3-Dimensional Protein Modeling of TP53 Mutations in Head and Neck Squamous Cell Carcinoma

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Background

- The most common mutation in head and neck squamous cell carcinoma (HNSCC) occurs in the tumor suppressor gene TP53.
- *TP53* encodes p53, which functions as an important tumor suppressor protein.
- Structurally, p53 is a multi-domain protein with 393 residues and 5 functional domains: an N-terminal transcription activation domain (1–44); a proline-rich regulatory domain (62–94); a DNA-binding domain (110–292); an oligomerization domain (325–363); and a C-terminal regulatory domain (363–393).
- It is estimated that 75% of all the mutations in *TP53* result from a substitution of a single amino acid with another (missense mutation).
- Understanding how individual amino acid variants affect protein function is crucial to genetic studies, particularly in oncogenesis.

Objectives

The aim of this study was to analyze the recently published Evolutionary Action Score of TP53 (EAp53) variants on a crystal structure of TP53. All HNSCC TP53 variants at published by Neskey et al. were plotted on a crystal structure of TP53. Qualitative conclusions were drawn about the location of the TP53 variants within the tertiary protein structure.

Methods

All protein modeling was performed using DeepView – Swiss-PdbViewer. Emamzadah et al. generated the crystal structure of TP53 used, in complex with DNA (Protein Data Bank Identification Code 4MZR).

Results

Examples of conclusions drawn by variant mapping include:

- p.Cys176, p.Leu194, and p.Arg248 which are not proximal in the protein by sequence but all co-localize to a particular DNA binding region of *TP53* and can behave similar clinically.
- p.Val143, p.Leu145, and p.Pro152 represent a region of the protein that results in a more benign clinical phenotype.

References

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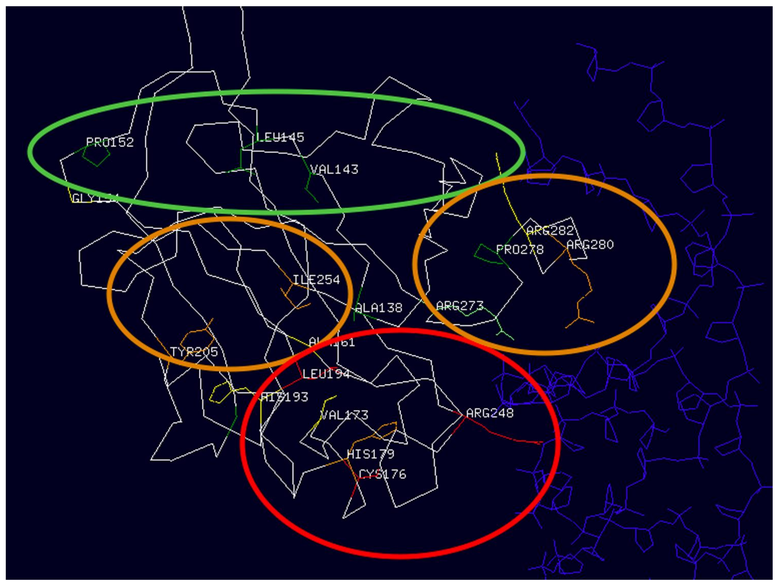

Figure 1. Crystal structure analysis of *TP53* (white backbone) bound to DNA (blue). The analyzed variants are highlighted with white text residues, with green representing the least clinically aggressive variants, yellow and orange more aggressive clinical variants, and red representing the most clinically aggressive variants.

Conclusions

- While clinical behavior does not model perfectly within the protein structure there are some interesting correlations that can be drawn that may, with validation, provide meaningful clinical information about the treatment and prognosis of HNSCC.

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