What is the diagnosis?

In view of his global developmental delay, aCGH was performed, and it came back negative. As there was concomitant movement disorder, frequent laughter and sleep disturbances, Angelman syndrome was suspected, and DNA methylation study was also performed. Methylation study showed amplification of the unmethylated paternal allele and absence of the methylated maternal allele of $SNRPN$ gene (Figure 2). The molecular diagnosis of Angelman syndrome was thus confirmed.

In order to determine the genetic mechanism behind the diagnosis of Angelman syndrome, DNA of the index patient and his parents was taken for uniparental disomy studies. The pattern of the short tandem repeat (STR) markers from chromosome 15 suggested that the index patient had a pair of identical chromosome 15 of paternal origin (Figure 3) in view of previous normal aCGH result. This was confirmatory of paternal uniparental disomy (UPD) 15.

What is Angelman syndrome?

Angelman syndrome is a neurodevelopmental disorder with reported incidence of one in 10,000 to one in 40,000.¹ It was first described by British paediatrician Harry Angelman in 1965, who referred to three children as 'puppet

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**Figure 2** DNA methylation study showing amplification of the unmethylated paternal allele and absence of methylated maternal allele of the $SNRPN$ gene in the index patient. PWS: Prader-Willi syndrome.
children’, with their unusual arm position and jerky movement. The term 'happy puppet syndrome' is no longer used owing to its derogatory implications. Nonetheless, children with Angelman syndrome share common behavioural phenotype with easy excitation, happy demeanor and frequent laughter; and are also hypermotoric with jerky movement and difficulty with balance. Like our index patient, they usually have normal prenatal and birth history, normal growth parameters at birth, normal biochemical profiles and brain imaging. Developmental delay usually becomes apparent by 6-12 months, followed by occurrence of seizure between 1 to 3 years. Most of them are severely intellectually impaired and do not have any spoken language at all, even though many of them can communicate using nonverbal communication system. For clinical and molecular findings of Chinese patients with Angelman syndrome in Hong Kong, a good summary has just been published by Luk et al.4

**What are the diagnostic criteria for Angelman syndrome?**

Consensus criteria for diagnosis of Angelman syndrome was published by an expert panel in 1995 and subsequently revised in 2005 (See Table 1).5,6

**What are the genetic anomalies associated with Angelman syndrome?**

The gene responsible for Angelman syndrome is UBE3A, located at chromosome 15q11-q13. The region also contains the SNRPN gene, which is used as a marker during methylation study in this case. UBE3A codes for an ubiquitin protein ligase, which may play a role in posttranslational processing of precursor proteins involved in synaptogenesis and at synaptic receptor level. This gene is paternally imprinted in the brain, meaning that the paternal copy of the gene is silenced and that expression of the gene depends entirely on the maternal copy. However, the gene remains normally expressed elsewhere in the body.

![Figure 3](image-url). Results of short tandem repeat (STR) markers from chromosome 15 showed paternal uniparental disomy (UPD) for chromosome 15 in the index patient. Three informative STR markers (D15S817, D15S533, and D15S188) showed homozygous alleles of paternal origin in the index patient, whereas three STR markers (D15S194, D15S1365, and D15S822) were uninformative.
| Consistent (100%) | Severe developmental delay, functionally severe  
|                  | Movement or balance disorder  
|                  | - Usually ataxic gait and/or tremulous limb movement  
|                  | - e.g. forward lurching, unsteadiness, clumsiness, quick jerky motions  
|                  | Behavioural uniqueness  
|                  | - Any combination of frequent laughter/smiling; apparent happy demeanor, easily excitable personality  
|                  | - Often with uplifted hand-flapping, or waving movements; hypermotoric behavior  
|                  | Speech impairment  
|                  | - None or minimal use of words  
|                  | - Receptive and non-verbal abilities higher than verbal ones  
| Frequent (>80%)  | Microcephaly  
|                  | Seizures  
|                  | - Any type; predominantly atypical absence myotonic seizures  
|                  | Abnormal EEG\(^7,8\)  
|                  | - 3 possible patterns (not correlated with clinical seizures):  
|                  | - Prolonged runs of 2-3 Hz large amplitude rhythmic delta activity with epileptiform discharges predominant in the frontal regions  
|                  | - Persistent rhythmic 4-6 Hz activity of large amplitude  
|                  | - Spikes and sharp waves mixed with 3-4 Hz components of high amplitude, mainly posterior and facilitated by eye closure  
| Associated (20-80%) | Appearance/dysmorphism  
|                   | - Hypopigmented skin, light hair and eye colour  
|                   | - Obesity (in older child)  
|                   | - Prognathia, wide mouth, widely spaced teeth  
|                   | - Flat occiput, occipital groove  
|                   | Oromotor problem  
|                   | - Protruding tongue, tongue thrusting  
|                   | - Suck or swallowing disorder  
|                   | - Frequent drooling, excessive chewing or mouthing behaviour  
|                   | Musculoskeletal/neurological  
|                   | - Truncal hypotonia (infancy)  
|                   | - Uplifted, flexed arm position during ambulation  
|                   | - Hyperactive lower limb jerks  
|                   | - Wide based gait with pronated or valgus positioned ankles  
|                   | - Scoliosis  
|                   | Behaviour/sleep problem  
|                   | - Abnormal sleep wake cycles, diminished need for sleep  
|                   | - Increased sensitivity to heat  
|                   | - Attention to/fascination with water, fascination with crinkly items such as certain papers and plastics  
|                   | - Abnormal food related behaviour  

**Table 1** Clinical features of Angelman syndrome (Adapted from Williams et al. 2006)\(^5\)
There are four ways in which UBE3A can be affected:\textsuperscript{3}
1. Deletion of maternal copy of UBE3A (65-75%)
2. Mutations of the maternal copy of UBE3A (5-11%)
3. Failure for expression of maternal copy of UBE3A due to imprinting defect (3%)
4. Paternal uniparental disomy (3-7%)

Most deletions and uniparental disomies are sporadic, where the recurrence rate is low. However, in cases due to maternally inherited UBE3A mutations,\textsuperscript{9,10} the recurrence risk can be as high as 50%. Half of the imprinting defects are also caused by maternal inheritance of a submicroscopic imprinting centre deletion.\textsuperscript{11} As such it is important to offer maternal screening in cases with UBE3A mutations or imprinting defects.

DNA methylation study is the first line investigation in the diagnostic algorithm of Angelman syndrome. If it is negative, then UBE3A mutation analysis should be performed. If it is positive, then the patient should be tested for microdeletion (either by fluorescent in situ hybridisation (FISH) or microarray, as in this case), and if there is no microdeletion, uniparental disomy testing should also be performed.\textsuperscript{3,11} If both are negative, then imprinting centre mutation analysis should be performed. If all of the above are negative, Angelman-like syndromes should be considered.

What are the differential diagnoses?

In around 10% of the suspected cases of Angelman syndrome, no abnormality with the UBE3A gene can be found.\textsuperscript{12} These are either due to some unknown genetic mechanism or misdiagnosis. Indeed there are many mimickers of Angelman syndrome, including various copy number variations and single gene disorders. Features that should alert one to a non-Angelman syndrome diagnosis include developmental regression (Rett syndrome, Christianson syndrome), MRI brain anomalies (Phelan-McDermid syndrome/2q13 deletion, Pitts Hopkins syndrome, FOXG1 haploinsufficiency syndrome) as well as congenital anomalies (Mowat Wilson syndrome).\textsuperscript{13,14}

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References