

**Table S8.** constraint enrichments and depletion across gene set

<b>Gene sets</b>	<b>Constrained (%)<sup>&amp;</sup></b>	<b>Unconstrained (%)</b>	<b>P<sup>^</sup></b>	<b>OR (95% CI)<sup>^</sup></b>
ExAC constrained	67.08	13.17	1.24E-121	184.81 (99.50, 366.52)
ClinGen haploinsufficient	60	10	6.45E-05	35.26 (4.22, 1621.15)
FMRP interactors	44.62	21.54	8.82E-16	14.95 (7.34, 31.81)
Dominant	26.03	35.62	5.13E-06	4.69 (2.36, 9.17)
Mice essential	19.72	33.33	1.78E-10	4.56 (2.84, 7.31)
Cell essential	18.18	36.36	2.25E-01	2.84 (0.25, 20.09)
GWAS hits	11.28	46.64	1.60E-02	1.64 (1.08, 2.47)
Recessive	3.23	72.58	1.04E-03	0.23 (0.06, 0.61)
Olfactory receptors	0	72.73	6.14E-01	0.00 (0.00, 3.31)

<sup>&</sup> sorted and listed in an descending order of proportions of constrained genes.

<sup>^</sup> *P* values and odds ratios with the 95% confidence intervals are calculated via two-sided Fisher's exact tests to assess the enrichment or depletion of constrained genes in the gene sets of interests.