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Humanization of yeast genes with multiple orthologous human genes reveal principles of functional divergence in paralogs

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The most deeply evolutionarily conserved human genes encode essential cellular machinery whose failures are linked to diverse diseases, from cancer to cardiovascular disease. Recent systematic studies have discovered extensive genetic polymorphism in these genes yet studying how these variations contribute to cellular function and overall human health remains a challenge. The remarkable extent to which protein-coding genes are still functionally equivalent between humans and yeast emphasizes the power even of distant organism for studying human gene function. We recently created hundreds of humanized yeast strains (>200) such that human genes can complement a lethal growth defect conferred by loss of the corresponding yeast gene with little or no effect on growth. Humanizability is not well-explained by sequence similarity between the human and yeast genes but is instead a property of specific protein complexes and pathways. We have further extended this work replacing the entire set of shared essential genes (>500 human genes) in yeast that have several co-orthologs in humans assaying for functional complementation. We find that duplicated human genes tend to differentially replace their yeast ortholog, rarely observing broad ability to replace within gene families. These results suggest that within-species paralogs do indeed diverge in function at a higher rate than between species orthologs. Thus, by extending the scope of humanization assays to include those yeast genes that have more than one human ortholog, we have successfully added 90 new human genes to our tested set (Total 310 - a 73% increase).

Speaker Biography

Aashiq H Kachroo did his PhD at the Indian Institute of Science, Bangalore, INDIA on the molecular evolution of new functions in bacteria. He did his first postdoctoral training at the University of Texas at Austin, USA with Dr. Makkuni Jayaram, studying the mechanisms of site-specific DNA recombination. In his second postdoctoral research at the University of Texas at Austin, USA with Dr. Edward Marcotte, he focused on understanding deep homologies in essential genes across vast evolutionary distances (yeast and humans) towards the development of humanized yeast. He is currently an Assistant professor at Concordia University, Montreal, Canada. His research interests span mechanisms of evolution of novel gene functions in bacteria, site-specific DNA recombination, and 'humanization' of critical pathways in yeast.

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