Linking Disease Models and Human Phenotypes: The Clinical Geneticist Perspective

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Disclosures

• Past-President of the American College of Medical Genetics and Genomics (ACMG)

• Funded research on
  – Genetics of autism spectrum disorders (DoD)
  – Mouse models for human developmental disorders of cholesterol synthesis (NIH)
Precision Medicine

• Possible through disruptive technology of NGS and advances in computational biology

• Clinical utility currently
  – Cancer diagnosis and personalized therapeutics
  – Diagnosis of rare Mendelian disorders

• Future expected clinical utility
  – Pharmacogenomics
  – Multifactorial disorders
Human Gene Discovery for Mendelian Phenotypes

Protein Coding Genes and Mendelian Phenotypes

Strategies for Exome Sequencing in Pediatrics

A  Multiple Unrelated Affected Subjects

All subjects have similar phenotypes.
Exome sequencing reveals many differences (X) from the reference genome.
Sequence changes are filtered to remove those seen in healthy controls.

Only gene 2 harbors a rare, potentially damaging sequence change in all subjects.

B  Trio Analysis

Gene 1  
Gene 2  
Gene 3  De novo change in gene 3

C  Recessive Analysis

Gene 1  
Gene 2  
Gene 3  
Recessive mutations in gene 2

Secondary Findings - Definitions

• **Primary Finding** – pathogenic alterations in gene(s) relevant to the diagnostic indication for which sequencing was ordered

• **Secondary Finding** – results of a deliberate search for pathogenic or likely pathogenic alterations in genes that are apparently unrelated to a diagnostic indication for which sequencing was ordered (also called incidental findings)
Secondary Findings in Clinical Sequencing

- Recommendations of ACMG & President’s Commission on Bioethics (2013)
- “Minimum list” of 56 actionable genes and specific mutations
  - Hereditary cancer genes, Marfan and related syndromes, inherited cardiomyopathies & arrhythmias, familial hypercholesterolemia, malignant hyperthermia
- Pathogenic variants in this gene list should be reported regardless of indication for clinical exome sequencing
  - Additional genes may be analyzed for incidental variants
  - Minimal list should be reported regardless of patient age
  - Patients/parents may “opt out” at time of consent
Secondary Findings

• Labs should seek and report only the types of variants listed (pathogenic)
  – Low prior likelihood of disease for secondary findings
  – Labs should list quality of coverage/data which may be lower than for diagnostic genes
• Clinician/team has responsibility to provide appropriate pre- and post-test counseling [should include qualified genetics professional(s)]
• List should be refined and updated at least annually
• No consensus or recommendations on reporting of secondary findings in research WES/WGS sequencing
Clinical Exome Sequencing

• High diagnostic yield (~25-40%)
  – Frequent de novo heterozygous mutations, some recurrent
  – Broadening of phenotypic spectrum for some classic syndromes; ≥1 phenotype ass’d with a single gene
• Importance of studying trios – higher yields in trios of ~40% vs ~25% if study DNA from proband only
• VUS and actionable secondary findings are common (the latter in ~1-5% of cases depending on lab)
• Requires team to interpret results, including clinicians
Types of Information on the Clinical Exome Report

• Variants/mutations likely or possibly related to the patient’s clinical phenotype
• Medically actionable variants in disease genes unrelated to the patient’s clinical phenotype (secondary findings)
• Carrier status for recessive Mendelian disorders
• Pharmacogenetic results
Who are the Best Candidates for Clinical Exome Sequencing?

• Specific phenotypes/disorders should lead to specific genetic testing (single gene, gene panel)
  – May be less coverage of specific genes/regions on WES
  – Longer TAT; ?higher cost; lower % reimbursement

• Testing prior to exome
  – Microarray analysis - MCA, intellectual disability (IDD), severe szs, severe ASD (low IQ, dysmorphic)
  – Low cost screening tests where appropriate
Utility of a Genetic Diagnosis

• Prevents additional unnecessary testing
• May help predict future medical complications
• May help tailor specific interventions
• May help predict function as an adult
• Will often provide better guidance concerning recurrence risks
• Will occasionally permit specific medical therapies that may significantly improve the outcome
Clinical Exome Sequencing Results at NCH Through 2/10/15

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<thead>
<tr>
<th>Category</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exomes Completed</td>
<td>131</td>
<td></td>
</tr>
<tr>
<td>Cause Identified (Pathogenic variant found related to disease)</td>
<td>55 (42%)</td>
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<tr>
<td>Likely Cause Identified (awaiting confirmation)</td>
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<td></td>
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<tr>
<td>Questionable Results (VUS, pathogenicity unclear)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Actionable Secondary Findings (BRCA1, MEN I, BRCA2)</td>
<td>3</td>
<td></td>
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Exome Sequencing Results at NCH – Implications for Management on 1st 100 Cases

- 19/41 (46%) with positive result had change in management beyond reproductive risk
  - 16/41 change in surveillance, including increased cancer risk (DKC)
  - 3/41 specific rx such as medication, diet (Lesch-Nyhan, AR disorder of creatine synthesis, novel sz/movement disorder)
- 20/41 clearly de novo – dramatic reduction in recurrence risk (?25% to <1%)
- 3 novel genes identified (PURA, VARS2, one pending)
Trends in Clinical Sequencing

• Expansion to carrier and population screening
• Move from gene identification to validation of variant pathogenicity; Need rapid, robust tools to validate potential disease-causing variants, particularly missense variants
• Move toward WGS, with assessment of chr rearrangements included in analysis; increased complexity of assessing non-coding variants
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  – Ben Kelly