BIOLOGY, MEDICINE, & NATURAL PRODUCT CHEMISTRY ISSN 2089-6514 (paper)
Volume 14, Number 2, October 2025 | Pages: 717-723 | DOI: 10.14421/biomedich.2025.142.717-723 ISSN 2540-9328 (online)

Investigating Genetic Vulnerability to Environmental Exposures and Associated Lung Diseases: A Bioinformatics Study

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Manuscript received: 04 June, 2025. Revision accepted: 18 September, 2025. Published: 01 October, 2025.

Abstract

Lung diseases induced by environmental exposures such as air pollution, cigarette smoke, and industrial particles remain a significant global health concern, contributing to high morbidity and mortality rates. Genetic variations are known to influence individual responses to environmental exposures, but the molecular mechanisms underlying these interactions are not well understood. This study aims to identify genetic variants, specifically Single Nucleotide Polymorphisms (SNPs), that may increase the risk of lung diseases using a bioinformatics approach. The analysis was conducted by integrating various public genetic databases, including PheWAS, GWAS Catalog, HaploReg v4.2, GTEx Portal, and Ensembl Genome Browser. SNPs were filtered based on p-value < 0.05 and odds ratio (OR) > 1. Missense mutations in selected SNPs were further analyzed for gene expression in lung tissue and distribution across populations. From an initial 151 SNPs, 86 met the statistical criteria, and six were identified as missense variants. Two genes, *TNIP1* and *PSMB8*, showed significantly high expression in lung tissue. SNP rs2071543 in *PSMB8* exhibited a strong correlation with increased gene expression and demonstrated notable allele frequency variation across populations. These findings suggest that genetic variations, particularly in *PSMB8*, may contribute to individual susceptibility to lung diseases induced by environmental exposures. This study highlights the importance of multidatabase analysis in identifying genetic biomarkers and provides a foundation for the development of precision therapies for multifactorial lung diseases.

Keywords: Bioinformatics study; environmental exposures; lung disease; PSMB8; rs2071543.

INTRODUCTION

Lung diseases remain one of the leading causes of morbidity and mortality worldwide. Conditions such as Chronic Obstructive Pulmonary Disease (COPD), Idiopathic Pulmonary Fibrosis (IPF), asthma, and lung cancer are showing increasing prevalence, particularly among populations exposed to harmful environmental factors (Victoni et al., 2021). The complex pathogenesis of these diseases reflects the involvement of multiple biological mechanisms, including oxidative stress, chronic inflammation, and innate genetic factors that may influence an individual's response to external exposures (Victoni et al., 2021). One of the key mechanisms contributing to lung tissue damage is oxidative stress, which results from an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defense systems. ROS can trigger inflammation, apoptosis, and tissue remodeling, ultimately leading to organ dysfunction over time (Victoni et al., 2021). This condition is further exacerbated by the limited effectiveness of conventional therapies for certain chronic lung diseases, such as COPD and IPF, highlighting the need for more targeted and specific therapeutic approaches (Harber et al., 2016).

Environmental and occupational factors have been identified as major contributors to the etiology of lung diseases. Individuals working in agriculture and livestock industries, for example, are at high risk of exposure to organic dust, which is known to trigger occupational asthma, chronic bronchitis, and even pulmonary fibrosis (Poole et al., 2024). Additionally, air pollution from motor vehicle emissions and industrial activities has been shown to significantly impair lung function, as evidenced by numerous epidemiological studies and meta-analyses (Adam et al., 2015). Synthetic food additives such as sodium nitrite, artificial coloring agents, and sulfites also contribute to impaired lung function, particularly in individuals with airway hyperresponsiveness (Aldabayan, 2025). These exposures can elicit abnormal immune responses, compromise epithelial integrity, and accelerate disease progression, especially in genetically susceptible individuals.

At the cellular and molecular levels, chronic lung diseases such as IPF have been associated with a programmed cell death mechanism known as ferroptosis

a process triggered by iron accumulation and oxidative stress. Unlike apoptosis or necrosis, ferroptosis represents a distinct cell death pathway and has emerged as a potential target in novel therapeutic research (He et al., 2022). Several genes, including CAV1, GDF15, NOS2, and CDKN2A, have been found to be dysregulated in the lung tissues of IPF patients and are all involved in ferroptosis-related regulatory pathways (He et al., 2022). These findings suggest that therapeutic strategies aimed at inhibiting or modulating ferroptosis pathways may offer innovative approaches for managing IPF and other lung diseases. Furthermore, chronic exposure to cigarette smoke plays a significant role in inducing systemic genetic alterations. A well-characterized molecular marker of smoke exposure is the SBS4 mutational signature, which is closely associated with carcinogenesis and lung tissue remodeling (Kim et al., 2022). Remarkably, this signature can be detected even in non-malignant lung tissues, indicating that environmental exposure can induce genetic changes long before clinical symptoms emerge (Kim et al., 2022; Valavanidis et al., 2009). The ROS present in cigarette smoke intensify oxidative stress, accelerate degenerative processes, and cause DNA damage (Valavanidis et al., 2009).

The extensive application of bioinformatics allows researchers to integrate diverse omics data—including transcriptomics, proteomics, and DNA mutation profiles to uncover previously hidden patterns of lung pathology (He et al., 2022). This approach has also been employed to assess immune responses to organic dust exposure and to identify disrupted signaling pathways resulting from food additive exposure (Aldabayan, 2025; Poole et al., 2024). In the era of precision medicine, such molecular understanding is crucial for designing therapies tailored to an individual's genetic profile. Therefore, multidisciplinary collaboration between clinical sciences, environmental toxicology, and bioinformatics is key to comprehensively understanding and managing lung diseases caused by external agents (Harber et al., 2016; He et al., 2022). By elucidating the complex interplay between environmental and genetic factors, we can pave the way for more personalized and effective prevention and treatment strategies.

This study aims to identify and analyze genetic variations (SNPs) that may increase the risk of lung disease due to exposure to external agents using a bioinformatics approach. Through this research, we hope to gain a more comprehensive understanding of the relationship between genetic factors and environmental exposures in the pathogenesis of lung diseases, thereby opening new avenues for the development of precision therapies in the future.

MATERIALS AND METHODS

This study employed a bioinformatics approach to identify genetic variations that may increase the risk of lung disease due to exposure to external agents. The analysis was conducted through the integration of various publicly accessible online genetic databases, including the GWAS Catalog, PheWAS Resources, HaploReg v4.2, GTEx Portal, and the Ensembl Genome Browser. The Genome-Wide Association Studies (GWAS) and Phenome-Wide Association Studies (PheWAS) databases were used as primary resources to identify associations between genetic variants particularly Single Nucleotide Polymorphisms (SNPs) and various disease phenotypes. Since its development by the National Human Genome Research Institute (NHGRI) in 2008, the GWAS Catalog has recorded over 38,000 associations between SNPs and disease phenotypes, including information about the involved polymorphic alleles (Burbelo et al., 2014). Meanwhile, the PheWAS database provides data on the relationships between over 3,000 SNPs and diverse clinical manifestations, making it a valuable tool for exploring genotype-phenotype associations on a broad scale (Pendergrass et al., 2012).

In the initial phase of the analysis, SNPs potentially associated with increased risk of lung disease due to environmental exposure were identified using PheWAS Resources. Selection of SNPs was based on a significance threshold of p-value < 0.05 and an odds ratio (OR) > 1, indicating a statistically meaningful increase in disease risk. SNPs meeting these criteria were then further analyzed to determine the presence of missense mutations, which refer to codon changes resulting in amino acid substitutions (Irham et al., 2023). This analysis was conducted using HaploReg v4.2, which provides in-depth information on structural genetic variations and epigenetic regulatory features. SNPs with identified missense mutations were subsequently evaluated for their expression in lung tissue using data from the GTEx Portal. The Genotype-Tissue Expression (GTEx) project offers comprehensive data on correlations between genetic variants and gene expression levels across various human tissues, including the lungs. This expression analysis, based on Expression Quantitative Trait Locus (eQTL) data, is crucial for identifying variants that are not only structural but also functionally significant in modulating gene activity within the target tissue (Ma'ruf et al., 2023). As a final step, the population distribution of the identified genetic variants was analyzed using the Ensembl Genome Browser (Ensembl genome browser 113). This database provides allele frequency data across diverse global populations, including those from the Americas, Africa, Europe, East Asia, and South Asia (Ma'ruf et al., 2023). This information is valuable for understanding the geographical and ethnic distribution of genetic risk factors and their potential public health implications across different regions.

RESULTS AND DISCUSSION

The initial phase of this study involved the identification of Single Nucleotide Polymorphisms (SNPs) potentially contributing to increased risk of lung disease due to exposure to external agents. This process was carried out using the PheWAS database, which yielded an initial list of 151 SNPs potentially associated with pathological conditions in lung tissue. To refine the scope of analysis and ensure statistical significance, a filtering process was applied based on the criteria of p-value < 0.05 and odds ratio (OR) > 1. This filtering resulted in 86 SNPs that met the criteria and were considered to have significant mutational potential. Details of these SNPs are presented in Table 1.

Table 1. SNPs form Phewas Database.

SNP	p-value	odds-ratio	SNP	p-value	odds-ratio	SNP	p-value	odds-ratio
rs2006996	0.0009142	2.379	rs6704644	0.03987	1.6	rs744910	0.02215	1.455
rs2237878	0.0001304	2.179	rs2237886	0.03513	1.598	rs727957	0.03989	1.455
rs1800961	0.02108	2.075	rs1408282	0.04102	1.581	rs1836127	0.01948	1.45
rs544368	0.0005663	1.97	rs12134279	0.01145	1.577	rs10744304	0.0209	1.449
rs7702057	0.04517	1.917	rs3099844	0.032	1.57	rs11031093	0.02643	1.44
rs737337	0.008276	1.814	rs3131296	0.02662	1.567	rs1927745	0.03301	1.436
rs12534221	0.002788	1.739	rs8321	0.04864	1.56	rs10737562	0.02732	1.431
rs12317459	0.001874	1.731	rs771767	0.007037	1.559	rs1000579	0.02406	1.43
rs2233287	0.01872	1.703	rs8023445	0.04503	1.556	rs2248359	0.02413	1.428
rs11618202	0.02869	1.696	rs17111394	0.01972	1.545	rs2208059	0.02464	1.428
rs13376333	0.000899	1.692	rs649891	0.01776	1.538	rs927675	0.02681	1.425
rs4952590	0.01132	1.692	rs6478108	0.006956	1.534	rs7072268	0.02769	1.423
rs6683071	0.004638	1.677	rs10475598	0.009451	1.53	rs2239633	0.02709	1.422
rs3131379	0.02038	1.665	rs12727642	0.0292	1.523	rs153734	0.04868	1.422
rs10488031	0.04744	1.665	rs1574192	0.008351	1.522	rs204993	0.04138	1.42
rs3117582	0.02062	1.662	rs2068888	0.009902	1.517	rs697739	0.03235	1.417
rs1549519	0.007362	1.647	rs2647044	0.01853	1.516	rs2814828	0.04725	1.415
rs655601	0.02947	1.643	rs6570507	0.01169	1.514	rs164898	0.03647	1.413
rs6062314	0.04578	1.641	rs2358944	0.04436	1.508	rs3923809	0.0354	1.407
rs10506458	0.02917	1.632	rs7871764	0.0161	1.485	rs470490	0.03335	1.402
rs1317209	0.008025	1.627	rs935334	0.03898	1.483	rs5751901	0.03682	1.4
rs8043440	0.0232	1.621	rs3748069	0.01702	1.482	rs8083346	0.04033	1.4
rs9357155	0.02425	1.619	rs378108	0.01635	1.477	rs2275215	0.0479	1.397
rs2681472	0.01006	1.617	rs1464500	0.01959	1.475	rs610604	0.04577	1.387
rs2681492	0.01059	1.612	rs6478109	0.01484	1.474	rs1364063	0.04131	1.379
rs1521882	0.009275	1.61	rs4924935	0.01962	1.462	rs4505848	0.04561	1.374
rs17291045	0.01915	1.607	rs1402837	0.02708	1.462	rs610932	0.04323	1.373
rs12101261	0.003302	1.602	rs12212193	0.01818	1.459	rs4838605	0.04946	1.368
rs10513789	0.007242	1.601	rs8047014	0.01916	1.458			

Subsequently, these 86 SNPs were further analyzed to determine whether they involved missense mutations, which are genetic code alterations resulting in amino acid substitutions in the encoded proteins. This analysis was performed using the HaploReg v4.2 database, which provides in-depth information on functional annotations and the impact of genetic mutations. The analysis identified six missense SNPs, each associated with one of the following gene symbols: HNF4A, *TNIP1*, FAM177B, VWA7, VWA7, and *PSMB8*. These six variants are listed in Table 2 and were selected for further analysis.

Table 2. Variants alleles of the prioritized SNPs.

Risk variants of alleles	Risk variants of alleles in close proximity with r2 >= 0.8	Gencode	Allele location
rs1800961		*HNF4A*	Missense
rs2233287	rs2233290	*TNIP1*	Missense
rs6683071		*FAM177B*	Missense
rs3131379	rs3101017	*VWA7*	Missense
rs3117582	rs3101017	*VWA7*	Missense
rs9357155	rs2071543	*PSMB8*	Missense

To evaluate the biological relevance of these genes, a gene expression analysis across multiple human tissues was conducted using data from the GTEx Portal, with a specific focus on lung tissue as the primary target of

environmental exposure. The results revealed that two genes, *TNIP1* and *PSMB8*, exhibited high expression levels in lung tissue. *TNIP1* showed a high expression with a median Transcripts Per Million (TPM) value of 113.8, ranking fourth among all analyzed tissues Figure 1. Meanwhile, *PSMB8* exhibited even higher expression in the lungs, with a median TPM of 172.5, also ranking as the fourth highest among lung-expressed genes Figure 2. These findings reinforce the hypothesis that both genes play a significant role in the pathological processes within the lungs resulting from environmental exposures.

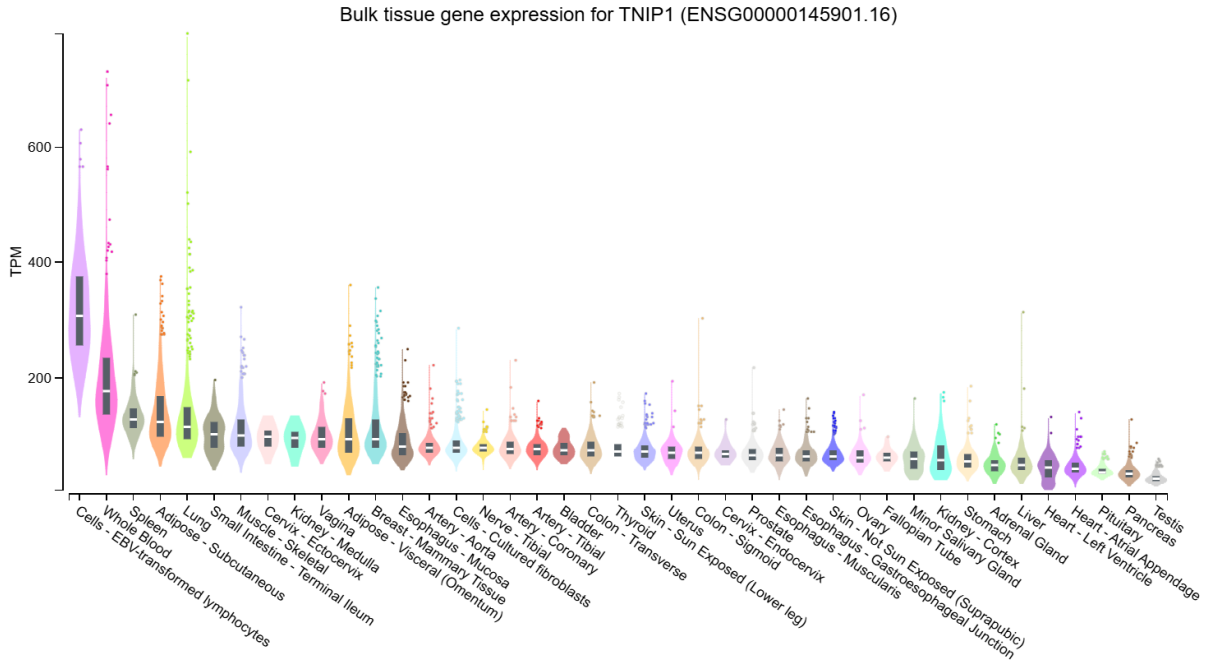

Figure 1. TNIP1 gene expression based on GTEx Portal analysis.

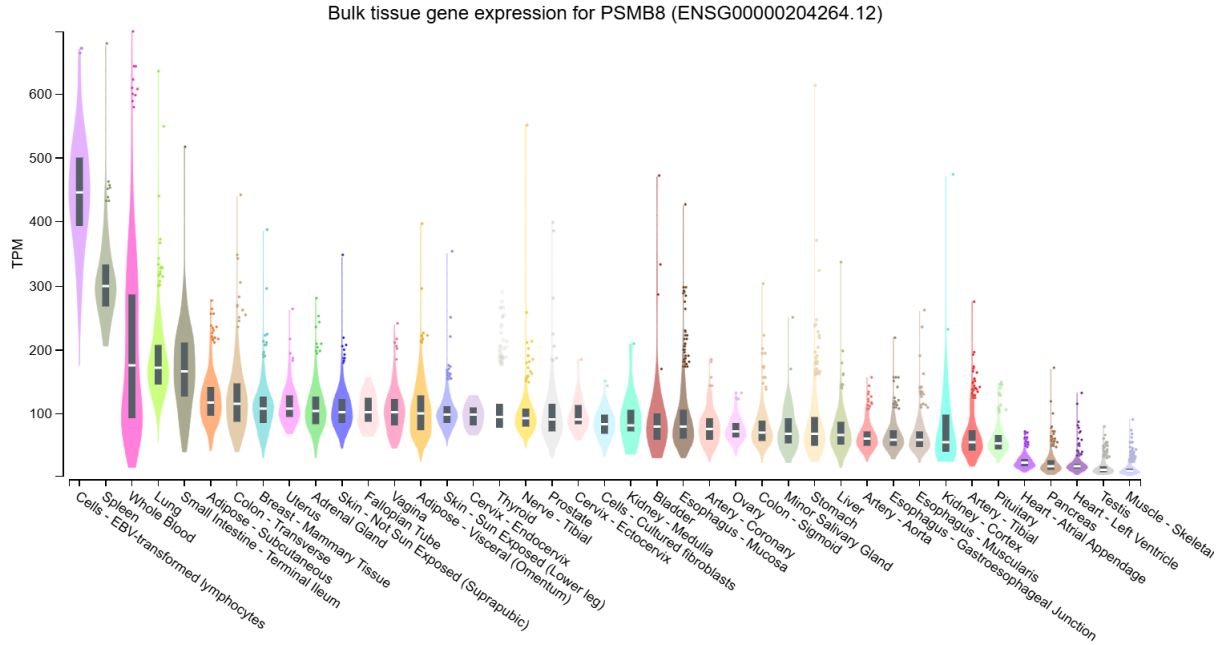

Figure 2. PSMB8 gene expression based on GTEx Portal analysis.

The next analysis focused on identifying relevant expression Quantitative Trait Loci (eQTLs) SNPs that influence gene expression levels in lung tissue. Based on GTEx data, one SNP, rs2071543, was identified as both previously selected and functionally involved in gene regulation. This SNP is associated with the gene *PSMB8*. Information regarding the major and minor alleles of rs2071543 is presented in Table 3. The GG genotype of

rs2071543 showed a stronger correlation with increased gene expression in lung tissue compared to the TT genotype, with a correlation coefficient of 0.81, indicating a significant regulatory effect on gene expression within the target organ. As part of the population-level analysis, the allelic distribution of rs2071543 was examined across different global ethnic groups using data from the Ensembl Genome Browser. The results revealed notable variation in allele frequencies among populations. The G allele showed the highest frequency in African populations, at 0.904 (1,195), followed by South Asian and European populations. In contrast, the lowest frequency of the G allele was observed in American populations, at 0.663 (230). For the T allele, the highest distribution was also found in African populations, while European populations exhibited the lowest frequency of this allele.

Table 3. Allele frequencies for PSMB8.

SNP ID	Position	Gene Symbol	Location	Allele		Allele Frequency			
				Ref	Aff	AFR	AMR	EUR	SAS
rs2071543	Chr6:32843852	*PSMB8*	Missense	G	T	G: 0.904 (1195) T: 0.096 (127)	G: 0.663 (230) T: 0.040 (14)	G: 0.730 (367) T: 0.024 (12)	G: 0.648 (317) T: 0.029 (14)

These findings indicate the presence of significant inter-population genetic variation associated with SNP rs2071543, which may contribute to differences in susceptibility to lung diseases triggered by environmental exposures. This highlights the importance of incorporating genomic and population-based approaches in understanding disease risk and in the development of more personalized and precision-based medical strategies.

Discussion

This study highlights a significant association between specific genetic variations and increased risk of lung diseases triggered by exposure to external agents. Out of 151 SNPs initially identified through the PheWAS database, 86 met the study's criteria, indicating their potential contribution to pulmonary disorders. Further analysis revealed that six of these variants were missense mutations, which cause amino acid substitutions in the resulting proteins. This is particularly important, as missense mutations can alter protein structure and function, potentially disrupting normal biological processes in lung tissue. Among these, the *TNIP1* and *PSMB8* genes demonstrated notably high expression levels in lung tissue, according to data from the GTEx Portal.

The *TNIP1* gene is known to be involved in regulating immune responses and inflammatory processes via the NF-κB pathway, which plays a central role in the pathophysiology of inflammatory lung diseases such as asthma and Chronic Obstructive Pulmonary Disease (Shamilov & Aneskievich, 2018). In contrast, the *PSMB8* gene encodes a subunit of the immunoproteasome, which is essential for antigen processing and the regulation of adaptive immune responses. The high expression of both genes in lung tissue supports the hypothesis that genetic variations in *TNIP1* and *PSMB8* may contribute to immune dysfunction and chronic inflammation in response to toxic exposures such as air pollution, cigarette smoke, and industrial particles.

The *PSMB8*, which encodes the β subunit of the immunoproteasome, plays a critical role in maintaining immune homeostasis, particularly in lung diseases induced by environmental exposures. Previous studies have shown that *PSMB8* polymorphisms are significantly associated with increased risk of hypersensitivity pneumonitis (HP) among bird breeders (Camarena et al., 2010). For instance, Camarena et al. (2010) reported that individuals carrying the *PSMB8* KQ genotype had an odds ratio of 7.25 for developing HP compared to healthy controls ($p = 0.000034$), suggesting that this genetic variant may lead to dysregulation of antigen processing and adaptive immune activation via the MHC class I pathway. Moreover, mutations in *PSMB8* have been implicated in CANDLE syndrome, a rare autoinflammatory disorder characterized by interferon dysregulation and elevated expression of inflammatory mediators such as IP-10, IL-6, and MCP-1. These mediators are also involved in chronic pulmonary diseases like COPD and fibrosis (Liu et al., 2012). The enhanced activation of the interferon pathway in such cases suggests that *PSMB8* mutations may induce damaging immune hyperactivity in lung tissue over time. Additionally, *PSMB8* has been linked to cellular transformation mechanisms following exposure to environmental carcinogens like cigarette smoke. Recent research demonstrated that chronic exposure to NNK, a carcinogenic compound in tobacco, significantly increases the expression of the long non-coding RNA *PSMB8*-AS1 in human bronchial epithelial cells (Ou et al., 2024). This lncRNA regulates the cell cycle by influencing CDK1 expression. Its silencing leads to G2/M phase arrest, reduced cell proliferation, and increased apoptosis, pointing to a potential epigenetic role for *PSMB8* in carcinogenic pathways.

Further studies in non-small cell lung cancer (NSCLC) have shown that immunoproteasome deficiency, including downregulation of *PSMB8*, is

associated with a mesenchymal phenotype and correlates with tumor recurrence and metastasis (Tripathi et al., 2016). On the other hand, high *PSMB8* expression and hypomethylation in lung adenocarcinoma (LUAD) tissues are linked to activation of anti-tumor immune pathways, presence of effector immune cells, and improved response to PD-1/PD-L1-based immunotherapy (Xie et al., 2022). These findings suggest that *PSMB8* through genetic mutation, lncRNA expression, or epigenetic modification holds potential as both a diagnostic biomarker and a precision therapeutic target in lung diseases associated with environmental exposure.

Our analysis also found that gene variants related to exposure-induced lung disease showed highest expression levels in several tissues, including EBV-transformed lymphocytes, blood, spleen, lungs, and adipose tissue. This expression pattern aligns with common clinical manifestations of pulmonary disease, such as lymphadenopathy, pulmonary infections, and systemic inflammation (Eckhardt & Wu, 2021). The discovery of mutagenic and pathogenic genetic variants warrants further laboratory and clinical investigation. Identifying such variants not only improves our understanding of disease susceptibility but also supports the development of diagnostic or prognostic biomarkers and specific therapeutic targets for future research (Adikusuma et al., 2021; Qureshi, 2020; Santri et al., 2022). These findings serve as a preliminary foundation for developing more effective biomarkers and therapeutic strategies for environmentally induced lung disease.

Overall, this study underscores the importance of a multi-database approach in identifying genetic biomarkers relevant to multifactorial diseases such as environmentally triggered lung disorders. The combination of SNP association analysis, mutation characterization, tissue-specific expression profiling, and population distribution provides a more comprehensive picture of the molecular mechanisms underlying disease susceptibility. While this research is limited as a preliminary study based on publicly available genomic and bioinformatics databases, it offers valuable insights that can guide further investigations. Future studies should aim to validate these findings in laboratory and clinical settings, and expand the scope to discover additional pathogenic variants. Thus, this research represents an important first step toward a deeper understanding of the genetic basis of lung disease and the development of more effective therapeutic approaches.

CONCLUSIONS

This study demonstrates the potential role of specific genetic variants, particularly *TNIP1* and *PSMB8*, in increasing susceptibility to lung diseases triggered by environmental exposures. Through an integrative bioinformatics approach, six missense SNPs were identified, with *PSMB8* variant rs2071543 showing significant expression in lung tissue and variation across global populations. The findings suggest that genetic predisposition, combined with environmental risk factors, may contribute to the pathogenesis of chronic lung conditions through immune and inflammatory dysregulation. These results underscore the value of genomic and population-based analyses in uncovering biomarkers for early detection and precision therapy. Although further experimental validation is needed, this study provides a foundational step toward the development of targeted strategies for the prevention and treatment of environmentally induced lung diseases.

Acknowledgements: We would like to express our gratitude to the Faculty of Medicine at Universitas Ahmad Dahlan, Yogyakarta, Indonesia.

Authors' Contributions: All authors contributed equally to the conception of the study, data acquisition, analysis, and interpretation for the manuscript.

Competing Interests: The authors declare no competing of interests.

Funding: This research received no external funding.

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