GENETIC MARKERS OF IDIOPATHIC AND CONGENITAL SCOLIOSIS AND DIAGNOSIS OF SUSCEPTIBILITY TO THE DISEASE: REVIEW OF THE LITERATURE*

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Inheritance of scoliosis has been studied for many decades, and it was found that it is usually complex, although the literature describes the families with a clear Mendelian principle of transmission of this disease through generations. Hence, it was necessary to try to find the genetic basis of the disease, that is, genes whose mutations can cause the development of scoliosis. And such mutations may serve as markers of the disease assisting in its diagnosis before the onset of spinal deformities. In cases of hereditary disorders of the spine, deformities often continue to evolve even after surgery. In all cases it is important to know what causes led to the development of scoliosis, and such information is certainly important in assessment of the risk of developing disease in a patient, because it allows predicting the effects of a particular mutation, as well as choosing a strategy and tactics of the treatment.
Key Words: idiopathic scoliosis, scoliosis inheritance, genetics.

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Idiopathic scoliosis [EC or (IS) Online Mendelian Inheritance in Man (OMIM) number 181800)] is characterized by the three-dimensional deformation of the thoracic and / or lumbar spine, and a torsion (twisting around the vertical axis) plays a leading role in mechanogenesis of deformation. If to define an idiopathic scoliosis as curvature of the spine (Cobb angle) of at least 10, it is the most frequent spinal deformity occurs in 0.5–10 % of adolescents in all human populations [52]. The impetuous development of the disease usually occurs in a period of rapid growth during adolescence and is characterized by two significant risk factors - growth potential and being female. The initial stages of the disease often stay unnoticed because they do not cause an obvious discomfort to the patients. Usually idiopathic scoliosis is detected incidentally during medical examinations for other reasons, in the course of routine medical inspections or school routine fluorography. Often, spinal deformities in children are identified at the stages when the Cobb angle is greater than 10°. Such children should get into the group of intensive observation and undergo frequent medical examinations in order to identify the progress in the development of the disease and to take the right and timely decision on the choice of method of treatment - conservative or surgical.

The definition of «idiopathic scoliosis» includes all spinal deformities which developed for no apparent reasons after birth (http://www.srs.org/). At the same time, congenital scoliosis stands out well in medicine, and it often means the spinal abnormalities, noticeable at birth. It has long been observed that idiopathic scoliosis often occurs in some families in a series of generations, and that gave the reason to believe the genetic nature of idiopathic scoliosis. It is also known that the development of spinal deformity can be caused not only by physical factors (environmental factors), but genetic reasons also. Inheritance of idiopathic scoliosis has been studied for many decades, and it was found out that this inheritance is generally complicated, although the literature describes the families with obvious Mendelian principle of transmission of this disease in the generations [10]. In general, population-based studies show that risk of spinal deformity among first degree relatives comprises 11.1 % compared to 2.4 % for second degree relatives and 1.1 % in third degree relatives [9, 54, 55]. Twin method is widely used in genetic researches, and it allows discriminating the influence of environmental factors from genetic factors in the occurrence and development of diseases. The method is based on the fact that identical twins have identical genomes, unlike fraternal twins whose genomes are similar only on 50%. If the disease occurs significantly more frequently among identical twins, then hereditary nature of this disease is obvious. A recent study in a large population samples with identical and fraternal twins reliably showed that idiopathic scoliosis is genetically determined [15]. It was naturally to try

to find the genetic basis of the disease, ie, the genes whose mutations can provoke the development of scoliosis. Such mutations may serve as markers of the disease, and they may be used for diagnosis of possible deformation of the spine before its clinical manifestation. Modern age-related classification of scoliosis (idiopathic and other forms) identifies the following forms, depending on the age of diagnosis of spinal deformity: infantile (up to 4 years), juvenile (4 to 10 years), adolescent scoliosis (11–20 years), and scoliosis of adults (over 20 years) [1]. However, numerous studies failed to identify age-specific genetic markers of idiopathic scoliosis, though a number of genes involved in the pathogenesis were identified. Congenital scoliosis is the second most frequent etiologic form of spinal deformities caused by vertebral abnormalities formed in utero (often in combination with abnormalities of ribs). These anomalies are extremely variable in severity, extent and rate of deformation progression, but they can be classified into three main groups: anomalies of formation (wedge-shaped vertebrae and hemivertebrae, butterfly-shaped vertebrae), anomalies of segmentation (abnormal segmentation of the spinal column at any level and any extension), and mixed anomalies [1]. Often, congenital anomalies of the spine are the result of genetic mutations occurring in different syndromes such as Klinefelter, Marfan, Klippel-Feil and others [8]. These mutations disrupt the work of individual genes or entire gene cascades responsible for the development and function of organs and tissues not related directly to the development of bones and musculoskeletal system as a whole. But the dysfunction of other organs can lead to anomalies in musculoskeletal system.

Genetic determination of spinal deformities

Mutations in the genes responsible for the process of embryonic development as a whole can cause the congenital spinal deformities. It is known a number of genes expressing at different stages of embryonic development, often in cycles «turning on» and «turning off», and driving the mechanisms of anlage and development of organs and tissues, eg, FGF, Wnt, Notch and other genes [38], and they, in turn, are managed by a number of regulatory genes. In these identified gene cascades, often multi-layered, the breakages (mutations in genes) may occur that results in disorders of development processes of bone tissue, and, consequently, to the abnormalities of spine and musculoskeletal system in whole. However, not all forms of congenital scoliosis are inherited. Being very complicated, the embryonic development is a very sensitive mechanism, and it reacts on many environmental factors which can affect the gene expression, not changing the genes themselves. Effects of alcohol, drugs and chemicals, diseases, and physical factors on mother organism during pregnancy are well-known, they often lead to abnormal fetal development that is expressed in the spine deformities or, in whole, abnormalities of the musculoskeletal system. It is obvious that it is impossible to predict the effects of a particular factor on the developing fetus, especially to evaluate the extent and direction of the influence. It is obvious that it is not possible to predict the effects of different factors on the developing fetus, especially to determine the extent and direction of the impact. Both for the patient and the physician it is highly important to know the causes of congenital scoliosis. The deformities caused by environmental factors are not inherited and, as a rule, has no relapses after surgical or non-surgical correction. However, in the case of inherited spinal deformities, they often continue to progress even after surgery. In all cases, it is critical to know the causes of scoliosis, since this gives the opportunity to predict the effects of a particular mutation, as well as to choose the treatment strategy and tactics. Scoliosis is not only and not so much a cosmetic defect, this is a range of serious problems that the patient and his/her parents inevitably face: severe progressive pain syndromes associated with early degenerative changes of the spine, abnormal position and function of internal organs (heart, lungs, large vessels, and diaphragm), psychological problems and associated problems of social adaptation and others. All this taken together leads to the need to make decision about extensive and traumatic surgical operation in many patients. Therefore, the maximum early diagnosis of scoliosis allowing timely to start an optimal treatment in each particular case, is very important [1]. A lot of attempts to identify genes associated with the development of scoliosis being done and have been done in the past decade. Table 1 shows some results of the findings.

The structure of the connective tissue

Structural proteins are those which are involved in extracellular matrix formation. Genes encoding fibrillin (FBN1), elastin (ELN), collagen type 1 A1 and A2 (COL1A1, COL1A2), collagen type 2 A1 (COL2A1), aggrecan (ACAN) have shown no association with idiopathic scoliosis in linkage analysis [4, 25, 29, 33, 63]. Montanaro et al. [31] in the study of a large sample of Italian triplets have shown that intragenic polymorphism of microsatellites (short tandem repeats) in 3' untranslated region of matrilin-1 gene (MATN1) was associated with adolescent idiopathic scoliosis. Other authors found a statistically significant association between SNP rs1065755 of the matrilin-1 gene and probability of adolescent idiopathic scoliosis [3]. Another SNP rs1149048 at the same gene was investigated by Chen et al [6, 7]. They have shown that carriers of GG genotype have a significantly higher risk of scoliosis than carriers of AA and AG genotypes. In addition, the GG genotype carriers incline to more severe deformity of the spine. Matrilin-1, also known as cartilage matrix protein, is a non-collagenous protein. It is involved in extracellular matrix formation being a bridging molecule that connects matrix components in cartilage to form a matrix network for the supporting efficiency of the spine [5]. Human genes of lysyl oxidase (LOX, LOX1, LOX2, LOX3, and LOX4) are involved in the modeling of collagen and

elastin. Despite on revealed association of these genes with scoliosis on animal models, studies of large human samples from American populations showed no evidence for this association [26]. Other studies did not find any reliable association of genes encoding matrix metalloproteinase (MMPs) and their inhibitors (TIMPs -tissue inhibitors of metalloproteinases), which are expressed during endochondral ossification, with scoliosis [23]. Although on small samples from Chinese populations [19, 20] a positive association of TIMP2 gene with curvature of the spine in the thoracic region was found, this result requires a confirmation on large independent samples. Nowak and colleagues [35] have found the differences in the expression level of TIMP2 MED13 genes in patients with juvenile and adolescent idiopathic scoliosis.

Table 1
Genes and their associations with scoliosis

Gene	Number of references	Number of positive associations	Number of negative associations
The structure of the connective tissue			
FBN1	1	0	1
ELN	1	0	1
COL1A1	1	0	1
COL1A2	2	0	2
COL2A1	1	0	1
ACAN	2	0	2
MATN1	3	2	1
TIMP2	1	1	0
MMP3	3	1	2
DPP9	1	0	1
LOX1, LOX2, LOX3, LOX4, LOX5	1	0	1
Bone formation and metabolism			
BMP4	1	0	1
LEP	1	0	1
CALM1	1	1	0
IL6	3	2	1
VDR	2	1	1
TNFRSF11B (OPG)	1	1	0
RANKL	1	0	1
RANK	1	0	1
Melatonin signaling pathway			
MTNR1A	3	0	3
MTNR1B	6	1	5
TPH1	3	1	2
ASMT (HIOMT)	1	0	1
AANAT (SNAT)	2	0	2
GPR50	1	0	1
Puberty and growth			
CYP17	1	0	1
ESR1 (alpha)	6	3	3
ESR2 (beta)	2	1	1
GPER (GPR30)	1	1	0
GHR	3	0	3
IGF1	3	1	2

Bone formation and bone tissue metabolism

A number of genes are the candidates on the role of markers of scoliosis, and they are associated with the formation of bones and their strength. Bone morphogenetic proteins (BMP) are polypeptide growth factors that enhance osteoblast differentiation. BMP4 is capable of stimulating de novo formation of cartilage and bone, so it was included in the study of association of its mutations with the development of scoliosis. However, no association of BMP4 gene with scoliosis was found in the Hungarian population [30]. Another gene (CALM1) – Calmodulin 1 – calcium dependent regulatory protein that manages the large number of proteins, plays a key role in the regulation of bone metabolism. It was assumed that it plays a role in the pathogenesis of scoliosis, and on a small sample from Chinese population an association of rs12885713 polymorphism with predisposition to double curvature of the spine was revealed [60]. In order to identify genes responsible for osteopenia accompanying the scoliosis, genes potentially associated with osteoporosis were examined. Positive correlation with a predisposition to the curvature of the spine for IL 6 gene was found in small samples from Italy [2], however, this correlation has not been confirmed on large samples from other populations [30]. Nevertheless, some IL6 (interleukin-6) variants have been associated with low bone mineral density of the lumbar spine in Korean women with scoliosis [22]. Apparently, CALM1, IL6, LEP and VDR genes are associated with susceptibility to the curvature of spine [47], and IL6, VDR, and OPG [12] genes - with low bone mineral density, and it requires the confirmation, according to Gorman et al [14]. On the other hand, Zhuang et al. [62] demonstrated that the frequencies

of CC genotype of CALM1 gene at -16C > T locus and homozygous genotype of growth hormone receptor (GHR) gene at I526L were statistically higher in patients with idiopathic scoliosis than in the controls. The frequency of combination of homozygous genotype I526L in the growth hormone receptor (GHR) gene with homozygous genotype in the melatonin receptor 1B (MTNR1B) gene at rs1562444 locus was significantly higher in patients with idiopathic scoliosis than in controls [41, 42].

Melatonin signaling pathway

Genes associated with melatonin, were considered as candidates for markers of scoliosis, because chickens and rats with low levels of melatonin (or no circulating melatonin) developed curvature of the spine, which could be prevented by the administration of melatonin. However, lack of significant differences in melatonin levels between people with scoliosis and healthy controls gave the basis to assume the involvement of other components of human melatonin signaling pathway to occurrence of scoliosis. Therefore, genes encoding melatonin receptors 1A (MTNR1A; Mel-1A-R) and 1B (MTNR1B; MT2; Mel-1B-R), as well as GPR50 were investigated for the role of scoliosis markers but no reliable association of these gene variants with scoliosis development was found [39, 40, 46]. For TPH1 gene (tryptophan hydroxylase) which is important in the biosynthesis of serotonin (melatonin precursor) a link with predisposition to the curvature of spine in a small sample of the Chinese population have been found [51], however, this association was not observed in large samples from Japan and the United States [34, 48]. Thus, significant correlation of genes involved in melatonin signaling pathway with predisposition to scoliosis has not been shown.

Puberty and growth

Since pathological scoliosis deformations coincide in time with rapid growth and sexual maturation of adolescents, genes involved in somatotrophs and androgen axes, were considered as potential markers of predisposition to scoliosis. The gene encoding cytochrome P450 17a-hydroxylase (CYP17) was considered as obvious candidate for a scoliosis marker due to its crucial role in the biosynthesis of androgens. However, in the sample of Japanese women its association with the development of scoliosis was not found [16]. Both forms of estrogen receptors ESR1 and ESR2 are expressed in osteoblasts and osteoclasts indicating that estrogen directly regulates osteoblast function. ESR1 gene has been extensively studied since it has PvuII (rs2234693) and XbaI (rs9340799) polymorphic loci. XbaI site polymorphism was identified as a factor of occurrence of scoliosis in samples of Chinese and Japanese patients; it was associated with predisposition to scoliosis, its progression, and abnormal growth of spine [11, 17, 53]. In other samples from Chinese population of patients with double spinal curvature an association of PvuII site with this form of scoliosis was found [49, 50]. Like for other groups of genes, the association of genes related to growth and sexual maturation, with predisposition to scoliosis was demonstrated only on small samples of patients [59], and this association has not been confirmed when the study were exposed to large samples [18]. A large group of Japanese researchers [21] were able to show the association between genetic variants of GPR126 gene and development of adolescent idiopathic scoliosis. GPR126 gene is highly expressed in cartilage, and knockdown of the gene in zebrafish causes a delay of ossification during spinal development. A team of Russian scientists in the study of a large sample of patients with adolescent idiopathic scoliosis from Central Russia have found that the allele -509T and genotype -509TT of the TGFB1 (beta subunit of transforming growth factor) gene were significantly associated with increased risk of idiopathic scoliosis in both females and males. Besides, polymorphism in TGFB1 gene was found responsible both for early onset of scoliosis and for severity of curvature in females [45]. In a small sample of the Korean population has shown an association SNPs rs2449539 in lysosomal-associated transmembrane protein 4 beta (LAPTM4B) and rs5742612 in the insulin-like growth factor 1 (IGF1) with a predisposition to scoliosis and degree of severity [32, 57, 58]. The correlation between SNPs rs12459350 in DOT1L gene and rs4794665 in C17orf67 gene with a predisposition to adolescent idiopathic scoliosis and the speed of growth during puberty was able to identify in representative sample from Chinese population [24]. Another group from China on a large sample has shown that SNPs rs11190870, rs625039, and rs11598564, located near LBX1 gene (ladybird homeobox 1) are associated with a predisposition to idiopathic scoliosis, but does not have regard to the degree of its severity [13]. However, the authors of the study of one of these SNPs on independent representative sample did show that rs11190870 is associated with degree of manifestation of scoliosis. According to them, patients with TT genotype have a greater angle of spinal curvature (Cobb angle) than patients with TC or CC genotype [19]. Zhou et al [61] have shown on reliably large sample a statistically significant association between a predisposition to scoliosis and degree of its severity and rs708567 in IL17RC gene (interleukin-17 receptor). Chinese scientists [43] have shown that polymorphism of NTF3 gene (neurotrophin 3) itself is not associated with the occurrence of adolescent idiopathic scoliosis, but polymorphism in the promoter of the gene, namely, rs11063714, is associated with degree of curvature of spine and progression of this curvature, and sensitivity of this distortion to surgical correction. Success of surgical correction of spinal curvature in idiopathic scoliosis may also be due to genetic markers of patient, and such association was shown by Xu et al. [56]. Patients with G-allele of rs9340799 polymorphic site in gene ER and A-allele of rs10488682 site in gene TPH-1 are prone to relapse after surgical correction of spinal deformity in idiopathic scoliosis. Miller and colleagues [27, 28] have analyzed a linkage between kyphoscoliosis manifestations and chromosomal regions and

identified a number of genes, which they considered as promising markers of the disease. In particular, the genes: Osteoblast-specific factor 2 or periostin, forkhead box O1A, A-kinase anchor protein 11, TBC1 domain family member 4 and glypican 5 by their opinion may be involved in the pathogenesis of kyphoscoliosis. Peng et al [37] have shown an association between certain polymorphic loci in the GPER gene (G-Protein Estrogen Receptor 1) and severity of scoliosis. Thus, all these data indicate that the majority of scoliosis is caused by genetic factors and, according to Ogilvie et al [36], almost all (97 %) of patients with adolescent idiopathic scoliosis have a hereditary predisposition to it. Table 2 summarizes some of the data about positive association of idiopathic scoliosis with mutations in certain genes, which are to some extent related to the pathogenesis of scoliosis. These genes, more precisely specific mutations in them, can be used in the design and creation of the diagnostic systems on different platforms to identify the genetic nature of scoliosis.

The potential of diagnosis of predisposition to scoliosis

All of the above gives an idea of practicability of test systems development for analysis of genetic predisposition to idiopathic scoliosis and identification of genetic causes of congenital scoliosis. The analysis of literature shows that major number of investigations aimed at finding genetic markers of scoliosis was performed on samples from South-East Asia: China, Korea and Japan, while the populations of Western Europe and North America are less studied. In Russia such studies, with one exception [45], was not carried out, and specific markers of scoliosis for this area were not described. So it have a sense to investigate a representative sample of patients with scoliosis of different etiology who were treated in the clinic of Novosibirsk Research Institute of Traumatology and Orthopedics in order to find population-specific markers of predisposition to scoliosis. Novosibirsk Research Institute of Traumatology and Orthopedics has a large patient database collected over 30 years. All the cases in this database are well characterized and classified, and therefore it is possible to find the linkages of any genetic markers with specific clinical forms of scoliosis. The database includes representatives of European race, as well Mongoloid race: Buryatia, Tuva, Khakassia, Yakutia and other East Asian and North Asian nations. Since they are relatives and have long-term historical ties with other nations of Eastern and Southeastern Asia, for which genetic markers of scoliosis are known, it is quite possible to find the same markers in Russian populations of Mongoloids as well. Representatives of European ethnicity in the Siberian region also have own characteristics due to active migration from the central regions of Russia and Eastern Europe and mixing with local and Central Asian Mongoloids. Own unique set of markers of predisposition to scoliosis could have formed among representatives of European ethnicity in the Siberian region. In addition, the Siberian population in general might be characterized by different, from other populations, frequencies of these markers. The results of the study are expected to be unique and will give the opportunity to make a list of genetic markers, which are the most represented in the region. An addition of the list of the revealed markers to the literature data in order to make it most informative will contribute to development of a test system for detecting genetic predisposition to scoliosis on the basis of DNA microchip technology. The PCR-based platform would be reasonable to use in the case of a small list of genetic markers, however, a set of genetic markers of scoliosis, in our opinion, is already large enough to apply the biochip technology for their analysis. DNA microchips for detection of specific mutations will allow a simultaneous analysis of all markers on the chip and will provide more complete information about genetic background of patient. This will substantially speed up, simplify and reduce the cost of the analysis and obtaining important information. Moreover, such a narrowly aimed DNA microchip will be not only a convenient tool for screening of patients, but it could also be used as

Table 2
Positive genetic association with idiopathic scoliosis

Gene	Number of the studied cases and healthy controls	Phenotype (Cobb angle)	Population
MATN1	50/100	>5°	Italian
	419/750	Not studied	Chinese
TIMP2	570/210	>20°	Chinese
MMP3	53/206	25–125°	Italian
CALM1	67 (40 with thoracic curve)/100	>30°	Chinese
IL6	53/206	25–125°	Italian
	198/120	>10°	Korean
VDR	198/120	>10°	Korean
TNFRSF11B (OPG)	198/0	>10°	Korean
MTNR1B	Stage I: 472/304 Stage II: 342/347 (umbilical cord blood controls)	>20°	Chinese
TPH1	103/107	>30°	Chinese
ESR1 (alpha)	202/174	25–125°	Chinese
	304/0	>10°	Japanese
	67 (40 with thoracic curve)/100	>30°	Chinese
ESR2 (beta)	218/140	12–135°	Chinese
GPER (GPR30)	389/338	>15°	Chinese
IGF1	506/227	>20°	Chinese

a research tool in the study of large and small local populations for identification of genetic markers of scoliosis.

Suchlike test systems allow the identification of a genetic predisposition to scoliosis during screening the population, or in the early stages of the disease by a doctor if the patient's family history of the disease. Information about genetic background of the disease will help your doctor to choose an appropriate method of treatment. Similar developments take place in the world, and the first test-systems have already been created. For example, ScoliScore™ AIS Prognostic Test http://www.scoliscore.com/Default1p68.html used in the US in a number of orthopedic clinics (http://www.indianaspinegroup.com/ http://www.schumacherchiropractic.com/What- is-ScoliScore-Test.html) and helps physicians to identify genetic causes of scoliosis and select a treatment strategy. In 2012, the leading vertebrological Journal "Spine" published the results of testing of "ScoliScore ™ AIS Prognostic Test", which clearly showed that prediction of the risk of developing the disease and the complexity of its course, made using the biochip, is much more accurate than those made by classical methods [44]. In Russia the patent «Method for predicting the risk of developing of idiopathic scoliosis in children» was registered under number 2456925. The method is based on polymerase chain reaction followed by restriction digestion of the PCR fragments. The presence of -509TT genotype predicts an increased risk of idiopathic scoliosis. An existence of -509CT and -509CC genotypes predicts the absence of risk for idiopathic scoliosis in children. The method allows predicting the risk of developing of idiopathic scoliosis in children on the basis of detection of the C-509T polymorphism in gene of transforming growth factor 1. However, this method implies only analysis of one genetic marker; while there far too more of these markers as demonstrated by the data of this review.

In this review, we analyzed more than 60 investigations related to the exploration and analysis of genetic factors that influence the predisposition to scoliosis. Despite the fact that such studies have been conducted for a long time, and they involve the genes associated with development of structure of connective tissue, formation and bone metabolism, Melatonin signaling pathways, sexual maturation and growth, the genetic basis of this etiology is still not clear, and forecast of appearance and development of scoliosis is some kind of art, rather than a routine medical procedure.

The phenotypic and genetic heterogeneity of scoliosis is the major difficulty for genetic investigations. Although, many of studies were carried out, but not all of them managed to find an expressed positive association of genetic markers and clinical form of scoliosis. It is expected that in the near future genomic studies will identify genetic factors that reliably associated with a predisposition to idiopathic and congenital scoliosis, and it will help to understand better their contribution to the pathogenesis of diseases. An important question is how these factors, individually and collectively, quantified the risk of disease. Quantitative analysis and stratification of datasets may also give a more precise definition of clinical subtypes within diagnoses. The identification of new genetic factors in the base of scoliosis will allow in the future calculating better the risk of occurrence and development of disease, and using less invasive form of therapy in the treatment.

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