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

Fang-fang Li1 | Wei-jun Chen1 | Dan Yao1 | Lin Xu1 | Ji-yang Shen1 | Yan Zeng1 | Zhuo Shi2 | Xiao-wei Ye3 | Dao-huan Kang4 | Bin Xu5 | Jie Shao1 | Chai Ji1

1Department of Child Health Care, The Children's Hospital, Zhejiang University School of Medicine, National Clinical Research Center for Child Health, Hangzhou, China
2Department of Pediatric Cardio-Thoracic Surgery, The Children's Hospital, Zhejiang University School of Medicine, National Clinical Research Center for Child Health, Hangzhou, China
3Department of Stomatology, The Children's Hospital, Zhejiang University School of Medicine, National Clinical Research Center for Child Health, Hangzhou, China
4Department of Ophthalmology, The Children's Hospital, Zhejiang University School of Medicine, National Clinical Research Center for Child Health, Hangzhou, China
5Department of Otorhinolaryngology-head and Neck Surgery, The Children's Hospital, Zhejiang University School of Medicine, National Clinical Research Center for Child Health, Hangzhou, China

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 (29.1%), 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

Correspondence
Chai Ji, The Children's Hospital, Zhejiang University School of Medicine, 57 Zhugan Xiang Road, Hangzhou, Zhejiang 310003, China. Email: 6198011@zju.edu.cn

Funding information
Foundation of the Education of Zhejiang Province, Grant/Award Number: Y201839556; Medical Science and Technology Project of Zhejiang Province, Grant/Award Number: 2021LY185; National Clinical Research Center for Child Health, Grant/Award Number: G20C0005; Natural Science Foundation of Zhejiang Province, Grant/Award Number: LQ19H090016
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 (Pober, 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 ≥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 ± 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 ± 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).

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 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 (χ² = 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 (χ² = 10.43, p < .001) and inguinal hernia (χ² = 14.24, p < .001) was higher in male while the incidence of VSD was higher in female (χ² = 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

| Year of birth | Number | Age at diagnosis, y | χ² | p 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.
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 ($\chi^2 = 13.26, p < .001$),
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, hypercalciemia 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.
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...
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 (Allegri 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.

ACKNOWLEDGEMENTS

We would like to thank all the patients and their families for their consent and support.

FUNDING INFORMATION

the study was supported by the National Clinical Research Center for Child Health (G20C0005), Natural Science Foundation of Zhejiang Province (LQ19H090016), Foundation of the Education of Zhejiang Province (Y201839556) and Medical Science and Technology Project of Zhejiang Province (2021KY185).

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).

ORCID
Fang-fang Li  https://orcid.org/0000-0002-5217-0728

REFERENCES
Allegri, L., Baldan, F., Mio, C., De Felice, M., Amendola, E., & Damante, G. (2020). BAZ1B is a candidate gene responsible for hypothyroidism in Williams syndrome. *European Journal of Medical Genetics*, 63(6), 103894.

Amel-Shahbazz, S., Behjati-Ardakani, M., Namayandeh, S. M., Vafaenasab, M., Andishmand, A., Moghimi, S., Negahdary, M., & Sarebanhassanabadi, M. (2014). The epidemiological aspects of congenital heart disease in central and southern district of Iran. *Advanced Biomedical Research*, 3, 233.

American Academy of Pediatrics. (2001). Health care supervision for children with Williams syndrome. *Pediatrics*, 107(5), 1192–1204.

Burcharth, J. (2014). The epidemiology and risk factors for recurrence after inguinal hernia surgery. *Danish Medical Journal*, 61(5), B4846.

Chen, W. J., Ji, C., Yao, D., & Zhao, Z. Y. (2017). Thyroid evaluation of children and adolescents with Williams syndrome in Zhejiang Province. *Journal of Pediatric Endocrinology & Metabolism*, 30(12), 1271–1276.

Collins, R. T., 2nd. (2018). Cardiovascular disease in Williams syndrome. *Current Opinion in Pediatrics*, 30(5), 609–615.

Collins, R. T., 2nd, Kaplan, P., Sones, G. W., & Rome, J. J. (2010). Long-term outcomes of patients with cardiovascular abnormalities and Williams syndrome. *The American Journal of Cardiology*, 105(6), 874–878.

de Sousa Lima Strafacci, A., Fernandes Camargo, J., Bertapelli, F., & Guerra Júnior, G. (2020). Growth assessment in children with Williams-Beuren syndrome: A systematic review. *Journal of Applied Genetics*, 61(2), 205–212.

Eisenberg, R., Young, D., Jacobson, B., & Boito, A. (1964). Familial supravalvar aortic stenosis. *American Journal of Diseases of Children*, 108, 341–347.

Elison, S., Stinton, C., & Howlin, P. (2010). Health and social outcomes in adults with Williams syndrome: Findings from cross-sectional and longitudinal cohorts. *Research in Developmental Disabilities*, 31(2), 587–599.

Ferrero, G. B., Biamino, E., Sorasio, L., Banaudi, E., Peruzzi, L., Forzano, S., Verdun di Cantogno, L., & Silengo, M. C. (2007). Presenting phenotype and clinical evaluation in a cohort of 22 Williams-Beuren syndrome patients. *European Journal of Medical Genetics*, 50(5), 327–337.

Fricke, T. A., d’Udekem, Y., Brizard, C. P., Wheaton, G., Weintraub, R. G., & Konstantinov, I. E. (2015). Surgical repair of supravalvar aortic stenosis in children with Williams syndrome: A 30-year experience. *The Annals of Thoracic Surgery*, 99(4), 1335–1341.

Fusco, C., Micale, L., Augello, B., Teresa Pellico, M., Menghini, D., Alfieri, P., Cristina Digilio, M., Mandriani, B., Carella, M., Palumbo, O., Vicari, S., & Merla, G. (2014). Smaller and larger deletions of the Williams Beuren syndrome region implicate genes involved in mild facial phenotype, epilepsy and autistic traits. *European Journal of Human Genetics*, 22(1), 64–70.

Honjo, R. S., Dutra, R. L., Furusawa, E. A., Zanardo, E. A., de Athayde Costa, L. S., Kulikowski, L. D., Bertola, D. R., & Kim, C. A. (2015). Williams-Beuren syndrome: A clinical study of 55 Brazilian patients and the diagnostic use of MLPA. *BioMed Research International*, 2015, 903175.

Howlin, P., & Udwin, O. (2006). Outcome in adult life for people with Williams syndrome—Results from a survey of 239 families. *Journal of Intellectual Disability Research*, 50(Pt 2), 151–160.

Kanwar, M. K., & Stehlik, J. (2020). Sex-related differences in heart disease: Another piece of the puzzle. *Journal of Cardiac Failure*, 26(6), 505–506.

Kim, Y. M., Cho, J. H., Kang, E., Kim, G. H., Seo, E. J., Tee, B. H., Choi, J. H., & Yoo, H. W. (2016). Endocrine dysfunctions in children with Williams-Beuren syndrome. *Annals of Pediatric Endocrinology & Metabolism*, 21(1), 15–20.

Kitagawa, H., Fujiki, R., Yoshimura, K., Oya, H., & Kato, S. (2011). Williams syndrome is an epigenome-regulator disease. *Endocrine Journal*, 58(2), 77–85.

Kozel, B. A., Barak, B., Kim, C. A., Mervis, C. B., Osborne, L. R., Porter, M., & Poiber, B. R. (2021). Williams syndrome. *Nature Reviews Disease Primers*, 7(1), 42.

Kruszka, P., Porras, A. R., de Souza, D. H., Moresco, A., Huckstadi, V., Gill, A. D., Boyle, A. P., Hu, T., Addissie, Y. A., Mok, G. T. K., Tekendo-Ngongang, C., Fiegen, K., Prijoles, E. J., Tanpaiboon, P., Honey, E., Luk, H. M., Lo, I. F. M., Thong, M. K., Muthukumarasamy, P., … Muenke, M. (2018). Williams-Beuren syndrome in diverse populations. *American Journal of Medical Genetics Part A*, 175(6), 1128–1136.

Li, D. Y., Faury, G., Taylor, D. G., Davis, E. C., Boyle, W. A., Mecham, R. P., Stenzel, P., Boak, B., & Keating, M. T. (1998). Novel arterial pathology in mice and humans hemizygous for elastin. *The Journal of Clinical Investigation*, 102(10), 1783–1787.

Lowery, M. C., Morris, C. A., Ewart, A., Brothman, L. J., Zhu, X. L., Leonard, C. O., Carey, J. C., Keating, M., & Brothman, A. R. (1995). Strong correlation of elastin deletions, detected by FISH, with Williams syndrome: Evaluation of 235 patients. *American Journal of Human Genetics*, 57(1), 49–53.

Marler, J. A., Sitcovsky, J. L., Mervis, C. B., Kistler, D. J., & Wightman, F. L. (2010). Auditory function and hearing loss in children and adults with Williams syndrome: Cochlear impairment in individuals with otherwise normal hearing. *American Journal of Medical Genetics Part C Seminars in Medical Genetics*, 154c(2), 249–265.

Martin, N. D., Smith, W. R., Cole, T. J., & Preece, M. A. (2007). New developmental trajectories for intellectual abilities, vocabulary abilities, and adaptive behavior. *American Journal of Medical Genetics Part C Seminars in Medical Genetics*, 169(2), 158–171.
Meyer-Lindenberg, A., Mervis, C. B., & Berman, K. F. (2006). Neural mechanisms in Williams syndrome: A unique window to genetic influences on cognition and behaviour. *Nature Reviews Neuroscience, 7*(5), 380–393.

Morris, C. A., Braddock, S. R., & Council on Genetics. (2020). Health care supervision for children with Williams syndrome. *Pediatrics, 145*(2), e20193761.

Nugent, E. W., Freedom, R. M., Nora, J. J., Ellison, R. C., Rowe, R. D., & Nadas, A. S. (1977). Clinical course in pulmonary stenosis. *Circulation, 56*(1 Suppl), I38–I47.

Pinelli, M., Terrone, G., Troglio, F., Squeo, G. M., Cappuccio, G., Imperati, F., Pignataro, P., Genesio, R., Nitch, L., del Giudice, E., Merla, G., Testa, G., & Brunetti-Pierri, N. (2020). A small 7q11.23 microduplication involving GTF2I in a family with intellectual disability. *Clinical Genetics, 97*(6), 940–942.

Pober, B. R. (2010). Williams-Beuren syndrome. *The New England Journal of Medicine, 362*(3), 239–252.

Pober, B. R., Johnson, M., & Urban, Z. (2008). Mechanisms and treatment of cardiovascular disease in Williams-Beuren syndrome. *The Journal of Clinical Investigation, 118*(5), 1606–1615.

Royston, R., Waite, J., & Howlin, P. (2019). Williams syndrome: Recent advances in our understanding of cognitive, social and psychological functioning. *Current Opinion in Psychiatry, 32*(2), 60–66.

Sadler, L. S., Pober, B. R., Grandinetti, A., Scheiber, D., Fekete, G., Sharma, A. N., & Urban, Z. (2001). Differences by sex in cardiovascular disease in Williams syndrome. *The Journal of Pediatrics, 139*(6), 849–853.

Silva, L. A. F., Kim, C. A., & Matas, C. G. (2018). Characteristics of auditory evaluation in Williams syndrome: A systematic review. *CoDAS, 30*(5), e20170267.

Stanley, T. L., Leong, A., & Pober, B. R. (2021). Growth, body composition, and endocrine issues in Williams syndrome. *Current Opinion in Endocrinology, Diabetes, and Obesity, 28*(1), 64–74.

Wessel, A., Gravenhorst, V., Buchhorn, R., Gosch, A., Partsch, C. J., & Pankau, R. (2004). Risk of sudden death in the Williams-Beuren syndrome. *American Journal of Medical Genetics Part A, 127a*(3), 234–237.

Writing Committee Members, Otto, C. M., Nishimura, R. A., Bonow, R. O., Carabello, B. A., Erwin, J. P., Gentile, F., Jneid, H., Krieger, E. V., Mack, M., & McLeod, C. (2021). 2020 ACC/AHA guideline for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association joint Committee on clinical practice guidelines. *Journal of the American College of Cardiology, 77*(4), e25–e197.

Yau, E. K., Lo, I. F., & Lam, S. T. (2004). Williams-Beuren syndrome in the Hong Kong Chinese population: Retrospective study. *Hong Kong Medical Journal, 10*(1), 22–27.

Zhao, C., & Pleasure, S. J. (2005). Frizzled9 protein is regionally expressed in the developing medial cortical wall and the cells derived from this region. *Brain Research Developmental Brain Research, 157*(1), 93–97.

**How to cite this article:** Li, F.-f., Chen, W.-j., Yao, D., Xu, L., Shen, J.-y., Zeng, Y., Shi, Z., Ye, X.-w., Kang, D.-h., Xu, B., Shao, J., & Ji, C. (2022). Clinical phenotypes study of 231 children with Williams syndrome in China: A single-center retrospective study. *Molecular Genetics & Genomic Medicine, 10*, e2069. [https://doi.org/10.1002/mgg3.2069](https://doi.org/10.1002/mgg3.2069)