Parvalbumin: Evolutionary Distance From Human Homologs and Allergenicity.

Diana Rozenshteyn
Computer Science Department
San Diego State University
San Diego, USA

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I. Introduction

Food allergy is a potentially life threatening health condition that can affect a person's life and well being. Food allergies are affecting close to 8% of children in the US with an allergy to fin fish accounting for 0.6% of the total percentage [1]. Up to 10.8% (>26 million) of US adults also suffer from food allergies with 0.9% of them being allergic to fin fish [2].

Parvalbumin (PRVB) is a low molecular weight Ca2+ binding protein that plays important role in muscle twitching and other biological processes [3]. PRVB gene family has two evolutionary distinct forms of the PRVB protein, $\alpha-$ and β-Parvalbumins [3]. Additionally, β-PRVB also has two isoforms, $\beta 1$ and $\beta 2$ [3].

β-PRVB are abundant in fish species, but absent from human muscles [4]. Humans carry $\alpha-$ form of the PRVB protein [3].

It is important to consider the high level of cross-reactivity in fish species. Cross-reactivity is "the recognition of distinct antigens by the same IgE antibody...which clinically manifests as reactions caused by antigens that are homologous to different species" [5]. A study by Borrego, J. T., Cuevas, J. M., & Garcia, J. T. (2003) estimated that 50% of individuals allergic to one kind of fish species are also allergic to a different fish species due to similarity among parvalbumins of different fish species.[6].

This paper investigates how the Human $\alpha-$Parvalbumin protein is different from its homologs from fish and non-fish species, and how that could potentially help in the insight of Parvalbumin related allergies. This topic is worth researching because fish allergy affecting a large number of people in the US and poses a serious health risk for the adults and children affected.

II. Hypothesis/Questions

The objective of this study is to research, with the help of bio-informatics tools such as Multiple Alignment Fast Fourier Transform (MAFFT) and MView, the similarities between $\alpha-$ and β-Parvalbumins among fish and non-fish species and the human $\alpha-$Parvalbumin and to see how close PRVBs proteins have to be similar across species to cause an allergic reaction.

III. Methods

A. mRNA Sequences

First, to obtain mRNA sequences from different fish and non-fish species to be compared, I used nucleotide search tool available on the National Center for Biological Information (NCBI) website which is run by the National Institute of Health (NIH), https://www.ncbi.nlm.nih.gov/. Keywords for the search parameters were Parvalbumin plus a species common or scientific name. I downloaded each mRNA sequence in the FASTA format from the NCBI website and assembled all sequences into one FASTA file. I choose 26 different species for this study.

Second, for each of the species I verified its allergenicity type, when available, on the website http://www.allergen.org. The site provides the systematic allergen nomenclature which is approved by the World Health Organization (WHO) and International Union of Immunological Societies (IUIS).

B. Multiple Sequence Alignment

I have used MAFFT web based tool to align mRNA sequences and to build phylogenetic tree, https://www.ebi.ac.uk/Tools/msa/mafft/.

Additionally, I have used MView web tool, https://www.ebi.ac.uk/Tools/msa/mview/, to calculate percent coverage and percent identity of all mRNA sequences with respect to a reference sequence. The reference sequence in this study is Human $\alpha-$PRVB.

MView defines percent coverage as:

$$\frac{\text{number of residues in row aligned with reference row}}{\text{length of ungapped reference row}} \text{x} 100$$

It also defines percent identity as:

$$\frac{\text{number of identical residues}}{\text{length of ungapped reference row over aligned region}} \text{x} 100$$

IV. Results

The summary of Parvalbumin mRNA sequences searches, including the species scientific and common names, accession codes and allergen type as specified by WHO and IUIS are presented in the Table I. It is important to point out that among non-fish species chicken and frog PRVBs are also on the list of known allergen types as specified by WHO and IUIS.

Phylogentic relation of fish and non-fish $\alpha-$ and β-PRVB is shown in the pylogenetic tree in the Fig 1. It is evident from the tree that non-fish PRVB samples are closely related variants of the human $\alpha-$PRVB and frog and fish species PRVBs are further removed on the tree from the human $\alpha-$PRVB.

TABLE I
FISH AND NON-FISH $\alpha-$ AND β-PARVALBUMINS.

Species	Common Name	Accession Code[a]	Protein	Allergen Type[b]
Homo sapiens	Human	BC096113.3	α-PRVB	none
Ovis aries	Sheep	XM_012175019.4	α-PRVB	none
Bos taurus	Cattle	FM178223.1	α-PRVB	none
Sus scrofa	Pig	FM994923.1	α-PRVB	none
Oryctolagus cuniculus	Rabbit	XM_002711409	α-PRVB	none
Gallus gallus	Chicken	FM994924.1	α-PRVB	Gal d8
Rana esculenta	Frog	AJ315959.1	α-PRVB	Ran e1
Rana esculenta	Frog	AJ414730.1	β-PRVB	Ran e1
Esox lucius	Pike	XM_010874231.3	β1-PRVB	none
Cyprinus carpio	Carp	KY784972.1	β-PRVB	Cyp c1
Salmo salar	Salmon	NM_001123717.1	β2-PRVB	Sal s1
Gadus morhua	Cod	XM_030349118.1	β1-PRVB	Gad m1
Gadus morhua	Cod	XM_030349776.1	β2-PRVB	Gad m1
Thunnus albacares	Yellowfin Tuna	FM178217.1	β1-PRVB	Thu a1
Ictalurus punctatus	Catfish	AF227795.1	β-PRVB	Pan h1
Micropterus salmoides	Largemouth Bass	FJ696957.1	β-PRVB	none
Paralichthys olivaceus	Japanese Flounder	AY953372.1	β-PRVB	none
Clupea harengus	Atlantic Herring	FM178222.1	β-PRVB	Clu h1
Lutjanus argentimaculatus	Mangrove Red Snapper	EF591789.1	β-PRVB	none
Gadus chalcogrammus	Walleye Pollock	AY035587.1	β-PRVB	none
Sebastes marinus	Ocean Perch	FM178219.1	β-PRVB	Seb m1
Oreochromis mossambicus	Mozambique Tilapia	DQ124253.1	β-PRVB	Ore m4
Xiphias gladius	Swordfish	XM_040135499.1	β-PRVB	Xip g1
Salvelinus fontinalis	Brook Trout	FM994928.1	β-PRVB	Onc m1
Epinephelus coioides	Grouper, orange-spotted	FJ426133.1	β-PRVB	none
Rastrelliger kanagurta	Indian Mackerel	KX527884.1	β-PRVB	Ras k1

[a]mRNA.
[b]as registered with WHO.

Visualization of the percent coverage as determined by MView Sequences alignment of fish and non-fish $\alpha-$ and β-PRVB is attached as a supplemental material file mview_alligment.html.

Percentage identity for $\alpha-$ and β-PRVB for all species was ordered by the similarity to the human α-PRVB sequence (Table II). In addition, percent identity of all species to the Cod β1-PRVB is also presented in the Table II. I choose Cod because it has been extensively used as a model in studies of allergy to fish [5]. As can be observed from the Table II, among all fish and non-fish species, Ocean Perch β-PRVB had the least similarity (57.8%) to the Human $\alpha-$PRVB. Chicken and Frog α-PRVBs had the least similarity (74.77 and 68.47%) with the Human $\alpha-$PRVB among non-fish species.

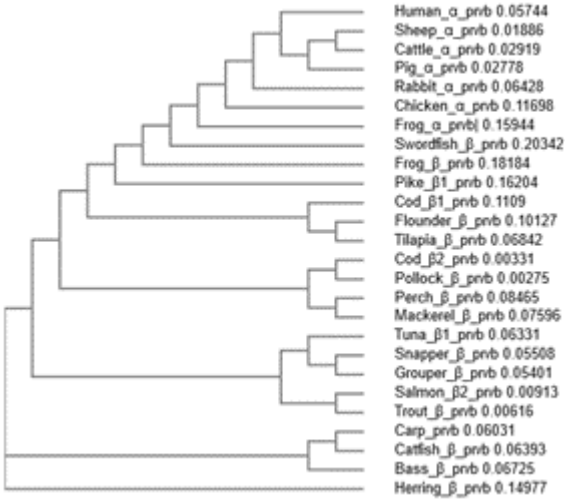

Fig. 1. Phylogenetic Tree.

V. DISCUSSION

With the help of bio-informatics tools such as MAFFT and MView, I analyzed the mRNA sequences of $\alpha-$ and β-Parvalbumins among fish and non-fish species and the Human $\alpha-$Parvalbumin. The results show that PRVB proteins with sequences identities less than 86.79% (the protein identity of Rabbit $\alpha-$PRVB to Human one) exhibit or have the potential to exhibit allergenicity (abnormal immune response) in humans, Tables I and II. Chicken and Frog PRVBs are on the list of known allergen types as specified by WHO and IUIS, and also show 74.77 and 68.47% similarity to the Human $\alpha-$Parvalbumin. Additionally, as can be seen in the pylogenetic tree in the Fig 1, chicken and frog $\alpha-$PRVBs are are further removed on the tree from the human $\alpha-$PRVB than all other non-fish species investigated in this study. Thus, while it is rare to have an allergy to chicken and frog $\alpha-$PRVBs, they still have the potential to cause an allergic reaction in highly sensitive individuals [3].

For all the fish species evaluated in this study, similarity to the Human $\alpha-$Parvalbumin varies between 64.85 to 57.58%. Most of the fish studied are also on the list of known allergen types as specified by WHO and IUIS, Tables I and II. In addition, fish species $\beta-$PRVBs are further removed on the pylogenetic tree from the human $\alpha-$PRVB than non-fish species 1.

Considering the results of this study, the strong cross-reactivity exhibited by the fish species and low degree of similarity between fish and human PRVBs, it is reasonable

TABLE II
PERCENT IDENTITY FOR $\alpha-$ AND β-PARVALBUMINS.

Common Name	Protein	Percent Identity, Human α-PRVB	Percent Identity, Cod β1-PRVB
Human	α-PRVB	100	59.70
Sheep	α-PRVB	89.79	61.52
Pig	α-PRVB	89.49	61.21
Cattle	α-PRVB	86.79	60.30
Rabbit	α-PRVB	86.79	60.91
Chicken	α-PRVB	74.77	61.52
Frog	α-PRVB	68.47	63.64
Carp	β-PRVB	64.85	73.94
Largemouth Bass	β-PRVB	64.24	76.06
Mozambique Tilapia	β-PRVB	63.94	78.79
Catfish	β-PRVB	63.64	75.76
Salmon	β2-PRVB	63.61	76.15
Brook Trout	β-PRVB	63.30	75.84
Grouper, orange-spotted	β-PRVB	62.42	73.64
Yellowfin Tuna	β1-PRVB	62.12	77.27
Mangrove Red Snapper	β-PRVB	61.52	71.21
Frog	β-PRVB	61.12	65.15
Atlantic Herring	β-PRVB	60.91	66.06
Japanese Flounder	β-PRVB	60.00	76.36
Walleye Pollock	β-PRVB	60.00	73.33
Cod	β1-PRVB	59.70	100
Cod	β2-PRVB	59.70	73.33
Pike	β1-PRVB	59.39	69.09
Swordfish	β-PRVB	58.56	60.61
Indian Mackerel	β-PRVB	57.88	74.85
Ocean Perch	β-PRVB	57.58	73.33

to conclude that individuals known to have allergy to one or more type of fish, should avoid all fin fish species.

In the feature studies, it would be interesting to take a closer look at the protein structure of the different PRVBs analysed in this study to see how this can contribute to the better understanding of the PRVBs allergenic potential across different species.

VI. REFERENCES

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