Stanford CF Family Day

CF Genetics

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CF Mutations

• How can we use them to diagnose?
• What do they mean about how severe the disease will be?
• How will we use info on mutations/genetics for new therapies?
CF Heredity – Autosomal Recessive

4% of Caucasians are carriers

Carrier  
<p>| |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>CF</td>
</tr>
<tr>
<td>Carrier</td>
</tr>
<tr>
<td>Carrier</td>
</tr>
<tr>
<td>Carrier</td>
</tr>
<tr>
<td>No CF Not Carrier</td>
</tr>
</tbody>
</table>
Diagnosis of Cystic Fibrosis

Evidence of Cystic Fibrosis

Transmembrane Regulator (CFTR) dysfunction

• Positive sweat test
• Abnormal nasal potential difference
• Two known CF-causing CFTR mutations

• Clinical signs of CF
  – Pulmonary
  – GI
  – Malnutrition
  – Obstructive Azoospermia

• A positive family history of CF

• A positive newborn screen (hypertrypsinoginemia)

CF is caused by mutations in CFTR

Cystic Fibrosis Transmembrane Conductance Regulator

- Identified in 1989, by positional cloning
- Codes for a chloride channel that is active in epithelial (lining) cells
- Located on Chromosome 7
- Made up of 170,000 nucleotides (base pairs) that code for 1480 amino acids (protein building blocks)
Cystic Fibrosis
Cloning and Genetics
What do we mean by a mutation?

Using the encyclopedia analogy, we have 23 “volumes” (chromosomes), containing ~20,000 “entries” (genes).
Genetic Mutations

Chromosomes consist of coiled up strands of DNA – which contain nucleotide base pair “codes” for all of our genes.
Genetic Mutation

These individual amino acids add together to make the CFTR protein (with 3D structure)
Types of Mutations in CFTR

- Missense – G551D

- Insertion/Deletion - F508del (deltaF 508)
  - Frameshift - 3659delC

- Nonsense – G542X

- Splice
  - 1898+1G->A
  - 3849+10kbC->T
There are almost 1900 different CFTR mutations

• The most common mutations – (F508del, G551D, R117H) – we know if they cause CF or not

• There are many more mutations that we do not know if they cause CF or not
  – Important point – there can be a mutation, that does not cause disease

• The Clinical and Functional TRanslation of CFTR (CFTR2) Project is designed to address all these unknown mutations
A new repository for clinical data associated with CFTR mutations

Gene information

CFTR1
(CF Mutation Database)

1898 mutations

Link by mutation

Clinical information

CFTR2

39,545 patients
Summary of clinical data collected

CFTR2 Database
39,545 patients
23 registries/clinics

CFTR Genotype
5276 patients with 1 mutation unknown
1674 patients with both mutations unknown
70,466 CF chromosomes with a mutation identified

Sweat Chloride Concentration
14,403 patients missing sweat data
250 measurements excluded
24,892 patients

Lung Function (FEV1%predicted)
16,204 patients missing PFT data
3 measurements <5 % predicted excluded
23,338 patients

Pancreatic Status
9309 unknown
30,236 patients
How do we determine which mutations cause CF and which ones don’t?

- **Clinically** consistent mutation
- **Functionally** consistent mutation
- **Genetically** consistent mutation

**CF-causing mutation**
Welcome to the Clinical and Functional Translation of CFTR (CFTR2) website

CFTR2 is a website designed to provide information about specific cystic fibrosis (CF) mutations to patients, researchers, and the general public. For each mutation included in the database, the website will provide information about:

- Whether the mutation causes cystic fibrosis when combined with another CF-causing mutation, and
- Information about the sweat chloride, lung function, pancreatic status, and pseudomonas infection rates in patients in the CFTR2 database with this mutation.

How to use this website

For patients and family members

This website provides information about specific CF mutations only. This website is intended for members of the general public who want to find out what we currently know about specific mutations related to cystic fibrosis. This includes:

- Cystic fibrosis (CF) patients,
- Family members of CF patients,
- People who are carriers of a CF mutation, and
- Parents whose baby has just been diagnosed with CF through newborn screening.

For health care providers/scientists

This section provides scientific and medical descriptions, intended for CF researchers, health professionals, and members of the general public that are looking for more in-depth, research-related information. Patients and their families are encouraged to visit the section "For patients and family members" first.

WHAT THIS SITE IS NOT INTENDED TO DO

- This website is not intended to help diagnose anyone with CF.
- For more information about CF, click here.

Note: *If you have questions about any of the information contained in this website, please consult your doctor.

Enter the site for CF patients, family members, or carriers

Enter the site for health care providers/scientists
<table>
<thead>
<tr>
<th>CLINICAL FEATURE (RANGE IN INDIVIDUALS WITHOUT CF)</th>
<th>AVERAGE OF ALL PATIENTS WITH MUTATION G551D AND MUTATION F508DEL</th>
<th>AVERAGE OF ALL PATIENTS WITH AT LEAST ONE F508DEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweat Chloride</td>
<td>104</td>
<td>99</td>
</tr>
<tr>
<td>(non-CF is less than 40mEq/L in children and older; less than 30mEq/L in infants)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung Function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>expressed as % predicted (non-CF 80%-120% predicted)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic Insufficiency</td>
<td>98%</td>
<td>90%</td>
</tr>
<tr>
<td>(0% of non-CF expected to be PI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>57%</td>
<td>54%</td>
</tr>
<tr>
<td>(0% of non-CF expected to have Pseudomonas)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average Age</td>
<td>18</td>
<td>18</td>
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How will CFTR2 help?

• It will provide a better resource to determine if a CFTR mutation:
  – Causes CF
  – Does not cause CF
  – Sometimes causes CF
BUT IF WE KNOW WHAT MUTATIONS SOMEONE HAS, CAN WE PREDICT HOW SEVERE THEIR DISEASE IS GOING TO BE?

Genotype-Phenotype Interactions
Lung function (FEV1% predicted)
Pancreatic status can be predicted from mutation class

I. RNA Expression

II. Folding and modification

III. Channel activation

IV. Channel function

V. Reduced expression

Welsh and Smith, Cell, 1993
CFTR Genotype

• May be useful to predict pancreatic status (pancreatic insufficiency – PI, or pancreatic sufficiency – PS)

• Requires however you to know whether a mutation is “severe” or “mild”
  – But there are many problems with these distinctions, and it requires that we know them!

Some Baltimore examples...
The Utz girl
F508del/F508del

Omar from the Wire
F508del/unknown

Edgar Allen Poe
F508del/3849+10kbC->T

Natty Boh guy
A455E/R117H
The Utz girl
F508del/F508del
PI from birth

Omar from the Wire
F508del/unknown
Could be PS or PI

Edgar Allen Poe
F508del/3849+10kbC->T
Likely PS, but may become PI as he gets older

Natty Boh guy
A455E/R117H
Likely PS, may have atypical CF presentation
We can not reliably predict lung function for anyone!

Edgar Allen Poe
F508del/3849+10kbC->T

Natty Boh guy
A455E/R117H
Specific Genotype

Mutations grouped by type or class

Specific Trait

Discrete variable: Pancreatic sufficient or pancreatic insufficient
Specific Genotype

Individual mutations

Specific Trait

Continuous variable: Sweat chloride or lung function
The relationship between $\log_{10} \text{CFTR function}$ and lung function is linear.
The relationship between $\log_{10}$ CFTR function and lung function is linear.

Mutations like F508del

Mutations like R117H
What does it this log linear relationship with CFTR function mean?

• We can use CFTR chloride function as a way of “defining” how bad a mutation is

• But – there is great variability in lung function for patients with the same mutation

• And – CFTR function plays less role in determining lung function than it does for sweat chloride or pancreatic function
What does it this log linear relationship with CFTR function mean?

• New drugs that have an affect restoring CFTR activity from mutations with low function will have the greatest effect on lung function

  – “a little bit of restored function will go a long way”
Are there other mutations that we can use VX-770 (ivacaftor/Kalydeco) to treat?

- Ivacaftor is being investigated for other mutations, keep in contact with your CF center about trials

- Other drugs, and combinations are being studied as well
  - Ataluren
  - VX-770/809
Summary

• There are many mutations in the CFTR gene, the CFTR2 project will help define which of those mutations cause CF

• For an individual person, the CFTR mutations they have may be helpful in predicting if they will need to take pancreatic enzymes, but there is too much variability to be able to predict what their lung function will be
Summary

• As new “mutation specific” therapeutics become available, CFTR2 will also be a resource for patients and CF caregivers to be able to determine if these drugs may be helpful for a given mutation
Take Home Points

• The reasons to get genotyped (if you are not already):
  – To aid with diagnosis (No absolutes)
  – NOT TO PREDICT HOW SEVERE DISEASE WILL BE
  – To be able to tailor therapy

• There is tremendous variability on the individual level
CFTR2 Team

Julian Zielenski

Vertex Pharmaceuticals and NIH
www.cftr2.org

• Online soon!

• Questions: psosnay@jhmi.edu