We claim:

1. A method of screening for genetic modifiers of tau aggregation, comprising:

(a) providing a population of cells comprising a Cas protein, a first tau repeat domain linked to a first reporter, and a second tau repeat domain linked to a second reporter,

wherein the cells are mammalian cells,

wherein the first reporter and the second reporter are fluorescent proteins, and wherein the first reporter and the second reporter are a fluorescence resonance energy transfer (FRET) pair;

(b) introducing into the population of cells a library comprising a plurality of unique guide RNAs that target a plurality of genes;

(c) culturing the population of cells to allow genome editing and expansion, wherein the plurality of unique guide RNAs form complexes with the Cas protein, and the Cas protein cleaves the plurality of genes resulting in knockout of gene function to produce a genetically modified population of cells;

(d) contacting the genetically modified population of cells with a tau seeding agent to produce a seeded population of cells,

wherein step (d) comprises culturing the genetically modified population of cells in the presence of conditioned medium harvested from cultured tau-aggregation-positive cells in which a tau repeat domain stably presents in an aggregated state, wherein the conditioned medium was harvested after being on confluent tau-aggregation-positive cells for 1 to 7 days;

(e) culturing the seeded population of cells to allow tau aggregates to form, wherein aggregates of the first tau repeat domain and the second tau repeat domain form in a subset of the seeded population of cells to produce an aggregation-positive population of cells; and

(f) determining abundance of each of the plurality of unique guide RNAs in the aggregation-positive population of cells identified in step (e) relative to the genetically modified population of cells in step (c),

wherein enrichment of a guide RNA in the aggregation-positive population of cells identified in step (e) relative to the cultured population of cells in step (c) indicates that the

gene targeted by the guide RNA is a genetic modifier of tau aggregation, wherein disruption of the gene targeted by the guide RNA enhances tau aggregation.

2. The method of claim 1, wherein the Cas protein is a Cas9 protein, optionally wherein the Cas protein is a *Streptococcus pyogenes* Cas9 protein, optionally wherein the Cas protein comprises SEQ ID NO: 21, and optionally wherein the Cas protein is encoded by a coding sequence comprising the sequence set forth in SEQ ID NO: 22.

3. The method of any preceding claim, wherein the Cas protein, the first tau repeat domain linked to the first reporter, and the second tau repeat domain linked to the second reporter are stably expressed in the population of cells, or

wherein nucleic acids encoding the Cas protein, the first tau repeat domain linked to the first reporter, and the second tau repeat domain linked to the second reporter are genomically integrated in the population of cells.

4. The method of any preceding claim, wherein each guide RNA targets a constitutive exon, optionally wherein each guide RNA targets a 5' constitutive exon, or

wherein each guide RNA targets a first exon, a second exon, or a third exon.

5. A method of screening for genetic modifiers of tau aggregation, comprising:

(a) providing a population of cells comprising a chimeric Cas protein comprising a nuclease-inactive Cas protein fused to one or more transcriptional activation domains, a chimeric adaptor protein comprising an adaptor protein fused to one or more transcriptional activation domains, a first tau repeat domain linked to a first reporter, and a second tau repeat domain linked to a second reporter,

wherein the cells are mammalian cells,

wherein the first reporter and the second reporter are fluorescent proteins, and wherein the first reporter and the second reporter are a fluorescence resonance energy transfer (FRET) pair;

(b) introducing into the population of cells a library comprising a plurality of unique guide RNAs that target a plurality of genes;

(c) culturing the population of cells to allow transcriptional activation and expansion, wherein the plurality of unique guide RNAs form complexes with the chimeric Cas protein and the chimeric adaptor protein, and the complexes activate transcription of the plurality of genes resulting in increased gene expression to produce a genetically modified population of cells;

(d) contacting the genetically modified population of cells with a tau seeding agent to produce a seeded population of cells,

wherein step (d) comprises culturing the genetically modified population of cells in the presence of conditioned medium harvested from cultured tau-aggregation-positive cells in which a tau repeat domain stably presents in an aggregated state, wherein the conditioned medium was harvested after being on confluent tau-aggregation-positive cells for 1 to 7 days;

(e) culturing the seeded population of cells to allow tau aggregates to form, wherein aggregates of the first tau repeat domain and the second tau repeat domain form in a subset of the seeded population of cells to produce an aggregation-positive population of cells; and

(f) determining abundance of each of the plurality of unique guide RNAs in the aggregation-positive population of cells identified in step (e) relative to the genetically modified population of cells in step (c),

wherein enrichment of a guide RNA in the aggregation-positive population of cells identified in step (e) relative to the cultured population of cells in step (c) indicates that the gene targeted by the guide RNA is a genetic modifier of tau aggregation, wherein transcriptional activation of the gene targeted by the guide RNA enhances tau aggregation.

6. The method of claim 5, wherein the Cas protein is a Cas9 protein, optionally wherein the Cas protein is a *Streptococcus pyogenes* Cas9 protein, and

wherein the chimeric Cas protein comprises the nuclease-inactive Cas protein fused to a VP64 transcriptional activation domain, optionally wherein the chimeric Cas protein comprises from N-terminus to C-terminus: the nuclease-inactive Cas protein; a nuclear localization signal; and the VP64 transcriptional activator domain, optionally wherein the chimeric Cas protein comprises SEQ ID NO: 36, and optionally wherein the chimeric Cas protein is encoded by a coding sequence comprising the sequence set forth in SEQ ID NO: 38, and

wherein the adaptor protein is an MS2 coat protein, and wherein the one or more transcriptional activation domains in the chimeric adaptor protein comprise a p65 transcriptional activation domain and an HSF1 transcriptional activation domain, optionally wherein the chimeric adaptor protein comprises from N-terminus to C-terminus: the MS2 coat protein; a nuclear localization signal; the p65 transcriptional activation domain; and the HSF1 transcriptional activation domain, optionally wherein the chimeric adaptor protein comprises SEQ ID NO: 37, and optionally wherein the chimeric adaptor protein is encoded by a coding sequence comprising the sequence set forth in SEQ ID NO: 39.

7. The method of claim 5 or 6, wherein the chimeric Cas protein, the chimeric adaptor protein, the first tau repeat domain linked to the first reporter, and the second tau repeat domain linked to the second reporter are stably expressed in the population of cells, or

wherein nucleic acids encoding the chimeric Cas protein, the chimeric adaptor protein, the first tau repeat domain linked to the first reporter, and the second tau repeat domain linked to the second reporter are genomically integrated in the population of cells.

8. The method of any one of claims 5-7, wherein each guide RNA targets a guide RNA target sequence within 200 bp upstream of a transcription start site, and

wherein each guide RNA comprises one or more adaptor-binding elements to which the chimeric adaptor protein can specifically bind, optionally wherein each guide RNA comprises two adaptor-binding elements to which the chimeric adaptor protein can specifically bind, optionally wherein a first adaptor-binding element is within a first loop of each of the one or more guide RNAs, and a second adaptor-binding element is within a second loop of each of the one or more guide RNAs, optionally wherein the adaptor-binding element comprises the sequence set forth in SEQ ID NO: 33, and

optionally wherein each of one or more guide RNAs is a single guide RNA comprising a CRISPR RNA (crRNA) portion fused to a transactivating CRISPR RNA (tracrRNA) portion, and the first loop is the tetraloop corresponding to residues 13-16 of SEQ ID NO: 17, and the second loop is the stem loop 2 corresponding to residues 53-56 of SEQ ID NO: 17.

9. The method of any preceding claim, wherein step (c) is 3 days to 9 days, optionally wherein step (c) is 6 days.

10. The method of any preceding claim, wherein the conditioned medium was harvested after being on confluent tau-aggregation-positive cells for 4 days.

11. The method of any preceding claim, wherein step (d) comprises culturing the genetically modified population of cells in 75% conditioned medium and 25% fresh medium.

12. The method of any preceding claim, wherein the genetically modified population of cells is not co-cultured with the tau-aggregation-positive cells.

13. The method of any preceding claim, wherein step (e) is 2 days to 6 days, optionally wherein step (e) is 4 days.

14. The method of any preceding claim, wherein abundance is determined by next-generation sequencing.

15. The method of any preceding claim, wherein a guide RNA is considered enriched if the abundance of the guide RNA relative to the total population of the plurality of unique guide RNAs is at least 1.5-fold higher in the aggregation-positive population of cells in step (e) relative to the cultured population of cells in step (c).

16. The method of any preceding claim, wherein step (f) comprises determining abundance of each of the plurality of unique guide RNAs in the aggregation-positive population of cells in step (e) relative to the cultured population of cells in step (c) at a first time point in step (c) and/or a second time point in step (c),

optionally wherein the first time point in step (c) is at a first passage of culturing the population of cells, and the second time point is in the middle of culturing the population of cells to allow genome editing and expansion or transcriptional activation and expansion, and

optionally wherein the first time point in step (c) is after three days of culturing, and the second time point in step (c) is after six days of culturing.

17. The method of claim 16, wherein a gene is considered a genetic modifier of tau aggregation, wherein disruption or transcriptional activation of the gene enhances tau aggregation, if:

(1) the abundance of a guide RNA targeting the gene relative to the total population of the plurality of unique guide RNAs is at least 1.5-fold higher in the aggregation-positive population of cells in step (e) relative to the cultured population of cells in step (c) at both the first time point in step (c) and the second time point in step (c); and/or

(2) the abundance of at least two unique guide RNAs targeting the gene relative to the total population of the plurality of unique guide RNAs is at least 1.5-fold higher in the aggregation-positive population of cells in step (e) relative to the cultured population of cells in step (c) at either the first time point in step (c) or the second time point in step (c).

18. The method of any preceding claim, wherein the following steps are taken in step (f) to identify a gene as a genetic modifier of tau aggregation, wherein disruption or transcriptional activation of the gene enhances tau aggregation:

(1) identifying which of the plurality of unique guide RNAs are present in the aggregation-positive population of cells produced in step (e);

(2) calculating the random chance of the guide RNAs identified in step (f)(1) being present using the formula nCn' * (x-n')C(m-n) / xCm,

wherein x is the variety of unique guide RNAs introduced into the population of cells in step (b),

wherein m is the variety of unique guide RNAs identified in step (f)(1),

wherein n is the variety of unique guide RNAs introduced into the population of cells in step (b) that target the gene, and

wherein n' is the variety of unique guide RNAs identified in step (f)(1) that target the gene;

(3) calculating average enrichment scores for the guide RNAs identified in step (f)(1),

wherein the enrichment score for a guide RNA is the relative abundance of the guide RNA in the aggregation-positive population of cells produced in step (e) divided by the relative abundance of the guide RNA in the cultured population of cells in step (c), and

wherein relative abundance is the read count of the guide RNA divided by the read count of the total population of the plurality of unique guide RNAs; and

(4) selecting the gene if a guide RNA targeting the gene is significantly below the random chance of being present and above a threshold enrichment score.

19. The method of any preceding claim, wherein the first tau repeat domain and/or the second tau repeat domain is a human tau repeat domain, and/or

wherein the first tau repeat domain and/or the second tau repeat domain comprises a pro-aggregation mutation, optionally wherein the first tau repeat domain and/or the second tau repeat domain comprises a tau P301S mutation; and/or

wherein the first tau repeat domain and/or the second tau repeat domain comprises a tau four-repeat domain; and/or

wherein the first tau repeat domain and/or the second tau repeat domain comprises SEQ ID NO: 11; and/or

wherein the first tau repeat domain and the second tau repeat domain are the same.

20. The method of any preceding claim, wherein the first tau repeat domain and the second tau repeat domain are the same and each comprises tau four-repeat domain comprising a tau P301S mutation.

21. The method of any preceding claim, wherein the first reporter is cyan fluorescent protein (CFP) and the second reporter is yellow fluorescent protein (YFP).

22. The method of any preceding claim, wherein the cells are human cells, optionally wherein the cells are HEK293T cells.

23. The method of any preceding claim, wherein the plurality of unique guide RNAs are introduced at a concentration selected such that a majority of the cells receive only one of the unique guide RNAs.

24. The method of any preceding claim, wherein the plurality of unique guide RNAs target 100 or more genes, 1000 or more genes, or 10000 or more genes, or

wherein the library is a genome-wide library.

25. The method of any preceding claim, wherein a plurality of target sequences are targeted on average in each of the targeted plurality of genes,

optionally wherein at least three target sequences are targeted on average in each of the targeted plurality of genes,

optionally wherein three to six target sequences are targeted on average in each of the targeted plurality of genes.

26. The method of any preceding claim, wherein the plurality of unique guide RNAs are introduced into the population of cells by viral transduction,

optionally wherein each of the plurality of unique guide RNAs is in a separate viral vector,

optionally wherein the plurality of unique guide RNAs are introduced into the population of cells by lentiviral transduction, and

optionally wherein the population of cells is infected at a multiplicity of infection of less than 0.3.

27. The method of any preceding claim, wherein the plurality of unique guide RNAs are introduced into the population of cells together with a selection marker, and step (b) further comprises selecting cells that comprise the selection marker,

optionally wherein the selection marker imparts resistance to a drug, optionally wherein the selection marker imparts resistance to puromycin or zeocin, and

optionally wherein the selection marker is selected from neomycin phosphotransferase, hygromycin B phosphotransferase, puromycin-N-acetyltransferase, and blasticidin S deaminase.

28. The method of any preceding claim, wherein the population of cells into which the plurality of unique guide RNAs are introduced in step (b) comprises greater than 300 cells per unique guide RNA.