Sorsby Fundus Dystrophy (SFD): Comprehensive Disease Characteristics Report

Disease: Sorsby Fundus Dystrophy (SFD) · **Causal gene: TIMP3** (Tissue Inhibitor of Metalloproteinases 3) **MONDO:** MONDO:0007640 · **OMIM:** 136900 (and allelic 188826, TIMP3) · **Gene locus:** 22q12.3 · **Inheritance:** Autosomal dominant, complete penetrance

Summary

Sorsby Fundus Dystrophy is a rare, fully penetrant **autosomal dominant macular degeneration** caused by heterozygous missense mutations in **TIMP3** (Tissue Inhibitor of Metalloproteinases 3; HGNC:11822), located on chromosome 22q12.3. The gene was identified as causal by Weber and colleagues in 1994 (PMID: 7894485). The large majority of pathogenic variants are missense changes that introduce or disrupt a **cysteine residue in the C-terminal domain** of TIMP-3 (e.g., Ser179Cys, Tyr168Cys, Tyr191Cys, Ser204Cys), producing an unpaired cysteine that promotes aberrant intermolecular disulfide bonding, protein dimerization/aggregation, and resistance to normal turnover. The misfolded protein is secreted but accumulates abnormally in **Bruch's membrane** beneath the retinal pigment epithelium (RPE), the histologic hallmark of the disease.

The accumulated mutant TIMP-3 drives disease through **three convergent mechanistic arms**: (1) a **degenerative arm**, in which thickened sub-RPE deposits impair nutrient/vitamin-A transport (producing night blindness and delayed dark adaptation) while oxidative and metabolic stress drive RPE death and geographic atrophy; (2) a **neovascular arm**, in which dysregulated TIMP-3/VEGFR2 competition permits choroidal and polypoidal neovascularization; and (3) an inferred **inflammatory arm**, in which loss of TIMP-3's unique inhibition of ADAM17/TACE increases TNF-α signaling. Clinically, patients present in the **third to sixth decade** with nyctalopia and delayed dark adaptation, progressing to macular neovascularization, geographic atrophy, and ultimately widespread chorioretinal atrophy with central then peripheral vision loss.

There is currently **no cure and no approved gene therapy**, but management is meaningful: early **intravitreal anti-VEGF** therapy preserves vision in neovascular disease when initiated promptly, **high-dose vitamin A** can improve rod-mediated dark adaptation, **anti-TNF-α (adalimumab)** controlled refractory neovascular disease in a case report, and **CRISPR base-editing** correction strategies are in preclinical development. Patient-derived iPSC-RPE models now faithfully recapitulate the sub-RPE deposits and have established that **excess accumulation of functional mutant TIMP3** — rather than loss of TIMP-3 function — is the primary driver of pathology.

Key Findings

Finding 1 — TIMP3 is the causal gene; dominant missense mutations cluster in the C-terminal domain and introduce cysteines

Sorsby Fundus Dystrophy is caused by heterozygous, germline mutations in **TIMP3** on chromosome 22q12.3. Approximately **21 pathogenic variants** are currently reported, predominantly missense substitutions that affect or introduce cysteine residues in the C-terminal domain of the mature protein — including the well-studied **Ser179Cys, Tyr191Cys, and Ser204Cys** variants, as well as Tyr168Cys, Tyr174Cys, Tyr177Cys, Tyr182Cys, Tyr137Cys, and the novel Arg107Cys. The introduction of an odd/unpaired cysteine promotes aberrant intermolecular disulfide bonding and protein dimerization. All reported variants are germline, heterozygous, and classified pathogenic or likely pathogenic under ACMG/AMP criteria.

A 2024 mechanistic review states: *"There are 21 mutations currently associated with SFD, with some variants (e.g., Ser179Cys, Tyr191Cys, and Ser204Cys) having been studied much more than others"* (PMID: 38601018). Newly reported variants continue to expand the spectrum, such as the **c.319C>T, p.(Arg107Cys)** variant proposed as likely pathogenic in a 51-year-old woman with presenile cataract and nyctalopia (PMID: 40714900), and the **p.Tyr137Cys** variant found in patients initially diagnosed with retinitis pigmentosa (PMID: 32715858).

Ontology suggestions: Gene — HGNC:11822 (TIMP3); MONDO:0007640 (Sorsby fundus dystrophy); SO:0001583 (missense_variant).

Finding 2 — Mutant TIMP3 accumulates in Bruch's membrane and drives RPE dysfunction via metabolic, oxidative, and angiogenic derangement

Patient-derived iPSC-RPE carrying TIMP3 **S204C** form thick sub-RPE deposits that recapitulate the SFD donor-eye phenotype. These cells show **reduced transepithelial electrical resistance**, elevated accumulation of TIMP3 monomer and dimer **despite unchanged TIMP3 mRNA**, and increased oxidative stress; CRISPR correction of S204C reverses the phenotype. A key study found SFD iPSC-RPE *"formed significantly more sub-RPE deposits (~6–90 μm in height) compared to control RPE at 8 weeks"* (PMID: 34929159).

Crucially, a proof-of-concept stem-cell study demonstrated that **excess accumulation of mutant TIMP3** — not loss of function — drives SFD. SFD-hiPSC-RPE exhibited *"basolateral accumulation of TIMP3 monomers, despite no change in TIMP3 gene expression"* and *"mutant TIMP3 retained matrix metalloproteinase activity,"* with *"increased expression of ECM proteins, endothelial cell interactions and angiogenesis-related pathways"* (PMID: 32666594). This supports a **gain-of-function / toxic-accumulation** model rather than simple haploinsufficiency.

Oxidative stress is a central downstream consequence. S179C mutant mouse RPE shows baseline up-regulation of antioxidant genes and heightened sensitivity to oxidative insult (sodium iodate), indicating *"the presence of a pro-oxidant environment in the RPE in the presence of Timp3 mutations"* (PMID: 32828705). Metabolically, *"Mutations in Tissue Inhibitor of Metalloproteinases 3 (TIMP3) cause Sorsby's Fundus Dystrophy (SFD)"* and increase RPE **glycolytic activity** while dysregulating **glutamine metabolism** (PMID: 39047907). Post-translational modification matters too: **deglycosylation increases the aggregation and angiogenic properties** of mutant TIMP3 (PMID: 36430707).

Ontology suggestions: GO:0006979 (response to oxidative stress); GO:0006096 (glycolytic process); GO:0001525 (angiogenesis); CL:0002586 (retinal pigment epithelial cell); UBERON:0001782 (Bruch's membrane).

Finding 3 — Clinical course: adult-onset night blindness progressing to CNV and geographic atrophy; anti-VEGF preserves vision if treated early

Early symptoms of SFD include **nyctalopia (night blindness), delayed dark adaptation**, and reduced low-luminance/contrast acuity, often with normal photopic best-corrected visual acuity (BCVA) initially. Scotopic testing demonstrates *"a delayed rod-intercept time"* (PMID: 34352251), consistent with early rod/dark-adaptation dysfunction. Onset is typically in the **third to sixth decade of life**. The disease course includes drusen-like deposits, rapidly

progressive geographic atrophy, and choroidal/polypoidal neovascularization leading to central vision loss (PMID: 25766588). A characteristically **reduced late-phase ICG-A fluorescence** is an early sign detectable in asymptomatic carriers and may be useful for early identification of at-risk individuals (PMID: 25766588).

Therapeutically, a systematic review of 31 cases (mean follow-up 54 months) *"reported satisfied to excellent responses to anti-VEGF therapy if patients were diagnosed and treated immediately after onset of symptoms,"* with 55% maintaining driving vision (PMID: 34070857). High-dose **vitamin A** can improve rod-mediated dark adaptation (PMID: 34352251; mechanism consistent with the classic rod-plateau findings in PMID: 9286267). **Anti-TNF-α (adalimumab)** controlled recurrent neovascularization over 18 months in one patient with the Ser204Cys variant (PMID: 34376817).

Ontology suggestions: HP:0000662 (nyctalopia); HP:0000512 (abnormal dark adaptation); HP:0007754 (macular dystrophy); HP:0011506 (choroidal neovascularization); HP:0001103 (macular atrophy).

Finding 4 — Historical gene discovery and human histopathology of the Bruch's membrane deposit

Weber et al. (1994) mapped the SFD locus to 22q13-qter and *"identified point mutations in the TIMP3 gene in affected members of two SFD pedigrees... predicted to disrupt the tertiary structure and thus the functional properties of the mature protein"* (PMID: 7894485) — the landmark discovery establishing TIMP3 causality. Six years later, Chong et al. (2000) analyzed a genetically confirmed SFD donor eye and showed that the sub-RPE deposit contained **collagens, elastin, glycosaminoglycans, lipids, and calcium**, with TIMP-3 immunoreactivity *"more extensive in the SFD eye"* and co-localizing with elastin, on a morphologically altered elastic layer of Bruch's membrane (PMID: 10711711). This provides the direct human-tissue anchor for the molecular model.

Finding 5 — Wild-type TIMP-3 is anti-angiogenic via VEGFR2 competition; SFD mutations dysregulate this axis

Wild-type TIMP-3 **competes with VEGF-A for binding to VEGFR2 (KDR)**, inhibiting downstream ERK and AKT phosphorylation and thereby suppressing endothelial proliferation, migration, and capillary formation. One study described *"tissue inhibitor of metalloproteinase (TIMP-3), which competed with vascular endothelial growth factor (VEGF-A) to bind to vascular endothelial growth factor receptor 2 (VEGFR2, KDR). This effect was related to inhibiting the*

phosphorylation of ERK and AKT" (PMID: 32762747). A TIMP-3-derived peptide (p700) *"binds to and inhibits a number of tyrosine kinase growth factor receptors (VEGFRs1-3, FGFRs 1-4 and PDGFRα)"* (PMID: 33504102), confirming the receptor-binding anti-angiogenic activity resides in TIMP-3. In SFD, mutant TIMP-3 dimerization impairs VEGFR2 inhibition (PMID: 37013036), and deglycosylation increases its angiogenic properties (PMID: 36430707) — providing the mechanistic basis for the choroidal neovascularization seen clinically and the clinical response to anti-VEGF therapy.

Ontology suggestions: GO:0001525 (angiogenesis); GO:0048010 (VEGF receptor signaling pathway); GO:0043066 (negative regulation of apoptotic process).

Finding 6 — TIMP-3 is the physiological inhibitor of ADAM17/TACE (TNF-α sheddase); the inferred inflammatory arm

Among the four TIMPs, **only TIMP-3 inhibits ADAM17/TACE**, the enzyme that sheds TNF-α and TNF receptors. Under basal conditions *"TACE was predominantly present as dimers at the cell surface… enabl[ing] efficient association with tissue inhibitor of metalloproteinase-3 (TIMP3) and silencing of TACE activity,"* while MAPK (ERK/p38) signaling shifts TACE to monomers and relieves inhibition (PMID: 22550340). Recombinant TIMP-3 blocks TACE-mediated shedding of TNF-α and TNFR1 in multiple tissues, including corneal epithelium (PMID: 19407014) and hepatic ischemia/reperfusion models (PMID: 17164725). This provides the biological rationale for anti-TNF (adalimumab) controlling SFD neovascular activity (PMID: 34376817). A review frames SFD within a broader context: *"Pathological changes in the ECM of Bruch's membrane have been described in both monogenic IRDs, such as Sorsby fundus dystrophy (SFD) and Doyne honeycomb retinal dystrophy (DHRD), as well as in the genetically complex age-related macular degeneration (AMD)"* (PMID: 36936905) — relevant to shared pathomechanism and differential diagnosis. Note: the inflammatory arm is **inferred** from TIMP-3 biology and a single case report, not yet demonstrated in SFD tissue at scale.

Ontology suggestions: GO:0006919 (TNF-mediated signaling); GO:0051044 (positive regulation of membrane protein ectodomain proteolysis); CHEBI — TNF-alpha; protein target ADAM17 (HGNC:195).

Mechanistic Model / Interpretation

Ordered causal chain (initiating lesion → clinical manifestation)

1. A **heterozygous missense mutation in TIMP3** (e.g., Ser204Cys) introduces an unpaired cysteine in the C-terminal domain → **leads to** an odd number of cysteine residues in the mature protein.
2. The unpaired cysteine **results in** aberrant intermolecular disulfide bonding → **leads to** mutant TIMP-3 **dimerization and aggregation** (demonstrated: PMID: 37013036).
3. The misfolded protein is still secreted and retains MMP-inhibitory activity but **resists normal turnover** → **results in** progressive **accumulation of TIMP-3 in Bruch's membrane** despite normal TIMP3 mRNA levels (demonstrated in iPSC-RPE: PMID: 32666594, PMID: 34929159; human tissue: PMID: 10711711).
4. Accumulated protein nucleates **thick sub-RPE deposits** containing elastin, collagen, GAGs, lipid, and calcium, thickening and altering Bruch's membrane → **the chain then branches into three arms:**

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                ┌─> ARM A (DEGENERATIVE): Thickened Bruch's membrane impairs
                │     nutrient/vitamin-A transport across RPE  ──> rod dysfunction,
                │     delayed dark adaptation, NIGHT BLINDNESS (early symptom)
                │     + pro-oxidant RPE environment & altered glycolysis/glutamine
Mutant TIMP-3   │     metabolism  ──> RPE death ──> GEOGRAPHIC ATROPHY
accumulation ─┤
in Bruch's      ├─> ARM B (NEOVASCULAR): Dysregulated mutant TIMP-3 loses control
membrane        │     of VEGF-A / VEGFR2 (KDR) competition  ──> endothelial
                │     ERK/AKT activation ──> CHOROIDAL / POLYPOIDAL NEOVASCULARIZATION
                │     ──> exudation, hemorrhage, disciform scar ──> CENTRAL VISION LOSS
                │
                └─> ARM C (INFLAMMATORY, inferred): Loss of TIMP-3 inhibition of
                      ADAM17/TACE ──> increased TNF-α / TNFR1 shedding ──> local
                      inflammation amplifying neovascular/degenerative injury
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1. Convergence of the three arms **results in** the full clinical picture: adult-onset nyctalopia → macular neovascularization and/or geographic atrophy → widespread chorioretinal atrophy, fibrosis, and choroidal thinning → **progressive central then peripheral vision loss**.

Upstream vs downstream

- **Upstream (initiating):** TIMP3 mutation → misfolding/dimerization → Bruch's membrane accumulation. These are shared across all patients and variants and are the logical targets for curative (gene-correction) therapy.
- **Downstream (effector):** oxidative stress, metabolic reprogramming, VEGFR2 dysregulation, TNF-α signaling. These are variant-independent convergence points and the targets of current symptomatic therapy (anti-VEGF, vitamin A, anti-TNF).

Cell types and tissues

Level	Structure	Ontology term
Organ	Eye / retina	UBERON:0000970 / UBERON:0000966
Primary site	Macula	UBERON:0005388
Key membrane	Bruch's membrane (sub-RPE deposits)	UBERON:0001782
Primary cell	Retinal pigment epithelial cell	CL:0002586
Affected cells	Rod photoreceptor (early), cone photoreceptor	CL:0000604 / CL:0000573
Vascular	Choroidal endothelial cells (neovascularization)	CL:0000115
Subcellular	ER (misfolding), extracellular matrix	GO:0005788 / GO:0031012

Section-by-Section Disease Characteristics

1. Disease Information

SFD is a rare autosomal dominant macular dystrophy with complete penetrance affecting the macula (PMID: 36197222). **Identifiers:** OMIM 136900 (phenotype) and 188826 (TIMP3 gene); MONDO:0007640; gene locus 22q12.3. **Synonyms:** SFD, Sorsby's fundus dystrophy, Sorsby pseudoinflammatory macular dystrophy, hereditary hemorrhagic macular dystrophy, fundus

dystrophy pseudoinflammatory of Sorsby. Information is derived primarily from **aggregated disease-level resources** (OMIM, Orphanet) and from case series/pedigrees — the disease is rare and no large EHR cohorts exist.

2. Etiology

Primary cause: monogenic — heterozygous dominant TIMP3 missense mutations (Finding 1). **Genetic risk:** the causal variant is sufficient for disease (complete penetrance); no established modifier genes. **Environmental risk/protective:** none established as causal; oxidative stress is a downstream amplifier, and antioxidant/vitamin-A status may modulate symptom severity (Findings 2, 3). **Gene–environment interaction:** mutant RPE shows heightened sensitivity to oxidative insult (PMID: 32828705), suggesting environmental oxidative load could modulate progression, though this is not clinically proven.

3. Phenotypes

Phenotype	Type	Onset	Progression	HPO
Night blindness / nyctalopia	Symptom	Early (3rd–6th decade)	Progressive	HP:0000662
Delayed dark adaptation	Functional sign	Early	Progressive	HP:0000512
Reduced contrast/low-luminance acuity	Sign	Early	Progressive	HP:0030532
Drusen-like sub-RPE deposits	Clinical sign	Early–mid	Progressive	HP:0011505
Choroidal/polypoidal neovascularization	Clinical sign	Mid	Episodic/ progressive	HP:0011506
Geographic/macular atrophy	Clinical sign	Mid–late	Progressive	HP:0001103
Central scotoma / central vision loss	Symptom	Mid–late	Progressive	HP:0000603
Widespread chorioretinal atrophy	Sign	Late	Progressive	HP:0000532

Severity is **moderate-to-severe** and progressive; quality-of-life impact is substantial due to loss of central (reading, driving) and eventually peripheral vision (PMID: 25766588, PMID: 34352251).

4. Genetic / Molecular Information

Causal gene: TIMP3 (HGNC:11822), 22q12.3. **Variants:** ~21 reported, predominantly **missense** introducing/affecting C-terminal cysteines; classified pathogenic/likely pathogenic (ACMG). Examples: Ser179Cys, Tyr168Cys, Tyr174Cys, Tyr177Cys, Tyr182Cys, Tyr191Cys, Ser204Cys (c.610A>T), Tyr137Cys (c.410A>G), Arg107Cys (c.319C>T), and the c.484G>A variant used in iPSC modeling (PMID: 38640637). **Origin:** germline, heterozygous. **Allele frequency:** extremely rare in gnomAD (private/near-private pathogenic variants). **Functional consequence:** toxic gain-of-function via accumulation — mutant protein retains MMP-inhibitory activity (PMID: 32666594); dimerization impairs VEGFR2 inhibition (PMID: 37013036). **Modifier genes/ epigenetics/chromosomal abnormalities:** none established for SFD.

5. Environmental Information

No established environmental, lifestyle, or infectious causes. Oxidative stress acts as a **downstream modifier** rather than an environmental cause (Finding 2). SFD is not infectious or zoonotic.

6. Mechanism / Pathophysiology

See the **Mechanistic Model** section above for the full ordered causal chain and three-arm branching. Molecular pathways: VEGF/VEGFR2–ERK/AKT (angiogenesis), ADAM17/TACE–TNF-α (inflammation), ECM/metalloproteinase homeostasis, glycolysis/glutamine metabolism, oxidative-stress response. Protein dysfunction: misfolding, aberrant disulfide dimerization, aggregation, impaired turnover. Biochemical hallmark: accumulation of a catalytically active but mislocalized/aggregated inhibitor.

7. Anatomical Structures Affected

Primary: **macula/retina → RPE → Bruch's membrane** (UBERON:0001782) → choroid. Secondary: photoreceptors (rods early, then cones), choroidal vasculature. Bilateral involvement is the rule, though inter-eye and intra-familial variability occurs (PMID: 10396378). Subcellular: ECM, ER. Body system: visual/nervous (special sense).

8. Temporal Development

Onset: adult, typically 3rd–6th decade; insidious/chronic. Some variants (e.g., Tyr174Cys) present earlier (3rd decade) with dark-adaptation problems, others (Tyr177Cys, Tyr182Cys) in the 6th decade with metamorphopsia/acuity loss (PMID: 25766588). **Progression:** chronic, lifelong, progressive — drusen-like deposits → neovascularization and/or geographic atrophy → widespread chorioretinal atrophy. Rate variable even within families (PMID: 10396378). **Critical window:** prompt detection and treatment of neovascularization is the key intervention opportunity (PMID: 34070857).

9. Inheritance and Population

Inheritance: autosomal dominant, **complete penetrance**, variable expressivity (including intra-familial). **Epidemiology:** rare (orphan disease; exact prevalence not well established). No anticipation, no documented germline mosaicism specific to SFD. Founder/geographic clustering has been described for specific variants; novel variants reported in Czech families (PMID: 38612555). Sex ratio ~equal (autosomal). Carrier frequency not applicable in the recessive sense (dominant disease).

10. Diagnostics

Clinical imaging: fundus exam (drusen-like deposits, atrophy), **OCT** and **OCT-angiography** (deposits, neovascular membranes), **fundus autofluorescence** (hyper-AF), **ICG-A** (characteristic reduced late-phase fluorescence — early sign, PMID: 25766588), **fluorescein angiography**. **Functional:** dark adaptation (delayed rod-intercept time), scotopic/ERG abnormalities (PMID: 34352251, PMID: 40714900). **Genetic testing:** single-gene TIMP3 testing or inherited-retinal-disease gene panels is **definitive and recommended**. **Differential diagnosis:** neovascular AMD (SFD often misdiagnosed as "wet AMD" in young patients, PMID: 36421778), retinitis pigmentosa (PMID: 32715858), Doyne honeycomb/malattia leventinese (EFEMP1), and other macular dystrophies. A strong family history of early-onset "wet AMD" should prompt TIMP3 testing.

11. Outcome / Prognosis

Not life-limiting — SFD affects vision, not survival. Prognosis for vision is **guarded but improved by early treatment**: 55% of anti-VEGF-treated patients maintained driving vision (PMID: 34070857). Without treatment, bilateral central vision loss and eventual widespread

chorioretinal atrophy are expected. **Prognostic factors:** promptness of neovascular detection/treatment is the dominant modifiable factor. Complications: disciform scarring, geographic atrophy, legal blindness.

12. Treatment

Modality	Agent/approach	Evidence	NCIT suggestion
Anti-VEGF (first-line for CNV)	Bevacizumab, ranibizumab, aflibercept	Favorable if early (PMID: 34070857, PMID: 25766588)	NCIT:C2039 (anti-VEGF therapy)
Vitamin A supplementation	High-dose vitamin A	Improves dark adaptation (PMID: 34352251, PMID: 9286267)	NCIT:C944 (Vitamin A)
Anti-TNF-α	Adalimumab	Controlled refractory CNV (case, PMID: 34376817)	NCIT:C1490 (Adalimumab)
Corticosteroid	Intravitreal triamcinolone	Inactivated CNV (case, PMID: 34376817)	NCIT:C874 (Triamcinolone)
Gene correction (experimental)	CRISPR base editing (ABE/GBE)	Preclinical bioinformatic feasibility (PMID: 36421778)	NCIT:C181947 (CRISPR)

No approved gene therapy exists (PMID: 36197222). Personalized medicine: base-editing strategies are inherently variant-specific (PMID: 36421778).

13. Prevention

No primary prevention (monogenic). **Secondary prevention:** cascade genetic testing of at-risk relatives, early ICG-A/OCT surveillance of carriers, and prompt treatment of incipient neovascularization. **Genetic counseling:** autosomal dominant 50% transmission risk; prenatal/preimplantation testing possible for known familial variants. Tertiary prevention: ongoing anti-VEGF for recurrent neovascular disease.

14. Other Species / Natural Disease

No naturally occurring SFD analog is established in companion animals or wildlife. The gene is conserved: **Timp3** orthologs exist in mouse (NCBI Gene 21859) and other vertebrates. No zoonotic or cross-species transmission (genetic disease).

15. Model Organisms

- **Patient-derived iPSC-RPE** (in vitro): the leading model — recapitulates sub-RPE deposits, reduced TEER, TIMP3 accumulation, oxidative/metabolic stress; CRISPR-correctable (PMID: 34929159, PMID: 32666594). iPSC lines established for S204C and c.484G>A variants (PMID: 38640637).
- **Mouse knock-in (Timp3 S179C):** recapitulates pro-oxidant RPE environment and heightened oxidative-stress sensitivity (PMID: 32828705).
- **Limitations:** mouse models do not fully reproduce the human macular neovascular phenotype (mice lack a macula); iPSC-RPE lack choroidal vasculature and long-term in-vivo aging. Databases: MGI (mouse), Cellosaurus (iPSC lines).

Evidence Base

PMID	Title (abbrev.)	Role
7894485	*TIMP3 mutations in Sorsby's fundus dystrophy* (Weber 1994)	Landmark gene identification (Finding 4)
10711711	*TIMP-3, collagen, elastin histopathology of SFD* (Chong 2000)	Human donor-eye deposit composition (Finding 4)
38601018	*Mechanisms of TIMP-3 accumulation in SFD* (review)	Variant spectrum; 21 mutations (Finding 1)
34929159	*ECM dysfunction in SFD patient-derived RPE*	iPSC-RPE sub-RPE deposits (Finding 2)
32666594	*Excess mutant TIMP3 as cause of SFD*	Gain-of-function / accumulation model (Finding 2)
32828705	*RPE oxidative-stress sensitivity in SFD*	Pro-oxidant RPE; mouse S179C (Finding 2)
39047907	*TIMP3 mutations alter glycolysis/glutamine*	Metabolic reprogramming (Finding 2)
36430707	*Deglycosylation increases aggregation/ angiogenesis*	PTM modulates pathogenicity (Findings 2, 5)
37013036	*All SFD mutations cause TIMP3 dimerization impairing VEGFR2*	Unifying dimerization mechanism (Finding 5)
32762747	*TIMP-3 competes with VEGF-A for VEGFR2*	Anti-angiogenic mechanism (Finding 5)
33504102	*TIMP3 peptide p700 inhibits VEGFR/FGFR/ PDGFR*	Receptor-binding activity (Finding 5)
22550340	*TACE dimerization and TIMP3 association*	TIMP-3 inhibits ADAM17/TACE (Finding 6)
19407014	*TIMP-3 blocks TNFR1 shedding in corneal epithelium*	TNF-α axis control (Finding 6)
17164725	*TIMP-3 inhibits TACE in hepatic injury*	TNF-α axis control (Finding 6)
34376817	*Anti-TNF-α (adalimumab) for SFD*	Clinical inflammatory-arm support (Findings 3, 6)
34070857	*Anti-VEGF for SFD MNV: systematic review*	Treatment efficacy (Finding 3)

PMID	Title (abbrev.)	Role
34352251	*Visual dysfunction/structure in SFD*	Early rod dysfunction; vitamin A (Finding 3)
25766588	*Novel mutations, phenotype, treatment*	Phenotype, ICG-A early sign (Finding 3)
36421778	*CRISPR base editing options in SFD*	Experimental gene correction (Finding 1, Treatment)
36936905	*ECM microenvironment in retinal disorders*	Shared pathomechanism/DDx (Finding 6)

Evidence-type mix: human clinical/genetic (Findings 1, 3, 4), in vitro iPSC and biochemistry (Findings 2, 5, 6), model organism (mouse S179C, Finding 2), and computational/bioinformatic (base editing, Finding 1).

Limitations and Knowledge Gaps

1. **Inflammatory arm is inferred, not proven in SFD.** The ADAM17/TACE–TNF-α mechanism rests on TIMP-3 biology from non-ocular tissues plus a single SFD case treated with adalimumab (PMID: 34376817). TNF-α levels in SFD retina/vitreous have not been systematically quantified.
2. **Conflicting dimerization data.** One iPSC study found TIMP3 dimers in both SFD and control cells and concluded dimerization does *not* drive pathology (PMID: 32666594), whereas others argue all SFD mutations converge on dimerization impairing VEGFR2 (PMID: 37013036). The precise toxic species (monomer accumulation vs dimer/aggregate) remains unresolved.
3. **No large epidemiological data** — prevalence, incidence, and natural-history cohorts are limited to case series; QoL has not been measured with standardized instruments (EQ-5D/SF-36).
4. **No model fully recapitulates human neovascularization** — mice lack a macula; iPSC-RPE lack choroid.
5. **Genotype–phenotype correlation** (e.g., why Tyr174Cys presents a decade earlier) is incompletely mapped.

6. **No approved disease-modifying therapy** exists; all curative approaches remain preclinical.

Proposed Follow-up Experiments / Actions

1. **Quantify TNF-α/ADAM17 activity directly in SFD models** (iPSC-RPE ± co-cultured immune/endothelial cells and S179C mouse RPE) to test whether the inflammatory arm is active in SFD tissue, and whether adalimumab normalizes it — converting an inferred mechanism to a demonstrated one.
2. **Resolve the toxic-species question** with quantitative, variant-matched assays comparing monomer accumulation, dimer formation, aggregation, and VEGFR2-binding across multiple variants in isogenic iPSC-RPE, reconciling PMID: 32666594 and PMID: 37013036.
3. **Advance CRISPR base-editing correction** (PMID: 36421778) from bioinformatic feasibility to functional rescue in patient iPSC-RPE, measuring deposit resolution, TEER recovery, and off-target/bystander edits (e.g., the predicted p.Ile205Thr bystander).
4. **Build a prospective natural-history registry** with standardized imaging (OCT, FAF, ICG-A), dark-adaptation testing, and QoL instruments to define progression rates, genotype–phenotype correlations, and treatment windows.
5. **Test antioxidant/vitamin-A combination prophylaxis** in carriers, given the pro-oxidant RPE environment (PMID: 32828705) and dark-adaptation benefit of vitamin A (PMID: 34352251).
6. **Evaluate deposit-clearance / ECM-remodeling strategies** targeting Bruch's-membrane accumulation upstream of all three disease arms.

Report compiled from a 5-iteration autonomous investigation: 6 confirmed findings, 42 papers reviewed. Evidence spans human clinical/genetic, in vitro iPSC-RPE, mouse model, biochemical, and computational sources.
