

Lung Disease, Immunodeficiency, and Chromosome Breakage Syndrome (LICS) — Comprehensive Disease Characterization

MONDO: MONDO:0014984 · **OMIM:** #617241 · **Gene:** *NSMCE3* (*NDNL2* / *MAGEG1*) · **Category:** Mendelian, autosomal recessive

Summary

Lung Disease, Immunodeficiency, and Chromosome Breakage Syndrome (LICS) is an ultra-rare, autosomal-recessive Mendelian disorder caused by **biallelic missense mutations in *NSMCE3*** (also called *NDNL2* / *MAGEG1*), a subunit of the **SMC5/6 genome-maintenance complex**. The disease was first defined in 2016 by whole-exome sequencing of four children from two unrelated kindreds who died of severe pulmonary disease in infancy following viral pneumonia, with combined T- and B-cell immunodeficiency and constitutional chromosome breakage [PMID: 27427983](#). LICS belongs to an emerging "SMC5/6 complexopathy" spectrum alongside *NSMCE2*- and *SMC5*-related microcephalic primordial dwarfism.

The central molecular lesion is destabilization of the SMC5/6 complex: the pathogenic variants **p.Leu264Phe (c.790C>T)** and **p.Pro209Leu (c.626C>T)** abolish NSE3's binding to its partner subunits within the NSE1/NSE3/NSE4 module. Because NSE3 directly binds double-stranded DNA and this module is required to load SMC5/6 onto chromatin, the variants collapse a DNA-binding/loading function, producing defective homologous recombination, sensitivity to replication stress, chromosome rearrangements, and micronuclei. The resulting cellular phenotype is cell-intrinsic.

Clinically, the defining and most lethal feature is **viral-triggered diffuse alveolar damage / pediatric acute respiratory distress syndrome (PARDS)** that progresses to irreversible interstitial fibrosis, refractory to corticosteroids and to hematopoietic stem-cell transplantation (HSCT). The immunodeficiency is variable (T-cell predominant) and does not fully explain the

lung disease. Death typically occurs in infancy to early childhood, though extended survival to 6.5 years and a fatal case at 11 years have been reported. A plausible but **inferred** amplifying mechanism links constitutional chromosome instability (micronuclei/chromatin bridges) to cGAS-STING/type-I-interferon signalling driving pulmonary fibrosis — this branch has not been directly demonstrated in LICS lung tissue. No curative therapy exists; management is supportive with genetic counselling for at-risk families.

Section 1 — Disease Information

Overview. LICS is a Mendelian chromosome-instability (chromosome-breakage) syndrome characterized by the triad of (1) severe, often fatal early-childhood lung disease (ARDS/PARDS), (2) combined (predominantly T-cell) immunodeficiency, and (3) spontaneous chromosome breakage/rearrangements with micronuclei. It is caused by destabilization of the SMC5/6 complex through biallelic *NSMCE3* mutations [PMID: 27427983](#).

Key identifiers.

Resource	Identifier
MONDO	MONDO:0014984
OMIM	#617241 (Lung disease, immunodeficiency, and chromosome breakage syndrome, LICS)
Gene (OMIM)	<i>NSMCE3</i> 608243
HGNC gene	<i>NSMCE3</i>
Cytogenetic locus	15q13
Inheritance	Autosomal recessive

Synonyms / alternative names. LICS; Lung disease–immunodeficiency–chromosome breakage syndrome; SMC5/6 complex deficiency due to *NSMCE3*; NDNL2-related / MAGEG1-related chromosome breakage syndrome.

Information source. Knowledge is derived from aggregated disease-level resources (OMIM, Orphanet) and a small number of primary case reports/series totaling roughly a dozen genetically confirmed patients worldwide. This is **not** EHR/individual-patient-registry derived — the literature base is case reports and small kindred studies.

Section 2 — Etiology

Primary cause (genetic). LICs is a monogenic disorder caused by biallelic (homozygous or compound-heterozygous) missense mutations in *NSMCE3*, which encodes a non-SMC element of the SMC5/6 complex essential for the DNA-damage response and chromosome segregation [PMID: 27427983](#).

Genetic risk factors. The disease-causing alleles are the risk factors themselves: - **c.790C>T, p.Leu264Phe** (rs199905054; homozygous in the original and 2021 cohorts; OMIM variant 608243.0001) - **c.626C>T, p.Pro209Leu** (NM_138704.3; compound-heterozygous; OMIM variant 608243.0002)

Consanguinity and founder effects increase homozygosity risk, consistent with the recessive inheritance and the recurrence of p.L264F across kindreds. No established modifier genes are documented, though variable immunophenotype suggests unidentified modifiers or stochastic/environmental contributions.

Environmental risk / trigger factors. Although the underlying defect is constitutional, **viral respiratory infection is the principal environmental trigger** of the lethal lung disease. In the original cohort, fatal pulmonary disease followed viral pneumonia [PMID: 27427983](#); multiple viral infections were implicated in subsequent cases.

Protective factors. None established. No protective variants or lifestyle/dietary factors are known for this ultra-rare disorder.

Gene–environment interaction. The core GxE axis is **germline SMC5/6 destabilization × viral infection → ARDS**. SMC5/6 is itself a broad-spectrum antiviral restriction factor (Section 6); loss of complex function may impair control of viral episomes while the genome-instability phenotype sensitizes the host to infection-driven immunopathology. This interaction is plausible but mechanistically incompletely resolved.

Section 3 — Phenotypes

LICS phenotypes cluster into three domains. Suggested HPO terms are provided; frequencies are qualitative given the small cohorts.

Phenotype	Type	Onset	Severity / course	Frequency	Suggested HPO
Severe lung disease / ARDS (diffuse alveolar damage, PARDS)	Clinical sign / imaging-histopathology	Infancy–early childhood	Severe, rapidly progressive, irreversible; often fatal	Core (defining); near-universal in symptomatic cases	HP:0002878 (Respiratory failure); HP:0002090 (Pneumonia); HP:0006536 (Obstructive lung disease)
Interstitial pulmonary fibrosis	Physical/histopathological	After viral insult	Progressive	Frequent	HP:0002206 (Pulmonary fibrosis)
Combined immunodeficiency (T-cell predominant)	Laboratory abnormality	Infancy	Variable (severe to limited)	Variable	HP:0005354 (Combined immunodeficiency)
Decreased T-cell count / proliferation	Laboratory abnormality	Infancy	Variable	Common in original cohort	HP:0005403 (Decreased T cell count); HP:0012177
Impaired antibody responses	Laboratory abnormality	Infancy	Variable	Common	HP:0004313 (Decreased antibody level)
Recurrent/viral respiratory infections	Symptom	Infancy	Variable; may be absent	Variable	HP:0002788 (Recurrent respiratory infections)
Chromosome breakage / rearrangements, micronuclei, marker chromosomes	Laboratory (cytogenetic)	Congenital (constitutional)	Stable cellular trait	Universal	HP:0040012 (Chromosome breakage)
Hypoglycemia		Infancy	Variable		

Phenotype	Type	Onset	Severity / course	Frequency	Suggested HPO
	Laboratory abnormality			Reported (2021+)	HP:0001943 (Hypoglycemia)
Hepatomegaly	Clinical sign	Infancy	Variable	Reported (2021+)	HP:0002240 (Hepatomegaly)

Age of onset: neonatal to early-childhood; **severity:** severe for the lung phenotype, variable for immunodeficiency; **progression:** lung disease is progressive and irreversible once triggered.

Quality of life. Given infant/early-childhood lethality, the dominant QoL burden is respiratory failure requiring intensive care; formal QoL instruments (EQ-5D/SF-36) are not applicable/not reported.

Supporting evidence: "Four children from two unrelated kindreds died of severe pulmonary disease during infancy following viral pneumonia with evidence of combined T and B cell immunodeficiency" [PMID: 27427983](#); "the immunological abnormalities can be limited and do not fully explain the LICS phenotype" [PMID: 33741030](#).

Section 4 — Genetic / Molecular Information

Causal gene. *NSMCE3* (NDNL2 / MAGEG1), OMIM 608243, cytogenetic locus **15q13**, encoding a non-SMC element 3 subunit of the SMC5/6 complex. NSE3/MAGEG1 is the founding member of the MAGE (melanoma-associated antigen) protein family and partners with the NSE4 kleisin (EID-family) subunit [PMID: 22536443](#).

Pathogenic variants.

Variant (cDNA)	Protein	Zygosity	dbSNP / OMIM allele	Functional consequence
c.790C>T	p.Leu264Phe	Homozygous (original + 2021 cohorts)	rs199905054 / 608243.0001	Abolishes NSE3–NSE4 binding
c.626C>T	p.Pro209Leu	Compound-heterozygous	NM_138704.3 / 608243.0002	Abolishes NSE3 binding to both NSE4 and NSE1

Variant classification: Pathogenic (ACMG/AMP) — biallelic, co-segregating, functionally validated. **Variant type:** missense. **Allele frequency:** rare; p.L264F (rs199905054) present at very low frequency in population databases, consistent with a recessive hypomorph. **Origin:** germline. **Functional consequence:** **loss of function** via complex destabilization — patient cells show undetectable NSE3 protein with secondarily decreased SMC5 and SMC6, increased genotoxin sensitivity, and defective homologous recombination; non-homologous end joining and V(D)J recombination are normal [PMID: 27427983](#).

Chromosomal abnormalities (acquired, in patient cells). Karyotyping of peripheral lymphocytes showed **multiple de novo supernumerary marker chromosomes**, chromosome rearrangements, and **micronuclei** — hallmarks of constitutional chromosome instability rather than a single recurrent rearrangement.

Modifier genes / epigenetics. No validated modifiers or disease-specific epigenetic marks are reported. The variable immunophenotype hints at modifiers but none are mapped.

Complexopathy context. Three SMC5/6 subunits now map to distinct recessive disorders: *NSMCE3* → LICS; *NSMCE2* (MMS21) → primordial dwarfism/insulin resistance/gonadal failure [PMID: 25105364](#); *SMC5* (in-frame Arg372 deletion) → microcephalic primordial dwarfism with chromosomal instability and insulin resistance [PMID: 36627765](#).

Section 5 — Environmental Information

Environmental factors. No chemical/radiation/occupational exposures are implicated in disease causation (the cause is genetic). However, patient cells are hypersensitive to **genotoxic/replication-stress agents** in vitro, meaning DNA-damaging exposures would be expected to be poorly tolerated.

Lifestyle factors. Not applicable (disease manifests in infancy/early childhood).

Infectious agents. Viral respiratory infection is the dominant disease trigger. Fatal pulmonary disease followed viral pneumonia in the index cases [PMID: 27427983](#); multiple viruses have been implicated across cases. No single causative pathogen is required — the host SMC5/6 defect converts common viral infection into lethal immunopathology. Mechanistically relevant, SMC5/6 restricts episomal DNA viruses (e.g., HBV cccDNA) [PMID: 42793236](#).

Section 6 — Mechanism / Pathophysiology

Ordered causal chain

1. **Biallelic NSMCE3 missense mutation** (p.L264F and/or p.P209L) → **results in** loss/abolition of NSE3 binding to NSE4 (and NSE1 for P209L) within the NSE1/NSE3/NSE4 module [PMID: 27427983](#).
2. Loss of intra-module interactions → **leads to** destabilization of the whole SMC5/6 complex (undetectable NSE3; secondary loss of SMC5 and SMC6) [PMID: 27427983](#).
3. Because the NSE1/NSE3/NSE4 module **binds double-stranded DNA** and is required for chromatin loading, complex destabilization → **leads to** reduced SMC5/6 association with chromatin [PMID: 26446992](#).
4. Impaired SMC5/6 chromatin function → **results in** defective homologous recombination and reduced tolerance of replication stress / DNA damage [PMID: 27427983](#).
5. Defective HR/replication-fork maintenance → **leads to** chromosome rearrangements, supernumerary marker chromosomes, and **micronuclei** (constitutional chromosome instability) [PMID: 27427983](#).
6. **Branch A (immune):** chromosome instability + loss of SMC5/6 → **results in** impaired lymphocyte development/function → T-cell–predominant combined immunodeficiency (variable) [PMID: 27427983](#).
7. **Branch B (shared apoptosis):** SMC5/6 dysfunction → **triggers** p53-dependent apoptosis (demonstrated for SMC5 depletion in zebrafish, rescued by p53 co-deletion) [PMID: 36627765](#) — likely contributing to cell loss across tissues.
8. **Trigger:** viral respiratory infection in this sensitized host → **leads to** diffuse alveolar damage / PARDS.

9. Diffuse alveolar damage with hyaline membranes, alveolar septal thickening → **progresses to** early interstitial fibrosis and metaplastic squamous alveolar epithelium (autopsy findings) → **results in** irreversible respiratory failure and death [PMID: 33741030](#).
10. **Inferred amplifying branch (not demonstrated in LICs):** micronuclei/chromatin bridges → cytosolic DNA → **cGAS** → **2'3'-cGAMP** → **STING** activation → chronic type-I-interferon/pro-inflammatory signalling → **fibrotic remodeling** of lung [PMID: 36876871](#); [PMID: 42559700](#).
Caveat: a single-cell cGAMP-reporter study found genotoxic-stress cGAS activation is a rare event not driven primarily by micronuclei enrichment [PMID: 42629426](#).

Mechanistic detail by category

- **Molecular pathways:** SMC5/6-mediated DNA repair/replication-fork maintenance and homologous recombination; SUMO/ubiquitin regulation (NSMCE2 is the complex's SUMO E3 ligase); p53-dependent apoptosis downstream of complex failure; inferred cGAS-STING/type-I-IFN innate-immune signalling.
- **Cellular processes:** Cell-cycle/replication-stress response, homologous recombination (GO:0000724 double-strand break repair via homologous recombination), chromosome segregation (GO:0007059), apoptosis (GO:0006915), innate immune/inflammatory signalling (GO:0002376).
- **Protein dysfunction:** Loss-of-function via complex destabilization — a scaffolding/assembly defect rather than catalytic loss. NSE3 directly binds dsDNA within the NSE1/NSE3/NSE4 module; mutating this surface reduces DNA binding and chromatin association in fission yeast and causes genotoxin hypersensitivity/cell death [PMID: 26446992](#).
- **Immune system involvement:** Primary combined immunodeficiency (variable, T-cell predominant); SMC5/6 is also an antiviral restriction factor that transcriptionally silences episomal viral genomes — the **NSE1/NSE3 subcomplex alone is sufficient to inhibit transcription in vitro**, and NSMCE3 knockdown promotes HBV proliferation [PMID: 41825673](#); [PMID: 42793236](#).
- **Tissue damage mechanisms:** Viral-triggered diffuse alveolar damage → interstitial fibrosis (hyaline membranes, septal thickening, squamous metaplasia).
- **Suggested GO/CL terms:** GO:0000724, GO:0007059, GO:0006915, GO:0140374 (antiviral innate immune response); cell types CL:0000084 (T cell), CL:0000236 (B cell), CL:0002063 (type II pneumocyte), CL:0000066 (epithelial cell), CL:0000057 (fibroblast).

Section 7 — Anatomical Structures Affected

- **Primary organ:** Lung (UBERON:0002048) — alveoli (UBERON:0002299), alveolar septa, alveolar epithelium.
 - **Secondary / systemic:** Immune system / lymphoid organs (bone marrow, thymus, peripheral lymphoid tissue); liver (hepatomegaly, UBERON:0002107) reported in later cases.
 - **Body systems:** Respiratory system (primary); immune/hematopoietic system; chromosomal instability is a whole-organism cellular trait.
 - **Tissue/cell level:** Alveolar epithelium (type II pneumocytes, CL:0002063), interstitial fibroblasts (CL:0000057), T lymphocytes (CL:0000084), B lymphocytes (CL:0000236).
 - **Subcellular level:** Nucleus/chromatin (GO:0000785), chromosome (GO:0005694), micronucleus; DNA-repair machinery. SMC5/6 is a nuclear chromatin-associated complex.
 - **Localization / lateralization:** Lung involvement is bilateral and diffuse (diffuse alveolar damage).
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Section 8 — Temporal Development

- **Onset:** Congenital genetic defect; clinical onset in infancy to early childhood, typically precipitated **acutely/subacutely by viral infection**.
 - **Progression:** Lung disease is rapidly progressive and irreversible once diffuse alveolar damage is established, evolving to interstitial fibrosis. Chromosome instability is a stable constitutional cellular trait.
 - **Disease course:** Progressive respiratory decline culminating in fatal respiratory failure; immunodeficiency ranges from severe to clinically limited.
 - **Duration / outcome:** Frequently fatal in infancy to early childhood (death reported at ~11 and 15 months in some cases), with extended survival to **6.5 years** in one patient [PMID: 33741030](#) and a fatal case at **11 years** (Chen 2025, [PMID: 40728043](#)).
 - **Critical period / window for intervention:** Prevention/aggressive control of viral respiratory infection in early childhood is the plausible window; no intervention reliably halts established lung disease.
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Section 9 — Inheritance and Population

- **Inheritance:** Autosomal recessive (biallelic *NSMCE3*) [PMID: 27427983](#).
 - **Epidemiology:** Ultra-rare; only ~a dozen genetically confirmed patients described worldwide across a handful of kindreds. Formal prevalence/incidence are not established (too few cases); Orphanet-level "ultra-rare."
 - **Penetrance / expressivity:** The lung/chromosome-breakage phenotype appears highly penetrant in biallelic patients; immunophenotype shows **variable expressivity** (severe to limited) [PMID: 33741030](#).
 - **Anticipation:** Not applicable (not a repeat-expansion disorder).
 - **Founder effect / consanguinity:** Recurrence of homozygous c.790C>T p.L264F across unrelated kindreds suggests a possible founder allele; recessive inheritance implies a consanguinity contribution in some families.
 - **Carrier frequency:** Not formally established; expected very low given rarity.
 - **Population demographics / sex ratio / geography:** No established ethnic predilection, sex bias, or geographic clustering; cases reported from multiple regions. Sex ratio not established.
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Section 10 — Diagnostics

Cytogenetics / chromosome breakage testing. Karyotype of peripheral lymphocytes reveals chromosome rearrangements, **supernumerary marker chromosomes**, and increased micronuclei; cells show hypersensitivity to replication stress/DNA-damaging agents and defective homologous recombination (with normal NHEJ and V(D)J recombination) [PMID: 27427983](#). Micronucleus/chromosome-breakage assays and genotoxin-sensitivity testing are informative.

Immunologic work-up. Decreased T-cell numbers, decreased T-cell proliferative responses, and impaired antibody responses with **normal B-lymphocyte numbers** — a combined, T-cell-predominant immunodeficiency; may be limited in some patients [PMID: 27427983](#); [PMID: 33741030](#).

Laboratory: Hypoglycemia reported in later cases; monitor hepatic status (hepatomegaly).

Imaging / histopathology. Chest imaging shows diffuse interstitial/alveolar disease (ARDS/PARDS). Lung histopathology: **classic diffuse alveolar damage with hyaline membranes, extensive alveolar septal thickening, early interstitial fibrosis, and metaplastic squamous alveolar epithelium** — without evidence of ongoing infection at autopsy [PMID: 33741030](#).

Genetic testing (definitive). Whole-exome (or whole-genome) sequencing established the diagnosis in the index families [PMID: 27427983](#). Recommended approach: **WES/WGS** or a chromosome-instability/primary-immunodeficiency gene panel including *NSMCE3*; confirmatory single-gene *NSMCE3* sequencing for known familial variants; functional confirmation (*SMC5/6* protein levels, HR assays). Chromosomal microarray/karyotype supports the breakage phenotype but does not identify the point mutation.

Clinical criteria / differential diagnosis. No formal consensus criteria exist. Differentials: other chromosome-breakage/instability syndromes — **Nijmegen breakage syndrome, ataxia-telangiectasia, Fanconi anemia, Bloom syndrome, ICF syndrome** — and *SMC5/6* complexopathies (*NSMCE2*, *SMC5* — which instead present with microcephalic primordial dwarfism and insulin resistance, distinguishing them from LICS). The distinctive LICS combination is **lethal viral-triggered lung disease + chromosome breakage + variable combined immunodeficiency**.

Screening. Carrier/cascade testing for known familial *NSMCE3* variants; prenatal/preimplantation genetic testing feasible in families with an identified genotype.

Section 11 — Outcome / Prognosis

- **Prognosis:** Poor. Frequently fatal in infancy to early childhood from progressive respiratory failure. Reported survival spans death before 2–3 years in the original cohort to extended survival of 6.5 years and a fatal case at 11 years [PMID: 33741030](#); [PMID: 40728043](#).
- **Disease-specific mortality:** Lung disease is the principal cause of death.
- **Complications:** Respiratory failure, recurrent/severe viral infections, interstitial fibrosis, hypoglycemia, hepatomegaly.
- **Recovery potential:** Low — established lung disease is irreversible and refractory to corticosteroids; **HSCT failed to cure** a patient, indicating the lung phenotype is cell-intrinsic (not corrected by immune reconstitution) [PMID: 33741030](#).

- **Prognostic factors:** Severity/recurrence of viral respiratory infection and the degree of lung involvement drive outcome; immunodeficiency severity is variable and does not fully predict the lethal lung phenotype.

Section 12 — Treatment

No curative therapy exists. Care is supportive and largely ineffective at reversing the lung disease.

- **Pharmacotherapy:** Corticosteroids (e.g., methylprednisolone) have been used but did not prevent death [PMID: 33741030](#). Antimicrobial/antiviral prophylaxis and immunoglobulin replacement are reasonable for the immunodeficiency component (supportive; NCIT: Corticosteroid Therapy; Intravenous Immunoglobulin Therapy).
- **Advanced therapeutics: Hematopoietic stem-cell transplantation failed to cure a patient** — consistent with a cell-intrinsic, non-hematopoietic lung mechanism [PMID: 33741030](#) (NCIT: Hematopoietic Stem Cell Transplantation). No gene/RNA/targeted therapies are available or trialed.
- **Supportive / rehabilitative:** Intensive respiratory support (oxygen, mechanical ventilation) for ARDS/PARDS; nutritional and infection management.
- **Experimental:** None registered specifically for LICS.
- **Treatment strategy / personalized medicine:** Genotype-guided diagnosis enables genetic counselling and infection-avoidance strategies; no molecularly targeted therapy exists. Theoretically, modulating downstream inflammatory amplifiers (e.g., cGAS-STING/type-I-IFN) is a conceptual target but entirely unproven for LICS.

Section 13 — Prevention

- **Primary prevention:** Not possible for the genetic defect. The most actionable measure is **minimizing/aggressively managing viral respiratory infection** in affected children, given the viral trigger of lethal lung disease (routine immunizations and infection-control measures are reasonable, though unproven to prevent the phenotype).
- **Secondary prevention:** Early molecular diagnosis; vigilant monitoring and prompt treatment of respiratory infections.

- **Tertiary prevention:** Supportive respiratory care to manage complications (limited efficacy).
- **Genetic screening / counselling:** Carrier testing, cascade testing, and prenatal/preimplantation genetic testing for families with a known *NSMCE3* genotype; genetic counselling regarding 25% recurrence risk in autosomal-recessive inheritance.
- **Behavioral/public-health/environmental:** Infection-avoidance guidance for the family; avoid unnecessary genotoxic exposures given cellular hypersensitivity.

Section 14 — Other Species / Natural Disease

- **Taxonomy / orthologs:** *NSMCE3*/*NSE3* is evolutionarily conserved. Orthologs/paralogs are well studied in *S. pombe* and *S. cerevisiae* (*Nse3*), *Arabidopsis*, and zebrafish; the mammalian ortholog is *NSE3*/*MAGEG1* [PMID: 22536443](#).
- **Natural disease in other species:** No naturally occurring LICS-equivalent disease is documented in companion animals or wildlife (OMIA); LICS is a human Mendelian disorder.
- **Comparative biology:** *SMC5/6* function is deeply conserved; yeast *nse3* DNA-binding mutants show reduced chromatin association and genotoxin hypersensitivity/cell death [PMID: 26446992](#), and *smc5*-knockout zebrafish show microcephaly/short length with p53-dependent apoptosis rescued by p53 co-deletion [PMID: 36627765](#) — illustrating conservation of the apoptotic response to complex dysfunction.
- **Transmission / zoonotic potential:** Not applicable (non-infectious, genetic disease).

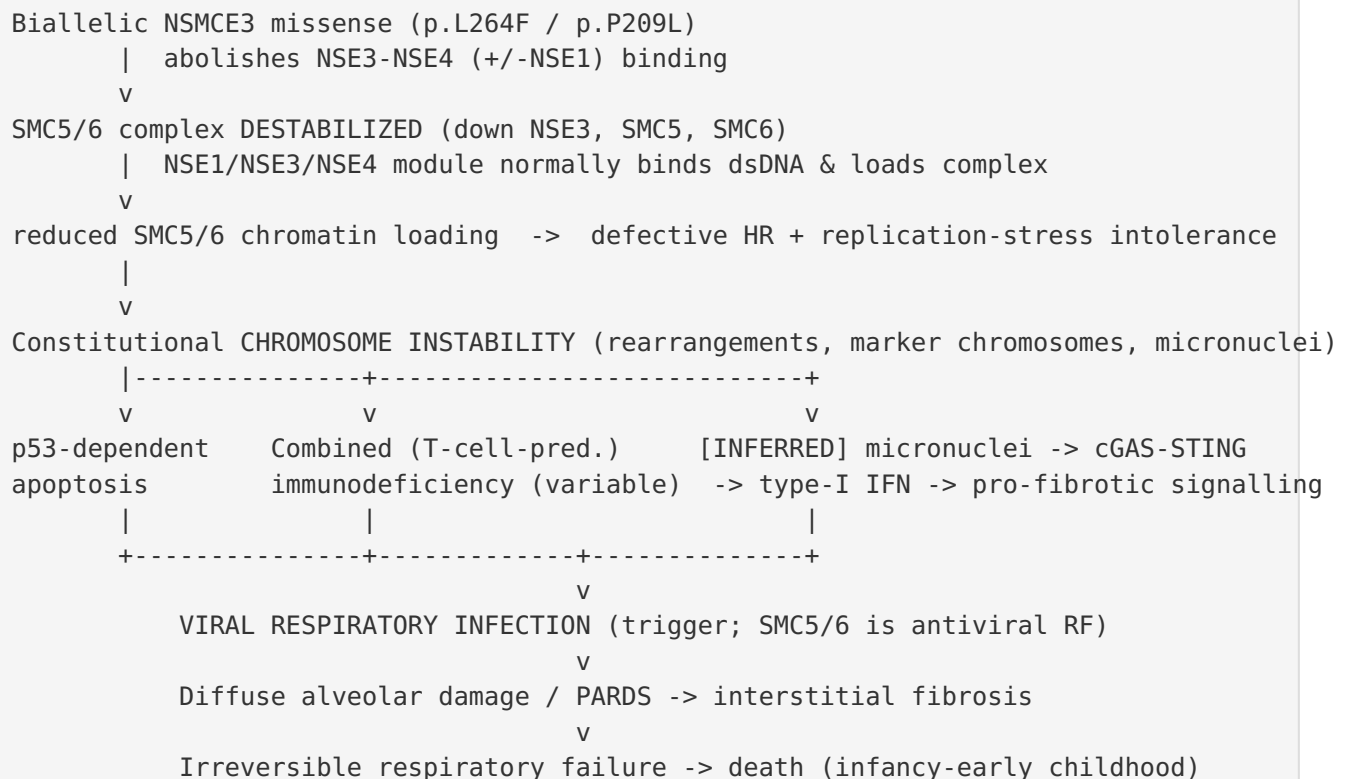
Section 15 — Model Organisms

- **Yeast (*S. pombe* / *S. cerevisiae*):** The foundational system for *NSE3* DNA-binding and chromatin-loading function. Hypomorphic *nse3* DNA-binding mutants show reduced *SMC5/6*–chromatin association and genotoxin hypersensitivity/cell death [PMID: 26446992](#) — directly relevant to the LICS loss-of-loading mechanism. Budding yeast illuminated *SMC5/6* regulation of *Sgs1*/*STR* recombination and SUMO-dependent control.
- **Zebrafish:** *smc5*-knockout reproduces microcephaly/short body length via **p53-dependent apoptosis** (rescued by p53 co-deletion) [PMID: 36627765](#) — a model for the *SMC5/6*

complexopathy spectrum (more directly for the SMC5/NSMCE2 dwarfism phenotypes than for LICS lung disease).

- **Cellular / in vitro:** Patient-derived cells are the principal LICS model, demonstrating undetectable NSE3 protein, secondary SMC5/SMC6 loss, defective HR, genotoxin hypersensitivity, chromosome rearrangements, and micronuclei [PMID: 27427983](#). In vitro reconstitution shows the NSE1/NSE3/NSE4 module binds dsDNA [PMID: 26446992](#) and the NSE1/NSE3 subcomplex suffices to inhibit transcription [PMID: 41825673](#).
- **Model limitations:** No dedicated mammalian model recapitulates the **viral-triggered lethal lung disease** that defines LICS; existing models capture chromosome-instability and apoptosis but not the pulmonary immunopathology. A conditional/humanized *Nsmce3* mouse challenged with respiratory virus is the key missing model.
- **Resources:** MGI, ZFIN, PomBase/SGD; Alliance of Genome Resources for orthology.

Mechanistic Model / Interpretation



The unifying interpretation is that a **scaffolding/assembly loss-of-function** in SMC5/6, driven by NSE3 destabilization, produces genome instability that is cell-intrinsic across tissues. Two phenotypic domains (immunodeficiency and chromosome breakage) are directly explained by impaired HR/genome maintenance in dividing cells. The **lethal lung phenotype is only partially explained** by the immunodeficiency (it is not corrected by HSCT, and immunodeficiency can be clinically limited), implying an additional cell-intrinsic lung-epithelial/fibrotic mechanism — for which the micronuclei → cGAS-STING → type-I-IFN → fibrosis axis is an attractive but **unproven, inferred** candidate. Viral infection is the universal clinical trigger, consistent with SMC5/6's dual role as both genome guardian and antiviral restriction factor.

Evidence Base

PMID	Title (abbrev.)	Role in this report
27427983	<i>Destabilized SMC5/6 complex leads to chromosome breakage syndrome with severe lung disease</i>	Primary/defining paper — identifies biallelic <i>NSMCE3</i> mutations, complex destabilization, clinical triad, cellular phenotypes
33741030	<i>New insights in phenotype and treatment of LICS</i>	Follow-up cohort (n=5): variable immunodeficiency, lung histopathology (DAD/fibrosis), HSCT failure, survival to 6.5 y
40728043	<i>Fatal lung disease caused by NSMCE3 mutation in an 11-year-old boy</i>	Extends age range of fatal disease to 11 years
26446992	<i>Chromatin association of SMC5/6 depends on NSE3 binding to DNA</i>	Mechanistic link — NSE3 DNA-binding module required for chromatin loading; mutants hypersensitive
22536443	<i>Analysis of the Nse3/MAGE-binding domain of Nse4/EID proteins</i>	NSE3/MAGEG1 identity and NSE4-kleisin partnership
36627765	<i>In-frame deletion of SMC5 — primordial dwarfism, instability, insulin resistance</i>	Complexopathy spectrum; p53-dependent apoptosis in zebrafish
25105364	<i>Hypomorphism in human NSMCE2 — primordial dwarfism and insulin resistance</i>	Complexopathy spectrum (differential diagnosis)
42793236	<i>The Multifunctional SMC5/6 Complex...Antiviral Restriction, and Human Disease</i>	SMC5/6 as broad-spectrum antiviral restriction factor
41825673	<i>Mechanism insights into Smc5/6 in HBV inhibition</i>	NSE1/NSE3 subcomplex suffices for transcriptional silencing
36592669	<i>Critical HBx residues for Smc5/6 interaction</i>	Viral evasion of SMC5/6 (host–virus axis)
36876871	<i>cGAS-STING signalling in cancer / chromosomal instability</i>	Supports inferred CIN→micronuclei→cGAS-STING axis
42559700		Links cGAS-STING/type-I-IFN to lung fibrosis (inferred branch)

PMID	Title (abbrev.)	Role in this report
	<i>Hyper-aging in systemic sclerosis — genome instability, inflammaging, fibrosis</i>	
42629426	<i>cGAMP reporter — cGAS activation by DNA damage</i>	Counter-evidence tempering the inferred micronuclei→cGAS branch

Limitations and Knowledge Gaps

1. **Extreme rarity.** Conclusions rest on ~a dozen patients across a few kindreds; no prevalence/incidence, penetrance, or carrier-frequency estimates are statistically robust.
2. **Lung mechanism unresolved.** The cell-intrinsic driver of lethal lung disease is not established. HSCT failure and limited immunodeficiency in some patients show the immune defect cannot fully explain the pulmonary phenotype.
3. **cGAS-STING branch is inferred, not demonstrated.** No study has shown cGAS-STING/type-I-IFN activation in LICS lung tissue, and single-cell data caution that micronuclei may not be the dominant cGAS activator [PMID: 42629426](#).
4. **No animal model of the lung phenotype.** Existing yeast/zebrafish/cell models capture genome instability and apoptosis but not viral-triggered lung immunopathology.
5. **No modifiers mapped** despite clear variable expressivity of immunodeficiency.
6. **No therapeutics.** All attempted treatments (corticosteroids, HSCT, supportive care) have failed to alter the lethal course.

Proposed Follow-up Experiments / Actions

1. **Generate a conditional/humanized *Nsmce3* (p.L264F) mouse** and challenge with respiratory virus to test whether lung epithelial SMC5/6 loss + viral trigger recapitulates diffuse alveolar damage/fibrosis.
2. **Directly test the cGAS-STING branch in LICS tissue:** measure cytosolic DNA, cGAMP, STING pathway activation, and type-I-IFN signatures in patient-derived lung organoids/airway epithelium and autopsy tissue; test STING/IFN inhibition for anti-fibrotic effect.

3. **Dissect cell-intrinsic lung epithelial vulnerability** using patient iPSC-derived alveolar type II cells under replication stress and viral infection.
 4. **Map modifiers of immunophenotype** via deeper genomic/transcriptomic profiling across the (small) patient set and unaffected carriers.
 5. **Define the antiviral-restriction contribution** of NSE3 loss to viral control in respiratory-relevant cells, linking SMC5/6's dual genome-guardian/antiviral roles to the infection trigger.
 6. **Establish an international LICS registry** to improve natural-history, prognosis, penetrance, and genotype–phenotype data.
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Evidence source legend: findings from [PMID: 27427983](#) and [PMID: 33741030](#) are **human clinical**; [PMID: 26446992](#), [PMID: 41825673](#), and [PMID: 22536443](#) are **in vitro / model organism (yeast)**; [PMID: 36627765](#) includes **zebrafish model** data; the cGAS-STING/fibrosis links ([PMID: 36876871](#), [PMID: 42559700](#), [PMID: 42629426](#)) are **extrapolated from other disease contexts** and flagged as inferred.

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