## Background

Cystic fibrosis (CF) is in the Caucasian population the most common metabolic disorder with autosomal recessive inheritance. The incidence is reported to be 1:2500 for individuals with this ethnic background. CF occurs also in non-Caucasian populations but is less common here. Multiple reports document the fact that the classical form of the disease occurs also in the Middle East population, indicating that CF mutations are also present in this ethnic group. An incidence of around 1:4000 is estimated based on recent molecular genetic studies.

Cystic fibrosis is characterized mainly by a severe respiratory tract disease and pancreatic dysfunction. The disease is highly variable in presentation and course. Some individuals have severe pulmonary and gastrointestinal affection, whereas others have relatively mild symptoms that develop during adolescence and young adulthood. CF is caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. The gene encodes a chloride channel protein. Dysfunction of the protein leads to a defect of chloride transport across the membranes. This in turn causes dehydration of the products of exocrine glands. The consequences are tenacious mucus in the lung, mucus plugs in the pancreas, and characteristically high sweat chloride levels.

Since the cloning of the *CFTR* gene in 1989 more than 1000 mutations have been identified so far (*). By applying the conventional Cystic Fibrosis Assay®, version 3 which is based on the oligo-ligation-assay technique (OLA) 32 common mutation sites within the *CFTR* gene can be analyzed.

The most common mutation which affects about 70% of Caucasians is a three base-pair deletion which results in the deletion of the amino acid phenylalanine at position 508 of the CTFR protein. This mutation is designated as DF508 or delta-F508. The 32 mutations tested with the conventional OLA represent approximately 90% of the mutations found in Caucasian CF mutation carriers. But by using this conventional analysis for other ethnic groups the rate of detected mutations can decrease significantly. For example it is estimated that the mutation detection rate with this method is around 33% for the Turkish population. For the Arabian population only 10 of the recurrent mutations are detectable with the conventional oligo-ligation-assay technique (Table 1).

Molecular genetic studies of the *CFTR* gene in the Arabian population revealed that even if the mutation DF508 occurs here, it might not be the most frequent allele in this ethnic group. In addition, some Arabian mutation carriers show alterations of the *CFTR* gene that have never been identified in Caucasian CF patients. Due to the small number of observations representative frequencies of CF mutations in the Arabian population can currently not be estimated.

Therefore testing for CF for Arabian individuals requires processing of a special mutation panel. **Bioscientia Center for Human Genetics has developed such a panel and can offer this specialized CF-testing on request now (Table 2).**

*The CF-mutation database is available at: http://www.genet.sickkids.on.ca/cftr-cgi-bin/FullTable

**Table 1: Mutations analyzed by the conventional Cystic Fibrosis Assay® version 3 (OLA-Test)**

| Location | Mutation | Location | Mutation |
|---|---|---|---|
| Exon 3 | **G85E**<br>394delTT | Exon 11 | **G542X** ,G551D<br>**R553X,** R560T<br>**S549R,** S549N |
| Exon 4 | R117H<br>I148T | Intron 12 | 1898+1G>A |
| Intron 4 | 621+1G>T | Exon 13 | 2184delA |
| Intron 5 | **711+1G>T** | Intron 14b | **2789+5G>A** |
| Exon 7 | 1078delT<br>R347P, R347H<br>R334W | Intron 16 | **3120+1G>A** |
| Exon 9 | A455E | Exon 19 | R1162X<br>3659delC |
| Exon 10 | **DF508**<br>DI507, V520F | Intron 19 | 3849+10kbC>T |
| Intron 10 | 1717-1G>A | Exon 20 | **W1282X**<br>3876delA, 3905insT |
| | | Exon 21 | **N1303K** |
| Mutations described for the Arabian population marked in bold letters. | | | |

**Table 2: Mutation panel expansion for Arabian population**

| Location | Mutation | Location | Mutation |
|---|---|---|---|
| Exon2/3 | CFTRdele2,3 | Intron 11 | 1811+2T>C<br>1812-1G>A |
| Exon 3 | R75X | Exon 13 | T665S, E672del<br>V754M, 2043delG<br>2183AA>G |
| Intron 3 | 406-2A>G | Exon 14b | 2766del8 |
| Exon 4 | Q98H, 425del42<br>E115X, Y122X<br>H139L, A141D | Exon 17b | R1066C |
| Exon 7 | 1161delC | Exon 19 | I1234V, K1177X |
| Intron 7 | 1248+1G>A | Exon 21 | 4010del4 |
| Exon 10 | 1548delG | Intron 21 | 4096-28G>A |
| Exon 11 | F533L | | |

## References


Bobadilla JL, Macek Jr M, Fine JP and Farrell PM. Cystic Fibrosis: A worldwide analysis of CFTR mutations – correlation with incidence data and application to screening. Human Mutation (2002) 19:575-606

Wahab AA, Janahi IA, Hebi S, al-Hamed M and Kambouris M. Cystic fibrosis in a child from Syria. Ann Trop Paediatr (2002) 22(1):53-5

Eskandarani HA. Cystic fibrosis transmembrane regulator gene mutations in Bahrain. J Trop Pediatr (2002);48(6):348-50

Kamboursi M, Banjar H, Moggari I, Nazer H, Al-Hamed M and Meyer BF. Identification of novel mutations in Arabs with cystic fibrosis and their impact on the cystic fibrosis transmembrane regulator mutation detection rate in Arab populations. Eur J Pediatr (2000) 159:303-309

Rawashdeh M and ManalH. Cystic fibrosis in Arabs: a prototype from Jordan. Ann Trop Peadiatr (2000) 20(4):283-6

Frossard PM, Lestringant G, Girodon E, Goossens M and Dawson KP. Determination of the prevalence of cystic fibrosis in the United Arab Emirates by genetic carrier screening. Clin genet (1999) 55,6:496

Laufer-Cahana A, Lerer I, Sagi M, Rachmilewitz-Minei T, Zamir C, Rivli and JR, Abeliovich D. Cystic fibrosis mutations in Israeli Arab patients. Human Mutation (1999) Mutation in Brief#277 online

Deseorges M, Mégarbané A, Guittard C, Carles S, Loiselet J, Demaille J and Claustres M. Cystic fibrosis in Lebanon: distribution of CFTR mutations among Arab communities. Hum Genet (1997) 100:279-283

el-Harith EA, Dork T, Stuhrmann M, Abu-Srair H, al-Shahiri A, Keller KM, Lentze MJ, Schmidtke J. Novel and characteristic CFTR mutations in Saudi Arab children with severe cystic fibrosis. J Med Genet (1997) 34(12):996-9

Al-Mobaireek K et al. Cystic fibrosis in Saudi Arabia: common and rare presentations. Annals of tropical pediatrics, 1995, 15:269-72

Nazer H et al. Cystic fibrosis in Saudi Arabia. European journal of pediatrics, 1989, 148:330-2


**p.t.o**

## Specimen Requirement

Sample material
2-3 ml EDTA blood sample in a monovette or vacutainer
Analysis time
approx. 4 to 8 weeks

Please request as “CF-middle east” in order to make sure that the appropriate analysis is performed. Furthermore, information about the ethnic background of the patient, clinical data and family history are essential prerequisites for an adequate interpretation of results.

## Contact/Address

bioscientia

Center for Human Genetics Ingelheim

Bioscientia
Int. Support Services Dept.
Konrad-Adenauer-Str. 17
55218 Ingelheim
Germany
Phone: ++49-6132-781-203, 224 or 165
Fax: ++49-6132-781-236
E-mail: int.support@bioscientia.com
Website: www.bioscientia.com

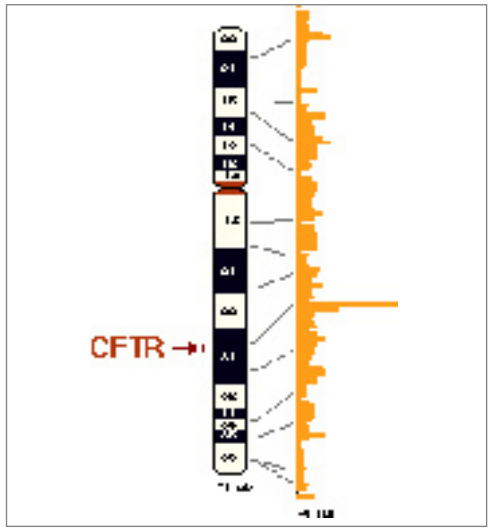
October 2006

bioscientia

Center for Human Genetics Ingelheim

# Molecular Diagnosis for Cystic Fibrosis

Special Mutation Panel For The Middle East




http://www.ncbi.nlm.nih.gov/SCIENCE96/Chr7.CFTR.gif