

Spastic Diplegia in a Haitian Girl with Angelman Syndrome

Kumarie Latchman¹  Margarita Nieto-Moreno¹ Roberto Lopez Alberola²

¹Department of Human and Translational Genetics, University of Miami Miller School of Medicine, Miami, Florida, United States

²Department of Neurology, University of Miami Miller School of Medicine, Miami, Florida, United States

Address for correspondence Kumarie Latchman, DO, Department of Human and Translational Genetics, University of Miami Miller School of Medicine, 1501 NW 10th Avenue, BRB 332, Miami, FL 33136, United States (e-mail: kxl604@miami.edu).

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Abstract

Spastic diplegia, a muscle hypertonia motor syndrome, can occur in conjunction with the characteristic abnormal movement features of Angelman syndrome (AS), a neurodevelopmental disorder with primary features of ataxic gait, happy demeanor, developmental delay, speech impairment, intellectual disability, microcephaly, and seizures. Spastic diplegia is classically associated with cerebral palsy (CP), an umbrella term encompassing developmental delay, abnormal brain magnetic resonance imaging findings, and various types of CP including spastic, ataxic, dyskinetic, and mixed types. We present a 12-year-old Haitian patient of African descent with AS due to a microdeletion involving the entire *UBE3A* (ubiquitin-protein ligase E3A) gene and spastic diplegia. She was initially given a clinical diagnosis of CP. Cases of AS in patients of African descent have been rarely reported and this case of severe spastic diplegia, unresponsive to medical intervention, reflects a rarely reported presentation of AS in patients of African descent and possibly the first reported case of a Haitian patient with this clinical presentation. Given that deletions are the most common mechanism resulting in AS, this case report provides supportive evidence that chromosome 15q11 deletion-type AS is most frequently associated with spastic diplegia, a more severe motor impairment phenotype in AS.

Keywords

- ▶ Angelman syndrome
- ▶ *UBE3A*
- ▶ spastic diplegia

Introduction

Spasticity can be associated with Angelman syndrome (AS), a neurodevelopmental disorder with an estimated prevalence of ~1 in 15,000 children.¹ The prevalence of AS appears to be highest in patients of Caucasian descent, and there is no known prevalence of AS in patients of African descent. The major clinical diagnostic features of AS include seizures, microcephaly, developmental delay, speech impairment, characteristic electroencephalogram (EEG) findings, gait abnormalities, and a happy demeanor.² Spastic diplegia, a common presentation of cerebral palsy (CP), is usually associated with severe spasticity of the bilateral lower limbs with minimal involvement of the upper extremities.³ Like CP, the exact pathophysiologic

mechanisms leading to spasticity in AS are currently unknown, and no clear relationship between a specific brain lesion and spasticity has been elucidated thus far. Dan et al provided evidence showing that different body motor mechanisms occur in patients with spastic diplegia associated with periventricular leukomalacia versus that in patients diagnosed with AS, providing a possible insight to variable underlying mechanisms of spasticity.⁴ Additionally, brain magnetic resonance imaging (MRI) of AS patients are usually characterized by delayed myelination and do not indicate specific brain structural anomalies.⁵ Although the mechanism for CP-related spastic diplegia is believed to be a static cerebral lesion associated with prematurity, the primary postulated mechanism for AS-related spasticity is the neuronal loss of function

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of maternally imprinted *UBE3A* (ubiquitin-protein ligase E3A) gene. The pathogenic mechanisms associated with AS, all resulting in neuronal loss of function of the *UBE3A* gene, include maternal chromosome 15q11 deletion, paternal uniparental disomy of chromosome 15 (UPD15), pathogenic *UBE3A* variants, and defects of the genomic imprinting mechanisms.

Established genotype-phenotype correlations indicate chromosome 15q11-q13 deletions are associated with more severe clinical presentations of AS.⁶ Developmentally, affected children with AS walk at a later age compared with unaffected children and ~10% of AS patients do not achieve ambulation for yet to be determined reasons.⁵ One possible explanation for the lack of ambulation in AS patients may be due to spasticity of the bilateral legs, and spastic diplegia has been studied as part of the abnormal movement mechanics in AS patients.⁴ Beckung et al showed that children with AS tend to have distal lower limb spasticity, ataxic-like gait, and stiff lower limbs.⁷ Dan et al showed that of 10 patients with AS, spasticity was more frequent in those with a maternal chromosome 15q11-13 deletion.⁴ It is possible that large deletions in the AS-Prader-Willi's syndrome region may involve the loss of genes outside the well-known associated breakpoint one to breakpoint three regions (BP1-BP3), and are correlated with a more severe phenotype.⁸ Four patients with larger deletions of 8 to 10 Mb were previously reported by Sahoo et al⁸, but none was reported to be nonambulatory or to have lower limb spasticity. Molfetta et al described a 15-year-old boy presenting with clinical features of CP such as spasticity of bilateral lower extremities, hypertonicity, and trunk hypotonia who was nonambulatory and did not speak. He was found to have a frameshift mutation in the *UBE3A* gene.⁹

In this report, we describe a rarely reported clinical presentation of AS in a 12-year-old Haitian patient of African descent with AS-related spastic diplegia unresponsive to medical intervention. A 180K Agilent microarray showed a 5.4-Mb deletion in the maternal 15q11.2-15q13.1 region including a complete deletion of the *UBE3A* gene in addition to deletion of other genes within the BP1-BP3 region, *ATP10A* (ATPase, Class V, type 10A), and part of the *SNRPN* (small nuclear ribonucleoprotein polypeptide N) gene (→**Fig. 1**). The function of the *UBE3A* gene in the pathogenesis of the movement disorder associated with AS is still unknown. As *UBE3A* is mainly located in the nucleus of neurons, the primary insult to neurons may occur in multiple areas of the central nervous system (CNS), including the cerebellum, the motor cortex, and the nigrostriatal pathway.⁵ Additionally, studies show that the *UBE3A* functions in monoubiquitylation, a membrane transport and transcriptional regulation pathway, and in polyubiquitylation, a protein degradation pathway. However, it is still unclear how these processes contribute to the overall CNS insult in AS.⁵ Based on limited data, we explore the potential genotype-phenotype correlation for the presence of spastic diplegia in AS and present this rarely reported clinical feature in a patient of African descent.

Case Presentation

The patient is a 12-year-old Haitian girl of African heritage with a clinical picture suggestive of CP. Her prenatal history was negative without pregnancy or birth-related complications. Perinatal history was unremarkable with a full-term delivery via cesarean section and no reported complications such as seizures, respiratory distress, hypotonia, or

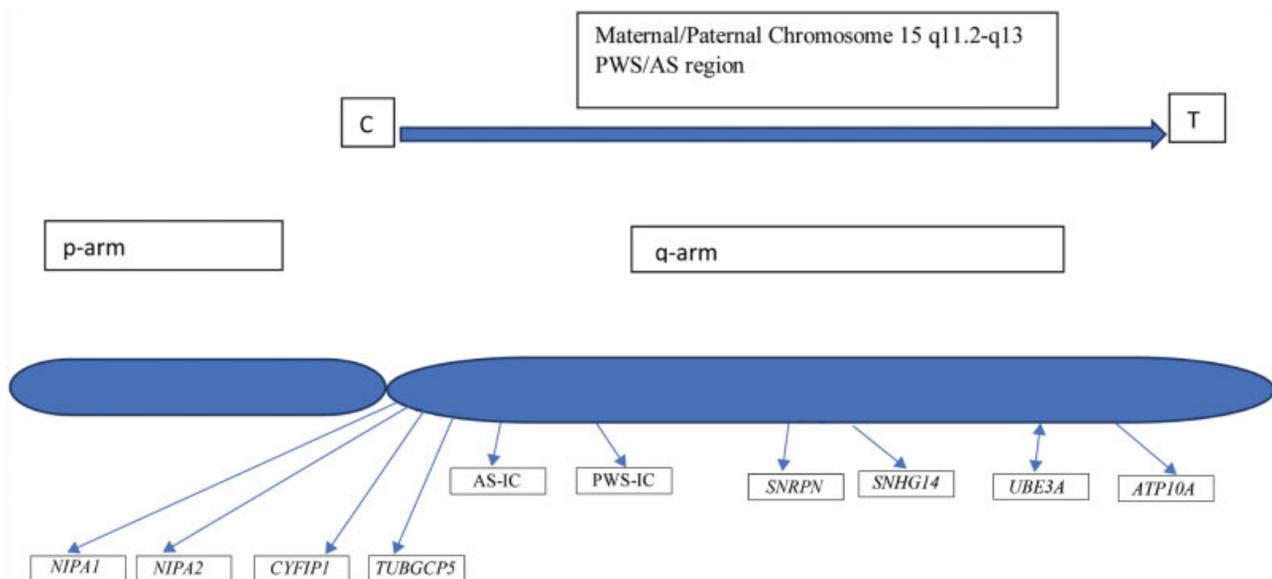


Fig. 1 Maternal and paternal chromosome 15q11.2-q13 PWS/AS region (not drawn to scale). AS-IC, Angelman syndrome imprinting center; C, centromere; *CYFIP1*, cytoplasmic fragile X mental retardation protein-interacting protein 1; T, telomere; *NIPAI*, nonimprinted gene in Prader-Willi's syndrome/Angelman syndrome chromosome region 1; *NIPAI2*, nonimprinted gene in Prader-Willi's syndrome/Angelman syndrome chromosome region 2; p, p arm; PWS-IC, Prader-Willi's syndrome imprinting center; q, q arm; *SNRPN*, small nuclear ribonucleoprotein polypeptide N; *TUBGCP5*, tubulin-gamma complex-associated protein 5.



Fig. 2 Patient aged 5 years old.

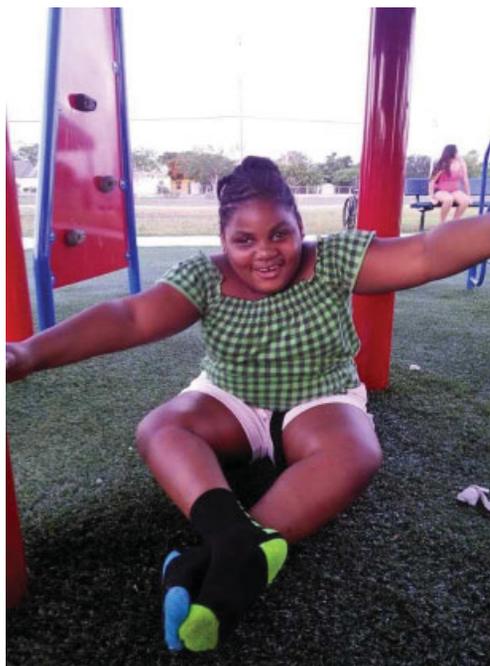


Fig. 4 Patient aged 7 to 8 years old.



Fig. 3 Patient aged 2 to 3 years old.

difficulty feeding. She was discharged on the third day of life. At less than 1 year of age, she had her initial presentation to the emergency room (ER) for seizures. She had numerous visits to the ER after the first year of life for persistent seizures. Records indicated that she initially presented to the genetics clinic at around 2 years of age for developmental delay, including motor and speech delay, but no testing was performed.

At 2 years of age, she was noted to have hypertonia of her bilateral lower legs and delayed motor milestones as

she was unable to stand without support. She eventually began toe-walking and established ambulation by 5 years of age. Her development was globally delayed; she never spoke and although she walked at 5 years old, it was mostly on her toes. She never learned to run, jump, or hop. She never learned to brush her teeth, dress herself, or become potty-trained. She was generally noted to have a happy demeanor but she also had aggressive behavior such as biting and grabbing. Her clinical diagnosis was CP and she was eventually treated at around 8 years of age with botulin injections for her bilateral lower leg spasticity. She later also had bilateral gastrocnemius extension repair and recession of her bilateral Achilles tendon. Although it was noted that she had fair improvement in the initial stages of treatment where she was able to stand and walk for short periods of time, botulin injections were eventually stopped due to sustained poor response and she continued to be nonambulatory. She continued with a clinical diagnosis of CP-related spastic diplegia and is currently managed pharmacologically with baclofen and clonazepam (► **Figs. 2–4**).

She was then lost to follow-up and presented to the genetics clinic at 11 years old with a history of nonambulation due to persistent spastic diplegia, intellectual disability, aphasia, and seizures. Additional history included abnormal EEGs and nonspecific brain MRIs. On physical examination, she was found to be normocephalic, severely obese with a wide mouth, almond-shaped eyes, small hands and feet, and spasticity of bilateral lower legs. She mostly made sounds but did not speak any words. Her mother reported that she may occasionally have outbursts of laughter. Her skin color appeared to be of similar color to her mother's skin color. On review of systems, she was noted to have passed the newborn hearing screen and records indicated that she did

not have hearing loss. She was also found to have sleep apnea, chronic constipation, obesity, and glucose intolerance requiring metformin treatment.

Diagnostic testing included an EEG at 2 years of age which showed generalized slowing with possible bilateral cortical dysfunction, a subtle diagnostic clue for AS. A video EEG at 5 years of age indicated a right frontal region run of spikes suggestive of epileptiform activity and a second video EEG at 9 years of age showed runs of 2 Hz spike and wave activity, lasting up to 10 seconds, and primarily observed in the bifrontal region. The most recent video EEG at 11 years of age showed frequent spikes and wave discharges at 2.5 to 3 Hz with bifrontal and mesial frontal predominance. Findings were interpreted as consistent with moderate to severe encephalopathy (→ **Table 1**). MRI at 24 months of age indicated nonspecific white matter signal abnormalities suggestive of a demyelination process. A repeat brain MRI at 9 years of age indicated resolution of the previously viewed white matter abnormalities with no other significant findings.

After the initial evaluation in the genetics clinic, a microarray (Agilent 180K) revealed an ~5.4 Mb interstitial deletion in the maternal 15q11.2q13.1 region, involving the *SNRPN* and *ATP10A* genes as well as other genes outside of the Prader-Willi/AS region, *TUBGCP5* (tubulin-gamma complex-associated protein 5), *CYFIP1* (cytoplasmic fragile X mental retardation protein-interacting protein 1), *NIPA1* (nonimprinted gene in Prader-Willi's syndrome/AS chromosome region 1), and *NIPA2* (nonimprinted gene Prader-Willi's syndrome/AS chromosome region 2). Commercial testing with methylation-specific multiplex ligation-dependent probe amplification for Prader-Willi's syndrome/AS found a heterozygous deletion for the *UBE3A* gene in the maternal chromosome 15q11.2 region. The deletion was noted to extend the past *UBE3A* gene and included the adjacent *ATP10A* gene and a part of the *SNRPN* gene; it was noted that this was not the classic recurrent rearrangement seen in up to 75% of AS patients.⁶

Discussion

The differential diagnosis of CP is broad and includes AS as well as numerous other neurodevelopmental conditions. The current patient presented with some known features of AS, although her features were more severe. Her inability to walk and speak, severe intellectual delay, and obesity are features known to occur in AS, but presentation of nonambulation and obesity are not classic features of AS. Although she had occasional outbursts of laughter, she also demonstrated aggressive behavior and she did not present with the typical flexed elbow and hand-flapping movements. Throughout her childhood, an early clinical diagnosis of AS was not made likely due to the combination of her less frequently reported features of AS primarily her severe obesity, normal head circumference, almond-shaped eyes, small hands and feet, and her progressive bilateral lower leg spasticity. Furthermore, as she is now 12 years old, it is likely that there were less literature evidence documenting the various atypical clinical presentations of AS a few years ago. As hereditary spastic diplegia can be associated with the possible gain of function of the *NIPA1* gene, we initially evaluated the possibility of an *NIPA1*-related spastic diplegia syndrome in this patient.¹⁰ This was unlikely as the entire *NIPA1* gene was found to be deleted which is not consistent with the current evidence citing missense variants as the possible mechanism leading to *NIPA1*-related gain-of-function spastic diplegia.¹¹ Essentially, in this Haitian girl of African descent, the clinical diagnosis of AS was less apparent and although AS is known to occur across all ethnic groups, no report regarding the prevalence or typical presentation of AS in patients of African descent was found.

Currently, genotype-phenotype correlation has been established for large deletions in AS such that larger maternal 15q11-q13 microdeletions tend to cause a more severe phenotype. For example, AS patients with larger deletions tend to have more severe seizures and speech delay. This was observed in the current patient as well (→ **Table 2**). Presently, few reports

Table 1 Specific EEG findings in AS

EEG findings ^a	Brain MRI findings ^b	Microarray	MS-MLPA for PWS/AS
Runs of 2 Hz spike and wave activity	Negative for structural abnormalities; demyelination	5.93 Mb deletion in chromosome 15q11.2q13.1 region	Heterozygous maternal <i>UBE3A</i> deletion of entire gene in 15q11.2

Abbreviations: AS, Angelman syndrome; BMI, body mass index; EEG, electroencephalogram; MRI, magnetic resonance imaging; MS-MLPA, methylation-specific multiplex ligation-dependent probe amplification; PWS, Prader-Willi's syndrome.

^aMultiple EEGs done, but this was the most pronounced finding.

^bMultiple brain MRIs performed.

Table 2 Phenotype of AS associated with large deletions in Chr 15q11 and clinical presence in current patient

Phenotype ⁸	Seizures	Microcephaly	Severe speech delay	Normal/low BMI	Hypopigmented hair/skin/eye
12 yo Haitian patient (African descent)	Y	N	Y	N	N

Abbreviations: AS, Angelman syndrome; BMI, body mass index; Chr, chromosome; N, no; Y, yes; yo, years old.

Table 3 Spastic diplegia in AS and associated genotype (current and previously reported patients)

Mechanism of AS	Number of reported patients with spastic diplegia
Maternal 15q11-13 deletion (size unknown)	6 ⁴
Maternal 15q11-13 deletion (5.4 Mb)	1 (current patient)
Paternal UPD	1 ⁴
Imprinting center defect	1 ⁴
<i>UBE3A</i> mutation	1 ⁹

Abbreviations: AS, Angelman syndrome; UPD, uniparental disomy.

have emphasized a potential genotype–phenotype correlation for the presence of spasticity in AS and based on current reported literature, it appears that spastic diplegia can occur in any of the various mechanisms involved in AS. Essentially, spasticity appears to be more frequently reported in the most common mechanism leading to AS, maternal chromosome 15q11–q13 microdeletions (→ **Table 3**). With this case presentation, we provide additional supportive evidence for a potential genotype–phenotype correlation for spastic diplegia and the possible correlation with maternal chromosome 15q11–13 deletion in AS.

The pathophysiologic mechanism for the loss-of-function *UBE3A* gene-associated spastic diplegia in AS is yet to be elucidated. Currently, *UBE3A* is known to be expressed in neuronal cells where imprinting is under the indirect regulation of *SNHG14* (small nucleolar RNA host gene 14).⁵ *SNHG14* is in turn regulated by the paternal *SNRPN* promoter region. Studies of *UBE3A* mouse models showed that only the 3' end of *UBE3A* in mouse neurons is imprinted. The transcriptional collision hypothesis postulates that essentially, the paternal *UBE3A* gene is always turned off due to a natural collision between the *UBE3A* and *SNHG14* resulting in the eventual degradation of the paternal *UBE3A* mRNA transcript.¹² Nonhomologous recombination, due to low copy number repeats, is associated with the most common mechanism for AS, microdeletion of the maternal 15q11.2–q13 region which also includes other gene clusters previously mentioned in the text. In the patient reported in this case, the entire *ATP10A*, telomeric to *UBE3A*, as well as a part of the *SNRPN* gene were also deleted. Mouse model for *ATP10A* (syntenic region for human chromosome 15q11 is on mouse chromosome 7) was shown not to be imprinted and is biallelically expressed in mice brain.¹³ Furthermore, *ATP10A*, which encodes an aminophospholipid translocase, may play a role in the modulation of body fat in mice. Previous reports hypothesized that the maternal deletion of *ATP10A* was likely associated with the obese phenotype observed in AS patients found to have large maternal 15q11 deletions.¹³ However, no similar association was postulated for spasticity or pronounced motor delay leading to non-ambulation in AS, (as previously mentioned in the text, ~10% of AS patients are nonambulatory for unknown reasons).

Additionally, Hogart et al concluded that human monoallelic *ATP10A* expression varied based on gender and other genetic factors and can be independent of imprinting.¹⁴ Thus, it is currently difficult to ascertain the physiologic impact of the deletion of *ATP10A* and other genes known to be clustered with *UBE3A*.

Note

This case report has not been simultaneously submitted for publication consideration in any other journal. Also, it has not been previously published elsewhere in any other journal or book.

Conflict of Interest

None declared.

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