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Stargardt macular dystrophy and therapeutic approaches

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ABSTRACT

Stargardt macular dystrophy (Stargardt disease; STGD1; OMIM 248200) is the most prevalent inherited macular dystrophy. STGD1 is an autosomal recessive disorder caused by multiple pathogenic sequence variants in the large *ABCA4* gene (OMIM 601691). Major advances in understanding both the clinical and molecular features, as well as the underlying pathophysiology, have culminated in many completed, ongoing and planned human clinical trials of novel therapies. The aims of this concise review are to describe (1) the detailed phenotypic and genotypic characteristics of the disease, multimodal imaging findings, natural history of the disease, and pathogenesis, (2) the multiple avenues of research and therapeutic intervention, including pharmacological, cellular therapies and diverse types of genetic therapies that have either been investigated or are under investigation and (3) the exciting novel therapeutic approaches on the translational horizon that aim to treat STGD1 by replacing the entire 6.8 kb *ABCA4* open reading frame.

INTRODUCTION

Stargardt macular dystrophy or Stargardt disease (STGD1; OMIM: 248200) is one of the most common macular dystrophies.^{1–8} STGD1 was first described by Karl Stargardt in 1909 and is characterised by bilateral progressive loss of visual acuity (VA) and central vision.⁹ There are three presentations of STGD1, childhood onset, adulthood onset and late onset, with earlier presentation being associated with a worse prognosis.^{3 7 10–20}

STGD1 typically presents with a variable degree of macular atrophy and yellow-white flecks at the level of the retinal pigment epithelium (RPE) (figure 1).^{8 10 11 14 21} However, there are a broad range of manifestations resulting in a large spectrum of clinical presentations, onset, progression, psychophysical and electrophysiological findings, as well as variable prognosis.^{6 10–13 15–20 22–32}

The global prevalence of STGD1 has been estimated at 1 per 6578.³³ Due to the progressive nature and often early onset of STGD1, patients typically face long-term health-related financial, emotional and psychological implications. Although information on the economic burden of STGD1 alone is not available, these impacts have been studied in a broad range of inherited retinal diseases (IRDs).³⁴ Some studies estimate the total

cost is over US\$27.5 billion per year among people aged 40 years and younger with eye disorders.^{35 36}

In 1997, disease-causing sequence variants in the *ABCA4* (ATP binding cassette subfamily A member 4; OMIM: 601691) gene were identified as the cause of STGD1³⁷; with more than 2000 variants found to date. The carrier frequency for a disease-causing variant in *ABCA4* may be as high as 1:20; although the true prevalence of retinopathy attributed to *ABCA4* variants is likely much higher than that of STGD1, given it can also cause other phenotypes including cone dystrophy, cone-rod dystrophy and rod-cone dystrophy.^{1 3 6 7 22 38} Moreover, the bone spicule pigmentation of *ABCA4*-associated retinopathy attributed to severe cone-rod dystrophy (formerly retinitis pigmentosa inversa) is now widely accepted as a sign of late-stage cone-rod dystrophy and peripheral degeneration, rather than rod-cone dystrophy.³⁹

An increasing amount of research on the clinical and molecular genetics of STGD1/*ABCA4* has been performed over the past 15 years. This has facilitated a growing understanding of the underlying pathophysiology, which has resulted in both completed and ongoing trials, as well as a broad range of planned clinical trials.^{6 7 40–42} Many types of interventions have been explored to treat STGD1, including pharmacological treatments, regenerative cell therapies^{43 44} and gene replacement/supplementation therapy.^{45 46} Increasingly, precision medicine focusing on particular variants and mechanisms has been gaining attention (including gene editing).^{7 42 47}

The aim of this review is to describe the phenotypic and genotypic characteristics, imaging findings, natural history and pathogenesis of the disease. Additionally, the characteristics of particular *ABCA4* variants, a pathogenicity assessment and a concise overview of the therapeutic landscape—past, present and future—will be presented.

DISEASE OVERVIEW

Gene family/gene function

The *ABCA4* gene is a large, highly polymorphic gene with an estimated size of 6819 bp encoding a 2,273-amino acid protein, including 50 exons.³⁷ *ABCA4*, formerly described as *ABCR*, is a member of the ABC transporter gene superfamily, encoding the retinal-specific transmembrane protein, a member of the ATP-binding cassette transporter superfamily.^{3 6 48} *ABCA4* contains two transmembrane domains, two



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glycosylated extracellular domains and two nucleotide-binding domains (figure 2A).^{3 6 48}

ABCA4 is localised along the rim of the rod/cone outer segment discs and is involved in the active transport of retinoids from photoreceptor to RPE in the retinoid cycle.^{48–51} The visual/retinoid cycle involves a series of enzyme-catalysed reactions that convert all-trans retinal, generated with photobleaching of rhodopsin/cone opsin, back to 11-*cis* retinal.^{48 50–53} All-trans retinal is released from the light-activated rhodopsin/cone opsin into the rod/cone outer segments to form a complex with phosphatidylethanolamine (PE), resulting in N-retinylidene-PE (N-ret-PE).^{6 48 54} This complex is then actively transported to the disc surface by ABCA4 (figure 2B,C). ABCA4 has also been shown to be expressed at lower levels in the RPE, where it may serve a similar function for the recycling of retinaldehydes.⁵⁴

Molecular genetics

The vast allelic heterogeneity of *ABCA4* is clearly demonstrated by the number of reported sequence variations (>2000) to date, resulting in macular dystrophy, cone dystrophy, cone-rod and rod-cone dystrophy.^{3 6–8} Due to this heterogeneity, establishing genotype-phenotype correlations is highly challenging. Likewise, the identification of *ABCA4* genetic characteristics related to intronic variants remains largely elusive, despite genetic sequencing advances. Deep intronic variants have been shown to significantly account for the missing heritability in STGD1 and have been associated with late-onset disease and mild phenotype.^{55–57} However, due to the highly polymorphic nature of the *ABCA4* gene, the genetic and pathogenic features of deep intronic variants remain difficult to characterise.

Null variants or variants predicted to be more deleterious are generally associated with earlier onset disease and characterised by a more severe, rapidly progressive phenotype, often with more generalised retinal involvement.^{6 8 11–13 16 25 26 32} Milder variants, such as missense variants, are often associated with later onset disease, typically milder, more slowly progressive and more likely isolated to the macula.⁵⁸ Although certain missense variants can produce severe functional effects similar to nulls (eg, p.Leu541Pro/p Ala1038Val (complex), p.Glu1022Lys, p.Cys1490Tyr, p.Glu1087Lys, p.Thr1526Met, p.Arg1640Trp and p.Cys2150Tyr p.Cys2150Tyr).^{13 16 25 26 58} The interaction between the variants (including disease-causing and benign variants) may also affect function.⁵⁹ Nevertheless, certain missense variants, including p.Arg2030Gln, are commonly observed in the mildest *ABCA4*-associated phenotype, late-onset/foveal sparing STGD1 (FS-STGD1).^{14 26}

While *ABCA4* allelic heterogeneity is high, there are founder variants associated with STGD1 in various racial and ethnic groups as well as differences in clinical features related to *ABCA4*-retinopathy.⁶ There have been larger cohort STGD1 studies featuring the genotypic profile and phenotypic correlations for the White populations in European/North American, although there are a limited number of studies for the Latin, Asian, African and other populations.^{5 8 32 60 61} However, further studies are required to better understand the clinical difference and effects across different ethnic and racial groups.

A category of rare hypomorphic alleles has also been characterised, which are typically observed in milder phenotypes with better prognosis.⁶² Lee *et al* showed that these hypomorphic variants can modulate the severity of the phenotype irrespective of the severity of the allele in trans.⁶² Notably, the mechanism of hypomorphic alleles or milder variants has been attributed to either reduced function of the ABCA4 protein produced in

normal amounts (ie, missense variants) or reduced production of a normal functioning protein (ie, splice variants). The aberrant splicing in the *ABCA4* gene and resulting variants, whose pathogenicity was previously unknown, has more recently been reclassified as pathogenic based on midi-gene and fibroblast assays.^{63 64}

Molecular mechanisms

Failure of transport due to ABCA4 dysfunction or mislocalisation leads to the inefficient removal of N-ret-PE from photoreceptor outer segments, resulting in an accumulation of bisretinoid compounds in the outer segment discs and ultimately in toxic levels of bisretinoid A2PE in photoreceptor membranes.^{48 49} A2PE is hydrolysed to form the highly toxic metabolite N-retinylidene-N-retinyl-ethanolamine (A2E), which accumulates as a major component of lipofuscin in RPE cells, and ultimately causes RPE dysfunction and death, with subsequent photoreceptor dysfunction/loss (figure 2D).⁵³

Previous studies of STGD1 mouse models (ie, *ABCA4* knockout) support the aforementioned pathogenesis; however, there are limitations such as lack of a macula in mice and the mild phenotype in mouse models showing a later-onset disease with slower degeneration than that of typical patients with STGD1.^{51 65} Moreover, there is data from multimodal high-resolution imaging studies in humans that in some cases photoreceptor cell loss may precede RPE cell dysfunction/loss.^{17 19 20 66 67}

Clinical aspects

Patients with STGD1 commonly present with progressive bilateral central vision loss. The onset is often in the first or second decades of life.^{11 12 24} The onset relates to the disease severity; an earlier onset disease is associated with more deleterious variants compared with adult-onset disease, which is more frequently due to missense variants.^{11–14 16 25–27}

Comprehensive investigations are crucial for clinical diagnosis and monitoring, including fundus photography, fundus autofluorescence (FAF) imaging, spectral-domain optical coherence tomography (SD-OCT) and electrophysiological assessment.^{1 3 6 7} Likewise, clinical classifications are useful to assess the disease severity associated with a particular genotype group.^{11 12 19 20 23 25 32}

At an early stage, ophthalmoscopy can reveal a normal retina or minimal retinal abnormalities, including foveal reflex abnormality, white macular dots and RPE disturbance, with or without vision loss.^{15–17} Retinal imaging with FAF, SD-OCT and electrophysiological assessment (including pattern, full-field and multifocal electroretinograms; PERG, FFERG, mfERG) are useful for diagnosis.^{42 68–70} Notably, children with STGD1 may not have retinal flecks on funduscopy or FAF at the early stage, but over time may develop these flecks associated with increasing macular atrophy.^{15 16} In very early childhood-onset disease with relatively preserved vision, macular atrophy involves the parafovea and spares the foveola, and these changes are preceded by fine, symmetrical, yellowish-white dots at the central macula in some cases and/or characteristic loss of outer nuclear layer transparency on SD-OCT.^{15–17}

Electrophysiological assessment is particularly helpful in providing better-informed advice on prognosis.¹¹ A classification of three functional phenotypes based on electrophysiological findings is well-established: group 1—severe PERG abnormality (macular dysfunction) with normal FFERGs; group 2—severe PERG abnormality with additional generalised cone dysfunction on FFERGs and group 3—severe PERG abnormality with additional generalised cone and rod dysfunction on FFERGs.^{11 22} A

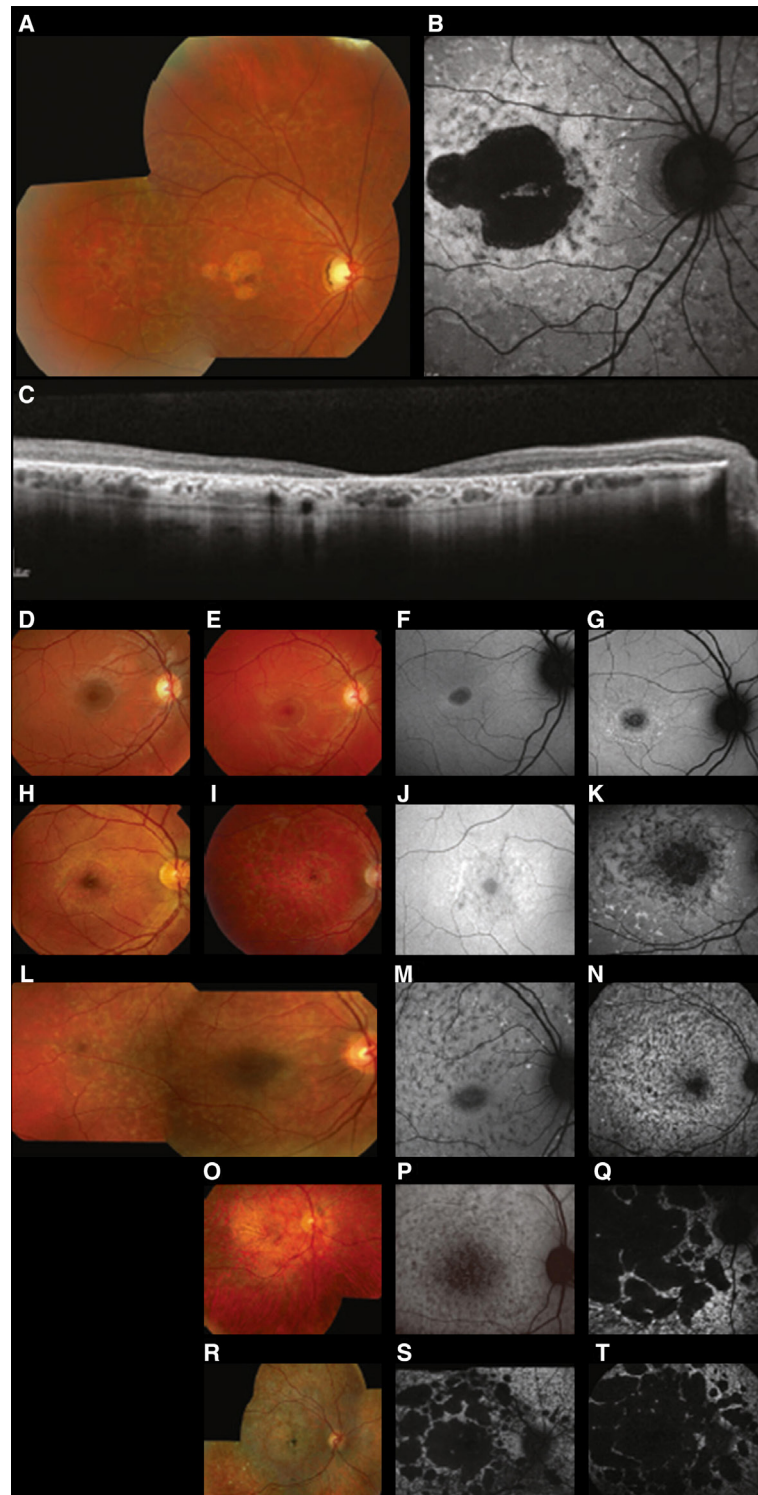


Figure 1 Representative cases of Stargardt disease (STGD1). Typical findings of Stargardt disease (STGD1; A–C). Fundus photograph of the right eye showing macular atrophy with yellow-white flecks at the level of the retinal pigment epithelium (RPE; A). Fundus autofluorescence (FAF) imaging identified an area of decreased autofluorescence (DAF) at the macula and multiple surrounding foci of abnormal AF (B). Spectral-domain optical coherence tomography (SD-OCT) demonstrated marked loss of outer retinal layers and RPE at the macula, with multiple hyper-reflective foci corresponding to flecks (C). A broad range of FAF patterns and progression over time in STGD1 are presented, with corresponding fundus photographs (D–T). FAF pattern can be classified into three types based on the area(s) of DAF and the background features (heterogeneous or homogeneous): type 1 (Baseline; F) to type 2 (follow-up; G), type 1 (baseline; J) to type 2 (follow-up; K), type 2 (baseline; M) to type 2 (follow-up; N), type 2 (baseline; P) to type 3 (follow-up; Q), type 3 (baseline; S) to type 3 (follow-up; T). Genetic information (*ABCA4*, Transcript ID: NM_000350.3; ENST00000370225.4): Case 1 (top row; : c.4139C>T, p.Pro1380Leu. Case 2 (second row; D–G): c.3322C>T, p.Arg1108Cys; c.6079C>T, p.Leu2027Phe. Case 3 (third row; H–K): c.768G>T; c.2588 G>C, p.Gly863Ala. Case 4 (fourth row; I–N): Unavailable. Case 5 (fifth row; O–Q): c.1622T>C, p.Leu541Pro; c.3113C>T, p.Alala1038Val; c.617_618delCG, p.Ser206ArgfsTer320. Case 6 (bottom row; R–T): c.5461–10T>C. *Permission to reuse the figure for publication in the journal has been obtained by the licensed content publisher, Springer Nature (Number: 5415100406042; License date: 23 October 2022).

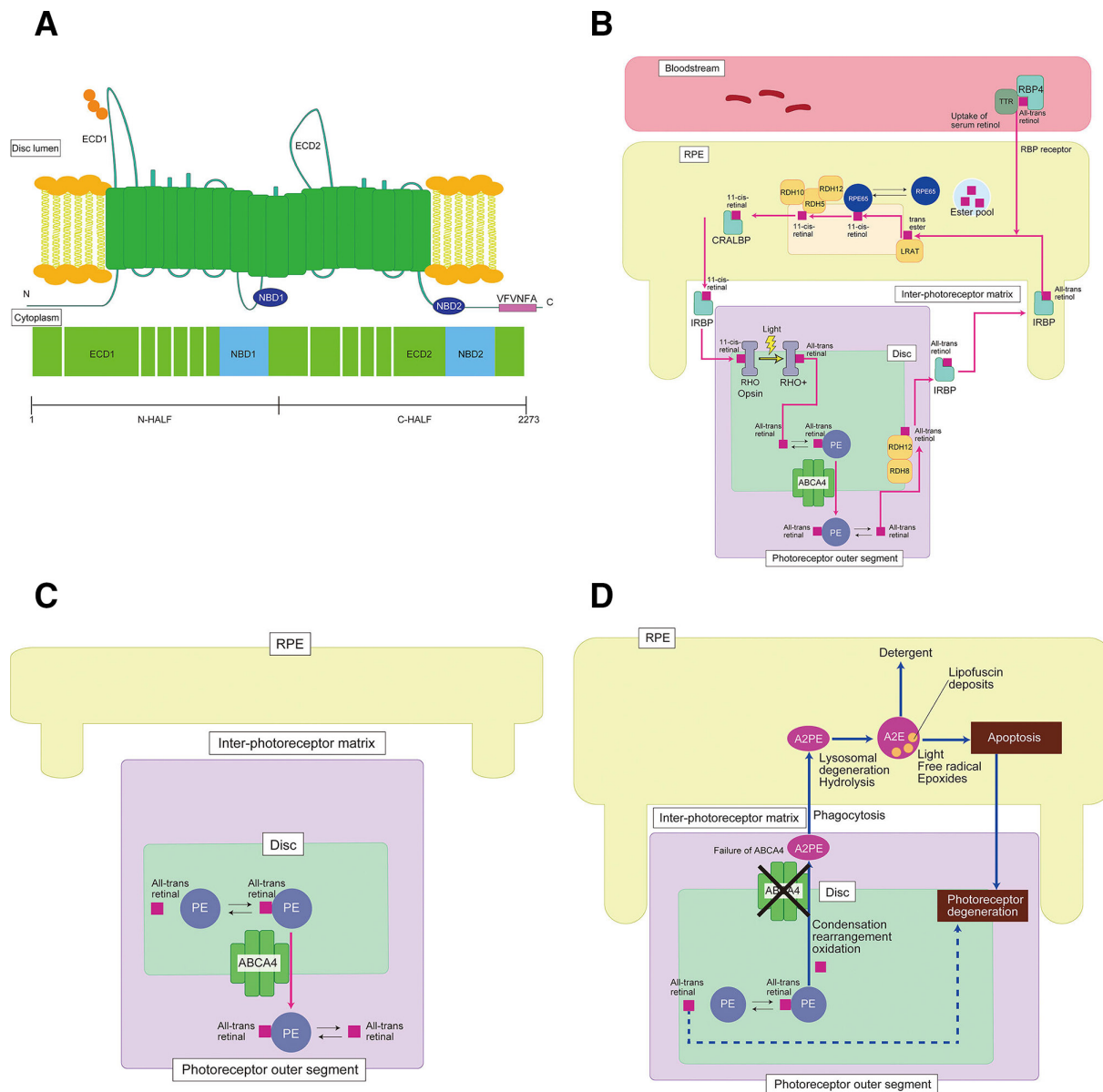


Figure 2 Molecular mechanisms of STGD1 (*ABCA4*-retinopathy) a schematic of *ABCA4* protein structure (A), the visual cycle (B), transport (C) and failure of transport leading to retinal degeneration (D). The *ABCA4* gene transcribes a large retina-specific *ABCA4* protein with two transmembrane domains (TMD), two glycosylated extracellular domains (ECD) and two nucleotide-binding domains (NBD) (A). All-trans retinal is released from the light-activated rhodopsin/cone opsin into the rod/cone outer segments (B) to form a complex with phosphatidylethanolamine (PE), resulting in N-ret-PE, then this complex is actively transported to the disc surface by *ABCA4* (C). Failure of this transport results in accelerated deposition of a major lipofuscin fluorophore (A2E) in the RPE, which causes RPE dysfunction and cell death, with subsequent photoreceptor cell loss over time (D).

longitudinal ERG study has confirmed the prognostic implications of the aforementioned ERG groups, with group 1 having the best prognosis; group 2 having an intermediate or variable prognosis; and group 3 having the worst prognosis.¹¹ All patients with initial rod ERG involvement demonstrated clinically significant electrophysiological deterioration; whereas, only 20% of patients with normal FFERGs at baseline showed clinically significant progression over time.¹¹ These findings are supported by the association with genotype grouping (eg, group 3 is associated with a greater prevalence of null variants), and are also relevant in the design, patient selection and monitoring of potential therapeutic interventions.^{11 16 20}

STGD1 with a later age of onset has been increasingly recognised. Patients with late-onset STGD1 often develop the FS phenotype (FS-STGD1).^{10 14 71} FS-STGD1 thereby is

characterised by relatively preserved VA and foveal structure and function in the early and intermediate stages of the disease.¹⁴ SD-OCT often exhibits outer retinal tubulation at the edge of atrophy, suggesting that the primary site of degeneration of this phenotype is the RPE and choroid.¹⁴ On the other hand, patients with foveal atrophy can manifest photoreceptor cell loss at the fovea at the early stage. Therefore, the presence of two distinct phenotypes—non-FS-STGD1, which is primarily childhood-onset and adulthood-onset STGD1, and FS-STGD1—suggests more than one disease mechanism in *ABCA4*-associated retinopathy.¹⁴ The fact that a different distribution of disease-causing variants exists between these two phenotypes appears to support this hypothesis.^{14 26}

Natural history

Natural history studies play a key role in advancing understanding of disease progression.^{20 24} Over the past 8 years, multicentre, international, large-cohort studies (>250 subjects) have been conducted: the retrospective and prospective Natural History of the Progression of Atrophy Secondary to Stargardt Disease (ProgStar) studies.²⁴ The aims were to characterise the natural history and identify sensitive, reliable and clinically relevant outcome measures, which could be employed in clinical trials.^{24 27–31} Here, we focus on FAF, given it has been prioritised in clinical trial endpoints to date.^{24 72 73}

In a ProgStar retrospective study of a subset of 224 eyes (mean age, 33.0±15.1 years), the total mean area of definitely decreased autofluorescence (DDAF) at the first visit was 2.6 mm², and the mean progression of DDAF was 0.51 mm²/year.⁷² In a prospective study with 12 months of observation, the mean area of DDAF at baseline was 3.93 mm², and the estimated progression of DDAF was 0.76 mm²/year.⁷³ The rate of progression was dependent on the initial size of the lesion in both studies, as previously reported by other longitudinal studies.^{12 74}

FAF imaging may serve as a monitoring tool for interventional clinical trials that aim to slow anatomical disease progression.^{20 42 67} Lesion size at baseline appears to be a strong predicting factor for lesion growth and can be partially accounted for by square root transformation.^{12 20 42 67 75}

Studies using en face SD-OCT and OCT angiography (OCTA) have shown that the area of photoreceptor ellipsoid zone (EZ) loss was 1.6-fold greater than the area of RPE atrophy, which suggests that photoreceptor degeneration may precede RPE loss in STGD1.⁷⁶ Moreover, OCTA showed that choriocapillary vascular density was abnormal even beyond the areas of photoreceptor EZ and RPE loss, supporting a complex chorioretinal-RPE pathophysiology due to ABCA4 dysfunction.⁷⁶ These findings may also be useful for developing end points in clinical trials.

THERAPEUTIC APPROACHES

Although there are currently no proven cures for STGD1, there are multiple treatment avenues being investigated. In addition to retinal prosthesis,⁷⁷ there are clinical trials of pharmacological agents, stem cell therapy and genetic therapies (see summary in table 1).^{3 6–8 40–42 45} Pharmacological therapies are arguably the most advanced and closest to potential approval as meaningful treatments.^{6 7 42}

Pharmacological therapy

Several pharmacological agents have been specifically developed that target different aspects of the retinoid cycle and are potentially beneficial in slowing or preventing progression in STGD (figure 3A), with some studies also reporting improvements in retinal and/or visual function (table 1).^{3 6 8 42}

The aims of these agents are either (1) lowering the formation of toxic products of the retinoid cycle by reducing delivery of vitamin A or inhibition of various enzymes participating in the cycle, including drugs such as emixustat,^{78–80} ALK-001, LBS-008, STG-001, fenretinide and A1120; or (2) directly targeting toxic metabolites such as A2E or pathways activated by these metabolites (eg, the complement cascade), including soraprazan and Avacincaptad pegol.

These drugs aim to impede formation of A2E and lipofuscin by either slowing the rate of vitamin A dimerisation (ALK-001),^{81 82} enhancing lipofuscin removal (soraprazan), imposing competitive inhibitory mechanisms on the retinal binding protein-4

(LBS-008 (tinlarebant), STG-001, fenretinide, vutrisiran and A1120), or modulating the activity of RPE65 (emixustat).⁷⁸

Many of these drugs have been or are currently in phase 1/2 or 3 trials (LBS-008: NCT03735810, emixustat: NCT03772665 and NCT03033108, ALK-001: NCT02402660) (table 1). Avacincaptad pegol, a complement C5 inhibitor, is also being investigated in a phase 2 trial (NCT03364153). Additional pharmacotherapeutic agents directly or indirectly targeting the visual cycle have been developed, including the complement-mediated response to accumulated by-products of the visual cycle.⁸³

Cellular therapies

For the management of advanced disease, cell replacement strategies offer potential benefit. A phase 1/2 clinical trial (NCT01469832) of human embryonic stem cell (hESC)-derived RPE cells for treating severe advanced STGD1 has been completed.^{43 84} Findings from the UK site of this trial identified subretinal hyperpigmentation consistent with the survival of viable transplanted hESC-derived RPE cells.⁸⁴ Borderline improvements in VA were noted in 4 of 12 patients; however, microperimetry did not demonstrate evidence of functional benefit at 12 months.⁸⁴ A phase 1 clinical trial testing the long-term safety and tolerability of hESC-derived RPE (NCT01625559) showed no adverse events, with favourable results.⁸⁵ Further trials are anticipated, including evaluation of combined RPE and photoreceptor transplants, which are either derived from hESCs or induced pluripotent stem cells (iPSC).

Trials involving autologous bone marrow-derived stem cells (BMSC; NCT01920867, NCT03011541, NCT03772938) are at various stages of completion. One study (NCT01920867) showed improvement in 61.8% of the eyes treated, with 76.9% of patients exhibiting VA improvement. Other studies involving BMSC treatment (NCT03772938, NCT03011541) are still active with no results yet reported.

Genetic therapies

Gene replacement therapy has been increasingly applied to photoreceptor diseases, aiming to slow or prevent further degeneration and/or improve function in early to intermediate stage disease.^{7 40–42 86} Preclinical studies in gene replacement showing phenotypic improvement in *abca4*^{-/-} mice have subsequently encouraged the development of human gene therapy trials.^{87 88} Adeno-associated virus (AAV) vectors have been the leading choice for gene delivery in human gene therapy; however, the AAV capsids exhibit limited cargo capacity. The *ABCA4* gene is far larger than the current AAV vector capacity.⁸⁷ Considering the larger cargo capacity of lentiviruses, subretinal injection of a lentiviral vector delivering *ABCA4* (SAR422459) was developed. The StarGen phase I/II trial for this therapy (NCT01367444) was terminated early, with a longer-term follow-up study ongoing (NCT01736592).⁸⁹ Although there were no safety concerns in either of these trials, there was no evidence of visual improvement.^{46 90}

Optogenetics represents a genetic therapy for advanced disease, where residual non-photoreceptor cells are made light sensitive by using AAV to deliver often an opsin-related photopigment.⁹¹ This approach is being explored in a Phase II clinical trial in STGD1, with AAV2 carrying a multicharacteristic opsin gene expression cassette (NCT05417126).⁹²

Future treatment options

In addition to treatments currently undergoing clinical trials, there are several therapeutic approaches on the horizon for

Table 1 Summary of therapeutic trials for Stargardt disease (STGD1; *ABCA4* retinopathy)

Mechanism	Treatment	Route	Phase	ClinicalTrials.gov identifier	Title	Summary results
Inhibition of vitamin A dimerisation	ALK-001	Oral	Phase 2 long-term follow-up	NCT04239625	Open-Label Extension: Tolerability and Effects of ALK-001 on Stargardt Disease	Active study
Inhibition of vitamin A dimerisation	ALK-001	Oral	Phase 2	NCT02402660	Phase 2 Tolerability and Effects of ALK-001 on Stargardt Disease	Reduction in growth rate of atrophic lesions, no change in BCVA, no reports of night blindness or impaired dark adaptation
Inhibition of vitamin A dimerisation	ALK-001	Oral	Phase 1	NCT02230228	Phase 1 Safety Study of ALK-001 in Healthy Volunteers	
RBP4 Inhibition	STG-001	Oral	Phase 2	NCT04489511	Study of STG-001 in Subjects With Stargardt Disease	Reported AEs: 6 patients low dose: 1 dry eye, 1 subretinal fluid, 1 skin disorder; 4 patients high dose: 1 chromatopsia, 1 delayed dark adaptation, 2 night blindness, 1 visual impairment, 1 dry skin
RBP4 Inhibition	Tinlarebant	Oral	Phase 3	NCT05244304	Study to Evaluate the Safety and Efficacy of Tinlarebant in the Treatment of Stargardt Disease in Adolescent Subjects Lesion(s) in Adolescent Subjects With STGD1	Active study
RBP4 Inhibition	Tinlarebant	Oral	Phase 1 Phase 2	NCT05266014	Dose-finding Study Followed by 2 year Extension Study to Evaluate Safety and Tolerability of Tinlarebant in Adolescent Subjects With Stargardt Disease	Preliminary safety results: 9/13 patients delayed dark adaptation, 9/13 xanthopsia/chromatopsia, 1/13 night vision impairment. No clinically significant findings in relation to general health. 8/13 gain in BCVA, trend for preventing/slowing atrophy on FAF, 6/13 narrowing of EZ defect
RBP4 Inhibition	Vutrisiran	Subcutaneous	Phase 3	Not yet registered	THEIA-A: A Phase 3 Global, Randomised, Double-Masked, Placebo-Controlled Study to Evaluate the Clinical Outcomes, Efficacy and Safety of Vutrisiran in Patients with Stargardt Disease Type 1 (STGD1)	Upcoming trial
Inhibition of visual cycle (RPE65)	Emixustat	Oral	Phase 3	NCT03772665	Safety and Efficacy of Emixustat in Stargardt Disease	No meaningful differences between treatment groups regarding macular atrophy
Inhibition of visual cycle (RPE65)	Emixustat	Oral	Phase 2	NCT03033108	Pharmacodynamic Study of Emixustat Hydrochloride in Subjects With Macular Atrophy Secondary to Stargardt Disease	Dose-dependent suppression of rod b-wave amplitude recovery post photobleaching, confirming emixustat's biological activity. AE: dark adaptation (11/23, 47.8%), erythropsia (5/23, 21.7%), vision blurred (4/23, 17.4%), photophobia (3/23, 13%), visual impairment (3/23, 13%), headache (2/23)
Inhibition of visual cycle	4-Methylpyrazole	Intravenous	Phase 1	NCT00346853	Phase 1 Pilot Study of 4-MP to Treat Stargardt Macular Dystrophy	No effect on dark adaptation in healthy probands, further studies suspended because substance doesn't seem to inhibit the visual cycle strong enough
Removal of lipofuscin	Soraprazan	Oral	Phase 2	EudraCT 2018-001496-20	A multinational, multi-centre, double-masked, placebo-controlled proof of concept trial to evaluate the safety and efficacy of oral soraprazan in Stargardt disease	Active study
Induce Autophagy	Metformin	Oral	Phase 1 Phase 2	NCT04545736	Oral Metformin for Treatment of <i>ABCA4</i> Retinopathy	Active study
Inhibition of complement C5	Zimura	Intravitreal	Phase 2	NCT03364153	Zimura Compared with Sham in Patients With Autosomal Recessive Stargardt Disease (STGD1)	Active study
Supplements	Omega-3 Fatty Acids	Oral		NCT03297515	Therapeutic Potential of Omega-3 Fatty Acids Supplementation in Dry Macular Degeneration and Stargardt Disease	Increase of BCVA in the active group after 24 weeks, score of a questionnaire on perceived vision and subjective mood higher in the active group at week 24, CAVE: patient cohort Stargardt+dry AMD, results not shown separately
Supplements	Docosahexaenoic acid (DHA)	Oral		NCT00420602	DHA Supplementation in Patients With STGD3	No beneficial effect over 8 years, poor compliance
Supplements	DHA	Oral	Phase 1	NCT00060749	Effect of DHA Supplements on Macular Function in Patients With Stargardt Macular Dystrophy and Stargardt-like Macular Dystrophy	No effect on macular function
Supplements	Saffron	Oral	Phase 1 Phase 2	NCT01278277	Saffron Supplementation in Stargardt's Disease	Short-term supplementation was well tolerated and had no detrimental effects on the electroretinographic responses of the central retina
Gene therapy (<i>ABCA4</i>)	SAR422459	Subretinal	Phase 1 Phase 2 Follow-up	NCT01736592	Phase I/II Follow-up Study of SAR422459 in Patients With Stargardt's Macular Degeneration	Treatment was well tolerated. No clinically significant changes in visual function tests were found to be attributable to the treatment. Reduction of flecks in one eye. 1 case of ocular hypertension. 27% of treated eyes showed exacerbation of retinal pigment epithelium atrophy on FAF.
Gene therapy (<i>ABCA4</i>)	SAR422459	Subretinal	Phase 1 Phase 2	NCT01367444	Phase I/IIA Study of SAR422459 in Participants With Stargardt's Macular Degeneration	Favourable safety profile
Optogenetics	vMCO-010	Intravitreal	Phase 2	NCT05417126	Safety and Effects of a Single Intravitreal Injection of vMCO-010 Optogenetic Therapy in Subjects With Stargardt Disease	Active study

Continued

Table 1 Continued

Mechanism	Treatment	Route	Phase	ClinicalTrials.gov identifier	Title	Summary results
Stem cells	hESC Derived RPE (MA09-hRPE)	Subretinal	Phase 2 Follow-up	NCT02941991	A Follow-up Study to Determine the Safety and Tolerability of Sub-retinal Transplantation of Human Embryonic Stem Cell Derived Retinal Pigmented Epithelial (hESC-RPE) Cells in Patients With Stargardt's Macular Dystrophy (SMD)	Active study
Stem cells	hESC Derived RPE (MA09-hRPE)	Subretinal	Phase 1 Phase 2	NCT01345006	Sub-retinal Transplantation of hESC Derived RPE (MA09-hRPE) Cells in Patients With Stargardt's Macular Dystrophy	No evidence of adverse proliferation, rejection, or serious ocular or systemic safety issues related to the transplanted tissue. 13/18px (72%) had patches of increasing subretinal pigmentation. BCVA improved in ten eyes, improved or remained the same in seven eyes, and decreased by more than ten letters in one eye, no similar improvements in untreated FE. Vision-related quality-of-life measures increased 3–12 months after transplantation.
Stem cells	hESC Derived RPE (MA09-hRPE)	Subretinal	Follow-up	NCT02445612	Long Term Follow-up of Sub-retinal Transplantation of hESC Derived RPE Cells in Stargardt Macular Dystrophy Patients	Active study
Stem cells	hESC Derived RPE (MA09-hRPE)	Subretinal	Phase 1 Phase 2	NCT01469832	Safety and Tolerability of Sub-retinal Transplantation of hESC-RPE Cells in Patients With SMD	Focal areas of subretinal hyperpigmentation, no evidence of uncontrolled proliferation or inflammatory responses. No meaningful improvements in BCVA, no benefit in microperimetry at 12 months, one case of localised retinal thinning and reduced sensitivity in the area of hyperpigmentation. No significant change in participant-reported quality of life.
Stem cells	hESC Derived RPE (MA09-hRPE)	Subretinal	Phase 1	NCT01625559	A Phase I, Open-Label, Prospective Study to Determine the Safety and Tolerability of Sub-retinal Transplantation of hESC-RPE (MA09-hRPE) Cells in Patients With SMD	No serious AEs occurred throughout the 3 year period following the injection of hESC-RPE cells. The functional and anatomical results were favourable, compared with the natural course of SMD reported in the ProgStar study.
Stem cells	hESC Derived RPE	subretinal	Phase 1 Phase 2	NCT02749734	Clinical Study of Subretinal Transplantation of Human Embryo Stem Cell Derived Retinal Pigment Epitheliums in Treatment of Macular Degeneration Diseases	Active study
Stem cells	hESC Derived RPE	subretinal	Phase 1 Phase 2	NCT02903576	Stem Cell Therapy for Outer Retinal Degenerations (sub retinal injections vs hESC RPE seeded on a polymeric substrate implanted in the subretinal space)	Active study
Stem cells	Autologous bone marrow-isolated stem/progenitor cells	Intravitreal	Phase 1	NCT03772938	Stem Cells Therapy in Degenerative Diseases of the Retina	No results from STGD group to date
Stem cells	Autologous bone marrow derived stem cells (BMSC)	Retrolubar, subtenon, intravitreal, intraocular, subretinal and intravenous		NCT03011541	Stem Cell Ophthalmology Treatment (SCOT) Study II	Active study
Stem cells	Autologous BMSC	Retrolubar, subtenon, intravitreal, intraocular, subretinal and intravenous		NCT01920867	Stem Cell Ophthalmology Treatment Study	21/34 eyes (61.8%) improved, 8/34 eyes (23.5%) remained stable, and 5/34 eyes (14.7%) showed continued progression. The average central vision improvement following treatment was 17.96% and ranged up to 80.5%. Of 17 patients treated, 13/17px (76.5%) showed visual acuity improvement in one or both eyes, 3/17px (17.6%) showed no net loss, and 1px worsened as a consequence of disease progression; 94.1% of patients had improved vision or remained stable. There were no AEs.

AE, adverse event; AMD, age-related macular degeneration; BCVA, best-corrected VA; FAF, fundus autofluorescence ; VA, visual acuity.

STGD1.⁹³ Anti-sense oligonucleotide (AON) treatments have exhibited great potential for the personalised treatment of patients that carry one of the *ABCA4* splice variants.^{55 57} Phase I/II clinical trials for the use of an AON-based therapeutic intravitreal injection to treat Leber congenital amaurosis (NCT03140969, NCT03913130), retinitis pigmentosa and Usher syndrome (NCT05085964) were conducted, but two of these studies (NCT03913130, NCT05085964) were terminated early for reasons unrelated to safety. Research involving the application of AON-based therapy has recently shown promise at preventing further deterioration in Stargardt disease models.⁹⁴

Other therapeutic methods being explored include gene therapy systems that use alternative delivery vectors. As mentioned above, there are fundamental limitations to using

AAVs in STGD1, principally cargo capacity, as well as concerns about immune reactions to the viral vector itself.^{95 96} Thus, future treatment methodologies that employ non-viral vectors—such as cationic lipids and lipid nanoparticles (LNPs)—would be potentially safer than viral vector options with respect to the absence of immunogenic viral proteins. LNPs have also shown robust capability to condense and deliver various nucleic acid molecules up to several million nucleotides,⁹⁷ while concurrently protecting the DNA/RNA cargo from unknown chromosomal position effects.^{98 99} However, the level of expression and transfection efficiency for non-viral vectors is typically much lower than viral vectors. Recent strategies such as PEGylation of LNPs or use of a pH-sensitive amino lipid have been shown to markedly enhance efficiency and targeting of ocular delivery.^{100 101}

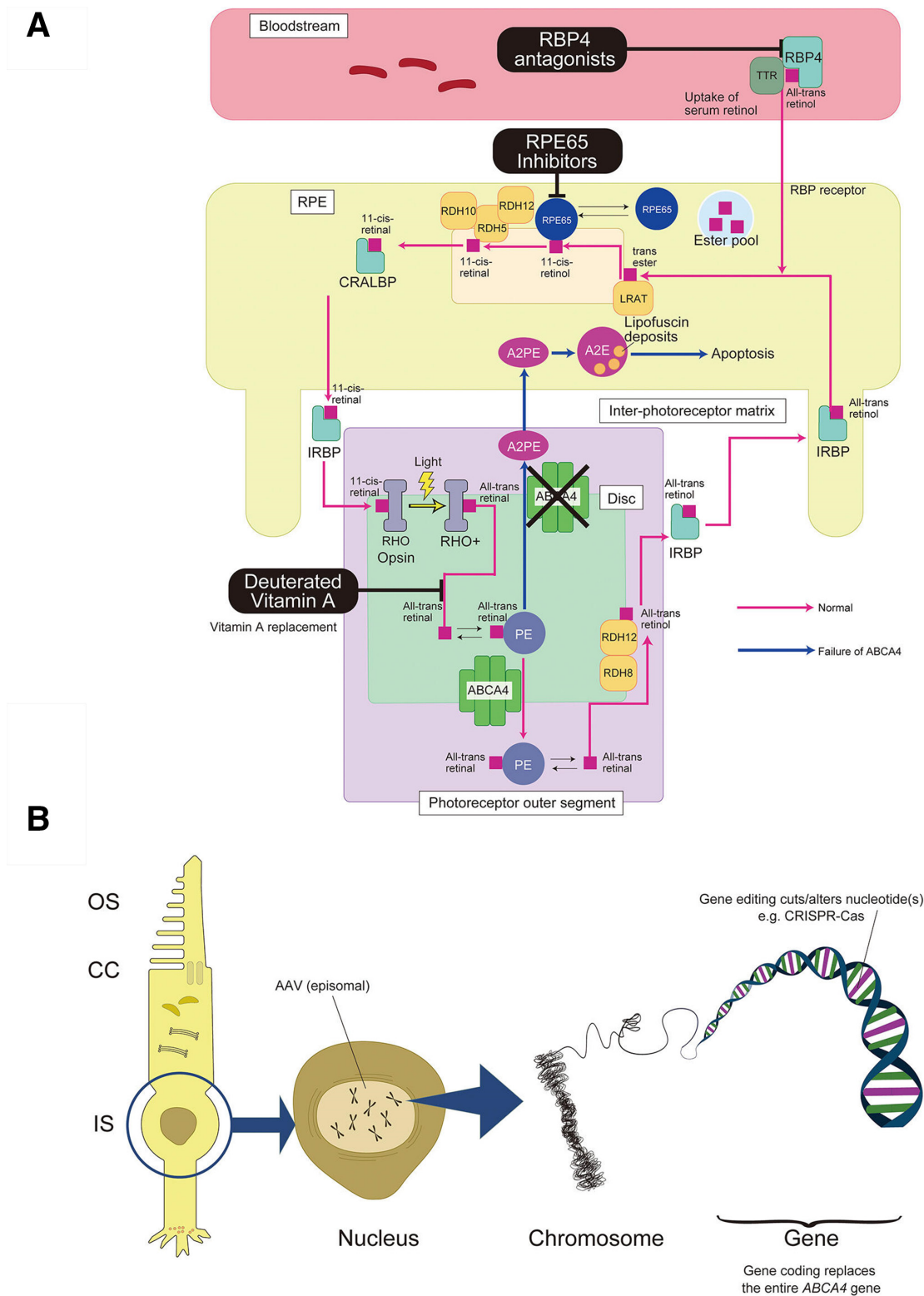


Figure 3 Current and future treatment agents for STGD1 A schematic showing (A) current pharmacological STGD1 treatment agents and (B) novel genetic therapies for STGD1. (A) Schematic showing the normal visual cycle (pink) and failure of transport due to *ABCA4* dysfunction (blue). Agents (RPE65 inhibitors, deuterated Vitamin A, RBP4 antagonists) lower the formation of toxic products of the retinoid cycle by enzymatic inhibition, reducing delivery of vitamin A, or antagonising the retinoid binding protein 4 (RBP4). (B) Schematic showing non-integrating episomal and integrating nuclear gene therapies. The *ABCA4* gene is expressed in retinal photoreceptors and the transporter is localised at the rim of rod and cone photoreceptors at the outer segment (OS), which connects to the inner segment (IS) via connecting cilium (CC). To target disordered transport due to *ABCA4* dysfunction, adeno-associated virus (AAV) therapies deliver the large 6.4 kb *ABCA4* gene (>4.7 kb AAV cargo limit) to the nucleus by splicing together fragments of the *ABCA4* gene, wherein the transgene remains in an episomal state. Gene editing therapies cut or alter single nucleotide(s) within the *ABCA4* gene via techniques such as CRISPR-Cas, which targets specific variants. Gene coding replaces the entire *ABCA4* gene via an engineered transposase, enabling its application to all variants, including exonic and intronic nucleotide variants, as well as structural variants.

Other approaches being developed include either using dual or triple AAV vectors to deliver full length *ABCA4* to the nucleus by splicing together fragments of the cDNA.^{102–104}

Novel CRISPR-based molecular tools have also emerged as a therapeutic option for STGD1 (figure 3B).¹⁰⁵ Recently, gene editing via CRISPR/Cas9 has been employed to correct pathogenic variants of *ABCA4* in human iPSCs (hiPSC) for STGD1 patients.¹⁰⁶ However, there are potential safety concerns associated with gene editing methods being developed for STGD1, namely the introduction of double-stranded breaks (DSBs) in the genome during editing. Gene editing systems such as CRISPR/Cas9 create DSBs, which run the risk of triggering error-prone endogenous DNA repair mechanisms that could otherwise cause unwanted effects.^{107–108} However, systems that exploit transposon-based mutagenesis—such as fish-derived Sleeping Beauty^{109–110} and insect-derived PiggyBac¹¹¹—may circumvent this issue. A potential drawback for such methods is that the DNA recognition sequence may be found throughout the human genome and thus the gene would not be targeted to a specific site. Thus, an ideal transposon-based system would be one that is mammal-derived and absent of immunogenic effects, with the capability to insert genetic material of unlimited size at a site-specific genomic target.

By combining features of the above systems, there is potential for developing much needed novel gene therapies that can transport a larger size DNA cargo (and avoid the introduction of DSBs) for STGD1 and other common IRDs such as *USH2A*-associated retinitis pigmentosa and Usher syndrome. For example, a novel DNA integrating platform developed by SalioGen Therapeutics—Gene Coding—combines many of the above-mentioned features (figure 3B). The technology uses a tissue-specific and cell-specific nanoparticle (NP) to co-encapsulate mRNA encoding a synthetic bioengineered, mammalian transposase and a DNA element containing the gene of interest for a specific disease target. Notably, the DNA element can contain large genetic cargos, such as *ABCA4*, or a combination of several genetic factors, since the NP does not have size limitations.

Several potential benefits of this type of technology are currently under investigation. First, NPs that target specific cell types such as photoreceptors and RPE are being developed.¹¹² Second, the NP capability to deliver large gene cargos is being exploited to deliver single or multiple genetic components and regulatory elements to control gene expression. Third, the non-viral nature of the DNA integration system may decrease the immunogenicity seen with viral delivery systems. Finally, in contrast to AAV therapies and non-viral gene editing technologies and gene therapies, the transposase avoids unwanted genomic effects by avoiding DSBs¹¹³ while integrating therapeutic genes at polynucleotide sites in the genome. All of these potential attributes may be important in treating degenerative retinal disorders such as STGD1, which is caused by multiple pathogenic variants in large genes.

CONCLUSIONS

STGD1 is one of the most common IRDs, presenting in childhood, early adulthood and in later life. This *ABCA4*-associated retinopathy is highly heterogeneous both clinically and genetically. The deep clinical and genetic characterisation that has been undertaken over the last 15 years has improved understanding of underlying disease mechanisms, natural history and outcome metrics, allowing multiple therapeutic trials to be conducted. Further trials are anticipated, including pharmacological in the

immediate term, with innovations towards the development of novel gene therapy approaches on the horizon.

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