Hereditary Cancer Syndromes

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February 28, 2017
Common Genetics Terms

—Gene: A hereditary unit consisting of a sequence of DNA that occupies a specific location on a chromosome and determines a particular characteristic in an organism.

—Locus: specific area on chromosome where the gene is found

—Trait: A distinguishing feature, a genetically determined characteristic or condition.

—Allele: Versions of a gene

—Genotype: the genetic makeup of an organism

—Phenotype: the physical appearance of an organism

—Pleiotropy: the ability of a gene to affect an organism in many ways

—Polygenic Inheritance: additive effect of 2 or more genes on a phenotypic character

—Phenocopy: the observed result of an environmentally induced, nongenetic alteration of a phenotype to a form that resembles the expression of a known genetic mutation.
Genetic Heterogeneity

- **Genetic heterogeneity:** A number of similar or identical phenotypes are caused by different genotypes
  - mutations at different loci (different genes)
    - locus heterogeneity
      - Hearing loss
  
- may be the result of different mutations at the same locus (same gene)
  - allelic heterogeneity means that different mutations within a single gene locus (forming multiple alleles of that gene) cause the same phenotypic expression.
  - For example, there are over 1000 known mutant alleles of the CFTR gene that cause cystic fibrosis.
Variation in the Phenotype

- **Penetrance**
  - the probability that a gene will have ANY phenotypic expression
    - it is an all or none concept
    - if some people with an appropriate genotype fail to express the phenotype, there is *reduced penetrance*

- **Expressivity**
  - Severity of the manifestations of the phenotype
  - when phenotypic severity varies among those with identical genotypes, variable expressivity is shown

- **Pleiotropy**
  - Multiple phenotypic effects of a single gene or gene pair
  - when the effects are not obviously related
Genotype vs. Phenotype

- **Same genotype** (genetic makeup) **different phenotype** (observed features)
  - Pleiotropy (single gene influences multiple phenotypic traits)
    - Ex. MSH6 associated w/ colon ca, endometrial ca, ovarian ca, etc.
  - Expressivity (different degrees of presentation)
    - Ex. APC gene mutations—classic vs. attenuated form

- **Same phenotype different genotype**
  - Ex. Breast cancer associated w/ mutations in BRCA, PTEN, TP53 or sporadic
Goals of Pedigree Analysis

1. Determine (suggest) the mode of inheritance: autosomal dominant (AD), autosomal recessive (AR), sex-linked, mitochondrial.

2. Determine the probability of inheriting a gene mutation for the offspring.
Obtaining a Family History

• 4 generations – list all maternal and paternal relatives, whether or not they have had cancer
  – Limited family structure (<2 females over age 45 on one side of the family) for HBOC
• Age at cancer diagnosis
• Pathology
• Age at death/cause of death
• History of oophorectomy or hysterectomy, CRC polyps—including number and pathology
• Ancestry
Basic Symbols

- Male (unaffected)
- Affected male
- Female (unaffected)
- Affected female
- Unknown sex
- Dead

Mating

Consanguineous mating

Offspring
Arrow points to proband
Modes of Inheritance

• **Autosomal Dominant**: affects both males and females in all generations.
  • Examples: Achondroplasia, Huntington disease, Neurofibromatosis types 1 & 2, and many, many more!
Modes of Inheritance

- **Autosomal Recessive**: offspring of 2 carrier parents can be affected. Usually only seen in one generation. Males and females affected and transmit.
  - Consanguinity may be apparent in parents of affected child.
    - Examples: Cystic Fibrosis, PKU, Wilson’s disease, and many more!
Modes of Inheritance

⦿ X-linked recessive: only sons of heterozygous mothers (carriers) can be affected, there is no father to son transmission. All daughters of an affected male will be carriers.

- Examples: Duchenne muscular dystrophy, Hemophilia A and B
- Females may rarely be affected due to non-random inactivation of X chromosome
Modes of Inheritance

- **X-linked dominant**: Males and females can be affected. All daughters of affected fathers are affected. No male to male transmission.

  - Example-
    - Hypophosphatemic rickets (X-linked hypophosphatemic rickets): increased phosphate wasting at proximal tubule (kidney)
Modes of Inheritance

- **Mitochondrial:** Transmission ONLY through the mother. Mitochondria are only inherited from the mother. All offspring of affected mothers are affected.
  - Variable expression due to heteroplasmy
  - The effect a mutation in mtDNA will have on a cell's function will therefore depend on the number of mutant organelles in a cell compared to the number of normal or "wild type", present. In this respect, each cell is analogous to an organism in which somatic mutation can produce mosaicism. Here the mixture of genotypes is termed heteroplasmy.

Example of a family tree showing members of a family in which runs an inheritance of a mitochondrial condition
(Adapted from: Greenwood Genetic Centre (1995): Counseling Aids for geneticists. Greenwood Genetic Centre, USA)
General Principles

- Causes of cancer
- Inheritance Patterns
- Importance of diagnosing a genetic disorder
All cancer is genetic, not all cancer is hereditary.
Cancer

- **Familial cancer** ~ 15-20%
  - More cases of a specific type(s) of cancer within a family than expected, but no specific pattern of inheritance
  - Age of onset variable
  - May result from chance clustering of sporadic cases
  - May result from common genetic background (low penetrance gene), similar environment and/or lifestyle factors

- **Hereditary cancer** ~ 5-10%
  - Early diagnosis
  - Bilateral cancers
  - Multiple primaries in an individual
  - Multiple affected family members
  - Spanning a number of generations
  - Rare cancers (ovarian cancer, male breast cancer)

- **Sporadic cancer** ~ 65-70%
  - Typical age of onset (older age)
  - Even if there is more than one case in the family, there is no particular pattern of inheritance
Hereditary Cancer Syndromes and Public Health

• ~5-10% of all cancers (with some exceptions)
• High risk of multiple primaries
• Occur at younger age
• Multiple family members affected
• Early identification would benefit from preventive care options
(Some) Hereditary Cancer Syndromes

- Hereditary Breast and Ovarian Cancer Syndrome (BRCA1 and BRCA2)
- HNPCC/Lynch Syndrome (MMR genes – MLH1, MSH2, MSH6, PMS2, and non-MMR gene EPCAM)
- FAP, AFAP and MAP (APC and MYH)
- Malignant melanoma (CDKN2A, CDK4)
- Hereditary Diffuse Gastric Cancer (CDH1)
- Von Hippel Lindau (VHL)
- Cowden Syndrome (PTEN)
- Neurofibromatosis type 1 and type 2 (NF1 and NF2)
- Li-Fraumeni Syndrome (TP53)
- Multiple endocrine neoplasia type 1 (MEN1)
- Multiple endocrine neoplasia type 2 (RET)
Hereditary Basis of Cancer

- Most inherited cancer syndromes are \textit{autosomal dominant- AD} (e.g. HBOC, HNPCC, FAP/AFAP, Cowden, Li-Fraumeni)

- Few are \textit{autosomal recessive- AR} (e.g. MYH-Polyposis, Fanconi Anemia)
Genetic Cancer Risk Assessment Component and Activities

1. Identify at-risk patients
2. Provide pretest counseling
3. Select and offer test
4. Provide informed consent
5. Disclose results
6. Provide post-test counseling and follow-up
Benefits and Limitations of Testing

Benefits

- Offers personalized hereditary cancer risk assessment
- Can provide information to help make medical management decisions to reduce cancer risk
- Important information for family members
- Reduced anxiety and stress

Limitations

- Testing does not detect all causes of hereditary cancer
- A negative result is most helpful when there is a known mutation in the family
<table>
<thead>
<tr>
<th>BREAST CANCER SYNDROMES</th>
<th>CANCERS/FEATURES</th>
<th>GENE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary Breast and Ovarian Cancer</td>
<td>Breast, ovarian, male breast, prostate, melanoma, pancreatic</td>
<td>BRCA1, BRCA2</td>
</tr>
<tr>
<td>Cowden Syndrome</td>
<td>Breast, thyroid, uterine, colon, renal</td>
<td>PTEN</td>
</tr>
<tr>
<td>Li-Fraumeni Syndrome</td>
<td>Breast, sarcoma, brain, adrenal cortical</td>
<td>TP53</td>
</tr>
<tr>
<td>Diffuse Gastric Cancer</td>
<td>Lobular breast, diffuse gastric</td>
<td>CDH1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COLON CANCER SYNDROMES</th>
<th>CANCERS/FEATURES</th>
<th>GENE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lynch Syndrome</td>
<td>Colon, uterine, ovarian, gastric, ureter, kidney, hepatobiliary, duodenal</td>
<td>MLH1, MSH2, MSH6, PMS2, EPCAM</td>
</tr>
<tr>
<td>Familial Adenomatous Polyposis</td>
<td>Colon, &gt;100 polyps, thyroid</td>
<td>APC</td>
</tr>
<tr>
<td>Attenuated Familial Adenomatous Polyposis</td>
<td>Colon, 10-100 polyps</td>
<td>APC</td>
</tr>
<tr>
<td>MYH-Associated Polyposis</td>
<td>Colon, up to 500 polyps</td>
<td>MUTYH</td>
</tr>
<tr>
<td>Juvenile Polyposis</td>
<td>Colon, hamartomatous polyps</td>
<td>SMAD4, BMPR1A</td>
</tr>
<tr>
<td>Juvenile Polyposis/Hereditary Hemorrhagic Telangetasia</td>
<td>Colon, hamartomatous polyps, HHT symptoms</td>
<td>SMAD4</td>
</tr>
<tr>
<td>Peutz-Jeghers Syndrome</td>
<td>Colon, testicular, breast, uterine</td>
<td>STK11</td>
</tr>
</tbody>
</table>

Adapted from: Lindor N. Concise Handbook of Familial Cancer Susceptibility Syndromes; Journal of the National Cancer Institute Monographs, No. 38, 2008.
Hereditary Breast and Ovarian Syndrome associated with mutations in the BRCA1/2 genes
BRCA1/2 genes: Mutation Penetrance

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Inherited Risk</th>
<th>General Population Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast - female</td>
<td>45 - 84%*</td>
<td>11-12%</td>
</tr>
<tr>
<td>- male</td>
<td>up to 8%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Ovarian and ovarian related</td>
<td>11 - 62%</td>
<td>1.5-2%</td>
</tr>
<tr>
<td>Prostate</td>
<td>20%</td>
<td>16.2%</td>
</tr>
</tbody>
</table>

- There is also an increased incidence of melanoma and/or pancreatic cancer in some families.

*Women who have already had breast cancer have up to a 20% risk to develop a new primary breast cancer within 5 years of their initial diagnosis, and up to a 60% risk in their lifetime.
Role of BRCA1&2 genes

- Tumor suppressor genes

- Primarily executing the DNA double-strand break repair by homologous recombination
HBOC (associated with mutations in BRCA1/2 genes) pedigree
Genetic Testing Results

- **Positive**
  - Deleterious (harmful) mutation identified

- **Negative**
  - Interpretation differs if a mutation has previously been identified in the family
    - Mutation known – true negative (cancer risk as general population)
    - Mutation unknown – uninformative (cancer risk increased compared with general population, but less than if having a BRCA mutation)

- **Variant of unknown significance**
  - The test identified a change in the BRCA1/2 genes but is not clear if the change is harmful or not.
Managing Hereditary Breast and Ovarian Cancer Risk
Management of BRCA Carriers

**Increased surveillance**
- For breast cancer, ovarian cancer, prostate cancer, melanoma and pancreatic cancer

**Medication**
- E.g. Tamoxifen, raloxifene (for breast cancer)
- Oral contraceptives (reduce the risk of ovarian cancer)

**Risk-reducing surgery**
- Bilateral mastectomy, bilateral salpingo-oophorectomy
New therapy:
PARP inhibitors

• Two genes are said to be in a **synthetic lethal** relationship if a mutation in either gene alone is not lethal but mutations in both cause the death of a cell.

• Inhibition of PARP[poly(adenosine-disposphate-ribose) polymerase] appears to selectively kill cells which lack functional BRCA.
PARP Inhibitors

• FDA approved for advanced ovarian cancer (certain conditions need to be met)

• There are currently a number of ongoing clinical studies in BRCA1/2 mutation carriers utilizing various PARP inhibitors in breast, prostate, pancreatic cancer patients
Colorectal Cancer Genetics

Sporadic

Familial

Rare CRC syndromes

HNPCC (2-5%)

FAP (1%)

from Burt, RW. Inheritance and Genetic Testing for Colon Cancer
Lynch syndrome (LS) or Hereditary non-polyposis colorectal cancer

- Germline mutations in one of four mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*).
- *MLH1* and *MSH2* germline mutations account for approximately 90%;
- *MSH6* mutations ~7%-10%; and
- *PMS2* mutations in fewer than 5%.
- Germline deletions in *EPCAM* (not a mismatch repair gene) inactivate *MSH2* in about 1% of individuals with Lynch syndrome.

## Cancer Risks in Individuals with Lynch Syndrome Age ≤70 Years Compared to the General Population

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>General Population Risk</th>
<th>Lynch Syndrome (MLH1 and MSH2 heterozygotes)</th>
<th>Risk</th>
<th>Mean Age of Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>5.5%</td>
<td>52%-82%</td>
<td>44-61 years</td>
<td></td>
</tr>
<tr>
<td>Endometrium</td>
<td>2.7%</td>
<td>25%-60%</td>
<td>48-62 years</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>&lt;1%</td>
<td>6%-13%</td>
<td>56 years</td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td>1.6%</td>
<td>4%-12%</td>
<td>42.5 years</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary tract</td>
<td>&lt;1%</td>
<td>1.4%-4%</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Urinary tract</td>
<td>&lt;1%</td>
<td>1%-4%</td>
<td>~55 years</td>
<td></td>
</tr>
<tr>
<td>Small bowel</td>
<td>&lt;1%</td>
<td>3%-6%</td>
<td>49 years</td>
<td></td>
</tr>
<tr>
<td>Brain/central nervous system</td>
<td>&lt;1%</td>
<td>1%-3%</td>
<td>~50 years</td>
<td></td>
</tr>
<tr>
<td>Sebaceous neoplasms</td>
<td>&lt;1%</td>
<td>1%-9%</td>
<td>Not reported</td>
<td></td>
</tr>
</tbody>
</table>

Aarnio et al [1999], Vasen et al[2002], American Cancer Society[2002], Hampel et al [2005], Ponti et al [2006], South et al [2008], Watson et al [2008], barrow et al [2009], Barrow et al [2009], Stoffel et al [2009]
Lynch syndrome - MMR genes

The DNA mismatch repair (MMR) mechanism in humans.
*Current Genomics, 2009, Vol. 10, No. 2*
Amsterdam Criteria: Clinical Diagnosis of Lynch syndrome (3-2-1)

Amsterdam Criteria

– **Three** or more family members, one of whom is a first-degree relative of the other two, with a confirmed diagnosis of colorectal cancer
– **Two** successive affected generations
– **One** or more colon cancers diagnosed before age 50 years
– FAP (Familial Adenomatous Polyposis) excluded

Amsterdam II Criteria

– **Three** or more family members, one of whom is a first-degree relative of the other two, with HNPCC-related cancers **
– **Two** successive affected generations
– **One** or more of the HNPCC-related cancers diagnosed before age 50 years
– FAP excluded

**Colorectal, endometrial, stomach, small intestinal, hepatobiliary, renal pelvic, or ureteral**

Bethesda Guidelines: Screening for Lynch syndrome
(criteria for microsatellite instability testing)

Colorectal cancer

- Under age 50
- With a synchronous or metachronous Lynch (HNPCC) tumor
- Under age 60 with histology consistent with Lynch (HNPCC) syndrome
  - tumor infiltrating lymphocytes, Crohn-like reaction, mucinous/signet ring differentiation, medullary growth pattern
- With a first-degree relative who has an HNPCC tumor <50
- With 2 or more first or second-degree relatives with HNPCC tumor

Pedigree of a Lynch syndrome family
Microsatellite Instability Testing

- Must have tumor and normal tissue (or normal control – blood sample)
- Most effective when combined with clinical information
- Studies of Lynch syndrome-associated adenomas suggest a slightly lower rate of MSI compared to invasive cancers, with approximately 80% of adenomas being MSI-high
- Approximately 20%-30% of endometrial cancers exhibit MSI, and as with colon cancers the majority are the result of somatic MLH1 promoter methylation

- **MSI-high** if more than two (or >30%) of the markers show instability
- **MSI-low** if one (or <30%) of the markers show instability
- **MSI-stable** if 0 (or 0%) of the markers show instability

Immunohistochemistry (IHC)

• Stain archived tumor tissue for MMR proteins

• Missing protein indicates which gene to sequence
  – MLH1 and PMS2
  – MSH2 and MSH6

• MLH1 can be lost by methylation or by somatic mutations
Management of Lynch syndrome

• Increased surveillance
  – Colorectal, endometrial, ovarian, urinary tract

• Risk reducing surgery
  – endometrial, ovarian

• Does surveillance help??
  – Detection of CRC at an earlier stage, to a 63% reduction of the risk of CRC and to a significant reduction of the mortality associated with CRC

What’s new?

• **Next Generation sequencing:**
  a high-throughput sequencing method that parallelize the sequencing process, producing thousands or millions of sequences at once.
High-penetrance, rare cancer predisposition genes
(Relative risk ≥ 5.0)

Moderate-risk alleles
(Relative risk ≥ 1.5 and < 5.0)

Genome-wide association studies
Low-penetrance, high-frequency risk alleles*
(Relative risk < 1.5)

Stadler ZK, J Clin Oncol. 2010 Sep 20;28(27):4255-67
Currently many clinical laboratories in US offer gene panel tests for hereditary cancer syndromes

**Syndrome-specific test** (e.g. BRCA1 and BRCA2 for HBOC)

**Cancer-specific** that include high penetrance gene panel

**Cancer-specific** including high- and moderate-penetrance genes

**Comprehensive cancer panels** (genes associated with multiple hereditary cancer syndromes)
Next Generation Sequencing (NGS) Panels

**Strengths**
- Allows the analysis of several genes concurrently
- May identify a cause/cancer syndrome that would not have otherwise been identified through single-gene testing
- Cost and time effective

**Limitations**
- Lack of evidence-based management guidelines for many of the rare syndromes (or gene mutations)
- High likelihood for Variants of Unknown Significance
- Several genes may not have clinical relevance to personal and family history

- NGS panels should be offered only in consultation with a cancer genetics professional (NCCN and SGO)
Tumor Genome Profiling

• Genetic mutations in tumors
• Used to identify mutations in genes that would guide personalized treatment
• “Incidental findings” a mutation in the tumor can actually be a germline mutation
Tumor genomic profiling for treatment

Examples:

• **Lung cancer.** Drugs that block the protein called EGFR may stop or slow down lung cancer. This may be more likely if the EGFR has certain mutations. Targeted therapy is also available for lung cancer with a mutation in the ALK gene.

• **Melanoma.** About half of melanomas have a mutation in the BRAF gene. FDA has approved several BRAF inhibitors. But these drugs can be dangerous if you do not have the BRAF mutation.
Issues in Genetic Counseling/Testing

• Blood sample (or other tissue sample)
• Non-directive counseling
• Informed consent
  - Positive, negative, variant of uncertain significance
• Insurance Discrimination/Genetic Privacy Laws
  - HIPAA, State Laws Governing Genetic Discrimination, Genetic Information Non-Discrimination Act (GINA)
• Minors
• Uninformative negative test result
• Family implications
• Support group information
Thank You!
Contact Information

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Fax: 716-845-5720