Spermatogenic Failure 72 (SPGF72): A Comprehensive Disease Characterization

Disease: Spermatogenic Failure 72 (SPGF72) **MONDO ID:** MONDO:0030809 **Causal gene: WDR19** (WD repeat domain 19 / IFT144; HGNC:18340; NCBI Gene 57728; OMIM *608151; UniProt Q8NEZ3) Category:** Mendelian, autosomal recessive

Summary

Spermatogenic Failure 72 (SPGF72) is an autosomal-recessive, nonsyndromic form of male infertility caused by biallelic loss-of-function variants in the gene *WDR19* (also called *IFT144*), which encodes a core subunit of the intraflagellar transport-A (IFT-A) complex. It is important to anchor this report on the gene rather than the serial-numbered disease name: *WDR19* is pleiotropic, and biallelic variants more commonly cause severe syndromic ciliopathies (Sensenbrenner/cranioectodermal dysplasia, nephronophthisis, Jeune asphyxiating thoracic dystrophy, Senior-Løken syndrome, retinitis pigmentosa). SPGF72 is the *nonsyndromic* end of this allelic spectrum, presenting purely as asthenoteratozoospermia with multiple morphological abnormalities of the sperm flagella (MMAF), without the renal, skeletal, retinal, or ectodermal features of the syndromic phenotypes.

The disease was defined by a single landmark report (PMID: 32323121) describing a proband from a consanguineous family who carried a homozygous *WDR19* missense variant (c.A3811G, p.K1271E). The proband had progressive sperm motility reduced to zero and flagella showing the MMAF spectrum (absent, short, bent, coiled, irregular-calibre tails). Scanning and transmission electron microscopy showed completely destroyed flagellar axonemal ultrastructure; immunofluorescence showed WDR19 absent from the sperm neck and flagellum, with mislocalization of its IFT partners IFT140 and IFT88. CT imaging and retinal examination explicitly excluded a syndromic ciliopathy, establishing the nonsyndromic nature of the condition.

Mechanistically, loss of WDR19 cripples retrograde intraflagellar transport within the six-subunit IFT-A complex during spermiogenesis, preventing proper assembly and maintenance of the sperm flagellar axoneme and abolishing motility. The inheritance is recessive, consistent

with population genetics data (gnomAD) showing that heterozygous WDR19 loss-of-function is well tolerated. There is no disease-modifying pharmacotherapy; however, intracytoplasmic sperm injection (ICSI) bypasses the motility defect and achieved clinical pregnancy in the index couple, consistent with favorable ICSI outcomes for MMAF generally. The principal limitation of current knowledge is that the human nonsyndromic phenotype rests on a single reported proband, and no dedicated *Wdr19* testis-specific knockout model has been published.

Key Findings

Finding 1 — Biallelic *WDR19* mutation causes nonsyndromic asthenoteratozoospermia (SPGF72)

Whole-exome sequencing of 65 individuals with asthenoteratospermia identified a proband carrying a homozygous *WDR19* variant c.A3811G (p.K1271E), inherited within a consanguineous family (PMID: 32323121). The authors state directly: *"We identified WDR19 as a novel pathogenic gene for male infertility caused by asthenoteratospermia in the absence of other ciliopathic phenotypes."* The clinical and laboratory picture was characteristic of MMAF: progressive motility decreased to zero, and the sperm flagella displayed multiple morphological abnormalities. SEM and TEM demonstrated completely destroyed flagellar ultrastructure, while immunofluorescence showed WDR19 absent from the sperm neck/flagella and its IFT-A partner IFT140 and IFT-B component IFT88 mislocalized. Critically, CT imaging and retinal examination excluded syndromic ciliopathy features, establishing the disorder as **nonsyndromic**. The couple achieved clinical pregnancy via ICSI: *"the MMAF subject harboring WDR19 variant and his partner successfully achieved clinical pregnancy through intracytoplasmic sperm injection (ICSI)."*

This single report is the defining evidence for SPGF72 as a discrete clinical entity and anchors the gene–disease relationship (WDR19 → nonsyndromic MMAF).

Finding 2 — *WDR19* is a pleiotropic IFT-A gene; the allelic spectrum ranges from severe syndromic ciliopathy to isolated SPGF72

WDR19 (IFT144) encodes a core component of the IFT-A complex required for retrograde intraflagellar transport. Biallelic *WDR19* variants cause a broad **syndromic ciliopathy spectrum**: Sensenbrenner syndrome / cranioectodermal dysplasia (CED4), nephronophthisis

(NPHP13), Jeune asphyxiating thoracic dystrophy / short-rib thoracic dysplasia, Caroli disease, and retinal dystrophy / Senior-Løken syndrome (PMID: 28621010; PMID: 29134781; PMID: 28332779). A review of renal phenotypes states: *"WDR19 has been reported as a causative gene of nephronophthisis-related ciliopathies. Patients with WDR19 mutations can show various extrarenal manifestations such as skeletal disorders, Caroli disease, and retinal dystrophy"* (PMID: 28621010).

Variable expressivity is marked: the same residue (homozygous p.Leu710Ser) can cause **either** isolated retinitis pigmentosa **or** Jeune syndrome (PMID: 25044745: *"analogous to homozygous p.Leu710Ser in WDR19 causing either isolated retinitis pigmentosa or Jeune syndrome"*). Against this backdrop, SPGF72 (PMID: 32323121) sits at the nonsyndromic extreme — a proband with asthenoteratospermia and **no** detectable ciliopathy features on CT or retinal imaging. This is a central interpretive point: the disease serial number ("Spermatogenic Failure 72") obscures that the causal gene is a well-known ciliopathy gene, and a researcher could easily confuse it with the more common syndromic WDR19 disorders.

Finding 3 — IFT-A dysfunction mechanistically links WDR19 loss to MMAF and sperm immotility

Intraflagellar transport is indispensable for sperm flagellum formation and male fertility (review PMID: 34815207). The mechanistic chain is supported by convergent model-organism and interaction evidence:

- **IFT140, WDR19's direct IFT-A partner:** germ-cell-specific *Ift140* knockout mice are infertile with reduced sperm number and motility, amorphous heads, short/bent flagella, and cytoplasmic vesicles (PMID: 29236364: *"IFT140 is a key regulator for male fertility and normal spermiogenesis in mice"*).
- **Testis IFT-A network:** DNAI4 interacts with IFT144 (WDR19) within the testis, and *Dnai4*-null mice show MMAF with downregulation of IFT-A members IFT140/IFT122/IFT121 (PMID: 42083518: *"Immunoprecipitation demonstrated an interaction between DNAI4 and the intraflagellar transport protein IFT144 within the testes"*).
- **Human corroboration:** in the WDR19 proband, IFT140 and IFT88 were mislocalized in sperm (PMID: 32323121).

Together these establish that WDR19 loss disrupts an IFT-A–dependent transport network required for building the sperm flagellar axoneme, recapitulating the MMAF phenotype.

Finding 4 — IFT-A is a six-subunit β-propeller/TPR complex (including WDR19) essential for flagellum assembly

Recent cryo-EM / cryo-electron tomography of IFT-A from *Tetrahymena* and *Chlamydomonas* resolved a **six-component complex** — WDR19/IFT144, IFT140, IFT122, WDR35/IFT121, IFT43, and TTC21B/IFT139 — that polymerizes laterally along anterograde IFT trains and sits between the IFT-B complex and the ciliary membrane (PMID: 36932088; PMID: 36593313; PMID: 36563665). A sperm-formation review states: *"Twenty-two IFT components form the IFT-A complex (six components) and IFT-B complex (sixteen components)"* and *"IFT is required to assemble these structures to form functional sperm"* (PMID: 40301266). Structurally, *"IFT-A is sandwiched between IFT-B and the ciliary membrane, consistent with its putative role in transporting transmembrane and membrane-associated cargoes"* (PMID: 36563665). WDR19 contributes β-propeller and α-solenoid (clathrin heavy-chain repeat) domains to this scaffold, consistent with a structural/cargo-adaptor role whose loss collapses retrograde transport.

Finding 5 — ICSI is effective for MMAF/asthenoteratozoospermia, with a caveat of possibly reduced embryo potential

Because the defect is in sperm motility and flagellar structure (not in the sperm genome or fertilizing capacity per se), **ICSI bypasses the defect**. Evidence:

Study	Cohort	Key outcome	PMID
Paris cohort	20 MMAF couples	*"ICSI outcomes for couples with MMAF do not differ from those of other couples requiring ICSI, irrespective of the genetic defect"*	34529793
DNAH2/6/10 MMAF	6 couples	Live birth in 5/6 via ICSI	40592014
Propensity-matched	n=38	*"decreased embryo developmental potential and compromised clinical outcomes in the MMAF cohort"*; lower cumulative live birth rate	38745955
WDR19 index case	1 couple	Clinical pregnancy achieved via ICSI	32323121

Overall, ICSI is the standard effective intervention, though some MMAF cohorts show modestly reduced embryo developmental potential.

Finding 6 — gnomAD constraint supports a recessive mechanism (WDR19 is heterozygous-LoF-tolerant)

Population constraint metrics for *WDR19* (ENSG00000157796; chr4:39,182,504–39,285,810, GRCh38) are consistent with recessive inheritance: **pLI ≈ 0** (1.76e-26); observed/expected LoF = 0.67 (121 observed vs ~180 expected); **LOEUF ≈ 0.78**; missense Z = 2.01; LoF Z = 3.73. These values indicate WDR19 is **not** haploinsufficient or LoF-intolerant at the heterozygous level, even though there is moderate overall depletion of LoF alleles. This fits the clinical picture that heterozygous carriers are unaffected and disease requires biallelic variants.

Finding 7 — WDR19 is a rare contributor within a heterogeneous MMAF gene landscape

MMAF is genetically heterogeneous. Recurrent causal genes include **DNAH1, CFAP43, CFAP44, CFAP69, FSIP2, WDR66, ARMC2**, among many others (PMID: 30686508; PMID: 30415212). *"Six genes (DNAH1, CFAP43, CFAP44, CFAP69, FSIP2, and WDR66) have been found to be recurrently associated with MMAF"* (PMID: 30686508). Exome sequencing of severe sperm motility disorders found disease-causing variants in 10/21 (48%) patients, and *"up to 50% of causality in patients with severe sperm motility disorders can be explained by pathogenic variants in at least 22 genes"* (PMID: 34089056). WDR19 is a **rare, recently added** MMAF gene (a single reported proband) that sits among the minority of unexplained/rare contributors.

Finding 8 — WDR19 orthologs, aliases, and domain architecture

NCBI/MyGene records: human *WDR19* = Gene **57728** (ENSG00000157796, cytoband 4p14); mouse *Wdr19* = Gene **213081** (chr5 C3.1); rat *Wdr19* = Gene **305349**; zebrafish *wdr19* = Gene **556414**; *C. elegans* ortholog **dyf-2**. Official aliases include ATD5, CED4, CFAP66, DYF-2, FAP66, **IFT144**, NPHP13, ORF26, Oseg6, PWDMP, **SPGF72**, SRTD5. The NCBI gene summary notes the protein *"contains six WD repeats … and a clathrin heavy-chain repeat"* (i.e., β-propeller plus α-solenoid architecture), and that mutations cause ciliopathies including Jeune, Sensenbrenner, Senior-Løken, nephronophthisis, and retinitis pigmentosa.

Finding 9 — Consolidated SPGF72 (WDR19) disease profile

SPGF72 (MONDO:0030809; gene *WDR19*/IFT144, HGNC:18340, NCBI 57728, OMIM *608151) is an autosomal-recessive nonsyndromic asthenoteratozoospermia with MMAF. The single reported proband carried homozygous* WDR19* c.A3811G/p.K1271E from a consanguineous family, with progressive motility of 0%, destroyed flagellar ultrastructure, WDR19 absent, and IFT140/IFT88

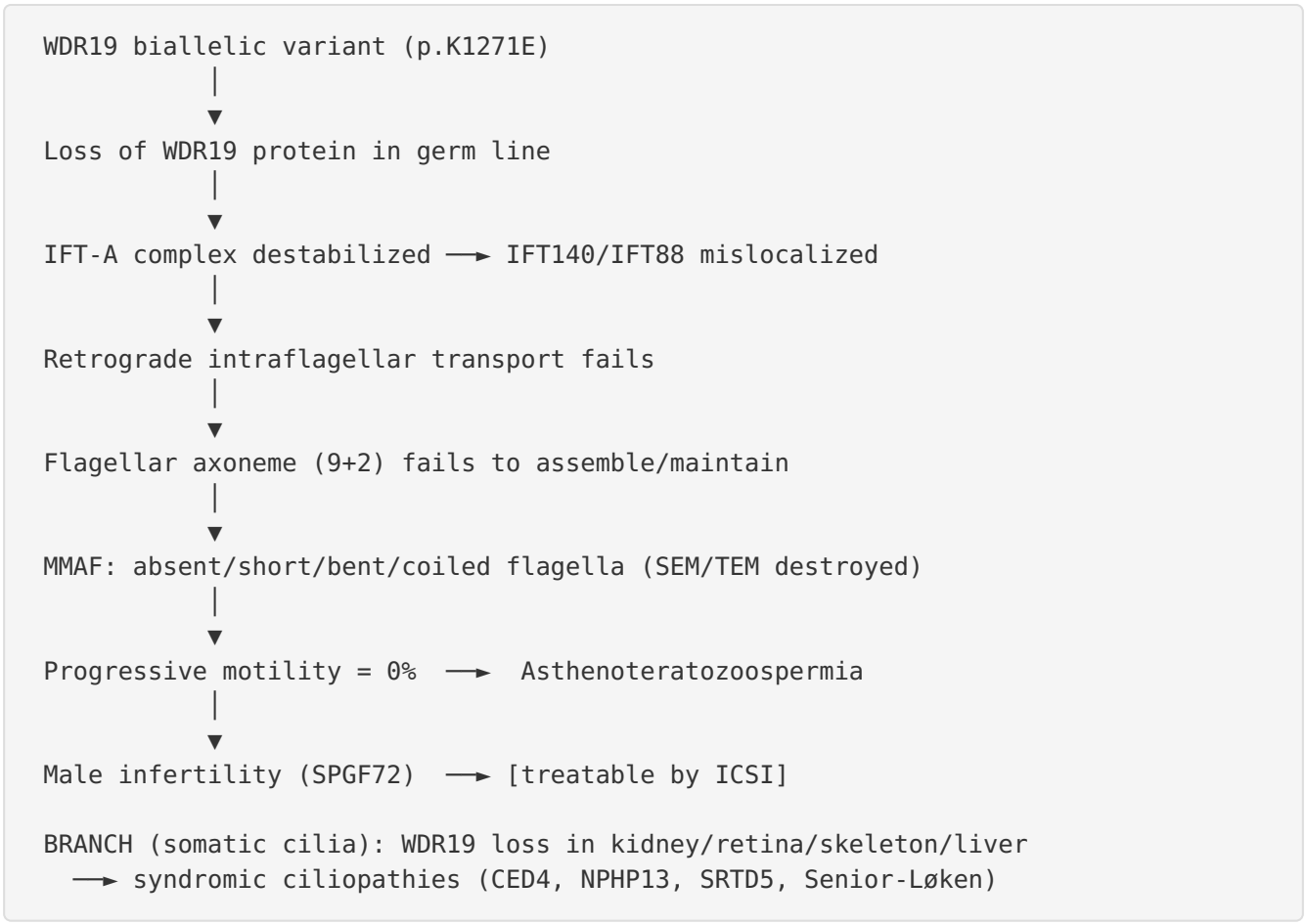
mislocalized (PMID: 32323121). The mechanism is IFT-A retrograde transport failure within a six-subunit complex. Treatment is ICSI; there is no disease-modifying drug and no environmental or infectious etiology.

Mechanistic Model / Interpretation

Ordered causal chain (initiating lesion → clinical manifestation)

1. **Biallelic loss-of-function/missense variant in *WDR19*** (e.g., homozygous c.A3811G, p.K1271E) **leads to** loss or destabilization of the WDR19/IFT144 protein in the male germ line (PMID: 32323121).
2. Absence of WDR19 **results in** destabilization of the six-subunit IFT-A complex and **mislocalization of partner proteins** IFT140 (IFT-A) and IFT88 (IFT-B) in differentiating spermatids (PMID: 32323121; mechanism inferred from IFT-A architecture, PMID: 36563665).
3. IFT-A destabilization **impairs retrograde intraflagellar transport** along the developing flagellar axoneme (inferred from IFT-A's established retrograde-transport and membrane-cargo role; PMID: 36932088).
4. Defective IFT **leads to** failure of proper assembly and maintenance of the flagellar "9+2" axoneme and accessory structures during spermiogenesis (supported by *Ift140* KO mouse spermiogenesis defects, PMID: 29236364; review PMID: 34815207).
5. Axonemal disassembly **results in** the **MMAF phenotype** — absent, short, bent, coiled, and irregular-calibre flagella with completely destroyed ultrastructure on SEM/TEM (PMID: 32323121).
6. Structurally defective flagella **cause** loss of progressive motility (reduced to 0%) → **asthenoteratozoospermia → male infertility / SPGF72** (PMID: 32323121).

Branch point: Because WDR19 is required in *all* cilia, the same gene's biallelic variants can instead (or additionally) impair primary and motile cilia in kidney, retina, skeleton, and liver → syndromic ciliopathies (CED4, NPHP13, SRTD5, Senior-Løken). The nonsyndromic SPGF72 outcome implies that the specific SPGF72 allele (p.K1271E) has a germ-cell/flagellum-predominant functional impact, sparing somatic ciliary function — an inference consistent with the marked variable expressivity documented for WDR19 alleles (PMID: 25044745).


WDR19 biallelic variant (p.K1271E)
Loss of WDR19 protein in germ line
IFT-A complex destabilized ⟶ IFT140/IFT88 mislocalized
Retrograde intraflagellar transport fails
Flagellar axoneme (9+2) fails to assemble/maintain
MMAF: absent/short/bent/coiled flagella (SEM/TEM destroyed)
Progressive motility = 0% ⟶ Asthenoteratozoospermia
Male infertility (SPGF72) ⟶ [treatable by ICSI]
BRANCH (somatic cilia): WDR19 loss in kidney/retina/skeleton/liver
⟶ syndromic ciliopathies (CED4, NPHP13, SRTD5, Senior-Løken)

Ontology annotations

Category	Term	ID
Disease	Spermatogenic failure 72	MONDO:0030809
Gene	WDR19	HGNC:18340 / NCBI 57728 / OMIM *608151
Phenotype	Male infertility	HP:0003251
Phenotype	Reduced sperm motility	HP:0012207
Phenotype	Asthenozoospermia	HP:0040031
Phenotype	Abnormal sperm morphology	HP:0012865
Anatomy	Testis	UBERON:0000473
Anatomy	Sperm flagellum	UBERON:0010314
Cell type	Spermatid	CL:0000018
Cell type	Spermatozoon	CL:0000019
GO-CC	Sperm flagellum	GO:0036126
GO-CC	Axoneme	GO:0005930
GO-CC	IFT particle A (IFT-A complex)	GO:0030991
GO-BP	Intraciliary retrograde transport	GO:0035721
GO-BP	Cilium assembly	GO:0060271
Treatment	Intracytoplasmic sperm injection (ICSI)	NCIT C18113

Section-by-Section Report

1. Disease Information

SPGF72 is a nonsyndromic autosomal-recessive male-infertility disorder characterized by asthenoteratozoospermia with MMAF, caused by biallelic *WDR19* variants. Identifiers: **MONDO:0030809**; gene *WDR19* (OMIM *608151; the phenotype-series OMIM number was not*

*recorded in the provided brief). Synonyms: SPGF72; WDR19-related nonsyndromic asthenoteratozoospermia. Information is derived from an aggregated disease-level / single-case report** source (PMID: 32323121), not large EHR cohorts.

2. Etiology

Causal factor is purely genetic: biallelic (homozygous in the index case) *WDR19* variants. The reported genetic risk context is **consanguinity** (index family was consanguineous). No environmental, infectious, lifestyle, or protective factors have been established for this specific disorder, and no gene–environment interactions are documented. gnomAD constraint (pLI≈0, LOEUF≈0.78) confirms heterozygous carriers are unaffected (recessive).

3. Phenotypes

Core phenotypes (all **laboratory/clinical-sign** abnormalities of semen): - **Male infertility** (HP:0003251) — the presenting complaint; adult onset at reproductive age; severe; stable (non-progressive); essentially 100% in affected (biallelic) individuals. - **Reduced/absent sperm motility — asthenozoospermia** (HP:0012207 / HP:0040031) — progressive motility reduced to 0%. - **Abnormal sperm morphology — MMAF** (HP:0012865) — absent, short, bent, coiled, irregular-calibre flagella; destroyed axonemal ultrastructure.

Quality-of-life impact is confined to reproductive function and the psychosocial burden of infertility; there is no systemic morbidity because the disorder is nonsyndromic. Onset is effectively congenital at the molecular level but clinically recognized in adulthood during infertility workup.

4. Genetic / Molecular Information

Causal gene: *WDR19* (IFT144), HGNC:18340, NCBI 57728, OMIM *608151, 4p14. Index variant: homozygous c.A3811G (p.K1271E), a missense variant (PMID: 32323121); germline origin. Functional consequence is loss of function** (protein absent from sperm by immunofluorescence). Across the WDR19 allelic series, variant types include missense, nonsense, splice, and frameshift. No modifier genes, epigenetic mechanisms, or chromosomal abnormalities are established for SPGF72. Population allele frequency of the specific variant is very low (consistent with a private/rare recessive allele).

5. Environmental Information

Not applicable. No environmental toxins, lifestyle factors, or infectious agents are implicated. The disorder is monogenic/recessive.

6. Mechanism / Pathophysiology

See the ordered causal chain above. In brief: WDR19 loss → IFT-A destabilization → failed retrograde intraflagellar transport → defective axoneme assembly → MMAF → immotility → infertility. Molecular pathway = intraflagellar transport (not a classical signaling cascade). Cellular process = cilium/flagellum assembly (spermiogenesis). Protein dysfunction = loss of a β-propeller/α-solenoid IFT-A scaffold subunit. No metabolic, immune, or inflammatory involvement is implicated.

7. Anatomical Structures Affected

- **Organ:** testis (UBERON:0000473); body system = male reproductive system.
- **Tissue/cell:** seminiferous epithelium germ cells — spermatids (CL:0000018) and spermatozoa (CL:0000019).
- **Subcellular:** sperm flagellum (GO:0036126 / UBERON:0010314), axoneme (GO:0005930), IFT particle A (GO:0030991).
- **Localization:** bilateral (both testes); no lateralization asymmetry. No secondary organ involvement (nonsyndromic).

8. Temporal Development

Onset is **congenital/developmental** at the cellular level (spermiogenesis is defective from puberty onward) but **clinically recognized in adulthood** at infertility evaluation. Course is **stable/non-progressive**: the defect is constitutive, not degenerative. No remission occurs spontaneously. The relevant "critical period" is the window of assisted-reproduction intervention (ICSI).

9. Inheritance and Population

Autosomal recessive, with complete penetrance for the reproductive phenotype in biallelic individuals (based on a single family). **Consanguinity** is a documented contributing factor. gnomAD shows WDR19 is heterozygous-LoF-tolerant. **Epidemiology:** extremely rare — SPGF72 is defined by a single reported proband; precise prevalence/incidence are unknown. Within

MMAF (itself a rare cause of male infertility), WDR19 is a minor contributor relative to DNAH1/CFAP43/CFAP44/etc. Affected sex is **male only** (the phenotype is male infertility). No founder effect is reported for WDR19 in SPGF72.

10. Diagnostics

- **Semen analysis** (LOINC-codable) showing severe asthenozoospermia / absent progressive motility with abnormal morphology.
- **Sperm ultrastructure:** SEM/TEM showing MMAF and destroyed axoneme.
- **Immunofluorescence:** WDR19 absent; IFT140/IFT88 mislocalized (research-grade confirmation).
- **Genetic testing:** whole-exome sequencing (how the gene was discovered) or targeted MMAF gene panels including *WDR19*; confirmatory Sanger of the biallelic variant. Chromosomal microarray, karyotyping, FISH, and mtDNA testing are **not** indicated for this monogenic nuclear-gene disorder.
- **Differential diagnosis:** other MMAF genes (DNAH1, CFAP43, CFAP44, CFAP69, FSIP2, WDR66, ARMC2, DNAH2/6/10) and — importantly — syndromic WDR19 ciliopathies, which must be excluded by renal/skeletal/retinal evaluation (CT, retinal imaging), as was done in the index case.

11. Outcome / Prognosis

No effect on survival or lifespan — the disorder is confined to fertility. Morbidity is reproductive/psychosocial only. **Prognosis for biological fatherhood is good with ICSI**: the index couple achieved clinical pregnancy, and MMAF cohorts broadly achieve good ICSI outcomes, with a caveat that some cohorts show modestly reduced embryo developmental potential and cumulative live-birth rates (PMID: 38745955).

12. Treatment

- **ICSI (NCIT C18113)** is the mainstay and is effective (PMID: 32323121; PMID: 34529793).
- **No pharmacotherapy, gene therapy, or disease-modifying treatment** exists or is in trials for this disorder.
- **Personalized medicine:** genotype (biallelic WDR19 LoF) guides counseling that natural conception is very unlikely but ICSI is appropriate; no pharmacogenomic considerations.

13. Prevention

- **Genetic counseling** for consanguineous couples and families with affected males.
- **Carrier/cascade screening** of relatives for the familial WDR19 variant.
- **Preimplantation genetic testing (PGT)** could prevent transmission of biallelic disease, though offspring of an affected father + non-carrier mother would be obligate heterozygous carriers (unaffected).
- No primary/secondary population prevention, immunization, or environmental intervention is applicable.

14. Other Species / Natural Disease

Orthologs: mouse *Wdr19* (NCBI 213081), rat *Wdr19* (305349), zebrafish *wdr19* (556414), *C. elegans* **dyf-2**. IFT/WDR19 function is deeply evolutionarily conserved across ciliated eukaryotes. No naturally occurring WDR19 male-infertility disease is catalogued in companion animals in the reviewed evidence; the conservation of IFT-A implies broad cross-species relevance for flagellar biology.

15. Model Organisms

No dedicated **testis-specific *Wdr19 knockout has been published for SPGF72. The most informative proxy is the germ-cell-specific Ift140 knockout mouse* (WDR19's direct IFT-A partner), which is infertile with reduced sperm number/motility and MMAF-like flagellar defects (PMID: 29236364), and the*** Dnai4-*null mouse**, which shows MMAF with downregulation of IFT-A members and a demonstrated DNAI4–IFT144 interaction in testis (PMID: 42083518). These models recapitulate the flagellar/infertility mechanism but not WDR19 specifically. Resource databases: MGI, IMPC, ZFIN, WormBase.

Evidence Base

PMID	Title (abbrev.)	Role in this report
32323121	*Novel homozygous WDR19 mutation … nonsyndromic asthenoteratospermia*	**Primary/defining evidence** for SPGF72: gene, variant, phenotype, ultrastructure, ICSI outcome
28621010	*Diversity of renal phenotypes in WDR19 mutations*	Documents syndromic WDR19 ciliopathy spectrum (contrast with nonsyndromic SPGF72)
25044745	*POC1B severe syndromic retinal ciliopathy*	WDR19 p.Leu710Ser variable expressivity (RP vs Jeune)
29134781 / 28332779	*Sensenbrenner/CED, WDR35*	IFT/CED gene-family context including WDR19
34815207	*Role of IFT in mammalian spermiogenesis*	IFT indispensable for sperm flagellum/ male fertility
29236364	*IFT140 essential for male fertility/ spermiogenesis*	Mouse model of WDR19's IFT-A partner recapitulates MMAF
42083518	*DNAI4 required for flagellum assembly/male fertility*	DNAI4–IFT144 testis interaction; IFT-A downregulation causes MMAF
36932088 / 36593313 / 36563665	*IFT-A structure / train assembly*	Six-subunit IFT-A architecture and retrograde role
40301266	*Intraflagellar Transport and Sperm Formation*	Defines WDR19 as 1 of 6 IFT-A subunits; IFT builds sperm
34529793	*ICSI in MMAF*	ICSI efficacy independent of genetic defect
40592014	*DNAH2/6/10 MMAF ICSI outcomes*	Live birth 5/6 via ICSI
38745955	*Decreased embryo potential in MMAF*	Caveat: reduced embryo/cumulative outcomes
34089056	*Exome sequencing in sperm motility disorders*	MMAF heterogeneity (~22 genes, ~50% yield)
30686508 / 30415212	*ARMC2 / CFAP69 MMAF*	Recurrent MMAF genes; differential diagnosis

Evidence source types: human clinical (single-case report) for the WDR19–SPGF72 link; model-organism (mouse) for the IFT-A mechanism; structural/computational (cryo-EM, AlphaFold) for IFT-A architecture; population-genetics (gnomAD) for inheritance mode.

Limitations and Knowledge Gaps

1. **Single human proband.** The entire human nonsyndromic WDR19 phenotype rests on one case (PMID: 32323121). Penetrance, expressivity, allelic range, and population frequency for SPGF72 are therefore essentially unknown. The gene–disease relationship would be classified as **limited** by ClinGen-style criteria until additional cases are reported.
2. **No dedicated WDR19 testis knockout.** The mechanism is inferred from IFT140 and DNAI4 models, not from direct WDR19 germ-cell perturbation. A conditional/germ-cell *Wdr19* knockout is the critical missing experiment.
3. **Variant-specific functional data absent.** Whether p.K1271E is a pure LoF or has flagellum-selective effects (explaining nonsyndromic sparing of somatic cilia) has not been functionally dissected.
4. **No epidemiology.** Prevalence, incidence, founder effects, and ethnic distribution are not quantifiable from one case.
5. **ICSI outcome generalization.** WDR19-specific ICSI data = 1 pregnancy; broader MMAF data apply by analogy and show a possible embryo-potential caveat.
6. **OMIM phenotype number.** The phenotype-series OMIM MIM number for SPGF72 was not recorded in the provided brief (gene OMIM = *608151).

Proposed Follow-up Experiments / Actions

1. **Case accrual / GeneMatcher.** Identify additional unrelated SPGF72 probands through MMAF cohorts and GeneMatcher to upgrade gene–disease evidence and define the allelic spectrum.
2. **Conditional germ-cell *Wdr19* knockout mouse.** Generate a Stra8-Cre or Ddx4-Cre conditional *Wdr19* deletion to test whether WDR19 loss directly causes MMAF and to determine why somatic cilia can be spared (flagellum-selective hypothesis).

3. **Variant functional assays.** Express p.K1271E in cell/ciliary models and in sperm-like systems to measure IFT-A stability, retrograde transport velocity, and IFT140/IFT88 localization versus wild type.
4. **Structural modeling.** Map p.K1271E onto the cryo-EM IFT-A structure to predict whether it disrupts a β-propeller interface, inter-subunit contact, or cargo-binding surface.
5. **ICSI outcome registry.** Pool WDR19/MMAF ICSI cases to quantify fertilization, embryo quality, and live-birth rates and to test whether WDR19 patients share the reduced embryo-potential signal seen in some MMAF cohorts (PMID: 38745955).
6. **Panel inclusion.** Ensure *WDR19* is included in clinical MMAF/male-infertility gene panels, with pre-test counseling to screen for latent syndromic ciliopathy features (renal, retinal, skeletal) given the gene's pleiotropy.

Report compiled from 5 discovery iterations, 9 confirmed findings, and 22 reviewed papers. Evidence base is dominated by a single human report (PMID: 32323121) supplemented by IFT-A structural biology and model-organism studies of partner genes.
