Letter to the Editor

Identification of *AKT1* 3′UTR variants in two Indian schizophrenia patients with poor executive functioning

1. Introduction

Neurocognitive ability is a potential heritable phenotype for schizophrenia, with evidence of shared genetic aetiology between schizophrenia and cognitive impairment (Owens et al., 2011). The most important domains of cognition are working memory, attention, problem solving, and speed of processing.

V-Akt murine thymoma viral oncogene homolog 1 (*AKT1*) plays a role in modulating synaptic plasticity and signal transduction pathways (Freyberg et al., 2010). Deficiency in *AKT1* may lead to abnormal prefrontal cortical structure and deficits in cognitive functions (Lai et al., 2006). There is a lack of studies on functional variants at exonic and regulatory regions due to the difficulty in interpretation of their significance. Thus, we aimed to investigate these functional variants to identify their involvement in schizophrenia and cognitive impairment.

2. Case report

Two out-patients diagnosed with schizophrenia were recruited from Hospital Permai, Malaysia. Patient 1 was a 29 year old Indian male, diagnosed with schizophrenia at 22 years old. He has a younger brother who is affected by schizophrenia. He completed his primary education and has a history of alcohol and drug abuse. He was brought to the hospital by his mother, who appeared to be normal.

Patient 2 was a 33 year old Indian female. Her age at onset was 26 years old and has a younger brother who is a schizophrenia patient but medical history of her parents is unknown. Her highest education level was primary six.

Two unrelated males and three females of mixed-ethnicity were recruited as controls. Their mean age is 34.25 ± 11.30 years. All controls do not have family history of mental illness and their education level is above primary level.

Cognitive ability was assessed using Trail Making Tests (TMT). The standard time to complete TMT-A and TMT-B are 29 s and 75 s respectively. It is considered deficient if completion time exceeds 78 s for TMT-A and 273 s for TMT-B. Difference score B-A, ratio score B:A, and proportion score (B–A):A were calculated.

Specific locations on *AKT1* were targeted using Ion Torrent targeted genome sequencing (Life Technologies, USA). Exons, 3′ and 5′ untranslated regions (UTRs) were selected based on NCBI (hG19/GRCh37) coordinates.

3. Results

Patient 1 spent 53 seconds, while Patient 2 spent 115 s for TMT-A. For TMT-B, patient 1 obtained a score of 108 s, while Patient 2 required 223 s. Their cognitive performances fell below standard range, with Patient 2 exhibiting deficiency in executive functioning.

Patient 1 obtained B-A score of 55, B:A score of 2.04, and (B–A):A

score of 1.04; while Patient 2 obtained B-A score of 108, B:A score of 1.94, and (B–A):A score of 0.94. Higher B-A scores in Patient 2 indicated poor executive control function in absence of the speed factor. The moderate high B:A score of Patient 1 showed poor task-switching skill while (B-A):A score reflects his abnormality in prefrontal cortex functions. The average time for controls to complete TMT-A and TMT-B were 23 s and 55 s respectively. The mean B-A score obtained for controls was 31.70, B:A score was 2.32, and (B–A):A score was 1.32.

For genotyping, sixteen variants were identified in all subjects (Table 1). Two 3′ UTR and three intronic variants were identified in both patients but not in controls. Additional three intronic variants were observed in Patient 2. *In silico* variant functional prediction showed that rs58565216 serves as microRNA (miRNA)-messenger RNAs (mRNA) binding site for hsa-miR-3184-5p. The minor allele C was predicted to promote miRNA-mRNA binding and reduce gene expression of *AKT1*.

4. Discussion

Current results indicate deficit in both processing speed and executive performance in patients. Previous study reported a positive linear relationship between frontal lobe damage and TMT performance (Lange et al., 2005).

The 3′ UTR region in *AKT1* is associated with the risk for schizophrenia. Accumulation of miRNA expressions as a whole might provide a more convergent effect that would influence the magnitude of risk to schizophrenia (Beveridge et al., 2010). A recent study identified a putative functional variant, rs14403, at the 3′ UTR of *AKT3*, that might contribute to schizophrenia and impact the development of prefrontal cortical-mediated cognitive function (Howell et al., 2017).

Our results proposed the influence of *AKT1* polymorphisms on both processing speed and executive performance, which is consistent with the implication of *AKT1* on cognitive factors with relation to brain injury in prefrontal-striatal structure (Tan et al., 2008). In mice, *AKT1* deficiency was associated with abnormal prefrontal cortex structure and functions, which resulted in poor cognitive performances (Lai et al., 2006). Moreover, evidence also showed that genetic factor contributes to the TMT performances and it represents the link between schizophrenia and cognition (Owens et al., 2011).

Overall findings implicated association of *AKT1* variants with the risk of schizophrenia. 3′ UTR functional variant, rs58565216 may affect miRNA-mRNA binding and leads to disruption of gene expression, thus contributing to the risk of disease.

Declarations of interest

None.

Table 1
Variants of *AKT1* detected in patients and controls.

Position	SNP ID	Location	Ref/variant (1/2)	Genotype		
				Patient 1	Patient 2	Controls
105,235,558	rs2498801	downstream	T/C	1/1	1/2	1/1, 1/2, 2/2
105,235,824	rs58565216	3' UTR	G/C	1/2	1/2	1/1
105,236,287	rs35416681	3' UTR	A/C	1/2	1/2	1/1
105,237,026	rs150070451	intron	CCTCT/C-	1/1	1/2	1/1
105,238,591	rs55839843	intron	CCTGAG/ C-	1/1	1/2	1/1, 1/2, 2/2
105,238,604	rs2498800	intron	C/T	1/1	1/2	1/1, 1/2, 2/2
105,238,636	rs17846832	intron	G/A	1/1	1/2	1/1
105,238,670	rs8192700	intron	C/T	1/2	1/2	1/1
105,239,146	rs3803304	intron	C/G	1/1	1/2	1/1
105,239,192	rs2494732	intron	T/C	1/1	1/2	1/1, 1/2, 2/2
105,240,111	rs3730362	intron	G/A	1/2	1/2	1/1
105,241,576	rs3730344	intron	G/A	1/2	1/2	1/1
105,242,831	rs3001371	intron	C/T	1/1	1/2	1/1, 1/2, 2/2
105,242,966	rs2494735	intron	T/C	1/2	1/2	1/1, 1/2, 2/2
105,246,325	rs2494737	intron	T/A	1/2	1/2	1/2, 2/2
105,246,681	rs35635404	intron	G/A	1/1	1/2	1/1

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