Proteins are the workhorse macromolecules of all organisms, performing a myriad of essential structural, regulatory, and catalytic tasks. Experimental discoveries related to mechanisms underlying protein structure and function are frequently made by analyzing the effects of amino acid residue substitutions at targeted positions. While such work is invaluable for design and engineering of new proteins with desired properties, it is also expensive and time consuming, leading to greater demand for reliable predictive models. Here we present a computational mutagenesis that empirically assesses relative change to overall protein structure due to residue replacements (residual score), and locally quantifies associated environmental perturbations at all positions (residual profile). Our approach utilizes a four-body, knowledge-based, statistical contact potential derived by applying Delaunay tessellation to a diverse dataset of protein structures. We illustrate how computed mutant residual scores correlate well with experimental relative functional changes, complementing the inherent nature of protein structure-function relationships. Additionally, residual profiles are used to develop accurate predictive models of mutant function through implementation of machine learning algorithms. (Received September 09, 2008)