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

Voice of the Patient – NIH October 2019

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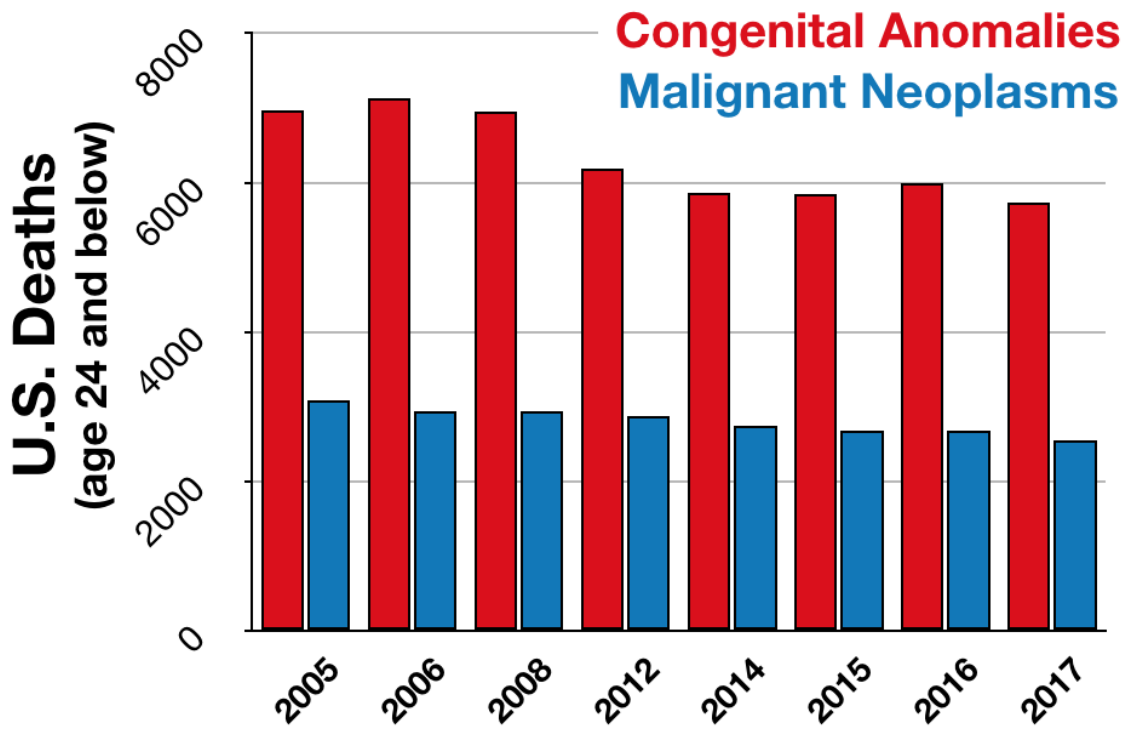
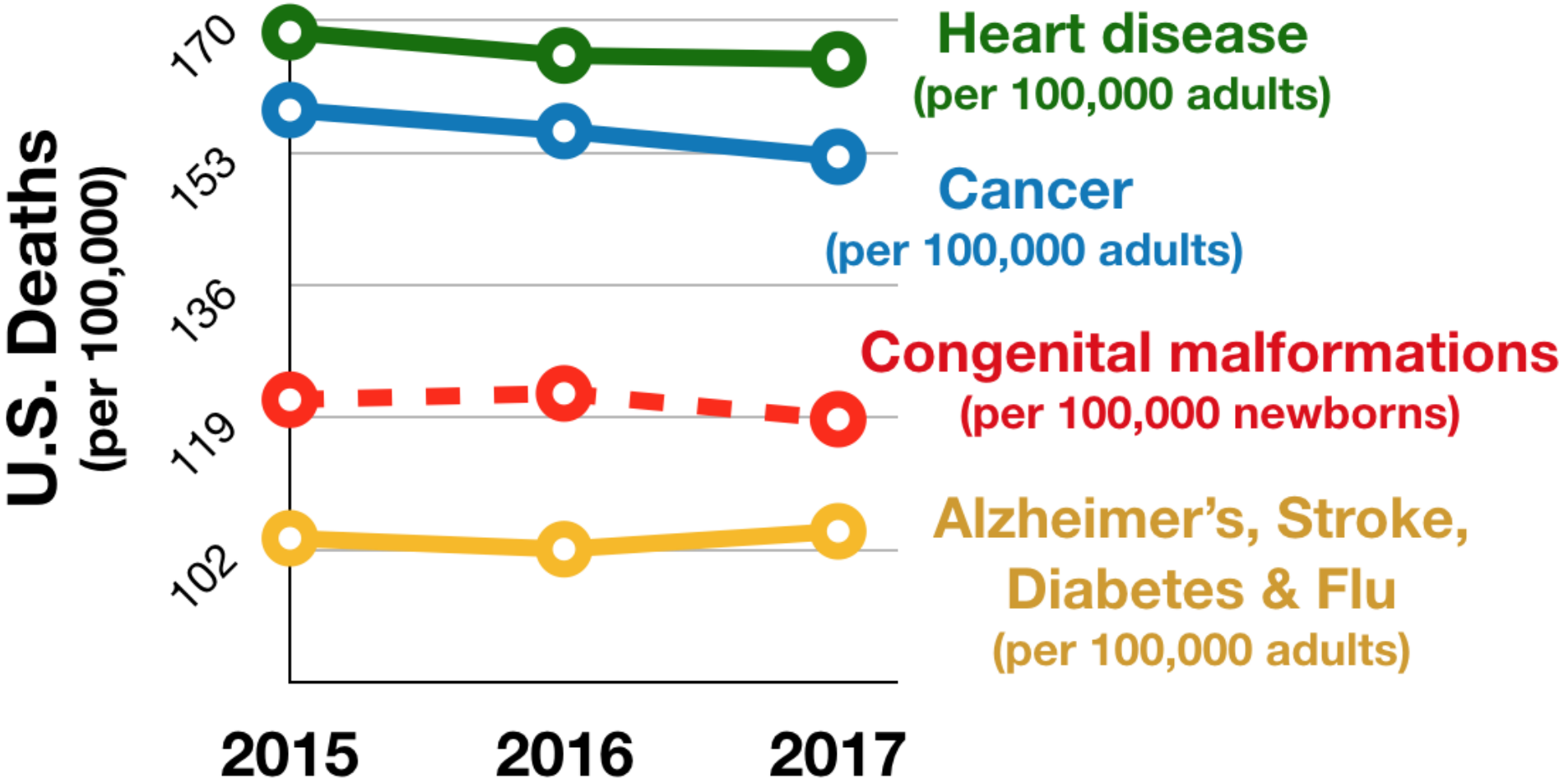
Impact of Rare disorders/Birth Defects

- 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



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

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

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-threating disease)

  } Combine to make pedigrees or multiple allele discovery unlikely

  - Standard genetic strategies for gene discovery are limited
- DNA sequencing
  - Inexpensive
  - Identify candidate genes efficiently
  - Transforms our insight into disease pathogenesis

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

LETTER

doi:10.1038/nature12723

The heterotaxy gene *GALNT11* glycosylates Notch to orchestrate cilia type and laterality

Marko T. Boskovski[1]*†, Shiaulou Yuan[1]*, Nis Borbye Pedersen[2], Christoffer Knak Goth[2], Svetlana Makova[1], Henrik Clausen[2], Martina Brueckner[1] & Mustafa K. Khokha[1]

CellPress

Developmental Cell
Article

RAPGEF5 Regulates Nuclear Translocation of β-Catenin

John N. Griffin,[1,2] Florencia del Viso,[1] Anna R. Duncan,[1] Andrew Robson,[1] Woong Hwang,[1] Saurabh Kulkarni,[1] Karen J. Liu,[2] and Mustafa K. Khokha[1,3,*]

Developmental Cell
Article

CellPress

WDR5 Stabilizes Actin Architecture to Promote Multiciliated Cell Formation

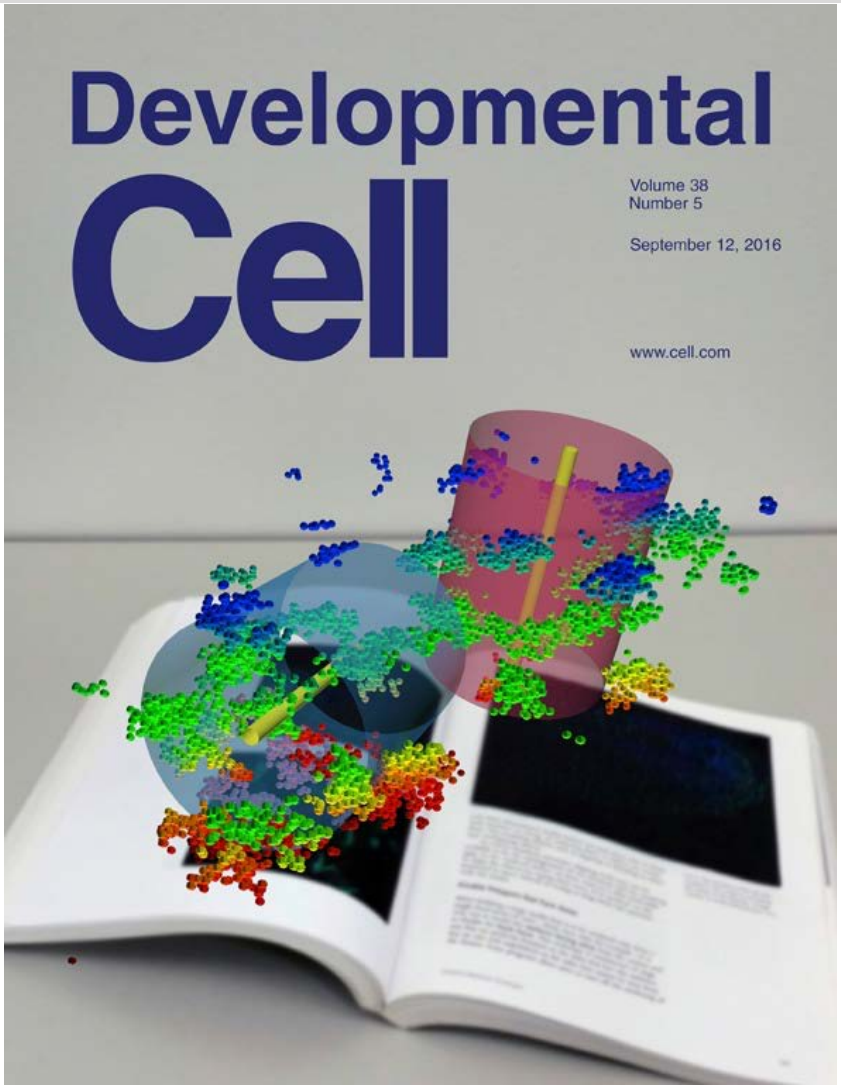
Saurabh S. Kulkarni,[1,2,3] John N. Griffin,[1,2,3] Priya P. Date,[1,2,3] Karel F. Liem, Jr.,[2] and Mustafa K. Khokha[1,2,3,4,*]

CellPress

Developmental Cell
Article

Congenital Heart Disease Genetics Uncovers Context-Dependent Organization and Function of Nucleoporins at Cilia

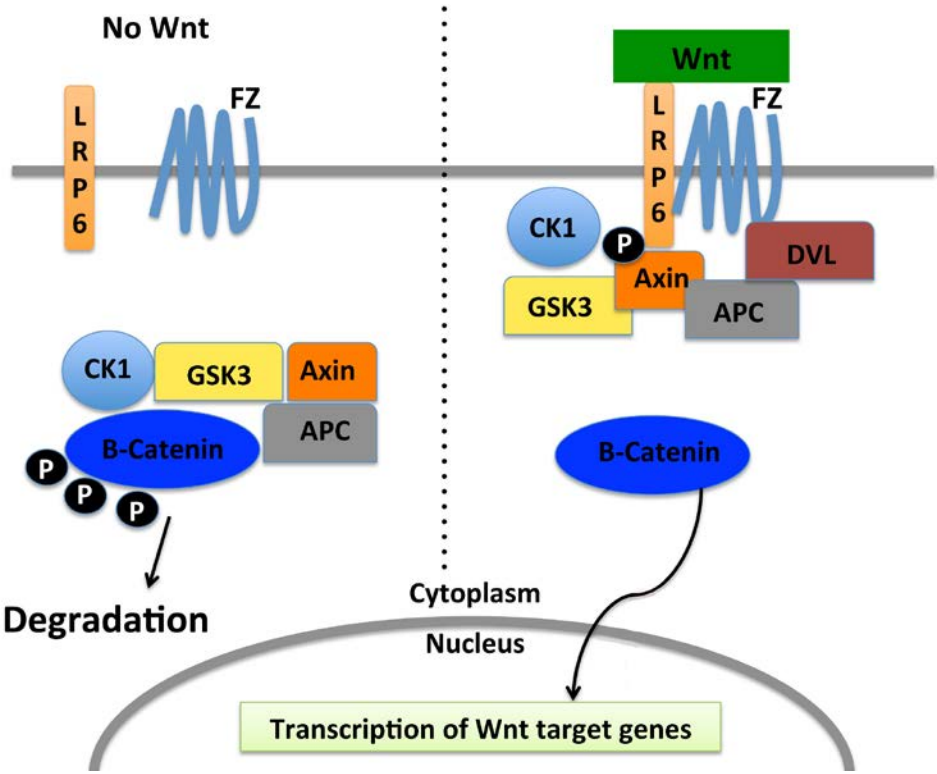
Florencia del Viso,[1,4] Fang Huang,[2,3,4] Jordan Myers,[2] Madeleine Chalfant,[2] Yongdeng Zhang,[2] Nooreen Reza,[1] Joerg Bewersdorf,[2] C. Patrick Lusk,[2,*] and Mustafa K. Khokha[1,5,*]



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**

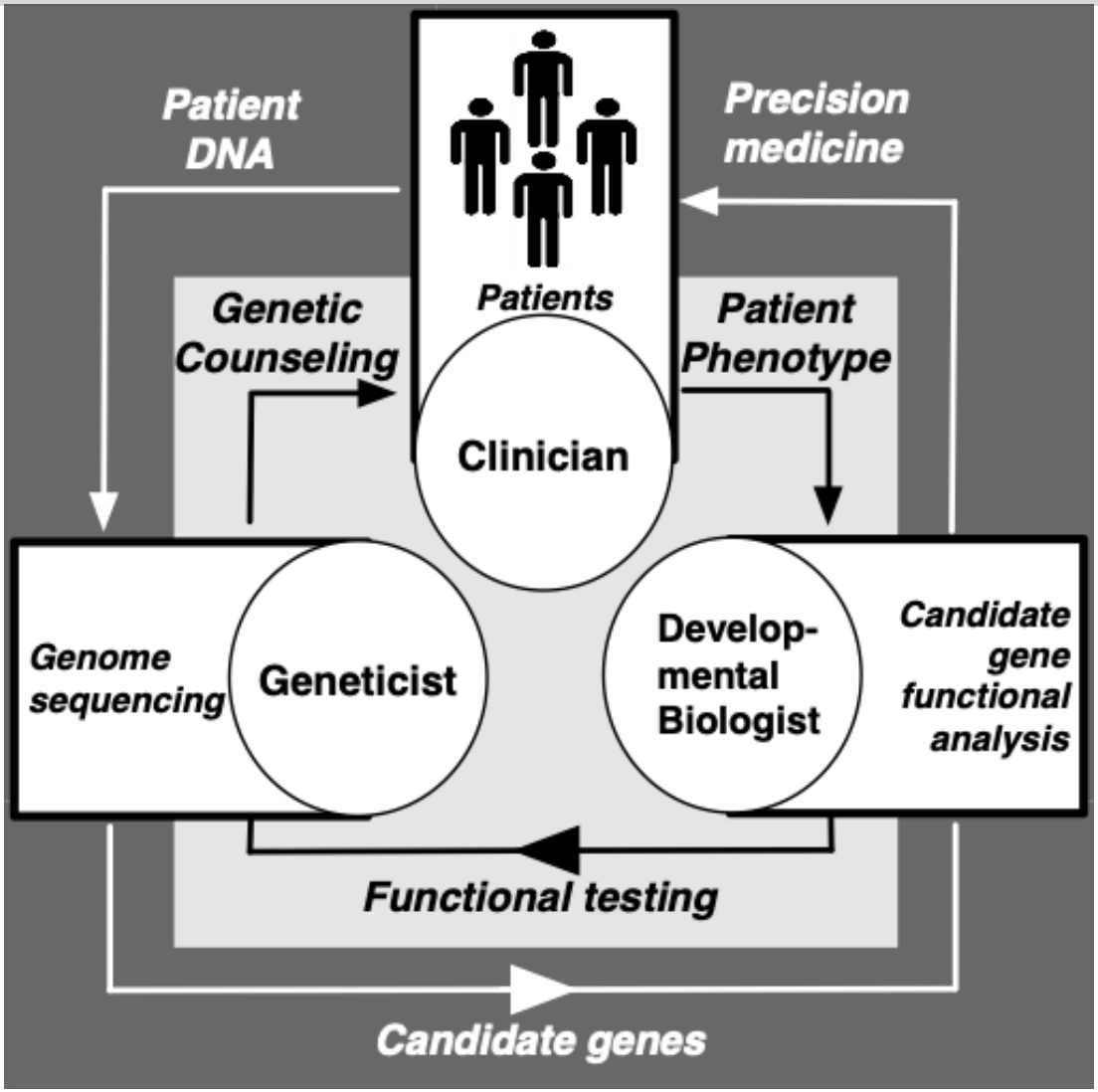


Return results to patients

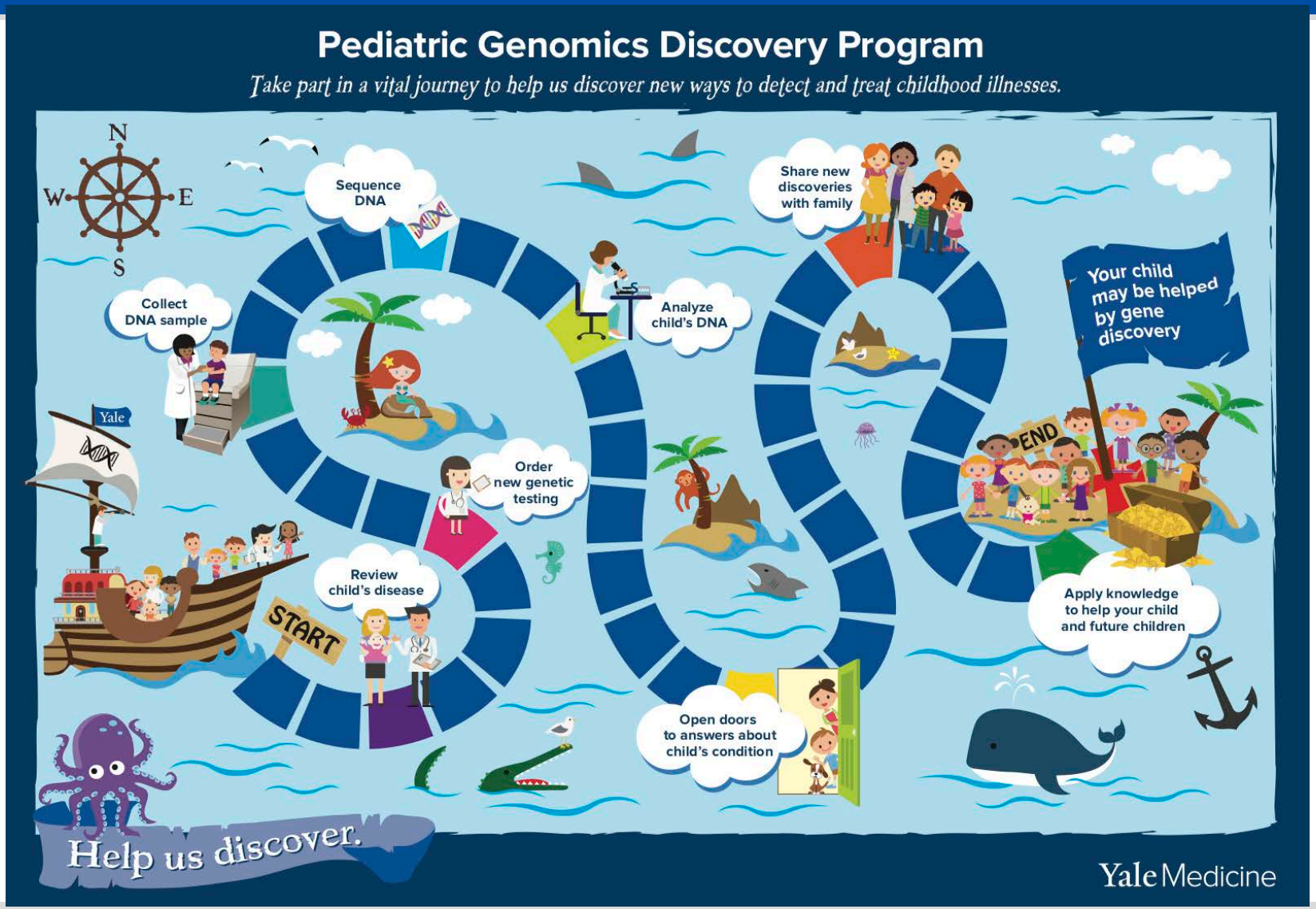
- Rare disorders – poor understanding of pathophysiology, parents become the experts – frustration, desperation
- Birth defects – diagnosis is descriptive not molecular
- DNA Sequencing
  - Why did this happen? What is going on?
    - Candidate genes may explain disease process
  - Will this happen to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



Pediatric Genomics Discovery Program



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

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Rare disease is devastating to families – hope from gene discovery

Voice of the Patient – NIH October 2019

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Lung disease – in infancy

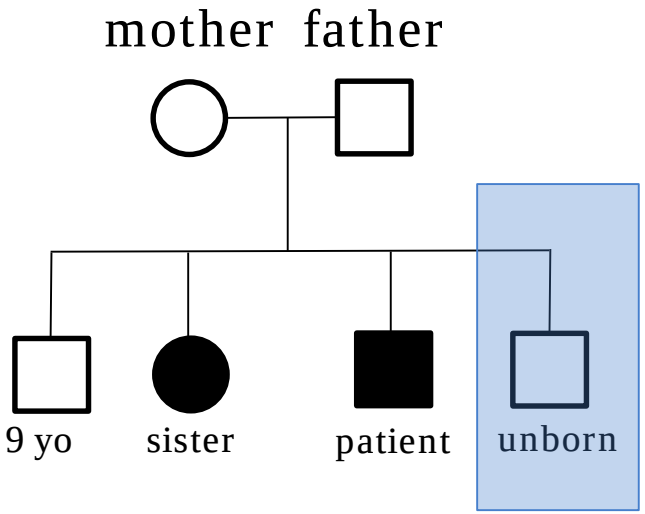
Onset of symptoms for proband and affected sib was around 1 year.

- 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

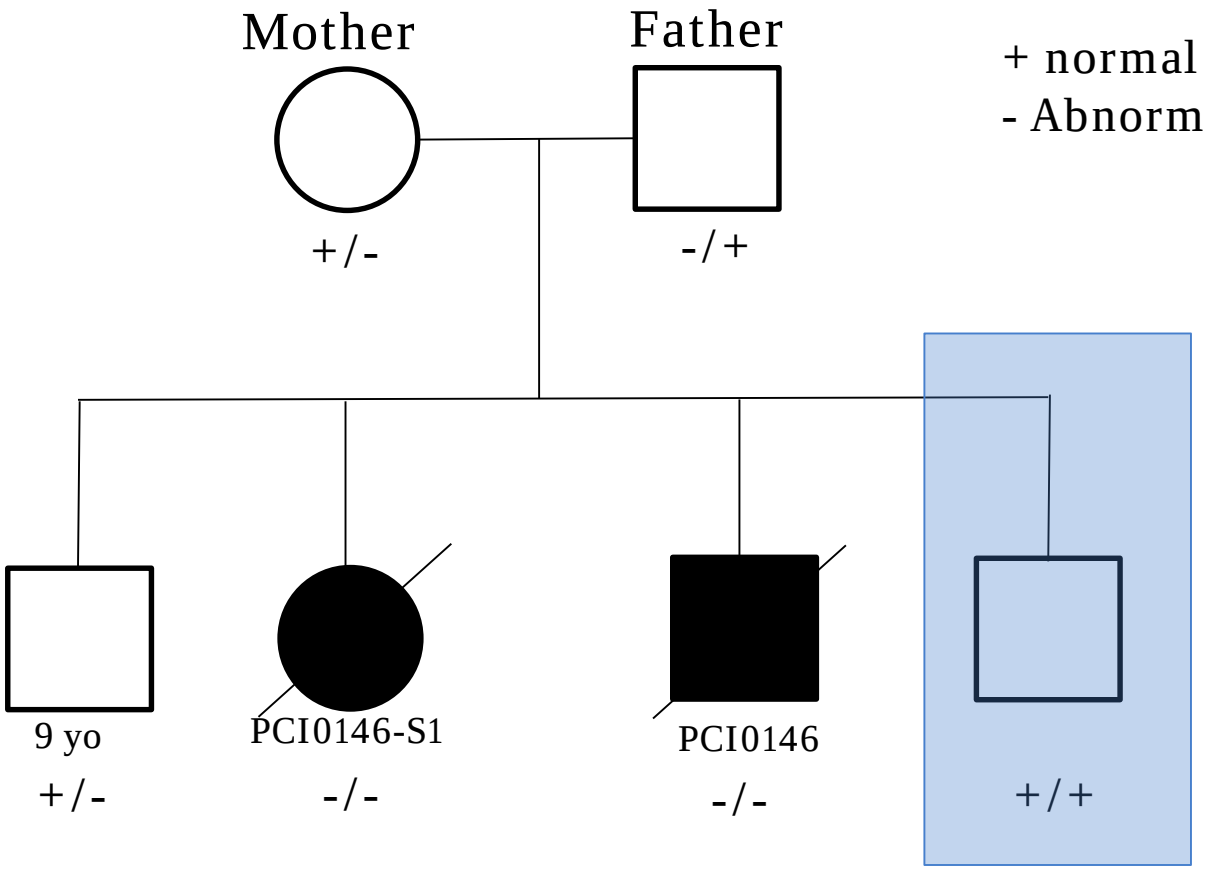
- Why study?



Variants in Exome Sequencing

Pos.	Gene		Variant	Intolerance	MAF ExAC_All	MAF ExAC_NFE	CADD	SIFT	PPH	Effect score	Father	Mother	S1
2:114500349_C/T	SLC35F5	solute carrier family 35, member F5	E224K	53.12%	0.0037	0.0058	20.6	T	B	1	Het	Ref	Ref
2:114508135_G/A	SLC35F5	solute carrier family 35, member F5	T95I	53.12%	0	0	21.1	T	P	2	Ref	Het	Het
3:49679930_C/T	BSN	bassoon presynaptic cytomatrix protein	P2888L	0.49%	0.0035	0.0052	18.33	T	B	2	Het	Ref	Het
3:49700582_G/A	BSN	bassoon presynaptic cytomatrix protein	R3664Q	0.49%	0.0029	0.0047	22.5	D	D	3	Ref	Het	Ref
16:784797_G/A	**NARFL**	**nuclear prelamin A recognition factor-like**	**R172X**	**91.39%**	**0**	**0**	**36**	**.**	**.**	**stopgain**	**Ref**	**Het**	**Het**
16:786403_A/C	**NARFL**	**nuclear prelamin A recognition factor-like**	**c.307-5T>G**	**91.39%**	**0.0001**	**0**	**.**	**.**	**.**	**0**	**Het**	**Ref**	**Het**

Impact on families



+ normal copy of gene
- Abnormal copy of gene