

CLAIMS

What is claimed is:

1. ~~1.~~ ~~1.~~ — A method of modulating expression of an OPA1 protein in a cell having a pre-mRNA that is transcribed from an OPA1 gene and that comprises a non-sense mediated RNA decay-inducing exon (NMD-exon), the method pharmaceutical composition comprising contacting an therapeutic agent or a vector encoding the therapeutic agent ~~to the cell, whereby the agent modulates splicing of the NMD-exon from the pre-mRNA, thereby modulating a level of processed mRNA that is processed from the pre-mRNA, and modulating the expression of the OPA1 protein in the cell,~~ wherein the therapeutic agent comprises an antisense oligomer ~~with at least 80% sequence identity to~~ a that comprises a sequence selected from the group consisting of SEQ ID NOs: 6-275 and 280-299, and a pharmaceutically acceptable excipient.
2. ~~The method of claim 1, wherein the agent:~~
 - ~~(a) binds to a targeted portion of the pre-mRNA;~~
 - ~~(b) modulates binding of a factor involved in splicing of the NMD-exon; or~~
 - ~~(c) a combination of (a) and (b).~~
3. ~~The method of claim 2, wherein the agent interferes with binding of the factor involved in splicing of the NMD-exon to a region of the targeted portion.~~
4. ~~The method of claim 2, wherein the targeted portion of the pre-mRNA is proximal to the NMD exon.~~
5. ~~The method of claim 2, wherein the targeted portion of the pre-mRNA is at most about 1500 nucleotides, about 1000 nucleotides, about 800 nucleotides, about 700 nucleotides, about 600 nucleotides, about 500 nucleotides, about 400 nucleotides, about 300 nucleotides, about 200 nucleotides, about 100 nucleotides, about 80 nucleotides, about 70 nucleotides, about 60 nucleotides, about 50 nucleotides upstream of 5' end of the NMD-exon.~~
6. ~~The method of claim 2, wherein the targeted portion of the pre-mRNA is at least about 1500 nucleotides, about 1000 nucleotides, about 800 nucleotides, about 700 nucleotides, about 600 nucleotides, about 500 nucleotides, about 400 nucleotides, about 300 nucleotides, about 200 nucleotides, about 100 nucleotides, about 80 nucleotides, about 70 nucleotides, about 60 nucleotides, about 50 nucleotides, about 40 nucleotides, about 30 nucleotides, about 20 nucleotides, about 10 nucleotides, about 5 nucleotides, about 4 nucleotides, about 2 nucleotides, about 1 nucleotides upstream of 5' end of the NMD-exon.~~
7. ~~The method of claim 2, wherein the targeted portion of the pre-mRNA is at most about 1500 nucleotides, about 1000 nucleotides, about 800 nucleotides, about 700 nucleotides, about 600 nucleotides, about 500 nucleotides, about 400 nucleotides, about 300 nucleotides, about 200~~

~~nucleotides, about 100 nucleotides, about 80 nucleotides, about 70 nucleotides, about 60 nucleotides, about 50 nucleotides downstream of 3' end of the NMD exon.~~

- ~~8.—The method of claim 2, wherein the targeted portion of the pre-mRNA is at least about 1500 nucleotides, about 1000 nucleotides, about 800 nucleotides, about 700 nucleotides, about 600 nucleotides, about 500 nucleotides, about 400 nucleotides, about 300 nucleotides, about 200 nucleotides, about 100 nucleotides, about 80 nucleotides, about 70 nucleotides, about 60 nucleotides, about 50 nucleotides, about 40 nucleotides, about 30 nucleotides, about 20 nucleotides, about 10 nucleotides, about 5 nucleotides, about 4 nucleotides, about 2 nucleotides, about 1 nucleotides downstream of 3' end of the NMD exon.~~
- ~~9.—The method of claim 2, wherein the targeted portion of the pre-mRNA is at most about 1500 nucleotides, about 1000 nucleotides, about 800 nucleotides, about 700 nucleotides, about 600 nucleotides, about 500 nucleotides, about 400 nucleotides, about 300 nucleotides, about 200 nucleotides, about 100 nucleotides, about 80 nucleotides, about 70 nucleotides, about 60 nucleotides, about 50 nucleotides upstream of genomic site GRCh38/hg38: chr3-193628509.~~
- ~~10.—The method of claim 2, wherein the targeted portion of the pre-mRNA is about 1500 nucleotides, about 1000 nucleotides, about 800 nucleotides, about 700 nucleotides, about 600 nucleotides, about 500 nucleotides, about 400 nucleotides, about 300 nucleotides, about 200 nucleotides, about 100 nucleotides, about 80 nucleotides, about 70 nucleotides, about 60 nucleotides, about 50 nucleotides upstream of genomic site GRCh38/hg38: chr3-193628509.~~
- ~~11.—The method of claim 2, wherein the targeted portion of the pre-mRNA is at most about 1500 nucleotides, about 1000 nucleotides, about 800 nucleotides, about 700 nucleotides, about 600 nucleotides, about 500 nucleotides, about 400 nucleotides, about 300 nucleotides, about 200 nucleotides, about 100 nucleotides, about 80 nucleotides, about 70 nucleotides, about 60 nucleotides, about 50 nucleotides downstream of genomic site GRCh38/hg38: chr3-193628616.~~
- ~~12.—The method of claim 2, wherein the targeted portion of the pre-mRNA is about 1500 nucleotides, about 1000 nucleotides, about 800 nucleotides, about 700 nucleotides, about 600 nucleotides, about 500 nucleotides, about 400 nucleotides, about 300 nucleotides, about 200 nucleotides, about 100 nucleotides, about 80 nucleotides, about 70 nucleotides, about 60 nucleotides, about 50 nucleotides downstream of genomic site GRCh38/hg38: chr3-193628616.~~
- ~~13.—The method of claim 2, wherein the targeted portion of the pre-mRNA is located in an intronic region between two canonical exonic regions of the pre-mRNA, and wherein the intronic region contains the NMD exon.~~
- ~~14.—The method of claim 2, wherein the targeted portion of the pre-mRNA at least partially overlaps with the NMD exon.~~
- ~~15.—The method of claim 2, wherein the targeted portion of the pre-mRNA at least partially overlaps with an intron upstream or downstream of the NMD exon.~~

- ~~16. The method of claim 2, wherein the targeted portion of the pre-mRNA comprises 5' NMD exon-intron junction or 3' NMD exon-intron junction.~~
- ~~17. The method of claim 2, wherein the targeted portion of the pre-mRNA is within the NMD exon.~~
- ~~18. The method of claim 2, wherein the targeted portion of the pre-mRNA comprises about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or more consecutive nucleotides of the NMD exon.~~
- ~~19. The method of any one of claims 1 to 18, wherein the NMD exon comprises a sequence with at least 80%, at least 90%, or 100% sequence identity to SEQ ID NO: 279.~~
- ~~20. The method of any one of claims 1 to 18, wherein the NMD exon comprises a sequence of SEQ ID NO: 279.~~
- ~~21. The method of claim 2, wherein the targeted portion of the pre-mRNA is within the non-sense mediated RNA decay inducing exon GRCh38/ hg38: chr3-193628509 to 193628616.~~
- ~~22. The method of claim 2, wherein the targeted portion of the pre-mRNA is upstream or downstream of the non-sense mediated RNA decay inducing exon GRCh38/ hg38: chr3-193628509 to 193628616.~~
- ~~23. The method of claim 2, wherein the targeted portion of the pre-mRNA comprises an exon-intron junction of exon GRCh38/ hg38: chr3-193628509 to 193628616.~~
- ~~24. The method of any one of claims 1 to 23, wherein the OPA1 protein expressed from the processed mRNA is a full-length OPA1 protein or a wild-type OPA1 protein.~~
- ~~25. The method of any one of claims 1 to 23, wherein the OPA1 protein expressed from the processed mRNA is a functional OPA1 protein.~~
- ~~26. The method of any one of claims 1 to 23, wherein the OPA1 protein expressed from the processed mRNA is at least partially functional as compared to a wild-type OPA1 protein.~~
- ~~27. The method of any one of claims 1 to 23, wherein the OPA1 protein expressed from the processed mRNA is at least partially functional as compared to a full-length wild-type OPA1 protein.~~
- ~~28. The method of any one of claims 1 to 23, or 25 to 27, wherein the OPA1 protein expressed from the processed mRNA is an OPA1 protein that lacks an amino acid sequence encoded by a nucleic acid sequence with at least 80% sequence identity to SEQ ID NO: 277.~~
- ~~29. The method of any one of claims 1 to 28, wherein the method promotes exclusion of the NMD exon from the pre-mRNA.~~

- ~~30. The method of claim 29, wherein the exclusion of the NMD exon from the pre-mRNA in the cell contacted with the agent is increased by about 1.1 to about 10 fold, about 1.5 to about 10 fold, about 2 to about 10 fold, about 3 to about 10 fold, about 4 to about 10 fold, about 1.1 to about 5 fold, about 1.1 to about 6 fold, about 1.1 to about 7 fold, about 1.1 to about 8 fold, about 1.1 to about 9 fold, about 2 to about 5 fold, about 2 to about 6 fold, about 2 to about 7 fold, about 2 to about 8 fold, about 2 to about 9 fold, about 3 to about 6 fold, about 3 to about 7 fold, about 3 to about 8 fold, about 3 to about 9 fold, about 4 to about 7 fold, about 4 to about 8 fold, about 4 to about 9 fold, at least about 1.1 fold, at least about 1.5 fold, at least about 2 fold, at least about 2.5 fold, at least about 3 fold, at least about 3.5 fold, at least about 4 fold, at least about 5 fold, or at least about 10 fold, compared to in the absence of the agent.~~
- ~~31. The method of any one of claims 1 to 30, wherein the method results in an increase in the level of the processed mRNA in the cell.~~
- ~~32. The method of claim 31, wherein the level of the processed mRNA in the cell contacted with the agent is increased by about 1.1 to about 10 fold, about 1.5 to about 10 fold, about 2 to about 10 fold, about 3 to about 10 fold, about 4 to about 10 fold, about 1.1 to about 5 fold, about 1.1 to about 6 fold, about 1.1 to about 7 fold, about 1.1 to about 8 fold, about 1.1 to about 9 fold, about 2 to about 5 fold, about 2 to about 6 fold, about 2 to about 7 fold, about 2 to about 8 fold, about 2 to about 9 fold, about 3 to about 6 fold, about 3 to about 7 fold, about 3 to about 8 fold, about 3 to about 9 fold, about 4 to about 7 fold, about 4 to about 8 fold, about 4 to about 9 fold, at least about 1.1 fold, at least about 1.5 fold, at least about 2 fold, at least about 2.5 fold, at least about 3 fold, at least about 3.5 fold, at least about 4 fold, at least about 5 fold, or at least about 10 fold, compared to in the absence of the agent.~~
- ~~33. The method of any one of claims 1 to 32, wherein the method results in an increase in the expression of the OPA1 protein in the cell.~~
- ~~34. The method of claim 33, wherein a level of the OPA1 protein expressed from the processed mRNA in the cell contacted with the agent is increased by about 1.1 to about 10 fold, about 1.5 to about 10 fold, about 2 to about 10 fold, about 3 to about 10 fold, about 4 to about 10 fold, about 1.1 to about 5 fold, about 1.1 to about 6 fold, about 1.1 to about 7 fold, about 1.1 to about 8 fold, about 1.1 to about 9 fold, about 2 to about 5 fold, about 2 to about 6 fold, about 2 to about 7 fold, about 2 to about 8 fold, about 2 to about 9 fold, about 3 to about 6 fold, about 3 to about 7 fold, about 3 to about 8 fold, about 3 to about 9 fold, about 4 to about 7 fold, about 4 to about 8 fold, about 4 to about 9 fold, at least about 1.1 fold, at least about 1.5 fold, at least about 2 fold, at least about 2.5 fold, at least about 3 fold, at least about 3.5 fold, at least about 4 fold, at least about 5 fold, or at least about 10 fold, compared to in the absence of the agent.~~
- ~~35. The method of any one of claims 1 to 34, wherein the agent comprises an antisense oligomer with at least 80%, at least 90%, or 100% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 36, 236, 242, 250, 280 283, 288, and 290 292.~~
- ~~36. The method of any one of claims 1 to 34, wherein the agent further comprises a gene editing molecule.~~

- ~~37. The method of claim 36, wherein the gene editing molecule comprises CRISPR-Cas9.~~
- ~~38. A method of modulating expression of an OPA1 protein in a cell having a pre-mRNA that is transcribed from an OPA1 gene, wherein the pre-mRNA comprises a coding exon, the method comprising contacting an agent or a vector encoding the agent to the cell, whereby the agent promotes exclusion of the coding exon from the pre-mRNA, thereby increasing a level of a processed mRNA that is processed from the pre-mRNA and that lacks the coding exon in the cell.~~
- ~~39. The method of claim 38, wherein the agent:~~
- ~~(a) binds to a targeted portion of the pre-mRNA;~~
 - ~~(b) modulates binding of a factor involved in splicing of the coding exon; or~~
 - ~~(c) a combination of (a) and (b).~~
- ~~40. The method of claim 39, wherein the agent interferes with binding of the factor involved in splicing of the coding exon to a region of the targeted portion.~~
- ~~41. The method of claim 39, wherein the targeted portion of the pre-mRNA is proximal to the coding exon.~~
- ~~42. The method of claim 39, wherein the targeted portion of the pre-mRNA is located in an intronic region immediately upstream of the coding exon.~~
- ~~43. The method of claim 39, wherein the targeted portion of the pre-mRNA is within a region spanning from 100 to 50, from 90 to 50, from 80 to 50, from 70 to 50, from 60 to 50, from 60 to 40, from 60 to 30, from 60 to 20, from 60 to 10, from 49 to 1, from 39 to 1, from 29 to 1, or from 19 to 1 nucleotides upstream of 5' end of the coding exon.~~
- ~~44. The method of claim 39, wherein the targeted portion of the pre-mRNA is within a region spanning from 49 to 1, from 39 to 1, from 29 to 1, or from 19 to 1 nucleotides upstream of 5' end of the coding exon.~~
- ~~45. The method of claim 39, wherein the targeted portion of the pre-mRNA is located in an intronic region immediately downstream of the coding exon.~~
- ~~46. The method of claim 39, wherein the targeted portion of the pre-mRNA is within a region spanning from 1 to 49, from 1 to 39, from 1 to 29, from 1 to 19, from 10 to 60, from 20 to 60, from 30 to 60, from 40 to 60, from 50 to 60, from 50 to 70, from 50 to 80, from 50 to 90, or from 50 to 100 nucleotides downstream of 3' end of the coding exon.~~
- ~~47. The method of claim 39, wherein the targeted portion of the pre-mRNA is within a region spanning from 1 to 49, from 1 to 39, from 1 to 29, or from 1 to 19 nucleotides downstream of 3' end of the coding exon.~~

- ~~48. The method of claim 39, wherein the targeted portion of the pre-mRNA at least partially overlaps with the coding exon.~~
- ~~49. The method of claim 39, wherein the targeted portion of the pre-mRNA at least partially overlaps with an intron immediately upstream or immediately downstream of the coding exon.~~
- ~~50. The method of claim 39, wherein the targeted portion of the pre-mRNA comprises 5' coding exon-intron junction or 3' coding exon-intron junction.~~
- ~~51. The method of claim 39, wherein the targeted portion is within the coding exon of the pre-mRNA.~~
- ~~52. The method of any one of claims 39 to 51, wherein the coding exon is an alternatively spliced exon.~~
- ~~53. The method of any one of claims 39 to 52, wherein the coding exon comprises a sequence with at least 80%, at least 90%, or 100% sequence identity to SEQ ID NO: 277.~~
- ~~54. The method of any one of claims 39 to 52, wherein the coding exon comprises SEQ ID NO: 277.~~
- ~~55. The method of claim 39, wherein the targeted portion of the pre-mRNA is immediately upstream of the coding exon GRCh38/hg38: chr3-193626092 to 193626202.~~
- ~~56. The method of claim 39, wherein the targeted portion of the pre-mRNA is within a region spanning from 49 to 1, from 39 to 1, from 29 to 1, or from 19 to 1 nucleotides upstream of genomic site GRCh38/hg38: chr3-193626092.~~
- ~~57. The method of claim 39, wherein the targeted portion of the pre-mRNA is immediately downstream of the coding exon GRCh38/hg38: chr3-193626092 to 193626202.~~
- ~~58. The method of claim 39, wherein the targeted portion of the pre-mRNA is within a region spanning from 1 to 49, from 1 to 39, from 1 to 29, or from 1 to 19 nucleotides downstream of genomic site GRCh38/hg38: chr3-193626202.~~
- ~~59. The method of claim 39, wherein the targeted portion of the pre-mRNA is within the coding exon GRCh38/hg38: chr3-193626092 to 193626202.~~
- ~~60. The method of claim 39, wherein the targeted portion of the pre-mRNA comprises an exon-intron junction of exon GRCh38/hg38: chr3-193626092 to 193626202.~~
- ~~61. The method of claim 39, wherein the targeted portion comprises about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or more consecutive nucleotides of the coding exon.~~

- ~~62. The method of claim 39, wherein the targeted portion of the pre-mRNA comprises a sequence with at least 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to a region comprising at least 8 contiguous nucleic acids of SEQ ID NO: 277.~~
- ~~63. The method of any one of claims 38 to 62, wherein the exclusion of the coding-exon from the pre-mRNA in the cell contacted with the agent is increased by about 1.1 to about 10 fold, about 1.5 to about 10 fold, about 2 to about 10 fold, about 3 to about 10 fold, about 4 to about 10 fold, about 1.1 to about 5 fold, about 1.1 to about 6 fold, about 1.1 to about 7 fold, about 1.1 to about 8 fold, about 1.1 to about 9 fold, about 2 to about 5 fold, about 2 to about 6 fold, about 2 to about 7 fold, about 2 to about 8 fold, about 2 to about 9 fold, about 3 to about 6 fold, about 3 to about 7 fold, about 3 to about 8 fold, about 3 to about 9 fold, about 4 to about 7 fold, about 4 to about 8 fold, about 4 to about 9 fold, at least about 1.1 fold, at least about 1.5 fold, at least about 2 fold, at least about 2.5 fold, at least about 3 fold, at least about 3.5 fold, at least about 4 fold, at least about 5 fold, or at least about 10 fold, compared to in the absence of the agent.~~
- ~~64. The method of any one of claims 38 to 63, wherein the method results in an increase in expression of the OPA1 protein in the cell.~~
- ~~65. The method of claim 64, wherein a level of the OPA1 protein expressed from the processed mRNA in the cell contacted with the agent is increased by about 1.1 to about 10 fold, about 1.5 to about 10 fold, about 2 to about 10 fold, about 3 to about 10 fold, about 4 to about 10 fold, about 1.1 to about 5 fold, about 1.1 to about 6 fold, about 1.1 to about 7 fold, about 1.1 to about 8 fold, about 1.1 to about 9 fold, about 2 to about 5 fold, about 2 to about 6 fold, about 2 to about 7 fold, about 2 to about 8 fold, about 2 to about 9 fold, about 3 to about 6 fold, about 3 to about 7 fold, about 3 to about 8 fold, about 3 to about 9 fold, about 4 to about 7 fold, about 4 to about 8 fold, about 4 to about 9 fold, at least about 1.1 fold, at least about 1.5 fold, at least about 2 fold, at least about 2.5 fold, at least about 3 fold, at least about 3.5 fold, at least about 4 fold, at least about 5 fold, or at least about 10 fold, compared to in the absence of the agent.~~
- ~~66. The method of claim 64, wherein a level of the OPA1 protein expressed from the processed mRNA in the cell contacted with the agent is increased by at least about 1.5 fold compared to in the absence of the agent.~~
- ~~67. The method of any one of claims 64 to 66, wherein the OPA1 protein expressed from the processed mRNA is a functional OPA1 protein.~~
- ~~68. The method of any one of claims 64 to 66, wherein the OPA1 protein expressed from the processed mRNA is at least partially functional as compared to a wild-type OPA1 protein.~~
- ~~69. The method of any one of claims 64 to 66, wherein the OPA1 protein expressed from the processed mRNA is at least partially functional as compared to a full-length wild-type OPA1 protein.~~

- ~~70. The method of any one of claims 64 to 69, wherein the OPA1 protein expressed from the processed mRNA comprises fewer proteolytic cleavage sites than an OPA1 protein encoded by a corresponding mRNA containing the coding exon.~~
- ~~71. The method of any one of claims 38 to 70, wherein the agent promotes exclusion of a non-sense mediated RNA decay inducing exon (NMD exon) from the pre-mRNA.~~
- ~~72. The method of claim 71, wherein the NMD exon comprises a sequence with at least 80%, at least 90%, or 100% sequence identity to SEQ ID NO: 279.~~
- ~~73. The method of claim 71, wherein the NMD exon comprises a sequence of SEQ ID NO: 279.~~
- ~~74. The method of any one of claims 64 to 73, wherein the OPA1 protein expressed from the processed mRNA comprises fewer proteolytic cleavage sites than an OPA1 protein encoded by a corresponding mRNA containing the coding exon.~~
- ~~75. The method of any one of claims 38 to 74, wherein the agent comprises an antisense oligomer with at least 80%, at least 90%, or 100% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 227-242, 250, 280-283, 288, and 290-292.~~
- ~~76. The method of any one of claims 38 to 74, wherein the agent comprises a gene editing molecule.~~
- ~~77. The method of claim 76, wherein the gene editing molecule comprises CRISPR-Cas9.~~
- ~~78. A method of modulating expression of an OPA1 protein in a cell having a pre-mRNA that is transcribed from an OPA1 gene, wherein the pre-mRNA comprises a coding exon, the method comprising contacting an agent or a vector encoding the agent to the cell,~~
~~wherein the agent comprises an antisense oligomer that binds to:~~
~~(a) a targeted portion of the pre-mRNA within an intronic region immediately upstream of a 5' end of the coding exon of the pre-mRNA; or~~
~~(b) a targeted portion of the pre-mRNA within an intronic region immediately downstream of a 3' end of the coding exon of the pre-mRNA;~~
~~whereby the agent increases a level of a processed mRNA that is processed from the pre-mRNA and that contains the coding exon in the cell.~~
- ~~79. The method of claims 78, wherein the coding exon is an alternatively spliced exon.~~
- ~~80. The method of claims 78 or 79, wherein the method promotes inclusion of the coding exon in the processed mRNA during splicing of the pre-mRNA in the cell.~~

- ~~81. The method of any one of claims 78 to 80, wherein the target portion of the pre-mRNA is within a region spanning from 100 to 50, from 100 to 60, from 100 to 70, from 100 to 80, or from 100 to 90 nucleotides upstream of a 5' end of the coding exon.~~
- ~~82. The method of any one of claims 78 to 80, wherein the target portion of the pre-mRNA is within a region spanning from 40 to 100, from 50 to 100, from 60 to 100, from 70 to 100, from 80 to 100, or from 90 to 100 nucleotides downstream of a 3' end of the coding exon.~~
- ~~83. The method of any one of claims 78 to 80, wherein the coding exon comprises a sequence with at least 80%, at least 90%, or 100% sequence identity to SEQ ID NO: 277.~~
- ~~84. The method of any one of claims 78 to 80, wherein the coding exon comprises SEQ ID NO: 277.~~
- ~~85. The method of any one of claims 78 to 80, wherein the targeted portion of the pre-mRNA is within a region spanning from 100 to 50, from 100 to 60, from 100 to 70, from 100 to 80, or from 100 to 90 nucleotides upstream of genomic site GRCh38/ hg38: chr3-193626092.~~
- ~~86. The method of any one of claims 78 to 80, wherein the targeted portion of the pre-mRNA is within a region spanning from 40 to 100, from 50 to 100, from 60 to 100, from 70 to 100, from 80 to 100, or from 90 to 100 nucleotides downstream of genomic site GRCh38/ hg38: chr3-193626202.~~
- ~~87. The method of any one of claims 78 to 86, wherein the inclusion of the coding exon in the processed mRNA in the cell contacted with the agent is increased by about 1.1 to about 10-fold, about 1.5 to about 10-fold, about 2 to about 10-fold, about 3 to about 10-fold, about 4 to about 10-fold, about 1.1 to about 5-fold, about 1.1 to about 6-fold, about 1.1 to about 7-fold, about 1.1 to about 8-fold, about 1.1 to about 9-fold, about 2 to about 5-fold, about 2 to about 6-fold, about 2 to about 7-fold, about 2 to about 8-fold, about 2 to about 9-fold, about 3 to about 6-fold, about 3 to about 7-fold, about 3 to about 8-fold, about 3 to about 9-fold, about 4 to about 7-fold, about 4 to about 8-fold, about 4 to about 9-fold, at least about 1.1-fold, at least about 1.5-fold, at least about 2-fold, at least about 2.5-fold, at least about 3-fold, at least about 3.5-fold, at least about 4-fold, at least about 5-fold, or at least about 10-fold, compared to in the absence of the agent.~~
- ~~88. The method of any one of claims 78 to 87, wherein the agent comprises an antisense oligomer with at least 80%, at least 90%, or 100% sequence identity to SEQ ID NO: 267.~~
- ~~89. A method of modulating expression of a target protein in a cell having a pre-mRNA transcribed from a gene that encodes the target protein, wherein the pre-mRNA comprises a coding exon and a non-sense mediated RNA decay inducing exon (NMD-exon), the method comprising contacting an agent or a vector encoding the agent to the cell,~~
- ~~wherein the agent promotes exclusion of both the coding exon and the NMD-exon from the pre-mRNA, thereby increasing a level of a processed mRNA that is processed from the pre-mRNA and that lacks both the NMD-exon and the coding exon in the cell.~~

~~90. The method of claim 89, wherein the agent:~~

- ~~(a) binds to a targeted portion of the pre-mRNA;~~
- ~~(b) modulates binding of a factor involved in splicing of the coding exon, the NMD exon, or both; or~~
- ~~(c) a combination of (a) and (b).~~

~~91. The method of claim 90, wherein the agent interferes with binding of the factor involved in splicing of the coding exon, the NMD exon, or both, to a region of the targeted portion.~~

~~92. The method of any one of claims 89 to 91, wherein the NMD exon is within an intronic region adjacent to the coding exon.~~

~~93. The method of claim 92, wherein the NMD exon is within an intronic region immediately upstream of the coding exon.~~

~~94. The method of claim 92, wherein the NMD exon is within an intronic region immediately downstream of the coding exon.~~

~~95. The method of any one of claims 90 to 94, wherein the targeted portion of the pre-mRNA is proximal to the coding exon.~~

~~96. The method of any one of claims 90 to 94, wherein the targeted portion of the pre-mRNA is located in an intronic region immediately upstream of the coding exon.~~

~~97. The method of any one of claims 90 to 94, wherein the targeted portion of the pre-mRNA is located in an intronic region immediately downstream of the coding exon.~~

~~98. The method of any one of claims 90 to 94, wherein the targeted portion of the pre-mRNA is located within the coding exon.~~

~~99. The method of any one of claims 90 to 94, wherein the targeted portion of the pre-mRNA is within a region spanning from 49 to 1, from 39 to 1, from 29 to 1, or from 19 to 1 nucleotides upstream of 5' end of the coding exon.~~

~~100. The method of any one of claims 90 to 94, wherein the targeted portion of the pre-mRNA is within a region spanning from 100 nucleotides upstream of the coding exon to 100 nucleotides downstream of the coding exon.~~

~~101. The method of any one of claims 89 to 100, wherein the coding exon is an alternatively spliced exon.~~

~~102. The method of any one of claims 89 to 101, wherein the coding exon comprises a sequence with at least 80%, at least 90%, or 100% sequence identity to SEQ ID NO: 277.~~

- ~~103. The method of any one of claims 89 to 101, wherein the coding exon comprises SEQ ID NO: 277.~~
- ~~104. The method of claim 90, wherein the targeted portion of the pre-mRNA is immediately upstream of the coding exon GRCh38/ hg38: chr3 193626092 to 193626202.~~
- ~~105. The method of claim 90, wherein the targeted portion of the pre-mRNA is immediately downstream of the coding exon GRCh38/ hg38: chr3 193626092 to 193626202.~~
- ~~106. The method of any one of claims 90 to 94, wherein the targeted portion of the pre-mRNA is within a region spanning from 49 to 1, from 39 to 1, from 29 to 1, or from 19 to 1 nucleotides upstream of GRCh38/ hg38: chr3 193626092.~~
- ~~107. The method of claim 90, wherein the targeted portion of the pre-mRNA is within a region spanning from 100 nucleotides upstream of genomic site GRCh38/ hg38: chr3 193626092 to 100 nucleotides downstream of genomic site GRCh38/ hg38: chr3 193626202. .~~
- ~~108. The method of claim 90, wherein the targeted portion of the pre-mRNA is within the coding exon GRCh38/ hg38: chr3 193626092 to 193626202.~~
- ~~109. The method of claim 90, wherein the targeted portion of the pre-mRNA comprises an exon-intron junction of the coding exon GRCh38/ hg38: chr3 193626092 to 193626202.~~
- ~~110. The method of claim 90, wherein the targeted portion comprises about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or more consecutive nucleotides of the coding exon.~~
- ~~111. The method of claim 90, wherein the targeted portion of the pre-mRNA is proximal to the NMD-exon.~~
- ~~112. The method of claim 90, wherein the targeted portion of the pre-mRNA is located in an intronic region immediately upstream of the NMD-exon.~~
- ~~113. The method of claim 90, wherein the targeted portion of the pre-mRNA is located in an intronic region immediately downstream of the NMD-exon.~~
- ~~114. The method of claim 90, wherein the targeted portion of the pre-mRNA is located within the NMD-exon.~~
- ~~115. The method of claim 90, wherein the targeted portion of the pre-mRNA is within a region spanning from 100 nucleotides upstream of the NMD-exon to 100 nucleotides downstream of the NMD-exon.~~
- ~~116. The method of any one of claims 89 to 115, wherein the NMD-exon comprises a sequence with at least 80%, at least 90%, or 100% sequence identity to SEQ ID NO: 279.~~
- ~~117. The method of claim 89, wherein the NMD-exon comprises SEQ ID NO: 279.~~

- ~~118. The method of claim 90, wherein the targeted portion of the pre-mRNA is immediately upstream of the NMD exon GRCh38/ hg38: chr3 193628509 to 193628616.~~
- ~~119. The method of claim 90, wherein the targeted portion of the pre-mRNA is immediately downstream of the NMD exon GRCh38/ hg38: chr3 193628509 to 193628616.~~
- ~~120. The method of claim 90, wherein the targeted portion of the pre-mRNA is within a region spanning from 100 nucleotides upstream of genomic site GRCh38/ hg38: chr3 193628509 to 100 nucleotides downstream of genomic site GRCh38/ hg38: chr3 193628616.~~
- ~~121. The method of claim 90, wherein the targeted portion of the pre-mRNA is within the NMD exon GRCh38/ hg38: chr3 193628509 to 193628616.~~
- ~~122. The method of claim 90, wherein the targeted portion of the pre-mRNA comprises an exon-intron junction of the NMD exon GRCh38/ hg38: chr3 193628509 to 193628616.~~
- ~~123. The method of claim 90, wherein the targeted portion comprises about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or more consecutive nucleotides of the NMD exon.~~
- ~~124. The method of any one of claims 89 to 123, wherein the exclusion of the coding exon from the pre-mRNA in the cell contacted with the agent is increased by about 1.1 to about 10 fold, about 1.5 to about 10 fold, about 2 to about 10 fold, about 3 to about 10 fold, about 4 to about 10 fold, about 1.1 to about 5 fold, about 1.1 to about 6 fold, about 1.1 to about 7 fold, about 1.1 to about 8 fold, about 1.1 to about 9 fold, about 2 to about 5 fold, about 2 to about 6 fold, about 2 to about 7 fold, about 2 to about 8 fold, about 2 to about 9 fold, about 3 to about 6 fold, about 3 to about 7 fold, about 3 to about 8 fold, about 3 to about 9 fold, about 4 to about 7 fold, about 4 to about 8 fold, about 4 to about 9 fold, at least about 1.1 fold, at least about 1.5 fold, at least about 2 fold, at least about 2.5 fold, at least about 3 fold, at least about 3.5 fold, at least about 4 fold, at least about 5 fold, or at least about 10 fold, compared to in the absence of the agent.~~
- ~~125. The method of any one of claims 89 to 124, wherein the exclusion of the NMD exon from the pre-mRNA in the cell contacted with the agent is increased by about 1.1 to about 10 fold, about 1.5 to about 10 fold, about 2 to about 10 fold, about 3 to about 10 fold, about 4 to about 10 fold, about 1.1 to about 5 fold, about 1.1 to about 6 fold, about 1.1 to about 7 fold, about 1.1 to about 8 fold, about 1.1 to about 9 fold, about 2 to about 5 fold, about 2 to about 6 fold, about 2 to about 7 fold, about 2 to about 8 fold, about 2 to about 9 fold, about 3 to about 6 fold, about 3 to about 7 fold, about 3 to about 8 fold, about 3 to about 9 fold, about 4 to about 7 fold, about 4 to about 8 fold, about 4 to about 9 fold, at least about 1.1 fold, at least about 1.5 fold, at least about 2 fold, at least about 2.5 fold, at least about 3 fold, at least about 3.5 fold, at least about 4 fold, at least about 5 fold, or at least about 10 fold, compared to in the absence of the agent.~~
- ~~126. The method of any one of claims 89 to 125, wherein the agent results in an increase in the level of the processed mRNA in the cell.~~

- ~~127. The method of claim 126, wherein the level of the processed mRNA in the cell contacted with the agent is increased by about 1.1 to about 10 fold, about 1.5 to about 10 fold, about 2 to about 10 fold, about 3 to about 10 fold, about 4 to about 10 fold, about 1.1 to about 5 fold, about 1.1 to about 6 fold, about 1.1 to about 7 fold, about 1.1 to about 8 fold, about 1.1 to about 9 fold, about 2 to about 5 fold, about 2 to about 6 fold, about 2 to about 7 fold, about 2 to about 8 fold, about 2 to about 9 fold, about 3 to about 6 fold, about 3 to about 7 fold, about 3 to about 8 fold, about 3 to about 9 fold, about 4 to about 7 fold, about 4 to about 8 fold, about 4 to about 9 fold, at least about 1.1 fold, at least about 1.5 fold, at least about 2 fold, at least about 2.5 fold, at least about 3 fold, at least about 3.5 fold, at least about 4 fold, at least about 5 fold, or at least about 10 fold, compared to in the absence of the agent.~~
- ~~128. The method of any one of claims 89 to 127, wherein the method results in an increase in expression of the target protein in the cell.~~
- ~~129. The method of claim 128, wherein a level of the target protein expressed from the processed mRNA in the cell contacted with the agent is increased by about 1.1 to about 10 fold, about 1.5 to about 10 fold, about 2 to about 10 fold, about 3 to about 10 fold, about 4 to about 10 fold, about 1.1 to about 5 fold, about 1.1 to about 6 fold, about 1.1 to about 7 fold, about 1.1 to about 8 fold, about 1.1 to about 9 fold, about 2 to about 5 fold, about 2 to about 6 fold, about 2 to about 7 fold, about 2 to about 8 fold, about 2 to about 9 fold, about 3 to about 6 fold, about 3 to about 7 fold, about 3 to about 8 fold, about 3 to about 9 fold, about 4 to about 7 fold, about 4 to about 8 fold, about 4 to about 9 fold, at least about 1.1 fold, at least about 1.5 fold, at least about 2 fold, at least about 2.5 fold, at least about 3 fold, at least about 3.5 fold, at least about 4 fold, at least about 5 fold, or at least about 10 fold, compared to in the absence of the agent.~~
- ~~130. The method of any one of claims 89 to 128, wherein the target protein is an OPA1 protein.~~
- ~~131. The method of claim 130, wherein a level of the OPA1 protein expressed from the processed mRNA in the cell contacted with the agent is increased by at least about 1.5 fold compared to in the absence of the agent.~~
- ~~132. The method of claim 130, wherein the OPA1 protein expressed from the processed mRNA is a functional OPA1 protein.~~
- ~~133. The method of claim 130, wherein the OPA1 protein expressed from the processed mRNA is at least partially functional as compared to a wild-type OPA1 protein.~~
- ~~134. The method of claim 130, wherein the OPA1 protein expressed from the processed mRNA is at least partially functional as compared to a full-length wild-type OPA1 protein.~~
- ~~135. The method of any one of claims 89 to 127, wherein the agent comprises an antisense oligomer with at least 80%, at least 90%, or 100% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 236, 242, 250, 280-283, 288, and 290-292.~~

~~136. The method of any one of claims 78 to 135, wherein the agent comprises a gene editing molecule.~~

~~137. The method of claim 136, wherein the gene editing molecule comprises CRISPR-Cas9.~~

~~2. 138. —The method of any one of claims 1 to 75 or 78 to 135, wherein the agent is an antisense oligomer (ASO)~~The pharmaceutical composition of claim 1, wherein the pharmaceutical composition comprises the therapeutic agent, and wherein the antisense oligomer comprises a backbone modification comprising a, a sugar moiety modification, or a combination thereof.

3. The pharmaceutical composition of claim 2, wherein the antisense oligomer comprises a phosphorothioate linkage or a phosphorodiamidate linkage.

~~4. 139. —The method of any one of claims 1 to 75 or 78 to 138, wherein the agent is an antisense oligomer (ASO) and~~The pharmaceutical composition of claim 3, wherein the antisense oligomer comprises a phosphorodiamidate morpholino, a locked nucleic acid, a peptide nucleic acid, a 2'-O-methyl moiety, a 2'-Fluoro moiety, or a 2'-O-methoxyethyl moiety; preferably, wherein the antisense oligomer comprises a 2'-O-methoxyethyl moiety; more preferably, wherein each nucleotide of the antisense oligomer comprises a 2'-O-methoxyethyl moiety.

~~140. The method~~pharmaceutical composition of any one of claims 1 ~~to 75 or 78 to 139-4,~~ wherein the ~~therapeutic agent is an antisense oligomer (ASO) and wherein the antisense oligomer comprises at least one modified sugar moiety.~~

~~141. The method of claim 140, wherein each sugar moiety is a modified sugar moiety.~~

~~5. 142. —The method of any one of claims 1 to 75 or 78 to 141, wherein the agent is an antisense oligomer (ASO) and wherein the antisense oligomer consists of from 8 to 50 nucleobases, 8 to 40 nucleobases, 8 to 35 nucleobases, 8 to 30 nucleobases, 8 to 25 nucleobases, 8 to 20 nucleobases, 8 to 15 nucleobases, 9 to 50 nucleobases, 9 to 40 nucleobases, 9 to 35 nucleobases, 9 to 30 nucleobases, 9 to 25 nucleobases, 9 to 20 nucleobases, 9 to 15 nucleobases, 10 to 50 nucleobases, 10 to 40 nucleobases, 10 to 35 nucleobases, 10 to 30 nucleobases, 10 to 25 nucleobases, 10 to 20 nucleobases, 10 to 15 nucleobases, 11 to 50 nucleobases, 11 to 40 nucleobases, 11 to 35 nucleobases, 11 to 30 nucleobases, 11 to 25 nucleobases, 11 to 20 nucleobases, 11 to 15 nucleobases, nucleotides, preferably from 12 to 50 nucleobases, 12 to 40 nucleobases, 12 to 35 nucleobases, 12 to 30 nucleobases, 12 to 25 nucleobases, 12 to 20 nucleobases, or 12 to 15 nucleobases~~20 nucleotides, more preferably 18 nucleotides.

~~6. 143. —The method~~pharmaceutical composition of any one of claims 1 ~~to 142-5,~~ wherein the composition comprises the vector, and wherein the vector comprises a viral vector encoding the therapeutic agent.

~~7. 144. —The method~~pharmaceutical composition of claim ~~143~~6, wherein the viral vector comprises an adenoviral vector, adeno-associated viral (AAV) vector, lentiviral vector, Herpes Simplex Virus (HSV) viral vector, or retroviral vector.

- ~~145. The method of any one of claims 1 to 144, wherein the method further comprises assessing mRNA level or expression level of the OPA1 protein.~~
- ~~146. The method of any one of claims 1 to 145, wherein the agent is a therapeutic agent.~~
- ~~147. A pharmaceutical composition comprising the therapeutic agent of claim 146 or a vector encoding the therapeutic agent of claim 146, and a pharmaceutically acceptable excipient.~~
- ~~148. A pharmaceutical composition, comprising a therapeutic agent or a vector encoding a therapeutic agent, and a pharmaceutically acceptable excipient, wherein the therapeutic agent comprises an antisense oligomer with at least 80% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 6-275 and 280-299.~~
- ~~149. The pharmaceutical composition of claim 148, wherein the therapeutic agent comprises an antisense oligomer with at least 80%, at least 90%, or 100% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 227-242 and 250.~~
- ~~150. The pharmaceutical composition of claim 148, wherein the therapeutic agent comprises an antisense oligomer with at least 80%, at least 90%, or 100% sequence identity to SEQ ID NO: 267.~~
- ~~151. The pharmaceutical composition of claim 148, wherein the therapeutic agent comprises an antisense oligomer with at least 80%, at least 90%, or 100% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 36, 236, 242, 250, and 280-299.~~
- ~~152. A composition, comprising an antisense oligomer with at least 80% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 6-275 and 280-299, wherein the antisense oligomer comprises a backbone modification, a sugar moiety modification, or a combination thereof.~~
- ~~153. The composition of claim 152, wherein the antisense oligomer has at least 80%, at least 90%, or 100% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 227-242 and 250.~~
- ~~154. The composition of claim 152, wherein the antisense oligomer has at least 80%, at least 90%, or 100% sequence identity to SEQ ID NO: 267.~~
- ~~155. The composition of claim 152, wherein the antisense oligomer has at least 80%, at least 90%, or 100% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 36, 236, 242, 250, and 280-299.~~
- ~~156. A pharmaceutical composition, comprising a therapeutic agent or a vector encoding the therapeutic agent, and a pharmaceutically acceptable excipient~~ [The pharmaceutical composition of any one of claims 1-7](#), wherein the therapeutic agent promotes exclusion of a [non-sense mediated RNA decay-inducing exon \(NMD exon\) and/or a coding exon](#) from a pre-mRNA, thereby increasing a level of a processed mRNA that is processed from the pre-mRNA

~~and that lacks the coding exon in a cell, and~~ wherein the pre-mRNA is transcribed from an *OPA1* gene and that comprises the ~~coding exon~~.

~~157. A pharmaceutical composition, comprising a therapeutic agent or a vector encoding the therapeutic agent, and a pharmaceutically acceptable excipient, wherein the therapeutic agent comprises an antisense oligomer that binds to a pre-mRNA that is transcribed from an OPA1 gene in a cell, wherein the antisense oligomer binds to:~~

~~(a) a targeted portion of the pre-mRNA within an intronic region immediately upstream of a 5' end of the coding exon of the pre-mRNA; or~~

~~(b) a targeted portion of the pre-mRNA within an intronic region immediately downstream of a 3' end of the coding exon of the pre-mRNA;~~

~~whereby the therapeutic agent increases a level of a processed mRNA that is processed from the pre-mRNA and that contains the coding exon in the cell.~~

~~8. 158.—A pharmaceutical composition, comprising a therapeutic agent or a vector encoding the therapeutic agent, and a pharmaceutically acceptable excipient, wherein the therapeutic agent promotes exclusion of both a coding exon and a non-sense mediated RNA decay inducing exon (NMD exon) from a pre-mRNA, thereby increasing a level of a processed mRNA that is processed from the pre-mRNA and that lacks the coding exon and the NMD exon in a cell, wherein the pre-mRNA is transcribed from an OPA1 gene in the cell and comprises the coding exon and the NMD and/or the coding exon.~~

9. 159.—The pharmaceutical composition of claim 1, wherein the antisense oligomer comprises:

(i) a sequence selected from the group consisting of SEQ ID NOs: 36, 227-242, 250, 267, and 280-299;

(ii) a sequence selected from the group consisting of SEQ ID NOs: 36, 227-230, 232-242, 280-283 and 288-295;

(iii) a sequence selected from the group consisting of SEQ ID NOs: 227-230, 232-242, 280-286, 288-299; or

(iv) a sequence selected from the group consisting of SEQ ID NOs: 227-230, 232-242, 280-283, and 288-295.

10. The pharmaceutical composition of claim 1, wherein the antisense oligomer comprises a sequence selected from the group consisting of 36, 236, 242, 250, or 267.

11. The pharmaceutical composition of any one of claims 1-10, further comprising a gene editing molecule or a polynucleotide encoding the gene editing molecule.

12. The pharmaceutical composition of claim 11, wherein the gene editing molecule comprises CRISPR-Cas9.

13. The pharmaceutical composition of any one of claims ~~147 to 158~~ 1-12, wherein the ~~pharmaceutical~~ composition is formulated for intracerebroventricular injection, intraperitoneal injection, intramuscular injection, intrathecal injection, subcutaneous injection, oral administration, synovial injection, intravitreal administration, subretinal injection, topical application, implantation, or intravenous injection; preferably, for intravitreal injection.

14. ~~160.~~—A composition comprising:

(a) an antisense oligomer that comprises a sequence selected from the group consisting of SEQ ID NOs: 6-275 and 280-299, wherein the antisense oligomer comprises a backbone modification, a sugar moiety modification, or a combination thereof; or

(b) a vector encoding the antisense oligomer.

15. The pharmaceutical composition of any one of claims ~~147 to 158, wherein 1-13 or the composition of claim 14 for use in treating or preventing a disease or condition.~~

Use of the pharmaceutical composition ~~is formulated for intravitreal injection.~~

~~161. The pharmaceutical composition of any one of claims 147 to 160, wherein the pharmaceutical composition further comprises a second therapeutic agent.~~

~~162. The pharmaceutical 1-13 or the composition of claim ~~161~~, wherein the second therapeutic agent comprises a small molecule.~~

~~163. The pharmaceutical composition of claim 161, wherein the second therapeutic agent comprises an antisense oligomer.~~

~~164. The pharmaceutical composition of claim 161, wherein the second therapeutic agent corrects intron retention.~~

~~165. The pharmaceutical composition or composition of any one 14 in the manufacture of claims 147 to 160, wherein the antisense oligomer is selected from the group consisting of Compound ID-NOs: 1-303.~~

~~166. A method of treating or reducing a medicament for the likelihood of developing a disease or condition in a subject in need thereof by modulating expression of an OPA1 protein in a cell of the subject, comprising contacting to cells of the subject the therapeutic agent of any one of claims 147 to 165.~~

16. ~~167.~~—The method of claim 166, wherein the treatment of a disease or condition, wherein the disease or condition

(i) is associated with a loss-of-function mutation in an OPA1 gene; or

~~168. —The method of claim 166 or 167, wherein the disease or condition~~(ii) is associated with haploinsufficiency of the OPA1 gene, and wherein the subject has a first allele encoding a functional OPA1 protein, and a second allele from which the OPA1 protein is not produced or produced at a reduced level, or a second allele encoding a nonfunctional OPA1 protein or a partially functional OPA1 protein.

~~169. The method of any one of claims 166 to 168, wherein the disease or condition comprises an eye disease or condition.~~

~~170. The method of any one of claims 166 to 168, wherein the disease or condition comprises ADOA-plus syndrome; a mitochondrial disorder; glaucoma; normal tension glaucoma; Charcot-Marie-Tooth disease; mitochondria dysfunction; diabetic retinopathy; age-related macular degeneration; retinal ganglion cell death; mitochondrial fission-mediated mitochondrial dysfunction; progressive external ophthalmoplegia; deafness; ataxia; motor neuropathy; sensory neuropathy; myopathy; Behr syndrome; brain dysfunction; encephalopathy; peripheral neuropathy; fatal infantile mitochondrial encephalomyopathy; hypertrophic cardiomyopathy; spastic ataxic syndrome; sensory motor peripheral neuropathy; hypotonia; gastrointestinal dysmotility and dysphagia; optic atrophy; optic atrophy plus syndrome; Mitochondrial DNA depletion syndrome-14; late-onset cardiomyopathy; diabetic cardiomyopathy; Alzheimer's Disease; focal segmental glomerulosclerosis; kidney disease; Huntington's Disease; cognitive function decline in healthy aging; Prion diseases; late-onset dementia and parkinsonism; mitochondrial myopathy; Leigh syndrome; Friedreich's ataxia; Parkinson's disease; MELAS (Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes); pyruvate dehydrogenase complex deficiency; chronic kidney disease; Leber's hereditary optic neuropathy; obesity; age-related systemic neurodegeneration; skeletal muscle atrophy; heart and brain ischemic damage; or massive liver apoptosis.~~

~~171. The method of any one of claims 166 to 168~~The use of claim 16, wherein the disease or condition comprises Optic atrophy type 1.

~~17. 172. —The method of any one of claims 166 to 168, wherein the disease or condition comprises~~ or autosomal dominant optic atrophy (ADOA).

~~18. 173. —The method~~Use of the pharmaceutical composition of any one of claims 1-13 or the composition of claim 166 or 167, 14 in the manufacture of a medicament for modulating expression of an OPA1 protein in a cell having a pre-mRNA that is transcribed from an OPA1 gene and that comprises a non-sense mediated RNA decay-inducing exon (NMD exon), wherein the ~~disease~~use ~~comprises~~

contacting the composition or condition is associated with an autosomal recessive mutation of the pharmaceutical composition to the cell, whereby the therapeutic agent modulates splicing of the NMD exon from the pre-mRNA, thereby modulating a level of processed mRNA that is processed from the pre-mRNA, and modulating the expression of the OPA1 protein in the cell.

19. Use of a therapeutic agent or a vector encoding the therapeutic agent in the manufacture of a medicament for modulating expression of an OPA1 protein in a cell having a pre-mRNA that is transcribed from an OPA1 gene, wherein the ~~subject has a first allele encoding from which~~ pre-mRNA comprises a coding exon, wherein the use comprises

contacting the therapeutic agent or the vector encoding the therapeutic agent to the cell, whereby the therapeutic agent promotes exclusion of the coding exon from the pre-mRNA, thereby increasing a level of a processed mRNA that is processed from the pre-mRNA and that lacks the coding exon in the cell.

20. The use of claim 19, wherein the coding exon comprises a sequence with at least 80%, at least 90%, or 100% sequence identity to SEQ ID NO: 277.

21. The use of claim 19 or 20, wherein the therapeutic agent:

(a) binds to a targeted portion of the pre-mRNA;

(b) modulates binding of a factor involved in splicing of the coding exon; or

(c) a combination of (a) and (b).

~~(i) OPA1 protein is not produced or produced at a reduced level compared to a wild-type allele; or~~

~~(ii) the OPA1 protein produced is nonfunctional or partially functional compared to a wild-type allele, and~~

~~a second allele from which:~~

~~(iii) the OPA1 protein is produced at a reduced level compared to a wild-type allele and the OPA1 protein produced is at least partially functional compared to a wild-type allele; or~~

~~(iv) the OPA1 protein produced is partially functional compared to a wild-type allele.~~

~~174. The method of any one of claims 166 to 173, wherein the subject is a human.~~

22. ~~175. — The method~~ The use of claim 21, wherein the targeted portion of the pre-mRNA comprises an exon-intron junction of exon GRCh38/ hg38: chr3 193626092 to 193626202.

23. The use of claim 21 or 22, wherein the targeted portion of the pre-mRNA comprises a sequence with at least 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to a region comprising at least 8 contiguous nucleic acids of SEQ ID NO: 277.

The use of any one of claims ~~166 to 173, wherein the subject is a non-human animal.~~

~~176. The method of any one of claims 166 to 173, wherein the subject is a fetus, an embryo, or a child.~~

~~177. The method of any one of claims 166 to 173, wherein the cells are ex vivo.~~

~~178. The method of any one of claims 166 to 173, wherein the therapeutic agent is administered by intracerebroventricular injection, intraperitoneal injection, intramuscular injection, intrathecal injection, subcutaneous injection, oral administration, synovial injection, intravitreal administration, subretinal injection, topical application, implantation, or intravenous injection.~~

~~24. 179. —The method of any one of claims 166 to 173~~19-23, wherein the therapeutic agent ~~is administered by intravitreal injection.~~comprises an antisense oligomer.

~~180. The method of any one of claims 166 to 179, wherein the method treats the disease or condition.~~