Ad/Soyad :
Cinsiyet :
Doğum Tarihi :

Örnek Toplama Tarihi :
Örnek Teslim Tarihi :
Örnek Türü :

ELM GENOMICS YENİ DOĞAN TARAMA TESTİ

Elm Genomics Yeni Doğan Tarama Testi tüm ekzom dizileme (WES) analizi sonucunda elde edilmiş varyant bilgisini kullanarak belirli hastalıklara sebebiyet verebilecek mutasyonları belirlemek amacıyla uygulanan bir testtir. Bu test ile öncelikle testin uygulandığı çocukta koruyucu tedavi ile oluşması ve ilerlemesi önlenebilecek hastalıklara sebebiyet verebilecek ve etkisi bilimsel çalışmalarda güçlü kanıtlar ile gösterilmiş mutasyonların tespit edilmesi amaçlanmıştır. Bu rapor içerisinde, analiz edilen örnekte bulunan etkisi yüksek olan mutasyonları ve bu mutasyonları tespit ederken uygulanan biyoinformatik analizlerin kalite parametreleri ile ilgili bilgileri bulabilirsiniz.

ANALİZ AYRINTILARI

Okumalar

Toplam Okuma Sayısı :
RDO* Okuma Sayısı :
RDO* Okuma Oranı :
RDO* Kaliteli Okuma Sayısı :
RDO* Kaliteli Okuma Oranı :
Ortalama Okuma Uzunluğu :

*RDO: Referans Diziye Oturan

Hedef Bölge

Referans Genom :
Hedef Bölge Uzunluğu :
Hedef Bölgenin Ortalama Derinliği :
Derinliği En Az 20 olan Baz Oranı :
Derinliği En Az 50 olan Baz Oranı :
Derinliği En Az 100 olan Baz Oranı :

AÇIKLAMALAR

Bu raporda sunulan genetik bilgi tüm ekzom dizileme (WES) yöntemi ile elde edilmiştir. Bu rapor çerçevesinde incelenen tüm hastalıklar ve genler EK AÇIKLAMALAR başlığı altında bulunabilir. Her hastalık için incelenen DNA bölgeleri ClinVar veritabanında o hastalık için patojenik olarak rapor edilmiş olması veya bilimsel literatürde güçlü kanıtlara dayalı bir yayının olması esas alınmıştır. Bu raporda sunulan, örneğe ait olduğu tespit edilen tüm varyantlar belirli katı filtrelerden geçirilmektedir. Aşağıdaki ölçütleri sağlayan varyantlar bu raporda verilmek üzere aday olarak belirlenmektedir:

- DP ≥ 15 (Kapsam değeri en küçük 15 olan)
- DP ≤ 10000 (Kapsam değeri en büyük 10000 olan)
- PAF ≤ %1(Patojenik alel frekansı %1 ve %1'den küçük olan)
- Etki büyüklüğü "yüksek" olan
- Ekzon bölgesinde, proteinin amino asit dizilimini ve aktivitesini değiştiren

İntronik ve proteine dönüşmeyen bölgelerde bulunan ve protein yapısını ve aktivitesini değiştirmeyen diğer varyantlar bu raporda gösterilmemiştir. Bu test kapsamında kullanıcının tüm genomu incelenmediği için, kullanıcı bakılan bölgeler dışında mutasyonlar da içerebilir. Bu sebeple kullanıcının herhangi bir hastalık konusunda riskinin belirtilmemiş olması o hastalık konusunda taşıyıcı olmadığı veya hastalık riskini içermediği anlamına gelmez. Bu rapordaki bilgiler sadece Ad/Soyad kısmında ismi yazılı örnek için geçerlidir. Dizileme sonrası elde edilen ham veri dosyaları yaygın ve halka açık olarak kullanılan programlar ile Broad Enstitüsü tarafından "En İyi Uygulamalar" olarak adlandırılan biyoinformatik yöntemler ile analiz edilmiştir. Veri analizi ile ilgili ayrıntılar "ANALİZ AYRINTILARI" bölümünde bulunabilir. DNA verisinin elde edilmesi için yapılmış olan laboratuvar çalışmaları Elm Genomics tarafından yapılmamıştır. Bu sebeple laboratuvar çalışmalarındaki hatalar nedeniyle veri analizinde oluşabilecek problemlerden Elm Genomics sorumlu değildir.Burada oluşturulan sonuçlar araştırma amacı ile bilimsel çalışmalara yardımcı olması maksadı ile hazırlanmıştır, teşhis koymak için kullanılamaz. Elm Genomics yazılımsal olarak ham verinin dosya formatını değiştirerek yetkili kurumun yazılımsal çözümünü sağlamıştır ve hiçbir şekilde tanı veya teşhis oluşturabilecek bir sonuç vermemektedir. Bu çalışmada hazırlanmış olan sonuçlar sadece T.C. Sağlık Bakanlığı tarafından ruhsatlandırılmış yetkili bir kurum ve/veya doktor nezaretinde kullanılabilir.

ÖZET SONUÇLAR

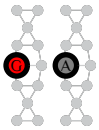
Patojenik Alel | Doğal Alel

Yüksek Etkili Varyantlar

Rapor edilebilecek yüksek etkili bir varyant tespit edilmemiştir.

Taşıyıcı Varyantlar

Genotip



Gen
CFTR

Kromozom:Pozisyon
chr7:117509071

Transkript
ENST00000003084.11

Kalıtım
AR

Varyasyon
c.202A>G (p.Lys68Glu)

Etki
MODERATE

Hastalık
Cystic Fibrosis

AYRINTILI SONUÇLAR

Gen
CFTR
Transkript
ENST00000003084.11
Varyasyon
c.202A>G
Protein Değişimi
p.Lys68Glu
Kromozom
chr7
Pozisyon
117509071
Derinlik
205
Kalıtım
AR
Etki
MODERATE
Hastalık
Cystic Fibrosis

Zigosite
Heterozygous
rsID
rs397508332
ExAC Frekansı
0.0002
esp6500 Frekansı
.
genomAD Frekansı
0.0002
1000g Frekansı
0.000399361
GME Türk Frekansı
0.000000
Genotipleme Tutarlılığı
%100.0
Varyant Çağırma Tutarlılığı
%100.0

CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR; CFTR

The CFTR gene encodes an ATP-binding cassette (ABC) transporter that functions as a low conductance Cl(-)-selective channel gated by cycles of ATP binding and hydrolysis at its nucleotide-binding domains (NBDs) and regulated tightly by an intrinsically disordered protein segment distinguished by multiple consensus phosphorylation sites termed the regulatory domain (summary by Wang et al., 2014).

Gene Function

In addition to functioning as a chloride channel, CFTR controls the regulation of other transport pathways. For example, patients with CF and the homozygous CFTR-deficient mouse have enhanced sodium ion absorption; this enhanced sodium ion absorption is corrected by addition of a wildtype copy of CFTR. CFTR and outwardly rectifying chloride channels (ORCCs) are distinct channels but are linked functionally via an unknown regulatory mechanism. Schwiebert et al. (1995) presented results from whole-cell and single-channel patch-clamp recordings, short-circuit current recordings, and ATP-release assays of normal, CF, and wildtype or mutant CFTR-transfected CF airway cultured epithelial cells indicating that CFTR regulates ORCCs by triggering the transport of the potent agonist, ATP, out of the cell. The results suggested that CFTR functions to regulate other chloride ion secretory pathways in addition to conducting chloride ion itself. A quality control system that rapidly degrades abnormal membrane and secretory protein is stringently applied to the CFTR protein; approximately 75% of the wildtype precursor and 100% of the delF508 variant (602421.0001) are rapidly degraded before exiting from the endoplasmic reticulum (ER). Jensen et al. (1995) demonstrated that CFTR and presumably other intrinsic membrane proteins are substrates for proteasomal degradation during their maturation within the endoplasmic reticulum. Chang et al. (1999) showed that export-incompetent CFTR proteins display multiple arginine-framed tripeptide sequences. Inactivation of 4 of these motifs by replacement of arginine residues at positions R29, R516, R555, and R766 with lysine residues simultaneously caused mutant delF508 CFTR protein to escape ER quality control and function at the cell surface. Chang et al. (1999) suggested that interference with recognition of these signals may be helpful in the management of CF. Younger et al. (2006) identified an ER membrane-associated ubiquitin ligase complex containing the E3 RMA1 (RNF5; 602677), the E2 UBC6E (UBE2J1), and derlin-1 (DERL1; 608813) that cooperated with the cytosolic HSC70 (HSPA8; 600816)/CHIP (STUB1; 607207) E3 complex to triage CFTR and delFl508. Derlin-1 retained CFTR in the ER membrane and interacted with RMA1 and UBC6E to promote proteasomal degradation of CFTR. RMA1 could recognize folding defects in delF508 coincident with translation, whereas CHIP appeared to act posttranslationally. A folding defect in delF508 detected by RMA1 involved the inability of the second membrane-spanning domain of CFTR to productively interact with N-terminal domains. Younger et al. (2006) concluded that the RMA1 and CHIP E3 ubiquitin ligases act sequentially in ER membrane and cytosol to monitor the folding status of CFTR and delF508. Randak et al. (1997) expressed NBF2 of CFTR as a soluble protein fused to maltose-binding protein in E. coli and found that it catalyzed hydrolysis of ATP to form ADP and Pi. The ADP product inhibited ATPase activity. NBF2 also hydrolyzed GTP to GDP and Pi. In the presence of AMP, however, the ATPase reaction was superseded by adenylate kinase activity, resulting in formation of 2 ADP molecules from ATP and AMP. Randak et al. (1997) identified a typical adenylate kinase-like AMP-binding site in NBF2. To determine the structural basis for the ATPase activity of CFTR, Ramjeesingh et al. (1999) studied the effect of mutations in the Walker A consensus motifs on ATP hydrolysis by the purified, intact protein. Mutation of the lysine residue in the Walker A motif of either NBF inhibited the ATPase activity of purified, intact CFTR protein by greater than 50%, suggesting that the 2 NBFs function cooperatively in catalysis. Surprisingly, the rate of channel gating was significantly inhibited only when the mutation was in the second NBF, suggesting that ATPase activity may not be tightly coupled to channel gating. Randak and Welsh (2003) demonstrated that full-length CFTR and the isolated nucleotide-binding domain-2 (NBD2) had ATPase and adenylate kinase activities following expression in HeLa cells. The adenylate kinase inhibitor Ap5A inhibited CFTR Cl- currents, and it inhibited channel activity by binding an ATP site and an AMP site. Adding AMP switched enzymatic activity of the NBD2 polypeptide from ATPase to adenylate kinase. ATP and AMP appeared to induce dimerization between NBD1 and NBD2, causing the channel to open. Randak and Welsh (2003) hypothesized that at physiologic AMP concentrations, the predominant reaction regulating channel activity is likely adenylate kinase. Jiang and Engelhardt (1998) reviewed the cellular heterogeneity of CFTR expression and function in the lung and the important implications for gene therapy of cystic fibrosis. Cystic fibrosis is characterized by persistent Pseudomonas aeruginosa colonization of the conducting airways leading to the migration of inflammatory cells, including polymorphonuclear leukocytes (PMNs), into the airways of CF patients. PMNs release a potent chemokinetic and chemoattractant, leukotriene B, during an inflammatory response, resulting in the further migration of inflammatory cells. Cromwell et al. (1981) demonstrated the existence of leukotrienes in the sputum of CF patients. The oxidative metabolites of arachidonic acid and the inflammatory cell-derived proteases have been implicated in the destruction and shedding of the airway epithelia observed in CF. Based on these observations, it has been proposed that antiinflammatory drugs might be useful in CF therapy. The nonsteroidal antiinflammatory drug (NSAID) ibuprofen inhibits 5-lipoxygenase and hence leukotriene formation, suggesting that ibuprofen may be useful in the treatment of CF. Its possible benefit in CF, with no apparent adverse effects, was reported by Konstan et al. (1995). However, other effects of ibuprofen may counteract therapeutic strategies designed to increase CFTR expression and/or function in secretory epithelia. Devor and Schultz (1998) evaluated the acute effects of ibuprofen and salicylic acid on cAMP-mediated Cl- secretion in both colonic and airway epithelia and found that at a pharmacologically relevant concentration the drugs inhibited chloride ion secretion across these epithelia and that this inhibition was due at least in part to the blocking of the CFTR Cl- channels. Wei et al. (1998) studied CFTR channel activity of mature R-domain mutants with point mutations at sites other than the predicted phosphorylation sites. Whole-cell chloride conduction was increased in Xenopus oocytes injected with H620Q-CFTR mRNA, but decreased in the E822K and E826K mutants compared to wildtype CFTR. Anion permeability and single-channel conductances did not differ from wildtype for any of the mutants. Cell-attached single channel studies in COS cells revealed that both open channel probability and/or the number of functional channels were either higher (H260Q) or lower (E822K and E826K) than in wildtype CFTR. These results suggested that sites other than the phosphorylation sites in the R-domain influence gating. Chanson et al. (1999) compared gap junctional coupling in a human pancreatic cell line harboring the delF508 mutation in CFTR and in the same cell line in which the defect was corrected by transfection with wildtype CFTR. Exposure to agents that elevate intracellular cAMP or specifically activate protein kinase A evoked chloride ion currents and markedly increased junctional conductance of CFTR-expressing cell pairs, but not in the parental cells. Thus, the expression of functional CFTR restored the cAMP-dependent regulation of junctional conductance as well as the chloride ion channel in CF cells. Consequently, defective regulation of gap junction channels may contribute to the altered functions of tissues affected in CF. Reddy et al. (1999) demonstrated that in freshly isolated normal sweat ducts, epithelial sodium channel (ENaC; see 600228) activity is dependent on, and increases with, CFTR activity. Reddy et

al.(1999) also found that the primary defect in chloride permeability in cystic fibrosis is accompanied secondarily by a sodium conductance in this tissue that cannot be activated. Thus, reduced salt absorption in cystic fibrosis is due not only to poor chloride conductance but also to poor sodium conductance. Weixel and Bradbury (2000) used in vivo cross-linking and in vitro pull-down assays to show that full-length CFTR binds to the endocytic adaptor complex AP2 (see 601024). Substitution of an alanine residue for tyrosine at position 1424 significantly reduced the ability of AP2 to bind the C terminus of CFTR. However, mutation to a phenylalanine residue, which is normally found in dogfish CFTR at this position, did not perturb AP2 binding. Taken together, these data suggest that the C terminus of CFTR contains a tyrosine-based internalization signal that interacts with the endocytic adaptor complex AP2 to facilitate efficient entry of CFTR into clathrin-coated vesicles. Wang et al. (2000) identified a hydrophilic CFTR-binding protein, CAP70, which is concentrated on the apical surfaces. CAP70 had previously been identified by Kocher et al. (1998) as PDZK1 (603831). The protein contains 4 PDZ domains, 3 of which are capable of binding to the CFTR C terminus. Linking at least 2 CFTR molecules via cytoplasmic C-terminal binding by either multivalent CAP70 or a bivalent monoclonal antibody potentiates the CFTR chloride channel activity. Thus, the CFTR channel can be switched to a more active conducting state via a modification of intermolecular CFTR-CFTR contact that is enhanced by an accessory protein. Moyer et al. (2000) reported that the C terminus of CFTR constitutes a PDZ-interacting domain that is required for CFTR polarization to the apical plasma membrane and interaction with the PDZ domain-containing protein EBP50 (604990). PDZ-interacting domains are typically composed of the C-terminal 3 to 5 amino acids, which in CFTR are gln-asp-thr-arg-leu. Point substitution of the leucine at position 0 with alanine abrogated apical polarization of CFTR, interaction between CFTR and EBP50, efficient expression of CFTR in the apical membrane, and chloride secretion. Point substitution of the threonine at position -2 with alanine or valine had no effect on the apical polarization of CFTR, but reduced interaction between CFTR and EBP50, efficient expression of CFTR in the apical membrane, and chloride secretion. By contrast, individual point substitution of any of the other amino acids in the PDZ domain had no effect on measured parameters. Moyer et al. (2000) concluded that mutations that delete the C terminus of CFTR may cause cystic fibrosis because CFTR is not polarized, complexed with EBP50, or efficiently expressed in the apical membrane of epithelial cells. CFTR regulates other transporters, including chloride-coupled bicarbonate transport. Alkaline fluids are secreted by normal tissues, whereas acidic fluids are secreted by mutant CFTR-expressing tissues, indicating the importance of this activity. Bicarbonate and pH affect mucin viscosity and bacterial binding. Choi et al. (2001) examined chloride-coupled bicarbonate transport by CFTR mutants that retain substantial or normal chloride channel activity. Choi et al. (2001) demonstrated that mutants reported to be associated with cystic fibrosis with pancreatic insufficiency do not support bicarbonate transport, and those associated with pancreatic sufficiency show reduced bicarbonate transport. Choi et al. (2001) concluded that their findings demonstrate the importance of bicarbonate transport in the function of secretory epithelia and in CF. Rowntree et al. (2001) showed that removal of a DNase I hypersensitive site (DHS) in intron 1 (185+10 kb) of CFTR abolished the activity of this DHS in transient transfection assays of reporter/enhancer gene constructs. Stable transfections of a human colon carcinoma cell line with CFTR-containing YACs showed that transcription from the DHS element-deleted YAC was reduced by 60% compared to the intact construct. In transgenic mice, deletion of the intron 1 DHS had no effect on expression in the lung, but reduced expression in the intestine by 60%. The authors concluded that the regulatory element associated with the intron 1 DHS is tissue-specific and is required for normal CFTR expression levels in the intestinal epithelium in vivo. Callen et al. (2000) developed a cAMP-mediated sweat rate test that allows the quantitative discrimination of CFTR function, thereby indicating CF genotype: CF, CF carrier, and non-CF. Callen et al. (2000) remarked that this test may be helpful in the diagnosis of ambiguous cases and in studies of new agents to increase the function of CFTR. In CFTR, an abbreviated polypyrimidine tract between the branch point A and the 3-prime splice site is associated with increased exon skipping and disease. However, many exons, both in CFTR and in other genes, have short polypyrimidine tracts in their 3-prime splice sites, yet they are not skipped. Hefferon et al. (2002) examined the molecular basis of the skipping of constitutive exons in mRNAs and the skipping of exon 9 in the CFTR gene. They reported observations in human, mouse, and sheep that placed renewed emphasis on deviations at 3-prime splice sites in nucleotides other than the invariant GT, particularly when such changes are found in conjunction with other altered splicing sequences, such as a shortened polypyrimidine tract. Hefferon et al. (2002) suggested that careful inspection of entire 5-prime splice sites may identify constitutive exons that are vulnerable to skipping. Using a quantitative mRNA assay at 14 time points through ovine gestation, Broackes-Carter et al. (2002) determined that CFTR expression was highest at the start of the second trimester followed by a gradual decline through to term. In contrast, epithelial sodium channel (SCNN1A; 600228) expression increased from the start of the third trimester. The authors proposed a role for CFTR in differentiation of the respiratory epithelium and suggested that its expression levels are not merely reflecting major changes in the sodium/chloride bulk flow close to term. Eidelman et al. (2002) found that NBF1 of CFTR interacted selectively with phosphatidylserine rather than phosphatidylcholine. In contrast, NBF1 with the delta-F508 mutation lost the ability to discriminate between these phospholipids. In mouse L cells expressing delta-F508 CFTR, replacement of phosphatidylcholine by noncharged analogs led to increased CFTR protein expression, suggesting that aberrant interaction between the delta-F508 NFB1 domain and phospholipid chaperones may contribute to the processing defect of the delta-F508 CFTR mutant. Plasma membrane expression of delta-F508 CFTR can be rescued in epithelial cells by culturing them at 27 degrees Celsius for 24 hours. By screening 100,000 diverse small molecules, Yang et al. (2003) found that tetrahydrobenzothiophenes could activate cold-induced membrane-associated delta-F508 CFTR, resulting in reversible Cl- conductance in transfected rat thyroid epithelial cells. Single-cell voltage clamp analysis showed characteristic CFTR currents. Activation required low concentrations of a cAMP agonist, mimicking the normal physiologic response. Reddy and Quinton (2003) reported phosphorylation- and ATP-independent activation of CFTR by cytoplasmic glutamate that exclusively elicits chloride but not bicarbonate conductance in the human sweat duct. They also showed that the anion selectivity of glutamate-activated CFTR is not intrinsically fixed, but can undergo a dynamic shift to conduct bicarbonate by a process involving ATP hydrolysis. Duct cells from patients with the delta-F508 CFTR mutation showed no glutamate/ATP-activated chloride or bicarbonate conductance. In contrast, duct cells from heterozygous patients with R117H (602421.0005)/delta-F508 mutations also lost most of the chloride conductance, yet retained significant bicarbonate conductance. Reddy and Quinton (2003) concluded that not only does glutamate control neuronal ion channels, but it can also regulate anion conductance and selectivity of CFTR in native epithelial cells. They proposed that the loss of this uniquely regulated bicarbonate conductance is most likely responsible for the more severe forms of cystic fibrosis pathology. Wang et al. (2003) demonstrated that endometrial epithelial cells possess a CFTR-mediated bicarbonate transport mechanism. Coculture of sperm with endometrial cells treated with antisense oligonucleotide against CFTR, or with bicarbonate secretion-defective CF epithelial cells, resulted in lower sperm capacitation and egg-fertilizing ability. These results were considered consistent with a critical role of CFTR in controlling uterine bicarbonate secretion and the fertilizing capacity of sperm, providing a link between defective CFTR and lower female fertility in CF. Sheep and human CFTR genes show a gradual decline in expression during lung development, from the early midtrimester through to term. Mouchel et al. (2003) identified a

novel5-prime exon of the sheep CFTR gene (ov1a) that occurs in 2 splice forms (ov1aL and ov1aS), which are both mutually exclusive with exon 1. CFTR transcripts, including ov1aL and ov1aS, were present at low levels in many sheep tissues; however, ov1aS showed temporal and spatial regulation during fetal lung development, being most abundant when CFTR expression starts to decline. Alternative 5-prime exons -1a and 1a in the human CFTR gene also showed changes in expression levels through lung development. Structural evaluation of ov1aL and ov1aS revealed the potential to form extremely stable secondary structures which would cause ribosomal subunit detachment. Further, the loss of exon 1 from the CFTR transcript removed motifs that are thought crucial for normal trafficking of the CFTR protein. Mouchel et al. (2003) hypothesized that recruitment of these alternative upstream exons may represent a novel mechanism of developmental regulation of CFTR expression. Fischer et al. (2004) found that vitamin C induced the opening of CFTR chloride channels by increasing the average open probability in the absence of detectable increased cAMP levels. Exposure of the apical airway surface to physiologic concentrations of vitamin C stimulated transepithelial chloride secretion. When instilled into the nasal epithelium of human subjects, vitamin C activated chloride transport. Fischer et al. (2004) concluded that cellular vitamin C, via its apical vitamin C transporter, is a biologic regulator of CFTR-mediated chloride secretion in epithelia. Vergani et al. (2005) used single-channel recording methods on intact CFTR molecules to directly follow opening and closing of the channel gates, and related these occurrences to ATP-mediated events in the nucleotide binding domains (NBDs). They found that energetic coupling between 2 CFTR residues, expected to lie on opposite sides of its predicted NBD1-NBD2 dimer interface, changes in concert with channel gating status. The 2 monitored side chains are independent of each other in closed channels but become coupled as the channels open. Vergani et al. (2005) concluded that their results directly link ATP-driven tight dimerization of CFTR's cytoplasmic nucleotide binding domains to opening of the ion channel in the transmembrane domains. This establishes a molecular mechanism, involving dynamic restructuring of the NBD dimer interface, that is probably common to all members of the ABC protein superfamily. Using proteomics to assess global CFTR protein interactions, Wang et al. (2006) showed that HSP90 (see 140571) cochaperones modulated HSP90-dependent stability of CFTR protein folding in the ER. Small interfering RNA-mediated partial silencing of the HSP90 cochaperone ATPase regulator AHA1 (AHSA1; 608466) in human embryonic kidney and lung cell lines rescued delivery of CFTR delta-F508 to the cell surface. Wang et al. (2006) proposed that failure of CFTR delta-F508 to achieve an energetically favorable fold in response to steady-state dynamics of the chaperone folding environment is responsible for the pathophysiology of CF. Using proteomic approaches, Thelin et al. (2007) showed that filamin (FLNA; 300017) associates with the extreme CFTR N terminus, and found that the disease-causing S13F mutation disrupts this interaction. Cell studies revealed that FLNA tethers plasma membrane CFTR to the underlying actin network, stabilizing CFTR at the cell surface and regulating the plasma membrane dynamics and confinement of the channel. In the absence of filamin binding, CFTR is rapidly internalized from the cell surface, where it accumulates prematurely in lysosomes and is ultimately degraded. Thelin et al. (2007) concluded that the CFTR N terminus plays a role in the regulation of the plasma membrane stability and metabolic stability of CFTR, and stated that S13F is the first missense mutation in CFTR found to disrupt a protein-protein interaction. Coimmunoprecipitation analysis and immunofluorescence microscopy by Cheng et al. (2002) showed that CAL (GOPC; 606845) interacted with the C terminus of CFTR in the Golgi. Functional analysis indicated that the CAL-CFTR interaction resulted in a reduction of the CFTR chloride current by a selective inhibition of cell surface CFTR expression; this could be reversed by competition from NHERF (604990). Cheng et al. (2010) showed that both syntaxin-6 (STX6; 603944) and CAL were involved in downregulation of CFTR via lysosome-mediated degradation. STX6 bound the N terminus of CFTR, and CAL independently bound the C terminus of CFTR. Overexpression of STX6 reduced cell surface expression of CFTR and caused its instability, but not in the absence of CAL and not in the presence of a lysosome inhibitor. Conversely, overexpression of a dominant-negative STX6 mutant or knockdown of STX6 resulted in CFTR stability. STX6 and CAL had no effect on the stability of delta-F508 CFTR, which is retained in the ER and undergoes ER-associated degradation. Cheng et al. (2010) concluded that STX6 and CAL function in the trans-Golgi network and direct trafficking of CFTR to the lysosome. By coimmunoprecipitation of transfected COS-7 and CHO-K1 cells, Rode et al. (2012) found that human testis anion transporter-1 (TAT1, or SLC26A8; 608480) interacted with the Cl- and HCO3- conductor CFTR. The 2 proteins colocalized at the equatorial segment of the human sperm head, with partial colocalization at the annulus. Similar colocalization was observed in mouse sperm. Voltage clamp experiments showed that TAT1 enhanced PKA (see 188830)-stimulated currents in CFTR-expressing Xenopus oocytes and stimulated cAMP-dependent CFTR-mediated iodide efflux in transfected CHO-K1 cells. TAT1 alone did not mediate iodide efflux in CHO-K1 cells and did not affect whole-cell conductance in Xenopus oocytes, suggesting that TAT1 is an electroneutral anion exchanger. Rode et al. (2012) concluded that TAT1 and CFTR cooperate in the regulation of Cl-/HCO3- fluxes required for sperm motility and capacitation. Using single-cell RNA sequencing and in vivo lineage tracing to study the composition and hierarchy of the mouse tracheal epithelium, Montoro et al. (2018) identified a rare cell type, the Foxi1 (601093)-positive pulmonary ionocyte; functional variations in club cells based on their location; a distinct cell type in high turnover squamous epithelial structures that they termed 'hillocks'; and disease-relevant subsets of tuft and goblet cells. Montoro et al. (2018) developed 'pulse-seq,' combining single-cell RNA-seq and lineage tracing, to show that tuft, neuroendocrine, and ionocyte cells are continually and directly replenished by basal progenitor cells. Ionocytes are the major source of transcripts of the CFTR in both mouse and human. Knockout of Foxi1 in mouse ionocytes caused loss of Cftr expression and disrupted airway fluid and mucus physiology, phenotypes that are characteristic of cystic fibrosis. Montoro et al. (2018) concluded that by associating cell type-specific expression programs with key disease genes, they had established a new cellular narrative for airway disease. Plasschaert et al. (2018) performed single-cell profiling of human bronchial epithelial cells and mouse tracheal epithelial cells to obtain a comprehensive census of cell types in the conducting airway and their behavior in homeostasis and regeneration. The analysis revealed cell states that represent known and novel cell populations, delineated their heterogeneity, and identified distinct differentiation trajectories during homeostasis and tissue repair. In addition, Plasschaert et al. (2018) identified a novel, rare cell type that they called the 'pulmonary ionocyte,' which coexpresses FOXI1, multiple subunits of the vacuolar-type H(+)-ATPase (V-ATPase), and CFTR. Using immunofluorescence, modulation of signaling pathways, and electrophysiology, Plasschaert et al. (2018) showed that Notch signaling (see 190198) is necessary and FOXI1 expression is sufficient to drive the production of the pulmonary ionocyte, and that the pulmonary ionocyte is a major source of CFTR activity in the conducting airway epithelium.

CYSTIC FIBROSIS; CF

Cystic fibrosis (CF) is classically described as a triad of chronic obstructive pulmonary disease, exocrine pancreatic insufficiency, and elevation of sodium and chloride concentration in sweat. Almost all males with CF are infertile due to congenital bilateral absence of the vas deferens. The disorder is associated with decreased longevity (summary by Cutting, 2002). For discussion of a phenotype consisting of bronchiectasis with or without elevated sweat chloride caused by mutation in the genes encoding the 3 subunits of the epithelial sodium channel, see BESC1 (211400).

ClinicalFeatures

The mildest extreme of CF is represented by patients not diagnosed until middle age (Scully et al., 1977). The phenotypic variability in CF was analyzed by Sing et al. (1982). In an inbred kindred in North Carolina, a mild form of cystic fibrosis was described by Knowles et al. (1989). There was 1 instance of mother-daughter involvement, the mother being related to her husband. One of the presumed homozygotes was a 62-year-old woman. Another was her 52-year-old sister, the mother of the affected proposita. The daughter was an intensive care nurse, the mother of a normal daughter. Manifestations in the family were predominantly pulmonary; pancreatic exocrine insufficiency was not a conspicuous feature, especially in the older patients. The 2 subgroups defined by the A and C haplotypes of polymorphisms closely linked to the CF locus on chromosome 7, reported by Estivill et al. (1987), have clinical differences in terms of the frequency of meconium ileus, pseudomonas infections, and pancreatic disease (Woo, 1988). Gasparini et al. (1990) described a RFLP DNA marker closely linked to the CF locus which showed an allelic correlation with severity of the disorder: the genotype 2/2 was associated with severe disease; the genotype 1/2 was overrepresented in patients with very mild clinical manifestations, including pancreatic insufficiency, absence of meconium ileus, and absence of Pseudomonas colonization. Meconium Ileus Allan et al. (1981) showed that sibs tend to show recurrence of meconium ileus as a feature of cystic fibrosis. The distal intestinal obstruction syndrome is a 'meconium ileus equivalent' that occurs in adolescents and adults with CF. It is the consequence of the abnormally viscid mucofeculant material in the terminal ileum and right colon, where the fecal stream is normally liquid. Typical features are recurrent episodes of RLQ pain with palpable mass in the right iliac fossa. Symptoms are exacerbated by eating. Mornet et al. (1988) determined the haplotype associated with cystic fibrosis in 41 families using 4 DNA probes, all of which are tightly linked to the CF gene. In 17 of the families an affected child had meconium ileus, and in the other 24 families there was a child without meconium ileus. A different haplotype was associated with the 2 types of families, suggesting that multiple allelism, i.e., different mutations at the same locus, accounts for CF with or without meconium ileus. Liver Disease Gaskin et al. (1988) found that 96% of patients with cystic fibrosis and evidence of liver disease had biliary tract obstruction, usually a stricture of the distal common bile duct. All patients without liver disease had normal intrahepatic and common-duct excretion of tracer. Bilton et al. (1990) described a case of cystic fibrosis complicated by common bile duct stenosis. Gabolde et al. (2001) showed that the presence of cirrhosis in patients with cystic fibrosis is significantly associated with either homozygous or compound heterozygous mutations in the MBL2 gene (154545), which encodes mannose-binding lectin (MBL). The authors compared 216 patients homozygous for the delta-F508 mutation (602421.0001) and found that 5.4% of those homozygous or compound heterozygous for wildtype mannose-binding lectin had cirrhosis, while 30.8% of those homozygous or compound heterozygous for mutant alleles had cirrhosis (p = 0.008). Approximately 3 to 5% of patients with cystic fibrosis develop severe liver disease defined as cirrhosis with portal hypertension. Bartlett et al. (2009) performed a 2-stage case control study enrolling patients with CF and severe liver disease with portal hypertension from 63 CF centers in the United States as well as 32 in Canada and 18 outside of North America. In the first stage, 124 patients with CF and severe liver disease, enrolled between January 1999 and December 2004, and 843 control patients without CF-related liver disease (all assessed at greater than 15 years of age) were studied by genotyping 9 polymorphisms in 5 genes previously studied as modifiers of liver disease in CF. In the second stage, the 2 genes that were positive from the first stage were tested in an additional 136 patients with CF-related liver disease, enrolled between January 2005 and February 2007, and in 1,088 with no CF-related liver disease. The combined analysis of the initial and replication studies by logistic regression showed CF-related liver disease to be associated with the SERPINA1 Z allele (107400.0011) (odds ratio = 5.04; 95% confidence interval, 2.88-8.83; p = 1.5 x 10(-8)). Bartlett et al. (2009) concluded that the SERPINA1 Z allele is a risk factor for liver disease in CF. Patients carrying the Z allele are at greater risk (odds ratio = approximately 5) of developing severe liver disease with portal hypertension. Pancreatic Insufficiency Approximately 15% of CF patients do not have pancreatic insufficiency, i.e., are 'pancreatic sufficient.' Kerem et al. (1989) performed linkage disequilibrium and haplotype association studies of patients in 2 clinical subgroups, one pancreatic insufficient (PI) and the other pancreatic sufficient (PS). Significant differences were found in allelic and haplotype distributions in the 2 groups. The data suggested that most of the CF-PI patients were descendants of a single mutational event at the CF locus, whereas the CF-PS patients resulted from multiple, different mutations. Corey et al. (1989) commented on the intrafamilial concordance for pancreatic insufficiency in CF. Devoto et al. (1989) studied the allele and haplotype frequencies of 5 polymorphic DNA markers near the CF locus in 355 CF patients from Belgium, the German Democratic Republic, Greece, and Italy who were divided into 2 groups according to whether or not they were taking supplementary pancreatic enzymes. The distributions of alleles and haplotypes revealed by 2 of the probes were always different in patients with or without pancreatic insufficiency in all the populations studied. In the case of 1 haplotype that was present in 73% of all the CF chromosomes in their sample, they found homozygosity in only 28% of patients without pancreatic insufficiency as contrasted with 64% who were homozygous and had pancreatic insufficiency. Like other workers, they concluded that this indicated that pancreatic insufficiency and sufficiency are associated with different mutations at the CF locus. Ferrari et al. (1990) studied the distribution of haplotypes based on 8 polymorphic DNA markers linked to CF in 163 Italian patients and correlated the findings with clinical presentation. Among 19 pancreatic sufficient patients, 6 (31.6%) showed at least 1 copy of a rare phenotype which was present in only 16 of 138 patients (11.6%) with pancreatic insufficiency. In addition, only 5 pancreatic sufficient patients were homozygous for the common 2,1 haplotype as compared with 88 patients (63.8%) with pancreatic insufficiency. Kristidis et al. (1992) likewise found intrafamilial consistency of the pancreatic phenotype, whether pancreatic sufficient or insufficient. Furthermore, the PS phenotype occurred in patients who had 1 or 2 mild CFTR mutations, such as arg117-to-his (602421.0005), arg334-to-trp (602421.0034), arg347-to-pro (602421.0006), ala455-to-glu (602421.0007), and pro574-to-his (602421.0018), whereas the PI phenotype occurred in patients with 2 severe alleles, such as phe508-to-del (602421.0001), ile507-to-del (602421.0002), gln493-to-ter (602421.0003), gly542-to-ter (602421.0009), arg553-to-ter (602421.0014), and trp1282-to-ter (602421.0022). Borgo et al. (1993) commented on the phenotypic intrafamilial heterogeneity displayed by an Italian family in which 3 sibs, 2 of whom were dizygotic twins, were compound heterozygotes for the delF508 (602421.0001) and the 1717,-1,G-A splicing mutation (602421.0008). While close intrafamilial concordance was found for exocrine pancreatic phenotype, the pulmonary phenotype varied widely. They suggested that interaction of the CFTR protein with tissue-specific proteins or the action of modifier loci (which may be operationally identical possibilities) plays a role in intrafamilial variability. Barreto et al. (1991) concluded that the father of a girl with severe CF also had CF but was mildly affected. The child was homozygous for the delta-F508 mutation associated with haplotype B; the father was a compound heterozygote for this mutation and a second CF mutation associated with haplotype C. Perhaps it should not be surprising that some patients with cystic fibrosis have no pancreatic lesions (Oppenheimer, 1972). Sharer et al. (1998) and Cohn et al. (1998) demonstrated that heterozygosity for CFTR mutations can lead to 'idiopathic' chronic pancreatitis, especially when the mutation is associated with the 5T allele of the variable number of thymidines in intron 8 of the CFTR gene. Pulmonary Disease Pier et al. (1996) provided an experimental explanation for the susceptibility of CF patients to chronic Pseudomonas aeruginosa

lunginfections. They found that cultured human airway epithelial cells expressing the delta-F508 allele of the CFTR gene were defective in uptake of P. aeruginosa compared with cells expressing the wildtype allele. P. aeruginosa lipopolysaccharide-core oligosaccharide was identified as the bacterial ligand for epithelial cell ingestion; exogenous oligosaccharide inhibited bacterial ingestion in a neonatal mouse model, resulting in increased amounts of bacteria in the lungs. The authors concluded that CFTR may normally contribute to a host-defense mechanism that is important for clearance of P. aeruginosa from the respiratory tract. Ernst et al. (1999) identified unique lipopolysaccharide structures synthesized by P. aeruginosa within CF patient airways. P. aeruginosa synthesized lipopolysaccharide with specific lipid A structures, indicating unique recognition of the CF airway environment. CF-specific lipid A forms containing palmitate and aminoarabinose were associated with resistance to cationic antimicrobial peptides and increased inflammatory responses, indicating that they are likely to be involved in airway disease. Because mannose-binding lectin (MBL), encoded by the MBL2 gene (154545), is a key factor in innate immunity, and lung infections are a leading cause of morbidity and mortality in CF, Garred et al. (1999) investigated whether MBL variant alleles, which are associated with recurrent infections, might be risk factors for CF patients. In 149 CF patients, different MBL genotypes were compared with respect to lung function, microbiology, and survival to end-stage CF (death or lung transplantation). The lung function was significantly reduced in carriers of MBL variant alleles when compared with normal homozygotes. The negative impact of variant alleles on lung function was especially confined to patients with chronic Pseudomonas aeruginosa infection. Burkholderia cepacia infection was significantly more frequent in carriers of variant alleles than in homozygotes. The risk of end-stage CF among carriers of variant alleles increased 3-fold, and the survival time decreased over a 10-year follow-up period. Moreover, by using a modified life table analysis, Garred et al. (1999) estimated that the predicted age of survival was reduced by 8 years in variant allele carriers when compared with normal homozygotes. Davies et al. (2000) found that MBL binds to Burkholderia cepacia, an important pathogen in patients with CF, and leads to complement activation, but that this was not the case for Pseudomonas aeruginosa, the more common colonizing organism in CF. Davies et al. (2000) suggested that patients with CF and mannose-binding lectin deficiency would be at a particularly high risk of B. cepacia colonization. The lack of binding to P. aeruginosa suggests that the effect of this organism on lung function in patients with MBL-deficient CF reflects a role for MBL, either in intercurrent infections with other organisms, or in the inflammatory process. In an association study involving 112 patients with cystic fibrosis, Yarden et al. (2004) found that patients with the MBL2 A/O or O/O genotypes were more likely to have a more severe pulmonary phenotype than patients with the A/A genotype (p = 0.002). No association was found between the MBL2 genotype and the age at first infection with P. aeruginosa. Yarden et al. (2004) concluded that it is very likely that MBL2 is a modulating factor in cystic fibrosis. Tarran et al. (2001) stated that there is controversy over whether abnormalities in the salt concentration or volume of airway surface liquid (ASL) initiate CF airway disease. Using CF mouse nasal epithelia, they showed that an increase in goblet cell number was associated with decreased ASL volume rather than abnormal Cl- concentration. Aerosolization of osmolytes in vivo failed to raise ASL volume. Osmolytes and pharmacologic agents were effective in producing isotonic volume responses in human airway epithelia but were typically short acting and less effective in CF cultures with prolonged volume hyperabsorption and mucus accumulation. These data showed that therapies can be designed to normalize ASL volume without producing deleterious compositional changes in ASL, and that therapeutic efficacy will likely depend on development of long-acting pharmacologic agents and/or an increased efficiency of osmolyte delivery. In 69 Italian patients with CF due to homozygosity for the delF508 mutation in the CFTR gene (F508del; 602421.0001), De Rose et al. (2005) found that those who also carried the R131 allele of the immunoglobulin Fc-gamma receptor II gene (FCGR2A; see 146790.0001) had a 4-fold increased risk of acquiring chronic Pseudomonas aeruginosa infection (p = 0.042). De Rose et al. (2005) suggested that FCGR2A locus variability contributes to this infection susceptibility in CF patients. Emond et al. (2012) used exome sequencing and an extreme phenotype study design to discover genetic variants influencing Pseudomonas aeruginosa infection in cystic fibrosis. Forty-three individuals with early age of onset of chronic P. aeruginosa infection (all below the tenth percentile of age at onset), and the 48 oldest individuals who had not reached chronic P. aeruginosa infection (all past the mean age of onset) were sequenced. After Bonferroni adjustment, a single gene, DCTN4, was significantly associated with time to chronic P. aeruginosa infection (naive P = 2.2 x 10(-6); adjusted P = 0.025). Twelve of the 43 individuals in the early extreme sample carried a missense variant in DCTN4, 9 a phe349-to-leu substitution (F349L; rs11954652) and 3 a tyr270-to-cys substitution (Y270C; rs35772018). None of the 48 individuals in the late P. aeruginosa extreme sample had either missense variant. Subsequently, 696 individuals with varied CFTR genotypes were studied. Seventy-eight participants were heterozygous and 9 were homozygous for the F349L (614758.0001) mutation; 15 were heterozygous for the Y270C (614758.0002) mutation; 1 individual was heterozygous for both mutations. The presence of at least 1 DCTN4 missense variant was significantly associated with both early age of first P. aeruginosa-positive culture (p = 0.01, hazard ratio = 1.4) and with early age of onset of chronic P. aeruginosa infection (p = 0.004, hazard ratio = 1.9). The risk was highest in individuals with less selective bias toward a P. aeruginosa-negative history, i.e., children enrolled before 1.5 years of age and 103 enrollees who participated in the study despite a history of P. aeruginosa-positive cultures. No significant interaction was found between CFTR genotypes and DCTN4 mutations, although power to detect such an interaction was low. Infertility Oppenheimer et al. (1970) suggested that characteristics of cervical mucus may account for infertility in females with cystic fibrosis. Congenital bilateral absence of the vas deferens (CBAVD; 277180) is a usual cause of male infertility in cystic fibrosis. It also occurs with CFTR mutations in heterozygous state, especially when associated with the polymorphic number of thymidines in intron 8, specifically the 5T allele. Carcinoma Siraganian et al. (1987) pointed to adenocarcinoma of the ileum in 3 males with cystic fibrosis. The diagnosis was made between ages 29 and 34 years. From a pancreatic adenocarcinoma developing in a 26-year-old patient with cystic fibrosis due to the phenylalanine-508 deletion, Schoumacher et al. (1990) established a cell line in which the cells showed morphologic and chemical characteristics typical of pancreatic duct cells and showed physiologic properties of CF cells. Schoumacher et al. (1990) suggested that the cell line, which had been stable through more than 80 passages over a 2-year period, could serve as a continuous cell line for studies of the CF defect. Bradbury et al. (1992) demonstrated that the CFTR protein is involved in cAMP-dependent regulation of endocytosis and exocytosis. In a study of pancreatic cancer cells derived from a CF patient, they found that plasma membrane recycling did not occur until normal CFTR was provided. Neglia et al. (1995) performed a retrospective cohort study of the occurrence of cancer in 28,511 patients with cystic fibrosis from 1985 through 1992 in the United States and Canada. The number of cases observed was compared with the number expected, calculated from population-based data on the incidence of cancer. They also analyzed proportional incidence ratios to assess the association between specific cancers and cystic fibrosis in Europe. The final results indicated that although the overall risk of cancer in patients with cystic fibrosis is similar to that of the general population, there is an increased risk of digestive tract cancers. They recommended that persistent or unexplained gastrointestinal symptoms in CF patients should be carefully investigated. Patients with cystic fibrosis have altered levels of plasma fatty acids. Affected tissues from cystic fibrosis knockout mice show elevated levels of arachidonic acid and decreased levels of docosahexaenoic acid. Freedman et al. (2004)

performedstudies of fatty acids in nasal and rectal biopsy specimens, nasal epithelial scrapings, and plasma from 38 patients with cystic fibrosis, and found alterations in fatty acids similar to those in the knockout mice. Other Features Delayed puberty is common among individuals with cystic fibrosis and is usually attributed to chronic disease and/or poor nutrition. However, delayed puberty has been reported as a feature of CF even in the setting of good nutritional and clinical status (Johannesson et al., 1997).

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