CLAIMS

What is claimed:

1. A computer-implemented method for generating a classifier for an obesity phenotype using a trait associated with obesity, the method comprising:

   (a) receiving in a computer system, regression weights obtained from a regression analysis between each genetic variant in a genetic dataset obtained from a sample obtained from each subject from a population of subjects and a value for a trait for each subject from the population of subjects, wherein each subject in the population of subjects is obese and the trait is associated with obesity;

   (b) selecting by the computer system, regression analysis weights from (a) for genetic variants located in, around or near a set of genes present in the genetic dataset and known to play a role in obesity;

   (c) calculating by the computer system, a gene risk score (GRS) for each gene in the set of genes, wherein the calculating comprises: (i) populating a function with the regression weights for the genetic variants from (b); and (ii) populating the function with one or more additional parameters selected from the group consisting of known or theoretical mechanistic role of each genetic variant on a gene from the set of genes, proximity of each genetic variant to a gene from the set of genes, dosage of genetic variants across an extended region of megabase pairs flanking a gene from the set of genes and any combination thereof, thereby calculating a gene risk score (GRS) for each gene in the set of genes;

   (d) inputting features that comprise the GRS for each gene in the set of genes along with non-genetic and/or multi-omic data for each subject from the population of subjects into a machine learning model on the computer system to select features that are predictive of an obesity phenotype; and

   (e) training by the computer system a classifier model to predict subjects from a training set of obese subjects as having a known value of the obesity phenotype by: (i) obtaining the features selected in (d) for each of the subjects from the training set of obese subjects; and (ii) inputting the features from (e)(i) into the classifier model, thereby generating a trained ML-GRS classifier for the obesity phenotype.

2. The computer-implemented method of claim 1, wherein the plurality of genetic variants comprises single nucleotide polymorphisms (SNPs).

3. The computer-implemented method of claim 1 or 2, wherein each gene in the set of genes is known or suspected to play a role in appetite regulation, energy expenditure, lipid metabolism or adipogenesis.
4. The computer-implemented method of claim 2, wherein the known or theoretical mechanistic role of the SNP: (a) is selected from the group consisting of synonymous mutation, nonsynonymous mutation, deletion or frameshift mutation and nonsense mutation; (b) affects the three-dimensional structure of the translated protein binding sites, protein-protein interaction sites and modification sites, wherein the modification sites are selected from the group consisting of phosphorylation, glycosylation and proteolytic site; or (c) comprises whether or not the SNP is within an intron, exon, enhancer region or regulatory region of the gene, a cis-regulatory element, a promoter region, a non-coding exonic region, a coding exonic region, intronic region, splice site, transcription factor binding site, epigenetic modification site, at a remote genomic location involved in a three-dimensional chromatin contact with the gene, or a cell-type-specific topological-associated domain that contains the gene.
5. The computer-implemented method of any one of the above claims, wherein the non-genetic and/or multi-omic data is selected from the group consisting of anthropometric data, metabolomic data, proteomic data, peptidomic data, epigenetic data, microbiome data, results from one or more questionnaires and any combination thereof.
6. The computer-implemented method of any one of the above claims, wherein the machine learning model comprises a forward feature selection, backward feature selection, or random feature sampling algorithm and a random forest, GBM, or linear predictor that iteratively selects a feature with a desired training accuracy using the random forest predictor in multiple rounds until no further training accuracy improvement is detected.
7. The computer-implemented method of any one of the above claims, wherein the GRSs of step (d) are normalized.
8. The computer-implemented method of any one of the above claims, wherein the classifier model is selected from the group consisting of a support vector classifier (SVC), gradient boosted machine (GBM), neural network (NN), convolutional neural network (CNN), logistic regression, classification and regression trees (CRT), Bayesian inference and clustering method.
9. The computer-implemented method of any one of the above claims, wherein

the obesity phenotype is selected from the group consisting of abnormal satiation, abnormal satiety, resting energy expenditure (REE) or hedonic/emotional eating.

10. The computer-implemented method of any one of the above claims, wherein the trait associated with obesity is one or more of the following: total kcal consumed to satiation (CTS) at an *ad libitum* meal, gastric emptying amount of time, resting metabolic rate from indirect calorimetry, or score from a behavioral questionnaire indicative of level of anxiety or depression for the subject.
11. The computer-implemented method of any one of the above claims, further comprising determining if a test subject is positive for the obesity phenotype by: (i) obtaining the selected features from 1(d) for the test subject; and (ii) inputting the selected features for the test subject into the trained ML-GRS classifier from 1(e), wherein the test subject is positive for the obesity phenotype if the trained ML-GRS classifier predicts the subject has a value of the trait indicating the subject has the obesity phenotype or negative for the obesity phenotype if the trained ML-GRS classifier predicts the subject has a value of the trait indicating the subject does not have the obesity phenotype.
12. The computer-implemented method of any one of the above claims, wherein the trait is total kcal consumed to satiation (CTS) at an *ad libitum* meal and the obesity phenotype is abnormal satiation, wherein if the trained ML-GRS classifier for the abnormal satiation obesity phenotype predicts the subject is above the sex-specific 75th percentile for CTS that subject is considered to possess a high CTS_{GRS} and is positive for the abnormal satiation phenotype or if the trained ML-GRS classifier for CTS predicts the subject is below the sex-specific 75th percentile for CTS that subject is considered to possess a low CTS_{GRS} and is negative for the abnormal satiation phenotype.
13. The computer-implemented method of claim 11, wherein the set of genes are two or more genes selected from GLP1R, UCP2, FTO, TCF7L2, MBOAT4 (GOAT), ADRA2A, GNB3, GPBAR1, LEP, LEPR, SH2B1, SIM1, NCOA1 (SRC1), PCSK1, TMEM18, NEGR1, BDNF, GPRC5B, GNPDA2, MTCH2, KCTD15, SEC16B, FAIM2, TNNI3K, LINGO1, FANCL, CADM2, PTBP2, NUDT3, OLFM4, HOXB5, NPY1R, NPY2R, NPY4R, NPY5R, NR1H4, SLC6A4, NTS, UCP3, ADIPOQ, CCK, DPP4, FGFR4, GHRL, MC4R, MC3R, POMC, AGRP, GIPR, CNR1, FAAH, GCG, CELA2A, PPARG, TFAP2B, APOE, TNFRSF11A or DYRK1B.

14. Use of a composition comprising phentermine/topiramate in the manufacture of a medicament for treating obesity in a subject suffering from obesity, wherein the subject is determined to possess a high CTS_{GRS} using the method of any one of claims 10-12.
15. Use of a composition comprising a GLP-1 agonist in the manufacture of a medicament for treating obesity in a subject suffering from obesity, wherein the subject is determined to possess a low CTS_{GRS} using the method of any one of claims 10-12.
16. The use of claim 14, wherein the GLP-1 agonist is selected from the group consisting of exenatide, liraglutide, albiglutide, dulaglutide, lixisenatide, semaglutide and tirzepatide.