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Genotype-phenotypic association of heterozygous deletion of the *TBX-6* gene in patients with congenital scoliosis

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Abstract

Introduction Congenital scoliosis is a multifactorial disease caused by abnormalities in vertebral development during embryogenesis. The *TBX6* gene, located at locus 16p11.2, plays a key role in somitogenesis, and the heterozygous deletion is associated with the development of specific phenotypes of congenital scoliosis (*TBX6*-associated congenital scoliosis, TACS). Despite numerous studies on the role of *TBX6* in the pathogenesis of congenital scoliosis, there is a paucity of data on the phenotypic manifestations of heterozygous 16p11.2 deletion.

The **objective** was to identify and confirm the TACS phenotype being associated with 16p11.2 deletions in the Russian patients.

Material and methods A single-center retrospective cohort study included 187 patients diagnosed with congenital scoliosis treated at the Turner National Medical Research Center for Pediatric Orthopedics and Traumatology between 2012 and 2021. Heterozygous deletion (16p11.2 region) were verified using MQRT-PCR. The deletion group consisted of 42 patients, and the control group included 145 probands. Clinical and radiological findings were reviewed to identify localization, type and multiplicity of vertebral anomalies and associated malformations. Descriptive statistics and Pearson's correlation coefficient were used for data processing.

Results Heterozygous deletion of *TBX6* was detected in 22.4 % of patients. The thoracic and lumbar spine were common localizations, while involvement of the cervical spine was not identified in the deletion group. Vertebral malformations were the most common anomaly in both study groups, but their prevalence was higher among patients with *TBX6* deletion (50 % vs. 43.4 %). Multiple spinal malformations were more common in the deletion group (50 % vs. 35 %). Associated internal organ defects were less common in patients with deletion (31 % vs. 43.4 %), while rib synostoses and Sprengel's disease were more common.

Discussion TACS is characterized by specific manifestations including multiple vertebral malformations in the thoracic and lumbar spine, rib synostoses and Sprengel's disease, which is consistent with the scientific literature.

Conclusion The findings indicate the need to include genetic testing for *TBX6* deletion in the diagnostic algorithm for congenital scoliosis to facilitate early detection and a personalized approach to treatment of this cohort of patients.

Keywords: congenital scoliosis, TACS, genetics, congenital spinal deformities, children

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INTRODUCTION

Congenital spinal deformities including congenital scoliosis (CS) are a challenge in pediatric orthopedics and are caused by abnormalities in vertebral development during embryogenesis [1]. Teratogenic factors and associated mutational damage to the genome, affecting the formation of the fetus in the first 6–8 weeks of embryogenesis, are considered to be critically significant causes leading to spinal malformations [2]. The incidence of CS, according to epidemiological studies, is 0.5–1 case per 1,000 newborns [3].

Developmental anomalies of the vertebrae, such as hemivertebrae, butterfly vertebrae and segmentation defects, can be the cause of progressive scoliosis and/or kyphosis leading to impaired cardiovascular and respiratory function and neurological deficit [4, 5]. Despite the advances in the diagnosis of the condition in young children, progressive congenital curvatures of the spine require high-tech and timely surgical treatment before the age of three in a significant cohort of patients [6].

Recent advances in molecular genetics allowed for identification of the genes responsible for congenital spinal deformities and congenital scoliosis [7, 8, 9]. The *TBX6* gene is one of the key factors determining the development of the spinal column; it is involved in somitogenesis, regulating the formation of the paraxial mesoderm that gives rise to vertebrae and ribs [10, 11]. Approximately 7.9–10.6 % of cases of congenital scoliosis are associated with *TBX6* mutations and can develop sporadically, with familial cases described in 1–3.4 % of patients [12]. Studies on experimental animal models have confirmed that hypomorphic alleles and deletions of *TBX6* lead to the formation of butterfly vertebrae and hemivertebrae [13]. The target is a heterozygous deletion at the site of chromosome 16p11.2 affecting the region of the short arm (p) of chromosome 16 where *TBX6* gene is located. Deletion is a type of genetic mutation with a particular region of DNA lost [14]. The loss results in changes in the structure of the gene or genes leading to the impaired functions. Homozygous deletion of 16p11.2 is embryonic lethal [15]. In the case of the *TBX6* gene, heterozygous deletion and other genotypes can characterize *TBX6*-associated congenital scoliosis (TACS), described by Liu et al. in 52 Chinese patients [16]. TACS is characterized by specific phenotypes and clinical manifestations including hemivertebrae and butterfly vertebrae, predominantly in the lower thoracic and lumbar spine [16].

Analysis of patient cohorts in China, Japan and the United States has shown that *TBX6* mutations are often associated with simple spinal malformations and are rarely associated with severe segmentation defects or intraspinal abnormalities [17]. The clinical role of the studies includes the development of predictive models, such as TACScore that help identify patients at high risk of having TACS [18]. However, heterozygous *TBX6* deletion and TACS phenotype have not been examined in Russian and European populations.

The **objective** was to identify and confirm the TACS phenotype being associated with 16p11.2 deletions in the Russian patients. Analysis of the findings allows us to identify characteristic phenotypes and determine the frequency of occurrence in the group of patients, and to assess the possible correlation with concomitant anomalies in the development of organs and systems.

MATERIAL AND METHODS

The design was a monocentric cohort retrospective study. The results of molecular genetic and clinical examination of 187 patients treated between 2012 and 2021 at the Turner National Medical Research Center for Pediatric Traumatology and Orthopedics were reviewed.

Inclusion criteria included verified diagnosis of congenital scoliosis based on a comprehensive clinical and radiological examination, absence of a positive genetic history, voluntary informed consent of patients or their legal representatives to participate in the study.

Exclusion criteria included patients whose diagnosis of congenital scoliosis was not confirmed during the examination; verified genetic syndromes in patients and/or their relatives, as well as refusal of the patient or legal representative to participate in the study. The study was performed in two stages. The first stage included molecular genetic testing for genomic DNA isolated from probands' peripheral blood leukocytes and aimed at finding deletions in the region of chromosome 16p11.2. Genomic DNA was isolated using a commercial reagent kit (Synthol, Moscow). A multiplex quantitative real-time polymerase chain reaction (PCR) method (MQRT-PCR) with fluorescently labeled TaqMan hybridization probes was used to detect heterozygous deletion of the TBX-6 gene. PCR was performed in 25 µl mixture containing 1×PCR buffer, 0.5 units of Taq DNA polymerase activity SynTaq (Syntol, Moscow), 3.5 mmol/l MgCl2, 200 µmol/l of each dNTP, 5 % dimethyl sulfoxide, 0.5 % formamide. The reaction mixture also contained 500 nmol/l of each oligonucleotide primer and 200 nmol/l of each fluorescently labeled PCR probe (Eurogen, Moscow). Testing was performed using the Bio-Rad CFX96 system (Bio-Rad, USA).

Clinical data of the selected patients were reviewed to determine the phenotypic manifestations of the disease at the second stage of the study. The probands were divided into two groups depending on the presence of heterozygous deletion. The group with the genotype of heterozygous deletion 16p11.2 consisted of 42 patients and 145 probands constituted the normal group. The analysis included data from medical records, radiography, multispiral computed tomography (MSCT) and magnetic resonance imaging (MRI) findings.

Descriptive statistics methods were used to evaluate the results. The Pearson's contingency coefficient was used to evaluate the significance of correlation.

RESULTS

Multiplex quantitative real-time PCR (MQRT-PCR) performed on 187 genomic DNA samples showed heterozygous deletion of 16p11.2 of the *TBX6* gene (*TBX6*/null genotype) verified in 42 probands. Clinical and instrumentation findings in the groups with heterozygous deletion (n = 42) and without it (norms) (n = 145) were analyzed at the second stage of the study through panoramic radiography of the spine in the supine position, MSCT to verify the localization and type of vertebral anomaly, MRI to rule out intracranial pathology. The average age of patients at the time of examination was (6.00 ± 2.73) years. There were 79 (42 %) male and 108 (57 %) female patients.

Localization of anomalies

The lumbar and thoracic spine were commonly involved segments in both groups among other localizations of spinal anomalies. With the majority of cases suffering from multiple spinal lesions, vertebral malformations the data are presented in absolute numbers. Patients of the normal group (Fig. 1 a) showed 394 maldeveloped vertebrae including 33 (8.5 %) localized in the cervical spine, 288 (73 %) in the thoracic spine and 73 (18.5 %) demonstrated lumbar involvement. The heterozygous deletion group (Fig. 1 b) demonstrated 104 abnormal vertebrae registered with 2 (1.9 %) localized in the cervical spine, 78 (75 %) in the thoracic spine and 24 (23 %) were lumbar involvement. The Pearson's contingency coefficient was used to evaluate the relationship between localization and heterozygous deletion. A positive value obtained (0.09) characterized the tightness of the stochastic relationship of random variables, which confirmed the correlation between the presence of a deletion and the localization of developmental anomalies.

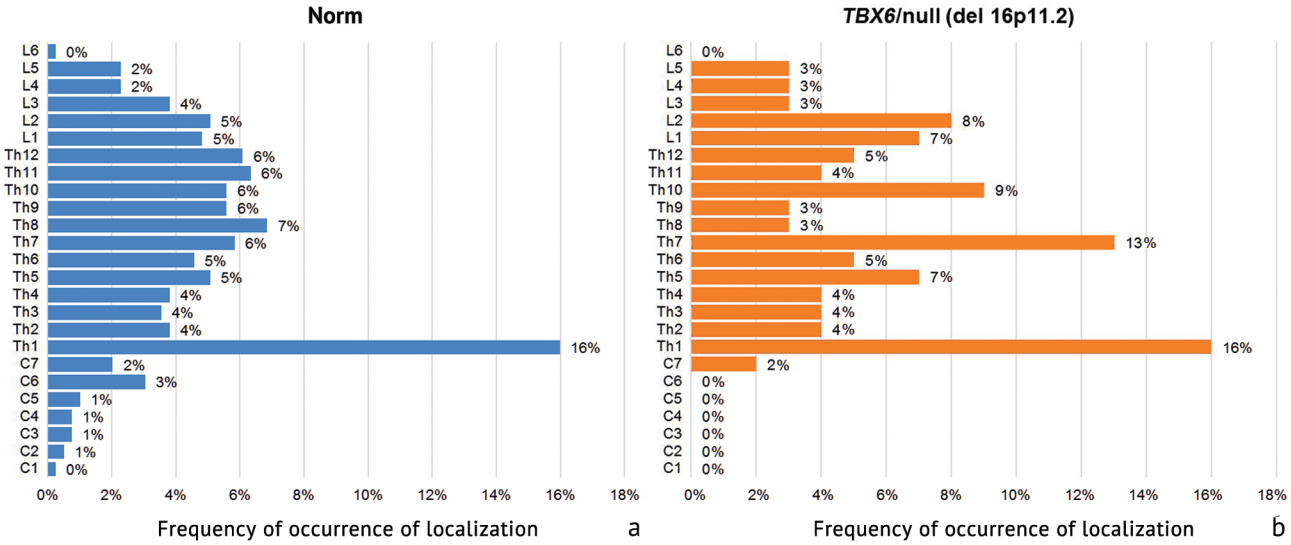

Fig. 1 Distribution of localizations of spinal developmental anomalies: (a) patients in the group without verified deletion (norm); (b) patients in the deletion group (*TBX6*/null)

Typological analysis

Developmental defects are divided into types (grades) in accordance with the generally accepted MacEwan classification that is expanded and supplemented to include defects of vertebral formation (hemivertebrae), impaired vertebral fusion (butterfly vertebrae), vertebral segmentation defects (non-segmented column) and their combinations. Single isolated hemivertebrae were commonly detected in the patients including 63 (43.4 %) in the group without verified deletion and 21 cases (50 %) in the deletion group (Fig. 2). The differences were found in the cohorts of patients with segmentation disorders (isolated non-segmented rods and combinations of non-segmented rods with hemivertebrae and butterfly vertebrae) with a total of 30.9 % in the normal group versus 21.4 % in the group with deletion.

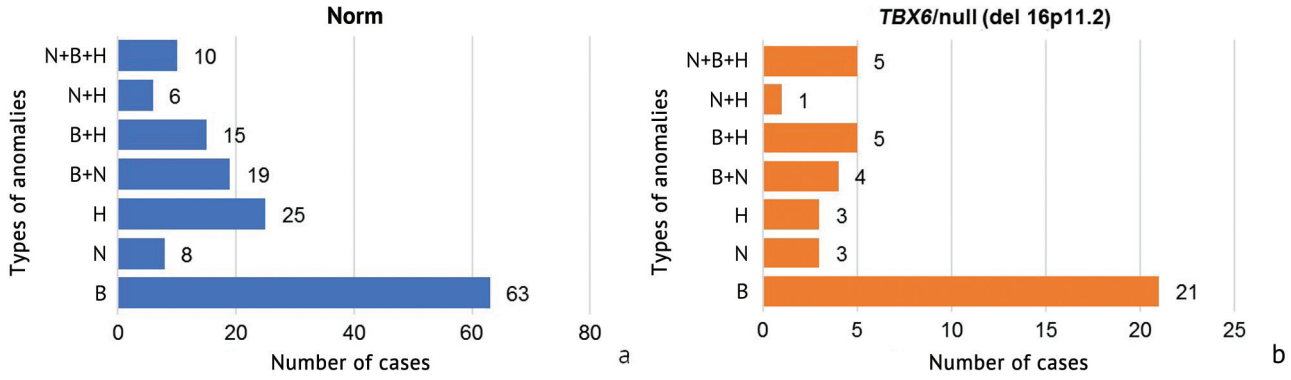

Fig. 2 Distribution of spinal malformations: (a) group without verified deletion (norm); (b) group of heterozygous deletion (*TBX6*/null). B — butterfly vertebra; N — non-segmented rod; H — hemivertebra and their combinations

Multiple spinal malformations were recorded in 51 patients (35 %) of the normal group and in 21 cases (50 %) in the heterozygous deletion group. Considering the proportion of multiple spinal involvement, it can be concluded that this type of developmental anomalies is more common in patients with heterozygous deletion. The Pearson coefficient was greater than the expected value (0.109 > 0.090) suggesting that there was a relationship between the presence of a deletion and the localization of the defect at a significance level of $p = 0.05$.

Associated developmental defects

Pre-admission tests and somatic examination of each patient revealed concomitant congenital spinal deformities, malformations of other organs and systems identified as (Table 1) minor cardiac anomalies, gastrointestinal malformations and urinary anomalies. Orthopedic conditions diagnosed included Sprengel's disease, diastematomyelia, Spina Bifida, tethered spinal cord syndrome, VATER and VACTERL associations, rib synostoses and other malformations (isolated cases of isolated tarsal coalitions, caudal regression syndrome, brachydactyly, aplasia of the fingers, polydactyly, Churg-Strauss syndrome, pituitary dwarfism, high myopia, lipomyeliomeningocele).

Table 1

Specification of associated developmental anomalies in patients

Developmental anomalies	Group			
	Norm		Heterozygous deletion	
	абс.	%	абс.	%
Minor cardiac anomalies (OOO, LVH, autonomic rhythm disturbances)	7	4.8	0	0
Gastrointestinal malformations (anal atresia, esophageal atresia)	5	3.4	0	0
Malformations of the urinary tract (aplasia, duplication, hypoplasia, renal dystopia)	6	4.1	0	0
Sprengel's disease	4	2.8	2	4.7
Diastematomyelia	7	4.8	0	
Spina Bifida	7	4.8	1	0.1
Tethered Cord Syndrome	1	0.6	0	
Synostosis of the ribs	15	10.3	7	16.6
VATER/VACTERL associations	5	3.4	1	2.3
Others	7	4.8	2	4.8
Total number of patients	64	43.8	13	28.5

DISCUSSION

Heterozygous deletion of the *TBX6* gene was detected at locus 16p11.2 in 22.4 % of patients with verified diagnosis of congenital scoliosis. This figure is greater than that reported in the world literature with the frequency of *TBX6*-associated mutations ranging from 7.9 % to 10.6 % in the Chinese, Japanese and North American populations [17]. Chromosomal local deletions and duplications including the 16p11.2 as the cause of congenital scoliosis phenotype was reported by Al-Kateb et al. [19]. Wu et al. [17] suggested that the impact and frequency of *TBX6* mutations determining development of congenital scoliosis vary depending on the population, indicating possible interaction with other genetic and environmental factors. In our opinion, the higher mutation frequency in the Russian cohort can be caused by regional characteristics of the population. Given the data obtained, a more extensive genetic profile of patients in the deletion group is of interest.

Analysis of the localization of spinal malformations revealed predominant lesions of the thoracic and lumbar spine in patients with and without *TBX6* deletion. However, the group with heterozygous deletion showed no anomalies in the cervical spine and anomalies in this localization was 8.4 % in the normal group. This is consistent with the findings reported by Liu et al. with involved lower thoracic and lumbar spine observed with the TACS phenotype [16]. This localization pattern may be related to the function of the *TBX6* gene in somitogenesis, which is critical for the formation of paraxial mesoderm at the spinal levels [20]. Heterozygous deletion of *TBX6* results in decreased

gene expression and impaired segmentation and vertebral formation [21]. White et al. reported a decrease in *TBX6* levels in mice leading to defects in somite formation and correlating with those observed in patients with spinal anomalies [22].

Typological analysis revealed that hemivertebrae were the most common type of skeletal anomalies in patients with *TBX6* deletion (50 %) and without it (43.4 %). The fact is consistent with the findings reported by Liu et al. emphasizing the importance of this morphological feature for determining the treatment strategy of congenital scoliosis and further dynamic observation [23]. Isolated segmentation disorders were not common in the group with a heterozygous deletion (7.2 % versus 17.2 % in the normal group) reflecting the specificity of *TBX6*-associated anomalies reported by Yang et al. The authors suggested that heterozygous *TBX6* mutations led to a decrease in gene expression rather than to the critical level required for the occurrence of complex segmentation defects [24].

Multiple spinal anomalies were detected in 50 % of patients with *TBX6* deletion that was much greater than the similar indicator in the normal group (35 %). This is consistent with the findings reported by Liu et al. [23], Wu et al. [25] and Feng et al. [26] who found multiple spinal defects being more common in patients with *TBX6* mutations. The mechanism emphasizes the more complex nature of the lesions in the cohort of patients and plays a clinical role in predicting the course of the disease and planning surgical treatment [27].

Associated malformations of visceras including cardiovascular, urinary and digestive anomalies were less common in patients with *TBX6* deletion compared to the normal group. These factors partially contradict the data reported by Liu et al. [16] on the high frequency of combined systemic anomalies indicating regional or methodological differences. In addition to that, the findings do not rule out the presence of other mutational injury to the genome in the normal group including microdeletions or polymorphisms of other genes. Powel et al. reported more common cardiac malformations detected in patients with *TBX6* mutations in a systematic review. [28] However, orthopedic anomalies including rib synostoses (16.6 %) and Sprengel's disease (4.7 %) are more characteristic of TACS, and Otomo et al. reported the more frequent cases of synostoses and rib hypoplasia or aplasia in patients with *TBX6* deletions [29]. Panigrahi et al. [30] reported a series of clinical observations of patients with congenital scoliosis and Sprengel's disease and suggested a positive correlation between *TBX6* mutations and the pathological position of the scapula. Yang et al. reported the occurrence of complex forms of congenital scoliosis being associated with developmental abnormalities of other organs and systems and complex oligogenic influence [31].

The study we present has a number of limitations. The patient sample is limited to one clinic reducing the possibility of extrapolating the results to a larger patient sample. The lack of whole-genome sequencing places restriction on the search of etiopathogenetic justifications for other concomitant developmental anomalies in the study groups. A greater cohort of patients is scheduled to be recruited for further investigations to explore regional and ethnic characteristics of patients with TACS. Another study is planned to assess the effect of heterozygous *TBX6* mutations on the occurrence of the dysplastic nature of the course of congenital scoliosis. This will help clarify the mechanisms of pathogenesis and improve approaches to early diagnosis of the pathological condition and treatment of patients with this pathology.

CONCLUSION

The findings obtained suggest that *TBX6*-associated scoliosis is characterized by vertebral malformations localized mainly in the thoracic and lumbar spine, with a predominance of hemivertebrae. The high frequency of rib synostoses and multiple anomalies requires further study to clarify the prognostic value of the manifestations.

Conflict of interest *None.*

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Ethical review *The study was approved by the Ethics Committee of the Turner National Medical Research Center of Pediatric Traumatology and Orthopedics of the Ministry of Health of the Russian Federation (Protocol No. 24-9 dated October 22, 2024).*

Informed consent *Written voluntary informed consent was obtained from patients and their legal representatives to participate in the scientific study and process personal data.*

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