## CASE REPORT

# Distal Arthrogryposis type 5 in an Italian family due to an autosomal dominant gain-of-function mutation of the *PIEZO2* gene

Gregorio Serra*  , Vincenzo Antona, Chiara Cannata, Mario Giuffrè, Ettore Piro, Ingrid Anne Mandy Schierz and Giovanni Corsello

**Abstract**

**Background:** Arthrogryposis multiplex congenita (AMC) is a group of clinically and etiologically heterogeneous conditions, characterized by prenatal onset contractures affecting two or more joints. Its incidence is about 1 in 3000 live births. AMC may be distinguished into amyoplasia, distal and syndromic arthrogryposis. Distal arthrogryposis (DA) predominantly affects hands and feet. It is currently divided into more than ten subtypes (DA1, DA2A/B, DA3–10), based on clinical manifestations, gene mutations and inheritance pattern. Among them, only a few patients with DA5 have been reported. It is associated to a gain-of-function pathogenic variant of the *PIEZO2* gene, encoding for an ion-channel necessary to convert mechanical stimulus to biological signals and crucial for the development of joints, neuromuscular and respiratory systems. Main clinical features include multiple distal contractures, short stature, ptosis, ophthalmoplegia and, in some cases, restrictive lung disease.

**Case presentation:** Hereby, we report on a four-generation Italian family with DA5. Our first proband was a newborn with prenatal suspicion of AMC. At birth, clinical findings were compatible with a DA diagnosis. Family history was positive for the mother with *short stature,* ophthalmoplegia, short neck, and contractures of the joints of distal extremities, and for three other relatives on the maternal side, including grandfather and great-grandmother, who all shared similar findings. Thus, we performed a next generation sequencing analysis (NGS) of the genes associated to AMC and of those involved in DA. The gain-of-function heterozygous mutation c.8181_8183delAGA (p.Glu2727del) of *PIEZO2* was identified in the proband, and the same mutation was also found in the mother, confirming the autosomal dominant inheritance of the condition.

**Conclusions:** Our patients contribute to the current DA5 genomic database, and to a better characterization of the disease. Clinicians may have suspicion of a DA diagnosis based on suggestive (also prenatal) clinical findings, which must be then confirmed by NGS analysis. Since natural history varies widely among different DA disorders, detection of the underlying causal variant is essential for the identification of the exact subtype, and to its adequate management, which must rely on a multidisciplinary and individualized approach.

**Keywords:** Arthrogryposis multiplex congenita, DA5, Ophthalmoplegia, *PIEZO2* gene, Gain-of-function mutation, NGS, Case report

## Background

Arthrogryposis Multiplex Congenita (AMC) is a group of clinically and etiologically heterogeneous conditions characterized by prenatal onset contractures affecting two or more joints. The incidence is estimated at about

*Correspondence: gregorio.serra@unipa.it

Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties "G. D'Alessandro", University of Palermo, Palermo, Italy

Serra *et al. Italian Journal of Pediatrics*        (2022) 48:133

Page 2 of 9

1 in 3000 live births, with female to male ratio 1:1 [1]. The pathogenic mechanism underlying arthrogryposis is the reduction of fetal movements, leading to an atypical increase of connective tissue around the joints (collagenosis) during development. This, in turn, further limits the joint movement and increases the contractures [2]. AMC has been described as a clinical feature in more than 400 specific disorders, and over 400 genes are currently associated to arthrogryposis [1, 2]. AMC may be classified into amyoplasia, distal (DA) and syndromic arthrogryposis [3]. DA predominantly affects hands and feet, and more than ten subtypes (DA1, DA2A and B, DA3–10) have been reported, based on clinical manifestations (including extra-articular findings), as well as gene pathogenic variants and inheritance pattern [1]. Distal arthrogryposis type 5 (DA5, MIM#108145) shows autosomal dominant inheritance, and its clinical features include multiple distal contractures, short stature, triangular face, ocular manifestations including deep-set eyes, ptosis and ophthalmoplegia, a textural peculiarity of the muscles to palpation described as "woody", and in some cases restrictive lung disease with pulmonary hypertension [2]. It is associated to a gain-of-function heterozygous variant of the *PIEZO2* (piezo type mechanosensitive ion channel type 2) gene, encoding for an ion-channel protein necessary to convert mechanical stimulus to biological signals and crucial for the development of joints, and neuromuscular and respiratory systems [4]. Only a few cases of DA5 have been described to date, although such condition is sometimes mistaken with the allelic phenotypes of *PIEZO2*, namely Gordon (GS) and Marden-Walker (MWS) syndromes, and/or with other

DAs subtypes [5]. Hereby, we report on an Italian family affected with DA5, in which target next generation sequencing (NGS) analysis revealed the pathogenic gain-of-function heterozygous variant c.8181_8183delAGA (p.Glu2727del) of the *PIEZO2* gene.

## Case presentation

A male newborn, first child of Italian nonconsanguineous parents, was born at $38 + 1$ weeks of gestation by caesarean section due to preeclampsia. Pregnancy was complicated by hypertension treated with methyldopa. Second trimester prenatal ultrasound (US) revealed oligohydramnios, flexed wrists, and bilateral clubfeet, raising the diagnostic suspicion of AMC. Apgar scores were 8, 8 and 9 at 1, 5 and 10 minutes respectively. At birth, anthropometric measurements were as follows: weight 2460 g (5th centile, − 1.65 standard deviation, SD), length 47 cm (12th centile, − 1.17 SD) and occipitofrontal circumference (OFC) 36 cm (95th centile, + 1.65 SD). Soon after birth, he was transferred to the neonatal intensive care unit due to mild respiratory distress, that required non-invasive ventilatory support by continuous positive airway pressure. At admission, physical examination showed high forehead, low anterior hairline, deep-set eyes, wide and depressed nasal bridge, bulbous nose, anteverted nares, long and thick philtrum, increased nasogenian folds and half-opened mouth with "whistling" appearance. The right posteriorly rotated ear with bilateral thick helix, and microretrognathia completed his craniofacial profile (Fig. 1a, b). *Pectus excavatum*, and increased tone ("woody") of the muscles of the abdominal wall were also observed. Anomalies of the extremities



**Fig. 1** **a** Patient's front view. High forehead, low anterior hairline, deep-set eyes, wide and depressed nasal bridge, bulbous nose, anteverted nares, long and thick philtrum, increased nasogenian folds and half-opened mouth with "whistling" appearance. **b**. Lateral view. Right posteriorly rotated ear with thick helix, and microretrognathia

Serra *et al. Italian Journal of Pediatrics*        (2022) 48:133

Page 3 of 9

included ulnar deviation of the hands, bilateral arachnodactyly, proximal set and short first and fifth fingers, with clinodactyly of the latters, in addition to talipes *equinus-varus-adductus-supinatus*, with overlapping toes, short and proximal set of the first (also straight and broad) and fifth toes (Fig. 2a, b). Neurological findings were a mild generalized hypotonia, poor reactivity, crying and suction, as well as decreased osteotendinous and archaic reflexes. Most of these phenotypic features were observed in the mother, who had short stature (height 150 cm), ophthalmoplegia, short neck, along with contractures of the joints of distal extremities. Furthermore, family history disclosed three further relatives (grandfather, aunt, and great-grandmother), on the maternal side, sharing overlapping clinical features.

The clinical course was characterized by the need of non-invasive ventilatory support during the first week of life. Due to lack of sucking/swallowing coordination, nasogastric tube feeding was initially required. Laboratory analyses including complete blood count, serum electrolytes, liver, kidney, and thyroid function tests showed normal results. Ophthalmologic examination revealed a bilateral decreased accommodation reflex, secondary to ophthalmoplegia. Except for mild enlargement of the left ventricle, major structural brain anomalies were ruled out on head US. Moreover, abdominal US documented no abnormalities, and the echocardiographic evaluation, revealed an isolated patent *foramen ovale*. Conversely, skeletal X-Ray confirmed the clinically observed abnormalities of the extremities, consisting of ulnar deviation of the hands, talipes *equinus-varus-adductus-supinatus*, in addition to proximal set and short first and fifth fingers and toes. No bone anomalies were identified in the proximal segments of the extremities, chest, spine and hips. Then, having considered the family history along with the clinical, laboratory and image findings, a targeted

next generation sequencing analysis (NGS) of the genes associated to AMC and of those involved in distal arthrogryposis and digital synostosis (Table 1) was performed. The gain-of-function heterozygous pathogenic variant c.8181_8183delAGA (p.Glu2727del) (Ref Seq NM_022068.3, based on genome build GRCh37/hg19) of the *PIEZO2* gene was identified in the proband, and the same mutation was also found in his mother. Genetic investigations of the other family members were not carried out due to restrictions related to the COVID-19 pandemic emergency occurring at the time of the hospital stay of our patient.

In the following months, the proband showed mild generalized hypotonia and developmental delay. However, he overcame his initial feeding difficulties, reaching adequate and exclusive bottle feeding with standard infant formula, at around 3 weeks of life. He was discharged from the Hospital at about 1 month of age, in good general condition but with poor weight gain and growth, and included in a multidisciplinary follow-up. Initial hearing screening, through transient evoked otoacoustic emissions (TEOAEs), showed abnormal results. To ascertain and characterize the hearing loss, an audiological assessment was started. It included brain auditory evoked response (BAER) evaluation at 3 months of age, which detected bilateral response threshold at 30 dB (decibel) HL (hearing level) according to mild hearing loss, that did not require any treatment. He underwent further ophthalmological assessments, which confirmed the previous findings compatible with ophthalmoplegia. He also performed hip US, which ruled out congenital dysplasia. Finally, an orthopedic evaluation was carried out, which counseled and prescribed the conservative Ponseti method for the management of bilateral clubfoot, consisting in manipulation, serial casting, and Achilles tendon tenotomy followed by foot abduction bracing. Indeed, he underwent reduction of the right foot
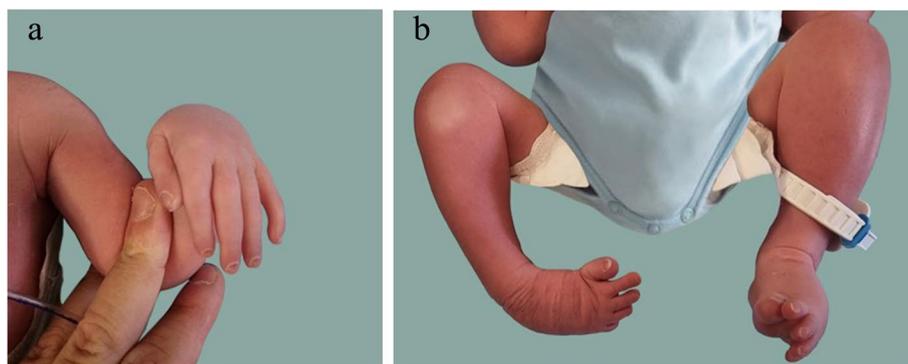


**Fig. 2** **a** Ulnar deviation of the hand, arachnodactyly, proximal set and short first, and fifth finger (showing also clinodactyly). **b** Talipes *equinus-varus-adductus-supinatus*, overlapping toes, with short, and proximal set of the first (also straight and broad) and fifth ones

Serra *et al. Italian Journal of Pediatrics*        (2022) 48:133

Page 4 of 9

**Table 1** Genes included and quality of target NGS analysis

| Name HGNC | Full name | OMIM | Coding sequence length (bases number) | >5x | Coverage% > 10x | >20x | Depth of medium | coverage (x) maximum |
|---|---|---|---|---|---|---|---|---|
| **Arthrogryposis multiplex congenita** | | | | | | | | |
| ADCY6 | Adenylate cyclase 6 | 600,294 | 3507 | 100.00 | 100.00 | 100.00 | 380.13 | 832 |
| ASCC1 | Activating signal cointegrator 1 complex subunit 1 | 614,215 | 1203 | 100.00 | 100.00 | 99.17 | 172.73 | 423 |
| CNTN1 | Contactin 1 | 600,016 | 3024 | 100.00 | 100.00 | 100.00 | 196.61 | 458 |
| CNTNAP1 | Contactin associated protein 1 | 602,346 | 4155 | 100.00 | 100.00 | 100.00 | 358.82 | 923 |
| DOK7 | Docking protein 7 | 610,285 | 1515 | 100.00 | 99.74 | 97.43 | 331.79 | 736 |
| ERGIC1 | Endoplasmic reticulum-golgi intermediate compartment 1 | 617,946 | 873 | 100.00 | 100.00 | 100.00 | 444.82 | 747 |
| FKBP10 | FKBP prolyl isomerase 10 | 607,063 | 1749 | 100.00 | 100.00 | 100.00 | 359.79 | 769 |
| GLE1 | GLE1 RNA export mediator | 603,371 | 2097 | 100.00 | 100.00 | 100.00 | 194.62 | 387 |
| KIF14 | Kinesin family member 14 | 611,279 | 4947 | 100.00 | 100.00 | 100.00 | 167.48 | 323 |
| LGI14 | Leucine rich repeat LGI family member 4 | 608,303 | 1614 | 100.00 | 100.00 | 100.00 | 222.95 | 429 |
| MUSK | Muscle associated receptor tyrosine kinase | 601,296 | 2610 | 100.00 | 100.00 | 100.00 | 222.38 | 508 |
| MYBPC1 | Myosin binding protein C, slow type | 160,794 | 3522 | 100.00 | 100.00 | 100.00 | 183.71 | 581 |
| MYOD1 | Myogenic differentiation 1 | 159,970 | 963 | 100.00 | 100.00 | 100.00 | 623.24 | 1438 |
| NUP88 | Nucleoporin 88 | 602,552 | 2226 | 100.00 | 100.00 | 100.00 | 206.06 | 482 |
| PIEZO2 | Piezo type mechanosensitive ion channel component 2 | 613,629 | 8259 | 100.00 | 100.00 | 99.94 | 191.65 | 677 |
| RAPSN | Receptor associated protein of the synapse | 601,592 | 1239 | 100.00 | 100.00 | 100.00 | 419.22 | 935 |
| SCARF2 | Scavenger receptor class F member 2 | 613,619 | 2598 | 100.00 | 100.00 | 100.00 | 209.97 | 618 |
| SYNE1 | Spectrin repeat containing nuclear envelope protein 1 | 608,441 | 26,394 | 100.00 | 100.00 | 100.00 | 193.42 | 680 |
| TRIP4 | Thyroid hormone receptor interactor 4 | 604,501 | 1746 | 100.00 | 100.00 | 100.00 | 140.63 | 238 |
| UBA1 | Ubiquitin like modifier activating enzyme 1 | 314,370 | 3177 | 100.00 | 100.00 | 100.00 | 215.59 | 532 |
| VIPAS39 | VPS33B late endosome and lysosome associated | 608,552 | 1854 | 100.00 | 100.00 | 100.00 | 218.34 | 597 |
| ZC4H2 | Zinc finger C4H2-type containing | 300,897 | 675 | 100.00 | 100.00 | 100.00 | 103.71 | 158 |
| **Distal arthrogryposis** | | | | | | | | |
| CHST14 | Carbohydrate sulfotransferase 14 | 608,429 | 1131 | 100.00 | 100.00 | 100.00 | 260.38 | 467 |
| DSE | Dermatan sulfate epimerase | 605,942 | 2877 | 100.00 | 100.00 | 100.00 | 206.13 | 547 |

Serra *et al. Italian Journal of Pediatrics*    (2022) 48:133

Page 5 of 9

**Table 1**  (continued)

| Name HGNC | Full name | OMIM | Coding sequence length (bases number) | >5x | Coverage% > 10x | >20x | Depth of medium | coverage (x) maximum |
|---|---|---|---|---|---|---|---|---|
| ECEL1 | Endothelin converting enzyme like 1 | 605,896 | 2328 | 100.00 | 100.00 | 98.80 | 248.47 | 929 |
| FBN2 | Fibrillin 2 | 612,570 | 8739 | 100.00 | 100.00 | 100.00 | 225.84 | 600 |
| MYBPC1 | Myosin binding protein C, slow type | 160,794 | 3522 | 100.00 | 100.00 | 100.00 | 183.71 | 581 |
| MYH3 | Myosin heavy chain 3 | 160,720 | 5823 | 100.00 | 100.00 | 100.00 | 211.55 | 551 |
| MYH8 | Myosin heavy chain 8 | 160,741 | 5814 | 100.00 | 100.00 | 99.47 | 191.77 | 746 |
| NALCN | Sodium leak channel, non-selective | 611,549 | 5217 | 100.00 | 100.00 | 100.00 | 177.57 | 395 |
| PIEZO2 | Piezo type mechanosensitive ion channel component 2 | 613,629 | 8259 | 100.00 | 100.00 | 99.94 | 191.65 | 677 |
| SLC35A3 | Solute carrier family 35 member A3 | 605,632 | 1104 | 100.00 | 100.00 | 100.00 | 156.35 | 264 |
| TNNI2 | Troponin I2, fast skeletal type | 191,043 | 549 | 100.00 | 100.00 | 100.00 | 355.52 | 890 |
| TNNT1 | Troponin T1, slow skeletal type | 191,041 | 837 | 100.00 | 100.00 | 100.00 | 196.36 | 370 |
| **Other genes** | | | | | | | | |
| ACTA1 | Actin alpha 1, skeletal muscle | 102,610 | 1134 | 100.00 | 100.00 | 100.00 | 250.29 | 714 |
| AGRN | Agrin | 103,320 | 6138 | 100.00 | 100.00 | 99.54 | 351.00 | 897 |
| BIN1 | Bridging integrator 1 | 601,248 | 1782 | 100.00 | 100.00 | 100.00 | 283.67 | 580 |
| CASK | Calcium/calmodulin dependent serine protein kinase | 300,172 | 2766 | 100.00 | 100.00 | 100.00 | 110.05 | 307 |
| CFL2 | Cofilin 2 | 601,443 | 501 | 100.00 | 100.00 | 100.00 | 142.68 | 262 |
| CHAT | Choline O-acetyltransferase | 118,490 | 2247 | 100.00 | 100.00 | 98.00 | 234.82 | 481 |
| CHRNA1 | Cholinergic receptor nicotinic alpha 1 subunit | 100,690 | 1374 | 100.00 | 100.00 | 100.00 | 219.81 | 422 |
| CHRNB1 | Cholinergic receptor nicotinic beta 1 subunit | 100,710 | 1506 | 100.00 | 100.00 | 100.00 | 257.88 | 591 |
| CHRND | Cholinergic receptor nicotinic delta subunit | 100,720 | 1554 | 100.00 | 100.00 | 100.00 | 326.22 | 666 |
| CHRNE | Cholinergic receptor nicotinic epsilon subunit | 100,725 | 1482 | 100.00 | 100.00 | 100.00 | 311.97 | 705 |
| CHRNG | Cholinergic receptor nicotinic gamma subunit | 100,730 | 1554 | 100.00 | 100.00 | 100.00 | 309.39 | 644 |
| COL6A2 | Collagen type VI alpha 2 chain | 120,240 | 3060 | 100.00 | 100.00 | 100.00 | 380.62 | 701 |
| COLQ | Collagen like tail subunit of asymmetric acetylcholinesterase | 603,033 | 1368 | 100.00 | 100.00 | 100.00 | 193.63 | 454 |
| DHCR24 | 24-dehydrocholesterol reductase | 606,418 | 1551 | 100.00 | 100.00 | 100.00 | 305.51 | 710 |

Serra *et al. Italian Journal of Pediatrics*     (2022) 48:133

Page 6 of 9

**Table 1**  (continued)

| Name HGNC | Full name | OMIM | Coding sequence length (bases number) | >5x | Coverage% > 10x | >20x | Depth of medium | coverage (x) maximum |
|---|---|---|---|---|---|---|---|---|
| DPAGT1 | Dolichyl-phosphate N-acetylglucosaminephosphotransferase 1 | 191,350 | 1227 | 100.00 | 100.00 | 100.00 | 209.58 | 349 |
| EGR2 | Early growth response 2 | 129,010 | 1431 | 100.00 | 100.00 | 100.00 | 313.71 | 523 |
| ERCC5 | ERCC excision repair 5, endonuclease | 133,530 | 3561 | 100.00 | 100.00 | 100.00 | 171.74 | 386 |
| ERCC6 | ERCC excision repair 6, chromatin remodeling factor | 609,413 | 4482 | 100.00 | 100.00 | 100.00 | 229.78 | 501 |
| EXOSC3 | Exosome component 3 | 606,489 | 828 | 100.00 | 100.00 | 99.88 | 292.51 | 690 |
| FHL1 | Four and a half LIM domains 1 | 300,163 | 972 | 100.00 | 100.00 | 98.66 | 96.30 | 207 |
| FKTN | Fukutin | 607,440 | 1386 | 100.00 | 100.00 | 100.00 | 198.58 | 376 |
| GBA | Glucosylceramidase beta | 606,463 | 1611 | 100.00 | 100.00 | 100.00 | 602.97 | 1174 |
| GBE1 | 1,4-alpha-glucan branching enzyme 1 | 607,839 | 2109 | 100.00 | 100.00 | 100.00 | 204.50 | 501 |
| GFPT1 | Glutamine-fructose-6-phosphate transaminase 1 | 138,292 | 2100 | 100.00 | 100.00 | 100.00 | 162.87 | 429 |
| GLDN | Gliomedin | 608,603 | 1656 | 100.00 | 100.00 | 100.00 | 157.95 | 407 |
| KAT6B | Lysine acetyltransferase 6B | 605,880 | 6222 | 100.00 | 100.00 | 100.00 | 276.88 | 1144 |
| KLHL40 | Kelch like family member 40 | 615,340 | 1866 | 100.00 | 100.00 | 100.00 | 307.58 | 611 |
| MPZ | Myelin protein zero | 159,440 | 747 | 100.00 | 100.00 | 100.00 | 293.78 | 823 |
| MTM1 | Myotubularin 1 | 300,415 | 1812 | 100.00 | 100.00 | 100.00 | 111.02 | 238 |
| MYH2 | Myosin heavy chain 2 | 160,740 | 5826 | 100.00 | 100.00 | 100.00 | 200.07 | 480 |
| NEB | Nebulin | 161,650 | 19,974 | 100.00 | 100.00 | 100.00 | 193.18 | 564 |
| PLOD2 | Procollagen-lysine,2-oxoglutarate 5-dioxygenase 2 | 601,865 | 2277 | 100.00 | 100.00 | 100.00 | 166.51 | 435 |
| PMM2 | Phosphomannomutase 2 | 601,785 | 741 | 100.00 | 100.00 | 100.00 | 202.86 | 369 |
| RARS2 | Arginyl-tRNA synthetase 2, mitochondrial | 611,524 | 1737 | 100.00 | 100.00 | 100.00 | 164.02 | 377 |
| SCO2 | SCO cytochrome c oxidase assembly protein 2 | 604,272 | 801 | 100.00 | 100.00 | 100.00 | 325.72 | 627 |
| TGFB3 | Transforming growth factor beta 3 | 190,230 | 1239 | 100.00 | 100.00 | 100.00 | 280.94 | 449 |
| TK2 | Thymidine kinase 2 | 188,250 | 798 | 100.00 | 100.00 | 99.25 | 212.26 | 474 |
| TNNT3 | Troponin T3, fast skeletal type | 600,692 | 771 | 100.00 | 100.00 | 100.00 | 286.03 | 564 |
| TPM3 | Tropomyosin 3 | 191,030 | 858 | 100.00 | 100.00 | 100.00 | 181.98 | 368 |
| TRPV4 | Transient receptor potential cation channel subfamily V member 4 | 605,427 | 2616 | 100.00 | 100.00 | 100.00 | 308.90 | 554 |

Serra *et al. Italian Journal of Pediatrics*     (2022) 48:133

Page 7 of 9

**Table 1** (continued)

| Name HGNC | Full name | OMIM | Coding sequence length (bases number) | >5x | Coverage% > 10x | >20x | Depth of medium | coverage (x) maximum |
|---|---|---|---|---|---|---|---|---|
| TSEN2 | tRNA splicing endonuclease subunit 2 | 608,753 | 1398 | 100.00 | 100.00 | 100.00 | 223.97 | 579 |
| TSEN54 | tRNA splicing endonuclease subunit 54 | 608,755 | 1581 | 100.00 | 99.11 | 97.28 | 273.41 | 462 |
| VRK1 | VRK serine/threonine kinase 1 | 602,168 | 1191 | 100.00 | 100.00 | 100.00 | 177.52 | 298 |
| ZBTB42 | Zinc finger and BTB domain containing 42 | 613,915 | 1269 | 100.00 | 100.00 | 100.00 | 372.32 | 655 |
| **Digital synostosis** | | | | | | | | |
| BHLHA9 | Basic helix-loop-helix family member a9 | 615,416 | 708 | 100.00 | 89.27 | 81.50 | 135.39 | 384 |
| BMPR1B | Bone morphogenetic protein receptor type 1B | 603,248 | 1599 | 100.00 | 100.00 | 100.00 | 210.72 | 332 |
| CHSY1 | Chondroitin sulfate synthase 1 | 608,183 | 2409 | 100.00 | 99.63 | 98.13 | 215.28 | 398 |
| FGF9 | Fibroblast growth factor 9 | 600,921 | 627 | 100.00 | 100.00 | 100.00 | 187.26 | 287 |
| GDF5 | Growth differentiation factor 5 | 601,146 | 1506 | 100.00 | 100.00 | 100.00 | 364.68 | 699 |
| GDF6 | Growth differentiation factor 6 | 601,147 | 1368 | 100.00 | 100.00 | 100.00 | 262.93 | 704 |
| IHH | Indian hedgehog signaling molecule | 600,726 | 1236 | 100.00 | 100.00 | 100.00 | 303.92 | 420 |
| NOG | Noggin | 602,991 | 699 | 100.00 | 100.00 | 100.00 | 416.59 | 809 |
| PCNT | Pericentrin | 605,925 | 10,011 | 100.00 | 100.00 | 99.91 | 207.88 | 569 |
| PTDSS1 | Phosphatidylserine synthase 1 | 612,792 | 1422 | 100.00 | 100.00 | 100.00 | 197.51 | 399vements restriction |

deformity with plaster casting, and a percutaneous Achilles tenotomy is at present planned.

The proband is now 4 months and 6 days old, and shows a poor growth: weight Kg 5.020 (<3rd centile, − 3 SD), length 58 cm (<3rd centile, − 3.01 SD), and head circumference 40.5 cm (14th centile, − 1.09 SD) (according to World Health Organization growth standards for neonatal and infant close monitoring) [6]. The child is presently placed in a rehabilitation program, including physiokynesiotherapy as well as occupational and manipulation treatment of the upper limbs, to improve the hands contractures. He has increased axial, upper and lower limbs and abdominal muscles' tone, and delayed motor development. Clinical examination and multiorgan US evaluations showed no further anomalies.

## Discussion and conclusions

DA was first classified by Hall, Reed, and Greene, as a heterogeneous group of disorders with congenital joint contractures, predominantly affecting hands and feet. Although originally described as autosomal dominant (AD) trait, it is well known that DA may also show autosomal recessive (AR) pattern of transmission [1, 2].

DA is presently classified into more than ten subtypes (DA1, DA2A and B, and DA3–10), depending on the pattern of contractures combined with extraarticular features [7]. Distal arthrogryposis type 5 (DA5), originally classified as type 2B, is characterized by short stature, characteristic *facies* with ocular manifestations, and AD trait [8, 9]. Nevertheless, other features have been added to the phenotype, including ophthalmoplegia, pulmonary dysfunction, and a textural peculiarity of the muscles to palpation, described as "woody". Its genotype was first identified by Coste et al. [7], through NGS, in three patients with the aforementioned clinical features and a heterozygous variant of *PIEZO2*. Such gene encodes for a large transmembrane protein (named from the Greek term πιεση, meaning pressure), belonging to components of mechanically (MA) or stretch-activated ion channels, found in many cells and tissues/organs (somatosensory neurons, dorsal root ganglions, inner ear hair, muscle and endothelial cells, osteoblasts, cartilage, urinary bladder,

Serra *et al. Italian Journal of Pediatrics*     (2022) 48:133

Page 8 of 9

lungs, kidneys, and gastrointestinal tract) [4]. Its action allows the phenomenon of mechanic transduction, which is the translation of mechanical force into biochemical signals. Therefore, it plays crucial roles in different processes, including perception and proprioception, pain and hearing, and further potential ones are assumed for the development of the skeletal, neuromuscular and respiratory systems during embryogenesis [10]. Indeed, the identification of *PIEZO2* pathogenic variants in DA5, as in the present family, has provided further insights into the potential pathogenic mechanisms of the disease [11]. Specifically, its clinical picture may be related to gain-of-function pathogenic variants leading to hyperactive PIEZO2 signaling and increased channel activity, which may decrease joint extension, lung or thorax expansion, and ocular movement (muscular fibrosis leading to contractures may be the cause of ophthalmoparesis) [12, 13]. It is uncertain whether the respiratory complications are age dependent [14]. The current absence of chest and lung involvement in the mother of our newborn may not rule out its possible appearance over time.

To date, *PIEZO2* missense, and frameshift (as the one here described, rsID 587,777,077, Ensembl transcript ENST00000503781.7, and reported in literature by some Authors [5, 7, 10]) pathogenic variants, account for the vast majority of variants. They have highly pleomorphic effects and different pathophysiological consequences [15, 16]. The clinical manifestations of *PIEZO2*-associated diseases display a great variation, as well [10]. Indeed, gain-of-function mutations of *PIEZO2* have been also linked with DA3 (also known as Gordon Syndrome, GS, MIM#114300), Marden-Walker Syndrome (MWS, MIM#248700) and other related diseases [12, 17]. GS is commonly mistaken with DA5, but it may be distinguished by the presence of cleft palate and bifid uvula, whereas ophthalmological, muscle, and respiratory problems are primarily observed in DA5 [15]. Other less frequent signs and symptoms seen in DA5 patients are *pectus excavatum* (33%, observed also in our patient), *trismus* (26%), metacarpal and metatarsal synostosis (25%), toe syndactyly (18%), neck webbing (8%, found in the mother of our newborn), and sensorineural hearing loss (6%, and also present in the proband) [15]. Differential diagnosis of DA5 also includes Aase-Smith Syndrome (MIM#147800), and Marden-Walker Syndrome (characterized by joint contractures, cleft palate, blepharophimosis, "immobile" *facies*, diminished muscular bulk, developmental delay and hindbrain malformations) [15].

Hereby, we report on a four-generation family with clinical pictures compatible with DA5, in which two members (the newborn proband and his mother) were found to have the same gain-of-function heterozygous pathogenic variant of *PIEZO2*. The present study contributes to the current genomic databases, and to a better characterization of the disease. Moreover, it highlights the age-dependent phenotypic variability, which may also be observed among family members.

Clinicians may suspect DA based on suggestive (also prenatal) clinical findings, which must be then confirmed by NGS analysis [18–22]. Since natural history varies widely among different DA disorders, identification of the underlying causal variant is essential. The existing classification of DAs is a helpful tool for the differential diagnosis. Indeed, the prompt recognition of signs and symptoms of DA in our patient, in addition to NGS analysis, has led to early identification of the exact subtype (DA5), and then to proper management.

Comorbidities and/or potential complications related to growth, feeding, development and behavior, musculoskeletal system, ophthalmological abnormalities, respiratory difficulties, and hearing defects should be prevented and/or reduced according to a multidisciplinary and individualized approach [23–26]. Enrollment in physical and occupational therapy may improve the fine motor skills in these subjects. Periodic ophthalmological examinations are recommended to rule out keratoconus, refraction problems or abnormalities of the retina, which may require correction, while hearing screening is able to early detect sensorineural hearing loss (as in our proband). Moreover, pulmonary function testing and echocardiography should be performed for the early diagnosis of restrictive pulmonary disease [15].

Further understanding of the physiological implications of gain-of-function mutations of *PIEZO2* is required to find the most effective management and treatment for each patient, and ultimately to improve the quality of life among patients with DA5 and *PIEZO2*-related phenotypes.

**Abbreviations**
AMC: Arthrogryposis Multiplex Congenita; BAER: Brain Auditory Evoked Response; DA: Distal Arthrogryposis; GS: Gordon Syndrome; MA: Mechanically Activated; MWS: Marden-Walker Syndrome; NGS: Next Generation Sequencing; OFC: Occipitofrontal Circumference; *PIEZO2*: Piezo type mechanosensitive ion channel type 2; TEOAE: Transient-Evoked OtoAcoustic Emissions; US: UltraSonography.

**Authors' contributions**
GC conceptualized the report, revised the manuscript and gave final approval of the version to be submitted. GS drafted the final version of the manuscript and took care of the patient. VA contributed to the acquisition and interpretation of genetical data. CC collected clinical data, revised the literature, and drafted the first version of the paper. MG revised the manuscript. EP performed neurological and developmental assessment. IAMS contributed in drafting the manuscript and took care of the patient. All authors approved the final manuscript as submitted.

Serra *et al. Italian Journal of Pediatrics*    (2022) 48:133

Page 9 of 9

## Declarations

**Ethics approval and consent to participate**
Written informed consent was obtained from parents at admission of their newborn. The study was approved by the Mother and Child Department of the University of Palermo (Palermo, Italy). All procedures performed in this report were in accordance with the ethical standards of the institutional and national research committee, and with the 1964 Helsinki declaration and its later amendments, or comparable ethical standards.

**Consent for publication**
Written informed consent for publication was obtained.

**Competing interests**
The authors declare that they have no competing interests.

## References

1.  Whittle J, Johnson A, Dobbs MB, Gurnett CA. Models of distal arthrogryposis and lethal congenital contracture syndrome. Genes (Basel). 2021;12(6):943.
2.  Desai D, Stiene D, Song T, Sadayappan S. Distal arthrogryposis and lethal congenital contracture syndrome - an overview. Front Physiol. 2020;25(11):689.
3.  Hall JG. Arthrogryposis (multiple congenital contractures): diagnostic approach to etiology, classification, genetics, and general principles. Eur J Med Genet. 2014;57(8):464.
4.  Okubo M, Fujita A, Saito Y, Komaki H, Ishiyama A, Takeshita E, et al. A family of distal arthrogryposis type 5 due to a novel PIEZO2 mutation. Am J Med Genet A. 2015;167A(5):1100.
5.  McMillin MJ, Beck AE, Chong JX, Shively KM, Buckingham KJ, Gildersleeve HI, Aracena MI, Aylsworth AS, Bitoun P, Carey JC, Clericuzio CL, Crow YJ, Curry CJ, Devriendt K, Everman DB, Fryer A, Gibson K, Giovannucci Uzielli ML, Graham JM Jr, Hall JG, Hecht JT, Heidenreich RA, Hurst JA, Irani S, Krapels IP, Leroy JG, Mowat D, Plant GT, Robertson SP, Schorry EK, Scott RH, Seaver LH, Sherr E, Splitt M, Stewart H, Stumpel C, Temel SG, Weaver DD, Whiteford M, Williams MS, Tabor HK, Smith JD, Shendure J, Nickerson DA; University of Washington Center for Mendelian Genomics, Bamshad MJ. Mutations in PIEZO2 cause Gordon syndrome, Marden-Walker syndrome, and distal arthrogryposis type 5. Am J Hum Genet. 2014 May 1;94(5):734.
6.  World Health Organization. Child growth standards 2021. https://www.who.int/tools/child-growth-standards/standards.
7.  Coste B, Houge G, Murray MF, Stitziel N, Bandell M, Giovanni MA, et al. Gain-of-function mutations in the mechanically activated ion channel PIEZO2 cause a subtype of distal arthrogryposis. Proc Natl Acad Sci U S A. 2013;110(12):4667.
8.  Pallotta R, Ehresmann T, Fusilli P. Occurrence of Dandy-Walker anomaly in a familial case of distal arthogryposis type IIB. Am J Med Genet. 2000;95(5):477.
9.  Williams MS, Elliott CG, Bamshad MJ. Pulmonary disease is a component of distal arthrogryposis type 5. Am J Med Genet A. 2007;143A(7):752.
10. Ma Y, Zhao Y, Cai Z, Hao X. Mutations in PIEZO2 contribute to Gordon syndrome, Marden-Walker syndrome and distal arthrogryposis: a bioinformatics analysis of mechanisms. Exp Ther Med. 2019;17(5):3518.
11. Li S, You Y, Gao J, Mao B, Cao Y, Zhao X, et al. Novel mutations in TPM2 and PIEZO2 are responsible for distal arthrogryposis (DA) 2B and mild DA in two Chinese families. BMC Med Genet. 2018;19(1):179.
12. Seidahmed MZ, Maddirevula S, Miqdad AM, Al Faifi A, Al Samadi A, Alkuraya FS. Confirming the involvement of PIEZO2 in the etiology of Marden-Walker syndrome. Am J Med Genet A. 2021;185(3):945.
13. Yamaguchi T, Takano K, Inaba Y, Morikawa M, Motobayashi M, Kawamura R, et al. PIEZO2 deficiency is a recognizable arthrogryposis syndrome: a new case and literature review. Am J Med Genet A. 2019;179(6):948.
14. Fang XZ, Zhou T, Xu JQ, Wang YX, Sun MM, He YJ, et al. Structure, kinetic properties and biological function of mechanosensitive piezo channels. Cell Biosci. 2021;11(1):13.
15. Zapata-Aldana E, Al-Mobarak SB, Karp N, Campbell C. Distal arthrogryposis type 5 and PIEZO2 novel variant in a Canadian family. Am J Med Genet A. 2019;179(6):1034.
16. Delle Vedove A, Storbeck M, Heller R, Hölker I, Hebbar M, Shukla A, et al. Biallelic loss of proprioception-related PIEZO2 causes muscular atrophy with perinatal respiratory distress, arthrogryposis, and scoliosis. Am J Hum Genet. 2016;99(5):1206.
17. Alisch F, Weichert A, Kalache K, Paradiso V, Longardt AC, Dame C, et al. Familial Gordon syndrome associated with a PIEZO2 mutation. Am J Med Genet A. 2017;173(1):254.
18. Piro E, Nardello R, Gennaro E, Fontana A, Taglialatela M, Mangano GD, et al. A novel mutation in KCNQ3-related benign familial neonatal epilepsy: electroclinical features and neurodevelopmental outcome. Epileptic Disord. 2019;21(1):87.
19. Serra G, Antona V, D'Alessandro MM, Maggio MC, Verde V, Corsello G. Novel SCNN1A gene splicing-site mutation causing autosomal recessive pseudohypoaldosteronism type 1 (PHA1) in two Italian patients belonging to the same small town. Ital J Pediatr. 2021;47(1):138.
20. Schierz IAM, Serra G, Antona V, Persico I, Corsello G, Piro E. Infant developmental profile of Crisponi syndrome due to compound heterozygosity for CRLF1 deletion. Clin Dysmorphol. 2020;29(3):141.
21. Nardello R, Plicato G, Mangano GD, Gennaro E, Mangano S, Brighina F, et al. Two distinct phenotypes, hemiplegic migraine and episodic Ataxia type 2, caused by a novel common CACNA1A variant. BMC Neurol. 2020;20(1):155.
22. Serra G, Antona V, Giuffré M, Li Pomi F, Lo Scalzo L, Piro E, et al. Novel missense mutation of the *TP63* gene in a newborn with Hay-Wells/Ankyloblepharon-ectodermal defects-cleft lip/palate (AEC) syndrome: clinical report and follow-up. Ital J Pediatr. 2021;47:196.
23. Serra G, Memo L, Coscia A, Giuffrè M, Iuculano A, Lanna M, et al. Recommendations for neonatologists and pediatricians working in first level birthing centers on the first communication of genetic disease and malformation syndrome diagnosis: consensus issued by 6 Italian scientific societies and 4 parents' associations. Ital J Pediatr. 2021;47:94.
24. Griffet J, Dieterich K, Bourg V, Bourgeois E. Amyoplasia and distal arthrogryposis. Orthop Traumatol Surg Res. 2021;107(1S):102781.
25. Serra G, Corsello G, Antona V, D'Alessandro MM, Cassata N, Cimador M, et al. Autosomal recessive polycystic kidney disease: case report of a newborn with rare PKHD1 mutation, rapid renal enlargement and early fatal outcome. Ital J Pediatr. 2020;46(1):154.
26. Haliloglu G, Topaloglu H. Arthrogryposis and fetal hypomobility syndrome. Handb Clin Neurol. 2013;113:1311.

## Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.