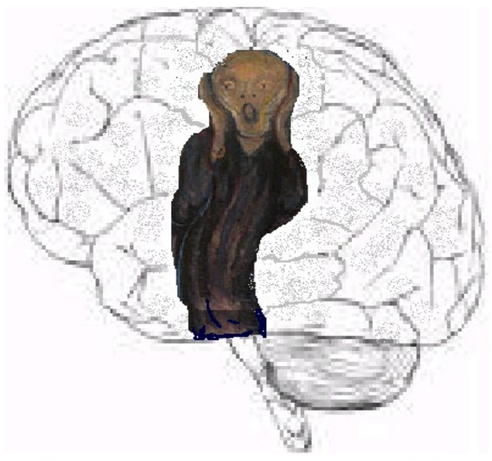

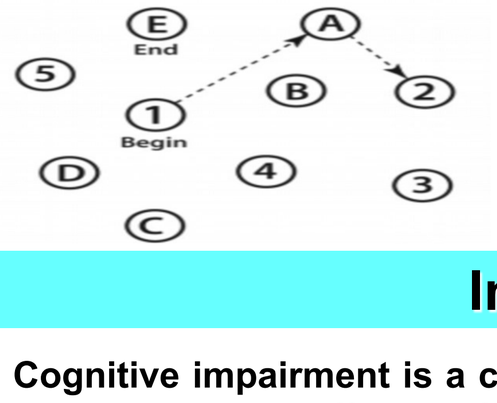

Microdeletions of Neurexin 1 (NRXN1) Conferring Risk of Cognitive Impairment: A Report of Family Cases with Schizophrenia

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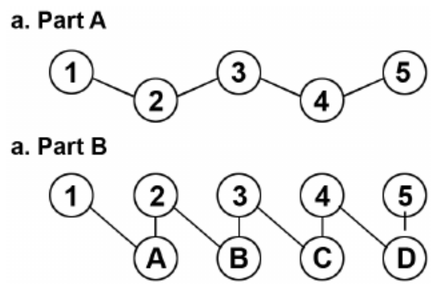

Introduction

Cognitive impairment is a core feature of schizophrenia. Studies found shared genetic effects of schizophrenia and cognitive impairment. NRXN1 gene on chromosome 2p, is responsible for low cognitive ability. Microdeletions in the NRXN1 gene have been associated with a range of neurodevelopmental disorders, including autism spectrum disorders, schizophrenia, intellectual disability, speech and language delay, epilepsy and hypotonia (Al Shehhi et al., 2019).

The objective of this study is to evaluate the relationship between the copy number variation (CNV) in NRXN1 gene and cognitive impairment in schizophrenia family patients .

Materials & Methods

Subjects

THREE schizophrenia families consisted of seven patients were recruited from Hospital Permai, Johor Bahru, Malaysia. They were diagnosed with schizophrenia and met the DSM-IV criteria. They were structurally interviewed by experienced psychiatrists using the Mini International Neuropsychiatric Interview (MINI). Informed consent was obtained.

Molecular Analysis

Peripheral blood samples were collected from all subjects. Genomic DNA has been extracted. A duplex TaqMan real-time quantitative polymerase chain reaction (qPCR) method used to call for CNVs of these seven regions. All assays were commercially available (Applied Biosystems, USA) (Table 1).

Statistical Analysis

The detected copy number with a cut-off value of less than 1.77 copies was designated as copy number loss, while the copy number with a value greater than 2.23 was classified as gained segment (Capizziet al., 2011).

Results

Cognitive functions

All patients took longer than average time to complete both tests (Figure 1).

For TMT-A, P1 and P4 have mild cognitive impairment (>78s).
P7 = marginal score (= 75s)

For TMT-B, P4 = Poorest Performance was achieved by (228s).
P3 = Highest Cognitive Performance (107s)

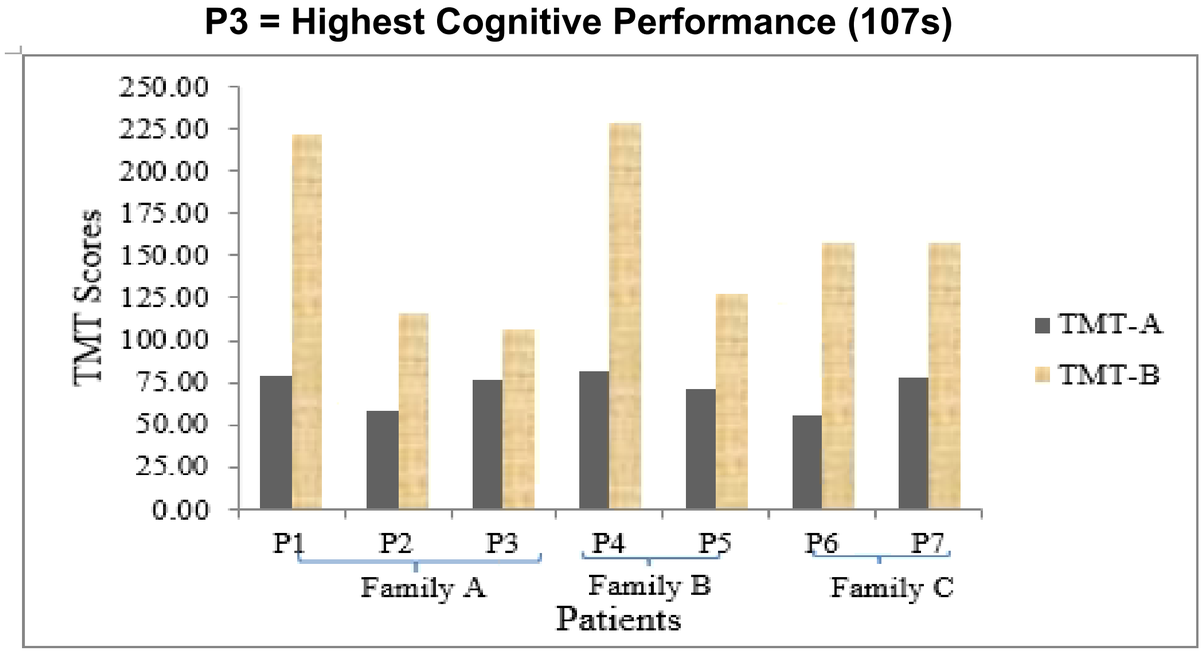

Figure 1: Cognitive performance of THREE families with schizophrenia.

CNV Analysis

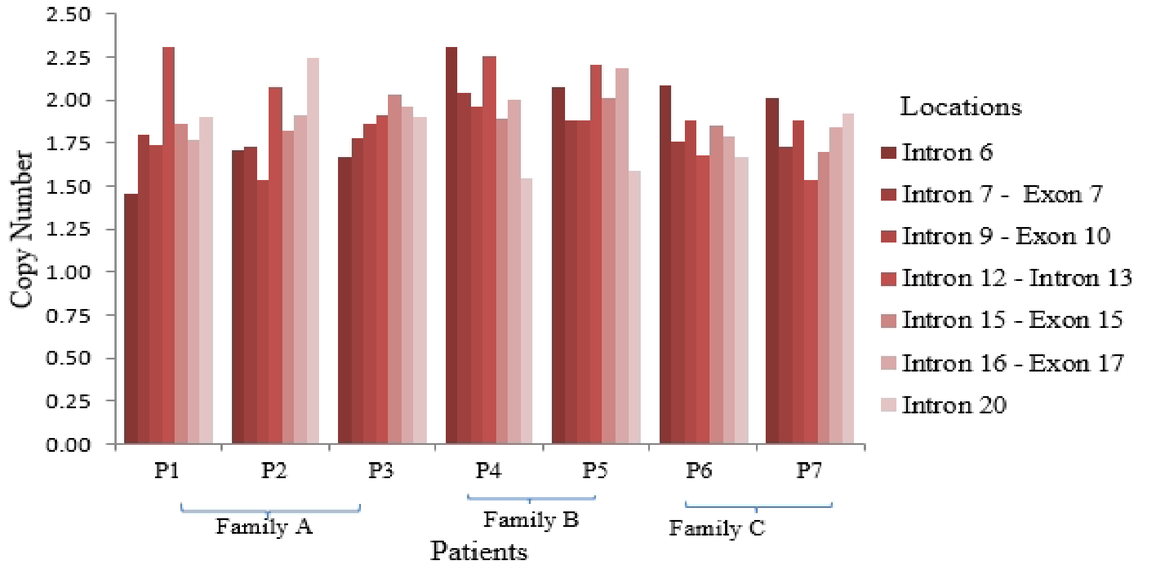

Figure 2: Copy gain and loss variations in selected regions of NRXN1 observed in THREE families with schizophrenia.

Among the seven studied NRXN1 regions, only two intronic deletions were detected. The genomic midpoint of NRXN1 is located in intron 5 (Hu et al, 2019). We observed both deletions were located in the 3' half (chr2: 49999147–chr2: 50658073, 658 kb) of the region shown in Figure 2.

Table 1: : Seven regions in NRXN1 gene in this study.

Assay	Location	Targeted position
Hs04655378_cn	Chr2:50916609	Intron 6
Hs01321892_cn	Chr2:50850463	Intron 7 – exon 7
Hs00349838_cn	Chr2:50780123	Intron 9 – exon 10
Hs01745979_cn	Chr2:50755753	Intron 12 – intron 13
Hs02921447_cn	Chr2:50724517	Intron 15 – exon 15
Hs02861396_cn	Chr2:50699549	Intron 16 – exon 17
Hs04692971_cn	Chr2:50428586	Intron 20

Discussion

In our study, we found deletions in more distal introns, which were intron 6 and intron 20 in schizophrenia patients with poorer cognitive performance.

Curran et al. (2013) found that deletions in the intron 3 and intron 5 in NRXN1 also confer neurodevelopment disorders.

One possible explanation is that some intronic deletions in NRXN1 can lead to the deletion of essential regulatory elements in the gene, such as alternative promoters, enhancers, or sequences involved in the complex splicing which generates various isoforms of NRXN1 mRNA (Curran et al., 2013).

In conclusion, we found deletions in the 5' half of the NRXN1 region are potential shared genetic risk factors for schizophrenia and cognitive impairment.

Acknowledgement

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