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Association Between PAI-1 4G/5G Genetic Polymorphism and Uncontrolled Allergic Asthma

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Abstract. Airway remodeling is a major challenge in the management of uncontrolled allergic asthma, despite standard therapy with a combination of inhaled corticosteroids (ICS) and long-acting bronchodilators (LABA). Increased levels of Plasminogen Activator Inhibitor-1 (PAI-1) are thought to play a role in this process, and the 4G/5G polymorphism in the PAI-1 gene is one of the genetic factors that affect it. This study aimed to analyze the association between the 4G/5G PAI-1 genetic polymorphism and uncontrolled allergic asthma. A case-control study was conducted at Wahidin Sudirohusodo General Hospital between January-March 2024 on 40 patients with allergic asthma and 40 non-asthmatic subjects. Diagnosis was made through prik test (+), bronchodilator test (+), and asthma control classification according to GINA criteria. All asthmatic patients received Budesonide-Formoterol therapy for 4 weeks. PAI-1 levels were measured and 4G/5G polymorphism was analyzed by RT-PCR. Results showed that PAI-1 levels were significantly higher in uncontrolled asthma patients and in individuals with the 4G/4G genotype compared to non-4G/4G (2.38 ± 0.770 vs 1.65 ± 0.714; p=0.001). The 4G/4G genotype was more common in uncontrolled asthma (OR: 5.8) and was associated with the risk of severe obstruction (OR: 11.6). Thus, it was concluded that the 4G/4G genotype in the PAI-1 gene is associated with increased PAI-1 levels, risk of uncontrolled allergic asthma, and more severe degree of airway obstruction. The implication of the results shows that genetic testing of PAI-1 has the potential to be a predictive biomarker in personalized asthma therapy strategies. This approach can help clinicians identify high-risk patients and tailor interventions early and effectively to prevent remodeling and reduce long-term morbidity.

Keywords: allergic asthma, 4G/5G PAI-1 polymorphism, genetic polymorphism, plasminogen activator inhibitor-1, asthma control.

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1. Introduction

Millions across the globe suffer from asthma, a persistent respiratory ailment. The 300 million sufferers show that asthma is not a rare disease, but a widespread condition that has a major impact on people's quality of life. Variations in prevalence from 1% to 18% indicate that the number of people with asthma varies by region or country, possibly influenced by environmental factors, genetics, health systems and lifestyle. With around 1,000 deaths per day, asthma is a chronic disease that needs to be taken seriously through prevention, appropriate treatment, and public education [1]. Therefore, serious efforts are needed in controlling asthma disease, one of which is through a predictive approach. Disease prediction has an important role in modern health systems because it helps early identification of individuals at risk before the appearance of clinical symptoms [2]. By recognizing potential risks earlier, preventive measures or medical interventions can be carried out in a more timely manner, thereby reducing the severity of the disease, reducing the number of complications, and saving long-term medical costs [3]

This long-standing respiratory condition is common, characterized by inflammation and narrowing of the airway, triggering symptoms such as wheezing, coughing, and difficulty taking in air. Asthma develops and worsens through a complex interaction of various factors, such as genetic factors, environmental influences, and immune system responses [1,4]. Allergic asthma is most often associated with allergic and eosinophilic airway inflamation. Patients with allergic asthma usually respond to ICS treatment, but some do not [5,6]. This is associated with airway remodeling [7–9].

In asthma, elevated levels of Plasminogen Activator Inhibitor-1 (PAI-1) have been associated with airway damage, particularly in patients with severe uncontrolled asthma. PAI-1 is a major protein in the fibrinolytic system that plays an important role in the process of fibrosis, extracellular matrix accumulation, and tissue remodeling, including the airway. Genetically, PAI-1 expression is affected by the 4G/5G polymorphism in the PAI-1 gene promoter at position -675 on chromosome 7q22. This variation occurs due to the insertion or deletion of one guanine (G) base, resulting in two allelic forms: 4G and 5G, where the 4G allele tends to increase PAI-1 expression more than the 5G allele.

Some studies suggest that the 4G allele may increase susceptibility to asthma or other allergic conditions due to its association with higher PAI-1 levels. However, the current findings are inconsistent as there was no statistically significant difference in the distribution of 4G/5G genotypes between asthmatics and healthy individuals, so it cannot be concluded that 4G/4G, 4G/5G, or 5G/5G genotypes directly increase the risk of asthma. This means that the presence of these genotypes alone is not a definitive indicator of asthma [10]. However, another study mentioned that the -675 4G/5G genetic variation in the PAI-1 gene still has the potential to be one of the causes of asthma [11]. This difference in results may be influenced by variations in gene-environment interactions that are unique to each population [12]. Thus, expanding the understanding of the association of PAI-1 genetic polymorphisms with allergic asthma, especially in the Indonesian population, can fill the existing knowledge gap and contribute to the development of personalized genetic-based therapy approaches.

Individuals who have two copies of the 4G allele (homozygous 4G/4G) in the PAI-1 genetic variant generally produce more PAI-1 protein than people who have at least one 5G allele (either 4G/5G or 5G/5G) [13–15]. Given that high PAI-1 levels result in changes in airway structure, airway over-sensitization (AHR), and allergic inflammation, PAI-1 is thought to be involved in the process of asthma. When activated in mast cells (MCs), the promoter part of PAI-1 containing the 4G allele shows greater transcriptional activity than the 5G variation. PAI-1 is a protein whose production can increase when the body is experiencing inflammation. Inflammation-inducing substances such as IL-1 and TNF-α stimulate cells to produce more PAI-1 as part of the body's immune response. The 4G allele of the PAI-1 gene leads to a significantly larger quantity of PAI-1 RNA being produced when compared to the 5G allele, as evidenced by scientific findings [13]. It is thought that the 4G/4G genotype may influence the degree of control and severity of atopic asthma. This is associated with higher levels of PAI-1, which causes more severe inflammation and structural changes, crete measures are necessary to enhance the monitoring and management of road maintenance moving forward. Previously, road maintenance was insufficient due to several challenges, including ineffective handling methods, a lack of trained

personnel, and limited equipment availability [16].

Thus, the aim of this study was to evaluate “whether there is an association between the 4G/5G genetic polymorphism in the plasminogen activator inhibitor-1 (PAI-1) gene and the incidence of uncontrolled allergic asthma, with a particular focus on the effect of this genetic variation on PAI-1 levels in the body?”. The benefits of these findings are of great clinical importance, as they can help identify asthma patients who are at high risk of developing uncontrolled conditions. By knowing the patient's genotype, clinicians can perform genetic screening and monitoring of PAI-1 levels as a predictive and preventive measure. This also has the potential to support the development of more personalized and targeted treatment strategies for people with allergic asthma, especially those who do not respond optimally to standard therapies.

2. Methods

This study was a case-control study conducted from January to March 2024 at Wahidin Sudirohusodo Hospital and Hasanuddin University Hospital, Makassar, Indonesia. The main objective of this study was to evaluate the association between the 4G/5G genetic polymorphism in the PAI-1 gene and serum PAI-1 levels in subjects with allergic asthma compared to control subjects without asthma. A total of 40 patients with allergic asthma and 40 non-asthmatic non-atopic control subjects were included in this study. Subjects from both groups were selected by purposive sampling technique, with matching based on age and gender. The diagnosis of allergic asthma was based on a positive bronchodilator test result (>12% increase in FEV1 after salbutamol 2 mg inhalation), a positive skin prick test against common inhalant allergens, and an assessment of the level of asthma control according to the Global Initiative for Asthma (GINA) guidelines.

The inclusion criteria for the case group included 18-50 years of age, not currently experiencing asthma exacerbations, not having comorbidities such as diabetes mellitus or active lung infection, not smoking, and having used maintenance therapy of a combination of inhaled corticosteroids and long-acting beta-agonists (ICS+LABA), namely Budesonide-Formoterol (160/4.5 mcg, 2x2/day), routinely for at least four weeks before the examination. Control subjects were healthy individuals with no history of asthma, allergy or atopy, and showed negative results on the bronchodilator test and skin prick test. To reduce potential bias, all examinations were performed by medical personnel who had standardized diagnostic procedures. The case-control design has the potential for selection and information bias, so subject selection and data collection were rigorous and uniform.

Serum plasminogen activator inhibitor-1 (PAI-1) levels were measured in all participants using standard immunologic methods. Analysis of 4G/5G genetic polymorphisms in the PAI-1 gene was performed using real-time polymerase chain reaction (RT-PCR) technique, which is a sensitive method for detecting specific genetic variations in gene promoter sequences. The process begins with DNA extraction from peripheral blood samples using a commercial kit, followed by amplification of target DNA fragments using specific primers for the 4G and 5G alleles. RT-PCR was run in 25 microliter volume reactions using a dedicated thermal machine, and amplification results were analyzed directly through fluorescence curves to identify genotypes. Genotypes were classified into three types: 4G/4G, 4G/5G, and 5G/5G, and further grouped into two analysis categories: 4G/4G (5G non-carrier) and non-4G/4G (5G allele carrier).

Data were analyzed quantitatively using descriptive and inferential statistics. Independent t-test was used to compare the mean PAI-1 levels between uncontrolled and controlled allergic asthma groups, as well as between 4G/4G and non-4G/4G genotypes. Chi-square test was used to analyze the association between PAI-1 genetic variation (4G/5G) with the incidence of allergic asthma, the level of asthma control, and the degree of airway obstruction. The odds ratio (OR) and 95% confidence interval (CI) were calculated to assess the risk, with the significance level set at $p < 0.05$.

This study has obtained ethical approval from the Ethics Committee of the Faculty of Medicine, Hasanuddin University with decision letter number 01186/H.4.8.4.5.31/PP.36-KOMETIK, and all participants signed informed consent before being involved in the study. All procedures were conducted in accordance with the principles of the 1964 Declaration of Helsinki and its revisions to ensure the

protection and ethics of human subjects in biomedical research.

3. Results and Discussion

This study included 40 cases of allergic asthma and 40 non-asthmatic individuals as controls, each consisting of 20 females and 20 males. Among the allergic asthma subjects, based on GINA Scoring, there were 15 uncontrolled asthma cases and 25 well-controlled asthma cases. All the subject with allergic asthma using ICS + LABA as treatment control.

Table 1. Characteristics of subjects

	allergic asthma	non-asthmatic	
Variable	n = 40	n = 40	P. Value
Age (years)	32.1 (7.7)	29 (7.4)	p = 0.081
Man	20	20	
Woman	20	20	

*Independent sample tests

Table 1 shows that the average age did not differ significantly between subjects with and without allergic asthma.

We found a significantly higher PAI-1 level in subjects with uncontrolled allergic asthma than in the controls

Table 2. Average PAI-1 levels based on the degree of allergic asthma control

Variable	Uncontrolled	Well Controlled	P. Value
	Allergic Asthma	Allergic Asthma	p = 0.081
PAI-1	2.45 (0.78)	1.58(0.73)	0.001

*Independent t tests

Then, when compared to non-4G/4G genotypes, 4G/4G genotypes had significantly higher PAI-1 levels.

Table 3. Distribution of mean serum PAI-1 levels, by 4G/4G genotype and non 4G/4G group

Variable	4G/4G	Non 4G/4G	p*
	n=7	n=33	p*
PAI-1	2.45 (0.78)	1.58(0.73)	0.001

*Independent t tests

Table 4. Incidence Pattern of Allergic Asthma Associated with 4G/5G Polymorphism of PAI-1 Gene

Genotype 4G/5G PAI-1 gene	N	**allergic asthma** n = 40	**non-asthmatic** n = 40	p value*	OR	95% CI
4G/4G	12	7 (58.3%)	5 (41.7%)	0.75	1.5	0.42-5.14
Non 4G/4G	68	33 (48.5%)	35 (51.5%)			

From the data presented in Table 4, it can be seen that in the group with the 4G/4G genotype of the PAI-1 gene, the proportion of subjects with allergic asthma was not significantly different compared to those without (58.3% vs 41.7%). Thus, this study concludes that the 4G/5G polymorphism of the PAI-1 gene does not increase the risk of allergic asthma.

Table 5. Distribution of uncontrolled allergic asthma cases based on 4G/5G genetic variation in PAI-1

gene

Genotype 4G/5G PAI-1 gene	n	**Uncontrolled allergic asthma** n = 15	**Well controlled allergic asthma n=25**	p value*	OR	95% CI
4G/4G	7	5 (33.3%)	2(28.6%)	0.05	5.8	0.95-34.7
Non 4G/4G	33	10 (30.3%)	23 (69.7%)			

*Chi Square test

Table 6. Distribution of severe airway obstruction cases based on 4G/5G genetic variation in PAI-1

Genotype 4G/5G PAI-1 gene	n	**FEV1 ≤ 50 n = 40**	**FEV1 > 50 n=40**	p value*	OR	95% CI
4G/4G	7	5 (71.4%)	2(28.6%)	0.03	11.6	1.83-75.08
Non 4G/4G	33	6 (17.6%)	27 (82.4%)			

*Chi Square test

Researchers wanted to find out whether genetic differences in the PAI-1 gene, particularly the 4G/5G variation, affect the severity of asthma. The main focus is on two important aspects, first, how controlled the asthma symptoms are; and second, how much obstruction or blockage occurs in the patient's airway. Therefore, Table 5 contains information on asthma control, while Table 6 shows the association of genotype with the degree of airway obstruction.

Subjects with the 4G/4G genotype of the PAI-1 gene, uncontrolled allergic asthma was more prevalent than controlled asthma. Similarly, in non-4G/4G subjects, the incidence of controlled allergic asthma was higher than that of uncontrolled allergic asthma. When calculating the risk, subjects with the 4G/4G genotype of PAI-1 had a 5.8 times higher risk of developing allergic asthma.

Table 6 shows that subjects with the 4G/4G genotype of the PAI-1 gene in allergic asthma had a higher incidence of FEV1% < 50 compared to FEV1% > 50 (71.4% vs 28.6%). Similarly, in non-4G/4G subjects with allergic asthma, the occurrence of FEV1 > 50% was higher compared to FEV1% < 50% (17.6% vs 82.4%). When calculating the OR, subjects with the 4G/4G genotype of the PAI-1 gene have an 11.6 times higher risk of severe obstruction (FEV1 <50%) compared to non-severe obstruction (CI: 1.83–75.08; p=0.03).

4. Discussion

The genes that influence asthma are divided into groups that affect risk through allergic sensitization, inflammation, and remodeling, as well as the therapeutic response to drugs. This study revealed that the 4G/5G genetic variation in the PAI-1 gene is not directly associated with an increased risk of developing allergic asthma in general. This means that the presence of this polymorphism does not significantly affect whether a person will suffer from allergic asthma or not. However, the results showed that the polymorphism has an important role in determining the severity of the disease, especially in cases of uncontrolled allergic asthma. Uncontrolled allergic asthma is often characterized by chronic inflammation and changes in airway structure, called remodeling.

Based on the results of the study, there was no significant difference in the presence of the 4G/4G genotype of the PAI-1 gene between individuals with allergic asthma and those without the condition. This study also showed that genetic variation in the form of the 4G/5G polymorphism in the PAI-1 gene did not differ significantly between individuals with asthma and healthy individuals. The distribution of the three types of genotypes, namely 4G/4G, 4G/5G, and 5G/5G, was relatively balanced in both groups, implying that the PAI-1 4G/5G polymorphism does not have a strong association with the incidence of allergic asthma in general. In other words, the presence of any of the three genotypes does not directly affect a person's likelihood of having asthma[17].

Comparing individuals with uncontrolled allergic asthma to those with well-controlled asthma, this study found that the former had noticeably higher PAI-1 levels. This is corroborated by other studies

that found that those with moderate to severe asthma had significantly greater blood PAI-1 levels than people with mild asthma [18].

Genetically, certain individuals may have a greater susceptibility to allergic disorders, and one of the contributing factors is variations or polymorphisms in the PAI-1 gene. This gene plays an important role in regulating the fibrinolytic system, which is responsible for dissolving fibrin clots in the body. When PAI-1 is overworked, the fibrinolysis process can be inhibited, which can contribute to chronic inflammatory conditions and airway remodeling. In this study, it was found that individuals with uncontrolled allergic asthma were more likely to carry the 4G/4G genotype of PAI-1 compared to asthmatics whose symptoms were well controlled.

Research shows that individuals with the 4G/4G genotype are at 5.8 times greater risk of developing uncontrolled allergic asthma. At the molecular level, PAI-1 gene expression is controlled through the interaction between the 4G/5G polymorphism site and the transcription factor upstream stimulatory factor-1 (USF-1). Since mast cells are the main producers of PAI-1, the regulation of this gene expression in these cells is very important in understanding the inflammatory mechanisms that occur in asthma. The 4G/5G polymorphism itself is a genetic variation in the form of addition (insertion) or deletion (deletion) of one guanosine nucleotide in the promoter of the PAI-1 gene, precisely at position -675. This small change turns out to have a big impact on the production level of PAI-1. In addition, it was shown that people who carry two 4G alleles (4G/4G genotype) tend to produce higher amounts of PAI-1 in their blood plasma compared to people who carry two 5G alleles (5G/5G genotype) [19–21].

The 4G/5G polymorphism in the PAI-1 gene itself occurs in the promoter part of the gene, an area that regulates when and how much the gene will be expressed. Several previous studies have proven that the presence of the 4G allele tends to increase PAI-1 expression because it does not contain repressor binding sites, thus producing more protein. In contrast, the 5G allele has inhibitory elements that suppress the gene's expression21. PAI-1 primarily functions to inhibit fibrinolysis, leading to fibrin buildup and elevated plasma PAI-1 levels. This disruption in normal fibrin degradation can contribute to thrombosis.

Recent research has revealed that the PAI-1 protein has a broader impact than just inhibiting the dissolution of blood clots (fibrinolytics). When PAI-1 is present in high concentrations, it can decrease the effectiveness of MMPs, enzymes that break down the extracellular matrix, including collagen and elastin. MMPs are essential in the process of tissue regeneration and repair. In addition, PAI-1 also affects the ability of cells to adhere to surrounding tissues (cell adhesion). When cell adhesion is impaired, normal processes such as cell migration and tissue healing may also be inhibited. The combined suppression of MMP activity and disruption of cell adhesion leads to changes in tissue structure and function, known as tissue remodeling [22].

It is thought that the processes of activating blood clotting pathways and inflammation can occur independently. Disruption of the balance between protease enzymes and their inhibitors is an important factor in the process of tissue repair and remodeling. PAI-1 is believed to be associated with fibrosis and ECM buildup after injury and chronic inflammation in the airways of asthmatic patients [23,24].

In this study, it was found that in allergic asthmatics with the 4G/4G genotype of the PAI-1 gene, the incidence of FEV1% <50 (severe obstruction) was much higher than FEV1% >50 (non-severe obstruction), with a ratio of 71.4% versus 28.6%. In addition, allergic asthmatics with the 4G/4G genotype had an 11.6 times greater risk of having severe obstruction in their airways compared to those with non-severe obstruction (CI: 1.83-75.08; p=0.03). Allergic asthma with the genotypic 4G/4G gene PAI-1 was more common with FEV1% < 50 compared than with FEV1% >50% (71.4% vs. 28.6%). Allergic asthma genotypic 4G/4G gene PAI-1 is more common with FEV1% < 50 compared than with FEV1% >50% (71.4% vs. 28.6%). Elevated PAI-1 levels have been linked to decreased lung function. In chronic inflammatory conditions of the respiratory tract associated with asthma, PAI-1 may contribute to the formation of obstruction or narrowing of the airways [25].

Polymorphisms in the PAI-1 gene affect PAI-1 levels in the body, which then play a role in extracellular matrix (ECM) buildup and subepithelial scar tissue formation during airway remodeling.

This causes asthma to become more difficult to control, with more severe airway obstruction, and suboptimal response to standard treatments such as combination inhaled corticosteroids (ICS) and long-acting beta-2 agonists (LABAs). PAI-1 contributes to airway structural changes and obstruction in cases of chronic inflammation due to asthma [26–28]. The limitation of this study is that it did not evaluate PAI- 1 levels before ICS + LABA therapy.

From the results of the study, it can be concluded that certain genetic variants, especially the 4G/4G genotype in the PAI-1 gene, have an important role in worsening the clinical condition of allergic asthma patients. Individuals with this genotype tend to have higher PAI-1 levels, which then results in airway remodeling and connective tissue buildup, as well as increased resistance to standard therapy. The result of this process is more severe airway obstruction and asthma symptoms that are difficult to control, despite optimal treatment. Compared to individuals with genotypes other than 4G/4G (such as 4G/5G or 5G/5G), those with the 4G/4G genotype are more prone to uncontrolled asthma and exhibit higher symptom severity.

5. Conclusion

This study shows that although the 4G/5G genetic variant in the PAI-1 gene does not directly increase an individual's risk of developing allergic asthma, it has a significant influence on disease severity and control. Individuals with the 4G/4G genotype showed higher serum PAI-1 levels, which were strongly correlated with severely impaired lung function (FEV1 < 50%) and uncontrolled asthma conditions. Compared to non-4G/4G individuals, those carrying the 4G/4G genotype had 11.6 times greater risk of severe airway obstruction and 5.8 times higher risk of uncontrolled allergic asthma. These findings indicate that the 4G/4G genotype of the PAI-1 gene may affect the effectiveness of standard therapies, such as the combination of ICS + LABA, through its role in airway inflammation and remodeling. Therefore, monitoring PAI-1 levels and detection of PAI-1 genotypes, particularly the 4G/4G variant, could potentially be used as genetic markers in clinical practice to help identify patients at risk of poor therapy response.

However, this study has some limitations. The relatively small sample size and uneven distribution between genotype groups may affect the statistical power and generalizability of the findings. In addition, this study has not explored other factors that may influence PAI-1 levels and asthma severity, such as environmental exposures, comorbidities or more complex immune responses. PAI-1 measurements were only taken once, so they may not reflect the dynamics of changes in levels during the course of the disease or therapy. For this reason, future studies are recommended to include larger samples and more diverse populations to confirm these findings more robustly. Longitudinal studies are also needed to evaluate changes in PAI-1 levels over time and its relationship with asthma control. In addition, exploration of possible therapeutic interventions targeting the PAI-1 pathway, as well as integration of genetic data with other biomarkers in personalized treatment approaches, are important steps to develop more effective allergic asthma management strategies in the future.

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