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CASE REPORT

Treatment-resistant schizophrenia with 22q11.2 deletion and additional genetic defects

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Abstract

We report a case of a 61-year-old female with 22q11.2 deletion syndrome (22q11.2DS) and a novel heterozygous nonsense variant in *MAP1A*, identified through whole-genome sequencing (WGS). The patient presented with intellectual developmental disorder, treatment-resistant schizophrenia (SCZ), and multiple congenital anomalies. Despite aggressive pharmacotherapy, she experienced persistent auditory hallucinations and negative symptoms. WGS revealed a 3 Mb deletion at 22q11.2 and a nonsense variant in *MAP1A* (c.4652T>G, p.Leu1551*). *MAP1A*, encoding microtubule-associated protein 1A, is crucial for axon and dendrite development and has been implicated in autism spectrum disorder and SCZ. The *MAP1A* variant may contribute to the severe psychiatric phenotype, as it is thought to influence synaptic plasticity, a process also affected by 22q11.2 deletion. This case highlights the importance of WGS in identifying additional pathogenic variants that may explain phenotypic variability in 22q11.2DS. Thus, WGS can lead to a better understanding of the genetic architecture of 22q11.2DS. However, further studies are needed to elucidate the role of secondary genetic contributors in the diverse clinical presentations of 22q11.2DS.

KEYWORDS
22q11.2 deletion syndrome, genetics: Human, schizophrenia: Clinical, treatment-resistant schizophrenia, whole-genome sequencing

1 | INTRODUCTION

22q11.2 deletion syndrome (22q11.2DS) is the most prevalent chromosomal microdeletion disorder, with an estimated occurrence of one in 3000–4000 live births, primarily resulting from nonallelic homologous recombination.[1] The main clinical features of 22q11.2DS include congenital heart disease, palatal anomalies, immune deficiencies, distinctive facial characteristics, and psychiatric disorders.[1] Notably, 22q11.2DS is recognized as one of the most potent genetic risk factors for schizophrenia (SCZ).[2] Intellectual developmental disorder (IDD), autism spectrum disorder (ASD), attention deficit/hyperactivity disorder (ADHD), or mood disorders are frequently observed in patients with 22q11.2DS.[2]

The 22q11.2 deletion region contains genes involved in neurodevelopment, several of which play crucial roles in synaptic function.[3] In line with this, abnormalities in synaptic function, including impaired dendrite and spine development, have been observed in a mouse model of 22q11.2DS.[4] These synaptic dysfunctions are thought to disrupt the neural circuitry between the hippocampus and prefrontal cortex.[5] Thus, synaptic and circuit-level disturbances may play a crucial role in the pathogenesis of psychiatric symptoms and cognitive deficits associated with 22q11.2 deletion.

The psychiatric manifestations and symptom severity in 22q11.2DS exhibit remarkable variability among affected individuals, and the penetrance of the deletion is incomplete.[2,6] While some patients may present with severe psychotic symptoms and develop SCZ, others may exhibit milder cognitive and behavioral impairments. This phenotypic variability and incomplete penetrance indicate that 22q11.2 deletion alone is not sufficient to explain the diverse clinical outcomes fully, and additional genetic factors likely contribute to the variable expressivity observed in 22q11.2DS. Rare genetic variants outside the 22q11.2 deletion region may contribute to the variability in psychiatric symptom expression in 22q11.2DS,[7] which indicates that these second-hit variants that affect genes related to synaptic function and neurodevelopment may modulate the risk of SCZ in individuals with 22q11.2DS. These findings highlight the potential role of genetic factors beyond the primary 22q11.2 deletion in shaping the phenotypic heterogeneity observed in this syndrome.

In this case report, we present a patient with treatment-resistant SCZ who carried the 22q11.2 deletion along with a psychiatric disorder-related variant (a nonsense variant in the *MAP1A* gene). MAP1A is involved in synaptic plasticity,[8] and the combination of 22q11.2 deletion and the *MAP1A* variant may have had an additive effect, resulting in severe psychiatric symptoms in this patient.

2 | CASE PRESENTATION

The patient was a 61-year-old female with moderate IDD and SCZ. Her medical history included ventricular septal defect, atrial septal defect, dysmorphic features, cleft palate, unspecified hernia, epilepsy with yearly generalized tonic–clonic seizures, hypocalcemia, allergic dermatitis, and dyslipidemia. She did not have significant immune dysfunction. Her mother had dementia with Lewy bodies, no other family member had psychiatric symptoms (Figure 1A). The patient was born as the first child among five siblings to parents who were both 23 years old at the time of her birth. A detailed developmental history could not be obtained. She was diagnosed with IDD at age 8 years and attended a special needs school. At age 12 years, she underwent surgical closure for atrial and ventricular septal defects. She had been free from symptoms of heart failure up to the time of this report. After graduation, she worked in cleaning or factory roles. She married at age 32 years but divorced a year later without having children. At age 36 years, she began experiencing hallucinations and delusional persecution, leading to a diagnosis of SCZ. She was hospitalized in a psychiatric ward and experienced auditory hallucinations in which a young man hurled abusive language at her even after hospitalization. Influenced by these auditory hallucinations, she experienced a constantly unstable mood and high irritability. She persistently engaged in impulsive behaviors such as breaking glass and overturning tables. She had delusions that the person appearing in her auditory hallucinations was after her assets. She experienced suicidal thoughts because of these auditory hallucinations and engaged in self-harm, cutting her own arms. Soliloquy was prominently observed. In her 40s, she was prescribed haloperidol (9 mg), risperidone (3 mg), chlorpromazine (100 mg), olanzapine (10 mg), levomepromazine (50 mg), clonazepam (3 mg), and carbamazepine (600 mg). The chlorpromazine equivalent dose of antipsychotics was 1300 mg. Anticonvulsants were prescribed for not only the management of epilepsy but also their mood-stabilizing effects. Despite this aggressive pharmacological intervention with multiple antipsychotics, her positive symptoms persisted, leading to a diagnosis of treatment-resistant SCZ (see the Supporting information).[9] Over a 20-year period, she was hospitalized more than 10 times. During her hospitalizations, she frequently felt agitated and called out, which led to complaints from other patients. In recent years, due to negative symptoms, she has shown little interest in her surroundings and has been leading a withdrawn lifestyle. At age 60 years, she was hospitalized in a general hospital because of tetany, convulsions, and diagnosed hypocalcemia. At the time, she had concurrent cellulitis as a spreading infection that triggered hypocalcemia. Medications at age 61 years were olanzapine (10 mg), risperidone (2 mg), and clonazepam (3 mg). Despite this treatment, she experienced persistent auditory hallucinations. Brain computed tomography performed at age 59 years showed bilateral basal ganglia calcifications (Figure 1B).

To investigate the underlying factors contributing to treatment-resistant SCZ, we performed whole-genome sequencing (WGS) (Details are provided in the Supporting information). As a result, a 22q11.2 deletion (hg38 chr22:18897001-21131000) was detected (Figure 1C). Thus, the patient was diagnosed with 22q11.2DS. In addition, a novel heterozygous nonsense variant in exon 4 of *MAP1A* was detected [NM_002373: c.4652T>G, p.Leu1551*; hg38 chr15:g.43526125T>G] (Figure 1D,E). *MAP1A* is highly conserved, with a probability of being loss-of-function intolerant score of 1. This variant is located on the middle of the gene (Figure 1D), resulting in

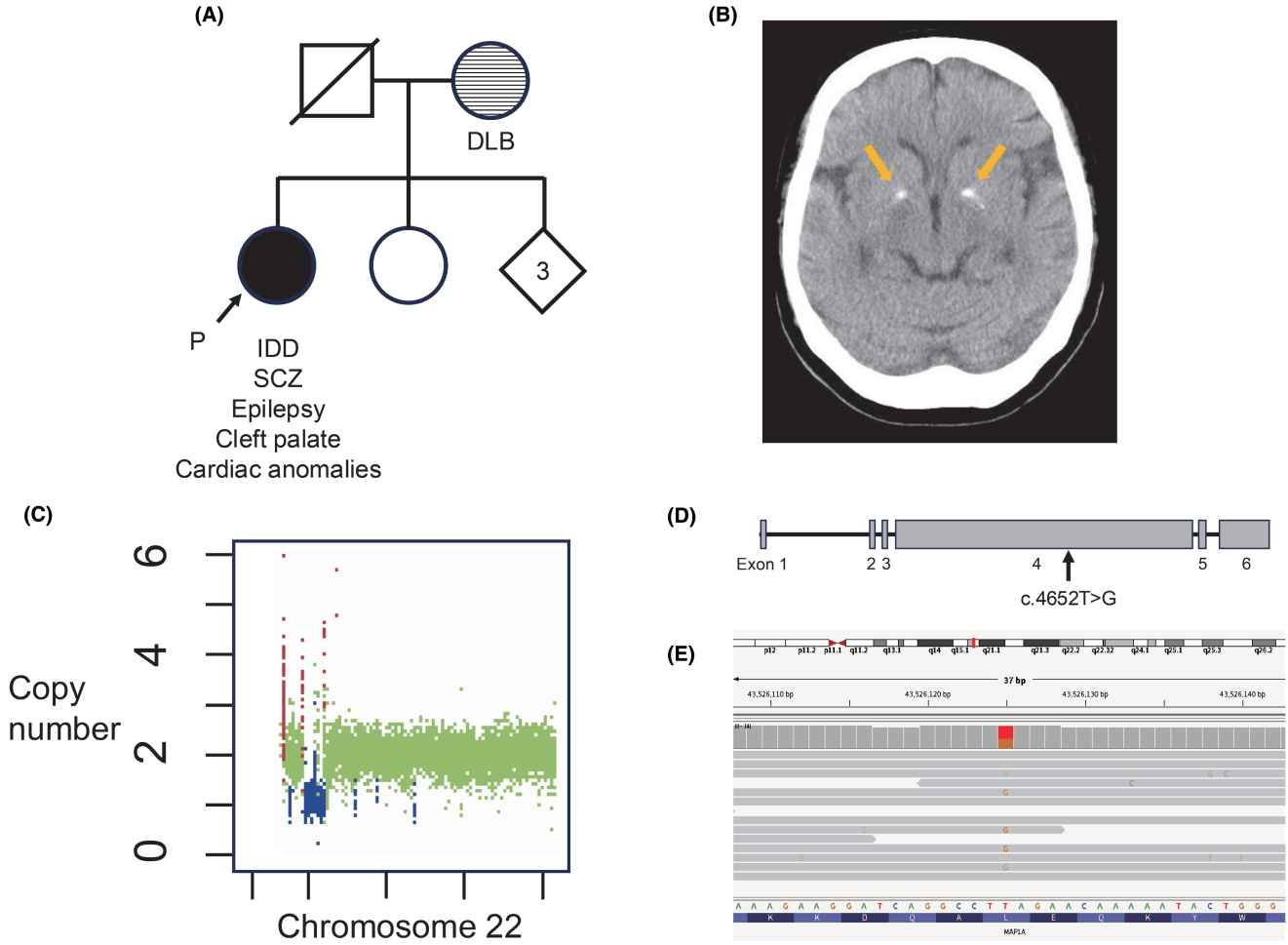

FIGURE 1 Clinical and genetic characterization of the patient. A) Pedigree of the patient's family. The proband is indicated by an arrow. Filled symbols represent affected individuals, and open symbols represent unaffected individuals. DLB, Dementia with Lewy bodies; IDD, Intellectual developmental disorder; SCZ, Schizophrenia. (B) Brain computed tomography image from when the patient was age 59 years. (C) The 22q11.2 deletion identified by Control-FREEC. The deletion is shown in blue. (D) Schematic representation of the exon structure of *MAP1A*. (E) Integrative Genomics Viewer snapshot of the *MAP1A* nonsense variant.

the production of truncated MAP1A protein. No other pathogenic variants, including STRs, were detected in this patient.

3 | DISCUSSION

In this report, we presented a case of a 61-year-old female with IDD, SCZ, and multiple comorbidities who exhibited treatment-resistant positive symptoms despite aggressive pharmacotherapy, frequent psychiatric hospitalizations, and negative symptoms. As mentioned above, patients with 22q11.2DS exhibit notable phenotypic variability.[2,6,7,10] If records from early childhood were available, a diagnosis of ASD and/or ADHD might have been made. The patient exhibited high irritability, which may have been attributable to her underlying sensory hypersensitivities,[11] leading to increased distress and agitation.

In addition to genetic factors, environmental factors may also contribute to the phenotypic variability in 22q11.2DS.[12] To the best of our knowledge, no clear environmental factors, such as poverty, abuse, or bullying, were identified. However, it is conceivable that the patient's experience of divorce before the onset of positive symptoms could have contributed to the development of SCZ, as stressful life events are known to be associated with an increased risk of psychosis.[13]

While there is no evidence for association between 22q11.2DS and treatment resistance, a recent study has reported an increased prevalence of pathogenic CNVs in individuals with treatment-resistant psychosis compared to those with treatment-responsive psychosis.[14] Moreover, we previously reported more severe phenotypes in patients with two pathogenic CNVs.[15] Based on these findings, we hypothesized that additional genetic factors might have contributed to the development of treatment resistance in this case.

We identified a nonsense variant in *MAP1A* by WGS in addition to 22q11.2DS. Large-scale whole-exome sequencing studies have reported that the *MAP1A* nonsense variant is strongly associated

with ASD.[16,17] Microtubule-associated protein (MAP) 1A, the protein coded by *MAP1A*, is predominantly expressed in neurons and crucial for the formation and development of axons and dendrites.[18] MAP1A interacts with postsynaptic density protein PSD-95[19] and DISC1 (Disrupted-In-Schizophrenia 1).[20] MAP1A anchors *N*-methyl-D-aspartate receptors to the cytoskeleton, stabilizes postsynaptic density scaffolds, and plays a crucial role in the maintenance of synaptic plasticity in the postsynapse.[8] The mouse model of 22q11.2DS presents abnormal synaptic plasticity in the presynapse.[4] Therefore, the 22q11.2 deletion and nonsense variants in *MAP1A* are both thought to influence synaptic plasticity, contributing to the severe phenotype observed in this patient. However, the inheritance pattern of the *MAP1A* variant was unknown, the extent to which this variant has influenced the patient's phenotype remains unclear, and further studies are needed to elucidate the role of secondary genetic hits in modulating the clinical presentation of individuals with 22q11.2DS.

In conclusion, we identified a 22q11.2 deletion and a nonsense variant in *MAP1A* in a patient with treatment-resistant SCZ. These findings indicate that WGS is crucial for gaining a deeper understanding of the genetic architecture of treatment-resistant SCZ. Furthermore, a nonsense variant in *MAP1A* was detected, which might explain the severe psychiatric phenotype. By utilizing WGS, it is possible to examine patients with 22q11.2DS in greater detail, potentially leading to a more comprehensive understanding of the patient's pathology and treatment options.

AUTHOR CONTRIBUTIONS

S.F. and I.K. designed the study. S.F. and I.K. performed the genetic analysis. S.F., I.K., S.A., H.K., and N.O. recruited the participants and/or collected DNA samples or phenotype data. S.F. and I.K. wrote the first draft of the manuscript, and the other authors commented on and refined the manuscript. All authors carefully read the manuscript and approved the final version for submission.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in this article and its supporting information files.

ETHICS STATEMENT

Approval of the Research Protocol by an Institutional Reviewer Board: This study was approved by the ethics committee of Nagoya University Graduate School of Medicine (2010-1033). This study complied with all the provisions of the Declaration of Helsinki.

Informed consent: Written informed consent was obtained from the patient.

Registry and the Registration No. of the Study/Trial: N/A.

Animal Studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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