Clinical and Experimental Health Sciences

Non-Structural Protein-13 Mutations in European Isolates of SARS-CoV-2 Changed Protein Stability

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ABSTRACT

Objective: Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) became one of the most important health problems of the 21st century. Non-structural protein-13 (nsp13/helicase) plays an important role in the replication of the viral genome and the viral life cycle. The SARS-CoV-2 genome has undergone thousands of mutations since the disease first appeared. Mutations pose a threat to the validity of therapeutics due to changes in protein structure. Modeling alterations caused by mutations in the viral proteome contributes to the development of effective antivirals. The changes in protein structure and stability caused by mutations seen in European isolates of SARS-CoV-2 were analyzed in the study with the aim of contributing to studies on the development of new anti-virals and the validity of existing therapeutics.

Methods: The changes in protein structure after mutation were modeled with deep learning algorithms. The alterations in protein stability were analyzed by SDM2, mCSM, DUET and DynaMut2.

Results: The mutation analysis revealed four (Pro77Leu, Gly170Ser, Tyr324Cys, and Arg392Cys) missense mutations in the nsp13 protein in European isolates of SARS-CoV-2. Mutations caused changes in protein structure (rmsd 0.294 Å) and stability ($-4.37 \leq \Delta\Delta G \leq .085$ kcal.mol^{-1}). The atomic interactions formed by the mutant residues in the three-dimensional conformation of the protein have changed.

Conclusions: The mutations seen in European isolates for nsp13 of SARS-CoV-2 may lead to the emergence of different phenotypes in terms of viral activity. For this reason, the study may contribute to the success of the fight against the virus with different treatment approaches in different regions.

Keywords: SARS-CoV-2, COVID-19, helicase, nsp13, mutation

1. INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the pathological agent of Coronavirus Disease-2019 (COVID19), one of the most important health problems of the 21st century, is a positive polarity RNA virus (1). SARS-CoV-2 has caused 704 million people to become ill and more than 7 million deaths since its emergence in December 2019 (2). The SARS-CoV-2 genome, which is 29.9 kb in size, consists of two overlapping open reading frames (ORF1ab and ORF1a), four structural proteins (spike, envelope, nucleocapsid and membrane) and six accessory proteins (ORF3a, ORF6, ORF7a, ORF7b, ORF8 and consists of ORF10) (3). The twelve open reading frames (ORFs) encoded by the RNA genome of SARS-CoV-2 regulate the viral cycle. Non-structural protein (nsp)−13 is one of sixteen non-structural proteins encoded by ORF1ab. nsp13 is a non-structural protein belonging to helicase superfamily 1B. SARS-CoV-2 helicase (nsp13) catalyzes a 5'–3' direction unwinding process in the presence of nucleotide three phosphate to transform duplex oligonucleotides (RNA or DNA) into single strands (4,5). Helicases perform numerous biological functions like as transcription, mRNA splicing, mRNA export, RNA stability, translation, mitochondrial gene expression, and nucleic acid packaging into virions. The SARS-CoV-2 helicase plays a vital role in the replication of the viral genome and the maintenance of the viral life cycle. Therefore, inhibition of the helicase of SARS-CoV-2 is one of the main targets of anti-viral drug studies (6–8). The genomes of RNA viruses face a high risk of mutation with each replication cycle (9). Thousands of mutations have been seen in the SARS-CoV-2 genome since the disease was first detected (10). These mutations resulted in significant changes in the clinical manifestations of the disease. For the SARS-CoV-2 genome, some of these mutations aggravated

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clinical findings, increased human-to-human transmission, and mortality rates, while others caused a decrease in the severity of the disease (11,12). Mutations also pose a threat to the validity of therapeutics due to changes in protein structure (13,14). Modeling alterations caused by mutations in the viral proteome contributes to the development of effective antivirals.

A thorough understanding of the functional roles and responses of viral genomes is necessary for success in controlling viral epidemics, which occur every eight years. In this study, the changes in protein structure caused by helicase mutations seen in European isolates of SARS-CoV-2 were investigated with the aim of contributing to the development of valid therapeutics.

2. METHODS

2.1. Study group, genome and proteome data

The mutation data for 1,616 European isolates were obtained from the NCBI Virus database (15). NC_045512.2 and YP_009725308.1 sequences were taken as reference for the SARS-CoV-2 virus nsp13 protein. The sequence data was aligned with the MAFFT (v7.511) multiple sequence alignment program L-INS-i algorithm (16). The scoring matrix BLOSUM 80, and 1 PAM was chosen for the amino acid sequences, and nucleotide, respectively (17,18). The gap opening penalty was used as 2.0. The mutated residues were analysed MegaXI (19). The detected mutant residue information was processed using MegaXI and the mutant nsp13 protein sequence was compiled.

2.2. Protein modelling and quality assessment

The changes caused by the mutations detected in the helicase protein structure were modeled using deep learning algorithms (20). 7NIO was used as a template in protein modelling (21). The quality evaluation of the created mutant protein models was made with QMEAN and MolProbity (22,23). The changes in mutant protein conformation were visualized with PyMOL.

2.3. Protein stability analyses

The changes in helicase protein stability and atomic interaction caused by nsp13 mutations of SARS-CoV-2 detected in European isolates were analysed with SDM2, mCSM, DUET, and DynaMut2 tools.

3. RESULTS

The mutation analysis revealed four (Pro77Leu, Gly170Ser, Tyr324Cys, and Arg392Cys) missense mutations in the nsp13 protein in European isolates of SARS-CoV-2 (Figure 1). Mutant sequence data were modeled on reference sequence (Figure 2).

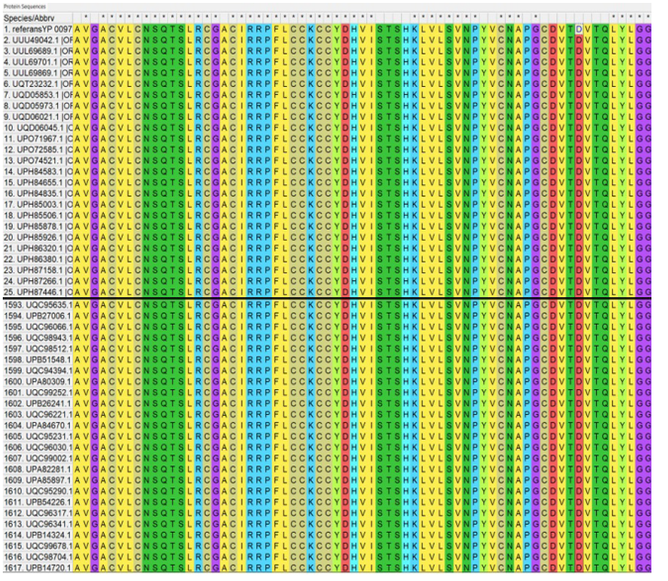

Figure 1. *Aligned sequence representation of the nsp13 protein of SARS-CoV-2 in European isolates*

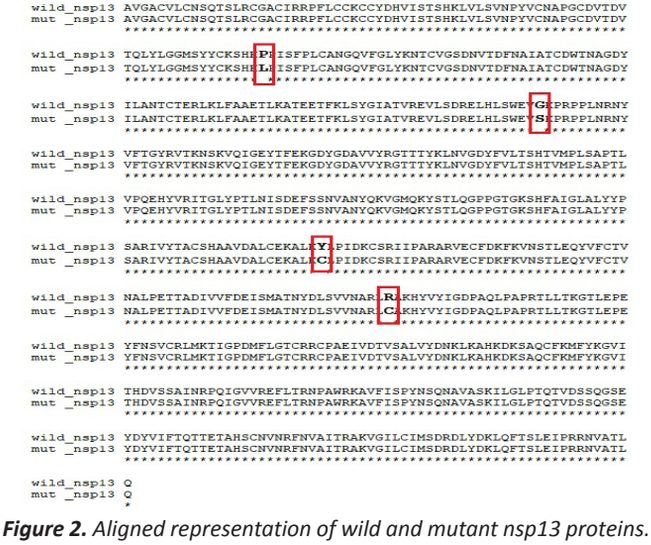

Figure 2. *Aligned representation of wild and mutant nsp13 proteins.*

The obtained mutant protein sequence data were modelled with the Robetta tool using deep learning algorithms. The quality of the mutant protein models created was highly reliable and within acceptable limits (Figure 3). Z-score was in the .55 ± .34 – .13 ± .32 range. Model confidence values were .88. Mutations caused changes in nsp13 protein conformation and topological structure. The rmsd value at superimpose was .294 Å (Figure 4). The Pro77Leu mutation in the nsp13 protein of SARS-CoV-2 caused a decrease in protein stability (-.58≤ ΔΔG≤.003 kcal.mol^{-1}). A change in the nsp13 tertiary structure atomic interaction was observed after the Pro77Leu mutation in the nsp13 protein of the SARS-CoV-2 European isolates. The tertiary structure stability provided by proline with one polar, one hydrogen bond, and two hydrophobic interactions at the 77th position in the wild type was provided with one polar and four hydrophobic interactions after the mutation (Figure 5).

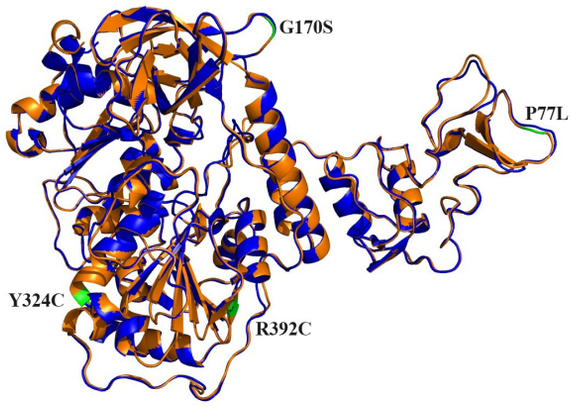

Figure 3. *Cartoon illustration of the nsp13 mutations detected in European isolates of SARS-CoV-2 on the protein tertiary structure.*

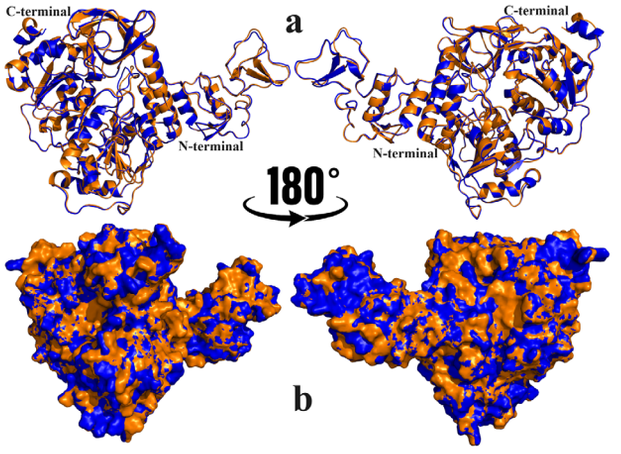

Figure 4. *Superimposed illustration of the nsp13 protein of SARS-CoV-2 (blue color indicates wild type nsp13, orange color indicates mutant type nsp13). a) Superimposed cartoon illustration of the nsp13 protein of SARS-CoV-2, b) Superimposed of the nsp13 protein of SARS-CoV-2.*

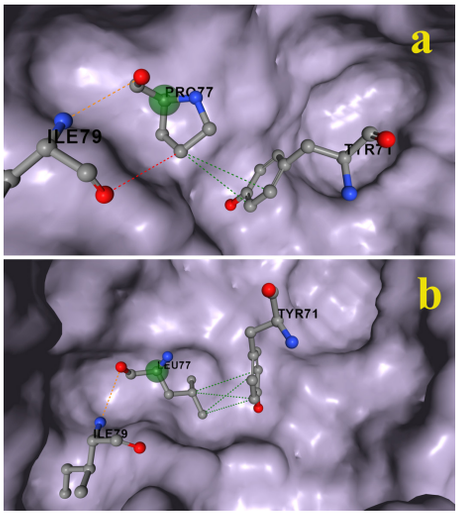

Figure 5. *Illustration of the change in the atomic interaction of residue 77 in the P77L mutation of nsp13 detected in European isolates of SARS-CoV-2. a) wild type nsp13, b) mutant type nsp13 (indicates that green dots-hydophobic, orange dots-polar interaction, red dots-hydrogen bond)*

The Gly170Ser mutation in the nsp13 protein of SARS-CoV-2 caused a decrease in protein stability (-4.37 ≤ ΔΔG ≤ - .75 kcal.mol^{-1}). A change in the tertiary structure atomic interaction was observed after the nsp13 protein Gly170Ser mutation in European isolates of SARS-CoV-2. While Glycine at the 170th position in the wild type ensured the stability of the tertiary structure with one polar interaction, it did not form an interaction with the surrounding residues after mutation.

The Tyr324Cys mutation in the nsp13 protein of SARS-CoV-2 caused a decrease in protein stability (-1.581 ≤ ΔΔG ≤ - .46 kcal. mol^{-1}). A change in the tertiary structure atomic interaction was observed after the Tyr324Cys mutation detected in the nsp13 protein in European isolates of SARS-CoV-2. The tertiary structure stability provided by Tyrosine at the 324th in the wild type with five polar, twelve hydrophobic, and one Van der Waals interaction was reduced to three polar, four hydrophobic interactions after mutation (Figure 6).

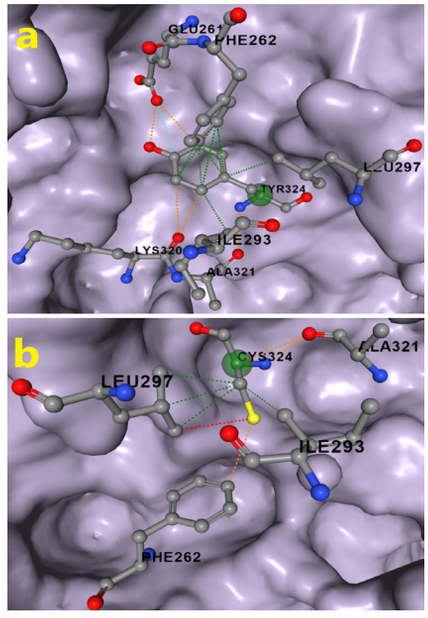

Figure 6. *Illustration of the change in the atomic interaction of residue 324 in the Y324C mutation of nsp13 detected in European isolates of SARS-CoV-2. a) wild type nsp13, b) mutant type nsp13 (indicates that green dots-hydophobic, orange dots-polar interaction, red dots-hydrogen bond)*

The Arg392Cys mutation in the nsp13 protein of SARS-CoV-2 caused a decrease in protein stability (-.496 ≤ ΔΔG ≤ .85 kcal. mol^{-1}). A change in the tertiary structure atomic interaction was observed after the nsp13 protein Arg392Cys mutation in European isolates of SARS-CoV-2. The tertiary structure stability provided by arginine with four polar interactions and one hydrogen bond at the 392th position in the wild type was reduced to four polar interactions after mutation (Figure 7).

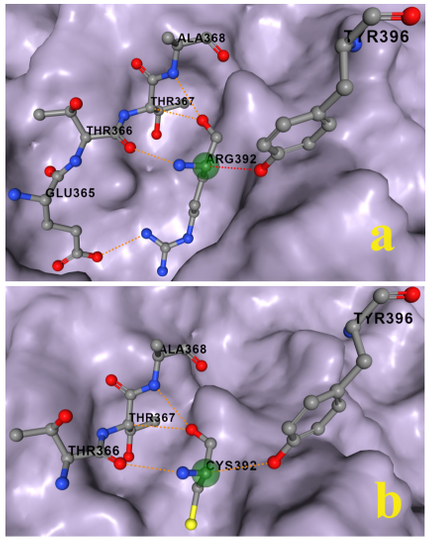

Figure 7. *Illustration of the change in the atomic interaction of residue 392 in the R392C mutation of nsp13 detected in European isolates of SARS-CoV-2. a) wild type nsp13, b) mutant type nsp13 (indicates that green dots-hydophobic, orange dots-polar interaction, red dots-hydrogen bond)*

4. DISCUSSION

The study revealed that mutations seen in European isolates of SARS-CoV-2 nsp13, an important antiviral target, caused changes in protein stability. The functional roles of proteins are formed by the dynamic movement and stability of their molecules (24,25). Mutations in the primary sequences of proteins can alter tertiary structure, stability and function (26,27).

Regional-based evaluation of mutations, especially in viral epidemics, is important in terms of the behavior of the virus in the cellular invasion process, the progression of the epidemic, and determination of treatment options (28). SARS-CoV-2 has undergone thousands of mutations since the beginning of the epidemic, resulting in significant changes in its genome and protein structure (29–31).

Many of these changes have emerged as viral properties such as increased affinity for the angiotensin-converting enzyme-2 receptor and faster host transmission (32–34). The increase of virus in the host cell is associated with increased replication cycle and helicase activity. The opposite is also possible. Viral proteome rearrangements caused by mutations in the virus can increase or decrease the virulence effect (35).

The interaction of active protein molecules and the target nucleic acid sequence in the activation and regulation of replication, transcription, and translation processes occurs with the contribution of special structural motifs such as zinc fingers (36,37). Zinc finger domain mutations cause changes in target nucleic acid/protein and protein/protein interactions (38–40). Our findings showed that the Pro77Leu mutation in the zinc finger region located at the N-terminus of SARS-CoV-2 nsp13 caused a decrease in protein stability ($\Delta\Delta G^{Pro77Leu}$ range from -.58 to +.003 kcal.mol^{-1}) and a change in its conformation. Considering the functional roles of zinc finger structural motifs, these changes in protein stability are likely to lead to significant changes in the functional properties of the helicase (41,42). Akbulut, in his in-slico study analysing the mutations seen in Chinese isolates, showed that mutations in the zinc finger structural motif located in the N-terminal region caused changes in protein structure and stability, and these changes resulted in a decrease in protein-nucleic acid affinity (35).

The mutations, Tyr324Cys and Arg392Cys, detected in the 1A domain of nsp13 of SARS-CoV-2 indicate a decrease in protein stability. Domains 1A and 2A of nsp13 of SARS-CoV-2 contain the Rossman fold, one of the common structural motifs in nucleotide binding regions. It is thought that the changes in stability caused by the two mutations in the 1A domain, where this structural motif, which stands out with its substrate binding properties, is located, may also trigger changes in the activity of the helicase. Grimes et al. in their study, they revealed that the Ala336Val mutation in the 1A domain preserved the ability of the SARS-CoV-2 helicase to associate with core replication proteins nsp 7, 8 and 12, but caused impairment in helicase unwinding and ATPase activity (43).

5. CONCLUSION

The study data revealed that four missense mutations detected in the helicase protein in European isolates of SARS-CoV-2 caused a decrease in protein stability. The mutations and resulting changes are not only a threat to the functional roles of viral proteins but are also important for the validity of existing therapeutics. Topological and stability changes in targeted therapeutic binding sites are important for the validity of developed therapeutics. The changes resulting from these mutations may increase or, conversely, reduce the effectiveness of inhibitors. The mutations seen in European isolates for nsp13 of SARS-CoV-2 may lead to the emergence of different phenotypes in terms of viral activity. For this reason, the study may contribute to the success of the fight against the virus with different treatment approaches in different geographical regions.

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Design of the study: EA
Acquisition of data for the study: MEA
Analysis of data for the study: MEA
Interpretation of data for the study: EA, MEA
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