Assessing Heritable Risks of Cancer in Children: The Role of Genes, Genomics, and Genetic Counseling

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The Role of Genes

Disclosure

Gail Tomlinson, M.D., Ph.D., has no relationships with commercial companies to disclose.

Lindsey Mette, MS, MScPH, CGC discloses the following relationships with commercial companies:
• Invitae, paid Genetic Counseling Advisory Board member

At the end of this presentation the participant will be able to:

1. Know the spectrum of types of genetic abnormalities in childhood cancer
2. Understand the role of the cancer genetic counselor
3. Characterize the benefits and limitations of new genetic testing technologies

Knudson’s “Two-Hit” Model

Modified from Time, Oct. 27, 1986

Timeline of Cancer Gene Discovery

Modified from Time, Oct. 27, 1986
Hereditary Cancer Accounts for Only a Small Portion of All Cancers

The Cancer Family History is the Key to:
- Accurate risk assessment
- Effective genetic counseling
- Appropriate medical follow-up

Adult vs. Pediatric Tumors

Adult Cancer
- Carcinomas
- Increase with age
- DNA repair + environment
- Multiple acquired genetic hits

Pediatric Cancer
- “Blastomas”
- Occur within range
- Developmental factors
- Key acquired genetic events

What Makes a Family History Plausible for a Cancer Predisposition Syndrome?

Number of somatic mutations in representative human cancers, detected by genome-wide sequencing studies.

Hallmarks of a Cancer Syndrome
- Young age of onset
  - Age is relative
- Multiple generations affected
- Bilateral cancers/multiple primaries
- Similar cancer types within family
- Constellation of cancer types or known syndromes
  - Breast – sarcoma
  - Hepatoblastoma - colon
Cancer Predisposition Inheritance

Most inherited predispositions are autosomal dominant

Most de novo mutations are new to an individual but passed down to future generations in autosomal dominant fashion

Classification of Major Cancer Predisposition Genes

- **Autosomal dominant**
  - RB1, WT1, APC, RET, VHL, NF1, NF2
  - BRCA1, BRCA2, Pten, TP53, hSNF5/INI1
  - MLH1, MLH2, MSH6, PMS2

- **Autosomal recessive**
  - BLM, DIS3L2
  - also MLH1, MLH2, MSH6, PMS2

- **X-linked**
  - GPC3, XLP

- **Tumor Suppressor**
  - RB1, WT1, APC, VHL, NF1, NF2, Pten, TP53, GPC3, hSNF5/INI1

- **Dominant Oncogenes**
  - RET, HRAS

- **DNA Repair Genes** (most are tumor suppressors)
  - MLH1, MLH2, MSH6, PMS2
  - BRCA1, BRCA2
  - BLM, XP

Selected Childhood Hereditary Cancer Syndromes

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Which children are at high genetic risk of cancer?

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Retinoblastoma

The Paradigm of Cancer
Genetic Predisposition

Features of Retinoblastoma

• 1 in 20,000 children
• Most common eye tumor in children
• Occurs in heritable and non-heritable forms
• Genetic studies of retinoblastoma formed cornerstone of cancer genetics

Age of Onset Restricted to First 4 Years of Life

Normal growth and maturation of retina provide an “at-risk” period
Risk is enhanced in germline mutation carriers

Genetic Features of Heritable Retinoblastoma

• Autosomal dominant transmission
• RB1 gene on chr 13 (first tumor suppressor gene discovered)
• Penetrance >90%
• Prototype for Knudson’s “two-hit” hypothesis

The RB1 Gene

• Large gene spanning 27 exons, with hundreds of known mutations
• Mutations of every type have been reported
• Almost every family has unique mutation
• Occasional family with large deletion or rearrangement
**De novo Mutations in Heritable Retinoblastoma**

- 80% of germline RB1 mutations are de novo
- Mutations occur on paternally derived chromosome possibly related to spermatogenesis

**Long-Term Mortality of Children with Heritable Retinoblastoma**

- Early detection saves vision
- RB1 status guides medical management
- Prevention of secondary cancers
- Screening of at-risk sibling

**Benefits of Retinoblastoma Screening**

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**Clinical Features of Beckwith-Wiedemann Syndrome**

- Large tongue
- Umbilical hernia
- Generalized overgrowth
- Normalization of growth with age
Chromosome 11p15 Region: Beckwith-Wiedemann Syndrome

- Overgrowth syndrome
- Imprinting of genes involved
- Wilms tumor in ~5% of cases
- Other tumor risks: hepatoblastoma, adrenocortical carcinoma

Recognition of BWS

- Possible at birth based on physical features
- Clinical testing for imprinted genes possible, but not always helpful
- Referral for surveillance or screening
  - Enhances early detection for Wilms, HB, ACC
  - High cure rates
  - Less therapy

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Wilms Tumor and Overgrowth

- Beckwith-Wiedemann Syndrome
- Simpson-Golabi-Behmel Syndrome

Li-Fraumeni Family

Li-Fraumeni Syndrome

- Rare autosomal dominant syndrome
- Early onset of bone and soft tissue sarcomas, breast cancer, brain cancer, leukemia, adrenocortical carcinoma, and other tumors
- Multiple primary tumors
- TP53 germline mutations associated with most cases
- Testing in children and adults raises important psychosocial issues
### Li-Fraumeni Syndrome

- **“I just don’t want to know”**
- Died 37
- Breast, 40
- Breast, 36 (Desires clinical testing)
- Osteosarcoma, 9
- Adrenocortical carcinoma, 10
- Glioblastoma multiforme, 37
- Breast, 36
- 36
- 37
- 9
- 7

### Tumor Genetic Profiling

- Overcomes traditional pathological classification limitations by determining the level of gene expression within the tumor, identifies potential drug treatments, response to treatment, and outcomes.
- Individualized Cancer Therapy (iCAT) multi-center study
- 100 patients (<30y, median 13.4y) with advanced high-risk, recurrent, or refractory extracranial solid tumors
  - 31% received an iCAT recommendation
  - 3% received matched therapy
  - 11% had a somatic mutation indicating the possibility of a cancer predisposition syndrome

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### TP53 Testing in Families

- Many families with Li-Fraumeni syndrome decline testing
  - Issues in testing for TP53 status in LFS
    - Lack of effective interventions
      - However recent surveillance protocols introduced
    - Possible adverse psychological outcomes
    - Inability of minors to provide adequate informed consent

### The Role of Genomics


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......and many panels of genes

Whole Exome Sequencing

- Simultaneous scanning of >95% of exons in the genome
- First proven effective in identifying causal genetic variants in 2009
  • More than 150 genes have been characterized through WES
- First offered as a clinical test in 2011
  • Instrumental in identifying underlying causes of neurological, cardiovascular, and multiple congenital anomalies

National Comprehensive Cancer Network

- St. Jude's study: 120 cancer patients <20 years old (median 6.9y)
  • Tested 565 genes, including 60 associated with autosomal dominant cancer predisposition
  • 52.3% leukemia, 21.9% CNS tumor, 25.6% non-CNS solid tumor
- Findings
  • 8.5% of patients harbored a mutation in a cancer predisposition gene
  • 8.6% CNS tumors vs. 16.7% non-CNS solid tumors
  • 3.6% after removing TP53-enriched rare tumors
  • 40% of patients had family history documented in medical record
  • 57% had mutation consistent with reported family history

American College of Medical Genetics Recommended Secondary Findings List

- Mutations found in the 56 genes on the list should be reported by the laboratory regardless of the indication for testing
- It is the responsibility of the ordering clinician to provide comprehensive pre- and post-test counseling to the patients

- BRCA1/2, TP53, STK11, MSH1/MSH2/MSH6/PMS2, APC, MUTYH, VHL, MEN1, RET, PTEN, RB1, SDH5/SDH6/SDH7/SDH8, TSC1/2, WT1, NF2
- COL1A1, FBN1/FGFR3/FGFR4/SMAAD3/ACTA2, MYH6/MYH11, MYBPC3, MYHC, 7Q7, TM1, TM4, MYL3-Act1, PKAAG2, GBA, MYL2, LAMN, RYR2, PKD2, DSP, DSG2, TMEAS3, DG3, KCNN1, KCN2, CNSA, LDB1, APB2, PCSK9, RYR1, CACNA1A
WES in developmental disorders

- Findings of the first 2000 patients tested with WES at Baylor
  - Molecular diagnosis reported for 504 patients (25.2%)
    - Neurological subgroup = 36.1%
  - 4.6% had medically actionable incidental findings
  - 3% had an incidental finding from the ACMG list

WES in pediatric cancer

- 150 pediatric patients with solid tumors (median age 7.4y)
- Germline WES
  - 10% (n=15) pathogenic mutation(s) underlying the patient’s phenotype
    - 13 Autosomal dominant
      - 8 with a known childhood cancer predisposition gene
      - 3 had not been considered for testing by clinical care team
      - 5 with a mutation not predisposing to childhood cancer (i.e. BRCA2)
    - 1 autosomal recessive, 1 X-linked

Genetic Counselors

- Master’s degree trained allied health professional
- Certified by the American Board of Genetic Counselors
- Trained to provide patient education and assess psychosocial risk factors or considerations related to genetic testing

WES in pediatric cancer

- Germline WES, continued
  - 6% (n=10) with a single mutation in a gene associated with an autosomal recessive cancer syndrome
  - 5% (n=8) had incidental findings, including 5 genes on the ACMG list
- Tumor WES
  - 3% somatic mutation with established clinical utility
  - 24% somatic mutation with potential clinical utility
    - Only 11% previously detected by routine clinical molecular testing (i.e. BRAF V600E)

In combination, tumor & germline WES revealed potentially clinically relevant alterations in 39% of patients

The Role of Genetic Counseling

Genetic Counseling is Integral to the Testing Process
Why Refer to a Genetic Counselor

- 3-generation pedigree and family risk assessment can be lengthy
- Need to determine whether testing is reasonable
- Complex syndromes and differential diagnoses
- Genetic testing options are rapidly evolving, as is insurance coverage
- Counseling process typically takes 60 minutes, sometimes much longer

Family Health History

- Provides accurate risk assessment
- Allows providers to identify other cancer risks
- Identifies informative family members
- Enables recommendation for appropriate cancer risk management strategies
- Enables accurate interpretation of genetic test results
- Limitations
  - Self-reported
  - Small families
  - Early, non-cancer deaths in the family
  - Prophylactic surgeries
  - Lack of family health communication /estranged families
  - Non-paternity or adoption

Typical Cancer Genetic Counseling Session

- Obtain and assess personal and family medical history
- Assess patient's understanding, risk perception, and motivation for testing
- Discuss basic genetics, inheritance, cancer genetics and genetic risk
- Help patients understand the risks, benefits, and limitations of testing
- Explain testing and follow-up procedures
- Educate patient on testing alternatives
- Discuss possible management options
- Obtain insurance approval for testing

Testing Considerations

- Single gene test vs. panel
- Which lab to use
- Which technology
- Blood, saliva, or fibroblast?
- Cost of test
- Likelihood of reimbursement
- Patient specific factors (BMT, active chemo)
- Ability to interpret results

Ethical Considerations in Genetic Testing of Minors

- Age of consent/assent
- Parent's right to know vs. child's right not to know
- Differences between diagnostic, predictive, and predispositional testing

Always remember the family history
**General Guidelines of Testing Children for Cancer Predisposition**

- Test only when
  - Test can be adequately interpreted
  - Intervention available
  - Benefit in early detection
- Obtain age-appropriate
  - Involvement in counseling process
  - Consent / Assent

**Possible Results of Genetic Testing**

- **Positive**
  - Explains cancer in the family
  - Allows for cascade testing and identification of at-risk patients
- **Negative**
  - True negative
    - Patient's cancer risk is similar to general population
    - No additional screening or surveillance recommended
  - Uninformative negative
    - Negative result without ability to rule out possibility of hereditary cancer syndrome
    - Occurs when an unaffected family member is the first to test
  - Variant of uncertain significance
    - May be mutation or polymorphism
    - Modified screening or surveillance may be warranted
    - Testing unaffected family members not recommended

**Psychosocial Aspects of Genetic Counseling**

- Discuss the various result scenarios
- Why does the patient want/not want testing?
- How will the results be used?
- How will this information change the patient's life – better? Worse?
- How will the patient communicate these results with the family?
- Do other family members want this information?
- Risks to children, telling children, testing children

**Post-test Psychosocial Considerations**

- Anxiety about increased cancer risk
- Concern for family members
- Reaction from family members
- Survivor guilt
- Depression
- A negative result may not alleviate anxiety
- Worry that surveillance may not be offered
- Family planning

**Genetic Discrimination**

- **GINA (Genetic Information Non-Discrimination Act)**
  - Federal law in 2008 protecting discrimination in employment and health insurance based on genetic test results
  - Does not prevent discrimination in life or long-term disability insurance
- **Affordable Care Act**
  - Eliminates discrimination based on pre-existing conditions
Questions?