Translating allelic heterogeneity to clinical practice: the CFTR2 project

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Disclosures

• Consultant for CF Foundation, Vertex Pharmaceuticals, Illumina, aTyr Pharma and Canon Biosciences

• Funded by CF Foundation, Aetna/U.S. Healthcare Endowed Chair and NIDDK

Author: Garry Cutting MD
The challenge

• Over 2700 Mendelian phenotypes with known causative gene (OMIM.org)
• Allelic heterogeneity is the rule
  – Many genes have >100 mutations
• Disease implications
  – Known (usually) for common mutations
  – Variably known for low frequency mutations (<5%)
  – Unknown (usually) for rare mutations (<1%)
• Clinical diagnostic DNA sequencing identifies all 3 types of mutation

Author: Garry Cutting MD
Need for accurate assessment of disease-liability of mutations

- Diagnosis of clinical cases
- Newborn screening
- Carrier screening
  - Pregnancy decisions
- Mutation-specific therapy

Author: Garry Cutting MD
Cystic Fibrosis

• 1 in 3,000 (Caucasians) and ~70,000 affected individuals in North America and Europe

• Caused by mutations in the CF Transmembrane conductance Regulator (CFTR) gene

• Disorder of epithelial ion and fluid transport; elevated sweat chloride concentration is diagnostic

• Life expectancy is ~37 years; obstructive lung disease responsible for 90% of mortality
Pathogenesis of lung disease in CF

Author: Garry Cutting MD

Source: CF Foundation
Cystic Fibrosis as a model for annotation of disease-causing alleles

• Over 1900 mutations identified
  – One mutation is common (p.Phe508del; 70% of CF alleles)
  – Twenty mutations are low frequency (15% of CF alleles)
  – Remainder (>1800) are rare (15% of CF alleles)

• Disease implications of most rare mutations is unknown
Collection of mutation data

Clinic

Laboratory

Cystic Fibrosis Mutation Database

1,903 mutations

39,689 patients

Author: Garry Cutting MD
Data collection facilitated by microattribution

“Curated and peer-reviewed phenotypic annotations (trait measurements and diagnostic categories) attached to gene variants (SNPs, mutations and structural alterations) and indexed to genome sequences could be further highlighted with quantitative counts of annotation activity and publication. *In this way, the intensity of effort and interest in specific areas of genotype-phenotype investigation would be evident to the genetics community, locus by locus*”

**Compete, collaborate, compel** Nature Genetics 39, 931 (2007)
Summary of data collected

CFTR2 database
39,689 patients; 25 clinics/registries

Genotype
70,777 chromosomes

160 mutations
with allele frequency ≥0.01%

4,377 patients
(5 registries/clinics) excluded*

Clinical data analysis
35,319 patients

Sweat chloride
(mmol/L)
24,913 patients^a

Lung function
(FEV1% predicted)
24,946 patients^b

Pancreatic status
(PS or PI)
30,236 patients^c

Author: Garry Cutting MD

Nature Genetics, accepted
How did we determine which mutations cause CF and which ones don’t?
A 3-pronged approach for assigning disease liability

**Clinically** consistent mutation
Average sweat [Cl⁻] ≥ 60 mEq/L

**Functionally** consistent mutation
< 10% of WT CFTR function

**Genetically inconsistent** mutation
Mutation found on non-transmitted ‘healthy’ CFTR gene in father of CF patient

Non-disease causing
Assignment of pathogenicity

159 mutations
≥0.01% frequency in CFTR2

127 mutations meet clinical AND functional criteria
19 mutations meet clinical OR functional criteria
13 mutations meet neither criteria

20 mutations are indeterminate
12 mutations are non CF-causing

Nature Genetics, accepted
Author: Garry Cutting MD
How is the mutation information being translated to practice?
• Improved genetic testing
  – Diagnosis (newborn screening; \( \sim 10^7 \) births/year)
  – Carrier screening (U.S couples; \( 1.2 \times 10^6 \)/year)

• Improved clinical care
  – CFTR2 website/ apps

• Mutation-specific therapies
  – Structure/function analysis

• Qualify clinical endpoints for molecular-based therapy
  – Mutation-Function-Trait correlations

Author: Garry Cutting MD
Improved clinical care: CFTR2.org

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 with this mutation.

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.

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

Author: Garry Cutting MD

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Summary: G542X is seen in 1651 patients in our worldwide CF database. Based on the combination of clinical and functional evaluation, this is a mutation that would cause CF. Based on the patients we have reviewed we would expect this mutation would be associated with pancreatic insufficient CF.

The information displayed below shows how we came to this decision:

- Clinical Characteristics
- Mutation Characteristics
- Functional Testing
- Literature Review
- Population Screening
- Bioinformatics Assessment

This mutation entry was last updated on: 1/19/2012
Patients with this mutation in the CFTR2 database have the following clinical characteristics:

- Average of 1007 patients carrying mutation G542X and mutation F508del
- Average of 1303 patients carrying mutation G542X and an ACMG mutation
- Average of 1327 patients carrying mutation G542X and a pancreatic insufficient mutation
- Average of 1651 patients carrying mutation G542X

### Clinical Characteristics

<table>
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<tr>
<th>CLINICAL FEATURE</th>
<th>AVERAGE OF ALL PATIENTS WITH MUTATION G542X</th>
<th>AVERAGE OF ALL PATIENTS</th>
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<tr>
<td>Sweat Chloride</td>
<td>99</td>
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<td><em>less than 30mEq/L in infants</em></td>
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<td>Lung function</td>
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<td>expressed as % predicted (non-CF 80%-120% predicted)</td>
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<tr>
<td>Pancreatic insufficiency</td>
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<td>87%</td>
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<td>Pseudomonas spp. (less than 1% of non-CF expected to have Pseudomonas spp.)</td>
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<td>53%</td>
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<td>Average Age</td>
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Author: Garry Cutting MD
Improved education via publicly available apps: CFGeneE
Mutation-specific therapy

Primary airway cells from a patient carrying G551D
Van Goor PNAS 2009

Lung function

CF patients carrying G551D Ramsey NEJM 2011
A model for translating allelic heterogeneity to clinical practice

Clinics

Laboratories

Patient Registries

Microattribution

Mutation repositories

Genotype-phenotype database

Phenotype-driven repositories

Author: Garry Cutting MD
CFTR2 Team

Julian Zielenski
Ruslan Dorfman

Vertex Pharmaceuticals and NIDDK R37 DK44003
## Contributors to CFTR2

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<thead>
<tr>
<th>Contributing country, registry, or clinic</th>
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## Contributors to Penetrance Study

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Thank you

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