# Genetics Corner: A Consultation for Wolf-Hirschhorn Syndrome

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**Case Summary:**

A 9-week-old female had a cleft palate, dysmorphic features, and poor growth caused by Wolf-Hirschhorn syndrome (WHS). She was seen in Genetics Clinic a few weeks after lab results, that had been drawn as a newborn, established the diagnosis. The fetal size was small for gestational age throughout the pregnancy, but fetal movements were normal. The baby was born at a nearby community hospital at term by vaginal delivery to a 22-year old G2P1 mother. The birth weight was 2.49 kg (Z -1.89). She did not require intensive care. She could not latch on to the breast, but she fed from a bottle. She referred bilaterally on her newborn hearing screen.

Chromosome analysis had been sent, without the family's knowledge, before the baby was discharged home with her mother. The results identified a deletion of chromosome 4 at 4p16: 46,XX,del(4)(p16), establishing the diagnosis of Wolf-Hirschhorn syndrome (WHS).

The mother received these abnormal chromosome results by phone when her pediatrician called her a few weeks later, while she was driving. The mother recalls being told only that her daughter had a "serious chromosome abnormality" and would be referred to Pediatric Genetics to discuss the results in detail.

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In the first weeks of life, she had frequent spit-ups while feeding. Gastroesophageal reflux was diagnosed. Her maternal grandmother was the first to notice her cleft palate at a few weeks of age.

**Genetics Evaluation:**

The family history was noncontributory. Her interval growth was poor: Weight 3.28 kg (Z -3.71). On physical exam, she had facial features consistent with WHS, including prominent glabella, hy-

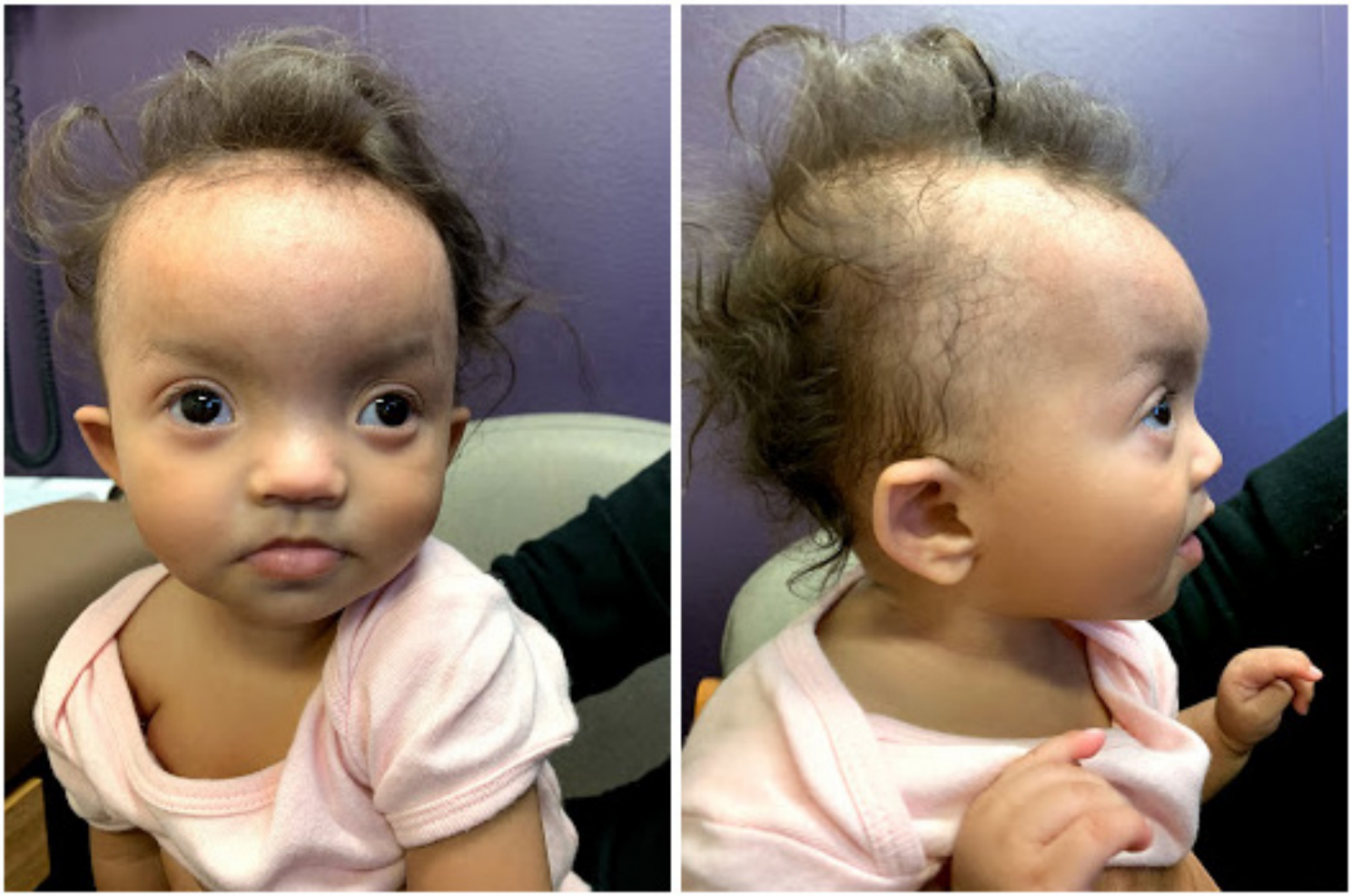

*Figure 1: This 12-month-old female has the classic facial features of Wolf-Hirschhorn syndrome. Note her widely-spaced eyes, broad and high forehead, prominent glabella, and arched eyebrows. Her philtrum is short.*

pertelorism, hypoplastic eyebrows, broad nasal bridge, v-shaped cleft of the soft palate, wandering eye movements, and hypotonia.

A same-day evaluation was arranged for her in the multidisciplinary Craniofacial team clinic for cleft palate evaluation, where she was given special bottles and instructed in feeding techniques for cleft palate. An echocardiogram and renal US were ordered: atrial septal defect and right ventricle dilation and right pelviectasis were detected. Chromosome microarray identified a 7.32 MB interstitial deletion of 4p16.3->p16.1: arr[hg19] 4p16.3p16.1(1,020,130-8,339,745)x1.

When she was evaluated again at 12 months of age, she was small but doing well developmentally. Her weight was 5.4 kg, (Z -4.45, but 50th%ile on the WHS syndrome specific growth charts.) She said, "mama," waved bye, responded to her name, and to sounds. She was socially engaged and “danced” for her mother. She bore weight well and stood with support but was not cruising.

**Discussion:**

Wolf-Hirschhorn syndrome (WHS), which is also called 4p minus syndrome, is caused by a variable deletion of the short arm of chromosome 4 (the “p” in p arm is an abbreviation for petit). WHS has a birth prevalence of 1 in 20,000-50,000 live births, and females predominate in a ratio of 2F:1M. Multiple congenital anomalies may contribute to the infant mortality of 17%.

WHS is characterized by a typical craniofacial appearance in infancy. The face is said to give the impression of a ‘Greek warrior helmet’ with a wide bridge of the nose in continuity with the prominent forehead and arched eyebrows. Microcephaly is common. In this patient, her providers recognized that her features were dysmorphic, but they were not confident enough to broach this with the mother. Her facial features are typical for WHS. There is a high anterior hairline with prominent glabella, widely spaced eyes, epicanthus, highly arched eyebrows, short philtrum, downturned corners of the mouth, and micrognathia small lower jaw). Poorly

## Breaking bad news

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| Set up the interview | Maintain privacy, sit down, have enough chairs for everyone, involve significant family members, as desired by parents, minimize interruptions, have tissues handy | |
| Assess parent perceptions | Ask parents how they think the infant is doing<br>What is their understanding of the situation | |
| Invite participation | Give parents the choice of how much information they would like to receive at that time | |
| Communicate effectively | Avoid jargon (aneuploidy, trisomy, syndrome), pause frequently to allow a response, use drawings or pictures, avoid being excessively blunt | |
| | **Use:**<br>“I’m sorry to have to tell you this”<br>“I know this is not good news for you” “ | **Avoid:**<br>“You knew….this was a possibility”<br>“I see this all of the time”<br>“I know what this must be like” |
| Address parents’ emotions | Listen, observe and acknowledge their emotions | |
| Provide summary of information and resources | End with a summary of recommendations. Keep it simple.<br>Give written information. | |

*Figure 2. Breaking bad news to the parents*

formed ears with pits/tags (1) are common. Other findings include feeding problems, including GE reflux, oral clefts, both cleft lip and/or cleft palate, skeletal anomalies (60%-70%), congenital heart defects (~50%), hearing loss (mostly conductive) (>40%), urinary tract malformations (25%), and structural brain abnormalities (33%). Seizures occur in 90-100% of children with WHS and can be triggered by fever. Almost one third later develop valproic acid-responsive atypical absence seizures (1).

***"The fact that this baby's medical providers did not diagnose her cleft palate at birth is unfortunate but not surprising. Needless to say, careful examination of the palate should be routine in all newborn babies, but especially in those who are small at birth, dysmorphic, or have trouble feeding. (It has been our personal observation that a tongue blade is more difficult to find in most nurseries than a high-frequency ventilator.) "***

All individuals with WHS have a variable degree of hypotonia, developmental delay, and later, intellectual disability. Poor growth is universal in WHS. Growth deficiency is of prenatal-onset, and it continues postnatally. WHS should be considered whenever a dysmorphic baby has an unexplained small size for gestational age.

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Approximately 50%-60% of individuals with WHS have a de novo deletion of 4p16; about 40%-45% have an unbalanced translocation with both a deletion of 4p and a partial trisomy of a different chromosome arm that can be inherited from an unaffected parent with a balanced chromosome translocation. Parental chromosome analysis with fluorescence in situ hybridization for 4p16 is recommended to rule out a cryptic balanced translocation in an unaffected parent.

Unfortunately, the manner in which this mother was informed of her daughter's diagnosis (by phone, while driving), was traumatic for her. The pediatrician did not offer any information about the condition, which also added to her anxiety. This news was all the more upsetting to this mother because it came as a surprise. She was unaware that her daughter's doctor suspected a problem. Then she had to wait for an appointment in our clinic to get any information about her daughter's condition.

With a little preparation, this situation can be avoided. It is better to prepare parents for the possibility of an abnormal result by letting them know whenever any consequential testing (genetic or otherwise) has been ordered prior to discharge. Let them know you will be calling them with the results as soon as it becomes available after discharge. When results are available, set up a time when both parents can be present and deliver the news in person. Use resources, such as GeneReviews, that provide useful summaries of many rare disorders: type "GeneReviews" in the search field at www.pubmed.gov to search through their offerings. Here are some practical tips to use when breaking the bad news to patients and family members based on the SPIKES 6-step protocol.

**Practical applications:**

1. Consider Wolf-Hirschhorn syndrome in dysmorphic infants who are small for gestational age.
2. Evaluate newborn infants for congenital anomalies when they are dysmorphic, SGA, or feed poorly without an explanation.
    a. Begin with a thorough physical examination and include the palate (find and use that tongue blade).
    b. Order imaging studies: echocardiogram, abdominal/renal and head ultrasounds
3. Apprise parents of genetic testing at the time the test is ordered. Share your concerns. Parents may be less anxious about it when you explain that you are trying to be thorough.
4. Use the protocol above when you have to break bad news. These steps help reduce the trauma for patients and families when receiving bad news
5. Consult the disorder summary at GeneReviews before speaking to the parents so you can offer basic information before referring to a specialist

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*References:*
1. *GeneReview summary on Wolf-Hirschhorn Syndrome by Battaglia, A., Carey, J., & South, S. https://www.ncbi.nlm.nih.gov/books/NBK1183/.*

*Permission was obtained from the patient's parents to distribute her picture for education purposes.*

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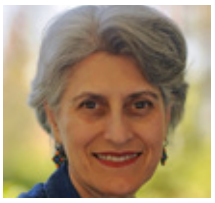

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