



**HAL**  
open science

## Blood groups of Neandertals and Denisova decrypted

Silvana Condemi, Stéphane Mazières, Pierre Faux, Costedoat Caroline,  
Andres Ruiz-Linares, Pascal Bailly, Jacques Chiaroni

► **To cite this version:**

Silvana Condemi, Stéphane Mazières, Pierre Faux, Costedoat Caroline, Andres Ruiz-Linares, et al.. Blood groups of Neandertals and Denisova decrypted. Human Evolution - From Fossils to Ancient and Modern Genomes 2021, Nov 2021, virtual conference, United Kingdom. hal-03517940

**HAL Id: hal-03517940**

**<https://hal.science/hal-03517940>**

Submitted on 8 Jan 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Scan me for data and more!

CONDEMI Silvana<sup>1</sup>, MAZIÈRES Stéphane<sup>1</sup>, FAUX Pierre<sup>1</sup>, COSTEDOAT Caroline<sup>1</sup>,  
 RUIZ-LINARES Andres<sup>1,2,3</sup>, BAILLY Pascal<sup>1,4</sup>, CHIARONI Jacques<sup>1,4</sup>

- 1 Aix Marseille Univ, CNRS, EFS, ADES, UMR 7268, Marseille, France
- 2 Department of Genetics, Evolution and Environment, and UCL Genetics Institute, University College London, London, United Kingdom
- 3 Ministry of Education Key Laboratory of Contemporary Anthropology and Collaborative Innovation Center of Genetics and Development, School of Life Sciences and Human Phenome Institute, Fudan University, Yangpu District, Shanghai, China,
- 4 Etablissement Français du Sang PACA-Corse, « Biologie des Groupes Sanguins », Marseille, France

Email: [stephane.mazieres@univ-amu.fr](mailto:stephane.mazieres@univ-amu.fr)

: @StphaneMazieres1

- Background**
- Red cell blood group systems are relevant to transfusion medicine and anthropology
  - Sporadic knowledge of their gene variation in archaic populations
- Aims**
- To explore the archaic gene variation of the key blood groups
  - To shed light on the late evolutionary history of Neandertal and Denisova

## Selection of the 4 probands

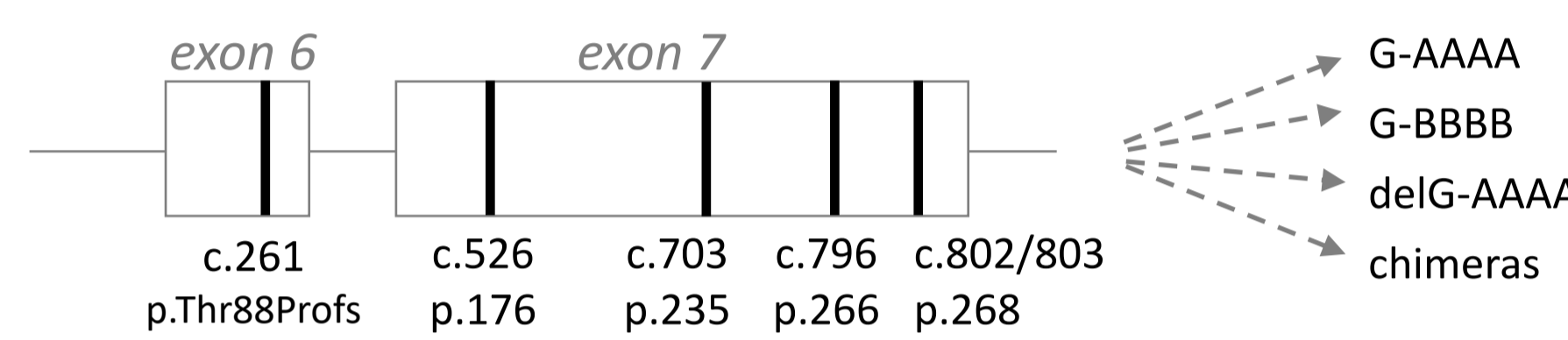
- High coverage
- Low contamination
- Unadmixed
- Few uncalled snps

Altai Neandertal  
 Vindija 33.19  
 Chagyrskaya 8  
 Denisova 3

## Caution items

- HG19: 5' strand and alignment with blood group *Locus Genomic References*

- ABO genotype calls : 5 key snps → enzyme activity



- *RHD* and *RHCE* haplotypes : The Human RhesusBase,



- Key indels: *ABO* c.261delG, c.1061delC, and *RHCE* 209bp

- Low-mapped variants : IGV → Mapping Quality threshold

## Allele exploration procedure

- Tabix
- Vcftools



Key snps & exons browsing:  
 \*bam & \*vcf files



- GT:DP:GQ:A:C:G:T:PL & PP
- Mapping quality 25
- Amino-acid changes



Alleles and inferred phenotypes

## Key blood group systems and their genes

ABO, H, Se (secretor)	<i>ABO, FUT1, FUT2</i>
Rh	<i>RHD, RHCE</i>
Kell, Kx	<i>Kell, XK</i>
Duffy	<i>DARC</i>
Kidd	<i>SLC14A1</i>
MNS	<i>GYPB</i>
Diego	<i>SLC4A1</i>

## Probable phenotypes from functional genotypes

### Altai Neandertal (130-90 ky)

**ABO** > A<sup>1</sup> (G-BAAA / G-BAAA), **SeSe**  
**partial RhD** > *RHD\*DIII type4 (602G, 733C) / RHD\*DIII type4 (602G, 733C)*  
**partial Rhce** > *RHCE\*ceEK / RHCE\*ce(48C, 410T, 712G)*  
**K- k+**, **Js(a+, b-)** > *KEL\*02/\*02, KEL\*06/\*06*  
**Fy(a-, b+)** > *FY\*02/\*02*  
**Jk(a+, b-)** > *JK\*01/\*01*  
**S-, s+** > *GYPB\*04/\*04*  
**Di(a-, b+)** > *DI\*01/\*01*

### Vindija 33.19 (65-50 ky)

**ABO** > B (delG-AAAA / G-BABB), **SeSe** (*rs1800028, c.571T, p.191stop*)  
**partial RhD** > *RHD\*DIII type4 (602G, 733C) / RHD\*DIII type4 (602G, 733C)*  
**partial Rhce** > *RHCE\*ceEK / RHCE\*ce(48C, 744C, 787G)*  
**K- k+**, **Js(a+, b-)** > *KEL\*02/\*02, KEL\*06/\*06*  
**Fy(a-, b+)** > *FY\*02/\*02*  
**Jk(a+, b-)** > *JK\*01/\*01*  
**S-, s+** > *GYPB\*04/\*04*  
**Di(a-, b+)** > *DI\*01/\*01*

### Chagyrskaya 8 (51-45 ky)

**ABO** : A<sup>1</sup> (delG-AAA / G-BAAA), **se** (*rs1800028, c.571T, p.191stop*)  
**partial RhD** > *RHD\*DIII type4 (602G, 733C) / RHD\*DIII type4 (602G, 733C)*  
**partial Rhce** > *RHCE\*ceEK / RHCE\*ce(48C, 410T, 800A)*  
**K- k+**, **Js(a+, b-)** > *KEL\*02/\*02, KEL\*06/\*06*  
**Fy(a-, b+)** > *FY\*02/\*02*  
**Jk(a+, b-)** > *JK\*01/\*01*  
**S-, s+** > *GYPB\*04/\*04*

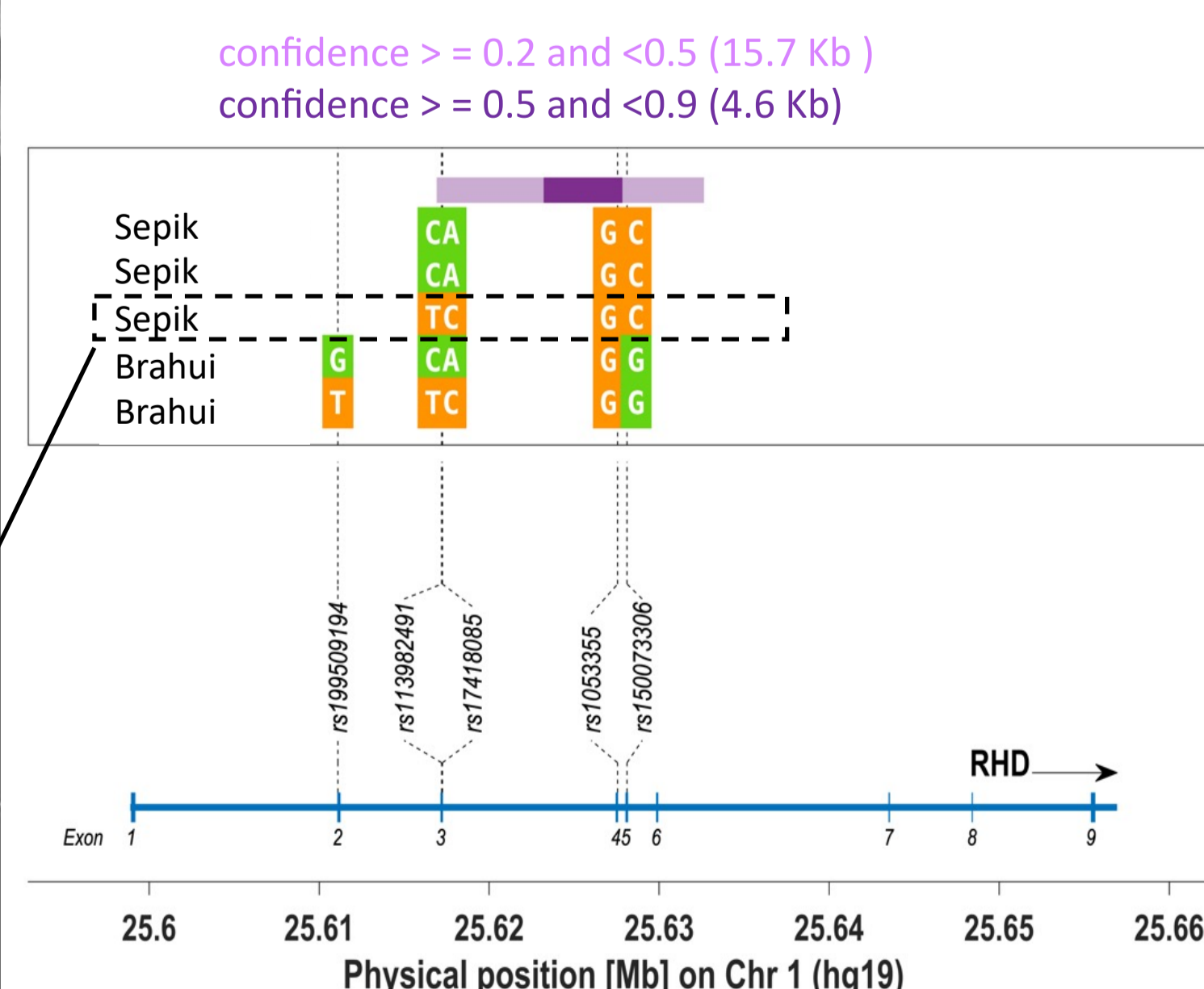
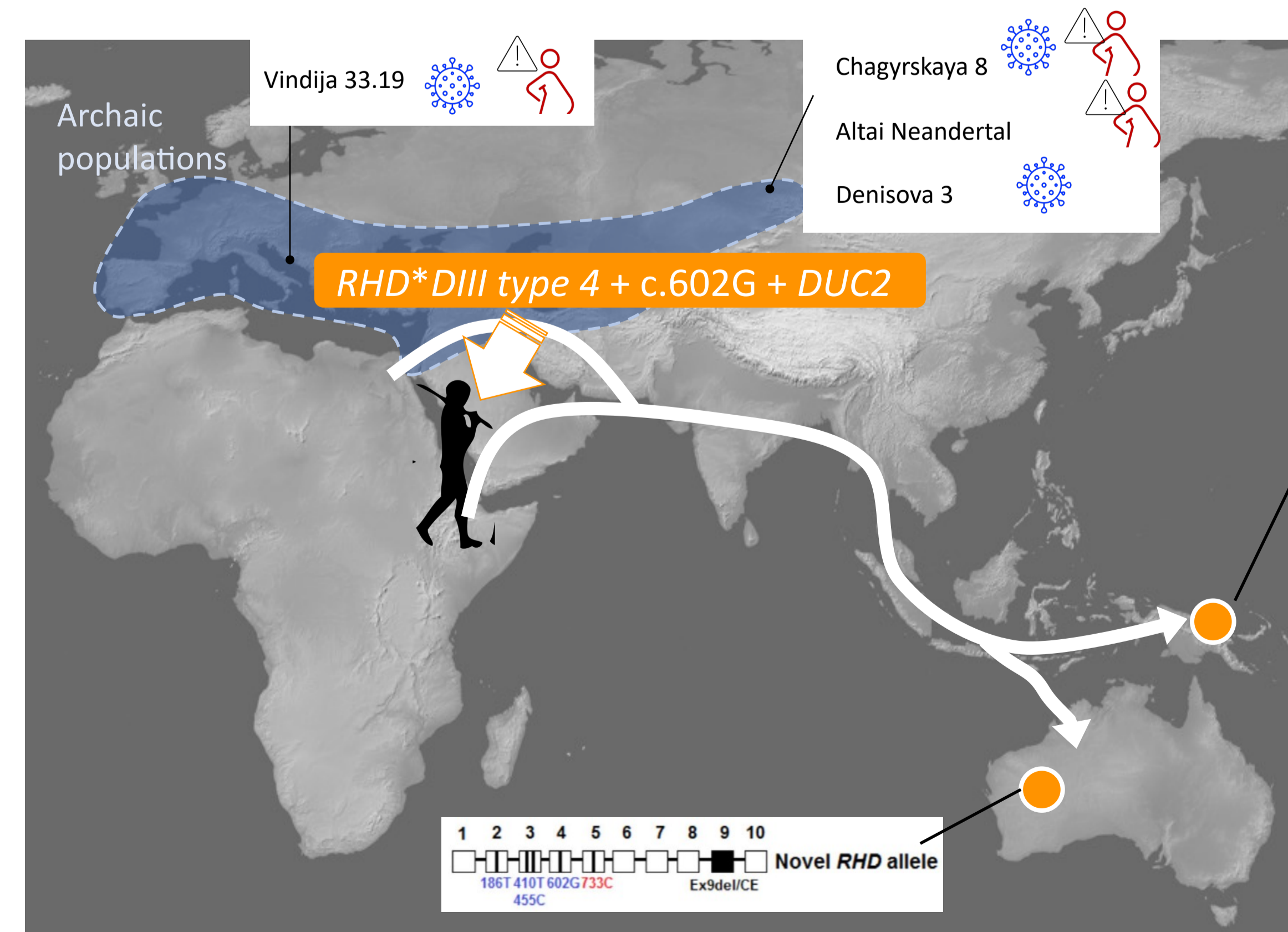
### Denisova 3 (76-52 ky)

**ABO** > O<sup>1</sup> (delG-AAAA / delG-AAAA), **Se/se** (*c.714A, p.237stop, undescribed*)  
**RhD** > *RHD\*D / RH\*D(19G, 186T, 410T, 929G)*  
**Rhce** > *RHCE\*ce(48C) / RhCE\*ce(48C)*  
**K- k+**, **Js(a-, b+)** > *KEL\*02/\*02, KEL\*07/\*07*  
**Fy(a-, b+)** > *FY\*02/\*02*  
**Jk(a+, b-)** > *JK\*01/\*01*  
**S-, s+** > *GYPB\*04/\*04*  
**Di(a-, b+)** > *DI\*01/\*01*

## Highlights

- Presence of the 3 ABO phenotypes
- Non-secretor alleles
- *DIII type 4, \*ceEK* → sub-Saharan background, → partial D, partial ce (RH:-18)
- Neandertal-specific *RHD* haplotype
- Denisova : unknown *RHD* (c.929A>G, Pro310Arg)
- Homozygous at 6 loci: K-k+, Fy(a-b+), Jk(a+b-), S-s+, Di(a-b+)
- Ancestral alleles: *DARC* (rs12075 "Fy<sup>b</sup>", c.125A, p.42Asp), *SLC4A1* (rs5036 "Memphis", c.166G, p.56Glu), *Kel* (rs8176038 "Js<sup>b</sup>", c.1790T>C, p. 597Pro)

## Evolutionary outcomes



- 1. Consolidation of an African origin**  
 Ancestral forms for RH, Kell, Duffy, Kidd, MNS and Diego  
 African clusters of *RHD, RHCE* variants  
 Absence of the antigen combination RhC, RhE, K, Fya, Jkb and S
- 2. Admixture before expansion towards Oceania**  
*RHD\*DIII type4* with c.602G and *DUC2* : only 2 cases in Australia & Papua New Guinea
- 3. Genetic signature of environmental pressure**  
 Polymorphism at the ABO level → balanced selection  
 Non-secretor *FUT2* snps → exposition to « Norovirus-like »
- 4. Neandertal demography at risk**  
 High level of homozygosity  
 Partial RhD, Rhc and Rhe antigens → risk of hemolytic disease of the foetus and the new born

**Acknowledgments**  
 • Centre de Calcul Intensif d'Aix-Marseille for granting access to its high performance computing resources.  
 • Céline Bon, Laure Ségurel and the two anonymous reviewers for their fruitful comments.

**References**  
 • Bokelman et al. 2019. A genetic analysis of the Gibraltar Neanderthals. PNAS, 116 (31) 15610-15615  
 • Meyer et al. A high-coverage genome sequence from an archaic Denisovan individual. Science. 2012; 338(6104):222-6.  
 • Mafessoni et al. A high-coverage Neandertal genome from Chagyrskaya Cave. Proc Natl Acad Sci U S A. 2020.  
 • Möller et al. ErythroGene: a database for in-depth analysis of the extensive variation in 36 blood group systems in the 1000 Genomes Project. Blood Advances. 2016; 1(3):240-9.  
 • Prüfer et al. The complete genome sequence of a Neandertal from the Altai Mountains. Nature. 2014; 505(7481):43-9.  
 • Prüfer et al. A high-coverage Neandertal genome from Vindija Cave in Croatia. Science. 2017; 358(6363):655-8.

• Schoeman EM, Roullis EV, Perry MA, Flower RL, Hyland CA. Comprehensive blood group antigen profile predictions for Western Desert Indigenous Australians from whole exome sequence data. Transfusion. 2019; 59(2):768-78.  
 • Thorvaldsdottir et al. Integrative Genomics Viewer (IGV): high-performance genomics data visualization and exploration. Brief Bioinform. 2013; 14(2):178-92.  
 • Wagner & Flegel. The Rhesus Site. Transfus Med Hemother. 2014; 41(5):357-63.  
 • Yamamoto et al. Molecular genetic basis of the histo-blood group ABO system. Nature. 1990; 345(6272):229-33.  
 • Yamamoto & Hakomori S. Sugar-nucleotide donor specificity of histo-blood group A and B transferases is based on amino acid substitutions. J Biol Chem. 1990; 265(31):19257-62.