CDG Discovery, Diagnosis and Outreach

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Our lab’s goals?
Entry points?
How do we discover CDGs?
How do we communicate with families?
How do we interact with other doctors and researchers?
What advances or slows our progress?
Your questions?
Who are we and what are our goals?

• Hud Freeze, PhD (not MD): basic scientist, glycobiologist, interested in glycosylation and glycosylation disorders for over 35 years.

• Bobby Ng, BS: Extraordinary scientist, insightful experimentalist, skilled technician, and excellent manager. Main contact in our lab.

• We share the same interest in science and helping families.

• **OUR GOALS**: Discover new types of CDG and try to understand the underlying science with the goal of making a difference for patients.
ENTRY POINTS?

• DNA sequencing results or transferrin testing
  – FAMILY CONTACTS US
  – PHYSICIAN CONTACTS US
Simple Biomarker for Patients with Glycosylation Disorders

N-glycosylation occurs at N-X-S/T/C

Control

Glyco-deficient
A Dynamic Interplay

Our lab is just a click away

PHYSICIANS

Basic Scientists

Families
How do we communicate with families?

- Either family or physician contacts us
- Obtain informed consent, clinical information physician contact. Evaluate results.
- Request skin cells, DNA, and serum from patient and sometimes other family members.
How do we discover CDGs?

• Patient samples in our hands
• Do assays to rule out (or in) suspected defects
• Suggest testing a CDG Panel of genes-If a known CDG is found then we usually stop
• If unknown, we send trio DNA to Center for Mendelian Genomics, UW for exome analysis
• Analyze results—THIS CAN TAKE A LONG TIME
• Validate defects in candidate genes—THIS CAN TAKE EVEN LONGER!
How do we interact with other doctors and researchers?

• If we find a new type of CDG, we ask others if they found them also.
• Not so simple
• We live in an academic setting where first discovery is prestigious and treasured, second place has much less value.
• The families are empowered to catalyze change by stressing the need to collaborate
THE PATIENT WILL SEE YOU NOW

The Future of Medicine is in Your Hands

Eric Topol
What advances or slows our progress?

• Quick response from families, efficient communication with physicians.
• Every family should receive and/or ask for periodic updates—we owe you that!
• Sometimes suspected defects turn out NOT to be defects. 1000’s of genetic changes happen, but only a few actually cause the disorder.
• Scientific research labs do not provide a “diagnostic service”. Licenced clinical labs must replicate our results.
Lab Strategy to identify CDG patients

- DNA from patients with abnormal transferrin glycosylation (blood and/or fibroblasts samples)
- Gene sequence in collaboration with University of Washington, Center for Mendelian Genomics
- Filter results, for best candidate (Bobby Ng)
- Sequencing and biochemical confirmation
- In two years we and our collaborators identified 7 new CDG defects
History of CDG in Our Lab by the Numbers

• 266 - Fibroblast lines
• 212 - Fibroblast lines with abnormal glycosylation
• 209 – Fibroblasts gene defect (65 PMM2-CDG)
• 64 - WES performed with UW-CMG
• 34 - Cases solved by WES (~ 2 years)
• 30 - Unsolved cases using WES analysis
• 7 - New Disorders discovered in ~ 2 years
• 4 – Number of potential new disorders
GLYCOSYLATION DISORDERS: A GROWING INDUSTRY

IN 2013—A NEW DISORDER EVERY 17 DAYS
Transferrin (Tf) does not detect all CDGs AND Some CDGs alter glycosylation homeostasis

- Disorders in several pathways do not change Tf.
- Even some predicted to change Tf, don’t.
- CDGs can disrupt homeostasis (balance) in a pathway
Hunting down my son's killer

I found my son's killer.

It took three years.

But we did it.
Matt Might and Cristina Cananova met in the spring of 2002, as twenty-year-old undergraduates at the Georgia Institute of Technology. Cristina was an industrial-design major with an interest in philosophy, Matt was a shy computer geek obsessed with "Star Trek." At first, Cristina took no notice of him, but the two soon became friends, and that fell...
WELL PLACED ADVOCATES INCREASE CDG AWARENESS