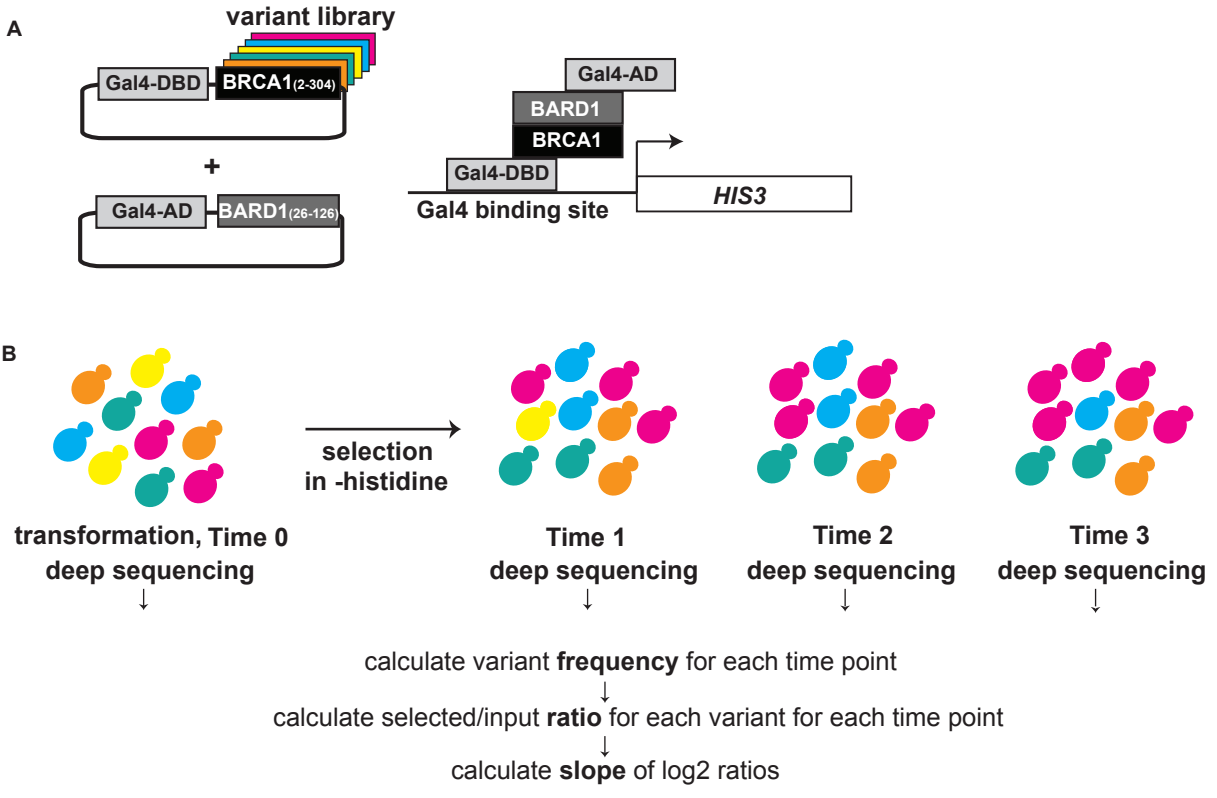

Figure S5 Diagram of the yeast-two-hybrid selection scheme to measure BRCA1-BARD1 binding.
(A) The barcoded allelic series of BRCA1(2-304) was fused to the carboxy-terminus of the Gal4 DNA-binding domain, and the BARD1(26-126) domain was fused to the carboxy-terminus of the Gal4 activation domain. Yeast harboring BRCA1 variants that bind to BARD1 drive the expression of the HIS3 reporter gene and therefore grow in media lacking histidine. **(B)** The two-hybrid reporter strain transformed with the plasmids encoding the BRCA1 allelic series and BARD1 was selected in triplicate in two separate experiments in media lacking histidine and containing 10 mM 3-amino-1,2,4-triazole (3-AT), a competitive inhibitor of the His3 enzyme. At mid-log phase, aliquots of the cultures were sampled and then back-diluted into fresh selective media and grown to mid-log phase two additional times. The BRCA1 plasmids were extracted at each of three time points and their barcodes were PCR amplified and sequenced. The barcodes associated with BRCA1(2-304) plasmids prepped from the yeast after each of the three time points of selection and the input population were deeply sequenced. We fit a linear curve to the log ratio of the frequency of each variant in the selected populations divided by its frequency in the input population and calculated the slope of that line, normalized again to stop codons (set to 0) and wild-type (set to 1).