

REVIEW PAPER

# Skeletal and dental abnormalities in patients with sex chromosome aberrations: a systematic case-based review

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## ABSTRACT

Sex chromosome aneuploidies (SCAs) are common chromosomal disorders characterised by an atypical number of sex chromosomes. Turner syndrome (TS), Klinefelter syndrome (KS), and Jacobs syndrome (JS) are associated with a wide spectrum of skeletal manifestations, including craniofacial and limb anomalies. This systematic review aimed to analyse the incidence of skeletal abnormalities in selected SCAs based on case reports. In this review, 55 articles were included from the MEDLINE/PubMed and Google Scholar databases, according to PRISMA guidelines. High-arched palate, skeletal class II, and cubitus valgus were most frequently demonstrated among TS patients. Patients with KS and JS most often presented micrognathia, hypertelorism, and flat nasal bridge in the craniofacial region. In contrast, radioulnar synostosis, clinodactyly, and pes planus could be observed in the limbs of KS patients. The presence of dysmorphic facial features and limb malformations may indicate SCAs, which are underdiagnosed in the general population due to a variety of phenotypes.

## KEY WORDS:

sex chromosome aneuploidy, Turner syndrome, Klinefelter syndrome, XYY syndrome.

## INTRODUCTION

Most chromosome aberrations are associated with numerous abnormalities in somatic and mental development. Aneuploidy, defined as the occurrence of one or more extra or missing chromosomes in the typical diploid set, occurs in at least 5% of all pregnancies [1, 2]. Sex chromosome aneuploidies (SCAs) are the most common chromosomal anomalies, with a total frequency of 1 in 400 [3]. SCAs include conditions in which there is an abnormal number of sex chromosomes [4], such as Turner syndrome (45,X), Klinefelter syndrome (47,XXY), or

Jacobs syndrome (47,XYY). These syndromes are a frequent cause of miscarriage in the first trimester of pregnancy.

Turner syndrome (TS) is a congenital genetic disease occurring in the female sex, with a prevalence of approximately 1 in 2500 newborn girls [5]. The characteristic clinical picture is associated with quantitative and/or structural aberrations of the X chromosome. The features of TS were first described in 1938 by Henry H. Turner, an Oklahoma physician, who published a description of 7 women with short stature, sexual infantilism, congenital webbed neck, cubitus valgus, and low hairline at the back of the neck [6]. However, earlier descriptions

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of this disease are known, e.g. by the Russian physician M.A. Shereshevky (1925) or the German paediatrician O. Ullrich (1930) [7, 8].

Another SCA, Klinefelter syndrome (KS), represents the most common form of sex chromosomal aneuploidy and affects approximately 1 in 650 newborn males [9, 10]. In 1942, H.F. Klinefelter *et al.* described 9 patients with a syndrome characterised by tall stature, gynecomastia, small firm testes, azoospermia, hyalinisation of the seminiferous tubules, elevated excretion of follicle-stimulating hormone (FSH), and hypogonadism [11]. In 1959 P.A. Jacobs and J.A. Strong demonstrated the presence of an extra X chromosome in the karyotype of KS patients [12]. About 90% of KS patients have the karyotype 47,XXY and 7% have mosaicism 46,XY/47,XXY. In contrast, karyotypes with a higher number of X chromosomes are very rare and represent 3% [10].

Lastly, Jacobs syndrome (JS), or XYY syndrome, is an aneuploidy resulting from an additional copy of the Y chromosome to the normal XY pair in men [13]. The presence of an extra Y chromosome was first described by Sandberg *et al.* in 1961 [14] and Jacobs *et al.* in 1965 [15]. Aberration occurs in approximately 1 out of 1000 live male births. About 85% of cases with XYY are never diagnosed due to variability of mild phenotypes [16]. Diagnosis is often late, with a median age at diagnosis of 17 years [17].

Moreover, skeletal disorders are quite common in sex chromosome aberrations. This article was written in memory of Prof. Jerzy Kosowicz. He was one of the world's first investigators to describe characteristic changes in the skeletal system occurring in many endocrinopathies (e.g. Turner syndrome, Klinefelter syndrome, hyperparathyroidism) [18-20]. The bone lesions that he discussed were repeatedly mentioned in Polish and foreign publications in the field of endocrinology, radiology, and orthopaedics. Accurate knowledge of X-ray changes has helped to clarify and improve the diagnostics in endocrine disorders and has enabled early diagnosis and treatment of these diseases.

Our systematic review aimed to assess whether the presence of specific bone symptoms in the craniofacial

and limb regions indicates selected sex chromosome aberrations such as Turner syndrome, Klinefelter syndrome, and Jacobs syndrome.

## MATERIAL AND METHODS

### SEARCH STRATEGY AND DATA EXTRACTION

This systematic review was conducted up to 15<sup>th</sup> August 2021, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines [21], using the MEDLINE/PubMed database. The search formulas combined in PubMed Advanced Search Builder included (Turner syndrome) AND ((skeletal\*) OR (synostosis) OR (craniofacial\*) OR (dental\*) OR (growth\*)), (Klinefelter syndrome) AND ((skeletal\*) OR (synostosis) OR (craniofacial\*) OR (dental\*) OR (growth\*)), and (XYY syndrome) AND ((skeletal\*) OR (synostosis) OR (craniofacial\*) OR (dental\*) OR (growth\*)). The results were filtered by article type (case reports), publication date (since 2000), and language (English). Additionally, relevant articles from Google Scholar were added.

Records were screened by the title, abstract, and full text by 2 independent investigators. Studies included in this review matched all the predefined criteria according to PICOS (“Population”, “Intervention”, “Comparison”, “Outcomes”, “Study design”) – Table 1. A detailed search flowchart is presented in Figure 1.

## RESULTS

In this systematic review, 55 papers following the search criteria were included. Figure 1 shows the detailed selection strategy of the articles. The inclusion and exclusion criteria are presented in Table 1.

Case reports were described in 26 different countries, considering a total of 79 patients. Table 2 presents basic data by type of SCA.

Among the included cases, 34 patients with Turner syndrome, 34 with Klinefelter syndrome, and 11 with Jacobs syndrome were described. The TS group was domi-

TABLE 1. Inclusion and exclusion criteria according to the PICOS

Parameter	Inclusion criteria	Exclusion criteria
Population	Patients with sex chromosomal abnormalities such as Turner syndrome, Klinefelter syndrome, and Jacobs syndrome – aged from 0 to 99 years	Patients with other coexisting genetic anomalies Patients without determined karyotype
Intervention	Not applicable	
Comparison	Not applicable	
Outcomes	Clinical and/or radiological description of skeletal abnormalities (craniofacial and limb)	Only bone density disorders
Study design	Case reports	Literature reviews, expert opinion, conference reports, case-control, cohort, and cross-sectional studies
	Published from January 2000 to August 2021	Not published in English

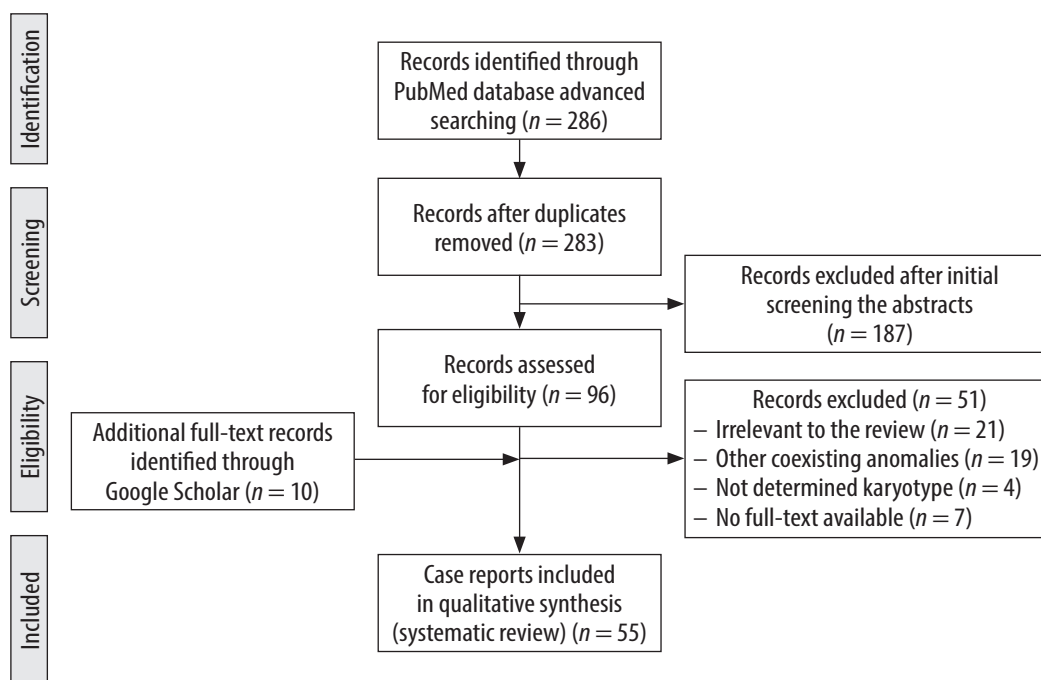


FIGURE 1. PRISMA flow diagram presenting the detailed search strategy

nated by patients with mosaicism, whereas the KS group was mainly patients with karyotype 49,XXXXY and the JS group with karyotype 47,XYY. Most of the articles described teenage patients. The majority of patients came from Asia, followed by Europe, as well as Americas and Africa. More than half of the patients had detailed reported radiographic findings in the craniofacial region and extremities.

Table 3 presents the numbers of selected bone symptoms in the craniofacial and limb regions found in patients from the included studies. In TS patients, irrespec-

tively of the karyotype, gothic palate and skeletal class II (manifested as mandibular retrognathia) with occasional crossbite predominated in the craniofacial region, as well as cubitus valgus in limb deformities. Because the most abundant karyotypes in selected KS patients were 47,XXY and 49,XXXXY, dysmorphic features such as hypertelorism, flat nasal bridge, and retracted midface associated with the presence of skeletal class III were most commonly observed. Limb abnormalities were most commonly presented by patients with karyotype 49,XXXXY and expressed as clinodactyly, radioulnar synostosis, and

TABLE 2. Basic data about included subjects by type of sex chromosome aneuploidies

	n	Age (median)	Origin, %				Radiological examination, %
			Europe	Asia	Americas	Africa	
Turner syndrome	34	10	29.4	53.0	17.6	—	64.7
Monosomy 45,X	10	10	40.0	40.0	20.0	—	80.0
Mosaicism	16	9.5	25.0	68.8	6.2	—	62.5
Structural X chromosome abnormality	8	11.5	25.0	37.5	37.5	—	50.0
Klinefelter syndrome	34	9	38.2	44.1	3.0	14.7	38.2
47,XXY	8	6.5	25.0	12.5	—	62.5	25.0
48,XXX	3	14	33.3	33.3	33.3	—	100.0
48,XXYY	2	29	—	100.0	—	—	50.0
49,XXXXY	20	11	50.0	50.0	—	—	30.0
Mosaicism (47,XXY/46,XX)	1	12	—	100.0	—	—	100.0
Jacobs syndrome	11	12	18.2	63.6	9.1	9.1	54.5
47,XYY	9	11	22.2	66.7	11.1	—	44.4
Mosaicism	2	13.5	—	50.0	—	50.0	100.0

— not reported

TABLE 3. Selected skeletal abnormalities in sex chromosome aneuploidies by karyotype based on included case reports

	Turner syndrome				Klinefelter syndrome						Jacobs syndrome									
	Monosomy 45,X		Mosaicism		Structural X chromosome abnormality		47,XXY	48,XXX	48,XXYY	49,XXXXY		Mosaicism (47,XXY/46,XX)		47,XXY	Mosaicism					
	n	Ref.	n	Ref.	n	Ref.	n	Ref.	n	Ref.	n	Ref.	n	Ref.	n	Ref.				
Craniofacial features	9	[22-28]	9	[24, 29-32]	8	[24, 33-37]	8	[38-41]	2	[42, 43]	1	[44]	19	[45-56]	7	[13, 57-62]	2	[63, 64]		
Microcephaly	-		-		-		-		-		-		9	[45, 49-51, 55]	2	[58, 60]	1	[63]		
Flat nasal bridge	-		-		1	[35]	1	[38]	-		-		13	[46-50, 56]	2	[57, 60]	1	[63]		
Hypertelorism	-		1	[30]	-		7	[38, 39, 41]	-		-		12	[45, 48-51]	3	[57, 59, 60]	1	[63]		
High-arched palate	6	[23, 24, 26, 27]	9	[24, 29-32]	6	[24, 33, 34, 36]	1	[38]	-		-		-		-		2	[63, 64]		
Cleft palate	-		-		-		-		-		-		3	[45, 47, 54]	1	[59]	-			
Micrognathia/ mandibular prognathism (skeletal class III)	1	[22]	1	[30]	1	[36]	6	[40, 41]	1	[42]	1	[44]	15	[45-49, 51-54]	3	[57, 61, 62]	-			
Microgenia/ mandibular retrognathia (skeletal class II)	7	[23-26, 28]	4	[24]	3	[24, 35, 37]	-		1	[43]	-		-		-		-			
Crossbite	4	[23-26]	2	[24]	-		-		1	[43]	-		1	[54]	-		-			
Taurodontism	-		-		-		1	[38]	1	[42]	1	[44]	3	[49, 54]	1	[13]	-			
Others	7	[23-26, 28]	6	[24, 32]	1	[35]	1	[40]	2	[42, 43]	-		8	[49, 53, 56]	3	[13, 57, 61]	-			
Limb deformities	1	[22]	7	[30, 32, 33, 65-67]	3	[33, 35, 37]	5	[41]	1	[55]	1	[68]	19	[45-53, 55, 56, 69]	1	[70]	3	[58, 62, 71]	2	[63, 64]
Radioulnar synostosis	-		-		-		-		-		-		9	[46, 49, 53]	1	[70]	1	[58]	1	[63]
Cubitus valgus	1	[22]	3	[30, 65, 66]	3	[33, 35, 37]	-		-		-		1	[53]	-		1	[64]	-	
Brachydactyly	-		2	[30]	-		-		-		-		-		-		-		-	
Clinodactyly	-		-		-		5	[41]	-		1	[68]	14	[45, 49, 51-53, 55, 56]	-		-		-	
Short metacarpals	-		1	[30]	-		-		-		-		-		-		-		1	[64]
Pes planus	-		-		-		-		1	[55]	-		6	[45, 49]	-		-		-	
Genu valgum	-		-		-		-		1	[55]	-		4	[48-50]	-		1	[71]	-	
Others	-		4	[32, 33, 65, 67]	2	[33, 35]	-		1	[55]	-		8	[49, 50, 55, 69]	-		2	[62, 71]	-	

- not reported

**TABLE 4.** Additional skeletal abnormalities in sex chromosome aneuploidies by karyotype based on included case reports

	Craniofacial features	Limb deformities
<b>Turner syndrome</b>		
Monosomy 45,X	Diastemas [23, 25], tremas [23], periodontal disease [23], maxillary or mandibular midline deviation [23, 25, 26], bimaxillary protrusion [23], open bite [23, 25], V-shaped maxillary dental arch [24], deep bite [28], facial asymmetry [25]	—
Mosaicism	V-shaped maxillary dental arch [24], plagiocephaly [32], diastemas [31], aggressive periodontitis [31]	Short upper limbs [33], short fingers [67], medial displacement of bilateral first toes [32], bilateral clubfoot [65]
Structural X chromosome abnormality	V-shaped maxillary dental arch [35], open bite [35], supernumerary teeth [35], enamel hypoplasia [35]	Short upper limbs [33], atrophy of right upper limb [35]
<b>Klinefelter syndrome</b>		
47,XXY	Impacted teeth [40], open bite [40], enamel defects [40]	—
48,XXXY	Large palatal torus [42], bimaxillary protrusion [43], open bite [43]	Hip dysplasia [55]
48,XXYY	—	—
49,XXXXY	Narrow forehead [53], brachycephaly [56], dental anomalies (such as delayed eruption, ectopic teeth, hypodontia, enamel defects) [49]	Tibiofibular synostosis [50], unilateral preaxial hexadactyly [49], hip dysplasia [49, 55], bilateral clubfoot [69], pes valgus [49]
Mosaicism (47,XXY/46,XX)	—	—
<b>Jacobs syndrome</b>		
47,XYY	Delayed eruption of permanent teeth [57, 61], bimaxillary protrusion [61], enlarged head circumference [61], facial asymmetry [61], macrodontia [13], agenesis of permanent maxillary lateral incisors [13]	Short hands [62], radial head dislocation [71], cubitus varus [71], hindfoot varus [71], pes cavus [71]
Mosaicism	—	—

— not reported

pes planus. JS patients rarely demonstrated specific skeletal changes. Among the observed features, the presence of hypertelorism, micrognathia, or radioulnar synostosis could be found.

Moreover, Table 4 shows examples of additional skeletal symptoms in the included cases. Most of the abnormalities were identified in the craniofacial bones, associated with significant malocclusion among the described patients. The other malformations involved both limbs with a slight predominance of the lower extremity.

## DISCUSSION

Although patients with SCAs demonstrate a variety of phenotypes, including bone and dental lesions, the proper diagnosis seems to be limited. Endocrine societies rarely recommend routine skeletal and craniofacial radiological examination for the diagnosis and management of these patients [72, 73]. Dual-energy X-ray absorptiometry (DXA) is the only radiological method recommended for bone mineral density (BMD) assessment. Most of the signs of skeletal changes are recognised on clinical

examination, and other tests serve only to supplement or confirm a previously made diagnosis. Additionally, some skeletal abnormalities do not need a detailed radiological evaluation because of the marginal impact on patients' quality of life. In contrast, dental manifestations may require expanded radiographic diagnosis, especially in patients presenting with malocclusion. In order to accurately assess the skeletal or dental nature of the bite disorder in orthodontic patients, a cephalometric radiograph is necessary [74]. It is also crucial to remember the screening role of panoramic radiographs that allow detection of such dental anomalies as taurodontism. However, especially in paediatric patients, radiation exposure safety must be considered [75].

## TURNER SYNDROME

The basis for the diagnosis of the TS is the result of the cytogenetic test. The gold standard for diagnosis is postnatal karyotyping [76]. The literature shows divergent information on the prevalence of karyotypes in TS, which can be explained by technological progress and increasingly

sensitive diagnostic methods [77]. As it currently stands, classical karyotype and mosaicism among TS patients account for 40-50% and 28-40%, respectively [72]. Furthermore, 99% of 45,X foetuses abort spontaneously [78]. The remaining group consists of TS patients with revealed structural X-chromosome aberrations.

A growing number of patients are diagnosed with TS during prenatal examination – mainly based on ultrasonography results. It is also possible to perform a prenatal karyotype analysis using chorionic villus sampling (CVS) or amniocentesis (AC) [76]. Moreover, molecular methods, such as Southern blotting, polymerase chain reaction (PCR), fluorescent PCR genotyping, or restriction fragment length polymorphism (RFLP), are used to detect TS in neonates [5].

Turner's syndrome demonstrates characteristic developmental defects or dysmorphic features that occur with different frequencies. In a newborn, TS may be suspected in the presence of so-called "stigmata": congenital lymphoedema of the hands and feet, extra folds of skin on the neck, high-arched palate or cleft palate, small mandible, nail dysplasia, low posterior hairline, broad chest with widely-spaced and hypoplastic nipples, and congenital hip dislocation [79]. A decelerated increase in body length is already observed in foetal life [76]. At birth, a lower weight (by approx. 500 g) and a shorter body length (by approx. 3 cm) are noticed [8]. However, this syndrome may be recognised later, e.g. during the diagnosis of short stature or primary amenorrhoea [80]. Slower growth rate in childhood, lack of pubertal growth spurt, and delayed growth end (approx. 20-21 years old) are observed [8]. Furthermore, osteoporosis is found in most patients with TS, especially in patients not treated with growth hormone and cyclic oestrogen/progesterone [81, 82].

It is believed that the deficit in height and skeletal deformities are due to the haploinsufficiency of the distal region of Xp, including the short stature homeobox (*SHOX*) gene (Xp22.33) [8, 26, 76, 83]. Moreover, *SHOX* mutations are also associated with Leri-Weill dyschondrosteosis (LWD) and idiopathic short stature (ISS) [84]. LWD is manifested with a wide spectrum of phenotypes, including short-normal stature to severe short stature with no, mild, or severe Madelung deformity. Langer *et al.* defined the LWD-specific radiological features in the upper extremity, such as triangularisation of the distal radial epiphysis with shortening of the ulnar segment, pyramidalisation of the distal carpal row, shortening and bowing of the distal radius, and widening of the articular space between the distal parts of radius and ulna. The Madelung deformity is also thought to be caused by decreased oestrogen levels, due to its essential role in closing the epiphyseal cleft [85]. Moreover, Binder *et al.* asserted that Turner girls tended to have an abnormal triangularisation of the distal radial epiphysis [83].

In addition to the stigmata mentioned above, Turner syndrome has typical bone defects concerning the axial

and appendicular skeleton. The most frequent bone symptoms comprise short fourth metacarpals, short neck, Madelung deformity, or genu valgum. In radiological diagnostics, the so-called "Kosowicz sign" concerns lunate bone displacement, thus reducing the carpal angle below 118° in Turner patients [86]. Also, knee joints are characteristically changed – the tibial metaphysis has mushroom-like enlargement or peaked projection on its medial surface [86]. Additionally, girls with TS usually have distinctive craniofacial features, such as gothic palate, crossbite, retrognathia with microgenia, and trigonocephaly [74, 79]. Furthermore, based on radiographs of the skull, Rzymiski and Kosowicz observed the following characteristic findings: increased angle of the skull base, smaller sella turcica, decreased dimensions of the mastoid processes, enlarged and thicker mandible (as in males), and excessive pneumatization of paranasal sinuses [87]. In reference to our recent unpublished study, including 37 TS patients with radiographs of the cranium and both extremities, the characteristic symptoms of TS, i.e. shortening of the fourth and fifth metacarpals, positive carpal sign, and elongation of fibula, occur with a frequency of nearly 100%, regardless of the karyotype. However, it has not been possible to determine the skeletal signs that would be pathognomonic for a selected karyotype. Also, Czyzyk *et al.* [88] pointed out the diversity of phenotype and karyotype characteristic for TS patients. In contrast, in our systematic review of case reports published after 2000, a negligible proportion of patients had detailed radiological examinations of the limbs. The majority of available papers focused on descriptions of craniofacial abnormalities based on cephalometric radiographs.

In differential diagnosis, Noonan syndrome presenting similar clinical symptoms should be considered (e.g. short stature, webbed neck, cardiac and renal disorders). However, this condition can affect both males and females because it is not associated with X-chromosomal abnormality [89].

#### KLINFELTER SYNDROME

According to National Danish Cytogenetic Registry Study, only about one-fourth of Klinefelter patients are diagnosed in their lifetime [90]. KS is very rarely recognised prior to puberty or adulthood due to variable phenotypes and clinical presentations, which are age related. In addition, Abramsky and Chapple estimated that less than 10% of expected cases were diagnosed by prenatal amniocentesis [91]. In children and adolescents, KS detection is based on typical features, such as underdeveloped genitalia, hypotonia, gynecomastia, or learning and behavioural problems due to mental retardation [10]. The diagnosis is usually made in adult men evaluated for infertility and hypogonadism [10, 92]. The diagnosis of KS should be confirmed by chromosome analysis on lymphocytes from peripheral blood [93, 94].

The number of the extra X chromosome is positively correlated with the severity of the KS phenotype. In patients with mosaicism (especially 46,XY/47,XXY), the clinical presentation is relatively mild, and bone radiological examination rarely shows abnormalities [95]. About half of KS boys manifest motor impairments associated with muscular hypotonia, articular hypermobility, pes planus, or genu valgum [10], as well as radioulnar synostosis or bilateral fifth finger clinodactyly [94]. Additionally, based on radiographs of the skull, Kosowicz and Rzymiski observed the following characteristic findings: decreased angle of the skull base, shortening of the anterior cranial fossa, shorter mandibular rami, and deepening of the posterior cranial fossa [19]. Among dental conditions, inter alia cleft palate, malocclusion, and taurodontism occur in KS. Furthermore, tall stature is partially implicated in hypogonadism in decelerated closure of epiphyseal plates. Also, *SHOX* overexpression results in accelerated growth velocity [10]. The number of X chromosomes is negatively correlated with the height in KS patients [93]. Delayed treatment with testosterone could lead to lowered muscle and bone mass, resulting in osteoporosis and a higher prevalence of hip and spine fractures [10, 90]. In our systematic review, similarly to TS patients, most included case reports were focused on craniofacial features based on cephalometric analysis.

Klinefelter syndrome should be differentiated from other growth disturbances, such as Marfan syndrome [96], acromegaly [97], or fragile X syndrome (FXS) [98].

#### JACOBS SYNDROME

Currently, prenatal diagnosis is made using preferably cell-free foetal DNA instead of invasive amniocentesis [99-101]. Postnatally, JS is detected by karyotyping from the patient's blood [91]. The main JS karyotype is 47,XYY, and other mosaics (e.g. 46,XY/47,XYY) are less common [17].

JS may be associated with mental disabilities, such as autism spectrum disorder (ASD) or attention deficit hyperactivity disorder (ADHD) [16]. It can also be related to behavioural problems (e.g. aggression, sociopathy) [102, 103]. JS patients are more predisposed to systemic disorders, including asthma, seizures, and tremors [16]. Also, males with JS are often fertile with normal external genitalia and can have healthy offspring [103].

The JS phenotypes could be expressed diversely. In JS patients, among the most common findings are tall stature, brachy- or clinodactyly, pes planus, and hypotonia. Radiologically, radioulnar synostoses can be observed [104]. Moreover, dental examination usually manifests as progenia with open bite, macrodontia, or taurodontism [16]. Hypertelorism is also a specific facial feature in JS. According to our systematic review, JS patients constituted a significant minority and manifest a diverse range of skeletal abnormalities.

The differential diagnosis of JS should include growth disorders, such as Marfan syndrome, Sotos syndrome, and Klinefelter syndrome [13].

#### STUDY LIMITATIONS

Our systematic review included only individual case reports that met the strict inclusion criteria. Therefore, the included patients may not reflect the actual occurrence of karyotypes in the given types of SCAs, because rarer and unique cases are more often published in reputable journals. The described skeletal lesions may not represent the population of patients with SCAs, but the goal of this review was to collect bone manifestations published in the literature. The selection of only one medical database (albeit the most popular) should be considered a study limitation. We know that there may be other non-included papers published in local journals not indexed in this database and written in languages other than English, which limits their availability.

#### CONCLUSIONS

Diagnosis and treatment of patients with SCAs require a multidisciplinary approach. Skeletal manifestations in the craniofacial and limb regions could help diagnose these reviewed sex chromosome aberrations. However, further observational studies on larger populations are advisable to determine the pathognomonic symptoms for selected genetic syndromes.

#### DISCLOSURE

The authors declare no conflict of interest.

#### REFERENCES

- Hassold T, Hunt P. To err (meiotically) is human: the genesis of human aneuploidy. *Nat Rev Genet* 2001; 2: 280-291.
- Mandrioli D, Belpoggi F, Silbergeld EK, et al. Aneuploidy: a common and early evidence-based biomarker for carcinogens and reproductive toxicants. *Environ Health Glob Access Sci Source* 2016; 15: 97.
- Tartaglia NR, Ayari N, Hutaff-Lee C, et al. Attention-deficit hyperactivity disorder symptoms in children and adolescents with sex chromosome aneuploidy: XXY, XXX, XYY, and XXYY. *J Dev Behav Pediatr* 2012; 33: 309-318.
- Le Gall J, Nizon M, Pichon O, et al. Sex chromosome aneuploidies and copy-number variants: a further explanation for neurodevelopmental prognosis variability? *Eur J Hum Genet* 2017; 25: 930-934.
- Cui X, Cui Y, Shi L, et al. A basic understanding of Turner syndrome: Incidence, complications, diagnosis, and treatment. *Intractable Rare Dis Res* 2018; 7: 223-228.
- Turner HH. A syndrome of infantilism, congenital webbed neck, and cubitus valgus. *Endocrinology* 1938; 23: 566-574.
- Ullrich O. Über typische Kombinationsbilder multipler Abartungen. *Z Kinderheilkd* 1930; 49: 271-276.

8. Lacka K. Turner's syndrome – correlation between karyotype and phenotype. *Endokrynol Pol* 2005; 56: 986-993.
9. Velissariou V, Christopoulou S, Karadimas C, et al. Rare XXY/XX mosaicism in a phenotypic male with Klinefelter syndrome: case report. *Eur J Med Genet* 2006; 49: 331-337.
10. Davis S, Howell S, Wilson R, et al. Advances in the interdisciplinary care of children with Klinefelter syndrome. *Adv Pediatr* 2016; 63: 15-46.
11. Klinefelter HF, Reifenstein EC, Albright F. Syndrome characterised by gynecomastia, aspermatogenesis without A-Leydigism, and increased excretion of follicle-stimulating hormone. *J Clin Endocrinol Metab* 1942; 2: 615-627.
12. Jacobs PA, Strong JA. A case of human intersexuality having a possible XXY sex-determining mechanism. *Nature* 1959; 183: 302-330.
13. Scheidt L, Sanabe ME, Diniz MB. Oral, physical, and behavioral aspects of patient with chromosome 47, XYY syndrome. *J Indian Soc Pedod Prev Dent* 2015; 33: 347-350.
14. Sandberg AA, Koepf GF, Ishihara T, et al. An XYY human male. *Lancet Lond Engl* 1961; 2: 488-489.
15. Jacobs PA, Brunton M, Melville MM, et al. Aggressive behavior, mental sub-normality and the XYY male. *Nature* 1965; 208: 1351-1352.
16. Bardsley MZ, Kowal K, Levy C, et al. 47, XYY syndrome: clinical phenotype and timing of ascertainment. *J Pediatr* 2013; 163: 1085-1094.
17. Stochholm K, Juul S, Gravholt CH. Diagnosis and mortality in 47, XYY persons: a registry study. *Orphanet J Rare Dis* 2010; 5: 15.
18. Kosowicz J. Changes in the medial tibial condyle: a common finding in Turner's syndrome. *Acta Endocrinol (Copenh)* 1959; 31: 321-323.
19. Kosowicz J, Rzymiski K. Radiological features of the skull in Klinefelter's syndrome and male hypogonadism. *Clin Radiol* 1975; 26: 371-378.
20. Kosowicz J, Baszko-Błaszyk D, Horst-Sikorska W, et al. Bone mineral density in primary hyperparathyroidism. *Pol Arch Med Wewn* 1999; 101: 131-138.
21. Page MJ, McKenzie J, Bossuyt P, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews [Internet]. *MetaArXiv*; 2020. Available from: <https://osf.io/v7gm2>
22. Gawlik A, Malecka-Tendera E. Hormonal therapy in a patient with a delayed diagnosis of Turner's syndrome. *Nat Clin Pract Endocrinol Metab* 2008; 4: 173-177.
23. Jivănescu A, Bratu AE, Naiche D, et al. Interdisciplinarity in oromaxillofacial dysmorphism rehabilitation of a patient with Turner syndrome. A clinical case report. *Romanian J Morphol Embryol Rev Roum Morphol Embryol* 2012; 53: 407-311.
24. Ahiko N, Baba Y, Tsuji M, et al. Investigation of maxillofacial morphology and oral characteristics with Turner syndrome and early mixed dentition. *Congenit Anom* 2019; 59: 11-17.
25. Marçal FF, Costa AC de F, Magalhães IA, et al. Orthodontic treatment and aesthetic rehabilitation in a patient with Turner syndrome: a case report. *Spec Care Dentist* 2020; 40: 498-505.
26. Cazzolla AP, Lo Muzio L, Di Fede O, et al. Orthopedic-orthodontic treatment of the patient with Turner's syndrome: review of the literature and case report. *Spec Care Dentist* 2018; 38: 239-248.
27. Kasagani SK, Jampani ND, Nutalapati R, et al. Periodontal manifestations of patients with Turner's syndrome: report of 3 cases. *J Indian Soc Periodontol* 2012; 16: 451-455.
28. Aristizábal JF, Smit RM. Two-phase orthodontic treatment in a patient with Turner syndrome: an unusual case of deep bite. *Cleft Palate-Craniofacial J* 2015; 52: e56-64.
29. Rodríguez L, Diego-Alvarez D, Lorda-Sanchez I, et al. A small and active ring X chromosome in a female with features of Kabuki syndrome. *Am J Med Genet A* 2008; 146A: 2816-2821.
30. Rohrer TR, Gassmann KF, Rauch A, et al. Growth of heterokaryotic monozygotic twins discordant for Ullrich-Turner syndrome during the first years of life. *Am J Med Genet A* 2004; 126A: 78-83.
31. Kasagani SK, Mutthineni RB, Jampani ND, et al. Report of a case of Turner's syndrome with localised aggressive periodontitis. *J Indian Soc Periodontol* 2011; 15: 173-176.
32. Posey JE, Mohrbacher N, Smith JL, et al. Triploidy mosaicism (45,X/68,XX) in an infant presenting with failure to thrive. *Am J Med Genet A* 2016; 170: 694-698.
33. Periquito I, Carrusca C, Morgado J, et al. Familial Turner syndrome: the importance of information. *J Pediatr Endocrinol Metab* 2016; 29: 617-620.
34. Nabhan ZM, Eugster EA. Monozygotic twins with Turner syndrome develop slipped capital femoral epiphysis on growth hormone therapy. *Pediatrics* 2006; 118: e1900-1903.
35. Andrade NS, Tenório JR, Gallottini M. Supernumerary teeth in a patient with Turner syndrome: an unusual finding. *Spec Care Dentist* 2019; 39: 538-542.
36. Mousavi S, Amiri B, Beigi S, et al. The value of a simple method to decrease diagnostic errors in Turner syndrome: a case report. *J Med Case Rep* 2021; 15: 79.
37. Hemani F, Niaz S, Kumar V, et al. A case of early diagnosis of Turner syndrome in a neonate. *Cureus* 2021; 13: e16733.
38. Hunter ML, Collard MM, Razavi T, et al. Increased primary tooth size in a 47, XXY male: a first case report. *Int J Paediatr Dent* 2003; 13: 271-273.
39. Bahillo-Curieses MP, Fournier-Carrera M, Morán-López J, et al. Klinefelter syndrome and short stature: an unusual combination. *Endocrine* 2011; 39: 294-295.
40. Parhiz A. A rare case of multiple impacted teeth in a Klinefelter patient. *J Craniomaxillofacial Res* 2014; 1: 66-68.
41. Mazen I, El-Ruby M, El-Bassyouni HT. Variable associations of Klinefelter syndrome in children. *J Pediatr Endocrinol Metab* 2010; 23: 985-989.
42. Joseph M. Endodontic treatment in three taurodontic teeth associated with 48, XXXY Klinefelter syndrome: a review and case report. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2008; 105: 670-677.
43. Capasso F, Panetta F, Ierardo G, et al. Klinefelter syndrome: case report. *Oral Implantol* 2009; 2: 27-36.
44. Krishnamoorthy S, Gopikrishna V. Endodontic management of a hypertaurodontic tooth associated with 48, XXXY syndrome: a review and case report. *J Conserv Dent* 2015; 18: 265-268.
45. Hou JW. 49, XXXXY syndrome. *Chang Gung Med J* 2004; 27: 551-554.
46. Pamuk BO, Torun AN, Kulaksizoglu M, et al. 49, XXXXY syndrome with autoimmune diabetes and ocular manifestations. *Med Princ Pract Int J Kuwait Univ Health Sci Cent* 2009; 18: 482-485.
47. Wei L, Liu Y, Sun S, et al. Case report of 49, XXXXY syndrome with cleft palate, diabetes, hypothyroidism, and cataracts. *Medicine (Baltimore)* 2019; 98: e17342.
48. Sumathipala D, Gamage T, Wijesiriwardena B, et al. An infant born to a mother with gestational diabetes presenting with 49, XXXXY syndrome and renal agenesis – a case report. *J Clin Res Pediatr Endocrinol* 2012; 4: 223-225.
49. Burgemeister AL, Daumiller E, du Bois G, et al. Clinical report of 8 patients with 49, XXXXY syndrome: delineation of the facial gestalt and depiction of the clinical spectrum. *Eur J Med Genet* 2019; 62: 210-216.
50. Nishimura T, Nii E, Urawa M, et al. Proximal tibiofibular synostosis with 49, XXXXY syndrome, a rare congenital bone anomaly. *J Orthop Sci* 2008; 13: 390-395.
51. Etemadi K, Basir B, Ghahremani S. Neonatal diagnosis of 49, XXXXY syndrome. *Iran J Reprod Med* 2015; 13: 181-184.



52. Dötsch J, Foerster W, Holl R, et al. Case of XXXXY syndrome. Development throughout adolescence and endocrine aspects. *Horm Res* 2000; 53: 154-156.
53. Kim HJ, Kim D, Shin JM, et al. 49,XXXXY syndrome with diabetes mellitus. *Horm Res* 2006; 65: 14-17.
54. Hata S, Maruyama Y, Fujita Y, Mayanagi H. The dentofacial manifestations of XXXXY syndrome: a case report. *Int J Paediatr Dent* 2001; 11: 138-142.
55. Simşek PO, Utine GE, Alikasıfoğlu A, et al. Rare sex chromosome aneuploidies: 49,XXXXY and 48,XXXY syndromes. *Turk J Pediatr* 2009; 51: 294-297.
56. Dissanayake VHW, Bandarage P, Pedurupillay CRJ, Jayasekara RW. A Sri Lankan child with 49,XXXXY syndrome. *Indian J Hum Genet* 2010; 16: 164-165.
57. Shah AH, Manjunatha BS, Bindayel NA, Khounganian R. Oral health management of a patient with 47,XYY syndrome. *BMJ Case Rep* 2013; 2013: bcr2013010408.
58. Franceschini P, Licata D, Guala A, et al. Radioulnar synostosis and XYY syndrome. *Clin Dysmorphol* 2000; 9: 77.
59. Chew FLM, Visvaraja S. 47 XYY and morning glory syndrome – a unique association. *J AAPOS* 2009; 13: 406-407.
60. Liao C, Fu F, Zhang L. Ring chromosome 13 syndrome characterized by high resolution array based comparative genomic hybridisation in patient with 47, XYY syndrome: a case report. *J Med Case Reports* 2011; 5: 99.
61. Hayashi-Sakai S, Sakai J, Kitamura T, et al. The clinical oro-facial findings of an 11-year-old Japanese boy with 47, XYY: a case report. *Pediatr Dent J* 2008; 18: 179-186.
62. Mahjoubi F, Akbary M, Shafegate Y. XYY karyotype in a mentally retarded man with prognathism and malformation of his hands and toe nails. *Balk J Med Genet* 2010; 13: 71-73.
63. Mutesa L, Jamar M, Hellin AC, et al. A new 48, XXYY/47, XYY syndrome associated with multiple skeletal abnormalities, congenital heart disease and mental retardation. *Indian J Hum Genet* 2012; 18: 352-355.
64. Liu ZH, Zhou SC, Du JW, et al. A patient with 46,XY/47,XYY karyotype and female phenotype: a case report. *BMC Endocr Disord* 2020; 20: 42.
65. Maciejewska-Jeske M, Czyzyk A, Meczekalski B. The Turner syndrome in patient with 45X/47XXX mosaic karyotype – case report. *Gynecol Endocrinol* 2015; 31: 526-528.
66. Güzel Erdal G, Balkan M. Turner syndrome with isochromosome Xq. *J Pediatr Genet* 2020; 9: 243-245.
67. Dinesh Kumar J, Venkataraman P, Ramachandran P, et al. Turner syndrome with mosaic 45,X(77%)/46,XR(X)(23%) (Turner mosaic with ring X chromosome): a case report. *Sri Ramachandra J Med* 2014; 7: 25-26.
68. Alhalabi MM, Alhalabi M. 48,XXYY syndrome presenting with long-term infertility and newly observed neck deformities: a case report. *J Med Case Reports* 2020; 14: 58.
69. Patacchiola F, Sciarra A, Di Fonso A, et al. 49,XXXXY syndrome: an Italian child. *J Pediatr Endocrinol Metab* 2012; 25: 165-166.
70. Mohd Nor NS, Jalaludin MY. A rare 47 XXY/46 XX mosaicism with clinical features of Klinefelter syndrome. *Int J Pediatr Endocrinol* 2016; 2016: 11.
71. Butler D, Offiah AC, Wilson L, Roposch A. Congenital radial head dislocation in XYY-syndrome: case report and review of the literature. *Curr Orthop Pract* 2009; 20: 203-208.
72. Gravholt CH, Andersen NH, Conway GS, et al. Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. *Eur J Endocrinol* 2017; 177: G1-70.
73. Zitzmann M, Aksglaede L, Corona G, et al. European academy of andrology guidelines on Klinefelter Syndrome Endorsing Organization: European Society of Endocrinology. *Andrology* 2021; 9: 145-167.
74. Borkowska M, Gawlik A, Hankus M, Małecka-Tendera E. Dental abnormalities and orthodontic disorders in Turner's syndrome patients. *Pediatr Endocrinol Diabetes Metab* 2016; 21: 143-148.
75. Arthurs OJ, van Rijn RR, Granata C, et al. European Society of Paediatric Radiology 2019 strategic research agenda: improving imaging for tomorrow's children. *Pediatr Radiol* 2019; 49: 983-989.
76. Ranke MB, Saenger P. Turner's syndrome. *Lancet Lond Engl* 2001; 358: 309-314.
77. Wojda A, Kołowska J, Łącka K, et al. Chromosome aberrations and cell mosaicism in Turner's syndrome – examinations with using of FISH. *Ginekol Pol* 1997; 68: 56-65.
78. Saenger P, Wikland KA, Conway GS, et al. Recommendations for the diagnosis and management of Turner syndrome. *J Clin Endocrinol Metab* 2001; 86: 3061-3069.
79. Bondy CA. Turner Syndrome Study Group. Care of girls and women with Turner syndrome: a guideline of the Turner Syndrome Study Group. *J Clin Endocrinol Metab* 2007; 92: 10-25.
80. Morgan T. Turner syndrome: diagnosis and management. *Am Fam Physician* 2007; 76: 405-410.
81. Łącka K, Korczowska I, Milewska A, Łącki JK. Bone mineral density and biochemical markers of osteoporosis in adult patients with Turner syndrome. *Pediatr Pol* 2005; 80: 280-282.
82. Suganuma N, Furuhashi M, Hirooka T, et al. Bone mineral density in adult patients with Turner's syndrome: analyses of the effectiveness of GH and ovarian steroid hormone replacement therapies. *Endocr J* 2003; 50: 263-269.
83. Binder G, Fritsch H, Schweizer R, et al. Radiological signs of Leri-Weill dyschondrosteosis in Turner syndrome. *Horm Res* 2001; 55: 71-76.
84. Hirschfeldova K, Solc R, Baxova A, et al. SHOX gene defects and selected dysmorphic signs in patients of idiopathic short stature and Léri-Weill dyschondrosteosis. *Gene* 2012; 491: 123-127.
85. Langer LO. Dyschondrosteosis, a hereditary bone dysplasia with characteristic roentgenographic features. *Am J Roentgenol Radium Ther Nucl Med* 1965; 95: 178-188.
86. Leszczyński S, Kosowicz J. Radiologic changes in the skeletal system in Turner's syndrome – review of 102 cases. *Prog Radiol* 1965; 510-517.
87. Rzymiski K, Kosowicz J. The skull in gonadal dysgenesis. A roentgenometric study. *Clin Radiol* 1975; 26: 379-384.
88. Czyzyk A, Lacka K, Krawczynski MR, et al. Analysis of phenotype and karyotype of children born from mothers with 45,X/46,XX mosaicism. *Endocrinologist* 2010; 20: 283-285.
89. Roberts AE, Allanson JE, Tartaglia M, et al. Noonan syndrome. *Lancet Lond Engl* 2013; 381: 333-342.
90. Bojesen A, Juul S, Gravholt CH. Prenatal and postnatal prevalence of Klinefelter syndrome: a national registry study. *J Clin Endocrinol Metab* 2003; 88: 622-626.
91. Abramsky L, Chapple J. 47,XXY (Klinefelter syndrome) and 47,XYY: estimated rates of and indication for postnatal diagnosis with implications for prenatal counselling. *Prenat Diagn* 1997; 17: 363-368.
92. Forti G, Corona G, Vignozzi L, et al. Klinefelter's syndrome: a clinical and therapeutical update. *Sex Dev* 2010; 4: 249-258.
93. Lanfranco F, Kamischke A, Zitzmann M, Nieschlag E. Klinefelter's syndrome. *Lancet* 2004; 364: 273-283.
94. Visootsak J, Graham JM. Klinefelter syndrome and other sex chromosomal aneuploidies. *Orphanet J Rare Dis* 2006; 1: 42.
95. Radicioni AF, Ferlin A, Balercia G, et al. Consensus statement on diagnosis and clinical management of Klinefelter syndrome. *J Endocrinol Invest* 2010; 33: 839-850.
96. Yuan SM, Jing H. Marfan's syndrome: an overview. *Sao Paulo Med J Rev Paul Med* 2010; 128: 360-366.

97. Meazza C, Gertosio C, Giaccherio R, et al. Tall stature: a difficult diagnosis? *Ital J Pediatr* 2017; 43: 66.
98. Ciaccio C, Fontana L, Milani D, et al. Fragile X syndrome: a review of clinical and molecular diagnoses. *Ital J Pediatr* 2017; 43: 39.
99. Margiotti K, Cesta A, Dello Russo C, et al. Cell-free DNA screening for sex chromosomal aneuploidies in 9985 pregnancies: Italian single experience. *BMC Res Notes* 2020; 13: 167.
100. Kypri E, Ioannides M, Touvana E, et al. Non-invasive prenatal testing of fetal chromosomal aneuploidies: validation and clinical performance of the veracity test. *Mol Cytogenet* 2019; 12: 34.
101. Zheng Y, Wan S, Dang Y, et al. Non-invasive prenatal testing for detection of trisomy 13, 18, 21 and sex chromosome aneuploidies in 8594 cases. *Ginekol Pol* 2019; 90: 270-273.
102. Marcus AM, Richmond G. The XYY syndrome. Review with a case study. *Can Psychiatr Assoc J* 1970; 15: 389-397.
103. Kim IW, Khadilkar AC, Ko EY, Sabanegh ES. 47,XYY syndrome and male infertility. *Rev Urol* 2013; 15: 188-196.
104. Sirota L, Zlotogora Y, Shabtai E, et al. 49,XYYYY. A case report. *Clin Genet* 1981; 19: 87-93.