

THE GENE POLYMORPHISMS OF *COL1A1* AND *VDR* IN CHILDREN WITH SCOLIOSIS

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Background. Identification of the genetic prerequisites for development of spinal deformity.

Aim. The aim of the study was to assess the frequency of distribution of alleles and genotypes for polymorphisms –3731A/G (Cdx2) and +61968T/C (TaqI) of the VDR gene and –1997G/T and +1245G/T (Sp1) of the COL1A1 gene in children with scoliosis of various etiologies and in healthy children.

Materials and methods. Clinical genetic testing was performed in 154 children with congenital scoliosis, 145 children with idiopathic scoliosis, and 278 children without an orthopedic pathology. The molecular genetic testing was performed by PCR.

Results. Genotype tt/GG VDR gene incidence is twice as high in children with congenital scoliosis than in children who do not have scoliosis (11% and 5.2% of cases, respectively; $\chi^2 = 4.17$; $df = 1$; $p = 0.04$).

Conclusion. We have found that children with the allele carriers t(C) and genotype tt(CC) in patients with congenital scoliosis were significantly more likely than children without scoliosis spinal deformity.

Keywords: congenital scoliosis, idiopathic scoliosis, polymorphism, genes.

ИССЛЕДОВАНИЕ ПОЛИМОРФИЗМОВ ГЕНОВ *COL1A1* И *VDR* У ДЕТЕЙ СО СКОЛИОЗОМ

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Актуальность. Выявление генетических предпосылок развития деформации позвоночника.

Цель работы — провести сравнительный анализ распределения частоты аллелей и генотипов по полиморфизмам –3731A/G (Cdx2) и +61968T/C (TaqI) гена VDR и –1997G/T и +1245G/T (Sp1) гена COL1A1 у пациентов со сколиотической деформацией позвоночника различной этиологии и у детей без ортопедической патологии. Проанализировать взаимосвязь исследованных молекулярно-генетических маркеров с развитием сколиоза.

Материалы и методы. Клинико-генетическое обследование было проведено у 154 детей с врожденным сколиозом, 145 детей с идиопатическим сколиозом и 278 пациентов без ортопедической патологии. Молекулярно-генетическое тестирование осуществлялось методом ПЦР.

Результаты. Генотип tt/GG гена VDR встречается в группе детей с врожденным сколиозом более чем в 2 раза чаще, чем в группе детей, не имеющих сколиотической деформации позвоночника, соответственно в 11 и 5,2 % случаев ($\chi^2 = 4,17$; $d. f. = 1$; $p = 0,04$).

Заключение. Нами выявлено, что дети — носители аллеля t(C) и генотипа tt(CC) среди пациентов с врожденным сколиозом встречались достоверно чаще по сравнению с детьми, не имеющими сколиотической деформации позвоночника ($\chi^2 = 6,79$; d. f. = 2; $p = 0,03$).

Ключевые слова: врожденный сколиоз, идиопатический сколиоз, полиморфизм, гены.

Introduction

Scientists and clinicians have been involved in the search for etiologic factors of spinal deformities in children for several centuries. The emergence of molecular, genetic, and biochemical technologies enabled evaluation of scoliosis (which is far from complete at the present stage of medical development) from more fundamental positions [1, 2].

Spinal deformities that are found in the postnatal period are congenital. However, curvature of the spine also can be due to vertebral anomalies that may manifest during growth and development of a child with anatomically normal structure, in which case the scoliosis is idiopathic (IS). Regardless of the nature of the deformity, scoliosis is a multifactorial disease, the formation of which is due to genetic determinants and environmental factors [3].

In connection with the development of IS and congenital scoliosis, the candidate genes were studied; that is, the epidermal growth factor gene [4], *DLL3* [5], *WNT3A* [6], *TBX6* [7], and so forth. The genes whose products are involved in the processes of bone metabolism and osteogenesis are considered as “candidate” genes that contribute to the formation of spinal deformities. Among many genes in this group, the vitamin D receptor gene (*VDR*) and the type I collagen gene (*COL1A1*) are considered to be particularly significant [8].

It is known that vitamin D and its active metabolites have a key role in phosphoric calcium homeostasis and bone metabolism, and regulate the growth and differentiation of cells in various target organs [9-10]. Vitamin D is a ligand for a nuclear receptor encoded by the *VDR* gene and it is a regulator of the activity of many target genes through its interaction with specific DNA sequences in the promoter regions of these genes [11]. Under the influence of calcitriol or vitamin D₃, the expression of the type I collagen gene decreases [12, 13].

The organic matrix of bones is represented by 95% type I collagen, and its amino acid structure is encoded by the *COL1A1* gene [14].

The *VDR* gene is located on chromosome 12q12-14. It consists of 60,000 nucleotide pairs and includes 10 exons and 8 introns [14]. Several polymorphisms of the length of the restriction fragments (RFLPs) in the *VDR* gene have been identified (BsmI, TaqI, ApaI, FokI, polyadenyl mononucleotide [poly (A) repeat]). Functional mutations in this gene affect mineral metabolism and mineral density of bone tissue [14]. The site for the TaqI-restrictase is located inside the 9th exon. This polymorphism is characterized by the replacement of thymine (T) with cytosine (C; rs731236). In a number of studies, the connection of this polymorphism of the *VDR* gene with bone mineral density [8] has been noted, as well as with diseases, such as osteoporosis [14], chronic periodontitis [15], and type 1 diabetes mellitus [16].

The *Cdx2* polymorphism (rs11568820) is located in the promoter region of the *VDR* gene and is associated with decreased bone mineral density [17], an increased risk of fractures, in particular, the spine [18], and colorectal cancer [19]. Suh et al. [20] analyzed the distribution of alleles and genotypes according to the *Cdx2* polymorphism of the *VDR* gene in 198 girls with IS of II to IV degrees and in healthy girls. There were no significant differences in their frequencies, or in bone mineral density values in children with IS carriers of different alleles and genotypes of *Cdx2* polymorphism of the *VDR* gene [20]. At the same time, a number of studies have revealed a decrease in bone mineral density values in children with IS [21, 22], and osteopenia has been considered as a risk factor for the progressive course of IS [23].

In studies on the polymorphism of Sp1 (rs1800012) located in the first intron of the *COL1A1* gene, an association of allele s with reduced bone mineral density, osteoporosis, and fracture risk was revealed [24]. Some studies have proved that in carriers of the allele s in the homozygous

and heterozygous states there is an impairment of the collagen function and a predisposition to osteoporosis [25]. In addition, the decrease in bone mineral density was observed in carriers of certain combinations of genotypes, -1997G/T (PCOL2) and +1245G/T (Sp1) of the *COL1A1* gene [26, 27].

Analysis of the data of previous studies led to the conclusion that structural changes in the genes of the *VDR* and type I collagen can be associated with the development of congenital and acquired spinal deformities. The aim of this study was to evaluate the molecular and genetic testing of the -3131A/G (Cdx2) and +61968T/C (TaqI) *VDR* genes and -1997G/T (PCOL2) and +1245G/T (Sp1) of the *COL1A1* gene in patients with scoliotic deformity of various etiologies and healthy children. We subsequently studied the distribution of frequencies of alleles and genotypes according to the polymorphisms studied, and analysis of the relationship between the studied molecular and genetic markers with the development of scoliosis.

Materials and methods

From 2008 to 2011, we examined 195 children 6 months to 17 years old with congenital scoliosis. Children with scoliotic spinal deformity in the structure of various genetic syndromes were excluded from the study (41 patients). Comparison group 1 consisted of 145 patients (12–18 years old) with IS of II to IV degrees of severity, who were treated on an inpatient basis in the clinic of spine pathology and neurosurgery of the Turner Scientific and Research Institute for Children's orthopedics. Comparison group 2 included 278 children (aged 1–18 years) who did not show signs of spinal deformity at the time of examination (the unstable impaired posture was allowed). These patients underwent outpatient examination for diseases not related to skeletal pathology. All patients voluntarily signed the informed consent to participate in the study.

Table 1 shows the distribution of the study groups of children by sex and age.

Table 1

Distribution of children in the study groups by sex and age

Sex group	Congenital scoliosis <i>n</i> , %	Average age (years)	IS <i>n</i> , %	Average age (years)	Control <i>n</i> , %	Average age (years)
Boys	63 (40.9)	7.2 (+0.4)	15 (10.3)	15.4 (+0.1)	124 (44.7)	11.2 (+0.2)
Girls	91 (59.1)		130 (89.7)		154 (55.3)	
Total	154		145 (100)		278 (100)	

DNA for the study was isolated from peripheral blood leukocytes via a standard phenol-chloroform extraction method. The TaqI and Cdx2 polymorphisms of the vitamin D receptor gene (*VDR*) were determined via the RFLP method with the use of the restrictases TaqI and Cdx2. The Sp1 polymorphism of the $\alpha 1$ gene of the collagen type I chain (*COL1A1*) was determined via the RFLP method with the use of the BseII restrictase. The 1997G/T (rs1107946) polymorphism of the $\alpha 1$ gene of the collagen type I chain (*COL1A1*) was determined by the RFLP method using the BstMAI restrictase.

Statistical data processing was performed using Statistica 5.5 software (Stat-Soft, Inc.). The Hardy–Weinberg equilibrium was used to assess the correspondence of the distribution of genotypes on the polymorphic markers

studied. The Pearson χ^2 criterion was used for comparative analysis of the frequency distribution of alleles and genotypes based on the studied polymorphisms in the patients with congenital and idiopathic scoliosis, as well as in children without scoliotic deformity. The differences at $P < 0.05$ were considered statistically significant.

The presence of the relationship of certain genotypes with the development of scoliotic deformity was determined by the odds ratio (OR) value, which is an indicator reflecting how many times the probability of being in the “case” group (patients) differs from the probability of being in the “control” group (healthy) for the carrier of a certain genotype (allele) according to the studied polymorphisms of the *VDR* and *COL1A1* genes: $OR = (A/B)/(C/D)$, where *A* and *B* are the number of patients having and not

having a mutant allele, respectively; and *C* and *D* are the number of healthy patients having and not having a mutant genotype or allele, respectively. According to *OR*, this genotype is supposed to be associated with the risk of development of the disease: *OR* = 1 indicates the lack of relation of this genotype with the risk of development of the disease, *OR* > 1 indicates the increased risk of development of the disease, while *OR* < 1 indicates a negative association of the DNA marker with development of the pathology. For calculations, the Calculator software for calculating statistics in case-control studies was used (available in the public domain at <http://test.tatotili.ru/calculator.php>). For *OR*,

a confidence interval (CI) at a 95% significance level was calculated.

Results and discussion

Distribution of frequencies of alleles and genotypes of *VDR* and *COL1A1* genes on all the studied polymorphisms in the analyzed samples of the patients examined corresponded to the Hardy-Weinberg equilibrium. The results of the allele and genotype distribution on polymorphisms of the *VDR* gene as +61968T>C, -3731A>G, and those of the *COL1A1* gene as +1245 G>T, -1997 G>T in patients with congenital and acquired scoliosis, and children without spinal deformities are shown in Table 2.

Table 2

The distribution of frequencies of alleles and genotypes of the genes *VDR* (+61968T>C, -3731A>G) and *COL1A1* (+1245 G>T, -1997 G>T) in groups of patients T with congenital and IS, and children without spinal deformity

Genes. alleles. genotypes	Frequencies of alleles and genotypes		
	Congenital scoliosis	Control	IS
<i>VDR</i>			
TaqI (+61968T/C)	<i>n</i> = 154	<i>n</i> = 271	<i>n</i> = 145
T/T	0.396	0.498	0.448
T/t (T/C)	0.455	0.421	0.428
t/t (C/C)	0.149	0.081	0.124
Statistics	$\chi^2 = 6.79$; d. f. = 2; <i>p</i> = 0.03		$\chi^2 = 2.31$; d. f. = 2; <i>p</i> = 0.31
T*	0.623	0.708	0.662
t**	0.377	0.292	0.338
Statistics	$\chi^2 = 6.51$; d. f. = 1; <i>p</i> = 0.01		$\chi^2 = 1.91$; d. f. = 1; <i>p</i> = 0.17
Cdx2(-3731A/G)	<i>n</i> = 154	<i>n</i> = 269	<i>n</i> = 145
A/A	0.052	0.026	0.028
A/G	0.266	0.279	0.310
G/G	0.682	0.695	0.662
Statistics	$\chi^2 = 1.94$; d. f. = 2; <i>p</i> = 0.38		$\chi^2 = 0.48$; d. f. = 2; <i>p</i> = 0.79
A	0.185	0.165	0.183
G	0.815	0.835	0.817
Statistics	$\chi^2 = 0.53$; d. f. = 1; <i>p</i> = 0.47		$\chi^2 = 0.40$; d. f. = 1; <i>p</i> = 0.53
<i>COL1A1</i>			
Sp1 (+1245 G/T)	<i>n</i> = 154	<i>n</i> = 276	<i>n</i> = 145
S/S (G/G)	0.675	0.714	0.724
S/s (G/T)	0.292	0.272	0.248
s/s (T/T)	0.032	0.014	0.028
Statistics	$\chi^2 = 1.88$; d. f. = 2; <i>p</i> = 0.39		$\chi^2 = 1.07$; d. f. = 2; <i>p</i> = 0.59
S*	0.821	0.850	0.848
s**	0.179	0.150	0.152
Statistics	$\chi^2 = 1.17$; d. f. = 1; <i>p</i> = 0.28		$\chi^2 = 0.00$; d. f. = 1; <i>p</i> = 0.96
<i>PCOL2</i>			
(-1997 G/T)	<i>n</i> = 154	<i>n</i> = 268	<i>n</i> = 145
G/G	0.701	0.690	0.697
G/T	0.253	0.280	0.262
T/T	0.045	0.030	0.041
Statistics	$\chi^2 = 0.94$; d. f. = 2; <i>p</i> = 0.62		$\chi^2 = 0.48$; d. f. = 2; <i>p</i> = 0.79
G	0.828	0.830	0.828
T	0.172	0.170	0.172
Statistics	$\chi^2 = 0.01$; d. f. = 1; <i>p</i> = 0.93		$\chi^2 = 0.01$; d. f. = 1; <i>p</i> = 0.92

Note: d.f. is the number of degrees of freedom; T* and S* are alleles having no site for the restrictase; t** and s** are alleles having a site for the restrictase.

Comparative analysis of frequencies of alleles and genotypes on polymorphism +61968T>C of the *VDR* gene in the children with and without scoliotic deformity of the spine revealed differences in their distribution. Among patients with congenital scoliosis, children who were carriers of allele t(C) (0.377 vs 0.292; $\chi^2 = 6.51$; d.f. = 1; $P = 0.01$) and the genotype tt(CC) (0.149 vs 0.081; $\chi^2 = 6.79$; d.f. = 2; $P = 0.03$) were more common compared to children without scoliotic deformity. The OR for carriers of the TT genotype was 0.66 (95% CI, 0.44–0.99), and for the genotype tt(CC) it was 1.99 (95% CI, 1.07–3.70). It is possible that carriership of the *VDR* gene allele t can be regarded as a marker of increased risk of the development of congenital scoliosis. Comparative analysis of the distribution of alleles and genotypes on polymorphism –3731A>G of the gene *VDR* and the polymorphisms (+1245 G>T, –1997 G>T) of the *COL1A1* gene revealed no significant differences in the children with congenital and IS. There also were no significant differences in the distribution of alleles and genotypes on the

studied polymorphic markers when comparing their frequencies among patients with different types of scoliosis and the control group.

Analysis of the distribution of alleles and genotypes combinations of the *VDR* gene (+61968T>C,–3731A>G) was conducted in patients with congenital and IS and in the children without spinal deformity (Table 3). Carriership of the genotype tt/GG of the *VDR* gene (+61968T>C,–3731A>G) is found in the children with congenital scoliosis more than two times more often than in the children without scoliosis (11% and 5.2% of cases, respectively; $\chi^2 = 4.17$; d.f. = 1; $P = 0.04$). This genotype was detected in 8.7% of children with IS. There were no statistical differences in the carriership of this genotype in the patients with IS and in children without scoliotic deformity of the spine.

Analysis of the distribution of combinations of alleles and genotypes of the *COL1A1* gene (+1245 G>T,–1997 G>T) was performed in patients with congenital and IS and children without spinal deformity (Table 4).

Table 3

The distribution of genotype combinations of alleles and genotypes of *VDR* (+61968T>C,–3731A>G) in patients with congenital and IS and in children without spinal deformity

Gene, polymorphisms	Genotype combinations	Congenital scoliosis <i>n</i> (%)	IS <i>n</i> (%)	Control <i>n</i> (%)
<i>VDR</i> +61968T>C–3731A>G	TT/GG	42 (27.2)	45 (31.0)	93 (34.5)
	TT/AA	3 (1.9)	0	3 (1.2)
	TT/AG	16 (10.4)	20 (13.7)	40 (14.8)
	tt/GG	17 (11.0)	12 (8.7)	14 (5.2)
	tt/AA	1 (0.7)	1 (0.4)	1 (0.4)
	tt/AG	5 (3.2)	5 (3.5)	6 (2.3)
	Tt/GG	44 (28.6)	39 (26.9)	79 (29.3)
	Tt/AA	4 (2.7)	3 (2.0)	5 (1.9)
	Tt/AG	22 (14.3)	20 (13.8)	28 (10.4)

Table 4

The distribution of combinations of alleles and genotypes of *COL1A1* (+1245 G>T,–1997 G>T) in patients with congenital and IS and in children without spinal deformity

Gene, polymorphisms	Genotype combinations	Congenital scoliosis (<i>n</i> , %)	IS (<i>n</i> , %)	Control (<i>n</i> , %)
<i>COL1A1</i> +1245 G > T / –1997 G > T	ss/GG	5 (3.2)	4 (2.7)	8 (3.0)
	ss/TT	0	0	0
	ss/TG	0	0	0
	SS/GG	67 (43.5)	68 (46.9)	120 (44.9)
	SS/TT	6 (3.9)	6 (4.1)	7 (2.6)
	SS/TG	31 (20.1)	32 (22.2)	63 (23.5)
	Ss/GG	36 (23.5)	29 (20.0)	57 (21.2)
	Ss/TT	1 (0.6)	0	0
	Ss/TG	8 (5.2)	6 (4.1)	13 (4.8)
	N		154	145

It should be noted that ss/TT and ss/TG genotypes were not found in children either with or without scoliosis. There was no difference in the distribution of combinations of alleles and genotypes of *COL1A1* (+1245 G>T, -1997 G>T) in patients with congenital scoliosis and children without spinal deformity ($\chi^2 = 3.08$; d.f. = 6; $P > 0.05$), as well as in patients with IS and children without scoliosis ($\chi^2 = 1.07$; d.f. = 6; $P > 0.05$). There was no difference in the distribution of combinations of alleles and genotypes of *COL1A1* (+1245 G>T, -1997 G>T) in patients with congenital and IS ($\chi^2 = 1.92$; d.f. = 6; $P > 0.05$).

Conclusions

Thus, our results indicated that there were significantly more children who were carriers of allele t(C) and genotype tt(CC) among patients with congenital scoliosis compared to children without scoliotic spinal deformity. The genotype tt/GG of the gene *VDR* was found in children with congenital scoliosis more than 2 times more often than in children without scoliotic spinal deformity.

For a more reliable assessment of the contribution of gene polymorphism, the products of which are involved in bone metabolism and in the development of congenital and acquired spine deformities, further studies involving more extensive patient samples are required.

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