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*TBX6*基因对儿童先天性脊柱畸形发展的影响

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论证。脊柱先天性畸形是一组严重的脊椎先天性缺陷，在临床上表现为轴肌骨骼系统的孤立病理，以及与内脏和其他系统先天性缺陷相关的疾病。最近，在大约11%的病例中*TBX6*基因被确定为先天性脊柱侧凸的遗传原因。这种脊柱侧凸亚型与TBX6相关的先天性脊柱侧凸相区别。其表型特征为下胸椎和腰椎区域的蝶形椎体和半椎体，没有明显的脊髓畸形。

目的是研究和评估来自国内外专门研究先天性脊柱侧凸候选基因*TBX6*的科学出版物的数据。

材料与方法。从科学电子数据库PubMed、Cochrane图书馆、科学网、SCOPUS、MEDLINE、eLibrary、Cyberleninka获得了撰写文献综述的科学出版物。纳入标准：系统评价、荟萃分析、多中心研究、对照队列研究、先天性脊柱畸形患者的非对照队列研究。排除标准：临床病例、观察结果、会议记录、遗传综合征中的先天性脊柱侧弯、与神经系统缺陷相关的先天性脊柱侧弯。

结果。为实现这一目标，研究了70篇关于先天性脊柱侧弯*TBX6*候选基因研究数据的评估和分析的科学出版物。选择了49个，其中国内 – 2个，其余 – 国外出版物，提供有关导致人类和动物先天性脊柱畸形的基因的分子分析信息。

结论。对该主题的研究工作的分析表明*TBX6*基因突变的显着影响存在，导致先天性脊柱侧弯的出现。在阐明先天性脊柱畸形发生的遗传因素和临床表型的分子病因学方面取得的进展为根据潜在的遗传病因学进一步细化先天性脊柱侧凸症状的分类提供了机会。

关键词：先天性脊柱畸形；先天性脊柱侧弯；*TBX6*基因；孩子们。

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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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论证

儿童先天性脊柱畸形(CDC)被认为是中轴骨骼最严重和致残的病理。CDC的患病率约为每1000名新生儿0.5-1.0 [1-2]。椎体异常是由于胚胎发生的前6周，由于暴露于致畸因子和基因组突变损伤而导致的形成或分割过程中断[3-4]。在CDC中最常见的是先天性脊柱侧凸——早期脊柱侧凸最复杂的类型之一[5]。脊柱最常见的畸形，导致先天性畸形过程的进行性，是对椎骨形成的破坏。脊椎的缺陷会导致严重的畸形、神经系统紊乱和胸部器官生长受限，这可能是心肺功能不全综合征的原因[6]。为了防止儿童出现神经功能缺陷和脊柱先天性畸形，有必要及时发现渐进性曲度并进行早期手术治疗[7]。

先天性脊柱侧凸主要是散发性的，很少发展为单基因疾病。在1-3.4%的先天性脊柱侧凸病例中发现有沉重的先天性脊柱畸形家族史。患者多发性脊柱缺陷的存在将其兄弟姐妹畸形的风险增加到2.5-3%[8-9]。高达17%的先天性脊柱侧凸患者报告近亲存在CDC，这表明脊柱畸形的遗传易感性[10]。

确定先天性脊柱畸形病因的遗传因素将有助于更好地了解其发病机制和预测畸形的发展。在了解脊柱畸形的病因和进展方面的最新进展是由遗传数据驱动的。例如，Notch信号通路中的突变包括*DLL3*、*MESP2*、*LFNG*、*HES7*、*RIPPLY2*和*NOTCH2*基因，以及其他基因的变体，例如*PAX1*、*SLC35A3*、*TBXT*、*FBN1*、*PTK7*、*SOX9*、*FLNB*和 *HSPG2*导致脊柱先天畸形[11-14]。最近*TBX6*突变的杂合变异也被确定为约11%患者先天性脊柱侧弯的遗传原因[15]。

研究先天畸形发生的遗传先决条件是一项重要而紧迫的任务。了解这种现象的生物学性质，可以进行有针对性的预防和制定诊断措施，从而在儿童生命的最初几年就可以识别以发育异常为背景的渐进过程的脊柱畸形椎体[16]。反过来，这将允许早期手术干预。

目的是研究和评估来自国内外专门研究先天性脊柱侧凸候选基因*TBX6*的科学出版物的数据。

材料与方法

为实现这一目标，研究了70篇关于先天性脊柱侧弯*TBX6*候选基因研究数据的评估和分析的科学出版物。其中49份已鉴定，国内 - 2份，其余为国外出版物，这些出版物提供了导致人类和动物URT基因的分子分析信息。从科学电子数据库PubMed、Cochrane图书馆、科学网、SCOPUS、MEDLINE、eLibrary、Cyberleninka获得了撰写文献综述的科学出版物。审查期间为2008年至2021年1月。本综述包含了2008年之前发表的一些文献来源，因为它们包含了在后来的出版物中没有反映的重要信息。

使用以下关键词进行文献检索："先天性脊柱侧弯"（congenital scoliosis）、"先天性脊柱畸形"(congenital vertebral malformation)、"*TBX6*基因"（*TBX6*基因）、"16p11.2染色体"（16p11.2染色体）、*TBX6*介导的基因(TBX6-mediated genes)、双等位基因突变 (bi-allelic mutation)、脊椎动物分割(vertebrate segmentation)、体节发生(somitogenesis)。

*纳入标准：*系统评价、荟萃分析、多中心研究、对照队列研究、先天性脊柱畸形患者的非对照队列研究。

*排除标准：*临床病例、观察结果、会议记录、遗传综合征中的先天性脊柱侧弯、与神经系统缺陷相关的先天性脊柱侧弯。

结果与讨论

符合纳入标准的主要出版物的信息列在表中。

在人类中，脊椎起源于体节，通过一个称为体节发生的过程，这是许多与基因相关的信号通路的协调工作[17]。与体细胞发生相关的基因突变或对称基因调控的破坏可能最终导致CDC的出现[18]。

在脊椎动物胚胎发生中，轴旁中胚层来源于祖细胞，最初位于胚胎的表层，后来在原肠形成过程中内化并形成前体中胚层(PSM)。随后，旁轴中胚层经历分割,并且位于神经管的外侧[19]。原始条纹分化成大量细胞，称为尾芽[20]。位于胚胎后端的尾芽含有促进后续组织形成的PSM前体[21]。在这个过程中，体节的结构逐渐同步和有节奏地形成。体节产生脊柱的椎骨、肌肉、肌腱和韧带[22]。SCM体节的胚胎发育受多种因素的调节。这些因素相互作用的详细机制已经通过几个模型进行了说明，包括广泛接受的时钟波前模型[23]。在时钟波前模型中，PSM逐渐

表格主要出版物信息

作者	出版年代	国家	样本容量	突变患者数	突变类型	脊柱病理学
Shimojima et al. [41]	2009	日本	3	2	16p11.2删除	半脊椎畸形
Ghebranious et al. [33]	2008	美国	50	3	错义突变	违反脊柱的形成和分割
Fei Qi et al. [38]	2010	中国	254	17	删除16p11.2区域 + + TCA 单倍型	违反脊柱的形成和分割
Sparrow D.B. et al. [37]	2013	澳大利亚	5	3	终止密码子	脊椎骨骨发育不良
Al-Kateb et al. [43]	2014	美国	15	-	删除和复制16p11.2区域	违反脊柱的形成和分割
Wu N. et al. [45]	2015	中国	237	23	零选项TBX6	违反脊柱的形成和分割
Baschal E.E. et al. [44]	2015	美国	42	–	–	家族性特发性脊柱侧弯
Lefebvre M. et al. [35]	2017	法国	56	4	16p11.2删除	脊柱节段障碍
Takeda K. et al. [39]	2017	日本	94	9	错义突变	违反脊柱的形成和分割
Otomo N. et al. [36]	2019	日本	200	10	16p11.2删除，错义突变	违反脊柱的形成和分割，脊椎肋骨发育不良
Liu J. et al. [46]	2019	中国	497	58	TBX6 LoF	反脊柱的形成和分割，X-XII肋骨发育不全
Chen W. et al. [47]	2020	中国	523	43	TBX6 LoF	违反脊柱的形成和分割
Yang Y. et al. [48]	2020	中国	584	28	MEOX1, MEOX2, Mesp2, MYOD1, Myf5, RIPPLY1和RIPPLY2	违反脊柱的形成和分割
Feng X. et al. [49]	2020	中国	67	4	16p11.2/TBX6删除	违反脊柱的形成和分割

被分割成重复体节，由Notch、WNT和FGF信号通路的周期性激活驱动[24]。在体节发生中，分割发生在体节形成之后，此时形成的体节接收时钟信号[25]。例如，MESP2由NICD（Notch path）和TBX6激活。MESP2最初在体节的有限区域（一个片段的长度）中表达，然后在片段的后半部分区域表达RIPPLY1和RIPPLY2，从而根据区域定义体节的未来边界信号动作[26，27]。下游靶基因*RIPPLY2*被激活，被认为是MESP2和TBX6的负反馈抑制剂。这个过程有助于定义新形成的节段的前缘。MESP1和MESP2的失活导致旁轴中胚层的形成受损[28]。

*T-box*基因编码参与调控发育过程的转录因子。*TBX6*基因位于16p11.2区域，是系统发育保守基因家族的成员[29，30]。正如我们所看到的，*TBX6*基因是后体节形成所必需的，也是中胚层正确旁轴分化和分割不可或缺的组成部分[31，32]。

Ghebranious和合著者表明*T*和/或*TBX6*基因的突变可导致脊柱先天性畸形[33]。

基于对小鼠和人体模型基因分型结果的分析时，White和合著者（2005）表明*TBX6*可能是与先天性脊柱侧弯相关的潜在候选基因组[34]。当*TBX6*与Notch配体相互作用时，这些表型类似于一些人类先天性缺陷的表型，例如脊椎肋骨发育不良和先天性脊柱侧弯[35，36]。

Sparrow和合著者(2013)利用全异域测序法研究了一个具有脊椎钢表型的马其顿家族的三代人。在5名家庭成员中，3人有脊柱钢质偶发性腹腔镜的临床表现和放射学证据，2人没有临床表现。经证实，三个受影响的家庭成员在*TBX6*基因中具有杂合无义突变，而两个没有临床表现的纯合野生型，表明在鉴定出具有完全外显性突变的家庭中与疾病隔离[37]。

据报道，*TBX6*基因的几个单核苷酸多态性(SNP)与脊柱先天性畸形有关。Fei和合著者在254名中国人的*TBX6*基因中对它们进行基因分型（其中先天性脊柱侧弯患者127例，对照组127例）。两个SNP分析rs2289292（SNP1，外显子8）和rs3809624（SNP2,5'-非翻译区）在病例和对照之间存在显着差异（分别为$p=0.017$和$p=0.033$）。单倍型分析显示

SNP1/SNP2病例与先天性脊柱侧弯之间存在显着关联(p=0.017) [38]。

一项病例对照关联研究首先在中国人群中进行[39]。该研究确定了两个与先天性脊柱侧弯相关的TBX6单核苷酸多态性。2015年开展了*TBX6*基因的分子遗传学研究，在华南地区先天性脊柱侧弯患者队列中发现了核苷酸序列变异的复杂杂合遗传[39，40]。在10%的患者中，在染色体16p11.2上发现了杂合缺失，其中包括*TBX6*基因或*TBX6*基因中的移码突变。有趣的是，对于不同的等位基因，所有在*TBX6*基因中具有杂合无效突变的患者都有一个共同的单倍型。这种先天性脊柱侧弯的原因是由罕见的无效突变和亚型单倍型的复杂遗传引起的，在日本和欧洲队列研究后得到进一步证实。这些研究还在94名先天性脊柱侧弯患者中的9名和56名先天性脊柱侧弯患者中分别发现了*TBX6*基因中类似的双等位基因变异[40]。

Shimojima和合著者（2009）报告了一名发育迟缓、腹股沟疝、T_{10}、T_{12}和L_3半椎体的3岁男孩；缺少右侧XII肋骨和左侧XII肋骨发育不全。患者的16p11.2缺失为593kb，母亲的缺失与染色体微阵列分析确定的相同[41，42]。

Al-Kateb和合著者（2014)分析了从10名具有CDC染色体16p11.2缺失的患者获得的X射线数据。其中8人患有先天性脊柱侧弯，其余人患有特发性脊柱侧弯。他们进一步回顾了先前报道的5名具有16p11.2区域重排和类似骨骼异常的患者，并得出结论，其中2名患有先天性脊柱侧弯，而其余的患有特发性脊柱侧弯[43]。

Baschal和合著者(2015)对42名家族性特发性脊柱侧弯患者进行了Sanger测序，并未发现该疾病与*TBX6*基因相关[44]。

Wu和合著者澄清了TBX6无效变异和常见的亚型TBX6等位基因共同导致先天性脊柱侧凸的发展。在161例CDC患者组中，发现先天性脊柱侧凸患者有17例异型TBX6-零突变.本组包括12例16p11.2染色体反复缺失，包括*TBX6*基因和5个单核苷酸变异（1个无义突变和4个阅读框移位突变）。鉴定出具有染色体16p11.2微缺失的表型正常个体和这种微缺失携带者中先天性脊柱侧弯的不协调家族表型表明，*TBX6*等位基因之一中存在杂合无效突变不足以导致先天性脊柱侧弯[45]。

Liu和合著者(2019)对497例先天性脊柱侧凸患者进行了大规模的分子遗传学研究，结果发现*TBX6*基因突变发生率为10%（n=52）。作者区分了一种遗传上新型的先天性脊柱侧弯-TBX6 相关的先天性脊柱侧弯(TABS)。TABS表型的特征是下胸椎和腰椎区域的蝶形椎体和半椎体没有明显的脊髓畸形[46]。

Liu和合著者(2019)已发展基于表型数据和临床可测量的内表型预测TABC的TACScore模型。TACScore包括以下标准：位于下胸椎和腰椎(T_8-S_5)的分段半椎体/蝴蝶椎骨、椎体畸形的数量、椎管内缺陷的存在以及肋骨畸形的类型[46]。

基于分子遗传学研究Chen和合著者(2020)创建了TABS基因给药模型。在推定的模型中，TABS患者的表型随着*TBX6*基因的特征性突变而不同。由杂合亚型单倍型或双等位亚型单倍型引起的TBX6功能的轻微丧失可以被认为是可接受的突变剂量，不会导致CDC表型。然而，一个杂合的严重低形或无效等位基因仍会导致先天性脊柱侧弯。严重的亚型或无效等位基因与轻度亚型单倍型的组合导致先天性脊柱侧凸的高外显率，导致最常见的TABS表型[47]。

Yang和合著者(2020)在584名先天性脊柱侧弯患者中，对*TBX6*介导的候选基因*MEOX1*、*MEOX2*、*MESP2*、*MYOD1*、*MYF5*、*RIPPLY1*和*RIPPLY2*进行了遗传研究。TABS表型的特征是下胸椎和腰椎区域的蝶形椎体和半椎体没有明显的脊髓畸形[46]。

Feng和合著者(2021)分析了一组先天性脊柱侧弯患者，发现在67名患者中有3名（4.5%），杂合TBX6变异与先天性脊柱侧弯相关[49]。

结论

本综述中介绍的国内外作者的科学出版物可以集中获取有关先天性脊柱侧弯遗传危险因素等儿科骨科急迫问题的主要方面的最新信息。对这方面工作的分析表明，*TBX6*基因突变对先天性脊柱侧凸的发生有显著影响。

阐明CDC的遗传因素和临床表型的分子病因学的进展为根据潜在遗传病因学进一步细化先天性脊柱侧凸症状分类提供了机会。这种遗传分类可以导致创建用于预测儿童先天性脊柱畸形进展的模型。

附加信息

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