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CASE REPORT

A Japanese patient with a 2p25.3 terminal deletion presented with early-onset obesity, intellectual disability and diabetes mellitus: A case report

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ABSTRACT

2p25.3 deletion syndrome is a rare genetic disorder that accompanies various phenotypic features, including early-onset obesity and intellectual disability. Here, we report the first Japanese case of this deletion associated with severe obesity and diabetes mellitus. Microarray-based comparative genomic hybridization analysis identified a 3.1-Mb deletion of distal chromosome band 2p25.3, which was suspected as de novo. The patient also presented bilateral cataracts and adolescent-onset muscular weakness of the upper limbs, both of which were uncommon in previously reported cases. It is possible that these symptoms are also important clinical features suggestive of this syndrome.

INTRODUCTION

Recent advances in genetic approaches, such as genome-wide association studies and microarray-based comparative genomic hybridization, have identified numerous obesity-related genetic variants and abnormalities. Recently, several reports described individuals with 2p25.3 aberrations characterized by various symptoms, such as early-onset obesity, intellectual disability, developmental delay and strabismus[1,2]. Here, we report the first Japanese case of early-onset severe obesity associated with a terminal 2p25.3 deletion, who showed several uncommon features, such as bilateral cataracts, adolescent-onset muscular weakness and diabetes mellitus.

CASE REPORT

A 31-year-old Japanese woman was referred to Osaka University Hospital (Suita, Osaka, Japan) for the treatment of obesity and diabetes. She was born as the third child of unrelated healthy parents. Although she did not show any remarkable abnormalities, including muscular hypotonia, during the neonatal period, significant weight gain became apparent as early as 1 month after birth (Figure 1). Her motor development was normal, but she presented speech developmental delay and learning disabilities. Menarche occurred at 12 years-of-age, and she had a history of oligomenorrhea, probably due to obesity. When she was a high school student, she was aware of muscular weakness of the upper limbs, which gradually worsened. Her bodyweight had steadily increased, reaching >100 kg at 20 years-of-age. Gynecological examination found no evidence of polycystic ovarian syndrome. When she was 31 years-of-age, her blood test showed a fasting plasma glucose level of 255 mg/dL and glycosylated hemoglobin level of 9.7%, revealing severe diabetes mellitus. Then, she was admitted to our hospital for the treatment of obesity and diabetes.

At admission, she received no medication, except for progesterone replacement therapy. Her height, bodyweight and body mass index were 157.2 cm, 122.3 kg and 49.5 kg/m^2, respectively. She showed no distinct facial and body features, except

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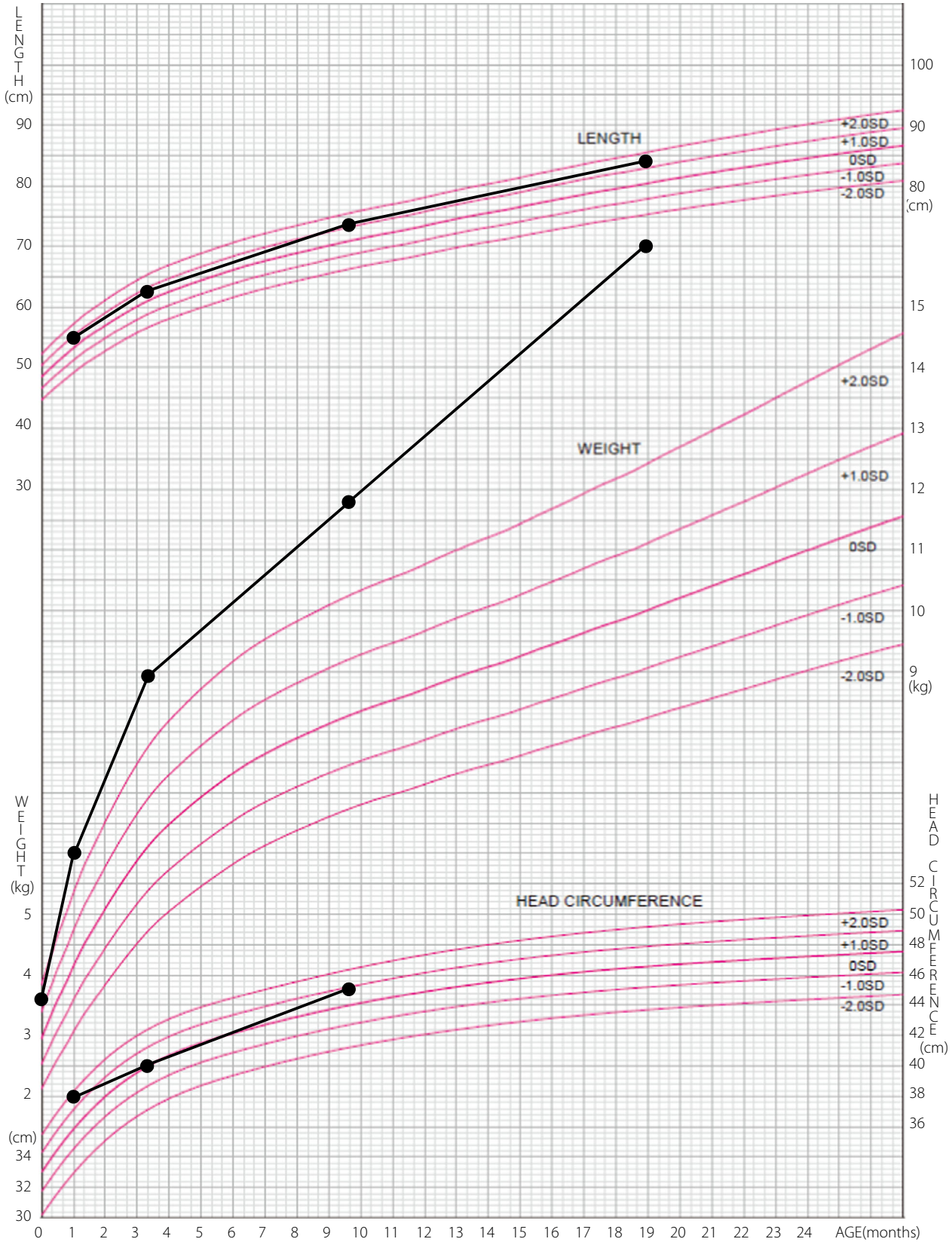

Figure 1 | The patient's growth charts from birth to 24 months. A significant weight gain (>2 standard deviations above the normal mean) was observed at 1 month after birth, and thereafter the patient's bodyweight had steadily increased. Information about length and head circumference at birth was not available. The source of growth charts for Japanese girls (0–24 months) is reprinted with permission from the Japanese Society for Pediatric Endocrinology.

for intermittent left external strabismus. Ophthalmological examination showed bilateral cataracts without diabetic retinopathy. Her intelligence quotient, determined by the Wechsler Adult Intelligence Scale, 3rd edition, was 54, indicating mild intellectual disability. Her laboratory data showed no indication of abnormalities in pituitary, adrenal and thyroid hormones (Table 1). Brain magnetic resonance imaging and abdominal computed tomography found no significant abnormalities except fatty liver. Abdominal computed tomography also showed visceral fat accumulation (visceral fat area at umbilical level 174 cm^2) with an excessive accumulation of subcutaneous fat (subcutaneous fat area at umbilical level 613 cm^2).

When hospitalized, muscular weakness of the upper limbs made it difficult for the patient to twist a plastic bottle open. Neurological examinations in both lower limbs were normal. In contrast, muscle strengths of the upper limbs were reduced to a degree of manual muscle test 4. In addition, her maximal handgrip strengths were as low as 5 kg/5 kg, despite the preserved fat-free mass evaluated by dual-energy X-ray absorptiometry (Table 2). Although we could not carry out muscle biopsy, there were no abnormalities in the motor nerve

Table 1 | Patient's laboratory data on admission

Variable	Result	Reference range	Variable	Result	Reference range
Blood cell counts and biochemical examinations			Hormonal examinations		
WBC (/μL)	7,410	3,300–9, 400	ACTH (pg/mL)	45	7–63
RBC ($\times10^4$/μL)	538	390–510	Cortisol (μg/dL)	15.4	4–18.3
Hemoglobin (g/dL)	14.2	12–15	DHEA–S (μg/dL)	216.5	25.9–460.2
Platelets ($\times10^3$/μL)	301	130–320	GH (ng/mL)	0.23	0.13–9.88
Total protein (g/dL)	6.8	6.4–8.1	IGF–1 (ng/mL)	119	129–304
Albumin (g/dL)	3.6	3.6–4.7	Prolactin (ng/mL)	11.6	4.1–27.9
AST (U/L)	62	<40	LH (mIU/mL)	2.9	1.1–8.1
ALT (U/L)	151	<40	FSH (mIU/mL)	6.7	4–14.2
γGTP (U/L)	31	8–51	Estradiol (pg/mL)	54	17–362.3
CK (U/L)	64	54–286	TSH (μIU/mL)	1.73	0.45–3.72
Creatinine (mg/dL)	0.4	0.5–0.9	FT4 (ng/dL)	1.5	0.8–1.7
Uric acid (mg/dL)	4.9	2.5–5.5	FT3 (pg/mL)	2.9	2.1–3.1
Sodium (mmol/L)	136	138–145	Adiponectin (μg/mL)	7.2	
Potassium (mmol/L)	3.9	3.6–4.8	Leptin (ng/mL)	94.1	
Calcium (mmol/L)	2.12	2.1–2.5	Autoantibodies		
Phosphorus (mmol/L)	1.2	0.9–1.5	ANA	<1:40	<1:40
T-Chol (mg/dL)	155	150–220	C–ANCA (U/mL)	<1.0	<3.5
Triglyceride (mg/dL)	71	30–150	P–ANCA (U/mL)	<1.0	<3.5
HDL-Chol (mg/dL)	48	40–80	Jo–1 Ab (U/mL)	<1.0	<10
LDL-Chol (mg/dL)	102	<140	ARS Ab (INDEX)	<5.0	<25
Vitamin B_1 (μg/dL)	4.4	2.6–5.8	AChR Ab (pmol/mL)	<0.2	<0.2
Vitamin B_{12} (pg/mL)	339	211–911	Diabetes marker		
Urine examinations			FPG (mg/dL)	204	70–110
U-CPR (μg/day)	99.5	48.7–97.7	Hemoglobin A1c (%)	10.4	4.6–6.2
U-Albumin (mg/day)	8.5	<10	IRI (μIU/L)	16.1	1.1–9.0
U-Cortisol (μg/day)	38.6	11.2–80.3	GAD Ab (U/mL)	<5	<5

γGTP, γ-glutamyl transpeptidase; AChR Ab, anti-acetylcholine receptor antibody; ACTH, adrenocorticotropic hormone; ALT, alanine aminotransferase; ANA, anti-nuclear antibody; ARS Ab, anti-aminoacyl-tRNA synthetase antibody; AST, alkaline phosphatase; C-ANCA, cytoplasmic antineutrophil cytoplasmic antibody; CK, creatine kinase; CPR, connecting peptide immunoreactivity; DHEA-S, dehydroepiandrosterone-sulfate; FPG, fasting plasma glucose; FSH, follicle-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; GAD Ab, anti-GAD antibody; GH, growth hormone; HDL-Chol, high-density lipoprotein cholesterol; IGF-1, insulin-like growth factor 1; IRI, immunoreactive insulin; Jo-1 Ab, anti-Jo-1 antibody; LDL-Chol, low-density lipoprotein cholesterol; LH, luteinizing hormone; P-ANCA, myeroperoxidase antineutrophil cytoplasmic antibody; PTH, parathyroid hormone; RBC, red blood cells; T-Chol, total cholesterol; TSH, thyroid-stimulating hormone; U, urinary; WBC, white blood cells.

Table 2 | Body composition results from dual-energy X-ray absorptiometry

	BMC (kg)	Fat mass (kg)	Fat-free mass (kg)	% Fat mass
Right arm	0.18	5.2	4.0	55.4
Left arm	0.17	5.1	3.9	55.7
Trunk	0.64	28.4	31.7	46.8
Right leg	0.4	6.4	9.6	39
Left leg	0.38	6.5	10.4	37.6
SMI (kg/m^2)	11.3			

Skeletal muscle index (SMI) was calculated by following the formula using the results of dual-energy X-ray absorption; muscle mass of arms and legs (kg) / height (m)^2. BMC, bone mineral content.

conduction study, magnetic resonance imaging of the cervical spine, and autoantibodies related to myositis and myasthenia gravis (Table 1).

We carried out further assessments of the patient's genetic background because of early-onset severe obesity accompanied by intellectual disability. By fluorescent *in situ* hybridization, no deletion was observed in chromosome 15q11.2, known as a causative region for Prader–Willi syndrome. Conventional G-banded chromosome analysis showed a loss of the distal region of the short arm of chromosome 2. Furthermore, microarray-based comparative genomic hybridization analysis identified a 3.1-Mb terminal deletion at chromosome band 2p25.3; arr [GRCh37] 2p25.3(42444_3172043) × 1 (Figure 2). No other pathogenic copy number variation was detected by microarray-based comparative genomic hybridization other than the 2p25.3 region. Both parents declined to be genotyped, but no relative showed similar clinical characteristics, suggesting the possibility of a de novo origin in this case. After 22 days of hospitalized treatment, her bodyweight was reduced to 116.6 kg by calorie restriction, together with remarkably improved glycemic control by taking 1,500 mg of metformin and 50 mg of sitagliptin. The clinical course over 2 years after discharge is shown in Figure S1.

DISCUSSION

To date, there have been 26 reported cases of a 2p25.3 deletion, sharing common clinical features of early-onset obesity and intellectual disability. To the best of our knowledge, this is the first report of this deletion in Japan.

Myelin transcription factor 1 gene (*MYT1L*) has been proposed as a strong candidate gene responsible for 2p25.3 deletion syndrome[3], because inheritance of *MYT1L* is classified into an autosomal dominant pattern in the Online Mendelian Inheritance in Man (https://omim.org/) and the probability of loss-of-function intolerance score of *MYT1L* is "1" in the Genome Aggregation Database (https://gnomad.broadinstitute.org/), indicating loss-of-function intolerance. Thus, *MYT1L* is the only gene in 2p25.3 that related to haploinsufficiency as a pathomechanism. *MYT1L* expresses mainly in the brain, suggesting its significant role in controlling appetite and cognitive function. Patients with single nucleotide variants in *MYT1L* show very similar characteristics, such as early-onset hyperphagic obesity and intellectual disability, to 2p25.3 deletion carriers[4]. In contrast, Windheuser *et al.* recently reported nominally significant evidence that overweight/obesity was more prevalent in patients with microdeletions in 2p25.3 than those with mutations affecting *MYT1L* only[5]. In addition to *MYT1L*, transmembrane protein 18 gene (*TMEM18*), which expresses widely in the brain including the hypothalamus, and acid phosphatase 1 gene, which expresses in adipocytes, are also reported as a possible association with the development of obesity in 2p25.3 deletion syndrome[2]. In addition, from the genome-wide association studies catalog (https://genome.gov/gwastudies/), several candidate single-nucleotide polymorphisms for obesity and/or body mass index were identified in the *TMEM18*, *SH3Y1* and *SNTG2* genes mapped to 2p25.3. Thus, contributions of the single-nucleotide polymorphism haplotypes in such genes cannot be denied.

The present case is unique in bilateral cataracts and progressive muscular weakness of the upper limbs, as these symptoms are uncommon in patients with a 2p25.3 deletion. Previously, only one patient was reported to show unilateral cataract at 8 years-of-age[2]. Peroxidasin gene (*PXDN*), located on 2p25.3, is essential for eye development in mice[6], and subjects with homozygous mutations in *PXDN* showed congenital cataracts[7]. Although some 2p25.3-deleted patients showed muscular hypotonia in the neonatal and infant period, adolescent-onset muscle weakness has not so far been reported in patients with a 2p25.3 deletion. However, recent genome-wide association studies results showed that single-nucleotide polymorphisms near *TMEM18* are associated with grip strength[8]. The complication of diabetes has also not been found in previous reports, despite the strong association of this syndrome with severe obesity. Compared with white people, Asian people are more susceptible to developing diabetes by weight gain[9], which might be involved in early disease progression in the present patient. In addition, patients reported in previous papers were relatively young (mostly <15 years), and, therefore, a further increase in the number of patients and follow-up studies is necessary to elucidate the long-term clinical course of this syndrome, including the incidence of cataracts, muscle weakness and diabetes.

In conclusion, we first report a Japanese patient with a 2p25.3 terminal deletion. In addition to early-onset obesity, this patient presented bilateral cataracts and upper limb weakness.

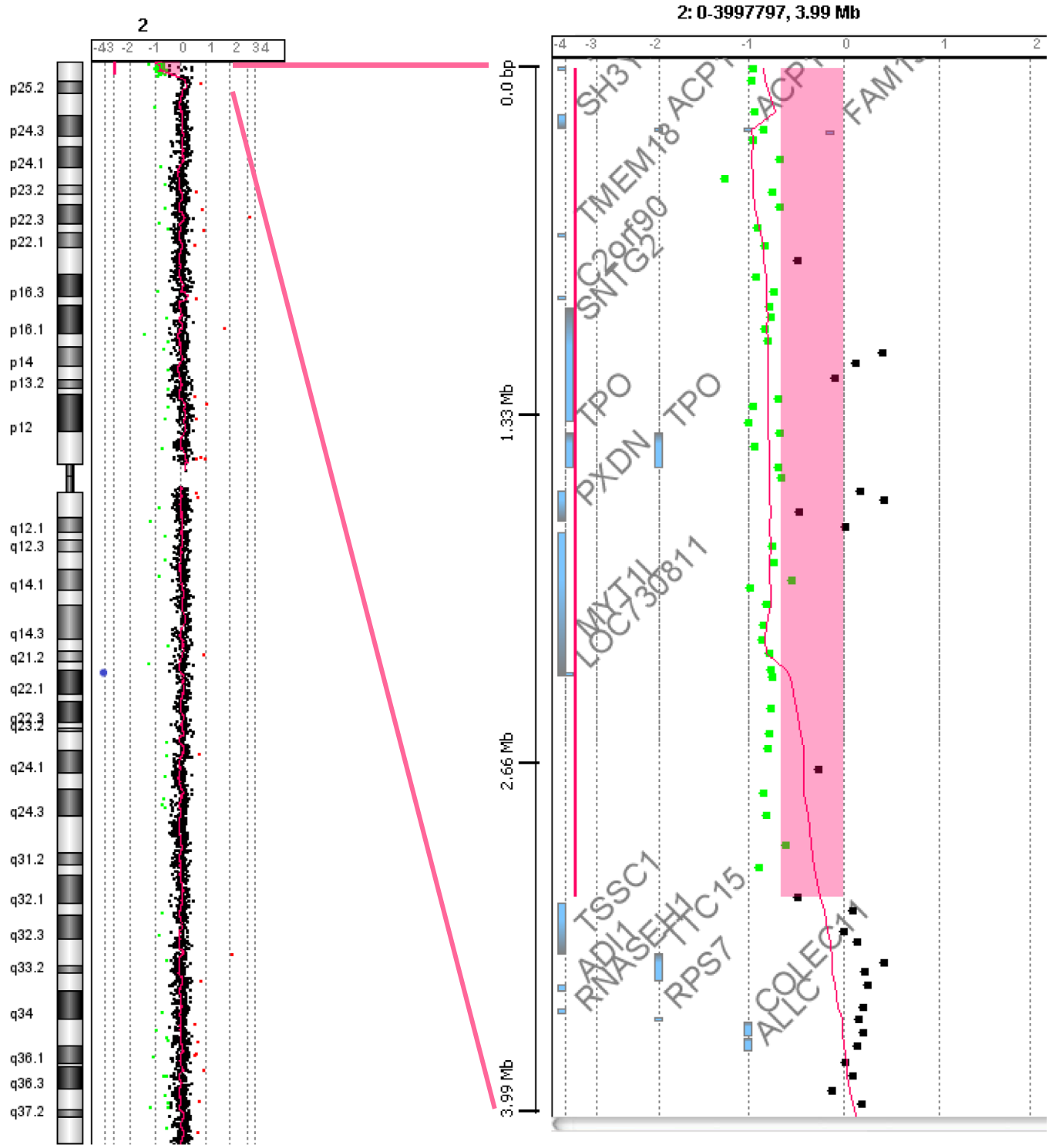

Figure 2 | Results of microarray-based comparative genomic hybridization (aCGH) for chromosome 2. The aCGH analysis was carried out using the Agilent SurePrint G3 Human CGH microarray kit 60K (Agilent Technologies, Santa Clara, CA, USA), as described previously[10]. The deleted region is shown by the red zone. The result of the aCGH analysis is shown by Chromosome View (left) and Gene View (right) constructed with Agilent Genomic Workbench software version 7.0 (Agilent Technologies). The deletion region of the 2p terminal region identified by Chromosome View (left) is expanded by Gene View (right). Dots indicate the genomic positions and signal log2 ratio of the array probes. Black dots indicate normal copy, whereas red and green dots indicate more/<0.5 of log2 ratio, respectively.

Although causal relationships are as yet uncertain, these symptoms might also be important phenotypic features allowing us to suspect the existence of such a rare genetic disorder.

ACKNOWLEDGMENTS

None.

DISCLOSURE

The authors declare no conflict of interest.
Approval of the research protocol: N/A.
Informed consent: Written informed consent was obtained from both the patient and her mother before genetic analysis.
Approval date of Registry and the Registration No. of the study/trial: N/A.
Animal studies: N/A.

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SUPPORTING INFORMATION

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

Figure S1 | The clinical course of the present patient after hospitalized treatment.