

Systems Biology of Biomarker Sets

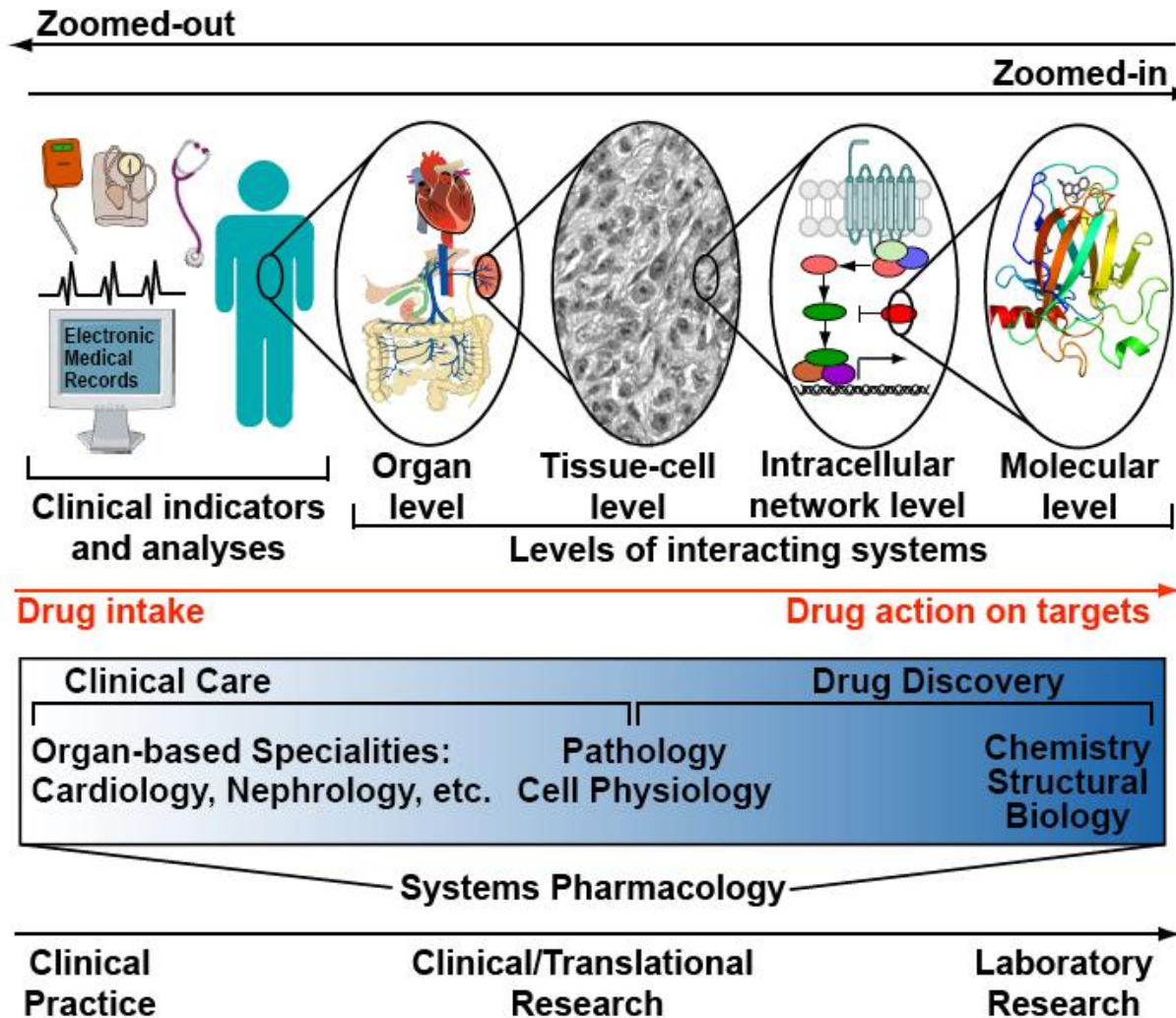


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What is Systems Biology

- An approach that looks at how parts come together to form a functional system
- Uses computational approaches to drive understanding
 - Network Analyses*
 - Differential Equation-based models*
such as Pharmacokinetic and Pharmacodynamic models
- *Understanding of the HOW and WHY of complex functions*
Predictive Insights :
 - Safety Biomarkers*
 - Drug Targets*
 - Approaches for Combination Therapy*

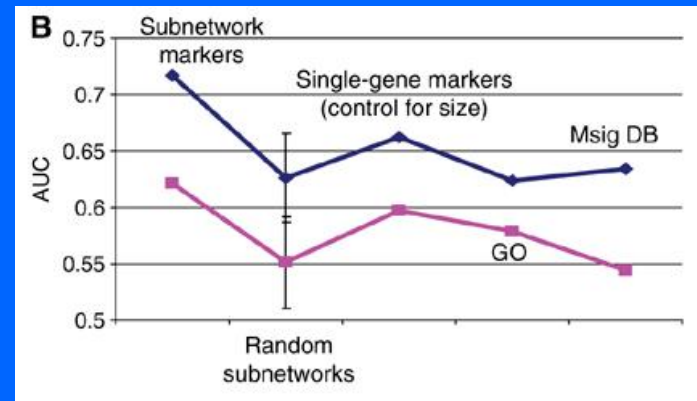
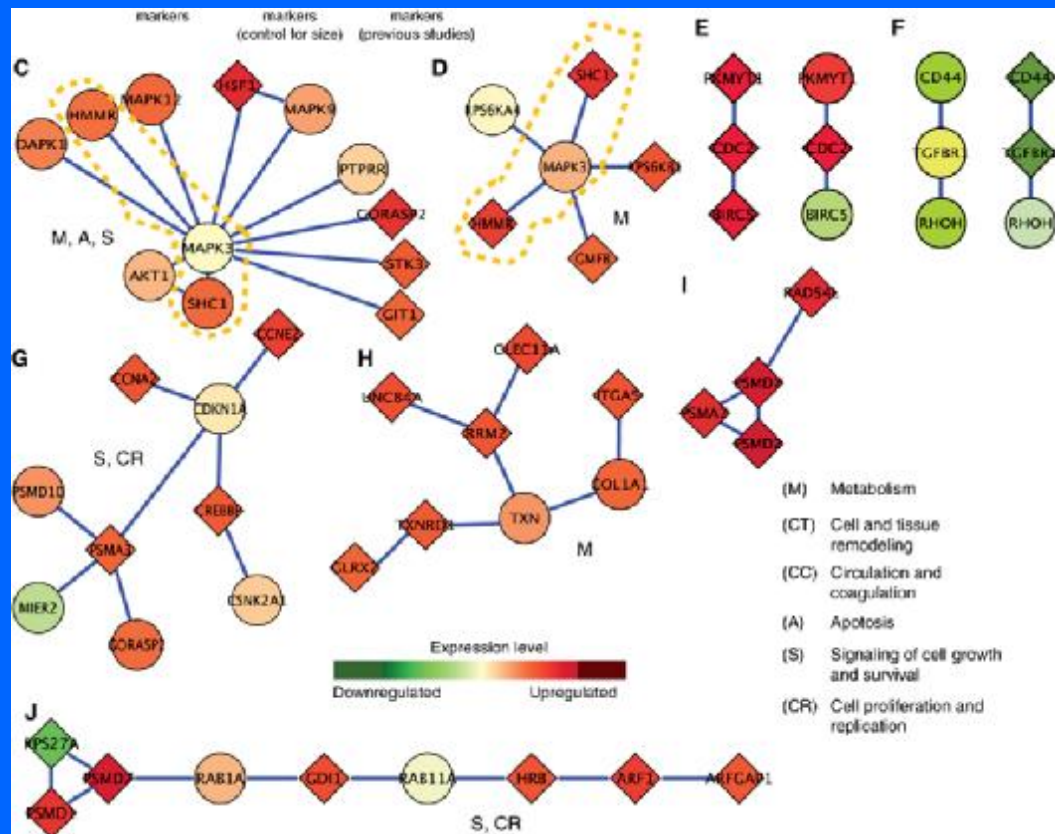
Why do we need Systems Biology to identify and predict Biomarker Sets?



Disease and drug action originate at the level of cellular components but physiological effects (e.g. symptoms, drug action) are at the organismal levels.

Unraveling such complexity requires a systems approaches

Predictive Network Biomarker Sets for Breast Cancer



Network of Biomarkers perform better than single gene biomarkers

Chuang HY, Lee E, Liu YT, Lee D, Ideker T. Network-based classification of breast cancer metastasis. *Mol Syst Biol.* 2007;3:140. Epub 2007 Oct 16

Multiple sets of markers for breast cancer progression and recurrence

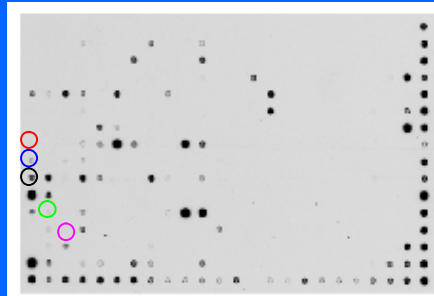
MammaPrint (FDA Approved Breast Cancer Diagnostic)
Based on studies by van't Veer L.J. (Nature 415: 530)
(70 genes)

Wang et al Lancet 365: 671 - Rotterdam signature
(76 genes)

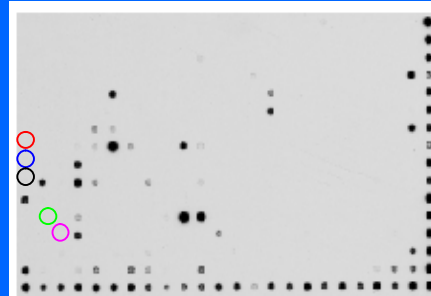
Only 3 genes in common between the two sets – Each set predicts less successfully on the others data set

HOW MIGHT THE TWO SETS BE RELATED ?

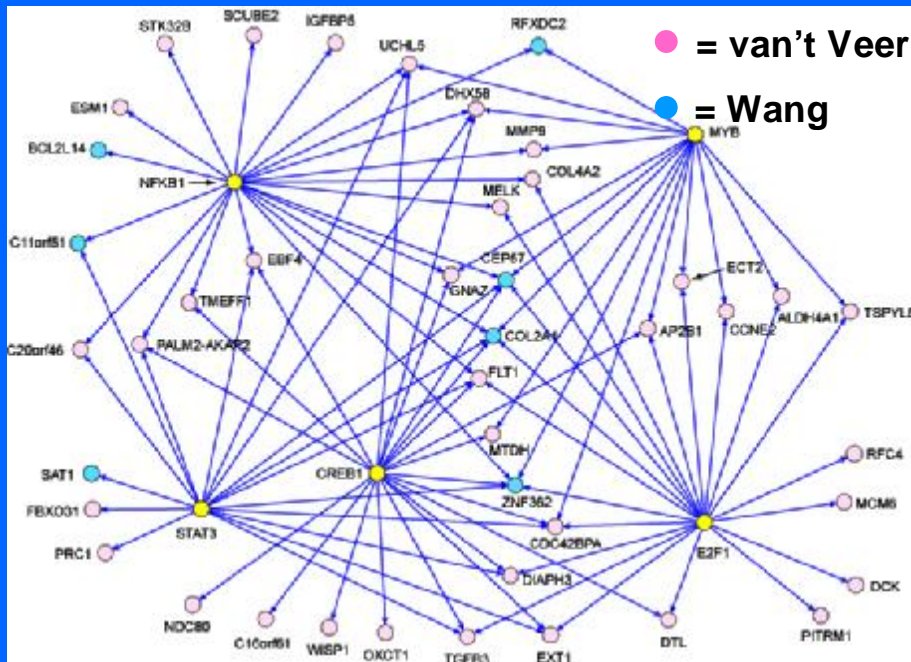
Linking breast cancer biomarker set genes to upstream transcription factors and signaling



SKBR3

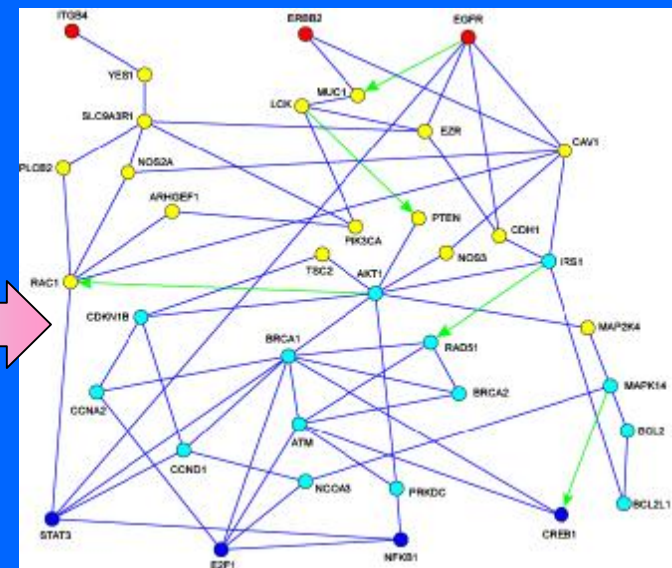


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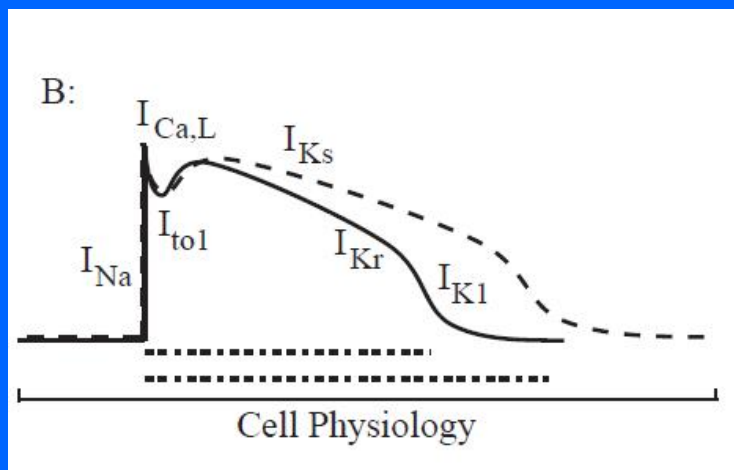
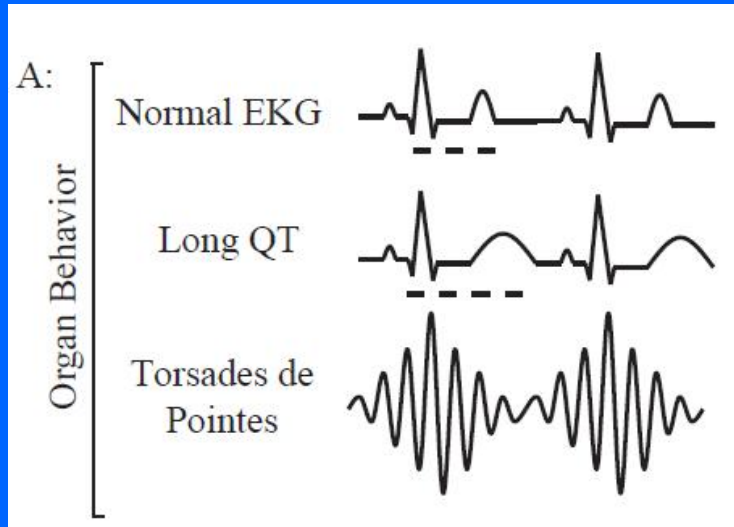


Transcription factor activity profiling and network analyses help identify relationship upstream mutated disease genes and prognostic gene expression signatures

Helps explain multiple signatures



Congenital Arrhythmia Syndromes and Relationship to Drug-induced Arrhythmias

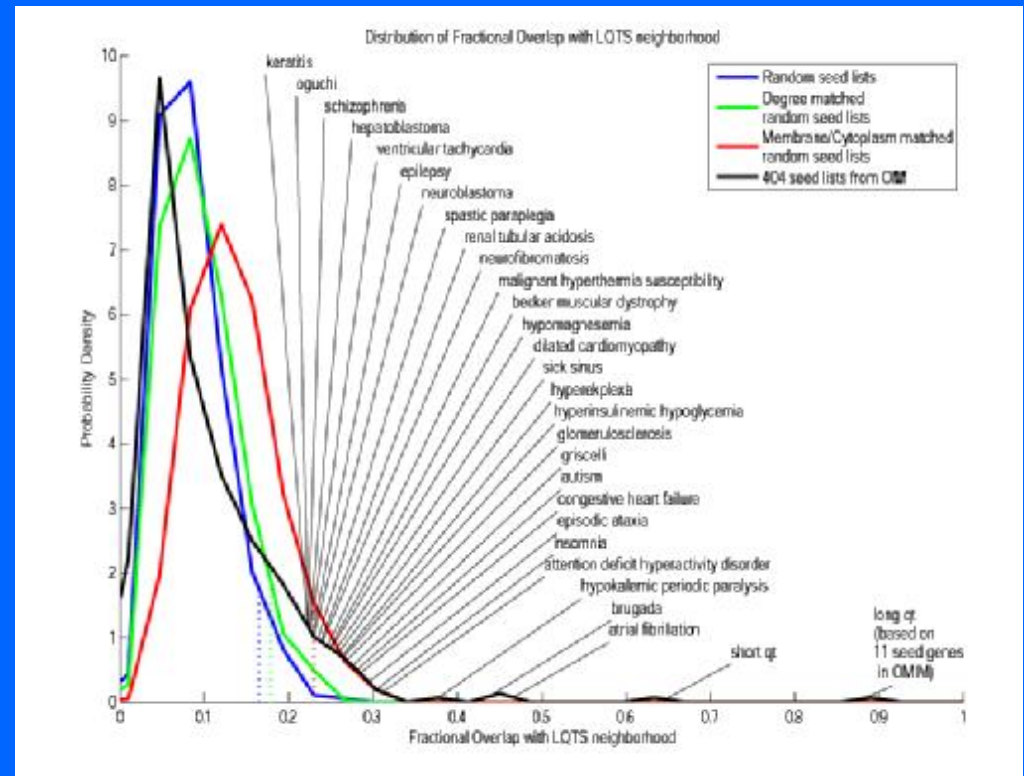
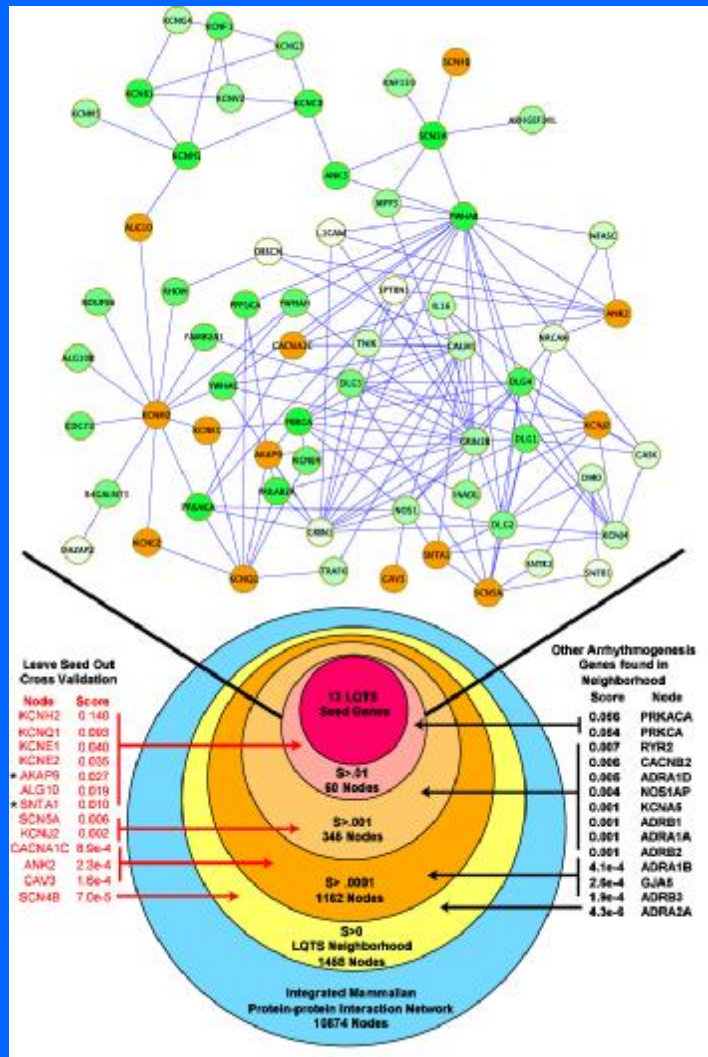


C: Genes associated with congenital and acquired LQTS.

Gene Symbol	Full Gene Name	Function	LQT Phenotype
KCNQ1	potassium voltage-gated channel, KQT-like subfamily, member 1	$\downarrow I_{Kr}$	LQT1
KCNH2	potassium voltage-gated channel, subfamily H (eag-related), member 2	$\downarrow I_{Kr}$	LQT2
SCN5A	sodium channel, voltage-gated, type V, alpha subunit	$\uparrow I_{Na}$	LQT3
ANK2	ankyrin 2, neuronal	Altered Targeting of Ca^{2+} control proteins	LQT4
KCNE1	potassium voltage-gated channel, Isk-related family, member 1	$\downarrow I_{Ks}$	LQT5
KCNE2	potassium voltage-gated channel, Isk-related family, member 2	$\downarrow I_{Kr}$	LQT6
KCNJ2	potassium inwardly-rectifying channel, subfamily J, member 2	$\downarrow I_{K1}$	LQT7
CACNA1C	calcium channel, voltage-dependent, L type, alpha 1C subunit	$\uparrow I_{Ca,L}$	LQT8
CAV3	caveolin 3	$\uparrow I_{Na}$	LQT9
SCN4B	sodium channel, voltage-gated, type IV, beta	$\uparrow I_{Na}$	LQT10
AKAP9	A kinase (PRKA) anchor protein (yotiao) 9	$\downarrow I_{Ks}$	LQT11
ALG10	asparagine-linked glycosylation 10 homolog (yeast, alpha-1,2-glycosyltransferase)	Protects I_{Kr} from drug blockade	Reduced susceptibility to LQTS

Seth Berger

Disease Gene Neighborhoods in the Cellular Network



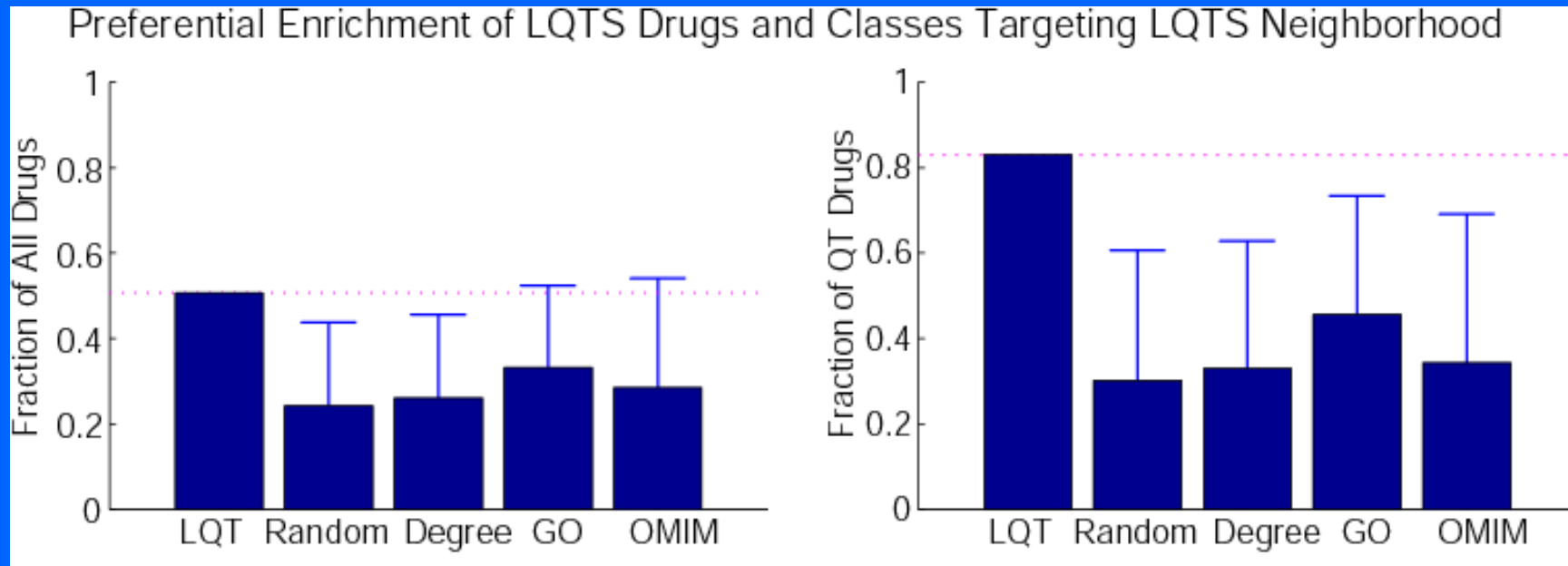
Relatively unique networks can be constructed around genes involved in disease states.

These networks can explain relationships between diseases

Can these networks explain drug side effects?

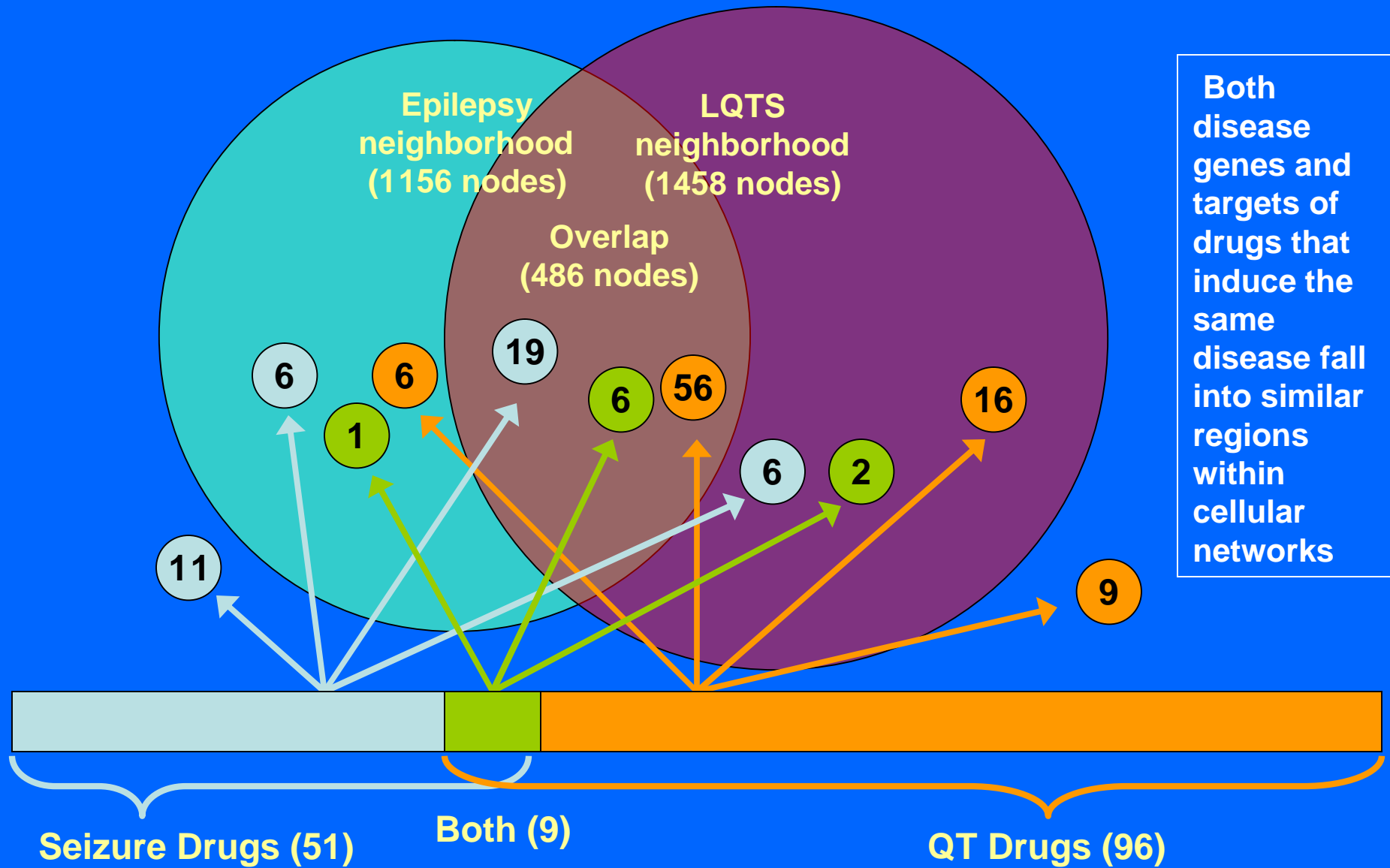
Yes, we can ! at least for LQTS

Relationships between the Genomics and Systems Pharmacology of LQTS



There is an enrichment of QT prolonging drugs that target the LQTS neighbourhood. Drugs as a whole are not enriched in this neighbourhood

Comparing the Genomics and Systems Pharmacology of Arrhythmias and Seizures



Systems Biology for Toxicity Assessment in Early Drug Development

- **Systems Biology approaches identify networks selective for diseases and drug action**
- **These networks can provide insight into the pathogenesis of adverse events and suggest alternative targets with equivalent effects.**

Implicit assumption: For a disease drug induced pathophysiology and congenital syndrome share common mechanisms

Systems Biology for Multimarker Panels

- Individual biomarkers are less informative than multimarker panels
 - Diseases and side effects arise from multiple interacting factors
- Networks allow integration of multiple sources of information into a framework that may provide prediction of disease outcomes and drug toxicity

**Multimarker networks may yield superior panels
For both disease outcome and drug toxicity**