

**Supplemental Fig S1** Example of contingency table used to quantify intolerance of mutations of a reference allele at a near-splice site position (D+6 T allele)

	Num. of mutations disrupting the reference allele	Num. of reference alleles - Num. of mutations
pLI < 0.9	3978	44837.3
pLI > 0.9	1183	19442.8

Chi-squared statistics and odds ratios are used to test for association between pLI status and mutation rates, or in other words whether loss-of-function intolerant genes (genes with pLI > 0.9) are significantly devoid of mutations compared to other genes. In this example (D+6 T allele), chi-squared statistic = 122.7 and odds ratio = 1.46.