Further provided is a codon-optimized sequence of the CNGA3 gene, which is provided as SEQ ID NO:8.

Also provided are vectors, such as viral vectors, comprising the expression constructs disclosed herein. The expression construct is preferably delivered using a vector derived from adenovirus serotype 8 (AAV8) or an alternative strong AAV serotype.

The disclosure also provides methods of using the nucleic acids, transcriptional control units (TCUs), optimized gene sequences, expression constructs, and vectors for the treatment and/or prevention of retinal disorders or dystrophies, including but not limited to cone dystrophies such as Achromatopsia.

In one aspect, the present disclosure provides a transcriptional control unit (TCU) of up to 2500 nucleotides in length comprising in a 5' to 3' direction:

(a) a Locus Control Region (LCR) comprising

(i) SEQ ID NO 1; or

(ii) a sequence having at least 90% sequence identity to said sequence (a)(i); and

(b) a promoter element comprising SEQ ID NO: 16 and

(i) at least the last 200 nucleotides of SEQ ID NO: 17; or

(ii) a sequence having at least 90% sequence identity to said sequence (b)(i);

said TCU exhibiting cone photoreceptor-specific promoter activity.

Accordingly, in one ~~aspect~~ example, the disclosure provides:

a transcriptional control unit (TCU) of up to 2500 nucleotides in length comprising in a 5' to 3' direction:

(a) a Locus Control Region (LCR) comprising

(i) SEQ ID NO 1; or

(ii) a sequence having at least 90% sequence identity to said sequence (a)(i); and

(b) a promoter element comprising

(i) at least 200 nucleotides of either SEQ ID NO: 2 or SEQ ID NO: 17; or

(ii) a sequence having at least 90% sequence identity to said sequence (b)(i);

said TCU exhibiting cone photoreceptor-specific promoter activity.

In one example, promoter element (b) may optionally comprise at least the last 200 or the last 500 nucleotides of either SEQ ID NO: 2 or SEQ ID NO: 17, or a sequence having at least

90% sequence identity to the last 200 or the last 500 nucleotides of either SEQ ID NO: 2 or SEQ ID NO: 17.

According to any one of the above examples, promoter element (b) may comprise at least 200 nucleotides of SEQ ID NO: 3, optionally wherein promoter element (b) also comprises a sequence of at least 10 contiguous nucleotides selected from nucleotides 1 to 35 of SEQ ID NO:3, or a sequence comprising at least 10 contiguous nucleotides selected from a sequence having at least 90% sequence identity to nucleotides 1 to 35 of SEQ ID NO:3.

According to any one of the above examples, promoter element (b) may comprise SEQ ID NO: 3 [529 bp promoter element in hG1.7] or SEQ ID NO:5 [247 bp promoter element in hG1.4] or a sequence having at least 90% sequence identity to SEQ ID NO:3 or SEQ ID NO: 5.

CLAIMS

1. A transcriptional control unit (TCU) of up to 2500 nucleotides in length comprising in a 5' to 3' direction:

(a) a Locus Control Region (LCR) comprising

(i) SEQ ID NO 1; or

(ii) a sequence having at least 90% sequence identity to said sequence (a)(i); and

(b) a promoter element comprising SEQ ID NO: 16 and

(i) at least the last 200 nucleotides of ~~either SEQ ID NO: 2 or~~ SEQ ID NO: 17; or

(ii) a sequence having at least 90% sequence identity to said sequence (b)(i);

said TCU exhibiting cone photoreceptor-specific promoter activity.

~~2. The TCU of claim 1, wherein (b) comprises:~~

~~(i) at least the last 200 nucleotides of either SEQ ID NO: 2 or SEQ ID NO: 17, or~~

~~(ii) a sequence having at least 90% sequence identity to said sequence (i);~~

~~said TCU exhibiting cone photoreceptor-specific promoter activity.~~

2~~3~~. The TCU of claim 1~~2~~, wherein (b) comprises:

(i) at least the last 500 nucleotides of ~~either SEQ ID NO: 2 or~~ SEQ ID NO: 17, or

(ii) a sequence having at least 90% sequence identity to said sequence (i);

said TCU exhibiting cone photoreceptor-specific promoter activity.

3~~4~~. The TCU of any one of the preceding claims, wherein (b) comprises at least 200 nucleotides of SEQ ID NO: 3.

4~~5~~. The TCU of any one of the preceding claims, wherein (b) comprises a sequence of at least 10 contiguous nucleotides selected from nucleotides 1 to 35 of SEQ ID NO:3, or a sequence comprising at least 10 contiguous nucleotides selected from a sequence having at least 90% sequence identity to nucleotides 1 to 35 of SEQ ID NO:3.

5~~6~~. The TCU according to any one of the preceding claims, wherein (b) comprises:

(i) SEQ ID NO: 3; or

(ii) a sequence having at least 90% sequence identity to said sequence (i);

said TCU exhibiting cone photoreceptor-specific promoter activity.

~~7. The TCU of claim 6, wherein nucleotides 1934 to 1939 (GGGCCG) of SEQ ID NO:2 are replaced by SEQ ID NO:16.~~

6~~8~~. The TCU of claim 5~~6~~, wherein the TCU comprises SEQ ID NO: 4 or SEQ ID NO:15.

7~~9~~. The TCU of any one of claims 1 to 3~~4~~, wherein the promoter element comprises SEQ ID NO: 5.

8~~10~~. The TCU of claim 7~~9~~, wherein the TCU comprises SEQ ID NO: 6.

9~~11~~. An expression construct comprising the TCU of any one of the preceding claims, operably linked to a sequence to be expressed in a cone photoreceptor-specific manner.

10~~2~~. The expression construct according to claim 9~~11~~, wherein the operably linked sequence is *CNGA3*, *CNGB3*, *PDE6C*, *PDE6H*, *GNAT2*, *KCNV2* or *CACNA2D4*.

11~~3~~. The expression construct according to claim 10~~2~~, wherein the operably linked sequence comprises SEQ ID NO: 7, 8, 9, 10, 11, 12, 13 or 14, or that has at least 80% sequence identity to SEQ ID NO: 7, 8, 9, 10, 11, 12, 13 or 14 and has the ability to rescue cone photoreceptor function.

12~~4~~. The expression construct according to claim 10~~2~~ or 11~~3~~, wherein the operably linked sequence comprises SEQ ID NO: 8, or that has at least 80% sequence identity to SEQ ID NO: 8 and has the ability to rescue cone photoreceptor function.

135. A vector comprising the TCU according to any one of claims 1 to 810 or an expression construct according to any one of claims 911 to 1214.

146. The vector according to claim 135 which is a viral vector.

157. The vector according to claims 146, which is an adeno-associated virus (AAV) vector.

168. The vector according to claim 157, wherein the vector comprises an AAV genome or a derivative thereof.

179. The vector according to claim 168, wherein the vector comprises an AAV genome or a derivative thereof, and wherein the AAV capsid is derived from AAV8.

1820. The vector according to claim 179, wherein the AAV capsid is derived from AAV8 and the expression construct is defined according to any one of claims 911 to 1214.

1921. The vector according to claim 1820, wherein the operably linked sequence is *CNGA3*.

202. The vector according to any one of claims 1618 to 1921, wherein said derivative is a chimeric, shuffled or capsid modified derivative.

213. The vector according to any of claims 1618 to 202, wherein said AAV genome is from a naturally derived serotype or isolate or clade of AAV.

224. The vector according to claim 213, wherein said AAV genome is from AAV serotype 2 (AAV2), AAV serotype 4 (AAV4), or AAV serotype 8 (AAV8) and/or wherein the capsid is derived from AAV8.

235. The vector according to claim 224, wherein the genome is derived from AAV2 and the capsid is derived from AAV8.

246. A host cell that contains a vector of any one of claims 135 to 235 or produces a viral vector of any one of claims 135 to 235.

257. The cell according to claim 246 that is a HEK293 or HEK293T cell.

268. A pharmaceutical composition comprising a vector of any one of claims 135 to 235 and a pharmaceutically acceptable carrier.

279. The vector according to any one of claims 135 to 235 for use in preventing or treating retinal disorders.

2830. Use of a vector according to any one of claims 135 to 235 in the manufacture of a medicament for the treatment or prevention of retinal disorders.

2931. Use of a vector according to any one of claims 135 to 235 in the manufacture of a medicament for the treatment or prevention of retinal disorders in a patient in need thereof, comprising that a therapeutically effective amount of the vector is to be administered to said patient.

302. The vector according to claim 279, or the use of claim 2830 or 2931, wherein the retinal disorder is Achromatopsia.

313. The vector according to claim 279 or 302, or the use of any one of claims 2830 to 302, wherein the treatment or prevention is by administration of the vector according to any one of claims 135 to 235 to a patient by direct retinal, subretinal or intravitreal injection.

324. The vector, or use, ~~or method~~ according to claim 313, wherein said vector is to be administered directly into the retinal, subretinal space or intravitreal space.