Nuances in Prenatal Carrier Screening

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Objectives – Carrier Screening

• Review available evidence:
  • Unique role: Women through all stages of life
  • Family history: Refer for counseling
  • Preconception/Prenatal
  • “Ethnicity” versus Universal – benefits & limitations
    • Hemoglobinopathies
    • Ashkenazi/Eastern European
    • Cystic Fibrosis
    • Fragile X
    • Spinal Muscular Atrophy
  • Basics of Carrier Screening

Successful Screening Program

• Disease
  • Considerable clinical severity
  • Frequency
• Test
  • Reliable
  • Timely
  • Cost effective/ relatively inexpensive
    • Afford carrier screen & prenatal diagnosis
• Appropriate counseling & education
  • Non-directive

Successful Screening Program

• Prevention
  • Forgo pregnancy
  • Adoption
  • Donor
  • IVF-PGD
  • Prenatal diagnosis with option of termination
• Additional benefit
  • Preparation
  • Education
  • Delivery at an appropriate institution
Geographic ancestry

- “Ethnicity” based
- Founder effect
  - Close proximity
    - Religious, geographical, political
    - In general, asymptomatic
  - Advantage
    - Sickle cell anemia
  - Does not apply to all single gene disorders
    - Tay Sachs vs. Spinal Muscular Atrophy (SMA)
  - Unique California population

Case

- 22 year old G1P0 Thai woman presents at 22 wks for routine prenatal care
- Do you offer her Hemoglobinopathy screening?
- If so, What tests?
- What if she described her ethnicity as
  - Southern Chinese, Middle Eastern, African?
  - Mixed?
  - Not sure?

Structure of hemoglobin

Beta globin genes

- b1
- b2

Alpha globin genes

- a1
- a2
- a3
- a4

Hemoglobin protein

Chromosome 11

Chromosome 16

Hemoglobinopathies – ACOG

- ACOG (2007)
  - African, SE Asian, Mediterranean (ACOG)
    - “higher risk” for hemoglobinopathies - offer screening
    - Hgb Electrophoresis/HPLC
    - CBC with MCV
  - Low risk
    - Northern European, Japanese, Native American, Inuit, Korean
**Hemoglobinopathies – Sickle Cell**

- Most common disorder: Hgb
  - β chain of hemoglobin
- Sub-Saharan descent
  - Carrier rate: 1 in 12
  - Advantage
- ~1 in 600 with SSA in US
- Diagnosis: Hgb Electrophoresis

**Hemoglobinopathies – Sickle cell**

- More comprehensive
  - African American, African, Mediterranean (Greek, Italian), Turkish, Arabic, Southern Iranian, Asian Indian, Brazilian, Central American
- Others?
  - Confirmed Hgb (α & β) abnormalities in CA by Newborn Screening
    - Asian (43%)
    - Black (27%)
    - Latin (3%)
    - Other/Unknown (27%)

**Thalassemias**

- β thalassemia
  - Southeast Asian, Pacific Islander, Middle Eastern, Indian, Chinese, Mediterranean, African (not African American)
  - Low MCV → Hgb Electrophoresis
- α thalassemia
  - Mediterranean (Italy, Greece), East Asian (China, Thailand), Middle Eastern (Turkey, Pakistan), Central Asia (West India), African American
  - Low MCV
    - No evidence of iron deficiency
    - Offer partner & patient molecular testing

**Hemoglobinopathies – Who?**

- Hemoglobin H (α – thalassemia)
- CA New born screening
  - Laotian/Thai (26%) Mixed Asian (7%)
  - Vietnamese (9%) Multiple race (16%)
  - Cambodian (5%) Other (7%)
  - Filipino (15%)
  - Chinese (15%)
Screen for Thalassemia?

- Mean corpuscular volume (MCV)
  - 80fL
  - Others suggest 85fL (Chan LC et al 2001)
    - Those at greatest risk
      - Southern Chinese, Thai/Lao
    - 80fL at UCSF

Case - continued

- 22 year old G1P0 Thai woman presents at 22 wks for routine prenatal care
- Thai – α thal, β thal
- Southern Chinese - α thal; (East Asia - β thal)
- Middle Eastern
  - α thal
  - β thal (Turkey, Pakistan)
  - SSA (Southern Iranian, Turkish, Arabic)
- African – SSA, α thal (Not African American),
- Mixed ethnicity/Not sure?
  - Consider Hgb electrophoresis, MCV

Case - 2

- 37 year old G1P0 woman of Eastern European descent, thinks Ashkenazi presents for preconception visit
- She wants information on carrier screening

Ashkenazi/East European

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<thead>
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<th>Detection rate</th>
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**Geographic Ancestry**

- Tay Sachs
  - Pennsylvania Dutch
  - Louisiana Cajun
  - French Canadian

**Case - 2**

- 37 year old G1P0 woman of Eastern European descent, she thinks Ashkenazi presents for preconception visit
- She wants information on carrier screening
  - ACOG – standard of care
  - ACMG - ? All nine
    - Refer for counseling?
    - Commercial company carrier screen?
      - >100 diseases, ~$350
Case- 3

- 29 year old G1P0 White woman presents at 12 weeks and is concerned about cystic fibrosis (CF)
  - Her husband is from Africa and neither have a personal or family history of CF.
  - Your patient’s carrier screening is negative.
    - ACMG 23 mutation panel reveals no mutations
    - Is this enough mutations?
    - What is their risk of having an affected child?
    - What if mother was a carrier?

ACMG/ACOG Guidelines (2005)

- CF testing should be offered to:
  - Individuals with a family history of CF
  - Partners of individuals with CF
  - Couples in whom one or both partners are Caucasian & who are currently planning a pregnancy or seeking prenatal care
  - Testing should be made available to couples who are of other ethnicities

ACMG/ACOG Guidelines (2005)

- Reality: 2/3 of all Ob/Gyn’s perform CF carrier testing on all of their patients, regardless of ethnicity
- Why?
  - Increasing difficulty in assigning one ethnicity
- Does test performance differ from one ethnicity to another?
  - Limitations based on geographic ancestry
  - Decreased sensitivity is acceptable if patient understands

CF screening

- CFTR gene
  - > 1300 mutations
- ACMG/ACOG recommendation:
  - 23 most common mutations
    - ‘Classic’ – severe disease
    - 0.1%
- DNA test
- Not sequencing
**CF Detection Rates by Mutation Analysis (ACMG 23 mutation panel)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Incid</th>
<th>Carrier</th>
<th>Detect</th>
<th>Risk After (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashkenazi</td>
<td>1/2300</td>
<td>1/24</td>
<td>94%</td>
<td>1/83,000</td>
</tr>
<tr>
<td>European</td>
<td>1/2500</td>
<td>1/25</td>
<td>88%</td>
<td>1/21,000</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1/13,500</td>
<td>1/46</td>
<td>57%</td>
<td>1/18,000</td>
</tr>
<tr>
<td>African-Am</td>
<td>1/15,100</td>
<td>1/62</td>
<td>69%</td>
<td>1/54,000</td>
</tr>
<tr>
<td>Asian-Am</td>
<td>1/35,100</td>
<td>1/90</td>
<td>~30%</td>
<td>1/75,000</td>
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**Case: Fetal risk?**

- **Patient:** Negative
  - Pre-test risk: 1/25-29
  - After negative test: ~1/208
- **Partner:** No test
  - Risk of partner carrier status: 1/62 (pretest)
- **Risk of affected fetus after mom’s (-) result:**
  - (Mom) $\frac{1}{2} \times 1/208 = 1$ in 103,000

**Fetal risk if Mom was POS?**

- **Patient:** (+) → Refer
  - Risk: 1/2
- **Partner:** (-)
  - Pretest risk: 1/62
  - After (-) test: 1/186
- **Risk of affected fetus:**
  - (MOM) $\frac{1}{2}$
  - (DAD) $\frac{1}{2} \times 1/186 = 1$ in 744

**Carrier Screening & Cystic Fibrosis**

- Mutation analyses may **reduce** but **do not eliminate** the chance of having an affected child
- Mutations tested are those most frequently detected in disease (>0.1%)
  - Frequencies of mutations vary in different ethnic/racial backgrounds
- Expanded panels – 23, 32, 35 (UCSF), 97 etc...
  - Know about your laboratory’s panel
Case 4

26 yo G1P0 at 10 weeks with a family history of a younger brother with cognitive disability who “looks different” than other family members. On further questioning her mother had early menopause.

- For which causes of cognitive deficiency is screening available?
- What is the risk to her fetus?
- What if her family history was negative?

Fragile X Syndrome

- Heritable cognitive and developmental disability
  - 1/3600 in males & 4,000-6000 females
- Males
  - 2nd most common form of cog impairment in males
  - Varies – borderline to severe
  - Behavior abnormalities, including autism
  - Anxiety, especially social anxiety
  - Unique cranio-facial characteristics
- Females
  - If affected, usually less severe
  - Premature ovarian failure
  - Cognitive abnormalities
  - Tremor ataxia

Fragile X – Who is at risk?

- Family h/o Fragile X or undiagnosed MR, autism
- Known maternal premutation or full mutation
- Women with h/o elevated FSH (<40 years) or ovarian failure of unknown etiology
- Family h/o premature ovarian failure, tremor/ataxia
- Women who request testing
- Those with intermediate alleles are not at risk of having an affected child

Fragile X Syndrome

- Fragile Site: Xp27.3
- Trinucleotide expansion (CGG)_n
  - Normal (<44)
  - Intermediate or “gray zone” (45-54)
  - Pre mutation (55-199)
  - Full mutation (>200)
- Meiosis expansion
  - 56 repeats lowest known expansion to affected

Known maternal premutation or full mutation

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Fragile X – Carrier Rate

Pre & Full mutation → Fetus at risk
- Low risk women (negative family history)
  - 1 in 113-549
- Suspicious family history
  - 1 in 83
- Family history of Fragile X
  - 1 in 4 (28.8%)
- History of premature ovarian failure
  - 1 in 10

Risk of Expansion to Full Mutation

<table>
<thead>
<tr>
<th>Category</th>
<th>(CGG)n</th>
<th>% to Full Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate</td>
<td>55-59</td>
<td>(3.7%)</td>
</tr>
<tr>
<td>Premutation</td>
<td>60-69</td>
<td>(5.3%)</td>
</tr>
<tr>
<td>&quot;&quot;</td>
<td>70-79</td>
<td>(31.1%)</td>
</tr>
<tr>
<td>&quot;&quot;</td>
<td>80-89</td>
<td>(57.8%)</td>
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<td>(80.1%)</td>
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<tr>
<td>&quot;&quot;</td>
<td>100-200</td>
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Fragile X – Universal Screening?

ACMG & ACOG: No population screening
- Complex inheritance
- Variation in phenotype in females
- Need for formal genetic counseling
  - Difficult to understand complexities of testing
- But...reliable testing, severe phenotype, presumed cost effectiveness, desirability
  - Thus, if formal counseling – offer Fra X?

Case 4

- 26 yo G1P0 at 18 weeks with a family history of a younger brother with mental retardation (MR) who “looks different” than other family members. On further questioning her mother had early menopause. The fetus is male on ultrasound

Frag X – CGG repeats 80, 23

- What causes of MR can we screen for?
- Is her fetus at risk?
- What if her family history was negative?
Case 5

- 32 yo woman at 16 weeks heard a story on the radio about spinal muscular atrophy and wants carrier screening. Family history is negative.

Should you offer testing?
How do you test?
Limitations of testing?

Spinal Muscular Atrophy (SMA)

- Autosomal recessive
- 2nd most common fatal AR disorder
- SMN1 (survival motor neuron) gene deletions
  - SMN2 may influence severity of SMA
  - Genetics complicated in 3-4%
- No features of SMA and two copies of SMA1 on one chromosome
  - Parents not identified as a carrier
  - 2% de novo deletion

Spinal Muscular Atrophy (SMA)

- Progressive muscle weakness and paralysis
  - α motor neurons
  - Type I (Werdnig-Hoffman) - most severe
    - Death prior to 2 years (respiratory failure)
  - Type II
  - Type III

Spinal Muscular Atrophy (SMA)

- Universal screening?
  - Disease is severe (in most cases)
  - Limited treatment available
  - Reliable testing
  - High pan ethnic carrier frequency (1 in 40-60)
Spinal Muscular Atrophy (SMA)

- ACMG vs. ACOG
- ACMG
  - Offer routine carrier screening
- ACOG
  - No routine screening
    - Limitations in prediction of SMA type w/o Fam Hx
    - No data on education, counseling, preferences, utility measurements, cost effectiveness
    - False negative rate

Carrier screening

- Geographic ancestry vs. Universal
  - Follow ACOG guidelines
  - Capable of screen for Hgb, CF, Ashkenazi
  - Educate – limitations of screening
  - Patient preferences
  - Admixture of your patient population
  - Refer when needed – family history
  - ?Fra X, SMA

Case 5

- 32 yo woman at 16 weeks heard a story on the radio about spinal muscular atrophy and wants carrier screening. Family history is negative

Should you offer testing? - ?refer

How do you test? – SMN1 carrier screening

Limitations of testing? – false positive

References

Ashkenazi Jewish/Eastern European


References

Hemoglobinopathies

Cystic Fibrosis

References

Spinal Muscular Atrophy

References

Fragile X