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Research Article

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A Turner Patient Presenting Dicentric Ring X-Chromosome and Intellectual Disability

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Abstract

A ring chromosome is the result of fusion of the proximal ends following a break in both arms of a chromosome. Formation of a dicentric ring which is a rare event occurs as a consequence of either U-type exchange or due to misrepair of the DNA strand breaks. The proband in our study clinically presented as Turner syndrome with intellectual disability. Chromosomal analysis revealed her karyotype to be 45,X[50]/46,X,r(X)(p11q13)[30]/46,X,dic r(X;X)(p11q13;p11q13) [20] which was further confirmed using specialized banding techniques and fluorescence *in situ* hybridization. Intellectual disability in our patient could have been due to the active ring X chromosome. To the best of our knowledge this is the first case of a stable dicentric ring X chromosome associated with both Turner syndrome and intellectual disability. This report describes the genotypic and phenotypic features exhibited by the patient.

Keywords: Dicentric ring X; Intellectual disability; Ring chromosome; Turner syndrome

Introduction

Turner syndrome (TS) is caused by either complete or partial absence of the second sex chromosome X or Y, resulting in haploinsufficiency of several genes. Monosomy of X is the only complete non-mosaic monosomy that is compatible with existence [1]. Any loss of genetic material has more detrimental effect on normal growth and development of the fetus compared to its gain. The most common findings of the non-mosaic TS patients are short stature, edema (puffy hands and feet), cubits valgus, webbed neck, widely spaced nipples, flat chest, skeletal deformities, cystic hygroma and cardiac or renal anomalies. Isochromosome Xq is the most common structural rearrangement followed by the ring X chromosome, deletions of the X chromosome and Y chromosome abnormalities with or without mosaicism in patients with TS [1]. Haploinsufficiency of genes that are expressed by inactive X chromosomes accounts for these phenotypes [2]. A ring chromosome is the outcome of joining of the proximal ends following breaks occurring in the distal arms of the chromosome leading to loss of genetic material. Depending on the material lost, the size of the ring chromosomes may vary. Secondary abnormalities linked with instability of the ring chromosomes include monosomy due to its loss, two ring chromosomes, interlocked rings and a dicentric ring chromosome. The larger dicentric ring occurs as a result of a single crossover event between the sister chromatids of a replicated ring chromosome. Eventually unstable ring structures get lost during further cycles leading to monosomy [3]. This report details a Turner individual showing mosaicism for dicentric ring X chromosome, the first of its kind, and intellectual disability.

Case Report

The 15-year old proband, who is the first child of second-degree consanguineous parents, was referred for Primary Amenorrhea (PA) with a clinical suspicion of Turner syndrome. She was short (119 cm) and weighed 36 kg. Her arm span was 118 cm and her secondary sexual characters were of Tanner stage I. The other clinical features included low posterior hairline, widely spaced nipples, short webbed neck, stubby fingers and toes, pigmented naevi all over her body and cubitus valgus (Figure 1). She exhibited moderate Intellectual Disability (ID) with her mental age being 7 years and bone age 13 years. MRI of brain showed a normal cerebral parenchyma, ventricular system, sella bilateral orbits and posterior fossa structures. Further investigation for ID was not performed due to non-cooperation of her parents. An echocardiogram showed stable cardiac state with presence of normal valves and chambers. EEG report showed no paroxysmal discharges and they were within normal limits.

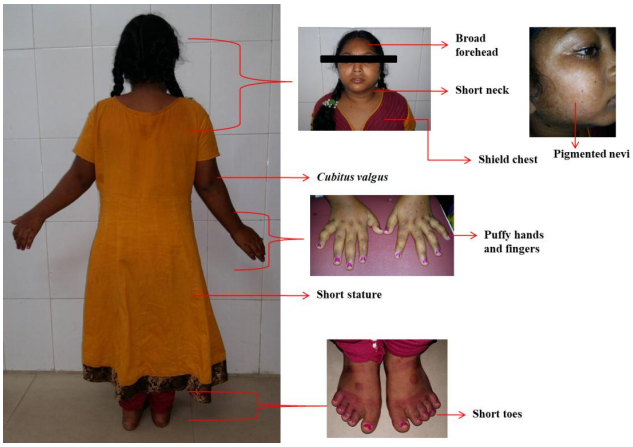

Figure 1: Clinical features seen in our Turner mosaic patient.

The proband was reported to suffer from moderate to severe conductive hearing loss of right ear and minimal hearing loss in left ear. Her external genitalia were infantile. Physical examination showed presence of vagina (1.2 cm) and her uterus could not be made out. USG of pelvis could not visualize either uterus or ovaries. The thyroid function test exhibited normal values (Triiodothyronine (T3)-1.4 pg/ml; Thyroxine (T4)-1.13 ng/dl; Thyroid-stimulating hormone (TSH)-1.9 µIU/ml). GH stimulation test revealed normal range of stimulation response (0.49 ng/ml). Endocrine profiling of the patient revealed elevated level of follicle stimulating hormone (FSH – 79 IU/L) and normal levels of luteinizing hormone (LH – 12 mIU/ml) and prolactin (20.2 ng/ml).

Routine analysis of GTG-banded chromosomes from cultured lymphocytes was done as per standard protocols and the abnormalities were designated following ISCN (2016) guidelines. The karyograms

were prepared using Applied Spectral Imaging Systems BandView (version 6.0) software. She showed a mosaic karyotype 45,X[50]/46,X,r(X)(p11q13)[30]/46,X,dic r(X;X)(p11q13;p11q13)[20]. A representative karyogram from the three different cell lines is shown in Figure 2. Figures 3a and 3b illustrate the CBG-banded ring X chromosome and the dicentric ring X chromosome respectively. Differential replication pattern of X chromosomes studied using a final 5-bromodeoxyuridine pulse followed by staining with Hoechst 33258 and then Giemsa [4] revealed darkly stained, normal X, ring X and dicentric ring X chromosomes suggesting that the abnormal X chromosomes have escaped inactivation (Figures 3c-3e).

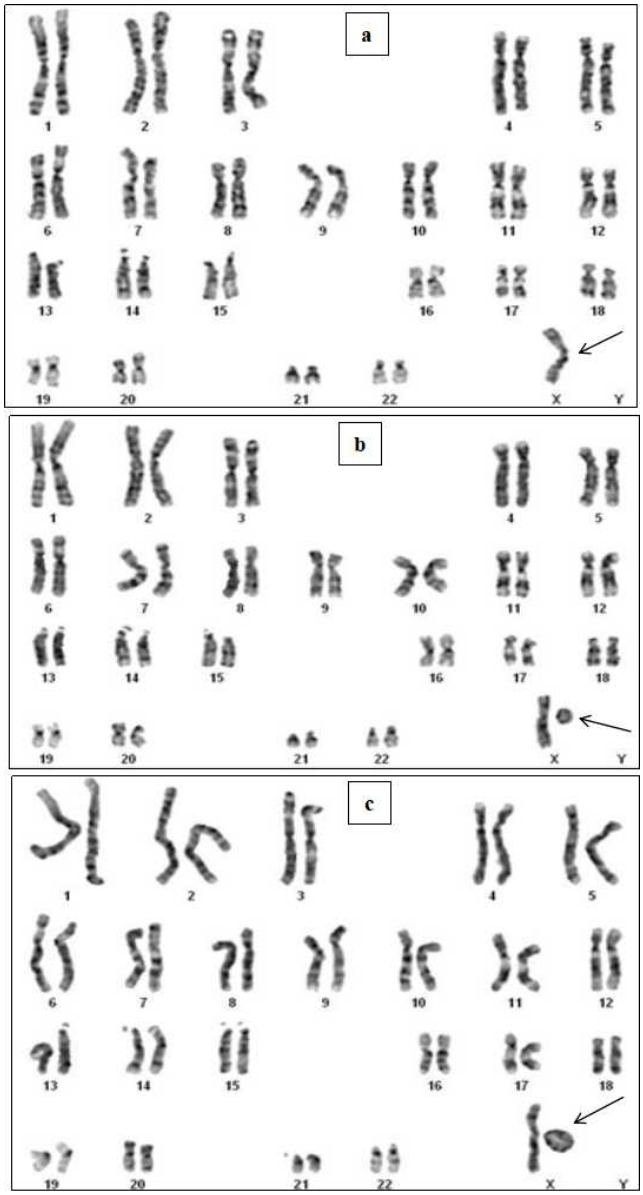

Figure 2: GTG-banded karyogram of the proband exhibiting 45,X chromosomal pattern (a) ring X chromosome in 46,X,r(X) cell (b) and dicentric ring X chromosome in 46,X,dic r(X;X) cell (c) (indicated by arrows).

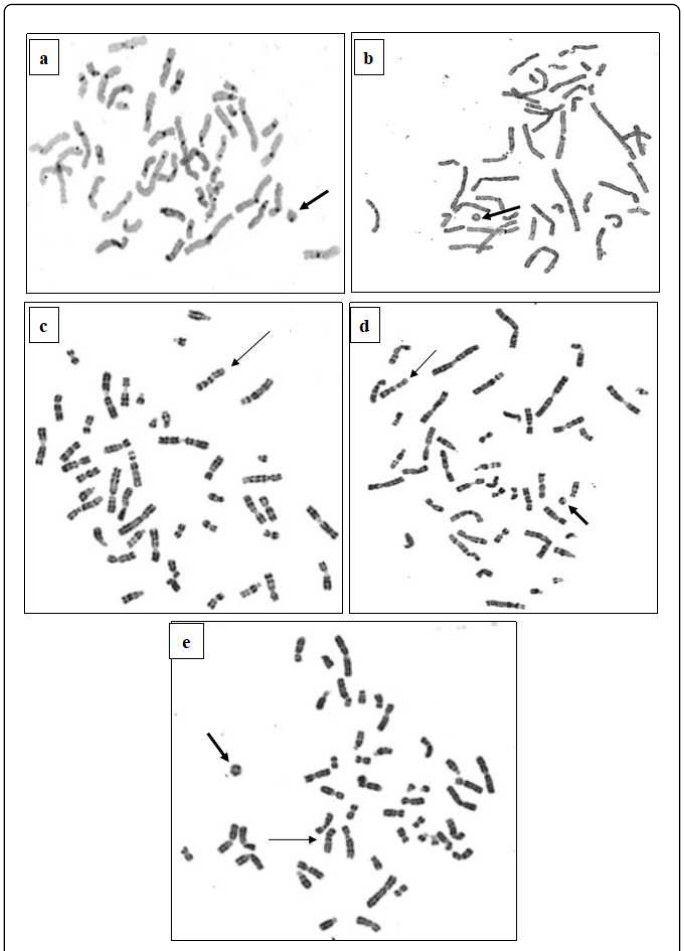

Figure 3: CBG-banded metaphase of the proband showing ring X chromosome in 46,X,r(X) cell(a) and dicentric ring X chromosome in 46,X,dic r(X;X) cell (b) (indicated by arrows); Metaphase showing normal X in 45,X cell (c) and both normal X and early replicating ring X (thick arrow) in 46,X,r(X) cell (d) and both normal X and early replicating dicentric ring X (thick arrow) in 46,X,dic r(X;X) cell (e), the normal X is shown by a thin arrow.

Degree of mosaicism was further confirmed by scoring fluorescence *in situ* hybridization (FISH) signals on metaphases and interphases employing alphoid probe for the centromeric region of the X chromosome following manufacturer's instructions and analysing using ASI Systems FISHView (version 6.0) software. A single signal on the normal X chromosome in 45, X cells and two signals, one each on the normal X and ring X chromosome in 46,X,r(X) cells were seen. On the other hand, one and two signals on the normal X and dicentric ring X chromosome respectively were observed in 46,X,dic r(X;X) cells (Figures 4a-4c). Figures 4d-4f displays the FISH images with centromeric alphoid probe for the X chromosome (FITC green) and locus-specific probe for XIST region (Texas red) showing typical pattern of hybridization (a red and a green signal) on the normal X chromosome in all the three cell lines and on the monocentric ring X in 46,X,r(X) cells. Two sets of red and green signals were seen on the dicentric ring X in 46,X,dic r(X;X) cells and these findings confirm the presence of the XIST region on the ring chromosomes. The presence of positive signals with centromere and XIST probes confirm the

breakpoints as Xp11 and Xq13. Chromosomal microarray analysis which would help not only in the identification of the exact breakpoints but also the genes responsible for the phenotype could not be performed due to non-cooperation of her parents. PCR amplification of cDNA using XIST primers to determine the activity of the X chromosomes could also not be carried out.

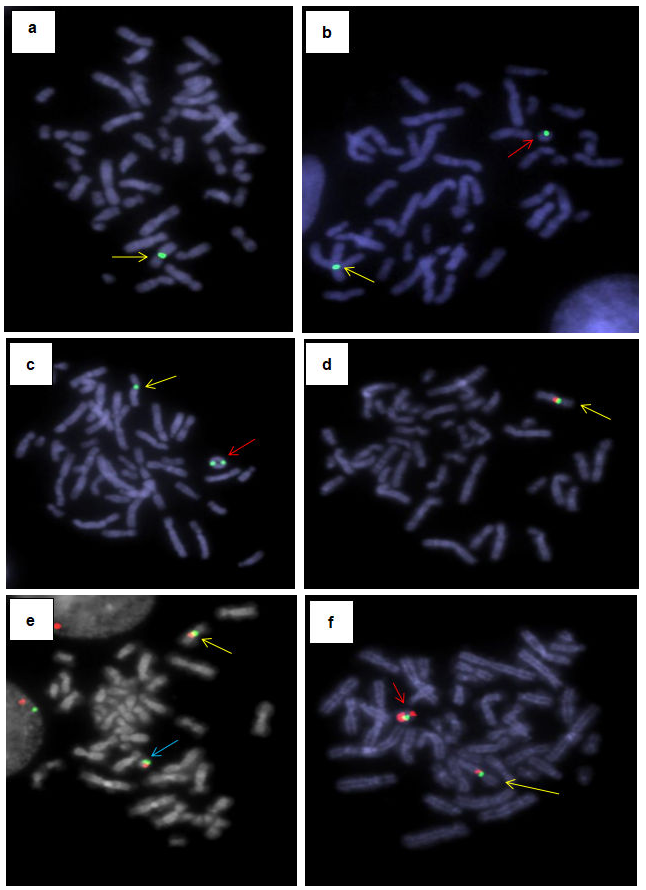

Figure 4: Metaphase FISH using centromeric alphoid probe for chromosome X (FITC green) showing single hybridization signal on the normal X in 45,X cell(a) two signals corresponding to normal X and r(X) (red arrow) in 46,X,r(X) cell (b) and three signals corresponding to one normal X and two centromeres on the dicentric ring X (red arrow) in 46,X,dic r(X;X) cell (c); Metaphase FISH using centromeric alpha satellite probe for chromosome X (FITC green) and locus-specific probe for XIST region (Texas Red) showing hybridization to normal X in 45,X cell (d) to monocentric ring X (blue arrow) in 46,X,r(X) cell (e) and to the dicentric ring X (red arrow) in 46,X,dic r(X;X) cell (f) the normal X is shown by an yellow arrow.

Discussion

The presence of ring chromosome is a rare event compared to the other structural abnormalities. A break in both chromosomal arms followed by subsequent fusion of wrecked ends, results in the formation of ring chromosome with loss of genetic material [5]. Other possible mechanisms proposed for ring formation are contiguous inverted duplication and terminal deletion. There are also cases with no significant deletion and rings formed by telomere-telomere fusion referred to as the 'ring syndrome' or the 'McClintock' mechanism [3,5,6]. The most common features observed in patients with ring chromosomes involving both autosomes and sex chromosomes are growth retardation, developmental delay, dysmorphic facial features, congenital malformations and ID [7]. The ring chromosomes result in formation of dicentric or interlocked rings during cell division, which later break and cause additional chromosomal abnormalities finally leading to ring loss [3]. The main cell line lacked the ring X chromosome bearing the 45,X karyotype in our proband also as in previously reported cases [6]. According to Kosztolányi (1987), a ring chromosome is presumed to be unstable when secondary aberrations were found in more than 5% of the mitoses counted [3]. This 'ring instability' causes either loss or gain of genes which possibly could result in various phenotypic features observed in the patients with similar rings [3,8]. The timing of replication, percentage of mosaicism, status of X-inactivation, positional effect of the genes and copy number variations are other determinants of phenotypic variability [3,5,9,10]. The rings are heterogeneous in nature due to inconsistent initial size and genetic makeup arising from any of the chromosomes [2]. The region of chromosome involved in deletion or rearrangement, and its corresponding genome sequence which contains crucial genes for development and growth are regarded liable for the phenotypes observed in these patients [3].

Guilherme et al., [6] had reported five cases of infertility and/or Turner syndrome with a ring derived from X chromosome. The 45,X main cell line was accompanied by others showing ring chromosome-induced imbalances in two of them. While one patient exhibited two ring X chromosomes, the other case showed two additional cell lines having a dicentric ring X chromosome and two copies of the dicentric in a low proportion of the metaphases. Our proband is the first case of Turner syndrome showing a stable dicentric ring X chromosome [seen in 20 percent of the cells] to the best of our knowledge. A dicentric ring chromosome forms as a result of either the U-type exchange where break in one arm of the double stranded DNA re-establishes by fusion of both chromatids and when the chromosome arm which encompasses inverted low copy repeats, folds and recombines. The single cross over happening between two ring sister chromatids also results in a large ring with two centromeres. When the dicentric ring chromosome breaks due to mitotic instability it results in formation of either two monocentric rings with add-on deletions or duplications or they move into a single daughter cell leaving the other monosomic for the X chromosome [11]. The 'dynamic tissue-specific mosaicism' is contributed by aberrant cross overs of the sister chromatid [7]. Figure 5 depicts a schematic representation of the formation of the various abnormalities including the dicentric ring.

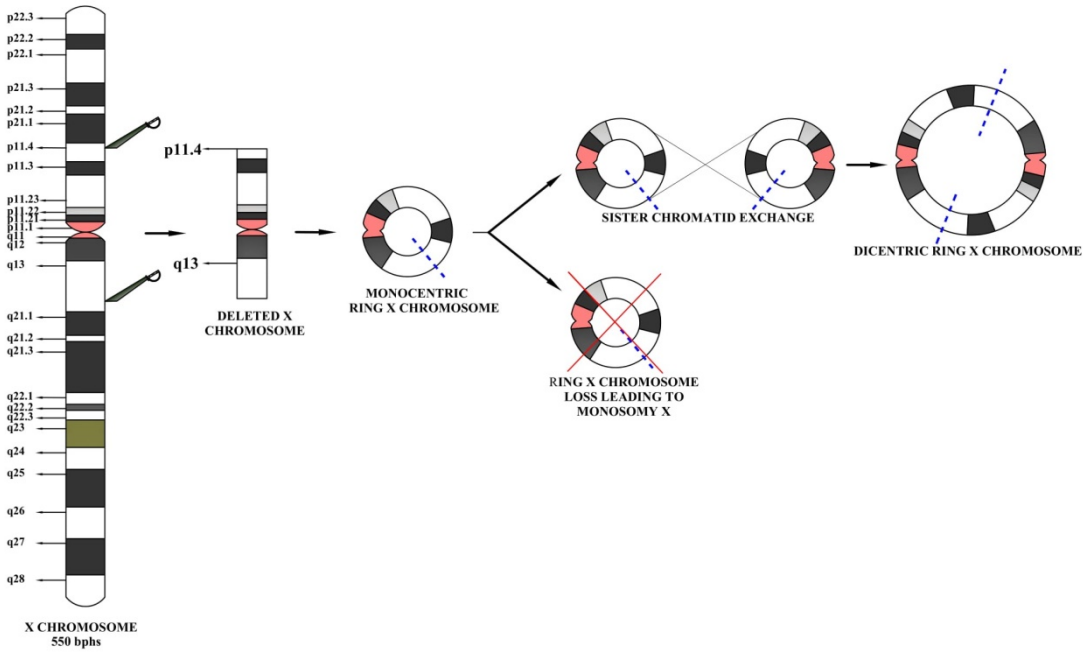

Figure 5: Schematic representation of the formation of ring X chromosome and its instability leading to production of other cell lines with dicentric ring X chromosome and monosomy X as observed in the patient. *Blue line denotes the fusion of the two broken ends.

The incidence of ring X chromosomes are 3.5 times higher compared to the autosomal rings [12]. Ring X chromosome mosaicism has been reported to occur in 6%-15% of the TS patients [1,5,9,13]. Smaller the ring size, greater is the deletion and closer is its phenotype to monosomy X. These females with 46,X,r(X) karyotype may resemble TS individuals in their characteristics such as short stature, peripheral edema, typical facial features, low neck hairline, ovarian dysgenesis, hypothyroidism, glucose intolerance, cardiac abnormalities and endocrine disorders. Mental Retardation (MR), learning disability, autism spectrum disorders, craniofacial abnormalities, dermatological problems and structural brain abnormalities are other severe phenotypes more frequently observed in those with a small ring X [1,5,9,14]. Diabetes, hypothyroidism, hypertension, auricular malformations, middle ear disease and hearing impairment, osteoporosis and bone fractures are associated morbidities of TS that increase with age [15,16]. Not only the absence of the second X chromosome is accountable for these features, but also the genomic imbalance arising due to deletions, additive influences of the associated genes in the cascade and their altered expression are linked to the resulting phenotypes [10]. Absence of XIST region or lack of its expression resulting in functional disomy of the otherwise inactive X-related genes along with monosomy of crucial active X-linked genes could also be contributory [17]. Our proband exhibited most of the characteristic features of Turner syndrome such as short stature, PA, cubitus valgus and pigmented naevi all over her body. Short stature affects more than 95% of the TS patients and is ascribed to the haploinsufficiency of *SHOX* (short-stature homeobox-containing gene) gene localized on the short arm (Xp22.33) of X chromosome [18]. This gene is expressed in the pharyngeal arch, limbs, osteogenic cells, bone marrow and fibroblasts [1]. *SHOX* promotes differentiation and inhibits proliferation of hypertrophic growth plate chondrocytes, absence of which results in excessive proliferation thus causing premature fusion of the growth plate [19]. Short metacarpals, high palate, cubitus valgus, mesomelia, Léri-Weill dyschondrosteosis and Madelung wrist deformity are other abnormalities associated with *SHOX* gene haploinsufficiency [1]. About 15% of genes on the X chromosome are identified to escape inactivation with major proportion residing in the short arm [10,20]. These non-inactive genes are crucial for the normal ovarian development and preservation [20]. Until 14 weeks of gestation, TS patients usually have normal ovaries. Subsequently the absence of the second X chromosome i.e., absence of non-inactivated genes, causes degeneration or atresia of ovaries resulting in depleted follicular reserve which eventually leads to streak ovaries and estrogen deficiency [18,20]. Molecular studies identified the Xq21.33-Xq22.1 region to be crucial, since it contains genes responsible for thyroid hormone signaling, insulin receptor signaling, chromatin organization, meiosis and cell cycle regulation, which when altered leads to ovarian dysfunction [5]. Further animals studies have

linked absence of *AR* exon 1 and its proteins to follicular decline [14]. This could explain the presenting complaint of PA and concurs with non-visualization of ovaries in our patient. However, spontaneous menarche and spontaneous pregnancy was reported to occur in 28% and 7.4% of the TS patients with mosaicism for ring X chromosome respectively [21].

Examining the active status of the ring chromosome irrespective of the size and frequency is always crucial in cases presenting unusual phenotypic features [22]. Replication and methylation studies are indirect methods used in clinical cases for determining the activation status of X and FISH for confirming its presence [17,18]. FISH analysis confirmed presence of an intact XIST on the ring X in the proband which as per Lyon's hypothesis might inactivate the additional copy of X. However, both the ring and the dicentric ring X chromosomes appeared to be darkly stained and replicating synchronously with all other chromosomes in the differential replication staining technique suggesting that they might have escaped inactivation and remain active [23,24].

The proband had moderate intellectual disability (ID) and partial hearing loss which is in agreement with the earlier reports on ring X chromosome abnormality [9,22]. Migeon et al., [23] described a TS patient with severe Mental Retardation (MR) and multiple congenital abnormalities carrying three cell lines including monosomy X, ring X and deletion of distal Xq. Both the abnormal X chromosomes were active and did not express XIST, even with XIC present. Only one of the seven ring X patients lacking XIST locus presented severe phenotypes such as MR, facial dysmorphism and congenital anomalies. Absence of XIST expression, large Xp region on ring and associated maternal uniparental disomy were attributed as causes [24]. Further, the authors proposed the presence of a mild phenotype in the remaining six patients to be due to i) absence of disomy of critical sequences responsible for a severe phenotype, ii) mosaicism leading to absence of the ring from tissues crucial to the phenotype and iii) presence of XIST expression in some tissues. Partial or incomplete X-inactivation due to absence of other downstream factors, inefficient spreading, failure to undergo conformational changes during inactivation by the abnormal X chromosome, and/or incomplete selection in favour of cells with normal balance of gene expression are other possible causes hypothesized to explain the abnormal phenotypes seen in patients with XIST region but missing expression [18]. Yoshizawa et al., [22] reported on an active ring X in a patient with MR, TS and partial hearing loss of left ear which is comparable to our study. Their proband had a mosaic ring X cell line with deletion of the XIST region and absence of X-inactivation was ascribed to unusual Turner features like MR and syndactyly.

Tomkins et al., [17] reported small r(X) in a 3½-year-old girl containing XIST locus but failing to express it causing the derivative to be active. Developmental delay, facial dysmorphism along with short stature presented by the proband was attributed to the functional disomy. She also had a variant sequence at the promoter region of the XIST linked to non-random X inactivation, but presence of the same in the grandmother with normal inactivation explains the complexity of the mechanism [17]. Kalkan et al., [14] presented a TS case with mosaic ring, wherein the proband presented ID along with Turner features which he attributes to the gain of other regions/genes such as AR from X chromosome other than XIST. Bernard et al., [21] reported a case of mosaicism involving ring X chromosome inherited from the mother causing ID and other Turner features in the proband. Reports on inheritance of mosaic ring X chromosome in two generations are available [18]. It is hypothesised to result from transmission of an unstable chromosome prone to either ring opening or to post-zygotic ring re-formation [25]. Maternal inheritance of ring X chromosome is on a higher side compared to the paternal owing to impaired male meiosis [8].

The risk towards ID and learning disabilities increases in patients with ring X chromosome and approximately 20-86% of them present ID [18]. The risk for attention deficit hyperactivity disorder is 18 times more in TS patients [26]. About 27% of genes responsible for ID and genes which influence social cognition, spatial intelligence and emotional regulation are mapped to X chromosome [20]. Reports associating neurological genes, *KDM5C* (Xp11.22), *USP9X* (Xp11.4), *NLGN4* (Xp22.3) and *OPHN1* (Xq12) to ID are available in the literature [9-12,20]. Imaging studies comparing normal and TS patients have identified differences in neuroanatomical regions, most commonly reduced grey matter and increased temporal lobe regions caused by hormonal fluctuations. Decreased production of sex hormones as a result of atresia has a direct effect on the neurodevelopment, particularly in the regions with high sex-steroid receptors [26,27]. The activity status and the ratio of mosaic X ring cell line in Central Nervous System (CNS) matters the most since, the mitosis in CNS ceases at early fetal life causing ratio difference in the cell lines compared to the lymphocytes which replicate continuously causing instability and tissue specific mosaicism [22].

Chronic or recurrent otitis media (with incidence of 68%) resulting in conductive hearing loss is the most consistent high frequency neurological abnormality reported in childhood TS patients [15,26]. Estrogen and estrogen-related receptors are important regulators and lack of these along with *SHOX*-gene deficiency is hypothesized to affect inner ear formation causing hearing loss [15]. Low set ears, cupped auricles, narrowing of the external auditory canal and abnormally protruding ears are common external ear anomalies linked to TS [15]. Autoimmune diseases, urinary congenital malformations and aortic aneurism formation are other TS associated phenotypes with possible link to inactivation escape genes [10]. Literature reports associating microcephaly, seizures, contractures, prune belly syndrome, diaphragmatic hernia and severe CNS abnormalities *viz.*, agenesis of the corpus callosum, anencephaly and total dorsal rachischisis to r(X) are available [18]. Patients with mosaic X ring have higher chance of having metabolic syndrome characterized by elevated liver enzymes *viz.*, Gamma-glutamyltransferase and alanine transaminase than monosomy patients. The risk for diabetes mellitus (elevated HbA1c) and hypertension is also high in this group [16,27].

Conclusion

In conclusion, lack of XIST-mediated silencing leading to failure of dosage compensation and consequently functional disomy and/or trisomy of genes, size of the ring and the level of mosaicism could all contribute to the observed severe TS phenotype in our proband who exhibited mosaicism for a ring X chromosome and a stable dicentric ring X chromosome. It is recommended that chromosomal analysis along with FISH may be more helpful in determining the frequency of the different mosaic cell lines.

Novel Insights

1. This is the first case of a stable dicentric ring X chromosome in an individual with both Turner syndrome and intellectual disability.

2. Presence of XIST region but absence of its expression leading to active ring X and dicentric ring X chromosomes underlies the severe phenotype in the proband.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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Statement of Ethics

The study was approved by the institutional ethical committee and informed consent was obtained from the proband's parents for participating in the study and publication of images.

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