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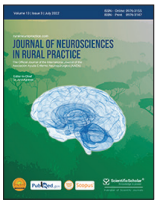

Review Article

Chromosome Xp22.3 deletion syndrome with X-linked ichthyosis, Kallmann syndrome, short stature, generalized epilepsy, hearing loss, attention deficit hyperactivity disorder, and intellectual disability – A rare report with review of literature

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ABSTRACT

Chromosome Xp22.3 deletion syndrome is a very rare contiguous gene deletion syndrome with variable phenotype due to the deletion of genes from the distal short arm of the X chromosome (Xp), including the short-stature homeobox (*SHOX*), anosmin-1 (*ANOS1),* arylsulfatase *(ARSL),* neuroligin-4 (*NLGN4),* and steroid sulfatase (*STS)* genes. We have reviewed the available literature on the chromosome Xp22.3 deletion syndrome. A 10-year-old boy presented with global developmental delay, generalized epilepsy, decreased hearing, and hyperactivity. He had no significant family history. Examination revealed microcephaly, short stature, and dry and scaly skin lesions on the trunk. He had thick arched eyebrows, a depressed nasal bridge, a long philtrum, high arched palate, retrognathia, brachytelephalangy, brachymetatarsia, and mild scoliosis. Brainstem-evoked response audiometry testing revealed moderate hearing loss. Magnetic resonance imaging showed cerebellar tonsillar ectopia. Clinical exome sequencing revealed a likely pathogenic contiguous deletion (~8.10 Mb) spanning genomic location chrX:g.(_630898)_(8732037_)del encompassing *ANOS1, ARSL, NLGN4X, SHOX,* and *STS* genes. We have reviewed the available literature for reported associations of Chromosome Xp22.3 deletion syndrome and report a novel association of X-linked ichthyosis, Kallmann syndrome, global developmental delay, short stature, bilateral hearing loss, generalized epilepsy, attention deficit hyperactivity disorder, and intellectual disability.

Keywords: Chromosome Xp22.3 deletion syndrome, X-linked ichthyosis, Kallmann syndrome, Short stature, Generalized epilepsy

INTRODUCTION

Chromosome Xp22.3 deletion syndrome is a very rare contiguous gene deletion syndrome with variable phenotype, depending on the large terminal or interstitial codeletions of adjacent genes that are physically clustered. This contiguous gene syndrome is due to the deletion of genes from the distal short arm of the X chromosome (Xp), including the *short-stature homeobox* (*SHOX), anosmin-1* (*ANOS1),* arylsulfatase *(ARSL),* neuroligin-4 (*NLGN4),* and steroid sulfatase (*STS)* genes.[1] This syndrome is characterized by X-linked ichthyosis (XLI), Kallmann syndrome (KS), short stature, generalized epilepsy, neurodevelopmental disorders including autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), and intellectual disability (ID), sensorineural hearing loss, strabismus, and bony deformities including chondrodysplasia punctata (CDP), obesity, and ocular albinism.[1-3] The other dysmorphism features reported are frontal bossing, hypertelorism, depressed nasal bridge, high-arched palate, retrognathia, and flat occiput.[4,5] Based on the deletion lengths, the clinical phenotypes occur independently from each other or in various combinations as a contiguous gene syndrome.[6] Only about 34 cases have been reported in the literature. Here, we report a case of Xp22.3 deletion syndrome (8.1 Mb contiguous deletion), including *ANOS1, ARSL, NLGN4X, SHOX,* and *STS* genes, along with a review of available literature [Table 1].

CASE PRESENTATION

A 10-year-old boy presented with global developmental delay, decreased hearing since birth, and hyperactivity. He also had a history of generalized tonic-clonic seizures since five years of age, with 1–2 episodes/year. He was first

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born to third-degree consanguineously married parents. The antenatal and perinatal periods were unremarkable. There was no significant family history. On examination, he had a height of 116 cm (−3.5Z, stunting), a weight of 25.2 Kg (−1.3Z), body mass index of 18.7 kg/m^2, and a head circumference of 53 cm. The upper-to-lower segment ratio (US: LS) was 0.93. The mid-parental height was 159 cm. He had coarse facies with thick arched eyebrows, long philtrum, retrognathia, depressed nasal bridge, high arched palate, brachytelephalangy, brachymetatarsia, and mild scoliosis [Figure 1a-c]. He had dry, scaly skin lesions over the axilla, lateral side of the chest, and abdomen, suggestive of ichthyosis [Figure 1d-f]. On genitalia examination, he had a stretched penile length of 3.5 cm and a testicular volume of <2cc (Tanner staging – G1, no axillary and pubic hair). The rest of the systemic examination was normal, with no organomegaly. Fundus examination was normal. Based on the clinical presentation, the possibilities of multiple sulfatase deficiency and Sjogren–Larsson syndrome were considered.

He had a normal hemogram, renal, liver, and thyroid function tests, and a normal bone metabolic profile. He had normal cortisol levels (9.92 [3.09–16.66] µg/dL), low levels of testosterone (7.0 [241–827] ng/dL), luteinizing hormone (0.21 [2.8–6.8] mIU/mL), prolactin (50.4 [87–392] mIU/L), and insulin growth factor 1 (9.05 [131–490] ng/mL). The testing for smell with common odors revealed anosmia in the index child. The urinary testing for mucopolysaccharides was negative. Ultrasonogram study of the abdomen and pelvis was normal. The 2D echocardiography study was normal. The skeletal survey revealed abnormal development of distal phalanges of bilateral 1st – 4th fingers, coxa valga, and mild concavity with enlarged intervertebral discs in the lower thoracic and lumbar regions. Magnetic resonance imaging showed a normal pituitary gland, crowded posterior fossa with effacement of the fourth ventricle, and cerebellar tonsillar ectopia. Brain-evoked auditory response testing revealed bilateral moderate (60 dB) hearing loss. Clinical exome sequencing revealed a contiguous deletion of size (~8.10 Mb), spanning genomic location chrX:g.(_630898)_(8732037_)del encompassing multiple genes including *ANOS1, ARSL, NLGN4X, SHOX, STS* was detected, suggestive of chromosome Xp22.3 deletion syndrome. The child is currently on a multidisciplinary follow-up.

LITERATURE SEARCH

A literature review was performed from the year 2023 to the oldest available report in English on Chromosome Xp22.3 deletion syndrome from the PubMed/MEDLINE, Google Scholar, and SCOPUS databases. All articles describing Chromosome Xp22.3 deletion syndrome were identified, and duplicates were removed. A total of 34 cases (excluding the index child) have been described in the literature and are summarized in Table 2.

DISCUSSION

The genetic analysis of the index child revealed a contiguous deletion of size (~8.10 Mb) in terminal Xp22.3 region encompassing multiple genes, including *ANOS1 (KAL1), ARSL, NLGN4X, SHOX,* and *STS*, suggestive of chromosome Xp22.3 deletion syndrome [Figure 2]. This deletion was classified as a "likely pathogenic" copy number variation based on the American College of Medical Genetics guidelines.[7] The index child's distinctive features were ichthyosis, global developmental delay, short stature, bilateral hearing loss, and hyperactivity. In the index child, along with signs of hypogonadism and anosmia, KS was diagnosed.

The deletions of the Xp22.31 – p22.33 region result in contiguous gene syndromes with various phenotypical combinations of XLI, KS, short stature, CDP, developmental delay, ASD, ID, strabismus, obesity, ocular albinism, and bilateral hearing loss [Table 1].[1,8-10] The XLI (MIM#308100) is characterized by dry, dark-colored scales over the trunk and limbs, which is due to deletions of *STS* gene.[11] The absence of *STS* causes the accumulation of cholesterol sulfate in the stratum corneum, resulting in impaired skin permeability and hyperkeratosis.[12] The *ANOS1* gene is located near the *STS* gene near the Xp22.3 locus, and the deletion of the *ANOS1* gene causes X-linked KS. The *ANOS1* gene encodes the anosmin-1 protein, which is present in the cerebral cortex and olfactory system. Ansomin-1 also mediates the adhesion and the axonal migration of gonadotrophin-releasing hormone (GnRH) neurons.[10] KS (MIM#308700) is due to deficiency of GnRH and hypoplasia of olfactory bulbs and is characterized by hypogonadotropic hypogonadism, anosmia/hyposmia, and other features may include cleft lip/palate, hearing loss, and unilateral renal agenesis.[10]

SHOX on the Xp gene is a homeobox gene involved in skeletal development and maturation. *SHOX*-related disorders have a highly variable phenotypic spectrum ranging from short stature to Leri-Weill dyschondrosteosis, which consists of a triad of mesomelia, short stature, and Madelung deformity (MD) (MIM#300582).[13] *ARSL* gene encodes *ARSL*, a member of the sulfatase family that is essential for the composition of bone and cartilage matrix.[14] The deletion of these genes results in short stature and X-linked chondrodysplasia punctata-1 (CDPX1). CDPX1 (MIM#302950) is characterized by brachytelephalangy – short distal phalanges, CDP – stippled epiphyses, nasomaxillary hypoplasia, short stature, hearing loss, vertebral abnormalities including dysplastic and hypoplastic vertebrae, developmental delay, ID, and cataracts.[14]

NLGN4X gene encodes the cell surface proteins of neurons. They are involved in forming and remodeling the synapses

Table 1: Genes of interest in Xp22.3 region and its phenotypes.

S. No	Location	Genes		MIM	Phenotype	Phenotype MIM
1.	Xp22.31	*ANOS1*	Anosmin-1	300836	Kallmann syndrome	308700
2.	Xp22.31	*STS*	Steroid sulfatase	300747	Ichthyosis	308100
3.	Xp22.32	*NLGN4X*	Neuroligin-4	300427	ASD, ID	300495
4.	Xp22.33	*ARSL*	Arylsulfatase-L	300180	Chondrodysplasia punctata, Short stature	302950
5.	Xp22.33	*SHOX*	Short stature homeobox	312865	Short stature LWD, MD	300582

ASD: Autism spectrum disorder; ID: Intellectual disability; LWD: Leri-Weill dyschondrosteosis; MD: Madelung deformity; MIM: Online Mendelian inheritance in man.

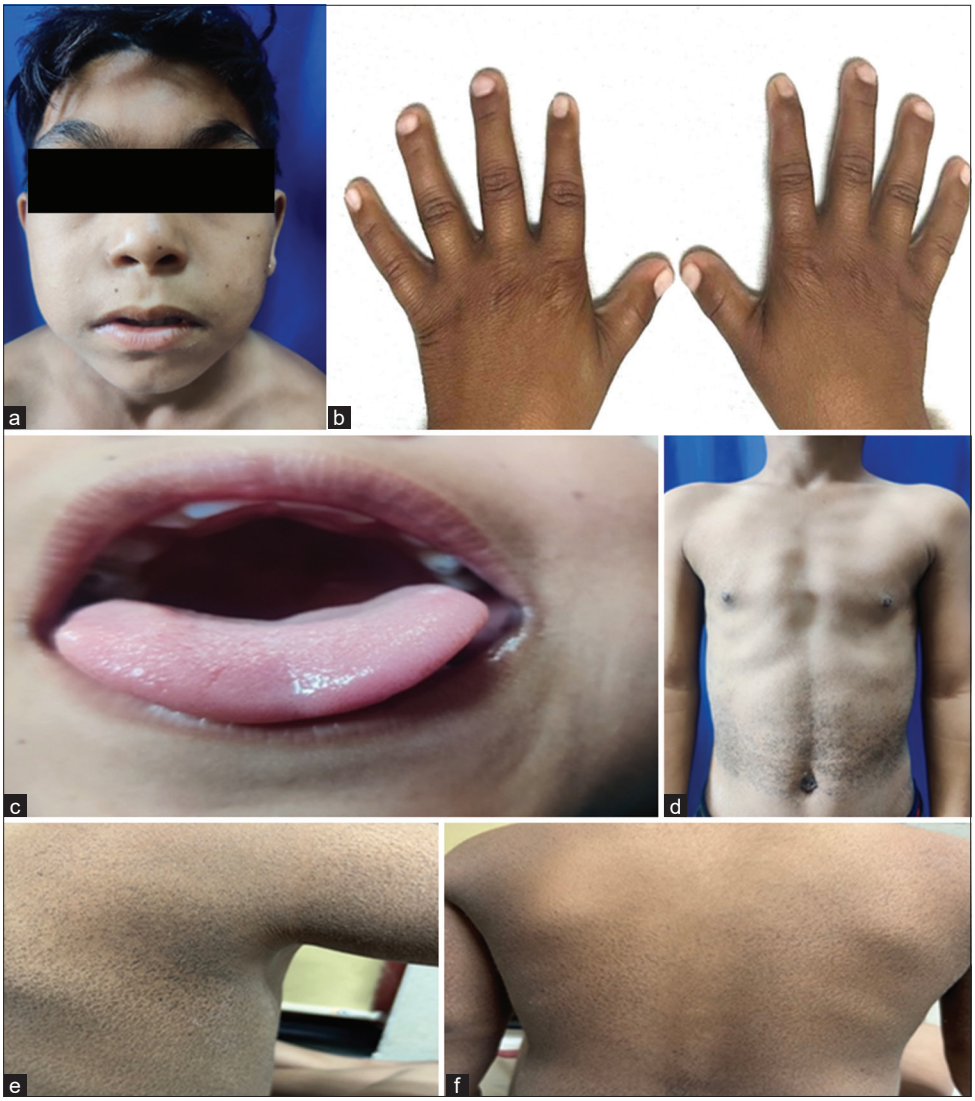

Figure 1: Clinical features in the Index Child. (a-f) shows dysmorphic features and Ichthyosis. (d) shows pectus excavatum. (a) Facial dysmorphism, (b) brachytelephalangy, (c) high-arched palate, (d) ichthyosis over the abdomen, (e) ichthyosis over the axilla, (f) ichthyosis over the back.

in the central nervous system. The deletion of *NLGN4X* causes X-linked ASD (MIM#300495) and X-linked ID (MIM#300495).[15-19] The deletion of other genes, including variably charged protein X-A (*VCX*-A), can also result in

Table 2: Summary of Xp22.3 deletions and phenotype associations reported in literature.

S. No	Author/year	Deletions	Age	Sex	Ich	SS	KS	CDP	MD	LWD	Epilepsy	ASD	ADHD	ID	OA	HL
1.	Ballabio *et al.* 1988[20]	Xp22.3	6y	M	+	+	−	+	−	−	+	−	−	+	−	−
2.			6y	M	+	−	−	−	−	−	−	−	−	+	−	−
3.	Bick *et al.* 1989[21]	Xp22.31	2.5m	M	+	−	+	+	−	−	−	−	−	−	−	−
4.	Meindl *et al.* 1993[22]	Xp22.3 9.9 Mb	9y	M	+	+	+	+	−	−	−	−	−	+	+	−
5.	Schwinger *et al.* 1996[23]	Xp22.32	10y	F	−	+	−	−	−	−	−	−	−	−	−	−
6.	Spranger *et al.* 1999[18]	Xp22.3	5y	M	−	+	−	−	+	+	+	−	+	−	−	+
7.	Gohlke *et al.* 2000[24]	Xp22.3	8y	M*	+	−	+	−	−	−	+	−	−	+	−	−
8.			8y	M*	+	−	+	−	−	−	+	−	−	+	−	−
9.	Doherty *et al.* 2003[1]	Xp22.3	24y	M	+	+	−	−	−	+	+	−	−	+	−	−
10.			22y	M	+	+	−	−	−	+	+	−	+	−	−	−
11.	Boycott *et al.* 2003[19]	Xp22.3 6 Mb	24y	M	−	−	−	−	−	−	+	−	+	+	−	−
12.			23y	M	−	+	−	−	+	−	−	−	+	−	−	−
13.	Lonardo *et al.* 2007[9]	Xp22.3 5.5 Mb	13y	M	+	+	−	+	−	−	−	−	+	+	−	+
14.	Macarov *et al.* 2007[15]	Xp22.3	2y	M	+	−	+	−	−	−	−	−	−	−	−	−
15.			22y	M	+	−	+	−	−	−	−	−	−	−	−	−
16.			48y	M	+	−	+	−	−	−	−	−	−	+	−	−
17.	Melichar *et al.* 2007[25]	Xp22.31 9.6 Mb	1m	M	+	−	An	+	−	−	−	−	−	−	+	+
18.	Puusepp *et al.* 2008[26]	Xp22.3	16y	F	−	+	−	−	+	−	+	+	+	+	−	−
19.	Mochel *et al.* 2008[17]	Xp22.3 3.7 Mb	17y	M	+	+	+	−	−	−	−	−	−	−	−	−
20.	Van Steensel *et al.* 2008[4]	Xp22.3 8.4 Mb	21y	M	+	+	−	−	−	−	+	−	−	+	−	−
21.	Bukvic *et al.* 2010[8]	Xp23.33 7.7 Mb	3y3m	M	+	−	−	−	+	−	−	−	+	−	−	−
22.			1y8m	F	−	−	−	−	−	−	−	−	−	−	−	−
23.	Palka-Bayard-de-Volo *et al.* 2012[27]	Xp22.3 6.8 Mb	11y	F	−	+	−	−	−	−	−	−	−	+	−	−
24.	Khelifa *et al.* 2013[5]	Xp22.3 2 Mb	14y	M	+	−	−	−	−	−	+	−	−	+	−	−
25.	Xu *et al.* 2015[28]	Xp22.3 1.6 Mb	–	M	+	−	+	−	−	−	−	−	−	−	−	−
26.			–	M	+	−	+	−	−	−	−	−	−	−	−	−
27.	Vrečar *et al.* 2015[29]	Xp22.33 3 Kb	9y	M	−	−	−	+	−	−	−	−	−	−	−	+
28.	Berges-Raso *et al.* 2017[30]	Xp22.3 4.7 Mb	39y	M	+	−	+	−	−	−	−	−	−	−	−	−
29.	Amasdl *et al.* 2017[2]	Xp22.33 3.1Mb	6y	M	−	+	−	−	−	−	−	−	−	−	−	+
30.			22y	M	−	+	−	−	−	−	−	−	−	−	−	+
31.	Nagai *et al.* 2017[16]	Xp22.31 2.7 Mb	6m	M	+	−	+	−	−	−	−	−	−	−	−	−
32.	Sait *et al.* 2020[3]	Xp22.33 8.3 Mb	20y	M	+	+	+	−	−	−	−	−	−	+	−	−
33.	Ma *et al.* 2020[10]	Xp22.31 3.9 Mb	14y	M	+	−	+	−	−	−	−	−	−	−	−	−
34.		Xp22.3 5.8 Mb	19y	M	+	−	+	−	−	−	−	−	−	−	−	−
35.	Index Study 2023	Xp22.32 8.1 Mb	10y	M	+	+	+	−	−	−	+	−	+	+	−	+

An: Anticipated, F: Female, M: Male, m: months, y: years, *Monozygotic twins. ASD: Autism spectrum disorder, ADHD: Attention deficit hyperactivity disorder, CDP: Chondrodysplasia punctata, HL: Hearing loss, Ich: Ichthyosis, ID: Intellectual disability, KS: Kallmann syndrome, LWD: Leri-Weill dyschondrosteosis, MD: Madelung deformity, OA: Ocular albinism, SS: Short stature

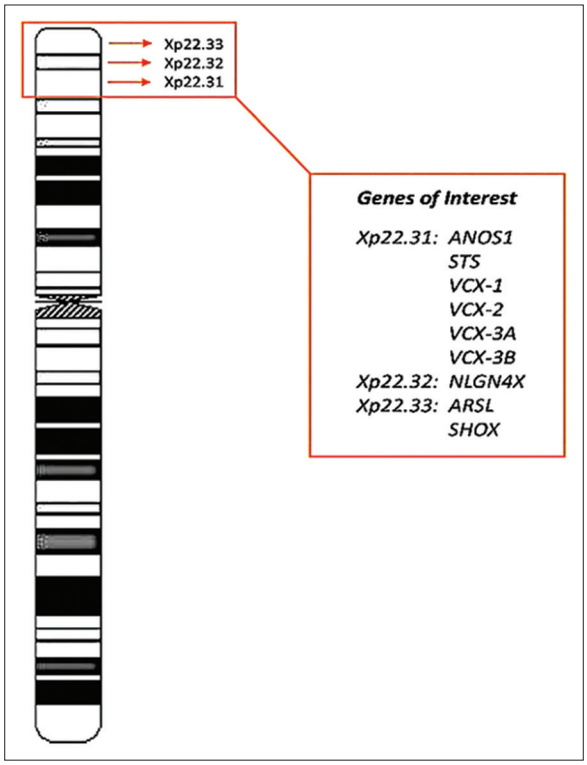

Figure 2: Chromosome Xp22.3 region with associated significant Genes. G-banding Ideogram of X chromosome (800 bphs resolution) showing Xp22.3 region with the Genes of Interest.

X-linked ID. The deletions of *NLGN4X* and *VCX*-A can cause variable phenotypes, including normal intellect.[5,15-17] Recently, in these associated contiguous gene syndromes involving Xp22.3, ADHD has been reported.[1,9,18,19]

In Xp22.3 microdeletions, cortical heterotopias, hypoplasia of corpus callosum, mild enlargement of sella turcica, olfactory bulb dysplasia (KS patients), and Dandy–Walker malformation have been reported.[4,8,10] Similarly, cerebellar tonsillar ectopia was noted in the index child, which has not been reported in the literature. The available literature on contiguous Xp22.3 deletion was reviewed and summarized in Table 2.

Limitations

The literature search included articles published only in the English language.

CONCLUSION

Contiguous gene syndromes exhibit complex disease phenotypes stemming from the microdeletion of multiple adjacent contiguous genes. These phenotypical associations serve as valuable indicators for the diagnosis, underscoring the critical role of recognizing them in establishing diagnoses and multimodal management planning for these patients.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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