Genetic Carrier Identification in Newborn Screening

Michael Watson, PhD, FACMG

Executive Director

American College of Medical Genetics

Presented to the Advisory Committee on Heritable Disorders in Newborns and Children

November 8, 2017

ACMG

Disclosures

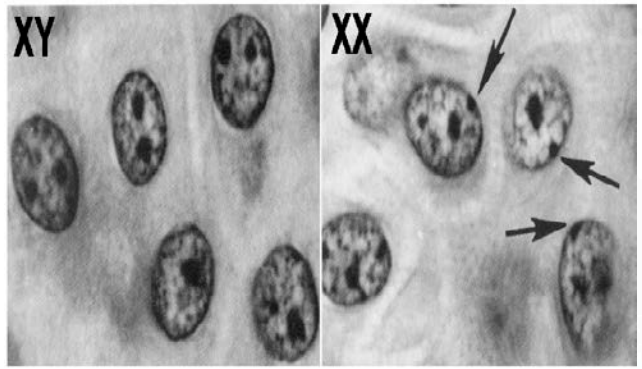
- None to report

Outline

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

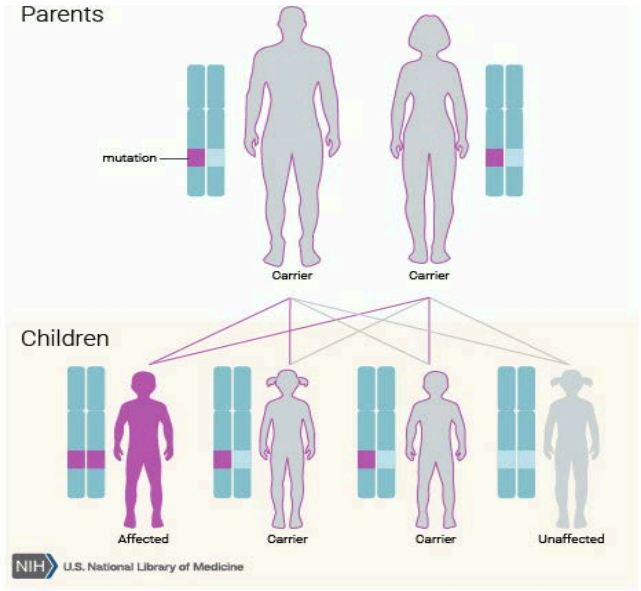
Carrier Types by Mode of Inheritance

- 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



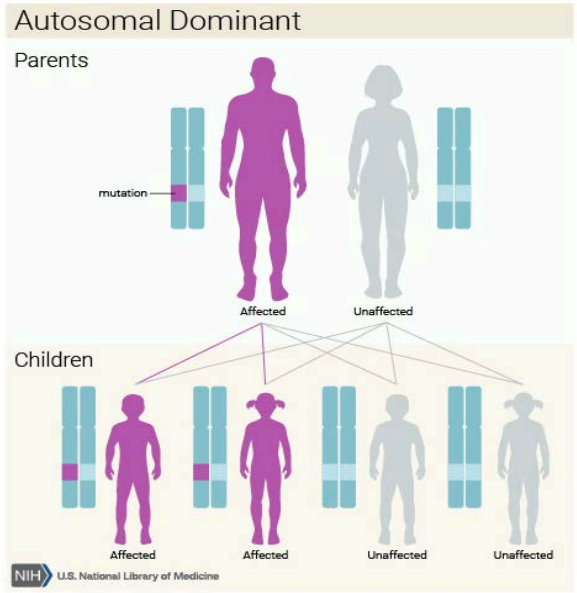
- Some conditions bring a mix of these into consideration (e.g., SMA)

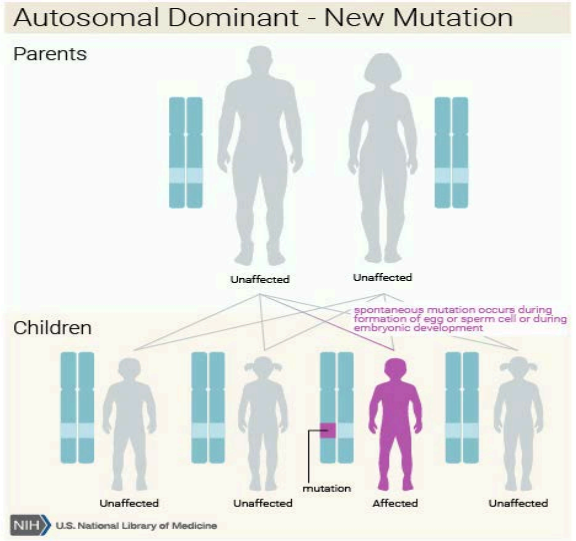
Autosomal Recessive Carriers in NBS (e.g., CF)



- 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

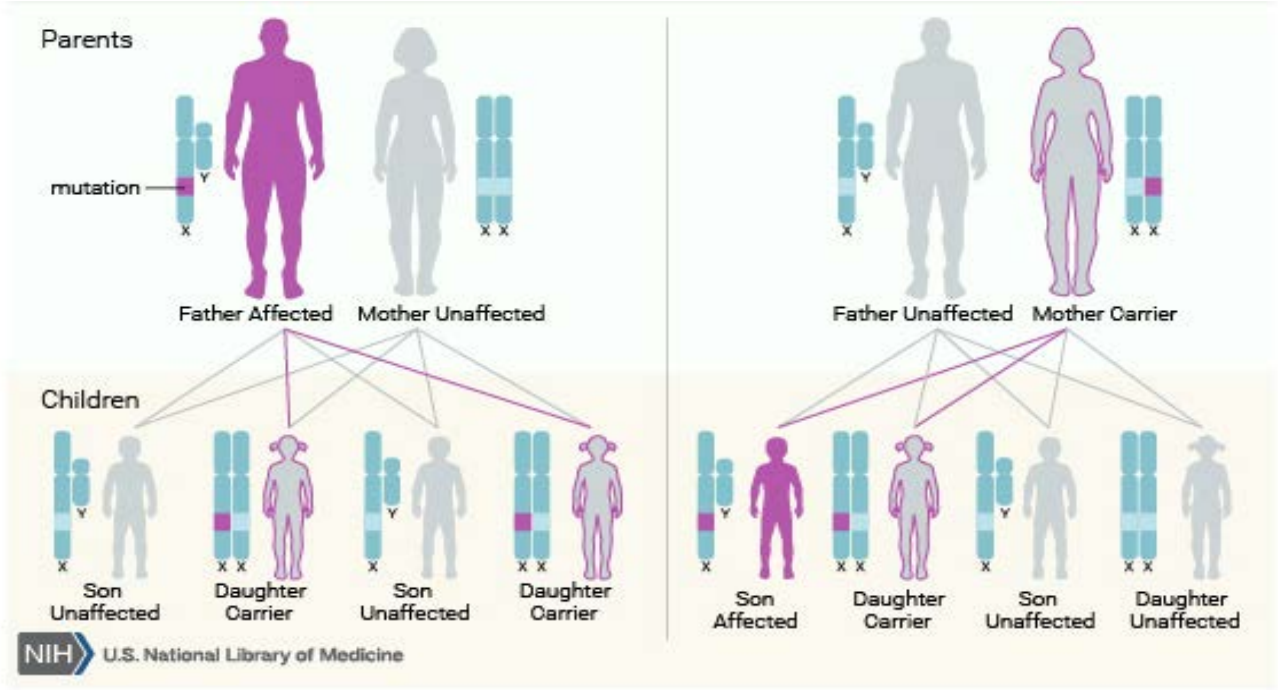




- Parent may be:
  - Penetrant (clinically affected)
  - Nonpenetrant (clinically unaffected)
  - New mutation (clinically unaffected)
- Examples (Huntington Disease, Neurofibromatosis, Familial Hypercholesterolemia)

ACMG

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)

ACMG

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?**

ACMG

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