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Correlation between fragile x- syndrome and ataxia

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Date of Submission: 18/2/ 2020

Abstract :

The fragile X syndrome, an X-linked dominant disorder with reduced penetrance, is one of the most common forms of inherited mental retardation. The cognitive, behavioral, and physical phenotype varies by sex, with males being more severely affected because of the X-linked inheritance of the mutation

Fragile X-associated tremor/ataxia syndrome is a progressive neurodegenerative disease that occurs in premutation carriers of 55-200 CGG repeats in FMR1 and is characterized by kinetic tremor, gait ataxia, parkinsonism, executive dysfunction, and neuropathy. [(1)]

Introduction :

Fragile X syndrome (FXS) is one of the most common inherited cause of mental retardation . In the vast majority of cases, this X-linked disorder is caused by expansions of a CGG repeat in the 5′-untranslated (UTR) region of the FMR1 gene that arises due to the meiotic instability of certain alleles of this repeat tract. FXS causing alleles, or full mutations, contain 200 or more copies of the repeat that are hypermethylated and transcriptionally silenced. The unstable alleles that give rise to full mutations are called premutations and are associated with phenotypes distinct from FXS. The mutational mechanism, combined with the location of this gene on the X chromosome, leads to remarkable inheritance patterns in which the relevant alleles are passed from intellectually normal men through their unaffected daughters and then to affected sons. Clinical phenotype. Individuals with FXS may present with such as (large head) (long narrow face) (large ears) (large forehead) (flat feet) (loose joints) (otitis media), (seizures), and (gastrointestinal problems).

The fragile X-associated tremor/ataxia syndrome (FXTAS) is a neurodegenerative disorder that affects carriers, principally most common males after 50 years of age and it is a Premutation expansions (55-200 CGG repeats) of the fragile X mental retardation 1 (FMR1) gene are frequent in the general population, The main clinical features described in this syndrome are cerebellar ataxia and intention tremor. Additional documented symptoms include short-term memory loss, executive functional deficits, cognitive decline, parkinsonism, peripheral neuropathy, lower-limb proximal muscle weakness, and autonomic dysfunction.

The aim of study that Fragile X syndrome (FXS) is one of the most common inherited cause of mental retardation. (FXTAS) is a neurodegenerative disorder that affects carriers, principally most common males after 50 years old and it is a Premutation expansions of the fragile X mental retardation 1.[2]

Materials and Methods :

A meta-analysis was conducted of all published genetic screens for expanded FMR1 alleles to assess the prevalence and CGG-repeat size bias of FMR1premutation alleles in those populations.[3]

Result :

frequency of the full mutation was 1.4 per 10,000 males and 0.9 per 10,000 females in the total population. The premutation frequency was 11.7 per 10,000 males and

34.4 per 10,000 for females in the total population. The prevalence of female carriers of the premutation in the normal was 34.4 per 10,000 population. In men with late-onset cerebellar ataxia, the prevalence of premutation alleles (1.5%) was greater than expected based on its prevalence in the general population (2%) for age of onset >50 years . Meta-analysis of CGG-repeat data for screened patients with premutation alleles shows a shift to larger repeat size than in the general population of premutation alleles were larger than 70 repeats in the patients screened, whereas only approximately 22% of premutation alleles are larger than 70 repeats in the general population.[4]

Discussion :

The fragile X syndrome, an X-linked dominant disorder with reduced penetrance, is one of the most common forms of inherited mental retardation. The cognitive, behavioral, and physical phenotype varies by sex, with males being more severely affected because of the X-linked inheritance of the mutation. The disorder-causing mutation is the amplification of a CGG repeat in the 5′ untranslated region of FMR1 located at Xq27.3. FMR1 is a polymorphic CGG repeat coincident with a rare fragile site on the X chromosome known as FRAXA. the inducible FRAXA fragile site was developed as a cytogenetic marker and proved valuable in diagnosing this nonspecific form of X-linked mental retardation. The fragile X CGG repeat has four forms: common (6–40 repeats), intermediate (41–60 repeats), premutation (61–200 repeats), and full mutation (>200–230 repeats). Although no effective cure or treatment exists for the fragile X syndrome, all persons affected with the syndrome are eligible for early intervention services.

Intermediate alleles are larger repeats that may or may not be transmitted stably from parent to offspring. Thus, these alleles overlap the boundary between common and premutation alleles.While intermediate alleles may be unstable, very few expand to the disorder-causing mutation in the next generation. Recent evidence, in fact, suggests that intermediate alleles identified among families with the fragile X syndrome are more susceptible to disorder-causing expansions in the next generation compared with intermediate alleles identified in the general population. To date, 59 repeats is the smallest size known to expand to the disorder-causing mutation in the next generation within a family with the fragile X syndrome.

usually expand in the next generation. The size of the repeat expansion is positively correlated with maternal CGG repeat size, with >90 repeats almost always expanding to the full mutation in the next generation. The transition from premutation to full mutation is thought to occur prezygotically. In contrast to the female germline, paternal transmission of the full mutation to the offspring is rare. Recent studies suggest that selection against full mutation in sperm is responsible for the differences observed between female and male germline transmissions .

We have chosen to define premutations as 61–200 repeats since these repeats are always unstable and have been found to expand to the full mutation. Premutations of smaller size are found in families with the fragile X syndrome; however, these smaller sized premutations found in the general population may or may not be unstable. Thus, the estimate of premutations in represent the lower limits of premutation carriers.

The full mutation in males in the general population (1 in 4,000) and the fact that only females can transmit the full mutation to their offspring, the expected prevalence among females affected with the fragile X syndrome is approximately 1 in 8,000 to 1 in 9,000 in the general population.The full mutation allele is the form associated with the fragile X syndrome phenotype. All full mutations identified to date are derived from premutation or full mutation alleles from the previous generation. The full mutation allele leads to hypermethylation and deacetylation of FMR1, which effectively shuts down transcription of the gene.the full mutation and premutation, are directly related to the expression of the fragile X syndrome phenotype.

Fragile X–associated tremor/ataxia syndrome: is an "adult onset"neurodegenerative disorder, usually affecting males over 50 years of age. Females comprise only a small part of the FXTAS population, and their symptoms tend to be less severe. FXTAS affects the neurologic system and progresses at varying rates in different individual. Fragile X syndrome diagnosed with: Parkinson's disease ,Alzheimer's disease ataxias and Tremors. All individuals with FXTAS are premutation carriers of the FMR1 (Fragile X) gene female premutation carriers can also be affected by Fragile X-associated primary ovarian insufficiency (or FXPOI), another of the conditions associated with the change in the FMR1 gene. Ages 50-59 the chance is about 17%.Ages 60-69 about 38%.Ages 70-79 about 47%.Over 80 years old, about 75% will develop symptoms of FXTAS.[5]

Conclusion:

Research on FXTAS is just beginning; however, it is already evident that this disorder is distinct in both the population at risk and the mechanism of disease formation from fragile X syndrome, although both disorders are associated with the same gene (FMR1). FXTAS must be considered in the clinical workup of all families with the FMR1 mutation. Genetic counseling should include a discussion of FXTAS and neurological symptoms in older carriers and, as the prevalence and risks are clarified, these issues should be explained to families. Further research regarding the predisposing factors, either environmental or genetic, in carriers is needed. A number of treatments may be clinically beneficial at this time, including medications to improve tremor, anxiety, and cognitive decline; controlled clinical studies are needed to test the efficacy of these interventions.[6]

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