Spermatogenic Failure 16 (SPGF16) — Comprehensive Disease Report

Disease: Spermatogenic Failure 16 (SPGF16) · **Causal gene:** *SUN5* (SPAG4L / TSARG4) **OMIM:** 617187 · **MONDO:** MONDO:0014961 · **HGNC:** HGNC:16252 · **Category:** Mendelian (autosomal recessive)

Summary

Spermatogenic Failure 16 (SPGF16) is a non-syndromic, autosomal-recessive form of male infertility caused by biallelic loss-of-function variants in *SUN5* (also named SPAG4L or TSARG4), a testis-specific inner-nuclear-membrane LINC-complex protein. SPGF16 is the molecular-genetic designation for the most common genetic subtype of **acephalic spermatozoa syndrome (ASS)** — a severe teratozoospermia in which the ejaculate is dominated by headless ("decapitated") sperm tails, detached heads, and sperm whose heads and tails are joined by a fragile, abnormal junction. *SUN5* mutations are reported in roughly **33–47% of ASS cases**, making it the single most frequently identified cause of the syndrome.

Mechanistically, SUN5 is a SUN-domain protein that localizes to the base of the sperm head (the head–tail coupling apparatus, HTCA). It physically bridges the sperm nucleus to the proximal centriole/flagellum: its nucleoplasmic side binds the nuclear-membrane protein **LaminB1**, while its other side binds the cytoskeletal GTPase **Septin12** and cooperates with **CENTLEIN** and **PMFBP1**. In situ cryo-electron tomography shows SUN5 forms an extensive **hexagonal protein lattice** in the nuclear envelope at this junction. When SUN5 is absent, the Septin12-associated proximal centriole separates from the nucleus, the head–tail junction fails, and sperm heads detach from their tails during spermiogenesis or ejaculation — producing the acephalic phenotype. *Sun5*-knockout mice recapitulate the human disease, confirming a conserved, autosomal-recessive mechanism.

Clinically, SPGF16 presents as isolated primary male infertility. Affected men have **normal virilization, normal testicular volume, and normal endocrine function**; there are no systemic or syndromic features. Diagnosis rests on semen analysis and sperm morphology (H&E staining, transmission electron microscopy showing head–tail junction defects)

confirmed by *SUN5* sequencing (WES/Sanger) and absent SUN5 protein on immunofluorescence/Western blot. Because the defect is purely structural and the detached heads frequently contain intact genetic material, **intracytoplasmic sperm injection (ICSI) is an effective treatment**, with reported fertilization, embryo, and pregnancy rates that are favorable (one cohort: 81.5% fertilization, 81.8% good-quality embryos, 100% pregnancy among SUN5 patients). This report synthesizes 8 confirmed findings across 26 reviewed papers into a complete, section-by-section knowledge-base entry.

---

1. Disease Information

Overview. SPGF16 is a Mendelian, autosomal-recessive male infertility disorder. It is the genetic-nomenclature label (OMIM phenotype series "Spermatogenic failure") for *SUN5*-related **acephalic spermatozoa syndrome (ASS)**, a rare and severe teratozoospermia defined by a predominance of headless spermatozoa in the ejaculate. ASS is described as "a severe teratospermia with decaudated, decapitated, and malformed sperm, resulting in male infertility" (PMID: 38870534).

Key identifiers.

Resource	Identifier
OMIM (phenotype)	617187 (Spermatogenic failure 16)
MONDO	MONDO:0014961
Causal gene	*SUN5* (HGNC:16252; NCBI Gene 140732; Ensembl ENSG00000167098; UniProt Q8TC36)
Gene OMIM	*SUN5* 613942
ICD-10	N46 (male infertility) — no SPGF16-specific code
ICD-11	GB04 (male infertility) — no specific code
MeSH	Closest: "Infertility, Male"; "Teratozoospermia"

Synonyms: spermatogenic failure 16; SPGF16; spermatogenic failure type 16; SUN5 azoospermia; azoospermia caused by mutation in SUN5; *SUN5*-related acephalic spermatozoa syndrome; acephalic spermatozoa syndrome (ASS, when SUN5-caused); headless spermatozoa.

Information source. The knowledge base here is derived from **aggregated disease-level resources** (OMIM, MONDO, gnomAD) plus **individual-patient case reports and small cohort studies** (WES-based gene discovery and ICSI outcome cohorts, predominantly from China). There is no large EHR-derived dataset; the evidence is primarily case-level clinical/genetic literature plus mouse models.

---

2. Etiology

Primary cause — genetic. SPGF16 is caused by **biallelic (homozygous or compound-heterozygous) loss-of-function variants in *SUN5***. The landmark discovery study performed "whole-exome sequencing in two unrelated infertile men and subsequent variant filtering identified one homozygous (c.824C>T [p.Thr275Met]) and one compound heterozygous (c.1006C>T [p.Arg356Cys] and c.485T>A [p.Met162Lys]) SUN5 (also named TSARG4) variants" (PMID: 27640305). *SUN5* is the most frequently identified ASS cause: "Mutations in the SUN5 gene have been identified most frequently (33-47%) in ASS cases" (PMID: 38870534).

Genetic risk factors. The only established risk factor is inheritance of two pathogenic *SUN5* alleles. **Consanguinity** increases the risk of homozygosity — multiple reported cases arise from consanguineous or first-cousin unions (e.g., two infertile brothers of first-cousin parents, PMID: 40977202). No susceptibility loci or validated modifier genes have been established for SPGF16 specifically.

Environmental risk factors. None established. SPGF16 is a monogenic structural sperm defect; it is not attributable to toxins, lifestyle, occupational exposure, age, or infection. These classic male-infertility risk factors are not implicated in this Mendelian subtype.

Protective factors. None identified. Heterozygous carriers are fertile (recessive inheritance); a single wild-type allele is "protective" in the Mendelian sense, but there are no described protective variants or environmental protective factors.

Gene–environment interactions. No gene–environment interaction has been documented for SPGF16. The phenotype is driven by the genotype essentially deterministically (high penetrance in biallelic LoF).

3. Phenotypes

SPGF16 is **non-syndromic**: the phenotype is confined to the reproductive system. Affected men present with primary infertility and otherwise normal health.

Phenotype	Type	HPO term (suggested)	Characteristics
Male infertility	Clinical sign	HP:0003251 (Male infertility)	Post-pubertal/ congenital onset; severe; stable; ~100% of affected men
Acephalic/headless spermatozoa	Laboratory (semen) abnormality	HP:0012874 (Abnormal sperm morphology) / teratozoospermia	Predominant finding; severe
Abnormal sperm head–tail junction	Laboratory abnormality	HP:0012874	Fragile junction in the minority of "intact" sperm
Asthenozoospermia / abnormal motility	Laboratory abnormality	HP:0008669 (Abnormal spermatogenesis)	Detached tails may retain motility; whole-sperm motility impaired
Normal external genitalia / testicular volume	Normal finding (exclusionary)	—	Documented normal exam
Normal endocrine/ hormonal profile	Normal finding	—	FSH/LH/testosterone typically normal

Clinical documentation: "Male external genitalia developed normally, bilateral testicles were normal in volume, and bilateral epididymis and spermatic vein were palpated without nodules, cysts, and tenderness. Repeated semen analysis showed that a large number of immature sperm could be seen, and they had the ability to move" (PMID: 34393249). The core teratozoospermia is "decaudated, decapitated, and malformed sperm" (PMID: 38870534).

Onset / severity / progression / frequency. Onset is effectively **congenital** at the cellular level but **manifests post-pubertally** as infertility when reproduction is attempted. Severity is high (near-absolute natural infertility). The condition is **stable and non-progressive** — it does not worsen over time nor cause systemic morbidity. Frequency of the acephalic phenotype among affected men approaches 100% of sperm being abnormal.

Quality-of-life impact. The impact is confined to **reproductive function and its psychosocial consequences** (infertility-related distress, family planning burden). There is no physical disability, pain, or reduced life expectancy. No disease-specific QoL instrument (EQ-5D/SF-36) data exist for SPGF16; impact is inferred from the general infertility literature.

---

4. Genetic / Molecular Information

Causal gene. *SUN5* (Sad1 and UNC84 domain containing 5), aliases **SPAG4L** and **TSARG4**. HGNC:16252; NCBI Gene 140732; Ensembl ENSG00000167098; chromosome **20q11.21** (GRCh38 chr20:32,983,773–33,004,433); **13 exons**; **377-amino-acid** protein (UniProt Q8TC36); reference transcript **NM_080675**. *SUN5* encodes a testis-specific SUN-domain nuclear-envelope protein and a member of the LINC (Linker of Nucleoskeleton and Cytoskeleton) complex.

Pathogenic variant spectrum. Variants span **missense, frameshift, nonsense, splice-site, and large structural deletions**. Representative pathogenic alleles and their gnomAD v4 exome allele frequencies:

Variant (cDNA)	Protein	Class	gnomAD v4 AF
c.381del	p.Val128SerfsTer7	Frameshift (recurrent, most common)	3.97×10^{-5} (AC 58)
c.824C>T	p.Thr275Met	Missense	1.78×10^{-5}
c.1066C>T	p.Arg356Cys	Missense	1.73×10^{-5}
c.1067G>A	p.Arg356His	Missense	8.3×10^{-6}
c.1043A>T	p.Asn348Ile	Missense	1.87×10^{-5}
c.775G>A	p.Gly259Ser	Missense	5.5×10^{-6}
c.340G>A	p.Gly114Arg	Missense	2.7×10^{-6}
c.1072C>T	p.Arg358Ter	Nonsense	6.9×10^{-6}
c.485T>A	p.Met162Lys	Missense	—
c.1006C>T	p.Arg356Cys	Missense	—
c.829C>T	p.Gln277*	Nonsense	—
c.211+1insGT	splice	Splice-site	—
c.879dupC	p.(fs)	Frameshift	—
c.1073G>A	p.Arg358Gln	Missense	—
Large deletion (partial *EFCAB8*/*BPIFB2* + complete *SUN5*)	—	Structural (CNV)	—

The structural deletion was reported alongside a novel missense allele: "one novel homozygous missense mutation (c.775G>A; p.G259S) and one compound heterozygous including one reported missense mutation (c.1043A>T; p.N348I) and a large deletion that contains partial EFCAB8 … and BPIFB2 … and complete SUN5 (NM_080675)" (PMID: 34159570). Additional alleles include the homozygous c.879dupC frameshift (PMID: 40977202) and homozygous c.1073G>A (p.Arg358Gln) (PMID: 40740627).

Variant classification (ACMG/AMP). Pathogenic/likely pathogenic for biallelic LoF and recurrent hotspot missense alleles (notably codon 356/358). Classification criteria typically invoked: PVS1 (null variants), PM2_Supporting (rare in gnomAD), PP4 (phenotype match), PM3 (recessive, in trans), and functional evidence (absent sperm SUN5).

Allele frequency / origin. All pathogenic alleles are **rare germline** variants at carrier-level frequencies (AF ≤ ~4×10^{-5}). None are somatic. The recurrent frameshift c.381del is the most common.

Functional consequence. Loss of function — mutations abolish or destabilize SUN5 protein, eliminating the nucleus-to-flagellum anchor. Patient sperm show absent SUN5 on immunostaining/Western blot.

Constraint. gnomAD v4 shows *SUN5* is **LoF-tolerant** (pLI ≈ 0; observed/expected LoF = 0.82; LOEUF = 1.05; mis_z = 0.98; lof_z = 1.13). There is no depletion of heterozygous LoF alleles — exactly as expected for a gene whose only essential function is in recessive male fertility (gnomAD v4; context in PMID: 34159570).

Modifier genes / epigenetics / chromosomal abnormalities. No validated modifier genes. No disease-specific epigenetic mechanism described (SUN5 participates in nuclear mRNA recruitment/export in spermatogenesis, PMID: 39108207, but this is a normal function, not an epigenetic disease mechanism). The only "chromosomal abnormality" relevant is the large CNV deletion encompassing *SUN5* noted above.

---

5. Environmental Information

Environmental factors: None established. SPGF16 is a monogenic disorder; toxins, radiation, and pollution are **not applicable**. **Lifestyle factors:** None established (smoking, diet, alcohol are not causal for this Mendelian subtype). **Infectious agents: Not applicable** — no infectious trigger.

This section is essentially negative: SPGF16 is a purely genetic, structural sperm defect.

---

6. Mechanism / Pathophysiology

Ordered causal chain

1. **Biallelic LoF mutation in *SUN5* → leads to** loss or destabilization of the testis-specific SUN-domain protein SUN5 in developing male germ cells (demonstrated: absent SUN5 on patient sperm immunostaining).
2. **Absence of SUN5 at the sperm-head base → results in** failure to assemble the nuclear-envelope hexagonal lattice and head–tail coupling apparatus (HTCA) during spermiogenesis (demonstrated by cryo-ET; PMID: 41855266).
3. **Loss of the LaminB1–SUN5–Septin12 bridge → leads to** separation of the Septin12-associated proximal centriole from the nucleus (demonstrated in *Sun5*-KO mice; PMID: 38870534).
4. **Breakage of the head-to-tail junction → results in** mechanical uncoupling of the sperm head from the flagellum.
5. **During spermiogenesis/epididymal transit/ejaculation** → the fragile or absent junction **causes** the head and tail to detach → **acephalic (headless) spermatozoa** and detached heads in the ejaculate.
6. **Headless/malformed sperm cannot fertilize an oocyte naturally → results in** primary male infertility (the clinical manifestation of SPGF16).

Branch (downstream network): SUN5 acts within a multi-protein HTCA scaffold. The adaptor **CENTLEIN** links SUN5 to **PMFBP1**; in its absence "the absence of Centlein sets SUN5 and PMFBP1 apart, the former close to the sperm head and the latter in the decapitated tail" (PMID: 34389728). Other HTCA partners — **CCDC113**, **CCDC188**, **CEP250**, **TSGA10**, **SPATA20**, **SPATC1L**, **BRDT**, and **ZMYND15** (which interacts directly with SUN5) — cause overlapping ASS phenotypes when mutated, placing SUN5 at the hub of head–tail anchoring.

Mechanistic detail

- **Molecular pathways / complex:** LINC complex (SUN–KASH), nuclear-envelope–cytoskeleton coupling. SUN5 "connected the nucleus by interacting with LaminB1 and connected the proximal centriole by interacting with Septin12. The binding between SUN5 and Septin12 promoted their aggregation together in the sperm neck. The disruption of the LaminB1/SUN5/Septin12 complex by Sun5 deficiency caused separation of the Septin12-proximal centriole from the nucleus, leading to the breakage of the head-to-tail junction" (PMID: 38870534).

- **Cellular processes:** Spermiogenesis — nuclear-envelope remodeling, implantation-fossa/basal-plate formation, centriole–nucleus tethering. SUN5 dynamically relocates during germ-cell development: "In pachytene spermatocytes, it is located in a membranous compartment… In round spermatids, it progresses to the Golgi and the NE before to be located to the tail/head junction in epididymal sperm… Sun5 is not, as initially reported, facing the acrosome but is in fact excluded from this zone" (PMID: 25775128).
- **Protein dysfunction:** Loss of function of a SUN-domain transmembrane protein; truncating and destabilizing missense alleles eliminate the functional anchor. Structural data: "sperm-specific SUN5 localizes to the base of the head in human, mouse, and boar sperm. By applying in situ cryoelectron tomography, we find an extensive hexagonal lattice in the nuclear envelope in this region" (PMID: 41855266).
- **Tissue damage mechanism:** Mechanical failure (not inflammatory/ischemic) — the head–tail junction physically fractures.
- **Immune / metabolic involvement:** None.

Ontology suggestions

- **GO (biological process):** GO:0007283 spermatogenesis; GO:0007286 spermatid development; GO:0048515 spermatid differentiation; GO:0007097 nuclear migration; LINC-complex / nuclear-membrane tethering.
- **GO (cellular component):** GO:0005637 nuclear inner membrane; GO:0005635 nuclear envelope; GO:0034993 (SUN–KASH / LINC); sperm neck / head–tail coupling apparatus.
- **CL (cell type):** CL:0000018 spermatid; CL:0000017 spermatocyte; CL:0000019 sperm; CL:0000015 male germ cell.

---

7. Anatomical Structures Affected

- **Organ level (primary):** Testis (UBERON:0000473) — specifically the seminiferous tubules (UBERON:0001343) where spermiogenesis occurs; and the spermatozoon itself (UBERON:0000408 / CL:0000019). **Secondary:** none — no other organ is affected.
- **Body system:** Male reproductive system (UBERON:0000079) only.
- **Tissue / cell level:** Germinal epithelium of the seminiferous tubule; affected cells are **spermatids and spermatozoa** (CL:0000018 spermatid; CL:0000019 sperm). Somatic Sertoli/Leydig cells and the endocrine axis are unaffected (normal testosterone/testicular volume).

- **Subcellular level:** The lesion is at the **sperm head–tail coupling apparatus / neck**, at the interface of the **nuclear envelope / inner nuclear membrane** (GO:0005637), the **implantation fossa (basal plate)** of the nucleus, and the **proximal centriole**. GO cellular components: nuclear inner membrane (GO:0005637), nuclear envelope (GO:0005635).
- **Localization:** Site = base of the sperm head / sperm neck; systemic to essentially all sperm (not a lateralized anatomical defect). UBERON: sperm (UBERON:0000408); testis (UBERON:0000473).

---

8. Temporal Development

- **Onset:** Congenital at the molecular/cellular level (the defect is present from first spermatogenesis at puberty); **clinically recognized in adulthood** when infertility is investigated. Onset pattern is **chronic/insidious** (silent until reproduction attempted).
- **Progression: Stable, non-progressive.** There are no disease stages; the sperm defect is constant across the reproductive lifespan. Disease course is a **chronic, lifelong** structural infertility with no spontaneous remission.
- **Critical period:** The vulnerable window is **spermiogenesis** (round-to-elongating spermatid stage) when the HTCA is built. There is no developmental window for correction; the therapeutic "window" is at **assisted reproduction (ICSI)**, which bypasses the defect.

---

9. Inheritance and Population

- **Inheritance: Autosomal recessive.** Biallelic pathogenic variants are required; heterozygous carriers are fertile and asymptomatic. Consistent with gnomAD LoF-tolerance (pLI ≈ 0).
- **Penetrance:** Effectively **complete** for the sperm phenotype in biallelic LoF individuals.
- **Expressivity:** Relatively consistent (acephalic spermatozoa), though the proportion of headless vs. fragile-junction vs. malformed sperm varies between individuals.
- **Epidemiology:** ASS overall is **rare** (no precise prevalence/incidence figures; considered a rare form of severe teratozoospermia). Within ASS, *SUN5* accounts for **33–47%** of cases (PMID: 38870534). No cases-per-100,000 estimate is available.

- **Consanguinity / founder effects:** Consanguinity elevates homozygosity risk; several reported families are consanguineous. No classical founder haplotype is established, though the recurrent c.381del frameshift is the most common allele in gnomAD.
- **Carrier frequency:** Individual pathogenic alleles are rare (AF ≤ ~4×10^{-5}); aggregate carrier frequency is low but non-trivial given allelic heterogeneity.
- **Population demographics:** Most reported cohorts are **Han Chinese**, reflecting study ascertainment rather than proven ethnic predilection; cases also reported from Iran and elsewhere. **Sex:** affects males only (a reproductive phenotype); the genotype can be carried by either sex. **Age distribution:** reproductive-age men.

---

10. Diagnostics

Clinical / laboratory workup: - **Semen analysis + sperm morphology** (H&E staining): predominance of headless tails, detached heads, and malformed sperm; "a large number of immature sperm… they had the ability to move" (PMID: 34393249). - **Transmission electron microscopy (TEM):** demonstrates head–tail junction/HTCA defects and abnormal neck structures. - **Hormonal panel:** FSH, LH, testosterone — typically **normal**, distinguishing from hypogonadotropic/primary testicular failure. - **Physical exam / scrotal ultrasound:** normal testicular volume, no varicocele/obstruction. - **Immunofluorescence / Western blot: absent SUN5** in spermatozoa confirms the molecular defect.

Genetic testing: - **Single-gene / panel testing of *SUN5*** is first-line given its dominant contribution; targeted Sanger confirmation of candidate variants. - **Whole-exome sequencing (WES)** is the workhorse for discovery and for cases negative on *SUN5* (to assess *PMFBP1, TSGA10, CEP250, CCDC188, CCDC113, SPATA20, SPATC1L, BRDT, ZMYND15*). - **CMA / CNV analysis** is warranted because large deletions encompassing *SUN5* occur (PMID: 34159570). - Karyotyping/FISH/mtDNA/repeat-expansion testing: not specifically indicated for SPGF16 (karyotype normal in typical cases; useful to exclude other azoospermia causes).

Clinical criteria / differential diagnosis: Diagnosis = morphological ASS + biallelic *SUN5*. Differential includes other ASS genes (PMFBP1, TSGA10, CEP250, CCDC188, CCDC113, etc.), globozoospermia (DPY19L2 — round-headed, acrosome defect), MMAF, and obstructive/non-obstructive azoospermia. SUN5 is distinguished by its specific role at the head–tail junction (not the acrosome; PMID: 25775128) and its favorable ICSI prognosis.

Screening: No population newborn/carrier screening exists. **Cascade carrier testing** of relatives and partner carrier testing are reasonable once a proband's variants are known.

---

11. Outcome / Prognosis

- **Survival / mortality / morbidity:** SPGF16 has **no effect on survival, life expectancy, or physical health.** The only "morbidity" is **infertility** and its psychosocial burden.
- **Disease course:** Stable, lifelong infertility; no complications in the conventional medical sense.
- **Recovery / treatment response:** Natural fertility is essentially absent, but **ICSI yields favorable reproductive outcomes** (see Treatment). In a SUN5 cohort: "The rates of fertilization, good-quality embryos and pregnancy for five patients with SUN5 mutations following ICSI were 81.5%, 81.8% and 100%, respectively" (PMID: 29329387).
- **Prognostic factors:** The genetic cause predicts ICSI prognosis — *SUN5* and *PMFBP1*/*TSGA10* generally carry **favorable** ICSI outcomes, whereas some genes (e.g., *SPATA20* loss of function, proximal-centriole-deficient *TSGA10*, certain *CEP250*/*CCDC188* cases) may give poorer outcomes. Notably, not all SUN5 ICSI attempts succeed — two ICSI cycles failed to achieve pregnancy in one c.879dupC case (PMID: 40977202).

---

12. Treatment

There is no pharmacological cure; management is reproductive, centered on ICSI.

Intervention	Role in SPGF16	NCIT (suggested)	Evidence
Intracytoplasmic sperm injection (ICSI)	First-line; bypasses the structural defect by injecting a sperm head (or intact sperm) directly into the oocyte	NCIT:C92531 (Intracytoplasmic Sperm Injection)	Favorable outcomes (PMID: 29329387)
IVF with ICSI (ART)	Framework for ICSI	NCIT:C19829 (In Vitro Fertilization)	—
Genetic counseling	Inform recurrence risk, carrier/partner testing	NCIT:C15417 (Genetic Counseling)	—
Preimplantation genetic testing (optional)	Consider when both partners carry risk alleles	—	—

Pharmacotherapy / pharmacogenomics: Not applicable. **Gene/cell/RNA therapies:** None clinical; purely conceptual (the defect is germ-cell structural and not currently a gene-therapy target). **Surgical:** Sperm retrieval is generally unnecessary because sperm are present in the ejaculate (the problem is morphology, not count/azoospermia); standard ejaculate sperm are used for ICSI. **Experimental:** No SPGF16-specific registered trials identified.

Treatment outcome nuance: Because the detached head usually retains an intact nucleus, injecting it supports fertilization; however, selecting a sperm/head with an intact centriolar/genetic complement matters — mis-injection of a head plus detached tail produced fertilization failure in a related *CCDC188* case (PMID: 41004021), underscoring the importance of gene-specific prognosis.

13. Prevention

- **Primary prevention:** Not possible (congenital genetic). **Genetic counseling** for consanguineous couples and families with affected relatives is the principal preventive measure.
- **Secondary prevention / screening: Carrier screening** of partners and **cascade testing** of relatives once a proband's *SUN5* genotype is defined; **preimplantation genetic testing (PGT)** and **prenatal testing** are options for couples at recurrence risk.

- **Tertiary prevention:** ICSI to achieve pregnancy; counseling that affected/carrier status may be transmitted depending on partner genotype.
- **Immunization / behavioral / public-health / environmental / prophylaxis measures:** Not applicable — no environmental or infectious component.
- **Counseling (ontology):** NCIT:C15417 Genetic Counseling.

---

14. Other Species / Natural Disease

- **Taxonomy / orthologs:** Human *SUN5* has a mouse ortholog **Sun5** (NCBI Gene **76407**; MGI:**1923657**; Ensembl **ENSMUSG00000027480**). SUN5 protein localizes to the sperm-head base in **human, mouse, and boar (pig)** (PMID: 41855266), indicating evolutionary conservation of its function across mammals.
- **Natural disease in other species:** No naturally occurring *SUN5* ASS has been catalogued in OMIA for companion animals/livestock; the boar data are experimental/structural, and mouse data are from engineered knockouts.
- **Comparative biology:** The mechanism (head–tail anchoring via a SUN-domain LINC protein) is conserved; mouse knockouts faithfully reproduce the human phenotype (see §15). One caveat: for some *other* ASS genes mouse and human phenotypes diverge (e.g., *CEP250* knock-in mice show azoospermia rather than classic ASS; PMID: 39726222), but *SUN5* is concordant across species.
- **Transmission / zoonosis:** Not applicable.

---

15. Model Organisms

- **Model type:** Mammalian — **mouse (*Mus musculus*)** is the principal model.
- **Genetic models: Sun5-knockout mice** (constitutive null). At least two independent lines:
- Shang et al., 2017, *eLife* — "Essential role for SUN5 in anchoring sperm head to the tail" (PMID: 28945193).
- Zhang et al., 2024 — "we generated Sun5 knockout mice, which presented the phenotype of ASS," used to map the LaminB1–SUN5–Septin12 bridge (PMID: 38870534).

- **Phenotype recapitulation: High** — Sun5-null males reproduce human acephalic spermatozoa syndrome (sperm heads detached from tails), validating the causal mechanism.
- **Limitations:** Mice do not model the ICSI-specific clinical outcome variability seen in humans; most lines are constitutive nulls rather than patient-variant knock-ins, so allele-specific (missense) effects are less explored.
- **Applications:** Dissecting HTCA assembly, SUN5 interaction partners (LaminB1, Septin12, CENTLEIN, PMFBP1), and nuclear-envelope lattice architecture.
- **Resources:** MGI (Sun5, MGI:1923657); IMPC/IMSR for availability.

Mechanistic Model / Interpretation

```
Biallelic LoF in SUN5 (missense/frameshift/nonsense/splice/CNV)
         │  (loss of testis-specific SUN-domain protein)
         ▼
No SUN5 at sperm-head base  ──►  Hexagonal NE lattice & HTCA fail to assemble
         │                                    (cryo-ET; <a href="https://pubmed.ncbi.nlm.nih.gov
         ▼
LaminB1 – SUN5 – Septin12 bridge disrupted
         │                          ├── CENTLEIN/PMFBP1 mis-sorted (<a href="https://pubmed.ncbi
         ▼                          └── CCDC113/CCDC188/CEP250/ZMYND15 network destabilized
Septin12–proximal centriole separates from nucleus  (<a href="https://pubmed.ncbi.nlm.nih.gov/3
         ▼
Head-to-tail junction breaks
         ▼
Acephalic (headless) spermatozoa + detached heads in ejaculate
         ▼
Primary male infertility  ──►  rescued by ICSI (favorable outcomes; <a href="https://pubmed.ncb
```

Upstream vs downstream: The initiating lesion (upstream) is the *SUN5* mutation; the most proximal molecular consequence is failure of the nuclear-envelope LINC bridge; downstream are the structural head–tail breakage and the clinical infertility. SUN5 is a **hub** — many ASS genes converge on the same HTCA, so SUN5 loss both directly breaks the bridge and indirectly mislocalizes partner proteins.

Evidence Base

PMID	Title (abbrev.)	Role
27640305	*Biallelic SUN5 Mutations Cause Autosomal-Recessive Acephalic Spermatozoa Syndrome*	**Landmark** — establishes SUN5 causality; original variants
38870534	*SUN5 interacts with LaminB1 and Septin12…*	Core mechanism; 33–47% ASS; KO mouse ASS
41855266	*SUN5 forms a regular protein lattice…*	Cryo-ET hexagonal lattice; cross-species localization
34389728	*The missing linker between SUN5 and PMFBP1…*	Places SUN5 in HTCA (CENTLEIN/PMFBP1)
25775128	*Dynamics of Sun5 localization…*	Dynamic relocalization; excluded from acrosome
28945193	*Essential role for SUN5 in anchoring sperm head to the tail*	Foundational KO mouse
29329387	*…SUN5 mutations have a favorable pregnancy outcome from ICSI*	Treatment outcome data
34159570	*Novel Mutation and Deletion in SUN5…*	Structural deletion; LoF-tolerant constraint
34393249	*Genetic analysis of three ASS cases…*	Clinical exam/semen findings
39108207	*SUN5… recruitment/export of nuclear mRNA*	Additional SUN5 function
40977202, 40740627	Novel SUN5 variants (c.879dupC; c.1073G>A)	Expand variant spectrum; variable ICSI outcome
42522282, 39671309, 41004021, 39726222	ZMYND15/CCDC113/CCDC188/CEP250 ASS genes	Context: SUN5 as HTCA hub; differential genes

Consistency: All primary sources converge — SUN5 is the most common ASS gene, acts at the head–tail junction, is conserved in mouse models, and is ICSI-amenable. The principal nuance is **variable ICSI success** (most cohorts favorable; occasional failures), suggesting additional factors (e.g., centriole/genetic integrity of the injected head) modulate outcome.

Limitations and Knowledge Gaps

1. **Ascertainment bias:** Most cohorts are Han Chinese and small; true population prevalence, ethnic distribution, and carrier frequencies are not precisely quantified.
2. **ICSI outcome heterogeneity:** Reported rates are favorable but based on few patients; occasional failures (e.g., PMID: 40977202) indicate incomplete predictability. Prognostic biomarkers for ICSI success are undefined.
3. **Genotype–phenotype correlations:** Whether specific missense vs. truncating alleles predict ICSI prognosis or residual sperm quality is not resolved.
4. **Mechanistic completeness:** The full stoichiometry/architecture of the SUN5–LaminB1–Septin12–CENTLEIN–PMFBP1 complex and the exact developmental timing of junction failure are still being mapped.
5. **No standardized QoL or natural-history data** specific to SPGF16.
6. **Modifier genes/epigenetics:** None established; unexplored.

Proposed Follow-up Experiments / Actions

1. **Multi-center ICSI outcome registry** for *SUN5* ASS, stratified by variant class, to define prognostic predictors and quantify fertilization/live-birth rates with confidence intervals.
2. **Patient-variant knock-in mouse/organoid models** (e.g., p.Thr275Met, p.Arg356Cys) to test allele-specific effects beyond constitutive knockout.
3. **High-resolution structural studies** (cryo-ET/cryo-EM) of the complete HTCA lattice with and without SUN5 partners to refine the assembly model.
4. **Centriole/genome-integrity assessment of detached heads** to explain ICSI failures and develop sperm-selection criteria.

5. **Broaden population screening** (gnomAD-informed carrier panels) across diverse ancestries to estimate true carrier frequency and detect founder alleles.
6. **Functional validation pipeline** for VUS in *SUN5* (expression, localization, interaction assays) to support ACMG classification and clinical reporting.

Report compiled from 8 confirmed findings across 26 reviewed primary and secondary sources. Evidence types: human clinical/genetic (case reports, WES cohorts, ICSI outcome studies), model organism (Sun5-KO mouse), in vitro (co-IP/IF/WB), and structural/computational (cryo-ET, gnomAD constraint).
