You are cordially invited to a Computational Genomics Seminar

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*"*Uncovering the regulatory function of variants that shaped human evolution*"*

Wednesday, May 15 at 11:15

School of Computer Science, Check Point Building, Room 420

**Abstract:** Changes to gene regulation are key drivers of human evolution. However, our ability to predict the effects of sequence variants on expression is limited. Consequently, the effects of most human variants remain unknown. Here, we used massively parallel reporter assays to experimentally determine the regulatory effect of each of the hundreds of thousands of single-nucleotide variants that emerged and spread to fixation in human evolution. Using a range of skeletal, adipose, skin, and neural cells, we compared the functional output of the ancestral and the derived allele for each of the 71,443 variants distinguishing modern humans from Neanderthals and Denisovans, as well as the 541,851 variants distinguishing all human lineages from other great apes. We found that 15% of the variants arose in active regulatory elements, and that 20% of these altered human expression levels. To identify genes affected by expression-altering variants, we generated human-chimpanzee hybrid cells, where expression differences between the species are driven solely in *cis* (i.e., by nearby variants). We found that genes controlling the vocal tract, face, and cerebellum were particularly enriched in regulatory changes, suggesting that these systems might have experienced unique selective pressures. Finally, we identified specific variants that likely contributed to human-specific traits, including in *SATB2*, a key skeletal and neural regulator, and in *IRF4*, a regulator of skin pigmentation. Overall, this work uncovers functionally important variants in deep and recent human evolution, and elucidates their role in shaping human adaptations.

Host: Prof. Ron Shamir, School of Computer Science, Tel Aviv University