COMMENTARY

Outcomes of FMR1 disorder and diagnosis

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Arif F. Outcomes of FMR1 disorder and diagnosis. J Clin Gen Genomics. 2021;4(3):3.

DESCRIPTION

Males and females with intellectual disability or developmental delay of unknown cause. Males with mysterious autism spectrum ailment and females with unexplained autism spectrum ailment and the presence of an additional indicator: phenotype compatible with FXS, family history of X-linked neurodevelopmental ailments, or premature ovarian failure, ataxia, or tremors in near relations.

Fragile X-associated tremor/ataxia syndrome

Males and females who are facing late-onset intention tremor and cerebellar ataxia of unknown reason. Men and women with dementia may also be measured, if ataxia, Parkinsonism, or tremor is also present. Males and females with multiple system atrophy, cerebellar subtype. Fragile X-associated primary ovarian insufficiency. Females with unexplained primary ovarian insufficiency or failure before age 40 years.

Diagnosis

Diagnosis of an FMR1 disorder is established through use of specialized molecular genetic testing. It should be noted that typical multigene panels and comprehensive genomic are useful only when no CGG repeat expansion is detected but FXS is still suspected. FMR1 relevant disorders are caused by CGG trinucleotide repeat expansion in 5' UTR of FMR1 with abnormal gene methylation for most alleles with more than 200 repeats. Normally, a definite diagnosis of FXS needs presence of a full-mutation repeat size while diagnosis of FXTAS or FXPOI is related with a premutation sized repeat.

Allele Scope

FMR1 alleles are categorized according to number of 5' UTR CGG trinucleotide repeats and methylation status of repeat region. However, distinction between allele groups is not absolute and must be made by considering both family history and repeat instability. Size boundary between intermediate and premutation groups listed below is not precise and caution is guided. For a summary of types of FMR1 alleles and clinical status of individuals with expanded alleles. Stability of alleles of fewer than 90 repeats is deeply influenced by number of AGG interspersions within CGG repeat sequence, both with respect to risk for size change in intermediate alleles and small premutations and expansion to a full mutation in premutation alleles more than about 60 repeats. This information should be used when suitable for counseling families about expansion risk. See Anticipation for full information on factors such as AGGs that effect FMR1 CGG repeat stability. Alleles of this size have little meiotic or mitotic instability and are typically transmitted without any increase or decrease in repeat number. Though, some instability in normal repeats has been reported, with alleles that contain no AGG interspersions having a greater likelihood to be unstable. Population distribution of FMR1 repeat alleles shows highest percentage of individuals with approximately 29-31 repeats, smaller but significant percentages cluster around 20 and 40 repeats.

Intermediate alleles do not cause FXS. But, about 14% of intermediate alleles are unstable and may expand into premutation range when transmitted by mother. They are not known to increase to full mutations; therefore, offspring are not at increased threat for FXS. Historically, largest repeat included in intermediate range has been 54, use of 54 as upper limit for normal alleles is a conservative estimate reflecting observations that transmission of alleles with 54 or fewer repeats from mothers to their offspring has not resulted in an affected individual to date. Conservative nature of estimate also reflects potential imprecision in laboratory measurement of repeat number during diagnostic testing, however, to date no transmission of alleles with 55 or fewer repeats is known to have resulted in an affected individual.

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Received date: *October 01, 2021*; **Accepted date:** *October 15, 2021*; **Published date:** *October 22, 2021*