Cystic Fibrosis Transmembrane Conductance Regulator

**Alternative Names**
- CFTR
- ATP-BINDING Cassette, Subfamily C, Member 7
- ABCC7
- ABC35
- cAMP-Dependent Chloride Channel
- MRP7

**Record Category**
- Gene locus

**WHO-ICD**
- N.B.: Classification not applicable to gene loci.

**Incidence per 100,000 Live Births**
- N/A to gene loci

**OMIM Number**
- 602421

**Mode of Inheritance**
- Autosomal recessive

**Gene Map Locus**
- 7q31.2

**Description**
The cystic fibrosis transmembrane regulator (CFTR) gene codes for the CFTR protein; a chloride channel protein that helps in the transportation of chloride ions and water molecules across the cell membranes of lungs, liver, pancreas, and skin. CFTR is a member of the ATP-binding cassette family of membrane transport proteins, but appears to be unique within this family by functioning as an ion channel rather than an active transporter protein. CFTR binds to ATP in order to open the channel for chloride ion transport across the membrane. This transport of chloride ions helps in controlling the movement of water in tissues and thereby, maintains the fluidity of mucus and other secretions. The CFTR protein contains twelve transmembrane alpha-helices that are presumed to form the pore region by which chloride ions cross the membrane. Functional evidence implicates transmembranes 1 and 6 as playing key roles in forming the pore and interacting with chloride ions to determine the functional permeation properties.

Mutations in the gene that disrupt the proper folding of the protein lead to loss of chloride ion transport. This, consequently results in a disruption of the chloride and water balance required to maintain the thin mucus in the airway and digestive tract. In addition, non-functional CFTR gene also lead to defects in the sodium ion channel, ENaC, leading to further loss of water in the upper airway. The mucus, therefore, gets thickened and sticky, leading to the characteristic signs and symptoms of Cystic Fibrosis (CF). CFTR gene mutations have also been implicated in the disorder Congenital Bilateral Absence of the Vas Deferens (CBAVD), characterized by an absence of vas deferens since birth. Interestingly, studies have indicated that mutations in the CFTR gene could also protect carriers against Salmonella typhi, the bacteria causing typhoid fever.

**Molecular Genetics**
The CFTR gene, located on chromosome 7q31.2, is approximately 250 Kb in length, and codes for an mRNA with 27 exons. The CFTR protein consists of 1480 amino acids, and weighs 168 kDa. Expression of the genes is normally seen in the endothelial cells of the umbilical vein, lung microvasculature, RBCs, pancreas, lung epithelia, sweat glands, colon, parotid glands, and the liver.

Over 1000 mutations have been identified in the CFTR gene. However, CF causing mutations are mainly clustered in the nucleotide binding domains of the protein. In fact, more than 70% of patients with cystic fibrosis show a single mutation that involves the deletion of three nucleotides of exon 10, within
the first nucleotide binding domain, resulting in the deletion of phenylalanine at position 508 in the protein product. This mutation is commonly referred to as delta F508. The mutated protein is unable to fold in a proper fashion, and is destroyed by the cellular degradation pathway. Most of the other mutations causing cystic fibrosis are rare and are called “private mutations”. The delta F508 is also the most common mutation seen among patients with CBAVD. However, some other mutations have been identified to be specific for CBAVD, with the exclusion of CF. These include the splice site variant IVS8-5T.

Epidemiology in the Arab World

Bahrain

Eskandarani (2002) undertook a study to identify the CFTR gene mutations existing in the Bahraini population. The study group included 19 Bahraini children (12 males, 7 females; mean age: 5.4 years) belonging to 13 unrelated families. The rate of consanguinity among these families was 77%. Genetic screening for 15 CFTR mutations common in the Arab population was performed on all patients using RFLP and/or ARMS-PCR. Eight mutations were detected in these patients, most common of which were: 2043delG (30.8%), 548A-T (19.3%), 4041C-G (7.7%), and delta F508 (7.7%). Both 2043delG and 548A-T mutations are rare in other populations, indicating that these mutations could have originated from the region. Homozygosity for the mutations was observed in six of the families, whereas six families were heterozygous for two mutations. One of the families was of Persian origin, and all three children from this family showed homozygous mutations for delta F508.

Jordan

Kakisk (2001) investigated the CFTR gene mutations in 72 Jordanian children (37 males and 35 females) with cystic fibrosis (CF). Mutations were determined by using a multiplex heteroduplex shift analysis followed by direct sequencing on blood taken from all patients and 42 parents. Twenty different mutations were detected in the CFTR gene and five of those mutations were found for the first time (296+9A-T, T338M, T760M, 3679delA, and G1244D). Since a large number of mutations were identified among Jordanians, Kakish (2001) suggested that it might be the result of ethnic diversity of the Jordanian population reflecting the country’s complex history. Surprisingly, low incidence of the Delta F508 mutation was found among the patients (6.3%) that could be explained on the basis of the founding population and the high mortality among patients carrying this severe mutation resulting in under-representation in the studied cases.

Lebanon

In order to identify the distribution of CFTR mutations in the Lebanese population Desgeorges et al. (1997) studied 20 unrelated Lebanese Arab families, with at least one CF-affected child. DNA was collected from a total of 89 individuals from these families, including patients, their parents, and healthy siblings. Analysis of the DNA using denaturing gradient gel electrophoresis and direct sequencing following PCR, allowed identification of 10 mutations that accounted for 87.5% of the CFTR alleles. The most common of these mutations were: delta F508 (37.5%), W1282X (15.6%), and N1303K (9.4%). Two novel putative mutations were also identified; E672del, a single amino acid deletion in the regulatory domain caused by deletion of nucleotides 2145 to 2148 (GAA), and 4096-28G-A, occurring at the putative branch point involved in the splicing of intron 21. The E672del mutation was identified in a 4-year old boy, who presented with pancreatic insufficiency without pulmonary disease, whereas the girl with the 4096-28G-A mutation presented with major malnutrition and severe pulmonary distress, and deceased at 4-months of age. In both these patients, the second defective allele could not be characterized. About 48.3% of the mutant genes were identified on haplotype backgrounds that were found to be absent on wild-type genes. Interestingly, about 66% of the delta F508 chromosomes from the Maronite community were associated with the 7T allele at locus IVS8(T)n; an association representing Central and Northern Europe. In all other communities the mutation was linked to the 9T allele, which is more Mediterranean in its occurrence. Desgeorges et al. (1997) hypothesized that this was the original haplotype on which the delta F508 mutation occurred, and a recombination later with the Central European haplotype was responsible for the 7T-delta F508 association.

Oman

Romey et al. (1999) undertook a study aiming at comparing ethnic, clinical, and genetic data from patients with the S549R mutation in the CFTR gene. Of the cystic fibrosis patients selected for the study, a total of 16 (10 males and 6 females) were from UAE and Oman. DNA analysis identified all the 16 patients to be homozygous for the S549R mutation. Although none of the children had presented with
meconium ileus at birth, all of them presented with insufficiency of the pancreas, severe lung disease, high rate of pulmonary infection, and rapid pulmonary decline. Three of the patients died of pulmonary failure. This phenotypic severity was found to be in contrast to that seen by the authors in patients of other ethnicities (French and Spanish) who carried the combined complex allele [-102T>A+S549R(T>G)]. The authors surmised that the [-102T>A] modification may alter the severity of the S549R mutation.

Frossard et al. (2000) performed mutation analysis on 15 Omani families (12 true Omani Bedouin families, and three Omani nationals of Baluchi origin) with a total of 16 CF-affected children. The CFTR genes of these patients were screened for S549R (T-G) and delta F508 mutations. Eleven patients (69%), all of Bedouin descent, were found to be homozygous for the S549R (T-G) mutation. On the other hand, two patients (12.5%) of Baluch descent were found to be homozygous for delta F508. Thus, these two mutations accounted for 81% of the CF patients and 87% of the families with CF. CFTR mutations in the remaining three patients could not be detected.

Palestine

By direct sequencing of exon 21, Shoshani et al. (1994) revealed a 4-bp deletion, TATT, at position 4010 of the coding sequence. This frameshift mutation is expected to create a termination codon (TAG) 34 amino acids downstream of the mutation. This alteration is likely to be a disease-causing mutation since it is predicted to create a truncated polypeptide that lacks the second ATP binding domain. The patient is of Arab origin and inherited this deletion from her father. The CFTR chromosome carries the D121 haplotype. Her other CFTR chromosome has the asn1303-to-lys mutation.

Saudi Arabia

El-Harith et al. (1997) undertook mutation analysis of 15 Saudi Arabian children affected with CF from 12 families. They identified six mutations in the CFTR gene, detectable by PCR with subsequent restriction enzyme digestion, that would allow the detection of 70% of Saudi CFTR mutations. The most frequent of these were: 3120 +1G-A, N1303K, and 1548delG. Two mutations, 1548delG and 406-2A-G, were identified for the first time. Most of the patients were found to present with severe forms of the disease.

In a study performed by Eskandarani (2002) to identify the CFTR gene mutations in Bahraini CF patients, one of the families studied was of Syrian origin. Mutation analysis of two affected siblings from this family identified homozygous mutation for 2043delG [See also Bahrain >Eskandarani, 2002].

Tunisia

Messoued et al. (2005) performed mutation analysis on 390 Tunisian CF patients belonging to 383 families to identify the CFTR mutations present in the Tunisian population. A total of 17 mutations were identified in this population, the most frequent of which were: delta F508 (50.74%), followed by G542X, W1282X, and N1303K. Four novel mutations were also identified; these included: T665S, 2766 del8, F1166C, and L1043R.

United Arab Emirates

The first study to identify the genetic mutations responsible for cystic fibrosis among the UAE national population was undertaken by Frossard et al. (1994). Eight families with one child suffering from CF and a group of 30 random unrelated UAE nationals were used for the study. Mutation analysis was performed on the patients, following PCR amplification of 17 CFTR exons, by denaturing gradient gel electrophoresis (DGGE) and direct genomic sequencing. Surprisingly, the delta F508 mutation was not detected in any of the patients. Instead multiplex amplification of exons 11, 14b, and 17b enabled the identification of a CF causing mutation in exon 11, designated as S549R, in 75% of the mutated chromosomes. This mutation is expected to disrupt the function of the first nucleotide binding region and, therefore, expresses in a severe form of CF. Confirmation of this high frequency for this mutation in CF patients in larger scale studies was expected to be helpful for screening for CF mutations in the UAE population. Two other polymorphisms, though not causing CF, detected in the population included M470V and a silent E528E. The M470V polymorphism was present in 50% of the patients and 40% of the studied UAE national population. The E528E polymorphism was noted in 10% of the national population. The identification of these polymorphisms was expected to be of importance in following the co-segregation of the CF alleles within family members affected with the disease and enabling easy prenatal detection. Few years later, Frossard et al. (1998) and Dawson and Frossard (1999) studied 17 unrelated UAE national families, with a total of 20 children affected with cystic fibrosis. Patients from all ten families of Bedouin
descent were found to be homozygous for the S549R (T-G) mutation on exon 11, whereas their parents were found to be heterozygous. On the other hand, all patients from families of Baluch origin were homozygous for the delta F508 mutation, suggesting that this mutation was introduced to the UAE as well as Europe from Baluchistan some 40,000-50,000 years ago (Dawson and Frossard, 2000a and 2000b). Both these mutations identified have been shown to affect the processing of the CFTR protein, leading to its degradation, and therefore, resulting in very severe forms of the disease. It was also noted that all patients were homozygous for the respective mutation; a fact attributable to the consanguinity prevalent in the population. A study of the variables associated with the presentation of the disease (Frossard et al., 1999a) revealed that in individuals homozygous for the R549, the symptoms were very severe, with early age of presentation, very high sweat chloride levels, universal pancreatic insufficiency, and early colonization with P. aeruginosa. Furthermore, Frossard et al. (1999b) studied the clinical severity of the disease in UAE national CF affected patients, homozygous for the S549R mutation. Results indicated that the mutation was sever in its form, with low age of diagnosis (1.0 year). Detailed radiological analyses in 12 children with CF who were homozygous for S549R (T-->G) revealed a diversity of pulmonary changes that included marked hyperinflation in early infancy in conjunction with inflammation of the interstitium. After 2 years of age, signs of central airway involvement occurred in association with early signs of pulmonary hypertension.

In order to determine the prevalence of these mutated alleles in the national population, Dawson and Frossard (1999) and Frossard et al. (1999c) screened a sample of 400 unrelated UAE nationals (200 males, 200 females) for these mutations. Six carriers were detected by this screening, and the carrier rate was calculated at 1:100 for S549R, and 1:200 for delta F508. The number of UAE nationals affected with cystic fibrosis in the national population was estimated at 1:15,876.

In 2001, Dawson and Frossard (2001a) compared the clinical severity associated with the two cystic fibrosis (CF) mutations S549R(T-->G) and deltaF508. Clinical and biochemical variables of CF were compared in two age- and sex-matched groups of CF children in the United Arab Emirates. The clinical severity of mutations S549R(T-->G) and deltaF508 showed comparable patterns, with very low Shwachman scores and high sweat chloride levels. Dawson and Frossard (2001a) concluded that patients homozygous for the CF mutations deltaF508 and S549R(T-->G) have a severe clinical presentation and illness and are indistinguishable on clinical grounds. Dawson and Frossard (2001b) further suggested that the founding chromosomes for the S549R(T-->G) may have originated in Bedouins of eastern Arabia. More recently, Saleheen and Frossard (2006) reported an Emirati CF patient homozygous for the 3120+1 G-A mutation.

[See also: Oman > Romey et al., 1999].

References
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Dawson KP, Frossard PM. A hypothesis regarding the origin and spread of the cystic fibrosis mutation deltaF508. QJM. 2000a; 93(5):313-5. PMID: 10825408
Frossard PM, Dawson KP, Das SJ, Alexander PC, Girodon E, Goossens M. Identification of cystic

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Cystic Fibrosis

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http://www.genecards.org/cgi-bin/carddisp.pl?gene=CFTR&search=CFTR&suff=txt
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