The Undiagnosed Diseases Network: A resource for challenging cases

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Disclosures

- Jill Rosenfeld Mokry receives salary support from Baylor Genetics Laboratories, a clinical genetic testing laboratory.

Overview

- What is the UDN?
- Lessons from the NIH
- Case example

Why study the undiagnosed?

- Diagnostic odysseys have high costs: emotional and financial
- Lack of a diagnosis
  - Creates concern or suspicion
  - Challenges the patient-physician relationship
- Personalized, precision medicine
- Advancement of scientific knowledge

Gahl *et al.* 2015 JAMA

Goals of the UDN

- Provide patients who have been extensively evaluated with an accurate diagnosis
- Use new genomic technologies to aid in diagnosis
- Assess phenotyping approaches
- Identify novel diseases
- Uncover new information about the causes of disease
- Identify potential therapeutic targets

Who is in the Network?

7 Clinical sites:

- Baylor College of Medicine
- Duke Medical Center
- Harvard-affiliated hospitals
- NIH Undiagnosed Diseases Program
- Stanford Medical Center
- UCLA Medical Center
- Vanderbilt University Medical Center

2 Sequencing cores:

- Baylor College of Medicine
- HudsonAlpha/Illumina

1 Coordinating center:

- Harvard Medical Center

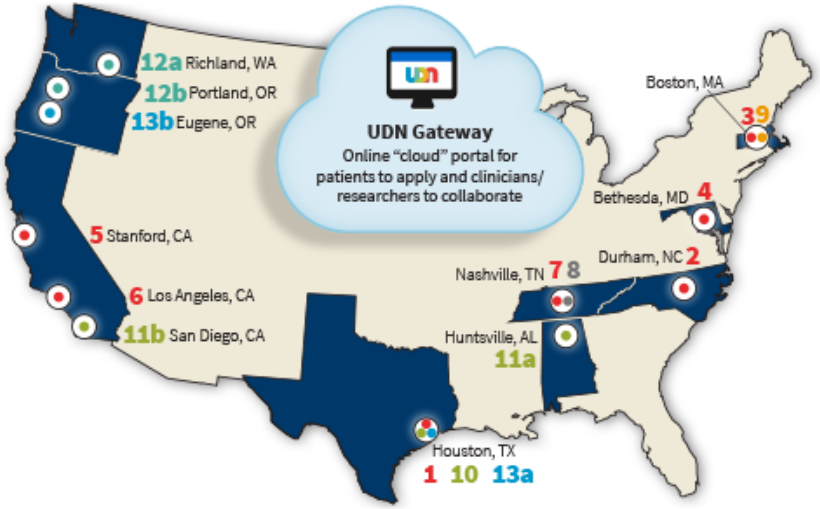
Additional resources

Model organisms screening center:

- Baylor College of Medicine
- University of Oregon

Metabolomics core:

- Battelle Pacific Northwest National Laboratories
- Oregon Health & Science University



Central biorepository:

- Vanderbilt University Medical Center

History: The Undiagnosed Diseases Program (UDP)

- Started in 2008 at the NIH
- 2008-2014:
  - Received over 10,000 inquiries
  - Reviewed records of over 3300 applicants
  - 800 patients evaluated
    - 40% pediatric
    - 30% adults with disease onset in childhood
- ~10% receive diagnosis of rare or novel disease

Tifft & Adams 2014 Curr Opin Pediatr

Types of diagnoses

- **Extremely rare diseases**
  - Ehlers-Danlos syndrome, musculocontractural type I [*CHST14*]
  - Early-onset myopathy, areflexia, respiratory distress, and dysphagia [*MEGF10*]
- **Rare presentations of known diseases**
- **Blended phenotypes of multiple diseases**
- **Novel diseases**
  - Calcification of joints and arteries [*NT5E*]
  - Familial distal myopathy [*HINT3*]

Gahl *et al.* 2012 Genet Med

Lessons learned at the UDP

- Whole-exome sequencing can be most economical when multiple gene candidates are being considered.
- Sequencing of family members can be a powerful tool to help filter and interpret variants found on whole-exome sequencing.
- Accurate and meticulous phenotyping is essential.
- Multidisciplinary collaborations are critical to making diagnoses.

Gahl *et al.* 2012 Genet Med

The UDN process

Undiagnosed Diseases Network

Patient applies online, supplying a physician's referral letter

Patient is assigned to a clinical site, where application is reviewed and medical records are gathered

Patient is informed of decision of acceptance into study

Patient travels to clinical site for study visit: up to 5 days of consultations and clinically indicated tests

Diagnosis, therapy, and/or further basic research

TEXAS Society of Genetic Counselors

Working with the UDN

- Referring providers may participate in discussions about their patients.
- Summary of UDN workup is provided back to family and referring provider.
- Publications
  - Referring physicians invited to be co-authors
  - The network is also listed as a co-author

Patient volume

- Phase I (through April 2018)
  - 135 patients per clinical site
  - Current rate of 50 patients per year
  - At BCM: 75 patients accepted, 39 evaluated

- Phase II to run into 2023
  - Patient volume not yet specified

Case example

- 8- and 3-year-old brothers with a working diagnosis of mitochondrial encephalomyopathy plus
- Prenatal onset of disorder
- Developmental, neurologic, and metabolic features

	TH (8yo)	ZH (3yo)
Prenatal	Severe **polyhydramnios**, **LGA**	
At birth	**Arthrogryposis**	No arthrogryposis
Cardiac	**ASD**, **dysplastic pulmonary valve** with **pulmonic stenosis**, **biventricular hypertrophy**	
	Prolonged QTc	–
Feeding	**Failure to thrive** necessitating gastrostomy	
Metabolic	Intermittent **hypoglycemic episodes** with metabolic acidosis and ketosis	
	Cyclic vomiting requiring hospitalization	
Neurologic	**Hypotonia**, mild **developmental delays**	
	Iatrogenic stroke, seizures, hemiparesis, cerebral volume loss	

The diagnostic odyssey

- Metabolic testing, including metabolomics and CDG studies
- Muscle biopsies
- Endocrine evaluations
- Renal evaluations
- MRIs, EEGs
- Genetic testing
  - Karyotype, microarray
  - RASopathy panel
  - Mitochondrial sequencing
  - Whole exome sequencing (proband only)

UDN evaluation

- Evaluations for siblings:
  - Genetics
  - Neurology
  - Cardiology
  - Ophthalmology
  - General pediatrics
  - Skeletal surveys
  - EEGs
- Lab studies:
  - Lactate & metabolomics repeat both siblings
  - Urine organic acids (TH)
  - Complete family WES studies – reanalysis
  - RNAseq both siblings' fibroblasts and blood

UDN findings

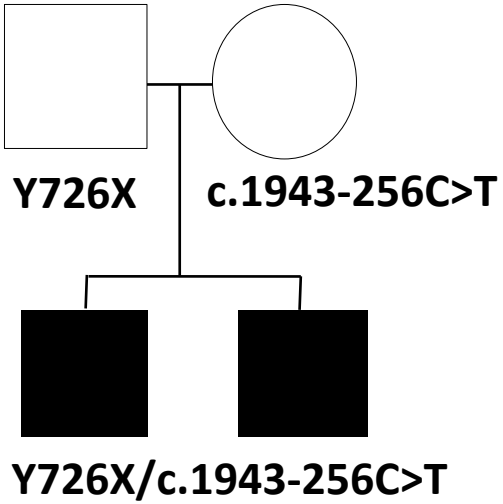
TH

- EEG – spike and polyspike and slow wave activity
- Skeletal survey – Thoracolumbar kyphosis
- Cardiology – pulmonary valve thickening, mild ventricular septal hypertrophy, slightly prolonged QT interval
- Labs – Global MAPS – mild elevations of several long fatty acids, lactate nl

ZH

- EEG – spike and polyspike and slow wave activity
- Brain MRI – Chiari I, otherwise normal
- Cardiology – mild dilation of the main pulmonary artery and branch pulmonary arteries, mild concentric left ventricular hypertrophy
- Labs – Global MAPS – no perturbations in tested pathways, lactate nl

Exome analysis of quad



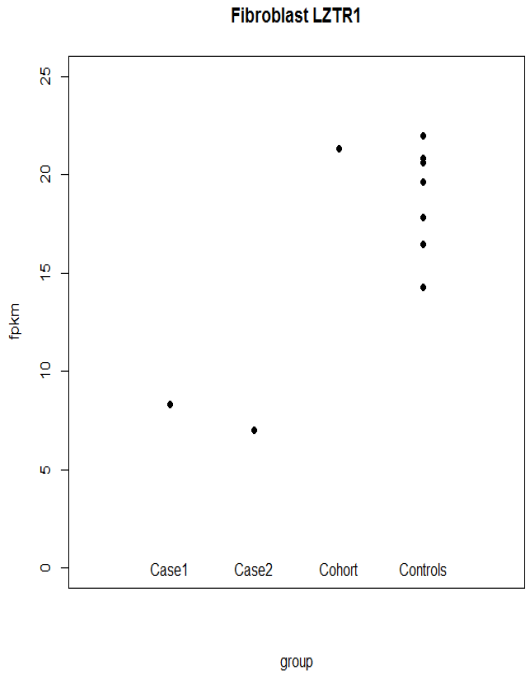
- Compound heterozygous, *LZTR1*
  - Dominant missense variants cause Noonan
  - Dominant missense or nonsense variants cause Schwannomatosis

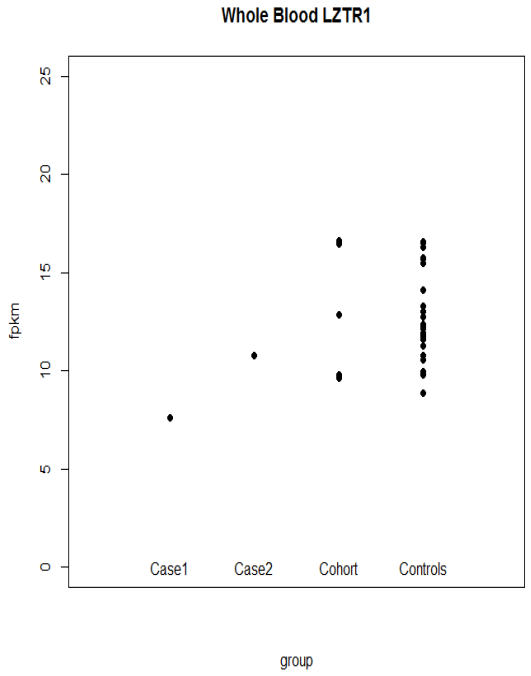
RNAseq, *LZTR1*

	Tissue	Variant Reads	Total Reads
ZH	Whole Blood	17	38
ZH	Fibroblast	12	30
TH	Whole Blood	11	30
TH	Fibroblast	18	38

- Variant (paternal nonsense allele) observed in ~50% of reads, thus escape of nonsense-mediated decay.
- Alternative splicing not seen.

RNAseq





- Overall reduced expression, and given escape of NMD, this suggests diminished expression on both alleles (maternal and paternal allele)
- Sequencing of ZH's genome has not identified any additional *LZTR1* variants.

Additional research

- Studies on patients' cells
  - SeaHorse assay – mild alterations
  - ERK is downregulated
  - CRISPR in progress to study effect of intronic variant
- *Drosophila* studies in model organisms core
  - Knockout does not have a phenotype
  - Crossing knockout with RAS gain-of-function line
- Identified 2 collaborators with 4 additional families with recessive Noonan-like syndrome & *LZTR1* variants

Conclusion

- In efforts to find a diagnosis, UDN leverages technologies and resources that may otherwise be unavailable.
- Through collaborative phenotyping and in-depth genotyping, UDN is providing diagnoses, discovering new disease genes, and providing phenotypic expansion.
- UDN seeks to provide value to participating patients and referring physicians.

Seeking partners to make referrals

- Patients initiate application process online or via phone
  - http://undiagnosed.hms.harvard.edu
  - 1-844-RINGUDN
  - Please supply your patient with a referral letter.
- Contact UDN team at BCM for more information
  - PI: Dr. Brendan Lee
  - Coordinator: Jill Mokry, MS
  - Undiagnosed.diseases@bcm.edu
  - 713-798-5440