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ARTICLE

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A rare variant of African ancestry activates 8q24 lncRNA hub by modulating cancer associated enhancer

Kaivalya Walavalkar[1], Bharath Saravanan[1,2], Anurag Kumar Singh[1], Ranveer Singh Jayani[3], Ashwin Nair[1,2], Umer Farooq[1,4], Zubairul Islam[1,2], Deepanshu Soota[1], Rajat Mann[1], Padubidri V. Shivaprasad[1], Matthew L. Freedman[5,6,7], Radhakrishnan Sabarinathan[1], Christopher A. Haiman[8] & Dimple Notani[1✉]

Genetic variation at the 8q24 locus is linked with the greater susceptibility to prostate cancer in men of African ancestry. One such African ancestry specific rare variant, rs72725854 (A>G/T) (~6% allele frequency) has been associated with a ~2-fold increase in prostate cancer risk. However, the functional relevance of this variant is unknown. Here we show that the variant rs72725854 is present in a prostate cancer-specific enhancer at 8q24 locus. Chromatin-conformation capture and dCas9 mediated enhancer blocking establish a direct regulatory link between this enhancer and lncRNAs PCAT1, PRNCR1 and PVT1. The risk allele ('T') is associated with higher expression of PCAT1, PVT1 and c-myc in prostate tumors. Further, enhancer with the risk allele gains response to androgen stimulation by recruiting the transcription factor SPDEF whereas, non-risk alleles remain non-responsive. Elevated expression of these lncRNAs and c-myc in risk allele carriers may explain their greater susceptibility to prostate cancer.

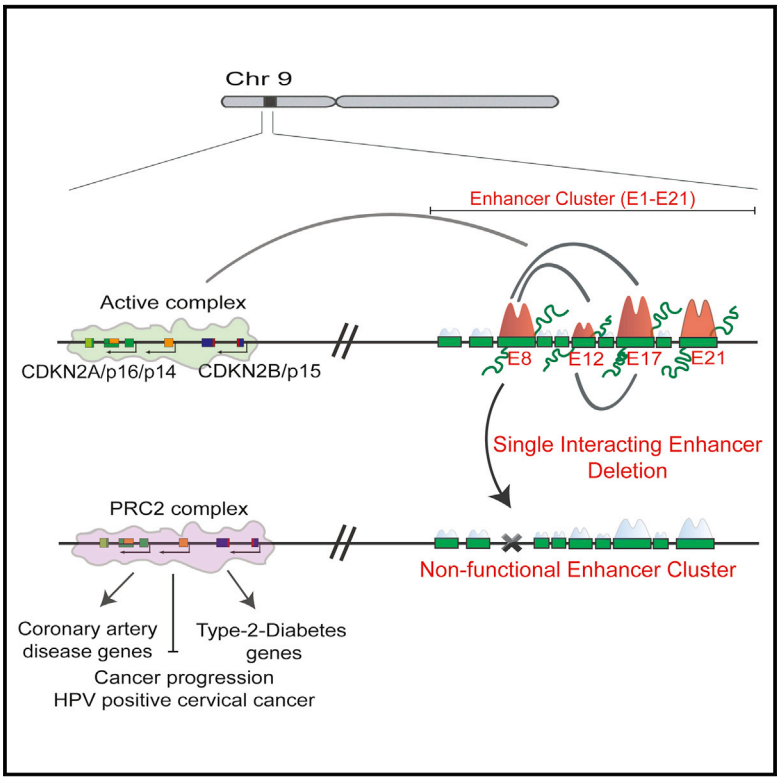
[1] Genetics and Development, National Centre for Biological Sciences, Tata Institute of Fundamental Research, Bangalore, Karnataka 560065, India. [2] Sastra Deemed University, Thanjavur, Tamil Nadu 613401, India. [3] Howard Hughes Medical Institute, Department of Medicine, University of California San Diego, 9500 Gilman Drive, La Jolla, CA 92037, USA. [4] Trans-Disciplinary University, IVRI road, Bangalore, Tamil Nadu 560064 Karnataka, India. [5] Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA 02215, USA. [6] The Eli and Edythe L. Broad Institute, Cambridge, MA 02142, USA. [7] Centre for Functional Cancer Epigenetics, Dana-Farber Cancer Institute, Boston, MA 02215, USA. [8] Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA 90007, USA. ✉email: dnotani@ncbs.res.in

Cell Reports

Article

An interdependent network of functional enhancers regulates transcription and EZH2 loading at the INK4a/ARF locus

Graphical abstract



Highlights

- Only a few enhancers from the dense multi-enhancer cluster regulate the *INK4a/ARF* locus
- Functional enhancers are not defined by high levels of H3K27ac or eRNAs
- Deletion of a single functional enhancer renders the entire SE non-functional
- Enhancer activation prevents EZH2 loading onto the *INK4a/ARF* promoters

Authors

Umer Farooq, Bharath Saravanan, Zubairul Islam, ..., Sweety Meel, Sudha Swaminathan, Dimple Notani

Correspondence

dnotani@ncbs.res.in

In brief

A dense enhancer cluster adjacent to the *INK4a/ARF* locus is the most reproducible GWAS hotspot. Using a series of enhancer deletions, Farooq et al. show that only a subset of enhancers loop with promoters. These interacting enhancers form a single functional unit that relies completely on each enhancer for the gene regulation.

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