Identification and sizing of GAA trinucleotide repeat expansion, investigation for D loop variations, haplogroup association and mitochondrial deletions in Iranian patients with Friedreich’s Ataxia

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Friedreich's ataxia (FA) is the commonest genetic cause of ataxia and is associated with the expansion of a GAA repeat in intron 1 of the frataxin gene. Iron accumulation in the mitochondria of patients with FA would result in hypersensitivity to oxidative stress. Mitochondrial DNA (mtDNA) could be considered a candidate modifier factor for FA disease, since mitochondrial oxidative stress is thought to be involved in the pathogenesis of this disease. We studied 52 Iranian patients (61 females and 9 males) from 21 unrelated families. DNA from each patient was extracted and frequency and length of (GAA) n repeat was analyzed using a long-Range PCR test. Also we investigated impact of GAA size on neurological findings, age of onset and disease development. In order to identify polymorphic sites, genetic background and also to find out any possible association between FA and mtDNA haplogroups (hg), the complete non-coding region of mitochondrial DNA from FA patients harbouring GAA trinucleotide expansions was sequenced. Alignment were made with the Revised Cambridge Reference Sequence (rCRS) and any differences recorded as single base substitution(SBS), numerical changes in C-tract(PCT),insertions and deletions. Homozygous GAA expansion was found in 41 (81 %) of all cases. In 4 cases (14%), no expansion was observed, ruling out the diagnosis of Friedreich's ataxia. In cases with GAA expansions, ataxia, scoliosis and pes cavus, cardiac abnormalities and some neurological findings occurred more frequently than in our patients without GAA expansion. Molecular analysis was imperative for diagnosis of Friedreich's ataxia, not only for typical cases, but also for atypical ones. Diagnosis bases only on clinical findings is limited, however, it aids in better screening for suspected cases that should be tested. Our results also showed that none of our patients had association with D-loop haplogroups, but the rate of D-loop variations was higher in FA patients than control. MtDNA deletions were present in 57% of our patients representing mtDNA
damage which may be due to Iron accumulation in mitochondria.

كلمات كليني:
Friedreich's ataxia, mtDNA, Haplogroup, D-loop

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