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Angelman Syndrome: Consensus for Diagnostic Criteria

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The Scientific and Research Advisory Committee of the Angelman Syndrome Foundation recently solicited input from scientists involved in the study of Angelman syndrome to establish consensus about the clinical profile and diagnostic criteria of Angelman syndrome. Tables I, II, and III are intended to assist in the evaluation and diagnosis of Angelman syndrome especially for those unfamiliar with this clinical disorder. These criteria are applicable for the three major types of AS: molecular deletions involving the critical region (deletion positive), uniparental disomy (UPD), and non-deletion/non-UPD [Chan et al., 1993].

The diagnosis of Angelman syndrome is currently a clinical diagnosis that can be confirmed by laboratory testing in about 80% of cases. Individuals whose developmental history conforms to that described in Table I and who have all of the clinical findings of groups A and B in Table II should have a chromosome study as well as molecular analysis by FISH, polymorphism analysis, or methylation testing to look for alterations in 15q11-q13. A positive genetic test (Table III) may confirm the diagnosis, but a normal result does not exclude the diagnosis. In individuals with fewer clinical findings, a positive genetic test is presumptive evidence for Angelman syndrome. The judgement of the clinician is crucial when genetic testing is negative and clinical findings suggest the syndromic diagnosis. For individuals with no deletion or uniparental disomy, the clinician should be reasonably certain that the clinical findings in Tables I and II are present if the diagnosis of Angelman syndrome is still considered [Clayton-Smith, 1993; Zori et al., 1992].

In about 20% of individuals whose clinical presentation is characteristic of Angelman syndrome, genetic laboratory studies of chromosome 15 will be normal. These individuals are currently termed the nondeletion, nondisomy type. It is in the families of these individuals where familial recurrence is a possibility, whether methylation patterns are normal or abnormal. Although affected nondeletion, nondisomy sibs have been shown to share molecular haplotypes of the maternal 15 chromosome, there is currently no diagnostic test applicable to these individuals. Diagnosis in these situations remains clinical, although that may change as new testing and additional insight into the molecular cause of Angelman syndrome evolves.

The clinical diagnosis of Angelman syndrome usually is not suspected during the first year of life but becomes a more frequent diagnostic consideration between 1-4 years of age [Fryburg et al., 1991; Magenis et al., 1990]. Angelman syndrome can be diagnosed in the first year (6-12 months) if the diagnosis is given due consideration. An abnormal EEG may be the first sign for diagnostic evaluation [Boyd et al., 1988]. During infancy, other clinical disorders can mimic the features of Angelman syndrome. These include Rett syndrome, non-specific cerebral palsy, Lennox-Gastaut "syndrome" [Dulac and N'Guyen, 1993], static encephalopathy with mental retardation, infantile autism, and alpha thalassemia X-linked mental retardation (ATR-X) syndrome [Ogle et al., 1994].

TABLE I. Angelman Syndrome: Developmental History and Laboratory Findings

(These findings are useful as inclusion criteria but deviations should not exclude diagnosis.)

1. Normal prenatal and birth history with normal head circumference. Absence of major birth defects.
2. Developmental delay evident by 6-12 months of age.
3. Delayed but forward progression of development (no loss of skills).
4. Normal metabolic, hematologic and chemical laboratory profiles.
5. Structurally normal brain using MRI or CT (may have mild cortical atrophy or dysmyelination).

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TABLE II. Angelman Syndrome: Clinical Characteristics

A. Consistent (100%)

- Developmental delay, functionally severe
- Speech impairment, none or minimal use of words; receptive and non-verbal communication skills higher than verbal ones
- Movement or balance disorder, usually ataxia of gait and/or tremulous movement of limbs
- Behavioral uniqueness: any combination of frequent laughter/smiling; apparent happy demeanor; easily excitable personality, often with hand flapping movements; hypermotoric behavior; short attention span

B. Frequent (more than 80%)

- Delayed, disproportionate growth in head circumference, usually resulting in microcephaly (absolute or relative) by age 2
- Seizures, onset usually <3 years of age
- Abnormal EEG, characteristic pattern with large amplitude slow-spike waves (usually 2-3/s), facilitated by eye closure

C. Associated (20-80%)

- Flat occiput
- Occipital groove
- Protruding tongue
- Tongue thrusting; suck/swallowing disorders
- Feeding problems during infancy
- Prognathia
- Wide mouth, wide-spaced teeth
- Frequent drooling
- Excessive chewing/mouthing behaviors
- Strabismus
- Hypopigmented skin, light hair and eye color (compared to family), seen only in deletion cases
- Hyperactive lower limb deep tendon reflexes
- Uplifted, flexed arm position especially during ambulation
- Increased sensitivity to heat
- Sleep disturbance
- Attraction to/fascination with water

TABLE III. Angelman Syndrome: Genetic Testing Abnormalities

(Number of tests necessary and order of testing may vary. Chromosome study is necessary in all suspected cases to rule out chromosome rearrangements or other chromosome disorders.)

1. High resolution G-banded chromosome study showing deletion of 15q11-q13. Because of the possibility of false positive and negative results from this study, G-banding should not be used as a stand-alone test but should be confirmed by FISH, polymorphism, or methylation analysis.
2. Abnormal fluorescence in situ hybridization (FISH) indicating a deletion of cloned 15q11-q13 DNA sequences that are included in the Angelman syndrome deletion overlap region. Use of a pericentromeric FISH probe enhances ability to detect subtle translocation.
3. DNA polymorphism analysis showing absence of maternal alleles at 15q11-q13 loci, which may result either from maternal deletion or from paternal uniparental disomy.
4. Characteristic DNA methylation pattern (i.e., paternal imprint only) of 15q11-q13 cloned DNA sequences using methylation-sensitive restriction endonucleases. An abnormal methylation pattern in individuals without 15q11-q13 deletion is not a stand-alone test for uniparental disomy.

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June, 1999 Addendum concerning 22q:

Sometimes individuals with a clinical diagnosis of AS have normal results on all genetic tests available for AS to date. Does this mean that he or she does not have AS? Not necessarily. The tests currently available are not able to detect 100% of AS cases; so there will be a percentage of individuals who do, in fact, have AS despite the previous normal results. It is also possible for other conditions or genetic abnormalities to have a clinical presentation similar to AS without actually having this diagnosis. One such genetic abnormality results from a deletion of the end (telomere) of the long arm of chromosome 22 (22q13). Case reports of individuals with a 22q13 deletion do suggest some overlap, although it is important to note that there is a great deal of variability between individuals with known 22q13 deletions. This variability is probably related to the amount of genetic material that is missing. The characteristics that are most consistent among individuals with a deletion of 22q13 include hypotonia, absence or delay of speech, and developmental delay. In some cases other features include unsteady gait, dysmorphic facial features, and seizures. This deletion can be detected by a FISH probe specific for the telomere of chromosome 22. Families considering this testing should know that 22q telomere FISH is currently not standard of care for individuals with a clinical diagnosis of AS and normal genetic studies. It is advised that families discuss this testing option with their geneticist or genetic counselor before proceeding.

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