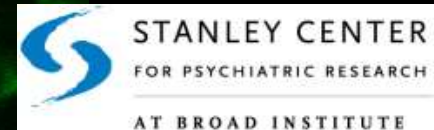


# Understanding Schizophrenia Risk: Emerging Genetics and Biological Mechanisms

**Beth Stevens**

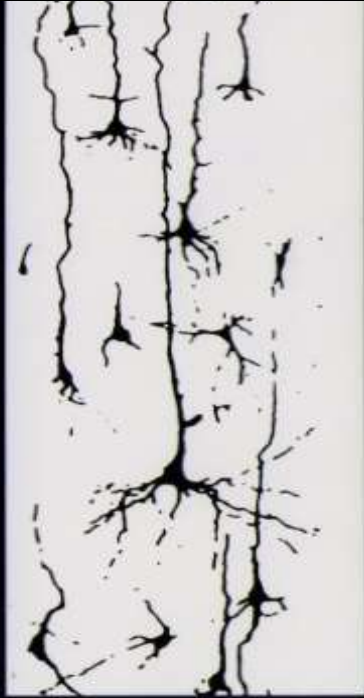


FM Kirby Neurobiology Center  
Boston Children's Hospital, HMS  
Broad Institute



10  $\mu$ m

# Could Pruning Help Us Understand Age of Onset of Schizophrenia?



birth



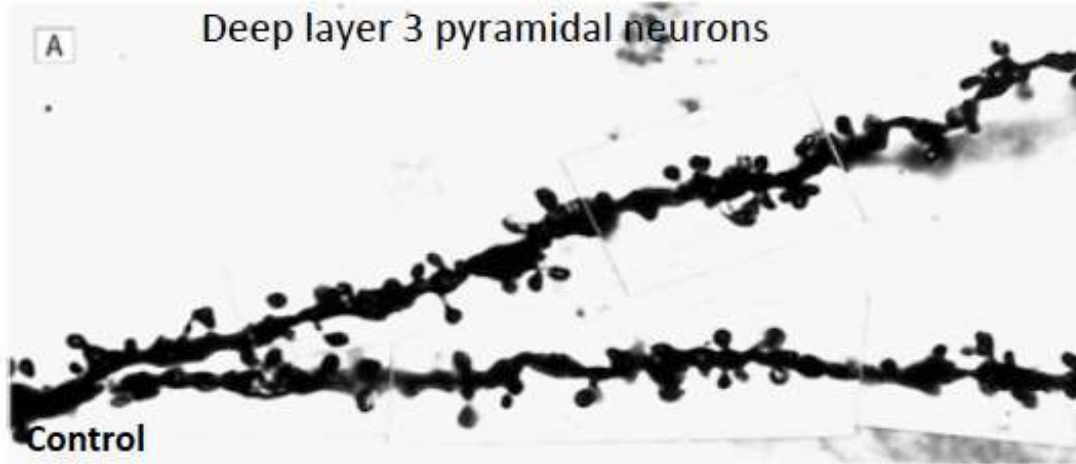
6 years



14 years



# Hypothesis: Pruning Defects Underlie Pathobiology of Schizophrenia



Loss or less formed?

Cause or Consequence?

Mechanisms?

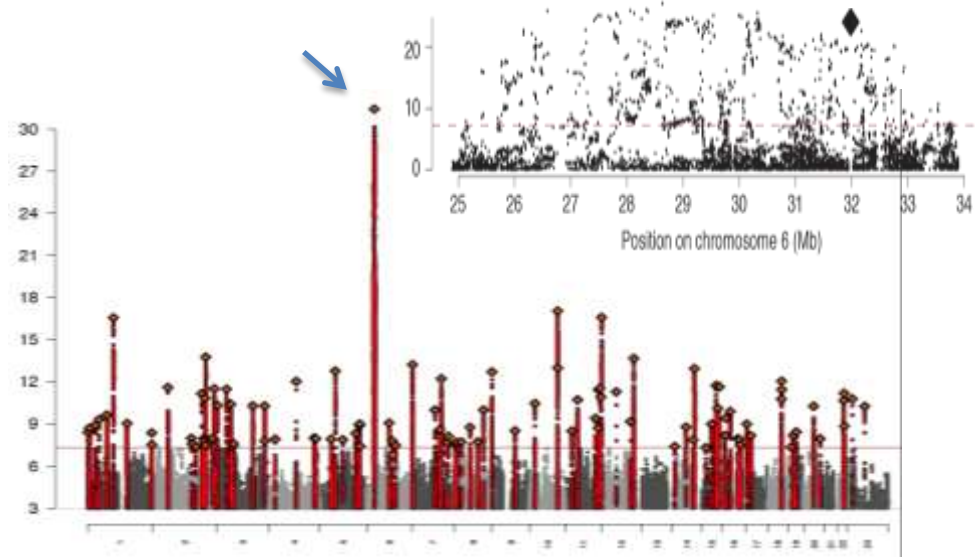
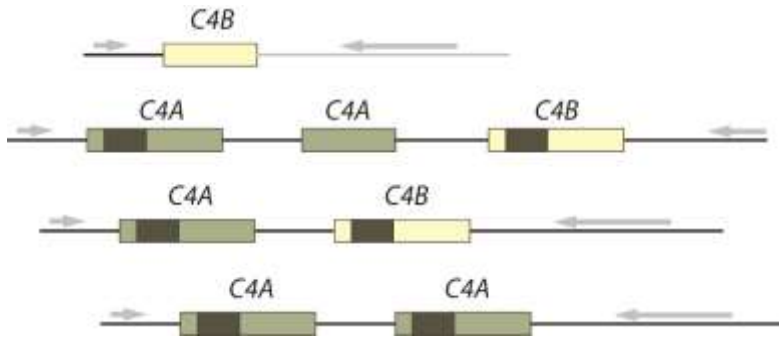
# Human Genetics Implicates Complement C4 In Schizophrenia



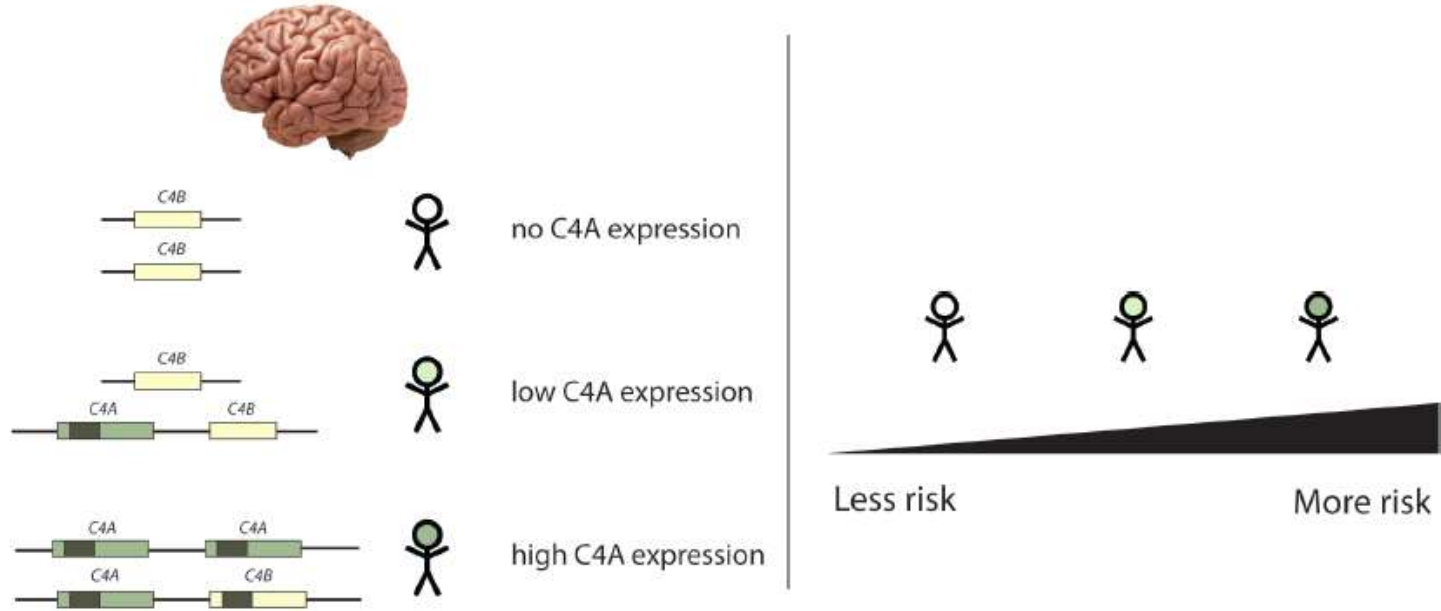
**Aswin Sekar**  
MD/PhD student



**Steve McCarroll**

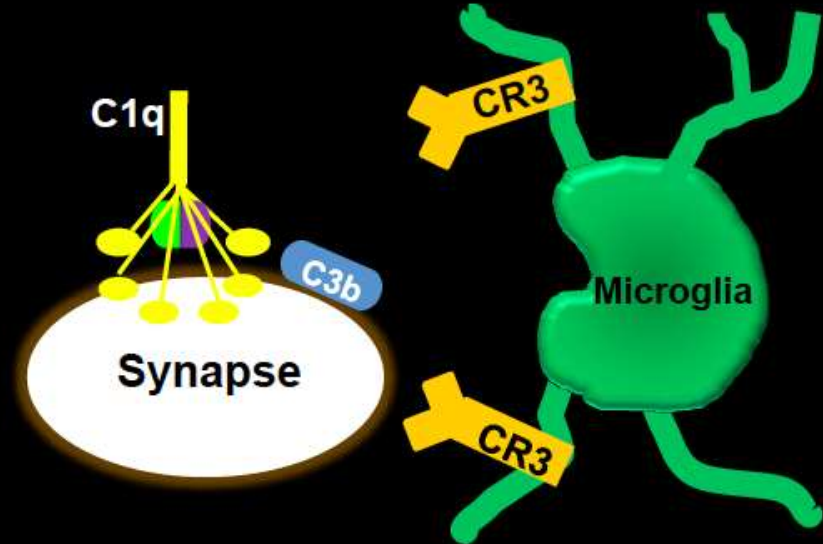
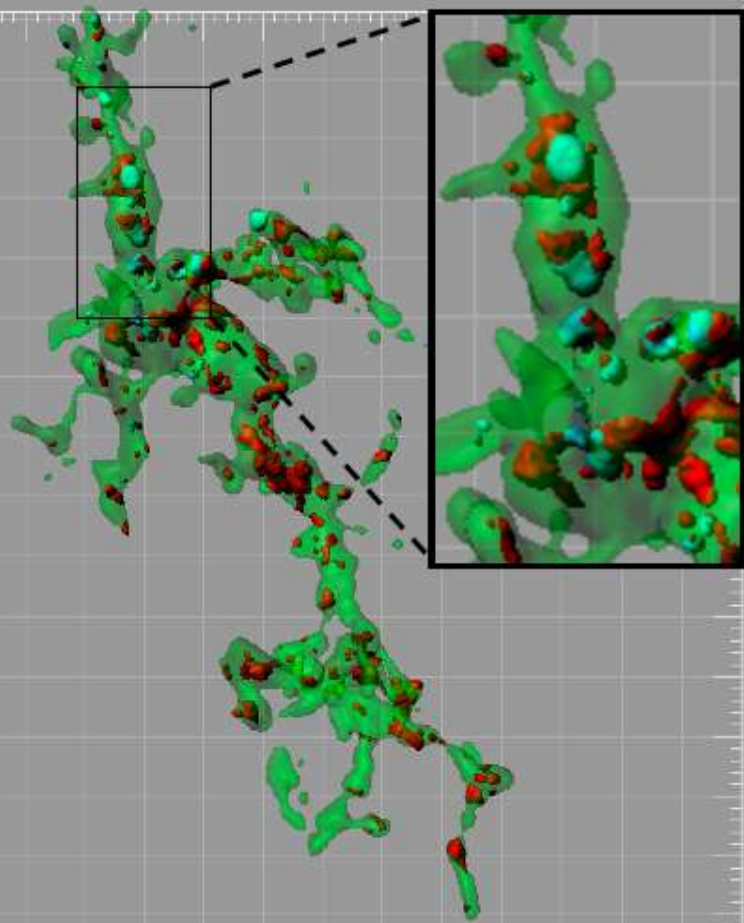


# Alleles of *C4* shape schizophrenia risk in proportion to their effect on *C4A* expression

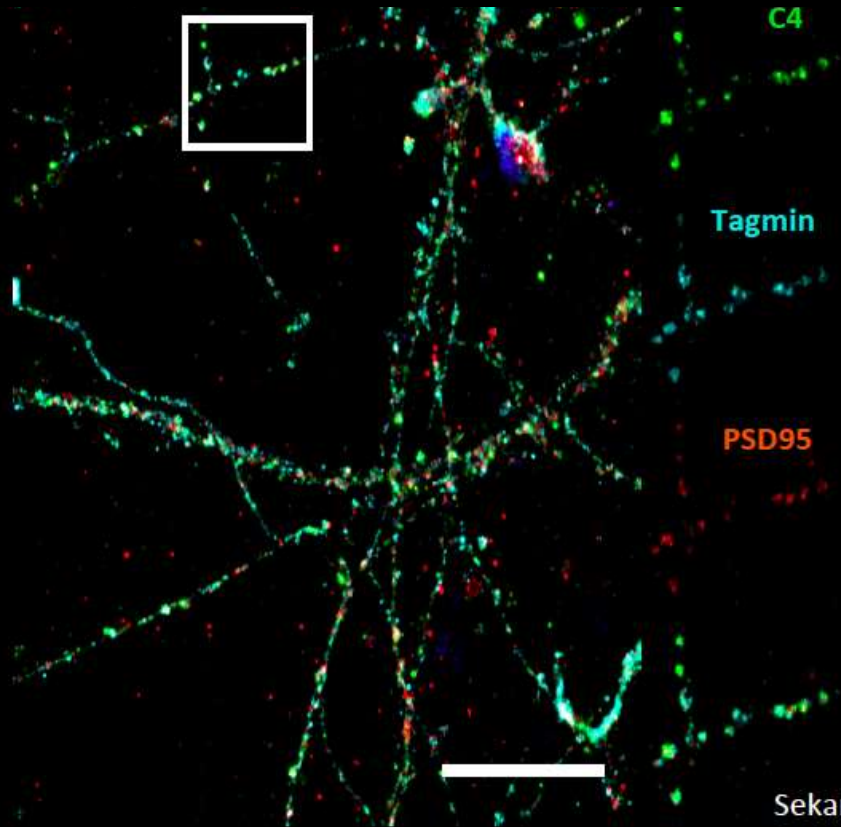




# Complement “Tags” Synapses For Elimination in the Healthy Developing Brain

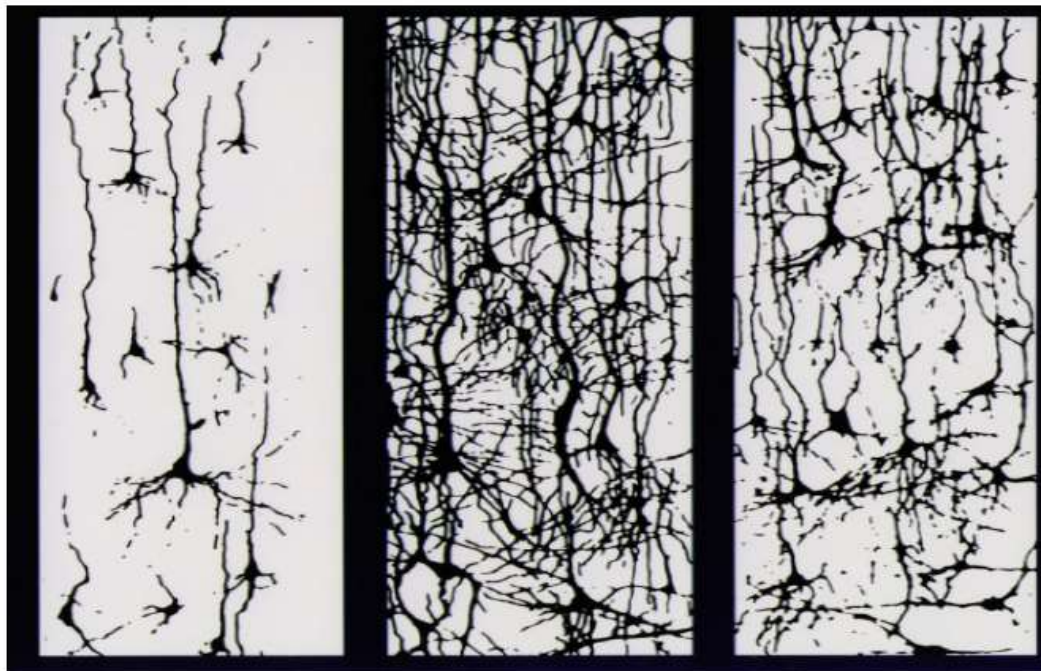


# Hypothesis: Excessive Pruning Contributes to Pathobiology of Schizophrenia





## 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)**

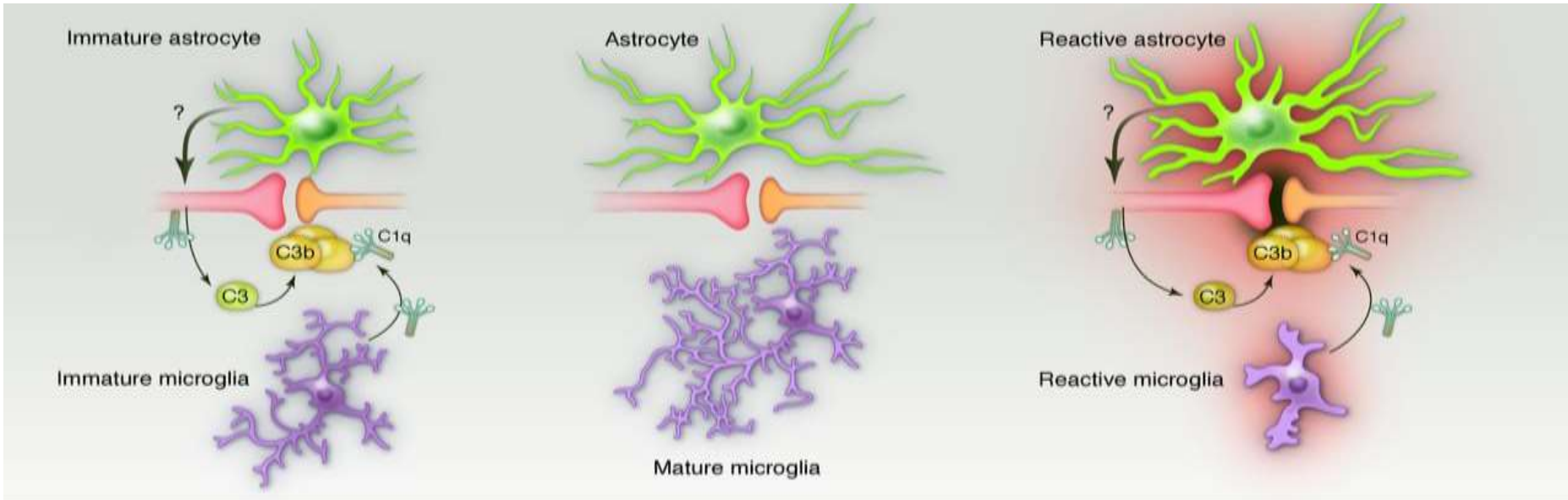


# A Common Mechanism of Synapse Loss and Cognitive Dysfunction ?

## 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?**