From Genetics To Therapeutics: Uncovering And Manipulating The Circuitry Of Non-coding Disease Variants

Abstract: Perhaps the greatest surprise of human genome-wide association studies (GWAS) is that 90% of disease-associated regions do not affect proteins directly, but instead lie in non-coding regions with putative gene-regulatory roles. This has increased the urgency of understanding the non- coding genome, as a key component of understanding human disease. To address this challenge, we generated maps of genomic control elements across 127 primary human tissues and cell types, and tissue-specific regulatory networks linking these elements to their target genes and their regulators. We have used these maps and circuits to understand how human genetic variation contributes to disease and cancer, providing an unbiased view of disease genetics and sometimes re-shaping our understanding of common disorders. For example, we find evidence that genetic variants contributing to Alzheimer's disease act primarily through immune processes, rather than neuronal processes. We also find that the strongest genetic association with obesity acts via a master switch controlling energy storage vs. energy dissipation in our adipocytes, rather than through the control of appetite in the brain. We also combine genetic information with regulatory annotations and epigenomic variation across patients and healthy controls to discover new disease genes and regions with roles in Alzheimer's disease, heart disease, prostate cancer, and to understand their pleiotropic effects by integration with electronic health records. Lastly, we develop systematic technologies for systematically manipulating these circuits by high-throughput reporter assays, genome editing, and gene targeting in human cells and in mice, demonstrating tissue-autonomous therapeutic avenues in Alzheimer's disease, obesity, and cancer. These results provide a roadmap for translating genetic findings into mechanistic insights and ultimately therapeutic treatments for complex disease and cancer.

Bio: Manolis Kellis is a Professor of Computer Science at MIT, an Institute Member of the Broad Institute of MIT and Harvard, a member of the Computer Science and Artificial Intelligence Lab at MIT, and head of the MIT Computational Biology Group (compbio.mit.edu). His research spans an unusually broad spectrum of areas, including disease genetics, epigenomics, gene circuitry, non-coding RNAs, comparative genomics, and phylogenetics. He has helped direct several large-scale genomics projects, including the Roadmap Epigenomics project, the ENCODE project, the Roadmap Epigenomics Project, the Genotype Tissue-Expression (GTEx) project, and comparative genomics projects in mammals, flies, and yeast. He received the US Presidential Early Career Award in Science and Engineering (PECASE) by US President Barack Obama, the NSF CAREER award, the Alfred P. Sloan Fellowship, the Technology Review TR35 recognition, the AIT Niki Award, and the Sprowls award for the best Ph.D. thesis in computer science at MIT. He has authored more than 150 journal publications, which have been cited more than 47,000 times. He lived in Greece and

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