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In-Silico Identification of Novel Resistant Genes for Fungal Pathogen *Fusarium oxysporum* f. sp. cubense Race 4: Causative Agent of Banana Vascular Wilt Disease

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Abstract

Cavendish, the most widely grown banana cultivar, is relatively resistant to Race 1 of *Fusarium oxysporum* f. sp. cubense (Foc1) that caused widespread Panama disease during the first half of the 20th century but is susceptible to Tropical Race 4 of the Foc (Foc TR4), a threat to world banana production. Foc TR4 can spread into the vascular system of banana roots during the early infection process. The genome of the diploid species *Musa acuminata*; the ancestor of majority of the triploid banana cultivars has recently been sequenced. The identification for the resistant gene in this cultivar is a challenge for the researchers as the resistant gene against Foc4 has not been identified, the major focus of this research work was to identify the pathogenic genes and some resistant genes against those pathogenic genes, to get some better results for the laboratory work. The four resistant genes I, I-1, I-2, and I-3 were identified which provides resistance against Foc4 in banana. About three pathogenic genes SIX1 (SIX1A, SIX1B, SIX1C), SIX2, and SIX8 of Foc4 were identified. Out of these pathogenic genes SIX8 showed the greatest number of interactions with the resistant proteins. So it is proposed that I-1, I-2 and I-3 genes can be used in the further research work for providing better improvements of the resistive cultivars in banana.

Keywords: SIX; Resistance; Pathogenecity; Foc4; Banana; Fol

Introduction

Fusarium wilt of banana (Panama infection), brought about by the soil borne *Fusarium oxysporum* f. sp. *cubense* (Foc), is a common disease in the banana (Musa spp.) generation inclusively [1-3]. Foc can affect the several types of Musa and Heliconia, their strains have been arranged into four physiological races. Race1 is pathogenic to 'Gros Michel'(aaa) and "Silk" (AAB) [4]; Race 2 just influences the crossbreed triploid Bluggoe (ABB) [5], and the race 4 attacks Cavendish cultivars, and all the cultivars susceptible to races 1 and 2, viewed as the most vital on the fact that it influences the cultivars which deliver more than 80% of the world's bananas [3,6]. The race 4 segregates are subdivided into subtropical race 4 (St4) and tropical race 4 (Tr4). The St4 segregate causes disease in Cavendish bananas in the subtropics [6-8], and Tr4 isolates are pathogenic both under tropical and subtropical conditions [9-12]. In South China, Fusarium wilt of Xiang Jiao (AAA, Cavendish bananas) was initially reported in Guangdong Province in 2001 [13], which brought about by Tr4 [14]. Till date, there are fewer fungicides accessible to control Fusarium wilt of banana. Chemical control is troublesome in light of the fact, that the chlamydospores can make holes in the soil. The best alternative is planting resistant cultivars, for example, Fusarium wilt-resistant bananas chose by means of genetic variations from tissue [15], and transgenic bananas [16,17]. Notwithstanding, Fusarium wilt of banana is still a significant danger to banana production around the world. Quarantine policies and Foc free tissue culture planting materials are the vital methodologies to counteract the spread of infection [18].

The asexual fungus Foc produces three kinds of asexual spores including macroconidia, microconidia and chlamydospore in its life cycle, empowering it to scatter and survive. It imparts a comparable disease cycle to *F. oxysporum* f. sp. *lycopercisi* (Fol) thus, brings about tomato wilt disease. Firstly, Foc conidia develop and form fungal hyphae under different supplement conditions and in the host plant environment. Further, fungal hyphae spread around and colonize at the surface of the root. After that, the fungal hyphae would cross the epidermis, attack and colonized the xylem vessels of the root. After effectively contaminating banana roots, the pathogen develops at the rhizome and pseudo stem, causes the demise of the tissue or the whole plant. Lastly, the fungal hyphae and spores on the debris of the banana plant might fall into the soil through rainwater and restart another contamination cycle. Tenuously, disease and colonization of banana plants by the fungal pathogen dependably bring about the wilting and yellowing of the lower parts of the leaves. Internally, discoloration of rhizomes and necrosis of vascular bundles in pseudo stem can be observed in seriously infected banana plants.

As a saprophyte, Foc can persevere in soil for quite a while. When it perceives and sees the stimuli from host plants, it starts polluting host bananas from the area of roots. Few powerful alternatives for dealing with this ineradicable pathogen, as fungicides are generally ineffectual [3]. In this manner, figuring successful control systems for fusarium wilt of bananas is a thing of extraordinary desperation and obliges better understanding of the fungal pathogen, particularly its genome. IN the earlier years, the genomes of the tomato pathogen Fol and the maize pathogen *F. verticillioides* were sequenced, the *Fusarium* similar genomics highlights the ancestry genomic locales in Fol that are in charge of the polyphyletic root of host specificity [4].

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Materials and Methods

An *in vitro* investigation of the physiological phenotypes of tomato suggested that recognition of I genes in the tomato are the vital events for vigorous defense, fungal development inhibition, induction of Peroxidase in the *in vitro* dual culture and ion leakage induced by the cultural filtrates of the Fol pathogen can be markers of resistance [19].

The study of the genomic similarity between the Foc4 and Fol

Foc4 shares a similar infection cycle with *F. Oxysporum* f. sp. *lycopersici* (Fol) creating tomato wilt ailment, for the determination of genomic similarity between Foc4 and Fol phylogenetic analysis was done by the help of the phylogeny (FR tool) [20].

Identification of the pathogenic regions in *Fusarium oxysporum* f. sp. *cubense* Race 4

The information about the pathogenic SIX1a, SIX1b, SIX1c, SIX2 and SIX8 proteins of the fungus were obtained through literature [21].

Idenification of the resistant genes for the *Fusarium oxysporum* f. sp. *cubense* Race 4

The resistant genes of tomato; I, I-1, I-2, I-3 against the pathogenic proteins were identified [22]. These resistant genes can be proposed for the resistance in banana against Foc4 as both Foc4 and Fol pathogens have the same cycle of infection in the hosts.

Sequence retrieval

The amino acid sequences of pathogenic SIX1, SIX2, and SIX8 proteins were retrieved through NCBI database. The protein sequences of resistant I, and I-2 genes were retrieved through UniprotKb and I-1 and I-3 were retrieved through Sol Genomics Network database [23].

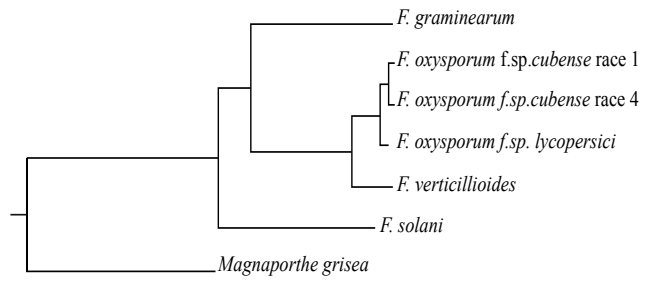

Figure 1: Thehylogenetic tree that represents similarity in the genomes of Foc race4 (*F. oxysporum* f. sp. *cubense* race 4) and Fol (*F. oxysporum* f. sp. *lycopersici*).

3D Models generation

3D models of all the retrieved protein sequences were built by the phyre2 server and validated by Errat server.

Docking of resistant protein structures with pathogenic protein structures

The resistant I, I-1, I-2, I-3 proteins were docked with SIX, SIX2, and SIX8 proteins one by one in Autodock Vina and their amino acid interactions were analyzed in discovery studio software.

Results and Discussion

Through the literature certain characteristics of Foc4 like that of Fol have been identified. These are a) the similarity in the genome, confirmed by phylogenetic analysis shown in Figure 1(b). The similarity in the infection cycle, c) the similar genes that are involved in the pathogenicity.

Here, the focus was to identify the resistant genes against pathogenic proteins and to perform computational analysis of the functionality of the resistant proteins with the assistance of docking procedure, and the interactive analysis of these pathogenic and resistant proteins. The SIX1, SIX2 and SIX8 genes were identified as pathogenic genes and I, I-1, I-2 and I-3 were identified as resistant genes. The 3D structures developed for all the proteins of pathogenic and resistant genes are shown in Figures 2 and 3.

Several *in vitro* studies have performed by researchers for the identification of Foc4 as a pathogen of the banana [24,25]. Saraswathi et al. [26] conducted an *in vitro* experiment for the identification of Fusarium wilt by using fusaric acid and culture filtrate. Late inquires about on Fol, the causal agent of Fusarium wilt of tomato, have elucidated the roles of a few SPs in pathogenicity in the Fol-tomato pathosystem [23]. The SIX proteins SIX1 (Avr3), SIX3 (Avr2) and SIX4 (Avr1) work as either Avr protein (effector) included in the inconsistent cooperation or destructiveness components involved in the perfect associations among tomato and Fol [23]. Scientists are keen on looking Foc4 congregations to distinguish the orthologs of the SIX-coding genes, in particular SIX1-SIX8. The researches have revealed that three orthologs of SIX1 are also found in Foc4 genome, namely SIX1a-SIX1c.

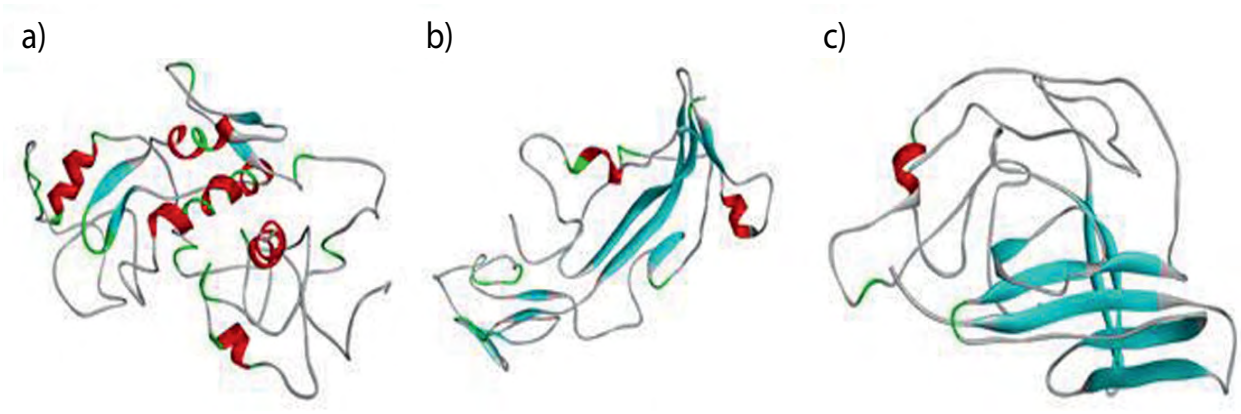

Figure 2: The 3D models of Pathogenic proteins identified for Foc race4 a)SIX1 pathogenic protein b) SIX2 pathogenic protein c) SIX8 pathogenic protein.

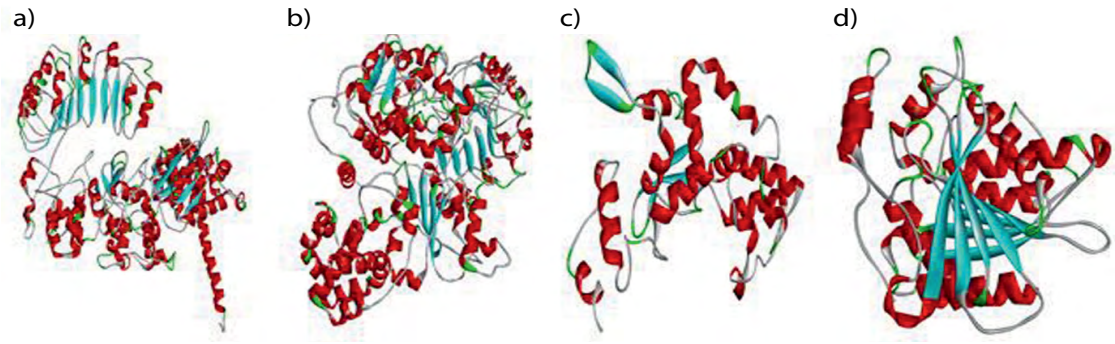

Figure 3: The 3D models of resistant proteins suggested against the Foc race4 a) I resistant protein b) I-1 resistant protein c) I-2 resistant protein d) I-3 resistant protein.

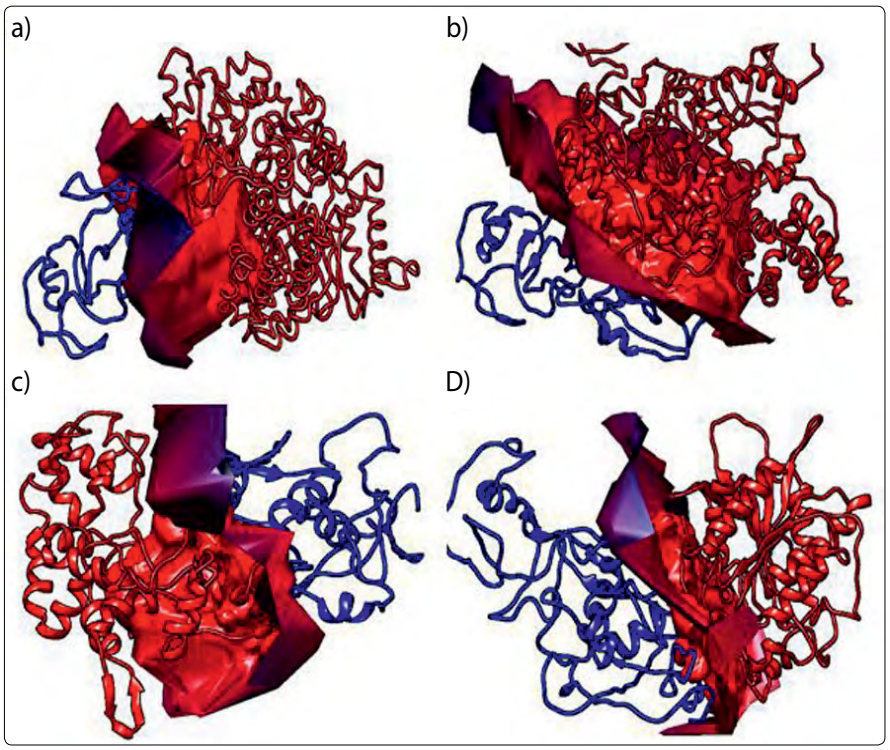

Figure 4: The docking results of Six1 protein of FOC4 and I resistant genes of FOL, the red ribbons represent the ligand whereas blue ribbons represents the receptors. The binding region between two protein structures is represented by the inter-protein surface. a) Six1-I docked complex b) Six1-I-1 docked complex c) Six1-I-2 docked complex d) Six1-I-3 docked complex.

Also, Foc4 has one copy of SIX2, SIX6 and SIX8. Furthermore, the Foc4 contains SIX2 and SIX8 genes that are truant in different races of Foc, hence it is further accepted that SIX2 and SIX8 genes may have roles in the infection of Cavendish banana "Brazil".

Usually, the resistant varieties are generally created by resistant wild types and existing cultivars developed for their properties like great taste, shape and shade. Reproducing of resistant cultivars is an alternative approach to chemical treatment, limiting environmental and consumer risks. Four race-specific R genes for resistance to this pathogen have been genetically mapped in tomato and introgressed into commercial tomato cultivars from wild tomato species [27-34]. The genes I-1 and I-3 are located on chromosome 7, whereas I and I-2 are known to be on the short and long arms of chromosome 11, respectively. The gene I-2 confers resistance to Fol race 2.

The docking studies done to determine the interaction among both resistant and pathogenic proteins further confirmed that, the I, I-1, I-2 and I-3 can be used as resistant genes against Foc race 4. The docking results are shown in Figures 4-6.

Docking strategies authorizes the investigators to monitor a database of compounds and foresees the robust inhibitors in the light of diverse scoring functions [35,36]. Similarly, Morris and Lim stated that Molecular docking is a vigorous tool in the fields of the computer-aided drug design and structural molecular biology. The purpose of docking is to anticipate the major binding modes of a ligand with a recognised 3D structure of a protein [34].

The surface is usually designed in the docked complexes to determine the antigenicity of proteins and to analyze the regions of hydrophobicity between a protein molecule. Such a method can

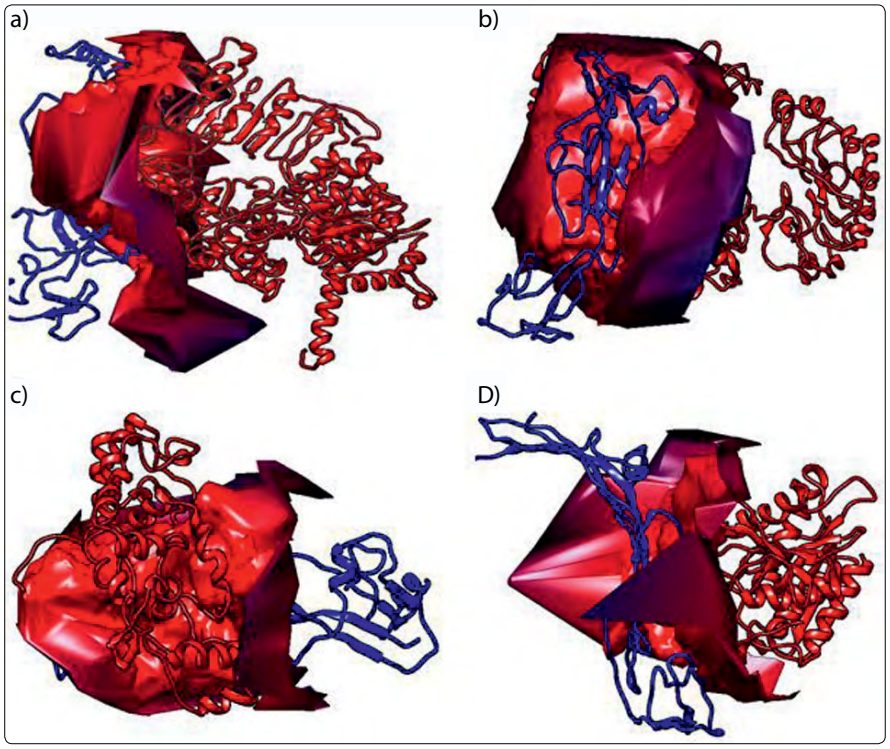

Figure 5: The docking results of Six2 protein of FOC4 and I resistant genes of FOL, the red ribbons represent the ligand whereas blue ribbons represents the receptors. The binding region between two protein structures is represented by the inter-protein surface. a) Six2-I docked complex b) Six2-I-1 docked complex c) Six2-I-2 docked complex d) Six2-I-3 docked complex.

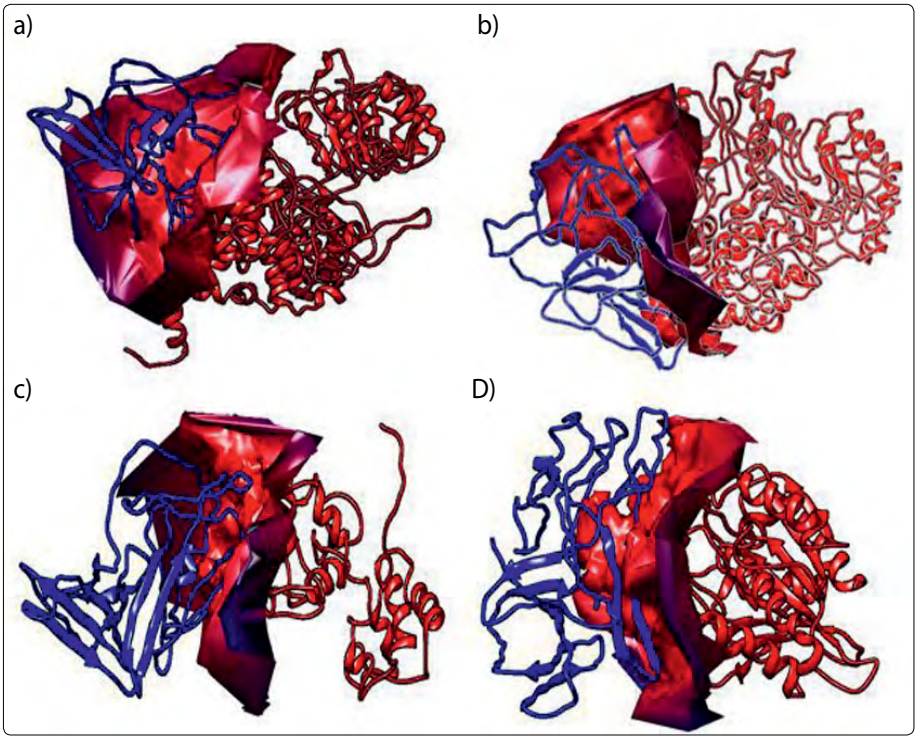

Figure 6: The docking results of Six8 protein of FOC4 and I resistant genes of FOL, the red ribbons represent the ligand whereas blue ribbons represents the receptors. The binding region between two protein structures is represented by the inter-protein surface. a) Six8-I docked complex b) Six8-I-1 docked complex c) Six8-I-2 docked complex d) Six8-I-3 docked complex.

appropriately locate the major antigenic sites on the surface proteins of most well characterized infectious organisms [35].

The bonds formed between the pathogenic proteins and resistant protein complexes are shown in Table 1.

The amino acids, which demonstrated better interactions in each docked complex are shown in Tables 2-4.

When two proteins are docked to each other, one protein can form a complex with another protein, this can steadfastly predict which amino acid residues are situated in the contact site of the protein. Diverse features of interactive sites, such as hydrophobicity, residue tendencies, size, shape, solvent accessibility, and residue pairing inclinations are calculated by examining the interactions between two proteins in a docked complex [36]. Same approach of determining the interactive amino acid residues was used in this research work to know about the other properties of proteins.

SIX1-I, SIX2-I, SIX8-I	Hydrogen bonds Salt bridges Pi donor bonds Pi cation bonds Pi anion bonds Pi sigma bonds Pi sulfur bonds Stacked pi pi bonds T shaped pi bonds Amide pi bonds Pi Alkyl bonds Alkyl alkyl bonds
SIX1-I-1, SIX2-I-1, SIX8-I-1	Hydrogen bonds Salt bridges Pi donor bonds Pi cation bonds Pi anion bonds Pi sigma bonds Pi sulfur bonds Stacked pi pi bonds T shaped pi bonds Amide pi bonds Pi Alkyl bonds Alkyl alkyl bonds Sulfur bonds
SIX1-I-2, SIX2-I-2, SIX8-I-2	Hydrogen bonds Pi donor bonds Pi cation bonds Pi anion bonds Pi sigma bonds Pi sulfur bonds Stacked pi pi bonds T shaped pi bonds Pi Alkyl bonds Alkyl alkyl bonds Sulfur bonds
SIX1-I-3, SIX2-I-3, SIX8-I-3	Hydrogen bonds Pi donor bonds Pi cation bonds Pi anion bonds Pi sigma bonds Pi sulfur bonds Stacked pi pi bonds T shaped pi bonds Pi Alkyl bonds Alkyl alkyl bonds

Table 1: Bonds formed between the docked complexes of pathogenic SIX1, SIX2, SIX8 proteins and resistant I, I-1, I-2, I-3 proteins.

	SIX1-I	**SIX1-I-1**	**SIX1-I-2**	**SIX1-I-3**
Common interacting amino acids	MET1	MET1	PRO52	MET1
	ALA2	PRO3	ASP53	ARG156
	LEU8	VAL7	LYS54	THR159
	LEU9	ASN104	LEU57	ARG160
	LEU12	ARG106	TRP59	ALA161
	LEU115	VAL107	ASN60	CYS162
	LEU118	ASP110	ASP61	PRO163
	CYS119	LYS148	MET63	ARG191
	ARG122	PRO149	GLU96	GLU193
	PRO186	SER150	PHE98	VAL194
	VAL187	ARG152	GLU100	LYS195
	CYS188	GLU153	ARG103	ASP199
	ARG191	ARG154	ASP105	ILE200
	GLU193	ASP155	ARG106	GLY201
	VAL194	ARG156	VAL107	ILE202
	LYS195	VAL158	THR136	TYR211
	ASP196	THR159	ARG139	GLU213
	ARG197	ARG160	THR141	TYR280
	ILE200	ALA161	LYS143	
	HIS203	CYS162	LYS148	
	GLU205	PRO163	VAL151	
	THR209	GLN166	ARG152	
	TYR211	ARG179	ARG156	
	ASP243	HIS181	MET227	
	TYR245	VAL183	ASN232	
	LYS246	THR209	TYR234	
	ARG263	TYR211		
	THR271	PHE235		
	ARG273	TYR237		

Table 2: The interacting amino acids between the docked complex of SIX1 to I, I-1, I-2 and I-3 proteins.

In docked complexes proteins interact with each other or numerous small molecules with a high specificity to form a complex. A comprehensive understanding of the protein-ligand interactions is thus vital to understanding biology at the molecular level. Furthermore, information of the mechanisms accountable for the protein-ligand recognition and binding likewise simplify the discovery, design, and development of drugs [37].

From Tables 2-4 it was observed that the common interacting amino acids among all the docked complexes were Leu, Met, Pro, Phe, Ala, Gly and Lys. The SIX1 protein demonstrated grater interactions with I and I-1 resistant proteins, SIX2 protein demonstrated grater interactions with I and I-2 resistant proteins, whereas the SIX8 protein represented grater interactions with I, I-1 and I-3 proteins. From the above observations, it is suggested that all the I, I-1, I-2, and I-3 resistant proteins can be used as a remedy to provide resistance against the Foc4 to prevent the banana vascular wilt disease.

Fernandes et al. performed *in vitro* analysis to analyze the significance of SGE1 gene expression in the Foc virulence through post-transcriptional silencing method using a double-stranded RNA hairpin. Their analysis discovered that the Foc agents were capable to spread the rhizomes and pseudostems of the inoculated banana plants [38].

Based on previous wet lab experiments conducted to confirm the Foc4 pathogenecity against banana, this *in silico* analysis can be further utilized in wet labs to confirm the I genes resistance against Foc.

Conclusion

In this study, the four resistant genes are revealed to use against Foc4 in banana i.e., gene, I-1, I-2, and I-3 results that Foc4 is closely related to the tomato vascular wilt pathogen Fol by the phylogenetic analysis. It is also revealed that there is a higher similarity in the genomes of Foc4 and Fol. Therefore; the I genes of tomato can also be induced in banana to provide resistance against Foc. This investigation can help the scientists to further work to develop the resistance in banana. This will eventually lead to the improvement of Fusarium wilt disease resistance in banana.

Conflict of Interest

This research work is unique and has not been submitted to any other journal. None of the authors have challenged conflicts of interest.

	SIX2-I	SIX2-I-1	SIX2-I-2	SIX2-I-3
Common interacting amino acids	TRP7	PRO22	ILE16	ALA15
	VAL8	ASN85	SER17	SER17
	LEU10	CYS116	ALA19	PRO22
	ASP29	TRP117	PRO22	ALA23
	LYS48	ASP159	GLY24	GLY24
	TYR56	ASN162	ASP25	ASP25
	HIS58	GLY163	HIS32	ASP114
	ARG60	PHE165	PHE103	CYS116
	ASP78	PRO166	ARG108	TRP117
	GLU80	HIS169	ASP114	MET143
	LEU82	CYS171	TYR115	ARG144
	LEU83	ASN173	CYS116	ASN146
	ASN85	SER174	TRP117	ASP147
	GLU86	ASP175	ARG118	HIS169
	TRP164	ASN181	ASP119	ALA170
	PHE165	HIS182	THR141	CYS171
	GLN177	ARG183	SER142	
	TYR179		MET143	
	ASN181		PHE157	
	HIS182		TYR161	
	LEU185		TRP164	
	VAL188		HIS169	
	TYR193		CYS171	
	ASP195		ASN173	
	HIS196		SER174	
	ARG205		ARG183	
	ASN208			
	SER222			
	ASN223			
	GLY224			
	ALA226			

Table 3: The interacting amino acids between the docked complex of SIX2 to I, I-1, I-2 and I-3 proteins.

	SIX8-I	SIX8-I-1	SIX8-I-2	SIX8-I-3
Common interacting amino acids	CYS116	ALA17	ASP115	ALA75
	LEU119	LEU18	CYS116	ASP76
	TRP126	HIS43	LEU119	THR151
	ARG129	CYS94	GLU120	LYS156
	GLU130	ALtA95	ARG179	VAL158
	ASP132	LYS156	ASP181	ARG168
	PRO137	VAL158	SER207	LYS169
	ARG179	ARG160	MET208	ILE171
	TYR184	ARG168	GLU209	ARG172
	ALA206	ARG172	PRO210	LYS174
	MET208	LYS174	TRP212	HIS183
	GLU209	TYR184	ASN213	TYR184
	PRO210	SER188	PHE214	ARG189
	TRP212	ARG189	ASP215	GLN220
	ASN213	PHE193	PHE224	PHE222
	PRO216	MET208	PHE226	PHE224
	SER217	GLU209	PRO228	PRO228
	PHE222	PHE226		PRO230
	PHE224	THR227		ASN231
	PHE226	PRO230		ARG234
	PRO228	ARG234		GLN236
				GLY237
				THR238
				ASN240
				LEU241
				ALA242

Table 4: The interacting amino acids between the docked complex of SIX to I, I-1, I-2 and I-3 proteins.

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