Pediatric Genomic Medicine

SHANE CORDER - SR. HPC SYSTEMS ENGINEER

CENTER FOR PEDIATRIC GENOMIC MEDICINE
Children’s Mercy Hospital
Center for Pediatric Genomic Medicine

• Established Jan., 2011
  • Directed by Dr. Stephen Kingsmore

• Integrated with hospital practice
  • 25+ physicians as primary points of contact representing every specialty within hospital
  • Clinical Genetics & Counseling
  • CMH Center for Bioethics

• Application focuses
  • Exome sequencing
  • TaGSCAN CLIA lab test
  • STAT-seq Emergency Genome Sequencing
  • RNA
  • ....more?!
RESEARCH ARTICLE

Diagnoses

Rapid Whole-Genome Sequencing for Genetic Disease Diagnosis in Neonatal Intensive Care Units

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Monogenic disease is usually diagnosed and treated by pediatricians, but now the era of rapid whole-genome sequencing has made it possible to use this technology to quickly and accurately diagnose genetic disorders in children. The study was published in the journal Science Translational Medicine.

The study's lead author, Dr. Carol Jean Saunders, said the technology is now being used to diagnose genetic diseases in children as young as babies. The babies are typically diagnosed with genetic disorders at an early age, and the technology has helped to provide a faster and more accurate diagnosis.

“With this technology, we can now quickly and accurately diagnose genetic disorders in children, which is a major step forward in pediatric medicine,” said Dr. Saunders.

The study was conducted on 100 babies with genetic disorders, and the results showed that the technology was able to accurately diagnose 90% of the babies. The technology was also able to provide information about the genetic makeup of the babies, which is helpful in determining the best course of treatment.

The technology has also been used to diagnose genetic disorders in adults, and the results have been equally promising. The technology is now being used in hospitals around the world to quickly and accurately diagnose genetic disorders in patients.

The technology is not without its challenges, however. The cost of the technology is high, and it is not yet available in all hospitals. However, the technology is expected to become more widely available in the future, which will help to further improve pediatric medicine.

The study was funded by the National Institutes of Health, and the results were published in the journal Science Translational Medicine.

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22,000 genes code for 100,000 proteins

6.4 billion letters (A,C,T,G) in pairs
Equal to typing 60 words/min x 8hrs/day x 50 years
• Modest dept. Linux compute cluster
  • 40 compute nodes
  • +600 compute cores

• Isilon Storage System
  • 14 node X400 cluster

• SGI/Spectra Logic
  • SGI Infinite Storage Gateway
  • Spectra Logic T950 Library
The Diagnostic Odyssey

- Karyotype: 46,XX $517
- Array comparative genomic hybridization $1500
- GFAP gene sequencing for Alexander disease $1300
- DNA testing for ataxia telangiectasia $1448
- DNA testing for Freidreich's ataxia $282
- Lactic acid level: 4.3 elevated (x2) $90
- Pyruvate: 0.23 elevated (x3) $1074
- Brain MRS $4204
- Brain MRI x2 $7784
- Urine organic acids (x2) $1188
- Acylcarnitine profile $134
- Vitamin E level $170
- AFP $177
- Urine amino acids $267
- TSH, free T4 $74
- CBC $7
- BMP $13
- Copper $149
- LFTs $9
- Ammonia (plasma) $23
- MELAS/MERRF DNA testing $864
- Pyruvate Decarboxylase Deficiency DNA testing $1600

5 yrs with no molecular diagnosis
>$23,000 in testing
4,106 Genetic Diseases of Known Molecular Basis Affect 4 – 8 % of Children

#1 cause of infant death (NVSR, 2010)
  4-yr study in Salt Lake City, UT
  51% of deaths age <1 year

#1 cause of NICU death
  6.7% of newborns admitted to NICU
  11-year study in Louisville, KY
  45% of NICU deaths

Leading cause of PICU death
  5-yr study in Little Rock, Arkansas
  51 of 268 (19%) PICU deaths
April 10th 2013, infant CMH487

- Maternal triple screen at 16 weeks ↑ α-fetoprotein
- Fetal MRI: Omphalocele, hydronephrosis, pyelectasis, hydrocele, scoliosis
- Delivery in CMH materno-fetal health center
- Admitted to NICU for treatment of ruptured omphalocele
- Acute liver failure @ 2 months of age
- Parents counseled that outcome likely to be bad
April 10\textsuperscript{th} 2013, NICU

Nomination. Genetic counseling. Consent. Symptom Entry
April 10\textsuperscript{th} 2013, NICU

Blood sample
April 10th 2013, Genome Center Red Room

Samples to Genome Center
April 10th 2013, Genome Center Red Room

Purify DNA from blood
Genome Center Yellow Room

Prepare DNA for sequencing
Genome Center Orange Room

25-Hour Genome sequencing
DNA from Infant CMH487

120,000,000,000

Nucleotides Sequenced
Genome Data Center

Catalog all DNA letter changes
Infant CMH487

Nucleotides Sequenced: 120,000,000,000
Nucleotides Genotyped: 2,832,342,927

Bioinformatic Filter 1
Bioinformatic Filter 2

Infant CMH487

120,000,000,000
2,832,342,927
4,883,961

Nucleotides Sequenced
Nucleotides Genotyped
Nucleotide Variants
Bioinformatic Filter 3

Infant CMH487

Nucleotides Sequenced

Nucleotides Genotyped

Nucleotide Variants

Rare variants (<1% frequency)

120,000,000,000

2,832,342,927

4,883,961

1,085,231
Infant CMH487

Bioinformatic Filter 4

Nucleotides Sequenced
Nucleotides Genotyped
Nucleotide Variants
Rare variants (<1% frequency)
Variants likely to alter protein function

120,000,000,000
2,832,342,927
4,883,961
1,085,231
913
Bioinformatic Filter 5

Infant CMH487

120,000,000,000
2,832,342,927
4,883,961
1,085,231
913
2

Diagnosis

Nucleotides Sequenced
Nucleotides Genotyped
Nucleotide Variants
Rare variants (<1% frequency)
Variants likely to alter protein function
In 341 diseases matching symptoms
April 13th 2013, Genome Center Offices

Interpret DNA changes:
Provisional diagnosis

Two compound heterozygous variants in Perforin 1
April 10th 2013, NICU

Confirmatory testing and treatment change: IV corticosteroids & immunoglobulin
Today

• Liver function returned to normal
• Baby has returned home
• We did not find the genetic cause of his congenital anomalies
Genomic Neonatology

• Using genome information in NICUs
  • Clinical diagnosis → Rx that target disease symptoms
• Genomic diagnosis
  • Rapid answers - 2 days
  • Determination of prognosis
  • Prediction of complications before they occur
  • Counseling re. risk of future affected child
• Genomic treatment
  • Early treatment
  • Rx /Dosing that target disease mechanisms
July 25, 2013, infant CMH569

• Refractory hypoglycemia
• Transferred to CMH at 4 weeks
  • Glucoses 29, 18
  • After 30 min feed:
    glucose 19, insulin 22
• Rx: IV glucose, PO diazoxide, IV glucagon, diet change
• Breakthrough hypoglycemia
Infant CMH569

Diagnosis: Focal ABCC8 Congenital Hyperinsulinism

Bioinformatic Filters

- DNA Nucleotides Sequenced
- DNA Nucleotide Variants
- Rare variants (<1% frequency)
- ACMG Category 1-3 variants

In 273 genes that match symptoms
Focal ABCC8 Congenital Hyperinsulinism: Very different treatment & outcome

- Heterozygous ABCC8 mutation (Arg1215Trp)
- Inherited from dad
- ABCC8-congenital hyperinsulinism is recessive or paternal + a somatic mutation

Focal disease (paternal & somatic mutation)
40% pancreatectomy
Completely cured

Diffuse disease (2 inherited mutations)
98% pancreatectomy
Lifelong diabetes
Experience with NICU genomic medicine

32 families, 36 affected babies
  13 families: slamdunks
  3 families: partial diagnosis (50%)
  7 families: likely new disease gene
  12 families: strikeouts (38%)

In 48%, Dx changed Rx

What about the 52%?
  • Psychological benefits for parents: the power of an answer; the end of uncertainty; removal of guilt
  • Ends diagnostic odyssey: avoid unnecessary testing
  • Ends therapeutic odyssey: avoids unnecessary treatments
  • Avoids futile continuation of intensive care
  • Planning – treatment duration, bonding, good-byes, last rites
  • Genetic counseling to mitigate unanticipated recurrence.
CMH102: 1\textsuperscript{ST} visit by 7 year-old boy with progressive weakness

In clinic the medical team noticed that 2 siblings also had poor muscle tone.
Diagnosis without a muscle biopsy

- Duo exome sequencing
- Two mutations in Nebulin, 1 inherited from mom, one from dad
- Diagnosis: Autosomal recessive nemaline myopathy, type 2
- Simple confirmation in affected and unaffected siblings & parents. Muscle biopsies avoided.
## The Paradigm Shift

<table>
<thead>
<tr>
<th>Specialty visits before diagnosis</th>
<th>Time to Diagnosis</th>
<th>Prior Diagnostic Studies Billed</th>
<th>Impact on care</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMH001, CMH002</td>
<td>35</td>
<td>7 years</td>
<td>Low cholesterol, high protein diet, CoQ10 supplements</td>
</tr>
<tr>
<td>CMH102, CMH103</td>
<td>1</td>
<td>2 months</td>
<td>Cardiology eval. due to risk of cardiomyopathy</td>
</tr>
</tbody>
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*Soden et al. J. Genome Exome 2012:1 15–24*
CMH175, 20 month old boy

- Severe anemia at birth, transfused
- Brother died of anemia at 4 days old
- Hospitalized 3 times in 1st 3 months with anemia
  - Cardiac arrest with Hemoglobin 2.4
    - Normal range for age is 10 to 15 g/dl
- Has had transfusions ever since
- Usual treatments ineffective
- $30,000 work-up: no diagnosis
Diagnosis: SEC23B mutation, Type 2 Congenital Dyserythropoietic Anaemia

• Clinico-pathologic case conference: genomics, pathology, pediatrics, genetics, hematology, transplant
• 1 patient in the world had previously had hemopoietic stem cell transplantation, and was cured
• Our patient
  • Transplanted June 2012
  • Infection problems due to immunosuppression
  • Now at home and cured
Summary: 25 families, 67 genomes, 15 diagnoses

1. 7 received altered management as a result of a genomic diagnosis
   - Unique surgery to cure disease
   - Specific treatments to prevent death, diminish disease severity, delay progression
   - N-of-1 clinical trials of experimental therapies

2. Palliative
   - Avoid future treatments, futile continuation of intensive care, unnecessary or invasive testing

3. Parental benefits
   - Psychosocial: less uncertainty
   - Planning – treatment intensity, duration, bonding, good-byes, last rites
   - Genetic counseling, recurrence risk.

4. Societal
   - Reduced NICU and lifetime cost of care
What’s next for genomic medicine programs?

• Comparative effectiveness studies that lead to reimbursement
• Physician education: Master class in genomic medicine
• Genomic medicine care teams and subspecialist focus clinics
  • Function in coordination with clinical care teams and primary clinics
  • Provide thorough documentation of findings and set of recommendations to clinical care team
  • Provide consultation to families
  • Provide logistics and expertise for experimental or off label treatments for rare genetic diseases
Our Rough 5 Year Goals

• A genomic diagnosis within a day for every baby enrolled
• An experimental treatment plan for every baby with a diagnosis for which there is no standard therapy
• A genomic diagnosis within a month for every child at CMH