Submitter name: Wei Zhang
Submitted email:

A global transcriptional network connecting noncoding mutations to changes in tumor gene expression

Wei Zhang[1], Ana Bojorquez-Gomez[1], Daniel Ortiz Velez[2], Guorong Xu[3], Kyle Sanchez[1], John Paul Shen[1], Kevin Chen[2], Katherine Licon[1], Collin Melton[4], Katrina Olson[1,5], Michael Ku Yu[1], Justin K. Huang[1], Hannah Carter[1], Emma Farley[1,5], Michael Snyder[4], Stephanie Fraley[2], Jason F. Kreisberg[1], Trey Ideker[1,2]

[1]Department of Medicine, University of California, San Diego; [2]Department of Bioengineering, University of California San Diego; [3]Center for Computational Biology and Bioinformatics, University of California, San Diego; [4]Department of Genetics, Stanford University School of Medicine; [5]Division of Biological Sciences, University of California San Diego

Although cancer genomes are replete with noncoding mutations, the effects of these mutations remain poorly characterized. Here we perform an integrative analysis of 930 tumor whole genomes and matched transcriptomes, identifying a network of 193 noncoding loci in which mutations disrupt target gene expression. These 'somatic eQTLs' (expression quantitative trait loci) are frequently mutated in specific cancer tissues, and the majority can be validated in an independent cohort of 3,382 tumors. Among these, we find that the effects of noncoding mutations on *DAAM1*, *MTG2* and *HYI* transcription are recapitulated in multiple cancer cell lines and that increasing *DAAM1*expression leads to invasive cell migration. Collectively, the noncoding loci converge on a set of core pathways, permitting a classification of tumors into pathway-based subtypes. The somatic eQTL network is disrupted in 88% of tumors, suggesting widespread impact of noncoding mutations in cancer.