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IdopNetwork as a genomic predictor of drug response

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Abstract

Given the multifactorial feature of drug response, portraying its systematic control mechanism is, despite being challenging, crucial for pharmacogenomic research. We describe a new norm of statistical mechanics to reconstruct informative, dynamic, omnidirectional, and personalized networks (idopNetworks) that cover all pharmacogenomic factors and their interconnection, interdependence, and mechanistic role. IdopNetworks can characterize how cell-cell crosstalk is mediated by genes and proteins to shape body-drug reactions and identify key roadmaps of information flow and propagation towards drug efficacy and toxicity. We argue that idopNetworks could potentially gain insight into the genomic machineries of drug response and provide scientific guidance to design drugs whose potency is maximized at a lower dose.

Keywords: drug response, gene regulatory network, idopNetwork, statistical mechanics, cell-cell crosstalk

Networks are fundamental to body-drug reactions

There is great inter-individual variability in how a drug acts on the body, leading to physiological effects at its specific site [1-5]. Traditional genomic approaches have been instrumental for identifying significant factors, such as genes, proteins, metabolites, pathways, or microbes, which cause variation in drug response [6-9]. However, these approaches based on a reductionist thinking have limited power to portray the overall atlas of pharmacogenomic control, making it difficult to translate pharmacogenetics into a clinical practice. Drug response involves multifactorial mechanisms [10,11], which can better be described as a dynamic system [12], where its constituent components interact with each other to form an intricate network. For this reason, network modeling may hold a great promise to unveil the genomic machineries of drug response.

As a commonly used approach, network tools have well been developed in physical

and social sciences [13,14]. The use of networks to biological, biomedical and pharmacological problems starts after a massive amount of omics data has been produced at a reasonably low cost [15-18]. However, most existing networks are still far from reaching a standard at which pharmacological mechanisms can be revealed at high resolution. For example, correlated-based networks can only estimate the strength of interactions, but failing to identify their causality, whereas Bayesian network can find the direction of interactions but cannot estimate their strength and sign [19]. More recently, a new norm of statistical mechanics has been proposed [20-23], which can distill all drug response-related factors into idopNetworks. Such networks enable us to chart the detailed atlas of how each pharmaco-agent interacts with every other one to mediate drug response.

Topology theory [24] is implemented into idopNetworks to better understand how a pharmacogenomic network functions. Based on network topology diagrams, the best placements for each pharmacological factor (i.e., node) and the optimal path for information flow from one node to the next can be determined. With a well-defined and planned-out network topology, pharmacologists can more easily locate key factors and their pathways to improve pharmacogenetic translation efficiency. GLMY theory, pioneered by S.-T. Yau and co-workers [25-27], to describe the path homology of digraphs has increasingly emerged as a mathematical tool to extract the topological features of data that persist across multiple scales. For example, this tool can capture the connected components or holes in networks, which serve as indicators of node importance [28,29]. By estimating the existence and distribution of structural holes in networks, network comparison and classification can be made [30].

This article aims to introduce idopNetworks into the pharmacological research community. We describe the basic principle of idopNetwork reconstruction from omics data collected in commonly designed genomic studies of drug response. We show that the integration of GLMY theory into pharmacogenomic idopNetworks can leverage the genomic studies of drug response to a new height in both theory and applications. We demonstrate the utilization and usefulness of idopNetworks by analyzing and interpreting a published genomic dataset from an antipsychotic study.

A framework for pharmacogenomic idopNetworks

Network pharmacology has emerged as a new discipline to understand drug actions and interactions with multiple targets [15,18]. Reconstructing genomic interactome networks in pharmacological response to medications from omics data is the key first step towards the translation of network pharmacology. Nodes in pharmacogenomic networks are biological agents, such as genes, proteins, metabolites, or pathways related to drug response, which are linked by lines termed edges. The edges represent the nature of how different agents interact with each other, usually unknown to pharmacologists but inferable from genomic data. Although many approaches are available for inferring pharmacogenomic networks, idopNetworks shall represent one of the advanced tools to reconstruct the most detailed networks from a wide spectrum of data domains.

IdopNetworks are derived from the seamless integration of many disciplines, including evolutionary game theory, allometrical scaling law, and graph theory. By analyzing and modeling omics data collected from a pharmacological experiment or practice, such networks can be used to study drug response. Consider a drug aimed to treat a disease. Drug response occurs if this drug produces any physiological and pathological processes in terms of effectiveness and adverse reactions. For a regular design of pharmacogenomic research, biological agents at pre- and post-intervention of the drug are measured, from which a set of significant agents associated with drug response are identified. A classic reductionist-based approach aims to find single significant agents by comparing and testing the difference of abundance of each agent between pre- and post-intervention (Fig. 1A). Significant agents can serve as a predictive biomarker of drug response; for example, BRAF V600E mutations were detected as a biomarker to be associated with response to BRAF inhibitors in melanoma [31]. This approach ignores the existence of inter-agent interaction and dependence, making it difficult to find the true role of individual significant agents. For example, by statistical testing, agent 1 is differentially expressed between pre- and post-intervention (Fig. 1A), indicating that this agent can be used as a biomarker of drug response. However, this differentiated expression may be due to change in its regulatory relationship with other agents; e.g., it is promoted by agent 6 at pre-

intervention, but promoted, to a much larger extent, by both agents 2 and 3 at post-intervention (Fig. 1B). A similar phenomenon is held for differentially expressed agent 3.

To model how different agents interact with each other to mediate drug response, we view each sample (e.g., an individual, an organ, a tissue, or even a cell) as an ecosystem consisting of many interdependent agents. We collect the data of these agents before and after a drug is administrated. Following game theory, we argue that each agent attempts to maximize the amount of its expression ("payoff") by adopting an optimal strategy, in response to other agents [32]. This attempt proceeds until the Nash equilibrium is reached, at which no agent can alter its expression by changing its own strategy (holding all other agents' expression fixed). Game theory is combined with evolutionary biology to generate evolutionary game theory [33] in which the Nash equilibrium was refined by the notion of evolutionarily stable strategy (ESS). Sun et al. [22] developed a system of mixed ordinary differential equations (mODEs) to characterize the dynamic change of ESS. In pharmacogenomic studies, such mODEs characterize the abundance levels of different genes expressed at pre- or post-intervention. The mODE of each gene in the system contains two terms: the first specifying the independent expression component derived from the intrinsic strategy of this gene and the second specifying the dependent expression component from its extrinsic influence by other genes. We code the independent components as nodes and the dependent components as edges into pharmacogenomic networks at pre- or post-intervention (Fig. 1B). These networks are idopNetworks because they are fully informative (characterized by bidirectional, signed, and weighted interactions), dynamic (modeling how interactions change across time and space), omnidirectional (complete identification of all direct and indirect interactions for each node), and personalized (discerning sample-specific variability in network structure).

In general, mODEs are built from temporal data. However, such data are difficult or impossible to collect because of technical, economic or ethical reasons. Chen et al. [20] introduced niche theory to define the "productivity" of each sample (ecosystem) by summing the expression values of all agents (coined ecosystem index). Thus, the power law is used to describe allometric scaling relationships between the expression of individual agents and ecosystem index [34]. These relationships are implemented

into mODE to formulize quasi-dynamic mODE (qdMODE) in which the time derivative is replaced by the ecosystem index derivative [35]. The formulation of qdMODE makes it idopNetwork a widespread use across various data domains. Rather than comparing the differentiated expression of a single gene at pre- or post-intervention, idopNetworks, by implementing GLMY theory, can find topological features in gene co-regulation that cause intervention-induced differences. This approach promotes a paradigm shift of pharmacogenomic studies from a reductionist thinking to a systems-oriented thinking. Systems pharmacology holds great promise to rationally design the next generation of drugs with improved therapeutic safety and efficacy.

A concept of proof: How idopNetworks work

As one of the largest types of prescribed drugs to treat mental health problems including schizophrenia, bipolar disorder, depression, dementia, and autism among other clinical conditions [36-38], antipsychotic drugs would induce weight gain, which are indirectly responsible for psychosis relapses [39]. Crespo-Facorro et al. [40] identified 115 genes that are differentially expressed in the antipsychotic-induced weight gain (AIWG) group (18 patients) before and after 3 months of intervention and 156 differentially expressed genes in the no weight gain group (18 patients) before and after 3 months of intervention. Although these discoveries provide a first step toward explaining the genomic causes of AIWG, they are still far away from a mechanistic understanding of how individual genes influence AIWD directly or through indirect pathways.

To address the above issue, we reconstruct idopNetworks for both the weight gain group and the no weight gain group before and after intervention using a complete set of 45,281 genes profiled in Crespo-Facorro et al.'s [40] study. We view each sample (patient) as an ecosystem and calculate ecosystem index by summing the values of expression over all genes for each sample. The relationship between the expression level of each gene and ecosystem index across samples can be fitted by the power equation, but with great inter-gene variability in the shape of the power curve (Fig. 1S). As our goal to demonstrate how idopNetworks is useful for revealing the genomic mechanisms of drug response, we focus our presentation on comparing

network differences for the no weight gain group before and after intervention.

Given a large number of genes considered, we implement functional clustering [41,42] to classify all genes into 67 and 61 distinct modules pre- and post-intervention, respectively (Fig. 2S). If the number of genes within a module is still too large, we further implement functional clustering to classify them into distinct submodules. This process repeats until the number of genes within a unit reaches Dubar's number, i.e., a "cognitive" limit of genes, beyond which members within a community cannot establish stable mutual relationships [43-45]. After a series of classification, we assign each gene into a Dunbar community, which encompasses all of its virtually existing interactions. We reconstruct idopNetworks of all Dunbar communities for the no weight gain group before and after intervention. As example, our analysis is focused on idopNetworks containing several genes detected to be differentially expressed pre- and post-intervention by standard statistical approaches. Such genes should be regarded as target genes of practical significance because they can inhibit psychotic symptoms but with no influence on weight gain.

Gene *OTOF* is observed to increase its expression dramatically from pre- to post-intervention for the no weigh gain group. *OTOF* encodes otoferlin, a critical protein at the synapse of auditory sensory cells, whose absence causes impaired release of synaptic vesicles, making it interrupted to transmit signals from the ear to the brain [46,47]. Increasing expression of *OTOF* helps patients improve their psychotic state. IdopNetworks containing this gene reconstructed before and after 3 months of intervention are illustrated in Figure 2A, from which *OTOF* is found to be promoted by *PLOD2* pre-intervention but inhibited by *POUSF1* post-intervention. A detailed decomposition analysis shows that the antipsychotic-induced function of *OTOF* depends on the expression of the other gene (Fig. 2A). It displays a much lower level of independent gene expression (due to its intrinsic capacity) before than after antipsychotic intervention. *OTOF* is only slightly promoted by *PLOD2* pre-intervention, making its observed expression level to be quite close to its independent expression level, yet it is heavily inhibited by *POUSF1* post-intervention, leading to its observed expression level to be much lower than its observed expression level. This finding suggests that the expression of *OTOF* post-intervention can be further strengthened by repressing the expression of negative regulator *POUSF1* via gene

editing, which can potentially improve drug efficacy in treating psychotic diseases. It is interesting to note that gene *POUSF1*, as a hub of inhibiting many other genes in the post-intervention network, promotes the proliferation, migration, and invasion of gastric cancer cells [48]. This implies that the repression of *POUSF1* may not only enhance the efficacy of antipsychotic drugs, but also inhibit the development of gastric cancer. It appears that antipsychotic-drug efficacy can be increased through releasing the expression of gene *LOC100190986* via the repression of *CCDC85C* (Fig. 2B).

Decreasing expression of gene *HBG1* is positively associated with the efficacy of antipsychotic drugs (Fig. 2C). It is only slightly promoted by *BLVRB* pre-intervention, but it is strikingly promoted by *PCGF5* and also inhibited by *RBM38* to a similar extent. In practice, by silencing the expression of *PCGF5*, the expression level of *HBG1* can be largely reduced, leading to the increase of antipsychotic-drug efficacy. As shown in Figure 2D, decreasing the expression of AnKRD22 can help improve drug efficacy. However, the independent expression of this gene increases considerably from pre- to post-intervention, which suggests that this gene cannot be used alone as a target to treat psychotic diseases, rather than using a dyad composed of it and its negative regulator *SPTSSB*. By reconstructing IdopNetworks of each differentiated gene, we can better understand the mechanistic underpinnings of how these genes function to determine drug response.

Leveraging idopNetworks to pharmacogenomic translation

IdopNetworks are often too complicated to ascertain explicit patterns of information flow. Path homology, known as GLMY homology theory, has emerged as an advanced tool in algebraic topology to dissect the topological architecture of digraphs [25-27]. This theory has been used to reveal the mechanistic pathways of how each node flows its signal to every other one in many fields including material synthesis [49], complex disease etiology [23], and ecological functioning of the soil microbiome [50]. We implement GLMY theory to characterize the topological features of idopNetworks pre- and post-intervention.

Figure 3 illustrates the GLMY dissection of idopNetworks involving gene OTOF pre- and post-intervention for the no weight gain group. Pre- and post-intervention idopNetworks display similar 0- and 1-dimensional homologies, but while the former has no 2-dimensional homology, the latter is characterized by such homologies. This difference suggests that post-intervention networks are much complex in structure and function than pre-intervention networks. It is interesting to note that OTOF and POU5F1 establishes an antagonistic relationship through one 1-dimensional homology and eight 2-dimensional homologies. Such multiple pathways make it possible and feasible to promote the expression of *OTOF* to enhance the efficacy and safety of antipsychotic drugs by knocking out *POU5F1*. Both *OTOF* and *POU5F1* inhibit *LEFRS* (lowly expressed in rheumatoid fibroblast-like synoviocytes)[51]. The silence of *POU5F1* can enhance the expression of *LERFS*, which is detected to inhibit rheumatoid synovial aggression and proliferation. From this perspective, *POU5F1* should be chosen as a central target for genomic editing not only to improve drug efficacy, but also to repress gastric cancer and rheumatoid arthritis.

Efficacy genes and toxicity genes are combined into a network

The most desirable drug should possess the following features: high efficacy, low toxicity (side effects), low chance of drug resistance, low cost, and low deleterious effect on the environment [52]. In treating psychotic diseases, antipsychotic drugs produce side effects, i.e., weight gain, which may lead to psychosis relapses. Crespo-Facorro et al.'s [40]design allows us to distinguish between specific genes for drug efficacy or drug toxicity and common genes for both drug processes. This information can be used to design optimal therapeutic strategies that maximize drug efficacy and minimize drug toxicity. The value of this information can be leveraged by implementing idopNetworks.

For a gene, if its expression is different between before and after intervention for the no weight gain group, then it is certain that this gene is associated with antipsychotic drug response. However, if a gene is differentially expressed pre- and post-intervention for the weight gain group, then we cannot precisely judge whether this gene is only responsible for either weight gain or drug response, or both. Based on

this analysis, we classify all genes into four categories:

(1) Weight gain-specific genes, i.e., those whose expression has no difference pre- and post-intervention for the no weight gain group but displays a difference pre- and post-intervention for the weight gain group;

(2) Weight gain-drug response antagonism genes, i.e., those whose expression displays a difference pre- and post-intervention for the no weight gain group but has no difference pre- and post-intervention for the weight gain group. The former suggests that these genes are responsible for antipsychotic drugs, whereas the latter implies that the direction by which these genes are associated with drug response and weight gain is different, which cancels out to zero;

(3) Weight gain-drug response cooperation genes, i.e., those whose expression displays a difference pre- and post-intervention for the no weight gain group, with this difference becoming dramatically increased for the weight gain group;

(4) Neutral genes to weight gain and drug response, i.e., those whose expression has no difference pre- and post-intervention for both no weight gain group and weight gain group.

In clinical practice, different gene therapies for optimizing drug response against drug toxicity should be developed, depending on which category of genes is used. For category 1, weight gain can be controlled by regulating their expression, although they may be not related to drug response. If genes of this category to be considered for minimizing weight gain are independent of genes for drug response, drug toxicity and drug efficacy can be manipulated separately. The second category of genes governs the antagonism between weight gain and drug response; i.e., their positive effect on antipsychotic drug response is associated with their negative effect on weight gain. Then, if the strategy for gene therapy is designed to increase drug efficacy based on the decomposition of gene expression in the no weight gain group, drug toxicity can automatically reduce at the same time.

The third category of genes mediates weight gain-drug response cooperation, which

means that the increasing drug efficacy (improving psychotic diseases) is often associated with the increasing drug toxicity (weight gain). The therapeutic use of this category of genes may lead to the change of both pharmacological features, which thus should be considered with caution. We find that the majority of genes belong to category (4), in which a gene participates neither in weight gain nor in drug response according to traditional statistical inference. When the idopNetwork model decomposes the overall expression level of such a gene into its independent component and dependent component, we find that these two components may each display different ecosystem index-varying trajectories between before and after intervention. For example, gene *SPT8* is observed to be neutral for wight gain and drug response, but its independent component is strikingly larger after than before intervention for both no weight gain group and weigh gain group (Fig. 4). The independent component is promoted by positive regulators pre-invention, but inhibited by negative regulators post-intervention, which leads the observed expression level to be similar after and before intervention. While traditional analysis claims no clinical usefulness of SPT8, the idopNetwork model excavates its hidden information which can be translated into clinical practice to enhance drug efficacy. For the no weight gain group, knocking out the expression of *OLIG2* may promote the function of *SPTB*, in which case drug efficacy can be improved. For the weight gain group, we can elevate drug efficacy by repressing the expression of H2AC7, but at a risk of weight gain. As can be seen, idopNetworks provide a powerful tool to reveal the genomic machineries of drug efficacy, drug safety, and drug side-effects, producing information of greater value for the clinical practice of translational genomics.

Concluding remarks

Network pharmacology presents an immense implication for how drug response can be more comprehensively defined and cohered into a mechanistic network and how this information is implemented to resolve the current problems that challenge the drug discovery industry. Despite the recognized role of networks in understanding pharmacology, however, we are still less knowledgeable about the application of network pharmacology mainly because of the lack of such informative

pharmacological networks. In this article, we introduce an advanced network model – idopNetworks into pharmacological research. The remarkable merit of this model lies in its capacity to contextualize pharmaco-genes, pharmaco-proteins, or pharmaco-metabolites into a cohesive network, in which a detailed atlas of how each agent interacts with every other agent to mediate pharmacological response can be traced and monitored by an emerging topology theory – GLMY homology theory.

IdopNetworks demonstrated multifaceted functionalities, including how each gene functions independently, how it functions depending on other genes, and whether a gene affects a single or multiple pharmacological processes. IdopNetworks classify all genes into different categories based on how they act in different types of drug response, from which the genomic machineries of drug efficacy vs. drug toxicity can be determined. All these pieces of information can be amplified from GLMY-based topology analysis. In summary, idopNetworks and their topological dissection give insight into the hidden knowledge of pharmacogenomics. The logical analysis of idopNetworks can be utilized to understand the pharmacogenomic mechanisms as well as to invent novel solutions for current pharmacological problems, reaching the goal of optimizing drug benefits but minimizing drug side-effects.

Declaration of interests

The authors have no conflicts of interest to declare.

Data and code availability

Research data used for writing this review were downloaded from Crespo-Facorro et al. [40]. Computer code for idopNetwork reconstruction is available on GitHub (https://github.com/chejincan/BIMSA-DrugNetwork).

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Figure Legends

Figure 1 A scheme of analyzing drug response data collected pre- and post-intervention. (**A**) Significance t-tests for intervention-dependent differences based on individual agents 1 – 6. Solid thick and thin lines represent highly significant and significant differences, whereas broken lines represent no significance. The size of circles is proportional to the abundance level of agents. (**B**) An actual case of genomic control over drug response, in which different agents interact with each other in a complicated manner different before and after intervention. Red and blue arrowed lines represent promotion and inhibition, respectively, with the thickness of lines proportional to the strength of interaction.

Figure 2 Pre- and post-intervention idopNetworks at the gene level from specific modules involving differentially expressed genes *OTOF* (**A**), *ANKRD22* (**B**), *HBG1* (**C**), and *LOC100190986* (**D**) by t-tests, respectively, for the no weight gain group. Upper panel: Genomic interaction networks, where the above-mentioned genes are shown in red. Red and blue arrowed lines represent promotion and inhibition, respectively, with the thickness of lines proportional to the strength of interaction. Lower panel: Decomposition of the observed expression trajectory of a gene (as a function of ecosystem index) (blue line) into its independent component trajectory (red line) and dependent component trajectory (green line). The names of regulator genes are given proximal to green lines.

Figure 3 The GLMY dissection of *OTOF*-related idopNetworks pre- and post-intervention for the no weight gain group. Left panel: genomic interaction networks. Middel panel: Homology numbers ($\beta_0,\ \beta_1,\ \beta_2$) across filtration at different dimensions. Right panel: Concrete homological features at dimensions 1 and 2.

Figure 4 Decomposition of the observed expression trajectory of *OTOF* (as a function of ecosystem index) (blue line) into its independent component trajectory (red line) and dependent component trajectory (green line) pre- and post-intervention for no weight gain and weigh gain groups, respectively. The names of regulator genes are given proximal to green lines.

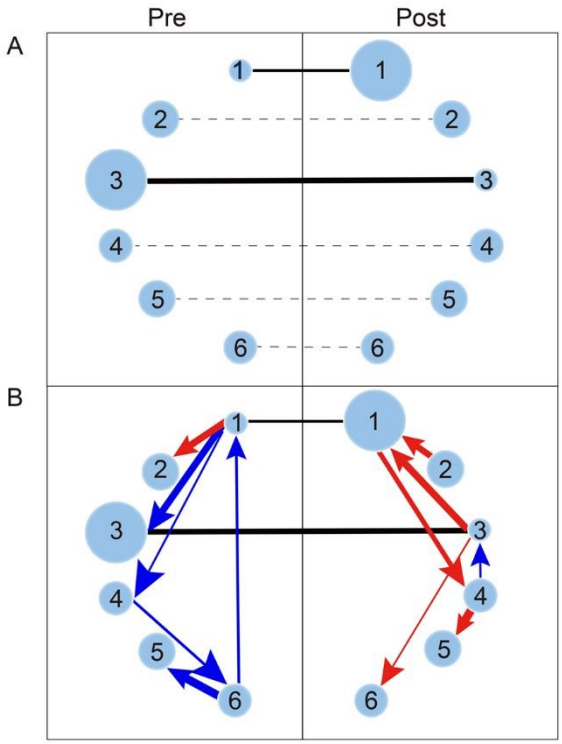
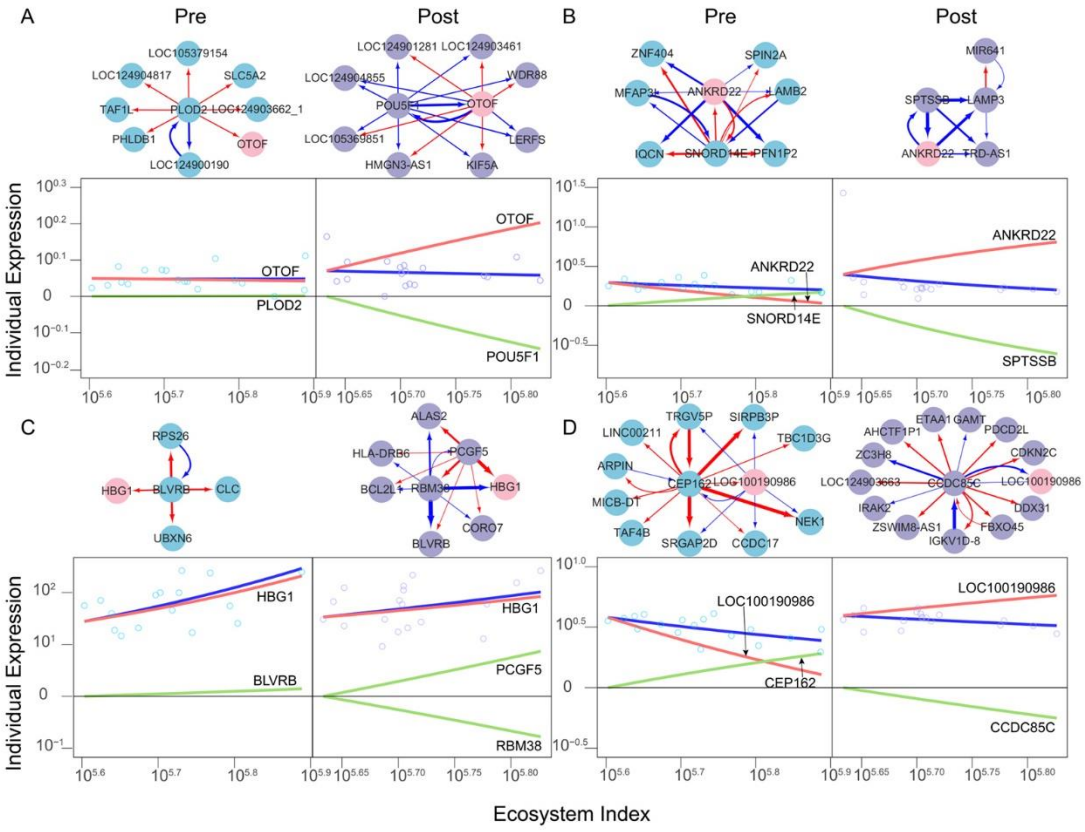


Figure 1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POU5F1
ANKRD22
SNORD14E
SPTSSB
HBG1
BLVRB
PCGF5
RBM38
LOC100190986
CEP162
CCDC85C

Figure 2

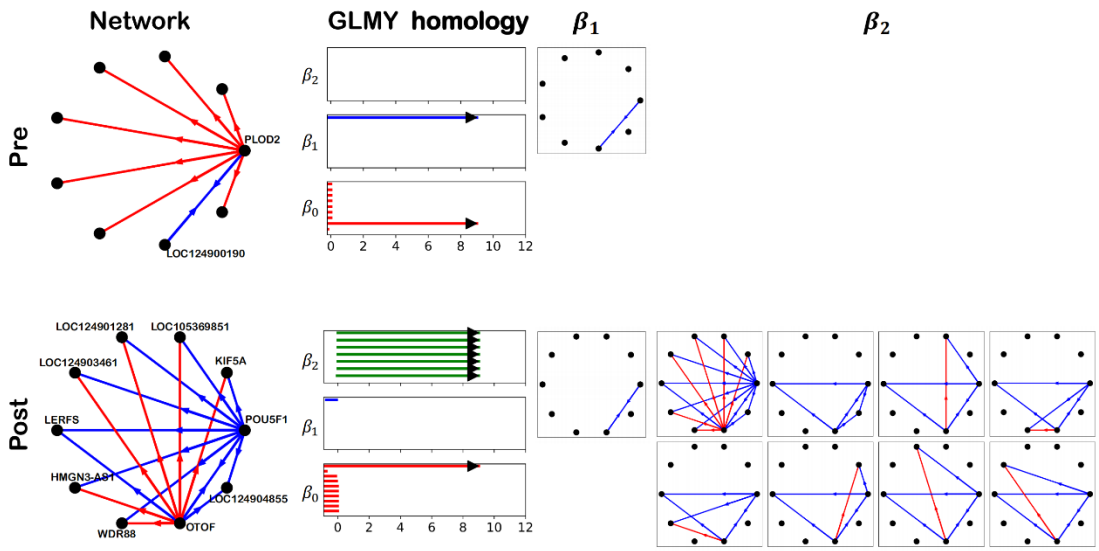
Network
GLMY homology
β_1
β_2
Pre
PLOD2
LOC124900190
β_2
β_1
β_0
0 2 4 6 8 10 12
Post
LOC124901281
LOC105369851
LOC124903461
KIF5A
LERFS
POU5F1
HMGN3-AS1
LOC124904855
WDR88
OTOF

Figure 3

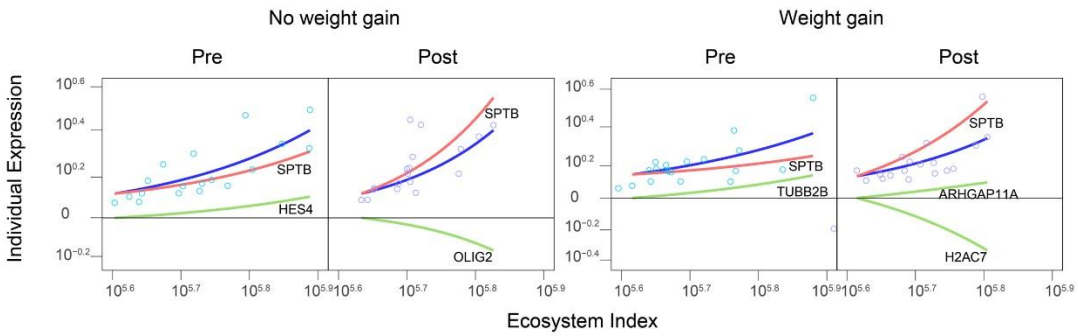
No weight gain
Weight gain
Pre
Post
Pre
Post
Individual Expression
SPTB
HES4
SPTB
OLIG2
SPTB
TUBB2B
SPTB
ARHGAP11A
H2AC7
Ecosystem Index

Figure 4