Supplementary Materials

Table S1. Demographic model parameter estimates from synonymous sites.

	n_{chr}	θ_S	N_1	T_1[a]	N_2	T_2	N_C	T_C
LuCamp	2596	4261.2	0.08984	0.01	1.0512	0.07304	31.270	0.01158
1kG	864	5984.9	0.08469	0.01	1.1007	0.07043	53.283	0.02009
ESP	2600	6415.1	0.11949	0.01	1.3111	0.05254	98.65	0.01502
LuCamp	24	4438.9	0.07554	0.01	0.8703	0.10652	53.09[b]	0.01311
1kG	24	6122.4	0.07447	0.01	0.9606	0.08805	93.23[b]	0.01991
ESP	24	6735.6	0.08887	0.01	0.9787	0.08434	63.79[b]	0.01758

Note: See Figure S3 for a pictorial representation of the model.
Parameter descriptions:
N_i: Population size relative to the ancestral population
T_i: Time, in units of $2N_{ANC}$ generations (N_{ANC} is the ancestral population size)
θ_S: The population mutation rate of synonymous sites.
[a]T_1 is fixed in this model.
[b]These estimates are unreliable and can range from 50-200 with no appreciable change in the fit of the model.

Table S2. Parameters used to scale the DFE in terms of *s*.

	n_{chr}	θ_S	L_{NS}/L_S	θ_{NS}	μ	L_S+L_{NS}	L_S	L_{NS}	N_{ANC}
LuCamp	2596	4261.2		10652.9	1.8×10^{-8}	20,043,582	5,726,738	14,316,844	10334
1kG	864	5984.9	2.5	14962.3	1.8×10^{-8}	26,673,114	7,620,890	19,052,224	10907
ESP	2600	6415.1		16037.7	1.8×10^{-8}	31,427,992	8,979,426	22,448,566	9922
LuCamp	2596	4261.2		9843.3	1.5×10^{-8}	20,043,582	6,055,463	13,988,119	11728
1kG	864	5984.9	2.31	13825.1	1.5×10^{-8}	26,673,114	8,058,343	18,614,771	12378
ESP	2600	6415.1		14818.8	1.5×10^{-8}	31,427,992	9,494,862	21,933,130	11261
LuCamp	24	4438.9		11097.3	1.8×10^{-8}	20,043,582	5,726,738	14,316,844	10766
1kG	24	6122.4	2.5	15306.0	1.8×10^{-8}	26,673,114	7,620,890	19,052,224	11158
ESP	24	6735.6		16839.0	1.8×10^{-8}	31,427,992	8,979,426	22,448,566	10418
LuCamp	24	4438.9		10253.9	1.5×10^{-8}	20,043,582	6,055,463	13,988,119	12217
1kG	24	6122.4	2.31	14142.7	1.5×10^{-8}	26,673,114	8,058,343	18,614,771	12663
ESP	24	6735.6		15559.2	1.5×10^{-8}	31,427,992	9,494,862	21,933,130	11823

Parameter descriptions:

θ_S: The population scaled synonymous mutation rate

θ_{NS}: The population scaled nonsynonymous mutation rate

L_S: The number of synonymous sites

L_{NS}: The number of nonsynonymous sites

N_{ANC}: The ancestral population sizes computed from $\theta_S=4N_{ANC}\mu L_S$

Table S3. Inference using Fit∂a∂i on the African-American dataset from Boyko et al. (2008).

	∂a∂i[a]	Boyko et al.
N_{curr}/N_{anc}	3.352	3.296
T_{exp}	7067	6809
	fit∂a∂i	**Boyko et al.**
α **(shape)**	0.179	0.184
β **(scale)**	3161	2488
$\mathbf{0 \le \lvert s \rvert < 10^{-4}}$	27.7%	27.9%
$\mathbf{10^{-4} \le \lvert s \rvert < 10^{-4}}$	14.1%	14.7%
$\mathbf{10^{-2} \le \lvert s \rvert < 10^{-3}}$	20.9%	21.9%
$\mathbf{10^{-2} \le \lvert s \rvert}$	37.3%	35.5%

Notes: Population sizes are reported relative to the ancestral population size, and times are reported in units of generations. The scale parameter of the gamma distribution is scaled in terms of the ancestral population size. The proportion of new mutations in each range of selective effects was computed from the gamma distribution.

[a]Demographic inference was done using the standard framework of ∂a∂i.

Table S4. Maximum likelihood estimates for the various DFEs under different mutation rate assumptions.

Dataset	n_{chr}	Distribution	Parameters[a]			$0 \le \lvert s\rvert < 10^{-5}$	$10^{-5} \le s < 10^{-4}$	$10^{-4} \le \lvert s\rvert < 10^{-3}$	$10^{-3} \le \lvert s\rvert < 10^{-2}$	$10^{-2} \le \lvert s\rvert$	Log-likelihood	$\lvert\Delta AIC\rvert$[b]
						$\mu=1.5\times10^{-8}$, $L_{NS}/L_S=2.31$						
1kG EUR	864	gamma	--	**0.186**	**875**	0.237	0.127	0.192	0.266	0.178	-1450.5	0
		neu+gamma	**0.031**	**0.199**	**820.6**	0.242	0.122	0.191	0.270	0.176	-1450.8	2.6
		neu+exp+let	**0.312**	**0.509**	**41.48**	0.216	0.026	0.199	0.279	0.279	-1472.0	45
		discrete	--	--	--	**0.286**	**0.099**	**0.222**	**0.305**	0.089	-1453.4	9.8
ESP EUR	2600	gamma	--	**0.169**	**1327.4**	0.248	0.118	0.173	0.240	0.220	-3012.6	2.6
		neu+gamma	**0.092**	**0.207**	**1082.3**	0.263	0.104	0.167	0.249	0.217	-3010.3	0
		neu+exp+let	**0.341**	**0.504**	**63.90**	0.343	0.016	0.132	0.340	0.169	-3071.6	122.6
		discrete	--	--	--	**0.334**	**0.041**	**0.201**	**0.306**	0.118	-3029.5	40.4
LuCamp	2596	gamma	--	**0.215**	**562.1**	0.205	0.131	0.212	0.298	0.154	-3334.7	13.8
		neu+gamma	**0.164**	**0.338**	**367.7**	0.241	0.091	0.194	0.332	0.141	-3326.8	0
		neu+exp+let	**0.304**	**0.613**	**66.56**	0.306	0.019	0.161	0.413	0.101	-3337.8	22
		discrete	--	--	--	**0.309**	**0.024**	**0.247**	**0.372**	0.049	-3334.2	16.8
						$\mu=1.8\times10^{-8}$, $L_{NS}/L_S=2.5$						
1kG EUR	864	gamma	--	**0.181**	**1585.1**	0.217	0.112	0.169	0.243	0.259	-1452.1	0
		neu+gamma	**0.01**	**0.184**	**1554.8**	0.220	0.111	0.168	0.244	0.258	-1452.5	2.8
		neu+exp+let	**0.288**	**0.470**	**41.53**	0.290	0.022	0.168	0.275	0.244	-1472.0	41.8
		discrete	--	--	--	**0.259**	**0.088**	**0.201**	**0.279**	0.174	-1454.2	8.2
ESP EUR	2600	gamma	--	**0.164**	**2527.8**	0.229	0.105	0.152	0.216	0.298	-3008.6	0
		neu+gamma	**0.032**	**0.176**	**2326.6**	0.234	0.101	0.150	0.218	0.297	-3008.6	2
		neu+exp+let	**0.315**	**0.466**	**63.88**	0.316	0.013	0.110	0.321	0.240	-3071.6	128
		discrete	--	--	--	**0.307**	**0.032**	**0.178**	**0.284**	0.199	-3032.5	51.8
LuCamp	2596	gamma	--	**0.203**	**1082.1**	0.192	0.114	0.181	0.268	0.245	-3335.9	2.6
		neu+gamma	**0.027**	**0.216**	**1017.5**	0.197	0.109	0.178	0.271	0.244	-3335.9	4.6
		neu+exp+let	**0.281**	**0.566**	**66.51**	0.283	0.016	0.134	0.390	0.178	-3337.8	8.44
		discrete	--	--	--	**0.278**	**0.027**	**0.211**	**0.352**	0.132	-3332.6	0

[a]The bolded parameters were directly inferred and are denoted in the following order. Gamma: α (shape), β (scale). Neutral+gamma: p_{neu}, α (shape), β (scale). The scale parameters are in terms of $2N_{ANC}s$. Neutral+exp+lethal: p_{neu}, p_{exp}, λ (rate). For the discrete DFE, the

proportion of each bin is directly inferred. Note, there are only four free bins because the mass in all of the bins together is constrained to sum to 1.

[b]Change in AIC relative to the model with the lowest AIC.

Table S5. A comparison of our three best-fitting DFEs to previously inferred DFEs.

n_{chr}	Dataset	DFE	p_{neu}	α (shape)	β (scale)	$0 \le \lvert s \rvert < 10^{-5}$	$10^{-5} \le \lvert s \rvert < 10^{-4}$	$10^{-4} \le \lvert s \rvert < 10^{-3}$	$10^{-3} \le \lvert s \rvert < 10^{-2}$	$10^{-2} \le \lvert s \rvert$	Log-likelihood
24	Boyko et al. (AFR)	gamma	--	0.184 (0.158-0.206)	2488 (1062 - 6159)	0.183 (0.123-0.266)	0.096 (0.075-0.12)	0.147 (0.120-0.167)	0.219 (0.191-0.228)	0.355 (0.222-0.491)	--
		neu+gamma	0.148 (0.000 – 0.235)	0.344 (0.178 – 0.790)	1900 (280-12300)	0.189 (0.235-0.300)	0.050 (0.001-0.151)	0.110 (0.004-0.222)	0.232 (0.027-0.257)	0.419 (0.070-0.733)	--
	Boyko et al. (EUR)	gamma	--	0.206	2263	0.151	0.092	0.147	0.231	0.379	--
		neu+gamma	0.239	1.09	800	0.240	0.006	0.068	0.455	0.232	--
180*	Eyre-Walker et al.[a]	gamma	--	0.23 (0.19-0.27)	1845 (833-4032)	0.134 (0.076-0.223)	0.094 (0.066-0.122)	0.159 (0.122-0.188)	0.259 (0.223-0.266)	0.354 (0.202-0.513)	--
400	Li et al.[b]	neu+gamma	0.2	4	11.1*	0.200	0.012	0.775	0.013	0.000	--
				$\mu=1.8\times10^{-8}$, $L_{NS}/L_S=2.5$							
864	1000 Genomes (EUR)	gamma	--	0.181 (0.175-0.185)	1585.1 (1451.9-1796.6)	0.217 (0.212-0.223)	0.112 (0.111-0.113)	0.169 (0.165-0.172)	0.243 (0.235-0.249)	0.259 (0.252-0.266)	-1452.1
		neu+gamma	0.010 (0.001-0.036)	0.184 (0.178-0.200)	1554.8 (1340.5-1724.4)	0.220 (0.212-0.228)	0.111 (0.105-0.112)	0.168 (0.164-0.172)	0.244 (0.237-0.252)	0.258 (0.251-0.265)	-1452.5
		discrete	--	--	--	0.259 (0.203-0.311)	0.088 (0.005-0.165)	0.201 (0.163-0.243)	0.279 (0.251-0.305)	0.174 (0.160-0.188)	-1454.2
2600	ESP (EUR)	gamma	--	0.164 (0.160-0.168)	2527.8 (2284.9-2742.1)	0.229 (0.223-0.234)	0.105 (0.104-0.106)	0.152 (0.150-0.155)	0.216 (0.212-0.221)	0.298 (0.294-0.302)	-3008.6
		neu+gamma	0.032 (0.012-0.089)	0.176 (0.168-0.203)	2326.6 (1936.4-2591.9)	0.234 (0.228-0.244)	0.101 (0.091-0.104)	0.150 (0.145-0.153)	0.218 (0.212-0.225)	0.297 (0.294-0.301)	-3008.6
		discrete	--	--	--	0.307 (0.252-0.331)	0.032 (0.001-0.114)	0.178 (0.141-0.200)	0.284 (0.269-0.300)	0.199 (0.193-0.207)	-3032.5
2596	LuCamp	gamma	--	0.203 (0.197-0.207)	1082.1 (999.3-1184.4)	0.192 (0.188-0.198)	0.114 (0.113-0.115)	0.181 (0.177-0.184)	0.268 (0.261-0.273)	0.245 (0.238-0.251)	-3335.9
		neu+gamma	0.027 (0.005-0.104)	0.216 (0.201-0.262)	1017.5 (813.8-1150.4)	0.197 (0.190-0.215)	0.109 (0.093-0.113)	0.178 (0.169-0.182)	0.271 (0.263-0.283)	0.244 (0.237-0.250)	-3335.9

		discrete	--	--	--	0.278 (0.221-0.303)	0.027 (0.001-0.110)	0.211 (0.167-0.234)	0.352 (0.330-0.373)	0.132 (0.124-0.142)	-3332.6
	1000 Genomes (EUR)	gamma	--	0.183 (0.170-0.197)	1534.8 (1018.8-2311.4)	0.216 (0.206-0.225)	0.113 (0.107-0.119)	0.171 (0.158-0.185)	0.246 (0.225-0.268)	0.255 (0.220-0.285)	-53.8
		neu+gamma	0.051 (0.017-0.179)	0.209 (0.186-0.339)	1256.8 (451.4-1834.4)	0.221 (0.212-0.244)	0.105 (0.074-0.113)	0.169 (0.155-0.180)	0.256 (0.233-0.323)	0.248 (0.189-0.279)	-54.1
		discrete	--	--	--	0.155 (0.092-0.279)	0.262 (0.056-0.366)	0.053 (0.001-0.249)	0.495 (0.002-0.556)	0.034 (0.001-0.384)	-53.2
	ESP (EUR)	gamma	--	0.159 (0.147-0.172)	3349.2 (2020.4-5585.4)	0.230 (0.221-0.240)	0.102 (0.096-0.108)	0.147 (0.135-0.160)	0.207 (0.187-0.229)	0.315 (0.280-0.345)	-54.1
24		neu+gamma	0.084 (0.027-0.221)	0.201 (0.161-0.388)	2112.3 (480.8-4144.3)	0.240 (0.232-0.260)	0.092 (0.058-0.102)	0.146 (0.132-0.154)	0.223 (0.192-0.297)	0.300 (0.224-0.327)	-54.2
		discrete	--	--	--	0.216 (0.130-0.323)	0.172 (0.001-0.304)	0.086 (0.001-0.251)	0.373 (0.001-0.577)	0.153 (0.001-0.428)	-54.0
	LuCamp	gamma	--	0.189 (0.172-0.205)	2050.3 (1256.3-3583.5)	0.193 (0.183-0.204)	0.105 (0.099-0.111)	0.161 (0.146-0.177)	0.239 (0.210-0.266)	0.302 (0.261-0.339)	-51.1
		neu+gamma	0.113 (0.024-0.205)	0.278 (0.195-0.509)	951.5 (267.7-2078.6)	0.208 (0.195-0.233)	0.085 (0.044-0.105)	0.161 (0.145-0.172)	0.280 (0.233-0.383)	0.266 (0.180-0.310)	-50.9
		discrete	--	--	--	0.262 (0.119-0.301)	0.049 (0.001-0.268)	0.209 (0.003-0.290)	0.257 (0.001-0.600)	0.222 (0.001-0.425)	-50.9
μ=1.5×10^{-8}, L_{NS}/L_S =2.31											
	1000 Genomes (EUR)	gamma	--	0.186 (0.181-0.191)	875.0 (787.9-978.0)	0.237 (0.231-0.243)	0.127 (0.125-0.128)	0.192 (0.188-0.197)	0.266 (0.259-0.272)	0.178 (0.171-0.186)	-1450.5
		neu+gamma	0.031 (0.004-0.104)	0.199 (0.186-0.238)	820.6 (670.2-908.3)	0.242 (0.233-0.256)	0.122 (0.109-0.127)	0.191 (0.185-0.195)	0.270 (0.263-0.282)	0.176 (0.167-0.183)	-1450.8
864		discrete	--	--	--	0.286 (0.240-0.333)	0.099 (0.012-0.169)	0.222 (0.182-0.264)	0.305 (0.271-0.334)	0.089 (0.071-0.107)	-1453.4
2600	ESP (EUR)	gamma	--	0.169 (0.165-0.174)	1327.4 (1211.9-1439.2)	0.248 (0.242-0.254)	0.118 (0.117-0.119)	0.173 (0.170-0.177)	0.240 (0.235-0.246)	0.220 (0.214-0.224)	-3012.6

		neu+gamma	0.092 (0.026-0.158)	0.207 (0.179-0.251)	1082.3 (880.3-1261.5)	0.263 (0.250-0.277)	0.104 (0.091-0.114)	0.167 (0.160-0.173)	0.249 (0.241-0.259)	0.217 (0.211-0.221)	-3010.3
		discrete	--	--	--	0.334 (0.284-0.363)	0.041 (0.001-0.115)	0.201 (0.165-0.228)	0.306 (0.285-0.324)	0.118 (0.110-0.126)	-3029.5
		gamma	--	0.215 (0.207-0.220)	562.1 (525.9-620.8)	0.205 (0.199-0.213)	0.131 (0.130-0.132)	0.212 (0.207-0.215)	0.298 (0.290-0.303)	0.154 (0.147-0.161)	-3334.7
2596	LuCamp	neu+gamma	0.164 (0.110-0.215)	0.338 (0.281-0.415)	367.7 (295.4-455.7)	0.242 (0.223-0.260)	0.091 (0.072-0.107)	0.194 (0.183-0.203)	0.332 (0.313-0.352)	0.141 (0.129-0.152)	-3326.8
		discrete	--	--	--	0.309 (0.260-0.332)	0.024 (0.001-0.099)	0.247 (0.201-0.269)	0.372 (0.347-0.395)	0.049 (0.039-0.060)	-3334.2
		gamma	--	0.183 (0.170-0.197)	1534.8 (1018.8-2311.4)	0.221 (0.212-0.230)	0.115 (0.109-0.122)	0.175 (0.161-0.189)	0.250 (0.228-0.272)	0.239 (0.204-0.271)	-53.8
	1000 Genomes (EUR)	neu+gamma	0.051 (0.017-0.179)	0.209 (0.186-0.339)	1256.8 (451.4-1834.4)	0.226 (0.217-0.247)	0.108 (0.077-0.116)	0.173 (0.160-0.187)	0.260 (0.237-0.329)	0.232 (0.170-0.264)	-54.1
		discrete	--	--	--	0.155 (0.092-0.279)	0.262 (0.056-0.366)	0.053 (0.001-0.249)	0.495 (0.002-0.556)	0.034 (0.001-0.384)	-53.2
		gamma	--	0.159 (0.149-0.171)	2001.6 (1390.4-2898.3)	0.254 (0.244-0.263)	0.113 (0.106-0.118)	0.162 (0.150-0.173)	0.224 (0.205-0.240)	0.247 (0.222-0.274)	-54.1
24	ESP (EUR)	neu+gamma	0.127 (0.031-0.249)	0.231 (0.167-0.424)	1084.0 (338.2-2202.3)	0.264 (0.250-0.287)	0.096 (0.062-0.112)	0.162 (0.147-0.176)	0.254 (0.216-0.332)	0.224 (0.148-0.269)	-54.3
		discrete	--	--	--	0.256 (0.170-0.355)	0.169 (0.001-0.304)	0.101 (0.001-0.294)	0.425 (0.001-0.515)	0.050 (0.001-0.355)	-54.0
		gamma	--	0.189 (0.175-0.206)	1307.8 (806.7-2071.6)	0.214 (0.201-0.226)	0.117 (0.110-0.124)	0.179 (0.162-0.198)	0.258 (0.233-0.283)	0.232 (0.190-0.269)	-51.1
	LuCamp	neu+gamma	0.113 (0.024-0.205)	0.278 (0.195-0.509)	951.5 (267.7-2078.6)	0.211 (0.199-0.235)	0.089 (0.048-0.108)	0.166 (0.150-0.177)	0.286 (0.237-0.391)	0.248 (0.156-0.295)	-50.9
		discrete	--	--	--	0.262 (0.119-0.301)	0.049 (0.001-0.268)	0.209 (0.003-0.290)	0.257 (0.001-0.600)	0.222 (0.001-0.425)	-50.9

Note: We present our results assuming that that L_{NS}/L_S=2.31 and μ=1.5×10^{-8}, or, alternatively, L_{NS}/L_S=2.5 and μ=1.8×10^{-8}. The latter provides a direct comparison to Boyko et al. (2008).

[a]The DFE of Eyre-Walker et al. (2006) is rescaled assuming an ancestral population size of N=10,000 diploids. Additionally, this dataset is comprised of 320 autosomal genes, in contrast to the exome sequencing datasets presented here.

[b]The DFE of Li et al. (2010) is scaled by a population size of N=52,097 diploids.

Table S6. Masking singletons has little effect on inference of the DFE.

		With singletons		Singletons masked	
Dataset	**Distribution**	**Parameters**	**Log-likelihood**	**Parameters**	**Log-likelihood**
1kG EUR	gamma	α=0.186, β=875	-1450.5	α=0.186, β=866	-1444.1
	neu+gamma	p_{neu}=0.031, α=0.199, β=820.6	-1450.8	p_{neu}=0.088, α=0.232, β=662	-1444.9
ESP EUR	gamma	α=0.169, β=1327.4	-3012.6	α=0.162, β=1630.9	-2999.5
	neu+gamma	p_{neu}=0.092, α=0.207, β=1082.3	-3010.3	p_{neu}=0.0232, α=0.170, β=1530.7	-2999.8
LuCamp	gamma	α=0.215, β=562.1	-3334.7	α=0.213, β=587.1	-3327.2
	neu+gamma	p_{neu}=0.164, α=0.338, β=367.7	-3326.8	p_{neu}=0.1696, α=0.352, β=338.3	-3318.9

Notes: We assumed L_{NS}/L_S=2.31 and μ=1.5×10^{-8} for these calculations. α denotes the shape parameter and β denotes the scale parameter. The scale parameter is scaled by the ancestral population size.

Table S7. The DFE of new mutations and the DFE of segregating sites.

Sample	**α (shape) MLE**	**β (scale) MLE**
True DFE of new mutations	0.187	0.0356
Gamma distribution fit to s (s is known)		
segregating variants, $2n$=24	0.112	0.00201
segregating variants, $2n$=864	0.164	0.00634
new mutations	0.187	0.0356
Gamma distribution inferred from SFS with Fit∂a∂i and multinomial likelihood		
$2n$=24	0.163	2.39*
$2n$=864	0.194	0.0248
Gamma distribution inferred from SFS with Fit∂a∂i and Poisson likelihood		
$2n$=24	0.166	0.0497
$2n$=864	0.189	0.0364

Notes: These results represent a single simulation replicate. We show that Fit∂a∂i infers the DFE of new mutations correctly for many replicates in Figure S7. These DFEs are scaled in terms of s. *The estimated scale parameter is likely inaccurate due to the small sample size as well as the fact the multinomial likelihood was used.

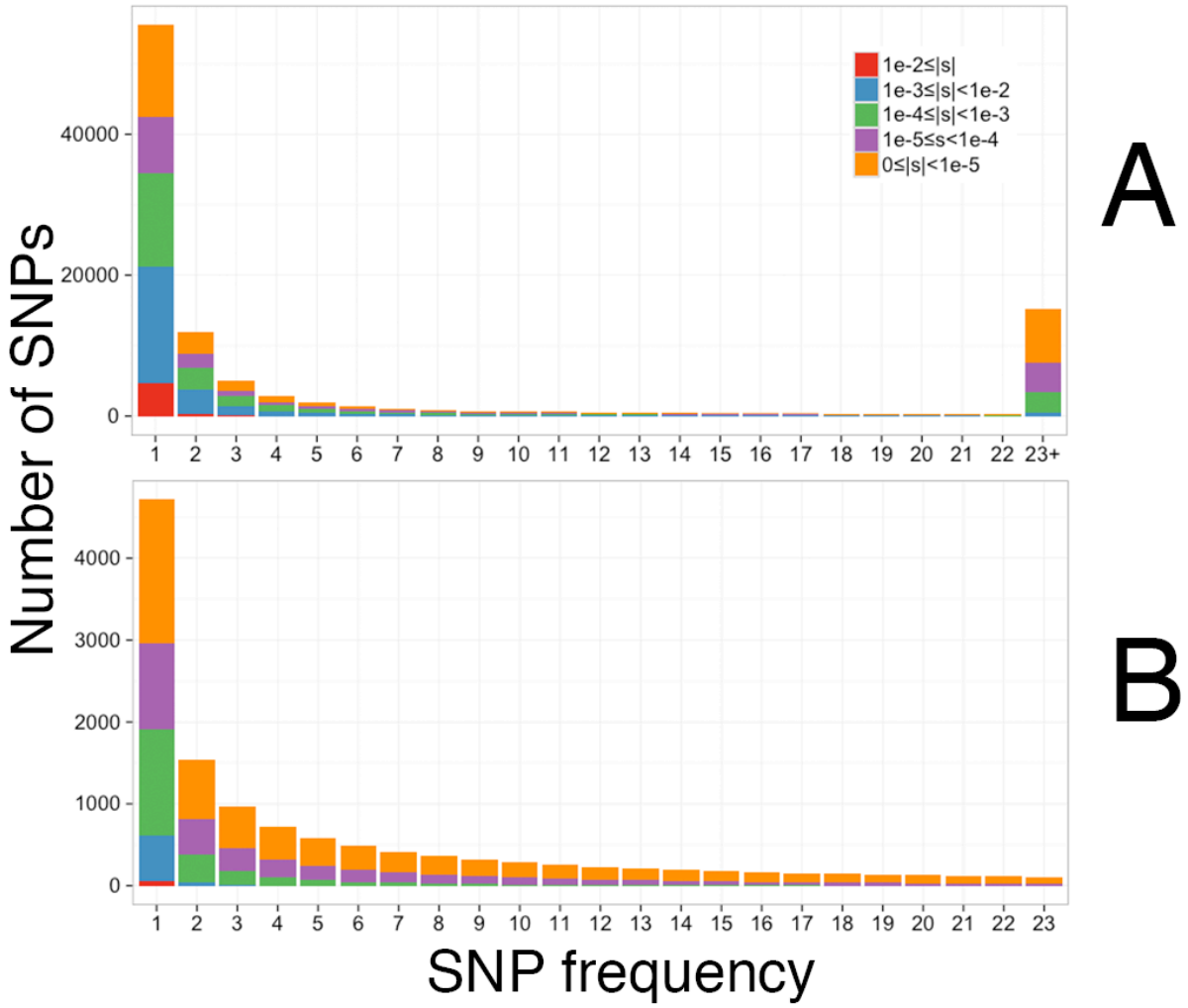

Figure S1. The expected contribution of mutations with various selective effects to the nonsynonymous SFS in (A) a sample of 2596 chromosomes and (B) a sample 24 chromosomes under the demographic model and DFE inferred from the full LuCamp dataset. Note that fewer than 1000 moderately to strongly deleterious mutations (blue and red) are segregating in the small sample, while more than 20,000 of them are predicted to be segregating in the large sample.

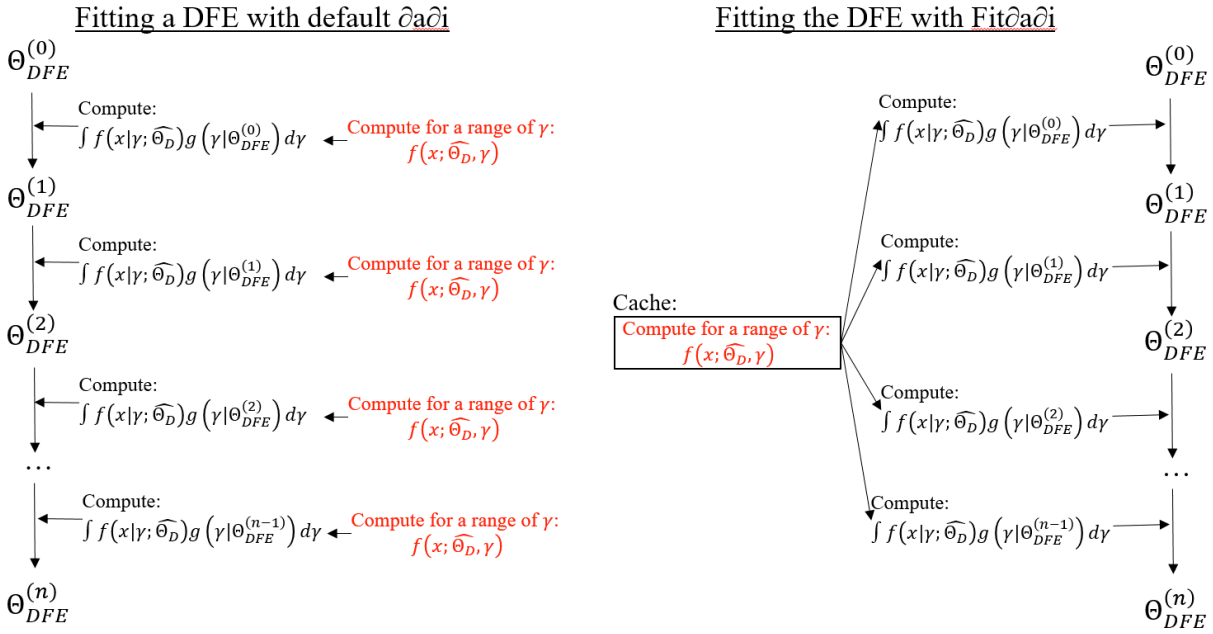

Figure S2. A flow chart depicting the efficiency of Fit∂a∂i compared to the default implementation of ∂a∂i. Fitting a DFE with the default implementation of ∂a∂i is slow because the same frequency spectra must be calculated for each step in the optimization of the DFE. We compute the spectra once and call the saved frequency spectra for each optimization step.

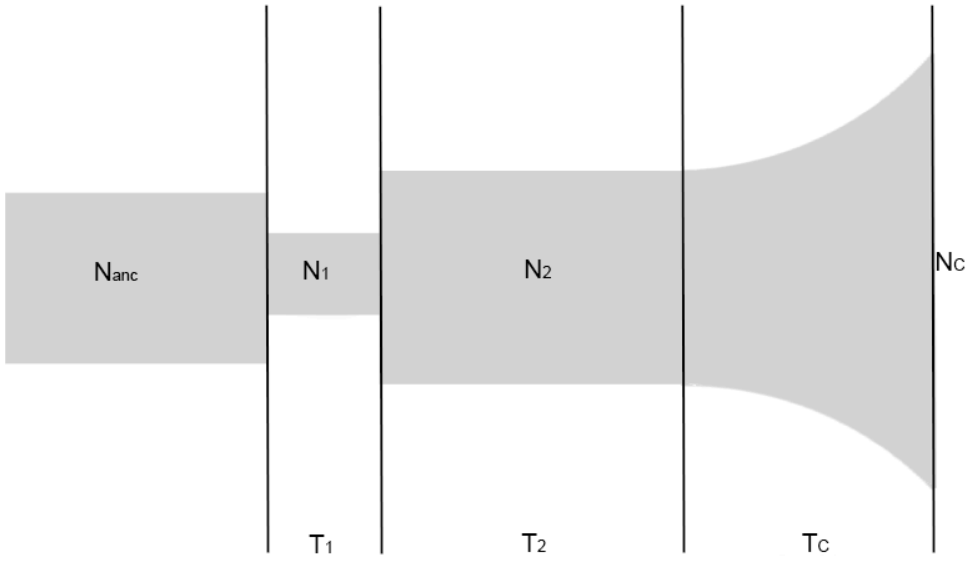

Figure S3. A pictorial representation of the demographic model fit to the SFS of synonymous sites of our datasets. The times denote the length of time of each epoch. See Table S1 for the parameter values we inferred from the data.

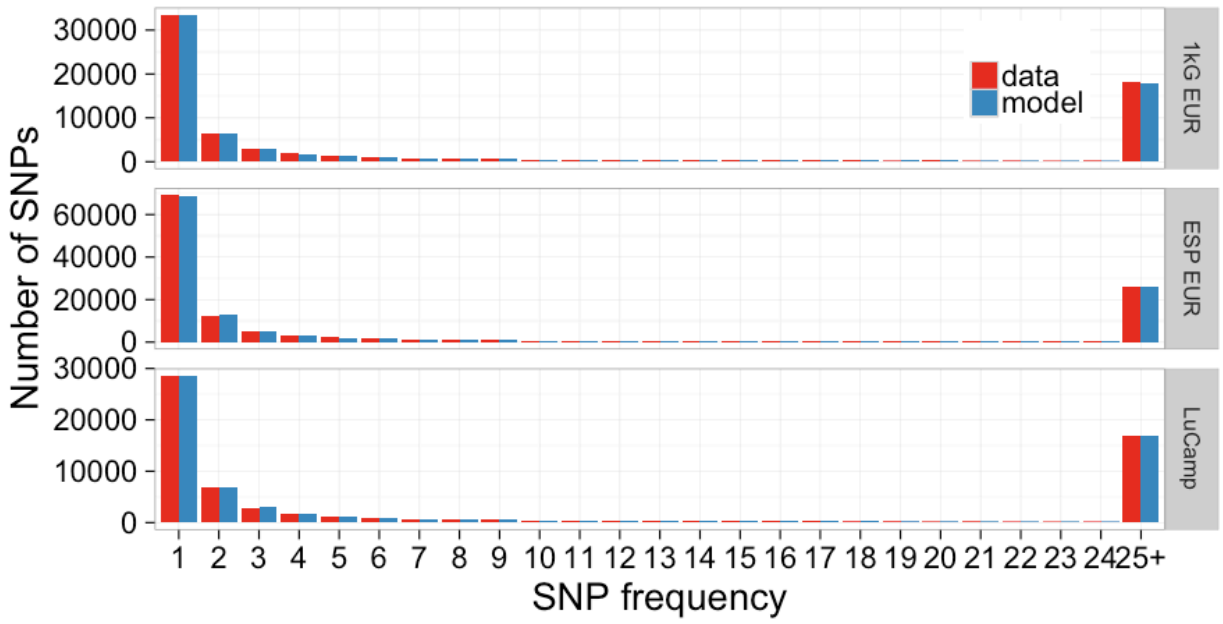

Figure S4. Comparison of the observed synonymous SFS to the SFS from the best fitting demographic model. Each SFS has been folded, then truncated to 25 entries. All the alleles of frequency 25 or greater in the folded frequency spectrum are summed into the last entry. Because these demographic models were fit using the multinomial likelihood, the model SFS has been scaled by θ_S.

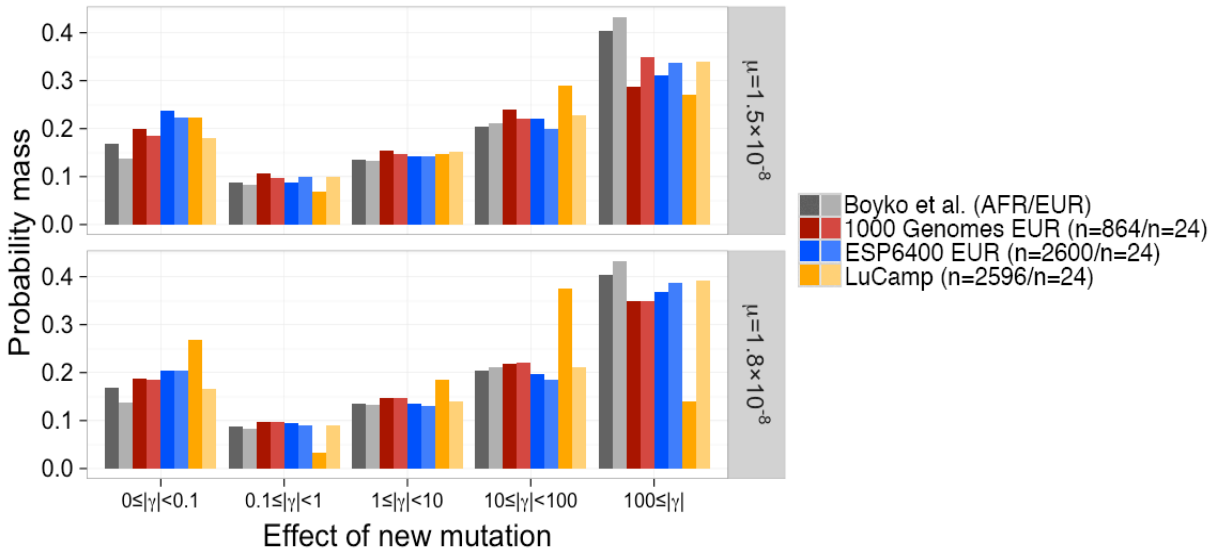

Figure S5. The distribution of population-scaled selection coefficients (γ=2*Ns*) of new mutations for our best-fit DFEs compared to Boyko et al. (2008). This figure is the same as **Figure 4**, except estimates are scaled by twice the ancestral population size. Results are presented for the best fit DFE to each full dataset and the best fit DFE when the data were projected down to *n*=24 chromosomes. Our DFEs predict more nearly neutral mutations ($0 \leq |2Ns| < 0.1$) and fewer strongly deleterious mutations ($100 \leq |2Ns|$) than Boyko et al. (2008), regardless of the mutation rate or the manner in which selection coefficients are parameterized (**Figure 4**). The top panel denotes our favored mutation rate while the bottom panel denotes the mutation rate used by Boyko et al. (2008).

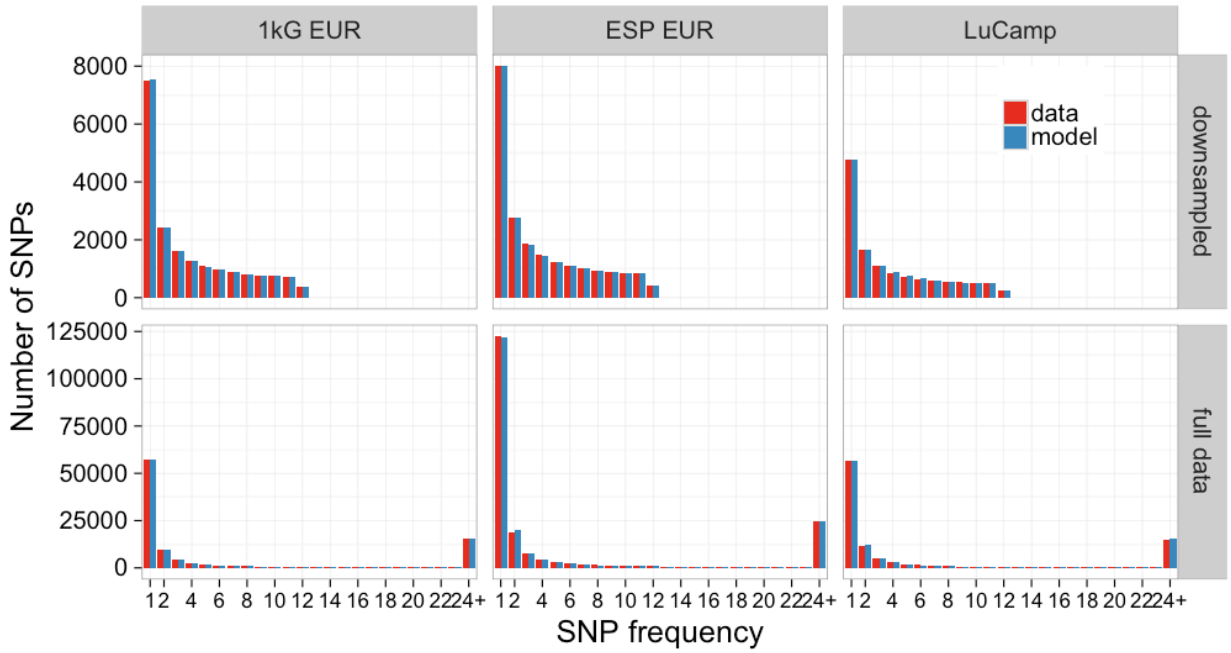

Figure S6. Comparison of the observed nonsynonymous SFS to the SFS from the best fitting demographic and selective models. For the full data, the discrete, neutral+gamma, and neutral+gamma are the best fitting DFEs to the 1000 Genomes, ESP, and LuCamp datasets, respectively. To the downsampled datasets, the neutral+gamma, gamma, and gamma DFEs are the best fitting DFEs to the 1000 Genomes, ESP, and LuCamp datasets, respectively. Each SFS has been folded, then truncated to 25 entries. All the alleles of frequency 25 or greater in the folded frequency spectrum are summed into the last entry.

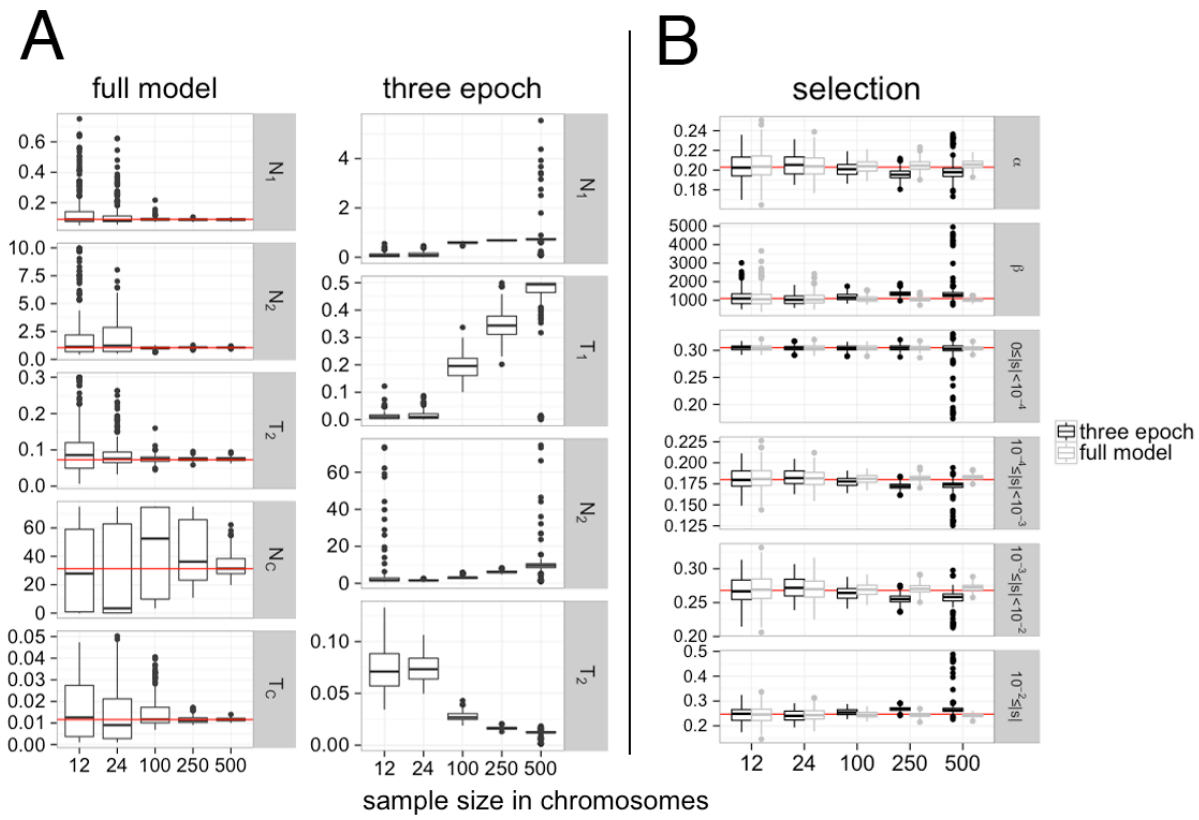

Figure S7. Mis-specification of the demographic model has little effect on selection inference from small samples. Two hundred datasets were simulated under the demographic model fit to the LuCamp synonymous SFS (Table S1, Figure S3) for a range of sample sizes. True values are depicted with a red line. (A) Parameter estimates of the correct demographic model (full model) and a three epoch model fit to the simulated data. (B) Parameter estimates of the gamma DFE as well as the proportions of each range of selective effect for a range of sample sizes assuming L_{NS}/L_S=2.5 and μ=1.8×10^{-8} (α=0.203, β=1082.1). The shape and scale parameters are directly inferred, and the proportions are computed from the gamma distribution. For the full model, sample size does not bias inference of selection. The accuracy of the selection inference conditioned on the three epoch demography declines with increasing sample size because the simple demographic model cannot account for the excess of rare variation in the data. The boxes cover the first and third quartiles, and the band represents the median. The whiskers cover the highest and lowest datum within 1.5 times the interquartile range from the first and third quartiles. Lastly, any data outside that region are plotted as outlier points.

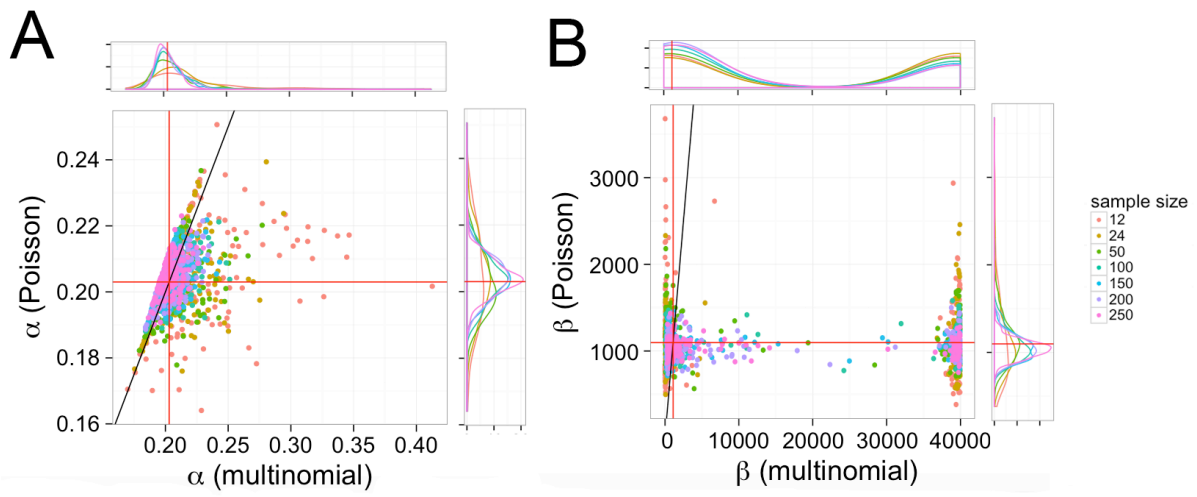

Figure S8. Fitting only the curvature of the SFS is insufficient for estimating the scale parameter of the gamma DFE, especially at small sample sizes. Depicted are the relative performances of the multinomial and Poisson likelihoods when fitting a gamma DFE to 200 simulated datasets of varying sample sizes. The multinomial likelihood only fits the curvature of the SFS while the Poisson likelihood accounts for the total number of SNPs in the data. Simulations were performed using the demographic model and gamma DFE inferred from the LuCamp dataset, assuming L_{NS}/L_S=2.5 and μ=1.8×10^{-8} (α=0.203, β=1082.1). True parameter values are depicted with a red line, and the slope of the black line is 1. The density plots describe the marginal densities of the MLEs of the simulation replicates. (A) Shape parameter (α) of the gamma distribution. (B) Scale parameter (β) of gamma distribution. Note the bimodal distribution of the MLEs of the scale parameter at the optimization boundaries when the multinomial likelihood is used.

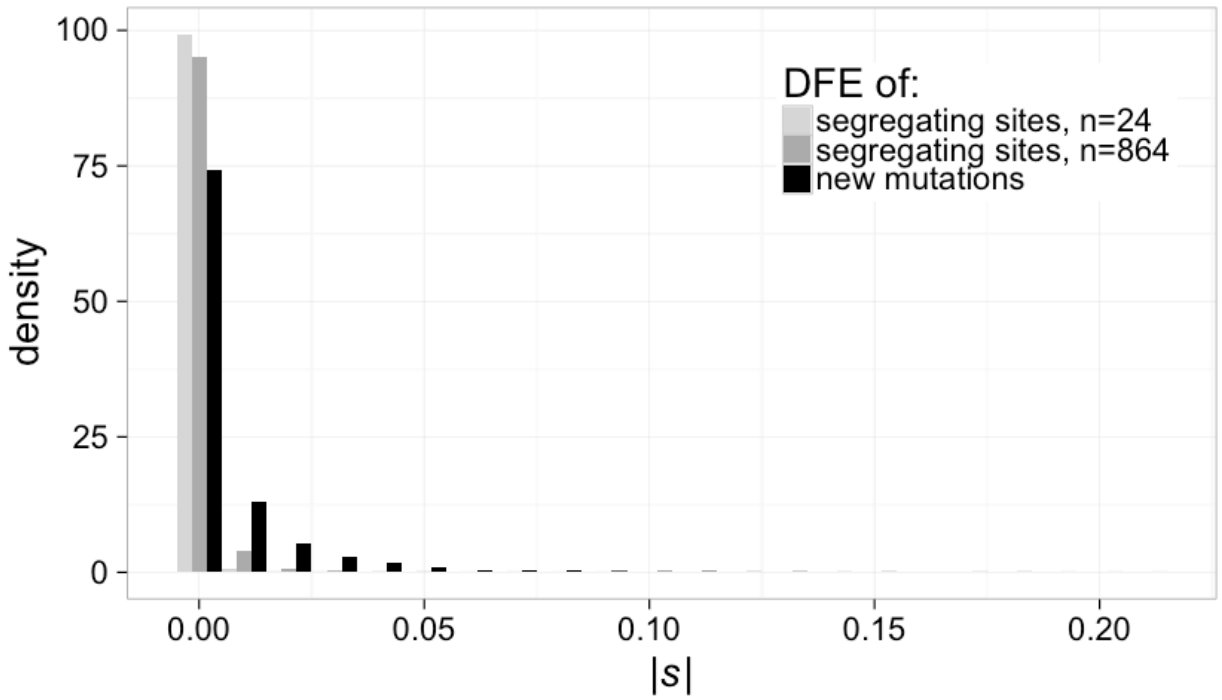

Figure S9. The DFE of segregating sites versus the DFE of new mutations. DFEs from three different simulations are shown as discretized histograms. In the first two, the selection coefficients of only the segregating variants in samples of size n=24 and n=864 chromosomes were tallied. In the third, the selection coefficients of new mutations (which could be segregating, fixed, or lost) were tallied. The DFEs of only segregating sites show a distinct skew towards neutrality, reflecting that strongly deleterious variants are less likely to be found segregating in smaller samples. Additionally, our simulations show a clear distinction between the DFE of new mutations and that of segregating variants.

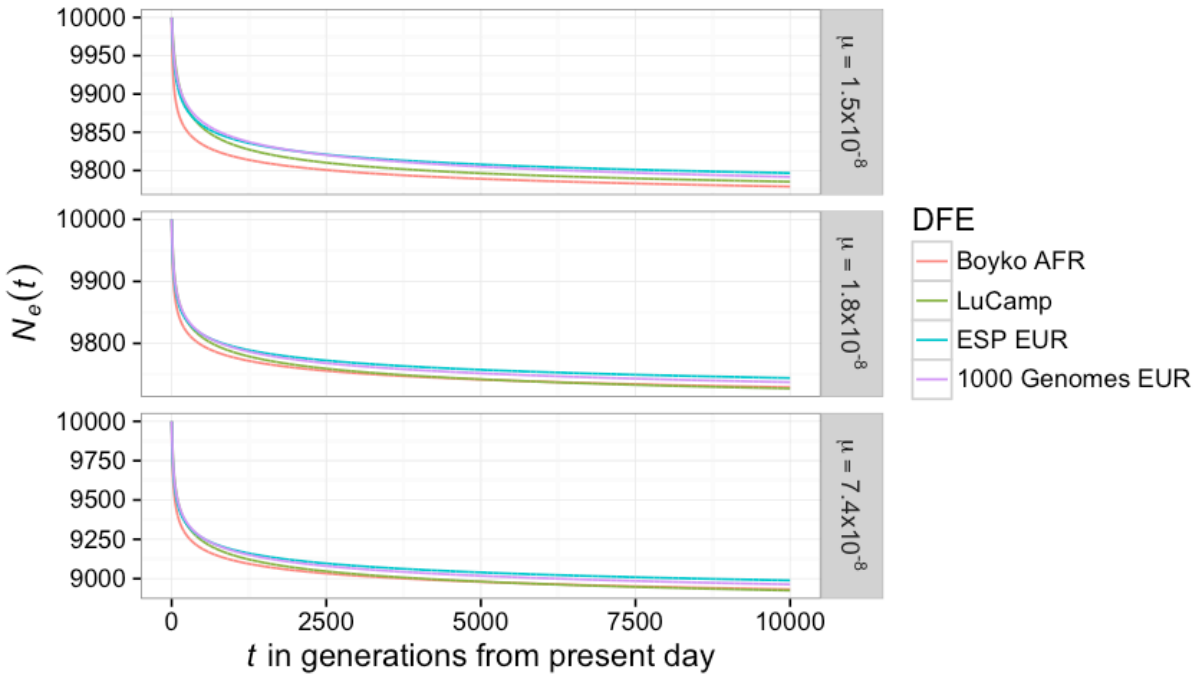

Figure S10. The reduction in genetic diversity due to background selection as a function of time. The reduction in N_e was computed using the deterministic approximation in Nicolaisen and Desai (2013), assuming: a chromosome of length 100Mb with 1.5% coding sequence; a recombination rate of 1×10^{-8} per bp; mutation rates similar to those used in our study as well as the deleterious mutation rate of McVicker et al. (2009) of $7.4\text{x}10^{-8}$ per bp; and the DFEs inferred in our study as well as that of Boyko et al. (2008). Except the DFE from Boyko et al. (which assumed a mutation rate of 1.8×10^{-8}), the DFEs used to compute the reduction in diversity for the various mutation rates are the best-fitting gamma or neutral+gamma DFEs inferred using their respective mutation rates. The DFEs used for the mutation rate of 7.4×10^{-8} are the best-fitting DFEs inferred assuming the mutation rate was 1.8×10^{-8}. These calculations assume a constant population size of 10,000 diploids, and values of N_e less than 10,000 are due to background selection reducing linked neutral diversity.