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The influence of the *TBX6* gene on the development of congenital spinal deformities in children

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BACKGROUND: Congenital deformities of the spine are a group of serious congenital defects of the vertebrae, which can manifest themselves in the clinical picture as an isolated pathology of the axial musculoskeletal system, and are associated with congenital defects of internal organs and other systems. Recently, the *TBX6* gene has been identified as the genetic cause of congenital scoliosis in about 11% of cases. This subtype of scoliosis is classified as TBX6-associated congenital scoliosis. The TBX6-associated congenital scoliosis phenotype is characterized by butterfly-shaped vertebrae and hemivertebrae in the lower thoracic and lumbar regions without pronounced malformations of the spinal cord.

AIM: Our aim is to study and evaluate data from foreign and domestic scientific publications devoted to the study of the candidate gene for congenital scoliosis *TBX6*.

MATERIALS AND METHODS: The following databases of scientific publications such as PubMed, Cochrane Library, Web of Science, SCOPUS, MEDLINE, e-Library, Cyberleninka were used to write this review. The inclusion criteria were systematic reviews, meta-analyses, multicenter studies, controlled cohort studies, uncontrolled cohort studies of patients with congenital spinal deformities. The exclusion criteria were clinical cases, observations, conference proceedings, congenital scoliosis in genetic syndromes, congenital scoliosis associated with defects of the nervous system.

RESULTS: In order to achieve this goal, 70 scientific publications were studied relating to the data analysis of the candidate gene for congenital scoliosis *TBX6*. Among 49 publications that were identified, 2 were domestics, and the rest were foreign publications. These studies provided information on the molecular analysis of genes that cause congenital spinal deformities in humans and animals.

CONCLUSIONS: An analysis of the published research work on this topic indicates the presence of a significant effect of mutations in the *TBX6* gene, leading to the appearance of congenital scoliosis.

Advances in elucidating the genetic contribution to the development of congenital spinal deformities and the molecular etiology of clinical phenotypes may uncover the opportunities for further refinement of the classification of signs of congenital scoliosis in accordance with the underlying genetic etiology.

Keywords: congenital spinal deformity; congenital scoliosis; *TBX6* gene; children.

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О влиянии гена *TBX6* на развитие врожденных деформаций позвоночника у детей

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Обоснование. Врожденные деформации позвоночника представляют собой группу серьезных врожденных дефектов позвонков, которые могут проявляться в клинической картине как изолированной патологией осевого опорно-двигательного аппарата, так и состояниями, ассоциированными с врожденными дефектами внутренних органов и других систем. В последнее время ген *TBX6* был идентифицирован как генетическая причина врожденного сколиоза примерно в 11 % случаев. Данный подтип сколиоза выделяют как TBX6-ассоциированный врожденный сколиоз. Для его фенотипа характерны бабочковидные позвонки и полупозвонки в нижнем грудном и поясничном отделах без выраженных пороков развития спинного мозга.

Цель — изучение и оценка данных зарубежных и отечественных научных публикаций, посвященных исследованию гена-кандидата врожденного сколиоза *TBX6*.

Материалы и методы. Научные публикации для написания литературного обзора были получены из научных электронных баз данных PubMed, Cochrane Library, Web of Science, SCOPUS, MEDLINE, eLibrary, Cyberleninka. Критерии включения: систематические обзоры, метаанализы, мультицентровые исследования, контролируемые когортные исследования, неконтролируемые когортные исследования пациентов с врожденными деформациями позвоночника. Критерии исключения: клинические случаи, наблюдения, материалы конференций, врожденный сколиоз при генетических синдромах, врожденный сколиоз, ассоциированный с пороками нервной системы.

Результаты. Для достижения поставленной цели было изучено 70 научных публикаций, касающихся оценки и анализа данных по исследованию гена-кандидата врожденного сколиоза *TBX6*. Было выделено 49, из них отечественных — 2, остальные — зарубежные публикации, в которых приведены сведения о молекулярном анализе генов, вызывающих врожденную деформацию позвоночника у людей и животных.

Заключение. Анализ изученных исследовательских работ по данной теме свидетельствует о наличии значимого влияния мутаций гена *TBX6*, приводящих к появлению врожденного сколиоза. Успехи в выяснении генетического вклада в развитие врожденной деформации позвоночника и молекулярную этиологию клинических фенотипов открывают возможности для дальнейшего уточнения классификации признаков врожденного сколиоза в соответствии с лежащей в его основе генетической этиологией.

Ключевые слова: врожденная деформация позвоночника; врожденный сколиоз; ген *TBX6*; дети.

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BACKGROUND

In children, congenital deformities of the spine (CDS) are the most severe and disabling pathology of the axial skeleton. The prevalence of CDS is about 0.5–1.0 per 1000 newborns [1–2]. Vertebral anomalies occur due to malfunctions in the formation or segmentation processes in the first six weeks of embryogenesis due to exposure to teratogenic factors and mutational damage to the genome [3–4]. Among the CDS, the most common is congenital scoliosis – one of the most complex types of early scoliosis [5]. The most common malformation of the spine, contributing to the progressive nature of the course of congenital deformity, is a violation of the formation of the vertebrae. Defects of the vertebrae can lead to significant deformity, neurological disorders, and restriction of the growth of the chest organs, which can be the cause of the syndrome of cardiopulmonary insufficiency [6]. To prevent neurological deficits and prevent the development of gross CDS in children, timely detection of progressive forms of curvature and early surgical treatment is necessary [7].

Congenital scoliosis is predominantly sporadic and rarely develops as a monogenic disease. A burdened family history of congenital spinal deformities is detected in 1%–3.4% of cases of congenital scoliosis. The presence of multiple spinal defects in a patient increases the risk of malformation in his siblings to 2.5%–3% [8–9]. Up to 17% of patients with congenital scoliosis report the presence of CDS in their next of kin, which indicates a genetic predisposition to spinal deformities [10].

The identification of the genetic factors of the etiology of congenital spinal deformities will help better understand the pathogenesis and predict the development of deformities. Genetic data drive recent advances in understanding the etiology and progression of spinal deformities. For example, mutations in the Notch signaling pathway, including the *DLL3, MESP2, LFNG, HES7, RIPPLY2*, and NOTCH2 genes, and variants of other genes such as *PAX1, SLC35A3, TBXT, FBN1, PTK7, SOX9, FLNB,* and *HSPG2*, cause congenital deformities spine [11–14]. Recently, heterozygous variants of the TBX6 mutation have also been identified as a genetic cause of congenital scoliosis in about 11% of patients [15].

The study of the genetic prerequisites for the occurrence of congenital malformations is an essential and urgent task. Understanding the biological nature of this phenomenon allows conducting targeted prevention and development diagnostic measures. It makes it possible to identify spinal deformities in the first years of a child's life, which is characterized by a progressive course against the background of anomalies in the development of the vertebral bodies [16]. In turn, this will provide for early surgical intervention.

The study aimed to evaluate the data from international and national scientific publications for studying the candidate gene for congenital scoliosis *TBX6*.

MATERIALS AND METHODS

For this study, a total of 70 scientific publications were studied regarding the assessment and analysis of data on the study of the candidate gene for congenital scoliosis *TBX6*. Among them, 49 were identified, 2 national and 47 international publications, which provided information on the molecular analysis of genes that cause CDS in humans and animals. Scientific publications were obtained from scientific electronic databases such as PubMed, Cochrane Library, Web of Science, SCOPUS, MEDLINE, eLibrary, Cyberleninka. The period under review is from 2008 to January 2021. Several literature sources published earlier than 2008 are included in this review, as they contained important information that was not reflected in later publications.

The literature search was carried out using the following keywords: "congenital scoliosis" (congenital scoliosis), "congenital vertebral malformation", "*TBX6* gene" (gene *TBX6*), "chromosome 16p11.2" (chromosome 16p11. 2), TBX6-mediated genes, biallelic mutation, vertebrate segmentation, and somitogenesis.

Inclusion criteria: systematic reviews, meta-analyses, multicenter studies, controlled cohort studies, uncontrolled cohort studies of patients with congenital spinal deformities.

Exclusion criteria: clinical cases, observations, conference proceedings, congenital scoliosis in genetic syndromes, congenital scoliosis associated with defects of the nervous system.

RESULTS AND DISCUSSION

Information on the main publications that meet the inclusion criteria is presented in the table.

In humans, vertebrae originate from somites through somitogenesis, which is the harmonious work of many signaling pathways related to genes [17]. Thus, mutations in genes associated with somitogenesis or a violation of symmetric gene modulation may ultimately contribute to the emergence of CDS [18].

In vertebrate embryogenesis, the paraxial mesoderm is derived from progenitors initially located in the surface layer of the embryo, which later internalizes during gastrulation and forms the presomitic mesoderm (PSM). Subsequently, the paraxial mesoderm undergoes segmentation and is located on the lateral sides of the neural tube [19]. The primordial streak differentiates into a mass of cells called the tailbud [20]. The caudal bud, located at the

Table. Information about the main publications

Authors	Year of publication	Country	Sample size	Number of patients with mutations	Mutation type	Spinal pathology
Shimojima et al. [41]	2009	Japan	3	2	Deletion 16p11.2	Semivertebrae
Ghebranious et al. [33]	2008	USA	50	3	Missense mutation	Disorder of the spine formation and segmentation
Fei Qi et al. [38]	2010	China	254	17	Deletion of the region 16p11.2 + TSA_ galotype	Disorder of the spine formation and segmentation
Sparrow D.B. et al. [37]	2013	Australia	5	3	Stop codon	Spondylo-costal dysostosis
Al-Kateb et al. [43]	2014	USA	15	-	Deletion and duplication of the region 16p11.2	Disorder of the spine formation and segmentation
Wu N. et al. [45]	2015	China	237	23	Null variants of TBX6	Disorder of the spine formation and segmentation
Baschal E.E. et al. [44]	2015	USA	42	–	–	Familial idiopathic scoliosis
Lefebvre M. et al. [35]	2017	France	56	4	Deletion 16p11.2	Disorder of the spine segmentation
Takeda K. et al. [39]	2017	Japan	94	9	Missense mutation	Disorder of the spine formation and segmentation
Otomo N. et al. [36]	2019	Japan	200	10	Deletion 16p11.2, missense mutation	Disorder of the spine formation and segmentation, spondylocostal dysostosis
Liu J. et al. [46]	2019	China	497	58	TBX6 LoF	Disorder of the spine formation and segmentation, aplasia of X–XII ribs
Chen W. et al. [47]	2020	China	523	43	TBX6 LoF	Disorder of the spine formation and segmentation
Yang Y. et al. [48]	2020	China	584	28	MEOX1, MEOX2, Mesp2, MYOD1, Myf5, RIPPLY1, and RIPPLY2	Disorder of the spine formation and segmentation
Feng X. et al. [49]	2020	China	67	4	16p11.2/TBX6 deletion	Disorder of the spine formation and segmentation

posterior end of the embryo, contains precursors of the SCM that promote subsequent tissue formation [21]. In this process, the structure of the somite is gradually formed synchronously and rhythmically. As a result, somites give rise to vertebrae, muscles, tendons, and ligaments of the spine [22]. Several factors regulate the embryonic development of somites from SCM. The underlying mechanisms of interactions of these factors have been illustrated by several models, including the widely accepted clock wavefront model [23]. In the clock wavefront model, the PSM is gradually segmented into repeating somites driven by periodic activation of the Notch, WNT, and FGF signaling pathways [24]. In somitogenesis, the segmentation occurs after the formation of somites, when the formed somites receive a clock signal [25]. For example, MESP2 is activated by NICD (Notch path) and TBX6. MESP2 is initially expressed in a limited region of the somite (the length of one segment). Then RIPPLY1 and RIPPLY2 are expressed in the region of the posterior half of the segment, thus defining the future boundaries of the somite following the region of

signal action [26, 27]. Finally, the downstream target gene *RIPPLY2* is activated, a negative feedback inhibitor of MESP2 and TBX6. This process contributes to the definition of the anterior border of the newly formed segment. In addition, the inactivation of MESP1 and MESP2 leads to impaired paraxial mesoderm formation [28].

T-box genes encode transcription factors involved in the regulation of developmental processes. For example, the *TBX6* gene, located in the 16p11.2 region, is a phylogenetically conserved gene family [29, 30]. As we can see, the *TBX6* gene is required to form the posterior somites and as an indispensable component for the correct paraxial differentiation and segmentation of the mesoderm [31, 32].

A study by Ghebranious et al.(2008) suggested that mutations in the *T* and/or *TBX6* genes can lead to congenital malformations of the spine [33].

White et al. (2005), based on the analysis of the genotyping results of a mouse and human model suggested that *TBX6* may be a potential candidate genome associated with congenital scoliosis [34]. When *TBX6* interacts with the Notch ligand, these phenotypes are similar to the phenotypes of some human congenital defects, such as spondylocostal dysostosis and congenital scoliosis [35, 36].

Sparrow et al. (2013) used total exome sequencing to study three generations of a Macedonian family with a spondylocostal phenotype. Of the five family members, three had clinical signs and radiological evidence of spondylocostal dysostosis, and two had no clinical manifestations. Thus, it was confirmed that three affected family members had a heterozygous nonsense mutation in the *TBX6* gene. At the same time, two members without clinical manifestations were homozygous wild-type, indicating segregation with the disease in a family where the mutation with full penetrance was identified [37].

Several single nucleotide polymorphisms (SNPs) of the *TBX6* gene have been reported to be associated with congenital malformations of the spine. Fei et al. genotyped them in the *TBX6* gene among 254 ethnic Chinese (including 127 patients with congenital scoliosis and 127 patients from the control group). The two SNP analyzes rs2289292 (SNP1, exon 8) and rs3809624 (SNP2,5'-untranslated region) differ significantly between cases and controls ($p = 0.017$ and $p = 0.033$, respectively). Haplotype analysis showed a significant association between SNP1 / SNP2 cases and congenital scoliosis ($p = 0.017$) [38].

A case-control association study was first performed in a Chinese population [39]. The study identified two *TBX6* SNPs associated with congenital scoliosis. In 2015, a molecular genetic analysis of the *TBX6* gene was carried out. The complex heterozygous inheritance of nucleotide sequence variants was identified in a cohort of patients with congenital scoliosis among residents of South China [39, 40].

In 10% of patients, a heterozygous deletion was found on chromosome 16p11.2, which included the *TBX6* gene or a frameshift mutation in the *TBX6* gene. Interestingly, all patients with heterozygous null mutations in the *TBX6* gene had a common haplotype for a different allele. This cause of congenital scoliosis, caused by the complex inheritance of rare null mutations and a hypomorphic haplotype, was fCDSher confirmed after studies in Japanese and European cohorts. These studies also identified similar biallelic variants in the *TBX6* gene in 9 out of 94 and 4 out of 56 patients with congenital scoliosis [40].

A study by Shimojima et al. (2009) reported a 3-year-old boy with developmental delay, inguinal hernia, T_{10}, T_{12}, and L_3 hemivertebrae; missing right XII rib, and hypoplasia of the left XII rib. The patient had a 593 kb deletion of 16p11.2, and the mother had the same deletion identified by chromosomal microarray analysis [41, 42].

Al-Kateb et al. (2014) analyzed X-ray data obtained from 10 patients with a deletion on chromosome 16p11.2 with CDS. Eight of them had congenital scoliosis, and the rest had idiopathic scoliosis. They further reviewed 5 previously reported patients with 16p11.2 region rearrangement and similar skeletal abnormalities and concluded that 2 of them had congenital scoliosis, while the rest had idiopathic scoliosis [43].

Baschal et al. (2015) performed Sanger sequencing in 42 patients with familial idiopathic scoliosis and did not reveal an association of the disease with the *TBX6* gene [44].

Subsequently, Wu et al. clarified that *TBX6*-null variants and common hypomorphic *TBX6* alleles contribute to congenital scoliosis. In a group of 161 patients with CDS, 17 heterozygous *TBX6*-null mutations were found in individuals with congenital scoliosis. This group included 12 cases of recurrent deletion of chromosome 16p11.2, including the *TBX6* gene, and five single nucleotide variants (1 nonsense mutation and four mutations with a shift in the reading frame). Identification of phenotypically normal individuals with microdeletions of chromosome 16p11.2 and dissonant familial phenotypes of congenital scoliosis in carriers of this microdeletion suggested the presence of heterozygous null mutations in one of the *TBX6* alleles is not enough to cause congenital scoliosis [45].

Liu et al. (2019) conducted a large-scale molecular genetic study of 497 patients with congenital scoliosis. As a result, it was found that mutations of the *TBX6* gene occur in 10% patients ($n = 52$). The authors identified a genetically new type of congenital scoliosis – *TBX6*-associated congenital scoliosis (TACS). Butterfly-shaped vertebrae and hemivertebrae characterize the TACS phenotype in the lower thoracic and lumbar regions without pronounced spinal cord malformations [46]. Further, this study developed

a TACScore model to predict TACS based on phenotypic data and clinically measurable endophenotypes. TACScore includes the following criteria: segmented hemivertebrae/butterfly vertebrae located in the lower thoracic and lumbar spine (T_8–S_5), the number of vertebral malformations, the presence of intraspinal defects, and the type of rib malformations [46].

Based on molecular genetic studies, Chen et al. (2020) created a TACS gene dosing model. In the putative model, the phenotypes of patients with TACS differ along with the characteristic mutations in the *TBX6* gene. The insignificant loss of *TBX6* function caused by a heterozygous hypomorphic haplotype or a biallelic hypomorphic haplotype can be considered an acceptable mutation dose that does not lead to the CDS phenotype. However, one heterozygous severe hypomorphic or null allele will still lead to congenital scoliosis. A severe hypomorphic or null allele combined with a mild hypomorphic haplotype causes high penetrance of congenital scoliosis, leading to the most common TACS phenotype [47].

Yang et al. (2020) performed a genetic study of *TBX6*-mediated candidate genes *MEOX1, MEOX2, MESP2, MYOD1, MYF5, RIPPLY1,* and *RIPPLY2* in 584 patients with congenital scoliosis. It was found that a single mutation in these genes does not determine the phenotype of congenital scoliosis; however, the combined effect of mutant variants in several genes can synergistically lead to the disease [48].

Feng et al. (2021) analyzed a group of patients with congenital scoliosis and found that in 3 out of 67 patients (4.5%), heterozygous *TBX6* variants are associated with congenital scoliosis [49].

CONCLUSION

The scientific publications of national and international authors presented in this review make it possible to obtain up-to-date comprehensive information on the main aspects of such an urgent problem for pediatric orthopedics as genetic risk factors for congenital scoliosis. The analysis of work on this topic indicates the presence of a significant effect of mutations in the *TBX6* gene, leading to the appearance of congenital scoliosis.

Advances in elucidating the genetic contribution to the development of CDS and the molecular etiology of clinical phenotypes open up opportunities for further refinement of the classification of signs of congenital scoliosis per the underlying genetic etiology. Furthermore, this genetic classification can lead to models for predicting the progression of congenital spinal deformities in children.

ADDITIONAL INFORMATION

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