

Ethics Debate

Tuesday April 23

Aaron Gitler/Stuart Kim

American College of Medical Genetics and Genomics

ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing

Robert C. Green, MD, MPH^{1,2}, Jonathan S. Berg, MD, PhD³, Wayne W. Grody, MD, PhD⁴⁻⁶, Sarah S. Kalia, ScM, CGC¹, Bruce R. Korf, MD, PhD⁷, Christa L. Martin, PhD, FACMG⁸, Amy McGuire, JD, PhD⁹, Robert L. Nussbaum, MD¹⁰, Julianne M. O'Daniel, MS, CGC¹¹, Kelly E. Ormond, MS, CGC¹², Heidi L. Rehm, PhD, FACMG^{2,13}, Michael S. Watson, MS, PhD, FACMG¹⁴, Marc S. Williams, MD, FACMG¹⁵, Leslie G. Biesecker, MD¹⁶

Ethics Debate

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NEWS & ANALYSIS

GENOME SEQUENCING

Return of Unexpected DNA Results Urged

Jennifer Couzin-Frankel

Geneticists, ethicists, and physicians reacted with shock to recommendations released last week by the American College of Medical Genetics and Genomics (ACMG): that patients undergoing genomic sequencing should be informed whether 57 of their genes put them at risk of serious disease in the future, even if they don't want that

But many experts contacted by *Science*, other than those on the ACMG working group, panned the recommendations. "They say that labs and

Height Exercise from Thursday

Choose Your Sex

Male

Female

Mother's Height

60

cm

in

Father's Height

63

cm

in

Your Actual Height

68

cm

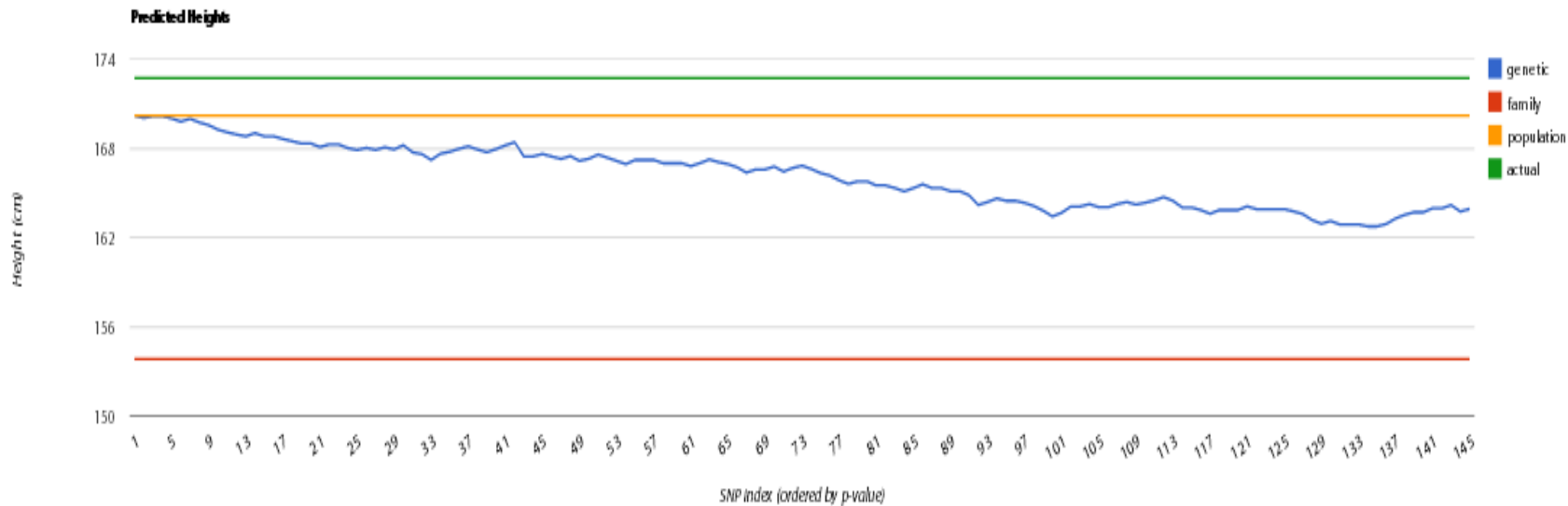
in

Predict My Height

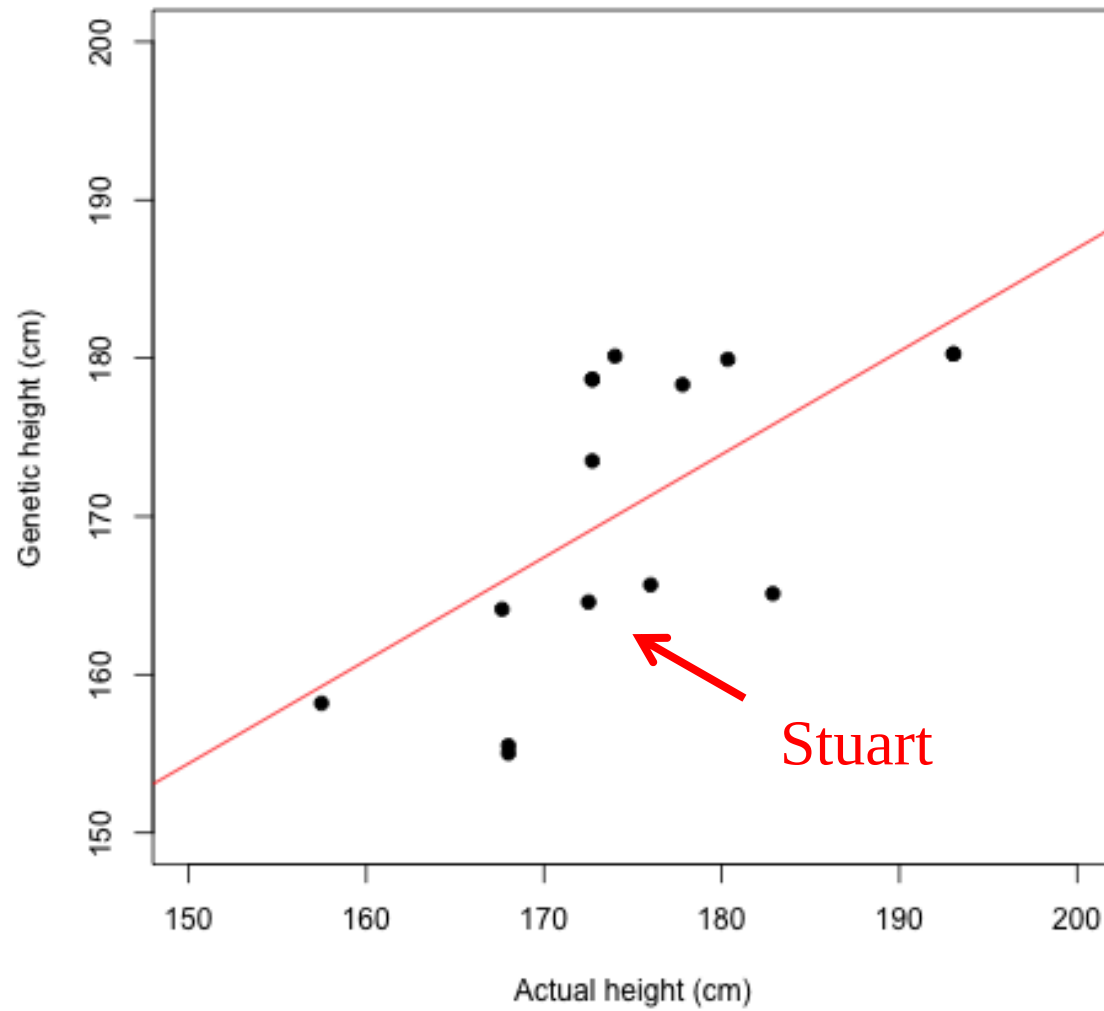
Stuart's height results

Genetic	Family	Population	Actual
163.92 cm	153.82000000000002 cm	170.2 cm	172.72 cm

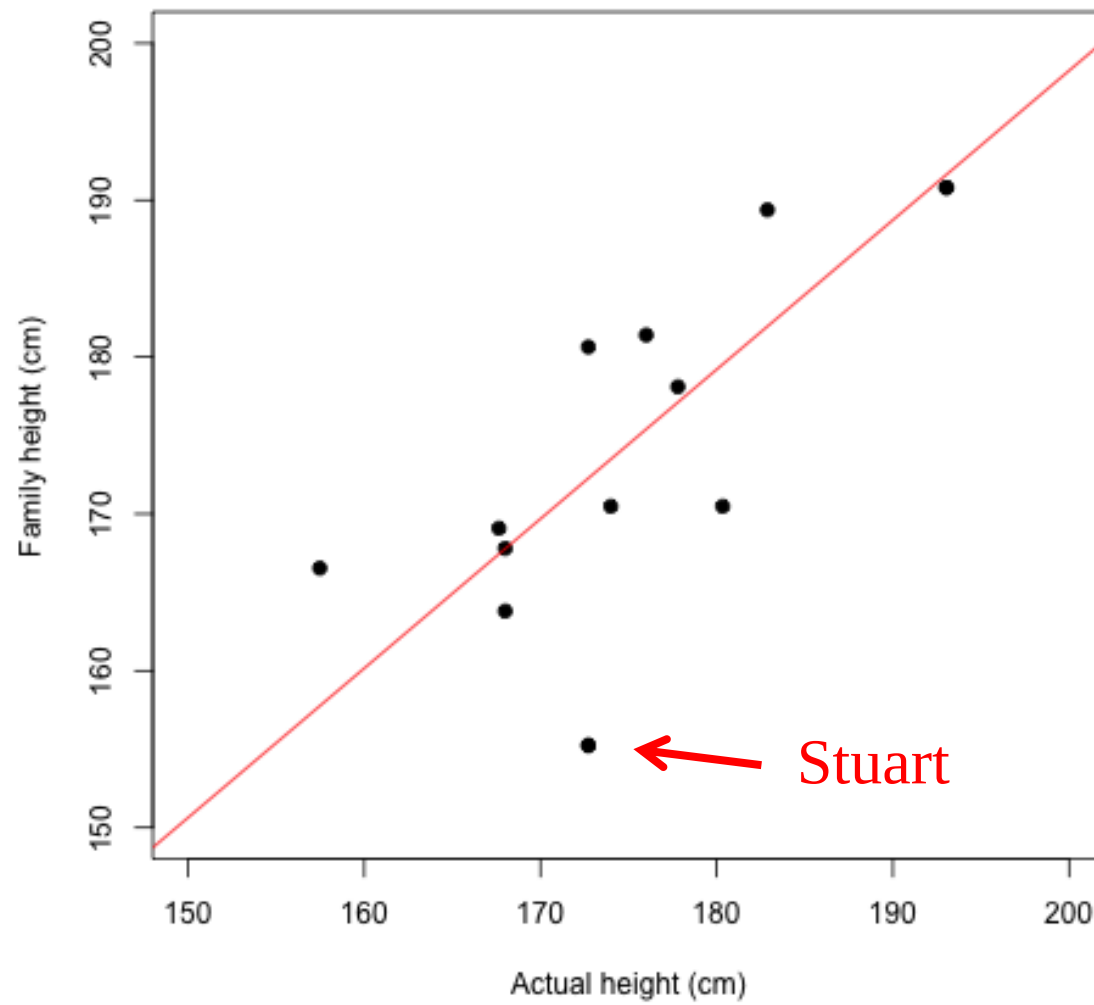
[Submit my SNPs](#)



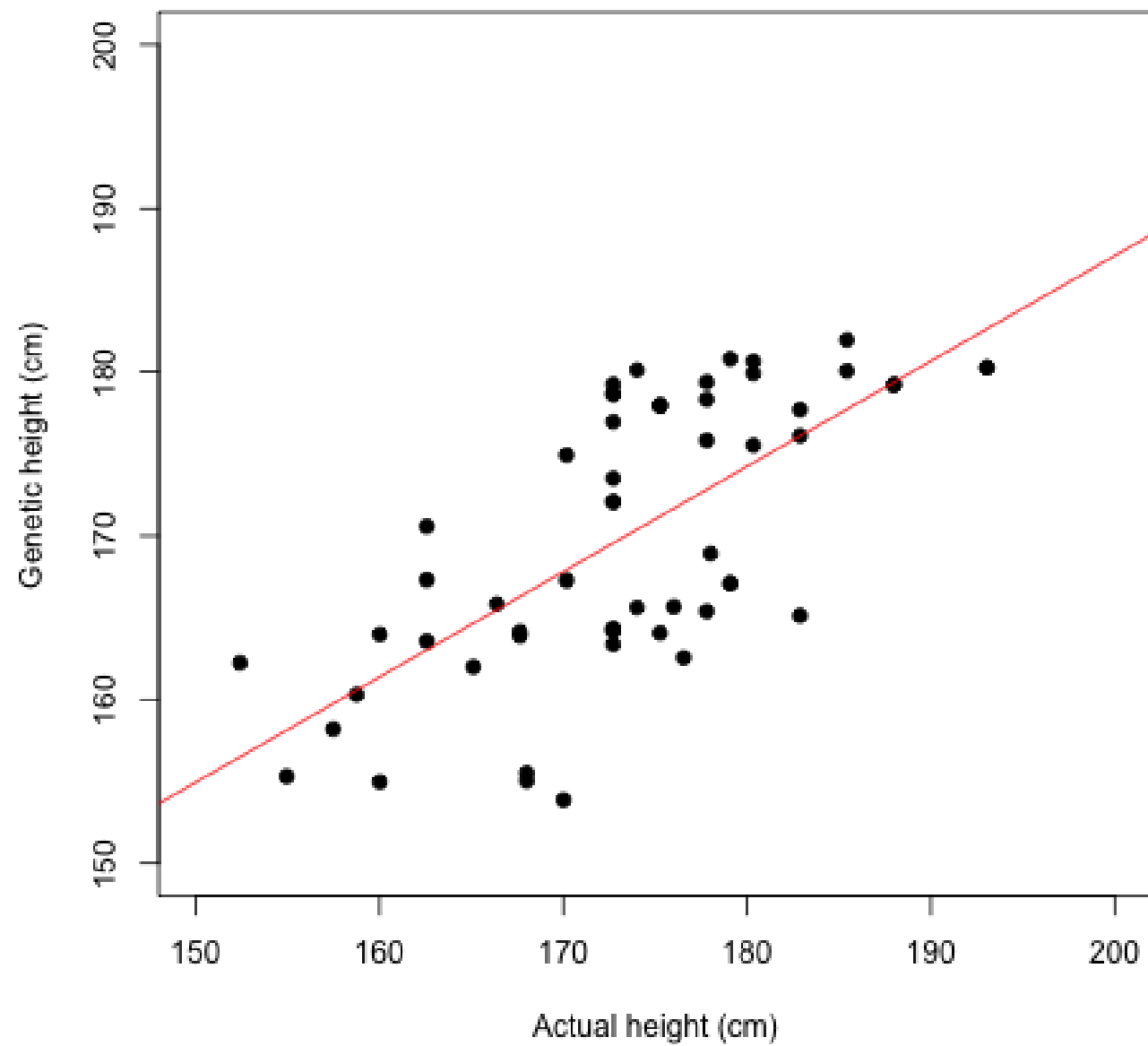
Actual vs predicted genetic height, correlation= 0.355



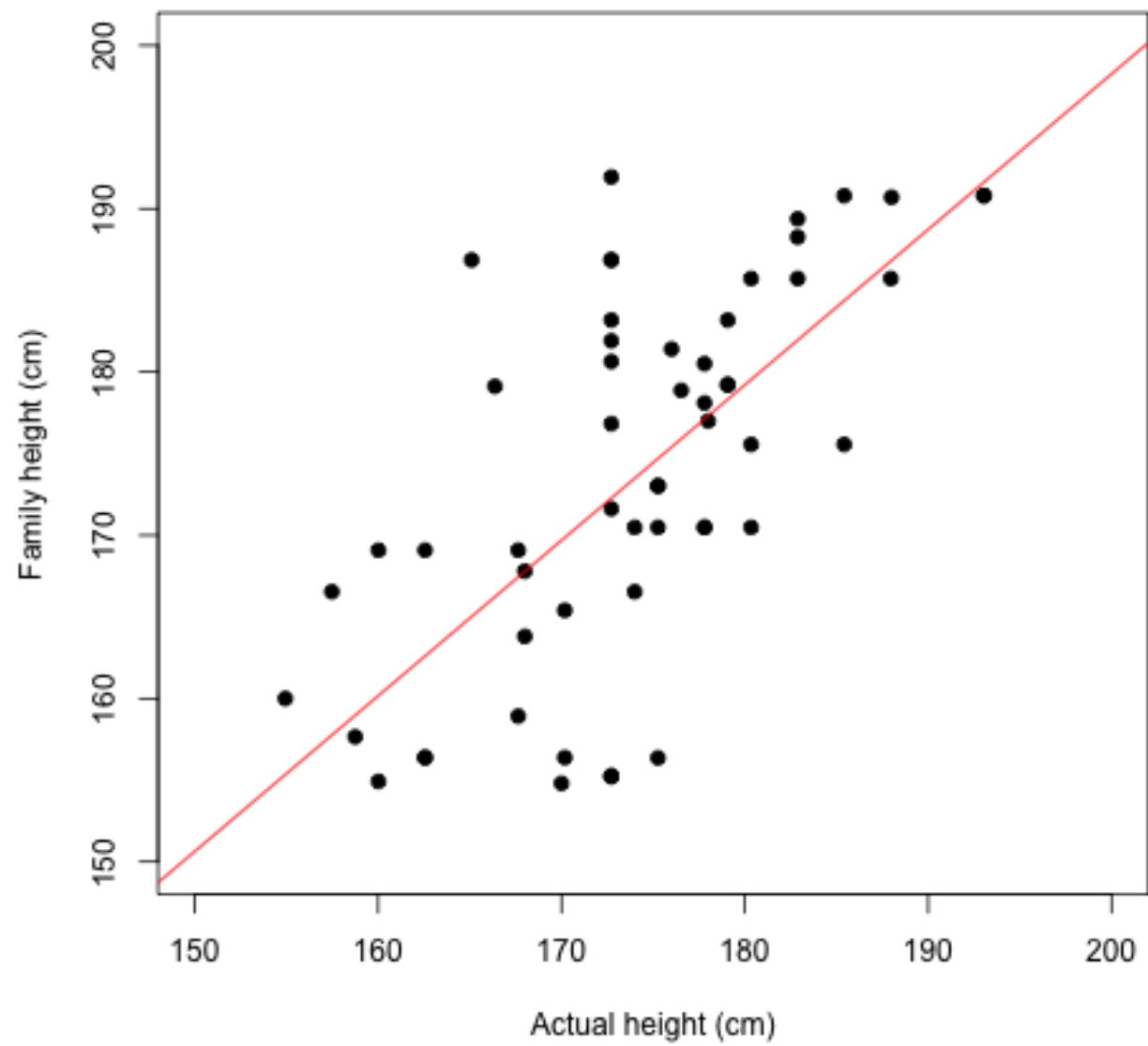
Actual vs predicted family height, correlation= 0.477



Actual vs predicted genetic height, correlation= 0.453



Actual vs predicted family height, correlation= 0.454



Lessons Learned

1. Individual height SNPs have very small effects
2. The aggregate score from 145 SNPs can have medium predictive power ($R \sim 0.45$).
3. From Visscher et al., 2010 the aggregate score from thousands of SNPs increases predictive power ($R \sim 0.65$).
4. Missing heritability for height? Large number of genes each with small effect.
5. Similar approaches could work for other complex traits, such as Type 2 diabetes, cardiovascular disease, etc.

Neandertals



Svante Paabo

RESEARCH ARTICLE

A Draft Sequence of the Neandertal Genome

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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 Schultz¹, Ayinuer Aximu-Petri¹,
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Eric S. Lander², Carsten Russ², Nathaniel Novod², Jason Affourtit⁹, Michael Egholm⁹, Christine Verna²¹,
Pavao Rudan¹⁰, Dejana Brajkovic¹¹, Željko Kucan¹⁰, Ivan Gušić¹⁰, Vladimir B. Doronichev¹²,
Liubov V. Golovanova¹², Carles Lalueza-Fox¹³, Marco de la Rasilla¹⁴, Javier Fortea^{14,¶}, Antonio Rosas¹⁵,
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,†} and Svante Pääbo^{1,†}

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Neandertals

First appear in the European fossil record about 400,000 years ago

Lived in Europe and Western Asia as far east as Southern Siberia and as far south as the Middle East

came into contact with modern humans from at least 80,000 years ago

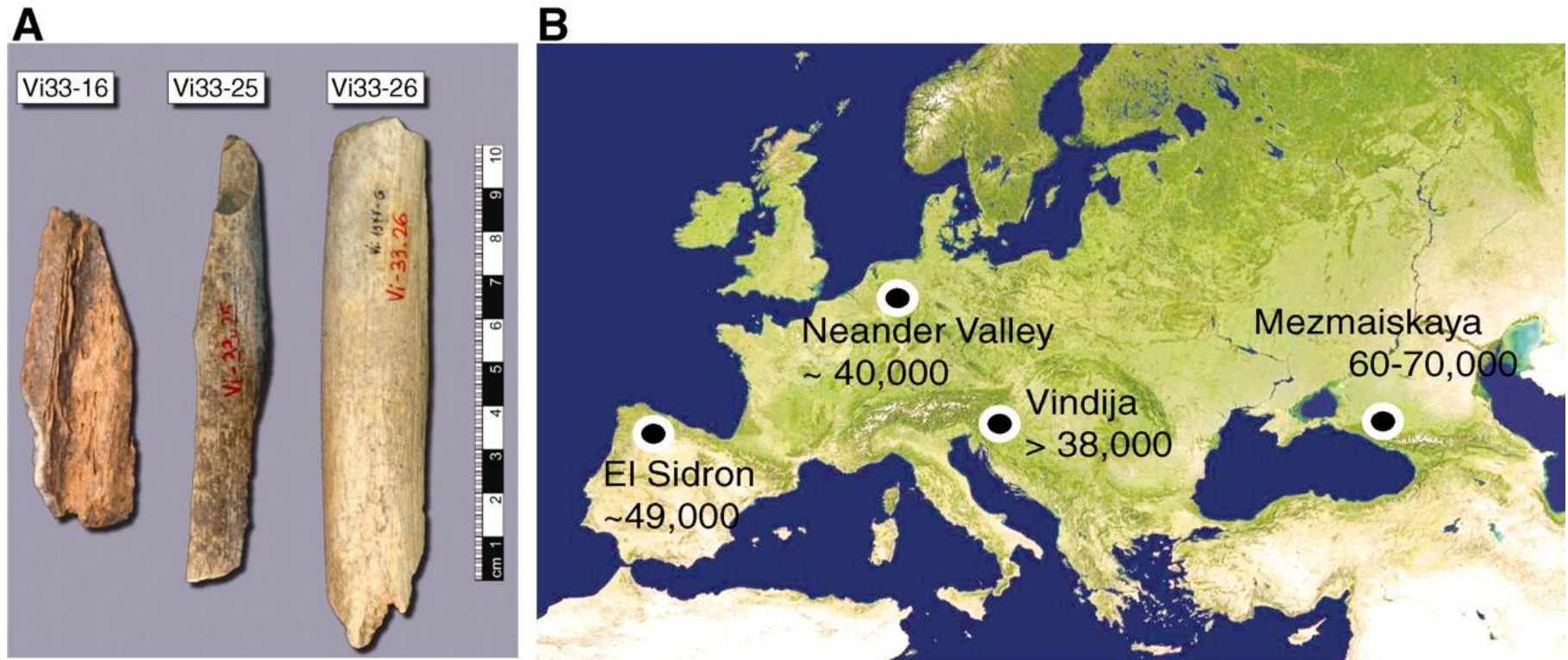
Neandertals

Neanderthal cranial capacity is thought to have been as large as babies or larger as adults than *Homo sapiens*

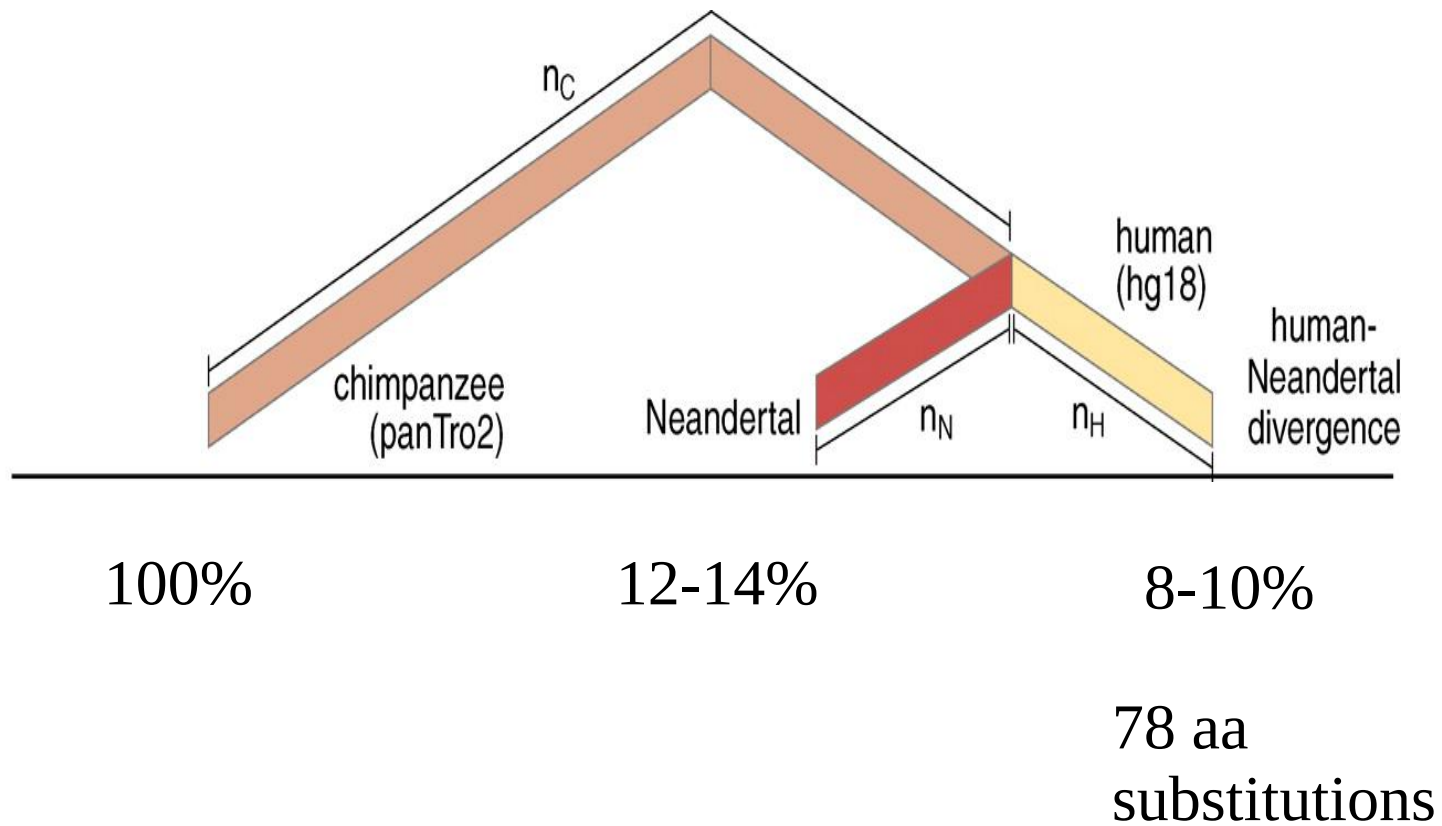
Neandertals were heavily built with robust bone structure.

They were much stronger than *Homo sapiens*, having particularly strong arms and hands

Samples and sites from which DNA was retrieved.



R E Green et al. Science 2010;328:710-722



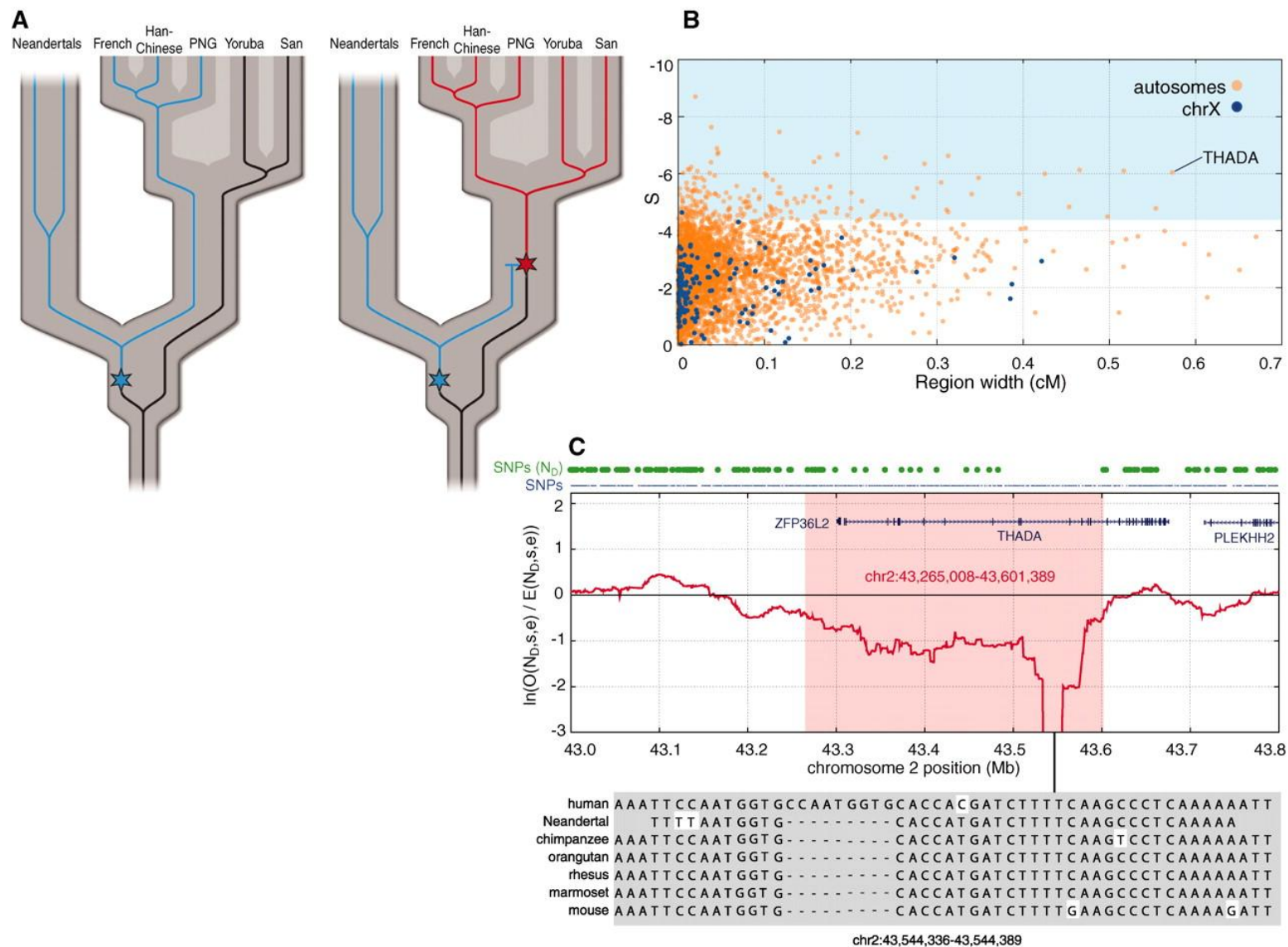
R E Green et al. Science 2010;328:710-722

Table 2. Amino acid changes that are fixed in present-day humans but ancestral in Neandertals. The table is sorted by Grantham scores (GS). Based on the classification proposed by Li *et al.* in (87), 5 amino acid substitutions are radical (>150), 7 moderately radical (101 to 150), 33 moderately conservative (51 to

100) and 32 conservative (1 to 50). One substitution creates a stop codon. Genes showing multiple substitutions have bold SwissProt identifiers. (Table S15 shows the human and chimpanzee genome coordinates, additional database identifiers, and the respective bases.) Genes with two fixed amino acids are indicated in bold.

ID	Pos	AA	GS	Description/function
RPTN	785	*/R	—	Multifunctional epidermal matrix protein
GREB1	1164	R/C	180	Response gene in estrogen receptor–regulated pathway
OR1K1	267	R/C	180	Olfactory receptor, family 1, subfamily K, member 1
SPAG17	431	Y/D	160	Involved in structural integrity of sperm central apparatus axoneme
NLRX1	330	Y/D	160	Modulator of innate immune response
NSUN3	78	S/F	155	Protein with potential SAM-dependent methyl-transferase activity
RGS16	197	D/A	126	Retinally abundant regulator of G-protein signaling
BOD1L	2684	G/R	125	Biorientation of chromosomes in cell division 1-like
CF170	505	S/C	112	<i>Uncharacterized protein: C6orf170</i>
STEAD1	336	C/S	112	Metalloreductase, six transmembrane epithelial antigen of prostate 1
F16A2	630	R/S	110	<i>Uncharacterized protein: family with sequence similarity 160, member A2</i>
LTK	569	R/S	110	Leukocyte receptor tyrosine kinase
BEND2	261	V/G	109	<i>Uncharacterized protein: BEN domain-containing protein 2</i>
O52W1	51	P/L	98	Olfactory receptor, family 52, subfamily W, member 1
CAN15	427	L/P	98	Small optic lobes homolog, linked to visual system development
SCAP	140	I/T	89	Escort protein required for cholesterol as well as lipid homeostasis
TTF1	474	I/T	89	RNA polymerase I termination factor
OR5K4	175	H/D	81	Olfactory receptor, family 5, subfamily K, member 4
SCML1	202	T/M	81	Putative polycomb group (PcG) protein

Fig. 4 Selective sweep screen.



R E Green et al. Science 2010;328:710-722

Table 3. Top 20 candidate selective sweep regions.

Region (hg18)	S	Width (cM)	Gene(s)
chr2:43265008-43601389	-6.04	0.5726	ZFP36L2;THADA
chr11:95533088-95867597	-4.78	0.5538	JRKL;CCDC82;MAML2
chr10:62343313-62655667	-6.1	0.5167	RHOBTB1
Changes in THADA (T2D gene) may have affected aspects of energy metabolism in early modern humans.			
chr2:176635412-176978762	-5.86	0.3481	HOXD11;HOXD8;EVX2;MIX2;HOXD1;HOXD10;HOXD13;HOXD4;HOXD12;HOXD9;MIR10B;HOXD3
chr11:71572763-71914957	-5.28	0.3402	CLPB;FOLR1;PHOX2A;FOLR2;INPPL1
chr7:41537742-41838097	-6.62	0.3129	INHBA
chr10:60015775-60262822	-4.66	0.3129	BICC1
chr6:45440283-45705503	-4.74	0.3112	RUNX2;SUPT3H
chr1:149553200-149878507	-5.69	0.3047	SELENBP1;POGZ;MIR554;RFX5;SNX27;CGN;TUFT1;PI4KB;PSMB4
chr7:121763417-122282663	-6.35	0.2855	RNF148;RNF133;CADPS2
chr7:93597127-93823574	-5.49	0.2769	
chr16:62369107-62675247	-5.18	0.2728	
chr14:48931401-49095338	-4.53	0.2582	
chr6:90762790-90903925	-4.43	0.2502	BACH2
chr10:9650088-9786954	-4.56	0.2475	

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chr10:62343313-62655667	-6.1	0.5167	RHOBTB1
chr21:37580123-37789088	-4.5	0.4977	DYRK1A
chr10:83336607-83714543	-6.13	0.4654	NRG3
chr14:100248177-100417724	-4.84	0.4533	MIR337;MIR665;DLK1;RTL1;MIR431;MIR493;MEG3;MIR7
chr3:157244220-157507502	-4	0.425	KCNAB1
chr11:3			
chr2:17			OXD10;HOXD13;13
chr11:7			
chr7:41			
chr10:6			
chr6:45			
chr1:149553200-149878507	-5.69	0.3047	SELENBP1;POGZ;MIR554;RFX5;SNX27;CGN;TUFT1;PI4KB;PSMB4
chr7:121763417-122282663	-6.35	0.2855	RNF148;RNF133;CADPS2
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DYRK1A is thought to underlie some of the cognitive impairment associated with having three copies of chromosome 21

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chr2:43265008-43601389	-6.04	0.5726	<i>ZFP36L2;THADA</i>
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chr21:37580123-37789088	-4.5	0.4977	<i>DYRK1A</i>
chr10:83336607-83714543	-6.13	0.4654	<i>NRG3</i>
chr14:100248177-100417724	-4.84	0.4533	<i>MIR337;MIR665;DLK1;RTL1;MIR431;MIR4</i>
chr3:157244328-1575			
chr11:30601000-3099			
chr2:176635412-176978762	-5.86	0.3481	<i>HOXD11;HOXD8;EVX2;MTX2;HOXD1;HOXD</i> <i>HOXD4;HOXD12;HOXD9;MIR10B;HOXD3</i>
chr11:71572763-71914957	-5.28	0.3402	<i>CLPB;FOLR1;PHOX2A;FOLR2;INPPL1</i>
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chr10:60015775-60262822	-4.66	0.3129	<i>BICC1</i>
chr6:45440283-45705503	-4.74	0.3112	<i>RUNX2;SUPT3H</i>
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chr6:90762790-90903925	-4.43	0.2502	<i>BACH2</i>
chr10:9650088-9786954	-4.56	0.2475	

NRG3 is associated with schizophrenia

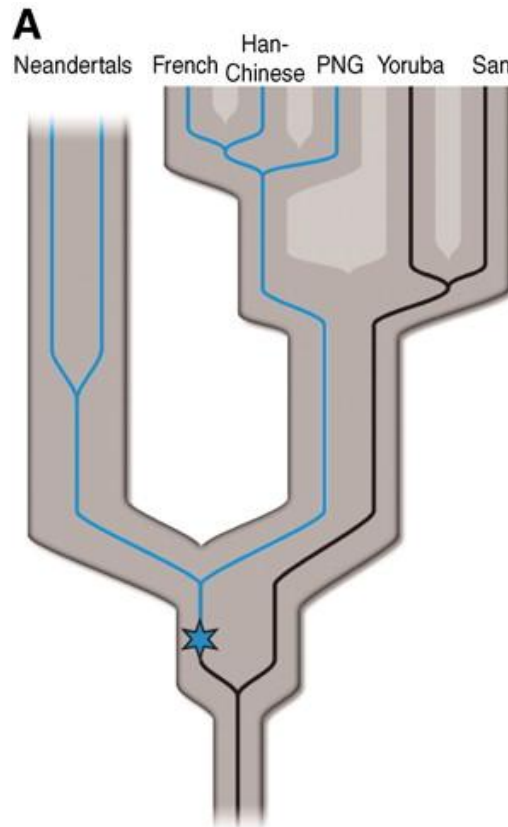
Supplementary Online Materials 17

Non-African haplotypes match Neandertal at an unusual rate

Weiwei Zhai, David Reich and Rasmus Nielsen*

* To whom correspondence should be addressed (rasmus_nielsen@berkeley.edu)

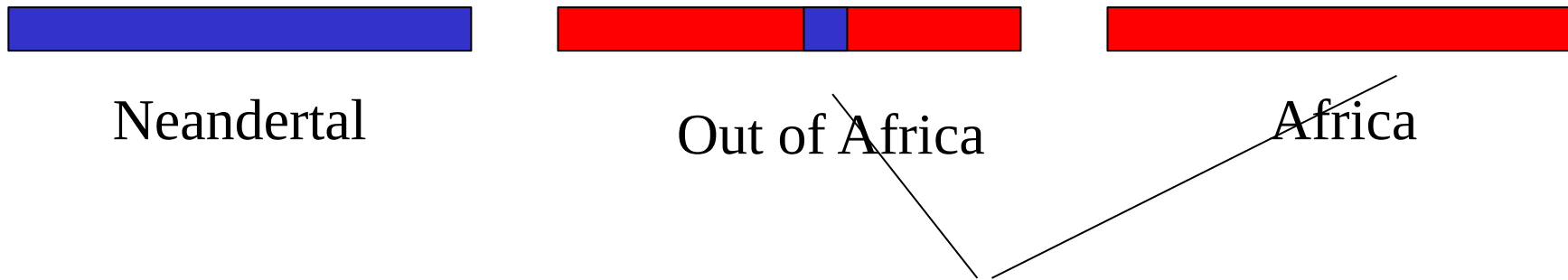
Page 150 out of ~200.



Scenario for Neandertal gene flow into OOA genomes.

The Neandertals are equally close to Europeans and East Asians. However, the Neandertals are significantly closer to non-Africans than to Africans

R E Green et al. Science 2010;328:710-722



Step 1: candidate region

In a 50 kb region, search for regions in which OOA is very different from Africa

Step 2: compare to Neandertal

Look for cases in which there is high match to the Neandertal sequence across many SNPs. The OOA/Neandertal allele should be derived, not ancestral

Neandertal Alleles

Use at your own risk.

[Compute my Neandertal Index](#)

Neandertal

Are you a neandertal?

You have **12** out of 82 Neandertal alleles.

Running total

dbSNP	Derived Allele	Ancestral Allele	Out of Africa Allele	Genotype	Count
10800485	C	T	C	CT	1
6670818	G	A	G	AA	0
10915846	A	G	A	GG	0
16845098	C	T	C	CT	1
17503834	C	T	C	TT	0

Same as Chimp

Same as Neandertal allele

Your genotype

Neandertal



White Paper 23-05

Neanderthal Ancestry Estimator

Authors:

Eric Y. Durand edurand@23andme.com

Created: 5 December 2011

Last Edited: 8 January 2012

Summary:

Neanderthal ancestry estimator is a 23andMe feature that enables customers to find out how much of their genome is of Neanderthal ancestry. This document is a technical description of the feature.

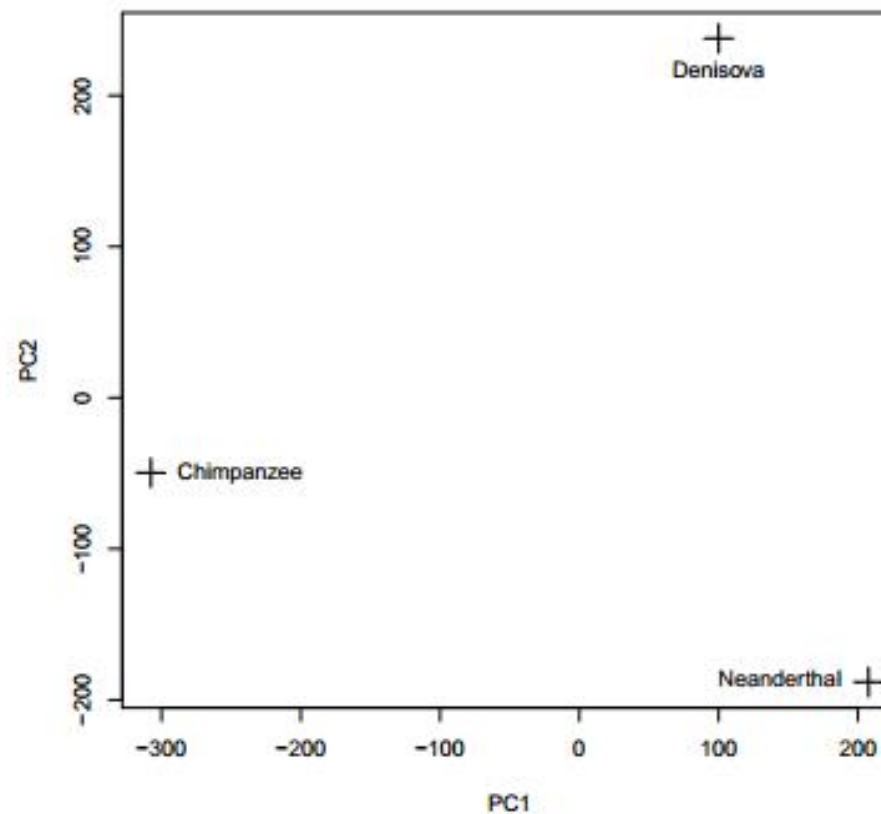


Figure 1: PCA on the Neanderthal, Denisovan and Chimpanzee genomes. We used the subset of the genomes that was defined on the 23andMe genotyping platform. PC1 differentiates archaic humans from the Chimpanzee while PC2 separates Neanderthal from Denisova.

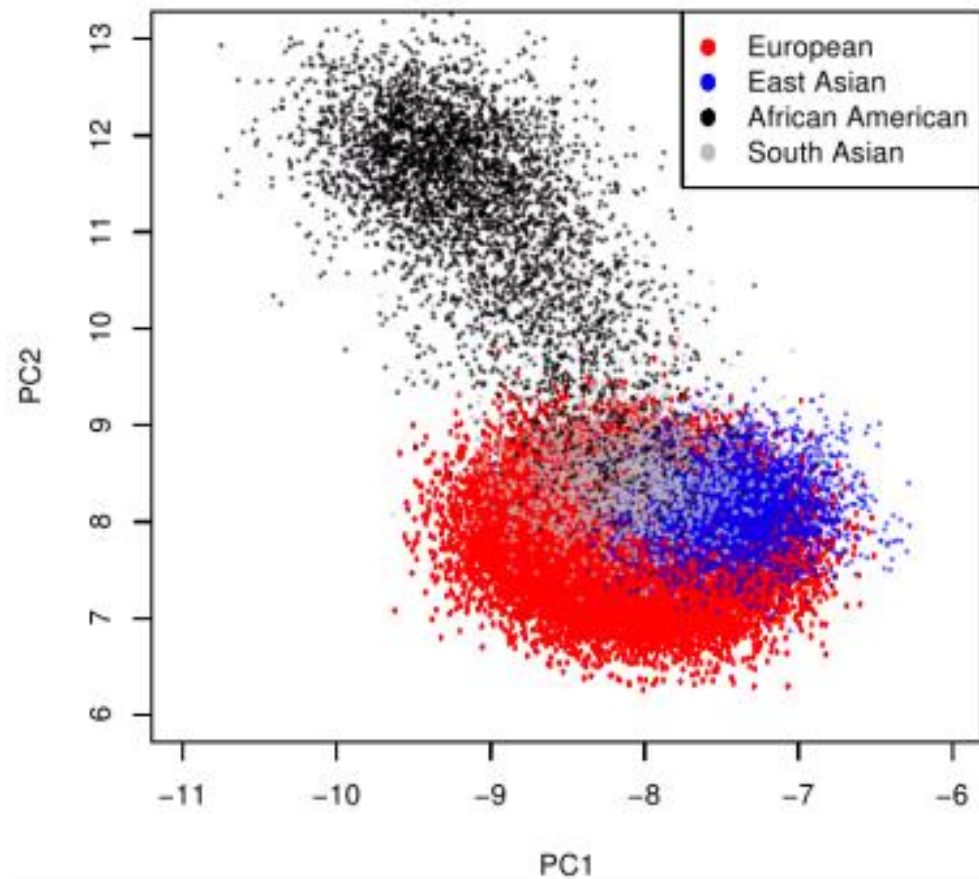


Figure 2: Projection of customer genotypes onto PC1 and PC2. Customers of European, East-Asian and South-Asian ancestry are shifted towards Neanderthal compared to African-Americans.

Got Neanderthal DNA?

An estimated **2.5%** of your DNA is from Neanderthals.

stuart kim (You)



2.5%

35th percentile

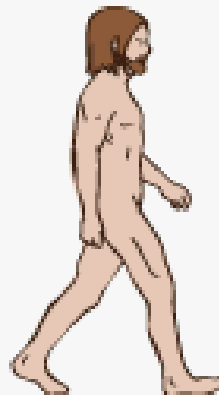
Average Eastern
Asian user



2.6%

MODERN HUMANS

Higher brow
Narrower shoulders
Slightly taller



NEANDERTHALS

Heavy eyebrow ridge
Long, low, bigger skull
Prominent nose with
developed nasal chambers
for cold-air protection

