



**Figure 1 | Genome-wide screen for L1 activators and suppressors in K562 cells.** **a**, Schematic for the screen. **b**, Schematic for the L1-G418<sup>R</sup> retrotransposition. **c**, CasTLE analysis of (n = 2) independent K562 genome-wide screens. Genes at 10% FDR cutoff colored in blue, CasTLE likelihood ratio test<sup>11</sup>. **d**, The maximum effect size (center value) estimated by CasTLE from two independent K562 secondary screens with 10 independent sgRNAs per gene. Bars, 95% credible interval (CI). L1 activators, red; L1 suppressors, blue; insignificant genes whose CI

include 0, gray. **e**, L1-GFP retrotransposition in control (infected with negative control sgRNAs, hereinafter referred to as 'Ctrl') and mutant K562 cells as indicated. GFP(+) cell fractions normalized to Ctrl. Center value as median. n = 3 biological replicates per gene. **f**, RT-qPCR measuring endogenous L1s expression in mutant K562 cells, normalized to Ctrl. Center value as median. n = 3 technical replicates per gene. \*\*P < 0.01; \*\*\*P < 0.001; two-sided Welch t-test.