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Short Communication

De novo duplication of Xq22.1→q24 with a disruption of the *NXF* gene cluster in a mentally retarded woman with short stature and premature ovarian failure

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Abstract

Objective: To present molecular cytogenetic characterization of a *de novo* duplication of Xq22.1→q24 in a mentally retarded woman with short stature and premature ovarian failure.
Materials and Methods: A 19-year-old woman presented with psychomotor retardation, developmental delay, mental retardation, short stature, low body weight, general muscle hypotonia, distal muscle hypotrophy of the lower extremities, elongated digits, scanty pubic and axillary hair, hypoplastic external female genitalia, and secondary amenorrhea but no clinical features of Pelizaeus-Merzbacher disease. Conventional cytogenetic analysis revealed a karyotype of 46,X,dup(X)(q22.1q24). Fluorescence *in situ* hybridization determined a direct duplication with a linear tandem orientation. Array comparative genomic hybridization demonstrated partial trisomy Xq [arr cgh Xq22.1q24 (101,490,234–119,070,188 bp)×3] with a 17.6-Mb duplication.
Results: The duplicated region contained *NXF2B*, *NXF4*, *NXF3*, *PLP1*, and *PGRMC1* genes. There was a disruption of the *NXF* gene cluster of Xcen-*NXF5-NXF2-NXF2B-NXF4-NXF3*-Xqter.
Conclusion: A duplication of Xq22.1→q24 with a disruption of the *NXF* gene cluster in female patients can be associated with clinical manifestations of mental retardation in addition to short stature and premature ovarian failure.

Keywords: Duplication of Xq; Mental retardation; *NXF* gene cluster; *PGRMC1*; Premature ovarian failure

Introduction

Males with duplications of X chromosome [dup(X)] have functional partial disomy X and clinical abnormal features. In cases of dup(Xp) involving a duplication of Xp21.2, the males will manifest sex reversal, ovarian formation, and female or ambiguous genitalia because of disomic expression of the

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DAX1 gene [1,2]. A duplication of the entire short arm of X chromosome has been reported to be associated with sex reversal, tetralogy of Fallot, and the Dandy-Walker anomaly in an XY fetus [3]. Males with dup(Xq) have features of short stature, mental retardation, feeding problems, microcephaly, facial dysmorphism, hypotonia, and hypoplastic genitalia [4–7]. Prader-Willi syndrome-like phenotype, such as hypotonia, feeding problems, and genital hypoplasia, may appear in males with proximal Xq (Xq21.1-q21.31) duplications [8] or distal Xq (Xq25-qter) duplications [6,9–11].

Females with dup(X) may or may not present phenotypic abnormalities. The phenotypic abnormalities in females with dup(Xp) include developmental delay, macrosomia, facial dysmorphism, congenital heart defects, structural central nervous system anomalies, macrocephaly, and mental retardation [12]. The phenotypic abnormalities in females with dup(Xq) include short stature, developmental delay, facial dysmorphism, and gonadal dysgenesis [13–15]. Herein, we present molecular cytogenetic analysis of a *de novo* duplication of Xq22.1→q24 in a mentally retarded woman with short stature and premature ovarian failure (POF).

Materials, methods, and results

The 19-year-old woman was the second child of a healthy and unrelated Taiwanese couple. The mother was 32 years old and the father was 36 years old at her birth. The maternal family history was unremarkable. The paternal family had a history of depression. Her 23-year-old brother was healthy and normal. She was born at term by normal smooth vaginal delivery with a birth weight of 2,300 g (<3rd centile), a head girth of 33.2 cm (<3rd centile), and a body length of 50 cm (90th centile). Psychomotor retardation, developmental delay, and severe mental retardation had been noted since childhood. Brain ultrasound at the age of 4 months showed ventricular dilation, and brain computed tomography scan at the age of 1 year showed mild prominence of the lateral ventricles and prominent frontal horn and temporal horn. Menarche occurred at the age of 17 years, and the menstruation was irregular. Her last menstrual period occurred 6 months ago. At the age of 19 years, the patient's weight was 31 kg and height was 142 cm. Physical examination showed general muscle hypotonia, distal muscle hypotrophy of the lower extremities, breast budding

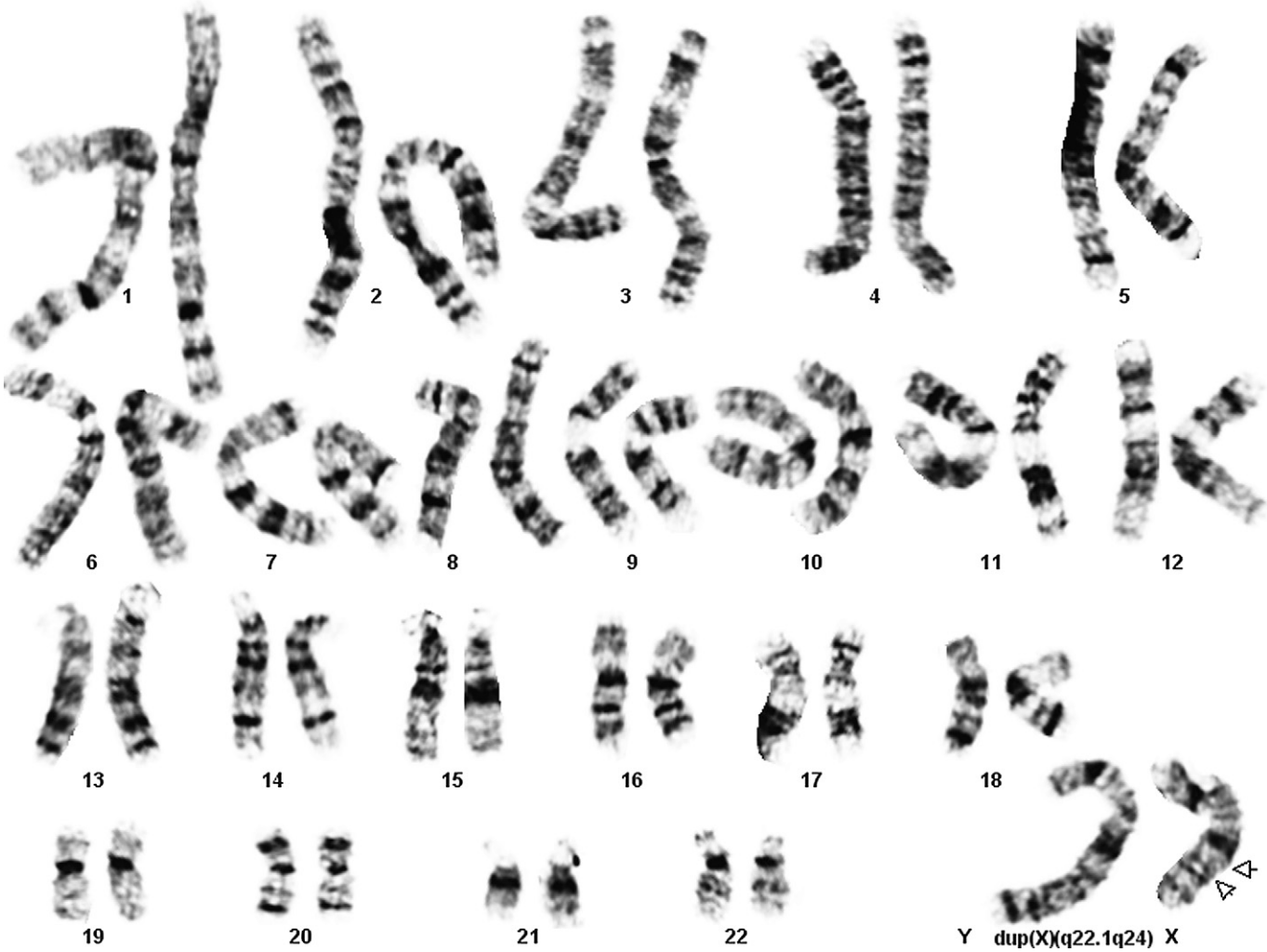

Fig. 1. A 46,X,dup(X)(q22.1q24) karyotype. The arrows indicate the breakpoints.