Why study Rare diseases?

Lynne A. Wolfe, CRNP
NIH-Undiagnosed Diseases Program Site Coordinator, NHGRI
Gold Rare Disease Symposium May 2019
Prevalence of Rare Disease

US definition:
• Fewer than 200,000 people (about 1/1,575)

European definition:
• Rarer than 1 in 2,000 individuals

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

Living with an undiagnosed or rare disease is complex with many stakeholders and yet it is very isolating for the person/family experiencing it.
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
Diagnosis/Closure
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
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, Megan S. Kane, Miao He, Lynne A. Wolfe, Xue Li, Micho A. Rainha, Katherine R. Chao, William P. Bone, Cornelius F. Boerkoel, William A. Gahl, Camilo Toro

Neurodegeneration Brain Iron Accumulation (NBIA) aka Infantile Neuroaxonal Dystrophy

Figure 1 Clinical and radiographic approach to NBIA.
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
## Vineland Adaptive Behavior Scales II

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

Youngest sibling not affected, not a carrier
New Mechanism of Disease
COG4 Saul Wilson Syndrome
First described in 1982, gene identified 2018
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
COG4 Saul Wilson Syndrome

Short fingers especially the finger tips

Severe Club feet even after casting and/or corrective surgery
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

Control

Patients’
Is there a treatment?
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
Biallelic mutations in CAD, impair de novo pyrimidine Biosynthesis and decrease glycosylation precursors

Bobby G. Ng††, Lynne A. Wolfe2,†, Mie Ichikawa1, Thomas Markello2, Miao He4, Cynthia J. Tifft2,3, William A. Gahl2,3 and Hudson H. Freeze1,*

Human Molecular Genetics, 2015, Vol. 24, No. 11
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.
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
Data Sharing Tools
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.

![Diagram showing relationships between Your Patient, Similar Patient, Clinical Expert, and Research Expert.]

[Diagram showing relationships between Your Patient, Similar Patient, Clinical Expert, and Research Expert.]

Your Patient

Similar Patient

Clinical Expert

Research Expert
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$^2$

https://mygene2.org/MyGene2/
Closed Data Sharing Spectrum

- 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

https://www.phenomecentral.org/
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


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
MatchMaker Exchange (MME)

Connects findings between case-matching sites

https://www.matchmakerexchange.org/
Acknowledgements the UDP Team

William A. Gahl  Yan Huang  Mitchell Goheen  Marie Morimoto  Tito Onyekweli
Cyndi Tifft  Brianna Glase  Mary Gordon  Shino Shimada  Anabella Roman
David Adams  Vivian Del Valle  Laura Brown  Deb Mosbrook  Joan Rentsch
Camilo Toro  Brigitte Osorio  Jose Salas  Barbara Pusey  Chris Lau
Donna Novacic  Guoyun Yu  John Macdowall  Nick Balanda  Blythe Hospelhorn
Maria Acosta  Adam Brown  Maisam Jafri  Daron Ross  Prashant Sharma
Andrea Gropman  Val Maduro  Ayat Abdelbaki  Austin Kim  Liz Burke
Tom Markello  Joan Rentsch  Mary Hackbarth  Brigitte Osorio  Jose Salas
Colleen Wahl  Barbara Pusey  Chris Lau  Guoyun Yu  John Macdowall
Lynne Wolfe  Deb Mosbrook  Joan Rentsch  Brigitte Osorio  Jose Salas
Catherine Groden  Ellen MacNamara  Jean Johnston  Tyra Estwick  John Yang
Precilla D’Souza  Rena Godfrey  Ellen MacNamara  Jean Johnston  Tyra Estwick
Rena Godfrey  Ellen MacNamara  Jean Johnston  Tyra Estwick  John Yang
Ellen MacNamara  Jean Johnston  Tyra Estwick  John Yang  David Draper
Mary Hackbarth  Yan Huang  Mitchell Goheen  Marie Morimoto  Tito Onyekweli
Our patients and families

NIH  NHGRI
The Forefront of Genomics®