European Cystic Fibrosis Society

Journal of Cystic Fibrosis
The Official Journal of the European Cystic Fibrosis Society

Cystic Fibrosis Research News

Title:
HOW THE SWEAT GLAND REVEALS LEVELS OF CFTR ACTIVITY

Lay Title:
Measuring CFTR function and relating it to health.

Authors:
Jeffrey J Wine

Affiliations:
Departments of Psychology and Pediatrics
Stanford University and Stanford University School of Medicine

What was your research question?
CFTR is an ion channel that causes CF when its activity (defined as number of channels times how well each one works) is near zero. Amazingly, pills are now available that partially improve the activity of certain kinds of CFTR that are not working correctly. The research question was 'How can we use sweat testing to estimate levels of CFTR function?'

Why is this important?
Is CF something you either have or don't have? We know that CFTR activity can range from zero to more than average levels detected in healthy individuals. People with CF have little or no CFTR activity. CF carriers have, on average, half as much as non-carriers do. It is unclear how much CFTR activity is restored when people are taking modulators that partially fix CFTR. The sweat test is the easiest way to measure CFTR activity, but researchers do not fully understand its relationship to CFTR activity.

What did you do?
This review looked at different methods for measuring CFTR activity, and at attempts to relate those measures to sweat test results (sweat chloride levels). We first explored results from a special type of sweat test that has a more direct relation to CFTR activity compared to methods such as sweat chloride or FEV1. It showed that CF carriers have half the normal levels of CFTR activity. We then asked: what mathematical functions best describe the relationship between average values from sweat tests given to groups of CF, carrier and non-carrier individuals?

What did you find?
We found that logarithmic (log) functions worked best to describe the relationship (see graph). We found that sweat chloride values decrease most rapidly for small increases in CFTR activity in the range

between zero and 10% of normal activity. Sweat chloride levels then changes progressively more slowly as CFTR activity increased towards 100%, so that values for carriers and non-carriers are similar (mean sweat chloride values in mmol/L: CF 102, carrier 28, healthy control 20. The shapes of the log functions (curves on the graph) were sensitive to the value assigned to CFTR activity in individuals with CF with the highest average sweat chloride values (102 mmol/l). Here the log curves, fell much more steeply when the value was increased from zero to 1% of normal activity (blue, grey and black curves on graph) than when it was assigned as 5% of normal activity (red curve on graph).

What does this mean and reasons for caution?

An important lesson from this review is that CFTR modulators appear to restore somewhat less CFTR activity than we thought. That is actually good news, because it means that the huge clinical benefits conferred by modulators can be improved further. However, there are uncertainties about which log function is best. . It is important to choose the correct function, because they each make different predictions for the CFTR activity that correlates with the sweat chloride level that potentially indicates CF (60 mmol/l). Indeed, we may need to use a more complex mathematical function to describe the relationship. In addition, all biological assays, including sweat tests, have unknown sources of variability that require repeated measures and averaging across groups. This is one of the challenges faced by personalized medicine.

What's next?

A great deal of information collected over the years is available in databases such as CFTR2 and in patient registries maintained by organizations such as ECFS and CFF. Continued refinement and mining of this information is improving the researcher's ability to provide the CF community with better information for making clinical decisions.

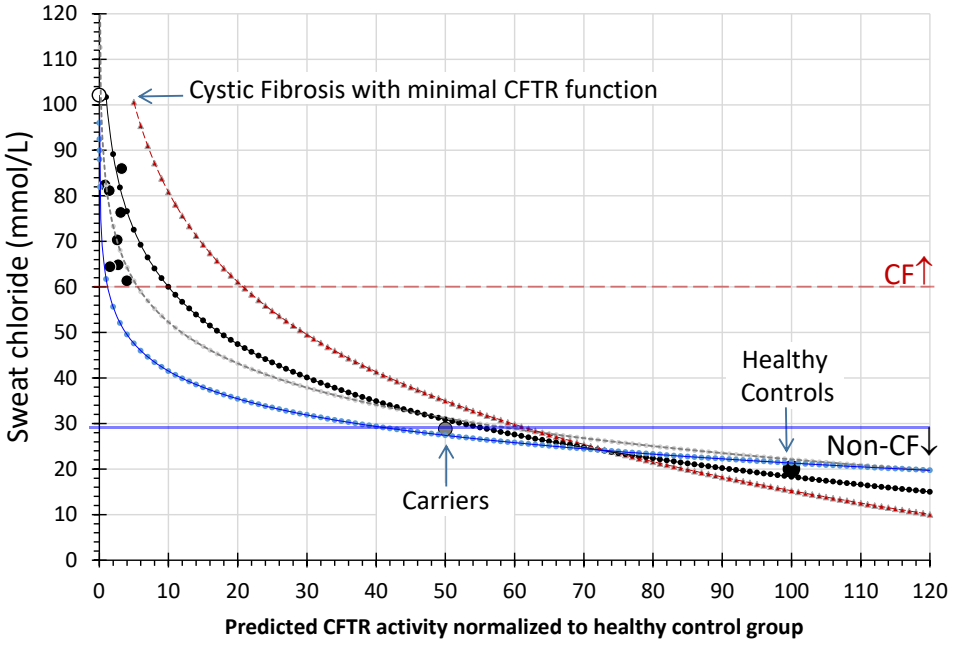
Original manuscript citation in PubMed

https://pubmed.ncbi.nlm.nih.gov/35184981/

European Cystic Fibrosis Society

Journal of Cystic Fibrosis
The Official Journal of the European Cystic Fibrosis Society

Cystic Fibrosis Research News



Sweat chloride levels predict CFTR activity. The evidence favours a logarithmic relation. The graph shows four possible functions based on the CFTR activity assigned to CF individuals who have minimal function mutations (0.01, 0.22, 1 and 5%). The resulting functions make different predictions for CFTR activity at the diagnostic level of sweat chloride (60, dashed line). The points between 60-90 on the sweat chloride scale are for groups (n>30) with CFTR mutations that confer partial function and milder CF. Sweat chloride values used for CF, carriers and healthy controls are 102, 28 and 20 mmol/L respectively.

cfresearchnews@gmail.com