# Neanderthal genes in modern humans

## A review of recent findings from ancient and modern DNA on hominin evolution and natural selection on humans

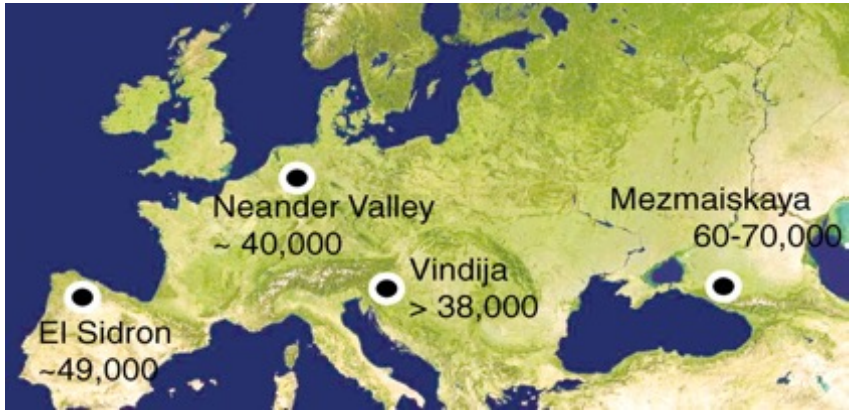
5.11.2018

Turun eläin- ja kasvitieteellinen seura

Päivi Onkamo

# Introgression!

- Genomic studies have shown that Neanderthals interbred with modern humans, and that non-Africans today are the products of this mixture
- **First shown by Green et al. in Science 2010**
- Identified a number of genomic regions that may have been affected by positive selection in ancestral modern humans, genes involved in metabolism and in cognitive and skeletal development





Green et al. 2010

# Introgression!

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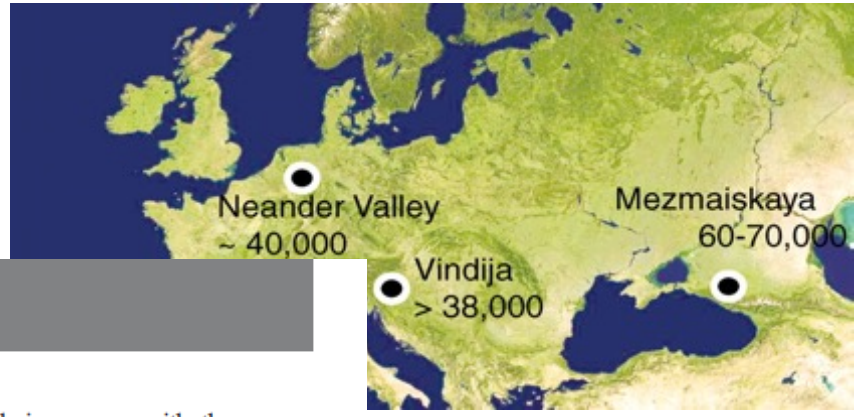



RESEARCH ARTICLE

## A Draft Sequence of the Neandertal Genome

Richard E. Green,[1]*†‡ Johannes Krause,[1]†§ Adrian W. Briggs,[1]†§ Tomislav Maricic,[1]†§ Udo Stenzel,[1]†§ Martin Kircher,[1]†§ Nick Patterson,[2]†§ Heng Li,[2]† Weiwei Zhai,[3]†‖ Markus Hsi-Yang Fritz,[4]† Nancy F. Hansen,[5]† Eric Y. Durand,[3]† Anna-Sapfo Malaspinas,[3]† Jeffrey D. Jensen,[6]† Tomas Marques-Bonet,[7,13]† Can Alkan,[7]† Kay Prüfer,[1]† Matthias Meyer,[1]† Hernán A. Burbano,[1]† Jeffrey M. Good,[1,8]† Rigo Schultz,[1] Ayinuer Aximu-Petri,[1] Anne Butthof,[1] Barbara Höber,[1] Barbara Höffner,[1] Madlen Siegemund,[1] Antje Weihmann,[1] Chad Nusbaum,[2] Eric S. Lander,[2] Carsten Russ,[2] Nathaniel Novod,[2] Jason Affourtit,[9] Michael Egholm,[9] Christine Verna,[21] Pavao Rudan,[10] Dejana Brajkovic,[11] Željko Kucan,[10] Ivan Gušic,[10] Vladimir B. Doronichev,[12] Liubov V. Golovanova,[12] Carles Lalueza-Fox,[13] Marco de la Rasilla,[14] Javier Fortea,[14]¶ Antonio Rosas,[15] Ralf W. Schmitz,[16,17] Philip L. F. Johnson,[18]† Evan E. Eichler,[7]† Daniel Falush,[19]† Ewan Birney,[4]† James C. Mullikin,[5]† Montgomery Slatkin,[3]† Rasmus Nielsen,[3]† Janet Kelso,[1]† Michael Lachmann,[1]† David Reich,[2,20]*† Svante Pääbo[1]*†

Neandertals, the closest evolutionary relatives of present-day humans, lived in large parts of Europe and western Asia before disappearing 30,000 years ago. We present a draft sequence of the Neandertal genome composed of more than 4 billion nucleotides from three individuals. Comparisons of the

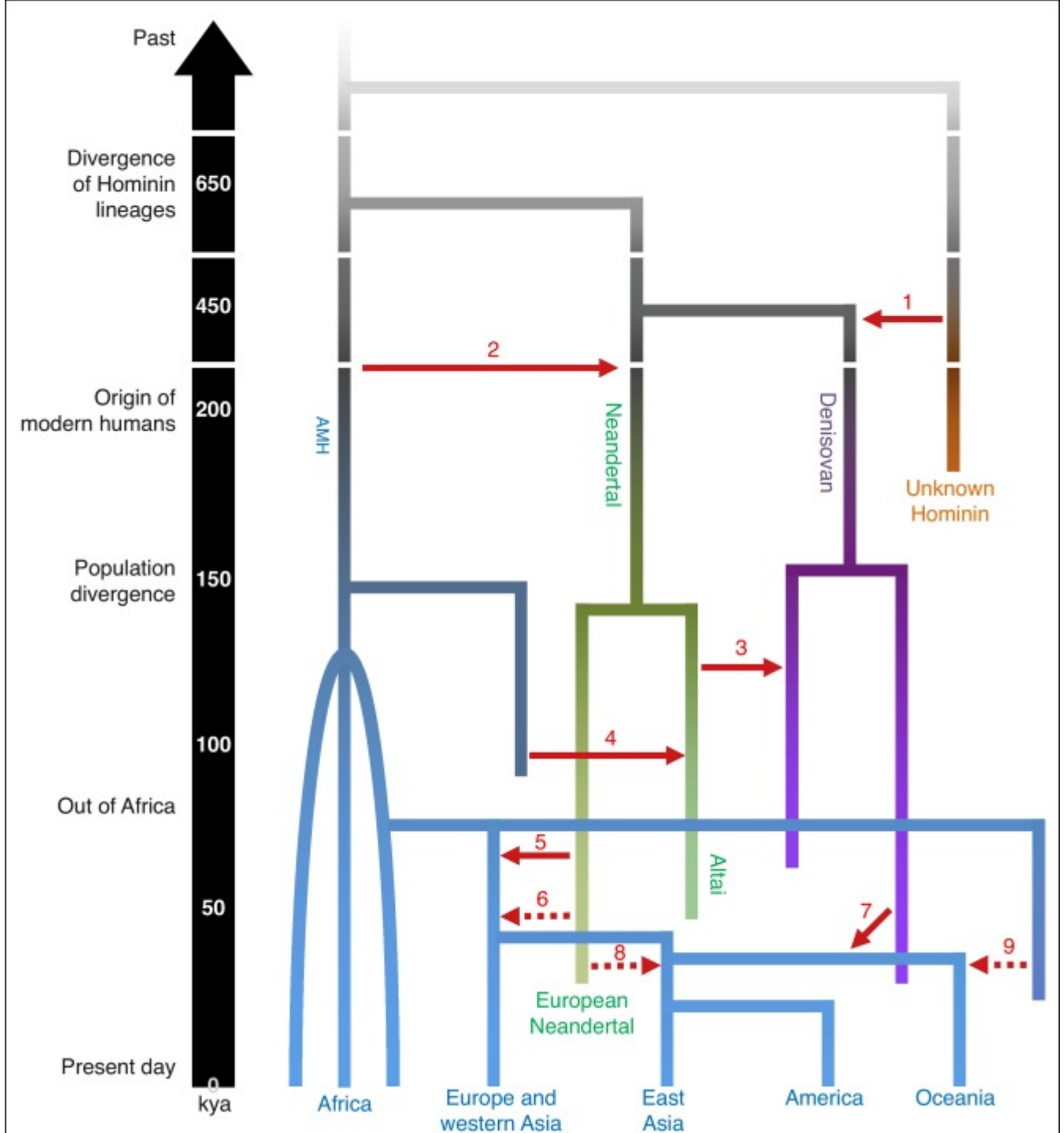
changed parts of their genome with the ancestors of these groups.

Several features of DNA extracted from Late Pleistocene remains make its study challenging. The DNA is invariably degraded to a small average size of less than 200 base pairs (bp) (*21*, *22*), it is chemically modified (*21*, *23*–*26*), and extracts almost always contain only small amounts of endogenous DNA but large amounts of DNA from microbial organisms that colonized the specimens after death. Over the past 20 years, methods for ancient DNA retrieval have been developed (*21*, *22*), largely based on the polymerase chain reaction (PCR) (*27*). In the case of the nuclear genome of Neandertals, four short gene sequences have been determined by PCR: fragments of the *MC1R* gene involved in skin pigmentation (*28*), a segment of the *FOXP2* gene involved in speech and language (*29*), parts of the ABO blood group locus (*30*), and a taste receptor gene (*31*). However, although PCR of ancient DNA can be multiplexed (*32*), it does not allow the retrieval of a large proportion of the genome of an organism.

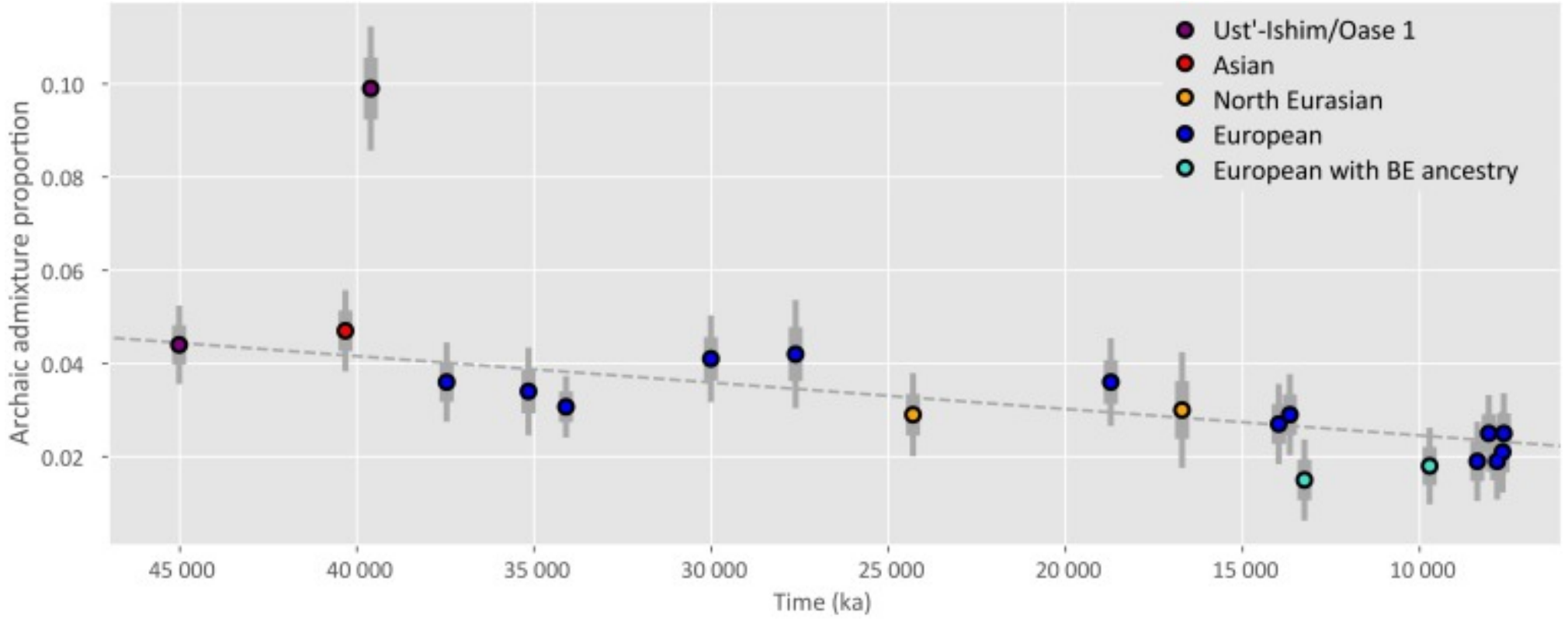

Green et al. 2010

- Since, a number of studies published
- Interbreeding occurred among many hominin groups in the Late Pleistocene

Fig. Schematic representation of human evolution
1: 2.5–5.8% Denisova genome from archaic hominin, diverged 0.9–1.4 mya
4: 1.0–7.1% gene flow from AMH into Altai Neanderthals
5,6,8,9: multiple introgressions from Neanderthals into various modern human populations
7: Denisova introgression resulting in about 2–4% Denisovan DNA in Melanesia



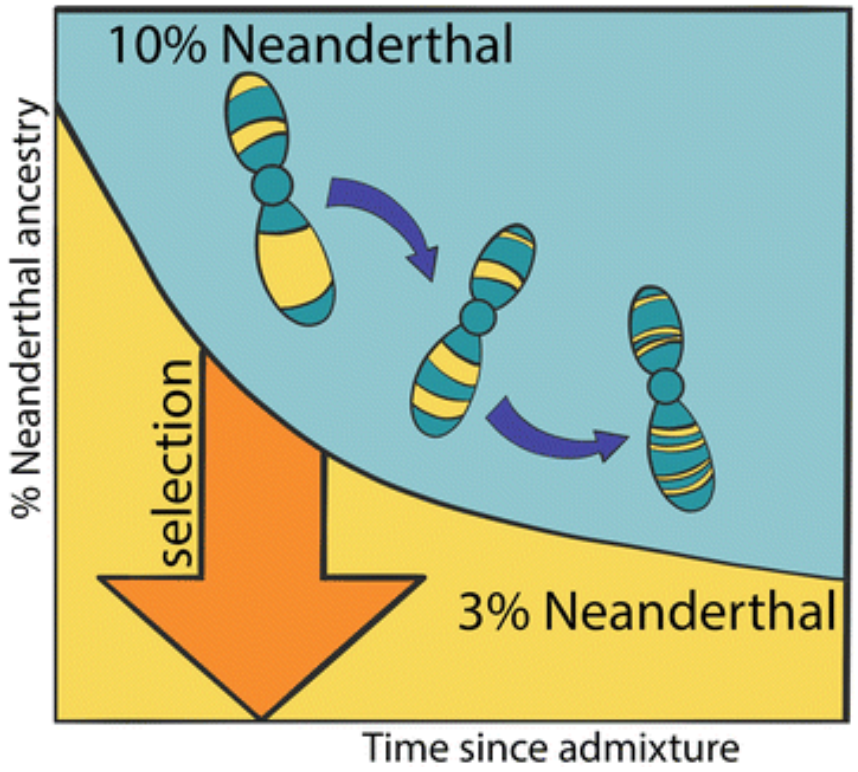
A gradual decline in archaic ancestry in Europeans dating from ~37 to 14 ka suggests that purifying selection lowered the amount of Neanderthal ancestry first introduced into ancient modern humans.




Trends in Genetics

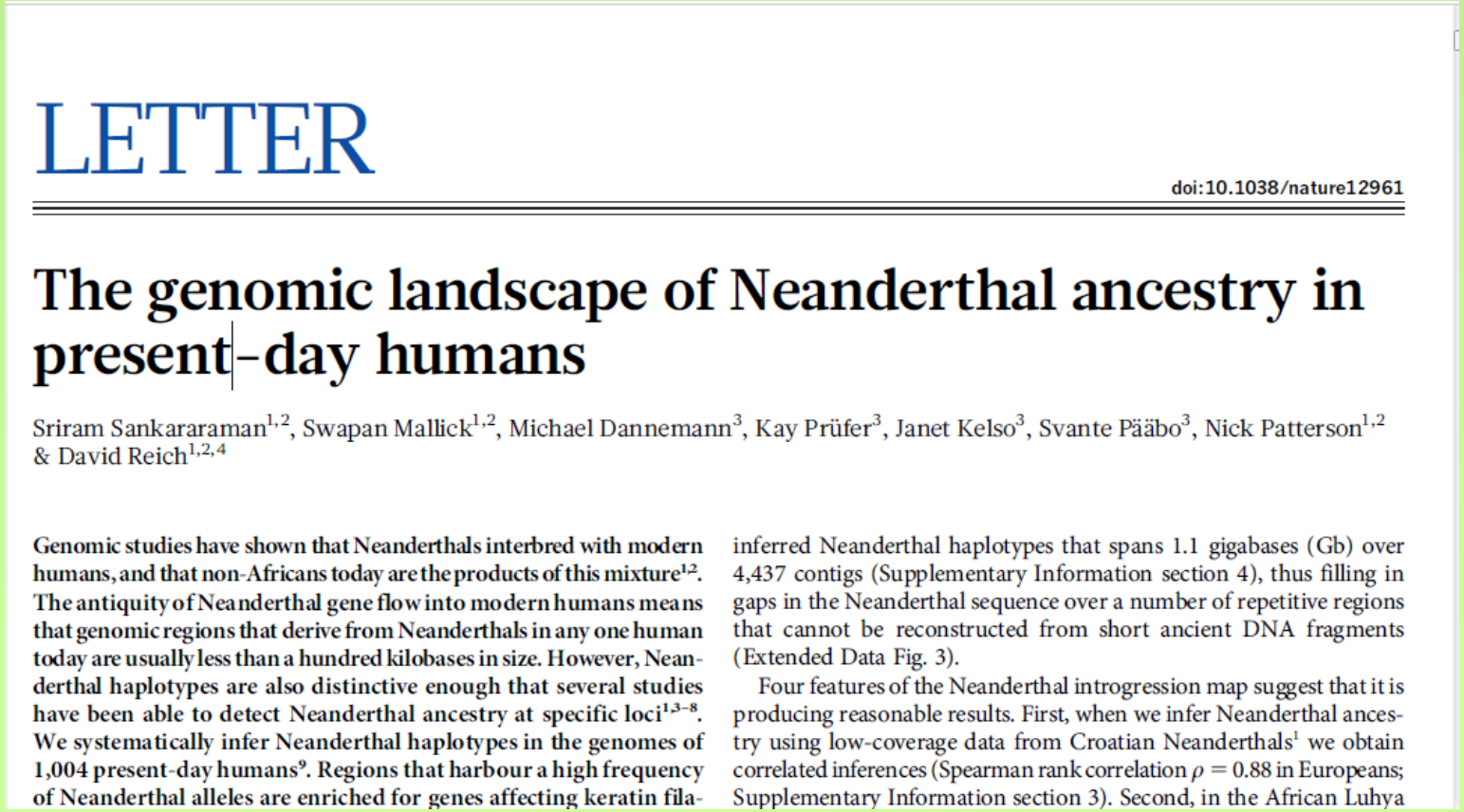
Yang & Fu 2018

- The antiquity of Neanderthal gene flow into modern humans means that genomic regions that derive from Neanderthals in any one human today are usually less than a hundred kilobases in size
- However, Neanderthal haplotypes are distinctive enough -> detectable from modern human ancestry



# The genomic landscape of Neanderthal ancestry in present-day humans

- Sankararaman et al. Nature 2014
- An unexpected finding is that regions with reduced Neanderthal ancestry are enriched in genes, implying selection to remove genetic material derived from Neanderthals.



LETTER

doi:10.1038/nature12961

## The genomic landscape of Neanderthal ancestry in present-day humans

Sriram Sankararaman[1,2], Swapan Mallick[1,2], Michael Dannemann[3], Kay Prüfer[3], Janet Kelso[3], Svante Pääbo[3], Nick Patterson[1,2] & David Reich[1,2,4]

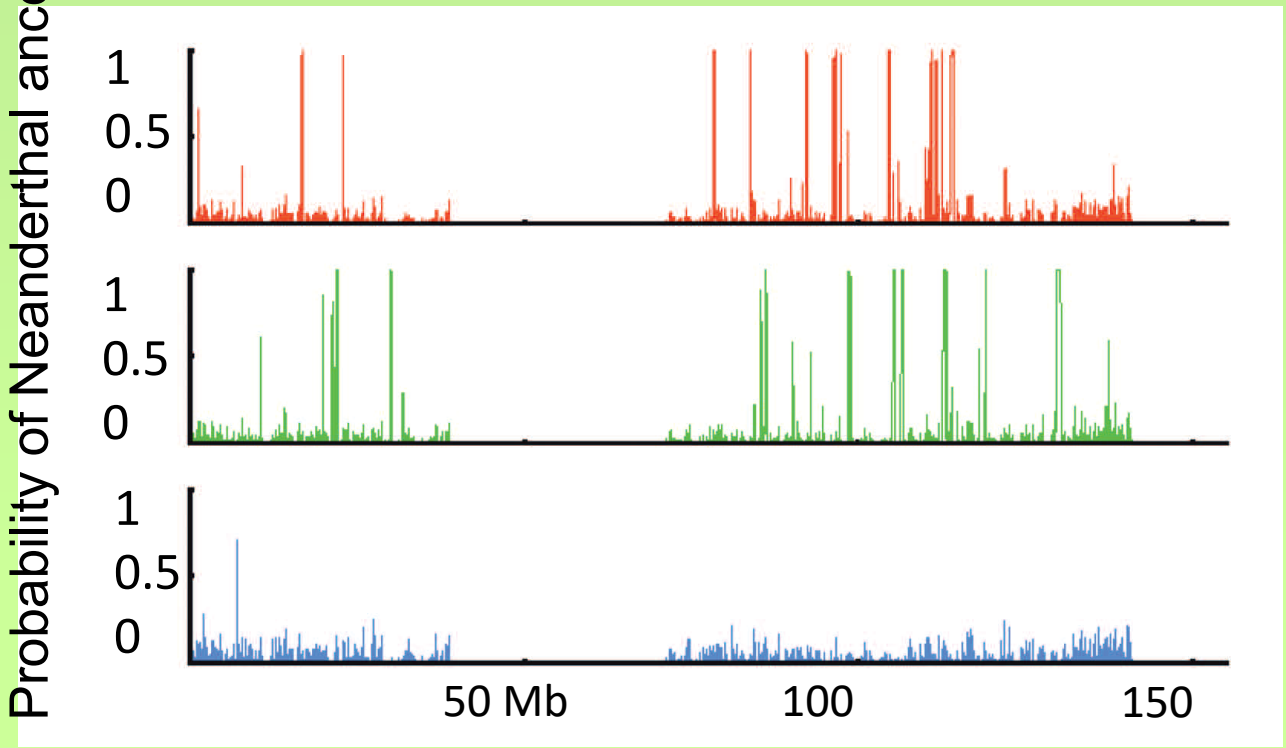
**Genomic studies have shown that Neanderthals interbred with modern humans, and that non-Africans today are the products of this mixture[1,2]. The antiquity of Neanderthal gene flow into modern humans means that genomic regions that derive from Neanderthals in any one human today are usually less than a hundred kilobases in size. However, Neanderthal haplotypes are also distinctive enough that several studies have been able to detect Neanderthal ancestry at specific loci[1,3–8]. We systematically infer Neanderthal haplotypes in the genomes of 1,004 present-day humans[9]. Regions that harbour a high frequency of Neanderthal alleles are enriched for genes affecting keratin fila-**

inferred Neanderthal haplotypes that spans 1.1 gigabases (Gb) over 4,437 contigs (Supplementary Information section 4), thus filling in gaps in the Neanderthal sequence over a number of repetitive regions that cannot be reconstructed from short ancient DNA fragments (Extended Data Fig. 3).

Four features of the Neanderthal introgression map suggest that it is producing reasonable results. First, when we infer Neanderthal ancestry using low-coverage data from Croatian Neanderthals[1] we obtain correlated inferences (Spearman rank correlation $\rho = 0.88$ in Europeans; Supplementary Information section 3). Second, in the African Luhya

# Maps of Neanderthal ancestry

Individual maps; the marginal probability of Neanderthal ancestry for one European-American, one east-Asian and one sub-Saharan-African phased genome across chromosome 9.




European individual (CEU)

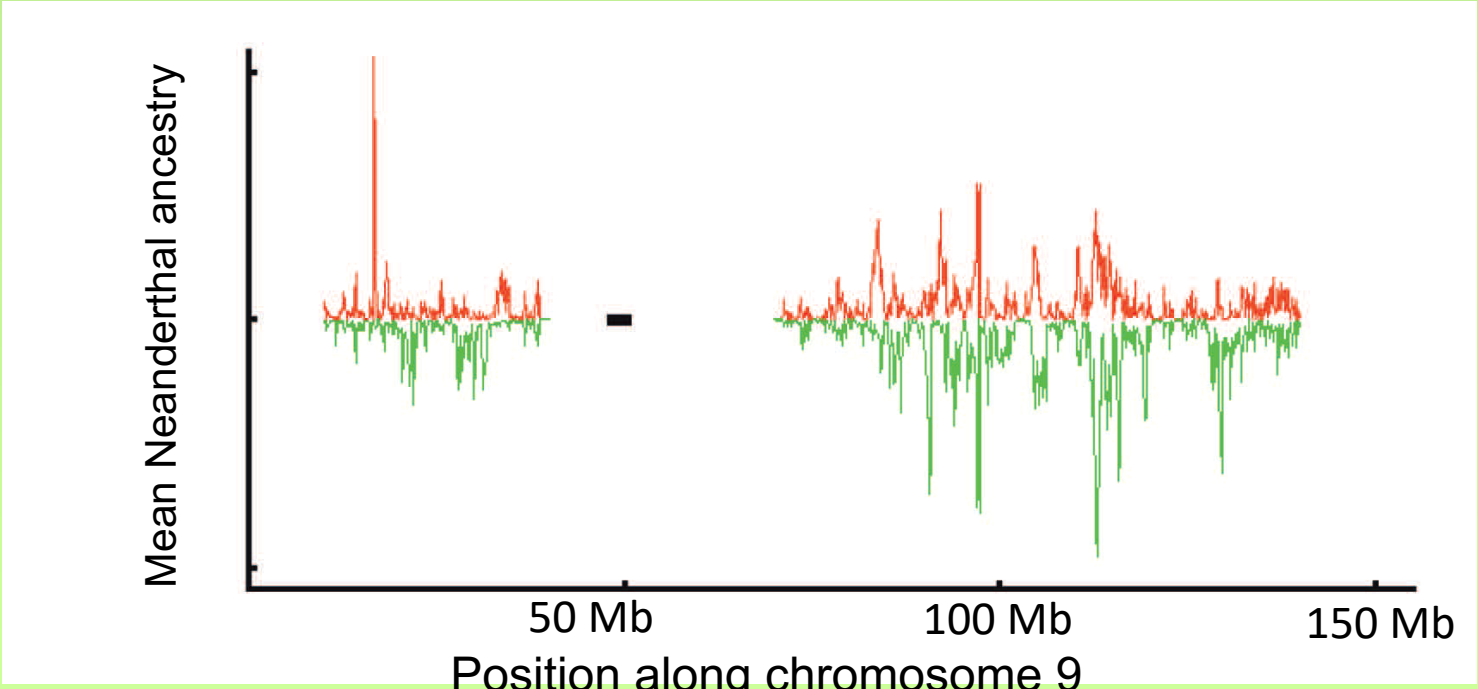
East-Asian individual (CHB )

Sub-Saharan-African Individual (LWK)

Sankararaman et al. Nature 2014

# Mean Neanderthal ancestry

Highest location-specific percentages: 62% in east-Asian and 64% in European populations



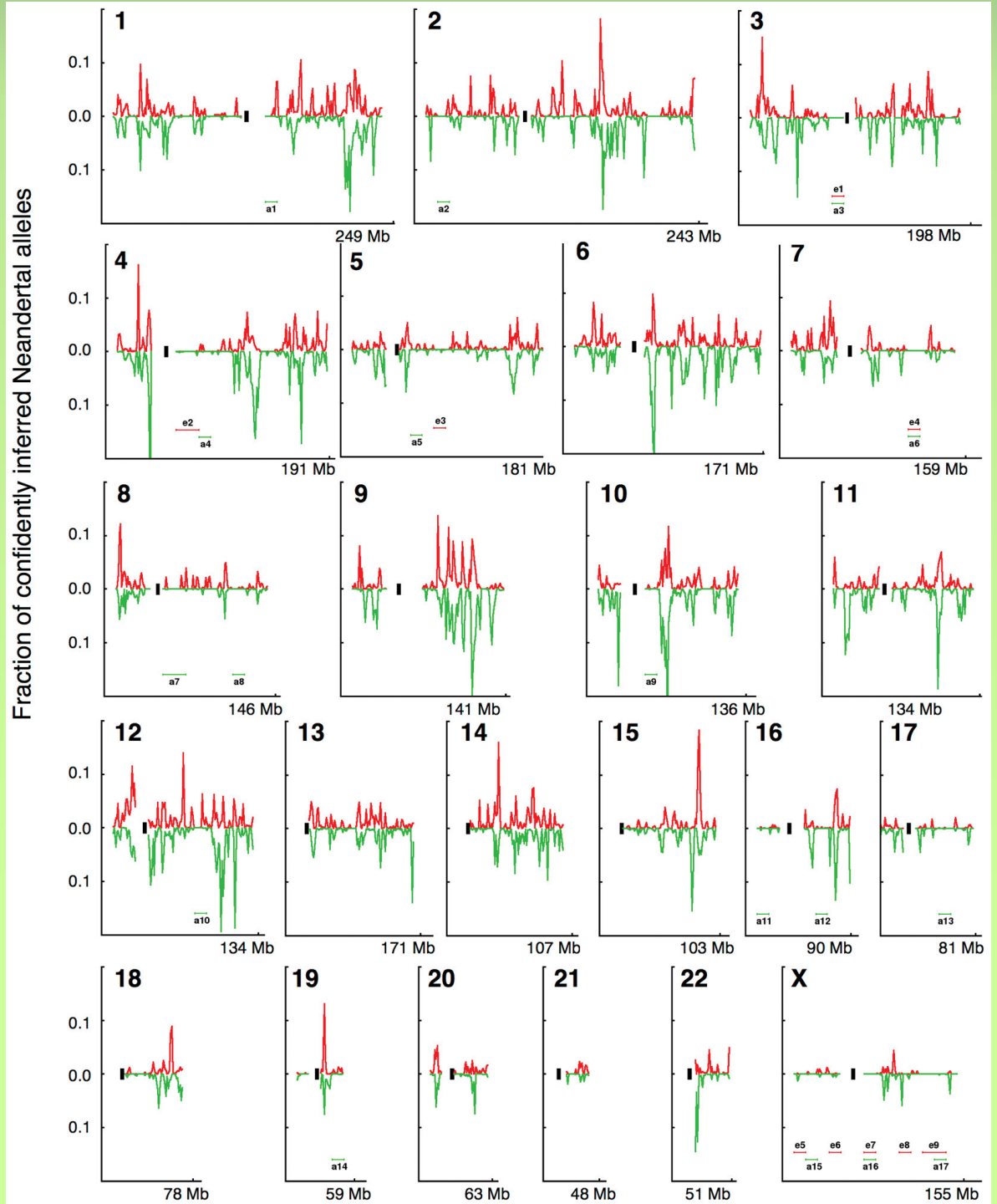

European individuals (red) and east-Asian individuals (green), averaged across all individuals from each population in non-overlapping 100-kb windows on chromosome 9. The black bar denotes the coordinates of the centromere.

Sankararaman et al. Nature 2014

# Maps of Neanderthal ancestry

Whole genome map of Neandertal ancestry in European and East Asian populations

Sankararaman et al. Nature 2014



## Genome-wide estimates of Neandertal ancestry

| | Population | Individuals | Neandertal ancestry (%) Autosomes | X |
|---|---|---|---|---|
| Europeans | CEU | 85 | 1.17±0.08 | 0.21±0.17 |
| | FIN | 93 | 1.20±0.07 | 0.19±0.14 |
| | GBR | 89 | 1.15±0.08 | 0.20±0.15 |
| | IBS | 14 | 1.07±0.06 | 0.23±0.18 |
| | TSI | 98 | 1.11±0.07 | 0.25±0.20 |
| East Asians | CHB | 97 | 1.40±0.08 | 0.30±0.21 |
| | CHS | 100 | 1.37±0.08 | 0.27±0.21 |
| | JPT | 89 | 1.38±0.10 | 0.26±0.21 |
| Americans | CLM | 60 | 1.14±0.12 | 0.22±0.16 |
| | MXL | 66 | 1.22±0.09 | 0.21±0.15 |
| | PUR | 55 | 1.05±0.12 | 0.20±0.15 |
| Africans | LWK | 97 | 0.08±0.02 | 0.04±0.07 |
| | ASW | 61 | 0.34±0.22 | 0.07±0.11 |

**Population abbreviations**

CEU: Utah Residents (CEPH) with Northern and Western European Ancestry
GBR: British in England and Scotland
IBS: Iberian population in Spain
TSI: Toscani in Italia
CHB: Han Chinese in Beijing, China
CHS: Southern Han Chinese
JPT: Japanese in Tokyo, Japan
CLM: Colombians from Medellin, Colombia
MXL: Mexican Ancestry from Los Angeles USA
PUR: Puerto Ricans from Puerto Rico
LWK: Luhya in Webuye, Kenya
ASW: Americans of African Ancestry in SW USA

Sankararaman et al. Nature 2014

## Extended Data Table 1

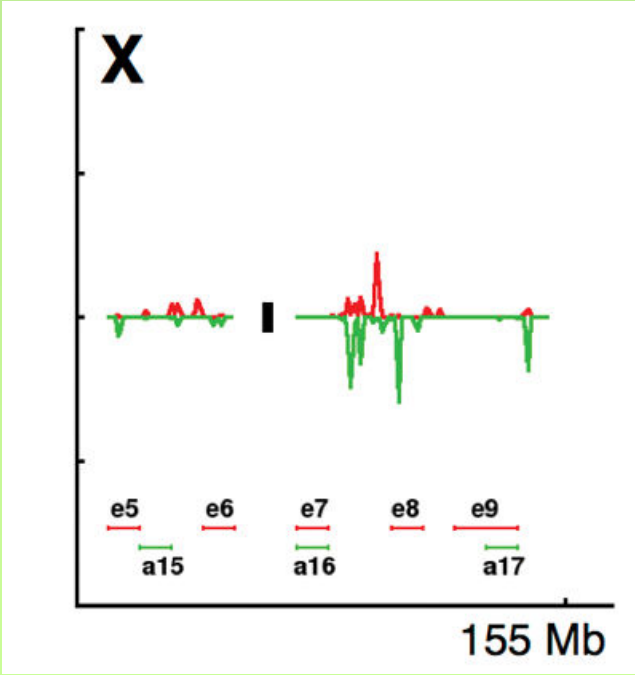
Gene categories enriched or depleted in Neandertal ancestry. Enrichment of Gene Ontology categories in genes with depleted or elevated Neandertal ancestry was assessed using the hypergeometric test implemented in the FUNC package. We report Family-wise error rate P-values (FWER) associated with each GO category (P-values corrected for the testing of multiple categories).

| Biological pathway (GO categorization) | Neandertal ancestry | Europe FWER | East Asian FWER |
|---|---|---|---|
| nucleic acid binding (molecular_function, GO:0003676) | Depleted | 0.018 | 0.032 |
| RNA processing (biological_process, GO:0006396) | Depleted | 0.004 | 0.049 |
| ribonucleoprotein complex (cellular_component, GO:0030529) | Depleted | <0.001 | 0.027 |
| organelle part (cellular_component, GO:0044422) | Depleted | <0.001 | 0.037 |
| intracellular organelle part (cellular_component, GO:0044446) | Depleted | <0.001 | 0.025 |
| mRNA metabolic process (biological_process, GO:0016071) | Depleted | <0.001 | 0.014 |
| nuclear lumen (cellular_component, GO:0031981) | Depleted | 0.039 | 0.017 |
| nuclear part (cellular_component, GO:0044428) | Depleted | 0.005 | 0.022 |
| keratin filament (cellular_component, GO:0045095) | Enriched | <0.001 | <0.001 |

Sankararaman et al. Nature 2014

# Unexpectedly low Neanderthal ancestry on the X chromosome

- In many species genes responsible for reduced male fertility map to the X chromosome -> could explain why the X chromosome was more resistant to introgression of Neanderthal ancestry than the autosomes.
- Genes that are specific to testes were enriched in regions of low Neanderthal ancestry
- Interbreeding of Neanderthals and modern humans introduced alleles onto the modern human genetic background that were not tolerated, which probably resulted in part from their contributing to male hybrid sterility.

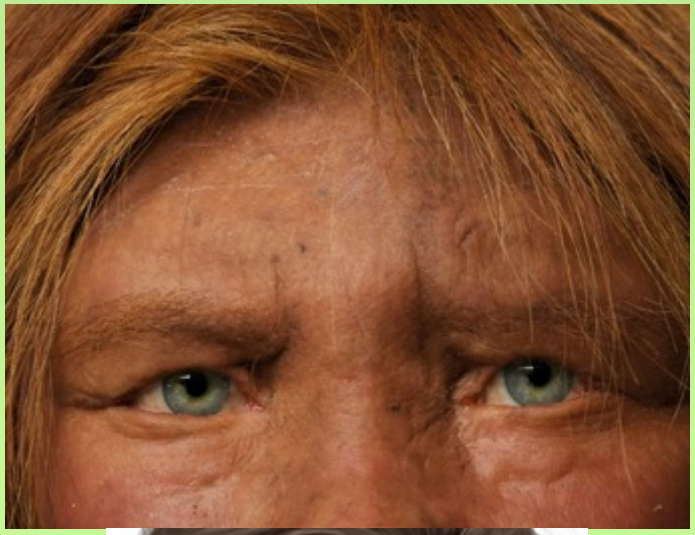



- Particularly remarkable when compared with mixed populations of present-day humans – no convincing signals of selection against alleles inherited from one of the mixing populations
- 5x time separation between Neanderthals and modern humans, compared to present-day European and west-African populations → the biological incompatibility is still far greater.

Sankararaman et al. Nature 2014

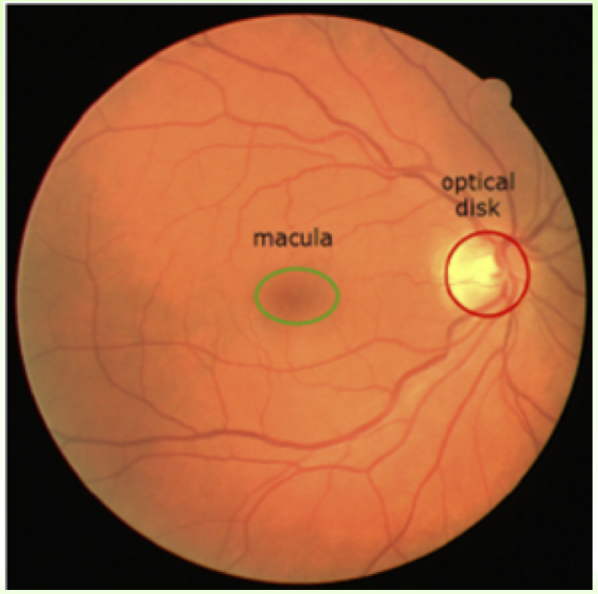
# Modern human genes with the highest inferred Neanderthal ancestry

- Genes involved in keratin filament formation significantly enriched in Neanderthal ancestry in European and east-asian populations -> Neanderthal alleles that affect skin and hair may have helped modern humans to adapt to non-African environments.
- Alleles of Neanderthal origin that overlap alleles that have been associated with **phenotypes of medical relevance:**
  - Lupus (systemic autoimmune disease, can affect many different body systems — joints, skin, kidneys, blood cells, brain, heart and lungs)



# Alleles of Neanderthal origin with possible medical relevance

- Biliary cirrhosis (autoimmune disease of the liver, “sappikirroosi”)
- Crohn’s disease (inflammatory bowel disease)
- Optic-disk size (the point in the eye where the optic nerve fibers leave the retina. "The Blind Spot")
- Smoking behavior
- IL-18 levels (induces cell-mediated immunity following infection with microbial products like lipopolysaccharide)
- Type 2 diabetes
- Progesterone receptor PGR locus. Deleterious missense allele in Neanderthal genome, later introgressed in modern human populations. Preterm birth, ovarian cancer. (Li et al. 2018)

# Immune genes!

- Deschamps M, Laval G, Fagny M, Itan Y, Abel L, Casanova J-L, Patin E, Quintana-Murci L. Genomic signatures of selective pressures and introgression from archaic hominins at human innate immunity genes. Am J Hum Genet. 2016;98:5–21. 3.
- Quach H, Rotival M, Pothlichet J, Loh Y-HE, Dannemann M, Zidane N, Laval G, Patin E, Harmant C, Lopez M, et al. Genetic adaptation and Neandertal admixture shaped the immune system of human populations. Cell. 2016; 167:643–56. e617.
- For example, parts of human leucocyte antigen (*HLA*) alleles were derived from archaic humans, which provided advantages for survival for ancestry of modern humans after the out-of-Africa expansion

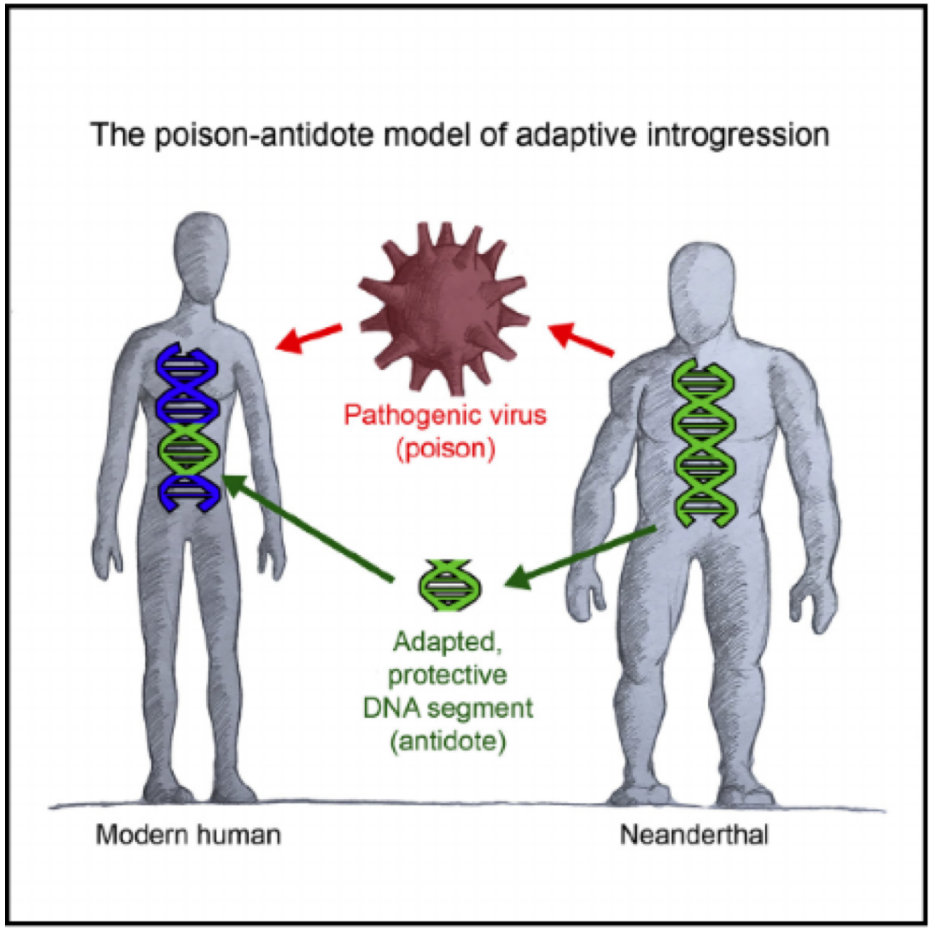
# Introgression of Neandertal- and Denisovan-like haplotypes contributes to adaptive variation in human Toll-like receptors.

Dannemann M, Andrés AM, Kelso J Am J Hum Genet. 2016;98:22–33.

- A cluster of three Toll-like receptors (TLR6-TLR1-TLR10) in modern humans carries three distinct archaic haplotypes, indicating repeated introgression from archaic humans.
  - Two of these haplotypes are most similar to the Neandertal genome, and the third haplotype is most similar to the Denisovan genome.
- The Toll-like receptors are key components of innate immunity and provide an important first line of immune defense against bacteria, fungi, and parasites.
- The unusually high allele frequencies and unexpected levels of population differentiation indicate that there has been local positive selection on multiple haplotypes at this locus.
- Archaic-like alleles underlie differences in the expression of the TLR genes and are associated with reduced microbial resistance and increased allergic disease in large cohorts

# RNA viruses drove adaptive introgression between Neanderthals and modern Humans

- Neanderthals and modern humans interbred and exchanged viruses
- Neanderthal DNA introgressed in modern humans helped them adapt against viruses
- Neanderthal DNA-based adaptation was particularly strong against RNA viruses in Europeans
- Ancient epidemics can be detected through the lens of abundant host genomic adaptation



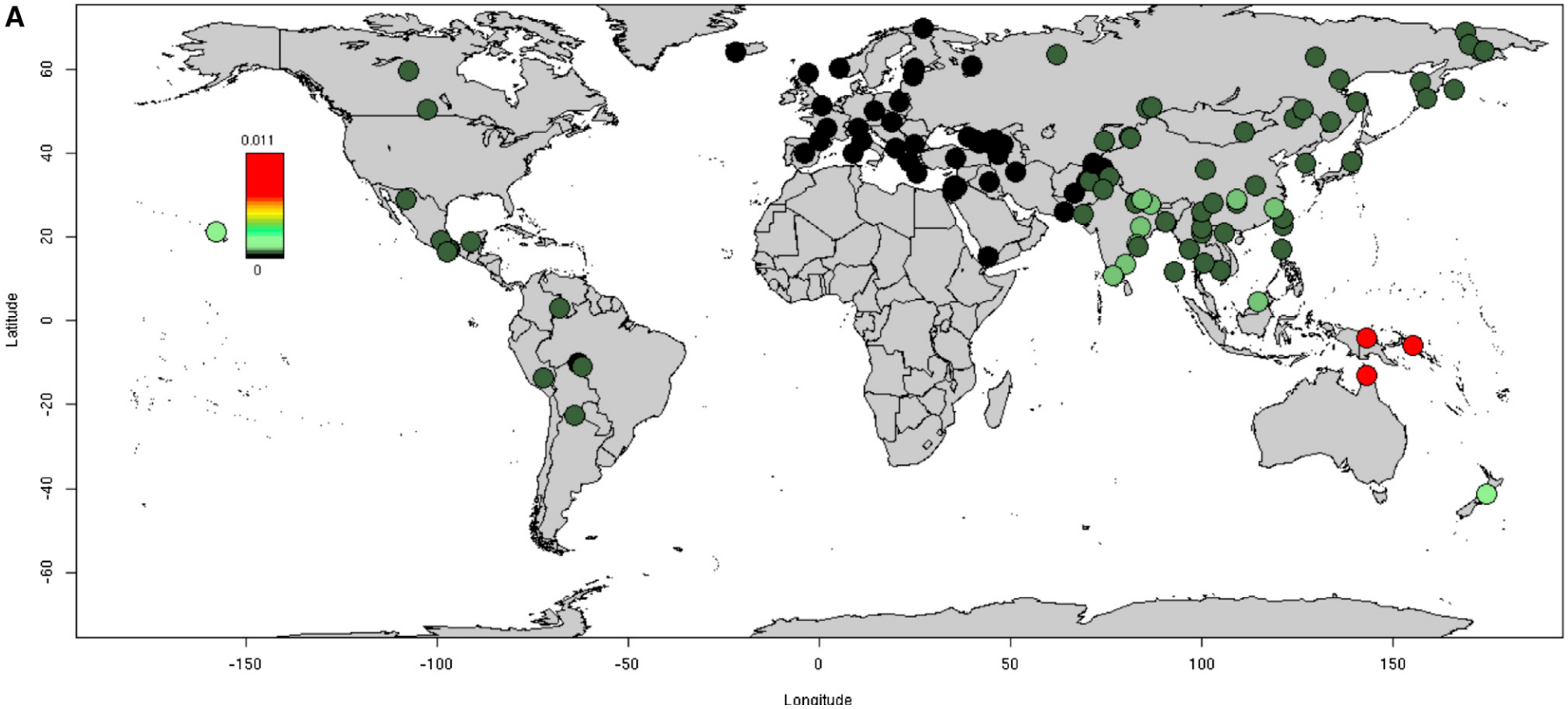

Enard & Petrov 2018

# Denisovan ancestry

- Denisovan admixture into modern humans occurred after Neanderthal admixture
- There is more Denisovan ancestry in South Asians than expected; Some present-day humans derive up to 5% of their ancestry from archaic Denisovans, an even larger proportion than the 2% from Neanderthals
- Denisovan ancestry, just like Neanderthal ancestry, has been deleterious on a modern human genetic background, as reflected by its depletion near genes.
- The reduction of both archaic ancestries is especially pronounced on chromosome X and near genes more highly expressed in testes than other tissues
- This suggests that reduced male fertility may be a general feature of mixtures of human populations diverged by >500,000 years.

Sankararaman et al. 2016

Variation in Denisovan Ancestry Proportion. The color scale is not linear to allow saturation of the high Denisova proportions in Oceania (bright red) and better visualization of the peak of Denisova proportion in South Asia.

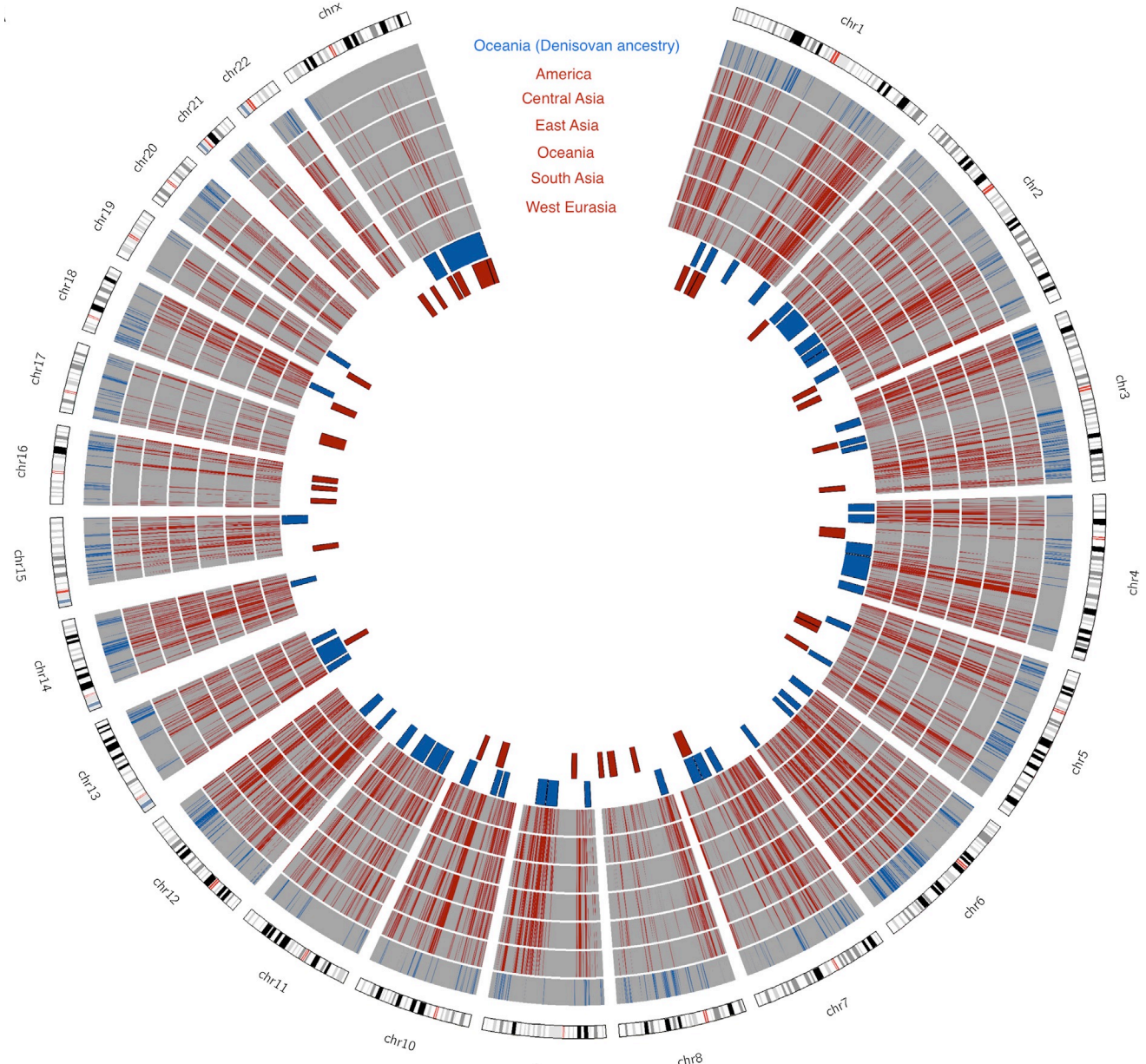



Sankararaman et al. 2016

# Fine-Scale Maps of Denisovan and Neanderthal Introgression

- Non-overlapping 100 kb windows that have non-zero inferred archaic ancestry in each of six populations (blue, Denisova; red, Neanderthal).
- In the innermost rings, deserts (windows >10 Mb).
- The desert on chromosome 7 contains the FOXP2 gene, which probably has role in enabling modern human speech and language
- The finding that this region is also a desert of Denisovan ancestry strengthens the evidence that the modern human version of this gene may be critical for modern human biology

Sankararaman et al. 2016



# The phenotypic legacy of admixture between modern humans and Neandertals

- Simonti et al. 2016 studied contribution of common Neandertal variants to over 1000 electronic health record (EHR)–derived phenotypes in ~28,000 adults of European ancestry.
- Showed that a large number of Neanderthal variants at different loci influence risk of a number of disease traits, including depression, skin lesions, and blood-clotting disorders, and that Neanderthals contributed both risk and protective alleles for these traits
- Discovered and replicated associations of Neandertal alleles with neurological, psychiatric, immunological, and dermatological phenotypes.
- Neandertal alleles together explained a significant fraction of the variation in risk for depression and skin lesions resulting from sun exposure (actinic keratosis)
- Individual Neandertal alleles were significantly associated with specific human phenotypes, including hypercoagulation and tobacco use.

Simonti et al. 2016 Science

# The Contribution of Neanderthals to Phenotypic Variation in Modern Humans

Dannemann and Kelso 2017 AJHG

- Genetic contribution of Neanderthals to non-disease phenotypes in modern humans
- Baseline phenotypes collected for 112,000 individuals by the UK Biobank
- 136 phenotypes, including diet, cognitive functions, physical measurements, and self-reported medical conditions for which data were available for at least 80,000 individuals
- 822,111 SNPs screened

# Archaic alleles with genome-wide-significant phenotype associations

**Table 1. Archaic Alleles with Genome-wide-Significant Phenotype Associations**

| Phenotype | Meta-phenotype | Tag aSNP | Association p Value | Neanderthal Allele Frequency | Data Type | Archaic Haplotype (hg19) | Overlapping Gene(s) | Missense |
|---|---|---|---|---|---|---|---|---|
| Hair color (natural before graying) | sun exposure | chr16: 89,947,203 (rs62052168) | $3.7 \times 10^{-202}$ | 0.097 | categorical | chr16: 89,813,988–90,008,296 | *SPIRE1, TCF25, MC1R, TUBB3, FANCA* | – |
| Skin color | sun exposure | chr6: 45,553,288 (rs115127056) | $4.21 \times 10^{-30}$ | 0.075 | categorical | chr6: 45,533,261–45,680,205 | *RUNX2* | – |
| Ease of skin tanning | sun exposure | chr9: 16,804,167 (rs10962612) | $1.59 \times 10^{-22}$ | 0.77 | categorical | chr9: 16,720,122–16,804,167 | *BNC2* | – |
| Hair color (natural before graying) | sun exposure | chr14: 92,793,206 (rs77004437) | $4.56 \times 10^{-21}$ | 0.089 | categorical | chr14: 92,767,097–92,801,297 | *SLC24A4* | – |
| Skin color | sun exposure | chr9: 16,904,635 (rs62543578) | $1.6 \times 10^{-14}$ | 0.19 | categorical | chr9: 16,891,561–16,915,874 | *BNC2** | – |
| Comparative height size at age 10 years | early life factors | chr19: 31,033,240 (rs56199929) | $3.97 \times 10^{-14}$ | 0.16 | categorical | chr19: 30,982,165–31,041,053 | *ZNF536* | – |
| Pulse rate (automated reading) | blood pressure | chr6: 121,947,984 (rs55913590) | $6.48 \times 10^{-14}$ | 0.029 | continuous | chr6: 121,910,814–122,062,861 | *GJA1** (MIM: 121014) | – |
| Morning or evening person (chronotype) | sleep | chr2: 239,316,043 (rs75804782) | $3.57 \times 10^{-10}$ | 0.12 | categorical | chr2: 239,316,043–239,470,654 | *ASB1* | A 2 |
| Skin color | sun exposure | chr11: 89,996,325 (rs74918882) | $5.54 \times 10^{-10}$ | 0.041 | categorical | chr11: 89,996,325–90,041,511 | *CHORDC1** | – |
| Impedance of leg (left) | impedance measures | chr15: 84,716,986 (rs12902672) | $1.46 \times 10^{-9}$ | 0.27 | continuous | chr15: 84,703,470–85,114,447 | *ADAMTSL3* (MIM: 609199), *GOLGA6L4* | A ( 8 |

More than 20 variants in MC1R have been shown to alter hair color in humans

However the archaic haplotype is UNDERREPRESENTED in red-haired individuals

- Associated with skin pigmentation in Europeans
- Archaic allele present at freq 66% in Europeans, and is associated with increased incidence of childhood sunburn, poor tanning and increased risk of keratosis
- Shows recent positive selection in Europeans, perhaps indicating their importance in recent local adaptation.
- Interestingly, a second, less-frequent (19%) archaic haplotype near BNC2 shows strong associations with darker skin pigmentation

**Table 1.** *Continued*

| Phenotype | Meta-phenotype | Tag aSNP | Association p Value | Neanderthal Allele Frequency | Data Type | Archaic Haplotype (hg19) | Overlapping Gene(s) | Missense Mutations | Associated eQTLs | FDR ILS Test |
|---|---|---|---|---|---|---|---|---|---|---|
| Incidence of childhood sunburn | sun exposure | chr9: 16,804,167 (rs10962612) | $1.49 \times 10^{-9}$ | 0.77 | continuous | chr9: 16,720,122–16,804,167 | *BNC2* | – | *BNC2*: muscle (skeletal) | $1.62 \times 10^{-12}$ |
| Sitting height | body-size measures | chr10: 70,019,371 (rs12571093) | $1.52 \times 10^{-9}$ | 0.16 | continuous | chr10: 70,009,572–70,059,496 | *PBLD* (MIM: 612189) | – | *PBLD*: muscle (skeletal), brain (cortex), brain (caudate; basal ganglia), brain (putamen; basal ganglia)<br>*ATOH7* (MIM: 609875): artery (coronary), breast (mammary tissue), skin (not sun exposed; suprapubic), minor salivary gland, adrenal gland, pancreas, esophagus (gastresophageal junction), colon (transverse), adipose | 0.002 |
| Hair color (natural before graying) | sun exposure | chr6: 503,851 (rs71550011) | $2.91 \times 10^{-9}$ | 0.07 | categorical | chr6: 503,851–544,833 | *EXOC2* | | | |
| Daytime dozing or sleeping (narcolepsy) | sleep | chr10: 94,711,457 (rs112294410) | $4.09 \times 10^{-9}$ | 0.017 | categorical | chr10: 94,574,048–94,756,023 | *EXOC6* | – | – | $<2.2 \times 10^{-22}$ |
| Impedance of leg (right) | impedance measures | chr15: 84,716,986 (rs12902672) | $5.54 \times 10^{-9}$ | 0.27 | continuous | chr15: 84,703,470–85,114,447 | *ADAMTSL3*, *GOLGA6L4* | *ADAMTSL3* (chr15: 84,706,461) | *NMB*: muscle (skeletal), minor salivary gland, adrenal gland, pancreas, esophagus (muscularis), esophagus (mucosa), stomach, small intestine | $1.17 \times 10^{-5}$ |

Individuals with blonde hair show a higher frequency of the Neanderthal haplotype at EXOC2

suggesting reduced body fat composition

- more than half of the significantly associated alleles are related to skin and hair traits

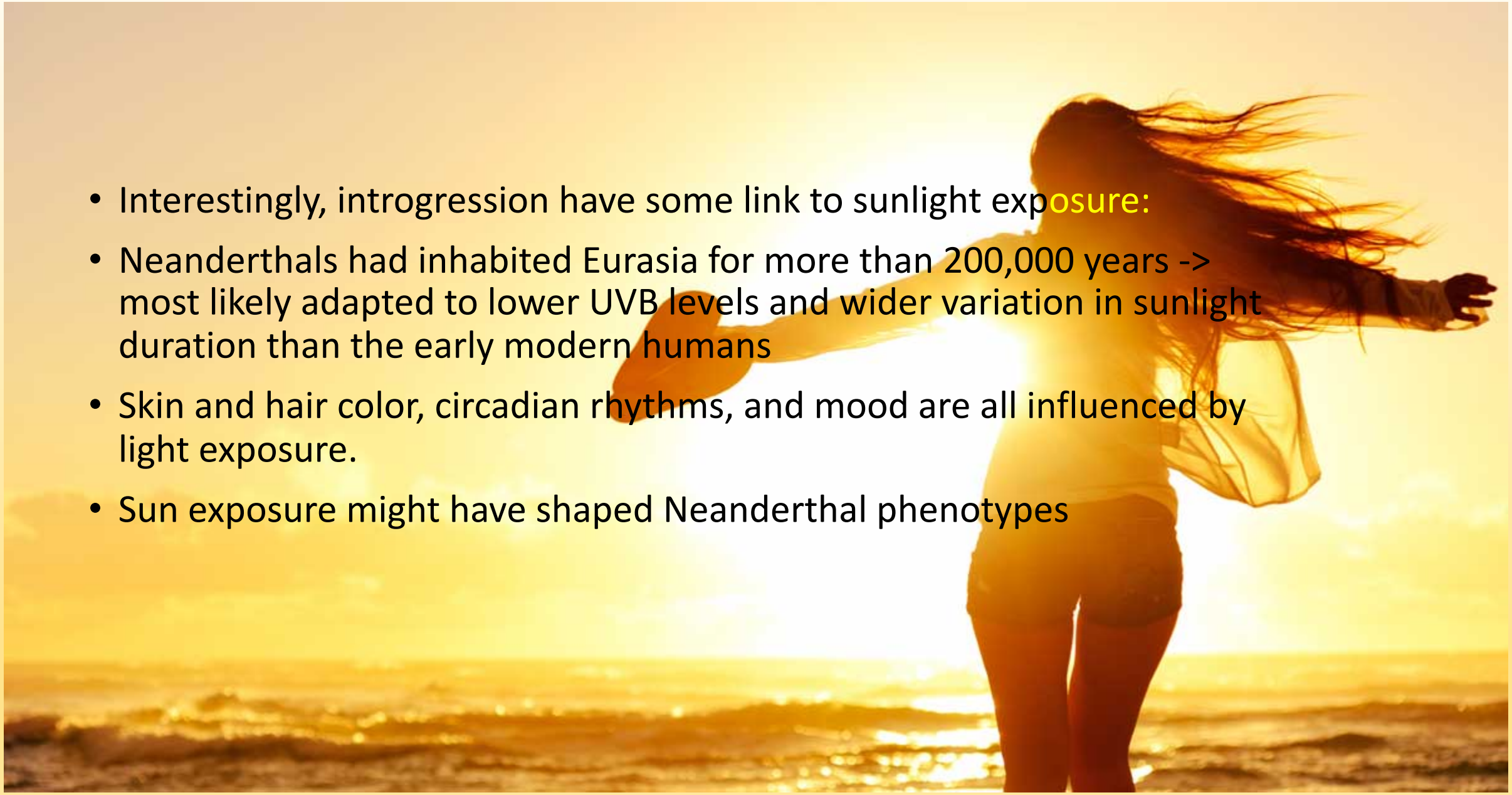
# Continued: **The Contribution of Neanderthals to Phenotypic Variation in Modern Humans**

Dannemann and Kelso 2017 AJHG

- Archaic alleles near ASB1[#] and EXOC6* are associated with a preference for being an ‘‘evening person’’ and an increased tendency for daytime napping and narcolepsy
- The phenotype of increased frequencies of ‘unenthusiasm or disinterest in the last 2 weeks’ was significantly associated with an archaic haplotype nearest gene CDH6
- Four phenotypes, all behavioral, to which Neanderthal alleles contribute more phenotypic variation than non-archaic alleles: chronotype, loneliness or isolation, frequency of unenthusiasm or disinterest in the last 2 weeks, and smoking status
- Some of the psychiatric and metabolic phenotypes, such as obesity, identified in Simonti et al were not replicated in Dannemann & Kelso

# Ankyrin Repeat And SOCS Box Containing 1

*Exocyst Complex Component 6, one of the components of a multiprotein complex required for exocytosis.

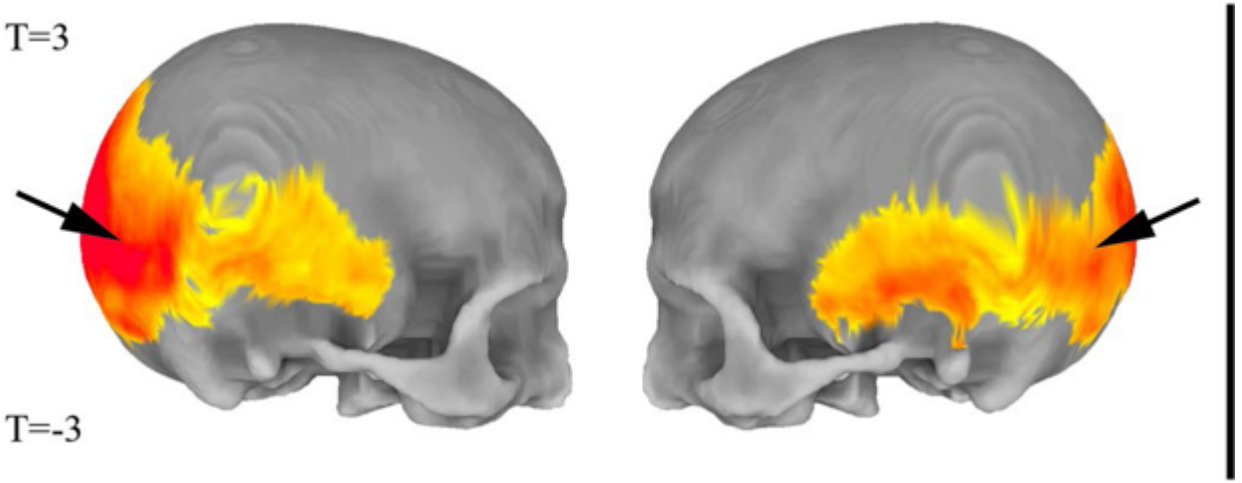


- Interestingly, introgression have some link to sunlight exposure:
- Neanderthals had inhabited Eurasia for more than 200,000 years -> most likely adapted to lower UVB levels and wider variation in sunlight duration than the early modern humans
- Skin and hair color, circadian rhythms, and mood are all influenced by light exposure.
- Sun exposure might have shaped Neanderthal phenotypes

# Neanderthal-derived genetic variation shapes modern human cranium and brain

Gregory et al. Sci Rep 2017

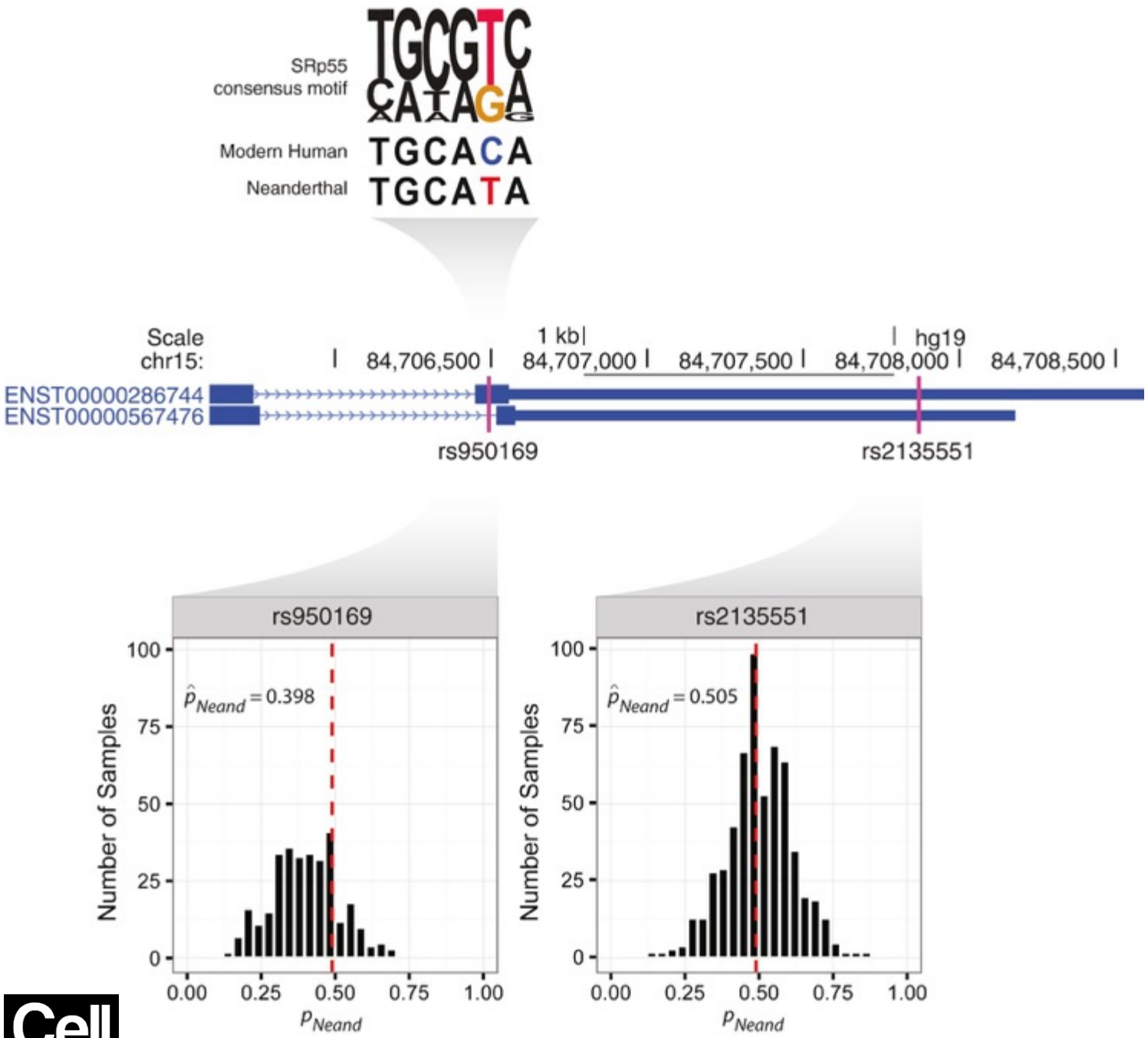
- Using MRI in a large cohort of healthy individuals of European-descent, the amount of Neanderthal-originating polymorphism carried in living humans is related to cranial and brain morphology.
- higher “NeanderScore” is associated with skull shapes resembling those of known Neanderthal cranial remains, particularly in occipital and parietal bones.
- Higher NeanderScore findings in t and intraparietal sulcus.
- This work provides insights into a suggests that Neanderthal-derive functional in the contemporary p



# Impacts of Neanderthal-introgressed sequences on the landscape of human gene expression

McCoy et al 2017 Cell

- Regulatory variation influencing gene expression is a key contributor to phenotypic diversity, both within and between species.
- One-quarter of Neanderthal-introgressed haplotypes show *cis*-regulatory effects
- Introgressed regulatory variants add to genomic complexity and phenotypic diversity
- Neanderthal alleles are downregulated in genes expressed in the brain and testes
- Widespread expression differences between Neanderthal and modern human alleles
- Brain regions and testes exhibited significant downregulation of Neanderthal alleles relative to other tissues, consistent with natural selection influencing the tissue-specific regulatory landscape.




- Height and schizophrenia-associated introgression tag SNP (rs950169) in *ADAMTSL3* shows evidence of allele-specific expression (ASE ) mediated by an effect on splicing regulation.
- The Neanderthal-introgressed (T) allele of this variant is predicted to increase binding of the SRp55 splicing factor compared to the modern human (C) allele and splice out a portion of exon 30 containing the SNP itself.
- Patterns of ASE (histograms) are consistent with this model of splicing regulation.

McCoy et al 2017 Cell

# Functional implications of Neandertal introgression in modern humans

Dannemann et al. 2017 *Genome Biology* **18**:61

- Gene expression changes are more often associated with Neandertal ancestry than expected
- The introgressed non-synonymous variants tend to have less predicted functional effect on modern human proteins than mutations that arose on the human lineage.
- Conversely, introgressed alleles contribute proportionally more to expression variation than non-introgressed alleles.
- **Higher frequency archaic variants** contribute significantly more to gene expression changes than lower frequency archaic variants
- -> at least some of the archaic alleles that modify gene expression may have been driven to higher frequencies by positive selection
- Changes in gene expression are likely to have important adaptive effects in humans

- **Major influence of Neandertal introgressed alleles is through their effects on gene regulation**