We claim:

1. A method of screening for genetic vulnerabilities associated with tau aggregation, comprising:

(a) providing an aggregation-positive population of cells and an aggregation-negative population of cells, wherein each population of cells comprises 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,

wherein the aggregation-positive population of cells comprises aggregates of the first tau repeat domain linked to the first reporter and the second tau repeat domain linked to the second reporter, and

wherein the aggregation-negative population of cells does not comprise aggregates of the first tau repeat domain linked to the first reporter and the second tau repeat domain linked to the second reporter;

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

(c) determining abundance of each of the plurality of unique guide RNAs at a plurality of time points over a time course in each population of cells,

wherein the plurality of time points comprises at least three time points, wherein there is more than 1 day between each time point,

wherein depletion of a guide RNA in the aggregation-positive population of cells but not in the aggregation-negative population of cells or a faster rate of depletion of a guide RNA over the time course in the aggregation-positive population of cells relative to the aggregation-negative population of cells indicates that the gene targeted by the guide RNA

exhibits synthetic lethality with tau protein aggregates and is a genetic vulnerability associated with 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 populations 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 populations 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 vulnerabilities associated with tau aggregation, comprising:

(a) providing an aggregation-positive population of cells and an aggregation-negative population of cells, wherein each population of cells comprises 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,

wherein the aggregation-positive population of cells comprises aggregates of the first tau repeat domain linked to the first reporter and the second tau repeat domain linked to the second reporter, and

wherein the aggregation-negative population of cells does not comprise aggregates of the first tau repeat domain linked to the first reporter and the second tau repeat domain linked to the second reporter;

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

(c) determining abundance of each of the plurality of unique guide RNAs at a plurality of time points over a time course in each population of cells,

wherein the plurality of time points comprises at least three time points, wherein there is more than 1 day between each time point,

wherein depletion of a guide RNA in the aggregation-positive population of cells but not in the aggregation-negative population of cells or a faster rate of depletion of a guide RNA over the time course in the aggregation-positive population of cells relative to the aggregation-negative population of cells indicates that activation of the gene targeted by the guide RNA exhibits synthetic lethality with tau protein aggregates and is a genetic vulnerability associated with 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 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.

10. 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.

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

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

13. 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.

14. 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.

15. 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, and

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

16. The method of any preceding claim, wherein the plurality of unique guide RNAs are introduced into the populations 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 populations of cells by lentiviral transduction, and

optionally wherein the populations of cells are infected at a multiplicity of infection of less than 0.3.

17. The method of any preceding claim, wherein the plurality of unique guide RNAs are introduced into the populations 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.

18. The method of any preceding claim, wherein the populations of cells into which the plurality of unique guide RNAs are introduced in step (b) each comprise greater than 500 cells per unique guide RNA.

19. The method of any preceding claim, wherein the time course in step (c) is more than 1 week, optionally wherein the time course in step (c) is more than 2 weeks.

20. The method of any preceding claim, wherein the time course in step (c) comprises 10 to 15 cell doublings.

21. The method of any preceding claim, wherein the plurality of time points in step (c) comprises four time points or six time points.

22. The method of any preceding claim, wherein there is more than 2 days between each time point in step (c), and

optionally wherein there is between 3 to 4 days between each time point in step (c).

23. The method of any preceding claim, wherein a gene is considered to exhibit synthetic lethality with tau protein aggregates in step (c) if a guide RNA targeting the gene is depleted in the aggregation-positive population of cells but not in the aggregation-negative population of cells,

optionally wherein a gene is considered to exhibit synthetic lethality with tau protein aggregates in step (c) if a guide RNA targeting the gene has a faster rate of depletion over the time course in the aggregation-positive population of cells relative to the aggregation-negative population of cells.

24. The method of any preceding claim, wherein a guide RNA is considered depleted in step (c) if the abundance of the guide RNA at each time point is less than or equal to the abundance of the guide RNA at the preceding time point, or

wherein a guide RNA is considered depleted in step (c) if the abundance of the guide RNA at each time point after the second time point is less than or equal to the abundance of the time point two time points prior.

25. The method of any preceding claim, wherein a gene is considered to exhibit synthetic lethality with tau protein aggregates in step (c) if more than 30% of the guide RNAs in the library that target the gene are depleted in the aggregation-positive population of cells but not in the aggregation-negative population of cells,

optionally wherein a gene is considered to exhibit synthetic lethality with tau protein aggregates in step (c) in any one of the following situations:

(1) there is one guide RNA in the library that targets the gene, and the one guide RNA is depleted in the aggregation-positive population of cells but not in the aggregation-negative population of cells;

(2) there are two guide RNAs in the library that target the gene, and at least one of the two guide RNAs is depleted in the aggregation-positive population of cells but not in the aggregation-negative population of cells;

(3) there are three guide RNAs in the library that target the gene, and at least one of the three guide RNAs is depleted in the aggregation-positive population of cells but not in the aggregation-negative population of cells;

(4) there are four guide RNAs in the library that target the gene, and at least two of the four guide RNAs is depleted in the aggregation-positive population of cells but not in the aggregation-negative population of cells;

(5) there are five guide RNAs in the library that target the gene, and at least two of the five guide RNAs is depleted in the aggregation-positive population of cells but not in the aggregation-negative population of cells; and

(6) there are six guide RNAs in the library that target the gene, and at least three of the six guide RNAs is depleted in the aggregation-positive population of cells but not in the aggregation-negative population of cells.

26. The method of any preceding claim, wherein the method is repeated at least three times in at least three different experiments, and a gene is considered to exhibit synthetic lethality with tau protein aggregates if it is considered to exhibit synthetic lethality with tau protein aggregates in more than 50% of the at least three different experiments.

27. The method of any preceding claim, wherein the time course in step (c) is more than 2 weeks,

wherein the plurality of time points in step (c) comprises six time points,

wherein there is between 3 to 4 days between each time point in step (c),

wherein a guide RNA is considered depleted in step (c) if the abundance of the guide RNA at each time point after the second time point is less than or equal to the abundance of the time point two time points prior, and

wherein a gene is considered to exhibit synthetic lethality with tau protein aggregates in step (c) if more than 30% of the guide RNAs in the library that target the gene are depleted in the aggregation-positive population of cells but not in the aggregation-negative population of cells.