

[CASE REPORT]

Copy Number Variations in a Case with Intractable Epilepsy, Intellectual Disability, and Hereditary Neuropathy with Liability to Pressure Palsies Having a 17p12 Deletion

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Abstract:

Some copy number variations (CNVs) in DNA are associated with the development of pathological phenotypes. Regarding the diagnosis of recurrent radial nerve palsies, a 73-year-old female patient with intractable epilepsy and intellectual disability was diagnosed with duplicated 15q11.1-11.2, in addition to a deletion of 17p12, causing hereditary neuropathy with liability to pressure palsies. CNVs in 15q11.1-11.2 have been reported in patients with schizophrenia and autism. Although CNVs are also sometimes seen in healthy individuals, duplicated 15q11.1-11.2 could be associated with CNS symptoms in this patient.

Key words: copy number variation, hereditary neuropathy with liability of pressure palsies, intractable epilepsy, intellectual disability

(Intern Med Advance Publication)

(DOI: 10.2169/internalmedicine.4811-24)

Introduction

Some copy number variations (CNVs) in DNA are associated with the development of pathological phenotypes including cardiovascular diseases, autoimmune diseases, cancer, and neurodegenerative diseases (1, 2). CNVs have been identified as important risk factors for neuropsychiatric disorders such as schizophrenia, autism, intellectual disability, and depression (3).

I herein describe a female patient who was followed up for intractable epilepsy and intellectual disability. The patient's chromosome was analyzed to diagnose recurrent radial nerve palsy. A duplication of 15q11.1-11.2 was discovered as a candidate cause of epilepsy and intellectual disability.

Case Report

A 73-year-old woman presented with a loss of control of her left hand. She had intractable epilepsy since her late twenties and intellectual disability and had been followed up for eight years. She was not a diabetic or alcohol drinker. A

neurological examination revealed left radial nerve palsy. She had experienced radial nerve palsy four years previously, and it recurred three months previously. The palsy in the right radial nerve resolved completely. She had a medical history of miscarriage, surgery for cervical canal stenosis, and sepsis after acute pyelonephritis. She was admitted to the hospital several times for epilepsy, which included either a complex partial seizure or secondary generalized convulsion. The patient was treated with levetiracetam, valproate, zonisamide, and lacosamide. However, epileptic attacks were observed at least once a month. The patient's parents were unconsanguineous. She had a healthy son. The patient was hyperlogically insensitive. The Wechsler Adult Intelligence Scale-III, performed at the age of 68 years, was VIQ 61, PIQ 59, and FIQ 57. The electroencephalogram detected generalized spike and wave complexes. Computed tomography (CT) of her head did not reveal cortical dysplasia, ischemic lesions, or brain tumors. A nerve conduction study (NCS; Table) was performed during the first episode of radial nerve palsy. The amplitude of the motor and sensory nerve action potentials decreased. The conduction velocity was different among her nerves, from normal to a severe decrease, thus suggesting a mixture of demyelination and ax-

Table. Nerve Conduction Study at the First Episode of Radial Nerve Palsy.

Motor Nerve Conduction Study							
	TL (msec)	MCV (m/sec)	CMAP (mV)	Temporal Dispersion	Conduction Block	F wave Minimal Latency	F wave Occurrence
R Median	6.0	37.7	3.8	(-)	(-)	41.8	1/16
L Median	5.8	52.9	5.0	(-)	(-)	31.0	2/16
R Ulnar	5.8	35.1	3.6	(-)	(-)	39.7	3/16
L Ulnar	5.1	39.2	5.7	(-)	(-)	35.1	6/16
R Radial	2.9	61.2	1.9	(-)	(-)		
L Radial	2.7	49.6	1.1	(-)	(-)		
R Tibial	5.0	22.7	0.13	(+)	(-)	Not evoked	
Sensory Nerve Conduction Study							
	TL (msec)	SCV (m/sec)	SNAP (μ V)	Temporal Dispersion	Conduction Block		
R Median	4.3	34.9	2.0	(-)	(+)		
L Median	4.6	35.1	2.2	(-)	(+)		
R Ulnar	9.6	11.5	1.4	(+)	(+)		
L Ulnar	5.8	21.6	2.0	(+)	(+)		
R Radial	3.5	39.0	7.6	(-)			
L Radial	3.3	42.9	4.5	(-)			
R Sural	Not evoked						

TL: terminal latency, MCV: motor nerve conduction velocity, CMAP: compound muscle action potential, SCV: sensory nerve conduction velocity, SNAP: sensory nerve action potential

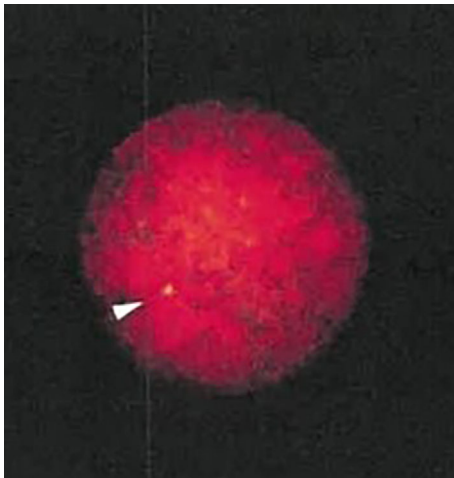


Figure 1. Fluorescent *in situ* hybridization to *PMP22* revealed heterozygous deletion of *PMP22*. Arrowhead indicates hybridized *PMP22*.

onal degeneration. On the second NCS after left radial nerve palsy, the motor nerve conduction velocity (MCV) of the ulnar nerve at the elbow (the usual compression sites) was 33.3 m/s bilaterally. The distal MCVs of the ulnar nerves were 36.6 m/s and 26.7 m/s (right and left), respectively. Although there was no family history of neuropathy, three cases of radial nerve palsy indicated hereditary neuropathy with liability to pressure palsies (HNPP). Fluorescent *in situ* hybridization (FISH) revealed deletion of *PMP22* (Fig. 1). However, since intractable epilepsy and intellectual disability are uncommon features of HNPP, her chromosome was analyzed further. G-banding test revealed that her karyotype

was 46, XX. Chromosomal microarray analysis (CMA) revealed gain of 5q21.2-21.3 (165-219 kb, GRCh37:5:104366033-104531844) and 15q11.1-11.2 (2.28-2.40 Mb, GRCh37:15:20416244-22698581), and loss of 10q11.2 (198-296 kb, GRCh37:10:46949255-47147501) and 17p12 (1.33-1.42Mb, GRCh37:17:14111772-15442066, Fig. 2).

Discussion

Repetitive radial nerve palsies were due to HNPP caused by the deletion of *PMP22* located on 17p12. The alterations in NCS at non-compression sites suggested the progression of HNPP. Smith-Magenis syndrome (SMS) is a disease resulting from the deletion of 17p11.2. Its symptoms include intellectual disability, insomnia, behavioral abnormalities, minor physical abnormalities, and epilepsy. The causal gene was *RAI1*. When the deletion in 17p was long, HNPP was complicated. Since CNVs of the contiguous gene *PMP22-RAI1* have been reported (4, 5), the chromosome was examined using CMA. However, *RAI1* was not included in the deleted region, and SMS deposits were ruled out. The size and location of the deleted site suggest that the deletion could result from two 24-kb low copy number repeats (CMT 1A-REPs), which are most frequently found in patients with HNPP (6, 7). The genes included in the 17p12 deletion in this case were *COX10*, *CDRT15*, *HS3ST3B1*, *MGC12916*, *LOC101928475*, *CDRT7*, *CDRT8*, *PMP22*, *MIR4731*, *TEKT3*, *TVP23C-CDRT4*, *CDRT4*, *CDRT3*, and *TVP23C*. Among these genes, biallelic *COX10* variants with *PMP22* deletions resulted in Leigh syndrome and HNPP. However, monoallelic *COX10* deletions do not cause Leigh syndrome (8). Al-

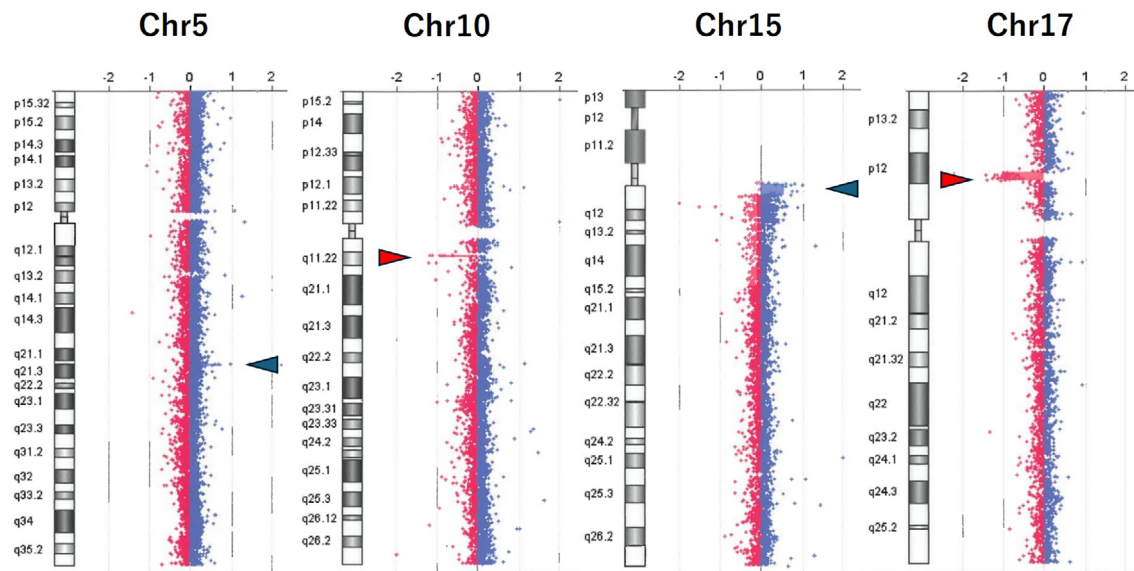


Figure 2. Chromosomal microarray analysis. Results of chromosomes 5, 10, 15, and 17 are shown. Blue columns and blue arrowheads are gains. Red columns and red arrowheads are losses.

though the sequence of *COX10* in another allele was not determined, the patient was not considered to have Leigh syndrome based on her clinical course and brain CT results. No other gene in this region has been reported to be associated with either intellectual disability or epilepsy.

CMA revealed another unexpected deletion, 10q11.22. No report has been found in association with intellectual disability and epilepsy with a brief deletion of 10q11.22. The genes in this region were *LOC101927699*, *LOC102724593*, *LOC102724488*, *SYT15*, *GPRIN2*, *NPY4R2*, *NPY4R*, *LINC00842*, and *HNRNPA1P33*. None of these have been reported to be related to intellectual disability or epilepsy. Deletion of 10q11.22 has been reported to be pathogenic to recurrent pregnancy loss (9).

CMA revealed two duplications. Duplication of 15q11.1-11.2 has been reported in schizophrenia patients (10). The patient also had a 22q11.2 deletion, which is known as DiGeorge syndrome. Another study reported that the deletion of 15q11.1-11.2 was one of the CNVs found in autistic children (11). A longer duplication, 15q11.1-13.1, is known to result in Dup15q syndrome characterized by hypotonia, developmental delay, epilepsy, and autism (12). The duplicated region in this case was included in the duplicated region of patient 14 with Dup15q syndrome in Borlot's report (13) and in an 11-month-old infant in Lu's report (14). Genes on the duplicated 15q11.1-11.2 in this case were *CHEK2P2*, *HERC2P3*, *LOC102723534*, *GOLGA6 L6*, *GOLGA8CP*, *NBEAP1*, *POTEB3*, *MIR3118-2*, *MIR3118-3*, *MIR3118-4*, *POTEB*, *POTEB2*, *NF1P2*, *MIR5701-2*, *MIR5701-3*, *MIR5701-1*, *LINC01193*, *LINC02203*, *FAM30C*, *LOC646214*, *CXADRP2*, *LOC101927079*, *OR4M2*, *OR4N4C*, *OR4N4*, *OR4N3P*, *IGHV1OR15-1*, *LOC102724760*, *IGHV1OR15-3*, *LOC642131*, *MIR1268A*, *REREP3*, *MIR4509-1*, *MIR4509-2*, and *MIR4509-3*. Among them, except for the pseudogene, non-protein coding gene, and micro RNA, *GOLGA6 L6*,

POTEB2, *POTEB*, *OR4M2*, and *OR4N4* overlapped in this case and a closely similar case reported by Takahashi et al. (10). However, a duplication of 15q11.1-11.2 was found in the controls in the database of genomic variants (GRCh37/hg19 at <http://dgv.tcag.ca/dgv/app/home>). It is still unknown which gene is responsible for neuropsychiatric disorders, such as schizophrenia and autism, and whether this duplication is a normal variant or pathogenic. A brief duplication of 5q21.2-21.3 contained *RAB9BP1*. However, no relationship between CNV or *RAB9BP1* and intellectual disability or epilepsy has previously been reported.

4.8-9.5% of the genome in healthy population contributes to CNV, and approximately 100 genes when completely deleted have no effect on the phenotype (15). Most CNV are located near pericentromeric regions (16). Iafrate et al. identified 255 loci of large-scale CNVs in 55 human DNA samples. In their report, a duplication of 15q11.1-11.2 was not present (16). This case report has limitations in concluding that a duplication of 15q11.1-11.2 could be associated with intractable epilepsy and intellectual disability in this patient. Other factors such as metabolic diseases, cannot be completely ruled out. CNVs of the patient's parents and son were not performed. However, considering the significance of the duplication of 15q11.1-11.2, it is important to accumulate other cases similar to this patient.

In conclusion, CMA should be considered in the diagnosis of patients presenting with unknown intractable epilepsy and intellectual disability, although the interpretation of the clinical importance of CNVs is limited.

The authors state that they have no Conflict of Interest (COI).

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