The Extreme of "No One Left Behind": Undiagnosed Patients

Rare Disease Day at the United Nations

New York City, February 21, 2019

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UDP
(May 19, 2008)

- **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
- 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 (2008-2019)

- Medical Records: >4000
- Admitted & Evaluated: >1200
- Children: ~40%
- Neurological: ~50%
- Some diagnosis: ~30%
- Publications 180

65 Year-old Man with Recurrent Meningitis

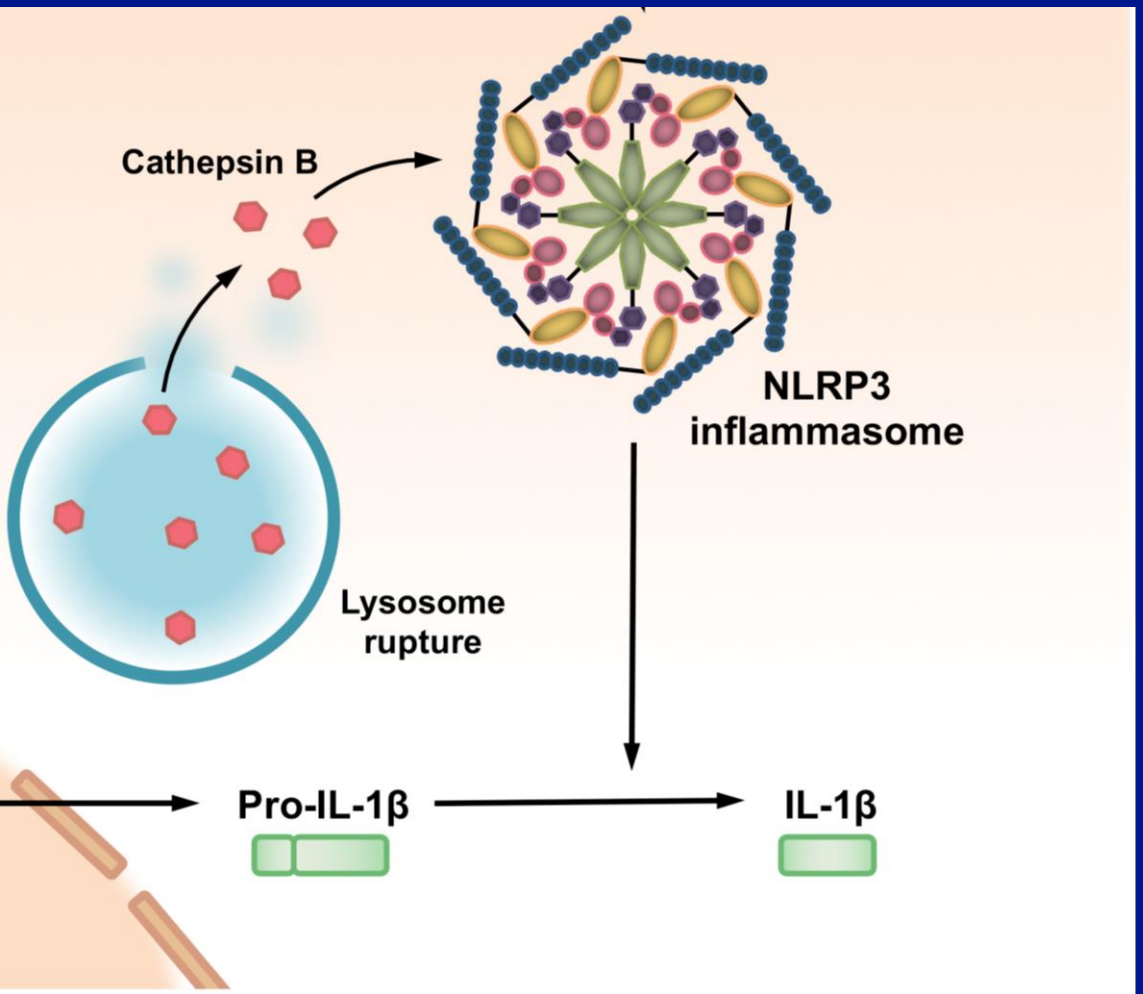
- Age 59 - First episode of meningitis; followed by autoimmune sensorineural hearing loss
- Acute: Headache, unsteady gait
- Chronic: Uses wheelchair, memory decline
- Age 59-65 – 27 more episodes
- LPs: Lymphocytic pleiocytosis
- Aseptic; steroid responsive
- Negative imaging; negative rheumatology evaluation
- Normal labs, including CRP, ESR
- No diagnosis at Emory, Cleveland Clinic, Mayo (Fl), Hopkins

65 Year-old Man with Recurrent Meningitis

- Exomes: Thr915Met in NLRP3
- NLRP3: Familial cold autoinflammatory syndrome or Muckle-Wells syndrome
- Heterozygous; gain of function

Donna Novacic, MD

- NLRP3 is part of the Inflammasome.
- A gain of function mutation will increase IL-1 activity.



- We treated with the IL-1 receptor inhibitor, anakinra
- In 4 hours, he walked and talked normally

Diagnoses

Very Very Rare Diagnoses

- 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)

More Diagnoses

- EMARRD (Early myopathy, AReflexia, Respiratory distress, Dysphagia) due to *MEGF10* mutations
- Neurodegeneration due to *BTK* mutation
- Cognitive & motor decline with *C19orf12* muts
- Waardenburg type 2 due to *SOX10* deletion
- SLE with cerebellar ataxia and anti-GWB Abs
- GM2 gangliosidosis and Sanfilippo disease
- TEMPI syndrome with erythrocytosis muts
- Choreo-acanthocytosis due to *VPS13A*
- Aicardi-Goutieres due to *RNASEH2B, A* muts
- SPG11, NPC1, STIM1, GARS, A-T, NGLY1, MNGIE, CAV3

Expansion

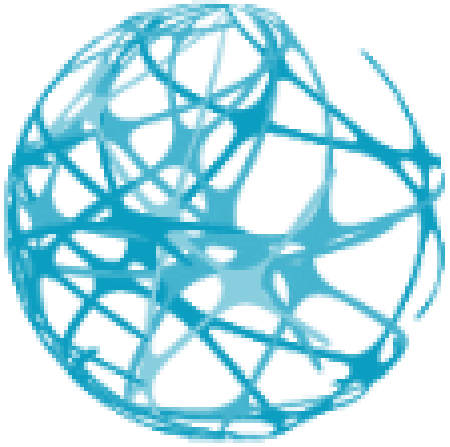
The Undiagnosed Diseases Network (UDN)

- UDP, 7 (now 12) Clinical Sites, Coordinating Center, 2 Sequencing Cores, Metabolomics Core, Model Organisms Screening Center, Central Repository
- Formal data sharing agreements
- Consent: PII to be shared within UDN, de-identified data with others.
- First patients: August 2015.

Worldwide Access: UDNI

Undiagnosed Diseases Network International(UDNI): White Paper for Global Actions to Meet Patient Needs

Molecular Genetics and Metabolism 116:223-5, 2015.



Undiagnosed
Diseases Network
INTERNATIONAL

Website:

http://www.udninternational.org/

UDNI Meetings

(NIH Common Fund, Wilhelm Foundation, Local Sponsors)

- Rome September 2014
- Budapest – June 2015
- Vienna – February 2016
- Tokyo – November 2016
- Stockholm – August 2017
- Naples – June 2018
- Delhi – April 2019

Undiagnosed Diseases Programs

- W. Australia
- Japan
- Austria
- Spain
- Sweden
- India
- Turkey
- Canada
- Hong Kong
- China
- Korea
- France
- Thailand
- Italy

CONCLUSIONS: Rare and Undiagnosed Diseases Programs

- Require strong phenotyping of patients
- Foster new disease discovery
- Lead to insights into common diseases
- Help desperate patients
- Often require functional studies
- Sometimes do not need NGS
- Hugely benefit from data sharing
- Have captured the interest of industry
- Are needed throughout the world