Genetic Carrier Identification in Newborn Screening

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Disclosures

• None to report
Outline

- Types of carrier states
- Uses of carrier information
- Impact of technologies on detection of carriers
- Implications for:
  - Policy
Carrier Types by Mode of Inheritance

- Autosomal recessive traits and SNV (e.g. CF)
- Autosomal dominant traits
- X-linked traits
  - Recessive
- Non-traditional
  - Germ-line mosaicism
  - Copy number and genetic phasing (e.g., SMA)
  - Repeated sequences (e.g. Fra(X))
  - Mitochondrial

- Some conditions bring a mix of these into consideration (e.g., SMA)
Autosomal Recessive Carriers in NBS (e.g., CF)

- Biochemically detected
  - Often not well discriminated from normal or affected
- Molecularly detected in NBS program
  - Second tier
    - CF
    - LSDs in some states; health care system in most
  - Issues
    - Variants of uncertain significance (VUS)
Autosomal Dominant

- Parent may be:
  - Penetrant (clinically affected)
  - Nonpenetrant (clinically unaffected)
  - New mutation (clinically unaffected)
- Examples (Huntington Disease, Neurofibromatosis, Familial Hypercholesterolemia)
X-linked Recessive (e.g., Fabry)

- Non-random X-chromosome inactivation may cause clinical phenotype
  - Often milder than in males
  - Examples (Fabry, X-linked Adrenoleukodystrophy)

- X-Linked Dominant Example (Ornithine transcarbamylase deficiency, OTC)
Nontraditional Carrier: Triplet Repeat Amplification (e.g., Fragile X)

• Premutations
  – Intermediate number of repeats that predispose to full amplification due to meiotic instability
    • May have nonclassical phenotype (e.g., Fragile X-Associated Tremor Ataxia Syndrome in older males)
      • 1 per 250 females; 1 per 800 males)

• Full mutations
  – Clinically affected (e.g., Fragile X Syndrome)
Nontraditional Carriers: Gene Copy Numbers and Phase (e.g., SMA)

- Due to repeat sequences in SMN1 and SMN2, there is possibility of gain or loss of a full gene copy on one of the two chromosome 5s
  - One chromosome may contain 2 copies of SMN1 while other chromosome has no copy
    - They have the right amount of the SMN1 protein but can pass the chromosome with no SMN1 gene
    - May go undetected in absence of long read sequencing that shows them to be in cis phase (on same chromosome) rather than trans (on different chromosomes)
  - Also causes variation in number of SMN2 genes (0-5)
  - Population variation with Hispanic carrier (2+0) rate ~1/100
Nontraditional Variation on Unaffected Carrier

- Somatic mosaicism
  - Present in some cell lineages but not all
    - Detectable in tests of lymphocyte or fibroblasts
    - Germ-line mosaicism
      - Cells with mutation in gonads only (i.e., germ line egg)
Uses of Carrier Information

• Clinical relevance to the individual
  – Varies with mode of inheritance and ability to distinguish carriers from normal or affected individuals

• Clinical relevance to family members
  – Cascade testing
    • The rarer the better
  – Reproductive decision-making

• NBS predicated on identifying infants with treatable conditions
  – Ethical dilemma: If not clinically relevant to individual, do we withhold incidental information or require someone to possess it.
When is Carrier Status Clinically Relevant to the Individual

• Autosomal recessives are usually without clinical impact though are often milder forms of disease

• X-linked recessives can have clinical implications for female carriers due to nonrandom X-chromosome inactivation; can be severe form

• Premutation repeat sequences and late-onset disease
Carriers and Conditions in Newborn Screening

• Sickle cell anemia
  – 8-10% of African Americans
  – Reporting of carrier state to providers and families recommended by CORN in 1989
  – Clinical considerations for carriers in high altitude and highly exertional exercise

• Cystic fibrosis
  – Reporting of 2nd tier molecular results to those with one clear pathogenic variant and VUSs that are reported for follow-up
    • Most VUSs get down classified to benign
  – Carrier rates and disease incidence vary by population origin

• X-linked adrenoleukodystrophy
  – 1 per 17,000 births with 20% of females with symptoms by adulthood
  – 1 per 21,000 newborn males
  – 1 per 14,000 newborn females are carriers

• Are mild forms of disease the target of NBS?
• Can the workforce digest the volume?
Policies that Impact Carrier Screening Result Reporting

- General recommendation to not test children unless test result is direct benefit to the child
- Most NBS programs report carrier status when detected with high PPV test but don’t include following up on autosomal recessives unless detected molecularly

Main Issues in NBS
- When to report only or report and follow-up?
  - Are some proportion of the ‘carriers’ clinically affected with early or late onset forms?
  - Is the disease in affected ‘carriers’ mild or severe and is it treatable by the same intervention used in severe forms?
Thanks