The NIH Undiagnosed Diseases Program: A Work in Progress

Cynthia J. Tifft, MD, PhD

TMF-Workshop: Registries for patients with undiagnosed rare diseases 21 November 2013

6% of patients contacting the NIH Office of Rare Disorders do not have a diagnosis



In the United States 6% of the general population suffers from a rare disorder

The NIH Undiagnosed Diseases Program

Launched in May, 2008 as a 5 year pilot project with two main objectives:

- 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 "House of Hope"

집은 별한 집은

27 Institutes and Centers 1200 physician investigators credentialed at the NIH Clinical Center

THE ME ME COM

UDP Operations

- Adult and pediatric directors triage records for review by appropriate specialists
- Directors synthesize reviews and make a final disposition
- Patients/referring physicians are informed
 - Accepted patients are admitted for a I week evaluation
 - The majority of patients who are not accepted receive personalized letters with recommendations for further work up

Physician request received, and acknowledged. Additional information requested

variable

Case accepted and meets inclusion criteria for another active NIH Clinical Center study

Case accepted and placed in cue for NIH admission; workup plans formulated by PUDP team Chart sorted, scanned and sent to reviewers; pathology slides reviewed; imaging reviewed by pediatric neuroradiologist Data collection on standardized forms stored electronically

4-6 weeks

Case Presented at monthly PUDP screening meeting by 1° reviewer

Additional workup with home team requested; specific recommendation made

variable

If additional suggested workup unrevealing, then reconsider for NIH admission Case declined. •Diagnosis already established. •Additional workup unlikely to yield diagnosis. •Inadequate workup (standard testing options not exhausted)

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
 - Unaffected sibling
 - Additional affected members with the same or very similar phenotype
 - Consanguineous families

UDP Process



Good Response/Some Success

8000 inquiries

- 3000 medical records reviewed
 - 650 participants accepted into program
 - Diverse symptoms, > 1/2 neurologic, ~1/3 pediatric
 - 24% offered some diagnostic results/clarification
 - Range from named syndromes to well understood diseases
 - 76% not able to be provided any diagnostic clarification

Major Phenotypes

	<u>Applicants</u>	<u>Accepted</u>
Cardiovascular	40	22
Dermatology	47	8
Endocrine	33	13
Fibromyalgia/CFS	79	3
Gastrointestinal	106	13
Hematology	23	7
Immunology	63	15
Neurology	512	164
Pulmonary	28	14
Renal	19	10
Rheumatology	56	19
Female	60%	56%

Age distribution of PUDP applicants



Age in years

Pediatric UPD 2008-2013

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 28 Conventional testing

Selected Diagnoses

NT5E/calcification	KCTD7/ataxia	SMS/neuro and bone
Call Fleming	MBTPS2/Ichthyosis	ARH3/neuropathy
SPG7/HSP	CI9orfI2/neuro	SOX10/Waardenburg
ABCA4/Stargardt	C9orf72/dementia	AFG3L2
Joubert Syndrome	24 hydroxylase def	GRIN2A/neuro
IgG4 sclerosing fibrosis	CHST14	GRIN2B/neuro
Dejerine-Sottas	LMNB1/leukodyst.	DNAH1/ciliopathy
Pitt Hopkins	FA2H	RAII/Smith Magenis

What about the 75% of cases unsolved...

- Good candidate genes in an additional 59 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





Challenge: Establishing Disease Causation

- Given our selection criteria, a minority of wellworked-up undiagnosed diseases will be known diseases.
- We hypothesize that a significant number of the remainder have "new" diseases:
 - Undiscovered disease-gene associations
 - Multiple contributing genes
 - Environment-gene interactions
 - Diseases caused by non-coding DNA changes

19 y/o, 9 kg

Each patient, each family becomes a research project...



Revised UDP Process



Improve Exome Analysis for Families: The Diploid Aligner

NextGen Sequencing that is Population and Parent Aware at both Alignment and Genotyping

Ontological Mapping of Phenotype

Create Research-Grade Dataset

Signs and Symptoms (Phenotype) mapped to standard ontology (HPO) GROWTH PARAMETERS

Small for gestational age Delete - Clear details assuming near term birth. Exact gestational age at birth not a... Severe short stature Delete · Add details

Decreased body weight Delete · Add details

Short stature Delete · Add details

CRANIOFACIAL

Craniofacial disproportion Delete · Clear details

cranium > face

Frontal bossing Delete · Add details

Expanded Hypothesis Generation from Untargeted (Agnostic) Screens

Exome Glycome Metabolome Exome/Genome sequencing CSF, Plasma, Urine N- and Olinked glycans CSF and Urine Metabolomics CSF Lipidomics CSF/plasma/urine isoprostanes CSF/plasma/urine acylcarnitines

Prioritize/deprioritize DNA sequence candidates +/- stand alone findings

Broaden Opportunities for Collaboration

Active/Passive Collaborator Recruitment Active Collaborator Discovery Identify established investigators Automate from phenotypes Passive Collaborator Discovery Searchable case database dbGaP PhenomeCentral Cohort Creation Automate from phenotypes

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.

UDPICS Work Flow

UDPICS Design

NIH/NHGRI/UDP LIMS 24/7 Network Diagram

UDPICS is fully integrated with

- Phenotips
- FreezerPro .
- Sciency
- EzColony .
- The system can be customized to meet specific individualized requirements

UDP 2146/2156

UMS 24/7 - Mozilla Firefox	A DECEMBER OF	The second s	Second	
https://udplims.nhgri.nih.gov/#			☆ マ C Google	
🗘 LABMATRIX P🖬 XWikiLogin \$xwiki.ge 🗌 LIMS 24/7				
UDP Integrated Collaboration S	ystem			Dr. Cynthia Tifft <u>Loqout</u>
<u></u>	💽 _2156 × 🧊 UDP_2156 Exome Sequencing 2 × 🧊 UDP_2	156 Exome Analysis 2 🎽 🦁 Exome Sequencings 🎽 🧔 Glycomics Results UDI	PM-26 🎽 🧑 UDP_2156 SNP Analysis 🎽 🥥 UDP_2146 🎽 🧔 Labmatrix Legacy - Phen	otype Legacy Files 🎽 🥥 Phenotypes 🎽 🕑
🛃 Quick Links 🛛 🕀			🞸 - Search Subjects: Live search requir	es a minimum of 2 characters.
C Explorer				
	<u>UDP 2146</u>			
	Updated By: Elizabeth Lee 11/15/2013, 03:58 PM		Created By:	Dr. Murat Sincan 06/28/2013, 04:33 PM
Settings And Preferences				ADD DIAGNOSIS
S 45 8 📿 🤉	ID	10795	·	
🗧 Users	Name	UDP_2146		CONTACT +
Ser Groups	SubjectType	Patient		FAMILY OR HOME TEAM
Sec. 10	Formatted Name			
Evternal Pluging	First Name			PATIENT
	Middle Name			COMMUNICATION
Liner Defined Fields	Last Name			FAR, FOLLOWUP OR FINAL LETTER
Subject Types	Attending	Dr. Tifft		
88 Subject Type Groups	Primary Clinician	Gretchen Golas, NP		ρατιενίτ
Subject Workflows	Patient Case	Pediatric		INFORMATION
🔓 Subject Tasks	Affected_status	Affected		UPDATE PATIENT INFORMATION
🗄 🧰 Advanced	Proband	Yes		
Q About LIMS 24/7	Relationship to Proband	Proband		REQUEST REVIEW
	Date of Birth	04/21/2002		
	Age	11		+
	M/F	Male		SCANING &
	Fatrier	UDP_3467		SORTING SEND FOR SCANNING & SORTING
	Family	UDD 3146		
	MDN	46.62.40.4		DEJEOT
Subject Type Groups	Phenotips Complete	Yes		REJECT
Subject Workflows	Phenotips Confirmed by	C. Tifft		
을 Subject Tasks	Phenotips	25		UPDATE PATIENT INFORMATION
🗄 🧰 Advanced	LM Phenotype	Neuro		
O About LIMS 24/7	Patient Safety Status	Routine		
	Notes	REAL PATIENT		REQUEST REVIEW
	Vials in FreezerPro	<u>16</u>		
	Number of DNA Vials	2		SCANING &
	SNP Analysis	UDP 2146 SNP Analysis		SORTING SEND FOR SCANNING & SORTING
	SNP Report	<u>12</u>		
	Exome Analysis	2	Ξ.	
	Exome Sequencing	2		REJECT
	Attribute 1	Admitted		
	Consents	2		SCREENING
	Collaborations	2		MEETING
	Full Name			
	Mortality Status	Alive		
	Infortilo	No		ACCEPT - NO UDP

UDP 2146/2156

LMS 24/7 Pedigree Tree UDP.2146

NIH Clinical Center Phenotyping

Monda	08/12/13	Tuesda	y 08/13/13	Wedne	sday 08/14/13	Thursda	y 08/15/13	Friday	08/16/13
7:00a	Admissions	7:00a		7:00a		7:00a		7:00a	
7:30a		7:30a		7:30a		7:30a		7:30a	
8:00a		8:00a		8:00a	DEXA	8:00a		8:00a	
8:30a		8:30a	Skeletal survey	8:30a		8:30a	OT with Hanna	8:30a	
			-				if additional time needed		
9:00a		9:00a		9:00a	Physiatry w/ Dr. Paul	9:00a		9:00a	
9:30a		9:30a	EEG in 7SW Neuro Testing	9:30a		9:30a	Nutrition consult at bedside	9:30a	
							w/ Jennifer Myles		
10:00a	Neuropsych w/ Dr. Thurm	10:00a		10:00a		10:00a		10:00a	
10:30a	- meet at the bedside	10:30a		10:30a	OT w/ Hanna	10:30a		10:30a	
11:00a		11:00a	PT w/ Mina	11:00a		11:00a	Sedated brain MRI and eye	11:00a	
11:30a		11:30a		11:30a		11:30a	exam	11:30a	
							EMG in the PACU w/		
12:00p		12:00p		12:00p		12:00p	Dr. Floeter	12:00p	
12:30p		12:30p		12:30p	Eye consult in OP-11	12:30p		12:30p	
					w/ Dr. Zein				
1:00p		1:00p	Neuro w/ Paul Lee	1:00p		1:00p		1:00p	
1:30p		1:30p	at the bedside	1:30p		1:30p		1:30p	
2:00p	Pre-anesthesia	2:00p		2:00p		2:00p		2:00p	
2:30p		2:30p		2:30p		2:30p		2:30p	
3:00p		3:00p		3:00p		3:00p		3:00p	
3:30p		3:30p		3:30p		3:30p		3:30p	
4:00p		4:00p		4:00p		4:00p		4:00p	
4:30p		4:30p		4:30p		4:30p		4:30p	
5:00p		5:00p		5:00p		5:00p		5:00p	
6:00p		6:00p		6:00p		6:00p		6:00p	
7:00p		7:00p		7:00p		7:00p		7:00p	
8:00p		8:00p		8:00p		8:00p		8:00p	
9:00p		9:00p		9:00p		9:00p		9:00p	

Phenotype entry populates

PHENO **TIPS**

JICK PHENOTYPE SEARCH:	Enter keywords and choose among suggested ontology terms
Weight for age	CURRENT SELECTION
Y >97th Stature for age	EYE DEFECTS
Image: Non-State Imag	Esotropia Delete Clear details
Head circumference for age	Intermittent Mittendorf dot OD small congenital cataract outside the visua
NAYN <3rd	Cataract Delete - Add details
MA Y N Hemihypertrophy	EAR DEFECTS
Other	Recurrent otitis media Delete · Add details
(enter free text and choose among suggested ontology terms)	CARDIAC
CRANIOFACIAL	Ventricular septal defect Delete Clear details
MA Y N Craniosynostosis	small membranous with very small left to right shunt made restrictive fro
NAYN Cleft upper lip	RESPIRATORY
MA Y N Abnormal facial shape	
Other	With Upper Respiratory Infection Triggers
(enter free text and choose among suggested ontology terms)	Pectus excavatum Delete · Add details
	MUSCULOSKELETAL
EYE DEFECTS	Contractures of the joints of the lower limbs Delete - Add details
MA Y N Abnormality of the cornea	
NA Y N Coloboma	BEHAVIOR, COGNITION AND DEVELOPMENT
MAYN Abnormality of the anterior chamber	Global developmental delay Delete · Clear details
A Abnormality of the refina	profound

GANTT chart tracks progress of project

UMS 24/7 - Mozilla Firefox	
s Edit View History Bookmarks Tools Help	
UMS24/7 +	
) ֎ https://udplims.nhgri.mih.gov/#	<u> </u>
LABMATRIX Par XWikiLogin SxwikiLogin Sxw	
	Dr. Cynthia Tifft Logout
🔍 🕐 2156 Exome Sequencing 2 × 👧 UDP 2156 Exome Analysis 2 × 👰 Exome Sequencings × 👰 Glycomics Results UDPM-26 × 👩 UDP 2156 SNP Analysis × 👰 UDP 2146 × 🥥 Labratrix Legacy - Phenotype Legacy Files × 👩 Ph	enotypes × SUDP 2146 × P
Churk Links 🗇	mum of 2 characters
	2 Filler
Search Queries Mon 14 Oct 2013 Mon 21 Oct 2013 Mon 28 Oct 2013 Mon 24 Nov 2013 Mon 11 Nov 2013 Mon 18 Nov 2013 Mon 25 Nov 2013 Mon 02 Dec 2	013 Mon 09 Dec 2013
Settings And Preferences Workflow States M T W T F S S M T	FSSMTWTFSS
UDP Inage UDP Inage UDP Inage UDP Inage	
Upr 2140 Exone Alignment UUPr 2140 Exone Alignment UU	_
To below County Service County Servi	
Conset Decision Control C	
External ruggins Conservo Connect autors 2	
a Luminity Settings - Set Later Conversion Settings - Set Later Conversion Setting - Set Later Conversion Setting -	
Subject Damod Holes Exome Analysis	
😵 Subject Type Groups v UDP 2146 Exome Analysis	
Subject Workflows Exome Analysis Complete	
s sugject tasks Exome Analysis	
Quality Check Exome Report Quality Check Exome Report Amanda Links	
Exome Analysis Complete Exome Analysis Complete	
VDP 2146 Exome Alignment 2 UDP 2146 Exome Alignment 2	
Receive Lane Files Receive Lane Files 💊 Elise Flynn	
VDP 2146 Exome Sequencin	
Complete Annotation Pipeli Dr. Thomas Markello	
DNA Sent for Exome DNA Sent for Exome	
VDP 2146 Exome Sequencing	
Complete Annotation Pipeli Elise Valkanas	
DNA Sent for Exome DNA Sent for Exome	
Electronic Callaboration LIDPU 25	

UDP 2146/2156 Compound Het for MED23

exon26:c.3638A>G:p.H1213R

exon29:c.3988C>T:p.R1330X

Mediator Complex

Multi-subunit RNA polymerase II transcriptional regulator

Collaboration with Dr. Zhao to generate drosophila model to functionally validate phenotype has promising preliminary results.

Hashimoto S, Boissel S, Zarhrate M, Rio M, Munnich A, Egly JM, Colleaux L. MED23 mutations links intellectual disability to dysregulation of immediate early gene Expression. (2011) *Science* 333:1161-3.

Undiagnosed Diseases Program

Program Snapshot

With advances in genomic sequencing and medicine, it is now possible to examine patients with rare genetic diseases at a level that allows physicians and scientists to find the "needle in a haystack". Often times, one small change (mutation) in a genetic sequence can cause an individual to develop disease symptoms. To increase the capacity for this type of research, the Undiagnosed Diseases Program (UDP) is establishing an Undiagnosed Diseases Network (UDN) to diagnose both rare and new diseases. Furthermore, through the support of mechanistic studies, the Network hopes to aid in management strategies for the patients. This program will advance laboratory and clinical research, building upon the experience and expertise of the NIH Intramural UDP and similar programs, to enhance coordination and collaboration among laboratory and clinical researchers across multiple centers. The Network will benefit from having the capacity to share data and approaches widely throughout the scientific community.

New Funding Opportunity Announcement (Administrative Supplement)!

The Undiagnosed Diseases Program is seeking applications for gene function studies to investigate rare and undiagnosed diseases. Please see the full details <u>here</u>.

New Funding Opportunity Announcement!

The Undiagnosed Diseases Program is seeking applications for a Coordinating Center for an Undiagnosed Diseases Network (UDN). Please see the full details <u>here</u>.

Read more ...

Undiagnosed Diseases Network

A cry for help.....

elp. Bear. Doctors, My name is Taylor Im 11 reats 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 Im faking or Im stressed but their not in my body. I'v always canted to become an actiess or model + mabye even try a singing carrier but this sickness is not helping got closer to forfilling my dreams, 111111111 I cry evrey night before I go to bed because what Im going through I NEED HELP! Please please It you guys are a really good doctor than please try to help the Figure out what's wronge with me. From: Taylor

"A small group of thoughtful people <u>could</u> change the world. Indeed, it's the only thing that ever has."

-Margaret Mead

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

It Takes a Village...

Willam A. Gahl

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

Charité Hospital, Berlin Peter Robinson

University of Toronto Michael Brudno

Oregon Health Sciences University Melissa Haendel and the Monarch Consortium

<u>Children's Hospital Philadelphia</u> Michael Bennett Miao He

Case Western Reserve University Charles Hoppel

Sanger Institute, Cambridge University Damian Smedley University of Cinncinati Bruce Aronow

<u>NHGRI</u> Shawn Burgess

<u>University of Miami</u> Grace Zhai Gennaro D'Urso

University of California, Los Angeles Shuo Lin

NIH Intramural Sequencing Center Jim Mulliken

<u>NIH Clinical Center</u> > 50 physician scientists who volunteer their time and expertise