

A Case of Schizophrenia with Chromosomal Microdeletion of 17p11.2 Containing a Myelin-Related Gene *PMP22*

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Abstract: We report a patient with schizophrenia who had a chromosomal deletion of 17p11.2 containing a myelin-related gene *PMP22* by using comparative genomic hybridization (CGH) array and quantitative PCR. Since genetic linkage to 17p11, reduced expression of *PMP22*, and alterations in myelination have previously been reported, this report further suggests an etiological role of *PMP22* in schizophrenia.

Keywords: Schizophrenia, *PMP22*, 17p11.2.

INTRODUCTION

Chromosomal aberrations found in patients with schizophrenia have provided possibly important insights into the molecular mechanism of the illness [1,2], although such aberrations are rare [3]. For example, 22q11 deletion syndrome (22q11DS) is a well known risk factor for schizophrenia [4]. *DISC1*, which is one of promising candidate genes of schizophrenia, was found as a disrupted gene by chromosomal translocation [5,6]. In this context, we have been screening chromosomal abnormalities by using the array comparative genomic hybridization (CGH) in 42 schizophrenia subjects and found a patient who had a chromosomal microdeletion of 17p11.2 containing the myelin-related gene, *PMP22*. *PMP22* is causal to Charcot-Marie-Tooth neuropathy type 1A (CMT1A) [7] and hereditary neuropathy with liability to pressure palsies (HNPP) [8]. Three copies of *PMP22* (duplication) result in CMT1A, while one copy (deletion) in HNPP. Patients with CMT1A have reduced nerve conduction velocities [9]. HNPP is characterized by diverse sensory or motor nerve palsies which are often precipitated by minor trauma.

CASE REPORT

Case History

The proband was 32-year-old man who was the first child of reportedly unrelated parents. He had a surgical operation

for inguinal herniation when he was 2 months old. According to his mother, the development of his verbal communication was delayed. When he was 11 years old, he lost consciousness for a few minutes with no apparent external event inducing such loss of consciousness; however, no abnormality was detected with electroencephalography or the computed tomography (CT) scan of the head immediately after the loss of consciousness. The CT film is not available now because the brain CT scan was carried out more than 20 years ago in another hospital. He entered ordinary elementary and junior high schools without receiving any special education. Although he went on to enter a high school, he dropped out at the age of 17 years. When he was 19 years old, auditory hallucination and delusion of persecution developed. Six months later, he started antipsychotic treatment at a psychiatric clinic. Then he was introduced to our hospital to control his psychotic symptoms and adverse effects (tremor) induced by the antipsychotics with a clinical diagnosis of schizophrenia and mental retardation. Finally, his psychiatric symptoms and tremor were controlled by 100mg floropipamide, 2mg trihexyphenidyl, and 1mg biperiden. He had never showed motor paralysis or sensory disturbance. His intelligence quotient (IQ) was 42 by the Wechsler adult intelligence scale-revised (WAIS-R) [10] at the age of 29 years. Laboratory tests for blood and urine did not show any abnormality. His final diagnoses were schizophrenia and mental retardation, according to the structured interview of DSM-IV [11, 12].

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This study was approved by the ethics committee of the National Center of Neurology and Psychiatry, Tokyo, Japan. Written informed consent was obtained from the proband and his parents to perform chromosomal examination, and publish this case report.

Family History

His father was a professor of a university and his mother was a housewife with normal social function. Structural interview by Mini-International Neuropsychiatric Interview [13,14] did not indicate any present or past psychiatric diagnosis in his parents. The proband had a younger sister who had no current or past history of psychiatric illness according to the parents.

Array CGH Findings

The proband participated in our ongoing screening of chromosomal abnormalities in a series of patients with schizophrenia. Chromosomal abnormalities were assessed with the array CGH method developed by Miyake *et al.* [15] using a newly developed 4.2K microarray with 4,235 FISHed BAC clones. A typical 1.4-Mb microdeletion at 17p11.2, containing *PMP22*, was identified. The deletion was also confirmed by fluorescence *in situ* hybridization (FISH) analysis (Fig. 1).

Quantitative PCR for Copy Number Variation

We examined copy number of *PMP22* for the proband and his parents by the quantitative PCR of genomic DNA. TaqMan probes were chosen, and delta-delta Ct method was applied, according to a previous study [16]. Quantitative PCR was done with the ABI prism 7900 (Applied Biosystems, Foster city, CA, USA). A Delta-delta Ct value around 0.5 indicates that the copy number of the gene is one and the value around 1 means two copies. The delta-delta Ct values of the proband, his father, and his mother were 0.65, 0.50, and 1.06, respectively, suggesting that the microdeletion of the proband was transmitted from his father.

Neurological Assessment

A clinical neurologist assessed neurological symptoms of the proband. However, no symptom of HNPP was apparent including abnormality of deep tendon reflex. A nerve conduction study was carried out for the proband; however, the result was within normal limit except for the distal motor latency of right tibial nerve. He does not show *pes cavus* or hammer toes. These findings are incongruent with the phenotype of *PMP22* deletion described by Mouton *et al.* [17]. His father did not report any neurological symptoms, either, although a nerve conduction study was not carried out for him.

DISCUSSION

We report a case of schizophrenia who had a microdeletion of chromosome 17p11.2 containing a myelin-related gene, *PMP22*. To our knowledge, this is the first report of such a case. Chromosomal microdeletion was confirmed by FISH and RT-PCR in addition to the initial array CGH method. Thus it is unlikely that the detected deletion was an

artifact, although the case we report here was asymptomatic with respect to HNPP and had no clear family history of HNPP. Mouton *et al.* [17] investigated 99 individuals with the 17p11.2 deletion in 22 families and found that fourteen individuals showed no symptom. Thus asymptomatic individuals like our case seem to be not rare.

It is possible that coexistence of schizophrenia and the deletion of 17p11.2 in the proband may have occurred by simple coincidence. The absence of psychiatric history in the proband's father, who had the same deletion, further supports such a possibility. However, it is also possible that incomplete penetrance of the genetic effect of the deletion may explain the discrepancy in psychiatric condition between the proband and his father. Indeed, several lines of evidence in addition to our case have suggested that *PMP22* may play a role in the pathogenesis of schizophrenia. Dracheva *et al.* [18] reported that mRNA of *PMP22* was reduced in the hippocampus and anterior cingulate cortex in post mortem brains of schizophrenia. *PMP22* is highly expressed and plays a critical role in functions of oligodendrocytes, which accords with previous studies indicating the oligodendrocyte dysfunction in schizophrenia [19,20,21]. Decreased number of perineuronal oligodendrocytes was reported in the prefrontal cortex of patients with schizophrenia [22]. Transgenic mice which have oligodendrocyte dysfunction have increased levels of dopamine receptors and transporters [23]. Then defects in white matter can cause hyper-dopaminergic symptoms (e.g. delusion and hallucination). Reduced fraction anisotropy in white matter of patients with schizophrenia by a diffusion tensor imaging study [24] may due to oligodendrocyte dysfunction. Oligodendrocytes produce trophic factors such as brain derived neurotrophic factor (BDNF) [25] and neuregulins (NRGs) [26]. BDNF and NRG1 are believed in playing an important role in the etiology of schizophrenia. *PMP22* dysfunction may decrease the function of BDNF [27] and NRG1 [28]. Finally, some genome wide linkage studies provide evidence for linkage to 17p11.2-q25.1 in schizophrenic pedigrees [29,30,31]. To further elucidate the possible role of *PMP22* in schizophrenia, molecular genetic studies and psychiatric examination on individuals with CMT1A and HNPP are warranted.

CONCLUSIONS

In conclusion, we found a patient with schizophrenia who had a chromosomal microdeletion of 17p11.2 containing *PMP22*, a gene critical to oligodendrocyte functions. Since reduced expression of *PMP22*, alterations in oligodendrocyte functions, and genetic linkage to 17p11 have previously been reported, our case further supports an etiological role of *PMP22* in schizophrenia.

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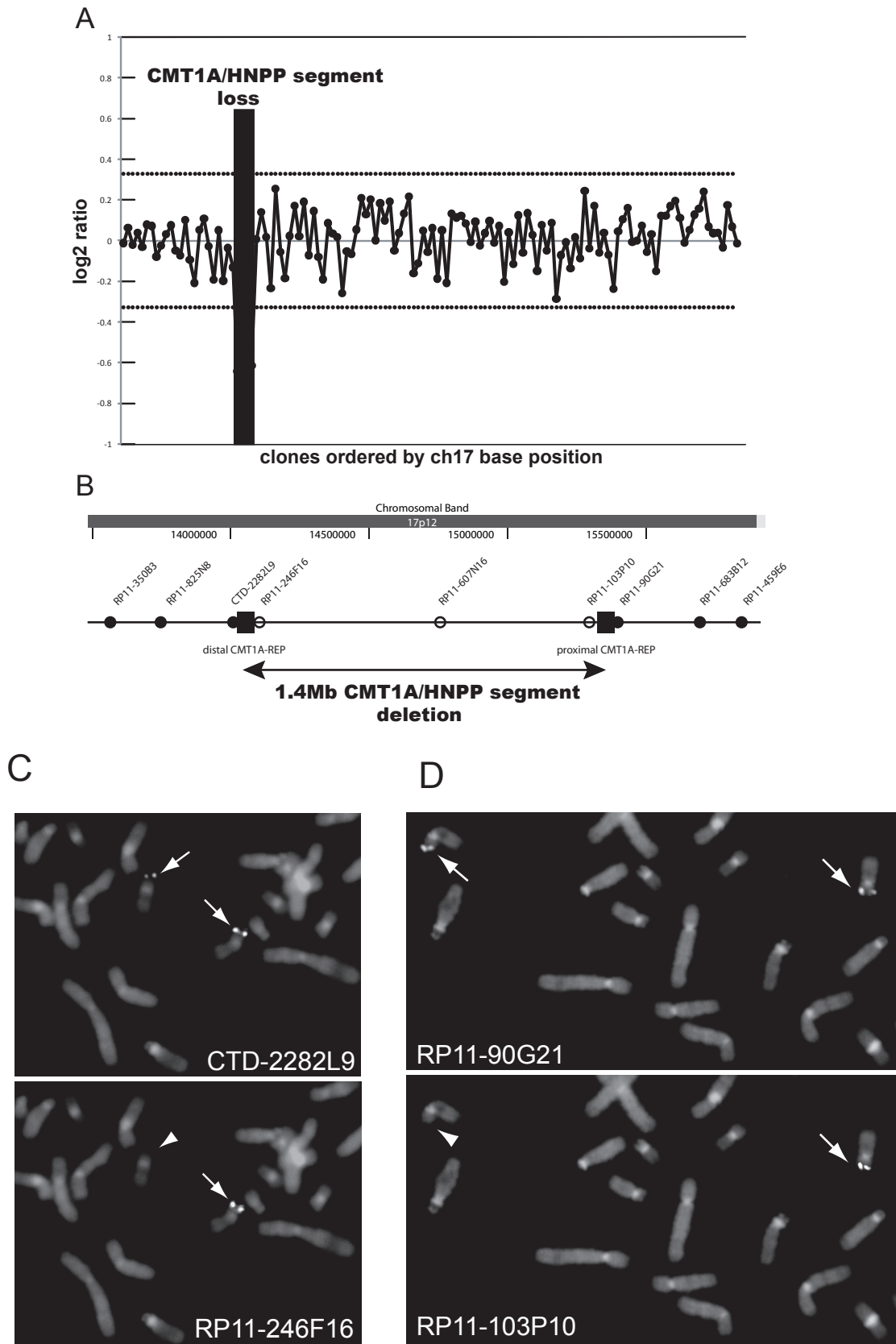


Fig. (1). (A) Microarray CGH analysis showing deletions at CMT1A/HNPP locus. (B) Schematic presentation of BAC clones delineating the CMT1A/HNPP deletion in the patient. Open circle: BAC clone deleted in the patient, closed circle: BAC clone not deleted in the patient. Closed square: low copy repeat which may have mediated genomic rearrangements. A common 1.4-Mb deletion of HNPP occurs between proximal CMT1A-REP and distal CMT1A-REP. (C,D) BAC FISH analysis in the proband. Arrows show intact signals in 17p11.2 region. Arrow heads show the loss of signal in 17p11.2 region. Clone positions are indicated in Fig. (1B).

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