The Genetics of FASD: Accelerating Research Advances

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Presenter Disclosure

• Tatiana Foroud, Ph.D.
• No relationships with commercial interests
• No sources of bias or conflicts of interest
Objectives

1. Describe how genetics may play a role in the risk for FASD

2. Integrate online research opportunities for families with FASD
Why do some individuals develop FASD and other do not – even though there is similar prenatal alcohol exposure?

• What factors might be important?
  – Environment in and around the mother?
    • Example: microbiota
  – Genetics in the mother or the fetus
    • Example: DNA, epigenetics
How could genetics be important in FASD?

- Everyone’s DNA is slightly different
- There may be some DNA changes that make some individuals more susceptible to the effects of alcohol exposure \textit{in utero}
Collaborative Initiative on Fetal Alcohol Spectrum Disorders

• Multidisciplinary approach to study human FASD
  – Dysmorphology evaluation
  – Neuropsychological assessment
  – Facial image
  – MRI
  – Demographic information
Genetic Analysis Sample

- All subjects had prenatal alcohol exposure
- Classified based on dysmorphology evaluation

<table>
<thead>
<tr>
<th>Dysmorphology</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAS</td>
<td>46</td>
</tr>
<tr>
<td>No FAS</td>
<td>66</td>
</tr>
</tbody>
</table>

- Initial Analysis: Compared FAS to No FAS
DNA Whole Exome Sequencing

Exons are the coding region of a gene. Changes in the DNA sequence of an exon can change how the resulting protein works.
Analysis Strategy

All with prenatal alcohol exposure

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PROTECTIVE EFFECT:
Individuals who do not develop FAS carry certain variants

RISK EFFECT:
Individuals who develop FAS carry certain variants
Genetic Analysis Results
Top hit: mTOR pathway

- CRIPAK
  - p=4.50x10^{-7}

- Let’s unpack what underlies the association...
CRIPAK: Cystine-Rich PAK1 Inhibitor

<table>
<thead>
<tr>
<th></th>
<th>FAS</th>
<th>No FAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene Carrier (GC)</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Non Gene Carrier (NonGC)</td>
<td>23</td>
<td>66</td>
</tr>
</tbody>
</table>

p=4.50x10^{-7}

- Individuals without FAS do NOT carry these variant in CRIPAK
- Only individuals with FAS carry these variants in CRIPAK
  - Variants increase risk of FAS
Gene carriers (GC) had reduced hippocampal volume (p=0.0013)

# GC = 10
# nonGC = 91
Gene carriers (GC) made more errors on a spatial working memory task (p=0.025)

# GC = 22
# nonGC = 175
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Model organisms

In vitro studies

mTOR

Human studies
**KIF2A: Kinesin Family Member 2A Cilia Pathway**

<table>
<thead>
<tr>
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<th>FAS</th>
<th>No FAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene Carrier (GC)</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>Non Gene Carrier (NonGC)</td>
<td>45</td>
<td>53</td>
</tr>
</tbody>
</table>

$p=2.91 \times 10^{-4}$

- Only 1 individual *with* FAS carries these variants in *KIF2A*
- 13 or 14 individuals *without* FAS carry these variants in *KIF2A*
  - Variants *decrease* risk of FAS (protective)
Gene carriers (GC) had significantly increased caudate volume (p=0.007)

# GC = 19
# nonGC = 82
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Model organisms

In vitro studies

cilia

Human studies
Challenges

Genetic studies require large samples sizes to identify robust, reproducible results
A web portal with a novel, online consenting process to create a large cohort

Web Portal (https://digfasd.org)
DiG FASD: Inclusion Criteria

• Children and adults
• History of known or suspected prenatal alcohol exposure
• Internet access
• Digital camera / smartphone / tablet
• Willing to provide saliva
• English speaking
Why develop an online cohort?

• Allows many more eligible participants and families to participate in research
• Allows us to understand why some individuals with prenatal alcohol exposure develop FASD while others do not
• Allows larger studies to be undertaken
• Creates opportunities for online interventions
• Creates opportunities for involvement with other studies
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Data Available

• Researchers can apply for data collected as part of the CIFASD Consortium
  – [https://cifasd.org/resources/informatics-core-resources/](https://cifasd.org/resources/informatics-core-resources/)