Why study Rare diseases ?

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Gold Rare Disease Symposium May 2019

National Human Genome Research Institute

The Forefront of Genomics®

Prevalence of Rare Disease

US definition:

- Fewer than 200,000 people (about 1/1,575)

European definition:

- Rarer than 1 in 2,000 individuals

Prevalence of some single-gene disorders[*citation needed*]

Disorder prevalence (approximate)	
Autosomal dominant	
Familial hypercholesterolemia	1 in 500
Polycystic kidney disease	1 in 1250
Neurofibromatosis type I	1 in 2,500
Hereditary spherocytosis	1 in 5,000
Marfan syndrome	1 in 4,000[2]
Huntington's disease	1 in 15,000[3]
Autosomal recessives	
Sickle cell anaemia	1 in 625
Cystic fibrosis	1 in 2,000
Tay–Sachs disease	1 in 3,000
Phenylketonuria	1 in 12,000
Mucopolysaccharidoses	1 in 25,000
Lysosomal acid lipase deficiency	1 in 40,000
Glycogen storage diseases	1 in 50,000
Galactosemia	1 in 57,000
X-linked	
Duchenne muscular dystrophy	1 in 7,000
Hemophilia	1 in 10,000
Values are for liveborn infants	

https://en.wikipedia.org/wiki/Genetic_disorder

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Rare Diseases are Common as a Group

- Using the US definition, 1 in 10 US citizens have a rare disease
- Most are genetic
- Many remain undiagnosed for many years
- New rare diseases continue to be discovered & may be characterized

https://www.who.int/genomics/public/geneticdiseases/en/index2.html

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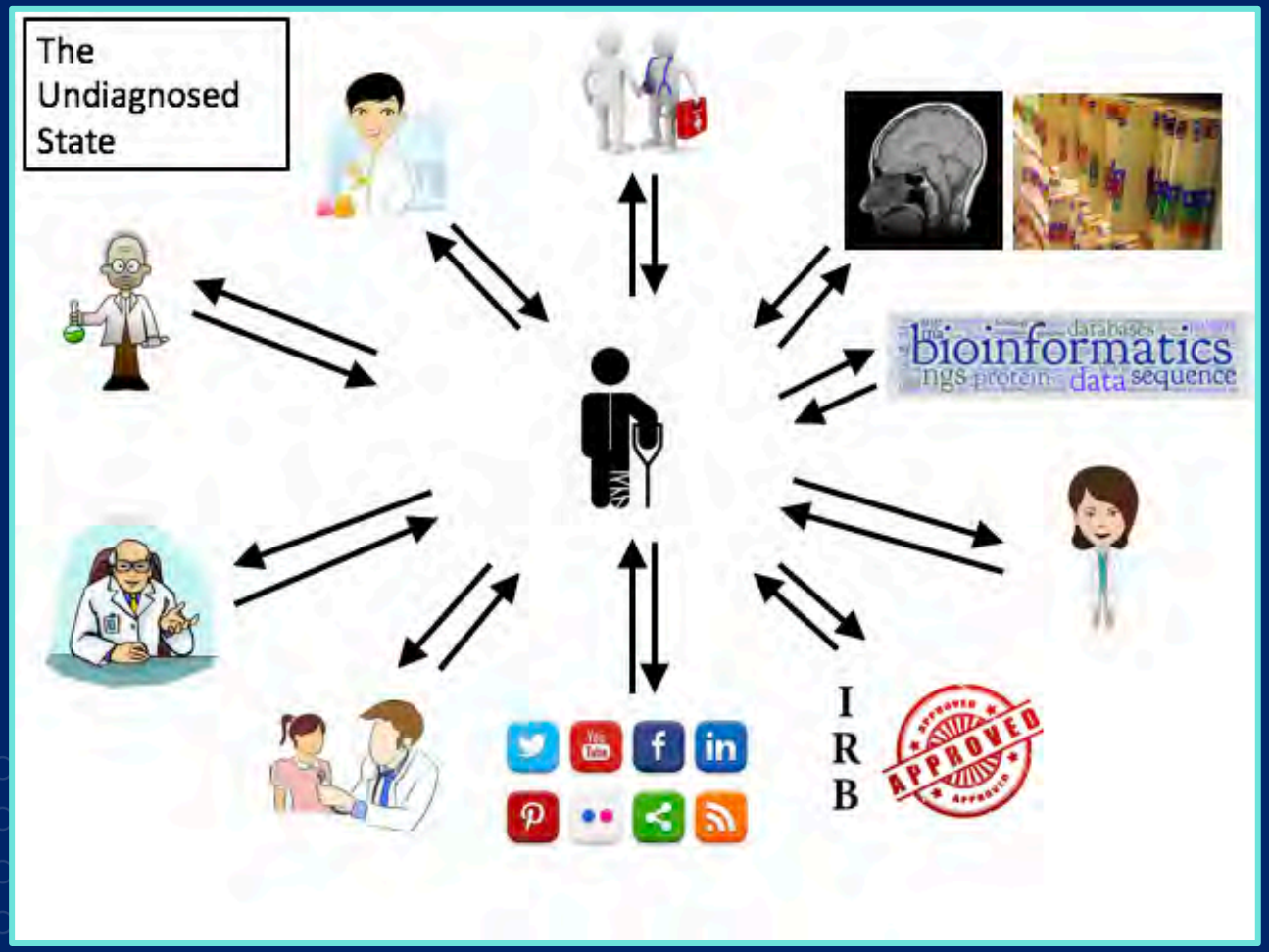
Living with an Undiagnosed/Rare Disease



Living with an undiagnosed or rare disease is complex with many stakeholders and yet it is very isolating for the person/family experiencing it

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Importance of studying Rare diseases

- What do I/my child have?
  - Diagnosis
  - Closure
- Why did it happen?
  - Genetic basis
  - Pathogenesis/Mechanism of disease/Cell biology
- What will happen now?
  - Prognosis
  - Natural History
- Is there a treatment?
  - Not always to cure the disorder but can improve quality of life
- Will it happen to other family members?
  - Recurrence risk for a young family
  - Genetic counseling for childbearing siblings and other family members

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Diagnosis/Closure

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UDP 5185

- Upgaze palsy
- Optic nerve atrophy
- Cerebellar atrophy
- Truncal Hypotonia
- Axonal Neuropathy
- Losing skills

Older sibling not affected, not a carrier

Referred to Disease Expert for further research

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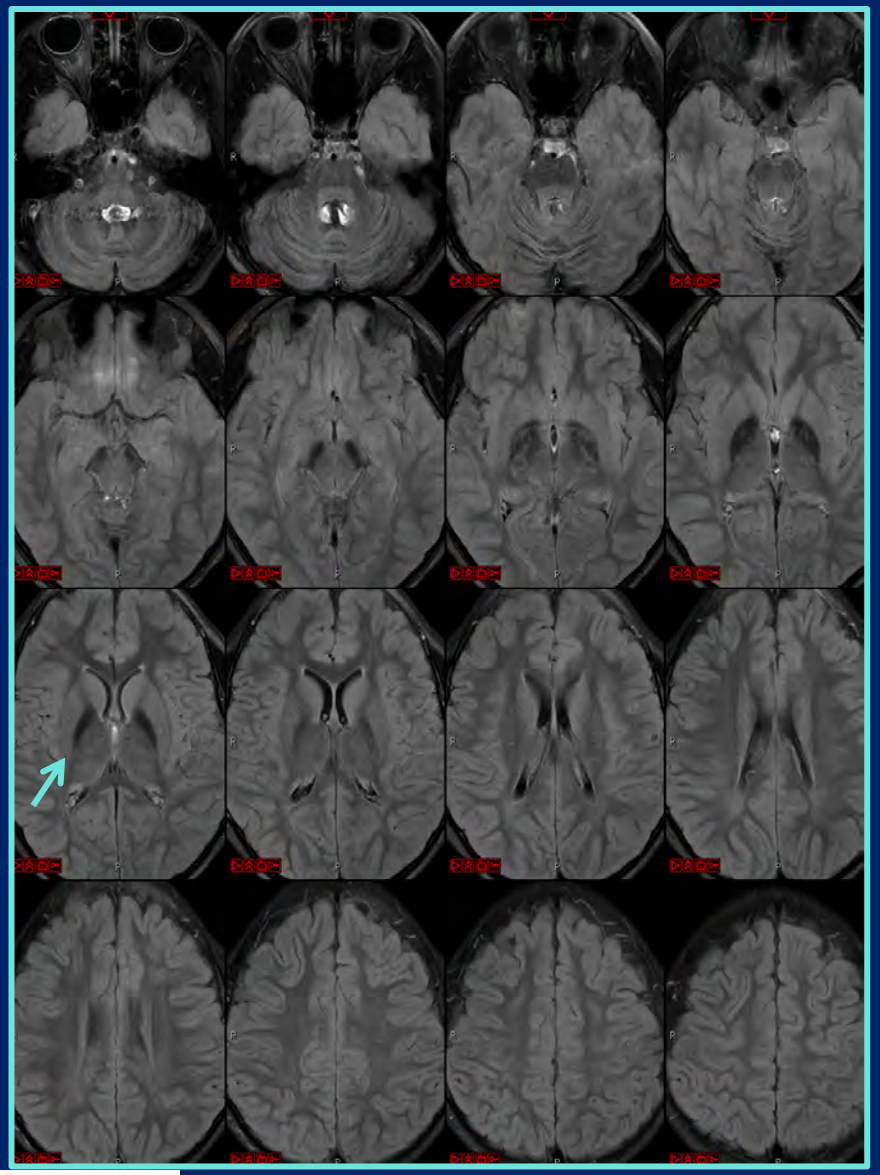
Brain MRI

Iron accumulation in the globus pallidus

Neurodegeneration Brain Iron Accumulation (NBIA) due to *PLA2G6* Duplication exons 4-7 c.426?_1077+[2] (known) and c.950G>T (p.Gly317Val) (novel)



Disruption of Golgi morphology and altered protein glycosylation in PLA2G6-associated neurodegeneration

Mariska Davids,[1,2] Megan S Kane,[1,2] Miao He,[3,4] Lynne A Wolfe,[1,2] Xueli Li,[3,4] Mohd A Raihan,[3,4] Katherine R Chao,[1,2] William P Bone,[1,2] Cornelius F Boerkoel,[1,2] William A Gahl,[1,2] Camilo Toro[1,2]

Davids M, *et al*. *J Med Genet* 2015;**0**:1–10. doi:10.1136/jmedgenet-2015-103338

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Neurodegeneration Brain Iron Accumulation (NBIA) aka *Infantile* Neuroaxonal Dystrophy

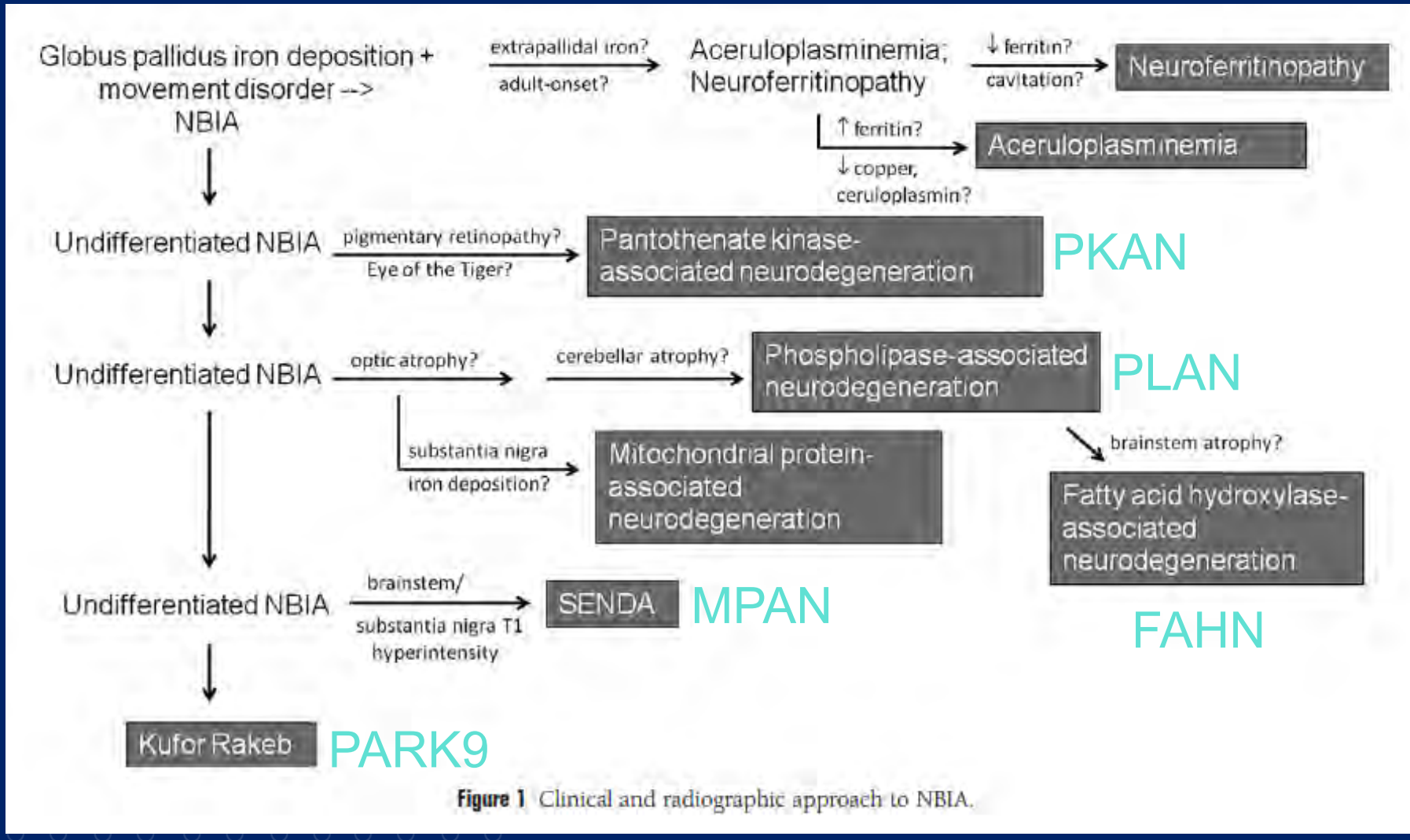

Figure 1 Clinical and radiographic approach to NBIA.

Semin Pediatr Neurol 19:67-74 2012

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UDP 5433, 5434, 5736

- Below 3rd centile on all growth parameters
- Nystagmus, ptosis, cataract with probable retinal degeneration
- Declining cognitive function with age
- Resting tremor
- Scoliosis
- Ataxic gait with demyelinating peripheral neuropathy
- General weakness & easy fatigue

ERCC6 c.2008C>T (p.R670W); and c.208C>T (p.R70W)
Cockayne Syndrome is one of three known Nucleotide Excision Repair disorders & causes premature aging

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Vineland Adaptive Behavior Scales II

Youngest sibling not affected, not a carrier

	VT	LT	TT	ST
Chronological Age	2 years	5 years	7 years, 1 month	8 years, 10 months
Communication	101	85	88	81
Receptive Age Equivalent	2 years, 2 months	2 years, 6 months	4 years, 7 months	3 years, 11 months
Expressive Age Equivalent	2 years, 3 months	3 years, 6 months	8 years	7 years
Daily Living	105	91	76	71
Socialization	112	105	83	76
Motor	96	91	70	75
Gross Motor Age Equivalent	2 years, 3 months	3 years, 5 months	2 years, 4 months	2 years, 9 months
Fine Motor Age Equivalent	1 year, 10 months	5 years, 1 month	5 years, 7 months	5 years, 10 months
Adaptive Behavior Composite	104	91	80	74

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New Mechanism of Disease

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COG4 Saul Wilson Syndrome

First described in 1982, gene identified 2018

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COG4 Saul Wilson Syndrome

- Growth
  - Intrauterine growth retardation
  - Delayed growth & severe short stature
- Dysmorphic Facial features
  - Prominent forehead early > tall forehead with age
  - Prominent veins
- Ophthalmologic
  - Congenital Cataracts
  - Retinal Pigmentary changes
- Combined sensori-neuro & conductive hearing loss
- Immunological
  - Congenital Neutropenia
  - Frequent ear & respiratory infections
- Skeletal
  - Congenital Club feet
  - Unique Skeletal dysplasia with Odontoid hypoplasia
  - Severe progressive osteoporosis requiring joint replacements

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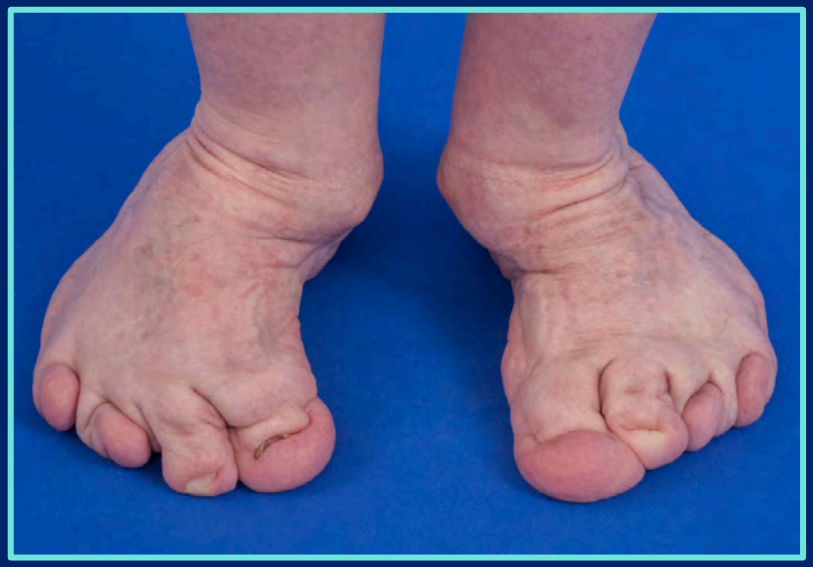
COG4 Saul Wilson Syndrome

Short fingers especially the finger tips

Severe Club feet even after casting and/or corrective surgery



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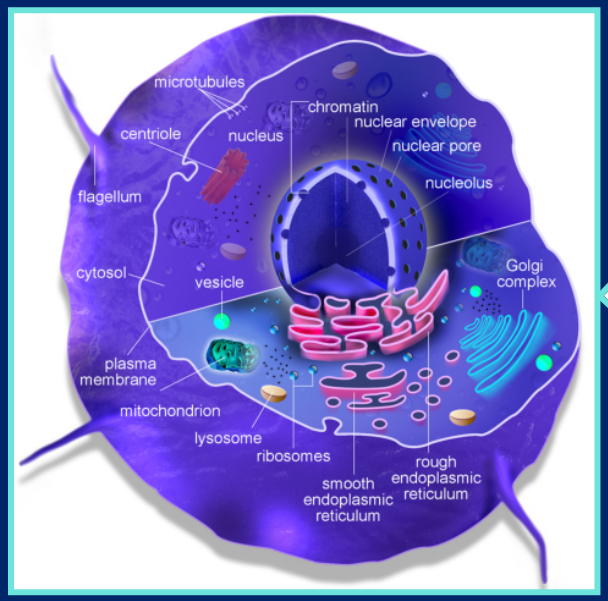
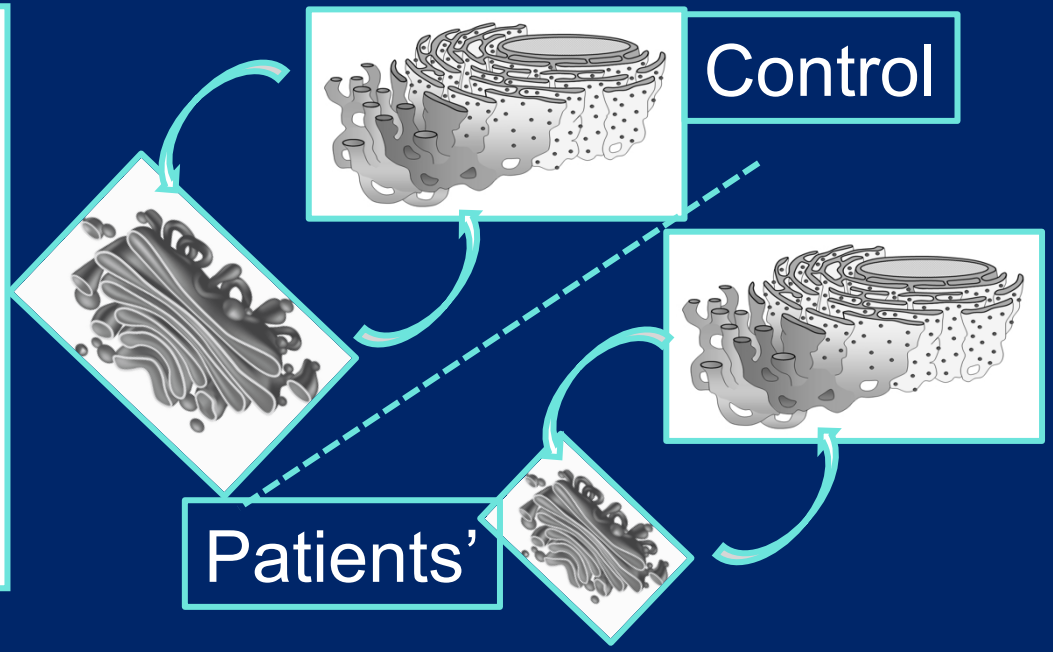
COG4 Saul Wilson Syndrome

A Recurrent *De Novo* Heterozygous COG4 Substitution Leads to Saul-Wilson Syndrome, Disrupted Vesicular Trafficking, and Altered Proteoglycan Glycosylation

The American Journal of Human Genetics *103*, 553–567, October 4, 2018

COG4 p.Gly516Arg





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Is there a treatment ?

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UDP 4003

- Seizures
- Mild delays in fine motor & speech
- Chronic anemia
- Splenomegaly
- Mild sensory neuropathy

CAD c.1843-1G>A; c.6071G>A (p.R2024Q) both novel
25% recurrence risk

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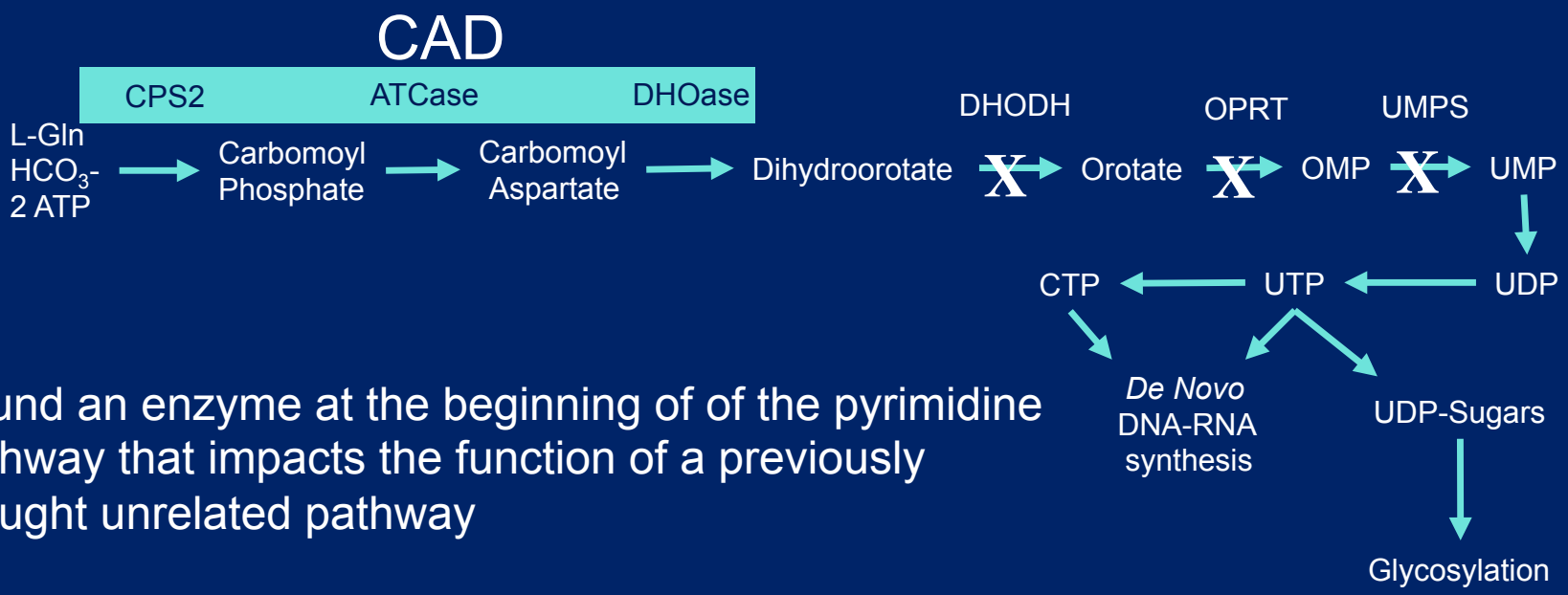
UDP 4003



Found an enzyme at the beginning of of the pyrimidine pathway that impacts the function of a previously thought unrelated pathway

Treatable with Xuriden (Triacetyluridine)

Biallelic mutations in CAD, impair de novo pyrimidine Biosynthesis and decrease glycosylation precursors

Bobby G. Ng[1†], Lynne A. Wolfe[2,†], Mie Ichikawa[1], Thomas Markello[2], Miao He[4], Cynthia J. Tifft[2,3], William A. Gahl[2,3] and Hudson H. Freeze[1,*]
Human Molecular Genetics, 2015, Vol. 24, No. 11

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Importance of Identifying Rare diseases

- Discovering new diseases generally leads to more cases being identified, better characterization of the spectrum of disease, and the possibility of treatments (even for common diseases) however this means a lot of data needs to be obtained and then shared

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Challenges of Data Sharing

- Patient privacy
- Time associated collecting & reviewing relevant data in the academic or research setting
- Academic credit, intellectual property
- Structured file conventions and sizes
- Applicable laws
- Language and basic science translation

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Data Sharing Tools

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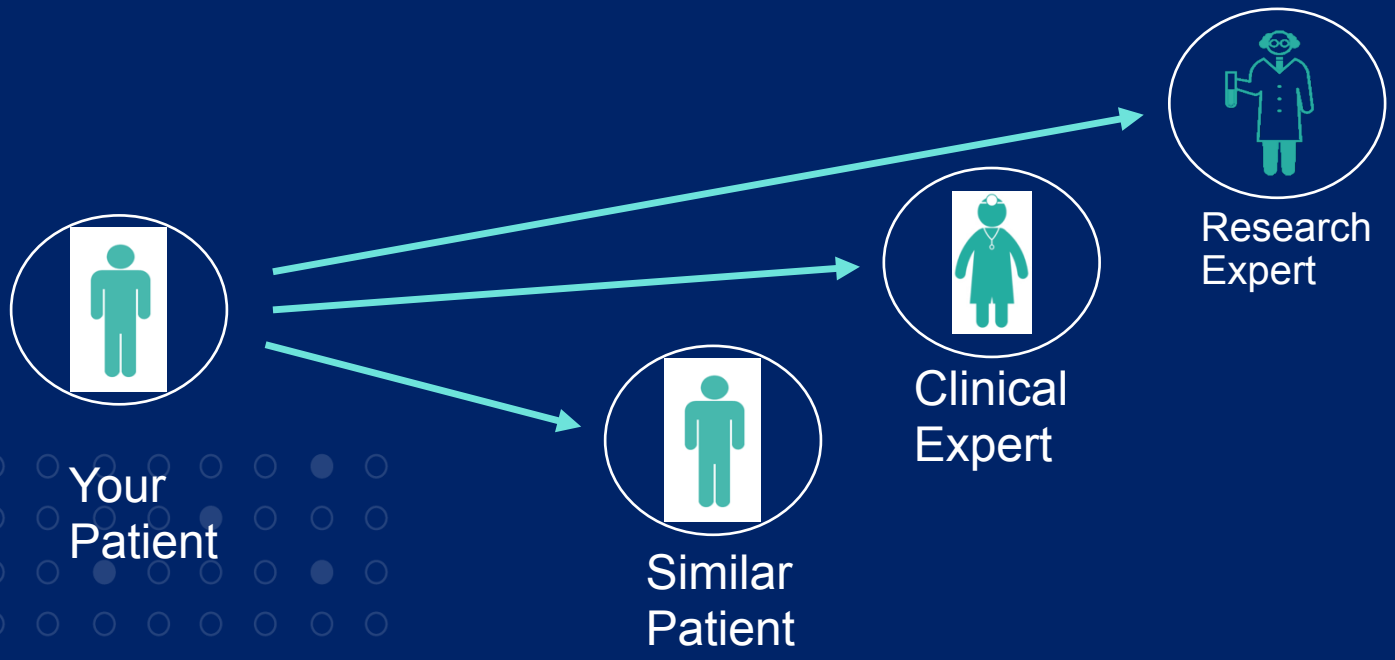
Goals of Data Sharing

- Identify additional cases to build cohorts for research and establish communities for families
- Identify clinical and research experts to explore disease-causation hypotheses



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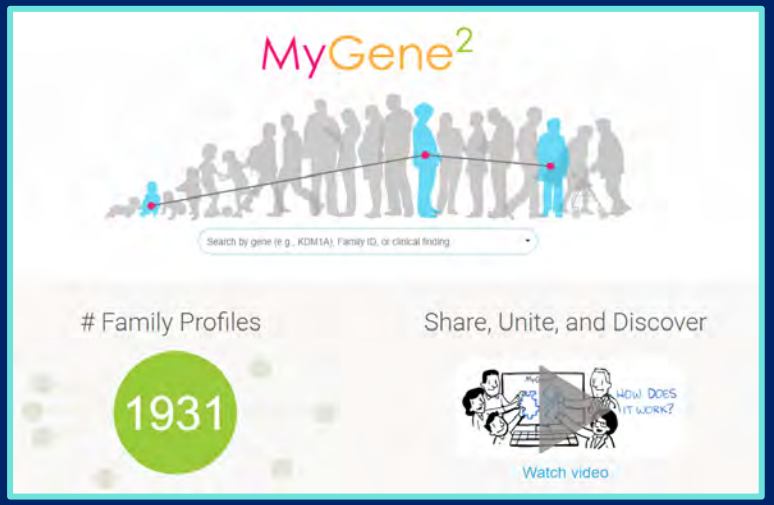
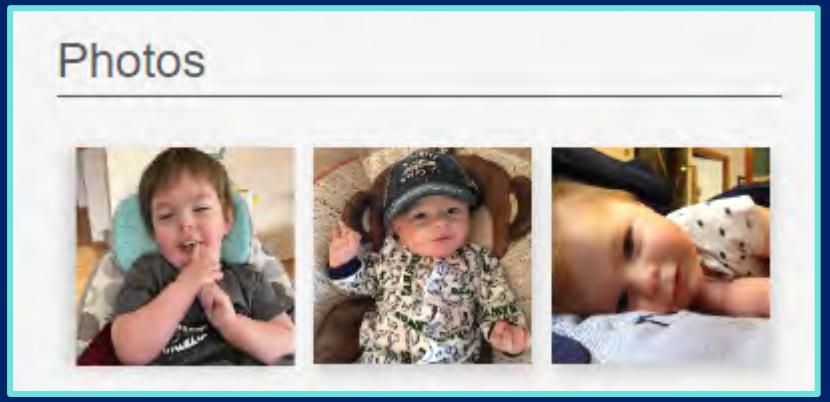
Open Data Sharing

- Person with illness has full access to data and can edit data
- Any data contributors can view all cases and contact other participants
- Family can add data that shows identity of person with illness
- Example: MyGene^2





Candidate Variant ID	Het group	Gene	Inheritance	Chr:Position	Alleles
3013	30133014	ALG14	autosomal recessive (compoun...	chr1:95530570	C>A
3014	30133014	ALG14	autosomal recessive (compoun...	chr1:95448759	A>T
3017		NRSN1	unknown / other	chr6:24146136	T>C

https://mygene2.org/MyGene2/

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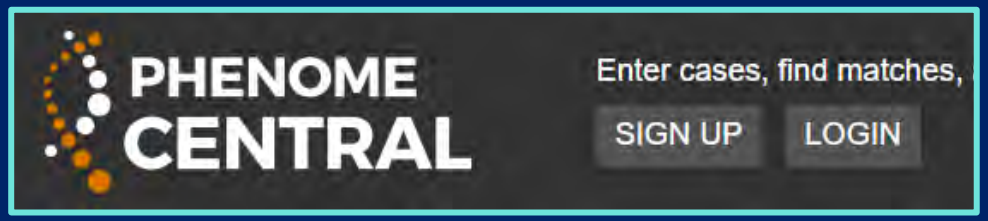
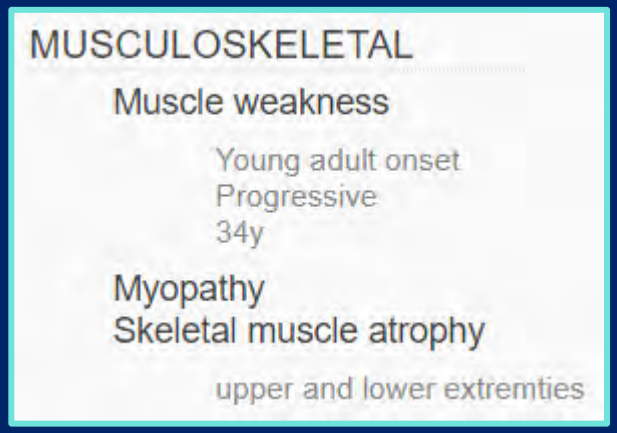
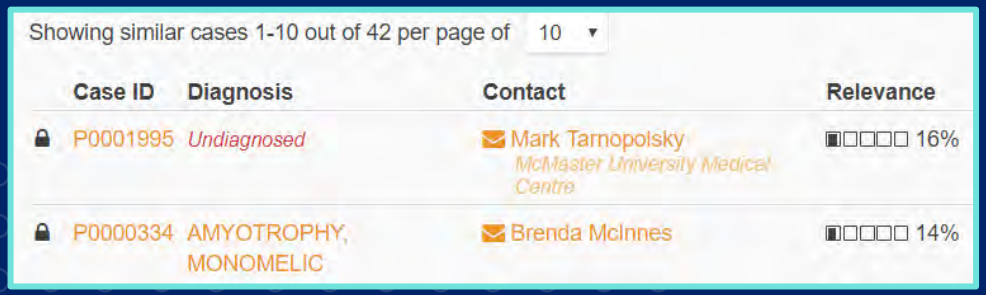
Closed Data Sharing Spectrum







https://www.phenomecentral.org/

- Submissions only edited by the submitter
- May share limited information
  - Only gene name
  - Human Phenotype Ontology (HPO) terms to describe illness
- Does not include information about patient's identity
- Site allows user to control access to submissions
- Example: PhenomeCentral

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Human Phenotype Ontology

- A standardized language for describing clinical signs and symptoms
- HPO terms arranged as a graph from less specific to more specific
- Allows computational comparison of cases

Less Specific

More Specific

HP:0000240
Abnormality of Skull Size

HP:0040195
Decreased Head Circumference

HP:0000252
Microcephaly

HP:0011541
Congenital Microcephaly

HP:0000253
Progressive Microcephaly

HP:0005484
Postnatal Microcephaly

http://www.sciencemag.org/news/2016/03/zika-virus-kills-developing-brain-cells

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MatchMaker Exchange (MME)

Connects findings between case-matching sites

https://www.matchmakerexchange.org/

Acknowledgements the UDP Team

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Adam Brown
Maisam Jafri
Daron Ross
Ayat Abdelbaki
Austin Kim
Robin Yoon

Our patients and families

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