The NIH Undiagnosed Network: hope for more families and links to the International Rare Diseases Community

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RareX/ICORD 2016,
Cape Town, South Africa
20 October 2016
Every rare disease was once an undiagnosed disease!!

In rare and undiagnosed diseases, collaboration is EVERYTHING!!
In the beginning... 2007 6% of patients contacting the NIH Office of Rare Disorders Research did not have a diagnosis. For those who did, 33% took 1 to 5 years, 15% took > 5 years to obtain it!
The NIH Undiagnosed Diseases Program 2008-2015

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
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
Working hypotheses...

- An extremely rare disease with expanded phenotype
- An unusual presentation of a more common disease
- More than one disease....
- A new disease/gene association

Number of applicants vs. Age in years
UDP Model

Comprehensive Record Evaluation

Selection: Clinical Criteria, Family Structure, Objective Findings

Extensive Clinical Evaluation and Testing

HGMD Diagnosis or Strong Candidate Genes

Family Exome and SNP Chip

Biospecimen Collection

Create a Research Grade Data Set

Active/Passive Collaborator Recruitment

New disease discovery
Without accurate phenotyping, exome/genome analysis is uninterpretable!

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**Informed Consent**

**Genetic Counseling**

**Sedate Day**

**Wrap-Up**
HPO terms:
a common language
Clinician:
Raine syndrome
Researcher:
Candidate 
model system?
Long hallux
Midface 
retusion
Abnormality of 
upper lip
Abnormality of 
toe
Abnormal joint 
morphology
abnormal head 
shape
prominent ears
Cleft palate
Exaggerated 
Cupid's bow
Bowing of the 
long bones
Long hallux
Arthrogryposis 
multiplex 
congenita
Midface 
retrusion
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
Cleft lip
abnormal 
limb long 
bone morphology
digit 1 phenotype
ephyseal plate 
morphology
short snout
lowered ear position
Phenotype similarity across patients or 
….any organism
https://code.google.com/p/owltools/wiki/OwlSim
Filtered Variants, Family vs No Family

Exome analysis
- 360 families
- 1329 exomes

Average Family Size
- Pediatric patients 4.1
- Adult patients 3.3

Variant Filtration Procedure

Analysis of DNA Sequence Variants Detected by High-Throughput Sequencing
UDP Integrated Collaboration System (UDPICS) Facilitates Active Collaboration

**UDP Staff**
- Patient identifiers
  - Medical records
  - Photos & videos
  - Consents & Communications
  - Pedigrees
  - Exome/genome
  - HPO phenotyping
  - Candidate genes
  - Biospecimens

**Collaborators**
- De-identified information
  - Pedigrees
  - HPO clinical phenotype & de-identified medical records
  - List of candidate variants with bioinformatic documentation
  - Available biospecimens

*Each patient’s disease is a unique research project!*
Matchmaker Exchange Facilitates Passive Collaboration
Inquiries 7585
Medical Records 3124 (41%)
Acceptances 966 (31%)
  – Pediatric probands 348 (36%)
  – Female 519 (54%)
  – Neurologic phenotype (>50%)
  – International patients
Diagnoses 176 in 150 (20%)
  – Pediatric diagnoses 93 (33%)
The Undiagnosed Diseases Network
To **extend the success** of the NIH Undiagnosed Diseases Program (UDP) into an Undiagnosed Diseases Network (UDN), composed of UDN Clinical Sites including the UDP, a Coordinating Center, and UDN Core Laboratories, **forming a sustainable national resource** to diagnose both rare and new diseases, **advance laboratory and clinical research**, **enhance global coordination and collaboration** among laboratory and clinical researchers, and **share resulting data and approaches** throughout the scientific and clinical communities.
The Undiagnosed Diseases Network

18 Institutions

234 Investigators

- Network-wide Protocol
- Central IRB
- Data Sharing and Use Agreement

“Best practices” to share with the clinical and research communities and with patients

Gateway Launched Sept 2015!
http://undiagnosed.hms.harvard.edu/apply/
Identified patient information is available to all sites to aid in diagnosis through a common Date Sharing and Use Agreement.
Help from patient advocates...

The team is composed of dedicated runners from around the world who will not only spend their personal time training for the marathons, but also host numerous events to raise funds and engage people in the cause. (Learn more about the runners at: [www.running4rare.org](http://www.running4rare.org))

The funds raised by the Running for Rare Team will support the NORD/Undiagnosed Diseases Network (UDN) Patient Assistance Program. This program provides financial assistance to families who have exhausted all other alternatives for seeking a diagnosis. NORD will help cover the basic diagnostic testing needed for patients and families to apply into the Undiagnosed Diseases Network.
Patient Online Application

https://undiagnosed.hms.harvard.edu/apply/
Sharing of “Best Practices”

UDN Manual of Operations

The UDN Manual of Operations is a handbook that details the network’s research conduct and protocols in order to facilitate consistent adherence across all institutions participating in the study. This is a dynamic document that will be updated throughout the duration of the study to reflect amendments and refinements. Each update that is approved by the UDN Steering Committee will be posted on this page.

Current

183 Pages, 2.7 MB

Archive

Previous versions of the manual
Empowering Patients

Find Matching Patients

Discovering new diseases with the internet: How to find a matching patient

In this blog post, Matt Might describes ways you can use the internet to find more patients with the same rare genetic disorder, including

- Setting up your own patient-finding web site
- Creating content for the web site
- Editing Wikipedia
- Setting Google alerts
- Buying Google AdWords
- Using gene names for domain names
- Minor search engine optimization
- Using Google analytics and webmaster tools to find “cloaked” patients
- Standard registries
• UDN has received 994 applications
  – Accepted 380 participants
  – Completed 137 evaluations
• UDN has made diagnoses*
  – 24 confirmed
  – 10 clinical
  – 11 strong candidates

*numbers as of 10/12/2016
GENERAL AIMS

Improve the level of diagnosis and care for patients with undiagnosed diseases through the development of *common 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 laboratory data* (including genotyping, phenotyping, and documentation of environmental exposures).

Create an integrated and collaborative community across *multiple Countries* and among *laboratory and clinical investigators* prepared to investigate the pathophysiology of these newly recognized and rare diseases.

[www.udninternational.org](http://www.udninternational.org)
udni@iss.it
Teamwork and the global community...

Ablepharon macrostomia syndrome

Mosaicism in 1st generation (fertile)
**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*
“A small group of thoughtful people could change the world. Indeed, it’s the only thing that ever has.”

-Margaret Mead
Acknowledgements

**UDP**
- William Gahl
- Stephen Groft
- David Adams
- May Malicdan
- Camilo Toro
- cast of > 100 others

**UDN**
- William Gahl
- Anastasia Wise
- 234 Investigators
- many, many others

**UDNI**
- Domenica Taruscio
- William Gahl
- Helene & Mikk Cederroth
- Investigators from 13 countries