

Cystic Fibrosis

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Key Points

- Cystic fibrosis (CF) is an autosomal recessive condition. A person with CF has two *CFTR* mutations, one inherited from each parent.
- Molecular genetic testing for CF usually involves testing for a defined panel of 23-100 mutations in the *CFTR* gene, out of more than 1000 mutations so far identified. The mutation detection rate among CF carriers and patients with CF varies depending on ethnic background and the specific panel of mutations offered by the laboratory.
- If the father of a child with CF has been tested and found not to carry a *CFTR* mutation, there are four possible explanations:
 - The *CFTR* mutation he carries was not included in the genetic testing panel used;
 - Paternity of the child was misassigned;
 - A laboratory error occurred; OR
 - Very rarely, a new *CFTR* mutation might arise in the affected child, or the child might inherit two *CFTR* mutations from the mother.
- If misassigned paternity is a consideration, this possibility should ideally be addressed with the child's mother before ordering genetic testing and before disclosing genetic test results to the child's father.

Learning Objectives

Participants will be able to:

- Explain issues of carrier testing for CF as they relate to ethnic minority groups;
- Provide possible explanations for unexpected genetic test results for CF in which the baby's father does not carry one of the mutations identified in the baby;
- Describe counseling approaches if genetic test results suggest misassigned paternity.

See [GeneReview: CFTR-Related Disorders](#).

Family History Issues

Cystic fibrosis can occur in the absence of family history of the disease. Cystic fibrosis is inherited in an autosomal recessive manner, meaning that both parents of an affected individual are usually carriers of a mutation in the *CFTR* gene. A *CFTR* mutation can be transmitted from generation to generation with no affected individuals in the family. However, if a carrier has a child with another carrier, they are at risk of having an affected child.

Red Flags



Symptoms suggestive of cystic fibrosis include **chronic sinopulmonary disease** (chronic cough and sputum production, chronic wheeze and air trapping, obstructive lung disease on lung function tests, persistent bacterial colonization, chronic chest radiograph abnormalities, digital clubbing) and **gastrointestinal/nutritional abnormalities** (malabsorption/pancreatic insufficiency, distal intestinal obstructive syndrome, rectal prolapse, recurrent pancreatitis, meconium ileus, chronic hepatobiliary disease, failure to thrive, hypoproteinemia, fat-soluble vitamin deficiencies).

Case 13. Parents Concerned about Risk of Having a Child with Cystic Fibrosis

Mrs. R, a white woman, sought counseling from her primary care physician prior to conceiving her first child because she was concerned about her risk of having a child with cystic fibrosis. Her brother died of the disease at age eight years, prior to the availability of molecular genetic testing for CF. Realizing the potential risk of CF occurring in Mrs. R's children, Mrs. R's primary care physician referred her to a genetic counselor for genetic counseling and genetic testing.

The genetic counselor explained to Mr. and Mrs. R that CF is an autosomal recessive condition. Both parents must be carriers for their child to be at risk

of inheriting this disease. Mrs. R has a 2/3 chance of being a carrier (since her brother was affected and she is unaffected) and Mr. R has a 1/28 chance of being a carrier (the carrier frequency in the general non-Hispanic white population). Mr. and Mrs. R elected to have carrier testing for cystic fibrosis. The 25-mutation panel typically used for carrier testing (recently reduced to 23 mutations; see [Watson et al 2004](#)) detects about 85-90% of mutations in non-Hispanic whites (see [GeneReview: CFTR-Related Disorders, Table 1; Table 8](#)).

Mrs. R was found to be a carrier for the delta F508 mutation in *CFTR*. Her husband's test did not identify any *CFTR* mutation. The couple was informed that their results showed the risk of having a child with CF to be approximately 1/1000. This risk estimate takes into account the fact that a negative result cannot eliminate the possibility that Mr. R is a carrier (he may have a *CFTR* mutation that was not included in the 23-mutation panel). Thus, they could not be completely assured that they will not have a child with CF.

Mrs. R became pregnant. Her newborn baby was generally healthy but exhibited chronic wheezing, a symptom of CF. Because of Mrs. R's family history, he was tested for CF using sweat chloride testing at age three months. His sweat chloride test was positive. Mr. and Mrs. R were notified of the results and requested genetic testing of their child.

The molecular genetic testing of the *CFTR* gene indicate that the baby carries two mutations: delta F508 and G542X. Mr. and Mrs. R have not yet been notified of the results.

Clinical Care Issues

How could the child have two mutations in the *CFTR* gene if Mr. R's carrier testing was negative?

The possible explanations include:

- The mutation was not included in the carrier testing panel used to determine Mr. R's carrier status. Over 1000 mutations have been detected in the *CFTR* gene, but the most commonly used [testing panel for CF carriers](#) includes 23 mutations and detects approximately 85-90% of mutations in non-Hispanic whites. Test panels including a larger number of mutations are often used in testing of an affected

individual, so sometimes the affected child is tested with an expanded panel that includes a mutation not included in the father's carrier test. However, in this case, the baby carries the delta F508, inherited from his mother and the G542X mutation, inherited from his father; the G542X mutation **is** included in the 23-mutation panel used to test Mr. R. Mr. R's carrier test should have detected this mutation.

- Missigned paternity. This is probably the most likely explanation, particularly given that Mr. R was tested for the G542X mutation. Although definitive studies are lacking, misassigned paternity has been estimated to occur in 1% to 10% of pregnancies.
- Lab error. If Mr. R's carrier test result is erroneous, and he is a carrier of the G542X mutation, each subsequent child of Mr. and Mrs. R would have a 25% risk for having CF.
- A new mutation in the *CFTR* gene. Although a rare genetic event, the occurrence of a de novo mutation in the normal *CFTR* gene inherited from the father has been reported and could also explain this situation. (Another rare genetic event, uniparental disomy, can result in a child inheriting two copies of a *CFTR* mutations from one parent; this mechanism would not apply in this case, because it would result in the inheritance of two copies of the same *CFTR* mutation.)

How should the possibility of misassigned paternity be addressed with this family?

Most geneticists would recommend that the possibility of misassigned paternity be discussed first privately with Mrs. R. If Mrs. R indicates that her husband may not be the biological father of the child, the physician needs to have a discussion with Mrs. R about options for how the results of the genetic test will be disclosed to Mr. R. The physician should point out that the father has legal status in relationship with the child so Mr. R must be informed of the results if he asks.

Risk Assessment

Cystic fibrosis is inherited in an autosomal recessive manner; the children of two carriers have a 25% risk of being affected. The risk for CF in Mr. and Mrs. R's future pregnancies is dependent upon whether Mr. R is the father of the affected child or whether another genetic explanation is confirmed.

Role of ethnicity in CF

If Mr. and Mrs. R had been Hispanic or non-white, the genetic counselor

would have provided them with race-specific carrier frequency information about CF. The CF carrier frequency is lower among Hispanics and non-whites, varying in one report from 1/46 in Hispanic Americans to 1/90 among Asian Americans [Richards et al 2002]. Another report found the carrier frequency is 1/61 in African Americans [Hamosh et al 1998]. Before carrier testing, the probability that Mrs. R is a carrier would remain 2/3 since her brother was affected with CF, but the chance that Mr. R is a carrier would depend on his racial/ethnic group.

The mutation detection rate of the panels used to determine carrier status of individuals of racial/ethnic minorities should also be considered. For example, the original 25-mutation panel detects 57% of *CFTR* mutations in the Hispanic population; an expanded panel, including 70 to 86 mutations, is likely to detect up to 72% of mutations in the *CFTR* gene among Hispanics [Heim et al 2001]. For mutation detection rates with the standard 25-mutation panel in various ethnic groups, see *GeneReview: Table 1*.

Genetic Counseling and Testing

Genetic counseling provides an opportunity for Mr. and Mrs. R to learn more about autosomal recessive inheritance, genetic testing, and the implications of the CF diagnosis for their family.

What is the optimal genetic testing strategy for the family?

This question would be approached initially through a discussion of the different possible explanations with Mrs. R. The genetic counselor who was involved with this family could be helpful in determining the type of testing options for the family and which laboratory may be able to provide more information. If Mr. R had not been tested for the specific mutation identified in the baby, an expanded mutation panel including that mutation could be offered to Mr. R.

The subsequent testing done depends upon the results of the physician's discussion with Mrs. R regarding the possibility of misassigned paternity:

- If another man could be the father of the baby, he could be offered testing to determine if he carries the G542X mutation.
- If Mrs. R is certain that Mr. R is the baby's father, carrier testing should be offered again to Mr. R to determine if a laboratory error was made.
- Evaluation to determine if a de novo mutation occurred in the baby's *CFTR* gene inherited from Mr. R may be available if other possible

explanations are eliminated.

Interventions

Preventive care. Strategies exist to manage the pulmonary and gastrointestinal complications associated with cystic fibrosis (see [GeneReview: Management](#)).

Other clinical management. Referral to a regional CF Center is recommended for individuals known to have CF or those in whom the diagnosis is being considered. A local CF clinical care center can be identified by contacting the [CF Foundation](#). Most patients followed at a CF Center are evaluated quarterly by a multidisciplinary team consisting of physicians, nurses, respiratory therapists, dietitians, social workers, and genetic counselors. Frequent monitoring and increased use of appropriate medications in the management of CF have resulted in improved outcomes [[Johnson et al 2003](#)].

Ethical/Legal/Social/Cultural Issues

Given the new diagnosis of CF in this family, this case shares many issues with [Case 12](#). Some additional issues in this case include:

- Possible need for psychosocial support
- Communication with Mr. and Mrs. R about paternity
- Medical error

Possible need for psychosocial support. If Mrs. R indicates that Mr. R may not be the father of the baby, this could pose a considerable strain on their marriage and parenting roles, particularly given the child was recently diagnosed with a chronic illness. A meeting with a social worker may help determine sources of psychosocial support for this couple.

Communication with Mr. R about paternity. If Mr. R is not the baby's father, the physician and other health care workers may be in a difficult situation. If Mrs. R requests that the physician not reveal the baby's genetic test results to Mr. R, a problematic situation may arise in which Mr. R requests information about these results directly from the physician. Ideally, the physician and Mrs. R should decide together how such a request will be handled so that the physician can respect the needs of both parents while providing honest and accurate information. The physician must document all

conversations in the medical record; Mr. R, as the baby's legal father, would have access to these records and may choose to request them at any time.

Medical error. If it is determined that Mr. R's laboratory test results were inaccurate, the physician must explain the situation to the parents. Many institutions have policies concerning disclosure of medical error.

Resources

- **Cystic Fibrosis Foundation**

6931 Arlington Road, 2nd Floor
Bethesda, MD 20814-5200

Phone: 800-FIGHTCF (800-344-4823); 301-951-4422

Fax: 301-951-6378

Email: info@cff.org

- **Cystic Fibrosis Trust**

11 London Road
Bromley
Kent BR1 1BY
England

Phone: 020 8464 7211

Fax: 020 8313 0472

After hours: 020 8464 0623

- **Medline Plus Health Information: Cystic Fibrosis**

- **Connecticut Children's Medical Center**

[Pediatric to Adult Care Transition for CF](#)


This site has a basic protocol for the transfer of patients from pediatric to adult care.

- **Institute of Child Health**

Great Ormond Street Hospital for Children NHS Trust

This site answers some basic questions about their transition program.

- American Society of Human Genetics and American College of Medical Genetics (1995) [Points to consider](#): ethical, legal, and psychosocial implications of genetic testing in children and adolescents

- American College of Medical Genetics (2000) [Statement](#) on genetic testing for cystic fibrosis
- [Cystic Fibrosis Medicine](#)
- [National Library of Medicine Genetics Home Reference Cystic Fibrosis](#)
- [GeneTests Online Medical Genetics Information Resource](#)
- [GeneReviews, GeneTests Online Medical Genetics Information Resource](#)
- [GeneTests Resources for *CFTR*-Related Disorders](#) 

References

[CFTR-Related Disorders GeneReview, References](#)

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