
DTU

22126: Next Generation Sequencing Analysis
DTU - January 2026
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FUNCTIONAL VARIATION

Types of Genetic Variation

- SNPs (single nucleotide polymorphisms)
- Indels (small insertions and deletions)
- Structural variants
  - Large deletions/insertions
  - Copy number variants (CNVs)
  - Inversions
  - Translocations

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Reflection prompt (1 min):

"Which type of variant do you think would be hardest to detect with short-read sequencing? Why?"

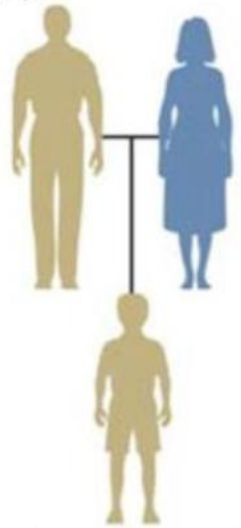
Germline vs Somatic vs Mosaic

- Germline:
  - Inherited, present in all cells
- Somatic:
  - Arise during life (especially in cancer)
- Mosaic:
  - A mixture of genotypes in the same individual
- Allele fraction expectations differ across contexts

Germline vs Somatic vs Mosaic

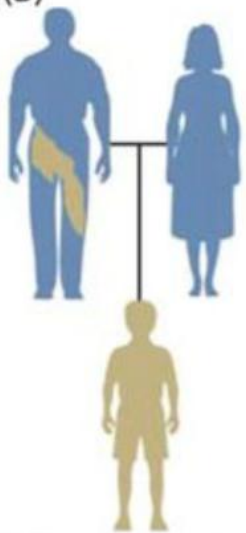
Inherited

(A)



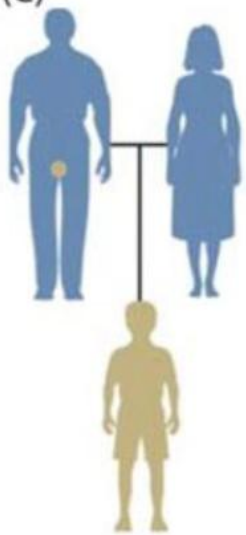
Father has mutation in all cells and transmits it on to his child. Child is heterozygous in every cell.

(B)



Father has mosaic mutation that affects germline and somatic cells. Child is heterozygous in every cell.

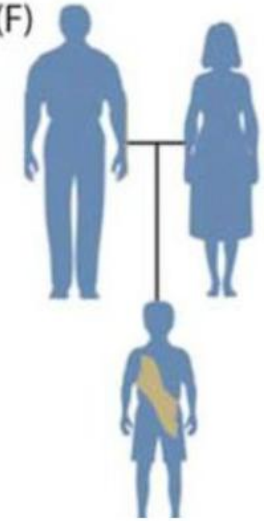
(C)



Father has germline mosaic mutation. Child is heterozygous in every cell.

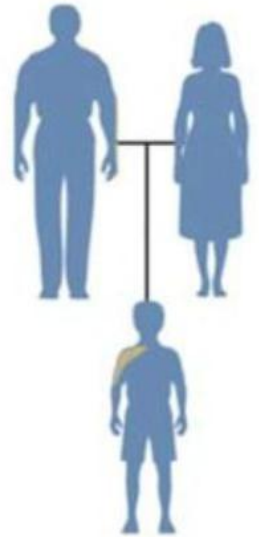
Somatic

(F)



Child has mosaic somatic mutation that occurrs early in postzygotic development and is present in a percentage of his cells.

(G)

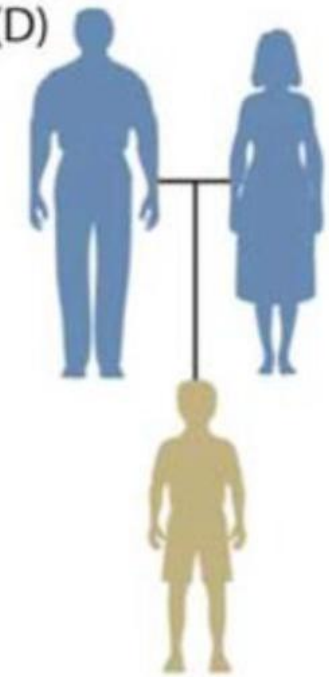


Child has mosaic mutation that occurrs later in development and affects fewer cells (e.g. skin cells)

De novo mutations

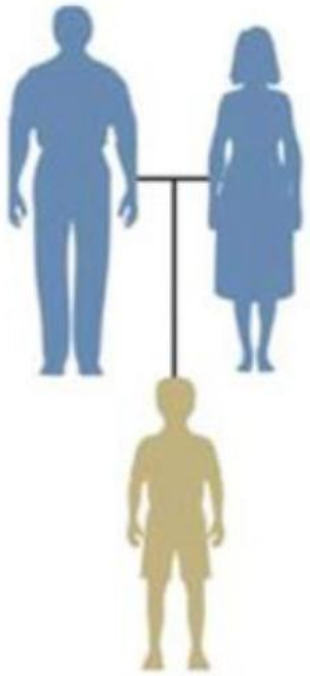
De novo

(D)



Father has mutation in a single sperm cell and transmits it to the child. Child is heterozygous in every cell.

(E)



Mutation occurs in zygote within first few cell divisions. Child is heterozygous in every cell.

Why Variant Calling Matters

- Human disease genetics (rare disease, Mendelian inheritance)
- Somatic mutations in cancer
- Microbial genomics and outbreak tracing
- Population genomics and evolution
- Agriculture and breeding programs

Neaderthal DNA + COVID-19

Neaderthal DNA + COVID-19

Article | Published: 30 September 2020

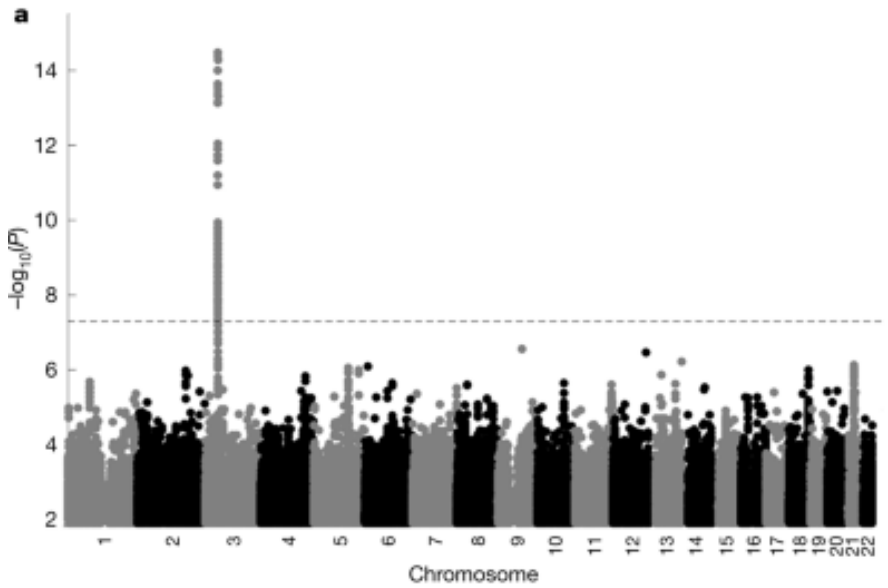
The major genetic risk factor for severe COVID-19 is inherited from Neanderthals

Hugo Zeberg & Svante Pääbo

Nature **587**, 610–612 (2020) | Cite this article

Neaderthal DNA + COVID-19

- GWAS identified a chr3 cluster linked to COVID-19 respiratory failure
- Strongest common genetic predictor of severe disease
- ~50-kb genomic segment defined by shared variants
- Segment is Neanderthal-derived
- Carried by:
  - ~50% of individuals in South Asia
  - ~16% in Europe



Neaderthal DNA + COVID-19

RESEARCH ARTICLE | GENETICS |

A genomic region associated with protection against severe COVID-19 is inherited from Neandertals

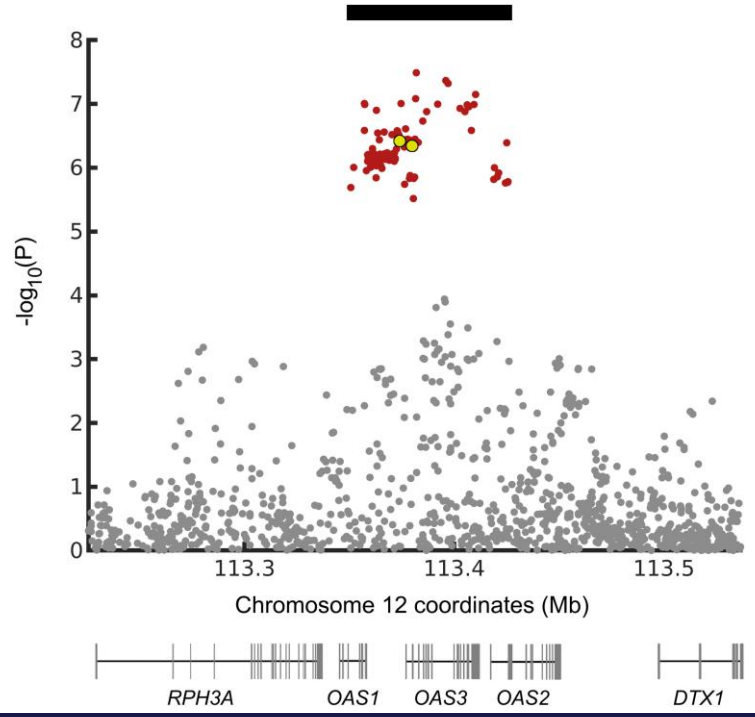
Hugo Zeberg and Svante Pääbo Authors Info & Affiliations

Contributed by Svante Pääbo, January 22, 2021 (sent for review December 21, 2020; reviewed by Tobias L. Lenz and Lluis Quintana-Murci)

February 15, 2021 | 118 (9) e2026309118 | https://doi.org/10.1073/pnas.2026309118

Neaderthal DNA + COVID-19

- Chr12 Neanderthal-derived haplotype less frequent in ICU cases
- Region influences antiviral response to RNA viruses
- Neanderthal haplotype = protective effect
- Moderate frequency worldwide outside Africa



Polar bear evolution

Polar bear evolution

Home › BMC Genomics › Article

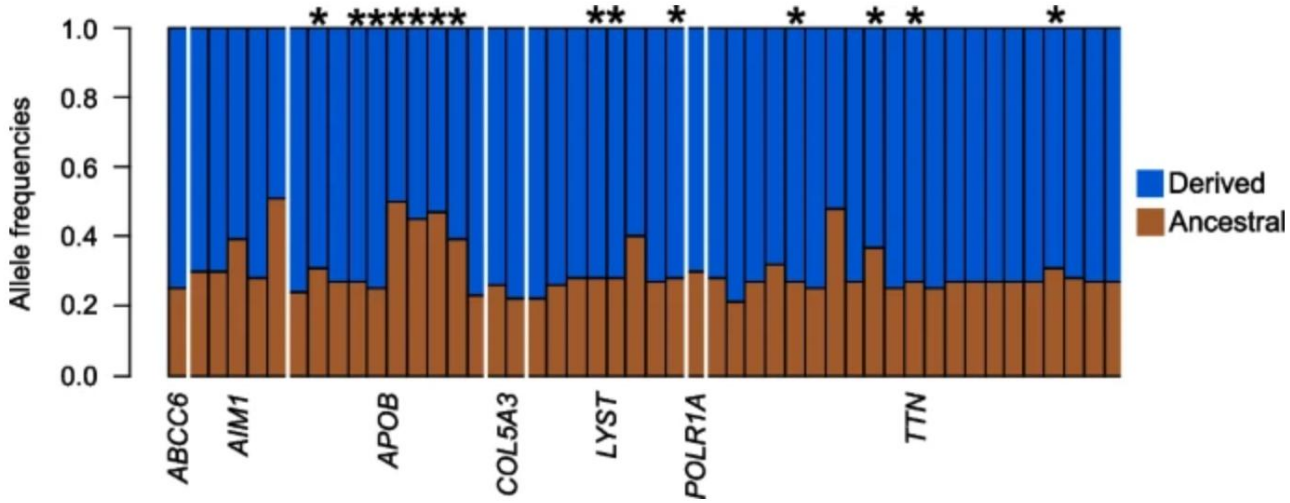
Late Pleistocene polar bear genomes reveal the timing of allele fixation in key genes associated with Arctic adaptation

Research | Open access | Published: 16 September 2024

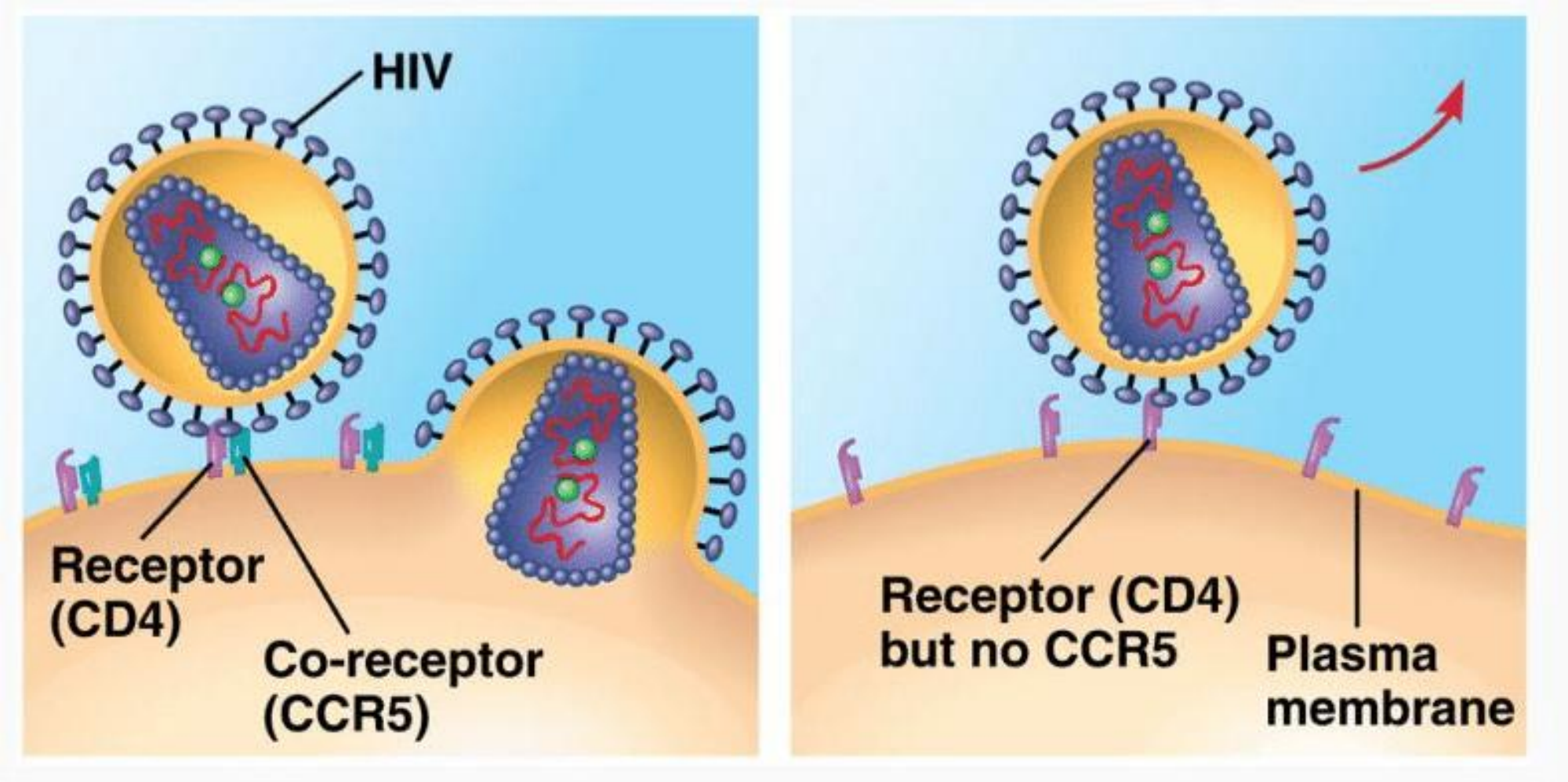
Volume 25, article number 826, (2024) Cite this article

Polar bear evolution

- Whole-genome data to study rapid Arctic adaptation
  + ancient genomes (70–130k years old)
- No fixed de novo mutations in modern polar bears
- Many adaptive variants were fixed before 70,000 years ago
- Genes involved in
  - Cardiovascular function
  - Metabolism
  - Pigmentation



CCR5-Δ32 mutation + HIV



CCR5-Δ32 mutation + HIV

RESEARCH ARTICLE | GENETICS |

Legacy of a magic gene—*CCR5-Δ32*: From discovery to clinical benefit in a generation

Stephen J. OBrien Authors Info & Affiliations

Contributed by Stephen J. OBrien; received December 14, 2023; accepted January 22, 2024; reviewed by George Duncan and Meredith Yeager

This contribution is part of the special series of Inaugural Articles by members of the National Academy of Sciences elected in 2018.

March 8, 2024 | 121 (12) e2321907121 | https://doi.org/10.1073/pnas.2321907121

CCR5-Δ32 mutation + HIV

- CCR5-Δ32 mutation:
  - –32-bp deletion giving near-complete HIV resistance in homozygotes
- A single recent mutation rising to ~10% in Europeans
- Clinical applications:
  - –CCR5-targeting HIV entry inhibitors developed
  - –Δ32/Δ32 stem-cell transplants enabled multiple functional HIV “cures”