SCREEN FOR EXPANDED FMR1 ALLELES IN PATIENTS WITH ESSENTIAL TREMOR AND CEREBELLAR ATAXIA

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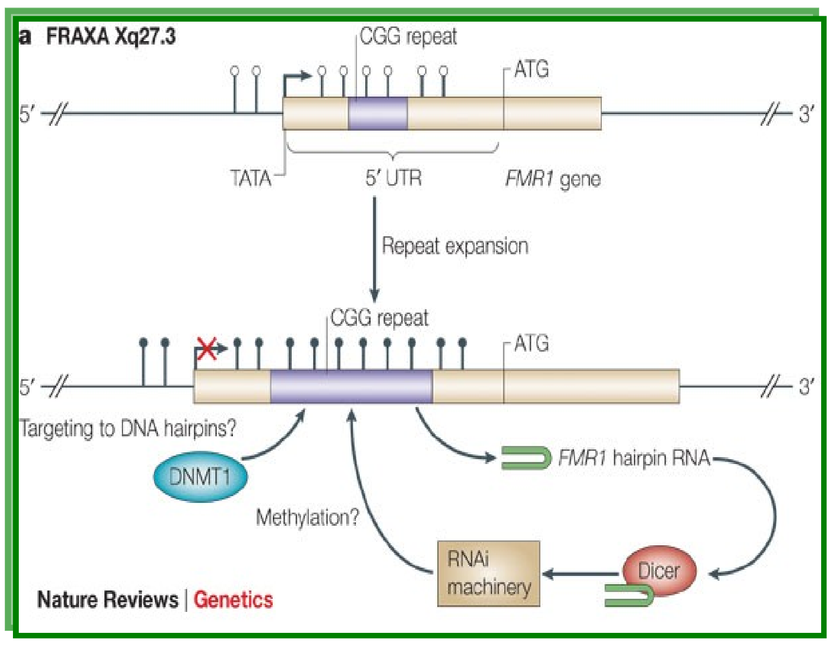
INTRODUCTION

Fragile X–associated tremor/ataxia syndrome (FXTAS) is a late-onset neurodegenerative disorder that affects some but not all carriers of small, noncoding CGG-repeat expansions (55–200 repeats; premutation) within the fragile X gene (FMR1). Principal features of FXTAS include intention tremor, cerebellar ataxia, Parkinsonism, memory and executive function deficits, autonomic dysfunction, brain atrophy with white matter disease, and cognitive decline. Although FXTAS was originally considered to be confined to the premutation range, rare individuals with a gray zone (45–54 repeats) or an unmethylated full mutation (>200 repeats) allele have now been described, the constant feature of the disorder remaining the requirement for FMR1 expression, in contradistinction to the gene silencing mechanism of fragile X syndrome.



METHODS AND PATIENTS

From our data base, we retrospectively selected 100 male patients , older than 50 years, with Parkinsonism and Ataxia who were referred to us for testing of the spinocerebellar ataxia (SCA 1, 2, 3, 6, 7, 8,12,17) genes and who were found to be negative; 203 patients with PD, 30 patients with ET and 370 healthy subjects enrolled during a previous study on aging. We also included four individuals, two of which (exhibiting parkinsonian symptoms) were from a fragile X mental retardation pedigree, whereas the remaining two cases had intention tremor and postprandial hypotension. All participants were male subjects who had the same ethnic background and gave written informed consent. Genomic DNA was extracted from peripheral blood. Fragment were measured by comparison with previously sequenced alleles. PCR products were visualized on agarose gel and compared to a control with 30 CGGs; PCR products that appeared larger were further analyzed by automated fragment analysis in a 3500 DNA Analyzer (Applied Biosystems) for assessment of repeat number. Premutation status was established for alleles with 55-200 CGGs.

RESULTS

We did not detect *FMR*1 premutation genotype in any patients with PD and ET or in any healthy controls. Concerning the allele distribution, no difference was found between PD patients and controls (Fig.1). On the contrary, the last four patients carried premutation-size alleles. In particular, the two subjects with parkinsonian symptoms and family history of fragile X syndrome carried, respectively, 57 and 90 CGG repeats. As regards the two subjects with intention tremor and postprandial hypotension, on of them had 73 CGG repeats and the second one were a male, uncommon mosaic for a premutation (90 CGG repeats) and a normal-size allele.

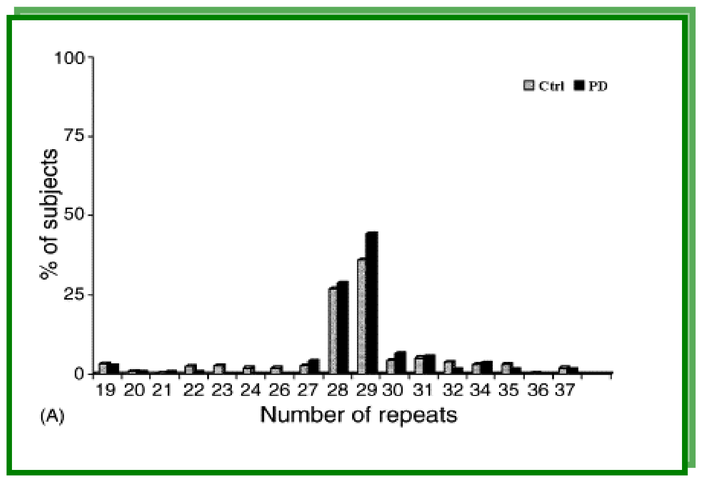


Fig. 1: *Fig. 1. (A) Distribution of FRAXA CGG repeats in the X chromosomes from male subjects with Parkinson's disease (black columns) and from normal male controls (grey columns). No significant difference was observed between patients and controls (χ2 = 24.46; P = 0.071).*

CONCLUSIONS

In this study, we found four patients with an FMR-1 premutation. In four of them, a definite diagnosis of FXTAS could be made, based on the proposed diagnostic clinical and radiological criteria for FXTAS. The repeat sizes observed in our patients range from 55 to 89. In conclusion we recommend that FMR-1 analysis should be included in the molecular diagnostic work-up in the group of male ataxia and parkinsonism patients older than 50 years. Our data, in agreement with other authors, show that premutated alleles are rare in PD as well as in ET. Thus the presence of postprandial hypotension or a positive family history of fragile X syndrome, beside the peculiar T2-hyperintense signal in middle cerebellar peduncles, can be considered an important indication for *FMR1* expansion genetic testing.

REFERENCES

Lozano R, Rosero CA, Hagerman RJ. Fragile X spectrum disorders. Intractable Rare Dis Res. 2014 Nov;3(4):134-46.

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