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CASE REPORT

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Functional insights into a rare X–autosome rearrangement: Xq23–12p13 translocation in primary amenorrhea and recurrent depression

İlyas Yücel#, Gülbahar Güzel Erdal*#, Mahir Binici, Diclehan Oral, Mahmut Balkan, Elif Ademoğlu, Selahattin Tekeş, Mert İpekçi

Institute of Medical Sciences, Department of Medical Biology and Genetics, Dicle University, Diyarbakır, Turkey

ABSTRACT

Background: Chromosomal translocations, particularly X–autosome rearrangements, are rare and can produce complex clinical phenotypes even in carriers who appear phenotypically normal.

Case presentation: We present a female patient with primary amenorrhea, hypergonadotropic hypogonadism, and recurrent major depressive episodes. Cytogenetic analysis revealed a previously unreported karyotype: 46,X,t(X;12)(Xpter→Xq24::12p13→12pter;Xqter→Xq24::12p13→12qter). Array-CGH analysis confirmed that the translocation was balanced and no pathogenic copy number alterations were detected. As both parents' karyotypes were normal, this rearrangement arose de novo.

The Xq23 region contains genes involved in neuronal activity, synaptic transmission, and behaviour regulation, such as *TRPC5*, *HTR2C*, *PAK3*, *AMMECR1,* and nearby gene *PLS3*. The 12p13 region, on the other hand, harbours genes associated with calcium signalling, NMDA receptor function, and neurotrophic support, such as *TNFRSF1A*, *CACNA1C*, *GRIN2B*, *FKBP4*, and *NTF3*. *PLS3* and *AMMECR1* may influence cytoskeletal structure and neuronal migration. The proximity of these loci may lead to changes in gene expression through interaction with regulatory elements. This combination may explain the possible genetic basis for the simultaneous occurrence of gonadal insufficiency, primary amenorrhoea, and neuropsychiatric findings.

Computational analyses suggest that these genes may jointly modulate neuroplasticity, hypothalamic–pituitary–gonadal axis function, and neuroinflammatory responses.

Conclusions: This case highlights the importance of cytogenetic, molecular, and computer-assisted analyses in evaluating X–autosomal translocations in patients with unexplained amenorrhoea or recurrent depressive symptoms. Furthermore, candidate genes at breakpoints emerge as potential targets for future functional and clinical studies.

Keywords: *CACNA1C*, de novo karyotype, *GRIN2B*, hypergonadotropic hypogonadism, *in silico* analysis, primary amenorrhea, *TRPC5*, X–autosome translocation

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INTRODUCTION

Chromosomal translocations are structural rearrangements resulting from the abnormal exchange of genetic material between non-homologous chromosomes. Reciprocal translocations occur in approximately 0.2% of the general population, while X–autosome translocations are much rarer [1]. Balanced translocation carriers are mostly phenotypically normal; however, they carry a risk of infertility, spontaneous miscarriage, and unbalanced gamete production [1].

Amenorrhoea is defined as the absence of menstruation in women of reproductive age and can be primary or secondary in type [2–4]. Primary amenorrhoea, particularly when associated with hypergonadotropic hypogonadism (HH), may suggest an underlying chromosomal abnormality or gonadal dysgenesis [5,6]. HH is associated not only with infertility but also with cardiovascular problems, bone density loss, and neuropsychiatric complications.

X–autosome translocations are rarely reported in the literature and usually involve chromosomes 15, 21, and 22. Such translocations can cause gonadal dysfunction, premature ovarian failure, or psychiatric symptoms even in individuals who appear phenotypically normal [7,8]. The clinical phenotype depends on the X chromosome inactivation pattern and whether critical genes at the breakpoints are affected [9–11].

* Corresponding author: Gülbahar Güzel Erdal, Institute of Medical Sciences, Department of Medical Biology and Genetics, Dicle University, Diyarbakır, Turkey. E-mail: gulbaharguzel@yahoo.com
# These authors contributed equally to this work and share first authorship

The Xq23 region contains genes such as *TRPC5*, *HTR2C*, *PAK3*, *AMMECR1*, and *PLS3* which are associated with cognitive function, synaptic transmission, and neurodevelopment [12]. The 12p13 region contains genes such as *TNFRSF1A*, *CACNA1C*, *GRIN2B*, *FKBP4*, and *NTF3*, which play a role in calcium signalling, synaptic regulation, and stress-related neuropsychiatric processes [13-17]. Disruption of these genes or their regulatory elements may lead to pleiotropic effects affecting both endocrine and neuropsychiatric systems.

This study presents a female patient with a history of primary amenorrhoea, hypergonadotropic hypogonadism, and recurrent major depressive episodes, who carries a de novo balanced X–autosomal translocation 46,X,t(X;12)(Xpter→Xq24::12p13→12pter;Xqter→Xq24::12p13→12qter). The functional and clinical effects of this rare chromosomal rearrangement were investigated using cytogenetic, molecular, and in silico analyses. This is the first report of translocations involving the Xq23 and 12p13 regions, providing new insights into the genotype–phenotype relationship in X–autosomal translocations.

METHODS

The study was approved by the Ethics Committee of Dicle University, Diyarbakır, Turkey (approval no: 2020/266, 26 November 2020).After obtaining informed consent, peripheral blood lymphocytes were cultured, and cytogenetic analysis was performed using GTG banding. Fifty metaphases were evaluated according to ISCN 2020 criteria [18] using a Zeiss microscope, and karyotyping was carried out with Ikaros software to detect structural chromosomal abnormalities.

To further characterize the chromosomal rearrangement, array comparative genomic hybridization (array-CGH) was performed using the Agilent GenetiSure Cyto 8x60K microarray. This platform scans the genome with ~100 kb resolution (median probe spacing ~7.1 kb). Data were compared with the NCBI Human Genome Build 38 reference genome and analyzed with CytoGenomics v5.2.1.4 (Agilent). Results were cross-referenced with DGV, DECIPHER, OMIM, and ClinVar databases, and pathogenic copy number variations (CNVs) were classified according to ACMG-ClinGen guidelines (PMID: 33731880). Array-CGH confirmed the presence of a balanced translocation with no pathogenic CNVs detected, supporting cytogenetic findings.

Hormonal evaluation included FSH, LH, estradiol, TSH, prolactin, total testosterone, and DHEA-S, measured using standard automated assays. Clinical and psychiatric assessments were conducted, and pedigrees were constructed following ISCN 2020 guidelines to investigate family history.

Finally, *in silico* analyses were performed to assess potential functional effects of genes at the translocation breakpoints, focusing on candidate genes (e.g., *TRPC5*, *HTR2C*, *PAK3*, *AMMECR1*, *TNFRSF1A*, *CACNA1C*, *GRIN2B*, *FKBP4*, and *NTF3*) that may contribute to gonadal dysfunction and neuropsychiatric phenotypes observed in the patient.

CASE PRESENTATION AND FINDINGS

The patient presented with primary amenorrhea, hypergonadotropic hypogonadism, and recurrent major depressive episodes over six years, including multiple suicide attempts. Family history revealed fourth-degree consanguinity between parents, with only a maternal aunt reporting early menopause (Figure 1).

Cytogenetic analysis of the patient revealed a terminal translocation of the Xq23 segment onto 12p13, resulting in the karyotype: 46,X,t(X;12)(Xpter→Xq24::12p13→12pter;Xqter→Xq24::12p13→12qter). Metaphase spread analysis confirmed the translocation (Figure 2), and GTG banding showed no net loss or gain of chromosomal material, indicating a structurally balanced translocation (Figure 3A). Analysis of the parents' karyotypes was normal, confirming that the translocation occurred de novo (Figures 3B, 3C).

Array-CGH analysis detected no pathogenic copy number alterations, confirming the balanced nature of the translocation. *In silico* analysis identified genes located at the Xq23 and 12p13 breakpoints. In the Xq23 region, *TRPC5*, *HTR2C*, *PAK3*, *AMMECR1*, and *PLS3* were identified; in the 12p13 region, *TNFRSF1A*, *CACNA1C*, *GRIN2B*, *FKBP4*, and *NTF3* genes were identified. The combination of these genes suggests potential molecular interactions that could cause the simultaneous onset of gonadal dysfunction and neuropsychiatric symptoms.

Laboratory evaluation revealed elevated FSH (89.75 mIU/mL) and LH (79.03 mIU/mL), low estradiol (16.05 pg/mL), and normal TSH, prolactin, and androgen levels (total testosterone: 0.43 ng/mL; DHEA-S: 188.9 µg/dL). Detailed laboratory findings are summarized in Table 1.

Table 1. Laboratory findings

Parameter	Value	Normal Range
FSH	89.75 mIU/mL	1.50–12.40
LH	79.03 mIU/mL	0.50–18.00
Estradiol	16.05 pg/mL	20.00–350.00
TSH	2.40 mIU/L	0.40–4.00
Prolactin	14.80 ng/mL	4.00–23.00
Total Testosterone	0.43 ng/mL	0.20–0.80
DHEA-S	188.90 µg/dL	35.00–430.00

Abbreviations: DHEA-S – dehydroepiandrosterone sulfate, FSH – follicle-stimulating hormone, LH – luteinizing hormone, TSH – thyroid-stimulating hormone.

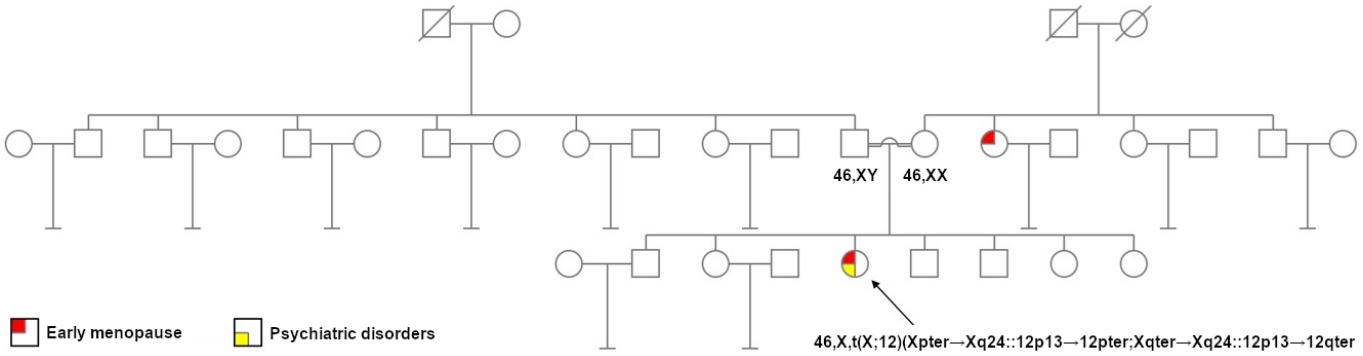

Figure 1. Pedigree of the patient showing family relationships and relevant reproductive history.

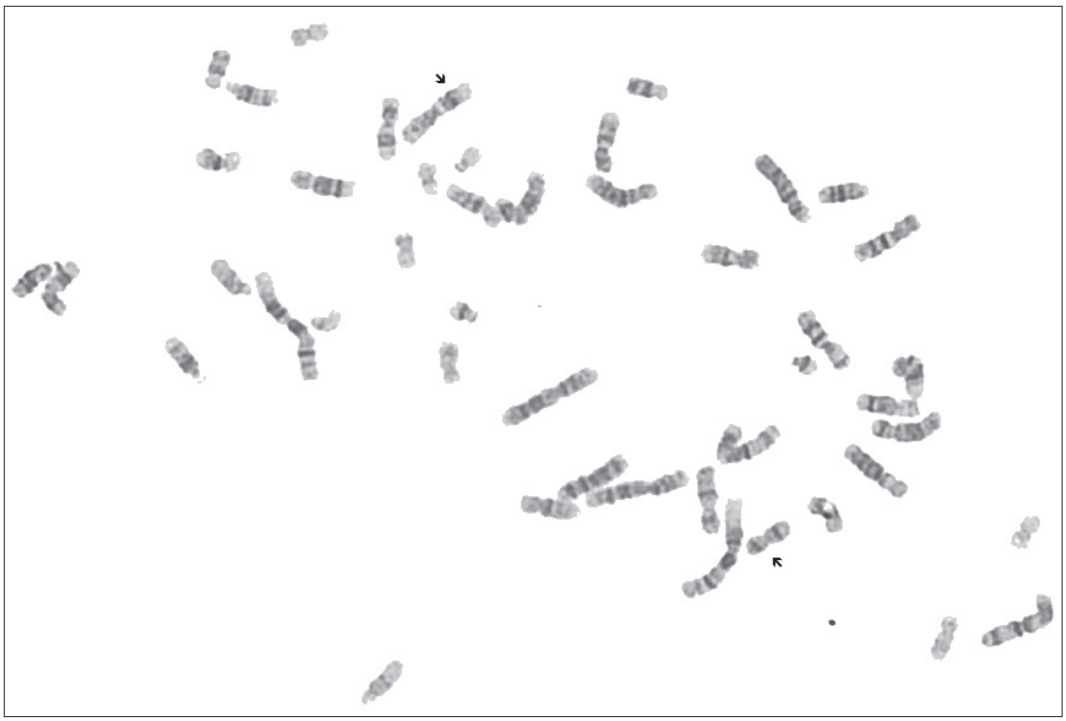

Figure 2. Metaphase of the patient, showing the balanced Xq23–12p13 translocation.

DISCUSSION

Chromosomal rearrangements, particularly X–autosome translocations, are a significant source of phenotypic variability due to their potential to disrupt critical genes and regulatory networks. Balanced translocations generally do not result in net DNA loss or gain; however, if critical genes for neurodevelopment, endocrine regulation, or synaptic function are located at the breakpoints, they can lead to clinically meaningful phenotypes [19,20]. X–autosome translocations are of particular importance because genes critical for excitatory neurotransmission, learning, memory, and antidepressant response may be affected [19–21].

In this case, cytogenetic analysis revealed a de novo 46,X,t(X;12)(Xpter→Xq24::12p13→12pter;Xqter→Xq24::12p13→12qter) karyotype. This confirms the translocation of the Xq23 terminal segment to 12p13. Array-CGH supported the balanced translocation interpretation by showing no pathogenic copy number alterations. The combination of cytogenetic and molecular analyses strengthened the structural characterisation of the translocation and enabled the evaluation of candidate genes that could contribute to the observed clinical phenotype. The case presented with primary amenorrhoea, hypergonadotropic hypogonadism, and recurrent major depressive episodes over six years, highlighting the pleiotropic effects of the breakpoint genetic disruption.

The Xq23 region contains several genes that play critical roles in neuronal and endocrine functions. *TRPC5* regulates synaptic calcium flux and neuronal excitability; this may be associated with primary amenorrhoea and mood disorders by affecting HPG axis regulation and synaptic plasticity [22]. *HTR2C* is a serotonin receptor expressed in various brain regions, including the hypothalamus, amyg-

dala, and anterior cingulate; it plays a role in neurobehavioural modulation, feeding behaviour, and stress response; therefore, its disruption may increase depressive symptoms [23-24]. *PAK3* is a gene encoding p21-activated kinase and has been associated with cognitive impairments, neurobehavioural abnormalities, and self-injurious behaviour in some cases; its haploinsufficiency may contribute to the patient's neuropsychiatric phenotype [25].

The 12p13 breakpoint region contains many genes involved in neuropsychiatric and gonadal function. *TNFRSF1A* may contribute to neuroimmune interactions that could affect mood by regulating inflammatory signalling [26]. *CACNA1C* encodes the L-type calcium channel subunit and is essential for synaptic plasticity; it is associated with bipolar disorder and mood dysregulation (rs1006737) [27]. *GRIN2B* encodes the NMDA receptor subunit and is critical for excita-

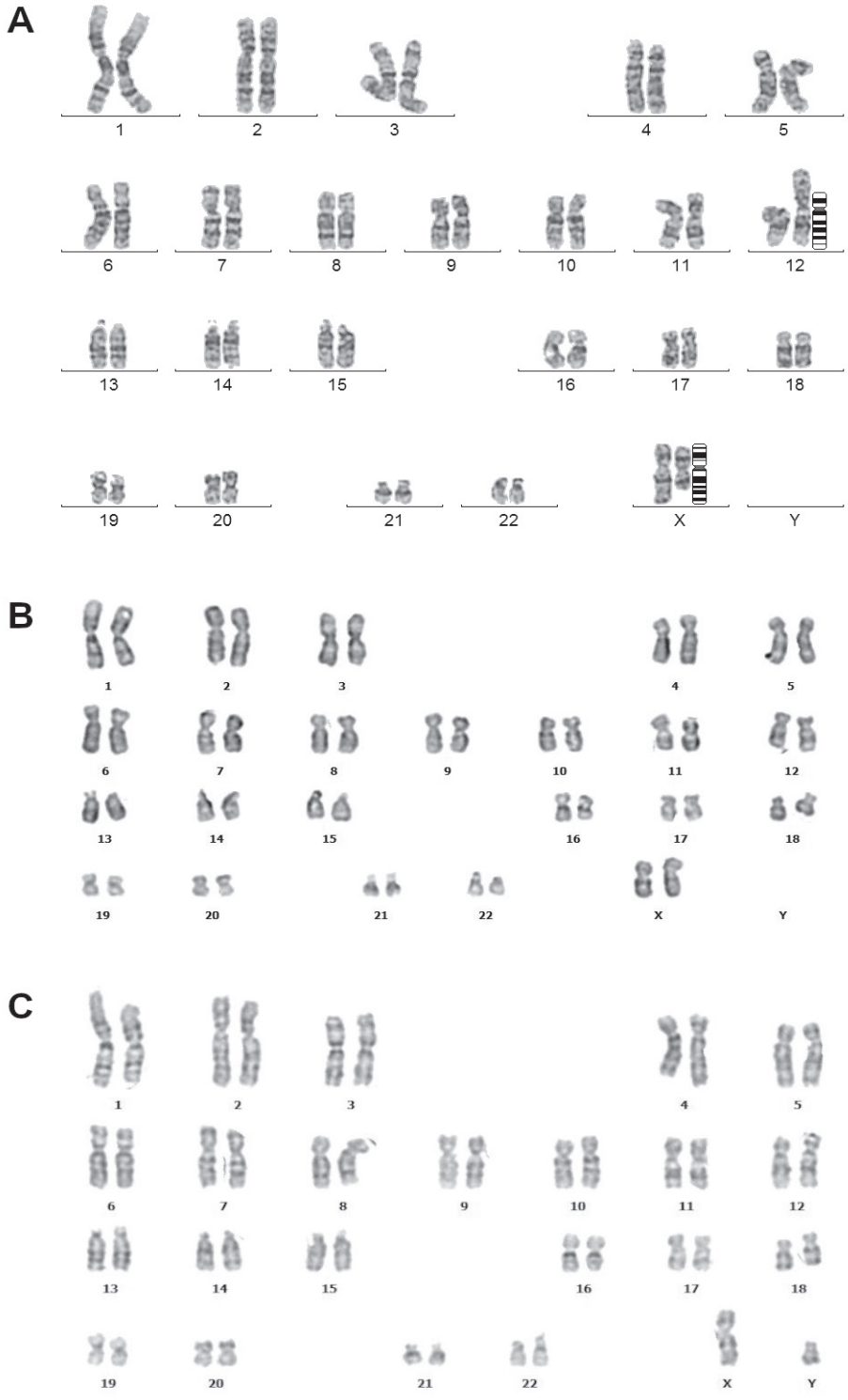

Figure 3. Karyotype analysis

(A) Patient karyotype, showing the Xq23 translocation onto chromosome 12p13; (B) Mother karyotype, demonstrating a normal chromosomal complement; (C) Father karyotype, demonstrating a normal chromosomal complement.

tory neurotransmission, learning, memory, and antidepressant response [28–29]. *FKBP4*, as a co-chaperone regulating glucocorticoid receptor activity, may influence the stress response and the HPG axis [30]. *NTF3*, located at 12p13, and *NTF4*, a neurotrophin located outside the breakpoint regions, are expressed in various brain regions and support neuronal survival, differentiation, and synaptic plasticity; alterations in their expression have been associated with depressive phenotypes [31–32]. The Xq23 and 12p13 breakpoint regions contain several candidate genes with potential effects on neuropsychiatric and gonadal function (Table 2).

Additional candidate genes in breakage regions may also affect cytoskeletal and synaptic organisation. *PLS3*, an actin-binding protein, plays a role in neuronal migration and morphogenesis; it may contribute to neurodegenerative processes [33-35]. *AMMECR1*, whose function is not fully understood, shares homology with AMME complex genes and may affect nuclear or cytoskeletal organisation [36]. These genes may contribute mildly to neurodevelopmental outcomes, creating a predisposition to depressive phenotypes. Furthermore, astrocyte-derived synaptogenesis factors *SPARCL1* and *CHRDL1*, although not located at the breakpoint regions, may influence hippocampal circuits and depressive phenotypes by regulating excitatory synapse formation and AMPAR clustering [37,38]. A schematic representation of the neurological and psychiatric effects of candidate genes at Xq23 and 12p13 breakpoints is shown in Figure 4.

The intersection of Xq23 and 12p13 genetic disruptions likely creates a complex network effect. Haploinsufficiency of Xq23 genes (*TRPC5*, *HTR2C*, *PAK3*, *AMMECR1*, *PLS3*) combined with 12p13 genes (*TNFRSF1A*, *CACNA1C*, *GRIN2B*, *FKBP4*, *NTF3*) may collectively disrupt neuroendocrine signalling, synaptic plasticity, neuroinflammation, and mood regulation. Although Array-CGH does not show pathogenic copy number changes, the juxtaposition of these loci may create a positional effect on transcription, enhancer-promoter interactions, or chromatin topology. This situation may explain the co-occurrence of primary amenorrhoea, hypergonadotropic hypogonadism, and major depressive disorder.

Phenotypic variability in X-autosomal translocations involves genes located on Xq23 as well as autosomal regions such as 12p13. This variability is influenced by environmental, epigenetic, and stochastic factors, and incomplete penetrance and variable expressivity are frequently observed. Comprehensive endocrine, neuropsychiatric, and molecular profiling is therefore essential to fully capture clinical outcomes [10–12]. Functional interactions between candidate genes may enhance pleiotropic effects; for example, *TRPC5*-derived calcium signalling may modulate neurotrophin activity (*NTF3*, *NTF4*) [39],while *CACNA1C* and *GRIN2B* may influence synaptic plasticity [40], converging with *FKBP4*-regulated glucocorticoid receptor pathways to affect mood and stress responses [41].

Furthermore, the interaction between neurotrophic support (*NTF3*, *NTF4*) [42], cytoskeletal regulation (*PLS3*, *AMMECR1*) [43-44], and astrocytic modulation (*SPARCL1*, *CHRDL1*) [45-46], demonstrates that both neuronal and glial components contribute to the neuropsychiatric phenotype. Disruption of this network may lead to alterations

Table 2. Candidate genes associated with the Xq23–12p13 translocation breakpoints and related neurodevelopmental pathways

Gene	Chromosome region	Function / Role	Related clinical / functional effect	References
TRPC5	Xq23	Calcium channel, regulates synaptic excitability and neuronal calcium flux	Modulates HPG axis, synaptic plasticity, mood regulation	[22]
HTR2C	Xq23	Serotonin receptor, involved in behavior and stress response	Depression, behavioral modulation, feeding behavior	[23,24]
PAK3	Xq23	p21-activated kinase, synaptic development	Cognitive impairments, neurobehavioral abnormalities	[25]
AMMECR1	Xq23	Potential role in nuclear and cytoskeletal organization	Mild neurodevelopmental effects, cytoskeletal organization	[36]
PLS3	Xq23	Actin-binding protein, neuronal migration and morphogenesis	Neurodegenerative susceptibility, cytoskeletal integrity	[33–35]
TNFRSF1A	12p13	Inflammatory signaling, NF-κB pathway	Neuroimmune interactions, mood regulation	[26]
CACNA1C	12p13	L-type calcium channel, synaptic plasticity	Bipolar disorder, mood dysregulation	[27]
GRIN2B	12p13	NMDA receptor subunit, excitatory neurotransmission	Learning, memory, antidepressant response	[28,29]
FKBP4	12p13	Glucocorticoid receptor co-chaperone	HPA/HPG axis regulation, stress response	[30,41]
NTF3	12p13	Neurotrophin, supports neuronal survival and differentiation	Synaptic plasticity, depressive phenotypes	[31,42]
NTF4	19q13.33	Neurotrophin, synaptic support	Synaptic plasticity, depressive phenotypes	[32,42]
SPARCL1	4q22.1	Astrocyte-derived synaptogenesis factor	Excitatory synapse formation, hippocampal circuits	[37,45]
CHRDL1	Xq23	BMP antagonist, regulates synapse formation	AMPAR clustering, modulation of depressive phenotypes	[38,46]

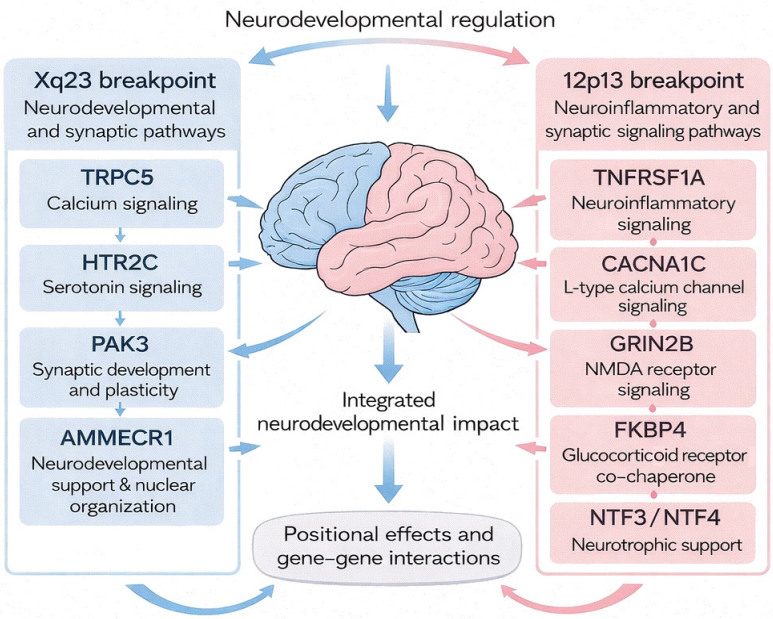

Figure 4. Schematic representation of neurological and psychiatric pathways involving candidate genes at the Xq23 and 12p13 breakpoints

in HPG axis feedback, synaptic plasticity, and susceptibility to depression. Serotonergic modulation (*HTR2C*) provides a multi-layered mechanistic perspective by integrating effects at the neurotransmitter level [47].

Consequently, this case demonstrates that coordinated disruption of multiple candidate genes, even in balanced translocations, can lead to pleiotropic phenotypes and highlights the importance of combining cytogenetic, microarray, and in silico analyses. Future studies should clarify the mechanistic contributions of these genes through functional genomics, chromatin conformation analyses, and transcriptomic profiling, and guide potential therapeutic interventions. The significance of this finding also lies in the understanding that even balanced translocations can lead to complex phenotypic outcomes when genetic, molecular, and clinical data are integrated. Xq23 deficiency may affect the expression of genes such as *TRPC5*, *HTR2C*, *PAK3*, *AMMECR1*, and *PLS3*, which could disrupt synaptic plasticity, neuroendocrine function, and cognitive behaviour. The juxtaposition of the 12p13 region may disrupt the regulatory elements of genes such as *TNFRSF1A*, *CACNA1C*, *GRIN2B*, *FKBP4*, and *NTF3*, thereby affecting inflammation, neurotrophic support, cytoskeletal organisation, and synaptic development.

In particular, the effect of *TRPC5* and *CACNA1C* on calcium signalling, the modulation of NMDA receptor function by *GRIN2B*, and the regulation of the glucocorticoid response by *FKBP4* may contribute to the combined disruption of mood, stress response, and gonadal axis regulation in the central nervous system. Alterations in *HTR2C* may influence depression and behavioural phenotypes via serotonin signalling. *NTF3* supports synaptic plasticity and neuronal survival, while *PLS3* and *AMMECR1* may increase neurodegenerative susceptibility by affecting cytoskeletal integrity and cellular morphology. *SPARCL1* and *CHRDL1* provide additional modulation via astrocyte-derived synaptogenesis.

This finding demonstrates that even in a balanced translocation, the juxtaposition of breakpoints can lead to clinically meaningful pleiotropic phenotypes through positional effects and haploinsufficiency mechanisms. Furthermore, the absence of pathogenic CNVs in microarray analysis suggests that this condition is related to disrupted regulatory interactions rather than copy number alterations. This emphasises the importance of not only karyotype and microarray data but also in silico and functional analyses in the evaluation of X–autosome translocations.

This study has several limitations. Only a single case is reported, limiting generalizability. Functional experimental validation was not performed; genetic mechanisms are inferred from in silico predictions. Also, environmental and epigenetic factors may contribute to psychiatric phenotypes and could not be fully controlled in this study.

CONCLUSIONS

We report the first case of a de novo balanced X-autosomal translocation involving Xq23 and 12p13 in a female patient with primary amenorrhoea, hypergonadotropic hypogonadism, and recurrent major depressive episodes. Cytogenetic and array CGH analyses confirm the balanced nature of the rearrangement, and normal karyotypes in the parents indicate its de novo origin.

This case highlights the clinical importance of integrating detailed cytogenetic evaluation with *in silico* functional analyses to understand complex phenotypes

arising from rare chromosomal rearrangements. Even phenotypically normal balanced X-autosome translocation carriers may exhibit variable endocrine and neuropsychiatric phenotypes due to disruption of critical gene networks. Our findings underscore the importance of both gonadal and neuropsychiatric evaluations in patients with similar chromosomal abnormalities and highlight the need for future functional studies to elucidate the precise molecular mechanisms underlying phenotypic variability in X-autosomal translocation carriers.

In conclusion, this case presents the molecular and clinical characterisation of a balanced Xq23–12p13 translocation and highlights the necessity for comprehensive analysis in rare chromosomal rearrangements. Genes on Xq23, such as *TRPC5*, *HTR2C*, and *PAK3*, and genes on 12p13, such as *TNFRSF1A*, *CACNA1C*, *GRIN2B*, *FKBP4*, *NTF3*, *NTF4*, *PLS3*, *AMMECR1*, *SPARCL1*, and *CHRDL1*, play a critical role in explaining phenotypic variability and pleiotropy. In the future, functional genomic studies, chromatin conformation and transcriptome analyses may provide further insight into the mechanistic contributions of these genes and identify potential therapeutic targets.

ABBREVIATIONS

CLIA – chemiluminescence immunoassay

DHEA – dehydroepiandrosterone sulfate

FSH – follicle-stimulating hormone

HH – hypogonadotropic hypogonadism

HPG – hypothalamic-pituitary-gonadal axis

LH – luteinizing hormone

TSH – thyroid-stimulating hormone

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None.

AUTHORS' CONTRIBUTION

GGE and İY contributed equally to this work and share first authorship: conceived and designed the study, coordinated the workflow, contributed to the interpretation of the clinical, cytogenetic, and molecular findings, and critically revised the manuscript for important intellectual content.

GGE performed *in silico* analyses and drafted the manuscript.

MB and ST performed and interpreted the array comparative genomic hybridization (array-CGH) analyses.

DO and MB performed and interpreted the GTG-banded karyotype analysis according to ISCN 2020 criteria.

Mİ and EA contributed to clinical data collection, hormonal evaluation, and pedigree analysis.

All authors have read and approved the final version of the manuscript.

CONFLICT OF INTEREST

None to declare.

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