Building the Rare Disease Research Community: Columbia University’s DISCOVER Program

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-a borderless initiative mapping the future for regional and international collaboration

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Michael Welling, Chair
Partner, Meridian Risk Management

Joanne Gere, Executive Director
Thank You to our Community Partners, Alliance Partners, and Participants!
Building the Rare Disease Research Community: Columbia University's DISCOVER Program

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Objectives

• To recognize the genetic basis for some conditions in children
• Understand the clinical utility of genetic testing
• Understand how to utilize the results of genetic testing in clinical care and develop new treatments
Why a diagnosis matters

• Ends the diagnostic odyssey which may involve invasive/expensive tests
• Prognosis, ability to tailor health maintenance
• Identifies treatment options
• Risk of recurrence, ability to prevent having other affected children if desired
• Closure about how this happened
Why accurate predictions matter

• Ability to tailor health maintenance and prioritize health threats in real time
• Increase alertness/monitoring to maintain health
• Ability to take steps to prevent disease, ideally using real time data
• Provide reassurance or minimize ambiguity
• Assist with life planning
Reduced Sequencing Costs Enables New Screening Tests
Exome sequencing

• Sequencing of the exome (all coding exons of all genes)
  – ~1.5% of the genome (30Mb)
  – ~20,500 genes

• Capture of the exons

• Sequence using NextGen technology

• Generates a massive amount of data which needs to be filtered
Not all Genetic Conditions Run in Families

*De novo* mutations are a common cause of severe conditions in children
Seizures

- 9 year old female
- Seizures and dyskinesia at birth, microcephaly, intellectual disability
- No known family history of similar symptoms
Positive for a mutation in SLC2A1 Causing GLUT1 deficiency syndrome

GLUT1 deficiency syndrome is due to the inability to transport glucose to the brain

Diagnostic Implications:

In individuals with SLC2A1 mutations, a ketogenic diet often improves seizure control and reduces paroxysmal events, although cognitive impairment persists.

Mutation-specific testing for the SLC2A1 mutation showed this was a de novo mutation.
Prenatal case

• Fetus at 28 wks gestation
  • Anatomy scan normal
  • Fetal echocardiogram normal
  • Hydropic
  • Irregular heartbeat
  • No family history of sudden cardiac death/arrest, syncope, seizures
• Goal of genetic testing was to administer early therapy/neonatal management
Results: KCNH2 mutation

• Pathogenic variant in KCNH2 previously reported as de novo in a neonate with:
  – Neg family history and parents with normal QTc
  – fetal bradycardia
  – torsades de pointes
  – 2:1 atrioventricular block
  – QTc=544 ms
  – Heart failure
  – Infant asymptomatic at 3 months following therapy with propranolol and a pacemaker

• Our patient reported to match this presentation
  – Patient treated with beta blocker and is doing well
WES STUDY, Nature 2013

• De Novo Mutations
  • Not Increased in CHD
  • Non-Randomly Distributed
    • Chromatin Remodeling Implicated
  • ~10-20% of CHD
• Large Number of Genes (~500)
Most of the Burden of De novo Variants is for CHD Associated with Other Congenital Anomalies and Neurodevelopmental Differences
## Functional categories of candidate risk genes

<table>
<thead>
<tr>
<th>Function group</th>
<th>Genes recurrently mutated in PCGC</th>
<th>Genes mutated once in CHD cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromatin modification genes</td>
<td>KDM5B, KMT2D/MLL2, CHD7, CHD4, POGZ</td>
<td>ARID1B, EP300, TLK2, KAT6A, KANSL1, KAT6B, KMT2C, NSD1, KDM6B</td>
</tr>
<tr>
<td>Kinase signaling</td>
<td>SOS1, PTPN11, PPL</td>
<td>BRAF</td>
</tr>
<tr>
<td>Pre-mRNA splicing</td>
<td>RBFOX2</td>
<td>CDK13, SF3B1, SNACP5</td>
</tr>
<tr>
<td>Post-translational regulation</td>
<td>NAA15</td>
<td>CUL3, ASB17</td>
</tr>
<tr>
<td>TGF-beta, Notch, Wnt</td>
<td>SMAD2, NOTCH1, JAG1, ZEB2</td>
<td>CTNNB1, MED13L, SMAD4</td>
</tr>
<tr>
<td>Cellular structure</td>
<td>KRT13, DTNA, FBN1</td>
<td>GJA10, SBF1, TFE3, NCKAP1</td>
</tr>
<tr>
<td>Other</td>
<td>MYH6, CAD, RABGAP1L, GANAB, AHNAK</td>
<td>ATIC, FGF12, TANC2, KLF2</td>
</tr>
</tbody>
</table>
DISCOVER

The **Diagnosis Initiative: Seeking Care and Opportunities with Vision for Exploration and Research**

- Program for undiagnosed diseases
- Multidisciplinary team of over 50 expert clinicians and researchers who provide specialized, coordinated, and compassionate care.
- Access to advanced genetic and genomic technologies and cutting edge research leading to accurate clinical diagnosis.

To initiate a referral, please contact our coordinator at **212-342-4622** or by email at **thediscoverprogram@cumc.columbia.edu**

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**Columbia University Department of Pediatrics**
College of Physicians and Surgeons

**DISCOVER**
The Program for Undiagnosed Diseases

**NewYork-Presbyterian Morgan Stanley Children's Hospital**
Novel Disease Gene Diseases We Have Identified

Mutations in ZFET are the cause of a new Syndrome including Short stature, developmental delay and Congenital Heart Defects

De novo POZG2 mutations are associated with neurodevelopmental disorders and microcephaly

De novo mutations in PURA are associated with hypotonia and developmental delay

Mutations in ARID2 are associated with intellectual disabilities

Fetal Diagnosis Therapy

Whole-Exome Sequencing Reveals CLCNKB Mutations in a Case of Sudden Unexpected Infant Death
Genes for CHD overlap with those causing NDD
Family Partnerships
Yield of Exome Sequencing by Clinical Indication

Genetics in Medicine. 2015. PMID: 26633542
Cost Analysis Before WES
(without including cost of the hospitalization)

- Imaging Cost: $5,979
- Laboratory Tests Cost: $1,221
- Other Testing (including biopsy): $887
- Genetic testing /Karyotype/ Chromosome microarray: $14,425

Total Cost: $22,512
Rapid, comprehensive genetic diagnostics
The mission of SPARK – an online, long-term study – is simple. We want to speed up research and advance our understanding of autism. Help spark better futures for all individuals and families affected by autism.
SPARK: Simons Foundation Powering Autism Research through Knowledge

To recruit, engage, and retain 50,000 individuals with ASD and their biological family members to:

- Identify causes of ASD
- Accelerate clinical research
- Enable genotype-driven research
- Accelerate effective treatments
- WES will be performed and monogenic causes of autism will be CLIA confirmed and returned to families
- Option for return of secondary findings, but these will not be sought

SPARKforAutism.org
SPINAL MUSCULAR ATROPHY (SMA)
NEWBORN SCREENING
The result of SMA newborn screening

14 months old
Mechanisms for Weight Regulation

Barsh and Schwartz 2002
Setmelanotide Trial for Obesity

- MC4R agonist
- Outcome measures
  - Body weight
  - Hunger
  - Metabolic parameters
  - Blood pressure
  - Body composition/energy expenditure

TREATMENT: Targeted Research and Exploration
Advancing Trial Models, Editing, and Next-generation Therapies

• Case finding
• Natural history
• Outcome measures/biomarker
• Reagents
  – Induced pluripotential stem cells, differentiated cells, organoids, mouse models
• Determine disease mechanism
• Strategically identify best therapeutic option
  – Small molecular, biologics, stem cells, gene therapy, gene editing
• Preclinical trials
  – Rodent studies, large mammal, nonhuman primate
• Clinical trials
Conclusions

• We need to diagnose individuals with genetic conditions faster and more efficiently and get onto treatment and support

• The diagnosis provides prognostic information that is helpful for management, but most conditions still cannot be cured

• Population based screening for genetic disorders is possible and important as treatments are identified
Acknowledgements

Patients and their families

PCGC consortium

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NERI

Cincinnati Children’s Hospital (Pete White)

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Questions???

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Research Community Resources