NCATS Advisory Council
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NCATS Partnerships with NIH Common Fund

THE UNDIAGNOSED DISEASES NETWORK

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Undiagnosed Diseases Program
(May 19, 2008)

• **Goals:**
  - To assist patients with unknown disorders to reach an accurate diagnosis
  - To discover new diseases that provide insight into human physiology and genetics
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
Political Inquiries

Congress 35
NIH Director 23
Secretary HHS 4
White House 1

Congressional Visits to NIH UDP ~6
UDP Numbers

• Inquiries: ~10,000
• Medical Records: >3300
  ~2500 Rejected
  >900 Accepted
  ~800 on UDP service; 130 other services
  ~40% children
• Types of Cases
  Roughly half are neurological; some of these are mitochondrial
  Many complex pediatric genetic disorders
• Some diagnosis in ~25%
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 (just reported as disease)
- Cytosolic PEPCK deficiency due to PCK1 muts
- KDCT7 in two sibs with ataxia, Sz (2 families)
- Nephrolithiasis & 24-hydroxylase deficiency (few families)
- Congenital Disorder of Glycosylation type 2b (2nd and 3rd cases in world)
- Adducted Thumb-Clubfoot Syndrome & CHST14 mutations (1st case in U.S.)
- Spinocerebellar ataxia, myoclonic epilepsy & AFG3L2 muts (1st AR case)
- Autosomal Dominant Leukodystrophy & LMNB1 duplication (~10 in world)
- Adenylosuccinate lyase def. (~60 cases)
- Hereditary Muscular Neuropathy type 6 due to IGHMBP2 muts (oldest pt. known)
- Fatty acid 2-hydroxylase def. (~50 cases)
New Disease Genes

- Arterial Calcification due to Deficiency of CD73; \textit{NT5E} mutations
- Developmental delay & anemia; \textit{CAD}
- Ablepharon macrostomia; \textit{TWIST2}
- Short stature, osteoporosis; \textit{ATP6V1H}
- Skin & hair abnormalities; \textit{HEPHL1}
- Developmental delays; \textit{PRUNE}
UDN Objectives

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
Undiagnosed Diseases Network

Coordinating Center (1 award)

Clinical Sites (NIH UDP and 6 awards)

Gene Function (3-6 per year)

DNA Sequencing Cores (2 awards)

Model Organisms (1 award)

Metabolomics (1 award)
Seven clinical sites, a coordinating center, two DNA sequencing cores, a metabolomics core, a model organisms screening center, and a central biorepository.
UDN Coordinating Center

• Coordinate UDN network-wide activities
• Facilitate collaboration amongst laboratory and clinical researchers
• Develop innovative analytical approaches
• Share data and approaches
• RFA-RM-12-020
Seven clinical sites, a coordinating center, two DNA sequencing cores, a metabolomics core, a model organisms screening center, and a central biorepository.
Patients: 10 FY14, 25 FY15, 50 per year FY16-17

Sequence: 35 FY15, 140 per year FY16-17

- Provide clinical evaluation in one week
- Accept un-insured and under-insured patients
- Evaluate patients with disorders in any clinical specialty
- RFA-RM-13-004

UDP: ~150 patients and ~400 sequenced per year FY14-17
Seven clinical sites, a coordinating center, two DNA sequencing cores, a metabolomics core, a model organisms screening center, and a central biorepository.
UDN Sequencing Cores

Provide UDN DNA sequencing and CLIA variant validation

- Raw sequence results within at most a **two-week turnaround** time
- Over **4 years**, sequence ~**3,300** UDN patients and their family members (average 3.5 sequences per family)
- Generate **clinical reports**
- **RFA-RM-13-018**

**Year 1 and 2**

Baylor College of Medicine = Exomes
HudsonAlpha with Illumina = Genomes

www.illumina.com/
Seven clinical sites, a coordinating center, two DNA sequencing cores, a metabolomics core, a model organisms screening center, and a central biorepository.
Model Org Screening Center

- Evaluate the pathogenicity and function of ~200 gene variants per year for 3 years
- Establish a screening platform involving at a minimum Drosophila and zebrafish models
- Analyze the function of UDN gene variants in the context of the respective UDN patient's disease phenotype
- RFA-RM-14-016

Awarded September 2015
Seven clinical sites, a coordinating center, two DNA sequencing cores, a metabolomics core, a model organisms screening center, and a central biorepository.
Metabolomics Core

• Provide comprehensive analytical methods, analyses, technologies, and **metabolomics expertise** to the UDN to aid in clinical diagnosis

• **Investigate potential mechanisms** underlying phenotypic changes in patients

• RFA-RM-15-001

Awarded September 2015
Seven clinical sites, a coordinating center, two DNA sequencing cores, a metabolomics core, a model organisms screening center, and a central biorepository.
UDN Central Biorepository

- Coordinate sample shipments to/from UDN investigators and to outside collaborators
- Organize and store the UDN samples at -80°C (or colder) with a plan for sample tracking
- Half of collected aliquots will go to the UDN Central Biorepository

Awarded September 2015
Seven clinical sites, a coordinating center, two DNA sequencing cores, a metabolomics core, a model organisms screening center, and a central biorepository.
Gene Function Studies

- Support **gene function studies** in collaboration with the UDN
- Investigate the underlying genetics, biochemistry and/or pathophysiology of newly diagnosed diseases in association with the respective gene variant(s) identified through the UDN
- PA-13-076, RM-13-003, RM-14-005, RM-15-004

To date: 20 Awards
QUESTIONS?
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Note: *Indicates incomplete data or data not applicable.
- Kearns-Sayre with cerebral folate deficiency
- Neuroaxonal dystrophy with spheroids
- Call-Fleming syndrome (vascular strokes)
- CSF tetrahydrobiopterin deficiency
- Spastic paraplegia due to \textit{SPG7} mutations
- Hereditary Spastic Paraplegia with \textit{SPG4} muts
- Stargardt’s due to \textit{ABCA4} mutations
- Noonan syndrome due to \textit{PTEN} mutation
- Amyotrophic lateral sclerosis with \textit{SOD1} mut
- GM1 gangliosidosis due to \textit{GLB1} mutations
- Progressive supranuclear palsy
- Joubert syndrome
- Telomerase deficiency
- IgG4 sclerosing fibrosis
- Anti-synthetase syndrome
- **NOD2** mutations (father & child)
- **FOXG1** mutation in 2 year old
- Dejerine-Sottas syndrome/hypertrophic neuro
- **POLG1** in late-onset ataxia
- **DNAH1** ciliopathy
- SLE with cerebellar ataxia and anti-GWB Abs
- Smith-Magenis syndrome with **RAI1** mutation
- Pitt-Hopkins syndrome with **TCF4** mutation
- Amyloid myopathy
- Dystonia, dysarthria due to **ND3** mito mut