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Correlation of the Interferon Gamma Point +874 A/T Gene Polymorphism with the Occurrence of Schizophrenia

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Abstract: Schizophrenia is a mental illness characterized by delusions and hallucinations. Several investigations have revealed that the immune system and genetic factors have a role in the development of schizophrenia. Interferon gamma is one of the genes thought to have a role in the development of schizophrenia, and many studies have reported the involvement of interferon-gamma (IFN-γ) in neuropsychiatry. This study aims to determine the relationship between the Interferon-γ +874 A/T Gene Polymerphism with the incidence of Schizophrenia. A case control study was conducted at the hospital. Ernaldi Bahar Palembang for 3 months (February-April). There were 100 samples that met the inclusion criteria, of which 50 patients were cases and 50 respondents were healthy controls. Analysis of data using computerized data processing applications. The sampling method in this study is the matching sampling method. The results showed that the frequency of the A allele in the case group was 50 and in the control group was 69, while the frequency of the T allele in the case group was 50 and the control group was 31. The analysis of the results showed that the frequency of the T allele was higher in the schizophrenia group than the control group with value (p = 0.006), with an OR value of 2.226. There was a significant relationship between the case group and the control group. Individuals with the T allele have a 2,226 higher risk of developing schizophrenia than individuals with the A allele.

Keywords: Gamma Point +874 A/T; Gene Polymorphism; Interferon; Schizophrenia

Introduction

Mental health is still a significant health problem in the world, including in Indonesia (Subu et al., 2021). According to WHO data, there are around 35 million people affected by depression, 60 million people affected by bipolar disorder, 21 million affected by schizophrenia, and 47.5 million affected by dementia (Sulistiani et al., 2021; Yusuf et al., 2022). Schizophrenia is a serious mental disorder accompanied by disorganization or decline in personality function, causing disability and causing the sufferer to become a burden on the family and society (Digal, 2020; Ismail et al., 2023). Schizophrenia is a type of psychosis that can be accompanied by symptoms of hallucinations and delusions (Gaebel & Salveridou-Hof, 2023; Pietkiewicz et al., 2021). Schizophrenia usually begins in early adulthood, between the ages of 15 and 25 years and men tend to experience schizophrenia than women (Häfner, 2019).

Schizophrenia has a prevalence of 1% of the world's population or an average of 0.85%. The incidence of schizophrenia is 1 per 10,000 people per year. The incidence of schizophrenia can be found spread across various regions. The prevalence of schizophrenia based on gender, race and culture is the same. Women tend to experience milder symptoms, fewer hospitalizations and better social functioning in the community than men (Sommer et al., 2023). The prevalence of schizophrenia sufferers in Indonesia is 0.3 to 1% and usually appears around the age of 15 to 45 years (Setiawati & others, 2020). However, there are also those aged 11 to 12 years

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who already suffer from schizophrenia. If Indonesia's population is around 200 million people, it is estimated that around 2 million people suffer from schizophrenia (Arafa, 2022).

Basic Health Research in 2018 showed that the prevalence of schizophrenia/psychosis in Indonesia was 7% per 1000 households (Rastafary & Tondok, 2021). This shows that out of 1000 households, there are 70 households that have household members (ART) with severe schizophrenia (Farida & PH, 2022). It is known that the profile data from the Palembang City Health Service (2017) shows that the number of visits for mental disorders was around 53,655 people and in 2018 it increased to 56,389 people (Putri et al., 2020). This is reinforced by data from the Palembang City Social Service, there was an increase in outreach to ODGJ from 2017, namely 7285 people and in 2018 it increased to 9597 people and in 2019, it rose again to 10,175 people (Putri et al., 2020).

The results of several studies show that there are several theories regarding the pathogenesis of schizophrenia, one of which is the involvement of the immune system and also genetic factors (Ajami et al., 2014). It is thought that the neural, endocrine, and immune systems influence each other through the activity of cytokines, hormones, and neurotransmitters. Activation of the immune system causes behavioral, neuroendocrine, and neuropathological changes in the central nervous system. These changes occur due to the interaction of cytokines with their receptors on neurons and glial cells in the brain (Ferro et al., 2021).

Genes encoding cytokines related to the central nervous system are thought to influence the incidence of schizophrenia (Dawidowski et al., 2021). Several genes are thought to have a role in the development of schizophrenia, including the genes encoding tumor necrosis factor-alpha (TNF-alpha), interleukin (IL-1), IL-6, and IL-10. Several studies have reported the involvement of interferon-gamma (IFN-γ) in neuropsychiatric disorders (Cordeiro et al., 2022; Srinivas et al., 2016).

IFN-γ is a cytokine that activates the expression of the strongest gene indoleamine 2,3-dioxygenase (Pallotta et al., 2022). Cytokines influence the synthesis of monoamine neurotransmitters by monoaminergic mechanisms through transcription and activation of IDO. An enzyme that causes low Tryptophan levels, resulting in depletion. Serotonin causes a decrease in serotoninergic neurotransmission, triggering mental disorders and depression accompanied by changes in the immune system. The IFN-γ protein is encoded by a single gene located on chromosome 12 (12q15). The A to T transition single nucleotide polymorphism (SNP) at +874 (rs2430561) was associated with increased expression of IFN-γ mRNA and serum IFN-γ cytokines (Anuradha et al., 2008). The expression of the interferon-γ cytokine gene in schizophrenia patients was significantly higher than that of healthy controls (Chen et al., 2021).

So far there are not many results regarding the relationship between the Interferon Gamma +874 A/T gene polymorphism and the incidence of schizophrenia in the population in Indonesia. Therefore, researchers intend to determine the relationship between the Interferon Gamma +874 A/T gene polymorphism and the incidence of schizophrenia in the population of South Sumatra.

Method

Research Area Determination Method

This research is an observational study with a case control approach (case control study). The population of this research is the schizophrenic patient population of South Sumatra at the Ernaldi Bahar Mental Hospital in Palembang and a healthy control group (Family/staff at the Ernaldi Bahar Mental Hospital) in March-April 2021.

The inclusion criteria in this study were patients who were clinically diagnosed with schizophrenia by a psychiatric specialist who was > 20 years old. Meanwhile, the criteria for a healthy control group could be the patient's family or Ernaldi Bahar Hospital staff who do not have a history of mental disorders and are not taking antipsychotic drugs and are > 20 years old. A total of 50 groups of schizophrenic subjects and 50 groups of healthy controls. All subjects have agreed and signed the informed consent.

DNA isolation

Take 200 µl of blood into a sterile 1.5 ml tube. Then wash with 1000 µL of PBS pH 7.4, then centrifuge at 5,000 rpm for 5 minutes, the supernatant is discarded (Trempe et al., 2022). This stage is repeated 2-3 times. After that, the supernatant was discarded, then 500 µL of 0.5% saponin was added, mixed well using a vortex. Incubate for 24 hours in a refrigerator -20oC. Next, vortex again so that it melts immediately, then centrifuge at a speed of 12,000 rpm for 10 minutes. The supernatant was discarded. Add 1000 µL PBS, centrifuge at 5000 rpm for 10 minutes, discard the supernatant, repeat 2x until the supernatant is clear. The supernatant was discarded, 50 µl of Chelex was added and 100 µl of ddH2O was added. Then incubate/boil in boiling water (using a heatlock device) for 5 minutes then vortex then centrifuge at 1000 rpm for 1 minute. Next, it is incubated in boiling water for 10 minutes, then centrifuged at 12,000 rpm for 10 minutes. The DNA will be in the supernatant (DNA containing water). Then this part was transferred into a sterile tube and stored at -20^{o}C.

PCR-RFLP

The PCR-RFLP method was carried out using patient and control genotypes in the IFN-y +874 A/T variant. A total of 176 bp IFN-y +874 A/T, forward primer 5'-GATTTTATTCTTACAACACACAAAATCAAAATCAAGAC-3' and reverse primer 5'-GCAAAGCCACCCCACTATAA-3' were used. PCR is performed with these steps. Denaturation at an initial stage at 95oC for 10 minutes, followed by 34 cycles of denaturation at 95oC for 30 seconds, annealing at 55oC for 1 minute and extension at 72oC for 1:30 minutes. The last cycle carried out final extension for 5 minutes at a temperature of 72oC.

The PCR reaction was carried out by mixing 3.5 µl ddH2O, 1 µl Buffer, 0.5 µl HinFI Enzyme into each 0.2 ml Eppendorf tube for all case and control samples. Add 10 µl of amplicon into each tube then Spin down (Vortex). Then put the tube into a heating device (Heat Lock) to incubate for 2 hours at a temperature of 37ºC. After incubating for two hours, perform gel electrophoresis. Put 0.3 µl of 50 bp marker into the agarose gel well. Insert an aliquot of 0.5 µl into the agarose well provided.

Connect the electrophoresis device with 100 Volts, 400 mAh voltage, for 30 minutes. After electrophoresis, visualization is carried out using Gel-Doc equipment made by BIO-RAD Laboratories USA which is connected to a computer. Next, the results were observed on a computer using the Quantity One program to see the presence of gamma interferon gene polymorphisms for the A/A genotype at 176 bp, the A/T genotype at 176,148,28bp and the T/T genotype at 148, 28 bp.

Statistic analysis

Data were analyzed univariately and bivariately (Gannon et al., 2023). Univariate analysis will assess the characteristics of respondents in the form of prevalence, age, gender (Chong et al., 2020). Bivariate data analysis will assess the relationship between the INF-γ +874 A/T gene polymorphism and the incidence of schizophrenia (Pinto, 2019), analyzed using the Chi-square test to compare the proportion of alleles and genotypes in each group.

Result and Discussion

Subject Characteristics

In table 1, it is divided into 3 age group categories, namely 21-30 years old (32%), 31-40 years old (44%) and 41-50 years old (24%). Based on gender, the frequency of male gender in the case group was 30 people (60%) and in the healthy control group it was 35 people (70%). The frequency of female gender in the case group was 20 people (40%) and in the healthy control group was 15 people (30%).

Table 1. Subject Characteristics based on age

Respondent's age (year)	Frequency	Percentage %
21 - 30	32	32
31 - 40	44	44
41 - 50	24	24
Total	100	100

Table 2. Subject Characteristics based on Sex

Respondent's Sex	Groups	
	Case (50)	Group (50)
Men (n,%)	30 (60%)	35 (70%)
Women (n,%)	20 (40%)	15 (30%)
Total	50 (100%)	50 (100%)

Frequency distribution of the genotype of the Interferon Gamma Gene +874 A/T PCR and RFLP results in Table 2, the frequency distribution of TT, AT, and AA genotypes in the case group is 12 (24%), 26 (42%), and 12 (24%), respectively. The frequency distribution of TT, AT, and AA genotypes in the control group was 8 (16%), 16 (32%), 26 (52%), respectively. The frequency distribution of TT, AT, and AA genotypes in all research subjects was 20 (20%), 42 (42%), and 38 (38%). It was found from these results that the frequency of the TT and AT genotypes was higher in the case group than in the control group.

Table 3. Frequency distribution of the Interferon Gamma +874 A/T genotype

Variabel		Groups		Total	*P-value*
		Case n (%)	Control n (%)	n (%)	
Polimorfisme Gen Interferon Gamma +874 A/T	TT (Mutan homizigot)	12 (24)	8 (16)	20 (40)	0,015*)
	AT (Mutan heterozigot)	26 (42)	16 (32)	42 (74)	
	AA (Wild type)	12 (24)	26 (52)	38 (76)	
	Amount	50 (100)	50 (100)	100 (100)	

Genetic analysis of IFN-γ +874 A/T was examined in the case and control groups (Liu et al., 2011; Paul-Samojedny et al., 2011). Table 3 shows the allele and genotype frequency distribution of the two groups. The A/T genotype frequency of the case group was found to be higher than that of the control group, accounting for 42% and 32%, respectively, p = 0.015. For allele frequency, the T allele in the case group was 50% and the

control was 31%, while the A allele in the case group was 50% and in the controls 69%, p = 0.006, OR = 2.226.

Table 4. Genotype and allele frequencies of interferon +874A/T polymorphism

	Case		Control		p	OR (95 CI)
Genotype	n	%	n	%		
A/A	12	24%	26	52%		
A/T	26	42%	16	32%	0.015	
T/T	12	24%	8	16%		
Alel						
A	50	50%	69	69%		2.226
					0.006	(1.250-
T	50	50%	31	31%		3.965)

Analysis of the Correlation of the Polymorphism of the Interferon Gene Promoter Gamma point +874 A/T Polymorphism with the Occurrence of Schizophrenia in the Population of South Sumatra.

In this study, the analysis of the relationship between the gamma interferon gene promoter polymorphism point +874 A/T and the incidence of schizophrenia in the population of South Sumatra is the analysis of the relationship between TT and AA genotype polymorphisms, the relationship analysis of AT and AA genotype polymorphisms, the relationship analysis of TT and AA genotype polymorphisms, and the analysis of relationship between TT-AT and AA genotype polymorphisms.

Frequency distribution of the genotype (TT vs AA) of IFN-γ +874 A/T in the TT genotype frequency in the case group (24%), controls (16%), while the frequency of the AA genotype in the case group (24%), controls (52 %) there is a significant difference with p value = 0.037; OR = 3.250 (CI = 1.054-10.020).

Frequency distribution of the genotype (AT vs AA) of IFN-γ +874 A/T in the AT genotype frequency in the case group (32.5%), controls (20%), while the frequency of the AA genotype in the case group (15%), controls (32.5%) there is a significant difference with p value = 0.007; OR = 3.521 (CI = 1.396-8.879).

Frequency distribution of the genotype (TT vs AT) of IFN-γ +874 in the TT genotype frequency in the case group (19.4%), controls (8%), while the frequency of the AT genotype in the case group (41.9%), controls (25.8%) no there is a significant difference with a p value = 0;886 OR = 0.923 (0.310-2.746). Analysis of the Relationship between the IFN-γ Gene Promoter Polymorphism point +874A/T genotype (TT-AT vs AA) with the incidence of schizophrenia in the South Sumatran population.

The relationship between the +874 A/T point gene polymorphism and the Interferon gene promoter gammagenotype (TT-AT vs AA) was calculated using the chi-square test between the mutant type genotypes (TT and AT) and the wild type genotype (AA). Based on Table 6 in the case group, it appears that the TT and AT mutant genotypes appear more frequently, namely 76% compared to the wild type genotype which is only 24%. In the control group, the wild type genotype appeared more yati by 52% compared to the mutant genotype which was only 48%. The results of the analysis showed a significant difference between the genotype frequencies (TT-AT vs AA) in the case group and the control group (p = 0.004) with an OR value = 3.431 (1.461-8.057).

Table 5. Analysis of the Relationship between Polymorphisms of the INF-γ gene genotype point +874 A/T with the incidence of Schizophrenia

Genotipe	Case	Control	*p-value*	OR (95% CI)
	n (%)	n (%)		
TT	12 (20.7)	8 (13.8)	0.037*)	3.250 (1.054-
AA	12 (20.7)	26 (44.8)		10.020)
AT	26 (32.5)	16 (20)	0.007	3.521 (1.396-8.879)
AA	12 (15)	26(32.5)		
TT	12 (19.4)	8 (12.9)	0.886*)	0.923 (0.310-2.746)
AT	26 (41.9)	16 (25.8)		

Table 6. Analysis of the Relationship between the IFN-γ Gene Promoter Polymorphism point +874A/T genotype (TT-AT vs AA) with the incidence of schizophrenia

Genotipe	Case	Control	*p-value*	OR (95% CI)
	n (%)	n (%)		
TT-AT	38 (76)	24 (48)	0.004*)	3.431 (1.461-
AA	12 (24)	26 (52)		8.057)
Total	50 (100)	50 (100)		

Based on research subject data, the incidence of schizophrenia was more common in the population aged 31-40 years in the case group (Correll et al., 2022), namely 24 respondents (23.2%). The results of this research are supported by the Global Epidemiology and Burden of Schizophrenia study by Charlson et al., 2018, which provides data on the global prevalence of schizophrenia. According to this study, around 70.8% of schizophrenia disorders are found in the 25-54 year age range, with the highest prevalence in the 30-40 year age group (Hakulinen et al., 2019). In research subjects with a control group, there were 20 respondents (20.7%) in the population aged 31-40 years.

Analysis of the Relationship between Interferon Gamma Gene Allele Polymorphisms and the incidence of Schizophrenia. Respondents in the case group with the interferon gamma gene polymorphism +874 A/T with the T allele (50%) had a greater percentage than respondents in the control group (31%). These results are also supported statistically where there is a significant relationship between the interferon gamma gene allele

polymorphism and the incidence of schizophrenia, where respondents with the T allele have a risk factor for schizophrenia 2.226 times compared to respondents with the A allele.

Conclusion

Based on research subject data, the incidence of schizophrenia was more common in the population aged 31-40 years in the case group, namely 24 respondents (23.2%). The results of this research are supported by the Global Epidemiology and Burden of Schizophrenia study by Charlson et al., 2018, which provides data on the global prevalence of schizophrenia. According to this study, around 70.8% of schizophrenia disorders are found in the 25-54 years age range, with the highest prevalence in the 30-40 years age group. In research subjects with a control group, there were 20 respondents (20.7%) in the population aged 31-40 years.

Author Contributions

This article was written by three authors who worked together at every stage to complete this article, namely A.F.L, E.M.S, and Z.H.

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Conflicts of Interest

The authors declare no conflict of interest.

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