treats the obesity and hyperphagia associated with POMC-MC4R pathway genetic defect disorders with fewer safety issues.

SUMMARY OF THE ~~INVENTION~~DISCLOSURE

In an aspect, there is provided a use of an agonist of the melanocortin-4 receptor (MC4R) at a daily dosage of about 0.1 mg to about 10 mg in the manufacture of a medicament for treating a disorder in a subject in need thereof,

wherein the disorder comprises

a disorder characterized by a hypermethylated POMC gene and

wherein the agonist is a structure of Formula (I):

$$(R^2R^3)\text{-}A^1\text{-}c(A^2\text{-}A^3\text{-}A^4\text{-}A^5\text{-}A^6\text{-}A^7\text{-}A^8\text{-}A^9)\text{-}A^{10}\text{-}R^1 \quad \text{(I)},$$

wherein:

A^1 is Acc, HN—$(CH_2)_m$—C(O), L- or D-amino acid, or deleted;

A^2 is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Asp, or Glu;

A^3 is Gly, Ala, β-Ala, Gaba, Aib, D-amino acid, or deleted;

A^4 is His, 2-Pal, 3-Pal, 4-Pal, Taz, 2-Thi, 3-Thi, or (X^1, X^2, X^3, X^4, X^5)Phe;

A^5 is D-Phe, D-1-Nal, D-2-Nal, D-Trp, D-Bal, D-(X^1, X^2, X^3, X^4, X^5)Phe, L-Phe or D-(Et)Tyr;

A^6 is Arg, hArg, Dab, Dap, Lys, Orn, or HN-CH($(CH_2)_n$-N(R^4 R^5))-C(O);

A^7 is Trp, 1-Nal, 2-Nal, Bal, Bip, D-Trp, D-2-Nal, D-Bal or D-Bip;

A^8 is Gly, D-Ala, Acc, Ala, 13-Ala, Gaba, Apn, Ahx, Aha, HN-$(CH_2)_s$-C(O), or deleted;

A^9 is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Dab, Dap, Orn, or Lys;

A^{10} is Acc, HN-$(CH_2)_t$-C(O), L- or D-amino acid, or deleted;

R^1 is OH or NH_2;

each of R^2 and R^3 is, independently for each occurrence, selected from the group consisting of H, (C_1-C_{30})alkyl, (C_1-C_{30})heteroalkyl, (C_1-C_{30})acyl, (C_2-C_{30})alkenyl, (C_2-C_{30})alkynyl, aryl(C_1-C_{30})alkyl, aryl(C_1-C_{30})acyl, substituted (C_1-C_{30})alkyl, substituted (C_1-

C_{30})heteroalkyl, substituted (C_1-C_{30})acyl, substituted (C_2-C_{30})alkenyl, substituted (C_2-C_{30})alkynyl, substituted aryl(C_1-C_{30})alkyl, and substituted aryl(C_1-C_{30})acyl;

each of R^4 and R^5 is, independently for each occurrence, H, (C_1-C_{40})alkyl, (C_1-C_{40})heteroalkyl, (C_1-C_{40})acyl, (C_2-C_{40})alkenyl, (C_2-C_{40})alkynyl, aryl(C_1-C_{40})alkyl, aryl(C_1-C_{40})acyl, substituted (C_1-C_{40})alkyl, substituted (C_1-C_{40})heteroalkyl, substituted (C_1-C_{40})acyl, substituted (C_2-C_{40})alkenyl, substituted (C_2-C_{40})alkynyl, substituted aryl(C_1-C_{40})alkyl, substituted aryl(C_1-C_{40})acyl, (C_1-C_{40})alkylsulfonyl, or -C(NH)-NH_2;

m is, independently for each occurrence, 1, 2, 3, 4, 5, 6 or 7;

n is, independently for each occurrence, 1, 2, 3, 4 or 5;

s is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

t is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

X′, X^2, X^3, X^4, and X^8 each is, independently for each occurrence, H, F, Cl, Br, I, (C_{1-10})alkyl, substituted (C_{1-10})alkyl, (C_{2-10})alkenyl, substituted (C_{2-10})alkenyl, (C_{2-10})alkynyl, substituted (C_{2-10})alkynyl, aryl, substituted aryl, OH, NH_2, NO_2, or CN.

In an ~~aspect~~example, provided herein is a method of treating Prader Willi Syndrome (PWS) in a subject in need thereof, comprising:

administering an agonist of the melanocortin-4 receptor (MC4R) at a daily dosage of about 0.1 mg (e.g., 0.1 mg +/- 5%) to about 10 mg (e.g., 10 mg +/- 5%),

wherein the agonist is a MC4R agonist described herein, e.g., the agonist is

$$(R^2R^3)\text{-}A^1\text{-}c(A^2\text{-}A^3\text{-}A^4\text{-}A^5\text{-}A^6\text{-}A^7\text{-}A^8\text{-}A^9)\text{-}A^{10}\text{-}R^1 \qquad \text{(I)},$$

wherein:

A^1 is Acc, HN—$(CH_2)_m$—C(O), L- or D-amino acid, or deleted;

A^2 is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Asp, or Glu;

A^3 is Gly, Ala, β-Ala, Gaba, Aib, D-amino acid, or deleted;

A^4 is H is, 2-Pal, 3-Pal, 4-Pal, Taz, 2-Thi, 3-Thi, or (X^1, X^2, X^3, X^4, X^5)Phe;

A^5 is D-Phe, D-1-Nal, D-2-Nal, D-Trp, D-Bal, D-(X^1, X^2, X^3, X^4, X^5)Phe, L-Phe or D-(Et)Tyr;

A^6 is Arg, hArg, Dab, Dap, Lys, Orn, or HN-CH($(CH_2)_n$-N(R^4 R^5))-C(O);

A^7 is Trp, 1-Nal, 2-Nal, Bal, Bip, D-Trp, D-2-Nal, D-Bal or D-Bip;

A^8 is Gly, D-Ala, Acc, Ala, 13-Ala, Gaba, Apn, Ahx, Aha, HN-$(CH_2)_s$-C(O), or deleted;

A^9 is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Dab, Dap, Orn, or Lys;

A^{10} is Acc, HN-$(CH_2)_t$-C(O), L- or D-amino acid, or deleted;

R^1 is OH or NH_2;

each of R^2 and R^3 is, independently for each occurrence, selected from the group consisting of H, $(C_1$-$C_{30})$alkyl, $(C_1$-$C_{30})$heteroalkyl, $(C_1$-$C_{30})$acyl, $(C_2$-$C_{30})$alkenyl, $(C_2$-$C_{30})$alkynyl, aryl$(C_1$-$C_{30})$alkyl, aryl$(C_1$-$C_{30})$acyl, substituted $(C_1$-$C_{30})$alkyl, substituted $(C_1$-$C_{30})$heteroalkyl, substituted $(C_1$-$C_{30})$acyl, substituted $(C_2$-$C_{30})$alkenyl, substituted $(C_2$-$C_{30})$alkynyl, substituted aryl$(C_1$-$C_{30})$alkyl, and substituted aryl$(C_1$-$C_{30})$acyl;

each of R^4 and R^5 is, independently for each occurrence, H, $(C_1$-$C_{40})$alkyl, $(C_1$-$C_{40})$heteroalkyl, $(C_1$-$C_{40})$acyl, $(C_2$-$C_{40})$alkenyl, $(C_2$-$C_{40})$alkynyl, aryl$(C_1$-$C_{40})$alkyl, aryl$(C_1$-$C_{40})$acyl, substituted $(C_1$-$C_{40})$alkyl, substituted $(C_1$-$C_{40})$heteroalkyl, substituted $(C_1$-$C_{40})$acyl, substituted $(C_2$-

C_{40})alkenyl, substituted (C_2-C_{40})alkynyl, substituted aryl(C_1-C_{40})alkyl, substituted aryl(C_1-C_{40})acyl, (C_1-C_{40})alkylsulfonyl, or -C(NH)-NH_2;

m is, independently for each occurrence, 1, 2, 3, 4, 5, 6 or 7;

n is, independently for each occurrence, 1, 2, 3, 4 or 5;

s is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

t is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

X′, X^2, X^3, X^4, and X^8 each is, independently for each occurrence, H, F, Cl, Br, I, ($C_{1\text{-}10}$)alkyl, substituted ($C_{1\text{-}10}$)alkyl, ($C_{2\text{-}10}$)alkenyl, substituted ($C_{2\text{-}10}$)alkenyl, ($C_{2\text{-}10}$)alkynyl, substituted ($C_{2\text{-}10}$)alkynyl, aryl, substituted aryl, OH, NH_2 , NO_2 , or CN,

thereby treating PWS.

In examples~~embodiments~~, the subject has or is identified as having a loss of function mutation in the 15q11-q13 region of chromosome 15.

In examples~~embodiments~~, the subject has or is identified as having a mutation (e.g., loss of function mutation) in the MAGEL2 gene.

In examples~~embodiments~~, the daily dosage is 0.1 mg to 10 mg. In examples~~embodiments~~, the daily dosage is about 0.1 mg to about 7.5 mg. In examples~~embodiments~~, the daily dosage is about 0.1 mg to about 5 mg. In examples~~embodiments~~, the daily dosage is about 0.1 mg to about 2.5 mg. In examples~~embodiments~~, the daily dosage is about 0.1 mg to about 2 mg. In examples~~embodiments~~, the daily dosage is about 0.1 mg to about 1 mg. In examples~~embodiments~~, the daily dosage is about 0.2 mg to about 10 mg. In examples~~embodiments~~, the daily dosage is about 0.2 mg to about 7.5 mg. In examples~~embodiments~~, the daily dosage is about 0.2 mg to about 5 mg. In examples~~embodiments~~, the daily dosage is about 0.2 mg to about 2.5 mg. In examples~~embodiments~~, the daily dosage is about 0.2 mg to about 2 mg. In examples~~embodiments~~, the daily dosage is about 0.2 mg to about 1.5 mg. In examples~~embodiments~~, the daily dosage is about 0.2 mg to about 1 mg. In examples~~embodiments~~, the daily dosage is about 0.3 mg to about 10 mg. In examples~~embodiments~~, the daily dosage is about 0.3 mg to about 7.5 mg. In examples~~embodiments~~, the daily dosage is about 0.3 mg to about 5 mg. In examples~~embodiments~~, the daily dosage is about 0.3 mg to about 2.5 mg. In examples~~embodiments~~, the daily dosage is about 0.3 mg to about 2 mg. In examples~~embodiments~~, the daily dosage is about 0.3 mg to about 1.5 mg. In examples~~embodiments~~, the daily dosage is about 0.3 mg to about 1 mg. In examples~~embodiments~~, the daily dosage is about 0.25 mg (e.g., 0.25 mg) to about 0.5 mg (e.g., 0.5 mg). In examples~~embodiments~~, the daily dosage is about 0.5 mg (e.g., 0.5 mg) to about 0.75 mg (e.g., 0.75 mg). In examples~~embodiments~~, the daily dosage is about 0.25 mg (e.g., 0.25 mg). In

examplesembodiments, the daily dosage is about 0.5 mg (e.g., 0.5 mg). In examplesembodiments, the daily dosage is about 0.75 mg (e.g., 0.75 mg) to about 1.25 mg (1.25 mg). In examplesembodiments, the daily dosage is about 1 mg (e.g., 1 mg). In examplesembodiments, the daily dosage is about 1.25 mg (e.g., 1.25 mg) to about 2 mg (e.g., 2 mg). In examplesembodiments, the daily dosage is about 1.5 mg (e.g., 1.5 mg). In examplesembodiments, the daily dosage is about 2 mg (e.g., 2 mg).

In examplesembodiments, the method comprises administering the agonist in a unit dosage suitable for injection, e.g., subcutaneous injection, to the subject.

In examplesembodiments, the unit dosage comprises about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, or 2 mg of the agonist.

In examplesembodiments, the unit dosage is disposed within a delivery device, e.g., a syringe (e.g., prefilled syringe),an implantable device, a needleness hypodermic injection device, an infusion pump (e.g., implantable infusion pump), or an osmotic delivery system.

In examplesembodiments, the agonist is administered subcutaneously, e.g., by subcutaneous injection.

In examplesembodiments, the agonist is administered daily over a period of at least 3 weeks, e.g., at least 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, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 weeks or more, or at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months or more, or at least 1, 2, 3, 4 years or more.

In examplesembodiments, the subject is obese, e.g., severely obese.

In examplesembodiments, the subject has early onset severe obesity.

In examplesembodiments, the subject is hyperphagic.

In examplesembodiments, the subject has a body mass index (BMI) greater than 25 kg/m^2 (e.g., ≥25, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 kg/m^2 or greater) prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.

In examplesembodiments, the subject has a body mass index (BMI) greater than 35 kg/m^2 (e.g., ≥36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 kg/m^2 or greater) prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.

In examplesembodiments, the subject has a body mass index (BMI) greater than 40 kg/m^2 (e.g., ≥41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55 kg/m^2 or greater) prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.

In examplesembodiments, the subject has a body mass index (BMI) greater than 45 kg/m^2 (e.g., ≥46, 47, 48, 49, 50, 51, 52, 53, 54, 55 kg/m^2 or greater) prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.

In examplesembodiments, the subject has a BMI higher than the 85-95th percentile prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.

In examplesembodiments, the subject has failed one or more previous therapies, e.g., exercise, diet, or behavioral therapies, prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.

In examplesembodiments, the subject has a lower body weight after administration of the agonist than before administration of the agonist.

In examplesembodiments, administration of the agonist results in a reduction of weight in the subject compared to the weight of the subject before treatment of about 1 kg to 3 kg after 1 week of treatment, or about 1 kg to 6 kg after 2 weeks of treatment, or about 2 kg to 12 kg after 4 weeks of treatment, or about 4 kg to 24 kg after 8 weeks of treatment, or about 8 kg to 48 kg after 16 weeks of treatment.

In examplesembodiments, administration of the agonist results in weight loss in the subject at a rate of about 1-2 kg/week, e.g., about 2 kg/week, e.g., over a period of 1-2 weeks of treatment or longer, 2-4 weeks of treatment or longer, 4-8 weeks of treatment or longer, 8-16 weeks of treatment or longer, 16-32 weeks or longer, or 32-64 weeks or longer.

In examplesembodiments, administration of the agonist results in a reduction in hunger level (e.g., a lower score on the Likert hunger scale, e.g., a lower score by at least 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 points) in the subject compared to the hunger level of the subject before treatment, e.g., results in abolishment of hunger (e.g., a score of 0 on the Likert hunger scale) in the subject, e.g., after 1-2 weeks of treatment or longer, 2-4 weeks of treatment or longer, 4-8 weeks of treatment or longer, or 8-16 weeks of treatment or longer.

In examples~~embodiments~~, administration of the agonist results in no detectable/significant decrease in resting energy expenditure (REE) in the subject, e.g., over a period of 24 hours, one week, or 30 days or longer, e.g., as compared to a control REE (e.g., the REE in the subject prior to treatment or a predetermined REE, e.g., in subjects of similar pre-treatment BMI, e.g., when expressed as REE per kg of lean body mass).

In examples~~embodiments~~, administration of the agonist results in an increase in resting energy expenditure (REE) in the subject, e.g., over a period of 24 hours, one week, or 30 days, or longer e.g., as compared to a control REE (e.g., the REE in the subject prior to treatment or compared to a predetermined REE, e.g., in subjects of similar pre-treatment BMI, when expressed as REE per kg of lean body mass, e.g., after a similar level of weight loss has been attained by fasting).

In examples~~embodiments~~, administration of the agonist results in a reduction in food intake by the subject compared to a control (e.g., the food intake of the subject prior to treatment), e.g., wherein the food intake is daily food intake or food intake over a period of 24 hours, or one week.

In examples~~embodiments~~, administration of the agonist results in a reduction in food intake of at least 100 kilocalories, e.g., at least 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 525, 550, 575, 600, 1000 kilocalories or more, compared to a control (e.g., the food intake of the subject prior to treatment or a predetermined food intake level), e.g., wherein the food intake is daily food intake or food intake over a period of 24, hours, or one week.

In examples~~embodiments~~, administration of the agonist results in a reduction in food intake of at least 5 kcal/kg/day, e.g., 5, 10, 20, 30, 40, 50, 60, 70, 80, or 90 or more kcal/kg/day. In embodiments, the reduction in food intake is relative to the food intake at baseline. In embodiments, the baseline food intake is at least 100 kcal/kg/day, e.g., for a pediatric subject at about 1 year of age. In examples~~embodiments~~, the baseline food intake is at least 40 kcal/kg/day, e.g., for a pediatric subject, e.g., in late adolescence.

In examples~~embodiments~~, administration of the agonist results in a reduction in waist circumference of the subject compared to a control (e.g., the waist circumference of the

subject prior to treatment), as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.

In examples~~embodiments~~, administration of the agonist results in a reduction in waist circumference of at least 2 cm (e.g., at least 2, 3, 4, 5, 6, 7, 8, 9, 10 cm or more) in the subject compared to a control (e.g., the waist circumference of the subject prior to treatment), as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.

In examples~~embodiments~~, administration of the agonist results in no detectable increase in blood pressure (e.g., diastolic and/or systolic blood pressure) of the subject compared to the blood pressure of the subject prior to treatment, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.

In examples~~embodiments~~, administration of the agonist results in a reduction in blood pressure (e.g., diastolic and/or systolic blood pressure) of the subject compared to the blood pressure of the subject prior to treatment, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.

In examples~~embodiments~~, administration of the agonist results in a reduction in systolic blood of the subject of at least 3 mmHg (e.g., at least 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7 mmHg or more) compared to the blood pressure of the subject prior to treatment, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.

In examples~~embodiments~~, administration of the agonist results in a reduction in diastolic blood pressure of the subject of at least 4 mmHg (e.g., at least 4, 7, 7.5, 8, 8.5, 9, 9.5, 10 mmHg or more) compared to the blood pressure of the subject prior to treatment, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.

In examples~~embodiments~~, the subject is a mammal, e.g., a human.

In examples~~embodiments~~, the agonist is Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 (SEQ ID NO: 140).

In examples~~embodiments~~, the method further comprises acquiring knowledge of the genotype of the subject, e.g., acquiring knowledge of the genotype the 15q11-q13 region of chromosome 15 or of the MAGEL2 gene.

In examples~~embodiments~~, the agonist is administered in response to the detection of a predetermined sequence, e.g., a mutation, in 15q11-q13 region of chromosome 15 or in the MAGEL2 gene.

In examples~~embodiments~~, the knowledge is acquired directly, e.g., from a sample (e.g., a blood, serum, urine, or tissue (e.g., biopsy) sample) from the subject.

In examples~~embodiments~~, the predetermined sequence, e.g., mutation, is detected in a nucleic acid by a method chosen from one or more of: a nucleic acid hybridization assay, an amplification-based assay, a PCR-RFLP assay, real-time PCR, sequencing, screening analysis, FISH, spectral karyotyping or MFISH, comparative genomic hybridization, *in situ* hybridization, SSP, HPLC or mass-spectrometric genotyping.

In examples~~embodiments~~, the predetermined sequence, e.g., mutation, is detected in the subject.

In examples~~embodiments~~, the predetermined sequence, e.g., mutation, is detected in a nucleic acid molecule or a polypeptide in a sample from the subject.

In examples~~embodiments~~, the sample comprises cells from a blood, serum, urine, or tissue (e.g., biopsy) from the subject.

In examples~~embodiments~~, the knowledge is acquired from another party, e.g., wherein the party is the subject, a caregiver, a physician, an endocrinologist, a hospital, clinic, third-party payor, insurance company or government office.

In examples~~embodiments~~, the method comprises:

responsive to a determination of the presence or absence the predetermined sequence, e.g., mutation, in the subject, one or more of:

(1) identifying or selecting the subject as having Prader Willi Syndrome (PWS); and/or

(2) identifying or selecting the subject as likely or unlikely to respond to the agonist.

In examples~~embodiments~~, the presence of the predetermined sequence, e.g., mutation, is detected in the subject, and responsive to that determination, the method comprises identifying the subject as having Prader Willi Syndrome (PWS).

In examplesembodiments, the presence of the predetermined sequence, e.g., mutation, is detected in the subject, and responsive to that determination, the method comprises identifying the subject as likely to respond to the agonist.

In examplesembodiments, the subject has or is identified as having PWS.

In an aspectexample, provided herein is a method of treating a disorder in a subject in need thereof, comprising:

administering an agonist of the melanocortin-4 receptor (MC4R) at a daily dosage of about 0.1 mg (e.g., 0.1 mg +/- 5%) to about 10 mg (e.g., 10 mg +/- 5%),

wherein the disorder is chosen from:

(i) Prader Willi Syndrome (PWS);

(ii) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the POMC gene;

(iii) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the PCSK1 gene;

(iv) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the MAGEL2 gene;

(v) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the leptin receptor gene;

(vi) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the leptin gene;

(vii) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the 5-HT2c receptor gene;

(viii) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the nescient helix loop helix 2 (NhHL2) gene;

(ix) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the pro-hormone convertase gene;

(x) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the carboxypeptidase E (CPE) gene;

(xi) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the single-minded 1 (SIM1) gene;

C_{40})alkenyl, substituted (C_2-C_{40})alkynyl, substituted aryl(C_1-C_{40})alkyl, substituted aryl(C_1-C_{40})acyl, (C_1-C_{40})alkylsulfonyl, or -C(NH)-NH_2;

m is, independently for each occurrence, 1, 2, 3, 4, 5, 6 or 7;

n is, independently for each occurrence, 1, 2, 3, 4 or 5;

s is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

t is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

X′, X^2, X^3, X^4, and X^8 each is, independently for each occurrence, H, F, Cl, Br, I, (C_{1-10})alkyl, substituted (C_{1-10})alkyl, (C_{2-10})alkenyl, substituted (C_{2-10})alkenyl, (C_{2-10})alkynyl, substituted (C_{2-10})alkynyl, aryl, substituted aryl, OH, NH_2 , NO_2 , or CN.

In examples~~embodiments~~, the subject comprises one or more mutations, e.g., from one or more genes described herein.

In examples~~embodiments~~, the disorder is Prader Willi Syndrome (PWS).

In examples~~embodiments~~, the subject has or is identified as having a loss of function mutation in the paternal allele of the 15q11-q13 region of chromosome 15.

In examples~~embodiments~~, the subject has or is identified as having a mutation, e.g., loss of function mutation, in the MAGEL2 gene.

In examples~~embodiments~~, the disorder is characterized by one or more mutations (e.g., loss of function mutations) in the POMC gene.

In examples~~embodiments~~, the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional POMC allele and one non-functional POMC allele.

In examples~~embodiments~~, the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two distinct non-functional POMC alleles, e.g., having a POMC null genotype.

In examples~~embodiments~~, the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a homozygous POMC null genotype.

In examples~~embodiments~~, the disorder is characterized by one or more mutations (e.g., loss of function mutations) in the PCSK1 gene.

In examples~~embodiments~~, the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional PCSK1 allele and one non-functional PCSK1 allele.

In examples~~embodiments~~, the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two non-functional PCSK1 alleles, e.g., having a PCSK1 null genotype.

In examples~~embodiments~~, the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a homozygous PCSK1 null genotype.

In examples~~embodiments~~, the disorder is characterized by one or mutations (e.g., loss of function mutations) in the MAGEL2 gene.

In examples~~embodiments~~, the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional MAGEL2 allele and one non-functional MAGEL2 allele, including the subjects where the remainingfunctional allele is silenced by maternal imprinting, as result of which the subject is a functional MAGEL2 null patient.

In examples~~embodiments~~, the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two mutated non-functional MAGEL2 alleles, e.g., having a MAGEL2 null genotype.

In examples~~embodiments~~, the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a MAGEL2 null genotype.

In examples~~embodiments~~, the disorder is characterized by one or mutations (e.g., loss of function mutations) in the leptin receptor gene.

In examples~~embodiments~~, the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional leptin receptor allele and one non-functional leptin receptor allele.

In examples~~embodiments~~, the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two non-functional leptin receptor alleles, e.g., having a leptin receptor null genotype.

In examples~~embodiments~~, the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a leptin receptor null genotype.

In examples~~embodiments~~, the disorder is characterized by one or mutations (e.g., loss of function mutations) in the leptin gene.

In examplesembodiments, the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional leptin allele and one non-functional leptin allele.

In examplesembodiments, the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two non-functional leptin alleles, e.g., having a leptin null genotype.

In examplesembodiments, the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a leptin null genotype.

In examplesembodiments, the disorder is characterized by one or mutations (e.g., loss of function mutations) in the 5-HT2c receptor gene.

In examplesembodiments, the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional 5-HT2c receptor allele and one non-functional 5-HT2c receptor allele.

In examplesembodiments, the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two non-functional 5-HT2c receptor alleles, e.g., having a 5-HT2c receptor null genotype.

In examplesembodiments, the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a 5-HT2c receptor null genotype.

In examplesembodiments, the disorder is characterized by one or mutations (e.g., loss of function mutations) in the nescient helix loop helix 2 (NhHL2) gene.

In examplesembodiments, the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional NhHL2 allele and one non-functional NhHL2 receptor allele.

In examplesembodiments, the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two non-functional NhHL2 alleles, e.g., having a NhHL2 null genotype.

In examplesembodiments, the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a NhHL2 null genotype.

In examplesembodiments, the disorder is characterized by one or mutations (e.g., loss of function mutations) in the pro-hormone convertase gene.

In examplesembodiments, the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional pro-hormone convertase allele and one non-functional pro-hormone convertase allele.

In examplesembodiments, the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two non-functional pro-hormone convertase alleles, e.g., having a pro-hormone convertase null genotype.

In examplesembodiments, the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a pro-hormone convertase null genotype.

In examplesembodiments, the disorder is characterized by one or mutations (e.g., loss of function mutations) in the carboxypeptidase E (CPE) gene.

In examplesembodiments, the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional CPE allele and one non-functional CPE allele.

In examplesembodiments, the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two non-functional CPE alleles, e.g., having a CPE null genotype.

In examplesembodiments, the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a CPE null genotype.

In examplesembodiments, the disorder is characterized by one or mutations (e.g., loss of function mutations) in the single-minded 1 (SIM1) gene.

In examplesembodiments, the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional SIM1 allele and one non-functional SIM1 allele.

In examplesembodiments, the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two non-functional SIM1 alleles, e.g., having a SIM1 null genotype.

In examplesembodiments, the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a SIM1 null genotype.

In examplesembodiments, the disorder is characterized by a hypermethylated POMC gene (e.g., hypermethylated at a POMC intron, e.g., at a CpG island of the POMC gene, e.g., comprising a methylated cytosine, e.g., a 5'methyl cytosine).

In examplesembodiments, the disorder is characterized by a defect in the POMC-MC4R pathway other than:

(a) a heterozygous POMC mutation characterized by the presence of one functional POMC allele and one non-functional POMC allele,

(b) a heterozygous leptin mutation characterized by the presence of one functional leptin allele and one non-functional leptin allele,

(c) a heterozygous melanocortin-4 receptor (MC4R) mutation characterized by the presence of one functional MC4R allele and one non-functional MC4R allele, or

(d) a pro-hormone convertase mutation (e.g., loss of function mutation).

In examplesembodiments, the daily dosage is 0.1 mg to 10 mg. In embodiments, the daily dosage is about 0.1 mg to about 7.5 mg. In examplesembodiments, the daily dosage is about 0.1 mg to about 5 mg. In examplesembodiments, the daily dosage is about 0.1 mg to about 2.5 mg. In examplesembodiments, the daily dosage is about 0.1 mg to about 2 mg. In examplesembodiments, the daily dosage is about 0.1 mg to about 1 mg. In examplesembodiments, the daily dosage is about 0.2 mg to about 10 mg. In examplesembodiments, the daily dosage is about 0.2 mg to about 7.5 mg. In examplesembodiments, the daily dosage is about 0.2 mg to about 5 mg. In examplesembodiments, the daily dosage is about 0.2 mg to about 2.5 mg. In examplesembodiments, the daily dosage is about 0.2 mg to about 2 mg. In examplesembodiments, the daily dosage is about 0.2 mg to about 1.5 mg. In examplesembodiments, the daily dosage is about 0.2 mg to about 1 mg. In examplesembodiments, the daily dosage is about 0.3 mg to about 10 mg. In examplesembodiments, the daily dosage is about 0.3 mg to about 7.5 mg. In examplesembodiments, the daily dosage is about 0.3 mg to about 5 mg. In examplesembodiments, the daily dosage is about 0.3 mg to about 2.5 mg. In examplesembodiments, the daily dosage is about 0.3 mg to about 2 mg. In examplesembodiments, the daily dosage is about 0.3 mg to about 1.5 mg. In examplesembodiments, the daily dosage is about 0.3 mg to about 1 mg. In examplesembodiments, the daily dosage is about 0.25 mg (e.g., 0.25 mg) to about 0.5 mg (e.g., 0.5 mg). In examplesembodiments, the daily dosage is about 0.5 mg (e.g., 0.5 mg) to about 0.75 mg (e.g., 0.75 mg). In examplesembodiments, the daily dosage is about 0.25 mg (e.g., 0.25 mg). In examplesembodiments, the daily dosage is about 0.5 mg (e.g., 0.5 mg). In examplesembodiments, the daily dosage is about 0.75 mg (e.g., 0.75 mg) to about 1.25 mg (1.25 mg). In examplesembodiments, the daily dosage is about 1 mg (e.g., 1 mg). In examplesembodiments, the daily dosage is about 1.25 mg

(e.g., 1.25 mg) to about 2 mg (e.g., 2 mg). In examples~~embodiments~~, the daily dosage is about 1.5 mg (e.g., 1.5 mg). In examples~~embodiments~~, the daily dosage is about 2 mg (e.g., 2 mg).

In examples~~embodiments~~, the method comprises administering the agonist in a unit dosage suitable for injection, e.g., subcutaneous injection, to the subject.

In examples~~embodiments~~, the unit dosage comprises about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, or 2 mg of the agonist.

In examples~~embodiments~~, the unit dosage is disposed within a delivery device, e.g., a syringe (e.g., prefilled syringe),an implantable device, a needleness hypodermic injection device, an infusion pump (e.g., implantable infusion pump), or an osmotic delivery system.

In examples~~embodiments~~, the agonist is administered subcutaneously, e.g., by subcutaneous injection.

In examples~~embodiments~~, the agonist is administered daily over a period of at least 3 weeks, e.g., at least 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, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 weeks or more, or at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months or more, or at least 1, 2, 3, 4 years or more.

In examples~~embodiments~~, the subject is obese, e.g., severely obese.

In examples~~embodiments~~, the subject has early onset severe obesity.

In examples~~embodiments~~, the subject is hyperphagic.

In examples~~embodiments~~, the subject has a body mass index (BMI) greater than 25 kg/m^2 (e.g., ≥25, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 kg/m^2 or greater) prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.

In examples~~embodiments~~, the subject has a body mass index (BMI) greater than 35 kg/m^2 (e.g., ≥36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 kg/m^2 or greater) prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.

In examples~~embodiments~~, the subject has a body mass index (BMI) greater than 40 kg/m^2 (e.g., ≥41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55 kg/m^2 or greater) prior to

administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.

In examples~~embodiments~~, the subject has a body mass index (BMI) greater than 45 kg/m^2 (e.g., ≥46, 47, 48, 49, 50, 51, 52, 53, 54, 55 kg/m^2 or greater) prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.

In examples~~embodiments~~, the subject has a BMI higher than the 85-95th percentile prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.

In examples~~embodiments~~, the subject has failed one or more previous therapies, e.g., exercise, diet, or behavioral therapies, prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.

In examples~~embodiments~~, the subject has a lower body weight after administration of the agonist than before administration of the agonist.

In examples~~embodiments~~, administration of the agonist results in a reduction of weight in the subject compared to the weight of the subject before treatment of about 1 kg to 3 kg after 1 week of treatment, or about 1 kg to 6 kg after 2 weeks of treatment, or about 2 kg to 12 kg after 4 weeks of treatment, or about 4 kg to 24 kg after 8 weeks of treatment, or about 8 kg to 48 kg after 16 weeks of treatment.

In examples~~embodiments~~, administration of the agonist results in weight loss in the subject at a rate of about 1-2 kg/week, e.g., about 2 kg/week, e.g., over a period of 1-2 weeks of treatment or longer, 2-4 weeks of treatment or longer, 4-8 weeks of treatment or longer, 8-16 weeks of treatment or longer, 16-32 weeks or longer, or 32-64 weeks or longer.

In examples~~embodiments~~, administration of the agonist results in a reduction in hunger level (e.g., a lower score on the Likert hunger scale, e.g., a lower score by at least 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 points) in the subject compared to the hunger level of the subject before treatment, e.g., results in abolishment of hunger (e.g., a score of 0 on the Likert hunger scale) in the subject, e.g., after 1-2 weeks of treatment or longer, 2-4 weeks of treatment or longer, 4-8 weeks of treatment or longer, or 8-16 weeks of treatment or longer.

In examplesembodiments, administration of the agonist results in no detectable/significant decrease in resting energy expenditure (REE) in the subject, e.g., over a period of 24 hours, one week, or 30 days or longer, e.g., as compared to a control REE (e.g., the REE in the subject prior to treatment or a predetermined REE, e.g., in subjects of similar pre-treatment BMI, e.g., when expressed as REE per kg of lean body mass).

In examplesembodiments, administration of the agonist results in an increase in resting energy expenditure (REE) in the subject, e.g., over a period of 24 hours, one week, or 30 days, or longer e.g., as compared to a control REE (e.g., the REE in the subject prior to treatment or compared to a predetermined REE, e.g., in subjects of similar pre-treatment BMI, when expressed as REE per kg of lean body mass, e.g., after a similar level of weight loss has been attained by fasting).

In examplesembodiments, administration of the agonist results in a reduction in food intake by the subject compared to a control (e.g., the food intake of the subject prior to treatment), e.g., wherein the food intake is daily food intake or food intake over a period of 24 hours, or one week.

In examplesembodiments, administration of the agonist results in a reduction in food intake of at least 100 kilocalories, e.g., at least 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 525, 550, 575, 600, 1000 kilocalories or more, compared to a control (e.g., the food intake of the subject prior to treatment or a predetermined food intake level), e.g., wherein the food intake is daily food intake or food intake over a period of 24, hours, or one week.

In examplesembodiments, administration of the agonist results in a reduction in food intake of at least 5 kcal/kg/day, e.g., 5, 10, 20, 30, 40, 50, 60, 70, 80, or 90 or more kcal/kg/day. In examplesembodiments, the reduction in food intake is relative to the food intake at baseline. In examplesembodiments, the baseline food intake is at least 100 kcal/kg/day, e.g., for a pediatric subject at about 1 year of age. In examplesembodiments, the baseline food intake is at least 40 kcal/kg/day, e.g., for a pediatric subject, e.g., in late adolescence.

In examplesembodiments, administration of the agonist results in a reduction in waist circumference of the subject compared to a control (e.g., the waist circumference of the

subject prior to treatment), as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.

In examples~~embodiments~~, administration of the agonist results in a reduction in waist circumference of at least 2 cm (e.g., at least 2, 3, 4, 5, 6, 7, 8, 9, 10 cm or more) in the subject compared to a control (e.g., the waist circumference of the subject prior to treatment), as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.

In examples~~embodiments~~, administration of the agonist results in no detectable increase in blood pressure (e.g., diastolic and/or systolic blood pressure) of the subject compared to the blood pressure of the subject prior to treatment, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.

In examples~~embodiments~~, administration of the agonist results in a reduction in blood pressure (e.g., diastolic and/or systolic blood pressure) of the subject compared to the blood pressure of the subject prior to treatment, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.

In examples~~embodiments~~, administration of the agonist results in a reduction in systolic blood of the subject of at least 3 mmHg (e.g., at least 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7 mmHg or more) compared to the blood pressure of the subject prior to treatment, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.

In examples~~embodiments~~, administration of the agonist results in a reduction in diastolic blood pressure of the subject of at least 4 mmHg (e.g., at least 4, 7, 7.5, 8, 8.5, 9, 9.5, 10 mmHg or more) compared to the blood pressure of the subject prior to treatment, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.

In examples~~embodiments~~, the subject is a mammal, e.g., a human.

In examples~~embodiments~~, the agonist is Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 (SEQ ID NO: 140).

In examples~~embodiments~~, the method comprises acquiring knowledge of the genotype of the subject, e.g., acquiring knowledge of the genotype of, e.g., of a mutation in:

the POMC gene;

the PCSK1 gene;

the MAGEL2 gene;

the leptin receptor gene;

the leptin gene;

the 5-HT2c receptor gene;

the nescient helix loop helix 2 (NhHL2) gene;

the pro-hormone convertase gene;

the carboxypeptidase E (CPE) gene;

the single-minded 1 (SIM1) gene; or

a POMC-MC4R pathway gene.

In examples~~embodiments~~, the agonist is administered in response to the detection of a predetermined sequence, e.g., a mutation, in a gene described herein.

In examples~~embodiments~~, the method comprises acquiring knowledge of the state of methylation of the POMC gene (e.g., hypermethylated at a POMC intron, e.g., at a CpG island of the POMC gene, e.g., comprising a methylated cytosine, e.g., a 5'methyl cytosine).

In examples~~embodiments~~, the agonist is administered in response to the detection of hypermethylation.

In examples~~embodiments~~, the knowledge is acquired directly, e.g., from a sample (e.g., a blood, serum, urine, or tissue (e.g., biopsy) sample) from the subject.

In examples~~embodiments~~, the predetermined sequence, e.g., mutation, is detected in a nucleic acid by a method chosen from one or more of: a nucleic acid hybridization assay, an amplification-based assay, a PCR-RFLP assay, real-time PCR, sequencing, screening analysis, FISH, spectral karyotyping or MFISH, comparative genomic hybridization, *in situ* hybridization, SSP, HPLC or mass-spectrometric genotyping.

In examples~~embodiments~~, the predetermined sequence, e.g., mutation, is detected in the subject.

In examples~~embodiments~~, the predetermined sequence, e.g., mutation, is detected in a nucleic acid molecule or a polypeptide in a sample from the subject.

In examples~~embodiments~~, the state of methylation, e.g., hypermethylation, e.g., methylated cytosine, is detected by a method chosen from one or more of: mass spectrometry, methylation-

specific PCR, sequencing of bisulfite treated DNA, HpaII tiny fragment Enrichment by Ligation-mediated PCR Assay, ChIP-on-chip assay, restriction landmark genomic scanning, methylated DNA immunoprecipitation, molecular break light assay for DNA adenine methyltransferase activity, methyl sensitive Southern blotting, or high resolution melt analysis.

In examples~~embodiments~~, the hypermethylation, e.g., methylated cytosine, is detected in the subject.

In examples~~embodiments~~, the hypermethylation, e.g., methylated cytosine, is detected in a nucleic acid molecule in a sample from the subject.

In examples~~embodiments~~, the sample comprises cells from a blood, serum, urine, or tissue (e.g., biopsy) from the subject.

In examples~~embodiments~~, the knowledge is acquired from another party, e.g., wherein the party is the subject, a caregiver, a physician, an endocrinologist, a hospital, clinic, third-party payor, insurance company or government office.

In examples~~embodiments~~, the detection of the predetermined sequence arises from a collaboration with another party.

In examples~~embodiments~~, the method comprises:

responsive to a determination of the presence or absence of (a) the predetermined sequence, e.g., mutation, and/or (b) hypermethylation in the subject, one or more of:

(1) identifying or selecting the subject as having Prader Willi Syndrome (PWS);

(2) identifying or selecting the subject as having a disorder characterized by one or more mutations in the POMC gene, e.g., POMC deficiency;

(3) identifying or selecting the subject as having a disorder characterized by one or more mutations in the PCSK1 gene, e.g., PCSK1 deficiency;

(4) identifying or selecting the subject as having a disorder characterized by one or more mutations in the MAGEL2 gene, e.g., MAGEL2 deficiency;

(5) identifying or selecting the subject as having a disorder characterized by one or more mutations in the leptin receptor gene, e.g., leptin receptor deficiency;

(6) identifying or selecting the subject as having a disorder characterized by one or more mutations in the leptin gene, e.g., leptin deficiency;

(7) identifying or selecting the subject as having a disorder characterized by one or more mutations in the 5-HT2c receptor gene, e.g., 5-HT2c receptor deficiency;

(8) identifying or selecting the subject as having a disorder characterized by one or more mutations in the NhHL2 gene, e.g., NhHL2 deficiency;

(9) identifying or selecting the subject as having a disorder characterized by one or more mutations in the pro-hormone convertase gene, e.g., pro-hormone convertase deficiency;

(10) identifying or selecting the subject as having a disorder characterized by one or more mutations in the CPE gene, e.g., CPE deficiency;

(11) identifying or selecting the subject as having a disorder characterized by one or more mutations in the SIM1 gene, e.g., SIM1 deficiency;

(12) identifying or selecting the subject as having a disorder characterized by a hypermethylated POMC gene, e.g., POMC deficiency;

(13) identifying or selecting the subject has having a disorder characterized by one or more mutations in a POMC-MC4R pathway gene, e.g., POMC-MC4R pathway deficiency; and/or

(14) identifying or selecting the subject as likely or unlikely to respond to the agonist.

In examples~~embodiments~~, the presence of the predetermined sequence, e.g., mutation (e.g., mutation in MAGEL2 and/or mutation in the paternal allele of the 15q11-q13 region of chromosome 15) is detected in the subject, and responsive to that determination, the method comprises identifying the subject as having Prader Willi Syndrome (PWS).

In examples~~embodiments~~, the presence of the predetermined sequence, e.g., mutation (e.g., mutation in the POMC gene) is detected in the subject, and responsive to that determination, the method comprises identifying the subject as having a disorder characterized by one or more mutations in the POMC gene, e.g., POMC deficiency.

In examples~~embodiments~~, the presence of the predetermined sequence, e.g., mutation (e.g., mutation in the PCSK1 gene) is detected in the subject, and responsive to that determination, the method comprises identifying the subject as having a disorder characterized by one or more mutations in the PCSK1 gene, e.g., PCSK1 deficiency.

In examplesembodiments, the presence of the predetermined sequence, e.g., mutation (e.g., mutation in the leptin receptor gene) is detected in the subject, and responsive to that determination, the method comprises identifying the subject as having a disorder characterized by one or more mutations in the leptin receptor gene, e.g., leptin receptor deficiency.

In examplesembodiments, the presence of the predetermined sequence, e.g., mutation (e.g., mutation in the leptin gene) is detected in the subject, and responsive to that determination, the method comprises identifying the subject as having a disorder characterized by one or more mutations in the leptin gene, e.g., leptin deficiency.

In examplesembodiments, the presence of the predetermined sequence, e.g., mutation (e.g., mutation in the 5-HT2c receptor gene) is detected in the subject, and responsive to that determination, the method comprises identifying the subject as having a disorder characterized by one or more mutations in the 5-HT2c receptor gene, e.g., 5-HT2c receptor deficiency.

In examplesembodiments, the presence of the predetermined sequence, e.g., mutation (e.g., mutation in the NhHL2 gene) is detected in the subject, and responsive to that determination, the method comprises identifying the subject as having a disorder characterized by one or more mutations in the NhHL2 gene, e.g., NhHL2 deficiency.

In examplesembodiments, the presence of the predetermined sequence, e.g., mutation (e.g., mutation in the pro-hormone convertase gene) is detected in the subject, and responsive to that determination, the method comprises identifying the subject as having a disorder characterized by one or more mutations in the pro-hormone convertase gene, e.g., pro-hormone convertase deficiency.

In examplesembodiments, the presence of the predetermined sequence, e.g., mutation (e.g., mutation in the CPE gene) is detected in the subject, and responsive to that determination, the method comprises identifying the subject as having a disorder characterized by one or more mutations in the CPE gene, e.g., CPE deficiency.

In examplesembodiments, the presence of the predetermined sequence, e.g., mutation (e.g., mutation in the SIM1 gene) is detected in the subject, and responsive to that determination, the method comprises identifying the subject as having a disorder characterized by one or more mutations in the SIM1 gene, e.g., SIM1 deficiency.

In examplesembodiments, the presence of the predetermined sequence, e.g., mutation (e.g., mutation in a gene described herein) is detected in the subject, and responsive to that determination, the method comprises identifying the subject as having a disorder characterized by one or more mutations in a POMC-MC4R pathway gene, e.g., POMC-MC4R pathway deficiency.

In examplesembodiments, the presence of the hypermethylation in the POMC gene is detected in the subject, and responsive to that determination, the method comprises identifying the subject as having a disorder characterized by a hypermethylated POMC gene, e.g., POMC deficiency.

In examplesembodiments, the presence of the predetermined sequence, e.g., mutation, or the hypermethylation, is detected in the subject, and responsive to that determination, the method comprises identifying the subject as likely to respond to the agonist.

In examplesembodiments, the subject has or is identified as having PWS or a disorder characterized by one or more mutations in the POMC, PCSK1, MAGEL2, leptin receptor, leptin, 5-HT2c receptor, NhHL2, pro-hormone convertase, CPE, SIM1, or other POMC-MC4R pathway gene, e.g., POMC-MC4R pathway deficiency.

In an exampleaspect, provided herein is a method of treating a disorder chosen from:

(i) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the PCSK1 gene;

(ii) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the MAGEL2 gene;

(iii) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the leptin receptor gene;

(iv) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the 5-HT2c receptor gene;

(v) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the nescient helix loop helix 2 (NhHL2) gene;

(vi) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the carboxypeptidase E (CPE) gene;

(vii) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the single-minded 1 (SIM1) gene;

A^8 is Gly, D-Ala, Acc, Ala, 13-Ala, Gaba, Apn, Ahx, Aha, HN-$(CH_2)_s$-C(O), or deleted;

A^9 is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Dab, Dap, Orn, or Lys;

A^{10} is Acc, HN-$(CH_2)_t$-C(O), L- or D-amino acid, or deleted;

R^1 is OH or NH_2;

each of R^2 and R^3 is, independently for each occurrence, selected from the group consisting of H, (C_1-C_{30})alkyl, (C_1-C_{30})heteroalkyl, (C_1-C_{30})acyl, (C_2-C_{30})alkenyl, (C_2-C_{30})alkynyl, aryl(C_1-C_{30})alkyl, aryl(C_1-C_{30})acyl, substituted (C_1-C_{30})alkyl, substituted (C_1-C_{30})heteroalkyl, substituted (C_1-C_{30})acyl, substituted (C_2-C_{30})alkenyl, substituted (C_2-C_{30})alkynyl, substituted aryl(C_1-C_{30})alkyl, and substituted aryl(C_1-C_{30})acyl;

each of R^4 and R^5 is, independently for each occurrence, H, (C_1-C_{40})alkyl, (C_1-C_{40})heteroalkyl, (C_1-C_{40})acyl, (C_2-C_{40})alkenyl, (C_2-C_{40})alkynyl, aryl(C_1-C_{40})alkyl, aryl(C_1-C_{40})acyl, substituted (C_1-C_{40})alkyl, substituted (C_1-C_{40})heteroalkyl, substituted (C_1-C_{40})acyl, substituted (C_2-C_{40})alkenyl, substituted (C_2-C_{40})alkynyl, substituted aryl(C_1-C_{40})alkyl, substituted aryl(C_1-C_{40})acyl, (C_1-C_{40})alkylsulfonyl, or -C(NH)-NH_2;

m is, independently for each occurrence, 1, 2, 3, 4, 5, 6 or 7;

n is, independently for each occurrence, 1, 2, 3, 4 or 5;

s is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

t is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

X′, X^2, X^3, X^4, and X^8 each is, independently for each occurrence, H, F, Cl, Br, I, ($C_{1\text{-}10}$)alkyl, substituted ($C_{1\text{-}10}$)alkyl, ($C_{2\text{-}10}$)alkenyl, substituted ($C_{2\text{-}10}$)alkenyl, ($C_{2\text{-}10}$)alkynyl, substituted ($C_{2\text{-}10}$)alkynyl, aryl, substituted aryl, OH, NH_2, NO_2, or CN.

In examples~~embodiments~~, the disorder is characterized by a homozygous POMC mutation (e.g., loss of mutation), e.g., characterized by a POMC null genotype.

In examples~~embodiments~~, the disorder is characterized by a compound heterozygous POMC mutation (e.g., characterized by the presence of two non-functional alleles) e.g., characterized by a POMC null genotype.

In examples~~embodiments~~, the mutations are mutations described herein, e.g., p.Lys51Term g.A6851>T and p.Arg145ProfsX12 g.7134delG.

In examples~~embodiments~~, the disorder is characterized by one or more mutations (e.g., loss of function mutations) in the PCSK1 gene.

In examplesembodiments, the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional PCSK1 allele and one non-functional PCSK1 allele.

In examplesembodiments, the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two non-functional PCSK1 alleles, e.g., having a PCSK1 null genotype.

In examplesembodiments, the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a PCSK1 null genotype.

In examplesembodiments, the disorder is characterized by one or mutations (e.g., loss of function mutations) in the MAGEL2 gene.

In examplesembodiments, the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional MAGEL2 allele and one non-functional MAGEL2 allele.

In examplesembodiments, the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two non-functional MAGEL2 alleles, e.g., having a MAGEL2 null genotype.

In examplesembodiments, the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a MAGEL2 null genotype.

In examplesembodiments, the disorder is characterized by one or mutations (e.g., loss of function mutations) in the leptin receptor gene.

In examplesembodiments, the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional leptin receptor allele and one non-functional leptin receptor allele.

In examplesembodiments, the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two non-functional leptin receptor alleles, e.g., having a leptin receptor null genotype.

In examplesembodiments, the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a leptin receptor null genotype.

In examplesembodiments, the disorder is characterized by a homozygous leptin mutation (e.g., loss of mutation), e.g., characterized by a leptin null genotype.

In examplesembodiments, the disorder is characterized by a compound heterozygous leptin mutation (e.g., characterized by the presence of two non-functional alleles) e.g., characterized by a leptin null genotype.

In examplesembodiments, the disorder is characterized by one or mutations (e.g., loss of function mutations) in the 5-HT2c receptor gene.

In examplesembodiments, the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional 5-HT2c receptor allele and one non-functional 5-HT2c receptor allele.

In examplesembodiments, the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two non-functional 5-HT2c receptor alleles, e.g., having a 5-HT2c receptor null genotype.

In examplesembodiments, the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a 5-HT2c receptor null genotype.

In examplesembodiments, the disorder is characterized by one or mutations (e.g., loss of function mutations) in the nescient helix loop helix 2 (NhHL2) gene.

In examplesembodiments, the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional NhHL2 allele and one non-functional NhHL2 receptor allele.

In examplesembodiments, the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two non-functional NhHL2 alleles, e.g., having a NhHL2 null genotype.

In examplesembodiments, the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a NhHL2 null genotype.

In examplesembodiments, the disorder is characterized by one or mutations (e.g., loss of function mutations) in the carboxypeptidase E (CPE) gene.

In examplesembodiments, the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional CPE allele and one non-functional CPE allele.

In examples~~embodiments~~, the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two non-functional CPE alleles, e.g., having a CPE null genotype.

In examples~~embodiments~~, the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a CPE null genotype.

In examples~~embodiments~~, the disorder is characterized by one or mutations (e.g., loss of function mutations) in the single-minded 1 (SIM1) gene.

In examples~~embodiments~~, the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional SIM1 allele and one non-functional SIM1 allele.

In examples~~embodiments~~, the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two non-functional SIM1 alleles, e.g., having a SIM1 null genotype.

In examples~~embodiments~~, the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a SIM1 null genotype.

In examples~~embodiments~~, the disorder is characterized by a hypermethylated POMC gene (e.g., hypermethylated at a POMC intron, e.g., at a CpG island of the POMC gene, e.g., comprising a methylated cytosine, e.g., a 5'methyl cytosine).

In examples~~embodiments~~, the subject has or is identified as having a hypermethylated CpG island in the POMC gene, e.g., at the intron2-exon3 boundary of the POMC gene.

In examples~~embodiments~~, the disorder is characterized by a defect in the POMC-MC4R pathway other than a POMC mutation, e.g., a heterozygous POMC mutation characterized by the presence of one functional POMC allele and one non-functional POMC allele.

In examples~~embodiments~~, the disorder is characterized by a defect in the POMC-MC4R pathway other than a leptin mutation, e.g, a heterozygous leptin mutation characterized by the presence of one functional leptin allele and one non-functional leptin allele.

In examples~~embodiments~~, the disorder is characterized by a defect in the POMC-MC4R pathway other than a MC4R mutation, e.g., a heterozygous melanocortin-4 receptor (MC4R) mutation characterized by the presence of one functional MC4R allele and one non-functional MC4R allele.

In examples~~embodiments~~, the disorder is characterized by a defect in the POMC-MC4R pathway other than a pro-hormone convertase mutation.

In examples~~embodiments~~, the method comprises administering the agonist in a unit dosage suitable for injection, e.g., subcutaneous injection, to the subject.

In examples~~embodiments~~, the unit dosage comprises about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, or 2 mg of the agonist.

In examples~~embodiments~~, the unit dosage is disposed within a delivery device, e.g., a syringe (e.g., prefilled syringe),an implantable device, a needleness hypodermic injection device, an infusion pump (e.g., implantable infusion pump), or an osmotic delivery system.

In examples~~embodiments~~, the agonist is administered subcutaneously, e.g., by subcutaneous injection.

In examples~~embodiments~~, the agonist is administered daily over a period of at least 3 weeks, e.g., at least 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, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 weeks or more, or at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months or more, or at least 1, 2, 3, 4 years or more.

In examples~~embodiments~~, the subject is obese, e.g., severely obese.

In examples~~embodiments~~, the subject has early onset severe obesity.

In examples~~embodiments~~, the subject is hyperphagic.

In examples~~embodiments~~, the subject has a body mass index (BMI) greater than 25 kg/m^2 (e.g., ≥25, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 kg/m^2 or greater) prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.

In examples~~embodiments~~, the subject has a body mass index (BMI) greater than 35 kg/m^2 (e.g., ≥36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 kg/m^2 or greater) prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.

In examples~~embodiments~~, the subject has a body mass index (BMI) greater than 40 kg/m^2 (e.g., ≥41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55 kg/m^2 or greater) prior to

administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.

In examples~~embodiments~~, the subject has a body mass index (BMI) greater than 45 kg/m^2 (e.g., ≥46, 47, 48, 49, 50, 51, 52, 53, 54, 55 kg/m^2 or greater) prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.

In examples~~embodiments~~, the subject has a BMI higher than the 85-95th percentile prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.

In examples~~embodiments~~, the subject has failed one or more previous therapies, e.g., exercise, diet, or behavioral therapies, prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.

In examples~~embodiments~~, the subject has a lower body weight after administration of the agonist than before administration of the agonist.

In examples~~embodiments~~, administration of the agonist results in a reduction of weight in the subject compared to the weight of the subject before treatment of about 1 kg to 3 kg after 1 week of treatment, or about 1 kg to 6 kg after 2 weeks of treatment, or about 2 kg to 12 kg after 4 weeks of treatment, or about 4 kg to 24 kg after 8 weeks of treatment, or about 8 kg to 48 kg after 16 weeks of treatment.

In examples~~embodiments~~, administration of the agonist results in weight loss in the subject at a rate of about 1-2 kg/week, e.g., about 2 kg/week, e.g., over a period of 1-2 weeks of treatment or longer, 2-4 weeks of treatment or longer, 4-8 weeks of treatment or longer, 8-16 weeks of treatment or longer, 16-32 weeks or longer, or 32-64 weeks or longer.

In examples~~embodiments~~, administration of the agonist results in a reduction in hunger level (e.g., a lower score on the Likert hunger scale, e.g., a lower score by at least 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 points) in the subject compared to the hunger level of the subject before treatment, e.g., results in abolishment of hunger (e.g., a score of 0 on the Likert hunger scale) in the subject, e.g., after 1-2 weeks of treatment or longer, 2-4 weeks of treatment or longer, 4-8 weeks of treatment or longer, or 8-16 weeks of treatment or longer.

In examplesembodiments, administration of the agonist results in no detectable/significant decrease in resting energy expenditure (REE) in the subject, e.g., over a period of 24 hours, one week, or 30 days or longer, e.g., as compared to a control REE (e.g., the REE in the subject prior to treatment or a predetermined REE, e.g., in subjects of similar pre-treatment BMI, e.g., when expressed as REE per kg of lean body mass).

In examplesembodiments, administration of the agonist results in an increase in resting energy expenditure (REE) in the subject, e.g., over a period of 24 hours, one week, or 30 days, or longer e.g., as compared to a control REE (e.g., the REE in the subject prior to treatment or compared to a predetermined REE, e.g., in subjects of similar pre-treatment BMI, when expressed as REE per kg of lean body mass, e.g., after a similar level of weight loss has been attained by fasting).

In examplesembodiments, administration of the agonist results in a reduction in food intake by the subject compared to a control (e.g., the food intake of the subject prior to treatment), e.g., wherein the food intake is daily food intake or food intake over a period of 24 hours, or one week.

In examplesembodiments, administration of the agonist results in a reduction in food intake of at least 100 kilocalories, e.g., at least 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 525, 550, 575, 600, 1000 kilocalories or more, compared to a control (e.g., the food intake of the subject prior to treatment or a predetermined food intake level), e.g., wherein the food intake is daily food intake or food intake over a period of 24, hours, or one week.

In examplesembodiments, administration of the agonist results in a reduction in food intake of at least 5 kcal/kg/day, e.g., 5, 10, 20, 30, 40, 50, 60, 70, 80, or 90 or more kcal/kg/day. In examplesembodiments, the reduction in food intake is relative to the food intake at baseline. In examplesembodiments, the baseline food intake is at least 100 kcal/kg/day, e.g., for a pediatric subject at about 1 year of age. In examplesembodiments, the baseline food intake is at least 40 kcal/kg/day, e.g., for a pediatric subject, e.g., in late adolescence.

In examplesembodiments, administration of the agonist results in a reduction in waist circumference of the subject compared to a control (e.g., the waist circumference of the

subject prior to treatment), as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.

In examples~~embodiments~~, administration of the agonist results in a reduction in waist circumference of at least 2 cm (e.g., at least 2, 3, 4, 5, 6, 7, 8, 9, 10 cm or more) in the subject compared to a control (e.g., the waist circumference of the subject prior to treatment), as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.

In examples~~embodiments~~, administration of the agonist results in no detectable increase in blood pressure (e.g., diastolic and/or systolic blood pressure) of the subject compared to the blood pressure of the subject prior to treatment, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.

In examples~~embodiments~~, administration of the agonist results in a reduction in blood pressure (e.g., diastolic and/or systolic blood pressure) of the subject compared to the blood pressure of the subject prior to treatment, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.

In examples~~embodiments~~, administration of the agonist results in a reduction in systolic blood of the subject of at least 3 mmHg (e.g., at least 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7 mmHg or more) compared to the blood pressure of the subject prior to treatment, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.

In examples~~embodiments~~, administration of the agonist results in a reduction in diastolic blood pressure of the subject of at least 4 mmHg (e.g., at least 4, 7, 7.5, 8, 8.5, 9, 9.5, 10 mmHg or more) compared to the blood pressure of the subject prior to treatment, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.

In examples~~embodiments~~, the subject is a mammal, e.g., a human.

In examples~~embodiments~~, the agonist is Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 (SEQ ID NO: 140).

In examples~~embodiments~~, the method comprises acquiring knowledge of the genotype of the subject, e.g., acquiring knowledge of the genotype of, e.g., of a mutation in:

the POMC gene;

the PCSK1 gene;

the MAGEL2 gene;

the leptin receptor gene;

the leptin gene;

the 5-HT2c receptor gene;

the nescient helix loop helix 2 (NhHL2) gene;

the carboxypeptidase E (CPE) gene; or

the single-minded 1 (SIM1) gene.

In examples~~embodiments~~, the agonist is administered in response to the detection of a predetermined sequence, e.g., a mutation, in a gene described herein.

In examples~~embodiments~~, the method comprises acquiring knowledge of the state of methylation of the POMC gene (e.g., hypermethylated at a POMC intron, e.g., at a CpG island of the POMC gene, e.g., comprising a methylated cytosine, e.g., a 5'methyl cytosine).

In examples~~embodiments~~, the agonist is administered in response to the detection of hypermethylation.

In examples~~embodiments~~, the knowledge is acquired directly, e.g., from a sample (e.g., a blood, serum, urine, or tissue (e.g., biopsy) sample) from the subject.

In examples~~embodiments~~, the predetermined sequence, e.g., mutation, is detected in a nucleic acid by a method chosen from one or more of: a nucleic acid hybridization assay, an amplification-based assay, a PCR-RFLP assay, real-time PCR, sequencing, screening analysis, FISH, spectral karyotyping or MFISH, comparative genomic hybridization, *in situ* hybridization, SSP, HPLC or mass-spectrometric genotyping.

In examples~~embodiments~~, the predetermined sequence, e.g., mutation, is detected in the subject.

In examples~~embodiments~~, the predetermined sequence, e.g., mutation, is detected in a nucleic acid molecule or a polypeptide in a sample from the subject.

In examples~~embodiments~~, the state of methylation, e.g., hypermethylation, e.g., methylated cytosine, is detected by a method chosen from one or more of: mass spectrometry, methylation-specific PCR, sequencing of bisulfite treated DNA, HpaII tiny fragment Enrichment by Ligation-mediated PCR Assay, ChIP-on-chip assay, restriction landmark genomic scanning,

methylated DNA immunoprecipitation, molecular break light assay for DNA adenine methyltransferase activity, methyl sensitive Southern blotting, or high resolution melt analysis.

In examples~~embodiments~~, the hypermethylation, e.g., methylated cytosine, is detected in the subject.

In examples~~embodiments~~, the hypermethylation, e.g., methylated cytosine, is detected in a nucleic acid molecule in a sample from the subject.

In examples~~embodiments~~, the sample comprises cells from a blood, serum, urine, or tissue (e.g., biopsy) from the subject.

In examples~~embodiments~~, the knowledge is acquired from another party, e.g., wherein the party is the subject, a caregiver, a physician, an endocrinologist, a hospital, clinic, third-party payor, insurance company or government office.

In examples~~embodiments~~, the detection of the predetermined sequence arises from a collaboration with another party.

In examples~~embodiments~~, the detection of the hypermethylation arises from a collaboration with another party.

In examples~~embodiments~~, the method comprises:

responsive to a determination of the presence or absence of (a) the predetermined sequence, e.g., mutation, and/or (b) hypermethylation in the subject, one or more of:

(1) identifying or selecting the subject as having a disorder characterized by one or more mutations in the PCSK1 gene, e.g., PCSK1 deficiency;

(2) identifying or selecting the subject as having a disorder characterized by one or more mutations in the MAGEL2 gene, e.g., MAGEL2 deficiency;

(3) identifying or selecting the subject as having a disorder characterized by one or more mutations in the leptin receptor gene, e.g., leptin receptor deficiency;

(4) identifying or selecting the subject as having a disorder characterized by one or more mutations in the 5-HT2c receptor gene, e.g., 5-HT2c receptor deficiency;

(5) identifying or selecting the subject as having a disorder characterized by one or more mutations in the NhHL2 gene, e.g., NhHL2 deficiency;

(6) identifying or selecting the subject as having a disorder characterized by one or more mutations in the CPE gene, e.g., CPE deficiency;

(7) identifying or selecting the subject as having a disorder characterized by one or more mutations in the SIM1 gene, e.g., SIM1 deficiency;

(8) identifying or selecting the subject as having a disorder characterized by a hypermethylated POMC gene, e.g., POMC deficiency;

(9) identifying or selecting the subject has having a disorder characterized by one or more mutations in a POMC-MC4R pathway gene, e.g., POMC-MC4R pathway deficiency;

(10) identifying or selecting the subject as having a disorder characterized by a defect in the POMC-MC4R pathway other than a POMC mutation;

(11) identifying or selecting the subject as having a disorder characterized by a defect in the POMC-MC4R pathway other than a leptin mutation;

(12) identifying or selecting the subject as having a disorder characterized by a defect in the POMC-MC4R pathway other than a MC4R mutation;

(13) identifying or selecting the subject as having a disorder characterized by a defect in the POMC-MC4R pathway other than a prohormone convertase mutation;

(14) identifying or selecting the subject as having a disorder characterized by a homozygous POMC mutation;

(15) identifying or selecting the subject as having a disorder characterized by a compound heterozygous POMC mutation;

(16) identifying or selecting the subject as having a disorder characterized by a homozygous leptin mutation;

(17) identifying or selecting the subject as having a disorder characterized by a compound heterozygous leptin mutation; and/or

(18) identifying or selecting the subject as likely or unlikely to respond to the agonist.

In examples~~embodiments~~, the presence of the predetermined sequence, e.g., mutation (e.g., mutation in MAGEL2) is detected in the subject, and responsive to that determination, the method comprises identifying the subject as having Prader Willi Syndrome (PWS).

In examplesembodiments, the presence of the predetermined sequence, e.g., mutation (e.g., mutation in the PCSK1 gene) is detected in the subject, and responsive to that determination, the method comprises identifying the subject as having a disorder characterized by one or more mutations in the PCSK1 gene, e.g., PCSK1 deficiency.

In examplesembodiments, the presence of the predetermined sequence, e.g., mutation (e.g., mutation in the leptin receptor gene) is detected in the subject, and responsive to that determination, the method comprises identifying the subject as having a disorder characterized by one or more mutations in the leptin receptor gene, e.g., leptin receptor deficiency.

In examplesembodiments, the presence of the predetermined sequence, e.g., mutation (e.g., mutation in the 5-HT2c receptor gene) is detected in the subject, and responsive to that determination, the method comprises identifying the subject as having a disorder characterized by one or more mutations in the 5-HT2c receptor gene, e.g., 5-HT2c receptor deficiency.

In examplesembodiments, the presence of the predetermined sequence, e.g., mutation (e.g., mutation in the NhHL2 gene) is detected in the subject, and responsive to that determination, the method comprises identifying the subject as having a disorder characterized by one or more mutations in the NhHL2 gene, e.g., NhHL2 deficiency.

In examplesembodiments, the presence of the predetermined sequence, e.g., mutation (e.g., mutation in the CPE gene) is detected in the subject, and responsive to that determination, the method comprises identifying the subject as having a disorder characterized by one or more mutations in the CPE gene, e.g., CPE deficiency.

In examplesembodiments, the presence of the predetermined sequence, e.g., mutation (e.g., mutation in the SIM1 gene) is detected in the subject, and responsive to that determination, the method comprises identifying the subject as having a disorder characterized by one or more mutations in the SIM1 gene, e.g., SIM1 deficiency.

In examplesembodiments, the presence of the predetermined sequence, e.g., mutation (e.g., mutation in a gene described herein) is detected in the subject, and responsive to that determination, the method comprises identifying the subject as having a disorder characterized by one or more mutations in a POMC-MC4R pathway gene, e.g., POMC-MC4R pathway deficiency.

In examplesembodiments, the presence of the hypermethylation in the POMC gene is detected in the subject, and responsive to that determination, the method comprises identifying the subject as having a disorder characterized by a hypermethylated POMC gene, e.g., POMC deficiency.

In examplesembodiments, the presence of the predetermined sequence, e.g., mutation (e.g., homozygous POMC mutation) is detected in the subject, and responsive to that determination, the method comprises identifying the subject as having a disorder characterized by a homozygous POMC mutation, e.g., POMC deficiency.

In examplesembodiments, the presence of the predetermined sequence, e.g., mutation (e.g., compound heterozygous POMC mutation) is detected in the subject, and responsive to that determination, the method comprises identifying the subject as having a disorder characterized by a compound heterozygous POMC mutation, e.g., POMC deficiency.

In examplesembodiments, the presence of the predetermined sequence, e.g., mutation (e.g., homozygous leptin mutation) is detected in the subject, and responsive to that determination, the method comprises identifying the subject as having a disorder characterized by a homozygous leptin mutation, e.g., leptin deficiency.

In examplesembodiments, the presence of the predetermined sequence, e.g., mutation (e.g., compound heterozygous leptin mutation) is detected in the subject, and responsive to that determination, the method comprises identifying the subject as having a disorder characterized by a compound heterozygous leptin mutation, e.g., leptin deficiency.

In examplesembodiments, the presence of the predetermined sequence, e.g., mutation, or the hypermethylation, is detected in the subject, and responsive to that determination, the method comprises identifying the subject as likely to respond to the agonist.

In examplesembodiments, the subject has or is identified as having a disorder characterized by one or more mutations in the PCSK1, MAGEL2, leptin receptor, 5-HT2c receptor, NhHL2, pro-hormone convertase, CPE, SIM1, or other POMC-MC4R pathway gene, e.g., POMC-MC4R pathway deficiency.

In examplesembodiments, the subject has or is identified as having a disorder characterized by a homozygous or compound heterozygous mutation in one or more of the POMC or leptin gene, e.g., POMC deficiency or leptin deficiency.

In as exampleaspect, provided herein is a unit dosage of an agonist described herein, wherein the unit dosage contains 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, or 2 mg of the agonist.

In examplesembodiments, the unit dosage contains 0.5 mg of agonist.

In examplesembodiments, the unit dosage contains 1.0 mg of agonist.

In examplesembodiments, the unit dosage contains 1.5 mg of agonist.

In examplesembodiments, the unit dosage is suitable for injection, e.g., subcutaneous injection.

In examplesembodiments, the unit dosage is disposed in a delivery device suitable for injection, e.g., subcutaneous injection.

In examplesembodiments, the unit dosage is disposed in a syringe or pen-type injector suitable for injection, e.g., subcutaneous injection.

In examplesembodiments, the agonist is Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 (SEQ ID NO: 140).

In an exampleaspect, provided herein is a method of evaluating a subject, comprising:

acquiring information that identifies the subject as having or not having a predetermined sequence, e.g., mutation, in the 15q11-q13 region of chromosome 15 or in the MAGEL2 gene,

wherein identification of the subject as having the mutation identifies the patient as more likely to have improved symptoms following treatment with a MC4R agonist (e.g., a MC4R agonist described herein), and identification of the subject as not having a mutation in the 15q11-q13 region of chromosome 15 or in the MAGEL2 gene identifies the patient as being less likely to have improved symptoms following treatment with a MC4R agonist, e.g., a MC4R agonist described herein.

In another exampleaspect, provided herein is a method of evaluating a subject, comprising:

acquiring information that identifies the subject as having or not having a predetermined sequence, e.g., mutation, in one or more of:

the POMC gene;

the PCSK1 gene;

the MAGEL2 gene;

the leptin receptor gene;

the leptin gene;

the 5-HT2c receptor gene;

the nescient helix loop helix 2 (NhHL2) gene;

the carboxypeptidase E (CPE) gene; or

the single-minded 1 (SIM1) gene;

wherein identification of the subject as having the predetermined sequence, e.g., mutation, identifies the patient as more likely to have improved symptoms following treatment with a MC4R agonist (e.g., a MC4R agonist described herein), and identification of the subject as not having the predetermined sequence, e.g., mutation, identifies the patient as being less likely to have improved symptoms following treatment with a MC4R agonist, e.g., a MC4R agonist described herein.

In accordance with any method described herein, in examples~~embodiments~~, the improved symptoms comprise one or more of:

(a) a decrease in body weight;

(b) a decrease in waist circumference;

(c) a decrease in hunger level;

(d) a decrease in food intake level; and/or

(e) a lack of decrease or an increase in resting energy expenditure.

In examples~~embodiments~~, the mutation is a loss of function mutation.

In examples~~embodiments~~, the mutation is a homozygous mutation, e.g., homozygous loss of function mutation.

In examples~~embodiments~~, the mutation is a heterozygous mutation.

In examples~~embodiments~~, the heterozygous mutation is a compound heterozygous mutation (e.g., characterized by the presence of two non-functional alleles).

In examples~~embodiments~~, the heterozygous mutation is characterized by the presence of one functional allele and one non-functional allele.

In examples~~embodiments~~, the method further comprises providing a report to another party, e.g., wherein the party is the subject, a caregiver, a physician, an oncologist, a hospital, clinic, third-party payor, insurance company or government office.

In examplesembodiments, said report is in electronic, web-based, or paper form.

In examplesembodiments, the report identifies the presence or absence of the mutation in the subject, and optionally includes an identifier for the subject from which the information was obtained.

In examplesembodiments, the report comprises:

information on the genotype (e.g., presence or absence of the predetermined sequence, e.g., mutation) of the subject;

information on prognosis or suggested therapeutic options, e.g., MC4R agonists;

information on the likely effectiveness of a therapeutic option, e.g., MC4R agonist, the acceptability of a therapeutic option, or the advisability of applying the therapeutic option to the subject; and/or

information, or a recommendation on, the administration of the therapeutic option (e.g., MC4R agonist).

In examplesembodiments, the agonist is Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 (SEQ ID NO: 140).

In an exampleaspect, provided herein is a method of selecting a subject having Prader Willi Syndrome (PWS), comprising:

acquiring knowledge of the genotype of the subject, e.g., acquiring knowledge of the genotype of the paternal allele of the 15q11-q13 region of chromosome 15 or of the MAGEL2 gene;

wherein the acquiring step comprises determining the presence or absence of a predetermined sequence, e.g., mutation in the paternal allele of the 15q11-q13 region of chromosome 15 or in the MAGEL2 gene; and

wherein the presence of the predetermined sequence, e.g., mutation, identifies the subject as having PWS.

In an exampleaspect, provided herein is a method of selecting a subject having a POMC-MC4R pathway deficiency, comprising:

(i) acquiring knowledge of the genotype of the subject, e.g., acquiring knowledge of the genotype of, e.g., of a mutation in:

the POMC gene;

the PCSK1 gene;

the MAGEL2 gene;

the leptin receptor gene;

the leptin gene;

the 5-HT2c receptor gene;

the nescient helix loop helix 2 (NhHL2) gene;

the carboxypeptidase E (CPE) gene; or

the single-minded 1 (SIM1) gene;

wherein the presence of the mutation identifies the subject as having a POMC-MC4R pathway deficiency; or

(ii) acquiring knowledge of the state of methylation of the POMC gene (e.g., hypermethylated at a POMC intron, e.g., at a CpG island of the POMC gene, e.g., comprising a methylated cytosine, e.g., a 5'methyl cytosine),

wherein the presence of the hypermethylation at the POMC intron identifies the subject as having a POMC-MC4R pathway deficiency.

In accordance with any method described herein, in examples~~embodiments~~, the method further comprises administering an agonist of the melanocortin-4 receptor (MC4R) to the subject, e.g., an agonist described herein, e.g., setmelanotide.

In examples~~embodiments~~, the mutation is a loss of function mutation.

In examples~~embodiments~~, the mutation is a homozygous mutation, e.g., homozygous loss of function mutation.

In examples~~embodiments~~, the mutation is a heterozygous mutation.

In examples~~embodiments~~, the heterozygous mutation is a compound heterozygous mutation (e.g., characterized by the presence of two distinct non-functional alleles).

In examples~~embodiments~~, the heterozygous mutation is characterized by the presence of one functional allele and one non-functional allele.

In examples~~embodiments~~, the agonist is Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 (SEQ ID NO: 140).

(xiii) a disorder characterized by a defect in the POMC-MC4R pathway other than:

(a) a heterozygous POMC mutation characterized by the presence of one functional POMC allele and one non-functional POMC allele,

(b) a heterozygous leptin mutation characterized by the presence of one functional leptin allele and one non-functional leptin allele,

(c) a melanocortin-4 receptor (MC4R) mutation (e.g., loss of function mutation), or

(d) a pro-hormone convertase mutation (e.g., loss of function mutation).

optionally wherein the agonist is administered at a daily dosage of about 0.1 mg (e.g., 0.1 mg +/- 5%) to about 10 mg (e.g., 10 mg +/- 5%).

Additional examples~~embodiments~~ in accordance with any method described herein include those that follow.

In examples~~embodiments~~, the MC4R agonist is a compound of Formula I, wherein:

A^1 is A6c, Arg, D-Arg, Cha, D-Cha, hCha, Chg, D-Chg, Gaba, Ile, Leu, hLeu, Met, β-hMet, 2-Nal, D-2-Nal, Nip, Nle, Oic, Phe, D-Phe, hPhe, hPro, Val, or deleted;

A^2 is Asp, Cys, D-Cys, hCys, D-hCys, Glu, Pen, or D-Pen;

A^3 is D-Abu, Aib, Ala, β-Ala, D-Ala, D-Cha, Gaba, D-Glu, Gly, D-Ile, D-Leu, D-Tle, D-Val, or deleted;

A^4 is H is or 3-Pal;

A^5 is D-Bal, D-1-Nal, D-2-Nal, D-Phe, D-Trp, or D-(Et)Tyr;

A^6 is Arg, or hArg;

A^7 is Bal, Bip, 1-Nal, 2-Nal, Trp, D-Trp;

A^8 is A6c, D-Ala, Aha, Ahx, Ala, β-Ala, Apn, Gaba, Gly or deleted;

A^9 is Cys, D-Cys, hCys, D-hCys, Lys, Pen, or D-Pen;

A^{10} is Thr, or deleted,

wherein at least one of A^3 or A^8 is deleted, but not both, or pharmaceutically acceptable salts thereof.

In examples~~embodiments~~, the MC4R agonist is not an adrenocorticotropic hormone (ACTH).

In examples~~embodiments~~, the MC4R agonist is not melanotan-II (MT-II) (Ac-Nle-cyclo[Asp-His-D-Phe-Arg-Trp-Lys]-NH_2) (SEQ ID NO: 562).

In examplesembodiments, the MC4R agonist comprises 8 amino acids or more.

In examplesembodiments, the MC4R agonist is Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 (SEQ ID NO: 140) or a pharmaceutically acceptable salt thereof.

In examplesembodiments, the MC4R agonist is Hydantoin(C(O)-(Arg-Gly))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH_2 (SEQ ID NO: 500) or a pharmaceutically acceptable salt thereof.

In examplesembodiments, the MC4R agonist is a tripeptide D-Phe-Arg-Trp (SEQ ID NO: 560) or a pharmaceutical salt thereof.

In examplesembodiments, the MC4R agonist is a peptide that includes D-Phe-Arg-Trp (SEQ ID NO: 560) or a pharmaceutical salt thereof.

In examplesembodiments, the MC4R agonist is a peptide that includes an acetylated tripeptide Ac-D-Phe-Arg-Trp-NH_2 (SEQ ID NO: 561) or a pharmaceutical salt thereof.

In examplesembodiments, the MC4R agonist is c[Hydantoin(C(O)-(Glu-D-Ala))-His-D-Phe-Arg-Trp-Dap]-NH_2 (SEQ ID NO: 496) or a pharmaceutically acceptable salt thereof.

In examplesembodiments, the MC4R agonist is Hydantoin(C(O)-(Nle-Gly))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH_2 (SEQ ID NO: 501) or a pharmaceutically acceptable salt thereof.

In examplesembodiments, the MC4R agonist is Hydantoin(C(O)-(Gly-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2 SEQ ID NO: 506) or a pharmaceutically acceptable salt thereof.

In examplesembodiments, the MC4R agonist is Hydantoin(C(O)-(Ala-Gly))-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 (SEQ ID NO: 507) or a pharmaceutically acceptable salt thereof.

In examplesembodiments, the MC4R agonist is Hydantoin(C(O)-(D-Arg-Gly))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH_2 (SEQ ID NO: 515) or a pharmaceutically acceptable salt thereof.

In examplesembodiments, the MC4R agonist is Hydantoin(C(O)-(Gly-D-Arg))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH_2 (SEQ ID NO: 535) or a pharmaceutically acceptable salt thereof.

In examplesembodiments, the MC4R agonist is Hydantoin(C(O)-(Gly-Arg))-c(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH_2 (SEQ ID NO: 531) or a pharmaceutically acceptable salt thereof.

In examplesembodiments, the MC4R agonist is Ac-c(Cys-Glu-His-D-2-Nal-Arg-Trp-Ala-Cys)-$(Pro)_2$-Lys-Asp-NH_2 (SEQ ID NO: 468) or a pharmaceutically acceptable salt thereof.

In examplesembodiments, the MC4R agonist is Ac-c(Cys-Glu-His-D-2-Nal-Arg-1-Nal-Ala-Cys)-$(Pro)_2$-Lys-Asp-NH_2 (SEQ ID NO: 470) or a pharmaceutically acceptable salt thereof.

In examplesembodiments, the MC4R agonist is Ac-c(Cys-Glu-His-D-2-Nal-Arg-Bal-Ala-Cys)-$(Pro)_2$-Lys-Asp-NH_2 (SEQ ID NO: 471) or a pharmaceutically acceptable salt thereof.

In examplesembodiments, the MC4R agonist is Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-β-Ala-Cys)-$(Pro)_2$-Lys-Asp-NH_2 (SEQ ID NO: 472) or a pharmaceutically acceptable salt thereof.

In examplesembodiments, the MC4R agonist is Ac-c(Cys-Glu-His-D-2-Nal-Arg-2-Nal-Aib-Cys)-$(Pro)_2$-Lys-Asp-NH_2 (SEQ ID NO: 473) or a pharmaceutically acceptable salt thereof.

In examplesembodiments, the MC4R agonist is c[Hydantoin(C(O)-(Asp-Aic))-D-2-Nal-Arg-Trp-Lys]-NH_2 (SEQ ID NO: 492) or a pharmaceutically acceptable salt thereof.

In examplesembodiments, the MC4R agonist is c[Hydantoin(C(O)-(Asp-A6c))-D-2-Nal-Arg-Trp-Lys]-NH_2 (SEQ ID NO: 489) or a pharmaceutically acceptable salt thereof.

In examplesembodiments, the MC4R agonist is Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)- NH_2 (SEQ ID NO: 139) or a pharmaceutically acceptable salt thereof.

In examplesembodiments, the MC4R agonist is Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH2 (SEQ ID NO: 36) or a pharmaceutically acceptable salt thereof.

In examplesembodiments, the MC4R agonist is D-Phe-c(Cys-His-D-Phe-Arg-Bip-β-Ala-D-Cys)-Thr-NH2 (SEQ ID NO: 81) or a pharmaceutically acceptable salt thereof.

In examplesembodiments, the MC4R agonist is D-Phe-c(Cys-His-D-Phe-hArg-Bip-β-Ala-D-Cys)-Thr-NH2 (SEQ ID NO: 83) or a pharmaceutically acceptable salt thereof.

In examplesembodiments, the MC4R agonist is D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-NH2 (SEQ ID NO: 84) or a pharmaceutically acceptable salt thereof.

In examplesembodiments, the MC4R agonist is D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-NH2 (SEQ ID NO: 82) or a pharmaceutically acceptable salt thereof.

In examplesembodiments, the MC4R agonist is any MC4R agonist described in US 2014/0329743 A1, incorporated herein by reference.

In examplesembodiments, the MC4R agonist is any MC4R agonist described in WO2014/144260 A1, incorporated herein by reference.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this ~~invention~~ disclosure belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present ~~invention~~disclosure, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting. Headings, sub-

headings or numbered or lettered elements, e.g., (a), (b), (i) etc, are presented merely for ease of reading. The use of headings or numbered or lettered elements in this document does not require the steps or elements be performed in alphabetical order or that the steps or elements are necessarily discrete from one another. Other features, objects, and advantages of the ~~invention~~ disclosure will be apparent from the description and drawings, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

The following detailed description of preferred embodiments of the invention will be better understood when read in conjunction with the appended drawings. For the purpose of illustrating the invention, there are shown in the drawings embodiments which are presently preferred. It should be understood, however, that the invention is not limited to the precise arrangements and instrumentalities of the embodiments shown in the drawings.

FIGs. 1A and 1B are graphs that show the effects on cumulative food intake suppression following treatment with setmelanotide (RM-493 at 0.1 mg/kg (mpk)) versus vehicle in Magel2-null (Magel2) and wildtype (WT) mice. FIG. 1A is an enlarged version of the inset in FIG. 1B and shows cumulative food intake through 3 hours post-dosing. FIG. 1B shows cumulative food intake through overnight.

FIG. 2 is a set of graphs showing the change in body weight in wild-type obese humans after 2 or 4 weeks of treatment with setmelanotide.

FIGS.3A-D show food intake over time in wild-type and *db/db* mice administred vehicle or setmelanotide.

FIGS.3A and 3D are graphs that show food intake as a function of time in wild-type mice and *db/db* mice at varying concentrations of setmelanotide..

FIGS. 3E-and 3F are graphs that summarize the effects of food intake over time in wild-type (FIG. 3E) or *db/db* mice (FIG. 3F) administered vehicle or 0.0554 mpk, 0.137 mpk, , 0.344 mpk or 1.37 mpk setmelanotide.

CLAIMS

1. A method of treating Prader Willi Syndrome (PWS) in a subject in need thereof, comprising:

administering an agonist of the melanocortin-4 receptor (MC4R) at a daily dosage of about 0.1 mg (e.g., 0.1 mg +/- 5%) to about 10 mg (e.g., 10 mg +/- 5%),

wherein the agonist is a MC4R agonist described herein, e.g., the agonist is

(R^2R^3)-A^1-*c*(A^2-A^3-A^4-A^5-A^6-A^7-A^8-A^9)-A^{10}-R^1 (I),

wherein:

A^1 is Acc, HN-$(CH_2)_m$-C(O), L- or D-amino acid, or deleted;

A^2 is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Asp, or Glu;

A^3 is Gly, Ala, β-Ala, Gaba, Aib, D-amino acid, or deleted;

A^4 is H is, 2-Pal, 3-Pal, 4-Pal, Taz, 2-Thi, 3-Thi, or (X^1, X^2, X^3, X^4, X^5)Phe;

A^5 is D-Phe, D-1-Nal, D-2-Nal, D-Trp, D-Bal, D-(X^1, X^2, X^3, X^4, X^5)Phe, L-Phe or D-(Et)Tyr;

A^6 is Arg, hArg, Dab, Dap, Lys, Orn, or HN-CH((CH_2)$_n$-N(R^4R^5))-C(O);

A^7 is Trp, 1-Nal, 2-Nal, Bal, Bip, D-Trp, D-2-Nal, D-Bal or D-Bip;

A^8 is Gly, D-Ala, Acc, Ala, 13-Ala, Gaba, Apn, Ahx, Aha, HN-$(CH_2)_s$-C(O), or deleted;

A^9 is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Dab, Dap, Orn, or Lys;

A^{10} is Acc, HN-$(CH_2)_t$-C(O), L- or D-amino acid, or deleted;

R^1 is OH or NH_2;

each of R^2 and R^3 is, independently for each occurrence, selected from the group consisting of H, (C_1-C_{30})alkyl, (C_1-C_{30})heteroalkyl, (C_1-C_{30})acyl, (C_2-C_{30})alkenyl, (C_2-C_{30})alkynyl, aryl(C_1-C_{30})alkyl, aryl(C_1-C_{30})acyl, substituted (C_1-C_{30})alkyl, substituted (C_1-C_{30})heteroalkyl, substituted (C_1-C_{30})acyl, substituted (C_2-C_{30})alkenyl, substituted (C_2-C_{30})alkynyl, substituted aryl(C_1-C_{30})alkyl, and substituted aryl(C_1-C_{30})acyl;

each of R^4 and R^5 is, independently for each occurrence, H, (C_1-C_{40})alkyl, (C_1-C_{40})heteroalkyl, (C_1-C_{40})acyl, (C_2-C_{40})alkenyl, (C_2-C_{40})alkynyl, aryl(C_1-C_{40})alkyl, aryl(C_1-C_{40})acyl, substituted (C_1-C_{40})alkyl, substituted (C_1-C_{40})heteroalkyl, substituted (C_1-C_{40})acyl, substituted (C_2-C_{40})alkenyl, substituted (C_2-C_{40})alkynyl, substituted aryl(C_1-C_{40})alkyl, substituted aryl(C_1-C_{40})acyl, (C_1-C_{40})alkylsulfonyl, or -C(NH)-NH_2;

m is, independently for each occurrence, 1, 2, 3, 4, 5, 6 or 7;

n is, independently for each occurrence, 1, 2, 3, 4 or 5;

s is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

t is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

X′, X^2, X^3, X^4, and X^8 each is, independently for each occurrence, H, F, Cl, Br, I, (C_{1-10})alkyl, substituted (C_{1-10})alkyl, (C_{2-10})alkenyl, substituted (C_{2-10})alkenyl, (C_{2-10})alkynyl, substituted (C_{2-10})alkynyl, aryl, substituted aryl, OH, NH_2, NO_2, or CN,

thereby treating PWS.

2. The method of any of the preceding claims, wherein the subject has or is identified as having a loss of function mutation in the 15q11-q13 region of chromosome 15.

3. The method of claim 2, wherein the subject has or is identified as having a mutation (e.g., loss of function mutation) in the MAGEL2 gene.

4. The method of any of claims 1-3, wherein the daily dosage is 0.1 mg to 10 mg.

5. The method of claim 4, wherein the daily dosage is about 0.1 mg to about 7.5 mg.

6. The method of claim 4, wherein the daily dosage is about 0.1 mg to about 5 mg.

7. The method of claim 4, wherein the daily dosage is about 0.1 mg to about 2.5 mg.

8. The method of claim 4, wherein the daily dosage is about 0.1 mg to about 2 mg.

9. The method of claim 4, wherein the daily dosage is about 0.1 mg to about 1 mg.

10. The method of any of claims 1-3, wherein the daily dosage is about 0.2 mg to about 10 mg.

~~11. The method of claim 10, wherein the daily dosage is about 0.2 mg to about 7.5 mg.~~

~~12. The method of claim 10, wherein the daily dosage is about 0.2 mg to about 5 mg.~~

~~13. The method of claim 10, wherein the daily dosage is about 0.2 mg to about 2.5 mg.~~

~~14. The method of claim 10, wherein the daily dosage is about 0.2 mg to about 2 mg.~~

~~15. The method of claim 10, wherein the daily dosage is about 0.2 mg to about 1.5 mg.~~

~~16. The method of claim 10, wherein the daily dosage is about 0.2 mg to about 1 mg.~~

~~17. The method of any of claims 1-3, wherein the daily dosage is about 0.3 mg to about 10 mg.~~

~~18. The method of claim 17, wherein the daily dosage is about 0.3 mg to about 7.5 mg.~~

~~19. The method of claim 17, wherein the daily dosage is about 0.3 mg to about 5 mg.~~

~~20. The method of claim 17, wherein the daily dosage is about 0.3 mg to about 2.5 mg.~~

~~21. The method of claim 17, wherein the daily dosage is about 0.3 mg to about 2 mg.~~

~~22. The method of claim 17, wherein the daily dosage is about 0.3 mg to about 1.5 mg.~~

~~23. The method of claim 17, wherein the daily dosage is about 0.3 mg to about 1 mg.~~

~~24. The method of any of claims 1-3, wherein the daily dosage is about 0.25 mg (e.g., 0.25 mg) to about 0.5 mg (e.g., 0.5 mg).~~

~~25. The method of any of claims 1-3, wherein the daily dosage is about 0.5 mg (e.g., 0.5 mg) to about 0.75 mg (e.g., 0.75 mg).~~

~~26. The method of claim 24, wherein the daily dosage is about 0.25 mg (e.g., 0.25 mg).~~

~~27. The method of 24 or 25, wherein the daily dosage is about 0.5 mg (e.g., 0.5 mg).~~

~~28. The method of any of claims 1-3, wherein the daily dosage is about 0.75 mg (e.g., 0.75 mg) to about 1.25 mg (1.25 mg).~~

~~29. The method of claim 28, wherein the daily dosage is about 1 mg (e.g., 1 mg).~~

~~30. The method of any of claims 1-3, wherein the daily dosage is about 1.25 mg (e.g., 1.25 mg) to about 2 mg (e.g., 2 mg).~~

~~31. The method of claim 30, wherein the daily dosage is about 1.5 mg (e.g., 1.5 mg).~~

~~32. The method of claim 30, wherein the daily dosage is about 2 mg (e.g., 2 mg).~~

~~33. The method of any of the preceding claims, comprising administering the agonist in a unit dosage suitable for injection, e.g., subcutaneous injection, to the subject.~~

~~34. The method of claim 33, wherein the unit dosage comprises about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, or 2 mg of the agonist.~~

~~35. The method of claim 33 or 34, wherein the unit dosage is disposed within a delivery device, e.g., a syringe (e.g., prefilled syringe),an implantable device, a needleness hypodermic injection device, an infusion pump (e.g., implantable infusion pump), or an osmotic delivery system.~~

~~36. The method of any of the preceding claims, wherein the agonist is administered subcutaneously, e.g., by subcutaneous injection.~~

~~37. The method of any of the preceding claims, wherein the agonist is administered daily over a period of at least 3 weeks, e.g., at least 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, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 weeks or more, or at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months or more, or at least 1, 2, 3, 4 years or more.~~

~~38. The method of any of the preceding claims, wherein the subject is obese, e.g., severely obese.~~

~~39. The method of any of the preceding claims, wherein the subject has early onset severe obesity.~~

~~40. The method of any of the preceding claims, wherein the subject is hyperphagic.~~

~~41. The method of any of the preceding claims, wherein the subject has a body mass index (BMI) greater than 25 kg/m^2 (e.g., ≥25, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 kg/m^2 or greater) prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.~~

42. The method of any of the preceding claims, wherein the subject has a body mass index (BMI) greater than 35 kg/m^2 (e.g., ≥36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 kg/m^2 or greater) prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.

43. The method of any of the preceding claims, wherein the subject has a body mass index (BMI) greater than 40 kg/m^2 (e.g., ≥41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55 kg/m^2 or greater) prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.

44. The method of any of the preceding claims, wherein the subject has a body mass index (BMI) greater than 45 kg/m^2 (e.g., ≥46, 47, 48, 49, 50, 51, 52, 53, 54, 55 kg/m^2 or greater) prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.

45. The method of any of the preceding claims, wherein the subject has failed one or more previous therapies, e.g., exercise, diet, or behavioral therapies, prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.

46. The method of any of the preceding claims, wherein the subject has a lower body weight after administration of the agonist than before administration of the agonist.

47. The method of any of the preceding claims, wherein administration of the agonist results in a reduction of weight in the subject compared to the weight of the subject before treatment of about 1 kg to 3 kg after 1 week of treatment, or about 1 kg to 6 kg after 2 weeks of treatment, or about 2 kg to 12 kg after 4 weeks of treatment, or about 4 kg to 24 kg after 8 weeks of treatment, or about 8 kg to 48 kg after 16 weeks of treatment.

~~48. The method of any of the preceding claims, wherein administration of the agonist results in weight loss in the subject at a rate of about 1-2 kg/week, e.g., about 2 kg/week, e.g., over a period of 1-2 weeks of treatment or longer, 2-4 weeks of treatment or longer, 4-8 weeks of treatment or longer, 8-16 weeks of treatment or longer, 16-32 weeks or longer, or 32-64 weeks or longer.~~

~~49. The method of any of the preceding claims, wherein administration of the agonist results in a reduction in hunger level (e.g., a lower score on the Likert hunger scale, e.g., a lower score by at least 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 points) in the subject compared to the hunger level of the subject before treatment, e.g., results in abolishment of hunger (e.g., a score of 0 on the Likert hunger scale) in the subject, e.g., after 1-2 weeks of treatment or longer, 2-4 weeks of treatment or longer, 4-8 weeks of treatment or longer, or 8-16 weeks of treatment or longer.~~

~~50. The method of any of the preceding claims, wherein administration of the agonist results in no detectable/significant decrease in resting energy expenditure (REE) in the subject, e.g., over a period of 24 hours, one week, or 30 days or longer, e.g., as compared to a control REE (e.g., the REE in the subject prior to treatment or a predetermined REE, e.g., in subjects of similar pre-treatment BMI, e.g., when expressed as REE per kg of lean body mass).~~

~~51. The method of claim 50, wherein administration of the agonist results in an increase in resting energy expenditure (REE) in the subject, e.g., over a period of 24 hours, one week, or 30 days, or longer e.g., as compared to a control REE (e.g., the REE in the subject prior to treatment or compared to a predetermined REE, e.g., in subjects of similar pre-treatment BMI, when expressed as REE per kg of lean body mass, e.g., after a similar level of weight loss has been attained by fasting).~~

~~52. The method of any of the preceding claims, wherein administration of the agonist results in a reduction in food intake by the subject compared to a control (e.g., the food intake of the~~

subject prior to treatment), e.g., wherein the food intake is daily food intake or food intake over a period of 24 hours, or one week.

53. The method of claim 52, wherein administration of the agonist results in a reduction in food intake of at least 100 kilocalories, e.g., at least 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 525, 550, 575, 600, 1000 kilocalories or more, compared to a control (e.g., the food intake of the subject prior to treatment or a predetermined food intake level), e.g., wherein the food intake is daily food intake or food intake over a period of 24, hours, or one week.

54. The method of any of the preceding claims, wherein administration of the agonist results in a reduction in waist circumference of the subject compared to a control (e.g., the waist circumference of the subject prior to treatment), as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.

55. The method of claim 54, wherein administration of the agonist results in a reduction in waist circumference of at least 2 cm (e.g., at least 2, 3, 4, 5, 6, 7, 8, 9, 10 cm or more) in the subject compared to a control (e.g., the waist circumference of the subject prior to treatment), as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.

56. The method of any of the preceding claims, wherein administration of the agonist results in no detectable increase in blood pressure (e.g., diastolic and/or systolic blood pressure) of the subject compared to the blood pressure of the subject prior to treatment, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.

57. The method of any of the preceding claims, wherein administration of the agonist results in a reduction in blood pressure (e.g., diastolic and/or systolic blood pressure) of the subject compared to the blood pressure of the subject prior to treatment, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.

~~58. The method of claim 57, wherein administration of the agonist results in a reduction in systolic blood of the subject of at least 3 mmHg (e.g., at least 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7 mmHg or more) compared to the blood pressure of the subject prior to treatment, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.~~

~~59. The method of claim 57, wherein administration of the agonist results in a reduction in diastolic blood pressure of the subject of at least 4 mmHg (e.g., at least 4, 7, 7.5, 8, 8.5, 9, 9.5, 10 mmHg or more) compared to the blood pressure of the subject prior to treatment, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.~~

~~60. The method of any of the preceding claims, wherein the subject is a mammal, e.g., a human.~~

~~61. The method of any of the preceding claims, wherein the agonist is Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 (SEQ ID NO: 140).~~

~~62. The method of any of the preceding claims, comprising acquiring knowledge of the genotype of the subject, e.g., acquiring knowledge of the genotype the 15q11-q13 region of chromosome 15 or of the MAGEL2 gene.~~

~~63. The method of claim 62, wherein the agonist is administered in response to the detection of a predetermined sequence, e.g., a mutation, in 15q11-q13 region of chromosome 15 or in the MAGEL2 gene.~~

~~64~~1. ~~A method of treating a disorder in a subject in need thereof, comprising:~~

~~administering~~ Use of an agonist of the melanocortin-4 receptor (MC4R) at a daily dosage of about 0.1 mg ~~(e.g., 0.1 mg +/- 5%)~~ to about 10 mg ~~(e.g., 10 mg +/- 5%),~~ in the manufacture of a medicament for treating a disorder in a subject in need thereof,

wherein the disorder ~~is chosen from:~~comprises

~~(i) Prader Willi Syndrome (PWS);~~

~~(ii) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the POMC gene;~~

~~(iii) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the PCSK1 gene;~~

~~(iv) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the MAGEL2 gene;~~

~~(v) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the leptin receptor gene;~~

~~(vi) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the leptin gene;~~

~~(vii) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the 5-HT2c receptor gene;~~

~~(viii) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the nescient helix loop helix 2 (NhHL2) gene;~~

~~(ix) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the pro-hormone convertase gene;~~

~~(x) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the carboxypeptidase E (CPE) gene;~~

~~(xi) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the single-minded 1 (SIM1) gene;~~

~~(xii)~~ a disorder characterized by a hypermethylated POMC gene and~~(e.g., hypermethylated at a POMC intron, e.g., at a CpG island of the POMC gene, e.g., comprising one or more methylated cytosines, e.g., a 5'methyl cytosine); or~~

~~(xiii) a disorder characterized by a defect in the POMC-MC4R pathway other than:~~

~~(e) a heterozygous POMC mutation characterized by the presence of one functional POMC allele and one non-functional POMC allele,~~

~~(f) a heterozygous leptin mutation characterized by the presence of one functional leptin allele and one non-functional leptin allele,~~

~~(g) a melanocortin-4 receptor (MC4R) mutation (e.g., loss of function mutation),~~

~~(h) a pro-hormone convertase mutation (e.g., loss of function mutation);~~

~~(i) a mutation in a gene associated with Bardet-Biedl syndrome (e.g., a mutation in *BBS1-BBS20*); or~~

~~(j) a mutation in a gene associated with Alström syndrome,~~

wherein the agonist is a ~~MC4R agonist described herein, e.g., the agonist is~~structure of Formula (I):

$$(R^2R^3)\text{-}A^1\text{-}c(A^2\text{-}A^3\text{-}A^4\text{-}A^5\text{-}A^6\text{-}A^7\text{-}A^8\text{-}A^9)\text{-}A^{10}\text{-}R^1 \qquad \text{(I)},$$

wherein:

A^1 is Acc, HN—$(CH_2)_m$—C(O), L- or D-amino acid, or deleted;

A^2 is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Asp, or Glu;

A^3 is Gly, Ala, β-Ala, Gaba, Aib, D-amino acid, or deleted;

A^4 is H-is, 2-Pal, 3-Pal, 4-Pal, Taz, 2-Thi, 3-Thi, or (X^1, X^2, X^3, X^4, X^5)Phe;

A^5 is D-Phe, D-1-Nal, D-2-Nal, D-Trp, D-Bal, D-(X^1, X^2, X^3, X^4, X^5)Phe, L-Phe or D-(Et)Tyr;

A^6 is Arg, hArg, Dab, Dap, Lys, Orn, or HN-CH($(CH_2)_n$-N(R^4 R^5))-C(O);

A^7 is Trp, 1-Nal, 2-Nal, Bal, Bip, D-Trp, D-2-Nal, D-Bal or D-Bip;

A^8 is Gly, D-Ala, Acc, Ala, 13-Ala, Gaba, Apn, Ahx, Aha, HN-$(CH_2)_s$-C(O), or deleted;

A^9 is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Dab, Dap, Orn, or Lys;

A^{10} is Acc, HN-$(CH_2)_t$-C(O), L- or D-amino acid, or deleted;

R^1 is OH or NH_2;

each of R^2 and R^3 is, independently for each occurrence, selected from the group consisting of H, (C_1-C_{30})alkyl, (C_1-C_{30})heteroalkyl, (C_1-C_{30})acyl, (C_2-C_{30})alkenyl, (C_2-C_{30})alkynyl, aryl(C_1-C_{30})alkyl, aryl(C_1-C_{30})acyl, substituted (C_1-C_{30})alkyl, substituted (C_1-

C_{30})heteroalkyl, substituted (C_1-C_{30})acyl, substituted (C_2-C_{30})alkenyl, substituted (C_2-C_{30})alkynyl, substituted aryl(C_1-C_{30})alkyl, and substituted aryl(C_1-C_{30})acyl;

each of R^4 and R^5 is, independently for each occurrence, H, (C_1-C_{40})alkyl, (C_1-C_{40})heteroalkyl, (C_1-C_{40})acyl, (C_2-C_{40})alkenyl, (C_2-C_{40})alkynyl, aryl(C_1-C_{40})alkyl, aryl(C_1-C_{40})acyl, substituted (C_1-C_{40})alkyl, substituted (C_1-C_{40})heteroalkyl, substituted (C_1-C_{40})acyl, substituted (C_2-C_{40})alkenyl, substituted (C_2-C_{40})alkynyl, substituted aryl(C_1-C_{40})alkyl, substituted aryl(C_1-C_{40})acyl, (C_1-C_{40})alkylsulfonyl, or -C(NH)-NH_2;

m is, independently for each occurrence, 1, 2, 3, 4, 5, 6 or 7;

n is, independently for each occurrence, 1, 2, 3, 4 or 5;

s is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

t is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

X′, X^2, X^3, X^4, and X^8 each is, independently for each occurrence, H, F, Cl, Br, I, (C_{1-10})alkyl, substituted (C_{1-10})alkyl, (C_{2-10})alkenyl, substituted (C_{2-10})alkenyl, (C_{2-10})alkynyl, substituted (C_{2-10})alkynyl, aryl, substituted aryl, OH, NH_2, NO_2, or CN.

~~65. The method of claim 64, wherein the disorder is Prader Willi Syndrome (PWS).~~

~~66. The method of 64 or 65, wherein the subject has or is identified as having a loss of function mutation in the paternal allele of the 15q11-q13 region of chromosome 15.~~

~~67. The method of claim 65 or 66, wherein the subject has or is identified as having a mutation, e.g., loss of function mutation, in the MAGEL2 gene.~~

~~68. The method of claim 64, wherein the disorder is characterized by one or more mutations (e.g., loss of function mutations) in the POMC gene.~~

~~69. The method of any of claim 68, wherein the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional POMC allele and one non-functional POMC allele.~~

~~70. The method of claim 68, wherein the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two distinct non-functional POMC alleles, e.g., having a POMC null genotype.~~

~~71. The method of claim 68, wherein the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a homozygous POMC null genotype.~~

~~72. The method of claim 64, wherein the disorder is characterized by one or more mutations (e.g., loss of function mutations) in the PCSK1 gene.~~

~~73. The method of claim 72, wherein the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional PCSK1 allele and one non-functional PCSK1 allele.~~

~~74. The method of claim 72, wherein the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two non-functional PCSK1 alleles, e.g., having a PCSK1 null genotype.~~

~~75. The method of claim 72, wherein the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a homozygous PCSK1 null genotype.~~

~~76. The method of claim 64, wherein the disorder is characterized by one or mutations (e.g., loss of function mutations) in the MAGEL2 gene.~~

~~77. The method of claim 76, wherein the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional MAGEL2 allele and one non-functional MAGEL2 allele, including the subjects where the remainingfunctional allele is silenced by maternal imprinting, as result of which the subject is a functional MAGEL2 null patient.~~

~~78. The method of claim 76, wherein the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two mutated non-functional MAGEL2 alleles, e.g., having a MAGEL2 null genotype.~~

~~79. The method of claim 76, wherein the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a MAGEL2 null genotype.~~

~~80. The method of claim 64, wherein the disorder is characterized by one or mutations (e.g., loss of function mutations) in the leptin receptor gene.~~

~~81. The method of any of claim 80, wherein the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional leptin receptor allele and one non-functional leptin receptor allele.~~

~~82. The method of claim 80, wherein the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two non-functional leptin receptor alleles, e.g., having a leptin receptor null genotype.~~

~~83. The method of claim 80, wherein the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a leptin receptor null genotype.~~

~~84. The method of claim 64, wherein the disorder is characterized by one or mutations (e.g., loss of function mutations) in the leptin gene.~~

~~85. The method of any of claim 84, wherein the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional leptin allele and one non-functional leptin allele.~~

~~86. The method of claim 84, wherein the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two non-functional leptin alleles, e.g., having a leptin null genotype.~~

~~87. The method of claim 84, wherein the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a leptin null genotype.~~

~~88. The method of claim 64, wherein the disorder is characterized by one or mutations (e.g., loss of function mutations) in the 5-HT2c receptor gene.~~

~~89. The method of any of claim 88, wherein the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional 5-HT2c receptor allele and one non-functional 5-HT2c receptor allele.~~

~~90. The method of claim 88, wherein the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two non-functional 5-HT2c receptor alleles, e.g., having a 5-HT2c receptor null genotype.~~

~~91. The method of claim 88, wherein the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a 5-HT2c receptor null genotype.~~

~~92. The method of claim 64, wherein the disorder is characterized by one or mutations (e.g., loss of function mutations) in the nescient helix loop helix 2 (NhHL2) gene.~~

~~93. The method of any of claim 92, wherein the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional NhHL2 allele and one non-functional NhHL2 receptor allele.~~

~~94. The method of claim 92, wherein the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two non-functional NhHL2 alleles, e.g., having a NhHL2 null genotype.~~

~~95. The method of claim 92, wherein the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a NhHL2 null genotype.~~

~~96. The method of claim 64, wherein the disorder is characterized by one or mutations (e.g., loss of function mutations) in the pro-hormone convertase gene.~~

~~97. The method of claim 96, wherein the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional pro-hormone convertase allele and one non-functional pro-hormone convertase allele.~~

~~98. The method of claim 96, wherein the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two non-functional pro-hormone convertase alleles, e.g., having a pro-hormone convertase null genotype.~~

~~99. The method of claim 96, wherein the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a pro-hormone convertase null genotype.~~

~~100. The method of claim 64, wherein the disorder is characterized by one or mutations (e.g., loss of function mutations) in the carboxypeptidase E (CPE) gene.~~

~~101. The method of any of claim 100, wherein the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional CPE allele and one non-functional CPE allele.~~

~~102. The method of claim 100, wherein the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two non-functional CPE alleles, e.g., having a CPE null genotype.~~

~~103. The method of claim 100, wherein the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a CPE null genotype.~~

~~104. The method of claim 64, wherein the disorder is characterized by one or mutations (e.g., loss of function mutations) in the single-minded 1 (SIM1) gene.~~

~~105. The method of any of claim 104, wherein the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional SIM1 allele and one non-functional SIM1 allele.~~

~~106. The method of claim 104, wherein the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two non-functional SIM1 alleles, e.g., having a SIM1 null genotype.~~

~~107. The method of claim 104, wherein the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a SIM1 null genotype.~~

~~108. The method of claim 64, wherein the disorder is characterized by a hypermethylated POMC gene (e.g., hypermethylated at a POMC intron, e.g., at a CpG island of the POMC gene, e.g., comprising a methylated cytosine, e.g., a 5'methyl cytosine).~~

~~109. The method of claim 64, wherein the disorder is characterized by a defect in the POMC-MC4R pathway other than:~~

(e) a heterozygous POMC mutation characterized by the presence of one functional POMC allele and one non-functional POMC allele,

(f) a heterozygous leptin mutation characterized by the presence of one functional leptin allele and one non-functional leptin allele,

(g) a heterozygous melanocortin-4 receptor (MC4R) mutation characterized by the presence of one functional MC4R allele and one non-functional MC4R allele, or

(h) a pro-hormone convertase mutation (e.g., loss of function mutation);

(i) a mutation in a gene associated with Bardet-Biedl syndrome (e.g., a mutation in *BBS1-BBS20*); or

(j) a mutation in a gene associated with Alström syndrome.

1102. The method use of any of claims 64-109claim 1, wherein the daily dosage is 0.1 mg to 10 mg.

111. The method of claim 110, wherein the daily dosage is about 0.1 mg to about 7.5 mg.

112. The method of claim 110, wherein the daily dosage is about 0.1 mg to about 5 mg.

113. The method of claim 110, wherein the daily dosage is about 0.1 mg to about 2.5 mg.

114. The method of claim 110, wherein the daily dosage is about 0.1 mg to about 2 mg.

115. The method of claim 110, wherein the daily dosage is about 0.1 mg to about 1 mg.

116. The method of any of claims 64-109, wherein the daily dosage is about 0.2 mg to about 10 mg.

~~117. The method of claim 116, wherein the daily dosage is about 0.2 mg to about 7.5 mg.~~

~~118. The method of claim 116, wherein the daily dosage is about 0.2 mg to about 5 mg.~~

~~119. The method of claim 116, wherein the daily dosage is about 0.2 mg to about 2.5 mg.~~

~~120. The method of claim 116, wherein the daily dosage is about 0.2 mg to about 2 mg.~~

~~121. The method of claim 116, wherein the daily dosage is about 0.2 mg to about 1.5 mg.~~

~~122. The method of claim 116, wherein the daily dosage is about 0.2 mg to about 1 mg.~~

~~123. The method of any of claims 64-109, wherein the daily dosage is about 0.3 mg to about 10 mg.~~

~~124. The method of claim 123, wherein the daily dosage is about 0.3 mg to about 7.5 mg.~~

~~125. The method of claim 123, wherein the daily dosage is about 0.3 mg to about 5 mg.~~

~~126. The method of claim 123, wherein the daily dosage is about 0.3 mg to about 2.5 mg.~~

~~127. The method of claim 123, wherein the daily dosage is about 0.3 mg to about 2 mg.~~

~~128. The method of claim 123, wherein the daily dosage is about 0.3 mg to about 1.5 mg.~~

~~129. The method of claim 123, wherein the daily dosage is about 0.3 mg to about 1 mg.~~

~~130. The method of any of claims 64-109, wherein the daily dosage is about 0.25 mg (e.g., 0.25 mg) to about 0.5 mg (e.g., 0.5 mg).~~

~~131. The method of any of claims 64-109, wherein the daily dosage is about 0.5 mg (e.g., 0.5 mg) to about 0.75 mg (e.g., 0.75 mg).~~

~~132. The method of claim 130, wherein the daily dosage is about 0.25 mg (e.g., 0.25 mg).~~

~~133. The method of 130 or 131, wherein the daily dosage is about 0.5 mg (e.g., 0.5 mg).~~

~~134. The method of any of claims 64-109, wherein the daily dosage is about 0.75 mg (e.g., 0.75 mg) to about 1.25 mg (1.25 mg).~~

~~135. The method of claim 134, wherein the daily dosage is about 1 mg (e.g., 1 mg).~~

~~136. The method of any of claims 64-109, wherein the daily dosage is about 1.25 mg (e.g., 1.25 mg) to about 2 mg (e.g., 2 mg).~~

~~137. The method of claim 136, wherein the daily dosage is about 1.5 mg (e.g., 1.5 mg).~~

~~138. The method of claim 136, wherein the daily dosage is about 2 mg (e.g., 2 mg).~~

~~139~~3. The ~~method~~ use of ~~any of claims 64-138~~claim 1, ~~comprising administering~~ wherein the agonist is to be administered in a unit dosage suitable for injection~~, e.g., subcutaneous injection, to the subject~~.

~~140. The method of claim 139, wherein the unit dosage comprises about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, or 2 mg of the agonist.~~

~~141. The method of claim 139 or 140, wherein the unit dosage is disposed within a delivery device, e.g., a syringe (e.g., prefilled syringe),an implantable device, a needleness hypodermic injection device, an infusion pump (e.g., implantable infusion pump), or an osmotic delivery system.~~

~~142. The method of any of claims 64-141, wherein the agonist is administered subcutaneously, e.g., by subcutaneous injection.~~

~~143. The method of any of claims 64-142, wherein the agonist is administered daily over a period of at least 3 weeks, e.g., at least 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, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 weeks or more, or at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months or more, or at least 1, 2, 3, 4 years or more.~~

~~14~~4. The ~~method~~ use of ~~any of~~ claim~~s 64-143~~1, wherein the subject is obese~~, e.g., severely obese.~~

~~145. The method of any of claims 64-144, wherein the subject has early onset severe obesity.~~

~~146. The method of any of claims 64-145, wherein the subject is~~ or hyperphagic.

~~147. The method of any of claims 64-146, wherein the subject has a body mass index (BMI) greater than 25 kg/m^2 (e.g., ≥25, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 kg/m^2 or greater) prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.~~

~~148. The method of any of claims 64-147, wherein the subject has a body mass index (BMI) greater than 35 kg/m^2 (e.g., ≥36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 kg/m^2 or greater) prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.~~

~~149. The method of any of claims 64-148, wherein the subject has a body mass index (BMI) greater than 40 kg/m^2 (e.g., ≥41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55 kg/m^2 or greater) prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.~~

~~150. The method of any of claims 64-149, wherein the subject has a body mass index (BMI) greater than 45 kg/m^2 (e.g., ≥46, 47, 48, 49, 50, 51, 52, 53, 54, 55 kg/m^2 or greater) prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.~~

~~151~~5. The ~~method~~ use ~~of any~~ of claim~~s 64-150~~1, wherein the subject:

has failed one or more previous therapies~~, e.g., exercise, diet, or behavioral therapies,~~ prior to administration of the agonist~~, e.g., at the time the agonist is prescribed,~~ or at the time of the first administration.

~~152. The method of any of claims 64-151, wherein the subject has a lower body weight after administration of the agonist than before administration of the agonist.~~

~~153~~6. The ~~method~~ use of ~~any of~~ claim~~s 64-152~~1, wherein ~~administration of~~ the agonist to be administered results in ~~a~~ one or more of:

(i) reduction of weight in the subject compared to the weight of the subject before treatment of about 1 kg to 3 kg after 1 week of treatment, or about 1 kg to 6 kg after 2 weeks of

treatment, or about 2 kg to 12 kg after 4 weeks of treatment, or about 4 kg to 24 kg after 8 weeks of treatment, or about 8 kg to 48 kg after 16 weeks of treatment;.

154. The method of any of claims 64-153, wherein administration of the agonist results in (ii) weight loss in the subject at a rate of about 1-2 kg/week;, e.g., about 2 kg/week, e.g., over a period of 1-2 weeks of treatment or longer, 2-4 weeks of treatment or longer, 4-8 weeks of treatment or longer, 8-16 weeks of treatment or longer, 16-32 weeks or longer, or 32-64 weeks or longer.

155. The method of any of claims 64-154, wherein administration of the agonist results in a reduction in (iii) hunger level (e.g., a lower score on the Likert hunger scale, e.g., a lower score by at least 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 points) in the subject compared to the hunger level of the subject before treatment;, e.g., results in abolishment of hunger (e.g., a score of 0 on the Likert hunger scale) in the subject, e.g., after 1-2 weeks of treatment or longer, 2-4 weeks of treatment or longer, 4-8 weeks of treatment or longer, or 8-16 weeks of treatment or longer.

156. The method of any of claims 64-155, wherein administration of the agonist results in (iv) no detectable/significant decrease in resting energy expenditure (REE) in the subject, e.g., over a period of 24 hours, one week, or 30 days or longer, e.g., as compared to a control REE; (e.g., the REE in the subject prior to treatment or a predetermined REE, e.g., in subjects of similar pre-treatment BMI, e.g., when expressed as REE per kg of lean body mass).

157. The method of claim 156, wherein administration of the agonist results in(v) an increase in resting energy expenditure (REE) in the subject, e.g., over a period of 24 hours, one week, or 30 days, or longer e.g., as compared to a control REE; (e.g., the REE in the subject prior to treatment or compared to a predetermined REE, e.g., in subjects of similar pre-treatment BMI, e.g., when expressed as REE per kg of lean body mass, e.g., after a similar level of weight loss has been attained by fasting).

~~158. The method of any of claims 64-157, wherein administration of the agonist results in~~(vi) a reduction in food intake by the subject compared to a control ~~(e.g., the food intake of the subject prior to treatment)~~, ~~e.g.,~~ wherein the food intake is daily food intake or food intake over a period of 24 hours, or one week~~;~~.

~~159. The method of claim 158, wherein administration of the agonist results in~~(vii) a reduction in food intake of at least 100 kilocalories~~, e.g., at least 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 525, 550, 575, 600, 1000 kilocalories or more,~~ compared to a control ~~(e.g., the food intake of the subject prior to treatment or a predetermined food intake level), e.g.~~, wherein the food intake is daily food intake or food intake over a period of 24~~,~~ hours~~, or one week.~~;

~~160. The method of any of claims 64-159, wherein administration of the agonist results in~~(viii) a reduction in waist circumference of at least 2 in the subject compared to a control ~~(e.g., the waist circumference of the subject prior to treatment)~~, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment~~;~~.

~~161. The method of claim 160, wherein administration of the agonist results in a reduction in waist circumference of at least 2 cm (e.g., at least 2, 3, 4, 5, 6, 7, 8, 9, 10 cm or more) in the subject compared to a control (e.g., the waist circumference of the subject prior to treatment), as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.~~

~~162. The method of any of claims 64-161, wherein administration of the agonist results in~~(ix) no detectable increase in blood pressure ~~(e.g., diastolic and/or systolic blood pressure)~~ of the subject compared to the blood pressure of the subject prior to treatment, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment~~;~~.

~~163. The method of any of claims 64-162, wherein administration of the agonist results in~~(x) a reduction in blood pressure ~~(e.g., diastolic and/or systolic blood pressure)~~ of the subject compared to the blood pressure of the subject prior to treatment, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment;~~.~~

~~164. The method of claim 163, wherein administration of the agonist results in~~(xi) a reduction in systolic blood pressure of the subject of at least 3 mmHg ~~(e.g., at least 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7 mmHg or more)~~ compared to the blood pressure of the subject prior to treatment, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment;~~.~~ and

~~165. The method of claim 163, wherein administration of the agonist results in~~(xii) a reduction in diastolic blood pressure of the subject of at least 4 mmHg ~~(e.g., at least 4, 7, 7.5, 8, 8.5, 9, 9.5, 10 mmHg or more)~~ compared to the blood pressure of the subject prior to treatment, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.

~~166~~7. The ~~method~~ use of ~~any of~~ claim~~s 64-165~~1, wherein the subject is a mammal~~, e.g., a human~~.

~~167~~8. The ~~method~~ use of ~~any of~~ claim~~s 64-166~~1, wherein the agonist is Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 (SEQ ID NO: 140).

~~168. The method of any of claims 64-167, comprising acquiring knowledge of the genotype of the subject, e.g., acquiring knowledge of the genotype of, e.g., of a mutation in:~~

~~the POMC gene;the prohormone convertase gene, including the PCSK1 gene;~~
~~the MAGEL2 gene;~~
~~the leptin receptor gene;~~
~~the leptin gene;~~
~~the 5-HT2c receptor gene;~~

~~the nescient helix loop helix 2 (NhHL2) gene;~~

~~the carboxypeptidase E (CPE) gene;~~

~~the single-minded 1 (SIM1) gene;~~

~~a POMC-MC4R pathway gene;~~

~~*BBS1-BBS20*);~~

~~*ALMS1*,~~

~~BDNF, MCH1R, MCH, NTRK2,SIM1, ENPP1, COH1, CNR1, NPC1, c-MAF, PTER, FTO, TMEM18 (childhood), SDCCAG8, TNKS/MSRA, GNPDA2 (childhood), NEGr1, INSIG2, KCTD15, NROB2, and 16p11.2 deletions (including the SH2B1 gene).~~

~~.~~

~~169. The method of claim 168, wherein the agonist is administered in response to the detection of a predetermined sequence, e.g., a mutation, in a gene in claim 168.~~

~~170. A method of treating a disorder chosen from:~~

~~(i) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the PCSK1 gene;~~

~~(ii) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the MAGEL2 gene;~~

~~(iii) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the leptin receptor gene;~~

~~(iv) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the 5-HT2c receptor gene;~~

~~(v) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the nescient helix loop helix 2 (NhHL2) gene;~~

~~(vi) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the carboxypeptidase E (CPE) gene;~~

~~(vii) a disorder characterized by one or more mutations (e.g., loss of function mutations) in the single-minded 1 (SIM1) gene;~~

(viii) a disorder characterized by a hypermethylated POMC gene (e.g., hypermethylated at a POMC intron, e.g., at a CpG island of the POMC gene, e.g., comprising a methylated cytosine, e.g., a 5'methyl cytosine);

(ix) a disorder characterized by a defect in the POMC-MC4R pathway other than:

(e) a POMC mutation, e.g., a heterozygous POMC mutation characterized by the presence of one functional POMC allele and one non-functional POMC allele,

(f) a leptin mutation, e.g., a heterozygous leptin mutation characterized by the presence of one functional leptin allele and one non-functional leptin allele,

(g) a melanocortin-4 receptor (MC4R) mutation, or

(h) a prohormone convertase mutation;

(x) a disorder characterized by a homozygous POMC mutation (e.g., loss of function mutation), e.g., characterized by a POMC null genotype;

(xi) a disorder characterized by a compound heterozygous POMC mutation (e.g., characterized by the presence of two non-functional alleles) e.g., characterized by a POMC null genotype;

(xii) a disorder characterized by a homozygous leptin mutation (e.g., loss of function mutation), e.g., characterized by a leptin null genotype;

(xiii) a disorder characterized by a compound heterozygous leptin mutation (e.g., characterized by the presence of two non-functional alleles) e.g., characterized by a leptin null genotype,

(xiv) a disorder characterized by a mutation in a gene associated with Bardet-Biedl syndrome (e.g., a mutation in *BBS1-BBS20*); or

(xv) a disorder characterized by a a mutation in a gene associated with Alström syndrome,

in a subject in need thereof, comprising administering an agonist of the melanocortin-4 receptor (MC4R),

wherein the agonist is a MC4R agonist described herein, e.g., the agonist is

$(R^2R^3)\text{-}A^1\text{-}c(A^2\text{-}A^3\text{-}A^4\text{-}A^5\text{-}A^6\text{-}A^7\text{-}A^8\text{-}A^9)\text{-}A^{10}\text{-}R^1$ (I),

wherein:

A^1 is Acc, HN—$(CH_2)_m$—C(O), L- or D-amino acid, or deleted;

A^2 is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Asp, or Glu;

A^3 is Gly, Ala, β-Ala, Gaba, Aib, D-amino acid, or deleted;

A^4 is H is, 2-Pal, 3-Pal, 4-Pal, Taz, 2-Thi, 3-Thi, or (X^1, X^2, X^3, X^4, X^5)Phe;

A^5 is D-Phe, D-1-Nal, D-2-Nal, D-Trp, D-Bal, D-(X^1, X^2, X^3, X^4, X^5)Phe, L-Phe or D-(Et)Tyr;

A^6 is Arg, hArg, Dab, Dap, Lys, Orn, or HN-CH((CH_2)$_n$-N(R^4-R^5))-C(O);

A^7 is Trp, 1-Nal, 2-Nal, Bal, Bip, D-Trp, D-2-Nal, D-Bal or D-Bip;

A^8 is Gly, D-Ala, Acc, Ala, 13-Ala, Gaba, Apn, Ahx, Aha, HN-(CH_2)$_s$-C(O), or deleted;

A^9 is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Dab, Dap, Orn, or Lys;

A^{10} is Acc, HN-(CH_2)$_t$-C(O), L- or D-amino acid, or deleted;

R^1 is OH or NH_2;

each of R^2 and R^3 is, independently for each occurrence, selected from the group consisting of H, (C_1-C_{30})alkyl, (C_1-C_{30})heteroalkyl, (C_1-C_{30})acyl, (C_2-C_{30})alkenyl, (C_2-C_{30})alkynyl, aryl(C_1-C_{30})alkyl, aryl(C_1-C_{30})acyl, substituted (C_1-C_{30})alkyl, substituted (C_1-C_{30})heteroalkyl, substituted (C_1-C_{30})acyl, substituted (C_2-C_{30})alkenyl, substituted (C_2-C_{30})alkynyl, substituted aryl(C_1-C_{30})alkyl, and substituted aryl(C_1-C_{30})acyl;

each of R^4 and R^5 is, independently for each occurrence, H, (C_1-C_{40})alkyl, (C_1-C_{40})heteroalkyl, (C_1-C_{40})acyl, (C_2-C_{40})alkenyl, (C_2-C_{40})alkynyl, aryl(C_1-C_{40})alkyl, aryl(C_1-C_{40})acyl, substituted (C_1-C_{40})alkyl, substituted (C_1-C_{40})heteroalkyl, substituted (C_1-C_{40})acyl, substituted (C_2-C_{40})alkenyl, substituted (C_2-C_{40})alkynyl, substituted aryl(C_1-C_{40})alkyl, substituted aryl(C_1-C_{40})acyl, (C_1-C_{40})alkylsulfonyl, or -C(NH)-NH_2;

m is, independently for each occurrence, 1, 2, 3, 4, 5, 6 or 7;

n is, independently for each occurrence, 1, 2, 3, 4 or 5;

s is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

t is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

X′, X^2, X^3, X^4, and X^8 each is, independently for each occurrence, H, F, Cl, Br, I, (C_{1-10})alkyl, substituted (C_{1-10})alkyl, (C_{2-10})alkenyl, substituted (C_{2-10})alkenyl, (C_{2-10})alkynyl, substituted (C_{2-10})alkynyl, aryl, substituted aryl, OH, NH_2, NO_2, or CN.

171. The method of claim 170, wherein the disorder is characterized by a homozygous POMC mutation (e.g., loss of mutation), e.g., characterized by a POMC null genotype.

~~172. The method of claim 170, wherein the disorder is characterized by a compound heterozygous POMC mutation (e.g., characterized by the presence of two non-functional alleles) e.g., characterized by a POMC null genotype.~~

~~173. The method of claim 172, wherein the mutations are p.Lys51Term g.A6851>T and p.Arg145ProfsX12 g.7134delG.~~

~~174. The method of claim 170, wherein the disorder is characterized by one or more mutations (e.g., loss of function mutations) in the PCSK1 gene.~~

~~175. The method of claim 174, wherein the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional PCSK1 allele and one non-functional PCSK1 allele.~~

~~176. The method of claim 174, wherein the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two non-functional PCSK1 alleles, e.g., having a PCSK1 null genotype.~~

~~177. The method of claim 174, wherein the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a PCSK1 null genotype.~~

~~178. The method of claim 170, wherein the disorder is characterized by one or mutations (e.g., loss of function mutations) in the MAGEL2 gene.~~

~~179. The method of claim 178, wherein the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional MAGEL2 allele and one non-functional MAGEL2 allele.~~

~~180. The method of claim 178, wherein the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two non-functional MAGEL2 alleles, e.g., having a MAGEL2 null genotype.~~

~~181. The method of claim 178, wherein the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a MAGEL2 null genotype.~~

~~182. The method of claim 170, wherein the disorder is characterized by one or mutations (e.g., loss of function mutations) in the leptin receptor gene.~~

~~183. The method of any of claim 182, wherein the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional leptin receptor allele and one non-functional leptin receptor allele.~~

~~184. The method of claim 182, wherein the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two non-functional leptin receptor alleles, e.g., having a leptin receptor null genotype.~~

~~185. The method of claim 182, wherein the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a leptin receptor null genotype.~~

~~186. The method of claim 170, wherein the disorder is characterized by a homozygous leptin mutation (e.g., loss of mutation), e.g., characterized by a leptin null genotype.~~

~~187. The method of claim 170, wherein the disorder is characterized by a compound heterozygous leptin mutation (e.g., characterized by the presence of two non-functional alleles) e.g., characterized by a leptin null genotype.~~

~~188. The method of claim 170, wherein the disorder is characterized by one or mutations (e.g., loss of function mutations) in the 5-HT2c receptor gene.~~

~~189. The method of any of claim 188, wherein the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional 5-HT2c receptor allele and one non-functional 5-HT2c receptor allele.~~

~~190. The method of claim 188, wherein the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two non-functional 5-HT2c receptor alleles, e.g., having a 5-HT2c receptor null genotype.~~

~~191. The method of claim 188, wherein the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a 5-HT2c receptor null genotype.~~

~~192. The method of claim 170, wherein the disorder is characterized by one or mutations (e.g., loss of function mutations) in the nescient helix-loop-helix 2 (NhHL2) gene.~~

~~193. The method of any of claim 192, wherein the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional NhHL2 allele and one non-functional NhHL2 receptor allele.~~

~~194. The method of claim 192, wherein the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two non-functional NhHL2 alleles, e.g., having a NhHL2 null genotype.~~

~~195. The method of claim 192, wherein the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a NhHL2 null genotype.~~

~~196. The method of claim 170, wherein the disorder is characterized by one or mutations (e.g., loss of function mutations) in the carboxypeptidase E (CPE) gene.~~

~~197. The method of any of claim 196, wherein the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional CPE allele and one non-functional CPE allele.~~

~~198. The method of claim 196, wherein the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two non-functional CPE alleles, e.g., having a CPE null genotype.~~

~~199. The method of claim 196, wherein the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a CPE null genotype.~~

~~200. The method of claim 170, wherein the disorder is characterized by one or mutations (e.g., loss of function mutations) in the single-minded 1 (SIM1) gene.~~

~~201. The method of any of claim 200, wherein the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional SIM1 allele and one non-functional SIM1 allele.~~

~~202. The method of claim 200, wherein the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two non-functional SIM1 alleles, e.g., having a SIM1 null genotype.~~

~~203. The method of claim 200, wherein the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a SIM1 null genotype.~~

~~204. The method of claim 170, wherein the disorder is characterized by a hypermethylated POMC gene (e.g., hypermethylated at a POMC intron, e.g., at a CpG island of the POMC gene, e.g., comprising a methylated cytosine, e.g., a 5'methyl cytosine).~~

~~205. The method of claim 204, wherein the subject has or is identified as having a hypermethylated CpG island in the POMC gene, e.g., at the intron2-exon3 boundary of the POMC gene.~~

~~206 The method of claim 170, wherein the disorder is characterized by a defect in the POMC-MC4R pathway other than a POMC mutation, e.g., a heterozygous POMC mutation characterized by the presence of one functional POMC allele and one non-functional POMC allele.~~

~~207. The method of claim 170, wherein the disorder is characterized by a defect in the POMC-MC4R pathway other than a leptin mutation, e.g, a heterozygous leptin mutation characterized by the presence of one functional leptin allele and one non-functional leptin allele.~~

~~208. The method of claim 170, wherein the disorder is characterized by a defect in the POMC-MC4R pathway other than a MC4R mutation, e.g., a heterozygous melanocortin-4 receptor (MC4R) mutation characterized by the presence of one functional MC4R allele and one non-functional MC4R allele.~~

~~209. The method of claim 170, wherein the disorder is characterized by a defect in the POMC-MC4R pathway other than a pro-hormone convertase mutation.~~

~~210. The method of any of claims 170-209, comprising administering the agonist in a unit dosage suitable for injection, e.g., subcutaneous injection, to the subject.~~

211. The method of claim 210, wherein the unit dosage comprises about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, or 2 mg of the agonist.

212. The method of claim 210 or 211, wherein the unit dosage is disposed within a delivery device, e.g., a syringe (e.g., prefilled syringe),an implantable device, a needleness hypodermic injection device, an infusion pump (e.g., implantable infusion pump), or an osmotic delivery system.

213. The method of any of claims 170-211, wherein the agonist is administered subcutaneously, e.g., by subcutaneous injection.

214. The method of any of claims 170-213, wherein the agonist is administered daily over a period of at least 3 weeks, e.g., at least 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, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 weeks or more, or at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months or more, or at least 1, 2, 3, 4 years or more.

215. The method of any of claims 170-214, wherein the subject is obese, e.g., severely obese.

216. The method of any of claims 170-215, wherein the subject has early onset severe obesity.

217. The method of any of claims 170-216, wherein the subject is hyperphagic.

218. The method of any of claims 170-217, wherein the subject has a body mass index (BMI) greater than 25 kg/m^2 (e.g., ≥25, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45,

~~46, 47, 48, 49, 50 kg/m^2 or greater) prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.~~

~~219. The method of any of claims 170-218, wherein the subject has a body mass index (BMI) greater than 35 kg/m^2 (e.g., ≥36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 kg/m^2 or greater) prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.~~

~~220. The method of any of claims 170-219, wherein the subject has a body mass index (BMI) greater than 40 kg/m^2 (e.g., ≥41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55 kg/m^2 or greater) prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.~~

~~221. The method of any of claims 170-220, wherein the subject has a body mass index (BMI) greater than 45 kg/m^2 (e.g., ≥46, 47, 48, 49, 50, 51, 52, 53, 54, 55 kg/m^2 or greater) prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.~~

~~222. The method of any of claims 170-221, wherein the subject has failed one or more previous therapies, e.g., exercise, diet, or behavioral therapies, prior to administration of the agonist, e.g., at the time the agonist is prescribed, or at the time of the first administration.~~

~~223. The method of any of claims 170-222, wherein the subject has a lower body weight after administration of the agonist than before administration of the agonist.~~

~~224. The method of any of claims 170-223, wherein administration of the agonist results in a reduction of weight in the subject compared to the weight of the subject before treatment of about 1 kg to 3 kg after 1 week of treatment, or about 1 kg to 6 kg after 2 weeks of treatment,~~

~~or about 2 kg to 12 kg after 4 weeks of treatment, or about 4 kg to 24 kg after 8 weeks of treatment, or about 8 kg to 48 kg after 16 weeks of treatment.~~

~~225. The method of any of claims 170-224, wherein administration of the agonist results in weight loss in the subject at a rate of about 1-2 kg/week, e.g., about 2 kg/week, e.g., over a period of 1-2 weeks of treatment or longer, 2-4 weeks of treatment or longer, 4-8 weeks of treatment or longer, 8-16 weeks of treatment or longer, 16-32 weeks or longer, or 32-64 weeks or longer.~~

~~226. The method of any of claims 170-225, wherein administration of the agonist results in a reduction in hunger level (e.g., a lower score on the Likert hunger scale, e.g., a lower score by at least 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 points) in the subject compared to the hunger level of the subject before treatment, e.g., results in abolishment of hunger (e.g., a score of 0 on the Likert hunger scale) in the subject, e.g., after 1-2 weeks of treatment or longer, 2-4 weeks of treatment or longer, 4-8 weeks of treatment or longer, or 8-16 weeks of treatment or longer.~~

~~227. The method of any of claims 170-226, wherein administration of the agonist results in no detectable/significant decrease in resting energy expenditure (REE) in the subject, e.g., over a period of 24 hours, one week, or 30 days or longer, e.g., as compared to a control REE (e.g., the REE in the subject prior to treatment or a predetermined REE, e.g., in subjects of similar pre-treatment BMI, e.g., when expressed as REE per kg of lean body mass).~~

~~228. The method of claim 227, wherein administration of the agonist results in an increase in resting energy expenditure (REE) in the subject, e.g., over a period of 24 hours, one week, or 30 days, or longer e.g., as compared to a control REE (e.g., the REE in the subject prior to treatment or compared to a predetermined REE, e.g., in subjects of similar pre-treatment BMI, e.g., when expressed as REE per kg of lean body mass, e.g., after a similar level of weight loss has been attained by fasting).~~

~~229. The method of any of claims 170-228, wherein administration of the agonist results in a reduction in food intake by the subject compared to a control (e.g., the food intake of the subject prior to treatment), e.g., wherein the food intake is daily food intake or food intake over a period of 24 hours, or one week.~~

~~230. The method of claim 229, wherein administration of the agonist results in a reduction in food intake of at least 100 kilocalories, e.g., at least 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 525, 550, 575, 600, 1000 kilocalories or more, compared to a control (e.g., the food intake of the subject prior to treatment or a predetermined food intake level), e.g., wherein the food intake is daily food intake or food intake over a period of 24, hours, or one week.~~

~~231. The method of any of claims 170-230, wherein administration of the agonist results in a reduction in waist circumference of the subject compared to a control (e.g., the waist circumference of the subject prior to treatment), as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.~~

~~232. The method of claim 231, wherein administration of the agonist results in a reduction in waist circumference of at least 2 cm (e.g., at least 2, 3, 4, 5, 6, 7, 8, 9, 10 cm or more) in the subject compared to a control (e.g., the waist circumference of the subject prior to treatment), as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.~~

~~233. The method of any of claims 170-232, wherein administration of the agonist results in no detectable increase in blood pressure (e.g., diastolic and/or systolic blood pressure) of the subject compared to the blood pressure of the subject prior to treatment, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.~~

~~234. The method of any of claims 170-233, wherein administration of the agonist results in a reduction in blood pressure (e.g., diastolic and/or systolic blood pressure) of the subject~~

~~compared to the blood pressure of the subject prior to treatment, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.~~

~~235. The method of claim 234, wherein administration of the agonist results in a reduction in systolic blood of the subject of at least 3 mmHg (e.g., at least 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7 mmHg or more) compared to the blood pressure of the subject prior to treatment, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.~~

~~236. The method of claim 234, wherein administration of the agonist results in a reduction in diastolic blood pressure of the subject of at least 4 mmHg (e.g., at least 4, 7, 7.5, 8, 8.5, 9, 9.5, 10 mmHg or more) compared to the blood pressure of the subject prior to treatment, as measured 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more after initiation of treatment.~~

~~237. The method of any of claims 170-236, wherein the subject is a mammal, e.g., a human.~~

~~238. The method of any of claims 170-237, wherein the agonist is Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 (SEQ ID NO: 140).~~

~~239. The method of any of claims 170-238, comprising acquiring knowledge of the genotype of the subject, e.g., acquiring knowledge of the genotype of, e.g., of a mutation in:~~

- ~~the POMC gene;~~
- ~~the PCSK1 gene;~~
- ~~the MAGEL2 gene;~~
- ~~the leptin receptor gene;~~
- ~~the leptin gene;~~
- ~~the 5-HT2c receptor gene;~~
- ~~the nescient helix loop helix 2 (NhHL2) gene;~~
- ~~the carboxypeptidase E (CPE) gene;~~
- ~~the single-minded 1 (SIM1) gene.;~~

~~any of the BBS1-BBS20 genes;~~

~~the ALMS1 gene,~~

~~or the BDNF, MCH1R, MCH, NTRK2,SIM1, ENPP1, COH1, CNR1, NPC1, c-MAF, PTER, FTO, TMEM18 (childhood), SDCCAG8, TNKS/MSRA, GNPDA2 (childhood), NEGr1, INSIG2, KCTD15, or NROB2 gene, or 16p11.2 deletions (including the SH2B1 gene).~~

~~240. The method of claim 239, wherein the agonist is administered in response to the detection of a predetermined sequence, e.g., a mutation, in a gene in claim 239.~~

~~241. The method of any of claims 170-238, comprising acquiring knowledge of the state of methylation of the POMC gene (e.g., hypermethylated at a POMC intron, e.g., at a CpG island of the POMC gene, e.g., comprising a methylated cytosine, e.g., a 5'methyl cytosine).~~

~~242. The method of claim 241, wherein the agonist is administered in response to the detection of hypermethylation.~~

~~243. A unit dosage of an agonist described herein, wherein the unit dosage contains 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, or 2 mg of the agonist.~~

~~244. The unit dosage of claim 243, which contains 0.5 mg of agonist.~~

~~245. The unit dosage of claim 243, which contains 1.0 mg of agonist.~~

~~246. The unit dosage of claim 243, which contains 1.5 mg of agonist.~~

~~247. The unit dosage of any of claims 243-246, suitable for injection, e.g., subcutaneous injection.~~

~~248. The unit dosage of any of claims 243-247, disposed in a delivery device suitable for injection, e.g., subcutaneous injection.~~

~~249. The unit dosage of any of claims 243-248, disposed in a syringe suitable for injection, e.g., subcutaneous injection.~~

~~250. The unit dosage of any of claims 243-249, wherein the agonist is Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 (SEQ ID NO: 140).~~

~~251. The method of claim 64, wherein the disorder is characterized by one or mutations (e.g., loss of function mutations) in a BBS1-19, or 20 gene.~~

~~252. The method of claim 96, wherein the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional BBS1-19, or 20 allele and one non-functional BBS1-19, or 20 allele.~~

~~253. The method of claim 96, wherein the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two non-functional BBS1-19, or 20 alleles, e.g., having a BBS1-19, or 20 null genotype.~~

~~254. The method of claim 96, wherein the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a BBS1-19, or 20 null genotype.~~

~~255. The method of claim 64, wherein the disorder is characterized by one or mutations (e.g., loss of function mutations) in an ALMS1 gene.~~

~~256. The method of claim 255, wherein the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional ALMS1 allele and one non-functional ALM1 allele.~~

~~257. The method of claim 256, wherein the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two non-functional ALMS1 alleles, e.g., having an ALMS1 null genotype.~~

~~258 The method of claim 256, wherein the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having an ALMS1 null genotype.~~

~~259. The method of claim 64, wherein the disorder is characterized by one or more mutations (e.g., loss of function mutations) in the BDNF, MCH1R, MCH, NTRK2,SIM1, ENPP1, COH1, CNR1, NPC1, c-MAF, PTER, FTO, TMEM18 (childhood), SDCCAG8, TNKS/MSRA, GNPDA2 (childhood), NEGr1, INSIG2, KCTD15, or NROB2 gene, or 16p11.2 deletions (including the SH2B1 gene).~~

~~260. The method of claim 250, wherein the subject is or is identified as being a heterozygous carrier of the mutation(s), e.g., having one functional allele and one non-functional allele of the BDNF, MCH1R, MCH, NTRK2,SIM1, ENPP1, COH1, CNR1, NPC1, c-MAF, PTER, FTO, TMEM18 (childhood), SDCCAG8, TNKS/MSRA, GNPDA2 (childhood), NEGr1, INSIG2, KCTD15, or NROB2 gene, or 16p11.2 deletions (including the SH2B1 gene).~~

~~261. The method of claim 250, , wherein the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two non-functional alleles, e.g., having a null genotype, of of the BDNF, MCH1R, MCH, NTRK2,SIM1, ENPP1, COH1, CNR1, NPC1, c-MAF, PTER, FTO, TMEM18 (childhood), SDCCAG8,~~

~~TNKS/MSRA, GNPDA2 (childhood), NEGr1, INSIG2, KCTD15, or NROB2 gene, or 16p11.2 deletions (including the SH2B1 gene).~~

5