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An Unrecognized Case of Fragile X Syndrome

By Heather Workman, MS, CGC and Leslie Willis, BS, MB(ASCP)^{CM}

Case Study

A 3 year-old Caucasian male with a history of global developmental delay was referred to the genetic counseling clinic to review Comparative Genomic Hybridization (CGH) microarray results of unknown significance. Previous genetic testing included high-resolution chromosomes (normal: 46, XY) and CGH microarray (results of unknown significance). The CGH microarray results proved

Case Discussion

CGH microarray and high-resolution chromosomes are an important and cost-effective first line test for the child with unexplained developmental delays. However, this technology is not able to detect patients affected with FXS.

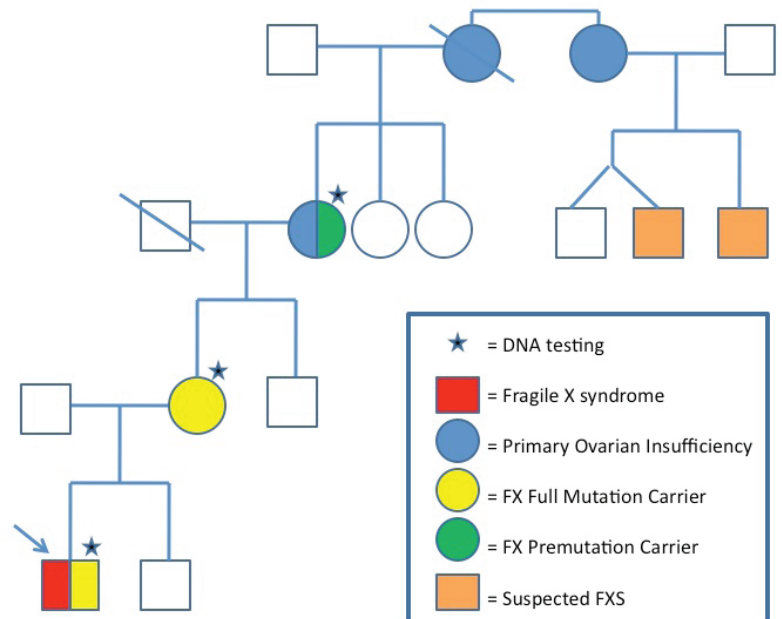
An accurate diagnosis of Fragile X syndrome has far-reaching implications for the patient and the family. Notably, patients with FXS may benefit from minocycline drug therapy, which has minimal side effects and has been shown to decrease irritability and improve behavior. Also, patients with FXS should have regular ophthalmologic exams and are at risk for joint complications and mitral valve prolapse related to connective tissue laxity.

to be noncontributory to the history of developmental delay. A four-generation pedigree showed that the child's maternal grandmother had a 57-year-old male cousin with mental retardation (MR) of unknown etiology. Further investigation into the maternal family history revealed primary ovarian insufficiency (POI) in the child's maternal grandmother. Given the child's global developmental delay, family history of MR and POI, Fragile X syndrome (FXS) testing was ordered. The diagnosis of Fragile X

syndrome was confirmed when the child was found to carry a full mutation (300-600 CGG repeats) in the FMR-1 gene. FXS testing was offered to the child's brother, mother and maternal grandmother. The child's developmentally typical brother had a normal test (30 CGG repeats). The child's mother was found to be a full-mutation carrier (250-400 CGG repeats) and the child's maternal grandmother was found to be a premutation carrier (109 CGG repeats) consistent with her history of POI.

Females with full mutations are also at risk for the physical, cognitive and behavioral concerns seen in males with a full mutation, but only half will display symptoms. In this case, the child's mother was a full-mutation carrier and had no symptoms of FXS.

Females with premutations are at risk for primary ovarian insufficiency and Fragile X Tremor Ataxia syndrome (FXTAS). The lifetime risk for both of these conditions approaches 20 percent in females. Males with premutations have a 75 percent risk to develop FXTAS



Featured Specialists



Heather Workman, MS, CGC

Heather Workman, a board-certified genetic counselor, has worked in the genetics department at Dayton Children's for five years. Heather graduated from the University of Cincinnati/Cincinnati Children's Hospital Medical Center Genetic Counseling Program.



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Medical Genetics at Dayton Children's

The department of medical genetics evaluates children and adults for a wide variety of indications. Clinical genetic services are available at the main campus and genetic counseling services are available at the main campus, Beavercreek and Warren County Dayton Children's locations and at Samaritan North Cancer Care Center. The genetics department also includes a cytogenetics laboratory and a molecular and biochemical laboratory.

over their lifetime. Symptoms of FXTAS include late onset ataxia, intention tremor, Parkinsonism, short-term memory loss, and cognitive decline.

As additional information was gathered about the child's family in our case study, it was noted that the maternal grandmother's mother and maternal aunt also had POI. The additional family history of POI led to a suspected diagnosis of FXS in the maternal grandmother's first cousin with MR of unknown etiology. This family later reported that the individual's brother also had MR of unknown etiology. The family was informed that these two individuals were likely to have FXS.

The diagnosis of FXS in this child was significant in many ways. The child was started on minocycline therapy, which

has been shown to be effective in males with FXS. The family was given appropriate genetic counseling on the inheritance of FXS including explanations of X-linked inheritance and maternal anticipation. Genetic testing was offered to at-risk family members. The child's parents were provided with accurate recurrence risks for future children and the child's maternal grandmother was provided with an explanation for her POI and notification of her risk for FXTAS. In addition, extended at-risk females were offered genetic counseling and testing.

FXS is a common genetic cause of developmental delay affecting 1:4000 males (approximately 1:143 women carry a premutation). The American College of Medical Genetics recommends FXS testing in males and females

with mental retardation, autism or developmental delay. FXS testing along with high-resolution chromosomes and CGH microarray should be completed as initial genetic testing in the child with unexplained developmental delay. This case also illustrates the usefulness of an extended family history focusing on additional family members with MR, POI or symptoms of FXTAS.

References

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