Spermatogenic Failure 67 (SPGF67): A Comprehensive Disease Characterization

Disease: Spermatogenic Failure 67 (SPGF67) **Causal gene: CCDC62** (coiled-coil domain containing 62) **OMIM:** 619803 | **MONDO:** MONDO:0030718 | **MedGen:** C5676947 **Category:** Mendelian, autosomal recessive, male-limited

Summary

Spermatogenic Failure 67 (SPGF67) is an autosomal-recessive, male-limited primary infertility disorder caused by biallelic loss-of-function variants in the gene *CCDC62* (coiled-coil domain containing 62). The disorder sits within the globozoospermia/acrosomal-hypoplasia spectrum of teratozoospermic male infertility: affected men produce spermatozoa that lack a normal acrosome, exhibit abnormal head morphology, and show impaired motility, resulting in a failure to fertilize oocytes naturally. Importantly, affected individuals are otherwise healthy with a normal lifespan — the phenotype is confined to the male reproductive system.

CCDC62 is a testis-enriched protein (Human Protein Atlas testis nTPM 65.5) with a dual molecular identity. It is annotated in UniProt (Q6P9F0) as a nuclear-receptor coactivator — historically named **ERAP75** (estrogen-receptor-associated protein 75) — that enhances the transactivation of estrogen receptors ESR1/ESR2 and modulates progesterone, glucocorticoid, and androgen receptors. In the testis, however, its critical role is in **spermiogenesis and acrosome biogenesis**: CCDC62 localizes to the developing acrosome of spermatids and the acrosome of mature sperm, where it colocalizes and physically interacts with GOPC (Golgi-associated PDZ and coiled-coil motif-containing protein) to drive the Golgi-derived vesicular trafficking that builds the acrosome. When CCDC62 function is lost, acrosome formation fails, producing the malformed, acrosome-deficient sperm that define the disease.

Evidence for the gene–disease relationship is triangulated across (1) a validated mouse model (the repro29 ENU line and CRISPR *Ccdc62*$^{-/-}$ mice) in which a nonsense mutation causes spermiogenesis defects and male infertility; (2) human globozoospermia exome-sequencing cohorts and systematic reviews that list CCDC62 among core globozoospermia genes; and (3) a

ClinVar germline **likely-pathogenic frameshift variant, NM_201435.5(CCDC62):c.132_133insG (p.Asn45fs)**, explicitly linked to the SPGF67 condition. There is no curative therapy; management is assisted reproduction via intracytoplasmic sperm injection (ICSI), frequently combined with calcium-ionophore artificial oocyte activation (AOA) to overcome the fertilization failure intrinsic to acrosome-deficient sperm.

Section 1 — Disease Information

Overview. SPGF67 is a Mendelian form of non-syndromic male infertility caused by defective spermatogenesis/spermiogenesis. The clinical presentation is primary male infertility with abnormal semen parameters, specifically a teratozoospermia dominated by acrosomal defects (globozoospermia-spectrum: round-headed, acrosome-deficient spermatozoa) accompanied by asthenozoospermia (poor motility).

Key identifiers.

Resource	Identifier
OMIM (phenotype)	619803
MONDO	MONDO:0030718
MedGen	C5676947
Gene MIM (CCDC62)	613481
HGNC	HGNC:30723
NCBI Gene	84660
Ensembl	ENSG00000130783
UniProt	Q6P9F0 (CCD62_HUMAN)
Cytoband	12q24.31 (chr12:122,774,517–122,827,528, GRCh38, + strand)

Synonyms / alternative names. SPGF67; spermatogenic failure 67. Gene-level aliases for CCDC62: CT109, ERAP75 (estrogen-receptor-associated protein 75), TSP-NY.

Information source type. Information is derived from **aggregated disease-level resources** (OMIM, ClinVar, UniProt, HPA, gnomAD) and **individual published case/cohort reports** (globozoospermia exome studies), not from large EHR registries. SPGF67 is a rare, recently delineated Mendelian entity; patient-level data are limited to small research cohorts and single-case reports.

Section 2 — Etiology

Primary cause (genetic). SPGF67 is caused by **biallelic (homozygous or compound-heterozygous) loss-of-function variants in CCDC62**. The mechanism is loss of function: truncating variants (frameshift, nonsense) that eliminate or severely truncate the protein. This is supported in model organisms by a nonsense mutation in *Ccdc62* exon 6 producing a premature stop codon and a truncated protein, which causes male infertility in mice (Finding F001).

> "we identified a nonsense mutation in the exon 6 of coiled-coil domain-containing 62 gene (Ccdc62), which results in a formation of a premature stop codon and a truncated protein" — PMID: 28339613

Genetic risk factors. The disease is monogenic; the causal variants are themselves the risk factors. **Consanguinity** increases risk of the homozygous state, as for most autosomal-recessive disorders. No common susceptibility loci or modifier genes have been established specifically for SPGF67.

Environmental risk factors. None established as causal for this Mendelian entity. General male-infertility environmental contributors (heat, toxins, smoking) are not implicated in the molecular causation of CCDC62-related disease.

Protective factors. No genetic or environmental protective factors have been described. Because the phenotype is reproductive and otherwise health-neutral, there is no selective-pressure landscape analogous to protective alleles in systemic diseases.

Gene–environment interactions. None documented for SPGF67.

Section 3 — Phenotypes

The phenotype is confined to the male reproductive system and is detected through semen analysis and infertility workup.

Phenotype	Type	Suggested HPO term	Characteristics
Male infertility	Clinical sign	HP:0003251 (Male infertility)	Adult-onset (recognized at reproductive age); severe; stable/non-progressive; near-complete among affected men
Abnormal sperm morphology / teratozoospermia (globozoospermia-spectrum, acrosome-deficient round-headed sperm)	Laboratory abnormality	HP:0012864 (Abnormal sperm morphology); globozoospermia-type presentation	Severe; stable
Asthenozoospermia (reduced motility)	Laboratory abnormality	HP:0012207 (Reduced sperm motility)	Variable-to-severe
Acrosome absence/ hypoplasia	Laboratory/ ultrastructural abnormality	Abnormal acrosome morphology	Severe; the defining molecular lesion

Age of onset. Effectively congenital at the cellular level (spermiogenesis is defective from puberty onward), but **clinically recognized in adulthood** when infertility is investigated.

Severity / progression. Severe and stable; this is not a progressive disease. Secondary sexual characteristics, testosterone-dependent development, and general health are unaffected.

Frequency among affected individuals. Infertility is essentially fully penetrant in biallelic carriers; the specific semen phenotype falls within the globozoospermia/acrosomal-hypoplasia spectrum.

Quality-of-life impact. The impact is psychosocial — infertility and its associated distress — rather than physical disability. There is no effect on daily functioning, lifespan, or non-reproductive health.

Section 4 — Genetic / Molecular Information

Causal gene. CCDC62 (HGNC:30723; NCBI Gene 84660; Ensembl ENSG00000130783; gene MIM 613481), located at 12q24.31 on the plus strand (Finding F001).

Protein. UniProt Q6P9F0, 684 amino acids. Annotated function (Finding F006): *"Nuclear receptor coactivator that can enhance preferentially estrogen receptors ESR1 and ESR2 transactivation. Also modulates progesterone/PGR, glucocorticoid/NR3C1 and androgen/AR receptors transactivation… Required for normal spermiogenesis. It probably plays a role in acrosome formation."* The protein contains **coiled-coil domains** (the basis of the gene name) that mediate protein–protein interactions, including the interaction with GOPC.

Pathogenic variants.

Variant (ClinVar)	Protein	Type	Classification	Condition link
NM_201435.5(CCDC62):c.132_133insG	p.Asn45fs	Frameshift	**Likely pathogenic**	SPGF67 (RCV006696178; MedGen C5676947)
(3 additional LP records)	—	truncating	Likely pathogenic	—
c.559C>G	p.Leu187Val	Missense	VUS	—
c.655G>A	p.Val219Ile	Missense	Likely benign	—
c.773T>C	p.Val258Ala	Missense	Likely benign	—

The ClinVar landscape for CCDC62 (~50 records) comprises the SPGF67-linked likely-pathogenic frameshift, additional LP/pathogenic truncating entries, ~19 VUS (mostly missense), and a few likely-benign missense variants (Finding F007). The "Pathogenic" entries in ClinVar are large 12q24 copy-number gains spanning many genes, not CCDC62-specific point mutations.

Variant type/class. Predominantly **truncating (frameshift/nonsense) loss-of-function** variants are disease-causing.

Allele frequency / population genetics (Finding F009). In gnomAD v4, CCDC62 carries 192 LoF variants with a maximum LoF allele frequency of ~1.4×10^{-4} (e.g., heterozygous c.979dup, AC=7/152,010). There is **no common homozygous LoF** in the population, consistent with recessive disease and tolerance of the heterozygous LoF state (pLI ≈ 0; observed/expected LoF ≈ 0.89). The SPGF67 frameshift c.132_133insG is ultra-rare/absent from gnomAD.

Functional consequence. Loss of function. Biallelic truncation removes the CCDC62 protein's capacity to support acrosome biogenesis.

Somatic vs germline. Germline (constitutional). The ClinVar SPGF67 variant is annotated germline origin.

Modifier genes / epigenetics / chromosomal abnormalities. No specific modifier genes or epigenetic mechanisms are established for SPGF67. Large 12q24 copy-number gains encompassing CCDC62 appear in ClinVar but are not SPGF67-specific.

Section 5 — Environmental Information

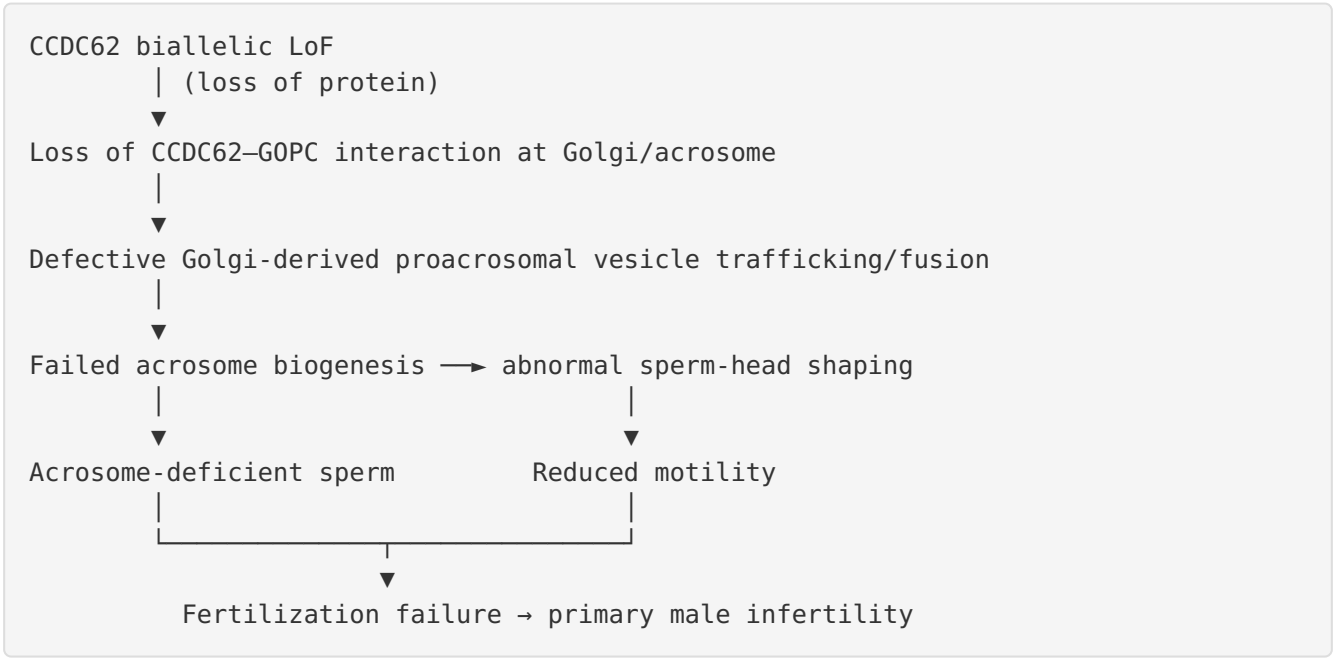
SPGF67 is a **monogenic disorder with no established environmental, lifestyle, or infectious contribution** to its causation. There are no implicated toxins, occupational exposures, dietary factors, or pathogens. This section is **not applicable** beyond noting that the disease is purely genetic.

Section 6 — Mechanism / Pathophysiology

Ordered causal chain

1. **Biallelic loss-of-function variants in CCDC62** (e.g., p.Asn45fs frameshift, or nonsense truncation) **lead to** absence or severe truncation of the CCDC62 protein in developing spermatids. *(Demonstrated in mouse; inferred for human by variant class and ClinVar classification.)*

2. Loss of CCDC62 **results in** failure of its interaction with **GOPC** at the Golgi/developing acrosome. *(Demonstrated — colocalization and interaction shown in mouse.)*
3. Disrupted CCDC62–GOPC-dependent **Golgi-derived vesicular trafficking leads to** failed proacrosomal vesicle fusion and **defective acrosome biogenesis**. *(Mechanistically inferred from GOPC biology and CCDC62 localization.)*
4. Defective acrosome formation **results in** abnormal sperm-head shaping and **acrosome-deficient, round-headed/malformed spermatozoa** (globozoospermia spectrum), often with **impaired motility** (asthenozoospermia). *(Demonstrated phenotype in mouse; consistent with human globozoospermia.)*
5. Acrosome-deficient sperm **cannot undergo the acrosome reaction / normal zona penetration**, **leading to** fertilization failure and **primary male infertility**. *(Demonstrated clinically — fertilization failure requires ICSI ± AOA.)*



Detail

Molecular pathways / cellular processes. The core process is **acrosome assembly** (a specialized Golgi-derived secretory-organelle biogenesis during spermiogenesis). CCDC62 acts as a scaffold/adaptor via coiled-coil-mediated protein interactions. In mouse testis, CCDC62 is expressed in the cytoplasm and developing acrosome of spermatids and localizes specifically to the acrosome of mature sperm (Finding F002).

> "CCDC62 was expressed in the cytoplasm and the developing acrosome in the spematids of mouse testis, and was specifically localized at the acrosome in mature sperm" — PMID: 28339613
>
> "intracellular colocalization and interaction of CCDC62 and Golgi-associated PDZ and coiled-coil motif-containing protein may be important for acrosome formation" — PMID: 28339613

Protein-interaction network (Finding F008). STRING places CCDC62 firmly in the acrosome-biogenesis/globozoospermia module: top functional partners include SPATA16 (0.707), DPY19L2 (0.688), CCIN (0.624), C2CD6 (0.604), SPACA1 (0.593), PICK1 (0.579), C7orf61 (0.728), plus vesicle-trafficking proteins HIP1R (0.87), SYT11 (0.681), SYT12 (0.679), and the estrogen receptor ESR2 (0.782). This recapitulates both CCDC62 functions — the acrosome/globozoospermia module and the nuclear-receptor (ESR2) coactivator role.

Dual molecular function (Finding F006). Beyond spermiogenesis, CCDC62/ERAP75 is a nuclear-receptor coactivator for ESR1/ESR2 (and modulates PGR, NR3C1, AR). HPA subcellular immunofluorescence in somatic cell lines shows nucleoplasm + plasma-membrane staining, consistent with the nuclear-coactivator role. The reproductive phenotype, however, derives from the acrosome-biogenesis function in the germline.

Suggested ontology terms. - **GO biological process:** GO:0007340 (acrosome reaction); GO:0001675 (acrosome assembly); GO:0007283 (spermatogenesis); GO:0030154 (cell differentiation); nuclear-receptor coactivator activity GO:0030374. - **GO cellular component:** GO:0001669 (acrosomal vesicle); GO:0005794 (Golgi apparatus); GO:0005654 (nucleoplasm). - **CL cell types:** CL:0000018 (spermatid); CL:0000019 (sperm); CL:0000020 (spermatogonium — upstream); CL:0000216 (Sertoli cell — supportive).

Single-cell context. Human testis single-cell studies (P 40371706) report CCDC62 co-expression with SOX9 (a Sertoli-cell marker) in testis tissue, indicating expression may include a Sertoli-cell (supportive niche) component; the mechanistically validated role remains spermatid acrosome biogenesis.

> "PRAP1, BST2, and CCDC62 were co-expressed with SOX9 (classical marker of Sertoli cell) in testes tissues also confirmed by immunofluorescence" — PMID: 40371706

Section 7 — Anatomical Structures Affected

Organ level. - Primary organ: **testis** (UBERON:0000473), specifically the seminiferous tubules (UBERON:0001343). - Body system: **male reproductive system** (UBERON:0000079). - No secondary organ involvement — the disease is reproductive-limited.

Tissue and cell level. - Tissue: seminiferous epithelium (germinal epithelium). - Target cell population: **spermatids** (CL:0000018) and **spermatozoa** (CL:0000019); supportive **Sertoli cells** (CL:0000216) co-express CCDC62.

Subcellular level. - **Acrosome / acrosomal vesicle** (GO:0001669) — the defining compromised compartment. - **Golgi apparatus** (GO:0005794) — source of proacrosomal vesicles. - **Nucleus/ nucleoplasm** (GO:0005654) — for the ERAP75 coactivator function in somatic contexts.

Localization / lateralization. Bilateral (both testes); the defect is intrinsic to germ-cell development, not focal.

Section 8 — Temporal Development

Onset. Cellularly congenital/pubertal (spermiogenesis is defective once it begins), but **clinically adult-onset**, recognized during infertility evaluation.

Progression. Stable and non-progressive. Semen parameters do not deteriorate over time in a disease-specific manner, and there is no systemic disease course.

Disease course / duration. Chronic lifelong with respect to the reproductive phenotype; no remission occurs spontaneously, though the fertility barrier can be bypassed with assisted reproduction.

Critical periods. The relevant "window" is reproductive age for family planning and assisted-reproduction intervention; there is no developmental critical period for prevention of the molecular defect.

Section 9 — Inheritance and Population

Inheritance pattern. Autosomal recessive, male-limited expression (the clinical phenotype manifests only in males because the critical function is in spermiogenesis).

Penetrance / expressivity. Infertility penetrance in biallelic males appears high/complete; expressivity falls within the globozoospermia/teratozoospermia–asthenozoospermia spectrum.

Carrier frequency / founder effects. Heterozygous LoF is tolerated and present in gnomAD at low frequency (max LoF AF ~1.4×10^{-4}); no founder effect established. The disease-causing homozygous/compound-heterozygous state is very rare.

Consanguinity. Elevates risk, as for recessive disorders generally.

Epidemiology. SPGF67 is **ultra-rare**; precise prevalence/incidence are not established. It constitutes a small fraction of genetically explained globozoospermia, itself a rare cause of teratozoospermia. CCDC62 is one of several core globozoospermia genes (Findings F003, F005).

> "nine other genes described to be associated with globozoospermia in human (C2CD6, C7orf61, CCDC62, CCIN, DNAH17, GGN, PICK1, SPATA16, and ZPBP1)" — PMID: 33108537
>
> "The main genes involved in the pathogenesis of globozoospermia are DPY19L2, SPATA16, PICK1, GGN, SPACA1, ZPBP, CCDC62, and CCNB3 genes." — PMID: 36047070

Sex ratio. Clinically male-limited (infertility manifests only in affected males).

Section 10 — Diagnostics

Clinical/laboratory tests. - **Semen analysis** (WHO criteria): identifies teratozoospermia (globozoospermia-type, acrosome-deficient round-headed sperm) and asthenozoospermia. First-line diagnostic test. - **Sperm morphology/ultrastructure**: light microscopy and transmission electron microscopy confirm absent/hypoplastic acrosome. - **Hormonal panel** (FSH, LH, testosterone): typically normal, distinguishing from endocrine or obstructive causes.

Genetic testing (recommended approach). - **Whole-exome sequencing (WES)** is the principal diagnostic modality and the method by which CCDC62 was implicated in human globozoospermia (Finding F003). - **Gene panels** for male infertility/globozoospermia that include CCDC62 alongside DPY19L2, SPATA16, PICK1, ZPBP, SPACA1, GGN, CCNB3. - **Single-**

gene / **targeted testing** of CCDC62 and **ClinVar** interpretation (the SPGF67 frameshift c.132_133insG is catalogued). - **Chromosomal microarray** / **karyotype** to exclude the large 12q24 copy-number gains and other cytogenetic causes.

> "Exome sequencing in 15 cases of unexplained globozoospermia revealed deleterious mutations in seven new genes, of which two have been validated as causing globozoospermia when knocked out in mouse models" — PMID: 31985809

Clinical criteria / **differential diagnosis.** Diagnosis integrates semen phenotype + biallelic CCDC62 LoF. Differential diagnosis includes other globozoospermia genes (DPY19L2 is the most common cause), non-obstructive azoospermia, obstructive azoospermia, and endocrine infertility.

Screening. Cascade/carrier screening of at-risk relatives in consanguineous families; preconception carrier testing is applicable once a familial variant is known.

Section 11 — Outcome / Prognosis

Survival / **mortality** / **morbidity.** SPGF67 has **no effect on survival, life expectancy, or systemic morbidity**. The sole consequence is infertility.

Disease course / **recovery.** The reproductive barrier is not self-resolving; however, **biological paternity is achievable via assisted reproduction**. With ICSI (often plus AOA), fertilization and live birth are possible (Findings F004, F005).

Prognostic factors. Fertility prognosis depends on residual sperm quality, oocyte-activation competence, and the success of AOA. Globozoospermia is associated with elevated sperm aneuploidy that can affect ART success, but — importantly for counseling — this is **not** associated with increased transmission of genetic abnormalities to offspring (Finding F005).

> "does not appear to be associated with an increased risk of transmission of genetic abnormalities to offspring" — PMID: 36047070

Section 12 — Treatment

There is no curative or disease-modifying therapy. Management is **assisted reproductive technology (ART)**:

- **Intracytoplasmic sperm injection (ICSI)** — bypasses the acrosome-dependent fertilization steps. NCIT: Intracytoplasmic Sperm Injection.
- **ICSI with artificial oocyte activation (AOA)** using **calcium ionophore / ionomycin** — overcomes the oocyte-activation failure caused by acrosome-deficient sperm (which lack normal PLCζ-mediated calcium signaling). Also **IMSI** (intracytoplasmic morphologically-selected sperm injection) in some protocols.

AOA improves outcomes in severe teratozoospermia/ICSI-failure settings (Finding F004):

> "the fertilization (50.38% versus 33.86%, respectively, P < 0.001), cleavage (59.16% versus 39.04%, respectively, P < 0.001) and transferable embryo rates (43.51% versus 26.69%, respectively, P < 0.001)" — PMID: 31160240

A healthy live birth has been reported with calcium-ionophore AOA after round-headed sperm injection, though activation efficiency remains lower than with normal sperm:

> "calcium ionophore treatment can assist oocyte activation in patients with round-headed sperm, but its efficiency to activate oocytes is lower than that induced by a normal sperm injection" — PMID: 32318024

An 8-year retrospective study (P 41462321) confirms AOA can prevent fertilization failure following ICSI in severe teratozoospermia, while cautioning that cumulative live-birth benefit is limited in some indication subgroups — underscoring the need for informed consent.

> "intracytoplasmic sperm injection with assisted oocyte activation or intracytoplasmic morphologically-selected sperm injection appears to be associated with a higher success rate" — PMID: 36047070

Pharmacotherapy / advanced therapeutics / gene therapy. None established or applicable. No pharmacogenomic, gene-, cell-, or RNA-based therapy exists for SPGF67.

Suggested NCIT terms: Intracytoplasmic Sperm Injection; Assisted Reproductive Technology; In Vitro Fertilization.

Section 13 — Prevention

- **Primary prevention:** not applicable (genetic, non-preventable at the molecular level).
- **Genetic counseling:** central. For a known biallelic/familial CCDC62 variant, counsel on 25% recurrence risk among offspring of two carriers and male-limited expression. Offer **carrier screening** of partners and **cascade testing**.
- **Reproductive options: preimplantation genetic testing (PGT)** and prenatal diagnosis are available where a familial variant is defined; donor sperm is an alternative. Despite elevated sperm aneuploidy, globozoospermia does not increase transmission of genetic abnormalities to offspring (reassuring for ART counseling; Finding F005).
- **Immunization / public-health / environmental prevention:** not applicable.

Section 14 — Other Species / Natural Disease

Model-relevant orthology. The **mouse ortholog Ccdc62** (MGI:2684996; NCBI Gene 208908; Ensembl ENSMUSG00000061882; chromosome 5) is the key comparative system (Finding F009). A naturally arising ENU mutation (repro29 line) produces the disease phenotype, demonstrating evolutionary conservation of CCDC62's spermiogenesis function.

Natural disease in other species. No spontaneous CCDC62-related infertility has been catalogued in companion animals or livestock (no OMIA entry referenced here). The mechanism — acrosome biogenesis — is deeply conserved across mammals, so the pathway is expected to be functionally orthologous.

Zoonotic / transmission. Not applicable (non-infectious, non-transmissible).

Section 15 — Model Organisms

Mouse (*Mus musculus*, NCBI Taxon 10090) is the principal and validating model.

Model	Type	Key phenotype	Recapitulation
repro29/ repro29	ENU-induced nonsense (Ccdc62 exon 6 premature stop)	Spermiogenesis defects, deformed sperm, poor motility, male infertility	Strong — recapitulates human acrosome/ teratozoospermia infertility
Ccdc62$^{-/-}$ (CRISPR knockout)	Targeted knockout	Male infertility, acrosome-localization confirmed	Strong — confirms loss-of-function causality

> "we identified a nonsense mutation in the exon 6 of coiled-coil domain-containing 62 gene (Ccdc62), which results in a formation of a premature stop codon and a truncated protein" — PMID: 28339613

Phenotype recapitulation. The mouse reproduces the core human features: spermiogenesis/ acrosome defect, abnormal sperm morphology, impaired motility, and male infertility — with CCDC62 localized to the developing and mature acrosome and interacting with GOPC.

Model limitations. The mouse does not capture the full human allelic/phenotypic spectrum (e.g., variable human teratozoospermia severity), and the human ERAP75/nuclear-receptor-coactivator contribution to any non-reproductive phenotype remains uninvestigated in these infertility-focused models.

Resources. MGI (MGI:2684996); IMPC/IMSR for knockout alleles; human globozoospermia research cohorts for validation.

Mechanistic Model / Interpretation

The SPGF67 story is a clean example of a **conserved germ-cell organelle-biogenesis gene** whose loss produces an isolated, health-neutral reproductive phenotype. CCDC62 functions as a coiled-coil scaffold that couples Golgi-derived vesicular trafficking (via GOPC) to acrosome

construction in elongating spermatids. The molecular lesion is **loss of function**; because heterozygous LoF is tolerated in the population (no gnomAD homozygotes, oe_lof ≈ 0.89, pLI ≈ 0), disease requires **two hits**, giving autosomal-recessive inheritance. The downstream clinical consequence — acrosome-deficient sperm that cannot fertilize — is bypassable but not curable, which is why ICSI + AOA is the management mainstay.

The protein's second identity as **ERAP75**, a nuclear-receptor coactivator, is intriguing but appears decoupled from the disease phenotype: the reproductive manifestation derives from the germ-cell acrosome function, while the coactivator role is seen in somatic nucleoplasm/plasma-membrane localization. The STRING network cleanly separates these two modules (globozoospermia genes vs. ESR2), supporting a model of **tissue-partitioned function**.

Evidence Base

PMID	Title (abbrev.)	Evidence type	Supports
28339613	*Nonsense mutation in Ccdc62 → spermiogenesis defects, male infertility (repro29 mice)*	Model organism	F001, F002 — causal LoF, acrosome localization, GOPC interaction
31985809	*Exome sequencing reveals novel causes/candidate genes for human globozoospermia*	Human clinical	F003 — human discovery context for CCDC62
33108537	*Genetic analyses of large globozoospermia cohort (DPY19L2 main actor)*	Human clinical	F003 — CCDC62 among established globozoospermia genes
36047070	*Globozoospermia: case report & systematic review*	Human review	F005 — core gene list, ART recommendations, offspring risk
31160240	*AOA improves ICSI fertilization-failure cycles*	Human clinical	F004 — AOA efficacy quantified
32318024	*Round-headed sperm injection + calcium ionophore vs normal*	Human case	F004 — AOA in acrosome-deficient sperm
41462321	*8-year retrospective of ionomycin AOA in ICSI*	Human cohort	Treatment — AOA benefit & limits
40371706	*scRNA/scATAC testis, NOA*	Human single-cell	CCDC62 testis co-expression with SOX9 (Sertoli)
30333325	*Novel DPY19L2 variants in Chinese globozoospermia*	Human clinical	Globozoospermia differential/ context

Limitations and Knowledge Gaps

1. **Sparse human genetic evidence.** SPGF67 rests on a limited number of human cases plus one ClinVar likely-pathogenic frameshift (c.132_133insG, p.Asn45fs). The full human allelic spectrum, genotype–phenotype correlation, and penetrance estimates are not established.
2. **No formal epidemiology.** Prevalence/incidence and carrier frequency for the disease state are unquantified.
3. **Phenotype boundary.** It is unresolved whether human CCDC62 disease is strictly globozoospermia or a broader teratozoospermia/oligo-astheno-teratozoospermia spectrum; cohort-level semen characterization is lacking.
4. **Dual-function uncertainty.** Whether the ERAP75/nuclear-receptor-coactivator role contributes anything to the human phenotype (or any subclinical endocrine effect) is unknown.
5. **Treatment outcome data are indirect.** AOA/ICSI efficacy data come from general severe-teratozoospermia/globozoospermia populations, not CCDC62-genotyped cohorts.
6. **Variant interpretation.** Most CCDC62 ClinVar variants are VUS; functional assays to reclassify missense variants are needed.

Proposed Follow-up Experiments / Actions

1. **Aggregate additional human cases** via GeneMatcher/Matchmaker Exchange to firm up the gene–disease relationship and define penetrance and the semen-phenotype spectrum.
2. **Functional validation of VUS** (minigene/splicing assays; acrosome-biogenesis rescue in cell or organoid systems) to reclassify the ~19 CCDC62 VUS in ClinVar.
3. **Mechanistic dissection of the CCDC62–GOPC axis** — map the coiled-coil interaction interface and test whether patient truncations abolish GOPC binding and proacrosomal vesicle fusion.
4. **Genotype-specific ART outcome study** — track ICSI ± calcium-ionophore AOA fertilization/live-birth rates specifically in CCDC62-biallelic patients.
5. **Single-cell testis profiling** of CCDC62 across spermatogenic stages (and in Sertoli cells, given SOX9 co-expression) to resolve the germ-cell vs. supportive-niche contribution.
6. **Evaluate the ERAP75 function** in germ cells to determine whether nuclear-receptor coactivation has any reproductive relevance, using domain-separation mutants.

Report compiled from 9 confirmed findings and 9 reviewed papers across 5 investigation iterations. Evidence types: model organism (mouse), human clinical/cohort, in vitro/annotation (UniProt, STRING, HPA, ClinVar, gnomAD).