



Cross-sectional analysis and trend of vertebral and associated anomalies in Chinese congenital scoliosis population: a retrospective study of one thousand, two hundred and eighty nine surgical cases from 2010 to 2019

Guanfeng Lin¹ · Xiran Chai¹ · Shengru Wang¹ · Yang Yang¹ · Jianxiang Shen¹ · Jianguo Zhang¹

Received: 25 November 2020 / Accepted: 26 April 2021 / Published online: 1 June 2021
© SICOT aisbl 2021

Abstract

Purpose The objective of this article is to report associated anomaly incidences of a large CS cohort and analyze interrelationships among vertebral anomaly types and associated abnormalities.

Methods We retrospectively searched and extracted medical records of 1289 CS inpatients surgically treated in our institute from January 2010 to December 2019. All patients have taken spine X-ray, CT, MRI, echocardiogram, urogenital ultrasound, and systemic physical examination. We analyzed information on demographics, CS types, and associated anomalies.

Results CS type was found to be 49.1% for failure of formation (FF), 19.5% for failure of segmentation (FS), and 31.4% for mixed defects (MD). Intraspinous defects were found in 29.4% patients (16.0% for FF, 45.4% for FS, 40.5% for MD), cardiac in 13.7% (12.3% for FF, 14.3% for FS, 15.6% for MD), genitourinary in 5.8% (4.1% for FF, 6.0% for FS, 8.4% for MD), gastrointestinal in 3.6% (4.7% for FF, 1.6% for FS, 3.0% for MD), and musculoskeletal in 16.4% (10.3% for FF, 19.9% for FS, 23.7% for MD). The intraspinal and musculoskeletal defect incidences were significantly higher in patients with failure of segmentation and mixed defects. We also observed a decreasing trend for intraspinal and musculoskeletal defect incidences as well as a tendency for more failure of formation and less failure of segmentation from 2010 to 2019.

Conclusions The intraspinal and musculoskeletal defect incidences were higher in patients with failure of segmentation and mixed defects. Strong interrelationships were found between intraspinal and musculoskeletal defects and among cardiovascular, genitourinary, and gastrointestinal defects. From 2010 to 2019, the proportion of patients with failure of formation increased significantly, causing a decrease in the intraspinal and musculoskeletal defect incidences over time. Female sex, failure of segmentation, and mixed defects could be considered risk factors for more associated anomalies in CS individuals, which would help surgeons in medical management and prenatal consultation.

Keywords Congenital scoliosis · Associated anomalies · Vertebral anomaly type · Retrospective analysis

Introduction

Congenital scoliosis (CS) is the lateral curvature of the spine resulting from vertebral deformities that develop during four to six weeks of gestation and are present at birth.

CS was reported to occur at a ratio of approximately 1 in every 1000 live births [1]. Congenital scoliosis is caused by abnormal vertebral development, and a multifactorial aetiology of CS is universally accepted [2–4]. While certain genetic and environmental factors have been implicated in congenital scoliosis [5–9], the aetiology of most CS remains unclear.

It is widely observed in clinical practice that CS patients usually have comorbidities of other congenital abnormalities. Among all kinds of congenital defects, intraspinal, cardiovascular, and genitourinary defects are the most common. Several previous studies have reported the incidences of different congenital defects

✉ Jianguo Zhang
jgzhang_pumch@yahoo.com

¹ Department of Orthopedic Surgery, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital (PUMCH) Peking Union Medical College (PUMC) & Chinese Academy of Medical Sciences (CAMS), 1st Shuaifuyuan Hutong, Beijing 100730, People's Republic of China

in CS patients [7, 10–19]. However, the incidences varied greatly in different studies, and the interrelationship among these anomalies and the trend in recent years has not been fully clarified.

We retrospectively analyzed information from 1289 CS patients who were admitted for congenital scoliosis from January 2010 to December 2019 in our institute. The objective of this article is to report anomaly incidences of a large CS cohort and analyze interrelationships among vertebral anomaly types and associated abnormalities.

Material and methods

We retrospectively searched for cases who were admitted for congenital scoliosis from January 2010 to December 2019 in our institute from the inpatient database using ICD-10 codes (Q67.501, Q67.502). In total, 1289 inpatients are included in our study.

The CS types (namely failure of formation, failure of segmentation, and mixed defects) were diagnosed from the patients' X-ray and spine CT [20, 21]. Echocardiogram, urogenital ultrasound, spine imaging, including MRI, X-ray and CT, and systemic physical examination were undertaken in all patients to screen and diagnose associated anomalies.

After automated extraction of patient information from the inpatient database, all patients' medical records, including imaging reports, were reviewed and re-evaluated case by case to minimize missing data.

Statistical analysis

Descriptive statistics are expressed as the mean \pm standard deviation for continuous variables and percentage (%) for categorical variables. The chi-square test was used to evaluate the relationships between categorical variables. *P* value < 0.05 was considered to indicate a statistically significant result. Statistical analysis was performed using IBM SPSS Statistics 23. Statistical graphs were plotted using Graphpad Prism 7.

Results

In total, 1289 CS patients were included in our study. The mean patient age was 12.4 ± 8.1 years old, and 54.0% were female (Table 1). Annual trends in age and sex structures were similar from 2010 to 2019.

Typical X-rays and spine CT 3D-reconstructions of three CS types were shown in Fig. 1.

Among all 1289 CS patients, failure of formation was seen in 633 patients (49.1%), failure of segmentation in 251 patients (19.5%), and mixed defects in 405 patients (31.4%). The distribution of different vertebral anomaly types in male and female patients is presented in Table 1. There are significantly more cases with failure of formation and less failure of segmentation and mixed defects in male patients. Among the patients with congenital scoliosis, 39 patients had a constellation of abnormalities as part of a syndrome (Table 2).

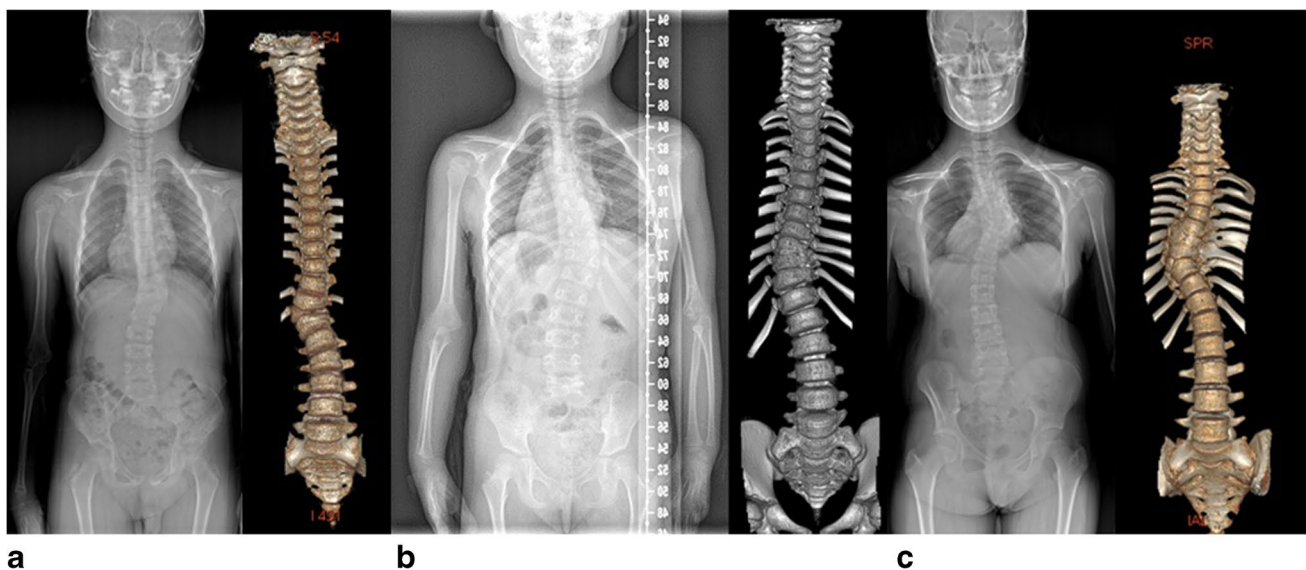


Fig. 1 Typical X-ray and CT 3D-reconstruction of three CS types, **a** X-ray and CT 3D-reconstruction of a patient with failure of formation (a hemivertebrae between T11 and T12) **b** X-ray and CT 3D-reconstruction of a patient with failure of segmentation (T9 to T11 seg-

mentation defect), **c** X-ray and CT 3D-reconstruction of a patient with mixed defects (T9 hemivertebrae, T6 to T8 segmentation defect and fused ribs)

Table 1 Demographic details of congenital scoliosis patients isolated from our hospital database and distribution of vertebral anomaly types in male and female patients

Demographic information							
Sample size (<i>n</i>)	1289						
Age	Mean	12.4 ± 8.1					
Sex	Male	593		46.0%			
	Female	696		54.0%			
Distribution of vertebral anomaly types							
Anomaly type	Male		Female		Total	<i>P</i>	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	
Failure of formation	346	58.3%	287	41.2%	633	49.1%	<i>p</i> < 0.001
Failure of segmentation	81	13.7%	170	24.4%	251	19.5%	<i>P</i> < 0.001
Mixed defects	166	28.0%	239	34.3%	405	31.4%	<i>P</i> < 0.05

Within those syndromes, Klippel-Feil syndrome ($n=23$) and VACTERL association ($n=11$) were the most common.

The incidences of associated defects in different systems and those incidences reported by previous studies are summarized in Table 3. Intraspinial defects were found in 379 (29.4%) out of 1289 CS patients, cardiovascular defects in 177 patients (13.7%), genitourinary defects in 75 patients (5.8%), gastrointestinal defects in 46 patients (3.6%), and musculoskeletal defects in 211 patients (16.4%). We also found five patients with auricular defects (2 with congenital deafness and 3 with microtia) and nine patients with cleft lip and palate (Table 4).

The numbers of specific associated anomalies in this CS series are summarized in Table 4. Among 379 patients with intraspinal defects, diastematomyelia, syringomyelia, and tethered cord were the first three most frequent defects in our series, with incidences of 19.3% ($n=249$), 13.2% ($n=170$), and 9.1% ($n=117$), respectively. There were 125 male patients (21.1%) and 254 female (36.5%) patients with intraspinal defects (Fig. 2a). The incidence of intraspinal defects was significantly lower in men than in women ($p<0.001$). Intraspinial anomalies were found in 101 patients (16.0%) with failure of formation, 114 patients (45.4%) with failure of segmentation, and 164 patients (40.5%) with

mixed defects (Fig. 2b). The patients with failure of segmentation and mixed defects were found to have significantly higher incidence of intraspinal defects.

In this study, 177 patients (13.7%) were found to have cardiovascular abnormalities (Table 4). Valvular malformation was the most frequent defect with an incidence of 6.3%. The cardiovascular abnormalities had almost the same incidence between sexes (Fig. 2a). Patients with failure of segmentation and mixed defects had a slightly higher frequency of cardiovascular abnormalities, but the difference was not significant ($p=0.495$) (Fig. 2b).

Genitourinary anomalies were found in 75 patients (5.8%) where a single kidney and an ectopic kidney were the most frequent comorbidities (Table 4). There was no significant difference between sexes (Fig. 2a), but patients with failure of segmentation and mixed defects did have a significantly higher incidence of genitourinary defects ($p<0.05$) (Fig. 2b). The incidence of gastrointestinal anomalies was 3.6% in our study. Accessory spleen and anal atresia were the most frequent. There was no significant difference between sexes or vertebral anomaly types.

Musculoskeletal defects were found in 211 patients (16.4%), most of which were rib defects (Table 4). Non-significantly higher incidence ($p=0.076$) and significantly higher incidence ($p<0.001$) were observed in female patients and patients with failure of segmentation and mixed defects respectively (Fig. 2a, 2).

As for the level of congenital spinal defects, there were 5.7% ($n=74$) of patients had cervical spine involved, 78.1% ($n=1008$) had thoracic spine involved and 33.6% ($n=434$) had lumbar spine involved. Intraspinial and musculoskeletal defects had higher incidences in patients with cervical and thoracic spine involved than in patients with lumbar spine involved (33.8% vs. 33.4% vs. 20.7% for intraspinal defects; 28.4% vs. 19.1% vs. 9.0% for musculoskeletal defects). No difference with statistical significance was observed in the incidences of cardiac, urogenital, and gastrointestinal defects among three groups (Table 5).

Table 2 Associated syndromes in our CS cohort

Syndromes	Number
Klippel-Feil	23
VACTERL association	11
Jarcho-Levin	2
Goldenhar	1
Klinefelter	1
Porteaus	1
Ehlers-Danlos	1
Freeman-Shelton	1
Congenital insensitive to pain with anhidrosis	1
Total	39

Table 3 Incidences of associated anomalies in different systems and key findings in our study and previous studies

	Intraspinal	Cardiovascular	Genitourinary	Gastrointestinal	Musculoskeletal	Key findings
Basu et al. [7]	37%	26%	21%	-	-	FS and MD had higher incidences of associated anomalies
Rai et al. [11]	-	-	26.7%	-	-	Genitourinary anomalies were positively associated with musculoskeletal, gastrointestinal and cardiac defects
Liu et al. [12]	24.5%	14.1%	-	-	-	Intraspinal defects were more common in female and older patients
Shen et al. [13]	43%	18%	12%	5.3%	4.9%	FS and MD had higher incidences of intraspinal defects; Patients with thoracic hemivertebrae had higher incidence of intraspinal defects
Hassan et al. [14]	21.8%	-	-	-	-	Rib and intraspinal anomalies were significantly associated
Gupta et al. [16]	47%	-	-	-	-	FS and MD had higher incidences of intraspinal defects
Evin et al. [15]	-	55%	-	-	-	-
Eliane et al. [17]	10%	21%	17.1%	15%	21.7%	Only a minority of patients had a syndromic diagnosis to explain their CS
Ahmet et al. [18]	53.7%	27.1%	27.8%	-	-	Intraspinal, cardiac and renal anomalies were associated
Mohanty et al. [19]	21%	-	-	-	-	FS had higher incidence of cord anomalies; Cord anomalies were not associated with other organ defects
Our study	29.4% (n=379)	13.7% (n=177)	5.8% (n=75)	3.6% (n=46)	16.4% (n=211)	Female, FS and MD had higher incidences of associated anomalies; Strong interrelationships between intraspinal and musculoskeletal defects and among cardiac, urogenital and gastrointestinal defects

FS, failure of segmentation; MD, mixed defects; CS, congenital scoliosis

The interrelationship between different organ defects is shown in Fig. 3. Intraspinal defects were found in 44.9% of patients with musculoskeletal defects, an incidence significantly higher than that in the total CS population. Cardiac, genitourinary, and gastrointestinal defects were found to have a strong interrelationship with each other, although the association between cardiac and genitourinary defects was not significant. A significant correlation between genitourinary and musculoskeletal defects was also observed.

After analyzing incidence changes in different associated anomalies during the last ten years (Fig. 4a), we found that intraspinal and musculoskeletal defects had an obvious decreasing trend from 2010 to 2019. Similarly, the proportion of failure of formation in our center had an obvious increasing tendency, while the proportion of failure of segmentation obviously decreased during the last ten years (Fig. 4b).

Discussion

Several independent studies covering different ethnic populations have been published in recent years. However, most of these studies did not cover and analyze all common associated anomalies of CS and their interrelationship but focused only on one or two certain systems. Therefore, we conducted this study to fully depict the distribution, incidences and interrelationship of vertebral anomaly types and associated anomalies. To the best of our knowledge, this is the largest CS series of the Chinese population so far. In our study, a total of 1289 CS patients were included and all their medical records, including imaging examination reports, were reviewed and re-evaluated.

In all CS patients, 49.1% were typed as failure of formation, 19.5% as failure of segmentation, and 31.4% as mixed defects. This distribution was similar to that in previous studies [7, 14, 16, 18, 19]. We also found that failure of

Fig. 2 Interrelationship of different associated anomalies, sexes and vertebral anomaly types, a Interrelationship between different associated anomalies and sexes. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, b Interrelationship between different associated anomalies and vertebral anomaly types. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

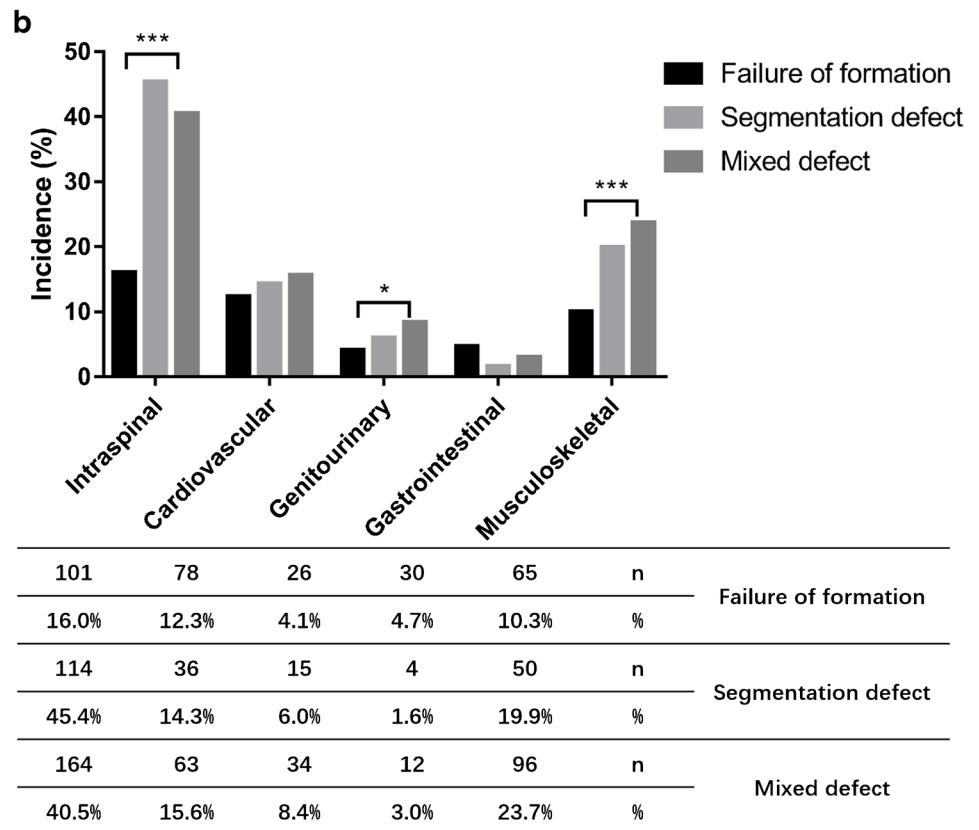
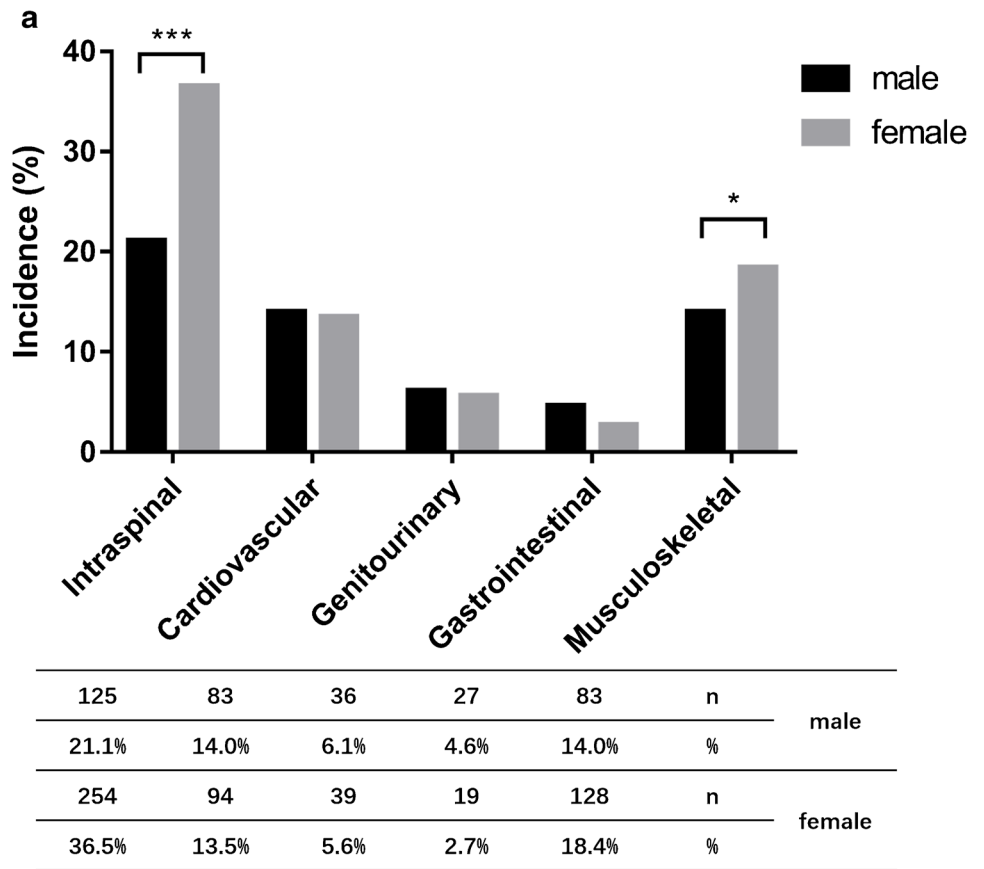


Table 4 Incidences of associated organ defects

System	Defects	N	%
Intraspinal	Diastematomyelia	249	19.3%
	Syringomyelia	170	13.2%
	Tethered cord	117	9.1%
	Low conus	49	3.8%
	Chiari malformation	26	2.0%
	Intraspinal cyst/mass	21	1.6%
	Spinal meningocele	17	1.3%
	Total	379	29.4%
Cardiac	Valvular malformation	81	6.3%
	Atrial septal defect	40	3.1%
	Ventricular septal defect	18	1.4%
	Patent ductus arteriosus	16	1.2%
	Dilation of coronary sinus	15	1.2%
	Tetralogy of fallot	9	0.7%
Total	177	13.7%	
Genitourinary	Single kidney	18	1.4%
	Ectopic kidney	12	0.9%
	Dysplasia of uterus/testicle	13	1.0%
	Urethra defects	8	0.6%
	Abnormal renal pelvis	7	0.5%
Total	75	5.8%	
Musculoskeletal	Lib defects	161	12.5%
	Upper limb bone deformity	7	0.5%
	Lower limb bone deformity	23	1.8%
	Hip dysplasia	10	0.8%
	Total	211	16.4%
Gastrointestinal	Accessory spleen	19	1.5%
	Anal atresia	16	1.2%
	Oesophagus atresia	4	0.3%
	Total	46	3.6%
Auricular	Microtia	3	0.2%
	Congenital deafness	2	0.2%
	Total	5	0.4%
Cleft lip and palate		9	0.7%

formation was significantly more common in male patients, whereas failure of segmentation or mixed defects were significantly more common in female patients. This finding contradicts the studies of Hassan et al. [14] and Ahmet et al.

[18], which showed that failure of segmentation and mixed defects were more common in male patients than in females. This contradiction of type distribution in sex might suggest that different ethnic groups have different pathogenesis of CS.

The incidence of intraspinal anomalies was 29.4%, which was in the range of previous studies [7, 12–14, 16–19]. The most common associated anomaly of intraspinal defect was diastematomyelia, with an incidence of 19.3%, followed by syringomyelia (13.2%) and tethered cord (9.1%). This result was in accordance with the studies in the Chinese population [12, 13], but contradicted the studies of Basu et al. [7], Gupta et al. [16], and Ahmet et al. [18]. This discrepancy suggests that the spectrum of associated intraspinal anomalies varies among different ethnic and geographical populations. Based on our clinical practice, a low conus without tethered cord usually presents no symptom and needs no intervention. As to tethered cord, surgical treatment is always the first choice, and the purpose of operation is to release the tethered spinal cord. Membranous diastematomyelia does not require any treatment unless the patient has obvious neurologic deficit, while the treatment of bony diastematomyelia usually needs the cooperation of orthopedic surgeons and neurosurgeons. Asymptomatic intraspinal defects can only be found by spinal MRI, so we recommend routine spinal MRI screening before surgery.

Moreover, our data indicated that female patients and patients with failure of segmentation or mixed defects have a significantly higher incidence of intraspinal defects ($p < 0.001$), which is consistent with previous studies. Thus, we recommend that female sex, failure of segmentation, or mixed defects should be considered as risk factors for intraspinal defects, and spinal MRI should be performed for patients with these risk factors. The association of CS and genetic factors has been proven by many previous studies. Among those genetic factors, chromosome aneuploidies, chromosomal deletion, or insertion and gene point mutation are the most common. Chromosome aneuploidies, such as trisomy 22, and chromosomal deletion or insertion, such as 10 Mb 9q33.1q34.11 deletion, are considered as more severe mutation and are associated with non-isolated vertebral malformation [22]. On the other hand, compound inheritance of a rare null mutation and a hypomorphic allele of TBX6 was confirmed to account for up to 11% of congenital

Table 5 Summary of information on the level of congenital spine defect

Level of spine defect	Cervical (C)	Thoracic (T)	Lumbar (L)
% (n) in total population	5.7% (n = 74)	78.1% (n = 1008)	33.6% (n = 434)
Intraspinal defects	33.8%	33.4%	20.7%
Musculoskeletal defects	28.4%	19.1%	9.0%
Cardiac defects	13.5%	14.6%	13.1%
Urogenital defects	9.5%	5.6%	6.9%
Gastrointestinal defects	6.8%	3.5%	4.4%

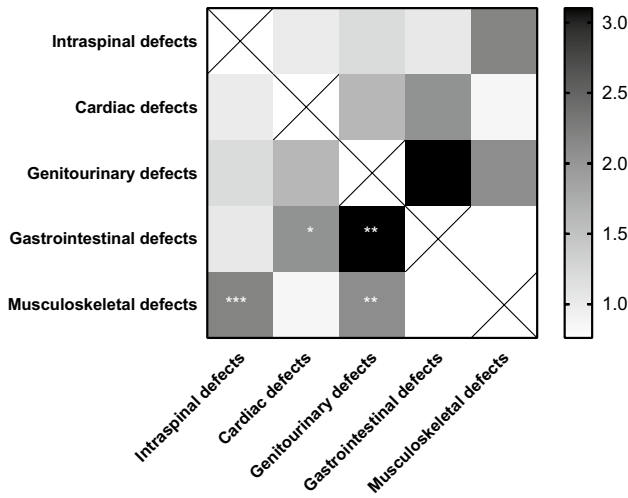


Fig. 3 Interrelationship of different associated anomalies. The depth of color refers to the odds ratio between two associated defects, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

scoliosis cases [9], and patients with perturbations in TBX6 dosage only present simple hemivertebrae/butterfly vertebrae at lower part of the spine and have very low incidences of intraspinal anomalies [23]. With the decrease of TBX6 expression, the spinal phenotype would become more severe [24]. As for CS types, compared with failure of formation, especially simple hemivertebrae, failure of segmentation and mixed defects are usually regarded as more severe spinal defects. Thus, we hypothesized that more severe genetic factors, such as chromosome aneuploidies, chromosomal deletion or insertion, and severe alteration of gene dosage, are associated with more severe spinal defects, including FS and MD, and higher incidence of other organ malformation, especially intraspinal defects. But this needs to be further studied and clarified.

Regarding the comparison between congenital scoliosis and idiopathic scoliosis, Johan et al. [25] systematically reviewed 8622 patients with idiopathic scoliosis (IS) in 51 studies and reported a 11.4% incidence of intraspinal defects with syrinx and Chiari malformation the most common. The author also reported intraspinal defect incidence of 16–21% in patients with early-onset scoliosis, which is higher than that in patients with late-onset scoliosis. Several other independent studies also reported the intraspinal defect incidences of 2% to 18% in IS population [26–29] and found that juvenile IS had higher incidences of intraspinal defects than adolescent IS (27% vs. 14%). The result that the incidence of intraspinal defects in patients with CS is higher than that in patients with IS but comparable to that in patients with EOS, including juvenile IS, suggests some similarities in pathogenic mechanism between CS and EOS, such as genetic factors or embryonic factors. But this hypothesis needs to be further clarified.

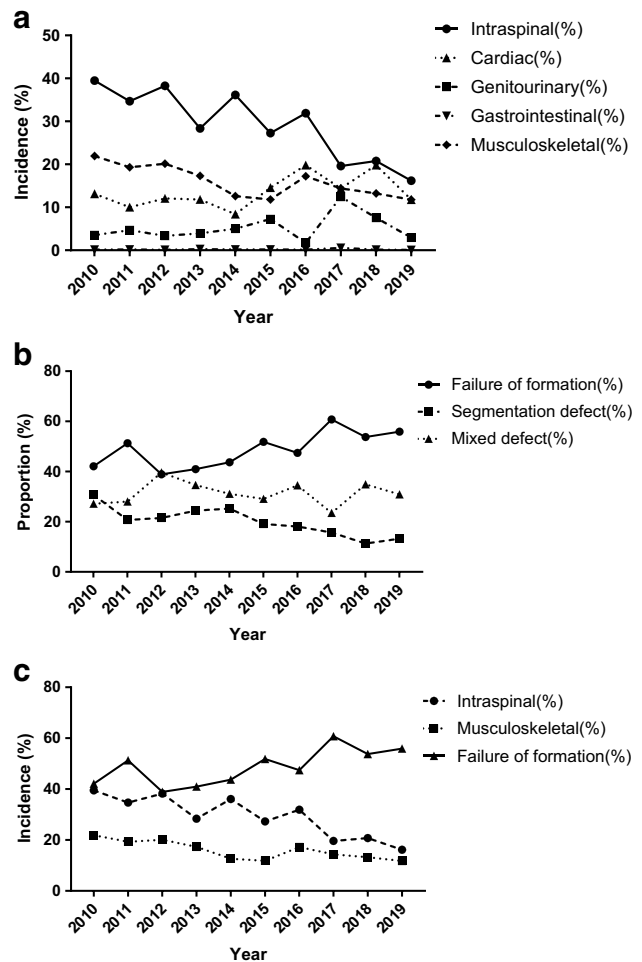


Fig. 4 Trends in incidences of different associated anomalies and vertebral anomaly types from 2010 to 2019, **a** Trends in incidences of different associated anomalies, **b** Trends in vertebral anomaly types from 2010 to 2019, **c** Association between trends in incidences of different associated anomalies and trends in vertebral anomaly types from 2010 to 2019

Apart from intraspinal anomalies, 442 patients (34.3%) had at least one associated anomaly in other organs. Cardiovascular defects were found to have an incidence of 13.7% in our study, which was within the range of early reports [7, 12, 13, 15, 17, 18]. The most frequently associated defect was valvular malformation, followed by atrial septal defect. This result was in line with Liu et al. [12] and Shen et al. [13] but inconsistent with Basu et al. [7] and Eliane et al. [17]. The incidences of atrial septal defect, ventricular septal defect, and patent ductus arteriosus were much lower in the Chinese population. We supposed that as China is still a developing country, patients with congenital heart disease from economically underdeveloped areas may prioritize treatment of heart disease; thus, they are unable to have their CS treated surgically due to economic burden.

The incidence of genitourinary defects (5.8%) was lower in our study than in previous studies [7, 11, 13, 17, 18]. In our hospital, urogenital ultrasound is a routine examination for CS patients, but intravenous pyelogram was an uncommon examination. As some defects of genitourinary system, such as duplex systems in the urogenital system, are hard to judge using ultrasound only, the incidence of genitourinary defects might be underestimated in our study. The most common genitourinary defects were single kidney and ectopic kidney. In our clinical practice, these genitourinary defects, such as unilateral kidney, seldom cause damage to renal function or require medical management in CS populations, and thus can only be found in routine screening using urinary ultrasound.

The frequency of gastrointestinal anomalies in our series (3.6%) was also lower in our study than previous studies [13, 17]. We supposed the reason was as follow. Most gastrointestinal anomalies reported in previous studies in Chinese population were hypersplenotrophy, which is not a clinically meaningful manifestation and cannot be distinguished with splenomegaly caused by other diseases. Apart from hypersplenotrophy, incidence of other gastrointestinal anomalies in our series was comparable to previous studies. In our clinical practice, patients suffering from anal or oesophagus atresia would come across relevant and severe gastrointestinal symptoms in fetal period and called for surgery as soon as possible.

Musculoskeletal anomalies (16.4%) were observed to have a higher incidence than in the report by Shen et al. (4.9%) [13]. However, in our study, most musculoskeletal anomalies were rib defects, which were not counted as musculoskeletal anomalies in their study. After excluding these rib defects, the incidence and distribution of musculoskeletal anomalies was comparable. CS individuals with rib defects tend to have more severe and progressive curves as rib defects lead to additional forces that cause extra deformities.

Regarding the interrelationship between other organ defects and sex, Ahmet et al. [18] reported no significant association between cardiac and renal defects and sex. This study expanded the analysis into more systems and observed a similar finding: none of the cardiovascular, genitourinary, or gastrointestinal defects was significantly associated with sex, although female patients did have a higher incidence of musculoskeletal defects.

In regard to the interrelationship between vertebral anomaly types and associated defects, patients with failure of segmentation or mixed defects were found to have a higher incidence of anomalies in other organs. Specifically, other than intraspinal defects, genitourinary, and musculoskeletal defects were found to have significantly higher incidences in patients with failure of segmentation and mixed defects. This significant interrelationship between associated anomalies

and vertebral anomaly types may indicate that patients with failure of segmentation or mixed failure had much greater embryonic injury [7], either genetic or environmental, in the development of the spine, which had a more serious influence on adjacent organs.

The significant interrelationship between intraspinal defects and musculoskeletal defects observed in our study has never been reported. In our series, most musculoskeletal defects were rib abnormalities such as fused rib or rib absence. The rib is an important component of the bony structure of the thorax, which is derived from somites in the early embryonic stage [30]. The same embryonic origin of the rib and vertebrae and the close correlation of the development of the notochord and somites might give rise to the strong interrelationship of vertebral anomalies, intraspinal defects, and musculoskeletal defects found in our study.

Another interesting finding regarding the interrelationship between different organ defects is that cardiovascular, genitourinary, and gastrointestinal defects were strongly interrelated with each other, which is a new discovery. This interrelationship among cardiac, genitourinary, and gastrointestinal defects might be explained by their germ layer origins and common developmental process. For example, the gastrointestinal system and urinary tract both originate from the endoderm, while the cardiovascular system, reproductive system, and kidney all derive from the mesoderm [31]. In addition, the studies on VACTERL association, the phenotype spectrum of which covers vertebral defects, anal atresia, cardiac defects, and renal defects, might provide some explanation for this interrelationship. The familial clustering phenomenon of VACTERL was found by Solomon et al. [32], suggesting a genetic role in its causality. Later, Hilger et al. [33] revealed *ZIC3* and *FOXF1* to be related to VACTERL association. These genetic factors also help to explain the interrelationship in our study. Certain signaling pathways might also be involved. TGF- β family signaling functions in the development of both the mesoderm and endoderm and thus has the potential to affect the normal morphogenesis of certain organs [34].

Furthermore, we found an obvious decrease in the incidences of intraspinal and musculoskeletal defects from 2010 to 2019. The distribution of vertebral anomaly types was also observed to change apparently during these ten years. In short, more patients with failure of formation and fewer patients with failure of segmentation were surgically treated in our center. This tendency might be explained by either the distribution shift of vertebral anomaly types in our population or the preference of patients in our hospital. As intraspinal and musculoskeletal defects were strongly associated with different vertebral anomaly types, the distribution shift of vertebral anomaly types might contribute to the decrease in their incidence. As expected, we noted a strong negative correlation between the tendency of the proportion of failure of formation and the trend of incidences of intraspinal and

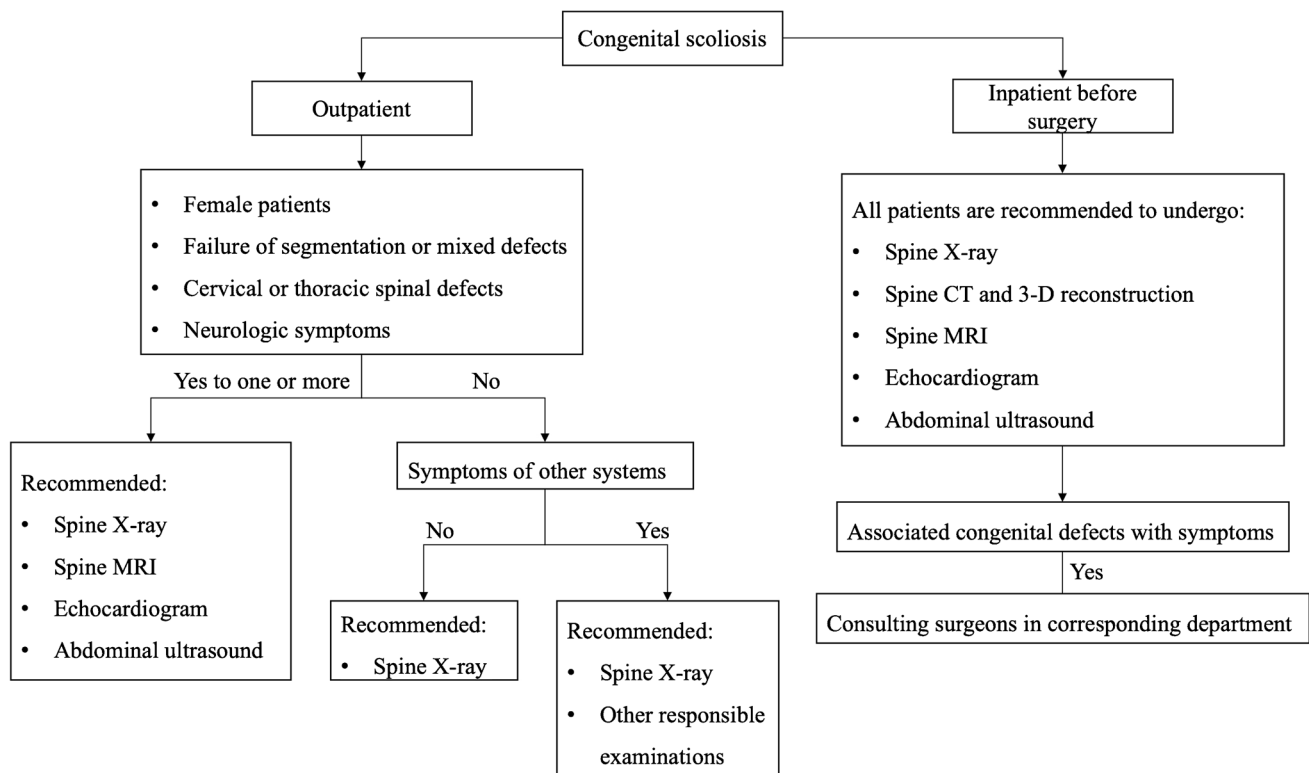


Fig. 5 Diagnostic algorithm

musculoskeletal defects (Fig. 4c). This result further demonstrated that patients with failure of formation could present with a lower incidence of intraspinal and musculoskeletal defects in a dynamic model.

Generally, our study has two major strengths. First, to our knowledge, this is one of the largest CS cohorts in the Chinese population. Second, we not only comprehensively analyzed the incidences and interrelationships but also first introduced the trends of vertebral anomaly types and all common associated anomalies in the last decade. However, as this is a retrospective study of extracted medical records, the quality and reliability of this study were largely influenced by the recorders, imaging interpreters and the medical record quality.

In a conclusion, our study found that associated anomalies, especially intraspinal anomalies, had much higher incidences in female patients (36.5% vs. 29.4% for intraspinal anomalies), patients with failure of segmentation (45.4% vs. 29.4%), and patients with mixed defects (40.5% vs. 29.4%). Thus, female sex, failure of segmentation, and mixed defects could be considered risk factors for CS patients, which deserves more attention from surgeons in medical management and prenatal consultation. Based on these results and our clinical experience, we recommended that a thorough screening for associated anomalies be performed for outpatients with one or more

risk factors and all inpatients before surgery (Fig. 5). However, as genetic factors may play a role, the incidences and interrelationship of specific associated anomalies might be discrepant in different ethnicities. Therefore, it is important to run similar studies to provide further clarification and comparison on such findings in different ethnicities.

Authors' contributions Conceptualization: Guanfeng Lin and Jianguo Zhang; methodology: Guanfeng Lin, Xiran Chai and Yang Yang; formal analysis and investigation: Guanfeng Lin, Xiran Chai; writing—original draft preparation: Guanfeng Lin, Xiran Chai; writing—review and editing: Guanfeng Lin, Xiran Chai, Shengru Wang, Yang Yang, Jianxiong Shen, and Jianguo Zhang; funding acquisition: Yang Yang, Shengru Wang, and Jianguo Zhang; resources: Jianxiong Shen, Jianguo Zhang; supervision: Jianguo Zhang.

Funding The study was supported by grants from National Natural Science Foundation of China (No. 81972037, 81902178), National Key Research & Development Program of China (No. 2017YFC1104902), Beijing Natural Science Foundation (No. L192015), Fundamental Research Funds for the Central Universities (No. 3332019021), and China Postdoctoral Science Foundation (No. 2020M670008ZX).

Declarations

Ethics approval Approval for the study was obtained from the ethics committee at Peking Union Medical College Hospital.

References

- Giampietro PF, Blank RD, Raggio CL et al (2003) Congenital and idiopathic scoliosis: clinical and genetic aspects. *Clin Med Res* 1(2):125–136. <https://doi.org/10.3121/cmr.1.2.125>
- Batra S, Ahuja S (2008) Congenital scoliosis: management and future directions. *Acta Orthop Belg* 74(2):147–160
- Giampietro PF, Raggio CL, Blank RD, McCarty C, Broeckel U, Pickart MA (2013) Clinical, genetic and environmental factors associated with congenital vertebral malformations. *Mol Syndromol* 4(1–2):94–105. <https://doi.org/10.1159/000345329>
- Li Z, Yu X, Shen J (2015) Environmental aspects of congenital scoliosis. *Environ Sci Pollut Res Int* 22(8):5751–5755. <https://doi.org/10.1007/s11356-015-4144-0>
- Chen Y, Liu Z, Chen J et al (2016) The genetic landscape and clinical implications of vertebral anomalies in VACTERL association. *J Med Genet* 53(7):431–437. <https://doi.org/10.1136/jmedgenet-2015-103554>
- Giampietro PF (2012) Genetic aspects of congenital and idiopathic scoliosis. *Scientifica (Cairo)* 2012:152365. <https://doi.org/10.6064/2012/152365>
- Basu PS, Elsebaie H, Noordeen MH (2002) Congenital spinal deformity: a comprehensive assessment at presentation. *Spine (Phila Pa 1976)* 27(20):2255–2259. <https://doi.org/10.1097/00007632-200210150-00014>
- Hensinger RN (2009) Congenital scoliosis: etiology and associations. *Spine (Phila Pa 1976)* 34(17):1745–1750. <https://doi.org/10.1097/BRS.0b013e3181abf69e>
- Wu N, Ming X, Xiao J, Wu Z et al (2015) TBX6 null variants and a common hypomorphic allele in congenital scoliosis. *N Engl J Med* 372(4):341–350. <https://doi.org/10.1056/NEJMoa1406829>
- Beals RK, Robbins JR, Rolfe B (1993) Anomalies associated with vertebral malformations. *Spine (Phila Pa 1976)* 18(10):1329–1332. <https://doi.org/10.1097/00007632-199308000-00012>
- Rai AS, Taylor TK, Smith GH, Cumming RG, Plunkett-Cole M (2002) Congenital abnormalities of the urogenital tract in association with congenital vertebral malformations. *J Bone Joint Surg Br* 84(6):891–895. <https://doi.org/10.1302/0301-620x.84b6.11814>
- Liu YT, Guo LL, Tian Z, Zhu WL, Yu B, Zhang SY, Qiu GX (2011) A retrospective study of congenital scoliosis and associated cardiac and intraspinal abnormalities in a Chinese population. *Eur Spine J* 20(12):2111–2114. <https://doi.org/10.1007/s00586-011-1818-2>
- Shen J, Wang Z, Liu J, Xue X, Qiu G (2013) Abnormalities associated with congenital scoliosis: a retrospective study of 226 Chinese surgical cases. *Spine (Phila Pa 1976)* 38(10):814–818. <https://doi.org/10.1097/BRS.0b013e31827ed125>
- Ghandhari H, Tari HV, Ameri E, Safari MB, Fouladi DF (2015) Vertebral, rib, and intraspinal anomalies in congenital scoliosis: a study on 202 Caucasians. *Eur Spine J* 24(7):1510–1521. <https://doi.org/10.1007/s00586-015-3833-1>
- Bozcali E, Ucpunar H, Sevcen A, Balioglu MB, Albayrak A, Polat V (2016) A retrospective study of congenital cardiac abnormality associated with scoliosis. *Asian Spine J* 10(2):226–230. <https://doi.org/10.4184/asj.2016.10.2.226>
- Gupta N, Rajasekaran S, Balamurali G, Shetty A (2016) Vertebral and intraspinal anomalies in Indian population with congenital scoliosis: a study of 119 consecutive patients. *Asian Spine J* 10(2):276–281. <https://doi.org/10.4184/asj.2016.10.2.276>
- Beauregard-Lacroix E, Tardif J, Camurri MV et al (2017) Retrospective analysis of congenital scoliosis: associated anomalies and genetic diagnoses. *Spine (Phila Pa 1976)* 42(14):E841–E847. <https://doi.org/10.1097/BRS.0000000000001983>
- Sevcen A, Misir A, Ucpunar H, Balioglu MB, Gur V, Akinci S (2019) The incidence and interrelationship of concomitant anomalies in congenital scoliosis. *Turk Neurosurg* 29(3):404–408. <https://doi.org/10.5137/1019-5149.JTN.24429-18.2>
- Mohanty SP, Pai Kanhangad M, Narayana Kurup JK, Saiffudeen S (2020) Vertebral, intraspinal and other organ anomalies in congenital scoliosis. *Eur Spine J* 29(10):2449–2456. <https://doi.org/10.1007/s00586-020-06450-3>
- McMaster MJ, Ohtsuka K (1982) The natural history of congenital scoliosis. A study of two hundred and fifty-one patients. *J Bone Joint Surg Am* 64(8):1128–47
- Winter RB, Moe JH, Wang JF (1973) Congenital kyphosis. Its natural history and treatment as observed in a study of one hundred and thirty patients. *J Bone Joint Surg Am* 55(2):223–256
- Lemire GT, Beauregard-Lacroix E, Campeau PM et al (2020) Retrospective analysis of fetal vertebral defects: associated anomalies, etiologies, and outcome. *Am J Med Genet A* 182(4):664–672. <https://doi.org/10.1002/ajmg.a.61468>
- Liu J, Wu N, Deciphering Disorders Involving S, study CO, Yang N et al (2019) TBX6-associated congenital scoliosis (TACS) as a clinically distinguishable subtype of congenital scoliosis: further evidence supporting the compound inheritance and TBX6 gene dosage model. *Genet Med* 21(7):1548–1558. <https://doi.org/10.1038/s41436-018-0377-x>
- Chen W, Lin J, Wang L, Li X, Zhao S et al (2020) TBX6 missense variants expand the mutational spectrum in a non-Mendelian inheritance disease. *Hum Mutat* 41(1):182–195. <https://doi.org/10.1002/humu.23907>
- Heemskerk JL, Kruyt MC, Colo D, Castelein RM, Kempen DHR (2018) Prevalence and risk factors for neural axis anomalies in idiopathic scoliosis: a systematic review. *Spine J* 18(7):1261–1271. <https://doi.org/10.1016/j.spinee.2018.02.013>
- Winter RB, Lonstein JE, Heithoff KB, Kirkham JA (1997) Magnetic resonance imaging evaluation of the adolescent patient with idiopathic scoliosis before spinal instrumentation and fusion. A prospective, double-blinded study of 140 patients. *Spine (Phila Pa 1976)* 22(8):855–858. <https://doi.org/10.1097/00007632-199704150-00005>
- Do T, Frasc C, Burke S, Widmann RF, Rawlins B, Boachie-Adjei O (2001) Clinical value of routine preoperative magnetic resonance imaging in adolescent idiopathic scoliosis. A prospective study of three hundred and twenty-seven patients. *J Bone Joint Surg Am* 83(4):577–579. <https://doi.org/10.2106/00004623-200104000-00014>
- Inoue M, Minami S, Nakata Y et al (2005) Preoperative MRI analysis of patients with idiopathic scoliosis: a prospective study. *Spine (Phila Pa 1976)* 30(1):108–114. <https://doi.org/10.1097/01.brs.0000149075.96242.0e>
- Rajasekaran S, Kamath V, Kiran R, Shetty AP (2010) Intraspinal anomalies in scoliosis: an MRI analysis of 177 consecutive scoliosis patients. *Indian J Orthop* 44(1):57–63. <https://doi.org/10.4103/0019-5413.58607>
- Kaplan KM, Spivak JM, Bendo JA (2005) Embryology of the spine and associated congenital abnormalities. *Spine J* 5(5):564–576. <https://doi.org/10.1016/j.spinee.2004.10.044>
- Kiecker C, Bates T, Bell E (2016) Molecular specification of germ layers in vertebrate embryos. *Cell Mol Life Sci* 73(5):923–947. <https://doi.org/10.1007/s00018-015-2092-y>

32. Solomon BD, Pineda-Alvarez DE, Raam MS, Cummings DA (2010) Evidence for inheritance in patients with VACTERL association. *Hum Genet* 127(6):731–733. <https://doi.org/10.1007/s00439-010-0814-7>
33. Hilger AC, Halbritter J, Pennimpede T et al (2015) Targeted resequencing of 29 candidate genes and mouse expression studies implicate ZIC3 and FOXF1 in human VATER/VACTERL association. *Hum Mutat* 36(12):1150–1154. <https://doi.org/10.1002/humu.22859>
34. Zinski J, Tajer B, Mullins MC (2018) TGF-beta family signaling in early vertebrate development. *Cold Spring Harb Perspect Biol* 10 (6).<https://doi.org/10.1101/cshperspect.a033274>

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.