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Research Letter

Detection of mosaic balanced homologous acrocentric rearrangement rea(21q21q) in a woman with repeated pregnancy losses

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A 40-year-old G2P0 phenotypically normal woman was referred for cytogenetic investigation because of a history of repeated pregnancy losses. The woman had normal external genitalia, polycystic ovary syndrome and irregular menstrual cycles. She had experienced two spontaneous abortions. Chromosome preparations from the blood lymphocyte culture revealed a karyotype of 45,XX,der(21;21)(q10;q10)[16]/46,XX[23]/47,XX,+21[1] (Fig. 1). Repeated blood sampling from blood lymphocytes revealed a karyotype of 45,XX,der(21;21)(q10;q10)[10]/46,XX[30]. Cytogenetic analysis of the blood lymphocytes from her husband, a 43-year-old phenotypically normal man, revealed a karyotype of 46,XY.

Cytogenetic analysis is an indispensable part of the etiological investigation in couples with recurrent miscarriages [1]. The mean reported frequency of chromosome aberrations in couples with recurrent miscarriage is about 5–7%, and Robertsonian translocations account for 10–20% of chromosome aberrations [1–4]. In a study of 1743 couples with recurrent miscarriage, Fryns and Van Buggenhout [1] found chromosome aberrations in 93 couples (5.3%), which is a 30-fold increase compared to the general population. In their study, approximately 66.7% of chromosome aberrations detected were reciprocal translocations, 9.7% were Robertsonian translocations, 10% were inversions and 7.5% were numerical sex-chromosome abnormalities. Elghezal et al [2] found chromosome aberrations in 6.9% (97/1400) couples with recurrent miscarriages, including X-chromosome aneuploidy (33%), reciprocal translocations (30%), inversions (16%) and Robertsonian translocations (12%). Meza-Espinoza et al [3] found chromosome aberrations in 5.5% (52/939) couples with reproductive disorders, including reciprocal translocations (55.7%), Robertsonian translocations (19.2%) and inversions (3.8%). Ozawa et al [4] found chromosome aberrations in 4.9% (114/2324) couples with repeated pregnancy losses, including reciprocal translocations (65%), Robertsonian translocations (20%) and inversions (9%).

The present case was associated with mosaic balanced rea(21q21q) and repeated pregnancy losses. Detection of mosaic or non-mosaic balanced rea(21q21q) in couples with repeated pregnancy losses is unusual. Carriers of non-mosaic rea(21q21q) are unable to produce normal offspring, since all the gametes should be either nullisomic or disomic for the chromosome involved in the rearrangement. The rea(21q21q) Down syndrome progeny of the carriers of rea(21q21q) can survive to the second trimester or even to term [5], and such carriers may therefore be ascertained through their abnormal children. Recurrence of unbalanced rea(21q21q) has been shown to be associated with low-level parental mosaicism or gonadal mosaicism [6]. Kovaleva and Shaffer [6] found that parents of unbalanced rea(21q21q) offspring were more often found to be mosaic. In families with recurrent *de novo* rea(21q21q) Down syndrome, several reports have demonstrated mosaicism for rea(21q21q) in the skin or ovary of one parent, but normal karyotypes in the parental blood lymphocytes [7–11] and a very low level of mosaic rea(21q21q) in the blood lymphocytes of one parent [12].

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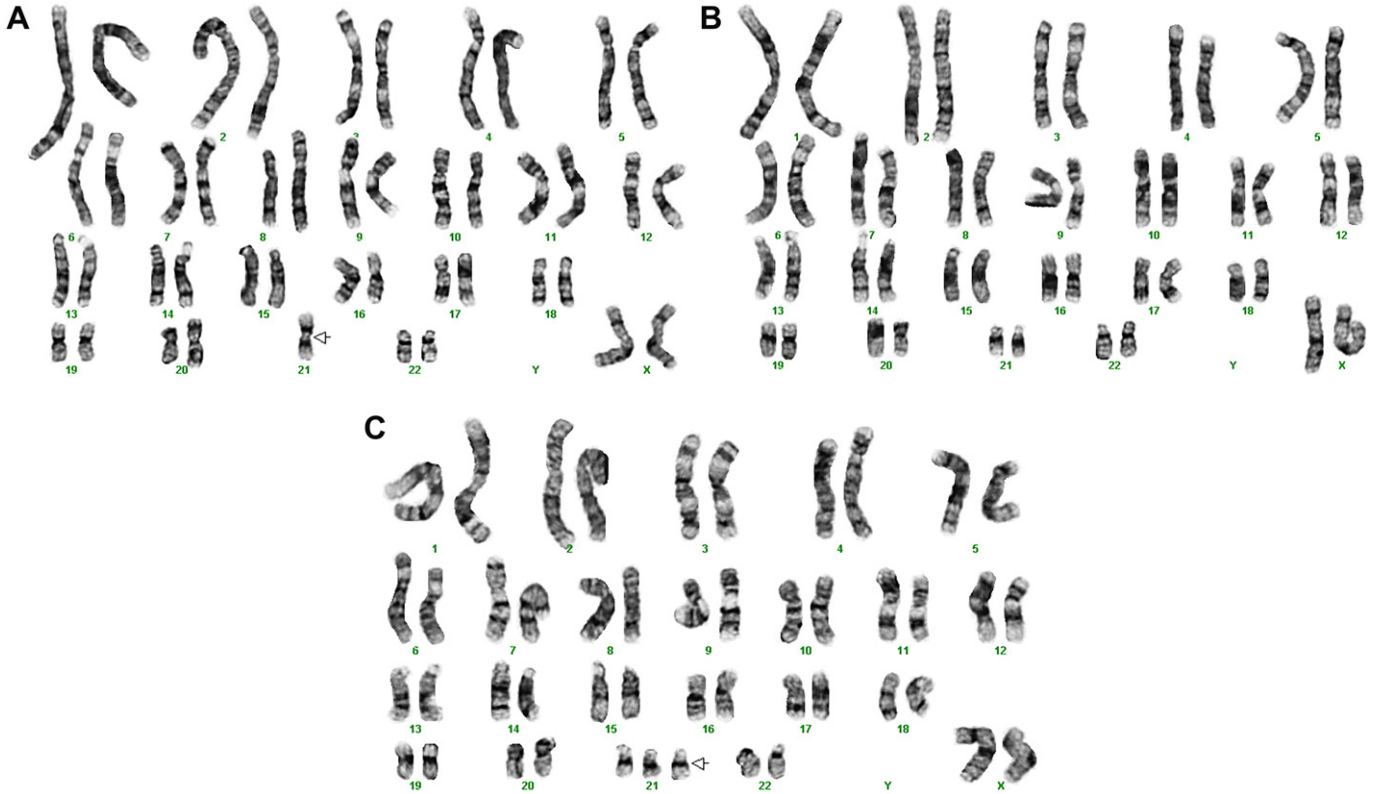

Fig. 1. (A) A karyotype of 45,XX,der(21;21)(q10;q10). The arrow indicates a homologous acrocentric rearrangement rea(21q21q); (B) a karyotype of 46,XX; (C) a karyotype of 47,XX,+21. The arrow indicates a free extra chromosome 21.

Carriers of non-mosaic and mosaic rea(21q21q) may be associated with abortions, in addition to liveborn and stillborn babies with Down syndrome. Lawton et al [13] reported five spontaneous abortions in a mother who was a carrier of non-mosaic rea(21q21q). Lucas et al [14] reported five spontaneous abortions in a couple with a paternal carrier of non-mosaic rea(21q21q). Furbetta et al [15] reported four spontaneous abortions in a mother who was a carrier of non-mosaic rea(21q21q). Jacobs et al [8] reported four spontaneous abortions in a mother who was a carrier of mosaic rea(21q21q) or 46,XX[993]/45,XX,der(21;21)(q10;q10)[7]. Lakshminarayana [16] reported seven spontaneous abortions in a maternal carrier of non-mosaic rea(21q21q) and three spontaneous abortions in a couple with a paternal carrier with non-mosaic rea(21q21q). Sudha and Gopinath [17] reported four spontaneous abortions in a mother who was a carrier of non-mosaic rea(21q21q) and nine spontaneous abortions in a couple with a paternal carrier with non-mosaic rea(21q21q). Robinson et al [18] reported three spontaneous abortions in a mother who was a carrier of non-mosaic rea(21q21q).

Carriers of balanced homologous or heterologous acrocentric rearrangements involving chromosome 21 may carry very low-level mosaicism for a cell line with trisomy 21, but without phenotypic abnormalities [11,19]. Gross et al [19] reported two spontaneous abortions in a maternal carrier of the karyotype 46,XX,i(21q)[1]/45,XX, rob(21;22)(q10;q10)[59] in blood lymphocytes. The mother was phenotypically normal and had two children with i(21q) Down syndrome. Skin fibroblasts had the balanced cell line of rob(21q22q), whereas in the ovarian biopsy, about 1/3 of the cells exhibited unbalanced rea(21q21q). Yu et al [11] reported five spontaneous abortions in a mother who was a carrier of low-level mosaicism for a cell line with an unbalanced 46,XX,+21,der(21;21)(q10;q10) karyotype in skin fibroblasts. The mother had a karyotype of 46,XX in blood lymphocytes. Cytogenetic analysis of two of the five abortions revealed unbalanced rea(21q21q) Down syndrome. The present case was a phenotypically normal woman with 25–40% mosaicism for balanced rea(21q21q) and very low-level mosaicism (1/40 cells) for free trisomy 21; she was found to have the chromosome aberration simply because of repeated pregnancy losses. Such patients are at a high risk for infertility, recurrent miscarriages and aneuploid offspring.

This is the first report of the detection of mosaic balanced homologous acrocentric rearrangement rea(21q21q) and low-grade trisomy 21 mosaicism in a couple with repeated pregnancy losses. We emphasize that couples with repeated pregnancy losses should undergo detailed cytogenetic analysis and comprehensive clinical evaluation.

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