

take the

# GENETIC CHALLENGE

test your knowledge of clinical genetics

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## What is Your Diagnosis?

### CHIEF COMPLAINT CHIEF COMPLAINT

A 36-month-old Caucasian male, Robert, is referred for developmental delay and history of hypotonia.

### PAST MEDICAL HISTORY

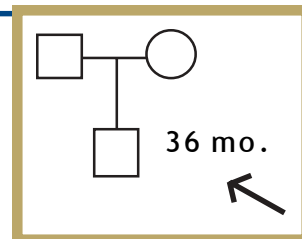
Robert was born with generalized hypotonia and had early problems with feeding. His mother states that he babbled and cooed as an infant and understands what they tell him, however, he has never spoken. He didn't sit until his first birthday and he only recently began to walk, but his gait is unsteady. Robert likes to constantly chew on something, and his mother usually carries a hard plastic toy (he chews up softer ones) to accommodate him. He had a normal hearing examination and normal karyotype at 14 months of age.

### PHYSICAL EXAMINATION

You note that Robert has minor facial anomalies including dolicocephaly, puffiness around the eyes, large ears, a wide nasal bridge, full cheeks, and a pointy chin. He does not make eye contact. In addition, his toenails are thin and peeling off.

### FAMILY HISTORY

The family history is unremarkable. Robert's parents are not related to each other. See pedigree.



Test yourself: answer these questions before reading the answers on page 2.

1. Robert has already had a normal standard chromosome analysis. What laboratory test(s) should you order *next* to determine Robert's diagnosis?

- A. Extended banding chromosome analysis
- B. Subtelomeric chromosome analysis
- C. Methylation studies
- D. Array CGH
- E. All of the above

2. What is the diagnosis for your patient?

- A. Angelman syndrome
- B. Autism
- C. Tricho-rhino-phalangeal syndrome
- D. 22q13 deletion/Phelan-McDermid syndrome
- E. Prader-Willi syndrome

3. Robert is the firstborn child in this family. What is the recurrence risk for future pregnancies?

- A. <<1%
- B. 25%
- C. 50%
- D. Depends on whether his lab abnormality is de novo or not

4. What percentage of cases like Robert's will extended banding chromosome analysis *miss*?

- A. Up to 12%
- B. Up to 25%
- C. Up to 32%
- D. Extended banding chromosome analysis will not detect Robert's condition.

Take the Genetic Challenge! will feature one or more genetic cases per month to test your knowledge of clinical genetics. We hope you find these cases interesting and educational. Questions or comments, please call: 1-800-366-1502 or visit us on the webat: [www.genetics.emory.edu](http://www.genetics.emory.edu).

continued next page

If you answered 1) B, 2) D, 3) D, 4) C,  
for each question, congratulations! You have  
mastered this month's Genetic Challenge!

## FOLLOW-UP

You order subtelomeric chromosome analysis (question 1) because you suspect that Robert has some type of microdeletion syndrome, such as 22q13 deletion syndrome, also called Phelan-McDermid syndrome (question 2). (Although fluorescence in situ hybridization, or FISH for 22q13 can also be ordered alone, a subtelomere study will pick up the 22q13 deletion as well as other subtelomeric abnormalities associated with Robert's clinical presentation). His results show a terminal deletion without any type of associated chromosome rearrangement, indicating a *de novo* occurrence. For this reason the recurrence risk in future pregnancies is considered to be negligible (question 3). Prior to the availability of subtelomeric chromosome analysis, you would have considered ordering extended banding chromosome studies in cases like Robert's. Although the diagnosis of 22q13 deletion syndrome is infrequently found via extended banding karyotype, this technique does not show the chromosome ends clearly, and misses up to 32% of cases resulting from submicroscopic deletions (question 4).

## ABOUT PHELAN-MCDERMID SYNDROME

Approximately 6% of idiopathic mental retardation results from cryptic subtelomeric chromosome rearrangements. First described in 1985, 22q13 deletion/Phelan-McDermid syndrome is a relatively widespread and underdiagnosed cause of mental retardation. Phelan, et al. (1988) identified the breakpoint of this microdeletion syndrome at 22q13.31, and have also published the largest study to date (2001), characterizing 37 patients, comparing them to 24 previously published cases. The major findings of global developmental delay, generalized hypotonia, absent or delayed speech, minor anomalies of the face, head, ears, and hands, and normal to advanced growth, overlap with many other conditions, particularly Angelman syndrome, autism, tricho-rhino-phalangeal syndrome, and Prader-Willi syndrome.

The prevalence of 22q13 deletion/Phelan-McDermid syndrome is unknown. Although three-quarters of the cases have been diagnosed in children under the age of 5, 25% are older than this, with a range of age at diagnosis from prenatal to 33 years. The 22q13 deletion/Phelan-McDermid syndrome family support group website, [www.22q13.org](http://www.22q13.org), lists the following characteristics of patients:

- Hypotonia (97%)
- Normal to accelerated growth (95%)
- Increased tolerance to pain (86%)
- Thin, flaky toenails (78%)
- Large, fleshy hands (68%)
- Prominent, poorly formed ears (65%)

22q13  
deletion/  
Phelan-  
McDermid  
syndrome  
is a  
relatively  
widespread  
and  
under-  
diagnosed  
cause of  
mental  
retardation.  
In 20% of  
cases the  
deletion  
is due to  
an  
unbalanced  
chromosome  
translocation.

- Pointed chin (62%)
- Dolicocephaly (57%)
- Ptosis (57%)
- Tendency to overheat and lack of perspiration (51%)
- Chewing on non food items such as clothing, bedding, toys (70%)
- Teeth grinding
- Tongue thrusting
- Hair pulling
- Aversion to clothes

#### **Characteristics present in less than 50% of patients:**

- Epicanthal folds (fold over inner corner of eye)
- Syndactyly (webbing) between 2nd and 3rd toes
- Fair skin
- Puffy eyelids
- Deep set eyes
- Long eye lashes
- Full cheeks
- Wide nasal bridge
- Full eyebrows
- Minor anomalies of head, ears, hands, feet, and face
- Seizures
- Strabismus
- Anomalies of the spine
- Vision difficulties that result in extensive use of peripheral vision and poor depth perception

#### **Developmental Delays include:**

- Absent to severely delayed speech
- Rolling over – average 8 months (range 3-24 months)
- Crawling – average 16 months (range 7-36 months)

Behaviorally, many fall within the autistic spectrum.

## **ETIOLOGY & RECURRENCE RISK**

Phelan-McDermid syndrome results from loss of genetic material near the terminal end of the long arm of one copy of chromosome 22. Although more paternal than maternal germline deletions are reported, a parent of origin effect on phenotype has not been observed. Affected individuals may have the 22q13 deletion in all cells examined or be mosaic (i.e. have a mixture of cell types, usually some normal and some abnormal) for the condition. This loss can occur from a terminal (or very rarely) an interstitial deletion or insertion, unbalanced translocation, or ring chromosome formation. In one study of 56 patients using microsatellite analysis and FISH, the size of the 22q13 deletion ranged from 130 kb to over 9 Mb, with little correlation to phenotypic severity.

Most of the time the 22q13 deletion occurs sporadically (de novo) and therefore has a negligible recurrence risk for future pregnancies. In 20% of cases the deletion is due to an unbalanced chromosome translocation. In about 80% of cases the unbalanced rearrangement is inherited from a healthy parent who carries a balanced translocation. A balanced translocation carrier has an increased risk for chromosome malsegregation in all of their pregnancies. Abnormalities in offspring will depend upon which chromosomes are involved in the unbalanced rearrangement. The balanced translocation carrier parent therefore will be at increased risk not only for 22q13 deletion syndrome, but other chromosome abnormalities as well, depending on the specific rearrangement.

PROSAP2/SHANK3 is a gene that is important in brain development, and is at the 22q13 location and therefore lost when this segment of the chromosome is deleted. The loss of PROSAP2/SHANK3 is thought to be responsible for the major neurological features (mental retardation, delay of expressive speech) in Phelan-McDermid syndrome.

## REFERENCES

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- Wilson, et al. Molecular characterisation of the 22q13 deletion syndrome supports the role of haploinsufficiency of SHANK3/PROSAP2 in the major neurological symptoms. Journal of Medical Genetics 2003;40:575-584 .
- [www.22q13.org](http://www.22q13.org)

*This issue of "Take the Genetic Challenge!" was written by Catherine Tesla, MS, CGC, with edits by Katy Phelan, PhD.*

### Emory Department of Human Genetics

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If you have additional questions regarding Phelan-McDermid syndrome, please call Emory Genetics at 1-800-366-1502 or (404) 778-8500 and ask for the Genetic Counselor On-Call, or fill out the information below, and fax this page to: FAX (404) 778-8559. Thank you.

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