

# Network-based drug target discovery

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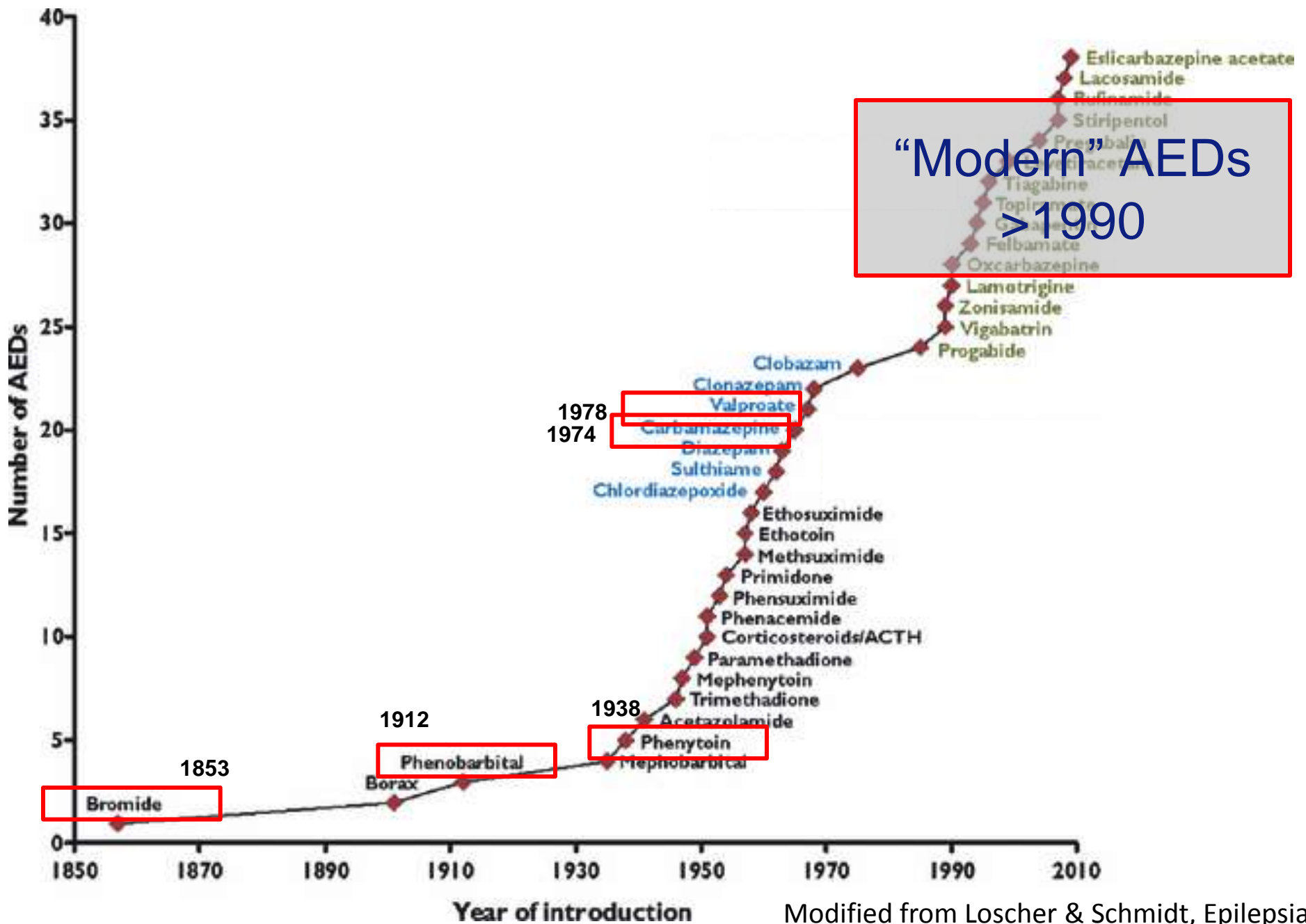
# Structure of Talk

- Part 1: Limitations of currently available anti-epilepsy drugs
- Part 2: Network approaches to new drug target discovery
- Part 3: Application to epilepsy

# EPILEPSY

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- A common, serious neurological disorder
- Lifetime risk of epileptic seizure is 4%
- Active epilepsy affects 1 in 200 people
- Young people with epilepsy: 24X more likely to die than members of the general population
- Stigma, social exclusion and under-employment
- Costs the UK NHS £1bn/year



Modified from Loscher & Schmidt, Epilepsia

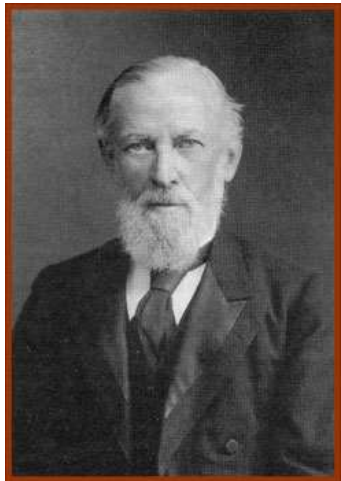
# Prognosis of epilepsy

## Prospective cohorts of newly treated epilepsy

30% of patients fail to remit despite maximal medical therapy

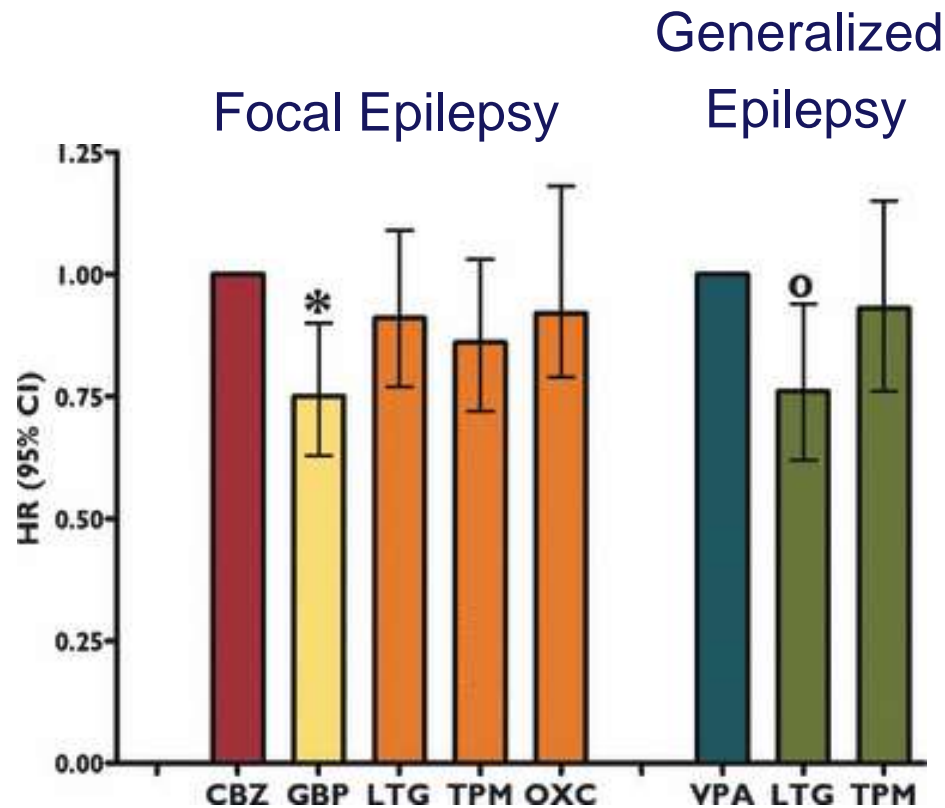
Schmidt and Sillanpaa. *Curr Opinion Neurol* 2012

Gowers (1881) 30% of newly treated patients failed to remit with Bromide

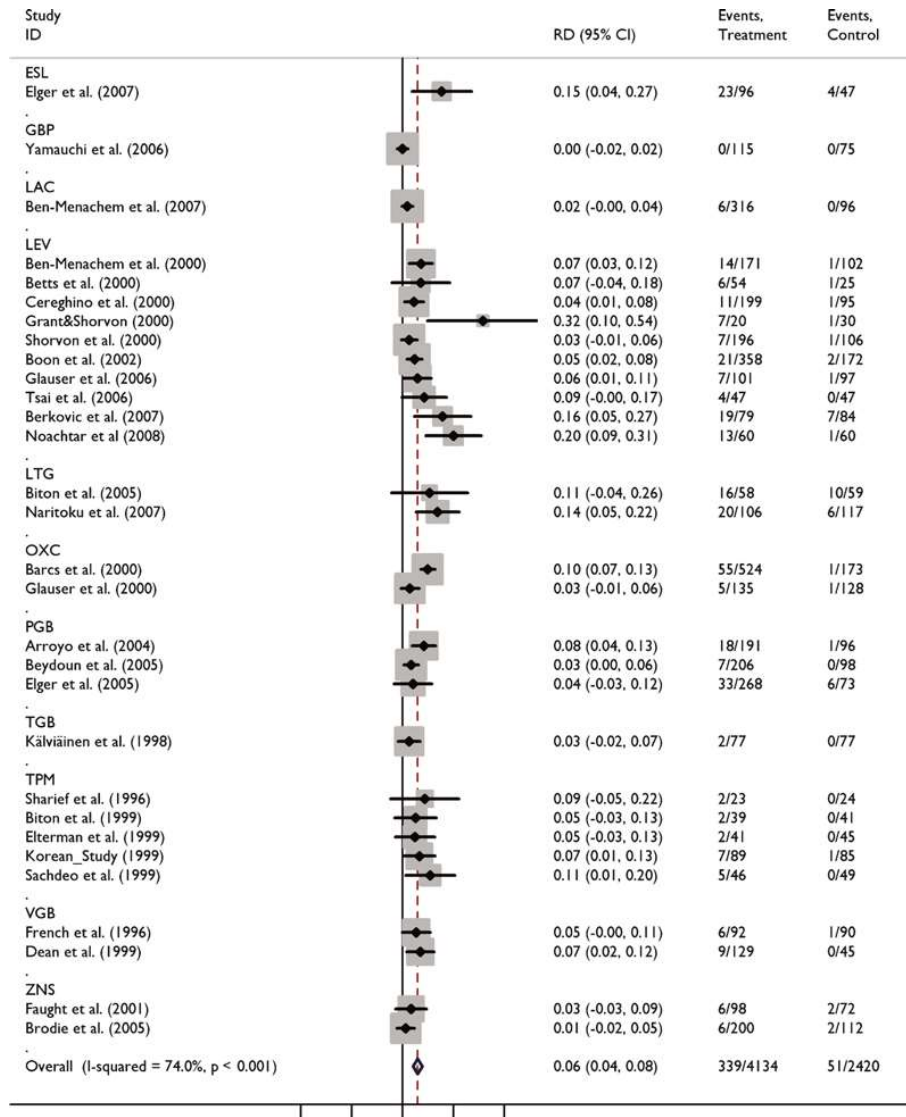


Gowers WR. In, *Epilepsy and other chronic convulsive diseases: their causes, symptoms & treatment*. Churchill: London; 1881

# Comparative efficacy of old and new AEDs: time to 12-month remission of seizures



# Placebo-corrected efficacy (seizure freedom) for all AED licensing trials since 1996



Overall pooled-risk for Sz freedom = 6%

# Clinically important PK interactions

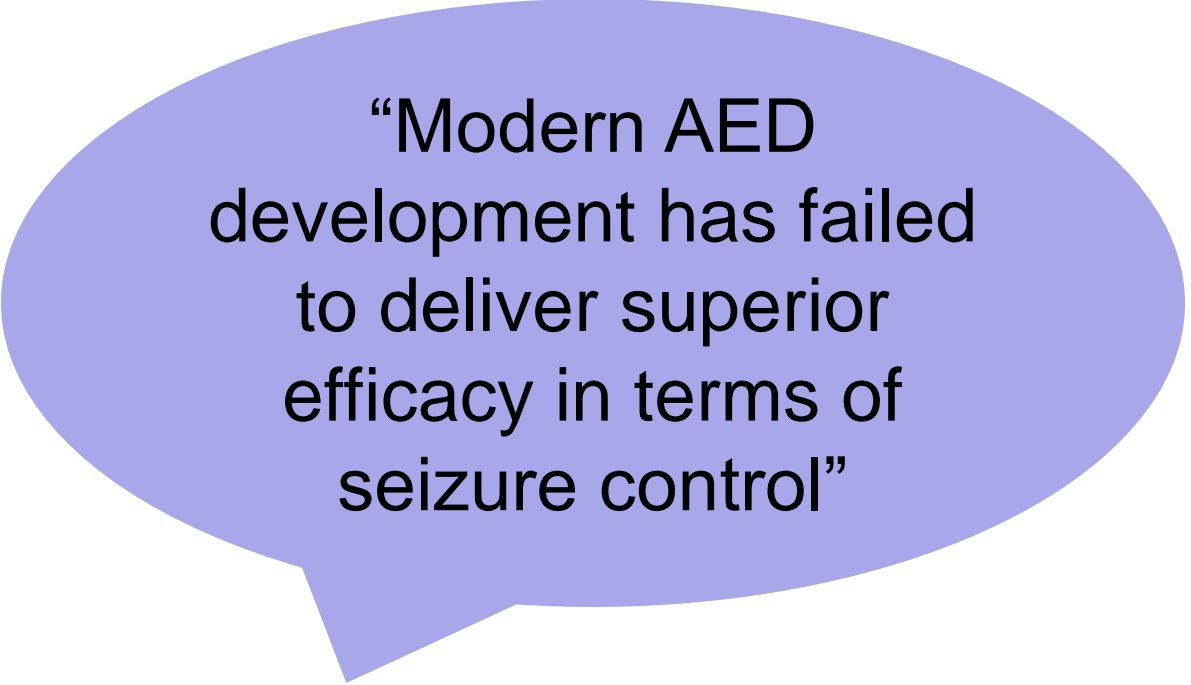
## AED / AED interactions

AED	Number
PHT	20
CBZ	17
VPA	16
PB	14
OXC	8
TPM	8
ZNS	7
ETS	6
LTG	6
TGB	4
VGB	1
<b>GBP</b>	<b>0</b>
<b>LEV</b>	<b>0</b>
<b>PGB</b>	<b>0</b>
<b>LCM</b>	<b>0</b>

## AED / non-AED interactions

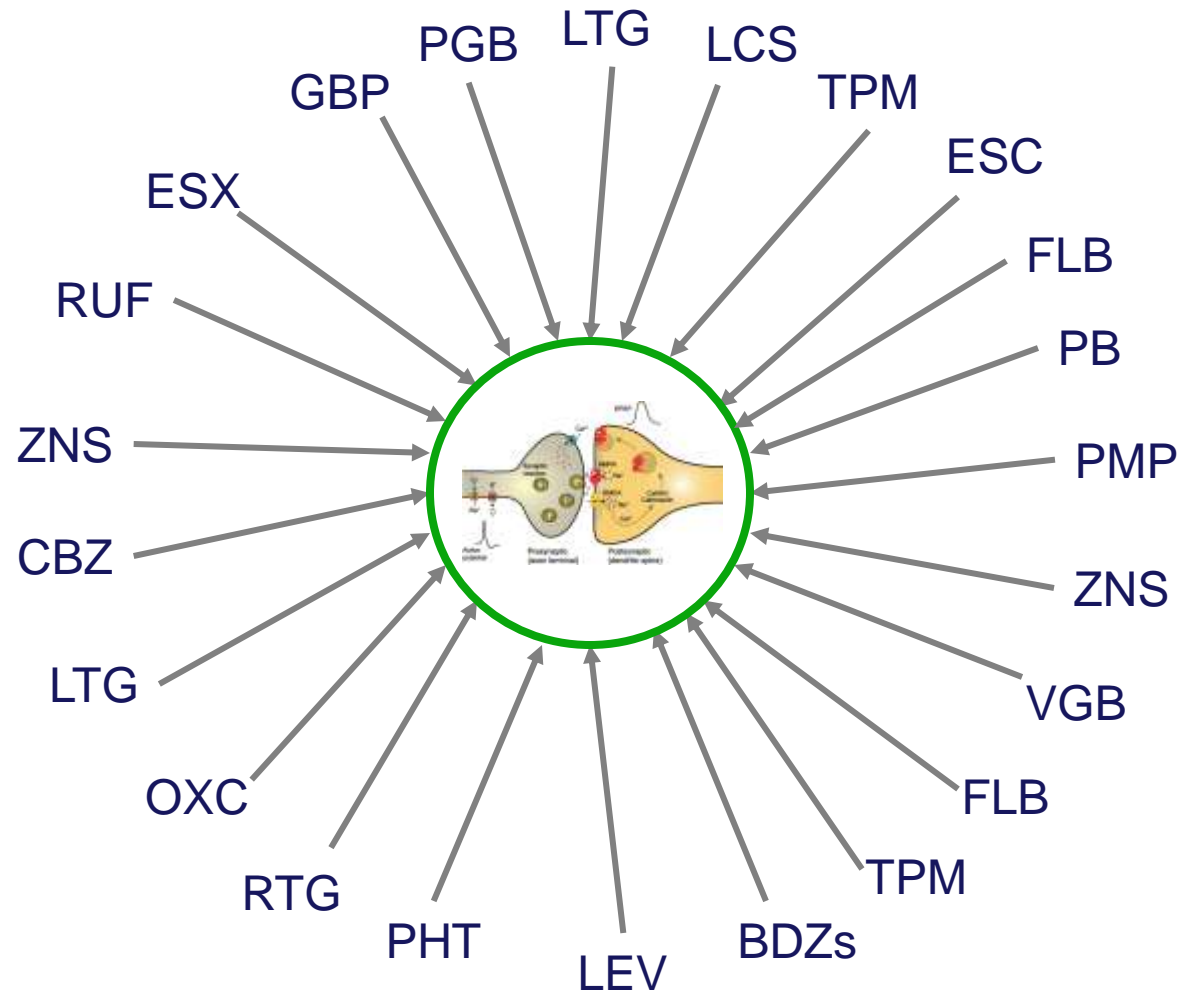
AED	Number
PHT	Many 100s
CBZ	
VPA	
PB	
ETS	
TPM	10
LTG	6
OXC	5
GBP	2
ZNS	1
TGB	1
<b>VGB</b>	<b>0</b>
<b>LEV</b>	<b>0</b>
<b>PGB</b>	<b>0</b>
<b>LCM</b>	<b>0</b>



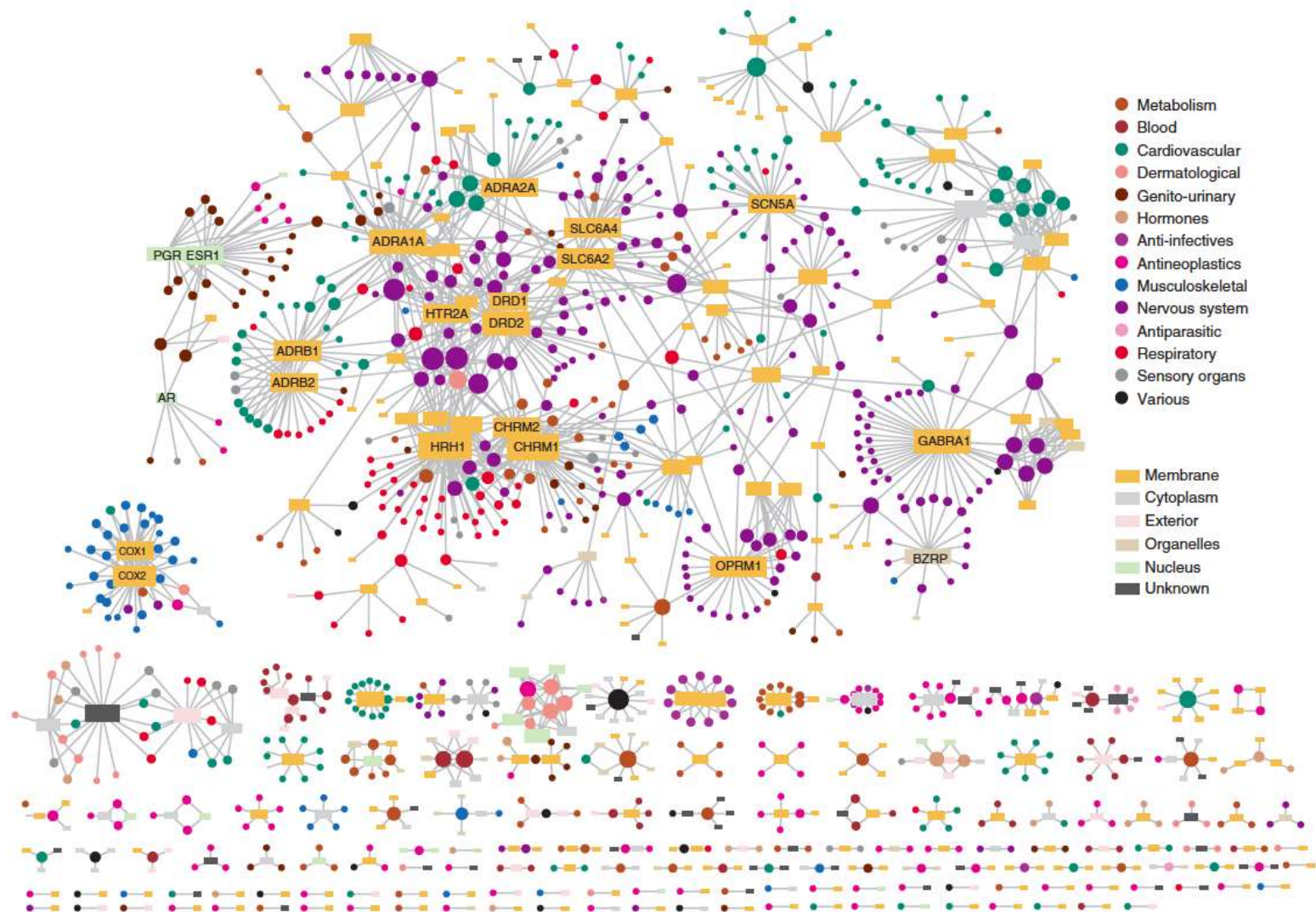


**“Modern AED  
development has failed  
to deliver superior  
efficacy in terms of  
seizure control”**

# The antiepileptic drug target network



# Drug-Target Network: 1,178 FDA-approved drugs in 2007 and their 394 target proteins (drug-target ratio 3:1)

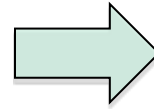
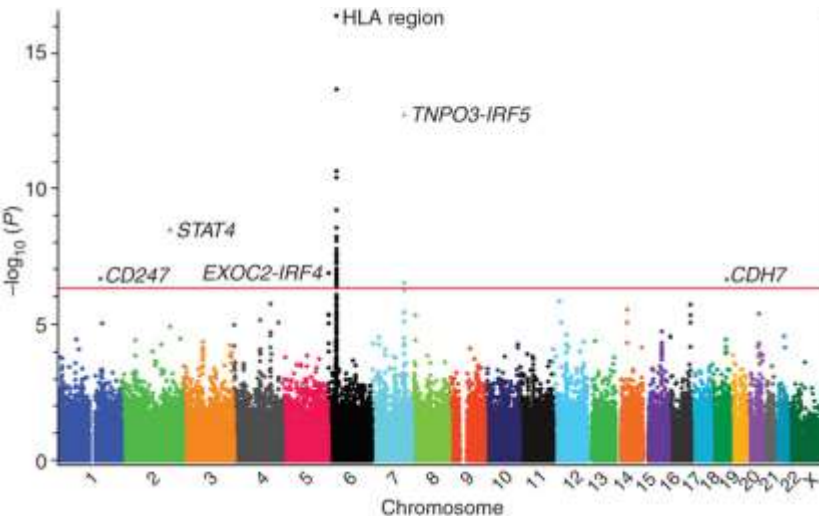


# Need to increase the pool of drug targets

- Better efficacy
- Target novel causal molecular pathways and not just focus on existing mechanisms

# Traditional genetic approach

Genome-wide association studies  
(GWAS)



**Hundreds of loci associated  
with human disease**

## Major Limitations

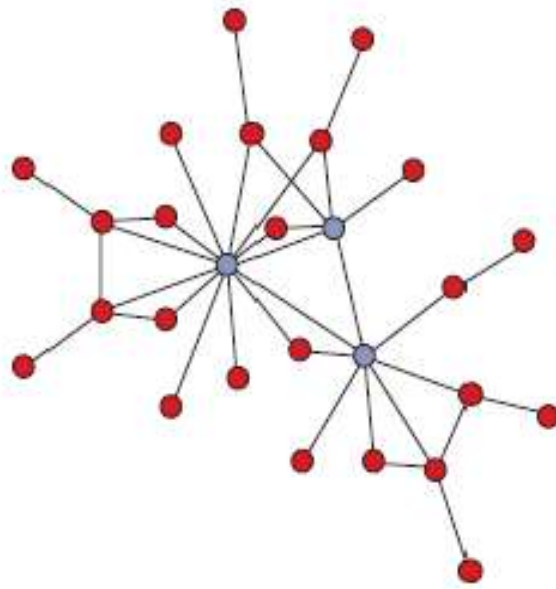
- Rarely identify the causal pathway
- Rarely inform new drug targets

# Beyond single-gene approaches: Network-based drug target discovery

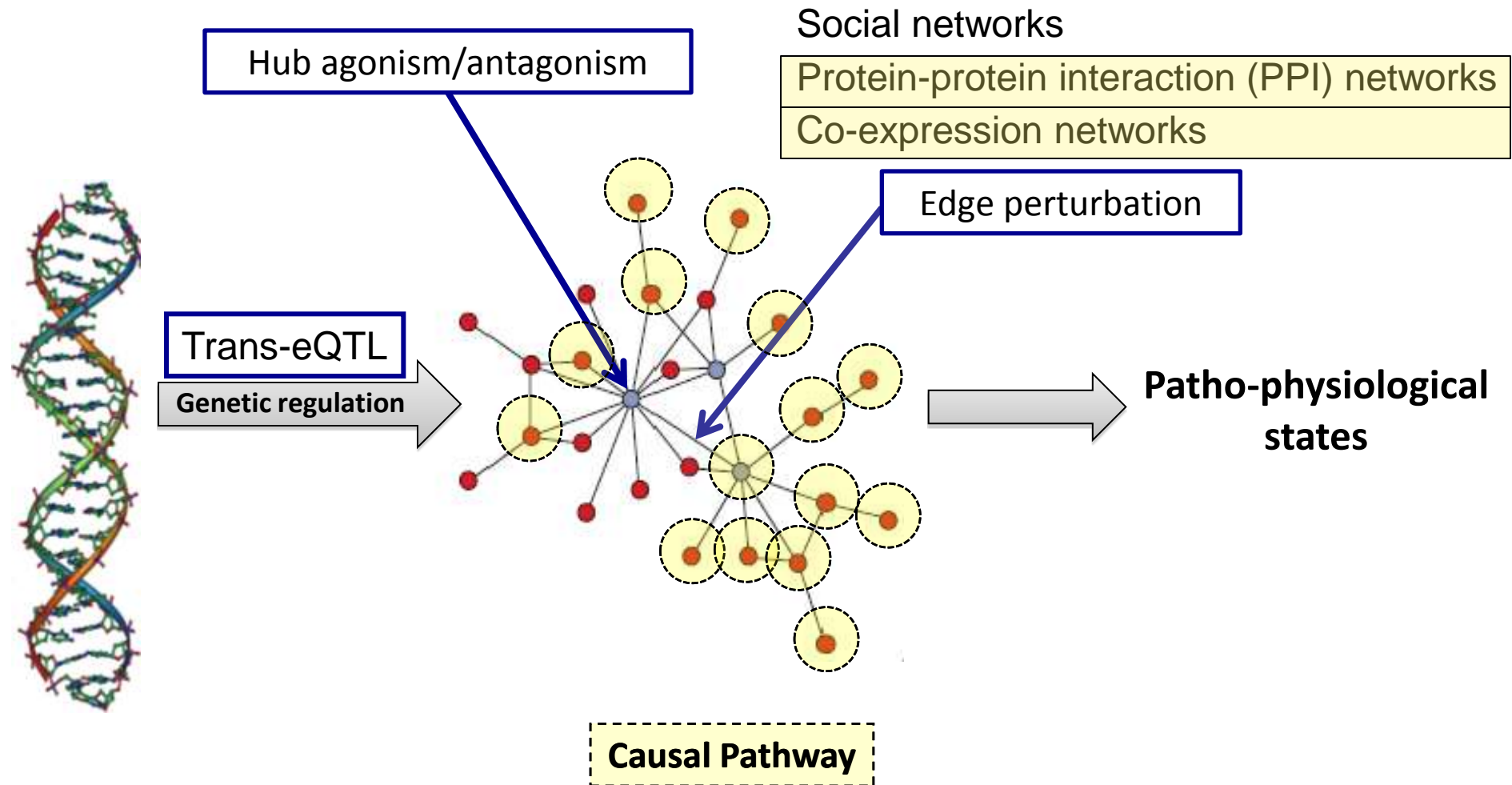
Social networks

Protein-protein interaction (PPI) networks

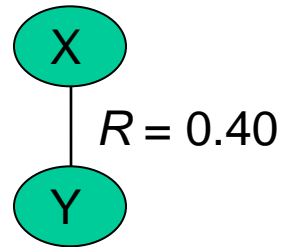
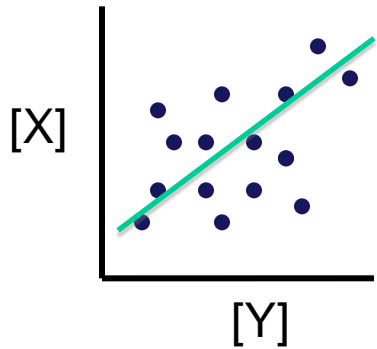
Co-expression networks



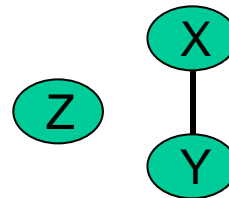
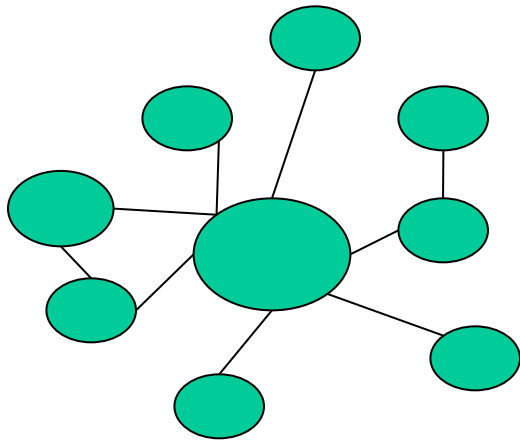
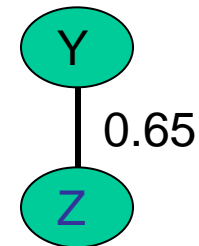
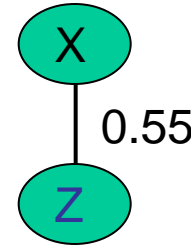
# Beyond single-gene approaches: Network-based drug target discovery



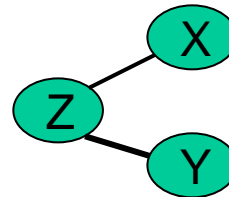
# Co-expression networks using partial correlations (e.g., GGM)



but...



conditional dependence = edge



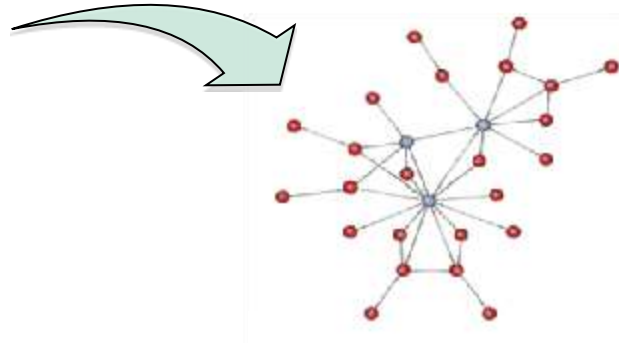
conditional independence = no edge

Partial correlation matrix describes the correlation between all possible gene pairs conditioned on **all** other genes in the genome



# Integrative Network Genomics and Medicine

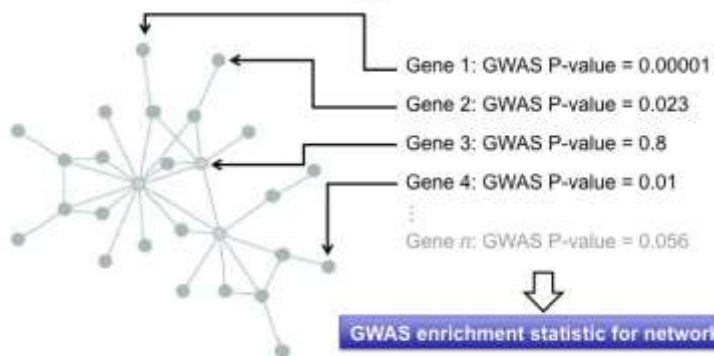
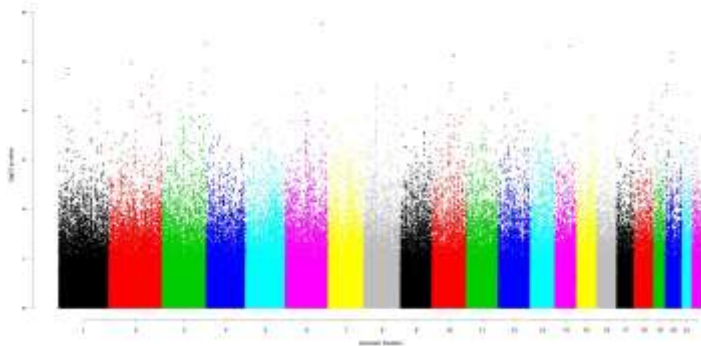
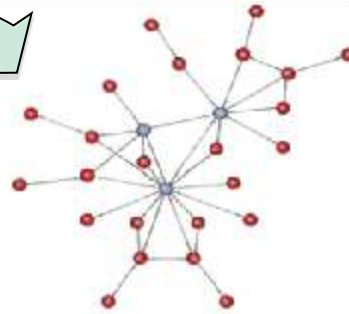
gene expression data  
from relevant tissue



# Integrative Network Genomics and Medicine

gene expression data  
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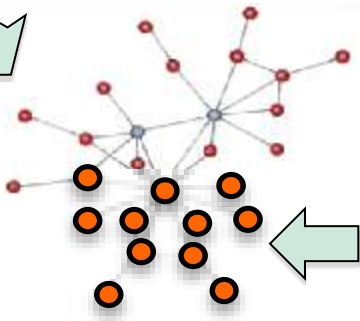
networks associated to  
disease by GWAS



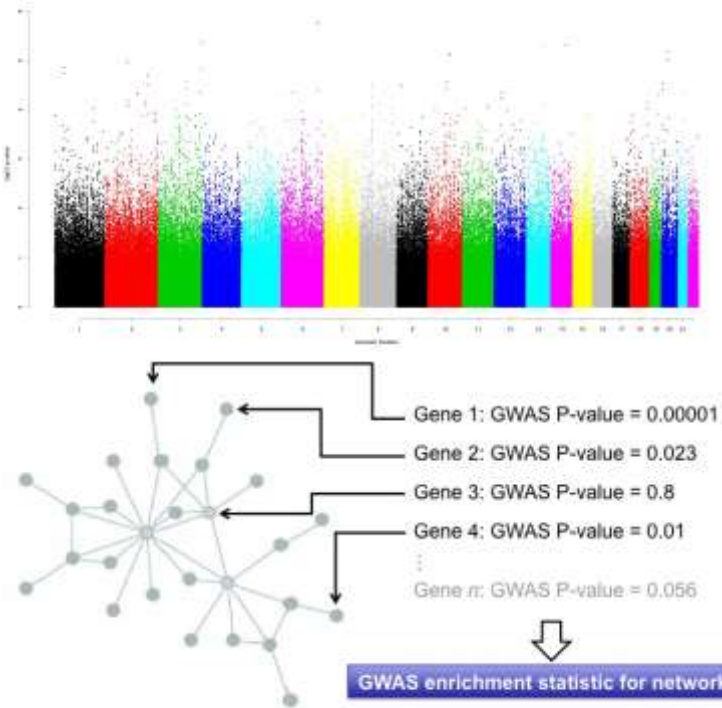
# Integrative Network Genomics and Medicine

gene expression data  
from relevant tissue

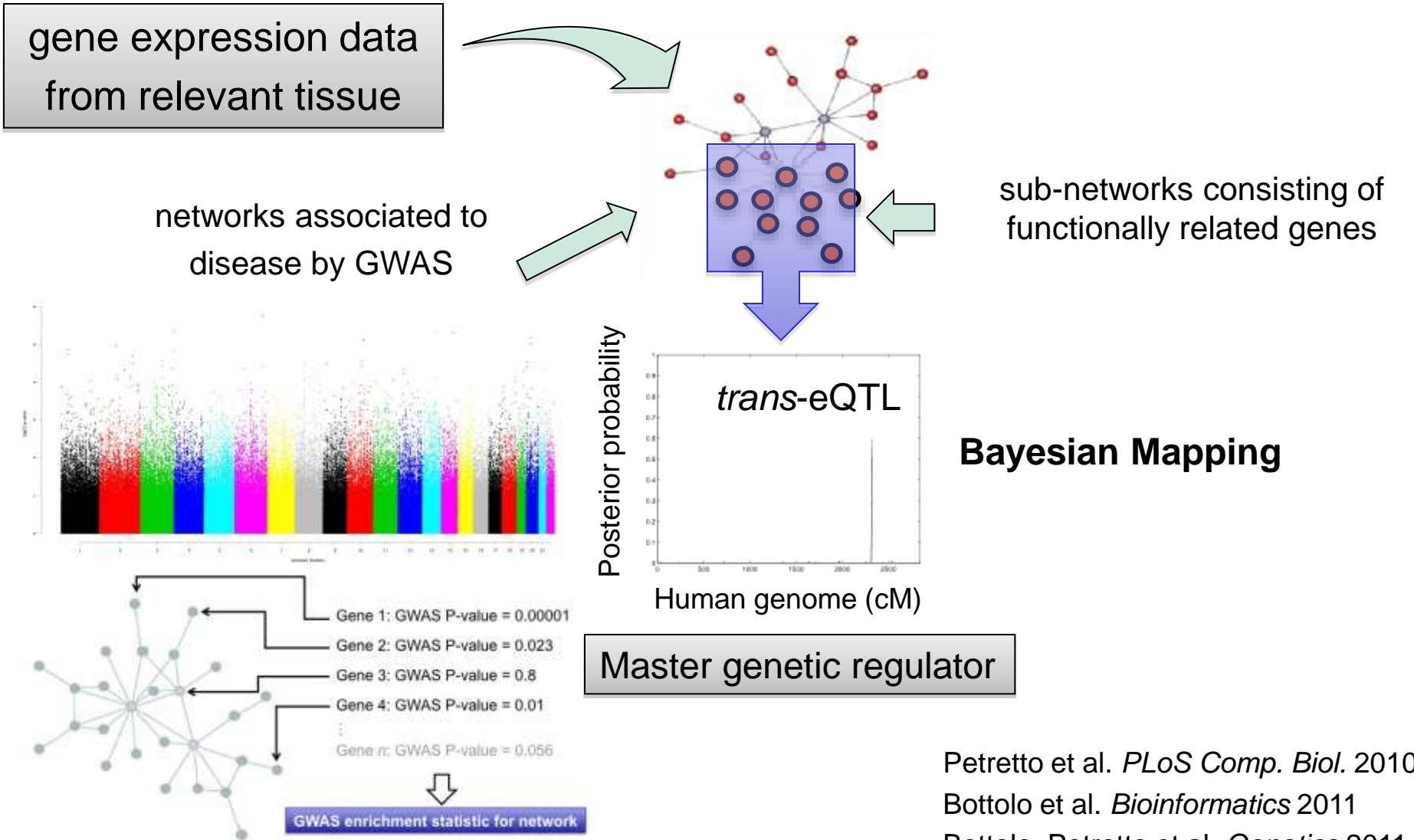
networks associated to  
disease by GWAS



sub-networks consisting of  
functionally related genes



# Integrative Network Genomics and Medicine

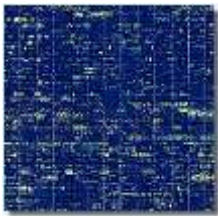


Petretto et al. *PLoS Comp. Biol.* 2010  
Bottolo et al. *Bioinformatics* 2011  
Bottolo, Petretto et al. *Genetics* 2011  
Heinig et al., *Nature* 2010

# Integrative Network Genomics: application to human epilepsy

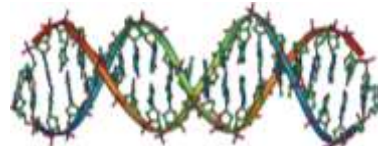
N=131 patients with temporal lobe epilepsy (TLE)

Gene expression  
in hippocampus



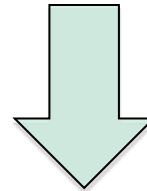
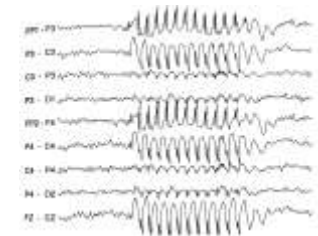
+

Genotype (SNP) data



+

Clinical data

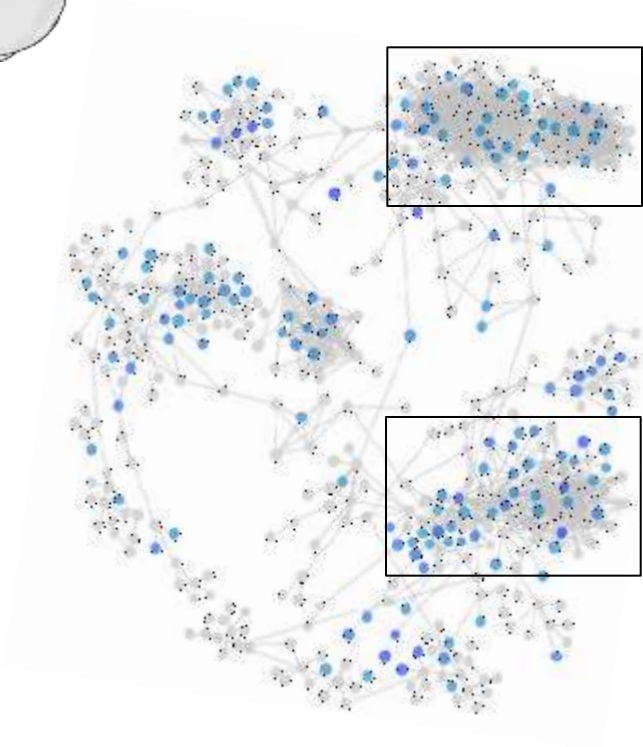


Integrate multi-level data using  
network approaches to identify  
new drug targets for epilepsy

# Integrative Genomics and Medicine

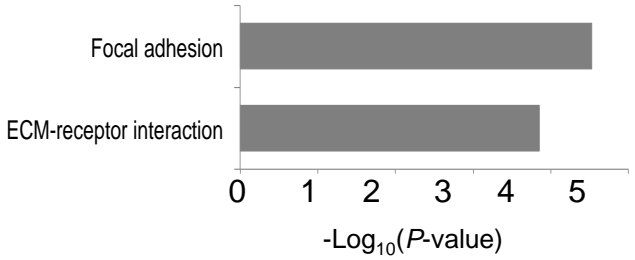
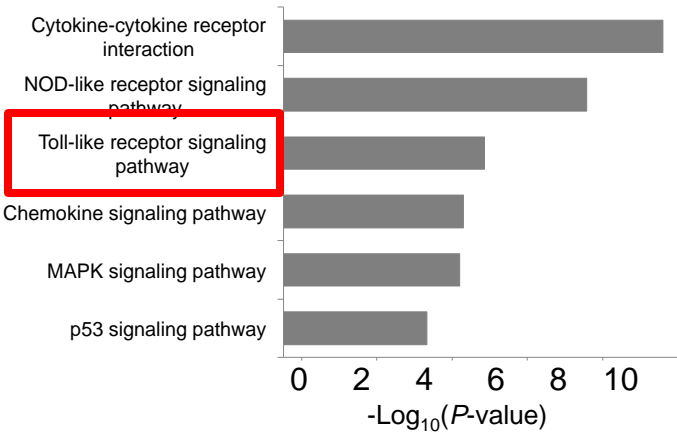


N=131



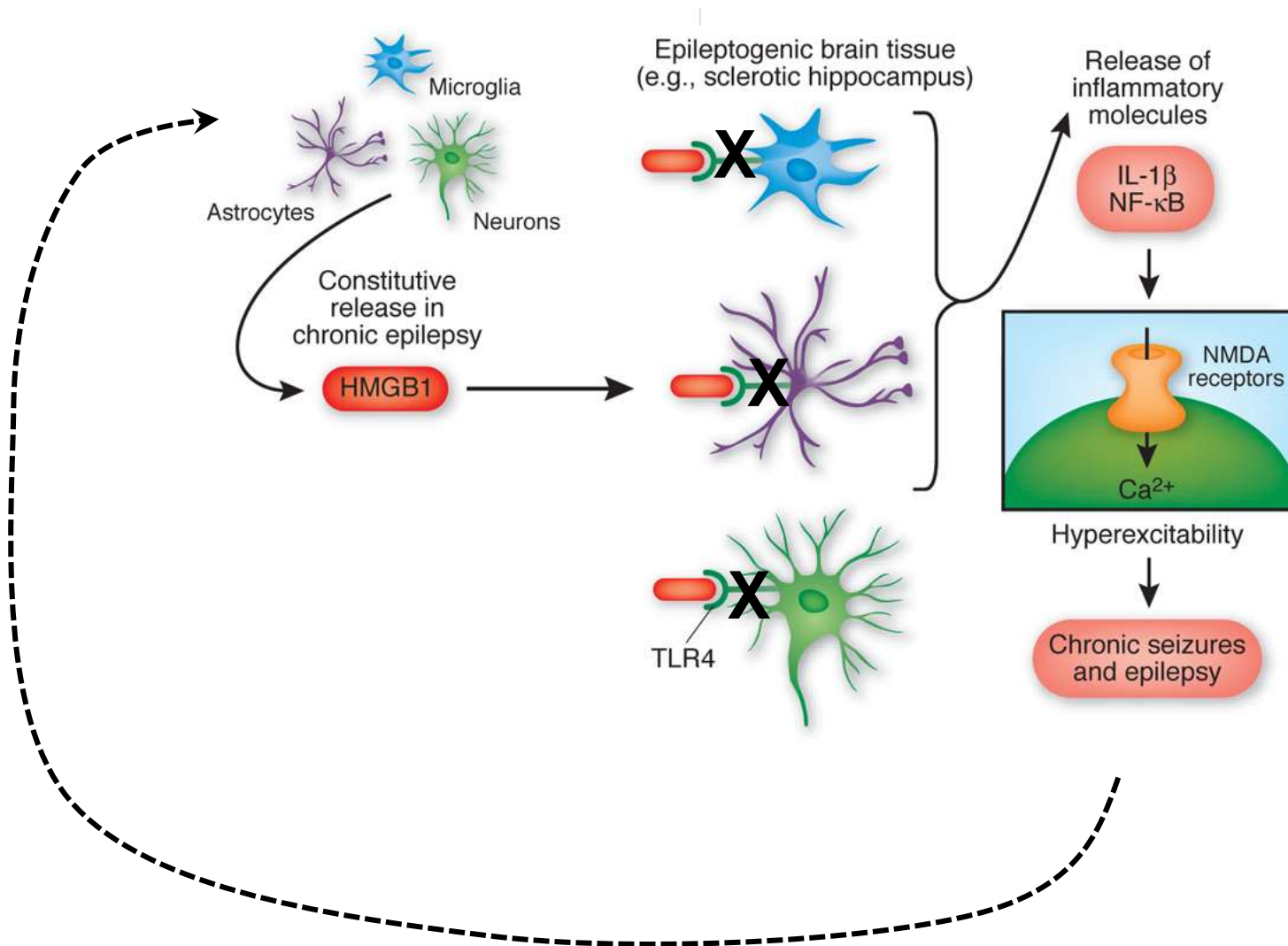
Module-1

Module-2



# Toll-like receptor (TLR) signaling and epilepsy

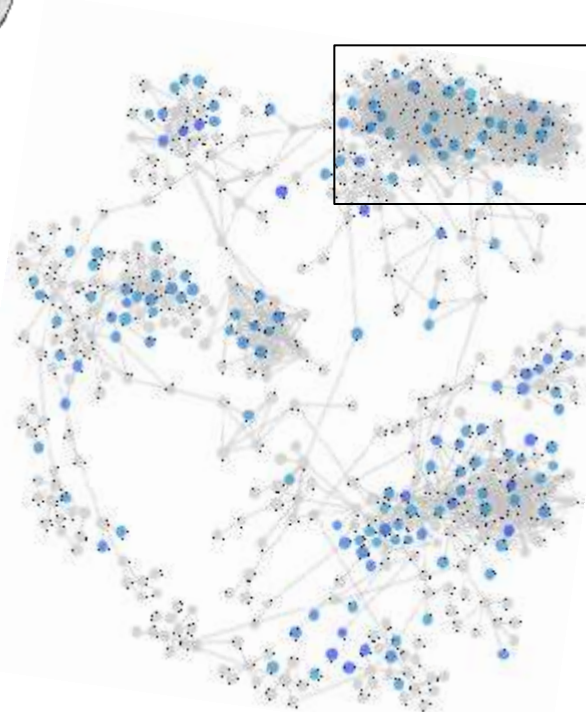
Maroso et al., *Nat Med* 2010



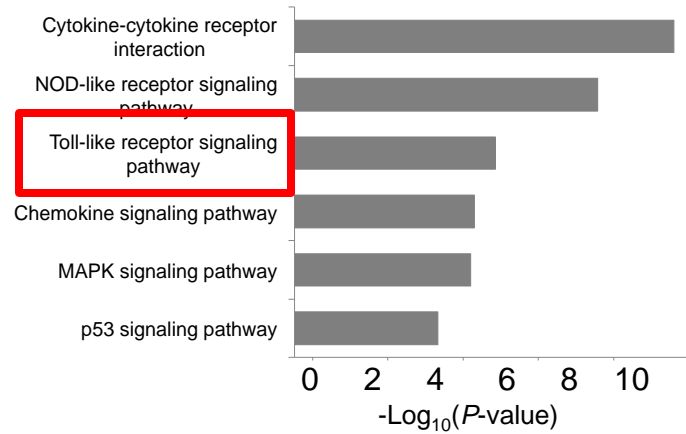
# Integrative Genomics and Medicine



N=131

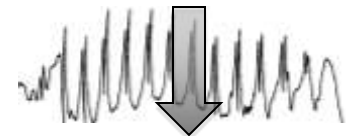
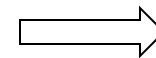


Module-1



Hypothesis

INFLAMMATION

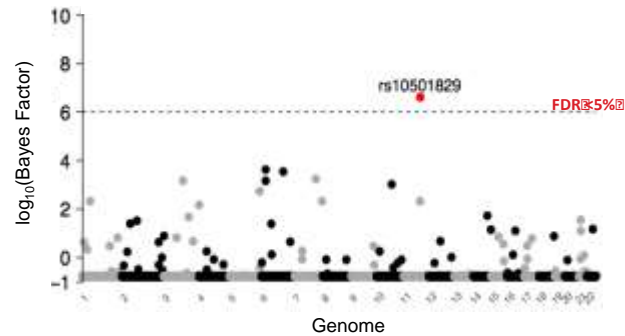


SEIZURES



# Integrative Genomics and Medicine

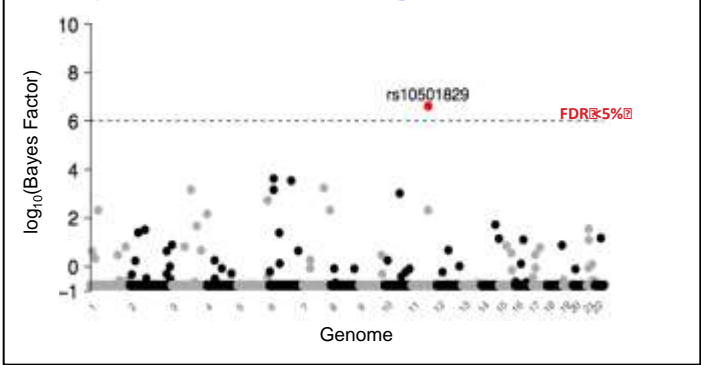
## Bayesian mapping of Module-1



Master genetic control by gene on Chr 11

# Integrative Genomics and Medicine

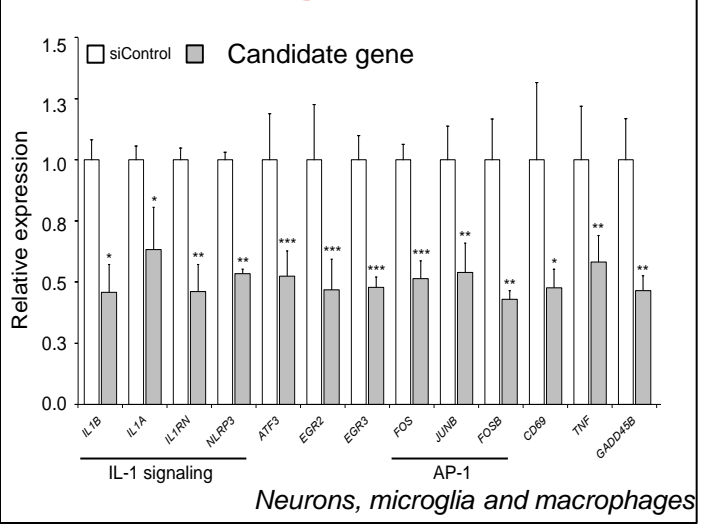
## Bayesian mapping of Module-1



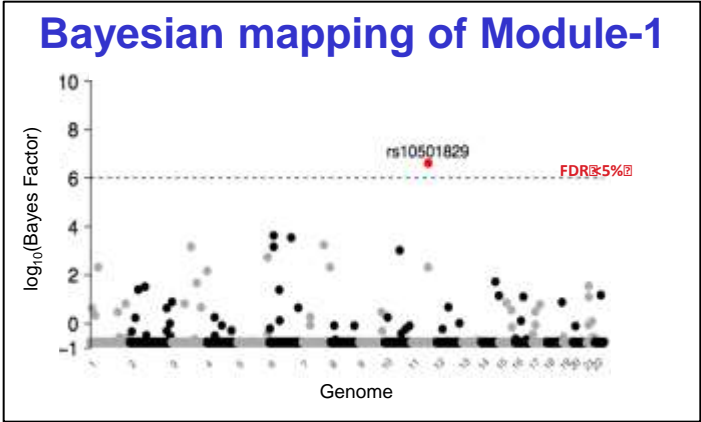
## Master genetic control by gene on Chr 11



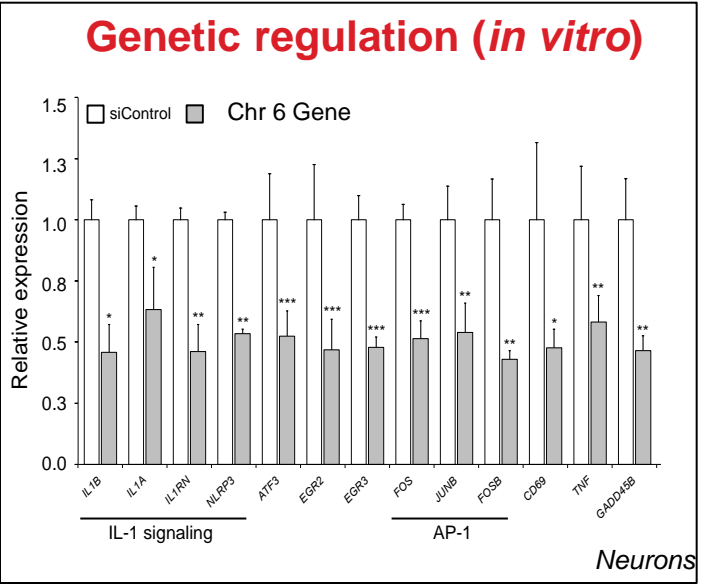
## Genetic regulation (*in vitro*)



# Integrative Genomics and Medicine



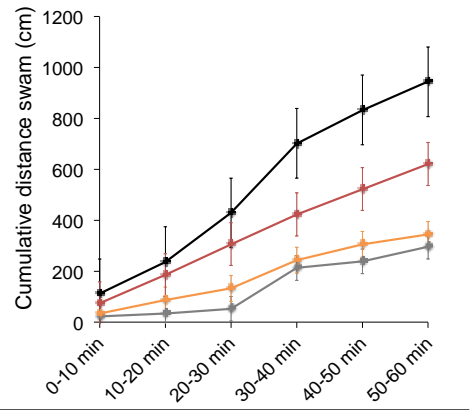
Master genetic control by gene on Chr 11



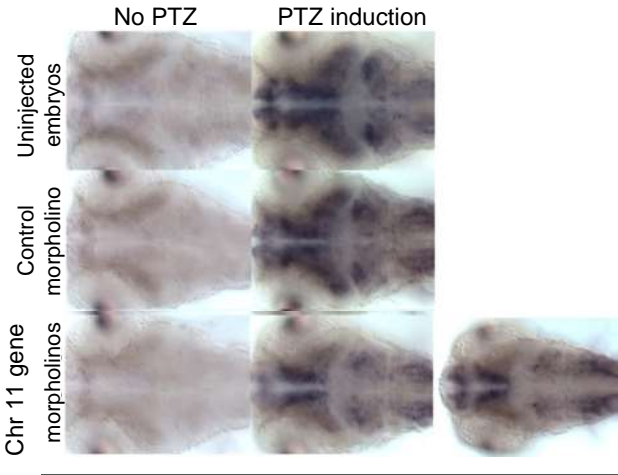
## GENE KD has seizure-suppressing properties *in vivo*

*Zebrafish model of PTZ-induced epileptic seizures*

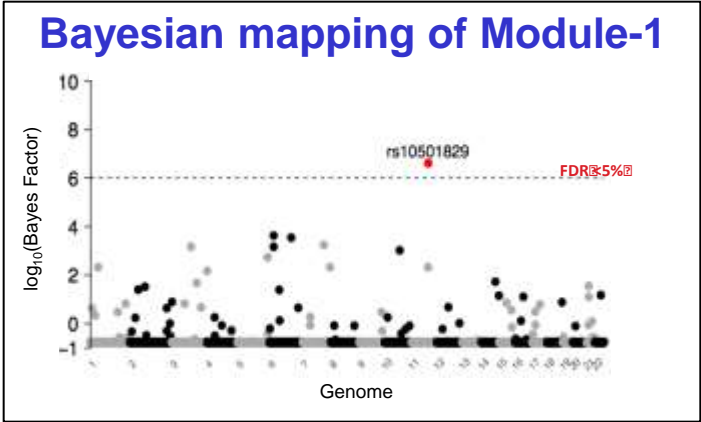
1. Reduced locomotor activity



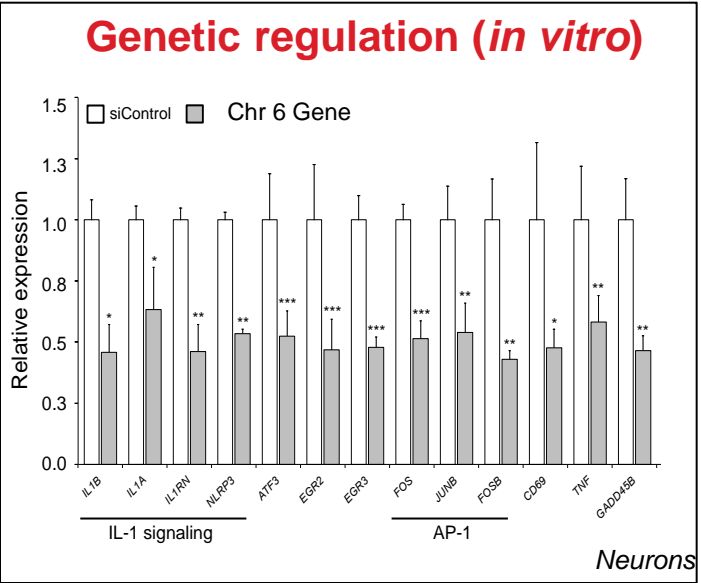
2. Reduced *c-fos* expression (*in situ*)



# Integrative Genomics and Medicine



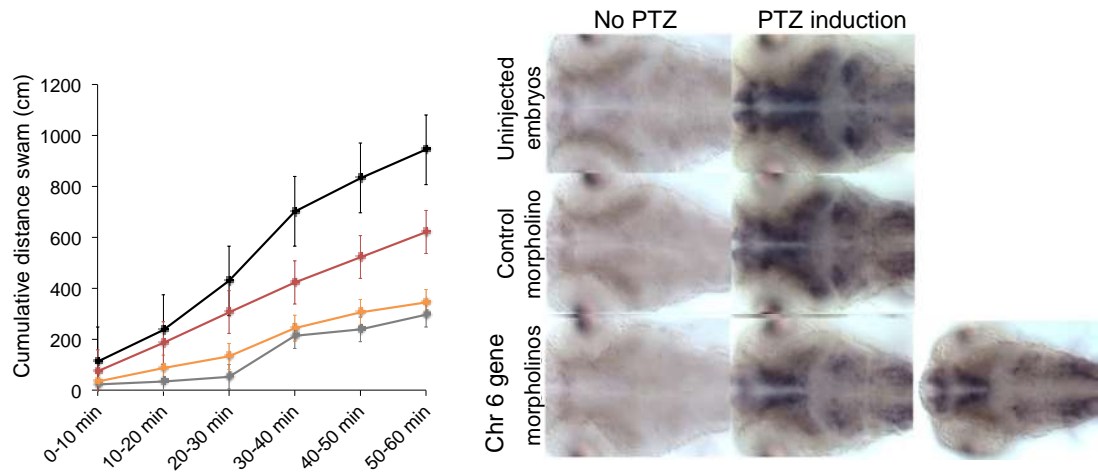
Master genetic control by gene on Chr 11



## **GENE KD has seizure-suppressing properties *in vivo***

*Zebrafish model of PTZ-induced epileptic seizures*

1. Reduced locomotor activity
2. Reduced *c-fos* expression (*in situ*)



Chr 11 gene regulates a co-expression network in human epileptic hippocampus and inhibition has seizure-suppressing effects *in vivo*



**Potential new target for epilepsy**

IP protection ongoing

Imperial Innovation Primer Fund grant awarded (PI)

**Systems-genetics**

Identify gene networks  
driving disease states

**Genetic  
regulators  
of disease**

Potential targets for  
disease modification

Industrial  
partnerships

Dr Michael Johnson  
Dr Enrico Petretto