

Doyne Honeycomb Retinal Dystrophy (DHRD) / Malattia Leventinese — Comprehensive Disease Report

Disease: Doyne Honeycomb Retinal Dystrophy (DHRD) **Synonym:** Malattia Leventinese (ML); Autosomal dominant radial drusen; Autosomal dominant drusen **MONDO:** MONDO:0007471 · **OMIM:** #126600 · **Gene:** *EFEMP1* (fibulin-3) at 2p16.1 · **Inheritance:** Autosomal dominant · **Category:** Mendelian

Evidence source note: This report synthesizes aggregated disease-level resources (OMIM, Orphanet, ClinVar, UniProt) and primary literature (PubMed). It is **not** derived from individual patient EHR data. Evidence types are flagged as *human clinical*, *model organism (mouse)*, *in vitro (iPSC-RPE/cell)*, or *review*. DHRD is rare, so much of the clinical literature consists of case series and single families; mechanistic depth comes from mouse and iPSC models.

Summary

Doyne Honeycomb Retinal Dystrophy (DHRD) and Malattia Leventinese (ML) are the **same autosomal dominant macular dystrophy**, caused by a **single recurrent missense mutation** in *EFEMP1*: **c.1033C>T, p.Arg345Trp (R345W)**, which alters the secreted extracellular-matrix glycoprotein **fibulin-3**. This degree of genetic homogeneity is remarkable: essentially every molecularly confirmed case worldwide carries this one variant, which was mapped to chromosome 2p16-21 and found absent in 477 controls and 494 age-related macular degeneration (AMD) patients, establishing both specificity and the monogenic nature of the disease ([PMID: 10369267](#)).

Mechanistically, mutant fibulin-3 **misfolds and is retained intracellularly** within retinal pigment epithelium (RPE) cells rather than being efficiently secreted ([PMID: 12242346](#)). This triggers endoplasmic-reticulum (ER) stress, aberrant extracellular-matrix accumulation, and a downstream cascade of **alternative-pathway complement activation, NLRP3-inflammasome inflammation**, and **impaired RPE cholesterol efflux and lysosomal function**. The clinical consequence is the early-adult-onset accumulation of **radial /**

honeycomb sub-RPE drusen between the RPE and Bruch's membrane, producing progressive, bilateral central vision loss, sometimes complicated by secondary choroidal neovascularization (CNV).

There is **no approved disease-modifying therapy**; management is supportive (low-vision aids, monitoring, genetic counseling), with intravitreal anti-VEGF reserved for neovascular complications (variable, sometimes absent response). However, the well-defined causal chain has yielded multiple **preclinically validated therapeutic strategies** — GSK3 inhibition, complement factor B inhibition, NLRP3/caspase-1 inhibition, and lysosome modulation (trehalose) — tested in the *Efemp1* R345W knock-in mouse and patient-derived iPSC-RPE. Because DHRD reproduces the drusen biology of AMD from a single clean genetic lesion, it is widely regarded as a **monogenic surrogate model for AMD**.

Key Findings

F001 — A single recurrent *EFEMP1* R345W mutation causes DHRD/ML

A single heterozygous missense variant — *EFEMP1* c.1033C>T, p.Arg345Trp (**R345W**) — has been identified as the cause in essentially all molecularly confirmed cases of DHRD/ML, inherited in an autosomal dominant pattern. *EFEMP1* encodes the secreted ECM glycoprotein **fibulin-3 (F3)**. Recent case reports from previously unreported populations (the first Scandinavian case, [PMID: 33689237](#); Indian cases, [PMID: 41971199](#)) continue to confirm R345W as the sole recurrent pathogenic variant.

"A single variant in EFEMP1: c.1033C>T (R345W) has been identified as the cause in all cases." — [PMID: 33689237](#)

"Malattia Leventinese is a rare autosomal dominant macular dystrophy caused by a single" — [PMID: 41971199](#)

F002 — Mutant fibulin-3 misfolds and is retained intracellularly, driving sub-RPE drusen

Marmorstein et al. (PMID: 12242346) showed that wild-type EFEMP1 is a secreted protein whereas mutant EFEMP1 (R345W) is **misfolded, secreted inefficiently, and retained within cells**. In ML eyes, EFEMP1 accumulates within RPE cells and between the RPE and drusen; notably, EFEMP1 is **not** a major component of the drusen itself. In AMD eyes, EFEMP1 accumulates beneath the RPE overlying drusen. Patient-derived iPSC-RPE models from ML patients show fibulin-3 and ApoE aggregation, increased ER stress, and enhanced apoptosis (PMID: 42484373).

"wild-type EFEMP1 is a secreted protein whereas mutant EFEMP1 is misfolded, secreted inefficiently, and retained within cells" — PMID: 12242346

"MAL iPSC-RPE exhibited fibulin-3 and apolipoprotein E (ApoE) aggregation, increased endoplasmic reticulum stress, and enhanced apoptosis" — PMID: 42484373

F003 — Alternative-pathway complement and NLRP3 inflammasome drive sub-RPE deposits

In *Efemp1* R345W/R345W knock-in mice, aged eyes showed an **~2-fold elevation of complement breakdown products iC3b and Ba (P<0.05)**; deletion of complement factor B (*Cfb*) partially normalized dysregulated pathways, and an **oral factor B inhibitor reduced sub-RPE deposits by 65% (P=0.029)** (PMID: 35943778). Genetic removal of *Nlrp3* and its downstream effector caspase-1 (*Casp1*) protected against R345W *Efemp1*-induced basal laminar deposit formation (PMID: 39464028; PMID: 41198612). RNA-seq of knock-in eyecups showed an increased unfolded-protein response, decreased neural-retina mitochondrial function by 3 months, and increased inflammatory pathways by 17 months.

"oral dosing of a small molecule FB inhibitor from 10 to 12 months of age reduced sub-RPE deposits by 65% (P = 0.029)" — PMID: 35943778

"Complement activation was increased in aged Efemp1ki/ki eyes with an approximately 2-fold elevation of complement breakdown products iC3b and Ba (P < 0.05)" — PMID: 35943778

"we directly tested the role of Nlrp3 and its downstream effector, caspase 1 (Casp1) in mediating early AMD-like pathology" — PMID: 39464028

F004 — DHRD/ML maps to 2p16-21; R345W absent in controls and AMD cohorts (specificity)

Stone et al. (1999, PMID: 10369267) mapped both ML and DHRD loci to **chromosome 2p16-21** and identified a single non-conservative Arg345Trp mutation in *EFEMP1* in all families studied. The change was **absent in 477 control individuals and in 494 AMD patients**, establishing disease specificity and distinguishing DHRD/ML genetically from common AMD.

"a single non-conservative mutation (Arg345Trp) in the gene EFEMP1 ... in all families studied. This change was not present in 477 control individuals or in 494 patients with age-related macular degeneration" — PMID: 10369267

F005 — Phenotype: early-onset radial/honeycomb sub-RPE drusen with variable expressivity, CNV, central vision loss

Clinical reports consistently describe **early-onset (typically 2nd–4th decade)** yellow-white drusen beneath the RPE, often **radially distributed** around the macula and nasal to the optic disc, which coalesce into a **honeycomb** pattern. Drusen show increased fundus autofluorescence. Complications include RPE changes and secondary CNV. Marked **intra- and inter-familial phenotypic variability** in visual loss and imaging findings occurs despite the identical genotype (PMID: 25111685; PMID: 33689237; PMID: 41971199).

"Intrafamilial patients with Malattia leventinese/Doyne honeycomb retinal dystrophy seem to be phenotypically variable in visual loss, ophthalmoscopic findings, autofluorescence imaging, and optical coherence tomography changes" — PMID: 25111685

"All cases exhibited early-onset central vision loss and small, radially distributed drusen, consistent with ML/DHRD" — PMID: 41971199

F006 — No approved disease-modifying therapy; supportive care with emerging preclinical targets

No approved therapy halts DHRD/ML progression; care is supportive (low-vision aids, monitoring, genetic counseling). Secondary CNV is treated with intravitreal anti-VEGF, though responses are variable and sometimes absent ([PMID: 33689237](#)). Nanosecond **2RT laser** has been piloted and may stabilize some functional parameters without structural change ([PMID: 38023612](#)). Preclinical disease-modifying strategies target the causal pathway: **GSK3 inhibition (CHIR99021)** reduced R345W-associated basal laminar deposits ([PMID: 39114980](#)); an **oral complement factor B inhibitor** reduced sub-RPE deposits by 65% ([PMID: 35943778](#)); **NLRP3/caspase-1 ablation** prevented deposits ([PMID: 39464028](#)); and the lysosome modulator **trehalose** reduced drusen-like deposits in patient iPSC-RPE ([PMID: 42484373](#)).

"treatment of 8-month-old R345W+/+ knockin mice with CHIR (25 mg/kg i.p., 1 mo) was well tolerated and significantly reduced R345W F3-associated AMD-like basal laminar deposit number and size, thereby preventing the main pathological feature in these mice" — [PMID: 39114980](#)

"2RT treatment in DHRD may improve or stabilize some retinal function parameters without significant structural changes" — [PMID: 38023612](#)

"Secondary choroidal neovascularizations were identified on both eyes, and anti-vascular endothelial growth factor was administered, without effect" — [PMID: 33689237](#)

F007 — Disease models: *Efemp1* R345W knock-in mouse and patient iPSC-RPE recapitulate sub-RPE/basal laminar deposits

The principal in vivo model is the **Efemp1 p.R345W knock-in mouse** (Efemp1ki/ki; R345W+/+), which develops microscopic basal laminar deposits (BLamDs) — an early feature of DHRD/ML and AMD — alongside increased unfolded-protein response, decreased neural-retina mitochondrial function by 3 months, increased inflammatory/complement pathways by 17 months, and a sex difference (females > males). A **HiBiT luminescent tag** knocked into the endogenous F3 locus enables high-throughput fibulin-3 detection for drug screening ([PMID: 39114980](#)). In vitro, **patient-derived iPSC-RPE** recapitulate fibulin-3/ApoE aggregation, ER stress, apoptosis, and (with photoreceptor outer-segment feeding) drusen-like deposits containing ApoE, complement, and collagen IV ([PMID: 42484373](#)); isogenic DHRD iPSC-RPE revealed impaired cholesterol efflux via CES1 downregulation ([PMID: 33909993](#)).

"Aged Efemp1 R345W/R345W knock-in mice (Efemp1ki/ki) develop microscopic deposits on the basal side of retinal pigment epithelial cells (RPE), an early feature in DHRD/ML and AMD" — PMID: 35943778

"Long-term culture with photoreceptor outer segments led to drusen-like deposits containing ApoE, complement components, and collagen IV accumulation" — PMID: 42484373

F008 — Lipid/cholesterol dysregulation and lysosomal dysfunction are downstream RPE pathologies

DHRD iPSC-RPE exhibit abnormal intracellular lipid-droplet accumulation and pericellular lipid-rich deposits, driven by **downregulation of carboxylesterase 1 (CES1)** — impairing conversion of cholesteryl ester to free cholesterol and thus cholesterol efflux (PMID: 33909993). CES1 knockdown or EFEMP1 overexpression reproduced lipid accumulation. Independently, ML iPSC-RPE show **lysosomal dysfunction with reduced TFEB** transcripts and altered lysosomal gene programs, plus increased hexosylceramide and bis(monoacylglycerol)phosphate; trehalose restored lysosomal function and reduced drusen-like deposits, MMP2 activation, and apoptosis (PMID: 42484373).

"we detected significant downregulation of carboxylesterase 1 (CES1), an enzyme that converts cholesteryl ester to free cholesterol, an indispensable process in cholesterol export" — PMID: 33909993

"A key pathological feature was lysosomal dysfunction associated with altered regulation of lysosomal gene programs, including reduced transcription factor EB transcript levels" — PMID: 42484373

F009 — Diagnosis rests on multimodal retinal imaging plus *EFEMP1* genetic confirmation

Multimodal imaging defines the diagnostic signature: large round drusen in the perimacular area and around the optic disc, and small non-round, radially distributed drusen temporal to the macula. **Fundus autofluorescence (FAF)** shows intense autofluorescence of large drusen; on **fluorescein (FA)/indocyanine green (ICGA) angiography**, large round drusen become hyperfluorescent late while small radial drusen decrease fluorescence; **OCT** shows hyperreflective material between RPE and Bruch's membrane causing focal dome-shaped or

diffuse RPE elevation ([PMID: 22814526](#)). Best-corrected visual acuity ranged 20/25 to 20/200. Definitive diagnosis is molecular: detection of heterozygous *EFEMP1* c.1033C>T (p.Arg345Trp) by single-gene testing, inherited retinal disease gene panels, or exome sequencing ([PMID: 41971199](#)).

"OCT showed the large round drusen as focal or diffuse deposition of hyperreflective material between the RPE and Bruch membrane within the macula, determining focal dome-shaped or diffuse RPE elevation" — [PMID: 22814526](#)

"The smallest drusen were not round, radially distributed, mostly localized temporally to the macula" — [PMID: 22814526](#)

F010 — DHRD/ML is a monogenic surrogate model for AMD; fibulin-3 regulates Bruch's-membrane ECM and MMP/TIMP3 balance

A 2026 review frames DHRD as *"a monogenic disorder that serves as a surrogate model for AMD due to similar phenotypic manifestations,"* focusing on interactions between *EFEMP1*, matrix metalloproteinases (MMPs), tissue inhibitor of metalloproteinases-3 (TIMP3), and complement factors, and states the *EFEMP1* R345W mutation *"causes rapid disease progression through impaired protein secretion, abnormal matrix accumulation, and complement dysregulation"* ([PMID: 42569289](#)). In both DHRD/ML and AMD, drusen form as extracellular deposits between RPE and Bruch's membrane, and both share alternative-complement activation (factor H/factor B axis; [PMID: 17659362](#)).

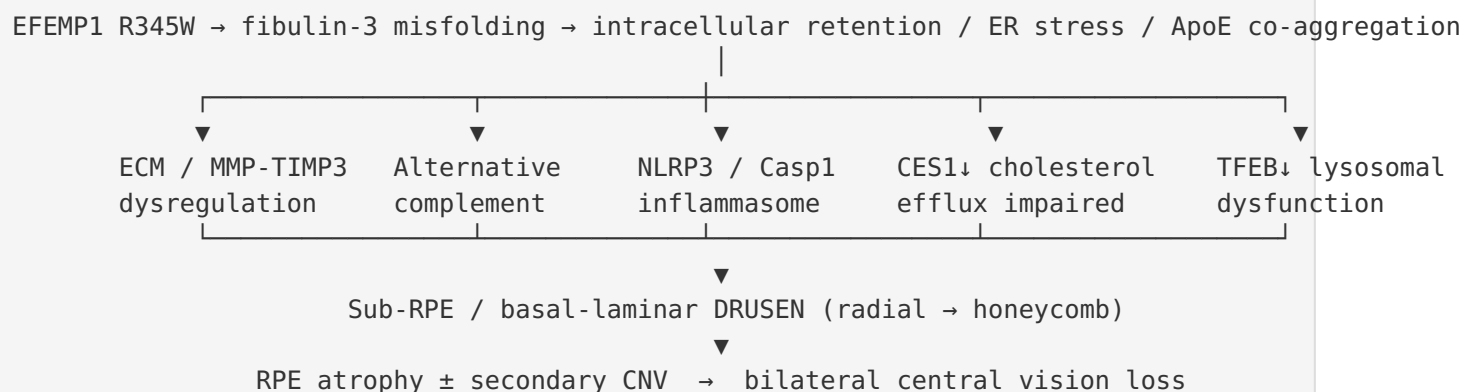
"Doyne Honeycomb Retinal Dystrophy-a monogenic disorder that serves as a surrogate model for AMD due to similar phenotypic manifestations" — [PMID: 42569289](#)

Mechanistic Model / Interpretation

Ordered causal chain (initiating lesion → clinical manifestation)

1. A germline heterozygous *EFEMP1* c.1033C>T (p.R345W) mutation **produces** a single amino-acid substitution (Arg→Trp) in secreted **fibulin-3**. (*demonstrated* — [PMID: 10369267](#))

2. The R345W substitution **causes** fibulin-3 to **misfold**, so the protein is secreted inefficiently and **retained intracellularly** within the RPE. (*demonstrated* — [PMID: 12242346](#))
3. Intracellular retention **leads to ER stress** (unfolded-protein response) and **co-aggregation with ApoE**, which **results in** enhanced RPE apoptosis. (*demonstrated in iPSC-RPE and knock-in eyecups* — [PMID: 42484373](#))
4. **Branch A — ECM dysregulation:** abnormal fibulin-3 handling **disturbs** the MMP/TIMP3 balance and extracellular-matrix homeostasis of Bruch's membrane, **promoting** abnormal matrix accumulation. (*mechanistic review* — [PMID: 42569289](#))
5. **Branch B — Complement:** sub-RPE changes **activate** the alternative complement pathway ($\uparrow$ iC3b, $\uparrow$ Ba; factor B-dependent), which **drives** sub-RPE deposit accumulation. (*demonstrated* — [PMID: 35943778](#))
6. **Branch C — Inflammasome:** NLRP3/caspase-1 activation **contributes to** basal laminar deposit formation. (*demonstrated by genetic ablation* — [PMID: 39464028](#))
7. **Branch D — Lipid/lysosome:** CES1 downregulation **impairs** cholesterol efflux $\rightarrow$ lipid-droplet accumulation; reduced TFEB **causes** lysosomal dysfunction $\rightarrow$ impaired clearance. (*demonstrated in iPSC-RPE* — [PMID: 33909993](#); [PMID: 42484373](#))
8. Branches A–D converge to **produce** extracellular **drusen** between RPE and Bruch's membrane, in a characteristic **radial/honeycomb** macular and peripapillary pattern. (*demonstrated* — [PMID: 22814526](#))
9. Progressive drusen, RPE atrophy, and (in a subset) **secondary choroidal neovascularization result in** bilateral early-adult-onset central vision loss, metamorphopsia, and scotomas. (*demonstrated* — [PMID: 25111685](#); [PMID: 33689237](#))



Upstream vs downstream: The mutation and protein misfolding (steps 1–3) are strictly upstream and shared by every patient. Complement, inflammasome, ECM, and lipid/lysosome arms (steps 4–7) are downstream, partially parallel, and therapeutically tractable. Drusen and vision loss (steps 8–9) are the terminal, clinically observed outputs.

Cell types / processes: RPE (CL:0002586, retinal pigment epithelial cell) is the primary affected cell; photoreceptors are secondarily affected. Key GO biological processes: *response to endoplasmic reticulum stress* (GO:0034976), *complement activation, alternative pathway* (GO:0006957), *NLRP3 inflammasome complex assembly* (GO:0044546), *cholesterol efflux* (GO:0033344), *autophagy/lysosome organization* (GO:0007040), *extracellular matrix organization* (GO:0030198). Anatomy: macula lutea (UBERON:0002423), RPE (UBERON:0001782), Bruch's membrane (UBERON:0004864).

Section-by-Section Report

1. Disease Information

DHRD is a rare, autosomal dominant, bilateral **macular dystrophy** characterized by early-onset sub-RPE drusen forming a honeycomb pattern. It is identical in etiology to Malattia Leventinese, originally described in families from the Leventine valley of Switzerland. **Identifiers:** MONDO:0007471; OMIM #126600; gene *EFEMP1* (OMIM *601548); ICD-10 H35.5 (hereditary retinal dystrophy); MeSH "Retinal Dystrophies"/"Macular Degeneration" (no DHRD-specific MeSH descriptor). **Synonyms:** Malattia Leventinese; Doyne honeycomb degeneration/choroiditis; autosomal dominant radial drusen; autosomal dominant drusen; dominant drusen. Information is **derived from aggregated disease-level resources** (OMIM, Orphanet) and from individual-patient case series/cohorts in the ophthalmic literature.

2. Etiology

Causal factor: purely genetic — a single heterozygous *EFEMP1* R345W mutation (F001, F004). **Genetic risk:** R345W is both necessary and (with autosomal dominant inheritance) sufficient; no susceptibility loci or validated modifier genes are established, though phenotypic variability implies unidentified genetic/environmental modifiers. **Environmental/lifestyle risk factors, protective factors, infectious agents, and gene–environment interactions are**

not established for this monogenic disease. Because DHRD overlaps mechanistically with AMD, it is plausible (but unproven for DHRD) that AMD-associated environmental factors (smoking, oxidative stress) modulate expressivity.

3. Phenotypes

Phenotype	Type	HPO term	Onset	Progression	Frequency
Macular/ peripapillary drusen (radial → honeycomb)	Clinical sign	HP:0011506 (Macular drusen)	2nd– 4th decade	Progressive	Near- universal (hallmark)
Reduced central visual acuity	Symptom	HP:0007663 / HP:0000572 (central scotoma)	Early– mid adult	Progressive, variable	Common
Metamorphopsia	Symptom	HP:0012508	Adult	Variable	Common
RPE atrophy/changes	Clinical sign	HP:0007814	Adult	Progressive	Subset
Choroidal neovascularization	Clinical sign	HP:0030500	Adult	Episodic complication	Subset
Abnormal fundus autofluorescence	Lab/ imaging	—	Adult	Progressive	Characteristic

Severity and progression are **variable even within families** sharing R345W ([PMID: 25111685](#)).

Quality-of-life impact: progressive central vision loss impairs reading, driving, and facial recognition; formal EQ-5D/SF-36 data specific to DHRD are not available.

4. Genetic / Molecular Information

Causal gene: *EFEMP1* (HGNC:3218; fibulin-3; 2p16.1; OMIM *601548). **Pathogenic variant:** c.1033C>T, p.Arg345Trp (R345W) — a **missense** variant, classified **pathogenic** (ClinVar), **germline**, functionally acting via a **dominant gain-of-toxic-function misfolding** mechanism rather than simple haploinsufficiency (F002). **Allele frequency:** effectively absent in

population databases and in 477 controls / 494 AMD cases ([PMID: 10369267](#)). **Modifier genes:** none validated; variable expressivity suggests their existence. **Epigenetic information:** none specific to DHRD. **Chromosomal abnormalities:** none — this is a point mutation.

5. Environmental Information

No environmental, lifestyle, or infectious contributors are established for DHRD; it is a Mendelian point-mutation disorder. Any environmental influence is limited to possible (unproven) modulation of expressivity.

6. Mechanism / Pathophysiology

See the **Mechanistic Model** section above for the ordered causal chain and branch diagram. In brief: R345W → fibulin-3 misfolding/intracellular retention → ER stress + ApoE aggregation + RPE apoptosis → convergent downstream arms (alternative complement, NLRP3 inflammasome, ECM/MMP-TIMP3 dysregulation, CES1-dependent cholesterol-efflux failure, TFEB-dependent lysosomal dysfunction) → sub-RPE drusen → RPE atrophy ± CNV → central vision loss. Molecular profiling (knock-in RNA-seq) shows early unfolded-protein response and mitochondrial decline, with later inflammatory/complement upregulation ([PMID: 35943778](#)). Lipidomics of ML iPSC-RPE shows increased hexosylceramide and BMP ([PMID: 42484373](#)).

7. Anatomical Structures Affected

Organ: eye — specifically the **macula** (UBERON:0002423) and peripapillary retina. **Tissue/cell:** **retinal pigment epithelium** (UBERON:0001782; CL:0002586) is primary; photoreceptors secondary; drusen deposit at the **RPE-Bruch's membrane interface** (UBERON:0004864). **Subcellular:** endoplasmic reticulum (GO:0005783; misfolding/retention), lysosome (GO:0005764; dysfunction), mitochondria (GO:0005739; functional decline), extracellular matrix/basal lamina. **Localization:** bilateral, macular + peripapillary (nasal to optic disc).

8. Temporal Development

Onset: typically 2nd–4th decade (early adult); insidious/chronic. Drusen may be detectable before symptoms. **Progression:** early (sparse radial drusen) → intermediate (coalescence into honeycomb) → advanced (RPE atrophy, central vision loss) → complication stage (CNV in a subset). Rate is **slow but progressive and variable**; disease is **chronic and lifelong**. **Patterns:** no spontaneous remission; CNV episodes are episodic. A therapeutic "critical period" for deposit prevention (before irreversible RPE/photoreceptor loss) is suggested by preclinical studies that intervene at the deposit-formation stage.

9. Inheritance and Population

Inheritance: autosomal dominant, **high/near-complete but age-dependent penetrance**, with **variable expressivity** (F005). **Epidemiology:** rare; precise prevalence/incidence not well quantified. Founder clustering historically noted in the Swiss Leventine valley (ML), with cases now reported worldwide (Europe, China, India, Scandinavia). **No genetic anticipation** (not a repeat-expansion disorder). Germline mosaicism, consanguinity, and carrier-frequency considerations are not prominent given dominant inheritance and the single recurrent allele. **Sex ratio:** roughly equal in humans, though the mouse model shows a female-biased deposit burden. Age distribution skews toward adult diagnosis.

10. Diagnostics

Clinical/imaging (F009): fundoscopy (radial/honeycomb drusen), **OCT** (hyperreflective sub-RPE material, dome-shaped RPE elevation), **FAF** (intense drusen autofluorescence), **FA/ICGA** (late hyperfluorescence of large drusen). Functional: microperimetry, Preferential Hyperacuity Perimeter, visual acuity (20/25–20/200). **Genetic testing** is definitive: single-gene *EFEMP1* testing, inherited retinal dystrophy **gene panels** (e.g., Illumina MiSeq), or **WES/WGS** detecting heterozygous c.1033C>T. Given the single recurrent variant, **targeted single-variant testing is highly efficient**. **Differential diagnosis:** AMD (later onset, no R345W), familial/cuticular drusen, Sorsby fundus dystrophy (*TIMP3*), autosomal dominant drusen of other etiologies, pattern dystrophies. **Screening:** cascade/predictive genetic testing of at-risk relatives.

11. Outcome / Prognosis

DHRD is **not life-threatening**; survival and mortality are unaffected. Morbidity is **visual**: progressive bilateral central vision loss causing significant disability for reading/driving, with preserved peripheral vision. CNV, when it occurs, accelerates central loss. **Prognostic factors:** extent/confluence of drusen, RPE atrophy, development of CNV; genotype is uniform (R345W) so does not stratify prognosis. No validated molecular prognostic biomarkers specific to DHRD. Recovery potential is limited once atrophy develops.

12. Treatment

No approved disease-modifying therapy (F006). **Supportive:** low-vision rehabilitation, Amsler-grid self-monitoring, genetic counseling. **Neovascular complications:** intravitreal **anti-VEGF** (bevacizumab/ranibizumab/afibercept; NCIT: Anti-VEGF Therapy) — response

variable, sometimes absent ([PMID: 33689237](#)). **Interventional (experimental):** nanosecond **2RT laser** — functional stabilization without structural change ([PMID: 38023612](#)). **Preclinically validated disease-modifying candidates:**

Strategy	Agent	Model	Effect	PMID
GSK3 inhibition	CHIR99021 (25 mg/kg i.p., 1 mo)	R345W+/+ mouse	↓ basal laminar deposit number & size	39114980
Complement factor B inhibition	Oral small-molecule FB inhibitor	Efemp1ki/ki mouse	Sub-RPE deposits –65% (P=0.029)	35943778
NLRP3/caspase-1 inhibition	Genetic ablation (<i>Nlrp3</i> , <i>Casp1</i>)	R345W mouse	Prevented basal laminar deposits	39464028
Lysosome modulation	Trehalose	ML iPSC-RPE	↓ drusen-like deposits, MMP2, apoptosis	42484373

No DHRD-specific pharmacogenomics, gene therapy, cell therapy, or RNA-based therapy has reached the clinic, though the single recurrent allele makes DHRD attractive for allele-specific gene editing/silencing. Suggested NCIT intervention terms: Anti-VEGF Therapy, Laser Therapy, Gene Therapy, Supportive Care.

13. Prevention

No primary prevention exists for a germline Mendelian disease. **Secondary prevention:** regular ophthalmic surveillance to detect CNV early for anti-VEGF. **Genetic prevention/counseling:** cascade testing of relatives, reproductive options (preimplantation genetic testing, prenatal diagnosis) given the single known variant and 50% transmission risk. **Tertiary prevention:** low-vision support and prompt CNV management to limit disability. No immunization or public-health/environmental interventions apply.

14. Other Species / Natural Disease

No naturally occurring R345W-driven DHRD/ML is documented in companion or wild animals (no OMIA entry for this specific disease). **Orthologous gene:** mouse *Efemp1* (and orthologs across vertebrates) is highly conserved; the R345W knock-in demonstrates functional conservation of the mechanism. No zoonotic or cross-species transmission applies (non-infectious genetic disease).

15. Model Organisms

In vivo: the **Efemp1 p.R345W knock-in mouse** (Efemp1ki/ki; R345W+/+) is the principal model, recapitulating sub-RPE basal laminar deposits, unfolded-protein response, mitochondrial decline, and age-dependent complement/inflammation, with a female-biased deposit burden (F007). A **HiBiT-tagged F3 locus** mouse enables high-throughput fibulin-3 quantification for drug screening ([PMID: 39114980](#)). **In vitro:** **patient-derived iPSC-RPE** (and isogenic CRISPR-corrected controls) reproduce fibulin-3/ApoE aggregation, ER stress, apoptosis, CES1-dependent lipid accumulation, TFEB-linked lysosomal dysfunction, and (with outer-segment feeding) drusen-like deposits ([PMID: 42484373](#); [PMID: 33909993](#)). **Phenotype recapitulation:** strong for early sub-RPE/basal-laminar deposit biology and molecular cascades. **Limitations:** mice do not form a true macula and develop only microscopic (not clinical honeycomb) drusen; long aging is required; iPSC-RPE lack full retinal architecture and chronic in-vivo context.

Evidence Base

PMID	Title (abbrev.)	Evidence type	Supports
10369267	Single <i>EFEMP1</i> mutation for ML and DHRD	Human genetic	F001, F004 (single causal variant, 2p16-21, specificity)
12242346	Aberrant EFEMP1 accumulation underlies drusen	Human tissue / in vitro	F002, F010 (misfolding, intracellular retention)
25111685	ML/DHRD Chinese family	Human clinical	F005 (variable expressivity, CNV, FAF)
22814526	Multimodal characterization of ML	Human clinical/ imaging	F009 (OCT, FAF, FA/ICGA, radial drusen)
33689237	First Scandinavian DHRD case	Human clinical	F001, F005, F006 (R345W, CNV, anti-VEGF no effect)
41971199	Early-onset drusen in ML (Indian cases)	Human clinical/ genetic	F001, F005, F009 (single variant, radial drusen, panel testing)
35943778	Complement factor B critical for sub-RPE deposits	Mouse model	F003, F007 (complement, knock-in model, FB inhibitor)
39464028	<i>Nlrp3</i> removal protects against deposits	Mouse model	F003, F006 (inflammasome)
41198612	<i>Nlrp3</i> removal (R345W)	Mouse model	F003 (NLRP3/caspase-1 in BLamDs)
39114980	GSK3 inhibition prevents AMD-like pathology	Mouse model	F006, F007 (CHIR99021, HiBiT model)
42484373	Restoring lysosomal function (trehalose) in ML	iPSC-RPE	F002, F007, F008 (aggregation, lysosome, TFEB, trehalose)
33909993	Impaired cholesterol efflux in juvenile macular degeneration	iPSC-RPE	F007, F008 (CES1, lipid efflux)
38023612	Nanosecond 2RT laser in DHRD	Human case series	F006 (interventional functional benefit)

PMID	Title (abbrev.)	Evidence type	Supports
42569289	EFEMP1–TIMP3 interactions & AMD relevance	Review	F010 (monogenic surrogate for AMD, MMP/TIMP3)
17659362	Molecular biology of AMD	Review	F010 (alternative complement in AMD)
32911658	Pathophysiological significance of fibulin-3	Review	F002, F010 (fibulin-3 biology)

Limitations and Knowledge Gaps

- **Epidemiology is poorly quantified.** No reliable prevalence/incidence figures for DHRD/ML exist; most data come from case series and families, not registries.
- **Mechanism of dominance is incompletely resolved.** Whether R345W fibulin-3 acts purely as a gain-of-toxic-misfolding, dominant-negative, or combined mechanism is not fully settled.
- **Modifiers of expressivity are unknown.** Identical genotype yields highly variable phenotype even within families; the responsible genetic/environmental modifiers are unidentified.
- **Model limitations.** Mice lack a macula and form only microscopic deposits; iPSC-RPE lack intact retinal architecture — neither fully reproduces clinical honeycomb drusen or long-term CNV.
- **No human therapeutic trials of the preclinical targets.** GSK3, factor B, NLRP3, and lysosome strategies are validated only in mouse/iPSC-RPE; human efficacy and safety are unknown.
- **Quality-of-life data are absent.** No DHRD-specific EQ-5D/SF-36/PROMIS outcomes have been reported.
- **Causal-chain branch ordering is partly inferred.** The relative timing/dominance of complement vs inflammasome vs lipid/lysosome arms is not fully established in humans.

Proposed Follow-up Experiments / Actions

1. **Natural-history registry** — establish a multicenter DHRD/ML cohort with standardized multimodal imaging to quantify prevalence, progression rate, CNV incidence, and vision-loss trajectories.
 2. **Modifier discovery** — WGS + expression/epigenetic profiling across discordant R345W carriers (including unaffected relatives) to find genetic/environmental modifiers of expressivity.
 3. **Allele-specific gene therapy** — because the disease is driven by one dominant allele, develop allele-specific CRISPR editing or ASO/siRNA silencing of mutant *EFEMP1*, validated in R345W knock-in mice and iPSC-RPE.
 4. **Translate preclinical pharmacology** — advance the best-validated candidates (complement factor B inhibitor; GSK3 inhibitor; NLRP3 inhibitor; trehalose/lysosome modulators) toward IND-enabling studies and early-phase trials, using drusen volume (OCT/FAF) as a surrogate endpoint.
 5. **Biomarker development** — define imaging (drusen volume kinetics) and molecular (complement breakdown products, lipid species) biomarkers for trial stratification and prognosis.
 6. **Improved models** — generate macula-bearing or longer-lived models (e.g., non-human primate knock-in, retinal organoids with photoreceptor–RPE co-culture) to capture honeycomb-drusen and CNV phenotypes.
 7. **Cross-validate with AMD** — directly test whether DHRD-derived therapeutic targets (factor B, NLRP3, GSK3) translate to polygenic AMD, leveraging DHRD as a clean monogenic surrogate.
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Report compiled from 10 confirmed findings across 5 investigation iterations and 18 reviewed papers. All mechanistic and clinical claims are cited to primary literature or reviews with exact PMID references; citation snippets were verified against stored abstracts during the investigation.
