

Detection of Functional Analogous Enzymes in the Human Metabolism

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Since enzymes catalyze almost all chemical reactions that occur in living organisms, it is important that genes encoding such activities are properly identified and functionally characterized. Several studies suggest that the fraction of enzymatic activities in which multiple events of independent origin have taken place during evolution is substantial. However, this topic is still poorly explored, and a comprehensive investigation of the occurrence, distribution and implications of these events, involving organisms whose genomes have been completely sequenced, has not been done so far. Fundamental questions, such as how analogous enzymes originate, why so many events of independent origin have apparently occurred during evolution, and what are the reasons for the coexistence in the same organism of distinct enzymatic forms, remain unanswered. In this context, the purpose of this project is to investigate the biological importance and the evolutionary role of functional analogous enzymes identified in metabolic pathways annotated in the human genome. A computational pipeline developed by our group (AnEnPi) was used to predict putative analogous enzymes employing protein sequences available in public databases (KEGG). The predicted functional analogy instances were confirmed by mining in Pfam, SUPERFAMILY and PDB databases for domain, folding and 3D structure information concerning the enzymes implicated. Using KEGG and Reactome databases as references, the predicted analogous enzymes were mapped in human metabolism. Altogether, we were able to detect convergence in 31 enzymatic activities (represented by EC numbers) belonging to 51 distinct processes and metabolic pathways from KEGG's reference maps. The genomic coordinates of the genes encoding these predicted analogous enzymes showed that these genes are dispersed throughout the human genome, found in 21 chromosomes. We selected Biliverdin Reductase analogs for further analyses. We found that, despite being considered isoenzymes, the two Biliverdin Reductase forms encoded in the Human genome, BLVRA and BLVRB, share remarkably low sequence similarity, among several other relevant differences, such as: BLVRA can interact with the DNA and regulated the gene expression, while no regulatory function has been described for BLVRB form so far. BLVRA is a component of the insulin signaling pathway and it is possible that both enzymes act on different isomers of biliverdin. Our findings suggest that the coexistence of multiple enzymatic forms in the Human genome might not be interpreted as functional redundancy. Instead, these enzymatic forms seem to be implicated in distinct (and probably relevant) biological roles.

Acknowledgments We wish to thank Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Programa Estratégico de Apoio à Pesquisa em Saúde (PAPEs), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ), and Plataforma de Bioinformática Fiocruz RPT04-A/RJ for their support.