Issa and Elhady
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Cytogenetic abnormalities in a sample of females with premature ovarian failure

Noha M. Issa[1,2*] and Ghada M. Elhady[2]

Abstract

Background: Premature ovarian failure (POF) is a complex heterogeneous disorder characterized by the triad of amenorrhea, hypergonadotropinism, and hypoestrogenism in women before the expected age of menopause. In most POF patients, the etiology is idiopathic. X chromosome abnormalities are known to be responsible for many POF cases but the effect of sex chromosome low level mosaicism on ovarian function still remains unclear. The aim of this study was to investigate the prevalence and type of cytogenetic abnormalities as well as low-level sex chromosome mosaicism in Egyptian females with POF.

Results: The present study recruited thirty women with POF and thirty women with normal reproductive history as a control group. Conventional cytogenetic analysis was carried out on POF patients in order to detect cytogenetic abnormalities. FISH on interphase and metaphase nuclei from patients with normal karyotype as well as from thirty control women with normal reproductive history was performed using X, Y, and 18 centromeric probes to evaluate low-level sex chromosome mosaicism. Conventional cytogenetic analysis of peripheral blood lymphocytes demonstrated chromosomal aberrations in 7 cases. FISH revealed that the rate of X chromosome mosaicism was significantly higher in POF patients than in the control group.

Conclusion: We concluded that X chromosome abnormalities including low level mosaicism may be underlying the pathology of POF as increased mosaicism may lead to accelerated oocyte aging and premature follicular atresia.

Keywords: Premature ovarian failure, Chromosomal abnormalities, Karyotyping, FISH analysis, Low level mosaicism

Background

Premature ovarian failure (POF) may be characterized by absence of menarche (primary amenorrhea) or premature depletion of ovarian follicles (secondary amenorrhea) for at least 4–6 months before the age of 40 years [1]. Gonadotrophins are elevated (FSH $\geq$40 mIU/ml) and estrogen is in the menopausal range (0 to 30 pg/mL) [2]. POF occurs in ~1% of the general female population before 40 years old [2]. Its incidence according to age is approximately 10/100,000 in women aged 15 to 29 years and 79/100,000 in women aged 30 to 39 years [2]. The prevalence of familial POF has been reported as 12.5% to 50% with widely varying percentages in series [2–4].

POF is a heterogeneous disorder with a wide range of etiologies, mainly genetic, cytogenetic, iatrogenic, infectious, metabolic, and autoimmune that may or may not be genetic [5–7]. Among genetic causes of POF, chromosome abnormalities are the most common, and POF has been frequently linked to X-chromosome abnormalities, ranging from numerical defects, deletions, X-autosome translocations, and isochromosomes [8–10]. However, apart from the Turner syndrome phenotype characterized by X-chromosome monosomy, the implication of mosaic X-chromosome monosomy has been reported but remains controversial particularly in cases with low-level mosaicism 45,X/46,XX and/or 47,XXX and the precise impact of this low-level sex-chromosome mosaicism in ovarian function is unknown [11, 12]. Moreover,

*Correspondence: issanoha@yahoo.com; noha.esaa@alexu.edu.eg
[2] Department of Human Genetics, Medical Research Institute, Alexandria University, Alexandria, Egypt
Full list of author information is available at the end of the article

conventional cytogenetic analysis involves routine scanning of no more than 30 metaphases. Thus, a low mosaicism cannot be properly estimated using this technique. Interphase fluorescence in situ hybridization (FISH) using centromeric probes is the best means to scan a large number of cells to evaluate more precisely numerical chromosomes mosaicism [13].

The aim of this study is to investigate the prevalence and type of cytogenetic abnormalities in 30 Egyptian females with POF. Moreover, we assessed an analysis on X chromosome aneuploidy, by means of FISH on interphase and metaphase nuclei, to evaluate low-level sex chromosome mosaicism rate, trying to add further evidence that there is a correlation between advanced and increased loss of X chromosome and POF.

Methods

This study was carried out on 30 women with POF recruited from Medical Research Institute, Alexandria University. Inclusion criteria were (1) primary amenorrhea or secondary amenorrhea for at least 6 months duration prior to the age of 40 years. (2) FSH levels ≥ 40 IU/. All of the patients underwent a complete clinical assessment, including complete medical and gynecological history, in order to exclude patients with conditions known to induce POF (chemo- or radiotherapy, ovarian surgery, or autoimmune diseases). Pelvic ultrasound had been done for all patients. Patients with typical Turner stigmata were also excluded. Family history was obtained. Positive family history considered if there is another first- or second-degree relative had either POF or early menopause (menopause before 45 years old). POF is considered as familial when the index case had at least two affected family members with POF [14]. The study was approved by the Ethical Research Committee (ID:10RG#:10RG0008812), Medical Research Institute, Alexandria University. A written consent was obtained from each patient included in the study.

Conventional cytogenetics

Cytogenetic analysis was performed on GTG-banded metaphase chromosomes prepared from peripheral lymphocyte cultures, using a standard protocol that generated 450–550 band resolutions [15]. A minimum of 30 metaphases per patient were analyzed. If any cell among the 30 showed an aneuploid cell (45,X or 47,XXX), an additional 20 cells were counted. The only tissue studied routinely was blood, for which reason this report is confined to lymphocyte analysis only. Chromosome polymorphisms, for example pericentic inversion of chromosome 9 and centromeric heterochromatin variants, were recorded but classified as normal.

FISH analysis

Among patients with normal constitutional karyotypes, FISH analysis of interphase lymphocyte preparations was performed on 26 patients with POF (12 patients with primary amenorrhea and 14 with secondary amenorrhea) to detect low level mosaicism of monosomy X or trisomy X with normal cell line. FISH study was performed on nuclei conserved from chromosomal preparations used for karyotyping. Thirty control women aged between 17 and 37 years and with normal reproductive history were also studied using interphase FISH to establish the range of normality.

FISH technique was performed using Cytocell aquarius kit (REF: LPA 002) for X chromosome centromere, Xp11.1- q11.1 (DXZ1) Green, Y chromosome centromere, Yp11.1-q11.1 (DYZ3) Orange, and chromosome 18 centromere, 18p11.1- q11.1 (D18Z1) Blue probe combination. Probes and slides preparations as well as hybridization and washing techniques were performed according to manufacturing protocols as follows: cell samples were spotted onto a clean super frosted slides; each slide was labeled with the patient's name, date, probe name, and type of sample. The slides were incubated in 2× SSC/0.5% NP40 or 2× SSC, at room temperature (RT) for 2 min, then dehydrated through 70%, 90%, and 100% ethanol series, 2 min each at RT, then they were allowed to air dry. After initial denaturation for 5 min at 74 °C, the slides were hybridized with 10 µl of probe mixture at 37 °C overnight. When the hybridization time was completed, the slides were washed using 0.4× SSC/0.3NP-40 kept in 72 ± 1 °C and 2× SSC/0.1%NP-40 kept at RT for 2 min each. The slides were dehydrated through 70%, 90%, and 100% ethanol 1 min each at RT. Finally, counterstain was applied to the slides. The slides were screened under fluorescent microscope (Olympus microscope BX51/61) equipped with single band-pass filter (DAPI/ Green , Red and Blue). Image capture was done using a color digital JAI progressive scan CCD camera (Olympus, Japan), and the software CytoVision (Applied Imaging, UK). The results of hybridization were assessed by number of signals interphase cells. A total of 500 interphase nuclei from each patient were analyzed. Only cells with monosomy X and trisomy X were taken into consideration to determine the frequency of X chromosome aneuploidy. Cells with other X chromosome anomalies (e.g., tetrasomy X) were neglected as they were small categories and hence irrelevant.

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Qualitative data were described using number and

Table 1 Demographic and clinical data of the POF patients

	Mean ± SD.
Age (years)	
Patients	20.83 ± 4.58
Controls	25.90 ± 6.62
Age at menarche	13.94 ± 1.24
Age of onset of menstrual dysfunction	17.81 ± 3.96
Age of amenorrhea	19.12 ± 4.32
Body mass index (BMI)	22.14 ± 3.23
LH	49.22 ± 12.02
FSH	100.53 ± 29.81

percent. Quantitative data were described using mean ± standard deviation. Chi-square test was performed for categorical variables to compare between different groups. Significance of the obtained results was judged at the 0.05% level.

Results

Clinical characteristics and demographic data

Table 1 summarizes the demographic and clinical data of the POF patients included in the study. From 30 POF patients, 14 patients presented with primary amenorrhea and 16 with secondary amenorrhea, with the mean age of diagnosis 19.12 ± 4.32 years old. Patients' BMI was 22.14 ± 3.23, LH and FSH levels were 49.22 ± 12.02 (normal range: (4–25 IU) and 100.53 ± 29.81 (normal range, 10–75 IU) respectively, and no specific somatic abnormalities were detected. Five cases (16.66%) were found to have one first- or second-degree relative with POF and 3 (10%) familial cases were identified. Ultrasound findings in POF patients were summarized in Table 2. Of 14 cases with primary amenorrhea, 9 (64.28%) were found to have streak gonads and hypo plastic uterus and 5 patients (35.71%) were with small sized uterus and ovaries, while in POF patients with secondary amenorrhea, low ovarian volume were found in 7 (43.75%) cases, thin endometrial interface in 6 (37.5%) cases, and normal size uterus and ovaries in 3 (18.75%) cases.

Chromosomal abnormalities

Conventional cytogenetic analysis of peripheral blood lymphocytes revealed chromosomal aberrations in 7 cases (23.3%) (Table 3). Among those 7 cases, 3 patients (42.9%) showed structural chromosomal aberrations (two patients with primary amenorrhea and one patient with secondary amenorrhea) and 4 patients (57.1%) showed numerical aberrations (two patients with primary amenorrhea and two with secondary amenorrhea). Two of The structural aberrations (66.7%) were non mosaic which included partial deletion of the long arm of one X chromosome in one patient with secondary amenorrhea and X-autosome translocation in the other with primary

Table 2 The ultra sound finding detected in patients with primary amenorrhea and in patients with secondary amenorrhea

Ultra sound findings	Number of cases with primary amenorrhea	%	Number of cases with secondary amenorrhea	%
Streak gonads (absent ovaries) and hypo plastic uterus	9	64.28	/	0
Small size uterus with small ovaries	5	35.71		0
Low ovarian volume	/	0	7	43.75
Normal size uterus with thin endometrial interface	/	0	6	37.5
Normal size uterus and ovaries	/	0	3	18.75
Total	14	100	16	100

Table 3 Chromosomal aberrations in POF patients

Type of amenorrhea in POF patients (primary or secondary)	Type of chromosomal aberration (numerical or structural)	No. of patients	Karyotype
Chromosomal aberrations in POF patients with primary amenorrhea	Structural chromosomal aberrations	2	45,X[22]/46,X,add(X)(q28)[28]
			46,X,t(X;9)(q26;q21)
	Numerical chromosomal aberrations	2	mos 47,XX,+ mar[4]/46,XX[46]
			mos 45,X[4]/46,XX[46]
Chromosomal aberrations in POF patients with secondary amenorrhea	Structural chromosomal aberrations	1	46,X,del(Xq)(q13-qter)
	Numerical chromosomal aberrations	2	46,XX, inv (9)(p11q13)[42]/45,X, inv (9)(p11q13)[5]/47,XXX, inv(9)(p11q13)[3]
			mos 45,X[4]/46,XX[46]

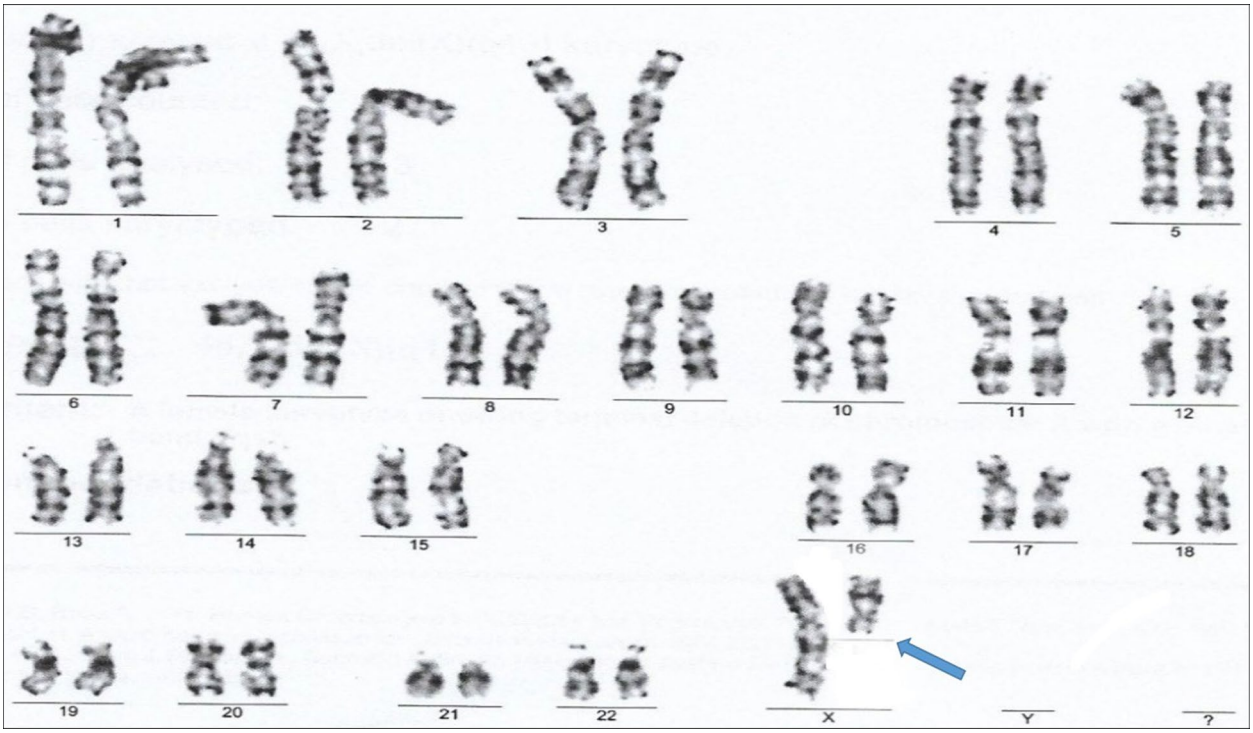

Fig. 1 Female karyotype with partial deletion of the long arm of an X chromosome with a break in band Xq13 [46,X,del(Xq)(q13-qter)]

amenorrhea (Figs. 1 and 2). This X autosome translocation was de novo as her parents were analyzed cytogenetically and they were normal. Mosaicism has been detected in primary amenorrhea patient (33.3%) with structural aberrations who had 2 cell lines one with 45,X and the other cell line with 46,X,add(X)(q28), and this additional material on the long arm of X chromosome is de novo and of unknown origin as parental karyotyping has been performed and revealed normal results (Fig. 3). One patient has been detected to have pericentric inversions of chromosome 9 and considered as a normal polymorphism. All numerical aberrations were mosaic with the presence of two or more cell lines with different proportion, one normal cell line with 46,XX, and the other cell lines either 45,X, 47,XXX or 47,XX,+mar of unknown origin as FISH analysis which has been performed for chromosomes X in this patient revealed normal result. The frequency of chromosomal aberrations detected in patients with primary amenorrhea (28.6%) was higher than that detected in patients with secondary amenorrhea (18.75%) (Table 4).

FISH analysis of interphase nuclei from peripheral blood lymphocytes prepared from the reference group revealed monosomy of X chromosome in 2.6% of cells (1.8–3.4%), double X signal in 97% of cells (97–97.4%), and triple signals in 0.4% of cells (0.2–0.8%). No four signals cells were detected. As regard POF patients group, there were 6.9% cells (2.6–40%) with monosomy X, 91% of cells (56.2–96.2%) with double X signal, 2% of cells (0–3.8%) with triple X signals, and 0.1% of cells (0–0.4%) with four signals (Table 5). Only cells with double signals of chromosome 18 have been included to ensure great hybridization efficiency (18-X: 2/1-2/2-2/3 and 2/4) (Fig. 4a–c).

By means of statistical analysis using χ^2 test for variance to compare between POF patients and reference group, there was a significant difference between the data distribution of the two groups ($P < .001$) (Table 5).

Discussion

A great number of causes have been implicated in POF, and in many cases the underlying genetic etiology remains unknown. Familial POF is considered when the patient has two or more affected family members with POF. Ten percent of our patients were reported as familial. In previous studies, familial POF incidence has been reported to be between 4 and 33% [3, 4, 10, 14, 16–19]. Chromosomal aberrations have been detected in several patients with POF worldwide. It was documented that two intact X chromosomes is necessary for normal ovarian development and function [20]. Chromosomal study on peripheral blood lymphocytes from POF

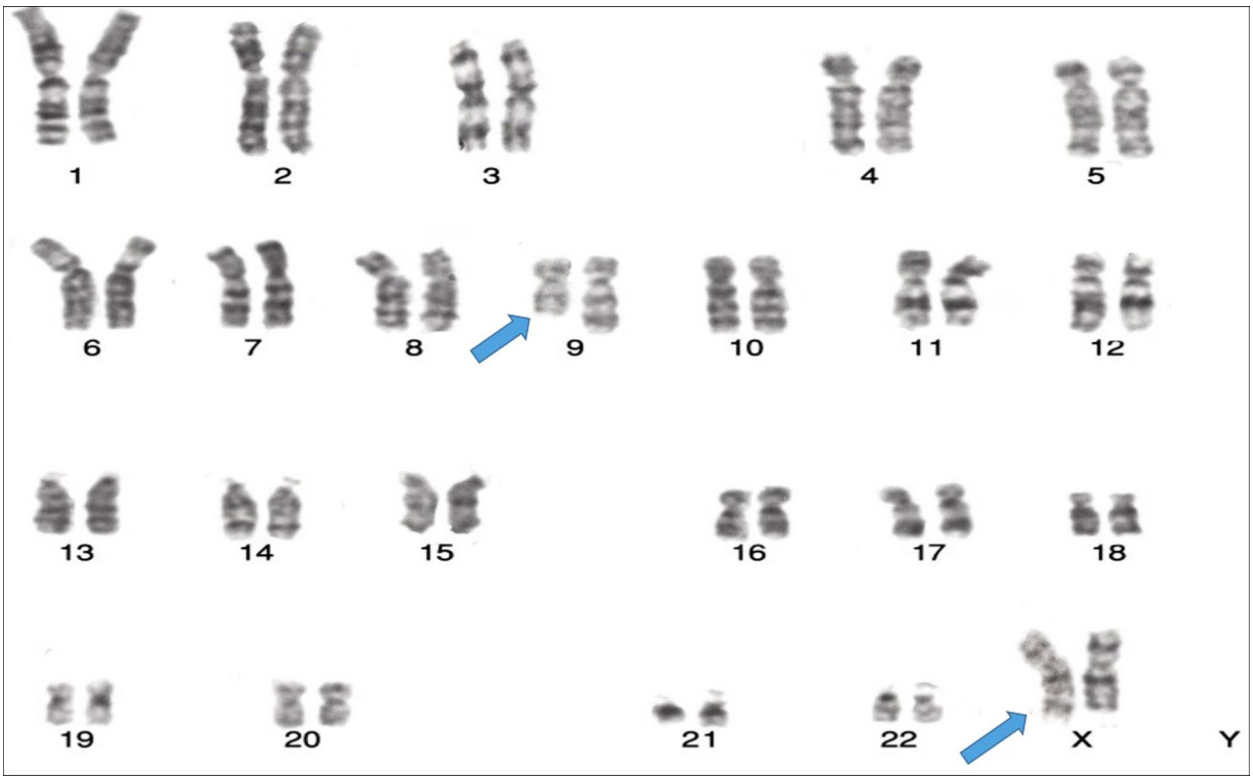

Fig. 2 Female karyotype with a reciprocal translocation between an X chromosome and a 9 chromosome with breakpoints at bands Xq26 and 9q21 (46,X,t(X;9)(q26;q21))

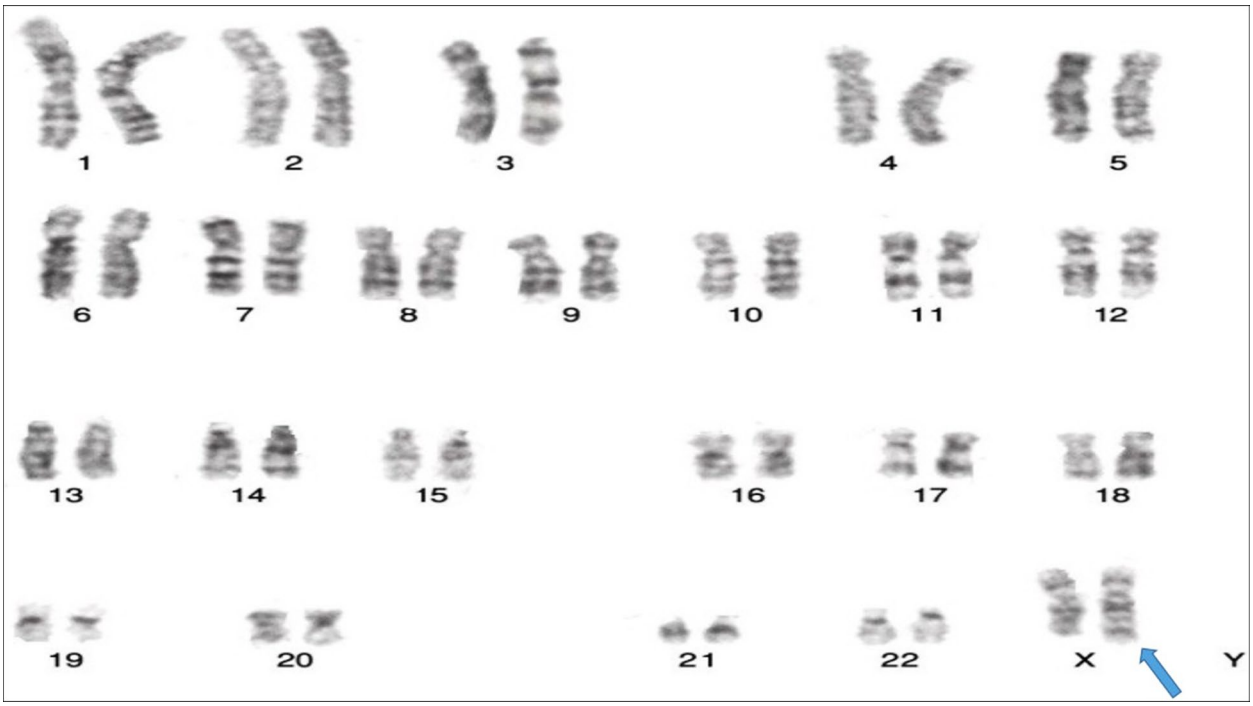

Fig. 3 Female karyotype with additional material of unknown origin attached to band Xq28 (46,X,add(X)(q28))

Table 4 The frequency of chromosomal abnormalities detected in patients with primary amenorrhea and that detected in patients with secondary amenorrhea

	Chromosomal abnormalities detected in patients with:		*p* value
	Primary amenorrhea	Secondary amenorrhea	
Number	**4/14**	**3/16**	**0.675**
%	28.6%	18.75%	

p: *p* value for comparing between primary and secondary

patients is considered as an essential method for detection of cytogenetic abnormalities in those patients [21]. It was postulated that premature centromeric division (PCD) may be a possible mechanism by which numerical abnormalities of chromosomes can occur [22]. Moreover, there were different mechanisms by which X chromosome mosaicism may accelerate follicular atresia. These mechanisms may include aberrant pairing of chromosomes during meiosis, absence or increased expression of X linked genes which may influence oocyte maturation, and impaired genetic control which may lead to aberrant meiosis and oocyte atresia [23].

In the present work, 23.3% of POF patients were found to have chromosomal aberrations. This result was consistent with that reported in many studies of different populations and higher than that detected in others (Table 6) [8, 17, 24–32]. We attributed this variation to the difference in the sample size, selection criteria or ethnicity. There was no significant difference between the frequency of chromosomal abnormalities detected in patients with primary amenorrhea and with that detected in patients with secondary amenorrhea ($P > 0.05$). X chromosome numerical and structural abnormalities were the most frequent. The numerical aberrations were more frequently mosaic than the structural ones. Four patients (13.3%) were found to have numerical chromosomal aberrations, 45,X cell lines were reported in 3 of them in mosaic form with a normal cell line that represented the majority of cells and these results were consistent with the fact that there is a necessity of two intact X chromosomes for normal ovarian function [20]. The fourth patient was found to have a marker chromosome in a few cells; we confirmed that this marker did not belong to the sex chromosomes after doing the FISH analysis using X and Y probes and we could not determine the relation between this marker chromosome and amenorrhea in that patient. The structural aberrations were mainly in the long arm of the X chromosome, and this data is of interest because two critical regions for POF have been documented which are Xq13-Xq21 (POF2) and Xq23-Xq27(POF1) [33, 34]. For more than a decade, POF has been associated with deletions of X-chromosome; deletions within these critical regions were detected in POF patients in several previous studies, and they concluded that these regions contain critical genes that are essential for proper ovarian function [35–39]. In the present study, one patient was found to have a large terminal deletion in the long arm of one X chromosomes in all examined metaphases. This deletion was within the critical regions for POF and we suggested that the occurrence of POF in this patient may be due to haploinsufficiency of X-linked genes that may be having a role in normal ovarian function. The parents were not available so we could not decide if this deletion is de novo or inherited. X-autosome balanced translocations in which the breakpoints occur in a critical region of the X chromosome may be associated with POF. The mechanism by which these balanced translocations can cause POF is either due to destruction of X linked genes essential for normal ovarian function such as aminopeptidase gene, XPNPEP2, effect of position alteration, or due to chromosomal effect such as impairing X inactivation or inhibition of mitotic pairing [40]. The effect of position alteration can be explained by the effect of POF2 critical region in down-regulation of ovarian expressed autosomal genes translocated to the X chromosome in order to reach an equal level of gene expression between the X chromosome and the autosomes. In most POF patients with X, autosome balanced translocations the breakpoints were clustered in POF2 region. Moreover, it was found that only deletions involving POF1 region were associated with POF, while large interstitial deletions of POF2 were not as it is gene poor region. POF2 region has a highly heterochromatic organization, which could be responsible for POF

Table 5 FISH analysis on interphase nuclei data and statistical analysis

	One signal (1/2)	Two signals (2/2)	Three signals (3/2)	Four signals (4/2)	Total
Controls	394 (2.6%)	14476 (97%)	65(0.4%)	0 (0%)	**14935**
Patients	897 (6.9%)	11845 (91%)	261 (2%)	7 (0.1%)	**13,010**
***p* value**	**< 0.001***	**< 0.001***	**< 0.001***	**0.005***	

p: *p* value for comparing between patients and controls

* Statistically significant at $p \leq 0.05$

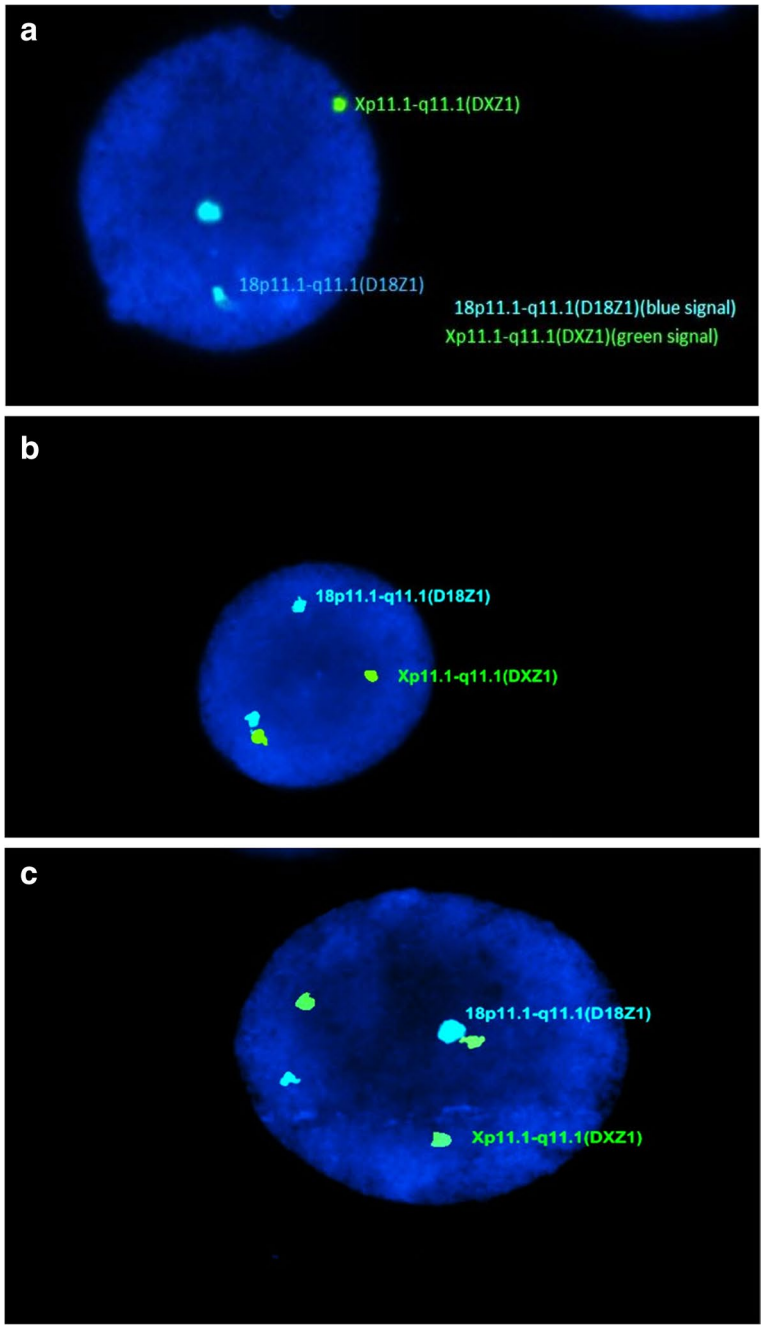

Fig. 4 FISH analysis on interphase nuclei. FISH was performed using alpha satellite probes of X (green) and and 18 (aqua) chromosomes. The images show the different categories of signals detected: **a** monosomy X mosaicism (one X signal and two 18 signals). **b** Disomy X (two X signals and two 18 signals). **c** Trisomy X (three X signals and two 18 signals)

through alteration of the epigenetic modifications of autosomal genes through a position effect [41, 42].

In this study X-autosome translocation has been detected in one patient, where the break point was in Xq26 which exists within the POF1 critical region. In this case, the translocation is de novo as her parents showed normal karyotyping results. Another de novo structural abnormality that was detected in the present study is the presence of an additional material on the long arm of the X chromosome in a mosaic form with 45,X cell line.

Table 6 Summary of frequency of chromosomal abnormalities in different population studies of POF

Population	Frequency of chromosomal abnormalities (%)	Reference
American	25.4	Rebar and Connoly (1990) [24]
Chilean	32.0	Castillo et al. (1992) [25]
English	2.5	Davision et al. (1998) [26]
American	13.3	Devi and Benn (1999) [8]
Chinese	12.5	Zhang et al (2003) [27]
French	8.8	Portnoi et al. (2006) [28]
Turkish	25.3	Ceylaner et al. (2010) [17]
Dutch	12.9	Janse et al. (2010) [29]
Tunisian	10.8	Lakhal et al. (2010) [30]
Italian	10.0	Baronchell et al. (2011) [31]
Indian	24%	Kumar et al. (2012) [32]
Egypt	23.3	Present study

Spectral karyotyping is not available in our lab so it was difficult to identify the origin of this additional material and to decide if it has a role in POF or not. Pericentric inversion of chromosome 9 was considered as a common polymorphism in the general population but, with unclear mechanism. Several studies have reported that there is a high frequency of chromosome 9 pericentric inversion among infertile females [43–45]. unfortunately, there were no sufficient studies reporting the frequency of this balanced structural aberrations in POF. In the present study, one patient was found to have a pericentric inversion in chromosome 9 which was associated with numerical mosaicism of the X chromosome and the relation between this inversion and the associated mosaicism was unclear.

By indefinite mechanism, 45,X karyotype is associated with ovarian dysfunction and whenever there is a mosaicism with normal cell line 46, XX, the number of ovarian follicles increase till they reach the maximum with the lowest percentage of 45,X cells [46]. In some patients, this mosaicism is too low in peripheral blood lymphocytes to be detected by conventional cytogenetic techniques but is still of great implication on ovarian function as the level of mosaicism may be different in different tissues including ovaries [47]. Evaluating this low level of 45,X mosaicism in POF patients may give a clue to the mechanism by which this mosaicism can affect the ovarian function. FISH analysis is a sensitive technique for detection of this mosaicism and can detect even very low mosaicism that cannot be detected by conventional cytogenetics [11, 48, 49]. Comparing the detection rate for mosaicism by both techniques in previous studies revealed that FISH can detect about 74% of cases while metaphase chromosomal analysis can detect only about 6% at a confidence level of 95% [50, 51]. Based on these findings, we performed FISH analysis for POF patients with normal karyotypes to detect low level mosaicism of X chromosome. We used chromosome 18 centromeric probe as a reference signaling in order to evaluate the hybridization efficiency, Moreover, we have a reference group for validation. We reported a high percentage of X chromosome aneuploidy especially for monosomy X in POF patients compared to the reference group. In particular, we searched for mosaicism in a reference group of non-affected females to establish the level of the physiological mosaicism (Table 3). As regards the POF patients group, we reported that there was a statistical significant higher percentage rate of cells with one signal (6.9%) and with 3 signals (2%) ($P < .001$, χ^2 test). These findings were in harmony with previous studies [30, 31, 51]. Guttenbach et al. reported 3.3% of X monosomy in a group of normal females aged 16–50 years and similar results were reported by Lakhal and colleagues who found 2.33% of X monosomy in the control group [30, 51]. Baronchelli et al. found that the percentage of monosomy X is 2.7% in the reference group [31]. By comparing our reference group, literature reference groups, and our POF patients group, we found that there was a significant increase in X chromosome monosomy in our POF group (6.9% of monosomy X, $P < .001$) and we suggested that this low level mosaicism may be the underlying cause of ovarian function cessation in those patients. Similar results were reported in previous studies [30, 31, 51]. They compared between POF patient group and a general population group as well as control groups and concluded that the low-level mosaicism of the X chromosome may be the origin of POF pathology as it may be attributed to the lack of adequate number of follicles due to earlier oocyte aging [31].

Intact X chromosomes have a pivotal role in development and maintenance of ovarian function. Low level mosaicism of numerical X chromosome anomalies could influence survival rate and accelerate ovarian cells aging by different mechanisms that may include; decrease in the number of germ cells or acceleration of its postnatal destruction and early oocyte atresia [52]. The X chromosome has a great role in POF pathology as females showing monosomy X or trisomy X are predisposed to POF development. Although most triple X females reported to have normal ovarian function and normal fertility but some of them exhibit late onset menarche, menstrual disturbance, and POF [53, 54]. Considering the previous data and our data, it is possible to hypothesize that X chromosome mosaicism could be the underlying pathological etiology of POF which may be explained by early aging of oocyte and premature follicular atresia.

Causes of POF are an area of great research potential. Understanding of the ovarian failure underlying mechanisms may facilitate the development of new era of management for POF patients as well as for ovarian function optimization in normal women who are asking for fertility time expansion or enhancement of fertility for the purpose of assisted reproductive technology (ART).

The strength to our study is that it is the first study that performed on POF Egyptian population. But the limitation may be related to the small sample size, as larger sample size may allow more detection of chromosomal abnormalities and better understanding of the underlying mechanisms of POF.

Conclusion

Considering our data, we concluded that X chromosome aberrations including low level mosaicism may be related to POF pathology as premature follicular atresia may be due to accelerated oocyte aging associated with increased mosaicism. Cessation of ovarian function in POF patients is irreversible so early diagnosis by conventional cytogenetic analysis or by FISH technique may be of great importance to give genetic counseling for those females and to advise them for early conception or oocyte harvesting and preservation. Moreover, new molecular techniques particularly next-generation sequencing (NGS), is a powerful tool to identify genome wide variants including chromosomal abnormalities and could contribute to understanding of POF pathology that will help in providing a proper genetic counseling.

Abbreviations

ART: Assisted reproductive technology; CGH: Comparative genomic hybridization; CNV: Copy number variation; FISH: Fluorescent In Situ Hybridization; POF: Premature ovarian failure.

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Authors' contributions

NMI: conceptualized the study, collection and analysis of primary data, shared in the lab work, interpretation of data, initial manuscript preparation, and submission. GME: shared in the selection of participants, clinical examination of the studied cases, shared in the lab work, revision of the manuscript. All authors approved the final version of the manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of the Medical Research Institute (10 GR 0008812). An informed written consent was obtained from all participants in the study according to the Declaration of Helsinki.

Consent for publication

Consent for publication in MEFS journal was obtained from all authors.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Department of Medical Genetics, Faculty of Medicine, King Abdul-Aziz University, Jeddah, Saudi Arabia. [2]Department of Human Genetics, Medical Research Institute, Alexandria University, Alexandria, Egypt.

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