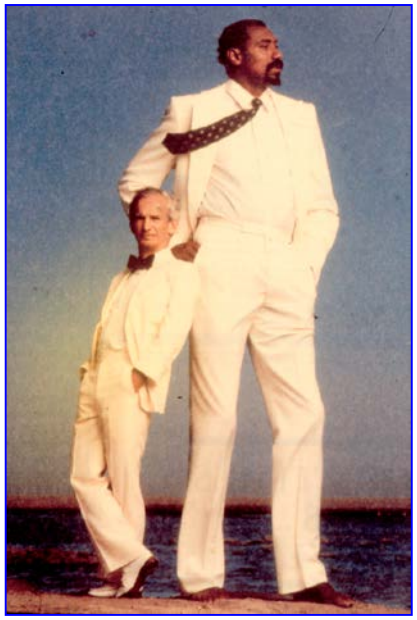
Genetic Basis of Human Disease and Implications for Germline Editing

Human Diseases and Traits



Rare, Mendelian
Cystic fibrosis,
Huntington Disease,
Diastrophic Dysplasia …

Common, polygenic
Heart disease, Alzheimer's
Schizophrenia, Height, Obesity
Intelligence? . . .

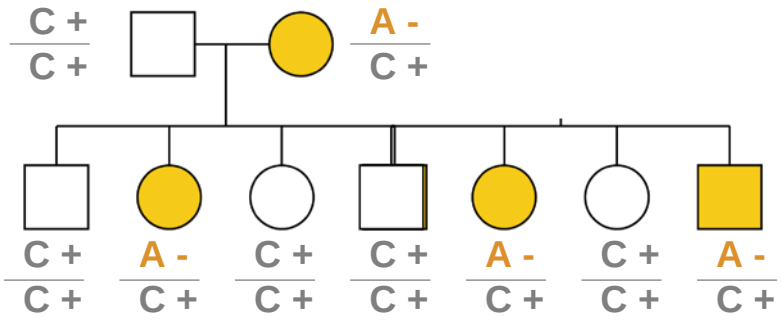
Avoid all cases of severe genetic disease
Eliminate disease alleles from population

Eliminate disease risk
'Enhance' human population

What do we know about disease genes?

1. Principles for Mapping Disease Genes

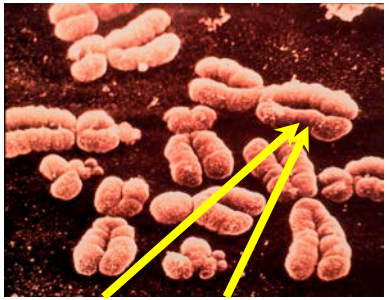
(1980s)



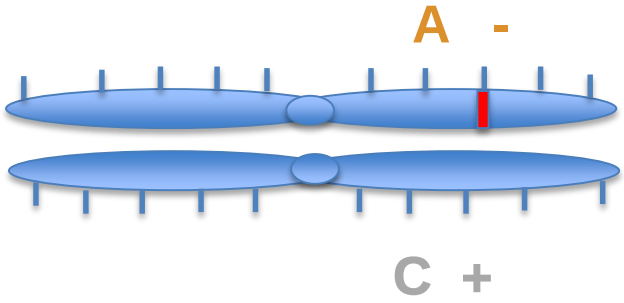
Mapping Disease Genes: Rare, Mendelian

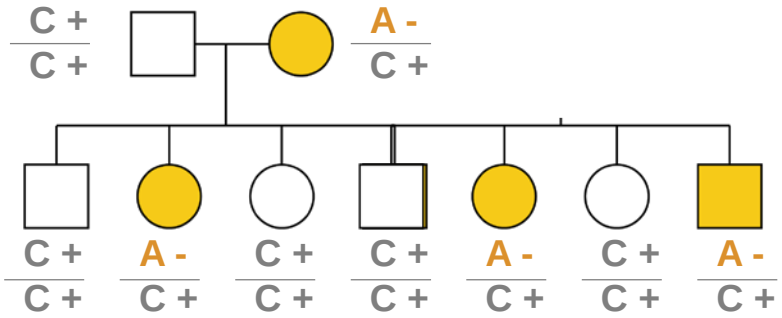
Rare Inherited: Monogenic

Linkage Mapping in Families

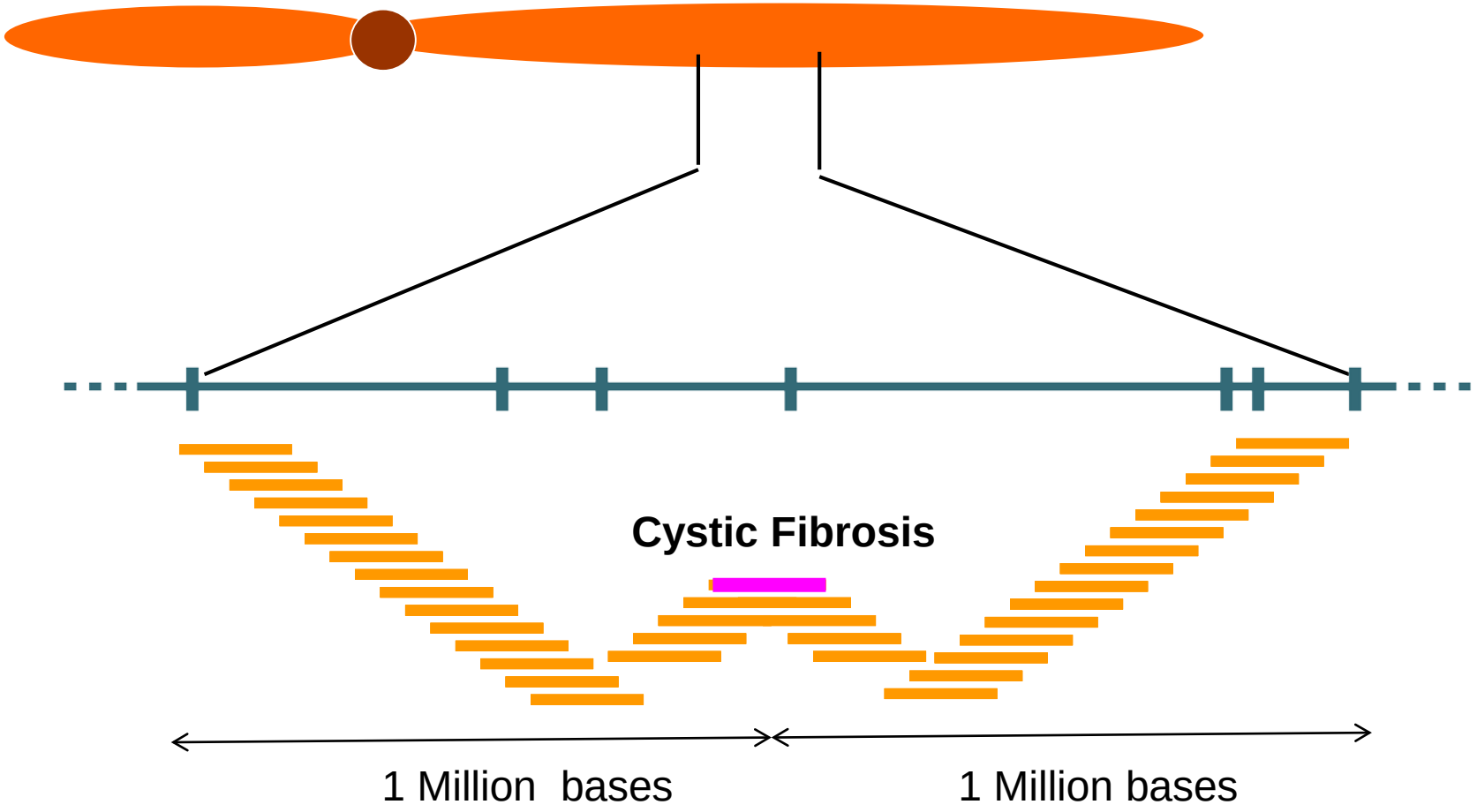


A/C Disease Gene





From Gene Mapping to Gene Discovery



Cystic Fibrosis Gene

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Cystic Fibrosis Gene

‘Big data’ analysis reveals function

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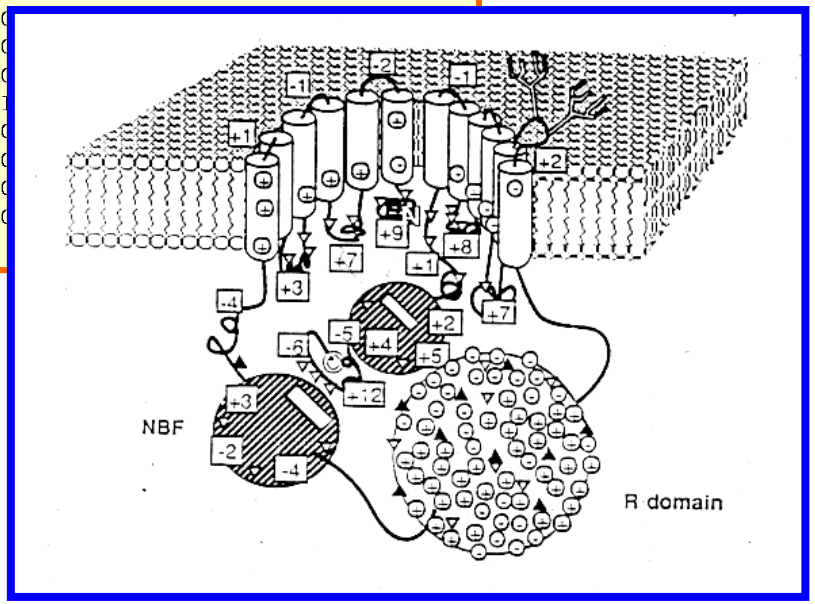
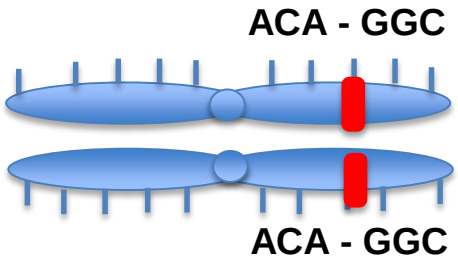


Mapping Disease Genes: Rare, Mendelian

Rare Inherited: Monogenic

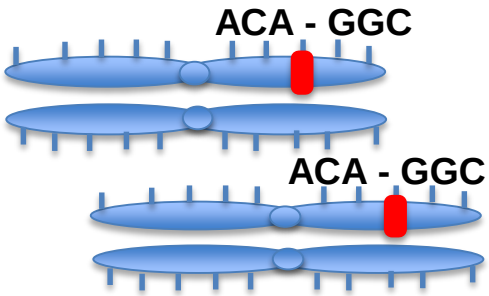
Linkage Mapping without Families

Homozygosity Mapping: Inbred individuals



Denser Genetic Map

Ancestral Segment (LD) Mapping: Isolated Populations



Even Denser Genetic Map!

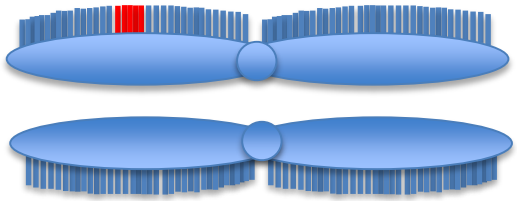
Mapping Disease Genes: Common Diseases

Common Inherited: Polygenic

Association mapping in populations

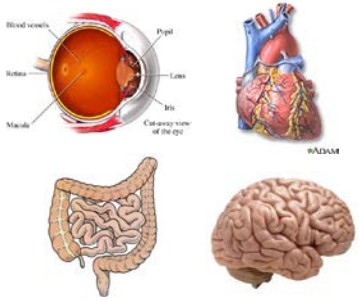
Ancestral segments (LD): isolated populations

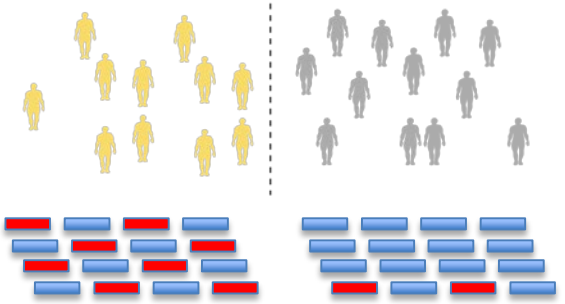
Finland



Denser genetic map!

Ancestral segments (LD): general populations



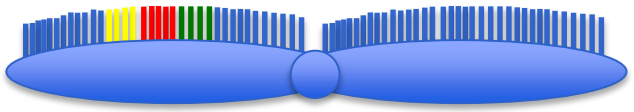


Mapping Disease Genes: Common Diseases

Common Variant Association Studies

High-resolution haplotype structure in the human genome

Mark J. Daly[1], John D. Rioux[1], Stephen F. Schaffner[1], Thomas J. Hudson[1,2] & Eric S. Lander[1,3]

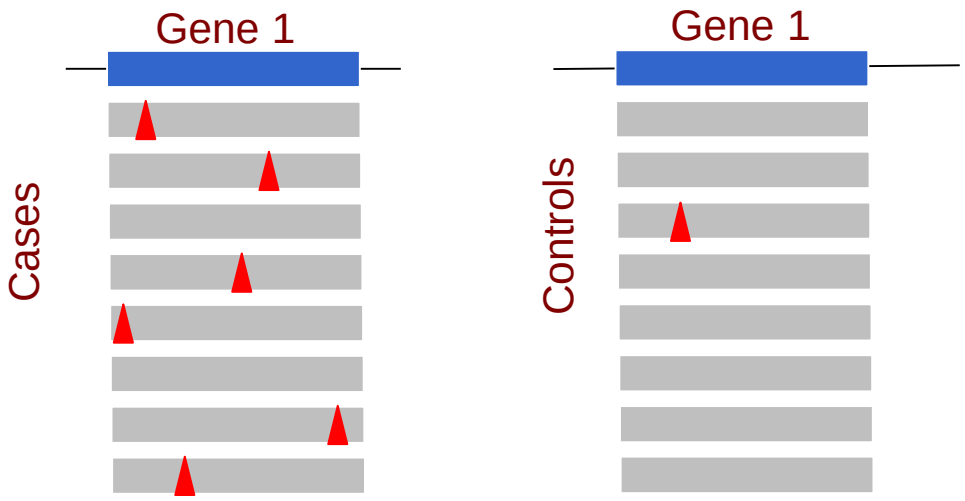


Need:

Catalog of
- all common variants (~1%)
- local haplotype structure

Technology to genotype
huge sample collections
for millions of SNPs

Rare Variant Association Studies



Need:

Technology to sequence
huge sample collections
for full exome or genome

2. Mapping the Human Genome

(1990-2003)

From Principles to Practice

Human Genome Project (1990-2003)

- Genetic map: Genetic landmarks to trace inheritance
- Physical map: DNA fragments covering the chromosomes
- Sequence: DNA sequence (3 billion bases)
- Gene List: Identification of all genes

Information freely available without restriction

Draft: (90%)

June 2000 Announced

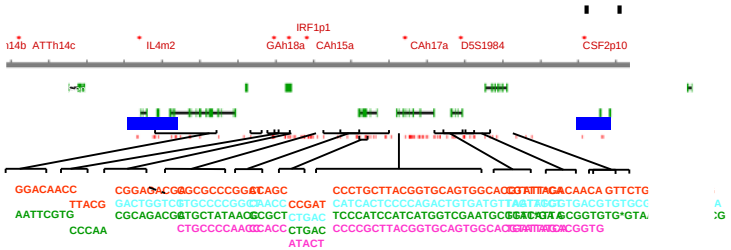
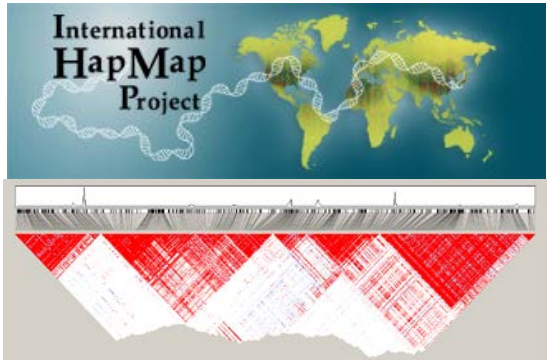
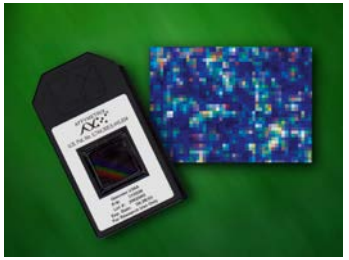
Feb 15, 2001 Publish

Finished (99.3%)

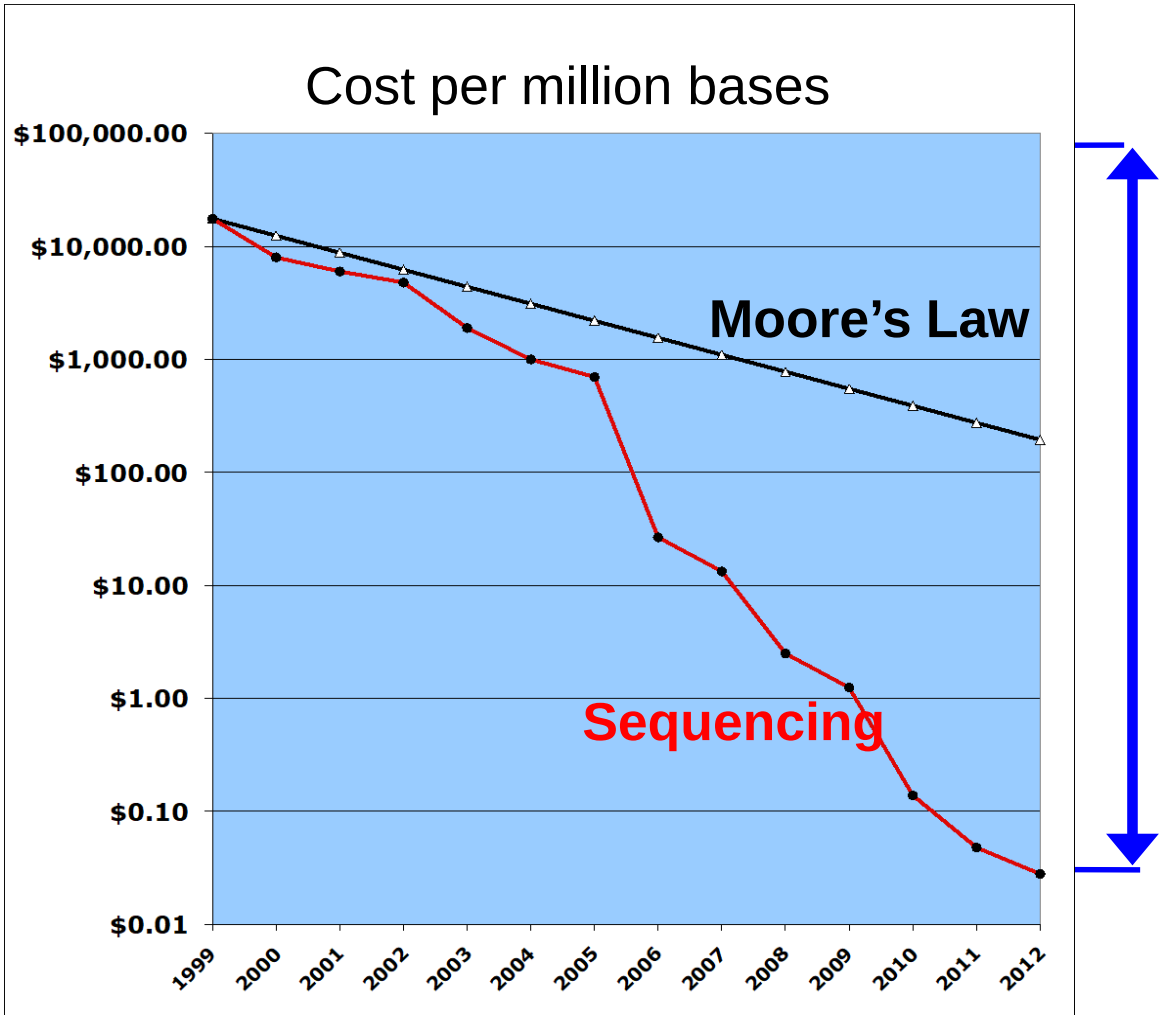
Apr 25, 2003 Completed

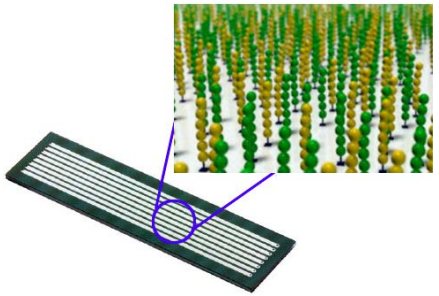
Oct 2004 Published

Catalog of all *common* genetic variation in humans

	Common variants	Correlation structure	Genotyping
1998	4,000	—	1 at a time
2001	A map of human genome sequence variation containing 1.42 million single nucleotide polymorphisms The International SNP Map Working Group 1.4 million	High-resolution haplotype structure in the human genome Mark J. Daly[1], John D. Rioux[1], Stephen F. Schaffner[1], Thomas J. Hudson[1,2] & Eric S. Lander[1,3] 	 10s
2007	 >10 million		 1 Million

New DNA sequencing technology: Can discover all *rare* variants in individuals

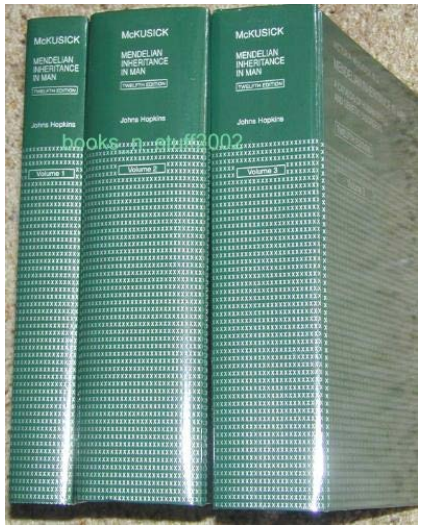




~2,000,000-fold decrease in cost over decade

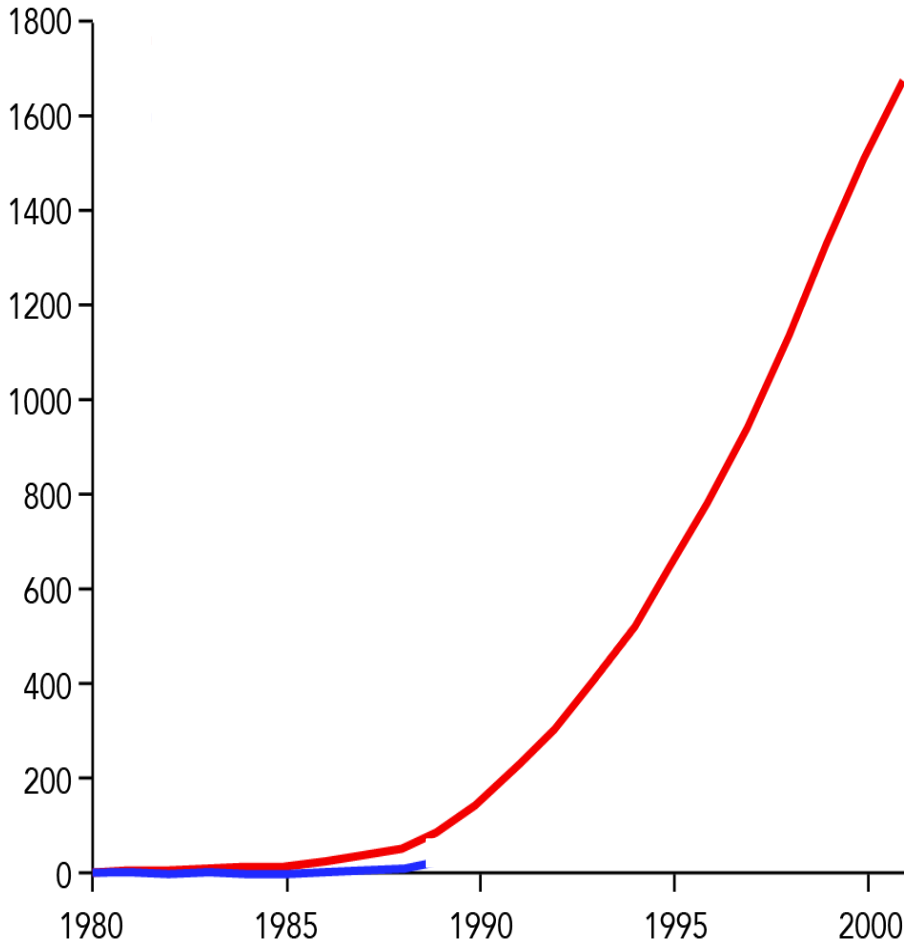
3. Mapping Disease Genes

(2000 - 2006)



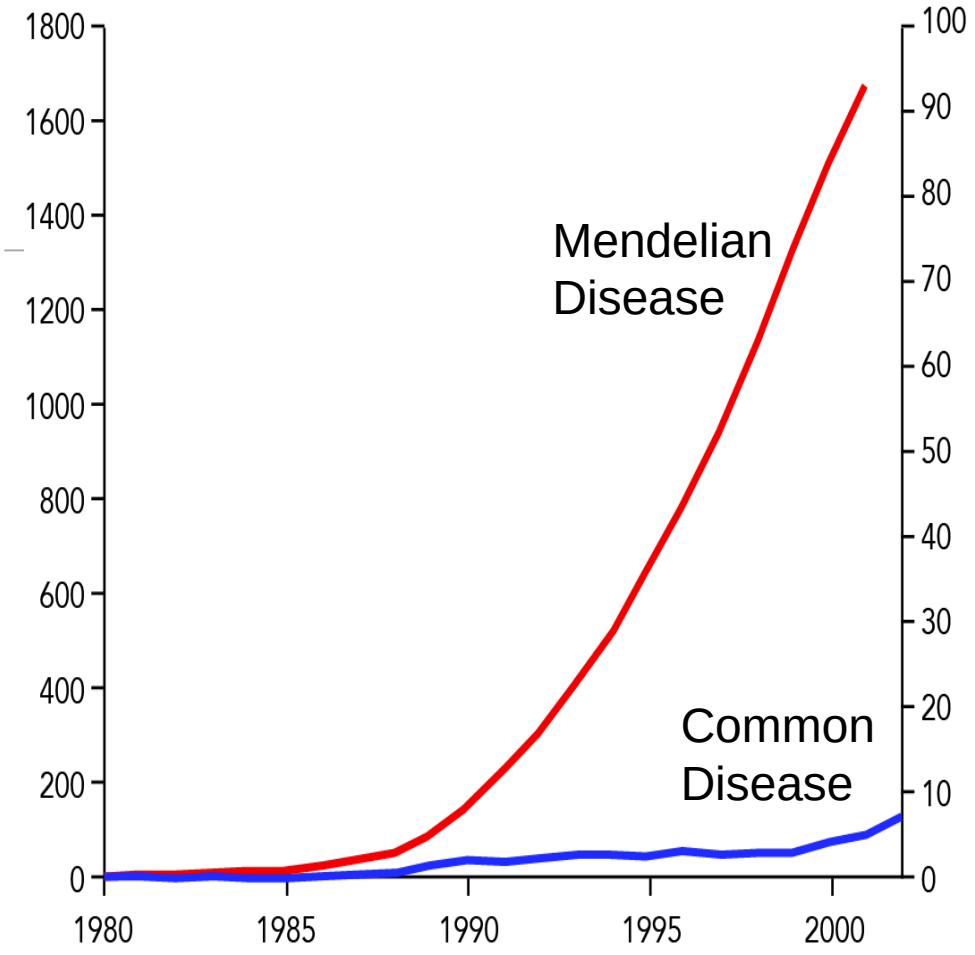
Mendelian Inheritance in Man

Family-based linkage mapping



Mendelian disease genes	
1990 (pre HGP)	~70
2001	~1700
2015	~4000

Family-based linkage mapping



Common Disease

Largely fails:
< 10 genes found

Exceptions instructive:

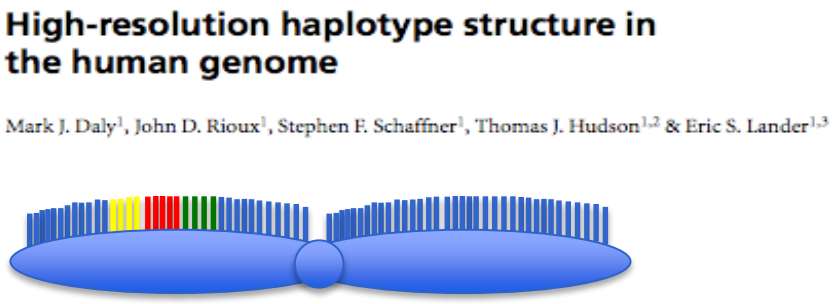
- APOE – Alzheimer's
- NOD2 – Crohn's
- CFH – Macular degeneration
- HLA – immune disorders

Different than Mendelian disease

Common variants *with odds ratios of 2-5*

Population-based mapping of common disease

Common Variant Association Studies (CVAS) – aka GWAS



Need:

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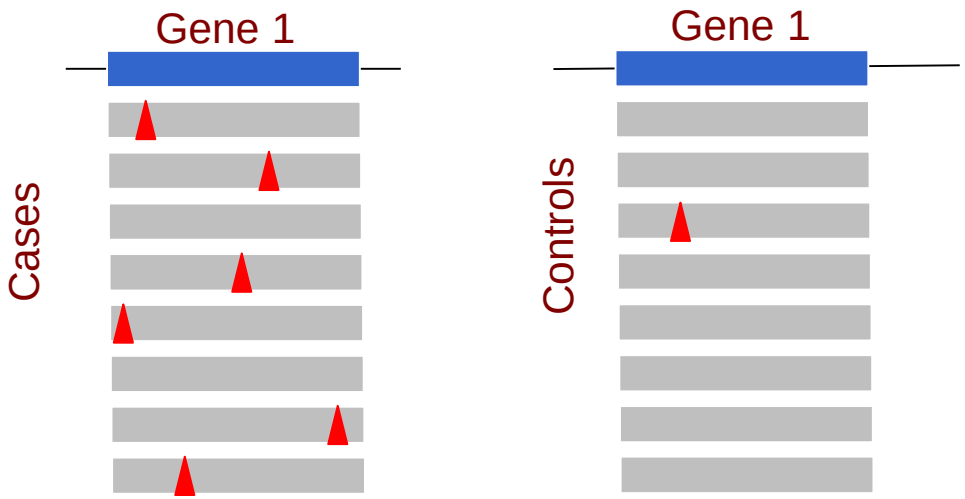
Technology to genotype
huge sample collections
for millions of SNPs

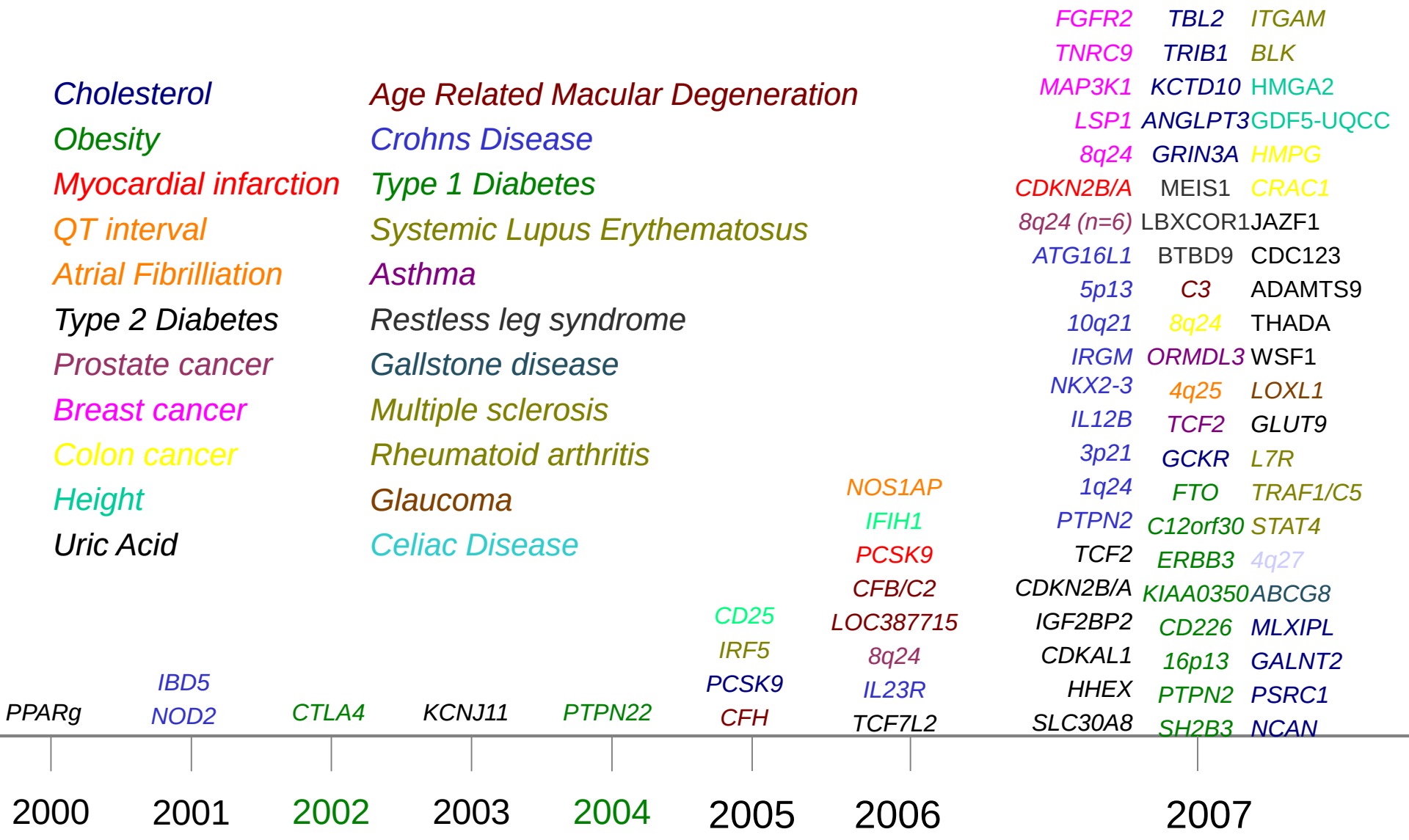
Rare Variant Association Studies (RVAS)



Need:

Technology to sequence
huge sample collections
for full exome or genome

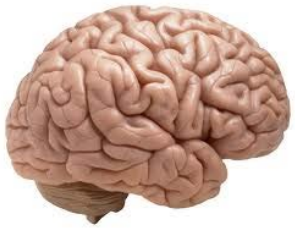
Genetic variants affecting human diseases



Schizophrenia

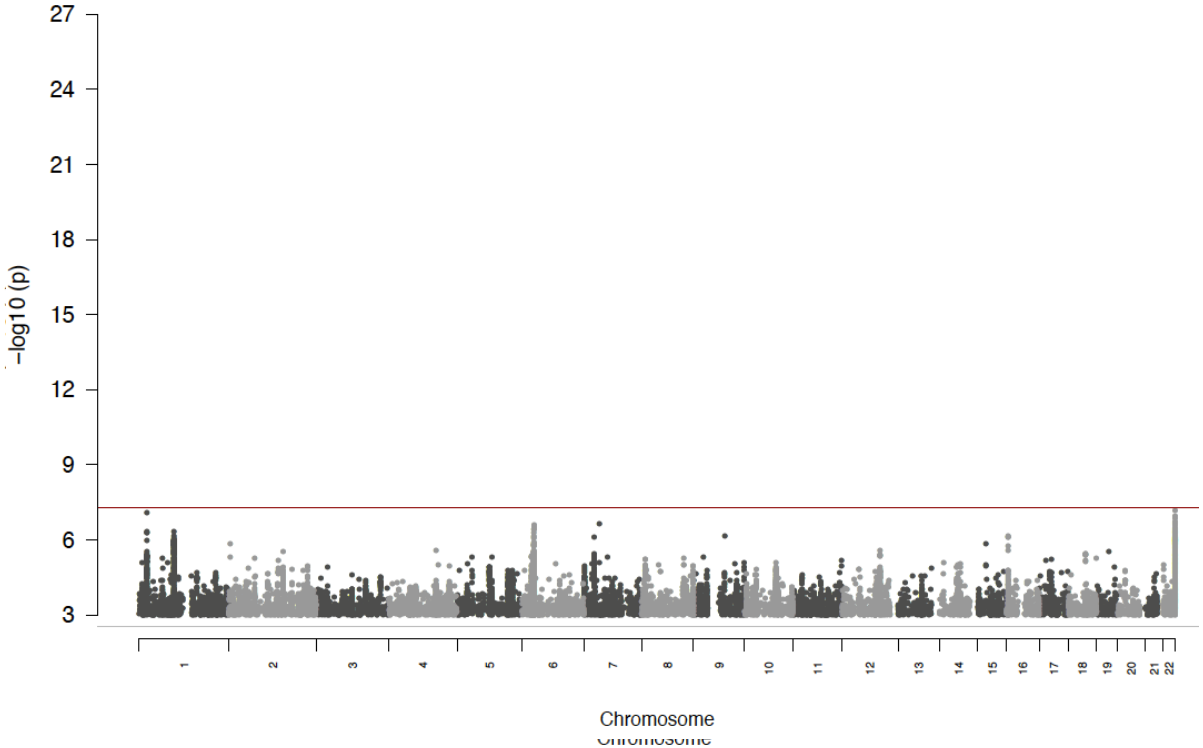


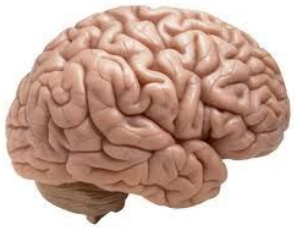
Mark Daly
Steven McCarroll
Beth Stevens



Schizophrenia

6,000 people 0 genes!

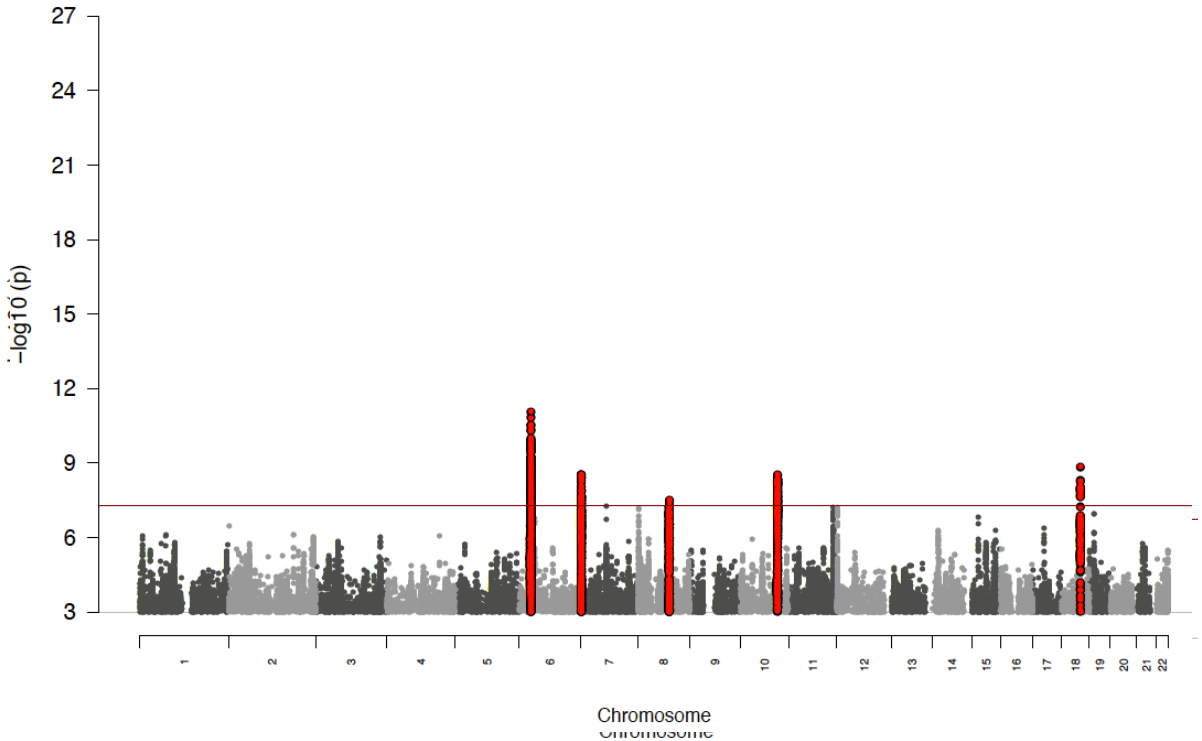


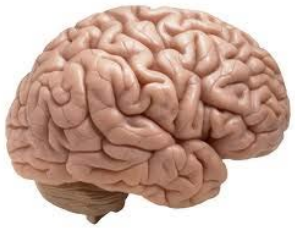


Schizophrenia

20,000 people

5 genes

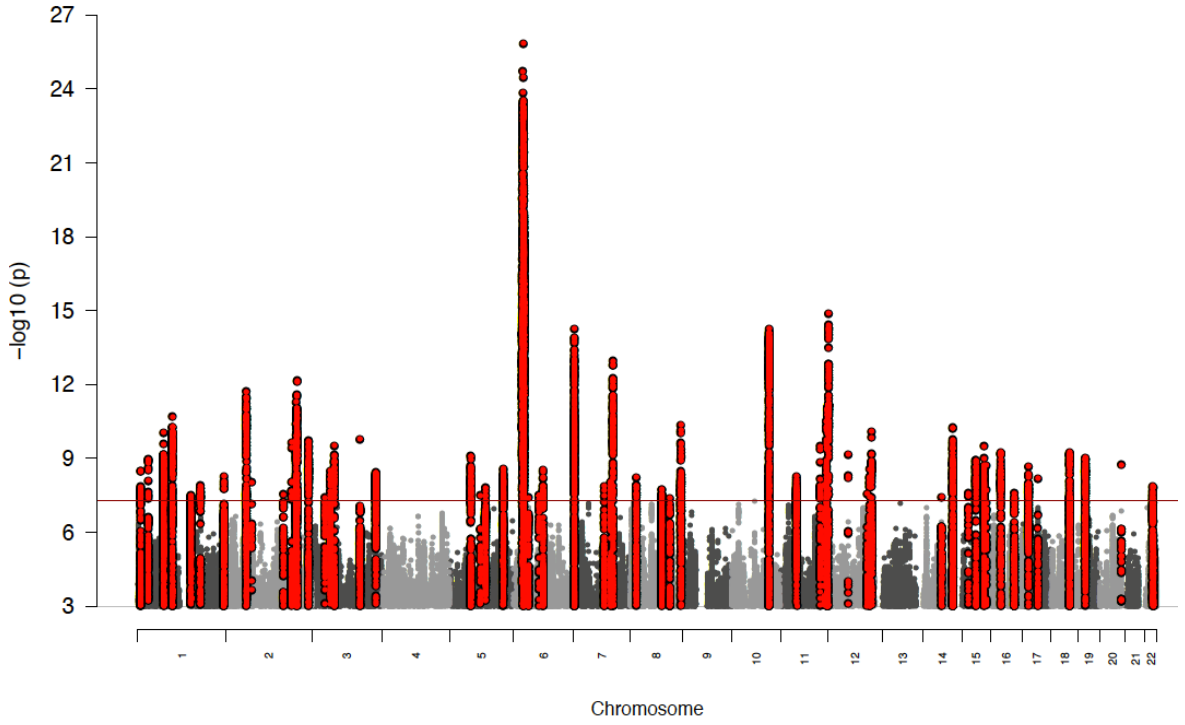


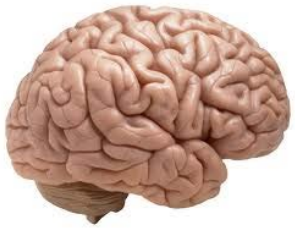


Schizophrenia

50,000 people

62 genes

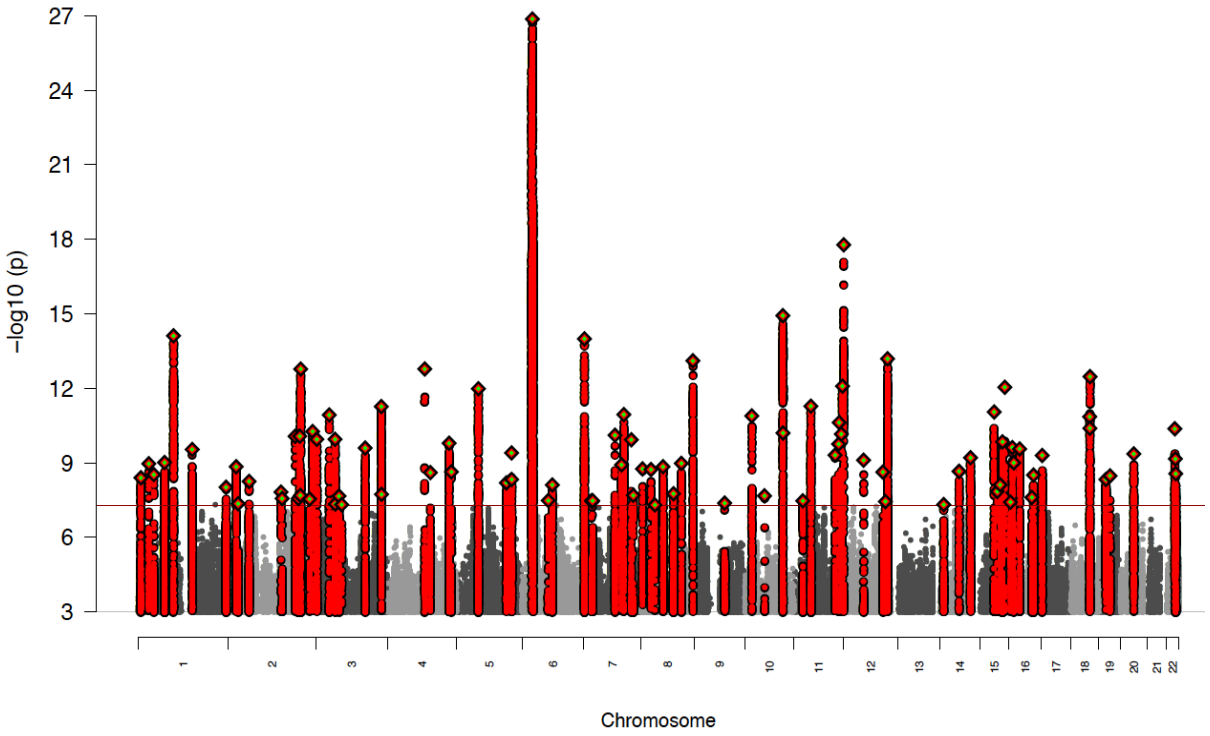


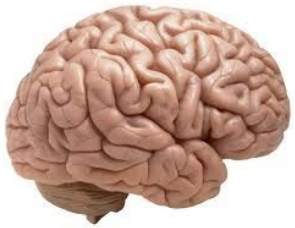


Schizophrenia

110,000 people

108 genes !





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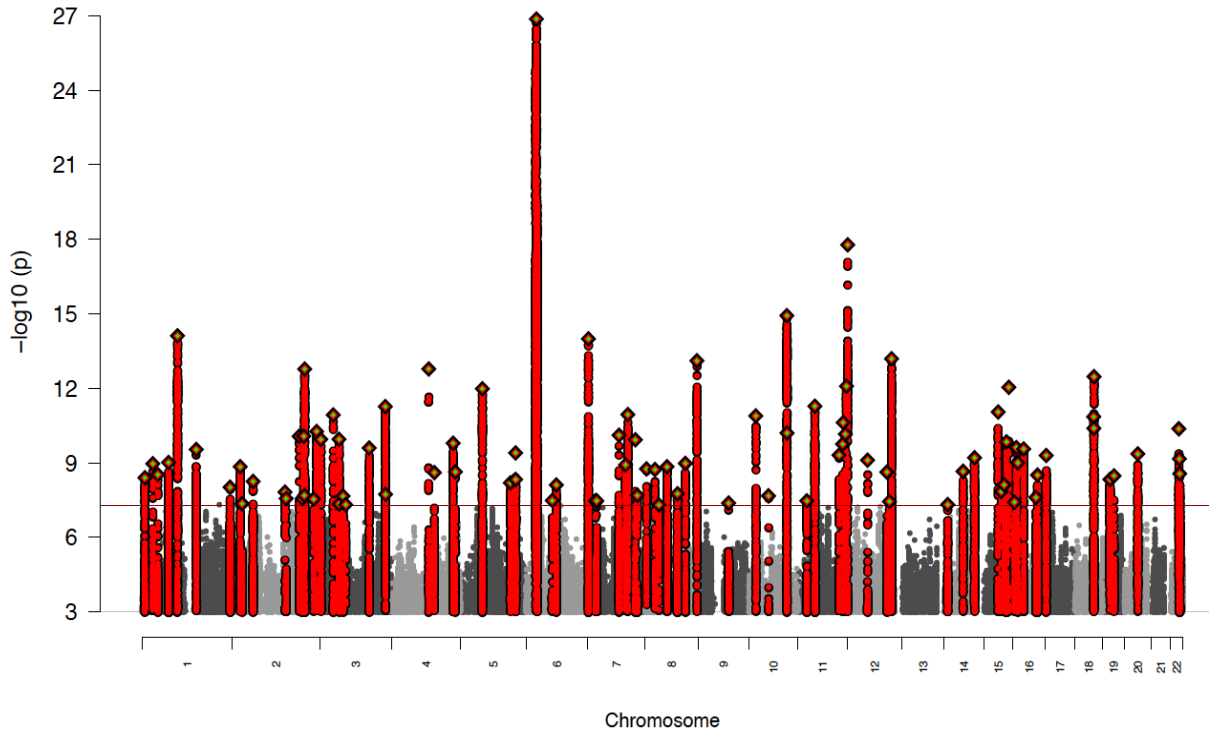
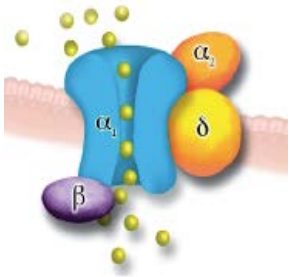
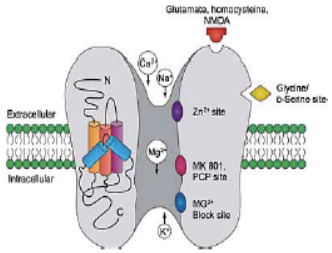


Calcium channels

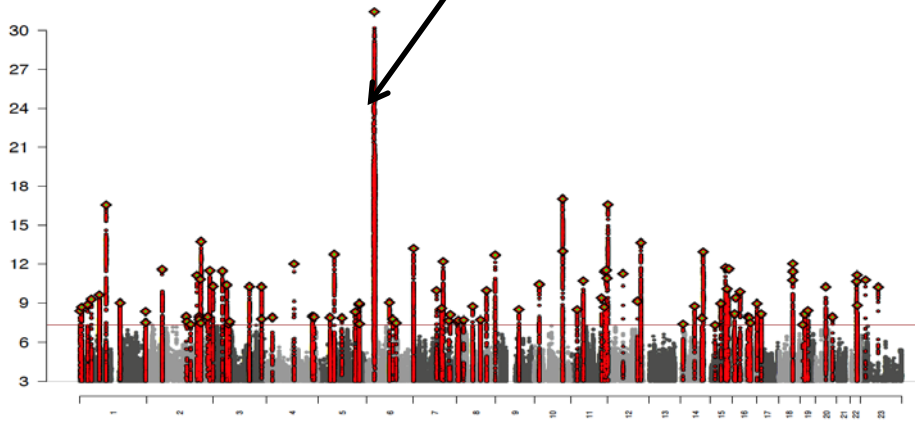


Glutamate signaling

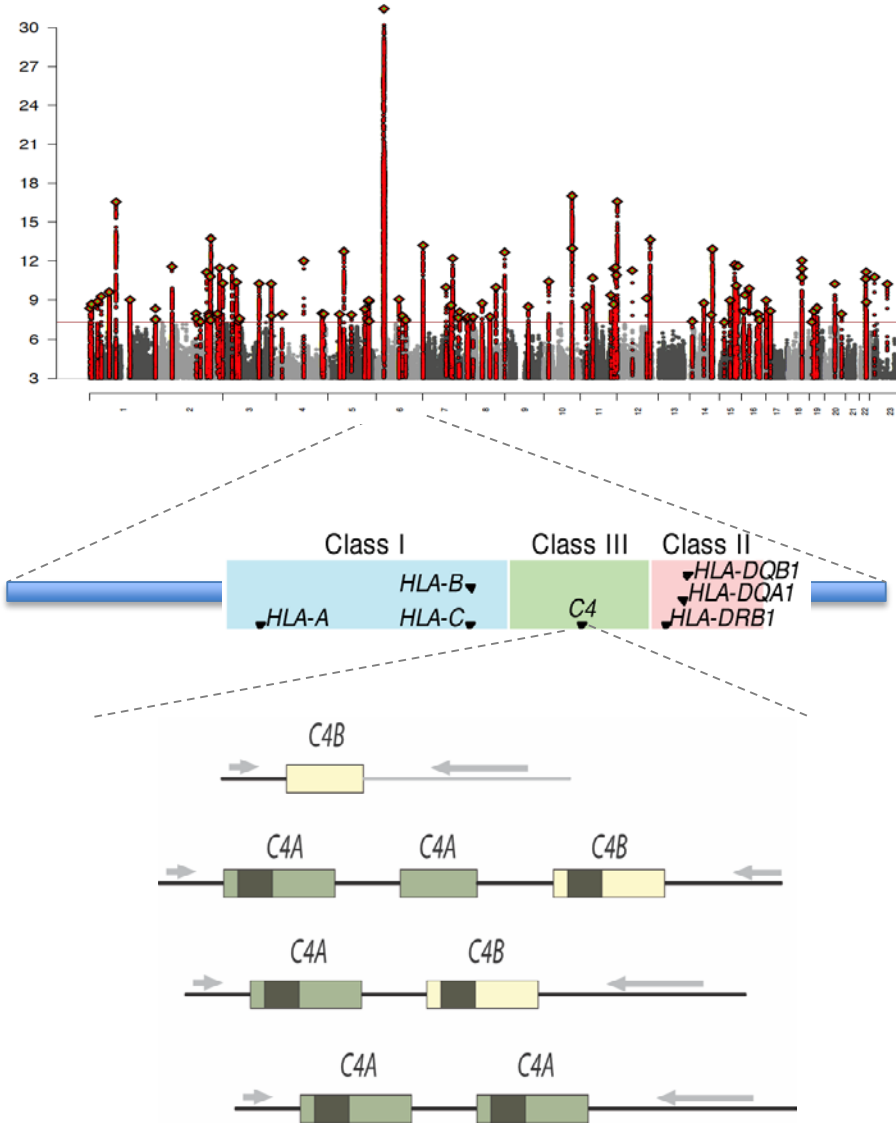


Strongest gene effect is on Chromosome 6

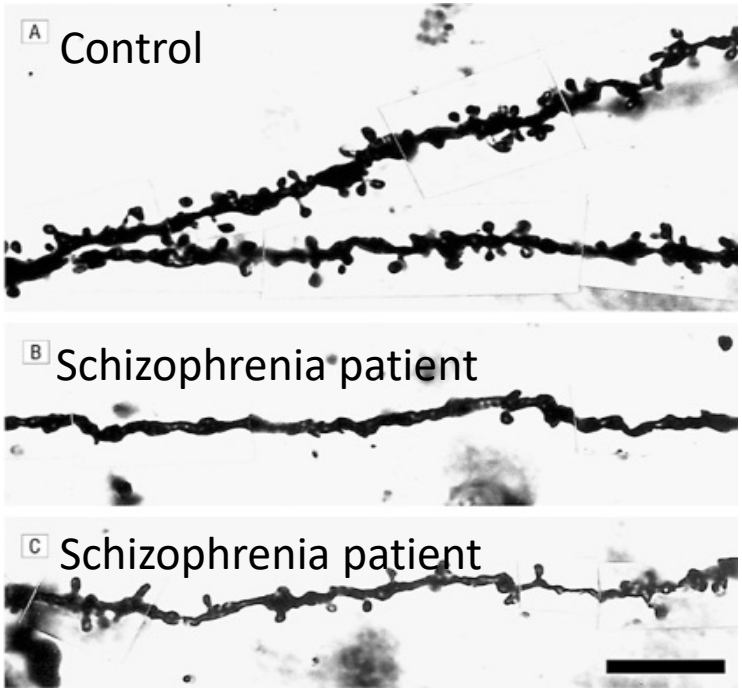
Gene region involved in Immune system ($p<10^{-30}$)



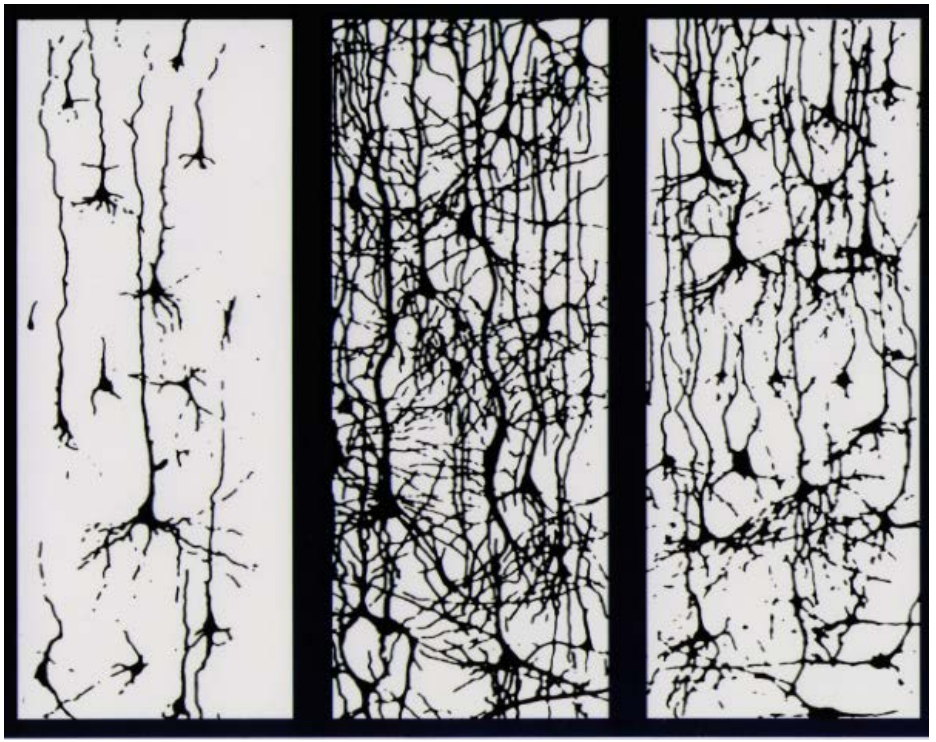
Schizophrenia gene identified: C4



Synaptic pruning in normal development and schizophrenia



Loss of synapses
in brains from
schizophrenic patient



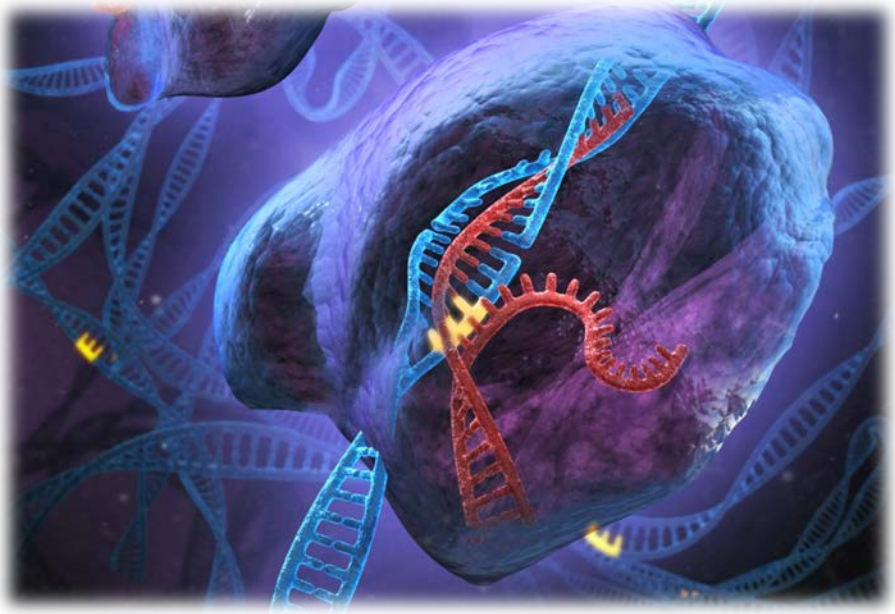
Extensive pruning
in adolescence and early adulthood
(time of schizophrenia onset)

Schizophrenia: A disease of excess synaptic pruning?

Idea:

Can schizophrenia be
treated or prevented
by affecting synaptic pruning?

4. Implications for Germline Editing

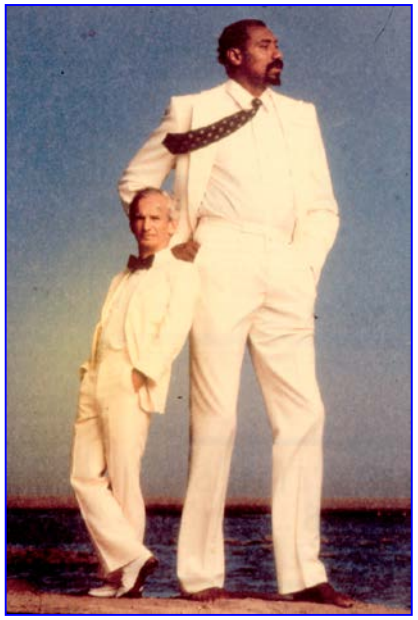


Human Diseases and Traits

Rare, Mendelian

Cystic fibrosis,
Huntington Disease,
…

Avoid all cases of severe genetic disease
Eliminate disease alleles from pop'n

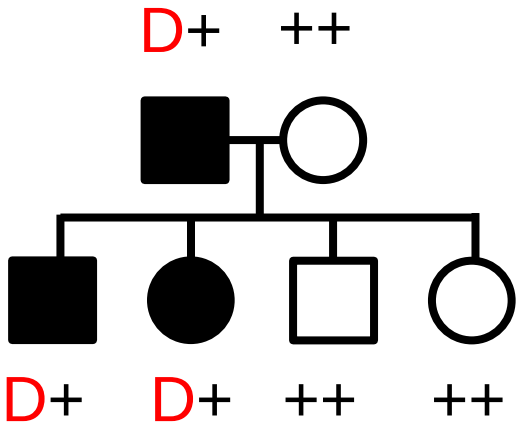


Common, polygenic

Heart disease, Alzheimer's
Schizophrenia, Height, Obesity
Intelligence? . . .

Decrease disease risk
'Enhance' human population

Rare Mendelian Disease: Dominant



Heterozygous parent

Half of offspring affected

Half of offspring *un*affected

Can use pre-implantation diagnostics (PGD

PGD+germline editing adds relatively little*

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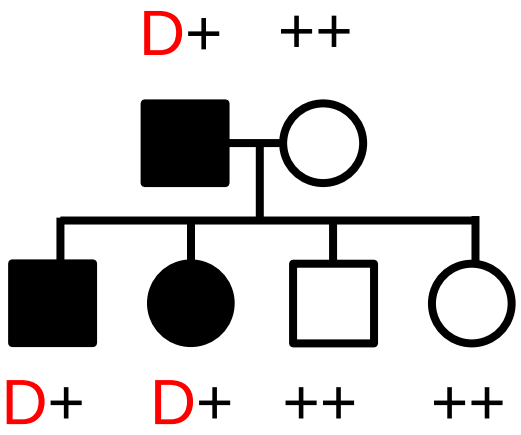

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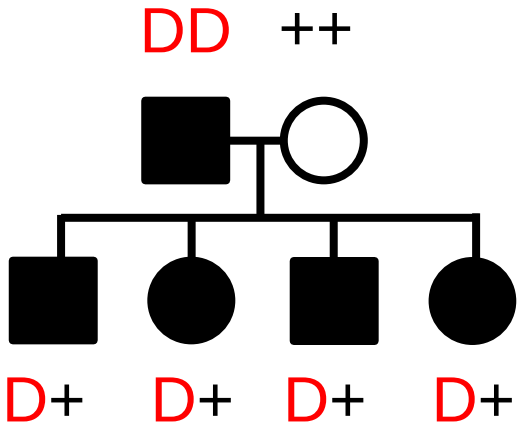


Homozygous parent

All offspring affected

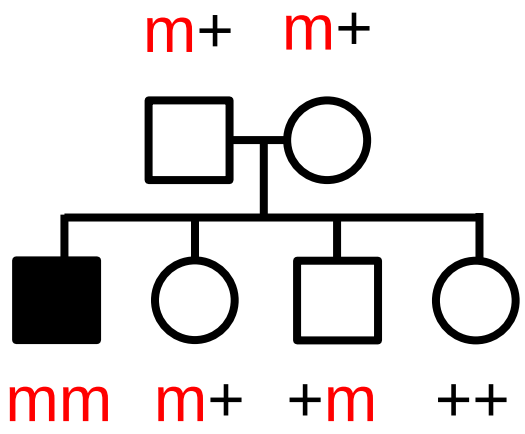
Germline editing would be useful

Homozygotes are extremely rare

For Huntington's disease,

only *dozens* of cases found worldwide

Rare Mendelian Disease: Recessive



Heterozygous unaffected parents

One-quarter of offspring affected

To avoid affected offspring:

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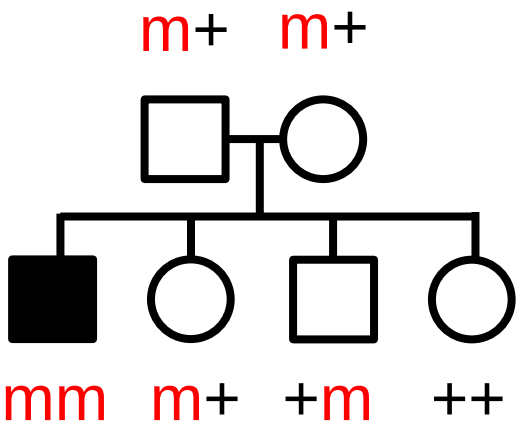
Rare Mendelian Disease: Recessive



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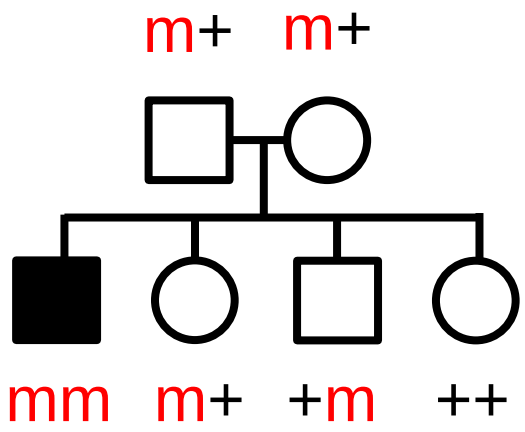
To avoid most cases of devastating genetic diseases, the most important intervention would be ensuring access to genetic testing so carrier couples know they are at risk

To eliminate disease alleles from population, we'd all need to use IVF – since we all carry multiple disease genes in heterozygous state

Rare Mendelian Disease: Recessive



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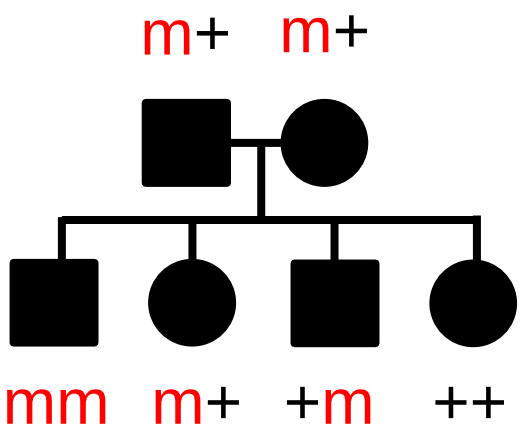


Homozygous parents

All offspring affected

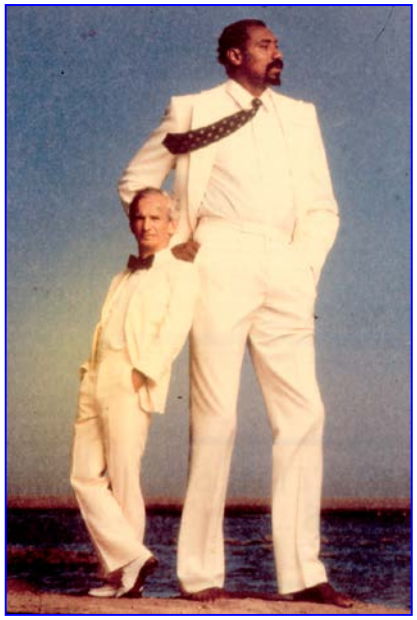
Germline editing would be useful

Very rare, unless brought together by disease

E.g.: Deaf parents with mutations in same gene

Human Diseases and Traits

Rare, Mendelian
Cystic fibrosis,
Huntington Disease,
…



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Heart disease, Alzheimer's
Schizophrenia, Height, Obesity
Intelligence? . . .

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'Enhance' human population

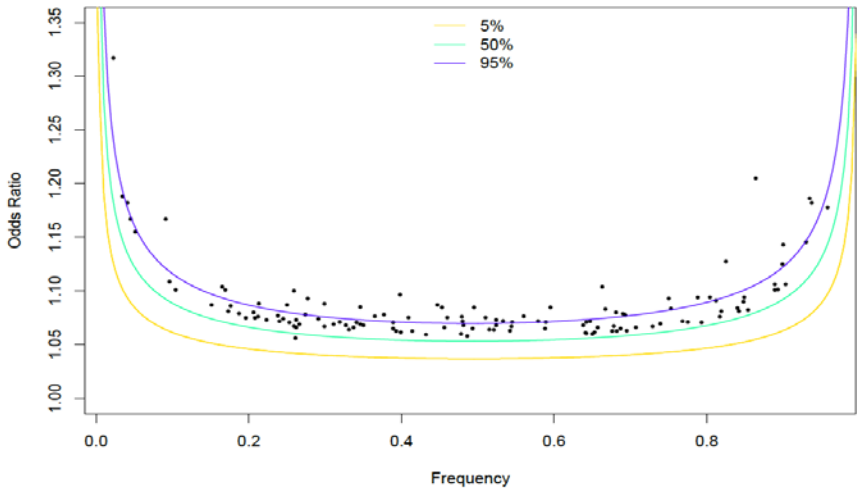
Common, Polygenic Disease

Genetic variants have modest effects

- Handful: 3-5-fold
- 99+%: <1.2-fold

Why?

- Selection keeps strong alleles at low frequency
- Disease processes are buffered



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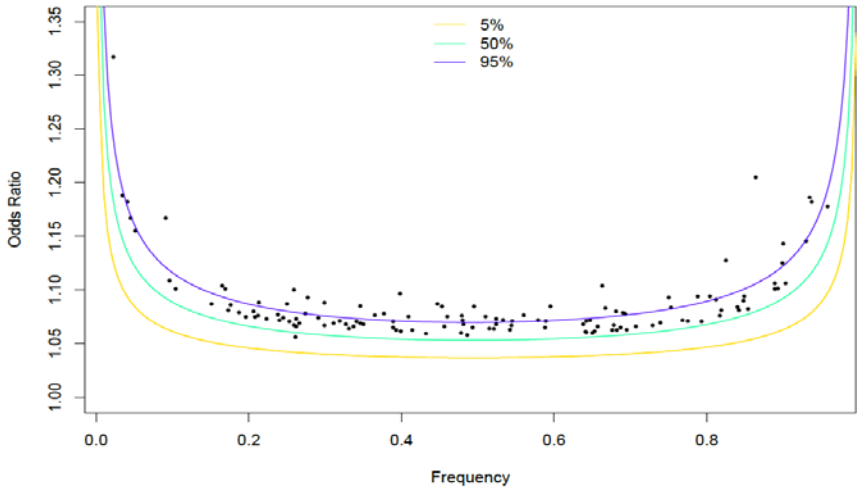

Why?

Selection keeps strong alleles at low frequency

Disease processes are buffered

<u>Schizophrenia</u>

Population 1% risk

C4 gene 1.1% risk

Polygenic risk score

- Top 100 loci (statistically significant) Top decile: ~3% risk
- Top 10,000 loci (only a fraction significant) Top decile: ~10% risk

Common, Polygenic Disease

Is there a free lunch?

Genetic variants have ‘pleiotropic’ effects

and environmental interactions

Inflammatory bowel disease

	Lower risk of:	Higher risk of:
FUT2	Norovirus	Crohn's & Type 1 diabetes
IFIH1	Type 1 diabetes	Crohn's disease
RNF186	Ulcerative colitis	Chronic kidney disease

Viral infection

	Lower risk of:	Higher risk of:
CCR5	HIV	West Nile (13x higher risk for fatal cases)

Common, Polygenic Disease: Germline editing

Avoid deleterious variants?

- Most have very small effects
- Those with large effects usually rare: treat like Mendelian

Bestow protective variants with *large* effects?

- Very few examples overall
- Moreover, want common (to assess impact in homozygotes)
  - ideally, with **no downsides** (undesired pleiotropic effects)

Common, Polygenic Disease: Germline editing

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Best candidates:

- ApoE2, 3 vs. ApoE4 (3%) Higher Alzheimer's risk
- PCSK9 null (<2%) Lower LDL levels, heart attack risk

Common, Polygenic Disease: Germline editing

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Currently, very few such examples

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Best candidates:

- ApoE2, 3 vs. ApoE4 (3%) Higher Alzheimer's risk
- PCSK9 null (<2%) Lower LDL levels, heart attack risk

Still, we have incomplete knowledge about pleiotropic effects

If alleles are so good, why aren't they at higher frequency?

Summary and Conclusion

Rare, Mendelian diseases

- Vast majority of cases can be addressed by IVF and PGD
- Some cases of compelling need, although rare
- If we wish to avoid devastating genetic diseases, most important intervention is ensuring couples have access to genetic testing to know they are at risk

Common, Polygenic diseases

- Thousands of genes being identified
  — revealing disease processes, pointing to therapeutic hypotheses
- For vast majority of variants, impact on risk is small
- Currently, *at most* a few plausible variants for editing

Conclusion

- Genetic basis of human disease is complex
- We still have a lot to learn
- Before making permanent changes to the human gene pool, we should use great caution

Breakout Sessions

List of Breakout Sessions is in your program

The same five sessions will be held on Tues and Wed

Room sizes vary—equilibrate

Staff (green badges) will be outside auditorium to direct you to rooms

Breakout sessions will end at 7pm

Reception to follow in Great Hall