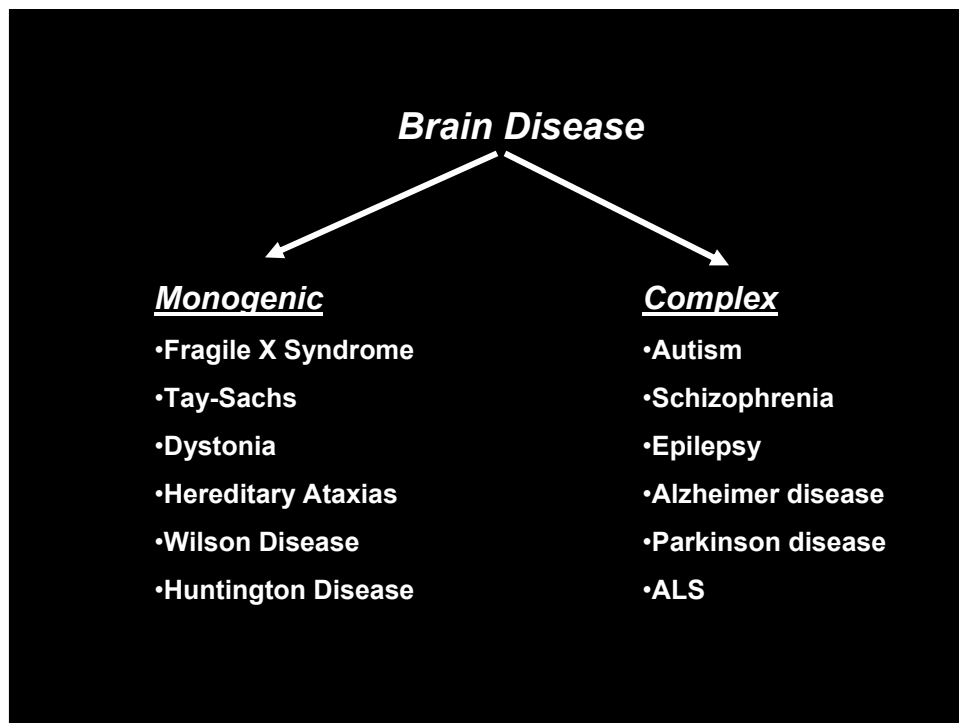


Monogenic vs. Complex Disorders: Isolating the molecular defects of Alzheimer's Disease

Scott A. Small
Columbia University



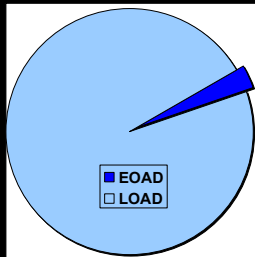
Alzheimer Disease

Monogenic

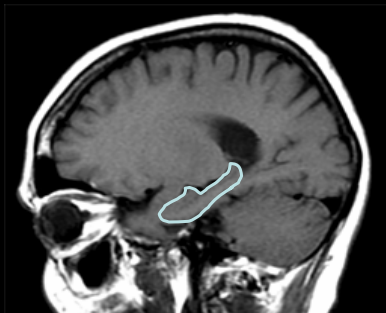
- Early Onset Alzheimer Disease (EOAD)
- Familial
- 5%

Complex

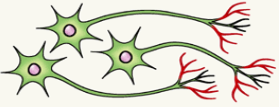
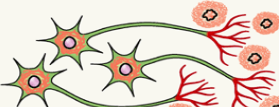
- Late-Onset Alzheimer Disease (LOAD)
- Sporadic
- 95%



Anatomy

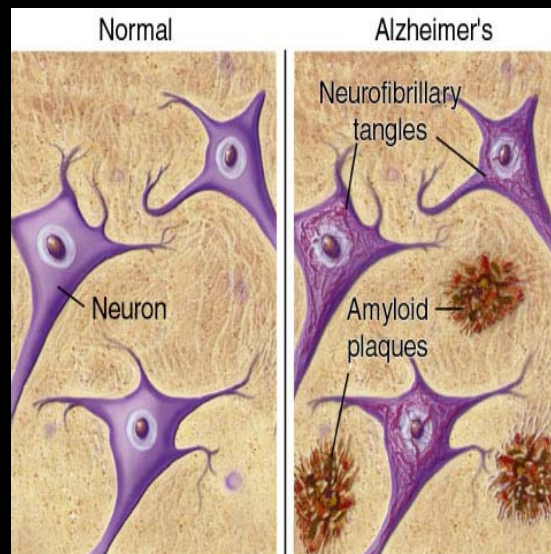


Pathophysiology

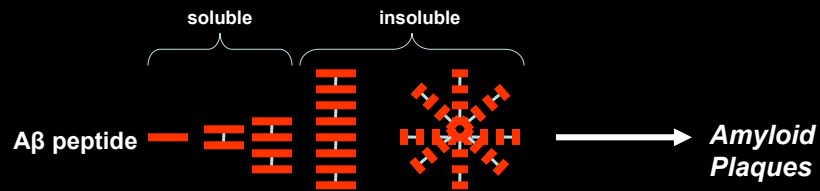
Stage	Key feature	Imaging
Normal		
Cell sickness stage		Functional imaging
Histological stage		Histological imaging
Cell death stage		Volumetric imaging

Small SA, Nature Neuroscience, 2005

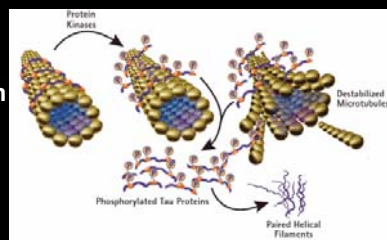
Histology



Histology

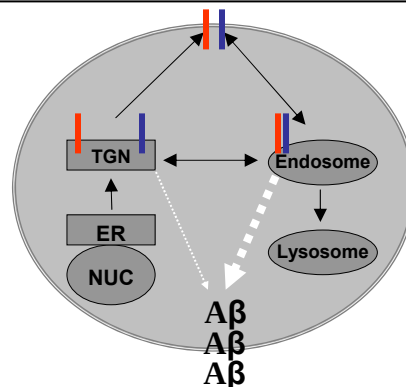
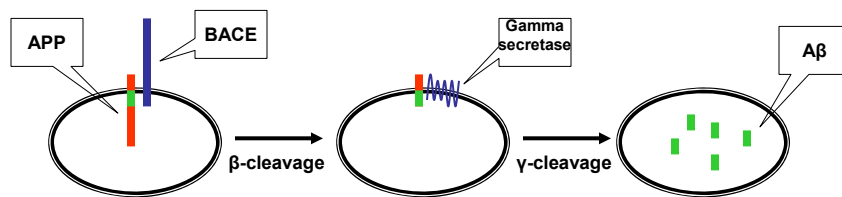


Tau protein



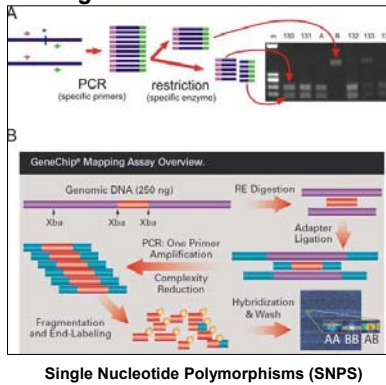
Neurofibrillary Tangles

Molecular & Cell Biology



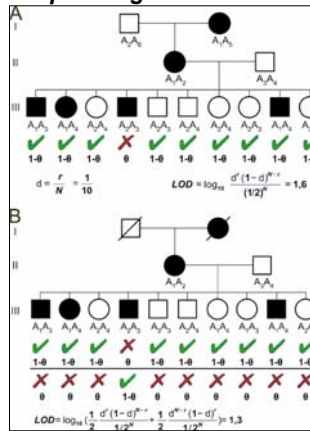
Molecular Defects in Monogenic Disorders

Molecular Techniques: Large-Scale Genetic Profiles



Single Nucleotide Polymorphisms (SNPs)

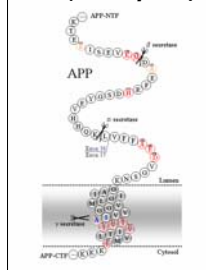
Statistical Models: Pinpointing Genetic Defect



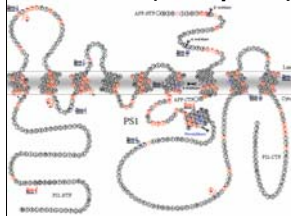
1. Law of "Segregation of Characteristics."
2. Law of "Independent Assortment".

Molecular Defects in Early-Onset AD

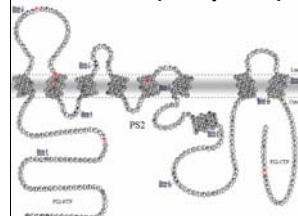
APP(ch21q21.3)



Presenilin1 (ch14q24.13)

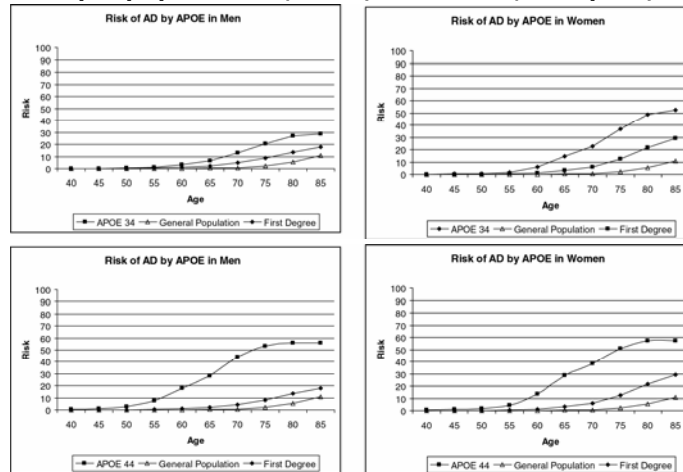


Presenilin2 (ch1q31.42)

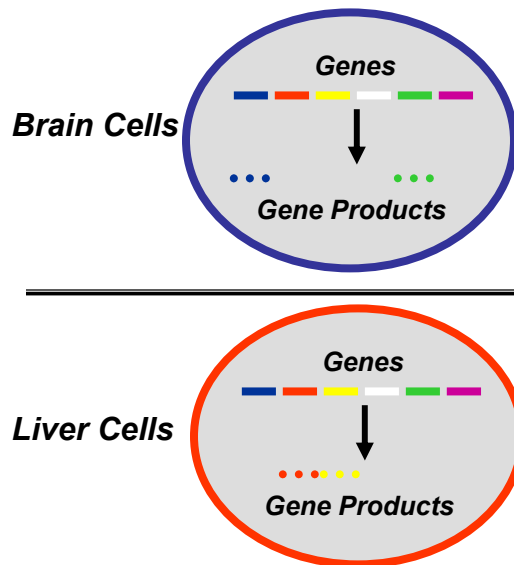


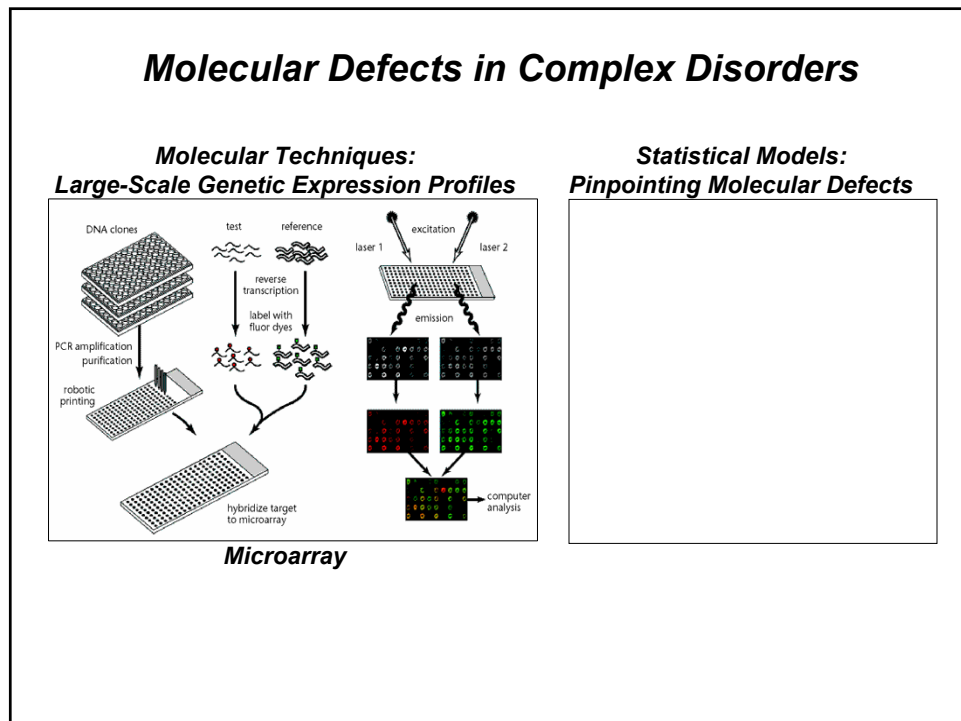
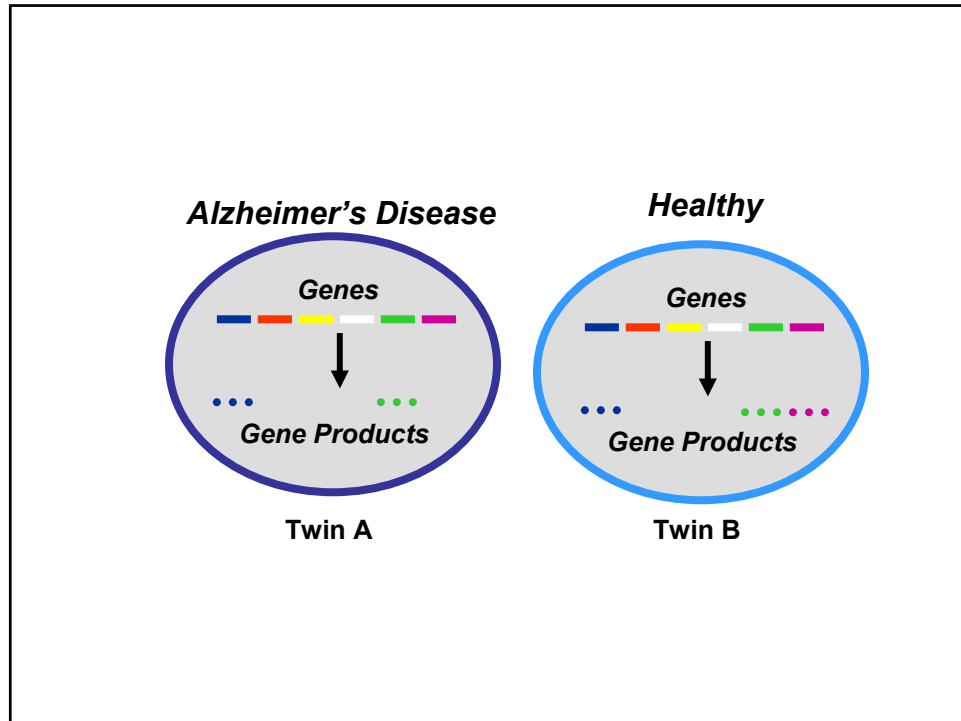
Molecular Defects in Late-Onset AD

Apolipoprotein E (APOE): $\epsilon 2$, $\epsilon 3$, $\epsilon 4$ (ch19q13.2)



Roberts JS, et al, J Geriatr Psychiatry Neurol, 2005

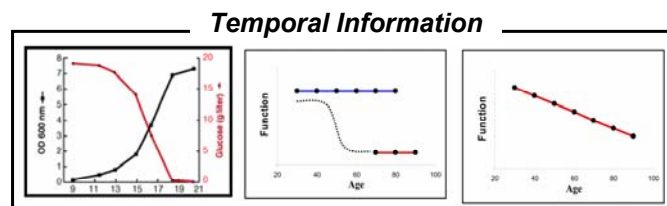
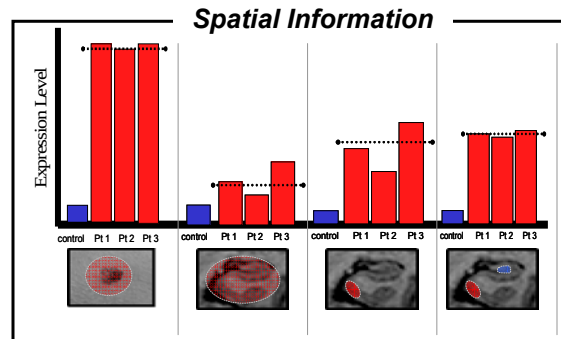




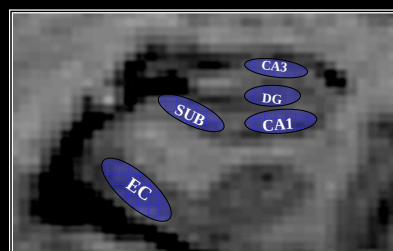
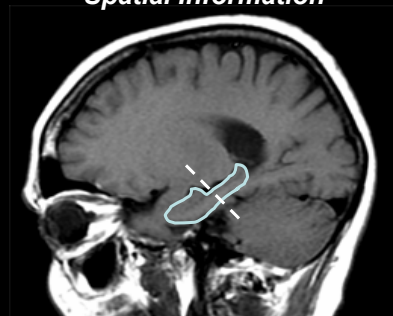
Brain Microarray: Finding Needles in Molecular Haystacks

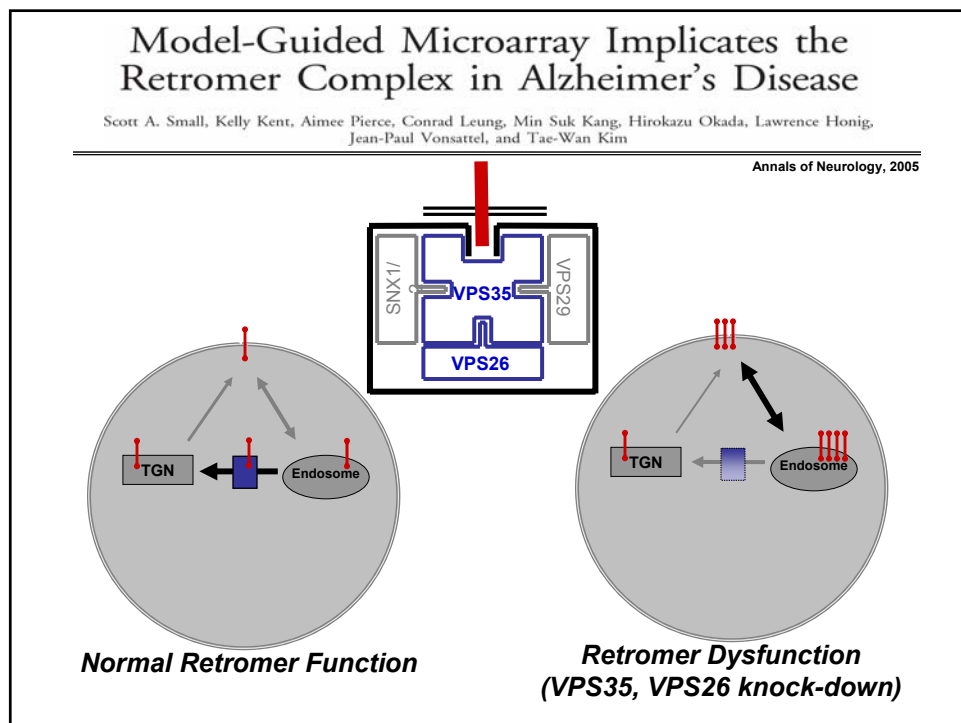
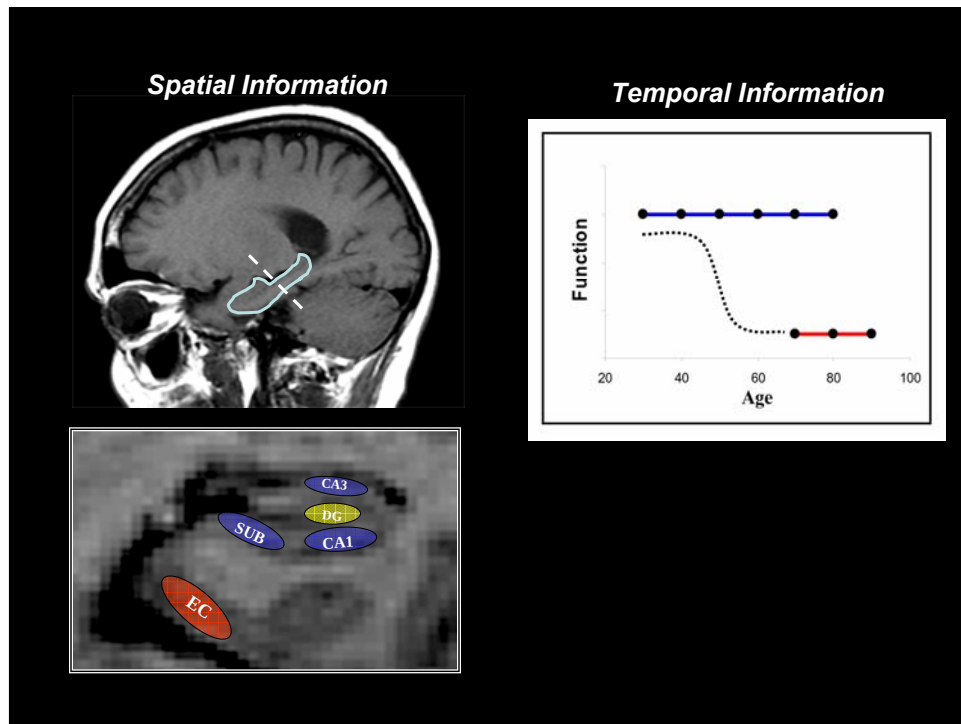
Nicole M. Lewandowski and Scott A. Small

The Journal of Neuroscience, November 9, 2005 • 25(45)



Spatial Information

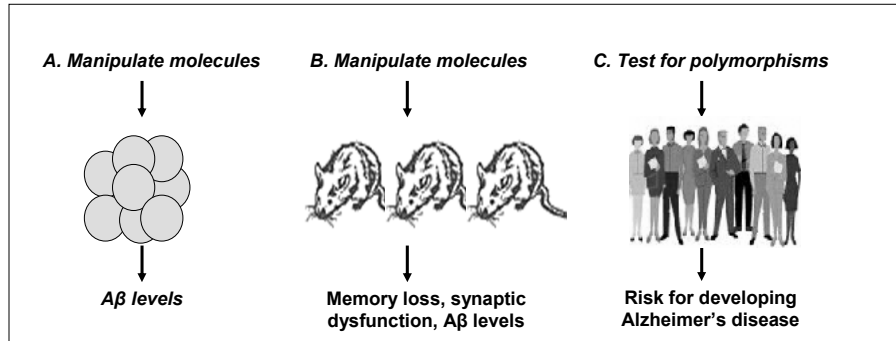




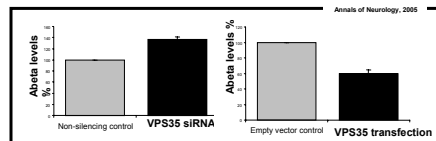
Brain Microarray: Finding Needles in Molecular Haystacks

Nicole M. Lewandowski and Scott A. Small

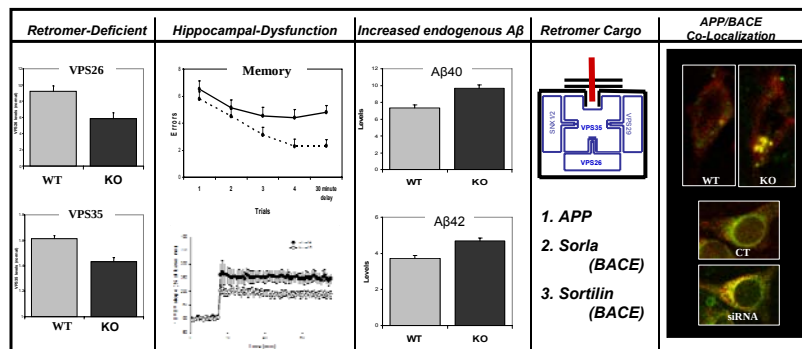
The Journal of Neuroscience, November 9, 2005 • 25(45)



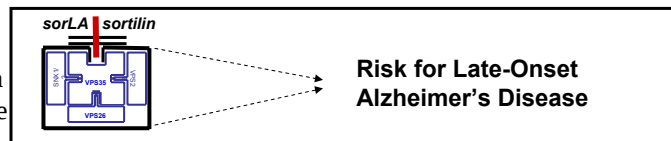
Cell Culture



Mouse Models

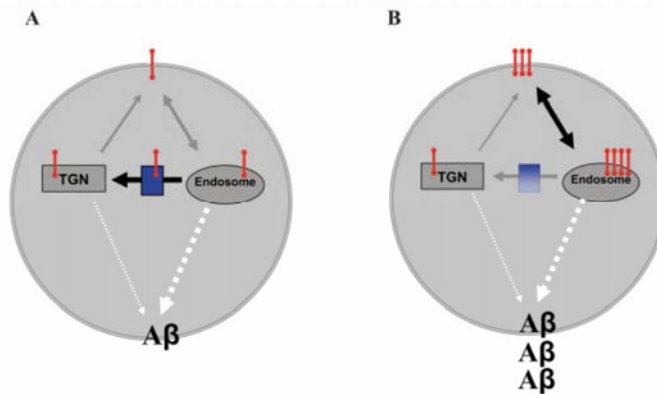


Human Disease



Model-Guided Microarray Implicates the Retromer Complex in Alzheimer's Disease

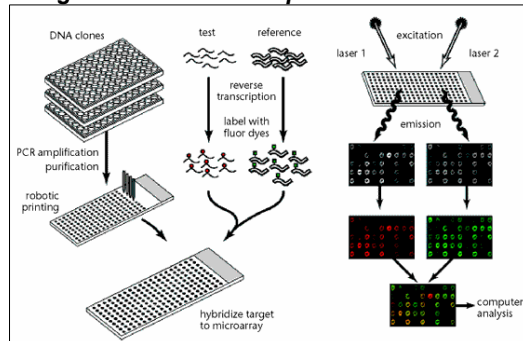
Scott A. Small, Kelly Kent, Aimee Pierce, Conrad Leung, Min Suk Kang, Hirokazu Okada, Lawrence Honig, Jean-Paul Vonsattel, and Tae-Wan Kim



Annals of Neurology, 2005

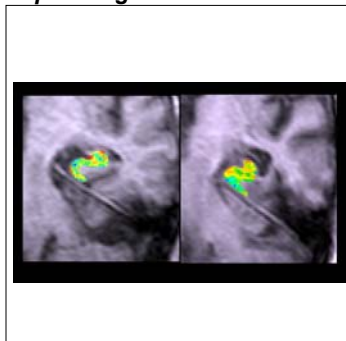
Molecular Defects in Complex Disorders

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Microarray

Statistical Models: Pinpointing Molecular Defects



Functional Imaging

