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Research Letter

Babies born from three young infertile sisters with premature ovarian insufficiency caused by inherited fragile X syndrome: An intergenerational report

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To the Editor,

Fragile X syndrome (FXS) is a common cause of inherited premature ovarian insufficiency (POI) in young women and intellectual disability in male offspring. Discovered in 1991 [1], the *FMR1* gene is associated with a DNA sequence comprising of repeated CGG trinucleotides. Currently, four diagnostic categories are defined according to the sizes of the CGG repeats: full mutation (FM), >200 repeats; premutation (PM), 55–199 repeats; intermediate (or gray zone), 45–54 repeats; and unaffected carriers, <45 repeats [2]. PM carriers have been identified in 3% of women with sporadic POI and up to 11% of women with familial POI [2]. Currently, the molecular mechanisms underlying POI are not clear; however, FM appears to protect females from developing POI [3,4].

FXS screening is not covered by health insurance in Taiwan because of the rare prevalence of PM alleles, with incidence as low as 1/1674 in contrast to that of Caucasian populations (3.3–3.7%) [5]. FXS screening in such a low prevalence country should be reserved for patients with suspected hereditary disease. At least two tertiary reproductive centers and our university-based reproductive center were unaware of POI in the older sister until consecutive siblings turned out to have similar findings.

Most clinicians have opted for assisted reproductive technology (ART) alone rather than investigating the underlying causes of POI. Owing to the advancement of ART, infertility specialists have decreased awareness of the possible causes for POI. The following is a brief family history of the three sisters seeking ART. The three sisters underwent the same protocol of ovulation induction, and achieved live births after *in vitro* fertilization/embryo transfer at our center. (Table 1) They were diagnosed incidentally as being carriers of a PM of the *FMR1* gene antenatally, which may explain their POI at a young age (by 30 years). Here, we report on the number of triplet repeats in *FMR1* gene mutation among three infertile female siblings and the extent of intergenerational differences in mutation status (Figure 1).

The American College of Medical Genetics and the American College of Obstetrics and Gynecology suggest *FMR1* testing for patients presenting with elevated follicle-stimulating hormone levels, infertility, and/or POI, especially when there is a family history of POI, FXS, or undiagnosed mental retardation [2].

The PM may become longer repeats, or even FM, in the next generation. The risk of expanding from the maternal PM to an FM in the offspring depends on the size of the repeats and is frequently unpredictable [6].

In conclusion, women with familial POI who are at an increased risk of having an *FMR1* PM should undergo fragile X testing. Clinicians should inform carriers about the implications of the *FMR1* gene PM and make appropriate referrals to genetic counselors for the lifelong health risks for the family members and offspring.

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Table 1
Patient characteristics and ART protocols.

	Oldest sister	Middle sister	Youngest sister
Age	34	32	31
Duration of infertility	3	1	2
Previous IVF cycle	0	0	1
AMH (ng/mL)	0.24	0.29	0.68
Cycle day 3 FSH/LH (IU/L)	31.1/11.3	9.4/3.3	10.3/4.1
Male factor	−	+	−
Ovulation-stimulation protocol	GnRH antagonist		
rFSH (d)	200 IU (8)	200 IU (8)	200 IU (8)
rLH (d)	150 IU (8)	150 IU (8)	150 IU (8)
Cetrotide (d)	0.125 mg (3)	0.125 mg (4)	0.125 mg (4)
Growth hormone (d)	4 IU (5)	4 IU (5)	4 IU (5)
Oocyte retrieval in first IVF cycle	1	1	3
Oocyte retrieval in second IVF cycle	2	4	4
Surplus frozen embryos	0	2	2
Embryo transferred	2	2	2
Embryo quality	4G2F5/2G2F5	9G3F15/7G3F5	8G1/6G3
Transfer day	D + 2	D + 3	D + 3
Newborn weight (g)	2814	3040	2530
Gestational age	36 wk 5 d	38 wk 2 d	39 wk
Baby's sex	Male	Male	Female
Baby's CGG repeats	29/	65/	29/30

AMH = Anti-Müllerian hormone; ART = Assisted reproductive technology; FSH = Follicle stimulating hormone; GnRH = Gonadotropin releasing hormone; IVF = In vitro fertilization; LH = Luteinizing hormone; rFSH = Recombinant follicle stimulating hormone; rLH = Recombinant Luteinizing hormone.

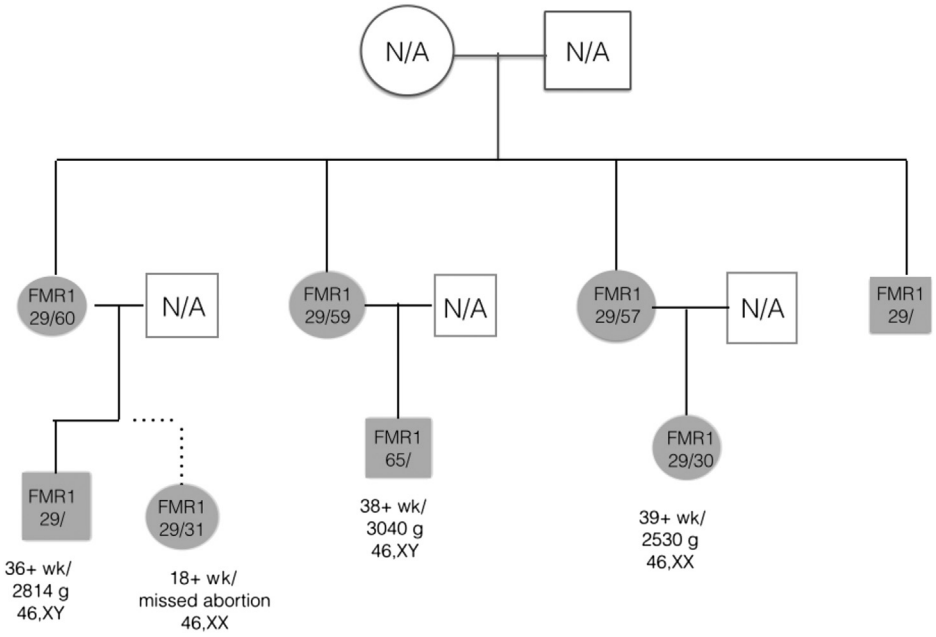

Figure 1. Family pedigree of the siblings with FXS syndrome. FXS = fragile X syndrome; N/A = no analysis.

Conflicts of Interests

The authors have no conflicts of interest relevant to this article.

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