The NIH Undiagnosed Diseases Program: Medicine for the 21st Century

16 October 2015
Xth International Conference on Rare Diseases and Orphan Drugs
Cynthia J. Tifft, M.D., Ph.D.
Director, NIH Pediatric Undiagnosed Diseases Program
I have no conflicts of interest to disclose
It Takes a Village…

Willam A. Gahl

Cynthia Tifft
David Adams
Camilo Toro
Dennis Landis
Fred Gill
Grace Park
John Schreiber
Ariane Soldatos
Johannes Dastgir
Paul Lee
Tyler Pierson

Gretchen Golas
Lynne Wolfe
Catherine Groden
Michele Nehrebecky
Colleen Wahl
Rena Godfrey

Joy Bryant
Jean Johnston
Casey Hadsall
Val Robinson
David Draper

Cheryl Hipple
Jose Salas
Joan Rentsch
Anabella Roman
Lisa Gardner
Quentin Whitley

Neil Boerkoel
Tom Markello
Murat Sincan
Praveen Cherukuri

Karin Fuentes Fajardo
Valerie Muduro
Hannah Carlson-Donohoe
Jacqueline Brady
Aditi Trehan
Dimitre Simeonov
John Accardi
May Malicdan
Yan Huang
Shira Ziegler
Tim Gall
Taylor Davis
Charles Markello
Roxanne Fischer
William Bone
Amanda Links
Elise Flynn
Elise Valkanas
Collaborators…the expanded village

<table>
<thead>
<tr>
<th>Charité Hospital, Berlin</th>
<th>University of Cincinnati</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peter Robinson</td>
<td>Bruce Aronow</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>University of Toronto</th>
<th>NHGRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michael Brudno</td>
<td>Shawn Burgess</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oregon Health Sciences University</th>
<th>University of Miami</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melissa Haendel and the Monarch Consortium</td>
<td>Grace Zhai</td>
</tr>
<tr>
<td></td>
<td>Gennaro D’Urso</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Children’s Hospital Philadelphia</th>
<th>University of California, Los Angeles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michael Bennett</td>
<td>Shuo Lin</td>
</tr>
<tr>
<td>Miao He</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Case Western Reserve University</th>
<th>NIH Intramural Sequencing Center</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charles Hoppel</td>
<td>Jim Mulliken</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sanger Institute, Cambridge University</th>
<th>NIH Clinical Center</th>
</tr>
</thead>
<tbody>
<tr>
<td>Damian Smedley</td>
<td>&gt; 50 physician scientists who volunteer their time and expertise</td>
</tr>
</tbody>
</table>

> 50 physician scientists who volunteer their time and expertise
Every rare disease was once an undiagnosed disease!!
6% of patients contacting the Office of Rare Disorders do not have a diagnosis.
The unmet need...

- Of the 6000 calls to the NIH Office of Rare Diseases Research in 2007, nearly 400 (6%) were from patients who did not have a diagnosis.

- Of the callers who did have a diagnosis
  - 33% took 1-5 years to receive that diagnosis and,
  - 15% took >5 years.
The Dream:
The NIH Undiagnosed Diseases Program

Launched in May, 2008 as a 5 year pilot project with two main objectives that reflect the mission of the NIH:

- **Public Service**
  - To provide answers to patients with mysterious conditions that had long eluded diagnosis

- **Biomedical Research**
  - To advance medical knowledge by providing insight into human physiology and the genetics of rare and common diseases
The dreamers...

Steve Groft

Bill Gahl
UDP Model

1. Comprehensive Record Evaluation
2. Selection: Clinical Criteria Family Structure
3. Extensive Clinical Evaluation and Testing
   - HGMD Diagnosis if Possible
   - Family Exome and SNP Chip
   - Biospecimen Collection
   - Strong Candidate Genes
   - Active Collaborator Recruitment
   - New disease discovery

NATIONAL HUMAN GENOME RESEARCH INSTITUTE
Division of Intramural Research
UDP Operations

- Applications are received, acknowledged, and additional records, radiographs, photos, or pathology slides are requested.
- Charts are organized and scanned electronically.
- Adult and pediatric directors triage records for review by appropriate specialists.
- Directors synthesize specialist reviews and make a final disposition.
- Patients and referring physicians are informed of the decision.
All UDP applicants are desperate--

- Everyone gets something from the UDP
  - Complete charts are organized
  - Every chart is read thoroughly by specialists
  - Applicants not accepted (75%) & their physicians receive a personal letter with recommendations for further work up
  - Accepted applicants (25%) receive a one week inpatient evaluation at the NIH Clinical Center in Bethesda, Maryland
Optimizing Selection Criteria

- Patients more likely to be selected
  - Objective documented physical or biochemical finding
  - Completely evaluated in an academic medical setting
  - Family structure favorable to genetic analysis
    - Both parents available for blood samples
    - Additional family members with the same phenotype
    - Unaffected siblings
    - Consanguineous families
<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inquiries</td>
<td>7585</td>
<td></td>
</tr>
<tr>
<td>Medical Records</td>
<td>3124</td>
<td>(41%)</td>
</tr>
<tr>
<td>Acceptances</td>
<td>966</td>
<td>(31%)</td>
</tr>
<tr>
<td>Pediatric probands</td>
<td>348</td>
<td>(36%)</td>
</tr>
<tr>
<td>Female</td>
<td>519</td>
<td>(54%)</td>
</tr>
<tr>
<td>Neurologic phenotype</td>
<td></td>
<td>(~50%)</td>
</tr>
<tr>
<td>Diagnoses</td>
<td>176 in 150</td>
<td>(20%)</td>
</tr>
<tr>
<td>Pediatric diagnoses</td>
<td>93</td>
<td>(33%)</td>
</tr>
</tbody>
</table>

* UDP statistics 2008-2015*

* As of October 12, 2015
# Major Phenotypes

<table>
<thead>
<tr>
<th>Category</th>
<th>Applicants (N=1006)</th>
<th>Accepted (N=288)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>4%</td>
<td>8%</td>
</tr>
<tr>
<td>Dermatology</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Endocrine</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Fibromyalgia/CFS</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Hematology</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Immunology</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td><strong>Neurology</strong></td>
<td><strong>51</strong></td>
<td><strong>57</strong></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Renal</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Rheumatology</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th>Applicants</th>
<th>Accepted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>60%</td>
<td>56%</td>
</tr>
</tbody>
</table>
Pediatric applicants

Number of applicants

Age in years

1  2  3  4  5  6  7  8  9  10  11  12  13  14  15  16  17  18  19  20  21  22  23  24  25  26  27  28  29  30  31
UDP Process

Selection: Clinical Criteria
Family Structure

Comprehensive Record Evaluation

Extensive Clinical Evaluation and Testing

Strong Candidate Genes

Family Exome and SNP Chip

Biospecimen Collection

Active Collaborator Recruitment

New disease discovery

New disease discovery
phenotype

- the observable properties of an organism that are produced by the interaction of the genotype and the environment

- Without accurate phenotyping, exome/genome analysis is uninterpretable.

- Careful phenotyping is everything!!
Phenotyping in the UDP

- Starts when charts are received
- Becomes more focused as charts are reviewed and patient accepted
- Expands during the patient evaluation
- Comes together once all clinical and diagnostic testing is received
# Scheduling the evaluation...

<table>
<thead>
<tr>
<th>F.P.</th>
<th>DOB</th>
<th>MR #</th>
<th>UDP#</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Monday 02/10/2014</td>
<td>Tuesday 02/11/2014</td>
<td>Wednesday 02/12/2014</td>
<td>Thursday 02/13/2014</td>
<td>Friday 02/14/2014</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7:00a Admissions</td>
<td>7:00a</td>
<td>7:00a</td>
<td>7:00a</td>
<td>7:00a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7:30a</td>
<td>7:30a</td>
<td>7:30a</td>
<td>7:30a</td>
<td>7:30a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8:00a</td>
<td>8:00a</td>
<td>8:00a</td>
<td>8:00a</td>
<td>8:00a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8:30a</td>
<td>8:30a</td>
<td>8:30a</td>
<td>8:30a</td>
<td>8:30a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9:00a History and physical on 1NW Inpatient Unit</td>
<td>9:00a</td>
<td>9:00a</td>
<td>9:00a</td>
<td>9:00a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9:30a</td>
<td>9:30a</td>
<td>9:30a</td>
<td>9:30a</td>
<td>9:30a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10:00a</td>
<td>10:00a</td>
<td>10:00a</td>
<td>10:00a</td>
<td>10:00a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10:30a</td>
<td>10:30a</td>
<td>10:30a</td>
<td>10:30a</td>
<td>10:30a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11:00a</td>
<td>11:00a</td>
<td>11:00a</td>
<td>11:00a</td>
<td>11:00a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11:30a</td>
<td>11:30a</td>
<td>11:30a</td>
<td>11:30a</td>
<td>11:30a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12:00p</td>
<td>12:00p</td>
<td>12:00p</td>
<td>12:00p</td>
<td>12:00p</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12:30p</td>
<td>12:30p</td>
<td>12:30p</td>
<td>12:30p</td>
<td>12:30p</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:00p</td>
<td>1:00p</td>
<td>1:00p</td>
<td>1:00p</td>
<td>1:00p</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:15p</td>
<td>1:15p</td>
<td>1:15p</td>
<td>1:15p</td>
<td>1:15p</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:30p</td>
<td>1:30p</td>
<td>1:30p</td>
<td>1:30p</td>
<td>1:30p</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2:00p</td>
<td>2:00p</td>
<td>2:00p</td>
<td>2:00p</td>
<td>2:00p</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2:30p</td>
<td>2:30p</td>
<td>2:30p</td>
<td>2:30p</td>
<td>2:30p</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3:00p</td>
<td>3:00p</td>
<td>3:00p</td>
<td>3:00p</td>
<td>3:00p</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3:30p</td>
<td>3:30p</td>
<td>3:30p</td>
<td>3:30p</td>
<td>3:30p</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4:00p</td>
<td>4:00p</td>
<td>4:00p</td>
<td>4:00p</td>
<td>4:00p</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4:30p</td>
<td>4:30p</td>
<td>4:30p</td>
<td>4:30p</td>
<td>4:30p</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5:00p</td>
<td>5:00p</td>
<td>5:00p</td>
<td>5:00p</td>
<td>5:00p</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6:00p</td>
<td>6:00p</td>
<td>6:00p</td>
<td>6:00p</td>
<td>6:00p</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7:00p</td>
<td>7:00p</td>
<td>7:00p</td>
<td>7:00p</td>
<td>7:00p</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8:00p</td>
<td>8:00p</td>
<td>8:00p</td>
<td>8:00p</td>
<td>8:00p</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9:00p</td>
<td>9:00p</td>
<td>9:00p</td>
<td>9:00p</td>
<td>9:00p</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Informed Consent**
- **Genetic Counseling**
- **Sedate Day**
- **Wrap-Up**
Choreography of pediatric sedation day...

Pediatric anesthesia services in MRI suite to accomplish multiple studies under a single 3-5 hour sedation:

- Brain MRI/MRS
- Lumbar puncture
- Skin biopsy
- Eye exam
- Brainstem evoked response
- Dysmorphology exam
- Dental exam
- EMG/NCV
- Large blood draws
- Catheterization for urine sample
- Minor surgical procedures
Pediatric UDP: First 5 years

- Patients Evaluated: 215 (193 families)
  - Patients diagnosed: 56 (26%)
    - Two families had 3 diagnoses each
    - Nine families had 2 or more affected sibs
    - Two patients had a deceased sib with the same phenotype
  - Genetic diagnoses made: 50
    - Next Gen/SNP analysis: 22
    - Conventional testing: 28
  - May excellent candidate genes not previously linked to human disease
UDP Process

Selection: Clinical Criteria
Family Structure

Comprehensive Record Evaluation

Extensive Clinical Evaluation and Testing

Strong Candidate Genes

Family Exome and SNP Chip

Biospecimen Collection

Active Collaborator Recruitment

New disease discovery

National Human Genome Research Institute
Working hypotheses…

- An extremely rare disease
- More than one disease…. 
- An unusual presentation of a more common disease 
- An entirely new disease
Extremely rare disease
UDP 1846

- 5 year old with adducted thumbs, clubbed feet, hypotonia, and bleeding disorder
UDP 1846
Phenotype suggests candidate gene

- SNP array shows 26 Mb of homozygosity unique to the patient containing 72 genes.
- One gene fits clinical picture: \textit{CHST14}
- Patient homozygous for G>C in exon 14.

\textit{CHST14} encodes dermatan-4-sulfotransferase 1 important for the formation of dermatan sulfate which is fibrinolytic.
- Could one prevent the bruising/bleeding by treating with dermatan sulfate?

The Phenotype of the Musculocontractural Type of Ehlers-Danlos Syndrome due to \textit{CHST14} Mutations

Andreas R. Janecke,\textsuperscript{1,2*} Ben Li,\textsuperscript{3} Manfred Boehm,\textsuperscript{4} Birgit Krabichler,\textsuperscript{2} Marianne Rohrbach,\textsuperscript{5} Thomas Müller,\textsuperscript{2} Irene Fuchs,\textsuperscript{1} Gretchen Golas,\textsuperscript{6} Yasuhiro Katagiri,\textsuperscript{7} Shira G. Ziegler,\textsuperscript{6} William A. Gahl,\textsuperscript{6} Yael Wilnai,\textsuperscript{8} Nicoletta Zoppi,\textsuperscript{9} Herbert M. Geller,\textsuperscript{7} Cecilia Giunta,\textsuperscript{5} Anne Slavotinek,\textsuperscript{3} and Beat Steinmann\textsuperscript{5}
Extremely rare disease with expanded phenotype
UDP 2146, 2156

MED23-Associated Intellectual Disability in a Non-Consanguineous Family

Aditi Trehan,¹,² Jacqueline M. Brady,¹,² Valerie Maduro,¹,² William P. Bone,¹,² Yan Huang,¹,² Gretchen A. Golas,¹,² Megan S. Kane,² Paul R. Lee,³ Audrey Thurm,⁴ Andrea L. Gropman,¹,⁵ Scott M. Paul,⁶ Gilbert Vezina,⁷ Thomas C. Markello,² William A. Gahl,¹,² Cornelius F. Boerkoel,² and Cynthia J. Tifft¹,²*
Filtered Variants, Family vs No Family

Analysis of DNA Sequence Variants Detected by High-Throughput Sequencing

David R. Adams,1,2* Murat Sincan,2 Karin Fuentes Fajardo,1 James C. Mullikin,3† Tyler M. Pierson,1,4 Camilo Toro,1 Cornelius F. Boerkoel,1 Cynthia J. Tiffit,1,3 William A. Gahl,1,2,3 and Tom C. Markello5
Exome analysis in the UDP

Exome analysis
- 360 families
- 1329 exomes

Average Family Size
- Pediatric patients 4.1
- Adult patients 3.3
UDP Process Revised

Selection: Clinical Criteria
Family Structure

Comprehensive Record Evaluation

Extensive Clinical Evaluation and Testing

Strong Candidate Genes

Family Exome and SNP Chip

Biospecimen Collection

Glycome Metabolome

Active Collaborator Recruitment

New disease discovery

New disease discovery
11 year old Male
- Dysmorphic facial features
- Global developmental delay
- Spastic paraparesis
- Truncal hypotonia
- Bilateral hearing loss
- Optic atrophy
- Cerebral atrophy, small corpus callosum, low NAA
- Multiple fractures
- Leukocytosis
- Generalized aminoaciduria
- Hypogammaglobulinemia
- Normal carbohydrate deficient transferrin

6 year old Female
- Dysmorphic facial features
- Global developmental delay
- Generalized hypotonia
- Neonatal seizures
- Cerebral folate deficiency
- Optic atrophy
- Cerebral atrophy, small corpus callosum, low NAA
- Leukocytosis
- Hypogammaglobulinemia
- Normal carbohydrate deficient transferrin
Urine glycans prove key role.

- Glu4 or Glu3Man1
- Tetrasaccharide
- Mannosyl-Oligosaccharide Glucosidase (MOGS-CDG)

Diagnosis: MOGS-CDG
Glycosylation, Hypogammaglobulinemia, and Resistance to Viral Infections

Mohammed A. Sadat, M.D., Ph.D., Susan Moir, Ph.D., Tae-Wook Chun, Ph.D., Paolo Lucio, M.D., Ph.D., Gerardo Kaplan, Ph.D., Lynne Wolfe, N.P., Matthew J. Memoli, M.D., Miao He, Ph.D., Hugo Vega, M.D., Ph.D., Leo J.Y. Kim, B.A., Yan Huang, Ph.D., Nadia Hussein, B.E., Elma Niervas, M.D., Raquel Mitchell, Ph.D., Mary Garofalo, R.N., Aaron Louie, B.Sc., Derek C. Ireland, Ph.D., Claire Grunes, Raffaele Cimbro, Ph.D., Vyomesh Patel, Ph.D., Genevieve Holzapfel, Ph.D., Daniel Salahuddin, B.Sc., Tyler Bristol, M.S., David Adams, M.D., Beatriz E. Marciano, M.D., Madhuri Hegde, M.D., Yuxing Li, Ph.D., Katherine R. Calvo, M.D., Ph.D., Jennifer Stoddard, B.S., J. Shawn Justement, M.S., Jerome Jacques, M.S., Debra A. Long Priel, M.S., Danielle Murray, M.A., Peter Sun, Ph.D., Douglas B. Kuhn, Ph.D., Cornelius F. Boerkoel, M.D., Ph.D., John A. Chiorini, Ph.D., Giovanni Di Pasquale, Ph.D., Daniela Verhelyi, M.D., Ph.D., and Sergio D. Rosenzweig, M.D., Ph.D.

- Vaccinations and Titers
  - Tetanus  -> (+) protective titers
  - Diphtheria -> (+) protective titers
  - HiB        -> (+) protective titers
  - Pneumococcal  -> (+) protective titers
  - Measles   -> (-) protective titers
  - Mumps      -> (-) protective titers
  - Varicella  -> (-) protective titers
More than one disease in a non-consanguineous family
Careful phenotyping is key

- Sibling pair with recurrent episodes of ketotic hypoglycemia
Three rare diseases in one Sib pair: *RAI1, PCK1, GRIN2B* mutations associated with Smith–Magenis Syndrome, cytosolic PEPCK deficiency and NMDA receptor glutamate insensitivity

David R. Adams a,b, Hongjie Yuan c, Todd Holyoak d, Katrina H. Arajs d, Parvin Hakimi g,h, Thomas C. Markello a, Lynne A. Wolfe a, Thierry Vilboux b, Barbara K. Burton e,f, Karin Fuentes Fajardo a, George Grahame i, Conisha Holloman j, Murat Sincan a, Ann C.M. Smith a, Gordon A. Wells k,l, Yan Huang a, Hugo Vega a, James P. Snyder k, Gretchen A. Golas a, Cynthia J. Tifft a, Cornelia F. Boerkoel a, Richard W. Hanson g, Stephen F. Traynelis c, Douglas S. Kerr g,h,i, William A. Gahl a,b

- PCK1 mutation for enzyme PEPCK
- Smith Magenis Syndrome (RAI1)
- PCK1 mutation for enzyme PEPCK
- GRIN2B mutation for ID phenotype
Unusual presentation of a more common disease
UDP 5316

- **GARS**
  - Glycyl tRNA synthetase
  - Charcot-Marie-Tooth disease, type 2D
  - Distal hereditary motor neuronopathy type VA
  - Autosomal dominant
New disease/gene association
UDP 3866

Mosaicism in 1st generation (fertile)

Ablepharon macrostomia syndrome
**TWIST2**

c.223G>A(p.E75K)

Transcription factor

Group A helix-loop-helix transcription factor (E box)

Mesenchyme and craniofacial and dermis in embryogenesis plus cell maintenance

Autosomal dominant

7 families with Ablepharon macrostomia

10 families with Barber-Say syndrome

**TWIST2** (NM_057179)
Families with Arterial/Joint Capsule Calcification

(A) Family 1

(B) Family 1: VI-5

(C) X-rays showing calcification in different areas of the body

(D) Enlarged view of a hand and foot showing calcification

(E) Full body X-ray showing calcification in the joints and bones
The finding of additional families and strong candidate genes led to gene discovery.

Could adenosine or an adenosine analog decrease calcification in the major vessels of individuals with atherosclerosis?
Expanding the vision...
What about the 75% of cases unsolved…

- Good candidate genes in an additional 70 families (quartets on average)
  - Mendelian consistent, rare, good coverage, and predicted deleterious, BUT
  - Gene is not associated with any known disease
  - Gene associated with known disease, but not our phenotype
UDP Process Revised & Extended

Selection: Clinical Criteria
Research Criteria

Comprehensive Record Evaluation

Extensive Clinical Evaluation and Testing

Glycome Metabolome

Family Exome & SNP Chip

Biospecimen Collection

Strong Candidate Genes

Create Research-Grade Dataset

Active/Passive Collaborator Recruitment
UDP Integrated Collaboration System

- A patient centric information, process management and communications system designed to improve productivity and collaboration.
- Enables UDP leaders to manage each patient’s disease as a unique research project with unique experimental design and cohort of collaborators.
### Quick Phenotype Search:

#### Craniofacial
- **Y** N Craniosynostosis
- **Y** N Cleft upper lip
- **Y** N Cleft palate
- **Y** N Abnormal facial shape

**Other**
(enter free text and choose among suggested ontology terms)

#### Eye Defects
- **Y** N Visual impairment
- **Y** N Abnormality of the cornea
- **Y** N Coloboma
- **Y** N Abnormality of the anterior chamber
- **Y** N Cataract
- **Y** N Abnormality of the retina
- **Y** N Abnormality of the optic nerve
- **Y** N Microphthalmos
- **Y** N Nystagmus
- **Y** N Strabismus

**Other**
(enter free text and choose among suggested ontology terms)

#### Ear Defects
- **Y** N Deafness
  - **Y** N Sensorineural
  - **Y** N Conductive
  - **Y** N Preauricular pit
  - **Y** N Preauricular skin tag
  - **Y** N Abnormality of the outer ear
  - **Y** N Abnormality of the inner ear

### Current Selection

#### Growth Parameters
- Decreased body weight
  - Neonatal onset
  - Slow progression

#### Craniofacial
- Cleft upper lip
  - Delete - Clear details
  - No additional information.

#### Eye Defects
- Cataract
  - Delete - Add details

#### Ear Defects
- Abnormality of the outer ear
  - Delete - Add details

#### Musculoskeletal
- Hip osteoarthritis
  - Delete - Add details

#### Behavior, Cognition and Development
- Repetitive compulsive behavior
  - Delete - Add details
- Multim
  - Delete - Add details
- Self-injurious behavior
  - Delete - Add details
- Attention deficit hyperactivity disorder
  - Delete - Add details
- Behavioural/Psychiatric abnormality
  - Delete - Clear details
  - No additional information.
Phenotype similarity across patients or any organism

- Cleft palate
- Exaggerated Cupid's bow
- Bowing of the long bones
- Long hallux
- Arthrogryposis multiplex congenita
- Midface retrusus
- Protruding ears

- Cleft palate
- Abnormality of upper lip
- Limb long bone phenotype
- Abnormality of toe
- Abnormal joint morphology
- Abnormal head shape
- Prominent ears

- Cleft palate
- Abnormal limb long bone morphology
- Digit 1 phenotype
- Epiphyseal plate morphology
- Short snout
- Lowered ear position

https://code.google.com/p/owltools/wiki/OwlSim

Courtesy M. Haendel
Finding the second case... Matchmaker Exchange
No good deed goes unpunished…
The Undiagnosed Diseases Network
1. **Improve the level of diagnosis and care** for patients with undiagnosed diseases

2. **Facilitate research** into the etiology of undiagnosed diseases

3. **Create an integrated and collaborative research community** to identify improved options for optimal patient management
Seven clinical sites, a coordinating center, two DNA sequencing cores, a metabolomics core, a model organisms screening center, and a central biorepository.

The NIH site will continue to enroll about 150 patients per year, each of the clinical sites will ultimately enroll about 50 patients per year.
A cry for help.....

Help.

Dear Doctors,

My name is Taylor. I'm 11 years old and I have a sickness that no one can figure out. I need your help and I need it badly. I'm sick and tired of people telling me I'm faking or I'm stressed but they're not in my body. I've always wanted to become an actress or model & maybe even try a singing career but this sickness is not helping me get closer to fulfilling my dreams. I cry every night before I go to bed because of what I'm going through. I NEED HELP! Please please if you guys are a really good doctor than please try to help & figure out what's wrong with me.

From: Taylor
“A small group of thoughtful people could change the world. Indeed, it’s the only thing that ever has.”

-Margaret Mead