Association between Cathecol -O-Methyltransferase (COMT) Val 158 Met Polymorphisms and Psychosocial Stressors in Torajanese Schizophrenic Patients

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Abstract

Objective*s:* TheTorajanese has a ritual tradition for the dead and marriage ceremonies from generation to generation on a large-scale; this is one of the cultural factor that influences the evolution of genetic adaptation. Increased incidence of schizophrenia annually is often associated with Cathecol-O-Methyltransferase (COMT) Val 158 Met polymorphisms as one of the genes causing schizophrenia. This study was aimed to determine the association between Cathecol -O- Methyltrnasferase Val 158 Met polymorphisms and psychosocial stressors with schizophrenia in Torajanese schizophrenia patients.

Method: This was a quantitative study with a cross-sectional analytical description. There were 210 subjects divided equally into 3 groups, namely the Torajanese schizophrenia group with three subsequent generations (n = 70), normal Torajanese group (n = 70) and normal non-Torajanese group (n = 70). This study was conducted at Hasanuddin University Hospital and its network. PCR and RFLP examination were used for Cathecol-O-Methyltransferase (COMT) Val 158 Met polymorphism. Questionnaire was used to assess the psychosocial stressors.

Result*:* There was a significant difference in the distribution of genotypes between the Torajanese schizophrenia group and the normal Torajanese group, between the normal Torajanese group and the the normal non-Torajanese group ($p < 0.05$). There were 3 genotypes in Cathecol -O-Methyltransferase (COMT) Val 158 Met polymorphisms in Torajanese, namely Val/Val, Val/Met and Met/Met; and for the 140 subjects of the Torajanese, the amount of Val/Val genotypes was 104 (74.3 %) subjects, Val/Met genotype was 32 (22.9%) subjects and Met/Met genotype was 4 (2.9%) subjects. It was found that 66 (47.1%) subjects had psychosocial stressors and 74 (52.9%) subjects didn't have psychosocial stressor.

Conclusion: There was a significant relationship between Cathecol -O-Methyltransferase (COMT) Val 158 Met polymorphisms and Torajanese schizophrenia group. There was a significant association between psychosocial stressors and Torajanese schizophrenia group. There was no significant difference in PANSS scores on the COMT Val 158 Met polymorphism genotypes.

Keywords: *Schizophrenia, Cathecol-O-Methyltransferase (COMT) Val 158 Met polymorphism, psychosocial stressors, PANSS, Torajanese*

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Introduction

Human have biological plasticity, or an ability to adapt biologically to our environment.The human body readily responds to changing environmental stresses in a variety of biological and cultural ways. When an environmental stress is constant and lasts for many generations, successful adaptation may develop through biological evolution. Those individuals who inherit a trait that offers an advantage in responding to particular stresses are more likely to survive longer and pass on more of their genes to the next generation. This is evolution through natural selection. Biological adaptation varies in their length of time, anywhere from a few seconds for a reflex to a lifetime for developmental acclimatization or genetics. The biological changes that occur within an individual's lifetime are also referred to as functional adaptations. What type of adaptation is activated often depends on the severity and duration of stressors in the environment. Genetic adaptations can occur when stressor is constant and lasts for many generations (1). Genetic change in response to environmental stresses usually takes many generations to become widespread in a population. Fortunately, we also have other ways of responding more quickly as individuals during our own lifetime. Adaptations is reserved for inheritable genetic changes developed in a population over a long period of time. Charles Darwin and Alfred Wallace (1858) famously proposed that positive selection could explain the many marvelous adaptation that suit organism to their environments and lifestyles, and this simple process remains the central explaination for all evolutionary adaptation yet today. (2) Whatever the determinants of mutation rates in humans, they seem to have comparable effects on diversity and divergence. Thus, there is currently no need to assume that natural selection has shaped genome wide patterns of variability in humans, although it has undoubtedly shaped patterns of variation in some genomic regions. In human at least, the great majority of mutations are thought to be selectively neutral(3) the frequency of some of these neutral genetic variants (alleles) increases simply by chance, and the resulting genetic drift is thought to be the most commonprocess in human evolution. (4)

The Torajanese has a ritual tradition for the dead and marriage ceremonies from generation to generation on a large-scale; this is one of the cultural factor that influences the evolution of genetic adaptation. The results of Basic Health Research (Riskesdas) 2018, showed that prevalence of schizophrenia in Indonesia in 2013 by 1.7% per mile increased to 7% per mile in 2018, and South Sulawesi province became the sixth highest schizophrenic province in Indonesia. Data from Health District Office of Tana Toraja showed that 593 people suffer from schizophrenia.

Schizophrenia is a severe mental illness with a global incidence close to 1%. Convergent data had shown that both genetic and environmental factors were involved in the development of this disorder. (5,6) Schizophrenia has been subjected to detailed genetic epidemiological investigation. The results of numerous families, twin, and adoption studies show conclusively that risk of illness is increased among the relatives of affected individuals and that this is the result largely of genes rather than shared environment. (7,8) In the children and siblings of individuals with schizophrenia, the increase in risk is around 10-folds, and somewhat less than this in parents. The latter finding is probably explained by a reduction in the reproductive opportunities, drive, and possibly fertility of affected individuals. Five recent systematically ascertained studies using modern diagnostic criteria report monozygotic (MZ) concordances estimated at 41–65% compared with dizygotic (DZ) concordances of 0–28%, resulting in an estimated broad heritability of 85%.(9) Polymorphic variations in genes that reside in the deleted region, in the remaining chromosome,may contribute to differences in susceptibility to psychiatric disorders between patients with the same deletion. Such variations could affect the biological functions of the gene products and may be particularly important because the amount of mRNA and protein produced in 22q11.2DS individuals is expected to be reduced due to the deletion, as was demonstrated in a mouse model of 22q11.2DS. (10)

The catechol-O-methyltransferase (COMT) gene, which is located in the 22q11 microdeletion, has been considered as a candidate gene for schizophrenia because of its function of degrading catecholamines including dopamine. (11) The catechol-O-methyltransferase (COMT) gene plays an important role in the metabolic inactivation of DA and norepinephrine in regions with a paucity of DAT expression, specifically in the frontal cortex (12). A common functional polymorphism of this gene involves an amino acid substitution of methionine (Met) for valine (Val) which changes the activity of the enzyme. Val homozygotes have 3–4 times higher COMT enzyme activity, resulting in increased catabolism of catecholamines in frontal regions compared to Met-homozygotes [13]. In human, similar results have been reported as Val-homozigotes appear more stress resistant. (14,15,16) Val allele loading may generate stress-resistance in combination with suboptimal cognitive performance. (17,18) The Val158Met functional polymorphism among the COMT polymorphisms leads to a fourfold reduction in enzyme activity, and this variation of enzyme activity presumably affects the risk of schizophrenia. (19,20)The preponderance of the COMT literature, primarily focused on schizophrenia, links impaired cognition with the Val allele of the Val158Met polymorphism. For example, Val/Val homozygotes have lower sensorimotor gating levels (21). In contrast, the Met allele has been associated with aggressive behavior (22) and suicidality (23) in schizophrenia patients. These observations are consistent with the hypothesis proposed by Bilder et al, (24) that the Met allele confers an increase in tonic catecholamine function, which putatively leads to a decreased ability to plan adaptive responses to novel situations. Thus, features of behavioral overactivity may be associated with the presence of the Met allele.

A number of studies had shown a relationship between COMT Val 158 Met polymorphism and schizophrenia, including research by NurayAltintas, et al, 2018 in ManisaTurkey.(25) S- Al-Asmary, et al in 2014 on the Arab population. (26) Research conducted by EM Sutrisna, 2016 on Javanese,(27) GwennyIchsan Prabowo's research, 2018 in East Java. (28) However, there were also studies that showed no relationship between COMT Val 158 Met polymorphism with schizophrenia, such as research conducted by Chen et al., 2011 on Han ethnicity in Taiwan.(29) Hung Jing Kang et al, 2010 in Korean society,(30) Wen Jun Li, et al. 2012 in the Han Chinese population,(31) Tovilla-Zarate C. et al research on the Mexican population.(32) So it can be concluded that the relationship of COMT Val 158 Met gene polymorphism with schizophrenia depends on geography and ethnicity.

In our study, we aimed to investigate the Catechol-OMethyltransferase (COMT) Val158Met polymorphism in individuals with chronic schizophrenia in Torajanese

Material and Methods

Subjects

There were 210 subjects divided equally into 3 groups, namely the Torajanese schizophrenia group with three subsequent generations (n = 70), normal Torajanese group (n = 70) and normal non-Torajanese group (n = 70). Seventy Torajan schizophrenia patients (male/female=45/25) were recruited fromHasanuddin University Hospital and its network. One independent experienced psychiatrist diagnosed each patient on the basis of the Structured Clinical Interview for DSM-V. All schizophrenic patients were chronic, with at least 6 month of illness, were Torajanese with three subsequent generations and were between 20 and 45 years old (mean 34.50 +6.71years), minimum junior high school for educational level, no history of cardiovascular diseases, endocrine and metabolic disorders, kidney disorders, liver disorders, drug addiction, had no history of head trauma, seizures or fever. Seventy healthy Torajanese controls (male/female=25/45) without current or past psychiatric history were selected from the local Makassar and Makale area. They were 20 - 45 years old (mean 32.34 ±4.41 years), minimum junior high school for educational level, no history of cardiovascular diseases, endocrine and metabolic disorders, kidney disorders, liver disorders, drug addiction, had no history of head trauma, seizures or fever.

Seventy healthy Non Torajanese controls (male/female=27/43) without a current or past psychiatric history were selected from the local Makassar and Makale area. They were from 20 - 45 years old (mean 24.16 +5.72 years), minimum junior high school for educational level, no history of cardiovascular diseases, endocrine and metabolic disorders, kidney disorders, liver disorders, drug addiction, had no history of head trauma, seizures or fever.

All subjects provided with written informed consent and the protocol approved by the Hasanuddin University Medical Ethnic Committee. The demographic data of the participants are presented in Table 1.

Genotyping

We extracted genomic DNA for the polymerase chain reaction (PCR) from the whole blood sample using standard protocols. Genomic DNA was isolated from 200 µL venous blood using a spin column format kit . (EuroGold^{TM} Blood DNA mini kit, Euroclone, Italy). The procedure was carried out according to the manufacturer recommendations. It was followed byPCR amplification of the SNP-containing fragment A 108 bp DNA fragment containing the SNP was amplified using the PCR method. The sequence of the reverse primer used was selected as to anneal to and modify the constant recognition sequence of NlaIII found in close proximity to the SNP under study through a mismatch. The PCR reaction was carried out in a total volume of 20 µL containing 100-150 ng genomic DNA as the template, 0.5 µM of each primer (synthesized by VBC-Biotech, Austria), 2.3 mM MgCl2, 200 µM of each dNTP, 1X Taq buffer (10 mM Tric-HCl pH 8.4, 50 mM KCl) and 0.75 units of Taq DNA polymerase (Fermentas, Lithuania). PCR amplification was carried out in a MasterCycler® thermal cycler (Eppendorf, Germany) with an initial denaturation step at 94^0C for 5 min followed by 32 cycles of 94^0C for 30 sec, 62^0C for 30 sec and 72^0C for 10 sec, and a final extension step at 72^0C for 5 min. The sequences for the forward and reverse primers were 5′-CGAGGCTCATCACCATCGAGATC-3′ and 5′-CTGACAACGGGTCAGGAATGCA-3′, respectively.

For Restriction Digestion , the whole volume of the unpurified PCR product was mixed with 1 µL of FastDigest® NlaIII enzyme (Fermentas®, Lithuania), 2 µL of 10X FastDigest® green buffer and 17 µL of nuclease free water to make up a total volume of 40 µL. Digestion was ensured to be complete following incubation at 37^0C for 15-20 min. Tris-Borate-EDTA (TBE) buffer was used for electrophoresis. TBE was used at a concentration lower than that commonly used (only 0.2X) in order to decrease electric conductivity allowing the application of electric field strength as high as 16 V/cm. This resulted in sharp bands and short electrophoresis time and separation distance. Agarose gel was used as the separation medium with a concentration of 2.5 %. Ethidium Bromide was incorporated into the gel with a concentration of 1 µg/mL. The gel was illuminated withWiseDoc® gel documentation system (DaihanScietific, South Korea) and directly photographed using a handheld digital camera. Results Digestion of the amplified fragment with NlaIII showed 3 bands in heterozygotes (108, 72 and 36 bp) The amplified fragment remained intact in Val homozygotes after digestion, with agarose gel electrophoresis showing a single 108 bp band. In Met homozygotes, 2 bands were produced (72 and 36 bp) [(33)]

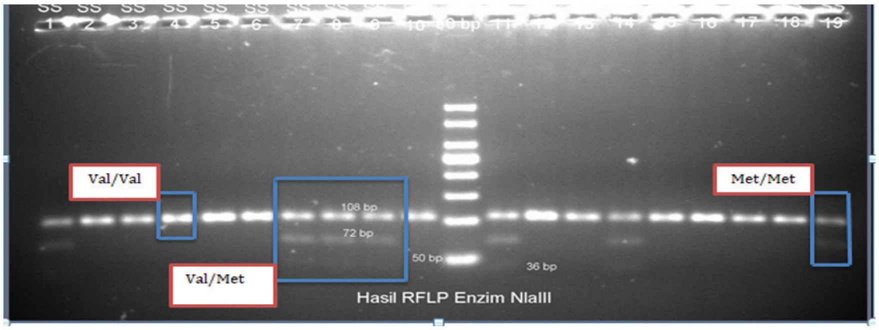

Figure 1: Val158Met COMT polymorphism as detected by the proposed PCR-RFLP method. The electrophoretogram shows genotypes for 6 different subjects. A single band (108 bp) indicates a homozygous genotype for the high activity allele (HH). The presence of 2 bands (72 and 36 bp) is indicative of a homozygous genotype for the low activity allele (LL). Heterozygous genotype (LH) is characterized by the presence of 3 fragments (108, 72 and 36 bp).

Clinical Assessment

A psychiatrist, who had previously completed a training session in rating the positive and negative syndrome scale (PANSS), assessed the patient's psychopathology using this scale.

Statistical Analysis

Deviation from Hardy–Weinberg equilibrium was calculated by Chi-square tests. The

Statistical analysis was performed using the SPSS ver. 22.0 for Windows. Chi-squared test were used for the statistical analyses of the data.

Results

The demographic characteristics of subjects are described and compared in Table 1. The Torajanese schizophrenia group included 70 subjects (45 males and 25 females), with a mean age of 34.50 ± 6.71 (range: 20-45) years , the normal Torajanesegroup included 70 subjects (25 males and 45 females), with a mean age of 32,34 ± 4.41 (range:22-45) years, the normal Torajanese group included 70 subjects (27 males and 43 females), with a mean age of 24,16± 5,72 (range:20-38) years,

The mean age of the research subjects was SD 30.33 + 7.21. The proportion of sex of the research subjects was seen as more female than male, namely female as much as 113 people (53.8%) and male as much as 97 people (46.2%). Eeducation level were divided in 4 divisions, namely junior high school, Senior high school, 3-year-diploma, Bachelor/Master. Senior high school education is the largest (41.0%), then undergraduate and masters (40.5%), 3-year-diploma (12.6%), and junior high school education (5.7%).

Table 1.Demographic Characteristics of Patients with Schizophrenia and Normal Torajanese and Normal Non Torajanese (N = 210)

Characteristics	Torajanese Schizophrenia		Normal Torajanese		Normal Non-Torajanese		Total	
	N	Percen-tage (%)	N	Perce-tage %	N	Percen-tage %	N	Percen-tage (%)
Age (mean, SD)	34.50 +6.71		32.34+ 4.41		24.16+ 5.72		30.33+ 7.21	
Gender								
male	45	64.3%	25	35.7%	27	38.6%	97	46.2%
women	25	35.7%	45	64.3%	43	61.4%	113	53.8%
Eduation								
Junior high school	12	17.1%	0	0.0%	0	0.0%	12	5.7%
Senior high School	48	68.6%	0	0.0%	38	54.3%	86	41.0%
3-year diploma	3	4.3%	23	32.9%	1	1.4%	27	12.9%
Bachelor/Masters	7	10.0%	47	67.1%	31	44.3%	85	40.5%
Total	70	100.0%	70	100.0%	70	100.0%	210	100.0%

Primary data,2020

Table 2 show The distribution of the Met/Met genotype in the Torajanese schizophrenia group consisted of 3 subjects (4.3%), in the normal Torajanesegroup there was 1 subject (1.43%), and none (0.0%) in the Normal Non Torajanese group. The distribution of the Val/Met genotype in the Torajanese schizophrenia group was 21 subjects (30%), 10 subjects in the normal Torajanese (14.28%) and quite high in Normal Non Torajanese group as many as 26 subjects (37.1%).). The distribution of the Val / Val genotype in the Torajanese schizophrenia group was 46 subjects (65.7%), the Normal Torajanese group was 59 subjects (84.29%) and Normal Non Torajanese was 44 subjects (62.9%). Of all the samples, it was found that the highest number was the Val/Val genotype as many as 148 subjects (70.5%), then the Val/Met genotype was 58 subjects (27.8%) and the lowest was the Met/Met genotype as many as 4 subjects (1.9%)

Table 2 Torajanese Schizophrenia and Normal Torajanese and Normal Non Torajanese genotype frequency

Genotype	Torajanese Schizophrenia		Normal Torajanese		Normal Non Torajanese		Total	
	N	%	n	%	n	%	n	%
Met/Met	3	4.3%	1	1.4%	0	0.0%	4	1.9%
Val/Met	21	30.0%	10	14.28%	26	37.1%	58	27.6%
Val/Val	46	65.7%	59	84.29%	44	62.9%	148	70.5%
Total	70	100.0%	70	100.0%	70	100.0%	210	100.0%

Table 3 showed a significant association between the Cathecol O-Methyltransferase (COMT) Val158Met polymorphisms and Schizophreniaof Torajanese (n=140, p=0,039). The COMTval158met polymorphism in normal Torajanesegroup andTorajanese schizophrenic group were 3 genotypes, namely Val/Val, Val/Met and Met/Met. Genotype distribution of Val/Val genotype in the Torajanese schizophrenia group as much as 46 (65.7%) which was lower thanin the normal Torajanese group as much as 59 (84.29%). Thesewere different for theVal/Met genotype(21 or 30.0%) and Met/Met genotype (3 or 4.3%), whichwere higher in the Torajanese schizophrenia group compared to normal Torajanese group (Val/Met 10 or 14.28% andMet/Met 1 or1,4%)

Table 3.Relationship between schizophrenia and Genotype

Genotype	Schizophrenia Torajanese		Normal Torajanese		Total		P Value
	n	%	n	%	n	%	
Met/Met	3	4.3%	1	1.4%	4	2.9%	0.039
Val/Met	21	30.0%	10	14.28%	32	22.9%	
Val/Val	46	65.7%	59	84.29%	104	74.3%	
Total	70	100.0%	70	100.0%	140	100.0%	

* Chi Square Test

Table 4 showed no significant differences between COMT Val158Met polymorphism with PANSS inTorajanese Schizophrenia group (PANSS positive symptom, p = 0.178; PANSS negative symptoms, p = 0.949; PANSS general psychopathology, p = 0.362; Total PANSS, p = 0.586). PANSS Positive symptoms on Val / Val genotype (median-16) lower than theVal/ Met and Met/Met genotypes which shared the same median (median=19), meaning that the met allele had an influence on PANSS positive symptoms.

Table 4. Comparison of the PANSS Value according to the Genotype of the Torajanese Schizophrenia Group (N=70)

Genotype	Positive Symptoms		Negative Symptoms		General Psychopathology		Total	
	Median	Min – Max	Median	Min – Max	Median	Min – Max	Median	Min - Max
Met/Met	19	14 – 28	14	13 – 19	41	30 – 48	74	57 – 95
Val/Met	19	14 – 33	14	8 – 29	33	25 – 59	66	50 – 121
Val/Val	16	7 – 33	14	7 – 33	33	16 – 78	64	32 – 134
P Value	0,178		0,949		0,362		0,586	

Kruskal Wallis test

Table 5 showed psychosocial stressors in the Torajanese schizophrenia group including family problems 23 (38.3%), professionproblems 17 (28.3%), problems with the social environment 12 (20%), economic problems 5 (8.3%), educational problems 2 (3,3%) and health problems 1 (1,7%). While those with unclear or psychosocial problems 10 (14.28%)

Table 5. Distribution of Psychosocial Stressors in the Toraja Ethnic Schizophrenia Group (N=70)

Stressor	Met/Met		Val/Met		Val/Val		Total	
	N	%	n	%	n	%	N	%
Ekonomic	0	0.0%	0	0.0%	5	100.0%	5	8,3%
Family	2	8.7%	7	30.4%	14	60.9%	23	38,3%
Health	0	0.0%	0	0.0%	1	100.0%	1	1,7%
Profession	1	5.9%	7	41.2%	9	52.9%	17	28,3%
Education	0	0.0%	0	0.0%	2	100.0%	2	3,3%
Problems with the social environment	0	0.0%	5	41.7%	7	58.3%	12	20%
There is no	0	0,0 %	2	20,0%	8	80,0%	10	14,28%
Total	3	4,3%	21	30,0%	46	65,7%	70	100.0%

Discussion

In our study, Cathecol O-Methyltransferase (COMT) Val158Met polymorphism in the Torajanese schizophrenia, normal Torajanese group and normal non Torajanese group remain in equilibrium according to the calculation of the genotype frequency with the Hardy-Weinberg equilibrium .

In this study,, the polymorphism of Cathecol O-Methyltransferase (COMT) Val158Met in the normal Torajanese group was 84.29% for Val/Val genotype, 14.28% for Val/Met genotype and 1.43% for Met/Met genotype. Meanwhile, the polymorphism of Cathecol O-Methyltransferase (COMT) Val18 Met in the normal non Torajanese group generally was 66.9% for Val/Val genotype, and 37.1% for Val/Met genotype. Here, it could be seen that the percentage of the Val/Val genotype and the Met/Met genotype in the normal Torajanese group is higher, while the Val/Met genotype was lower than the normal non Torajanese group, This could be influenced by the uniqueness of the culture that becomes a moral burden, and indirectly as a continuous stressor from generation to generation.

So that in order to continue life and continue to carry out customary habits, the normal Torajanese group will choose genotypes that have high stress resistance. The existence of the Torajanese which had existed since 3000-1,500 BC, with the environment and culture that is very inherent in the community makes the population adapted. The basic assumption of adaptation develops from an evolutionary understanding that umans always trying to adapt to themselves and their natural surroundings, both biologically / genetically and culturally.

Cathecol O-Methyltransferase (COMT) Val158Met polymorphism resulted in 3 genotypes namely Val/Val, Val/Met and Met/Met. Based on several studies conducted by Collip D et al., Walder DJ et al. And Van Winkel R et al. In humans, it was reported that the homozygous val allele is more resistant to stress than the met allele form. (14,15,16). So that the normal Torajanese population then experienced adaptations in the form of genetic evolution by creating a new equilibrium to increase their resistance to stress. Where initially it has a similar balance to the normal non-Torajanese population with a val/val genotype image of around 62.9 percent but in order to adapt to the environment and culture, the normal Torajanese population increases stress resistance by increasing the genotype percentage. Val/Val becomes 84.29 percent, so that the normal Torajanese population has a new equilibrium following the hardy-Weinberg law, the new balance in the normal Torajanese population is the percentage of the Val/Val genotype 84.29%, the Val/Met genotype 14.28% and Met/Met genotype 1.43%. This equilibrium occured because a population adapts to its environment, not only through culture, but also through genotypic adaptation. This was in accordance with the theory of Futyyma, DJ which states that these differences in allele and genotype frequencies are in accordance with the theory of evolution which states that if two different populations adapt to different environments, then each population will accumulate differences in differences that occur in gene pool (differences in allele and genotype frequencies).(34)

When the Torajanese population experiences a deviation from the normal balance of the Torajanese population, it tends to experience schizophrenia. The picture obtained from the COMT Val158Met polmorphism in the Torajanese schizophrenia population was the percentage of the Val/Val genotype 65.7%, the Val/Met genotype 30%, and the Met / Met genotype 4.3%. Based on the chi square statistical test in theTorajanese schizophrenia group with the normal Torajanese group, with the p value 0.039 (<0.05) which meant that the distribution of COMT Val158Met polymorphism in these two populations is significantly different, especially in the percentage of the Val/Val genotype. The percentage of Val/Val genotypes in the Torajanese schizophrenia group (65,7%) had mutations or deviations whichwere lower than the normal Torajanese(84.29%), so the Torajanese schizophrenia group has mutations or deviations whichwere lower than normal, so they tended not to strong against stressors and prone to suffered schizophrenia. Similar results had been reported as Val-homozigotes appeared more stress resistant. (14,15,16)

Our study shows that there is a relationship between Cathecol-O-Methytransferase (COMT) Val158Met polymorphism and the incidence of Torajanese schizophrenia. This is in accordance with several studies such as Nuray Altintas, et al, 2018 in ManisaTurkey.(25) S- Al-Asmary, et al in 2014 on the Arab population. (26)

The median value of positive symptoms based on PANNS in the Torajanese schizophrenia group showed that the Val/Val genotype which had a median value of 16, was lower than Val/Met genotype and Met/Met genotype which shared the same median value of 19. The median general psychopathology based on PANSS in theTorajanese schizophrenia group,Val/Valgenotype andVal/Met genotypes shared the same median value of 33 which were lower than Met/Met genotypes(41). This was in accordance with the research of Goldman et al, and Montag et al. Met allele in COMT Val158Met polymorphism is associated with emotional instability, warrior-worrier hypothesis, anxiety and traits (35,36) with anxiety and related traits in empirical studies (37,38,39,40, 41). Although statistically there was no significant difference between the PANSS values of the COMT Val 158 Met polymorphism in Torajanese schizophrenia patients.

In this study, an overview of psychosocial stressors in the Torajaneseschizophrenia group was obtained in the form of family problems 23 (38.3%), professions 17 (28.3%), problems with the social environment 12 (20%), economic problems 5 (8.3%) , education problems 2 (3.3%) and health problem 1 (1.7%). Likewise, the relationship between stressors and the incidence of schizophrenia was significant, there was also a possibility of interactions among stressors which could cause schizophrenia. From this study, it was found that the incidence of Torajanese schizophrenia, apart from being related to the Cathecol-O-Methyltransferase (COMT) Val158Met polymorphism was also amplified by the presence of psychosocial stressors. This was in accordance with research conducted by Arman Marwing, 2011 which found that the direct impact of stress on a subject who had a vulnerable background or absence of resources, such as the absence or lack of income and productive assets, and low education tended to be suffering from heavier stress (42) so that he had the potential to suffer from a mental disorder in this case schizophrenia. The greater or more stressors, the more likely to suffer from schizophrenia, this was in accordance with the theory that stresses could cause an increase in the secretion of the neurotransmitter glutamate (GABA precursor compound) in the limbic system, causing neurotransmitter imbalance. An imbalance of the neurotransmitter glutamate itself could trigger schizophrenia (43).

Limitation

Some limitations in our study have to be pointed out. More samples and controls are needed for the accuracy of the study and better results. The study was only limited to examining the COMT val 158 Met polymorphism, so we could not see the interaction of other COMT chain polymorphisms or other genes such as the DRD2 / ANKK1 polymorphisms, BDNF, ANK3, CACNA1C, DRD2, DPP10 and GSK3B, to assess the involvement of other genes in the the incidence of schizophrenia. This study did not see the multivariate relationship between psychosocial stressors and COMT val 158 met polymorphisms in the Torajanese.

Conclusion

There was a significant relationship between Cathecol -O-Methyltransferase (COMT) Val 158 Met polymorphisms and Torajanese schizophrenia group. There was a significant association between psychosocial stressors and Torajanese schizophrenia group. There was no significant difference in PANSS scores on the COMT Val 158 Met polymorphism genotypes.

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Source of Support: Self

Ethical Clearance: Ethical clearance and funding were not necessary as it was a retrospective study that included the only collection of data.

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