# Gene Discovery
## Progressive Supranuclear Palsy
## Corticobasal Degeneration

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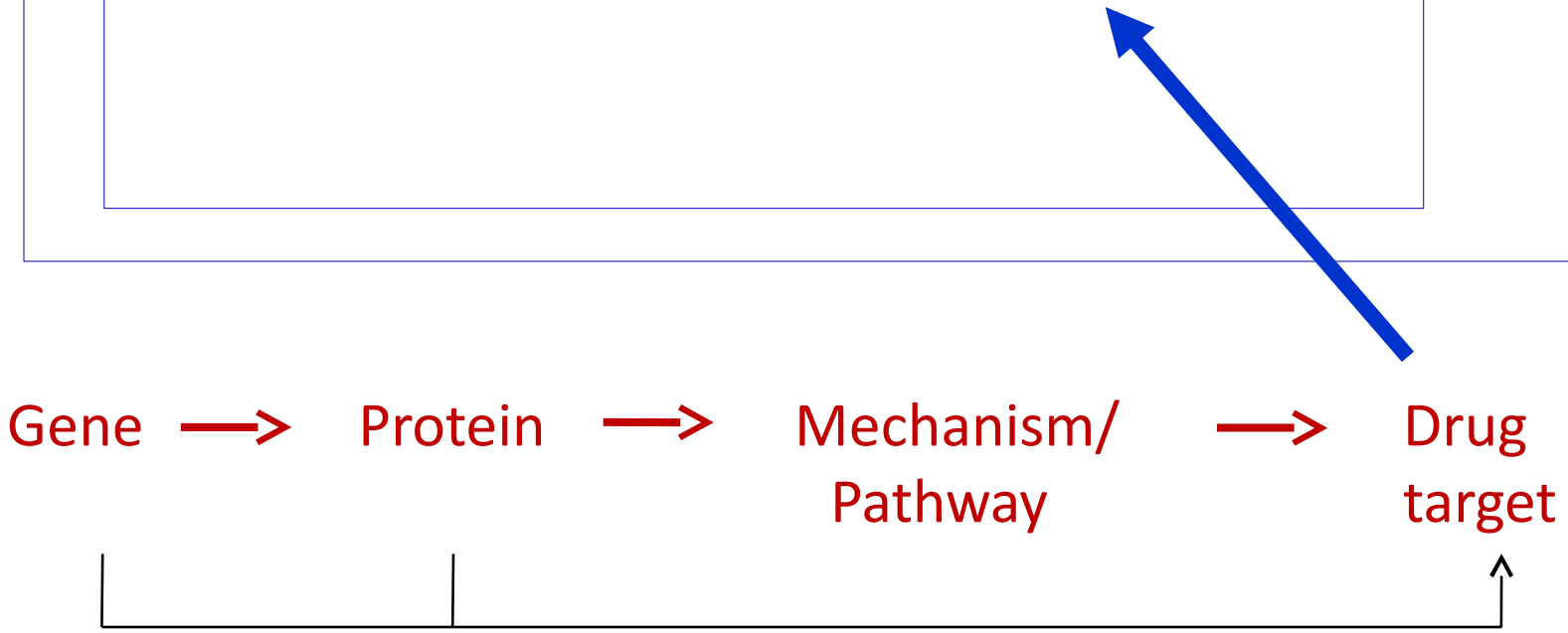
# Human disease genetics

- Study human disease mechanisms directly in humans
- Prediction
- Mechanism
- Drug targets

# Human disease genetics

Does this work?



*PCSK9* Coronary artery disease

2006 → 2011 → 2016

# Drug targets – supported by genetics

Visscher *et al*. Am J. Hum. Genet. 101, 5-22 (2017)

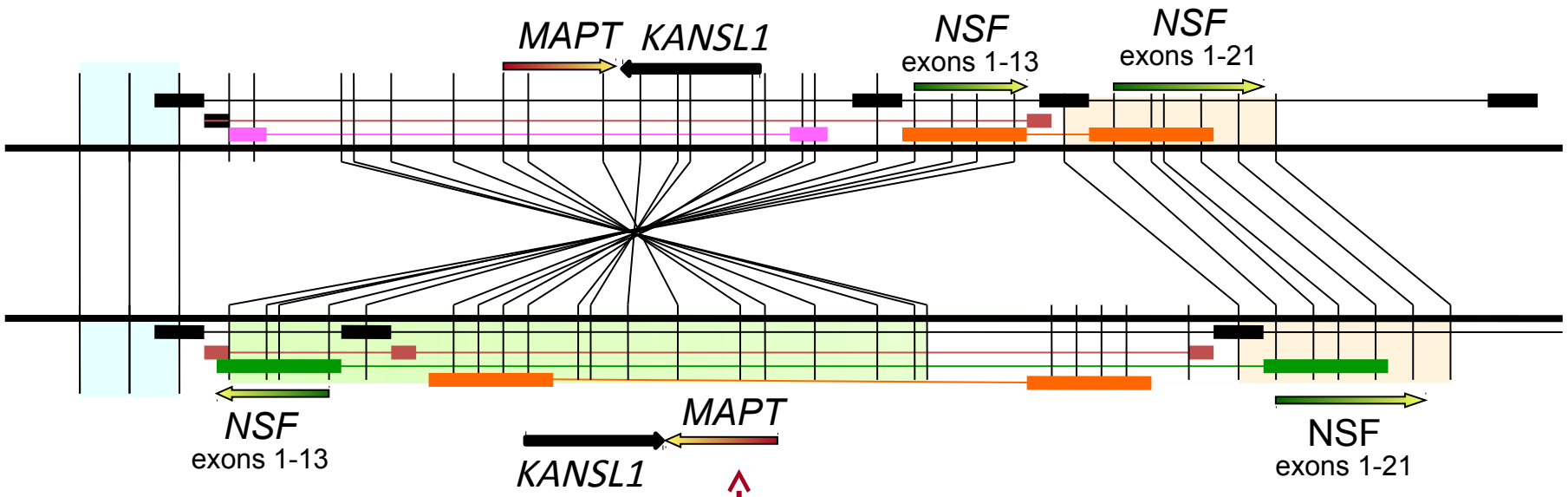
| Target | Disorder | Drug |
|---|---|---|
| **HMG co-A reductase** | **Heart disease** | **statins** |
| NPC1L1 | Heart disease | Zetia (ezetimibe) |
| **PCSK9** | **Heart disease** | **monoclonal antibody** |
| VCAM1 | MS | natalizumab |
| IL2RA | MS | daclizumab |
| TNF-α | RA | infliximab |
| SLC30A8/KCNJ11 | Type 2 diabetes | ZnT-8 antagonists/Glyburide |
| PADI | Rheumatoid Arthritis | BB-Cl-amidine/Toclilizumab |
| TNFR1/PTGER4/TYK2 | Ankylosing Spondylitis (AS) | TNF-inhibitors/NSAIDS/fostamatinib |
| IL23A | Psoriasis (Ps) | Risankizumab |
| RANKL/ESR1 | Osteoporosis | Denosumab/Raloxifene and HRT |
| DRD2 | Schizophrenia | anti-psychotics |
| IL12B | AS, Ps, Psoriatic arthritis | Ustekinumab |
| ANGPTL3 | Heart disease | monoclonal Ab/antisense oligos |
| APOC3 | Heart disease | antisense oligos |

# PSP Genetics

## *MAPT* mutations

| | PSP | CBD | |
|---|---|---|---|
| exon 1 | R5L | | |
| exon 10 | S285R, Δ296, G303V, S305S | | N296H, N296N, P301S |
| intron 10 | E10+11, E10+16 | | |
| exon 13 | G415S | | |

**H1**

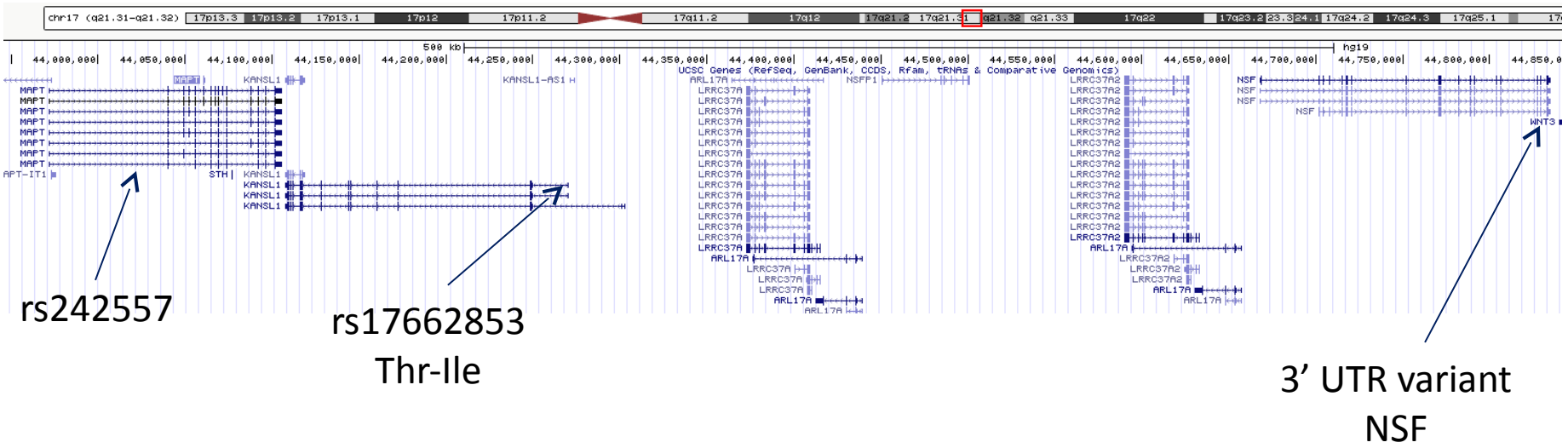



Stefansson *et al* (2005) Nature Genet. 37, 129

**H2**

*MAPT* encodes tau – protein in neurofibrillary tangles

863 kb




Interpretations:

- *KANSL1* is tagging a regulatory element that alters *MAPT* expression/splicing
- *KANSL1* variant influences risk for PSP through activity of the KANSL1 protein

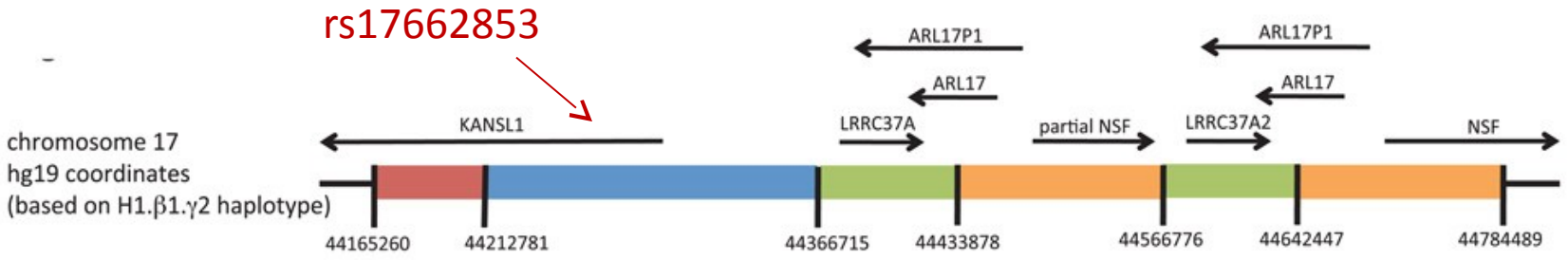

| | YRI | CHB+CHS | CEU |
|---|---|---|---|
| H1.β1.γ4 | 0.01 | 0.08 | 0.01 |
| H1.β1.γ3 | 0.07 | 0.31 | 0.17 |
| H1.β1.γ2 | 0.49 | 0.18 | 0.10 |
| H1.β1.γ1 | 0.43 | 0.42 | 0.26 |

PSP risk

One copy of *KANSL1* 5' end

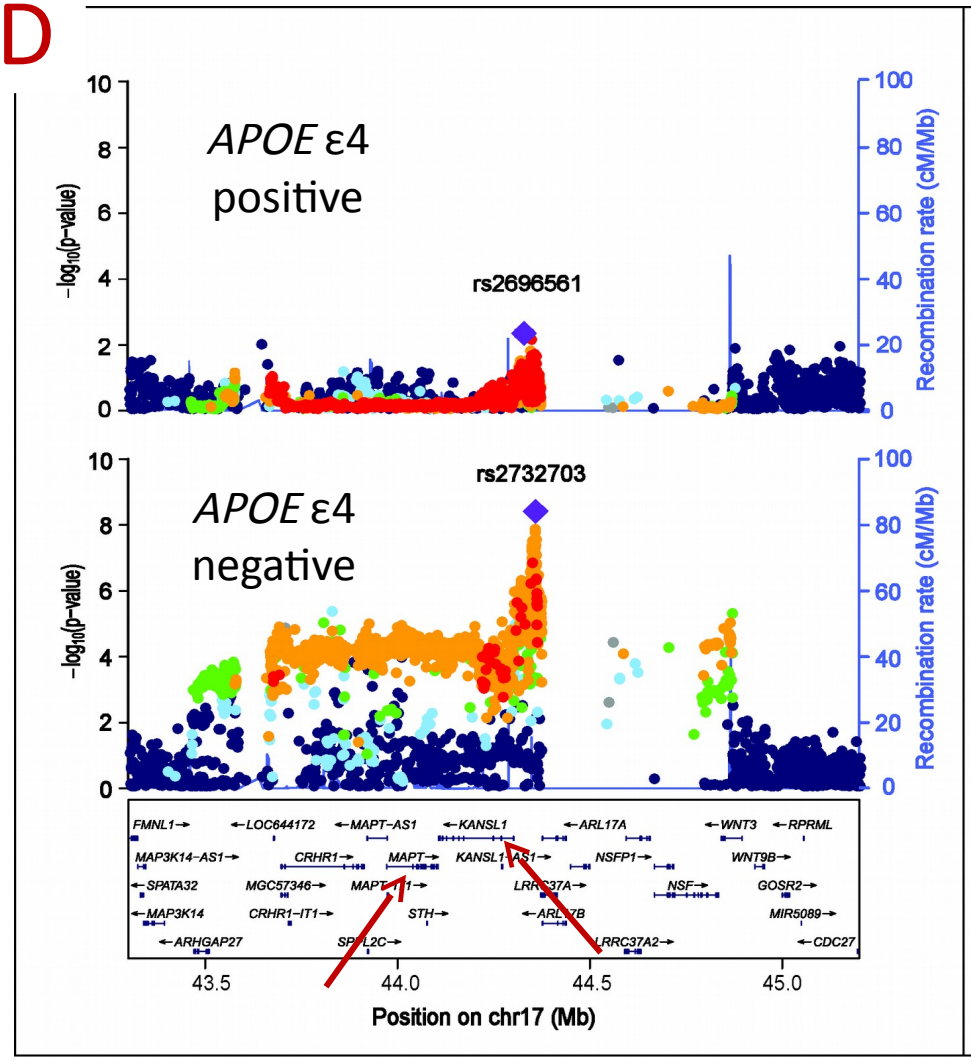
One – four copies NSF 5' end

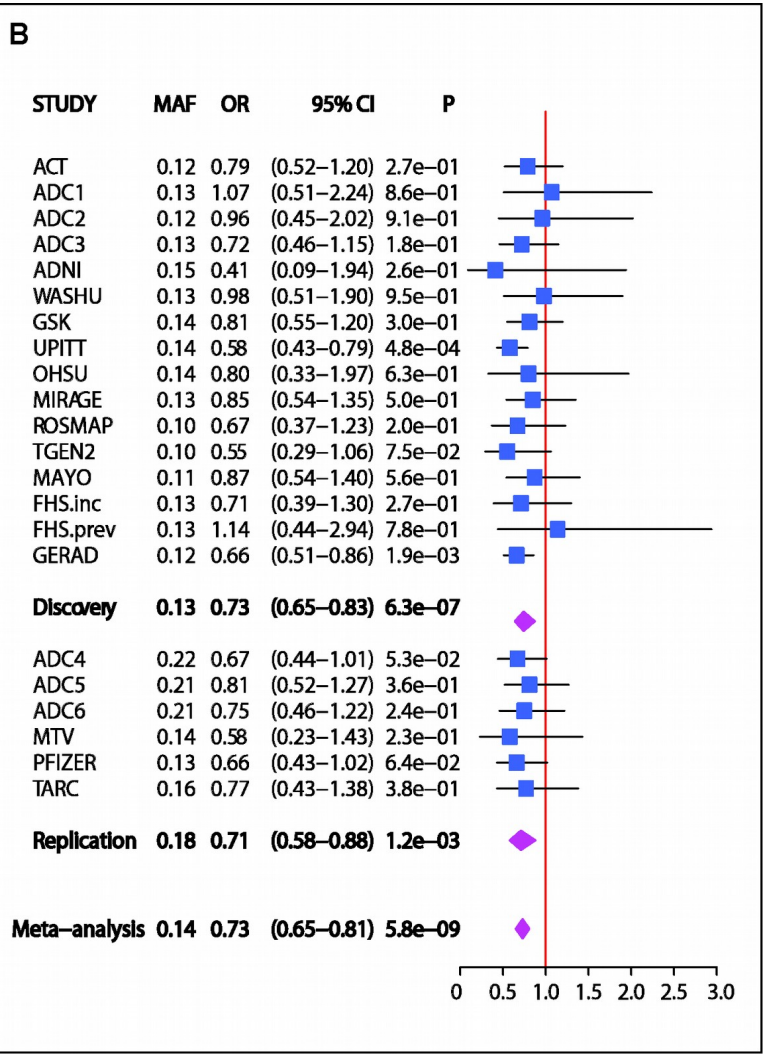
One copy of NSF 5' end




Boettger et al., Nature Genetics **44**:8, 2012

# AD



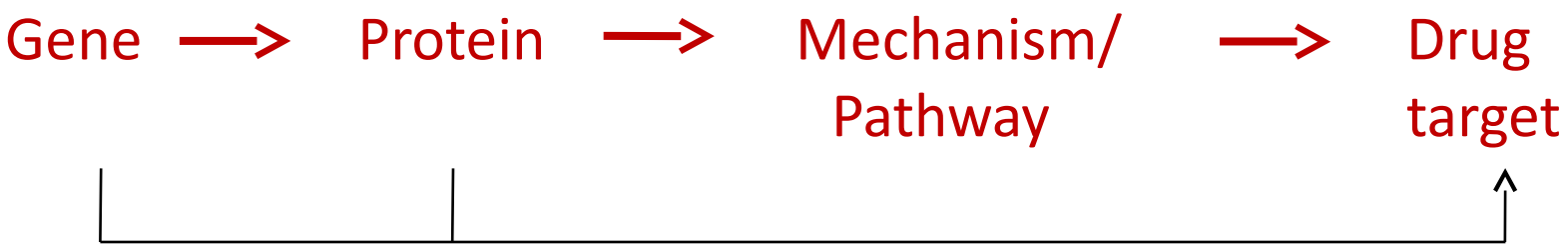




| SNP | CH | Closest Gene/Region | Meta-Analysis | |
|---|---|---|---|---|
| | | | OR (95% CI) | P |
| rs2732703 | 17 | KANSL1/LRRC37A | 0.73 (0.65-0.81) | $5.8 \times 10^{-9}$ |

## PSP Genetics

- GWAS array data
- Whole exome sequence data
- Whole genome sequence data
- Imputed genotypes

Combined approaches



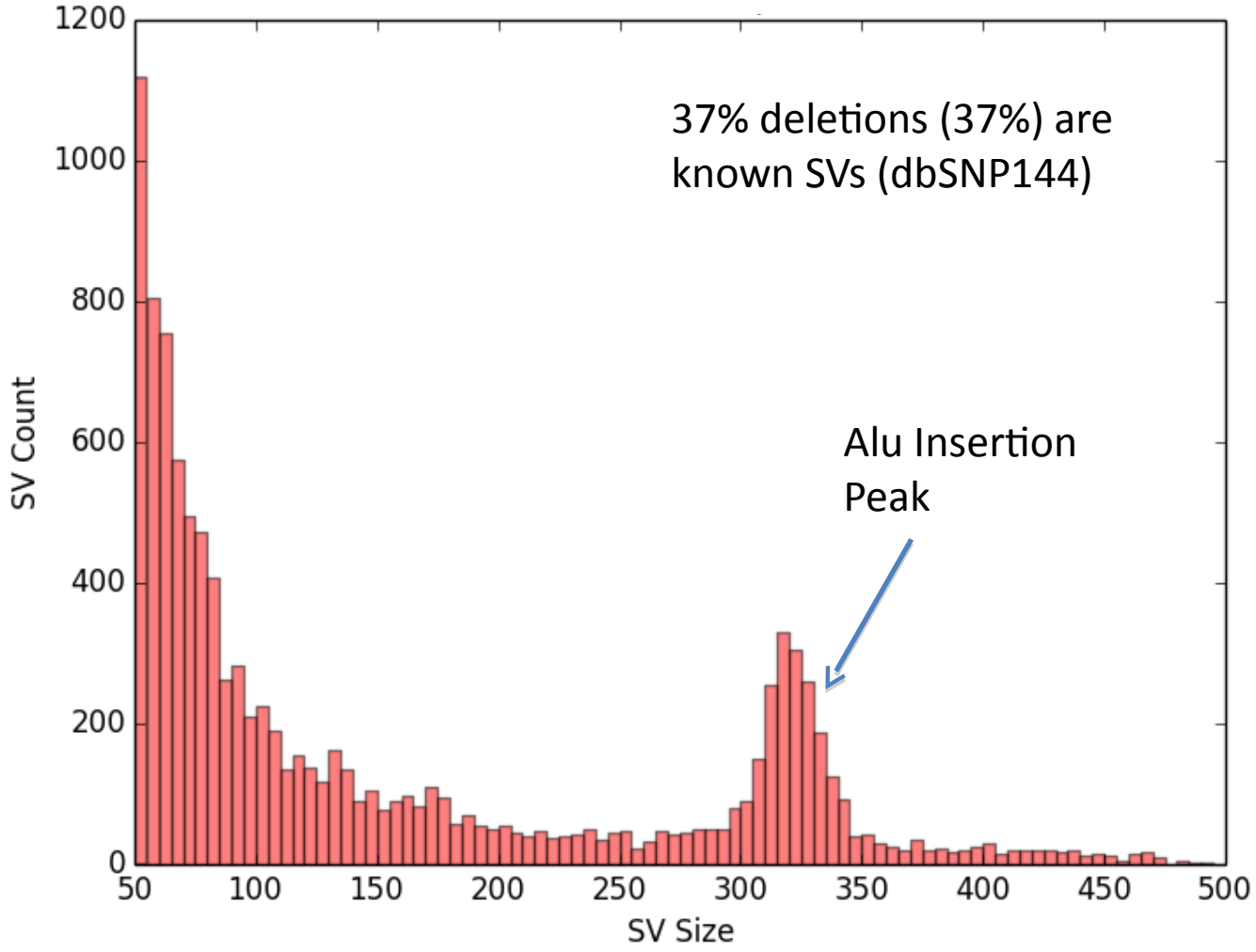
## PSP Genetics:

- 700 WES
- 2,000 WGS
- Controls: ~8,000 (ideal?)
- Controls available: ~5,000 for WES, 1,600 for WGS

## Challenges:

- Cases sequenced at different times and different platforms
- Controls sequenced separately from cases
- Controls sequenced at different times and different platforms
- WES capture – different reagents
- Case/control **data** needs to be identically processed
- Methods to detect structural variants not reliable

# Deletion Size Frequency
# 50-500 bp



Alzheimer's Disease Sequence Project, TOPMed, and others

**Controls**

## WES

5,000 unrelated AD cases

**5,000 elderly normal controls – Caucasians (non-Hispanics)**

MESA 4,300 - 2,000 Caucasians

GCAD: Call all data – **HG38**

Generate **gVCF** files: GATK
ATLAS (?)

Consensus call set

Harmonized project level VCF - all data sets

Goal: All variant positions called in all data sets

# Model Organisms and Tauopathies
# Gene Discovery
# Loss-of-function mutations

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- Associate Professor - Department of Medicine, University of Washington
- Acting Director – Research at the Geriatric Research Education and Clinical Center, Seattle VA

# PSP/CBD GWAS Collaborators

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Thank you