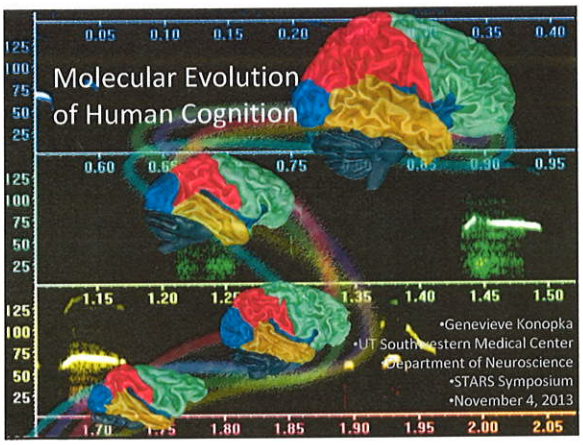
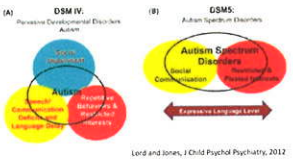


AUTISM

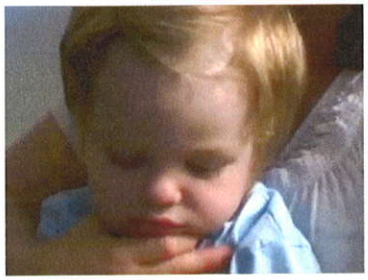


Lord and Jones, J Child Psychol Psychiatry, 2012

Autism (or ASD) is a human-specific disorder

1 in 88 in the US:
>800,000 children in US (plus adults)

Autism: a human disorder

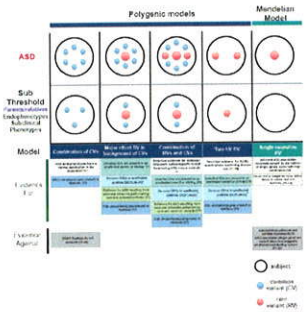


UC Davis

ASD: complex genetic architecture but a starting point

Concordance Rates:

MZ twins: 50-90%
DZ twins: 0-30%
Siblings: 3-26%



Berg and Geschwind *Genome Biology* 2012

Enrichment of ASD genes at the synapse

Delorme et al., Thomas Bourgeron 2013 *Nat Med*

How can we connect genetics/genomics to brain-relevant phenotypes in a meaningful way for a human-specific disease?

Current state-of-the-art for ASD research

Traditional Approach

Patients → Identify genes and mutations → Disease ← Treat

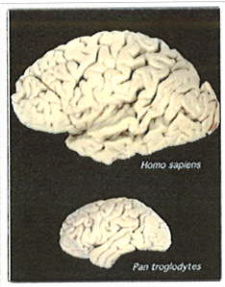
Social impairment→ social preference test

Repetitive behaviors→ grooming

Communication→ USVs

Rescue with one of a few drugs: risperidone, various receptor agonist/antagonists

BUT a mouse is not a small human.....



Todd Preuss

A different way to approach these disorders is to work from the

hypothesis that vulnerability to disorders of cognition emerged as a consequence of the evolution of cognition itself

Many Features have Contributed to human Evolution

- LANGUAGE is Arguably the most Compelling & Unique human Feature
- And is disrupted in many cognitive disorders

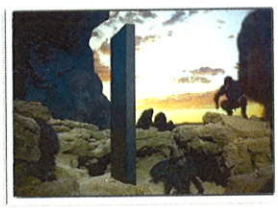
Can we uncover the origins of human language at a genetic and molecular level?

And use this information to provide insight into neurodevelopmental disorders such as autism

Where do we Even Start?

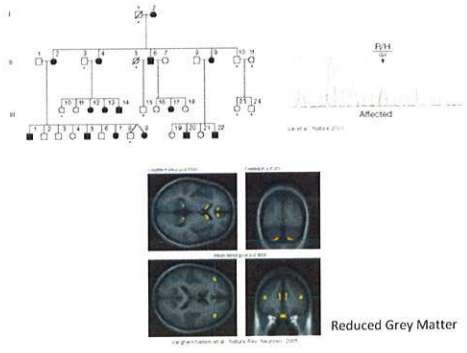
1) Candidate approach

2) Hypothesis-generating approach

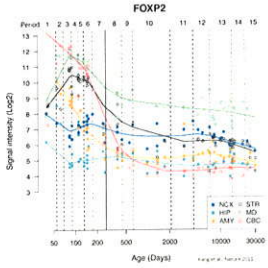


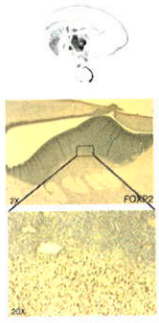
Can Changes to a Single Gene Dramatically Alter a Complex Human Trait?

FOXP2: a "Language" Gene

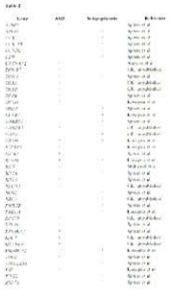


FOXP2: Expressed in the Right Place at the Right Time

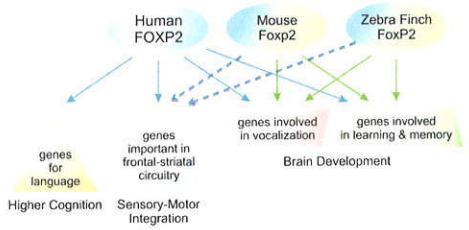




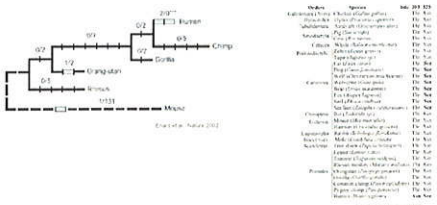
FOXP2 Target Genes Associated with Disease



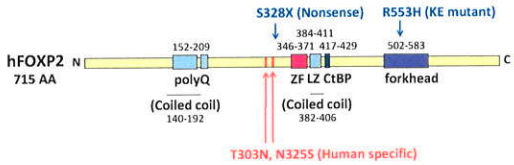
Conserved Functions of FOXP2



Accelerated Evolution of FOXP2



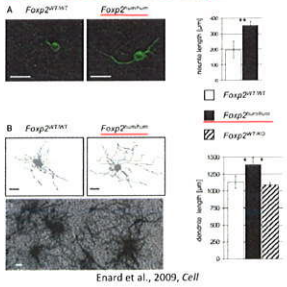
Features of human FOXP2 protein



	T303N	N325S
Human	TSSNTSKASP PITHHSIVNG QSSVISARRD	
Chimp	TSSTTSKASP PITHHSIVNG QSSVINARRD	
Gorilla	TSSTTSKASP PITHHSIVNG QSSVINARRD	
Orang	TSSTTSKASP PITHHSIVNG QSSVINARRD	
Macaque	TSSTTSKASP PITHHSIVNG QSSVINARRD	
Rat	TSSTTSKASP PITHHSIVNG QSSVINARRD	
Mouse	TSSTTSKASP PITHHSIVNG QSSVINARRD	

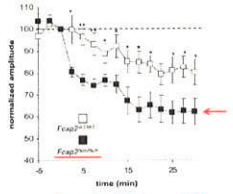
Humanized Version of Foxp2 in mouse

1. Increased dendrite length

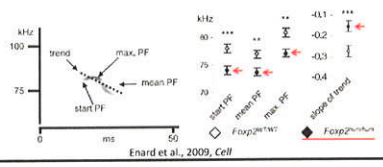


Enard et al., 2009, *Cell*

2. Increased long-term depression (LTD) in medium spiny neurons (MSNs)

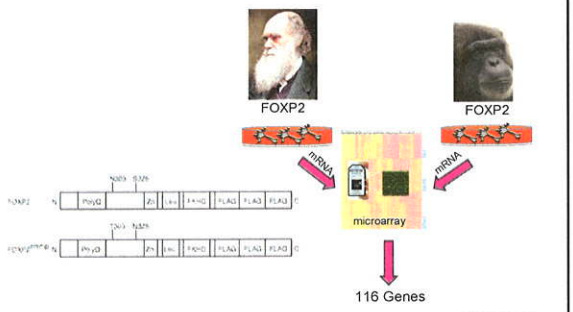


3. Altered structure of pup Isolation calls



Enard et al., 2009, *Cell*

Human and Chimpanzee FOXP2 Have Differential Targets



Genes are Involved in Motor and Craniofacial Development

People:

FGF14	SCA27
PPP2R2B	SCA12
COL9A1	Stickler syndrome (craniofacial abnormalities)
GJA12	ataxia and mental retardation
ROR2	Robinow syndrome (dysmorphic facial features)

Mice:

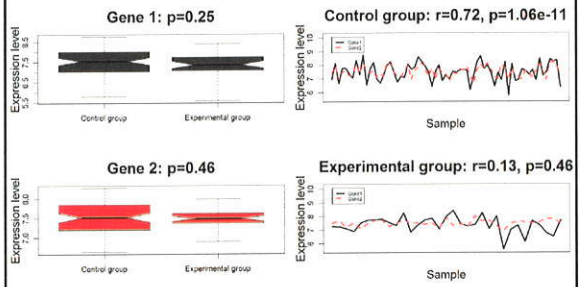
CACNB2	Abnormal craniofacial development (perinatal lethal)
ENPP2	Abnormal forebrain development (embryonic lethal)
PDGFRA	Craniofacial defects (perinatal lethal)
DCN	Craniofacial defects

Moving beyond differential expression

- Each gene is treated as an individual entity
- How to prioritize for further study?

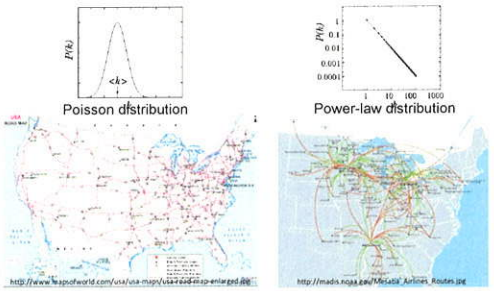
Oldham & Geschwind, 2009

Real data: what differential expression doesn't show

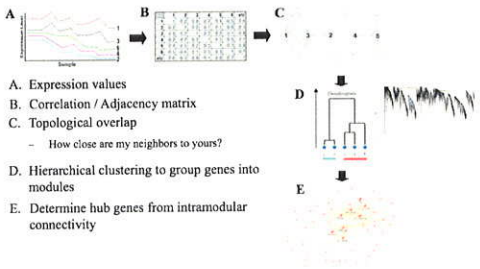


Oldham & Geschwind, 2009

Complex networks can be better modeled using a scale free approach



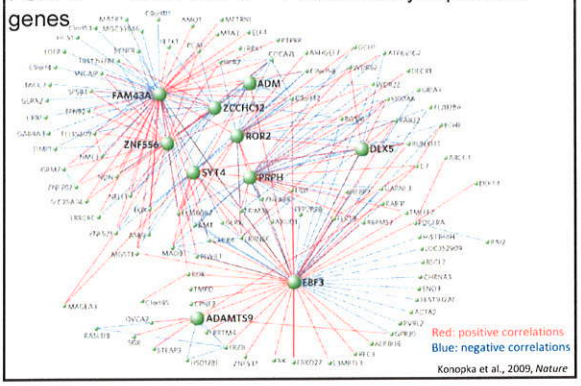
Weighted Gene Co-expression Network Analysis



A. Expression values
B. Correlation / Adjacency matrix
C. Topological overlap
   - How close are my neighbors to yours?
D. Hierarchical clustering to group genes into modules
E. Determine hub genes from intramodular connectivity

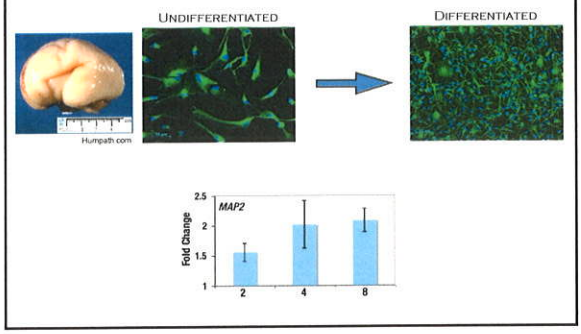
Jeremy Miller

Visualization of one of the modules containing FOXP2^{human} and FOXP2^{chimp} differentially expressed genes

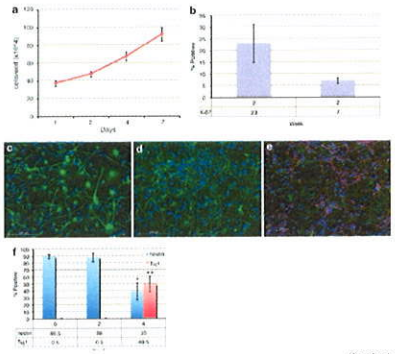


Konopka et al., 2009, *Nature*

Using human fetal neuronal cells as a model system

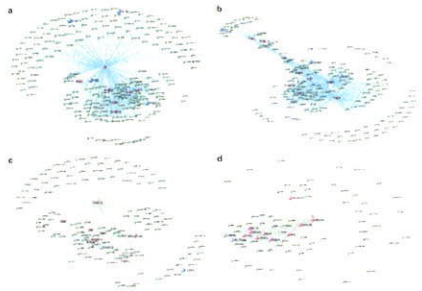


Differentiation of hNPs



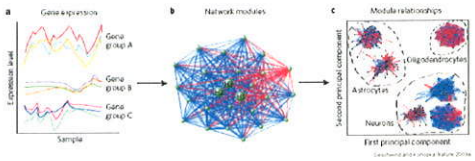
Konopka et al., 2012 *Mol Psych*

Identification of modules enriched for ASD genes during hNP differentiation



Konopka et al., 2012 *Mol Psych*

Power of the systems-level network approach



Network structure is robust, reproducible and real (Oldham, Konopka et al. *Nat Neuro* 2008).

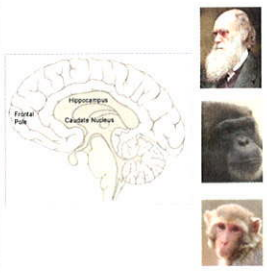
A gene's network position is biologically meaningful

Groups of co-expressed genes called modules correspond to key elements of biological function (Konopka et al., *Nature* 2009b).

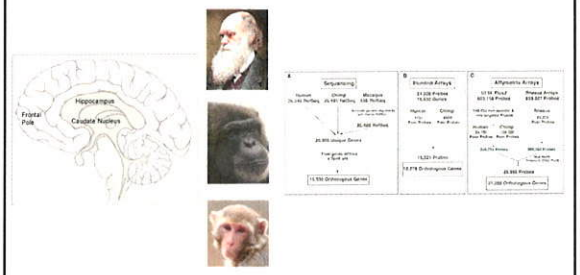
The most central, "hub" genes are important (Konopka et al., *Neuron* 2012).

This structure serves as a basis for identification of biological meaningful insights

Can we identify human-specific patterns of gene expression on a global scale?

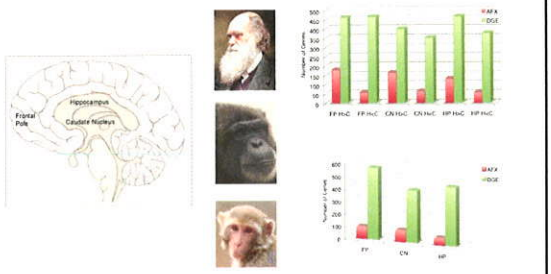


Can we identify human-specific patterns of gene expression on a global scale?



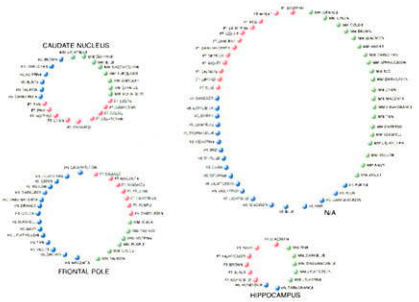
Konopka et al., 2012, *Neuron*

Can we identify human-specific patterns of gene expression on a global scale?



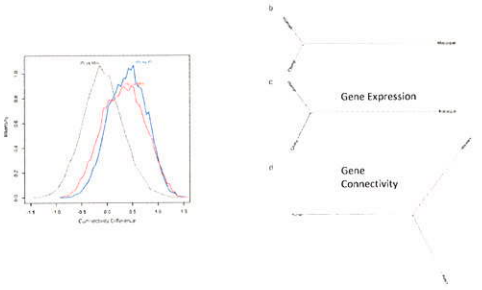
Konopka et al., 2012, *Neuron*

Connectivity among module eigengenes: enrichment of human-specific FP modules



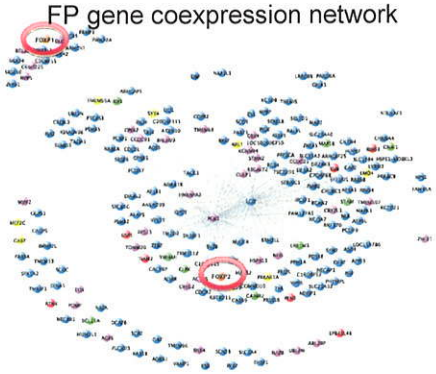
Konopka et al., 2012, *Neuron*

Brain Network Connectivity Among Primates



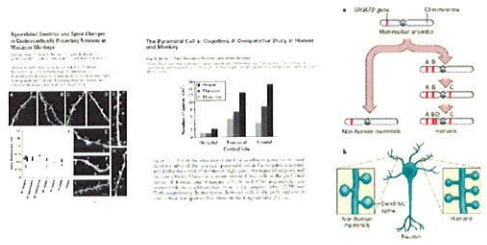
Konopka et al., 2012, *Neuron*

Visualization of a human-specific FP gene coexpression network



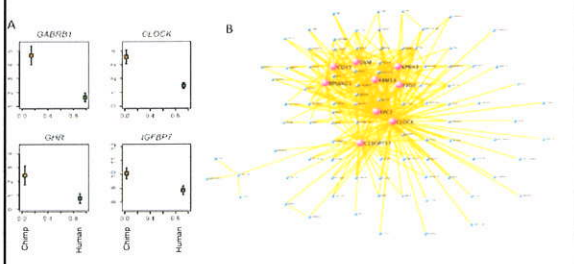
Konopka et al., 2012, *Neuron*

Spines: unique feature of human neuronal morphology



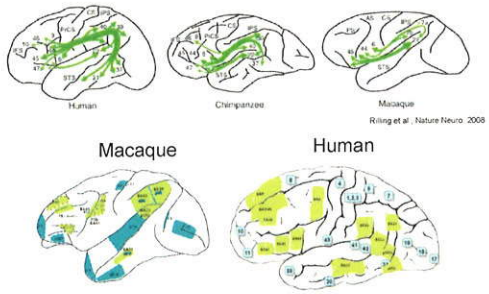
Geschwind & Konopka, *Nature 2012*
Review of :
Dennis et al., *Cell 2012*
Charrier et al., *Cell 2012*

CLOCK: a candidate for human-specific cortical function



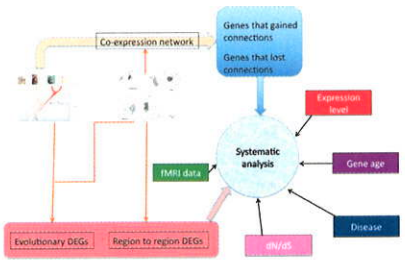
Zeng, Konopka et al., 2012, *AJHG*
Konopka et al., 2012, *Neuron*

Identify Human-Specific Patterns of Gene Expression in "Language" Areas



Riling et al., Nature Neuro. 2008

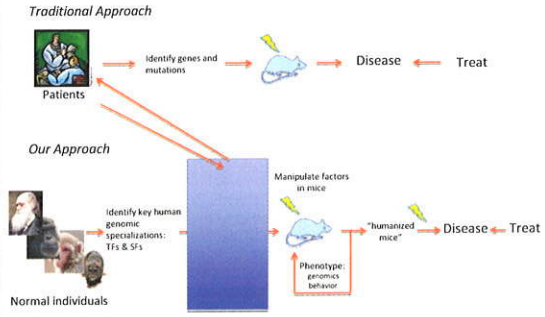
Integration of Multiple Approaches to Identify Human-Specific Modifications



Conclusions

- The study of evolutionary important single genes can provide insight into complex cognitive processes.
- Differentiation of primary human neural progenitors (hNPs) is a good model for *in vivo* brain development.
- hNPs can be used to model ASD signaling pathways at a genome-wide level.
- Network analyses can provide novel insights into large gene expression datasets.
- Evolutionary comparisons provide a unique perspective into cognitive disorders.

Multiple approaches to understand human-specific cognitive disorders



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