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CLINICAL REPORT

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Terminal Deletions of the Long Arm of Chromosome X That Include the *FMR1* Gene in Female Patients: A Case Series

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Terminal deletions on the X chromosome in female patients may be detected as part of a work up for infertility, premature ovarian insufficiency (POI) or in screening for fragile X carrier status. We present the clinical, cytogenetic and molecular features of four patients with terminal deletions of chromosome X that include the *FMR1* gene, and discuss biological and genetic implications of this deletion. Providers should be aware of possible identification of Xq27 deletions as a potential outcome of fragile X screening. © 2011 Wiley-Liss, Inc.

Key words: fragile X; Xq deletion; premature ovarian insufficiency; non-random X inactivation

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INTRODUCTION

Terminal deletions at Xq27 in female patients may be detected as part of a work up for infertility or premature ovarian insufficiency (POI). Such deletions may also be detected after an abnormal finding in screening women for fragile X, a common cause of inherited mental retardation. We present four female patients with terminal deletions of chromosome Xq that include the fragile X mental retardation 1 (*FMR1*) gene and summarize their clinical, cytogenetic and molecular features.

CLINICAL REPORTS

Patient 1

The patient presented for genetic counseling to discuss her abnormal karyotype results, which were obtained at another institute. She was 42 years old, gravida 1, para 0010. She reported symptoms of premature ovarian insufficiency present since age 34, particularly hot flashes. She reported secondary amenorrhea since age 39. Premature ovarian insufficiency was diagnosed at age 40 based on her elevated FSH. Her thyroid and adrenal functions were reported as normal. She had normal intelligence, normal stature, and no dysmorphic features. At the time of assessment she was considering in vitro fertilization with egg donation. Her family history was negative for fertility problems, POI, or mental retardation.

Chromosomal analysis revealed an abnormal female karyotype with a terminal deletion of a segment of the long arm of X chromosome, involving q27–q28 (Fig. 1). Molecular analysis of the *FMR1* gene by PCR showed 29 CGG repeats. However, Southern analysis with *Eco*RI/*Eag*I, and probe StB12.3 showed one unmethylated 2.8 kb fragment representing the normal active X; the normal methylated 5.2 kb fragment representing the inactive X was absent [Oberle et al., 1991]. These results are consistent with a deletion of the *FMR1* gene region on one X chromosome and skewed X inactivation in favor of the normal X.

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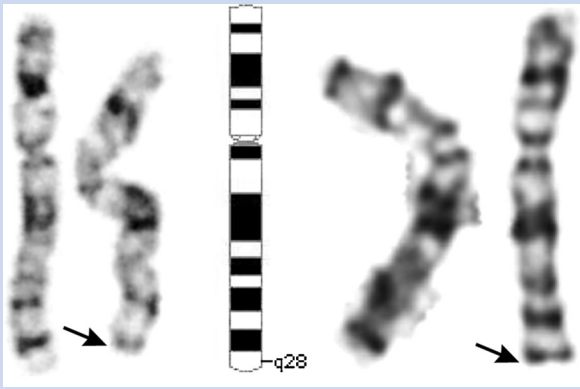

FIG. 1. The X chromosomes of patients 1 and 4. The X chromosomes from patient 1 are on the left and from patient 4 on the right. The X chromosomes with the Xq deletion are on right side of each pair. An arrow indicates the deletion. An idiogram of the X is placed between the chromosome pairs.

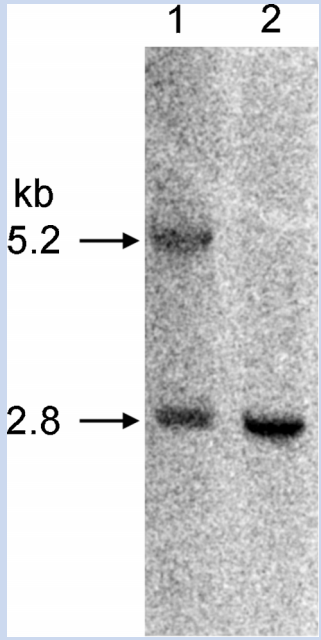

FIG. 2. *FMR1* Southern analysis of patient 2 with a deletion of Xq27.3 to terminus. DNA was digested with *Eco*RI/*Eag*I and hybridized with probe StB12.3. Lane 1: normal female with the 2.8 kb fragment representing the normal active X chromosomes and the 5.2 kb fragment representing the normal inactive X chromosomes. Lane 2: patient with Xq27.3 deletion with the 2.8 kb fragment reflecting complete skewing of the X inactivation patterns.

Comparative genomic hybridization (CGH) was performed using the custom designed Agilent microarray, which includes 44,000 probes, with probe density of 5–10 kb in clinically relevant regions, including sub-telomeres, peri-centromeres, and the common microdeletion/duplication regions according to the human genome build hg18. The patient was found to harbor an 11 Mb terminal deletion within the region of Xq27.3–28 [arr cgh Xq27.3–28(143,513,379–154,888,082)x1].

Patient 2

The 34-year-old gravida 1 para 0 patient was nondysmorphic, and had normal stature and intelligence. Amniocentesis, performed for increased risk of aneuploidy on Quad screening revealed that the female fetus carried a deletion on the long arm of the X chromosome, possibly at q27.3 to terminus. Chromosome analysis of the mother revealed that she carried the same deletion. Molecular analysis of the fragile X locus to define better the breakpoint showed 29 repeats by PCR and one unmethylated fragment of 2.8 kb on Southern analysis (Fig. 2). Analysis of the androgen receptor and fragile X genes showed complete skewing with the normal X active in both mother and fetus. Prenatal analysis of a second pregnancy indicated that the female fetus inherited the same Xq27 deletion and also had skewed X inactivation. Follow-up of the daughters at 5 and 3 years of age showed normal growth and development.

Patient 3

This 34-year-old gravida 5 para 3013 woman had no personal or family history of infertility. She had normal stature and intelligence, and is nondysmorphic. She has three daughters. During her fourth pregnancy she was screened for fragile X, and identified to carry a single *FMR1* repeat in the normal range (30 CGG repeats), as well as a single 2.8 kb fragment on Southern analysis. High resolution chromosome analysis of the patient showed a deletion of Xq27.3 to terminus, which was also confirmed by FISH (Fig. 3).

Patient 4

The 19-year-old gravida 1 para 0 woman was screened for fragile X during her current pregnancy. She had no family history of POI or infertility. She was nondysmorphic and had normal intelligence and stature. She was found to carry a single 30 repeat *FMR1* allele and a single 2.8 kb fragment on Southern analysis. The initial cytogenetic studies failed to identify any chromosome abnormality. Following detection of the *FMR1* results, the cytogenetic laboratory re-examined the Xq27.3 region and identified a deletion from Xq27 to terminus (Fig. 1). BAC array with a resolution of ~1 Mb showed that the deletion size was ~9.5 Mb [arr cgh Xq27.3q28(145,344,165–154,845,961)X1]. Coordinates are according to the human genome build hg18. The patient declined any additional studies for the pregnancy.

METHODS

Chromosome Analysis and Array Based Comparative Genomic Hybridization

The chromosome analysis was performed through clinical laboratories Quest and CytogenX. A whole genome chromosomal microarray for Patient 1 was performed with custom designed 44 K oligoarray, using the Agilent platform, which has ~50 kb resolution in targeted regions based on the hg18 build of the human genome

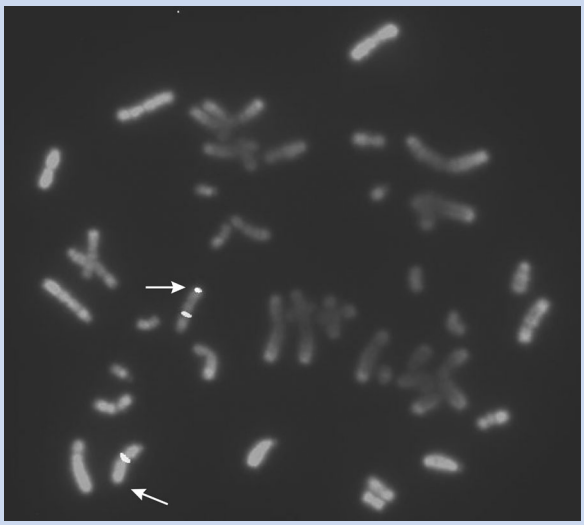

FIG. 3. FISH performed on patient 3, showing lack of hybridization of the telomere probe to the deleted X chromosome.

sequence. Aberrations were confirmed by FISH. Comparative genomic hybridization for Patient 4 was performed with the Quest bacterial artificial chromosome (BAC) array, which equates to an average of 1 BAC/Mb across the genome, and additional coverage at subtelomeric and pericentromeric regions. Coordinates are given according to the human genome build hg18.

PCR and Southern Molecular Analysis

Genomic DNA was isolated from peripheral blood (5–10 ml) with a Flexigene kit (Qiagen, Valencia, CA). Polymerase chain reaction (PCR) and Southern analysis of the fragile X locus CGG repeat region [Nolin et al., 2003] were used to determine fragile X status. Briefly, the FMR1 CGG repeat region was amplified by PCR, the products were separated by denaturing polyacrylamide gel electrophoresis, transferred to nylon membrane and hybridized with an alkaline phosphatase-linked probe complementary to the triplet repeat sequence. The fractionated PCR products were visualized by chemiluminescence. Southern analysis of genomic DNA *Eco*RI–*Eag*I digestion products was performed using radiolabeled StB12.3 DNA as a probe [Rousseau et al., 1991; Nolin et al., 2003]. Southern analysis autoradiograms were visualized by phosphorimaging: a Fujifilm BAS-MS imaging plate read by a Fujifilm FLA-7000 plate reader (Fujifilm, Stamford, CT).

DISCUSSION

The four patients had cytogenetically visible terminal deletions involving Xq27 and the *FMR1* gene situated at Xq27.3 (Table I). The patients varied in their presentation. Two were identified because of initial cytogenetic analysis (Patients 1 and 2) and two (Patients 3 and 4) because of abnormal findings in routine maternal fragile X testing. Patient 1 was diagnosed with POI, while Patient 2 was identified because of the fetal karyotype obtained following a Quad screen. CGH, performed for two patients, showed deletions of ~11 and 9.5 Mb. According to the UCSC human genome browser assembly hg19, the deleted areas contain over 100 genes, with more than half not fully characterized. Xq27-ter is a gene rich region with many genes associated with severe/lethal X-linked syndromes. It is unlikely that the deletion sizes in the cases were identical. Two of our patients with CGH studies differed and even in familial cases of Xq deletions, intra-familial phenotypic variability exists [Rossetti et al., 2004].

The four females, and the two daughters of Patient 2 with the Xq deletion have normal intelligence and stature indicating the deletion is compatible with a normal phenotype. Each of the females has completely skewed X inactivation as evidenced by the fragile X analysis with only the normal X as the active X chromosome. The fact that the deletion is never expressed because of extreme skewing explains the lack of somatic abnormalities. The two daughters of Patient 2 inherited the Xq deletion from their mother indicating that the deletion is not lethal in oocytes. The skewed X inactivation pattern, however, does suggest that the deletion is lethal at a cellular level early in development and that only the cells with the normal X as the active chromosome survive. The Xq deletions are likely to be lethal in males because of the many essential genes contained within the deleted regions. However, Schmidt et al. [1990] reported on a 5-year-old girl with del Xq27.1–q27.3 who was phenotypically normal but developmentally delayed, in whose fibroblasts the deleted X was preferentially early replicating. Probst et al. [2007] reported on a 6-year-old girl with intellectual disabilities and mild dysmorphic features and a ~2.7 Mb microdeletion of Xq27.3 and the *FMR1*, whose peripheral leukocytes showed random X inactivation. Perhaps the smaller size of the deletions in these patients did not result in skewing.

As fragile X screening of pregnant women becomes increasingly common, the identification of Xq deletions similar to the ones

TABLE I. Clinical Features of Patients With Xq and *FMR1* Deletions

	Age	Fertility status	Xq27–28 deletion (Mb)	CGG repeat	Southern analysis *Eco*RI/*Eag*I
Case 1	42	POI	11	29	2.8 kb, unmethylated
Case 2	35	Pregnant	No CGH	29	2.8 kb, unmethylated
Case 3	34	Pregnant	No CGH	30	2.8 kb, unmethylated
Case 4	19	Pregnant	9.5	30	2.8 kb, unmethylated

described here, may also increase. The identification of a deletion from Xq27 to terminus is unlikely to have serious consequences on the phenotype of live born females with inheritance of a normal paternal X chromosome if complete skewing of X inactivation in favor of the normal X occurs. Whether the deletion is associated with problems such as POI remains to be seen. Males that inherit the deleted X chromosome probably result in a miscarriage.

POI is defined as secondary hypergonadotropic amenorrhea of 6 months' duration, occurring prior to age 40 years [Coulam, 1982; Toniolo and Rizzolio, 2007]. Its prevalence is 1% of the female population [Coulam et al., 1986; Luborsky et al., 2003], with variable etiologies. It can be due to an autoimmune disease, and concomitant autoimmune hypothyroidism or hypoadrenalism should be ruled out [LaBarbera et al., 1988; Kim et al., 1997; Bakalov et al., 2002; Nelson et al., 2005]. It can be caused by abnormalities of the X chromosome. It is caused by variable single gene disorders, as seen in galactosemia (*GALT1*), bleoharophimosis–ptosis–epicanthus inversus syndrome (*FOXL2*), and polyendocrinopathy with mucocutaneous candidiasis (*AIRE*) [Fassnacht et al., 2006; Portnoi et al., 2006]. It can also be caused by a premutation of the *FMR1* gene [Allingham-Hawkins et al., 1999].

Vegetti et al. [1998] found that genetic abnormalities accounted for 31% of the causes for POI in his patients. Rebar and Connolly [1990] and Portnoi et al. [2006] reported cytogenetic abnormalities in 13% and 8.8% of their respective cohorts. The association between X chromosome deletions and POI is well established [Davison et al., 1998; Zinn et al., 1998]. Patients with POI due to distal Xq deletions were described by Fitch et al. [1982], Tharapel et al. [1993], Maraschio et al. [1996], Davison et al. [1998], and Marozzi et al. [2000]. Marozzi concluded that a critical region, which was termed POF1 by Tharapel, is located at Xq26.2–q28. Eggermann et al. [2005] narrowed this region, by reporting POI in a woman with familial Xq27.2-qter deletion. It is possible, however, that concomitant microduplications or translocations were not identified when karyotyping alone was performed, as was shown by Tachdjian et al. [2008].

Our first patient presented with POI, which is unlikely to be related to a deleted *FMR1* gene. The proposed cause of POI in *FMR1* premutation carriers is excess of the *FMR1* mRNA [Tassone et al., 2000; Kenneson et al., 2001; Coffey et al., 2008], which is not expected to occur when one allele is deleted, and the other has a normal number of CGG repeats. Similarly, a deletion of *FMR1* does not pose a risk of fragile X tremor ataxia syndrome, which is also secondary to excess *FMR1* mRNA [Hagerman et al., 2004; Al-Hinti et al., 2007; Coffey et al., 2008; Rodriguez-Revenga et al., 2009]. The other three patients have shown no evidence of developing POI although it is possible they undergo POI at a later time period. The unmasking of recessive genes on the non-deleted X may also possibly account for the difference in the fertility phenotype in our group of patients.

In conclusion, physicians and genetic counselors should be aware of the possible identification of Xq deletions as a potential outcome of fragile X screening. We recommend that patients with premature ovarian insufficiency be referred for genetic counseling, cytogenetic analysis and molecular analysis of the *FMR1* gene. Comparative genomic hybridization may assist in delineation of chromosome X deletions and possibly in identification of genes involved in POI.

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