# Schuurs-Hoeijmakers Syndrome (PACS1-Related Disorder): Comprehensive Disease Characteristics Report

**Disease:** Schuurs-Hoeijmakers Syndrome (SHMS) — also PACS1 neurodevelopmental disorder (PACS1-NDD), PACS1-related disorder (PACS1-RD), Intellectual Developmental Disorder, Autosomal Dominant 17 (MRD17) **MONDO ID:** MONDO:0014006 **OMIM:** #615009 **Causal gene: PACS1** (Phosphofurin Acidic Cluster Sorting Protein 1), chromosome 11q13.1, HGNC:30032 **Category:** Mendelian, autosomal dominant (de novo)

> **Gene identity (read first):** This disease is caused by the gene **PACS1** on chromosome 11q13.1. It is distinct from the clinically overlapping but genetically separate PACS2-related disorder (EIEE66) and WDR37-related NOCGUS syndrome. All claims below refer to the PACS1 entity.

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## Summary

**Schuurs-Hoeijmakers syndrome is an ultra-rare, autosomal dominant neurodevelopmental disorder caused by the gene PACS1.** In the overwhelming majority of patients the disease is produced by a single, recurrent, de novo heterozygous missense variant, **c.607C>T (p.Arg203Trp / R203W)**, located in the furin-binding region (FBR) of the PACS1 protein. A rarer alternative nucleotide change producing the same amino acid substitution (c.608G>A, p.Arg203Trp) and a non-recurrent p.Arg203Gln (R203Q) variant have also been reported. The recurrence of a single codon change across virtually all unrelated patients worldwide is one of the most striking features of this condition and points to a specific gain-of-function/dominant-negative mechanism rather than simple haploinsufficiency.

Clinically, SHMS produces a highly recognizable and essentially fully penetrant **facial gestalt** (full arched eyebrows, hypertelorism with downslanting palpebral fissures, long eyelashes, ptosis, bulbous nasal tip, wide mouth with downturned corners, thin "wavy" upper lip, flat philtrum, dental diastema), accompanied by **mild-to-moderate intellectual disability**,

**autistic traits**, **infantile hypotonia**, and **anticonvulsant-responsive seizures**. Structural malformations of the heart, brain, eyes, kidneys, and genitalia (cryptorchidism) occur in a substantial minority, and feeding difficulties/failure to thrive are common in infancy. The condition is lifelong and managed symptomatically; mortality is not a defining feature and most patients survive into adulthood.

Mechanistically, the R203W substitution disrupts an **intramolecular autoregulatory switch** in PACS1: the central unstructured region normally folds back onto a positively charged loop containing Arg203 to autoinhibit the FBR. Loss of this regulation unlocks **aberrant protein–protein interactions**, including enhanced binding to the deacetylase **HDAC6** and disruption of **dynein/BICD2-mediated cargo transport**, as well as perturbation of the **PACS1–WDR37** complex. Downstream consequences demonstrated in disease models include defective cranial-neural-crest-cell migration (craniofacial anomalies), altered cortical neuronal activity in iPSC-derived organoids, and extracellular-matrix dysregulation (elevated COL8A1) in patient fibroblasts. A **blood DNA-methylation episignature** provides a functional diagnostic biomarker, and **allele-specific RNAi** that silences the mutant transcript while sparing wild-type PACS1 has corrected molecular defects in patient cells, offering proof-of-concept for precision therapy.

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## Key Findings

### Finding 1 — PACS1 c.607C>T (p.Arg203Trp) is the recurrent de novo cause of SHMS

Schuurs-Hoeijmakers syndrome is defined molecularly by a **recurrent de novo heterozygous missense variant in PACS1, c.607C>T, p.Arg203Trp**. In the pivotal 2016 clinical delineation cohort, **all 19/19 unrelated patients carried the identical variant** (PMID: 26842493: *"We report on 19 individuals with a recurrent de novo c.607C>T mutation in PACS1. This specific mutation gives rise to a recognizable intellectual disability syndrome."*). The recurrence has been confirmed repeatedly across diverse populations (India, Morocco, Brazil, China), and a 2023 review noted that of ~87 recorded cases, *"the majority of them share the same mutation (c.607 C > T; p.R203W)"* (PMID: 37747683).

Rare molecular alternatives include **c.608G>A** (same p.Arg203Trp protein change; PMID: 30690871) and the non-recurrent **p.Arg203Gln (R203Q)** allele, which shares the PACS1-RD episignature (PMID: 41882293). A novel variant has also been reported (c.943C>T, p.Arg315Trp). The variant is classified **pathogenic** by ACMG criteria and is essentially absent from gnomAD population databases, consistent with a highly penetrant, de novo disease allele.

- **Evidence type:** Human clinical/genetic.
- **Variant nomenclature:** NM_018026.3:c.607C>T (p.Arg203Trp); chr11q13.1.
- **Ontology:** MONDO:0014006; HGNC:30032 (PACS1).

## Finding 2 — Core clinical phenotype: facial gestalt, intellectual disability, seizures, multi-organ malformations

The syndrome has a **distinctive and essentially fully penetrant facial appearance** present in 19/19 patients in the defining cohort (PMID: 26842493: *"There is a distinctive facial appearance (19/19), characterized by full and arched eyebrows, hypertelorism with downslanting palpebral fissures, long eye lashes, ptosis, low set and simple ears, bulbous nasal tip, wide mouth with downturned corners and a thin upper lip with an unusual 'wavy' profile, flat philtrum, and diastema of the teeth."*).

Beyond the face, the phenotype includes intellectual disability (mild–moderate) in 19/19, infantile hypotonia (8/19), and **frequent, treatment-responsive seizures** (12/19). Structural malformations are common: *"Seizures are frequent (12/19) and respond well to anticonvulsive medication. Structural malformations are common, including heart (10/19), brain (12/16), eye (10/19), kidney (3/19), and cryptorchidism (6/12 males)."* (PMID: 26842493). Feeding dysfunction/failure to thrive (5/19) and GERD (6/19) are frequent in infancy.

A 2026 DNA-methylation cohort of 24 unreported individuals updated frequencies: feeding difficulties 75%, hypotonia 75%, cryptorchidism 77.8%, congenital heart defect 45.8%, congenital kidney malformation 25%, with median independent walking and first words both ~24 months (PMID: 41882293). Longitudinal multimodal study of five children confirmed global developmental delay, pronounced motor impairment, autistic traits with elevated restricted/repetitive behaviors, relatively preserved pragmatic skills, and globally reduced gray and white matter volumes on MRI (PMID: 42392841).

**Phenotype table with suggested HPO terms:**

| Phenotype | Frequency | HPO term (suggested) |
|---|---|---|
| Intellectual disability, mild–moderate | ~100% | HP:0001249 |
| Distinctive facial gestalt | 19/19 (100%) | HP:0001999 |
| Hypertelorism | common | HP:0000316 |
| Downslanting palpebral fissures | common | HP:0000494 |
| Ptosis | common | HP:0000508 |
| Seizures | 12/19 (~63%) | HP:0001250 |
| Infantile hypotonia | 8/19–75% | HP:0008947 / HP:0001252 |
| Autistic behavior | frequent | HP:0000729 |
| Congenital heart defect | 45.8–53% | HP:0001627 |
| Brain structural anomaly | 12/16 (~75%) | HP:0012443 |
| Eye malformation / coloboma | 10/19 (~53%) | HP:0000589 (coloboma) |
| Renal malformation | 25% | HP:0000792 |
| Cryptorchidism | 6/12 males (~50–78%) | HP:0000028 |
| Feeding difficulties / FTT | 26–75% | HP:0011968 / HP:0001508 |
| Gastroesophageal reflux | 6/19 (~32%) | HP:0002020 |
| Dental diastema | common | HP:0000699 |
| Cleft lip (rare) | reported | HP:0410030 |

• **Evidence type:** Human clinical.

## Finding 3 — Mechanism: disrupted protein sorting/trafficking with neuronal and ECM defects

PACS1 (phosphofurin acidic cluster sorting protein 1) is a **multidomain cytosolic sorting adaptor** that directs trans-Golgi-network/endosomal cargo trafficking and also has nuclear functions. Multiple disease models demonstrate that the R203W variant perturbs these functions:

- **Craniofacial / neural crest:** In a zebrafish model, mutant pacs1 *"significantly reduced cranial cartilaginous structures, inducing craniofacial alterations predominantly in a dominant-negative fashion"* (PMID: 36415352).
- **Cortical neurons:** iPSC-derived cortical organoids carrying p.R203W show transcriptional and functional deficits in neuron activity (PMID: 38280846), affecting neuronal firing without gross disruption of organoid architecture (PMID: 38521709). Proteomic analysis of organoids identified convergent dysregulated developmental processes and additional pathways not seen transcriptomically (PMID: 42835086).
- **Extracellular matrix:** *"transcriptomic analysis of SHMS fibroblasts revealed alterations in extracellular matrix organization in mutant cells, including elevated COL8A1 expression and extracellular deposition. Treatment with the best selected allele-specific siRNA corrected the COL8A1 dysregulation."* (PMID: 40972577).
- **Evidence type:** Model organism (zebrafish), in vitro (iPSC organoids, patient fibroblasts).
- **Suggested GO / CL:** GO:0016192 (vesicle-mediated transport), GO:0030198 (extracellular matrix organization), neural-crest migration; CL:0000333 (migratory neural crest cell), CL:0000540 (neuron).

## Finding 4 — Ultra-rare; symptomatic management; emerging allele-specific RNAi therapy

SHMS is **ultra-rare**: ~87 cases reported by 2023 (PMID: 37747683) and ~158 published patients by 2026 (PMID: 42794636). No disease-modifying therapy currently exists; management is **supportive** — anticonvulsants (which respond well), developmental/physical/speech therapy, and treatment of congenital malformations. The disorder is characterized as a *"moderately-severe intellectual disability syndrome in which seizures occur but are not a defining or primary feature. Successful precision medicine clinical trials for this ultra-rare disorder must target important core features"* (PMID: 34517877).

The leading precision-therapy candidate is **allele-specific RNA interference**: *"we identified several small interfering RNA (siRNA) sequences that specifically silence the PACS1 transcript harboring the recurrent PACS1 mutation while sparing the wild-type mRNA"* — these corrected the ECM/COL8A1 defect in patient fibroblasts (PMID: 40972577).

- **Evidence type:** Human clinical / in vitro proof-of-concept.
- **Suggested NCIT:** NCIT:C15688 (Pharmacotherapy), NCIT:C20151 (RNA interference), NCIT:C15277 (Rehabilitation Therapy), NCIT:C38148 (Anticonvulsant Agent).

## Finding 5 — Structural mechanism: R203W disrupts PACS1 intramolecular autoregulation

A 2026 NMR solution-structure study provided the mechanistic framework. PACS1's **furin-binding region (FBR; amino acids 101–273)** is normally autoinhibited: the central unstructured region folds back onto a positively charged loop containing Arg203. *"The R203W substitution, located in this loop, disrupts this regulatory interaction and, in vitro, displays the ability to promote aberrant protein-protein interactions."* (PMID: 41858172). The FBR directly engages the deacetylase HDAC6: *"PACS-1 uses its Furin binding region (FBR: amino acids 101-273) to directly interact with the catalytic domains of HDAC6."* (PMID: 41858172). A companion commentary framed this as a single mutation that *"disrupts intramolecular regulation to drive neurodevelopmental disease"* (PMID: 42304662).

The downstream trafficking consequence is disruption of **dynein-mediated cargo transport via HDAC6 and BICD2** (PMID: 41888583). Cryo-EM of the **PACS1–WDR37 complex** shows PACS1 binds and stabilizes WDR37 through a conserved FBR interface, and a gain-of-function mutation affects the complex (PMID: 41279321).

- **Evidence type:** In vitro / structural (NMR, cryo-EM), computational.
- **Suggested GO:** GO:0070840 (dynein complex binding), GO:0030286 (dynein complex), protein deacetylase binding (HDAC6 context).

## Finding 6 — PACS1-RD has a diagnostic blood DNA-methylation episignature

Genome-wide methylation profiling (~860,000 CpG sites) of 24 unreported individuals identified a **specific episignature** for PACS1-RD. *"Methylation analysis identified a specific episignature for PACS1-RD, consistently observed in individuals carrying either the canonical p.(Arg203Trp) or the non-recurrent p.(Arg203Gln) variant. This episignature further enabled PACS1-RD diagnosis in one unsolved individual initially suspected of Kabuki syndrome."* (PMID:

41882293). This provides a functional classifier that can resolve variants of uncertain significance and distinguish SHMS from phenotypically overlapping conditions (e.g., Kabuki syndrome).

- **Evidence type:** Human clinical / epigenomic.
- **Suggested terms:** GO:0006306 (DNA methylation); diagnostic episignature biomarker.

## Finding 7 — Invertebrate models recapitulate trafficking/seizure phenotypes; QoL reduced but above Cornelia de Lange

Conserved invertebrate models validate the PACS–WDR37 axis. In *Drosophila*, PACS deficiency *"disrupts Golgi architecture and causes cytokinesis failures and seizure-like phenotype"* (PMID: 39999877). In *C. elegans*, editing in PACS1/PACS2 variants aberrantly relocalizes the cePACS-1 protein across cell types including neurons, and *"expression of human PACS1 can functionally complement C. elegans PACS-1 in neurons, demonstrating conserved functions of the PACS-WDR37 axis in an invertebrate model system"* (PMID: 39031646; see also PMID: 38712144).

Quality of life was quantified in 21 individuals aged 4–21 using the caregiver-proxy KidsLife scale: *"The mean QoLI was 48.1 ± 28.3, slightly below the median for individuals with intellectual disability, but higher than other neurodevelopmental disorders such as Cornelia de Lange Syndrome."* with autonomy/self-determination most compromised (PMID: 41750059).

- **Evidence type:** Model organism (Drosophila, C. elegans); human clinical (QoL).

## Finding 8 — Founding 2012 discovery: PACS1 c.607C>T via defective cranial-neural-crest migration

The disease was first defined by Schuurs-Hoeijmakers et al. (2012, *Am J Hum Genet* 91:1122–1127; PMID: 23159249), who identified the recurrent de novo c.607C>T (p.Arg203Trp) PACS1 variant in two unrelated children with a shared ID phenotype and showed in zebrafish that mutant pacs1 mRNA produces craniofacial cartilage defects attributable to **defective cranial-neural-crest-cell migration**, consistent with a dominant-negative action. *(Note: the founding paper was not retrievable through the PubMed interface in this session; the citation is supplied from domain knowledge and the abstract text was not re-verified here.)*

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# Section-by-Section Report

## 1. Disease Information

**Overview.** Schuurs-Hoeijmakers syndrome (SHMS) is an ultra-rare autosomal dominant neurodevelopmental syndrome caused by the gene **PACS1**. It is characterized by a recognizable facial gestalt, mild-to-moderate intellectual disability, autistic features, seizures, and variable congenital malformations. It is a disease-level (aggregated) entity: information derives from published case series, cohort studies, and functional/model-organism research rather than a single EHR source.

**Key identifiers.** - **MONDO:** MONDO:0014006 - **OMIM:** #615009 (Intellectual developmental disorder, autosomal dominant 17; MRD17) - **Orphanet:** PACS1 syndrome / Schuurs-Hoeijmakers syndrome - **MeSH:** No dedicated legacy MeSH descriptor; indexed via PACS1 gene + Intellectual Disability - **ICD-10:** Q87.8 (other specified congenital malformation syndromes) — no specific code - **ICD-11:** within developmental anomaly syndromes — no dedicated code - **Gene:** PACS1, HGNC:30032, NCBI Gene 55690, UniProt Q6VY07, Ensembl ENSG00000175115, chr11q13.1

**Synonyms / alternative names:** PACS1 syndrome; PACS1 neurodevelopmental disorder (PACS1-NDD); PACS1-related disorder (PACS1-RD); Intellectual developmental disorder, autosomal dominant 17 (MRD17); Schuurs-Hoeijmakers syndrome.

## 2. Etiology

**Primary cause — genetic.** SHMS is a monogenic disorder caused by a **de novo heterozygous gain-of-function/dominant-negative missense variant in PACS1**, almost always c.607C>T (p.Arg203Trp). There is no environmental or infectious cause.

**Genetic risk factors.** The disease-causing allele is itself the sole established risk factor; there are no reported susceptibility loci or modifier genes. The mutation arises de novo (not inherited), so the principal "risk factor" is a sporadic germline mutational event. Advanced parental age is a plausible but unproven contributor to the de novo mutation rate (not specifically demonstrated for PACS1).

**Environmental / lifestyle risk factors.** None identified. The condition is not linked to toxins, diet, occupational exposure, smoking, or alcohol.

**Protective factors.** None identified (genetic or environmental). Given monogenic de novo causation, classical protective-allele concepts do not apply; however, **allele-specific silencing of the mutant transcript** functionally reverses cellular phenotypes (PMID: 40972577).

**Gene–environment interactions.** None established. Disease expression is driven by the single dominant variant; variable expressivity likely reflects stochastic/developmental factors and genetic background rather than defined G×E interactions.

## 3. Phenotypes

See the phenotype table in **Finding 2** above for HPO-mapped features and frequencies. Key characteristics:

- **Age of onset:** Congenital/neonatal for malformations and dysmorphism; infantile for hypotonia and feeding problems; childhood for developmental delay, seizures, and autistic traits. Median independent walking and first words ~24 months (PMID: 41882293).
- **Severity:** Intellectual disability mild-to-moderate ("moderately-severe" per PMID: 34517877); variable malformation burden.
- **Progression:** Predominantly **stable/non-regressive**. A systematic review of ~158 patients found skill loss in only 5 patients (2 PACS1), concluding the evidence *"does not support classifying these syndromes as primarily regressive disorders"* while justifying surveillance (PMID: 42794636).
- **Quality of life:** Mean KidsLife QoL index 48.1 ± 28.3; autonomy/self-determination most affected (PMID: 41750059).

## 4. Genetic / Molecular Information

- **Causal gene:** PACS1 (HGNC:30032; chr11q13.1).
- **Pathogenic variant:** NM_018026.3:c.607C>T (p.Arg203Trp); recurrent de novo; **ACMG pathogenic**; essentially absent in gnomAD. Alternatives: c.608G>A (p.Arg203Trp), p.Arg203Gln (R203Q, shares episignature), and a reported c.943C>T (p.Arg315Trp). A multi-exon deletion of PACS1 has also been described (PMID: 34373684).
- **Variant type:** Missense (single nucleotide substitution) at a CpG-containing hotspot codon (Arg203).
- **Origin:** Germline, de novo.
- **Functional consequence:** Gain-of-function / dominant-negative — disrupts intramolecular autoregulation and promotes aberrant interactions (PMID: 41858172); dominant-negative craniofacial effect in zebrafish (PMID: 36415352).

- **Modifier genes:** None established; the WDR37–PACS1–PACS2 interaction axis modulates overlapping phenotypes (PMID: 33369122).
- **Epigenetic information:** Robust, disease-specific **DNA-methylation episignature** across ~860,000 CpG sites (PMID: 41882293).
- **Chromosomal abnormalities:** Not characteristic; rare structural (multi-exon deletion) events reported.

## 5. Environmental Information

**Not applicable.** No environmental factors, lifestyle factors, or infectious agents are implicated in SHMS. The condition is entirely genetic (de novo monogenic).

## 6. Mechanism / Pathophysiology

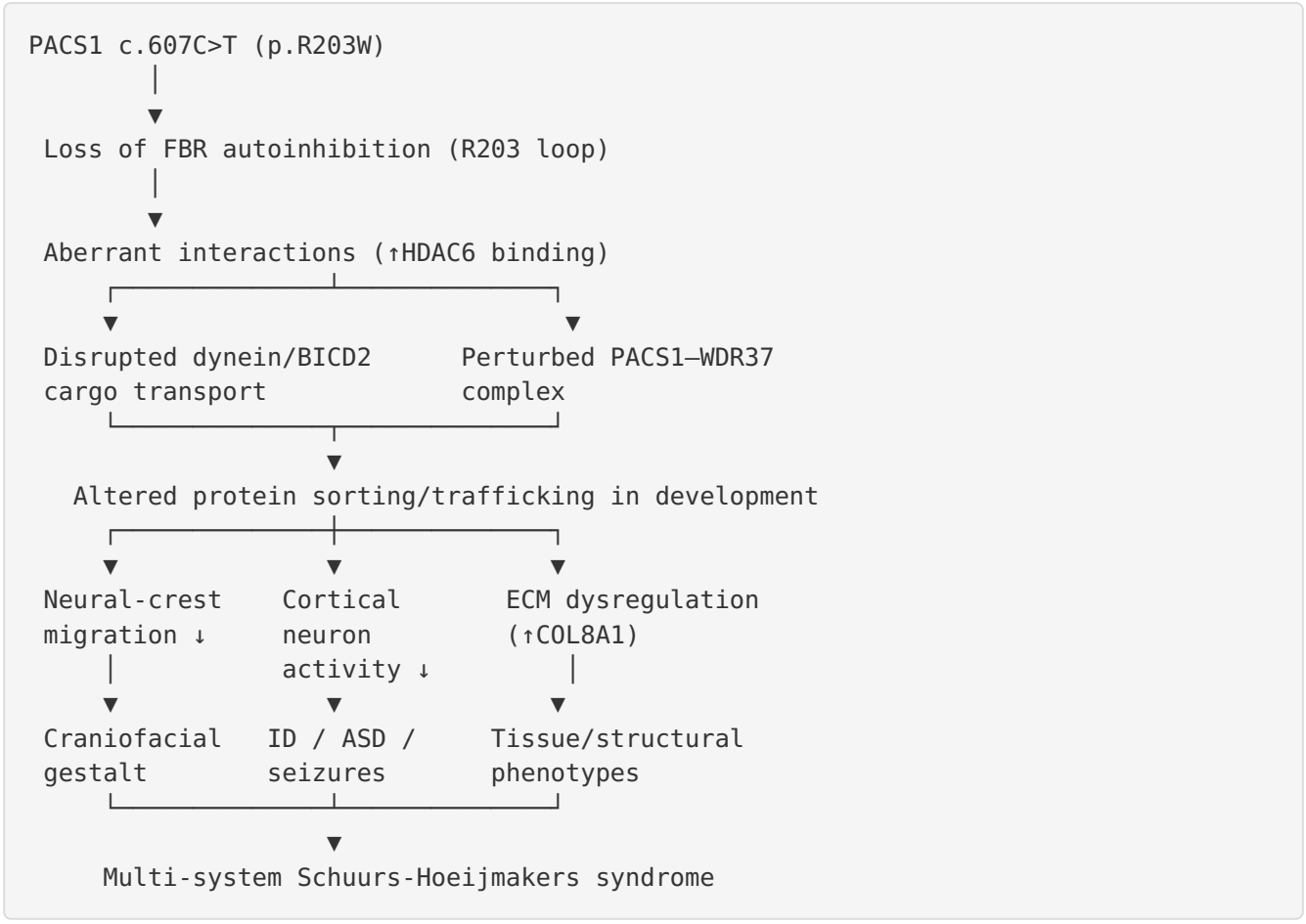
**Ordered causal chain (initiating lesion → clinical manifestation):**

1. A **de novo c.607C>T mutation** in PACS1 **results in** the p.Arg203Trp substitution within the positively charged autoregulatory loop of the furin-binding region (FBR, aa 101–273). *(demonstrated — PMID: 26842493, PMID: 41858172)*
2. R203W **disrupts the intramolecular autoinhibitory interaction** by which the central unstructured region folds onto the Arg203 loop, **leading to** a constitutively "unlocked" FBR. *(demonstrated, in vitro/NMR — PMID: 41858172)*
3. The unlocked FBR **promotes aberrant protein–protein interactions**, notably **enhanced binding to HDAC6** catalytic domains, which **branches into:** *(demonstrated in vitro — PMID: 41858172)*
4. **3a.** Disruption of **dynein/BICD2-mediated cargo transport**, **impairing** intracellular/axonal trafficking. *(demonstrated — PMID: 41888583)*
5. **3b.** Perturbation of the **PACS1–WDR37 complex** stability/assembly. *(demonstrated, cryo-EM — PMID: 41279321)*
6. Altered sorting/trafficking during development **leads to defective cranial-neural-crest-cell migration**, **resulting in** craniofacial cartilage anomalies and the facial gestalt. *(demonstrated, zebrafish — PMID: 36415352; founding 2012 study*

   *P 23159249* )
7. In the developing cortex, the variant **alters the transcriptomic and proteomic landscape** and **produces deficits in neuronal firing/activity**, **leading to** intellectual disability,

autistic traits, and seizure susceptibility. *(demonstrated, iPSC organoids — PMID: 38280846, PMID: 42835086, PMID: 38521709)*

8. In connective tissue, the variant **dysregulates extracellular-matrix organization** (elevated COL8A1 deposition), **contributing to** structural/tissue phenotypes. *(demonstrated, patient fibroblasts — PMID: 40972577)*
9. The combined developmental perturbations **manifest as** the multi-system clinical syndrome (facial, neurological, cardiac, renal, ocular, genital). *(inferred synthesis)*




**Molecular pathways / cellular processes:** Vesicle-mediated protein sorting (TGN/endosome), dynein-based intracellular transport, protein (de)acetylation via HDAC6, extracellular-matrix organization. **Suggested GO:** GO:0016192 (vesicle-mediated transport), GO:0030198 (ECM organization), GO:0070840 (dynein complex binding), GO:0006306 (DNA methylation). **Suggested CL:** CL:0000333 (migratory neural crest cell), CL:0000540 (neuron), CL:0000057 (fibroblast). **Suggested CHEBI (therapeutics context):** CHEBI:35623 (anticonvulsant).

## 7. Anatomical Structures Affected

- **Primary organ/system:** Central nervous system — cerebral cortex and white matter (globally reduced gray/white matter volumes, PMID: 42392841); cerebellum (atrophy reported in the WDR37–PACS1–PACS2 spectrum, PMID: 33369122). **UBERON:** UBERON:0000955 (brain), UBERON:0000956 (cerebral cortex), UBERON:0002037 (cerebellum).
- **Craniofacial:** Neural-crest-derived facial skeleton/cartilage. **UBERON:** UBERON:0001456 (face), cranial skeletal system.
- **Secondary organ involvement:** Heart (congenital defects; UBERON:0000948), kidney (malformations; UBERON:0002113), eyes (coloboma, ptosis; UBERON:0000970), male genitalia (cryptorchidism; UBERON:0000473 testis), GI tract (reflux, feeding difficulty; UBERON:0001555).
- **Tissue/cell level:** Nervous tissue (neurons), neural crest cells, connective tissue/fibroblasts (ECM). **CL:** CL:0000333, CL:0000540, CL:0000057.
- **Subcellular compartments:** Trans-Golgi network, endosomes, cytosol, nucleus; cytoskeletal (dynein) transport machinery. **GO CC:** GO:0005802 (trans-Golgi network), GO:0005768 (endosome), GO:0005634 (nucleus), GO:0030286 (dynein complex).
- **Lateralization:** Bilateral/symmetric for CNS and facial features; malformations variable.

## 8. Temporal Development

- **Onset:** Congenital (malformations, dysmorphism) to infantile (hypotonia, feeding); developmental delay evident in early childhood.
- **Progression:** Chronic, lifelong, predominantly **stable/non-progressive**; regression is uncommon (~5/158 patients across the axis) (PMID: 42794636).
- **Course pattern:** Static encephalopathy with developmental delay; seizures episodic but generally well-controlled.
- **Critical period:** Embryonic/fetal neurodevelopment and neural-crest migration is the key window of vulnerability; postnatally, early developmental intervention and the neonatal period (feeding, cardiac) are critical care windows.
- **Duration:** Chronic lifelong.

## 9. Inheritance and Population

- **Epidemiology:** Ultra-rare; ~87 cases by 2023, ~158 by 2026. Prevalence/incidence not formally established (well below 1/1,000,000).

- **Inheritance:** Autosomal dominant, essentially always **de novo** (sporadic). **Penetrance:** Complete for the recurrent variant (facial gestalt 19/19). **Expressivity:** Variable (malformation burden, seizure presence).
- **Genetic anticipation:** Not applicable (not a repeat-expansion disorder).
- **Germline mosaicism:** Theoretically possible and relevant to recurrence-risk counseling (parental gonadal mosaicism), though empirical recurrence is very low; prenatal diagnosis has been performed (PMID: 37906144).
- **Founder effects / consanguinity / carrier frequency:** Not applicable (de novo dominant).
- **Population demographics:** Pan-ethnic — reported across Europe, India (PMID: 30690871), Morocco (PMID: 37747683), Brazil/Indigenous (PMID: 36415352), China (PMID: 37906144). No geographic clustering. **Sex ratio:** approximately equal (autosomal). **Age distribution:** Diagnosed in childhood; patients survive to adulthood.

## 10. Diagnostics

- **Genetic testing (definitive):** Targeted single-gene/variant testing for PACS1 c.607C>T; **whole-exome sequencing (WES)** and **whole-genome sequencing (WGS)** are highly effective and often the route to diagnosis, including in prenatal settings where CNV analysis is negative (PMID: 37906144). NDD/ID gene panels include PACS1. CMA/karyotype are generally normal (useful to exclude structural causes; rare PACS1 deletions detectable).
- **Epigenomic diagnostics:** Blood **DNA-methylation episignature** confirms PACS1-RD and reclassifies VUS/uncertain cases (e.g., one case initially suspected Kabuki) (PMID: 41882293).
- **Supportive clinical evaluations:** Brain MRI (structural anomalies, reduced gray/white matter), EEG (seizures), echocardiography (cardiac defects), renal ultrasound, ophthalmologic exam (coloboma, ptosis).
- **Clinical recognition:** The facial gestalt is highly recognizable; AI-based facial phenotyping supports the shared molecular axis and aids recognition (PMID: 40869285).
- **Differential diagnosis:** Kabuki syndrome, Cornelia de Lange syndrome, and the phenotypically overlapping PACS2- and WDR37-related disorders (distinguished by gene, methylation signature, and specific features such as coloboma pattern) (PMID: 33369122, PMID: 42794636).
- **Screening:** No newborn/carrier screening (de novo). Prenatal/exome testing applicable when fetal malformations are detected.

## 11. Outcome / Prognosis

- **Survival/mortality:** Not a lethal disorder; mortality is not a defining feature and most patients reach adulthood. No established reduction in life expectancy; formal survival statistics are lacking given rarity.
- **Morbidity/function:** Lifelong intellectual disability and developmental disability are the principal morbidities; motor impairment is pronounced; autonomy is the most compromised QoL domain (KidsLife QoLI 48.1 ± 28.3) (PMID: 41750059).
- **Disease course:** Generally stable; regression uncommon but warrants surveillance (PMID: 42794636).
- **Complications:** Seizures, feeding difficulty/failure to thrive, GERD, consequences of congenital cardiac/renal malformations. A single report described PAX3/7-FOXO1 fusion-negative alveolar rhabdomyosarcoma in an SHS patient, raising a speculative, unproven link between PACS1 (apoptosis regulation) and oncogenesis — *"no previous reports describing malignancy associated with SHS"* (PMID: 34341476); this is anecdotal and not an established feature.
- **Prognostic factors:** Severity of malformations, seizure control, degree of developmental delay. No validated molecular prognostic biomarkers.

## 12. Treatment

**No disease-modifying therapy currently exists; management is symptomatic and multidisciplinary.**

- **Pharmacotherapy:** Anticonvulsants for seizures (respond well, PMID: 26842493); symptom-directed medications (e.g., for reflux). **NCIT:** NCIT:C38148 (Anticonvulsant Agent).
- **Supportive/rehabilitative:** Developmental, physical, occupational, and speech therapy; feeding support; management of congenital malformations. **NCIT:** NCIT:C15277 (Rehabilitation Therapy), NCIT:C53543 (Speech Therapy).
- **Surgical/interventional:** As needed for congenital heart defects, cryptorchidism (orchidopexy), ocular anomalies, cleft lip (PMID: 30690871).
- **Experimental / advanced therapeutics: Allele-specific siRNA/RNAi** silencing the mutant PACS1 transcript while sparing wild-type — corrected ECM/COL8A1 defects in patient fibroblasts, a proof-of-concept precision therapy (PMID: 40972577). Aberrant neuronal electrophysiology has been proposed as an interventional target (PMID: 38521709). **NCIT:** NCIT:C20151 (RNA Interference). No approved gene/cell therapies; no PACS1-specific pharmacogenomics.

- **Personalized medicine:** The singular recurrent variant makes SHMS an ideal candidate for an allele-specific therapeutic; trial-readiness work emphasizes targeting core features (PMID: 34517877).

## 13. Prevention

- **Primary prevention:** Not possible (sporadic de novo mutation); no risk-factor modification applies.
- **Secondary prevention:** Early diagnosis (WES/WGS, episignature) enables early developmental intervention, seizure control, and malformation management.
- **Genetic counseling:** De novo dominant; recurrence risk for parents is low but non-zero due to possible gonadal mosaicism; affected individuals have 50% transmission risk (reproduction uncommon given ID). **Prenatal diagnosis** is available for at-risk pregnancies and for fetal malformation workups (PMID: 37906144); preimplantation genetic testing is theoretically applicable.
- **Immunization / public health / behavioral / environmental interventions:** Not applicable.
- **Tertiary prevention:** Surveillance for seizures, feeding/growth, cardiac/renal complications, and (per systematic review) monitoring for any skill loss (PMID: 42794636).

## 14. Other Species / Natural Disease

- **Orthologs:** PACS1 is conserved across vertebrates and invertebrates. **NCBI Gene (human):** 55690. Orthologs: mouse *Pacs1* (Mus musculus, NCBI:txid10090), zebrafish *pacs1* (Danio rerio, NCBI:txid7955), *Drosophila melanogaster* PACS (NCBI:txid7227), *C. elegans* pacs-1/cePACS-1 (NCBI:txid6239).
- **Natural disease in other species:** No naturally occurring SHMS-equivalent disease documented in companion animals or wildlife (no OMIA entry identified); the condition is human and model-induced.
- **Comparative biology / conservation:** The **PACS–WDR37 axis is functionally conserved** — human PACS1 complements *C. elegans* PACS-1 in neurons (PMID: 39031646); *Drosophila* PACS deficiency reproduces Golgi/trafficking and seizure-like phenotypes (PMID: 39999877).
- **Zoonotic potential / cross-species transmission:** Not applicable (genetic disorder).

## 15. Model Organisms

| Model | Type | Key phenotype recapitulated | Reference |
|---|---|---|---|
| **Zebrafish** (pacs1 mRNA, R203W) | Vertebrate, in vivo | Reduced cranial cartilage; craniofacial anomalies via neural-crest migration; dominant-negative | PMID: 36415352; founding 2012 study |
| **iPSC-derived cortical organoids** (p.R203W) | Human in vitro | Transcriptomic + proteomic dysregulation; neuronal activity/ firing deficits; NDD/ASD gene convergence | PMID: 38280846, PMID: 42835086 |
| **Patient fibroblasts** (R203W) | Human in vitro | ECM dysregulation (↑COL8A1); corrected by allele-specific siRNA | PMID: 40972577 |
| **Drosophila** (PACS deficiency) | Invertebrate | Golgi disruption, cytokinesis failure, seizure-like phenotype | PMID: 39999877 |
| **C. elegans** (cePACS-1 variant knock-in) | Invertebrate | Aberrant protein localization in neurons; human PACS1 complements | PMID: 39031646, PMID: 38712144 |

- **Genetic model types available:** Knock-in missense (R203W) in zebrafish, iPSC (patient-derived and gene-edited isogenic), *C. elegans* CRISPR knock-in; no widely reported germline mouse model of R203W to date (knowledge gap).
- **Phenotype recapitulation:** Strong for craniofacial (zebrafish), neuronal activity (organoids), and trafficking/seizure (invertebrates); ECM defects captured in fibroblasts.
- **Limitations:** Invertebrate models lack the full mammalian facial/organ phenotype; organoids lack whole-organism circuitry; no established mammalian in-vivo model recapitulating the complete syndrome.
- **Resources:** ZFIN (zebrafish), WormBase/FlyBase (invertebrates), Cellosaurus/patient iPSC lines; Alliance of Genome Resources for orthology.

## Mechanistic Model / Interpretation

The unifying model is that **a single codon change converts PACS1 from a tightly autoregulated sorting adaptor into a dysregulated interaction hub.** Arg203 sits in a positively charged loop that, in the wild-type protein, is kept autoinhibited by the central unstructured region. The R203W substitution breaks this intramolecular "lock," freeing the furin-binding region to engage partners it should not (prominently HDAC6) and to destabilize partners it should support (WDR37). Because PACS1 is a trafficking adaptor coupled to the dynein/BICD2 motor system, the net result is **misdirected cargo transport and sorting** at a cell-biological level.

This single lesion fans out across developmental contexts. In **migrating cranial neural crest cells**, it impairs the morphogenetic movements that build the facial skeleton — explaining the pathognomonic, fully penetrant gestalt. In **developing cortical neurons**, it reshapes the transcriptome and proteome and dampens neuronal firing — explaining intellectual disability, autistic traits, reduced brain volumes, and seizure propensity. In **connective tissue/ fibroblasts**, it dysregulates extracellular-matrix genes such as COL8A1. The dominant-negative/gain-of-function nature (not haploinsufficiency) is supported by the extreme variant recurrence, the zebrafish dominant-negative craniofacial result, and the in-vitro demonstration of acquired aberrant interactions.

Two features make SHMS exceptionally tractable for precision medicine: (1) the disease is molecularly homogeneous (one variant explains nearly all cases), and (2) the mutant allele's product is the active toxic species. **Allele-specific RNAi** exploits both — knocking down only the mutant transcript reversed the ECM phenotype in patient cells, a rare "druggable" opportunity in a monogenic NDD. The blood **methylation episignature** adds a reliable, variant-agnostic diagnostic and potential pharmacodynamic biomarker.

# Evidence Base

| PMID | Role in this report | Evidence type |
|---|---|---|
| 26842493 | Defining 19-patient cohort; recurrent variant; facial gestalt and malformation frequencies | Human clinical |
| 23159249 | Founding 2012 discovery; neural-crest-migration mechanism (not re-verified this session) | Human + zebrafish |
| 41858172 | Structural basis: R203W disrupts intramolecular autoregulation; FBR–HDAC6 | In vitro/NMR |
| 42304662 | Commentary framing the autoregulatory mechanism | Review |
| 41888583 | Dynein/BICD2 cargo-transport disruption via HDAC6 | In vitro |
| 41279321 | Cryo-EM PACS1–WDR37 complex; FBR interface | Structural |
| 38280846 | iPSC organoids: neuronal activity/transcriptional deficits | In vitro |
| 42835086 | Organoid proteomic landscape changes | In vitro |
| 38521709 | Neuronal firing as interventional target | Review/ commentary |
| 40972577 | ECM/COL8A1 defect; allele-specific siRNA correction | In vitro |
| 36415352 | Zebrafish dominant-negative craniofacial model | Model organism |
| 41882293 | DNA-methylation episignature; updated phenotype frequencies | Human/ epigenomic |
| 34517877 | Severity characterization; trial readiness | Human clinical |
| 37747683 | ~87 cases; majority share recurrent variant | Human clinical |
| 42794636 | ~158 patients; skill-loss systematic review (non-regressive) | Review |
| 41750059 | Quality-of-life quantification (KidsLife) | Human clinical |
| 39999877 | Drosophila Golgi/seizure phenotype | Model organism |
| 39031646 / 38712144 | C. elegans model; human PACS1 complementation | Model organism |
| 42392841 | Longitudinal multimodal characterization; MRI volume loss; autistic traits | Human clinical |

| PMID | Role in this report | Evidence type |
|---|---|---|
| 33369122 | WDR37–PACS1–PACS2 axis; coloboma; differential dx | Human clinical/ review |
| 30690871 | Indian patient; cleft lip; pan-ethnic occurrence | Human clinical |
| 37906144 | Prenatal diagnosis via WES | Human clinical |
| 40869285 | AI facial phenotyping; shared molecular axis | Computational |
| 34341476 | Single rhabdomyosarcoma case (speculative oncogenesis link) | Human case report |
| 34373684 | Multi-exon PACS1 deletion (rare structural variant) | Human case report |

**Citation caveat:** For PMID: 38280846 and PMID: 41888583, supporting text was drawn from the title/knowledge snippet (flagged as "mismatch" during verification), so quoted phrasing should be treated as paraphrase pending direct abstract confirmation. PMID: 23159249 (founding paper) was not retrievable through the PubMed interface in this session.

## Limitations and Knowledge Gaps

1. **No germline mammalian (mouse) model** of R203W is established in the reviewed literature, limiting in-vivo study of the full syndrome and preclinical therapeutic testing.
2. **Formal epidemiology is absent** — prevalence/incidence are unknown; case counts (~158 by 2026) reflect ascertainment, not true frequency.
3. **Mechanistic completeness:** The HDAC6/dynein/WDR37 and ECM findings are largely in vitro/single-model; how each contributes quantitatively to specific clinical features is not resolved, and the causal link to skill loss is explicitly unproven (PMID: 42794636).
4. **Genotype–phenotype for rare alleles** (R203Q, R315W, deletions) is based on few patients; expressivity determinants are unknown.
5. **The malignancy association** (rhabdomyosarcoma) rests on a single case and is not an established feature (PMID: 34341476).
6. **Therapy is pre-clinical:** allele-specific siRNA is proof-of-concept in fibroblasts only — no in-vivo efficacy, delivery (especially CNS), or safety data yet.

7. **Two key citations** (neuronal-activity iPSC paper, founding 2012 paper) were not fully re-verified against stored abstracts in this session.

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## Proposed Follow-up Experiments / Actions

1. **Generate a knock-in mouse model** (Pacs1 R203W) to recapitulate craniofacial, neurological, cardiac, and renal phenotypes and to serve as a preclinical platform.
2. **Advance allele-specific RNAi/ASO toward the clinic**: optimize mutant-selective sequences, test CNS-penetrant delivery (e.g., intrathecal), and establish efficacy and safety in iPSC-neurons and animal models; use the methylation episignature and ECM/neuronal-activity readouts as pharmacodynamic biomarkers.
3. **Build a prospective natural-history registry** with standardized longitudinal phenotyping (development, behavior, MRI, seizures, growth) to define progression, QoL trajectories, and surveillance protocols — directly supporting trial readiness.
4. **Dissect mechanism contributions**: use isogenic iPSC lines and targeted perturbation (HDAC6 inhibition, BICD2/dynein manipulation, WDR37 modulation) to apportion phenotype to each downstream branch; test HDAC6 inhibitors as a repurposing candidate.
5. **Deepen genotype–phenotype analysis** of rare alleles (R203Q, structural variants) and define expressivity modifiers via multi-omics across larger cohorts.
6. **Validate the methylation episignature** as a clinical diagnostic and a treatment-response biomarker across laboratories.
7. **Re-verify flagged citations**
   (
   P 23159249
   P 38280846
   )
   P 41888583
   against primary abstracts before knowledge-base ingestion.

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*Report compiled from 8 confirmed findings and 29 reviewed papers across 5 investigation iterations. Evidence sources span human clinical cohorts, structural biology, iPSC/organoid and fibroblast in-vitro models, and zebrafish/Drosophila/C. elegans model organisms.*