Significance of Phenotype Correlation in Genetic Testing and Genetic Counseling : A Case Report

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Abstract

A five-year-old boy referred for post-test genetic counseling in view of global developmental delay, intellectual disability, autism spectrum disorder, hyperactivity & normal whole exome sequencing report. His sibling also had similar phenotype. In addition to the above mentioned phenotype, proband had flapping of hands, stereotypic behavior, characteristic elongated face and large prominent ears with significant family history. We suspected Fragile X Syndrome and suggested methylation specific PCR testing. It revealed expanded CGG repeats in proband and his brother, suggestive for Fragile X syndrome and mother is a carrier. The family were counseled about the condition, risk and management. This case highlights the importance of phenotype correlation and suggestion of appropriate testing to establish correct diagnosis and plan appropriate management. Disease specific Hagerman clinical checklist can be used for screening of Fragile X syndrome.

Background

- Fragile X syndrome is an X-linked trinucleotide CGG repeat expansion single-gene disorder caused by methylation-induced FMR1 gene silencing at Xq27.3.
- It exists in four allelic forms: Normal FMR1 allele has 5–44 CGG , Intermediate or gray zone has 45–54 repeats, Premutation has repeats 55–200 CGG repeats and Full mutations (FM) have unstable methylated allele with >200 CGG repeats causing Fragile X syndrome.
- It is the most prevalent inherited cause of mild-to-severe intellectual disability and the most common monogenic cause of autism spectrum disorder.
- Physical features include a elongated narrow face with a prominent jaw and forehead, large ears and hyper extensible joints

Case Presentation

Referral Reason: A 5 year old boy referred for post test genetic counseling with Autism spectrum disorder, speech delay, hyperactive and intellectual disability.

Pedigree

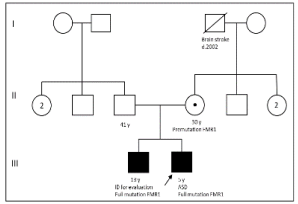
- Born to Non consanguineous parents
- Brother also had similar phenotype
- Asymptomatic Mother with respect to premature ovarian failure /Mild ID.

Birth History

- Full term by LSCS
- Birth weight 3.5 Kg, Cried at Birth

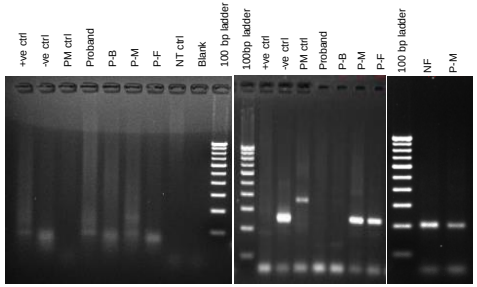
Clinical Features

- Autism spectrum disorder
- Speech delay
- Flapping of hand
- Elongated Face
- Prominent large Ears
- Stereotypic behavior
- Facial dysmorphism



Diagnostic Workup

- Whole exome sequencing done elsewhere revealed no significant variants .
- In view of classic phenotype, strong family history and Increased score of 19 in Hagerman checklist suggested Methylation specific PCR(MS-PCR) for fragile X syndrome for proband , his affected brother and the importance of premutation carrier screening for mother was also discussed
- MS-PCR confirmed FXS in both proband and his affected brother
- Carrier Screening for Mother revealed heterozygous premutation allele /Normal allele



Key: ctrl-control, +ve-positive, -ve-negative, NT-Non treated, PM-Premutation, bp-Basepair

MS PCR results

S. No	Members	Types of Mutation	CGG Repeats
1	Proband(P)	Full Mutation	>200 repeats
2	Brother(P-B)	Full Mutation	>200 repeats
3	Mother(P-M)	Pre Mutation	55-200 repeats
4	Father(P-F)	Normal	5-44 repeats

Hagerman Checklist Score

Clinical Features	Proband	P-Brother
Mental Retardation	2	2
Hyperactivity	2	2
Short attention span	2	2
Tactile defensive	1	1
Hand-flapping	2	2
Hand-biting	0	0
Family history	2	2
Poor eye contact	2	1
Perseverative speech	2	2
Hyperextensible MP joints	2	2
Large or prominent Ears	2	2
Large testicles(Macroorchidism)	0	0
Simian crease or sydney line	0	0
TOTAL	19	18

Genetic Counseling

- The family were counseled about the nature of the condition, history and mode of inheritance.
- Recurrence risk : 50% of male will be affected & 50% of female will be carrier.
- Prenatal Testing, Preimplantation Genetic testing and other reproductive options were also discussed with the family.
- Since Mother is a permutation carrier, her increased risk for primary ovarian insufficiency (FXPOI) and Fragile X associated tremor / ataxia syndrome (FXTAS) was also discussed.

Conclusion

- The family was concerned about not getting diagnosis Inspite of performing and spending for WES.
- Phenotype assessment and family history is very important to decide on a testing strategy.
- For fragile X syndrome, increased Hagelman clinical checklist score will enhance our detection and help in planning cost effective diagnostic testing.
- Pretest genetic counseling is very important to apprehend family about the necessity of testing, test advantages, limitations, detection capabilities, alternative tests, TAT and extended family testing.
- This case study highlights the importance of phenotyping, choosing appropriate testing for the diagnosis, management and prevention in this NGS Era.

Reference

Zhou Y, Law HY, Boehm CD, Yoon CS, Cutting GR, Ng IS, Chong SS. Robust fragile X (CGG)n genotype classification using a methylation specific triple PCR assay. J Med Genet. 2004 Apr;41(4):e45. doi: 10.1136/jmg.2003.012716. PMID: 15060121; PMCID: PMC1735740.