Xpansion Interpreter®

Fragile X *FMR1* Gene: Impact of AGG Interruptions on CGG Repeat Expansion

Xpansion Interpreter® is the first clinically available laboratory-developed *FMR1* test to determine the total number of CGG repeats and number of AGG interruptions. These AGG insertions "interrupt" the unstable CGG sequence and provide additional insight into how likely select premutation carriers are of having a child with fragile X syndrome (FXS). FXS affects approximately 1 in 3,600 – 4,000 males and 1 in 4,000 – 6,000 females worldwide and is the most common inherited cause of intellectual disability and autism.

CATEGORIES OF FRAGILE X MUTATIONS

CATEGORY	NUMBER OF REPEATS	CLINICAL FEATURES
Normal	<45	• Normal • Offspring have normal-size gene region
Intermediate/ Gray zone (unaffected)	45-54	• Normal • Not at risk for passing a full mutation to next generation • **Possible candidate for Xpansion Interpreter**
Premutation (carrier)	55-200	• Typically intellectually normal • Females at risk for having children with fragile X syndrome • **Strong candidate for Xpansion Interpreter (55-90 repeat range)**
Full mutation	>200	• >99% males and most females have clinical features of fragile X syndrome

WHO TO TEST

Use the criteria below to identify patients who may be appropriate for testing with Xpansion Interpreter.

- Known intermediate and premutation fragile X carriers (45-90 CGG repeats)
- Family history of fragile X or fragile X-related disorders[1]
- Family history of unexplained intellectual disability, developmental delay or autism
- Personal or family history of female infertility
- Relevant fragile X-related disorders include fragile X-associated primary ovarian insufficiency (FXPOI) and fragile X-associated tremor/ataxia syndrome (FXTAS)

Asuragen®

TESTING SERVICE

Asuragen's Xpansion Interpreter® testing service employs three different PCR reactions for each DNA sample. Capillary electrophoresis (CE) of the products of one PCR reaction, called repeat-primed PCR, examines this distribution to allow accurate determination of total repeat size. Characteristic signal "dips" occur at the site of AGG interruptions. Additional information is needed to determine the exact locations of the AGGs in females because the presence of two alleles creates interpretation challenges. Two additional PCR reactions allow resolution of the AGG position and number in females. Through specialized training to interpret the results from all three PCR reactions, the Asuragen CLIA laboratory staff that run Xpansion Interpreter are able to definitively determine the location of the AGG interruptions within CGG repetitive sequences.

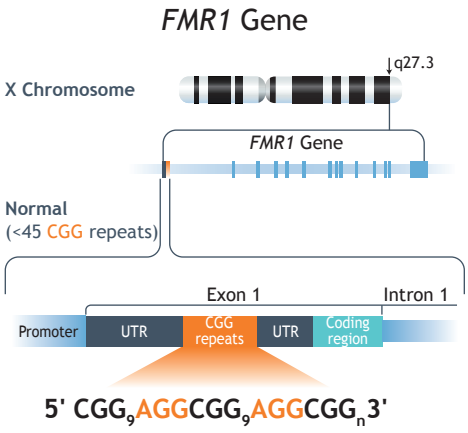

Figure 1. Diagram of *FMR1* gene and AGG locations.

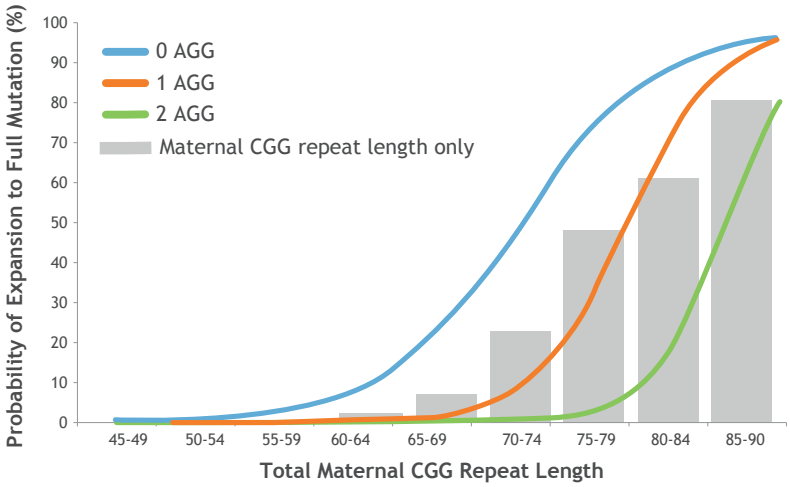

Figure 2. Impact of AGG interruptions on risk of expansion to full mutation.

Determining the number of AGG interruptions provides a more accurate assessment risk of CGG expansion within the FMR1 gene. The graph to the left represents 876 mother-to-offspring transmissions and illustrates the probability of expansion to a fragile X full mutation in the next generation based on the total number of maternal CGG repeats alone (grey bars) or the number of AGG interruptions present (colored lines). The data are taken from published results (Nolin *et al.*, 2013 and Nolin *et al.*, 2014).

CONTACT US

Xpansion Interpreter (AGG interruption testing) is provided as a service to specific carrier screening laboratories throughout the United States. If you would like information on how to obtain XI, please contact us: 1.877.772.8018 • clinicallabsupport@asuragen.com

Do not send CONFIDENTIAL Patient and Protected Health Information to this email address. Please send all Patient and Protected Health Information to Asuragen via fax at 1.512.681.5205 or call Asuragen Client Services at 1.877.772.8018.

PUBLICATIONS AND RESOURCES

For more information and published articles please visit:
asuragen.com/portfolio/genetics/xpansion-interpreter/

Asuragen®

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Xpansion Interpreter® is a Laboratory Developed Test (LDT). The analytical and clinical performance characteristics have not been reviewed or approved by the U.S. FDA.

[1]Monaghan et al. ACMG Standards and Guidelines for fragile X testing: a revision to the disease-specific supplements to the Standards and Guidelines for Clinical Genetics Laboratories of the American College of Medical Genetics and Genomics. Genet Med. 2013 doi:10.1038/gim.2013.61.

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