SMARCC1-associated Developmental Dysgenesis Syndrome — Comprehensive Disease Report

MONDO ID: MONDO:0700123 · **Causal gene:** *SMARCC1* (BAF155; HGNC:11104; OMIM gene 601732; UniProt Q92922) · **Classification:** Mendelian, autosomal-dominant BAFopathy (subclass of MONDO:0700120) · **Synonym:** SMARCC1-related BAFopathy

Summary

SMARCC1-associated Developmental Dysgenesis Syndrome is an autosomal-dominant, de-novo-dominated Mendelian neurodevelopmental disorder caused by haploinsufficient/damaging variants in *SMARCC1*, the gene encoding BAF155 — the core scaffold subunit of the BAF (mammalian SWI/SNF) ATP-dependent chromatin-remodeling complex. The disease was defined by Singh et al. (2024) through a large genetic-association study of ventriculomegalic trios, in which rare, protein-altering de novo *SMARCC1* variants surpassed genome-wide significance. The clinical core comprises cerebral ventriculomegaly / congenital hydrocephalus, aqueductal stenosis, corpus callosum abnormalities, developmental delay, and structural cardiac defects, with variable expressivity.

Mechanistically, the disorder is not a disease of impaired cerebrospinal fluid (CSF) dynamics but of **genetic disruption of prenatal neural stem/progenitor biology**. SMARCC1/BAF155 is a scaffold subunit that controls BAF-complex stability; its loss destabilizes the complex and dysregulates the epigenetic landscape of neural progenitors — elevating the repressive histone mark H3K27me3 (via control of the demethylases UTX/JMJD3), de-repressing Wnt signaling, and shifting the balance toward excess progenitor proliferation and impaired neuronal differentiation. Downstream, pro-neurogenic transcription factors NEUROD2 and MAB21L2 are dysregulated. In vivo *Xenopus tropicalis* modeling recapitulated both aqueductal stenosis and cardiac defects and was rescued by wild-type but not patient-variant SMARCC1, establishing loss-of-function pathogenicity.

The entity is newly described and minimally curated: MONDO places it under BAFopathy and links it to *SMARCC1*, but there are **no OMIM/Orphanet/ICD cross-references and no curated HPO phenotype annotations yet**, so all phenotype terms here are literature-derived. Population frequency, penetrance, prognosis, and treatment are therefore characterized qualitatively. Management is supportive and follows general congenital-hydrocephalus practice (CSF diversion via shunt or endoscopic third ventriculostomy, developmental support). No targeted or disease-specific therapy exists.

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1. Disease Information

Overview. SMARCC1-associated Developmental Dysgenesis Syndrome is a Mendelian BAFopathy caused by germline (overwhelmingly de novo) variants in *SMARCC1*, which encodes **BAF155**, a core scaffold subunit of the BAF/mSWI/SNF chromatin-remodeling complex. It manifests as a prenatal brain developmental disorder with variable cerebral ventriculomegaly, aqueductal stenosis, corpus callosum anomalies, developmental delay, and cardiac defects (Findings F001, F006; PMID: 38128548).

Key identifiers.

Resource	Identifier	Status
MONDO	MONDO:0700123	Confirmed (name: "SMARCC1-associated developmental dysgenesis syndrome"); subclass of MONDO:0700120 (BAFopathy)
Causal gene	*SMARCC1* (HGNC:11104; OMIM 601732; Ensembl ENSG00000173473; chr3p21.31)	Confirmed
OMIM (disease/ phenotype)	Not recorded	No dedicated phenotype MIM yet
Orphanet	Not recorded	—
ICD-10 / ICD-11	Not recorded	—
MeSH	Not recorded	—
UniProt (protein)	Q92922 (SMARCC1/BAF155, 1105 aa)	Confirmed

The MONDO term and its parentage/gene link were verified via EBI OLS4 and the Monarch Initiative API (Findings F011, F012).

Synonyms. SMARCC1-related BAFopathy (MONDO synonym); informally "SMARCC1 BAFopathy."

Information source. Derived from **aggregated disease-level resources and primary literature**, principally the defining cohort study (Singh et al. 2024) combining whole-exome sequencing of 2,697 ventriculomegalic trios with functional modeling — a research cohort rather than routine EHR. MONDO/Monarch provide ontology placement but no patient-level data.

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2. Etiology

Primary cause — genetic. The disease is caused by rare, protein-altering, predominantly **de novo** variants in *SMARCC1*. Singh et al. identified six such variants at highly conserved residues in key functional domains, exceeding genome-wide significance in a cohort of 2,697

ventriculomegalic trios / 8,091 exomes (2016–2023) versus 1,798 control exomes (Findings F001, F006; PMID: 38128548). An independent clinical-exome cohort separately identified de novo/loss-of-function *SMARCC1* variants and classified it as a BAFopathy gene (Finding F001; PMID: 34906496).

Genetic risk architecture. The core mechanism is **haploinsufficiency**: *SMARCC1* is extremely intolerant to loss of function (gnomAD v2.1.1 pLI ≈ 1.00, observed/expected LoF = 43/147.4 = 0.29, LOEUF = 0.38, LoF Z = 7.30; missense Z = 3.01) — a constraint profile consistent with a single damaging allele being sufficient to cause disease (Finding F004). No susceptibility loci or polygenic contributors are established for this monogenic disorder; modifier genes are not yet defined.

Environmental / protective / lifestyle factors. None are established. As a de novo dominant developmental disorder, there are no documented environmental triggers, protective alleles, dietary or lifestyle modifiers, infectious agents, or gene-environment interactions — *not applicable / not available* for this entity (Section 5 likewise).

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3. Phenotypes

Because MONDO:0700123 carries **zero curated HPO annotations** (Finding F012, Monarch API disease-to-phenotype count = 0), all phenotype terms below are **literature-derived** from the defining cohort and should be treated as provisional frequencies.

Phenotype	Type	Suggested HPO	Onset	Notes / frequency (qualitative)
Cerebral ventriculomegaly	Imaging/structural sign	HP:0002119 (Ventriculomegaly)	Congenital/ prenatal	Core feature; variable presence
Congenital hydrocephalus	Clinical sign	HP:0000238 (Hydrocephalus)	Congenital	Core; neurosurgically treated in cohort
Aqueductal stenosis	Structural sign	HP:0002410 (Aqueductal stenosis)	Congenital	Prominent; recapitulated in frog model
Corpus callosum abnormality	Structural sign	HP:0001273 (Abnormal corpus callosum)	Congenital	"Common" in cohort
Developmental delay	Behavioral/ neurodevelopmental	HP:0001263 (Global developmental delay)	Infancy/ childhood	Common
Structural cardiac defect	Physical/structural	HP:0001627 (Abnormal heart morphology)	Congenital	Common; recapitulated in *Xenopus*

Characteristics. Onset is congenital/prenatal for structural brain and cardiac features; developmental delay emerges in infancy–childhood. Severity and progression are **variable** — the defining paper explicitly describes "variable presence of cerebral ventriculomegaly, aqueductal stenosis, developmental delay and a variety of structural brain or cardiac defects" (PMID: 38128548, Finding F006). Quantitative frequencies, QoL instruments (EQ-5D/SF-36/ PROMIS), and per-phenotype severity grading are **not yet available**.

4. Genetic / Molecular Information

Causal gene. *SMARCC1* (BAF155), HGNC:11104, OMIM 601732, Ensembl ENSG00000173473, chr3:47,585,269–47,782,106 (3p21.31). Encodes a 1105-aa core/scaffold subunit of the BAF complex (UniProt Q92922).

Protein domain architecture and variant localization (Finding F011; PMID: 33953332, PMID: 28438634):

Domain	Residues (aa)	Function
N-terminal module	28–302	DNA contact / assembly
— MarR-like (putative DNA-binding)	38–164	DNA binding
— BRCT (N)	168–211	Protein interaction
— Chromo domain	217–245	Chromatin engagement
— BRCT (C)	261–285	Protein interaction
SWIRM domain	449–546	Binds SMARCB1/BAF47 (complex assembly)
SANT domain	618–669	Histone-tail / DNA binding
Disordered regions	296–439, 745–860, 956–1028, 1041–1105	Flexible linkers

Pathogenic de novo variants cluster at highly conserved residues within these functional domains (Findings F006, F011).

Variant classification and population frequency. ClinVar contains **287** *SMARCC1* records — **68 Pathogenic, 17 Likely pathogenic**, remainder VUS/benign (Finding F010); note this count mixes germline developmental submissions with somatic/cancer classifications, so it is an upper bound on developmental-disease variants. Variant types in the developmental syndrome are **missense (de novo, conserved residues)** and predicted loss-of-function (nonsense/frameshift/splice); pathogenic alleles are effectively **absent from population databases** (gnomAD), consistent with de novo origin and strong constraint.

Origin and functional consequence. Germline **de novo** in the developmental syndrome; functional consequence is **loss of function / haploinsufficiency** (not gain-of-function or dominant-negative, per rescue data). A distinct **somatic** role exists in cancer (Finding F009): somatic *SMARCC1* deletion acts as a **tumor suppressor** (oral squamous cell carcinoma, PMID: 26934577; biallelic loss in malignant mesothelioma, PMID: 24916674). >20–25% of human cancers carry mutations in SWI/SNF/BAF subunit genes (PMID: 35158202). These somatic contexts are mechanistically and clinically separate from the germline developmental disorder.

Modifier genes. Not yet defined.

Epigenetic information. The disease mechanism is intrinsically epigenetic: BAF complexes globally control H3K27me2/3 by modulating the demethylases UTX and JMJD3 (PMID: 26986003, Finding F003). A disease-specific methylation episignature for *SMARCC1* is **not yet reported**.

Chromosomal abnormalities. Large 3p21.31 interstitial deletions encompassing *SMARCC1* (among many genes) have been described with developmental delay and dysmorphism (PMID: 27385966), but phenotypes in those cases are contiguous-gene effects (e.g., *SETD2*), not the isolated *SMARCC1* syndrome.

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5. Environmental Information

Not applicable. No environmental, lifestyle, or infectious factors are established for this monogenic de novo dominant disorder. No toxins, radiation, occupational exposures, dietary factors, or pathogens are implicated.

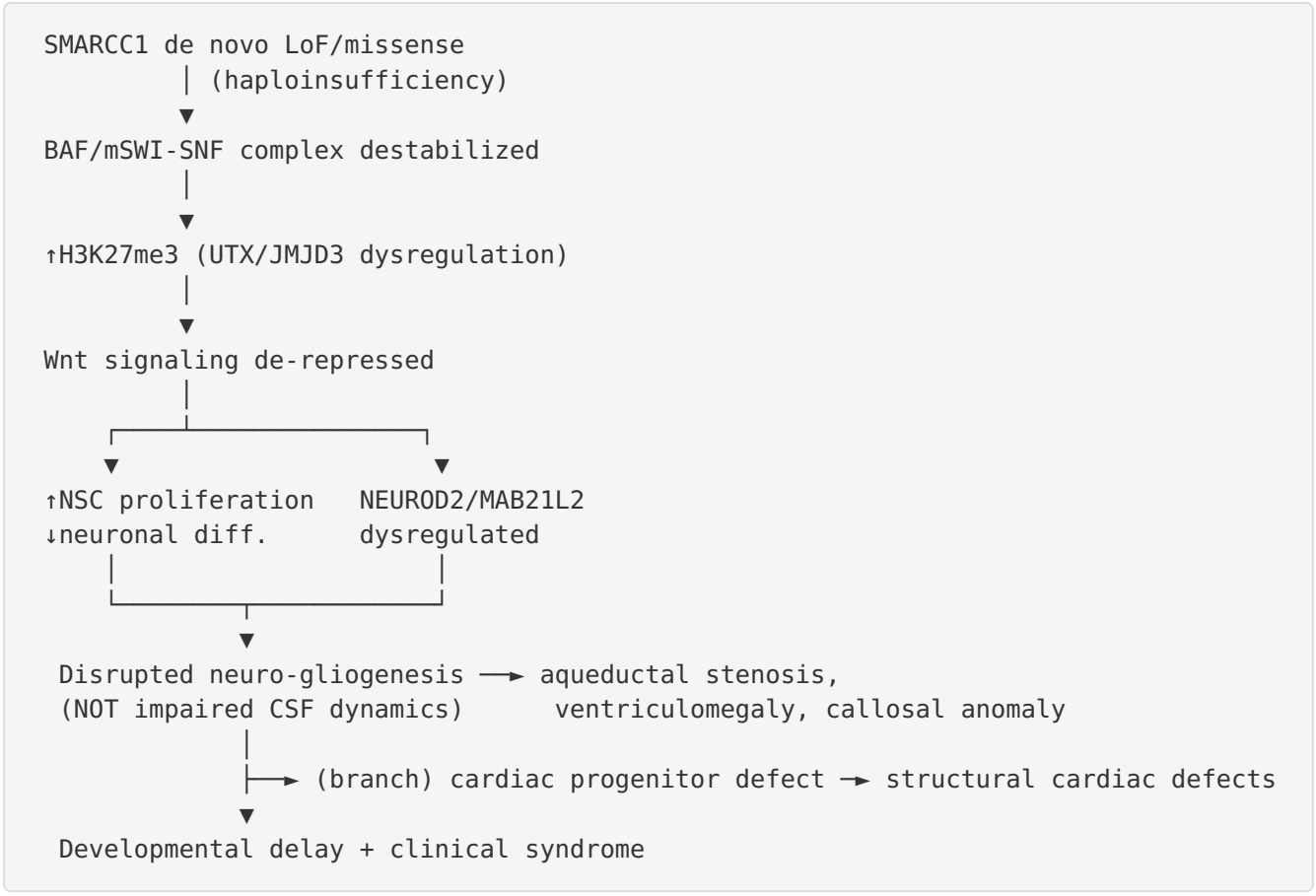
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6. Mechanism / Pathophysiology

Ordered causal chain

1. A **de novo damaging/loss-of-function variant in *SMARCC1*** (missense at conserved domain residues, or LoF) arises in the germline → **reduces functional BAF155 (haploinsufficiency)** (demonstrated: genetic constraint pLI≈1, de novo enrichment; F004, F006).

2. Reduced BAF155 scaffold → **destabilizes the BAF (mSWI/SNF) chromatin-remodeling complex**, because BAF155 regulates complex stability and assembly (demonstrated in mouse/in vitro; F003; PMID: 31020615).
3. BAF dysfunction → **loss of BAF-mediated control over H3K27 demethylases UTX/JMJD3 → global increase in repressive H3K27me2/3** (demonstrated in mouse forebrain; F003; PMID: 26986003).
4. Altered histone-methylation balance (↑H3K27me3 on neuronal-differentiation genes; ↑H3K4me2 on proliferation genes) → **de-repression of Wnt signaling** (demonstrated in mouse late corticogenesis; F005; PMID: 29779894).
5. Wnt de-repression → **increased proliferation of neuroepithelial-like neural stem cells and impaired neuronal differentiation** (demonstrated; F005).
6. Imbalanced progenitor proliferation/differentiation → **dysregulation of midgestational neurogenesis transcription factors NEUROD2 and MAB21L2** (demonstrated across human fetal brain and *Xenopus*; F007; PMID: 38128548).
7. Disrupted neuro-gliogenesis → **structural brain dysgenesis: aqueductal stenosis, cerebral ventriculomegaly/hydrocephalus, corpus callosum anomalies** — i.e., the primary lesion is developmental, *not* impaired CSF dynamics (inferred for human from model + cohort transcriptomics; supported by F002; PMID: 33077954).
8. **Branch — cardiac:** BAF dysfunction in cardiac progenitors → **structural cardiac defects** (demonstrated by *Xenopus* knockdown recapitulation and rescue; F007).
9. Brain dysgenesis + hydrocephalus → **developmental delay and the clinical syndrome** (clinical observation; F006).



Molecular pathways: Wnt signaling (de-repressed; KEGG hsa04310); chromatin remodeling / histone methylation (H3K27me2/3; H3K4me2). **Cellular processes:** neural stem cell proliferation (GO:0050767 regulation of neurogenesis), neuronal differentiation (GO:0030182), chromatin remodeling (GO:0006338), histone H3-K27 methylation (GO:0070734). **Protein dysfunction:** loss of scaffold function → complex instability (not aggregation). **Cell types:** neural stem/progenitor cells (CL:0000047 neuronal stem cell; CL:0000031 neuroblast; CL:0000681 radial glial cell), cardiac progenitors. **Subcellular:** nucleus / nuclear chromatin (GO:0000785 chromatin; GO:0016514 SWI/SNF complex; GO:0071564 npBAF complex). **Multi-omics / functional genomics:** cross-species transcriptomics (human fetal brain RNA-seq + *Xenopus*) converging on shared neurogenesis genes (F007); *Xenopus* knockdown-rescue as the in vivo functional assay (F007).

Upstream nodes = SMARCC1 loss → BAF instability → histone-methylation shift; downstream = Wnt/progenitor imbalance → transcription-factor dysregulation → structural malformation.

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7. Anatomical Structures Affected

- **Primary organ: brain** (UBERON:0000955), especially **cerebral ventricles** (UBERON:0002285 lateral ventricle), **cerebral aqueduct** (UBERON:0002289; aqueductal stenosis), **corpus callosum** (UBERON:0002336), neocortex and hippocampus (implicated by BAF-loss cortical models, F005).
- **Secondary / branch organ: heart** (UBERON:0000948) — structural cardiac defects.
- **Body systems:** central nervous system (developmental) and cardiovascular system.
- **Tissue/cell level:** neuroepithelium / neural stem & progenitor cells (CL:0000047, CL:0000681 radial glia, CL:0000031 neuroblast); cardiac progenitor cells.
- **Subcellular:** nucleus / chromatin (GO:0000785); BAF/SWI-SNF complex (GO:0016514, GO:0071564).
- **Localization / lateralization:** midline and bilateral CNS structures; ventriculomegaly typically bilateral. Precise lateralization not systematically reported.

8. Temporal Development

- **Onset:** congenital/prenatal for brain and cardiac malformations (detectable as fetal/neonatal ventriculomegaly); developmental delay apparent in infancy–childhood. Onset pattern is **chronic/congenital**, arising during **midgestational neurogenesis** — the critical developmental window (F002, F007).
- **Progression:** structural malformations are fixed at birth; hydrocephalus may require intervention. Developmental delay is generally **stable to slowly evolving** rather than neurodegenerative. Formal natural-history/longitudinal data are **not available**.
- **Critical period:** fetal neuro-gliogenesis (midgestation) is the window of vulnerability and the only plausible window for mechanistic intervention — likely inaccessible postnatally.
- **Remission:** none intrinsic; hydrocephalus is managed surgically (symptomatic, not curative).

9. Inheritance and Population

- **Inheritance pattern:** autosomal dominant, overwhelmingly **de novo** (F001, F006).
- **Penetrance / expressivity:** expressivity is explicitly **variable**; penetrance not precisely quantified given small cohort.
- **Anticipation / mosaicism / founder effects / consanguinity:** not reported / not applicable (de novo dominant, not a repeat-expansion or recessive disorder). Germline/gonadal mosaicism is a theoretical source of recurrence risk.
- **Carrier frequency:** not applicable (de novo dominant); pathogenic alleles essentially absent from gnomAD.
- **Epidemiology:** prevalence and incidence are **not established** — the syndrome is newly defined from a research cohort and carries no Orphanet/registry prevalence figure. It represents a rare, genetically defined subset within the broader congenital-hydrocephalus and BAFopathy populations.
- **Demographics / geography / sex ratio / age distribution:** no population-specific enrichment, geographic clustering, or sex bias established; affected individuals are identified in the prenatal/pediatric period.

For context, the broader Coffin-Siris/Nicolaides-Baraitser BAFopathy family may account for ~1% of intellectual disability (PMID: 25249037, F008) — but *SMARCC1* disease is a distinct, much rarer entity within that family.

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10. Diagnostics

- **Genetic testing is the definitive diagnostic.** Trio **whole-exome sequencing (WES)** or **whole-genome sequencing (WGS)** identifying a de novo damaging *SMARCC1* variant is the basis of diagnosis (the entity was defined by trio WES; F001, F006). Single-gene testing and BAFopathy/congenital-hydrocephalus **gene panels** including *SMARCC1* are appropriate. **Chromosomal microarray** may detect 3p21.31 deletions but typically as contiguous-gene events (PMID: 27385966).
- **Variant interpretation:** ACMG/AMP classification against ClinVar (68 P / 17 LP records; F010); de novo occurrence (PS2), absence from gnomAD (PM2), and conserved functional-domain location support pathogenicity.

- **Imaging:** fetal/neonatal cranial ultrasound and brain **MRI** demonstrate ventriculomegaly, aqueductal stenosis, and callosal anomalies; **echocardiography** for cardiac defects.
- **Laboratory biomarkers / metabolomics / proteomics / liquid biopsy:** no specific biochemical biomarker exists; diagnosis is molecular/radiological.
- **Clinical criteria:** no formal consensus criteria yet (newly defined).
- **Differential diagnosis:** other BAFopathies — Coffin-Siris syndrome (*ARID1B, ARID1A, SMARCB1, SMARCA4, SMARCA2, SMARCE1, ARID2*) and Nicolaides-Baraitser syndrome — which share BAF-subunit etiology but are distinguished by coarse facial features, sparse scalp hair, hypertrichosis, and fifth-digit nail/phalanx hypoplasia rather than the prominent **congenital hydrocephalus/aqueductal stenosis** of SMARCC1 disease (F008; PMID: 34906496, PMID: 35813374, PMID: 27264197). Also consider other monogenic congenital-hydrocephalus genes (e.g., *TRIM71*, *CCDC88C*, *MPDZ*; PMID: 29983323).
- **Screening:** no population or newborn screening exists; **cascade testing** is generally uninformative given de novo origin.

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11. Outcome / Prognosis

Prognostic data specific to SMARCC1 disease are **limited/not formally reported**. Outcome is driven by the severity of hydrocephalus and associated brain/cardiac malformations and by developmental delay. By analogy to genetic congenital hydrocephalus, morbidity relates to neurodevelopmental impairment and shunt-dependence complications (pediatric VP-shunt 30-day failure ~13.8%; PMID: 42829386). **Survival, mortality, 5/10-year outcomes, QoL measures, and validated prognostic biomarkers are not available** for this specific entity. Disease course is chronic/lifelong with stable (non-degenerative) neurodevelopmental impairment.

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12. Treatment

No disease-specific or targeted therapy exists. Management is **supportive and symptomatic**, following general congenital-hydrocephalus and neurodevelopmental care:

- **Neurosurgical CSF diversion** for hydrocephalus — ventriculoperitoneal shunting (NCIT: Ventriculoperitoneal Shunt) or **endoscopic third ventriculostomy (ETV)**, particularly for

obstructive/aqueductal-stenosis physiology (supporting surgical literature: PMID: 42886343, PMID: 42829386).

- **Cardiac management** for structural defects (cardiology/surgical as indicated).
- **Developmental support** — physical, occupational, and speech therapy; early intervention (NCIT: Rehabilitation Therapy).
- **Pharmacotherapy / pharmacogenomics / gene / cell / RNA / targeted / immunotherapy:** none established or applicable.
- **Experimental:** no disease-specific trials (no NCT identifiers) target *SMARCC1* disease. Mechanistically, the epigenetic link (↑H3K27me3 via EZH2/demethylase axis) is of conceptual interest — EZH2 inhibition (GSK126) rescued a *Baf155*-CKO myeloid phenotype in mice (PMID: 33207205) — but this is **not** a validated therapy and the prenatal critical window likely limits translational feasibility.

13. Prevention

- **Primary prevention:** none available (de novo mutation; not preventable by risk-factor modification or immunization).
- **Secondary prevention:** prenatal detection of ventriculomegaly on ultrasound/MRI can prompt genetic evaluation and delivery/neurosurgical planning.
- **Genetic counseling:** recurrence risk for parents of a child with a confirmed de novo variant is low but non-zero due to possible **gonadal mosaicism**; prenatal/preimplantation testing is feasible if a familial variant is identified. Counseling per NSGC/ACMG principles is recommended.
- **Public health / behavioral / environmental / prophylaxis:** not applicable.

14. Other Species / Natural Disease

- **Orthologs:** *Smarcc1* is conserved across mammals (mouse *Smarcc1*), zebrafish (*smarcc1a/b*), *Xenopus tropicalis* (*smarcc1*), and other vertebrates. BAF-complex function is deeply evolutionarily conserved.

- **Natural disease in other species:** no naturally occurring companion-animal or wildlife disease specifically attributed to *SMARCC1* is catalogued (no established OMIA entry). Veterinary relevance is currently limited to experimental models.
- **Comparative biology:** BAF/SMARCC1 roles in embryonic development, lineage specification, and neural progenitor regulation are conserved from frog to human (PMID: 26952987, PMID: 29779894); a zebrafish study linked BBS6 to Smarcc1a in congenital heart disease (PMID: 28753627).
- **Transmission / zoonosis:** not applicable (genetic disorder).

15. Model Organisms

Model	Type	Manipulation	Phenotype recapitulation	Reference
Xenopus tropicalis	Vertebrate (amphibian)	*smarcc1* knockdown; WT vs variant rescue	**Recapitulated aqueductal stenosis AND cardiac defects**; rescued by WT but not patient-variant SMARCC1; shared NEUROD2/MAB21L2 dysregulation with human fetal brain	PMID: 38128548 (F007)
Mouse (*Mus musculus*)	Mammalian	*Baf155/Baf170* conditional KO (forebrain); *Baf155* CKO	↑H3K27me3, impaired forebrain development; de-repressed Wnt, ↑NSC proliferation, impaired neuronal differentiation	PMID: 26986003, PMID: 29779894 (F003, F005)
Mouse blastocyst/ embryo	Mammalian	BAF155 up/ down-regulation	Lineage-specification defects (pluripotency-marker dysregulation)	PMID: 26952987
Zebrafish (*Danio rerio*)	Vertebrate	*smarcc1a/bbs6* manipulation	Congenital-heart-disease-relevant transcriptional changes	PMID: 28753627

Strengths: The *Xenopus* model is the strongest disease-specific validation — it reproduces both the neural (aqueductal stenosis) and cardiac arms of the human phenotype and provides variant-level loss-of-function proof via rescue. Mouse BAF155-loss models illuminate the upstream epigenetic (H3K27me3/Wnt) mechanism. **Limitations:** mouse studies use conditional/compound knockouts rather than the human heterozygous de novo state; no reported germline heterozygous *Smarcc1* mouse that fully mirrors the human syndrome; iPSC/organoid models of patient variants are not yet published.

Mechanistic Model / Interpretation

The evidence converges on a single coherent model: **SMARCC1 disease is a chromatinopathy of fetal neurogenesis.** A de novo hit reduces functional BAF155 below the dose the developing brain tolerates (haploinsufficiency, pLI≈1). Because BAF155 is the scaffold that holds the BAF complex together, its loss has an outsized, complex-wide effect — explaining why a single damaging allele is pathogenic. The destabilized complex loses grip on the H3K27-methylation machinery, tipping progenitors toward Wnt-driven over-proliferation and away from neuronal differentiation, and derailing the NEUROD2/MAB21L2 neurogenic program during the narrow midgestational window. The resulting malformed neural tube/ventricular system manifests as aqueductal stenosis and ventriculomegaly, with a parallel branch in cardiac progenitors producing heart defects. Crucially, the hydrocephalus is a **downstream developmental consequence, not a primary plumbing failure** — reframing a "neurosurgical" phenotype as a chromatin-remodeling disorder (F002).

This model cleanly separates the **germline developmental** context (haploinsufficiency → malformation) from the **somatic oncogenic** context (SMARCC1 as a tumor suppressor whose loss drives cancer), unifying them under the theme that SMARCC1 dosage is critical across distinct cellular programs.

Evidence Base

PMID	Role	How it supports the findings
38128548	**Defining study**	Names the syndrome; genome-wide-significant de novo *SMARCC1* variants in 2,697 trios; *Xenopus* rescue; NEUROD2/MAB21L2 (F001, F006, F007)
34906496	Independent cohort	De novo/LoF *SMARCC1* in clinical-exome BAFopathy cohort; genotype-first constraint approach (F001, F004, F008)
33077954	Mechanistic framing	Genetic disruption of neuro-gliogenesis, not CSF dynamics, is the primary CH pathomechanism (F002)
31020615	Protein function	BAF155 as core/scaffold regulating BAF stability (F003)
26986003	Epigenetic mechanism	BAF controls H3K27me2/3 via UTX/JMJD3; forebrain development (F003, F005)
29779894	Mechanism	BAF loss → Wnt de-repression → ↑NSC proliferation, impaired differentiation (F005)
33953332	Structure	N-terminal MarR/chromo/BRCT module architecture (F011)
28438634	Structure	SWIRM domain binds BAF47/SMARCB1 (F011)
26934577 / 24916674 / 35158202	Somatic contrast	SMARCC1 as tumor suppressor; SWI/SNF in >20% cancers (F009)
25249037	Epidemiologic context	BAFopathy/CSS ~1% of intellectual disability (F008)

Constraint metrics (pLI, LOEUF) were retrieved directly from the gnomAD GraphQL API; ClinVar counts from NCBI E-utilities; MONDO parentage/gene link from the Monarch Initiative API and EBI OLS4.

Limitations and Knowledge Gaps

1. **Newly defined, minimally curated entity:** no OMIM phenotype MIM, Orphanet, ICD, or MeSH code; **zero curated HPO annotations** (F012). All phenotype frequencies are literature-derived from a single defining cohort.
2. **Small patient numbers:** six de novo variants underpin the definition; penetrance, expressivity ranges, prevalence/incidence, sex ratio, and natural history are not quantified.
3. **Prognosis and treatment:** no disease-specific outcome data, QoL measures, prognostic biomarkers, or targeted therapies; management is extrapolated from general congenital-hydrocephalus practice.
4. **Mechanistic inferences:** the human causal chain from histone-methylation shift → Wnt → malformation is strongly supported in mouse/frog but partly **inferred** for human; the EZH2-inhibition rescue is from a non-neural mouse model and is not a validated therapy.
5. **ClinVar counts** mix germline and somatic submissions, inflating the apparent germline pathogenic-variant pool.
6. No patient-derived iPSC/organoid models or human methylation episignature yet.

Proposed Follow-up Experiments / Actions

1. **Curate HPO annotations** for MONDO:0700123 from the Singh 2024 cohort and future cases, with explicit frequencies, to enable automated phenotype-driven diagnosis.
2. **Establish a patient registry / GeneMatcher recruitment** to quantify prevalence, penetrance, expressivity, sex ratio, and natural history.
3. **Patient-specific iPSC-derived cerebral organoids** carrying the de novo variants to test, in a human system, the predicted H3K27me3 increase, Wnt de-repression, and NEUROD2/MAB21L2 loss, and to screen candidate modulators (e.g., EZH2 inhibitors) for developmental-window rescue.
4. **Generate a heterozygous germline *Smarcc1* mouse** matching the human dosage state to test faithful recapitulation and therapeutic windows.
5. **Define a DNA-methylation episignature** for clinical variant classification (reclassifying VUS).
6. **Cross-reference OMIM/Orphanet/ICD** submissions to formalize identifiers and align the knowledge base.

7. **Structure-function mapping** of each pathogenic variant onto Q92922 domains (MarR/chromo/BRCT module, SWIRM) to predict genotype–phenotype correlation and assembly impact.

Evidence source legend: human clinical/genetic (38128548, 34906496, 33077954, 29983323, 27385966, 25249037); model organism (38128548 *Xenopus*; 26986003, 29779894, 26952987, 33207205 mouse; 28753627 zebrafish); in vitro/structural (31020615, 33953332, 28438634, 35158202); somatic/computational constraint (26934577, 24916674, gnomAD/ClinVar APIs).
