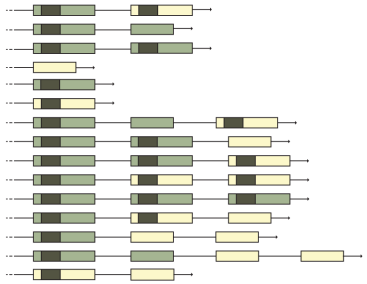
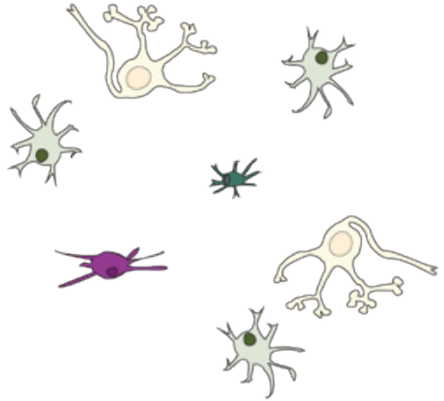


Emerging genetics in schizophrenia: Real challenges for creating animal models

Steven A McCarroll, PhD
Stanley Center for Psychiatric Research, Broad Institute
Department of Genetics, Harvard Medical School

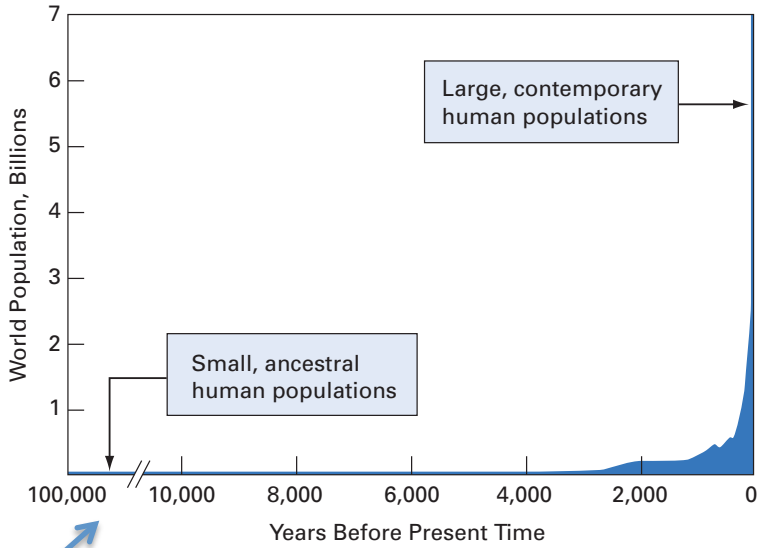


NASEM Workshop on Therapeutic Development in the Absence of Preclinical Animal Models of Disease
12 Sept, 2016

Summary

- Real early victories toward revealing genetic architecture of schizophrenia in humans
- These results present great challenges for modeling in animals

Human genetics strategies



Rare variation

Rare/private to individuals and families

Ascertainable by sequencing

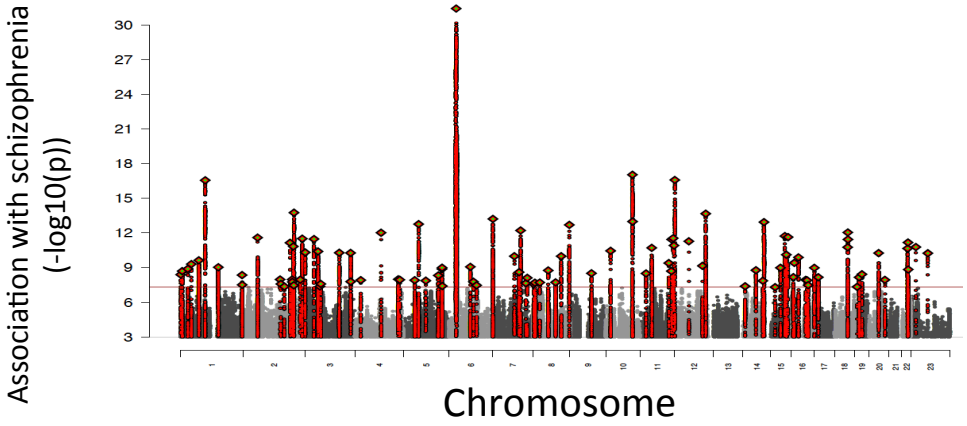
Scz has lacked segregating, Mendelian forms analogous to PD or EOAD

Common variation

Present in most/all populations today

Relationship to phenotypes measured in GWAS

Common variation



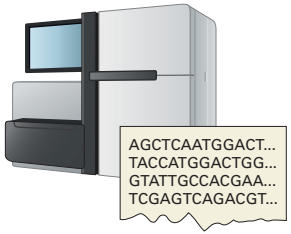
Psychiatric Genomics Consortium, *Nature* 2014

- 108 (going on 150) loci have variation that associates with schizophrenia in populations; highly replicated, statistically strong

BUT

- **Polygenicity**: exerts risk via many small effects rather than one large, "model-able" effect
- Tends to involve mechanisms other than change in protein-coding sequence – challenging to identify functional alleles and define analogous mutation in mice

Rare variation



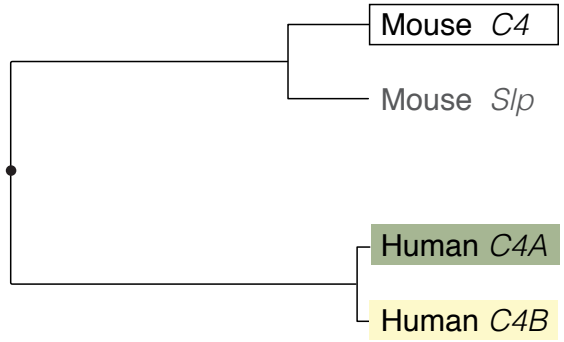
- Rare, recurring CNVs (22q, 15q13, others) –affecting many genes – an early hit in GWAS studies
- As whole-exome and whole-genome sequencing allow scaling to cohorts >10k, fine-scale variants likely to begin to implicate specific genes (e.g. *SETD1*, Singh et al., *Nat Neurosci.* 2016)

BUT

- **Polygenicity**: No one locus explains even 1% of cases (Genovese *et al.*, *Nat Neurosci*, in press, based on sequence from 5k Scz cases + 50k others)
- **Partial penetrance**: environmental and genetic modifiers (including common variation) still matter (even the human is an imperfect model for other humans)
- Constellations of phenotypes: typically present in **syndromic** cases with ID, epilepsy, other neurodevelopmental defects

Gene evolution can also challenge modeling in animals

Example: Complement component 4 (*C4*)



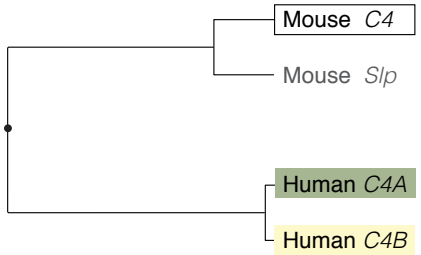
C4A dosage affects Scz risk

C4B dosage doesn't affect Scz risk

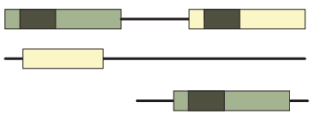
Sekar et al., *Nature* 2016

Moving human *C4* genes into mice

Jessy Presumey, Allison Bialas, Mike Carroll (ongoing work)

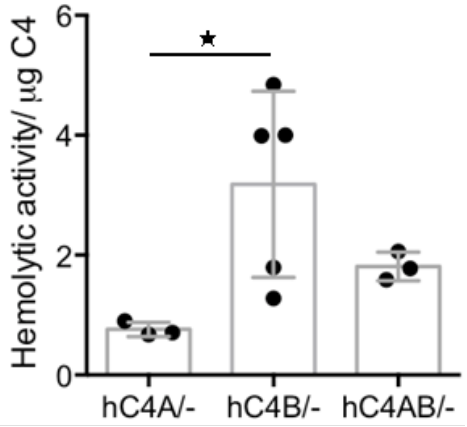


Generation of BAC tg mice:

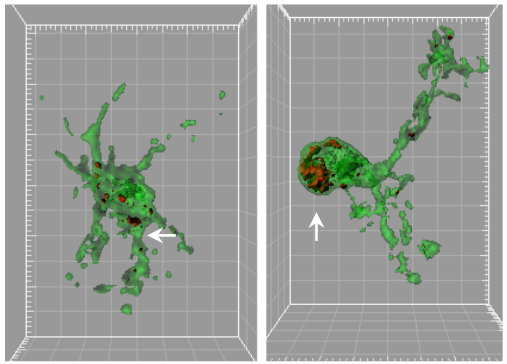


180 Kb
182 Kb
42 Kb

Hemolytic activity



Engulfment of synapses by microglia

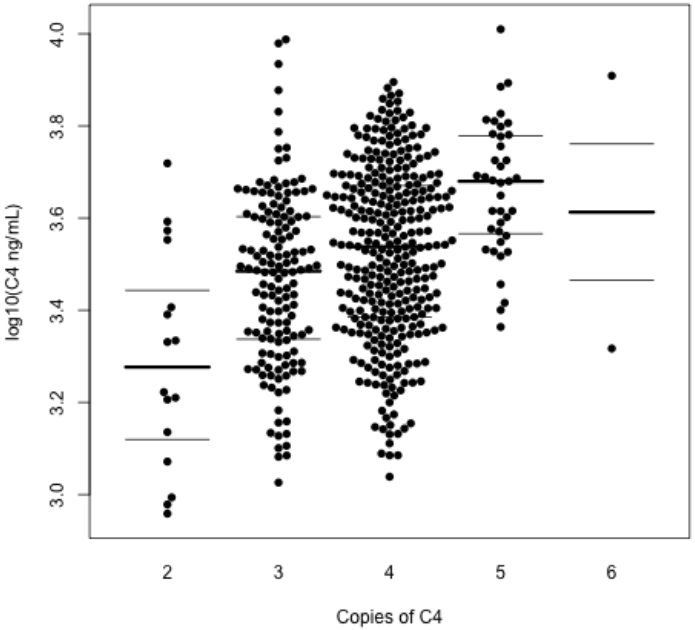


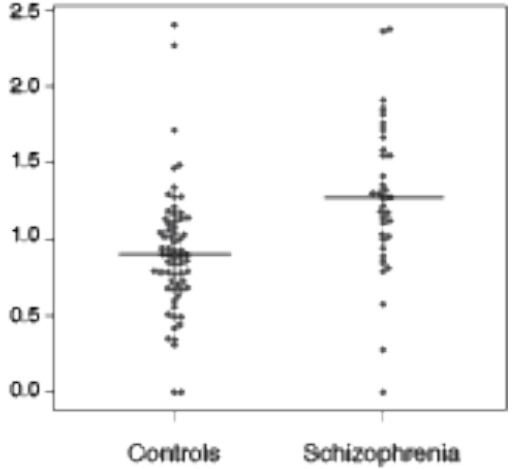
C4-/- C4A

Focus is on cellular, physiological (not behavioral) phenotypes

Other uses of genetic results include to nominate potential biomarkers for human studies

e.g. C4 protein in CSF:





ongoing work

Summary

- Real genetic progress in schizophrenia, but may not lend itself to animal “models of disease”
- Most useful levels of analogy in mice etc. may be for phenotypes at molecular/cellular/circuit level (rather than behavior/disease)