A report of schizophrenia in a patient with chromosome 3p26 deletion

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ABSTRACT

A 41-year-old female patient presented at a psychiatric clinic at Ramathibodi Hospital. She was diagnosed as having schizophrenia 11 years ago (under the DSM-IV-TR criteria). She appeared to have poor insight and poor compliance. She had both visual and auditory hallucination. She also had suicidal thought, but never attempted because of embarrassment. The patient's past medical record and family history showed that she consumed 1-2 bottles of alcohol per day. She has already been divorced twice. Her parents were also divorced. Other members in her family have no psychiatric history. Single nucleotide polymorphism (SNP) array revealed a 4.7-Mb deletion on the short arm of chromosome 3 within bands p26.1-3p26.3 encompassing *CNTN4* and *CNTN6*, which are genes associated with intellectual disability/developmental delay (ID/DD), growth retardation, and dysmorphic features. This deletion results in chromosome 3p26 deletion syndrome and is linked to autism spectrum disorders (ASD). Multiple genes in the aberrant region play a role in synaptogenesis, synaptic transmission, and neurological development. Interestingly, chromosomal aberration in this region has not been previously reported to be associated with schizophrenia. This finding suggests that patients with 3p26 microdeletion have a potential to exhibit neuropsychiatric symptoms and that 3p26 might be a novel candidate locus for schizophrenia.

Keywords: schizophrenia; CNV; SNP array; 3p26 microdeletion

INTRODUCTION

Schizophrenia (SZ) is a severe and chronic mental disorder that causes a wide range of psychological symptoms. Patients often completely lose touch with reality. They may experience delusion and hallucination. They also have a disruption of normal emotions such as lack of motivation, difficulty beginning and sustaining relationships. Schizophrenia is multifactorial in origin in which the disorder is contributed by both genetic and environmental factors. The onset of schizophrenia usually occurs between late adolescence and early adulthood (Owen *et al*., 2016). It affects approximately 1% of the population worldwide (Buckley, 2008). In the Thai population, the prevalence of schizophrenia at ages 15-59 is 8.8 per 1,000 (Phanthunane *et al*., 2010).

One of the principle factors playing a role in the development of schizophrenia is genetic predisposition which we focus in this study. It is previously known that many different genes contribute to the susceptibility of the disorder, and the risk is higher in people who have relatives with this mental illness (Kendler and Diehl, 1993). Several evidences demonstrated that copy number variations (CNVs), an important component of genetic variation, encompass genes leading to dosage imbalances. These imbalances might be an underlying cause of many diseases including neurodevelopmental/neuropsychiatric disorders.

Chromosomal microarray analysis (CMA) including array comparative genomic hybridization (aCGH) and single nucleotide polymorphism (SNP) array are commonly used for CNV detection. CMA can provide the diagnosis of microduplication/ microdeletion syndromes, which can be further explained on the basis of genotype–phenotype correlations. In this study, we report a female schizophrenic patient with terminal 3p26.3 deletion.

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The common clinical manifestations of 3p26.3 deletion include facial dysmorphic features, developmental delay, learning difficulties, ptosis and other eyesight issues, hypotonia, kidney problems, and heart conditions. However, these characteristics are absent in this patient who mainly exhibits neuropsychiatric phenotypes. We therefore propose the 3p26.1-3p26.3 regions as a novel candidate locus for schizophrenia.

MATERIALS AND METHODS

Ethics statement

This research project has been reviewed and approved by the Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine Ramathibodi Hospital, Mahidol University, based on the Declaration of Helsinki, protocol number ID 09-59-48. Patient was recruited from a psychiatric clinic at Ramathibodi Hospital.

Single Nucleotide Polymorphism (SNP) array assay and data analysis

A total of 200 ng genomic DNA was screened for SNP and CNV using the Infinium CytoSNP-850K v1.1 BeadChip kit (Illumina, USA). Data produced from Infinium assays was initially analyzed using Illumina GenomeStudio V2011.1 software. CNV analysis was performed using BlueFuse Multi 4.3 software. The clinical interpretation of CNVs was subsequently assessed based on contents from several databases including DGV (MacDonald *et al*., 2014), DECIPHER (Firth *et al*., 2009), ISCA/ClinGen (http://www.iscaconsortium.org/), Thai CNV (Suktitipat *et al*., 2014), and Thai ASD cohort (Hnoonual *et al*., 2017).

Functional annotation

Gene annotation was conducted by WEB-based GEne SeT AnaLysis Toolkit (http://www.webgestalt.org/).

RESULTS AND DISCUSSION

Case presentation

A 41-year-old female patient was diagnosed with paranoid schizophrenia. She appeared to have poor insight and poor compliance. She had delusion and both visual and auditory hallucinations. She was employed and had history of excessive alcohol consumption. She once had a thought to commit suicide, and that she was controlled by black magic. She had euthymic mood with intermittent aggression. Her speech was relevant and coherent. She had no history of developmental delay (speech and motor). She denied other comorbidities or underlying diseases. Other members in her family have no psychiatric history (Figure 1).

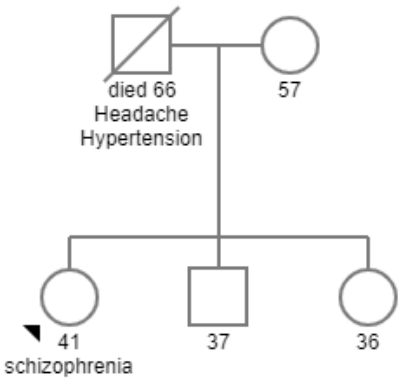

Figure 1 A 2-generation pedigree chart of our patient's family in which the proband is indicated by black arrow. Unfilled shapes without arrow indicate unaffected individuals. Squares and circles represent males and females respectively.

SNP array results

SNP-based CMA (Illumina Infinium CytoSNP-850Kv1.1 BeadChip) identified a 4.7-Mb deletion of chromosomal bands 3p26.1-3p26.3 encompassing 9 OMIM genes; *CHL1* (*607416), *CNTN6* (*607220), *CNTN4* (*607280), *IL5RA* (*147851), *TRNT1* (*612907), *CRBN* (*609262), *SUMF1* (*607939), *SETMAR* (*609834), *ITPR1* (*147265) as shown in Table 1. The log R ratio (LRR) and B allele frequency (BAF) plots (Figures 2A & 2B) from BlueFuse Multi 4.3 software indicated a large terminal deletion covering the aforementioned genes as shown in the UCSC hg19 Genome Browser (Figure 2C). Interestingly, this deletion was known to be associated with 3p deletion syndrome, however the association of schizophrenic phenotype has not been previously reported. 3p deletion syndrome is a rare contiguous gene disorder involving the disruption of the terminal of short (p) arm of chromosome 3. Individuals with this deletion typically have dysmorphic features, developmental delay, intellectual disability, ptosis, prominent nose or nasal bridge, and growth retardation (Fernandez *et al*., 2008; Pohjola *et al*., 2010). The deletion that we found contained *CNTN4* and *CNTN6*, which regulate the neuronal network formation and play an important role in various neurodevelopmental disorders such as autism spectrum disorder, seizures, and attention deficit hyperactivity disorder (Hu *et al*., 2015; Repnikova *et al*., 2020). These two genes are the members of the neural immunoglobulin superfamily that function as

an axon-associated cell adhesion molecule. They are mainly expressed in brain (Mu *et al*., 2018; Zeng *et al*., 2002). A recent case report indicated the association between *CNTN6* and schizophrenia in a patient with schizophrenia and epilepsy whose microarray finding showed a 200-Kb deletion of chromosome 3p26.3 encompassing exons 21 and 22 of *CNTN6* (Juan-Perez *et al*., 2018). This evidence strongly suggests that *CNTN6* deletion may be responsible for the schizophrenia phenotype seen in our 3p26 microdeletion syndrome patient. Other deleted genes, *CHL1* and *CRBN*, also are abundantly expressed in brain and are considered as critical genes for mental development (Cuoco *et al*., 2011). *ITPR1* acts as second messenger enriched in cerebellar Purkinje cells. Of note, most of the genes in the aberrant region have neurological functions.

Since most reported 3p26 microdeletion cases are *de novo* (Cuoco *et al*., 2011; Malmgren *et al*., 2007; Pohjola *et al*., 2010), and the parental samples of this patient was not available, familial segregation was not analysed.

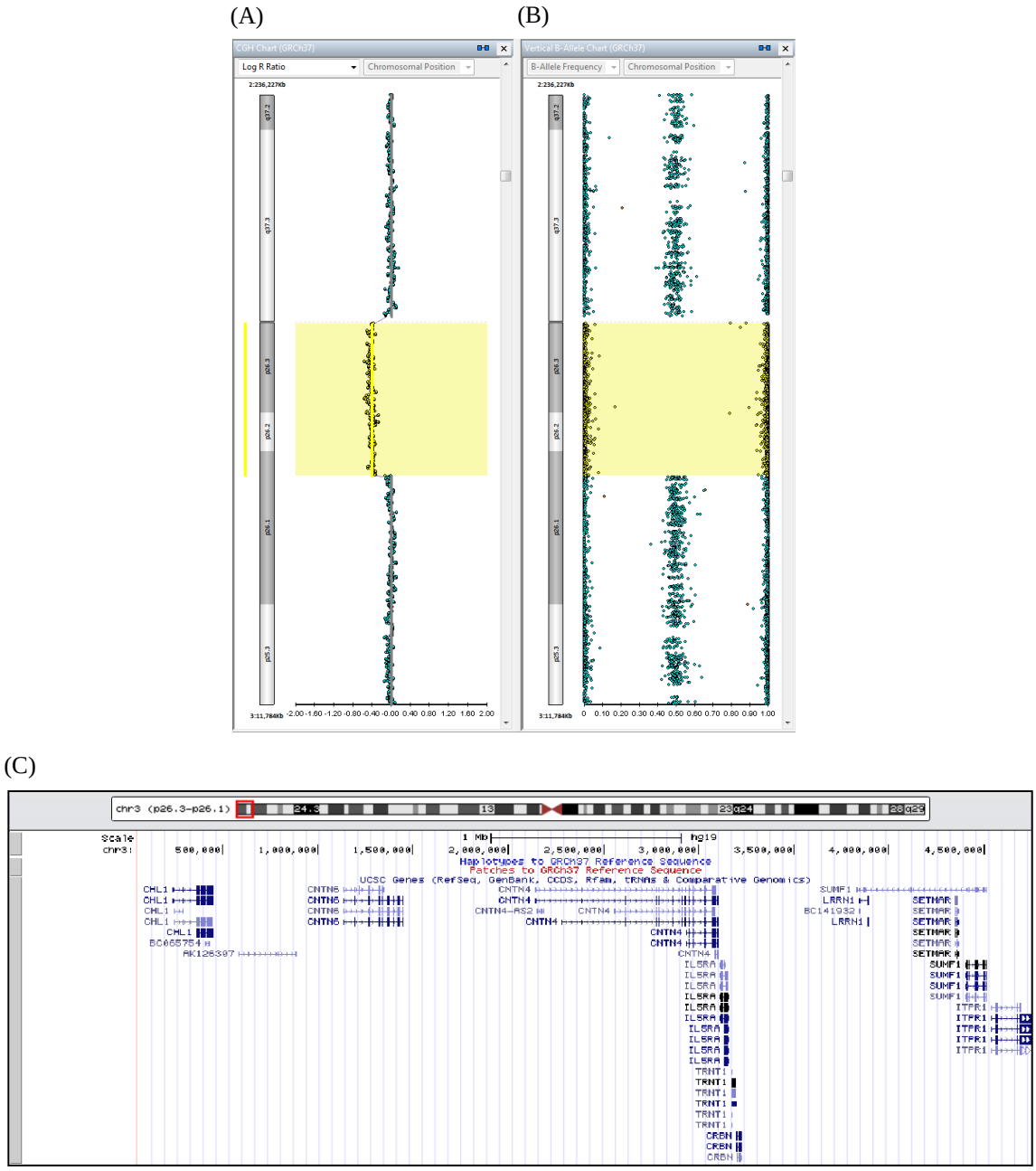

Figure 2 The LRR (A) and BAF (B) plots revealing a terminal deletion of chromosome 3p26.1-3p26.3 covering 9 OMIM genes (C) in our patient as shown in pale yellow highlight.

Functional annotation

Due to the compelling results in which no previous report provides the apparent explanations on genotype-phenotype correlation in this patient, we sought to explore the possible biological insights of the genes in the deleted region using the *in silico* method. WebGestalt was then used for gene annotation. Those 9 OMIM genes spanning chromosome 3p26.1-3p26.3 region were annotated based on the context of biological process. The most significant enrichment result was "gene set: GO:0097485 neuron projection guidance" with the *P*-value of 0.00041554. This gene set is associated with the process in which the migration of a neuron projection is directed to a specific target site in response to a combination of attractive and repulsive cues. Three out of 9 genes in this deleted region mapped within this gene set (gene set size: 260) as shown in Figure 3. These 3 genes include *CHL1*, *CNTN4*, and *CNTN6*, all of which play a critical role in neuronal development (Table 2).

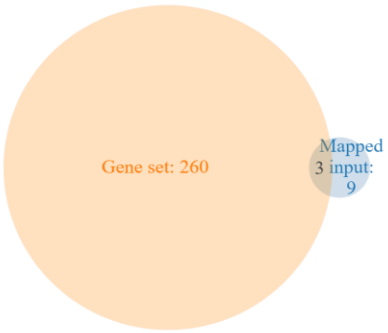

Figure 3 A Venn diagram showing 3 out of 9 genes mapped within GO:0097485.

Directed acyclic graph (DAG) was also created in order to see the plausible biological process network (Figure 4). The colored gradient of dark to light blue is based on the small to large number of FDR value respectively. The critical gene sets consisted of GO:0097485 neuron projection guidance, GO:0061564 axon development (the neighborhood), and GO:0008037 cell recognition. Likewise, the recent studies reported that gene polymorphisms related to axon guidance pathway probably confer the risk of schizophrenia (Wang *et al*., 2018). Moreover, the unusual effect of neuron projection can result from the alterations of white matter neuron which is considered as one of the pathogenesis of schizophrenia (Connor *et al*., 2011). Altogether, these results support that the disruption of genes in chromosome 3p26.1-3p26.3 region, which are associated with the projection of neuron and neuronal development, has a potential to cause additional neuropsychiatric phenotypes other than those of neurodevelopment commonly seen in patients with terminal 3p deletion.

To our knowledge, our patient is among the first reported cases of chromosome 3p26 deletion with schizophrenia, thus establishing schizophrenia as a possible new phenotype of this syndrome. Our findings also provide the plausible explanations why the neuropsychiatric phenotypes can result from the aberration at 3p26.1-3p26.3, and suggest this region as a novel candidate locus for schizophrenia. However, due to the challenges in conducting a detailed genotype-phenotype correlation resulting from incomplete penetrance, variable expressivity, and the possible existence of additional unknown genetic aberrations shared by most neuropsychiatric and neurodevelopmental disorders (Girirajan and Eichler, 2010), further studies using a larger sample size should help verify the schizophrenia phenotype in this syndrome.

Table 1 Pathogenic CNV identified in our patient.

Chromosome band	Chromosome position (hg19)	Loss/gain	Size (bp)	Genes
3p26.3-3p26.1	chr3:61,495-4,750,674	loss	4,689,180	*CHL1*, *CNTN6*, *CNTN4*, *IL5RA*, *TRNT1*, *CRBN*, *SUMF1*, *SETMAR*, *ITPR1*

Table 2 The 3 genes that were mapped within gene set: GO:0097485.

Gene symbol	Gene name	Entrez gene ID
CHL1	cell adhesion molecule L1 like	10752
CNTN4	contactin 4	152330
CNTN6	contactin 6	27255

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