Review

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Does Localisation of BPIFB4 Support Its Proposed Function in Extending Healthy Longevity?

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Abstract

In 2015 a polymorphic variant of *Bactericidal/permeability-increasing protein (BPI) Fold containing Family B Member 4* (*BPIFB4*) was genetically associated with longevity. Following on from this intriguing observation, a literature has developed that suggests that this poorly characterised secreted protein, plays a pleiotropic role in maintaining human health and extending lifespan. In this article we briefly review what is known about BPIFB4 and discuss how its sites of expression may impact on these proposed functions.

Keywords: BPIFB4; longevity; health lifespan; gene expression; protein localisation; olfactory epithelium; nasal

Perspectives

Genetics play a clear role in determination of lifespan and understanding the genetic components of healthy longevity will be important in improving quality of life and combating chronic diseases.

Variations in *BPIFB4*, a gene initially identified in the nasal cavity, have been associated with longevity and a number of studies have implicated the secreted protein with functions that may contribute to healthy longevity.

We review the distribution of mammalian BPIFB4 and propose that its restricted distribution may not allow this protein to perform the pleiotropic roles that have recently been ascribed to it. Instead we believe that the true function of BPIFB4 will reside in the nasal cavity and remains unresolved.

Introduction

BPIFB4 is a member of the BPI/LBP/PLUNC family of secreted proteins [1,2]. Members of the family contain either one, (BPIFAn), or two (BPIFBn) structural domains that were first identified in BPI and Lipopolysaccharide binding protein (LBP), key host defence lipid transfer proteins. Similar domains are also found in cholesteryl ester transfer protein (CETP) and phospholipid transfer protein (PLTP). These domains form a twisted, anti-parallel beta-sheet barrel that has the ability to bind lipids. Subsequently the BPI fold containing proteins were assigned to the larger Tubular Lipid Binding Protein (TULIP) family [3]. Although the functions of BPI, LBP, CETP and PLTP are well recognised, the function of members of the BPIF branch of the protein family remains unclear, despite the original suggestion that they function in host defence [1].

The BPIF protein family has been described in the past three decades, with members of the family predominantly being found in the respiratory, nasopharyngeal, and oral epitheliums [4]. *BPIF* genes are rapidly evolving and are highly divergent between species. Human *BPIF* genes are located on a gene locus on chromosome 20q11, and comprise eight functional genes along with four pseudogenes (Figure 1A). The mouse locus on chromosome 2 contains thirteen functional members

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and a single pseudogene. All mammals have single loci containing differing numbers of genes with the greatest diversity being seen in the *BPIFA* subfamily [5].

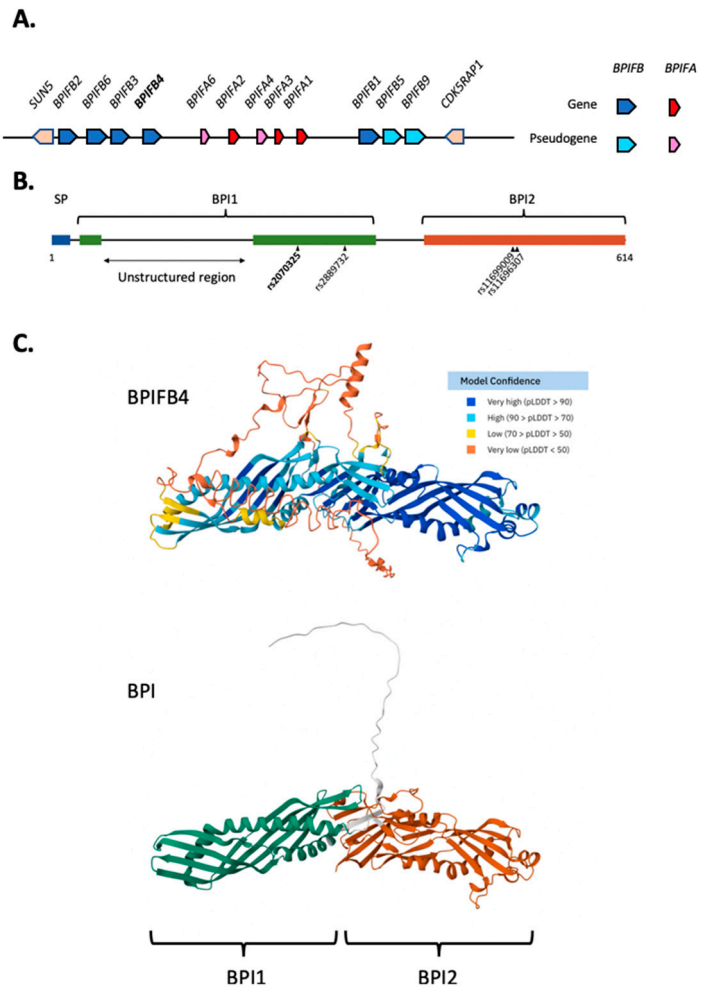

Figure 1. Genomic context, domain organisation and structure of BPIFB4. Organisation of the human *BPIF* gene locus showing the position of *BPIFB4*. *BPIFB* genes are in blue (pseudogenes are in turquoise) and *BPIFA* genes are in red (pseudogenes are pink). **A.** Schematic representation of human BPIFB4 protein. The position of the BPI1 (green) and BPI2 (red) domains are shown along with the position of the polymorphic variants seen in LAV-BPIFB4. The insertion of the unstructured region is shown in the BPI1 domain. **B**. The structure of human BPIFB4 from alphafold (https://alphafold.ebi.ac.uk/entry/AF-P59827-F1) is presented above that of human BPI (https://alphafold.ebi.ac.uk/entry/AF-P17213-F1). The unstructured region is predicted with very low confidence. The two domains of BPI are shown in different colours. **C.**

BPIFs generally show low protein homology between both orthologs and paralogs, with for example, human and mouse BPIFB1 having around 50% identity [6]. However, BPIFs maintain a conserved intron/exon structure and similar protein length. *BPIFA*s generally have 8-9 exons and encode proteins between 220-270 amino acids whereas *BPIFBs* generally have 15-16 exons and encode proteins between 450-500 amino acids in length. The shorter BPIF proteins are homologous to the N-terminal BPI (BPI1) domain, whilst the BPIFB proteins are homologous to both the N- and C-terminal BPI (BPI2) domains [6]. It has been suggested that a loss of the C-terminal domain of a *BPIFB* gene gave rise to the *BPIFA* gene branch early in mammalian evolution [6]. The "complete" BPIF family (composed of *BPIFA* and *BPIFB* genes) is found in placental mammals, whereas some *BPIFB* genes (including *BPIFB4*) are found in birds and amphibians [7,8].

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Background on BPIFB4

BPIFB4 (as *Ry2g5*) was initially identified by subtractive hybridization of genes highly-expressed in rat olfactory mucosa and *in situ* hybridization showed that the gene was localised to the Bowman's glands [9]. It was later shown that *BPIFB4* was expressed in human nasal mucosa [1], and murine olfactory epithelium (OE) [10]. Consistent with this localised expression, BPIFB4 has been identified in olfactory cleft mucus [11]. *BPIFB4* exhibits some significant differences in both sequence conservation and genomic organisation when compared to other *BPIFB* genes. Principally, the gene includes two exons towards the 5' end that are significantly different to those of other family members. One is much shorter than that seen in the other *BPIF* genes and there is also the inclusion of large exon (508bp in the human gene) that encodes a peptide sequence that is unique to BPIFB4 (Figure 1B), resulting in the production of a protein that is 614 amino acids long. This sequence is inserted into the BPI1 domain and is predicted to form unstructured loops that are outside of the well-defined BPIF structural fold [6] (Figure 1C). The functional significance of this difference remains unclear. The other striking difference between BPIFB4 and other BPIFB proteins is the very high level of sequence similarity between orthologs. For example, the pairwise identity between human and mouse proteins is 85% with the highest level of similarity seen in the BPI1 domain. These two observations identify BPIFB4 as being somewhat different to other BPIF family members.

A Role for BPIFB4 in Longevity and Human Health?

BPIFB4 was essentially unstudied until a paper was published in 2015 suggesting that the protein may function to regulate longevity [12]. This suggestion arose following the validation of a common non-synonymous polymorphic variant in *BPIFB4* (rs20700325, V268I), identified in a genome wide association study in long lived individuals (LLIs) in Italy, as being associated with longevity in two independent cohorts from Germany and the USA [12]. This SNP, located the N-terminal BPI1 domain was associated with three additional common non-synonymous variants (rs2889732, T320N; rs11699009, F527L and rs11696307, T533I) (Figure 1B) and generates a haplotype that the authors called a longevity associated variant (LAV). These SNPs have not been identified in other cohort studies,[13]. In the original paper the authors provide some biochemical evidence from *in vivo* and *in vitro* studies, for the action of the LAV in modulating endothelial function and angiogenesis [12]. The same group reported that serum BPIFB4 levels were elevated in LLIs and could be used to stratify their health status [14]. Since that time a literature has developed that appears to suggest that BPIFB4 plays a pleiotropic role in regulating human cardiovascular health, frailty and longevity (reviewed by Montella et al 2021 [15]). Some of this has focused on therapeutic effects of LAV-BPIFB4, with the hypothesis that gene therapy of the LAV could promote longevity. For example, overexpression of LAV was shown to prevent progression of frailty in old mice [16], prevents type 2 diabetes complications in mice [17], and protects against cardiac ischaemia in mice [18]. Endogenous BPIFB4 staining has also been shown to be reduced in tissue from ischemic heart failure compared to non-diseased tissue [19]. In addition, it has also been shown to be protective in a mouse model of Huntington's disease [20]. Studies have also linked BPIFB4 with Chronic Obstructive Pulmonary Disease (COPD) [21,22] and nonsteroidal anti-inflammatory drug (NSAID)-induced enteropathy [23]. High circulating levels of BPIFB4 in LLIs may be associated with an anti-inflammatory myeloid cell profile [24]. The majority of this data has been published by a related research group

Although this and other data is intriguing perhaps it is important to revisit what is known about the localisation of BPIFB4 to see if there is a rational basis for these suggested roles in the maintenance of wellbeing.

Simply put, does localisation of BPIFB4 support a potential role in longevity and lifespan?

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Expression and Localisation of BPIFB4

As outlined above *Bpifb4*, was identified as being differentially expressed in rat OE [9] and was subsequently shown to be expressed in the human and mouse nasal mucosa [1,10]. The protein was also identified in human nasal cleft mucus by proteomics [11] but has not been localised in these regions at the protein level. Unbiased transcriptional analysis of human OE showed that *BPIFB4*, as well as *BPIFB3* and *BPIFB6* were amongst the most tissue enriched and highly expressed genes when compared against 17 other tissues, including blood and heart [25]. A second transcriptional study showed that *BPIFB4* was the second most highly expressed transcript in human OE and very highly expressed in the OE of multiple additional species, including macaques, dogs, rats and mice [26]. Although this data confirms that *BPIFB4* is highly expressed in the nose, the olfactory regions are not well studied compared with most other tissues and so direct comparisons of expression levels between tissues cannot easily be made. For example, the Human Protein Atlas (HPA) [27] contains no olfactory tissues. The same is true for single cell RNA sequencing (scRNAseq) data in the Chan Zuckerberg CELLxGENE data repository [28] which contains no specific data from the human OE. However, these databases do enable assessment of *BPIFB4* expression in a very wide range of other tissues.

So Where Is BPIFB4 Expressed in This Data?

In bulk RNAseq data in the HPA, *BPIFB4* is shown to be expressed at low levels in pituitary (8.2 normalised transcripts per million (nTPM)) and <1 nTPM in parathyroid, choroid plexus, salivary gland, testes, heart muscle, and adipose tissue. scRNAseq data in the HPA show low expression of BPIFB4 in oocytes (3.7 nTPM) and respiratory epithelial cells (<2.6 nTPM) but three distinct sets in the HPA show no expression of BPIFB4 in immune cells.

scRNAseq and single nuclei (sn)RNAseq offers unparalleled power to detect gene expression in individual cells and have transformed our understanding to tissue and cell-type specific gene expression. CELLxGENE contains expression data from over 90 million single cells from over 60 tissues and represents the largest repository of scRNAseq data [28]. If BPIFB4 is abundantly expressed in tissue/cell types represented in the data sets then this should be clear to see.

In CELLxGENE, there is very little evidence of BPIFB4 being expressed above background levels. In cells where BPIFB4 has been suggested by the recent literature to be functional/expressed, less than 0.02% of cells express the gene (Table 1). In the vasculature BPIFB4 is expressed in 3 of 349,303 cells, in endothelial cells 284 of >1.9 million cells are positive and in heart tissue, which has been suggested to contain abundant levels of BPIFB4 [17,19], 701 of >2.4 million cells express the gene. Less than 0.004% of total leukocytes are positive and even when these are broken down into distinct cell lineages no specific leukocyte cell population is shown to express the gene. In nose tissue (which may contain some OE) 0.1% of total cells are positive. When numbers of cells expressing a gene are so low in this type of data, it is difficult to be confident that the gene is truly expressed. It remains a formal possibility that *BPIFB4* expression is both context and disease responsive and conditions that induce expression of the gene are not captured in these databases. However, the gene has not been noted to be differentially expressed in experimental studies, for example it was not found to be differentially expressed in scRNAseq data from individuals with heart failure [29].

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Table 1. BPIFB4 positive cell numbers in selected single cell populations. BPIFB4 positivity data was extracted from selected cells/tissues in the Gene Expression application of CellXGene. https://cellxgene.cziscience.com/gene-expression.

Tissue	Total cells	Positive cells	% $^{+}$ve cells
Vasculature	349,303	3	0.00057
Heart	2,467,698	701	0.003
Endothelial cells	1,902,491	284	0.015
Leukocytes	9,768,207	399	0.004
Lung	3,843,366	664	0.017
Nose	311,828	326	0.105

Although CELLxGENE contains no OE tissues, a number of scRNAseq data sets have been generated from nasal and olfactory tissue that show *BPIFB4* expression. In data from cells isolated from the human olfactory cleft, *BPIFB4* is enriched in Bowman's gland cells [30]. *Bpifb4* is also highly enriched in Bowman's gland ductular cells from the mouse OE [31]. More recently snRNAseq data from porcine OE also identified *BPIFB4* in Bowman's gland cells [32]. This data is all consistent with the first paper describing localisation of rat *Bpifb4* [9].

At the protein level, the HPA does not display any localisation data for BPIFB4 and there are no robustly validated commercial antibodies for the protein. BPIFB4 contains a signal peptide (Figure 1B) and is predicted to be secreted. Does the protein, at approximately 65kDa enter the circulation? Although BPIFB4 has been reported in serum, with levels determined by ELISA [14], it is only found in one of 158 data sets in the human plasma peptide atlas [33]. It is also not present in heart, blood vessel or blood cell data sets in the Peptide Atlas [34], which shows only 20 of >800 studies contain BPIFB4 (Figure 2). Proteomics studies have shown however, that BPIFB4 is present in human nasal tissue [35,36], nasal cleft mucus [11,37], and nasal lavage [38]. It has also been identified in nasal secretions in mice [39]. So, available proteomic data also supports the view that BPIFB4 is predominantly found in the nasal/olfactory regions.

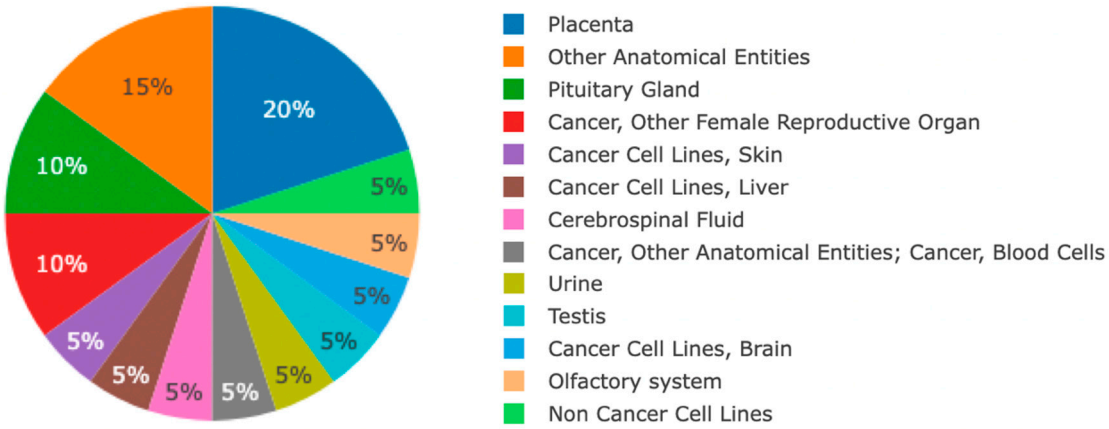

Figure 2. Distribution of BPIFB4 in data sets represented in the Human Peptide Atlas. BPIFB4 (P59827) is present in 20 of 837 data sets in the 2025-1 build of the Human Peptide Atlas. https://peptideatlas.org/builds/human/.

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Closing Thoughts

Although some population studies have demonstrated that there is a correlation between LAV-BPIFB4 and longevity and there is an emerging literature suggesting that BPIFB4 plays a role in maintaining health, it remains unclear if the protein is expressed in the appropriate places to function in this manner. Objective analysis of existing data supports the contention that BPIFB4 is highly expressed in the nasal and OE and is not highly expressed in the vasculature, the heart and in leucocytes. Even though absence of evidence is not evidence of absence, it seems unlikely that BPIFB4 is highly expressed or localised in these tissues and therefore it calls into question some of the proposed functional roles of BPIFB4. We believe that the true function of BPIFB4 remains to be identified but will likely be associated with the OE. This will require further study.

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Data Availability Statement: Peptide Atlas: https://peptideatlas.org/. The Human Protein Atlas: https://www.proteinatlas.org/. CellXGene, Gene Expression application: https://cellxgene.cziscience.com/gene-expression

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Conflict of Interest: The authors report no conflicts of interest

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