Genetic Testing ACT Sheet
Fragile X [FraX] Syndrome

Condition Description: Abnormalities of the fragile X mental retardation (*FMR-1*) gene cause three distinct conditions: Fragile X Syndrome (mental retardation with or without autism/autism spectrum disorder); premature ovarian failure (POF); and Fragile X-associated Tremor Ataxia Syndrome (FXTAS).

Major Indications for Ordering Fragile X Testing: Fragile X testing may be considered in males and females with mental retardation and autism or autism spectrum disorder, females with premature ovarian failure, and older males with progressive development of intention tremor and ataxia with or without dementia.

YOU SHOULD TAKE THE FOLLOWING ACTIONS:

- Inform individual/family of the test result.
- Refer for genetic evaluation and counseling.
- Obtain consultation for evaluation, early intervention, and management of mental retardation, autism, developmental delay, neurological disorders or infertility, as appropriate.

Diagnostic Evaluation: Mentally retarded males with intermediate and premutation repeat sizes may require immunohistochemical staining of lymphocytes for FMR protein to establish causation. Mosaicism may also be found. There are rare forms associated with FMR gene deletions.

Clinical Considerations: Fragile X syndrome is the most common inherited form of mental retardation. Approximately 1/3 of affected children have autism or autism spectrum disorders. As an X-linked disorder, it affects males more severely than females. It is caused by an increased number (>200 – full mutation) of DNA repeats (trinucleotide-CGG) sequences in the FMR1 gene, normal alleles of which have ~5 to ~44 repeats. Severity of mental retardation cannot be predicted based on repeat length. Females with premutations (~55 to ~200 repeats) are at high risk for POF. Males with a "full" mutation usually have mental retardation in the mild to moderate range. Approximately 70% of females with the full mutation have an IQ of 85 or lower; and the majority present with learning disabilities, although mental retardation occurs in about 25%. Young males with the premutation often have ADHD and occasionally social deficits. Older males (>50 yrs.) and some females with a premutation may develop the FXTAS, characterized by intention tremor, ataxia, neuropathy and cognitive decline. Premutations can expand to full mutations in the next generation, particularly in carrier females, that is a premutation carrier can have a child with a full mutation. Individuals with repeat numbers of "intermediate" size (~45 to ~54 repeats) may expand to full mutations over more than one generation, meaning that children of individuals with an intermediate repeat could inherit a gene that has undergone expansion to premutation size with the attendant risks.

Additional Information:

Gene Tests/Gene Clinics
American College of Medical Genetics—Practice Guideline
American College of Medical Genetics—Laboratory Guideline
American Academy of Pediatrics

Referral (local, state, regional and national):

Testing
Clinical Services
Find Genetic Services

ACMG
American College of Medical Genetics and Genomics
Translating Genes Into Health®

LOCAL RESOURCES: Insert State newborn screening program web site links

State Resource site *(insert state newborn screening program website information)*

Name	
URL	
Comments	

Local Resource Site *(insert local and regional newborn screening website information)*

Name	
URL	
Comments	

APPENDIX: Resources with Full URL Addresses

Additional Information:

Gene Tests/Gene Clinics
http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=fragileX

Genetics Home Reference
http://ghr.nlm.nih.gov/condition=fragilexsyndrome

American College of Medical Genetics -Practice Guideline
http://www.acmg.net/StaticContent/StaticPages/FragileX.pdf

American College of Medical Genetics - Laboratory Guideline
http://www.acmg.net/Pages/ACMG_Activities/stds-2002/fx.htm

Referral (local, state, regional and national):

Testing
http://www.ncbi.nlm.nih.gov/sites/GeneTests/lab/clinical_disease_id/2366?db=genetests

Clinical Services
http://www.ncbi.nlm.nih.gov/sites/genetests/clinic?db=genetests

Find Genetic Services
http://www.acmg.net/GIS/Disclaimer.aspx

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