GENETIC COUNSELING, FAMILY HISTORY, GENETIC TESTING

How to make the most of these resources
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Objectives

• Provide a brief description of genetic counseling
• Discuss useful tools and considerations when reviewing a family history
• Provide a basic understanding for the genetics of NF
Genetic Counseling

• What is it?
  • A bridge between genetics and the general population
  • Provides a patient friendly explanation of genetics and genetic disorders
  • Uses psychosocial cues and interaction to help determine the effects of genetics and genetic disorders on an individual/family
Genetic Counseling

- Who performs genetic counseling?
  - Physicians
  - Nurses
  - Genetic Counselors

- In what settings is this done?
  - Prenatal
  - Pediatric
  - Adult
  - Other
Key Components of Genetic Counseling

• Establish a background on the patient
  • Values and social background for the patient
  • Medical history of the patient
  • FAMILY HISTORY

• Explain how genetics currently affects the patient
  • Provide summaries of the genetics and natural history of particular genetic disorders
  • Explain current genetic testing options
  • Provide resources on genetic disorders

• Serve as a resource for any advancements within genetics
Family History

• What is important?
  • Relationships: Different diseases are inherited in different patterns
  • Ages of onset: help to rule in/out genetic disorders
  • Details: medical details can be essential
  • Ancestry: helps to rule in/out genetic disorders
An Example

Café-au-lait spots and freckling

Café-au-lait spots

Tumors

Cancer
Neurofibromatosis Type 1

- Chromosome 17
- *NF1* gene
- Autosomal Dominant
- 1:3,500 incidence
- 50% chance to have a brand new mutation
- Gene change does not provide information on clinical presentation
- >95% detection rate for genetic testing
An Example

Café-au-lait spots and freckling

Tumors
- Lipomas, CALs, Learning disability

Cancer
- Stage 1 Lung cancer, smoker

>30 Café-au-lait spots
Legius syndrome

- Chromosome 15
- \textit{SPRED1} gene
- Autosomal Dominant
- No CNS tumors
- Less frequent than NF1
  - $\approx20\%$ with family history of CAL spots and freckling only
  - $\approx2\%$ of total population of CAL spots and freckling only
Segmental/Mosaic NF1

- More than one cell line within the body
- May require more complex genetic testing
- Seen in “founder” patients
- Leads to variable risk of inheritance to the next generation

[Diagram showing segmental/mosaic NF1]

An Example

Ancestry: Irish

Breast Cancer

2 large CALs and freckling on face and arms

Ancestry: Irish

60

3 CALs, Schwannomas

45

Tumors

Vestibular Schwannoma

Cancer

14

8
Neurofibromatosis Type 2

- Chromosome 22
- *NF2* gene
- Autosomal Dominant
- Later onset
- 1:33-40,000
- 50% brand new in family
- >92% detection rate with family history
- 25-30% cases can be mosaic
Schwannomatosis

- Chromosome 22
- *SMARCB1* gene
- Adult onset
- Schwannomas
- More compared to NF2
- Low detection rates in blood
- Tumor testing available
An Example

Ancestry: African American

- Breast Cancer, diagnosed at 46
- Bilateral Breast Cancer, diagnosed at 40 and 45
- d. 52
- CAL spots and freckling

Ancestry: African American

- CAL spots
- Tumors
- Cancer
- Sickle cell disease
Importance of Genetic Testing

Beneficial in making a diagnosis

- Helpful for those with:
  - Unclear clinical presentations
  - Mild clinical presentations
  - Mosaicism

REPORT MUTATION ANALYSIS NEUROFIBROMATOSIS TYPE 1 – TODAY

<table>
<thead>
<tr>
<th>Patient Name: Doe, John</th>
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<tbody>
<tr>
<td>Date of Birth: 1/2/03</td>
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<tr>
<td>Family #: NF56</td>
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<tr>
<td>Lab ID#: M123456</td>
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<tr>
<td>Date Collected: 7/8/00</td>
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<tr>
<td>Date Initiated: 7/8/00</td>
</tr>
<tr>
<td>Address: 720 20th St South, Birmingham, AL 35204</td>
</tr>
<tr>
<td>Telephone / Fax Number: 205-999-9999/205-555-5555</td>
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</tbody>
</table>

Indications for testing: 7 y/o boy presenting with >6 CALS and bilateral inguinal and axillary freckling. Father is reported to have several CALS.

Result and interpretation:

A heterozygous truncating mutation in the NF1 gene was identified in the patient Doe, John; i.e. c.8709C>T (p.Ala2933Thr). No other possibly damaging alteration was found after comprehensive NF1 mutation analysis.

This finding confirms the diagnosis of NF1 in this patient.

Comprehensive NF1 mutation analysis detects the pathogenic mutation in >95% of non-familial NF1 patients fulfilling the NIH diagnostic criteria.

Genetic counseling should be offered to explain the implication of the test result. Counseling should include information about the implications of testing, residual risks, reproductive and medical options.

Method:

Comprehensive NF1 mutation analysis starts with extraction of DNA from the blood sample of the patient. Another aliquot of the blood sample is used to start a short-term culture of phytohemagglutinin stimulated lymphocytes. Total RNA is extracted from phytohemagglutinin-treated cultures and cDNA is prepared.

Four intragenic microsatellite polymorphisms, i.e., IVS27 CAGT (Lazaro et al., 1993), A444T, IVS27 (Xu et al., 1995), IVS37 T363G (Lazaro et al., 1993) and 1 exonic marker, i.e., NF1-1, are analyzed as a first approach to determine whether 2 copies of the NF1 gene are likely to be present. If no heterozygous signal is observed for any of these markers, FISH analysis is performed using PACs 9298F and 1002G3 to confirm or rule out the presence of a total gene deletion.

Then, the total coding region of the NF1 gene is analyzed by long-range RT-PCR and direct cycle sequencing starting from 3 overlapping RT-PCR fragments spanning exons 1-27b, 12b-34 and exons 32-49. Sequencing is performed using dye-terminator chemistry on an ABI PRISM 3730xl capillary sequencer. NF1 exon 1 is hereby sequenced at the gDNA level. If no mutation is identified by direct sequencing, a multiplex ligation probe assay (MLPA) is performed in order to detect copy number changes (deletions/duplications) in the coding region of the NF1 gene.

A routine cytogenetic analysis is NOT performed.

Mutations are described to conform to the ICGV recommendations with nucleotide 1 being the A of the ATG translation initiation codon in the NF1 RefSeq NM_000267.3, and corresponding NF1 protein RefSeq NP_000265.1.

This test was developed and its performance determined by the Medical Genomics Laboratory. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes. Pursuant to the requirements of CLIA '88, this laboratory has established and verified the test's accuracy and precision.

Ludwine Messiaen, Ph.D.
Director, Medical Genomics Laboratory

Bruce Korf, M.D., Ph.D.
Chairman, Department of Genetics
Importance of Genetic Testing

Can help with future research studies

- Genotype-phenotype correlations
- Clinical trials

http://chgr.org/about.html
Importance of Genetic Testing

Can help with assessing recurrence risk

- Risks for:
  - Parents
  - Siblings
  - Children

U.S. National Library of Medicine
Importance of Genetic Testing

Can help with assessing recurrence risk for future pregnancies

• Testing options:
  • Chorionic villus sampling (CVS)
    • 10-13 weeks gestation
  • Amniocentesis
    • 15-21 weeks gestation
  • Pre-implantation genetic diagnosis
    • Before the embryo is implanted into the uterus
In Summary

• Check on the details!
• Think “outside” box
• Know your relationships
• Be sure to update your physician
• Talk with your family about important medical diagnoses
• Share your testing results with relevant family members