Published in final edited form as:

Am J Med Genet A. 2023 July ; 191(7): 1711–1721. doi:10.1002/ajmg.a.63192.

Quantitative measures of motor development in Angelman syndrome

Jessica Duis[1,2,3], **Austin Skinner**[1], **Robert Carson**[4], **Arnaud Gouelle**[5,6], **Melanie Annoussamy**[7], **Jill L. Silverman**[8], **Susan Apkon**[9], **Laurent Servais**[10,11], **James Carollo**[1,9]

[1]Center for Gait & Movement Analysis (CGMA), Children's Hospital Colorado, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA

[2]Section of Genetics and Inherited Metabolic Disease, Department of Pediatrics, Children's Hospital Colorado, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA

[3]Section of Pediatrics, Special Care Clinic, Department of Pediatrics, Children's Hospital Colorado, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA

[4]Department of Pediatrics, Vanderbilt University Medical Center, Nashville, Tennessee, USA

[5]Université de Reims Champagne-Ardenne, PSMS (Performance, Santé, Métrologie, Société), Reims, France

[6]Gait and Balance Academy, ProtoKinetics, Havertown, Pennsylvania, USA

[7]Sysnav, Vernon, France

[8]MIND Institute and Department of Psychiatry and Behavioral Sciences, University of California Davis School of Medicine, Sacramento, California, USA

[9]Department of Physical Medicine & Rehabilitation, Children's Hospital Colorado, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA

[10]Department of Paediatrics, Oxford University, Oxford, UK

[11]Division of Child Neurology, Centre de References des Maladies Neuromusculaires, Department of Pediatrics, University Hospital Liege & University of Liege, Liege, Belgium

Abstract

Angelman Syndrome is a rare neurodevelopmental disorder characterized by developmental delay, lack of speech, seizures, intellectual disability, characteristic behavior, and movement disorders. Clinical gait analysis provides the opportunity for movement quantification to investigate an observed maladaptive change in gait pattern and offers an objective outcome of change. Pressure-

Correspondence: Jessica Duis Children's Hospital Colorado, University of Colorado, Anschutz Medical Campus, 13123 E 16th Ave, Aurora, CO 80045, USA. jessica.duis@childrenscolorado.org.

AUTHOR CONTRIBUTIONS

Jessica Duis conceptualized and designed the study, guided the collection of data, analyzed the data, contributed to and edited the manuscript. Austin Skinner assisted with data analysis, contributed to and edited the manuscript. Robert Carson contributed to data collection and edited the manuscript. Arnaud Gouelle collected control data, analyzed data and edited the manuscript. Melanie Annoussamy analyzed the data and edited the manuscript. Jill L. Silverman was co-PI on the grant. Susan Apkon provided mentorship, reviewed and provided insight into the data and edited the manuscript. Laurent Servais reviewed the data and edited the manuscript. James Carollo provided insight into the data, reviewed the data and edited the manuscript.

sensor-based technology, inertial and activity monitoring, and instrumented gait analysis (IGA) were employed to define motor abnormalities in Angelman syndrome. Temporal–spatial gait parameters of persons with Angelman Syndrome (pwAS) show deficiencies in gait performance through walking speed, step length, step width, and walk ratio. pwAS walk with reduced step lengths, increased step width, and greater variability. Three-dimensional motion kinematics showed increased anterior pelvic tilt, hip flexion, and knee flexion. PwAS have a walk ratio more than two standard deviations below controls. Dynamic electromyography showed prolonged activation of knee extensors, which was associated with a decreased range of motion and the presence of hip flexion contractures. Use of multiple gait tracking modalities revealed that pwAS exhibit a change in gait pattern to a flexed knee gait pattern. Cross-sectional studies of individuals with AS show a regression toward this maladaptive gait pattern over development in pwAS ages 4–11. PwAS unexpectedly did not have spasticity associated with change in gait pattern. Multiple quantitative measures of motor patterning may offer early biomarkers of gait decline consistent with critical periods of intervention, insight into appropriate management strategies, objective primary outcomes, and early indicators of adverse events.

Keywords

Angelman syndrome; gait; genetics; movement disorders; muscle spasticity; neurodevelopmental disabilities; outcome measures

1 | INTRODUCTION

Angelman Syndrome (AS) is a rare genetic neurodevelopmental disorder (NDD) characterized by developmental delay, impaired receptive and expressive communication skills, motor and balance deficits, severe intellectual disability, and seizures (Williams, 2010). Motor impairments affect every individual with AS and are more prevalent than other commonly associated symptoms (Bird, 2014; Gentile et al., 2010). AS is caused by the loss of maternal expression of the gene *UBE3A* (ubiquitin-protein ligase E3A/E6AP) (Jiang et al., 1998; Matsuura et al., 1997; Sutcliffe et al., 1997). Due to brain-specific imprinting, the paternal allele is silenced. Loss of the maternal *UBE3A* expression causes deficiency isolated to the brain (Sutcliffe et al., 1997; Yamasaki et al., 2003).

The most common motor problems reported include spasticity, ataxia of gait, tremor, and muscle weakness (Grieco et al., 2018). Current literature suggests that individuals with AS demonstrate muscle weakness in the trunk and asymmetry in strength and spasticity of the upper and lower extremities (Beckung et al., 2004). Motor impairment studied in persons with AS (pwAS) using the 6-minute walk test and 4-stair climb lack rigor, and reproducibility.

Many pharmaceutical clinical trials in NDDs have failed to show clinical impact, which may be explained by intrinsic lack of efficacy, but also by limitations in outcome measures sensitive enough to pick up meaningful change (Erickson et al., 2017). The Clinical Global Impression-Severity (CGI-S) and CGI-Improvement, which evaluate if the patient is doing better or worse were recently selected in many NDD trials, including in AS (Kolevzon et al., 2021), and illustrate the need of more sensitive, reliable outcome measures due to inconsistences between providers and the subjective nature of the evaluation.

Antisense oligonucleotides (ASOs), aimed at unsilencing paternal *UBE3A* are underway in human trials (NCT04428281, NCT04259281, NCT05127226). Clinically relevant outcome measures are necessary to evaluate the utility of ASOs and additional personalized therapies such as gene replacement therapy, which are on the horizon. In addition, clinical data from other NDDs, such as spinocerebellar ataxia, Noonan syndrome, Phelan-McDermid Syndrome, and Dup15q Syndrome show a strong relationship between degree of motor impairment and other behavioral domains such as cognition, suggesting quantitative motor measures offer an objective primary outcome and a surrogate marker of clinically meaningful change in other domains of interest in clinical trials (Ackerly et al., 2003; Burdekin et al., 2020; Costales & Kolevzon, 2015; Dhamne et al., 2017; Pierpont et al., 2009; Soorya et al., 2018; Wilson et al., 2020; Zwanenburg et al., 2016). This is conceivably the case for pwAS, in whom we know motor planning and coordination plays a role in deficits such as apraxia impacting expressive language delays.

In this study, we sought to define changes in gait performance utilizing a gait mat, which measures temporal–spatial parameters of walking, deploying a wearable, inertial sensor for activity monitoring and gait measurement in the home environment and finally utilizing Instrumented Gait Analysis (IGA) to characterize the 3D joint kinematics, kinetics, and muscle activity during walking to functionally assess the changes in pattern and performance that may correlate with mobility decline. Knowledge of evolving gait changes is essential to include for future clinical trial design for AS as this may be evolving over time and correlate quantitatively to other characteristics of the disorder and recently reported serious adverse events in an ASO trial (NCT04259281).

2 | METHODS

2.1 | Human subjects

Human studies were approved by the Institutional Review Board at University of Colorado and Vanderbilt University. Consent was obtained from caretakers for participation in research. They provided written informed consent to participation and publication of research. Participants were examined in three groups. Nineteen subjects, five of which also enrolled in the wearable activity-monitoring study, were recruited prospectively to participate in temporal–spatial gait studies using a gait mat. Two of these subjects were excluded from analysis due to poor data capture from subjects running across the walkway or not remaining on the walkway for full data capture. Five additional subjects were identified retrospectively from the Center for Gait and Movement Analysis (CGMA) at Children's Hospital Colorado, a nationally accredited clinical motion laboratory. Data from a total of 22 subjects were included (Table 1).

Basic definitions of gait parameters are as follows for those not otherwise cited or described in text. Step length is the distance from the foot strike of one foot to the foot strike of the contralateral foot. Stride length is the distance from one foot strike to the next foot strike of the ipsilateral foot. Cadence is the number of steps taken per minute. Step width is the mediolateral distance between both feet.

2.2 | Analysis of temporal–spatial gait parameters

A Zeno Walkway (ProtoKinetics, Havertown, PA) was used to capture temporal–spatial parameters of gait as reported by Grieco et al. (2018). Data were used to compute the following parameters: walking speed, step length, cadence, walk ratio (i.e., the ratio between step length and cadence) (Bogen et al., 2018), step width, and the enhanced Gait Variability index (eGVI) (Gouelle et al., 2018). Normative data was obtained from Gouelle et al. (2016). The selected gait parameters in typically developing (TD) controls were grouped to match with the age groups in our pwAS, resulting in references composed by 30 TD 4–6-year-old children and 43 aged 8–11 years. Speed, step length, cadence, walk ratio, and step width were normalized by the height and/or the gravitational constant, *g*, according to the recommendations of Hof (1996).

2.3 | Activity monitoring

The ActiMyo® device (Sysnav, France) was used to monitor patient movements in a real-life setting using magneto-inertial sensors in three dimensions (Lilien et al., 2019). Daytime use of sensors worn on both ankles for at least 14-days at baseline was collected in 5 pwAS, ages 4–11 years. Variables characterizing ambulation and gait were generated: the 95th percentile of the stride length (SL95C), the 95th percentile of stride velocity (SC95C), the coefficient of variation of stride velocity (CVSV), the coefficient of variation of stride length, and the stride duration. Individuals were age-matched with 45 healthy controls recorded in Liege, Belgium (Ethical approval number: CHR 1646).

2.4 | Three-dimensional instrumented gait analysis

All individuals had a physical exam by a licensed physiotherapist. Physical examination included passive range of motion measurements by goniometer and Modified Ashworth spasticity testing on the lower extremities. Each child was fitted with reflective markers in accordance with the Conventional Gait Model (Davis et al., 1991; Kadaba et al., 1985; Leboeuf et al., 2019). Marker trajectories were obtained using a 13-camera, 3D motion capture system (Vantage V8, Vicon Motion Systems, USA) sampling at 120 Hz. Ground reaction forces were simultaneously acquired using 10 force platforms (model FP 4060–10, Bertec Corp., USA). Dynamic electromyography (EMG) electrodes (Trigno Avanti, Delsys, USA) were placed bilaterally on the rectus femoris, vastus lateralis, hamstrings, anterior tibialis, peroneals, and gastrocnemius. Each pwAS made at least three passes through the walkway at a self-selected, comfortable walking speed. All data processing was completed using Vicon Nexus 2 software before final computations with MATLAB (Mathworks Inc., Natick, MA) using standard laboratory procedures. Sagittal plane kinematics presented herein (Figure 3a–c) underwent additional processing to calculate the average joint angles during stance periods of all gait cycles of the representative trial. Each subject was compared to age-matched normal ranges for kinematics, kinetics, and EMG patterns to simplify interpretation. Gait deviation index (GDI) was calculated to quantify each individuals' 3D gait pattern relative to a TD reference set (Figure 3d) (Schwartz & Rozumalski, 2008). GDI is a normalized composite measure of gait pattern that compares nine joint angles from the subject to the same joint angles of a normal reference over the entire gait cycle, using principle component analysis (Schwartz & Rozumalski, 2008). Scores between 90 and 100 are considered normal patterns, with every 10 points equal to 1 standard deviation from the average composite score from the TD reference. A 5-point difference is considered clinically significant.

2.5 | Statistical analysis

Statistical analysis was conducted using GraphPad PRISM software or IBM SPSS Statistics. Non-parametric alternative tests (Mann–Whitney *U* test) were used for comparison of temporal–spatial subcomponents of human gait data. Two-way ANOVA was used to analyze human spatial subcomponent data with factors of age group and diagnosis (Figure 1). Cross-sectional temporal–spatial data were analyzed using two-way ANOVA with planned post-hoc comparisons within age and between groups.

3 | RESULTS

Persons with AS typically walked slower, with reduced step lengths, greater step widths, and greater variability by assessment on the Zeno walkway ($N = 17$) relative to typically developing peers, although there was significant inter-subject variability (Table 2). Seven of the 17 children (41%) had a walking speed at least 1 standard deviation below typically developing peers, while four (24%) had a speed more than 1 standard deviation above typically developing peers; the remaining six children (35%) were less than 1 standard deviation above or below typically developing peers. All pwAS ($N = 17$) with slower speeds had shorter step lengths, while faster speeds were achieved by a mix of higher cadence and longer step lengths. All pwAS had a smaller step length than typically developing controls. Eight/17 (47%) had step lengths shorter than typically developing peers by more than two standard deviations for *z*-scores. The walk ratio (i.e., ratio of step length to cadence) ranged from −5.4 to 1.3, with 9/17 (53%) of the subjects having a walk ratio more than two standard deviations below typically developing peers. Enhanced gait variability index (eGVI) was greater than 3.3 SDs above typically developing peers for all subjects. Except cadence (raw or normalized), all parameters demonstrated differences between pwAS and typically developing, with smaller speed, step length, walk ratio, higher step width, and eGVI observed in pwAS (Table 2).

Over development, gait patterns in pwAS studied on the Zeno Walkway show wider steps than typically developing children at all ages (Figure 1). While typically developing children showed increasing step lengths, pwAS maintained smaller steps and these steps were significantly shorter from age 6 onwards according to these data. At 6–8 years old, pwAS had a significantly higher cadence. Walk ratio increased across age in typically developing children, but pwAS maintained a similar, significantly lower, walk ratio. Similar to younger pwAS, older individuals showed normalized step width that was higher than typically developing range, with all *z*-scores between 2.2 and 8.3 SDs. All eGVI were beyond 3.3 *z*-scores (Table 2). Differences in temporal–spatial gait parameters were exacerbated when we compared *z*-scores with the 8–11-year-olds showing larger deviations from typically developing peers than 4–6-year-old pwAS compared to typically developing peers. Similar trends were observed in the IGA group. Walking speed, step width, and walk ratio decreased as compared to age matched controls. Step width was conversely increased in most individuals. In the IGA group GDI was collected. These *z*-scores ranged from approximately −3 to −8.38 indicating significantly deficient gait performance as compared to age matched controls (Table 3). These metrics are not completely analogous but both metrics indicate gait aberrations across each group. Notably there were less deficits in step width across the IGA group as opposed to the Zeno Walkway group.

We investigated the effect of altered gait patterns on activity levels of pwAS with a magneto-inertial sensor ($n = 5$) to quantitatively observe behavior in the home environment. PwAS tolerated the device for several hours during the day and repeatedly accepted the device. Individuals with AS walk less and at a slower stride speed than controls. Distance walked was normalized to the duration of activity recorded. PwAS presented with a distance walked per hour of data recording significantly lower than control subjects (Figure 2a, $U = 225$, $p = 0.000$). Stride velocity at the 95th percentile (Figure 2b, $U = 225$, $p = 0.000$) was lower in pwAS than in typically developing individuals. Inversely, the median stride duration was higher in pwAS. PwAS showed shorter stride lengths than typically developing controls ($U = 225$, $p = 0.000$). Interestingly, we noted that in Angelman the coefficient of variation of the stride velocity was on average 1.55 smaller in pwAS as compared to controls ($U = 225$, $p = 0.000$).

Six unique pwAS were analyzed, of which three patients had a single follow-up IGA. This resulted in a total of 9 IGA used for this analysis. Overall results revealed that pwAS demonstrated increased average anterior pelvic tilt relative to age-matched typically developing peers (Figure 3a). PwAS also demonstrated increased average hip and knee flexion relative to age-matched typically developing children (Figure 3b, c). PwAS displayed a kinematic pattern of movement typical of the flexed-knee gait pattern. Average GDI was 72.07, indicating that kinematics were on average 3 SD away from typically developing average kinematics (Figure 3d). Longitudinal IGA on three individuals showed that the flexed knee gait pattern was persistent across multiple time points, in which one patient showed signs of further developing an increased knee flexion gait pattern. Additionally, increased knee flexion resulted in increased demand on the quadriceps, as demonstrated by increased quadriceps EMG activity through stance period (Figure 4). These compensatory mechanisms can also be seen in sagittal plane kinetics, where a reduced internal hip flexion moment at terminal stance and pre-swing results in reduced hip flexor power generation during second double support (Figure 5). The knee kinetics show an extended internal knee extension moment directly related to the increased knee flexion throughout stance period, necessitating the increased quadriceps EMG activity noted above. Physical examination of the lower extremities demonstrated that pwAS had a normal passive range of motion at the hip; however, had tightness at the hamstrings and quadriceps, as assessed by popliteal angle and knee extension respectively (Table 4). Furthermore, it was found that half of the participants (3 pwAS) had a hip flexion contracture, as assessed by the Thomas test (Table 4).

Modified Ashworth tests showed little to no spasticity, in which patients experienced a slight increase in spasticity, mainly in the shank (gastrocnemius, posterior tibialis, toe flexors), while most pwAS experienced no spasticity at all (Table 4).

4 | DISCUSSION

Our analysis of motor development in AS revealed a decline in mobility associated with sustained knee flexion or "crouch" gait pattern. Crouch gait is a pattern that commonly refers to excessive dorsiflexion at the ankle in combination with excessive flexion at the knee and hip, typically found in individuals with cerebral palsy (Rodda et al., 2006; Rodda et al., 2012; Rodda & Graham, 2001; Vuillermin et al., 2011). It allows for individuals to generate larger ground reaction force profiles (Hoang & Reinbolt, 2012), which is theorized to improve stability for individuals with motor impairments by maintaining a lower center of gravity. While the gait pattern of the five participants in this study are most appropriately defined as a "flexed-knee gait," understanding the functional impacts of this common pattern in pwAS represents an important area for future research. The increased knee flexion and increased step width may suggest balance deficits consistent with clinical observation or fall risks that should be monitored or could be used for clinical trial outcomes.

Our data also suggests that there are a number of consequences of altered gait in this population. Temporal–spatial measures (Figure 1) demonstrate that pwAS spend greater time in stance relative to swing period. EMG data showed increased demand on the quadriceps, which is demonstrated by prolonged activation throughout stance period. This finding exemplifies inefficiency of the flexed-knee gait pattern, in which AS individuals require a longer duty cycle from the knee extensors, potentially reducing their endurance and leading to a more sedentary lifestyle with significant impact on quality of life and cardiovascular health implications (Heyn et al., 2019). These increased demands at the hips, knees, and ankles result in gait inefficiencies that require prolonged muscle firing in the quadriceps and gastrocnemius to remain upright. This likely also holds true in gluteus maximus firing throughout stance though this was not recorded in our IGA cohort. Inefficiencies from prolonged activation of the quadriceps fatigues the individual much faster relative to the typical bipedal gait pattern; this is supported by inertial findings consistent with decreased distanced traveled normalized to the duration during which activity was recorded (Figure 2).

The absence of spasticity by use of the modified Ashworth scale was an unexpected finding given the classic description of spasticity in pwAS (Table 4). This finding is important to further explore given the frequent use of botulinum toxin in this population, which could lead to further weakness or gait impairments in the absence of spasticity (Beckung et al., 2004).

Our work is limited by the small number of participants and that this study was cross-sectional rather than longitudinal. Nevertheless, our study demonstrated that wearing a device to study gait and activity levels in a real-life setting may be accepted by children with AS. It also revealed that all individuals with AS equipped with a wearable magneto-inertial sensor present with a lower stride length, and decreased performance at the 95 percentile for speed in comparison to controls like what has been described in neuromuscular diseases such as Duchenne muscular dystrophy or spinal muscular atrophy (Chabanon et al., 2018). Work is ongoing to develop more specific outcomes in the non-controlled environment that account not only for reduced performances, but also for ataxia. PwAS had abnormal patterns at different ages, including a consistently wider stride and shorter steps while TD children maintain a narrow, stable stride, and increase in their step length as they age. Additionally, it is important to note that variability in gait may be influenced by cognitive difficulties in this population influencing completion of walking tasks, thus confounding interpretation of variability measures. We acknowledge that due to our small sample of retrospective data, we cannot generalize these kinematic and physical examination findings to the greater Angelman population; however, this methodology remains of great interest for quantitative measurement of gait development in clinical trials, especially considering recently reported serious adverse events in an ASO trial.

The idea to tailor attention on gait is gaining momentum for Rett syndrome, neurofibromatosis, Down syndrome, and other NDDs (Hampton et al., 2004). We identified a decline in mobility and functionally characterized this decline with kinematics to show that pwAS develop a flexed-knee gait pattern. This work can be expanded to other NDDs, such as Phelan-McDermid Syndrome, Duplication15q Syndrome, and autism spectrum disorders, for which there is a growing body of evidence that there exists a relationship between degree of motor deficit and other behavioral domains, such as social communication and cognition (Copping et al., 2016; DiStefano et al., 2016; Shumway et al., 2011; Soorya et al., 2018). Gait showed convincing evidence as a robust, reliable, consistent, and objective phenotype. As an outcome measure, it may be employed immediately with a high predictive value for therapeutic testing and clinical trials at a time when gene therapy by antisense oligonucleotides is underway in human trials. In addition, many forthcoming trials of personalized treatments such as viral vector therapy are threatened by a lack of primary objective and quantitative endpoints.

ACKNOWLEDGMENTS

Angelman Gait Group: Alex Tagawa, Fenna Phibbs, Damien Eggenspieler, Lucas Moore, Stela P. Petkova.

This study was generously supported by a grant awarded to Jessica Duis and Jill L. Silverman from the Foundation for Angelman Syndrome Therapeutics and NICHD (HD103526).

Jessica Duis and Laurent Servais have consulted for GeneTX Bio HD103526 therapeutics and Roche.

Melanie Annoussamy is employed by Sysnav.

Arnaud Gouelle was employed by ProtoKinetics.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

Ackerly S, Vitztum C, Rockley B, & Olney B (2003). Proximal femoral resection for subluxation or dislocation of the hip in spastic quadriplegia. Developmental Medicine and Child Neurology, 45(7), 436–440. 10.1017/s0012162203000823 [PubMed: 12828396]

Beckung E, Steffenburg S, & Kyllerman M (2004). Motor impairments, neurological signs, and developmental level in individuals with Angelman syndrome. Developmental Medicine and Child Neurology, 46(4), 239–243. 10.1017/s0012162204000398 [PubMed: 15077701]

Bird LM (2014). Angelman syndrome: Review of clinical and molecular aspects. The Application of Clinical Genetics, 7, 93–104. 10.2147/TACG.S57386 [PubMed: 24876791]

Bogen B, Moe-Nilssen R, Ranhoff AH, & Aaslund MK (2018). The walk ratio: Investigation of invariance across walking conditions and gender in community-dwelling older people. Gait & Posture, 61, 479–482. 10.1016/j.gaitpost.2018.02.019 [PubMed: 29494821]

Burdekin ED, Fogel BL, Jeste SS, Martinez J, Rexach JE, DiStefano C, Hyde C, Safari T, & Wilson RB (2020). The neurodevelopmental and motor phenotype of SCA21 (ATX-TMEM240). Journal of Child Neurology, 35(14), 953–962. 10.1177/0883073820943488 [PubMed: 32705938]

Chabanon A, Seferian AM, Daron A, Pereon Y, Cances C, Vuillerot C, De Waele L, Cuisset JM, Laugel V, Schara U, Gidaro T, Gilabert S, Hogrel JY, Baudin PY, Carlier P, Fournier E, Lowes LP, Hellbach N, Seabrook T, … NatHis-SMA Study Group. (2018). Prospective and longitudinal natural history study of patients with Type 2 and 3 spinal muscular atrophy: Baseline data NatHis-SMA study. PLoS One, 13(7), e0201004. 10.1371/journal.pone.0201004 [PubMed: 30048507]

Copping NA, Berg EL, Foley GM, Schaffler MD, Onaga BL, Buscher N, Silverman JL, & Yang M (2016). Touchscreen learning deficits and normal social approach behavior in the Shank3B model of Phelan-McDermid Syndrome and autism. Neuroscience, 345, 155–165. 10.1016/j.neuroscience.2016.05.016 [PubMed: 27189882]

Costales JL, & Kolevzon A (2015). Phelan-McDermid syndrome and SHANK3: Implications for treatment. Neurotherapeutics, 12(3), 620–630. 10.1007/s13311-015-0352-z [PubMed: 25894671]

Davis RB, Õunpuu S, Tyburski D, & Gage JR (1991). A gait analysis data collection and reduction technique. Human Movement Science, 10(5), 575–587. 10.1016/0167-9457(91)90046-z

Dhamne SC, Silverman JL, Super CE, Lammers SHT, Hameed MQ, Modi ME, Copping NA, Pride MC, Smith DG, Rotenberg A, Crawley JN, & Sahin M (2017). Replicable in vivo physiological and behavioral phenotypes of the Shank3B null mutant mouse model of autism. Molecular Autism, 8, 26. 10.1186/s13229-017-0142-z [PubMed: 28638591]

DiStefano C, Gulsrud A, Huberty S, Kasari C, Cook E, Reiter LT, Thibert R, & Jeste SS (2016). Identification of a distinct developmental and behavioral profile in children with Dup15q syndrome. Journal of Neurodevelopmental Disorders, 8, 19. 10.1186/s11689-016-9152-y [PubMed: 27158270]

Erickson CA, Davenport MH, Schaefer TL, Wink LK, Pedapati EV, Sweeney JA, Fitzpatrick SE, Brown WT, Budimirovic D, Hagerman RJ, Hessl D, Kaufmann WE, & Berry-Kravis E (2017). Fragile X targeted pharmacotherapy: Lessons learned and future directions. Journal of Neurodevelopmental Disorders, 9, 7. 10.1186/s11689-017-9186-9 [PubMed: 28616096]

Gentile JK, Tan WH, Horowitz LT, Bacino CA, Skinner SA, Barbieri-Welge R, Bauer-Carlin A, Beaudet AL, Bichell TJ, Lee HS, Sahoo T, Waisbren SE, Bird LM, & Peters SU (2010). A neurodevelopmental survey of Angelman syndrome with genotype-phenotype correlations. Journal of Developmental and Behavioral Pediatrics, 31(7), 592–601. 10.1097/DBP.0b013e3181ee408e [PubMed: 20729760]

Gouelle A, Leroux J, Bredin J, & Megrot F (2016). Changes in gait variability from first steps to adulthood: Normative data for the gait variability index. Journal of Motor Behavior, 48(3), 249–255. 10.1080/00222895.2015.1084986 [PubMed: 26392028]

Gouelle A, Rennie L, Clark DJ, Megrot F, & Balasubramanian CK (2018). Addressing limitations of the gait variability index to enhance its applicability: The enhanced GVI (EGVI). PLoS One, 13(6), e0198267. 10.1371/journal.pone.0198267 [PubMed: 29856818]

Grieco JC, Gouelle A, & Weeber EJ (2018). Identification of spatio-temporal gait parameters and pressure-related characteristics in children with Angelman syndrome: A pilot study. Journal of

Applied Research in Intellectual Disabilities, 31(6), 1219–1224. 10.1111/jar.12462 [PubMed: 29737626]

Hampton TG, Stasko MR, Kale A, Amende I, & Costa AC (2004). Gait dynamics in trisomic mice: Quantitative neurological traits of down syndrome. Physiology & Behavior, 82(2–3), 381–389. 10.1016/j.physbeh.2004.04.006 [PubMed: 15276802]

Heyn PC, Tagawa A, Pan Z, Thomas S, & Carollo JJ (2019). Prevalence of metabolic syndrome and cardiovascular disease risk factors in adults with cerebral palsy. Developmental Medicine and Child Neurology, 61(4), 477–483. 10.1111/dmcn.14148 [PubMed: 30663044]

Hoang HX, & Reinbolt JA (2012). Crouched posture maximizes ground reaction forces generated by muscles. Gait & Posture, 36(3), 405–408. 10.1016/j.gaitpost.2012.03.020 [PubMed: 22542242]

Hof AL (1996). Scaling gait data to body size. Gait & Posture, 4(3), 222–223. 10.1016/0966-6362(95)01057-2

Jiang YH, Armstrong D, Albrecht U, Atkins CM, Noebels JL, Eichele G, Sweatt JD, & Beaudet AL (1998). Mutation of the Angelman ubiquitin ligase in mice causes increased cytoplasmic p53 and deficits of contextual learning and long-term potentiation. Neuron, 21(4), 799–811. [PubMed: 9808466]

Kadaba MP, Wootten ME, Gainey J, & Cochran GV (1985). Repeatability of phasic muscle activity: Performance of surface and intramuscular wire electrodes in gait analysis. Journal of Orthopaedic Research, 3(3), 350–359. 10.1002/jor.1100030312 [PubMed: 4032106]

Kolevzon A, Ventola P, Keary CJ, Heimer G, Neul JL, Adera M, & Jaeger J (2021). Development of an adapted clinical global impression scale for use in Angelman syndrome. Journal of Neurodevelopmental Disorders, 13(1), 3. 10.1186/s11689-020-09349-8 [PubMed: 33397286]

Leboeuf F, Reay J, Jones R, & Sangeux M (2019). The effect on conventional gait model kinematics and kinetics of hip joint centre equations in adult healthy gait. Journal of Biomechanics, 87, 167–171. 10.1016/j.jbiomech.2019.02.010 [PubMed: 30808499]

Lilien C, Gasnier E, Gidaro T, Seferian A, Grelet M, Vissiere D, & Servais L (2019). Home-based monitor for gait and activity analysis. Journl of Visualized Experiments, (150). 10.3791/59668

Matsuura T, Sutcliffe JS, Fang P, Galjaard RJ, Jiang YH, Benton CS, Rommens JM, & Beaudet AL (1997). De novo truncating mutations in E6-AP ubiquitin-protein ligase gene (UBE3A) in Angelman syndrome. Nature Genetics, 15(1), 74–77. 10.1038/ng0197-74 [PubMed: 8988172]

Pierpont EI, Pierpont ME, Mendelsohn NJ, Roberts AE, Tworog-Dube E, & Seidenberg MS (2009). Genotype differences in cognitive functioning in Noonan syndrome. Genes, Brain, and Behavior, 8(3), 275–282. 10.1111/j.1601-183X.2008.00469.x [PubMed: 19077116]

Rodda J, & Graham HK (2001). Classification of gait patterns in spastic hemiplegia and spastic diplegia: A basis for a management algorithm. European Journal of Neurology, 8(Suppl 5), 98–108. 10.1046/j.1468-1331.2001.00042.x [PubMed: 11851738]

Rodda JM, Graham HK, Nattrass GR, Galea MP, Baker R, & Wolfe R (2006). Correction of severe crouch gait in patients with spastic diplegia with use of multilevel orthopaedic surgery. The Journal of Bone and Joint Surgery. American Volume, 88(12), 2653–2664. 10.2106/JBJS.E.00993 [PubMed: 17142416]

Rodda JM, Scheffer IE, McMahon JM, Berkovic SF, & Graham HK (2012). Progressive gait deterioration in adolescents with Dravet syndrome. Archives of Neurology, 69(7), 873–878. 10.1001/archneurol.2011.3275 [PubMed: 22409937]

Schwartz MH, & Rozumalski A (2008). The gait deviation index: A new comprehensive index of gait pathology. Gait & Posture, 28(3), 351–357. 10.1016/j.gaitpost.2008.05.001 [PubMed: 18565753]

Shumway S, Thurm A, Swedo SE, Deprey L, Barnett LA, Amaral DG, Rogers SJ, & Ozonoff S (2011). Brief report: Symptom onset patterns and functional outcomes in young children with autism spectrum disorders. Journal of Autism and Developmental Disorders, 41(12), 1727–1732. 10.1007/s10803-011-1203-3 [PubMed: 21360021]

Soorya L, Leon J, Trelles MP, & Thurm A (2018). Framework for assessing individuals with rare genetic disorders associated with pro-found intellectual and multiple disabilities (PIMD): The example of Phelan McDermid syndrome. The Clinical Neuropsychologist, 32(7), 1226–1255. 10.1080/13854046.2017.1413211 [PubMed: 29265961]

Sutcliffe JS, Jiang YH, Galijaard RJ, Matsuura T, Fang P, Kubota T, Christian SL, Bressler J, Cattanach B, Ledbetter DH, & Beaudet AL (1997). The E6-Ap ubiquitin-protein ligase (UBE3A) gene is localized within a narrowed Angelman syndrome critical region. Genome Research, 7(4), 368–377. [PubMed: 9110176]

Vuillermin C, Rodda J, Rutz E, Shore BJ, Smith K, & Graham HK (2011). Severe crouch gait in spastic diplegia can be prevented: A population-based study. Journal of Bone and Joint Surgery. British Volume (London), 93(12), 1670–1675. 10.1302/0301-620X.93B12.27332

Williams CA (2010). The behavioral phenotype of the Angelman syndrome. American Journal of Medical Genetics. Part C, Seminars in Medical Genetics, 154C(4), 432–437. 10.1002/ajmg.c.30278 [PubMed: 20981772]

Wilson RB, Elashoff D, Gouelle A, Smith BA, Wilson AM, Dickinson A, Safari T, Hyde C, & Jeste SS (2020). Quantitative gait analysis in duplication 15q syndrome and nonsyndromic ASD. Autism Research, 13(7), 1102–1110. 10.1002/aur.2298 [PubMed: 32282133]

Yamasaki K, Joh K, Ohta T, Masuzaki H, Ishimaru T, Mukai T, Niikawa N, Ogawa M, Wagstaff J, & Kishino T (2003). Neurons but not glial cells show reciprocal imprinting of sense and antisense transcripts of Ube3a. Human Molecular Genetics, 12(8), 837–847. [PubMed: 12668607]

Zwanenburg RJ, Ruiter SA, van den Heuvel ER, Flapper BC, & Van Ravenswaaij-Arts CM (2016). Developmental phenotype in Phelan-McDermid (22q13.3 deletion) syndrome: A systematic and prospective study in 34 children. Journal of Neurodevelopmental Disorders, 8, 16. 10.1186/s11689-016-9150-0 [PubMed: 27118998]

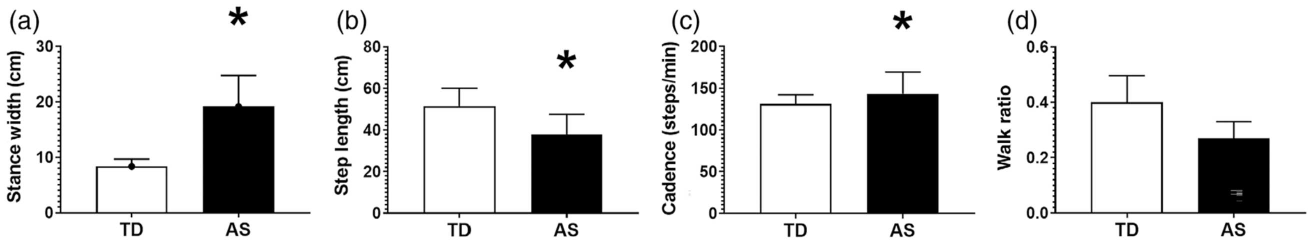

FIGURE 1.

Over development, gait patterns in AS children studied on the Zeno Walkway show a regression toward maladaptive gait. (a) pwAS exhibited wider stances than TD children at all ages. (b) While TD children showed increasing step lengths, pwAS maintained smaller steps and these steps were significantly shorter from age 6 onwards. (c) pwAS and TD children showed different cadences by age. At 6–8 years old, AS children had a significantly higher cadence. (d) Walk ratio increased across age in TD children, but AS children maintained a similar, significantly lower, walk ratio.

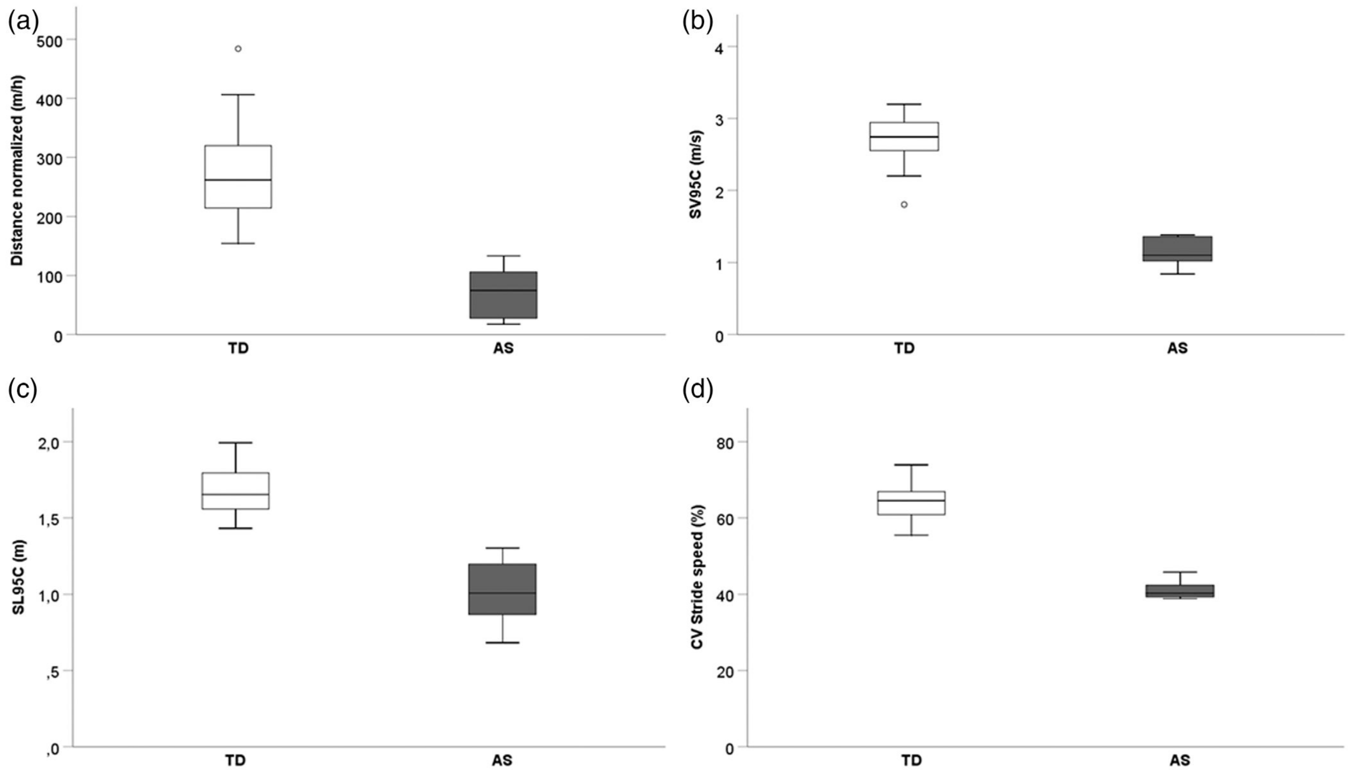

FIGURE 2.

pwAS walk less and with slower stride velocity compared to TD peers. (a) Data collected in five subjects using the ActiMyo® wearable device on bilateral ankles (a, b) Distance walked normalized to the duration during which activity was recorded. Individuals with AS present with a lower distance walked per hour of recording data compared to TD subjects. (b) pwAS compared to TD showed decreased stride velocity. (c) 95th Centile of stride length was lower in individuals with AS. (d) Individuals with AS had lower variability in their stride speed.

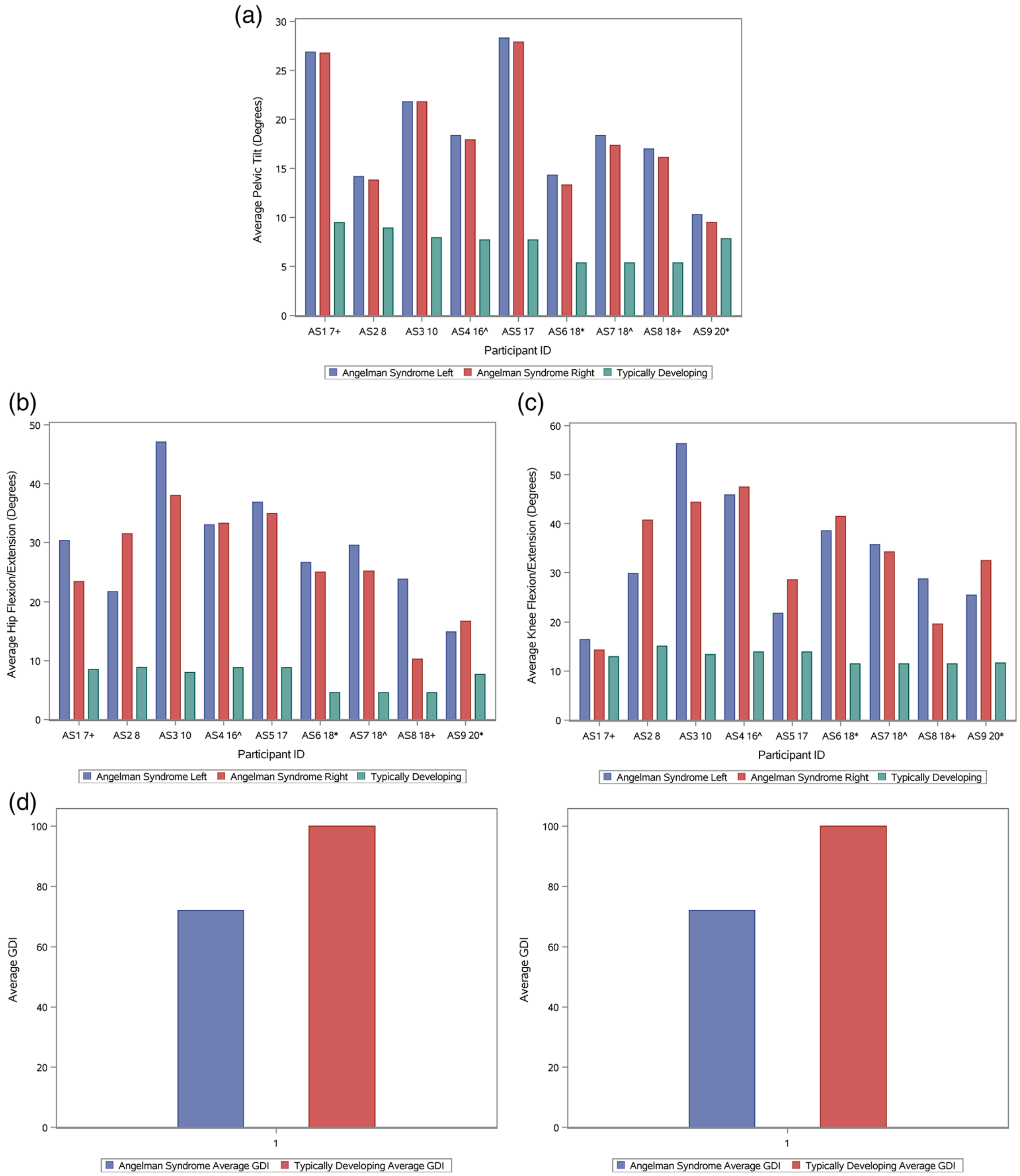

FIGURE 3.

pwAS demonstrate a flexed knee gait pattern which correlates with abnormal electromyographic patterns. (a) pwAS showed markedly increased anterior pelvic tilt relative to age-matched TD subjects with no apparent age dependence. (b) pwAS showed increased average hip flexion over stance period of the gait cycle relative to TD subjects. At all ages, there was a substantive increase in hip flexion, which is consistent with anterior pelvic tilt and flexed knee gait. (c) pwAS consistently demonstrated increased knee flexion over stance period. (d) Gait Deviation Index from the 3D gait analysis was reduced in pwAS. This cohort demonstrated global motor deficits as evidenced by a mean GDI of 71·4.

Though this cohort is small ($n = 5$), this overall motor deficit is reflected throughout our study. Bars represent mean ± SD.

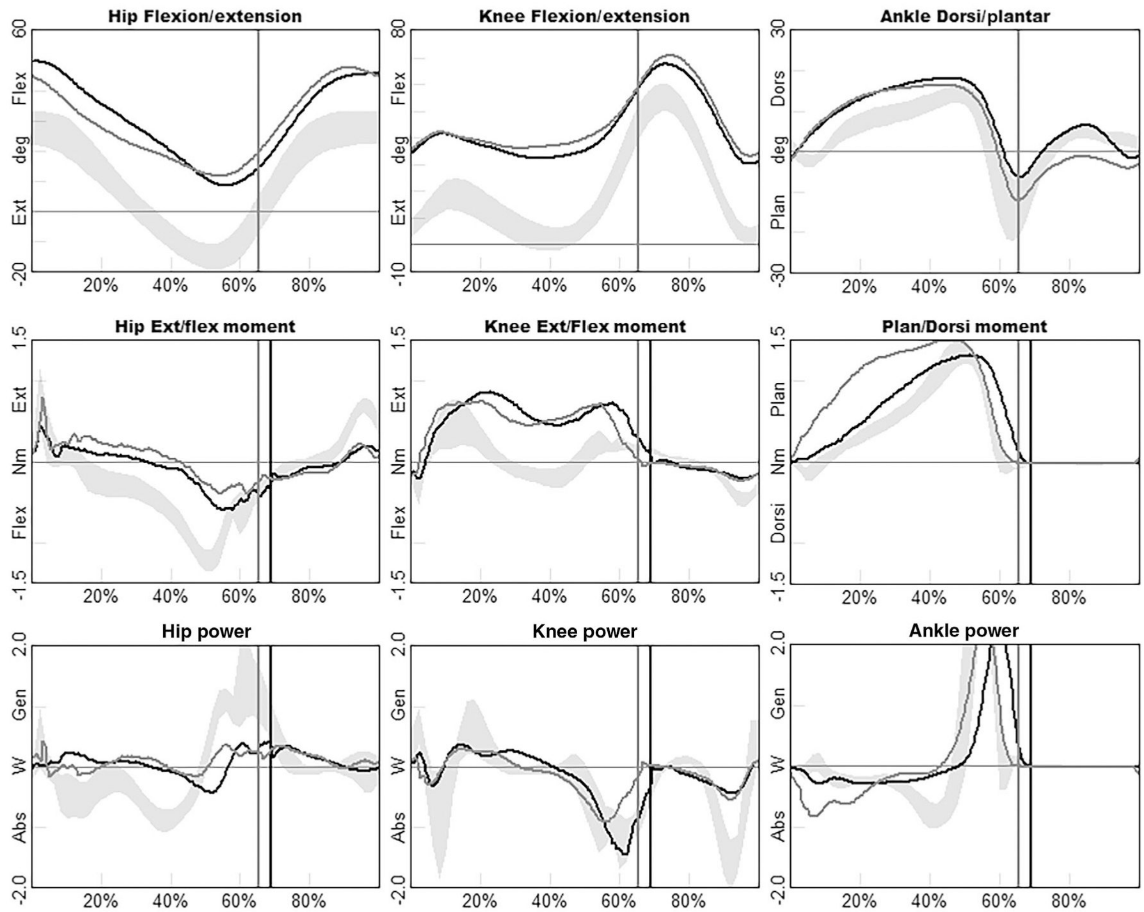

FIGURE 4.

Electromyographic data for an 18-year-old pwAS, generated from IGA, was representative of all five Individuals in this cohort. EMG activation timing from typically developing individuals is shown in black bars across the bottom of each panel. Vertical lines indicate the boundary between stance and swing period. Patient data is shown as a processed waveform.

Author Manuscript
Author Manuscript
Author Manuscript

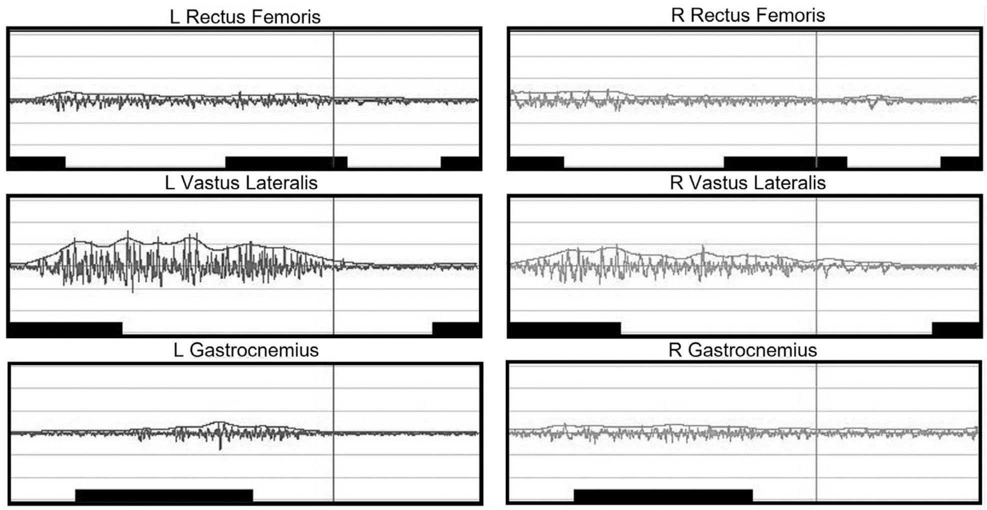

FIGURE 5.

Representative sagittal plane kinematic and kinetic report for an 18-year-old pwAS generated from a full instrumented gait analysis. Patient data is shown in black lines (left) and gray lines (right) with reference ranges from TD controls shown as gray bands. Vertical lines indicate the boundary between stance and swing period.

TABLE 1

Patient demographic and clinical characteristics.

	n	%
Sex		
Female	8	34.8
Male	15	65.2
AS diagnosis		
Uniparental disomy	4	17.4
Deletion class I	4	17.4
Deletion class II	5	21.7
Deletion (unspecified)	5	21.7
Abnormal methylation	1	4.4
Mutation of UBE3A	4	17.4
Study cohort		
Zeno Walkway	17	73.9
ActiMyo Activity Monitoring[a]	5	21.7
Three-dimensional Instrumented Gait Analysis	6	26.1

[a]All subjects in the ActiMyo cohort were part of the Zeno Walkway cohort.

TABLE 2

Normalized temporal–spatial *z*-scores calculated from Zeno Walkway gait analyses of 17 children with AS.

Age	Angelman origin	Walking speed z score	Step length z score	Cadence z score	Step width z score	EGVI z score	Adjusted walking speed z score	Adjusted step length z score
4	Deletion class II	−2.84563	−3.88562	−0.47115	11.4451	2.94101	−2.6822	−3.63777
4	Uniparental disomy	−2.39543	−2.95504	−0.73452	8.4549	3.32014	−1.93099	−2.2195
5	Deletion class I	−0.32847	−0.78833	0.47148	7.0639	2.88818	−0.5066	−1.03552
5	Deletion class II	3.50489	2.47254	2.27488	2.7222	2.03756	2.72188	1.55477
5	Deletion	2.11869	1.9108	0.73339	3.3677	2.9764	2.33464	2.19223
5	Deletion	−3.57752	−4.68048	−0.89196	15.9983	4.34439	−3.34798	−4.30302
5	Deletion class I	−0.62241	−0.01823	−1.17211	13.5991	2.38625	−0.6521	−0.06583
6	Mutation of UBE3A	−0.52967	−2.42806	2.14275	3.5224	3.15942	−0.11835	−2.0469
6	Deletion class I	−0.95132	−2.10123	1.10821	9.7056	4.08405	−0.51849	−1.65255
6	Uniparental disomy	−0.14784	−2.30592	2.64955	1.8806	2.55005	−0.34514	−2.48248
6	Deletion	1.56416	−2.1111	4.78144	4.9839	3.60944	2.56034	−1.36684
6	Uniparental disomy	−0.70753	−2.03277	1.64506	5.7124	3.02291	0.22716	−1.08935
8	Deletion class I	−1.46658	−1.57775	−0.55122	8.0245	4.01837	−1.05172	−1.07473
9	Deletion	−4.55715	−4.38802	−2.06832	5.7596	8.41422	−4.18994	−3.8941
10	UPD	−4.7167	−4.95049	−1.1118	4.568	9.44088	−4.55794	−4.74906
10	Mutation of UBE3A	1.90083	−1.46721	5.0742	2.2883	5.18303	1.6551	−1.67011
11	Deletion	−5.63689	−5.70241	−2.17719	5.6192	8.8642	−5.72557	−5.82465

TABLE 3

Normalized temporal–spatial *z*-scores calculated from instrumented gait analyses of nine children with AS.

Unique study ID	Age	Walking speed z score	Step length z score	Cadence z score	Step width z score	GDI z score	Adjusted walking speed z score	Adjusted step length z score	Adjusted step width z score	Adjusted walk ratio z score
1	7	−5.6172	−6.9153	−4.15606	4.26111	−4.6937	−4.98093	−6.42286	3.92071	−2.52325
5	8	−0.8883	1.62614	−2.47717	−0.2357	−4.4818	−2.25403	−1.67751	−0.8856	1.07263
6	10	−3.8979	−3.9844	−2.7773	0.97549	−8.3887	−4.28873	−5.02778	0.58544	−2.23734
4	16	−2.6353	−2.7253	−3.61985	−0.5803	−7.5884	−1.99481	−1.85886	−1.04145	−0.84912
2	17	−2.0912	−3.1102	−0.62101	3.3601	−6.8602	−1.12495	−1.37809	8.20766	−1.90724
3	18	−3.3823	−3.1219	−2.48062	−0.38	−4.9764	−3.23249	−3.53004	−0.56514	−1.59065
4	18	−3.9484	−3.7947	−3.01882	0.91483	−4.9717	−3.55296	−3.83933	0.97499	−1.46925
1	18	−5.9153	−6.7233	−4.69289	−0.228	−5.3018	−5.08507	−6.21029	0.35033	−3.14514
3	20	−2.3605	−2.7827	−0.77494	0.78629	−3.0092	−2.39151	−3.25569	0.56953	−2.60354

Note: Adjusted measures accounted for height, in which both the patient and normal database accounted for a patient’s height.

TABLE 4

Physical examination data of 3D gait analysis cohort.

Patient (identified by age)	Hamstrings L/R	Quadriceps L/R	Peroneals L/R	Post. Tib. L/R	Toe flexors L/R	Gastrocnemius L/R	Hip flexion L/R	Hip extension L/R	Knee flexion L/R	Knee extension L/R	Thomas test L/R	Popliteal angle L/R
7[1]	*a*	*a*	*a*	*a*	*a*	*a*	120°/115°	10°/10°	140°/140°	5°/0°	0°/0°	−25°/−20°
8[1]	0/0	0/0	0/0	0/0	1/1	1/1	100°/90°	0°/0°	125°/120°	−5°/-5°	10°/10°	−65°/−50°
10	0/0	0/0	0/0	0/0	0/0	0/0	110°/110°	15°/15°	140°/140°	−20°/-20°	0°/0°	−70°/−60°
17[2]	0/0	0/0	0/0	0/0	0/0	0/0	95°/90°	0°/0°	130°/140°	−15°/−15°	10°/10°	−60°/−60°
18	*a*	*a*	*a*	*a*	*a*	*a*	110°/[a]	5°/5°	155°/155°	−5°/10°	*a*	−60°/−40°
18[3]	0/0	0/0	0/0	0/0	0/0	0/0	95°/105°	−5°/−5°	140°/145°	−10°/-10°	10°/10°	−65°/−70°
18	0/0	0/0	0/0	0/1+	0/0	1+/1+	105°/125°	0°/0°	140°/140°	0°/0°	0°/0°	−50°/−60°
18[2]	0/0	0/0	0/0	0/0	0/0	0/0	100°/95°	0°/0°	130°/135°	−10°/-10°	20°/10°	−65°/−60°
20[3]	0/0	0/0	1/1	1/1	2/1	1/1	100°/100°	0°/0°	140°/140°	10°/−15°	5°/5°	−75°/−70°

Note: Modified Ashworth scored from 0 to 4 with 0 = Normal, 1 = Slight increase with catch and release, 1+ = slight increase with catch, 2 = marked increase, 3 = considerable increase, 4 = rigid. Normative ranges as follows: Hip Flexion (0–120°) Hip Extension (0–30°) Knee Flexion (0–135°) Knee Extension (0°) Popliteal Angle (−20 to −15°). Superscript identifies whether the patient had a follow-up assessment.

Those with superscript of the same number represent patients with follow up.

[a]No physical exam data available.