

## SUMMARY

**[0015]** A method and system that detects regulatory drug networks in humans using bioinformatics and computational methods such as machine learning and deep learning. The foundation for these methods is the ability to reveal previously unrecognized drug pharmacogenomic networks through interrogation of pharmacogenomic regulatory interactions embedded within the functional three-dimensional (3D) topology of the human genome using mutations that stratify drug response in large human populations. These spatial regulatory interactions provide the architecture for the pharmacogenomic network for most psychotropic and anti-neoplastic drugs.

**[0016]** There now exists an enormous amount of extant data that can be used to computationally map drug pathways *in lieu* of additional experiments in animal and cellular models and without resorting to the use of sophisticated probabilistic inference methods. These knowledge-based methods described herein can be used to reconstruct drug pharmacogenomic networks acting in different cell types and tissues and deconstruct these networks into constitutive parts that mediate different on-target and off-target mechanisms of a drug, validated *post hoc* using bioinformatics analysis.

**[0017]** These methods differ from studies that require experimental perturbation of the biology of cells or tissues following drug exposure, or those that entirely depend on the centrality of learning machines for pathway mapping. An important part of the process of determining whether a single nucleotide polymorphism (SNP: may be a single base pair change or a short insertion/deletion) that has been significantly associated with a specific drug response is the use of different machine learning algorithms for determination of probable mechanistic causality. Nonetheless, the primary mapping methods are based on 3D genome structure and an existing knowledge base drawn from multiple public data sources and/or from experimental data or proprietary data.

**[0017a]** In one aspect, the present disclosure provides a computer-implemented method for identifying a pharmacogenomic network of a drug, the method executed by one or more processors programmed to perform the method, the method comprising:

obtaining, by one or more processors, a plurality of single nucleotide polymorphisms (SNPs) correlated with drug response or adverse events for a ~~psychotropic particular~~ drug;

identifying, by the one or more processors, a drug pharmacogenomic network for the ~~psychotropic particular~~ drug based on ~~a set of~~ target genes associated with the plurality of SNPs;

deconstructing, by the one or more processors, the drug pharmacogenomic network into a plurality of drug pharmacogenomic sub-networks using a topology of sub-network types selected from two or more of: a chromatin remodeling sub-network type, a drug efficacy sub-network type, a drug adverse events sub-network type, a pharmacokinetic enzymes and hormones sub-network type, a systemic pharmacokinetics sub-network type, or an immune system adverse events sub-network type by:

organizing the target genes into functional subsets based on functionality of each of the target genes using iterative gene set optimization to identify a plurality of drug pharmacogenomic sub-networks for the psychotropic drug corresponding to each of the functional subsets; and

providing, by the one or more processors, an indication of the drug pharmacogenomic network and indications of the plurality of drug pharmacogenomic sub-networks for display.

**[0017b]** In another aspect, the present disclosure provides a computing device for identifying a pharmacogenomic network of a drug, the computing device comprising:

a communication network,

one or more processors; and

a non-transitory computer-readable memory coupled to the one or more processors and storing thereon instructions that, when executed by the one or more processors, cause the computing device to:

obtain a plurality of single nucleotide polymorphisms (SNPs) correlated with drug response or adverse events for a ~~psychotropic particular~~ drug;

identify a pharmacogenomic network for the ~~psychotropic particular~~ drug based on ~~a set of~~ target genes associated with the plurality of SNPs;

deconstruct the drug pharmacogenomic network into a plurality of drug pharmacogenomic sub-networks using a topology of sub-network types selected from two or more of: a chromatin remodeling sub-network type, a drug efficacy sub-network type, a drug adverse events sub-network type, a pharmacokinetic enzymes and hormones sub-network type, a systemic pharmacokinetics sub-network type, or an immune system adverse events sub-network type by:

organizing the target genes into functional subsets based on functionality of each of the target genes using iterative gene set optimization to identify a plurality of drug pharmacogenomic sub-networks for the psychotropic drug corresponding to each of the functional subsets; and

provide, via the communication network, an indication of the drug pharmacogenomic network and indications of the plurality of drug pharmacogenomic sub-networks for display.

**[0017c]** In another aspect, the present disclosure provides a method for identifying a combination of drugs to test as a therapeutic for a particular disease, the method executed by one or more processors programmed to perform the method, the method comprising:

obtaining, by one or more processors, a first plurality of single nucleotide polymorphisms (SNPs) correlated with drug response or adverse events for a first psychotropic drug;

obtaining, by one or more processors, a second plurality of SNPs correlated with drug response or adverse events for a second psychotropic drug;

identifying, by the one or more processors, a first drug pharmacogenomic network for the first psychotropic drug based on a first set of genes associated with the first plurality of SNPs;

identifying, by the one or more processors, a second drug pharmacogenomic network for the second psychotropic drug based on a second set of genes associated with the second plurality of SNPs;

identifying, by the one or more processors, a first drug response phenotype associated with the first set of genes in the first drug pharmacogenomic network that is complementary to a second drug response phenotype associated with the second set of genes in the second drug pharmacogenomic network using gene set enrichment to identify the complementary first and second drug response phenotypes; and

re-purposing a combination of the first and second drug to test as a therapeutic for a particular disease.

**[0018]** Figure 1D illustrates an exemplary model for how the system integrates and processes multi-scale data using machine learning and deep learning for pharmacogenomic network reconstruction. This strategy for mapping drug networks provides insight into the *mechanistic* on- and off-target effects, laying a foundation for subsequent preclinical studies;

**[0019]** Figure 1E shows a method for the detection of drug pharmacogenomic networks in humans, which may be executed by a server device. The first step in the method includes extracting significant SNPs that have been associated with a specific drug response. The majority of these SNPs have been published in genome-wide association studies (GWAS) and phenome-wide association studies (PheWAS), and there is also a wealth of unbiased, peer-reviewed scientific publications where such data may be obtained. To improve the accuracy of the location of the SNP it is processed, by the server device, using the automated pharmacoepigenomics informatics pipeline (PIP) described with reference to Figures 4B, 4D, and 4E of U.S. Patent Application No. 15/977,347 filed on May 11, 2018, incorporated by reference herein. Once imputation and annotation has been performed to further characterize the

WE CLAIM:

1. A computer-implemented method for identifying a pharmacogenomic network of a drug, the method executed by one or more processors programmed to perform the method, the method comprising:

obtaining, by one or more processors, a plurality of single nucleotide polymorphisms (SNPs) correlated with drug response or adverse events for a particular-psychotropic drug;

identifying, by the one or more processors, a drug pharmacogenomic network for the particular-psychotropic drug based on ~~a set of~~target genes associated with the plurality of SNPs;

deconstructing, by the one or more processors, the drug pharmacogenomic network into a plurality of drug pharmacogenomic sub-networks using a topology of sub-network types selected from two or more of: a chromatin remodeling sub-network type, a drug efficacy sub-network type, a drug adverse events sub-network type, a pharmacokinetic enzymes and hormones sub-network type, a systemic pharmacokinetics sub-network type, or an immune system adverse events sub-network type by:-

organizing the target genes into functional subsets based on functionality of each of the target genes using iterative gene set optimization to identify a plurality of drug pharmacogenomic sub-networks for the psychotropic drug corresponding to each of the functional subsets; and

providing, by the one or more processors, an indication of the drug pharmacogenomic network and indications of the plurality of drug pharmacogenomic sub-networks for display.

2. The method of claim 1, wherein identifying a drug pharmacogenomic network for the particular-psychotropic drug based on a set of genes associated with the plurality of SNPs includes:

comparing, by the one or more processors, the plurality of SNPs to a database of SNPs to identify additional SNPs that are linked to the plurality of SNPs using a topologically associating domain (TAD) boundary within a chromosome territory, wherein the plurality of SNPs and additional SNPs are included in a set of candidate variants;

performing, by the one or more processors, a mapping of 3D spatial connections using the set of candidate variants as probes within chromatin data to determine interconnections

between the target genes correlated with drug response or adverse events for the particular psychotropic drug;

performing, by the one or more processors, a pathway analysis on the target genes associated with the set of candidate variants to filter the target genes to identify a set of genes which are causally related to the particular-psychotropic drug; and

identifying, by the one or more processors, the drug pharmacogenomic network for the particular-psychotropic drug based on the identified set of genes.

3. The method of claim 2, further comprising:

performing, by the one or more processors, a bioinformatics analysis on the drug pharmacogenomic network to ensure a most significantly associated drug to the plurality of drug pharmacogenomic sub-networks is the particular-psychotropic drug.

~~4. The method of claim 3, wherein deconstructing the drug pharmacogenomic network into a plurality of drug pharmacogenomic sub-networks includes:~~

~~organizing, by one or more processors, the set of genes into functional subsets using iterative gene set optimization to identify a plurality of drug pharmacogenomic sub-networks for the particular drug corresponding to each of the functional subsets.~~

45. The method of claim 43, wherein performing a bioinformatics analysis on the drug pharmacogenomic network includes:

validating, via bioinformatics, the drug pharmacogenomic network and the plurality of drug pharmacogenomic sub-networks for the particular-psychotropic drug.

65. The method of claim 54, wherein validating the drug pharmacogenomic network and the plurality of drug pharmacogenomic sub-networks for the particular-psychotropic drug includes:

comparing the drug pharmacogenomic network and the plurality of drug pharmacogenomic sub-networks for the particular-psychotropic drug to one or more of:  
terms from a gene ontology or medications database,

canonical biological pathway in cells or tissues where the ~~particular~~ psychotropic drug acts, or

xenobiotic upstream regulators in the cells or the tissues where the ~~particular~~ psychotropic drug acts.

**76.** The method of claim 2, wherein performing a pathway analysis on target genes associated with the subset of intermediate candidate variants to filter the target genes includes identifying, by the one or more processors, a set of candidate drug pharmacogenomic network genes by identifying a subset of the target genes that form a statistically significant interconnected pathway expressed in a tissue associated with the ~~particular~~ psychotropic drug.

**87.** The method of claim 2, further comprising:  
analyzing each gene in the set of candidate drug pharmacogenomic network genes according to at least one of: a function of the gene in context of the ~~particular~~ psychotropic drug, a set of mutations within the gene, or a pattern of expression of the gene relative to a neuroanatomical substrate, as defined by RNA expression data, functional imaging, or other integrative multiscale data indicating where the ~~particular~~ psychotropic drug is known to act;  
analyzing other genes and functional genomic elements including long noncoding RNA based on each gene in the set of candidate drug pharmacogenomic network genes; and  
adding or removing genes to or from the set of candidate drug pharmacogenomic network genes based on the analysis.

**98.** The method of claim **78**, wherein analyzing each gene in the set of candidate drug pharmacogenomic network genes according to a pattern of expression of the gene relative to a neuroanatomical substrate includes:

comparing each gene in the set of candidate drug pharmacogenomic network genes to a neuromap indicating the neuroanatomical substrate for the ~~particular~~ psychotropic drug; and

filtering genes from the set of candidate drug pharmacogenomic network genes that are not expressed in a same neuroanatomical region as the ~~particular~~ psychotropic drug.

~~109~~. The method of any one of claims 1-~~98~~, further comprising:  
determining, by the one or more processors, one or more spatial contacts including TADs based on the plurality of single nucleotide polymorphisms (SNPs) correlated with drug response or adverse events for the ~~particular-psychotropic~~ drug, wherein the one or more spatial contacts are differentially expanded and suppressed.

~~110~~. The method of any one of claims 1-~~109~~, wherein the drug pharmacogenomic network includes one of more defining characteristics of functional spatial genomics, including at least one of:

- mutations that impact enhancer-promoter pairs,
- promoter-promoter pairs,
- super enhancer-promoter pairs,
- regulatory RNAs,
- euchromatin or heterochromatin state,
- topologically-associating domains (TADs), or
- lamina-associating domains (LADs).

~~1211~~. The method of any one of claims 1-~~1110~~, further comprising:  
storing, by the one or more processors, the indication of the drug pharmacogenomic network and indications of the plurality of drug pharmacogenomic sub-networks for the ~~particular-psychotropic~~ drug in a database as a reference set to compare and score input patient pharmacogenomic networks for the same ~~particular-psychotropic~~ drug to determine efficacy and adverse events when treating the patient for a condition or disease.

~~132~~. The method of any one of claims 1-~~1211~~, further comprising:  
identifying, by the one or more processors, a set of molecular pharmacodynamic targets within one of the plurality of drug pharmacogenomic sub-networks for a same or similar clinical indication as the specified drug.

~~1413~~. The method of claim ~~132~~, wherein the set of molecular pharmacodynamic targets within one of the plurality of drug pharmacogenomic sub-networks and the ~~particular~~

psychotropic drug act in a human brain, and a majority of members of a pathway for the molecular pharmacodynamic target are expressed in the same regions of the human brain as the particular-psychotropic drug.

~~15~~14. The method of any one of claims 1-~~14~~13, further comprising:  
re-purposing a drug based on underlying loci of pharmacogenomic enhancer SNPs related to the plurality of drug pharmacogenomic sub-networks within the topology of sub-network types.

156. The method of any one of claims 1-~~15~~14, further comprising:  
re-purposing a combination of drugs to test as a therapeutic after determination that physiological mechanisms demonstrate that complementarity between sub-network characteristics of two or more drugs offers a more optimal therapy for a particular disease or disease states than a single particular drug.

~~17~~16. The method of claim ~~16~~15, wherein re-purposing a combination of drugs includes re-purposing valproic acid and ketamine as a combinatorial therapeutic for neurological and neuropsychiatric disorders.

~~18~~17. The method of any one of claims 1-~~17~~6, wherein the particular-psychotropic drug is one of: valproic acid, ketamine, lithium, lamotrigine, or clozapine, ~~or~~ warfarin.

189. A computing device for identifying a pharmacogenomic network of a drug, the computing device comprising:

a communication network,

one or more processors; and

a non-transitory computer-readable memory coupled to the one or more processors and storing thereon instructions that, when executed by the one or more processors, cause the computing device to:

obtain a plurality of single nucleotide polymorphisms (SNPs) correlated with drug response or adverse events for a particular-psychotropic drug;

identify a pharmacogenomic network for the ~~partieular~~ psychotropic drug based on ~~a set of~~ target genes associated with the plurality of SNPs;

deconstruct the drug pharmacogenomic network into a plurality of drug pharmacogenomic sub-networks using a topology of sub-network types selected from two or more of: a chromatin remodeling sub-network type, a drug efficacy sub-network type, a drug adverse events sub-network type, a pharmacokinetic enzymes and hormones sub-network type, a systemic pharmacokinetics sub-network type, or an immune system adverse events sub-network type by:

organizing the target genes into functional subsets based on functionality of each of the target genes using iterative gene set optimization to identify a plurality of drug pharmacogenomic sub-networks for the psychotropic drug corresponding to each of the functional subsets; and

provide, via the communication network, an indication of the drug pharmacogenomic network and indications of the plurality of drug pharmacogenomic sub-networks for display.

2019. The computing device of claim 198, wherein to identify a pharmacogenomic network for the ~~partieular~~ psychotropic drug based on a set of genes associated with the plurality of SNPs, the instructions further cause the computing device to:

compare the plurality of SNPs to a database of SNPs to identify additional SNPs that are linked to the plurality of SNPs using a topologically associating domain (TAD) boundary within a chromosome territory, wherein the plurality of SNPs and additional SNPs are included in a set of candidate variants;

perform a mapping of 3D spatial connections using the set of candidate variants as probes within chromatin data to determine interconnections between the target genes correlated with drug response or adverse events for the ~~partieular~~ psychotropic drug;

perform a pathway analysis on the target genes associated with the set of candidate variants to filter the target genes to identify a set of genes which are causally related to the ~~partieular~~ psychotropic drug; and

identify the drug pharmacogenomic network for the ~~partieular~~ psychotropic drug based on the identified set of genes.

2120. A method for identifying a combination of drugs to test as a therapeutic for a particular disease, the method executed by one or more processors programmed to perform the method, the method comprising:

obtaining, by one or more processors, a first plurality of single nucleotide polymorphisms (SNPs) correlated with drug response or adverse events for a first psychotropic drug;

obtaining, by one or more processors, a second plurality of SNPs correlated with drug response or adverse events for a second psychotropic drug;

identifying, by the one or more processors, a first drug pharmacogenomic network for the first psychotropic drug based on a first set of genes associated with the first plurality of SNPs;

identifying, by the one or more processors, a second drug pharmacogenomic network for the second psychotropic drug based on a second set of genes associated with the second plurality of SNPs;

identifying, by the one or more processors, a first drug response phenotype associated with the first set of genes in the first drug pharmacogenomic network that is complementary to a second drug response phenotype associated with the second set of genes in the second drug pharmacogenomic network using gene set enrichment to identify the complementary first and second drug response phenotypes; and

re-purposing a combination of the first and second drug to test as a therapeutic for a particular disease.

2221. The method of claim 2120, wherein re-purposing the combination of the first and second psychotropic drug to test as the therapeutic for the particular disease includes:

the first psychotropic drug to be administered at a first time; and

the second psychotropic drug to be administered at a second time later than the first time.