Changing Substrate Specificity by Remodeling Domain Interfaces in Glutathione Transferases.

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I present a comprehensive bioinformatics analysis of the major isozyme subfamilies of the cytoplasmic Glutathione Transferases (GSTs). This analysis illuminates the structure and architecture of the GSTs and predicts the amino acids responsible for reorienting the glutathione binding domain and the substrate binding domain relative to each other. This reorientation allows different isozyme groups to accommodate different categories of substrates. The predictions are generated from a symmetric cross entropy measure that identifies the residues within each isozyme group that are most diagnostic of group membership. These residues are, in effect, a distributed sequence motif that serves to uniquely identify the isozyme family to which a sequence belongs and hence greatly reduces the ambiguity in determining whether homologous sequences are paralogs or orthologs. The cross entropy analysis is integrated with other analyses to create a comprehensive picture of the evolution of the cytoplasmic Glutathione Transferase isozyme families and their adaptation to binding new classes of substrates. The cytoplasmic Glutathione Transferases are medically important in eliminating drugs and chemotherapeutic agents from the body and play an important role in resistance to drugs or xenobiotics in other species.