GENETIC TESTING RESULTS

Fragile X Syndrome Testing

bionano laboratories

Patient Name: SAMPLE	**Provider Name:** SAMPLE	**Sample Type:** Buccal
Patient Date of Birth: SAMPLE	**Provider Phone:** SAMPLE	**Sample Collected:** SAMPLE
Patient Sex: SAMPLE	**Provider Fax:** SAMPLE	**Sample Received:** SAMPLE
Patient ICD-10 code(s): R62.5	**Provider Institution:** SAMPLE	**Order Date:** SAMPLE
Accession Number: SAMPLE		**Report Date:** SAMPLE

Test Result Summary: Full mutation

The fragile X syndrome testing revealed a full mutation allele in the *FMR1* gene.

CGG Repeats: >200 (full expansion; a CGG repeat expansion within the *FMR1* gene was detected)

Clinical Interpretation and Discussion

These results are clinically significant. Over 200 repeats were found in one copy of the *FMR1* gene. Follow up methylation studies are recommended.

Fragile X syndrome is a genetic disorder affecting approximately one in 5,000 male births and one in 10,000 female births (PMID: 20301558). It is the most common inherited cause of intellectual disability and autism spectrum disorder (ASD).

Fragile X syndrome is characterized by a constellation of neurocognitive disorders, physical symptoms, and other medical concerns (PMIDs: 20301558, 28960184, 28617938, 28617074, 20396595, 27672537, 17497108). Typically, symptoms are more significant in males than females and include:

- Variable degrees of intellectual disability, with males typically in the moderate-to-severe range, while females are usually in the mild-to-moderate range.
- Behavioral symptoms such as ASD, anxiety, distractibility, attention deficit hyperactivity disorder (ADHD), and sensory processing and integration issues may be seen.
- People with fragile X syndrome have a higher risk for seizures, heart conditions, gastroesophageal reflux disease, otitis media, sleep difficulties, strabismus, and toileting problems.
- Variable physical symptoms such as loose joints, hypotonia, macrocephaly, and specific facial characteristics may be apparent.

When a diagnosis of fragile X syndrome is made, testing can be considered for at-risk maternal relatives. This is important for determining recurrence risk and other related health risks such as fragile X-associated tremor ataxia syndrome (FXTAS), fragile X-associated primary ovarian insufficiency (FXPOI) or fragile X-associated neuropsychiatric disorder (FXAND; PMIDs: 33443313, 30483160, 20301558).

Healthcare supervision guidelines and expert opinion statements are available for individuals with fragile X

syndrome (PMIDs: 21518720, 27672537). An evaluation by a medical geneticist is recommended to discuss this result and determine if additional assessments would be useful.

Methylation analysis of the *FMR1* gene was not completed on the submitted sample. It is expected that the presence of a full mutation CGG repeat results in methylation of the *FMR1* gene, which renders it non-functional. To confirm the methylation status and the diagnosis of fragile X syndrome, follow up methylation analysis may be considered (PMIDs: 33998336, 10331602). Please call a Bionano Laboratories genetic counselor at 801-931-6191 to discuss the sample requirements and testing process for methylation analysis.

References

For more information about the *FMR1* gene or fragile X syndrome, please see the Online Mendelian Inheritance in Man (OMIM) database: http://www.omim.org

The references in this report can be found by searching the PubMed IDs (PMID) from the PubMed home page: http://www.ncbi.nlm.nih.gov/pubmed/

For more information on how to use PubMed, see the following tutorial: http://www.nlm.nih.gov/bsd/disted/pubmedtutorial/cover.html

Genetic Counseling and Family Resources

This genetic test looked at genetic variations that lead to a specific genetic condition, fragile X syndrome. The specific genetic variation that causes fragile X syndrome is called a triplet or trinucleotide repeat expansion in the *FMR1* gene. The *FMR1* gene contains a tract of DNA bases where the base pairs C-G-G (a triplet) are repeated. It is normal for a person to have from 5-54 of these triplet repeats. Higher numbers of CGG repeats lead to developmental challenges or medical problems.

Bionano Laboratories genetic counselors are available by phone to speak with providers or the family about this test result. You can schedule a time to speak with a Bionano Laboratories genetic counselor by calling 801-931-6191.

A genetic counselor can help review what these results mean for an individual and family members, background on genetics, and discuss additional resources or next steps that may be helpful. Additionally, the genetic counselor may review medical, developmental, and family history of the person tested. This will help the genetic counselor better answer questions about how a specific result may impact the family.

To best prepare for a genetic counseling session, it may be helpful for a family to create a list of questions. Additionally, it may help to review some information on fragile X syndrome or background on basic genetic concepts. The following resources are a good place to start for information about a variety of genetic topics:

This document provides information on genetic variants affecting the *FMR1* gene: http://Bionano Laboratories.box.com/FRX-images

MedlinePlus: This website can be used to find information about genetic topics, genes, specific genetic conditions, and broad topics like autism spectrum disorder. It also provides links to other websites for more in-depth information about genetic conditions, patient support and advocacy resources, and relevant clinical trials. https://medlineplus.gov/genetics

National Fragile X Foundation
http://www.fragilex.org

Fragile X Research and Treatment Center
This clinic has a wide variety of ongoing research studies involving fragile X syndrome and FXTAS.
http://www.ucdmc.ucdavis.edu/mindinstitute/research/fragilex/index.html

FRAXA Research Foundation
http://www.fraxa.org

Methodology & Limitations

FMR1 CGG repeat size was assessed using AmplideX PCR/CE FMR1 Reagents (kit#49402 Asuragen, Austin, TX). All results are reported in reference to Human Genome 19, Human Build 37. Clinical Comments: Fragile X syndrome is caused by an expansion of a CGG repeat in the *FMR1* gene located on chromosome Xq27.3 in 99% of cases. Specifically, the expanded CGG repeats lead to methylation and lack of FMR1 protein. There are rare *FMR1* mutations including missense mutations and gene deletions which also cause fragile X syndrome. Interpretation of the CGG repeat is based on the following:

Number of CGG Repeats	Interpretation
5-44 (unmethylated)	Normal
45-54 (unmethylated)	Grey Zone/Intermediate
55-199 (unmethylated)	Premutation
200 and up (methylated)	Full mutation

Variability of CGG repeats: Reported CGG repeat sizes may vary by +/- 1 for repeats less than 60, by +/- 2-4 for repeats from 60-120, and by +/- 10 for repeats over 120. Individuals with a full expansion will show a range of repeat sizes. This interpretation is based on the clinical and family relationships provided and the current understanding of fragile X syndrome. Genetic counseling is recommended to fully understand these test results.

Assay method and limitations: The analytical sensitivity is >99%. False positive or negative results are rare, but can happen due to low level mosaicism, rare genetic variants, or primer site mismatches. Methylation testing is recommended if CGG repeats are >75.
References: Hagerman RJ et al. *Mol Autism*. 2010; 1:12; Chen L et al. *Genet Med*. 2011; 3:528-38; Filipovic Sadic et al. *Clin Chem*. 2010; 56:399-408; Chen L et al. *J Mol Diagn*. 2010; 12:589–600; Sherman S et al. *Genet Med*. 2005; 7:584-87.

Disclaimer: This test and its performance characteristics were determined by Gene by Gene, a CAP accredited (CAP Number 7212851) and CLIA certified Clinical Laboratory located at 1445 North Loop West, Suite 820 Houston, TX 77008. The U.S. Food and Drug Administration (FDA) has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use. The results are not intended to be used as the sole means for clinical diagnosis or patient management decisions.

Gene by Gene, Ltd. is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high complexity clinical laboratory testing (CLIA# 45D1102202). Gene by Gene CLIA Laboratory Director: Rachel L. Beddard M.D.

Lineagen, Inc.'s (DBA Bionano Laboratories) CMA interpretation and reporting service is certified under CLIA (CLIA# 46D2042721).
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