R.C.P.U. NEWSLETTER

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Looks like Angelman syndrome but isn't – What is in the differential?

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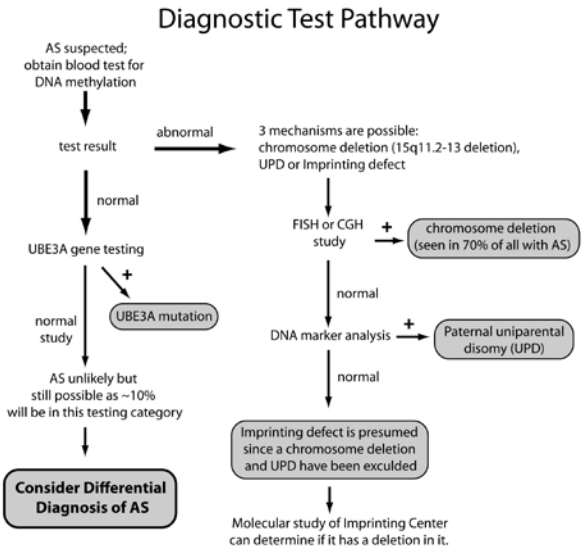
Angelman syndrome

Angelman syndrome is a neurobehavioral disorder characterized by developmental delay, progressive microcephaly, ataxic gait, absence of speech, seizures and a characteristic behavioral phenotype which includes happy demeanor and spontaneous bouts of laughter. AS was originally called the "Happy Puppet Syndrome" in its description by Harry Angelman in 1965 in an attempt to describe the upheld hands, clumsy gait and happy demeanor of individuals with this condition. The incidence is estimated to be between 1 in 15,000 and 1 in 20,000 live births. Angelman syndrome (AS), and its counterpart Prader-Willi syndrome (PWS), are recognized as classical examples of genomic imprinting because both syndromes can be associated with de novo deletions in the highly mutable 15q11-q13 region. The difference between the two is in the parent of origin of the deletion, as PWS results from deletions in the paternally derived chromosome and AS results from deletions in the maternally derived chromosome. The presence of both maternally and paternally imprinted gene(s) in this region is further evidenced by discovery of maternal uniparental disomy (UPD) in some individuals with PWS and paternal UPD in some individuals with Angelman syndrome.



Differential Diagnosis of Angelman syndrome (AS)

Individuals with AS-like features often present with psychomotor delay and/or seizures and the differential diagnosis can be broad, encompassing such non-specific entities as cerebral palsy, static encephalopathy, autism and mitochondrial encephalomyopathy. Tremulousness and jerky limb movements, seen in most individuals with AS may help distinguish it from these conditions (see table below for other helpful distinguishing features). Specific syndromes that mimic AS are reviewed below. Table 1 provides a methodology for testing for AS the options if AS testing is negative.

Christianson syndrome, an X-linked AS-like disorder, is caused by mutations in the *SLC9A6* gene. The clinical features include apparently happy disposition, severe cognitive delays, ataxia, microcephaly and a seizure disorder [Christianson et al., 1999; Gilfillan et al., 2008]. Some may have cerebellar and brain stem atrophy [Gilfillan et al., 2008]. Although seizures are present in both conditions, the EEG pattern appears to be different. AS typically shows a generalized high amplitude, slow spike/wave (1.5-3 Hz) pattern while those with *SLC9A6* mutations lack the AS EEG pattern and have a more rapid (10-14 Hz) background frequency [Gilfillan et al., 2008] Individuals with *SLC9A6* disorder may have thinner body appearance and may lose ambulation beyond 10 years of age.

Mowat-Wilson syndrome can present with findings that suggest AS [Zweier et al., 2005], including happy affect, prominent mandible, upturned prominent ear lobes, diminished speech, microcephaly, and constipation. Some have Hirschsprung disease. Mowat-Wilson syndrome results from heterozygous mutations in *ZEB2* or from deletions in the entire gene.

The characteristic features of Pitt-Hopkins syndrome are mental retardation, wide mouth and distinctive facial features, and intermittent hyperventilation followed by apnea [Zweier et al., 2007]. It may have overlapping features with AS such as microcephaly, seizures, ataxic gait and happy personality. Diurnal hyperventilation is a salient feature in some and occurs after three years of age [Peippo et al., 2006]. Mutation and deletion screening for the *TCF4* gene is available.

Infant girls with Rett syndrome having seizures and severe speech impairment can resemble infants with AS, but those with AS do not have a regressive course and do not lose purposeful use of their hands as do girls with Rett syndrome. Older girls with undiagnosed Rett syndrome may also have features that resemble AS, leading to the erroneous clinical diagnosis

of AS [Watson et al., 2001]. Testing for mutations of *MECP2* is widely available.

Sometimes infants with Prader-Willi syndrome who present with feeding difficulties and muscle hypotonia are misdiagnosed as having AS because the 15q11.2-q13 deletion, detected by CGH or FISH, was not proven by DNA methylation analysis to be of maternal origin.

Chromosome microdeletion disorders can also mimic some of the features of AS, especially the 22q13.3 deletion (Phelan–McDermid) syndrome [Precht et al., 1998]. This condition may present with nondysmorphic facial features, absent or minimal speech, and moderate to severe developmental delay, sometimes with behavioral features in the autism spectrum. Microdeletions of the 2q23.1 region may result in severe speech delay, seizures, behavioral disorders and microcephaly. Some individuals present with an AS-like phenotype [van Bon et al., 2010; Williams et al., 2009]. Other microdeletion disorders such as 1p36.3 deletion, and more recently discovered ones detected by array-CGH (molecular chromosome testing), may be associated with some features of AS [Brunetti-Pierri et al., 2008; Sharkey et al., 2009]

Some individuals with autism spectrum disorder may have features that mimic those in AS. Noteworthy among these are absent speech, hypermotoric activities and seemingly aloof or inattentive behaviors. Individuals with autism are often distinguishable from AS because of their agile and adept fine and gross motor abilities, often exhibited during motor stereotypies. They may also lack microcephaly or any history of seizures. Although there are reports indicating autism-like features in AS, there is usually prosocial behavior in AS as opposed to the social disinterest present in those with autism. [Bonati et al., 2007; Peters et al., 2008; Steffenburg et al., 1996; Trillingsgaard and Ostergaard 2004].

associated with profound developmental delay, facial dysmorphism, protruding tongue, happy demeanor, genital abnormalities and alpha thalassemia. Language is usually very limited. Genital abnormalities are observed in 80% of children and range from undescended testes to ambiguous genitalia. Alpha-thalassemia is not always present or detectable. Diagnosis can be established by mutation testing in the ATRX gene [Gibbons 2006; Gibbons et al., 2008].

Adenylosuccinate lyase deficiency results in accumulation of succinylpurines leading to psychomotor retardation, autistic features, hypotonia, and seizures [Spiegel et al., 2006]. Motor apraxia, severe speech deficits, excessive laughter, a very happy disposition, hyperactivity, a short attention span, mouthing of objects, tantrums and stereotyped movements have been reported in female sibs by Gitiaux et al. [Gitiaux et al., 2009]. Diagnostic testing involves detection of succinylaminoimidazole carboxamide riboside (SAICA riboside) and succinyladenosine (S-Ado) in cerebrospinal fluid, urine, and to a lesser extent in plasma.

Please refer to the table below for additional information that compares these AS-mimicking conditions. Most conditions are quite varied in their clinical presentation and genetic testing to rule them out can be complicated. Nevertheless, the table attempts to present some broad clinical features that may help point to a possible mimicking condition.

Table of clinical features that may help distinguish between syndromes. Overlap and variation of features occurs so absence or presence of a feature does not rule in or out the possible condition.

	AS	PHS	SL9A6	Rett	ATRX	Aden-S def.	MWS	Autism	Other Microdeletion	Mito
Microcephaly	+		+	+	+		+		±	
Seizures	+	+	+	+	+	+	+	±	±	+
Speech impairment	+	+	+	+	+	+	+	+	+	+
Ataxia	+		+	+		+				
Stereotypical movements	±			+				+		
Tremulous/jerky limb movements	+									
Happy disposition	+	+	+	±	+	±	+		±	
Abnormal MRI		+	+				±		±	±
Hyperventilation/apnea		+		+						
Hirschsprung disease		±					+			
Lack of hand use				+						
Prominent jaw/chin	+						+			
Wide mouth	+	+					+			
Upturned ear lobes							+			
Genital anomalies					+				±	
Congenital heart defect					+		+		+	
Occurs in males only			+		+					
Occurs in females only				+						
Neuro-regression with age			+	+						+

AS: Angelman syndrome; PHS: Pitt-Hopkins syndrome; SL9A6: X-linked Angelman-like syndrome (aka Christiansen); ATR-X: alpha-thalassemia-X mental retardation syndrome; Aden-S def.: Adenylosuccinate lyase deficiency; MWS: Mowat-Wilson syndrome; Other-micro: other microdeletion conditions; Mito: nonspecific mitochondrial encephalomyopathy

X-linked alpha thalassemia mental retardation (ATR-X) syndrome in males is

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About the RCPU

The Raymond C. Philips Research and Education Unit began in 1978 when the legislature established section 393.20, F.S., of what is now known as the "prevention" legislation. It is named after Raymond C. Philips, who was the Superintendent of Gainesville's Tacachale (formerly Sunland) Center for 38 years, and was an acknowledged state and national leader in services for mentally retarded persons. The Unit is located on the Tacachale campus and is funded through a contract with the Department of Children and Families and the Department of Health.

The purpose of the R.C.P.U. is to treat, prevent, and/or ameliorate mental retardation through medical evaluations, education and research. The unit provides direct evaluations and counseling to families and promotes service, education, and prevention projects.
Some of the conditions currently under study at the RCPU involve Angelman, Velo-Cardio-Facial, Prader-Willi, Fragile X, Williams and Smith-Lemli-Opitz syndromes.

The R.C. Philips Unit is a resource for all Floridians interested in the diagnosis, treatment and prevention of mental retardation. Staff members are available for consultation and for educational programs for health professionals and for the community at large.

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