CLAIMS

1. An isolated polynucleotide comprising a nucleotide sequence encoding Complement Factor H-like Protein 1 (FHL1)~~I (CFI)~~, wherein the nucleotide sequence has at least 75~~85~~% sequence identity to SEQ ID NO: 12~~10~~.

2. The isolated polynucleotide of claim 1, wherein the nucleotide sequence is SEQ ID NO: 12~~10~~.

3. The isolated polynucleotide of claim 1 or 2, wherein the polynucleotide comprises an adeno-associated virus (AAV) inverted terminal repeat (ITR) at its 5' end and an AAV ITR at its 3' end, preferably wherein the AAV ITRs are AAV2 or AAV8 ITRs, more preferably wherein the AAV ITRs are AAV2 ITRs.

4. The isolated polynucleotide of any one of claims 1 to 3, wherein the nucleotide sequence encoding FHL1 is operably linked to a promoter, preferably wherein the promoter is a CMV promoter or a CAG promoter.

5. The isolated polynucleotide of claim 4, wherein the promoter has the nucleotide sequence of SEQ ID NO: 5 or SEQ ID NO: 13, or a nucleotide sequence having at least 75%, 80%, 85% 90%, 95%, 96%, 97%, 98% or 99% identity to SEQ ID NO: 5 or SEQ ID NO: 13.

6. The isolated polynucleotide of any one of claims 1 to 5, wherein the nucleotide sequence encoding FHL1 is operably linked to a WPRE regulatory element, preferably wherein the WPRE regulatory element is a WPRE3 regulatory element.

7. The isolated polynucleotide of claim 6, wherein the WPRE regulatory element has the nucleotide sequence of SEQ ID NO: 7 or SEQ ID NO: 15, or a nucleotide sequence that has at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identity to SEQ ID NO: 7 or SEQ ID NO: 15.

8. The isolated polynucleotide of any one of claims 1 to 7, wherein the nucleotide sequence encoding FHL1 is operably linked to a poly-A signal, preferably wherein the poly-A signal is a Bovine Growth Hormone poly-A signal.

9. The isolated polynucleotide of claim 8, wherein the poly-A signal has the nucleotide sequence of SEQ ID NO: 6 or SEQ ID NO: 14, or a nucleotide sequence that has at least

75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identity to SEQ ID NO: 6 or SEQ ID NO: 14.

10. The isolated polynucleotide of any one of claims 1 to 9, wherein the nucleotide sequence encoding FHL1 is operably linked to a CMV promoter; a WPRE regulatory element; and a poly-A signal.

~~3. An isolated polynucleotide comprising a nucleotide sequence encoding Complement Factor H-like Protein 1 (FHL1), wherein the nucleotide sequence has at least 75% sequence identity to SEQ ID NO: 12.~~

~~4. The isolated polynucleotide of claim 3, wherein the nucleotide sequence is SEQ ID NO: 12.~~

11~~5~~. A vector comprising the polynucleotide of any preceding claim.

12~~6~~. The vector of claim 11~~5~~, wherein the vector is an adeno-associated viral (AAV) vector.

13~~7~~. The vector of claim 11~~5~~ or 12~~6~~, wherein the vector is in the form of a viral vector particle.

14~~8~~. The vector of claim 13~~ 7~~, wherein the viral vector particle is an AAV vector particle that comprises ~~an~~ AAV2 or AAV8 capsid proteins, preferably wherein the AAV vector particle comprises an AAV2 genome and AAV2 capsid proteins (AAV2/2), an~~d~~ AAV2 genome and~~or~~ AAV8 capsid proteins (AAV2/8), or an AAV8 genome and AAV8 capsid proteins (AAV8/8).

~~9. The vector of any one of claims 5-8, wherein the nucleotide sequence encoding the CFI or FHL1 is operably linked to a CMV promoter; a WPRE regulatory element; and/or a poly-A signal.~~

15~~10~~. A cell comprising the polynucleotide of any one of claims 1-104~~,~~ or

~~11.~~ a~~A~~ cell transduced with the vector of any one of claims 11-14~~5-9~~.

16~~12~~. A pharmaceutical composition comprising the polynucleotide, vector or cell of any preceding claim in combination with a pharmaceutically acceptable carrier, diluent or excipient.

17~~13~~. The polynucleotide or~~,~~ vector ~~or cell~~ of any one of claims 1-14~~1~~ for use in therapy~~,~~.

~~14. The polynucleotide, vector or cell of any one of claims 1-11~~ preferably for use in treating or preventing a complement-mediated disorder of the eye.

18~~15~~. The polynucleotide or~~,~~ vector ~~or cell~~ for use according to claim 17~~14~~, wherein the disorder is age-related macular degeneration (AMD) or diabetic retinopathy, preferably AMD~~.~~.

~~16. The polynucleotide, vector or cell for use according to claim 15,~~ more preferably wherein the AMD is dry AMD.

19~~17~~. The polynucleotide or~~,~~ vector ~~or cell~~ for use according to ~~any one of~~ claim~~s~~ 17 or 18~~13-16~~, wherein:

(i) the formation of geographic atrophy is prevented or reduced, and/or the amount of geographic atrophy is reduced, and/or~~.~~

~~18. The polynucleotide, vector or cell for use according to any one of claims 13-17, wherein~~ (ii) the progression of geographic atrophy is slowed; and/or~~.~~

~~19. The polynucleotide, vector or cell for use according to any one of claims 13-18, wherein~~ (iii) there is at least a 10% reduction in the increase in geographic atrophy area over the 12 months following administration to a treated eye of a subject, relative to an untreated eye over the same period; and/or~~.~~

~~20. The polynucleotide, vector or cell for use according to any one of claims 13-19, wherein~~ (iv) administration of the polynucleotide or~~,~~ vector ~~or cell~~ increases the level of C3b-inactivating and iC3b-degradation activity in a subject, or in an eye, such as in the retinal pigment epithelium (RPE), of a subject, optionally to a level that exceeds a normal level in a subject, or eye or RPE thereof.

20~~21~~. The polynucleotide or ~~,~~vector ~~or cell~~ for use according to any one of claims 17-19~~13-20~~, wherein the polynucleotide or~~,~~ vector ~~or cell~~ is administered intraocularly~~.~~.

~~22. The polynucleotide, vector or cell for use according to any one of claims 13-21,~~ wherein the polynucleotide or ~~,~~vector ~~or cell~~ is administered to the eye of a subject by subretinal, direct retinal, suprachoroidal or intravitreal injection~~.~~.

~~23. The polynucleotide, vector or cell for use according to any one of claims 13-22,~~ more preferably wherein the polynucleotide or ~~,~~ vector or cell is administered to the eye of a subject by subretinal injection.

~~24. A method of treating or preventing a complement-mediated disorder of the eye comprising administering the polynucleotide, vector or cell of any one of claims 1-11 to a subject in need thereof.~~

~~25. A method of providing Complement Factor I (CFI) and/or Complement Factor H-like Protein 1 (FHL1) to a subject, comprising delivering the polynucleotide, vector or cell of any one of claims 1-11 to the eye of the subject.~~

21. Use of a polynucleotide or vector of any one of claims 1-14 for the manufacture of a medicament for treating or preventing a complement-mediated disorder of the eye.

22. The use according to claim 21, wherein the disorder is age-related macular degeneration (AMD) or diabetic retinopathy, preferably AMD, more preferably wherein the AMD is dry AMD.

23. The use according to claim 21 or 22, wherein:

(i) the formation of geographic atrophy is prevented or reduced, and/or the amount of geographic atrophy is reduced; and/or

(ii) the progression of geographic atrophy is slowed; and/or

(iii) there is at least a 10% reduction in the increase in geographic atrophy area over the 12 months following administration to a treated eye of a subject, relative to an untreated eye over the same period; and/or

(iv) administration of the polynucleotide or vector increases the level of C3b-inactivating and iC3b-degradation activity in a subject, or in an eye, such as in the retinal pigment epithelium (RPE), of a subject, optionally to a level that exceeds a normal level in a subject, or eye or RPE thereof.

24. Use of a polynucleotide or vector of any one of claims 1-14 for the manufacture of a medicament for improving or restoring reading speed in a subject in a subject suffering

from an eye disorder such as AMD and/or mitigating reduction in reading speed associated with an eye disorder such as AMD.

25. Use of a polynucleotide or vector of any one of claims 1-14 for the manufacture of a medicament for reducing or preventing loss of photoreceptors and/or the retinal pigment epithelium (RPE).

26. The use according to any one of claims 21-25, wherein the polynucleotide or vector is administered intraocularly, preferably wherein the polynucleotide or vector is administered to the eye of a subject by subretinal, direct retinal, suprachoroidal or intravitreal injection, more preferably wherein the polynucleotide or vector is administered to the eye of a subject by subretinal injection.