https://scilett-fsg.uitm.edu.my/
Vol. 15(2) JUNE 2021

ISSN: 1675-7785
eISSN: 2682-8626

DOI: 10.24191/sl.v15i2.13831

Association of COMT Polymorphism and Academic Achievement among Female Undergraduate Students

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Received: 4 March 2021; Accepted: 20 May 2021; Published: 15 June 2021

ABSTRACT

Academic achievement may be influenced by catechol-O-methyltransferase (COMT) polymorphism. A common functional polymorphism of COMT, the rs4680 is consistently being involved in the modulation of dopaminergic pathway and prefrontal cortex function which may predominantly affect cognitive functions. A total of 197 female participants were recruited in this study. The score of student's grade point average (GPA) from the latest previous semester was used as the measurement of academic achievement. The COMT polymorphism was genotyped using tetra primer allele specific polymerase chain reaction. The findings indicated that there were 8 (4.1 %), 72 (36.5 %), and 117 (59.4 %) participants harbouring Met/Met, Met/Val, and

https://scilett-fsg.uitm.edu.my/
Vol. 15(2) JUNE 2021

ISSN: 1675-7785
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Val/Val genotype for COMT polymorphism respectively. All the genotype distributions of COMT polymorphism were consistent with Hardy-Weinberg equilibrium ($\chi^2 = 0.495$, $p > 0.05$). The one-way analysis of variance (ANOVA) result demonstrated that participants bearing Met/Met genotype had a better achievement in GPA as compared to the other COMT genotypes ($p = 0.001$). These findings support evidence that the affective role of COMT polymorphism might overwhelm cognitive abilities in measures of academic achievement like GPA.

Keywords: *COMT polymorphism, rs4680, academic achievement, grade point average*

INTRODUCTION

Education a is unique investment and academic achievement is a key component of it. Academic achievement has always been contemplated to be a crucial factor in educational life of an individual [1]. An excellent academic achievement is the main element for students to success in academic life. A good academic achievement is always desired by students, and it also becomes a primary focus for educational institutions and countries. In Malaysia, this is in line with the vision of becoming an international and regional education hub in ASEAN [2]. Therefore, students are under a great deal of pressure because of the competition and long-term planning for obtaining an excellent academic achievement, as well as the effect it will have of their future and educational opportunities.

Apart from that, students with a good academic achievement may be able to create a good valuable potential for themselves such as attaining higher financial success and employment rates. Meanwhile, students who fail to perform well in academic may reduce their potential abilities especially in their educational life. A poor academic achievement causes students to delay or extend their study, and this will eventually lead to a loss of interest to continue their study [3]. Moreover, if the failure rate of students is too high, the image and performance of educational institutions will be badly affected [4].

Many studies have been conducted to determine factors that influence academic achievement. Cognitive abilities are the primary focus as the one of the most search predictors of academic achievement since the beginning of the educational research. In fact, individual differences in cognitive function is caused by a significant influence of genetics with dopamine-related polymorphism among the most investigated candidate genes [5]. The effect of dopamine exerts on the cognition involving working memory, attention, and other execution functions [6]. In human cognition, the study of the biological basis of individual differences considered the catecholamine dopamine as a main candidate [7]. The role of dopamine in mediating human cognitive abilities and behavioural process has been widely accepted as it is postulated to be an essential neurotransmitter that regulates the function of the prefrontal cortex [8]. Therefore,

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Vol. 15(2) JUNE 2021
ISSN: 1675-7785
eISSN: 2682-8626

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genes participating in dopamine pathways make good candidates for relationship study in academic achievement.

Catechol-O-methyltransferase (COMT) is a methylation enzyme that catalyses the degradation of the first stage of extracellular catecholamines including dopamine through methyl group transfer of hydroxyl group of catecholamines to S-adenosylmethionine [9]. The COMT is widely expressed in the human brain and, it accounts for 60 % of the degradation of dopamine in the prefrontal cortex [7]. Hence, COMT is a vital regulator with regard to the modulation of dopamine level, cognitive functioning, and neural activity of the prefrontal cortex [8]. The *COMT* gene encodes for COMT enzyme is located on the chromosome 22q11.21 and it consists six exons. Moreover, *COMT* gene is the most studied gene affecting dopamine-mediated functions [10].

In human, a single nucleotide polymorphism on the *COMT* gene moderately leads to the individual differences in prefrontal dopamine and causes increased signal-to-noise ratio [11]. The *COMT* gene harbours a functional polymorphism that produces amino acid substitution at the protein level from valine (Val) to methionine (Met) at residue 158 known as Val158Met or rs4680 which is associated with differential COMT activity [12]. This polymorphism consists of wild type allele, encodes for Val, carries guanine (G) nucleotide and mutant type allele, encodes for Met, carries adenine (A) nucleotide [13].

The Met allele carrier of COMT polymorphism is less effective in metabolizing dopamine because the carrier is more thermolabile at temperatures 37°C, while the Val allele carrier has a higher stability [14]. The dopamine degradation in the prefrontal cortex of homozygous Met allele carrier is slower as the carrier synthesises enzyme with three to four-fold lower activity as compared to the homozygous Val allele carrier [13]. Meanwhile, heterozygous Val/Met carrier demonstrated an intermediate level of enzymatic activity. In other words, the less efficient COMT enzyme among individual with Met/Met genotype leaves dopamine in the synapse over longer period of time whereas the efficient COMT enzyme among individual with Val/Val genotype breaks down dopamine faster leaving little dopamine in the synapse [15].

The first study investigated the relationship between COMT polymorphism and cognition reported a better significant performance of individuals bearing Met/Met genotype in the Wisconsin Card Sorting Test [16]. Apart from that, individual who carry at least one copy of Met allele demonstrated to have advantage in working memory and attentional tasks [17]. The reduce activity among individual harbouring Met/Met genotype has been associated with enhanced cognitive functions as evidence from recent study on Caucasian population [18]. A study by Mestrovic et al. (2017) reported that the presence of one or two copies of Met alleles of COMT polymorphism might be beneficial in cognitive performance involving working memory tasks [6]. In contrast, a study conducted in a Chinese cohort demonstrated that participants habouring Met/Met genotype tended to perform poorer in an annual national competitive entrance examination as compared to the other genotype groups [8]. It was suggested that the poorer performance among participants bearing Met/Met genotype was due to the due to the

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Vol. 15(2) JUNE 2021

ISSN: 1675-7785
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predominant role of stress and emotional vulnerability [8]. Within the given frame of references, it is reasonable to presume that academic achievement can be influenced by the cognitive effects of the COMT polymorphism [18].

Since cognitive abilities are known to predict academic achievement, it is possible that COMT polymorphism could be related to academic achievement *via* effects it has on cognitive measure. Given that most of the previous studies examined the influence of COMT polymorphism on cognitive abilities reported more on Caucasian population, we aim to target our own population to identify the effect of the polymorphism specifically on the undergraduate university students specifically in Malaysia. Although many studies reported various factors that could affect academic achievement, the research involving genetic polymorphism particularly COMT polymorphism as the potential factor influencing academic achievement is still scanty in our population. Therefore, considering the important role of COMT in cognitive abilities which predominantly affect academic achievement, we compared the GPA score of female undergraduate university students with different COMT genotype groups.

EXPERIMENTAL

Participants

A total of 197 female undergraduate students from the Faculty of Health Sciences, Universiti Teknologi MARA Puncak Alam Campus participated in this study. The mean age of the participants was 21.74 years (SD: 1.353; age range; 20-27 years). Participants were recruited from two programmes: Bachelor of Nursing (Honours) and Bachelor of Medical Laboratory Technology (Honours). This study was approved by the Research Ethics Committee of Universiti Teknologi MARA (Reference Number: REC/365/16). The participants were all explained explicitly about the aims, protocols, potential risks, and benefits of the study. The participants were also informed that their identity and personal information would be kept strictly confidential, and they could withdraw from the study at any point of time without mentioning reasons for doing so. Written consent form was obtained from all participants at the beginning of the study.

Academic Achievement

Academic achievement was operationalized *via* Grade Point Average (GPA). All participants were required to provide their current score of GPA from the previous semester. GPA refers to the cumulative grade of the students that was calculated by averaging course

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grades of the previous semester. The scores of GPA range from 2.10 (average pass) to 4.00 (excellent).

Genomic DNA Extraction

A whole blood sample was collected from each participant. Genomic DNA was extracted from the blood samples using E.Z.N.A® Blood DNA Mini Kit (Omega, USA) following the instruction manual by the manufacturer and DNA were stored at -20 °C .

Genotyping of COMT Polymorphism

The COMT polymorphism (rs4680) was identified by allele specific polymerase chain reaction (PCR). The in-house designed primers for the reaction were as following: 5' - CTG TGC TCC CTC TCC TCC GTC CCC AAC-3' and 5' - CTG AGC TGC TGG GGG GGT CTT TCC TCA G - 3'. The amplification mixture contained, 2 µl of DNA template (50 ng/µl), 2 µl of 1X ThermoPol Buffer, 0.32 µl of 0.16 mM of dNTPs, 0.1 µl of 0.5 U *Taq* DNA Polymerase, sterile distilled water, and respective primers. Samples were amplified with an initial 2 minutes at 95 °C for initial denaturation followed by 20 seconds at 95 °C for denaturation, 20 seconds at 60 °C for primer annealing, 30 seconds at 68 °C for extension, and 5 minutes at 68 °C for final extension in a total of 30 cycles (TaKaRa, Japan).

The amplified products were checked by electrophoresis in 3.5 % agarose gel at 200 V for 40 minutes using PCR mix solution with known heterozygous DNA template as positive control and PCR mix solution without DNA template as negative control. Alleles were visualized by ethidium bromide staining according to amplified fragment sizes: common amplicon (393 bp), Val allele (249 bp), and Met allele (216 bp) using gel documentation system (PerkinElmer, USA). The selected amplified products were then purified using E.Z.N.A® Gel Extraction Kit (Omega, USA) following the instruction manual by the manufacturer and the purified products were sent for validation using the forward primer by the third party. The resulting sequence data was used to interrogate the nucleotide collection from Genebank database (https://blast.ncbi.nlm.nih.gov/Blast) using Basic Local Alignment Search Tool (BLAST) algorithm and orientation utilizing the SnapGene® software, v.4.3.10 (GSL Biotech, USA).

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Statistical Analysis

All statistical analysis was performed using Statistical Package for Social Sciences (SPSS) software version 20 (Chicago, IL, USA). The subjects were grouped according to their COMT genotypes (Met/Met, Met/Val, and Val/Val). The χ^2 test was used to test the Hardy-Weinberg equilibrium. The statistical significance of academic achievement measured by GPA score among the three COMT genotype groups was determine using one-way ANOVA. A probability $p < 0.05$ was set as evidence of statistically significance.

RESULTS AND DISCUSSION

A total of 197 participants were recruited among female undergraduate students from Faculty of Health Sciences UiTM. The allele specific PCR technique was performed to determine the COMT polymorphism. The representative gel image of COMT polymorphism with bands produced of 393bp for common amplicon, 249 bp for Val allele, and 216 bp for Met allele is displayed in Figure 1. The genotype distributions of the participants are presented in Table 1. Out of 197 participants, 8 (4.1 %) were homozygous for Met allele, 72 (36.5 %) were heterozygous, and 117 (59.4 %) were homozygous for Val allele for COMT polymorphism. The genotypes were not sampled selectively as the observed genotypes were consistent with the expected Hardy-Weinberg equilibrium ($\chi^2 = 0.495$, $p > 0.05$).

The academic achievement measured by current GPA score of the participants in the different COMT genotype groups was analysed using one-way ANOVA. Individual harbouring Met/Met genotype was shown to have higher mean score of GPA followed by individual bearing homozygous Val/Val genotype and individual with heterozygous Met/Val genotype (Table 2). In addition to that, the relationship between the COMT genotype groups and the GPA score of each participant was further examined. The finding revealed that there was a significant difference in GPA score among three different groups of COMT genotype. Particularly, post-hoc Tukey analysis demonstrated that Met/Met carriers obtained significantly higher GPA score as compared to the Val/Val carriers and heterozygous Met/Val carriers as presented in Table 2.

Academic achievement is highly portrayed the educational status of an individual [1]. The influence of COMT polymorphism on academic achievement was investigated in this study since the polymorphism plays a vital role in individual differences in human cognition which partially could affect student's achievement in academic. The highest COMT genotype distribution was among individual harbouring Val/Val genotype followed by individual bearing heterozygous Met/Val and individual with homozygous Met/Met genotype. The distribution is consistent with other finding that demonstrated the significantly higher frequency of Met/Met genotype of COMT polymorphism within Asian populations than in Caucasian populations [19].

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Vol. 15(2) JUNE 2021

ISSN: 1675-7785
eISSN: 2682-8626

DOI: 10.24191/sl.v15i2.13831

Apart from that, the major finding of this study is indicated that participant harbouring homozygous Met allele tended to have a better academic achievement as compared to the other COMT genotype groups. This finding is in parallel with previous studies done by Mestrovic et al. (2017) and Bueno (2019) that demonstrated a significant better performance in Met/Met carriers than Val/Val carrier [6,20]. The better performance by individual with homozygous Met allele because the carrier could induce higher activity in prefrontal cortex where the neuronal circuits involved in working memory are occur [20].

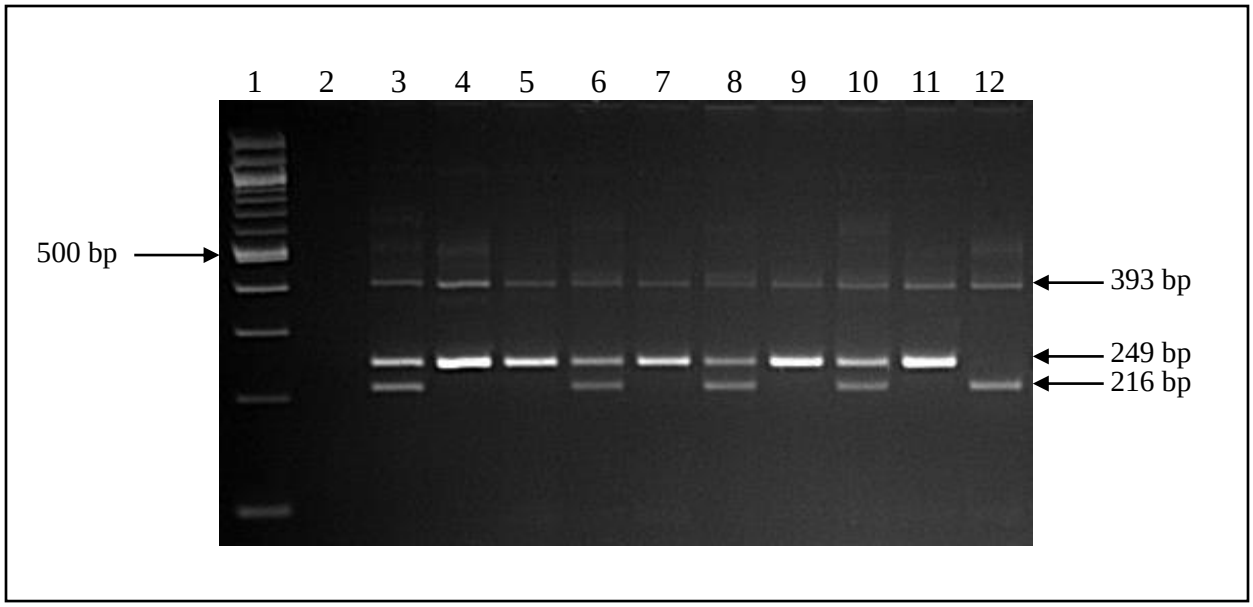

Figure 1: Representative gel image of COMT polymorphism. Lane 1: 100bp ladder, lane 2: negative control, lane 3: positive control, lane 4 – 12: representative DNA samples of participants.

Table 1: COMT genotype distributions.

COMT genotypes	N	Percentage (%)	χ^2	*p* - value
Met/Met	8	4.1		
Met/Val	72	36.5	0.495	0.781
Val/Val	117	59.4		

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Table 2: Mean GPA score in participants with different COMT genotype groups.

COMT Genotype	N	GPA Score	F	*p* – value	Post-hoc Tukey (*p*)
Met/Met	8	3.75 ± 0.248	7.872	0.001	MM > VV** MM > MV**
Met/Val	72	3.25 ± 0.361			
Val/Val	117	3.35 ± 0.343			

GPA score (Mean ± SD)

* $p < 0.05$

** $p < 0.01$

In addition to that, normal dopamine release helps the Met/Met carrier to perform better in cognitive tasks under non-stressful conditions [21]. In a related study in which a subset of the subjects comprised of the subjects from our study, it was found that 75.5% of the female subjects experienced normal and mild stress [22]. Furthermore, students bearing the Met allele need a good educational environment to develop full potential for superior cognitive skills which could eventually affect their academic achievement [18]. There is an association reported between individual with Met allele and increased anxiety, major depression, and emotional stability and vulnerability when the carrier is exposed to stress or educational distress [8]. Several studies also reported the negative impact of emotional vulnerability and academic adversity could influence academic achievement [8,23]. Therefore, these discoveries strengthen the present result by suggesting that the individuals with the Met/Met genotype could obtain good GPA score because of the non-stressful condition and good educational environment throughout their study.

In contrast to that, the stressful conditions cause the performance of Met/Met carriers to drop due to the increased prefrontal dopamine release [21]. Otherwise, the increased of prefrontal dopamine due to stressful condition would be beneficial to the Val/Val carriers since they are more vulnerable to stress as compared to the Met/Met carriers. This could be explained by the inverted U hypothesis of prefrontal dopamine which stated that performance is enhanced by moderate increase of dopamine synaptic level but impeded when dopamine level surpasses certain optimal level [24]. Besides, this hypothesis implied that too little or too much dopamine activity in prefrontal cortex could affect cognitive abilities hence leading to impaired cognitive functioning in homozygous Met carrier [25]. Thus, the contradictory findings could be due to other additional factors such as environmental factor that possibly liked together with genetic factors which eventually exert more significant effect on academic achievement.

This study showed concrete evidence that genetic factor particularly a functional polymorphism in *COMT* gene plays a significant role in individual differences in academic achievement. The genotype profile of the students could help educational practitioners and university authorities to create more understanding on the individual cognitive abilities in

https://scilett-fsg.uitm.edu.my/
Vol. 15(2) JUNE 2021
ISSN: 1675-7785
eISSN: 2682-8626

DOI: 10.24191/sl.v15i2.13831

academic. Furthermore, educators could help students by providing priority to courses that suit the strongest cognitive abilities of the students. In any programme, students use their cognitive abilities to improve their quality of study. The strongest cognitive abilities may differ for each student, for example certain students may have advantage in working memory while others may have advantage in logic and reasoning skills. Students who are unable to utilize their strongest cognitive abilities will cause them to lose interest in learning. Therefore, educators could help students by suggesting the best courses that fit the strongest cognitive ability of the student. This would eventually lead to increase interest in learning and enhance the academic performance of the student.

However, there are some limitations in this study. The participants recruited were all female students. This was based on convenience sampling method whereby approximately 90% of Health Sciences undergraduate students at UiTM Puncak Alam were female. This study limits generalizability since participants were female undergraduate university students. In general, males and females demonstrate differences in cognitive abilities. Hence, future studies on male participants and gender comparison will be needed to show if these tenets will either be differently applied especially regarding the role of dopamine activity of COMT polymorphism on cognitive abilities which may influence student's academic achievement.

Hitherto, academic achievement could be influenced by many additional and combination of other factors besides genetic factors because of the complexity that underlies cognitive behaviour. Thus, due to the lack of measurement of cognitive abilities on the student's academic achievement, the current study creates a slight gap to establish the connection between cognitive functioning of COMT polymorphism on the student's achievement in academic. Therefore, it would be captivated to conduct meticulous hypothesis examining this issue by analysing more solid information regarding the cognitive abilities and environmental information of the students. In addition, the further studies involving students from different faculty and other universities are also important to validate the effect of COMT polymorphism on academic achievement of university students especially in Malaysia.

CONCLUSION

In this study, the genotype distribution of the female students was the highest among Val/Val carriers followed by Val/Met carriers and Met/Met carriers. Students harbouring homozygous Met allele for COMT polymorphism demonstrated a significantly higher academic achievement measured by GPA score as compared to the students bearing homozygous Val allele and heterozygous Val/Met. The data of this study will be helpful to educators to monitor and personalized strategies in improving student's academic achievement. Thus, the further analysis on the effect of COMT polymorphism on the academic achievement by cognitive measures may be beneficial in establishing the interaction between these variables.

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Vol. 15(2) JUNE 2021

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eISSN: 2682-8626

DOI: 10.24191/sl.v15i2.13831

ACKNOWLEDGMENTS

The authors would like to acknowledge the support of Universiti Teknologi Mara (UiTM) and Faculty of Health Sciences, Universiti Teknologi MARA, Puncak Alam Campus, Malaysia for providing the facilities and financial support on this research and all the participants. This work was supported by Universiti Teknologi MARA, Malaysia [Bestari Perdana Research Grant (600-IRMI/DANA 5/3/BESTARI (P) 006/2018), DUCS 2.0 Research Grant (600-UiTMSEL (PI. 5/4) 008/2020) and Integrative Pharmacogenomics Institute (iPROMISE), Universiti Teknologi MARA, Malaysia grant (241810/2017/RMJJ/14)].

CONFLICT OF INTEREST STATEMENT

The authors agree that this research was conducted in the absence of any self-benefits, commercial or financial conflicts and declare absence of conflicting interests with the funders.

REFERENCES

[1] Hassan, R. (2017). Personality traits and academic achievement among college students. *Scholarly Research Journal for Interdisciplinary Studies*, *4*(29), 4382–4388.

[2] Seman, K., & Ismail, Z. (2019). Big Five Personality Traits on Academic Performance Among Foundation Students. *Asian Social Science and Humanities Research Journal (ASHREJ)*, *1*(2), 28-35.

[3] Ab Razak, W. M. W., Baharom, S. A. S., Abdullah, Z., Hamdan, H., Abd Aziz, N. U., & Anuar, A. I. M. (2019). Academic Performance of University Students: A Case in a Higher Learning Institution. *KnE Social Sciences*, 1294-1304.

[4] Osman, Z., Mohamad, W., Mohamad, R. K., Mohamad, L., & Sulaiman, T. F. T. (2018). Enhancing Students'academic Performance in Malaysian Online Distance Learning Institutions. *Asia Pacific Journal of Educators and Education*, *33*, 19-28.

[5] Bellander, M., Bäckman, L., Liu, T., Schjeide, B. M. M., Bertram, L., Schmiedek, F., Lindenberger, U., & Lövdén, M. (2015). Lower baseline performance but greater plasticity of working memory for carriers of the val allele of the COMT Val^{158}Met polymorphism. *Neuropsychology*, *29*(2), 247.

[6] Mestrovic, A. H., Tudor, L., Perkovic, M. N., Erjavec, G. N., Petrovic, Z. K., Strac, D. S., Konjevod, M., & Pivac, N. (2018). Significant association between catechol-O-methyltransferase (COMT) Val158/108Met polymorphism and cognitive function in veterans with PTSD. *Neuroscience Letters*, *666*, 38-43.

[7] Geller, S., Wilhelm, O., Wacker, J., Hamm, A., & Hildebrandt, A. (2017). Associations of

https://scilett-fsg.uitm.edu.my/
Vol. 15(2) JUNE 2021

ISSN: 1675-7785
eISSN: 2682-8626

DOI: 10.24191/sl.v15i2.13831

the COMT Val158Met polymorphism with working memory and intelligence–A review and meta-analysis. *Intelligence*, *65*, 75-92.

[8] Yeh, T. K., Chang, C. Y., Hu, C. Y., Yeh, T. C., & Lin, M. Y. (2009). Association of catechol-O-methyltransferase (COMT) polymorphism and academic achievement in a Chinese cohort. *Brain and Cognition*, *71*(3), 300-305.

[9] Kazantseva, A., Malykh, S., & Khusnutdinova, E. (2016). Molecular Genetic Investigations of Personality: From Candidate Genes to Genome-wide Associations. In *Behavioural Genetics for Education* (pp. 130-154). Palgrave Macmillan, London.

[10] Dickinson, D., & Elvevåg, B. (2009). Genes, cognition and brain through a COMT lens. *Neuroscience*, *164*(1), 72-87.

[11] Panitz, C., Sperl, M. F., Hennig, J., Klucken, T., Hermann, C., & Mueller, E. M. (2018). Fearfulness, neuroticism/anxiety, and COMT Val158Met in long-term fear conditioning and extinction. *Neurobiology of Learning and Memory*, *155*, 7-20.

[12] Gervasini, G., Gonzalez, L. M., Mota-Zamorano, S., Gamero-Villarroel, C., Carrillo, J. A., Flores, I., & Garcia-Herraiz, A. (2018). Association of COMT Val158Met polymorphism with psychopathological symptoms in patients with eating disorders. *Current Molecular Medicine*, *18*, 65-70.

[13] Chen, J., Lipska, B. K., Halim, N., Ma, Q. D., Matsumoto, M., Melhem, S., ... & Weinberger, D. R. (2004). Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): effects on mRNA, protein, and enzyme activity in postmortem human brain. *The American Journal of Human Genetics*, *75*(5), 807-821.

[14] Lotta, T., Vidgren, J., Tilgmann, C., Ulmanen, I., Melen, K., Julkunen, I., & Taskinen, J. (1995). Kinetics of human soluble and membrane-bound catechol O-methyltransferase: a revised mechanism and description of the thermolabile variant of the enzyme. *Biochemistry*, *34*(13), 4202-4210.

[15] Berryhill, M. E., Wiener, M., Stephens, J. A., Lohoff, F. W., & Coslett, H. B. (2013). COMT and ANKK1-Taq-Ia genetic polymorphisms influence visual working memory. *PloS one*, *8*(1).

[16] Egan, M. F., Goldberg, T. E., Kolachana, B. S., Callicott, J. H., Mazzanti, C. M., Straub, R. E., Goldman, D., & Weinberger, D. R. (2001). Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proceedings of the National Academy of Sciences*, *98*(12), 6917-6922.

[17] Mier, D., Kirsch, P., & Meyer-Lindenberg, A. (2010). Neural substrates of pleiotropic action of genetic variation in COMT: a meta-analysis. *Molecular Psychiatry*, *15*(9), 918-927.

[18] Lehto, K., Akkermann, K., Parik, J., Veidebaum, T., & Harro, J. (2013). Effect of COMT Val158Met polymorphism on personality traits and educational attainment in a longitudinal population representative study. *European Psychiatry*, *28*(8), 492-498.

[19] Palmatier, M. A., Kang, A. M., & Kidd, K. K. (1999). Global variation in the frequencies of functionally different catechol-O-methyltransferase alleles. *Biological Psychiatry*, *46*(4), 557-567.

[20] Bueno i Torrens, D. (2019). Genetics and learning: how the genes influence educational

https://scilett-fsg.uitm.edu.my/
Vol. 15(2) JUNE 2021

ISSN: 1675-7785
eISSN: 2682-8626

DOI: 10.24191/sl.v15i2.13831

attainment. *Frontiers in Psychology*, 10(1622).

[21] Nocera, F. D., Ricciardi, O., Abate, G., & Bevilacqua, A. (2017). Does the catechol-o-methyltransferase (COMT) Val158Met human polymorphism influence procrastination?. *Journal of Biological Sciences*, *1*, 27-36.

[22] Fauzi, M. F., Anuar, T. S., Teh, L. K., Lim, W. F., James, R. J., Ahmad, R., ... & Salleh, M. Z. (2021). Stress, anxiety and depression among a cohort of health sciences undergraduate students: the prevalence and risk factors. *International Journal of Environmental Research and Public Health*, *18*(6), 3269.

[23] Goldman, D., Weinberger, D. R., & Malhotra, A. K., & Goldberg, T. E. (2009). The role of COMT Val158Met in cognition. *Biological Psychiatry*, *1*(65). e1-e2.

[24] Hamidovic, A., Dlugos, A., Palmer, A. A., & de Wit, H. (2010). Catechol-O-methyltransferase val158met genotype modulates sustained attention in both the drug-free state and in response to amphetamine. *Psychiatric Genetics*, *20*(3), 85.

[25] Meyer-Lindenberg, A., & Weinberger, D. R. (2006). Intermediate phenotypes and genetic mechanisms of psychiatric disorders. *Nature Reviews Neuroscience*, *7*(10), 818-827.