_____

1. Introduction

This document is one of a series related to Cystic Fibrosis (CF) that have been published by WHO since 1983. Most documents report joint meetings and workshops organized by WHO in association with various organizations devoted to CF, including the International Cystic Fibrosis (Mucoviscidosis) Association (ICFMA) now Cystic Fibrosis Worldwide, the Cystic Fibrosis Foundation (CFF), the European Cystic Fibrosis Thematic Network (ECFTN) and the European Cystic Fibrosis Society (ECFS). The meetings considered a range of topics including the Distribution of CF, Prospects for Treatment, Prevention of CF, Delivery of Health Care for CF in Developing Countries, Health Care Services for Adults with CF and, most recently, proposed a Classification of Cystic Fibrosis and Related Disorders [1].

The present document should be read in the light of its predecessors. It does not revisit areas, such as the diagnosis of CF, which remains clinical [1]. Rather, it attempts to set out what is known about the worldwide epidemiology of CF and related disorders. Thus, a meeting was convened to consider worldwide relevance of current clinical and genetic knowledge of CF in its various forms, and how the latter affect different populations. The report is intended to provide a point of reference for national and international health organizations, and to help them in planning diagnostic, advisory and therapeutic services for affected patients and their families.

2. Background

CF is a common autosomal recessive disorder usually found in populations of white Caucasian descent, such as those of Europe, North America and Australasia. CF is caused by mutations in the *CFTR* (Cystic Fibrosis Transmembrane conductance Regulator) gene. Each individual inherits one *CFTR* gene from his father and one *CFTR* gene from his mother, both genes are called *CFTR* alleles. Since CF is a recessive disease, CF will develop when deleterious mutations are found on both *CFTR* alleles. When a deleterious mutation is found on one *CFTR* allele, the individual is called a CF carrier. More than 1000 CF-causing *CFTR* mutations have been found (http://genet.sickkids.on.ca/cgi-bin/WebObjects/MUTATION). A CF patient can carry an identical CF-causing *CFTR* mutation on both *CFTR* alleles, or two different CF-causing *CFTR* mutations on both *CFTR* alleles.

While the earliest clear medical descriptions date from the 1930s [1], CF obviously existed prior to this date though had remained unrecognized. Its clinical features individually resemble those of other diseases such as pneumonia, bronchiectasis, asthma, failure to thrive, and coeliac disease. Indeed, where these conditions are prevalent CF may still lie unrecognized. Moreover, if clinicians believe that CF is absent from their population they will not consider it in a differential diagnosis. A better awareness of CF and the increasing availability of diagnostic tests - the sweat test and/or DNA tests - frequently leads to the identification of a higher number of affected individuals.

In the last two decades, CF has been increasingly diagnosed in Latin America, the Middle East, and populations derived from the Indian subcontinent that have emigrated to Western Europe, thus implying the presence of CF in significant numbers among the citizens of India and Pakistan who have remained in their homelands.

Reports from South Africa show the presence of CF in persons of pure African descent, thus demonstrating that the earlier observation of the presence of *CFTR* mutations in African Americans was not simply due to a mixture of European genes [2].

A small proportion of CF patients (<3 %) remains undiagnosed until adulthood [3]. Late CF diagnosis is mainly caused by the delayed expression and mild progression of clinical symptoms. It is associated with

_____

milder pulmonary disease, less pancreatic insufficiency, and the presence of milder *CFTR* mutations. Patients with late diagnosis have a better prognosis than those diagnosed early.

In the populations of Western Europe, North America and Australasia, there has been a significant increase in survival of CF patients during the last 2-3 decades, resulting in ageing CF populations. There are at least two reasons that account for this. First, the improvement in patient care and disease management and, secondly, improved diagnosis of CF may have included a higher proportion of mild or atypical cases. Moreover, neonatal screening, cascade screening, and prenatal diagnosis of *CFTR* mutations are expected to change the incidence of CF in time, as has been shown for the Brittany region in France, where a decrease of 30% in CF incidence has been observed during the last 10 years [4].

The identification of the *CFTR* gene in 1989 [5], the gene defective in CF, has been followed by the recognition of CF-related conditions which do not amount to "classical" CF, but have one or more of its characteristic features, e.g. congenital bilateral absence of the vas deferens (CBAVD), disseminated bronchiectasis, chronic pancreatitis, diffuse panbronchiolitis [1].

More than a decade has passed since the *CFTR* gene was identified, and more than 1200 mutations have been reported. It is therefore timely to review and assess what is known about the epidemiology of CF and its CF-related disorders worldwide.

3. Phenotypic variation in CF

Despite the sophisticated molecular technology available in genetic laboratories, CF remains a clinical diagnosis [1]. "Classical" CF is characterized by progressive lung disease, pancreatic dysfunction, elevated sweat electrolytes, and male infertility [1]. However, a wide variability in the clinical expression is found among patients. Up to 20% of affected infants are born with intestinal obstruction and present inspissated meconium (meconium ileus). Other patients are diagnosed with various modes of presentation from birth to adulthood and with considerable variability in the severity and rate of disease progression. Although progressive lung disease is the most common cause of mortality in CF, there is great variability in the age of onset and severity of lung disease in different age groups. Even within the same *CFTR* genotype, there is evidence that other genes, as well as environmental factors, make important contributions to the pulmonary phenotype.

The extent of pancreatic disease also varies. Most affected individuals suffer from pancreatic insufficiency (pancreatic insufficient CF, PI), but up to 15% of patients possess sufficient exocrine pancreatic function to permit normal digestion and are called pancreatic sufficient (PS). A small group of patients present typical, but usually relatively mild CF symptoms but have normal/borderline sweat tests, which are then referred to as "atypical CF". Variability is also found in male infertility. Almost all CF male patients are infertile due to congenital bilateral absence of the vas deferens (CBAVD); however occasional fertile CF male patients have been reported. The population incidence of CF varies between countries, and between ethnic groups within the same country (Table 1, Figure 1).

4. CF incidence and *CFTR* mutations

The spectrum and distribution of CF-causing *CFTR* mutations world-wide are given in Figure 2 and Table 2 (see poster insert). Data for sub-regions are given in Table 3 where only frequencies of *CFTR* mutations causing CF are given. These frequencies found in CF patients are unsuitable for calculating the frequencies of these mutations in the general population or other *CFTR*-related diseases.

_____

4.1 Europe

The incidence of CF is well documented in Europe. On average 1 in 2000-3000 new-borns are affected with CF. Even where populations appear relatively homogeneous, there may be marked local and regional variations. In France, for example, there is a very high incidence of CF in Northwest Brittany and a lower incidence in the South [6].

CFTR gene mutations have been well characterized in most European populations. In several Western-European countries, mutations are detected in more than 95% of the *CFTR* genes derived from CF patients.

The F508del *CFTR* mutation is the most common mutation causing CF. F508del. Frequencies vary from a maximum of 100% in the isolated Faroe Islands of Denmark, to a minimum of about 20% in Turkey. In central, northern, western, and north-eastern Europe, F508del has a frequency of about 70%.

Apart from F508del, 5 to 10 relatively frequent mutations contribute to 10%-15% of all CF-causing *CFTR* mutations, such as the G542X, N1303K, and G551D mutations. The G542X and N1303K mutations are most common in Mediterranean countries. Ethnic specific mutations are observed in some populations such as the Nordic mutation 394delTT, the 3905insT mutation in Switzerland, the R1162X mutation in Northeast Italy, and the Eastern Slavic CFTRdele2,3(21kb) mutation. The remaining mutations are heterogeneous, private, or limited to a small number of individuals.

4.2 Africa

There are no accurate CF prevalence figures for northern African countries bordering the Mediterranean, although small *CFTR* mutation detection studies have been done in Algeria and Tunisia, showing largely European mutations such as F508del, G542X and N1303K, albeit at different frequencies. Some unique mutations were identified in these populations.

The identification of *CFTR* mutations in individuals of sub-Saharan African origin presents evidence that CF is relatively common in Africa and is vastly under-diagnosed. The only systematic study comparing Causian Americans and African Americans concluded that the clinical manifestations are similar, and that the only difference was poorer nutrition in the African Americans [7]. The *CFTR* mutation profile in sub-Saharan Africans has revealed a common African mutation, 3120+1G$\rightarrow$A, which is found on about 46% of the *CFTR* alleles derived from patients [8]. Several rare mutations were also found, while the F508del mutation was not detected. In southern Africa there is a corrected carrier frequency of 1 in 42, with a calculated expected incidence of CF of 1 in 7056 in healthy Africans with little or no European admixture.

4.3 North America

The incidence of CF, based on derivative populations, is about 1 in 3500 in North America [9]. The *CFTR* mutations reflect the geographic origin of a current population with a strong relationship to Europe. About 10 CF-causing *CFTR* mutations are found at greater than 0.5% frequency in CF patients residing in the United States. These 10 mutations account for 79.7% of the identified CF-causing *CFTR* mutations.

The African *CFTR* mutation 3120+1G$\rightarrow$A is the second most prevalent allele in African American CF patients and is second only to the F508del mutation, which presumably emerged via ethnic admixture with Caucasians. Complete analysis of *CFTR* genes from African American CF patients allowed the detection of a mutation in 96% of the *CFTR* genes [2].

In Canada, most of the mutations again reflect a strong relation with the Caucasoid population of European origin. An important difference in ethnic origin is the proportion of populations tracing their origin to French or British ancestry. Therefore the mutations found in the respective regions of Canada reflect the ancestral French and British frequency. There is an east to west decrease in frequency of F508del, probably associated with increased ethnic diversity of the central and western Canadian populations, and a significant number of ethnic-specific rare mutations. Some mutations can reach higher frequencies in particular populations due to founder effects (e.g. M1101K in Hutterites [10]). A distinct mutation spectrum is also observed in the genetic isolate in the Saguenay-Lac St. Jean region of north-eastern Quebec where only three *CFTR* mutations (F508del, 58%; 621+1G→T, 23% and A455E, 8%) account for 89% of all *CFTR* alleles of CF patients [11].

4.4 Latin America

Latin America's ethnic makeup is very heterogeneous. In countries like Uruguay and Argentina, about 90% of the population is Caucasoid, whereas in others, for example Mexico, Colombia or Chile, between 57% and 85% is Mestizo (Caucasoid + Amerindian admixture). In addition, in Uruguay, Ecuador, Colombia, Venezuela and Brazil, the presence of descendants of African origin is important, although its percentage does not exceed 10%. The incidence of CF ranges respectively from 1/3900 to 1/8500 neonates in Cuba [12] and Mexico [13].

The F508del mutation is the most frequent CF-causing *CFTR* mutation in Latin America, with the highest frequency found in countries that have a higher Caucasoid contribution (e.g. 59% in Argentina), and a lower frequency in countries with a lower Caucasian contribution (e.g. 29% in Chile). The spectrum of mutations in Latin Americans of European extraction mimics that of the major southern European exploratory nations. The spectrum of *CFTR* mutations in Mestizo is less defined. In Latin America, all mutations described for the first time were found only once, suggesting the absence of other frequent mutations in this region of the world and indicating that each country has its own set of private, rare mutations. For example, 14% and 25% respectively of the Colombian and Mexican *CFTR* alleles of CF patients are rare and are unique to that country. This shows that the history of CF in Latin America is as complex as it is in Europe and North America.

4.5 Middle East

The incidence of CF in the Middle East varies according to the ethnic background and the degree of consanguinity. Consanguinity is claimed to be about 65% in the Arab world. Estimates range from 1 in 2,560 to 1 in 15,876.

A few mutations in the Middle East are shared with many other regions in the world, i.e. F508del, N1303K, W1282X and 3120+1G>A. Although F508del is much more frequent in Europe than in the Middle East, it is relatively common in Israel and the Lebanon. On the other hand, 3120+1G>A is more frequent in individuals of African descent and may have spread from African to Arabic populations.

There are mutations that appear to be more widely spread throughout the Near and Middle East but are rarely observed elsewhere. In some cases, these more frequent mutations may be specific for a subset of the people in the Middle East defined by a common ethnic or religious background, e.g. Bedouin tribes in the case of I1234V, Muslim Arabs in case of CFTRdele2(ins186), Christian Arabs in case of 4010delTAAT, the S549R(T>G) mutation in Bedouins from the United Arab Emirates and Oman, the 548A>T mutation in Bahrain, and the 1548delG mutation in Saudi Arabia [14-19].

_____

Thus, CF further illustrates that, in addition to its indigenous founder mutations, the geographic location and ethnic admixture has made the Middle East a "melting pot" of different genetic influences from outside and over time.

4.6 Asia

CF is normally rare in Asians and there are few reports of CF affected people of Asian origin. The exact incidence is not known but the predicted incidence for Asians in the United Kingdom (mainly Indian/Pakistani) is 1 in 10,000 [20] and 1 in 40,000 in the USA [21]. In India, the CF incidence is estimated to be 1 in 40,000 to 100,000 live births (S. Kabra, 2002, unpublished). In Japan, the estimated incidence is 1 in 100,000 to 350,000 live births, but is likely to be higher than anticipated (K. Yoshimura, 2002, unpublished).

There is limited information available from most Asian countries. According to the United Kingdom CF database, 88 (1.67%) out of 5,274 children with CF were from the Indian subcontinent, 63 were Pakistani, 12 Indian, 7 Bangladeshi, and 6 from other Asian regions (A. Mehta, 2002, unpublished). CF definitely exists in the Indian subcontinent but is probably less common than in Europe.

The frequency of F508del reaches about 60% in Pakistani CF patients, but is much lower in Indian (about 20%) and Japanese patients (about 10%). In 36 Asian CF patients in the United Kingdom (26 Southern Asians and 10 Central Asians), 26% were homozygous for F508del [22]. There are other rarer *CFTR* mutations in the Indian population, but no second frequent mutation could be detected, possibly because of the highly heterogeneous nature of the population. Although a limited number of patients have been studied, no single mutation has a frequency higher than 15%. In studies of Pakistani patients, some rarer mutations appear to be relatively frequent, however they are mostly found in homozygous state because of consanguinity [23]. In Japan, no mutation frequent for clinically diagnosed CF has been found.

4.7 Oceania

Given the historical emigration of Europeans to this region, the distribution of *CFTR* mutations reflects the European distribution of *CFTR* mutations.

5. CF-related disorders

Mutations in the *CFTR* gene are also involved in diseases that share part of the CF symptoms, such as CBAVD, obstructive azoospermia, disseminated bronchiectasis, diffuse panbronchiolitis, pulmonary emphysema, allergic bronchopulmonary aspergillosis, asthma, chronic pancreatitis and neonatal hypertrypsinaemia (Table 4). For some diseases, it should be noted that the discovery of an involvement of *CFTR* in disease is based on limited, or even single studies.

So far, most genetic studies of these *CFTR*-related diseases have been performed in Caucasian patients. There is little published information about the relative contribution of *CFTR* mutations to their incidence, compared with other genetic and environmental factors.

When *CFTR* is involved in this broader spectrum of *CFTR*-related disorders, many patients may carry a severe *CFTR* mutation on one *CFTR* allele. The spectrum of these severe *CFTR* mutations thus reflects the spectrum of mutations found in CF patients of the same population.

The other *CFTR* allele, or even both *CFTR* alleles, may carry a milder mutation that might be specific for the *CFTR*-related disease. Except for the IVS8-T5 polymorphism, these mutations are rather rare in the general population. The IVS8-T5 polymorphism is a mutation that can cause CBAVD, however with

_____

reduced penetrance. The IVS8-T5 polymorphism has a frequency of 5% in the Caucasian control population, while it has a frequency of 25% in CBAVD patients. When found in combination with other *CFTR* polymorphism(s) that reduce the amount of functional *CFTR*, a disease phenotype is very likely found [24]. The IVS8-T5 allele may also be involved in the other *CFTR*-related diseases. The percentage of *CFTR* genes that harbour a disease mutation varies between the different *CFTR*-related diseases. The highest proportion (79%) is found in CBAVD patients. In the other *CFTR*-related diseases, a lower proportion of mutations is found. In fact, the latter diseases may be multifactorial diseases in which *CFTR*, in some patients, might be one genetic component that contributes to the disease.

A different distribution of *CFTR* mutations is thus found in *CFTR*-related diseases compared to classic CF (Table 2). For example, the R117H *CFTR* mutation is found at a higher frequency in CBAVD patients compared to classic CF patients.

In non-Caucasian populations, data are scarce with regard to alleles conferring milder phenotypes such as CBAVD. The IVS8-T5 allele is a recurrent mutation in many populations, including the Middle East and East Asia. Data obtained for Jewish CBAVD patients, and studies from neighbouring countries such as Turkey and Egypt indicate that the IVS8-T5 allele, and probably certain other mild *CFTR* alleles, should be considered in these populations as well.

Of special interest is diffuse panbronchiolitis, which is a chronic inflammatory airway disease that affects East Asian populations exclusively. The respiratory manifestations are remarkably similar to those of CF. In Japan, a *CFTR* missense mutation or the IVS8-T5 allele was observed in 22% of the *CFTR* alleles derived from patients having diffuse panbronchiolitis.

6. Regions where CF appears to be under recognized

It is likely that cystic fibrosis and CF-related diseases are under-diagnosed in Latin America, Africa and the Indian continent due to the medical community's lack of knowledge of the disease, poor access to medical facilities and health care for CF patients, confounding diagnosis, a high infant mortality rate, and low life expectancy in general. Respiratory and gastro-intestinal problems associated with malnutrition are very common in developing countries, and the diagnosis of CF can therefore be missed due to a low index of suspicion.

In South Africa alone, it is expected that over 110 African CF babies are born annually. With an overall infant mortality rate of 52 per 1000, CF would only make up between 0.12 and 2.5% of the total. In South America, a lower incidence of CF is reported than one would expect on the basis of the frequency observed in Europeans and European migration to Latin America over the past 500 years. In India, based on a neonatal screening study of the F508del mutation, a carrier frequency of 1/50 to 1/66 was found. This has been calculated to produce as many infants affected with CF born annually as in the whole of Europe or North America (S. Kabra, 2002, unpublished).

CF disease is therefore clearly under-diagnosed in developing countries. In countries, such as Japan and the Gulf States of the Middle East, some under-diagnosis may exist, but most probably results from the medical community's lack of familiarity with CF. Under-representation of severe CF cases in some populations may modify the observed ratio of mild to severe cases. This could account for the unexplained low F508del incidence in some countries with a large proportion of Caucasians of European origin.

7. Regions, which appear to have no significant CF burden

The incidence of classic CF is less clear, but probably low in eastern Asia. It is rare in China and Japan, even in cities such as Hong Kong and Singapore where both western and eastern medicine is practised and

doctors are familiar with cystic fibrosis in Europeans. It is still possible that other factors, including genetic factors, may modify the phenotype in these populations, and the general medical community may not be sufficiently aware to detect a variant form of CF. On the other hand, the high incidence of CF elsewhere is explained by an heterozygote advantage in Caucasians. The low prevalence of CF in Asia may therefore be associated with the likely, but unproven scenario, that there are only a small number of CF-causing *CFTR* mutations in these populations because of the absence of a heterozygote advantage pressure in Asians.

The F508del mutation, which is the most common mutation in Europeans, is thought to be absent from east asian populations. However, the finding of Asian homozygous F508del CF patients in the United Kingdom [22] raises questions of whether the same mutation has arisen spontaneously in different populations, and why it should be so rare in east asians compared with its frequency in Europe, if the possibility of European input into the ancestry of these few Asian United Kingdom patients can indeed be ruled out.

On the other hand, CF-related diseases do exist in East Asia, and other *CFTR* mutations have been reported in some of them. Moreover, diffuse panbronchiolitis is exclusively found in east asian populations and a high proportion of the *CFTR* genes derived from such patients harbour a mutation. In this region, CFTR disease might possibly result in a diffuse panbronchiolitis phenotype, rather than a CF phenotype.

8. Other gene(s)

In many populations, mutation-screening assays of the complete coding region, and exon/intron junctions, of the *CFTR* gene have been performed permitting the detection of most *CFTR* mutations. However, the finding of a mutation in 100% of the *CFTR* genes analysed, is rarely observed. Even in most well characterized Northern European countries, a mutation cannot be identified in 1-3% of the *CFTR* genes (Table 2). In some populations the frequency of *CFTR* genes in which a mutation cannot be identified, even after extensive screening of the complete coding region and exon/intron junctions of the *CFTR* genes, is considerable: 25% in Turkey [25], 25% in Mexico [13] and 14% in Pakistan [23].

Possible explanations for failure to detect all mutations are: the diagnosis of cystic fibrosis is incorrect; the technique used for identifying mutations fails to detect the mutation e.g. the mutation is located deep in intronic regions of the *CFTR* gene or distant regulatory elements, or the mutation is caused by complete deletion or duplication of one or more exons, which are not detected with the screening protocols that are currently used; a combination of different *CFTR* mutations/polymorphisms causes a defective *CFTR* gene; the mutation is located in another gene than the *CFTR* gene, or a combination of these. Regarding the penultimate option, there have been reports that CF-like disease may occur which is not caused by defective *CFTR* [26,27].

9. *CFTR* mutation panels

For genetic testing and screening of *CFTR*, complete analysis of the *CFTR* gene is presently too laborious and expensive. In general, screening for selected mutations is routinely performed in genetic testing facilities.

In developed countries, the spectrum and distribution of *CFTR* mutations is well known. For genetic testing, a general rule would be that most common mutations that have been observed in the national or regional populations are those which are routinely screened. A typical cut-off would be to screen for all mutations having a frequency of 0.5%, or higher.

7

_____

In most European countries, when screening for the most frequent mutations (>0.5%) in a given population, a mutation will be identified in 90-95% of the *CFTR* genes derived from CF patients (Table 2). In large heterogeneous regions, such as North America, a cut-off of 0.1% would be more desirable; even then, no more than 88% of the mutations in *CFTR* genes in CF patients will be identified. A core mutation panel of 25 mutations has been recommended by the American College of Medical Genetics, which detects 83.7% of the mutations in *CFTR* genes of American CF patients [28]. It is clear that for individuals with a different ethnic background, the mutation panel relating to their region of genetic origin should be used. In addition, mutation panels developed for classic CF may miss several mutations that can be responsible for less severe CFTR-related diseases.

10. Recommendations

1. The spectrum and distribution of CF in developing countries is still not well known. It is therefore highly desirable to **collect this information** in order to improve the accuracy of the predicted incidence of CF, and to provide appropriate genetic services for CF patients and their families.

2. The **spectrum and distribution of CFTR mutations** in target populations should be defined by screening the complete *CFTR* gene in selected true CF patients (n=50-100) in a reliable laboratory. This will allow a suitable mutation panel to be set up, which can then be applied to determine the population incidence of CF and the *CFTR* mutations. This should be a priority in India and South Africa where there is good *prima facie* evidence that the true burden of CF is much greater than has been appreciated. Advanced research laboratories should be encouraged to collaborate with CF centers in developing countries by providing in-house *CFTR* screening on collected patients. Many past collaborations of this sort greatly contributed to the present knowledge of ethnic-specific mutation spectra.

3. Evidence of serious under-diagnosis of CF could most readily be obtained through (limited) **neonatal screening programmes**, particularly in countries where routine neonatal screening for conditions such as hypothyroidism is already being performed (some Latin American countries). Screening for the most common mutation(s) alone would allow the country to determine the approximate overall incidence of CF and *CFTR* mutations.

4. **Multicentre studies** may be more fruitful to delineate common mutations in eastern Asia. Indeed, from the Japanese experience it seems that a frequent mutation does not exist in east asian populations, in contrast to the Caucasian F508del mutation and black 3120+1G>A mutation. The finding of common mutation(s), although at a low frequency, in different Asian regions would be a prerequisite to determine the incidence of CF and *CFTR* mutations in this region of the world.

5. Insufficient knowledge of CF in the medical community in developing countries, as well as in non-Caucasian developed countries, contributes to the under-diagnosis of CF in these countries. Severe cases are missed because they die before the diagnosis has been considered. The medical community should therefore be made more aware of CF through the **teaching of CF to medical and other healthcare students and postgraduates**, so that typical and atypical cases (such as those presenting in adult life) can be correctly diagnosed and treated.

6. In some countries, poorly developed local laboratory services, a lack of experience of the optimal performance of the sweat test, and the unacceptable expense of DNA testing make it unlikely that the situation will improve in the near future. **National or regional reference laboratories** for sweat testing and genetic diagnosis, serving a large population, are therefore needed.

_____

7. **Cystic Fibrosis organizations** such as the American and Canadian CF Foundations, ECFTN, ECFS, the Latin American CF Association (LAFQ) and the Australasian CF Association would be sources of expert advice, and could facilitate the training of healthcare professionals.

8. **Genetic technology companies** should be encouraged to support these studies by providing suitable panels of mutations dependent on ethnic correlates, to enable these investigations to be performed in developing countries.

9. Genetic defects causing CF, **other than mutations in the coding region and exon/intron junctions of the CFTR gene, should be searched** for in populations where and after extensive screening, genes no mutation was identified in the *CFTR* coding region and their exon/intron junctions in a large percentage of *CFTR*. This will allow a more complete characterisation of the genetic defects in these populations, which may also be of relevance to other populations, especially in populations where no mutation can be identified on a rather small number of *CFTR* alleles and where such studies are difficult to undertake given the small sample size.

10. The incidence of CF-related diseases, or at least the proportion of these CF-related diseases in which CFTR is involved, is not well known. This is even true in the Caucasian populations. Except for CBAVD, CF-related disease incidence data are needed and further research encouraged, whether obtained from limited, or even single, small studies.

11. Where significant under-diagnosis of CF is demonstrated, appropriate responses from **governmental and professional** bodies are needed to ensure the delivery of reliable diagnostic, healthcare and advisory services to patients and their families.

11. List of Participants

Dr Calafell, Francesc. University 'Pompeu Fabra', Unitat de Biologia Evolutiva, Facultat de Ciències de la Salut i de la Vida, Doctor Aiguader 80, 08003 Barcelona, Catalonia, Spain.
Tel.: 34-93-542 28 41; Fax: 34-93-542 28 02; Email: Francesc.calafell@cexs.upf.es

Dr Cutting, Garry. Institute of Genetic Medicine, School of Medicine, The Johns Hopkins University, 600 North Wolfe Street, CMSC 1004, Baltimore, Maryland 21287-3914. USA
Email: gcutting@jhmi.edu

Dr Dodge, John **(Chairman)**. University of Wales Swansea, Child Health, Singleton Hospital, SA2 8QA Swansea, United Kingdom.
Tel.: 44-1792-205 666; Fax: 44-1792-285 244; Email: j.a.dodge@btinternet.com

Dr Des Georges, Marie. Public Health Hospital Medical School, Laboratoire de Génétique Moléculaire, Institut universitaire de recherche clinique, 641 Avenue du Doyen Gaston Giraud, 34093 Montpellier Cedex 5, France.
Tel.: 33-4-6741 5360; Fax.: 33-4-6741 5365; Email: marie.desgeorges@igh.cnrs.fr

Dr Dörk, Thilo. Hanover Medical School Clinic of Obstetrics and Gynaecology, Biochemistry and Tumour Biology, Podbielskistrasse 380, 30659 Hanover, Germany.
Tel.: 49-511-906 3911; Fax: 49-511-906 3433; Email: doerk.thilo@mh-hannover.de

Dr Durie, Peter. The Hospital for Sick Children, Division of Gastroenterology & Nutrition, Department of Pediatrics, 555 University Avenue, Room 1448, M5G 1X8 Toronto, Ontario, Canada.
Email: peter.durie@sickkids.ca

_____

Dr Eskandarani, Hamza. King Faisal University, College of Medicine, Department of Biochemistry 2114, 31451 Dammam, Saudi Arabia.
Tel.: 00966-5-582 1065; Fax: 00966-3-857 5329; Email: hamzahoo@yahoo.com

Dr Gruenert, Dieter. University of Vermont, Department of Medicine, Human Molecular Genetics., Burlington, VT 05405 , USA
Tel.: 1-802-656 8909; Fax: 1-802-656 8903; Email: dgruener@zoo.uvm.edu

Dr Kabra, Sushil. All India Institute of Medical Sciences, Department of Pediatrics; 110 029 Ansari Nagar, New Delhi, India.
Tel.: 91-11-659 3209; Fax: 91-11-686 2663; Email: skkabra@hotmail.com

Dr Keyeux, Genoveva. Instituto de Genética, Universidad Nacional de Colombia, Ciudad Universitaria, Bogota, Colombia.
Tel.: 57-1/316 50 00; Fax: 57-1/316 55 26; Email: gkeyeuxd@unal.edu.co

Dr Lewis, Peter. University of Bath, Department Medical Sciences Room 3E2.16 & Department of Mathematical Sciences, BA2 7AY Bath, United Kingdom.
Tel.: 44-1225 38 33 68; Fax: 44-1225 38 38 33; Email: P.A.Lewis@bath.ac.uk

Dr Macek, Milan Jr. Charles University, Inst. Of Biology & Med. Genetics, Department of Molecular Genetics, CF Center, V Uvalu 84, CZ 150 06 Prague, Czech Republic.
Tel.: 420-2-2443 9548; Fax.: 420-2-2443 3523; Email: milan.macek.jr@lfmotol.cuni.cz

Dr Modiano, Guido. University 'Tor Vergata', Department of Biology, Via della Ricerca scientifica, 00133 Roma, Italy.
Tel.: 39-06-725 94 341; Fax: 39-06-725 94 599; Email: modiano@bio.uniroma2.it

Dr Piazza, Alberto. University of Torino, Department of Genetics, Biology and Biochemistry via Santena 19, 10126 Torino, Italy.
Tel.: 39-11-670 6650; Fax: 39-11-670 6582; Email: alberto.piazza@unito.it

Dr Pignatti, Pier Franco. University of Verona, Department of Mother and Child – Biology and Genetics, Strada Le Grazie 8, 37134 Verona, Italy.
Tel.: 39-045-58 46 02; Fax: 39-045-80 98 180; Email: pierfranco.pignatti@univr.it

Dr Pivetta, Omar. Humboldt 1885, 1414 Buenos Aires, Argentina.
Tel.: 541-801 2326; Fax: 541-775 6050; Email: opivetta@hotmail.com

Dr Ramsay, Michele. National Health Laboratory Service and The University of the Witwatersrand, Department of Human Genetics, Johannesburg, South Africa.
Tel.:27 11 489 9214; Fax:27 11 489 9226; Email: michele.ramsay@nhls.ac.za

Dr Super, Maurice. Royal Manchester Children's Hospital, Clinical Genetics & CF Clinic, Hospital Road Pendlebury, M27 4HA Manchester, United Kingdom.
Tel.: 44-161-727 23 35; Fax: 44-161-727 23 33; Email: Maurice.super@man.ac.uk

Dr Yoshimura, Kunihiko. Department of Respiratory Medicine, Toranomon Hospital, 2-2-2 Toranomon, Minato-ku, 105-8470 Tokyo, Japan.
Tel.: 81-3-3588-1111 (ext.2012); Fax: 81-3-3582-7068; Email: kuniyosh@toranomon.gr.jp

_____

Dr Zielenski, Julian. The Hospital for Sick Children, Department of Genetics, 555 University Avenue , M5G 1X8 Toronto, Ontario, Canada.
Email: julian@genet.sickkids.on.ca

ECFTN representatives

Dr Cassiman, Jean-Jacques. KULeuven, Department for Human Genetics, Herestraat 49, 0&N6, 3000 Leuven, Belgium.
Tel.: 32-16-34 58 60; Fax: 32-16-34 59 97; Email: jean-jacques.cassiman@med.kuleuven.ac.be

Dr Cuppens, Harry (**Rapporteur**). KULeuven, Department for Human Genetics, Herestraat 49, 0&N6, 3000 Leuven, Belgium;
Tel.: 32-16-34 60 77 ; Fax: 32-16-34 59 97; Email: harry.cuppens@med.kuleuven.ac.be

WHO representative

Dr Boulyjenkov, Victor. Human Genetics Programme, Management of Noncommunicable Diseases, World Health Organization (WHO), 1211 Geneva, Switzerland.
Tel.: 41-22-791 3442; Fax: 41-22-791 4769; Email: boulyjenkovv@who.ch

ICF(M)A representatives

Dr Götz, Manfred. Wilhelminenhospital, Abt. f. Kinder- und Jugendheilkunde mit Infektionskrankheiten, Montleartstrasse 37, A1171 Vienna, Austria.
Tel.: 431-491-50 2808; Fax: 431-491-50 2809; Email: manfred.goetz@kif.wil.magwien.gv.at

Mrs Heidet, Liliane. WHO/ICFMA, Chemin de la Montagne 124, 1224 Chene Bougeries, Switzerland.
Tel.: 41-22-348 9452; Email: liliane.heidet@bluewin.ch

Mr Silver, Enrique. Vice-President of the ICF(M)A, Marne 3389, 11600 Montevideo, Uruguay.
Tel./Fax: 598-2-208-6849; Email: esilver@netgate.com.uy

Mr Weggen, Herman. Cystic Fibrosis Worldwide, P.O. Box 677, 5600 AR Eindhoven, Netherlands.
Tel : 31-492-599 069; Fax: 31-492-599 068. Email: president@cfww.org

Observers

Dr Kabra, Madhulika. All India Institute of Medical Sciences, Department of Pediatrics, Division of Genetics, 110 029 New Delhi, India.
Email: madhulikakabra@hotmail.com

Dr Romano, Luca. Istituto Gaslini, L.go gaslini 1, 16147 Genoa, Italy.
Tel.:39-10-563 6646; Fax: 39-10-377 3210; E-mail: lromano@mclink.it

_____

12. References

[1]   Dequeker, E., Accurso, F., Cabeza, S., Cassiman, J.-J., Corey, M., Davidson, A., Döring, G., Heidet, L., Heijerman, H., Kotsimbos, T., Mastella, G., Morrison, C., Pignatti, P.F., Strandvik, B., Tsui, L.-C. and Dodge, J. (2002) Classification of cystic fibrosis and related disorders. *J Cystic Fibrosis* 1, 5-8.

[2]   Macek, M., Jr., Mackova, A., Hamosh, A., Hilman, B.C., Selden, R.F., Lucotte, G., Friedman, K.J., Knowles, M.R., Rosenstein, B.J. and Cutting, G.R. (1997) Identification of common cystic fibrosis mutations in African-Americans with cystic fibrosis increases the detection rate to 75%. *Am J Hum Genet* 60, 1122-1127.

[3]   Gan, K.H., Geus, W.P., Bakker, W., Lamers, C.B. and Heijerman, H.G. (1995) Genetic and clinical features of patients with cystic fibrosis diagnosed after the age of 16 years. *Thorax* 50, 1301-1304.

[4]   Scotet, V., Audrezet, M.P., Roussey, M., Rault, G., Blayau, M., De Braekeleer, M. and Ferec, C. (2003) Impact of public health strategies on the birth prevalence of cystic fibrosis in Brittany, France. *Hum Genet* 113, 280-285.

[5]   Riordan, J.R., Rommens, J.M., Kerem, B.-S., Alon, N., Rozmahel, R., Grzelczak, Z., Zielenski, J., Lok, S., Plavsic, N., Chou, J.-L., Drumm, M.L., Iannuzzi, M.C., Collins, F.S. and Tsui, L.-C. (1989) Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. *Science* 245, 1066-1073.

[6]   Claustres, M., Guittard, C., Bozon, D., Chevalier, F., Verlingue, C., Ferec, C., Girodon, E., Cazeneuve, C., Bienvenu, T., Lalau, G., Dumur, V., Feldmann, D., Bieth, E., Blayau, M., Clavel, C., Creveaux, I., Malinge, M.C., Monnier, N., Malzac, P., Mittre, H., Chomel, J.C., Bonnefont, J.P., Iron, A., Chery, M. and Georges, M.D. (2000) Spectrum of CFTR mutations in cystic fibrosis and in congenital absence of the vas deferens in France. *Hum Mutat* 16, 143-156.

[7]   Hamosh, A., Fitz-Simmons, S.C., Macek, M., Jr., Knowles, M.R., Rosenstein, B.J. and Cutting, G.R. (1998) Comparison of the clinical manifestations of cystic fibrosis in black and white patients. *J Pediatr* 132, 255-259.

[8]   Goldman, A., Labrum, R., Claustres, M., Desgeorges, M., Guittard, C., Wallace, A. and Ramsay, M. (2001) The molecular basis of cystic fibrosis in South Africa. *Clin Genet* 59, 37-41.

[9]   Kosorok, M.R., Wei, W.H. and Farrell, P.M. (1996) The incidence of cystic fibrosis. *Stat Med* 15, 449-462.

[10]   Zielenski, J., Fujiwara, T.M., Markiewicz, D., Paradis, A.J., Anacleto, A.I., Richards, B., Schwartz, R.H., Klinger, K.W., Tsui, L.C. and Morgan, K. (1993) Identification of the M1101K mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene and complete detection of cystic fibrosis mutations in the Hutterite population. *Am J Hum Genet* 52, 609-615.

[11]   Rozen, R., De Braekeleer, M., Daigneault, J., Ferreira-Rajabi, L., Gerdes, M., Lamoureux, L., Aubin, G., Simard, F., Fujiwara, T.M. and Morgan, K. (1992) Cystic fibrosis mutations in French Canadians: three CFTR mutations are relatively frequent in a Quebec population with an elevated incidence of cystic fibrosis. *Am J Med Genet* 42, 360-364.

[12]   Collazo, T., Magarino, C., Chavez, R., Suardiaz, B., Gispert, S., Gomez, M., Rojo, M. and Heredero, L. (1995) Frequency of delta-F508 mutation and XV2C/KM19 haplotypes in Cuban cystic fibrosis families. *Hum Hered* 45, 55-57.

[13]   Orozco, L., Velazquez, R., Zielenski, J., Tsui, L.C., Chavez, M., Lezana, J.L., Saldana, Y., Hernandez, E. and Carnevale, A. (2000) Spectrum of CFTR mutations in Mexican cystic fibrosis patients: identification of five novel mutations (W1098C, 846delT, P750L, 4160insGGGG and 297-1G-->A). *Hum Genet* 106, 360-365.

[14]   el-Harith, E.A., Dork, T., Stuhrmann, M., Abu-Srair, H., al-Shahri, A., Keller, K.M., Lentze, M.J. and Schmidtke, J. (1997) Novel and characteristic CFTR mutations in Saudi Arab children with severe cystic fibrosis. *J Med Genet* 34, 996-999.

_____

[15] Banjar, H., Kambouris, M., Meyer, B.F., al-Mehaidib, A. and Mogarri, I. (1999) Geographic distribution of cystic fibrosis transmembrane regulator gene mutations in Saudi Arabia. *Ann Trop Paediatr* 19, 69-73.

[16] Kambouris, M., Banjar, H., Moggari, I., Nazer, H., Al-Hamed, M. and Meyer, B.F. (2000) 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* 159, 303-309.

[17] Frossard, P.M., Dawson, K.P., Das, S.J., Alexander, P.C., Girodon, E. and Goossens, M. (2000) Identification of cystic fibrosis mutations in Oman. *Clin Genet* 57, 235-236.

[18] Abdul Wahab, A., Al Thani, G., Dawod, S.T., Kambouris, M. and Al Hamed, M. (2001) Heterogeneity of the cystic fibrosis phenotype in a large kindred family in Qatar with cystic fibrosis mutation (I1234V). *J Trop Pediatr* 47, 110-112.

[19] Eskandarani, H.A. (2002) Cystic fibrosis transmembrane regulator gene mutations in Bahrain. *J Trop Pediatr* 48, 348-350.

[20] Goodchild, M.C., Insley, J., Rushton, D.I. and Gaze, H. (1974) Cystic fibrosis in 3 Pakistani children. *Arch Dis Child* 49, 739-741.

[21] Powers, C.A., Potter, E.M., Wessel, H.U. and Lloyd-Still, J.D. (1996) Cystic fibrosis in Asian Indians. *Arch Pediatr Adolesc Med* 150, 554-555.

[22] Callaghan, B.D., Carr, S., Balfour-Lynn, I. and Dinwiddie, R. (2002) Do asian cystic fibrosis patients have more severe disease than their caucasian peers in childhood? *Pediat Pulm* sp.24, 329-329.

[23] Malone, G., Haworth, A., Schwarz, M.J., Cuppens, H. and Super, M. (1998) Detection of five novel mutations of the cystic fibrosis transmembrane regulator (CFTR) gene in Pakistani patients with cystic fibrosis: Y569D, Q98X, 296+12(T>C), 1161delC and 621+2(T>C). *Hum Mutat* 11, 152-157.

[24] Cuppens, H., Lin, W., Jaspers, M., Costes, B., Teng, H., Vankeerberghen, A., Jorissen, M., Droogmans, G., Reynaert, I., Goossens, M., Nilius, B. and Cassiman, J.J. (1998) Polyvariant mutant cystic fibrosis transmembrane conductance regulator genes - The polymorphic (TG)m locus explains the partial penetrance of the T5 polymorphism as a disease mutation. *J Clin Invest* 101, 487-496.

[25] Kilinc, M.O., Ninis, V.N., Dagli, E., Demirkol, M., Ozkinay, F., Arikan, Z., Cogulu, O., Huner, G., Karakoc, F. and Tolun, A. (2002) Highest heterogeneity for cystic fibrosis: 36 mutations account for 75% of all CF chromosomes in Turkish patients. *Am J Med Genet* 113, 250-257.

[26] Mekus, F., Ballmann, M., Bronsveld, I., Dörk, T., Bijman, J., Tümmler, B. and Veeze, H.J. (1998) Cystic-fibrosis-like disease unrelated to the cystic fibrosis transmembrane conductance regulator. *Hum Genet* 102, 582-586.

[27] Groman, J.D., Meyer, M.E., Wilmott, R.W., Zeitlin, P.L. and Cutting, G.R. (2002) Variant cystic fibrosis phenotypes in the absence of CFTR mutations. *N Engl J Med* 347, 401-407.

[28] Bobadilla, J.L., Macek, M., Jr, Fine, J.P. and Farrell, P.M. (2002) Cystic fibrosis: a worldwide analysis of CFTR mutations--correlation with incidence data and application to screening. *Hum Mutat* 19, 575-606.

[29] Feuillet-Fieux, M.N.F., Ferrec, M.F., Gigarel, N.G., Boree, D.B., Sermet, L.S., Lenoir, G.L., Thuillier, L.T. and Bonnefont, J.P.B. (2003) Identification of four novel mutations in black CF patients. *J Cystic Fibrosis* 2, S8-S8.

[30] Jarvi, K., Zielenski, J., Wilschanski, M., Durie, P., Buckspan, M., Tullis, E., Markiewicz, D. and Tsui, L.C. (1995) Cystic fibrosis transmembrane conductance regulator and obstructive azoospermia. *Lancet* 345, 1578.

[31] Girodon, E., Cazeneuve, C., Lebargy, F., Chinet, T., Costes, B., Ghanem, N., Martin, J., Lemay, S., Scheid, P., Housset, B., Bignon, J. and Goossens, M. (1997) CFTR gene mutations in adults with disseminated bronchiectasis. *Eur J Hum Genet* 5, 149-155.

[32] Bombieri, C., Benetazzo, M., Saccomani, A., Belpinati, F., Gilè, L.S., Luisetti, M. and Pignatti, P.F. (1998) Complete mutational screening of the *CFTR* gene in 120 patients with pulmonary disease. *Hum Genet* 103, 718-722.

[33] Tzetis, M., Efthymiadou, A., Strofalis, S., Psychou, P., Dimakou, A., Pouliou, E., Doudounakis, S. and Kanavakis, E. (2001) CFTR gene mutations--including three novel nucleotide substitutions--and haplotype background in patients with asthma, disseminated bronchiectasis and chronic obstructive pulmonary disease. *Hum Genet* 108, 216-221.

[34] Miller, P.W., Hamosh, A., Macek, M., Jr., Greenberger, P.A., MacLean, J., Walden, S.M., Slavin, R.G. and Cutting, G.R. (1996) Cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations in allergic bronchopulmonary aspergillosis. *Am J Hum Genet* 59, 45-51.

[35] Lazaro, C., de Cid, R., Sunyer, J., Soriano, J., Gimenez, J., Alvarez, M., Casals, T., Anto, J.M. and Estivill, X. (1999) Missense mutations in the cystic fibrosis gene in adult patients with asthma. *Hum Mutat* 14, 510-519.

[36] Wang, X.J., Moylan, B., Leopold, D.A., Kim, J., Rubenstein, R.C., Togias, A., Proud, D., Zeitlin, P.L. and Cutting, G.R. (2000) Mutation in the gene responsible for cystic fibrosis and predisposition to chronic rhinosinusitis in the general population. *J Am Med* Ass 284, 1814-1819.

[37] Castellani, C., Benetazzo, M.G., Tamanini, A., Begnini, A., Mastella, G. and Pignatti, P. (2001) Analysis of the entire coding region of the cystic fibrosis transmembrane regulator gene in neonatal hypertrypsinaemia with normal sweat test. *J Med Genet* 38, 202-205.

[38] Sharer, N., Schwarz, M., Malone, G., Howarth, A., Painter, J., Super, M. and Braganza, J. (1998) Mutations of the cystic fibrosis gene in patients with chronic pancreatitis. *New Engl J Med* 339, 645-652.

[39] Cohn, J.A., Friedman, K.J., Noone, P.G., Knowles, M.R., Silverman, L.M. and Jowell, P.S. (1998) Relation between mutations of the cystic fibrosis gene and idiopathic pancreatitis. *New Engl J Med* 339, 653-658.

[40] Girodon, E., Sternberg, D., Chazouilleres, O., Cazeneuve, C., Huot, D., Calmus, Y., Poupon, R., Goossens, M. and Housset, C. (2002) Cystic fibrosis transmembrane conductance regulator (CFTR) gene defects in patients with primary sclerosing cholangitis. *J Hepatol* 37, 192-197.

[41] Sheth, S., Shea, J.C., Bishop, M.D., Chopra, S., Regan, M.M., Malmberg, E., Walker, C., Ricci, R., Tsui, L.C., Durie, P.R., Zielenski, J. and Freedman, S.D. (2003) Increased prevalence of CFTR mutations and variants and decreased chloride secretion in primary sclerosing cholangitis. *Hum Genet* 113, 286-292.

Acknowledgement

Table 1: Incidence of cystic fibrosis

COUNTRY	INCIDENCE (1 CASE PER X BIRTHS)
EUROPE	
Finland	**25,000**
Turkey	**<10,000**
Sweden	**7,300**
Poland	**6,000**
Northern Ireland (United Kingdom)	**5,350**
Russian Federation	**4,900**
Denmark	**4,700**
Estonia	**4,500**
Norway	**4,500**
Netherlands	**3,650**
Greece	**3,500**
Spain	**3,500**
Germany	**3,300**
Czech Republic	**2,833**
United Kingdom	**2,600**
Italy	**2,438**
France	**2,350**
Switzerland	**2,000**
Scotland (United Kingdom)	**1,984**
Ireland	**1,800**
USA	**3,500**
LATIN AMERICA	
Mexico	**8,500**
Brazil	**6,902**
Chile	**4,000**
Cuba	**3,900**
MIDDLE EAST	
United Arab Emirates	**15,876**
Bahrain	**5,800**
ASIA	
India	**40,000 - 100,000**
Japan	**100,000 - 350,000**
AFRICA	
South Africa (African population)	**7,056**
AUSTRALIA	**2,500**

_____

Table 3: Distribution and frequency of CF-causing *CFTR* mutations in specific sub-regions of countries

REGION	Detection rate (a) (n)	Number of mutations (b)	Detection rate of most frequent mutations (c)	Number of most frequent mutations (d)	Mutations (proportion) (e)
EUROPE					
Austria					
Austria (South-East: Styria)	0.807 (580)	25	0.773	11	F508del (0.621) / G542X (0.045) / CFTRdele2,3(21kb) (0.021) / R1162X (0.019) / R553X (0.017) / 457TAT>G (0.016) / G551D (0.012) 2183AA>G (0.007) / R117H, I148T, N1303K (0.005 each)
Austria (West: Tyrol)	1.000 (126)	14	1.000	14	F508del (0.746) / R1162X (0.087) / G542X, 2183AA>G, 2789+5G>A (0.024 each) / Q39X, R347P, G551D (0.016 each) *394delTT, L453del, 1717-1G>A, 1874insT-Y577F, M1101K, 4108delT (0.008 each)*
Austria (North-East + North-West)	0.907 (118)	10	0.907	10	F508del (0.703) / G542X (0.051) / 3849+10kbC>T (0.034) / R117H, R347P, G551D (0.025 each) 621+1G>T (0.017) / *I148T, 1248+1G>A, T1299I (0.008 each)*
Bulgaria					
Bulgaria (Bulgarians)	0.894 (405)	28	0.872	19	F508del (0.620) / N1303K (0.059) / G542X (0.042) / 1677delTA, R1070Q (0.020 each) / 3849+10kbC>T (0.015) G1244V+S912L (0.012) / 2184insA, W1282X (0.010 each) / G85E, Q220X, R347P, 2183AA>G, 2789+5G>A, 4374+1G>A (0.007 each) 306delTAGA, L88X(T>G) 1717-8A>G, G1244E (0.005 each)
Bulgaria (South-East; Turkish population)	*0.800 (60)*	9	0.800	9	F508del (0.533) / R347P (0.117) / Q220X (0.050) / *L137P, Q493R, 1677delTA, G542X, L571S, W1282X (0.017 each)*
Bulgaria (Roms)	*1.000 (41)*	2	1.000	2	F508del (0.980) / G542X (0.020)
France					
France (South-West: Aquitaine)	0.976 (212)	30	0.976	30	F508del (0.670) / G542X (0.047) / 1811+1.6kbA>G (0.038) / N1303K (0.028) / 1717-1G>A (0.024) / G85E, W1063X (0.014 each) 621+1G>T, 711+1G>T, A455E, I507del, 1717-8G>A, R1162X, S1235R (0.009 each) *D44G, R75X, E116K, R117H, L320X, R334W, Q414X, S492F, G551D, R553X, L558S (0.005 each)* *2789+5G>A, Y1092X(C>A), 3659delC, I1234V, 4005+1G>A (0.005 each)*
France (North-West: Caen)	0.972 (214)	41	0.972	41	F508del (0.668) / I507del (0.033) / G551D (0.023) / N1303K (0.019) / G542X, 2183AA>G, 2789+5G>A (0.014 each) 574delA, 1078delT, 1717-1G>A, S945L, R1162X, 3659delC (0.009 each) *237insA, E60X, G149R, 621+1G>T, H199Y, L206W, S364P, 1248+1G>A, S434X(TAA),*

REGION	Detection rate (a) (n)	Number of mutations (b)	Detection rate of most frequent mutations (c)	Number of most frequent mutations (d)	Mutations (proportion) (e)
France (West: Brittany)	0.997 (896)	62	0.3%: 0.938	0.3%: 20	*A455E, S466X(TAA) (0.005 each)* *Q493X, 1677delTA, R553X, E585X, D651H, G673X, R709X, E831X, W846X1, R851X, R1066C, Y1092X(C>A) (0.005 each)* *W1204X, 3849+10kbC>T, S1251N, 3905insT, 4006-1G>A (0.005 each)* F508del (0.750) / 1078delT (0.038) / G551D (0.037) / N1303K (0.013) / W846X1 (0.011) / 2789+5G>A (0.010) 1717-1G>A (0.009) / Y1092X(C>A) (0.008) / 4005+1G>A (0.008) / E60X, 621+1G>T, R347H (0.007 each) S492F, G542X, 3272-26A>G (0.006 each) / R117H (0.005) / G91R, I507del, R553X, W1282X (0.003 each)
France (Central-East: Grenoble)	0.946 (240)	31	0.867	12	F508del (0.688) / G542X, N1303K (0.046 each) / 3659delC (0.017) / R553X (0.013) 852del22, I507del, 2183AA>G, 2789+5G>A, 3600+11.5kbC>G, 3849+10kbC>T, W1282X (0.008 each)
France (South-East: Languedoc)	0.961 (406)	69	0.855	26	F508del (0.611) / G542X (0.052) / N1303K (0.025) / R334W (0.015) / 711+1G>T, 1717-1G>A (0.012 each) / 1811+1.6kbA>G (0.010) G85E, L206W, I507del, 2183AA>G, K710X, 2789+5G>A, S945L, Y1092X(C>A), R1158X, 3849+10kbC>T (0.007 each) Y122X, I175V, 1078delT, R347P, G551D, E585X, R1162X, 3737delA, W1282X (0.005 each)
France (Central: Lyon)	0.859 (1200)	47	0.3%: 0.830	0.3%: 19	F508del (0.689) / G542X (0.033) / N1303K (0.018) / W1282X (0.015) / 1717-1G>A (0.013) 2183AA>G (0.009) / R553X (0.008) / 711+1G>T (0.007) / R1162X (0.005) 1078delT, R334W, R347P (0.004 each) / G85E, I507del, G551D, K710X, Y1092X(C>A), 3659delC, 3905insT (0.003 each)
France (Central: Paris)	0.919 (470)	43	0.869	11	F508del (0.685) / G542X (0.045) / W1282X (0.021) / 1717-1G>A, R553X (0.017 each) / I507del (0.013) / N1303K (0.011) R117H, 3272-26A>G, S1235R, S1251N (0.006 each)
France (North-East: Rennes)	0.930 (298)	34	0.862	14	F508del (0.681) / G551D, N1303K (0.027 each) / 1078delT, G542X, 3272-26A>G (0.017 each) I507del (0.013) / Y1092X(C>A) (0.013) / G85E, 621+1G>T, 2789+5G>A (0.010 each) / F311L, 1248+1G>A, 1717-1G>A (0.007 each)
France (South-West: Toulouse)	0.944 (414)	50	0.867	18	F508del (0.643) / G542X (0.053) / N1303K (0.039) / 1811+1.6kbA>G (0.034) / 1717-1G>A (0.015) R334W (0.012) / R553X (0.010) / I507del, G551D, R792X, 4005+1G>A (0.007 each) 1717-8G>A, 2789+5G>A, Y1092X(C>A), R1162X, 3737delA, 3849+10kbC>T, 3905insT (0.005 each)
Germany					
Germany (South-East: Erlangen)	0.944 (250)	18	0.904	8	F508del (0.740) / G551D (0.064) / G542X (0.032) / N1303K (0.024) / 1717-1G>A (0.016) R553X (0.012) / R347P, 1342-2A>C (0.008 each)

REGION	Detection rate (a) (n)	Number of mutations (b)	Detection rate of most frequent mutations (c)	Number of most frequent mutations (d)	Mutations (proportion) (e)
Germany (East-Central: Leipzig)	0.995 (182)	16	0.995	16	F508del (0.742) / 3849+10kbC>T (0.038) / G551D, 2143delT (0.033 each) / R347P, CFTRdele2,3(21kb) (0.022 each) R117H, G542X, N1303K (0.016 each) / 394delTT, I507del, 2789+5G>A (0.011 each) *1717-1G>A, R553X, 2183AA>G, R1162X (0.005 each)*
Germany (Central: Hanover)	0.959 (1154)	76	0.15%: 0.920	0.15%: 31	F508del (0.719) / N1303K (0.025) / R553X (0.019) / R347P (0.018) / G542X (0.014) / CFTRdele2,3(21kb) (0.013) G551D, 3849+10kbC>T (0.012 each) / 1717-1G>A, 3272-26A>G (0.010 each) / 2789+5G>A (0.009) / 2143delT (0.007) 1078delT, I336K, 2183AA>G, W1282X (0.004 each) / R117H, R334W, 1342-2A>C, 2184insA, I1005R, Y1092X(C>A) (0.003 each) 3659delC (0.003) / E92X, 621+1G>T, I507del, 2184delA, 2991del32, R1066C, R1162X, S1251N (0.0015 each)
Germany (North: Mecklenburg)	0.832 (274)	15	0.803	7	F508del (0.679) / G542X, N1303K (0.033 each) CFTRdele2,3(21kb) (0.026) R553X (0.015) / R117H (0.011) / W1282X (0.007)
Germany (South-Central: Thuringia)	*0.897 (78)*	12	0.897	12	F508del (0.654) / 2789+5G>A (0.051) / 394delTT, G542X, R553X, 2183AA>G, CFTRdele2,3(21kb) (0.026 each) *G85E, R117H, R347P, G551D, 3849+10kbC>T (0.013 each)*
Germany (South-West: Neu-Ulm)	0.946 (386)	43	0.883	19	F508del (0.635) / N1303K (0.031) / R117H, G542X (0.026 each) / 1717-1G>A (0.023) / G551D (0.021) / M1101K (0.018) Q39X (0.016) / 2183AA>G, CFTRdele2,3(21kb) (0.013 each) / R553X, 3659delC (0.010 each) R347P, Y1092X(C>A) (0.008 each) / 2789+5G>A, R1162X, 3849+10kbC>T, 3905insT, W1282X (0.005 each)
Greece					
Greece (Northern: Thrace)	0.795 (132)	8	0.795	8	F508del (0.561) / 621+1G>T (0.121) / G542X (0.053) / R553X, E822X, N1303K (0.015 each) *R334W, 1717-1G>A (0.008 each)*
Greece (South-Central: Athens)	0.910 (874)	85	0.804	21	F508del (0.534) / 621+1G>T (0.057) / G542X (0.039) / N1303K (0.026) / 2789+5G>A (0.017) / 2183AA>G, E822X (0.014 each) R1158X (0.010) / 1677delTA, R1070Q (0.009 each) / G85E, R334W, W496X, 3272-26A>G (0.008 each) 711+3A>G, I507del, W1282X (0.007 each) / 574delA, 621+3A>G, 3120+1G>A (0.006 each) / D110H (0.005)
Italy					
Italy (South-East: Basciliata)	*0.923 (52)*	12	0.923	12	F508del (0.558) / 852del22, 2183AA>G (0.058 each) / G542X, G1244E, W1282X, N1303K (0.038 each) *1717-1G>A, S549R(A>C), L558S, Y849X, 3849+10kbC>T (0.019 each)*

REGION	Detection rate (a) (n)	Number of mutations (b)	Detection rate of most frequent mutations (c)	Number of most frequent mutations (d)	Mutations (proportion) (e)
Italy (South-East: Campania)	0.915 (340)	27	0.891	19	F508del (0.556) / N1303K (0.074) / G542X (0.050) / W1282X (0.035) / 1717-1G>A, 2183AA>G (0.024 each) / 4016insT (0.021) 711+1G>T, R553X, R1158X (0.015 each) / L1065P (0.012) / G1244E, 2522insC (0.009 each) G85E, I148T, G178R, E585X, 2789+5G>A, L1077P (0.006 each)
Italy (North-Central: Milano)	0.816 (1160)	67	0.3%: 0.779	0.3%: 30	F508del (0.500) / G542X (0.051) / N1303K (0.050) / 1717-1G>A (0.037) / 2183AA>G (0.015) / W1282X (0.014) R1158X (0.010) / D1152H (0.009) / R334W, R352Q, R553X, R1066H (0.008 each) 3849+10kbC>T (0.007) / R117H (0.005) / R347P, E585X, L1077P (0.004 each) M1V, G85E, D110E, 621+1G>T, G178R, E193K, T338I, D579G, 1898+1G>A, 2789+5G>A, F1052V, R1066C, 3659delC (0.003 each)
Italy (South-East: Plugia)	0.922 (374)	31	0.896	21	F508del (0.449) / N1303K (0.080) / G542X (0.072) / 4382delA (0.040) / 852del22 (0.032) / 1259insA (0.032) I502T, L1077P (0.019 each) / R553X, D579G, R1066C, 3849+10kbC>T, G1349D (0.016 each) R1158X, 4016insT (0.013 each) / 1717-1G>A (0.011) / R347P, 2183AA>G, 2789+5G>A (0.008 each) / G1244E, W1282X (0.005 each)
Italy (North-East:Veneto and Trentino-Alto Adige)	0.911 (225)	24	0.871	15	F508del (0.476) / R1162X (0.098) / 2183AA>G (0.093) / N1303K (0.040) / 711+5G>A, G542X (0.027 each) / 1717-1G>A (0.022) G85E, Q552X, R553X, 2789+5G>A (0.013 each) / 621+1G>T, 2790-2A>G, 3132delTG, W1282X (0.009 each)
Italy (Central: Rome)	0.867 (586)	37	0.809	13	F508del (0.558) / N1303K (0.087) / G542X (0.070) / W1282X (0.026) / S549R(A>C) (0.014) / 621+1G>T (0.012) / 1717-1G>A (0.009) G85E, R553X (0.007 each) / H139R, R347P, L1065P, L1077P (0.005 each)
Italy (Sardinia)	0.941 (186)	22	0.941	22	F508del (0.489) / T338I (0.151) / G542X, 2183AA>G (0.059 each) / N1303K (0.043) / 3849+10kbC>T (0.022) / G1244E (0.016) 991del5, 1706del17, 1717-1G>A, S912X (0.011 each) *S13F, G85E, 621+1G>T, 711+3A>G, L375F, 1601delTC, 2184insA, 2789+5G>A, H1054D, D1270N+R74W, 4016insT (0.005 each)*
Italy (North-East: Torino)	0.839 (316)	20	0.820	14	F508del (0.611) / G542X (0.051) / N1303K (0.035) / R347P, 2183AA>G, 2789+5G>A, R1162X (0.016 each) G85E, 1717-1G>A (0.013 each) / R117H (0.009) / 711+5G>A, R553X, S1235R, W1282X (0.006 each)
Italy (Central: Toscana)	0.775 (382)	19	0.762	14	F508del (0.455) / G542X, N1303K (0.050 each) / 2789+5G>A (0.037) / R347P (0.031) / 2183AA>G, L1065P (0.029 each) T338I, R553X (0.018 each) / W1282X (0.013) / G85E (0.010) / 1898+1G>A, 3849+10kbC>T (0.008 each) / 1717-1G>A (0.005)
Italy (North-East: Veneto)	0.904 (312)	29	0.869	18	F508del (0.487) / 2183AA>G, R1162X (0.074 each) / 711+5G>A (0.038) / N1303K (0.035) /1717-1G>A (0.026)

REGION	Detection rate (a) (n)	Number of mutations (b)	Detection rate of most frequent mutations (c)	Number of most frequent mutations (d)	Mutations (proportion) (e)
Italy (North-East: Friuli Venezia Giulia)	0.825 (126)	22	0.825	22	Q552X (0.019) / G85E, G542X, R553X, 2789+5G>A (0.016 each) / I507del (0.013) 621+1G>T, Q353X, 898+3A>G, 2790-2A>G, 3132delTG, W1282X (0.006 each) F508del (0.492) / N1303K (0.063) / G542X (0.048) / 2183AA>G (0.032) / 621+1G>T, 1717-1G>A, R1162X (0.024 each) *G85E, D110H, 677delTA, 711+1G>A, T338I, S466X(TAA), I507del, G551D, 2368del11, 2789+5G>A (0.008 each)* *F1052X, R1070Q, 3659delC, K1177R, 4016insT (0.008 each)*
Russian Federation					
Russian Federation (Central: Moscow)	0.743 (668)	21	0.731	13	F508del (0.534) / CFTRdele2,3(21kb) (0.057) / N1303K (0.027) / 2143delT, 2184insA (0.020 each) / G542X, W1282X (0.017 each) 3849+10kbC>T (0.011) / R334W (0.008) / 394delTT, 1677delTA, S1196X (0.006 each) / 3732delA (0.005)
Russian Federation (North: St. Petersburg)	0.707 (1706)	21	0.700	17	F508del (0.497) / CFTRdele2,3(21kb) (0.041) / 3821delT (0.025) / W1282X (0.022) / N1303K (0.016) / G542X (0.015) / 394delTT (0.012) 2143delT (0.011) / R553X (0.010) / R334W, 552insA (0.009 each) / 1677delTA (0.008) / S1196X (0.006) Y122X, 1366del5, 2184insA (0.005 each) / G551D (0.004)
Spain					
Spain (South: Andalucia)	0.683 (350)	8	0.683	8	F508del (0.434) / G542X (0.114) / R334W (0.049) / R1162X (0.029) / 2789+5G>A (0.023) / R117H, I507del, W1282X (0.011 each)
Spain (North-West: Castilla-Leon)	0.947 (114)	21	0.947	21	F508del (0.632) / G542X (0.061) / 711+1G>T, R334W (0.026 each) / 2789+5G>A, Q890X, R1066C, 2183AA>G (0.018 each) V232D, 1341G>A (0.018 each) */ R117H, W361R(T>A), 1215delG, S549R(T>G), 1717-1G>A, 1812-1G>A (0.009 each)* *1898+1G>A, G673X, 3849+1G>A, 3849+10kbC>T, N1303K (0.009 each)*
Spain (North-East: Barcelona)	0.971 (1498)	108	0.3%: 0.909	0.3%: 40	F508del (0.513) / G542X (0.079) / N1303K (0.033) / R334W, 1811+1.6kbA>G (0.020 each) / 711+1G>T (0.018) / R1162X (0.015) Q890X (0.014) / R1066C (0.013) / L206W, 2789+5G>A (0.012 each) / I507del (0.011) / G85E, 1609delCA (0.010 each) 712-1G>T, 2869insG (0.009 each) / 2183AA>G,3272-26A>G,W1282X (0.008 each) / 1078delT,2184insA (0.006 each) K710X, A1006E (0.006 each) / 621+1G>T, V232D, R553X, R709X, 3849+10kbC>T (0.005 each) / G85V, R347H (0.004 each) 296+3insT, P205S, R347P, S549R(T>G), G551D, 1812-1G>A, 1949del84, W1089X, Y1092X(C>A), CFTR50kbdel (0.003 each)

REGION	Detection rate (a) (n)	Number of mutations (b)	Detection rate of most frequent mutations (c)	Number of most frequent mutations (d)	Mutations (proportion) (e)
Turkey					
Turkey (Central and East: Ankara) (f)	_0.692 (78)_	25	1.4%: 0.500 (f)	1.4%: 10 (f)	F508del (0.154) / 2789+5G>A (0.064) / E92K (0.051) / R347H (0.051) / 2181delA, N1303K (0.039 each) G85E, M152V, 1677delTA, R1158X (0.026 each)
Turkey (West: Istanbul) (f)	0.589 (168)	30	0.7%: 0.476 (f)	0.7%: 11 (f)	F508del (0.250) / 1677delTA (0.054) / G542X (0.042) / 2183AA>G (0.036) / 2043delG, N1303K (0.018 each) 296+9A>T, D110H, L571S, F1052V, 3849+5G>A (0.012 each)
United Kingdom					
United Kingdom (Northern Ireland)	0.944 (412)	32	0.901	14	F508del (0.680) / G551D (0.051) / R117H (0.041) / R560T (0.029) / 621+1G>T, G542X (0.022 each) / I507del (0.017) E60X, 3659delC (0.007 each) / 1154insTC, R553X, 3120G>A, 2789+5G>A, N1303K (0.005 each)
United Kingdom (North-West England: Manchester)	0.999 (1754)	105	0.3%: 0.944	0.3%: 21	F508del (0.810) / G551D (0.035) / G542X (0.011) / 621+1G>T (0.010) 1898+1G>A (0.009) / R117H, R553X (0.007 each) / R560T, 3272-26A>G (0.006 each) / 3659delC, N1303K (0.005 each) 1717-1G>A, 2711delT (0.004 each) / G85E, 1078delT, 1154insTC, 1461ins4, Q493X, I507del, V520F, W1282X (0.003 each)
United Kingdom (North: Scotland)	0.912 (486)	25	0.885	13	F508del (0.681) / G551D (0.058) / G542X (0.047) / R117H (0.019) / P67L, 1717-1G>A (0.014 each) 621+1G>T, A455E, 3659delC, 3849+10kbC>T (0.008 each) / Q493X, N1303K (0.006 each)
United Kingdom (West: Wales)	0.995 (183)	17	0.995	17	F508del (0.716) / 621+1G>T (0.066) / 1898+1G>A (0.055) / G542X (0.027) / 1078delT, G551D (0.022 each) / R1283M (0.016) I507del, 1717-1G>A, R553X (0.011 each) / E60X, R117H, S549N, 3659delC, 3849+10kbC>T, 4016insT, N1303K (0.006 each)
MIDDLE EAST					
Israel					
Israel (Ashkenazi)	0.946 (261)	6	0.946	6	W1282X (0.479) / F508del (0.280) / G542X (0.088) / 3849+10kbC>T (0.058) / N1303K (0.035) / 1717-1G>A (0.008)
Israel (Non-Ashkenazi)	0.821 (106)	12	0.821	12	F508del (0.419) / 405+1G>A (0.123) / Q359K-T360K, W1282X (0.067 each) / G85E, D1152H (0.029 each) S549R(T>G), W1098X(TAG), 3849+10kbC>T, N1303K (0.019 each) / _G542X, Y1092X(C>G) (0.010 each)_
Israel (Arab population)	_0.918 (85)_	12	0.918	12	F508del (0.235) / N1303K (0.212) / 3120+1kbdel8.6kb (0.129) / W1282X (0.106) / G85E

REGION	Detection rate (a) (n)	Number of mutations (b)	Detection rate of most frequent mutations (c)	Number of most frequent mutations (d)	Mutations (proportion) (e)
					(0.082) / 2183AA>G (0.047) R75X, 4010delTAAT, CFTRdele2 (0.024 each) / _G542X, S549R(A>C), S549R(T>G) (0.012 each)_
AFRICA					
African American (g)	0.750 (148)	15	0.750	15	F508del (0.480) / 3120+1G>A (0.122) / R553X, A559T, 2307insA (0.020 each) / 405+3A>C, G480C, S1255X (0.014 each) _444delA, R334W, I507del, 1717-1G>A, G542X, S549N, G551D (0.007 each)_
South Africa (Bantu-speaking; African)	_0.607 (28)_	5	0.607	5	3120+1A>G (0.464) / _-94G>T, 2183delAA, 3196del54, G1249E (0.036 each)_
South Africa (mixed: Khoisan, Malay, European, African)	_0.744 (86)_	6	0.744	6	F508del (0.500) / 3120+1G>A (0.174) / G542X, G551D (0.023 each) / _3272-26A>G, R1162X (0.012 each)_
Central Africa (h)					_IVS2+28A>G (Senegal), Y109X (Cameroon), CFTRdele17a-18 (Senegal), IVS22+1G>A (Guiana)_

(a) Proportion of *CFTR* alleles derived from CF patients on which a mutation could be identified. (n) denotes the total number of *CFTR* alleles that were studied. This detection rate for each region is the maximum detection rate obtained so far, irrespective of the sensitivity of the screening assays used. In some countries, lower detection rates are indeed obtained because of the use of screening assays that have low sensitivities. The data given in 'italics/underlined' refer to studies in which less than 100 *CFTR* alleles were studied (either because of an incomplete study, or because they deal with small populations in which less than 50 CF patients (100 *CFTR* alleles) exist), and each mutation therefore contributes for 1% or more.

(b) The total number of *CFTR* mutations that have been found in CF patients of the respective population.

(c) Proportion of *CFTR* alleles derived from CF patients on which a mutation could be identified if one only screens for the most common mutations. In general, a common mutation is defined as a mutation having a frequency of 0.5%, or higher. If not specified, mutations having a frequency of 0.5%, or higher, are only considered. For populations in which more than 950 *CFTR* alleles were studied, all mutations having a frequency of 0.3%, or higher, are included. When a relatively low number of mutations is observed in a given population, mutations having a frequency lower than 0.3%-0.5% may be included, and the sensitivity rate is then specified. For South Africa, were a low number of *CFTR* alleles have been studied, all mutations are given.

(d) The total number of common mutations that are found in the respective population. See also the remarks given in (c).

(e) The mutations given in 'italics/underlined' are only found once, but given the low number of mutations that were studied, they contribute for 0.5%, or more than 0.5%, of all *CFTR* alleles. They might still be private mutations in that given population.

(f) Given the low number of *CFTR* alleles from CF patients on which a disease causing mutation is identified, and the heterogeneous nature of *CFTR* mutations, private mutations (which even contribute for more than 0.5%) are not given. Only mutations are included which were at least found twice in the given population.

(g) Data are derived from respective individuals living in another country, i.e. African American individuals.

(h) For Central Africa, given the scarce number of data, any mutation found is given. The country from which the patient, in which the mutation was found, originated is given between brackets [29]. The latter mutations were found once; they may in the end turn out to be private mutations.

Table 4: Proportion of *CFTR* mutations in CFTR-related diseases

Disease [a]	Proportion of mutant *CFTR* [b] alleles (n)	Proportion of CF *CFTR* [c] alleles (n)	Reference
CBAVD	0.789 (654)	(d)	[6]
Obstructive azoospermia *	0.235 (34)	0.088 (34)	[30]
Disseminated bronchiectasis	0.328 (64)	0.156 (64)	[31]
Disseminated bronchiectasis	0.304 (46)	0.130 (64)	[32]
Disseminated bronchiectasis	0.211 (38)	0.053 (38)	[33]
Diffuse Panbronchiolitis	0.220 (50)	(e)	K.Yoshimura
Allergic bronchopulmonary aspergillosis	0.500 (22)	0.318 (22)	[34]
Asthma	0.325 (40)	0.000 (40)	[33]
Asthma (f)	0.118 (288)	0.035 (288)	[35]
Pulmonary emphysema (f)	0.140 (50)	0.002 (50)	[32]
Chronic rhinosinusitis * (f)	0.079 (292)	0.034 (292)	[36]
Chronic bronchitis (f)	0.093 (54)	(e)	[32]
Hypertrypsinaemia	0.730 (48)	0.625	[37]
Chronic Pancreatitis *	0.119 (268)	0.067 (18)	[38]
Chronic Pancreatitis *	0.241 (54)	0.148 (54)	[39]
Primary sclerosing cholangitis (f)	0.156 (58)	0.017 (58)	[40]
Primary sclerosing cholangitis	0.184 (38)	0.000 (38)	[41]
Controls	0.059 (136)	0.002 (136)	[32]
Controls	0.087 (104)	(e)	[33]

(a) Except for the studies denoted with an asterisk, the complete coding region, and exon/intron junctions, of the *CFTR* genes were analysed.

(b) Including mild mutations such as IVS8-T5, R75Q.

(c)   Only severe CF-causing mutations are included.

(d)   Mutations were not detailed in order to discriminate severe and mild mutations

(e)   In absence of functional studies of mutations, only for a portion of the mutations, or even for none of the mutations, it can be determined if the mutation is severe or mild.

(f)   A trend is observed, but it is not significantly different from controls.

(n) Denotes the number of *CFTR* alleles studied.

Figure 1: Incidence of cystic fibrosis

■	1-4999
▨	5000-9999
▨	10000-49999
▨	>50000
□	CF not recorded

WHO 04.72