Females who carry an FMR1 premutation: Can research make a difference?

Claudine Kraan
For females who have an FMR1 PM this can be a confusing time

- Early menopause/hormonal changes/osteoporosis
- Healthy ageing
- Medical conditions (e.g. migraine, autoimmune disorder, thyroid disorders, hypertension, neuropathy, fibromyalgia, sleep apnoea).
- Difficulties with mathematics/inattention
- Psychological problems (e.g. social anxiety & depression)
- Increased stress

?  

- You might read this and think...’well that doesn’t sound like me!’
  This can be extremely frustrating
- Your GP or psychologist may not understand
- You may be told that you cannot have symptoms outside of FXPOI and FXTAS
Feeling uninformed
“Well I can’t say that I fully understand it enough to even be able to explain it to others”

“We thought she was really hot, and we bought her extra fans”

Different priorities
“I don’t make myself a priority because I’m always worried about everybody else and it’s not until something starts to happen to me that I think, oh maybe it’s something I should get checked out”

Negative experiences with healthcare providers
“Most doctors thought, ‘Oh you’re just fine’...so it took a couple of doctors to actually get that. Cause I was 25 when I went through, um, menopause”

(Espinol et al., 2015, J Genet Couns)
Our research program is aimed at improving current diagnostics and opening up new avenues for intervention and treatment of fragile X-associated disorders in females.

Cognitive neuroscience, psychiatry and neuroimaging (Monash University, UNSW)

Molecular biology, genetics and epigenetics (MCRI, VCGS and Cyto-molecular Diagnostics and Research Group)

Genetics Education and Health Research

Statistics

Darren H, Nellie Georgiou-Karistianis & John Bradshaw

Erin, Chriselle and Belinda
Our overarching goal is to generate research that will lead to tailored medical and psychiatric care for female carriers affected by fragile X-associated disorders.
Female carriers of the FMR1 premutation

WHY IS THIS RESEARCH IMPORTANT?

- ~1 in 150 females are estimated to be FMR1 premutation carriers (Seltzer et al., 2012, Am J Med Genet B)

- Up to 40% of all female carriers will show symptoms of psychiatric disorders

- About 8-16% will go on to develop problems related to healthy ageing

- There are other things that we don’t really understand. For example, reports indicate that some female carriers will have difficulty with motor coordination, mild difficulties with mathematics, problems with visuospatial processing & poor attentional control
Research into executive function

Executive function is an umbrella term that is used to describe inter-related cognitive processes that guide and monitor goal directed behaviour.
## Tests of executive function

### Working memory

The Letter Number Sequencing (LNS) test is designed to assess the ability to temporarily store and manipulate information.

**Example**

<table>
<thead>
<tr>
<th>Stimuli</th>
<th>Correct answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>F-7-L</td>
<td>7-F-L</td>
</tr>
<tr>
<td>T-9-A-3</td>
<td>3-9-A-T</td>
</tr>
<tr>
<td>8-D-6-G-1</td>
<td>1-6-8-D-G</td>
</tr>
</tbody>
</table>

**PM carriers performed the same as age- and IQ-matched controls**

### Response inhibition

The Hayling sentence completion task is based on the principle that you must selectively inhibit the more automatic response of correctly completing an unfinished sentence.

Most cats see very well at...........

pen (correct)

A error = night (wrong)
B error = dogs (semantically related)

**PM carriers performed much worse than age- and IQ-matched controls**
### Tests of executive function

#### Working memory

*Start a sentence...then forget what you were going to say....?*

*Forgot why you entered a certain room?*

**What can you do?**

- Strategies: Visualisation, word association, connect emotion or your senses, practice practice practice, write things down, pay attention

- **LOOK AFTER YOURSELF:** physical exercise, mental activity, good sleep, good diet.

#### Response inhibition

*Accidentally say the wrong thing at the wrong time (foot in mouth?!)*

*Impulsive? Or, can’t stop behaviour?*

**What can you do?**

- Relaxation, practice holding things back, learn to control your attention

- Therapy: Cognitive behavioural therapy? Find out if it is linked to something else, like OCD or ADHD

- Training: Some might say that brain training could also help..but the jury is still out (e.g. luminosity)

- **LOOK AFTER YOURSELF**
Research into psychiatric symptoms

Main focus
Social phobia
Depression

Highlighted by other studies
Generalised anxiety
ADHD
OCD
Bipolar disorder

“I WISH YOU HAD COME IN TO SEE ME SOONER: BEFORE YOUR PHOBUA STARTED RUNNING WILD”
Research into psychiatric symptoms

<table>
<thead>
<tr>
<th>Activity</th>
<th>PM</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>From questionnaire</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADHD-PI highly probable</td>
<td>25.7%</td>
<td>8.6%</td>
</tr>
<tr>
<td>Social anxiety highly probable</td>
<td>34.3%</td>
<td>11.4%</td>
</tr>
<tr>
<td>Depression highly probable</td>
<td>14.3%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Lifetime diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADHD-PI</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Social anxiety</td>
<td>31.4%</td>
<td>22.9%</td>
</tr>
<tr>
<td>Depression</td>
<td>37.1%</td>
<td>25.7%</td>
</tr>
</tbody>
</table>

(Kraan et al., 2013, Am J M Gen)

*35 females in each group*
## Research into how psychiatric symptoms relate to executive function

<table>
<thead>
<tr>
<th></th>
<th>Social anxiety</th>
<th>Depression</th>
<th>ADHD-PI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response Inhibition</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>58.3%</td>
<td>80.0%</td>
<td>55.6%</td>
</tr>
<tr>
<td>Average</td>
<td>41.7%</td>
<td>20.0%</td>
<td>44.4%</td>
</tr>
<tr>
<td>Excellent</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Working memory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>100%</td>
<td>50%</td>
<td>83.3%</td>
</tr>
<tr>
<td>Average</td>
<td>27.3%</td>
<td>9.1%</td>
<td>18.2%</td>
</tr>
<tr>
<td>Excellent</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

(Kraan et al., 2013, Am J M Gen)
Abnormal methylation of the FREE2 region was correlated with social anxiety, depression and problems in executive function.

So... can we use a simple blood or cheek swab test to find out who is most likely to have these problems?

Well, maybe. But first we need to validate our findings in another sample.

(Cornish et al., 2015, Neurology)
What else are we up to?

General health and well-being in women with an altered fragile X gene (i.e., fragile X carriers)

This online questionnaire study is part of Tahlia Pavalino’s psychology honors research project at Monash University, supervised by Claudine Kranz and Kim Cornish.

This research project will look at some common health issues that can be strongly associated with being a carrier of Fragile X.

The results of this study will be used to help women and their families as well as inform clinical professionals to provide more personalized treatment options for women.

This is an anonymous questionnaire and no identifying information will be collected.

The project will run from May 2015 until October 2015. The questionnaire will be open until August 2015.

If you would like more information about this research project please download a copy of the information and consent form or contact Tahlia Pavalino or Claudine Kranz.

Total of 17 women with useable data.

184 completed questionnaires.

We have data on all sorts of medical issues, social anxiety, depression level and family dynamics. There are plans to expand the age range in future investigations.

Looking at relationship to the gene, behaviour and age of menopause.

BIG THANK YOU !!!
Where are we headed?

- Longitudinal follow-up
- Validation
- Looking into ways to help those that are affected (e.g., brain training and/or cognitive behavioural therapy)
- Medication or not? Does level of FMR1 methylation matter for how well the treatment works?
- Looking at movement and how it relates to the FMR1 gene. Knowledge of these relationships will help us to understand FXTAS found more commonly in older males
- Contribute to national policy and practice (when we have enough data)
Acknowledgments

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Hunter genetics

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Female carriers and controls that
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Thank You!

Any Questions?