METHODS OF TREATING MELANOCORTIN-4 RECEPTOR PATHWAY-ASSOCIATED DISORDERS

CLAIM OF PRIORITY

This application claims priority to U.S. Application No. 63/082,867, filed on September 24, 2020, the entire contents of which are incorporated herein by reference.

BACKGROUND

The melanocortin 4 receptor (MC4R) is a heterotrimeric G-protein-coupled receptor that transduces signals by activating adenylate cyclase. MC4R is primarily expressed in neuronal tissue and plays a role in controlling feeding behavior and energy homeostasis by, for example, integrating an agonist signal provided by the α-melanocyte stimulating hormone (α-MSH), and an antagonist signal provided by the agouti-related peptide (AGRP).

MC4R is a part of the leptin-melanocortin pathway, also known as the POMC-MC4R pathway, which includes a number of proteins such as leptin, leptin receptors, pro-opiomelanocortin (POMC), and prohormone convertases including PCSK1, α-MSH, and others. In mammals, the hypothalamic POMC-MC4R pathway is part of the regulatory network of appetite and body weight.

SUMMARY ~~OF THE INVENTION~~

The present disclosure features, *inter alia*, treatments for diseases, disorders, and conditions related to the melanocortin-4 receptor (MC4R) pathway. In one ~~aspect~~example, the present disclosure comprises a method of treating a disease, disorder, or condition in a subject having an MC4R pathway agonizable gene with a compound (e.g., an MC4R agonist) or compositions thereof. In some ~~embodiments~~examples, the MC4R agonist is a compound of any one of Formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or (XII), (e.g., as described herein) or a pharmaceutically acceptable salt thereof. In one aspect, the present disclosure provides a use of a composition comprising a melanocortin-4 receptor (MC4R) agonist in the manufacture of a medicament for treating a disease, disorder, or condition, wherein the disease, disorder, or condition is related to an MC4R pathway agonizable gene selected from ARL6, RAI1, SRC1, BBS19, BBS21, CEP290, IFT74,

LZTFL1, MKS1, TRIM32, WDPCP, RPS6KA3, HTR2C, KSR2, PROK2, RAB23, MRAP2, AFF4, ADCY3, TUB, OTP, GPR101, TBX3, ACBD7, AGRP, CADM1, CADM2, CARTPT, CCDC28B, CCK, CNR1, CREBBP, CREBRF, CUL4B, DYRK1B, ENPP1, EP300, FMR1, FTO, GHRL, GIPR, GLP1R, INPP5E, INS, INSIG2, IRS1, IRS4, KCTD15, KIDINS220, MCHR1, MSRA, NDN, NEGR1, NLGN2, NPY, NR0B2, NTRK2, PCNT, PCSK2, PHF6, PMCH, PPARG, PYY, SDC3, SEC16B, SLC6A14, SNRPN, THRB, TMEM18, TMEM67, TRAPPC9, UCP1, UCP3, VPS13B, NRP1, NRP2, PLXNA1, PLXNA2, PLXNA3, PLXNA4, SEMA3A, SEMA3B, SEMA3D, SEMA3E, SEMA3F, SEMA3G, DNMT3A, RPGRIP1L, ISL1, TRPC5, PHIP, and MeCP2.

In some ~~embodiments~~examples, the subject has or is identified as having a mutation (e.g., a substitution mutation, a deletion mutation, or a polymorphism, e.g., a loss of function mutation) or an epigenetic modification in or at an MC4R pathway agonizable gene, e.g., as described herein. In some ~~embodiments~~examples, the MC4R pathway agonizable gene is selected

from ARL6, RAI1, SRC1, BBS19, BBS21, CEP290, IFT74, LZTFL1, MKS1, TRIM32, WDPCP, RPS6KA3, HTR2C, KSR2, PROK2, RAB23, MRAP2, AFF4, ADCY3, TUB, OTP, GPR101, TBX3, ACBD7, AGRP, CADM1, CADM2, CARTPT, CCDC28B, CCK, CNR1, CREBBP, CREBRF, CUL4B, DYRK1B, ENPP1, EP300, FMR1, FTO, GHRL, GIPR, GLP1R, INPP5E, INS, INSIG2, IRS1, IRS4, KCTD15, KIDINS220, MCHR1, MSRA, NDN, NEGR1, NLGN2, NPY, NR0B2, NTRK2, PCNT, PCSK2, PHF6, PMCH, PPARG, PYY, SDC3, SEC16B, SLC6A14, SNRPN, THRB, TMEM18, TMEM67, TRAPPC9, UCP1, UCP3, VPS13B, NRP1, NRP2, PLXNA1, PLXNA2, PLXNA3, PLXNA4, SEMA3A, SEMA3B, SEMA3D, SEMA3E, SEMA3F, SEMA3G, DNMT3A, RPGRIP1L, ISL1, TRPC5, PHIP, and MeCP2. In some ~~embodiments~~examples, the MC4R pathway agonizable gene is selected from ARL6, RAI1, SRC1, BBS19, BBS21, CEP290, IFT74, LZTFL1, MKS1, TRIM32, WDPCP, RPS6KA3, HTR2C, KSR2, PROK2, RAB23, MRAP2, AFF4, ADCY3, TUB, OTP, GPR101, TBX3, ACBD7, AGRP, CADM1, CADM2, CARTPT, CCDC28B, CCK, CNR1, CREBBP, CREBRF, CUL4B, DYRK1B, ENPP1, EP300, FMR1, FTO, GHRL, GIPR, GLP1R, INPP5E, INS, INSIG2, IRS1, IRS4, KCTD15, KIDINS220, MCHR1, MSRA, NDN, NEGR1, NLGN2, NPY, NR0B2, NTRK2, PCNT, PCSK2, PHF6, PMCH, PPARG, PYY, SDC3, SEC16B, SLC6A14, SNRPN, THRB, TMEM18, TMEM67, TRAPPC9, UCP1, UCP3, VPS13B, NRP1, NRP2, PLXNA1, PLXNA2, PLXNA3, PLXNA4, SEMA3A, SEMA3B, SEMA3D, SEMA3E, SEMA3F, SEMA3G, DNMT3A, RPGRIP1L, ISL1, and MeCP2. In some ~~embodiments~~examples, the MC4R pathway agonizable gene is selected from RAI1 and SRC1. In some ~~embodiments~~examples, the MC4R pathway agonizable gene is RAI1. In some ~~embodiments~~examples, the MC4R pathway agonizable gene is SRC1. In some ~~embodiments~~examples, the MC4R pathway agonizable gene is TRPC5. In some ~~embodiments~~examples, the MC4R pathway agonizable gene is PHIP. In some ~~embodiments~~examples, the MC4R pathway agonizable gene is PCSK1 N221D. In some ~~embodiments~~examples, the MC4R pathway agonizable gene is selected from a gene listed in Table 1, e.g., described herein.

In some ~~embodiments~~examples, the MC4R pathway agonizable gene is POMC, PCSK1, LEPR, LEP, MC4R, SDCCAG8, SH2B1, CPE, ALMS1, BBS1, BBS2,

BBS4, BBS5, BBS6, BBS7, BBS8, BBS9, BBS10, BBS12, BBS18, BBS20, GNAS, MC3R, NHLH2, SIM1, BDNF, NTRK2, MAGEL2, or a 16p11.2 deletion.

In some ~~embodiments~~examples, the subject carries, or is identified as carrying, a mutation in a MC4R pathway agonizable gene. In an embodiment, the subject is, or is identified as being, heterozygous for a mutation in the MC4R pathway agonizable gene.

In some ~~embodiments~~examples, a heterozygous subject carries, or is identified as carrying, a non-functional, e.g., mutant, e.g., null mutant, allele of the MC4R pathway agonizable gene and a functional or wildtype allele of the MC4R pathway agonizable gene.

In some ~~embodiments~~examples, a heterozygous subject carries, or is identified as carrying, a first non-functional, e.g., mutant, e.g., null mutant, allele of the MC4R pathway agonizable gene and a second non-functional or mutant, e.g., null mutant, allele of the MC4R pathway agonizable gene. For example, the subject is a compound heterozygous carrier having two distinct non-functional alleles.

In some ~~embodiments~~examples, the subject is, or is identified as, homozygous for a non-functional, e.g., mutant, e.g., null mutant, allele of an MC4R pathway agonizable gene.

In some ~~embodiments~~examples, the subject carries, or is identified as carrying, a mutation in a second MC4R pathway agonizable gene. In an embodiment, the subject is, or is identified as being, heterozygous for a mutation in the second MC4R pathway agonizable gene. In some ~~embodiments~~examples, a heterozygous subject carries, or is identified as carrying, a non-functional, e.g., mutant, e.g., null mutant, allele of the second MC4R pathway agonizable gene and a functional or wildtype, allele of the second MC4R pathway agonizable gene. In an embodiment, a heterozygous subject carries, or is identified as carrying, a first non-functional, e.g., mutant, e.g., null mutant, allele of the second MC4R pathway agonizable gene and a second non-functional or mutant, e.g., null mutant, allele of second the MC4R pathway agonizable gene. For example, the subject is a compound heterozygous carrier having two distinct non-functional alleles.

In some ~~embodiments~~examples, the subject is, or is identified as, homozygous for a non-functional, e.g., mutant, e.g., null mutant, allele of a second MC4R pathway agonizable gene.

The MC4R agonist, e.g., a compound of any one of Formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or (XII), or a pharmaceutically acceptable salt thereof, may be provided as a composition (e.g., a pharmaceutical composition) with a

pharmaceutically acceptable excipient. In an embodiment, the pharmaceutically acceptable excipient comprises a polyethylene glycol (e.g., a modified polyethylene glycol), a lipid (e.g., a neutral lipid or a phospholipid). In an embodiment, the pharmaceutically acceptable excipient comprises a modified polyethylene glycol. In an embodiment, the pharmaceutically acceptable excipient comprises a lipid, such as a neutral diacyl lipid or a phospholipid.

The MC4R agonist or composition thereof may be provided in a unit dosage form. For example, the unit dosage form may comprise between about 0.01 mg to 100 mg of the MC4R agonist. In an embodiment, the unit dosage form comprises between 0.1 mg and 100 mg, e.g., between 0.1 mg and 50 mg, 0.1 mg and 25 mg, 0.1 mg and 10 mg, 1 mg and 100 mg, 1 mg and 50 mg, 1 mg and 25 mg, 1 mg and 10 mg, 5 mg and 100 mg, 5 mg and 50 mg, 5 mg and 25 mg, 5 mg and 15 mg, or 5 mg and 10 mg.

The MC4R agonist or composition thereof may be administered to a subject daily, weekly or monthly. In an embodiment, the MC4R agonist or composition thereof is administered daily, e.g., once daily, twice daily, or three times daily. In an embodiment, the MC4R agonist or composition thereof is administered weekly, e.g., once every week, once every two weeks, once every three weeks. In ~~embodiments~~examples, the MC4R agonist or composition thereof 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 ~~embodiments~~examples, the method comprises administering the MC4R agonist or composition thereof in a unit dosage form suitable for injection, e.g., subcutaneous injection, to the subject. In ~~embodiments~~examples, the unit dosage form is disposed within a delivery device, e.g., a syringe (e.g., prefilled syringe), an implantable device, a needleless hypodermic injection device, an infusion pump (e.g., implantable infusion pump), or an osmotic delivery system. In ~~embodiments~~examples, the MC4R agonist is administered subcutaneously, e.g., by subcutaneous injection.

In ~~embodiments~~examples, the subject is obese, e.g., severely obese. In ~~embodiments~~examples, the subject has early onset severe obesity. In ~~embodiments~~examples, the subject is hyperphagic. In ~~embodiments~~examples, the subject experiences severe hunger. In ~~embodiments~~examples, 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 MC4R agonist, e.g., at the time the MC4R agonist is prescribed, or at the time of the first administration. In ~~embodiments~~examples, 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 MC4R agonist, e.g., at the time the MC4R agonist is prescribed, or at the time of the first administration. In ~~embodiments~~examples, 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 MC4R agonist, e.g., at the time the MC4R agonist is prescribed, or at the time of the first administration. In ~~embodiments~~examples, 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 MC4R agonist, e.g., at the time the MC4R agonist is prescribed, or at the time of the first administration.

In ~~embodiments~~examples, the subject has a BMI higher than the 85-95th percentile prior to administration of the MC4R agonist or composition thereof, e.g., at the time the MC4R agonist is prescribed, or at the time of the first administration.

In ~~embodiments~~examples, the subject has failed one or more previous therapies, e.g., exercise, diet, or behavioral therapies, prior to administration of the MC4R agonist or composition thereof, e.g., at the time the agonist is prescribed, or at the time of the first administration.

In ~~embodiments~~examples, the subject has a lower body weight after administration of the MC4R agonist or composition thereof than before administration of the agonist.

In ~~embodiments~~examples, administration of the MC4R agonist or composition thereof 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 ~~embodiments~~examples, administration of the MC4R agonist or composition thereof results in a reduction of BMI by

about 1%, 2%, 3%, 5%, 6%, 7%, 8%, 9%, 10%, or more, e.g., by at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 weeks or longer.

In ~~embodiments~~examples, administration of the MC4R agonist or composition thereof 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 ~~embodiments~~examples, administration of the MC4R agonist or composition thereof 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~~examples, the reduction in food intake is relative to the food intake at baseline. In ~~embodiments~~examples, the baseline food intake is at least 100 kcal/kg/day, e.g., for a pediatric subject at about 1 year of age. In ~~embodiments~~examples, the baseline food intake is at least 40 kcal/kg/day, e.g., for a pediatric subject, e.g., in late adolescence.

In ~~embodiments~~examples, administration of the MC4R agonist or composition thereof 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 ~~embodiments~~examples, administration of the MC4R agonist or composition thereof 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 ~~embodiments~~examples, administration of the MC4R agonist or composition thereof 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 ~~embodiments~~examples, administration of the MC4R agonist or composition thereof 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 ~~embodiments~~examples, administration of the MC4R agonist or composition thereof 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 ~~embodiments~~examples, administration of the MC4R agonist or composition thereof results in a reduction of hunger in a subject. The reduction of hunger may result in a reduction of food intake, decrease in resting energy expenditure (REE), reduction of weight, reduction in waist circumference, and/or reduction in blood pressure in the subject.

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

In ~~embodiments~~examples, the method further comprises acquiring knowledge of the genotype of the subject, e.g., acquiring knowledge of the genotype of an MC4R pathway agonizable gene, e.g., a gene listed in Table 1. In ~~embodiments~~examples, 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 ~~embodiments~~examples, the MC4R agonist or composition thereof is administered in response to the detection of a predetermined sequence, e.g., a mutation, MC4R pathway agonizable gene, e.g., a gene listed in Table 1. In ~~embodiments~~examples, 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 (e.g., DNA sequencing, e.g., next generation sequencing or Sanger method sequencing, bisulfite sequencing, or pyrosequencing), screening analysis, FISH, spectral karyotyping or MFISH, comparative genomic hybridization, *in situ* hybridization, SSP, HPLC, or mass-spectrometric genotyping. In ~~embodiments~~examples, the predetermined sequence, e.g., mutation, is detected in the subject. In ~~embodiments~~examples, the predetermined sequence, e.g., mutation, is detected in a nucleic acid molecule or a polypeptide in a sample from the subject. In ~~embodiments~~examples, the sample comprises cells from a blood, serum, urine, or tissue (e.g., biopsy) from the subject. In ~~embodiments~~examples, 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 a gene listed in

In some ~~embodiments~~examples, the compound is a compound of Formula (I) or a pharmaceutically acceptable salt thereof. In some ~~embodiments~~examples, the compound of Formula (I) 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 some ~~embodiments~~examples, the compound is a compound of Formula (II) or a pharmaceutically acceptable salt thereof. In some

~~embodiments~~examples, the compound of Formula (II) is Hydantoin(C(O)-(Arg-Gly))-cyclo(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH_2 (SEQ ID NO:13) or a pharmaceutically acceptable salt thereof. In some ~~embodiments~~examples, the compound of any one of Formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or (XII),is formulated as a pharmaceutical composition.

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. Other features, objects, and advantages of the disclosure will be apparent from the description and drawings, and from the claims.

DETAILED DESCRIPTION

The present disclosure is based at least in part on the discovery that targeting certain defects in the POMC-MC4R pathway, e.g., such as mutations in an MC4R pathway agonizable gene by using a MC4R agonist, may lead to significant weight loss, decrease in hunger, and/or an increase in energy expenditure in obese subjects. The disclosure is also based in part on the discovery that obese subjects having a defect (e.g., genetic defect) in an MC4R pathway agonizable genes are likely to exhibit a significantly greater response (e.g., in decreasing body weight and/or hunger and/or increasing energy expenditure) to an MC4R agonist than obese subjects not having such a defect.

Without being bound by theory, a MC4R agonist, such as a compound of any one of Formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or (XII), (e.g., as described herein), e.g., setmelanotide (i.e., Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2, SEQ ID NO: 140) or a pharmaceutically acceptable salt thereof, can act to replace a missing MC4R signaling step in subjects having a genetic defect

CLAIMS

1. ~~A~~Use of a composition comprising ~~method of treating a disease, disorder, or condition in a subject comprising administering to the subject~~ a melanocortin-4 receptor (MC4R) agonist in the manufacture of a medicament for treating a disease, disorder, or condition, wherein the disease, disorder, or condition is related to an MC4R pathway agonizable gene selected from ARL6, RAI1, SRC1, BBS19, BBS21, CEP290, IFT74, LZTFL1, MKS1, TRIM32, WDPCP, RPS6KA3, HTR2C, KSR2, PROK2, RAB23, MRAP2, AFF4, ADCY3, TUB, OTP, GPR101, TBX3, ACBD7, AGRP, CADM1, CADM2, CARTPT, CCDC28B, CCK, CNR1, CREBBP, CREBRF, CUL4B, DYRK1B, ENPP1, EP300, FMR1, FTO, GHRL, GIPR, GLP1R, INPP5E, INS, INSIG2, IRS1, IRS4, KCTD15, KIDINS220, MCHR1, MSRA, NDN, NEGR1, NLGN2, NPY, NR0B2, NTRK2, PCNT, PCSK2, PHF6, PMCH, PPARG, PYY, SDC3, SEC16B, SLC6A14, SNRPN, THRB, TMEM18, TMEM67, TRAPPC9, UCP1, UCP3, VPS13B, NRP1, NRP2, PLXNA1, PLXNA2, PLXNA3, PLXNA4, SEMA3A, SEMA3B, SEMA3D, SEMA3E, SEMA3F, SEMA3G, DNMT3A, RPGRIP1L, ISL1, TRPC5, PHIP, and MeCP2.

2. The use according to~~method of~~ claim 1, wherein the disease, disorder, or condition is characterized by a mutation (e.g., a substitution mutation, a deletion mutation, or a polymorphism) in the MC4R pathway agonizable gene.

3. The use according to~~method of~~ claim 2, wherein the subject is homozygous or heterozygous for the mutation in the MC4R pathway agonizable gene.

4. The use according to~~method of~~ claim 2, 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 MC4R pathway agonizable gene.

5. The use according to~~method of~~ claim 2, wherein the subject is or is identified as being a compound heterozygous carrier of the mutation(s), e.g., having two distinct non-functional alleles, e.g., having the MC4R pathway agonizable gene.

6. The use according to~~method of~~ claim 2, wherein the subject is or is identified as being a homozygous carrier of the mutation(s), e.g., having a homozygous null genotype of the MC4R pathway agonizable gene.

7. The use according to~~method of~~ claim 1, wherein the MC4R pathway agonizable gene is selected from RAI1 and SRC.

8. The use according to~~method of~~ claim 7, wherein the MC4R pathway agonizable gene is RAI1.

9. The use according to~~method of~~ claim 7, wherein the MC4R pathway agonizable gene is SRC.

10. The use according to~~method of~~ claim 1, wherein the disease, disorder, or condition is characterized by a plurality of mutations (e.g., at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 mutations) in the MC4R pathway agonizable gene.

11. The use according to~~method of~~ claim 10, wherein the plurality of MC4R pathway agonizable genes comprises RAI1 and SRC.

12. The use according to~~method of~~ claim 10, wherein the plurality of MC4R pathway agonizable genes further comprises SHH2.

13. The use according to~~method of~~ claim 1, wherein the disease, disorder, or condition is characterized by modulation (e.g., upregulation or downregulation) of the MC4R pathway agonizable gene.

14. The use according to~~method of~~ claim 1, wherein the disease, disorder, or condition comprises Bardet-Biedl syndrome, Alstrom Syndrome, Prader Willi syndrome, hypothalamic obesity, or Smith-Magenis syndrome.

~~15. The method of claim 1, wherein the disease, disorder, or condition comprises Bardet-Biedl syndrome.~~

~~16. The method of claim 1, wherein the disease, disorder, or condition comprises Alstrom Syndrome.~~

~~17. The method of claim 1, wherein the disease, disorder, or condition comprises Prader Willi syndrome.~~

~~18. The method of claim 1, wherein the disease, disorder, or condition comprises Smith-Magenis syndrome.~~

~~19. The method of claim 1, wherein the disease, disorder, or condition comprises hypothalamic obesity.~~

~~20~~15. The use according to~~method of~~ claim 1, wherein a symptom of the disease, disorder, or condition comprises obesity or hyperphagia.

~~21~~16. The use according to~~method of~~ claim 1, wherein the MC4R agonist ~~is~~ has the 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 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, Phe, D-1-Nal, D-2-Nal, D-Trp, D-Bal, D-(X^1, X^2, X^3, X^4, X^5)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^1~~X′~~, X^2, X^3, X^4, and X^5~~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.

~~22~~17. The use according to~~method of~~ claim 21, wherein A^1 is selected from Lys, D-Lys, Arg, and D-Arg.

~~23~~18. The use according to~~method of~~ claim 21, wherein A^2 and A^9 are each independently selected from Cys, hCys, and Pen.

~~24~~19. The use according to~~method of~~ claim 21, wherein A^3 is selected from Ala or D-Ala.

~~25~~20. The use according to~~method of~~ claim 21, wherein A^4 is selected from His and D-His.

~~26~~21. The use according to~~method of~~ claim 21, wherein A^5 is selected from Phe, D-Phe, D-1-Nal, and D-2-Nal.

~~27~~22. The use according to~~method of~~ claim 21, wherein A^6 is Arg.

~~28~~23. The use according to~~method of~~ claim 21, wherein A^7 is Trp.

~~29~~24. The use according to~~method of~~ claim 21, wherein A^8 and/or A^{10} is deleted.

~~30~~25. The use according to~~method of~~ claim 21, wherein R^1 is NH_2.

~~31~~26. The use according to~~method of~~ claim 21, wherein one of R^2 and R^3 is independently hydrogen and the other of R^2 and R^3 is independently (C_1-C_{30}) acyl (e.g., acetyl).

~~32~~27. The use according to~~method of~~ claim 1, wherein the MC4R agonist is Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 (SEQ ID NO: 140).

~~33~~28. The use according to~~method of~~ claim 1, wherein the MC4R agonist is formulated as a pharmaceutical composition.

~~34~~29. The use according to~~method of~~ claim 33, wherein the pharmaceutical composition further comprises a pharmaceutically acceptable excipient.

~~35~~30. The use according to~~method of~~ claim 33, wherein the pharmaceutical composition comprises a polyethylene glycol (e.g., a modified polyethylene glycol, e.g., mPEG-DSPE, e.g., mPEG-2,000-DSPE)

~~36~~31. The use according to~~method of~~ claim 1, comprising administering the MC4R agonist in a unit dosage suitable for injection, e.g., subcutaneous injection, to the subject.

~~37~~32. The use according to~~method of~~ claim 36, wherein the unit dosage form is disposed within a delivery device, e.g., a syringe (e.g., prefilled syringe),an implantable device, a needleless hypodermic injection device, an infusion pump (e.g., implantable infusion pump), or an osmotic delivery system.

~~38~~33. The use according to~~method of~~ claim 37, wherein the MC4R agonist is administered subcutaneously, e.g., by subcutaneous injection.

~~39~~34. The use according to~~method of~~ claim 1, wherein the subject is obese, e.g., severely obese.

~~40~~35. The use according to~~method of~~ claim 1, wherein the subject is hyperphagic.

~~41~~36. The use according to~~method of~~ claim 1, 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 MC4R agonist, e.g., at the time the MC4R agonist is prescribed, or at the time of the first administration.

~~42. The method of claim 1, 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 MC4R agonist, e.g., at the time the MC4R agonist is prescribed, or at the time of the first administration.~~

~~43~~37. The use according to~~method of~~ claim 1, wherein the subject has failed one or more previous therapies, e.g., exercise, diet, or behavioral therapies, prior to administration of the MC4R agonist, e.g., at the time the MC4R agonist is prescribed, or at the time of the first administration.

~~44~~38. The use according to~~method of~~ claim 1, wherein the subject has a lower body weight after administration of the MC4R agonist than before administration of the MC4R agonist.