NATIONAL HUMAN GENOME RESEARCH INSTITUTE Division of Intramural Research

The NIH Undiagnosed Diseases Program: Medicine for the 21st Century

16 October 2015

*X*th International Conference on Rare Diseases and Orphan Drugs

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Director, NIH Pediatric Undiagnosed Diseases Program

I have no conflicts of interest to disclose

It Takes a Village…

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Colleen Wahl
Rena Godfrey

Joy Bryant
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Casey Hadsall
Val Robinson
David Draper

Cheryl Hipple
Jose Salas
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John Accardi
May Malicdan
Yan Huang
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Tim Gall
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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

Children's Hospital Philadelphia
Michael Bennett
Miao He

Case Western Reserve University
Charles Hoppel

Sanger Institute, Cambridge University
Damian Smedley

University of Cinncinati
Bruce Aronow

NHGRI
Shawn Burgess

University of Miami
Grace Zhai
Gennaro D'Urso

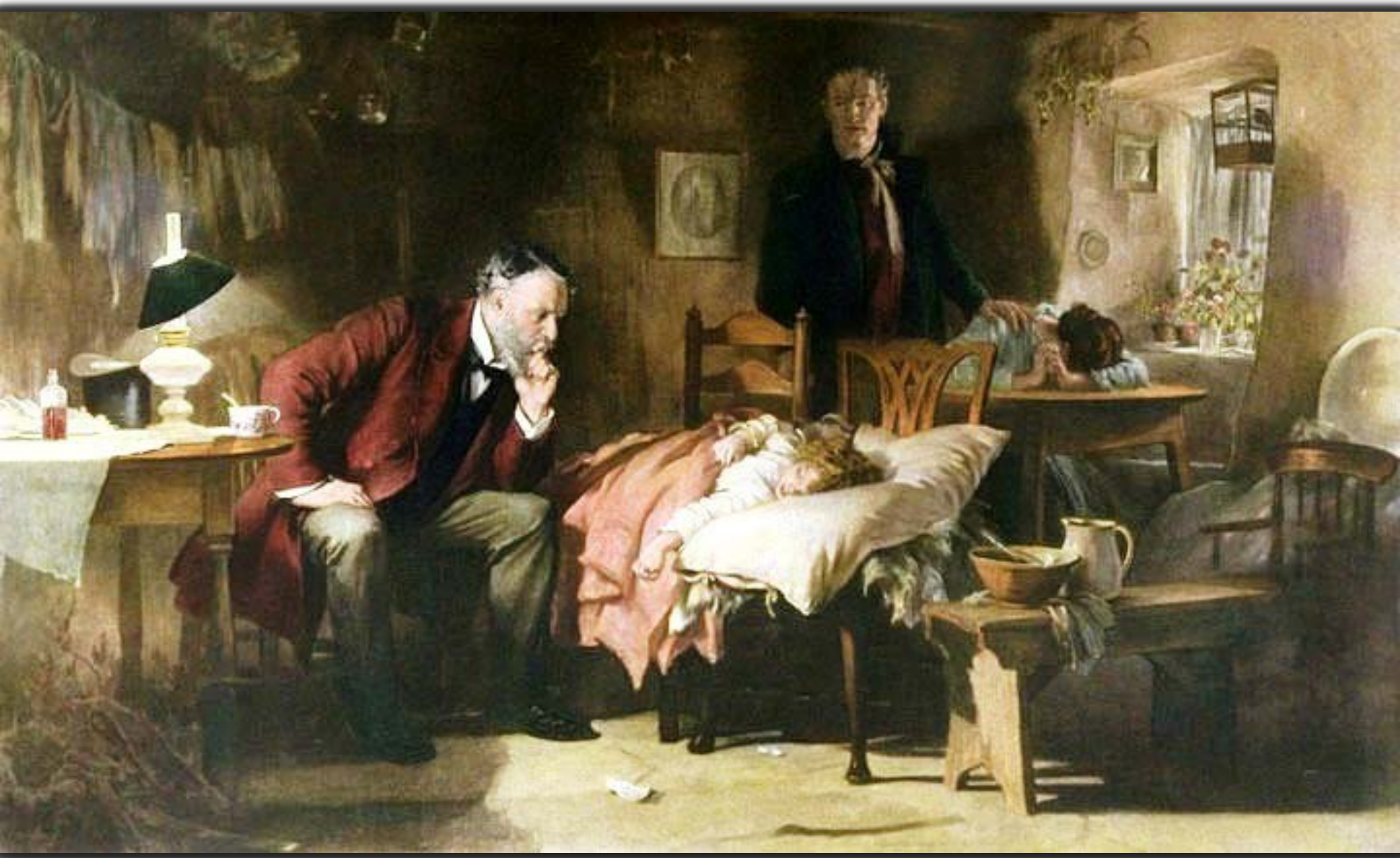
University of California, Los Angeles
Shuo Lin

NIH Intramural Sequencing Center
Jim Mulliken

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

Every rare disease was once an undiagnosed disease!!

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



The unmet need…

- Of the 6000 calls to the NIH Office of Rare Diseases Research in 2007, nearly 400 (6%) were from patients who did not have a diagnosis.

- Of the callers who did have a diagnosis
  - 33% took 1-5 years to receive that diagnosis and,
  - 15% took >5 years.

The Dream:

The NIH Undiagnosed Diseases Program

Launched in May, 2008 as a 5 year pilot project with two main objectives that reflect the mission of the NIH:

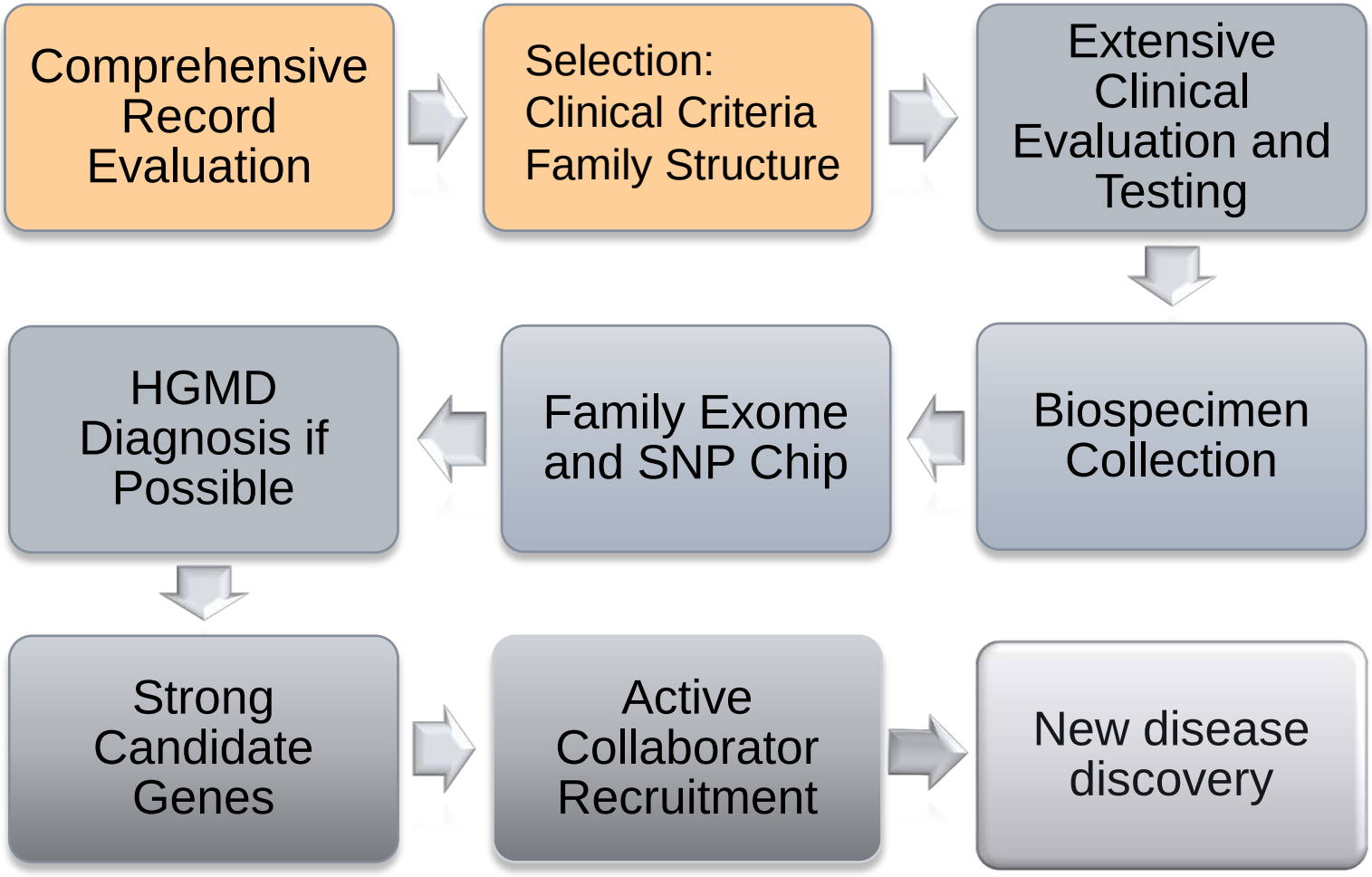
- Public Service
  - To provide answers to patients with mysterious conditions that had long eluded diagnosis
- Biomedical Research
  - To advance medical knowledge by providing insight into human physiology and the genetics of rare and common diseases

The dreamers…

Steve Groft

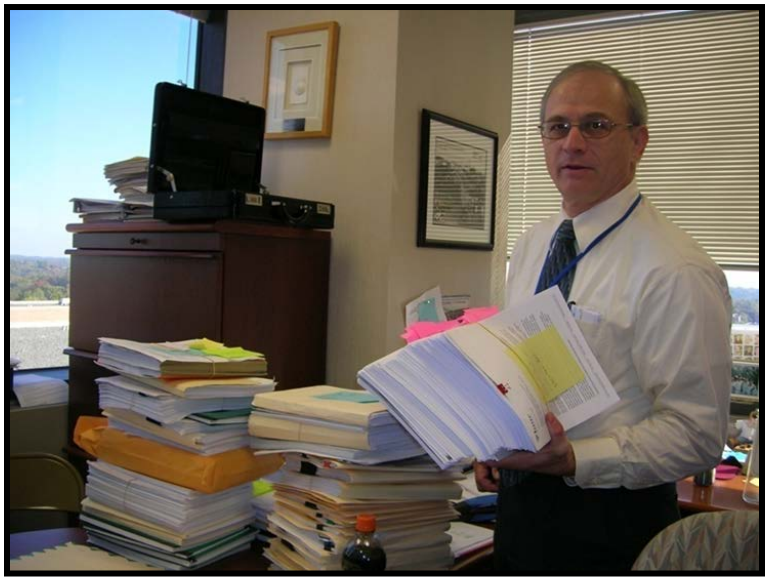
Bill Gahl

UDP Model


Comprehensive Record Evaluation
Selection: Clinical Criteria Family Structure
Extensive Clinical Evaluation and Testing
Biospecimen Collection
Family Exome and SNP Chip
HGMD Diagnosis if Possible
Strong Candidate Genes
Active Collaborator Recruitment
New disease discovery

UDP Operations

- Applications are received, acknowledged, and additional records, radiographs, photos, or pathology slides are requested.
- Charts are organized and scanned electronically.
- Adult and pediatric directors triage records for review by appropriate specialists
- Directors synthesize specialist reviews and make a final disposition
- Patients and referring physicians are informed of the decision.



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

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
    - Additional family members with the same phenotype
    - Unaffected siblings
    - Consanguineous families

UDP statistics 2008-2015*

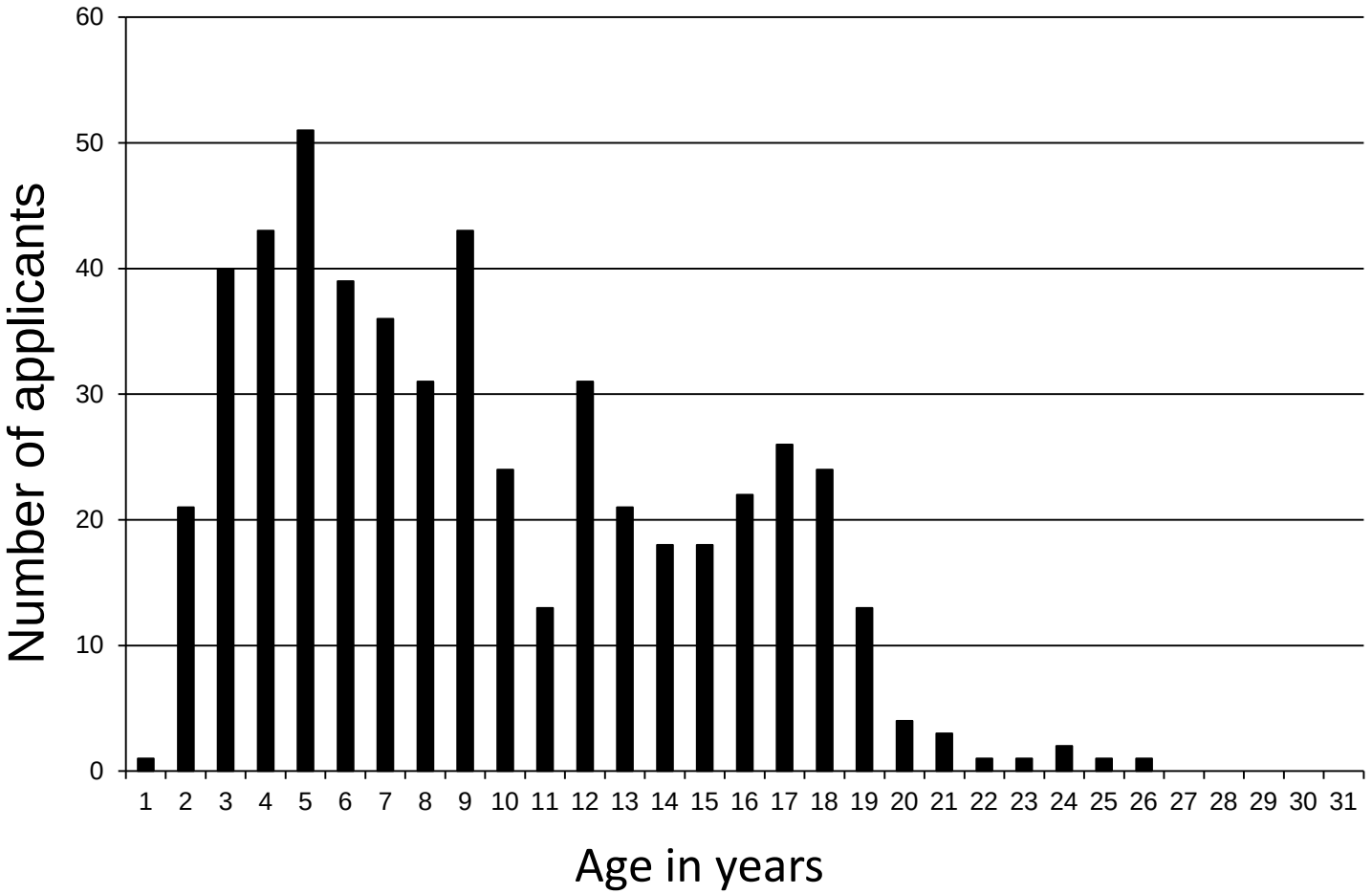
Inquiries	7585
Medical Records	3124 (41%)
Acceptances	966 (31%)
Pediatric probands	348 (36%)
Female	519 (54%)
Neurologic phenotype	(~50%)
Diagnoses	176 in 150 (20%)
Pediatric diagnoses	93 (33%)

* As of October 12, 2015

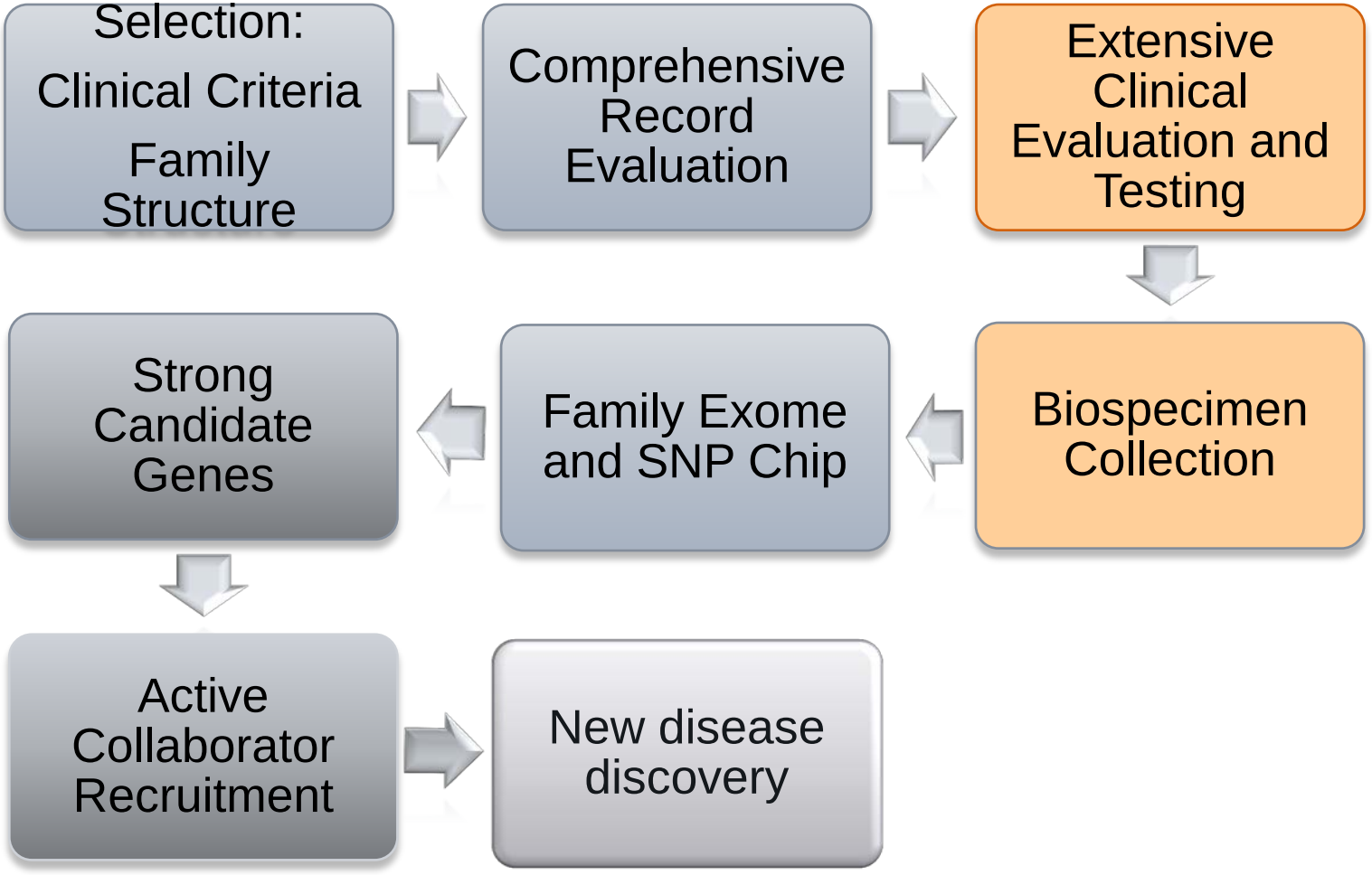
Major Phenotypes

	Applicants (N=1006)	Accepted (N=288)
Cardiovascular	4%	8%
Dermatology	5	3
Endocrine	3	5
Fibromyalgia/CFS	8	1
Gastrointestinal	10	4
Hematology	2	2
Immunology	6	5
Neurology	51	57
Pulmonary	3	5
Renal	2	3
Rheumatology	5	6
Female	60%	56%

Pediatric applicants



UDP Process


Selection:
Clinical Criteria
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New disease discovery

phe·no·type

- the observable properties of an organism that are produced by the interaction of the genotype and the environment
- Without accurate phenotyping, exome/genome analysis is uninterpretable.
- Careful phenotyping is everything!!

Phenotyping in the UDP

- Starts when charts are received
- Becomes more focused as charts are reviewed and patient accepted
- Expands during the patient evaluation
- Comes together once all clinical and diagnostic testing is received

Scheduling the evaluation…

	F.P.	DOB ********		MR # 71-91-81-9		UDP# 7478			
Monday	02/10/2014	Tuesday	02/11/2014	Wednesday	02/12/2014	Thursday	02/13/2014	Friday	02/14/2014
7:00a	Admissions	7:00a		7:00a		7:00a		7:00a	
7:30a		7:30a		7:30a	Sedate Day	7:30a		7:30a	
8:00a		8:00a	EKG	8:00a	Sedated brain MRI/MRS,	8:00a	Speech and swallow study	8:00a	OT w/ Becky
8:30a	Informed Consent	8:30a		8:30a	eye exam, skin biopsy,	8:30a	w/ Beth Solomon in	8:30a	in Rehab Medicine
					and LP		Radiology		
9:00a	History and physical	9:00a	Neuropsych w/ Dr. Thurm	9:00a		9:00a		9:00a	
9:30a	on 1NW Inpatient Unit	9:30a	~ meet at the bedside	9:30a	Genetic	9:30a	Abdominal U/S	9:30a	EEG in 7SW Neuro
					Counseling				Testing
10:00a		10:00a		10:00a		10:00a		10:00a	
10:30a		10:30a		10:30a		10:30a		10:30a	
11:00a		11:00a		11:00a	EMG in PACU	11:00a		11:00a	Clinical Photos
11:30a		11:30a		11:30a		11:30a	Eye appointment	11:30a	
							w/ Dr. Zein in OP-11		
12:00p		12:00p	Neurology w/ Dr. Paul Lee	12:00p		12:00p		12:00p	
12:30p		12:30p	at the bedside	12:30p		12:30p		12:30p	
1:00p	Audiology and ABR	1:15p		1:00p		1:00p		1:15p	DEXA scan in Nuclear
1:30p	in OP-5	1:30p		1:30p		1:30p		1:30p	Medicine
2:00p		2:00p	Pre-Anesthesia Clinic	2:00p	Nutrition w/ Jennifer Myles	2:00p		2:00p	PT w/ Zavera
2:30p		2:30p		2:30p	at the bedside	2:30p		2:30p	
3:00p	Physiatry w/ Dr. Paul	3:00p	Echocardiogram in 5NE-N	3:00p		3:00p		3:00p	
3:30p	in Rehab Medicine	3:30p		3:30p		3:30p		3:30p	
									Wrap-Up
4:00p		4:00p	Neurology w/ Dr. Toro	4:00p		4:00p		4:00p	
4:30p		4:30p	at the bedside	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	

Choreography of pediatric sedation day…

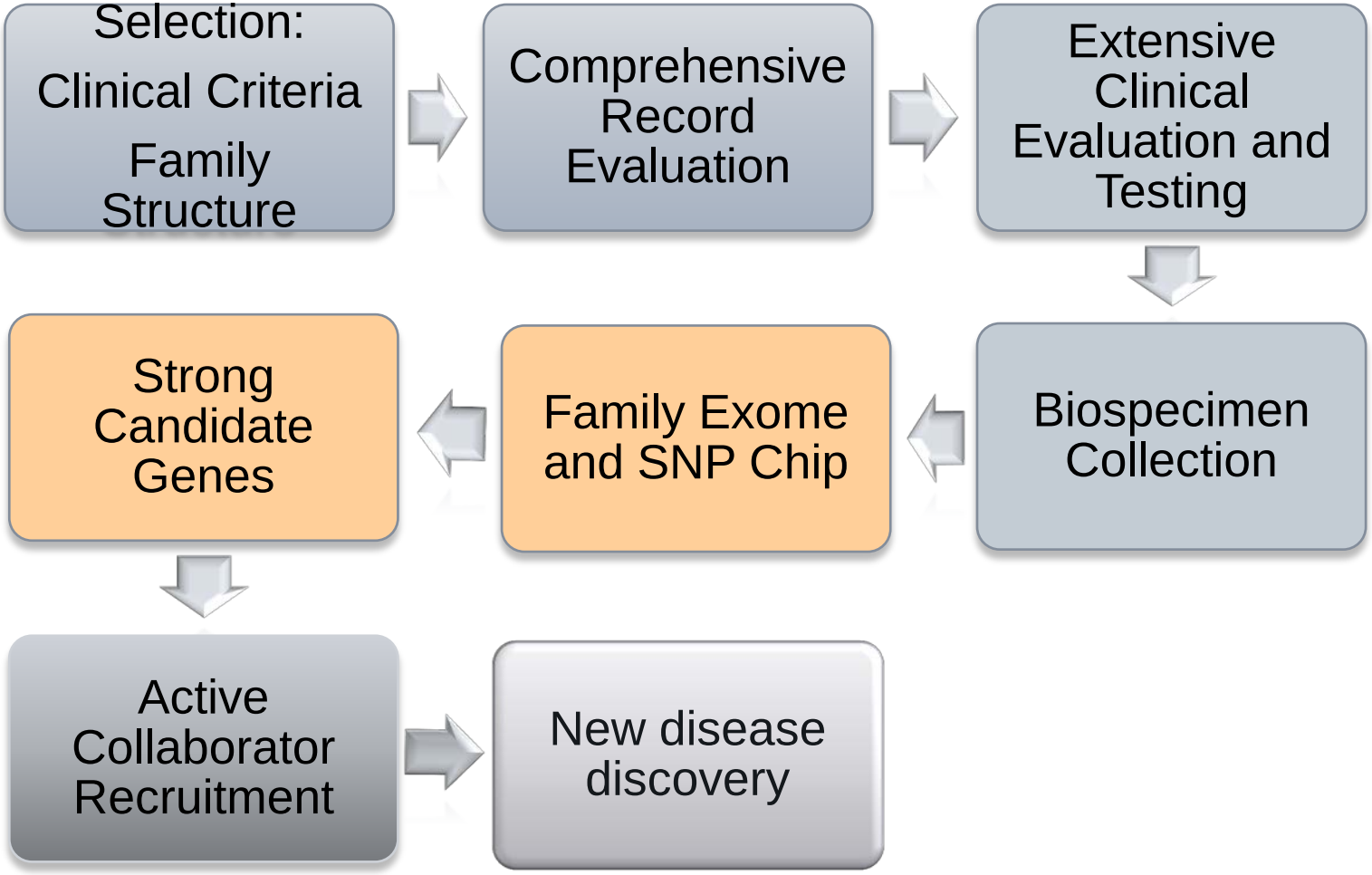
Pediatric anesthesia services in MRI suite to accomplish multiple studies under a single 3-5 hour sedation:

- Brain MRI/MRS
- Lumbar puncture
- Skin biopsy
- Eye exam
- Brainstem evoked response
- Dysmorphology exam
- Dental exam
- EMG/NCV
- Large blood draws
- Catheterization for urine sample
- Minor surgical procedures

Pediatric UDP: First 5 years

- 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
    - Conventional testing — 28
  - May excellent candidate genes not previously linked to human disease

UDP Process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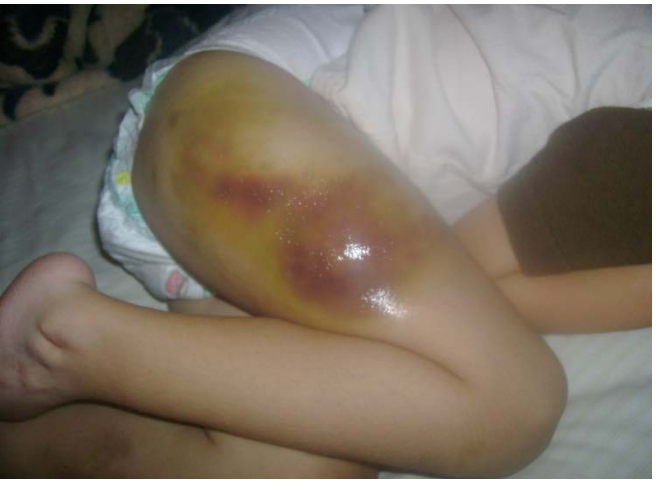
Working hypotheses…

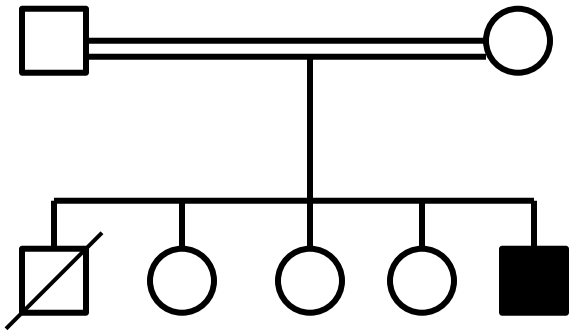
- An extremely rare disease
- More than one disease….
- An unusual presentation of a more common disease
- An entirely new disease

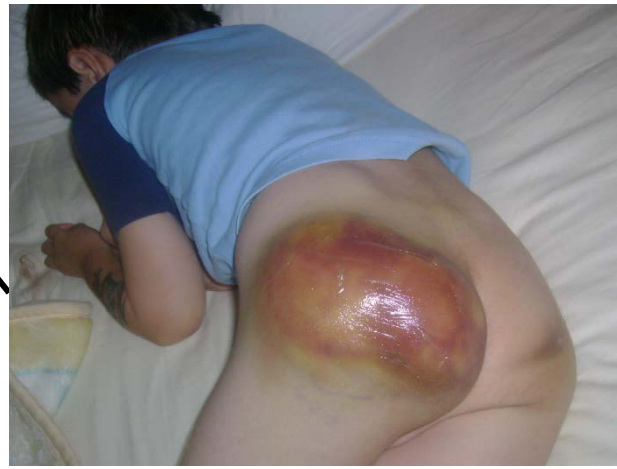
Extremely rare disease

UDP 1846

- 5 year old with adducted thumbs, clubbed feet, hypotonia, and bleeding disorder

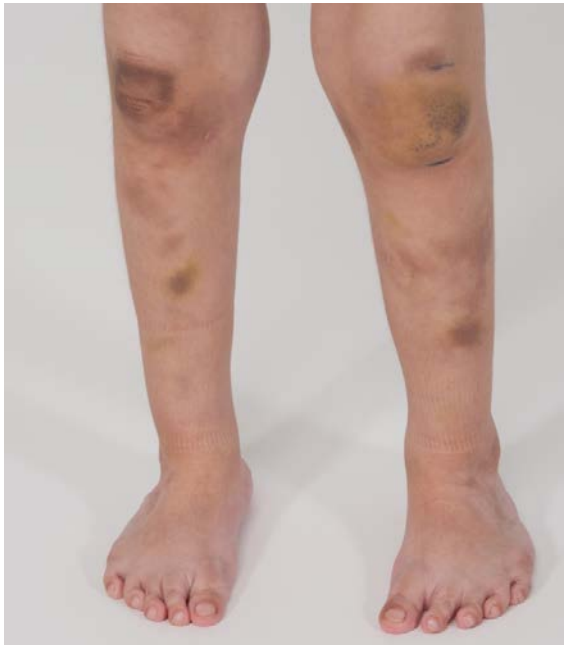
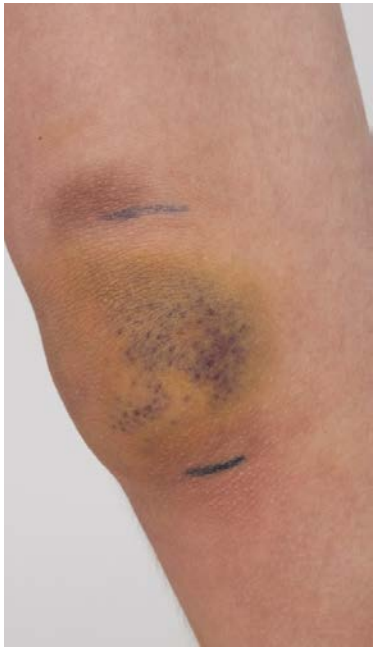
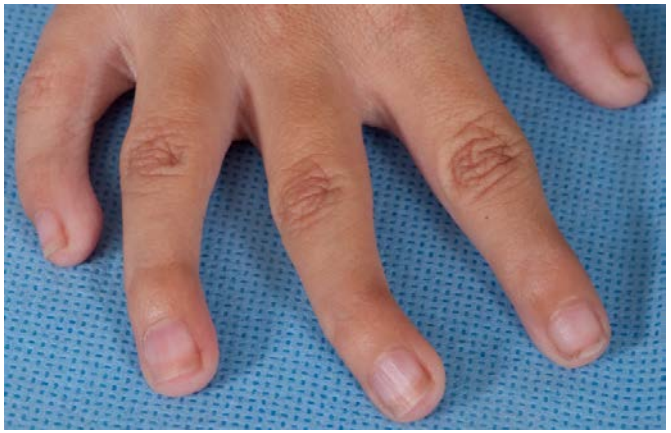
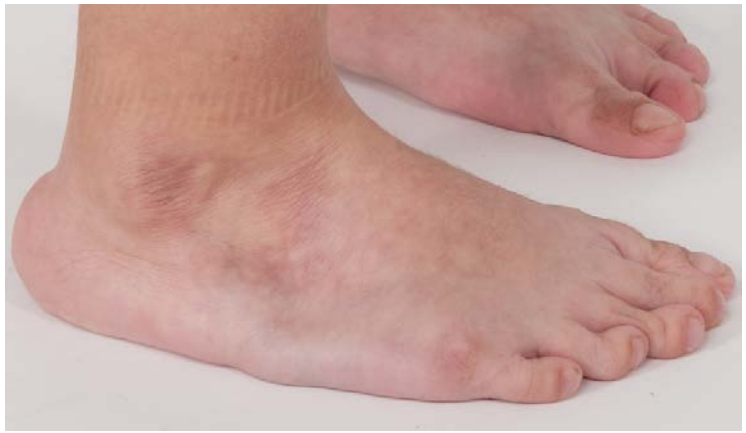






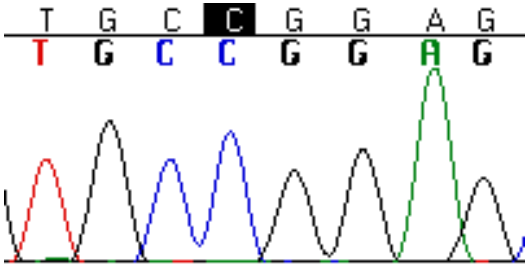
UDP 1846



Phenotype suggests candidate gene

- SNP array shows 26 Mb of homozygosity unique to the patient containing 72 genes.
- One gene fits clinical picture: *CHST14*
- Patient homozygous for G>C in exon 14.



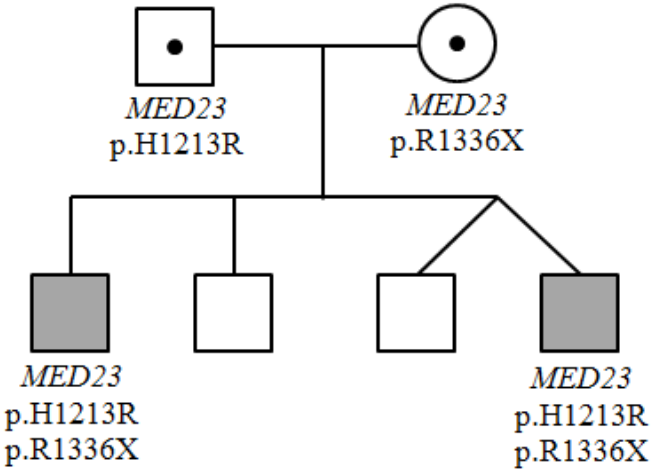
- *CHST14* encodes dermatan-4-sulfotransferase 1 important for the formation of dermatan sulfate which is fibrinolytic.
- Could one prevent the bruising/bleeding by treating with dermatan sulfate?

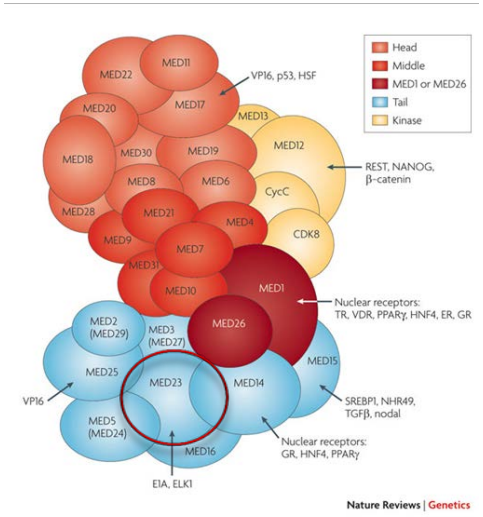
The Phenotype of the Musculocontractural Type of Ehlers-Danlos Syndrome due to *CHST14* Mutations

Andreas R. Janecke,[1,2]* Ben Li,[3] Manfred Boehm,[4] Birgit Krabichler,[2] Marianne Rohrbach,[5] Thomas Müller,[1] Irene Fuchs,[1] Gretchen Golas,[6] Yasuhiro Katagiri,[7] Shira G. Ziegler,[6] William A. Gahl,[6] Yael Wilnai,[8] Nicoletta Zoppi,[9] Herbert M. Geller,[7] Cecilia Giunta,[5] Anne Slavotinek,[3] and Beat Steinmann[5]

Extremely rare disease with expanded phenotype

UDP 2146, 2156

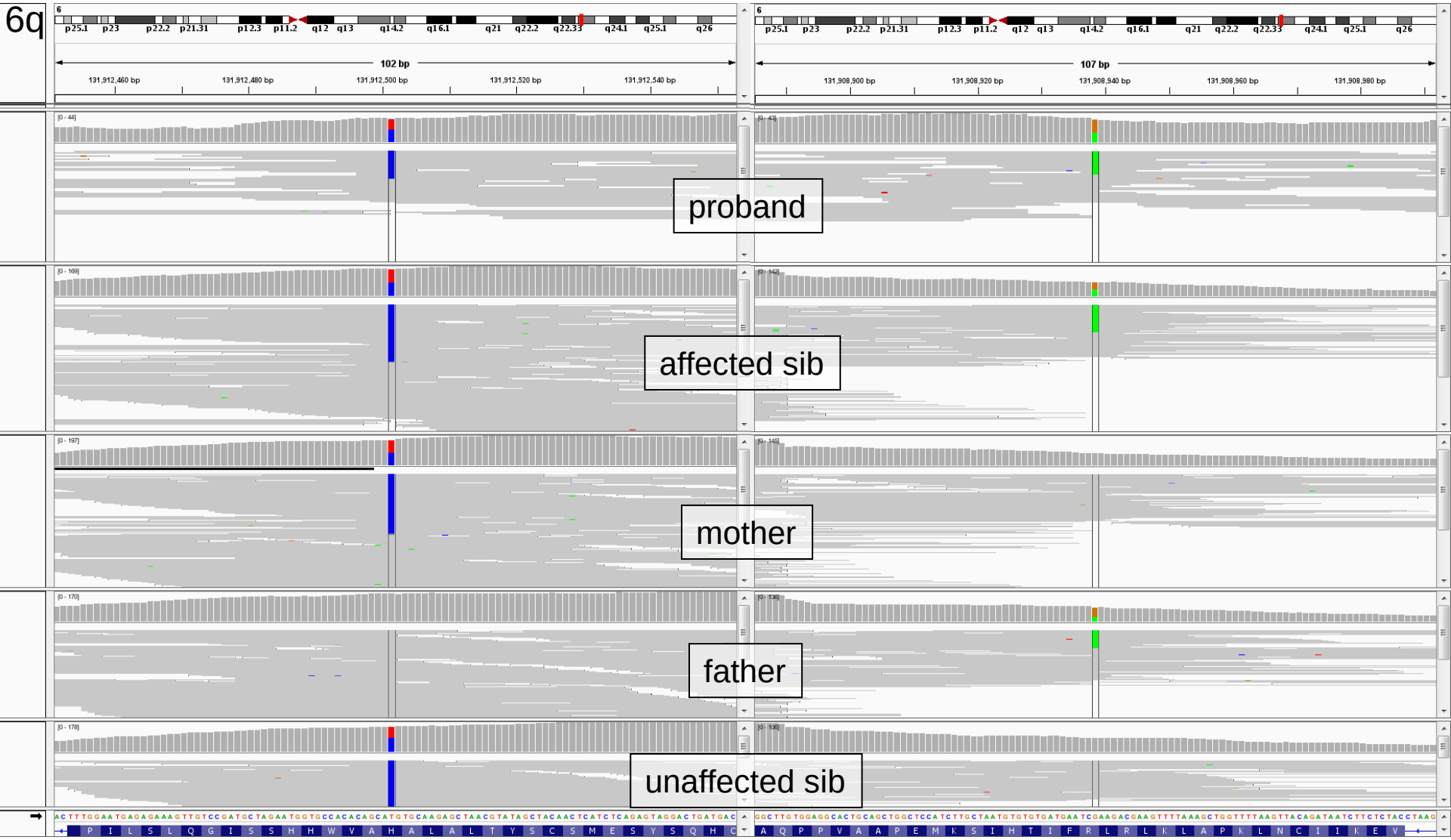




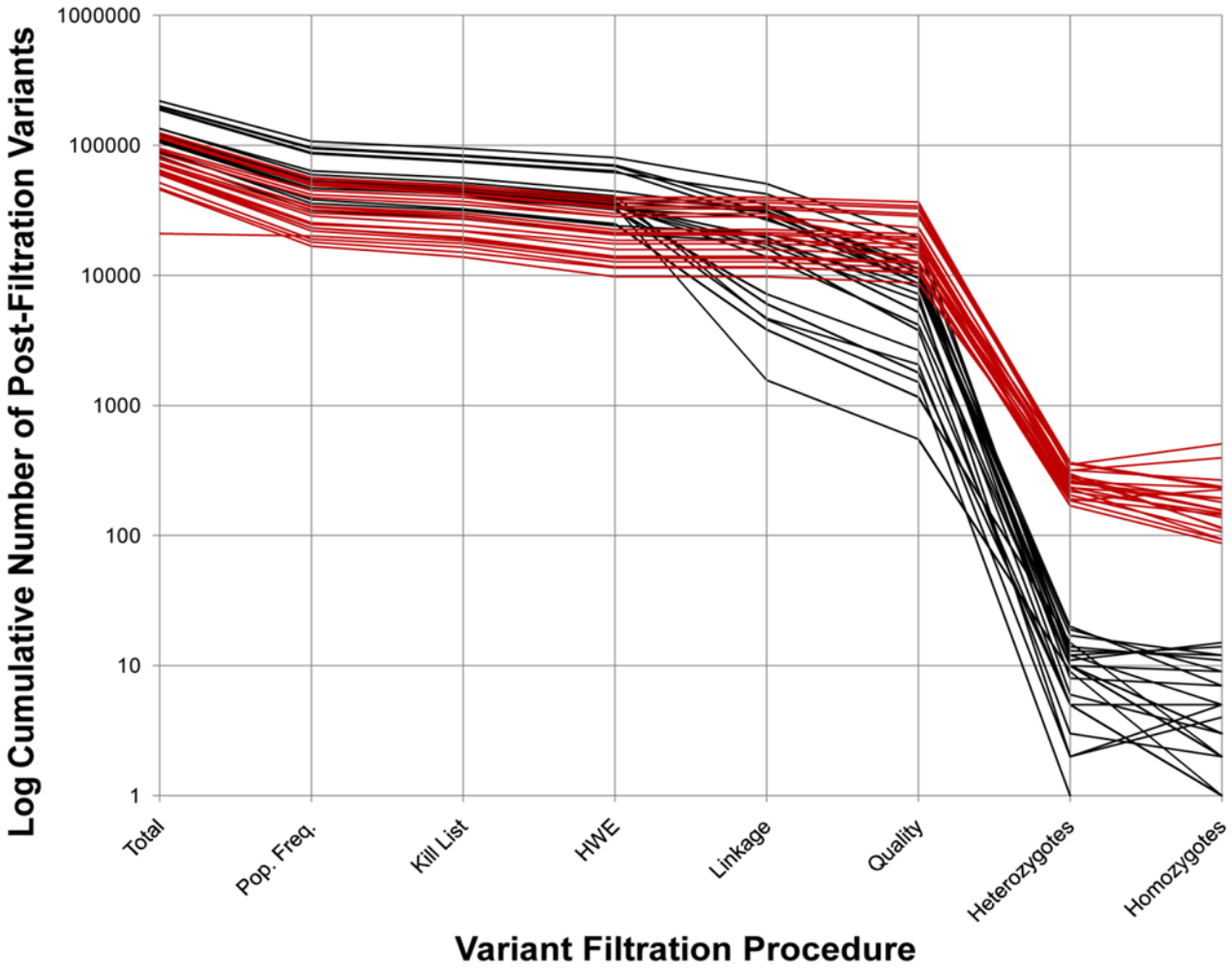
MED23-Associated Intellectual Disability in a Non-Consanguineous Family

Aditi Trehan,[1,2] Jacqueline M. Brady,[1,2] Valerie Maduro,[1,2] William P. Bone,[1,2] Yan Huang,[1,2] Gretchen A. Golas,[1,2] Megan S. Kane,[2] Paul R. Lee,[3] Audrey Thurm,[4] Andrea L. Gropman,[1,5] Scott M. Paul,[6] Gilbert Vezina,[5] Thomas C. Markello,[2] William A. Gahl,[1,2] Cornelius F. Boerkoel,[2] and Cynthia J. Tifft[1,2]*

UDP 2146,2156



Filtered Variants, Family vs No Family



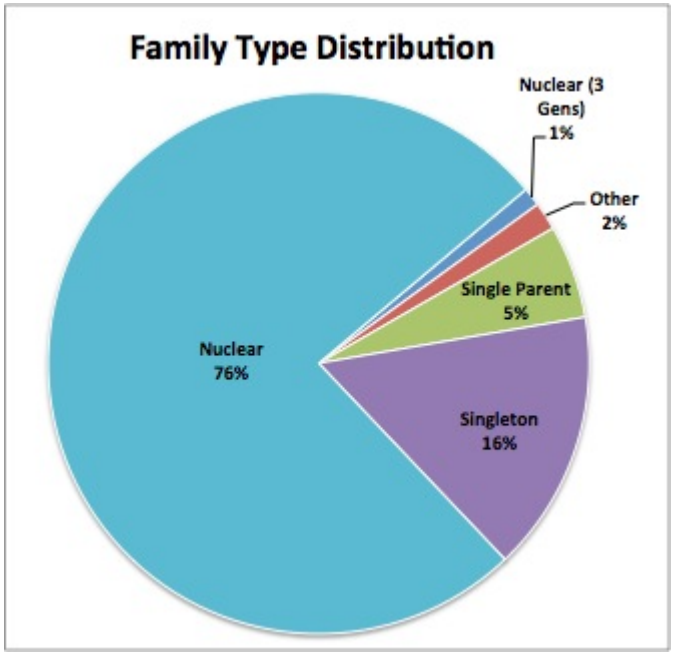
Analysis of DNA Sequence Variants Detected by High-Throughput Sequencing

HGVS HUMAN GENOME VARIATION SOCIETY www.hgvs.org

David R. Adams,[1,2*] Murat Sincan,[2] Karin Fuentes Fajardo,[1] James C. Mullikin,[5†] Tyler M. Pierson,[1,4] Camilo Toro,[1] Cornelius F. Boerkoel,[1] Cynthia J. Tifft,[1,3] William A. Gahl,[1,2,3] and Tom C. Markello[3]

NATIONAL HUMAN GENOME RESEARCH INSTITUTE
Division of Intramural Research

Exome analysis in the UDP



Exome analysis

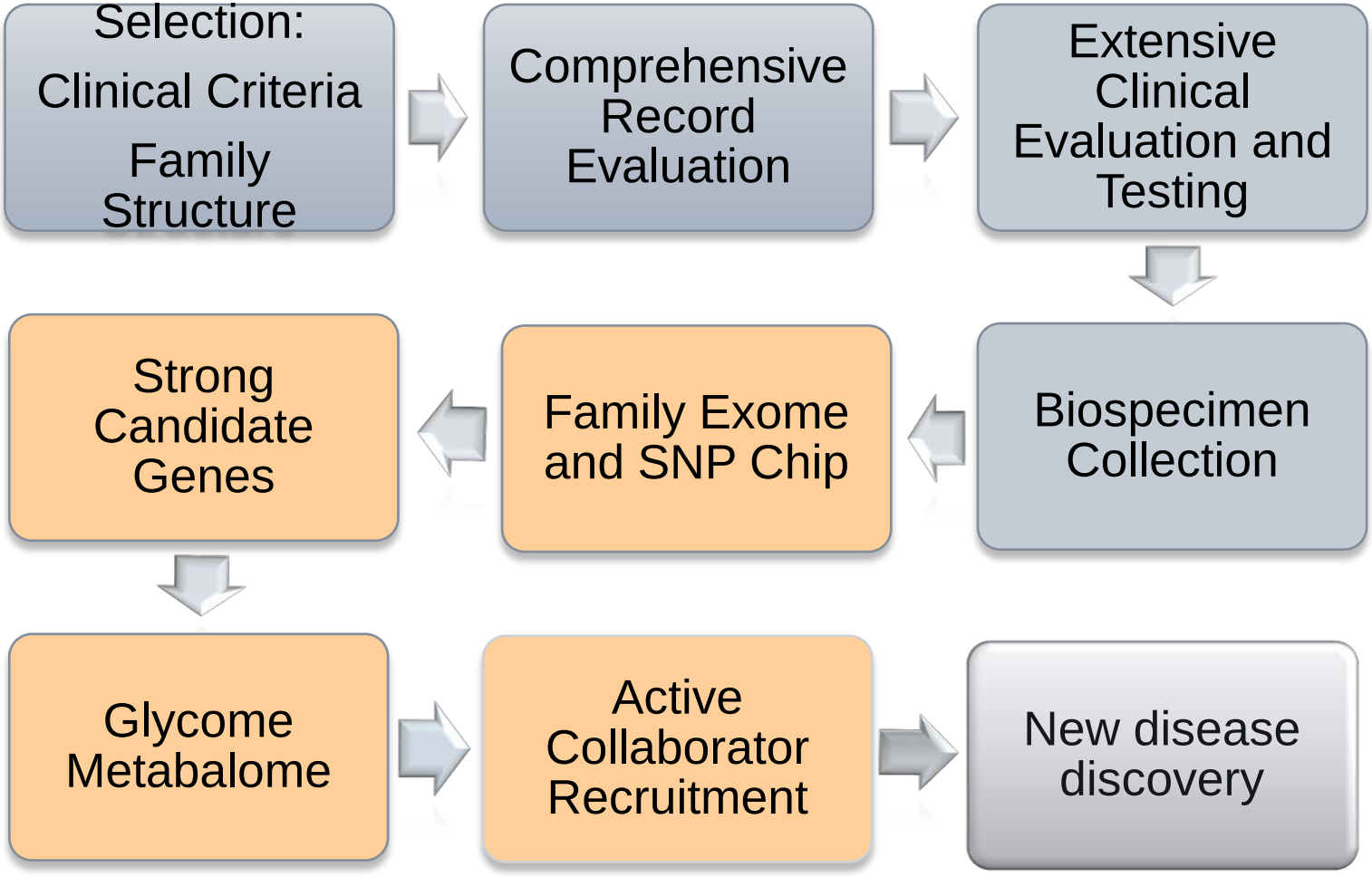
- 360 families
- 1329 exomes

Average Family Size

- Pediatric patients 4.1
- Adult patients 3.3

Family Type	Diagnosed	With Lead	Unsolved	In Pipeline
Singleton	7	2	43	4
Nuclear All	68	66	71	71
Single Parent	4	1	8	7
Other	1	0	5	0

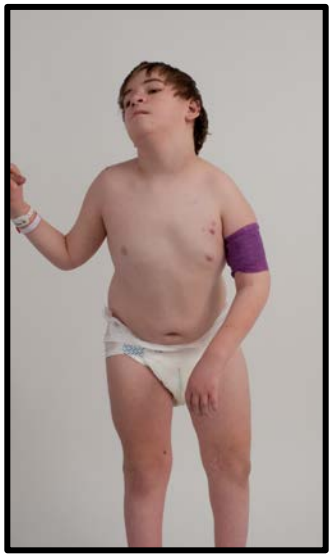
UDP Process *Revised*



UDP 887,1248

11 year old Male

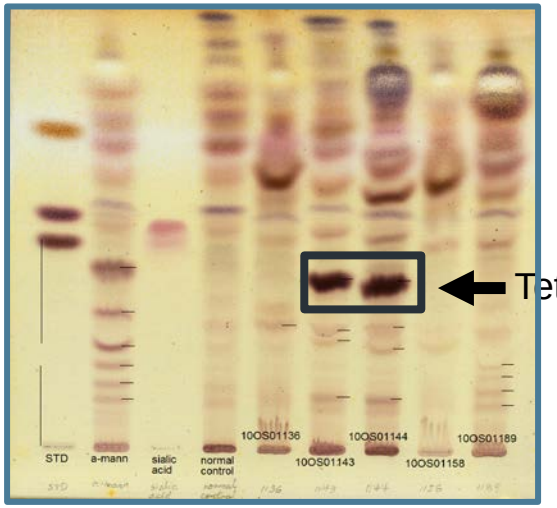
- Dysmorphic facial features
- Global developmental delay
- Spastic paraparesis
- Truncal hypotonia
- Bilateral hearing loss
- Optic atrophy
- Cerebral atrophy, small corpus callosum, low NAA
- Multiple fractures
- Leukocytosis
- Generalized aminoaciduria
- Hypogammaglobulinemia
- Normal carbohydrate deficient transferrin



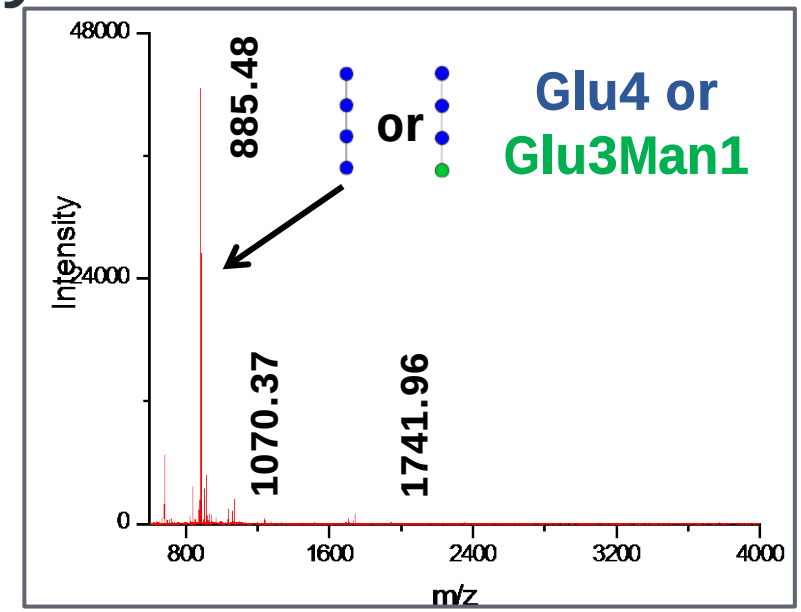
6 year old Female

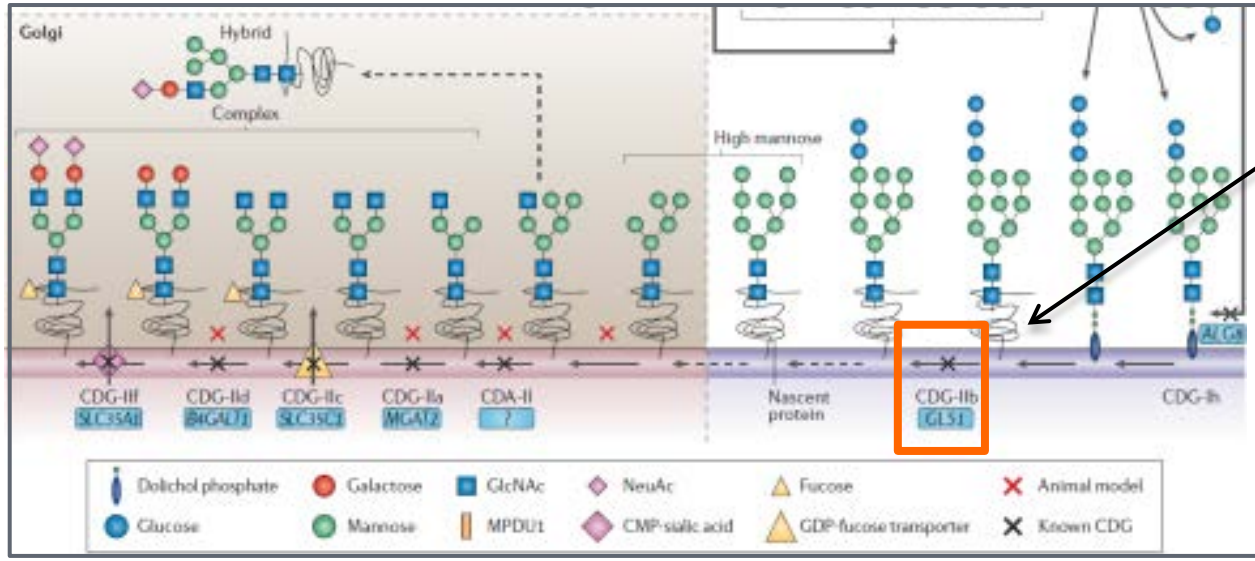
- Dysmorphic facial features
- Global developmental delay
- Generalized hypotonia
- Neonatal seizures
- Cerebral folate deficiency
- Optic atrophy
- Cerebral atrophy, small corpus callosum, low NAA
- Leukocytosis
- Hypogammaglobulinemia
- Normal carbohydrate deficient transferrin

Urine glycans prove key



Tetrasaccharide





Mannosyl-
Oligosaccharide
Glucosidase

Diagnosis--
MOGS-CDG

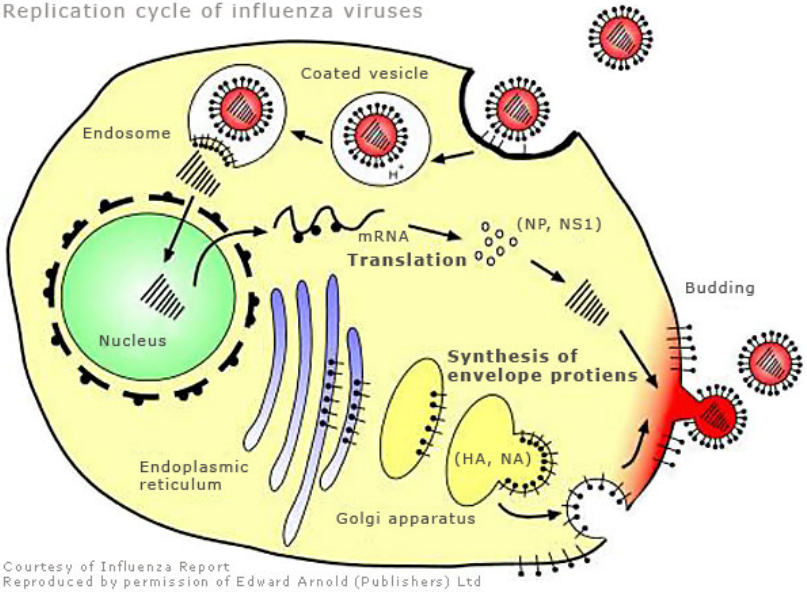
N ENGL J MED 370;17 NEJM.ORG APRIL 24, 2014

BRIEF REPORT

Glycosylation, Hypogammaglobulinemia, and Resistance to Viral Infections

Mohammed A. Sadat, M.D., Ph.D., Susan Moir, Ph.D., Tae-Wook Chun, Ph.D., Paolo Lusso, M.D., Ph.D., Gerardo Kaplan, Ph.D., Lynne Wolfe, N.P., Matthew J. Memoli, M.D., Miao He, Ph.D., Hugo Vega, M.D., Ph.D., Leo J.Y. Kim, B.A., Yan Huang, Ph.D., Nadia Hussein, B.E., Elma Nievas, M.D., Raquel Mitchell, Ph.D., Mary Garofalo, R.N., Aaron Louie, B.Sc., Derek C. Ireland, Ph.D., Claire Grunes, Raffaello Cimbro, Ph.D., Vyomesh Patel, Ph.D., Genevieve Holzapfel, Ph.D., Daniel Salahuddin, B.Sc., Tyler Bristol, M.S., David Adams, M.D., Beatriz E. Marciano, M.D., Madhuri Hegde, M.D., Yuxing Li, Ph.D., Katherine R. Calvo, M.D., Ph.D., Jennifer Stoddard, B.S., J. Shawn Justement, M.S., Jerome Jacques, M.S., Debra A. Long Priel, M.S., Danielle Murray, M.A., Peter Sun, Ph.D., Douglas B. Kuhns, Ph.D., Cornelius F. Boerkoel, M.D., Ph.D., John A. Chiorini, Ph.D., Giovanni Di Pasquale, Ph.D., Daniela Verthelyi, M.D., Ph.D., and Sergio D. Rosenzweig, M.D., Ph.D.

Replication cycle of influenza viruses



Courtesy of Influenza Report
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- Vaccinations and Titers

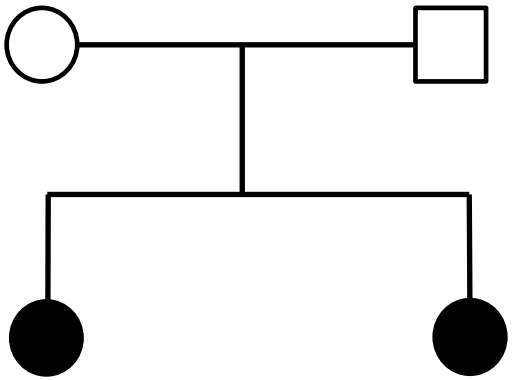
Tetanus -> (+) protective titers
Diphteria -> (+) protective titers
HiB -> (+) protective titers
Pnemoc. -> (+) protective titers
Measles -> (-) protective titers
Mumps -> (-) protective titers
Varicella -> (-) protective titers

More than one disease in a non-consanguineous family

Careful phenotyping is key

- Sibling pair with recurrent episodes of ketotic hypoglycemia

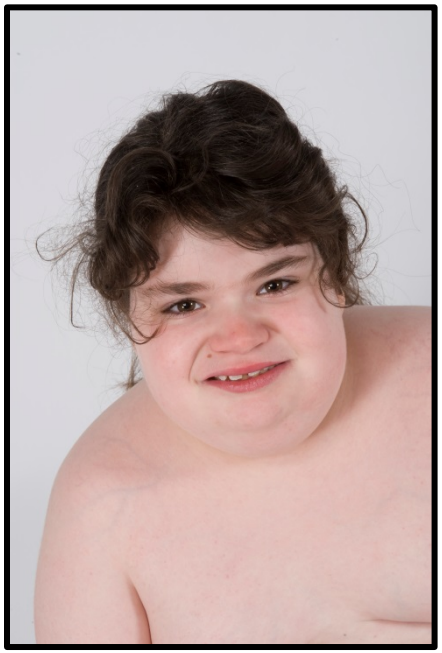




Three rare diseases in one Sib pair: *RAI1*, *PCK1*, *GRIN2B* mutations associated with Smith–Magenis Syndrome, cytosolic PEPCK deficiency and NMDA receptor glutamate insensitivity

David R. Adams [a,b], Hongjie Yuan [c], Todd Holyoak [d], Katrina H. Arajs [d], Parvin Hakimi [g,h], Thomas C. Markello [a], Lynne A. Wolfe [a], Thierry Vilboux [b], Barbara K. Burton [e,f], Karin Fuentes Fajardo [a], George Grahame [i], Conisha Holloman [j], Murat Sincan [a], Ann C.M. Smith [a], Gordon A. Wells [k,l], Yan Huang [a], Hugo Vega [a], James P. Snyder [k], Gretchen A. Golas [a], Cynthia J. Tifft [a], Cornelius F. Boerkoel [a], Richard W. Hanson [g], Stephen F. Traynelis [c], Douglas S. Kerr [g,h,i], William A. Gahl [a,b]

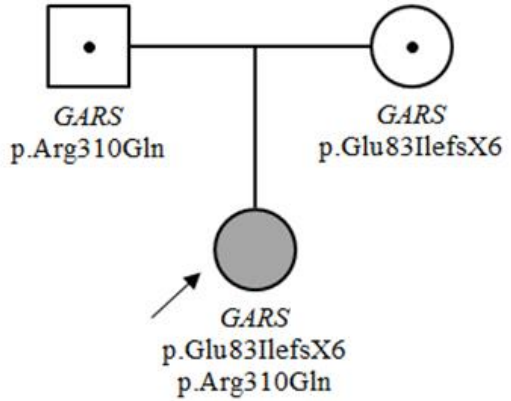
- PCK1 mutation for enzyme PEPCK
- Smith Magenis Syndrome (RAI1)

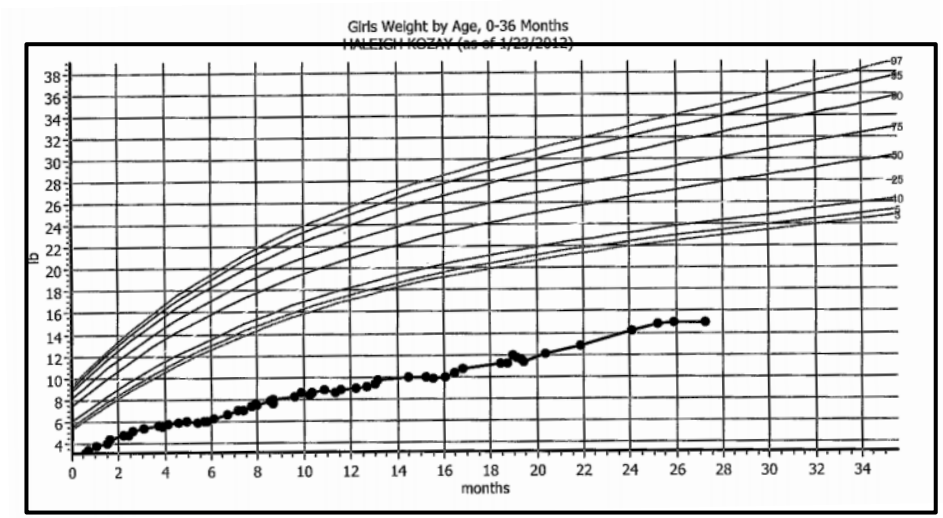


- PCK1 mutation for enzyme PEPCK
- GRIN2B mutation for ID phenotype

Unusual presentation of a more common disease

UDP 5316

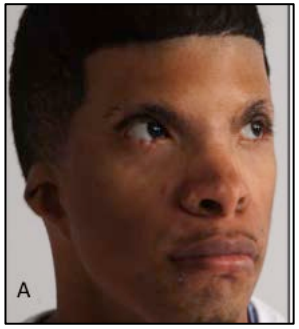




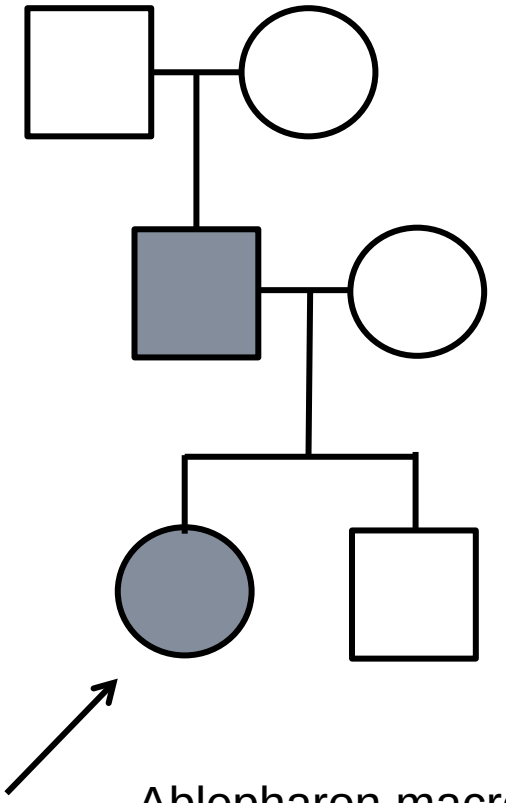
- GARS
  - Glycyl tRNA synthetase
  - Charcot-Marie-Tooth disease, type 2D
  - Distal hereditary motor neuronopathy type VA
  - Autosomal dominant

New disease/gene association

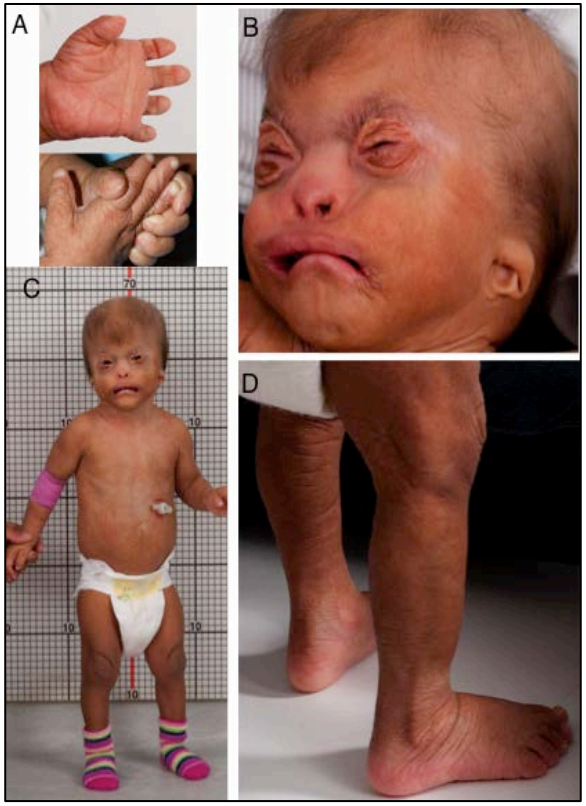
UDP 3866



Mosaicism in 1st generation (fertile)



Ablepharon macrostomia syndrome



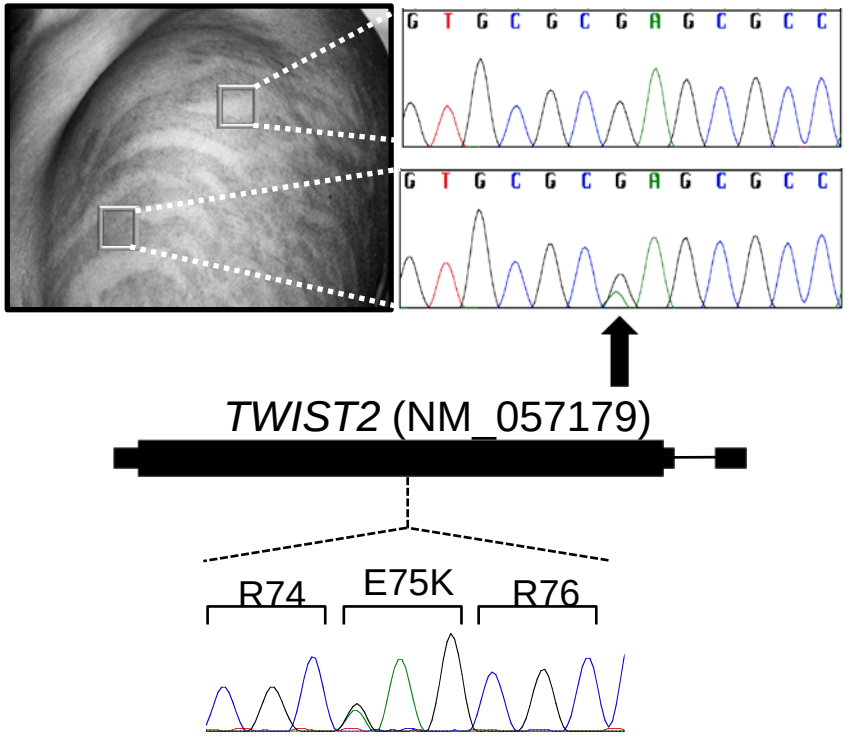
Recurrent Mutations in the Basic Domain of *TWIST2* Cause Ablepharon Macrostomia and Barber-Say Syndromes

Shannon Marchegiani,[1,2,31] Taylor Davis,[1,31] Federico Tessadori,[3,31] Gijs van Haaften,[4] Francesco Brancati,[5] Alexander Hoischen,[6] Haigen Huang,[7] Elise Valkanas,[1] Barbara Pusey,[1] Denny Schanze,[8] Hanka Venselaar,[6] Anneke T. Vulto-van Silfhout,[6] Lynne A. Wolfe,[1,9] Cynthia J. Tifft,[1,9] Patricia M. Zerfas,[10] Giovanna Zambruno,[11] Ariana Kariminejad,[12] Farahnaz Sabbagh-Kermani,[13] Janice Lee,[14] Maria G. Tsokos,[15] Chyi-Chia R. Lee,[15] Victor Ferraz,[16] Eduarda Morgana da Silva,[16] Cathy A. Stevens,[17] Nathalie Roche,[18] Oliver Bartsch,[19] Peter Farndon,[20] Eva Bermejo-Sanchez,[21] Brian P. Brooks,[22] Valerie Maduro,[1] Bruno Dallapiccola,[23] Feliciano J. Ramos,[24] Hon-Yin Brian Chung,[25] Cédric Le Caignec,[26] Fabiana Martins,[27] Witold K. Jacyk,[28] Laura Mazzanti,[29] Han G. Brunner,[6,30] Jeroen Bakkers,[3] Shuo Lin,[7] May Christine V. Malicdan,[1,9,*] Cornelius F. Boerkoel,[1] William A. Gahl,[1,9,*] Bert B.A. de Vries,[6] Mieke M. van Haelst,[4] Martin Zenker,[8,32] and Thomas C. Markello[1,32]

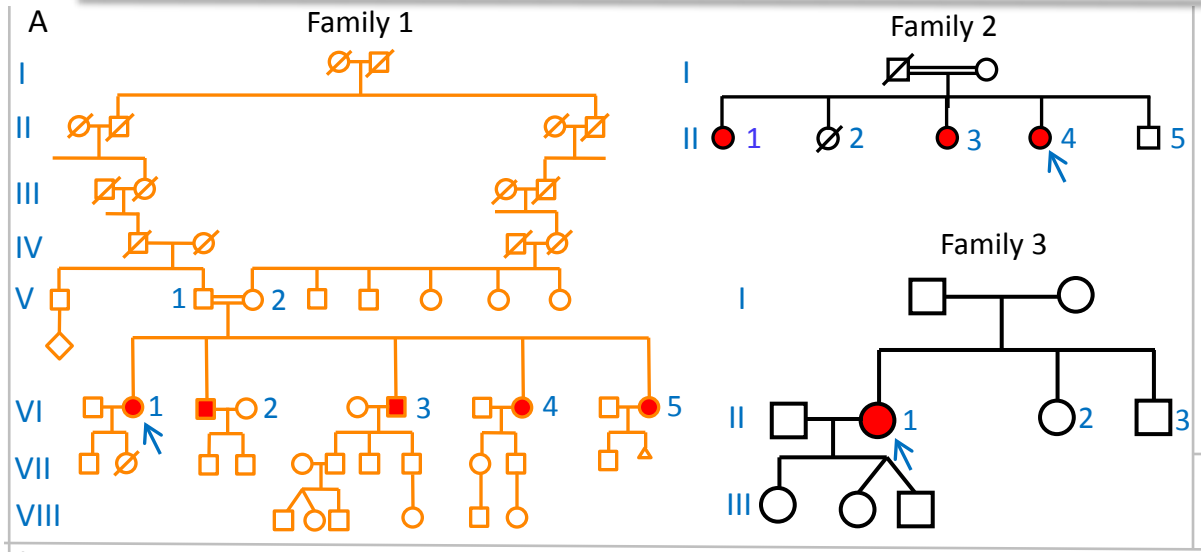
TWIST2:c.223G>A(p.E75K)

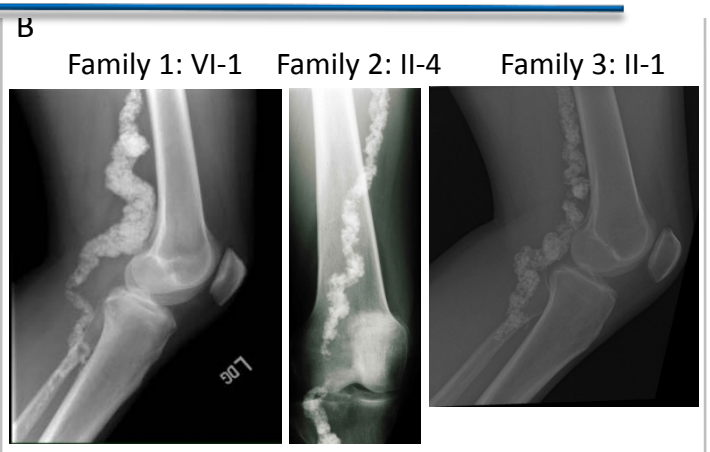
- Transcription factor
- Group A helix-loop-helix transcription factor (E box)
- Mesenchyme and craniofacial and dermis in embryogenesis plus cell maintenance
- Autosomal dominant

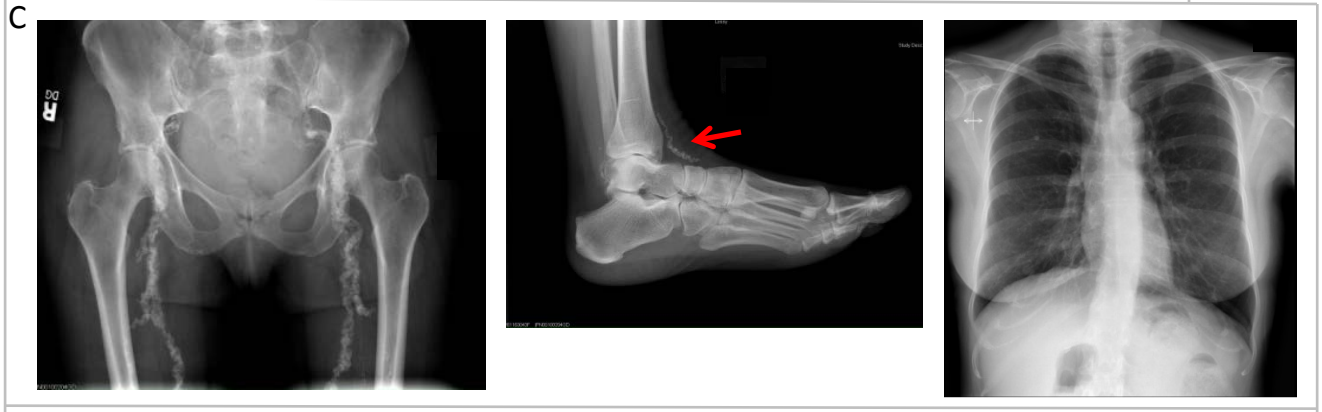
7 families with Ablepharon macrostomia
10 families with Barber-Say syndrome

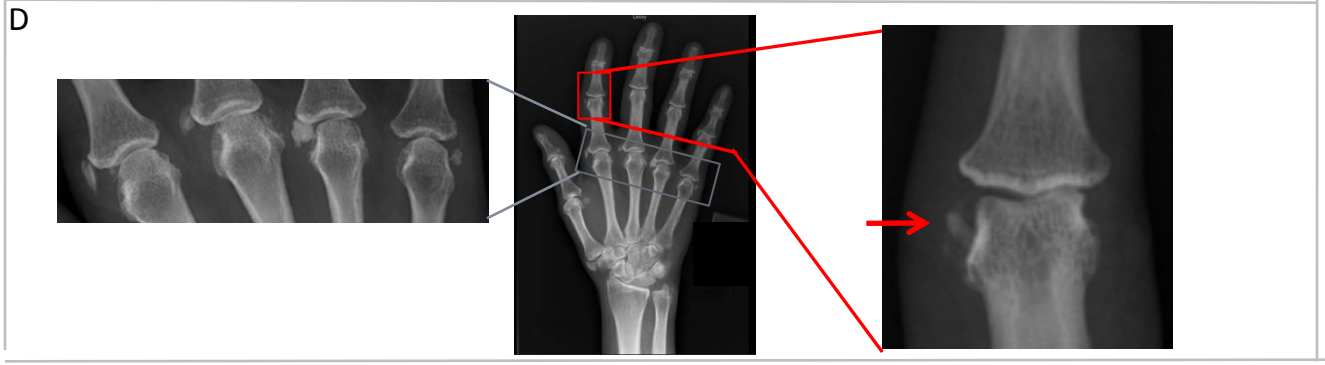


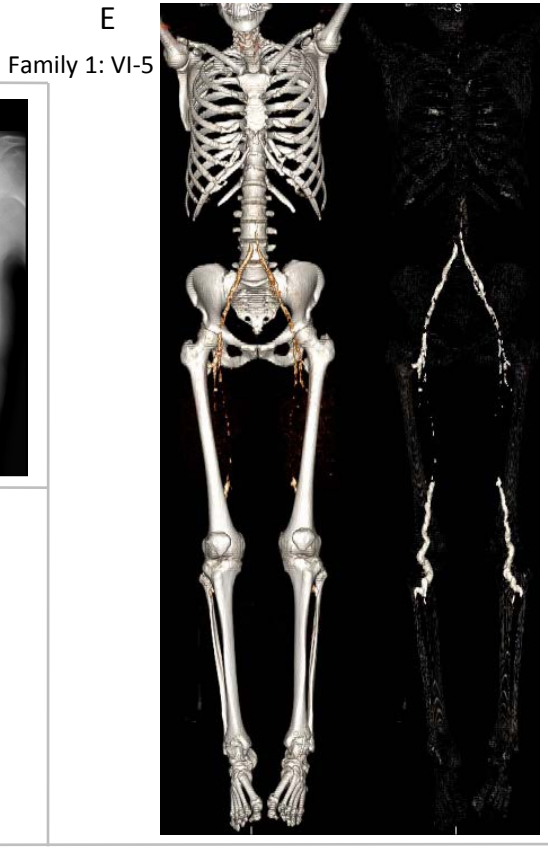
Families with Arterial/Joint Capsule Calcification









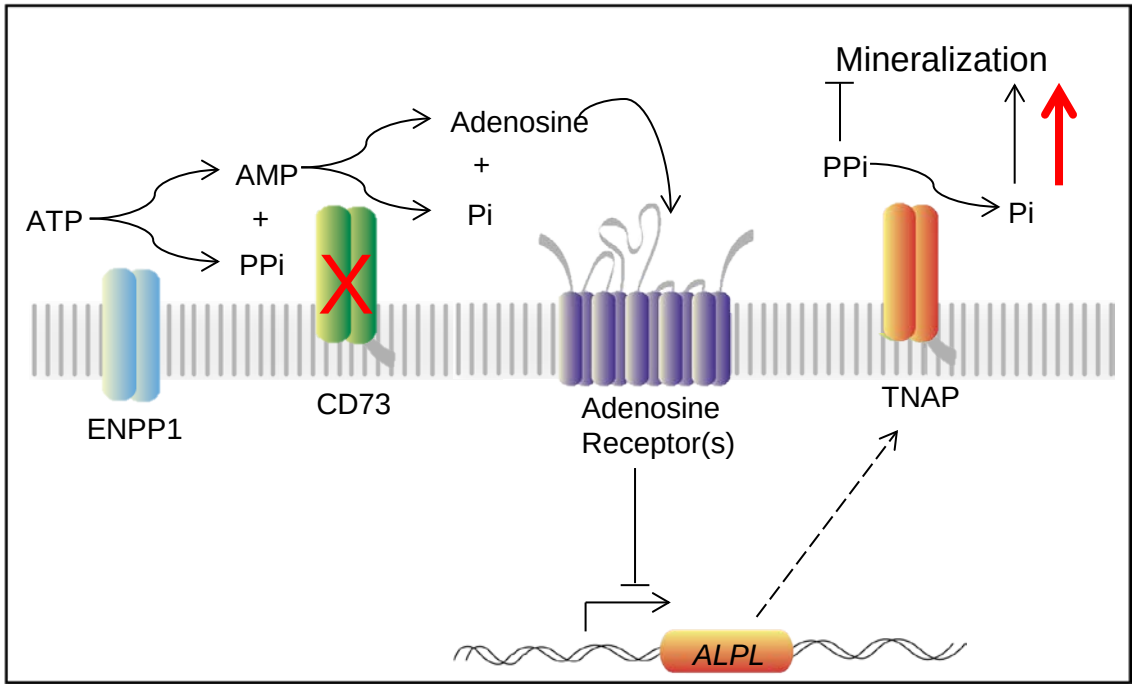


ORIGINAL ARTICLE

NT5E Mutations and Arterial Calcifications

Cynthia St. Hilaire, Ph.D., Shira G. Ziegler, B.A., Thomas C. Markello, M.D., Ph.D., Alfredo Brusco, Ph.D., Catherine Groden, M.S., Fred Gill, M.D., Hannah Carlson-Donohoe, B.A., Robert J. Lederman, M.D., Marcus Y. Chen, M.D., Dan Yang, M.D., Ph.D., Michael P. Siegenthaler, M.D., Carlo Arduino, M.D., Cecilia Mancini, M.Sc., Bernard Freudenthal, M.D., Horia C. Stanescu, M.D., Anselm A. Zdebik, M.D., Ph.D., R. Krishna Chaganti, M.D., Robert L. Nussbaum, M.D., Robert Kleta, M.D., Ph.D., William A. Gahl, M.D., Ph.D., and Manfred Boehm, M.D.

N Engl J Med 2011; 364:432-442 | February 3, 2011 | DOI: 10.1056/NEJMoa0912923



Courtesy S. Ziegler

The finding of additional families and strong candidate genes led to gene discovery.

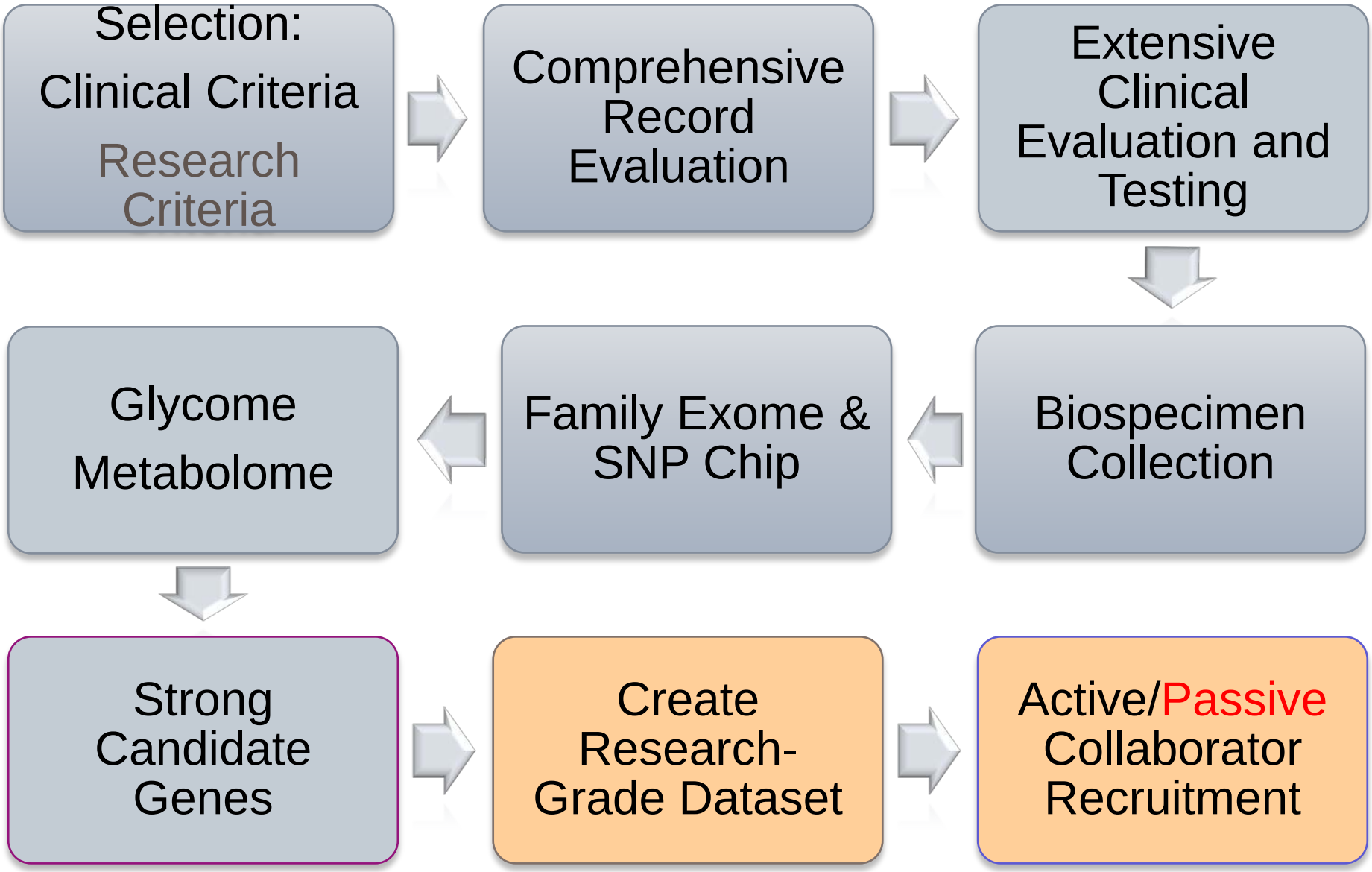
Could adenosine or an adenosine analog decrease calcification in the major vessels of individuals with atherosclerosis?

Expanding the vision…

What about the 75% of cases unsolved…

- Good candidate genes in an additional 70 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

UDP Process Revised & *Extended*



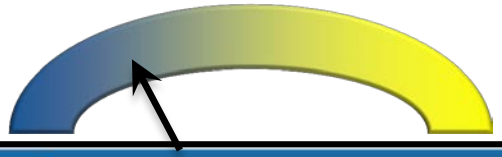
UDP Integrated Collaboration System

- 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.

PHENOTIPS

HPO terms

Specificity meter



QUICK PHENOTYPE SEARCH: Enter keywords and choose among suggested ontology terms

▼CRANIOFACIAL
- ▸ NA Y N Craniosynostosis
- ▸ NA **Y** N **Cleft upper lip**
- ▸ NA Y N Cleft palate
- ▸ NA Y N Abnormal facial shape

Other
(enter free text and choose among suggested ontology terms)

▼EYE DEFECTS
- ▸ NA Y N Visual impairment
- ▸ NA Y N Abnormality of the cornea
- ▸ NA Y N Coloboma
- ▸ NA Y N Abnormality of the anterior chamber
- ▸ NA **Y** N **Cataract**
- ▸ NA Y N Abnormality of the retina
- ▸ NA Y N Abnormality of the optic nerve
- ▸ NA Y N Microphthalmos
- ▸ NA Y N Nystagmus
- ▸ NA Y N Strabismus

Other
(enter free text and choose among suggested ontology terms)

▼EAR DEFECTS

Deafness
- NA Y N Sensorineural
- NA Y N Conductive
- NA Y N Preauricular pit
- NA Y N Preauricular skin tag
- ▸ NA **Y** N **Abnormality of the outer ear**
- ▸ NA Y N Abnormality of the inner ear

CURRENT SELECTION

GROWTH PARAMETERS

Decreased body weight Delete · Clear details
Neonatal onset
Slow progression

CRANIOFACIAL

Cleft upper lip Delete · Clear details
No additional information.

EYE DEFECTS

Cataract Delete · Add details

EAR DEFECTS

Abnormality of the outer ear Delete · Add details

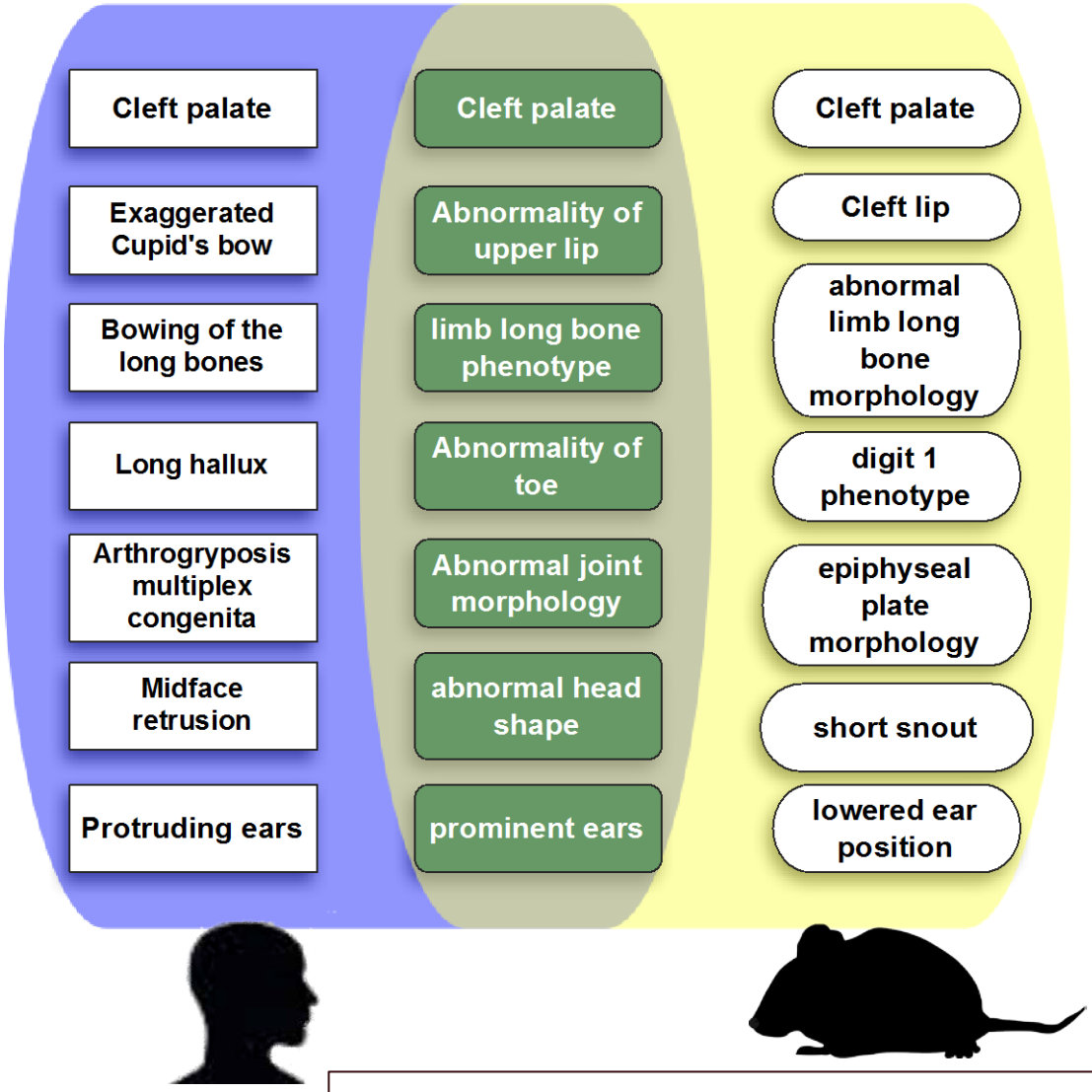
MUSCULOSKELETAL

Hip osteoarthritis Delete · Add details

BEHAVIOR, COGNITION AND DEVELOPMENT

Repetitive compulsive behavior Delete · Add details
Mutism Delete · Add details
Self-injurious behavior Delete · Add details
Attention deficit hyperactivity disorder Delete · Add details
Behavioural/Psychiatric Abnormality Delete · Clear details
No additional information.

Phenotype similarity across patients or ….any organism

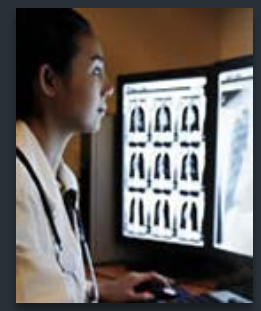


Courtesy M. Haendel

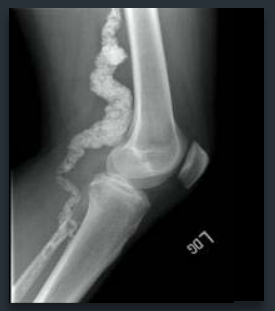
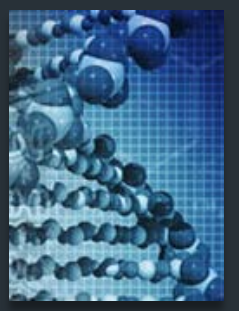
https://code.google.com/p/owltools/wiki/OwlSim

Finding the second case… Matchmaker Exchange

No good deed goes unpunished…





The Undiagnosed Diseases Network

NIH National Institutes of Health

Office of Strategic Coordination - The Common Fund

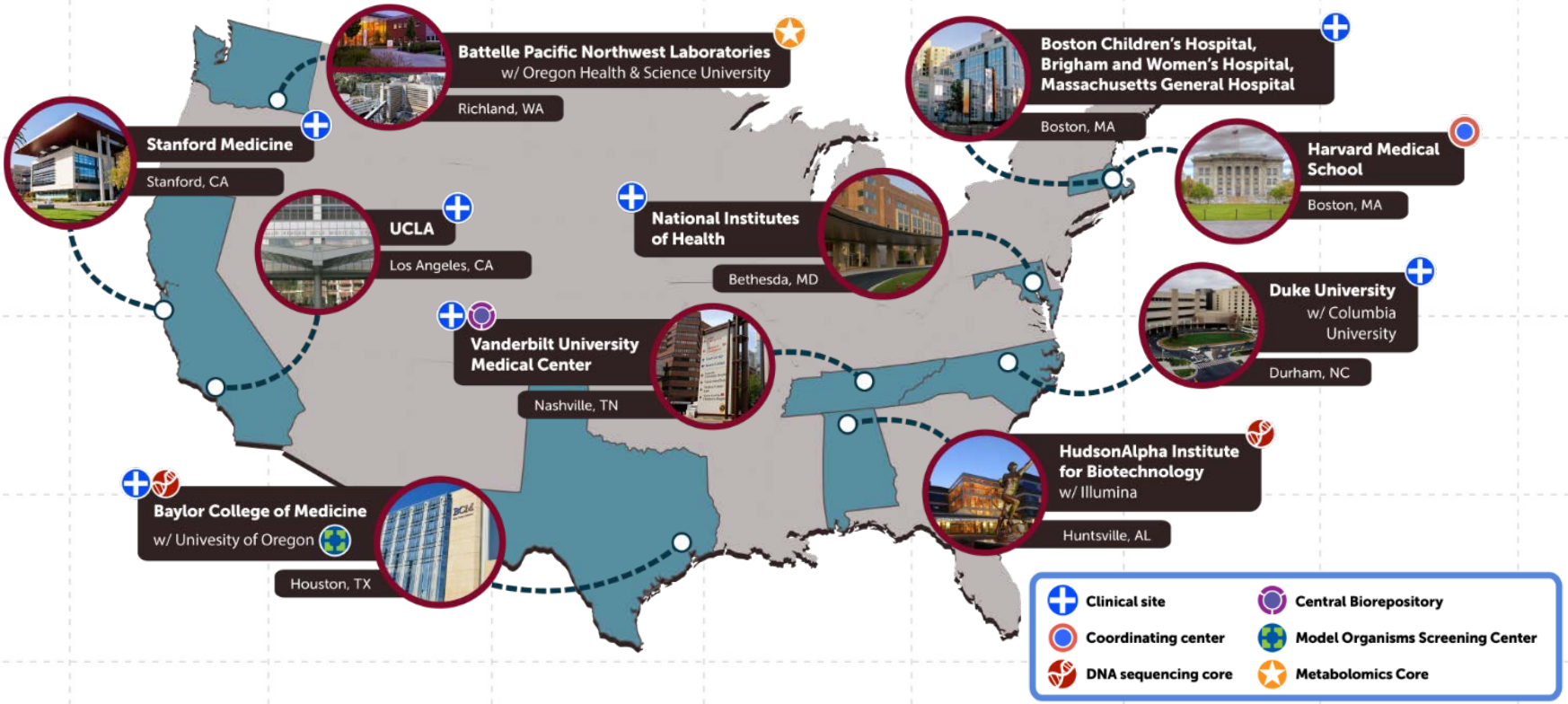
UDN Objectives

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

Undiagnosed Diseases Network

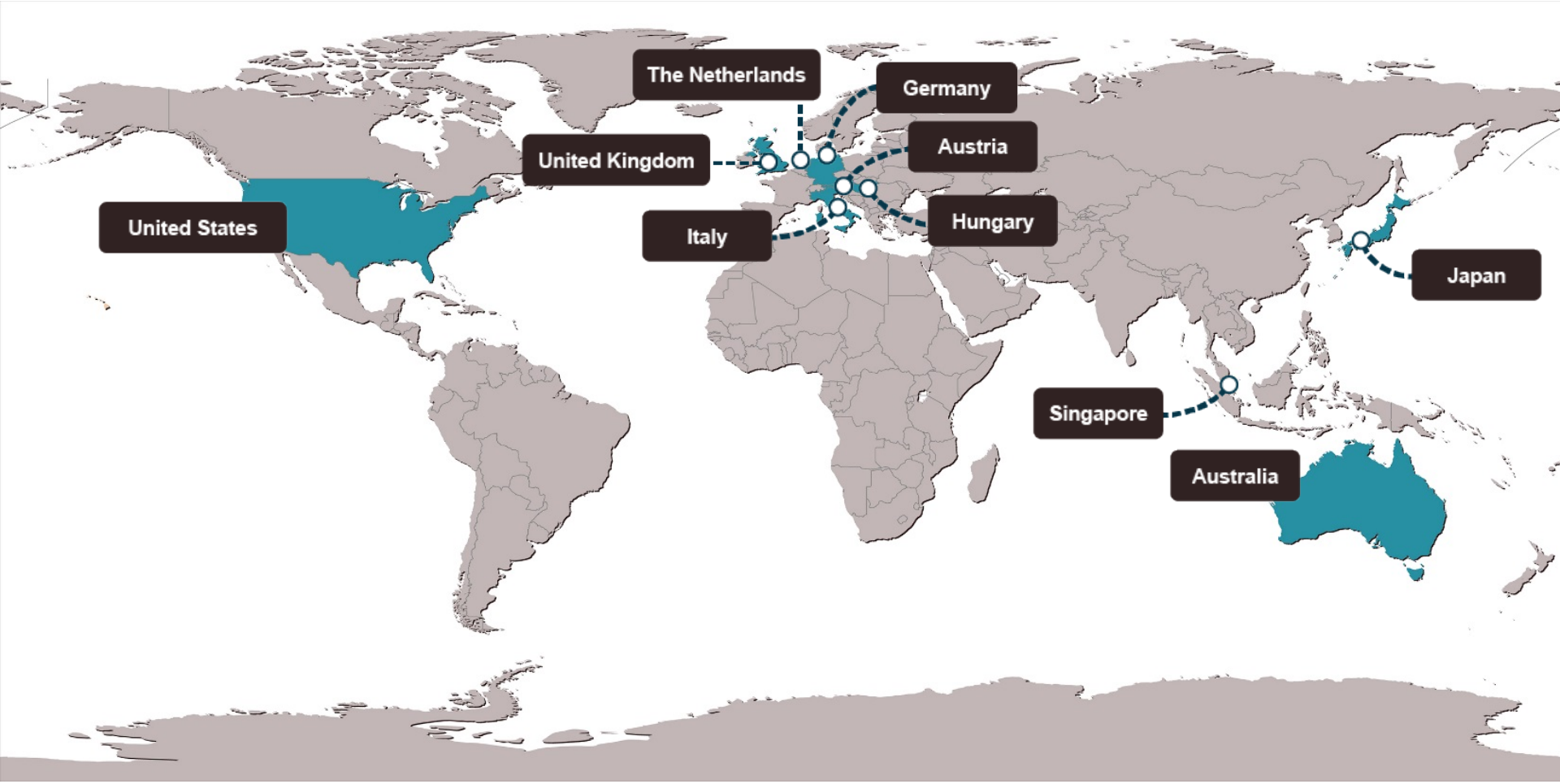
Seven clinical sites, a coordinating center, two DNA sequencing cores, a metabolomics core, a model organisms screening center, and a central biorepository



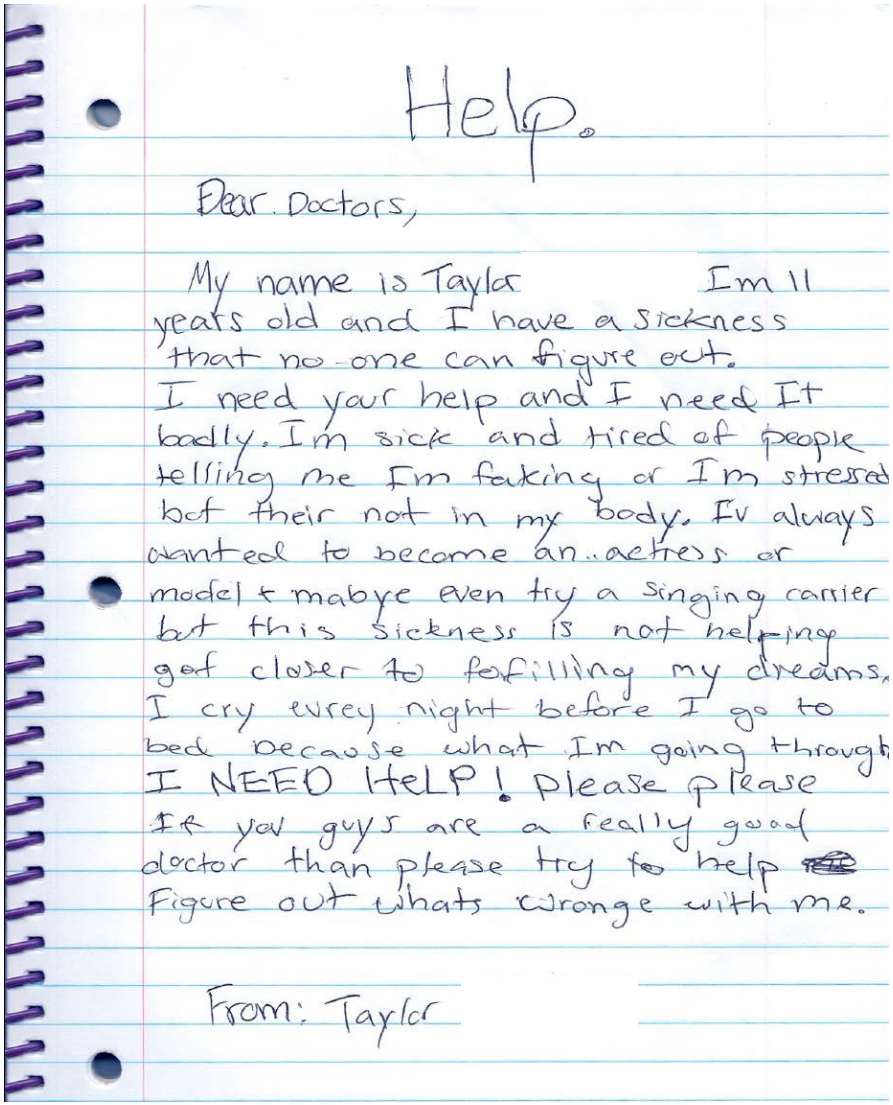
The NIH site will continue to enroll about 150 patients per year, each of the clinical sites will ultimately enroll about 50 patients per year.

Undiagnosed Diseases Network

Undiagnosed Diseases Network INTERNATIONAL



A cry for help…..



Help.

Dear Doctors,

My name is Taylor Im 11 years old and I have a sickness that no one can figure out. I need your help and I need It badly. Im sick and tired of people telling me Im faking or Im stressed but their not in my body. Iv always wanted to become an actress or model + mabye even try a singing carrier but this sickness is not helping get closer to fefilling my dreams. I cry every night before I go to bed because what Im going through I NEED HELP! please please If yor guys are a really good doctor than please try to help Figure out whats wrong with me.

From: Taylor

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

-Margaret Mead