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A Systematic Literature Review of TBX4 and SOX17 genes in Congenital Heart Disease with Pulmonary Arterial Hypertension Phenotype

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ABSTRACT

Pulmonary arterial hypertension (PAH) is a chronic and progressive vascular disorder manifested through increased pressure within the pulmonary arteries. It is widely associated with congenital heart disease (CHD) in pediatric patients, with cases related to CHD accounting for nearly 28 percent of all PAH occurrences. This condition severely affects the overall well-being and daily functioning of those diagnosed. Although the exact mechanism is not fully understood, various studies suggest the involvement of cellular and molecular factors, including genetic alterations. This study aimed to understand the association between genetic variants in SOX17 and TBX4 with the incidence of PAH-CHD. The methods used included a systematic literature review based on the PICO framework, from major academic databases namely PubMed, Google Scholar, Sinta, and Scimago. Articles were screened using the PRISMA method and managed through the Mendeley application. The results indicate that variants in the SOX17 and TBX4 genes are correlated to hereditary forms of PAH and may be associated with cardiac and thoracic vascular malformations. Early identification of these genes is crucial for more accurate diagnosis, risk prediction, and management of PAH-CHD.

KEYWORDS: Pulmonary arterial hypertension, TBX4, SOX17, Congenital Heart Disease

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INTRODUCTION

Pulmonary arterial hypertension (PAH) is a pathological disorder manifested by abnormally rising pressure in the pulmonary arterial system (1). This disorder contributes to a notably high mortality rate among both pediatric and adult populations, particularly when linked to congenital cardiac anomalies (1). PAH represents an uncommon vascular pathology, with a morbidity rate estimated at approximately 0.0001%-0.0002% (2)

Congenital heart disease (CHD), defined as a defect in the structural formation of the cardiovascular system which evident from birth, constitutes the predominant etiological factor of PAH (3). Epidemiological data indicate that the burden of PAH accompanied by CHD (PAH-CHD) reaches approximately 28% (4). Such structural abnormalities impose an increased hemodynamic burden, augment pulmonary blood flow, and elevate pulmonary arterial pressure, consequently fostering the onset of PAH. This progressive condition perpetuates circulatory overload and escalates myocardial strain, ultimately diminishing overall quality of life (5)

The mechanism of this condition is unclear, but some sources suggest the involvement of cellular and molecular factors that lead to pulmonary vascular remodeling (6). The predominant etiological factor underlying familial or hereditary pulmonary arterial hypertension (PAH) is a pathogenic alteration within the BMPR2 gene, initially marked in the year 2000. Following this discovery, numerous novel deleterious variants have been delineated across a spectrum of additional genetic loci, including TBX4, ATP13A3, GDF2, SOX17, AQP1, ACVRL1, SMAD9, ENG, KCNK3, CAV1, GDF2, and BMP10, thereby broadening the molecular landscape and playing a role in the pathobiology of PAH (7).

This literature review presents an overview of recent investigations into PAH-CHD from a genomic perspective, specifically SOX17 and TBX4, as genes at higher risk according to Adu et al., as well as from a bioinformatics perspective. It is hoped that this will contribute to understanding the mechanisms of PAH-CHD, aiding diagnosis and treatment.

RESEARCH METHOD

Methods and Materials

This research aims to (a) clarify the relationship between the SOX17 gene and congenital heart disease in the context of PAH, and (b) investigate the link between the TBX4 gene and congenital heart disease among individuals with PAH. Data acquisition follows the Population, Intervention, Comparison, and Outcomes (PICO) framework (8). The software Publish or Perish version 8 is employed to retrieve pertinent scholarly articles from databases including PubMed, Google Scholar, Sinta, and Scimago. The primary search keywords comprise “pulmonary arterial hypertension”, “congenital heart disease”, and “genomics”. Subsequently,

the gathered literature is systematically evaluated in light of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) model and predefined inclusion criteria. Subsequently, all extracted data are curated, organized, and administered through the Mendeley reference management platform to ensure methodological consistency and accuracy in documentation.

The implementation of the PICO framework in the article analysis is guided by formulating research questions based on its core components. Emphasis is first placed on defining the Population (P), specifying the research problem and identifying the subjects under investigation. Subsequently, attention is directed toward the Intervention (I) or primary focus of the study, followed by the Comparison (C) parameter used for analytical contrast, and culminating in the Outcome (O), which represents the synthesized research findings and implications.

Research Questions

a. Is there a relationship between the SOX17 gene and the PAH-CHD phenotype ?
b. Is there a relationship between the TBX4 gene and the PAH-CHD phenotype ?

Data collection

Based on the preliminary review, a wide range of relevant articles was identified. Consequently, the researcher established specific methodological criteria to determine article eligibility: (a) a minimum of 50% of the selected studies must employ field-based research methodologies, (b) at least 50% of the included articles must present empirical data, (c) only studies published between 2018 and 2023 will be considered, and (d) all articles must demonstrate clear relevance to the research objectives and contain the designated keywords.

Data Evaluation

At this stage, the collected data will be assessed using a structured set of predetermined questions. Each article will be evaluated and assigned a score according to its responses to these questions, as outlined below:

a. Was the article published in the period 2018-2025 ?
b. Does the article mention the terms " pulmonary arterial hypertension", "childhood congenital heart disease", "genomics"?
c. Does the article explain the purpose of the research regarding the relationship between the two genes and the occurrence of PAH-CHD?
d. Does the article refer to relevant theories or concepts?

Inclusion and Exclusion Criteria

Throughout the article selection phase, well-defined inclusion and exclusion parameters were implemented to uphold the relevance, validity, and methodological rigor of the chosen sources. The inclusion criteria comprised scholarly works centered on pediatric subjects diagnosed with PAH-CHD, along with investigations examining the genetic involvement of the SOX17 and TBX4 loci. Eligible studies were required to employ field-based research methods and include at least 50% empirical data. Additionally, only articles published between 2018 and 2023 that were directly relevant to the research objectives and contained the designated keywords were considered.

In contrast, the exclusion criteria comprised studies involving populations outside the pediatric cohort with PAH-CHD or those not addressing the SOX17 and TBX4 genetic components. The application of these criteria aims to ensure the selection of methodologically sound and contextually relevant articles capable of providing robust support for the research objectives.

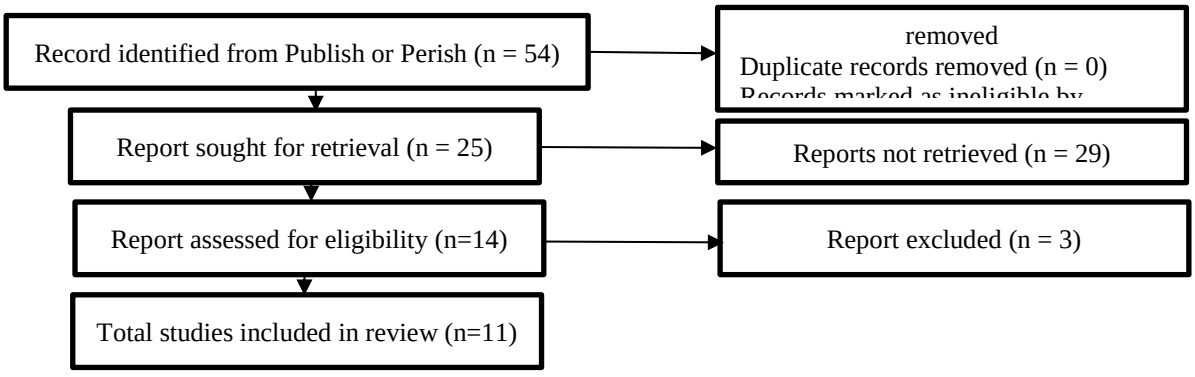

Figure 1: Search Results

RESULTS AND DISCUSSION

Pulmonary arterial hypertension (PAH) is an uncommon pathological disorder distinguished by structural remodeling of the pulmonary arterioles (9), ultimately inducing a progressive and persistent increase in pulmonary arterial pressure (PAP) (1). These vascular changes play a role in pulmonary vascular remodeling, which subsequently causes precapillary pulmonary hypertension

(PPH) and leads to progressive right ventricular dysfunction and failure. The principal genetic determinant of familial or hereditary pulmonary arterial hypertension (PAH) is a pathogenic mutation in the BMPR2 gene. However, numerous additional deleterious variants have been discovered in other genetic loci, such as TBX4, ATP13A3, GDF2, SOX17, AQP1, ACVRL1, SMAD9, ENG, KCNK3, CAV1, GDF2, and BMP10, thereby expanding the recognized molecular spectrum implicated in the etiology of PAH (6).

Relationship of SOX17 gene to PAH-CHD

Recent research has highlighted the pivotal function of SRY-related HMG-box factor 17 (SOX17) as a newly recognized susceptibility gene contributing to the molecular pathogenesis of pulmonary arterial hypertension (PAH), particularly in cases occurring alongside congenital heart disease (CHD). The SOX17 gene is essential for preserving arterial endothelial cell identity and vascular integrity, with its expression predominantly confined to arterial structures. Aberrant regulation or suppression of SOX17 expression can precipitate profound vascular malformations, such as excessive vascular sprouting, disruption of arterial architecture, and the emergence of large arteriovenous anomalies. Multiple studies have substantiated the pathogenic relevance of SOX17 as a genetic determinant of PAH corelated with CHD (PAH-CHD), as concisely presented in Table 1.

Table 1: Key Research Findings on SOX17 and PAH-CHD

Study (Year)	Key Findings Related to SOX17 and PAH-CHD
Zhao, et al (2023)	SOX17 has come to be recognized as a novel genetic determinant involved in the PAH pathogenesis. Pathogenic variants in this gene are frequently linked to CHD, occurrences of hemoptysis, and distinctive radiological manifestations. Furthermore, SOX17, together with several other genes, has been acknowledged as a major contributor to the molecular mechanisms underlying PAH associated with CHD (PAH-CHD) (4).
Zhu et al. (2018)	Whole-exome sequencing performed on 256 individuals diagnosed with PAH-CHD identified rare genetic variants within the SOX17 gene that are distinctively associated with pulmonary arterial hypertension secondary to congenital heart disease. These results furnish robust genetic evidence substantiating the pathogenic role of SOX17 in the development of PAH-CHD (1).
Welch et al. (2021)	SOX17 has been verified as a significant risk gene for PAH-CHD in pediatric patients, underscoring its critical role alongside other key genetic contributors such as Bone Morphogenetic Protein Receptor Type 2 (BMPR2) and TBX4 (10).
Montani et al. (2022)	Elucidated the functional role of SOX17, showing its key involvement in the development and maintenance of arterial endothelial cell specificity and integrity. Suppression of SOX17 expression in endothelial cells induces pronounced vascular hypersprouting, accompanied by compromised arterial integrity and the formation of extensive arteriovenous malformations (6).
Gallego-Zazo et al (2023)	The study unequivocally demonstrated that the SRY-related HMG factor 17 (SOX17) gene harbors rare genetic variants that are specifically and significantly associated with PAH-CHD (11).
Taha F and Southgate L (2022)	In congenital heart disease patients experiencing pulmonary hypertension, the SOX17 gene's involvement has been identified, with its effects mediated through the BMPR2 and TGF-beta signaling pathways (12).

These studies collectively establish SOX17 as an important genetic contributor to PAH-CHD, emphasizing its functional significance in vascular development and integrity, and its potential as a therapeutic target or diagnostic marker.

Relationship of TBX4 gene to PAH-CHD

In addition to SOX17, the T-BOX transcription factor 4 (TBX4) has been identified as another key genetic factor implicated in the pathogenesis of pulmonary arterial hypertension (PAH) among pediatric patients. Monoallelic pathogenic variants in the TBX4 gene represent the second most common hereditary cause of PAH in children. The pathogenic influence of TBX4 is especially evident in instances of severe perinatal cardiopulmonary dysfunction. Moreover, the interrelationship between congenital heart disease (CHD) and PAH holds considerable clinical significance. Elevated pulmonary blood flow, a hallmark feature among many CHD patients, can trigger adverse vascular remodeling within the pulmonary arteries, ultimately progressing to PAH. Epidemiological data suggest that approximately 5–10% of individuals with CHD eventually develop PAH. Table 2 presents a summary of pivotal findings concerning TBX4 and its association with pediatric PAH and CHD.

Table 2: Key Research Findings on TBX4 and its Association with PAH-CHD

Study (Year)	Key Findings Related to TBX4 and PAH-CHD
Prapaa et al. (2022)	Monoallelic pathogenic variants in the TBX4 gene are identified as the second most common hereditary cause of PAH in children. This study also notes that PAH in children can lead to or be associated with CHD (13).
Austin et al. (2022)	Highlights that TBX4 defects are frequently associated with severe perinatal cardiopulmonary disease, indicating its critical role in early lung and heart development (14).
Hernandez et.al (2022)	Discusses the mechanism by which CHD can lead to PAH, explaining that increased pulmonary blood flow in CHD patients can cause unfavorable vascular remodeling. Estimates that 5–10% of patients with CHD will develop PAH, underscoring the prevalence of this serious complication (15).
Zhao et al.	TBX4 has been identified as a novel risk gene implicated in the development of PAH. Cases of PAH

(2025)	resulting from pathogenic TBX4 variants are often linked to congenital heart disease (CHD), hemoptysis, and distinct radiological abnormalities (4).
Yoshida et al (2022)	TBX4 gene (T-box 4 transcription factor) have been consistently linked to severe outcomes, specifically manifesting as severe perinatal cardiopulmonary disease. This strong association powerfully underscores the critical and indispensable role of TBX4 in the intricate processes of early lung and heart development (16).

These findings collectively emphasize the genetic predisposition linked to TBX4 in pediatric PAH, as well as the mechanistic connection between increased pulmonary blood flow in CHD and the subsequent development of PAH

CONCLUSION

The present investigation was designed to assess and elucidate the complex relationship between two key genetic factors, SOX17 (SRY-related HMG factor 17) and TBX4 (T-box 4 transcription factor), and their role in the development of pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD) in children. Drawing upon the robust findings of this research and corroborating evidence from prior literature, it is evident that pathogenic variants within both SOX17 and TBX4 are strongly implicated in a distinct hereditary subtype of PAH. This genetically mediated form of PAH seldom presents in isolation; rather, it is frequently accompanied by an array of structural cardiac and thoracic vascular malformations. Collectively, these findings underscore the critical developmental roles of SOX17 and TBX4 in orchestrating the formation and maturation of the pulmonary vasculature and cardiac structures.

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