Alzheimer's Disease and Genetics

- Where are we now?
- What can genetics findings be used for?
- What do we expect to achieve?
- What is the final goal?

Is technology driving what we do?

Or

Is technology being used to answer questions?

Alzheimer's Disease and Genetics

- Where are we now?
- What can genetics findings be used for?
- What do we expect to achieve?
- What is the final goal?

Is technology driving what we do?

Or

Is technology being used to answer questions?

Where are we now?

Rare Variants

Early-Onset AD Rare variants
1. *APP* 2. *PSEN1* 3. *PSEN2*

Late-Onset AD Rare variants
1. *PSEN2 (early and late onset)* 2. *APP (protective variant)* 3. *TREM2* 4. *UNC5C* 5. *TREML2* 6. *PLXNA4* 7. *AKAP9*

1. *APOE*
2. *SORL1*
3. *CR1*
4. *CLU*
5. *PICALM*
6. *BIN1*
7. *CD2AP*
8. *EPHA1*
9. *MS4A4A*
10. *ABCA7*
11. *HLA-DRB5/HLA-DRB1*
12. *PTK2B*
13. *SLC24A4/RIN3*
14. *MAPT*

Closest gene

not CD33

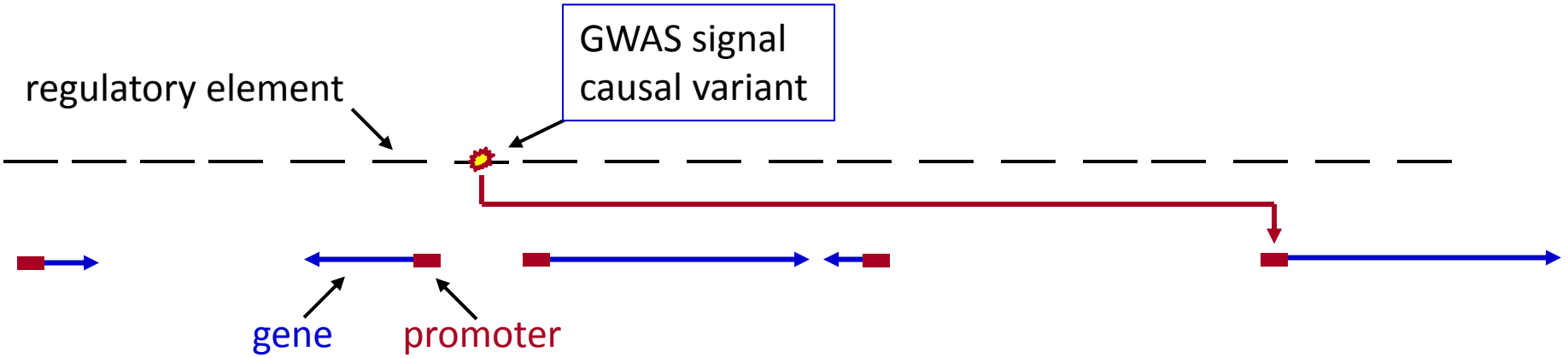
15. *CASS4*
16. *INPP5D*
17. *MEF2C*
18. *NME8*
19. *ZCWPW1*
20. *CELF1*
21. *FERMT2*
22. *TREM2L/TREM2*
23. *GLIS3*
24. *ABCG1*
25. *GalNAc*
26. Intergenic – chr 9
27. FRMD4A

Late-Onset AD
Common variants

- $P < 5 \times 10^{-8}$
- OR = 1.08 – 1.37, 5.22
- MAF = 3.9% - 49%

APOE

GWAS signals: 90-95% of causative variants are in non-promoter regulatory elements

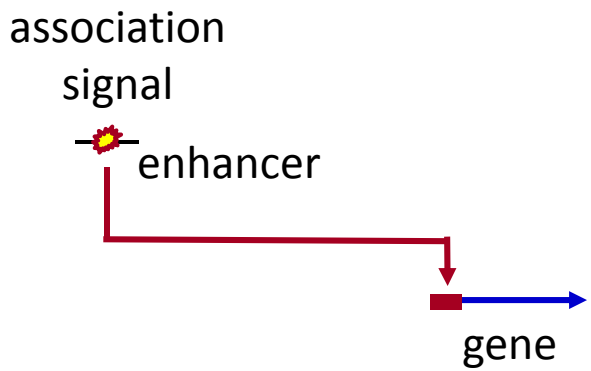


Genomic information

- eQTL (GTEX)
- Roadmap
- Encode
- Fantom 5

New Technology

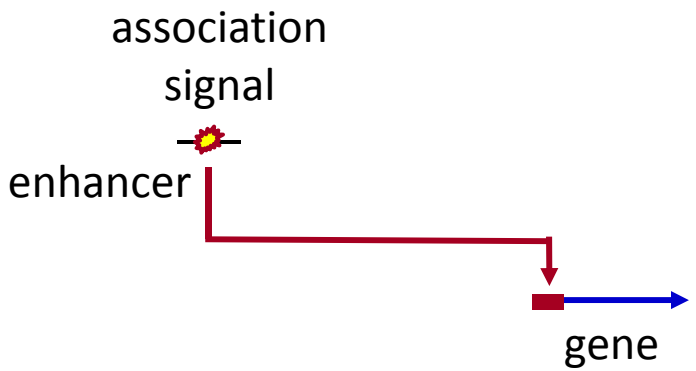
- Capture C methods
- CRISPR



Known AD Genes

1. *APP*
2. *PSEN1*
3. *PSEN2*
4. *APOE*
5. *SORL1*
6. *CR1*
7. *ABCA7*
8. *MAPT*
9. *TREM2*
10. *UNC5C*
11. *PLXNA4*
12. *AKAP*

Other GWAS loci



"New wine from old bottles"

Alzheimer's Disease and Genetics

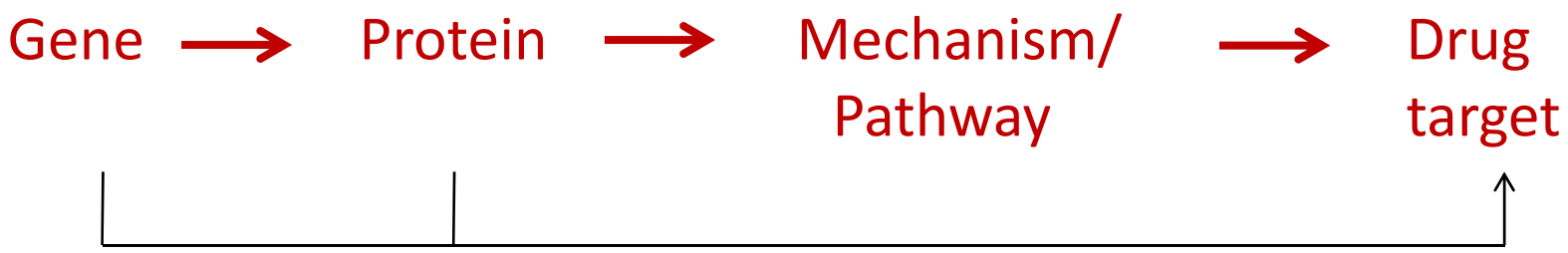
- Where are we now?
- What can genetics findings be used for?
- What do we expect to achieve?
- What is the final goal?

Is technology driving what we do?

Or

Is technology being used to answer questions?

- Prediction
- Mechanism
- Drug targets



- Prediction
- Mechanism
- Drug targets

APP
PSEN1
PSEN2

Autosomal dominant
Highly penetrant
Early-onset

Rare! (< 0.1%?)

Highly predictive

Applies to a very small number of cases

Used to design prevention trials

APOE

Genotype	Odds ratio (95% Confidence interval)	Control frequency (percent)	Case frequency (percent)
ε3/ε3	1.0 (referent)	60.9	36.4
ε2/ε2	0.6 (0.2 – 2.0)	0.8	0.2
ε2/ε3	0.6 (0.5 – 0.8)	12.7	4.8
ε2/ε4	2.6 (1.6 – 4.0)	2.6	2.6
ε3/ε4	3.2 (2.8 – 3.8)	21.3	41.1
ε4/ε4	14.9 (10.8 – 20.6)	1.8	14.8
ε4/ε4	35.07 (23.8 – 51.8)	onset age 60 – 69 years	

Farrer *et al*. JAMA 278, 1349: Genin *et. al.* Molec. Psychiatry 16, 903 (2011)

APOE

Genotype	Percent in Controls	Life Time Risk – Age 85 years (male/female)
ε3/ε3	60.9%	7% – 12%
ε3/ε4	21.3%	22% - 35%
ε4/ε4	1.8%	52% – 68%

Life-time risk – risk to develop AD between birth and a specific age (85 year in table above)

Genin *et. al.* Molec. Psychiatry 16, 903 (2011)

Other rare variant genes

- *TREM2*

TREM2

Variant	control carrier frequency	Odds ratio	p-value
R47H	0.4%	2.29	4.31×10^{-12}
R62H	1.26%	1.67	5.64×10^{-12}

Modest odds ratio
Semi-rare

Two additional loci:

- OR = 1.58 (risk allele frequency in controls = 1.28%)
- OR = 2.29 (risk allele frequency in controls = 0.4%)

African Americans	*ABCA7*	OR = **1.79 (CI, 1.47 – 2.12); risk allele controls = 7%**
Caucasians	*ABCA7*	OR = **1.11 (CI, 1.11 – 1.19) risk allele controls = 19%**

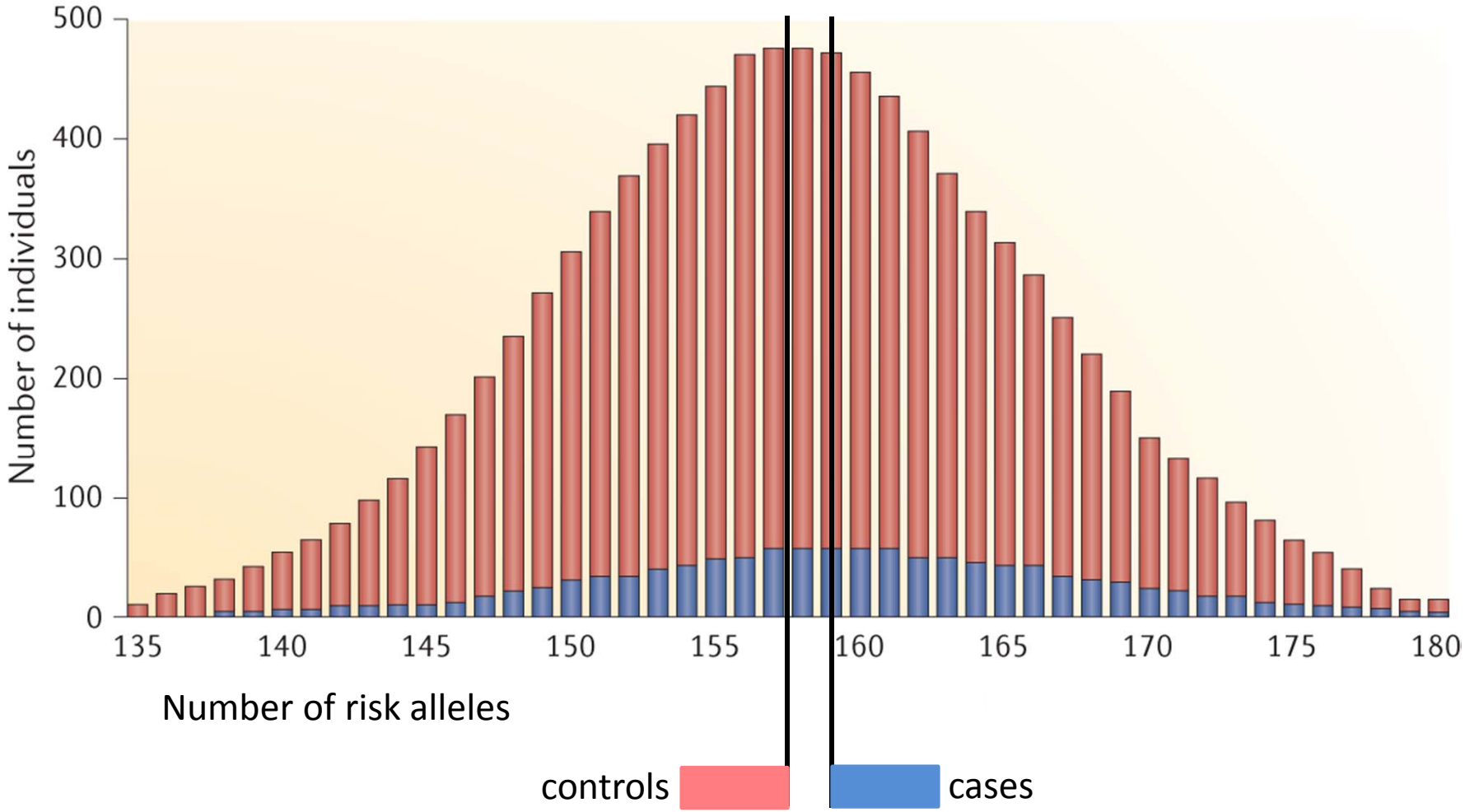
Reitz et al. JAMA 309, 1483 (2013)

Chr.	Closest gene[2]	MAF (SE)[3]	Overall	
			OR (95% CI)	Meta P-value
1	CR1	0.197 (0.012)	1.18 (1.14-1.22)	5.7×10^{-24}
2	BIN1	0.409 (0.017)	1.22 (1.18-1.25)	6.9×10^{-44}
6	CD2AP	0.266 (0.010)	1.10 (1.07-1.13)	5.2×10^{-11}
7	EPHA1	0.338 (0.010)	0.90 (0.88-0.93)	1.1×10^{-13}
8	CLU	0.379 (0.010)	0.86 (0.84-0.89)	2.8×10^{-25}
11	MS4A6A	0.403 (0.012)	0.90 (0.87-0.92)	6.1×10^{-16}
11	PICALM	0.358 (0.008)	0.87 (0.85-0.89)	9.3×10^{-26}
19	ABCA7	0.190 (0.012)	1.15 (1.11-1.19)	1.1×10^{-15}
6	HLA-DRB5/HLA-DRB1	0.276 (0.012)	1.11 (1.08-1.15)	2.9×10^{-12}
8	PTK2B	0.366 (0.012)	1.10 (1.08-1.13)	7.4×10^{-14}
11	SORL1	0.039 (0.004)	0.77 (0.72-0.82)	9.7×10^{-15}
14	SLC24A4/RIN3	0.217 (0.009)	0.91 (0.88-0.94)	5.5×10^{-9}
2	INPP5D	0.488 (0.018)	1.08 (1.05-1.11)	3.2×10^{-8}
5	MEF2C	0.408 (0.010)	0.93 (0.90-0.95)	3.2×10^{-8}
7	NME8	0.373 (0.012)	0.93 (0.90-0.95)	4.8×10^{-9}
7	ZCWPW1	0.287 (0.016)	0.91 (0.89-0.94)	5.6×10^{-10}
11	CELF1	0.316 (0.022)	1.08 (1.05-1.11)	1.1×10^{-8}
14	FERMT2	0.092 (0.009)	1.14 (1.09-1.19)	7.9×10^{-9}
20	CASS4	0.083 (0.006)	0.88 (0.84-0.92)	2.5×10^{-8}

Chr.	Closest gene[2]	MAF (SE)[3]	Overall	
			OR (95% CI)	Meta P-value
1	CR1	0.197 (0.012)	1.18 (1.14-1.22)	5.7×10^{-24}
2	BIN1	0.409 (0.017)	1.22 (1.18-1.25)	6.9×10^{-44}
6	CD2AP	0.266 (0.010)	1.10 (1.07-1.13)	5.2×10^{-11}
7	EPHA1	0.338 (0.010)	0.90 (0.88-0.93)	1.1×10^{-13}
8	CLU	0.379 (0.010)	0.86 (0.84-0.89)	2.8×10^{-25}
11	MS4A6A	0.403 (0.012)	0.90 (0.87-0.92)	6.1×10^{-16}
11	PICALM	0.358 (0.008)	0.87 (0.85-0.89)	9.3×10^{-26}
19	ABCA7	0.190 (0.012)	1.15 (1.11-1.19)	1.1×10^{-15}
6	HLA-DRB5/HLA-DRB1	0.276 (0.012)	1.11 (1.08-1.15)	2.9×10^{-12}
8	PTK2B	0.366 (0.012)	1.10 (1.08-1.13)	7.4×10^{-14}

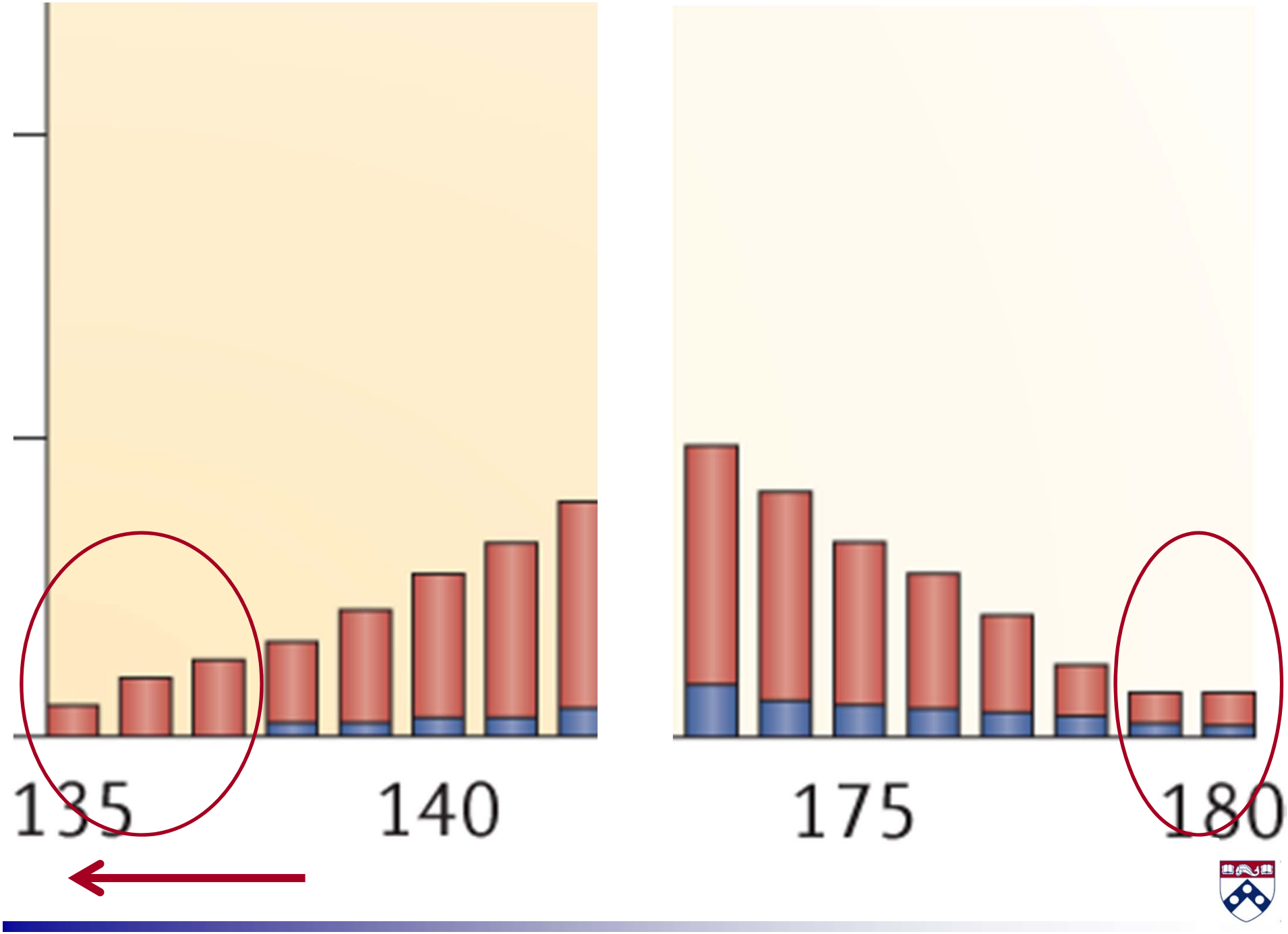
OR or (1/OR) range = 1.08 – 1.22

Prediction?



200 risk genes
Risk allele is common (0.1 – 0.9)
GRR = 1.04
Disease prevalence is 10%

Gibson (2012) Nature Review Genetics 13, 135


135
140
175
180

Prediction

- Some rare variants are highly predictive
- Some rare variants will be modestly predictive
- *APOE* is a major contributor to risk
- Common variants have a limited contribution to risk assessment

- Will find more common variants
- May find more rare-variants – modest predictive value
- Unlikely that a common large effect gene (*e.g. APOE*) will be found

- Prediction
- Mechanism
- Drug targets

Expected outcomes:

- Find genes that identify specific mechanisms
- Multiple genes in the same pathway
- Effect direction
  - High risk allele loss or gain of function
  - High-risk allele increase of decrease expression

Mechanisms/pathways

Aβ metabolism

APP, PSEN1, PSEN2

Innate immune system – microglial cells

TREM2, CR1, MS4 region, two new genes

Cholesterol metabolism (?)

APOE, ABCA7

Intracellular vesicle trafficking

SORL1, ABCA7

Synaptic dysfunction/membrane function

PICALM, BIN1, EPHA1

- Prediction
- Mechanism
- Drug targets

Can Genetic discoveries be used for drug target identification?

Alzheimer's Disease

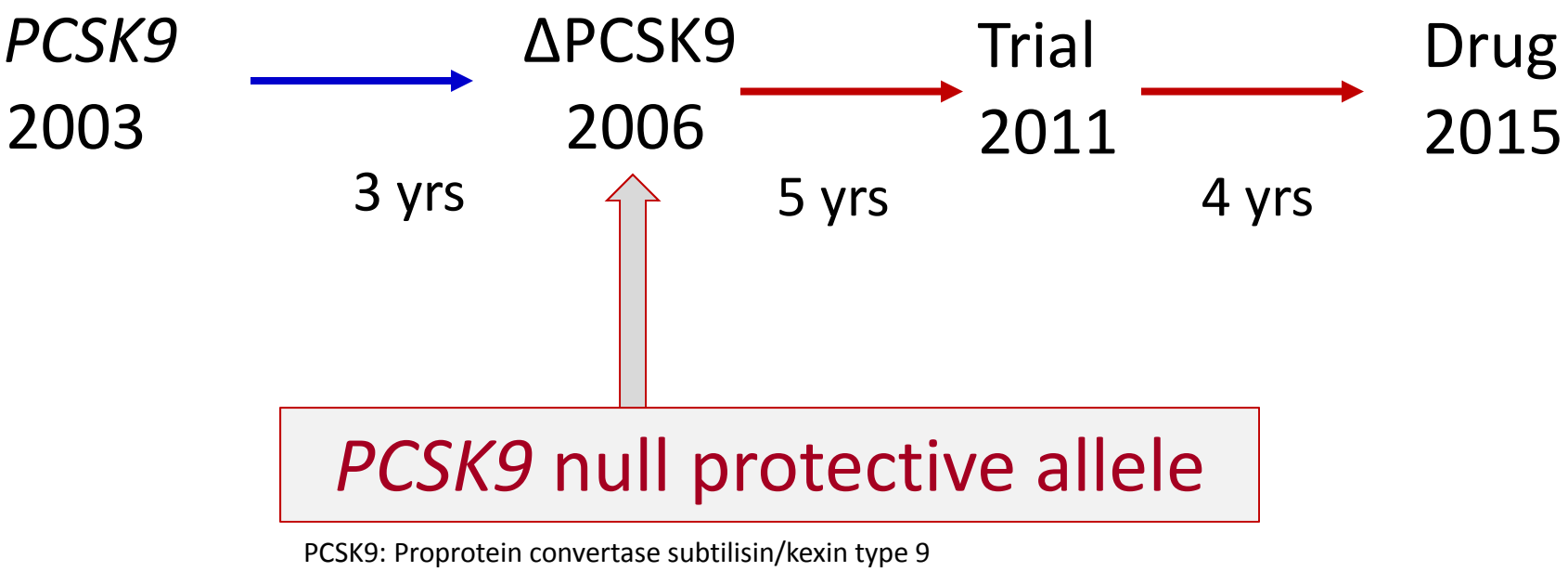
Aβ antibodies

Presenilin inhibitors

BACE1 inhibitors

APOE

Coronary artery disease



PCSK9: Proprotein convertase subtilisin/kexin type 9

What about small-effect genes and drug development?

NATURE | Vol 466 | 5 August 2010 p707

nature

ARTICLES

Biological, clinical and population relevance of 95 loci for blood lipids

A list of authors and their affiliations appears at the end of the paper.

Plasma concentrations of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides are among the most important risk factors for coronary artery disease (CAD) and are targets for therapeutic intervention. We screened the genome for common variants associated with plasma lipids in >100,000 individuals of European ancestry. Here we report 95 significantly associated loci ($P < 5 \times 10^{-8}$), with 59 showing genome-wide significant association with lipid traits for the first time. The newly reported associations include single nucleotide polymorphisms (SNPs) near known lipid regulators (for example, *CYP7A1*, *NPC1L1* and *SCARB1*) as well as in scores of loci not previously implicated in lipoprotein metabolism. The 95 loci contribute not only to normal variation in lipid traits but also to extreme lipid phenotypes and have an impact on lipid traits in three non-European populations (East Asians, South Asians and African Americans). Our results identify several novel loci associated with plasma lipids that are also associated with CAD. Finally, we validated three of the novel genes—*GALNT2*, *PPP1R3B* and *TTC39B*—with experiments in mouse models. Taken together, our findings provide the foundation to develop a broader biological understanding of lipoprotein metabolism and to identify new therapeutic opportunities for the prevention of CAD.

Gene*	P-value	Trait	Effect size (mg/dl)	drug
HMG co-A reductase	9×10^{-47}	TC	+2.84	statins
NPC1L1	3×10^{-11}	TC	+2.01	ezetimibe
PCSK9	2×10^{-28}	LDL	+2.01	alirocumab
APOE	9×10^{-147}	LDL	+7.14	none

ANALYSIS

nature genetics

The support of human genetic evidence for approved drug indications

Matthew R Nelson[1], Hannah Tipney[2], Jeffery L Painter[1], Judong Shen[1], Paola Nicoletti[3], Yufeng Shen[3,4], Aris Floratos[3,4], Pak Chung Sham[5,6], Mulin Jun Li[6,7], Junwen Wang[6,7], Lon R Cardon[8], John C Whittaker[2] & Philippe Sanseau[2]

Over a quarter of drugs that enter clinical development fail because they are ineffective. Growing insight into genes that influence human disease may affect how drug targets and indications are selected. However, there is little guidance about how much weight should be given to genetic evidence in making these key decisions. To answer this question, we investigated how well the current archive of genetic evidence predicts drug mechanisms. We found that, among well-studied indications, the proportion of drug mechanisms with direct genetic support increases significantly across the drug development pipeline, from 2.0% at the preclinical stage to 8.2% among mechanisms for approved drugs, and varies dramatically among disease areas. We estimate that selecting genetically supported targets could double the success rate in clinical development. Therefore, using the growing wealth of human genetic data to select the best targets and indications should have a measurable impact on the successful development of new drugs.

We estimate that selecting genetically supported targets could double the success rate in clinical development.

Drug targets

- Genetic studies can lead to successful drug development

- Effect size:
  - Does not predict druggability
  - Small effect genes are potential drug targets.

Tesla Syndrome

It's new
It's shiny
It must be better!

I want one!

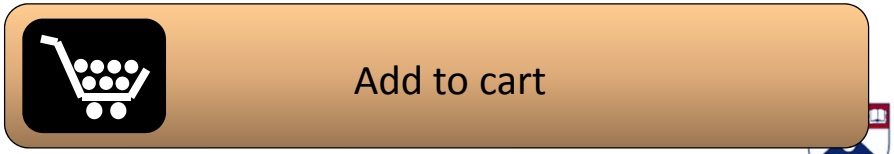
Business Day
Tesla's Model 3 Already Has 325,000 Preorders
BY BILL VLASIC APRIL 7, 2016

Tesla Syndrome

Is technology driving what we do?

Or

Are we using better technology to answer important questions?



Next Generation DNA sequencing

- whole exome
- whole genome

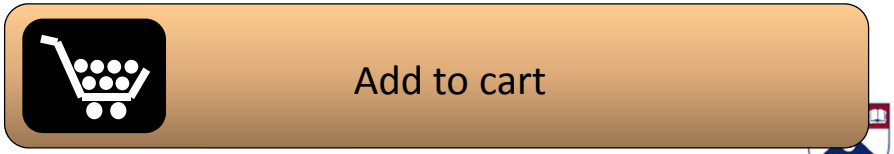
RNASeq

Histone acetylation/methylation

Methylation

DNase hypersensitivity

XYZomics



Whole exome sequencing

- DNA sequence for all (most) exons
- **~$600/sample**
- Coding/splice junction mutations
- 5’ and 3’ UTR
- Some small RNAs

Whole genome sequencing

- DNA sequence for all (most) 3×10^9 nucleotides
- **$1,250 – $1,350/sample**
- All coding, non-coding, intergenic mutations
- **Can get all (most) structural variants**

Pros - Whole exome sequencing

- cheaper
- Less costly to process data ($40/subject versus $140/subject)
- Easy (sort of) to interpret

Cons

- Miss 98% of genetic variability
- Limited resolution for structural variants

Pros - Whole genome sequencing

- Get all (most) mutations
- **Potential for all structural variants**

Cons

- More expensive to produce/process/store
- More difficult to interpret **ALL** the data

Genomic resources

- Encode
- RoadMap
- GTeX
- Fantom5
- Other databases

Enhance interpretation of intergenic and intronic genetic variation

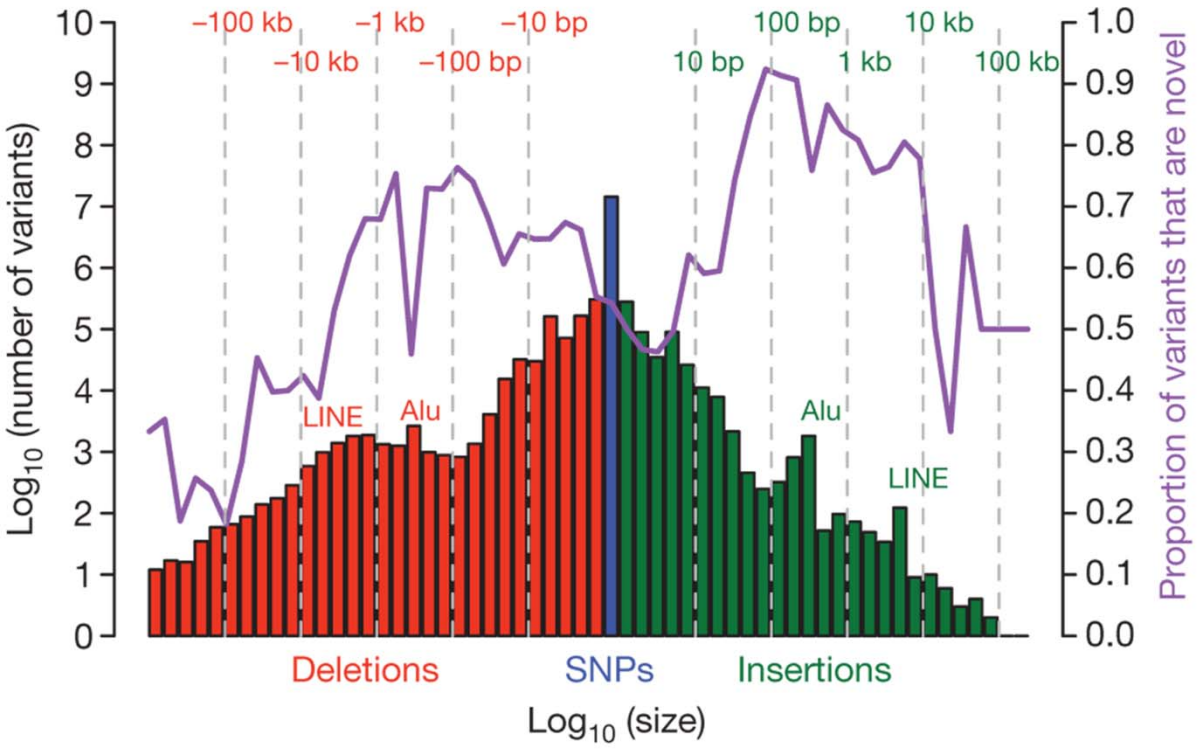
Structural Variants (SVs) Introduction

Type

- Insertions
- Deletions
- Inversions
- Translocations
- Copy number variation (CNV)

Size

- Inversely related to frequency
- 1bp to very large




ARTICLE

doi:10.1038/nature09534

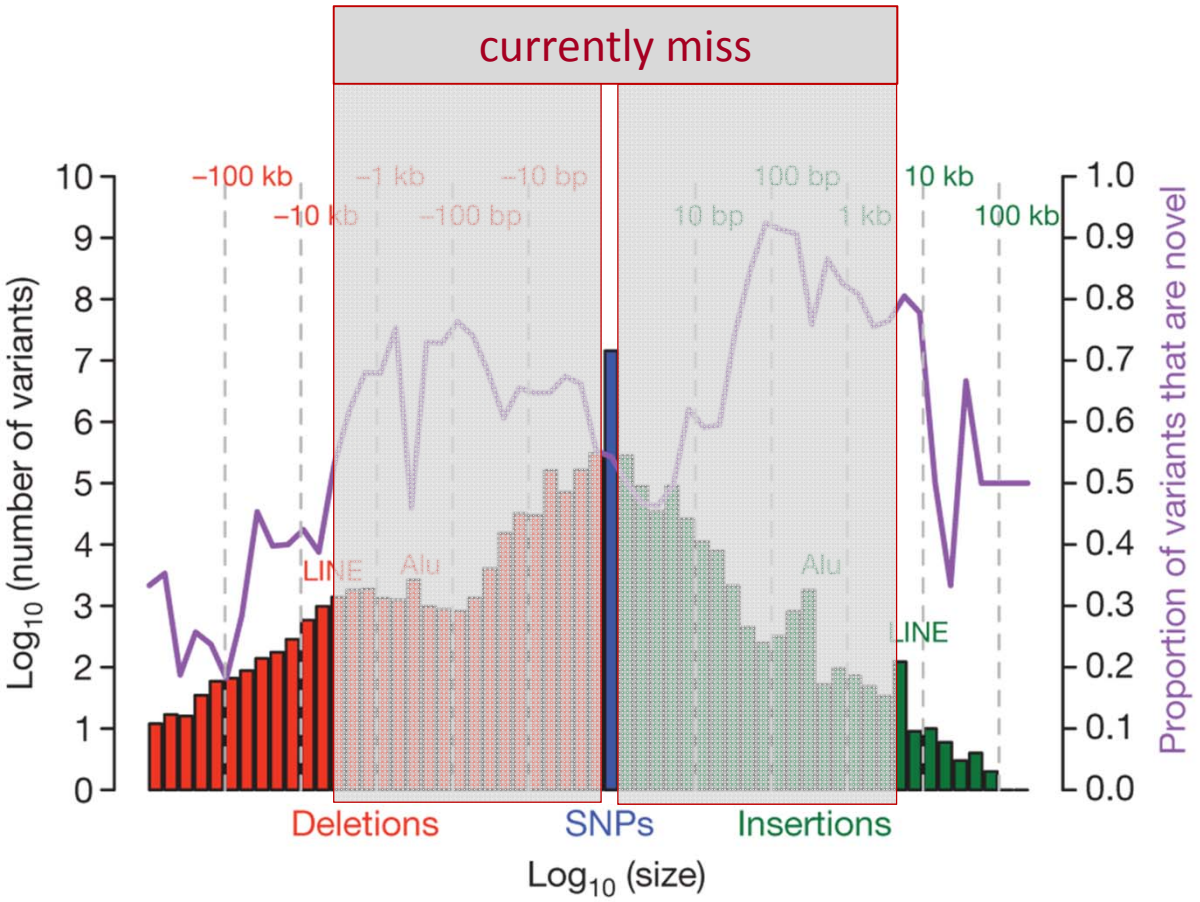
A map of human genome variation from population-scale sequencing

The 1000 Genomes Project Consortium*

*Lists of participants and their affiliations appear at the end of the paper.

28 OCTOBER 2010 | VOL 467 | NATURE | 1061

- SVs account for more of our genetic variability than single nucleotide variants (SNPs)



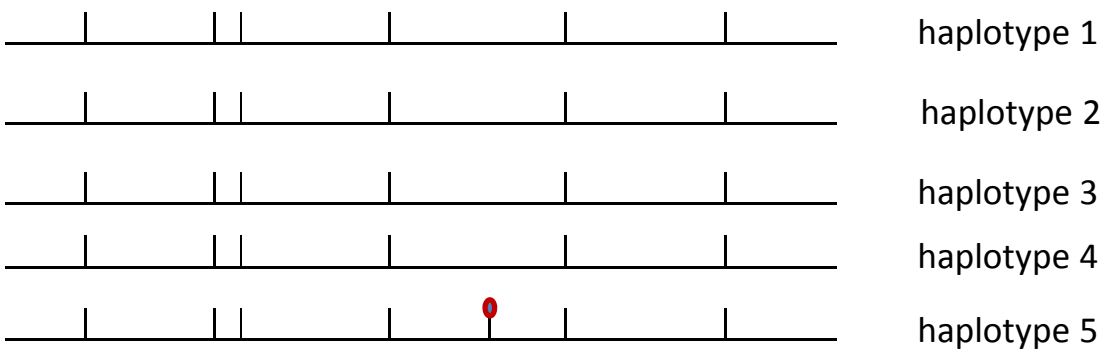
- Currently miss SVs in the 1 bp to ~5,000 bp range

Structural Variants (SVs)

- SVs - Alzheimer's disease/other neurologic disorders
  - *APP* duplication
  - *SNCA* duplication
  - *PSEN1* indel
  - *PMP22* deletion/duplication
  - *MAPT* inversion/CNVs
  - **Loss-of-function deletion – *ABCA7***

Whole genome sequencing will allow us to see SVs of all sizes – not previously genotyped

Imputation

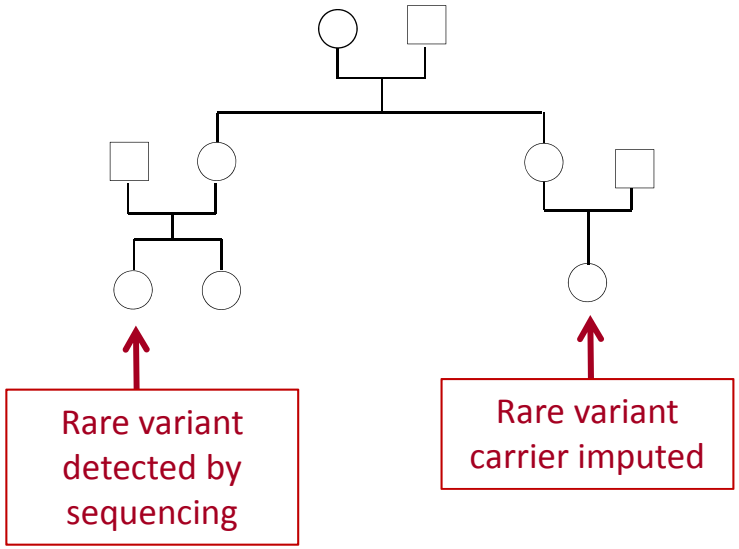


Reference panel

- 30,000 Genomes

1. Combined data from different genotyping platforms

2. **Test variants not directly genotyped: rare-variants**



Rare-Variant GWAS

Concordance: HRC vs. WGS

MAF Ranges	"Best Guess" % Concordance	"Stringent" % Concordance
0.2-1%	99.731	99.956
1-3%	99.522	99.924
3-5%	99.373	99.876
5-10%	99.389	99.847
10-15%	99.239	99.646
15-20%	99.068	99.424
Genotypes Used	90,251,702	76,642,843

- Hard-call genotypes from imputation
  - "Best Guess" – call goes to any genotype with prob>0.5
  - "Stringent" – call goes to genotypes only with prob>0.9
- Comparing HRC imputation of ADNI GWAS vs. ADNI WGS genotype calls in 213 ADNI samples
- Only looking at alternate genotype concordance (R/A; A/A)

Imputation:

- Uses existing GWAS genotypes
- Impute to an allele frequency of 0.1%

"New wine from old bottles"

- Most SVs
- Disease specific mutations
- Ethnic groups not in reference panel

Analyze rare variants not directly genotyped

Rare-Variant GWAS

Whole genome sequencing:

- detect all SVs
- detect rare variants not in reference panels
  (e.g. Alzheimer's disease – specific variants)
- variants in different ethnic groups

Use both whole genome sequencing and imputation

Future:

- Use imputed genotypes for replication studies
- Generate reference panels from:
  - Different ethnic groups
  - Disease populations
  - Sequence data processed for SVs

Goal: Completely resolve the genetics of AD – all genetic variation that alters risk

The longer the list of valid risk/preventative genes;

- The better the chance of finding a druggable target
- The more we will understand about disease mechanism

Alzheimer's Disease Genetics Consortium

University of Pennsylvania
- Li-San Wang
- Adam Naj
- Laura Cantwell
- Beth Dombroski
- Otto Valladeras
- Sherry Beecher

Mass. General
- Deborah Blacker

Standford
- Tom Montine

Mt. Sinai school of Medicine
- Alison Goate

University of Washington
- Bud Kukull
- Duane Beekly
- Debbie Tsuang

Indiana University
- Tatiana Foroud
- Kelly Michelle Faber

University of Miami
- Peggy Pericak-Vance
- Gary Beecher
- Eden Martin
- Kara Hamilton
- Brian Kunkle

Boston University
- Lindsay Farrer
- Kathryn Lunetta

Case Western
- Jonathan Haines
- Will Bush

Columbia
- Richard Mayeux
- Christiane Reitz
- Badri Vardarajan
- Jennifer Manly

NIA
- Marilyn Miller

NIA/NIH, Alzheimer's Association

The End