Chapter 6
Cystic Fibrosis, Primary Ciliary Dyskinesia, and Diffuse Panbronchiolitis: Hereditary and Non-hereditary—What Are the Roles of Genetic Factors in the Pathogenesis of These Diseases?

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Abstract Cystic fibrosis (CF), primary ciliary dyskinesia (PCD), and diffuse panbronchiolitis (DPB) are rare airway diseases. CF is the most common life-shortening genetic disorder in Caucasians, caused by mutations in a single gene on the long arm of chromosome 7 that encodes the cystic fibrosis transmembrane conductance regulator (CFTR). The predominant CFTR mutation is Phe508del, yet more than 2000 variants in this gene have been identified, which can be divided into six classes. Class II mutations, including Phe508del, cause retention of a misfolded protein in the endoplasmic reticulum and subsequent degradation in the proteasome. Patients with Class I, II, and III mutations, which are associated with loss of CFTR function, typically have a severe phenotype, whereas individuals with Class IV, V, and VI mutations, which retain residual CFTR function, have mild lung phenotypes and pancreatic sufficiency. PCD is usually inherited in an autosomal recessive manner and is genetically heterogeneous. Of the 30 mutations that are known to cause PCD, those affecting the *DNAH5*, *DNAI1*, *DNAAF1 (LRRC50)*, *LRRC6*, *CCDC39*, *CCDC40*, and *DNAH11 genes are found in* 15–21%, 2–9%, 4–5%, 3%, 2–10%, 2–8%, and 6% of patients, respectively. In terms of the relationship between phenotype and genotype, mutation of *DNAH5*, *DNAI1*, *DNAI2*, *DNAL1*, *CCDC114*, *TXNDC3 (NME8)*, *or ARMC4* results in loss of the outer dynein arms. In regard to DPB, an interaction of environmental and genetic factors is thought to underpin the disease. The most probable location for DPB susceptibility genes is thought to lie in a 200 kb major histocompatibility complex (MHC) class I region between *HLA-A* and *HLA-B*. This contains the DPB critical region 1 gene (*DPCR1*, chromosome 6p21.33), as well as *MUC21*, and the panbronchiolitis-related mucin-like genes 1 and 2 (*PBMUCL1* and *PBMCL2*). The fact that *DPCR1*, *MUC21*, *PBMUCL1*, and

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PBMUCL2 are all mucin or mucin-like genes is highly relevant for the excessive airway mucus secretion that is typical in DPB. In summary, CF and PCD are both hereditary disorders of mucociliary clearance that result in chronic upper and lower airways disease, while in DPB, it is thought that genetic factors may determine disease susceptibility.

Keywords Cystic fibrosis · Phe508del · Primary ciliary dyskinesia · *DNAH5* Diffuse panbronchiolitis · PBMUCL · Hereditary · Genetic factor

6.1 Introduction

Cystic fibrosis (CF), primary ciliary dyskinesia (PCD), and diffuse panbronchiolitis (DPB) are rare airway diseases. CF is the most common life-shortening genetic disorder in Caucasians in the United States. CF affects approximately 30,000 individuals in the United States and 70,000 individuals worldwide [1]. The functional failure of CFTR results in mucus retention and chronic infection. Early in life, airway infections are most commonly caused by *Staphylococcus aureus* and *H. influenzae*. As patients age, *P. aeruginosa* becomes the predominant infecting organism, and about 80% of patients with CF are infected with this organism by adulthood [2]. Subsequently, airway inflammation becomes harmful to the lungs. The development and delivery of drugs that improve the clearance of mucus from the lungs and treat the associated infection, in combination with the correction of pancreatic insufficiency and undernutrition by multidisciplinary teams, have resulted in remarkable improvements in quality of life and clinical outcomes in patients with CF, with median life expectancy now >40 years [3]. Innovative and transformational therapies that target the basic defect in CF have recently been developed and are effective in improving lung function and reducing pulmonary exacerbations [4].

PCD is a genetic disease that causes abnormalities in ciliary function, leading to impaired mucociliary clearance. PCD is rare, with an estimated prevalence of one in 20,000 live births (range, 1/10,000 to 1/40,000) [5]. Congenital abnormality of the primary cilia results in situs inversus in 50% of patients [6]. Cases with situs inversus are considered to show "Kartagener's syndrome" [7]. Decreased function of motile cilia causes chronic rhinosinusitis, otitis media with effusion, bronchiectasis, and infertility. The clinical features usually start with neonatal respiratory distress, with early-onset persistent rhinosinusitis and serous otitis media with hearing impairment and persistent daily wet cough [8]. PCD without situs inversus is underdiagnosed because prolonged chronic cough represents an important symptom that is seen in most patients. Diagnosis of PCD requires the presence of characteristic clinical phenotypes, in addition to either the identification of mutation in one of the genes known to be associated with PCD [9] or specific ciliary ultrastructural defects identified by transmission electron microscopy in biopsy samples of the respiratory epithelium [10]. Nasal nitric oxide concentration is extremely low in PCD and may

also therefore be useful for screening of the disease [11]. Diagnosis in the early stages is important to prevent progression of bronchiectasis and deterioration of lung function, by providing lifestyle guidance in regard to immunization, cessation of smoking, and the need for prompt therapy at the time of respiratory tract infection. Genetic counseling is necessary after definitive diagnosis since it is inherited in an autosomal recessive manner.

DPB has many similarities with CF, in that it is an inflammatory lung disease characterized by the chronic inflammation of bronchioles (small airways) in both lungs [12]. DPB can also present as one of the characteristic features of the lung in PCD [13]. The term *diffuse* means that lesions appear throughout both lungs, while *panbronchiolitis* refers to the inflammation that is found in the respiratory bronchioles. DPB causes severe coughing, large amounts of sputum, and exertional breathlessness, often associated with chronic sinusitis. Histopathologically, thickening of the terminal bronchiole walls with infiltration of lymphocytes, plasma cells, and foamy macrophages, leading to chronic neutrophilic inflammatory airway disease, are the predominant features [14]. The disease was first described by a Japanese group of clinicians as a new entity in the 1960s but was not accepted internationally because the disease had been reported predominantly in East Asia. Introduced to Western countries in the 1980s, cases were then recognized throughout Asia, as well as in Europe and the USA [15, 16]. According to a nationwide survey conducted in Japan [17], there appears to be no remarkable gender or age predominance for DPB, and a history of smoking or exposure to toxic fumes do not seem to be involved. In many cases, symptoms of chronic sinusitis first appear in the transition from child to adulthood, followed by the development of symptoms in the lower airways. In 1980, the prevalence of DPB was 11.1 cases per 100,000 people [18], but the number was reported to have decreased to only 3.4 cases per 100,000 in an unofficial survey conducted in 1995 [9]. The reason for this drop is presumed to be the positive effect of macrolide therapy given at an early stage [19], resulting in the appearance only of chronic sinusitis symptoms.

In patients with these three diseases, the associated infections and intense neutrophilic inflammatory responses lead to airway destruction, bronchiectasis, and obstructive lung disease, ultimately resulting in respiratory failure, which if left untreated, is fatal. This chapter is a discussion on the roles of genetic factors in the pathogenesis of these three diseases.

6.2 Genetic Factors in the Pathogenesis of CF

CF is a common autosomal recessive disorder caused by mutations in a single gene on the long arm of chromosome 7 that encodes the cystic fibrosis transmembrane conductance regulator (CFTR) protein [20–23]. The predominant mutation is Phe508del, although more than 2000 gene variants have been identified [24]. CFTR is a chloride-conducting transmembrane channel that regulates anion transport and mucociliary clearance in the airways (Fig. 6.1a) [25]. Wildtype CFTR is also

involved in the regulation of the inflammasome and the epithelial sodium channel (ENaC) [26]. The functional failure of CFTR results in hyper-inflammation, proteasome stress, reduced or absent anion transport, and hyper-reabsorption of Na+, which in turn leads to impaired innate immunity, mucus abnormalities, and reduced airway surface liquid (ASL) hydration and suboptimal mucociliary clearance. Together, these factors subsequently result in mucus retention, chronic infection, and local airway inflammation that is harmful to the lungs [25] (Fig. 6.1b). CFTR dysfunction mainly affects epithelial cells, although there is also evidence of a role for this protein in immune cells. CF affects several body systems; however, morbidity and mortality are mostly related to bronchiectasis, small airway obstruction, and progressive respiratory impairment. Important comorbidities caused by epithelial cell dysfunction present in the pancreas as malabsorption, in the liver as biliary cirrhosis, in the sweat glands as heat shock, and in the vas deferens as infertility. Mutations in the *CFTR* gene have different effects on the either production of the CFTR protein, its stability at the cell membrane, or functional defects in regard to chloride and bicarbonate transport. Most mutations in *CFTR* are missense alterations, but frameshift, splicing, and nonsense mutations, as well as in-frame deletions and insertions, have all been reported [27]. About 15% of identified genetic variants are not associated with clinical disease.

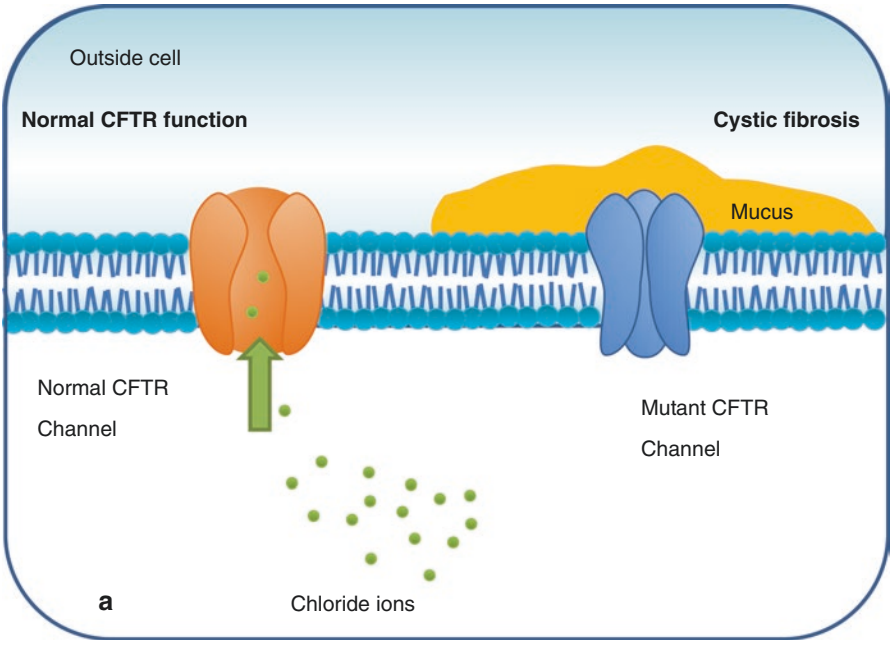


Fig. 6.1 (**a**) Schematic representation of pathology of cystic fibrosis. (**b**) Effects of CFTR dysfunction. ASL = airway surface liquid. CFTR = cystic fibrosis transmembrane conductance regulator. ENaC = epithelial sodium channel. Adapted from J Stuart Elborn [25]

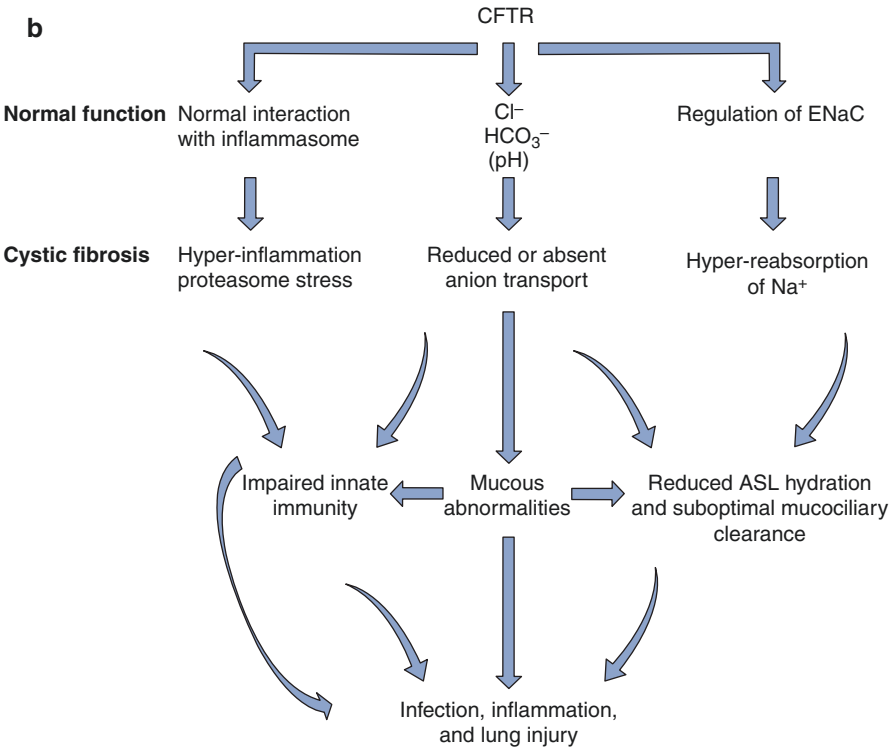


Fig. 6.1 (continued)

As shown in Fig. 6.2, mutations of the *CFTR* gene can be divided into six classes. Class I mutations, including Gly542X, Trp1282X, and Arg553X, result in no protein production. Class II mutations, including the most prevalent Phe508del variation, cause retention of a misfolded protein at the endoplasmic reticulum and subsequent degradation in the proteasome. Class III mutations, including Gly551Asp, Gly178Arg, and Gly551Ser, affect channel regulation, impairing the channel opening. Class IV mutants, including Arg117His, Arg347Pro, and Arg117Cys, show reduced conduction and a decreased flow of ions. Class V mutations cause substantial reduction in mRNA or protein or both. Class VI mutations, including 4326delTC, gln1412X, and 4279insA, cause substantial plasma membrane instability [28]. This classification system is helpful because it relates to the molecular and cellular processes in gene translation and protein processing and has some useful clinical correlates (Fig. 6.3). Patients with Class I, II, or III mutations are associated with no residual CFTR function and generally have a severe phenotype, whereas individuals with Class IV, V, or VI mutations have some residual CFTR function, with a mild lung phenotype and pancreatic sufficiency [29]. However, as with any system of classification, there are several oversimplifications with this approach. Phe508del, for example, is predominantly a Class II trafficking

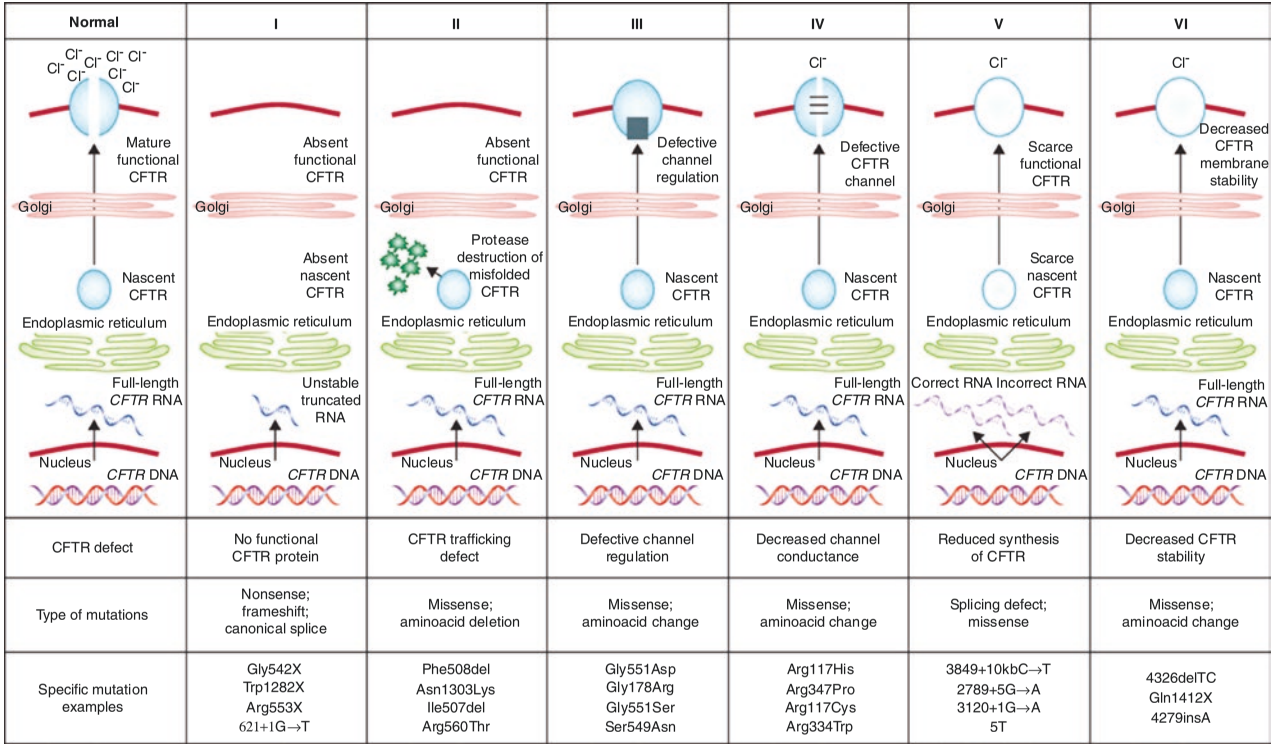
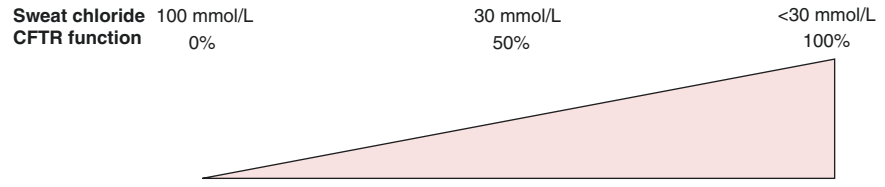


Fig. 6.2 Classes of CFTR mutations. Mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene can be divided into six classes. Class I mutations result in no protein production. Class II mutations (including the most prevalent, Phe508del) cause retention of a misfolded protein at the endoplasmic reticulum and subsequent degradation in the proteasome. Class III mutations affect channel regulation, impairing channel opening (e.g., Gly551Asp). Class IV mutants show reduced conduction, i.e., decreased flow of ions (e.g., Arg117His). Class V mutations cause substantial reduction in mRNA or protein or both. Class VI mutations cause substantial plasma membrane instability and include Phe508del when rescued by most correctors (rPhe508del). Reproduced from Boyle and De Boeck. Adapted from J Stuart Elborn [25]



Sweat chloride	100 mmol/L	30-60 mmol/L	<30 mmol/L
Lung phenotype	Bronchiectasis	Airway wall thickening	Normal airways
Bacteriology	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	Normal microbiome
Pancreatic function	None	50% pancreatic insufficiency	Normal pancreatic function
Male fertility	Infertile	Infertile	Fertile
Typical mutations	Gly542X	Arg117His (5T)	
	Phe508del	Arg334Trp	
	Gly551Asp	Ala55Glu	
	Class I-III mutations	Class IV-VI mutations	Healthy
		Heterozygote carrier	

Fig. 6.3 Relation between phenotype, genotype, and CFTR function in patients with cystic fibrosis, carriers, and healthy individuals. CFTR = cystic fibrosis transmembrane conductance regulator. Adapted from J Stuart Elborn [25]

mutation, with only around 3% of protein being trafficked to the cell membrane; however, the channel is not functional and thus has properties of a Class III gating mutation, in addition to having the decreased stability of a Class VI mutation [30]. Gene-based small-molecule therapies are currently being developed to restore CFTR function and thus improve the clinical outcomes of people with CF.

6.3 Genetic Factors in the Pathogenesis of PCD

As shown in Fig. 6.4 [9], pathogenesis associated with PCD begins with a defect in genes related to ciliary motility. PCD is usually inherited in an autosomal recessive manner, but the disorder is genetically heterogeneous, and cases of autosomal dominant or X-linked inheritance have also been reported [31]. In their review, Takeuchi et al. [9] described how impaired ciliary motility in embryos results in the *NODAL* gene being randomly expressed either to the right or the left of the body in this disease [32]. *NODAL* expressed to the right results in situs inversus *totalis* which is a known feature of Kartagener syndrome. When *NODAL* is expressed to the left, however, the heart develops in the normal location and PCD instead develops without situs inversus *totalis*. Decreased ciliary movement in motile cilia results in decreased mucociliary clearance, manifesting as rhinosinusitis, otitis media, pneumonia, bronchiectasis, infertility, and ectopic pregnancy. Mutations known to cause PCD have

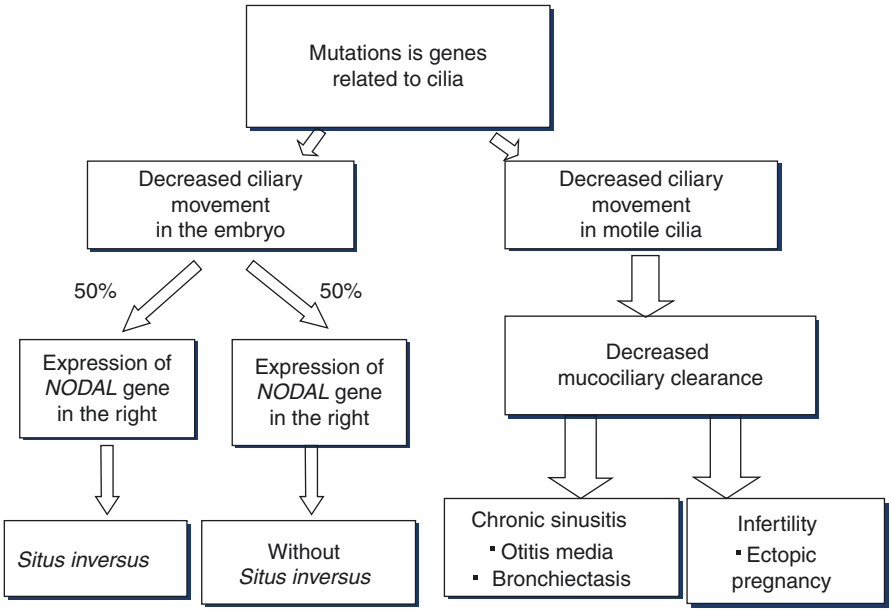


Fig. 6.4 Etiology of primary ciliary dyskinesia. All abnormalities start with mutations in genes related to cilia or ciliary movement. Decreased movement of primary cilia in the embryo results in expression of the *NODAL* gene on the right in approximately 50% of patients, causing situs inversus. Decreased movement of motile cilia causes decreased mucociliary clearance, which results in chronic sinusitis, otitis media, bronchiectasis, infertility, and ectopic pregnancy. Adapted from K Takeuchi [9]

been identified in 30 genes, as reviewed by Knowles et al. [33] and Takeuchi et al. [9]. These are shown in Table 6.1 [9] with the prevalence of *DNAH5*, *DNAI1*, *DNAAF1 (LRRC50)*, *LRRC6*, *CCDC39*, *CCDC40*, and *DNAH11 mutations among patients with PCD being* 15–21%, 2–9%, 4–5%, 3%, 2–10%, 2–8%, and 6%, respectively. Mutations in 30 of these genes account for the genetic etiology in approximately 70% of individuals affected with PCD [9, 34]; however, disease-causing mutations have yet to be identified for many patients with PCD.

Numerous mutations can arise in each of the genes involved in ciliary movement. This fact may help explain the wide variation in the degree of mucociliary dysfunction and disease severity among patients. In terms of the relationship between phenotype and genotype, mutation of *DNAH5*, *DNAI1*, *DNAI2*, *DNAL1*, *CCDC114*, *TXNDC3 (NME8)*, or *ARMC4* results in the loss of the outer dynein arms. Mutations in *DNAAF1 (LRRC50)*, *DNAAF2 (KTU)*, *DNAAF3 (C19orf51)*, *CCDC103*, *HEATR2*, *LRRC6*, *ZMYND10*, *DYX1C1*, *C21orf59*, *SPAG1*, or *CCDC151*, which code for proteins associated with the assembly of cilia, result in the loss of both outer and inner dynein arms. *CCDC39* and *CCDC40* mutations result in the loss of the inner dynein arms and abnormalities in axoneme structure. *RSPH1*, *RSPH4A*, and *RSPH9* code for radial spork proteins, with mutations resulting in the loss of central microtubules. Eighty-five percent of mutations represent loss-of-function

Table 6.1 List of genes causing primary ciliary dyskinesia and the relation to phenotypes

Locus name	Gene symbol	Structure of cilia	Percentage of PCD	Laterality defects
CILD3	*DNAH5*	Loss of outer dynein arms	15–21%	Possible
CILD1	*DNAI1*		2–9%	
CILD9	*DNAI2*		2%	
CILD16	*DNAL1*		NA	
CILD20	*CCDCI14*		6% of outer dynein loss	
CILD06	*TXNDC3(NME8)*		NA	
CILD23	*ARMC4*		NA	
CILD13	*DNAAF1(LRRC50)*	Loss of inner and outer dynein arms	4–5%	
CILD10	*DNAAF2(KTU)*		~2%	
CILD2	*DNAAF3 (C19orf51)*		NA	
CILD17	*CCDC103*		NA	
CILD18	*HEATR2*		NA	
CILD19	*LRRC6*		3%	
CILD22	*ZMYND10*		NA	
CILD25	*DYX1C1*		NA	
CILD26	*C21orf59*		NA	
CILD28	*SPAG1*		NA	
CILD30	*CCDC151*		NA	
CILD14	*CCDC39*	Loss of inner dynein arm and abnormalities of axoneme structure	2–10%	
CILD15	*CCDC40*		2–8%	
CILD24	*RSPH1*	Loss of central microtubules	NA	Absent
CILD11	*RSPH4A*		NA	
CILD12	*RSPH9*		NA	
CILD5	*HYDIN*	Occasional loss of central microtubules	NA	
CILD21	*DRC1(CCDC164,C2orf39)*	Loss of nexin link axonemal disorganization	NA	
CILD27	*CCDC65*		NA	
CILD29	*CCNO*	Decrease of cilia, centriole and basal bodies	NA	
	RPGR	Various	NA	
CILD7	*DNAH11*	Normal	6%	Possible
	OFD1	Not determined	NA	Absent

Adapted from K Takeuchi [9]

variants, while 15% are conservative missense mutations [33]. In 30% of PCD patients, cilial structures are normal under electron microscopy, meaning that genetic analysis represents the ultimate method of diagnosis in some patients. Takeuchi et al. [9], for example, have reported that they initially screen mutation hot spots on *DNAI1* and *DNAH5* by direct sequencing, but if no variants are detected in these loci, they then screen for variants in other genes using whole-exome sequencing.

6.4 Genetic Factors in the Pathogenesis of DPB

Although the cause of DPB remains unknown, the interaction of environmental and genetic factors appears to underpin the disease. Since DPB has been reported mainly in Japan and East Asia, it was initially suspected that a genetic predisposition unique to Asian descendants might determine disease susceptibility. Now, studies have shown that specific human leukocyte antigen (HLA) haplotypes are strongly associated with the development of DPB, such as HLA-B54 for Japanese patients [35] and HLA-A11 for Korean patients [36]. With this in mind, the most probable location for DPB susceptibility genes is thought to lie in a 200 kb major histocompatibility complex (MHC) class I region between *HLA-A* and *HLA-B* on chromosome 6, as shown in Fig. 6.5a [37]. This contains the DPB critical region 1 gene (*DPCR1*, chromosome 6p21.33) [38], as well as *MUC21*, and the panbronchiolitis-related

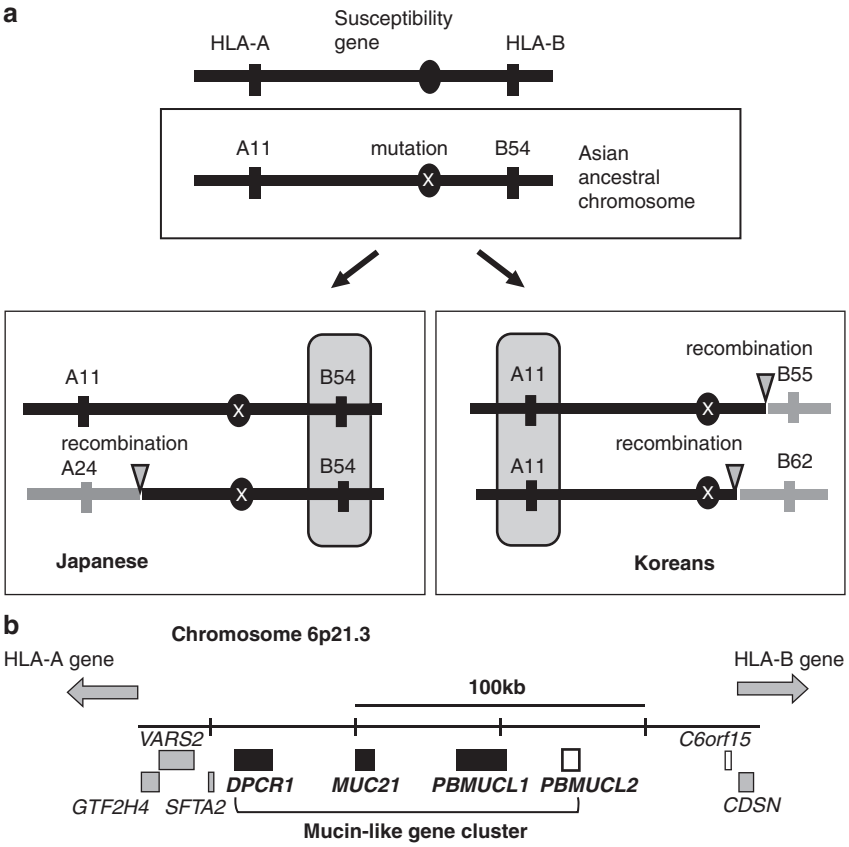


Fig. 6.5 (**a**) A hypothesis that may explain the findings that diffuse panbronchiolitis is associated with different HLA types in Japanese and Koreans. A disease susceptibility gene may be located between HLA-A locus and the HLA-B locus (see text for details). Adapted from: N Keicho [15]. (**b**) A novel mucin or mucin-like gene cluster in the HLA class I region on the short arm of chromosome 6 (6p21.3), members of which showed associations with diffuse panbronchiolitis. *DPCR1*, *MUC21*, *PBMUCL1*, and *PBMUCL2* are all mucin or mucin-like genes. Adapted from N Keicho [15]

mucin-like genes 1 and 2 (*PBMUCL1* and *PBMCL2*) [39] (Fig. 6.5b). The fact that *DPCR1*, *MUC21*, *PBMUCL1*, and *PBMUCL2* are all mucin or mucin-like genes [38, 40, 41] is highly relevant for the excessive airway mucus secretion that is typical in DPB. The HLA system contributes to appropriate immune responses through T-cell receptors, and thus, genetic predisposition in this disease may also involve defective immunity in the airways. Together with the number of familial cases, the high rate observed for current or past history of chronic sinusitis, and systematic failure of respiratory defense mechanisms, genetic susceptibility in the development and progression of DPB is quite possible.

Transmural and peribronchial infiltration by lymphocytes, the presence of plasma cells and lipid-engulfed foamy macrophages around the small airways, and large numbers of neutrophils and hypersecretion of mucus due to persistent bacterial infection in the large airways are the major characteristic aspects of DPB (Fig. 6.6). It is assumed that defective immunity caused by genetic predisposition results in both the persistent bacterial infection and the associated inflammatory disorders. It is generally accepted that key players in the development of DPB are neutrophils and T-lymphocytes, especially CD8+ cells, and cytokines such as interleukin 8 (IL-8) and macrophage inflammatory protein 1 (MIP-1). Cross sections of autopsied lung tissue from DPB patients show yellow nodules, mainly in the respiratory bronchioles [42]. Interstitial accumulation of foamy macrophages in the walls of the respiratory bronchioles and the surrounding interalveolar spaces (Fig. 6.7a) and thickened bronchiolar walls infiltrated by inflammatory cells (Fig. 6.7b) are found

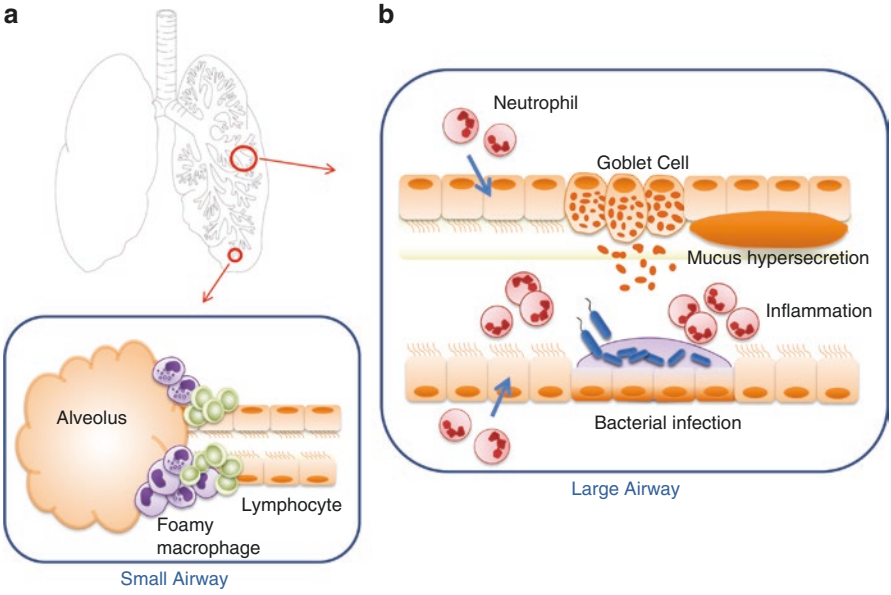


Fig. 6.6 Schematic representation of pathology of diffuse panbronchiolitis. Typical features seen include transmural accumulations of foamy macrophages, lymphocytes, and plasma cells in the small airways. The adjacent alveolar area tends not to be affected. Bacterial infections, along with a large number of neutrophils and mucus hypersecretion, are seen in large airways

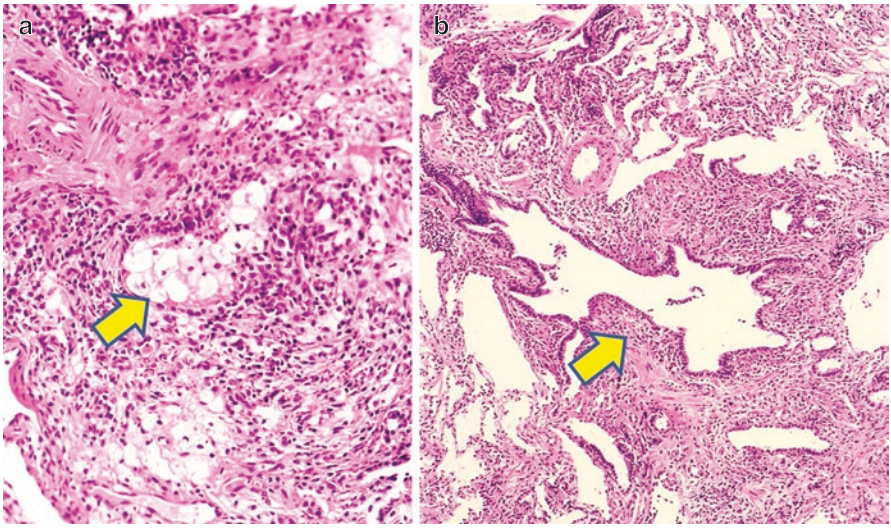


Fig. 6.7 (**a**) A respiratory bronchiole with the thickened wall infiltrated by inflammatory cells. (**b**) Interstitial accumulations of foamy macrophages in the wall of the respiratory bronchiole

in transbronchial lung biopsies from DPB patients. These histological features represent one of the distinctive characteristics of DPB [35], but their clinical significance remains uncertain.

6.5 Conclusion

CF and PCD are both hereditary disorders of mucociliary clearance that result in chronic upper and lower airways disease. In DPB, it is thought that genetic factors may determine disease susceptibility.

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