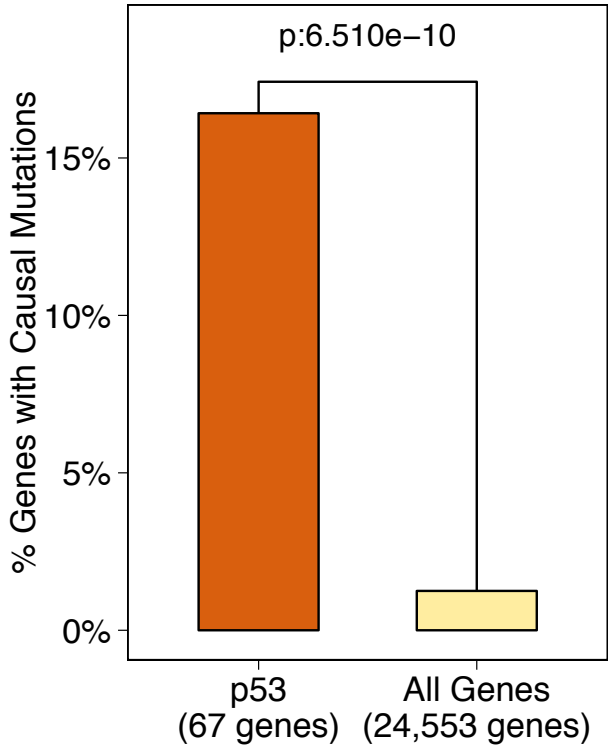
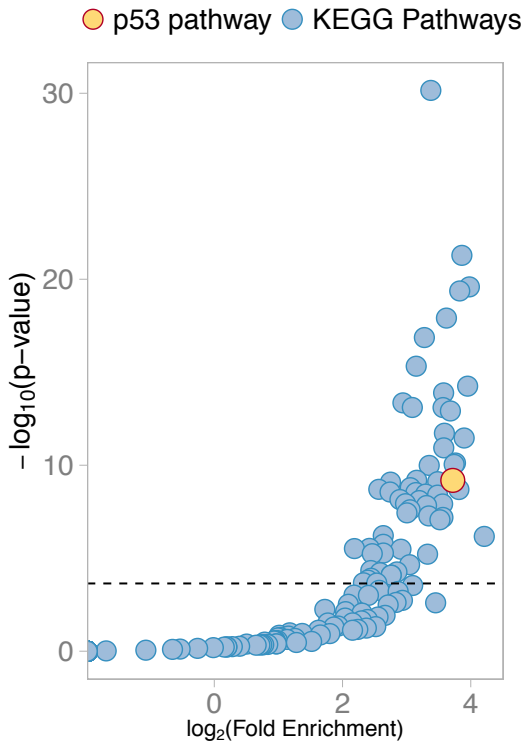
Supplementary Information S3. Somatic, causal mutations occur in a high proportion of p53 pathway genes. In order to define driver genes for this validation analysis, we used a list defined by Vogelstein et al.[1]. Specifically, using the supplementary table file (http://www.sciencemag.org/content/suppl/2013/03/27/339.6127.1546.DC1/1235122TablesS1-4.xlsx), we identified all somatically mutated driver genes by merging the genes found on the following sheets: Driver genes affected by subtle mutations" (Table S2A), "Driver genes affected by amplification or homozygous deletion" (Table S2B), "Rearrangements in carcinomas" (Table S3A), "Rearrangements in Mesenchymal Tumors" (Table S3B) and "Rearrangements in liquid tumors" (Table S3C). We used this list of 306 RefSeq genes to perform our standard enrichment analysis based on the hyper-geometric test, and correcting for multiple hypothesis testing using permutations (See Supplementary Information S1). **(A)** A bar graph of the percent of genes in the p53 pathway with known causal mutations compared to all annotated autosomal genes of the genome. 11 out of 67 genes in the p53 pathway (16.42%) are known to be causally mutated, which represents a significant 13.17-fold enrichment over the rest of the genes in the genome (p-value: 6.51E-10, adjusted p-value: 1.43E-7). **(B)** A scatter plot showing the fold enrichment of causally mutated genes on the x-axis (log-scale), and the adjusted p-value on the y-axis (-log10 scale). The horizontal line represents the 5% *Family Wise Error Rate* threshold (Bonferroni adjusted-p-value: 0.05). The enrichment of causal mutations in p53 pathway genes (in yellow) is compared to the other 220 annotated KEGG pathways (in blue). Overall, 26.82% pathways demonstrated significant enrichment of causally mutated genes.





1 Vogelstein, B. *et al.* Cancer genome landscapes. *Science* **339**, 1546-1558, doi:10.1126/science.1235122 (2013).