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Case Report

Unique Female Patient with *de novo* 6q22.31q27 Duplication and Xq28 Deletion: Case Report and Brief Literature Review

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Abstract

6q22.31q27 duplication and Xq28 deletion lead to two specific different rare chromosomal disorders. Partial trisomy 6q22.31q27 is a recognizable syndrome with a distinctive phenotype, and the most common finding in girls with Xqter deletions has been premature ovarian failure (POF) and secondary amenorrhea. To our knowledge, neither abnormality in one patient has yet been reported. A 10-year-old girl with de novo 6q22.31q27 duplication and Xq28 deletion was diagnosed by chromosomal microarray and confirmed by fluorescence in situ hybridization. The presence of two rare specific chromosomal disorders is possible and must be considered in genetic counseling. A second chromosomal abnormality may be considered in cases with a diagnosed syndrome but uncommon clinical features.

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Keywords
Cytogenetics; fluorescence in situ hybridization (FISH); dup(6q); del(X)(q28); chromosomal microarray (CMA)

1. Introduction

Partial trisomy of the long arm of chromosome 6 and Xq28 deletion are two rare specific chromosomal disorders.

Most patients with unbalanced translocations have partial trisomy 6q and partial monosomy of another chromosome. The co-existence of these two types of chromosomal anomalies, especially the monosomy of another chromosome, would usually make it complicated to clearly interpret the genotype-phenotype correlation of pure 6q duplication [1, 2].

This report describes a 10-year-old girl with a de novo 6q22.31q27 duplication and Xq28 deletion. To characterize the phenotype, the patient's clinical findings are compared with those of other reported patients with similar duplication of 6q and deletion of Xq28.

2. Case Report

2.1 Patient's Medical History

The patient was referred to the Department of Medical Genetics in Rabat for development delay and facial dysmorphism. The patient, a 10-year-old girl of a young and nonconsanguineous Moroccan couple (mother 28y, father 32y), was the family's second child. There were no health problems in the family or a history of miscarriages. She was delivered at 38 weeks of gestation, and the ultrasound scan in the third trimester showed intrauterine growth retardation.

Clinical manifestations included psychomotor delay, intellectual disability, joint contractures of both ankles, and generalized stiffness at articulations and facial dysmorphism with the following dysmorphic stigmata: carp-shaped mouth, micrognathia, frontal bossing, prominent eyes with hypertelorism, microcephaly, down slanting palpebral fissures and short neck.

The pre-analytic and post-analytic steps described in this work were performed for patients by the Department of Medical Genetics of the National Institute of Health as medical services in agreement with the tenets of the Declaration of Helsinki.

All ethical issues of the National Institute of Health in Rabat, Morocco, where the Department of Medical Genetics are in charge of an Intramural Advisory Committee.

Written informed consent was obtained from the patient's parents.

2.2 Classical Cytogenetics and Chromosomal Microarray Analysis

The patient's parents gave informed consent for this study. Venous blood (3 to 5 ml) acquired in a heparinized tube was taken from the patient and his parents for cytogenetic and molecular cytogenetic studies.

Further routine investigations included a brain MRI, abdominal ultrasound and an electroencephalogram.

Chromosome analyses from cultivated peripheral blood lymphocytes of proband and parents were done.

Chromosomal microarray (CMA) analyses by microarray Cyto Array (180K, GRCh37/hg19 – Agilent) were performed and evaluated by Agilent Cyto Genomics 5.1.2.1 software and tamper detection algorithm ADM-2 threshold value of 6.0.

2.3 Molecular Cytogenetics Analysis

Fluorescence in situ hybridization (FISH) according to standard procedures using a whole chromosome 6 probe (wcp 6), the locus-specific probe RP11-100A16 in 6q22.31 (hg19: 121,028,121-121,205,654) and a partial chromosome probe (pcpc) for short and long arm of X-chromosome as well a subtelomeric probe for Xqter.

3. Result

Chromosome analyses revealed normal karyotypes in both parents, but a karyotype: 46,X, der(X) of their daughter(Figure 1A).

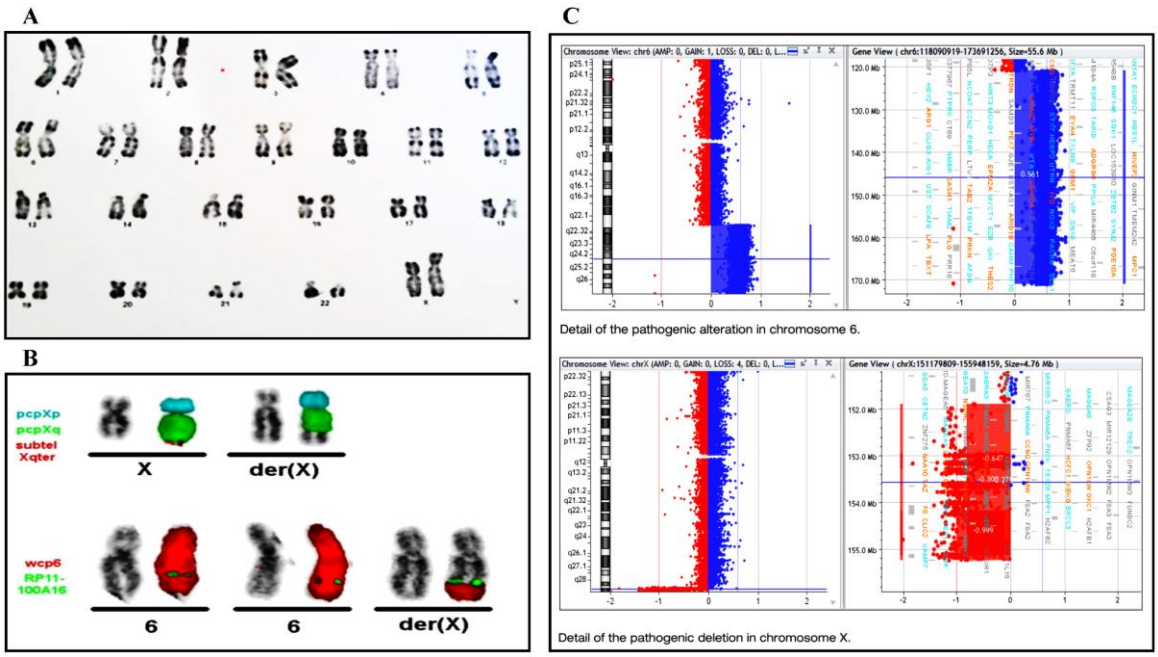

Figure 1 Techniques for Chromosomal Aberration Analysis (Karyotyping, FISH, and CGH). A) Karyotype of the patient-showing der(X). B) FISH was used to detect der(X) and 6. Using probes WCP (Whole chromosome painting) of chromosomes 6; locus-specific probe RP11-100A16, and a partial chromosome probe (pcpc) for the short and long arm of X-chromosome and subtelomeric probe for Xqter Results of FISH revealed the presence of a der(6)t(X;6)(q28;q22.31). C) Chromosomal aberration of the imbalances seen in CMA.

A 50.04 Mb heterozygote terminal duplication in 6q22.31q27(chr6:120,870,936_170,911,240) and a 3.338 Mb heterozygote terminal deletion in Xq28 (chrX:151,895,062_155,232,907) were detected (shown in Figure 1C).

FISH experiments further confirmed the presence of a der(6), classifying it as der(6)t(X;6)(q28;q22.31) as underlying chromosomal aberration of the imbalances seen in CMA (shown in Figure 1B).

4. Discussion and Conclusion

Various phenotypes have been described, and variable clinical signs exist for each chromosomal aberration. To our knowledge, the case reported here is the first in the literature involving the duplication of 6q22.31q27 and deletion of the Xq28 chromosomal region. An increased number of studies can help to identify chromosomal aberration causes and clinical effects more clearly.

The partial duplication of the long arm of chromosome 6 was described first by [De Grouchy et al., 1969], and since this time, other additional cases have been reported [3].

The phenotype's severity depends on the duplication's size and gene content.

In this study, we identified and selected all genes reported in the Online Mendelian Inheritance in Man (OMIM) database (https://www.omim.org/) and located in the deleted region (chrX:151895062_155232907) in Xq28 (see Table 1) and in the large 50.04 Mb duplication region 6q22.31-q27 (see Table 2) using UCSC genome browser tool (https://genome.ucsc.edu/) with pseudogene filtration. Here, we were able to select 73 genes in Xq28 deletion. Searching the ClinGen database (https://clinicalgenome.org/) for these genes revealed that, out of these 73 genes, 18 have been reported to have gene-disease validity (Table 1), with definitive, moderate, and/or limited classifications.

Table 1 Gene list in deletion region in Xq28 shown in UCSC and gene-disease validity from CLinGen database.

Genes located in (chrX:151895062_155232907) region using UCSC genome browser					**Gene-Disease Validity from CLinGen database with classification**	
ABCD1 *(MIM* 300371)*	***DUSP9*** *(MIM * 300134)*	***HCFC1*** *(MIM * 300019)*	***MTCP1*** *(MIM * 300116)*	***SSR4*** *(MIM * 300090)*	***ABCD1*** *HGNC:61 Definitive*	***SLC6A8*** *HGNC:11055 Definitive*
ARHGAP4 *(MIM * 300023)*	***EMD*** *(MIM * 300384)*	***IDH3G*** *(MIM * 300089)*	***NAA10*** *(MIM * 300013)*	***TAFAZZIN*** *(MIM * 300394)*	***ATP6AP1*** *HGNC:868 Definitive*	***TAFAZZIN*** *HGNC:11577 Definitive*
ATP2B3 *(MIM * 300014)*	***F8*** *(MIM * 300841)*	***IKBKG*** *(MIM * 300248)*	***NSDHL*** *MIM * 300275)*	***TEX28*** *(MIM * 300092)*	***BCAP31*** *HGNC:16695 Definitive*	
ATP6AP1 *(MIM * 300197)*	***F8A1*** *(MIM * 305423)*	***IRAK1*** *(MIM * 300283)*	***OPN1LW*** *(MIM * 300822)*	***TKTL1*** *(MIM * 300044)*	***BGN*** *HGNC:1044 Limited*	
AVPR2 *(MIM * 300538)*	***FAM3A*** *MIM * 300492)*	***L1CAM*** *(MIM * 308840)*	***PDZD4*** *(MIM * 300634)*	***TMEM187*** *(MIM * 300059)*	***DKC1*** *HGNC:2890 Definitive*	
BCAP31 *(MIM * 300398)*	***FAM50A*** *(MIM * 300453)*	***LAGE3*** *(MIM * 300060)*	***PLXNA3*** *(MIM * 300022)*	***TREX2*** *(MIM * 300370)*	***F8*** *HGNC:3546 Definitive*	
BGN *(MIM * 301870*	***FLNA*** *(MIM * 300017)*	***MAGEA1*** *(MIM * 300016)*	***PLXNB3*** *(MIM * 300214)*	***UBL4A*** *(MIM * 312070)*	***FLNA*** *HGNC:3754 Definitive/Limited*	
BRCC3 *(MIM * 300617)*	***FUNDC2*** *(MIM * 301042)*	***MAGEA10*** *(MIM * 300343)*	***PNCK*** *(MIM * 300680)*	***VBP1*** *(MIM * 300133)*	***G6PD*** *HGNC:4057 Definitive*	
CCNQ	***G6PD***	***MAGEA12***	***PNMA3***	***ZNF185***	***GDI1***	

*(MIM * 300708)*	*(MIM * 305900)*	*(MIM * 300177)*	*(MIM * 300675)*	*(MIM * 300381)*	*HGNC:4226 Moderate*
CETN2	***GAB3***	***MAGEA2***	***PNMA5***		***HCFC1***
*(MIM * 300006)*	*(MIM * 300482)*	*(MIM * 300173)*	*MIM * 300916)*		*HGNC:4839 Definitive*
CSAG1	***GABRA3***	***MAGEA2B***	***PNMA6A***		***IKBKG***
*(MIM * 300944)*	*(MIM * 305660)*	*(MIM * 300549)*	*MIM * 300917)*		*HGNC:5961 Definitive*
CTAG1A	***GABRE***	***MAGEA3***	***RENBP***		***L1CAM***
*(MIM * 300657)*	*(MIM * 300093)*	*(MIM * 300174)*	*(MIM * 312420)*		*HGNC:6470 Definitive*
CTAG1B	***GABRQ***	***MAGEA4***	***RPL10***		***MECP2***
*(MIM * 300156)*	*(MIM * 300349)*	*(MIM * 300175)*	*(MIM * 312173)*		*HGNC:6990 Definitive*
CTAG2	***GDI1***	***MAGEA6***	***SLC10A3***		***NAA10***
*MIM * 300396)*	*(MIM * 300104)*	*(MIM * 300176)*	*(MIM * 312090)*		*HGNC:18704 Definitive*
DKC1	***H2AB1***	***MECP2***	***SLC6A8***		***NSDHL***
*(MIM * 300126)*	*(MIM * 301037)*	*(MIM * 300005)*	*(MIM * 300036)*		*HGNC:13398 Moderate*
DNASE1L1	***HAUS7***	***MPP1***	***SRPK3***		***RPL10***
*(MIM * 300081)*	*(MIM * 300540)*	*(MIM * 305360)*	*(MIM * 301002)*		*HGNC:10298 Moderate*

Table 2 Gene list in duplication region in 6q22.31q27 (chr6:120870936_170911240) with OMIM numbers.

ACAT2	*100678	ESR1	*133430	L3MBTL3	*618844	PDE10A	*610652	SASH1	*607955	TBP	*600075
ADAT2	*615388	EYA4	*603550	LAMA2	*156225	PDE7B	*604645	SCAF8	*616024	TBPL1	*605521
AGPAT4	*614795	EZR	*123900	LATS1	*603473	PDE7B	*604645	SERAC1	*614725	TCF21	*603306
AHI1	*608894	FABP7	*602965	LPA	*152200	PERP	*609301	SERINC1	*614548	TCP1	*186980
AIG1	*608514	FAM120B	*612266	LPAL2	*611682	PEX3	*603164	SF3B5	*617847	TCP10	*187020
AKAP12	*604698	FBXO30	*609101	LTV1	*620074	PEX7	*601757	SGK1	*602958	TCTE3	*186977

AKAP7	*604693	FBXO5	*606013	MAN1A1	*604344	PHACTR2	*608724	SHPRH	*608048	TFB1M	*607033
ALDH8A1	*606467	FGFR1OP	*605392	MAP3K4	*602425	PHF10	*613069	SLC18B1	*613361	THBS2	*188061
ARG1	*608313	FNDC1	*609991	MAP3K5	*602448	PKIB	*606914	SLC22A1	*602607	THEMIS	*613607
ARHGAP18	*613351	FRMD1	*616919	MAP7	*604108	PLAGL1	*603044	SLC22A2	*602608	TIAM2	*604709
ARID1B	*614556	FUCA2	*136820	MAS1	*165180	PLEKHG1	*620134	SLC22A3	*604842	TMEM181	*613209
ASF1A	*609189	GJA1	*121014	MCM9	*610098	PLG	*173350	SLC2A12	*610372	TNFAIP3	*191163
BCLAF1	*612588	GPR126	*612243	MED23	*605042	PNLDC1	*619529	SLC35D3	*612519	TPD52L1	*604069
BRP44L	*614738	GPR31	*602043	MLLT4	*159559	PPIL4	*607609	SMOC2	*607223	TRDN	*603283
C6orf120	*616987	GRM1	*604473	MOXD1	*609000	PPP1R14C	*613242	SMPDL3A	*610728	TULP4	*619442
C6orf211	*616332	GTF2H5	*608780	MRPL18	*611831	PSMB1	*602017	SNX9	*605952	TXLNB	*611438
C6orf70	*615532	HBS1L	*612450	MTHFD1L	*611427	PTPRK	*602545	SOD2	*147460	ULBP1	*605697
CCDC28A	*615353	HEBP2	*605825	MTRF1L	*613542	QKI	*609590	STX11	*605014	ULBP2	*605698
CCN2	*121009	HECA	*607977	MYB	*189990	RAB32	*612906	STX7	*603217	ULBP3	*605699
CCR6	*601835	HEY2	*604674	MYCT1	*616805	RAET1E	*609243	STXBP5	*604586	UNC93A	*607995
CENPW	*611264	HINT3	*609998	NCOA7	*609752	RAET1G	*609244	SUMO4	*608829	UST	*610752
CEP85L	*618865	HIVEP2	*143054	NHSL1	*620171	RAET1K	*611047	SYNE1	*608441	UTRN	*128240
CITED2	*602937	HSF2	*140581	NKAIN2	*609758	RAET1L	*611047	SYNJ2	*609410	VIP	*192320
CLVS2	*616945	IFNGR1	*107470	NMBR	*162341	REPS1	*614825	TAAR1	*609333	VNN1	*603570
CNKSR3	*617476	IGF2R	*147280	NOX3	*607105	RGS17	*607191	TAAR2	*604849	VNN2	*603571
DACT2	*608966	IL20RA	*605620	NUP43	*608141	RMND1	*614917	TAAR5	*607405	VNN3	*606592
DLL1	*606582	IL22RA2	*606648	OLIG3	*609323	RNASET2	*612944	TAAR6	*608923	VTA1	*610902
DYNLT1	*601554	IPCEF1	*619948	OPRM1	*600018	RNF146	*612137	TAAR8	*606927	WAKMAR2	*618508
ECHDC1	*612136	IYD	*612025	PACRG	*608427	RNF217	*618592	TAAR9	*608282	WTAP	*605442
ENPP1	*173335	KATNA1	*606696	PARK2	*602544	RPS12	*603660	TAB2	*605101	ZBTB2	*616595
ENPP3	*602182	KIAA0408	*619236	PBOV1	*605669	RPS6KA2	*601685	TAGAP	*609667	ZC3H12D	*611106
EPB41L2	*603237	KIAA1244	*617411	PCMT1	*176851	RSPH3	*615876	TARID	*616058	ZDHHC14	*619295
EPM2A	*607566	KIF25	*603815	PDCD2	*600866	RSPO3	*610574	TBC1D32	*615867	7SK	*606515

The considerable size of the duplication makes it difficult to establish a straightforward genotype-phenotype correlation.

The phenotype of the duplication 6q syndrome is distinctive enough to be clinically recognizable. Full trisomy 6 is incompatible with fetal survival. However, it has been found in spontaneous abortions [4].

Very few patients have pure 6q duplication. Most patients carry partial monosomy of another chromosome, which would usually interpret the genotype-phenotype correlation of this duplication as challenging to make [1, 2].

Duplicated regions of the long arm of chromosome 6 display many common anomalies but define a clinically specific syndrome.

A review of the literature of similar patients with chromosomal rearrangements involving chromosome 6 is summarized in Table 3.

Table 3 Comparative features of patients with partial trisomy of the long arm of chromosome 6 in our case and published literature.

	Present case	**Erdel et al.**	**Dellacasa et al.**	**Bartalena et al.**	**Seel et al.**	**Taysi et al.**	**Pivnik et al.**	**Atli et al.**	**Conrad et al.**
Duplication segment	6q22.1-q27	6q23-qter	6q22.36-->qter	6q23----6qter	6q23.3–qter	6q22 to 6qter	6q23 → ter	6q23.3-q27:	6q22 to 6qter
Age	10 years	6 months	5 years	newborn	10 years	2-month-old	New born	8-month-old	22-month-old
Sex	F	M	M	M	M	M	M	F	F
Microcephaly	+	+	+	–	+	+	+	+	+
Short webbed neck	+	+	+	+	+	+	+	–	+
Prominent forehead	+	+	+	+	+	+	+	+	+
Down-slanting palpebral fissures	+	+	+	+	+	+	+	–	+
Acrocephaly	+	NS	NS	–	–	–	–	+	–
Abnormal palmar creases	+	+–	+	+–	+–	+–	+–	+–	+
Joint contractures	++	+	+	+	+	+	+	–	+
Foot anomaly	+	+	NS	+	+	+	+	+	+
Growth retardation	+	+	NS	+	+	+	+	+	+
High/cleft palate	–	+	NS	+	+	+	+	+	–
Low birth weight	+	+	NS	+–	+	+	+–	+	–
Hypertelorism	+	+	+	+	+	+	+	+	+
Carp shaped mouth	+	+	+	+	+	+	+	+	+
Micrognathia	+	+	+	+	+	+	+	+	+
Hand/finger anomaly	+	+	+	+	+	+	+	+	+
mental retardation	+	+	NS	NS	+	+	–	+	+
Low set ears	+	+	+	–	–	+	–	–	+
Cerebral anomaly	–	+	–	–	+	+	–	–	NS
Flat/broad nose	+	+	+	–	+	+	–	+	NS
Cardiac anomaly	–	+	–	+	+	+	+	+	+
Renal anomalies	–	NS	–	NS	+	NS	NS	NS	+

***NS, not specified**.

Of particular note is the similarity of the phenotype and the breakpoint duplication 6q22 to 6qter in our case with that presented by [5-7].

The duplicated segment in [8, 9] is slightly larger than the other cases [8-12]. The common duplicated segment is 6q23->q27. However, it has been suggested that the critical band involved in the expression of the phenotype of 6q duplication is located in this segment.

Almost all patients have in common microcephaly, frontal bossing, micrognathia, prominent eyes with hypertelorism, down-slanting palpebral fissures, short necks, and a carp-shaped mouth. Thus, the facial appearance allows the identification of the underlying chromosome abnormality.

Individuals with Partial Trisomy 6q may also have various internal organ malformations, such as cardiac or renal anomalies. Regarding cardiac anomaly, it has not been detected in our case but seen in 7 other compared patients [6-12]. Cardiac anomalies range from atrial septal defects to complex malformations. Therefore, children with partial duplication of 6q deserve a cardiac evaluation. The cases reported by [7-11] have also renal abnormalities.

All patients show psychomotor retardation. Motor development may be severely impaired due to multiple contractures and skeletal anomalies. They are seen in 7 of 8 patients reviewed. In our patients, they contribute to gross motor difficulties.

Duplications of 6q are the result of either an abnormal segregation of a balanced translocation or inversion carried by a parent or of a de novo unbalanced rearrangement, as in our case. Often, the duplication is combined with a deletion of the other chromosomal segment involved in the rearrangement.

The monosomic segment in our patient is Xq28; the phenotype of girls with X chromosome deletions has ranged from completely normal to severe phenotype. Characteristics of patients carrying chromosomal Xq28 rearrangements are summarized in Table 4.

Table 4 Features of patients with Xq deletion.

Age at diagnosis	Primary/Secondary amenorrhoea	Other features	Developmental delay	Chromosomal abnormality	De novo or inherited	Reference
6 years	-	mildly dysmorphic facies and obesity	Marked developmental delay	deletion at Xq27.3–Xq28	*de novo*	[13]
29 years	premature ovarian failure	-	-	Xq26 to Xqter deletion, includes FMR1	*de novo*	[14]
4 years	-	skewed X inactivation	global developmental delay	a hemizygous deletion of Xq27.3q28	*de novo*	[15]
34 years	Irregular menstruation	epicanthal fold and a mild	intellectual disability	deletion of Xq28-qter and trisomy for 8q13- qter.	-	[16]
13 years	-	myopathy	-	A large deletion at Xq28	*de novo*	[17]
36 years (the mom)	menopause occurred at age 39 years	mild edema of the dorsum of both hands and feet and	normal	46,X,del(X)(pter-- q26::qter)	-	[18]
9 years (the daughter)	Menarche occurred at age 11 years	hypoplastic, hyperconvex finger nails and toenails	normal	46,X,del(X)(pter-- q26::qter)	*inherited*	
47 years old	-	-	Normal	deletion at Xq28	*inherited*	[19]
11 years (daughter)		overweight	Normal			

Observations were made in the patients about features such as developmental delay and primary/secondary amenorrhoea. Still, these two last traits are variable due to age, so it is difficult to make firm conclusions about this. For some patients, the deletion did not appear severe due to the young age and the region's size deleted.

Individuals with terminal deletions at Xq28 show perturbations of ovarian function. Several studies have been proposed to explain the deletion that occurred on Xq. It has been suggested that there is a critical region for premature ovarian failure between Xq26.2 and Xq28 [4].

The long arm of the X chromosome (Xq) appears prone to structural rearrangements and is capable of translocating with other chromosomes. Petkovic et al. (2003) reported a case of a girl with a derivative X chromosome resulting from a translocation between chromosomes X and 6. Due to the age of this patient, the phenotypic features present in Xq deletions could not be fully evaluated, similar to our case [20].

The most common finding in girls with Xqter deletions has been premature ovarian failure (POF) and secondary amenorrhea [18]. It is related to deletion and other factors. X chromosome inactivation could be one of them. It is not well known when it takes place; slight differences in the time of skewing of X inactivation in germ cells or granulosa cells may alter the number of ovarian follicles and determine the age of onset of premature ovarian failure [21].

Our analysis of the clinical features of this case in comparison with existing literature demonstrates significant similarities with the phenotype observed in partial trisomy 6q. The 6q duplication observed in this patient is likely responsible for the abnormal clinical manifestations. This case study documents a rare chromosomal configuration and explores the complexities of genotype-phenotype correlation in the context of large-scale genomic alterations. Our findings provide a foundation for future research into similar chromosomal abnormalities and their clinical manifestations.

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Author Contributions

LA, ZE: Investigation, Writing–original draft, Methodology. ASb: Writing–review, editing and Validation. YE: Writing–original draft and editing. IR, ICJ performed the clinical evaluation. TL, ASe: Formal Analysis, Writing–review. AN: Validation, Writing–review and editing.

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Competing Interests

The authors have no conflicts of interest to declare.

Data Availability Statement

All data generated or analyzed during this study are included in this article [and/or] its supplementary material files.

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