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REVIEW ARTICLE

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# CHARACTERISTIC OF MORPHOLOGICAL CHANGES OF THE SPINE IN SELECTED MAMMAL SPECIES

Paulina Jundziłł-Bogusiewicz[1]✉, Joanna Gruszczyńska[1], Ivan Shuvar[2], Krzysztof Papis[3]

[1]Department of Animal Genetics and Conservation, Warsaw University of Life Sciences – SGGW, Ciszewskiego 8, 02-786 Warsaw, Poland
[2]Lviv National Agrarian University, Volodymyra Velykoho 1, Dubliany, Lviv Oblast, Ukraine
[3]Center of Translational Medicine, Warsaw University of Life Sciences – SGGW, Nowoursynowska 100, 02-797 Warsaw, Poland

## ABSTRACT

Morphological changes of the vertebrae, whether congenital or acquired, are more and more frequent causes of movement difficulties of both humans and other species of mammals. The most frequently diagnosed pathologies of the spine include: degenerative changes, congenital defects, inflammatory diseases, and proliferative changes. This article presents the characteristics of selected morphological changes in the spine, the reasons for their occurrence, and the diagnosis. Some of abnormalities have a genetic basis, sometimes already known, such as in the case of vertebral deformity syndrome in domestic cattle, which is caused by a mutation in the *SLC35A3* gene. At other times, the genetic factor is only speculated as in the case of human scoliosis – some studies indicate its autosomal dominant nature of inheritance.

**Key words:** morphological changes, spine, *SLC35A3* gene, human, dog

## INTRODUCTION

The spine is a kind of scaffolding that runs through quite a significant part of a body of both humans and other species of mammals. It consist of descriptive parts i.e., cervical, thoracic, lumbar, sacral, and caudal sections. The characteristic for each section is that it is made of vertebrae similar to each other. However, the vertebrae of the thoracic spine differ morphologically from the vertebrae of the lumbar spine. The exception is the cervical part – its first two vertebrae have a specific shape that allows the spine to be connected to the skull and gives this segment the greatest mobility. Despite all differences in the structure of individual vertebrae, they are connected with each other by special structures – the intervertebral joint, intervertebral disc and longitudinal ligaments. Articular joints connect the articular processes of adjacent vertebrae. In turn, the intervertebral disc connects the vertebral bodies with the peripheral fibrous ring and the nucleus pulposus located in the centre (these structures are not present in the sacral spine). Ligaments are structures running along the dorsal and ventral side of the vertebral bodies [Glinkowski and Ciszek 2004].

Among the many functions of the spine, its support function is more important in humans than in animals, which is associated with the upright position of a body. Although the spine itself has limited mobility due to its own ligamentous apparatus, it is also a site of attachment of many skeletal muscles, and therefore it is associated with the locomotion apparatus. In turn, the protective function of the spine consists not only in creating a bone tunnel for the spinal cord but also in reducing the loads acting on the spine through absorption shock [Panjabi and White 1980].

An important role in the formation of the spine is played by the dorsal cord, which is formed in 18–19. day of embryonic development and somites that derive from the paraxial mesoderm, which undergoes segmentation in the middle of the 4th week of foetal life. Somites develop along the long axis of the body (both cranial

✉ paulina_jundzill_bogusiewicz@sggw.edu.pl

and caudal) mainly under the control of genes from the wingless-type MMTV integration site family (WNT group). However, the homeobox genes (HOX) are responsible for the proper polarization and differentiation into sclerotomes, myotomes and dermatomes of individual somites in the 5th week of foetal life [Wellik 2009]. Sclerotomes form the proper basis for the development of the spine. On the 32nd day of development in the structure of the sclerotome, we can distinguish the upper, loose-cellular part, from which the vertebral body will form, and the lower, thick-celled part, from which the vertebral arch and the intervertebral disc will originate. Then the sclerotomes migrate to lay parallel to the long axis of the body after reaching the dorsal chord [Grzymisławska et al. 2012].

Back problems occur in about 80% of overweight people [Prostek and Kinalska 2013]. Thus, the genetic basis of overweight or obesity may indirectly affect the degeneration and pain of the spine [Pasiński and Pasińska 2008]. The most frequently diagnosed pathologies of the spine include degenerative changes, congenital defects, inflammatory diseases, and proliferative changes. According to Koszewski [2010], about 70% of adult Poles have experienced back pain in their lives; almost half (44%) are related to the lumbosacral region. In 23% of cases, due to pain in this section of the spine, there is a loss of fitness and temporary inability to work. Pain in the lumbosacral spine is the fifth most common cause of hospitalization in Poland, and in the United States it is the third most frequent cause of surgical interventions [Koszewski 2010]. In about 5% of cases, acute pain in the lumbar spine becomes chronic, i.e., it lasts for over three months [Stryła and Pogorzała 2012]. The most common cause of pains in the lumbar spine in humans is damage to the intervertebral disc [Koszewski 2010]. According to Radło et al. [2014], in 91% of cases pain was caused by discopathy.

Using imaging diagnostics, it was found that the most common changes in adults are: Baastrup's disease, when the spinous processes are positioned too close to each other and rub against each other during movement, causing pain, and scoliosis. These changes account for 14.2% and 13.7% of all observed changes in the spine, respectively. It has also been shown that ankylosis (stiffness, immobilization) of the sacroiliac joints and lack of anastomosis between the sacrum arches occurs in more than 6% of cases, followed by spondylolisthesis (cranial dislocation of several vertebrae), 5.2%, S1 lumbarisation (partial or complete absence of sacrum bone union), 5.2%, vertebral fissure (fissure present in the arch of a given vertebra), 4.2%, and L5 sacralisation (anastomosis of the last lumbar vertebra with the sacrum), 2.8% [Wójcik et al. 2015].

Similar results were obtained in studies conducted on children. According to Paprocka et al. [2008] among the five most common causes of back pain in children are hernia of the nucleus pulposus of the lumbosacral segment, 13.6%, systemic diseases including ankylosing spondylitis (AS, formerly Bechterew's disease) and osteoporosis, 11 5%, post-traumatic pain in the lumbosacral region, 9%, inflammatory processes, 6.9%, and developmental defects, 6.9%. In the studied population of children, the majority of patients aged 11–18 (72.8%). More than half of the children with diagnosed spinal pathologies (55%) were girls [Paprocka et al. 2008]. Studies on dogs indicate that the most common spine diseases in this species are: interverteble disc disease (IVDD), especially in chondrodystrophic breeds (i.e. Dachshund, Pekingese, Spaniels, Welsh corgi, French bulldogs, Shih-tzu, Beagle) [Griffin et al. 2009, Jeffrey et al. 2013], with symptoms from mild pain to complete paralysis; degenerative lumbosacral stenosis (DLSS) in German Shepherds and Labradors [Meij and Bergknut 2010] and Spondylosis in older large breed animals [Togini et al. 2014, Carnier et al. 2004]. Other species of mammals are very rarely under investigation.

## Degenerative changes

Degenerative changes mainly concern the intervertebral disc, which becomes dehydrated, loses its elasticity, and therefore its shock-absorbing function is impaired. The reasons for this phenomenon are not fully known. Lesions can also develop in the fibrous ring, which becomes weaker and weaker, eventually breaking. The nucleus pulposus then moves into the spinal canal. This condition is called the nucleus pulposus hernia [Glinkowski and Ciszek 2004].

Degenerative changes can also affect the joints of the spine and appear in the form of spondylosis and spondyloarthrosis. These are degenerative and generative changes occurring around the vertebral bodies, resulting in secondary changes in the vertebrae in the form of bone processes, the so-called osteophytes [O'Neill et al. 1999, Pye et al. 2007].

It should be mentioned that studies involving identical and fraternal twins demonstrated that after eliminating the influence of non-genetic factors (i.e. smoking or work-related loads, i.e., lifting weights), up to 75% of degenerative changes in the intervertebral discs depended on genetics factors [Sambrook et al. 1999].

## Congenital defects

Congenital malformations occur in the prenatal period, their cause is often unknown and/or they are multigene/multi-factorial in nature. Abnormalities in the development of human spine most often concern the thoracic and lumbar part. The most common congenital vertebral deformities include: insufficient development of a

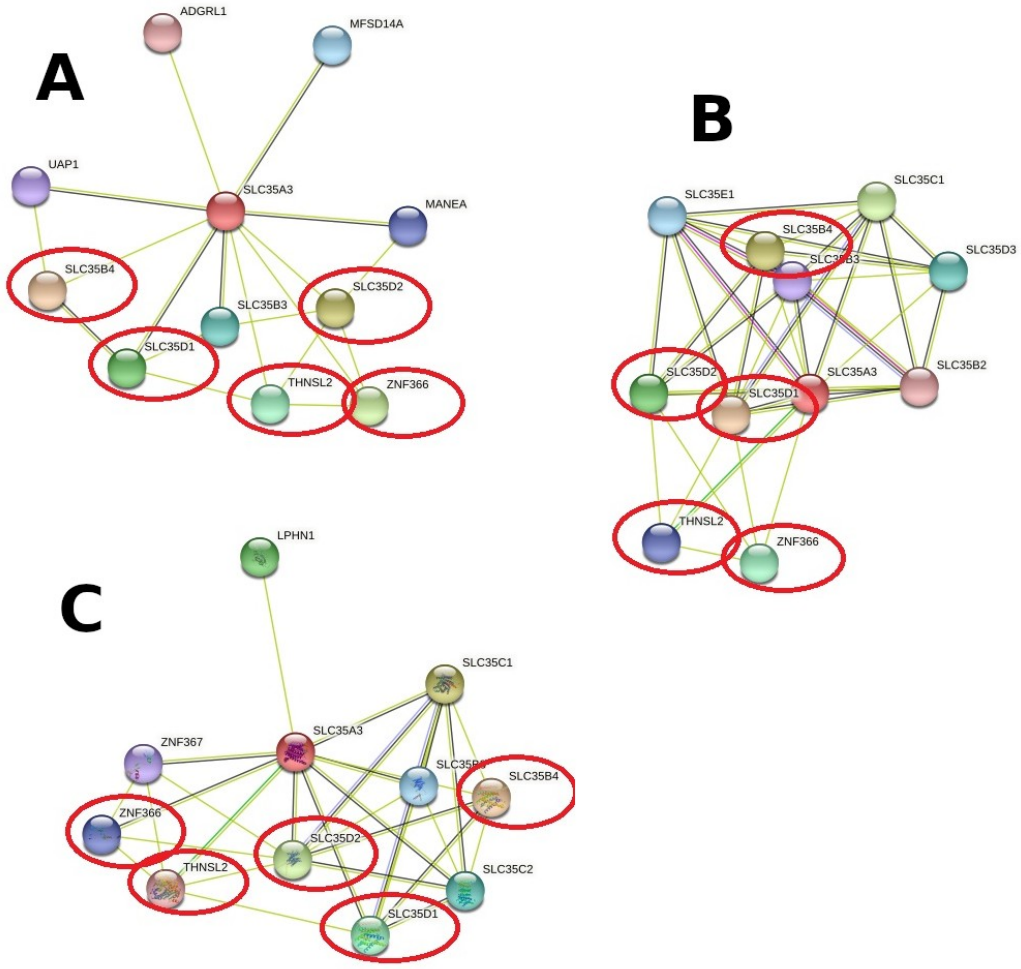


**Fig. 1.** Result of bioinformatics analysis for the *SLC35A3* gene. Functional links with other proteins for: a) domestic dog 0.616–0.680, b) cattle 0.760–0.875, c) human 0.704–0.951. Proteins common to the species studied are marked in red.

Software used: STRING v.11 [Szklarczyk et al. 2021].

part of the vertebrae, which results in the formation of a semi-vertebrae (Latin *hemivertebrae*) or a butterfly vertebrae, an incorrect connection between the vertebrae causing congenital bone union, a mixed defect, i.e., a specific connection of the semi-vertebrae with concrescence and multiple defects [Skwarcz and Majcher 2003]. The existence of any of the above-mentioned defects does not always result in any deformation of the spine. Contrary, single lesions usually do not give any symptoms and are detected accidentally during diagnostic tests for other diseases. It is estimated that even 33% of congenital defects of the spine occur in the semi-vertebrae [Skwarcz and Majcher 2003].

According to the research of McMaster and Singh [1999], the more anomalies found, the greater the curvature of the spine. Children are then born with congenital kyphosis and/or scoliosis. The results of the study were not influenced by the location of the lesions. The consequences of the spinal deformity that worsen with age include pressure on the spinal cord, and even paraparesis (McMaster and Singh [1999] describe such a case in a 28-year-old patient).

### Inflammatory diseases

Taking inflammation as a criterion, we can distinguish 2 groups. The first is seronegative spondyloarthropathies, i.e., a group of systemic diseases associated with the HLA B27 antigen of the main histocompatibility complex. The second is associated with the inflammation of individual subunits of the spine, e.g. inflammation of the intervertebral disc.

Seronegative spondyloarthritis includes, among others, ankylosing spondylitis (AS). Its first symptoms ap-

pear before the age of 40. Patients lack rheumatoid factor in the blood. This disease is more common in men than in women. It includes not only spinal arthritis, but also sacroiliac joints. The disease leads to a progressive limitation of the mobility of the spine in all planes, starting from the joints of the lumbar region, ending with the cervical region and the characteristic body shape [Dougados and Landewe 2009]. AS is a multifactorial disease with a previously unknown etiology, but if we take into account also genetic predisposition, the occurrence of this disease is largely correlated with the presence of the HLA B27 antigen. It has been found that up to 85% of patients are seropositive for this antigen [Vecellio et al. 2019]. There are also cases of familial ASS [Skomsvoll et al. 1995].

Inflammation of the movable part of the spine, i.e., the intervertebral disc, is rare (approximately 1/100,000 on average). The main cause is infection with Staphylococcus bacteria. The disease is characterized by local pain that worsens after exercise and in the laying position [Urbanowski et al. 2010].

### Proliferative processes

According to Fijuth et al. [2013], primary (benign and malignant) and secondary neoplasms of the spine should be distinguished. Benign tumours of the spine include, for example, osteoid, osteoma, osteoblastoma or giant cell carcinoma. On the other hand, malignant neoplasms include osteosarcoma, Ewing's sarcoma, chondrosarcoma, chordoma, and multiple or single myeloma.

Secondary neoplasms of the spine are mainly metastases to part of the body of a single vertebra or several vertebrae at the same time, most often in breast and prostate cancer [Fijuth et al. 2013].

### Genetic predisposition

Some of the abnormalities of the spine already occur in utero, others do not appear until later in life. This article describes congenital defects of the spine of known genetic origin. Sometimes they are isolated defects, i.e., those not accompanied by other changes, and sometimes they will be syndromes of various disease entities. One of such pathologies is congenital vertebral malformations (CVM), which in humans is associated with the occurrence of scoliosis. This syndrome also occurs in animals including in dogs and cattle (e.g. in the Holstein Friesian breed) [Thomsen et al. 2006, Fernandes et al. 2019].

### Vertebral deformity syndrome, congenital malformations of the vertebrae

The results of the conducted research suggest that genes associated with vertebral modelling defects, including paired box 1 gene (*PAX1*), delta like canonical notch ligand 3 gene (*DLL3*), solute carrier family 35 member A3 gene (*SLC35A3*), WNT family member 3 gene (*WNT3A*), T-box 6 gene (*TBX6*), are responsible for the syndrome of vertebral deformity in humans [Giampietro et al. 2013]. The *PAX1* gene is responsible for the correct ventromedial differentiation of the sclerotome in utero (formation of vertebral bodies and intervertebral discs) [Giampietro et al. 2003, Grzymisławska et al. 2012]. The *DLL3* gene is responsible for the proper structure of both vertebrae and intervertebral discs. The *TBX6* gene may play an important role in the pathogenesis of congenital scoliosis in the Chinese Han population [Fei et al. 2010]. The *WNT3* gene is important both in the formation of a normal dorsoventral axis during embryo development and is potentially oncogenic [Giampietro et al. 2003].

In cattle, the vertebral deformity syndrome is a recognized disease entity conditioned by changes in the *SLC35A3* gene sequence. A mutation at 559 nucleotide (substitution of thymine (T) for guanine (G) results in a lethal defect inherited as autosomal recessive. It causes miscarriages before day 260 of pregnancy, foetal growth retardation, vertebral malformations (semivertebrae, distorted vertebrae and ankylosis affecting especially the vertebrae around the cervico-thoracic junction) and bilateral symmetrical arthritis affecting the wrist and metacarpal joints [Thomsen et al. 2006]. Mutations in the *SLC35A3* gene has also been confirmed in people with curvatures of the spine [Edmondson et al. 2017] and with the following disease entity: autism spectrum disorder – epilepsy – arthrogryposis [Edvardson et al. 2013]. The *SLC35A3* gene acts as the uridine diphosphate N-acetylglucosamine (UDP-GlcNAc) transporter inside the Golgi apparatus [Ishida and Kawakita 2004].

The authors conducted bioinformatic analysis with the STRING v.11 program (Szklarczyk et al. 2021) for the *SLC35A3* gene of domestic dogs, domestic cattle, and human. The result indicates that among the proteins associated with the analysed protein SLC35A3, five of them are common to the species tested in this analysis, i.e. SLC35D1, SLC35D2, SLC35B4, ZNF366 and THNSL2 (Fig. 1). In addition, all analysed species showed the greatest (value above 0.68 in dog and above 0.80 in cattle and human) predicted functional relationship SLC35A3 with *SLC35D2* and *SLC35B4*.

Co-expression of the bovine *SLC35A3* gene was confirmed with the *SLC35D1* (coexpression score 0.098) *SLC35B3* (coexpression score 0.091), while with the *SLC35B3* (coexpression score 0.183), *SLC35B2* (coexpression score 0.070), and *SLC35C1* (coexpression score 0.076) in humans.

### Scoliosis

Scoliosis it is a lateral bend of the spine. It should be noted here that there is no physiological scoliosis, so

any, even slight, bending of the spine to the side must be treated as a pathology. We distinguish idiopathic scoliosis, the cause of which is undefined and often not accompanied by any other changes apart from curvature of the spine, and congenital scoliosis, which, as the name suggests, is related to deformities in foetal life. Scientists speculate that some cases of scoliosis in humans may be inherited as dominant autosomal trait [Wise et al. 2008], as cases have been reported in several generations in one family. Riseborough and Wynne-Davies [1973] showed that the risk of idiopathic scoliosis decreases with the next generation. The risk is respectively: for first degree relatives 11%, second degree relatives 2.4% and third degree relatives 1.4%.

Subsequent studies on humans indicate that in patients with idiopathic scoliosis certain mutation in the *CHD7* gene segment ($8q^{-1}2$) occurs very often. Although not encoding a protein, it is responsible for gene switching on. Such a defect does not hinder the production of the protein itself, but lowers its level. This is because the gene is turned off much more often than it should. The change in the amount of protein produced is very small. This is probably the reason why scoliosis develops slowly and shows symptoms only during the period of intense adolescence [Gao et al. 2007].

### Congenital bone fusion, synostosis

The most common form of vertebral synostosis (congenital bone fusion) is Klippel-Feil syndrome. It is characterized by the fusion of any two of the seven cervical vertebrae. It is presumed that the syndrome is caused by mutations in the *GDF6*, *GDF3* or *MEOX1* genes. The protein encoded by the *GDF6* gene is essential for the formation of bones and joints, including the vertebrae of the spine [Tassabehji et al. 2008]. The protein encoded by the *GDF3* gene, which is also involved in bone development, has a similar effect, but its role is still not fully understood [Ye et al. 2010]. In turn, a protein produced by the *MEOX1* gene, called the MoX-1 homeobox protein, regulates the process by which the vertebrae begin to separate from each other [McGaughran et al. 2003]. While the above genes are known to be involved in bone development, and in particular in vertebral formation, when any deficiency of one of these proteins leads to incomplete separation of the cervical vertebrae in people with Klippel-Feil syndrome is still under investigation.

### Hemivertebrae, semi-vertebrae

In the scientific literature, there is a different approach to the issues of distortion of vertebrae depending on the species to which such deformations relate. The semi-vertebrae are usually treated in humans as the cause of scoliosis and described only in this context and not as a separate disease entity. In animals, the opposite tendency is observed. Due to their horizontal position, the curvature of the spine itself is not as often the subject of research as the specific units of vertebral deformity that cause these curvatures, e.g., the aforementioned hemivertebrae.

The results of research by Goldstein et al. [2005] in Israel indicate that in humans the frequency of hemivertebrae per number of live births is 0.33/1000. As many as 88.5% of those children had concomitant congenital anomalies of other organs.

Hemivertebrae are also observed in other mammals, including in dogs, where we can trace some breed predisposition to its occurrence (e.g. French Bulldogs, Bulldogs and Pugs) and in domestic cattle [Ryan et al. 2017]. According to the experience of veterinarians, it is estimated that almost 100% of the examined French Bulldogs suffer from this condition. Often the changes themselves do not give any symptoms and are diagnosed by chance when diagnosing other diseases [Ryan et al. 2017]. The research by Ryan et al. [2019] describes the case of 100 dogs of the three breeds mentioned above. A total of 362 hemivertebrae were detected and 243 deformed vertebrae were found in 58 French Bulldogs.

According to the available literature, no candidate genes that might correspond to the formation of the hemivertebrae have been identified as of today. Trying to identify them in a domestic dog could possibly help diagnostics of some genetic spinal curvatures in humans.

### Imaging diagnostics

The best diagnostic methods of spine diseases are the imaging techniques: RTG, MR and CT.

RTG (radioisotope thermoelectric generator) is often used to detect developmental disorders (semi-vertebrae, butterfly vertebrae, curvature of the spine, transitional vertebrae), degenerative changes (osteophytes, intervertebral space narrowing), inflammations, neoplasms (features of neoplastic infiltration) and in the case of suspected trauma (compression fractures of vertebral bodies). On the other hand, X-ray images will not show structures such as the spinal cord and its meninges [Sąsiadek and Hendrich 2010]. It should also be borne in mind that with age the possibility of abnormalities detected during the examination increases, and the very finding of a change does not have to correlate with clinical symptoms. It is estimated that even 2/3 of the degenerative changes in intervertebral discs diagnosed in people over 50 do not show any symptoms [Świerkot 2006]. X-ray is the first tool used. For more accurate diagnostics, magnetic resonance and/or computed tomography are performed.

CT (computed tomography) examination enables an excellent assessment of the bone elements of the spine. It

is the method of choice in cases of severe spinal injuries. Currently, it is less frequently used for the diagnosis of degenerative diseases, although it sometimes exceeds the quality of MRI. It is used to confirm neoplastic changes that were unclear on X-rays. Computed tomography is also becoming more and more important in planning and monitoring the effects of spine surgery. Many procedures can be performed under CT control, for example, internal fixation [Sąsiadek and Hendrich 2010].

MR(magnetic resonance) allows for a precise assessment of both soft tissues and bone elements. The main indications for MRI of the spine are: degenerative disease (especially in the case of long-term pain), proliferative processes, inflammatory and demyelinating diseases, congenital defects and injuries. It is the only method that enables imaging of the spinal cord. Magnetic resonance imaging has one major drawback – it excludes patients with pacemakers or metallic implants from the examination [Sąsiadek and Hendrich 2010].

## SUMMARY

It is obvious that the achievements of modern medicine influence the fate and well-being of people and animals. Generally, they improve the comfort of their lives and even extend them. Human longevity and mainly sedentary lifestyle in developed countries will imply back problems. In addition, morphological changes in the vertebrae, whether congenital or acquired, will become more and more frequent causes of mobility difficulties. This will apply to both humans and other species of mammals.

Delving into the subject of genetic factors, one should be able to identify them well enough to limit the occurrence of congenital pathologies of the spine. While in animals it is relatively easier to control the process of selecting pairs for mating, or to carry out the procedure of *in vitro* fertilization, in humans these are controversial topics. It is therefore all the more important to know the genetic basis of selected spine defects and to apply earlier diagnostics in order to eliminate the effects of genetic changes in humans from birth, and even in utero.

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## CHARAKTERYSTYKA ZMIAN MORFOLOGICZNYCH KRĘGOSŁUPA WYBRANYCH GATUNKÓW SSAKÓW

### STRESZCZENIE

Zmiany morfologiczne kręgów, czy to wrodzone, czy nabyte stanowią, coraz częstsze przyczyny trudności z poruszaniem się zarówno ludzi, jak i innych gatunków ssaków. Do najczęściej diagnozowanych patologii kręgosłupa należą: zmiany zwyrodnieniowe, wady wrodzone, choroby o tle zapalnym, oraz zmiany rozrostowe. W niniejszym artykule przedstawiono charakterystykę wybranych zmian morfologicznych kręgosłupa, przyczyny ich występowania, a także diagnostykę. Część nieprawidłowości ma swoje podłoże genetyczne, niekiedy już znane jak w przypadku zespołu deformacji kręgów u bydła domowego, które powodowane jest przez mutację w genie *SLC35A3*. Innym razem czynnik genetyczny jest tylko przypuszczeniem naukowców jak w kwestii skoliozy u człowieka; niektóre badania wskazują na jej autosomalny dominujący charakter dziedziczenia.

**Słowa kluczowe:** zmiany morfologiczne, kręgosłup, gen SLC35A3, człowiek, pies

Paulina Jundziłł-Bogusiewicz https://orcid.org/0000-0002-3077-3042
Joanna Gruszczyńska https://orcid.org/0000-0001-6062-6353
Ivan Shuvar https://orcid.org/0000-0002-4149-1761
Krzysztof Papis https://orcid.org/0000-0001-5675-4061