All in the Family

How Genetic Counselors Facilitate Familial Genetic Testing

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Objectives

• Recognize different methodologies for performing family specific genetic testing

• Explain why positive control samples and a proband’s original test report are important for accurate testing

• Identify how genetic counselors can serve as a resource during the familial testing process
Why This Topic is Important

• Potential for false reassurance of a normal result
  – If we didn’t know what we were looking for or how to look for it, the family member may still be at risk.

• Original proband’s report, or providing a positive control is important but can take effort
  – Best to be prepared prior to testing family members
Why do Familial Testing?

- Medical management and recurrence risks
- Some OHPs opt for the SAME test as the proband
  - Targeted, site-specific testing is often cheaper and faster than the more comprehensive version that the proband had
  - Especially when dealing with NGS panels, or genomic microarray, it’s a better use of healthcare dollars to go searching only in the region with a genetic change
- Assumes you know how the proband was tested…
- Assumes you know exactly where to look…
Types of Proband Test Results

• Single gene testing
  – Gene(s) sequencing (Sanger or NGS panel)
  – Single gene del/dup testing

• Genomic testing
  – FISH
  – Microarray
  – Chromosome analysis
  – (Exome sequencing)
Familial Genetic Tests

• Recommended test to order on family members depends on several factors
  – How the proband was tested and what the results were
  – Clinical question for the family member – carrier status? Affected status? Recurrence risk?

• Methodology used for proband’s testing may not be appropriate for a family member

• There may be more than one option for familial testing each with pros and cons
Test Selection (sometimes)

PROBAND
Sequencing
del/dup (MLPA)
FISH
Array
Chromosomes

FAMILY MEMBER
Sequencing
del/dup (MLPA)
FISH
Array
Chromosomes
Testing Selection (more common)

**PROBAND**
- Sequencing
- del/dup (MLPA)
- FISH
- Array
- Chromosomes

**FAMILY MEMBER**
- Sequencing
- del/dup (MLPA)
- FISH
- Array
- Chromosomes
Brief Overview of Test Methods – Sequencing

Targeted mutation/exon

Modified from slide by Yuan Ji, PhD
Sequencing

Full-gene
MLPA

1. Denaturation and Hybridization
   - PCR primer sequence X
   - Hybridization sequence (left)
   - PCR primer sequence Y
   - Hybridization sequence (right)
   - Stuffer sequence

2. Ligation

3. PCR with universal primers X and Y
   - Exponential amplification of ligated probes only

4. Fragment analysis
FISH
Genomic Microarray

- Millions of DNA strands built up in each location
- 6.5 million locations on each GeneChip® array
- Actual strand = 25 base pairs

www.affymetrix.com
Genomic Microarray
Chromosome Analysis

http://www.spectral-imaging.com
So many options – now what?

• Ask a genetic counselor to help select and coordinate testing!

PROBAND
Sequencing
del/dup (MLPA)
FISH
Array
Chromosomes

FAMILY MEMBER
Sequencing
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FISH
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Genetic Counselor’s Role

• Test selection
  – Implication of results

• Test coordination
  – Obtaining reports, paperwork, and making sure lab is informed
  – Checking that family member and control samples are ordered correctly

• Interpretive comments

• Informing OHP about results
Proband Reports / Positive Controls

• Proband report and positive control are both important

• Controls ensure the test ordered would have identified the familial variant if present
  – Lab methodologies can be slightly different
  – Nomenclature for mutations can be different
  – Some familial testing might be possible without a control

• Control options:
  – Proband’s previous sample
  – New blood or buccal sample from proband
  – Maternal blood for fetal tests
Summary - Suggestions

• Involve genetics / genetic counselors
• Be prepared to obtain a report
• Investigate sooner rather than later
  – May avoid a proband redraw
Objectives

- Distinguish different methodologies for performing family specific genetic testing
- Explain why positive control samples and a proband’s original test report are important for accurate testing
- Understand how genetic counselors can serve as a resource during the familial testing process
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