disclosing novel compositions and methods useful for effective treatment, and potentially providing a cure, of the disease.

BRIEF SUMMARY

[0003] The application provides the first disclosure of genetic loci, including rs1921622 and/or other 574 sST2-associated genetic variants, and/or three-prime (3')-untranslated regions of sST2, upon being disrupted leading to diminished expression of soluble ST2 (sST2) protein, as a target for therapeutic intervention of Alzheimer's Disease through genetic manipulation. New compositions and methods for treating Alzheimer's Disease by way of suppression or elimination of the effects of genomic sequence encompassing rs1921622, other 574 sST2-associated genetic variants, or the three-prime (3')-untranslated regions of sST2 are therefore devised from this discovery.

[0003a] In one aspect, provided herein is a use of a composition comprising (1) one or more vectors encoding an endonuclease guided by a small guide RNA (sgRNA) and two sgRNAs targeting 3'-untranslated region (UTR) of sST2 gene; or (2) an antisense oligonucleotide targeting 3'-untranslated region (UTR) of sST2 gene/transcript in the manufacture of a medicament for treating Alzheimer's Disease (AD) or reducing risk of AD, wherein the medicament is to be administered to a person in need thereof.

[0003b] In another aspect, provided herein is a kit for treating Alzheimer's Disease (AD) or reducing risk of AD in a person in need thereof, comprising a container containing a composition comprising (1) one or more vectors encoding an endonuclease guided by a small guide RNA (sgRNA) and two sgRNAs targeting the 3'-UTR of the sST2 gene; or (2) an antisense oligonucleotide targeting the 3'-UTR of the sST2 gene transcript.**[0004]** As such, in a first example, this disclosure provides a method for treating Alzheimer's Disease in a person or reducing the person's risk for later developing Alzheimer's Disease. The claimed method comprises the step of administering to the person an effective amount of a composition disrupting a genomic sequence encompassing (i) rs1921622, and/or (ii) any one or more of other 574 sST2-associated genetic variants listed in Table 4 and Table 5, and/or (iii) 3'-untranslated region (UTR) of sST2 gene coding sequence or transcript.

[0005] In some examples, the claimed method comprises, prior to the administering step, sequencing at least a portion of the person's genome. In some examples, the person is deemed an APOE-ε4 carrier, either a heterozygote or

homozygote carrier. In other cases, the person is a non-APOE-ε4 carrier. In some cases, the person is a female. In some cases, the person is a male. In some examples, the person has an A allele at rs1921622. In some examples, the person has at least one allele at a specified genetic locus shown in Table 4. In some examples, the person has been diagnosed with AD. In some examples, the person is not yet diagnosed with AD but has known risk factors for AD such as family history of AD or carrying one or more genetic alleles known to increase AD risk, *e.g.*, as a female APOE-ε4 carrier. In some examples, the genomic sequence encompassing rs1921622 (or another genetic locus named in Table 4 or 5) comprises sequence about 300 basepairs upstream and downstream from rs1921622 (or another genetic locus in Table 4 or 5), preferably about 250, 200, 150, 100, 50, 30, or 20 basepairs upstream and downstream from rs1921622 (or another genetic locus in Table 4 or 5). In some examples, the composition comprising an siRNA, a microRNA, a miniRNA, a lncRNA,

or an antisense oligonucleotide targeting the genomic sequence encompassing rs1921622 (or another genetic locus in Table 4 or 5) or the 3'-UTR of the sST2 gene. In some examples, the composition comprises one or more vectors encoding an endonuclease guided by a small guide RNA (sgRNA) and two sgRNAs targeting two locations within the genomic sequence encompassing rs1921622 (or another genetic locus listed in Table 4 or 5) or the 3'-UTR of the sST2 gene. In some examples, the composition comprises one vector encoding a Cas9 nuclease and two sgRNAs. In some examples, the one or more vectors are one or more viral vectors. In some examples, the composition is administered by subcutaneous, intramuscular, intravenous, intraperitoneal, or intracranial injection or by oral or nasal administration. In some examples, the composition is administered in the form of a solution, a suspension, a powder, a paste, a tablet, or a capsule.

[0006] In a second example, the present disclosure provides a composition comprising an effective amount of one or more agents that disrupt a genomic sequence encompassing (i) rs1921622, and/or (ii) any one or more of other 574 sST2-associated genetic variants listed in Table 4 and Table 5, and/or (iii) 3'-untranslated region (UTR) of sST2 gene coding sequence or transcript, plus one or more physiologically acceptable excipient.

[0007] In some examples, the genomic sequence encompassing rs1921622 (or another genetic locus named in Table 4 or 5) comprises sequence about 300 bps upstream and downstream from rs1921622 (or another genetic locus in Table 4 or 5), preferably about 250, 200, 150, 100, 50, 30, or 20 bps upstream and downstream from rs1921622 (or another genetic locus in Table 4 or 5). In some examples, the composition comprising an siRNA, a microRNA, a miniRNA, a lncRNA, or an antisense oligonucleotide targeting the genomic sequence encompassing rs1921622 (or another genetic locus in Table 4 or 5) or the 3'-UTR of the sST2 gene. In some examples, the composition comprises one or more vectors encoding an endonuclease guided by a small guide RNA (sgRNA) and two sgRNAs targeting two locations within the genomic sequence encompassing rs1921622 (or another genetic locus listed in Table 4 or 5) or the 3'-UTR of the sST2 gene. In some examples, the composition comprises one vector encoding a Cas9 nuclease and two sgRNAs. In some examples, the one or more vectors are one or more viral vectors. In some examples, the composition is administered by subcutaneous, intramuscular, intravenous, intraperitoneal, or intracranial injection or by oral or nasal administration. In some examples, the composition is administered in the form of a solution, a suspension, a powder, a paste, a tablet, or a capsule.

[0008] In a third example, the present disclosure provides a kit for treating Alzheimer's Disease in a person or for reducing the person's risk of later developing Alzheimer's Disease. The kit comprises a first container containing a composition disrupting a genomic sequence encompassing rs1921622 (or another genetic locus in Table 4 or 5) or the 3'-UTR of the sST2 gene.

[0009] In some examples, the composition is formulated for subcutaneous, intramuscular, intravenous, intraperitoneal, or intracranial injection, or for oral or nasal administration. In some examples, the composition comprising an siRNA, a microRNA, a miniRNA, a lncRNA, or an antisense oligonucleotide targeting the genomic sequence encompassing rs1921622 (or another genetic locus in Table 4 or 5) or the 3'-UTR of the sST2 gene. In some examples, the composition comprises (1) one or more vectors encoding an endonuclease guided by a small guide RNA (sgRNA) and (2) two sgRNAs targeting two locations within the genomic sequence encompassing rs1921622 (or another genetic locus in Table 4 or 5) or the 3'-UTR of the sST2 gene. In some examples, the kit contains a composition comprising one vector encoding a Cas9 nuclease and two sgRNAs. In some examples, the kit further contains a second container containing agents for sequencing at least a portion of the person's genome (*e.g.*, the APOE-ε4 gene). Optionally, the kit also includes an instruction manual for administration of the composition.

[0010] Related to this example of the present disclosure, a use of one or more agents disrupting a genomic sequence encompassing rs1921622, and/or other 574 sST2-associated genetic variants, and/or 3'-untranslated regions of sST2 is further provided in accordance with the disclosure herein for the manufacturing of (1) a medicament for treating Alzheimer's Disease; and/or (2) a kit containing the medicament for treating Alzheimer's Disease.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] Figure 1. Diagrams illustrating IL-33/ST2 signaling. (a) Schematic showing the soluble ST2 (sST2) and full-length ST2 (ST2L) transcripts. (b) The IL-33/ST2 signaling pathways. IL-33, interleukin 33.

[0012] Figure 2. Circulating sST2 levels are associated with Alzheimer's disease and its pathologic changes. (a) Individual plasma soluble ST2 (sST2) levels stratified according to disease phenotype (n = 336 healthy controls [HCs], n = 277 patients with AD from the Chinese_cohort_1; linear regression test, T = 3.241, $^{**}P < 0.01$). Data are presented as box-and-whisker plots including maximum, 75th percentile, median, 25th percentile, and minimum

WHAT IS CLAIMED IS:

1. Use of a composition comprising (1) one or more vectors encoding an endonuclease guided by a small guide RNA (sgRNA) and two sgRNAs targeting 3'-untranslated region (UTR) of sST2 gene; or (2) an antisense oligonucleotide targeting 3'-untranslated region (UTR) of sST2 gene/transcript in the manufacture of a medicament for treating Alzheimer's Disease (AD) or reducing risk of AD, wherein the medicament is to be administered to a person in need thereof.

2. The use of claim 1, wherein at least a portion of the person's genome is prior sequenced.

3. The use of claim 1, wherein the person is an *APOE-ε4* carrier or a non-*APOE-ε4* carrier.

4. The use of claim 1, wherein the person is a female or a male.

5. The use of claim 1, wherein the person has been diagnosed with AD, or the person is not yet diagnosed with AD but has known risk factors for AD.

6. The use of claim 1, wherein the composition comprising an antisense oligonucleotide selected from hsST2-1 to hsST2-144 in Table 9.

7. The use of claim 1, wherein the composition comprising one or more vectors encoding an endonuclease guided by a small guide RNA (sgRNA) and two sgRNAs targeting the 3'-UTR of the sST2 gene.

8. The use of claim 7, wherein the composition comprises one vector encoding a Cas9 nuclease and two sgRNAs.

9. The use of claim 7 or 8, wherein the one or more vectors are one or more viral vectors.

10. The use of claim 1, wherein the composition is formulated for subcutaneous, intramuscular, intravenous, intraperitoneal, or intracranial injection or for oral or nasal administration.

11. The use of claim 10, wherein the composition is formulated in the form of a solution, a suspension, a powder, a paste, a tablet, or a capsule.

12. A kit for treating Alzheimer's Disease (AD) or reducing risk of AD in a person in need thereof, comprising a container containing a composition comprising (1) one or more vectors encoding an endonuclease guided by a small guide RNA (sgRNA) and two sgRNAs targeting the 3'-UTR of the sST2 gene; or (2) an antisense oligonucleotide targeting the 3'-UTR of the sST2 gene transcript.

13. The kit of claim 12, wherein the composition is formulated for subcutaneous, intramuscular, intravenous, intraperitoneal, or intracranial injection, or for oral or nasal administration.

14. The kit of claim 12, wherein the composition comprising an antisense oligonucleotide selected from hsST2-1 to hsST2-144 in Table 9.

15. The kit of claim 12, wherein the composition comprising one or more vectors encoding an endonuclease guided by a small guide RNA (sgRNA) and two sgRNAs targeting the 3'-UTR of the sST2 gene.

16. The kit of claim 15, wherein the composition comprises one vector encoding a Cas9 nuclease and two sgRNAs.

17. The kit of claim 12, further comprising a second container containing agents for sequencing at least a portion of the person's genome.

18. The kit of claim 12, further comprising an instruction manual for administration of the composition.