

Gordon Syndrome (Distal Arthrogryposis Type 3): A Comprehensive Disease Characteristics Report

Disease: Gordon Syndrome (Distal Arthrogryposis type 3, DA3) **MONDO ID:** MONDO:0007252 · **OMIM:** #114300 · **Category:** Mendelian (monogenic, autosomal dominant) **Causal gene:** *PIEZO2* (HGNC:26270) · **Report date:** 2026-10-14 · Evidence base: 32 papers reviewed, 7 confirmed findings.

Summary

Gordon Syndrome (GS), also called distal arthrogryposis type 3 (DA3), is a rare autosomal-dominant congenital contracture disorder. Its defining clinical triad is **camptodactyly** (permanently flexed fingers), **talipes equinovarus** (clubfoot), and **cleft palate**, usually accompanied by short stature and frequently by ptosis and a distinctive facies. GS is distinguished from the broader distal arthrogryposis family chiefly by the presence of cleft palate and short stature. The disease is caused by **heterozygous gain-of-function (GoF) missense variants in *PIEZO2*** (18p11.22), the gene encoding the principal mechanically activated cation channel for proprioception and touch. A single recurrent variant, **c.8057G>A / p.Arg2686His**, accounts for the majority of molecularly confirmed families and is statistically associated with the cleft-palate phenotype that defines GS.

Mechanistically, GS is a **channelopathy of mechanotransduction**. The GoF variants, concentrated in the C-terminal pore/inactivation module of *PIEZO2*, alter channel inactivation kinetics so that the channel carries excess mechanically activated current. In proprioceptive sensory neurons that innervate muscle spindles and tendons, this excessive mechanotransduction during fetal/postnatal development produces **neurogenic joint contractures**. This causal chain is directly demonstrated in mice: expressing a GoF *Piezo2* allele selectively in proprioceptors is sufficient to reproduce distal-arthrogryposis-like contractures, and the deficits are mitigated by botulinum toxin and by a *PIEZO2*-modulating dietary fatty acid. GS sits at one end of a **continuous dominant *PIEZO2* clinical spectrum** that

also includes distal arthrogryposis type 5 (DA5) and Marden-Walker syndrome (MWS); the same variant can produce different points on this spectrum, reflecting marked allelic heterogeneity and variable expressivity.

This report synthesizes evidence from exome-sequencing cohorts, biophysical electrophysiology, mouse and *C. elegans* models, and clinical case series to populate all 15 requested knowledge-base sections. Information is derived from **aggregated disease-level resources** (OMIM, Orphanet, published cohorts) rather than EHR-level individual-patient data. Where evidence is absent or not applicable (e.g., infectious agents, somatic variants, cancer survival statistics), this is stated explicitly.

Key Findings

Finding 1 — *PIEZO2* is the causal gene; recurrent p.Arg2686His defines Gordon Syndrome

Exome sequencing of five GS-affected families identified *PIEZO2* mutations in every family, establishing *PIEZO2* as the causal gene for Gordon syndrome (PMID: 24726473). In the pooled DA3/DA5/MWS cohort, *PIEZO2* mutations were found in **10/12 (83%) GS families, 24/29 (82%) DA5 families, and 1/2 MWS families**. Nine GS families carried the **identical c.8057G>A (p.Arg2686His)** allele, and the presence of cleft palate — the trait that distinguishes GS from other distal arthrogryposes — was **significantly associated with c.8057G>A (Fisher's exact test, adjusted $p < 0.0001$)**. The study states: "*Exome sequencing of five GS-affected families identified mutations in piezo-type mechanosensitive ion channel component 2 (PIEZO2) in each family*" and "*The presence of cleft palate was significantly associated with c.8057G>A (Fisher's exact test, adjusted p value < 0.0001).*" This firmly links a specific recurrent allele to the GS phenotype.

Finding 2 — Disease variants are gain-of-function, acting through altered channel inactivation

Patch-clamp electrophysiology of *PIEZO2* disease mutants shows a **gain-of-function** biophysical signature. Both the E2727del and I802F mutations cause the *PIEZO2*-dependent mechanically activated currents to **recover faster from inactivation**, and E2727del additionally **slows inactivation** — net effect, more channel activity for a given mechanical

stimulus (PMID: 23487782): "both E2727del and I802F mutations cause the PIEZO2-dependent, mechanically activated currents to recover faster from inactivation, while E2727del also causes a slowing of inactivation." Critically, "overexpression of mutated PIEZO2 cDNAs does not cause constitutive activity or toxicity to cells, indicating that the observed phenotype is likely due to a mechanotransduction defect." This excludes a toxic/misfolding mechanism and pins the disease on **altered mechanotransduction gating** rather than cell death. A bioinformatics survey (PMID: 30988732) corroborates that dominant mutations cluster in the C-terminal region and that GoF variants increase PIEZO2 channel activity, while recessive loss-of-function variants cluster N-terminally.

Finding 3 — The contractures are neurogenic: excessive proprioceptor mechanotransduction

The causal link between channel GoF and joint contractures is established in vivo. Expressing a gain-of-function *Piezo2* mutation **specifically in proprioceptive sensory neurons** that innervate muscle spindles and tendons is **sufficient to induce DA5-like contractures in mice**, via increased peripheral nervous-system activity during postnatal development (PMID: 36634173): "expression of a gain-of-function PIEZO2 mutation in proprioceptive sensory neurons that mainly innervate muscle spindles and tendons is sufficient to induce DA5-like phenotypes in mice." Importantly, the same study shows the phenotype is treatable at the mechanistic level: "botulinum toxin (Botox) and a dietary fatty acid that modulates PIEZO2 activity reduce DA5-like deficits." This identifies the **proprioceptive sensory neuron (CL:0000100)** as the critical cell type and reframes the contractures as a sensory-neuron-driven (neurogenic), not primarily myopathic or skeletal, process.

Finding 4 — Clinical triad frequencies and reduced, sex-influenced penetrance

Clinical cohort data quantify the core phenotype. Gordon's syndrome presents with short stature, stiff spine, **camptodactyly (89%), cleft palate (27%), and club feet (73%)** (PMID: 11718203). The original large pedigree established "autosomal dominant inheritance with reduced penetrance and variable expressivity. Penetrance appears to be more reduced in females than in males, and cleft palate is the least frequently manifested trait" (PMID: 458832). These data underpin the frequency annotations and inheritance characteristics below.

Finding 5 — Allelic dichotomy: dominant GoF (C-terminal) vs. recessive LOF (N-terminal/central)

PIEZO2 shows a clean **genotype–mechanism dichotomy**. Heterozygous **gain-of-function missense** mutations, mainly at the C terminus, cause dominant DA3 (Gordon)/DA5/MWS: *"heterozygous gain-of-function missense mutations, mainly localized at the C terminus, cause dominant distal arthrogryposis 3 (DA3), distal arthrogryposis 5 (DA5), or Marden-Walker syndrome (MWKS)"* (PMID: 27843126). In contrast, **biallelic loss-of-function** (frameshift/deletion) variants in the N-terminal/central regions cause a distinct **recessive** syndrome — *"leading to nonsense-mediated transcript decay and consequently to lack of PIEZO2 protein"* — characterized by muscular atrophy, perinatal respiratory distress (spontaneously resolving), arthrogryposis, scoliosis, and mild distal sensory loss. This dichotomy is essential for variant interpretation: the mechanism (and thus inheritance and recurrence risk) depends on variant type and location.

Finding 6 — Model organisms recapitulate the mechanism

Animal models validate both the normal function and the disease mechanism. Conditional deletion of *Piezo2* in mouse proprioceptors abolishes rapidly adapting mechanically activated currents and produces balance/coordination deficits — *"Piezo2 fulfills a critical role in a defined homogeneous population of proprioceptor neurons... demonstrating that this ion channel is essential for mammalian proprioceptive mechanotransduction"* (PMID: 27184818). A GoF knock-in mouse reproduces contractures (PMID: 36634173). In *C. elegans*, CRISPR knock-in of the conserved GoF variant **pezo-1[R2405P]** (equivalent to human *PIEZO2* **R2718P**, which causes DA5) is electrophysiologically gain-of-function and causes reproductive and actin-organization defects — *"a conserved gain-of-function variant pezo-1[R2405P] that in human PIEZO2 causes distal arthrogryposis type 5 (DA5; p. R2718P)"* (PMID: 38349741); the phenotype is suppressible by the F-actin regulator *gex-3/NCKAP1*, implicating the cytoskeleton in *PIEZO2* gating.

Finding 7 — Gordon Syndrome lies on a continuous *PIEZO2* spectrum

GS is not a discrete entity but one pole of a continuum. A review of individuals sharing the recurrent p.Arg2686His variant and other alleles demonstrates *"marked phenotypic variability—from Gordon syndrome to distal arthrogryposis type 5—underscoring allelic heterogeneity and variable expressivity"* (PMID: 41572728). An independent cohort describing a classic MWS patient with a C-terminal truncating variant (c.8237G>A/p.W2746*) alongside a GS girl with the prevalent c.8057G>A/p.R2686H further corroborates a dominant *PIEZO2* continuum (PMID: 36588752).

Mechanistic Model / Causal Chain

Ordered mechanistic sequence (initiating lesion → clinical manifestation)

1. A **heterozygous gain-of-function missense variant in *PIEZO2*** (most often c.8057G>A / p.Arg2686His), located in the C-terminal pore/inactivation module, **arises de novo or is inherited** (autosomal dominant). *[demonstrated —*

P 24726473

2. The variant **alters channel inactivation kinetics** — slowing inactivation and/or speeding recovery from inactivation — which **leads to** increased mechanically activated cation (Na⁺/Ca²⁺) current for a given mechanical stimulus (GoF). *[demonstrated in vitro —*

P 23487782

3. Excess *PIEZO2* current **results in** heightened mechanotransduction specifically in **proprioceptive sensory neurons** innervating muscle spindles and tendons. *[demonstrated —*

P 36634173

4. Heightened proprioceptor activity during **fetal and postnatal development leads to** increased peripheral nervous-system drive to developing muscle/joint units. *[demonstrated in mouse —*

P 36634173

5. Abnormal sensory-motor drive and reduced fetal movement **result in neurogenic joint contractures** (camptodactyly, clubfoot) and short stature. *[inferred for human; demonstrated phenotype in mouse model]*

Branch A (GS-defining): The p.Arg2686His allele is **statistically associated with cleft palate** (adjusted $p < 0.0001$), the trait distinguishing GS/DA3 from DA5 — the mechanism of the palatal branch (likely diminished fetal orofacial movement/mechanical patterning) is **inferred**. *[association demonstrated —*

P 24726473

mechanism inferred]

Branch B: Other C-terminal alleles shift the phenotype toward **DA5** (ptosis, ophthalmoplegia, no cleft palate) or **Marden-Walker syndrome** (CNS involvement), producing the continuous spectrum. *[demonstrated]* —

P 27843126

P 41572728

1. Contractures and craniofacial/skeletal anomalies **manifest at birth** as the congenital, non-progressive GS phenotype; variable expressivity and reduced (female-biased) penetrance modulate which features appear. *[demonstrated]* —

P 458832

Contrast with the recessive branch

PIEZO2 variant

```

├─ C-terminal MISSENSE, heterozygous — GAIN of function — ↑ mechanotransduction
│   └─ DOMINANT: DA3 (Gordon) / DA5 / Marden-Walker (a continuous spectrum)
└─ N-terminal/central FRAMESHIFT/DELETION, biallelic — NMD → NO protein — LOSS of function
    └─ RECESSIVE: muscular atrophy, perinatal respiratory distress,
        arthrogryposis, scoliosis, distal sensory loss
  
```

Pathways, processes, and ontology anchors

- **Molecular pathway:** Mechanically activated cation channel signaling / mechanotransduction (not a classic Wnt/MAPK/mTOR pathway). Gating is lipid-modulated — **phosphatidic acid and LPA are endogenous negative regulators of PIEZO2** (PMID: 39147733) — and cytoskeleton/ECM-coupled (PMID: 35586339).
- **GO biological process:** detection of mechanical stimulus (GO:0050982), proprioception, ion transmembrane transport (GO:0034220), sensory perception of touch (GO:0050975).
- **GO molecular function:** mechanosensitive monoatomic cation channel activity (GO:0140135).
- **GO cellular component:** plasma membrane (GO:0005886); PIEZO2 is a trimeric propeller-shaped plasma-membrane channel.
- **Cell type (CL):** proprioceptive/sensory neuron (CL:0000100), muscle-spindle-associated sensory neuron.

- **Upstream vs downstream:** Upstream = *PIEZO2* GoF variant → altered gating; midstream = excess proprioceptor mechanotransduction; downstream = neurogenic contractures and secondary skeletal/craniofacial manifestations.

Section-by-Section Report

1. Disease Information

Gordon Syndrome is a rare autosomal-dominant **distal arthrogryposis** characterized by the triad of camptodactyly, clubfoot, and cleft palate, usually with short stature. It is distinguishable from other distal arthrogryposes primarily by cleft palate and short stature.

Resource	Identifier
MONDO	MONDO:0007252
OMIM	#114300
Orphanet	ORPHA:375 (Gordon syndrome / distal arthrogryposis type 3)
MeSH	Arthrogryposis (indexed via Distal Arthrogryposis / <i>PIEZO2</i>)
ICD-10	Q74.3 (Arthrogryposis multiplex congenita) — no GS-specific code
ICD-11	LD28.1 / arthrogryposis grouping (no GS-specific code)
Gene	<i>PIEZO2</i> (HGNC:26270), 18p11.22

Synonyms / alternative names: Distal arthrogryposis type 3 (DA3); Camptodactyly–cleft palate–clubfoot; Gordon's syndrome. **Data source type:** Aggregated disease-level resources and published case series/cohorts (OMIM, Orphanet, PubMed) — **not** individual EHR data.

2. Etiology

- **Primary cause — genetic:** Heterozygous gain-of-function missense variants in *PIEZO2* (PMID: 24726473). No environmental, infectious, or toxic cause is implicated.
- **Genetic risk factors:** The causal variant itself is the risk factor; recurrent **p.Arg2686His** is by far the most common. No separate susceptibility loci or validated human modifier genes

are known (the *C. elegans* suppressor *gex-3/NCKAP1* is an experimental modifier of a PIEZO2 GoF phenotype — [PMID: 38349741](#)).

- **Environmental risk factors:** None established. As a monogenic congenital disorder, environmental exposures are not causal. Advanced paternal age is a general (not GS-specific) consideration for de novo variants.
- **Protective factors:** None genetic known. Experimentally, **phosphatidic acid/LPA** negatively regulate PIEZO2 ([PMID: 39147733](#)) and a dietary fatty acid reduces the contracture phenotype in mice ([PMID: 36634173](#)) — candidate protective/therapeutic modulators, not established human protective factors.
- **Gene–environment interactions:** Not applicable / none established for this monogenic disorder.

3. Phenotypes

Phenotype	HPO term (suggested)	Type	Frequency	Onset / course
Camptodactyly	HP:0012385	Clinical sign / physical	~89%	Congenital, non-progressive
Talipes equinovarus (clubfoot)	HP:0001762	Physical malformation	~73%	Congenital, non-progressive
Cleft palate	HP:0000175	Physical malformation	~27% (GS-defining; assoc. R2686H)	Congenital
Short stature	HP:0004322	Physical	Common	Congenital/childhood
Ptosis	HP:0000508	Clinical sign	Frequent (esp. DA5 end)	Congenital
Scoliosis / stiff spine	HP:0002650	Physical	Reported	Childhood, may progress
Distinctive facies	HP:0001999	Physical	Variable	Congenital
Bifid uvula	HP:0000193	Physical	Reported (mild palatal end)	Congenital
Mild intellectual disability / psychomotor delay	HP:0001256 / HP:0001263	Behavioral/ cognitive	Occasional (spectrum)	Childhood

Frequencies from [PMID: 11718203](#); psychomotor delay/ID occasionally reported ([PMID: 27714920](#)). **Severity:** mild to moderate, variable. **Progression:** congenital and essentially non-progressive (contractures static, though scoliosis can progress). **Quality-of-life impact:** contractures affect fine motor function and ambulation; cleft palate affects feeding/speech; most distal-arthrogryposis patients achieve independent ambulation and self-care ([PMID: 33104047](#)). No GS-specific EQ-5D/SF-36 data available.

4. Genetic / Molecular Information

- **Causal gene:** *PIEZO2* (HGNC:26270; NCBI Gene 63895; UniProt Q9H5I5), chromosome 18p11.22; phenotype OMIM #114300.
- **Pathogenic variants:** Predominantly **missense**, concentrated in the **C-terminal pore/inactivation module**. Recurrent GS allele: **c.8057G>A, p.Arg2686His**. Other spectrum alleles include p.Arg2718Leu/Pro, p.Glu2727del, p.Thr2221Ile, p.Ser2690Arg, p.Met998Ile, and truncating C-terminal p.W2746. *Novel GS alleles continue to be reported (e.g., c.8576G>A/p.Trp2859 in a fetus — PMID: 37587573).*
- **Variant classification (ACMG/AMP):** Recurrent C-terminal missense variants are classified pathogenic/likely pathogenic; several newly described alleles are initially VUS pending segregation/functional data.
- **Allele frequency:** Pathogenic GS alleles are **absent or ultra-rare** in gnomAD (consistent with a severe dominant developmental disorder).
- **Somatic vs germline:** **Germline** (constitutional). De novo occurrence is common; germline mosaicism is possible but rarely documented (PMID: 37587573).
- **Functional consequence: Gain of function** — altered inactivation increasing mechanically activated current (PMID: 23487782). Contrast: biallelic N-terminal LOF → recessive disease (PMID: 27843126).
- **Modifier genes:** None validated in humans; *gex-3/NCKAP1* modifies *PIEZO2* GoF in *C. elegans* (PMID: 38349741).
- **Epigenetic information:** No disease-specific DNA-methylation/histone data available.
- **Chromosomal abnormalities:** Not a feature of classic GS; rare intragenic *PIEZO2* duplications cause a distinct recessive phenotype (PMID: 41531622).

5. Environmental Information

Not applicable. GS is a monogenic germline disorder. No environmental factors, lifestyle factors, or infectious agents are implicated in causation or triggering. (Note: congenital myopathy co-occurrence and **malignant hyperthermia** susceptibility have been reported in isolated GS cases, relevant to anesthetic exposure — PMID: 24878349.)

6. Mechanism / Pathophysiology

See the **Mechanistic Model / Causal Chain** section above for the ordered sequence. In brief: C-terminal *PIEZO2* GoF variant → altered channel inactivation → excess mechanically activated current → hyperactive proprioceptive sensory-neuron mechanotransduction during

development → reduced fetal movement and neurogenic joint contractures → congenital GS phenotype, with the R2686H allele branching toward cleft palate and other alleles branching toward DA5/MWS. Key molecular detail: PIEZO2 gating is lipid-modulated (phosphatidic acid/LPA are negative regulators; [PMID: 39147733](#)) and cytoskeleton/ECM-coupled ([PMID: 35586339](#)). No primary metabolic, immune, oxidative-stress, or fibrotic mechanisms are involved; the disorder is a developmental channelopathy. GO/CL anchors as listed above.

7. Anatomical Structures Affected

- **Organ/system — primary:** Musculoskeletal system (hands/fingers, feet/ankles, spine), craniofacial structures (palate), peripheral **nervous system** (proprioceptive afferents — the mechanistic primary site). UBERON: skeletal joint (UBERON:0000982), manual digit (UBERON:0002389), foot (UBERON:0002387), secondary palate (UBERON:0001716), peripheral nerve.
- **Secondary involvement:** Extraocular muscles (ptosis/ophthalmoplegia at DA5 end), respiratory system (restrictive pulmonary function at the severe end, [PMID: 36317804](#)), vertebral column (scoliosis).
- **Tissue/cell level:** Peripheral sensory neurons (proprioceptors innervating muscle spindles/tendons) are the critical cell population — **CL:0000100**; secondarily skeletal muscle and periarticular connective tissue.
- **Subcellular level:** Plasma membrane mechanosensitive channel (GO:0005886); gating coupled to cortical actin cytoskeleton.
- **Localization / lateralization:** Contractures are typically **bilateral and symmetric** (hands and feet).

8. Temporal Development

- **Onset: Congenital** — contractures detectable prenatally by ultrasound (as early as ~13 weeks gestation; [PMID: 27714920](#)) and present at birth.
- **Onset pattern:** Developmental/congenital (not acute).
- **Progression:** Contractures are **non-progressive/static**; scoliosis may progress through growth and requires monitoring. No oncologic-style "stages."
- **Disease course:** Chronic/lifelong structural phenotype; the underlying channel defect is constitutive.
- **Remission:** No spontaneous remission; orthopedic interventions improve function.

- **Critical period:** Fetal/early-postnatal development is the window during which excess mechanotransduction produces contractures — identifying a potential **window for intervention** (cf. Botox/fatty-acid rescue in neonatal mice, [PMID: 36634173](#)).

9. Inheritance and Population

- **Epidemiology:** Very rare; precise prevalence/incidence not established. Orphanet classes GS/DA3 as <1/1,000,000. No reliable incidence figures.
- **Inheritance: Autosomal dominant** ([PMID: 458832](#)); frequent de novo occurrence.
- **Penetrance: Reduced/incomplete, and more reduced in females than males** ([PMID: 458832](#)).
- **Expressivity: Variable**, including intrafamilial variability and overlap across GS/DA5/MWS with identical alleles ([PMID: 41572728](#)).
- **Genetic anticipation:** Not a feature (not a repeat-expansion disorder).
- **Germline mosaicism:** Rarely documented but possible ([PMID: 37587573](#)).
- **Founder effects / consanguinity:** Not applicable to the dominant form (consanguinity is relevant to the **recessive** biallelic-LOF PIEZO2 disorder, [PMID: 27843126](#)).
- **Carrier frequency:** Not applicable (dominant).
- **Population demographics:** No ethnic predilection reported; cases described worldwide (Europe, China, Brazil, Saudi Arabia, Canada). Sex ratio: females may be under-ascertained owing to reduced female penetrance. Age distribution: diagnosed prenatally/at birth/in childhood.

10. Diagnostics

- **Clinical diagnosis:** Based on the triad (camptodactyly + clubfoot + cleft palate) plus short stature; physical exam and dysmorphology.
- **Imaging:** Prenatal **fetal ultrasound** detects contractures/clubfoot/micrognathia and can establish a prenatal diagnosis when combined with genetic testing ([PMID: 37587573](#)); skeletal radiographs for contractures/scoliosis.
- **Genetic testing (confirmatory, recommended):**
- **Single-gene *PIEZO2* sequencing or distal arthrogryposis / arthrogryposis gene panels** (Sanger confirmation of recurrent c.8057G>A is efficient when the phenotype is classic).
- **Whole-exome sequencing (WES)** — the discovery and workhorse modality ([PMID: 24726473](#), [PMID: 37587573](#)).

- **Whole-genome sequencing (WGS)** — useful when panels/WES negative.
- **Chromosomal microarray** — not diagnostic for point-variant GS, but detects the rare duplication/CNV forms ([PMID: 41531622](#)).
- Karyotype/FISH/mtDNA/repeat-expansion testing: **not applicable**.
- **Laboratory tests / biomarkers:** No specific biochemical biomarker; diagnosis is clinical + molecular. (Creatine kinase and muscle biopsy occasionally relevant when congenital myopathy co-occurs — [PMID: 24878349](#).)
- **Omics-based diagnostics:** Not routinely used.
- **Differential diagnosis:** Other distal arthrogryposes (DA1, DA2A/Freeman-Sheldon, DA2B/Sheldon-Hall — *TNNI2/TNNT3/TPM2/MYH3*), DA5 and Marden-Walker (allelic *PIEZO2*), multiple pterygium syndrome, amyoplasia, and syndromic cleft palate. Distinguishing features: **cleft palate + short stature favor GS/DA3**; ptosis/ophthalmoplegia favor DA5; CNS involvement/psychomotor delay favor MWS.
- **Screening:** No population newborn screen. **Cascade testing** of at-risk relatives and **prenatal/preimplantation genetic testing** available once the familial variant is known.

11. Outcome / Prognosis

- **Survival / life expectancy:** Generally **normal** for classic GS. Exception: the severe respiratory end of the *PIEZO2* spectrum can cause lethal neonatal respiratory insufficiency ([PMID: 36317804](#)).
- **Mortality:** No disease-specific mortality statistics for classic GS; mortality is concentrated in severe/respiratory cases.
- **Morbidity / disability:** Chiefly from contractures (hand function, ambulation), scoliosis, and cleft palate (feeding/speech). Most individuals with distal arthrogryposis achieve **independent ambulation and self-care** with orthopedic management ([PMID: 33104047](#)).
- **Quality of life:** No GS-specific validated QoL instrument data.
- **Complications:** Progressive scoliosis; feeding/speech difficulty from cleft palate; anesthetic risk including reported **malignant hyperthermia** in a GS case with congenital myopathy ([PMID: 24878349](#)).
- **Prognostic factors:** Specific *PIEZO2* allele and position on the spectrum (respiratory involvement worsens prognosis); severity of scoliosis and contractures.

12. Treatment

There is **no disease-modifying/curative therapy**; management is **supportive, orthopedic, and multidisciplinary**.

- **Orthopedic / surgical (NCIT: Orthopedic Procedure):** Serial **casting** and bracing for clubfoot (Ponseti-type), tendon-release/soft-tissue surgery for contractures, scoliosis management (bracing/spinal surgery). Distal-arthrogryposis orthopedic cohorts show good functional outcomes ([PMID: 33104047](#)).
- **Craniofacial surgery (NCIT: Palatoplasty):** Cleft palate repair with speech therapy follow-up.
- **Rehabilitation (NCIT: Physical Therapy / Occupational Therapy):** Physiotherapy, occupational therapy, and speech therapy for contractures, mobility, fine motor skills, and feeding/speech.
- **Pharmacotherapy:** No approved drug. **Mechanism-targeted candidates (experimental, preclinical):** **botulinum toxin** (NCIT: Botulinum Toxin) and a **PIEZO2-modulating dietary fatty acid** reduced DA-like deficits in mice ([PMID: 36634173](#)); **phosphatidic acid/LPA**-based PIEZO2 inhibition is a plausible future strategy ([PMID: 39147733](#)). These are **not** established human treatments.
- **Advanced therapeutics (gene/cell/RNA therapy):** None available; a GoF mechanism is in principle amenable to allele-selective silencing (ASO/siRNA) — conceptual only.
- **Anesthetic caution:** Given reported malignant hyperthermia/congenital myopathy associations, anesthetic planning should consider MH precautions ([PMID: 24878349](#)).
- **Personalized medicine:** Genotype confirms diagnosis and informs recurrence risk/prenatal options; no genotype-guided pharmacotherapy yet.

13. Prevention

- **Primary prevention:** Not possible (congenital genetic disorder). **Genetic counseling** is central: autosomal-dominant 50% transmission risk from an affected parent, with reduced (female-biased) penetrance and variable expressivity complicating counseling ([PMID: 458832](#)).
- **Secondary/tertiary prevention:** Early orthopedic intervention and scoliosis surveillance to prevent functional decline; palatoplasty and feeding/speech support.
- **Reproductive options:** Once the familial *PIEZO2* variant is identified — **prenatal diagnosis** (CVS/amniocentesis), **preimplantation genetic testing (PGT)**, and cascade testing of relatives.

- **Immunization / public-health / environmental interventions:** Not applicable.

14. Other Species / Natural Disease

- **Taxonomy / orthologs:** *PIEZO2* is evolutionarily conserved. Mouse ortholog *Piezo2* (*Mus musculus*, NCBI:txid10090); *C. elegans* ortholog *pezo-1* (*Caenorhabditis elegans*, NCBI:txid6239). Human variant positions map to conserved residues (e.g., human R2718P $\approx$ worm R2405P).
- **Natural disease in other species:** No well-documented naturally occurring Gordon-syndrome-equivalent in companion animals/wildlife (OMIA) identified in this review. Veterinary relevance: none established.
- **Comparative biology:** Disease mechanisms are evolutionarily conserved at the channel level — the worm GoF knock-in reproduces electrophysiological gain-of-function and physiological defects ([PMID: 38349741](#)); mouse *Piezo2* is essential for proprioception ([PMID: 27184818](#)).
- **Transmission / zoonosis:** Not applicable (non-infectious).

15. Model Organisms

Model	Type	Construct	Phenotype recapitulation	Reference
Mouse (<i>Mus musculus</i>)	Mammalian, in vivo	Proprioceptor-specific <i>Piezo2</i> GoF knock-in	High — sufficient to induce DA5-like contractures; Botox + dietary fatty acid rescue	PMID: 36634173
Mouse	Mammalian, in vivo	Conditional <i>Piezo2</i> knockout in proprioceptors	Validates normal function — loss abolishes RA mechanically activated currents, balance/coordination deficits	PMID: 27184818
<i>C. elegans</i>	Invertebrate	<i>pezo-1</i> [R2405P] CRISPR knock-in ($\approx$ human R2718P/DA5)	Moderate — GoF electrophysiology + reproductive/actin defects; suppressed by <i>gex-3</i> / <i>NCKAP1</i>	PMID: 38349741
HEK/heterologous cells	In vitro	PIEZO2 mutant cDNA (E2727del, I802F)	Biophysical GoF (altered inactivation); no toxicity	PMID: 23487782

- **Applications:** Dissecting channel gating, the neurogenic origin of contractures, the developmental critical period, and therapeutic screening (Botox, lipids, dietary fatty acids).
- **Limitations:** Mouse GoF studies modeled the DA5 allele/phenotype rather than the GS-specific cleft-palate branch; the orofacial/palatal mechanism remains uncharacterized in models. Invertebrate models cannot capture craniofacial/skeletal features.
- **Resources:** MGI (mouse), WormBase (*C. elegans*), Cellosaurus/ATCC (cell lines).

Evidence Base

PMID	Title (abbrev.)	Evidence type	Supports
24726473	<i>Mutations in PIEZO2 cause GS, MWS, and DA5</i>	Human exome cohort	F1 — causal gene, recurrent R2686H, cleft-palate association
23487782	<i>Gain-of-function PIEZO2 mutations cause a DA subtype</i>	In vitro electrophysiology	F2 — GoF via altered inactivation; no toxicity
36634173	<i>Excessive mechanotransduction in sensory neurons causes joint contractures</i>	Mouse in vivo	F3 — neurogenic mechanism; Botox/fatty-acid rescue
11718203	<i>Scoliosis in Gordon's syndrome</i>	Human clinical	F4 — triad frequencies
458832	<i>Gordon syndrome large pedigree</i>	Human pedigree	F4 — AD inheritance, reduced female penetrance, variable expressivity
27843126	<i>Biallelic loss of PIEZO2...</i>	Human + mechanism	F5 — dominant GoF vs recessive LOF dichotomy
27184818	<i>Critical role for Piezo2 in proprioceptive mechanotransduction</i>	Mouse in vivo	F6 — Piezo2 essential for proprioception
38349741	<i>F-actin factor suppresses DA5 PIEZO2 variant in C. elegans</i>	Invertebrate model	F6 — conserved GoF model; cytoskeletal modifier
41572728	<i>Expanding genotype-phenotype of MWS due to PIEZO2</i>	Human review	F7 — same variant → GS↔DA5 continuum
36588752	<i>Continuum in dominant PIEZO2 spectrum</i>	Human cohort	F7 — dominant PIEZO2 continuum
30988732	<i>Bioinformatics of PIEZO2 mutations</i>	Computational	F2/F5 — C-terminal dominant GoF vs N-terminal recessive LOF
39147733	<i>Phosphatidic acid negatively regulates PIEZO2</i>	In vitro/mouse	Mechanism/therapeutics — lipid modulation

PMID	Title (abbrev.)	Evidence type	Supports
37587573	<i>Novel PIEZO2 variant in a fetus (GS)</i>	Human case	Prenatal diagnosis; de novo/mosaicism
36317804	<i>Lethal respiratory course in PIEZO2 DA5</i>	Human case	Severe end of spectrum / prognosis
24878349	<i>GS with congenital myopathy / malignant hyperthermia</i>	Human cases	Anesthetic risk; comorbidity
27714920	<i>Familial GS with PIEZO2 mutation</i>	Human family	Prenatal detection; psychomotor-delay spectrum

Consistency of the evidence: The causal gene and GoF mechanism are supported convergently by human genetics (exome cohorts), in vitro electrophysiology, and two independent animal models — an unusually complete chain for a rare disorder. No study in this corpus contradicts the PIEZO2 GoF model for the dominant spectrum.

Limitations and Knowledge Gaps

- The cleft-palate branch is unexplained mechanistically.** p.Arg2686His is statistically linked to cleft palate, but no model explains how proprioceptor-channel GoF causes a palatal defect; this step is **inferred**, not demonstrated.
- Models target DA5, not GS specifically.** The pivotal mouse GoF study reproduced DA5-like contractures; no model reproduces the GS-defining cleft palate + short stature, so therapeutic rescue data may not transfer directly to GS.
- No epidemiology.** Prevalence, incidence, sex ratio, and natural-history/QoL data are not quantified for GS specifically.
- Therapeutics are preclinical.** Botox and fatty-acid/lipid modulation are promising but unproven in humans; no GS clinical trials (NCT identifiers) were identified.
- Variant interpretation of novel alleles.** Several reported variants remain VUS; functional assays are not routinely performed clinically.
- No human omics data** (transcriptomics/proteomics/metabolomics) for GS tissue.

7. **Penetrance/expressivity modifiers** in humans are uncharacterized (only a worm suppressor is known).

Proposed Follow-up Experiments / Actions

1. **Generate a GS-specific (R2686H) mouse knock-in** and assess craniofacial/palatal development to test whether proprioceptor GoF alone, or broader PIEZO2 expression (e.g., in cranial neural crest/orofacial tissues), produces cleft palate — resolving the unexplained branch.
 2. **Test lipid/fatty-acid and Botox interventions during the fetal critical window** in GS-relevant models, defining dose, timing, and whether palatal and skeletal phenotypes (not just contractures) are modifiable.
 3. **Develop allele-selective knockdown (ASO/siRNA)** against the recurrent R2686H allele as a mechanism-rational disease-modifying candidate.
 4. **Assemble an international GS/PIEZO2 registry** to quantify prevalence, penetrance by sex, genotype–phenotype correlations across the GS–DA5–MWS continuum, natural history, and validated QoL outcomes.
 5. **Systematic functional classification of VUS** (standardized patch-clamp inactivation assays) to accelerate ACMG reclassification and prenatal counseling.
 6. **Clinical anesthesia study** of malignant-hyperthermia/myopathy risk in PIEZO2 patients to issue evidence-based peri-operative guidance.
-

Report compiled from 5 autonomous investigation iterations; 7 confirmed findings; 32 papers reviewed. Evidence types span human clinical/genetic cohorts, in vitro electrophysiology, computational analysis, and mouse/C. elegans models. Information derived from aggregated disease-level resources and primary literature, not individual EHR data.
