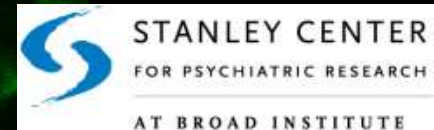


Understanding Schizophrenia Risk: Emerging Genetics and Biological Mechanisms

Beth Stevens

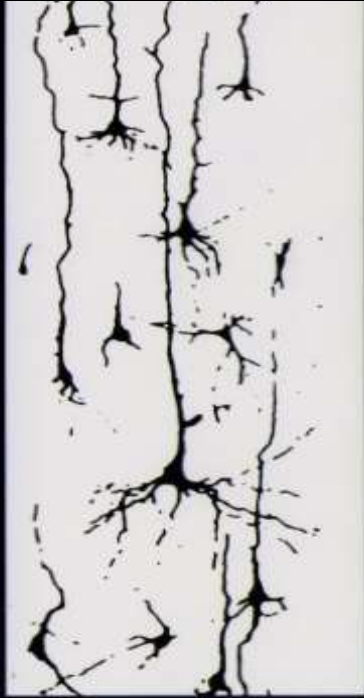


FM Kirby Neurobiology Center
Boston Children's Hospital, HMS
Broad Institute



10 μ m

Could Pruning Help Us Understand Age of Onset of Schizophrenia?



birth

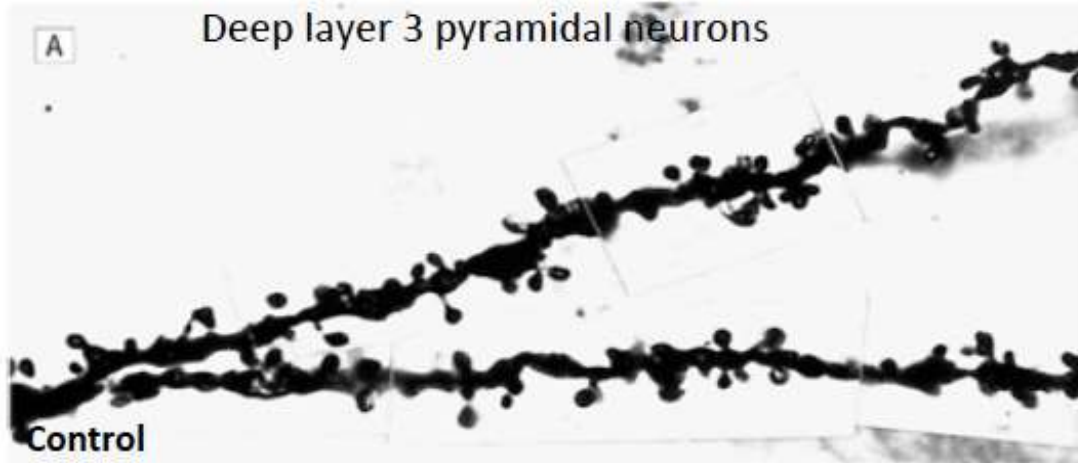


6 years



14 years

Hypothesis: Pruning Defects Underlie Pathobiology of Schizophrenia



Loss or less formed?

Cause or Consequence?

Mechanisms?

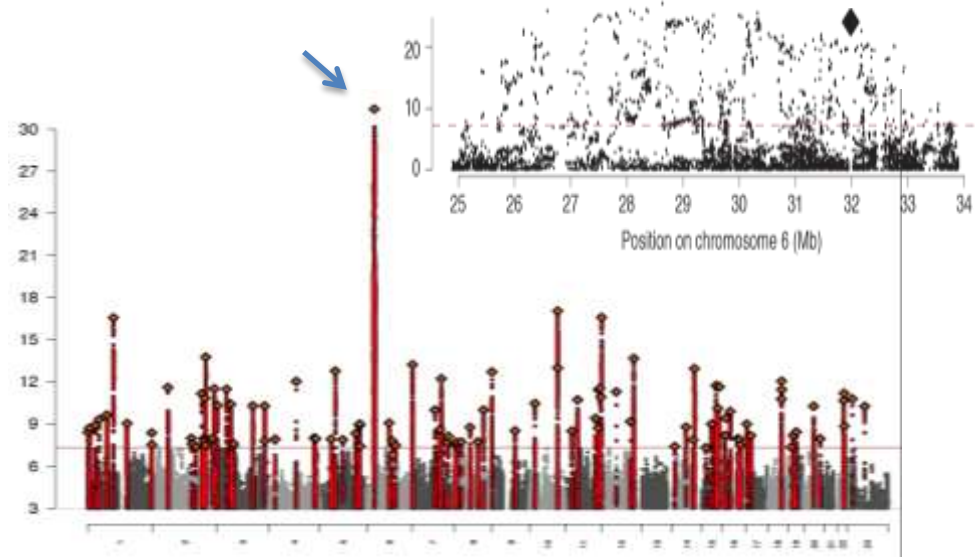
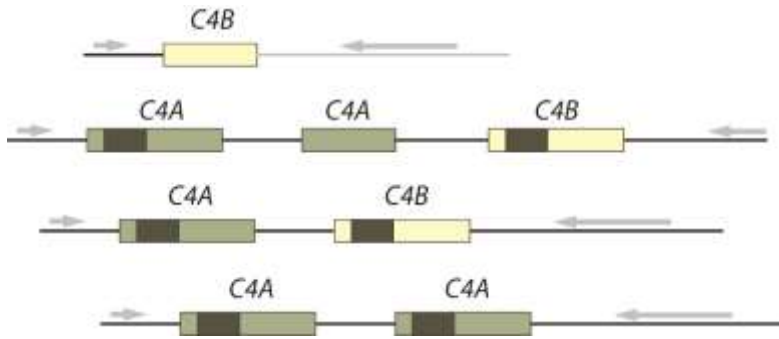
Human Genetics Implicates Complement C4 In Schizophrenia



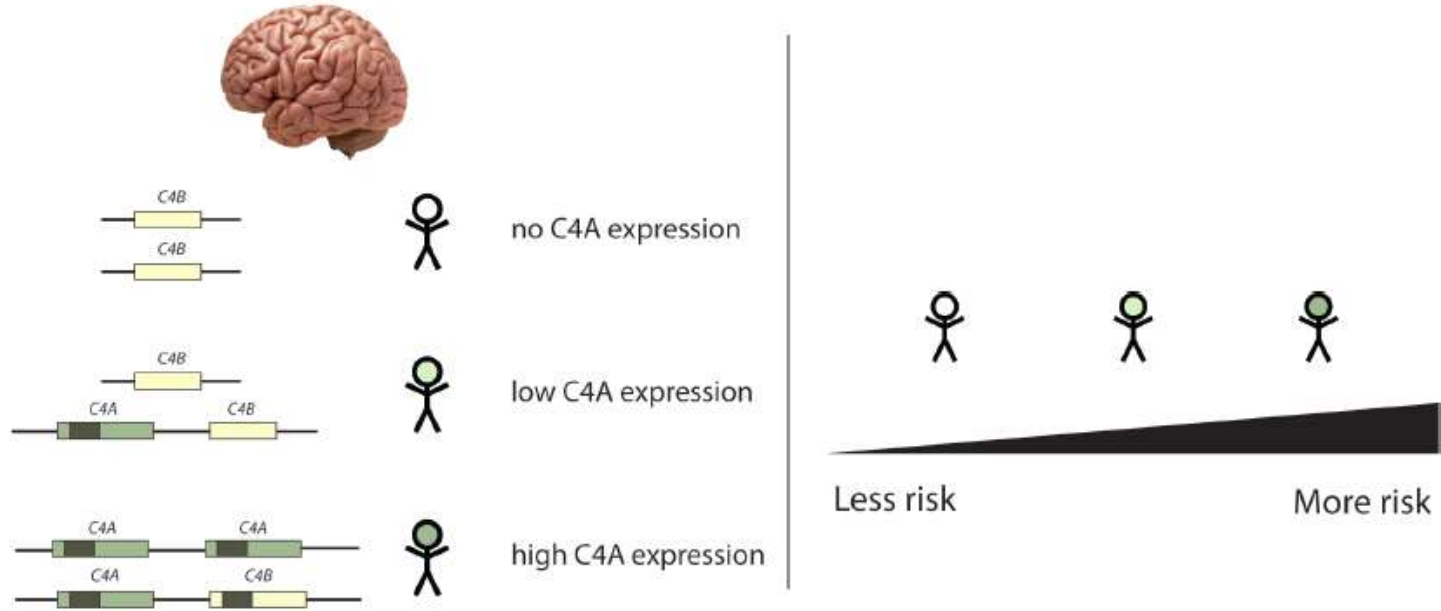
Aswin Sekar
MD/PhD student



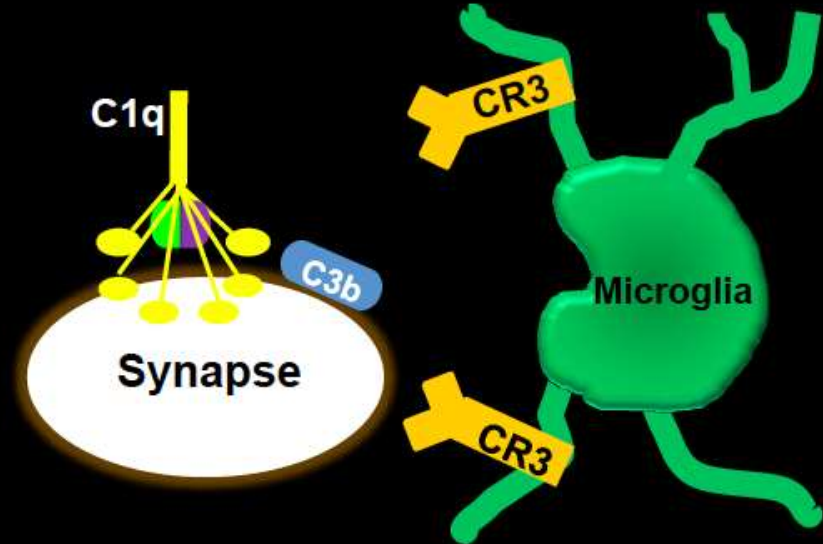
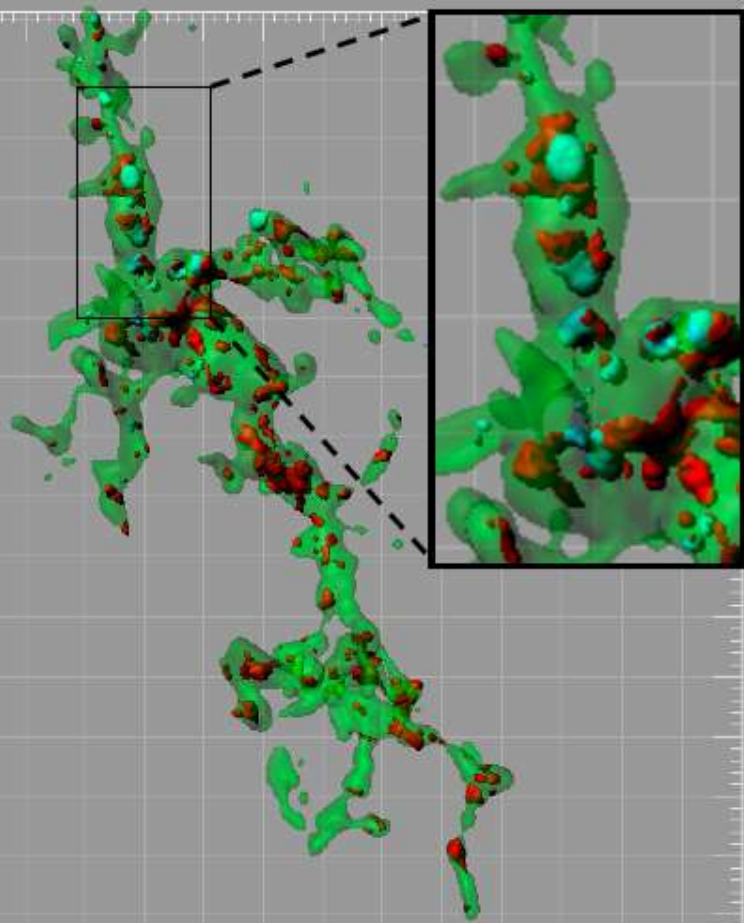
Steve McCarroll



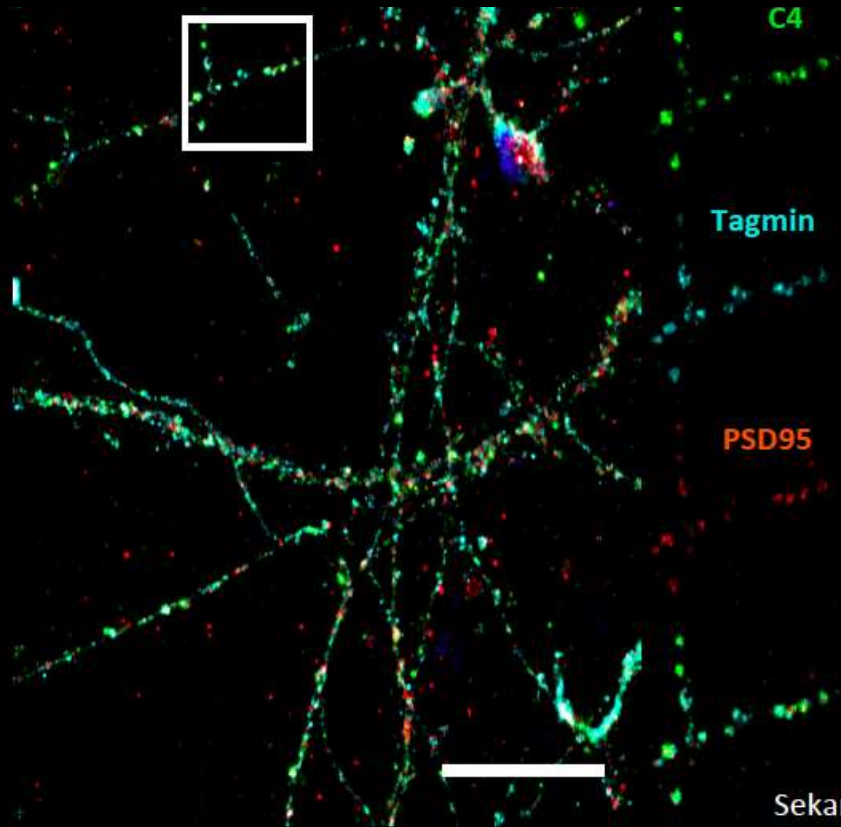
Alleles of *C4* shape schizophrenia risk in proportion to their effect on *C4A* expression



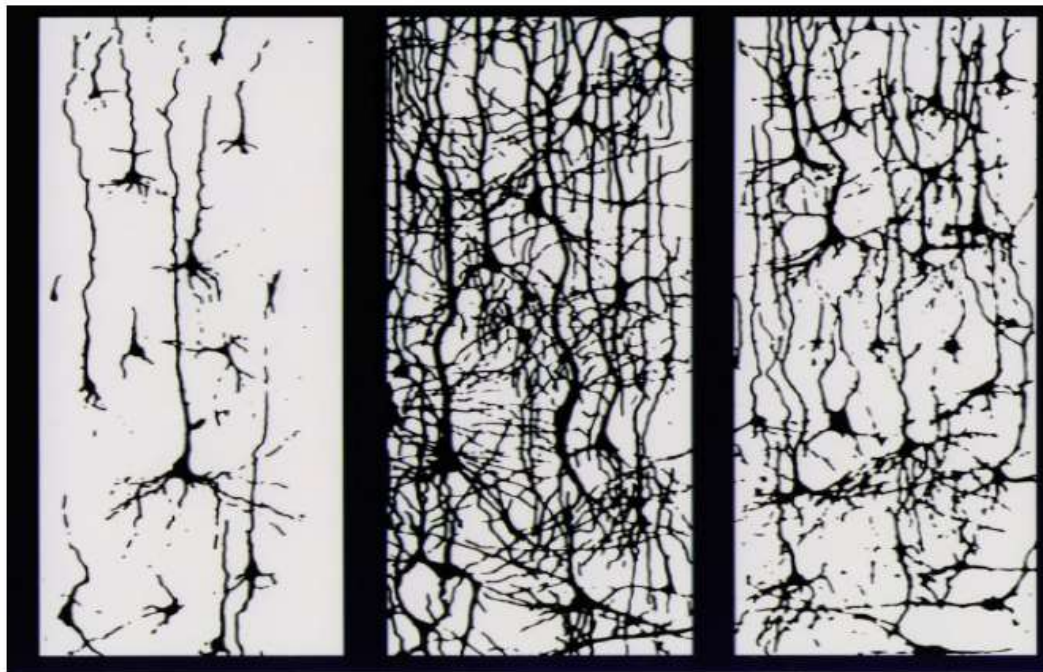
Complement “Tags” Synapses For Elimination in the Healthy Developing Brain



Hypothesis: Excessive Pruning Contributes to Pathobiology of Schizophrenia



Could Pruning Help Us Understand Age of Onset of Schizophrenia?



birth

childhood

adolescence

Might pruning expose other, pre-existing vulnerabilities?

Role of environment as a second hit?

Questions and Challenges:

Why is the Adolescent Brain Vulnerable?

How Does Environment Converge with Genetics to Increase Risk?

How and When to Intervene?

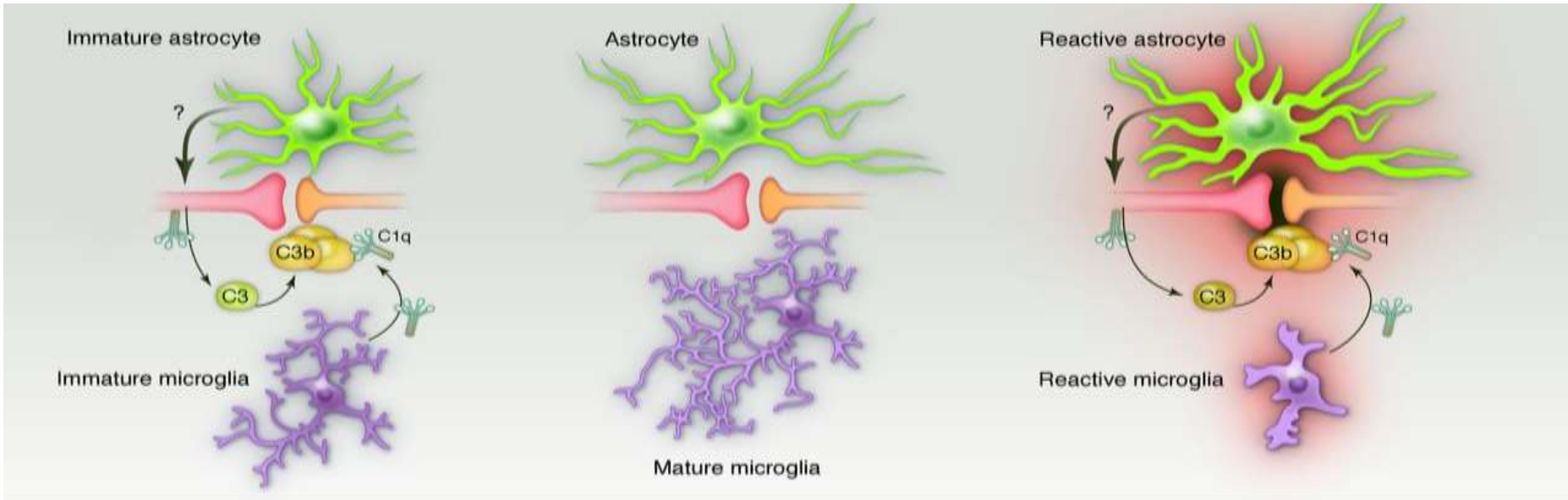
Need for New/Early Biomarkers (Imaging/PET, CSF, other)

A Common Mechanism of Synapse Loss and Cognitive Dysfunction ?

Developing Brain

Mature Brain

Disease



Alzheimer's Disease (Soyon Hong et al., Science 2016)

Glaucoma (Howell et al JCI 2011; Stevens et al.,2007)

FTD (Huang et al., Cell 2016)

Huntington's Disease (unpublished)

New Therapies?

New Biomarkers?