

# CYSTIC FIBROSIS

Cystic Fibrosis (CF) is caused by a recessively inherited defect of the cystic fibrosis transmembrane regulator (CFTR) protein. Over 1,000 mutations of the CFTR protein have been identified, but a single mutation ( $\Delta F508$ ), accounts for 2/3 of all the mutations worldwide. The incidence of CF in the U.S. is approximately 1:3,700 live births, being most frequent in non-Hispanic whites (1:2,500) but occurring in all racial and ethnic groups. Newborn screening for CF is currently done for all Oregon infants.

## Clinical Features

Mutations in the *CFTR* gene alter the structure, function or production of the transmembrane chloride channel protein that is critical to the normal functioning of multiple organs. These include the respiratory tract, pancreas, liver, sweat glands and genitourinary tract.

The first sign for 15-20% of infants with CF is meconium ileus, an intestinal obstruction that requires surgical correction and may indicate CF. Other symptoms of CF develop over time.

For infants without meconium ileus, the first symptoms include recurrent cough, wheezing, abdominal pain, loose stools and failure to thrive. Pancreatic insufficiency is present in 95% of CF cases, leading to severe nutritional deficiencies and malnutrition. Severely malnourished CF patients may suffer cognitive impairment as well. Respiratory symptoms may be absent in the neonatal period but develop in most individuals within the first year of life. Unfortunately, most of these symptoms are not specific to CF and may be confused with food allergies, celiac disease, asthma, bronchitis, or other disorders. Unless CF is diagnosed prenatally or the infant has meconium ileus, CF diagnosis is often delayed for months or years. In the absence of newborn screening, the average age at diagnosis is 14.5 months.

Most patients suffer progressive lung damage, although survival has improved dramatically and most patients now live into their 30's. Like most genetic disorders there are milder variants with proportionally fewer symptoms and a longer course.

## Causes of CF

CF is a recessively inherited defect in the CFTR protein. CFTR deficiency results in abnormal chloride transport and the formation of thick, sticky mucus, that in turn, leads to organ dysfunction and failure.

## Laboratory Tests

The newborn screening test measures trypsin, an enzyme produced in the pancreas that is transiently elevated in the blood of pancreatic insufficient CF

infants at birth. This is detected by immunoreactive trypsinogen (IRT) testing of neonatal dried blood spots. In Oregon, all infants are tested twice, once in the first few days of life and again around two weeks of age.

An elevated IRT on two screening specimens is an indication for diagnostic workup.

There are several issues to keep in mind regarding elevated IRT tests:

- Elevated IRT is **not diagnostic** of CF. False positives occur and are found in two out of three infants with high IRTs.
- Babies with meconium ileus may not have an elevated IRT, so this finding should lead to definitive testing for CF regardless of the IRT result.
- About 5% of babies with CF, who are pancreatic sufficient, will not have an elevated IRT. Thus a normal IRT at birth does not completely rule out CF. Children with recurrent respiratory problems, failure to thrive etc, may still need a CF work-up.

RESULTS	LIKELY CAUSES	ACTIONS
IRT >100 ng/mL (First NBS)	<ul style="list-style-type: none"> <li>▪ Cystic fibrosis</li> <li>▪ False positive</li> </ul>	Lab notifies practitioner by letter with request to repeat filter paper sample.
IRT >80 ng/mL (Second NBS)	<ul style="list-style-type: none"> <li>▪ Cystic fibrosis</li> <li>▪ False positive</li> </ul>	Lab emails results to consultants, who phones practitioner with recommendations. Lab notifies practitioner by FAX/mail.

### Confirmation

CF can be diagnosed by two different methods. The gold standard remains the sweat chloride test by a nationally standardized method and is recommended for infants with persistently elevated IRT. A chloride value in the sweat of >60 meq/L is diagnostic for CF, while a value of <30 meq/L effectively rules out CF. Infants whose chloride values fall in an intermediate range (30-60 meq/L) require follow-up.

DNA mutation analysis of the *CFTR* gene is another diagnostic method. However, the genetics of CF is complicated by the fact that there are over 1,000 different mutations of the *CFTR* gene. In the U.S., at least 70% of CF cases are caused by one specific mutation ( $\Delta F508$ ), another 25% of cases result from one of about 40 other mutations, and the remaining 5% result from any of the 1,000+ other mutations. Also, some persons with CF have two different mutations.

### Treatment

Treatment aims to ensure adequate nutrition and growth by supplementing pancreatic enzymes and vitamins and providing a high calorie diet. Daily chest physiotherapy and medications are required by most patients to loosen secretions. People with CF need rapid treatment of any chest infection

with antibiotics. Routine immunizations plus immunization against influenza and *Streptococcus pneumoniae* are recommended to help prevent chest infections.

### **Screening Practice Considerations**

- CF infants with meconium ileus or who are pancreatic sufficient may have **normal** IRT levels (false-negatives).
- Two-thirds of infants with elevated IRT on both newborn screening samples do NOT have CF; their IRT results are false-positive. For example, IRT may be falsely elevated in premature or sick infants.
- IRT levels in infants with CF will usually decline and be in the normal range by 3 months. Older infants suspected to have CF should have a sweat chloride or genetic test.