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Genetic and clinical spectrum of *PIEZO2*-related disorders: insights from a multicenter study of 26 patients

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ABSTRACT

PIEZO2 is a mechanosensitive ion channel essential for somatosensation, including proprioception, touch and interoception, enabling the detection of external and internal mechanical stimuli. Pathogenic variants in *PIEZO2* cause mechanosensitivity disorders, predominantly affecting musculoskeletal system. This multicenter study reports on 26 patients (14 females and 12 males; ages 1–51 years) from 23 independent families; 21 with biallelic and 5 with heterozygous variants. We identified 20 unique *PIEZO2* variants, including 14 novel variants. Patients with biallelic *PIEZO2* variants presented with hypotonia, joint contractures, feeding and respiratory difficulties,

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followed by delayed motor milestones and progressive scoliosis. Findings of disrupted proprioception along with areflexia were key neurological findings, and electrophysiologic studies showed sensory neuropathy. Clinical characteristics were distinct; however, there were considerable variations in disease severity. Heterozygous variants (*de novo* variants in three cases) exhibiting clinical features associated with *PIEZO2*-related disorders led to a heterogeneous disease spectrum, including distal arthrogryposis, restricted eye movements, ptosis, short stature, scoliosis, cleft palate, metacarpal/metatarsal synostosis, glaucoma, keratoconus, and restrictive pulmonary function. This is the largest cohort of patients with biallelic *PIEZO2* variants across ages. Our findings highlight the role of impaired proprioception in biallelic *PIEZO2*-related disease and channelopathy in heterozygous *PIEZO2*-related disorders, shaping diverse clinical presentations and expanding understanding of *PIEZO2*-related disorders.

1. Introduction

Piezo-type mechanosensitive ion channels (PIEZOs) are membrane proteins critical for mechanotransduction, the process by which mechanical stimuli are converted into changes in membrane potential [1, 2]. *PIEZO2* is a key sensor among gene families involved in mechanosensation, primarily expressed in mechanosensory neurons which detect and respond to internal and external mechanical stimuli [3]. These neurons are mainly located in specific subsets of dorsal root ganglia and other sensory ganglia (e.g., trigeminal, jugular, nodose) with sensory endings in specialized mechanosensory structures within muscles, tendons, joints, skin, and mucosa [4–11]. Abundantly present on axonal membranes, PIEZO2 is activated by mechanical stimuli that stretch axonal protrusions, triggering neuronal excitation [12].

Distal arthrogryposis (DA) is a group of rare disorders characterized by congenital contractures, primarily affecting the hands and feet. While initially described as an autosomal dominant trait, DA is now recognized to include diverse inheritance patterns and more than ten subtypes classified based on clinical features, extraarticular findings, gene variants, and inheritance patterns [13–16]. Among these, pathogenic variants in the *PIEZO2* gene contribute to the broad clinical spectrum of DA, resulting in varied presentations. During the last decade, several case studies demonstrated the role of biallelic *PIEZO2* variants in the pathogenesis of DA with impaired proprioception and touch (DAIPT, MIM 617,146), characterized by absent deep tendon reflexes, congenital contractures, neonatal hypotonia, respiratory challenges, and scoliosis [17–19]. On the other hand, heterozygous *PIEZO2* variants have been associated with conditions such as Gordon syndrome (GS), or DA type 3 (DA3, MIM 114,300), DA type 5 (DA5, MIM 108,145), and Marden-Walker syndrome (MWS, MIM 248,700) [20,21].

Previous literature is not only limited to single-case reports and small case series but also primarily focuses on snapshot clinical presentations or short-term observations. In this study, we aim to enhance our understanding of *PIEZO2*-related disorders by comprehensively analyzing clinical phenotypes in a relatively large patient cohort.

2. Patients and methods

In this nationwide, multicenter study, we included detailed phenotypic data on 26 patients diagnosed with *PIEZO2*-related disorders. The diagnosis was confirmed both clinically and genetically by the treating physicians, and genetic testing was performed at the participating centers.

Whole exome sequencing (WES) was performed for all cases, with a few exceptions. In Family 4, both patients (Patients 4 and 5) were diagnosed through single-gene analysis. Among the biallelic cases, two patients, Patient 21 (Family 20) and Patient 24 (Family 23), were diagnosed using Sanger sequencing following the diagnosis of their cousin (Patient 22, Family 20) or sibling (Patient 23, Family 23) by WES. Confirmation and family segregation analyses of the detected variants were performed using the Sanger sequencing method. Only the pathogenic variant(s) detected were sequenced in parents or relatives to determine inheritance. Segregation analysis could not be performed in four families (Families 11, 12, 17, and 23) due to lack of consent. Variant interpretation was performed according to the standards and guidelines of the American College of Medical Genetics and Genomics (ACMG) [22].

All patients underwent a study visit at these centers, and retrospective data were extracted from electronic medical records. To ensure consistency, standardized data collection templates were used. The study protocol was reviewed and approved by the Ethics Committee of Izmir Dr. Behcet Uz Children's Hospital (GOA-91, 12 DEC 2024). Written informed consent was obtained from all affected individuals and their parents for study participation and the publication of pseudo-anonymized data.

During the study visit, medical history was collected, including perinatal and family history, hypotonia, respiratory and feeding difficulties from the neonatal period onward, motor milestone development, cognitive development, facial characteristics, dysarthria/nasal speech, and musculoskeletal abnormalities such as scoliosis, contractures, hip dysplasia/dislocation, pes equinovarus, and joint hypermobility. Anthropometric measurements were recorded at birth, at subsequent time points, and at the current evaluation. Short stature was defined as a height equal to or less than two standard deviations (SD) below the mean, based on height charts for Turkish individuals. For children of non-Turkish descent, World Health Organization (WHO) charts were used. Data on neonatal intensive care unit (NICU) admissions, other hospitalizations, and surgeries were also collected.

A comprehensive neurological examination assessed cognitive status, cranial nerves, muscle tone and strength, deep tendon reflexes, and sensory deficits (e.g., vibration, joint position, touch, pain, and temperature). Detailed sensory assessments were conducted for all patients with biallelic variants if their age and developmental status allowed for testing. Among the five patients with heterozygous variants exhibiting clinical features associated with *PIEZO2*-related disorders, detailed proprioception and sensory assessments were performed in 2 patients (Patient 1 and Patient 5). The walking pattern was evaluated in all subjects who were ambulatory or able to walk with assistance at the time of the study visit. Additionally, patients were tested to determine whether their ability to reach a target deteriorated when they closed their eyes.

Laboratory evaluations included serum creatine kinase (CK) levels and routine biochemical tests. Radiographic assessments (e.g., cranial MRI, extremity X-rays, and scoliosis workup) and electrophysiological findings were reviewed.

Electrophysiological assessments included median and ulnar nerves (motor and sensory studies), tibial and peroneal nerves (motor study) and sural nerve (sensory study). Recorded parameters included compound muscle action potential amplitudes, sensory nerve action potentials, nerve conduction velocities and late responses including F wave and the soleal H-reflex.

Electrocardiography (ECG) records were examined for all patients, and ophthalmological evaluations were also reviewed. Urinary urgency and nocturnal enuresis were assessed in each patient if their age was appropriate.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS Inc.), version 24.0 for Windows. Mann Whitney U test was used to compare independent groups. Data were

expressed as n (%) or median (25th–75th percentiles; range), as appropriate.

3. Results

3.1. Cohort summary and genetic findings

A total of 26 patients from 23 independent families were diagnosed with *PIEZO2*-related disorders. The median age was 11 years (25–75 percentiles: 4–18 years; range: 1–51 years). The cohort included 14 females (54 %) and 12 males (46 %). Consanguinity was identified in 18 of the 26 cases (69 %). Among the 26 patients, 21 (81 %, from 19 families) were diagnosed with DAIPT. The remaining five patients (19 %, from four families) had heterozygous pathogenic variants in *PIEZO2:* three with *PIEZO2*-related DA5 (Patient 1, Patient 2, and Patient 3) and two with GS (Patient 4 and Patient 5, Family 4). Patient narratives are presented in the Supplemental File.

Genetic analysis revealed 20 unique *PIEZO2* variants in 26 patients, including 19 patients with homozygous variants, 2 with compound heterozygous variants, and 5 with heterozygous variants. Of these, 6 variants were previously reported, while 14 were novel.

The identified variants included six frameshift variants (five novel variants in exons 7, 28, 29, and 47, and one previously reported variant in exon 52), four missense variants (two novel variants in exon 5 and two previously reported variants in exons 38 and 52), six nonsense variants (four novel variants in exons 9, 11, 22, and 48, and two previously reported variants in exons 12 and 52), three noncoding variants (all novel, located in exons 17, 27, and 35), and one in-frame deletion (a previously reported variant in exon 52). A detailed list of individual variants is provided in Supplementary Table 1.

Heterozygous variants exhibiting clinical features associated with *PIEZO2*-Gain of function (GoF) related DA5, and GS were all located in exon 52, within the C-terminal region of the *PIEZO2* gene. Three patients with *PIEZO2*-related DA5 had *de novo* variants. Patients 1 and 3, from two unrelated families, carried the same *de novo* heterozygous variant, c.8181_8183del (p.Glu2727del) in *PIEZO2*, which was not detected in either parent. The variant was also absent in Patient 1′s unaffected sibling. Patient 3 was the only child in the family. Patient 2 carried a different *de novo* heterozygous variant, c.8208delA (p.Tyr2737Ilefs*7) in *PIEZO2*, which was not detected in either parent or in his unaffected brother.

We identified the *PIEZO2* variant c.8057G>*A* (p.Arg2686His) in Patient 5 and his daughter (Patient 4). Segregation analysis confirmed that the variant was not maternally inherited, as it was not detected in Patient 5′s mother. The father of Patient 5 had passed away 11 years earlier and could not be evaluated through genetic testing. He was reportedly clinically healthy and showed no signs of arthrogryposis. Although the variant is suspected to be *de novo* in Patient 5, this could not be definitively confirmed.

Biallelic variants were distributed throughout the gene. The novel c.744del variant was the most frequently detected homozygous variant in our cohort, identified in four unrelated patients. All variants detected in our cohort were classified based on ACMG guidelines (Supplementary Table 1). Among the previously reported variants, c.8152C>*T*, a nonsense variant, was identified in two patients with DAIPT from the same family. This variant was previously classified as a variant of uncertain significance (VUS) in the ClinVar database but was reinterpreted as "Likely Pathogenic" (PVS1, PM2) according to ACMG criteria. Transcripts carrying this variant would likely result in a truncated protein or be subject to nonsense-mediated decay. As expected, all parents of patients with biallelic variants who were tested for carrier status were found to be heterozygous carriers of the identified variants.

3.2. Characteristics of patients with biallelic PIEZO2 variants (Patients 6–26)

3.2.1. General characteristics and findings in neonatal and early infancy

The median age of patients with biallelic *PIEZO2* variants was 11 years (25th–75th percentiles: 4–15 years; range: 1–24 years), with 12 females (57 %) and 9 males (43 %). Consanguinity was identified in 16 patients (76 %). Birth weight was 3105 g (25th–75th percentiles: 2785–3290 g; range: 2275–3530 g).

Neonatal and early infancy features were commonly observed in patients with biallelic *PIEZO2* variants (Table 1), including hypotonia and feeding difficulties in all 21 patients, respiratory distress in 19 patients (91 %), and laryngeal stridor in 16 patients (76 %).

The median hospital stay during the neonatal and early infancy periods was 24 days (25th–75th percentiles: 15–45 days; range: 0–150 days) and was most often due to respiratory and feeding difficulties. One of the patients in this group (Patient 20) required a tracheostomy at 40 days of age, while another patient (Patient 22) underwent surgery for laryngomalacia at 5 months of age. Although all 21 patients experienced transient short-term feeding difficulties during the newborn period and early infancy, Patient 21 required a percutaneous endoscopic gastrostomy (PEG) at 8 months of age, which was used for feeding until the age of 3. At 15 years old, she still had difficulty swallowing liquids during oral feeding. Another patient who experienced prolonged feeding difficulties, Patient 22, was able to transition to oral feeding at 7 months.

3.2.2. Craniofacial and skeletal features

All 21 patients exhibited distinct craniofacial characteristics, including a prominent forehead, midface hypoplasia, prominent eyes, a long and broad nasal bridge, a thin upper lip, and a high-arched palate, with some variability. Several patients also presented with facial muscle weakness/hypomimia without ophthalmoplegia (Supplementary Figure 1A, a representative image from Patient 13 is shown in Fig. 1A). All patients had distal extremity contractures of varying severity (Supplementary Figure 1B and Supplementary Figure 1C, representative images are shown in Fig. 1B and Fig. 1C). In younger patients, contractures were typically milder, presenting as clenched hands, clinodactyly, or bilateral thumb flexion contractures, while older children and adults exhibited more pronounced contractures.

Additional physical findings in this group included pes equinovarus in 18 patients (86 %), joint hypermobility in 17 patients (81 %), umbilical hernia in 13 patients (62 %), hip dislocation/dysplasia in 11 patients (52 %), and short stature in 11 patients (52 %). The median height standard deviation score (SDS) was −3.37 (25th–75th percentiles: −3.72– −3.24; range: −3.98– −3.20).

Progressive scoliosis was a prominent feature, often worsening with growth (Supplementary Figure 1D, representative images from Patient 7 are shown in Fig. 1D). The youngest patient in the biallelic *PIEZO2* cohort, 12-month-old Patient 16, was the only patient who had not developed scoliosis. Another young patient, 20-month-old Patient 6, had mild scoliosis. Radiographs taken at 1 month of age in Patient 7 showed a normal spine, but by age 12, the patient developed severe scoliosis. Two patients required surgical correction due to scoliosis. Interestingly, Patient 22 had a history of using a brace for scoliosis starting at 18 months old, which resulted in significant improvement over 18 months. This patient also had spina bifida.

3.2.3. Neurological and electrophysiological findings

Neurological findings were consistent across patients with biallelic *PIEZO2* variants (Table 2). All patients had absent or decreased deep tendon reflexes and delayed motor milestones. Sensory deficits were noted in vibration perception (12/12, 100 %), discriminative touch (9/9, 100 %), and joint position sense (11/11, 100 %). Pain and temperature perception were normal (12/12, 100 %). Punctate touch on the glabrous skin of the forearm was preserved in all tested patients (11/11, 100 %). Mild dysarthria or nasal speech was detected in 10 of 19 patients

Table 1
Clinical findings from birth to infancy and physical findings based on medical history and physical exam at the study visit.

	Perinatal period		Birth to infancy					Physical findings						
	Birth weight (gram)	Gestational age	Hypotonia	Feeding difficulties	Respiratory insufficiency	Laryngeal stridor	Hospital stay for RI	Hip dislocation dysplasia	Pes equinovarus	Joint hypermobility	Scoliosis	Short stature	Umbilical hernia	Limited ocular motility / ptosis
P1	2850	term	–	+	+	–	7	–	+	–	+	+	–	+ / +
P2	2250	term	–	–	–	–	–	–	+	–	+	+	+	+ / +
P3	2800	term	–	–	–	–	–	–	+	–	–	+	–	+ / +
P4	1950	term	–	+	–	–	–	–	+	–	+	+	–	- / +
P5	NA	term	–	–	–	–	–	–	+	–	+	+	–	- / +
P6	2645	term	+	+	+	+	40	+	–	+	+	–	–	- / -
P7	3100	term	+	+	+	+	45	+	+	+	+	+	+	- / -
P8	3200	term	+	+	+	+	40	–	–	+	+	–	–	- / -
P9	3530	term	+	+	+	–	30	–	+	–	+	–	–	- / -
P10	2500	term	+	+	+	–	24	+	+	+	+	+	–	- / -
P11	3100	term	+	+	+	+	15	–	+	+	+	–	–	- / -
P12	3000	term	+	+	-	-	–	-	+	+	+	-	+	- / -
P13	3200	term	+	+	+	+	30	–	+	–	+	+	+	- / -
P14	3280	term	+	+	+	+	15	–	+	–	+	–	+	- / -
P15	2275	near term	+	+	+	+	15	+	+	+	+	–	+	- / -
P16	2820	term	+	+	+	+	22	–	+	+	–	+	+	- / -
P17	NA	term	+	+	+	+	120	–	+	–	+	+	+	- / -
P18	2500	near term	+	+	+	+	120	+	–	+	+	–	+	- / -
P19	2750	term	+	+	+	+	15	+	+	+	+	+	+	- / -
P20	3320	term	+	+	+	+	60	+	+	+	+	+	–	- / -
P21	3400	term	+	+	+	+	45	+	+	+	+	+	–	- / -
P22	3110	term	+	+	+	+	150	+	+	+	+	+	–	- / -
P23	3200	term	+	+	+	–	10	+	+	+	+	+	+	- / -
P24	3500	term	+	+	–	–	–	+	+	+	+	+	+	- / -
P25	3300	term	+	+	+	+	12	–	+	+	+	–	+	- / -
P26	3100	term	+	+	+	+	15	–	+	+	+	–	+	- / -

Term: gestational age ≥37; near term ≥34- <37; preterm <34 weeks. P: Patient; RI: Respiratory insufficiency.

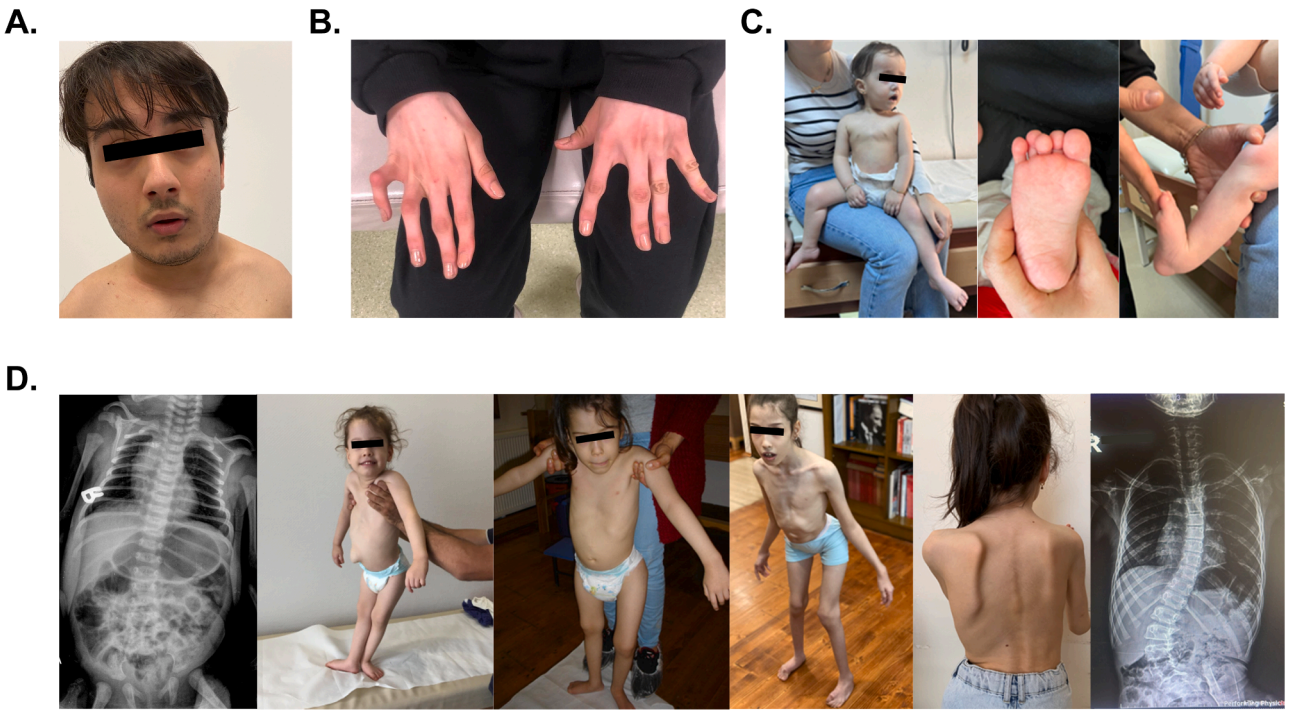

Fig. 1. Phenotypic features of patients with biallelic variants in *PIEZO2* **A.** Facial characteristics: Representative facial characteristics of patients with biallelic variants in *PIEZO2* are shown in Patient 13. These features include a prominent forehead, midface hypoplasia, prominent eyes, a long and broad nasal bridge, and a thin upper lip. Additionally, facial muscle weakness and reduced facial expression are noted. **B.** Hand abnormalities: The figure shows clinodactyly, camptodactyly, and bilateral thumb flexion contractures in Patient 19 from the cohort. A characteristic "duck-bill" deformity is observed (hyperextension of the interphalangeal joint with flexion of the metacarpophalangeal joint of the thumb). **C.** Foot abnormalities: All patients exhibited foot abnormalities (e.g., pes equinovarus, pes planus, pes cavovarus, overlapping toes, and joint hyperlaxity). Representative images from Patient 6 are presented here. **D.** Skeletal abnormalities: Most patients presented with hypotonia, scoliosis or kyphoscoliosis, and short stature. Representative images from Patient 7 are shown. Hypotonia, shoulder girdle muscle weakness, and sloping shoulders are evident. Progressive scoliosis was a prominent feature, often worsening with growth. While radiographs at 1 month of age appeared normal, by age 12, the patient developed severe scoliosis. Foot contractures are also apparent.

(52 %) with available assessments. Additionally, all 12 patients who were tested for their ability to reach a target showed deterioration when they closed their eyes and similarly experienced difficulties maintaining their posture.

Ambulation was delayed in all patients with biallelic *PIEZO2* variants. Among ambulatory patients (n = 9, 43 %), the median age at ambulation was 5 years (25th–75th percentiles: 3–6 years; range: 2–13 years). All ambulatory patients had sensorial ataxia and Romberg test was positive while eyes closed. Among patients who were not yet walking independently, the median age was 5 years (25th–75th percentiles: 3–9 years; range: 1–11 years), suggesting considerable intrafamilial variation in the severity of motor dysfunction.

Muscle biopsies were performed in four patients with biallelic *PIEZO2* variants. Muscle biopsy was normal in three patients (Patient 7, Patient 12, and Patient 13). Another patient's biopsy (Patient 21) showed nonspecific findings such as fiber size variation.

Electrophysiological studies revealed sensory neuropathy with normal motor nerve studies in 13 of 16 patients (81 %) and absent H reflexes in 11 of 11 patients (100 %).

Cognitive function was generally normal, except in two patients (10 %), one of whom had intellectual disability while the other had a language delay.

3.2.4. Other findings

One of the patients in this group (Patient 21) recently underwent polysomnography at age 15, which identified moderate sleep apnea; consequently, she began using a BiPAP device. Another patient (Patient 23) was diagnosed with diabetes mellitus at age 5. Her genetic testing revealed a heterozygous *HNF4A* c.724G>*A* (p.Val242Met) variant associated with maturity onset diabetes of the young (MODY), along with a novel nonsense variant in *PIEZO2* c.3247C>*T* (p.Arg1083*). She also presented with a tethered cord and neurogenic bladder.

3.3. Characteristics of patients with heterozygous PIEZO2 variants (Patients 1–5)

3.3.1. General characteristics and findings in neonatal and early infancy

The individual characteristics of patients with heterozygous *PIEZO2* variants are presented in Supplementary Table 1, Tables 1 and 2, and Fig. 2. The five patients with heterozygous *PIEZO2* variants had a median age of 22 years (25th–75th percentiles: 14–24 years; range: 1–51 years), with two females (40 %) and three males (60 %). Consanguinity was present in two patients (40 %). The median birth weight was 2525 g (25th–75th percentiles: 2100–2825 g; range: 1950–2850 g).

Patients with heterozygous *PIEZO2* variants had congenital contractures without joint hypermobility. Distal contractures of the fingers and pes equinovarus were observed at birth in all five patients, along with reduced wrist dorsiflexion and elbow extension. Phalangeal creases were absent, and palmar creases were poor in all five patients (Fig. 2).

All five patients in this group achieved their motor milestones normally. None of the five patients exhibited hypotonia during the neonatal and early infancy period. Instead, hypertonicity was observed in one patient (Patient 1) with *PIEZO2*-related DA5 as a newborn. Respiratory distress was noted in one patient (Patient 1), while transient feeding difficulties were reported in two patients (Patient 1 and Patient 4). In one of these cases (Patient 4), feeding difficulties were attributed to cleft palate as part of GS. Patient 1 was hospitalized for seven days during the neonatal period due to respiratory and feeding difficulties, along with a suspicion for sepsis. Other patients did not require hospitalization. None exhibited laryngeal stridor.

Table 2
Findings from neurological assessments and electrophysiological studies.

	Neurological findings					Defect of senses					Electrophysiological studies	
	Delayed motor development	Independent walking	Age at ambulation (years)	Cognitive delay	Dysarthria nasal speech	Absent or reduced DTRs	Vibration	Joint position	Touch	Pain temperature	Sensory nerve conduction abnormalities	H reflex
P1	–	+	1	–	–	–	–	–	–	–	–	+
P2	–	+	1	–	–	–	NA	NA	NA	NA	NA	NA
P3	–	–	–	–	NA	–	NA	NA	NA	NA	NA	NA
P4	–	+	1	–	–	–	NA	NA	NA	NA	NA	NA
P5	–	+	1.5	–	–	–	–	–	–	–	NA	NA
P6	+	–	–	–	NA	+	NA	NA	NA	NA	+	–
P7	+	–	–	–	+	+	+	+	+	–	+	–
P8	+	–	–	–	–	+	NA	NA	NA	NA	+	–
P9	+	–	–	–	–	+	NA	NA	NA	NA	+	NA
P10	+	–	–	–	–	+	+	NA	NA	–	+	NA
P11	+	+	3	–	+	+	+	+	+	–	+	–
P12	+	+	6	-	-	+	+	+	+	–	+	–
P13	+	+	6	–	+	+	+	+	+	–	NA	NA
P14	+	+	5	–	+	+	+	+	+	–	+	NA
P15	+	–	–	–	–	+	NA	NA	NA	NA	NA	NA
P16	+	–	–	–	+	+	NA	NA	NA	NA	–	NA
P17	+	–	–	+	+	+	NA	NA	NA	NA	NA	NA
P18	+	–	–	+	NA	+	NA	NA	NA	NA	NA	NA
P19	+	+	2	–	+	+	+	+	+	–	–	–
P20	+	–	–	–	+	+	+	+	+	–	+	–
P21	+	+	13	–	–	+	+	+	+	–	+	–
P22	+	–	–	–	–	+	NA	NA	NA	NA	+	–
P23	+	+	6	–	+	+	+	+	NA	–	+	NA
P24	+	+	3	–	+	+	+	+	NA	–	NA	NA
P25	+	–	–	–	–	+	NA	NA	NA	NA	–	–
P26	+	+	3,5	–	–	+	+	+	+	–	+	–

P: Patient; NA" Not available.

3.3.2. *Skeletal and neurological characteristics*

Short stature was a consistent finding among patients with heterozygous variants with all four subjects having height SDS below −2. The median height SDS was −3.28 (25th–75th percentiles: −3.46– −3.20; range: −3.98– −2.37). Compared to patients with biallelic *PIEZO2* variants, SDS was significantly lower in patients with heterozygous *PIEZO2* variants ($p = 0.041$).

The youngest patient (Patient 3) in this group had no scoliosis, while others with heterozygous *PIEZO2* variants had only mild, non-progressive or slowly progressing scoliosis. Patient 1 had mild leftward scoliosis (Cobb angle: 10.4°), which remained stable over four years (Fig. 2A). Two radiographs of Patient 2, taken ten years apart, showed no significant progression of scoliosis (14.2° vs. 18.4°; Fig. 2B). Similarly, Patient 5 had very mild scoliosis at age 51 (Fig. 2E). Other shared features included anteverted shoulders, pectus excavatum, a short, stiff neck and spinal rigidity. Metacarpal/metatarsal synostosis was another notable feature, present in four patients with heterozygous *PIEZO2* variants (Fig. 2A, Fig. 2B, Fig. 2D, Fig. 2E). A radiograph taken at 16 months of Patient 3 showed the absence of ossification centers in the carpal bones and tarsal bones, except for the calcaneus and talus (Fig. 2C).

Muscle strength, deep tendon reflexes, vibration, joint position sense, discriminative touch, temperature, and pain sensation were all normal in patients with heterozygous *PIEZO2* variants. No patient had dysarthria, distinguishing them from the recessive phenotype. All five patients had normal cognitive functions.

Motor and sensory nerve conduction studies, including H-reflex and F-latency responses, were evaluated only in Patient 1 and were found to be normal.

3.3.3. *Distinct characteristics of patients with PIEZO2-related DA5*

There were three patients with *PIEZO2*-related DA5. Patient 2, was previously reported with a limited clinical description [21]. Here, we provide a detailed phenotypic characterization and a longer follow-up of this patient along with others. Three patients with *PIEZO2*-related DA5 (Patient 1, Patient 2 and Patient 3), caused by *de novo* variants, had distinctive facial features, including a triangular face, deep-set eyes, mild ptosis, mild restriction of horizontal eye movements, and downward gaze with marked restriction in upward gaze, as well as a square chin and prominent ears (Fig. 2A–C). On physical examination, the muscles, particularly the paraspinal muscles, felt firm or woody. Respiratory function tests in Patient 1 and Patient 2 suggested mild restrictive lung disease, with minimal or no symptoms. Echocardiography revealed an enlarged pulmonary artery (1.7 cm) in Patient 1. Additionally, the same patient was diagnosed with Wolff-Parkinson-White (WPW) syndrome at age 12 after an ECG showed a short PR interval and delta waves, and an electrophysiological study identified a left-sided accessory pathway, which was successfully ablated with radiofrequency energy.

3.3.4. *Distinct characteristics of patients with Gordon syndrome*

Two patients in our heterozygous *PIEZO2* cohort had GS. A father and daughter with c.8057G>*A* variant had short stature, mild ptosis, a cleft palate (in the daughter), and contractures of the distal joints (Fig. 2D and Fig. 2E). These initial cases were classified as MWS by another group 20 years ago based on their phenotypic features and the absence of a genetic diagnosis at the time [23]. However, our re-evaluation identified the c.8057G>*A* variant, which accounts for most known cases of GS [21]. Additionally, since our patients have no brain malformations or cognitive impairment, their features align with a diagnosis of GS.

3.3.5. *Ophthalmologic findings of patients with heterozygous PIEZO2 variants*

Ophthalmological evaluation revealed mild ptosis and restricted eye movements in all three patients with *PIEZO2*-related DA5, while mild ptosis and narrow eyelids were noted in patients with GS. Another important ophthalmologic feature in patients with heterozygous *PIEZO2*

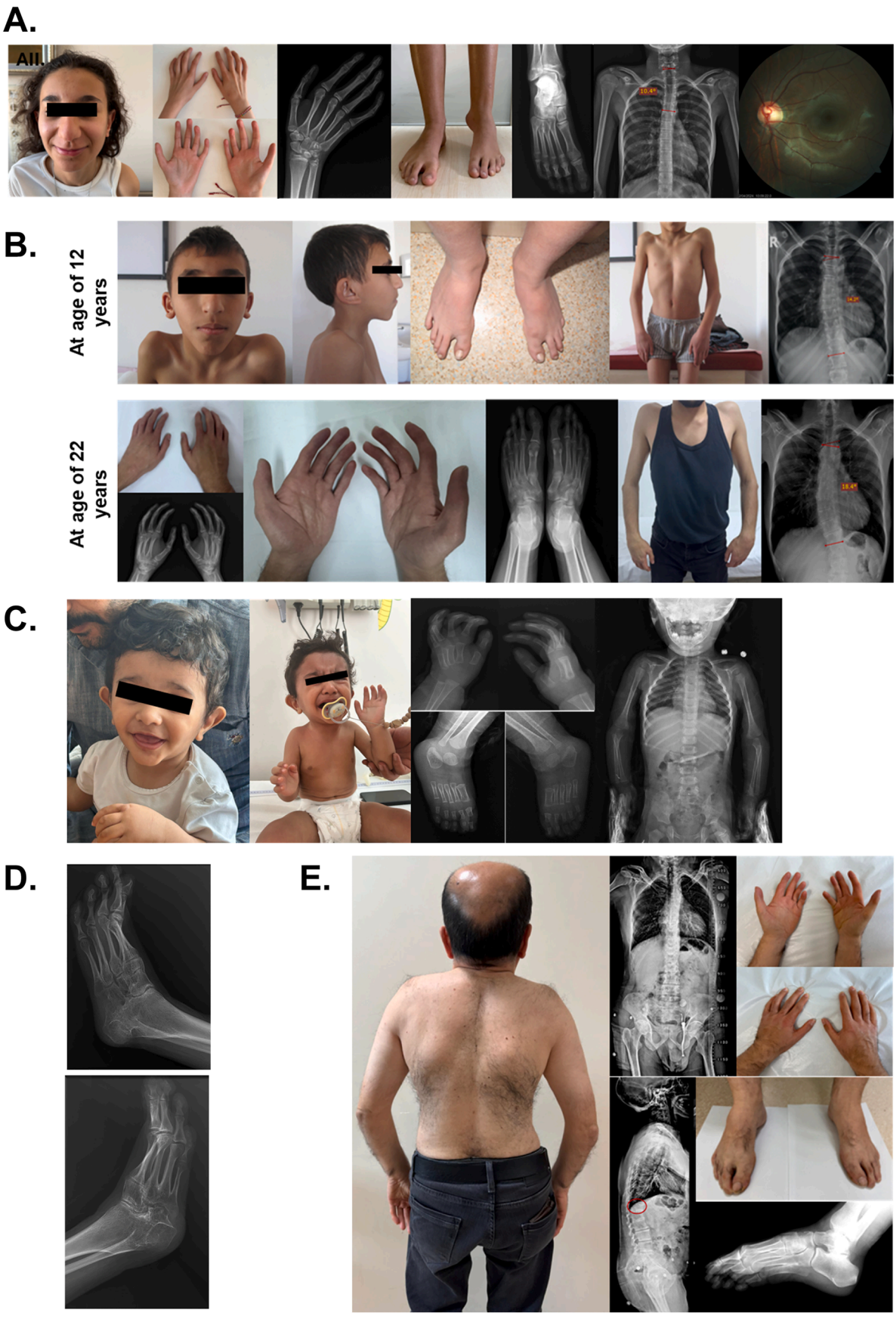

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Fig. 2. Characteristics of patients with heterozygous *PIEZO2* variants. **A.** Pictures from Patient 1 with *PIEZO2*-related distal arthrogryposis type 5 show distinctive craniofacial features, including a triangular facial shape, deep-set eyes, mild ptosis, arched eyebrows, a full nasal tip, a square chin, and large ears. The patient exhibits curved fingers with straight thumbs, bilateral camptodactyly, and clinodactyly of the fifth fingers, with absent phalangeal creases and poorly developed palmar creases. Ulnar deviation is visible on the wrist radiograph. Pictures also show tight heel cords, posteriorly located fifth toes, and a widely spaced gap between the first and second toes (sandal gap deformity). A foot radiograph reveals synostosis between the cuboid and cuneiform bones. Mild leftward scoliosis is present (Cobb angle: 10.4°). A color fundus image demonstrates advanced cupping of the optic nerve head, with a cup-to-disc ratio of 0.6–0.7. **B.** Pictures taken at the age of 12 years (at the time of diagnosis) of Patient 2 with *PIEZO2*-related distal arthrogryposis type 5 show distinctive craniofacial features (decreased facial expression, a triangular facial shape, deep-set eyes, mild ptosis, arched eyebrows, a full nasal tip, a square chin, and prominent ears with a thickened helix bilaterally). Pes planovalgus, short first and fifth toes, a wide gap between the first and second toes (sandal gap deformity) and posteriorly located fifth toes are also noted. Additional findings include a short and slightly webbed neck, hunched anteverted shoulders, pectus excavatum, mild elbow contractures, and reduced upper extremity mobility. Mild leftward scoliosis is present. Follow-up images taken at age 22 show no significant progression of scoliosis (14.2° vs. 18.4°). Hand pictures reveal curved fingers with straight thumbs, bilateral camptodactyly, and clinodactyly, with absent phalangeal creases and poorly developed palmar creases. Bilateral AP foot radiographs demonstrate synostosis between the navicular and cuneiform bones, as well as between the cuneiform bones themselves. **C.** Pictures from Patient 3 with *PIEZO2*-related distal arthrogryposis type 5 show distinctive craniofacial features, triangular face, mild ptosis, low anterior hairline, deep-set eyes, wide and depressed nasal bridge, square chin and large ears. Additional findings include a short, stiff neck, spinal rigidity, mild pectus excavatum. Limited finger extension, curved fingers with straight thumbs, bilateral camptodactyly, clinodactyly of the fifth fingers, and mild wrist flexion contractures are noted. The phalangeal flexion creases are absent, and the palmar creases are poorly developed. A radiograph taken at 16 months, shows absence of ossification centers in the carpal bones and tarsal bones (except for the calcaneus and talus). Anteroposterior vertebral radiograph shows no evidence of scoliosis. **D.** Lateral and oblique foot radiographs of both the right and left feet from Patient 4 with Gordon syndrome show synostosis in the distal tibiofibular, tibiotalar, talocalcaneal, and other proximal intertarsal joints. **E.** Pictures of Patient 5 with Gordon syndrome show short and stiff neck, anteverted shoulders, mild kyphoscoliosis, elbow contractures with reduced mobility of the upper extremities. The patient has stiff, tapering fingers with clinodactyly of the fifth fingers bilaterally, absent interphalangeal flexion creases. Other findings include pes cavus, sandal gap deformity and camptodactyly. A radiograph shows anterior wedging of the L1 vertebral body and kyphosis with mild scoliosis. Synostosis is detected between the base of the fourth metatarsal and the cuboid bone.

variants was glaucoma. Both patients with GS had glaucoma. Additionally, the father (Patient 5) developed corneal ectasia and cataracts in his 20 s, requiring multiple ophthalmologic interventions. His daughter (Patient 4) required medication and regular monitoring of intraocular pressure and corneal thickness. One patient with *PIEZO2*-related DA5 showed advanced optic nerve cupping (Fig. 2A), high-normal intraocular pressure, and retinal nerve fiber thinning at 13 years of age. The other patient with *PIEZO2*-related DA5, who is 22 years old, had keratoconus, which required corneal cross-linking.

4. Discussion

This multicenter study, the largest to date, explores the genetic and clinical spectrum of *PIEZO2*-related disorders. Our findings confirm distal joint contractures as a common feature across the spectrum, despite variability in severity and disease progression. While both deficient and excessive PIEZO2 activity contribute to these disorders, the distinct characteristics of biallelic (recessive) and heterozygous (dominant/*de novo*) variants reflect the presence of differing pathological mechanisms.

PIEZO2 is one of the largest human genes, consisting of 52 exons (transcript NM_022068.4, ENST00000503781.7). It encodes the large transmembrane PIEZO2 protein, which forms a homotrimeric channel composed of a central ion-conducting pore structure and three peripheral blades [24]. PIEZO2 mechanosensitivity depends on charged residues at the interface between the beam and C-terminal domain [25]. In addition, unique constriction sites near the C-terminus are thought to form a transmembrane gate regulated by the cap domain [24].

Biallelic variants of *PIEZO2* were found throughout the gene in our cohort of 21 patients and were primarily associated with the DAIPT phenotype. The novel biallelic c.744del variant was identified in four unrelated patients, suggesting a possible founder effect in Turkey. On the other hand, all heterozygous variants exhibiting clinical features associated with *PIEZO2*-related disorders were clustered in exon 52, consistent with previous reports, which described variants in the mid and C-terminal regions, a highly conserved domain crucial for ion-permeation channels [21,26,27]. *PIEZO2* related DA5 was caused by *de novo* variants in three of five patients, suggesting genetic instability and a higher spontaneous mutation rate in this region.

The cardinal difficulty and morbidity in DAIPT arise from impaired proprioception, making it challenging for affected individuals to perceive position of their body parts in space. Proprioception, often called the "sixth sense", allows the body to detect posture and movement by sensing changes in muscle length, tension, joint angles, and skin stretch [28]. It depends on specialized sensory organs such as muscle spindles, Golgi tendon organs, and low-threshold mechanoreceptors. PIEZO2 plays a crucial role in this process through mechanotransduction by transmitting mechanical signals through sensory neuron axons [1,4,8,12]. This process contributes both unconscious reflexes (e.g., patellar reflex) and conscious movements (e.g., touching one's nose with eyes closed), and light touch and vibration perception [5,29].

Despite preserved muscle strength, DAIPT patients in our cohort exhibited absent or reduced stretch reflexes, sensory ataxia, a positive Romberg sign, and impaired target-reaching with eyes closed. Punctate touch on hairy skin was preserved, suggesting the involvement of low-threshold mechanoreceptors independent of PIEZO2 to this sensation [8,18]. Temperature and pain sensations were tested normal. Electrophysiology studies confirmed sensory neuropathy, and absent H reflexes, indicating afferent arc dysfunction involving dorsal root ganglion neurons and type Ia fibers. These findings, along with neurological examination results, suggest that DAIPT represents a distinct mechanosensitivity disorder rather than a generalized ganglionopathy or posterior column impairment.

Lifelong proprioceptive deficits in DAIPT, likely beginning in early gestation, contribute to muscle and skeletal misalignment, leading to congenital and progressive deformities [30]. Animal studies confirm that deleting PIEZO2 in proprioceptive neurons, rather than bone-forming cells, leads to skeletal abnormalities resembling scoliosis and hip dysplasia, highlighting proprioception's crucial role in musculoskeletal structure [31].

Neurological characteristics were quite consistent in patients with DAIPT, on the other hand, we observed significant variations in motor impairment severity and deformity progression. In one instance, the use of spinal bracing initiated at 18 months improved alignment, highlighting the importance of early intervention. Earlier research suggests that proprioceptive illusions can be induced by longitudinal skin stretch, potentially generating sensory inputs from the skin and deep tissues [32]. Given that PIEZO2 channels may not play an active role in some specialized sensory structures, other stretch-sensitive ion channels in tactile afferents innervating these structures may contribute to detecting skin stretch and joint movement [33]. Physiotherapy and interventions aimed at enhancing proprioception may improve motor function and prevent complications if initiated early; however, further prospective collaborative studies are needed.

Our findings suggest that respiratory and feeding difficulties are major causes of morbidity in the neonatal period and early infancy in

DAIPT. The respiratory system, a highly sensitive sensory organ, depends on mechanoreceptors and chemoreceptors for proper ventilation. PIEZO2 plays a crucial role in lung volume regulation [34], as evidenced by PIEZO2-deficient mice that die from respiratory distress shortly after birth [9]. However, respiratory issues in DAIPT are likely multifactorial, with contributions from altered diaphragm and muscle dynamics, as well as tissue hyperextensibility possibly linked to collagen and extracellular matrix abnormalities. PIEZO2 is also expressed in sensory neurons of the supraglottic, subglottic, and tracheal respiratory epithelium, as well as basal cells of the proximal esophagus [10]. Proprioceptive dysfunction in the larynx may contribute to stridor, dysphonia, and dysphagia [31,32]. Most patients in our cohort exhibited laryngeal stridor, with one requiring surgery for laryngomalacia, supporting PIEZO2's involvement in upper airway development. Upper airway disruptions have also been linked to obstructive sleep apnea [35–38], and one patient with DAIPT required bilevel positive airway pressure (BiPAP) therapy for moderate sleep apnea.

Differential diagnosis of DAIPT includes several progressive disorders with early mortality. SMARD1, caused by *IGHMBP2* variants, presents between 3 and 6 months with hypotonia, distal weakness, and diaphragmatic paralysis, often requiring mechanical ventilation and leading to early death [35,36]. Unlike DAIPT, nerve conduction studies in SMARD1 typically reveal motor neuropathy, often accompanied by sensory neuropathy [39–41]. In DAIPT, neonatal respiratory distress may require temporary mechanical ventilation, but symptoms generally improve with age, and hypotonia and motor function gradually recover. Other neonatal-onset disorders with contractures include X-linked *UBA1* mutations (Kennedy syndrome) [42] and *GLE1* variants [43]. *TRPV4*-related disorders lead to a range of skeletal and neuromuscular conditions, including congenital distal spinal muscular atrophy (CDSMA) with DA and spinal muscular atrophy with scapuloperoneal and laryngeal weakness [41,42]. The most severe form, CDSMA with DA, presents with congenital distal contractures, mainly in the lower limbs, but unlike DAIPT, it involves pure motor neuron dysfunction without sensory involvement. Given DAIPT's nonspecific early presentations and the large size of the *PIEZO2* gene, whole-exome sequencing (WES) remains the most effective diagnostic tool. However, careful clinical evaluation is crucial to first rule out common causes of neonatal hypotonia (e.g., SMA, Prader-Willi syndrome, chromosomal anomalies, myotonic dystrophy type 1) before proceeding with WES. Electrophysiological findings may also be helpful.

A previous study showed that heterozygous variants associated with *PIEZO2*-related disorders cause a congenital channelopathy that disrupts inactivation, leading to prolonged channel opening and excessive mechanotransduction [20]. Coste et al. [20] investigated the functional effects of two heterozygous *PIEZO2* pathogenic variants, p.Glu2727del and Ile802Phe, identified in individuals with DA5. The study demonstrated that these heterozygous variants lead to mechanically activated currents with slower inactivation and faster recovery in the case of Glu2727del, and faster recovery alone in Ile802Phe, supporting a GoF mechanism. The authors further proposed that hyperactive PIEZO2 signaling during development underlies the observed phenotype, including restricted ocular movements, limited joint extension, and reduced thoracic expansion. Another study reporting on bioinformatic analyses of the previously identified heterozygous variants in patients with *PIEZO2*-related disorders suggested that these alterations may disrupt the secondary structure, solvent accessibility, or transmembrane positioning of the PIEZO2 protein, depending on the specific variant [26]. Such structural disruptions may contribute to GoF effects.

In our cohort, the Glu2727del variant, the GoF effects of which were previously studied by Coste et al. [20], was detected in two unrelated patients. Two additional patients from the same family carried a heterozygous missense variant, p.Arg2686His, and another patient had heterozygous p.Tyr2737Ilefs*7 variant. The p.Tyr2737Ilefs*7 variant in Patient 2 lies in exon 52, the final exon of the canonical transcript, and results from a single base pair deletion. While frameshift mutations typically indicate loss-of-function, exceptions may occur when transcripts escape nonsense-mediated decay (NMD), allowing truncated proteins to exert dominant, often GoF effects. Such mechanisms have been reported in genes like *ROR2* [OMIM #602,337], where C-terminal truncations cause brachydactyly type B1 by mislocalizing or constitutively activating the receptor, leading to dysregulated signaling and amputation-like phenotypes in the fingers [44]. Additionally, mouse studies have shown that even "knockout" frameshift alleles can leak through NMD and produce truncated proteins with unexpected GoF activity [45]. Based on these considerations, we hypothesize that this variant introduces a premature stop codon within the final exon, escapes NMD, and likely produces a C-terminally truncated protein with an altered reading-frame terminus. Clinically, this 22-year-old male displays features that closely overlap with those observed in patients carrying previously functionally validated GoF *PIEZO2* variants (e.g., p.Glu2727del), including short stature, mild restrictive pulmonary function, and slowly progressive scoliosis. These findings are consistent with the phenotype of *PIEZO2* GoF-related DA5. However, we acknowledge that this interpretation remains hypothetical in the absence of functional validation.

These variants present with a DA phenotype, often without significant motor delay but with potential multisystem involvement. It is hypothesized that overactive PIEZO2 causes pleiotropic effects on musculoskeletal system including ocular mucles, bones, and lung functions [46]. Patients with heterozygous variants in our study exhibited distinct facial and musculoskeletal features, suggesting a syndromic component of the heterozygous *PIEZO2* disorder spectrum. Animal studies suggest PIEZO2 activation during embryonic and early postnatal stages affects joint angles, whereas later activation has no impact, highlighting the importance of developmental timing [46].

Patients with *PIEZO2*-related DA5 can develop restrictive lung disease and pulmonary hypertension due to chronic hypoxia [47]. While the exact pathophysiology of restrictive lung disease remains unclear, increased channel activity may contribute to reduced joint extension and restricted lung and thoracic expansion. Although PIEZO2 expression in cardiac tissue is limited, heterozygous *PIEZO2* mutations may affect mechanosensitive ion channels involved in cardiac structure or electrical development, potentially contributing to accessory pathways.

Ophthalmologic findings were prominent in both *PIEZO2*-related DA5 and GS. All three patients with *PIEZO2*-related DA5 in our cohort had mild ptosis and restricted upward gaze due to fibrosis and contracture (rather than a neurological cause) [48]. One patient with *PIEZO2*-related DA5 had borderline high intraocular pressure, advanced optic nerve cupping, and retinal nerve fiber thinning. The other patient with *PIEZO2*-related DA5 required treatment for keratoconus. Both patients with GS exhibited mild ptosis and narrow eyelids and developed glaucoma. The father (Patient 5) also had corneal ectasia and cataracts, eventually requiring multiple ophthalmologic interventions. Although previous reports have described keratoconus [13], corneal thickening [49], isolated optic disc excavation [50], and mildly increased intraocular pressure in patients with *PIEZO2*-related DA5 [51], our study for the first time describes corneal ectasia and glaucoma development in GS. These findings highlight the crucial role of PIEZO2 in mechanosensation, particularly in corneal integrity and aqueous humor dynamics, where abnormal collagen arrangement in the corneal stroma may contribute to ophthalmological involvement. Dysregulated PIEZO2 function may increase the risk of vision impairment, including glaucoma, emphasizing the need for regular ophthalmologic screening in patients with heterozygous variants exhibiting clinical features associated with *PIEZO2*-related disorders.

Heterozygous *PIEZO2* variants contribute to a spectrum of overlapping syndromes with shared features and unique complications, reflecting variable expressivity rather than distinct entities. Traditionally these conditions are named based on their clinical characteristics, including ptosis and restricted eye movements in *PIEZO2*-related DA5, cleft palate in GS, and psychomotor retardation with central nervous

system involvement in MWS [21,48,52,53]. A father and daughter in our cohort were initially diagnosed with MWS [23], but reclassified as GS after genetic testing revealed the c.8057G>*A* variant and medical history reported cleft palate without cognitive impairment. McMillan et al. demonstrated a strong association between the c.8057G>*A* variant and cleft palate in GS [21]. Several other case examples support the presence of overlapping between these syndromes. For example, two patients with GS in the McMillan study were found to have ophthalmoplegia. Another previously reported case with the c.8057G>*A* variant presented with cleft palate and Dandy-Walker malformation [54].

In conclusion, this study improves our understanding of *PIEZO2*-related disorders, showing their wide range of symptoms and the need for personalized treatment. Early recognition of disease, genetic and phenotypic assessments, regular monitoring for complications, and timely intervention are critical for optimizing management, emphasizing the importance of a multidisciplinary approach. By deepening our knowledge of PIEZO2 function and associated clinical presentations, further research may pave the way for novel therapeutic strategies that can improve the lives of those affected with *PIEZO2*-related disorders.

Declaration of conflict of interest

We hereby confirm that none of the authors have any conflicts of interest.

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Authorship contribution statement

GA designed the study, performed data analysis, created tables and figures and wrote the manuscript. HT critically edited the manuscript. All other authors researched data and completed neurological, genetic, electrophysiological, and radiological assessments in their cases. GA and HT are the guarantors of this work and have full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors confirm that they have full access to all the data in the study and accept responsibility to submit for publication.

CRediT authorship contribution statement

Gulcin Akinci: Writing – original draft, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Berk Ozyilmaz:** Software, Investigation, Data curation. **Gulten Ozturk:** Investigation. **Mustafa Komur:** Investigation. **Ece Onel:** Investigation. **Didem Ardicli:** Investigation. **Hamide Betul Gerik-Celebi:** Investigation. **Aysima Ozcelik:** Investigation. **Sanem Yilmaz:** Investigation. **Ipek Dokurel Cetin:** Investigation. **Cagatay Gunay:** Investigation. **Gokcen Oz Tuncer:** Investigation. **Hilal Aydin:** Investigation. **Ayfer Sakarya Gunes:** Investigation. **Ozlem Yayici Koken:** Investigation. **Ipek Polat:** Investigation. **Aydan Degerliyurt:** Investigation. **Tamer Celik:** Investigation. **Yusuf Kenan Cetinoglu:** Investigation. **Omer Karti:** Investigation. **Sonay Sahan:** Investigation. **Burcu Karakayali:** Investigation. **Esra Isik:** Investigation. **Muhsin Elmas:** Investigation. **Bahtiyar Sahinoglu:** Investigation. **Hilmi Bolat:** Investigation. **Cem Karadeniz:** Investigation. **Ahmet Cevdet Ceylan:** Investigation. **Uluc Yis:** Investigation. **Dilsad Turkdogan:** Investigation. **Ayse Aksoy:** Investigation. **Sehime Gulsun Temel:** Investigation. **Haluk Topaloglu:** Investigation, Writing – review & editing.

Declaration of competing interest

The authors declare no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2025.105423.

Data availability

Some or all datasets generated during and/or analyzed during this study are not publicly available but are available from the corresponding author upon reasonable request.

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