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MutaProt: a web interface for structural analysis of point mutations

Eran Eyal, Rafael Najmanovich, Vladimir Sobolev and Marvin Edelman*

Department of Plant Sciences, Weizmann Institute of Science, Rehovot 76100, Israel

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ABSTRACT

Summary: A web-based tool, termed 'MutaProt', is described which analyses pairs of PDB files whose members differ in one, or two, amino acids. MutaProt examines the micro environment surrounding the exchanged residue(s) and can be searched by specifying a PDB ID, keywords, or any pair of amino acids. Detailed information about accessibility of the exchanged residue(s) and its atomic contacts are provided based on CSU software (Sobolev *et al.*, *Bioinformatics*, **15**, 327–332, 1999). An interactive 3D presentation of the superimposed regions around the mutation(s) is included. MutaProt is updated weekly.

Availability: http://www.bioinfo.weizmann.ac.il/MutaProt

Contact: eran.eyal@weizmann.ac.il

Point mutations have traditionally played a major role in assisting the biologist to analyse the function of a gene product. It is accepted that function and structure are closely related. Indeed, changes in protein conformation and stability are often accompanied by modifications in function. However, few tools for analysis of mutations from the structural point of view exist. This report presents such a tool devoted to structural implications of point mutations in proteins.

We have collected data from the PDB (Bernstein *et al.*, 1977) concerning structural distinctions between proteins in response to point differences in amino acids. A web site has been created which permits rapid searching of this data with links to detailed structural analysis of the mutation site. Our database, termed MutaProt, comprises pairs of PDB files that differ in one, or two, amino acids. Crystallographic files of resolution 3.5 Å or better were included. When submitted, MutaProt contained 9766 file pairs (single mutations—2801; double mutations—6965). The database is automatically kept up to date on a weekly basis.

MutaProt can be searched in three separate ways: by specifying a PDB ID, by entering keywords from the PDB file header, or by designating a particular pair of amino acids (Figure 1a). In addition, searches can be restricted to a particular level of residue solvent accessibility.

All the search methods eventually create a table of entries matching the search parameters. A cell in the table will contain one or more lines, depending on the number of PDB entries with the same sequence or the number of mutant files for the specific residue(s) being queried (Figure 1b). Activating a line in this table leads to detailed structural information concerning the environment of the mutation area. This includes the relative accessibility of the mutated residues, the displacement between equivalent atoms of the contacting residues, and a full list of contacts involving the mutated site and its surrounding residues (Figure 1c). A direct link to the relevant page of the CSU program (Sobolev *et al.*, 1999) provides contact analysis down to the atom–atom level.

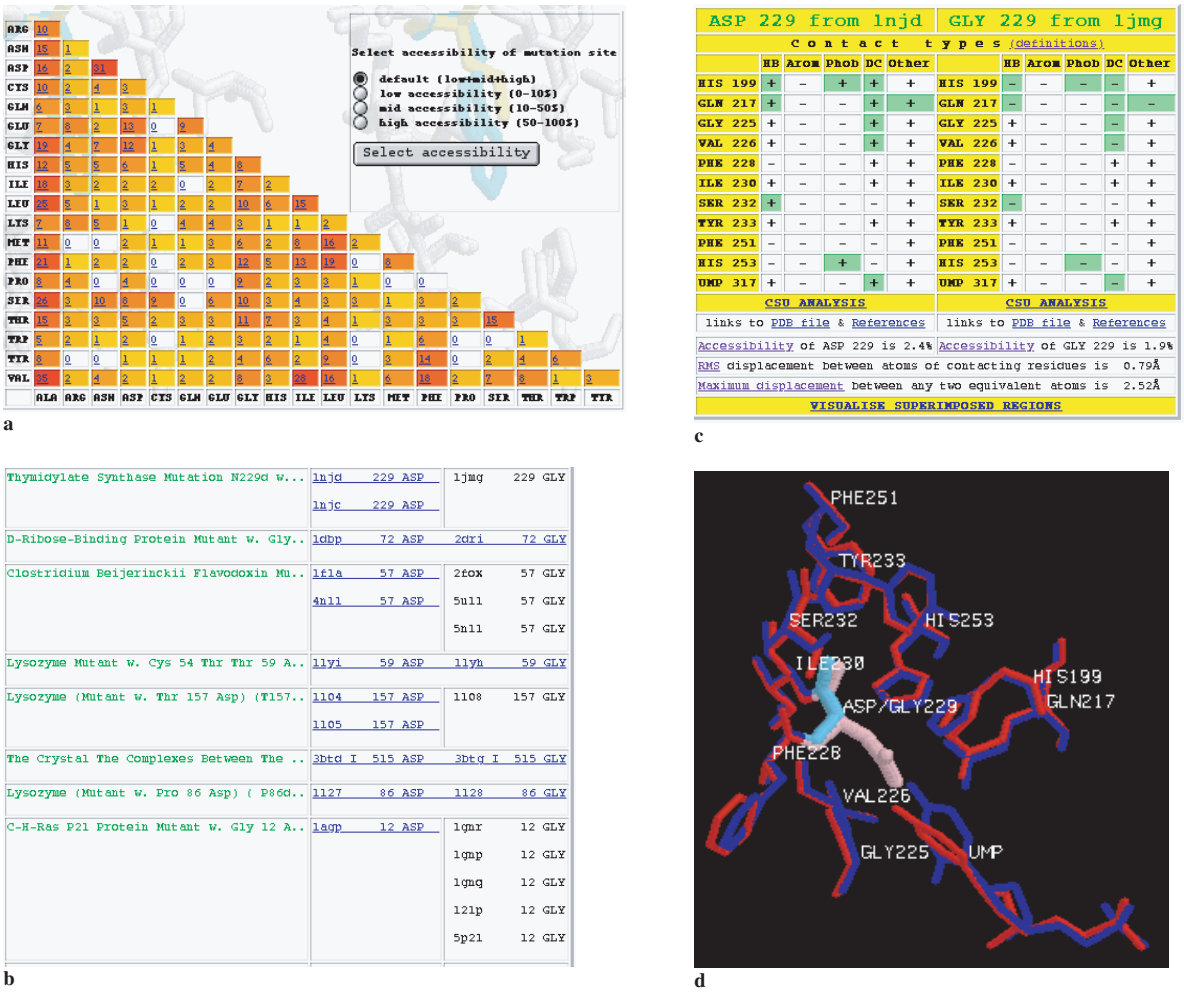
MutaProt employs CHIME (http://www.mdli.com) to visualise the superimposed mutated regions from both files. The presentation includes the amino acid pair undergoing change and their contacting residues (Figure 1d). The entire program was written in PERL using the CGI.pm module.

Several web sites provide information about mutations. Among them are PMD (Kawabata *et al.*, 1999) and ProTherm (Gromiha *et al.*, 1999, 2000), which provide mainly biochemical, thermodynamic and literature information along with some structural data and visualisation features. MutaProt is unique in providing detailed, on-line analysis of atomic contacts (Sobolev *et al.*, 1996), in using CSU definitions (Sobolev *et al.*, 1999) for contacting residues, and in providing a superimposed 3D presentation of the regions being compared.

APPLICATIONS

MutaProt is directly relevant to the fields of structural and molecular biology. It provides information relating to the influence of amino acid substitution on protein stability and backbone and side-chain flexibility. Such information is germane to planning site-directed-mutagenesis strategies.

*To whom correspondence should be addressed.



a b c d

Fig. 1. MutaProt web pages. (a) A matrix of PDB file pairs which differ by a single amino acid between pair members. The number in each cell is the amount of different point changes available for the amino acid pair. For example, clicking on the cell for ASP-GLY gives the table shown in (b). The first cell in (b) contains, on the left, two files (1njd and 1njc) of identical sequence; and, on the right, a 'mutant' partner file (1 jmg) with a single change at residue 229 (from ASP to GLY). Clicking on the 1njd-1jmg line in (b) results in the table shown in (c). This table lists all residues in contact with the 'mutated' amino acid (in our example, ASP/GLY 229), along with the specific type of contact (e.g. hydrogen bond, hydrophobic, aromatic, etc.). The root mean square and maximal differences between paired atoms are also furnished. A more detailed analysis of the environment of residue 229 (solvent accessible surface, putative hydrogen bonds, atomic contacts) is given by direct link to the relevant page of CSU ANALYSIS (Sobolev *et al.*, 1999). Finally, clicking on VISUALIZATION OF SUPERIMPOSED REGIONS produces a CHIME-derived, interactive 3D representation (as shown in (d)) of the superimposed region around the mutated residue from both files.

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