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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

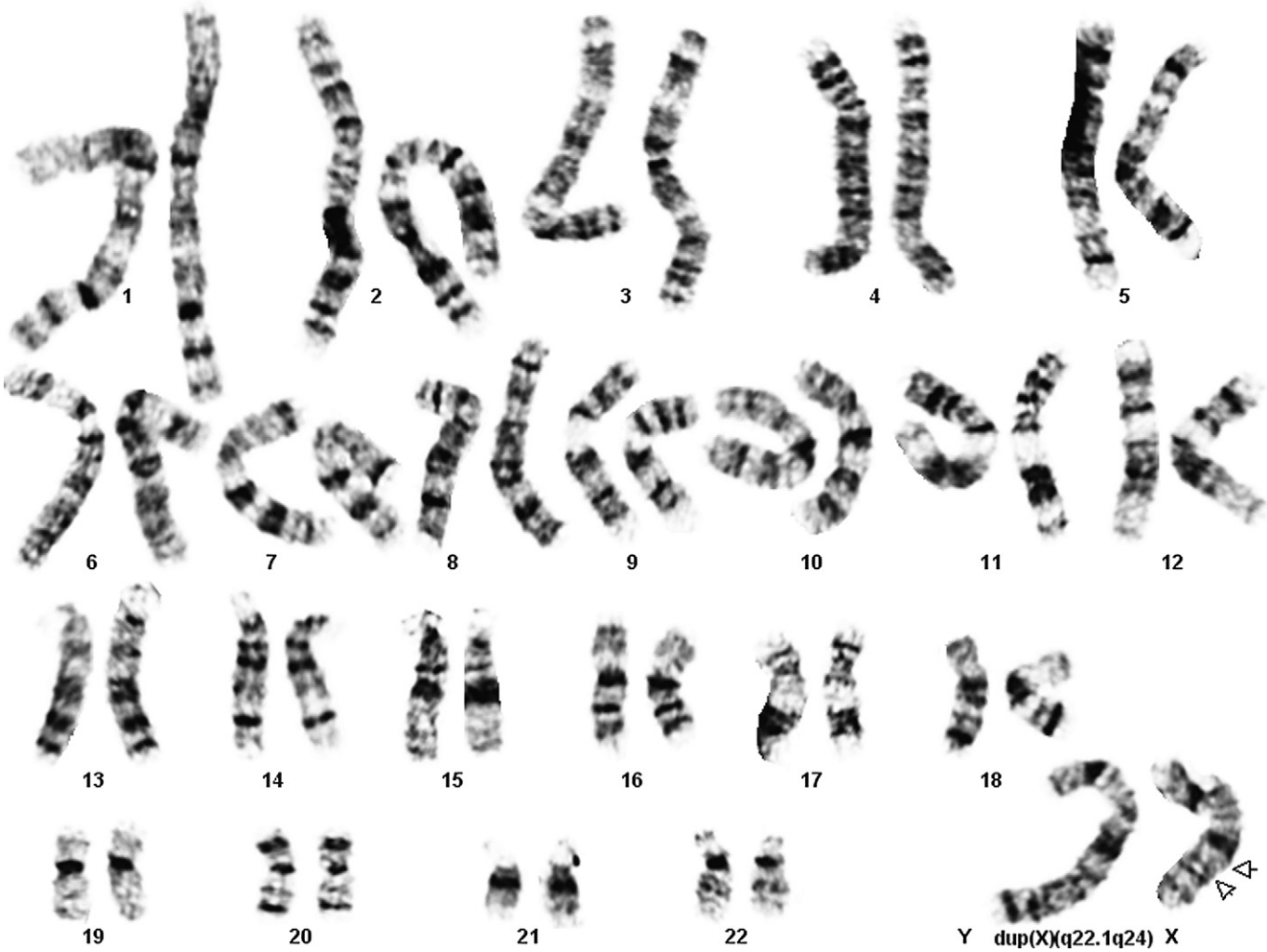

Fig. 1. A 46,X,dup(X)(q22.1q24) karyotype. The arrows indicate the breakpoints.

(Turner breast stage II), scanty pubic and axillary hair, and hypoplastic external female genitalia. Her digits were elongated. There were no clinical manifestations of facial dysmorphism, abnormal head movements, nystagmus, optic atrophy, ataxia, spasticity, or involuntary movements. The following measurements were obtained from laboratory studies follicle-stimulating hormone: 88.01 mIU/mL (normal females: <22 mIU/mL; postmenopausal females: 35–151 mIU/mL), estradiol: 3.10 pg/mL (postmenopausal females: <14 pg/mL), prolactin: 4.26 ng/mL (normal females, cyclic: 1–27 ng/mL; postmenopausal: 2–13 ng/mL), and thyroid-stimulating hormone: 1.65 μIU/mL (normal: 0.25–4 μIU/mL). Conventional cytogenetic analysis revealed a karyotype of 46,X,-dup(X)(q22.1q24) (Figs. 1 and 2). The parental karyotypes were normal. For fluorescence *in situ* hybridization determination of the orientation of the duplication, bacterial artificial chromosome (BAC) clones mapping to the duplicated genomic region of the X chromosome were used. The BAC clone RP11-34P3 encompassing the *PLP1* gene at Xq22 and the BAC clone RP11-22P2 encompassing the *PGRMC1* gene at Xq24 were applied. Fluorescence *in situ* hybridization mapping of the orientation of the duplication revealed that the rearrangement was a direct duplication with a linear tandem orientation (Fig. 3). Oligonucleotide-based array comparative genomic hybridization demonstrated partial trisomy Xq [arr cgh Xq22.1q24 (101,490,234–119,070,188 bp)×3] (NCBI Build 36) with a 17.6-Mb duplication (Fig. 4). The duplicated region contained *NXF2B*, *NXF4*, *NXF3*, *PLP1*, and *PGRMC1* genes, and there was a disruption of the *NXF* gene cluster of Xcen-*NXF5-NXF2-NXF2B-NXF4-NXF3*-Xqter (Fig. 5).

Discussion

The present case had a duplication of the *PLP1* gene but manifested no symptoms of Pelizaeus-Merzbacher disease (PMD). The *PLP1* gene (OMIM 300401) encodes proteolipid protein 1 which is the primary constituent of myelin in the central nervous system. PMD (OMIM 312080) is an X-linked recessive hypomyelinative leukodystrophy caused by mutations, deletions, duplications, or position effect rearrangements of the *PLP1* gene. PMD is characterized by nystagmus, spastic quadriplegia, ataxia, and developmental delay. Micro-

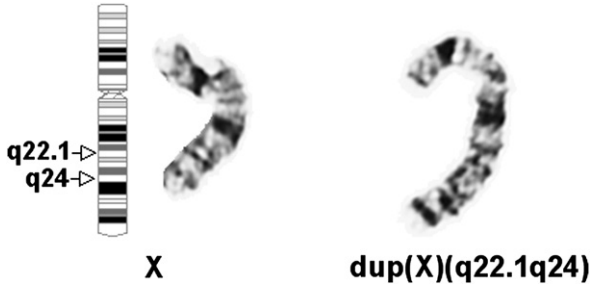

Fig. 2. Partial G-banded karyotype of the patient shows one normal X chromosome and one aberrant X chromosome that contains a duplicated segment between Xq22.1 and Xq24.

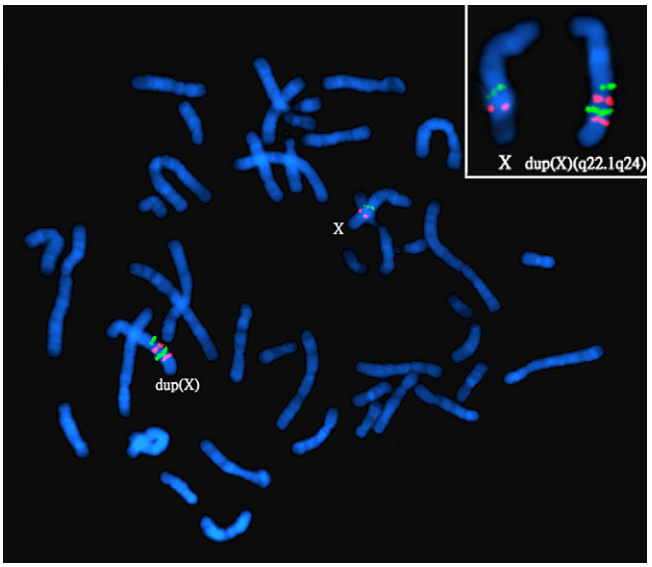

Fig. 3. Fluorescence *in situ* hybridization study using an Xq22-specific bacterial artificial chromosome (BAC) clone probe (spectrum green) (RP11-34P3) encompassing the *PLP1* gene and an Xq24-specific BAC clone probe (spectrum red) (RP11-22P2) encompassing the *PGRMC1* gene shows a direct duplication with a linear orientation of green-red-green-red. The inset shows the amplified dup(X)(q22.1q24) and chromosome X.

duplications encompassing the *PLP1* gene have been reported to be associated with PMD [16] and duplications of the *PLP1* gene is responsible for 50–75% of patients with PMD [17]. PMD can appear in patients with dup(Xq) involving a duplication of Xq22 [18,19]. Cremers et al [18] reported muscular hypotonia, growth retardation, psychomotor retardation, cryptorchidism, and PMD in a boy with dup(X)-(q13q22) at the age of 5 years. Carrozzo et al [19] reported multiple anomalies, brain hypomyelination, and ocular albinism in a girl with dup(X)(q21.32q24) at the age of 18 months. However, PMD may not appear in patients with dup (Xq) involving a duplication of Xq22 [20–22]. Steinbach et al [20] reported a male with dup(X)(q13q22) without clinical manifestations of PMD. Schwartz et al [21] reported a male with dup(X)(q21q24) with dysmorphic features and developmental delay but no features of PMD. Ida et al [22] reported a 5-year-old girl with functional disomy for Xq22-q23 with developmental and growth retardation but no features of PMD. The present case provides evidence that females with a duplication of Xq22-q24 involving *PLP1* can be associated with phenotypic abnormalities but no features of PMD.

The present case manifested POF and had a duplication of the *PGRMC1* gene. POF has been noted in females with dup(X)(q12qter) [23], dup(X)(q13.3q27.2) [24], dup(X)-(q22.3q27.3) [25], dup(X)(q22q23) [26], and dup(X)(q13q22) [27]. Recently, the *PGRMC1* gene has been implicated in POF [28,29]. Mansouri et al [28] reported two women, mother and daughter, with POF and t(X;11)(q24;q13). Giacomozzi et al [29] reported an adolescent girl with POF and t(X;15)-(q24;q26.3) involving partial Xq24 duplication. The *PGRMC1* gene (OMIM 300435) encodes progesterone receptor membrane component 1, which mediates the antiapoptotic action of

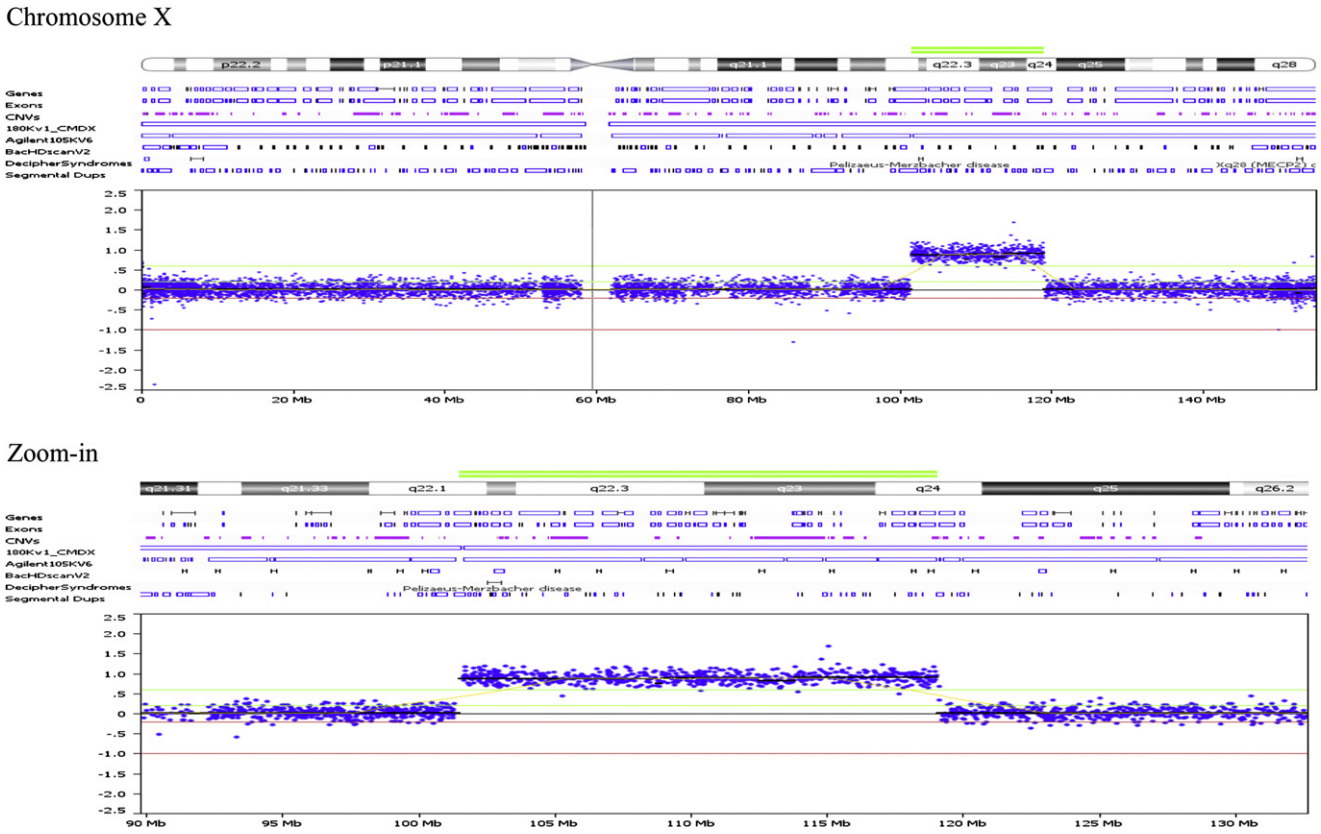

Fig. 4. Oligonucleotide-based array comparative genomic hybridization using Oligo HD Scan (CMDX, Irvine, CA, USA) shows a 17.6-Mb duplication in Xq22.1→q24 [arr cgh Xq22.1q24 (101,490,234–119,070,188 bp)×3] (NCBI Build 36).

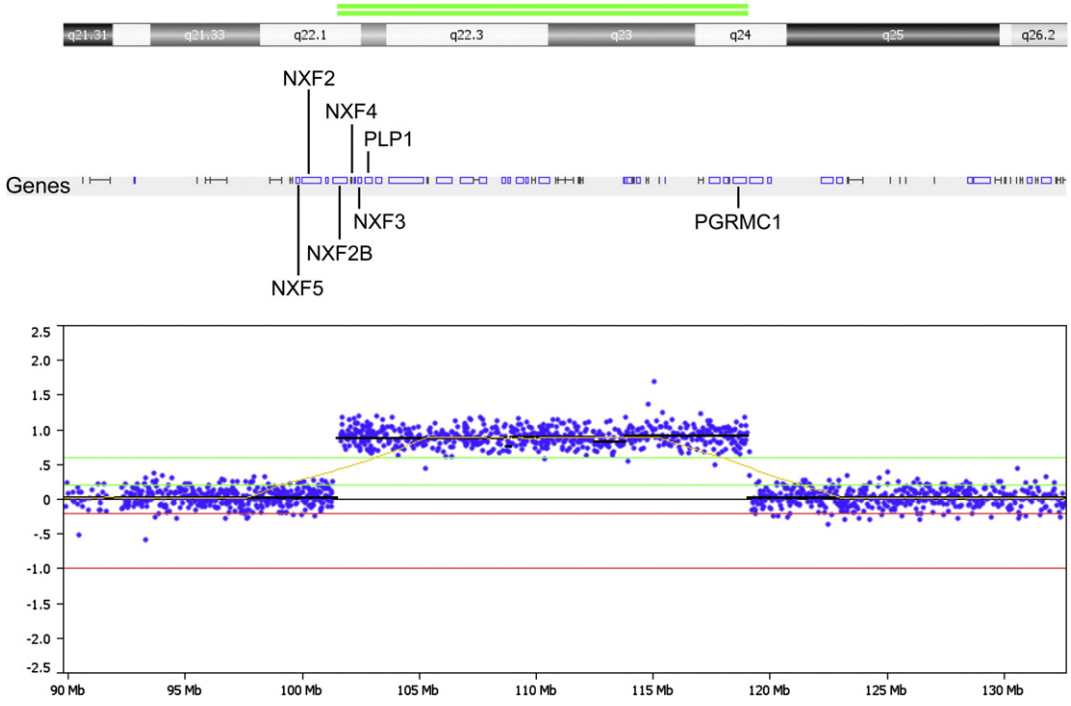

Fig. 5. Genomic context of the Xq22.1-q24 duplication in this patient adapted from the Human Genome Browser at UCSC hg18 (NCBI Build 36) [http://genome.ucsc.edu Human March 2006 assembly].

progesterone in ovarian cells. Altered PGRMC1 function may result in POF [28,29]. The present case provides evidence that females with dup(Xq) involving a duplication of Xq24 and the *PGRMC1* gene can be associated with POF.

The present case manifested mental retardation, a disruption of the *NXF* gene cluster of Xcen-*NXF5-NXF2-NXF2B-NXF4-NXF3*-Xqter, and duplications of *NXF2B* (101,519,072–101,613,388 bp), *NXF4* (101,691,549–101,713,277 bp), and *NXF3* (102,217,406–102,234,678 bp) (Build 36) genes. NXF2B, NXF4, and NXF3 belong to the proteins of the nuclear RNA export factor (NXF) family, which are associated with export of mRNAs from the nucleus to the cytoplasm [30]. Several reports have suggested that *NXF5* (100,973,741–100,999,205 bp) (Build 36) is a good candidate gene for X-linked mental retardation [31–33], and duplications harboring *NXF5* are associated with X-linked mental retardation. The present case had a breakpoint at Xq22.1. Frints et al [32] reported a 59-year-old male with mental retardation, short stature, general muscle wasting, and facial dysmorphism with inv(X)(p21.1q22.1) and a disruption of the *NXF* gene cluster of Xcen-*NXF5-NXF2-NXF4-NXF3*-Xqter. Grillo et al [34] reported a 7-year-old girl with severe mental retardation, autism, microbrachycephaly, hypotonia, distal hypotrophy of lower limbs, scoliosis, facial dysmorphism, and a 1.1-Mb deletion of chromosome Xq22.1 encompassing *NXF5*, *NXF2*, *NXF2B*, and *NXF4*. The present case had a disruption of the *NXF* gene cluster of Xcen-*NXF5-NXF2-NXF2B-NXF4-NXF3*-Xqter and duplications of *NXF2B*, *NXF4*, and *NXF3*. NXF2 regulates nucleocytoplasmic transport of specific mRNAs in neurons and male germ cells [35,36]. NXF2 also interacts with the fragile X mental retardation protein FRMP to promote the nucleocytoplasmic transport of specific mRNAs in neurons and male germ cells [35]. Both *NXF2* (101,356,936–101,468,287 bp) (Build 36) and *FRMP* are associated with *NXF1* mRNA and act to regulate its stability in neuronal cells [37]. A disruption of the *NXF* gene cluster and a gene dosage imbalance of *NXF2B*, *NXF4*, and *NXF3* genes in our patient may lead to a global impairment in neuronal mRNA export, resulting in a phenotype of severe mental retardation.

The present female patient was associated with dup(Xq) and major phenotypic abnormalities. The abnormal phenotype in females with dup(X) based on selective inactivation of the aberrant dup(X) chromosome is not predictable. Although females with dup(X) may present normal phenotype because of the prevention of genetic imbalance by preferential inactivation of the dup(X) chromosome, several reports have shown phenotypic abnormalities in females with selective inactivation of the dup(X) chromosome and an abnormal phenotype [38–42]. In a review of 35 females with dup(X) and selective inactivation of the aberrant dup(X) chromosome, Matsuo et al [38] found phenotypic abnormalities in 13 patients. Tihy et al [39] reported selective inactivation of the dup(X) chromosome in a 16-year-old female with a karyotype of 46,X,dup(X)-(q22.1q25), intrauterine growth restriction, body asymmetry, short stature, hypotonia, unilateral ptosis, microcephaly, developmental delay, and nystagmus. Volleth et al [40] reported preferential inactivation of the dup(X) chromosome in an 18-year-old female with a karyotype of 46,X,dup(X)-(q23q27-28), mental retardation, facial dysmorphism, developmental delay, and regular menstruation. Kokalj Vokac et al [41] reported selective inactivation of the dup(X) chromosome in a 32-year-old woman with a karyotype of 46,X,dup-(X)(p11.23p22.33), hypotonia, developmental delay, mental retardation, and facial dysmorphism. Armstrong et al [42] reported selective inactivation of the dup(X) chromosome in a 7-year-old girl with a karyotype of 46,X,dup(X)(q23.3q26), intrauterine growth restriction, short stature, hypotonia, unilateral ptosis, and a flat labia. The phenotypic diversity in females with dup(X) may be caused by functional disomy restricted to the duplicated X material [42], a tissue-dependent difference in the X-activation pattern, between the lymphocytes and other tissues [40], an interindividual difference in the X-inactivation pattern [43], incomplete inactivation of the duplicated X chromosomal segment, expression of recessive mutant genes on the active X chromosome, or disruption of a gene by rearrangement [15,24,44].

Acknowledgments

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