Supplementary Information for: "No evidence that selection has been less effective at removing deleterious mutations in Europeans than in Africans"

Supplementary Table 1: Sample sizes in each dataset

Dataset	Population	N
24 diverse genomes[1]	Denisova	1
	Neanderthal	1
	Mbuti	2
	San	2
	Mandenka	2
	Yoruba	2
	Dinka	2
	Papuan	2
	Sardinian	2
	Dai	2
	Karitiana	2
	Han	2
	French	2
Lohmueller[2]	African American	15
	European American	20
1000 Genomes[3]	ASW	61
	CEU	85
	CHB	97
	CHS	100
	CLM	60
	FIN	93
	GBR	89
	IBS	14
	JPT	89
	LWK	96
	MXL	64
	PUR	55
	TSI	98
	YRI	88
Exome Sequencing Project[4]	African American	1,088
	European American	1,351

ASW: African Ancestry in Southwest US; CEU: Utah residents (CEPH) with Northern and Western European ancestry; CHB: Han Chinese in Beijing, China; CHS: Han Chinese South; CLM: Colombian in Medellin, Colombia; FIN: Finnish from Finland; GBR: British from England and Scotland (GBR); IBS: Iberian populations in Spain; JPT: Japanese in Tokyo, Japan; LWK: Luhya in Webuye, Kenya; MXL: Mexican Ancestry in Los Angeles, CA; MXL: Mexican Ancestry in Los Angeles, CA; PUR: Puerto Rican in Puerto Rico; TSI: Toscani in Italia: YRI: Yoruba in Ibadan, Nigeria.

Supplementary Table 2: Version of Table 1 for sites with a consistent allele in apes

Data set	West Africans	Europeans	*R:* Relative accumulation of mutations					R^2: Relative accumulation of homozygous mutations				
			R(synonymous)	*R(All non-synonymous)*	*R(Benign)*	*R(Possibly damaging)*	*R(Probably damaging)*	*R^2(synonymous)*	*R^2 (All non-synonymous)*	*R^2 (Benign)*	*R^2 (Possibly damaging)*	*R^2 (Probably damaging)*
24 deep genomes	4	4	1.011 (0.014)	1.015 (0.015)	1.015 (0.019)	0.991 (0.039)	1.038 (0.038)	0.628 (0.015)	0.626 (0.018)	0.630 (0.021)	0.570 (0.043)	0.661 (0.052)
Celera exomes	15	20	0.990 (0.012)	1.012 (0.020)	1.018 (0.023)	1.009 (0.044)	0.991 (0.043)	0.599 (0.011)	0.572 (0.051)	0.585 (0.024)	0.604 (0.054)	0.572 (0.051)
1KG exomes	88	85	1.001 (0.012)	0.987 (0.013)	0.992 (0.016)	0.948 (0.029)	1.003 (0.028)	0.624 (0.013)	0.616 (0.014)	0.613 (0.017)	0.575 (0.031)	0.612 (0.035)
ESP exomes	1,088	1,351	1.007 (0.011)	0.999 (0.012)	0.993 (0.014)	0.984 (0.028)	1.040 (0.030)	0.603 (0.011)	0.594 (0.014)	0.585 (0.016)	0.551 (0.025)	0.628 (0.038)

Notes: This is the same analysis as Table 1, restricting to sites where chimpanzee and at least one of gorilla and orangutan have an allele call and all of the great apes are consistent (data from the EPO six-way primate alignment). ±1 standard errors are from a Weighted Block Jackknife. For the whole genomes, 2 Yoruba + 2 Mandenka represent West Africans, and 2 French + 2 Sardinian represent Europeans. For the 1000 Genomes Data (1KG), YRI represent West Africans and CEU Europeans. The Celera and ESP datasets use African Americans to represent people with West African ancestry.

Supplementary Table 3: Expansion of Table 2 into PolyPhen2 classes

Supplementary Table 3A – Synonymous mutations for all pairs of 24 deep genomes (bottom left) and 1000 Genomes populations (top right)

			IBS (Spanish)	GBR (British)	FIN (Finnish)	CEU (European)	JPT (Japanese)	CHS (Chinese)	CHB (Chinese)	PUR (Pu.Ric.)	MXL (Mexican)	CLM (Colom.)	YRI (Nigerian)	LWK (Kenyan)	ASW (Afr.Am.)	1KG
		TSI (98)	1.015 (0.004)	1.002 (0.003)	0.997 (0.004)	0.999 (0.003)	0.988 (0.008)	0.994 (0.009)	0.991 (0.008)	1.002 (0.003)	0.99 (0.005)	0.991 (0.004)	0.981 (0.009)	0.973 (0.008)	0.987 (0.007)	**TSI (Italian)**
			IBS (14)	0.987 (0.004)	0.982 (0.004)	0.984 (0.004)	0.974 (0.008)	0.98 (0.008)	0.977 (0.008)	0.988 (0.005)	0.976 (0.006)	0.976 (0.005)	0.97 (0.009)	0.962 (0.009)	0.975 (0.008)	**IBS (Spanish)**
	Denis-ova (1)			**GBR (89)**	0.995 (0.003)	0.997 (0.002)	0.986 (0.008)	0.992 (0.008)	0.989 (0.008)	1 (0.003)	0.988 (0.005)	0.989 (0.004)	0.979 (0.009)	0.972 (0.008)	0.985 (0.007)	**GBR (British)**
Neand-erthal	n/a	**Neand. (1)**			**FIN (93)**	1.002 (0.003)	0.991 (0.008)	0.997 (0.008)	0.994 (0.008)	1.005 (0.004)	0.993 (0.005)	0.994 (0.004)	0.983 (0.009)	0.976 (0.009)	0.99 (0.007)	**FIN (Finnish)**
Dinka	n/a	n/a	**Dinka (2)**			**CEU (85)**	0.989 (0.008)	0.994 (0.008)	0.992 (0.008)	1.003 (0.004)	0.991 (0.005)	0.991 (0.004)	0.981 (0.009)	0.974 (0.009)	0.988 (0.008)	**CEU (Eur.)**
Mand-enka	n/a	n/a	1.001 (0.013)	**Mand-enka (2)**			**JPT (89)**	1.007 (0.003)	1.004 (0.003)	1.014 (0.007)	1.003 (0.007)	1.003 (0.007)	0.99 (0.01)	0.983 (0.009)	0.997 (0.009)	**JPT (Japan.)**
Mbuti	n/a	n/a	0.99 (0.013)	0.993 (0.012)	**Mbuti (2)**			**CHS (100)**	0.997 (0.002)	1.008 (0.008)	0.997 (0.007)	0.997 (0.007)	0.986 (0.01)	0.978 (0.01)	0.992 (0.009)	**CHS (Chinese)**
San	n/a	n/a	0.979 (0.014)	0.975 (0.014)	0.982 (0.014)	**San (2)**			**CHB (97)**	1.01 (0.007)	0.999 (0.007)	1 (0.007)	0.988 (0.01)	0.98 (0.009)	0.994 (0.008)	**CHB (Chinese)**
Yoruba	n/a	n/a	0.981 (0.013)	0.981 (0.012)	0.99 (0.011)	1.004 (0.014)	**Yoruba (2)**			**PUR (55)**	0.989 (0.004)	0.989 (0.003)	0.979 (0.008)	0.972 (0.008)	0.986 (0.007)	**PUR (Pu.Ric.)**
Dai	n/a	n/a	0.969 (0.015)	0.971 (0.014)	0.978 (0.014)	0.994 (0.014)	0.988 (0.013)	**Dai (2)**			**MXL (64)**	1 (0.004)	0.988 (0.009)	0.981 (0.008)	0.995 (0.008)	**MXL (Mexican)**
French	n/a	n/a	0.966 (0.013)	0.971 (0.014)	0.977 (0.014)	0.991 (0.014)	0.984 (0.012)	0.995 (0.016)	**French (2)**			**CLM (60)**	0.988 (0.008)	0.98 (0.008)	0.995 (0.007)	**CLM (Colomb.)**
Han	n/a	n/a	0.99 (0.017)	0.992 (0.014)	0.996 (0.016)	1.013 (0.015)	1.009 (0.014)	1.029 (0.015)	1.028 (0.017)	**Han (2)**			**YRI (88)**	0.992 (0.003)	1.007 (0.003)	**YRI (Nigerian)**
Karit-iana	n/a	n/a	0.983 (0.017)	0.983 (0.015)	0.986 (0.016)	1.001 (0.016)	0.994 (0.014)	1.012 (0.015)	1.02 (0.017)	0.987 (0.018)	**Karitiana (2)**			**LWK (96)**	1.015 (0.003)	**LWK (Kenyan)**
Papuan	n/a	n/a	0.958 (0.015)	0.962 (0.015)	0.97 (0.015)	0.982 (0.015)	0.977 (0.013)	0.985 (0.016)	0.991 (0.016)	0.959 (0.016)	0.97 (0.016)	**Papuan (2)**			**ASW (61)**	
Sard-inian	n/a	n/a	0.976 (0.013)	0.972 (0.015)	0.978 (0.015)	0.996 (0.013)	0.987 (0.013)	1.004 (0.015)	1.01 (0.013)	0.978 (0.014)	0.991 (0.016)	1.018 (0.015)	**Sardinian (2)**			
Deep genomes	**Denis-ova**	**Neande r-thal**	**Dinka**	**Mand-enka**	**Mbuti**	**San**	**Yoruba**	**Dai**	**French**	**Han**	**Karitiana**	**Papuan**				

Notes: ±1 standard errors (parentheses) are based on a Weighted Block Jackknife. We highlight numbers >4 standard errors from expectation.

* $R_{X/Y}$ ratios involving the ancient Denisova and Neanderthal samples are not shown as fewer mutations are expected for these genomes than for present-day human genomes since divergence. Ratios are based on the accumulation of mutations observed in the population in the row divided by the accumulation of mutations observed in the population in the column. The number in parentheses indicates the number of samples per population.

Supplementary Table 3B – PolyPhen2 "Benign" mutations for all pairs of 24 deep genomes (bottom left) and 1000 Genomes populations (top right)

			IBS (Spanish)	GBR (British)	FIN (Finn)	CEU (Eur. Am.)	JPT (Jap.)	CHS (Chinese)	CHB (Chinese)	PUR (Pu.Ric.)	MXL (Mex)	CLM (Colom.)	YRI (Nigerian)	LWK (Kenyan)	ASW (Afr. Am.)	1KG
		TSI (98)	1.02 (0.006)	0.998 (0.004)	0.995 (0.005)	0.994 (0.004)	1 (0.013)	1.003 (0.014)	1 (0.014)	1.009 (0.005)	1.007 (0.008)	0.999 (0.006)	0.996 (0.015)	0.987 (0.014)	1.006 (0.012)	**TSI (Italian)**
			IBS (14)	0.979 (0.006)	0.976 (0.007)	0.974 (0.007)	0.983 (0.014)	0.985 (0.014)	0.982 (0.014)	0.991 (0.008)	0.988 (0.01)	0.981 (0.008)	0.982 (0.015)	0.972 (0.014)	0.991 (0.012)	**IBS (Spanish)**
	Denis-ova (1)			**GBR (89)**	0.996 (0.004)	0.995 (0.003)	1.002 (0.014)	1.005 (0.014)	1.001 (0.014)	1.011 (0.006)	1.008 (0.009)	1.001 (0.006)	0.997 (0.015)	0.988 (0.014)	1.008 (0.012)	**GBR (British)**
Neand-erthal	0.88 (0.053)	**Neand. (1)**			**FIN (93)**	0.999 (0.004)	1.005 (0.014)	1.008 (0.014)	1.004 (0.014)	1.014 (0.007)	1.012 (0.009)	1.004 (0.007)	1 (0.016)	0.991 (0.015)	1.011 (0.013)	**FIN (Finnish)**
Dinka	0.858 (0.039)	0.975 (0.044)	**Dinka (2)**			**CEU (85)**	1.006 (0.014)	1.009 (0.015)	1.006 (0.014)	1.015 (0.006)	1.013 (0.009)	1.005 (0.007)	1.001 (0.015)	0.992 (0.014)	1.012 (0.012)	**CEU (European)**
Mand-enka	0.85 (0.043)	0.97 (0.045)	0.996 (0.02)	**Mandenka (2)**			**JPT (89)**	1.003 (0.005)	0.999 (0.004)	1.008 (0.012)	1.006 (0.01)	0.999 (0.011)	0.996 (0.016)	0.986 (0.015)	1.006 (0.014)	**JPT (Japanese)**
Mbuti	0.882 (0.039)	1.016 (0.045)	1.024 (0.021)	1.022 (0.021)	**Mbuti (2)**			**CHS (100)**	0.996 (0.003)	1.005 (0.012)	1.003 (0.01)	0.995 (0.011)	0.993 (0.016)	0.984 (0.015)	1.003 (0.014)	**CHS (Chinese)**
San	0.897 (0.041)	1.03 (0.045)	1.006 (0.019)	1.009 (0.02)	0.988 (0.018)	**San (2)**			**CHB (97)**	1.009 (0.012)	1.007 (0.01)	0.999 (0.011)	0.996 (0.016)	0.987 (0.015)	1.007 (0.014)	**CHB (Chinese)**
Yoruba	0.84 (0.042)	0.963 (0.042)	0.98 (0.021)	0.987 (0.02)	0.963 (0.019)	0.976 (0.02)	**Yoruba (2)**			**PUR (55)**	0.998 (0.006)	0.99 (0.004)	0.989 (0.013)	0.98 (0.012)	0.999 (0.01)	**PUR (Pu.Ric.)**
Dai	0.851 (0.042)	0.982 (0.044)	0.984 (0.022)	0.984 (0.024)	0.965 (0.022)	0.976 (0.023)	1.001 (0.022)	**Dai (2)**			**MXL (64)**	0.992 (0.005)	0.991 (0.014)	0.982 (0.013)	1.001 (0.011)	**MXL (Mexican)**
French	0.844 (0.042)	0.967 (0.039)	0.986 (0.023)	0.987 (0.023)	0.964 (0.024)	0.978 (0.024)	1.004 (0.023)	0.998 (0.023)	**French (2)**			**CLM (60)**	0.997 (0.013)	0.988 (0.012)	1.007 (0.01)	**CLM (Colomb.)**
Han	0.857 (0.041)	0.963 (0.042)	0.998 (0.021)	1 (0.024)	0.981 (0.024)	0.998 (0.023)	1.022 (0.024)	1.022 (0.02)	1.021 (0.024)	**Han (2)**			**YRI (88)**	0.99 (0.004)	1.01 (0.005)	**YRI (Nigerian)**
Karitiana	0.836 (0.043)	0.945 (0.038)	0.95 (0.023)	0.954 (0.022)	0.931 (0.022)	0.942 (0.021)	0.965 (0.023)	0.954 (0.025)	0.955 (0.024)	0.935 (0.022)	**Karit-iana (2)**			**LWK (96)**	1.02 (0.005)	**LWK (Kenyan)**
Papuan	0.858 (0.042)	0.979 (0.042)	1 (0.024)	1.002 (0.023)	0.978 (0.024)	0.992 (0.022)	1.021 (0.023)	1.023 (0.023)	1.012 (0.022)	0.999 (0.025)	1.07 (0.028)	**Papuan (2)**			**ASW (61)**	
Sard-inian	0.864 (0.044)	0.97 (0.041)	0.983 (0.022)	0.992 (0.023)	0.969 (0.023)	0.979 (0.024)	1.009 (0.022)	1.003 (0.023)	1.001 (0.022)	0.987 (0.024)	1.047 (0.029)	0.991 (0.022)	**Sardinian (2)**			
Deep genomes	**Denis-ova**	**Neand-erthal**	**Dinka**	**Mandenka**	**Mbuti**	**San**	**Yoruba**	**Dai**	**French**	**Han**	**Karit-iana**	**Papuan**				

Notes: ±1 standard errors (parentheses) are based on a Weighted Block Jackknife. We highlight numbers >4 standard errors from expectation.

* *R*-ratios computed using Denisova and Neanderthal are normalized by the number of synonymous sites on each lineage, to adjust for the fewer mutations in the ancient sample than on present-day human lineages since divergence (the *R´* statistic described in the main text). Ratios involving Neanderthal and Denisova also remove C→T and G→A mutations to avoid high error rates due to ancient DNA degradation (Supplementary Table 7). Ratios are based on the accumulation of mutations observed in the population in the row divided by the accumulation of mutations observed in the population shown in the column. The number in parentheses indicates the number of samples per population.

Supp. Table 3C – PolyPhen2 "Possibly damaging" mutations for all pairs of 24 deep genomes (bottom left) and 1000 Genomes pops. (top right)

			IBS (Spanish)	GBR (British)	FIN (Finnish)	CEU European	JPT Japanese	CHS Chinese	CHB Chinese	PUR Pu.Ric.	MXL Mexican	CLM Colom.	YRI Nigerian	LWK Kenyan	ASW Afr. Am.	1KG
		TSI (98)	1.056 (0.013)	1.024 (0.008)	1.009 (0.012)	1.013 (0.008)	0.969 (0.025)	0.985 (0.027)	0.985 (0.026)	1.045 (0.012)	1.015 (0.018)	1.006 (0.012)	1.057 (0.031)	1.026 (0.028)	1.047 (0.024)	TSI (Italian)
			IBS (14)	0.969 (0.012)	0.955 (0.013)	0.959 (0.012)	0.921 (0.025)	0.936 (0.026)	0.935 (0.025)	0.991 (0.013)	0.963 (0.018)	0.954 (0.013)	1.014 (0.031)	0.984 (0.028)	1.002 (0.025)	IBS (Spanish)
	Denisova (1)			GBR (89)	0.985 (0.009)	0.989 (0.006)	0.948 (0.025)	0.963 (0.026)	0.963 (0.025)	1.021 (0.011)	0.992 (0.018)	0.983 (0.011)	1.038 (0.031)	1.007 (0.028)	1.027 (0.024)	GBR (British)
Neander-thal	0.769 (0.07)	Neand-erthal(1)			FIN (93)	1.005 (0.01)	0.961 (0.024)	0.977 (0.026)	0.977 (0.025)	1.036 (0.012)	1.007 (0.018)	0.998 (0.012)	1.05 (0.031)	1.019 (0.028)	1.04 (0.025)	FIN (Finnish)
Dinka	0.749 (0.06)	0.936 (0.071)	Dinka (2)			CEU (85)	0.958 (0.026)	0.973 (0.028)	0.973 (0.027)	1.031 (0.012)	1.002 (0.018)	0.993 (0.012)	1.046 (0.031)	1.015 (0.028)	1.036 (0.024)	CEU (European)
Mand-enka	0.788 (0.066)	0.982 (0.074)	1.075 (0.047)	Mand-enka (2)			JPT (89)	1.019 (0.01)	1.018 (0.009)	1.075 (0.025)	1.048 (0.023)	1.037 (0.022)	1.084 (0.033)	1.052 (0.03)	1.075 (0.029)	JPT (Japanese)
Mbuti	0.812 (0.064)	1.025 (0.079)	1.043 (0.05)	0.983 (0.044)	Mbuti (2)			CHS (100)	0.999 (0.007)	1.058 (0.025)	1.03 (0.024)	1.02 (0.022)	1.069 (0.033)	1.038 (0.03)	1.06 (0.029)	CHS (Chinese)
San	0.832 (0.064)	1.054 (0.078)	1.043 (0.044)	0.982 (0.038)	1.005 (0.042)	San (2)			CHB (97)	1.058 (0.025)	1.031 (0.023)	1.021 (0.022)	1.07 (0.033)	1.038 (0.031)	1.06 (0.029)	CHB (Chinese)
Yoruba	0.793 (0.063)	1.006 (0.073)	1.017 (0.039)	0.954 (0.036)	0.979 (0.041)	0.966 (0.035)	Yoruba (2)			PUR (55)	0.972 (0.014)	0.964 (0.009)	1.021 (0.026)	0.99 (0.024)	1.009 (0.019)	PUR (Pu.Ric.)
Dai	0.807 (0.066)	1.063 (0.086)	1.075 (0.048)	1.022 (0.047)	1.028 (0.052)	1.049 (0.051)	1.059 (0.048)	Dai (2)			MXL (64)	0.991 (0.011)	1.044 (0.029)	1.014 (0.027)	1.034 (0.023)	MXL (Mexican)
French	0.72 (0.056)	0.925 (0.071)	1.013 (0.048)	0.954 (0.044)	0.968 (0.045)	0.966 (0.044)	0.994 (0.048)	0.931 (0.042)	French (2)			CLM (60)	1.052 (0.028)	1.021 (0.025)	1.041 (0.022)	CLM (Colomb.)
Han	0.815 (0.066)	1.054 (0.088)	1.126 (0.049)	1.055 (0.049)	1.071 (0.05)	1.078 (0.049)	1.102 (0.051)	1.061 (0.048)	1.124 (0.051)	Han (2)			YRI 88)	0.97 (0.008)	0.988 (0.01)	YRI (Nigerian)
Karitiana	0.763 (0.066)	0.967 (0.082)	1.068 (0.052)	1.013 (0.048)	1.008 (0.051)	1.022 (0.049)	1.034 (0.048)	0.976 (0.048)	1.04 (0.053)	0.925 (0.051)	Karit-iana (2)			LWK (96)	1.018 (0.011)	LWK (Kenyan)
Papuan	0.759 (0.067)	0.981 (0.086)	1.071 (0.05)	1.008 (0.046)	1.019 (0.047)	1.037 (0.05)	1.05 (0.05)	0.998 (0.049)	1.068 (0.049)	0.952 (0.045)	1.012 (0.054)	Papuan (2)			ASW (61)	
Sardinian	0.767 (0.064)	0.985 (0.076)	1.031 (0.051)	0.968 (0.042)	0.965 (0.043)	0.975 (0.043)	1.013 (0.046)	0.937 (0.042)	1.003 (0.037)	0.881 (0.041)	0.961 (0.05)	0.946 (0.043)	Sardinian (2)			
Deep genomes	**Denisova**	**Neand-erthal**	**Dinka**	**Mand-enka**	**Mbuti**	**San**	**Yoruba**	**Dai**	**French**	**Han**	**Karit-iana**	**Papuan**				

Notes: ±1 standard errors (parentheses) are based on a Weighted Block Jackknife. We highlight numbers >4 standard errors from expectation.

* *R*-ratios computed using Denisova and Neanderthal are normalized by the number of synonymous sites on each lineage, to adjust for the fewer mutations in the ancient sample than on present-day human lineages since divergence (the *R´* statistic described in the main text). Ratios involving Neanderthal and Denisova also remove C→T and G→A mutations to avoid high error rates due to ancient DNA degradation (Supplementary Table 7). Ratios are based on the accumulation of mutations observed in the population in the row divided by the accumulation of mutations observed in the population shown in the column. The number in parentheses indicates the number of samples per population.

Supp. Table 3D – PolyPhen2 "Probably damaging" mutations for all pairs of 24 deep genomes (bottom left) and 1000 Genomes pops. (top right)

			IBS (Spanish)	GBR (British)	FIN (Finnish)	CEU European	JPT Japanese	CHS Chinese	CHB Chinese	PUR Pu.Ric.	MXL Mexican	CLM Colomb.	YRI Nigerian	LWK Kenyan	ASW Afr. Am.	1KG
		TSI (98)	1.025 (0.013)	1.004 (0.007)	1.03 (0.009)	1.012 (0.007)	1.014 (0.025)	1.029 (0.025)	1.024 (0.025)	1.026 (0.009)	1.042 (0.018)	1.022 (0.012)	0.998 (0.026)	0.981 (0.024)	1.008 (0.021)	**TSI (Italian)**
			IBS (14)	0.979 (0.013)	1.005 (0.014)	0.987 (0.013)	0.991 (0.028)	1.006 (0.028)	1.001 (0.028)	1.002 (0.014)	1.018 (0.022)	0.998 (0.016)	0.978 (0.026)	0.962 (0.025)	0.987 (0.021)	**IBS (Spanish)**
	Denis-ova (1)			**GBR (89)**	1.026 (0.008)	1.008 (0.007)	1.01 (0.026)	1.026 (0.026)	1.021 (0.026)	1.023 (0.01)	1.039 (0.019)	1.018 (0.013)	0.995 (0.027)	0.978 (0.025)	1.005 (0.022)	**GBR (British)**
Neander-thal	0.841 (0.099)	**Neand-ertal(1)**			**FIN (93)**	0.983 (0.008)	0.986 (0.024)	1.001 (0.025)	0.996 (0.025)	0.998 (0.011)	1.014 (0.017)	0.993 (0.012)	0.975 (0.026)	0.958 (0.024)	0.984 (0.021)	**FIN (Finnish)**
Dinka	0.918 (0.07)	1.048 (0.091)	**Dinka (2)**			**CEU (85)**	1.002 (0.025)	1.018 (0.025)	1.013 (0.025)	1.015 (0.01)	1.03 (0.018)	1.01 (0.013)	0.988 (0.026)	0.971 (0.024)	0.998 (0.021)	**CEU (European)**
Mandenka	0.94 (0.072)	1.083 (0.086)	1.029 (0.042)	**Mand-enka (2)**			**JPT (89)**	1.017 (0.009)	1.012 (0.009)	1.011 (0.023)	1.028 (0.02)	1.007 (0.022)	0.986 (0.028)	0.969 (0.026)	0.995 (0.024)	**JPT (Japanese)**
Mbuti	0.95 (0.075)	1.100 (0.088)	1.041 (0.041)	1.026 (0.04)	**Mbuti (2)**			**CHS (100)**	0.994 (0.007)	0.996 (0.022)	1.012 (0.02)	0.991 (0.021)	0.973 (0.028)	0.957 (0.026)	0.982 (0.024)	**CHS (Chinese)**
San	0.988 (0.071)	1.131 (0.089)	1.024 (0.039)	1.005 (0.04)	0.98 (0.038)	**San (2)**			**CHB (97)**	1.001 (0.022)	1.017 (0.021)	0.996 (0.021)	0.978 (0.027)	0.961 (0.026)	0.986 (0.024)	**CHB (Chinese)**
Yoruba	0.972 (0.076)	1.117 (0.099)	1.007 (0.035)	0.985 (0.039)	0.961 (0.036)	0.975 (0.036)	**Yoruba (2)**			**PUR (55)**	1.015 (0.014)	0.995 (0.008)	0.977 (0.022)	0.96 (0.021)	0.986 (0.017)	**PUR (Pu.Ric.)**
Dai	0.964 (0.079)	1.126 (0.101)	1.075 (0.046)	1.047 (0.046)	1.013 (0.044)	1.051 (0.04)	1.085 (0.041)	**Dai (2)**			**MXL (64)**	0.98 (0.012)	0.964 (0.027)	0.948 (0.026)	0.972 (0.022)	**MXL (Mexican)**
French	0.902 (0.076)	1.029 (0.089)	0.994 (0.045)	0.959 (0.044)	0.937 (0.044)	0.957 (0.04)	0.972 (0.039)	0.908 (0.039)	**French (2)**			**CLM (60)**	0.98 (0.024)	0.963 (0.023)	0.989 (0.019)	**CLM (Colomb.)**
Han	0.983 (0.079)	1.18 (0.097)	1.061 (0.047)	1.048 (0.048)	1.013 (0.039)	1.043 (0.041)	1.08 (0.043)	0.984 (0.041)	1.11 (0.053)	**Han (2)**			**YRI (88)**	0.983 (0.009)	1.01 (0.009)	**YRI (Nigerian)**
Karitiana	0.9 (0.081)	1.063 (0.093)	0.967 (0.047)	0.938 (0.047)	0.929 (0.045)	0.938 (0.044)	0.96 (0.044)	0.861 (0.041)	0.966 (0.046)	0.875 (0.046)	**Karit-iana (2)**			**LWK (96)**	1.027 (0.011)	**LWK (Kenyan)**
Papuan	0.913 (0.074)	1.051 (0.097)	1.006 (0.052)	0.974 (0.046)	0.964 (0.044)	0.979 (0.044)	0.995 (0.048)	0.924 (0.041)	1.02 (0.048)	0.911 (0.042)	1.046 (0.053)	**Papuan (2)**			**ASW (61)**	
Sardinian	0.931 (0.075)	1.069 (0.099)	1.02 (0.046)	0.969 (0.043)	0.958 (0.038)	0.969 (0.043)	0.988 (0.044)	0.919 (0.041)	1.014 (0.045)	0.917 (0.04)	1.052 (0.055)	1.008 (0.048)	**Sardinian (2)**			
Deep genomes	**Denisova**	**Neander-thal**	**Dinka**	**Mand-enka**	**Mbuti**	**San**	**Yoruba**	**Dai**	**French**	**Han**	**Karit-iana**	**Papuan**				

Notes: ±1 standard errors (parentheses) are based on a Weighted Block Jackknife. We highlight numbers >4 standard errors from expectation.

* *R*-ratios computed using Denisova and Neanderthal are normalized by the number of synonymous sites on each lineage, to adjust for the fewer mutations in the ancient sample than on present-day human lineages since divergence (the *R´* statistic described in the main text). Ratios involving Neanderthal and Denisova also remove C→T and G→A mutations to avoid high error rates due to ancient DNA degradation (Supplementary Table 7). Ratios are based on the accumulation of mutations observed in the population in the row divided by the accumulation of mutations observed in the population shown in the column. The number in parentheses indicates the number of samples per population.

Supplementary Table 4: Parameters of simulated demographic models

Gravel[5] [π_{Eur}/π_{Afr}=0.72]

Time in gens.	$2N_{Afr}$	$2N_{Eur}$
-300000 ≤ t < 3880	28948	
3880 ≤ t < 5000	28948	3,722
5000 ≤ t ≤ 5921	28948	$2064e^{.003858(t-5000)}$

Simple bottleneck [π_{Eur}/π_{Afr}=0.69]

Time in gens.	$2N_{Afr}$	$2N_{Eur}$
-300000 ≤ t < 3880	28948	
3880 ≤ t < 4080	28948	500
4080 ≤ t ≤ 5921	28948	28948

Tennessen[4] [π_{Eur}/π_{Afr}=0.70]

Time in gens.	$2N_{Afr}$	$2N_{Eur}$
-300000 ≤ t < 3880	28948	
3880 ≤ t < 5000	28,948	3,722
5000 ≤ t < 5716	28,948	$2064e^{.00307(t-5000)}$
5716 ≤ t ≤ 5921	$28948e^{.00166(t-5716)}$	$18900e^{.00195(t-5716)}$

Lohmueller[2] [π_{Eur}/π_{Afr}=0.70]

Time in gens.	$2N_{Afr}$	$2N_{Eur}$
-300000 ≤ t < 100002	15672	
100002 ≤ t < 101772	15556	11398
101772 ≤ t < 107706	51272	11398
107706 ≤ t ≤ 108580	51272	60060

Notes: All simulations use $\mu = 2\times10^{-8}$ and burn in from generation -250,000 to 0. The switch from sampling every 100 to every 1 generations occurs at generation +1000 for the three models that end at time 5,921, and at +99,000 for the Lohmueller model[2]. Summary statistics at the end of the simulation are shown.

Supplementary Table 5: Expected $R_{WestAfrica/Europe}$ for different models of demography

	$R(Non-synonymous)$	$R(Benign)$	$R(Possibly\ damaging)$	$R(Probably\ damaging)$
Estimated percentage of sites in each of three selective coefficient bins				
Percent of sites that are neutral	19%	27%	16%	9%
Percent of sites with weak selection coefficients: $s = -10^{-3}$	47%	60%	54%	27%
Percent of sites with strong selection coefficients: $s = -10^{-2}$	33%	13%	29%	64%
Model of history simulated				
Tennessen[4]	0.989	0.990	0.985	0.988
Gravel[5]	0.987	0.988	0.984	0.986
Lohmueller[2]	0.992	0.993	0.989	0.991

Notes: As described in the Supplementary Note, we assume that selective coefficients take on only one of three values: $s = 0$ ("neutral"), -10^{-3} ("weak"), and -10^{-2} ("strong"), and then fit the density in each of these bins using site frequency spectrum data under the assumption of mutations all acting additively with no epistasis. In the bottom section of the table, we show the value of $R_{WestAfrica/Europe}$ expected for each demographic model and distribution of selective coefficients. The expected values are less than two standard errors from 1 (using the empirically estimated Weighted Block Jackknife standard errors from Table 1), indicating that we do not expect there to be a clearly detectable difference in the accumulation of deleterious mutations comparing Europeans to West Africans.

Supplementary Table 6: $R_{African/Non\text{-}African}$-statistic stratified by coalescent time depth

PSMC point estimate of time depth (posterior decoding)*	***R(synonymous)***	***R(All non-synonymous)***	***R(Benign)***	***R(Possibly damaging)***	***R(Probably damaging)***
≥0.0008 expected divergence ≥800,000 years	1.046 (0.014)	1.050 (0.017)	1.063 (0.019)	0.976 (0.059)	1.025 (0.053)
0.0004-0.0008 expected divergence 400,000-800,000 years	1.018 (0.022)	1.026 (0.028)	1.005 (0.046)	1.028 (0.101)	1.012 (0.057)
<0.0004 expected divergence <400,000 years	1.008 (0.033)	1.009 (0.044)	0.931 (0.061)	1.017 (0.145)	1.146 (0.093)

Notes: ±1 standard errors are from a Weighted Block Jackknife. For this analysis, we compare 8=4×2 sub-Saharan African to 12=6×2 non-African phased genomes. We restrict to sites with a GATK genotype quality of ≥70, and that have a consistent genotype between GATK and samtools.

* We present two coalescent time estimates based on the PSMC. The first is the expected per-base pair sequence divergence for genealogies of this time depth. The second is a calibration to years, based on making the further assumption of a mutation rate of 0.5×10^{-9} / bp / year. (The dates would halve using another conventional mutation rate assumption of 1.0×10^{-9} / bp / year.)

Supplementary Table 7: Key statistics as a function of allelic substitution patterns

Substitution type	Benign	Possibly damaging	Probably damaging	Non-synonymous
$R_{WestAfrica/Europe}$				
C→T or G→A	0.981 (0.028)	0.942 (0.059)	0.978 (0.053)	0.976 (0.023)
T→C or A→G	1.035 (0.034)	0.995 (0.082)	0.941 (0.102)	1.023 (0.029)
A→C or T→G	1.016 (0.054)	1.127 (0.112)	1.183 (0.089)	1.082 (0.042)
C→A or G→T	1.001 (0.060)	1.213 (0.127)	1.113 (0.114)	1.065 (0.051)
A→T or T→A	1.017 (0.100)	0.995 (0.188)	0.927 (0.136)	1.001 (0.076)
C→G or G→C	0.971 (0.049)	0.957 (0.082)	1.078 (0.093)	0.989 (0.038)
All but C→T or G→A	1.018 (0.021)	1.053 (0.051)	1.073 (0.052)	1.033 (0.017)
All sites	1.002 (0.018)	1.007 (0.040)	1.031 (0.038)	1.008 (0.015)
$R'_{WestAfrica/Europe}$				
C→T or G→A	0.956 (0.030)	0.918 (0.058)	0.953 (0.049)	0.951 (0.025)
T→C or A→G	1.005 (0.043)	0.966 (0.084)	0.914 (0.099)	0.993 (0.038)
A→C or T→G	1.009 (0.080)	1.118 (0.134)	1.173 (0.134)	1.074 (0.084)
C→A or G→T	1.055 (0.087)	1.278 (0.146)	1.172 (0.145)	1.122 (0.084)
A→T or T→A	1.060 (0.143)	1.039 (0.209)	0.968 (0.158)	1.044 (0.117)
C→G or G→C	0.945 (0.064)	0.931 (0.096)	1.049 (0.106)	0.962 (0.060)
All but C→T or G→A	1.004 (0.029)	1.038 (0.052)	1.059 (0.051)	1.019 (0.024)
All sites	0.981 (0.022)	0.986 (0.041)	1.010 (0.037)	0.987 (0.019)
$R'_{AllModern/Denisova}$				
C→T or G→A	0.898 (0.035)	0.828 (0.065)	0.565 (0.033)	0.812 (0.027)
T→C or A→G	0.860 (0.046)	0.904 (0.120)	0.697 (0.091)	0.851 (0.042)
A→C or T→G	0.830 (0.119)	0.725 (0.143)	1.475 (0.313)	0.908 (0.117)
C→A or G→T	1.085 (0.127)	0.789 (0.123)	1.080 (0.189)	1.026 (0.103)
A→T or T→A	0.848 (0.162)	0.919 (0.228)	0.791 (0.227)	0.857 (0.149)
C→G or G→C	0.766 (0.075)	0.799 (0.118)	1.244 (0.207)	0.833 (0.072)
All but C→T or G→A	0.865 (0.039)	0.810 (0.058)	0.985 (0.070)	0.872 (0.034)
All sites	0.929 (0.029)	0.870 (0.046)	0.760 (0.035)	0.889 (0.024)
$R'_{AllModern/Neanderthal}$				
C→T or G→A	0.953 (0.040)	0.994 (0.094)	0.909 (0.059)	0.953 (0.033)
T→C or A→G	1.046 (0.056)	1.053 (0.126)	0.928 (0.156)	1.038 (0.051)
A→C or T→G	0.937 (0.105)	1.132 (0.197)	1.462 (0.283)	1.085 (0.105)
C→A or G→T	1.073 (0.125)	0.991 (0.160)	1.188 (0.201)	1.086 (0.112)
A→T or T→A	0.988 (0.214)	0.786 (0.208)	0.928 (0.224)	0.944 (0.168)
C→G or G→C	0.816 (0.070)	1.099 (0.173)	1.169 (0.185)	0.919 (0.077)
All but C→T or G→A	0.997 (0.037)	1.074 (0.079)	1.181 (0.092)	1.037 (0.036)
All sites	0.993 (0.026)	1.065 (0.062)	1.063 (0.054)	1.015 (0.025)
$R'_{Denisova/Neanderthal}$				
C→T or G→A	1.089 (0.060)	1.210 (0.147)	1.695 (0.160)	1.215 (0.055)
T→C or A→G	1.250 (0.098)	1.072 (0.182)	1.409 (0.277)	1.244 (0.087)
A→C or T→G	1.049 (0.184)	1.594 (0.447)	0.687 (0.201)	1.083 (0.170)
C→A or G→T	0.849 (0.128)	1.188 (0.266)	1.133 (0.251)	0.966 (0.136)
A→T or T→A	1.195 (0.275)	0.913 (0.272)	1.141 (0.387)	1.135 (0.218)
C→G or G→C	1.027 (0.138)	1.368 (0.323)	1.029 (0.204)	1.091 (0.126)
All but C→T or G→A	1.132 (0.068)	1.290 (0.118)	1.172 (0.140)	1.164 (0.059)
All sites	1.064 (0.044)	1.198 (0.090)	1.433 (0.096)	1.141 (0.040)

Notes: ±1 standard errors are from a Weighted Block Jackknife. Statistics computed using Denisova and Neanderthal are normalized by the number of synonymous sites on each lineage (the R' statistic). Red highlighting indicates a nominal $P < 0.001$ for $R < 1$ or $R' < 1$, and green highlighting indicates a nominal $P < 0.001$ for $R > 1$ or $R' > 1$. These results document a significantly higher rate of accumulation of deleterious mutations in Denisova than in present-day humans whether the analysis is performed over all sites, or excluding C→T and G→A sites which are known to be subject to high rates of error in ancient DNA. There is no significant evidence of a higher rate if accumulation of deleterious mutations in Neanderthals compared with present-day humans.

Supplementary Table 8: Biased gene conversion analysis for all population pairs

Supplementary Table 8A: Unnormalized $R_{X/Y}$ statistics: bottom left G/C→A/T, top right A/T→G/C

	Neand-erthal (1)	Denisova (1)	Dinka (2)	Mand-enka (2)	Mbuti (2)	San (2)	Yoruba (2)	Dai (2)	French (2)	Han (2)	Karitiana (2)	Papuan (2)	Sardin-ian (2)	
Denisova	1.06 (0.006)													**Neand-erthal**
Dinka	1.133 (0.004)	1.064 (0.004)												**Denisova**
Mandenka	1.132 (0.005)	1.063 (0.004)	1.01 (0.001)											**Dinka**
Mbuti	1.14 (0.005)	1.07 (0.004)	1.013 (0.002)	1.004 (0.001)										**Mand-enka**
San	1.137 (0.004)	1.065 (0.004)	1.002 (0.001)	0.994 (0.001)	0.99 (0.001)									**Mbuti**
Yoruba	1.125 (0.004)	1.056 (0.004)	0.994 (0.001)	0.985 (0.001)	0.981 (0.001)	0.992 (0.001)								**San**
Dai	1.142 (0.005)	1.071 (0.004)	0.992 (0.002)	0.984 (0.002)	0.98 (0.002)	0.991 (0.002)	0.999 (0.002)							**Yoruba**
French	1.11 (0.004)	1.045 (0.004)	0.986 (0.001)	0.978 (0.001)	0.975 (0.002)	0.985 (0.002)	0.992 (0.001)	0.992 (0.002)						**Dai**
Han	1.16 (0.005)	1.085 (0.004)	0.998 (0.001)	0.99 (0.001)	0.986 (0.002)	0.997 (0.002)	1.006 (0.001)	1.008 (0.001)	1.016 (0.001)					**French**
Karitiana	1.112 (0.005)	1.047 (0.004)	0.986 (0.002)	0.977 (0.002)	0.974 (0.002)	0.984 (0.002)	0.992 (0.002)	0.991 (0.002)	0.999 (0.002)	0.983 (0.002)				**Han**
Papuan	1.124 (0.005)	1.057 (0.004)	0.992 (0.002)	0.984 (0.002)	0.98 (0.002)	0.99 (0.001)	0.998 (0.001)	1 (0.002)	1.007 (0.002)	0.992 (0.002)	1.008 (0.002)			**Karitiana**
Sardinian	1.114 (0.004)	1.048 (0.004)	0.992 (0.002)	0.984 (0.001)	0.981 (0.002)	0.99 (0.002)	0.998 (0.001)	1 (0.002)	1.008 (0.001)	0.992 (0.001)	1.008 (0.002)	0.999 (0.002)		**Papuan**
	Neand-erthal	**Denisova**	**Dinka**	**Mand-enka**	**Mbuti**	**San**	**Yoruba**	**Dai**	**French**	**Han**	**Karitiana**	**Papuan**		

	Papuan	Karit-iana	Han	French	Dai	Yoruba	San	Mbuti	Mand-enka	Dinka	Denisova	Neander-thal	
Sardin-ian (2)	0.994 (0.002)	1.002 (0.002)	0.984 (0.002)	1.004 (0.001)	0.99 (0.002)	0.987 (0.002)	0.975 (0.002)	0.974 (0.002)	0.979 (0.002)	0.989 (0.002)	1.104 (0.003)	1.100 (0.003)	**Sardinian**
Papuan (2)		1.008 (0.002)	0.991 (0.002)	1.01 (0.002)	0.996 (0.002)	0.992 (0.002)	0.979 (0.002)	0.979 (0.002)	0.985 (0.002)	0.994 (0.002)	1.110 (0.003)	1.106 (0.003)	**Papuan**
Kariti-ana (2)			0.981 (0.002)	1.002 (0.002)	0.987 (0.002)	0.986 (0.002)	0.973 (0.002)	0.972 (0.002)	0.978 (0.002)	0.987 (0.002)	1.103 (0.003)	1.099 (0.003)	**Karitiana**
Han (2)				1.02 (0.002)	1.006 (0.001)	1 (0.002)	0.988 (0.002)	0.985 (0.002)	0.992 (0.002)	1.001 (0.002)	1.112 (0.003)	1.112 (0.003)	**Han**
French (2)					0.986 (0.002)	0.984 (0.002)	0.972 (0.002)	0.971 (0.002)	0.977 (0.002)	0.986 (0.002)	1.102 (0.003)	1.098 (0.003)	**French**
Dai (2)						0.996 (0.002)	0.983 (0.002)	0.981 (0.002)	0.987 (0.002)	0.997 (0.002)	1.109 (0.003)	1.108 (0.003)	**Dai**
Yoruba (2)							0.986 (0.001)	0.986 (0.001)	0.992 (0.001)	1.002 (0.001)	1.116 (0.003)	1.112 (0.002)	**Yoruba**
San (2)								1 (0.002)	1.006 (0.002)	1.015 (0.002)	1.128 (0.003)	1.125 (0.002)	**San**
Mbuti (2)									1.007 (0.001)	1.016 (0.001)	1.127 (0.003)	1.123 (0.003)	**Mbuti**
Mand-enka (2)										0.989 (0.002)	1.121 (0.003)	1.116 (0.003)	**Mandenka**
Dinka (2)											1.112 (0.003)	1.109 (0.003)	**Dinka**
Denisova (1)												0.998 (0.003)	**Denisova**
Neander-thal (1)													
	Papuan	**Karitiana**	**Han**	**French**	**Dai**	**Yoruba**	**San**	**Mbuti**	**Mand-enka**	**Dinka**	**Denisova**	**Neander-thal**	

Notes: Ratios are based on the accumulation of mutations observed in the population in the row divided by the accumulation of mutations observed in the population in the column. The number in parentheses indicates the number of samples per population. ±1 standard errors (parentheses) are based on a Weighted Block Jackknife. We highlight numbers >4 standard errors from expectation. We observe significant deviations from one in most pairwise comparisons. This could be due to different sequence error rates across samples which are small but significant given the small standard errors, or different mutation rates across samples. We therefore correct for such systematic differences across samples in Supplementary Table 6B by normalizing by the substitution rate differences at *G/C* and *A/T* sites, which are not subject to biased gene conversion. Ratios involving Neanderthal and Denisova remove C→T and G→A mutations to avoid high error rates due to ancient DNA degradation (Supplementary Table 7).

Supplementary Table 8B: Normalized $R'_{X/Y}$ statistics: bottom left G/C→A/T, top right A/T→G/C

				Papuan	**Karit-iana**	**Han**	**French**	**Dai**	**Yoruba**	**San**	**Mbuti**	**Mand-enka**	**Dinka**	**Denisova**	**Neander-thal**	
			Sardinian (2)	1.001 (0.003)	1.002 (0.003)	0.996 (0.003)	0.994 (0.003)	0.998 (0.003)	0.994 (0.003)	0.998 (0.002)	0.996 (0.002)	0.999 (0.003)	0.997 (0.002)	1.058 (0.003)	1.009 (0.003)	**Sardinian**
				Papuan (2)	1.001 (0.003)	0.995 (0.003)	0.994 (0.003)	0.996 (0.003)	0.994 (0.003)	0.997 (0.003)	0.996 (0.003)	0.998 (0.003)	0.996 (0.003)	1.059 (0.004)	1.008 (0.003)	**Papuan**
	Neander-thal (1)				**Karit-iana (2)**	0.993 (0.003)	0.992 (0.003)	0.994 (0.003)	0.993 (0.003)	0.996 (0.003)	0.994 (0.003)	0.998 (0.003)	0.995 (0.002)	1.057 (0.004)	1.008 (0.003)	**Karitiana**
Denisova	1.004 (0.007)	**Denisova (1)**				**Han (2)**	0.999 (0.003)	1.001 (0.003)	0.998 (0.003)	1.001 (0.003)	1 (0.003)	1.002 (0.003)	1 (0.002)	1.059 (0.004)	1.011 (0.003)	**Han**
Dinka	1.034 (0.005)	1.014 (0.005)	**Dinka (2)**				**French (2)**	1.003 (0.003)	0.999 (0.003)	1.002 (0.002)	1 (0.002)	1.004 (0.002)	1.001 (0.002)	1.06 (0.003)	1.01 (0.003)	**French**
Mand-enka	1.024 (0.005)	1.005 (0.005)	0.998 (0.002)	**Mand-enka (2)**				**Dai (2)**	0.997 (0.003)	1.001 (0.003)	0.998 (0.002)	1.001 (0.003)	0.999 (0.002)	1.059 (0.004)	1.009 (0.003)	**Dai**
Mbuti	1.028 (0.005)	1.009 (0.005)	0.997 (0.002)	1 (0.003)	**Mbuti (2)**				**Yoruba (2)**	1.003 (0.003)	1.002 (0.002)	1.005 (0.002)	1.004 (0.002)	1.063 (0.003)	1.013 (0.003)	**Yoruba**
San	1.023 (0.004)	1.002 (0.005)	0.987 (0.002)	0.99 (0.002)	0.989 (0.003)	**San (2)**				**San (2)**	0.999 (0.002)	1.002 (0.003)	1 (0.002)	1.061 (0.003)	1.013 (0.003)	**San**
Yoruba	1.025 (0.005)	1.006 (0.005)	0.995 (0.002)	0.998 (0.002)	0.997 (0.002)	1.009 (0.002)	**Yoruba (2)**				**Mbuti (2)**	1.003 (0.002)	1.001 (0.002)	1.063 (0.003)	1.013 (0.003)	**Mbuti**
Dai	1.041 (0.005)	1.023 (0.005)	0.995 (0.002)	0.998 (0.003)	0.997 (0.003)	1.009 (0.002)	1.000 (0.002)	**Dai (2)**				**Mand-enka (2)**	0.998 (0.002)	1.06 (0.003)	1.01 (0.003)	**Mandenka**
French	1.022 (0.004)	1.005 (0.005)	1.002 (0.002)	1.005 (0.002)	1.004 (0.003)	1.015 (0.002)	1.007 (0.002)	1.009 (0.003)	**French (2)**				**Dinka (2)**	1.06 (0.003)	1.012 (0.003)	**Dinka**
Han	1.054 (0.005)	1.033 (0.005)	0.997 (0.002)	1 (0.002)	1 (0.003)	1.01 (0.002)	1.003 (0.003)	1.003 (0.002)	0.995 (0.003)	**Han (2)**				**Denisova (1)**	0.945 (0.004)	**Denisova**
Karitiana	1.02 (0.005)	1.003 (0.005)	0.993 (0.003)	0.997 (0.003)	0.996 (0.003)	1.007 (0.003)	0.999 (0.003)	0.998 (0.003)	0.99 (0.003)	0.995 (0.003)	**Karitiana (2)**				**Neander-thal (1)**	
Papuan	1.025 (0.005)	1.009 (0.005)	0.995 (0.002)	0.997 (0.003)	0.997 (0.003)	1.008 (0.003)	1.000 (0.003)	0.999 (0.002)	0.992 (0.003)	0.997 (0.003)	1.001 (0.003)	**Papuan (2)**				
Sardinian	1.021 (0.005)	1.005 (0.005)	1.001 (0.002)	1.003 (0.002)	1.003 (0.002)	1.014 (0.002)	1.006 (0.002)	1.007 (0.003)	0.998 (0.003)	1.004 (0.003)	1.008 (0.003)	1.007 (0.003)	**Sardin-ian (2)**			
	Neander-thal	**Denisova**	**Dinka**	**Mand-enka**	**Mbuti**	**San**	**Yoruba**	**Dai**	**French**	**Han**	**Karitiana**	**Papuan**				

Notes: Ratios are based on the accumulation of mutations observed in the population in the row divided by the accumulation of mutations observed in the population in the column. The number in parentheses indicates the number of samples per population. ±1 standard errors (parentheses) are based on a Weighted Block Jackknife. We highlight numbers >4 standard errors from expectation. Ratios are normalized by the sum of $A \rightarrow T$, $T \rightarrow A$, $C \rightarrow G$ and $G \rightarrow C$ mutations on each lineage, producing an R' statistic that adjusts for differences in the rates of accumulations of mutations on different lineages since divergence, as well as the different ages of the samples. By normalizing, we highlight any differences in rates that are above and beyond these processes. Ratios involving Neanderthal and Denisova remove C→T and G→A mutations to avoid high error rates due to ancient DNA degradation (Supplementary Table 7).

Supplementary Table 9: R^2-statistic for all population pairs

	Dinka (2)										
Mand-enka	0.927 (0.038)	**Mand-enka (2)**									
Mbuti	0.956 (0.036)	1.025 (0.038)	**Mbuti (2)**								
San	0.907 (0.032)	0.962 (0.036)	0.949 (0.036)	**San (2)**							
Yoruba	0.92 (0.041)	0.99 (0.04)	0.969 (0.035)	1.029 (0.038)	**Yoruba (2)**						
Dai	1.601 (0.066)	1.684 (0.064)	1.609 (0.065)	1.681 (0.065)	1.713 (0.071)	**Dai (2)**					
French	1.448 (0.06)	1.528 (0.066)	1.454 (0.06)	1.513 (0.064)	1.541 (0.066)	0.879 (0.034)	**French (2)**				
Han	1.608 (0.059)	1.677 (0.07)	1.605 (0.064)	1.691 (0.068)	1.702 (0.072)	1.009 (0.036)	1.142 (0.045)	**Han (2)**			
Karitiana	2.141 (0.078)	2.228 (0.082)	2.091 (0.077)	2.147 (0.079)	2.239 (0.085)	1.468 (0.054)	1.619 (0.06)	1.455 (0.052)	**Karitiana (2)**		
Papuan	1.879 (0.07)	1.963 (0.078)	1.867 (0.058)	1.925 (0.064)	1.975 (0.067)	1.214 (0.048)	1.358 (0.048)	1.203 (0.049)	0.866 (0.032)	**Papuan (2)**	
Sardinian	1.524 (0.057)	1.603 (0.063)	1.522 (0.059)	1.579 (0.059)	1.612 (0.058)	0.936 (0.034)	1.064 (0.038)	0.933 (0.034)	0.655 (0.025)	0.787 (0.029)	**Sardin-ian (2)**
	Dinka	**Mand-enka**	**Mbuti**	**San**	**Yoruba**	**Dai**	**French**	**Han**	**Karitiana**	**Papuan**	

Notes: ±1 standard errors (parentheses) are based on a Weighted Block Jackknife. We highlight numbers >4 standard errors from expectation.

* For all population pairs, we show the $R^2_{X/Y}$ statistic. Ratios are based on the expected rate in the population in the row divided by the expected rate in the population in the column. Number in parentheses indicates the samples per population.

SUPPLEMENTARY NOTE

1 Inferred distributions of selection coefficients for PolyPhen-2 classes

1.1 Abstract

This note details the empirical fitting of the site frequency spectrum (SFS) from 1000 genomes data to determine the underlying distribution of fitness effects (DFE) for new mutations. Of particular interest is the DFE for PolyPhen-2 classes.

1.2 Aims and goals

Here we describe the technique used to analyze the distribution of selective effects of de novo mutations that form the distribution of fitness effects (DFE). Our primary aim is to infer this distribution from the site frequency spectrum of polymorphic non-synonymous alleles in the context of a given demographic history and total mutation rate. The de novo DFE in humans is in principle independent of population history and other demographic differences between individuals, allowing us to infer the distribution from a single fixed demography without loss of generality, provided the demographic inference is accurate.

1.3 Site frequency spectra

We use coding sequences from the 1000 genomes Yoruban (YRI) and Northern Europeans from Utah (CEU) populations to create a site frequency spectrum (SFS) in the form of a minor allele frequency (MAF) spectrum for both synonymous and non-synonymous sites. Additionally, we stratify the non-synonymous SFS by predicted PolyPhen-2 classes, labeled benign, possibly damaging, and probably damaging in order of increased predicted effect.

1.3.1 Simulated MAFs

Using the demographic inferences given in ref. 5, we simulate a genome of length 100Mb through the inferred demographic histories of European and African populations for a range of selective effects. In particular, the simulator tracks the derived allele frequencies of 10^8 independently evolving sites, in the infinite recombination limit with no linkage. Mutations

are introduced at a rate $\mu = 2 \times 10^{-8}$ per site per individual per generation. The population size is time dependent and reflects the demography associated with the population of interest. After completing roughly 5000 generations of recent demographic history, the allele frequencies are subsampled to the sample size of the associated 1000 genomes population sample, 88 for YRI and 85 for CEU. The results of this simulation provide expectations for the MAF for alleles with a single selective coefficient s. We simulate separately for $s = \{0, -10^{-3}, -10^{-2}\}$, which we consider to be neutral, weakly deleterious, and strongly deleterious, respectively. These selective coefficients are chosen to represent the range of realistic selective effects expected to be segregating in the human population. Alleles of stronger selective effect are likely to be absent in all but the largest population samples, and will be incorporated into the $s = -10^{-2}$ fitness class in our fit. These simulated MAFs provide the basis for our fit, as we will estimate the coefficients of their linear combination to determine the DFE.

1.4 Overall scale and target size

The number of bases simulated clearly overestimates the length of the human coding genome. The total coding genome is thought to be roughly $30Mb$ long, accounting for about 1% of the whole genome. Since estimates of both the mutation rate and target size are known to be relatively imprecise, we use the synonymous MAF to determine the overall rescaling for fitting our simulations to 1000 genomes data. Additionally, this method accounts for coverage issues, etc., assuming the same fraction of synonymous and non-synonymous sites are affected.

1.4.1 Scale factor for synonymous sites

Assuming synonymous sites are selectively neutral, we use a maximum likelihood fit with a single parameter to determine the scale factor for synonymous sites. The log likelihood is calculated as follows.

$$\log \mathcal{L} = \sum_{i=1}^{N} (D_i \log[F_i] - F_i) \tag{1}$$

Here D_i represents the i^{th} bin of the MAF from data, where $i \in [1, N]$ corresponds to allele count in the sample ranging from singletons at frequency $x = i/2N = 1/2N$ to alleles present in half of the haploid individuals at $x = N/2N = 1/2$. Similarly, F_i corresponds to counts in the fit to simulation, and is a function of fit parameters ϵ_k. For the present purposes, we are interested in determining the maximum likelihood for the following form of $F_i(\epsilon)$.

$$F_i(\epsilon) = \epsilon \; S_0^i \tag{2}$$

S_i^0 represents the i^{th} count of the MAF for the appropriately down-sampled neutral simulation with $s = 0$. The maximum log likelihood is given by the following expression.

$$\max[\log \mathcal{L}(\epsilon^{syn})] = \max \left[\sum_{i=1}^{N} (D_i \log[\epsilon^{syn} S_0^i] - \epsilon^{syn} S_0^i) \right] \tag{3}$$

We use the YRI synonymous MAF D_i^{YRIsyn} and the simulated YRI MAF for $s = 0$ to determine ϵ^{YRIsyn} numerically. The synonymous scale factor for YRI is determined by the maximum log likelihood value at $\epsilon^{YRIsyn} = 0.093$. Analogously, the synonymous scale factor for CEU has a maximum log likelihood value of $\epsilon^{CEUsyn} = 0.097$.

1.4.2 Scale factor for non-synonymous sites

Kruykov et al.[6] estimates the synonymous and non-synonymous fractions of the coding genome to be 0.32 and 0.68, respectively. This can be used to determine the appropriate scale factor for non-synonymous sites. The scale factor is simply the ratio of the total mutation rate in the target to the total simulated mutation rate.

$$\epsilon^{syn} = \frac{U_{syn}^{data}}{U^{sim}} = \frac{(\mu L_{syn})}{U^{sim}} \tag{4}$$

This can be solved for μ and substituted in to the non-synonymous expression to determine the non-synonymous scale factor.

$$\begin{aligned} \epsilon^{nonsyn} &= \frac{U_{nonsyn}^{data}}{U^{sim}} = \frac{(\mu L_{nonsyn})}{U^{sim}} \\ &= \frac{L_{nonsyn}}{L_{syn}} \epsilon^{syn} = \left(\frac{68}{32}\right) \epsilon^{syn} \end{aligned} \tag{5}$$

We find the following scale factors for the YRI and CEU simulated data.

ϵ_{nonsyn}^{YRI}	ϵ_{nonsyn}^{CEU}
0.198	0.207

1.4.3 Scale factors for PolyPhen-2 classes

The PolyPhen-2 software provides functional predictions that can be stratified into 3 classes: benign, possibly damaging, and probably damaging. One can compute the target size of these classes as a fraction of the total non-synonymous coding genome. This is accomplished by enumerating all possible point mutations from the hg19 human reference genome and classifying each mutation. We use the context dependent 64×4 weight matrix of single point mutations from a given triplet to all others[7]. Each of the 4^3 possible triplets has an associated matrix. Using HumVar, we compute approximate fractions for PolyPhen-2 classes found in the following table.

prediction	fraction (%)
benign	50.0
possibly damaging	16.7
probably damaging	33.3
unknown*	$\ll 1$

To confirm that this estimate is not biased by ancestry or recent demography, we stratify the human reference genome by predicted ancestry and find no substantial difference from these approximate values. From these fractions, we compute the appropriate scale factors for our fitting procedure.

ϵ^{YRI}_{benign}	$\epsilon^{YRI}_{possibly}$	$\epsilon^{YRI}_{probably}$
0.099	0.033	0.066

ϵ^{CEU}_{benign}	$\epsilon^{CEU}_{possibly}$	$\epsilon^{CEU}_{probably}$
0.104	0.035	0.069

1.5 Maximum Likelihood fit

Using the scale factors determined in the previous section, we compute the maximum log likelihood for a linear combination of selective effects. For simplicity, we choose to represent the DFE as a sum of several single s effect classes, rather than using a continuous functional form. We acknowledge that this three point mass model is a simplification of the true distribution of selection coefficients, but believe that it is useful for the purpose of obtaining a rough prediction of the expected value of the R-statistic for specific PolyPhen-2 classes.

$$\log \mathcal{L}(\{\alpha_k\}) = \sum_{i=1}^{N} \left(D_i \log[F_i(\{\alpha_k\})] - F_i(\{\alpha_k\})\right) \tag{6}$$

We use the following form for the fit function $F(\{\alpha_k\})$.

$$F_i(\{\alpha_k\}) = \epsilon^{nonsyn} \sum_k \alpha_k \; S_k^i = \epsilon^{nonsyn} \left(\alpha_0 \; S_0^i + \alpha_3 \; S_3^i + \alpha_2 \; S_2^i\right) \tag{7}$$

We employ the notation $k = 0$ for the simulated $s = 0$ MAF, $k = 3$ for the simulated $s = -10^{-3}$ MAF, and $k = 2$ for the simulated $s = -10^{-2}$ MAF. In this form, S_i^3 represents the MAF for the weakly selected sites, and α_3 is the fraction of the DFE that falls into this category. By estimating the maximum likelihood we can re-assemble the DFE in a rudimentary form as a fraction of mutations that fall into the category of neutral, weakly deleterious, and strongly deleterious. Since the overall scale factor is fixed, the α_k coefficients must be normalized with the following constraint.

$$\sum_k \alpha_k = 1 \tag{8}$$

This restricts the fit function as follows.

$$F_i(\{\alpha_k\}) = \epsilon^{nonsyn} \left(\alpha_0 \; S_0^i + \alpha_3 \; S_3^i + (1 - \alpha_0 - \alpha_3) \; S_2^i\right) \tag{9}$$

Note that for the present purposes, we have chosen 2 free parameters to fit, such that $\{\alpha_k\} = \{\alpha_0, \alpha_3\}$. For a 3 parameter fit with an additional nearly neutral class at $s = -10^{-4}$, for example, we simply introduce α_4 and S_4^i and modify the constraint $(\alpha_0 + \alpha_3 + \alpha_3 + \alpha_2) = 1$, with free parameters $\{\alpha_k\} = \{\alpha_0, \alpha_4, \alpha_3\}$. This method can be easily extended to fit an arbitrary number of parameters by including additional S_k^i for various selective effects. We have found this unnecessary for the present purposes, as it results in the effective overfitting of the DFE.

The maximum likelihood fit for 2 parameters is given simply by the following equations.

$$\max\left[\log \mathcal{L}(\alpha_0, \alpha_3)\right] = \max\left[\sum_{i=1}^{N} \left(D_i \log[F_i(\{\alpha_k\})] - F_i(\{\alpha_k\})\right)\right] \tag{10}$$

$$F_i(\{\alpha_k\}) = \epsilon^{nonsyn} \left(\alpha_0 \; S_0^i + \alpha_3 \; S_3^i + (1 - \alpha_0 - \alpha_3) \; S_2^i\right) \tag{11}$$

1.6 Results

Using the method outlined above, we compute the maximum likelihood fits for various PolyPhen-2 classes using YRI, CEU, and a joint measure that is the sum of the log likelihood functions of both YRI and CEU. Since the DFE should in principle be independent of demographic history, one can use the overlap of the independent measures in YRI and CEU in the form of the joint log likelihood (defined as a sum of the two log likelihoods) to produce a fit that is less sensitive to demographic errors in either of the two populations individually. The maximum log likelihood fit is summarized in the tables below. Errors are given for the joint fit, as this will be used in our subsequent analysis.

2 parameter fit (YRI)	neutral ($s = 0$)	weak ($s = -10^{-3}$)	strong ($s = -10^{-2}$)
all non-synonymous	0.20	0.44	0.36
benign	0.28	0.56	0.16
possibly damaging	0.17	0.50	0.34
probably damaging	0.09	0.25	0.66

2 parameter fit (CEU)	neutral ($s = 0$)	weak ($s = -10^{-3}$)	strong ($s = -10^{-2}$)
all non-synonymous	0.18	0.55	0.27
benign	0.26	0.68	0.06
possibly damaging	0.15	0.63	0.21
probably damaging	0.08	0.32	0.60

2 parameter fit (Joint)	neutral ($s = 0$)	weak ($s = -10^{-3}$)	strong ($s = -10^{-2}$)
all non-synonymous	0.19 $\pm$0.01	0.47 $\pm$0.04	0.33 $\pm$0.05
benign	0.27 $\pm$0.02	0.60 $\pm$0.07	0.13 $\pm$0.07
possibly damaging	0.16 $\pm$0.03	0.54 $\pm$0.11	0.29 $\pm$0.11
probably damaging	0.09 $\pm$0.01	0.27 $\pm$0.06	0.64 $\pm$0.06

1.6.1 Log Likelihood plots

The log likelihood surface for the two parameter fit can be visualized in a contour plot shown in Figure A. We note that the normalization condition $\sum_k \alpha_k = 1$ determines the strongly deleterious class uniquely. Figure B plots log likelihood contours for the benign, possibly damaging, and probably damaging PolyPhen-2 classes. We note a trend in the location of the maximum towards smaller values with increased predicted effect. All of the mass that vanishes in this process contributes to enhancing the weight of the strongly deleterious class. This is consistent with the stratification by PolyPhen-2 score, reinforcing our results.

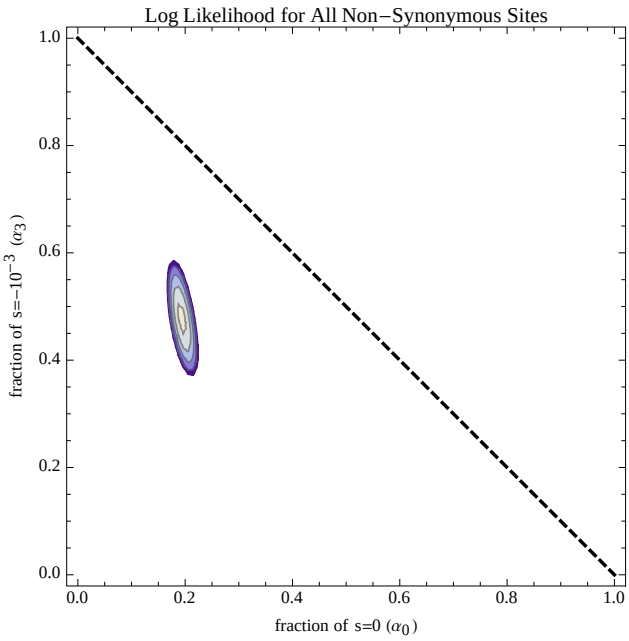

Figure A: The log likelihood plot for the joint inference from YRI and CEU data for all non-synonymous sites is shown for a two parameter fit. Contours are plotted representing two standard deviations from the peak. The coefficients of $s = 0$ and $s = -10^{-3}$, represented as (α_0,α_3), are plotted on the x and y axes, respectively. The fraction of strongly deleterious ($s = -10^{-2}$) sites in the DFE is constrained by the equation $\alpha_0 + \alpha_3 + \alpha_2 = 1$. This constraint restricts allowed values to below the dashed line. The maximum likelihood fit is located at $\{\alpha_0, \alpha_3, \alpha_2\} = \{0.19, 0.47, 0.33\}$.

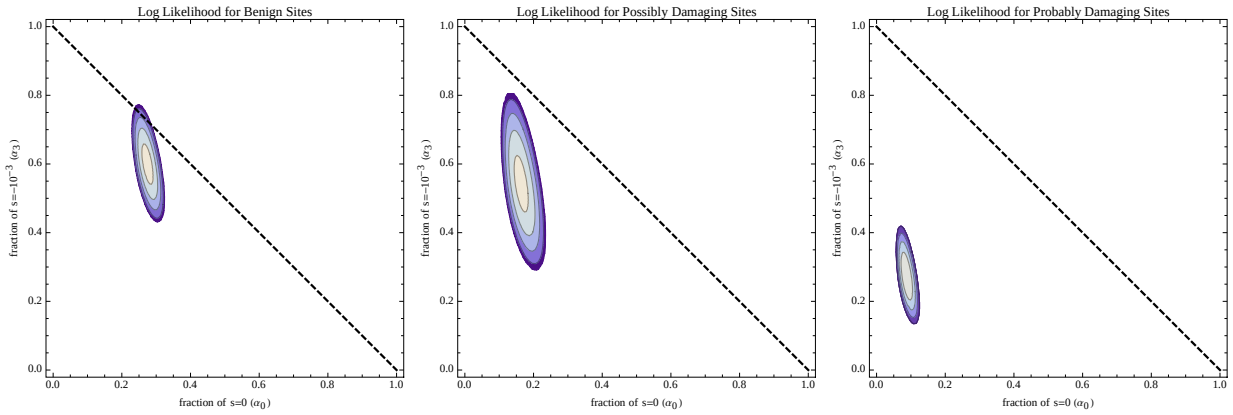

Figure B: Log Likelihood plots for the 2 parameter fit from the joint inference of YRI and CEU data are plotted for PolyPhen-2 classes. LEFT: Benign sites. MIDDLE: Possibly damaging sites. RIGHT: Probably damaging sites. All plots have axes (α_0,α_3) corresponding to neutral and weakly deleterious alleles and display two standard deviations from the maximum. The constraint $\alpha_0 + \alpha_3 + \alpha_2 = 1$ is satisfied, and only values below the dashed line are allowed. Note that the fit favors smaller fractions of neutral and weakly deleterious sites in favor of strongly deleterious sites with increasing PolyPhen-2 score, consistent with prediction.

1.7 Using the DFE to appropriately weight R

Here we use the inferred distribution of fitness effects, $\rho(s)$, to define an expected value $\langle R \rangle$ corresponding to the value of R that we expect to observe in population data. The appropriately weighted mutation load $\langle L \rangle$ for a given population is given by convoluting the load at different s values over the DFE.

$$\langle L \rangle = \int ds\ \rho(s)\ L(s) \tag{12}$$

This is true for both populations independently, since the DFE is roughly the same, allowing us to compute the expected $\langle R \rangle$ as follows.

$$\langle R \rangle = \frac{\langle L \rangle_{pop0}}{\langle L \rangle_{pop1}} = \frac{\int ds\ \rho(s)\ L^{pop0}(s)}{\int ds\ \rho(s)\ L^{pop1}(s)} \tag{13}$$

For the discretization of the DFE into neutral, weakly deleterious, and strongly deleterious components, this can be rewritten as the following sum.

$$\begin{aligned} \langle R \rangle &= \frac{\sum_k \alpha_k L^{pop0}(s_k)}{\sum_k \alpha_k L^{pop1}(s_k)} \\ &= \frac{\alpha_0 L^{pop0}(s=0) + \alpha_3 L^{pop0}(s=-10^{-3}) + \alpha_2 L^{pop0}(s=-10^{-2})}{\alpha_0 L^{pop1}(s=0) + \alpha_3 L^{pop1}(s=-10^{-3}) + \alpha_2 L^{pop1}(s=-10^{-2})} \end{aligned} \tag{14}$$

Here the α_k correspond to the fractions given in the results table above, and can represent appropriate values for all non-synonymous sites, or those for any of the PolyPhen-2 classes.

1.7.1 Computing $\langle R \rangle$, the weighted R statistic

Here, we calculate a weighted mutation load for population 0 (African) and population 1 (European) using fractions obtained from the maximum likelihood fits from the inferred distribution of fitness effects from Section 1.6 and from simulated mutation loads for average selection coefficients $s = \{0, -0.001, -0.01\}$. We calculated the weighted R statistic, denoted $\langle R \rangle$, as the ratio of the weighted mutation loads corresponding to population 0 and population 1. We calculate $\langle R \rangle$ for all non-synonymous sites, in addition to Polyphen classes, including benign, possibly damaging, and probably damaging sites (see tables below).

We calculated the expected $\langle R \rangle$ from simulations for four demographic models: Tennessen[4], Gravel[5], Lohmueller[2], and a simple bottleneck without exponential growth. We compare $\langle R \rangle$ from simulations with the R statistic observed in African Americans/European Americans from the Exome Sequencing Project (ESP) to assess the validity of different demographic models. Using this approach, we are unable to reject the Tennessen, Gravel and Lohmueller models, since $\langle R \rangle$ from these models are all within the 95% confidence intervals of R from ESP for all classes. The square bottleneck prediction is 2.09 standard errors from the empirical observation from the ESP measurement which is weakly suggestive that this model is not consistent with the data. These results suggest that this approach, the accumulation of deleterious mutations in two populations, along with the inferred DFE, can be a useful tool to evaluate the validity of different demographic models.

all non-synonymous sites	$\langle L \rangle_{pop0}$	$\langle L \rangle_{pop1}$	$\langle R \rangle$
Tennessen	0.000139	0.000140	0.989
Gravel	0.000138	0.000140	0.987
Lohmueller	0.000113	0.000114	0.992
Simple Bottleneck	0.000138	0.000141	0.978

benign	$\langle L \rangle_{pop0}$	$\langle L \rangle_{pop1}$	$\langle R \rangle$
Tennessen	0.000193	0.000195	0.990
Gravel	0.000192	0.000194	0.988
Lohmueller	0.000157	0.000158	0.993
Simple Bottleneck	0.000192	0.000196	0.979

possibly damaging	$\langle L \rangle_{pop0}$	$\langle L \rangle_{pop1}$	$\langle R \rangle$
Tennessen	0.000123	0.000125	0.985
Gravel	0.000123	0.000125	0.984
Lohmueller	0.000101	0.000103	0.989
Simple Bottleneck	0.000123	0.000126	0.973

probably damaging	$\langle L \rangle_{pop0}$	$\langle L \rangle_{pop1}$	$\langle R \rangle$
Tennessen	0.00006909	0.00006995	0.988
Gravel	0.00006887	0.00006982	0.986
Lohmueller	0.00005698	0.00005748	0.991
Simple Bottleneck	0.00006885	0.00007048	0.977

2 The proportion of non-synonymous sites is driven by neutral demographic history

2.1 Aims and Goals

We performed computer simulations of two models of demographic history (shown in Figure 3A) that differ qualitatively with regard to the history after the population split: (1) "Tennessen et al. 2012"[4], and (2) "Bottleneck and growth" . We tuned the parameters of the "Bottleneck and growth" model to match the Tennessen et al. 2012 (ref. 4) model both for the population split time (2,040 generations ago) and the final predicted heterozygosities at synonymous sites in both West Africans and Europeans.

2.2 Qualitative differences between the two models of demographic history

There is an important difference between the two models. For Tennessen et al. 2012 (ref. 4), West African populations are larger than European populations for most of the history since their split, and thus selection against weakly deleterious mutations would be expected to operate less effectively in European history. For the Bottleneck and Growth model, the opposite is the case.

Weighting of selection coefficients for Boyko et al. 2008				**Tennessen et al. 2012 demographic model results[4]**				**Bottleneck & Growth demographic model results**			
s	gamma density	bin width	Weight: proportional to (gamma) x (bin width)	segregating sites /bp	$L_{Afr\text{-}not\text{-}Eur}$	$L_{Eur\text{-}not\text{-}Afr}$	$R_{Afr/Eur}$	segregating sites /bp	$L_{Afr\text{-}not\text{-}Eur}$	$L_{Eur\text{-}not\text{-}Afr}$	$R_{Afr/Eur}$
-0.000001	1.8×10^{-1}	1.4×10^{-6}	0.029	2.8×10^{-3}	6.1×10^{-4}	6.1×10^{-4}	1	3.4×10^{-3}	6.2×10^{-4}	6.2×10^{-4}	1
-0.000002	1.1×10^{-1}	1.7×10^{-6}	0.021	2.8×10^{-3}	6.1×10^{-4}	6.1×10^{-4}	1	3.3×10^{-3}	6.1×10^{-4}	6.2×10^{-4}	1
-0.000005	5.1×10^{-2}	3.9×10^{-6}	0.022	2.8×10^{-3}	6.0×10^{-4}	6.0×10^{-4}	1	3.3×10^{-3}	6.1×10^{-4}	6.1×10^{-4}	1
-0.00001	2.9×10^{-2}	7.1×10^{-6}	0.023	2.7×10^{-3}	5.9×10^{-4}	5.9×10^{-4}	1	3.3×10^{-3}	5.9×10^{-4}	5.9×10^{-4}	1
-0.00002	1.7×10^{-2}	1.7×10^{-5}	0.033	2.6×10^{-3}	5.6×10^{-4}	5.6×10^{-4}	1	3.2×10^{-3}	5.6×10^{-4}	5.6×10^{-4}	0.99
-0.00005	8.2×10^{-3}	3.9×10^{-5}	0.036	2.3×10^{-3}	4.7×10^{-4}	4.8×10^{-4}	0.99	2.9×10^{-3}	4.7×10^{-4}	4.8×10^{-4}	0.99
-0.0001	4.7×10^{-3}	7.1×10^{-5}	0.037	1.9×10^{-3}	3.5×10^{-4}	3.6×10^{-4}	0.98	2.4×10^{-3}	3.5×10^{-4}	3.6×10^{-4}	0.97
-0.0002	2.7×10^{-3}	1.7×10^{-4}	0.053	1.4×10^{-3}	2.1×10^{-4}	2.1×10^{-4}	0.97	1.9×10^{-3}	2.1×10^{-4}	2.2×10^{-4}	0.95
-0.0005	1.3×10^{-3}	3.9×10^{-4}	0.057	8.7×10^{-4}	8.4×10^{-5}	8.9×10^{-5}	0.94	1.3×10^{-3}	8.3×10^{-5}	9.1×10^{-5}	0.91
-0.001	7.6×10^{-4}	7.1×10^{-4}	0.059	6.5×10^{-4}	4.1×10^{-5}	4.5×10^{-5}	0.92	9.8×10^{-4}	4.1×10^{-5}	4.6×10^{-5}	0.90
-0.002	4.3×10^{-4}	1.7×10^{-3}	0.084	4.9×10^{-4}	2.0×10^{-5}	2.2×10^{-5}	0.92	6.6×10^{-4}	2.0×10^{-5}	2.2×10^{-5}	0.94
-0.005	2.0×10^{-4}	3.9×10^{-3}	0.089	2.8×10^{-4}	8.0×10^{-6}	8.3×10^{-6}	0.97	3.0×10^{-4}	8.1×10^{-6}	8.1×10^{-6}	1
-0.01	1.1×10^{-4}	7.1×10^{-3}	0.090	1.6×10^{-4}	4.0×10^{-6}	4.0×10^{-6}	0.99	1.6×10^{-4}	4.0×10^{-6}	4.0×10^{-6}	1
-0.02	6.1×10^{-5}	1.7×10^{-2}	0.120	8.0×10^{-5}	2.0×10^{-6}	2.0×10^{-6}	1	7.9×10^{-5}	2.0×10^{-6}	2.0×10^{-6}	1
-0.05	2.4×10^{-5}	3.9×10^{-2}	0.105	3.2×10^{-5}	8.0×10^{-7}	8.0×10^{-7}	1	3.2×10^{-5}	8.0×10^{-7}	8.0×10^{-7}	1
-0.1	9.9×10^{-6}	7.1×10^{-2}	0.078	1.6×10^{-5}	4.0×10^{-7}	4.0×10^{-7}	1	1.6×10^{-5}	4.0×10^{-7}	4.0×10^{-7}	1
-0.2	2.9×10^{-6}	1.7×10^{-1}	0.056	8.0×10^{-6}	2.0×10^{-7}	2.0×10^{-7}	1	8.0×10^{-6}	2.0×10^{-7}	2.0×10^{-7}	1
-0.5	1.8×10^{-7}	3.9×10^{-1}	0.0077	3.2×10^{-6}	8.0×10^{-8}	8.0×10^{-8}	1	3.2×10^{-6}	8.0×10^{-8}	8.0×10^{-8}	1
-1	3.3×10^{-9}	2.9×10^{-1}	0.00011	1.6×10^{-6}	4.0×10^{-8}	4.0×10^{-8}	1	1.6×10^{-6}	4.0×10^{-8}	4.0×10^{-8}	1
Non-synonymous	N/A	1	1	7.6×10^{-4}	1.27×10^{-4}	1.29×10^{-4}	0.987	9.6×10^{-4}	1.28×10^{-4}	1.30×10^{-4}	0.983
Synonymous	N/A	N/A	N/A	2.8×10^{-3}	6.17×10^{-4}	6.17×10^{-4}	0.999	9.6×10^{-4}	6.21×10^{-4}	6.22×10^{-4}	0.998

2.3 Simulations

We simulated 10 billion base pairs for a selection coefficient of $s = 0$ ("synonymous sites") and 1 billion base pairs for each of 19 negative selection coefficients ("non-synonymous"), as shown in the table. For the total number of segregating non-synonymous sites, we weighted each of the 19 selection coefficients based on an inferred distribution of human selection coefficients from Boyko et al. 2008 (ref. 8) (the fit to European genetic variation data in which $-s$ follows a gamma distribution with α=0.206 and β=15,400). Specifically, we took the gamma density ("gamma density" in Table 1 of that paper), and multiplied it by the range of selection coefficients represented by that bin ("bin width"). We renormalized the products so that they summed to one.

For each simulation, we tabulated the number of segregating sites per generation over the last 3,000 generations of history assuming a sample size of 40 for both West Africans and 40 Europeans (we used a hypergeometric distribution to obtain the expected probability of each polymorphic site being heterozygous given that sample size).

2.4 Matching the empirical ratio of non-synonymous to synonymous sites

To obtain numbers for all non-synonymous sites we used the weights shown in the table to compute the expected rate of segregating sites per base pair in both West Africans and Europeans in each generation.

To compute the proportion of non-synonymous sites in each generation, we used the following equation, with the factor of 3.42 chosen to be what was needed for the proportion to equal the empirical value in ref. 2 (0.479). We note that this is only a scaling factor. Similar behaviors would be obtained with other scaling factors so the exact choice of scaling factor is not important for our qualitative results.

$$proportion\ nonsynonymous = \frac{3.42 \times nonsynonymous}{3.42 \times nonsynonymous + synonymous}$$

2.5 Detailed discussion of the simulation results

Figure 3B shows the temporal dynamics of the density of non-synonymous sites (per base pair), the density of synonymous sites, and the proportion of all sites that are non-synonymous. We only show results here for Europeans (in both simulated models, the West African population size changes very little and so the statistics hardly change, at least compared with Europeans).

Both simulated demographic models show the same qualitative feature as the simulations presented in ref. 2. Non-synonymous and synonymous segregating site densities are initially decreased in Europeans by the bottleneck for all classes of selection coefficients, with the proportional effect being larger for non-synonymous sites. In the recovery period, however, non-synonymous segregating site densities increase faster than synonymous ones. Thus, the total proportion of sites that are non-synonymous also increases in this period. In both simulated demographic models, the proportion of non-synonymous sites thus has a non-trivial behavior of initially falling and then rising, eventually passing the baseline as first observed by ref. 2.

Lohmueller et al. 2008 (ref. 2) argued that the observation of an elevated rate of non-synonymous sites in present-day Europeans (compared with West Africans as a baseline) is evidence of less effective natural selection to remove weakly deleterious mutations in European than in West African populations since their separation. If this is the case, it is surprising that the Bottleneck and Growth model where population sizes have been larger in European than in West Africans populations for most of their history shows the same qualitative effect.

What then is driving the rise in the proportion of non-synonymous sites in Europeans that begins within hundreds of generations after the bottleneck for both simulated models, if it is not reduced effectiveness of deleterious mutation in Europeans?

A key intuition that is helpful for understanding this behavior is that prior to the West African / European population split, the density of non-synonymous segregating sites is expected to have been much lower than the density of synonymous segregating sites due to the action of natural selection. This pattern would only have been intensified by the preferential loss of segregating sites for the non-synonymous class due to the out-of-Africa bottleneck, as our simulations show (Figure 3B).

Once the population began expanding, genetic drift would have been reduced and equilibrium would have favored a higher density of segregating sites both for non-synonymous and synonymous classes. The non-synonymous site class approaches its equilibrium relatively more quickly than the synonymous site class once the population grows, as the non-synonymous class experiences the same flux of new mutations as synonymous sites (actually an even higher flux, as the target size is larger). Since non-synonymous sites start out with a lower baseline density, the proportional rate of their approach to equilibrium is faster than for synonymous segregating sites, explaining our observation. Selected classes of mutations turn over more quickly, and thus approach equilibrium more quickly[9].

Supplementary References

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