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Review

PIEZO2 gene and its role in the development of distal arthrogryposis: A literature review

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BACKGROUND: PIEZO1 and PIEZO2 are mechanosensitive ion channel proteins; in humans, they are encoded by genes with identical names. PIEZO proteins convert mechanical signals into biochemical cellular responses following transduction. Recent data highlight the importance of this family of ion channel proteins in the regulation of physiological processes; however, many mechanisms remain unknown. Modern studies have proven that *PIEZO2* mutations lead to the development of various forms of distal arthrogryposis.

AIM: To analyze publications containing information on *PIEZO2* gene and its role in the development of distal forms of arthrogryposis.

MATERIALS AND METHODS: This study analyzed the results of a literature search in the open scientific literature databases of PubMed, Cochrane Library, and eLibrary. Consequently, 40 foreign, and domestic scientific sources were extracted from 1969 to 2022.

RESULTS: This study showed the relationship between *PIEZO2* mutations and the development of the distal forms of arthrogryposis. The study also presented the types of distal arthrogryposis and their clinical manifestations depending on the mutation of this gene. *PIEZO2* mutations with decreased function cause distal arthrogryposis with impaired proprioception and taction (autosomal recessive type of inheritance). *PIEZO2* mutations with gain-of-function cause distal arthrogryposis of types 3 and 5 (autosomal dominant inheritance).

CONCLUSIONS: An integrated approach to the diagnosis and molecular genetic study will allow us to choose the best techniques and treatment of patients with this pathology. The results are useful for doctors of various specialties.

Keywords: distal arthrogryposis; *PIEZO2* gene; mutations.

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Научный обзор

Ген *PIEZO2* и его роль в развитии дистальных форм артрогрипоза (обзор литературы)

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Обоснование. PIEZO1 и PIEZO2 — механочувствительные белки ионных каналов, которые у человека кодируются генами с идентичными названиями. Белки PIEZO в результате трансдукции преобразуют механические сигналы в биохимические клеточные реакции. Совокупность данных, накопленных в последнее время, подчеркивает важность этого семейства белков ионных каналов в регулировании физиологических процессов, но многие механизмы неизвестны до сих пор. Современные исследования доказали, что мутации гена *PIEZO2* приводят к развитию различных форм дистального артрогрипоза.

Цель — проанализировать публикации, содержащие информацию о гене *PIEZO2* и его роли в развитии дистальных форм артрогрипоза.

Материалы и методы. В статье представлены результаты поиска литературных источников в открытых базах научной литературы PubMed, Cochrane Library и eLibrary. Было выбрано 40 иностранных и отечественных публикаций за период с 1969 по 2022 г.

Результаты. В работе показана взаимосвязь мутации в гене *PIEZO2* с развитием дистальных форм артрогрипоза. Мутации, приводящие к снижению функции белка, в гене *PIEZO2* вызывают дистальный артрогрипоз с нарушением проприоцепции и осязания (аутосомно-рецессивный тип наследования). Мутации, обусловливающие усиление функции, в гене *PIEZO2* человека приводят к возникновению дистального артрогрипоза 3-го и 5-го типов (аутосомно-доминантный тип наследования).

Заключение. Редкая встречаемость дистальных типов артрогрипоза, сложность клинической диагностики определяют необходимость осуществления молекулярно-генетического исследования для верификации заболевания и выбора оптимальной тактики лечения. Данная статья будет полезна врачам различных специальностей.

Ключевые слова: дистальный артрогрипоз; ген *PIEZO2*; мутации.

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ЭКО•ВЕКТОР

BACKGROUND

Throughout life, a person encounters various mechanical forces. This process is called mechanosensing, which includes the conscious perception of tactile sense (somatosensory), control of posture (proprioception), and unconscious regulation of physiological functions such as breathing and heart rate (interoception). In each case, mechanical force activates special cells called mechanoreceptors that generate and transmit signals to the nervous system and body. The key stage in mechanosensing is the conformation of molecules expressed in mechanoreceptors, which results in the conversion of mechanical forces into electrochemical signals (the so-called mechanotransduction). Tactile sense, as one of the variants of mechanical sensations, is an integral part of daily living. This sensory system is extremely sensitive, remarkably accurate, and fast, allowing the localization of the smallest forces, such as the movement of a single hair strand, in a fraction of a second [1]. Unraveling the mechanisms by which the sensory system achieves these results has been a major challenge for scientists for more than a century, and only in the last decade, thanks to the discovery of PIEZO proteins in 2010, have we started to understand how this type of mechanosensing functions at the molecular level [1–4].

In humans, PIEZO1 and PIEZO2 are mechanosensitive ion-channel proteins encoded by identically named genes. These proteins are 47% identical to each other but differ from other ion-channel proteins in their large size (PIEZO1 and PIEZO2 have 2,521 and 2,752 amino acid residues, respectively) and structure resembling a three-blade propeller [2–4].

PIEZO proteins, as a result of transduction, convert mechanical signals into biochemical cellular reactions. The mechanical action on the cell membrane ensures the passage of cations through the PIEZO channels. Ca^{2+} entry into cells serves as the starting point for many biochemical signals, such as the regulation of gene expression, cytoskeletal remodeling, and protein transport. Recently, accumulated data emphasize the importance of this family of ion-channel proteins in the regulation of physiological processes; however, many mechanisms remain unknown [1, 2, 4].

PIEZO1 is produced in erythrocytes, lungs, bladder, pancreas, and uterine endometrium. It plays an important role in cell adhesion by maintaining integrin activation in the regulation of pulmonary vascular permeability and pulmonary blood flow, micturition (regulates bladder compliance), and erythrocyte hydration.

PIEZO2 is expressed in the neurons of the spinal ganglia, lungs, gastrointestinal tract, skin, and muscles (muscle spindle and Golgi organ). Special afferent fibers (proprioceptive neurons) transmit mechanical sensations from the muscle spindle and Golgi tendon organ to the spinal cord. PIEZO2 deficiency in proprioceptive neurons leads to impaired coordination and pathological limb positions. The PIEZO2 channel is important for the sensation of airway expansion and subtle tactile sense. Both PIEZO1 and PIEZO2 are also found in joint chondrocytes [1].

A *PIEZO1* mutation causes dehydrated congenital stomatocytosis, a rare form of hemolytic anemia, and lymphatic dysplasia. *PIEZO2* mutations impair proprioception, tactile and pain sensitivity, and urination and cause scoliosis, hip dysplasia, congenital contractures, arthrogryposis, perinatal respiratory distress syndrome, and muscle weakness [2].

PIEZO2 expression in proprioceptive neurons is essential for normal spinal and hip development. In mouse models, PIEZO2 deficiency in proprioceptive neurons leads to the development of scoliosis and hip dysplasia [1, 2].

Recent studies have demonstrated that *PIEZO2* mutations contribute to the development of distal arthrogryposis in various forms. Unlike amyoplasia (the most common form of congenital multiple arthrogryposis, clinically manifested by multiple contractures, aplasia or hypoplasia of the muscles, and occurring sporadically), distal forms of arthrogryposis are characterized by a predominance of hand and feet lesion and hereditary nature of the disease [5]. Decrease-of-function *PIEZO2* mutations cause distal arthrogryposis with impaired proprioception and tactile sense (autosomal recessive inheritance). Gain-of-function *PIEZO2* mutations result in distal arthrogryposis types 3 and 5 (autosomal dominant inheritance).

The work aimed to analyze publications containing information about *PIEZO2* and its role in the development of distal forms of arthrogryposis

MATERIALS AND METHODS

The study presents the results of a literature search on *PIEZO2* and its influence on the development of distal forms of arthrogryposis. The literature search was performed in the open electronic databases of PubMed, Cochrane Library, and eLibrary using the following keywords: *PIEZO2* gene, mutations, distal arthrogryposis, distal arthrogryposis type 3, Gordon syndrome, distal arthrogryposis type 5, distal arthrogryposis with proprioception, and touch disorders. Forty international and Russian studies were extracted from 1969 to 2022, of which 23 were published over the last 10 years.

RESULTS AND DISCUSSION

1. Gain-of-function *PIEZO2* mutations

Distal arthrogryposis type 3 (Gordon syndrome)

Gordon syndrome (DA3, GS, OMIM: 114300) is clinically characterized by camptodactyly, cleft palate, foot deformity, and autosomal dominant inheritance. The disease is caused

Table 1. Clinical manifestations of distal arthrogryposis type 3

Authors of the study, year	Number of cases	Sex	Age, years	Cleft palate	Bifurcation of the uvula	Deformity of the auricles	Ptosis	Altered palpebral fissure	Small mouth	Micrognathia	Chest deformity	Spinal deformity	Short stature	Short neck	Camptodactyly	Transverse palmar sulcus	Syndactyly	Ulnar deviation of the hands	Equinovarus deformity of the feet	Mental retardation	Cryptorchidism
Gordon H. et al., 1969 [6]	6	M	18	+											+			+	+		+
		M	22												+						
		F	?	+											+			+	+		
		M	60												+				+		
		F	0.2	+															+		
		F	?																+		
Say B. et al., 1980 [7]	1	M	5	+					+			+	+	+	+				+		
Robinow M. Johnson G.F., 1981 [13]	2	F	?					+					+		+	+			+		
		F	?					+				+	+		+		+		+		
Hall J.G. et al., 1982 [8]	6	F	?	+			+					+	+		+				+		
		M	?	+		+	+						+						+		
		?	?			+							+		+			+	+		
		M	?																+		
		?	?										+	+				+	+		
		M	?										+	+	+			+	+		
Ioan D.M. et al., 1993 [9]	3	M	56								+	+	+		+		+	+	+		
		F	26										+		+						
		M	10								+	+			+		+		+		
Courtens W. et al., 1997 [13]	2	M	2.4	+		+			+	+	+	+		+	+					+	+
		F	22	+		+			+				+	+	+	+					
Wild A. et al., 2001 [10]	1	F	13	+								+			+				+		
Botha S.J. et al., 2015 [11]	2	F	10	+			+								+				+		
		F	1.5	+											+				+		
Hajela R. et al., 2015 [13]	1	F	0.1	+					+										+		
Alisch F. et al., 2017 [12]	3	M	37		+		+	+	+		+		+	+	+				+	+	+
		M	4		+		+	+	+		+		+	+	+				+	+	
		M	0.1	+				+		+	+		+		+				+		
Roomaney I.A. et al., 2021 [13]	1	M	14			+		+					+	+	+						

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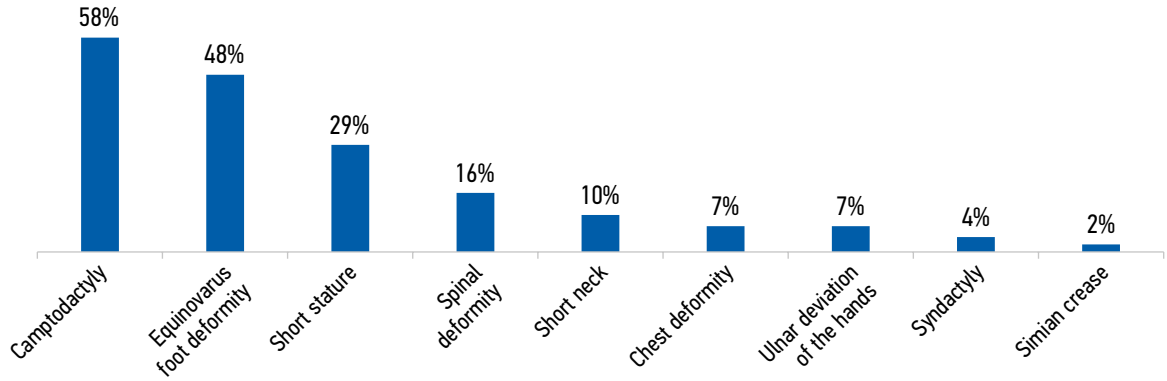

Fig. 1. Musculoskeletal pathologies in patients with distal arthrogryposis type 3

by a heterozygous *PIEZO2* mutation located on chromosome 18p11. This disease was first described by H. Gordon et al. in 1969 [6]. In the available literature, 28 cases of distal arthrogryposis type 3 have been reported (Table 1) [6–13].

The main clinical aspects of Gordon syndrome are camptodactyly, equinovarus foot deformity, and short stature. In 42% of cases, patients have a cleft palate; in 6% of cases, they have bifurcated uvula. Some patients have hypotension and decreased muscle mass. In 6% of cases, patients have moderate mental retardation. Studies have also described cases of cryptorchidism in this disease [6, 12, 14, 15].

Clinical manifestations of distal arthrogryposis type 3 are presented in Table 1 and Figs. 1 and 2.

Differential diagnostics of distal arthrogryposis type 3 should be performed with diseases such as the Aase–Smith syndrome (OMIM: 147800), Marden–Walker syndrome (MWS, OMIM: 248700), distal arthrogryposis type 5 (DA5, OMIM: 108145), Schwartz–Jampel syndrome (SJS1, OMIM: 255800), distal arthrogryposis type 1 (DA1, OMIM: 108120), and distal arthrogryposis type 2B (DA2B, OMIM: 601680) [15, 16].

Distal arthrogryposis type 5

Distal arthrogryposis type 5 (DA5, OMIM: 108145) is characterized by ocular abnormalities (most often ptosis, ophthalmoplegia, and/or strabismus) in combination with limb joint contractures. Patients have signs of facial dysmorphism such as hypomimia, triangular-shaped face, auricle deformity, deep-set eyes, and muscle rigidity (Fig. 3) [8, 15, 17–29]. Existing literature has described 41 cases of distal arthrogryposis type 5 (Table 2).

This disease is acquired in an autosomal dominant manner; for the first time, its genotype was identified by B. Coste et al. in 2013 [29]. A patient with similar clinical manifestations was first reported in 1939 by H.S. Altman and L.T. Davidson. Later B.D. Friedman and R.A. Heidenreich (1995) assessed the family history of the described patient and his son and regarded this case as distal arthrogryposis type 5 [8, 19].

An orthopedic examination revealed motion restriction in the spine, short neck, pectus excavatum, and scoliosis (often early progressing). In nearly half of the cases, patients have a short. A characteristic clinical sign of distal arthrogryposis type 5 is hand deformities, namely, finger contractures (camptodactyly), absence of folds in the projection of the interphalangeal joints, and clinodactyly of the fifth finger. Contractures of large joints of the extremities, more often the wrist and elbow and less often the shoulder, hip, and knee joints, were observed. The X-ray imaging of patients with distal arthrogryposis type 5 detects shortening of toes I and V, synostosis of the metacarpal and metatarsal bones, synostosis of the vertebrae, and scoliosis [26]. Other less common symptoms are toe syndactyly and cervical pterygium. Equinovarus deformity of the feet is characteristic (Fig. 4).

A distinctive clinical sign of distal arthrogryposis type 5 is an eye disorder, including ptosis, ophthalmoparesis, refraction disorders, degenerative changes in the retina, and optic nerve damage [25, 26]. A probable cause

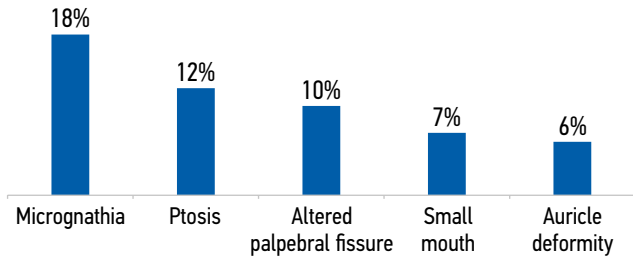

Fig. 2. Facial dysmorphism in patients with distal arthrogryposis type 3

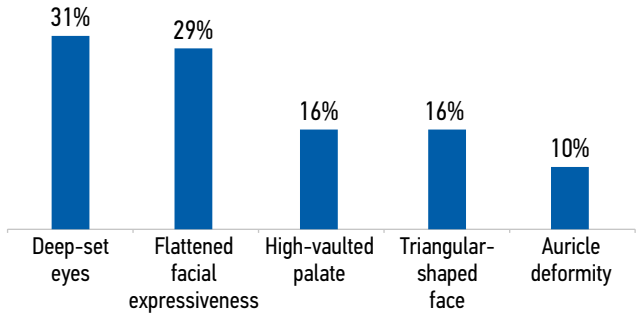

Fig. 3. Clinical manifestations of facial dysmorphism in patients with distal arthrogryposis type 5

Table 2. Clinical manifestations of distal arthrogryposis type 5

Authors of the study, year	Number of cases	Sex	Age, years	Short stature	Deep-set eyes	Ptosis	Impaired refraction	Ophthalmoparesis	Keratoconus	High-vaulted palate	Auricle deformity	Flattened facial expressiveness	Triangular-shaped face	Decreased muscle mass	Muscle rigidity	Stiffness of the spinal muscles	Short neck	Scoliosis	Camptodactyly	Absence of interphalangeal folds	Hand contracture	Wrist contracture	Contracture of the elbow joints	Contracture in the shoulder joints	Contracture in the hip joints	Contracture in the knee joints	Equinovar deformity of the feet	Heart pathology	Lung diseases	Chest deformity	Dimples on large joints
Hall J.G. et al., 1982 [8]	3	F	?	+		+		+			+	+					+			+		+	+				+				
		F	?						+																						
Lai M.M. et al., 1991 [17]	2	M	27	+	+	+		+		+																			+		+
		M	1.5																												
Schrander-Stumpel C.T. et al., 1993 [18]	1	M	18		+	+	+	+			+	+	+	+	+	+	+	+	+	+	+	+	+				+		+	+	
Friedman B.D., Heidenreich R.A., 1995 [19]	2	M	30			+																									
		M	63			+																									
Pallotta R. et al., 2000 [20]	3	F	12.5	+											+	+		+	+		+										
		M	14.5	+		+																									
		F	?	+																											
Beals R.K., Weleber R.G., 2004 [21]	7	M	?		+		+	+				+			+	+															
		F	?	+	+		+	+				+			+	+															
		F	?		+		+	+				+			+	+															
		F	?		+	+	+	+				+			+	+															
		M	?		+		+	+				+			+	+															
		M	?		+	+	+	+				+			+	+															
		M	?		+	+	+	+				+			+	+															
Sahni J. et al., 2004 [22]	4	M	53		+	+		+	+				+	+	+		+	+	+		+	+	+				+				
		F	28		+	+	+	+					+				+	+														
		F	28			+	+	+											+													
		F	?				+	+																								
Williams M.S. et al., 2007 [23]	3	F	47			+		+		+		+			+	+															
		M	19			+		+				+			+	+															
		M	48			+		+				+			+	+															
Castori M. et al., 2009 [24]	3	M	19			+	+								+	+															
		M	47			+	+	+				+																			
		M	76																												
Coste B. et al., 2013 [25]	3	F	35		+	+	+	+							+	+															
		M	5		+	+	+	+							+	+															
		F	38		+	+	+	+							+	+															
Okubo M. et al., 2015 [26]	4	F	13		+	+	+	+							+	+															
		M	8		+	+	+	+							+	+															
		F	7																												
		F	42		+	+		+							+	+															
Zapata-Aldana E. et al., 2019 [27]	4	M	1		+	+		+		+		+	+		+	+															
		F	?								+	+																			
		F	23		+	+	+	+							+	+															
		F	54		+	+	+	+							+	+															
Serra G. et al., 2022 [28]	1	M	0.4																												
Oliwa A. et al., 2022 [29]	1	M	0.3			+		+		+					+	+															+

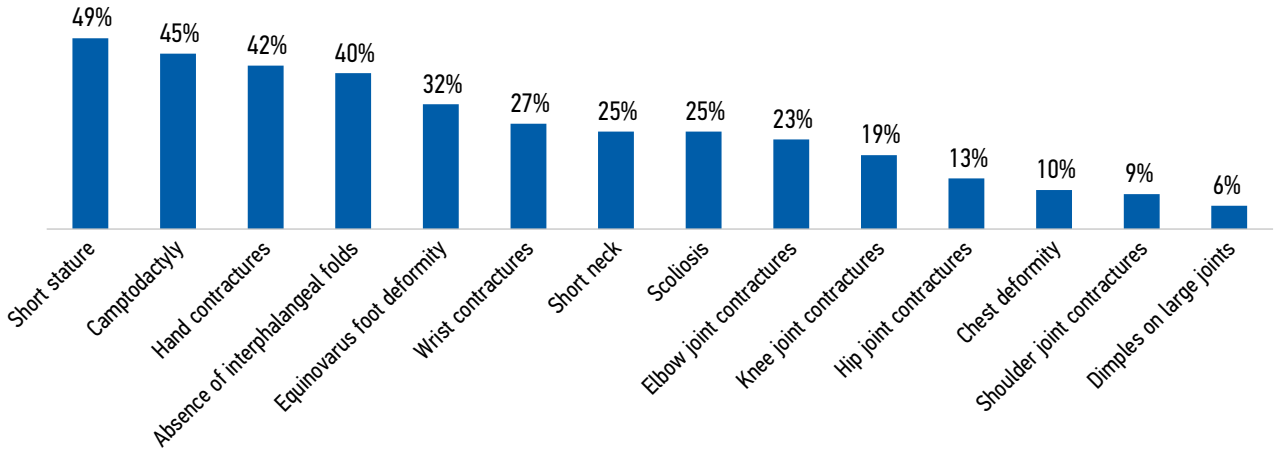

Fig. 4. Musculoskeletal pathologies in patients with distal arthrogryposis type 5

of ophthalmoparesis may be fibrosis of the eye muscles [21, 22] (Fig. 5).

In this arthrogryposis type, respiratory disorders are registered in 35% of cases. R.K. Beals and R.G. Weleber (2004) described four generations of the same family who suffered from severe obstructive-restrictive pulmonary dysfunction [21]. According to S. Dai et al. (2018), patients with severe distal arthrogryposis type 5 require tracheostomy [30]. M.S. Williams et al. (2007) reported a case of pulmonary hypertension in this arthrogryposis type [23].

Differential diagnostics of distal arthrogryposis type 5 should be performed with Marden–Walker syndrome, Gordon syndrome, and other types of distal arthrogryposis [15].

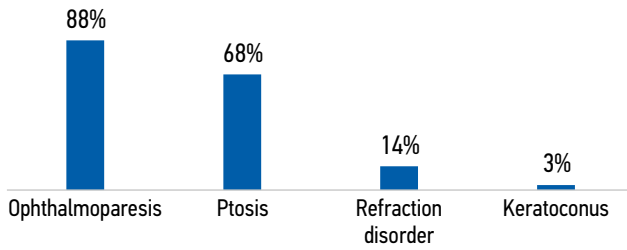

Fig. 5. Eye pathologies in patients with distal arthrogryposis type 5

2. Loss-of-function *PIEZO2* mutations

Distal arthrogryposis with impaired proprioception and tactile sense

In 2016, A. Delle Vedove et al. (2016) described 10 patients from four families with distal arthrogryposis, who were experiencing impaired proprioception and tactile sense [31]. This disease was caused by a *PIEZO2* mutation on chromosome 18p11 (OMIM: 613629). The authors concluded that PIEZO2 loss in afferent neurons in the spinal ganglia leads to impaired proprioception, muscle development, and function. This disease is inherited in an autosomal recessive manner [31].

In mouse experiments, complete deactivation of *PIEZO2* caused a lethal outcome in the perinatal period. Mice with PIEZO2 protein loss in mechanosensory neurons were diagnosed with severe impairments in motor coordination and limb rigidity [32].

Since 2016, new cases of distal arthrogryposis with impaired proprioception and tactile sense have been described. Existing literature presented 23 cases of this disease (Table 3) [31, 33–40].

Pathogenic loss-of-function *PIEZO2* mutations cause severe muscle hypotonia (90%), motor developmental

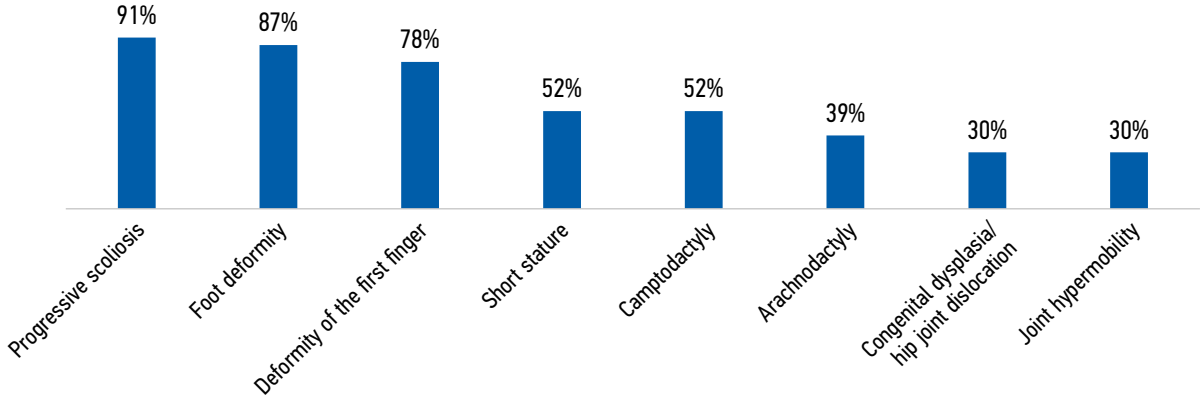

Fig. 6. Musculoskeletal pathologies in patients with distal arthrogryposis and impaired proprioception and tactile sense

Table 3. Clinical manifestations of distal arthrogryposis with impaired proprioception and tactile sense

Authors of the study, year	Number of cases	Sex	Age, years	Respiratory failure	Feeding problems	Hypotonia	Delayed motor development	Delayed start of walking	Start walking	Lack of deep reflexes	Dysarthria	Decreased proprioception	Axonal sensory neuropathy	Impaired mental function	Facial dysmorphism	Hypomimia/ptosis	short stature	Progressive scoliosis	Joint hypermobility	Camptodactyly	Arachnodactyly	Deformity of the first finger	Congenital dysplasia /hip joint dislocation	Foot deformity
Delle Vedove A. et al., 2016 [31]	10	M	5	+		+	+	+	5 years	+	+							+	+			+		+
		M	23	+		+	+	+	5 years	+	+	+					+	+				+		
		F	12	+	+	+	+			+	+		+			+	+	+						+
		M	15	+		+	+	+	6 years	+	+				+		+	+		+	+	+		+
		F	7	+		+	+	+	5 years	+	+				+		+			+	+			+
		M	27				+			+	+				+	+	+	+		+	+	+		+
		M	6	+	+	+	+	+	Does not go	+				+		+	+	+		+		+		+
		F	4			+	+	+	Does not go	+				+		+	+	+		+		+		
		F	25				+	+	8 years									+						
		M	25		+	+	+	+	5–6 years	+	+		+	+	+		+	+		+	+	+		+
Chesler A.T. et al., 2016 [33]	2	F	18			+	+	+	6–7 years	+		+	+					+		+	+	+	+	
		F	8			+	+	+	6–7 years	+		+	+					+		+	+	+	+	+
Mahmud A.A. et al., 2017 [34]	3	M	30			+	+	+	9 years	+		+					+	+		+	+	+		+
		F	23			+	+	+	6 years	+		+			+	+	+	+		+	+	+		+
		F	14			+	+	+	Does not go	+		+					+	+		+	+	+		+
Haliloglu G. et al., 2017 [35]	1	M	18		+	+	+	+	16 years		+	+	+		+			+	+			+	+	+
Behunova J. et al., 2018 [36]	1	M	3.5	+	+	+	+	+	Does not go	+	+				+			+	+					+
Yamaguchi T. et al., 2019 [37]	1	F	12		+	+	+			+		+	+		+		+	+	+	+		+	+	+
Oakley-Hannibal E. et al., 2020 [38]	1	F	9		+	+	+	+	2 years									+	+			+		+
Klaniewska M. et al., 2021 [39]	3	F	1	+	+	+	+	+	Does not go	+	+	+	+		+			+	+			+	+	+
		F	2.7		+	+	+	+	Does not go	+					+							+	+	+
		M	3.3	+	+	+	+	+	Does not go	+				+	+			+	+			+	+	+
Маркова Т.В. и др., 2021 [40]	1	F	3			+	+	+	Does not go		+							+						+

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delay (gait delay in 87% of cases), transient respiratory failure (39%), feeding problems in early infancy (43%), contractures of the joints of the upper and lower extremities, and progressive scoliosis. In the musculoskeletal system, feet and hand deformities (camptodactyly, arachnodactyly, and duckbill-shaped deformity of the first finger), short stature, joint hypermobility, and hip joint pathology (dysplasia or dislocation) are typical (Fig. 6).

Impaired proprioception is the main clinical sign of this disease. Patients have impaired balance and coordination, tactile sensitivity, areflexia, and dysarthria, and axonal neuropathy was diagnosed in nerve conduction studies [31, 33, 35, 37, 39] (Fig. 7).

In 17% of cases, patients have delayed cognitive functioning [31, 39].

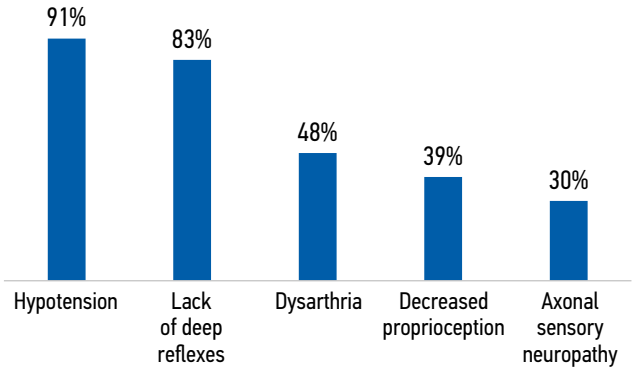

Fig. 7. Clinical manifestations in the nervous system of patients with distal arthrogryposis and impaired proprioception and tactile sense

CONCLUSION

This literature review revealed the importance of *PIEZO2* in the regulation of various physiological processes in the human body. Mutations of this gene cause distal arthrogryposis types 3 and 5 and distal arthrogryposis with impaired proprioception and tactile sense. The rare incidence of this pathology and complexity of clinical diagnosis warrant a molecular genetic study to verify the disease and select the optimal treatment approach.

ADDITIONAL INFORMATION

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