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Lung Function Decline is Delayed But Not Decreased in Patients With Cystic Fibrosis and the *R117H* Gene Mutation

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Abstract

Background: Patients with cystic fibrosis (CF) experience variable lung disease phenotypes. The *R117H* mutation is often associated with preserved lung function. Our objective was to compare the rate of lung function decline in patients with the *R117H* mutation and patients homozygous for the *F508del* mutation.

Methods: Rate of decline in percentage-of-predicted FEV_1 ($ppFEV_1$) was analyzed using the 2006-2010 US CF Foundation Patient Registry.

Results: 4-year rate of decline was slower in 156 *R117H* patients compared with 6251 *F508del* patients (−0.61 vs −2.03 $ppFEV_1$/year, $P<0.001$). Rates of decline in children were slower in *R117H* vs *F508del* patients (6-12 year-olds: +0.73 vs −1.91 $ppFEV_1$/year, $P<0.001$ and 13-17 year-olds: −1.55 vs −2.66 $ppFEV_1$/year, $P=0.046$), whereas rates in adults were not significantly different (18-24 year-olds: −1.52 vs −2.12, $P=0.26$ and ≥25 year-olds: −1.17 vs −1.40, $P=0.33$).

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AUTHORSHIP

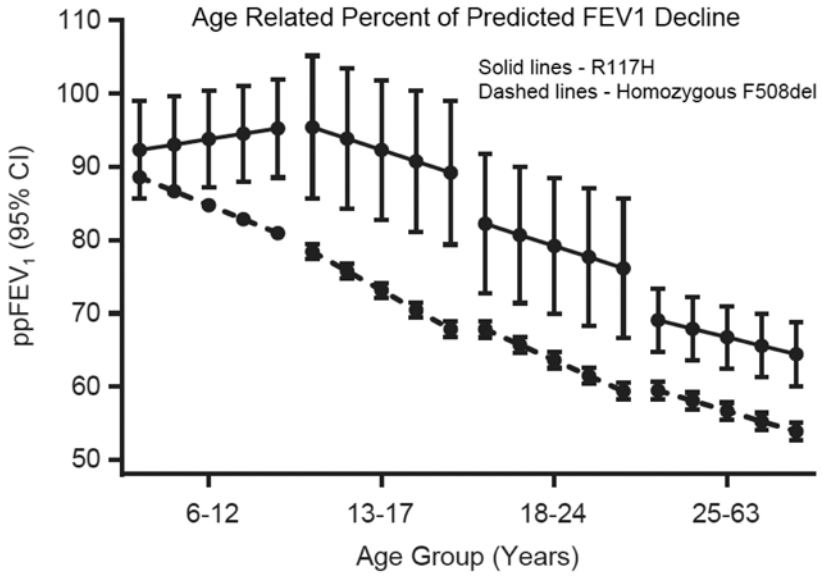
All authors contributed to the study design, interpretation of data, critically revising content, and final manuscript approval. In addition, **JSW**, **SJM**, and **DJP** contributed to data acquisition and **JSW**, **SJM**, **NM-H**, **DJP** and **RBM** contributed to data analysis and drafted the original work.

DISCLOSURES

This study was funded by Vertex Pharmaceuticals Incorporated. **JSW**, **EFM**, **MWK,** and **RBM** have received consultancy fees and their institutions have received financial support from Vertex Pharmaceuticals Incorporated for participation in clinical trials. **NM-H**, **GSS**, **CHG**, and **WJM** are members of the US CFF Patient Registry committee and their institutions have received financial support from Vertex Pharmaceuticals Incorporated for participation in clinical trials. **CHG** was also part of a research group that received a clinical research grant from Vertex Pharmaceuticals Incorporated. **JSW** is a former employee of, but currently does not consult for or own stock or stock options in Vertex Pharmaceuticals Incorporated. **DJP** and **SJM** are employees of ICON Clinical Research, which was paid by Vertex Pharmaceuticals Incorporated to provide analytical services for this study. No author declares any competing interests with this manuscript.

Conclusions: These findings are consistent with a delayed onset, but ultimately similar progression of lung disease in *R117H* and homozygous *F508del* patients.

GRAPHIC ABSTRACT



Keywords

cystic fibrosis; *R117H*; *F508del*; lung function; lung function decline

INTRODUCTION

Patients with cystic fibrosis (CF) experience a highly variable clinical disease. Some of this variation is explained by differences in function of the cystic fibrosis transmembrane conductance regulator (CFTR) protein. This protein function is in turn determined largely by the specific mutations present in the *CFTR* gene. Since the 1970s, investigators have described certain patients as having “mild” CF lung disease.(1, 2) Patients with this less severe disease tend to be diagnosed at an older age, are more likely pancreatic sufficient, and are not homozygous for the *F508del-CFTR* mutation.(3) However, even patients with “mild” disease are noted to develop lung pathology similar to typical patients with CF and exhibit progressive, ultimately fatal lung disease in adulthood.(4)

One of the more common mutations associated with this less severe form of disease, the *R117H-CFTR* mutation, was identified in 1990.(5) With this mutation the CFTR protein is present at the cell surface, but exhibits both conductance and gating defects.(6) This results in reduced CFTR function, although the degree of reduction is further modified by a poly-thymidine (poly-T) sequence on intron 8.(7) Historically, patients with this mutation have been diagnosed later in life, often due to male infertility, and almost always demonstrate pancreatic sufficiency.(8) However, many of these patients develop progressive, life-shortening lung disease.

Although patients with less severe CF typically experience some degree of symptomatic lung disease, it is not clear if loss of lung function occurs gradually throughout life or is delayed in onset and progresses more rapidly in later life. We designed this study to compare lung function decline in patients with the *R117H-CF* mutation on at least one allele to that in patients with the common *F508del-CFTR* mutation on both alleles. In addition, we wanted to answer the question "In patients with CF and the *R117H-CFTR* mutation, is lung disease as manifested by airway obstruction, early in onset but gradual, or delayed in onset but rapid?"

METHODS

Rate of lung function decline over 4 years was analyzed using percentage of predicted forced expiratory volume in 1 second ($ppFEV_1$)(9). Two retrospective cohorts of patients with CF and either ≥1 *R117H-CFTR* mutation or homozygous *F508del-CFTR* mutation were selected from the 2006 US CF Foundation Patient Registry (CFFPR). Data from 2006–2010 were used for the analysis since all CF centers were collecting encounter-based data by 2006 and we wanted to avoid any impact of patients enrolled in clinical trials of potential disease-modifying therapies (which started in 2011).

Since not all individuals with the *R117H-CFTR* mutation have clinical manifestations of CF, we excluded patients with presumed CFTR-related metabolic syndrome (CRMS).(10) This exclusion included individuals identified by newborn screening who had an *R117H-CFTR* mutation plus a sweat chloride level <60 mEq/mL or no sweat test result recorded. However, 2 patients meeting these criteria were included because they had been diagnosed due to the clinical presentation of failure to thrive prior to 1998 when *R117H-CFTR* mutation screening began.

Patients had to be ≥6 years old and have a baseline visit identified as the first recorded FEV_1 measurement in 2006. The last visit within 12 months of this baseline visit was considered the last baseline year visit. In addition to the baseline FEV_1, included patients had to have ≥3 values recorded with at least 1 during each of the second and fifth years of the study in order to assure all patients had 4 years of follow-up. All FEV_1 values recorded after the last baseline year visit and during the 4-year time span (2007–2010) were used to calculate an individual patient's annual $ppFEV_1$ rate of decline. All calculations of $ppFEV_1$ were based on Global Lung Initiative equations.(9) No post-lung transplant data were included.

Baseline demographics and clinical characteristics were derived from the first baseline year visit (age, sex, year of diagnosis, genotype, sweat chloride, "first visit" $ppFEV_1$), the last baseline year visit (height, weight, body mass index [BMI], microbiology) or from all recorded values during the baseline year (the highest value ["best"] $ppFEV_1$, CF related diabetes [CFRD], liver disease, intravenous [IV] antibiotic-treated pulmonary exacerbations [PEx]). Lack of comprehensive poly-T data meant that no analysis of this sequence was conducted.

The $ppFEV_1$ intercepts and slopes (rate of decline) were estimated for the *R117H* and *F508del* cohorts separately by age group and overall. These estimates reflect the linear

component of lung function decline over the 4 years of the trend (ie. the average rate of decline). Estimation and significance testing of the difference between mutation cohorts were conducted using a repeated-measures model that accounted for the correlation of values within patient. The model included mutation, age group, time (in years) since the last FEV_1 measurement in the baseline year, and all interactions. Overall estimates of intercept and slope were calculated by weighting each age group category according to the observed distribution pooled across mutation groups. In addition, intercept and slope were calculated separately for each age group from the same model. Final estimated intercepts and annual rates of decline with 95% confidence intervals were generated using the ESTIMATE statement within the MIXED procedure in SAS Version 9.4 (SAS Institute, Inc., Cary, NC).

A sensitivity analysis was performed using 2-year rates of lung function decline to include additional patients in the analysis that may have been excluded due to lack of complete 5-year data. For this analysis, a 2-year period was randomly chosen for each patient within each of the 4 age groups (6–12, 13–17, 18–24, and ≥25 years). Consequently, patients could contribute at most two 2-year periods. Patients were required to have ≥3 FEV_1 values recorded during the 2 years (spanning a minimum of 6 months), and all values were included in the analysis. Separate age group-specific repeated-measures models that accounted for the correlation of values within patient were used to estimate intercept and slope. These models included mutation, the starting year of measurement, time (years) since the first FEV_1 measurement in the 2-year period, and all interactions. Intercept and slope were calculated separately from each age group-specific model. Starting year was weighted equally.

RESULTS

The original dataset included 818 *R117H-CFTR* mutation patients and 13,632 homozygous *F508del-CFTR* mutation patients (Figure 1). After excluding 145 subjects with CRMS there were 673 *R117H-CFTR* mutation patients with CF. Of the patients ≥6 years old, 68% of the *R117H* patients were excluded due to missing data compared with only 38% of the *F508del* patients. Mortality or lung transplant accounted for exclusion in 5.7% of *R117H* patients and 13.3% of *F508del* patients. In total, 156 patients with the *R117H-CFTR* mutation and 6251 patients homozygous for the *F508del-CFTR* mutation met the selection criteria and were included in the 4-year analysis. At baseline, the *R117H* cohort was older, had a lower mean sweat chloride value, better nutritional status, and less CFRD or liver disease than the *F508del* cohort; however mean best $ppFEV_1$ values from the baseline year were not significantly different between cohorts (Table 1). At the end of the baseline year, the *R117H* cohort had a lower frequency of *Pseudomonas aeruginosa* and *Staphylococcus aureus* infection than the *F508del* cohort (Table 1). *Candida* species was slightly more common and *Aspergillus* species was less common in the *R117H* cohort. The *R117H* cohort experienced fewer IV-treated PEx during the baseline year, resulting in fewer hospitalizations and fewer home IV-antibiotic treatments than did the *F508del* cohort (Table 1). However, for patients experiencing ≥1 IV-treated PEx, the event rates were similar between cohorts.

R117H patients excluded from the analysis were similar to the included patients, although they had slightly lower sweat chloride levels and possibly milder disease as evidenced by significantly fewer being treated for a PEx during the baseline year (Supplemental Table 1).

The *CFTR* mutation on the second allele for the excluded *R117H* patients was (86% Class I, II, or III; 7% Class IV or V; 7% unknown) and for the included patients was (92% Class I, II, or III; 3% Class IV or V; 6% unknown). On the other hand, *F508del* patients excluded from the final analysis were at a worse stage of disease than included patients in multiple areas: older age, minimally higher sweat chloride levels, worse nutritional results, much lower baseline $ppFEV_1$, more CFRD and *Pseudomonas aeruginosa* culture positivity, but less *Staphylococcus aureus*, *Haemophilus influenzae*, and *Aspergillus* species culture positivity. Although fewer excluded patients had a PEx, they had an overall increased number of PEx and hospitalizations (Supplemental Table 1).

The recorded best baseline $ppFEV_1$ was similar between cohorts, although after adjusting for age the estimated overall $ppFEV_1$ intercept in the *R117H* cohort was significantly higher than in the homozygous *F508del* cohort (86.58 vs 76.54; $P<0.001$) (Table 2, Figure 2A). The estimated $ppFEV_1$ slope was not as steep and therefore rate of decline was slower in the *R117H* cohort than in the *F508del* cohort (−0.61 vs -2.03 $ppFEV_1$/year; $P<0.001$). However, estimated intercept and slope varied greatly by age group (Figure 2B). The rate of decline across age groups was consistently negative for the *F508del* cohort, ranging from −1.40 to −2.66 $ppFEV_1$/year (Table 3). In contrast, the *R117H* cohort had an increasing $ppFEV_1$ slope among 6–12 year olds, which became negative in the 13–17 year olds, although significantly less negative than in the *F508del* cohort (−1.55 vs −2.66 $ppFEV_1$/year $P=0.046$). In the older 18–24 and ≥25 year old age groups the rates of decline were not statistically different between *R117H* and *F508del* cohorts (Table 3). It should be noted that for this analysis the number of *R117H* patients in each age group was small. Although a minimum of 3 FEV_1 measurements was required, slope estimates were based on considerably more values in each cohort: *R117H* mean 13.5, median 12 (interquartile range of 9–17) and *F508del* mean 19.5, median 17 (interquartile range 13–23).

The 2-year sensitivity analysis included more patients (*R117H* n=329; *F508del* n=9,961) and showed similar trends in $ppFEV_1$ rate of decline by age group (Supplemental Table 2). Again the youngest *R117H* patients had a positive slope and the slope in older patients was not significantly different from *F508del* patients.

DISCUSSION

These analyses demonstrate that progressive lung disease occurs in patients with CF and either the *R117H-CFTR* mutation or homozygous *F508del-CFTR* mutation. Overall the $ppFEV_1$ rate of decline in the *R117H* cohort was significantly less steep than that in the *F508del* cohort. However, lung function decline varied greatly by age in both cohorts. Comparing this age-related pattern of decline between cohorts suggests that the deterioration of lung function in patients with CF and the *R117H-CFTR* mutation may only be delayed, and not necessarily lessened once chronic lung disease becomes established, compared with that in patients homozygous for the *F508del-CFTR* mutation.

Many factors influence lung function decline in patients with CF. In general, patients with higher lung function experience a more rapid rate of decline.(11, 12) Average baseline recorded lung function was similar between these 2 cohorts, indicating they were at a similar

stage of disease, although the *R117H* patients were significantly older than the *F508del* patients, suggesting they had a less severe disease. Additional risk factors for lung function decline (e.g. CF-related diabetes, *Pseudomonas aeruginosa* infection, and PEx) were present in both the *R117H* and *F508del* cohorts, although fewer patients in the *R117H* cohort had these known risk factors for lung function decline. Again, the difference in age between the cohorts is important since CF-related diabetes and *Pseudomonas aeruginosa* infection are both generally more common in older patients with CF.(13) Finally, one of the strongest predictors of mortality and a major risk factor for lung function decline is the frequency of PEx.(14) Patients with the *R117H-CFTR* mutation were nearly 40% less likely to experience a PEx, although if they did have an exacerbation in the prior year, the annual event rate was similar to that of the *F508del* patients. This suggests that once clinical lung disease is established in *R117H* patients, they progress in much the same way as *F508del* patients.

Although the overall rate of decline was quite different between the *R117H* and homozygous *F508del* cohorts, most striking was the ppFEV$_1$ slope when analyzed by age group. Marked differences were present in the youngest patients. During childhood, patients with CF and the *R117H-CFTR* mutation experienced almost no decline in lung function. However during adulthood, there was no evidence to suggest that the *R117H* patients lost function at a rate different from adults homozygous for the *F508del-CFTR* mutation. Because these adults with the *R117H-CFTR* mutation began with higher lung function, their parallel drop with the *F508del* patients suggests that, although they remain with higher overall lung function in adulthood, they experience a significant rate of decline. Thus when the clinician is faced with an adult patient who has the *R117H-CFTR* mutation, close monitoring is essential. Complacency with patients thought to have “mild” mutations may lead to missing early, potentially controllable lung disease, and risks the patient experiencing rapid lung function decline.

No attempt was made to match patients in these analyses given that these 2 mutation groups are known to have different clinical manifestations of CF disease. Additionally, no adjustments were made for sex or other factors when comparing these groups. We felt general population descriptions were useful to understand the clinical course of disease in these 2 mutation groups, recognizing that one cannot use the analysis to infer that any differences are independent effects of the *R117H* genotype in the individual patient. The estimated baseline ppFEV$_1$ was significantly higher in the *R117H* cohort in all age groups. However in adult patients, the estimated slope of lung function decline was not different between *R117H* and homozygous *F508del* patients. Older adults with typical CF lung disease are known to have a slower rate of lung function decline compared to younger patients, partly due to earlier death in patients with more rapid decline.(12) Indeed, in both of the *F508del* and *R117H* adult age groups, lung function decline was slightly less than in the adolescents. The fact that patient death or lung transplant excluded over twice as many homozygous *F508del* patients compared to the *R117H* patients potentially biases the results by excluding these patients with more severe lung disease.

An additional selection bias that might explain the appearance of delayed lung function decline in the *R117H* patients is the fact that the adult *R117H* patients were frequently diagnosed due to clinical symptoms, while younger patients were often detected by newborn

screening. Newborn screening for CF, including the *R117H-CFTR* mutation, is a recent development and the younger patients in this study probably include cases that will not develop clinical symptoms until a much later age, if at all. Thus the younger *R117H* patients probably represent a different distribution of disease severity from the older patients. However, since the drop in lung function appears to begin during adolescence and early adulthood, and since this study does not quantify risk factors for lung function decline, it is probably important that all children with the *R117H-CFTR* mutation be closely monitored.

This analysis does not address why this rapid loss of lung function appears to be delayed into adulthood for patients with the *R117H-CFTR* mutation. In addition to the potential for selection bias noted previously, differences in pathophysiology may be contributing. Patients with CF and the *R117H-CFTR* mutation have limited CFTR protein function, as opposed to almost no function in patients homozygous for the *F508del-CFTR* mutation. One theoretical possibility for rapid lung function decline would be a trigger event or sequence overwhelming this limited CFTR function. Following the trigger event, the patient might then experience lung function deterioration similar to typical patients with CF. A second theoretical possibility is that lung disease has been present throughout childhood but is not detected by spirometry lung function measurements until adulthood. In some ways this is similar to what occurs in patients with CF who have spirometry results in the normal range, yet still have neutrophilic airway inflammation.(15) Often this inflammation begins in early childhood and more sensitive lung function measurement techniques may be necessary to detect changes.(16) However, if the *R117H* patient has airway inflammation present throughout childhood, there would still be a need to explain the rapid decline in later life. Further study of younger patients with CF and the *R117H-CFTR* mutation is needed to better understand this delayed decline in $ppFEV_1$.

As with all epidemiologic studies, this analysis is limited by the available data. In the primary analysis there was a large discrepancy in the number of excluded patients with the *R117H-CFTR* mutation compared to the *F508del-CFTR* mutation. *R117H* patients had less frequent lung function testing, suggesting that they were not clinically followed as closely as the *F508del* patients. For this reason, a sensitivity analysis requiring only 2 years of data was conducted. This analysis more than doubled the number of included *R117H* and *F508del* patients yet showed similar patterns in the rate of lung function decline. These results suggest that the exclusion of milder *R117H* patients (lower sweat chloride and fewer PEx) and more severe *F508del* patients (lower lung function, more PEx, higher mortality) did not change the conclusion that the slope of FEV_1 decline was different in children, but similar in adult patients with either an *R117H-CFTR* mutation or homozygous for the *F508del-CFTR* mutation.

There are additional limitations to interpreting the data since this analysis is focused on patients with CF and the *R117H-CFTR* mutation. First, limited information was available concerning the polythymidine sequence in these patients. In the few patients with this information, 5T and 7T variants were present in all age groups; however, we were unable to evaluate these groups separately due to the small numbers. Second, patients with the *R117H-CFTR* mutation often fulfilled the diagnostic criteria for CRMS instead of CF. Recently, Ren and colleagues(17) studied the CFFPR to better understand this diagnosis and found

potential misclassification of these 2 diagnoses. We chose to use a strict definition of CF, requiring newborn screen detected patients to have a documented abnormal sweat chloride value in order for patients to be included in the analysis.(18) There is a possibility that patients with lower sweat chloride values may actually have clinical CF disease instead of CRMS. Third, not all subjects in the CFFPR had their genotype recorded. In 2010, 90.7% of patients in the CFFPR had genotype information and 1.4% had the *R117H-CFTR* mutation.(19) Fourth, the *R117H-CFTR* mutation is fairly common, and it is clear that not all individuals who have CF and the *R117H-CFTR* mutation have been diagnosed. Experience from newborn screening programs for CF has identified a much larger population of individuals with this mutation than historically have been diagnosed following clinical presentation. Since the adult *R117H* cohort in our analysis was diagnosed based on symptoms or family history and not neonatal screening, many individuals with less severe lung disease may exist, but have not yet been diagnosed. Additionally, the high prevalence of the *R117H-CFTR* mutation and lack of clinical disease in patients has led some newborn screening programs to exclude this mutation.(20) Finally, we used only one allele to define the *R117H* population, yet required the *F508del* patients to be homozygous for their mutation. Most of the *R117H-CFTR* mutation patients had an *F508del-CFTR* mutation on the second allele, although 4 of the 156 patients were paired with another “mild” Class IV or V mutation.(21)

Several conclusions can be drawn from these results. First, CRMS is fairly common and needs to be differentiated from CF in individuals with the *R117H-CFTR* mutation. Recently published guidelines recommend a complete evaluation of infants detected by newborn screening before giving them the diagnosis of CF.(18) Second, children with the *R117H-CFTR* mutation generally have stable lung function. Since we were unable to study if these patients were being treated with various therapies, it is not possible to say if therapies developed for typical CF are also of value in young *R117H* patients. Third, certain risk factors for lung function decline are less common in *R117H* patients and during adolescence and adulthood lung function is higher than that in homozygous *F508del* patients. However this does not mean that clinical monitoring should be lessened since, particularly for adults with the *R117H-CFTR* mutation, a rapid loss of lung function may occur. Finally, although there are differences between the $ppFEV_1$ rates of decline in the *R117H* and *F508del* cohorts in the younger age groups, there is no evidence to suggest they are different in adult patients. These findings are consistent with a delayed onset but ultimately similar lung disease progression in older patients with the *R117H-CFTR* mutation. Importantly, although this pattern occurs in *R117H* patients, further study is needed to see if a similar pattern exists in patients with CF and other “mild” CFTR gene mutations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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was previously, and **DP** and **GD** are currently, employed by Vertex Pharmaceuticals Incorporated and may own stock or stock options in the company.

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HIGHLIGHTS

- We questioned how the rate of lung function decline compares between patients with cystic fibrosis who have “mild” lung disease (related to the *R117H* CF gene mutation) and those with “typical” lung disease (homozygous for the *F508del* CF gene mutation)?
- We discovered that patients with cystic fibrosis and the *R117H* CF gene mutation experience a delayed, but ultimately similar decline in lung function.
- This suggestion of a delayed progression of lung disease provides an opportunity for better understanding the pathophysiology of cystic fibrosis related lung disease and clinically may lead to more effective intervention and monitoring of these patients.

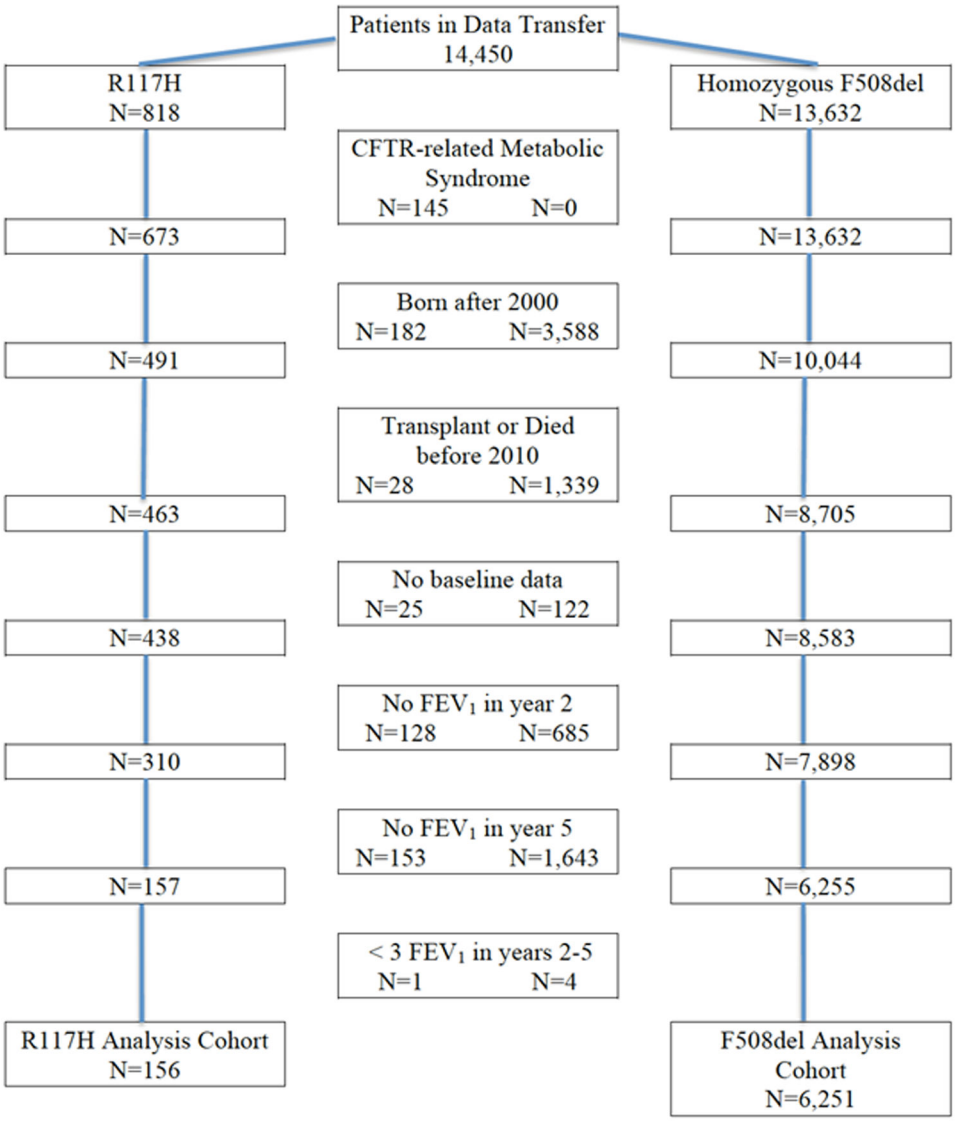

Figure 1.

STROBE diagram showing the derivation of the *R117H-CFTR* and homozygous *F508del-CFTR* mutation cohorts in the 4-year analysis.

CFTR, cystic fibrosis transmembrane conductance regulator; FEV_1, forced expiratory volume in 1 second.

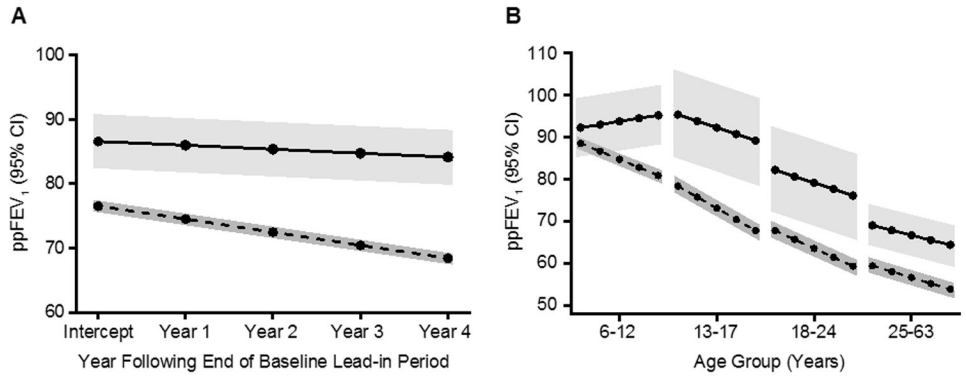

Figure 2.

Estimated ppFEV$_1$ intercept and slope by CFTR mutation (*R117H* or homozygous *F508del*) (Tables 2 and 3). Panel A: Overall estimates. *R117H-CFTR* mutation n=156, *F508del-CFTR* mutation n=6,251. Panel B: Estimates separated by age group. *R117H-CFTR* mutation ages 6–12 years, n=36; ages 13–17 years, n=17; ages 18–24 years, n=18; ages ≥25 years, n=85). *F508del-CFTR* mutation ages 6–12 years, n=2,398; ages 13–17 years, n=1,447; ages 18–24 years, n=1,278; ages ≥25 years, n=1,128.

Solid lines = *R117H-CFTR* mutation. Dashed lines = homozygous *F508del-CFTR* mutation. Shaded areas represent 95% Confidence Intervals.

ppFEV$_1$, percentage of predicted forced expiratory volume in 1 second.(9)

Table 1.

Baseline Demographic and Clinical Characteristics by Mutation.

Characteristic	*R117H* (n=156)	*F508del* (n=6251)	*P*-Value*
Age, years, mean (SD)	29.2 (17.2)	17.0 (9.1)	<0.001
Female, %	51.9	47.3	0.26
Year of CF diagnosis			
median	1998	1992	<0.001
min, max	1958, 2006	1949, 2006	
Sweat chloride	[n=126]	[n=5,729]	
mmol/L, mean (SD)	77.8 (23.9)	102.6 (16.3)	<0.001
Height *z*-score, mean (SD)	0.11 (1.03)	−0.51 (1.01)	<0.001
Weight *z*-score, mean (SD)	0.46 (1.14)	−0.41 (1.02)	<0.001
BMI *z*-score,		[n=6,250]	
mean (SD)	0.41 (1.07)	−0.20 (0.96)	<0.001
$ppFEV_1$ baseline first visit, mean (SD)	79.0 (22.2)	77.3 (23.0)	0.35
$ppFEV_1$ best baseline year value, mean (SD)	83.9 (22.4)	84.8 (22.3)	0.61
CF-related diabetes, %	7.1	15.5	0.004
Liver disease, %	0.6	4.1	0.029
Microbiology	[n=152]	[n=6,130]	
Staphylococcus aureus, %	36.2	54.1	<0.001
Pseudomonas aeruginosa, %	29.6	49.2	<0.001
Candida species, %	7.2	3.3	0.007
Stenotrophomonas maltophilia, %	5.3	7.7	0.27
Aspergillus species, %	3.9	8.9	0.034
Haemophilus influenzae, %	3.3	6.1	0.15
≥1 IV treatment for PEx, %	28.2	45.9	<0.001
≥1 hospitalization, %	21.2	40.8	<0.001
≥1 home IV antibiotic treatment, %	18.6	26.3	0.031
IV treatment for PEx events/year, mean (SD)	0.44 (0.84)	0.87 (1.31)	<0.001
Hospitalization events/year, mean (SD)	0.32 (0.74)	0.75 (1.22)	<0.001
Home IV antibiotic events/year, mean (SD)	0.25 (0.60)	0.41 (0.84)	0.020
IV treatment in patients with ≥1 PEx, mean (SD)	1.57 (0.87)	1.90 (1.33)	0.10

* *P*-Value obtained from *t*-test or chi-square test.

CF, cystic fibrosis; BMI, body mass index; max, maximum; min, minimum; $ppFEV_1$, percentage of predicted forced expiratory volume in 1 second; IV, intravenous; PEx, pulmonary exacerbation; SD, standard deviation.

Table 2.

Estimated Percentage of Predicted FEV_1 Intercept and Slope for *R117H* Patients (n=156) and *F508del* Patients (n=6,251)*

Parameter	Estimate	Standard Error	*P*-Value	Lower 95% CI	Upper 95% CI
Intercept ($ppFEV_1$)					
R117H	86.58	2.03	<0.001	82.60	90.55
F508del	76.54	0.26	<0.001	76.04	77.05
Difference	10.04	2.04	<0.001	6.03	14.04
Slope ($ppFEV_1$/year)					
R117H	−0.61	0.21	0.005	−1.03	−0.19
F508del	−2.03	0.02	<0.001	−2.07	−1.98
Difference	1.42	0.22	<0.001	1.00	1.84

*Repeated measures model adjusted for correlation within patient. Age group and mutation were fixed effects. All 2-way and 3-way interactions were included. Overall estimates of intercept and slope were calculated by weighting each age group category according to the observed distribution pooled across mutation groups.

CI, confidence interval; $ppFEV_1$, percentage of predicted forced expiratory volume in 1 second.

Table 3.

Age Group Specific Estimated Percentage of Predicted FEV_1 Intercept and Slope for *R117H* Patients and *F508del* Patients.*

Parameter	Estimate	Standard Error	*P*-value	Lower 95% CI	Upper 95% CI
6-12 year olds (*R117H* n=36, *F508del* n=2,398)					
Intercept ($ppFEV_1$)					
R117H	92.32	3.41	<0.001	85.65	99.00
F508del	88.59	0.42	<0.001	87.77	89.40
Difference	3.74	3.43	0.28	−2.99	10.46
Slope ($ppFEV_1$/year)					
R117H	0.73	0.34	0.032	0.06	1.39
F508del	−1.91	0.04	<0.001	−1.98	−1.84
Difference	2.64	0.34	<0.001	1.97	3.31
13-17 year olds (*R117H* n=17, *F508del* n=1,447)					
Intercept ($ppFEV_1$)					
R117H	95.40	4.99	<0.001	85.62	105.18
F508del	78.43	0.53	<0.001	77.38	79.47
Difference	16.97	5.02	<0.001	7.13	26.82
Slope ($ppFEV_1$/year)					
R117H	−1.55	0.55	0.005	−2.63	−0.47
F508del	−2.66	0.04	<0.001	−2.74	−2.57
Difference	1.11	0.55	0.046	0.02	2.19
18-24 year olds (*R117H* n=18, *F508del* n=1,278)					
Intercept ($ppFEV_1$)					
R117H	82.23	4.84	<0.001	72.73	91.72
F508del	67.81	0.57	<0.001	66.70	68.93
Difference	14.41	4.88	0.003	4.85	23.97
Slope ($ppFEV_1$/year)					
R117H	−1.52	0.53	0.004	−2.56	−0.49
F508del	−2.12	0.05	<0.001	−2.22	−2.02
Difference	0.60	0.53	0.26	−0.45	1.64
≥25 year olds (*R117H* n=85, *F508del* n=1,128)					
Intercept ($ppFEV_1$)					
R117H	69.05	2.22	<0.001	64.69	73.41
F508del	59.42	0.61	<0.001	58.23	60.62
Difference	9.63	2.31	<0.001	5.11	14.15
Slope ($ppFEV_1$/year)					
R117H	−1.17	0.23	<0.001	−1.62	−0.71
F508del	−1.40	0.06	<0.001	−1.51	−1.29
Difference	0.23	0.24	0.33	−0.24	0.70

*Repeated measures model adjusted for correlation within patients. Age group and mutation were fixed effects. All 2-way and 3-way interactions were included.

CI, confidence interval; ppFEV$_1$, percentage of predicted forced expiratory volume in 1 second.