An introduction to discovering genomic variation... Genome Wide Association Studies (GWAS)

Jeff Barrett

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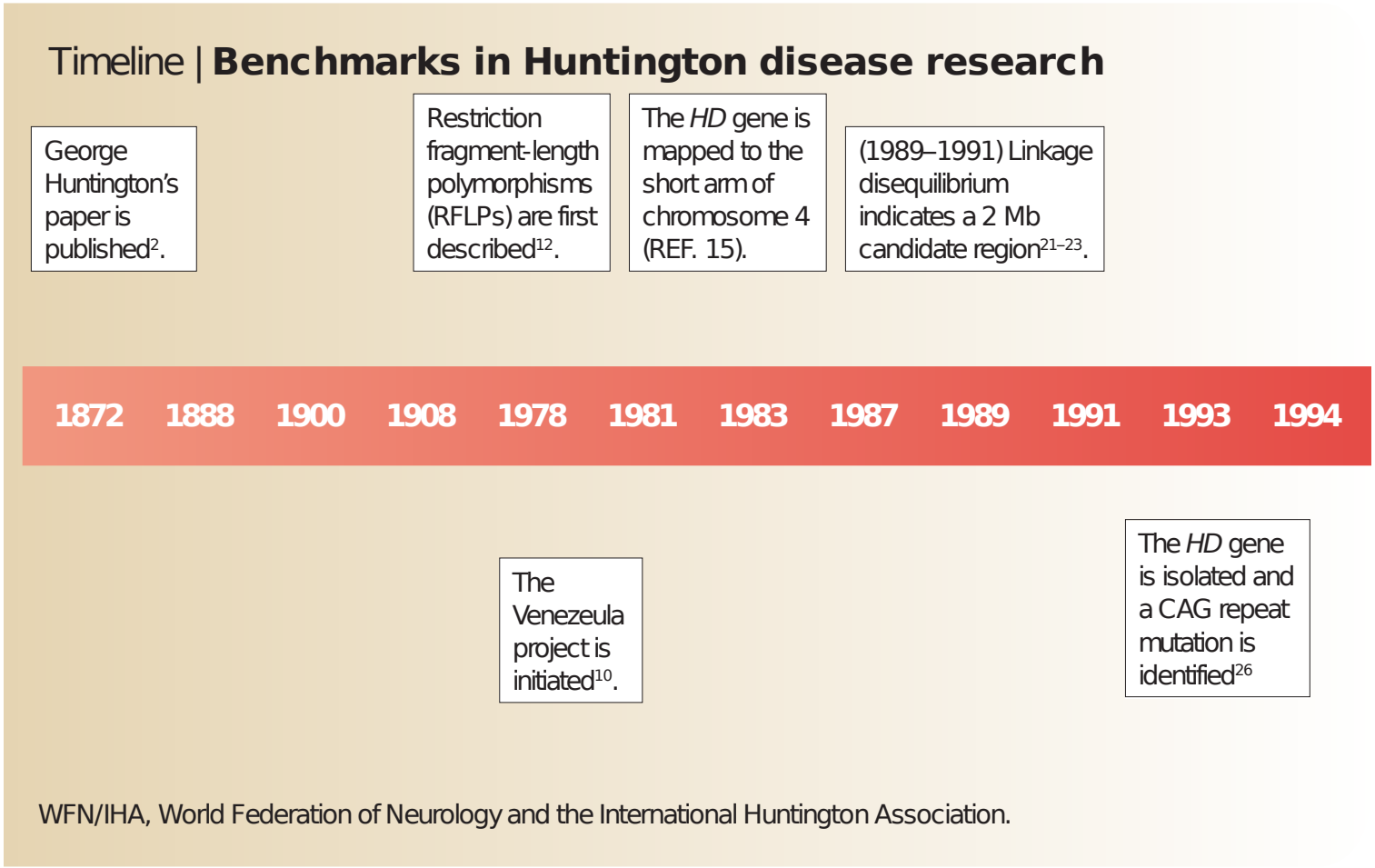
October 19, 2010

Early Mendelian gene mapping: *HD*



Mapping *HD* needed collaboration

Cell, Vol. 72, 971–983, March 26, 1993, Copyright © 1993 by Cell Press

A Novel Gene Containing a Trinucleotide Repeat That Is Expanded and Unstable on Huntington's Disease Chromosomes

The Huntington's Disease Collaborative Research Group*

***The Huntington's Disease Collaborative Research Group comprises:**

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†*Correspondence should be addressed to James F. Gusella.*

Introduction

“Figure 4”

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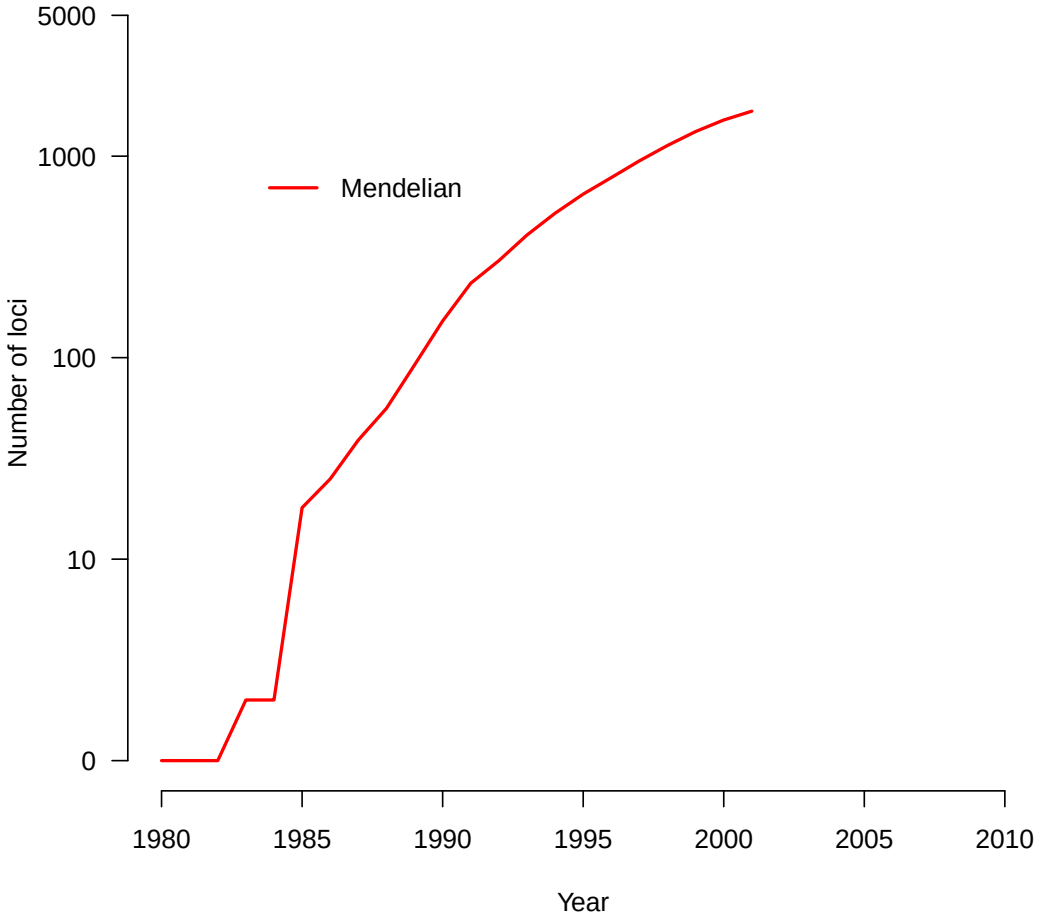
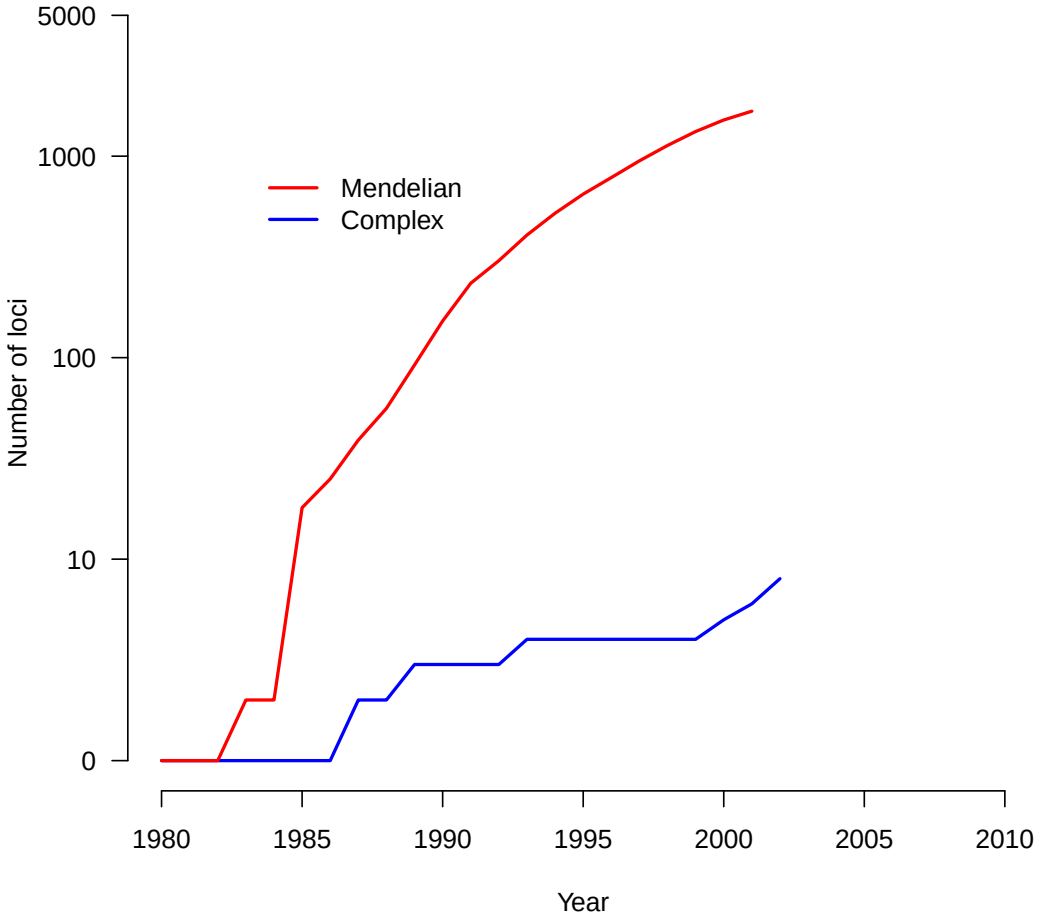
Mendelian gene mapping accelerated rapidly...



Adapted from Glazier *et al. Science.* 2002.

. . . but this success did not translate to complex disease



Adapted from Glazier *et al. Science.* 2002.

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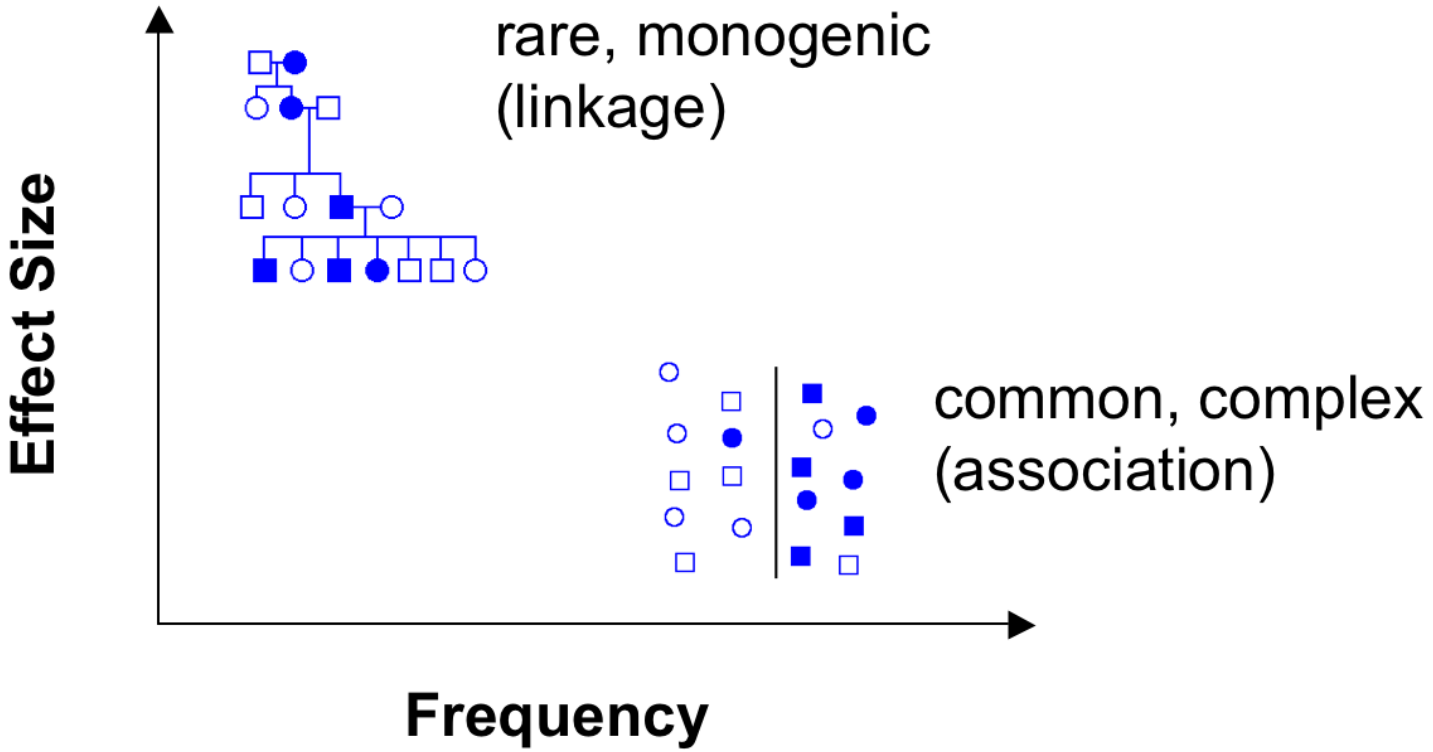
Different diseases need different methods of gene hunting



Obstacles to genome-wide association studies

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- Complete sequence of the human genome, followed by an extensive catalogue of common variation (especially SNPs) between individuals (no need to guess at functionally relevant genes).

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- An inexpensive and accurate means of genotyping hundreds of thousands of SNPs (practical implementation of possibilities above).
- Large collections of thousands of disease cases and healthy controls (to ensure power to find very weak effects).

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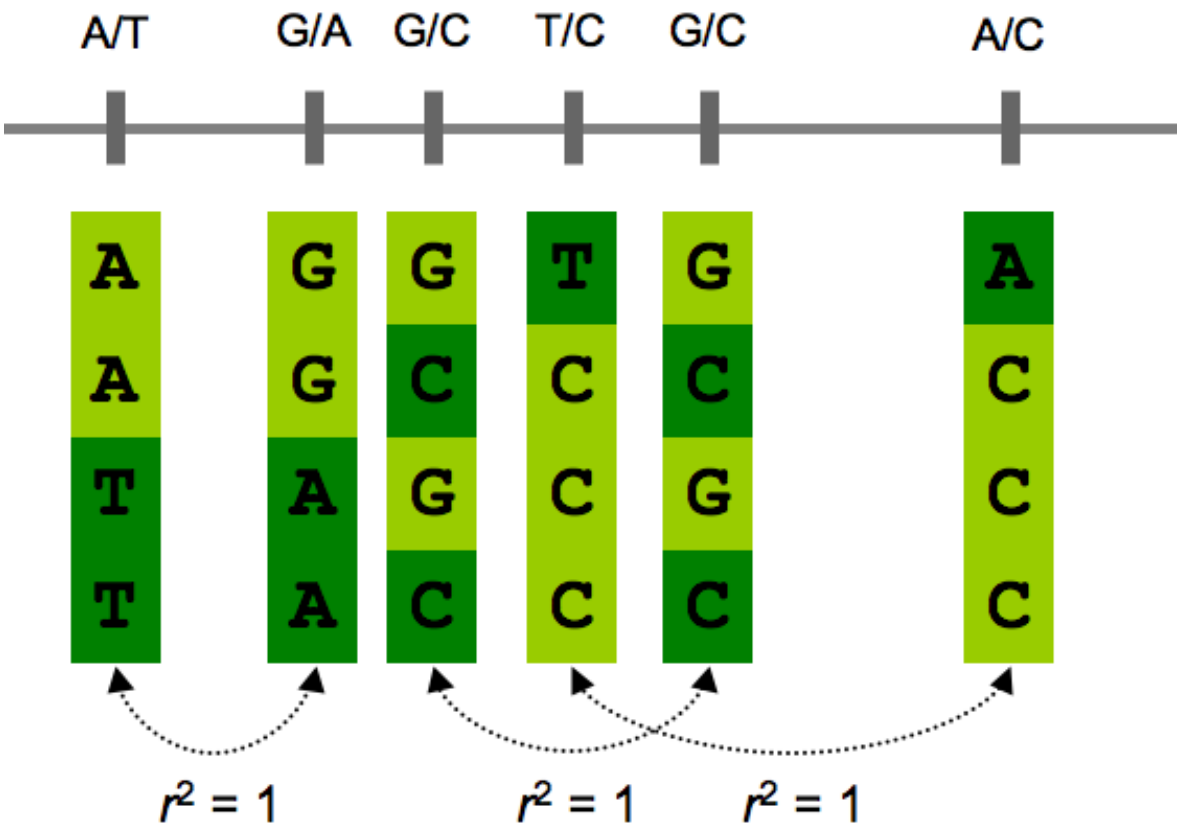
‘Tagging’ gains efficiency via LD



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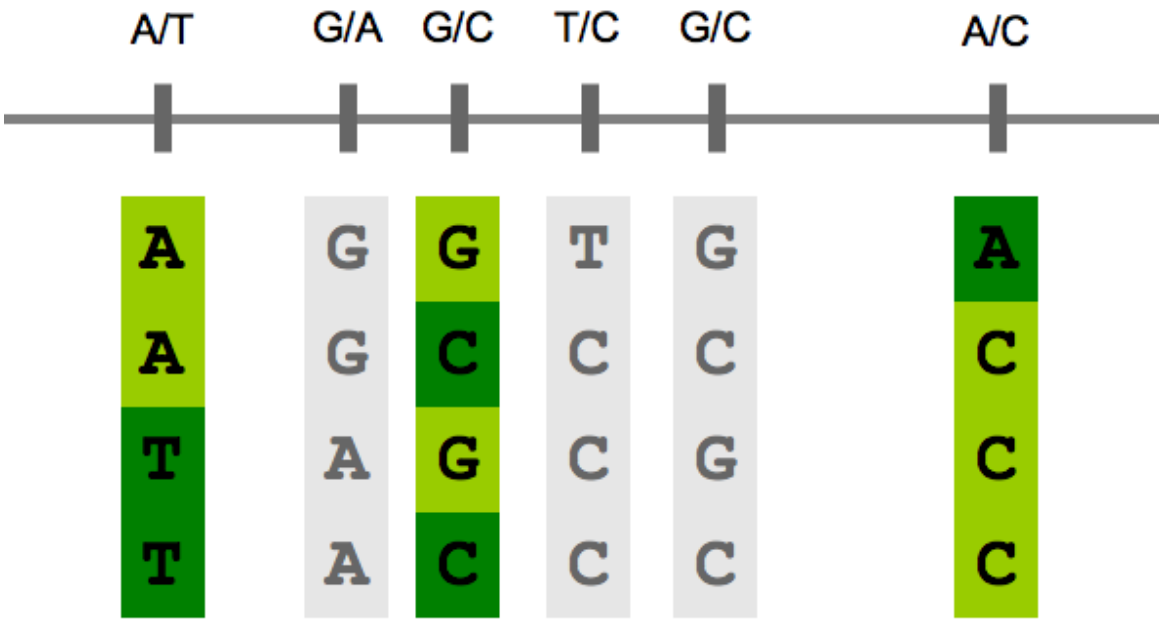

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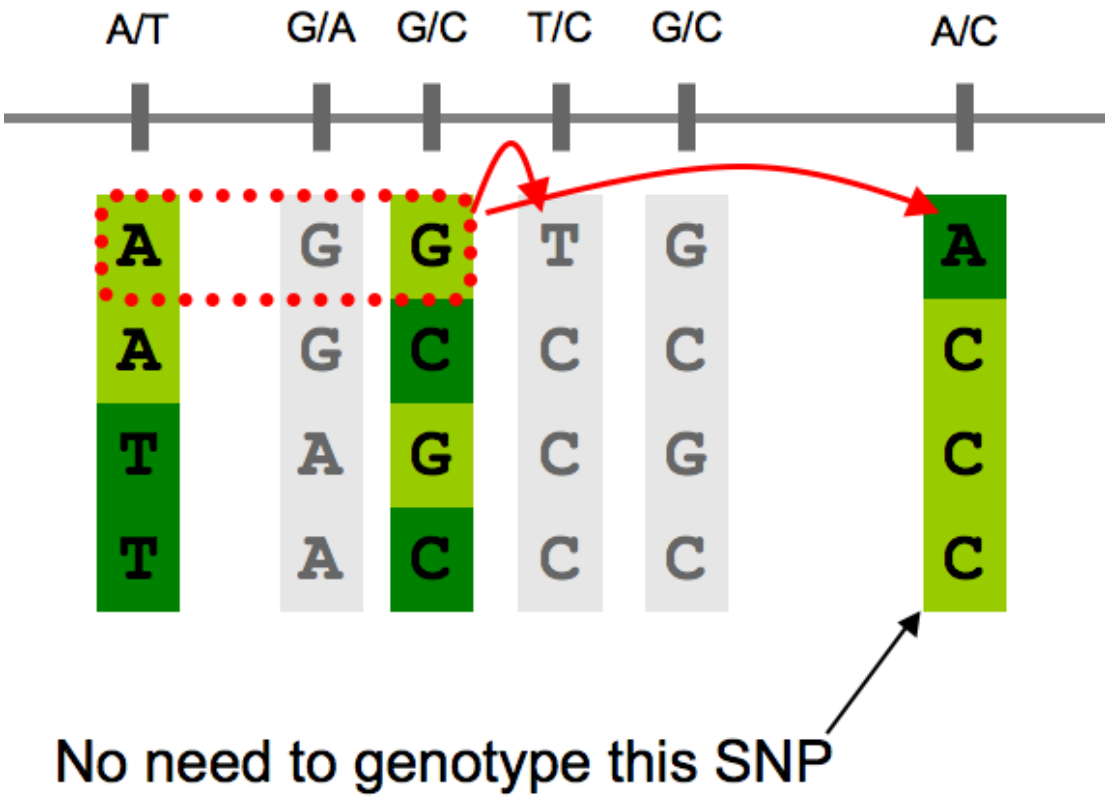
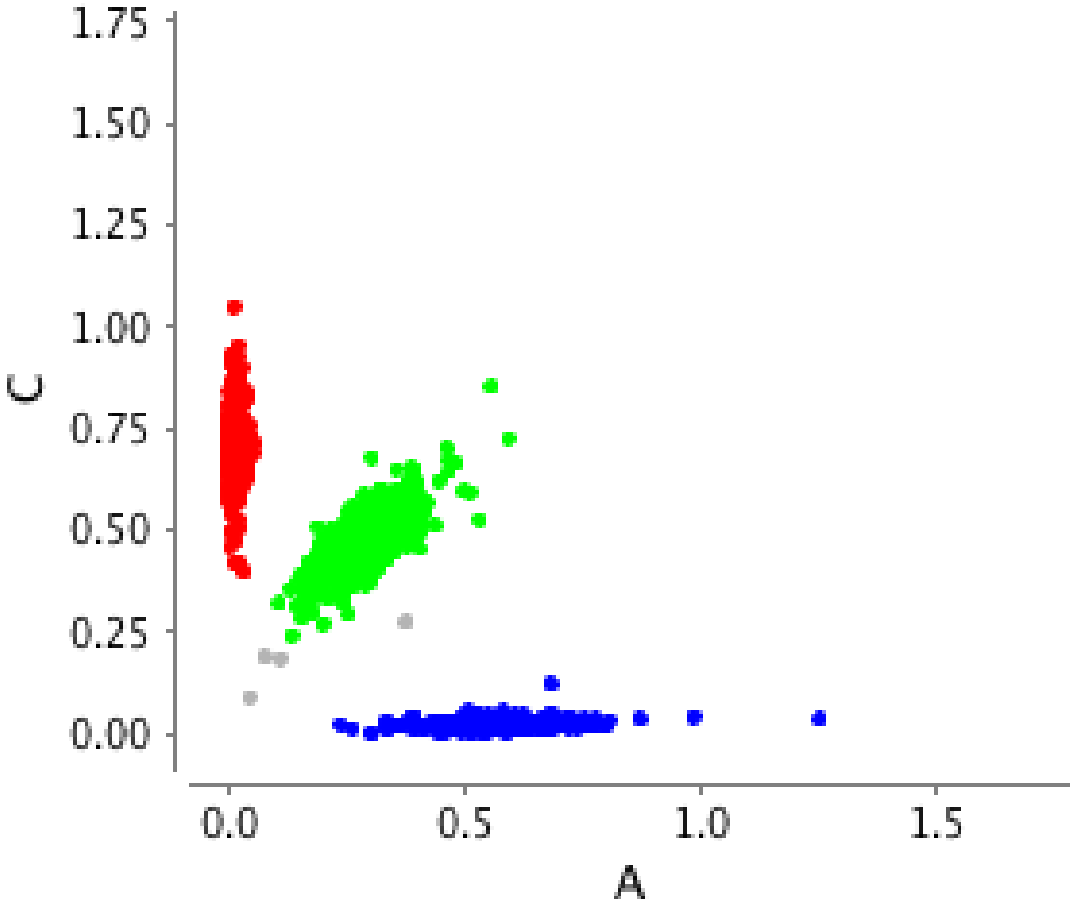


From intensity measurements to genotypes



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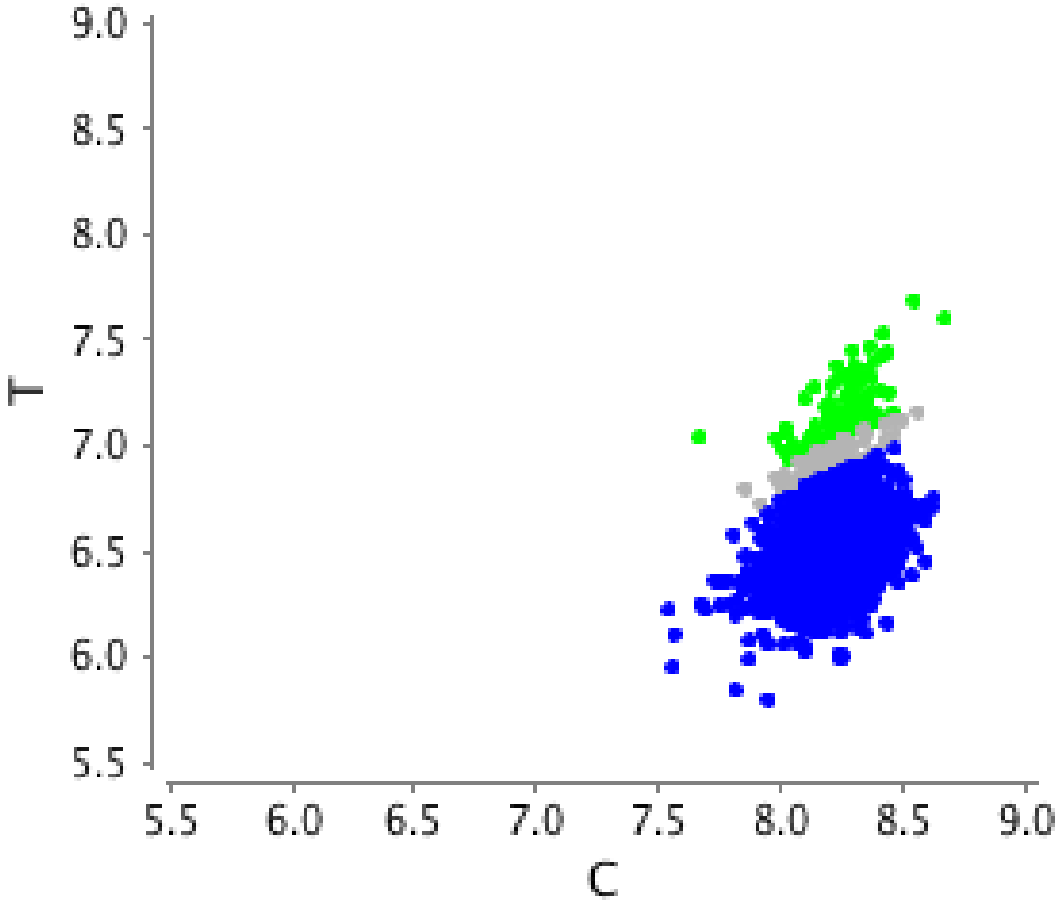

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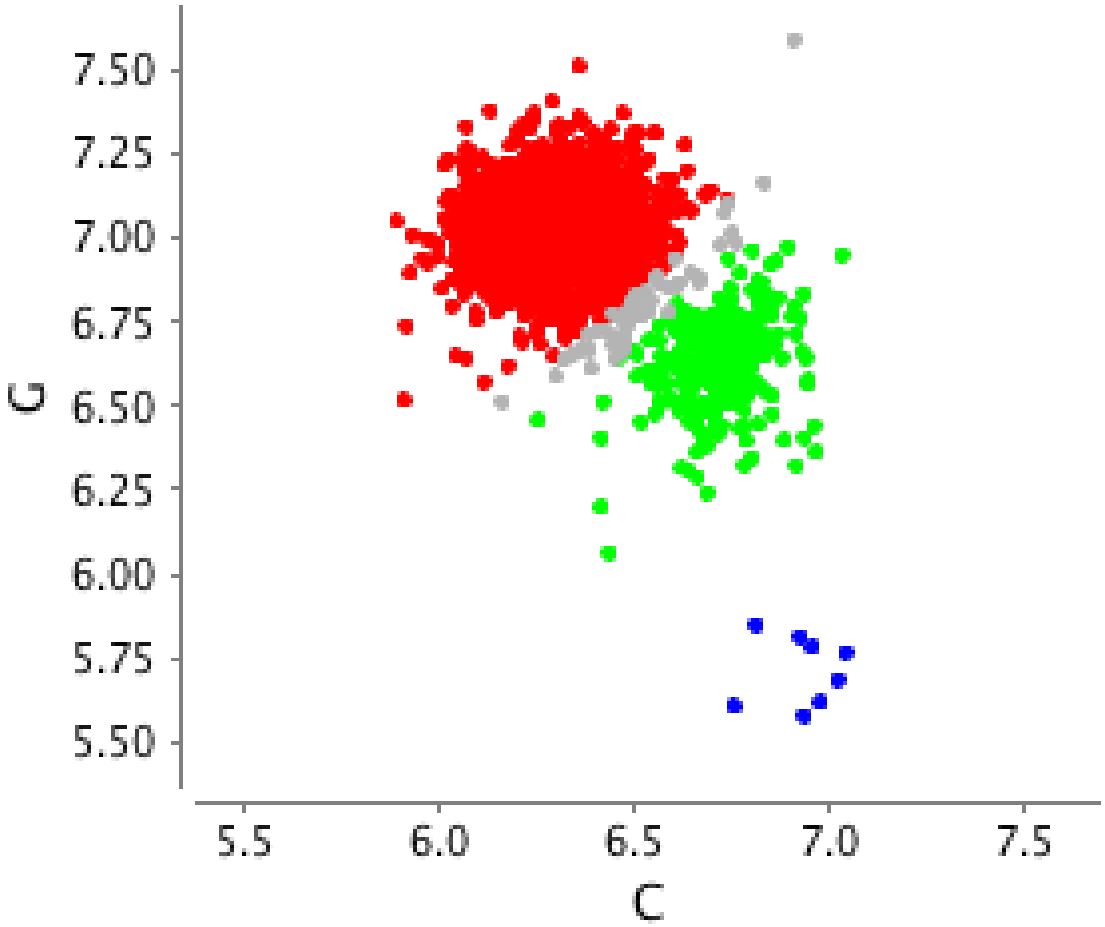

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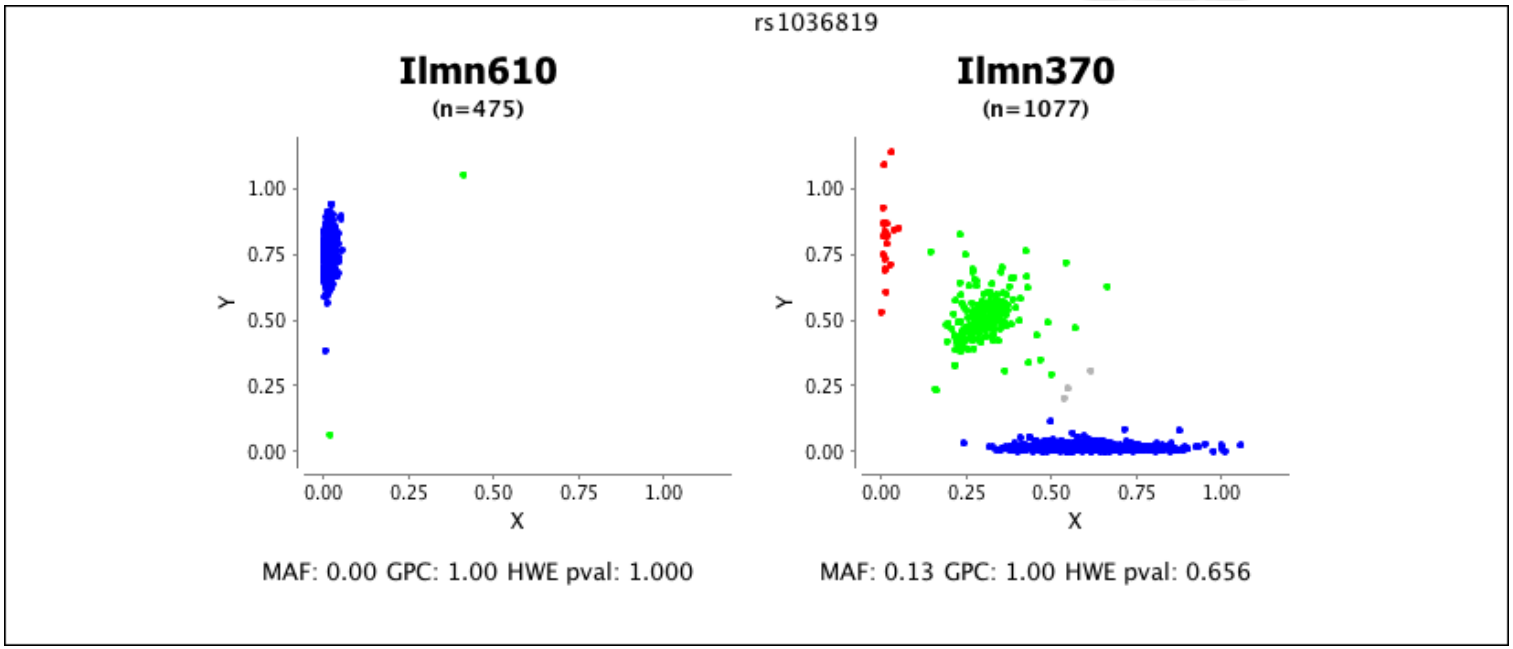
Clean data matters!

Sciencexpress Report

Genetic Signatures of Exceptional Longevity in Humans

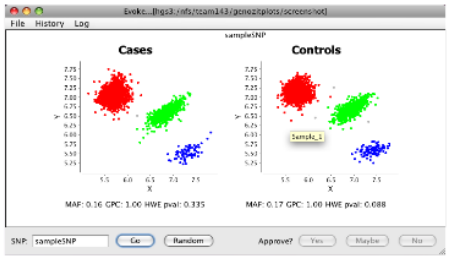
Paola Sebastiani,[1]* Nadia Solovieff,[1] Annibale Puca,[2] Stephen W. Hartley,[1] Efthymia Melista,[3] Stacy Andersen,[4] Daniel A. Dworkis,[3] Jemma B. Wilk,[5] Richard H. Myers,[5] Martin H. Steinberg,[6] Monty Montano,[3] Clinton T. Baldwin,[6,7] Thomas T. Perls[4]*



Genome wide association studies

A

B



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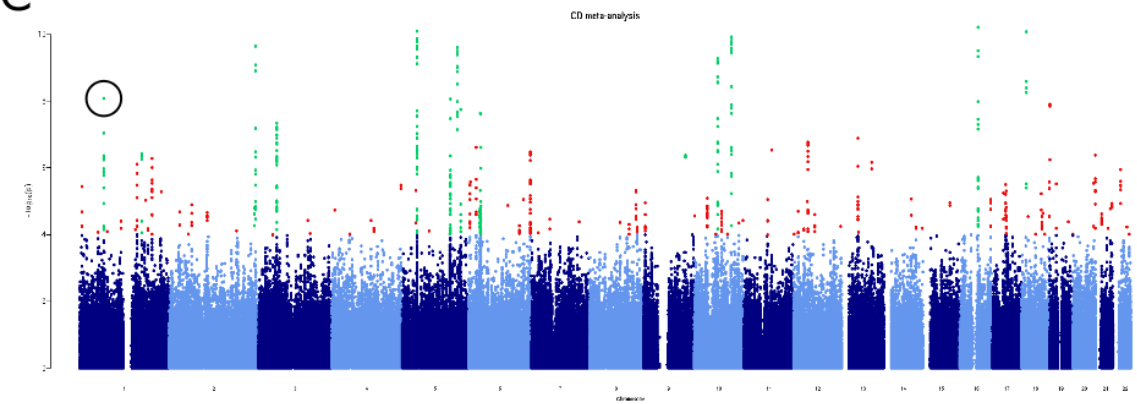

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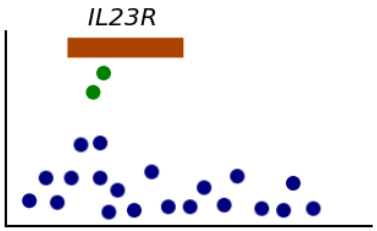
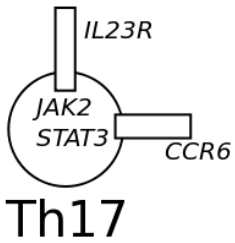


E



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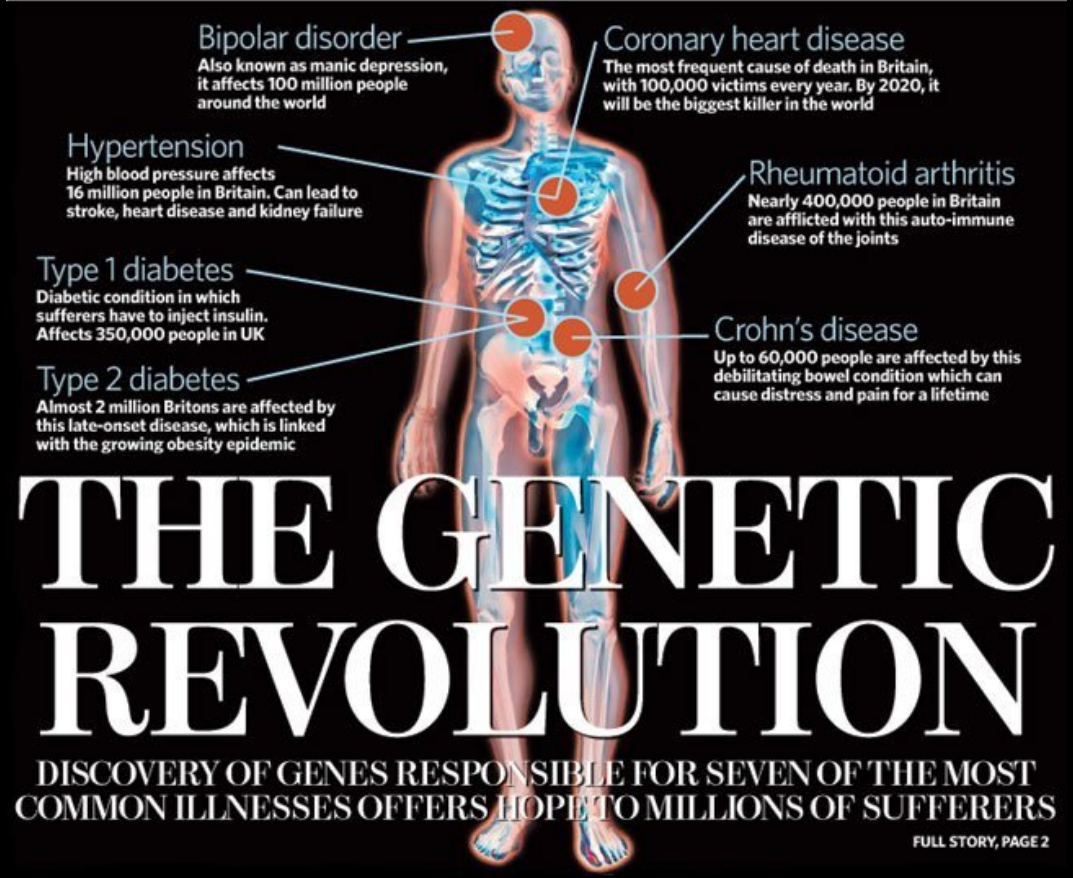
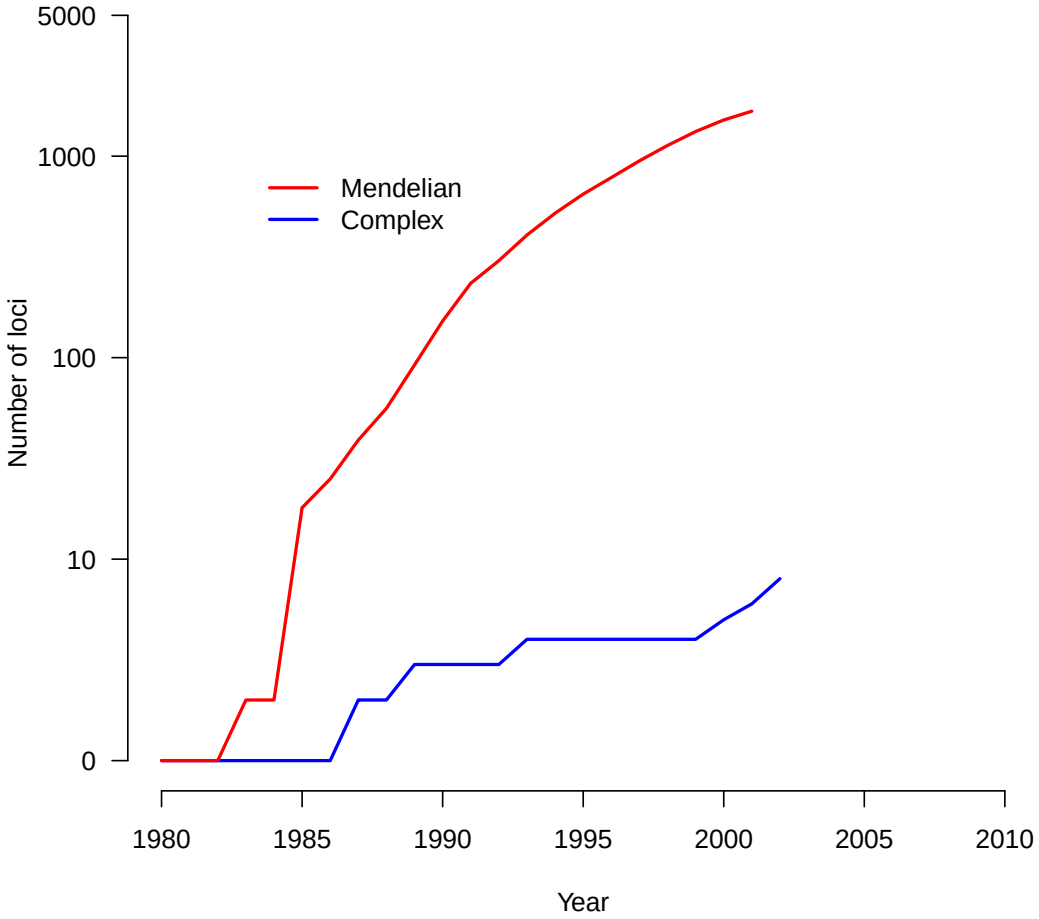


THE GENETIC REVOLUTION

DISCOVERY OF GENES RESPONSIBLE FOR SEVEN OF THE MOST COMMON ILLNESSES OFFERS HOPE TO MILLIONS OF SUFFERERS

FULL STORY, PAGE 2

GWAS revolutionized complex disease genetics



Adapted from Glazier *et al. Science.* 2002, and NHGRI GWAS catalog.

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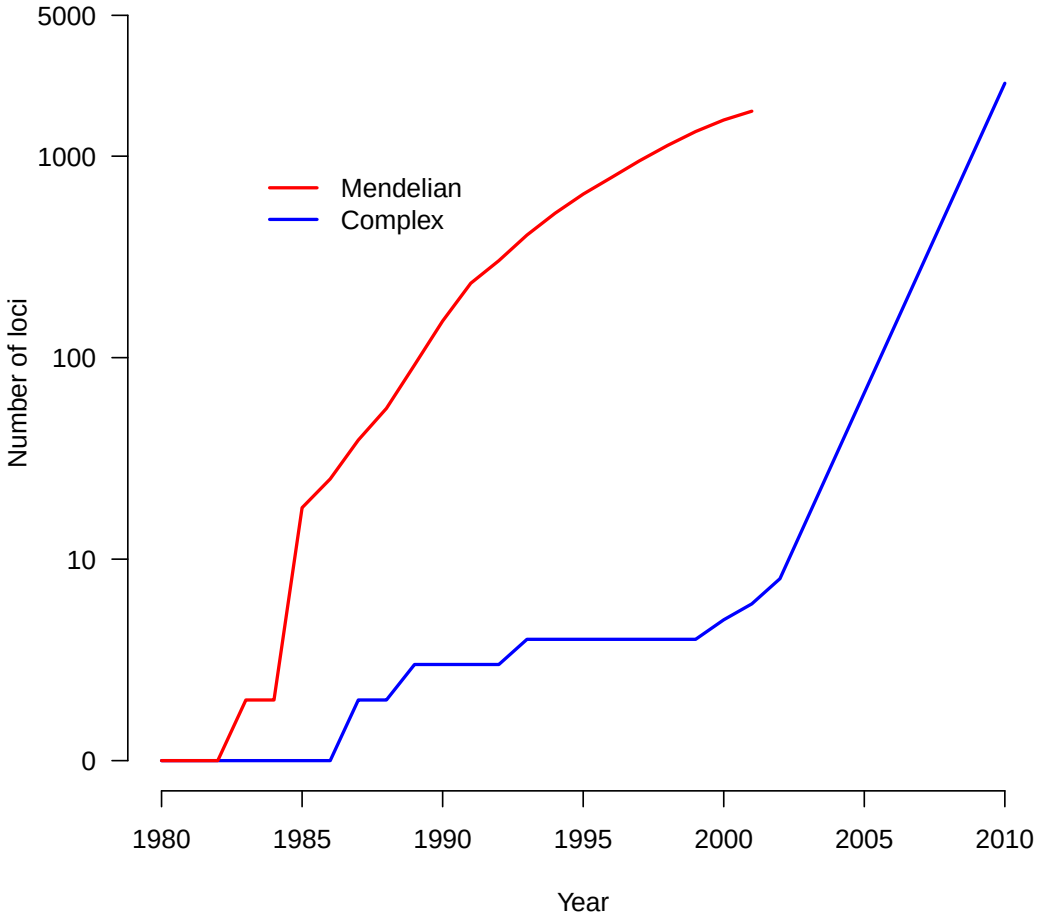

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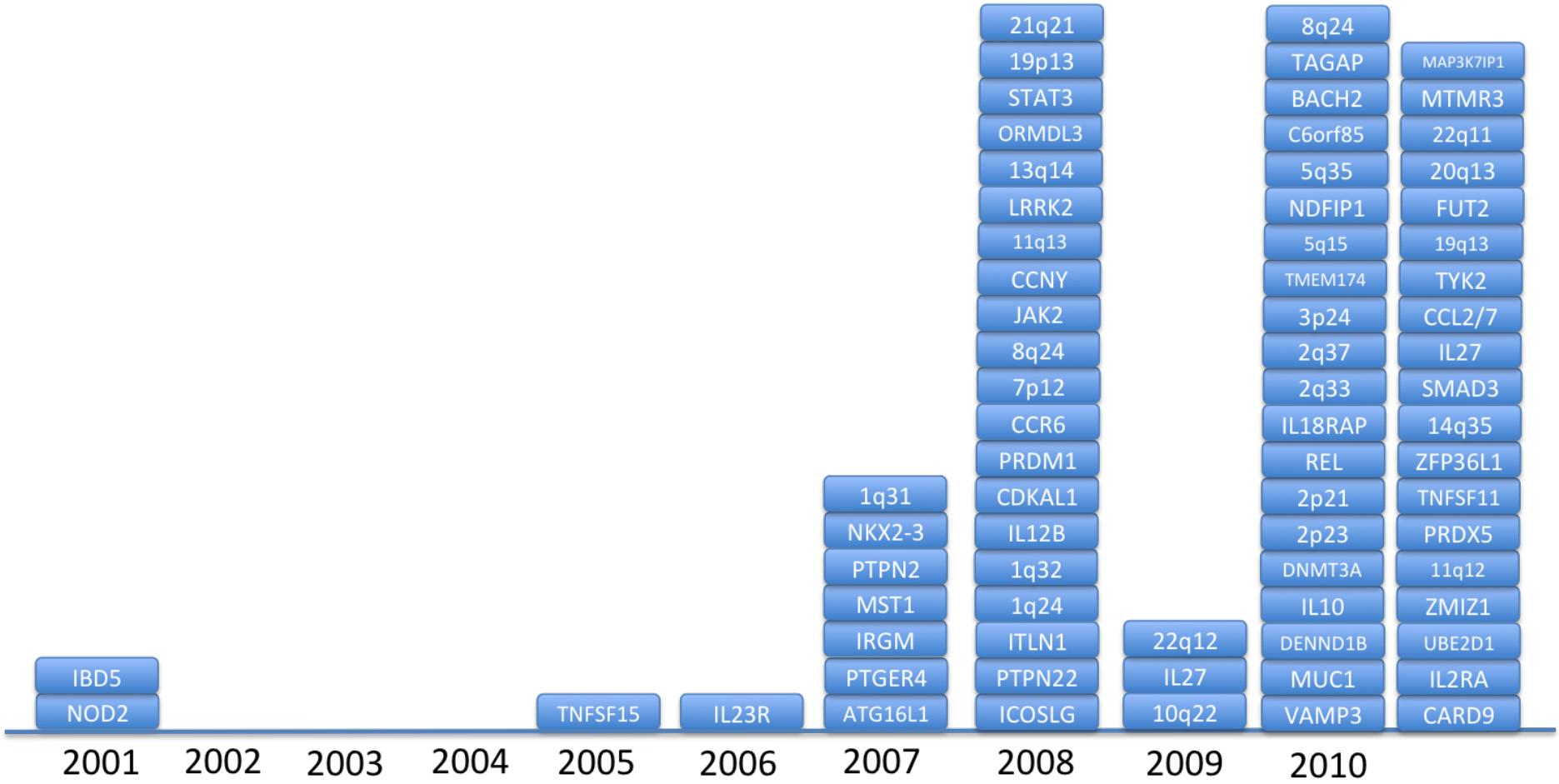
GWAS of Crohn's disease have been very successful

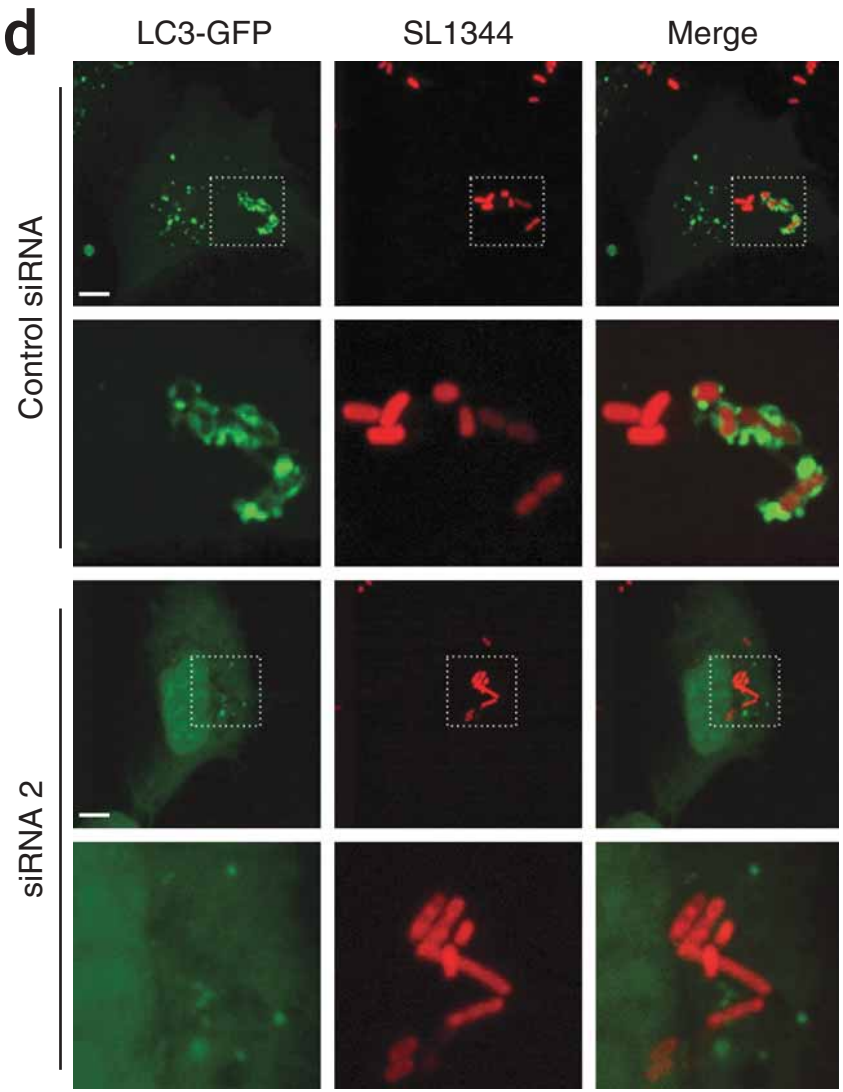


Disease genetics has two parallel goals

1. Understanding disease biology

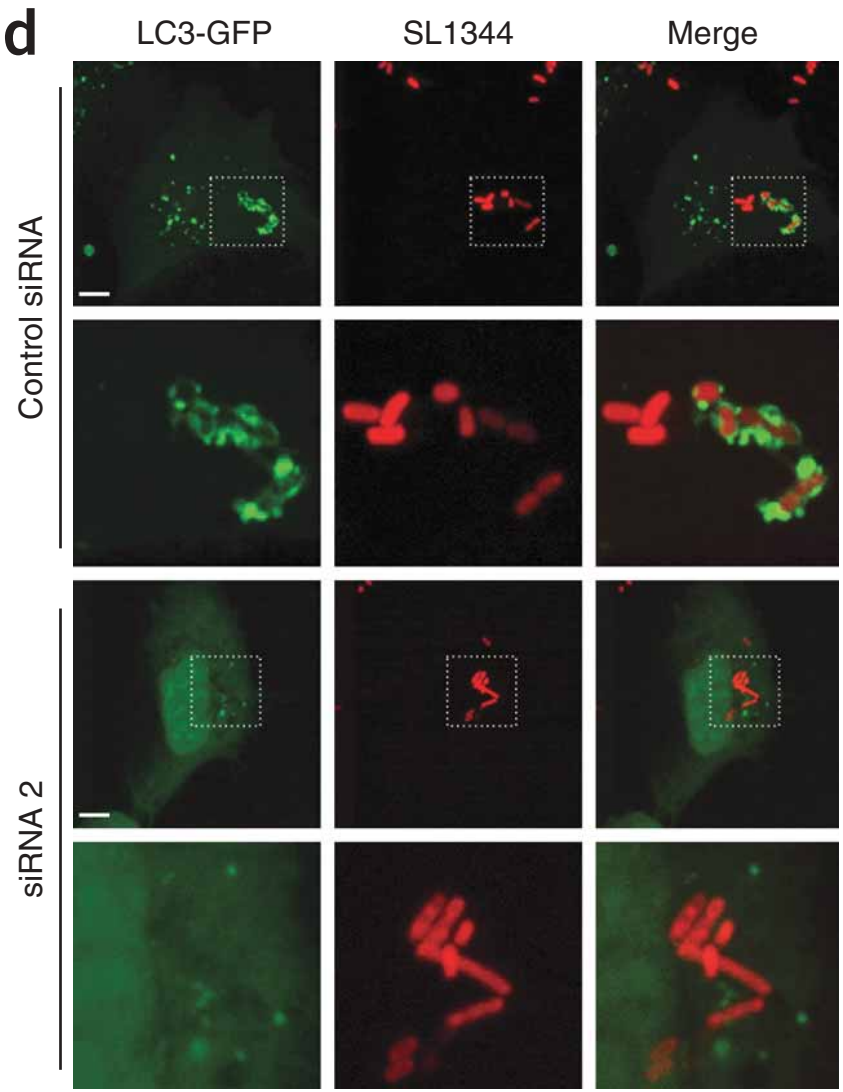
2. Predicting disease risk/outcome

Crohn's disease and autophagy



Rioux *et al. Nat Genet.* 2007.

Crohn's disease and autophagy



- Publications on autophagy and Crohn's before Hampe *et al.*: 0
- Pubs in subsequent three years: 92

Rioux *et al. Nat Genet.* 2007.

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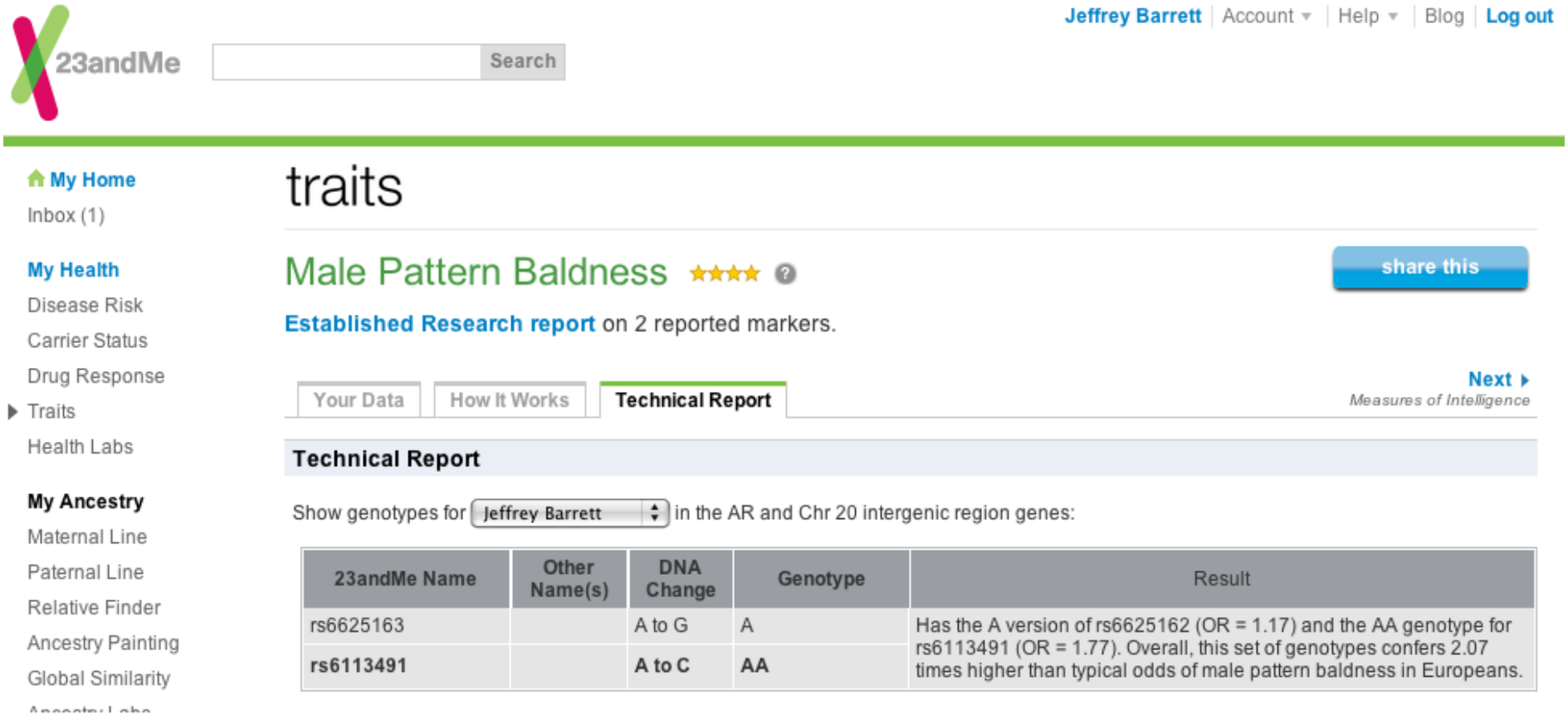
Can genes predict disease?



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UK10K: GWAS 2.0

UK 10K

RARE GENETIC VARIANTS IN HEALTH AND DISEASE

- 4,000 deeply phenotyped controls whole-genome sequenced.
- 6,000 cases (autism, schizophrenia, obesity, 8 rare) exome sequenced.
- Association analysis of low frequency and rare variation.
- *Might* be more useful in prediction.

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Conclusions

- Advances in disease genetics happen when technologists, clinicians, analysts come together in the right mix.
- GWAS have revolutionized our ability to link genomic function with disease.
- Progress has been slower on prediction, but we haven't given up hope yet!

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