


## ORIGINAL ARTICLE

# Clinical phenotypes study of 231 children with Williams syndrome in China: A single-center retrospective study

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## Abstract

**Background:** Williams syndrome (WS) is a multisystem neurodevelopmental disorder caused by microdeletions in 7q11.23. This study aims to characterize the clinical phenotypes of Chinese children with WS to help for the early diagnosis and intervention of this disease.

**Methods:** 231 children diagnosed with WS were retrospectively recruited to the study. Clinical data were analyzed to obtain the incidence of different clinical phenotypes. The occurrence of phenotypes and the influence of gender and age on the incidence of different phenotypes were analyzed.

**Results:** All WS exhibited facial dysmorphism (100.0%). The majority had neurodevelopmental disorder (91.8%), hoarseness (87.4%) and cardiovascular anomalies (85.7%). The incidence of short stature (46.9%), inguinal hernia (47.2%), hypercalciuria (29.10%), hypercalcemia (9.1%), subclinical hypothyroidism (26.4%) and hypothyroidism (7.4%) were relatively higher. Gender differences were found in supravalvular aortic stenosis (SVAS,  $p < .001$ ), ventricular septal defect (VSD,  $p < .05$ ), inguinal hernia ( $p < .001$ ), superior pulmonary stenosis (SVPS,  $p < .05$ ) and neurodevelopmental disorder ( $p < .05$ ). The incidence of neurodevelopmental disorder in WS increased with age ( $p < .05$ ) while cardiovascular

Fang-fang Li and Wei-jun Chen contributed equally to this manuscript.

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anomalies ( $p < .001$ ), short stature ( $p < .001$ ), hypercalciuria ( $p < .001$ ) and hypercalcemia ( $p < .01$ ) decreased with age.

**Conclusions:** Facial dysmorphism, neurodevelopmental disorder, hoarseness and cardiovascular anomalies were the most common phenotypes. Genetic testing should be suggested to confirm the diagnosis for children with the above abnormalities. Gender and age should be taken into account when making diagnosis and intervention.

#### KEYWORDS

age, children, clinical phenotype, gender, Williams syndrome

## 1 | INTRODUCTION

Williams syndrome (WS, OMIM#194050), also known as Williams-Beuren syndrome, is a rare gene microdeletion disorder with variable clinical phenotypes. The incidence of WS is 1/7500–1/20,000 in living birth (Meyer-Lindenberg et al., 2006). The typically contiguous deletion of 26–28 genes in the 7q11.23 of WS leading to a series of clinical phenotypes which include facial dysmorphisms known as “elfin face”, cardiovascular anomalies, connective tissue abnormalities, neurodevelopmental disorder, short stature, hearing loss, hypercalcemia and so on, mostly last for a lifetime (Poher, 2010). These phenotypes vary from person to person and cause a lot of troubles. Incidence of sudden death in individuals with WS is 25–100-fold higher compared to the age-matched normal population (Wessel et al., 2004). Neurodevelopmental disorder leads to learning problems, poor adaptability and employment difficulties. Almost all children with WS require multiple visits to the healthcare system for medical or surgical problems, which create huge financial and emotional burden on the individuals with WS and their families. The quality of the patients' life was reduced and only <10% adults with WS live independently (Howlin & Udwin, 2006).

It has been 60 years since WS was first reported by William and Buren (Kozel et al., 2021). Various clinical phenotypes have been well described in individuals with WS from European (Kruszka et al., 2018) and North American (American Academy of Pediatrics, 2001). In China, many clinicians are not familiar with the syndrome, which easily leads to inappropriate medical intervention. Doctors in primary hospitals may suggest increasing calcium and vitamin D intake for children with WS facing short stature, which unexpectedly increasing the risk of hypercalcemia. WS correlated researches started late in China and there were only limited and small sample reports (Yau et al., 2004). In

this study, we conduct a single-center retrospective study to characterize the clinical features of children with WS in China to help clinicians to know more about this disease and strive to alleviate complications and improve the quality of life in these patients and their families.

## 2 | METHODS

### 2.1 | Patients

Children diagnosed with WS in department of child health care of the Children's Hospital Affiliated to Zhejiang University School of Medicine were retrospectively recruited to the study between May 2001 and July 2021. The inclusion criteria required the subjects to have microdeletion in the gene 7q11.23 or clinical symptoms consistent with lowery score (Lowery et al., 1995). Patients with only *ELN* gene deletion, patients or family members refused to sign the informed consent, patients with insufficient birth information or clinical records were excluded.

### 2.2 | Data collection

Clinical data including demographics, family history, genetic test results and disease information were extracted from medical records. The incidence of phenotypes was calculated. These children were divided into four groups based on age: <1 years old (infancy), 1 to 2 years old (early childhood), 3 to 5 years old (preschool age), and  $\geq 6$  years old (school age). Written informed consent was obtained from the legal representative (relatives and/or guardians) of each study participant and this study was approved by the Ethics Committee of the Children's Hospital Affiliated to Zhejiang University School of Medicine (NO. 2019-IBR-122).

## 2.3 | Data analysis

The data were imported into SPSS version 21.0 software (SPSS Inc, Chicago, IL, USA) for analysis. Data conforming to normal distribution were expressed as mean  $\pm$  standard deviation (*SD*). Quantitative data were expressed as the median and interquartile range (IQR 25th–75th) or number with percentage when appropriate. Descriptive analysis was conducted to analyze the general characteristics of the patients. Chi-square, Mann–Whitney test or independent sample *T* test was used to compare sex differences. The trend of phenotype incidence with age were analyzed by binary logistic regression. *p* values < .05 were considered as statistically significant.

## 3 | RESULTS

### 3.1 | General characteristics of population

A total of 323 cases met the inclusion criteria, 92 cases were excluded due to insufficient data. 231 subjects were enrolled in the study, with 131 males (56.7%) and 100 females (43.3%). The median gestational age were 39 weeks (range 31.0–42.7 weeks), 24 were premature (10.4%), birth weight were  $2687.6 \pm 520.3$  grams and 114 (49.4%) were small for gestational age (SGA). The median age at diagnosis was 1.8 years old (range 0.1–10.3 years old). The birth weight of male was significantly higher than female ( $T = 2.39, p = .018$ ). There was no statistically significant difference in the remaining basic information among different genders ( $p > .05$ ) (Table 1).

**TABLE 1** Comparison of basic information between male and female

	Male	Female	Z/T/ $\chi^2$	<i>p</i> value
Age at diagnosis, y	1.8 (0.8–3.7)	1.9 (1.1–3.9)	–1.30	.195
Gestational age, w	$39.1 \pm 1.9$	$38.8 \pm 2.1$	1.06	.291
Premature, %	9.2%	14.0%	1.33	.249
Birth weight, g	$2758.1 \pm 527.0$	$2594.2 \pm 498.7$	2.39	<b>.018</b>
SGA, %	51.1%	47.0%	0.39	.532

Bold values indicate statistically significant.

**TABLE 2** Differences in age at diagnosis in children with WS in different years of birth

Year of birth	Number	Age at diagnosis, y	$\chi^2$	<i>p</i> value
≤2010	25	8.3 (6.5–9.8)	90.59	<.001
2011–2015	72	3.5 (1.5–5.6)*		
≥2016	134	1.2 (0.6–1.9)**		

\*  $p < .001$  when compare with birth year ≤2010; \*\*  $p < .001$  when compare with birth year within 2011–2015.

130 patients were diagnosed by chromosomal microarray analysis (CMA), 25 were diagnosed by multiplex ligation-dependent probe amplification (MLPA), 17 were diagnosed by whole exome sequencing (WES), 9 were diagnosed by fluorescence in situ hybridization (FISH), 50 refused genetic test but their phenotypes conformed to the WS diagnostic score (American Academy of Pediatrics, 2001). The diagnosis age difference was found in patients with different years of birth ( $\chi^2 = 90.59, p < .001$ ), which showed that the age at diagnosis was gradually decreasing (Table 2).

### 3.2 | The incidence of clinical phenotypes

The most common phenotypes of WS were facial dysmorphism (100.0%), neurodevelopmental disorder (91.8%), hoarseness (87.4%) and cardiovascular anomalies (85.7%) {SVAS (70.1%), SVPS (18.6%), PPS (35.5%), VSD (7.4%)}. The incidence of inguinal hernia (47.2%), short stature (45.9%), hearing loss (19.9%), hypercalcemia (29.1%), subclinical hypothyroidism (26.4%), hypercalcemia (9.5%) and hypothyroidism (7.4%) were relatively higher among general children. The incidence of SVAS ( $\chi^2 = 10.43, p < .001$ ) and inguinal hernia ( $\chi^2 = 14.24, p < .001$ ) was higher in male while the incidence of VSD was higher in female ( $\chi^2 = 5.57, p = .018$ ) (Table 3).

### 3.3 | The incidence of phenotypes varied with age

In this part, we explore the incidence of phenotypes changed with age groups by using binary logistic analysis. The incidence of neurodevelopmental disorder increased

TABLE 3 Clinical phenotypes in children with WS

Clinical phenotypes	Incidence		Male		Female	
	Number	%	Number	%	Number	%
Facial dysmorphisms	231/231	100.0%	131/131	100.0%	98/100	100.0%
Neurodevelopmental disorder	167/182	91.8%	98/107	91.6%	67/75	89.3%
Hoarseness	201/231	87.4%	112/131	85.5%	89/100	89.0%
Cardiovascular anomalies	198/231	85.7%	114/131	87.0%	84/100	84.0%
SVAS	162/231	70.1%	<b>103/131</b>	<b>78.6%</b>	<b>59/100</b>	<b>59.0%**</b>
SVPS	43/231	18.6%	24/131	18.3%	19/100	19.0%
PPS	82/231	35.5%	50/131	38.2%	32/100	32.0%
VSD	17/231	7.4%	<b>5/131</b>	<b>3.8%</b>	<b>12/100</b>	<b>12.0%*</b>
Inguinal hernia	109/231	47.2%	<b>76/131</b>	<b>58.0%</b>	<b>33/100</b>	<b>33.0%**</b>
Short stature	106/231	45.9%	65/131	49.6%	41/100	41.0%
Hearing loss	34/171	19.9%	20/92	21.7%	14/79	17.7%
Hypercalciuria	55/231	29.1%	35/109	32.1%	20/80	25.0%
Subclinical hypothyroidism	61/231	26.4%	33/131	25.2%	28/100	28.0%
Hypercalcemia	22/231	9.5%	12/131	9.2%	10/100	10.0%
Hypothyroidism	17/231	7.4%	11/131	8.4%	6/100	6.0%

Bold values indicate statistically significant.

\* $p < .05$  when compared with male; \*\* $p < .001$  when compared with male.

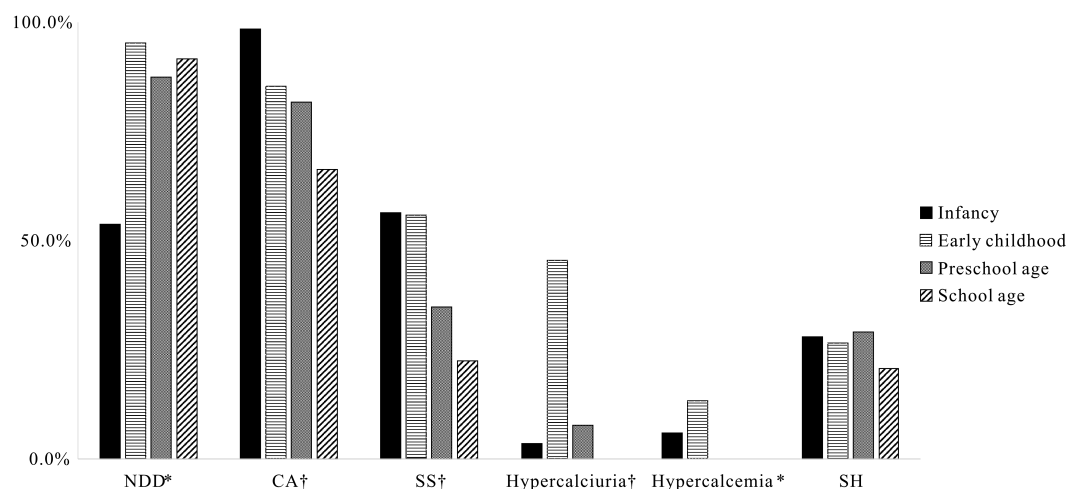


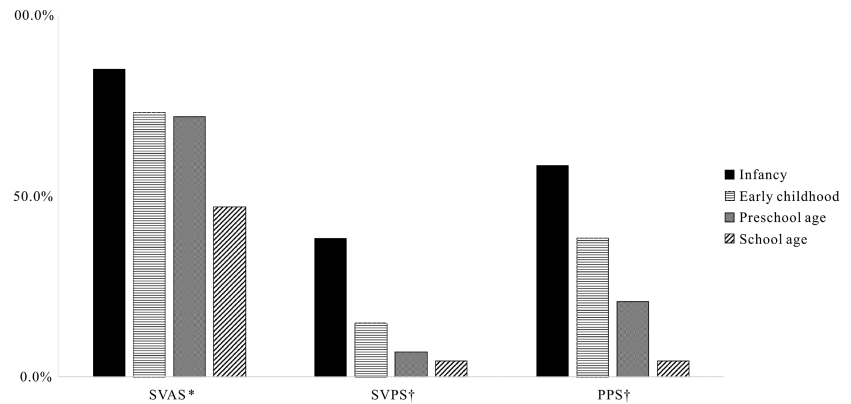
FIGURE 1 The incidence of phenotypes in different age groups. NDD, neurodevelopmental disorder, CA, cardiovascular anomalies, SS, short stature, SH, subclinical hypothyroidism; \* $p < .05$  when the phenotypes change with age were analyzed, † $p < .001$  when the phenotypes change with age were analyzed.

with age ( $p = .013$ ); The incidence of cardiovascular anomalies decreased with age ( $p < .001$ ), including SVAS ( $p = .040$ ), SVPS ( $p < .001$ ), PPS ( $p < .001$ ); The incidence of short stature and hypercalciuria decreased with age ( $p < .001$ ); The incidence of hypercalcemia decreased with age ( $p = .001$ ). However, this study did not show the effect of increasing age on the incidence of subclinical hypothyroidism ( $p = .475$ ) (Figures 1 and 2).

### 3.4 | Gender differences of phenotype incidences in different age groups

Gender differences were found in the incidence of part of phenotypes in different age groups. The incidence of neurodevelopmental disorder was higher in male in school age ( $\chi^2 = 6.11$ ,  $p = .013$ ), the incidence of SVAS was higher in male in preschool age ( $\chi^2 = 13.26$ ,  $p < .001$ ),

**FIGURE 2** The incidence of phenotypes of heart in different age groups. \* $p < .05$  when the phenotypes change with age were analyzed, † $p < .001$  when the phenotypes change with age were analyzed.



the incidence of SVPS was higher in female in infancy ( $\chi^2 = 4.50$ ,  $p = .034$ ). There were no gender differences in the remaining phenotypes in different age groups ( $p > .05$ ) (Figures 3 and 4).

## 4 | DISCUSSION

This study included large sample of Chinese children with WS. It showed the improvement of clinical diagnosis level and genetic testing technology in China as the age at diagnosis decreased with the birth year and most patients were diagnosed by CMA. Although the incidence of clinical phenotypes of WS like facial dysmorphism, cardiovascular anomalies, hoarseness, inguinal hernia, short stature, hypercalciuria, subclinical hypothyroidism, hypercalcemia were consistent with previous reports (de Sousa Lima Strafacci et al., 2020; Ferrero et al., 2007; Honjo et al., 2015; Kim et al., 2016; Morris et al., 2020; Stanley et al., 2021). This study still got some interesting results.

### 4.1 | Cardiovascular anomalies

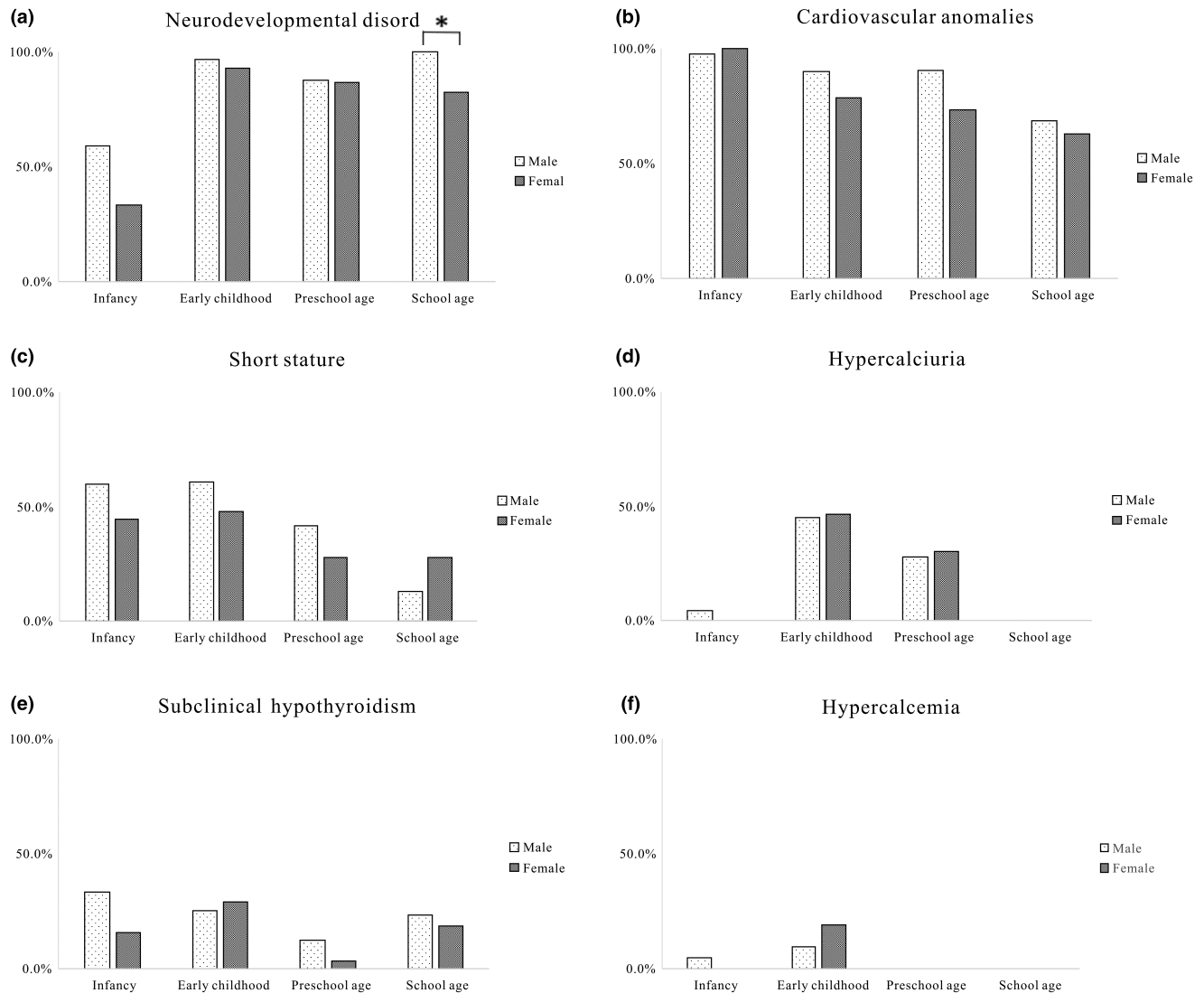
Cardiovascular anomalies, particularly SVAS, was usually the main reason for patients' visits (Pober et al., 2008). The cause of SVAS was often attributed to *ELN* deletion, which has been verified in animal studies (Li et al., 1998) and familial SVAS syndrome (Eisenberg et al., 1964). Different diagnostic criteria for supravalvular stenosis were adopted by different researchers in the past, resulted in a wide range of incidence of SVAS and PS, ranging from 35%–86% (Collins 2nd, 2018; Fricke et al., 2015) and 12%–61% (Collins 2nd, 2018; Collins 2nd et al., 2010), respectively. Reference criteria for diagnosis of supravalvular stenosis in this study were got from ACC/AHA guideline for the management of patients with valvular heart disease (Writing Committee Members et al., 2021) combined

with the literature on the high influence factor of WS with arterial stenosis (Nugent et al., 1977), more accurate conclusions could be obtained.

In this study, SVAS was the most common cardiac phenotype, followed by PPS and SVPS. The difference in gender in this study were different from the clinical impression that WS had no sex difference. SVAS and VSD incidence difference in gender were used reported (Amel-Shahbaz et al., 2014; Sadler et al., 2001). Female also showed a comparative advantage in other heart diseases such as myocardial injury and prognosis of some heart diseases (Kanwar & Stehlik, 2020). The effects of estrogen on vascular and cardiac cells may play a role in these differences. The higher incidence of SVPS in female in infancy may be due to insufficient number of cases, since there was no higher incidence of SVPS in female overall. By the way, this study found that the proportion of cardiovascular anomalies decreased with age, consistent with previous report that most WS do not require intervention during long-term follow-up, and the overall mortality has been low (Collins et al., 2010). It still requires vigilance that although with no statistically significant, the incidence of SVAS in male tended to rise before 5 years old, leading to a significant difference in the incidence of SVAS in gender in preschool age group. This study provided important prognostic information for WS in cardiac phenotype. Cardiac surgeries for children with WS should be treated with caution for the possibility of remission and regular monitoring of cardiac ultrasound is necessary.

### 4.2 | Neurodevelopmental disorder

The neurodevelopmental disorder in WS was expressed as poor motor development in infancy, global developmental delay before 5 years old and intellectual disability later. The Wechsler intelligence test was often used to evaluate the neurodevelopmental status of WS and the IQ was reported around 50–60, kept stable at least to mid-adulthood



**FIGURE 3** The incidence of phenotypes in male and female in different age groups. (a–f) The incidence of neurodevelopmental disorder, cardiovascular anomalies, short stature, hypercalciuria, subclinical hypothyroidism and hypercalcemia in male and female in different age groups, respectively. \* $p < .05$  when comparing gender difference.

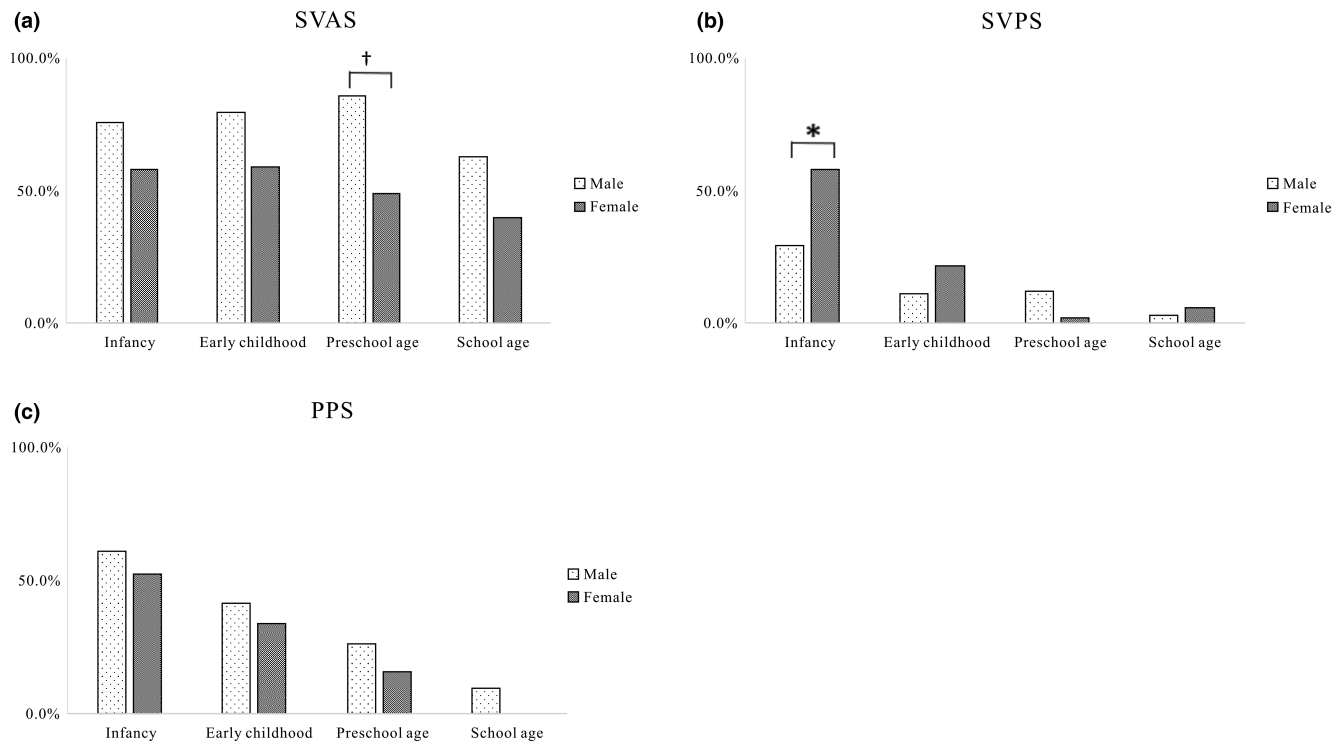
(Mervis & Pitts, 2015). These were thought to be associated with gene deletions. *FZD9* null mutants exhibit defects in learning and memory, reflecting hippocampus functional deficits (Zhao & Pleasure, 2005). *GTF2I* deletion was also significant while family members with the *GTF2I* duplication had intellectual disability, whereas the members with usual two copies of *GTF2I* had average intelligence (Pinelli et al., 2020). And *HIP1* deletion was associated with more severe intellectual disability (Fusco et al., 2014).

In this study, 91.8% WS were found with neurodevelopmental disorder. The incidence was relatively lower in the infancy group and increased with age, illustrating normal neurocognitive performance in the first year of children with WS may not be sustained thereafter. The lower incidence in school age female may due to

the limited number of cases, while no gender difference was found overall, and the IQ difference in gender was not apparent in previous reports (Royston et al., 2019). Cognitive uniqueness of WS was highlighted and individual assessment and management of individuals with WS were suggested. Appropriate parental expectations, behavior norms and mastery motivation in early stage may improve the adaptive behavior and academic performance of WS.

### 4.3 | Short stature

Short stature was common in WS, caused by heart disease, feeding difficulties, gastrointestinal diseases and



**FIGURE 4** The incidence of heart phenotypes in male and female in different age groups. (a–c) The incidence of SVAS, SVPS and PPS in male and female in different age groups, respectively. \* $p < .05$  when comparing gender difference; † $p < .001$  when comparing gender difference.

hypothyroidism (de Sousa Lima Strafacci et al., 2020). Once the diagnosis was made, WS-specific growth charts are available for plotting children's expected growth (Martin et al., 2007). In this study, the incidence of short stature was 45.9% and decreased with age. As it was mentioned earlier, 49.4% of WS was SGA at birth which anticipated its later stature. The weight advantage in male at birth has not been maintained. The incidence of short stature decreased with age may due to the timely remission of disease and proper nutritional supplementation. Although the use of growth hormone is not routinely recommended, it was still effective in WS with growth hormone deficiency.

#### 4.4 | Hearing loss

It was reported that 63% of children with WS had hearing loss (Marler et al., 2010). Gene deletion may play an important part in the auditory mechanisms (Silva et al., 2018). *GTF2IRD1* knockout mice showed impaired cochlear function. *LIMK1* deficiency results in reduced electrical motility of outer hair cells in cochlea. *ELN* deficiency may lead to abnormalities in the function of the middle ear system. The incidence of hearing loss in this study was lower than it was reported, which may be related to the younger

age of the subjects. Since the degree of hearing loss in WS increasing with age (Silva et al., 2018), it was necessary to follow up closely.

#### 4.5 | Inguinal hernia

Individuals with WS may have connective tissue disorder which made them prone to develop inguinal hernia. *ELN* deficiency may play an important part in this condition. In this study, nearly half of the patients had inguinal hernia, higher than it was reported, with 76 males and 33 females. Among them, 45% had hernia repairs surgery (40 males, 9 females), 5 children (4males, 1female) had more than two hernia repairs experience. Males were more likely to need repair surgery. While Burcharth found that female is one of risk factors for recurrence after inguinal hernia surgery (Burcharth, 2014), which seem to be inconsistent with what happens in children with WS. It indicates that inguinal hernia in WS has certain uniqueness.

#### 4.6 | Endocrine abnormality

Thyroid dysfunction due to defects in thyroid morphology was often reported in WS. Allegri reported that

*BAZ1B* deletion was involved in the thyroid developmental defects observed in part of WS patients and that some of these effects are putatively due to *PTEN* overexpression (Allegrì et al., 2020) (a phosphatase known to be involved in cell proliferation and apoptosis regulation, *PTEN* mRNA and protein levels increased when *BAZ1B* was silenced). Our team found that age under 6 years and existing thyroid abnormalities are risk factors for subclinical hypothyroidism (Chen et al., 2017). In this study, the sample size was enlarged and consistent rates of subclinical hypothyroidism and slightly higher rates of hypothyroidism were obtained. Yet now this study did not find the incidence of subclinical hypothyroidism decreased with age. This may relate to the diagnostic criteria in this study, since patients were recognized as having a positive result once in a certain age group. Interestingly, no thyroid dysfunction was found in patients with near adult in our group. It seems that age was still an important factor in thyroid function, but longer time window is needed to be validation.

Clinically actionable hypercalcemia in WS appears to be uncommon. Some patients with hypercalcemia are irritable and show poor oral intake, most cases were detected incidentally by laboratory testing. To date, no study has identified a definitive cause for hypercalcemia in WS, although a combination of endocrine, gut, and renal abnormalities had been reported. The *WSTF* gene deletion may play a role while serum calcium levels were increased in mice with inadequate *WSTF* gene expression (Kitagawa et al., 2011). In current study, the incidence of hypercalciuria and hypercalcemia decrease with age to even 0% in school and preschool age, respectively. Indicating that the occurrence of this symptom is mainly concentrated in a certain time window, and the prevention of high calcium in this time period should be focused.

## 5 | LIMITATIONS

This study was a retrospective study and many clinical data were not collected prospectively. 92 samples were excluded from 323 because records established earlier than 2010 were difficult to verify, which was a big pity. Cardiovascular anomalies diagnosed based on echocardiography results alone was still a limitation. Other phenotypes such as hypertension, diabetes, bowel problems, prematurely gray hair, early puberty, musculoskeletal anomalies like joint stiffness and scoliosis were more frequently happening in the older individuals with WS (Elison et al., 2010). The subjects in this study were relatively younger, so it was difficult to observe

the changes of disease spectrum throughout childhood. These are all areas that we will continue to track in the future.

## 6 | CONCLUSIONS

Our study is the first large sample research to describe the clinical phenotypes of children with WS in China. The results are similar to those reported in the European and North American population. For children with facial dysmorphism, neurodevelopmental disorder, hoarseness and cardiovascular anomalies, genetic testing should be suggested to confirm the diagnosis. Therefore, gender and age should be taken into account when making diagnosis and intervention. Regular physical examination, reasonable nutrition intake, early rehabilitation training and other targeted interventions should be taken to reduce the incidence of phenotypes to improve the quality of life in individuals with WS.

## AUTHOR CONTRIBUTIONS

Chai Ji conceptualized and designed the study, interpreted the data, reviewed and revised the manuscript for important intellectual content. Fang-fang Li and Wei-jun Chen collected the data, conducted the analysis, interpreted the data, drafted the initial manuscript, and revised the manuscript. Dan Yao, Lin Xu, Yan Zeng and Ji-yang Shen collected data and carried out the initial analyses and contributed to the important revision of the manuscript. Zhuo Shi, Xiao-wei Ye, Dao-huan Kang, Bin Xu and Jie Shao conceptualized and designed the study, reviewed and revised the manuscript for important intellectual content. All authors: approved the final content of the manuscript.

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## CONFLICT OF INTEREST

No financial have been received or will be received from any party related directly or indirectly to the subject of this article.



**DATA AVAILABILITY STATEMENT**

the datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

**ETHICS STATEMENT**

the study was approved by the Ethics Committee of the Children's Hospital Affiliated to Zhejiang University School of Medicine (NO. 2019-IBR-122).

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