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Original Article

The relationship between sweat chloride levels and mortality in cystic fibrosis varies by individual genotype

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Abstract

Rationale: The association between *CFTR* genotype, sweat chloride and mortality has been inconsistent, but no previous analyses have examined the association stratified by individual genotypes.
Objectives: To evaluate the genotype-specific association between sweat chloride and mortality.
Methods: The CFF Patient Registry was assessed and included all patients in the registry between 1996 and 2012 with at least one F508del allele. We excluded patients without a documented genotype or plausible sweat chloride level. The primary outcome was time to mortality during the observation period. We examined 15 genotypes using the three most prevalent alleles in each of 5 classes. We compared subgroups of sweat chloride using Kaplan-Meier curves, log-rank tests, and multivariable Cox PH models. The overall predictive value of sweat chloride on mortality was assessed using area under the receiver operating characteristic curves.
Measurements and main results: 18,893 subjects met inclusion criteria. Sweat chloride distribution was similar across genotypes in patients with class 1 mutations, but was significantly different across genotypes in mutation classes 2–5. The R117H/F508del genotype patients demonstrated an association between sweat chloride and mortality (HR: 1.32 for every 10 mmol/L increase in sweat chloride [95% CI 1.12–1.54]. There were also significant associations in patients with F508del/F508del, I507del/F508del, G551D/F508del and 2789 + 5G → A/F508del genotypes, though the clinical relevance for these genotypes is unclear.
Conclusions: There is significant variability in sweat chloride distribution across *CFTR* class 2–5 genotypes. The relationship between sweat chloride and mortality varies by genotype with a relatively strong relationship in R117H/F508del patients.
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Keywords: Cystic fibrosis; Sweat chloride; Mortality; CFTR genotype; Mutation

1. Background

Cystic fibrosis (CF) is an autosomal recessive disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene for which >2000 *CFTR* mutations have been identified [1–3]. The CFTR protein is an important regulator of chloride, bicarbonate and water transport in a variety of epithelial tissues, including the sweat duct, pancreas and airways [4,5]. The clinical phenotype varies widely in CF, which is partly attributable to the degree of residual CFTR function of different mutations [6–9]. *CFTR* genotypes are grouped into functional classes according to the resulting absence of CFTR protein or abnormal function. Most often five functional classes are identified: absent synthesis (class 1), processing defects (class 2), regulation or gating defects (class 3), altered conductance (class 4),

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and reduced synthesis (class 5) [9]. In some classifications a sixth class is included, but this generally has a very low prevalence. For the purposes of this review we chose to analyze classes 1–5. Patients with genotypes in functional classes 1–3 almost always have pancreatic insufficiency, are at high risk for early lung function decline and have decreased survival compared to lower-risk genotypes (functional classes 4 & 5) [10]. Even among patients with identical *CFTR* genotypes, the severity of disease may vary widely between individuals [11].

Important outcomes in CF, such as morbidity and mortality, are largely driven by progression of pulmonary disease [12,13]. However, one of the most common diagnostic tests for CF is an elevated sweat chloride level, which results from impaired reabsorption of chloride ions by CFTR in the sweat gland [14,15]. In addition to its utility as a diagnostic test, sweat chloride has been evaluated as a predictor of clinical outcomes and has been used as marker of CFTR restoration in clinical trials of CFTR modulator therapies [16,17]. However, reports on the relationship between sweat chloride values and mortality in CF have failed to discern a consistent relationship [18]. A previous study of 127 patients who are F508del homozygotes did not show any significant association of sweat chloride level with lung severity index [18]. A more recent analysis has suggested that sweat chloride concentration at diagnosis was not associated with mortality in patients who were broadly categorized into groups based on high risk (class 1–3) vs. low risk genotypes (class 4–5). However, there was an association of sweat chloride with mortality in patients whose genotypes could not be identified with routine testing [19]. Additionally, the relationship between CFTR modulator mediated sweat chloride change and clinical outcomes has also been difficult to demonstrate [20].

There are previous data that suggest that *CFTR* mutations impact *CFTR* expression and function differentially in different organ systems [21–24]. Thus, previous analyses assessing sweat chloride and mortality could have been confounded by the inclusion of multiple genotypes within a class and across multiple classes [19]. In fact, to our knowledge, no previous analysis has examined the predictive effect of sweat chloride on mortality within a specific *CFTR* genotype. Thus, we sought to determine whether sweat chloride as recorded in the CFF registry was associated with mortality when stratified by *CFTR* genotype.

2. Methods

Data from the Cystic Fibrosis Foundation Patient Registry (CFFPR) were examined retrospectively. The CF Patient Registry collects information on the health status of people with an established diagnosis of cystic fibrosis who receive care in CF Foundation-accredited care centers. This data can be used to study CF treatments and outcomes as well as to design CF clinical trials.

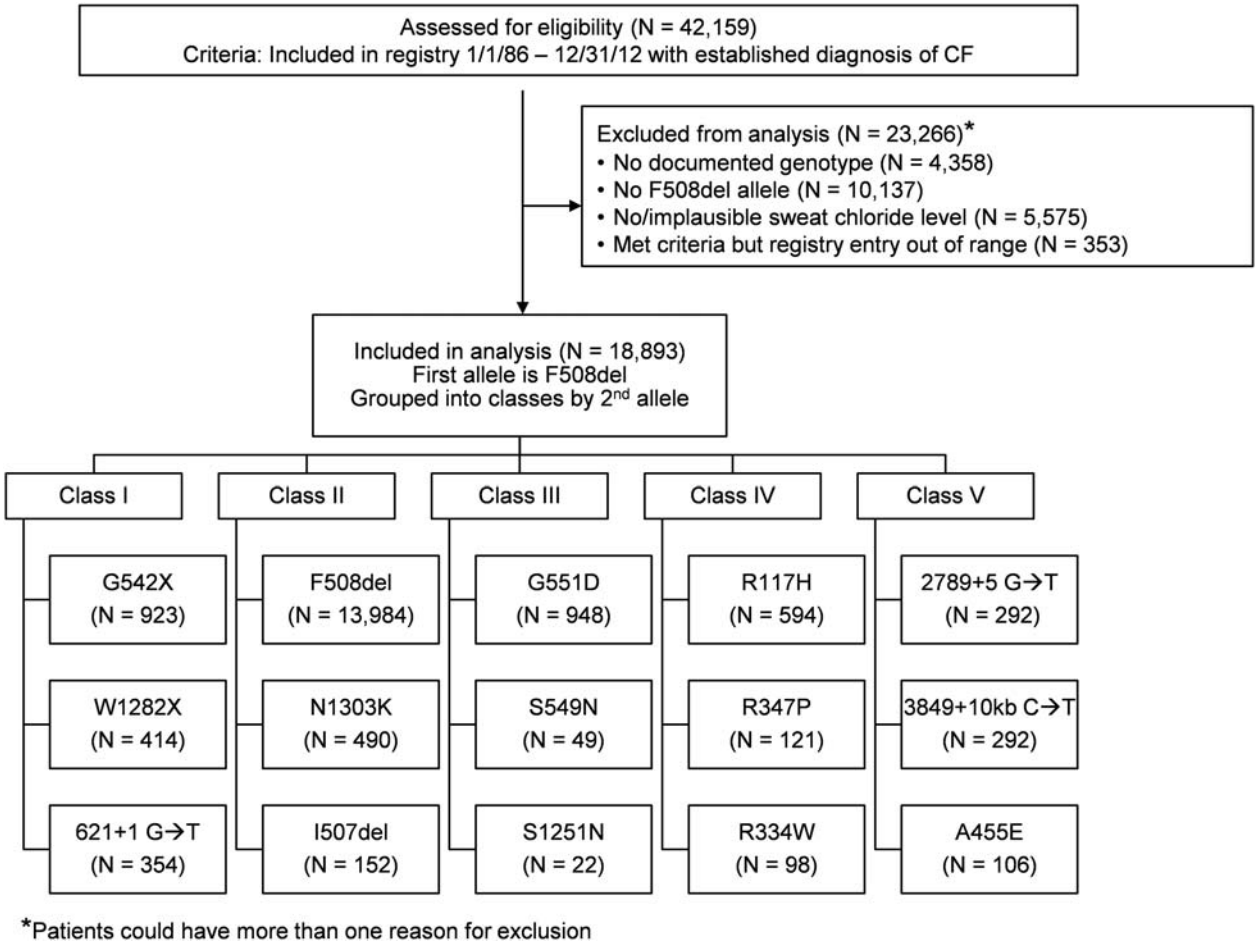

Fig. 1. CONSORT diagram of subject population.

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