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If Not Angelman, What Is It? A Review of Angelman-like Syndromes

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Angelman syndrome (AS) is caused by a lack of expression of the maternally inherited *UBE3A* gene in the brain. However, about 10% of individuals with a clinical diagnosis of AS do not have an identifiable molecular defect. It is likely that most of those individuals have an AS-like syndrome that is clinically and molecularly distinct from AS. These AS-like syndromes can be broadly classified into chromosomal microdeletion and microduplication syndromes, and single-gene disorders. The microdeletion/microduplication syndromes are now easily identified by chromosomal microarray analysis and include Phelan–McDermid syndrome (chromosome 22q13.3 deletion), *MBD5* haploinsufficiency syndrome (chromosome 2q23.1 deletion), and *KANSL1* haploinsufficiency syndrome (chromosome 17q21.31 deletion). The single-gene disorders include Pitt–Hopkins syndrome (*TCF4*), Christianson syndrome (*SLC9A6*), Mowat–Wilson syndrome (*ZEB2*), Kleefstra syndrome (*EHMT1*), and Rett (*MECP2*) syndrome. They also include disorders due to mutations in *HERC2*, adenylosuccinase lyase (*ADSL*), *CDKL5*, *FOXG1*, *MECP2* (duplications), *MEF2C*, and *ATRX*. Although many of these single-gene disorders can be caused by chromosomal microdeletions resulting in haploinsufficiency of the critical gene, the individual disorders are often caused by intragenic mutations that cannot be detected by chromosomal microarray analysis. We provide an overview of the clinical features of these syndromes, comparing and contrasting them with AS, in the hope that it will help guide clinicians in the diagnostic work-up of individuals with AS-like syndromes. © 2014 Wiley Periodicals, Inc.

Key words: Angelman syndrome; differential diagnoses; Phelan–McDermid syndrome; MBD5 deficiency; KANSL1 deficiency; Pitt–Hopkins syndrome; Christianson syndrome; Mowat–Wilson syndrome; Kleefstra syndrome; HERC2 deficiency; Adenylosuccinase lyase deficiency; ADSL deficiency; Rett syndrome; CDKL5 syndrome; FOXG1 syndrome; MECP2 duplication; MEF2C syndrome; ATRX

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INTRODUCTION

Angelman Syndrome (AS) is a diagnosis that should be considered in individuals who have severe developmental delay in combination with seizures, ataxia, hypermotoric behaviors, and absence of speech. However, only about 90% of these individuals have an identifiable molecular defect that results in the loss of expression of the maternally inherited *UBE3A* gene (encoding E6AP) in the brain, which is considered the *sine qua non* of AS [Ramsden et al., 2010; Williams et al., 2010a]. Over the last few years, many novel

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syndromes that mimic AS have been delineated and it is now recognized that some individuals who were clinically diagnosed with "test-negative AS" have one of these AS-like syndromes instead. In this overview, we summarize the key clinical features of the genetic syndromes that mimic AS to help clinicians determine which of these syndromes should be further considered in the differential diagnoses. This is an update of a similar review published in this journal by one of us (CAW) over a decade ago [Williams et al., 2001].

One of the major characteristics of AS is the relatively unusual developmental profile in which the cognitive abilities are stronger than the receptive language skills, which in turn are much stronger than the expressive language skills [Gentile et al., 2010]. Most individuals with AS do not speak, a minority speak a few single words, and only a few of the very highest functioning individuals are able to speak in short 3–4 word sentences. Another characteristic of AS is sleep dysfunction, including difficulties falling asleep and waking up multiple times at night, which has been reported in 70–80% of affected individuals. Behaviors that are characteristic of AS include a short attention span, an unusually happy demeanor, easily provoked laughter, mouthing of objects, and fascination with water [Angelman, 1965; Buntinx et al., 1995; Clayton-Smith and Laan, 2003; Williams et al., 2006; Tan et al., 2011]. Most individuals with AS enjoy social interactions and seek eye contact with adults. Among the facial features that have been observed in AS are a thin vermilion of the upper lip, widely spaced teeth in younger individuals, as well as mid-face retrusion and prognathism in older individuals. Constipation and gastroesophageal reflux are commonly reported by parents of children with AS. A recent study suggested that all children with AS, including those who have never had clinical seizures, have abnormal electroencephalographic (EEG) patterns such as background slowing, very high voltage slow delta activity, intermittent high-amplitude rhythmic theta activity, and focal, multifocal or generalized epileptiform abnormalities [Tan et al., 2011; Thibert et al., 2013]. The high voltage delta activity is typically present either in the occipital region, or less commonly, in the frontal region with admixed sharp waves giving it a "notched" appearance [Vendrame et al., 2012]. Clinical seizures affect up to 90% of individuals with AS; over 60% of those with seizures have more than one type of seizure, most commonly atypical absence, atonic, myoclonic, or generalized tonic-clonic seizures. Non-convulsive status epilepticus in the form of apparent lethargy, altered consciousness, "head drops" or myoclonic movements, is more common than convulsive status epilepticus, but epileptic spasms are rare [Thibert et al., 2009; Thibert et al., 2013]. Recently, studies using brain MRI with diffusion tensor imaging have revealed that some children with AS have global white matter abnormalities, delayed myelination, and hypoplastic corpus callosum [Peters et al., 2011; Tiwari et al., 2012].

CHROMOSOMAL MICRODELETION AND MICRODUPLICATION SYNDROMES

Chromosomal microdeletions or microduplications are a relatively common cause of severe intellectual disability and expressive language deficit. However, many of these chromosomal aberrations are not detectable by conventional G-banding karyotype; hence, a chromosomal microarray (i.e., microarray comparative genomic hybridization) analysis is indicated for all individuals with AS-like clinical features in whom genetic testing for AS has been unrevealing.

Although many rare chromosomal microdeletions and microduplications are associated with severe developmental disabilities as seen in AS, some microdeletions and microduplications result in specific AS-like presentations, which we will review here. Other AS-like disorders that were initially identified as chromosomal microdeletion syndromes but were subsequently found to be due to haploinsufficiency of a critical gene are discussed in the "Single Gene Syndromes" section below.

Phelan-McDermid Syndrome (Figure 1)

One of the first reported chromosomal mimics of AS was the chromosome 22q13.3 deletion (Phelan–McDermid) syndrome [Precht et al., 1998; Phelan and McDermid, 2012]. Like AS, this condition typically presents with moderate-to-severe global developmental delay with absent or minimal speech, neonatal hypotonia that may persist into adulthood, feeding difficulties in infancy, and mouthing behaviors. However, it is associated with normal or even rapid physical growth, large ears, large hands, and dysplastic toenails, which are features that are not typically associated with AS. Most of these individuals exhibit impaired social interactions and shun eye contact, which would be unusual for individuals with AS [Dhar et al., 2010; Phelan and McDermid, 2012]. Some demonstrate age-appropriate babbling and have "limited vocabulary until 3 or 4 years old" before they lose their expressive language skills, [Phelan and McDermid, 2012] which would also be unusual in children with AS. Although *SHANK3* has been implicated as the critical gene in the chromosome 22q13.3 deletion syndrome, haploinsufficiency of other genes in the region influences the phenotypic expression and severity of the syndrome [Dhar et al., 2010; Sarasua et al., 2011]. In particular, *MAPK8IP2* (also known as *IB2*) located upstream of *SHANK3* is deleted in most cases of chromosome 22q13.3 deletion syndrome, and complete lack of Mapk8ip2 resulted in a reduced ability of knock-out mice to learn and interact socially [Giza et al., 2010]. In a recent study of 10 children with chromosome 22q13.3 terminal deletions of varying sizes, it was found that nine of them had thin corpus callosum and seven had abnormal white matter, which are neuroanatomical findings that have also been observed in AS; however, 8 out of 10 also had abnormalities in their posterior fossa such as cerebellar vermis hypoplasia or enlarged posterior fossa, which are not typically seen in AS. The authors hypothesized that haploinsufficiency of *MAPK8IP2* and *PLXNB2* is responsible for the hindbrain abnormalities [Aldinger et al., 2013]. In a recent study of 32 individuals with Phelan–McDermid syndrome, 13 (41%) had clinical seizures, of whom seven had only febrile seizures. While all six subjects with afebrile seizures had abnormal EEGs, the majority of those with only febrile seizures had normal EEGs, which would be very unusual in AS [Soorya et al., 2013].

MBD5 Haploinsufficiency Syndrome (Figure 2)

Deletion of chromosome 2q23.1 resulting in haploinsufficiency of *MBD5* leads to an AS-like phenotype in many affected individuals.

FIG. 1. Facial features of Phelan–McDermid syndrome. [Reproduced from: Dhar SU, del Gaudio D, German JR, Peters SU, Ou Z, Bader PI, Berg JS, Blazo M, Brown CW, Graham BH, Grebe TA, Lalani S, Irons M, Sparagana S, Williams M, Phillips JA, 3rd, Beaudet AL, Stankiewicz P, Patel A, Cheung SW, Sahoo T. 2010. 22q13.3 deletion syndrome: Clinical and molecular analysis using array CGH. Am J Med Genet A 152A:573–581.]

This phenotype includes severe intellectual disability, motor delay, variable degrees of speech delay ranging from being completely non-verbal to being able to speak in short sentences, autistic and maladaptive behaviors, short attention span, seizures, and constipation than 80% of the affected individuals [Williams et al., 2010b; van Bon et al., 2010; Talkowski et al., 2011; Hodge et al., 2013]. Microcephaly was reported in more than 80% of individuals with chromosome 2q23.1 deletion but in only one out of eight individuals with disruptions or intragenic deletions in *MBD5* alone; similarly ataxia or unusual gait was reported in more than 70% of those with the chromosomal deletion but none in the four individuals with disruptions or deletions in *MBD5* alone [Hodge et al., 2013]. This suggests that other genes are probably responsible for the additional clinical features in individuals with chromosome 2q23.1 haploinsufficiency. The EEG patterns were non-specific and not consistent with those seen in AS, and normal EEG has been reported in at least one of these individuals [Jaillard et al., 2009; van Bon et al., 2010]. Facial features that have been reported in affected individuals include a broad forehead, structural nasal abnormalities such as a short nose and a depressed or broad nasal bridge, and a thick and everted vermilion of the lower lip, all of which would be atypical for AS. Similarly, a variety of minor skeletal abnormalities of the hands and fingers not typically seen in AS, including micromelia, brachydactyly, tapered fingers, and short fifth fingers, have been reported in many of these individuals [van Bon et al., 2010; Williams et al., 2010b; Talkowski et al., 2011].

KANSL1 Haploinsufficiency Syndrome (Koolen–de Vries Syndrome) (Figure 3)

The chromosome 17q21.31 deletion syndrome (Koolen–de Vries syndrome) presents with mild-to-moderate degrees of developmental delays and intellectual disability, but more severe speech and language delays. This condition resembles AS in that the cognitive development appears to be more advanced than the language development; however, "mild" intellectual disability would be extremely unusual in AS. Like children with AS, individuals with chromosome 17q21.31 deletion are hypotonic and consequently

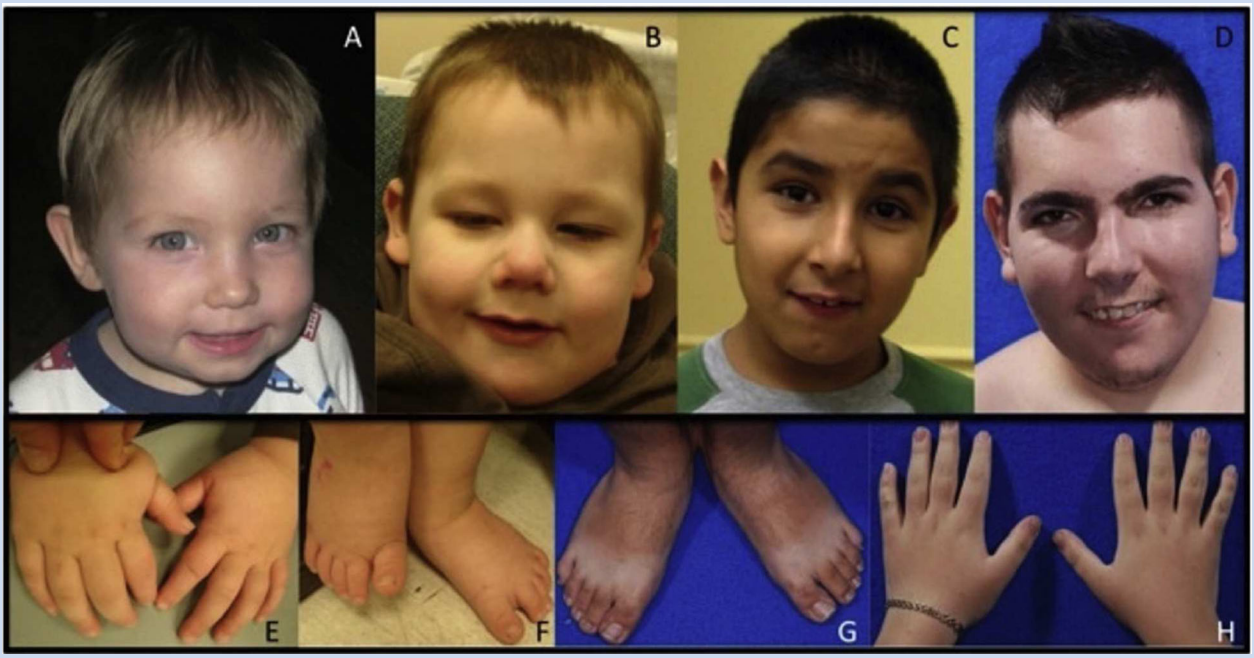

FIG. 2. Facial features and distal limbs of MBD5 haploinsufficiency syndrome. (E and F) Hands and feet of patient (B). (G and H) Hands and feet of patient (D). [Reprinted from: Talkowski ME, Mullegama SV, Rosenfeld JA, van Bon BW, Shen Y, Repnikova EA, Gastier-Foster J, Thrush DL, Kathiresan S, Ruderfer DM, Chiang C, Hanscom C, Ernst C, Lindgren AM, Morton CC, An Y, Astbury C, Brueton LA, Lichtenbelt KD, Ades LC, Fichera M, Romano C, Innis JW, Williams CA, Bartholomew D, Van Allen MI, Parikh A, Zhang L, Wu BL, Pyatt RE, Schwartz S, Shaffer LG, de Vries BB, Gusella JF, Elsea SH. 2011. Assessment of 2q23.1 microdeletion syndrome implicates MBD5 as a single causal locus of intellectual disability, epilepsy, and autism spectrum disorder. Am J Hum Genet 89:551–563, with permission from Elsevier.]

suffer from feeding difficulties in early childhood. They are also very friendly and happy, sometimes laughing easily or frequently. Hypersociability has been observed in some adults with this microdeletion syndrome. Seizures are common, but EEG findings have not been well described. The common findings occurring in 50–75% of these individuals that distinguish them from individuals with AS include: relative macrocephaly, facial dysmorphic features such as a tall or broad forehead, bulbous nasal tip, malformed or large ears, everted vermilion of the lower lip, and narrow or high palate; long fingers and joint laxity; and cryptorchidism [Dubourg et al., 2011; Wright et al., 2011; Egger et al., 2013; Koolen and de Vries, 2013]. Multiple nevi and generalized hyperpigmentation have been found to be very common in older individuals, which suggests that such pigmentation abnormalities may be a good diagnostic clue to this syndrome [Wright et al., 2011]. Recently, two independent groups showed that haploinsufficiency of *KANSL1* (previously known as *KIAA1267*) results in the chromosome 17q21.31 deletion syndrome phenotype [Koolen et al., 2012; Zollino et al., 2012]. Of the four subjects with mutations in *KANSL1* identified by these two groups, all had global developmental delay, hypotonia, unusually friendly and happy personality, a tall or broad forehead, and joint laxity; three out of four subjects had either a long face or large ears, or both. However, none of the four subjects had seizures [Koolen et al., 2012; Zollino et al., 2012]. In the two subjects identified by Koolen et al. [2012], one spoke his first words at 18 months of age while the other spoke her first words at 2 years of age [Koolen et al., 2012]. This suggests that haploinsufficiency of neighboring genes may modulate the phenotypic severity of the chromosome 17q21.31 deletion syndrome. It also suggests that individuals with *KANSL1* mutations do not truly resemble those with AS since it would be extremely unusual for even the most developmentally advanced children with AS to speak their first words before the age of 2 years.

SINGLE GENE SYNDROMES

Mutations in a number of individual genes can result in syndromes that mimic AS, particularly *TCF4* (Pitt–Hopkins syndrome), *SLC9A6* (Christianson syndrome), *ZEB2* (Mowat–Wilson syndrome), and *MECP2* (Rett syndrome). We review these disorders as well as emerging single-gene syndromes with AS-like clinical features.

Pitt–Hopkins Syndrome (Figure 4)

Pitt–Hopkins syndrome is caused by loss-of-function mutations in *TCF4* on chromosome 18q21.2. Like AS, individuals with Pitt–Hopkins syndrome have severe intellectual disabilities with a complete lack of or minimal expressive language, hypotonia, and widely spaced teeth.

FIG. 3. Facial features of KANSL1 haploinsufficiency syndrome (Koolen–De Vries syndrome). [Reproduced from: Koolen DA, de Vries BBA. KANSL1-related intellectual disability syndrome. In: Pagon RA, Adam MP, Bird TD, Dolan CR, Fong CT, Stephens K, editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2013. Available at: http://www.ncbi.nlm.nih.gov/books/NBK24676/, updated January 10, 2013, accessed: July 7, 2013.]

However, peripheral hypertonia is rare in individuals with Pitt–Hopkins syndrome in contrast to AS individuals who tend to become hypertonic in their limbs with increasing age. Seizures have been reported in only 40–50% compared to 65–90% in AS; the age of seizure onset in Pitt–Hopkins syndrome may also be older than that in AS. While individuals with Pitt–Hopkins syndrome generally have a "happy personality," tendencies towards self-aggression and violent behavioral outbursts have been reported. Although they have ataxic gaits like individuals with AS, they tend to develop their ability to walk at a much later age. Sleep difficulties are much less frequently reported than in AS; in fact, some of them are reported to have "slept in excess" in infancy. Other common findings in Pitt–Hopkins syndrome that can help to distinguish it from AS include abnormal helices of the ears, minor hand malformations such as extra or absent phalangeal flexion creases and persistent digit pads in 65–70%, severe chronic constipation of early onset in 70–75% of individuals, breathing abnormalities (typically episodic hyperventilation and/or apnea) in 55–65%, stereotypic hand movements in 40–60%, stereotypic head movements such as head rolling or rotation in 40–45%, and high myopia or strabismus in 80–89%. Of note, the age of onset of the breathing abnormalities is variable and in some individuals, it may resolve spontaneously after several months. Characteristic facial features that have been described in Pitt–Hopkins syndrome include deeply set eyes, malar prominence particularly in the older individuals, and full cheeks [Giurgea et al., 2008; Zweier et al., 2008; de Pontual et al., 2009; Marangi et al., 2012; Peippo and Ignatius, 2012; Whalen et al., 2012]. These facial features coarsen and the lower face protrudes more over time [Amiel et al., 2007]. It has been suggested that the presence of persistent digit pads in an individual with AS-like characteristics should raise the suspicion for Pitt–Hopkins syndrome, as well as chromosome 22q13.3 deletion syndrome and Mowat–Wilson syndrome [Lehalle et al., 2011]. Hypoplasia of the corpus callosum has been reported in both Pitt–Hopkins syndrome and AS individuals. Some individuals with Pitt–Hopkins syndrome also have ventricular dilatation, cerebellar atrophy, and vermian hypoplasia, none of which are typically seen in AS but are common in chromosome 22q13.3 deletion syndrome; in contrast, some AS individuals have delayed myelination and white matter abnormalities, which are not typically found in Pitt–Hopkins syndrome [Marangi et al., 2012; Whalen et al., 2012]. In a study examining the developmental profile of seven children and three adults with Pitt–

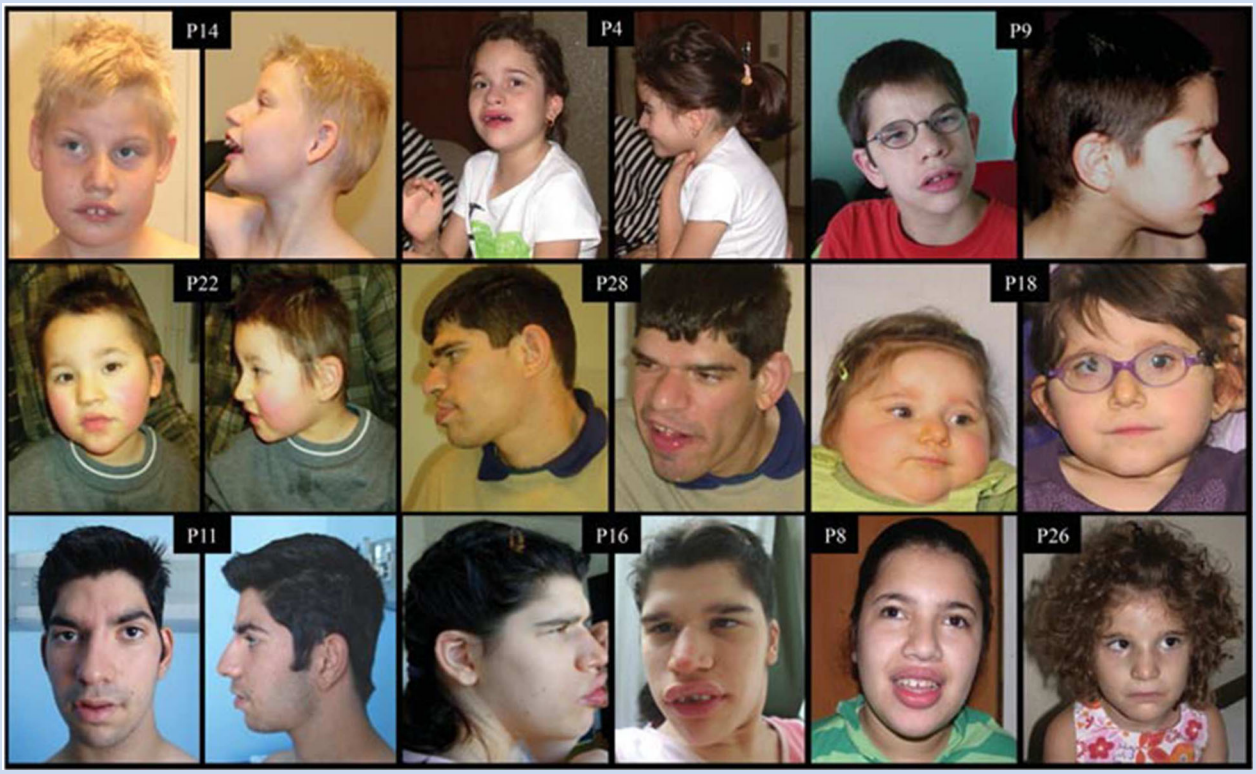

FIG. 4. Facial features of Pitt–Hopkins syndrome. Patient P4 had a large deletion that included the entire *TCF4* gene; P28 had a partial *TCF4* deletion; P8, P14, P16, and P22 had nonsense mutations; P9, P18, and P26 had frameshift mutations; and P11 had a missense mutation. [Reproduced from: Whalen S, Heron D, Gaillon T, Moldovan O, Rossi M, Devillard F, Giuliano F, Soares G, Mathieu-Dramard M, Afenjar A, Charles P, Mignot C, Burglen L, Van Maldergem L, Piard J, Aftimos S, Mancini G, Dias P, Philip N, Goldenberg A, Le Merrer M, Rio M, Josifova D, Van Hagen JM, Lacombe D, Edery P, Dupuis-Girod S, Putoux A, Sanlaville D, Fischer R, Drevillon L, Briand-Suleau A, Metay C, Goossens M, Amiel J, Jacquette A, Giurgea I. 2012. Novel comprehensive diagnostic strategy in Pitt–Hopkins syndrome: Clinical score and further delineation of the TCF4 mutational spectrum. Hum Mutat 33:64–72.]

Hopkins syndrome, all but the youngest child had better "motor" than "mental" (i.e., cognitive) skills, while their socialization skills appeared to be weaker than their daily living or communication skills [Van Balkom et al., 2012]. In contrast, AS children under 5 years of age have better cognitive than motor abilities, and better socialization than daily living or communication skills [Gentile et al., 2010]. These studies suggest that the developmental profile of Pitt–Hopkins syndrome may be quite different from that of AS.

Christianson Syndrome (Figure 5)

Christianson syndrome, an X-linked AS-like disorder, is caused by loss-of-function mutations in *SLC9A6* on chromosome Xq26.3 [Ohgaki et al., 2011; Xinhan et al., 2011]. The features shared with AS include severe intellectual disability with lack of speech, seizures, and ataxic gait in almost all affected individuals. There is also postnatal microcephaly and there may be a happy disposition with easily provoked laughter as well as excessive drooling. Some of them have very poor weight gain, resulting in a "gaunt" appearance in young adulthood. Teenagers often become non-ambulatory. The EEG findings have ranged from normal to "frontal high-amplitude 2–3 Hz" spike and wave activity that is consistent with Lennox–Gastaut syndrome [Schroer et al., 2010]. The most characteristic features that distinguish these individuals from AS are external ophthalmoplegia manifested as horizontal or vertical gaze palsies, as well as developmental regression with loss of motor skills, progressive atrophy of the inferior cerebellar vermis, increased glutamine–glutamate peak in the basal ganglia on magnetic resonance spectroscopy (MRS), and in some individuals, the practice of staring at their hands held up in front of their faces [Christianson et al., 1999; Gilfillan et al., 2008; Garbern et al., 2010; Schroer et al., 2010]. Some adults in an affected family have been reported to have dystonia, and two of these individuals were found to have tau depositions in their neurons and glial cells on post-mortem examination. These findings would be unusual in AS and suggest that dystonia and tau accumulation in neurons and glial cells may be part of the phenotype in Christianson syndrome [Garbern et al., 2010]. Although this condition appears to affect only males, some carrier females have been reported to have learning disabilities and/or behavioral issues, [Christianson et al., 1999; Schroer et al., 2010] and two probable female carriers in a single family were found to have Parkinsonian symptoms, with

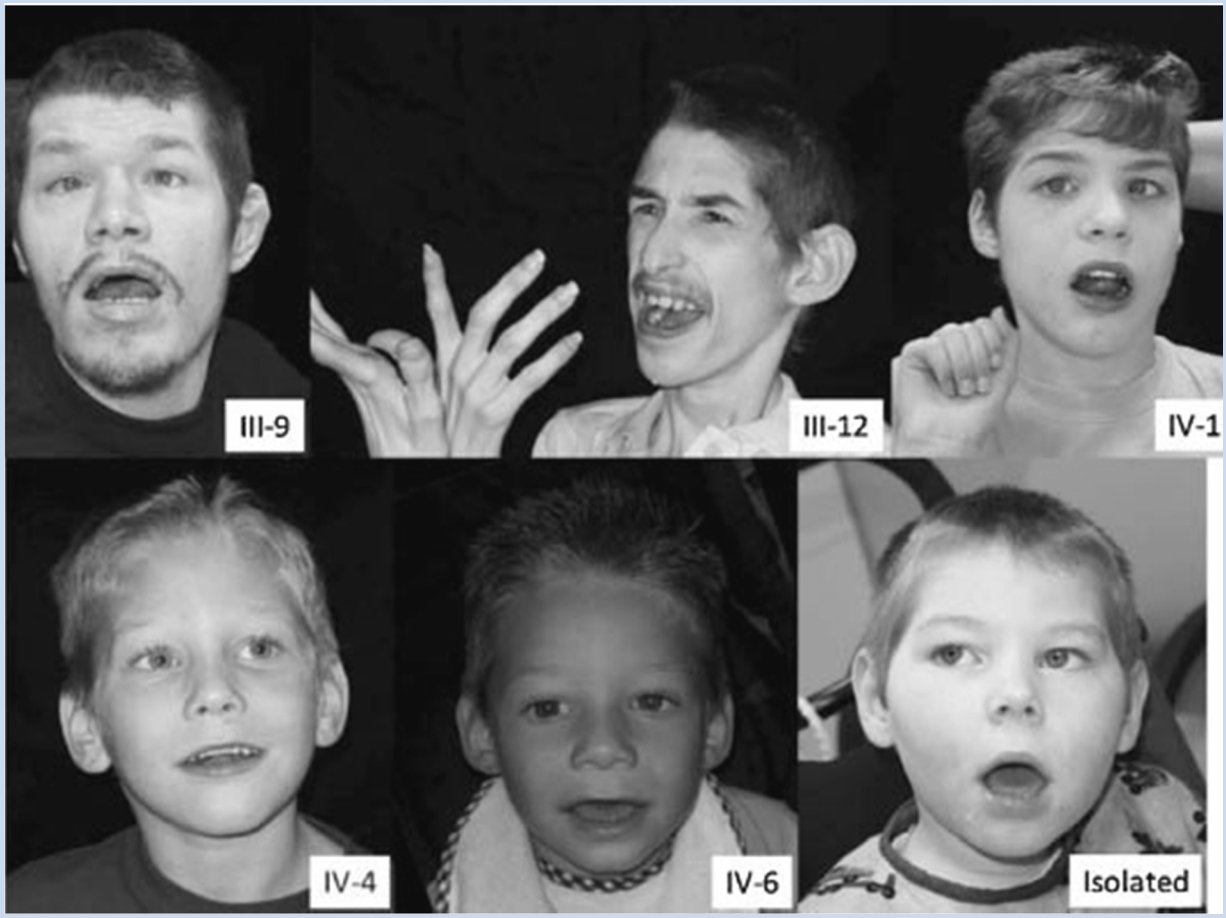

FIG. 5. Facial features of Christianson syndrome. Patients III-9, III-12, IV-1, IV-4, and IV-6 are from two generations of the same family. The "isolated" boy is from a different family. (III-9) At age 35 years; (III-12) At age 28 years; (IV-1) At age 15 years; (IV-4) At age 7 years; (IV-6) At age 14 months; (Isloated) At age 6 years. [Reproduced from: Schroer RJ, Holden KR, Tarpey PS, Matheus MG, Griesemer DA, Friez MJ, Fan JZ, Simensen RJ, Stromme P, Stevenson RE, Stratton MR, Schwartz CE. 2010. Natural history of Christianson syndrome. Am J Med Genet A 152A: 2775–2783.]

onset of symptoms during or after the sixth decade [Riess et al., 2013].

Mowat–Wilson Syndrome (Figure 6)

Mowat–Wilson syndrome, caused by haploinsufficiency of *ZEB2* (*ZFHX1B*) on chromosome 2q22.3, resembles AS in that all individuals have moderate-to-severe intellectual disability with minimal speech but have much better receptive than expressive language skills. Microcephaly, often of gradual post-natal onset, has been observed in more than 80% of the individuals studied. Seizures or EEG abnormalities have been observed in up to 89% of affected individuals. In a recent study of 22 individuals with Mowat–Wilson syndrome, the seizures typically started as focal-onset seizures progressing to atypical absence seizures, but the EEGs were either normal or had only mild background slowing at the onset of seizures, which would be very unusual in AS [Cordelli et al., 2013]. Hypoplasia of the corpus callosum was found in 44% of individuals in one series [Evans et al., 2012]. Some individuals also have a broad-based gait and walk with their arms upheld and elbows flexed as is sometimes seen in individuals with AS. Although Mowat–Wilson syndrome was first described in association with Hirschsprung disease, it is now apparent that fewer than 60% of individuals with Mowat–Wilson syndrome have biopsy-proven Hirschsprung disease; some individuals have chronic constipation without definite pathological evidence of Hirschsprung disease. The presence of congenital anomalies, including structural heart defects that frequently involve the pulmonary valve or arteries, hypospadias, and structural renal anomalies, distinguishes Mowat–Wilson syndrome from AS. Ophthalmologic abnormalities including microphthalmia, coloboma, strabismus, and cataracts are increasingly recognized [Garavelli and Mainardi, 2007; Adam et al., 2008]. In addition, in older children and adults, the characteristic facial gestalt of Mowat–Wilson syndrome allows it to be distinguished easily from AS. The facial features include hypertelorism with or without telecanthus, medially flared eyebrows that

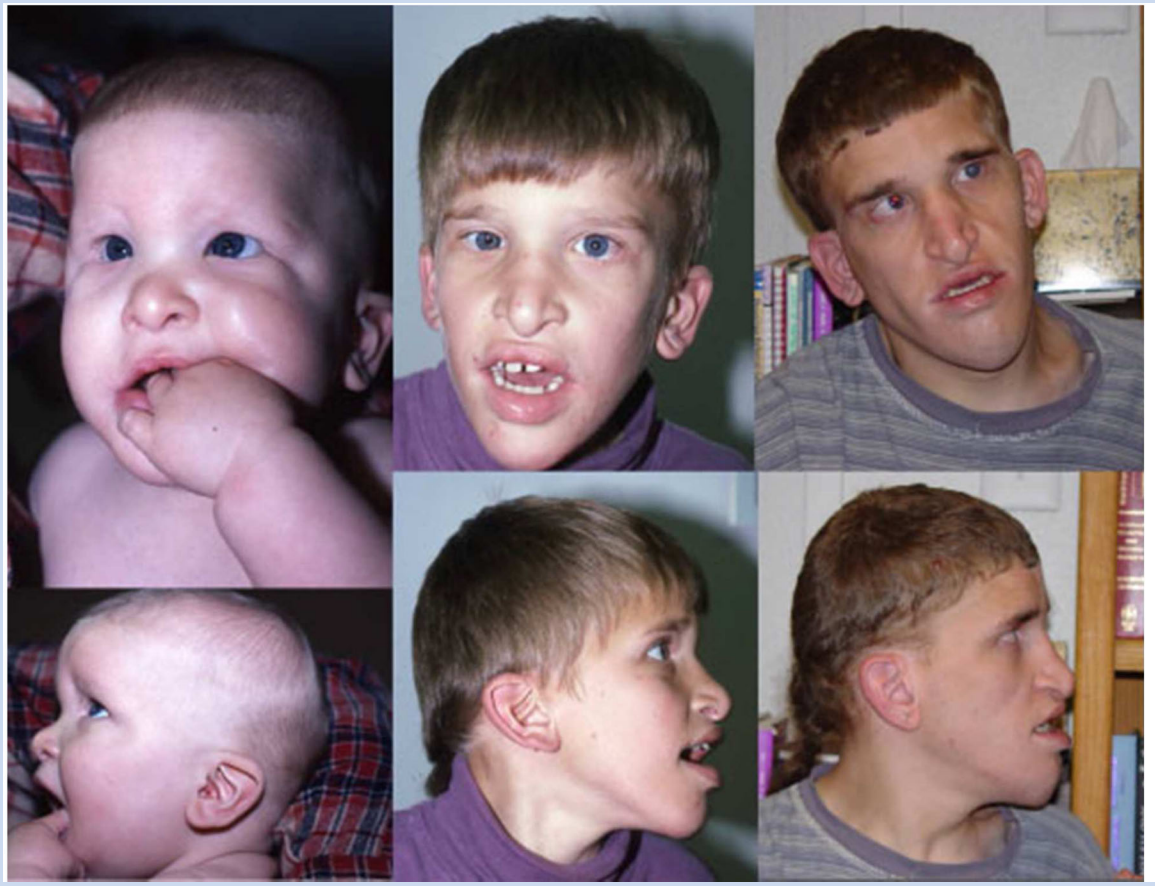

FIG. 6. Facial feature of the same patient with Mowat–Wilson syndrome in infancy, late childhood, and adulthood. [Reproduced from: Adam MP, Schelley S, Gallagher R, Brady AN, Barr K, Blumberg B, Shieh JT, Graham J, Slavotinek A, Martin M, Keppler-Noreuil K, Storm AL, Hudgins L. 2006. Clinical features and management issues in Mowat–Wilson syndrome. Am J Med Genet A 140:2730–2741.]

are sparse in the middle but become thicker and more horizontal with age, and uplifted ear lobes with a central depression (like "orecchiette" pasta or as seen in erythrocytes) that become less common with age. In older individuals there is an overhanging nasal tip, low-insertion columella, and prognathism [Adam et al., 2008; Garavelli et al., 2009]. Minor skeletal abnormalities in the limbs such as long, slender and tapered fingers, prominent digit pads, prominent interphalangeal joints, and calcaneovalgus deformities of the feet have been reported in many individuals [Garavelli and Mainardi, 2007; Adam et al., 2008]. In a study on the behavioral profile of 60 children and adults with Mowat–Wilson syndrome, it was found that 95% of them had mouthing behavior, a behavioral trait that is also commonly observed in AS; 87% exhibited teeth grinding (bruxism), which is rarely observed in AS, and 58% were found to "flick, tap, and twirl objects," which is also uncommon in AS. Although they have a "happy affect" and smile easily, only 20% of the Mowat–Wilson subjects "laughed or giggled for no obvious reason" and only 30% were "unrealistically happy or elated," both of which are common in AS. Unlike AS individuals, Mowat–Wilson syndrome individuals do not have a fascination with water [Evans et al., 2012].

Kleefstra Syndrome and Variants (Figure 7)

Kleefstra syndrome is caused by haploinsufficiency of *EHMT1* on chromosome 9q34.3. The clinical features that have been reported in both AS and Kleefstra syndrome include moderate-to-severe intellectual disability with minimal speech but better receptive language, hypotonia in childhood, sleep disturbances with multiple awakenings, midface retrusion, and prognathism. Facial features that differentiate Kleefstra syndrome from AS include synophrys and everted vermilion of the lower lip. Some mildly affected individuals have more than a hundred words in their vocabulary and speak in sentences, which would be very unusual in AS. In contrast, some of those with large deletions on chromosome 9q34 are unable to walk independently even at 5 years of age and have minimal verbal language; however, many are able to use simple signs or pictures to communicate their needs. In contrast to AS, only 30–40% of individuals with Kleefstra syndrome develop seizures and no consistent EEG patterns have been identified. Other features

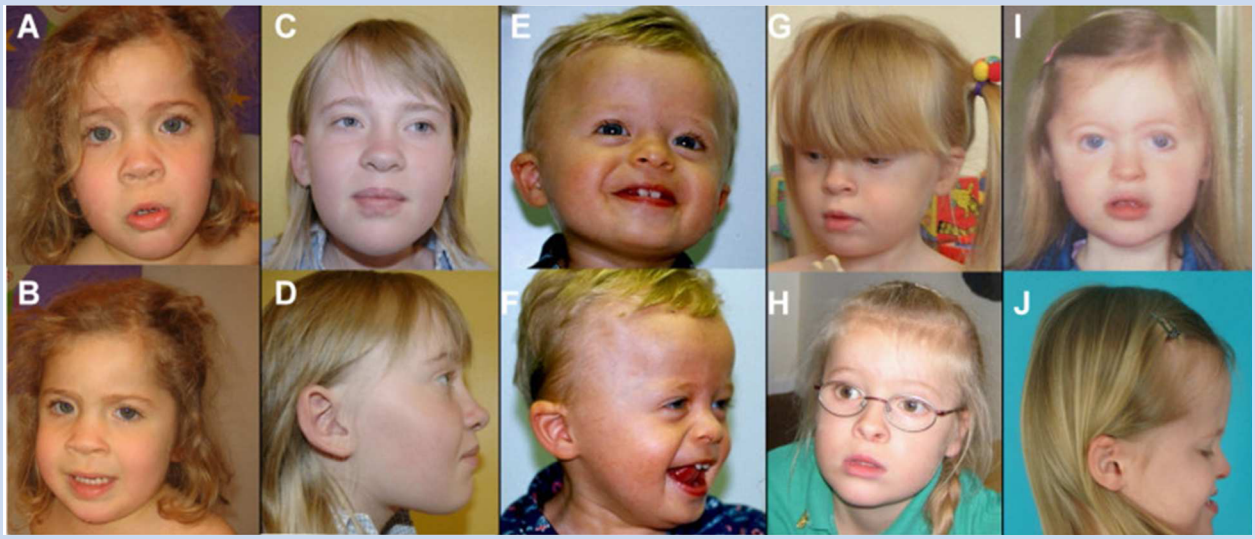

FIG. 7. Facial features of Kleefstra syndrome. [Reproduced from: Kleefstra T, van Zelst-Stams WA, Nillesen WM, Cormier-Daire V, Houge G, Foulds N, van Dooren M, Willemsen MH, Pfundt R, Turner A, Wilson M, McGaughran J, Rauch A, Zenker M, Adam MP, Innes M, Davies C, López AG, Casalone R, Weber A, Brueton LA, Navarro AD, Bralo MP, Venselaar H, Stegmann SP, Yntema HG, van Bokhoven H, Brunner HG. 2009. Further clinical and molecular delineation of the 9q subtelomeric deletion syndrome supports a major contribution of EHMT1 haploinsufficiency to the core phenotype. J Med Genet 46(9): 598–606, with permission from BMJ Publishing Group Ltd.]

of Kleefstra syndrome that can help to discriminate it from AS are childhood-onset obesity (25–45%), conotruncal and septal heart defects (40–50%), renal abnormalities including vesico-ureteric reflux (10–30%), male genital abnormalities (30–60%), and joint laxity, talipes equinovarus, or scoliosis (20–30%). While scoliosis has been observed in AS, joint laxity is uncommon. Similarly, although a small subset of children with AS develop food-seeking behavior and obesity, most children with AS are not obese. The behavioral profile in Kleefstra syndrome, observed in 50–75% of individuals, is characterized by aggression, self-mutilation, emotional outbursts, and autistic behaviors. These maladaptive behaviors may be more common in the older individuals. Some adolescents with Kleefstra syndrome develop unusual behaviors such as extreme apathy and catatonia, as well as mood disorders. Developmental regression, which would be unusual in AS, has been observed in some adolescents with Kleefstra syndrome [Kleefstra et al., 2009; Willemsen et al., 2012].

HERC2 Deficiency Syndrome

HERC2 on chromosome 15q13.1 encodes a protein that binds to and affects the ubiquitin ligase activity of E6AP. A homozygous c.1781C > T (p.Pro594Leu) mutation in *HERC2* has been identified in 22 members of four Amish and one mixed Amish-Mennonite families who presented with global developmental delay and intellectual disability, hypotonia, delayed independent ambulation at between 2½ and 5 years of age, and a broad-based gait with arms upheld and flexed at elbow when running. Although language development was delayed in all individuals, the expressive language abilities varied from non-verbal with only gestures to short sentences; their receptive language was generally stronger than their expressive language. Many of these individuals had short attention span and were very affectionate or sociable, but they were not reported to have frequent unprovoked laughter; some had aggressive behaviors such as hair-pulling and pushing. Features of autism spectrum disorder appeared to be frequent among those who were formally assessed. In most individuals, the severity of the intellectual disability ranged from mild to moderate. Afebrile seizures were uncommon, having been reported in only 2 out of these 22 individuals [Puffenberger et al., 2012; Harlalka et al., 2013]. Many of these findings are reminiscent of those observed in mildly affected AS individuals, but the lack of easily provoked laughter and the relatively mild intellectual disability in at least some of these individuals distinguish it from AS. Since all affected individuals reported to date have the same homozygous mutation, the phenotypic spectrum of *HERC2* deficiency syndrome remains to be determined.

Adenylosuccinase Deficiency

Adenylosuccinase (adenylosuccinate lyase) deficiency, an autosomal recessive inborn error of metabolism due to homozygous or compound heterozygous mutations in *ADSL* on chromosome 22q13.1, results in accumulation of succinylpurines in the cerebrospinal fluid, plasma, and urine, leading to severe intellectual disability, postnatal microcephaly, early-onset seizures, as well as poor eye contact and stereotypic hand movements in most individuals [Spiegel et al., 2006; Jurecka et al., 2012]. Spastic diplegia in lower limbs or tetraplegia can develop in late childhood resulting in the loss of motor skills [Perez-Duenas et al., 2012]. Cerebral atrophy

has been reported in those older than 2 months of age; other common brain MRI findings include cerebellar atrophy, delayed myelination, and hypoplasia of the corpus callosum [Jurecka et al., 2012]. Poor eye contact, as well as cerebral and cerebellar atrophy, distinguishes *ADSL* deficiency from AS. Of note, there is also a less severe form of *ADSL* deficiency ("Type II") associated with mild intellectual disability [Jurecka et al., 2013] as well as a neonatal lethal form, neither of which resembles AS in its clinical presentation. Diagnostic testing of *ADSL* deficiency involves detection of succinylaminoimidazole carboxamide riboside (SAICA riboside) and succinyladenosine (S-Ado) in cerebrospinal fluid, urine, and to a lesser extent plasma [Spiegel et al., 2006]. SAICA riboside in the urine can be screened for using thin-layer chromatography [de Bree et al., 1986] or the Bratton–Marshall test [Laikind et al., 1986], both of which are standard techniques that are performed in clinical diagnostic laboratories. Recently, it was reported that brain MRS over the occipitoparietal white matter in two such patients showed peaks corresponding to S-Ado and SAICA riboside, which suggests that brain MRS may be a useful diagnostic tool in these patients [Zulfiqar et al., 2013]. There are very few reports of seizures and EEG patterns in *ADSL* deficiency, but seizures were reported in all 3 patients in a small case series, with two of them having EEGs consistent with a burst-suppression pattern, which has not been reported in AS [Lundy et al., 2010].

Rett and "Variant Rett" Syndromes (Figure 8)

Heterozygous *MECP2* mutations on chromosome Xq28 in girls result in typical Rett syndrome, which presents with developmental regression that may stabilize or even improve over time, as manifested by the loss of "purposeful hand skills" and verbal language by the age of 5 years after a period of normal development for at least the first 6 months of life. They subsequently lose their ability to ambulate; some develop quadriplegia resulting in a "state of frozen rigidity," and they may have cold, atrophic feet in adulthood [Neul et al., 2010; Smeets et al., 2012]. However, a recent study suggests that some girls with typical Rett syndrome never acquire early language skills such as cooing and babbling [Marschik et al., 2013]. Nevertheless, developmental regression distinguishes typical Rett syndrome from AS in which regression is unusual unless seizures are poorly controlled. Girls with typical Rett syndrome also develop stereotypic hand movements, which would also be unusual in AS, and a dyspraxic gait, which could resemble the ataxic or broad-based gait in AS. Many individuals with Rett syndrome have abnormal breathing patterns including episodic hypoventilation and hyperventilation, which is also observed in Pitt–Hopkins syndrome, but not in AS. Both AS and Rett syndrome children seek eye contact, but those with Rett syndrome have a characteristically intense or dream-like stare. Bruxism, which would be atypical for AS, is observed in some girls with Rett syndrome. On the other hand, many girls with Rett syndrome develop seizures, impaired sleep patterns, inappropriate laughter, and scoliosis, all of which may be observed in individuals with AS. The EEG patterns that have been reported in individuals with Rett syndrome, which are distinct from those seen in AS, include generalized background slowing and/or loss of the occipital dominant rhythm, with further theta and delta slowing as these children continue to regress developmentally [Neul et al., 2010; Smeets et al., 2012; Christodoulou and Ho, 2012].

Mutations in *CDKL5* on chromosome Xp22.13 result in what has hitherto been known as early-seizure (Hanefeld) variant Rett syndrome, an X-linked disorder characterized by severe intellectual disability with lack of speech, generalized tonic-clonic seizures in the first 5 months of life that progress to infantile spasms and subsequently to refractory myoclonic epilepsy ("epileptic encephalopathy") in the majority of individuals, and bruxism. In contrast, seizures in AS tend to occur later in infancy or childhood and are more amenable to treatment. The EEG patterns in individuals with *CDKL5* mutations are unique and easily distinguishable from AS, at least in neonates and young infants, as the ictal pattern in neonates

FIG. 8. Normal facial features and midline stereotypic hand movements in Rett syndrome. [Photograph courtesy of Charles A. Williams, MD]

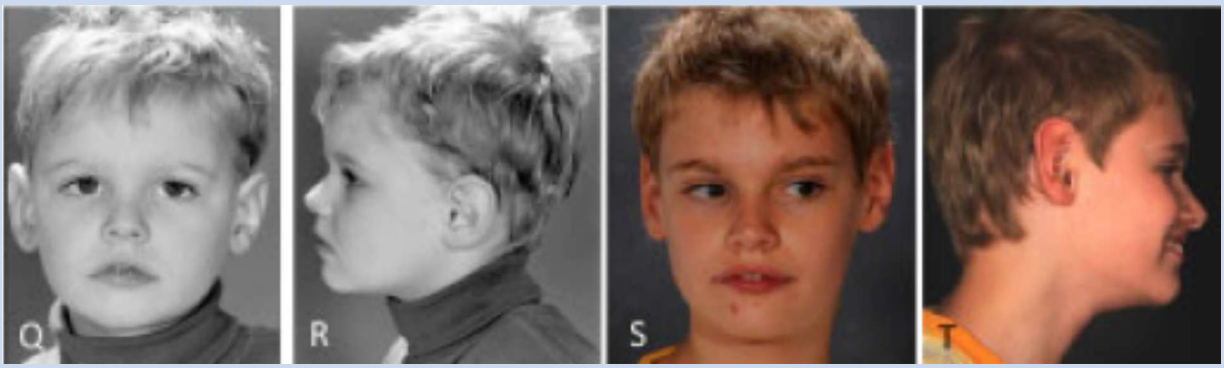

FIG. 9. Relatively normal facial feature of the same patient with MEF2C syndrome at age 3 (Q, R) and 14 years (S, T). [Reproduced from: Zweier M, Gregor A, Zweier C, Engels H, Sticht H, Wohlleber E, Bijlsma EK, Holder SE, Zenker M, Rossier E, Grasshoff U, Johnson DS, Robertson L, Firth HV, Cornelia K, Ekici AB, Reis A, Rauch A. 2010. Mutations in MEF2C from the 5q14.3q15 microdeletion syndrome region are a frequent cause of severe mental retardation and diminish MECP2 and CDKL5 expression. Hum Mutat 31:722–733.]

and young infants is an initial bilateral, synchronous electrodecrement followed by repetitive spikes and sharp waves [Guerrini and Parrini, 2012]. However, it has been proposed that individuals with *CDKL5* mutations have a distinct syndrome that is NOT part of the Rett syndrome spectrum because many of them do not meet the clinical diagnostic criteria for "atypical or variant Rett syndrome" as defined by the international RettSearch Consortium [Neul et al., 2010] due to their lack of developmental regression and lack of abnormal breathing, and the presence of the dysmorphic facial features. They should therefore be considered to have a "CDKL5 syndrome" instead [Fehr et al., 2013].

Heterozygous loss-of-function mutations in *FOXG1* on chromosome 14q12 result in the congenital (Rolando) variant of Rett syndrome which presents with severe intellectual disability with absent expressive language skills, early-onset postnatal microcephaly, generalized hypotonia, seizures with a variable age of onset ranging from infancy to teenage years, sleep disturbances, bruxism, dyskinesia of the hands, and poor eye contact with impaired social interaction. Brain MRI studies have revealed hypoplasia of the corpus callosum, as well as simplified gyral patterns and reduced white matter volume particularly in the frontal lobes, which are not typically associated with AS [Kortum et al., 2011; Florian et al., 2012].

Male *MECP2* Duplications

Duplication of the entire *MECP2* in males (i.e., "*MECP2* Duplication syndrome"), which can often be diagnosed by a high-resolution chromosomal microarray, results in severe intellectual disability with minimal speech, infantile hypotonia, motor developmental delay with ataxic gait but subsequent loss of ambulatory skills due to progressive spasticity of the lower limbs, recurrent respiratory tract infections including pneumonia and otitis media, abnormal involuntary movements such as choreiform movements and stereotypic hand movements, developmental regression, and seizures, which may be intractable; head circumference is usually normal [Ramocki et al., 2010; Van Esch, 2010, 2012]. The features

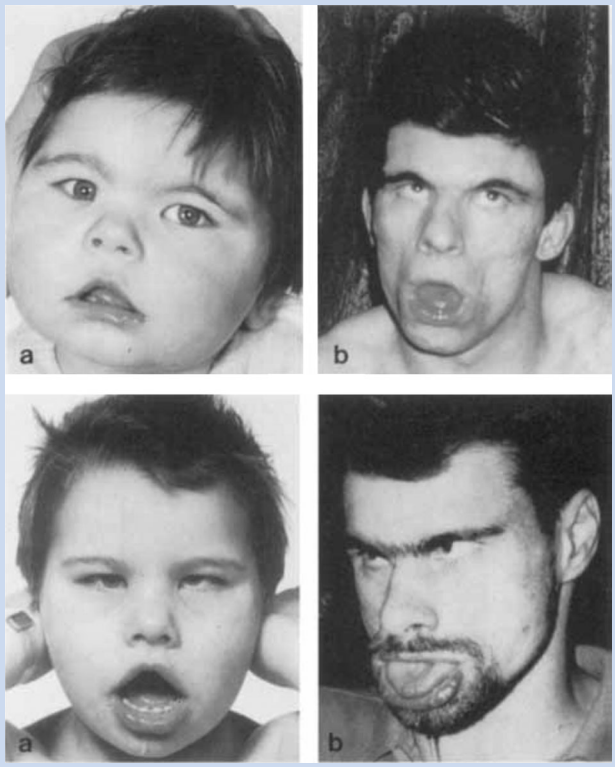

FIG. 10. Facial features of 2 patients with X-linked alpha-thalassemia/intellectual disability (mental retardation) syndrome: Top row: A patient at (a) 1½ years and (b) 23 years old; Bottom row: A different patient at (a) 4 years and (b) 26 years old. [Reproduced from: Gibbons RJ, Brueton L, Buckle VJ, Burn J, Clayton-Smith J, Davison BC, Gardner RJ, Homfray T, Kearney L, Kingston HM, Newbury-Ecob R, Porteous ME, Wilkie AO, Higgs DR. 1995. Clinical and hematologic aspects of the X-linked alpha-thalassemia/mental retardation syndrome (ATR-X). Am J Med Genet 55:288–299.]

TABLE I. Differentiating Clinical Features

Syndrome (gene)	Features shared with AS[a]	Unique or distinguishing features	Key references
22q13.3 deletion Phelan–McDermid syndrome	Hypotonia Feeding difficulties in infancy Mouthing behavior Hyperactivity Limited attention span Thin corpus callosum	Normal or rapid growth Large ears Large hands Dysplastic toenails Decreased socialization and poor eye contact May lose speech after 3–4 years old Brain MRI—Posterior fossa abnormalities	Dhar et al. [2010], Phelan and McDermid [2012], Aldinger et al. [2013]
2q23.1 deletion *MBD5* haploinsufficiency syndrome	Seizures Short attention span Constipation	Repetitive stereotypic behavior Hand/foot (skeletal) abnormalities Nasal abnormalities	van Bon et al. [2010], Hodge et al. [2013]
17q21.31 deletion *KANSL1* haploinsufficiency (Koolen–de Vries) syndrome	Hypotonia Seizures Feeding difficulties Friendly & happy disposition	Milder intellectual disability Multiple nevi, hyperpigmentation Relative macrocephaly Tall or broad forehead Large ears Long fingers Joint laxity Cryptorchidism	Koolen et al. [2012], Zollino et al. [2012], Koolen and de Vries [2013]
Pitt–Hopkins syndrome (*TCF4*)	Hypotonia Seizures Ataxic gait Happy personality Widely spaced teeth Corpus callosum hypoplasia	Dysmorphic ears Facial features coarsen with age High myopia Persistent digit pads Severe constipation Breathing abnormalities Stereotypic hand and head movements Self-aggression Cerebellar atrophy/vermian hypoplasia	Zweier et al. [2008], Giurgea et al. [2008], de Pontual et al. [2009], Marangi et al. [2012], Whalen et al. [2012]
Christianson syndrome (*SLC9A6*)	Postnatal microcephaly Hypotonia Seizures Ataxic gait Easy laughter Drooling	Developmental regression Horizontal/vertical gaze palsy Staring at own hands Brain MRI—progressive inferior cerebellar vermis ± hippocampal atrophy; Brain MRS—glutamate–glutamine peak in basal ganglia	Christianson et al. [1999], Gilfillan et al. [2008], Schroer et al. [2010]
Mowat–Wilson syndrome (*ZEB2*)	Microcephaly Hypotonia (infancy) Seizures Broad-based gait with arms upheld Mouthing behavior Corpus callosum hypoplasia	Congenital anomalies (heart defects, hypospadias) Thick medially flared eyebrows Uplifted ear lobes with central depression Minor hand and feet abnormalities Bruxism NO fascination with water EEG—Normal or mild slowing at seizure onset	Adam et al. [2008], Garavelli and Mainardi [2007], Evans et al. [2012]

TABLE I. (*Continued*)

Syndrome (gene)	Features shared with AS[a]	Unique or distinguishing features	Key references
Kleefstra syndrome (9q34.3 deletion,*EHMT1* haploinsufficiency)	Hypotonia (childhood) Seizures Sleep disturbance Midface retrusion, prognathism	Obesity (childhood-onset) Congenital anomalies (heart & genitourinary defects) Apathy, catatonia (adolescent-onset) Synophyrs	Kleefstra et al. [2009], Willemsen et al. [2012]
HERC2 deficiency syndrome	Hypotonia Broad-based gait with arms upheld Short attention span Affectionate	Laughter not easily provoked Seizures uncommon	Harlalka et al. [2013], Puffenberger et al. [2012]
Adenylosuccinase deficiency	Microcephaly Seizures Delayed myelination Corpus callosum hypoplasia	Poor eye contact Stereotypic hand movements Cerebral and/or cerebellar atrophy EEG—Burst-suppression pattern	Spiegel et al. [2006], Jurecka et al. [2012]
Typical Rett syndrome (*MECP2*)	Postnatal microcephaly Hypotonia Seizures Sleep disturbance Easily provoked/inappropriate laughter	Developmental regression Sterotypic hand movements Breathing abnormalities	Neul et al. [2010], Smeets et al. [2012]
CDKL5 syndrome	Hypotonia Sleep disturbances	Early-onset (<3 months age), sometimes intractable seizures Limited purposeful hand skills Poor eye contact Bruxism	Fehr et al. [2013]
FOXG1 haploinsufficiency syndrome	Postnatal microcephaly Hypotonia Seizures Sleep disturbance Hand dyskinesia Hypoplasia of corpus callosum	Poor eye contact Bruxism Hand dyskinesia Brain MRI—simplified gyri, reduced white matter volume	Kortum et al. [2011], Florian et al. [2012]
MECP2 duplication	Hypotonia Seizures	Developmental regression Recurrent respiratory infections Choreiform & stereotypic hand movements	Ramocki et al. [2010], Van Esch [2010], Van Esch [2012]
MEF2C haplo-insufficiency syndrome	Hypotonia Seizures Broad-based gait	Bruxism Hand stereotypy Poor eye contact	Zweier and Rauch [2012], Bienvenu et al. [2013]
Alpha-thalassemia/intellectual disability syndrome (*ATRX*)	Microcephaly Hypotonia Drooling Gastroesophageal reflux disease	Emotional lability Genitalia abnormalities Skeletal abnormalities Dysmorphic facial features (telecanthus)	Stevenson [2010], Gibbons [2012]

[a]In addition to global developmental delay/intellectual disability and absent or minimal speech.

that distinguish *MECP2* duplication syndrome from AS include recurrent respiratory infections, choreiform and stereotypic hand movements, and developmental regression. The EEG pattern typically shows an unusually slow background with "generalized slow spike and wave asynchronous discharge with frontotemporal predominance," which is different from the pattern seen in AS [Van Esch, 2012; Vignoli et al., 2012]. Female carriers of *MECP2* duplication have normal intellectual ability but tend to have neuropsychiatric manifestations such as depression and anxiety, and a "broad autism phenotype" [Ramocki et al., 2010]. However, emerging data suggest that some female carriers of *MECP2* duplication with random X-inactivation may have intellectual disability, speech delay, seizures, and recurrent infections [Bijlsma et al., 2012].

MEF2C Syndrome (Figure 9)

Haploinsufficiency of *MEF2C* on chromosome 5q14.3 results in severe global developmental delay and intellectual disability with absent speech, hypotonia, seizures, and (in those who are ambulatory) a wide-based gait, all of which are features common to AS. Strabismus has been reported in both *MEF2C* syndrome and AS, but it may be more common in *MEF2C* syndrome. Head circumference is typically normal in *MEF2C* syndrome, but some individuals with AS also have normal head circumference. On the other hand, bruxism, stereotypic movements of the hands such as clapping or hand-washing movements, and poor eye contact, none of which are typically associated with AS, have been identified in almost 50% of the *MEF2C* syndrome individuals reported [Zweier and Rauch, 2012; Bienvenu et al., 2013]. In a recent study, 54% of these individuals were found to have seizures—33% with early myoclonus (i.e., multifocal spike and wave on EEG) and 21% with epileptic spasms (hypsarrythmia), patterns which are not typically seen in AS [Paciorkowski et al., 2013]. About 1.3 Mb centromeric to *MEF2C* is the *RASA1* gene, mutations in which result in capillary malformation–arteriovenous malformation (CM-AVM) [Revencu et al., 2013]. As such, individuals who have a contiguous gene deletion resulting in haploinsufficiency of both *MEF2C* and *RASA1* present with the clinical features described above as well as CM-AVM. Interestingly, individuals with *MEF2C* point mutations and intragenic deletions have reduced expression of *MECP2* and *CDKL5*, at least in peripheral blood, which suggests that MEF2C regulates the expression of these two genes and might explain the partial phenotypic overlap between MEF2C syndrome and Rett and CDKL5 syndromes [Zweier et al., 2010].

X-Linked Alpha-Thalassemia/Intellectual Disability (Mental Retardation) Syndrome (Figure 10)

X-linked alpha-thalassemia/intellectual disability (mental retardation) syndrome, due to mutations in *ATRX* on chromosome Xq21.1, presents in males with variable degrees of intellectual disability ranging from mild to severe, and some individuals never acquire speech nor independent ambulation. As in AS, most individuals have hypotonia and drooling, many have gastroesophageal reflux disease, and some have chronic constipation. Most are described as "affable," but some are "emotionally labile" with episodes of laughter and crying. Skeletal abnormalities including delayed bone age, brachydactyly, bifid thumbs, vertebral anomalies, and chest wall deformities have been reported in up to 90% of these patients. Seizures have been reported in one-third of affected individuals. Unlike AS, most individuals have genital anomalies ranging from cryptorchidism and/or hypospadias to ambiguous genitalia in the more severe cases. Some distinctive facial features such as microcephaly, telecanthus, and everted vermilion of the lower lip have been described. Although some individuals have microcytic hypochromic anemia, many have normal red cell indices without anemia. Similarly, hemoglobin H inclusions can be seen on blood smear in some affected individuals, but these inclusions may be visible in only a small proportion (less than 1%) of the erythrocytes or completely absent in other affected individuals. Carrier females with highly skewed X-inactivation patterns appear to be asymptomatic [Stevenson, 2010; Gibbons, 2012].

Other Angelman-Like Syndromes

Heterozygous mutations in *STXBP1* on chromosome 9q34.11 result in an early-onset epileptic encephalopathy with burst-suppression on EEG (i.e., "Ohtahara syndrome"). These patients often have severe global developmental delay, lack of speech, hypotonia, and ataxia. However, the presence of hypsarrhythmia and burst-suppression on EEG distinguish these patients from those with AS [Deprez et al., 2010; Milh et al., 2011].

A patient with methylenetetrahydrofolate reductase (MTHFR) deficiency [Arn et al., 1998] and another patient with late-treated phenylketonuria [Dan et al., 2001] have been reported to have phenotypic features that mimic AS. However, no additional patients with these two inborn errors of metabolism have been reported to have phenotypic features that closely resemble AS. Moreover, these two patients have not had further investigations using current diagnostic tools such as chromosomal microarray, so it is possible that they have an undiagnosed AS-like condition in addition to their inborn errors of metabolism. Therefore, it is unclear whether these are true AS-mimicking conditions.

Table I summarizes the differentiating clinical features that can help distinguish AS from other mimicking conditions. Seizures, speech impairment, happy demeanor, and microcephaly are generally non-specific findings common to many of these AS-like syndromes. The features that are more helpful in discriminating these syndromes against AS include the presence of congenital malformations and evidence for developmental regression. A characteristic EEG "signature" of high amplitude delta activity in the occipital regions with admixed small spikes, giving it a "notched" appearance, [Dan and Boyd, 2003] can be a very sensitive, but not specific, screening test for AS.

CONCLUSIONS

Although conventional wisdom indicates that about 10% of individuals with a clinical diagnosis of AS do not have an identifiable molecular etiology, we believe that the vast majority of these individuals have an AS-like syndrome that is distinct from AS. It therefore behooves the clinician to make every effort to identify the true underlying genetic diagnosis in such patients before labeling them as having "test negative" AS.

Our review of these AS-like syndromes has revealed that many of them can be classified into two emerging classes of disorders based on either the molecular or cellular functions of their associated proteins—the chromatin-remodeling disorders due to mutations in genes such as *MECP2*, *ZEB2*, *EHMT1*, *MBD5*, *KANSL1*, *FOXG1*, and *ATRX*; and the "synaptopathies" (i.e., structural or functional defects in synapses) due to mutations in genes such as *SHANK3*. Further understanding of the interactions among these proteins and with E6AP may reveal new avenues for therapeutic interventions that target cellular processes rather than individual genes or proteins. Identifying the correct genetic diagnosis for patients who present with an AS-like condition is critical because the pathogenesis, potential treatment strategies, prognosis, and modes of inher-

itance can be very different. Recognition of the clinical phenotype can be helpful in guiding diagnostic strategies. The increasing use of exome/genome sequencing will facilitate the identification of more AS-like syndromes in the future, which in turn will help improve our understanding of the role of E6AP and the pathophysiology of AS and AS-like syndromes.

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