Luscan-Lumish Syndrome: Comprehensive Disease Characteristics Report

Disease Name: Luscan-Lumish Syndrome (LLS) **MONDO ID:** MONDO:0014916 **OMIM (phenotype):** #616831 · **OMIM (gene):** *612778 · Orphanet: ORPHA:457485 Category: Genetic (autosomal dominant overgrowth + neurodevelopmental disorder) Causal Gene:* SETD2* (HGNC:18420; NCBI Gene 29072; UniProt Q9BYW2; chromosome 3p21.31)

Summary

Luscan-Lumish syndrome (LLS) is an ultra-rare, autosomal-dominant overgrowth and neurodevelopmental disorder caused by heterozygous, near-universally *de novo* loss-of-function (LoF) variants in **SETD2**, the sole somatic histone H3 lysine-36 trimethyltransferase (H3K36me3). First delineated by Lumish and colleagues in 2015 in a girl with autism, intellectual disability, seizures, Chiari I malformation, and macrocephaly carrying a *de novo* frameshift variant (c.2028delT, p.P677LfsX19), the condition has since been reported in approximately 50 patients worldwide. The core clinical picture combines **postnatal overgrowth** — macrocephaly (near-universal), tall/advanced stature, and obesity (~50%) — with a highly penetrant **neurodevelopmental and behavioral phenotype**: intellectual disability (~83%), autism spectrum disorder (~89%), and behavioral difficulties (~100%), often with aggressive outbursts (~83%), speech and motor delay, and advanced carpal (bone) ossification. LLS is classified within the "Sotos-like" family of epigenetic overgrowth syndromes.

The molecular basis is dual. SETD2 is a **"chromatocytoskeletal" dual-function methyltransferase**: it writes H3K36me3 — essential for transcriptional fidelity (suppression of cryptic transcription), splicing, DNA repair, and genomic stability — and it also methylates **α-tubulin at Lys40 (α-TubK40me3)** and actin, linking it to microtubule/cytoskeletal function. Haploinsufficiency therefore simultaneously perturbs chromatin regulation and cytoskeletal dynamics. Model-organism work directly ties both arms to the phenotype: the H2A.z–Setd2–

H3K36me3 axis drives embryonic cortical neurogenesis (via *Nkx2-4*), and α-TubK40me3 is required for neuronal polarization and migration in the developing cortex, as well as for mitotic-spindle integrity.

Diagnosis is molecular — trio whole-exome or whole-genome sequencing, or overgrowth/intellectual-disability multigene panels — now reinforced by a distinctive **SETD2 DNA-methylation episignature** (EpiSign) that supports diagnosis and reclassifies variants of uncertain significance. Importantly, a genotype–phenotype dichotomy exists at the same locus: recurrent *de novo* missense variants at **codon 1740** produce clinically distinct, more severe, growth-*restricted* disorders — Rabin-Pappas syndrome (RAPAS, p.Arg1740Trp; MIM 620155) and autosomal-dominant intellectual developmental disorder 70 (MRD70, p.Arg1740Gln) — implying a non-LoF (e.g., gain-of-function or altered epigenetic-regulation) mechanism rather than simple haploinsufficiency. No disease-specific or curative therapy exists; management is entirely supportive and multidisciplinary.

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1. Disease Information

LLS is a monogenic **overgrowth-with-intellectual-disability syndrome** in the "Sotos-like" group. It is characterized by "*postnatal overgrowth, macrocephaly, obesity, speech delay, and advanced carpal ossification*" together with a strongly penetrant neurodevelopmental/behavioral profile (PMID: 31643139).

Key identifiers: - **OMIM (phenotype):** #616831 (Luscan-Lumish syndrome) - **OMIM (gene):** *612778 (*SETD2*)* - *Orphanet: ORPHA:457485 - MONDO: MONDO:0014916 - MeSH / ICD: No dedicated MeSH heading or specific ICD-10 code; captured under broad codes for congenital malformation syndromes / intellectual disability. ICD-11 would map to a rare-syndrome/developmental-anomaly category. - HGNC: HGNC:18420 (*SETD2*)*

Synonyms / alternative names: SETD2-related overgrowth syndrome; SETD2-related disorder; intellectual disability, autosomal dominant, with overgrowth (historical descriptions). Note that "SETD2-related disorders" is an umbrella now spanning three nosologically distinct entities: LLS, MRD70, and RAPAS (PMID: 37372360).

Source of information: Aggregated disease-level knowledge from published case reports/series (~50 patients) and mechanistic/model-organism studies — not from a large EHR cohort.

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2. Etiology

Primary cause (genetic). LLS is caused by heterozygous, intragenic **loss-of-function** variants in *SETD2*. Constitutional *SETD2* mutations are "*intragenic loss-of-function variants with truncating (69%) and missense (31%) mutations*" (PMID: 31643139). The founding case carried a *de novo* frameshift: "*a de novo c.2028delT (P677LfsX19) mutation in the SET domain-containing protein 2 (SETD2) gene, predicted to be gene-damaging*" (PMID: 26084711).

Genetic risk factors. The causal event is the *SETD2* LoF variant itself, arising *de novo*; there are no known susceptibility loci or modifier genes established for LLS. Large 3p21.31 deletions encompassing *SETD2* can reproduce part of the phenotype (PMID: 27385966).

Environmental risk factors / protective factors / gene–environment interactions. None established. As a *de novo* dominant Mendelian disorder, LLS has no recognized environmental, lifestyle, or infectious contribution, and no protective alleles or GxE interactions have been reported. Advanced paternal age is a general (non-specific) consideration for *de novo* single-nucleotide variants but is not documented specifically for LLS.

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3. Phenotypes

Per-phenotype frequencies derive chiefly from the Marzin (2019) cohort (n=13): "*neurodevelopmental disorders are common such as intellectual disability (83%), autism spectrum disorders (89%), and behavioral difficulties (100%) with aggressive outbursts (83%). A variety of features such as joint hypermobility (29%), hirsutism (33%), and naevi (50%) were also reported*" (PMID: 31643139).

Phenotype	Type	Frequency	Onset	Suggested HPO
Macrocephaly	physical	~all	postnatal/ childhood	HP:0000256
Behavioral difficulties	behavioral	~100%	childhood	HP:0000708
Autism spectrum disorder	behavioral	~89%	childhood	HP:0000729
Intellectual disability	cognitive	~83%	childhood	HP:0001249
Aggressive outbursts	behavioral	~83%	childhood	HP:0000718
Tall/advanced stature	physical	~50%	postnatal	HP:0000098
Obesity	physical	~50%	childhood	HP:0001513
Naevi	physical sign	~50%	variable	HP:0001054
Hirsutism	physical sign	~33%	variable	HP:0001007
Joint hypermobility	physical	~29%	childhood	HP:0001382
Speech delay	developmental	common	early childhood	HP:0000750
Motor delay	developmental	common	early childhood	HP:0001270
Advanced carpal ossification	radiographic	common	childhood	HP:0011834
Chiari I malformation	structural	reported subset	congenital	HP:0002344
Seizures	neurological	reported subset	childhood	HP:0001250
Facial dysmorphism	physical	reported	congenital	HP:0001999
Recurrent otitis media	clinical	reported	childhood	HP:0000403
Bilateral condylar hyperplasia	physical (rare)	single report	adolescence	—

Severity/progression: Variable expressivity, ranging from a mild adult overgrowth presentation "*without neurological symptoms*" (PMID: 33248444) to classic ID/ASD/overgrowth. Core neurodevelopmental features are generally stable (non-progressive) but lifelong. A rare/unusual manifestation, bilateral condylar hyperplasia, has been reported as part of the expanding phenotype (PMID: 40892041).

Quality-of-life impact: Driven mainly by ID, ASD, and behavioral difficulties (impact on communication, education, independence, and family/caregiver burden). Formal QoL instrument data (EQ-5D/SF-36/PROMIS) are not published for LLS.

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4. Genetic / Molecular Information

- **Causal gene:** *SETD2* (SET domain-containing 2), HGNC:18420, OMIM *612778, locus 3p21.31; encodes the sole somatic H3K36 trimethyltransferase.
- **Variant classification (ACMG/AMP):** Pathogenic/likely-pathogenic LoF variants; the SETD2 episignature helps reclassify VUS (PMID: 40104911).
- **Variant types:** Truncating (~69%: frameshift, nonsense, splice-site) and missense (~31%) (PMID: 31643139). Representative: c.2028delT (p.P677LfsX19) (PMID: 26084711).
- **Allele frequency:** Pathogenic variants are private/*de novo*; absent from population databases (gnomAD) — consistent with strong *SETD2* constraint against LoF.
- **Somatic vs germline:** LLS variants are **germline** (constitutional), *de novo*. Somatic *SETD2* LoF is a separate, well-established oncogenic event (renal cell carcinoma, leukemia, glioma).
- **Functional consequence:** Loss of function / haploinsufficiency for LLS. By contrast, codon-1740 missense variants likely act through a **non-LoF** mechanism (PMID: 32710489).
- **Modifier genes:** None established.
- **Epigenetic information:** A distinctive **DNA-methylation episignature** characterizes LLS/SETD2-related disorders and is detectable by EpiSign (PMID: 40104911).
- **Chromosomal abnormalities:** Interstitial **3p21.31 deletions** encompassing *SETD2* can produce overlapping features (developmental delay, ID, dysmorphism) (PMID: 27385966).

Genotype–phenotype dichotomy at codon 1740: Rabin (2020) identified 15 individuals with *de novo* codon-1740 variants — p.Arg1740Trp (n=12) → **RAPAS** (microcephaly, profound ID, multi-organ anomalies; MIM 620155) and p.Arg1740Gln (n=3) → **MRD70** (moderate-severe ID). "*The phenotype of Group 1 includes microcephaly, profound intellectual disability, congenital*

anomalies affecting several organ systems, and similar facial features," and "*the clinical features seen in individuals with variants affecting codon 1740 are more severe suggesting an alternative mechanism, such as gain of function, effects on epigenetic regulation, or posttranslational*" modification (PMID: 32710489).

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5. Environmental Information

No environmental, lifestyle, or infectious factors are known to cause or trigger LLS. It is a monogenic *de novo* dominant disorder. Obesity, when present, is a phenotypic feature partly amenable to lifestyle/nutritional management rather than an etiologic exposure (PMID: 29681085). No infectious agents apply.

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6. Mechanism / Pathophysiology

Central node — SETD2 dual enzymatic activity. SETD2 "*is a dual-function methyltransferase for histones and microtubules and plays an important role for transcriptional regulation, genomic stability, and cytoskeletal functions*" (PMID: 32710489); it has "*chromatocytoskeletal activity, methylating both histones and microtubules*" (PMID: 32620673).

Chromatin arm (H3K36me3). As the sole somatic H3K36me3 writer, SETD2 loss reduces transcriptional fidelity (allowing cryptic transcription), impairs co-transcriptional splicing, and compromises DNA repair and genomic stability. In the brain, the **H2A.z–Setd2–H3K36me3 axis** drives neurogenesis: "*H2A.z regulates embryonic neurogenesis by targeting Nkx2-4 through interaction with Setd2, thereby promoting H3K36me3 modification to activate the transcription of Nkx2-4*" (PMID: 29294103).

Cytoskeletal arm (α-TubK40me3). SETD2 methylates α-tubulin at Lys40; this mark is enriched in mouse cortex at E14–E16 and is required for neuronal migration: "*Knockdown of α-tubulin methyltransferase SETD2 at E14 leads to the defects in neuronal migration, which could be restored by overexpressing either a cytoplasm-localized SETD2 truncation or α-TubK40me3-mimicking mutant*" (PMID: 34226540). Loss also degrades spindle integrity: "*SETD2 is a dual-function methyltransferase important for methylation of histone H3 at lysine 36 and α-tubulin in spindle microtubules*" (PMID: 41827754), producing chromatin bridges, micronuclei, and

aneuploidy. The α-TubK40me3 regulatory triad comprises writer SETD2, reader PBRM1, and eraser KDM4A (PMID: 41171906); a Drosophila Set2 E741Q model confirms spindle defects (PMID: 38290049).

Candidate overgrowth mechanism. In one LLS case, patient cells "*showed enhanced tyrosine phosphorylation and transcriptional activity of signal transducer and activator of transcription 5b (STAT5b) and increased IGF-1 expression induced by GH*" (PMID: 33248444), implicating a GH→STAT5b→IGF-1 axis in postnatal overgrowth (single case; not yet generalized).

Suggested ontology terms: - **GO (BP):** histone H3-K36 trimethylation (GO:0010452); DNA repair (GO:0006281); microtubule cytoskeleton organization (GO:0000226); mitotic spindle organization (GO:0007052); neuron migration (GO:0001764); regulation of transcription elongation. - **GO (CC):** nucleus (GO:0005634); chromatin (GO:0000785); microtubule (GO:0005874); mitotic spindle (GO:0072686). - **CL:** neuron (CL:0000540); cortical projection neuron; radial glial/neural progenitor cell (CL:0000047). - **CHEBI:** S-adenosyl-L-methionine (CHEBI:15414, methyl donor).

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7. Anatomical Structures Affected

- **Organ/system level:** Central nervous system (primary) — cerebral cortex; brain (UBERON:0000956, UBERON:0000955), reflected in ID, ASD, seizures, and posterior-fossa Chiari I malformation. Skeletal system — macrocephaly, tall stature, advanced carpal ossification, rare condylar hyperplasia. Integument — naevi, hirsutism. Endocrine/growth axis — candidate GH/IGF-1 involvement.
- **Tissue/cell level:** Nervous tissue (cortical neurons, neural progenitors CL:0000047); connective tissue laxity (joint hypermobility).
- **Subcellular level:** Nucleus/chromatin (H3K36me3) and microtubule/mitotic spindle (α-TubK40me3).
- **Localization/lateralization:** Bilateral/systemic; no lateralization (condylar hyperplasia notably reported as bilateral, PMID: 40892041).

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8. Temporal Development

- **Onset:** Congenital-to-pediatric; overgrowth is characteristically **postnatal** (not prenatal). Developmental delay and behavioral features emerge in early childhood.
- **Progression:** Chronic, lifelong; core neurodevelopmental features are generally stable/non-progressive. No relapsing-remitting course; not a repeat-expansion disorder (no genetic anticipation).
- **Critical periods:** Embryonic cortical neurogenesis and neuronal migration (mouse E14–E16 equivalents) represent the mechanistic windows of vulnerability.

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9. Inheritance and Population

- **Epidemiology:** Ultra-rare — ~50 reported patients (PMID: 40104911); Orphanet prevalence <1/1,000,000 (ORPHA:457485). Precise incidence unknown.
- **Inheritance:** Autosomal dominant; near-universally *de novo*. Chen (2021) "*manually curate[d] 17 SETD2 de novo variants in 17 individuals from published literature*" (PMID: 33766796).
- **Penetrance/expressivity:** High penetrance with variable expressivity, from mild (no neurological symptoms, PMID: 33248444) to classic severe.
- **Recurrence risk:** Low for parents of an affected child (*de novo*), with a residual caveat for gonadal mosaicism.
- **Founder effects / consanguinity / carrier frequency:** None established; not a recessive/carrier disorder.
- **Demographics:** No ethnic predilection, geographic clustering, or clear sex bias; both sexes affected.

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10. Diagnostics

- **Recommended approach:** Molecular confirmation of a heterozygous pathogenic/likely-pathogenic *SETD2* variant.

- **Sequencing:** Trio **whole-exome (WES)** or **whole-genome (WGS)** sequencing; overgrowth/intellectual-disability **multigene panels** (which include *SETD2* alongside *NSD1*, *EZH2*, *NFIX*, *DNMT3A*, *PTEN*, etc.). Macrocephaly/ASD panels have detected pathogenic variants in such cohorts (PMID: 40282429).
- **Chromosomal microarray (CMA):** Detects 3p21.31 deletions encompassing *SETD2* (PMID: 27385966).
- **Epigenomic diagnostics:** The **SETD2 EpiSign DNA-methylation episignature** supports diagnosis and VUS reclassification — "*DNA methylation study by EpiSign assay confirmed the presence of an episignature profile compatible with SETD2-related disorders*" (PMID: 40104911).
- **Supportive workup:** Growth charts (macrocephaly/tall stature), skeletal survey (advanced bone age), brain MRI (Chiari I), EEG if seizures, developmental/ASD assessment.
- **Differential diagnosis:** Other Sotos-like epigenetic overgrowth syndromes — Sotos (*NSD1*), Weaver (*EZH2*), Malan (*NFIX*), Tatton-Brown-Rahman (*DNMT3A*), Beckwith-Wiedemann (11p15 imprinting), and PTEN hamartoma tumor syndrome. LLS is explicitly placed here: "*The SETD2 gene encoding a H3K36 trimethyltransferase is implicated in Sotos-like syndrome*" (PMID: 31643139).
- **Screening:** No newborn or carrier screening (de novo dominant); molecular testing is diagnostic, not screening.

11. Outcome / Prognosis

- **Survival/mortality:** Life expectancy is not clearly reduced in classical LLS; no disease-specific mortality data published.
- **Morbidity/function:** Driven by ID, ASD, and behavioral difficulties affecting communication, education, independence, and caregiver burden; obesity and Chiari I add complications.
- **Disease course:** Chronic, lifelong, generally stable neurodevelopmental features.
- **Tumor risk (uncertain):** SETD2 is a canonical tumor suppressor — "*SETD2 is the only known enzyme that catalyzes H3K36me3 in somatic cells and is implicated in tumor suppression across multiple cancer types*" (PMID: 40948406) — and a constitutional multi-tumor case exists, prompting discussion that "*given the implication of somatic SETD2 variants in benign and malignant tumors, the implication of these SETD2 constitutional*

variants in tumorigenesis is discussed" (PMID: 40104911). However, classical LLS cohorts have **not** established elevated cancer risk, and surveillance is **not** standardized.

- **Prognostic factors:** Variant type/position may influence severity (LoF → LLS overgrowth; codon-1740 → severe growth-restricted RAPAS/MRD70).

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12. Treatment

There is **no disease-specific or curative therapy**; management is supportive and multidisciplinary.

- **Developmental/rehabilitative:** Early intervention; speech, occupational, and physical therapy (NCIT rehabilitation-intervention terms).
- **Behavioral/ASD:** Behavioral therapy; pharmacologic management of aggression when indicated.
- **Neurological:** Anti-seizure medication for epilepsy; neurosurgical evaluation for symptomatic Chiari I malformation.
- **Metabolic:** Obesity prevention/nutritional management — "*prevention of obesity should be an important point of attention for patients diagnosed with a SETD2-related overgrowth syndrome*" (PMID: 29681085).
- **Advanced/experimental therapeutics:** No gene, RNA-based, cell, or targeted therapies are available or in clinical trials for LLS.
- **Pharmacogenomics:** No LLS-specific pharmacogenomic guidance.

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13. Prevention

- **Primary prevention:** Not applicable for a *de novo* dominant disorder.
- **Genetic counseling:** Convey typically low recurrence risk (with a caveat for possible parental gonadal mosaicism). Prenatal or preimplantation genetic testing is possible when a familial variant is known.
- **Secondary/tertiary prevention:** Developmental surveillance, obesity prevention, and management of complications (seizures, Chiari I).
- **Screening:** No population or newborn screening; cascade testing generally not applicable.

14. Other Species / Natural Disease

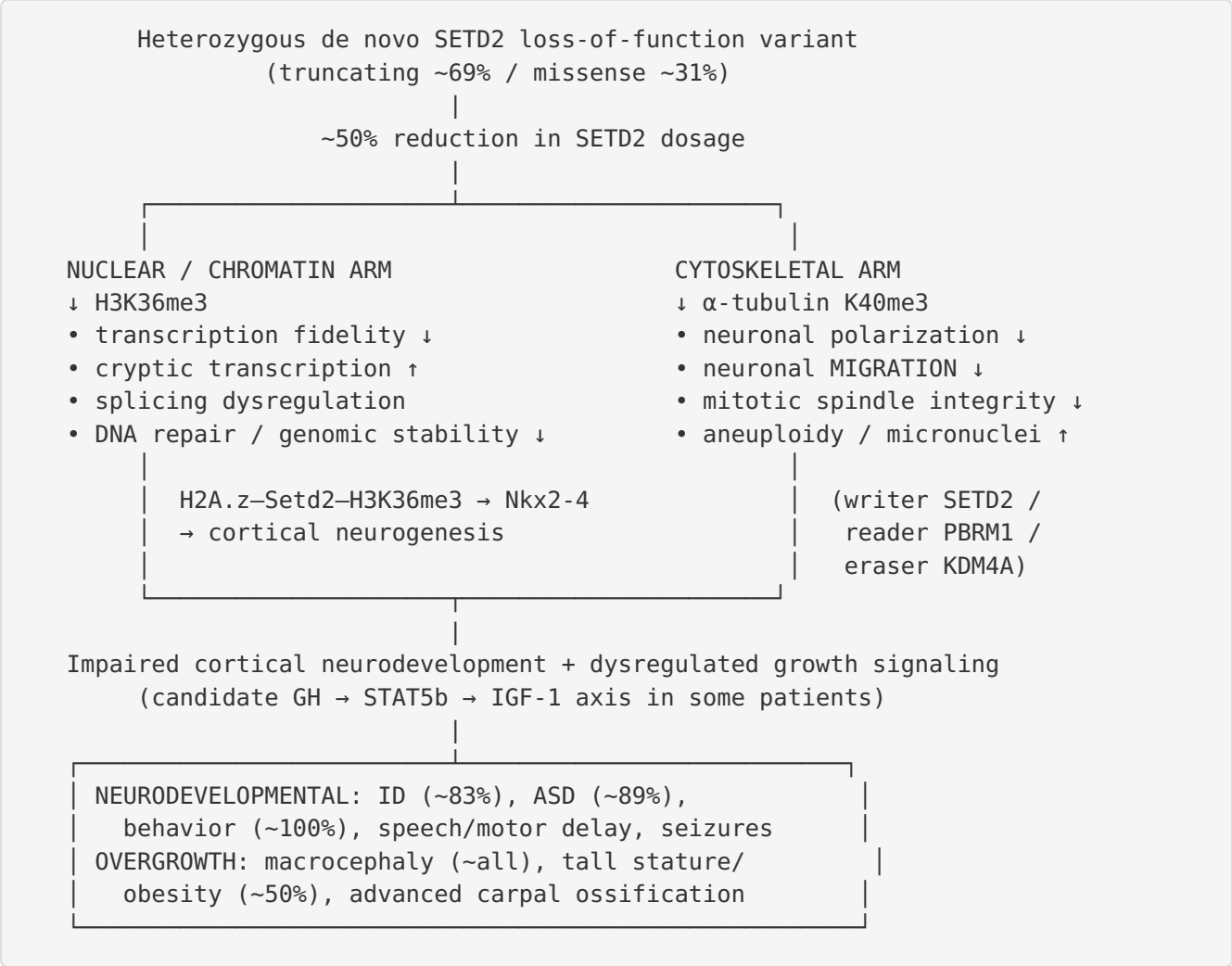
- **Orthologs:** *SETD2* is highly conserved — mouse *Setd2*, zebrafish *setd2*, Drosophila *Set2*, yeast *Set2*.
- **Natural disease:** No well-characterized naturally occurring animal equivalent of LLS is documented (no established OMIA entry); disease relevance is through engineered models.
- **Comparative biology:** The H3K36me3 methyltransferase function is deeply conserved: in zebrafish "*Setd2 is the only enzyme that catalyzes histone H3 lysine 36 trimethylation (H3K36me3) on virtually all actively transcribed protein-coding genes*" (PMID: 33088589); tumor-suppressor and spindle functions are conserved from Drosophila (PMID: 38290049) to mammals.
- **Zoonotic/transmission:** Not applicable (genetic disorder).

15. Model Organisms

Model	System	Key finding	Relevance to LLS	PMID
Mouse constitutive KO	Mammalian	Embryonic lethal (vascular/mesodermal defects)	Confirms essentiality; requires conditional/ het models	(established)
Mouse H2A.z brain-specific deletion	Mammalian	H2A.z–Setd2–H3K36me3 → *Nkx2-4* drives neurogenesis; deletion → cortical neurogenesis defects, abnormal dendrites, learning/memory deficits	Models neurodevelopmental arm	29294103
Mouse in-utero SETD2 knockdown (E14)	Mammalian	Neuronal migration defects; rescued by cytoplasmic SETD2 / α-TubK40me3 mimic / Taxol	Models cytoskeletal (migration) arm	34226540
Zebrafish *setd2*	Vertebrate	Sole H3K36me3 writer on transcribed genes; essential in development	Validates enzyme uniqueness	33088589
Drosophila *Set2* E741Q	Invertebrate	↓ H3K36me3 + mitotic-spindle defects	Models spindle/ genomic-stability arm	38290049

Model characteristics / limitations: Constitutive knockouts are embryonic lethal and cannot model the heterozygous adult phenotype; most models isolate one mechanistic arm (chromatin *or* cytoskeleton); behavioral and overgrowth features are not yet co-recapitulated in a single dose-accurate mammalian model. **Resources:** MGI (*Setd2*), ZFIN (*setd2*), FlyBase (*Set2*).

Mechanistic Model / Interpretation



Upstream → downstream logic: The *SETD2* LoF variant is the single upstream trigger. Its two enzymatic outputs (H3K36me3 and α-TubK40me3) act as parallel intermediate nodes. The chromatin arm predominantly explains transcriptional/growth dysregulation and neurogenesis defects; the cytoskeletal arm explains neuronal migration and mitotic phenotypes. Both converge on the developing cerebral cortex, yielding the combined overgrowth-plus-neurodevelopmental picture. The codon-1740 growth-restricted disorders (RAPAS/MRD70) at the same locus arise via a distinct (non-LoF) mechanism, showing that dosage and mechanism dictate divergent outcomes.

Evidence Base

PMID	Title (abbrev.)	Evidence type	Supports section(s)
26084711	*SETD2 mutation in a child with autism, ID, epilepsy* (Lumish 2015)	Human clinical (first case)	1, 2, 4
31643139	*SETD2-related overgrowth: four new patients + review* (Marzin 2019)	Human clinical (cohort n=13)	1–4, 10
32710489	*Genotype-phenotype at codon 1740 of SETD2* (Rabin 2020)	Human clinical + mechanism	4, 6
40104911	*Abnormal DNA methylation → syndromic multiple-tumor phenotype*	Human clinical + epigenetics	1, 4, 9, 10, 11
33248444	*LLS case: enhanced GH signaling*	Human clinical + in vitro	3, 6, 9
37372360	*Clinical heterogeneity / three distinct entities*	Human clinical	1, 4
33766796	*Mutation pattern & genotype-phenotype of SETD2* (Chen 2021)	Human clinical (curation)	9
29681085	*Two novel cases expanding the phenotype*	Human clinical	12
27385966	*3p21.31 interstitial deletion*	Human clinical (CNV)	4, 10
40282429	*Macrocephaly/ASD gene-panel cohort*	Human clinical	10
40892041	*Bilateral condylar hyperplasia in LLS*	Human clinical (case)	3
29294103	*H2A.z deletion → cortical neurogenesis defects*	Model organism (mouse)	6, 15
33088589	*Setd2 sole H3K36me3 writer (zebrafish)*	Model organism	6, 14, 15
34226540	*α-TubK40me3 required for neuronal migration*	Model organism (mouse)	6, 15
32620673	*Chromatocytoskeletal co-regulation by methylation*	Review/mechanism	6
41827754	*SETD2 inhibition → genomic instability*	In vitro/mechanism	6

PMID	Title (abbrev.)	Evidence type	Supports section(s)
41171906	*KDM4A is the α-tubulin demethylase*	In vitro/mechanism	6
38290049	*Drosophila Set2 E741Q → spindle defects*	Model organism	6, 14, 15
40948406	*SETD2 tumor suppression (KRAS model)*	Model organism/ mechanism	11
40755378	*Setd2 + Kras → JMML, MEK-inhibitor sensitivity*	Model organism	11
41654133	*SETD2 L1609P (leukemia) disrupts activity*	In vitro/structural	11
37921122	*Cellular/molecular functions of SETD2 in CNS*	Review	6

Limitations and Knowledge Gaps

1. **Small sample size.** All clinical conclusions rest on ~50 reported patients (largest single cohort n=13); frequency estimates carry wide confidence intervals and possible ascertainment bias toward severe cases.
2. **No natural-history or registry data.** Adult trajectories, life expectancy, and validated quality-of-life metrics are undocumented.
3. **Tumor risk unresolved.** SETD2 is a tumor suppressor and a constitutional multi-tumor case exists, but LLS-cohort cancer risk and the value of surveillance are unknown.
4. **Mechanistic attribution.** The relative contribution of the chromatin (H3K36me3) versus cytoskeletal (α-TubK40me3) arm to specific human phenotypes has not been dissected in patients.
5. **Intra-LLS genotype–phenotype.** Beyond the codon-1740 dichotomy, predictors of severity within LLS (truncation position, residual protein) are unestablished.
6. **No dose-accurate mammalian LLS model.** Constitutive KO is lethal; a heterozygous/ knock-in model co-recapitulating overgrowth and behavior is lacking.
7. **Overgrowth driver.** The GH/STAT5b/IGF-1 finding is from a single case and not generalized.

Proposed Follow-up Experiments / Actions

1. **Establish an international LLS registry** to aggregate genotype, phenotype frequencies, growth trajectories, tumor events, and QoL — powering robust penetrance/expressivity and prognosis estimates.
2. **Generate a dose-accurate mouse model** (*Setd2* heterozygous LoF or patient-specific knock-in) and phenotype for macrocephaly, cortical lamination, dendritic morphology, and behavior.
3. **Refine and standardize the SETD2 EpiSign episignature** for VUS reclassification and test whether episignature features distinguish LLS from RAPAS/MRD70 or correlate with severity.
4. **Prospective tumor-surveillance pilot** in constitutional *SETD2*-variant carriers to quantify malignancy risk and evaluate whether imaging/biochemical screening is justified.
5. **Dissect the two mechanistic arms** using separation-of-function alleles in patient iPSC-derived cortical organoids/neurons to map which clinical features track with each activity.
6. **Interrogate the GH/STAT5b/IGF-1 axis** across multiple patients (serum IGF-1; GH-stimulated STAT5b phosphorylation) to test generalizability and druggability of the overgrowth driver.
7. **Systematic genotype–phenotype meta-analysis** of all published *SETD2* variants (LLS vs. MRD70 vs. RAPAS) to build a mechanism-aware variant-interpretation framework.

Consensus Answer

Luscan-Lumish syndrome (MONDO:0014916; OMIM #616831) is an ultra-rare, autosomal-dominant, near-universally *de novo* overgrowth and neurodevelopmental disorder caused by heterozygous loss-of-function variants in *SETD2*, the sole somatic H3K36 trimethyltransferase. SETD2 haploinsufficiency reduces two methyl marks — histone H3K36me3 (transcriptional fidelity, splicing, DNA repair) and α-tubulin K40me3 (neuronal migration and mitotic-spindle integrity) — producing postnatal overgrowth, macrocephaly, obesity, intellectual disability (~83%), autism (~89%), and behavioral difficulties (~100%). Diagnosis is molecular (trio WES/WGS or overgrowth-ID panels plus a SETD2 DNA-methylation episignature), and management is entirely supportive and multidisciplinary because no disease-specific or curative therapy exists.