

22q11.2 Deletion Syndrome

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Key Points

- Primary care physicians may encounter situations in which a genetic diagnosis is now possible in an individual with developmental delay whose previous genetic workup was negative.
- Testing for small chromosomal deletions, such as 22q11.2 deletion syndrome, represents an example of the improved diagnostic capabilities of current genetic testing.
- 22q11.2 deletion syndrome includes a range of clinical findings, all caused by the same chromosomal deletion.
- Most individuals with the 22q11.2 deletion have a de novo deletion, meaning that neither of their parents has the deletion.
- To determine the recurrence risk of 22q11.2 deletion syndrome, parents of affected individuals should be tested for the deletion. Siblings should be tested if they have suggestive features.

Learning Objectives

Participants will be able to:

- Recognize a clinical situation for which a genetic evaluation may be worthwhile in an individual with developmental delay;
- Identify which family members should have genetic testing once a 22q11.2 deletion is identified.

Family History Issues

In about 85-95% of cases, the 22q11.2 deletion is a de novo occurrence. In the remaining cases, the deletion is also present in one of the parents.

Red Flags



In the neonatal period, red flags for 22q11.2 deletion syndrome include conotruncal heart malformations, palate abnormalities [midline cleft palate

and/or velo-pharyngeal insufficiency (VPI)], hypocalcemia, or immunodeficiency. In the childhood years, an individual may present with learning abnormalities and speech problems related to cleft palate or VPI. However, clinical presentation is highly variable due to the many associated findings [[McDonald-McGinn et al 2003](#)].

Case 17. A Sister with Learning Disability of Unknown Etiology

Brenda is a 30-year-old woman who would like to have children. She has come to you with a question about her risk of having a child with learning problems. Brenda's older sister, Cathy, is currently 32 years old and has a learning disability. Cathy was born with a cleft palate and she later developed a seizure disorder and schizophrenia. Brenda has brought copies of Cathy's medical records for you to review.

Medical records reveal the following history: Cathy was born with a cleft palate. No known birth trauma occurred. Brenda was born two years later, and Cathy's parents had a miscarriage of a fetus with a cleft palate two years after that. At age four, Cathy, who had always been somewhat "slow," had difficulty adjusting to a day care environment and was referred for further evaluation. Standardized testing indicated mildly to moderately delayed cognitive development, mildly delayed motor development, and significantly delayed language development.

Cathy's medical history at the time of her evaluation at age four was otherwise unremarkable. Physical examination revealed evidence of cleft palate repair but no other craniofacial abnormalities. Growth had been consistently at the 30th percentile, with normal head circumference. She had no abnormal skin findings. Chromosomal study and metabolic studies were normal. The family was counseled that no specific genetic etiology could be found. She was considered to have mild-to-moderate mental retardation of unknown, presumably multifactorial, etiology.

Cathy continued to have learning difficulties but was able to complete high school. As a young adult she had episodes of psychosis, thought to be temporal lobe epilepsy, and at least two grand mal seizures. Her psychiatrist and neurologist tried virtually every seizure and antipsychotic medicine with intermittent effect; however, steady deterioration occurred. She developed

sleep apnea and was unable to tolerate any treatment, including O₂. She eventually required hospitalization in a psychiatric locked ward to manage her preoccupation with frightening voices.

After reviewing this information, you called Brenda and told her that without knowing the precise diagnosis, it would be very difficult to tell her the chance she could have a child with similar problems. However, you recommended Cathy be re-evaluated by the local medical genetics clinic because clinical understanding of developmental problems and their associated complications had progressed considerably since Cathy's initial medical genetics evaluation in 1972 at age four.

Therefore, Cathy was seen by the local medical genetics clinic. Repeat chromosome studies revealed a deletion of chromosome 22 that includes band q11.2. This abnormality would not have been detected in the chromosomal studies done 28 years ago, and illustrates the sensitivity of new, more precise testing techniques. This deletion was confirmed using FISH (fluorescent in situ hybridization) testing.

Clinical Care Issues

What is the 22q11.2 deletion syndrome?

The 22q11.2 deletion syndrome is now known to encompass the phenotypes previously described as "diGeorge syndrome", "velocardiofacial syndrome", and "conotruncal anomaly face syndrome" (see [GeneReview: 22q11.2 Deletion Syndrome](#)). The most common manifestations are cardiac abnormalities, palatal abnormalities, learning disabilities, and characteristic facial features. Of these, Cathy has two: palatal abnormalities and learning disabilities. Her psychiatric problems are assumed to be part of the syndrome, but the frequency with which these features occur is not yet known. Molecular cytogenetic diagnosis, in this case the documentation of a specific small chromosomal deletion using FISH testing, has led to a re-evaluation of the epidemiology and definition of a syndrome. It is likely that many patients are yet to be identified, who, like Cathy, are either older or have somewhat atypical features of the syndrome as currently described. Some individuals with 22q11.2 deletion have very subtle findings and may not be recognized.

Significance of identifying the cause of Cathy's developmental delay

The ability to find specific causes for developmental delay has increased over time. Given advancing technology, it is especially important for the primary care physician to think "genetic causes" if no clear-cut etiology has been established in an individual with developmental delay. Considering a genetic etiology is particularly important when an individual has more than one malformation or when the family history reveals other similarly affected individuals.

Recognition of new syndromes and technological improvements in genetic testing — in particular, improved cytogenetic test methods and the introduction of molecular genetic testing — have led to an increasing ability to define specific genetic causes for problems like Cathy's. Thus, "normal" results on an evaluation performed 25 years ago do not preclude a genetic cause.

Recurrence risk

When a genetic diagnosis is made in a family, the recurrence risk — that is, the likelihood that the disease will occur in future children — needs to be considered. In this family, Cathy appears to be the only affected person. However, further evaluation is warranted. Brenda could have this deletion without manifesting obvious clinical signs, and if so, could pass it on to her children (see [Risk Assessment](#) and [Genetic Counseling and Testing](#)).

Risk Assessment

The 22q11.2 deletion is inherited in an autosomal dominant manner. This means that affected individuals such as Cathy have a 50% chance of passing the deletion to their offspring.

To determine the risk to Brenda's offspring, it is important to determine whether Cathy is the first individual in her family to have this condition or whether the deletion was inherited from her parents, in which case Brenda may also have inherited the deletion. In about 85-95% of cases, the 22q11.2 deletion is a de novo occurrence, but in the remaining cases, the deletion is also present in one of the parents. Results of FISH testing of Brenda for 22q11.2 deletion would determine if Brenda's children are at risk. Results of FISH testing of Brenda and Cathy's parents would determine if extended family members are at risk.

Genetic Counseling and Testing

Genetic testing

Routine chromosome analysis will reveal up to 15% of 22q11.2 deletions, but the majority will be detectable only by specific 22q11.2 FISH testing [Shprintzen 2001]. Deletions detectable only by FISH testing are usually called "microdeletions." In the workup of a patient suspected of having a 22q11.2 deletion, routine chromosome analysis should also be done to identify the few cases caused by chromosomal rearrangements involving the 22q11.2 region (<1% cases). Fewer than 5% of patients with suggestive clinical findings have no detectable deletion or chromosomal rearrangement of the 22q11.2 region after routine chromosome analysis and FISH testing.

Once the 22q11.2 deletion has been identified in an individual, FISH testing of both parents is used to determine if the deletion is inherited or de novo. If both parents of an individual with the 22q11.2 deletion syndrome have normal FISH studies, the deletion most likely occurred de novo in the affected individual. However, there is still a very small risk that a sibling could inherit the deletion, because germline mosaicism could have occurred in one of the parents [i.e., the situation in which the de novo chromosome deletion occurred in the germline (egg or sperm) of one of the parents, and thus was present in multiple gametes and could be passed on to more than one child]. Their mother's history of miscarriage of a fetus with cleft palate indicates that germline mosaicism is possible in the family.

FISH testing of Brenda will determine if she has the 22q11.2 deletion. If Brenda is found to have normal 22q11.2 FISH testing results, she is not at increased risk of having a child with 22q11.2 deletion syndrome. If Brenda has the deletion, she has a 50% chance of passing it on to her children.

Interventions

Treatment of individuals with 22q11.2 deletion syndrome is based on presenting symptoms and signs, and varies because of the highly variable clinical presentation. Depending on clinical problems of the individual patient, a multidisciplinary evaluation is often helpful, potentially involving the specialties of plastic surgery, speech pathology, otolaryngology, audiology, dentistry, cardiology, immunology, child development, child psychology, and other specialists [McDonald-McGinn et al 2003].

Ethical/Legal/Social/Cultural Issues

Relief of having a diagnosis

Cathy was not diagnosed 28 years ago because of lack of knowledge about this condition and limitations of the technology available at the time. A specific diagnosis in a child with developmental delay is often helpful to parents. A reassuring aspect of Cathy's diagnosis may be the knowledge that nothing the parents should have done or could have done would have prevented her condition. There are many support groups and counseling services that can continue to provide information and assistance to the family.

Resources

- **Max Appeal**
Landsowne House
Wollaston, Stourbridge
West Midlands, UK
DY8 1049
Phone: (+44) 0 138-482-1227
Email: info@maxappeal.org.uk
- **Velo-Cardio-Facial Syndrome Education Foundation**
Upstate Medical University, University Hospital
Jacobson Hall Room 707
750 East Adams Street
Syracuse, NY 13210
Phone: 315-464-6590
Fax: 315-464-6593
Email: info@vcfsed.org
- **Chromosome 22 Central**
237 Kent Avenue
Timmins, ON
Canada P4N 3C2
Phone: 705-268-3099
Email: a815@c22c.org
- **National Library of Medicine Genetics Home Reference**
[22q11.2 deletion syndrome](#)

- **GeneTests Resources for 22q11.2 Deletion Syndrome** 
- **GeneTests Online Medical Genetics Information Resource**

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