The NIH Undiagnosed Diseases Network

NIH Council of Councils
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William A. Gahl, MD, PhD
Clinical Director, NHGRI
Director, NIH Undiagnosed Diseases Program
Testing the feasibility of a national network that extends and expands upon the success of the intramural NIH Undiagnosed Diseases Program to:

- **Improve the level of diagnosis and care** for patients with undiagnosed diseases by developing protocols designed by a large community of investigators

- **Facilitate research** into the etiology of undiagnosed diseases by collecting and sharing standardized, high-quality clinical and lab data including genotyping, phenotyping, and environmental exposure histories

- **Create an integrated and collaborative research community** across multiple clinical sites and among lab and clinical investigators to investigate the pathophysiology of new and rare diseases
The UDN

1. The NIH Undiagnosed Diseases Program (UDP)
   - Background
   - Discoveries
   - Mysteries/Treatment
   - Diagnoses

2. Expansion to a Network

3. The Future
• Goals:
  – To assist patients with unknown disorders reach an accurate diagnosis
  – To discover new diseases that provide insight into human physiology and genetics
Intramural UDP Operations

• Applicants submit medical records
• Referring physician sends summary letter
• UDP Director triages submitted records
• Intramural NIH consultants review records
  – Many different specialties involved
  – Research oriented; not financially driven
• UDP Director makes final disposition
• Patients/physicians receive a standard letter; advice conferred in ~25% of cases
• If accepted, 1-week inpatient CC admission
UDP Numbers

- Medical Records: ~3500
- Admitted & Evaluated: ~1000
- Children: ~40%
- Neurological: ~50%
- Some diagnosis: ~25%
- Publications ~70
UDP Investigations

1. Patient phenotyping to rule out known diseases and describe new ones.

2. Genetic studies
   a. Commercial testing
   b. SNP arrays
   c. Exome sequencing

3. Functional studies (assays, model systems)
Discovery
5 Adult Siblings with these Clinical Symptoms and Signs:

- Intermittent claudication of calves, thighs, buttocks
- Chronic ischemic pain of the feet
- Joint pain in the hands
- Arterial calcification of lower extremities
- Spared coronary arteries
Femoral-Popliteal Artery Calcification
Parents were 3rd Cousins
SNP Array: Chromosome 6q14.3-6q21

Region of Identical Homozygosity

Dr. Tom Markello
Region of homozygosity: **22.4MB**
- 7977 total SNPs without a single A/B genotype in any locus
- 92 genes, about 902 exons
- No structural genes of the extracellular matrix
- One good candidate gene: **NT5E**, encoding CD73, an ecto-5’-nucleotidase

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T. Markello, C. St. Hilaire
NT5E Encodes CD73

AMP $\xrightarrow{\text{CD73}}$ Adenosine $+$ Pi
**NT5E Sequencing Analysis**

Family 1 (UDP)

- c.662C>A, S>X

Family 2 (Kleta)

- c.1073G>A, C>Y

Family 3 (Nussbaum)

- c.1069dupA/c.662C>A

*S. Ziegler*
Increased Fibroblast Staining for Alkaline Phosphatase

Control | Affected | Affected + Adenosine

Adenosine treatment of cells reduces alkaline phosphatase staining.

Rescue of Cell Calcification by a CD73 Lentivirus, Adenosine, or an Alkaline Phosphatase Inhibitor (Levamisole)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No Control</th>
<th>Control Lentivirus</th>
<th>CD73 Lentivirus</th>
<th>Adenosine</th>
<th>Levamisole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affected: VI-4</td>
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10 year-old boy and 5 year-old girl

- Facial dysmorphism, hypotonia, delays, hearing loss, nystagmus, seizures
- MRI: Diffuse atrophy, especially periventricular
- Labs normal, including transferrin IEF
- Urine glycan screening by MALDI (Dr. Miao He, Emory) confirmed hex4 band seen on TLC.
Oligosaccharide TLC

Dr. Miao He
Urine glycan MALDI profile

Glu4 or Glu3Man1

Dr. Miao He
Deficiency of Glucosidase I?

• In N-linked glycoprotein synthesis, Glc$_3$Man$_9$GlcNac$_2$ is transferred to polypeptides in the ER.
• Glucosidase I is the first trimming enzyme, removing the terminal glucose.
• Further trimming allows for creation of complex oligosaccharide on N-linked glycopolypeptides.
• Glucosidase I deficiency is Congenital Disorder of Glycosylation IIb (1 patient).
Mutation Analysis of Glucosidase I Gene

Both affected children are compound heterozygous for:

– Exon 2: c.370C>T, p.124Q>X

They are the 2\textsuperscript{nd} and 3\textsuperscript{rd} patients in the world with CDG IIb.
CDGIIb Patients

- Hypogammaglobulinemia
  - IgG 142 (504-1465 mg/dL)
  - IgA 18 (27-195 mg/dL)
  - IgM 25 (24-210 mg/dL)

- Why?
  - IgG, lacking oligosaccharides in patient, is rapidly degraded.
Hypo/agammaglobulinemia Evaluation: IgG Half-life in RAG1 SCID Mice

IgG half life: Control 21 days  
Patient 6 days

Dr. Sergio Rosenzweig
Despite hypogammaglobulinemia, CDGIIb patients do not get infections! 

WHY?
CDGIIb cells could be infected with virus, but once infected, they produced much less virus.
And the virus produced is 50-80% less infective, as gauged by the ability to produce a secondary infection.
Viral susceptibility model

Infections in WT cells

Glycosylation-Dependent
Primary infection

Glycosylation-Independent
Secondary infection

Infections in CDGIIb cells

Glycosylation-Dependent
Primary infection

Glycosylation-Independent
Secondary infection
Mysteries/Treatment
UDP 10237-25 year old man with contractures and skin ulcerations
Upper Extremities
Lower Extremities
Left lower extremity

Marcus Chen, MD
UDP 10237

• No diagnosis, but because the calcifications could be stimulating an inflammatory reaction, Dr. Lisa Rider (Rheum) suggested topical sodium thiosulfate.

• The thiosulfate salt of calcium is 250-10,000 times more soluble than the phosphate salt.
Diagnoses
Very Very Rare Diagnoses

- Myoclonus epilepsy without renal failure – due to SCARB2 mutations (5 in world)
- Ichthyosis Follicularis with Atrichia and Photophobia (IFAP) with MBTPS2 mutations (6 families in world)
- Neurodegeneration with brain iron due to c19orf12 mutations (20 families)
- ALS-Frontotemporal Dementia due to c9orf72 expansion
- Cytosolic PEPCK deficiency due to PCK1 muts
- KDCT7 in two sibs with ataxia, Sz (2 families)
- Nephrolithiasis & 24-hydroxylase deficiency (few families)
Very Very Rare Diagnoses

- Congenital Disorder of Glycosylation type 2b (2nd and 3rd cases in world)
- Adducted Thumb-Clubfoot Syndrome & \( \text{CHST14} \) mutations (1st case in U.S.)
- Spinocerebellar ataxia, myoclonic epilepsy & \( \text{AFG3L2} \) muts (1st AR case)
- Autosomal Dominant Leukodystrophy & \( \text{LMNB1} \) duplication (~10 in world)
- Adenylosuccinate lyase def. (~60 cases)
- Hereditary Muscular Neuropathy type 6 due to \( \text{IGHMBP2} \) muts (oldest pt. known)
- Fatty acid 2-hydroxylase def. (~50 cases)
Recent Diagnoses

- Spermine synthetase mutations with developmental delays (Snyder-Robinson)
- XP with dementia due to ERCC1 mutation
- Delays and seizures due to PIGT mutations and GPI anchor deficiency
- Stargardt syndrome, Pelger-Huet anomaly, and others with chromosome 1 isodisomy
- Movement disorder due to PLA2G6 mutations
- Osteopetrosis due to LRP5 mutation
- Mowat-Wilson syndrome due to ZEB2 mut
- Fahr’s disease due to PDGFRB mutations
- Spasticity & leucodystrophy due to DARS mut
- Leucodystrophy due to AARS2 mut
Recent Diagnoses

- Kohlschutter-Tonz syndrome (Sz, neurological regression) due to \textit{ROGDI} mutations
- Delays, hypotonia, strabismus due to biallelic \textit{UNC80} mutations
- CVID, aplastic anemia due to a \textit{CTLA4} mut
- Myofibrillar myopathy with de novo \textit{BAG3} mut
- X-linked intellectual disability, facial dysmorphisms due to \textit{RLIM} mutation
- Desminopathy
- Fatal Creutzfeldt-Jacob; PrPSc/PrP27-30
- Oculodentodigital Dysplasia due to \textit{GJA1} (connexin 43) mutations
- Chorea, hypomyelination-de novo \textit{TUBB4A} mut
Some UDP Communications

- Announcement May 19, 2008 (Dr. Zerhouni)
  - 90 patient advocacy groups; 25 reporting agencies

- Written press coverage
  - *Newsweek* article
  - Scores of newspaper articles
  - *NY Times Magazine, People Magazine* (!)
  - *Nature* article

- Television and Radio
  - NBC Nightly News
  - Fox Television (Chris Wallace); PBS
  - CNN (Dr. Sanjay Gupta)
  - ABC Today Show
  - 60 Minutes
  - Discovery
Political Inquiries

Congress 39
NIH Director 30
Secretary HHS 4
White House 1

Congressional Visits to NIH UDP ~6
Expansion to a UDN

- UDP, 7 Clinical Sites, Coordinating Center, 2 Sequencing Cores, Metabolomics Core, Model Organisms Screening Center, Central Repository
- Central NHGRI IRB; Reliance Agreements
- Formal data sharing agreements
- Consent: PII to be shared within UDN, de-identified data with others.
- First patients: August 2015.
Mapping UDP to UDN

1. Phenotyping -> 7 Clinical Sites
2. Genetics -> 2 Sequencing Cores
1. Functional studies -> Model Organism Screening Core; Gene Function initiatives
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.
The UDN Gateway

Click “Apply” button on any UDN website for more information

http://undiagnosed.hms.harvard.edu/apply/
Challenges of expanding Intramural UDP -> Extramural centers (UDN)

1. **Financial issues**
   - Billing for clinical vs research
   - Payment for patient travel
   - Ability to examine/study family members

2. **Practical issues**
   - Inpatient vs outpatient; sequence before visit?
   - Availability of diverse specialists
   - Time for consultants to discuss case together

3. **Research issues**
   - Need to expand the capacity to investigate the pathophysiology of new diseases
   - Federal/medical center data sharing
Progress – Toward Diagnosis

- Applications: 611
- Accepted: 220
- Evaluated: 40
- Diagnosed: 11
- Exomes sent: 189
- Genomes: 135
- Model Organism Genes: 52
- Metabolomics: Starting
- Collaborations: UCLA & Baylor; Duke

As of May 1, 2016; UDN opened August 2015
Progress - Toward Sharing

- Coordinating Center collecting data; available to Network, collaborators
- Submission to public databases
- UDN accepting applications for Collaborative Clinical Sites abroad
- Model Organisms Screening Core and Metabolomics Cores are discussing cases with clinicians
- International Undiagnosed Diseases Network
Manual of Operations Available!
http://undiagnosed.hms.harvard.edu/
Undiagnosed Diseases Network International (UDNI):
White Paper for Global Actions to Meet Patient Needs
Domenica Taruscio\textsuperscript{a}, Stephen C. Groft\textsuperscript{b}, Helene Cederroth\textsuperscript{c}, Béla Melegh\textsuperscript{d}, Paul Lasko\textsuperscript{e}, Kenjiro Kosaki\textsuperscript{f}, Gareth Baynam\textsuperscript{g}, Alexa McCray\textsuperscript{h}, William A. Gahl\textsuperscript{i}

\textit{Molecular Genetics and Metabolism 116:223-5, 2015.}

Website:
http://www.udninternational.org/
UDNI Meetings - Sharing

1. Meetings
- Rome September 2014
- Budapest – June 2015
- Vienna – February 2016
- Tokyo – November 2016
- Common Fund + Wilhelm Foundation

2. UDPs Operating
- Western Australia
- Japan
- Vienna
- Italy
New United States UDPs

- UDN has stimulated other groups to start UDPs.
- Sequencing but no research testing.
- Other sites look to UDN for collaborations, sharing, MOO.
- Sites include:
  - U. Alabama-Birmingham
  - Emory
  - Mayo
  - U. Utah
Issues for the UDN

1. Billing
2. Sequence before or after seeing patient
3. How to disseminate information
4. Sustainability of UDN model
5. Central support vs. Local support
Sustainability/Dissemination of the UDN

- FY18-22: Request Common Fund support; plan for future support.
- FY23->: No Common Fund support.
  - Extramural portion of UDN
    • NCATS? CTSAs? Central NIH Database?
    • Independent medical center support? Philanthropy?
  - Intramural
    • Supported by Clinical Center, consortium of ICs?
      - Reduced volume of new patients
      - Follow-up for previous patients
      - Disseminate new disease patients to ICs
      - Maintain UDPICs database