Systems Pharmacology

Ravi Iyengar
Department of Pharmacology and Systems Therapeutics
Mount Sinai School of Medicine
New York NY
Network Diagram of FDA Approved Drugs and their Targets (Human Gene Products)
Systems Pharmacology: Global Relationship Between Therapeutic Drugs and the Human Genome

Drugs and their targets as a bipartite graph

Many drug targets are part of networks, large and small

Each island is a network of interacting proteins

Avi Ma’ayan and Sherry Jenkins

Ma’ayan, Jenkins, Goldfarb, and Iyengar
Functional annotation of human drug targets

GO Gene Ontology validates our assumption that current drug targets are signaling proteins.

Ma’ayan, Jenkins, Goldfarb, and Iyengar
Relationship between Adverse Effects and the Human Genome

Table 1. Active ingredients can cause adverse effects through 12 different scenarios. The precursor, the active drug, or drug metabolites resulting from chemical processing of the drug, can interact with the intended target but cause the target to initiate undesired effects (scenarios 1, 5 and 9). The three possible different forms of the drug can interact with other unknown or undesired targets in the same cell type (scenarios 2, 6 and 10) or different cell types (scenarios 4, 8 and 12). Also, the three possible different forms of the drugs can cause unwanted effects by targeting the intended target but in the unintended cell type (scenarios 3, 7 and 11).

<table>
<thead>
<tr>
<th>Drug precursor</th>
<th>Scenario 1</th>
<th>Scenario 2</th>
<th>Scenario 3</th>
<th>Scenario 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active drug</td>
<td>Scenario 5</td>
<td>Scenario 6</td>
<td>Scenario 7</td>
<td>Scenario 8</td>
</tr>
<tr>
<td>Drug metabolites</td>
<td>Scenario 9</td>
<td>Scenario 10</td>
<td>Scenario 11</td>
<td>Scenario 12</td>
</tr>
</tbody>
</table>

There are likely to be multiple mechanisms underlying adverse effects

Ma’ayan, Jenkins, Goldfarb, and Iyengar
Some questions Systems Pharmacology can tackle

How do we go from such general analysis to specific situations?

After all drugs are designed to treat specific pathophysiolgies by interacting with specific targets!

Can network analysis be used to understand complex diseases and adverse events by drugs that are currently being used?
Build cellular networks using disease gene products as starting points.

Identify boundaries of functional neighborhoods (i.e. cellular interaction networks) of products of disease genes.

Do targets of drugs that cause the same clinical phenotype fall within the neighborhood?

Seth Berger
What can we find using Systems Pharmacology Approaches?

Predictions for new susceptibility genes (mutations and SNPs) for disease origins as well as adverse effects

Ranked list of cellular components that upon interaction with drugs can cause clinical phenotype (generally adverse effects)
Systems Pharmacology of Arrhythmias

Long QT Syndrome

Prolonged QT Interval on EKG
- Delayed repolarization after depolarization of cardiac ventricles
- Syncope, Sudden death, Ventricular arrhythmias, Torsades de Pointes

Congenital
- 10+ genes with known causative mutations
- Cardiac ion channels and related proteins

Acquired
- Metabolic disturbances
- Drug-induced

Many thanks to Dan Roden
Vanderbilt
Drug Induced LQTS

More than 70 FDA approved drugs

- Spanning several classes
- Direct HERG ion channel blockade
  - Most common
  - Degree of blockade is not directly related to risk of arrhythmia
- Channel trafficking
- Signal crosstalk
- Reduced repolarization reserve

Susceptibility and risk modifier genes for drug induced LQTS
Identifying the Disease Gene Neighborhood

Develop an Integrated Mammalian Protein-Protein Interaction (PPI) Database

Consolidated 9 publicly available protein-protein interaction databases

Biogrid, HPRD, MINT, PDZbase, Reactome, DIP, Intact, Mips, PhosphoELM

Used gene orthology (Jackson Labs and NCBI homologene) to merge non-human mammalian proteins and their human orthologs

Resulting Network contains:

10,351 nodes (gene products)
64,411 edges (interactions)
19,810 references
Identifying the Disease Gene Neighborhood

Identify Functional Node Distance

Usually Shortest Path
Bias for hubs (nodes with many connections)

We have used mean first passage time (MFPT)
To measure functional distance from the disease gene

Distance in a PPI network has been used to:
Identify functional modules
Annotate proteins with Gene Ontology Terms
Identify disease gene candidates
Calculating “Functional Distance” Between Nodes Using Random Walks

A random walker can step from any node to any adjacent node with equal probability. Mean First Passage Time describes number of steps on average it takes a random walker to walk from a specified node to another specified node.
10 genes with known causative mutations

Different mutations in some of same genes cause Short QT syndrome

1 gene (ALG10) annotated at as Reduced Susceptibility to LQTS

Mostly Cardiac Ion Channels and related Proteins

**Legend**

- $I_{\text{Ca,L}}$ (CACNA1C)
- $I_{\text{Na}}$ (SCN5A)
- $I_{\text{K}_{1}}$ (KCNJ2/Kir2.1)
- $I_{\text{K}_{s}}$ ($K_{\text{vLQT1}} + \text{minK}$)
- $I_{\text{T}_{o}}$ ($HERG + \text{MiRP1}$)

**Formulas**

- $HERG = \text{KCNH2} + \text{MiRP} = \text{KNCE2}$
- $K_{\text{vLQT1}} = \text{KCNQ1} + \text{minK} = \text{KCNE1}$

**Gene List**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCNQ1</td>
<td>potassium voltage-gated channel, KQT-like subfamily, member 1</td>
</tr>
<tr>
<td>(3784)</td>
<td></td>
</tr>
<tr>
<td>KCNH2</td>
<td>potassium voltage-gated channel, subfamily H (eag-related), member 2</td>
</tr>
<tr>
<td>(3757)</td>
<td></td>
</tr>
<tr>
<td>SCN5A</td>
<td>sodium channel, voltage-gated, type V, alpha subunit</td>
</tr>
<tr>
<td>(6331)</td>
<td></td>
</tr>
<tr>
<td>ANK2</td>
<td>ANK2 ankyrin 2, neuronal</td>
</tr>
<tr>
<td>(287)</td>
<td></td>
</tr>
<tr>
<td>KCNE1</td>
<td>potassium voltage-gated channel, Isk-related family, member 1</td>
</tr>
<tr>
<td>(3753)</td>
<td></td>
</tr>
<tr>
<td>KCNE2</td>
<td>potassium voltage-gated channel, Isk-related family, member 2</td>
</tr>
<tr>
<td>(9992)</td>
<td></td>
</tr>
<tr>
<td>KCNJ2</td>
<td>potassium inwardly-rectifying channel, subfamily J, member 2</td>
</tr>
<tr>
<td>(3759)</td>
<td></td>
</tr>
<tr>
<td>CACNA1C</td>
<td>calcium channel, voltage-dependent, L type, alpha 1C subunit</td>
</tr>
<tr>
<td>C (775)</td>
<td></td>
</tr>
<tr>
<td>CAV3</td>
<td>caveolin 3</td>
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<tr>
<td>(859)</td>
<td></td>
</tr>
<tr>
<td>SCN4B</td>
<td>SCN4B sodium channel, voltage-gated, type IV, beta</td>
</tr>
<tr>
<td>(6330)</td>
<td></td>
</tr>
</tbody>
</table>
LQTS Neighborhood

Statistical cutoffs from MFPT analysis to define boundaries of the LQTS neighborhood.

Even the biggest neighborhood has only 12.5% of the total nodes.

- ΔT > 10,000 (15 nodes)
- ΔT > 1,000 (100 nodes)
- ΔT > 100 (520 nodes)
- LQTS neighborhood ΔT > 0 (1310 nodes)
- Integrated mammalian network (10351 nodes)
Top 50 Ranked Nodes in the neighborhood

41 Nodes are 1-3 hops from Disease Genes

These include PKA and PKC
(See figure) And AKAP 9

Drugs which show QT prolongation as a side effect or LQTS and Torsades De Pointes as adverse events have targets that are within the LQTS-Neighborhood?

ArizonaCERT qtdrugs database

DrugBank database

Kilborn & Woolsey (2001) BMJ 322:672

<table>
<thead>
<tr>
<th>Rank</th>
<th>Node</th>
<th>Score</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KCNH2</td>
<td>50904</td>
<td>ibutilide_fumarate; propafenone</td>
</tr>
<tr>
<td>2</td>
<td>KCNQ1</td>
<td>34145.7</td>
<td>indapamide</td>
</tr>
<tr>
<td>5</td>
<td>KCNE1</td>
<td>23693.8</td>
<td>indapamide</td>
</tr>
<tr>
<td>10</td>
<td>KCNJ2</td>
<td>15781.3</td>
<td>levosimendan</td>
</tr>
<tr>
<td>11</td>
<td>CACNA1C</td>
<td>13500.9</td>
<td>magnesium_sulfate; ibutilide_fumarate; nicardipine</td>
</tr>
<tr>
<td>14</td>
<td>SCN5A</td>
<td>12792.7</td>
<td>quinidine; lamotrigine; indecainide; cocaine; benzonatate; enca</td>
</tr>
</tbody>
</table>
Top Network Analysis Identified Drug Targets

10 nodes in the networks with ranks from 43-84 show relevance to QT effect

Some nodes are disease genes for other diseases that also show QT prolongation as an associated pathophysiology

Some nodes are targets for drugs on ArizonaCERT QT drug base
**Initial Findings**

**MFPT Ranking** provides a continuum of scores, emphasizing “more specific interactors” as compared to highly connected hubs.

Known modulators of Torsadagenesis ranked highly
- Protein kinase C ranks 15
- Protein kinase A ranks 20.
- **AKAP9** ranks 19 ** Recently found mutation linked to LQTS! **
- **ADRA1D** and **ADRB1** and **ADRB2** rank within top half of the neighborhood
- **NOS1AP** (nitric oxide synthase 1 [neuronal] adaptor protein), a known modulator of QT interval, is ranked 367.
Targets of drugs that are associated with acquired LQTS are closer to the LQTS disease genes by 2:1 as compared to targets of drugs in general.

This suggests a region of protein-protein interaction space which, when targeted pharmaceutically, is more likely to cause QT interval prolongation or Torsade de Points.

Such a ranked list of genes can be used to screen for LQTS susceptibility polymorphisms in further studies.

New drug candidates can be screened for interactions with proteins in the list. Interactions may suggest that drug could have LQTS as an adverse effect.
Such a ranked list of genes can be used to screen for LQTS susceptibility polymorphisms in further studies.

Are the gene products found in myocytes?

New drug candidates can be screened for interactions with proteins in the list. Interactions may suggest that drug could have LQTS as an adverse effect.

Cell type and tissue type specification of gene products and cell type specific networks.