Genome variation and function 2

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Learning Outcomes

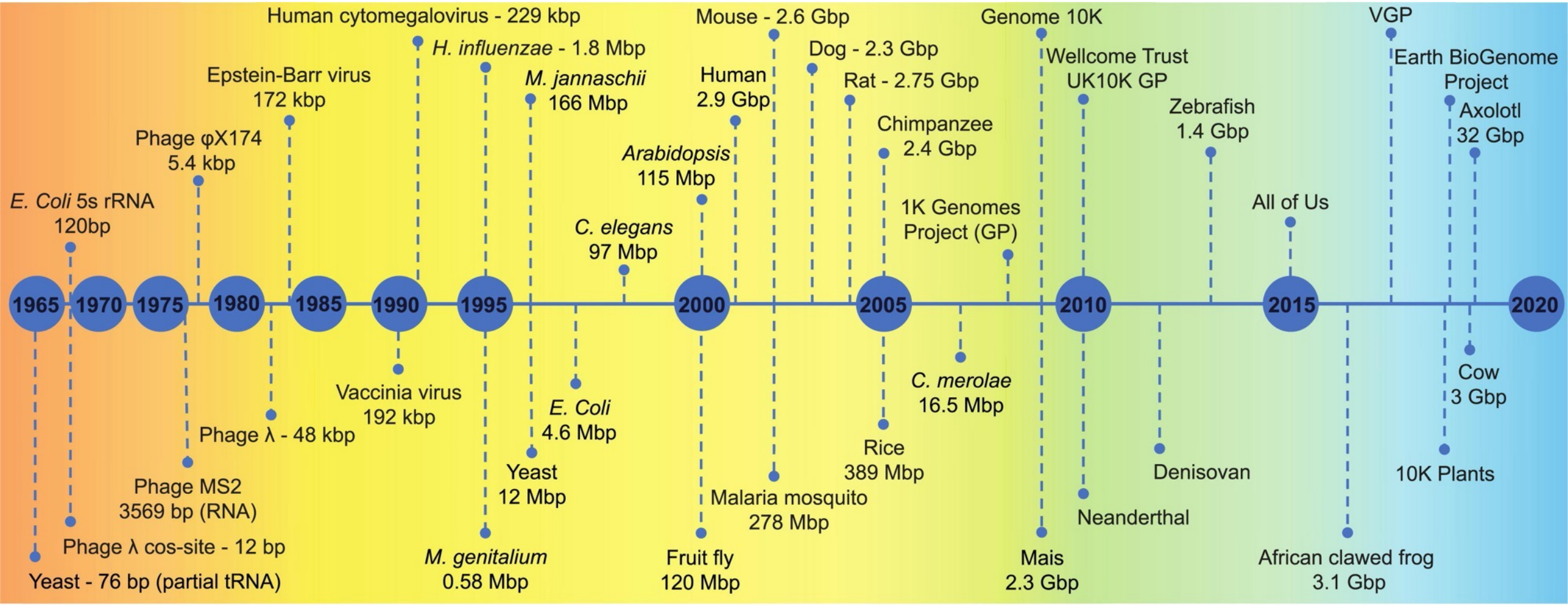
Prologue - Current topics in genomics

- Human genome sequence
- Nobel prize 2022

We will learn about:

- Methods and significance of functional genomics
- Challenges of human genomics

Brief Review: The timeline of genomics



https://www.sciencedirect.com/science/article/pii/S2001037019303277

The complete human genome (2022)

https://www.biorxiv.org/content/10.1101/2021.05.26.445798v1.full

- Adds nearly 200 million base pairs to the 2013 version of the human genome sequence.
- Lasers to scan long stretches of DNA isolated from cells — up to 20,000 base pairs at a time. (PacBio)
- Insight into traits/disease/evolution with further studies

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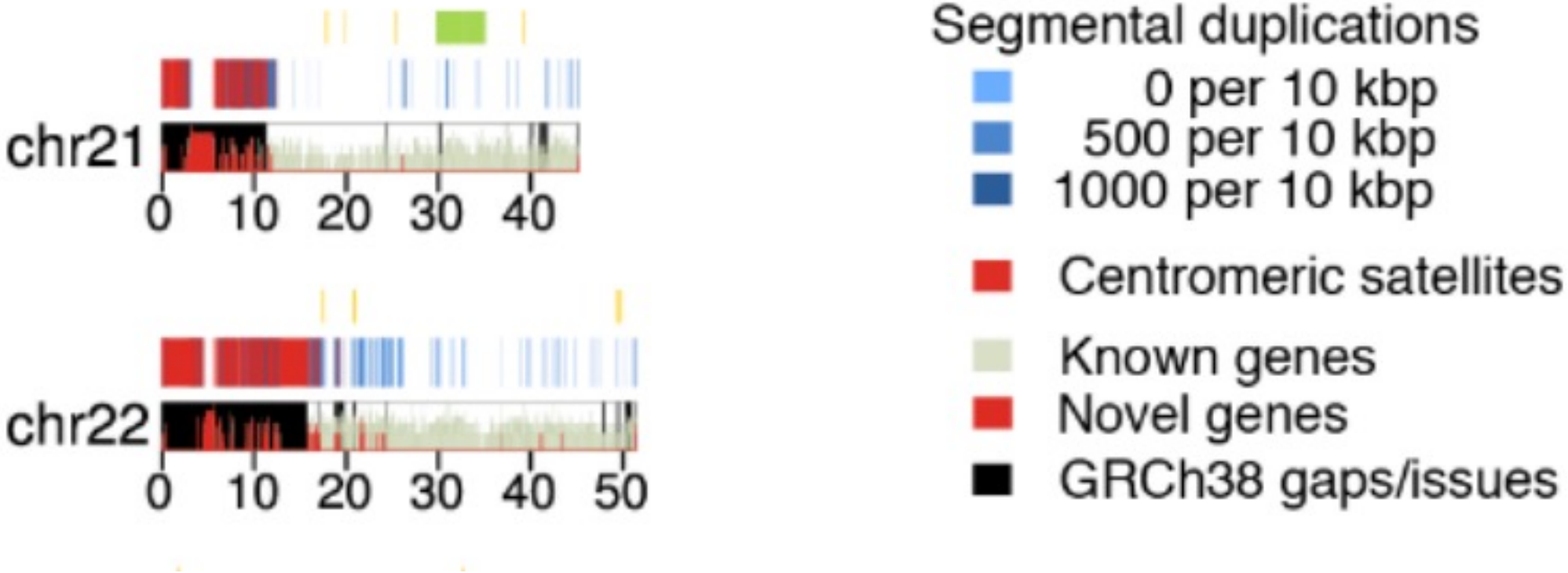


The latest technology

https://www.pacb.com/blog/the-evolution-of-dna-sequencing-tools/

First Generation

Sanger Sequencing
Maxam and Gilbert
Sanger Chain-termination

- Infer nucleotide identity using dNTPs then visualize with electrophoresis
- 500-1000 bp fragments

Second Generation
(Next Generation Sequencing)

454, Solexa,
Ion Torrent
Illumina

- High throughput from the parallelization of sequencing reactions
- ~50-500 bp fragments

Third Generation

PacBio
Oxford Nanopore

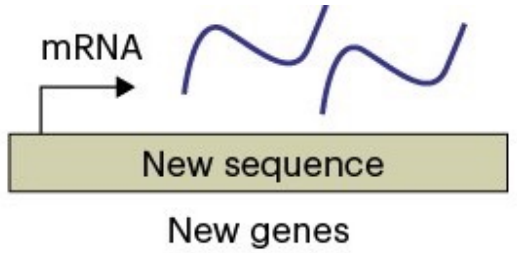
- Sequence native DNA in real time with single-molecule resolution
- Tens of kb fragments, on average

Short-read sequencing

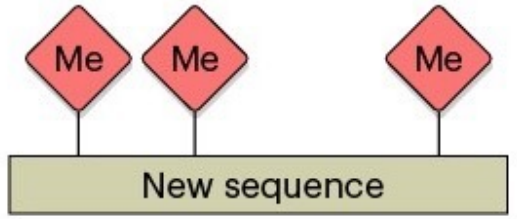
Long-read sequencing

Evolution/Function/Disease...

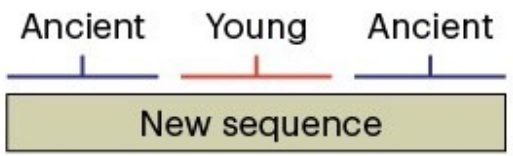
- New genes, epigenetic patterns and evolutionary features to be identified in previously unseen regions



New genes



New epigenetic patterns



New evolutionary features

https://www.nature.com/articles/d41586-021-01095-8

Ancient human genomics

Cell

Volume 90, Issue 1, 11 July 1997, Pages 19-30

1997

CellPress

Article

Neandertal DNA Sequences and the Origin

Science Contents ers Journals

2012

SHARE RESEARCH ARTICLE

A High-Coverage Genome Sequence from an Archaic Denisovan In

Matthias Meyer[1,*,‡], Martin K
Schraiber[4], Flora Jay[4], Kay Pr
Rohland[2,3], Arti Tandon[2,3], Mi
Dabney[1], Jay Shendure[6], Jac
Patterson[2], Aida M. Andrés[1],

nature
International journal of science

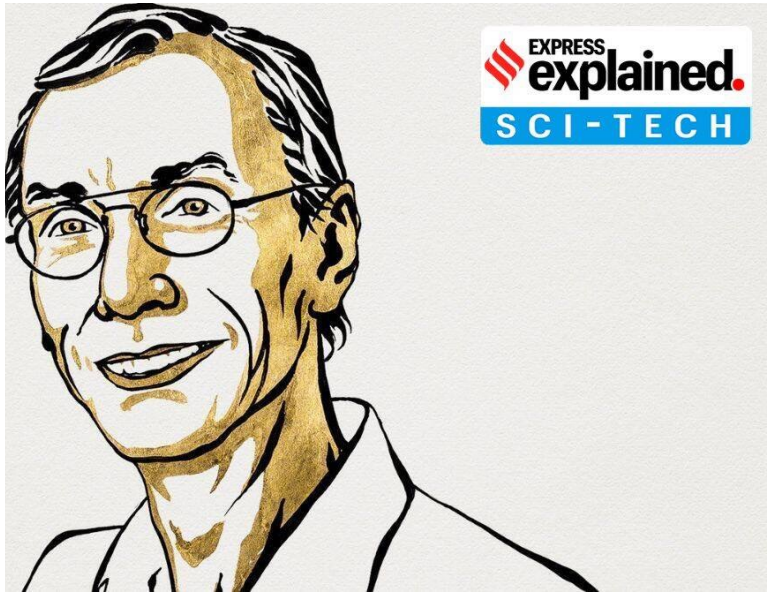
2014

Article | Published: 18 December 2013

The complete genome sequence of a Neanderthal from the Altai Mountains

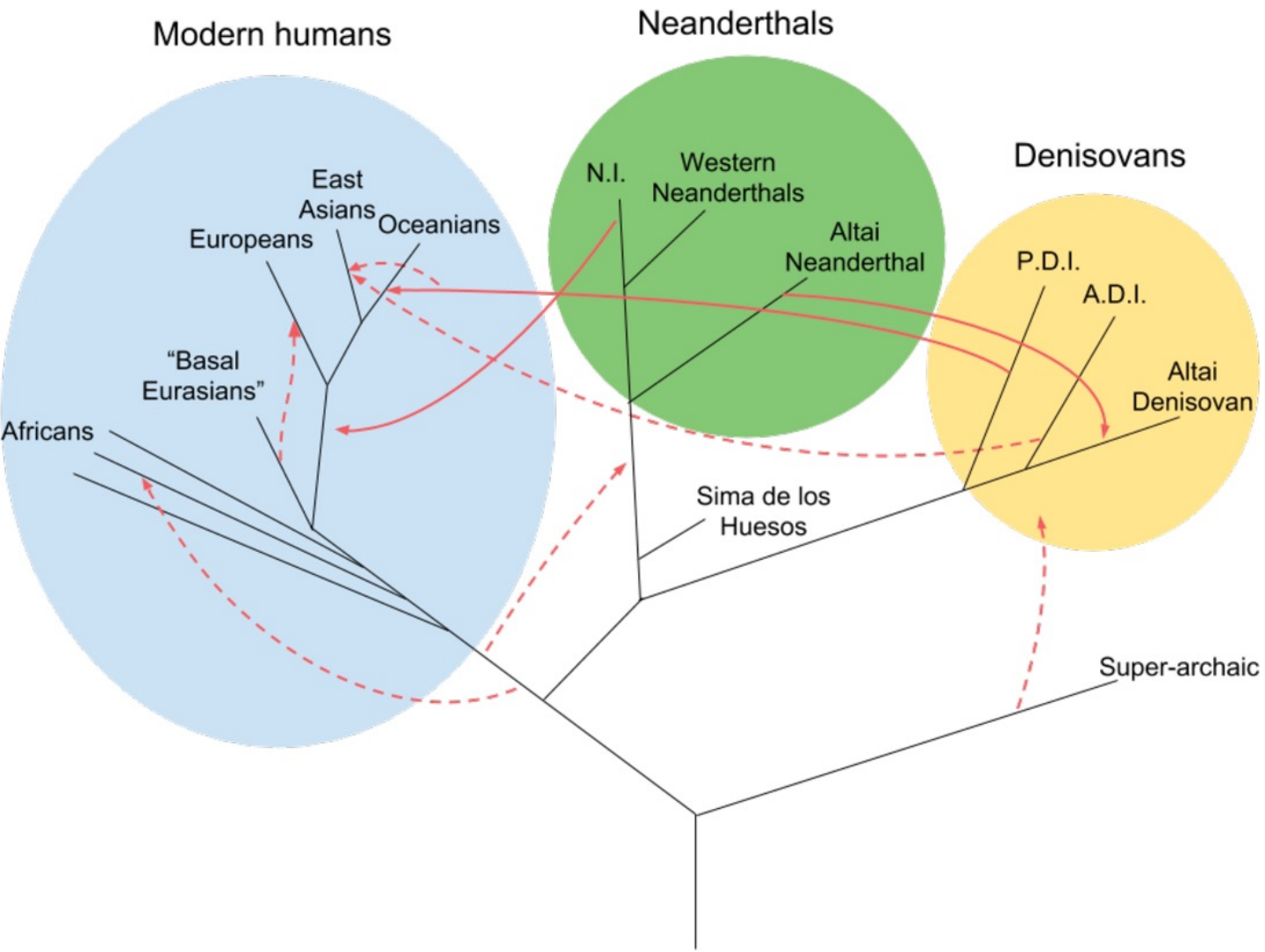
Kay Prüfer, Fernando Racimo [...] Svante Pääbo

Nature **505**, 43–49 (02 January 2014) | Download Citation



Nobel Prize in Medicine, 2022

Archaic Hominins



nature
International journal of science

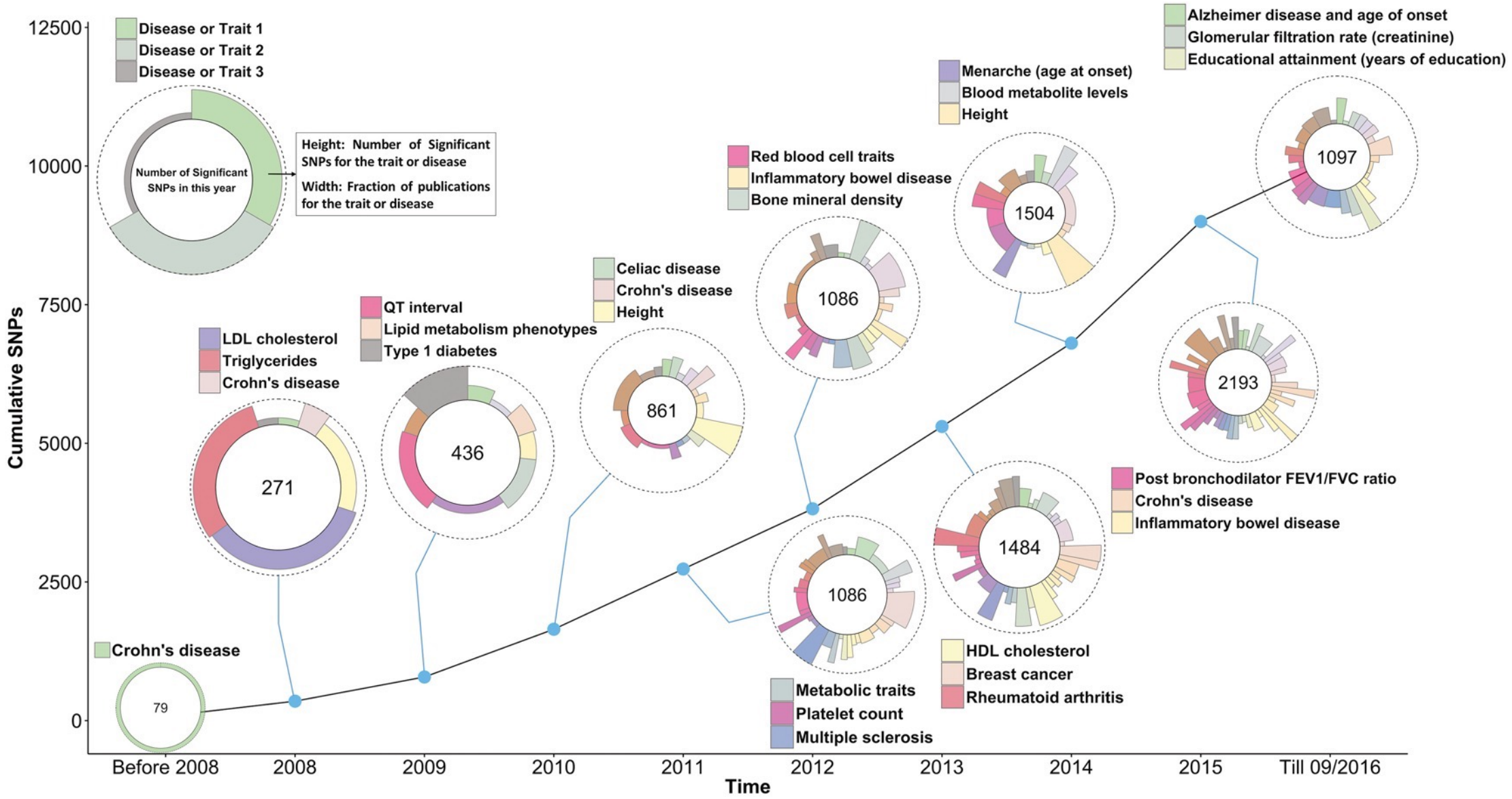
Letter | Published: 22 August 2018

The genome of the offspring of a Neanderthal mother and a Denisovan father

Viviane Slon, Fabrizio Mafessoni, Benjamin Vernot, Cesare de Filippo, Steffi Grote, Bence Viola, Mateja Hajdinjak, Stéphane Peyrégne, Sarah Nagel, Samantha Brown, Katerina Douka, Tom High Maxim B. Kozlikin, Michael V. Shunkov, Anatoly P. Derevianko, Janet Kelso, Matthias Meyer, Kay Prüfer & Svante Pääbo

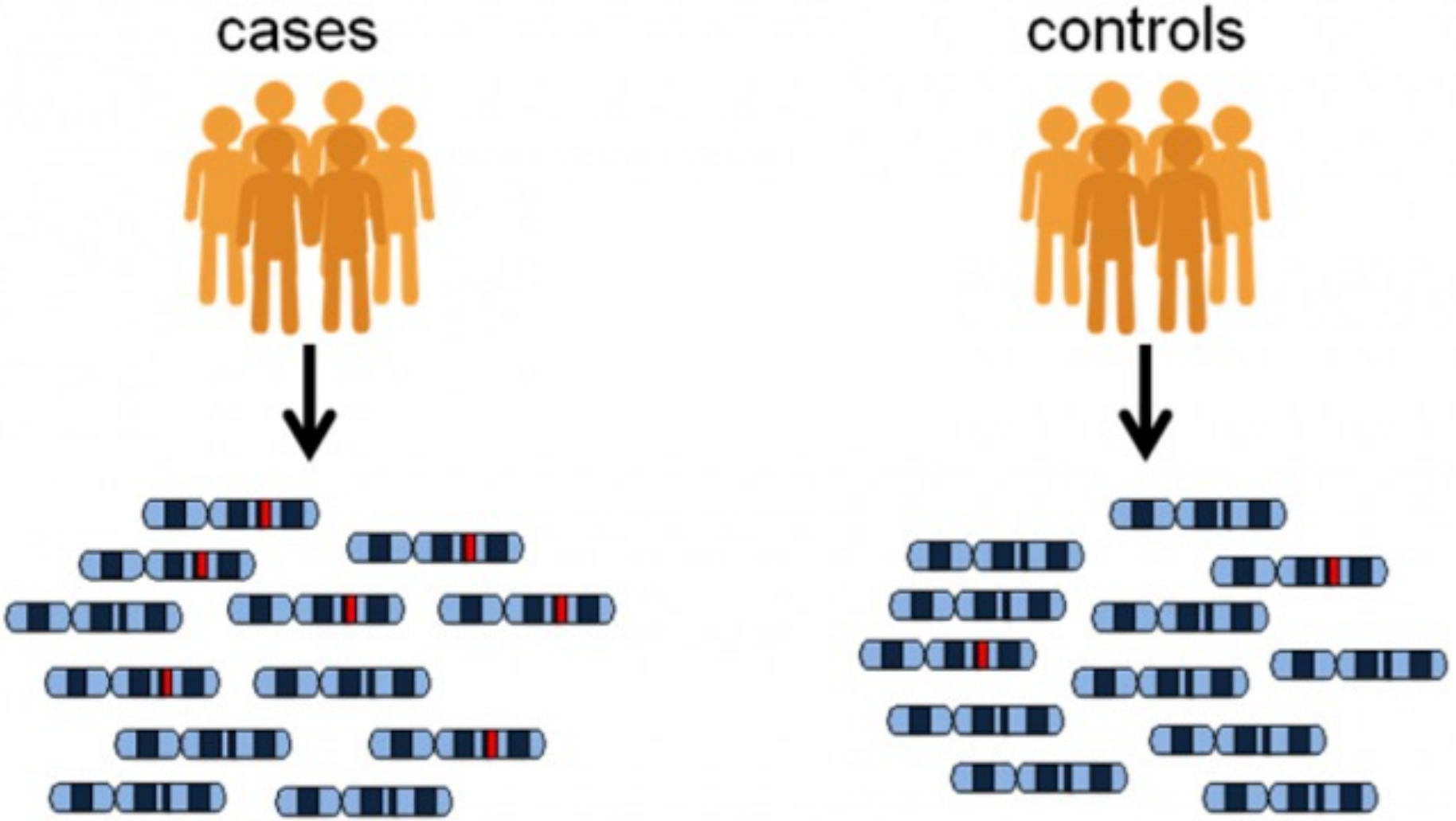
Nature **561**, 113–116 (2018) | Download Citation
27k Accesses | **45** Citations | **2542** Altmetric | Metrics

10 Years of genome-wide association studies

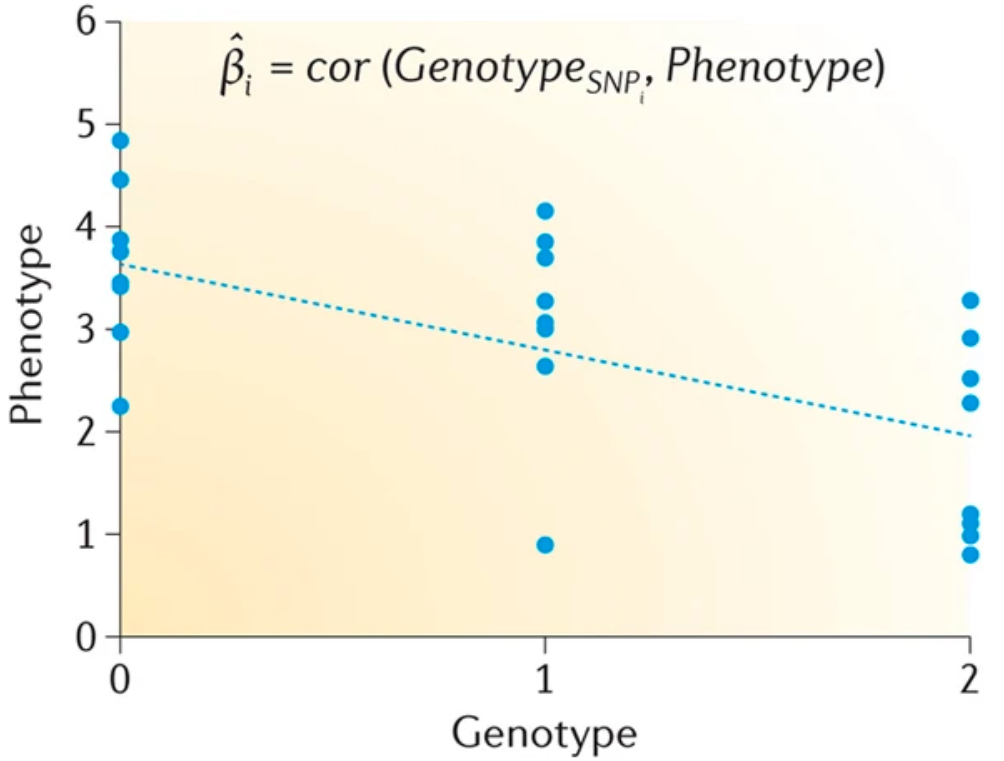


Visscher et al., 2017

Genome-wide association study (GWAS)

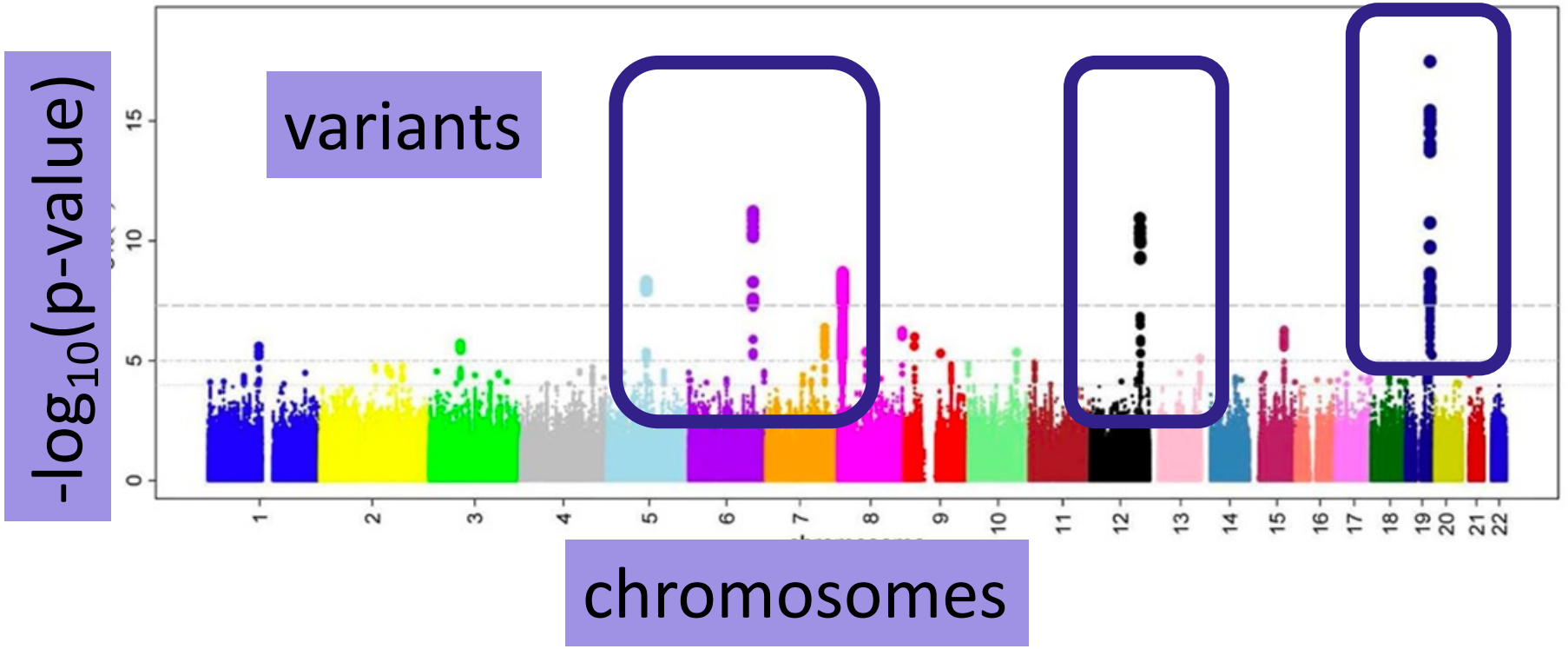


GWAS –
estimate the association between the phenotype and all observed variants



AA AT TT

How to read a Manhattan plot – a GWAS result representation



What is the p-value in GWAS?

the probability of obtaining results as extreme as the observed results of a statistical hypothesis test, assuming that the null hypothesis is correct.

- alternative hypothesis: the variant is associated with the trait
- null hypothesis: the variant is not associated with the trait

Multiple comparisons problem

However, When you conduct the for 100 variants, 5 of the genes can show $p < 0.05$ under the null hypothesis.

-> When you conduct the for 10,000 variants, 500 of the genes can show $p < 0.05$ under the null hypothesis (randomly, by chance).

There are various ways to “correct” this problem, considering how many times one conducts the same comparison.

Example:

Bonferroni correction - the local significance level is divided by the number of tests performed.

Why genome-wide analysis is beneficial

- Most quantitative traits are influenced by many genetic variants each with small effects
- **GWAS** can identify these individual genetic loci with small effects in a large enough sample
- **Polygenic score/breeding value** predicts phenotype based on genomic information aggregating the small effect of genetic variants

Desirable traits: mostly polygenic traits
Polygenic traits vs Mendelian traits

Mendelian traits: shaped by a single gene alone.

example: Wet or dry earwax, Face freckles

Polygenic traits: influenced by multiple (~ thousands) genes.

example: Hair color, height and most of quantitative (continuous) traits

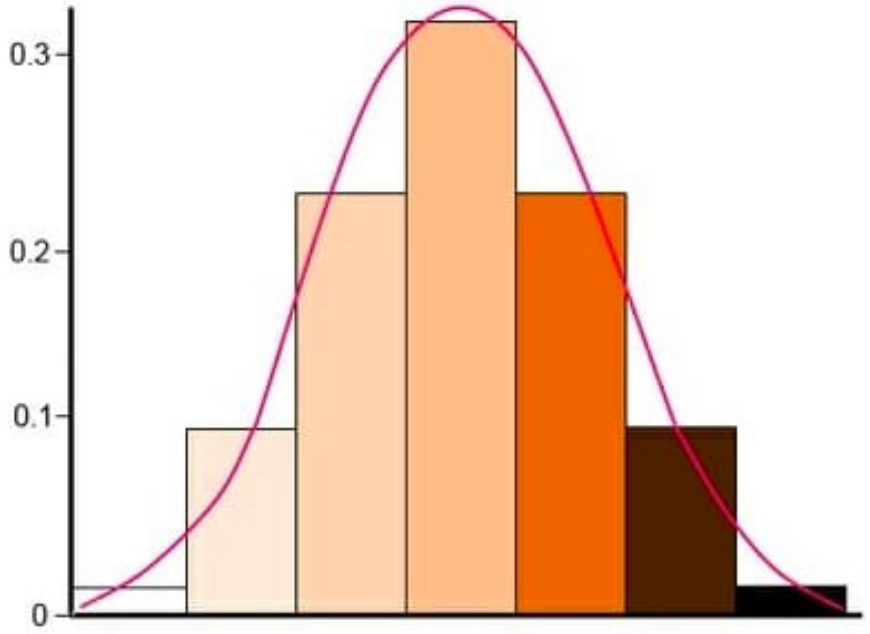
Polygenic trait: example (three loci, A, B and C affect color)

aabbcc (light color) x AABBCC (dark color)

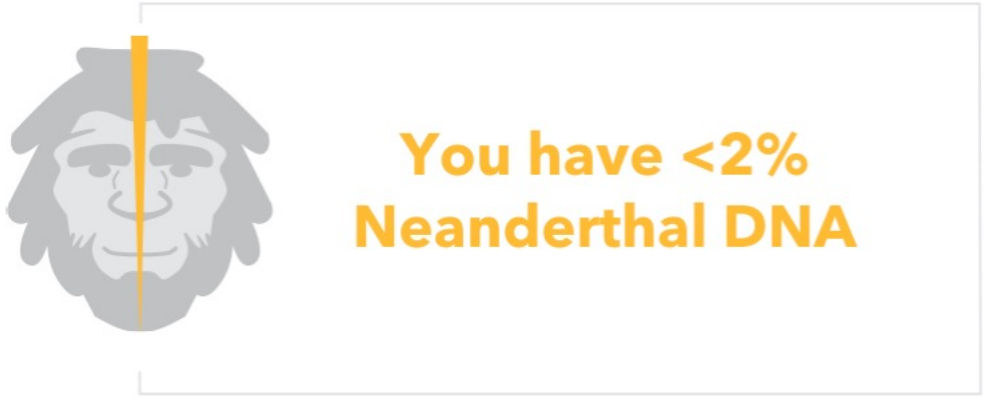
AaBbCc (intermediate)

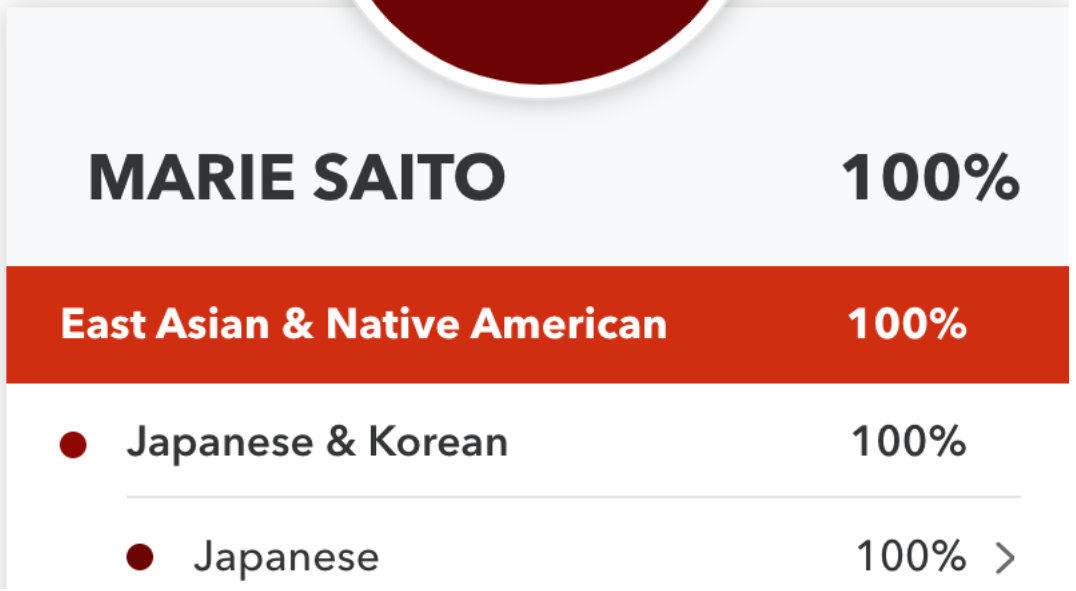
genotype and color

	ABC	*ABc*	*AbC*	*aBC*	*Abc*	*aBc*	*abC*	*abc*
ABC	6	5	5	5	4	4	4	3
ABc	5	4	4	4	3	3	3	2
AbC	5	4	4	4	3	3	3	2
aBC	5	4	4	4	3	3	3	2
Abc	4	3	3	3	2	2	2	1
aBc	4	3	3	3	2	2	2	1
abC	4	3	3	3	2	2	2	1
abc	3	2	2	2	1	1	1	0



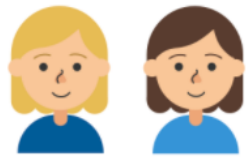
23andMe® Commercial DNA test





DNA Relatives

Get started with your predicted relationships, then connect and message to learn more.



Light or Dark Hair

MARIE, your genetics predict

67%
chance of **dark brown** hair

16%
chance of **black** hair

15%
chance of **light brown** hair

2%
chance of **dark blond** hair

<1%
chance of **light blond** hair

Eye Color

MARIE, your genetics predict

75%
chance of **dark brown** eyes

11%
chance of **light brown** eyes

9%
chance of **dark hazel** eyes

4%
chance of **light hazel** eyes

1%
chance of **green** eyes

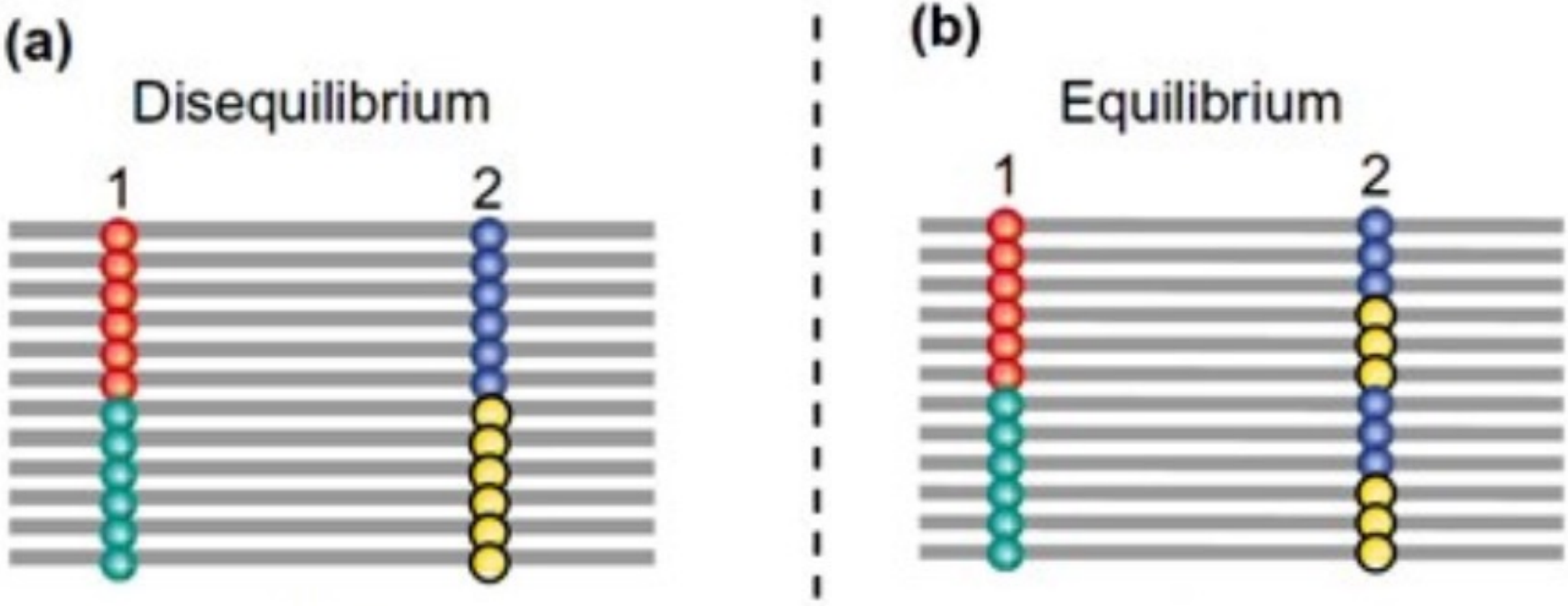
<1%
chance of **blue** eyes

<1%
chance of **greenish blue** eyes

Limitation of genome-wide association studies

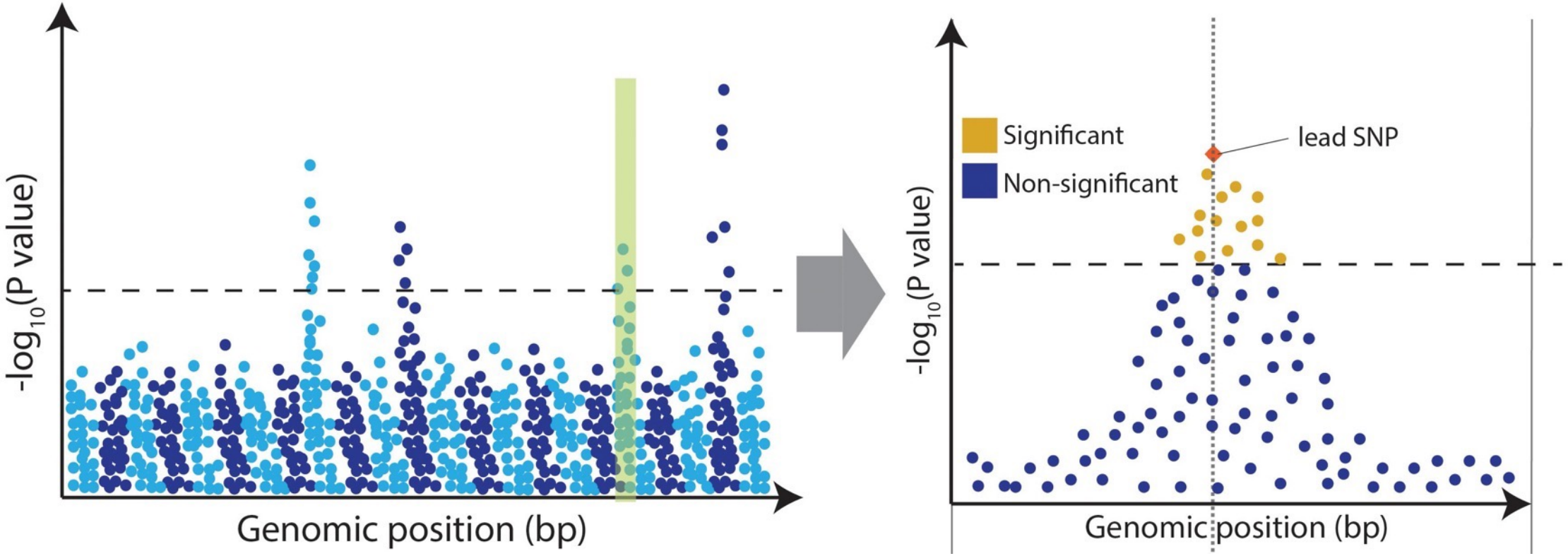
- The difficulty in figuring out true causal associations
- They tell us statistical associations, *not biological mechanisms*

The difficulty in figuring out *true causal associations*
- Linkage Disequilibrium



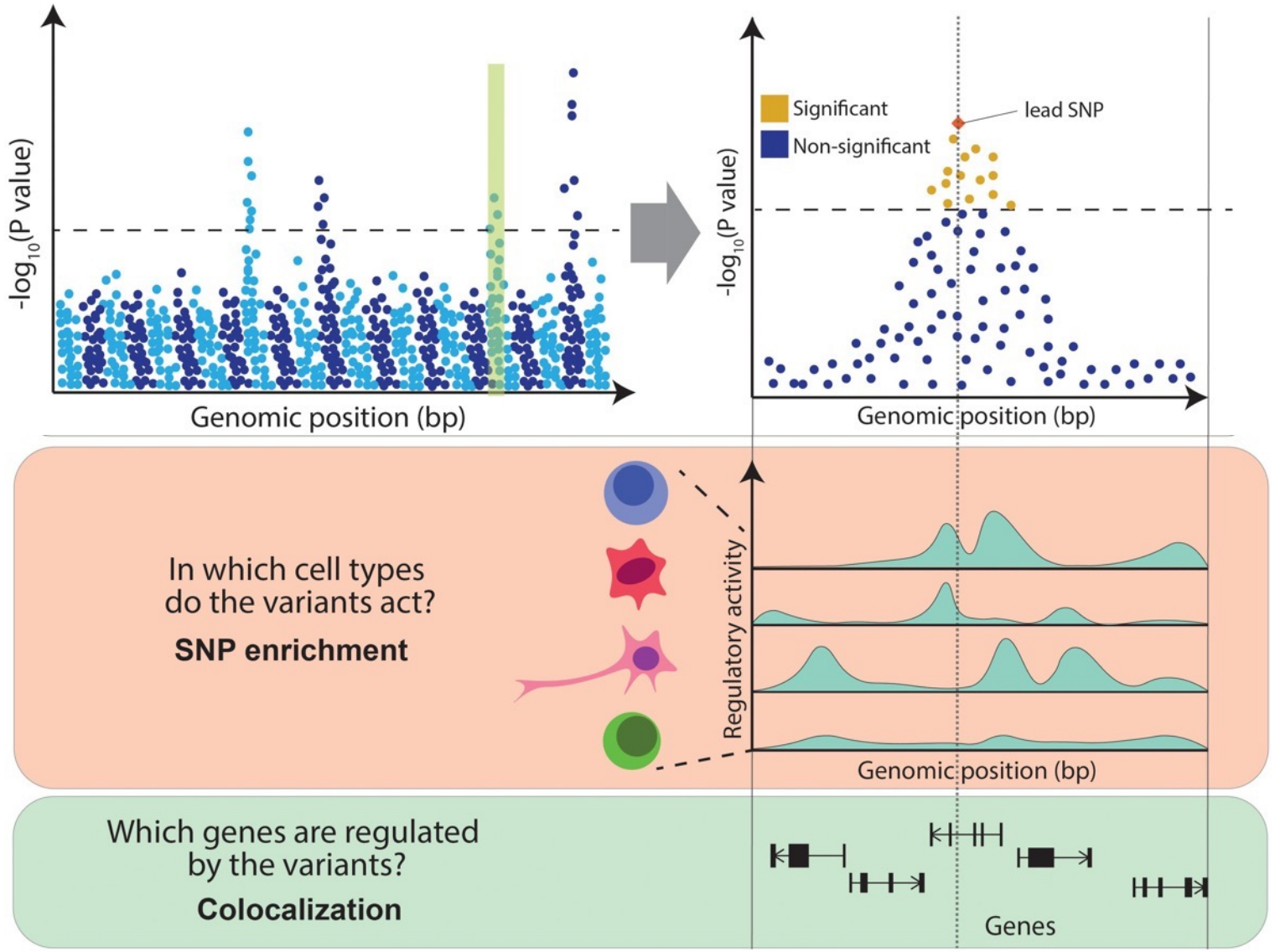
Rafalski. 2002. COPB 5: 94-100

The difficulty in figuring out true causal associations

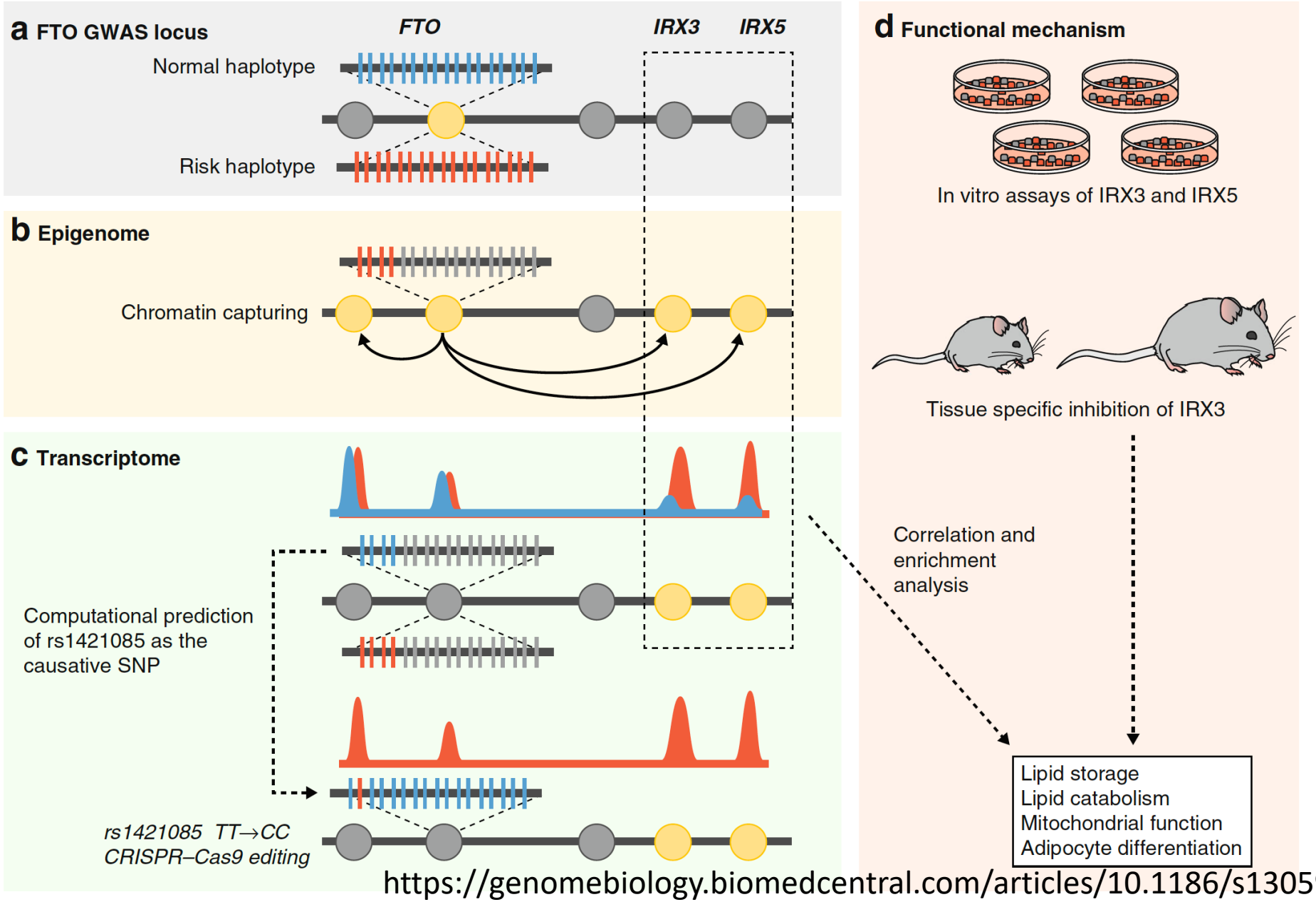


https://www.frontiersin.org/articles/10.3389/fgene.2020.00424/full

Multi-omics approach to narrow down causal associations



Multi-omics approach to narrow down causal associations



https://genomebiology.biomedcentral.com/articles/10.1186/s13059-017-1215-1

Hands-on exercise