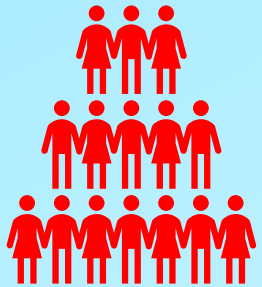
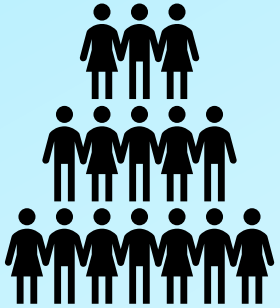
GWAS Are Used to Identify Novel AD Candidate Genes Using Large-Scale Genetic Information



AD population
Disease phenotype



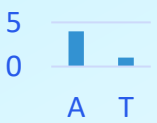
Control population
Without the disease phenotype

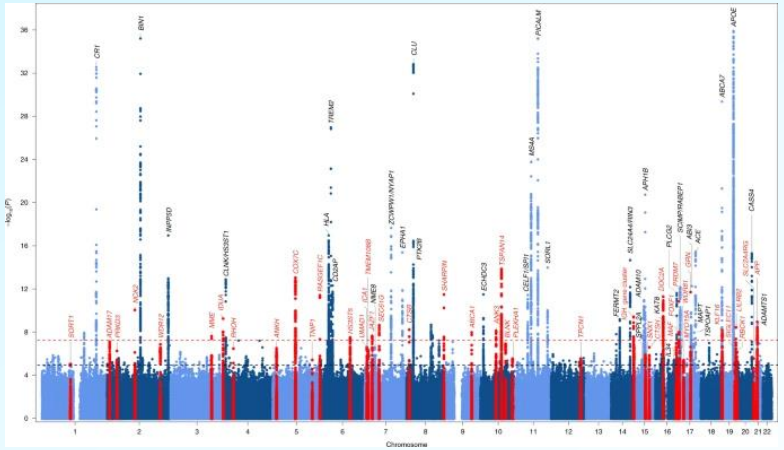
STEPS in GWAS:

- Enroll a large population of people that differ in the trait of interest
- Do a careful phenotype analysis
- Survey each person's genome for variation (called single-nucleotide polymorphisms, SNPS) in the genetic code
- Look for variants that are significantly more common in the disease population than in the control population
- These variants are map posts on the chromosome that are used to explore the nearby genes as candidate genes for AD
- **GWAS are useful for nominating candidate genes, but typically are unable to establish disease causality** (due to genetic linkage, lack of statistical power, multiple causative variants or genes).[1] Functional validation is needed through cell biology or animal studies

Identify single-nucleotide polymorphisms (differences) between populations

Control population	AD population
…CCTATGCTAC…	…CCTTTGCTAC…
…CCTATGCTAC…	…CCTTTGCTAC…
…CCTATGCTAC…	…CCTTTGCTAC…
…CCTTTGCTAC…	…CCTATGCTAC…
…CCTATGCTAC…	…CCTTTGCTAC…



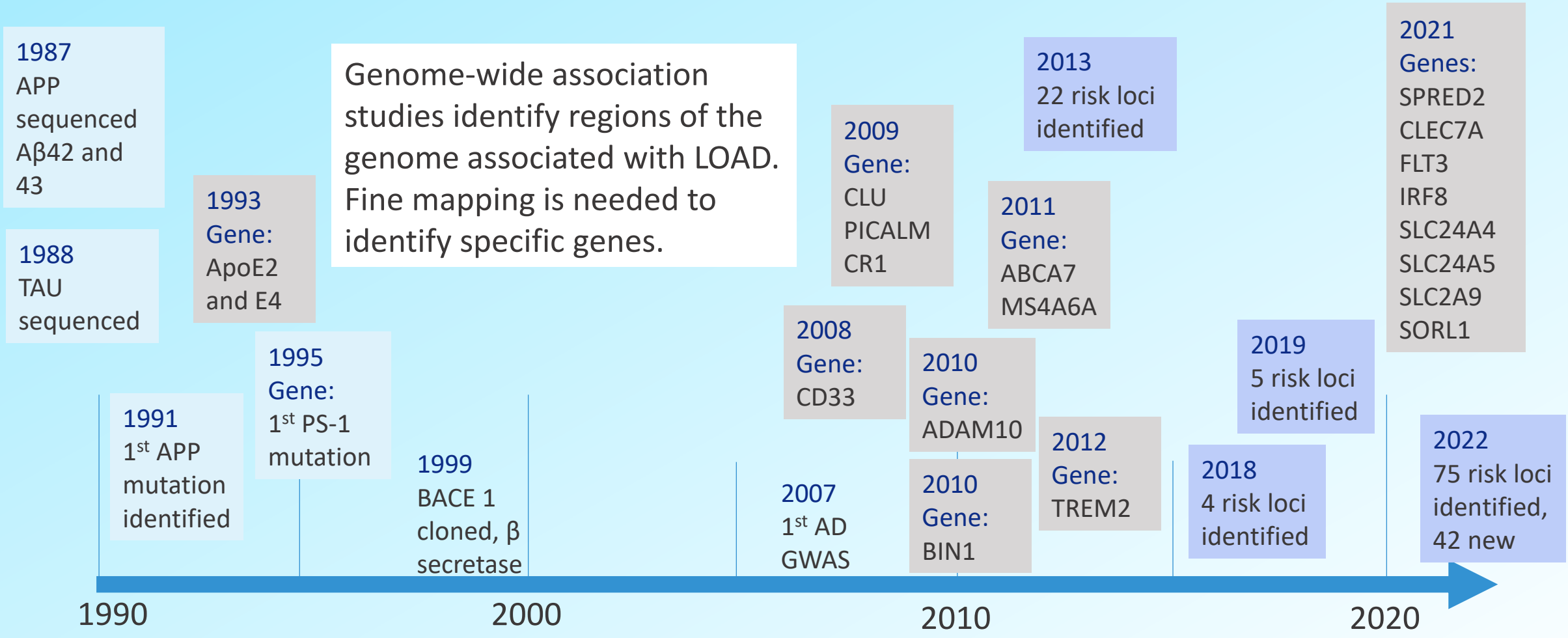


Bellenguez et al, CC by 4.0[2]

GWAS, genome-wide association studies.

1. Flister M et al. *Genome Res.* 2013;23:1996-2002; 2. Bellenguez C et al. *Nat Genet.* 2022;54:412-436.

GWAS Have Significantly Increased the Pace of AD Gene/Risk Loci Discovery



AlzForum. Accessed May 24, 2023. https://www.alzforum.org/timeline/alzheimers-disease;
Andrews SJ et al. *Lancet Neurol.* 2020;19:326-335; Jansen IE et al. *Nat Genet.* 2018; 51:404-413; Lemprière S. *Nat Rev Neurol.* 2021;17:659.

Susceptibility Loci Help Pinpoint Major Molecular Pathways Associated With LOAD

Gene	Molecular Pathway
ApoE, SORL1, CLU, CR1, PICALM, BIN1, ABCA7, CASS4, PLD3	Amyloid pathway
CLU, CR1, EPHA1, ABCA7, MS4A4A/MS4A6E, CD33, CD2AP, HLA-DRB5/DRB1, INPP5D, MEF2C, TREM2/TREML2	Immune system/inflammation
ApoE, CLU, ABCA7, SORL1	Lipid transport and metabolism
CLU, PICALM, BIN1, EPHA1, MS4A4A/MS4A6E , CD33, CD2AP, PTK2B, SORL1, SLC24A4/RIN3, MEF2C	Synaptic cell functioning/endocytosis
BIN1, CASS4, FERMT2	Tau pathology
PTK2B	Cell migration
MEF2C, PTK2B	Hippocampal synaptic function
CELF1, NME8, CASS4	Cytoskeletal function and axonal transport
INPPD5	Microglial and myeloid cell function
FBXL7	Phosphorylation-dependent ubiquitination

LOAD, late-onset Alzheimer's disease.

Reitz C. *Ann Translat Med.* 2016;4:107.