Spermatogenic Failure 23 (SPGF23 / TEX14): Comprehensive Disease Characteristics Report

Disease: Spermatogenic Failure 23 (SPGF23) **MONDO ID:** MONDO:0054727 · **OMIM:** #617707 · **Causal gene:** *TEX14* (MIM 605792) **Category:** Mendelian, autosomal recessive **Report date:** 2026-10-17

Summary

Spermatogenic Failure 23 (SPGF23) is a rare, autosomal-recessive Mendelian form of non-obstructive azoospermia (NOA) caused by biallelic loss-of-function mutations in *TEX14* (testis-expressed gene 14), located on chromosome 17q22. TEX14 encodes a 1,497-amino-acid, testis-restricted inactive serine/threonine (pseudo)kinase that serves as the essential structural scaffold of germ-cell **intercellular bridges (ICBs)** — stable cytoplasmic channels that connect developing male germ cells into a functional syncytium. When TEX14 is lost, these bridges fail to form, spermatogenesis arrests at the pachytene/meiotic stage (a "maturation arrest" histology), no mature spermatozoa are produced, and the affected man is azoospermic and infertile.

The molecular mechanism is well defined. TEX14 carries a conserved **GPPX$_3$Y motif** that binds the midbody protein **CEP55** with high affinity, competitively excluding the ESCRT-recruiting proteins ALIX (PDCD6IP) and TSG101. This converts what would be a transient cytokinetic midbody into a permanent intercellular bridge, arresting abscission so that daughter germ cells remain connected. These bridges enable cytoplasmic sharing of mRNAs and proteins required to complete meiotic DNA replication, chromosome synapsis, meiotic double-strand-break repair, and transposon repression. Loss of the bridges therefore produces downstream meiotic failure and genome-integrity defects, culminating in germ-cell arrest and azoospermia. The phenotype is strikingly **male-specific**: female *Tex14*-null mice lack embryonic ICBs yet remain fertile.

SPGF23 is a non-lethal, non-progressive, isolated reproductive disorder with no systemic features. Diagnosis relies on semen analysis (azoospermia), hormonal/karyotype workup to exclude other causes, and gene-panel or exome sequencing identifying biallelic *TEX14* variants; testicular histology shows meiotic/maturation arrest. There is no disease-modifying therapy. Management centers on assisted reproduction via microdissection testicular sperm extraction (micro-TESE) with intracytoplasmic sperm injection (ICSI); however, because SPGF23 causes complete (pre-spermatid) meiotic arrest, the probability of recovering usable spermatozoa is low. Genetic counseling is the principal preventive intervention.

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1. Disease Information

Overview. SPGF23 is an inherited male infertility disorder defined by non-obstructive azoospermia (absence of sperm in the ejaculate due to failed sperm production, not blockage) resulting from an intrinsic germ-cell defect. The spermatogenic program initiates normally through spermatogonial amplification and entry into meiosis but halts before the completion of the first meiotic division, so post-meiotic spermatids and spermatozoa are absent or severely depleted.

Key identifiers.

Resource	Identifier
OMIM (phenotype)	#617707 (Spermatogenic failure 23)
OMIM (gene)	605792 (*TEX14*)
MONDO	MONDO:0054727
Gene (NCBI)	56155 (*TEX14*)
UniProt	Q8IWB6
HGNC	*TEX14*
Cytoband	17q22
Mouse ortholog	*Tex14* (MGI)

Synonyms / alternative names: Spermatogenic failure 23; SPGF23; non-obstructive azoospermia due to *TEX14* deficiency; TEX14-related maturation (meiotic) arrest. In the broader literature the condition falls under "non-obstructive azoospermia (NOA)" and "maturation arrest / meiotic arrest."

Source of information. The entry is derived from **aggregated disease-level resources** (OMIM, ClinVar, UniProt) combined with **individual-patient reports** (consanguineous/affected families described by Gershoni et al. 2017, Fakhro et al. 2018, and a compound-heterozygous NOA patient in PMID: 40492599) and **model-organism data** (*Tex14*-null mouse, PMID: 16549803). It is not EHR-derived population data.

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2. Etiology

Primary cause — genetic. SPGF23 is monogenic: it is caused by **biallelic (homozygous or compound-heterozygous) loss-of-function mutations in *TEX14***. There is no environmental or infectious cause for this specific Mendelian entity; it is a germline genetic disorder of meiosis.

Genetic risk factors. The causal variants are LoF *TEX14* alleles. In the original human families the mutations were homozygous (consanguineous Iraqi-Jewish brothers, Gershoni et al. 2017; Jordanian brothers with maturation arrest, Fakhro et al. 2018). A recurrent **compound-heterozygous** genotype — c.802A>T (p.Ser268Cys) together with c.1021C>T (p.Arg341*) — was identified in an NOA patient with pachytene meiotic arrest and impaired intercellular-bridge assembly (PMID: 40492599). ClinVar (RefSeq NM_031272.5) catalogs 352* TEX14 *records, 42 classified pathogenic/likely-pathogenic, predominantly nonsense, frameshift, and canonical splice variants. Being autosomal recessive, carriers of a single allele are unaffected; consanguinity** increases homozygosity risk and is a documented contributor.

Environmental / lifestyle risk factors. Not applicable as a *cause* of SPGF23 — the disorder is fully genetic. General male-fertility risk modifiers (heat, gonadotoxins, smoking) are not established disease modifiers for this entity.

Protective factors. None established. No protective *TEX14* alleles or environmental modifiers are known. Given complete recessive inheritance with apparently complete penetrance in males, biallelic LoF essentially determines the phenotype.

Gene–environment interactions. No specific GxE interactions are documented for SPGF23. This is a classical high-penetrance Mendelian disorder in which genotype is the dominant determinant.

3. Phenotypes

The phenotype is reproductive and essentially monosystemic. There are no neurological, cardiac, skeletal, or other somatic manifestations.

Phenotype	Type	Onset	Severity	Frequency	Suggested HPO term
Non-obstructive azoospermia	Laboratory/ clinical	Post-pubertal (detected in adulthood)	Severe	Obligate (defining)	HP:0011961 (Azoospermia)
Male infertility	Clinical	Adult	Severe	~100% of affected males	HP:0003251 (Male infertility)
Meiotic / maturation arrest (spermatogenic arrest)	Histological	Adult	Severe	Characteristic	HP:0008669 (Abnormal spermatogenesis)
Decreased testicular size (variable)	Physical sign	Adult	Mild–moderate/ variable	Variable	HP:0008734 (Decreased testicular size)
Normal secondary sexual characteristics / normal androgens	(Context)	—	—	Typical	—

Phenotype characteristics. - **Age of onset:** Clinically manifest in adulthood, usually at infertility workup; biologically the defect begins at the onset of meiosis after puberty. - **Severity:** Severe with respect to fertility (complete azoospermia). - **Progression:** Stable/non-progressive. The germ-cell arrest is fixed; it is not a degenerative disorder. - **Frequency:** Azoospermia and infertility are obligate features in affected (biallelic) males.

Quality-of-life impact. The impact is confined to reproduction and its psychosocial sequelae (involuntary childlessness, distress associated with infertility). There is no effect on lifespan, physical functioning, or general health. No disease-specific QoL instrument has been applied to SPGF23 specifically.

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4. Genetic / Molecular Information

Causal gene. *TEX14* (testis-expressed 14), OMIM 605792, NCBI Gene 56155, UniProt Q8IWB6, chromosome 17q22. Transcript reference NM_031272.5; protein 1,497 aa.

Protein architecture (UniProt Q8IWB6): - Protein-kinase-like domain, residues ~227–518 — **catalytically inactive (pseudokinase)** - Conserved **CEP55-binding GPPX$_3$Y motif**, residues ~795–801 - Destruction box (D-box), residues ~852–860 - Ankyrin (ANK) repeats and multiple intrinsically disordered regions - **Testis-restricted expression**; subcellular localization to cytoplasm, midbody, and chromosome/centromere/kinetochore

Pathogenic variant spectrum (ClinVar, NM_031272.5). The spectrum is **dominated by loss-of-function alleles**, consistent with a LoF disease mechanism:

Variant type	Representative alleles
Nonsense	c.2943G>A (p.Trp981Ter); c.2944C>T (p.Gln982Ter); c.3549C>A (p.Cys1183Ter); c.3168C>A (p.Tyr1056Ter); c.3652A>T (p.Arg1218Ter); c.1021C>T (p.Arg341*)
Frameshift	c.1380dup (p.Ala461fs); c.899dup (p.Tyr300Ter); c.3482_3486del (p.Pro1161fs); c.3625_3628del (p.Ser1209fs); c.2650_2660del (p.Ser884fs)
Canonical splice-site	c.137-1G>A; c.4267+1G>A; c.2576+2T>G
Missense (likely pathogenic)	c.1490T>C (p.Leu497Pro), in the kinase-like domain
Missense (VUS)	p.Pro893Arg; p.Ala64Val; p.Asn83His; p.Glu1351Gly; p.Ser268Cys
Conflicting	c.1003C>T (p.Arg335Ter)

Classification follows ACMG/AMP criteria; the predominance of nonsense, frameshift, and splice variants supports **loss of function** as the mechanism. Variant counts: 352 total records, 42 pathogenic/likely-pathogenic.

Allele frequency. Pathogenic *TEX14* LoF alleles are individually rare in gnomAD, consistent with a recessive, reproduction-limiting disorder. Variants are **germline** in origin (somatic/COSMIC not applicable).

Functional consequence. Loss of function. Haploinsufficiency is not the issue — heterozygotes are fertile; biallelic LoF is required. The compound-heterozygous human variants disrupt intercellular-bridge assembly (PMID: 40492599).

Modifier genes. No validated clinical modifiers. Partner/pathway proteins include CEP55, ALIX (PDCD6IP), TSG101, KIF23/MKLP1, and RBM44; of these, RBM44 is dispensable (its knockout does not impair fertility; PMID: 21364893).

Epigenetics. No disease-specific methylation/chromatin signature is defined for SPGF23. Notably, loss of ICBs causes **retrotransposon derepression** during meiosis — an epigenetic/genome-defense consequence rather than a primary cause (PMID: 39929837).

Chromosomal abnormalities. Large 17q22 copy-number losses/gains encompassing *TEX14* exist in ClinVar/DECIPHER but are non-specific contiguous-gene CNVs, not the typical cause of isolated SPGF23. (Chromosomal causes of NOA generally — Klinefelter syndrome, Y-microdeletions — are distinct entities to exclude.)

5. Environmental Information

Environmental factors: None causal. SPGF23 is a Mendelian disorder. **Lifestyle factors:** None established as modifiers of this specific genotype–phenotype. **Infectious agents:** Not applicable — SPGF23 is not infectious or acquired.

(General NOA can have environmental/toxic contributors, but these do not apply to the *TEX14*-defined Mendelian entity.)

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6. Mechanism / Pathophysiology

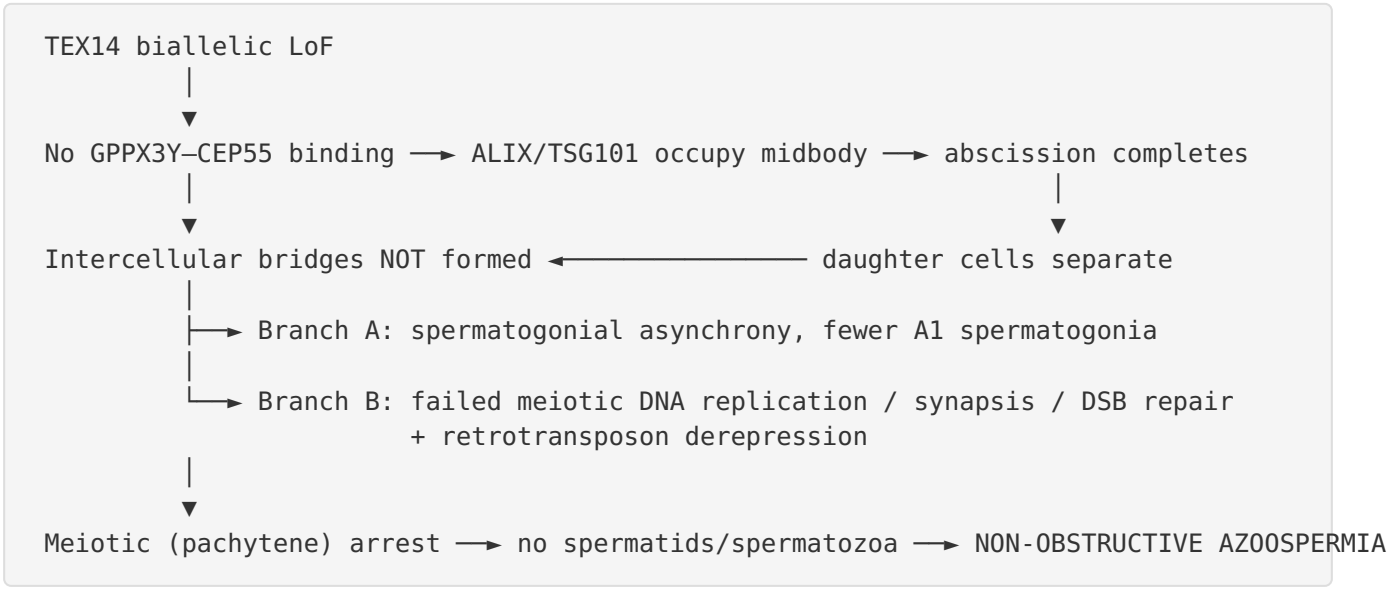
Causal chain (initiating lesion → clinical manifestation)

1. **Biallelic LoF mutation in *TEX14*** → leads to absence or non-functional TEX14 protein in germ cells. *(Demonstrated — human families and mouse knockout.)*
2. **Loss of TEX14** → the conserved GPPX$_3$Y motif is no longer available to bind CEP55, so TEX14 cannot outcompete ALIX/TSG101 at the midbody. *(Demonstrated biochemically — PMID: 20176808; simulation PMID: 37409705.)*
3. **ESCRT abscission machinery (ALIX/TSG101) is recruited to the midbody unopposed** → cytokinetic abscission proceeds to completion instead of being arrested. *(Inferred from the competitive-binding model.)*
4. **Daughter germ cells separate rather than remaining connected → intercellular bridges fail to form** (undetectable by EM in TEX14-null testis). *(Demonstrated — PMID: 16549803.)*
5. **Loss of ICBs abolishes cytoplasmic sharing** of mRNAs and proteins between connected germ cells. *(Demonstrated by scRNA-seq — PMID: 39929837.)*

Branch A → **Spermatogonial compartment:** reduced expansion of undifferentiated type-A spermatogonia and fewer differentiating A1 spermatogonia, with loss of synchrony from the type-B stage onward. *(PMID: 32438343.)*

Branch B → **Meiotic compartment:** germ cells fail to complete meiotic DNA replication, chromosome synapsis, and meiotic double-strand-break repair; retrotransposons are derepressed and retrotransposon-encoded proteins accumulate. *(PMID: 39929837.)*

1. **Meiotic progression halts before completion of the first meiotic division (pachytene/ meiotic maturation arrest)** → post-meiotic spermatids and spermatozoa are not produced. *(Demonstrated — PMID: 16549803.)*
2. **No mature sperm in testis/ejaculate → non-obstructive azoospermia → male infertility** (clinical manifestation). *(Demonstrated — human NOA patients.)*



Supporting detail

Molecular pathway — abscission control via CEP55/ESCRT. The central event is competition at the midbody. In somatic cells CEP55 recruits ALIX and TSG101 to activate ESCRT-III-mediated abscission. In germ cells, **TEX14's GPPX$_3$Y motif binds CEP55 strongly, blocking the homologous GPPX$_3$Y motifs of ALIX and TSG101**, thereby preventing ESCRT recruitment and arresting abscission to create a stable bridge (PMID: 20176808). Metadynamics simulations confirm TEX14's high affinity and low dissociation rate for CEP55 outcompete ALIX (PMID: 37409705). Reinforcing CEP55's central role, *Cep55* overexpression also causes male-specific sterility, acting through sustained PI3K/AKT signaling and loss of FOXO1 nuclear retention (PMID: 29683733).

Cellular processes. Arrested cytokinetic abscission (bridge formation); cytoplasmic/organelle sharing across the germ-cell syncytium; meiotic cell-cycle progression; DNA double-strand-break repair during meiotic recombination; transposon silencing. Downstream, disrupted bridges can produce **multinucleated giant cells** and apoptosis, as seen when ICBs are destabilized by FAR1 loss (PMID: 37039784) or YKT6 loss (PMID: 40528727).

Protein dysfunction. LoF alleles (nonsense/frameshift/splice) eliminate or truncate TEX14, removing the GPPX$_3$Y–CEP55 scaffolding function. TEX14 is a **pseudokinase** — its kinase-like domain is catalytically inactive — so it acts structurally, not enzymatically. Beyond bridges, TEX14 also contributes to **kinetochore–microtubule attachment during mitosis**, a second function (UniProt).

Transcriptomic / single-cell evidence. scRNA-seq shows ICBs enable transcript sharing between connected germ cells, and integrative RNA-seq of bridge-deficient testis reveals downregulation of late germ-cell developmental genes and upregulation of ECM/cell–cell-interaction genes (PMID: 39929837; PMID: 37039784).

Suggested ontology terms. - GO biological process: GO:0007283 (spermatogenesis); GO:0045172 (intercellular bridge / germline ring canal); GO:0007140 (male meiotic nuclear division); GO:0000281/GO:0007093 (cytokinesis/abscission regulation); GO:0010526 (retrotransposon silencing). - GO cellular component: GO:0045172 (intercellular bridge); GO:0030496 (midbody); GO:0000776 (kinetochore). - CL cell types: CL:0000020 (spermatogonium); CL:0000017 (spermatocyte); CL:0000019 (sperm); CL:0000216 (Sertoli cell, context).

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7. Anatomical Structures Affected

Organ level. - **Primary organ:** Testis (UBERON:0000473), specifically the seminiferous tubules (UBERON:0001343) / seminiferous epithelium. - **Body system:** Male reproductive system (UBERON:0000079). No secondary organ involvement; this is an isolated gonadal/germ-cell disorder.

Tissue and cell level. - Tissue: germinal (seminiferous) epithelium. - **Target cell populations:** male germ cells — spermatogonia (CL:0000020), spermatocytes (CL:0000017) — which fail to progress; spermatids/spermatozoa (CL:0000019) are absent. Sertoli cells (CL:0000216) remain and support the arrested epithelium.

Subcellular level. - **Intercellular bridge** (GO:0045172) — the structure that fails. - **Midbody** (GO:0030496) — site of the CEP55/TEX14/ESCRT decision. - **Kinetochore/centromere** (GO:0000776) — TEX14's secondary mitotic site. - Cytoplasm — the shared compartment lost when bridges fail.

Localization / lateralization. Bilateral (both testes affected); diffuse within the seminiferous epithelium.

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8. Temporal Development

Onset. Biologically, the defect manifests at the first wave of meiosis after pubertal activation of spermatogenesis; clinically it is detected in adulthood during infertility evaluation. Onset pattern is **chronic/insidious** — there is no acute event.

Progression. The disorder is **stable and non-progressive**. Spermatogenesis is arrested at a fixed developmental checkpoint (pachytene/meiotic division) rather than degenerating over time. Disease duration is **lifelong**, but it does not worsen systemically and does not shorten life.

Patterns. No spontaneous remission; no treatment-induced remission of the germ-cell defect (assisted reproduction bypasses, but does not cure, the block). The relevant "critical period" is developmental — the meiotic-entry window where the bridge-dependent syncytium is required.

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9. Inheritance and Population

Inheritance. Autosomal recessive (OMIM #617707). Affected individuals are homozygous or compound heterozygous for *TEX14* LoF alleles; heterozygous carriers are unaffected and fertile.

Penetrance / expressivity. In males, biallelic LoF appears **highly/completely penetrant** for azoospermia. Expressivity of secondary features (e.g., testicular volume) may be variable. **No genetic anticipation** (not a repeat-expansion disorder).

Sex-specificity. The requirement for TEX14 is **male-specific**. TEX14 is an essential component of both male and female embryonic ICBs, yet **female *Tex14*-null mice are fertile** while males are sterile (PMID: 19020301). Thus SPGF23 is a disorder of male fertility; female biallelic carriers would be expected to be unaffected for fertility.

Consanguinity / founder effects. Consanguinity is a documented contributor (homozygous cases in consanguineous families). No broad founder effect is established; individual rare alleles predominate.

Carrier frequency. Individual pathogenic *TEX14* alleles are rare in gnomAD; aggregate carrier frequency for SPGF23-causing biallelic genotypes is low but not precisely quantified.

Epidemiology. Precise prevalence/incidence of SPGF23 specifically are **not established**. Context: NOA affects ~1% of all men and is the most severe form of male infertility (PMID: 40658795); *TEX14* is one of many monogenic causes within this heterogeneous group and accounts for a small fraction of cases. The sex ratio is effectively male-only for the fertility phenotype.

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10. Diagnostics

Clinical tests. - **Semen analysis:** azoospermia on ≥2 centrifuged specimens (HP:0011961). Normal ejaculate volume with azoospermia points to a non-obstructive etiology when combined with hormones/volume. - **Hormonal profile:** FSH, LH, testosterone, inhibin B — to classify as non-obstructive (often elevated FSH) and exclude hypogonadotropic causes. - **Imaging:** scrotal ultrasound to assess testicular volume and exclude obstruction/varicocele. - **Biopsy/histopathology:** testicular histology shows **meiotic/maturation arrest** — germ cells present up to the spermatocyte stage, with absent or markedly reduced post-meiotic spermatids. This histological pattern is the hallmark.

Genetic testing (the definitive diagnostic route). - **Karyotype** and **Y-chromosome microdeletion (AZF)** screening first, to exclude Klinefelter syndrome and AZF deletions (the commonest chromosomal causes of NOA; see PMID: 42223426, PMID: 38511217). - **Whole-exome sequencing (WES)** or **NOA gene panels** including *TEX14* to detect biallelic variants. WES is an effective tool for genetic diagnosis of primary male infertility (PMID: 39267058), and targeted NGS panels increase diagnostic yield in idiopathic SPGF (PMID: 32655042). - Confirm biallelic status by **segregation/Sanger** and apply **ACMG/AMP** classification (biallelic LoF = pathogenic).

Biomarkers / omics-based prognostic diagnostics. Testicular transcript markers of post-meiotic germ cells correlate with sperm-retrieval success: post-meiotic markers are significantly reduced in maturation-arrest testes and in negative vs positive sperm-retrieval groups (PMID: 30054974). No validated circulating biomarker is SPGF23-specific.

Clinical criteria / differential diagnosis. No disease-specific criteria beyond azoospermia + meiotic arrest + biallelic *TEX14*. The differential diagnosis of NOA/maturation arrest includes Klinefelter syndrome, Y-microdeletions, Sertoli-cell-only syndrome (PMID: 41485595), and other single-gene meiotic-arrest genes (TEX11, TEX15, MEIOB, SYCP3, SOHLH1, NR5A1, SOX30, etc.) — distinguished by genetic testing.

Screening. Carrier/cascade screening within affected families; no population newborn screening (reproductive, non-lethal phenotype).

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11. Outcome / Prognosis

Survival / mortality. SPGF23 does **not affect survival, life expectancy, or mortality**. It is confined to reproductive function.

Morbidity / quality of life. Morbidity is reproductive (infertility) and psychosocial. No physical disability.

Disease course. Stable, lifelong, non-progressive.

Fertility prognosis (the key outcome). Because SPGF23 produces a **complete meiotic (pachytene) maturation arrest** with absent spermatids, the prognosis for recovering mature spermatozoa at **micro-TESE is poor**. Post-meiotic transcript markers are significantly lower in failed sperm-retrieval cases (PMID: 30054974), and a pre-spermatid arrest implies few or no retrievable sperm. Focal residual spermatogenesis cannot be excluded a priori, so micro-TESE may still be attempted, but with counseling about low yield.

Prognostic factors. Degree/completeness of the arrest; presence of any post-meiotic cells on histology; FSH and testicular volume (general NOA predictors).

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12. Treatment

No disease-modifying or curative therapy exists. There is no pharmacologic, gene, cell, or RNA therapy for the underlying germ-cell defect. Management is reproductive.

Intervention	Role in SPGF23	Suggested NCIT concept
Microdissection TESE (micro-TESE)	Surgical attempt to recover focal spermatozoa from testicular tissue; low expected yield given complete meiotic arrest	NCIT: Testicular Sperm Extraction
ICSI (intracytoplasmic sperm injection)	If any viable sperm are retrieved, used for assisted fertilization	NCIT: Intracytoplasmic Sperm Injection
Donor sperm / adoption	Family-building alternatives when retrieval fails	—
Genetic counseling	Risk assessment, family planning, cascade testing	NCIT: Genetic Counseling

- **Pharmacotherapy / hormonal therapy:** No evidence of benefit for a structural meiotic-arrest genotype (empirical gonadotropin/antiestrogen therapy used in some NOA is not expected to overcome a *TEX14*-null block).
- **Advanced therapeutics (gene/cell/RNA/targeted/immuno):** None available or in trials for SPGF23.
- **Experimental:** No SPGF23-specific registered trials identified.
- **Personalized medicine:** Genotype confirms etiology and informs realistic counseling about micro-TESE yield.

13. Prevention

Because SPGF23 is a non-lethal recessive reproductive disorder, "prevention" is reproductive-genetic rather than public-health.

- **Primary prevention:** Not applicable in the conventional sense; avoidance of the affected genotype is only possible via reproductive planning.

- **Genetic / reproductive prevention: Carrier screening** in relatives, **genetic counseling**, and, for couples at risk, **preimplantation genetic testing (PGT)** or prenatal diagnosis to inform reproductive choices. (Note: because affected males are infertile, transmission to offspring occurs only through assisted reproduction using retrieved sperm, in which case sons could inherit a pathogenic allele.)
- **Immunization / behavioral / environmental / prophylaxis:** Not applicable.
- **Counseling:** The principal preventive intervention — informs recurrence risk and reproductive options.

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14. Other Species / Natural Disease

- **Taxonomy / model species:** *Mus musculus* (NCBI Taxon 10090) is the principal model.
- **Orthologous gene:** mouse *Tex14* (MGI; NCBI Gene ortholog). The $GPPX_3Y$–CEP55 interaction and bridge function are **evolutionarily conserved** (PMID: 20176808); RBM44, another bridge protein, is conserved between mouse and human (PMID: 21364893).
- **Natural disease in other species / veterinary relevance:** No naturally occurring companion-animal or wildlife SPGF23 equivalent is documented (OMIA); intercellular bridges are, however, a conserved feature of metazoan germlines.
- **Comparative biology:** The male-specific essentiality of TEX14 (sterile males, fertile females) is conserved in mouse, mirroring the expected human sex-specific phenotype.
- **Zoonotic potential:** Not applicable (non-infectious genetic disorder).

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15. Model Organisms

Primary model — *Tex14*-knockout mouse. The *Tex14*$^{-/-}$ mouse is the foundational and highly faithful model of SPGF23.

Feature	Mouse *Tex14*$^{-/-}$	Human SPGF23	Concordance
Male fertility	Sterile	Infertile (azoospermic)	✔
Spermatogenic block	Halts before completion of the first meiotic division	Pachytene/meiotic maturation arrest	✔
Intercellular bridges	Absent (undetectable by EM)	Impaired bridge assembly	✔
Female fertility	Normal (fertile)	Expected unaffected (male-specific)	✔
Early meiotic markers	Expressed	—	✔

- **Model types:** Mammalian (mouse) germline knockout; also conditional/cell-type-specific models of related bridge genes (e.g., *Ykt6* cKO, PMID: 40528727; *Far1* KO, PMID: 37039784) that destabilize TEX14/ICBs secondarily.
- **Phenotype recapitulation:** Excellent — the mouse reproduces the azoospermia, meiotic arrest, and bridge loss, and provided the mechanistic framework (PMID: 16549803; PMID: 19020301).
- **Model limitations:** Human allelic heterogeneity (missense VUS, hypomorphs, potential focal residual spermatogenesis) is not fully captured by a null mouse; the complete-null mouse may be more severe than some human hypomorphic genotypes.
- **Applications:** Dissecting bridge biology, cytoplasmic sharing (scRNA-seq), meiotic DSB repair and transposon control, and testing whether residual spermatogenesis is ever achievable.
- **Resources:** MGI / IMSR for *Tex14* alleles.

Key Findings (with evidence)

Finding 1 — Biallelic *TEX14* LoF causes SPGF23 (NOA with meiotic arrest)

OMIM #617707 attributes SPGF23 to homozygous/biallelic *TEX14* mutation (17q22), autosomal recessive. Human families (Gershoni 2017; Fakhro 2018) and a recurrent compound-heterozygous genotype (c.802A>T p.Ser268Cys; c.1021C>T p.Arg341*) in an NOA patient with pachytene arrest and impaired bridge assembly establish causality in humans.* Tex14$^{-/-}$* mice are sterile with arrest before the first meiotic division.

> "we identified a novel compound heterozygous mutation in TEX14 (c.802A>T, p.S268C and c.1021C>T, p.R341*) in a patient with NOA" — PMID: 40492599 "Spermatogenesis in Tex14(-/-) mice progresses through the transit amplification of diploid spermatogonia and the expression of early meiotic markers but halts before the completion of the first meiotic division" — PMID: 16549803

Finding 2 — TEX14 builds intercellular bridges by converting CEP55 from abscission factor to bridge component

TEX14's conserved GPPX$_3$Y motif binds CEP55, competitively excluding ALIX/TSG101 and the ESCRT machinery from the midbody, arresting abscission to form a stable bridge. Without TEX14, bridges are undetectable by EM. Simulations confirm TEX14's high affinity/low dissociation outcompetes ALIX; *Cep55* overexpression independently causes male sterility.

> "an evolutionarily conserved GPPX3Y motif of TEX14 binds strongly to CEP55 to block similar GPPX3Y motifs of ALIX and TSG101 from interacting and localizing to the midbody" — PMID: 20176808 "In the absence of TEX14, intercellular bridges are not observed by using electron microscopy and other markers" — PMID: 16549803

Finding 3 — Intercellular bridges enable cytoplasmic sharing required for meiosis, DSB repair, synapsis, and transposon repression

In bridge-deficient male germ cells, meiotic DNA replication, synapsis, and DSB repair fail, and retrotransposons are derepressed with accumulation of retrotransposon-encoded proteins; scRNA-seq shows bridges enable transcript sharing. Bridge loss also causes spermatogonial asynchrony and, downstream (e.g., FAR1 loss), multinucleated giant cells.

> "germ cells fail to complete meiotic DNA replication, synapsis and meiotic double-strand break repair. They also derepress retrotransposons and accumulate retrotransposon-encoded proteins during meiosis" — PMID: 39929837 "intercellular bridges enable cytoplasmic exchange between connected germ cells in testes" — PMID: 39929837

Finding 4 — TEX14 requirement is male-specific

TEX14 is essential for both male and female embryonic bridges (with MKLP1/KIF23), but female *Tex14*-null mice are fertile while males are sterile — making SPGF23 a male-specific fertility disorder. RBM44, another bridge protein, is dispensable.

> "TEX14 is an essential component of male and female embryonic intercellular bridges" — PMID: 19020301

Finding 5 — Meiotic/maturation arrest predicts low surgical sperm-retrieval yield

Post-meiotic transcript markers are significantly reduced in maturation-arrest testes and lower in negative vs positive micro-TESE groups; SPGF23's complete pachytene arrest therefore implies a low-yield retrieval prognosis.

> "Post-meiotic markers were significantly reduced in negative vs. positive sperm retrieval groups" — PMID: 30054974

Finding 6 — TEX14 is a 1,497-aa testis-restricted inactive (pseudo)kinase with dual bridge/kinetochore roles

UniProt Q8IWB6: pseudokinase domain (227–518), GPPX$_3$Y CEP55-binding motif (795–801), D-box, ANK repeats; testis-restricted; localizes to cytoplasm, midbody, and kinetochore; required for intercellular bridges and for mitotic kinetochore–microtubule attachment; disease annotation SPGF23.

Finding 7 — ClinVar variant spectrum is LoF-dominated, confirming the LoF mechanism

352 *TEX14* records (42 P/LP); pathogenic alleles for SPGF23/NOA are overwhelmingly nonsense, frameshift, and canonical splice variants, with one likely-pathogenic kinase-domain missense (p.Leu497Pro) and several VUS missense — consistent with loss of function.

> "pathogenic biallelic TEX14 mutations are recurrent genetic etiologies of NOA in humans" — PMID: 40492599

Mechanistic Model / Interpretation

SPGF23 is best understood as a **structural disorder of the germ-cell syncytium**. The male germline is normally a connected network: after each mitotic/meiotic division, cells deliberately *fail* abscission and remain joined by intercellular bridges. This is not a byproduct but a programmed requirement — the bridges allow haploid and diploid cells to share transcripts and proteins so that the entire clone matures synchronously and so that genome-defense (transposon silencing) and meiotic recombination machinery are adequately supplied.

TEX14 is the molecular switch that creates these bridges. By binding CEP55 at the midbody, it blocks the ESCRT abscission pathway that would otherwise sever the cells. Remove TEX14 and the switch defaults to "abscission on": cells separate, the syncytium never forms, cytoplasmic sharing is lost, and the meiotic program stalls at pachytene. The ClinVar spectrum (nonsense/frameshift/splice) and the fertile-female/sterile-male dichotomy both point to simple loss of function as the disease mechanism, with no dominant-negative or gain-of-function

contribution required. The clinical endpoint — complete azoospermia with meiotic arrest — follows deterministically, which is why management is limited to assisted reproduction (with a sobering, low expected yield) and genetic counseling.

Evidence Base

PMID	Role	Contribution
16549803	Landmark (mouse)	TEX14 essential for bridges and male fertility; meiotic arrest phenotype
20176808	Mechanism	GPPX$_3$Y–CEP55 binding blocks ALIX/TSG101 abscission
19020301	Mechanism/sex-specificity	Embryonic bridges in both sexes; female fertile, male sterile
39929837	Downstream function	Bridges required for meiosis, DSB repair, transposon repression
32438343	Downstream function	Spermatogonial asynchrony without bridges
37039784	Corroborating	FAR1 loss disrupts TEX14/ICBs → giant cells, arrest
40528727	Corroborating	YKT6 loss destabilizes TEX14 bridges → meiotic arrest
29683733	Partner biology	CEP55 overexpression → male-specific sterility
37409705	Computational	Simulations confirm TEX14 outcompetes ALIX for CEP55
21364893	Contrast	RBM44 bridge protein dispensable — highlights TEX14's unique essentiality
40492599	Human causality	Recurrent compound-het TEX14 in NOA; disrupted bridge assembly
30054974	Prognosis	Post-meiotic markers predict sperm-retrieval success
32655042, 39267058, 38511217	Diagnostics	NGS/WES panels for SPGF/NOA diagnostic yield
41485595, 40658795, 42223426	Context/DDx	SCOS, NOA epidemiology, chromosomal causes to exclude

Limitations and Knowledge Gaps

1. **Epidemiology is unquantified.** Precise prevalence, incidence, and carrier frequency for SPGF23 specifically are not established; it is a minor fraction within the broad ~1% NOA population.
2. **Allelic heterogeneity and genotype–phenotype correlation.** Most functional evidence comes from null alleles/mouse knockout. Whether human missense/hypomorphic variants (several current VUS) produce partial phenotypes or permit focal residual spermatogenesis is not resolved.
3. **Micro-TESE yield in human SPGF23 is inferred,** largely from the maturation-arrest biology and marker studies rather than direct TEX14-cohort retrieval data; actual success rates are unreported.
4. **Human histopathology detail is limited** — bridge ultrastructure in human TEX14 patients is less characterized than in mouse.
5. **No disease modifiers or therapeutics** are known; no SPGF23-specific trials exist.
6. **Female carriers/homozygotes** — the male-specific prediction rests on mouse data; human female biallelic carriers are essentially unstudied.

Proposed Follow-up Experiments / Actions

1. **Assemble a *TEX14* patient registry** to quantify prevalence, allelic spectrum, testicular histology, and **micro-TESE success rates**, directly validating the low-yield prognosis.
2. **Functional validation of VUS** (p.Pro893Arg, p.Ala64Val, p.Asn83His, p.Glu1351Gly, p.Ser268Cys, p.Leu497Pro) via CEP55-binding assays and bridge-reconstitution in cell models to reclassify per ACMG.
3. **Single-cell/spatial transcriptomics of human TEX14 testis** to confirm the bridge-dependent cytoplasmic-sharing and transposon-derepression mechanisms seen in mouse.
4. **Correlate residual post-meiotic markers** (PMID: 30054974) with retrieval outcomes in genotype-confirmed SPGF23 to build a predictive tool.
5. **Humanized/knock-in mouse models** of specific patient missense alleles to test for hypomorphic phenotypes and any rescue windows.
6. **Genetic-counseling protocol** for families, including cascade carrier testing and reproductive options (PGT, donor sperm), given confirmed autosomal-recessive inheritance.

Evidence source types represented: human clinical (families, NOA cohorts, ClinVar, OMIM, UniProt), model organism (mouse Tex14/Cep55/Far1/Ykt6), in vitro (binding/IP), and computational (metadynamics).