparently sporadic cases. In addition, the BMPR2 gene was also found to be associated with idiopathic pulmonary arterial hypertension (IPAH), as the phenotypes of both diseases were similar. Approximately 70% of patients with FPAH have variants in the BMPR2 gene, of which there are no recurrent variants, and nearly 300 different variants have been identified to date. While less frequent than in FPAH, BMPR2 gene variants have also been identified in sporadic cases of IPAH, as well as in PAH associated with the use of anorexigens and PAH related to congenital heart diseases.[8,12]

The BMPR2 gene encodes bone morphogenetic protein receptor 2 (BMPR-II), which belongs to the TGF-B superfamily, and this gene is considered the primary genetic determinant of pulmonary arterial hypertension. It contains 13 exons and encodes the 1038-amino acid BMPR-II protein, which comprises a ligand-binding extracellular domain (exons 2 and 3), a transmembrane domain (exons 4 and 5), a highly conserved catalytic kinase domain (exons 6 to 11), and a cytoplasmic domain (exons 12 and 13). So far, of the more than 300 different variants identified, 30% are located in exon 12. [11]



**Figure 2** The BMPR2 gene, schematically represented in the image, consists of 13 exons. These exons are divided into several functional domains: exons 1 to 3 encode the extracellular ligand binding domain; exons 4 and 5 correspond to the transmembrane domain; exons 6 to 11 encode the kinase domain; exons 12 and 13 are responsible for the C-terminal cytoplasmic domain. The promoter and the start codon (ATG) at the beginning of the gene, as well as the stop codon (TGA) at the end of the gene can also be observed. Taken from Devendran.[7]

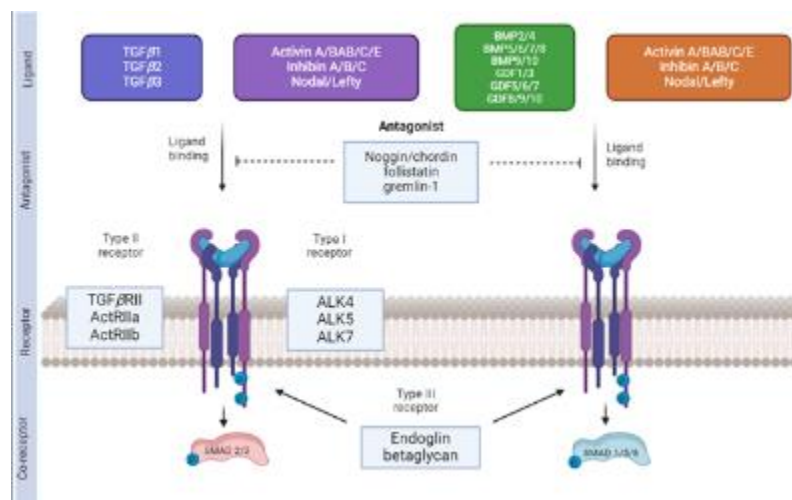
### 2.3. Regulation and signaling pathways

To understand the mechanism by which BMPR2 gene variants lead to pulmonary arterial hypertension, it is necessary to comprehend TGF- $\beta$  signaling. [3]

Activation of this signaling is crucial for PAH formation, regulating various processes such as cell proliferation and angiogenesis. TGF- $\beta$  levels are elevated in patients with PAH, according to clinical and experimental data. In PAH lungs, antiproliferative BMP signaling decreases, whereas elevated TGF- $\beta$  levels in the circulation increase vascular cell proliferation, leading to occlusive remodeling in the pulmonary vasculature. [13]

Ligand binding to the receptor, the type II receptor subunit phosphorylates the type I receptors, initiating two intracellular signaling cascades: the canonical (Smad-dependent) pathway and the non-canonical (Smad-independent) pathway. The small mothers against decapentaplegic (Smad) proteins are transcription factors that transduce the signal to the nucleus. Once phosphorylated, Smad1/5/8 or Smad2/3 form complexes with Smad4 and translocate to the nucleus. The non-canonical pathways, include the activation of phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt), extracellular signal-regulated kinase (ERK), p38 mitogen-activated protein kinase (MAPK), c-Jun N-terminal kinases (JNK), TGF-activated kinase (TAK1), and protein kinase C (PKC). The regulation of each of these pathways involves inhibitory Smad proteins, protein ligases, protein phosphatases, and microRNAs.[14]

Binding of the BMP ligand to the BMPR-II on the cell membrane triggers a cascade of phosphorylations involving Smad 1, 5, and 8 proteins. These, along with Smad 4, form a complex that translocates to the nucleus and modulates gene expression. Likewise, they participate in cell growth inhibition and apoptosis induction. [11]



**Figure 3** Schematic description of the TGF-beta superfamily. Abbreviations: ActRII (Activin Receptor Type 2); ALK (Activin Receptor-Like Kinase); AMH (Anti-Müllerian Hormone); AMHRII (Anti-Müllerian Hormone Receptor Type II); BMP (Bone Morphogenetic Protein); BMPRII (Bone Morphogenetic Protein Receptor Type II); GDF (Growth Differentiation Factor); IS (Inhibitor Substance); MIS (Müllerian Inhibiting Substance); Smad (Small Mothers Against Decapentaplegic); TGF $\beta$  (Transforming Growth Factor Beta); TGF $\beta$ R1I (Transforming Growth Factor Beta Receptor Type I). Taken from Birger. [14]

## 3. BMPR2 gene variants

### 3.1. Types of variants

Approximately 7% of patients with familial PAH carried a BMPR2 gene variation, with over 140 different variants described in these cases. A comprehensive study conducted in Germany involving 99 patients with IPAH found that 11 of them (12.2%) carried a BMPR2 gene variants, which is consistent with the reported 10% to 25% incidence of BMPR2 variants in cases of IPAH.[12,15]

Most of these variants are autosomal dominant and cause a production defect in the BMPR2 protein due to frameshift mutations, leading to BMPR2 haploinsufficiency as a pathogenic mechanism. BMPR2 assembles with a type of BMP type 1 receptor kinase (ALK 1) to transduce BMP ligand signaling through phosphorylation of SMAD transcription factors 1,

5, and 8. Loss-of-function variants have been associated with vascular pathology in the BMP type I receptor, ALK1 (ACVRL1), and its co-receptor endoglin, which has BMP9 and BMP10 as physiological ligands, with which they are also associated. These factors assemble on endothelial cells specifically, where they form a functional heteromeric signaling complex, indicating that the loss of this signaling is the basis of vascular dysfunction.[16]

To date, over 400 different BMPR2 gene variants associated with PAH have been identified. Of these, 25% are nonsense variants distributed across the gene, affecting the ligand-binding domain, intracellular kinase domain, and cytoplasmic tail regions [16]. However, nonsense variants in the cytoplasmic tail appear to be less severe than other BMPR2 variants, with a later age of onset, lower pulmonary vascular resistance, and more vasoreactivity. [17]

In a cohort study, it was described that people with PAH who had the BMPR2 gene variation were diagnosed at a younger age than non-carriers. Additionally, carriers were more likely to undergo a lung transplant and had a shorter time to death; similarly, carriers died younger than non-carriers. Therefore, carrying the variation makes the affected individuals more vulnerable.[18]

Heterozygosity in a BMPR2 variation is not necessary to cause heritable pulmonary arterial hypertension (HPAH), due to reduced penetrance with variable age and a lack of uniform severity, and possible phenotype modification caused by BMPR2 gene variants. This is because nonsense-mediated decay (NMD) pathway activation is involved, which is a mechanism used by the cell to destroy RNA transcripts that would produce harmful proteins. Due to its behavior, it is said that it can affect the phenotype, generating haploinsufficiency.[19]

### 3.2. Disease progression

The progression of PAH involves vascular remodeling, formation of thrombi within the blood vessels, and varying degrees of inflammation. [5]

Additionally, endothelial dysfunction disrupts the delicate balance between vasoconstrictors and vasodilators in the pulmonary circulation. In PAH, there is an increase in vasoconstrictors such as endothelin-1, angiotensin II, and serotonin, accompanied by a decrease in vasodilators or their signaling pathways, including nitric oxide and prostaglandins. This imbalance exacerbates pulmonary hypertension and serves as a key target for therapeutic intervention. [5]

Another hallmark of PAH is the development of thrombi within the blood vessels. Patients with PAH often exhibit a procoagulant state with evidence of abnormal platelet function, necessitating the frequent use of anticoagulants. [5]

While several new therapies for PAH have emerged, most aim to restore the balance between vasoconstrictor and vasodilator pathways, albeit with varying impacts on vascular remodeling. Despite treatment advances, the clinical course of PAH typically involves progressive deterioration, suggesting ongoing vascular remodeling. [5]

BMPR2 variants show decreased disease penetrance, with approximately 20% to 30% of carriers developing PAH, being particularly more prevalent in females compared to males, as indicated by data from the COMPERA and REVEAL registries. This underscores the complex nature of PAH, indicating the involvement of additional factors, whether environmental or genetic, which may influence disease susceptibility and progression.[20]

In patients with PAH, there is a significant decrease, of around 75%, in BMPR-II protein levels in both lung tissue and endothelial cells. This decrease exceeds what would be expected from haploinsufficiency and affects both patients without variants in BMPR2 and genetically non-predisposed rodent models. This phenomenon suggests that factors associated with the disease, regardless of variational status, suppress BMPR-II expression, supporting the notion that addressing this deficiency could be beneficial even for PAH patients lacking BMPR2 variants. [21]

Altered BMPR-II signaling has been shown to promote accelerated cell proliferation and, simultaneously, may contribute to disease onset by increasing the susceptibility of pulmonary endothelial cells to apoptosis. The loss of BMPR2 also leads to mitochondrial dysfunction and inflammation, suggesting a possible link between BMPR2 variants and mitochondrial dysfunction in PAH. [21]

Emerging therapies for PAH related to BMPR-II include strategies to restore functionality to mutated alleles or enhance BMPR-II signaling through functional receptors produced by the non-mutated allele. These strategies may involve the use of direct-reading compounds to promote the production of functional BMPR-II protein from mutated alleles. Additionally, approaches seeking to enhance BMPR-II-mediated signaling in endothelial cells are being explored, such

as the use of recombinant BMP ligands and small molecule agonists of BMP signaling. Inhibition of BMPR-II degradation has also shown promise, suggesting a potential pathway for disease prevention and signaling enhancement in pulmonary endothelial cells. [21]

### 3.3. BMPR2 and Estrogen Metabolism

The higher prevalence of PAH in females raises intriguing questions about how variants in BMPR2 interact with the metabolism of sex hormones. It is worth noting that estrogen plays a fundamental role in cardiovascular function by influencing epigenetic mechanisms. These mechanisms involve the regulation of miRNA expression, with notable gender disparities observed in the expression of miRNA and target genes in various conditions and diseases, such as metabolic disorders, neurodegenerative diseases, autoimmune disorders, and cancer. Compelling research indicates that the estrogen metabolite 16 $\alpha$ -hydroxyestrone (16 $\alpha$ OHE) exacerbates BMPR2-related PAH and contributes to insulin resistance by upregulating the miR-29 cluster. [20]

## 4. Conclusions

Variants in the BMPR2 gene represent the most common genetic cause of hereditary and IPAH. These variants the TGF- $\beta$  signaling pathway, leading to abnormal proliferation of pulmonary artery smooth muscle cells and increased susceptibility to apoptosis in endothelial cells. The consequent vascular remodeling, characterized by thickening of arterial walls, formation of plexiform lesions, and in situ thrombosis, plays a central role in the pathogenesis of PAH.

While current PAH therapies primarily aim to restore the imbalance between vasoconstrictors and vasodilators, they have a limited impact on the underlying vascular remodeling driven by BMPR2 deficiency. Therefore, emerging therapeutic strategies seek to restore BMPR2 functionality or enhance its signaling through approaches such as the use of read-through molecules, recombinant BMP ligands, and small molecule agonists. Additionally, the observed higher disease penetrance in female BMPR2 variation carriers suggests an important interaction with sex hormone metabolism that warrants further investigation.

Despite recent advances, PAH remains a devastating disease with significant morbidity and mortality. Continued research into the molecular mechanisms underlying BMPR2-related PAH, particularly the complex interplay between genetic and environmental factors, is crucial for the development of more effective therapeutic interventions that can target the root causes of the disease process. Ultimately, a deeper understanding of BMPR2 biology holds promise for improving clinical outcomes and quality of life for patients affected by this debilitating condition.

## Compliance with ethical standards

### *Disclosure of conflict of interest*

No conflict of interest to be disclosed.

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