A Case with Angelman Syndrome Carried *de novo* der(15q;15q) By *de novo* Paternal Uniparental Disomy

De novo Paternal Uniparental Dizomiyle Ortaya Çıkan *de novo* der(15q;15q) taşıyan Angelman Sendromlu Olgu

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Öz

Angelman sendromu (AS; OMIM 105830), tipik olarak maternal kromozom 15q11.2-q13 delesyonu, Ubiquitin-protein ligaz E3A (UBE3A) gen mutasyonları, paternal uniparental disomi (UPD), imprinting merkez mutasyonlarının neden olduğu konjenital bir nörogelişimsel bozukluktur. UPD taşıyan sporadik AS oranı %2-3 olarak bilinmektedir. AS hastalarının yaklaşık %2-3'ünde paternal UPD saptanmıştır. Birçok rapor, UPD ile ilişkili AS olgularının heterodizomik olduğunu ileri sürmüştür. Bu yazıda AS tanısı konulan dört yaşında bir hasta sunulmaktadır. Hastanın dilini dışarı çıkaran geniş bir ağzı, her iki parmağını esnetmesi, zeka geriliğiyle birlikte salyası akması, konuşamaması, uyku bölünmesi, kendine zarar verme davranışı gibi dismorfik özellikleri gözlenmiştir. Angelman sendromu olgularının tanısında elektroensefalogram (EEG) bulguları önemli olmakla birlikte olgumuzda spesifik EEG ve ayrıca manyetik rezonans görüntüleme bulguları saptanmamıştır. Olgumuzda konvansiyonel sitogenetik yöntemle başlayan tanı sürecinde yeni nesil dizileme yöntemi kullanılarak genetik analiz tamamlanmıştır. 15. kromozomda iki uzun kolun Robertson tipi translokasyonu saptanan hastanın karyotipi 45,XX,der(15;15)(q10;q10)dn olarak tanımlanmıştır. Haplotip analizi, vakanın taşıdığı *de novo* rob(15q;15q) translokasyonun paternal kökenli 15 numaralı kromozom olduğunu göstermiştir. Literatürde UPD'li AS olgularının klinik bulgularının mikrodelesyonlulara göre daha hafif olması nedeniyle 15. kromozomun UPD'sini taşıyan AS olgularının gözden kaçabileceğini düşündürmektedir. Bu nedenle, burada sunulan vaka, geleneksel sitogenetik tarafından belirlenen der(15;15) translokasyonlarında, bireyin UPD için değerlendirilmesi gerektiğini gösteren iyi bir örnektir.

Anahtar Kelimeler: Angelman Sendromu, Sitogenetik, Translokasyonlar, Uniparental Dizomi, Yeni Nesil Dizileme

Abstract

Angelman syndrome (AS; OMIM 105830) is a congenital neurodevelopmental disorder typically caused by maternal chromosome 15q11.2-q13 deletion, Ubiquitin-protein ligase E3A (UBE3A) gene mutations, paternal uniparental disomy (UPD), or imprinting center mutations. The rate of sporadic Angelman syndrome carrying UPD is known to be 2-3%. Paternal UPD has been detected in approximately 2-3% of AS patients. Many reports have suggested that patients with UPD-associated AS cases are heterodisomic. We reported a case of a 4-year-old patient diagnosed with AS. She presented with dysmorphic features, including a wide mouth with protruding tongue, flexion of both fingers, drooling with mental retardation, absence of speech, disrupted sleep, without self-injuring behavior. Although electroencephalogram (EEG) findings are important to diagnosing AS, specific EEG and also magnetic resonance imaging (MRI) findings were not detected in our case. In the diagnostic process, which began with conventional cytogenetics, genetic analysis was completed using the next-generation sequencing method. A Robertsonian-type translocation of two long arms in derivative chromosome 15 was detected, defining the patient's karyotype as 45,XX,der(15;15)(q10;q10)dn. Haplotype analysis confirmed the presence of paternal uniparental disomy, indicating that the case carried a *de novo* rob(15q;15q) translocation. The literature, suggests that AS cases with UPD may exhibit milder clinical features compared to those with microdeletion. Consequently, AS cases involving UPD of chromosome 15 can sometimes be overlooked. Therefore, the case presented here serves as an example highlighting the need to evaluate individuals with translocations involving der(15;15) identified through conventional cytogenetics for potential UPD.

Keywords: Angelman Syndrome, Cytogenetics, Next-Generation Sequencing, Translocations, Uniparental Disomy

Introduction

The frequency of Angelman syndrome is reported to be 1 in 15,000 and 1 in 20,000 individuals. Diagnosing Angelman syndrome involves considering clinical, behavioral, and developmental phenotypic features, along with electroencephalogram (EEG) findings. This diagnostic process is complemented by cytogenetic and molecular genetic analyses. Due to the gradual onset of signs and symptoms, which can overlap with other conditions, diagnosing the disease can be challenging (1). Genetic mechanisms associated with Angelman syndrome include the deletion of the 5-7 Mb 15q11.2-q13 region where the UBE3A gene resides, pathogenic intragenic deletions/insertions within the UBE3A gene, loss-of-function mutations involving missense, nonsense, or splice site mutations, and instances where both gene copies are inherited from the father, referred to as uniparental disomy (UPD). DNA methylation imprinting

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analyses aid in identifying these genetic anomalies in Angelman syndrome cases. Furthermore, cytogenetic methods have revealed chromosomal rearrangements, such as translocations and inversions, in some cases of Angelman syndrome (2).

In this report, cytogenetic testing was initially performed on a patient diagnosed with Angelman syndrome, followed by testing her family members to confirm the presence of a Robertsonian-type translocation involving two long arms of chromosome 15. The specific mild phenotype observed in the patient and the carrier of a *de novo* Robertsonian-type translocation involving two long arms of the derivative chromosome 15 suggested the need to confirm the presence of UPD in this case. Consequently, haplotype analysis was conducted on both the patient and her family to evaluate UPD.

Case

A 4-year-old girl was referred to a pediatric clinic due to the absence of speech. She had non-consanguineous parents and a healthy one-year-old sister. Her mother was 40 years old, and her father was 39. She was born via caesarian section after an uneventful first pregnancy, weighing 2800 g at birth. During her physical examination at the age of 4, she weighed 19.8 kg (90th percentile) and measured 106 cm in length (50-75th percentile), with a head circumference of 51 cm. She exhibited dysmorphic features such as a wide mouth with a protruding tongue, finger flexion, drooling, mental retardation, absence of speech, disrupted sleep, and the inability to run by the age of 4. She started walking at 22 months without a history of seizures. Notably, both brain MRI and EEG results were normal. At the age of 7, she underwent another physical examination, showing a weight of 29.4 kg (94th percentile), a length of 118.5 cm (40th percentile), and a head circumference of 50 cm.

Peripheral blood samples were obtained from the patient and her parents. GTG banding chromosome analysis was performed on peripheral blood lymphocytes using standard procedures, at a resolution of 550 bands. Subsequently, their karyotypes were determined following the guidelines of the International System for Human Cytogenetic Nomenclature 2020 (3). The patient's karyotype was identified as 45,XX,der(15;15)(q10;q10), while her parents' karyotypes were normal (Figure 1a, 1b, 1c).

Fluorescent In Situ Hybridization (FISH) was carried out on the patient using Cytocell's Prader-Willi/Angelman (SNRPN) probe (product no: LPU 005) designed for loci within the 15q11-q13 region, in addition to the 15qter subtelomere specific probe (clone 154P1), following the standard protocol. FISH analysis did not reveal any microdeletions in the Prader-Willi/Angelman region, confirming the presence of the same loci on each arm of the translocated chromosomes 15 (Figure 1d).

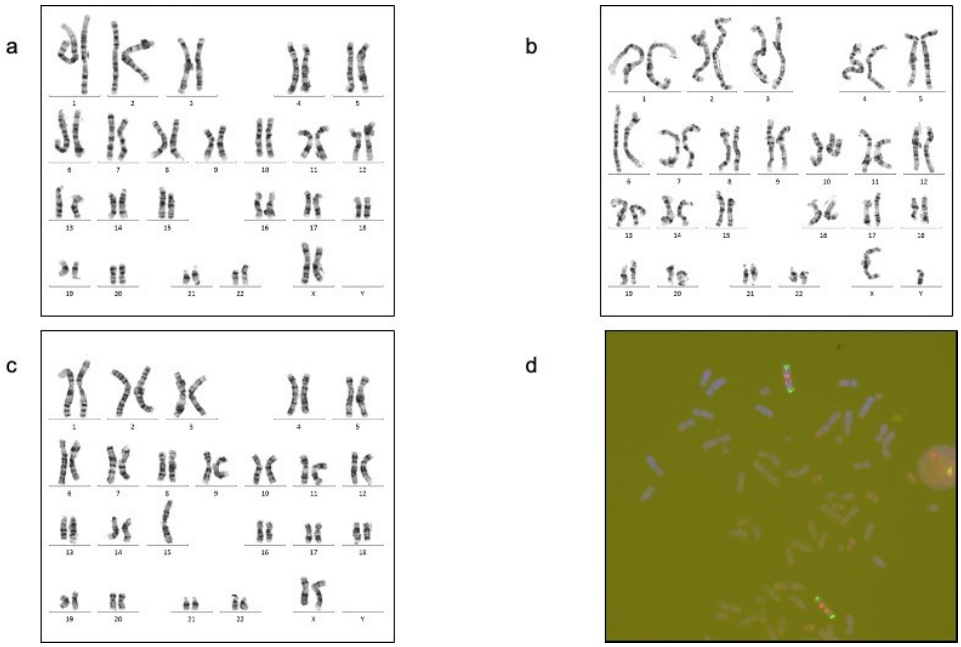

Figure 1. The karyotype analyses by conventional cytogenetic G-banding method (a,b,c). a) A normal karyotype of her mother. b) A normal karyotype of her father. c) A karyotype shows the case with apparently balanced *de novo* Robertsonian translocation 45,XX,der(15;15)(q10;q10)dn. d) A photograph from the Locus specific Fluorescent in situ hybridization (FISH) analysis. Locus-specific FISH analysis was carried out using Cytocell's Prader-Willi/Angelman (SNRPN) probe (product no: LPU 005), which was a red labeled specific for loci within the 15q11-q13 and the 15qter subtelomere specific probe (clone154P1) which was a green labeled. FISH detected two signals in the case for probe-specific Prader-Willi/Angelman (SNRPN) 15q11-q13 chromosomal region, indicating Robertsonian translocation of two long arms in derivative paternal chromosome 15.

To determine haplotype segregation on chromosome 15, Ion S5 system reads obtained from paired-end sequencing platforms were aligned to the human reference genome GRCh37 (hg19). Variants detected using next-generation sequencing-based methods were visualized using the Integrative Genomics Viewer (IGV) and assessed with Ion Reporter Software. To illustrate the heterodisomy, three variants within chromosome 15 were chosen: SMAD3 (RefSeq NM_005902.3) c.207-14678 G>A, ADAMTS7 (RefSeq NM_014272.3) c.744A>G(p.Val248=) and c.640T>C (p.Ser241Pro). For SMAD3 c.207-14678G>A, both the patient and the father exhibited a homozygous GG genotype, while the mother had an AA genotype. Concerning ADAMTS7 c.744A>G, the mother displayed a heterozygous genotype, whereas the father and the patient presented with a CC genotype. In the case of ADAMTS7 c.640T>C, the patient and her father were heterozygous, while the mother had the wild-type AA genotype. These findings suggest that the case inherited paternal heterodisomic UPD. Figure 2 shows the IGV view of the case, her mother, and father.

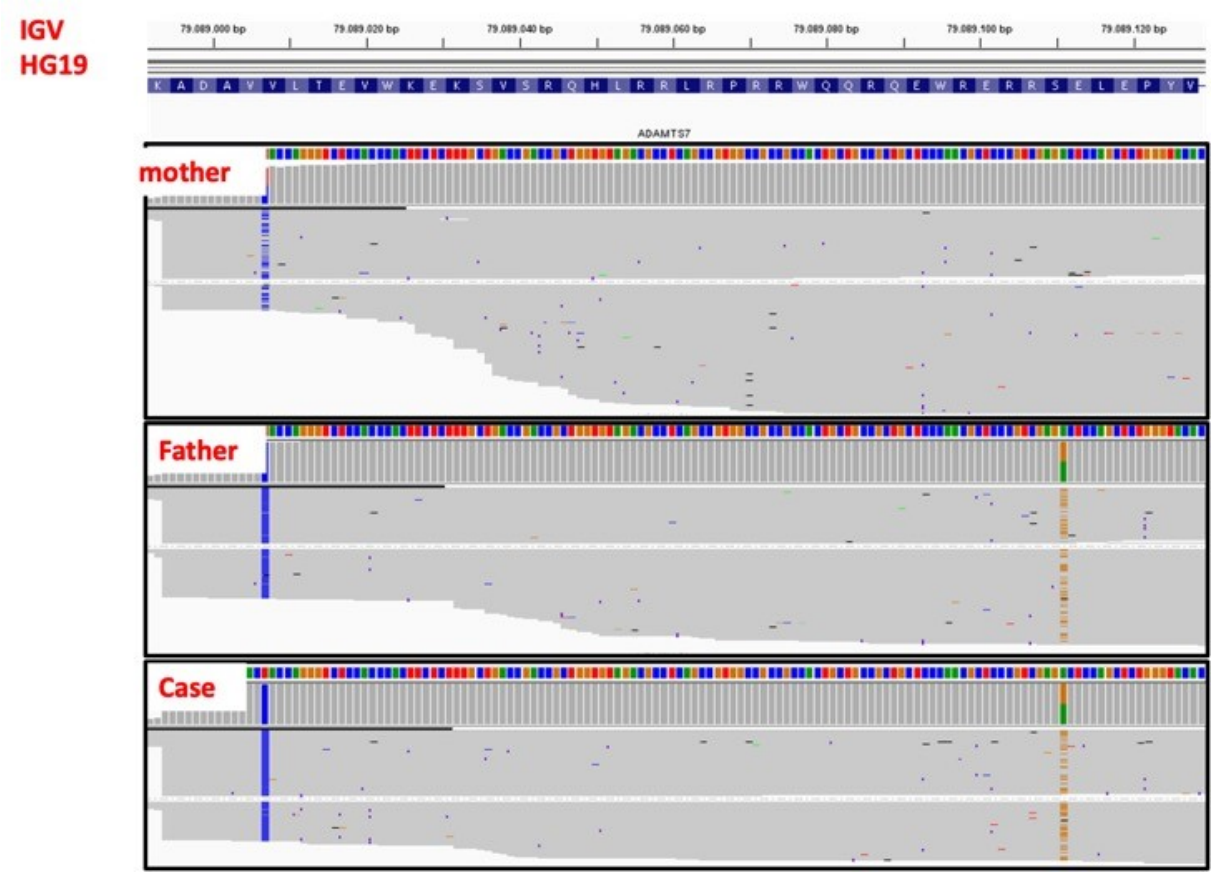

Figure 2. The case, her mother and father's IGV views are shown.

Discussion

In the patient we reported, a *de novo* 15;15 Robertsonian translocation occurred, and there was no familial history of Angelman syndrome. The literature indicates a sporadic occurrence rate of UPD-induced Angelman syndrome at approximately 2-3% (4).

The reason why maternal UPD15, leading to non-disjunction during meiosis, occurs ten times more frequently than paternal UPD15 remains unclear. However, post-zygotic gain or loss of paternal chromosome 15 is more likely to occur in both paternal and maternal UPD15 cases. Robinson et al. (5) reported that in 21 AS cases caused by paternal UPD15, the mean maternal and paternal ages were 33.4 and 39.4 years, respectively, higher than in controls. In our study, the parents' ages were 40 and 39, respectively, aligning with the older parental age observed in the literature. It's believed that paternal errors predominantly occur in the post-zygotic stage. Additionally, the non-disjunction event leading to nullisomy of chromosome 15, associated with older maternal age, typically occurs in the oocyte (5).

The NGS method was used to ascertain the presence of UPD in the patient with the Robertsonian translocation of 15;15. Subsequent segregation analysis confirmed the paternal origin of the disomy, indicating paternal heterodisomic UPD in the patient. It's established that around 2-3% of AS patients carry paternal UPD. Notably, prior reports

on UPD-associated AS cases have emphasized their heterodisomic nature (6). This suggests phenotypic differences between UPD and deletional cases, with UPD-associated AS cases displaying milder symptoms on chromosome 15 (5). Consequently, AS patients with UPD may go undiagnosed due to their less typical phenotype (7).

The first documented case of AS arising from *de novo* paternal uniparental heterodisomy was reported by Ramsden et al. (6) in 1996. This patient presented with typical Angelman syndrome features at age 4, including developmental delay, ataxia, jerky movements, absent speech, and a cheerful disposition. The determination of heterodisomic uniparental disomy was made through methylation analyses, revealing both 15 chromosomes to be of paternal origin (6).

In our patient, dysmorphic features such as a protruding tongue, mental retardation, sleep disturbances, inability to speak, drooling, and ataxia were observed. These clinical manifestations align with previously published reports (8). However, specific EEG and MRI findings were not observed in our patient. Subsequently, Li et al. (9) reported two cases: one, a 3-year-old female with paternal UPD at chromosome 15, displayed EEG and MRI abnormalities; the other case, a 3.5-year-old male with paternal UPD on 15q11-13, had no history of seizures, and the MRI result was normal, similar to our patient (4).

The specific EEG pattern associated with Angelman syndrome is determined by assessing electrophysiological parameters, either individually or in combination. Although crucial for clinical diagnosis, obtaining conclusive EEG results in a single test may be challenging. It's advisable to repeat the EEG examination as findings can vary over time within the same case (4). In our reported case, the EEG test produced normal results without any observed seizure activity. Tan et al.'s (8) 2011 study noted that among 92 AS patients aged 5-60 months diagnosed through molecular testing, 84 cases displayed abnormal EEG results. However, despite these abnormalities, clinical seizures were only evident in 65% of all cases (8).

Our patient's body mass index (BMI) was found to be >85%. This observation was supported by Tan et al. (8), who reported that almost half of the children with UPD/imprinting defects had a high BMI (>85%), despite facing feeding difficulties. Tan et al. (8) also noted that the BMI of our patient was recorded as >85%, aligning with our study's results. These findings strengthen the association between paternal UPD and higher BMI.

Furthermore, Table 1 in the literature details the karyotype and clinical features of cases similar to ours. Our case, highlighted in red in Table 1, shares similarities with these cases.

Genetic counseling should be recommended to families when Angelman syndrome arises sporadically. This counseling provides information about the risk of recurrence. As UPD occurred *de novo* in our case, we informed the family that the risk of UPD recurrence in their future offspring would be <1% (28).

Thomas Liehr (29) emphasized UPD as a chromosomal disorder that always requires examination at a chromosomal level. This approach aids in understanding the biological processes in individual patients (29). We believe that starting genetic tests for AS/PWS with cytogenetic analysis is crucial. This step serves as the initial stage in identifying uniparental disomy and comprehending the biological processes underlying such cases.

Conclusions

We reported that the case was a 4-year-old female carrying paternal heterodisomic UPD, leading to AS. In particular, since UPD carriers of AS patients have few of the phenotypic features of the syndrome, the presence of UPD in the first test will be demonstrated by conventional cytogenetics rather than molecular analysis. Also, we confirmed that AS patients with UPD have milder clinical symptoms as well as higher BMI than AS individuals with other underlying genetic abnormalities. Our data can lead to understanding phenotype-genotype correlation in AS carrying UPD.

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Conflict of interest statement

The authors declare that have no conflicts of interest.

Written consent: This study had an approval number was 2012-KAEK-20 and was obtained on 30/05/2022 from the ethics committee of Akdeniz University.

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265 **Table 1.** Clinical and karyotype comparison of our case with AS cases in the literature.

Karyotype	DD	Ataxic movement and gait	Unique behavioral features	Speech impairment	Micro-cephaly	Seizures	EEG abnormality	Hypo-pigmentation	Atypical dysmorphic features for AS	Family history	Reference number
45,XY,–10,–15,+t(10;15)(q26;q13)dn? (II-1)	n.d.	+	n.d.	n.d.	+	(+) ~14 y	+	n.d.	high bossed forehead, small mandible, hypoplastic maxillae, very high palate, short nose, flattened nares, short stature (<3rd centile at 15 y)	-	10
45,XY,–13,–15,+der(13),t(13;15)(p13;q13)mat (II-1)	DQ50 (2 y)	n.d.	n.d.	n.d.	-	(+) ~ 3 mo	n.d.	n.d.	telecanthus, long upper lip, higharched palate, broad nasal bridge, full nasal tip with flare of nasal alae	-	11
46,XX,–15,+der(22)t(15;22)(q13;q11)mat (II-2)	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	PWS in 2 relatives	12
45,XX,–6,–15,+der(6)t(6;15)(p25.3;q11.1)pat (I-2)	+	(+) walked at 2 y	n.d.	(+) no word 4.5 y	-	-	(+) typical for AS	+	epicanthic folds	PWS in cousin (caused by *de novo* paternal deletion)	13
45,XY,–8,–15,+der(8)t(8;15)(p23.3;q11)pat (I-2)	+	+	+	(+) no word 29 y	n.d.	(+) severe	(+) typical for AS	-	n.d.	-	14
45,XY,–10,–15,+der(10)t(10;15)(q26;q13) (II-1)	+	+	+	(+) no word	+	(+) severe	(+) typical for AS	(+) skin, eyes and hair	short stature (<3rd centile at 24 y)	-	15
45,XX,–3,–15,+der(3)t(3;15)(q29;q12) (II-1)	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	-	16
46,XX,–15,+der(14)t(14;15)(q11.2;q11.2)mat (II-2)	+	+	+	(+) no word	+	+	(+) typical for AS	n.d.	extreme short stature at 10 y	-	17
45,XY,–8,–15,+der(8)t(8;15)(p23.3;q13)mat (II-1)	+	(+) walked at 18 mo	+	began to babble at 8 mo	+	(+) ~18 mo	(+) typical for AS	(+) light red hair	protruding ears, short stature (<5th centile at 18 mo)	AS suspected in aunt	18
45,XY,der(15;15)(q10;q10)dn (I-1)	+	+	+	+	+	+	(+) typical for AS	-	some patients showed overgrowth	-	19
46,XX,–15,+der(14)t(14;15)(q11;q13)mat (II-2)	+	+	+	n.d.	+	+	+	n.d.	n.d.	PWS in 2 cousins	20
45,XX,–1,–15,+der(1)t(1;15)(p36.31;q13.1)mat (II-1)	+	+	- (did not smile or pay any attention to her surroundings)	n.d.	-	(+) from 7 mo	+	(+) skin, hair, irises	frontal bossing, hypertelorism, flat nasal root, apparently low-set ears with asymmetry and cupping, small hands and feet	-	21
45,XY,–15,–22,+der(22)t(15;22)(q13;p11) (II-1)	+	never walked alone at 30 y	n.d.	n.d.	n.d.	(+) ~ 3 y	n.d.	n.d.	n.d.	-	22
45,XY,–13,–15,+der(13)t(13;15)(q34;q15)mat (II-1)	n.d.	contractures and increased tone	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	sloping forehead, small anterior fontanel, very prominent nasal root, cup-shaped ear deforms; abnormal palmar creases	-	22

Karyotype	DD	Ataxic movement and gait	Unique behavioral features	Speech impairment	Micro-cephaly	Seizures	EEG abnormality	Hypo-pigmentation	Atypical dysmorphic features for AS	Family history	Reference number
45,XY,–1,–15,+der(1)t(1;15)(q44;q13)dn (II-1)	+	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	-	22
46,XX,–15,+der(22)t(15;22)(q13;q11.2)mat (II-2)	n.d.	gained head control but could not sit without support at 29 mo	n.d.	(+) no word: 23 mo	-	+	(+) typical for AS	n.d.	preauricular tag, preauricular pit, short stature (–2.4 SD at 23 mo)	22q11.2 deletion syndrome in brother	23
45,XX,–10,–15,+der(10)t(10;15)(q26;q13)mat (II-1)	DQ60 (10 mo)	-	-	n.d.	+	-	n.d.	(+) skin (-) hair and iris	n.d.	PWS in cousin	24
45,XY,–1,–15,+der(1)t(1;15)(q44;q12)mat (II-1)	n.d.	n.d.	+	(+) no word	+	-	n.d.	(+) face, iris	older brother, thin upper lip, overhanging nasal tip, large ears	-	25
45,XY,–1,–15,+der(1)t(1;15)(q44;q12)mat (II-1)	n.d.	n.d.	n.d. (autistic feature)	(+) no word	n.d.	-	n.d.	n.d.	younger brother, bushy eyebrows, overhanging nasal tip, bilateral low-set large ears		25
45,XX,–10,–15,+der(10)t(10;15)(q26.3;q11.2)mat (II-1)	Mode-rate delay	climbed stairs with support, but could not run or jump at 5 y	n.d. (autistic feature)	(+) spoke 4 disyllables at 5 y	+	-	(+) paroxysmal activity in the left and right occipital region	not hypo	low anterior hair implantation, bushy eyebrows, bilateral epicanthal folds, telecanthus, lips with absent Cupid's bow, slightly broad nasal bridge, prominent nose with a bulbous tip, short, broad, and smooth philtrum, hands with tapered fingers, broad thumbs and broad 2nd fingers	minor dysmorphic features in uncle and cousin	26
46,XX,–15,+der(13)t(13;15)(q14.1;q12) (II-2)	+	gained head control but could not sit at 24 mo; tonic spasmlike movement	(-) no happy demeanor	(+) no word at 24 mo	+	(-) tonic spasm like involuntary movement	(+) typical for AS	-	upslanted palpebral fissures, hypertelorism, thin lips with downturned corners of mouth, bilateral clinodactyly of 5th fingers	-	27
45,XX,der(15;15)(q10;q10)dn (I-2)	+	(+) broad-based gait, walked at 22 mo	disrupted sleep	+	-	-	-	-	(+) wide mouth with protruding tongue, flexion of both fingers and drooling	no family history to our knowledge	Present case

DD: Developmental Delay; mo: months; y: years, + : positive for the finding;, – : negative for the finding; n.d.: not described in the report, UPiD: uniparental isodisomy; UPhD: uniparental heterodisomy; I-1: Paternal UPiD; I-2: Paternal UPhD; II-1: Deletion and monosomy by maternal translocation; II-2: Deletion and trisomy by maternal translocation. This table adapted from Niida et al., 2016 (27).

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