Background

• The ongoing development of new genetic technologies has shed light on genetic variations associated with intellectual disability
• Our knowledge about the clinical implications of these genetic variations is constantly evolving
• The case of Fragile X Associated Disorders (FXAD) highlights complexities of genetic screening for intellectual disability

Fragile X Newborn Screening

• In 2005, FXS considered and rejected for inclusion in uniform newborn screening panel
• Low refusal rate if the screening is “opt out” as opposed to “voluntary”
• Pilot programs for Fragile X NBS underway

Should we screen newborns for FXS?

Traditional Newborn Screening Criteria:
- Diagnosis of condition for which screening should directly benefit the individual being tested
- Reducing morbidity and/or mortality

Who benefits from Newborn Screening for FXS?
- Newborns do not directly benefit
- No specific treatment or cure for FXS
- They can receive therapies without diagnosis based on developmental delays
- Parents benefit
- Enhanced future reproductive decision-making
- Family benefit
- Avoid diagnostic odyssey
- Societal benefit
- Scientific knowledge (ie, Natural history)

Does not meet traditional NBS criteria since the individual being screened do not directly benefit
- Proponents support notion that expanded benefit (ie, to family and society) sufficient to warrant population screening

An Ideal FMR-1 NBS program would ...

Be Mandatory or Voluntary?
- Mandatory: Acceptable if benefits outweigh risks
- Voluntary: Reasons why “reasonable” people would not want to
- Increase anxiety
- Results reveal potential risks of adult-onset FXAD for parents and other relatives

Screen for full mutation only or both full and premutations?
- Full mutation: Focuses only on genetic conditions that present in childhood
- Premutation: reveals increased risk of adult-onset conditions
  - May be useful for family cascade testing, though ethically debatable
  - Predictive genetic testing in childhood-not supported by many professional organizations

Screen males only or both genders?
- Males only: Virtually all males with FM are affected and could benefit; additional cost to separate samples
- Both Genders: 2/3 of females with FM will have some disabling consequences (genetic screening), however, 1/3 of females with FM will be normal, but labeled with FXS from birth which could inadvertently limit expectations

Discussion

Although FXAD do not meet traditional public health screening criteria, pilot programs are underway because a broader definition of benefits has been adopted and the screening technology exists. Based on stakeholder preferences, an ideal FXS NBS program would be voluntary, universally offered and able to identify both FMR-1 FM and PM; that is identify newborns at risk for FXS as well as adult-onset FXAD, FXPOI and FXTAS. Screening children for adult onset disorders is prohibited by many professional guidelines because of concerns of the child’s future privacy and confidentiality. Follow-up studies are necessary to understand the long-term psychological impact on individuals and families of learning this type of information in childhood.

NBS for FXAD is additionally complicated by complex genetic presentation. Mutations in a single gene lead to 3 distinct conditions. Even when the genotype is confirmed, there is uncertainty to develop the condition. As technology continues to evolve, in Down Syndrome and Alzheimer disease (APOE e4), ApoE genotyping will be increasingly recognized. Professional and patient education will be integral to any population screening program to ensure consent is informed and genetic counseling is effective and accurate for all families whose children screen positive.

Stakeholder Opinions

TABLE 1: Support for FXS NBS

<table>
<thead>
<tr>
<th>Genetic Health Professionals (GHP)</th>
<th>Mandatory</th>
<th>Voluntary</th>
</tr>
</thead>
<tbody>
<tr>
<td>25%</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>Developmental Behavioral Pediatrics (DBP)</td>
<td>35%</td>
<td>65%</td>
</tr>
<tr>
<td>Genetic counselors (GC)</td>
<td>20%</td>
<td>80%</td>
</tr>
<tr>
<td>Pediatricians*</td>
<td>31%</td>
<td>69%</td>
</tr>
<tr>
<td>of those supported universal NBS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TABLE 2: What FMR-1 mutation should FXS NBS identify?

<table>
<thead>
<tr>
<th>Males</th>
<th>Female</th>
<th>Both Genders</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM Only</td>
<td>PM and FM</td>
<td>Unsure</td>
</tr>
<tr>
<td>65%</td>
<td>27%</td>
<td>N/A</td>
</tr>
</tbody>
</table>

TABLE 3: What genders should FXS NBS screen?

<table>
<thead>
<tr>
<th>Males</th>
<th>Female</th>
<th>Both Genders</th>
</tr>
</thead>
<tbody>
<tr>
<td>91%</td>
<td>89%</td>
<td>N/A</td>
</tr>
</tbody>
</table>

According to stakeholders’ preferences, an ideal Fragile X NBS program would be: 1) Universally offered, 2) Require parental consent, 3) Screen both male and female infants and 4) Screen for both FM and PM

References


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