Full length article

Fragile x-associated premature ovarian failure in a large Turkish cohort: Findings of Hacettepe Fragile X Registry

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A R T I C L E   I N F O

Article history:
Received 22 May 2017
Received in revised form 8 September 2017
Accepted 14 December 2017
Available online xxx

Keywords:
Fragile X premutation
FMR1
Premature ovarian insufficiency

A B S T R A C T

Objective: To determine frequency of fragile X associated premature ovarian insufficiency (FXPOI) among Turkish premutation carriers.

Study design: FMR1 premutation is the single most common genetic cause of POI (FXPOI). Fragile X Registry at Hacettepe University has been reviewed for the frequency of FXPOI among female premutation carriers. Since 1991 when FMR1 testing was available, 760 individuals from 243 families have been registered. Actual data on menstrual status of female premutation carriers were gathered and analysed.

Results: Among 314 premutation-bearing females in the cohort, 268 could be reached for an update of their menstrual history; 107 adults were 40 or younger and 156 were older than 40 years of age, whereas the remaining 5 patients were prepubertal. Among 263 postpubertal females with premutations, 90 women stopped menstruating before or at 40 years of age (premature ovarian failure – POF), constituting 34.2% of our cohort. Additionally, one carrier of a gray zone allele experienced FXPOI. History of twinning was present once in 18 women (5.7%) and twice in two women (0.6%), none of the latter interestingly bearing a full-mutation.

Conclusions: FXPOI rates in the present cohort are higher than those reported in other populations. Higher FXPOI rates in Turkish premutation carriers might be a reflection of younger mean menopause age and higher POI rates in otherwise healthy Turkish women. Since POI is much more frequent among premutation carriers than in general population, testing for CGG repeat expansions in FMR1 should be included in the work-up.

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Introduction

Menopause is permanent cessation of menstrual cycles and the end of fertility. The median age at menopause is 50 years in most of the industrialized countries [1]. Premature ovarian insufficiency (POI) is considered in women younger than 40 years in whom amenorrhea of at least 4 months is associated with two serum FSH levels, obtained at least 1 month apart, in the menopausal range [2]. POI affects 1% of women below 40 (3) and 0.1% of those below 30 years of age [2,3].

POI is a broad definition which includes primary amenorrhea due to ovarian dysgenesis, as well as secondary amenorrhea due to early depletion of the ovarian reserve. Clinically, decreased fertility is the main feature of POI. The POI spectrum is further classified as 1) occult, if decreased fertility is the sole finding, 2) biochemical, when gonadotropin levels increase, or 3) overt, when menstrual cycles become irregular [4]. Premature ovarian failure (POF) refers to the irreversible last stage where the follicular reserve is completely depleted and menstrual cycles stop permanently [4,5].

POI is clinically and molecularly heterogeneous. Genetically, it is a multifactorial condition [6]. Underlying etiology may include chromosomal, genetic, infectious, iatrogenic, autoimmune, metabolic and toxic causes, and a large group remains idiopathic [6]. Families with multiple members affected by idiopathic POI suggest strong genetic component in etiology, and several genes have been detected in various families [6,7]. Furthermore, some well-delineated genetic disorders lead to autoimmune, hormonal,

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metabolic or toxic mechanisms of premature loss of ovarian reserve.

*FMR1* premutation is the single most common genetic cause of POI [4,7–9] and it is one of the oldest known causes [10]. It is responsible from 1.6 to 3.2% of sporadic POI and 11.5–16% of familial POI [4,8,11]. On the other hand, one in 130–250 of women are carriers of premutation and POI affects 15–24% of premutation carriers [4,8,10–12], corresponding to a high prevalence of *FMR1*-associated POI in general population.

Hacettepe University Children’s Hospital is one of the largest tertiary centers in central Anatolia, with approximately hundred thousand yearly admission. Since the discovery of *FMR1* in 1991 as the causative gene of fragile X syndrome (FXS), molecular analysis for CGG repeats has been performed at Hacettepe University, and families have been registered in the Fragile X Registry. For the purposes of this study, premutation bearing females registered since then have been reviewed for FXPOI.

**Materials and methods**

Primarily functioning as a Pediatric Genetics department of a Children’s Hospital, our Fragile X Registry mainly consists of individuals and families with FXS diagnosed in the pediatric age group. Thus, patients in the registry were mostly assigned either 1) on detection of full mutations causing FXS, 2) on detection of premutation alleles in cascade screening of available family members who were likely carriers. Less commonly, adult patients with suspected fragile X-associated tremor ataxia syndrome (FXTAS) or fragile X-associated premature ovarian insufficiency (FXPOI), without an index with FXS in the family, were tested for CGG repeat expansions.

Majority of the families in the registry are under periodic follow-up, mainly for FXS related morbidities. For purposes of the present study, female premutation carriers in the cohort were reviewed for the frequency of FXPOI and the age at POF. All families in the registry were contacted to survey more recent FXPOI events.

Diagnosis of POI in our cohort depended mainly on self-reporting by women and was not confirmed by two FSH levels above menopausal range. Considering that recall bias would decrease reliability of the data and also for the sake of simplicity and standardization, age at POF rather than the age at POI onset was surveyed, and age at cessation of menses was noted. Menstrual irregularity was also questioned, but was not included in the statistics.

Fragile X mutation analysis was performed by polymerase chain reaction and standard Southern blot testing [13]. Methylation status and CGG repeat numbers were determined in a subset of patients using methylation status kit, according to the manufacturer’s instructions [14].

The study was approved by Hacettepe University Non-interventional Clinical Research Ethics Board (Approval no: GO 17/322-20).

**Results**

Hacettepe Fragile X Registry includes 760 individuals from 243 families; 422 (55.5%) females and 338 (44.5%) males (Fig. 1). Among females, 33 were included in the registry without molecular testing but based on pedigree only; either as intellectually disabled daughters of carrier females or as obligate carrier relatives of affected males. For the purposes of this study, they were left out of the cohort, since mutation status was unknown. The remaining 389 females were all molecularly tested; 74 (19%) had full mutations, 309 (79.4%) had premutations, 4 (1%) had mosaicism of full mutation and premutation, one (0.3%) was a mosaic of normal and premutation alleles, and one (0.3%) had a normal and a gray zone (intermediate) allele; the latter was assigned due to decreased fertility and irregular menses starting at 19 years of age (Fig. 1).

Since the registry was formed over a period of 26 years, some of the families were lost to follow-up and could not be reached by phone. Among 74 full mutation bearing females 64 were available for the survey; 8 were prepubertal and 56 were postpubertal (42 were 40 years old or younger, 14 were above 40). Of postpubertal

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**Fig. 1.** Summary of the results in the present cohort. Boxes show numbers of female patients in each of the mutation groups, age distribution in relevant groups, and numbers of patients affected by FXPOI. Boxes at the bottom show numbers of FXPOI patients, distributed in three groups of reported age at ovarian failure (<20 years, 21–30 years, and 31–40 years).

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