

# MOWAT-WILSON SYNDROME IN A CHILD WITH LONGSTANDING CLINICAL DIAGNOSIS OF ANGELMAN SYNDROME

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## INTRODUCTION

One of the difficulties in dysmorphic diagnosis is the overlapping features found in many genetic syndromes. The availability of a laboratory test often enables the clinician to determine the correct diagnosis with greater certainty. Here we present a child followed for many years with a clinical diagnosis of Angelman syndrome who ultimately was determined to have Mowat-Wilson syndrome.

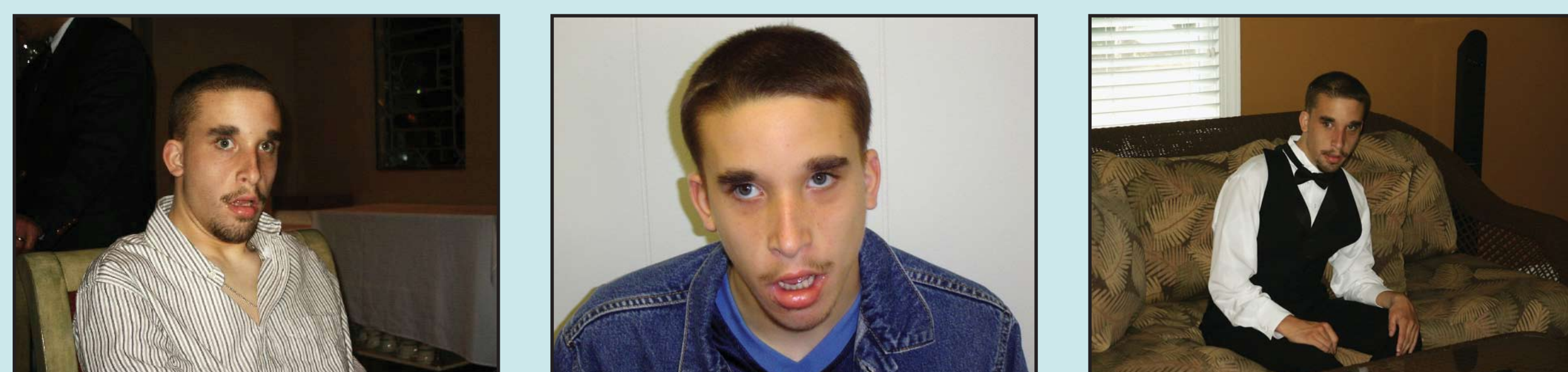
## CASE PRESENTATION

Cody was the term product of an uncomplicated pregnancy born to a 29 yr old G1P1 mother. He was a healthy newborn with normal growth parameters who was discharged home at age 3 days. His parents first became concerned at age 6 months when he was not reaching his milestones on time. He developed seizures at 1 ½ years. Cody walked at 3 ½ years old but had little to no speech. He has had multiple ear infections and had strabismus treated by patching.

Cody's family history is negative for consanguinity, birth defects, or mental retardation. He has two healthy younger siblings.

Cody was first seen at another genetics clinic at 6 years of age for seizures and developmental delays. His features and ataxic-like gait appeared to fit with Angelman syndrome. He had normal chromosome analysis, normal methylation studies for Angelman syndrome and normal UBE3A analysis. The family was counseled that he most likely fit with the small percentage of individuals with Angelman syndrome who had normal lab studies.

Cody presented in our clinic as a 15 year old young man who is nonverbal with mental retardation, seizure disorder, wide-based ataxic gait and happy demeanor. Our feeling was that now in adolescence, Cody had an evolving phenotype with changing facial features and behavioral phenotype that was a less secure fit with Angelman syndrome. We repeated AS methylation and UBE3A studies as well as ran chromosome microarray analysis which all returned normal results and we were unable to reach a diagnostic conclusion.



A few months after our visit, a family member came upon a PBS program called "The Key of G," which profiled a young man with Mowat-Wilson syndrome and noted similarities with Cody. We then sent testing for the ZEB2 gene on chromosome 2q22 which confirmed the diagnosis of Mowat-Wilson syndrome in Cody.

## THE KEY OF G

From the PBS website:

"THE KEY OF G tells the story of Gannet, a 22 year old man with severe disabilities, as he prepares to move out of his mother's home and into a San Francisco apartment with three musicians and artists as primary caregivers... Winner of the 2007 Golden Gate Award at the San Francisco International Film Festival, THE KEY OF G follows this unique household over several years as the usual difficulties and joys of group living are heightened by G's unique condition. Through the difficulties, relationships deepen and G's world continues to expand.

In the end, THE KEY OF G is the caregiver's story as much as it is Gannet's. As they come to rely on him as a friend, they realize that they are building something better than just an independent life for G: they are building a community of interdependence that benefits them all... along the way, [the film] challenges conventional notions about independence, empathy, and disability..."

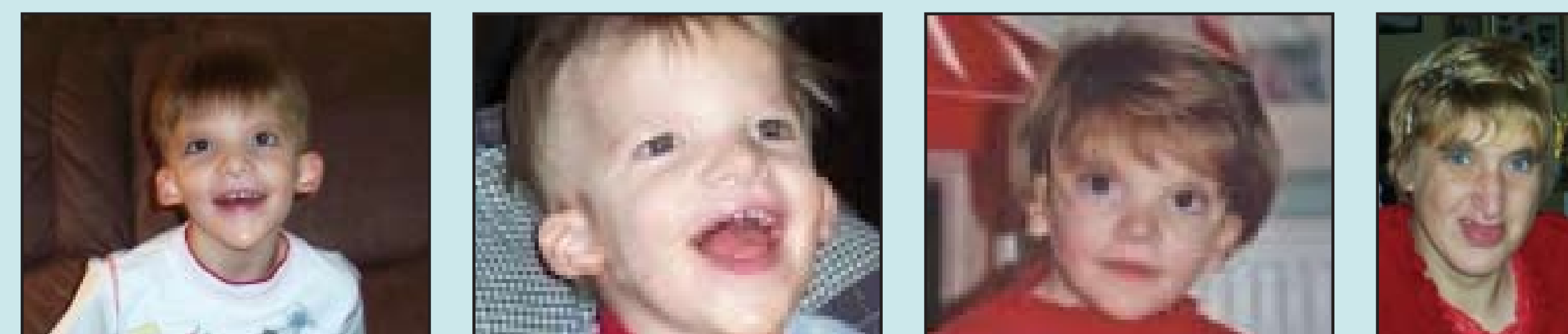


## MOWAT-WILSON SYNDROME

Mowat-Wilson syndrome can include mental retardation (typically moderate to severe), Hirschsprung disease, seizure disorder, and agenesis/hypogenesis of the corpus callosum. The facial phenotype is distinctive with deep set eyes, broad eyebrows with medial thickness and lateral sparseness, prominent nasal tip with columella extending below the alae nasi, telecanthus or hypertelorism, cupped ears with upswept lobes, and prominent, pointed chin with drooling. Some have microcephaly but most have normal height and weight. Most have a wide-based, ataxic-like gait. All have severely impaired verbal skills although receptive language is quite good. Many have cardiac findings and half will have Hirschsprung disease or constipation.

The ZEB2 gene (formerly called ZFX1B or SIP-1) stands for zinc finger E-box binding homeobox 2 and is located on chromosome 2q22. It is a transcriptional co-repressor involved in the transforming growth factor-beta signaling pathway and is widely expressed during embryological development. Most mutations found are either point mutations or deletions. Detection rate for those with typical Mowat-Wilson facial phenotype approaches 100%.

The majority of cases are sporadic with a recurrence risk of 1% or less expected. The prevalence is currently unknown but the condition is most likely underdiagnosed. This may change with the availability of laboratory diagnosis.

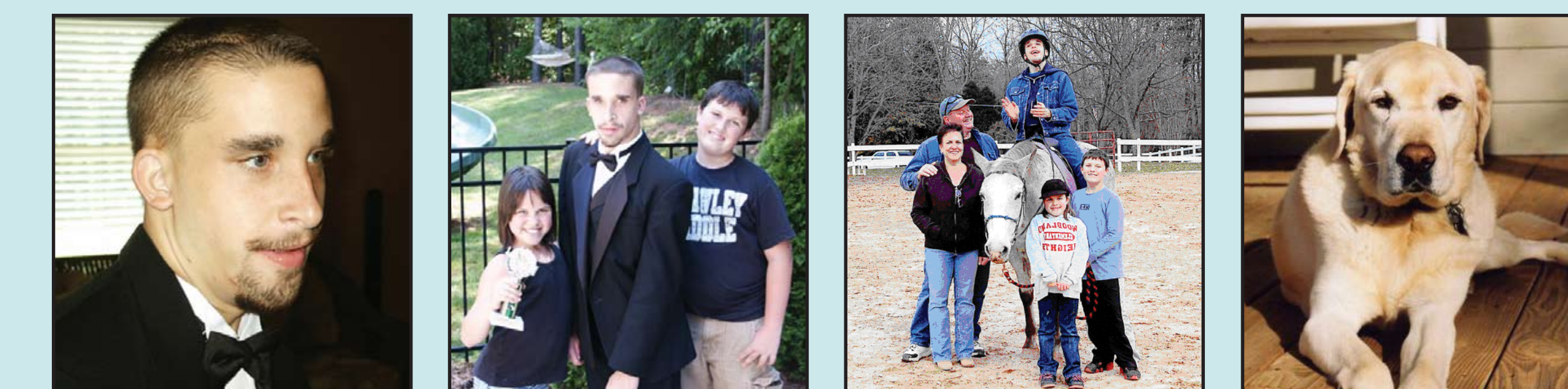


## TABLE

|  | Angelman syndrome | Mowat-Wilson syndrome |
|--|-------------------|-----------------------|
| <b>Features common to both</b>             |                   |                       |
| Mental retardation                         | +                 | +                     |
| Seizures                                   | +                 | +                     |
| Wide based gait                            | +                 | +                     |
| Wide spaced teeth                          | +                 | +                     |
| Constipation                               | +                 | +                     |
| Ophthalmologic findings                    | +                 | +                     |
| Prominent jaw                              | +                 | +                     |
| "Happy" disposition                        | +                 | +                     |
| Microcephaly                               | +                 | +                     |
| Verbal impairment                          | +                 | +                     |
| Frequent drooling                          | +                 | +                     |
| <b>Mowat-Wilson specific features</b>      |                   |                       |
| Hirschsprung disease                       | -                 | +                     |
| Cardiac findings                           | -                 | +                     |
| Hypertelorism                              | -                 | +                     |
| Elongated face                             | -                 | +                     |
| Distinctive eyebrows                       | -                 | +                     |
| Uplifted earlobes                          | -                 | +                     |
| Genitourinary (hypospadias)                | -                 | +                     |
| <b>Angelman syndrome specific features</b> |                   |                       |
| Flat occiput                               | +                 | -                     |
| Hypopigmentation                           | +                 | -                     |
| Disrupted sleep-wake cycles                | +                 | -                     |
| Fascination with water                     | +                 | -                     |

## SUMMARY

Today Cody is a handsome young man who recently attended his school prom and who enjoys time with his family and his service dog, Vito. Vito helps Cody feel more comfortable out in the community as well as increasing his social opportunities. Just like most teenage boys, Cody loves the ladies! Cody is currently in a self-contained class at school where he continues to receive physical, occupational and speech therapies. He ably communicates his wants/needs/interests by gestures and expression. Cody loves horseback riding (in a regular lesson stable) and riding his adapted tricycle. His family feels it is important to treat him like any other teenager and to help him create a life for himself within the community.



There is significant overlap of Mowat-Wilson syndrome and Angelman syndrome in children of young age. By adolescence, features of Mowat-Wilson syndrome should become more distinctive and allow differentiation of diagnosis. Availability of DNA based testing should help make a diagnosis of Mowat-Wilson syndrome at younger ages. Mowat-Wilson syndrome should be considered in children who have features seemingly consistent with Angelman syndrome but who have negative Angelman syndrome testing, and especially those with cardiac, GI findings and upswept earlobes.

## ACKNOWLEDGEMENTS

I would like to acknowledge Dr. Joseph Wagstaff (1955-2008) who saw this family with me in clinic, and who sadly and unexpectedly passed away earlier this year. Dr. Wagstaff was well known for his work on Angelman syndrome and was beloved by many families. I would also like to acknowledge Cody and his family for their persistence in getting to the bottom of this mystery and their willingness to help spread the word about Mowat-Wilson syndrome.

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