Strong association between genomic 3D structure and CRISPR cleavage efficiency

Shaked Bergman and Tamir Tuller

CRISPR is a gene editing technology which enables precise in-vivo genome editing; but its potential is hampered by its relatively low specificity and sensitivity. Improving CRISPR's on-target and off-target effects requires a better understanding of its mechanism and determinants. Here we demonstrate, for the first time, the chromosomal 3D spatial structure's association with CRISPR's cleavage efficiency, and its predictive capabilities. We used high-resolution Hi-C data to estimate the 3D distance between different regions in the human genome and utilized these spatial properties to generate 3D-based features, characterizing each region's density. We evaluated these features based on empirical, in-vivo CRISPR efficiency data and compared them to 425 features used in state-of-the-art models. The 3D features ranked in the top 4% of the features, and significantly improved the predictive power of LASSO and xgboost models trained with these features. The features indicated that sites with lower spatial density demonstrated higher efficiency. Understanding how CRISPR is affected by the 3D DNA structure provides insight into CRISPR's mechanism in general and improves our ability to correctly predict CRISPR's cleavage as well as design sgRNAs for therapeutic and scientific use.