Supplemental Material

Table S1. Estimates of *Nw*: the weighted change in N_e relative to 100 (and 99% CIs) of the one-step change model for S-to-W and W-to-S mutations categories in different recombination bins for datasets that include or exclude CpG-prone sites.

Recombination	Including CpG		Excluding CpG	
	Low	High	Low	High
S-to-W	330 (323 - 337)	435 (422 - 448)	221 (213 - 329)	234 (226 - 242)
W-to-S	100 (90 - 110)	14 (12 - 16)	99 (89 - 109)	18 (14 -21)
GC-conservative	135 (127 - 142)	100 (98 - 102)	123 (110 -135)	103 (96 - 108)
Total	193 (191-196)	186 (182 - 191)	221 (213 - 329)	234 (226 - 242)

Table S2. Pairwise Pearson's correlation coefficient and *p-v*alue between expression level and ω for different tissues.

Tissue	rho	p-value
Brain	-0.173	$< 2.2 \times 10^{-16}$***
Skin	-0.145	$< 2.2 \times 10^{-16}$***
Kidney	-0.126	$< 2.2 \times 10^{-16}$***
Muscle	-0.105	$< 4.5 \times 10^{-13}$***
Liver	-0.096	$< 5.5 \times 10^{-11}$***
Ovary	-0.139	$< 2.2 \times 10^{-16}$***
Testis	-0.009	0.471

*** denotes statistical significance at p < 0.001% level.

Table S3. Number of genes and bins used in the analysis of every explanatory variable

Variable	Number of bins	Number of genes per bin
Main analysis	1	7920
Recombination	3	2640
Expression level in brain	3	1986
Number of PPI	3	2640
Sex bias expression	3	fb = 2760 un = 2902 mb = 1845
Positive selected genes	1	79

Table S4. Total number of polymorphic and divergent sites included in the main analysis for different mutation categories.

		S-to-W	W-to-S	GC-conservative	Total
Polymorphic	4-fds	1712	1971	821	4504
	0-fds	1967	2295	762	5024
	Total	3679	4266	1583	9528
Divergence	4-fds	19542	47638	14408	81588
	0-fds	24007	29665	28189	81861
	Total	43549	77303	42597	163449

Table S5. R^2 between the observed and expected SFS for each mutation category.

Category	Bin	S-to-W	W-to-S	GC-conservative	Total
Average / Total	all	0.989	0.992	0.985	0.989
Recombination	Low	0.971	0.984	0.962	0.980
	Mid	0.987	0.966	0.945	0.987
	High	0.987	0.931	0.976	0.985
Expression level	Low	0.948	0.930	0.900	0.951
	Mid	0.991	0.967	0.974	0.989
	High	0.975	0.945	0.970	0.983
PPI	Low	0.983	0.930	0.977	0.983
	Mid	0.975	0.981	0.982	0.989
	High	0.991	0.969	0.907	0.981
Sex bias	Male-biased	0.995	0.969	0.925	0.990
	Unbiased	0.988	0.986	0.921	0.988
	Female-biased	0.948	0.954	0.970	0.972
Positive selection	Positively selected	0.718	0.890	0.691	0.920

All estimates are statistical significance at p < 0.001% significance level.
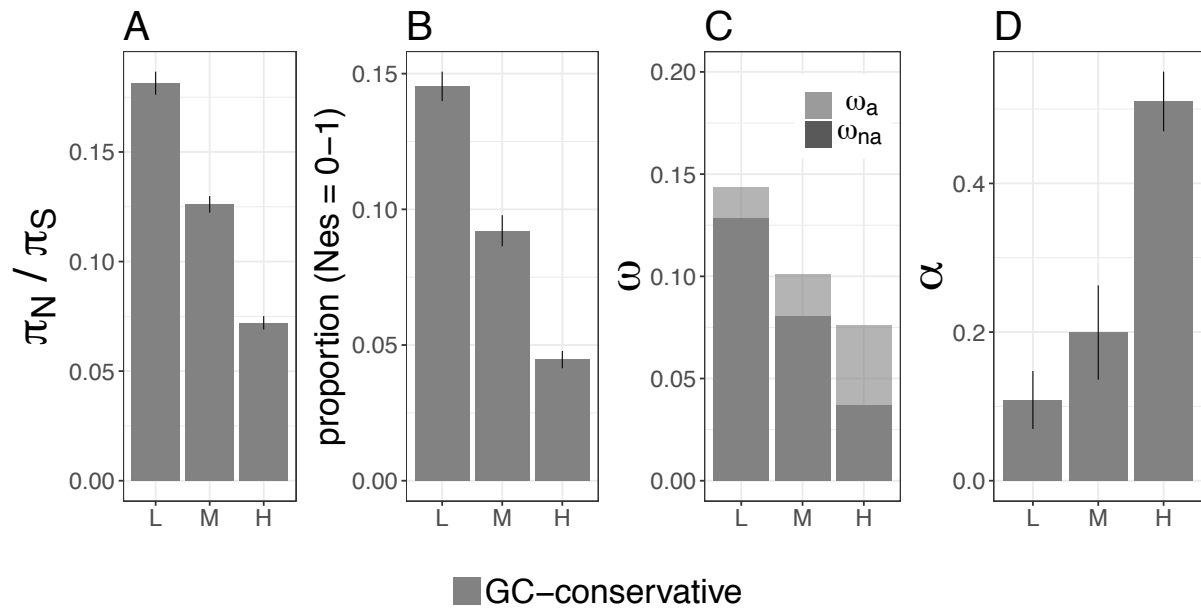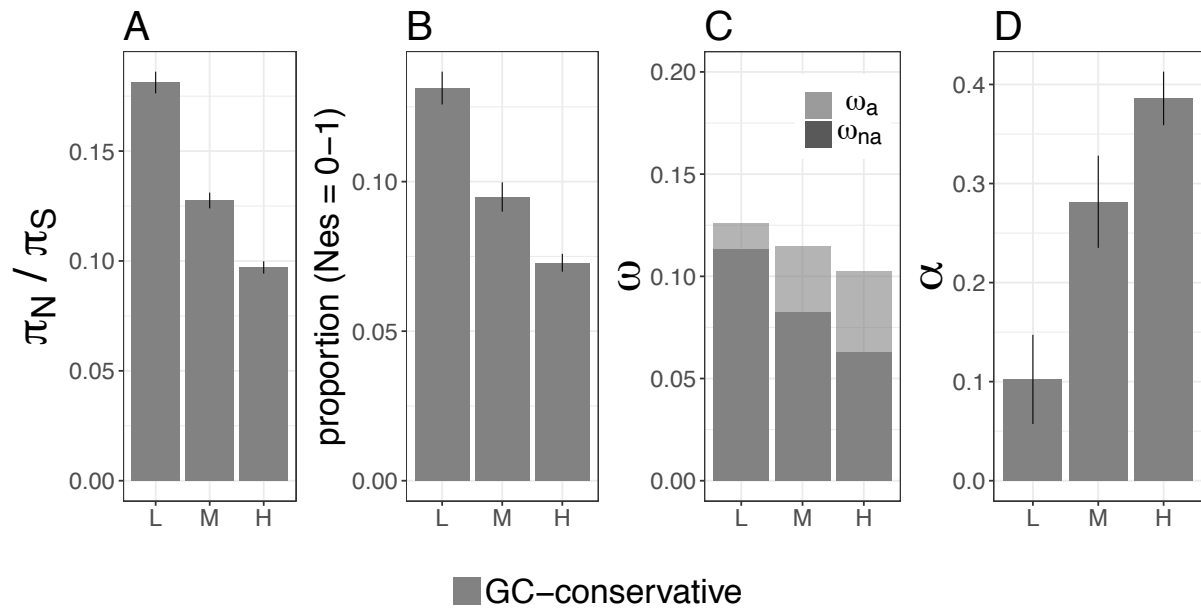
Figure S1. Estimates of five different test statistics and 99% confidence intervals for GC-conservative changes in genes with low (L), mid (M), and high (H) expression level in brain. A) π_N/π_S, B) proportion ($N_e s = 0\text{-}1$), i.e. the proportion of non-synonymous mutations for which $N_e s < 1$, C) ω, with the proportion of ω represented by ω_{na} and ω_a shown in bold and light colour, respectively, and D) α.
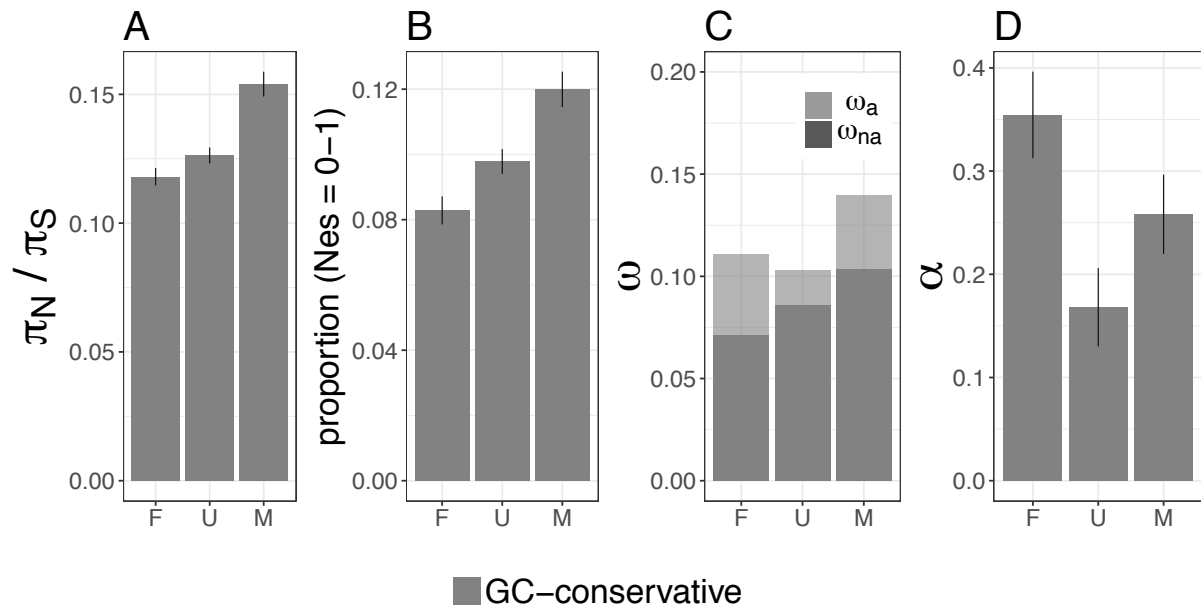
Figure S2. Estimates of five different test statistics and 99% confidence intervals for GC-conservative changes in genes with low (L), mid (M), and high (H) number of PPI. A) π_N/π_S, B) proportion ($N_e s$ = 0-1), i.e. the proportion of nonsynonymous mutations for which $N_e s < 1$, C) ω, with the proportion of ω represented by ω_{na} and ω_a shown in bold and light colour, respectively, and D) α.

Figure S3. Estimates of five different test statistics and 99% confidence intervals for GC-conservative changes in genes with female-biased (F), unbiased (U), and male-biased (M) expression. A) π_N/π_S, B) proportion ($N_e s = 0\text{-}1$), i.e. the proportion of non-synonymous mutations for which $N_e s < 1$, C) ω, with the proportion of ω represented by ω_{na} and ω_a shown in bold and light colour, respectively, and D) α.
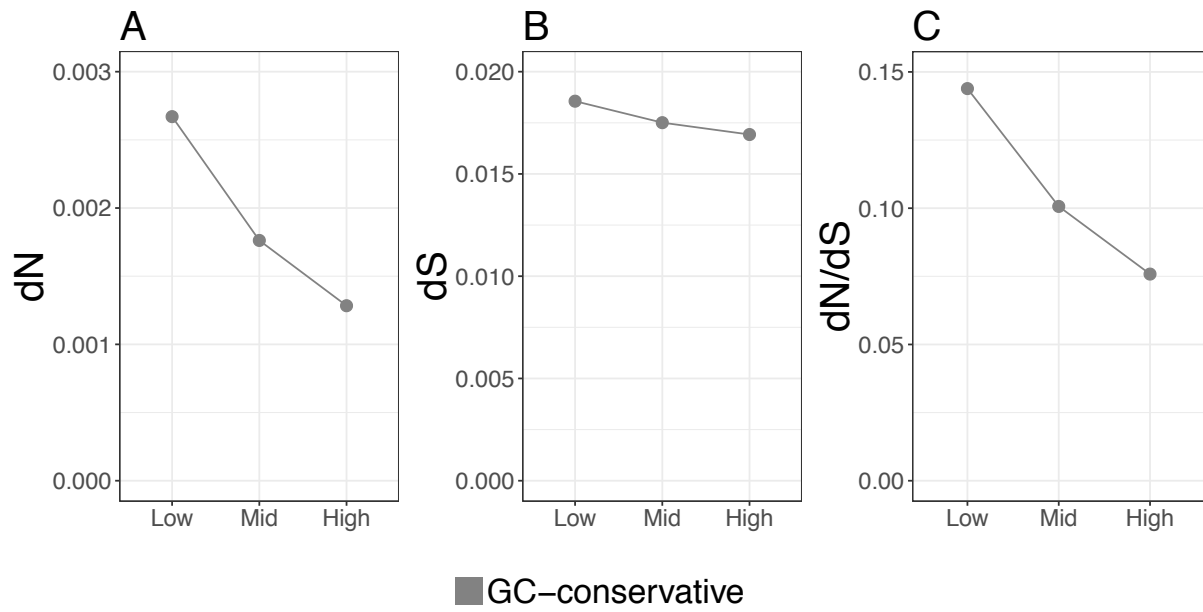
Figure S4. Estimates of divergence rates and rate ratios for GC-conservative changes in genes with low (L), mid (M), and high (H) expression level in brain. A) d_N, B) d_S, and C) d_N/d_S (ω).
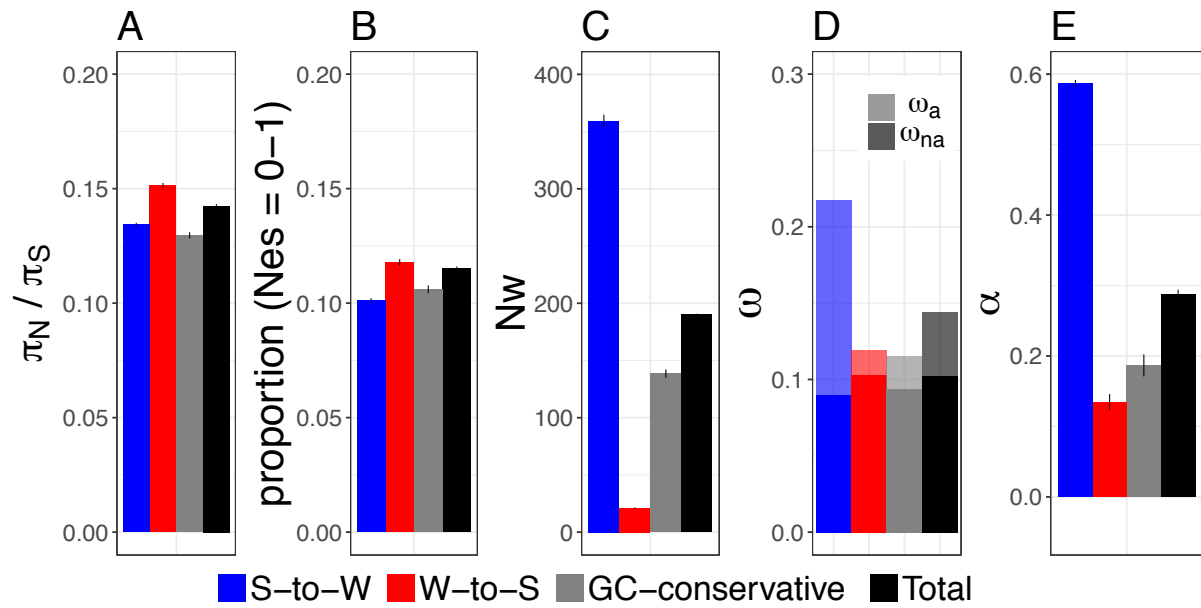
Figure S5. Estimates of six different test statistics and 99% confidence intervals for different mutation categories for a dataset including CpG-prone sites: S-to-W (blue), W-to-S (red), GC-conservative (grey) and all sites ('Total'; black). A) π_N/π_S, B) proportion ($N_es = 0$-1), i.e. the proportion of non-synonymous mutations for which $N_es<1$, C) N_w: the weighted change in N_e relative to 100, D) ω, with the proportion of ω represented by ω_{na} and ω_a shown in bold and light colour, respectively, and E) α.
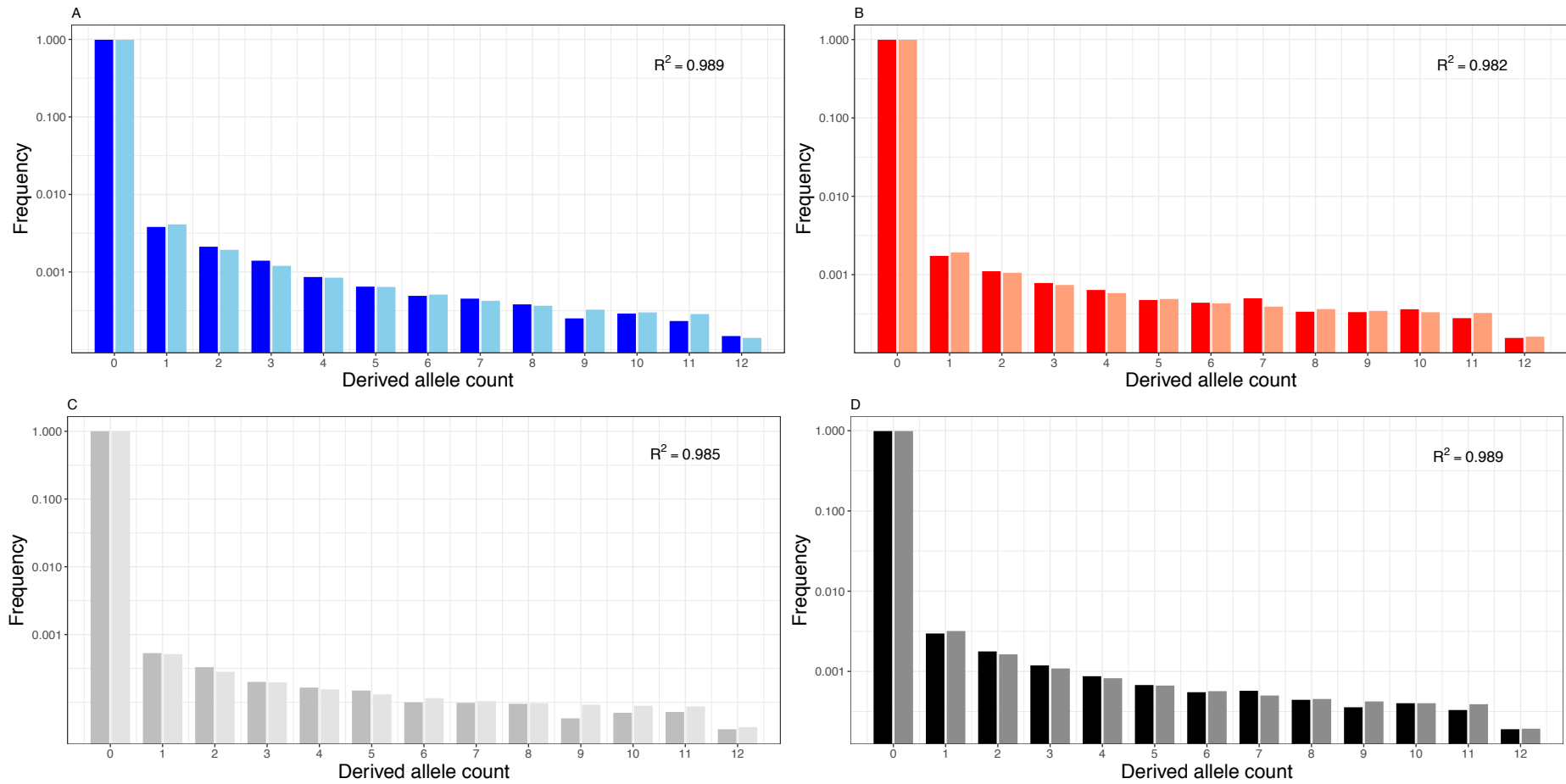
Figure S6. Observed (dark colour) vs expected (light colour) SFS of synonymous sites of the bets-fit model for each mutation category: A) S-to-W (blue), B) W-to-S (red), C) GC-conservative (grey), D) all mutations together (black).