

Research Article

Insights into the immune manipulation mechanisms of pollen allergens by protein domain profiling

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ABSTRACT

Plant pollens are airborne allergens, as their inhalation causes immune activation, leading to rhinitis, conjunctivitis, sinusitis and oral allergy syndrome. A myriad of pollen proteins belonging to profilin, expansin, polygalacturonase, glucan endoglucosidase, pectin esterase, and lipid transfer protein class have been identified. In the present *in silico* study, the protein domains of fifteen pollen sequences were extracted from the UniProt database and submitted to the interactive web tool SMART (Simple Modular Architecture Research Tool), for finding the protein domain profiles. Analysis of the data based on custom-made scripts revealed the conservation of pathogenic domains such as OmpH, PROF, PreSET, Bet_v_1, Cpl-7 and GAS2. Further, the retention of critical domains like CHASE2, Galanin, Dak2, DALR_1, HAMP, PWI, EFh, Excalibur, CT, PbH1, HELICc, and Kelch in pollen proteins, much like cockroach allergens and lethal viruses (such as HIV, HCV, Ebola, Dengue and Zika) was observed. Based on the shared motifs in proteins of taxonomically-dispersed organisms, it can be hypothesized that allergens and pathogens manipulate the human immune system in a similar manner. Allergens, being inanimate, cannot replicate in human body, and are neutralized by immune system. But, when the allergens are unremitting, the immune system becomes persistently hyper-sensitized, creating an inflammatory milieu. This study is expected to contribute to the understanding of pollen allergenicity and pathogenicity.

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1. Introduction

Allergies, the result of an agitated immune system (Parkin and Cohen, 2001) are a major cause of morbidity. The instances of these inflammatory health problems have soared in unprecedented manner in recent times. Atopy of individuals hinges on genetics, diet, environment and myriad other stochastic factors. Environmental warming, pollution, pesticides, chemical additives, and drugs etc. have been suspected or proven to be catalysts of these immune exacerbations. As new studies are unraveling the link between chronic inflammation and neurobehavioral disorders (such as schizophrenia, depression, multiple sclerosis, Alzheimer's disease etc.), cardiovascular disease, diabetes, cancer, autoimmune diseases (systemic lupus erythematosus) etc., allergies deserve wider understanding (de Punder and Pruimboom, 2013). Virtually, anything ranging from food, pollen, insects, cosmetics, latex, leather, chemicals, drugs, to metals, can be allergens. Biochemically, most of the allergens are either protease, protease inhibitors,

lectins, cofactors or enzyme manipulators. Common allergic symptoms include asthma, atopic dermatitis, urticaria, rhinitis, conjunctivitis, sinusitis, edema, abdominal pain, bronchospasm, and dyspnea (Baxi and Phipatanakul, 2010). Depending on the response of immune system towards the allergen, fatal conditions like hypotension, hypertension and anaphylactic shock can occur (Yoon et al., 2014).

Plant pollens are common allergens, causing pollinosis, degrading the quality of life during the blooming season of the year i.e. in winter and spring months (Gilles et al., 2012; Asam et al., 2014). Studies have shown that the vehicular exhausts promote pollen rupture, inducing airway inflammation (D'Amato et al., 2010). The allergenicity of each plant varies, not being restricted to any particular family, and it can span from gymnosperm to angiosperm, and monocot to dicot. Pollen allergen types can be exhaustively abundant, but most-studied are from the plants *Olea europaea* (Common olive), *Platanus acerifolia* (London plane tree), *Juniperus ashei* (Ozark white cedar), *Cryptomeria japonica* (Japanese cedar), *Juniperus virginiana* (Eastern red cedar), *Betula pendula* (European white birch), *Corylus avellana* (European hazel), *Ambrosia artemisiifolia* (Short ragweed), *Ligustrum vulgare* (Common privet), *Phleum pratense* (Common timothy grass), *Zea mays*

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(Maize), *Oryza sativa* subsp. japonica (Rice), *Phalaris aquatica* (Bulbous canary-grass), *Lolium perenne* (Perennial ryegrass), *Poa pratensis* (Kentucky bluegrass), *Artemisia vulgaris* (Mugwort), and *Nicotiana tabacum* (Common tobacco). The well-characterized pollens are Ole e (1, 10), Bet v (1-A, 1-B, 1-L, 1-D/H, 1-F/I, 1-M/N), Phl p (1, 5b), Amb a (3), Amb t (5), Lol p (1), Art v (1), Cor a 1, expansin (B1, B9, B10, B11), polygalacturonase (exo), glucan endo-beta-1,3-d-glucosidase, pectate lyase (1, 2, 3, 4, 5), profilin (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12), pectin esterase (1, 2), non-specific lipid transfer protein, peptidyl-prolyl cis-trans isomerase etc. (Hauser et al., 2010; Yadav et al., 2009). The pertinent data of plants and allergenic pollen proteins has been presented in Table 1. Each pollen protein type has multiple isoforms. In the present study, *in silico* analysis was carried out in order to understand the domain architecture of different pollens. The protein domains of the pollen allergens were compared among themselves and also with other virulent proteins such as cockroach allergens, and pathogenic viruses such as HIV (Human Immunodeficiency Virus), HCV (Hepatitis C virus), Ebola, Dengue and Zika.

2. Material and methods

The *in silico* analysis carried out for domain profiling of pollen proteins can be split into several steps as outlined below

a. Sequence retrieval from UniProt database

FASTA sequences of pollen proteins retrieved from publicly-available database UniProt (<http://www.uniprot.org/uniprot/>) (The UniProt Consortium, 2008) were used. The sequences belonging to different types of plant pollen were processed.

b. Multiple sequence alignment

The multiple sequence alignment (MSA) of 15 pollen sequences (with their UniProt accession numbers in brackets) such as Profilin-2 (A4GE39), Pectin esterase 1 (D8VPP5), Non-specific lipid-transfer (O04004), Profilin-2 (O24650), Lig v 1 (O82015), Amb

a 3 (P00304), Bet v 1-A (P15494), Ole e 1 (P19963), KBG 41 (P22285), Bet v (P43176), Expansin-B1 (P58738), Pectate lyase 1 (P81294), Exopolygalacturonase (Q6H9K0), Cor a 1 (Q08407), and Pha a 1 (Q41260) was performed using Clustal Ω program. The final figure of MSA was generated by ESript (<http://esript.ibcp.fr>), for better understanding of the conserved residues.

c. SMART platform for protein domains

Public platform SMART (Simple Modular Architecture Research Tool) (Ponting et al., 1999) was used for domain information of the pollen protein sequences. SMART identifies the domains, annotations, and assigns them to families and illustrates their topologies using HMMer (for alignment) and BLAST (for bit score).

d. Custom scripts development for domain distribution

Subsequently, the domain profiles in the pollen protein sequences and their distribution patterns were analyzed using scripts developed in Bash language. The scripts were constructed using the commands like awk, sort, grep, comm, and while loop. The scripts included pollen_protein_domains.sh, pollen_data_manipulations.sh and pollen_protein_common.sh. The script pollen_protein_domains.sh sorts the domains of each pollen protein alphabetically, counts the total number of domain for each protein and then conducts the comparison of domain profile between each pair of pollen proteins. The pair-wise comparison was done to find out the domain unique to a pollen protein. The script pollen_data_manipulations.sh uses the output of pollen_protein_domains.sh as input and finds the domains common to each pair of pollen proteins. The script pollen_protein_common.sh uses each pollen protein domain list and searches pathogenically-critical domains like PROF, AAI, DPBB_1, and PbH1 etc.

On executing the scripts, the generated output files were pollen_data, pollen_data_analysis and pollen_domain_consensus. The relevant and interesting findings were extracted from these result files. Domains common to all, shared among some and unique to some pollen protein sequences and the relevance of the

Table 1
Pollen allergens, their UniProt accession number, their plant sources and the SMART-predicted protein domains.

S. No.	Accession No.	Allergen	Plant	Domains	No. of Domain
1	A4GE39	Profilin-2	<i>Olea europaea</i> (Common olive)	PROF, Robl_LC7, SAA	3
2	D8VPP5	Pectin esterase1	<i>Olea europaea</i> (Common olive)	MBD, IG_FLMN, OmpH, YaeQ	4
3	O04004	Non-specific lipid-transfer	<i>Ambrosia artemisiifolia</i> (Short ragweed)	AAI, TNFR, PTN, DUF1899	4
4	O24650	Profilin-2	<i>Phleum pratense</i> (Common timothy grass)	PROF	1
5	O82015	Lig v 1	<i>Ligustrum vulgare</i> (Common privet)	PreSET	1
6	P00304	Amb a 3	<i>Ambrosia artemisiifolia</i> var. <i>elatoria</i> (Short ragweed)	–	0
7	P15494	Bet v 1-A	<i>Betula pendula</i> (European white birch)	Bet_v_1, Cpl-7, Lig_chan-Glu_bd, RAB, GAS2	5
8	P19963	Ole e 1	<i>Olea europaea</i> (Common olive)	ZnF_U1, IG, IGc2	3
9	P22285	KBG 41	<i>Poa pratensis</i> (Kentucky bluegrass)	Transmembrane region, FCD, DUF1907, CHASE2, Galanin, DHDPS, RL11, SMC_hinge, GCK, HBM, Ycel, PKS_TE, OmpH, MA, TOG, EB_dh, CHAD, BTAD, SRP54, EFG_IV, CBD_IV, Dak2, DALR_1, CTD, HWE_HK, HAMP	26
10	P43176	Bet v	<i>Betula pendula</i> (European white birch)	Bet_v_1, Cpl-7, PreSET, GAS2	4
11	P58738	Expansin-B1	<i>Zea mays</i> (Maize)	DPBB_1, NH, ShKT, Knot1, Amb_V_allergen, DISIN, CxxC_CXXC_SSSS, Gp_dh_N	8
12	P81294	Pectate lyase 1	<i>Juniperus ashei</i> (Ozark white cedar)	Amb_all, PbH1, HELICc, FA58C, PbH1, PbH1, MHC_II_beta, CHB_HEX, Kelch	9
13	Q6H9K0	Exopolygalacturonase	<i>Platanus acerifolia</i> (London plane tree)	PbH1, PbH1, PbH1, PbH1, PbH1, ZnF_C3H1, APC10, CBD_II, KR, CT	10
14	Q08407	Cor a 1	<i>Corylus avellana</i> (European hazel)	Bet_v_1, PWI, EFh	3
15	Q41260	Pha a 1	<i>Phalaris aquatica</i> (Bulbous canary-grass)	Transmembrane region, DPBB_1, CFEM, AWS, DISIN, LU, ClpB_D2-small, Integrin_B_tail, Excalibur	9

domains to allergenicity were analyzed. Based on the data obtained, the clusters were formed and tabulated. Further, the domains shared with cockroach allergen and lethal viral pathogens like HIV, HCV, Ebola, Dengue and Zika were determined and the results were presented. The hypotheses were formulated and insights were determined, which have relevance to the management of the pollen allergy. Fig. 1 shows the steps followed for the data analysis.

3. Results

The protein sequences of 15 pollen allergens (with UniProt accession numbers in brackets) Profilin-2 (A4GE39), Pectin esterase 1 (D8VPP5), Non-specific lipid-transfer (O04004), Profilin-2 (O24650), Lig v 1 (O82015), Amb a 3 (P00304), Bet v 1-A (P15494), Ole e 1 (P19963), KBG 41 (P22285), Bet v (P43176), Expansin-B1 (P58738), Pectate lyase 1 (P81294), Exopolysaccharonase (Q6H9K0), Cor a 1 (Q08407), Pha a 1 (Q41260) were used for *in silico* analysis. The multiple sequence alignment showed the presence of 5 conserved amino acid residues such as Ala, Ile, Leu and two Gly residues, among all 15 pollen allergens (Fig. 2). The short stretches of 5 to 6 amino acid residues matched at regular intervals within the sequences of P15494 (Bet v1-A), P43176 (Bet v), Q08407 (Cor a 1), O82015 (Lig v 1) and P19963 (Ole e 1), highlighting their potential involvement in allergenicity. Similarly, P58738 (Expansin-B1) and Q41260 (Pha a 1) showed short stretches of 5 to 6 amino acid residues along the protein sequence (Fig. 2). The peptide motifs or domains common to the groups of allergens was further analyzed by SMART, which distinguishes clearly among the allergens.

The cumulative number of SMART predicted domains was 72. The type and number of domains in the pollens varied from 1 (such as in Amb a 3 (P00304)) to 31 (such as in KBG 41 (P22285)). Frequently-occurring domains were PROF, AAI, DPBB_1, and PbH1. Multiple PbH1 motifs were displayed by pollen proteins such as

exopolysaccharonase protein (Q6H9K0) of *P. acerifolia* and pectate lyase 1 (P81294) of *J. ashei*. Other key domains are RobL_LC7, SAA, MBD, IG_FLMN, OmpH, YaeQ, TNFR, PTN, PreSET, Bet_v_1, Cpl-7, Lig_chan-Glu_bd, RAB, GAS2, ZnF_U1, IG, IGc2, FCD, CHASE2, Galanin, DHDPS, RL11, SMC_hinge, GCK, HBM, YceI, PKS_TE, MA, TOG, EB_dh, CHAD, BTAD, SRP54, EFG_IV, CBD_IV, Dak2, DALR_1, CTD, HWE_HK, HAMP, Cpl-7, PreSET, PWI, EFh, CFEM, AWS, LU, ClpB_D2-small, Integrin_B_tail, Excalibur, ZnF_C3H1, APC10, CBD_II, KR, CT, PbH1, HELICc, FA58C, MHC_II_beta, CHB_HEX, Kelch, NH, ShKT, Knot1, DISIN, CxxC_CXXC_SSSS, Gp_dh_N etc. The full names and functional roles of these domain acronyms have been elaborated later in the Discussion section. Some domains contained transmembrane alpha helices. SMART annotation of the pollen proteins revealed sections of them as low complexity regions. These regions are ambiguous, because the corresponding genomic parts are repetitive in their base composition which results in poor coverage during sequencing (Goldfeder et al., 2016; Warr et al., 2015). Some pollen proteins have domain of unknown functions (DUFs) as well, such as DUF1899 (in non-specific LTP of *A. artemisiifolia*) and DUF1907 (KBG 41 of *P. pratensis*). This information has been presented in Table 1.

A number of domains are shared among the pollen allergens. Such conserved domains include OmpH, PROF, PreSET, Bet_v_1, Cpl-7 and GAS2. The domains common to D8VPP5 (pectin esterase 1) and P22285 (KBG 41) was OmpH. The domain common to O24650 (profilin-2) and A4GE39 (profilin-2) was PROF; domain common to O82015 (Lig v 1) and P43176 (Bet v) was PreSET; domains common to P15494 (Bet v 1-A) and P43176 (Bet v) were Bet_v_1, Cpl-7 and GAS2; domain common to P15494 (Bet v 1-A) and Q08407 (Cor a 1) was Bet_v_1. Out of the 72 domains detected in the analyzed pollen proteins, 53 were varyingly present in cockroach allergens and lethal viral pathogens like HIV, HCV, Ebola, Dengue and Zika. Such conserved domains are BTAD, OmpH, HWE_HK, HAMP, DALR_1, DISIN, RobL_LC7, Kelch, CHAD, EFh, KR, RL11, HBM, ZnF_C3H1, CBD_II, Galanin, SAA, FA58C, DUF1907,

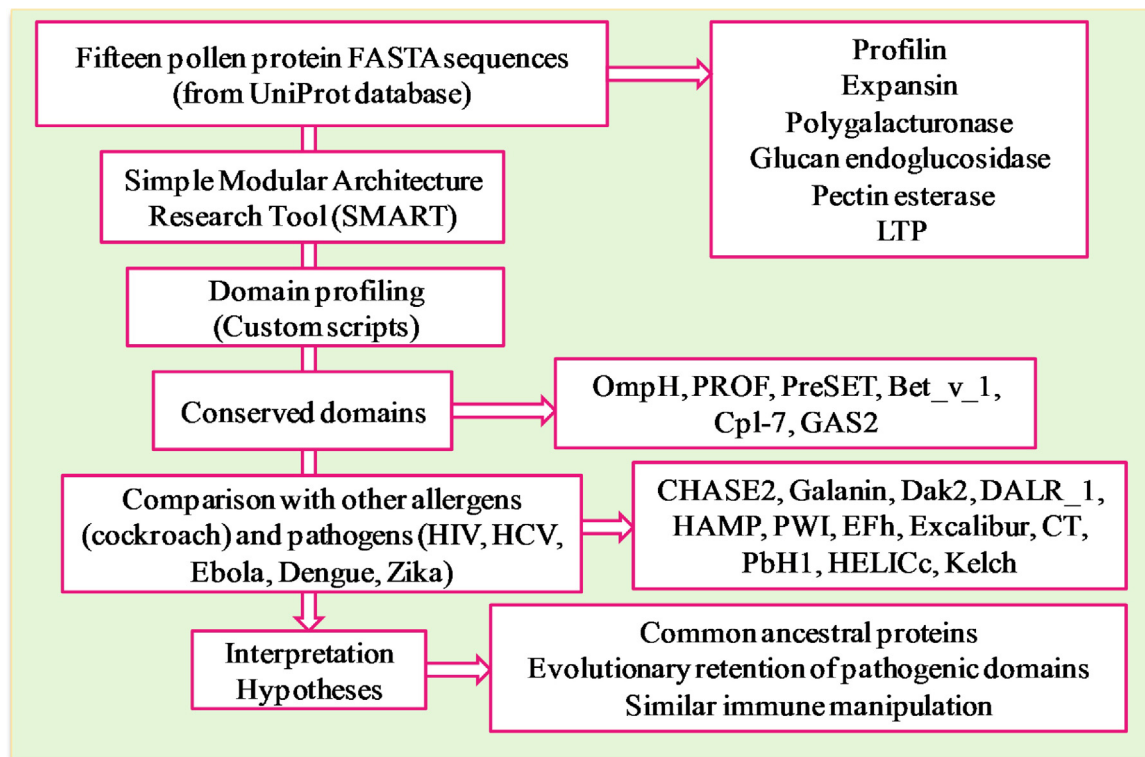


Fig. 1. Steps used in the study, the results and interpretation.

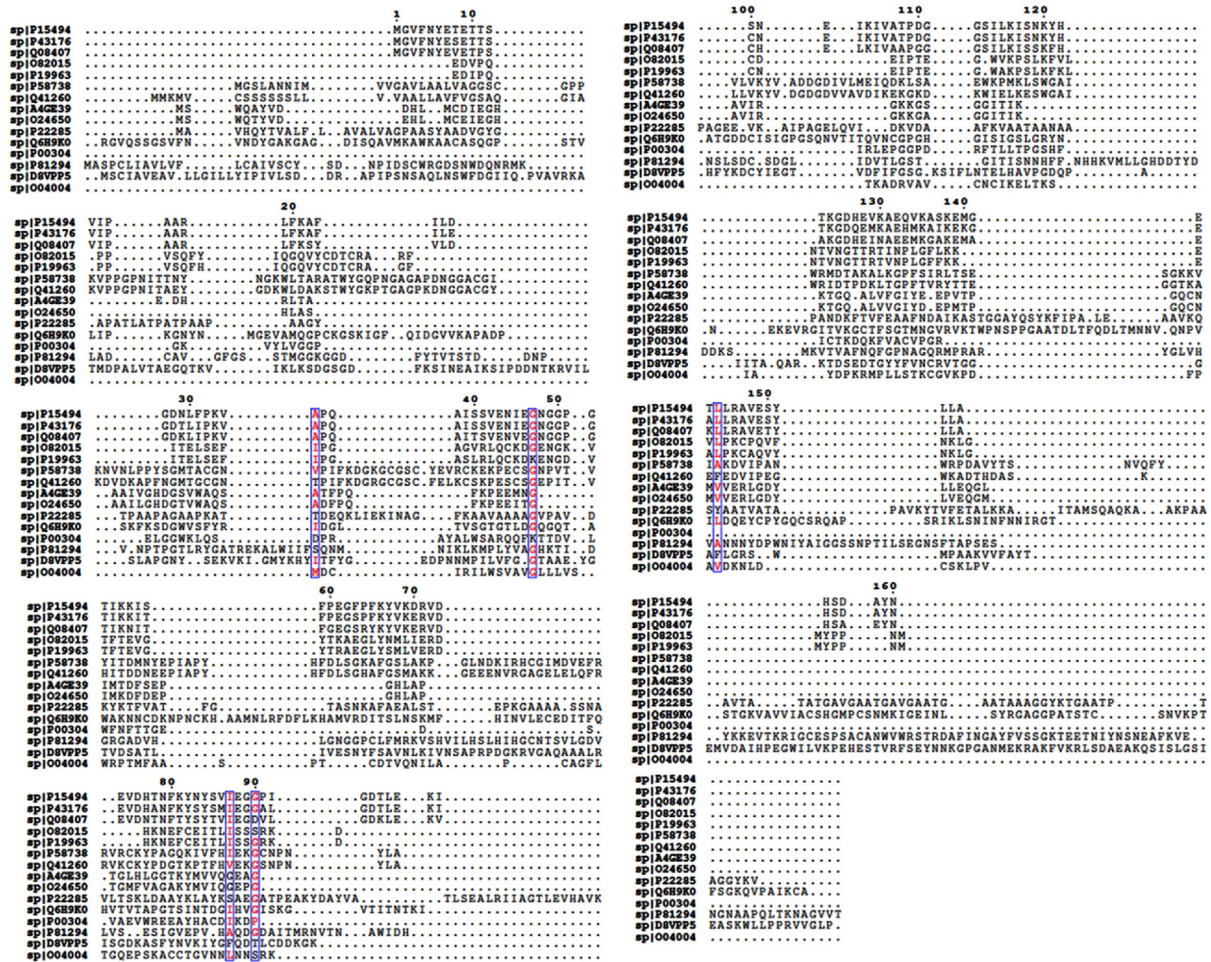


Fig. 2. Multiple sequence alignment of 15 pollen allergens (with UniProt accession numbers enclosed in brackets) Profilin-2 (A4GE39), Pectin esterase 1 (D8VPP5), Non-specific lipid-transfer (O04004), Profilin-2 (O24650), Lig v 1 (O82015), Amb a 3 (P00304), Bet v 1-A (P15494), Ole e 1 (P19963), KGB 41 (P22285), Bet v (P43176), Expansin-B1 (P58738), Pectate lyase 1 (P81294), Exopolysaccharanase (Q6H9K0), Cor a 1 (Q08407), Pha 1 (Q41260). The residues marked in red showed the conserved residues among the allergens. Table 1 can be consulted for origin of the pollen allergens. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

EB_{dh}, Dak2, Gp_{dh}_N, Lig_{chan}-Glu_{bd}, Amb_V allergen, Knot1, CxxC_CXXC_SSSS, FCD, Excalibur, YaeQ, ShKT, PROF, DPBB₁, NH, HELICc, MBD, PWI, PKS_{TE}, ClpB_{D2}-small, LU, Romo1, SMC_{hinge}, TNFR, AWS, CHASE2, CTD, RAB, CT, SRP54, GCK, DHDPS, MA, GAS2, Skp1. The detailed information has been presented in Table 2.

In nutshell, the interesting observation was that the Bet v protein essentially contains a GAS2 domain; PreSET domain is shared between Lig v and Bet v allergens. Human cell membrane manipulation property was suspected from the domains like MHC_{II}beta and Integrin_B-tail. Some other pathogenicity causing motifs in several pollens were identified, such as Omph in KGB41 allergen. Apart from this, other domains found in vicious viruses such as HIV, HCV, Ebola, Dengue and Zika include CHASE2, Galanin, Dak2, DALR₁, HAMP, PWI, EFh, Excalibur, CT, PbH1, HELICc, Kelch. *P. pratensis* (Kentucky bluegrass) particularly contains a large repertoire of domains, several of which have been detected in pathogenic viruses. All of these abbreviated domains and their pathogenic functions have been explained in the Discussion section. Fig. 1 shows the results in brief.

4. Discussion

Pollen allergens encompass several types of proteins. The studied allergens are non-enzymes like profilin (actin-binding protein), expansin (plant cell wall protein for plant cell growth and

fruit softening), non-specific LTPs, as well as enzymes like polygalacturonase, glucan endo-beta-1, 3-d-glucosidase, pectate lyase, pectin esterase, peptidyl-prolyl cis-trans isomerase etc. The characteristics of these allergens, gleaned from existing literature have been outlined below, in brief. Profilin constitutes a large family that exists in eukaryotes, including human and underlie several diseases. Spinal muscular atrophy (SMA) mediated by rho-kinase pathway involves hyper-phosphorylation of profilin 2a protein (Nölle et al., 2011). Mutation in profilin 1 (*pfn1*) gene has been implicated in inheritable amyotrophic lateral sclerosis (ALS), a lethal neurological disease (Wu et al., 2012). The reason has been explained as the interference in the conversion of monomeric actin into filamentous form, which leads to insoluble aggregate deposition, axon growth prevention and cytoskeletal network modification. An *in vivo* study revealed that the alteration in PFN1 protein levels leads to Fragile X syndrome, a robust cause of autism spectrum disorder (Michaelsen-Preusse et al., 2016). Over-expression of *pfn1* gene is associated with lower survival rate in clear cell renal cell carcinoma (CCRCC) patients. Profilin group plant allergens include Mal d 4, Pho d 2 etc. Expansin family of proteins occurs in plant cell walls, playing role in development and protection from stress. This family is highly diverse and a single plant has several subfamilies and a number of expansin genes (Shi et al., 2014). Immuno-reactant natriuretic peptides from some plants (such as potato) are related to this family. Germinating

Table 2

Pollen protein domain shared with cockroach allergen and lethal viral pathogens such as HIV, HCV, Ebola, Dengue and Zika.

S. No.	Domain	Pollen	Cockroach	HIV	HCV	Ebola	Dengue	Zika
1	BTAD	✓	✓		✓			
2	OmpH	✓	✓	✓				
3	HWHE_HK	✓			✓		✓	✓
4	HAMP	✓	✓		✓			✓
5	DALR_1	✓	✓	✓		✓		
6	DISIN	✓		✓	✓			
7	RobL_LC7	✓			✓		✓	✓
8	Kelch	✓			✓		✓	✓
9	CHAD	✓			✓		✓	✓
10	EFh	✓	✓				✓	
11	KR	✓				✓		
12	RL11	✓				✓		
13	HBM	✓	✓					
14	ZnF_C3H1	✓			✓			
15	CBD_II	✓			✓			
16	Galanin	✓			✓			
17	SAA	✓						✓
18	FA58C	✓				✓		
19	DUF1907	✓		✓				
20	EB_dh	✓					✓	
21	Dak2	✓			✓			
22	Gp_dh_N	✓			✓			
23	Lig_chan-Glu_bd	✓					✓	
24	Amb_V_allergen	✓			✓			
25	Knot1	✓			✓			
26	CxxC_CXXC_SSSS	✓		✓				
27	FCD	✓			✓			
28	Excalibur	✓			✓			
29	YaeQ	✓						✓
30	ShKT	✓					✓	
31	PROF	✓					✓	
32	DPBB_1	✓			✓			
33	NH	✓		✓	✓			
34	HELICc	✓	✓		✓			
35	MBD	✓				✓	✓	
36	PWI	✓						✓
37	PKS_TE	✓			✓			✓
38	ClpB_D2-small	✓		✓				✓
39	LU	✓			✓			✓
40	Romo1	✓			✓		✓	
41	SMC_hinge	✓		✓			✓	
42	TNFR	✓		✓	✓			
43	AWS	✓			✓		✓	
44	CHASE2	✓			✓			✓
45	CTD	✓		✓	✓			
46	RAB	✓	✓		✓			
47	CT	✓			✓			✓
48	SRP54	✓			✓		✓	
49	GCK	✓		✓	✓			
50	DHDPS	✓			✓		✓	
51	MA	✓	✓	✓				
52	GAS2	✓		✓				
53	Skp1	✓	✓	✓				

pollen has expansin protein to develop the tube for penetration into stigma (Cosgrove, 2000). These proteins might be binding to carbohydrate moieties of proteins in human body, leading to the immune activation. Polygalacturonase, an enzyme occurring in isozyme forms has been discovered to cause fruit softening by degradation of polyuronide and pectin matrix (García-Gago et al., 2009). Fleshy crops like tomato, and strawberry, often perish due to the activity of this enzyme. Italian cypress (*Cupressus sempervirens*) pollen allergens Cup s and *P. acerifolia* pollen Pla a were found to be these enzymes (Ibarrola et al., 2004). These enzymes form multi-protein complex, behaving like lectins. Glucan endo-1,3-beta-D-glucosidase hydrolyzes polysaccharides, belongs to pathogenesis-related PR2 group of proteins, and is found in fungi, plants, animals (like molluscs) etc. (Zakharenko et al., 2009). Role of this enzyme in germination and pollen tube growth justifies its presence in pollens and subsequent allergenicity in humans by meddling with

glycosyl moiety of other glycoproteins. Pectate lyase is an allergen from plants like tomato, common tobacco, juniper, cypress, cedar, common ragweed etc. It degrades pectate or related carbohydrates, liberating oligosaccharides, causing the loosening of plant tissues. Phytopathogenic bacterium like *Erwinia chrysanthemi* liberates pectate lyase C, which mediates soft rot disease. Pectate lyase-type allergens include Jun a, Cha o, Cry and Amb a (Pichler et al., 2015). Pectin esterase belongs to a multigene pectin methylesterase family, and exhibits considerable primary sequence variation, thus encompasses an array of isoforms. These esterases have been identified as allergens from a multitude of plants, including Chenopodiaceae family pollens, eggplant peel, tomato, apricot pulp, carrot, orange etc. A pectin esterase Ole e 11 from *O. europaea* (olive) pollen is a major allergen, established by various studies (Jimenez-Lopez et al., 2012; Salamanca et al., 2010). Polygalacturonase and pectate lyase shared high sequence homology (Ibarrola

et al., 2004). A transcriptomics study showed that all these related enzymes (polygalacturonase, pectate lyase and glucan endo-beta-1,3-glucosidase) can be clustered together in terms of functionality which include anther dehiscence, pollen wall rupture, tube emergence etc. (Rhee et al., 2015). Peptidyl-prolyl cis-trans isomerase (PPI) belongs to cyclophilin family, and is known to mediate myriad of cellular functions. PPIs carry out cis-trans isomerization of peptide bonds, with a role in protein folding, cell cycle and immunity (Shaw, 2002). Pin1, a cis-trans isomerase, serves as a component of the ribonucleoprotein complex, responsible for granulocyte-macrophage colony-stimulating factor (GM-CSF) mRNA stabilization (Shen et al., 2005). Some PPIs are part of the allergen repertoire of house dust mites (*Dermatophagoides farinae*) (An et al., 2013) and American cockroach (*Periplaneta americana*) (Ahmed et al., 2010).

LTPs are seed storage proteins and trypsin- α amylase inhibitors. These proteins are about 9 kDa allergens, found in several fruits (Rosaceae family fruits like apple, apricot, peach, cherry), vegetables (lettuce), nuts (walnut, hazelnut), latex, including pollens (plane tree) (Hartz et al., 2007). Most LTP allergens are non-specific, such as ns-LTP1 and ns-LTP2. Some well-studied allergens of this group are Mal d 3, Pru p 3 and Lac s (Hartz et al., 2007). Several of these allergens are pan-allergens, responsible for cross-reactivity and food allergy (such as oral allergy syndrome, edema, and gut disturbance) (Popescu, 2015; Santos and Van Ree, 2011). Bet v 1 profoundly occurring in birch pollen, causes cross-reactivity with other allergens such as Mal d 1 (apple), Api g 1 (celery) and Dau c 1 (carrot) (Asam et al., 2014; Fritsch et al., 1998; Levin et al., 2014; Smole et al., 2010). These plant allergens belong to pathogenesis-related (PR) allergenic proteins PR-10 (Zubini et al., 2009).

The crucial findings of the current work have been interpreted here, by referring to previously published data. The domain PROF binds to actin monomers, membrane polyphosphoinositides and poly-L-proline (Michaelsen-Preusse et al., 2016). AAI (alpha-amylase inhibitor) domain is a tetra-helix fold, which forms a part of LTP proteins. DPBB (double-psi beta-barrel) domains are N terminal motifs present in lipoproteins like expansins (such as Phl p). PbH1 (parallel β -helix 1) are repeats, abundant in exopolysaccharuronase and pectate lyase, are present in highly N-glycosylated protein and are involved in carbohydrate moiety recognition and/or modification. The pkhd1 (polycystic kidney and hepatic disease 1) gene product polyductin, associated with kidney disease and congenital hepatic fibrosis, contains these repeats (Gunay-Aygun et al., 2010; Igarashi, 2002; Menezes and Onuchic, 2006). OmpH (outer membrane protein H) domain has been found critical for pathogenesis (Lee et al., 2007). *Pasteurella multocida*, a Gram-negative bacterium causes animal (porcine atrophic rhinitis, bovine diseases), bird (avian fowl cholera) and human diseases, of which OmpH is a major surface antigen (Lee et al., 2007). Other enteric pathogenic bacteria like *Salmonella typhimurium*, *Escherichia coli*, and *Yersinia enterocolitica* have the ompH genes, which can be borne in plasmids as well. OmpH shares homology with the alpha helix of the HLA-B27 (human leukocyte antigen subtype) protein, which has been suspected to play role in inflammatory arthritis. The presence of this critical domain in pollen of grasses suggests similar pathogenicity mechanism.

Other domains worth-mentioning are Robl_LC7, YaeQ, PreSET, Bet_v_1, GAS2, CHAD, Integrin_B_tail, MHC_II_beta, DISIN, etc. Robl_LC7 (Roadblock/LC7 family) domains regulate dynein, a motor protein, and mediate several other adaptive functions (Koonin and Aravind, 2000). Mgl is a type of Robl_LC7, gene of which co-occurs with the gene encoding GTPases (such as Ras superfamily involved in transduction pathways) (Miertzschke et al., 2011; Wuichet and Søgaard-Andersen, 2015). Also, Robl_LC7 domain is grouped with profilin domain, under profilin-like clan.

YaeQ domain is the variation of PD-(D/E)XK motifs in nucleases and it generally occurs in hypothetical proteins (Guzzo et al., 2007). These domains show homology with transcription elongation protein RfaH and exhibit compensatory activity (Wong et al., 1998). PreSET is the N-terminal part of cysteine-rich Zn^{2+} binding SET domains in histone lysine methyltransferases (HMTase) (Binda et al., 2010). Bet_v_1 domain occurs in Bet v 1 proteins, which are homologues of profilins (Fritsch et al., 1998; Wensing et al., 2002). Allergenicity of Bet v 1 arises from its high acceptance of hydrophobic ligands (Asam et al., 2014). GAS2 (Growth-arrest-specific protein 2) domain manipulates actin microfilaments and binds to microtubules leading to cell division arrest (Zhang et al., 2011). CHAD (conserved histidine alpha-helical domain) is an α -helical domain with conserved histidines, chelating metal ions. It cross talks with CYTH domain present in adenylyl cyclases and the mammalian thiamine triphosphatases (Iyer and Aravind, 2002). Cell adhesion necessitates the binding of integrins with their ligands, which can be influenced by multiple domains. Integrin_B_tail (Integrin beta subunit cytoplasmic) domain is involved in cell adhesion (Bodeau et al., 2001). DISIN (disintegrin) domains inhibit ligands-receptor association. Disintegrin proteins and metalloproteases are together termed as ADAMs (A Disintegrin and Metalloprotease), which mediate cellular adhesion and recognition of sequences (Giebel and Zigrino, 2016; Huang et al., 2003). An ADAM with thrombospondin type 1 repeats-13 (ADAMTS13) inhibits platelet aggregation and arterial thrombosis, by the cleavage of von Willebrand factor (VWF) (Xiao et al., 2011). Canary grass pollen Pha a 1 DISIN induces pathogenesis, by interfering with the adhesion of integrins. MHC_II_beta (Class II histocompatibility antigen beta) domain is part of the MHC II glycoproteins expressed on antigen-presenting cells (APC) such as macrophages, dendritic cells and B lymphocytes. These components are critical as they display fragmented antigens for recognition by helper T cells and successive immune response (Vyas et al., 2008).

Domains present in the pathogenic viruses are discussed here. CHASE (cyclase/histidine kinase-associated sensing extracellular) is a conserved extracellular sensory domain that helps in perceiving the environmental changes. As the name indicates, this domain is present in signal transducing systems like histidine kinases, adenylyl cyclases, diguanylate cyclases, serine/threonine protein kinases, phosphodiesterases and methyl-accepting chemotaxis proteins. CHASE domains can be of many types based on functions, out of which CHASE2, -3, and -6 are well-studied. CHASE2 is a part of serine/threonine kinases, which is followed by transmembrane helices (Mascher et al., 2006; Zhulin et al., 2003). Adequate numbers of studies have reported their presence in bacteria (Cyanobacteria etc.) signal sensing proteins (Zhulin et al., 2003). But, their presence in viruses, and pollens, as observed in this study, is rather a new discovery. Galanin is a 29 amino acid-long neuropeptide that controls the growth hormone, insulin, somatostatin, adrenal secretion, smooth muscle activity etc (Kask et al., 1996). Galanin's endocrine regulation mediates the pain, inflammation, memory, learning, mood swings, feeding and sexual activities (Kask et al., 1996). Role of this peptide in neural diseases, angiogenesis, cancer, obesity, and diabetes has come forth as well (Poritsanos et al., 2009; Stevenson et al., 2012). Pathogenesis via the stimulation of phospholipase C (GAL_2) has been recognized (Lang et al., 2015). Dak2 (di-Mg $^{2+}$ ATP binding domain) domain is found in dihydroxyacetone kinases family, which helps bacteria to imbibe host fatty acids into their membrane phospholipids (Parsons et al., 2014). DALR is an anticodon binding domain of arginyl tRNA synthetase, made of alpha helices. In human, this domain-containing protein DALRD3 interacts with protein WDR6 and C3orf60, involved in autophagy and protein assembly, respectively (Grinchuk et al., 2010; Schyth et al., 2015). DALR_1

domain detected in pollen might have role in manipulating gene expression. HAMP, the acronym of Histidine kinases, Adenylyl cyclases, Methyl binding proteins, Phosphatases domains, are present in the transducing genes. This domain, containing helices and coiled coil regions, often undergo conformational changes, relaying signals for chemotaxis, pathogenesis, and biofilm formation (Airola et al., 2013, 2010; Hulko et al., 2006; Matamouros et al., 2015). PWI (proline-tryptophan-isoleucine) domains are present in pre-mRNA processing components, the spliceosome, and are known to bind RNA as well as DNA. PWI-like domains are present in N-terminal of helicases (e.g. Brr2) (Absmeier et al., 2015). EFh (EF-hand) are Ca^{2+} binding alpha helical domains of Miro GTPases, the Ca^{2+} sensors maintaining mitochondrial homeostasis (Suzuki et al., 2014). Trematode tegument proteins have this domain, which is characterized to show immunoglobulin-binding properties (Wu et al., 2015). Excalibur (extracellular calcium-binding region) is a domain of bacterial surface proteins, showing similarity with Ca^{2+} -binding loop of calmodulin-like EFh domains. CT or CTCK (C-terminal cystine knot-like) domains are present in growth factors such as TGF- β (transforming growth factor-beta), NGF (nerve growth factor), PDGF (platelet-derived growth factor) and GCH (human chorionic gonadotropins). The knot formed of six cysteine residues is conserved in the domain, though the proteins harboring them can assume multimeric forms, mediating an array of functions like cell growth, embryonic development, organogenesis, intercellular communication, differentiation, tissue repair and remodeling etc. This domain occurs in von Willebrand factor (VWF), a glycoprotein involved in cell adhesion and hemostasis, and mucins as well. PbH1 (parallel beta-helix repeats) are motifs present in many carbohydrate-lysing enzymes such as pectate lyase, rhamnogalacturonase etc. These domains are present in SHCBP1 (centralspindlin complex, made of motor protein MKLP1 and GTPase-activating protein MgcRacGAP), involved in cytokinesis initiation (Asano et al., 2014). These domains are also present in polyductin proteins, defect in which causes autosomal recessive polycystic kidney disease. HELICc (helicase domain near the C terminus) is part of RNA helicases, such as RIG-I (retinoic acid-inducible gene 1), MDA5 (melanoma differentiation-associated gene 5), and LGP2 (laboratory of genetics and physiology 2), involved in viral PAMPs (pathogen associated molecular patterns) recognition. These domains co-occur with other critical domains like DExD/H, and CARDs (caspase activation and recruitment domains). Kelch is a conserved domain with beta-propeller topology. This repeat-rich domain is widely present across organisms, from virus (Wang et al., 2014), plants to humans, and mediate protein-protein interactions. The kelch-like (KLHL) gene family is spread across multiple chromosomes in human, and several of their coded proteins bind to the E3 ligase cullin 3, playing role in ubiquitination, signaling (such as NF- κ B pathway inhibition), gene expression, actin binding and involved in several diseases.

Though homologies differ and the conserved amino acids are variably-preserved, an obvious evolutionary nexus between cellulases, hemicellulases, endoglucanases and expansins has come forth (Rhee et al., 2015). It indicates that all these proteins with varying functionality have evolved from the same primary protein sequence.

These findings indicate that pathogenic mode of action of the pollen allergens and the viral pathogens are not different. The only difference is that the latter is living, and can populate blood and other sterile niches of body (like pulmonary alveoli, nerves etc.), overpowering immune system by persistent provocation, leading to fatal diseases. This insight can be extended to other pathogens like bacteria, fungi, protozoa and helminthes, those induce immune system to go on overdrive, causing self-injury and death. On the other hand, pollen allergens or cockroach allergens, being

inanimate parts of living organisms, cannot replicate within or on human body. So, immune system can neutralize them, alleviating allergenicity. However, high dosage and repeated exposure of the allergens, inflame immune system to such an extent that these allergens, even without their replication ability can perturb neural and hormonal homeostasis. The shared domains between pollen allergens and cockroach allergens, such as OmpH, BTAD, HAMP, DALR_1, EFh, HELICc, RAB, MA, and Skp1 are conserved in at least one of the viral pathogens like HIV, HCV, Ebola, Dengue, and Zika. This observation from the current study has been exemplified by certain established reports. BTAD (Bacterial transcriptional activator domain) is present in Actinobacteria (Huang et al., 2015); OmpH is present in *Pasteurella multocida* (Okay et al., 2012); HWE_HK (HWE histidine kinase) is present in *Pseudomonas syringae* (Galperin, 2005; Lavín et al., 2007); HAMP (histidine kinases, adenylyl cyclases, methyl binding proteins, phosphatases) is present in *Escherichia coli* (Kishii et al., 2007) etc. Other information can be obtained from protein databases including SMART (Ponting et al., 1999). The fierce retention of conserved domains in virulence-associated protein suggests that below the superficial morphological differences, driven by various types of habitats and stressors, all pathogens have more or less the same arsenal that causes pathogenesis. This information might be useful for the drug repurposing approaches. This study also shed light on the causes of allergen cross-reactivity. Shared protein domains, such as PROF, LTP, Bet_v_1 in pollens and plant-based foods are the underlying cause of pollen-food allergy syndrome (PFS), following pollen exposure (Price et al., 2015). Since several of these plant cell wall enzymes are carbohydrate-active, the cleavage of glycosyl moiety on host protein might be activating the latter, leading to aberrant cascade of enzyme activation, driving cytokine release from immune cells and resulting in inflammation. Though at present, only a handful of plants are studied as the source of allergenic pollens, this study hypothesizes that given the conserved protein domains in pollen proteins, almost all plants are capable of allergenic pollen generation. Only a fraction of all exposed individuals suffers from the hypersensitizing effect of pollens, which can be attributed to host factors. Age, gender, and co-morbidities play role in hormonal and immune status of an individual, and resultant provocation by the hydrolyzing, adhesive, and cytoskeletal manipulative properties of pollen proteins. This *in silico* work generated interesting and persuasion-worthy results. This work can be further extended on a larger set of allergen protein sequences.

5. Conclusions

This study furnished the critical information regarding the pollen protein domain diversity. The presence of shared domains among animal-origin allergens, viral and bacterial pathogens, confirmed the evolutionary conservation and common mode of virulence. It also suggested that allergens and pathogens are not that different in manipulating human immunity, and the only distinction is that the latter is able to replicate and overwhelm the immune system beyond recuperation. However, the allergens, when ignored, become chronic, leading to neural and other tissue inflammation, therefore should not be trivialized.

Conflict of interest statement

The authors declare that there is no competing interest.

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