

We claim:

1. A rodent whose genome comprises a mutation in the penultimate exon of a *fibrillin-1* (*Fbn1*) gene,
wherein the rodent is heterozygous for the mutation,
wherein the mutation results in disruption or ablation of the asprosin C-terminal cleavage product of pro-fibrillin-1,
wherein expression of the mutant *Fbn1* gene results in a C-terminally truncated Fbn1 protein, and
wherein the rodent exhibits decreased body weight, decreased lean mass, and decreased fat mass when compared to a wild-type rodent.
2. The rodent of claim 1, wherein the mutant *Fbn1* gene is operably linked to an endogenous *Fbn1* promoter.
3. The rodent of claim 1 or 2, wherein the mutation is a frameshift mutation.
4. The rodent of any one of claims 1-3, wherein the mutation results in a premature termination codon, wherein the premature termination codon is in the penultimate or the final exon of the *Fbn1* gene.
5. The rodent of claim 4, wherein the premature termination codon is in the final exon or is less than 55 base pairs upstream of the last exon-exon junction in the *Fbn1* gene.
6. The rodent of any one of claims 1-5, wherein the mutation disrupts a basic amino acid recognition sequence for proprotein convertases of the furin family, and wherein the mutation is within 50 base pairs of the furin recognition sequence.
7. The rodent of any one of claims 1-6, wherein the C-terminally truncated Fbn1 protein has a positively charged C-terminus.
8. The rodent of any one of claims 1-7, wherein the C-terminally truncated Fbn1 protein is truncated at a position corresponding to a position between amino acids 2700 and

2790, between amino acids 2710 and 2780, between amino acids 2720 and 2770, between amino acids 2730 and 2760, or between amino acids 2737 and 2755 in the wild type mouse Fbn1 protein set forth in SEQ ID NO: 30 when the C-terminally truncated Fbn1 protein is aligned with SEQ ID NO: 30.

9. The rodent of claim 8, wherein:

(I) the C-terminally truncated Fbn1 protein is truncated such that the last amino acid is at a position corresponding to amino acid 2737, amino acid 2738, or amino acid 2755 in the wild type mouse Fbn1 protein set forth in SEQ ID NO: 30 when the C-terminally truncated Fbn1 protein is aligned with SEQ ID NO: 30;

(II) the C-terminally truncated Fbn1 protein is truncated such that the last amino acid is at a position corresponding to amino acid 2737 in the wild type mouse Fbn1 protein set forth in SEQ ID NO: 30 when the C-terminally truncated Fbn1 protein is aligned with SEQ ID NO: 30, and wherein the C-terminus of the C-terminally truncated Fbn1 protein consists of the sequence set forth in SEQ ID NO: 43 or 46;

(III) the C-terminally truncated Fbn1 protein is truncated such that the last amino acid is at a position corresponding to amino acid 2738 in the wild type mouse Fbn1 protein set forth in SEQ ID NO: 30 when the C-terminally truncated Fbn1 protein is aligned with SEQ ID NO: 30, and wherein the C-terminus of the C-terminally truncated Fbn1 protein consists of the sequence set forth in SEQ ID NO: 8 or 45; or

(IV) the C-terminally truncated Fbn1 protein is truncated such that the last amino acid is at a position corresponding to amino acid 2755 in the wild type mouse Fbn1 protein set forth in SEQ ID NO: 30 when the C-terminally truncated Fbn1 protein is aligned with SEQ ID NO: 30, and wherein the C-terminus of the C-terminally truncated Fbn1 protein consists of the sequence set forth in SEQ ID NO: 42 or 47.

10. The rodent of any one of claims 1-9, wherein the C-terminally truncated Fbn1 protein has a C-terminus consisting of the sequence set forth in SEQ ID NO: 8, 42, 43, 45, 46, or 47.

11. The rodent of any one of claims 1-10, wherein mRNA expressed from the mutant *Fbn1* gene escapes mRNA nonsense-mediated decay.

12. The rodent of any one of claims 1-11, wherein the mutated penultimate exon of the *Fbn1* gene comprises mutations corresponding to the mutations in SEQ ID NO: 26, 27, or 28 relative to the wild type mouse *Fbn1* penultimate exon sequence set forth in SEQ ID NO: 25 when the mutated penultimate exon is aligned with SEQ ID NO: 26, 27, or 28.

13. The rodent of any one of claims 1-12, wherein the C-terminally truncated Fbn1 protein consists of the sequence set forth in SEQ ID NO: 31, 32, or 33.

14. The rodent of any one of claims 1-13, wherein the mutation comprises an insertion or deletion that causes a -1 frameshift and results in a premature termination codon at the 3' end of the penultimate exon or the 5' end of the final exon of the *Fbn1* gene.

15. The rodent of claim 14, wherein:

(I) the mutation comprises an insertion in the penultimate exon that causes a -1 frameshift and results in a premature termination codon at the 5' end of the final exon of the *Fbn1* gene;

(II) the mutation comprises an insertion or deletion in the penultimate exon that causes a -1 frameshift and results in a premature termination codon at the 3' end of the penultimate exon of the *Fbn1* gene; or

(III) the C-terminally truncated Fbn1 protein has a positively charged C-terminus.

16. The rodent of claim 15, wherein:

(I) the insertion is between positions corresponding to positions 8179 and 8180 in the wild type mouse *Fbn1* coding sequence set forth in SEQ ID NO: 20 when the *Fbn1* gene comprising the mutation is aligned with SEQ ID NO: 20, and/or the premature termination codon is at a position corresponding to position 8241 in the wild type mouse *Fbn1* coding

sequence set forth in SEQ ID NO: 20 when the *Fbn1* gene comprising the mutation is aligned with SEQ ID NO: 20;

(II) the mutation comprises an insertion between positions corresponding to positions 8209 and 8210 in the wild type mouse *Fbn1* coding sequence set forth in SEQ ID NO: 20 when the *Fbn1* gene comprising the mutation is aligned with SEQ ID NO: 20, and/or the premature termination codon is at a position corresponding to position 8214 in the wild type mouse *Fbn1* coding sequence set forth in SEQ ID NO: 20 when the *Fbn1* gene comprising the mutation is aligned with SEQ ID NO: 20; or

(III) the mutation comprises a deletion starting at a position corresponding to position 8161 in the wild type mouse *Fbn1* coding sequence set forth in SEQ ID NO: 20 when the *Fbn1* gene comprising the mutation is aligned with SEQ ID NO: 20, and/or the premature termination codon is at a position corresponding to position 8214 in the wild type mouse *Fbn1* coding sequence set forth in SEQ ID NO: 20 when the *Fbn1* gene comprising the mutation is aligned with SEQ ID NO: 20.

17. The rodent of any one of claims 1-16, wherein the rodent exhibits:

(I) one or more of the following: decreased white adipose tissue normalized by body weight, decreased white adipose tissue in combination with preserved brown adipose tissue normalized by body weight, decreased body fat percentage, increased food intake normalized by body weight, and increased kyphosis;

(II) one or more of the following: increased metabolic rate, improved insulin sensitivity, normal glucose tolerance, normal serum cholesterol levels, normal serum triglyceride levels, and normal serum non-esterified fatty acid levels; or

(III) decreased white adipose tissue normalized by body weight and at least one of improved insulin sensitivity, normal glucose tolerance, normal serum cholesterol levels, normal serum triglyceride levels, and normal serum non-esterified fatty acid levels.

18. The rodent of any one of claims 1-17, wherein the rodent is a rat or a mouse.

19. The rodent of any one of claims 1-17, wherein the rodent is a rat.
20. The rodent of any one of claims 1-17, wherein the rodent is a mouse.
21. A rodent embryonic stem (ES) cell whose genome comprises a mutation in the penultimate exon of a *fibrillin-1* (*Fbn1*) gene,
wherein the rodent ES cell is heterozygous for the mutation,
wherein the mutation results in disruption or ablation of the asprosin C-terminal cleavage product of pro-fibrillin-1,
wherein expression of the mutant *Fbn1* gene results in a C-terminally truncated Fbn1 protein, and
wherein a rodent generated from the rodent ES cell exhibits decreased body weight, decreased lean mass, and decreased fat mass when compared to a wild-type rodent.
22. The rodent ES cell of claim 21, wherein the mutant *Fbn1* gene is operably linked to the endogenous *Fbn1* promoter.
23. The rodent ES cell of claim 21 or 22, wherein the mutation is a frameshift mutation.
24. The rodent ES cell of any one of claims 21-23, wherein the mutation results in a premature termination codon, wherein the premature termination codon is in the penultimate or the final exon of the *Fbn1* gene.
25. The rodent ES cell of claim 24, wherein the premature termination codon is in the final exon or is less than 55 base pairs upstream of the last exon-exon junction in the *Fbn1* gene.
26. The rodent ES cell of any one of claims 21-25, wherein the mutation disrupts a basic amino acid recognition sequence for proprotein convertases of the furin family, and wherein the mutation is within 50 base pairs of the furin recognition sequence.

27. The rodent ES cell of any one of claims 21-26, wherein the C-terminally truncated Fbn1 protein has a positively charged C-terminus.

28. The rodent ES cell of any one of claims 21-27, wherein the C-terminally truncated Fbn1 protein is truncated at a position corresponding to a position between amino acids 2700 and 2790, between amino acids 2710 and 2780, between amino acids 2720 and 2770, between amino acids 2730 and 2760, or between amino acids 2737 and 2755 in the wild type mouse Fbn1 protein set forth in SEQ ID NO: 30 when the C-terminally truncated Fbn1 protein is aligned with SEQ ID NO: 30.

29. The rodent ES cell of claim 28, wherein:

(I) the C-terminally truncated Fbn1 protein is truncated such that the last amino acid is at a position corresponding to amino acid 2737, amino acid 2738, or amino acid 2755 in the wild type mouse Fbn1 protein set forth in SEQ ID NO: 30 when the C-terminally truncated Fbn1 protein is aligned with SEQ ID NO: 30;

(II) the C-terminally truncated Fbn1 protein is truncated such that the last amino acid is at a position corresponding to amino acid 2737 in the wild type mouse Fbn1 protein set forth in SEQ ID NO: 30 when the C-terminally truncated Fbn1 protein is aligned with SEQ ID NO: 30, and wherein the C-terminus of the C-terminally truncated Fbn1 protein consists of the sequence set forth in SEQ ID NO: 43 or 46;

(III) the C-terminally truncated Fbn1 protein is truncated such that the last amino acid is at a position corresponding to amino acid 2738 in the wild type mouse Fbn1 protein set forth in SEQ ID NO: 30 when the C-terminally truncated Fbn1 protein is aligned with SEQ ID NO: 30, and wherein the C-terminus of the C-terminally truncated Fbn1 protein consists of the sequence set forth in SEQ ID NO: 8 or 45; or

(IV) the C-terminally truncated Fbn1 protein is truncated such that the last amino acid is at a position corresponding to amino acid 2755 in the wild type mouse Fbn1 protein set forth in SEQ ID NO: 30 when the C-terminally truncated Fbn1 protein is aligned with

SEQ ID NO: 30, and wherein the C-terminus of the C-terminally truncated Fbn1 protein consists of the sequence set forth in SEQ ID NO: 42 or 47.

30. The rodent ES cell of any one of claims 21-29, wherein the C-terminally truncated Fbn1 protein has a C-terminus consisting of the sequence set forth in SEQ ID NO: 8, 42, 43, 45, 46, or 47.

31. The rodent ES cell of any one of claims 21-30, wherein mRNA expressed from the mutant *Fbn1* gene escapes mRNA nonsense-mediated decay.

32. The rodent ES cell of any one of claims 21-31, wherein the mutated penultimate exon of the *Fbn1* gene comprises the mutations in SEQ ID NO: 26, 27, or 28 relative to the wild type mouse *Fbn1* penultimate exon sequence set forth in SEQ ID NO: 25.

33. The rodent ES cell of any one of claims 21-32, wherein the C-terminally truncated Fbn1 protein consists of the sequence set forth in SEQ ID NO: 31, 32, or 33.

34. The rodent ES cell of any one of claims 21-33, wherein the mutation comprises an insertion or deletion that causes a -1 frameshift and results in a premature termination codon at the 3' end of the penultimate exon or the 5' end of the final exon of the *Fbn1* gene.

35. The rodent ES cell of claim 34, wherein:

(I) the mutation comprises an insertion in the penultimate exon that causes a -1 frameshift and results in a premature termination codon at the 5' end of the final exon of the *Fbn1* gene;

(II) the mutation comprises an insertion or deletion in the penultimate exon that causes a -1 frameshift and results in a premature termination codon at the 3' end of the penultimate exon of the *Fbn1* gene; or

(III) the C-terminally truncated Fbn1 protein has a positively charged C-terminus.

36. The rodent ES cell of claim 35, wherein:

(I) the insertion is between positions corresponding to positions 8179 and 8180 in the wild type mouse *Fbn1* coding sequence set forth in SEQ ID NO: 20 when the *Fbn1* gene comprising the mutation is aligned with SEQ ID NO: 20, and/or the premature termination codon is at a position corresponding to position 8241 in the wild type mouse *Fbn1* coding sequence set forth in SEQ ID NO: 20 when the *Fbn1* gene comprising the mutation is aligned with SEQ ID NO: 20;

(II) the mutation comprises an insertion between positions corresponding to positions 8209 and 8210 in the wild type mouse *Fbn1* coding sequence set forth in SEQ ID NO: 20 when the *Fbn1* gene comprising the mutation is aligned with SEQ ID NO: 20, and/or the premature termination codon is at a position corresponding to position 8214 in the wild type mouse *Fbn1* coding sequence set forth in SEQ ID NO: 20 when the *Fbn1* gene comprising the mutation is aligned with SEQ ID NO: 20; or

(III) the mutation comprises a deletion starting at a position corresponding to position 8161 in the wild type mouse *Fbn1* coding sequence set forth in SEQ ID NO: 20 when the *Fbn1* gene comprising the mutation is aligned with SEQ ID NO: 20, and/or the premature termination codon is at a position corresponding to position 8214 in the wild type mouse *Fbn1* coding sequence set forth in SEQ ID NO: 20 when the *Fbn1* gene comprising the mutation is aligned with SEQ ID NO: 20.

37. The rodent ES cell of any one of claims 21-36, wherein the rodent generated from the rodent ES cell exhibits:

(I) one or more of the following: decreased white adipose tissue normalized by body weight, decreased white adipose tissue in combination with preserved brown adipose tissue normalized by body weight, decreased body fat percentage, increased food intake normalized by body weight, and increased kyphosis;

(II) one or more of the following: increased metabolic rate, improved insulin sensitivity, normal glucose tolerance, normal serum cholesterol levels, normal serum triglyceride levels, and normal serum non-esterified fatty acid levels; or

(III) decreased white adipose tissue normalized by body weight and at least one of improved insulin sensitivity, normal glucose tolerance, normal serum cholesterol levels, normal serum triglyceride levels, and normal serum non-esterified fatty acid levels.

38. The rodent ES cell of any one of claims 21-37, wherein the rodent is a rat or a mouse.

39. The rodent ES cell of any one of claims 21-37, wherein the rodent is a rat.

40. The rodent ES cell of any one of claims 21-37, wherein the rodent is a mouse.

41. A method of making a rodent whose genome comprises a mutation in the penultimate exon of the *fibrillin-1* (*Fbn1*) gene, comprising:

(a) introducing the rodent ES cell of any one of claims 21-40 whose genome comprises the mutation in the penultimate exon of the endogenous *Fbn1* gene into a rodent host embryo; and

(b) implanting and gestating the rodent host embryo in a surrogate mother to produce a genetically modified F0 generation rodent, thereby making the rodent whose genome comprises the mutation in the penultimate exon of the *Fbn1* gene.

42. The method of claim 41, further comprising modifying a rodent ES cell prior to step (a) to generate the rodent ES cell whose genome comprises the mutation in the penultimate exon of the *Fbn1* gene.

43. The method of claim 42, wherein the modifying step comprises:

(I) contacting the genome of the rodent ES cell with a Cas9 protein and a guide RNA that hybridizes to a guide RNA recognition sequence within a target genomic locus in the *Fbn1* gene, wherein the Cas9 protein cleaves the target genomic locus, and the *Fbn1* gene is modified to comprise the mutation;

(II) contacting the genome of the rodent ES cell with an exogenous repair template comprising a 5' homology arm that hybridizes to a 5' target sequence at a target genomic locus in the *Fbn1* gene and a 3' homology arm that hybridizes to a 3' target sequence at the target genomic locus, wherein the exogenous repair template recombines with the target genomic locus, and the *Fbn1* gene is modified to comprise the mutation; or

(III) contacting the genome of the rodent ES cell with a Cas9 protein, a guide RNA that hybridizes to a guide RNA recognition sequence within a target genomic locus in the *Fbn1* gene, and an exogenous repair template comprising a 5' homology arm that hybridizes to a 5' target sequence at the target genomic locus and a 3' homology arm that hybridizes to a 3' target sequence at the target genomic locus, wherein the Cas9 protein cleaves the target genomic locus, the exogenous repair template recombines with the target genomic locus, and the *Fbn1* gene is modified to comprise the mutation.

44. A method of making the rodent of any one of claims 1-20 whose genome comprises the mutation in the penultimate exon of the endogenous *Fbn1* gene, comprising:

(a) contacting the genome of a rodent one-cell stage embryo with:

(i) a Cas9 protein and a first guide RNA that hybridizes to a first guide RNA recognition sequence within a target genomic locus in the *Fbn1* gene, wherein the Cas9 protein cleaves the target genomic locus, and the *Fbn1* gene is modified to comprise the mutation; and/or

(ii) an exogenous repair template comprising a 5' homology arm that hybridizes to a 5' target sequence at the target genomic locus and a 3' homology arm that hybridizes to a 3' target sequence at the target genomic locus, wherein the exogenous repair template recombines with the target genomic locus, and the *Fbn1* gene is modified to comprise the mutation;

(b) implanting and gestating the modified rodent one-cell stage embryo in a surrogate mother to produce a genetically modified F0 generation rodent, thereby making the rodent whose genome comprises the mutation in the penultimate exon of the *Fbn1* gene.

45. The method of claim 43 or 44, wherein the exogenous repair template further comprises a nucleic acid insert flanked by the 5' homology arm and the 3' homology arm, optionally wherein the nucleic acid insert is homologous or orthologous to the target genomic locus.

46. A method of screening a compound for activity for ameliorating congenital lipodystrophy-like symptoms, comprising:

(a) contacting a subject rodent of any one of claims 1-20 with the compound;
and

(b) determining the presence of congenital lipodystrophy-like symptoms of the subject rodent relative to a control rodent not contacted with the compound, wherein the control rodent comprises the same *Fbn1* mutation as the subject rodent,

whereby activity for ameliorating congenital lipodystrophy-like symptoms is identified by decreased appearance of congenital lipodystrophy-like symptoms in the subject rodent compared with the control rodent.

47. The method of claim 46, wherein the symptoms comprise:

(I) one or more of the following: decreased body weight, decreased lean mass, decreased fat mass, decreased white adipose tissue normalized by body weight, decreased white adipose tissue in combination with preserved brown adipose tissue normalized by body weight, decreased body fat percentage, increased food intake normalized by body weight, and increased kyphosis;

(II) decreased white adipose tissue normalized by body weight; or

(III) decreased body weight, decreased lean mass, and decreased fat mass.

48. The method of any one of claims 41-47, wherein the rodent is a rat or a mouse.

49. The method of any one of claims 41-47, wherein the rodent is a rat.

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50. The method of any one of claims 41-47, wherein the rodent is a mouse.