

22q11.2 Deletion Syndrome: Diagnosis in a Newborn

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Key Points

Genetics

- Testing for the 22q11.2 deletion syndrome is performed by FISH (fluorescent in situ hybridization) analysis.
- A diagnosis of 22q11.2 deletion syndrome can lead to the identification of other affected family members.

ELSI

- A parent with developmental disability may need assistance and support with parenting, particularly when her child is born with a complex medical condition.
- All individuals, including those with developmental disability, have the legal right to make independent decisions about reproduction.

Learning Objectives

Participants will be able to:

- Determine the appropriate genetic testing strategy for family members when an individual is newly diagnosed with 22q11.2 deletion syndrome;
- Describe the psychosocial needs of parents with developmental disability.

Family History Issues

In 85-95% of cases, the 22q11.2 deletion is a de novo mutation, but in the remaining cases, the deletion is also present in one of the parents. When parents or siblings of an affected person have manifestations of the condition, it is more likely to be a hereditary case.

Red Flags



In the neonatal period, red flags 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 history of cleft palate or VPI. However, clinical presentation is highly variable due to the many associated findings [McDonald-McGinn et al 2003].

Case 18. Newborn with 22q11.2 Deletion Syndrome

Alice, the second daughter of Mr. and Mrs. P, was born with a cleft palate. Subsequently, she was noted to have developmental delay. Mild mental retardation was diagnosed at five years of age. She was placed in special education classes and graduated from high school. At age eight years, chromosome studies were obtained as part of a medical genetics evaluation, and revealed no abnormalities. No other genetic diagnosis was identified, and she was given the diagnosis of idiopathic mental retardation and coincidental cleft palate.

At age 20 years, Alice married and shortly thereafter became pregnant. Her daughter was born with a cleft palate and truncus arteriosus. As part of the workup, chromosome analysis, including FISH studies for 22q11.2 deletion, was performed. The FISH study on Alice's daughter revealed deletion 22q11.2. In retrospect, it seems likely that Alice has 22q11.2 deletion syndrome, and that her child has inherited it from her.

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, Alice's newborn daughter has two: a cleft palate and a cardiac malformation. Alice herself has two findings that are consistent with the 22q11.2 deletion: a cleft palate and a learning disability. 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 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.

New diagnosis of genetic condition

The diagnosis of 22q11.2 deletion provides information about etiology and prognosis. Alice's daughter (and Alice herself, if she has the deletion) may have other manifestations of this condition and may benefit from a medical genetics evaluation to determine what other workup is indicated.

Risk Assessment

Recurrence risk

Like all chromosomal microdeletion syndromes, 22q11.2 deletion is inherited in an autosomal dominant manner; that is, a person who has 22q11.2 deletion syndrome has a 50 percent chance of transmitting the chromosome 22 that contains the microdeletion to each offspring. Alice's risk of having future children with 22q11.2 syndrome (her recurrence risk) cannot be determined with certainty until she is tested. Although her medical history suggests the syndrome, testing is needed for confirmation. If she is confirmed to have the 22q11.2 deletion, she has a 50 percent risk of transmitting the deletion in each future pregnancy. In addition, further family testing should be considered (See [Genetic Counseling and Testing](#)).

Genetic Counseling and Testing

Testing for the 22q11.2 deletion

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 due to chromosomal rearrangements involving the 22q11.2 region (<1% cases). Deletion or chromosomal rearrangement of the 22q11.2 region is confirmed by routine chromosome analysis and FISH testing in more than 95% of patients with suggestive clinical findings.

Family testing after a diagnosis

After an individual is diagnosed to have the 22q11.2 deletion, testing of family members should be offered. In this case, Alice's medical history is consistent with the deletion syndrome. She can be tested by FISH analysis to determine whether she has the 22q11.2 deletion.

If Alice is found to have the 22q11.2 deletion, she may have inherited it from one of her parents. Even if her parents show no clinical evidence of the condition, they could have the deletion, because its manifestations can sometimes be very mild. If her parents choose to be tested and neither has the deletion, Alice may represent a de novo occurrence of the deletion.

Additionally, assuming Alice has the 22q11.2 deletion, her older sister should be offered testing. The results of testing would determine recurrence risk: if Alice's sister did not inherit the deletion, she cannot pass it on to her children.

Each family member should have the opportunity to decide whether to undergo testing, after receiving genetic counseling. Usually, the decision to undergo testing for parents and siblings of affected cases depends on the presence of medical problems in these individuals that might be explained by 22q11.2, or on their desire to use such information in reproductive planning.

Interventions

In the neonatal period, several tests are suggested for individuals with the 22q11.2 deletion, including serum calcium level, absolute lymphocyte count, echocardiogram, renal ultrasound examination, and a chest x-ray to evaluate for thoracic vertebral anomalies.

In addition, cardiac evaluation is indicated. Alice's daughter has already been diagnosed with a cardiac malformation; if Alice is found to have the 22q11.2 deletion, a cardiac evaluation may be indicated for her as well.

In general, 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

Like any parent dealing with this kind of information, Alice may need help coping with the impact of the diagnosis for her daughter and herself. Because she has developmental disability herself, she might need additional support. She should be encouraged to bring her partner, parents, or other family members to medical appointments to assist her in learning about her daughter's condition and in making decisions about her care.

Parental training and intervention for parents with developmental disability

When a parent has developmental disabilities, additional support and assessment may be needed. Public health and other community support organizations may begin by referring the parents to appropriate health resources or by providing them with appropriate training related to caring for their child. The ability of the parent to handle childcare responsibilities varies depending on his/her skills, the health needs of the child, and support available from other family members. In this case, Alice and her husband may be capable of providing parental care without additional assistance, but assessment of their daughter's care is appropriate.

If there is doubt about the skills of the parent, early monitoring and intervention is advocated for children who could be at risk. If the parent cannot provide the necessary care on his/her own, attempts to find alternative solutions should be made, such as providing home care support, or finding another supportive home environment where both the parent and child can stay. If a solution is not found, the child's well-being may require consideration of removal of the child from the parent's care and placement in a foster home. However, this approach should occur only after the failure of other solutions that would keep parents and children together. Inappropriately high standards for parenting and society's failure to provide adequate support and training have both been cited as reasons for overly frequent removal of children from the care of developmentally disabled parents [Finucane et al 1998].

Reproductive choice

If Alice has the 22q11.2 deletion, each subsequent child has a 50% of inheriting the deletion and having physical and developmental problems associated with this condition. She and her husband have the legal right to accept this risk in future pregnancies.

The right to reproductive autonomy is stressed because of a history of involuntary sterilization of women with developmental disabilities in the US and other developed countries. Involuntary sterilization of individuals with "feeble-mindedness" and other mental and physical disabilities was mandated by law in many states for a substantial part of the twentieth century (see [Eugenics Archive](#)). The Eugenics Movement, which was active in the US from the early 1900s to the 1940s, advocated this policy, and an estimated 60,000 individuals were sterilized as a result. Although state laws calling for involuntary sterilization were rescinded by the 1970s, this history remains an important example of the misuse of medical technology.

In supporting the reproductive rights of individuals with developmental disabilities, appropriate genetic counseling plays an important role. Abstract concepts in inheritance may be difficult to explain, and obtaining informed consent may also be difficult. Providing appropriate genetic counseling may require changes from usual practice, such as rephrasing or repeating information, providing information in more than one format, and taking additional time both to educate the patient and to ensure that the patient has had an opportunity to communicate his/her concerns.

Resources

- **Mental Retardation Association of America, Inc (MRAA)**
211 East 300 South, Suite 212
Salt Lake City, Utah 84111
Phone: 801-328-1574
- **American Association on Mental Retardation (AAMR)**
444 North Capitol Street NW, Suite #846
Washington DC 20001
Phone: 202-387-1968; 800-424-3688
Fax: 202-387-2193

Email: aamr@access.digex.net

- **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

- **Eugenics Archive, Cold Spring Harbor Laboratory**

- **National Library of Medicine Genetics Home Reference**

[22q11.2 deletion syndrome](#)

- **GeneTests Resources for 22q11.2 Deletion Syndrome**

- **GeneTests Online Medical Genetics Information Resource**

References

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