The fragile X syndrome (FXS) is defined as a loss of function disorder. The expansion and subsequent methylation of a CGG repeat in the 5' untranslated region (5'UTR) of the fragile X mental retardation 1 (FMR1) gene (chromosome locus Xq27), results in the deficit of the FMR1 gene-specific product. In general, the diagnosis of FMR1-related disorders, including POI in women, depends on the detection of a dynamic alteration in the FMR1 gene, including normal range alleles (6-50 CGG repeats), large sized mutations (50-200 CGG repeats), and full mutations (>200 CGG repeats) (Fig. 1) (Ooster & Willensem; 2008). Although several studies have been conducted to investigate the phenotype-genotype relationship in different populations, precise prevalence figures of the FMR1 premutation and full mutation alleles, and their association with FMR1-related disorders in Arab populations, are lacking (Bastaki et al., 2004; Iqbal MA et al., 2000). We report on a series of Jordanian subjects presenting symptoms ranging from learning disabilities to severe mental retardation, and 8 Jordanian POI patients, all of which were examined for X-chromosome abnormalities and the number of CGG repeats within the FMR1 gene between 2000 and 2010. Figure 1, A Jordanian Family Pedigree Highlighting the CGG Triplet Repeat Pattern of Inheritance. The change from normal CGG copy number to full mutation is a multistep process preceding over several generations characteristic of a dynamic mutation.

RESULTS

Among the cognitively impaired subjects, 45 and 11 patients were confirmed fragile X-positive by cytogenetic and southern blot analysis respectively, and surprisingly no carriers with premutations were observed. Interestingly, 6 of these symptomatic patients are unrelated individuals, with familial origins from the city of Karak, south of the capital Amman. Although further analysis is necessary, preliminary data indicates that Jordanian patients with mental retardation are carriers of the FMR1 full mutation allele, whereas patients showing mild to moderate cognitive disabilities are within the normal polymorphic range. Among the POI cases examined, the CGG repeat numbers were within the normal range, and only one female carried a premutated allele. Therefore, FMR1 premutations seem to be uncommon in sporadic cases of POI with no family history of FXS.

DISCUSSION

In general prescreening studies have proven to be very efficient in reducing the prevalence of FXS in populations were the FMR1 premutation frequency is high. Usually the identification of an individual in which the FMR1 repeat site is expanded triggers genetic counseling throughout the pedigree and subsequent prenatal testing. Therefore, future studies focusing on the prevalence of premutations within females of normal intelligence in different Arab populations are necessary. In addition, accumulating evidence associating candidate genes and X-chromosome abnormalities with POI necessitates screening of FMR1 premutations and cytogenetic analysis as part of the routine work-up for any women presenting with POI. Furthermore, comprehensive clinical, histological, morphological, and genetic studies relating to POI patients in Arab populations would be very informative.

REFERENCES