Rare Pediatric Diseases are common and demand mechanism discovery to understand the disease process

Voice of the Patient – NIH October 2019

Mustafa Khokha, MD
Director, Pediatric Genomics Discovery Program
Associate Professor, Yale University School of Medicine
Impact of Rare disorders/Birth Defects

- Combined, rare disorders are surprisingly common
  - 2% of population
  - 10% of hospital discharges
- Birth defects - #1 cause of infant mortality in the US
Impact of Rare disorders/Birth Defects

- **Heart disease** (per 100,000 adults)
- **Cancer** (per 100,000 adults)
- **Congenital malformations** (per 100,000 newborns)
- **Alzheimer’s, Stroke, Diabetes & Flu** (per 100,000 adults)

<table>
<thead>
<tr>
<th>Year</th>
<th>U.S. Deaths (per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>170</td>
</tr>
<tr>
<td>2016</td>
<td>153</td>
</tr>
<tr>
<td>2017</td>
<td>136</td>
</tr>
<tr>
<td>119</td>
<td>102</td>
</tr>
</tbody>
</table>
### Impact of Birth Defects

- In each age category
  - Birth defects are top 3 cause of death
  - In first decade of life – more children die due to birth defects than any other cause
  - Structural birth defects
  - Rare disorders – life-threatening

- Genetic basis – generally unknown

- Rare disease/Birth Defects individually are very rare – COMBINED – highly common and the major cause of childhood death

<table>
<thead>
<tr>
<th>Rank</th>
<th>&lt;1 Year</th>
<th>1-4</th>
<th>5-9</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Congenital Anomalies 4,580</td>
<td>Unintentional Injury 1,267</td>
<td>Unintentional Injury 718</td>
</tr>
<tr>
<td>2</td>
<td>Short Gestation 3,749</td>
<td>Congenital Anomalies 424</td>
<td>Malignant Neoplasms 418</td>
</tr>
<tr>
<td>3</td>
<td>Maternal Pregnancy Comp. 1,432</td>
<td>Malignant Neoplasms 325</td>
<td>Congenital Anomalies 188</td>
</tr>
<tr>
<td>4</td>
<td>SIDS 1,363</td>
<td>Homicide 303</td>
<td>Homicide 154</td>
</tr>
<tr>
<td>5</td>
<td>Unintentional Injury 1,317</td>
<td>Heart Disease 127</td>
<td>Heart Disease 75</td>
</tr>
<tr>
<td>6</td>
<td>Placenta Cord. Membranes 843</td>
<td>Influenza &amp; Pneumonia 104</td>
<td>Influenza &amp; Pneumonia 62</td>
</tr>
<tr>
<td>7</td>
<td>Bacterial Sepsis 592</td>
<td>Cerebrovascular 66</td>
<td>Chronic Low. Respiratory Disease 59</td>
</tr>
<tr>
<td>8</td>
<td>Circulatory System Disease 449</td>
<td>Septicemia 48</td>
<td>Cerebrovascular 41</td>
</tr>
<tr>
<td>9</td>
<td>Respiratory Distress 440</td>
<td>Benign Neoplasms 44</td>
<td>Septicemia 33</td>
</tr>
<tr>
<td>10</td>
<td>Neonatal Hemorrhage 379</td>
<td>Perinatal Period 42</td>
<td>Benign Neoplasms 31</td>
</tr>
</tbody>
</table>
Why study rare disorders?

• So why study?
  – Rare disorder - Impacts a single family, handful of families
  – Combined they are very common – 1 in 10 Americans
• Huge impact on child health
• physicians struggle to make correct diagnosis, patients respond unpredictably to therapy
  – Families – frustrated, isolated, desperate
  – Why did this happen? What is going on?
  – Will this happen to my next child?

• OPPORTUNITY
Extraordinary Opportunity

- Likely genetic basis for these disorders
  - Rarity
  - Locus heterogeneity
  - Serious illness (life-threatening disease)
  - Standard genetic strategies for gene discovery are limited

- DNA sequencing
  - Inexpensive
  - Identify candidate genes efficiently
  - Transforms our insight into disease pathogenesis

Combine to make pedigrees or multiple allele discovery unlikely
Sequencing is not enough

• Novel Gene discovery – pathogenesis

• 20,000 genes in our genome
  – Established causes of disease (25%)
  – No previous association with disease (75%)

• Understanding how the gene causes disease – powerful
  – Understand gene function – understand disease process
  – Creates opportunities to tailor diagnostics and therapy based on genotype
  – Predict complications, outcome
Three remarkable opportunities - Today

• Opportunity to convert descriptive diagnosis to molecular diagnosis

• Opportunity to discover new biology

• Opportunity to return these results to families desperate for answers
From patients, to fundamental science, to answers for families
Patient driven discovery -> Future therapy

- **Colorectal Cancer**
  - 3rd most common
  - 9.4 million people in 2015
  - 65% survival
  - 832,000 deaths

- **Colorectal Cancer + Wnt Pathway**
  - 90% of Colon cancer
  - APC, Axin1/2, β-catenin
  - Stabilize β-catenin
  - Blocking mechanism - β-catenin nuclear entry – **no one knows how**
Return results to patients

- Rare disorders – poor understanding of pathophysiology, parents become the experts – frustration, desperation
- Birth defects – diagnosis is descriptive not molecular
- DNA Sequencing
  - Why did this happen? What is going on?
    - Candidate genes may explain disease process
  - Will this happen to my next child?
    - Evaluate potential risk to next child based on the genetics

- Traditionally – Basic science offers therapies in the future
- Sequencing Era – basic science can immediately provide answers
Clinical – Basic Science Infrastructure

Diagram showing the integration of patient DNA, precision medicine, patient counseling, phenotype, clinician, geneticist, developmental biologist, candidate genes, and functional testing.
Pediatric Genomics Discovery Program

Help part in a vital journey to help us discover new ways to detect and treat childhood illnesses.
Summary:

- Extraordinary opportunity for rare disease/birth defects research

- To capitalize on this opportunity: Must address a number of problems
PROBLEM – Impact Underappreciated

- Impact of Birth Defects/Rare Disease on children is massive
- Underappreciated by the general public
- Resources - not proportional to the impact

- Why?
  - Premature infant in the palm of one’s hand
  - Unmistakable look of child with cancer
  - No heart tugging image of birth defect child – “cripple”

- Solution – Public education of the impact
  - Write in lay press
  - Alert our legislators, policy makers
PROBLEM – Rare diseases are rare

• So why study?
  – Impacts a single family, handful of families
  – Collectively common
• Rare disorders/birth defects
  – Families/Physicians - desperate for answers
  – Unsatisfying descriptive diagnoses – not molecular

• SOLUTION – change the research metric. Research to help patients today – return of results (even research results) to patients
• SOLUTION - Emphasize Patient driven gene discovery.
  – Patient as powerful motivator to “new” biology
  – Patient phenotype as powerful guide for pathogenesis discovery
  – Connect clinicians and basic scientists.
• To realize this potential – study patient derived genes – need disease models
Convert Clinical/Candidate Gene -> Basic Science

- Models for human disease
- Throughput for DNA sequencing is FAST…
- Create disease Models
  - Mouse models – throughput and cost
  - Non-mammalian models
  - Xenopus - F0 CRISPR – Gene to phenotype in 5 days
    - As similar to human without sacrifice on throughput – lungs, limbs
    - Annotated genome, Model Organism Database: Xenbase
    - National Xenopus Resource – animal stock center
  - Patient derived cells – animal models offer 3D architecture to model human disease. Test specific hypotheses in patient cells.
Convert Clinical/Candidate Gene -> Basic Science

- Fund studies of patients with rare disorders
  - Fund proposals to recruit patients and sequence – GM KidsFirst
  - Fund proposals to study candidate genes from patient driven gene discovery – basic science of novel genes
- To capitalize on return to patient – create basic science-clinical infrastructure
- PROBLEM#1: Diverse expertise: patients are seen by clinicians, exome sequencing requires bioinformatics, modeling of human disease and mechanism discovery requires basic scientists
- PROBLEM#2: Hypothesis generating not hypothesis driven
  - Grant proposal – recruit patients (broad), find candidate genes (unknown until patients recruited), discover cool biology that impacts patients (unknown until sequencing)
PROBLEM#1: Diverse Expertise

- SOLUTION: funding to emphasize collaboration

- Preliminary grants to bring complementary groups together and demonstrate that they can successfully work together

- Fund cooperative grants with multi-pronged approach
  - Clinician - Patient recruitment
  - Geneticist/Bioinformatics - Sequencing/Candidate gene analysis
  - Basic Scientists - Candidate gene screening/Mechanism discovery
  - R01s/PPG

- Foster training of **physician-scientists** – uniquely situated to simplify “three body problem”

- Productivity metric – papers & **return to patients**
PROBLEM#2: Hypothesis generating not hypothesis driven

• Solution: Specialized study sections/Institutes prioritize these applications.
• Patient Driven Gene Discovery → Basic Science
• Recruit patient -> Identify Candidate Gene -> screen in model systems -> Patient Phenotype -> Investigate mechanism
• Dependent Aims/”open ended”/unlikely to lead to mechanism – “risky”
• Not risky -> our group and many others
• Emphasize the impact of rare disorders
• Emphasize the impact directly on patients – return of results
Summary

- Birth defects/rare disorders – huge problem
- Rare disease – common collectively
- Gene identification is efficient – DNA sequencing
- Opportunity
  - Transform descriptive diagnoses to molecular understanding
  - Return of clinical/research result to patients
  - Exciting basic research avenues
- Public awareness - impact
- Collaborative infrastructure
- Model organisms – databases, stock centers
- Special Study sections/Institute priority
Acknowledgments

Yale New Haven Health

Rick D’Aquila
Cynthia Sparer

Paul Taheri
Kim Moriarty
Andrew Golus
Connie Branyan

NIH – NHLBI/NICHD
Sara and Jeffery Buell

Yale School of Medicine

Carolyn Slayman
(late)
Cliff Bogue
George Lister
Antonio Giraldez
Rare disease is devastating to families – hope from gene discovery

Voice of the Patient – NIH October 2019

Kendra Haifley
Lung disease – in infancy

Onset of symptoms for proband and affected sib was around 1 year.
- interstitial lung disease, pulmonary hypertension
- mild motor delay
- Path report of proband: lung alveolar proteinosis, pectus excavatum, Trach, GJ tube
- Oldest sib is 9 yrs and well, mother pregnant – fetus well to date
- Single family with disease with no known explanation
- Why study?
## Variants in Exome Sequencing

<table>
<thead>
<tr>
<th>Pos.</th>
<th>Gene</th>
<th>Variant</th>
<th>Intolerance</th>
<th>MAF ExAC All</th>
<th>MAF ExAC NFE</th>
<th>CAD</th>
<th>SIFT</th>
<th>PP/H</th>
<th>Effect score</th>
<th>Father</th>
<th>Mother</th>
<th>S1</th>
</tr>
</thead>
<tbody>
<tr>
<td>2:114500349_C/T</td>
<td>SLC35F5 solute carrier family 35, member F5</td>
<td>E224K</td>
<td>53.12%</td>
<td>0.0037</td>
<td>0.0058</td>
<td>T</td>
<td>B</td>
<td></td>
<td>1</td>
<td>Het</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>2:114508135_G/A</td>
<td>SLC35F5 solute carrier family 35, member F5</td>
<td>T95I</td>
<td>53.12%</td>
<td>0</td>
<td>0</td>
<td>T</td>
<td>P</td>
<td>2</td>
<td></td>
<td>Ref</td>
<td>Het</td>
<td>Het</td>
</tr>
<tr>
<td>3:49679930_C/T</td>
<td>BSN bassoon presynaptic cytomatrix protein</td>
<td>P288L</td>
<td>0.49%</td>
<td>0.0035</td>
<td>0.0052</td>
<td>T</td>
<td>B</td>
<td>2</td>
<td></td>
<td>Het</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>3:49700582_G/A</td>
<td>BSN bassoon presynaptic cytomatrix protein</td>
<td>R366_4Q</td>
<td>0.49%</td>
<td>0.0029</td>
<td>0.0047</td>
<td>D</td>
<td>D</td>
<td>3</td>
<td></td>
<td>Ref</td>
<td>Het</td>
<td>Ref</td>
</tr>
<tr>
<td>16:784797_G/A</td>
<td>NARFL nuclear prelamin A recognition factor-like</td>
<td>R172X</td>
<td>91.39%</td>
<td>0</td>
<td>0</td>
<td>36</td>
<td>.</td>
<td></td>
<td>stopgain</td>
<td>Ref</td>
<td>Het</td>
<td>Het</td>
</tr>
<tr>
<td>16:786403_A/C</td>
<td>NARFL nuclear prelamin A recognition factor-like</td>
<td>c.307-5T&gt;G</td>
<td>91.39%</td>
<td>0.0001</td>
<td>0</td>
<td>.</td>
<td>.</td>
<td>0</td>
<td></td>
<td>Het</td>
<td>Ref</td>
<td>Ref</td>
</tr>
</tbody>
</table>
Impact on families

Mother

Father

+/-  -/+

9 yo  PCI0146-S1  PCI0146
+/-  -/-  -/-

+ normal copy of gene
- Abnormal copy of gene

+/
++