JOURNAL OF MULTIDISCIPLINARY SCIENCES AND INNOVATIONS
VOLUME 5, ISSUE 06
MONTHLY JOURNALS
ISSN NUMBER: 2751-4390
IMPACT FACTOR: 9,08

GENETIC FACTORS IN THE DEVELOPMENT OF PULMONARY SYNDROME (COR PULMONALE)

G.M. Kutlikova
Kh.R. Rustamovna
Andijan Branch of Kokand University.
Faculty of Medicine.

Abstract. This study evaluates the profound role of genetic susceptibility in the pathogenesis and progression of pulmonary heart disease, clinically identified as cor pulmonale. Traditional paradigms have heavily emphasized environmental and acquired factors, yet contemporary molecular evidence demonstrates a strong genetic basis underlying individual variations in disease severity. This article provides a comprehensive analysis of genetic predispositions in conditions associated with chronic obstructive pulmonary disease and pulmonary arterial hypertension. Particular emphasis is placed on the regulatory functions of SERPINA1, the angiotensin-converting enzyme gene, interleukin-6, and the serotonin transporter gene. Furthermore, the transforming growth factor-beta and bone morphogenetic protein signaling pathways are extensively reviewed, with a focus on the BMPR2 gene. Through a synthesis of recent clinical and molecular genetic data, the critical importance of gene-environment interactions in the complex pathogenesis of cor pulmonale is delineated.

Keywords: Pulmonary heart disease, cor pulmonale, genetic factors, pulmonary hypertension, chronic obstructive pulmonary disease, BMPR2, genetic predisposition

INTRODUCTION

Pulmonary heart disease, widely recognized in clinical practice as cor pulmonale, represents a severe pathophysiological state characterized by the enlargement and eventual failure of the right ventricle [1]. This structural alteration of the myocardium occurs secondary to underlying disorders affecting the respiratory system or the pulmonary vasculature. The foundational hemodynamic anomaly in cor pulmonale is pulmonary hypertension, a condition driven by chronic elevation of pressure within the pulmonary arterial circuit and subsequent remodeling of the pulmonary vascular bed [1], [2].

Historically, the etiology of cor pulmonale was largely attributed to environmental exposures and behavioral risk factors. Extensive smoking history, chronic exposure to occupational irritants, and prolonged residence at high altitudes causing chronic alveolar hypoxia were considered the primary catalysts for pulmonary vascular remodeling [9]. However, clinical observations over the decades have highlighted a significant variance in patient outcomes when exposed to identical environmental stressors. Many individuals with severe chronic obstructive pulmonary disease or heavy smoking histories never develop significant pulmonary hypertension, whereas others develop rapid and fatal right ventricular failure [2].

This variance strongly suggests that environmental factors alone are insufficient to fully explain the disease's pathogenesis. The contemporary scientific consensus recognizes cor pulmonale as a highly complex, multifactorial syndrome where inherent

genetic susceptibility plays a pivotal role. Polymorphisms in specific genes govern how aggressively the pulmonary vasculature reacts to hypoxic stress, how inflammatory cascades are initiated and sustained, and how structural integrity is maintained within the lung parenchyma [3], [4]. The objective of this study is to thoroughly analyze the genetic factors contributing to pulmonary heart disease, specifically exploring genes related to pulmonary hypertension and chronic obstructive pulmonary disease, and to evaluate the critical gene-environment interactions that trigger clinical manifestation.

LITERATURE REVIEW

The investigation into the genetic basis of cor pulmonale necessitates an exploration of both structural lung disease genetics and the genetics of primary pulmonary vascular disorders. Previous research provides substantial insight into how variations in specific loci dictate pulmonary vascular tone, cellular proliferation, and extracellular matrix degradation.

The role of the SERPINA1 gene is one of the most comprehensively documented genetic factors in respiratory medicine. Mutations in this gene cause alpha-1 antitrypsin deficiency, a classical Mendelian disorder. Seminal reviews on chronic obstructive pulmonary disease genetics by Lomas and Silverman [6] and more recent exhaustive genomic studies by Cho et al. [7] emphasize that this deficiency leads to uninhibited neutrophil elastase activity. This enzymatic imbalance causes rapid, premature destruction of the alveolar walls, presenting as panacinar emphysema. Sotcan et al. established that the consequent massive loss of the pulmonary capillary bed directly elevates vascular resistance, inevitably leading to right ventricular overload and cor pulmonale, particularly when exacerbated by tobacco smoke [10]. Additionally, modern genome-wide association studies have identified polygenic variants such as MMP12, HHIP, and CHRNA3/5 that modify tissue repair and nicotine dependence, further altering the trajectory of chronic lung disease and secondary heart failure [7].

Beyond structural parenchymal degradation, genetic regulation of the pulmonary vascular response to hypoxia is critical. Shujaat et al. documented that polymorphisms in the serotonin transporter gene, specifically the 5-HTT promoter region, significantly alter vascular remodeling [2]. Serotonin functions not only as a potent vasoconstrictor but also as a mitogen for pulmonary arterial smooth muscle cells. Patients homozygous for the long allele, designated as the LL genotype, exhibit excessive cellular proliferation in the pulmonary microvasculature when exposed to hypoxia, precipitating severe pulmonary hypertension [2].

Equally important is the renin-angiotensin system. Angiotensin-converting enzyme is instrumental in generating angiotensin II, a robust constrictor of smooth muscle. Aldashev et al. conducted pivotal studies on high-altitude pulmonary hypertension among the Kyrgyz population, demonstrating a strong association between the angiotensin-converting enzyme insertion/deletion polymorphism and disease susceptibility [5]. Patients carrying the DD genotype demonstrated a significantly augmented rise in pulmonary arterial pressure during physical exertion compared to those with other genotypes [2], [5].

Inflammatory genetics also occupy a prominent space in current literature. Interleukin-6 is a pleiotropic cytokine heavily implicated in vascular remodeling. Eddahibi et al. revealed that the GG genotype at the −174G/C promoter polymorphism of the interleukin-6 gene is associated with significantly elevated mean pulmonary arterial pressures and a higher overall risk of developing pulmonary hypertension in patients with pre-existing lung disease [3]. This was further corroborated by Chaouat et al., who

highlighted that this genetic variant amplifies the inflammatory response to irritants like smoking, directly modifying vascular compliance [4].

Finally, the genetic landscape of hereditary pulmonary arterial hypertension provides the deepest understanding of isolated right ventricular failure. A profound paradigm shift occurred with the discovery of the central role of the transforming growth factor-beta and bone morphogenetic protein signaling pathways [8], [9]. Major genomic reviews indicate that mutations in the BMPR2 gene are the foremost risk factor for heritable pulmonary arterial hypertension [9], [11], [12]. Reduced signaling through the BMPR2 receptor disrupts normal cellular homeostasis, promoting endothelial apoptosis and driving the aggressive proliferation of underlying smooth muscle cells [11], [13]. Evans et al. published a comprehensive meta-analysis indicating that patients harboring BMPR2 mutations suffer from a significantly worse clinical prognosis and reduced survival rates compared to non-carriers [8]. Subsequent research expanded this genetic family to include ACVRL1, ENG, SMAD9, GDF2, CAV1, and KCNK3, cementing the highly heterogeneous nature of pulmonary vascular genetics [9], [14], [15].

METHODS

To construct this comprehensive analysis of genetic influences on cor pulmonale, a robust narrative review methodology was utilized. The research framework was designed to identify, extract, and synthesize peer-reviewed literature detailing molecular genetics, clinical manifestations, and physiological mechanisms related to pulmonary-cardiac syndrome.

A thorough search strategy was deployed focusing on high-impact academic databases including PubMed, Scopus, and the Web of Science. The primary conceptual targets were separated into two distinct categories to ensure broad coverage. The first category focused on chronic obstructive pulmonary disease and hypoxemic lung conditions, utilizing search terms such as chronic cor pulmonale, alpha-1 antitrypsin deficiency, SERPINA1, 5-HTT polymorphism, and hypoxic pulmonary vasoconstriction. The second category targeted primary pulmonary vascular diseases, utilizing terms including hereditary pulmonary arterial hypertension, BMPR2 mutations, transforming growth factor-beta pathway, and right ventricular hypertrophy.

Articles were screened for relevance based on their direct investigation of human genetic polymorphisms and their physiological link to pulmonary arterial pressure elevation or right ventricular structural changes. Both original genome-wide association studies and large-scale meta-analyses were included to capture both novel discoveries and established clinical consensus. Literature explicitly detailing the molecular mechanisms of the 5-HTT, ACE, and IL6 genes was prioritized due to their definitive links to variable clinical severity in hypoxic environments.

Data extraction involved categorizing the findings by gene, the associated primary pathology, the specific allele or mutation of interest, and the resultant clinical phenotype. Furthermore, specific attention was directed toward capturing data regarding gene-environment interactions, recognizing that genetic susceptibility often requires an external catalyst to manifest clinically. Extracted data were then synthesized into a structured framework dividing parenchymal-driven cor pulmonale from vascular-driven cor pulmonale to facilitate clear discussion.

RESULTS

The synthesis of the identified molecular and clinical data reveals a clear demarcation of how genetics influence the development of cor pulmonale. The results are

categorized into three primary mechanistic pathways driven by specific genetic alterations.

First, genetic variations leading to parenchymal destruction represent a major pathway to right ventricular failure. The data overwhelmingly confirms that SERPINA1 mutations are the most aggressive genetic driver of early-onset chronic obstructive pulmonary disease. The resultant alpha-1 antitrypsin deficiency allows proteolytic enzymes to degrade the extracellular matrix of the alveoli. This destruction inherently obliterates the surrounding capillary networks. The physiological result is a massive reduction in the cross-sectional area of the pulmonary vascular bed, forcing the right ventricle to pump against severely elevated physical resistance. Additional polygenic influences, such as variants in the MMP12 and HHIP loci, were found to modulate the rate of this tissue degradation and the lung's inherent sensitivity to injury [7].

Second, variations in genes controlling vasomotor tone and inflammation critically determine the severity of pulmonary hypertension in patients with existing lung disease. The extracted evidence demonstrates that the pulmonary vascular response to alveolar hypoxia is not uniform. Individuals with the LL genotype of the serotonin transporter gene (5-HTT) experience severe vascular remodeling characterized by smooth muscle hypertrophy due to abnormal cellular proliferation [2]. Similarly, the DD genotype of the angiotensin-converting enzyme gene is definitively linked to exaggerated pulmonary hypertensive responses during exertion, driven by unregulated renin-angiotensin activity [5]. Furthermore, patients carrying the GG genotype for the interleukin-6 promoter polymorphism experience a hyper-inflammatory state, accelerating the fibrous thickening of pulmonary arterial walls and elevating resting pulmonary arterial pressures [3].

Third, mutations within the transforming growth factor-beta signaling pathway constitute the primary genetic basis for hereditary pulmonary arterial hypertension. Data indicates that heterozygous pathogenic variants in the BMPR2 gene account for 70 to 80 percent of familial cases and up to 25 percent of sporadic cases [9], [11]. The primary phenotypic result of a BMPR2 mutation is the loss of growth-inhibitory signals. This leads to the pathological survival and proliferation of pulmonary artery smooth muscle cells alongside the apoptosis of the protective endothelial layer. Consequently, the arterial lumen narrows significantly, causing an extreme elevation in right ventricular afterload independent of any lung tissue damage. Furthermore, patients with BMPR2 mutations present with a more aggressive disease phenotype and higher mortality rates [8]. Extensive sequencing has also implicated genes such as ACVRL1, ENG, SMAD9, and GDF2, indicating that the structural integrity of the pulmonary vascular wall relies on a highly complex and genetically heterogeneous signaling network [9], [14], [15].

DISCUSSION

The integration of these diverse genetic findings underscores that cor pulmonale is not merely the end-stage consequence of long-standing environmental abuse, but a highly orchestrated outcome dictated by a patient's inherent genetic architecture. The most crucial finding emerging from current literature is the concept of penetrance and the absolute necessity of gene-environment interaction, often referred to in molecular biology as the "two-hit hypothesis."

Pathogenic variants in high-risk genes like BMPR2 are notably not fully penetrant. Clinical data reveals that only a fraction of individuals harboring this severe mutation actually progress to develop clinical pulmonary arterial hypertension and subsequent cor pulmonale [11]. This incomplete penetrance strongly suggests that the underlying genetic mutation acts as the primary susceptibility factor, or the first hit. However, an external

environmental trigger, the second hit, is required to initiate the aggressive vascular remodeling cascade. Recognized secondary triggers include hormonal fluctuations, chronic hypoxic exposure, exposure to toxins such as tobacco smoke or anorexigens, and severe viral or bacterial infections [9], [13].

This gene-environment synergy is equally visible in cases of cor pulmonale driven by chronic obstructive pulmonary disease. The presence of the LL genotype in the 5-HTT gene does not spontaneously cause pulmonary hypertension. Instead, it creates a highly sensitized vascular environment that, when exposed to the chronic hypoxia induced by prolonged smoking and emphysema, reacts with extreme and pathological vasoconstriction and remodeling [2]. Likewise, the baseline presence of the ACE DD genotype or the IL6 GG genotype creates a latent hyper-reactive and pro-inflammatory state that drastically magnifies the destructive consequences of environmental pollutants and alveolar hypoxia [2], [3].

Understanding these distinct genetic mechanisms holds profound implications for modern clinical practice. The identification of these genetic markers allows for the stratification of patients based on their intrinsic risk of developing right ventricular failure. A patient presenting with early-stage chronic lung disease who also tests positive for the 5-HTT LL genotype or the IL6 GG genotype should logically be monitored far more aggressively for signs of right ventricular strain. Furthermore, the identification of the central role of the transforming growth factor-beta and bone morphogenetic protein pathways in hereditary cases provides highly specific targets for novel pharmacological interventions. Rather than merely managing symptoms with traditional vasodilators, emerging therapies aimed at restoring BMPR2 signaling or inhibiting aberrant cellular proliferation hold the promise of actually halting or reversing the vascular remodeling process before irreversible cor pulmonale occurs.

Future research must prioritize expanding our understanding of the epigenetic modifications that bridge the gap between environmental exposures and genetic expression. Determining exactly how factors like chronic hypoxia silence or activate these identified gene loci will be the next critical step in preventing pulmonary heart disease.

CONCLUSION

Pulmonary-cardiac syndrome is an intricate, multifactorial condition where inherent genetic predisposition fundamentally governs the pathological processes of parenchymal destruction, adverse pulmonary vascular remodeling, and the consequent fatal increase in right ventricular afterload. Comprehensive molecular evidence confirms the central regulatory roles of SERPINA1 and broad polygenic loci in driving the structural lung damage that precedes cor pulmonale. Furthermore, specific gene polymorphisms including 5-HTT, ACE, and IL6 dictate the aggressiveness of the vascular response to hypoxic and inflammatory stressors. In primary vascular presentations, mutations targeting the BMPR2 gene and the broader transforming growth factor-beta pathway trigger catastrophic proliferative damage to the pulmonary arteries. Ultimately, the development of cor pulmonale represents a critical intersection between an individual's genetic vulnerabilities and specific environmental triggers, highlighting the necessity for advanced genetic screening and targeted molecular therapeutics in cardiovascular and respiratory medicine.

References

1. Shujaat, A., Minkin, R., & Eden, E. (2007). Pulmonary hypertension and chronic cor pulmonale in COPD. International Journal of Chronic Obstructive Pulmonary Disease, 2(3), 273-282.
2. Shujaat, A., Bajwa, A. A., & Cury, J. D. (2012). Pulmonary hypertension secondary to COPD. Pulmonary Medicine, 2012, 203952.
3. [3] Eddahibi, S., Chaouat, A., Tu, L., et al. (2006). Interleukin-6 gene polymorphism confers susceptibility to pulmonary hypertension in chronic obstructive pulmonary disease. Proceedings of the American Thoracic Society, 3(6), 475-476.
4. Chaouat, A., Naeije, R., & Weitzenblum, E. (2008). Pulmonary hypertension in COPD. European Respiratory Journal, 32(5), 1371-1385.
5. Aldashev, A. A., Sarybaev, A. S., Sydykov, A. S., et al. (2002). Characterization of high-altitude pulmonary hypertension in the Kyrgyz - association with angiotensin-converting enzyme genotype. American Journal of Respiratory and Critical Care Medicine, 166(10), 1396-1402.
6. Lomas, D. A., & Silverman, E. K. (2001). The genetics of chronic obstructive pulmonary disease. Respiratory Research, 2(1), 20-26.
7. Cho, M. H., Hobbs, B. D., Silverman, E. K., et al. (2022). Genetics of chronic obstructive pulmonary disease - understanding the pathobiology and heterogeneity of a complex disorder. The Lancet Respiratory Medicine, 10(5), 485-496.
8. Evans, J. D. W., Girerd, B., Montani, D., et al. (2016). BMPR2 mutations and survival in pulmonary arterial hypertension - an individual participant data meta-analysis. The Lancet Respiratory Medicine, 4(2), 129-137.
9. Aldred, M. A., Morrell, N.W., & Guignabert, C. (2022). New mutations and pathogenesis of pulmonary hypertension - progress and puzzles in disease pathogenesis. Circulation Research, 130(9), 1365-1381.
10. Sotcan, M. A., Vladeanu, A. M., & Tudorache, V. (2006). Alpha-1 antitrypsin deficiency and chronic cor pulmonale. Pneumologia, 55(4), 183-186.
11. Newman, J. H., Trembath, R. C., Morse, J. A., et al. (2004). Genetic basis of pulmonary arterial hypertension - current understanding and future directions. Journal of the American College of Cardiology, 43(12), 33S-39S.
12. Humbert, M., & Trembath, R. C. (2002). Genetics of primary pulmonary hypertension. Clinics in Chest Medicine, 23(4), 741-749.
13. Morrell, N. W., Aldred, M. A., Chung, W. K., et al. (2019). Genetics and genomics of pulmonary arterial hypertension. European Respiratory Journal, 53(1), 1801899.
14. Austin, E. D., & Loyd, J. E. (2014). The genetics of pulmonary arterial hypertension. Circulation Research, 115(1), 189-202.
15. Southgate, L., Machado, R. D., Gräf, S., & Morrell, N. W. (2020). Molecular genetic framework underlying pulmonary arterial hypertension. Nature Reviews Cardiology, 17(2), 85-95.
16. Garcia-Rivas, G., Jerjes-Sánchez, C., Rodriguez, D., et al. (2017). A systematic review of genetic mutations in pulmonary arterial hypertension. BMC Medical Genetics, 18(1), 82.