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IN-SILICO SCREENING AND MODELING OF DELETERIOUS nsSNPs IN HUMAN GENE FBN1 FOR MARFAN SYNDROME

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ABSTRACT: Marfan syndrome (MFS) is a common dominant inherited disorder that affects connective tissue, which is associated with mutation of the gene FBN1. The protein encoded by this gene contributes to the final structure of microfibrils. Single nucleotide polymorphisms (SNPs) of this gene links to variations in gene expression phenotypically among patients. Therefore SNPs would be the main target for identification and analysis, which may help in further diagnosis of such life-threatening disorder. In this study, various computational methods have been used to analyze the genetic variations and identify non-synonymous or amino acid-changing SNPs (nsSNP). It can quicken to evaluate a considerable outcome of a mutation before literally doing the lab work. In total, 475 high-risk nsSNPs have been identified using the NCBI SNPs database. Among these nsSNPs, residues are assigned to predict deleterious or disease-related nsSNP. The conservation of functional amino acid residues and secondary and tertiary structure predictions were also reported using various tools. Swiss-Pdb Viewer allows changing amino acid side chains, causing an artificial mutation to the model. Further, HOPE and Chimera software have managed to analyze the changing structures due to the mutation and the visualization of protein 3D structure. The present article points to lay out an overview and a future direction for genetic study of this rare hereditary disorder by *in silico* analysis.

INTRODUCTION: Marfan syndrome [MFS] is a genetic disorder that affects connective tissue [1], the fibers that maintain the structure of the body and provide cohesion and support internal organs [2]. This syndrome most commonly affects the heart [3, 4], eyes [5], blood vessels, and skeleton [2].

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MFS is a rare pleiotropic disease [6] with three distinctive clinical criteria such as Thoracic Aortic Aneurysm and/or Dissection [TAAD] [7, 8], Ectopia Lentis [EL] [9, 10] and Systemic Features [SFs, multisystemic manifestations] [2, 11, 12].

Features of the people with Marfan syndrome are mostly thin and tall having disproportionately long arms, legs, fingers and toes [9, 13]. The injuries caused by this syndrome can be vague or acute. If the aorta, the large blood vessel that carries blood from our heart to the rest of our body, of the patient is affected, the condition can become life-threatening [14]. Treatment usually includes medications to keep

the blood pressure low to reduce the strain on the patient's aorta [15]. Methodical checking for the damage progression is vital. Many people eventually require preventive surgery to repair the aorta [7, 16, 17, 18]. This genetic disease is associated with mutation of the gene FBN1 [9, 19, 20, 21], the gene encoding fibrillin-1 [22], a structural component of the extracellular matrix (ECM) [4, 23]. The gene is located on chromosome 15q21.1 [13, 24] and also involved in the regulation of transforming growth factor β (TGF-β) bio-availability [25, 26, 27, 28]. The protein encoded by this gene contributes to the final structure of microfibrils, a fine fibre that bears force giving structural support in elastic and non-elastic connective tissue throughout the body [9, 29].

In humans, three different genes (FBN1, FBN2, and FBN3) encode fibrillin proteins [9]. FBN1 is a 230 kb gene, containing 66 exons, which encodes the structural protein fibrillin-1 [30]. Fibrillin-1 is a glycoprotein with 2871 amino acids and is a large structural macromolecule with a molecular mass of ~320 kDa [9, 31]. This protein contributes to the integrity and function of all connective tissues. Fibrillins form 'microfibrils' with uniform diameters (~20 nm) [32] that are irregularly cross-striated or "banded". Fibrillinmicrofibrils have a characteristic structure consisting of light and dark or hollow areas that give the appearance of railroad tracks [33]. Fibrillin microfibrils exist as large bundles of microfibrils, as short individual microfibrils, or as the peripheral microfibril mantle around elastin in all elastic fibres [29, 34]. At the various types of connective tissue, fibrillin microfibrils are organized to best suit the functional integrity of the tissue [35].

An enormous number of SNPs have been predicted up to date; hence it is not practicable to study all SNPs [36]. Many bioinformatic approaches and tools can be used to pick the most damaging SNPs and to predict their effects on protein structure, stability and function [37]. These approaches are based on retrieving SNPs from databases and then filtering those using different tools. These tools can broadly be classified into two categories. The first category is made up of tools that make predictions based solely on the protein sequence (*e.g.*, SIFT, PROVEAN, PhD SNP). Meanwhile, the second one is made up of tools that integrate structural information when making predictions (*e.g.*, PolyPhen-2, SNAP) [38, 39]. However, none of these methods are perfect. For instance, it is significant to get consent from several different tools before deciding which SNPs to select for further, analysis. With rapidly increasing bioinformatics tools and algorithms with better predictive power, computational technologies can aid in predicting nsSNPs that are likely to have deleterious effects on FBN1 protein's structure, its expression, functions or disease susceptibility [40]. In this study, we performed a comprehensive *in silico* analysis of nsSNPs in coding regions in FBN1 gene using different structural bioinformatics tools.

METHODOLOGY:

Retrieval of SNPs: The SNP information of human FBN1 gene was obtained from the National Center for Biotechnology Information (NCBI) SNPs database, (dbSNP) (https://www. ncbi. nlm.nih. gov/SNP/) (accessed Nov.2018); nsSNPs in the coding regions were selected for investigation [41, 42].

Predicting the Most Deleterious nsSNPs by Different Bioinformatics Tools: The effects of nsSNPs on FBN1 protein structure and function were predicted using the following bioinformatics tools: SIFT Sorting Intolerant From Tolerant (http://sift.bii.astar.edu.sg/) [43, 44, 45] and Poly Phen-2 Phenotyping Polymorphism v2 (http:// genetics. bwh. harvard.edu/pph2/index.shtml) [46] were used to predict the deleterious nsSNPs [47]. To increase the accuracy of *in silico* techniques for prioritizing deleterious nsSNPs, the nsSNPs found to be deleterious by SIFT & PolyPhen-2 and furtherly analysed by SNAP2 Screening for Non-Acceptable Polymorphisms(https://rostlab.org/services/snap/)[48, 49, 50], PROVEAN Protein Variation Effect Analyzer (http://provean.jcvi.org) [48, 51], PhD-SNP Predictor of human Deleterious Single Nucleotide Polymorphisms (http://snps.biofold.org/phd-snp / phd-snp. html) [51, 52] and SNPs & GO (http://snps-and-go.biocomp.unibo.it/snps-and-go/) [49, 51].

Analysis of Protein Stability Changes: To analyse the stability changes of the target proteins, I-Mutant 3.*0 (*http:// gpcr. biocomp. unibo. It / cgi / predictors/I-Mutant3.0/I-Mutant3.0.cgi) was used which is an SVM based web server that predicts protein stability changes upon single point mutation starting from the protein structure or sequence.

This tool provides a free energy change value (DDG) and its direction, where positive value indicates that the mutated protein is of higher stability than the negative value. The DDG value is classified into largely unstable (DDG < −0.5 kcal/mol), largely stable (DDG>0.5kcal/mol), or neutral (-0.5≤ DDG≤0.5 kcal/mol) [48, 53].

Analysis of Protein Evolutionary Conservation: Con Surf (http://consurf.tau.ac.il/) was used to predict the conservation of amino acid positions in a protein molecule [54]. This bioinformatics tool is a web-server which can predict the conservation of amino acid positions in a protein using its phylogenetic homologous sequences. The conservation scores contain nine grades ranging from grade 1 (the most variable positions, turquoise colour) to grade 9 (the most conserved positions, maroon colour), with grade 5 being the inter-mediately conserved position (white colour) [53, 55, 56, 57]. Those highly conserved residues which are located at the risk nsSNPs were selected for further, analysis.

Modeling of 3D Protein Structure: By homology modeling [58], Swiss Model (https:// swissmodel. expasy. org/) was used to generate two natural 3D models of the corresponding proteins by using the FASTA sequence of the protein. The FASTA format of the protein can be acquired from Uniprot at Expasy database [59, 60, 61]. To construct a mutant type of each model, Swiss pdb viewer (https:// spdbv.vital-it.ch/)which is an application that provides a user-friendly interface allowing to analyze several proteins at the same time, was used. This tool helped to generate a mutant model at the specific position of the sequence [62, 63, 64, 65]. The resulting models were viewed using chimera version 1.8 which is an extensive program for visualization of molecular structures and analysis of protein 3D structure. Chimera packages are available from the Chimera website (http://www. cgl.ucsf.edu/chimera/) [65, 66, 67, 68].

Predicting Post Mutational Changes in the Protein: The impact from the mutation on the structure of the protein is predicted by using HOPE Have (y) Our Protein Explained (https:// www 3. cmbi. umcn. nl/hope/) which is a web-based tool that analyses the effects of the mutation on 3D structure and function of the protein. It collects information from different data sources like protein's 3D structure, Uniprot database, etc. The tool processes these data and generates a profound report that demonstrates and elucidates the effects of the mutation with figures and 3D structural visualization of mutated proteins [69, 70].

RESULTS AND DISCUSSION:

Retrieval of nsSNPs from dbSNP Database: The nsSNPs of FBN1 gene investigated in this work were retrieved from dbSNP. It contained a total of 54683 SNPs: 741 SNPs found to be pathogenic by clinical significance, 2687 were nsSNPs, 849 were coding synonymous, 180 were in non-coding regions, which comprises of 142 SNPs in 5′ untranslated region (UTR) region and 623 SNPs in 3′ UTR. The rest were in the intron region. Five non-synonymous coding SNPs were selected for the investigation.

Prediction of Deleterious nsSNPs: The selected five nsSNPs were assigned to SIFT, and three of them were predicted to be damaging. The nsSNPs were submitted in FASTA format as a query sequence to the web-server. SIFT analysis predicted that the scoring of nsSNPs was damaging (score is <=0.05), and nsSNPs had tolerated (score is >0.05) effects on the FBN1 gene **Table 1.** According to the Polyphen-2 results, two nsSNPs were predicted as "probably damaging" (rs137854468, rs137854462). To increase the accuracy of predictions, results of SIFT and PolyPhen-2 were joined, and SNPs with Poly Phen score> 0.90 and SIFT< 0.05 were selected. Accordingly, two nsSNPs passed both criteria and were classified as deleterious/damaging **Table 1.**

TABLE 1: LIST OF nsSNPs THAT PREDICTED AS DELETERIOUS BY BOTH SIFT AND POLYPHEN-2

dbSNP#rs	REF ALLELE	ALT ALLELE	Amino Acid Change	Sift Score	Sift Prediction	Polyphen Prediction	Polyphen Score
rs137854462	T	A	N548I	0	Deleterious	Probably Damaging	**0.99**
rs193922239	C	T	G2627R	0.001	Deleterious		
rs193922224	A	C	W217G	0.049	Deleterious		
rs111671429	G	A	Y170Y	1	Tolerated		
rs137854468	C	T	G1127S	0.058	Tolerated	Probably Damaging	1

All tools such as PhD-SNP, SNAP2 and PROVEAN accepted FASTA sequence as query except SNPs & GO, which accepts Uniprot accession id number as input.

SNPS & GO and PROVEAN confirmed the damaging effect of two nsSNPs (rs137854468 and rs137854462), whereas the nsSNPs rs137854468 found to be deleterious by only SNAP and rs137854462 by PhD-SNP **Table 2.**

TABLE 2: PREDICTION OF DELETERIOUS NSSNPS BY DIFFERENT BIOINFORMATIC TOOLS

dbSNPrs#		rs137854462	rs137854468
Amino acid change		N548I	G1127S
SNP&GO	Prediction	Neutral	Disease
	RI	8	8
PhD-SNP	Prediction	Disease	Neutral
	RI	0	2
SNAP2	Prediction	Neutral	Effect
	Score	-6	32
PROVEAN	Prediction	Deleterious	Deleterious
	Score	-5.371	-8.375

Prediction of Protein Stability: The two nsSNPs were predicted by I-Mutant as significantly decreasing the stability of the protein. It is confirmed that these nsSNPs were found to induce in decreasing the energy compared with native types **Table 3.**

TABLE 3: I-MUTANT 3.0 STABILITY PREDICTIONS FOR nsSNPs

dbSNPrs#	Amino Acid Change	Stability	RI	DDG
rs137854462	N548I	Decrease	2	-0.16
rs137854468	G1127S	Decrease	9	-1.26

Prediction of Conservation of the Substituent Residues: Analysis of the two deleterious nsSNPs with Con Surf revealed that all of them were located in highly conserved regions and predicted to have functional and structural impacts on FBN1 protein **Table 4.**

TABLE 4: CONSURF PREDICTIONS OF AMINO ACID CONSERVATION ACCOUNT FOR nsSNPs

dbSNPrs#	Residue Position	Conservation Score
rs137854462	N548	9
rs137854468	G1127	6

Analysis of 3D Structure:

Modeling of Native 3D Structure: By retrieving the FASTA sequence of the protein from Uniprot at Expasy database, a three-dimensional model of the gene FBN1 was to be created by homology modelling using the Swiss model platform.

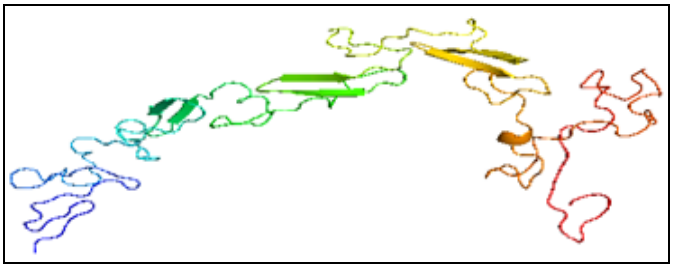

FIG. 1: 3D PROTEIN STRUCTURE MODEL WITH ASPARAGINE AT POSITION AT 548

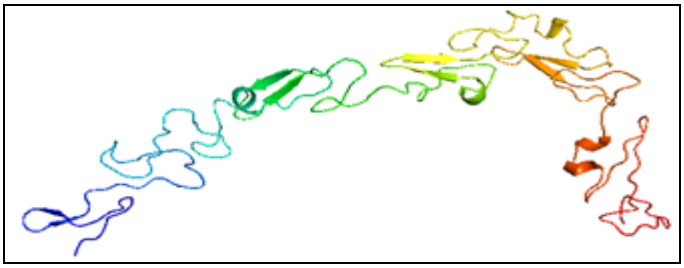

FIG. 2: 3D PROTEIN STRUCTURE MODEL WITH GLYCINE AT POSITION 1127

Constructing the Mutant Models by Swiss pdb Viewer: To construct two mutant models, Swiss pdb viewer, an application that provides a user-friendly interface allowing analysis of several proteins at the same time, was used. Swiss model repository is integrated with several external resources, such as Uniprot, *etc*.

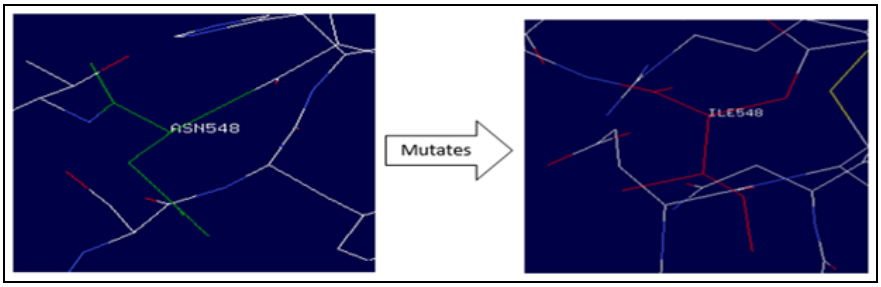

FIG. 3: nsSNP rs137854462 MUTATES THE AMINO ACID ASPARAGINE (GREEN) INTO ISOLEUCINE (RED) AT POSITION 548

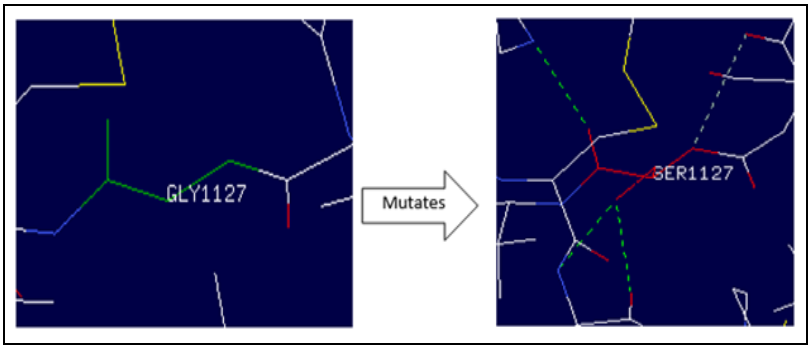

FIG. 4: nsSNP rs137854468 MUTATES THE AMINO ACID GLYCINE (GREEN) INTO SERINE (RED) AT POSITION 1127

Visualizing the 3D Models of Nature and Mutant Protein Structure: Chimera was used to visualize changes in the protein 3D structure due to deleterious nsSNPs. The following figures show the different 3D structures of the protein before and after mutation. The wild types were represented by the figures on the left while the mutants were on the right.

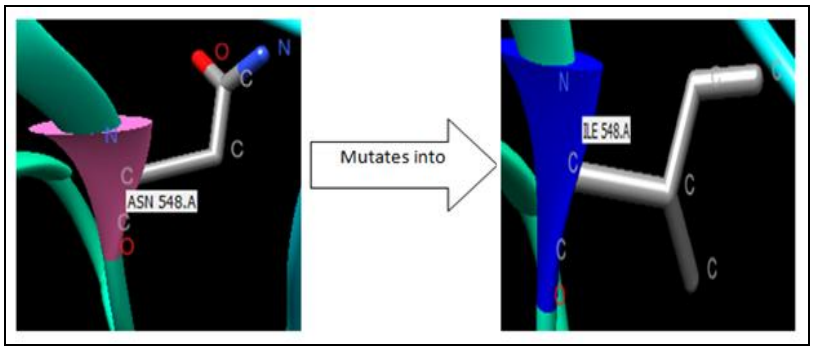

FIG. 5: THE 3D STRUCTURAL VISUALIZATION OF WILD TYPE ASPARAGINE (PINK COLOUR) AND MUTANT TYPE ISOLEUCINE (BLUE COLOUR) AT POSITION 548

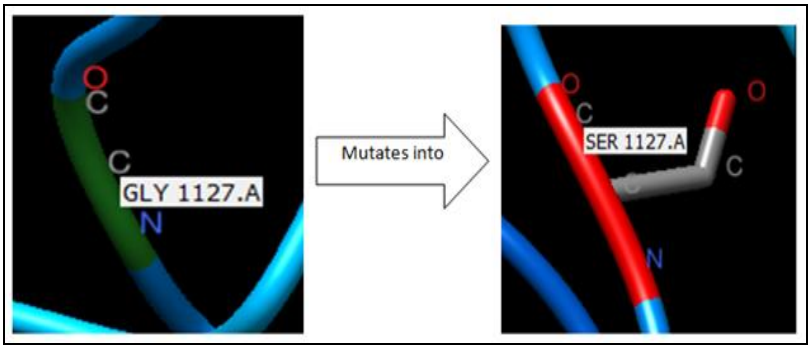

FIG. 6: THE 3D STRUCTURAL VISUALISATION OF WILD TYPE GLYCINE (GREEN COLOUR) AND MUTANT TYPE SERINE (RED COLOUR) AT POSITION 1127

Prediction of Post Translational Mutational Changes in the Protein Structure by Project HOPE: The 3D analysis of the wild-type and mutant protein structures was performed by project HOPE.

Mutation (rs137854462) of Asparagine into Isoleucine at Position 548 (N548I): For this variant, the mutant residue is smaller; this may cause the loss of external interactions. The wild-type residue was uncharged. The mutant residue is more hydrophobic than the wild-type residue. This mutant residue is located near a highly conserved position. The mutant residue is situated in a domain that is important for the binding of other molecules. The mutant residue is connected with residues in another domain. It is possible that the mutation might disturb the interaction between these two domains and as such, affect the function of the protein and thereby affect signal transfer from the binding domain to the activity domain.

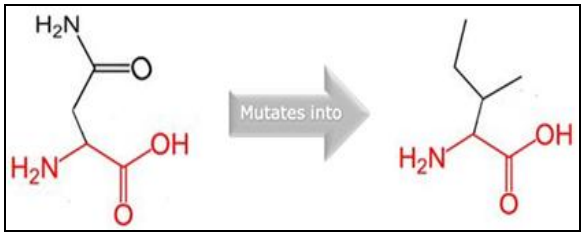

FIG. 7: THE MUTATION OF AN ASPARAGINE INTO AN ISOLEUCINE AT POSITION 548. The figure shows the schematic structures of the wild type (left) and the mutant type (right) amino acid; each amino acid is coloured red, except the side chain, unique for each amino acid, is coloured black.

Mutation (rs137854468) of Glycine into Serine at Position 1127(G1127S): The mutant residue is bigger than the wild-type residue. The protein has a new residue that has a different property from wild type due to the mutation, which can disturb this domain and abolish its function. The most flexible wild-type residue glycine is mutated into a less flexible mutant serine; this flexibility might be necessary for the protein's function. Mutation of this glycine can abolish this function. Mutation of a 100% conserved residue is usually damaging for the protein. The mutant residue is situated near a highly conserved position. The torsion angles for this residue are unusual. The only glycine is flexible enough to make these torsion angles, mutation into another residue will force the local backbone into an incorrect confirmation and will disturb the local structure.

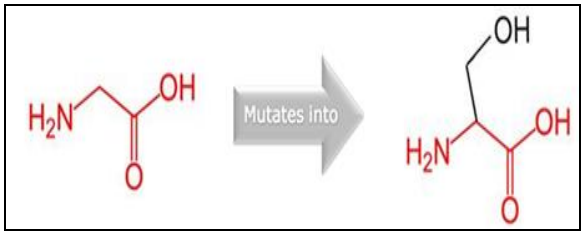

FIG. 8: THE MUTATION OF A GLYCINE INTO A SERINE AT POSITION 1127. The figure shows the schematic structures of the wild type (left) and the mutant type(right) amino acid, each amino acid is coloured red, except the side chain, unique for each amino acid, is coloured black.

CONCLUSION: It is not mandatory to focus on the study of nsSNPs to treat Marfan syndrome, but a mutation or an SNP can alter both the structure and function of a protein. This study shows multiple damaging effects which is possibly caused due to nsSNPs, with the help of various structural bioinformatics tools. The two main mutations shown are: Asparagine into Isoleucine at position 548(rs137854462) and Glycine into Serine at position 1127(rs137854468). These nsSNPs predicted on screening of Marfan related with FBN1 gene occur in a functional domain of the protein may be useful for further analysis using next-generation gene sequencing. Therefore, it may be helpful in advancing the diagnosis by surveying or scanning the disease-related nsSNPs beforehand.

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CONFLICTS OF INTEREST: We declare that we have no competing interests with anybody.

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