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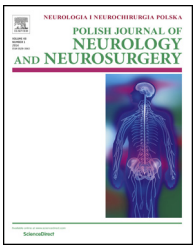

Review article

The role of polymorphisms of genes encoding collagen IX and XI in lumbar disc disease

Łukasz Janeczko [a,*], Magdalena Janeczko [b], Robert Chrzanowski [a], Grzegorz Zieliński [c]

[a] Neurosurgery Ward of St. Rafael Hospital, Krakow, Poland
[b] Department of Genetics, Polish-American Institute of Pediatrics, Krakow, Poland
[c] Department of Neurosugery, Military Hospital, Warsaw, Poland

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ABSTRACT

The intervertebral disc disease (IDD) is one of the most common musculoskeletal disorders. A number of environment and anthropometric risk factors may contribute to it. The recent reports have suggested the importance of genetic factors, especially these which encode collagen types IX and XI. The allelic variants in the collagen IX genes – *COL9A2* (Trp2) and *COL9A3* (Trp3) have been identified as genetic risk factors for IDD, because they interfere the cross-linking between collagen types II, IX and XI and result in decreased stability of intervertebral discs. Type XI collagen is a minor component of cartilage collagen fibrils, but it is present in the annulus fibrosus and nucleus pulposus of intervertebral discs. Some studies have shown the association between gene *COL11A1* polymorphism c.4603C>T and IDD. The frequency of 4603T allele was significantly higher in the patients with IDD than in the healthy controls.

1. Introduction

An intervertebral disc herniation is a primary cause of low back pain and physical impairment in about 70–85% patients younger than 45 years in Western civilizations [1]. A prevalence of the clinically significant lumbar disc disease in modern countries is estimated at about 5% [2]. The intervertebral discs show degenerative changes earlier than other musculoskeletal structures. The hyaline cartilage, which builds the upper and the lower surfaces of the intervertebral disc, consists of type II collagen (95%), type IX collagen (1%), type XI collagen (3%) and type X collagen [3,4].

The aetiology of intervertebral disc disease (IDD) is complicated, with various environmental risk factors such as mechanical injuries, age, gender, cigarette smoking, height, weight and exposure to vehicular vibration. It is still unclear at present, why the lumbar disc disease progresses to a severe condition in one group patients and does not in the others with similar environmental and anthropometric risk factors. Recently, many reports have indicated the significant participation of the genetic risk factors in a development of lumbar disc disease. There have been identified the several mutations of genes encoding the structural proteins of intervertebral disc, which may accelerate the intervertebral disc degeneration [4]. The genetic background of IDD was analyzed in family studies and

* *Corresponding author at*: Szpital im. św. Rafała, Oddział Neurochirurgii, ul. Bochenka 12, 30-693 Kraków, Poland.
E-mail address: soarer@o2.pl (Ł. Janeczko).

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twin studies. They indicated higher compliance rate of onset of IDD in monozygotic twins in comparison to dizygotic twins [5].

2. *COL9A2* gene polymorphism

Collagen IX is necessary to form heteropolymers of type II, IX and XI collagens [6]. It is composed of three chains: α-1, α-2 i α-3, encoded by the *COL9A1*, *COL9A2* i *COL9A3* genes [2]. The animal studies showed that transgenic mice harboring a mutation in the *COL9A1* gene had accelerated disc degeneration [7].

A genetic polymorphism is a variability in DNA sequence, which occurs in population with high frequency. Genetic polymorphism is the occurrence in the same population of two or more alleles at one locus, each with appreciable frequency, where the minimum frequency is typically taken as 1% [8].

The *COL9A2* gene polymorphism (Trp2) is a substitution of tryptophan for glutamine at codon 326, which disturbs forming of heterotrimers of collagen type II, IX and XI and may render intervertebral disc more fragile [1,2,4,9–13].

The role of *COL9A2* gene polymorphism (Trp2) in intervertebral disc disease was analyzed in many studies. Annunen et al. [9] showed the presence Trp2 allele in 6 out of 157 Finnish patients (3.8%) but in none of 174 individuals without the disease. The similar frequency of polymorphic allele Trp2 in patients with IDD was estimated by Paasilta et al. (4%) [3] and Karppinen et al. (3.8%) [10]. Wrocklage et al. [11] assessed the Trp2 allele frequency in 250 German patients with IDD as 1.2% [11].

The studies in Japanese population revealed the correlation between the *COL9A2* gene polymorphism (Trp2) in patients under 40 years and more severe disc degeneration. Higashino et al. included to the study 84 patients with the intervertebral disc herniation, who underwent discectomy. The severity of the IDD was calculated using a scoring system, which contained subjective symptoms, clinical signs, urinary bladder function and magnetic resonance images. The study results suggested that the Trp2 allele resulted in a six-fold increase in the risk of severe disc degeneration [4].

Knoeringer et al. analysed the influence of the *COL9A2* (Trp2) polymorphism on the reccurence rates of IDD. The study included 288 German patients with intervertebral disc herniation. Nevertheless, the mutated Trp2 allele was not detected in the patients samples with IDD [1]. The similar results were achieved by Greek scientists (Kales et al. [12]), who discovered the polymorphic allele Trp2 neither in 105 patients with IDD, nor in 102 patients in a control group.

3. *COL9A3* gene polymorphism

COL9A3 gene polymorphism (Trp3) is a substitution of tryptophan for arginine at codon 103, which may also render intervertebral disc more fragile. This polymorphism was analyzed in several studies [2,13,15].

Paassilta et al. proved in their study that a presence of at least one Trp3 allele increases risk of IDD about 3-fold in Finnish population. The case sample consisted of 171 patients with lumbar discopathy (diagnosed on the basis of clinical and radiological findings). The control samples consisted of 321 individuals without IDD. The frequency of the Trp3 allele was 12.2% in IDD group and was 4.7% among the controls [1]. The frequency of the Trp3 allele determined in Greek research (Kales et al. [12]) was considerably lower – 4.3%. The Trp3 allele was absent both in the case group and in the control group in Singaporeans (Lim et al. [14]).

4. *COL11A1* gene polymorphism

Type XI collagen is a cartilage-specific extracellular matrix important for cartilage fibril formation and for the extracellular matrix organization. It is composed of three α-chains: α-1, α-2 and α-3, which are encoded by *COL11A1*, *COL11A2* and *COL2A1*, respectively. Type XI collagen is present in the intervertebral discs, both in annulus fibrosus and nucleus pulposus. Type XI collagen is a quantitatively minor component of cartilage collagen fibrils, but it is essential for the interaction between proteoglycan aggregates and collagenes. Normally, *COL11A1* gene is highly expressed in the intervertebral discs, which suggest that it is critical for intervertebral disc metabolism.

COL11A1 gene polymorphism is a substitution of thymine for cytosine at position 4603 of nucleotide chain (c.4603C>T). Mio et al. identified the association between a polymorphism of the *COL11A1* gene (c.4603C>T) and lumbar disc herniation in Japanese population. In three studies, they recruited 130/179, 359/286 and 334/379 patients (respectively in the case group and the control group). The frequency of c.4603T allele was about 1,5-times higher in the cases than in the controls (the frequency of polymorphic allele in the control group was about 11.7%, and in the controls was about 7.1%). To clarify the functional impact of c.4603T allele an allelic difference of the mRNA expression was quantified. The expression level of the susceptibility allele c.4603T was significantly lower than that of the c.4603C allele. Mio et al. hypothesized that this SNP affects *COL11A1* transcription by altering mRNA stability. They also examined *COL11A1* expression in different tissues (including intervertebral discs). The *COL11A1* mRNA level was inversely correlated with the severity of disc degeneration evaluated by magnetic resonance images. Normal discs had a highly uniform structure, with intense immunostaining of type XI collagen in the nucleus pulposus cells and annulus fibrosus by immunohistochemistry. In degenerative discs, the immunostaining of type XI collagen around the nucleus pulposus cells was weak [15].

5. Conclusion

The genetic polymorphisms may influence the susceptibility of an organism for the risk factors. This may explain why the lumbar discopathy develops only in some of the patients with the same risk factors. The frequency of the particular polymorphisms shows the difference in various ethnic groups. In a Polish literature, still there has been no information about the studies assessing the influence of different genetic variants on IDD development. Proving the association between the genetic polymorphisms and IDD development in Polish

population could help to target a 'high-risk' subgroup and provide the basis for the development of new forms of prevention and treatment.

Conflict of interest

None declared.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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