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Article

Network Protein Interaction in Parkinson's Disease and Periodontitis Interplay: A Preliminary Bioinformatic Analysis

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Abstract: Recent studies supported a clinical association between Parkinson's Disease (PD) and periodontitis. Hence, investigating possible protein interactions between these two conditions is of interest. In this study, we conducted a protein-protein network interaction analysis with recognized genes encoding proteins for PD and periodontitis. Genes of interest were collected via GWAS database. Then, we conducted a protein interaction analysis using STRING database, with a highest confidence cut-off of 0.9. Our protein network cast a comprehensive analysis of potential protein-protein interactions between PD and periodontitis. This analysis may underpin valuable information for new candidate molecular mechanisms between PD and periodontitis and may serve new potential targets for research purposes. These results should be carefully interpreted giving the limitations of this approach.

Keywords: Parkinson's disease; Periodontitis; Periodontal disease; protein-protein network interaction; Bioinformatics

1. Introduction

Parkinson's disease (PD) is the second most frequent neurodegenerative condition, affecting primarily the central nervous system [1]. PD is clinically characterized by motor and non-motor symptoms, though its clinical onset and progression differ [2], and ultimately lead to disability and poor quality of life [3]. PD is age-dependent and is more prevalent in men [4,5]. Despite its cause is still unknown, a recent mendelian randomization research reported 12 exposures and risk of PD [6]. Further, the role of inflammation in PD has been widely investigated [7,8].

Periodontitis is a chronic dysbiotic and inflammatory disease of the periodontium and one of the most prevalent worldwide [9,10]. This condition presents inflamed gum and alveolar bone loss surrounding the teeth and may cause their loss [11]. Periodontitis has been highly associated with several systemic conditions, for instance diabetes [12], cardiovascular diseases [13,14], fertility-related conditions [15,16], rheumatic [17] or Alzheimer's Disease [18–20]. In most of these diseases, periodontitis shapes its influence through its chronic inflammatory burden and systemic bacteria spread.

The interplay between PD and periodontitis is still scarce, but a number of studies have revealed that the associated motor impairments and cognitive decline may hamper oral hygiene and deteriorate oral health [21,22]. Moreover, PD individuals seem to be at high risk of developing periodontitis [23–27], and this may lead to systemic leukocytosis [28]. Also, a nationwide study

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concluded that people with periodontitis were at more risk to develop PD [29], and one of the possible reasons may be genetic interactions, thus investigating such genetic relation would be of great research interest.

Studying possible biological mechanisms between these two diseases could be fruitful towards unexplored ways, and therefore bioinformatics is an appealing resource. In this sense, open-source genomic databases are important for the development of genetic discoveries, and possibly implementation of clinical decision thinking. For instance, protein-protein interaction (PPI) networks have been used to identify genes that are significant in the context of such associations [30–36].

To this end, we aimed to develop a PPI network between known genes of PD and periodontitis to identify potential biological mechanisms of interaction. Further, we tested the Blood-Brain Barrier permeability of proteins derived from the developed PPI network to investigate the possibility of moving into the brain.

2. Materials and Methods

2.1. Data Source

We searched The National Human Genome Research Institute-European Bioinformatics Institute Catalog of human Genome-Wide Association Studies (NHGRI-GWAS) [37]. This a comprehensive catalogue of reported associations from published Genome-Wide Association Studies (GWAS). We used a publicly available summary statistics dataset from periodontitis GWAS performed in up to 100,903 individuals of European, Asian, American and other ancestries [38–50] (Appendix S1).

For Parkinson's Disease, we used summary statistics dataset from periodontitis GWAS performed in up to 1,640,901 individuals of European, Asian, American, Subsarian African and other ancestries [51–88] (Appendix S2). GWAS data sets for both PD and periodontitis were derived from different populations as there are no GWAS data combining both conditions.

2.2. Protein-Protein Interaction Networks Functional Enrichment Analysis

The STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) database, complemented with heuristic methods of association and analysis, was used to investigate known and predicted PPI association for both PD and Periodontitis. The STRING database generates a network of PPI from high-throughput experimental data, literature, and predictions based on genomic context analysis [89,90]. The interactions in STRING are sourced from five main sources: Genomic Context Predictions, High-throughput Lab Experiments, (Conserved) Co-Expression, Automated Textmining and Previous Knowledge in Databases. Protein characteristics were obtained through the Universal Protein Resource [91].

2.3. Blood-Brain Barrier Permeability Analysis

Blood-Brain barrier permeability was predicted through the protein characteristics presented in the Protein Atlas Database [92]. Protein information (length, mass, prediction as a signal peptide, prediction as transmembrane protein) as well RNA expression within brain tissues allowed to foresee the possibility of passing.

2.4. Data management, test methods and analysis

Data was uploaded through GWAS website and handled with Microsoft Office Excel. PPI network was rendered via STRING database version 10.5 We set the highest confidence cut-off in this interaction analysis (of 0.9). In the resulting PPI network, proteins are presented as nodes which are connected by lines whose thickness represents this confidence level.

3. Results

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3.1. Protein-Protein Interaction Analysis

Using the STRING online tool, we found 100 nodes with 66 PPI relationships (Figure 1). The properties of the network were analysed, indicating that the network of PPIs had more interactions among themselves than what would be expected for a random set of proteins of similar size, drawn from the genome. Such an enrichment indicates that the proteins are, at least, partially biologically connected (p-value = 1.89e-05). From an expected number of 14 edges, it was cast a final number of 33 edges (average node degree = 0.66; average local clustering coefficient = 0.27).

Interestingly, we found possible PPIs between PD and periodontitis known associated genes (Figure 1, Table 1). The least likely association is between DLG2 and NLGN1 (Score = 0.966), as DLG2 is a common gene for both conditions. The remaining interactions were as follows: THSD4 and SEMA5A; ACTN1 and ACTN2 with FAM49B and TPM1; SMURF2 was establishing a connection between PARK2 and PSMA8; multiple interactions of IGF2R with HIP1R, GAK, SF3GL2 and AAK1; HLA-DOA with HLA-DRA. Further, we detail the physiological characteristics and localization of each interaction protein (Table 2).

Table 1. Score results between PD and periodontitis genes identified in the network interaction.

Genes for PD	Genes for Periodontitis	Score
TPM1	ACTN2	0.995
DLG2	NLGN1	0.966
TPM1	ACTN1	0.961
APOE	ABCA1	0.921
HLA-DRA	HLD-DOA	0.918
NSF	IGF2R	0.917
HIP1R	IGF2R	0.916
GAK	IGF2R	0.916
SH3GL2	IGF2R	0.907
PARK2	SMURF2	0.906
AAK1	IGF2R	0.903
SEMA5A	THSD4	0.902
FAM49B	ACTN1	0.901
FAM49B	ACTN2	0.901

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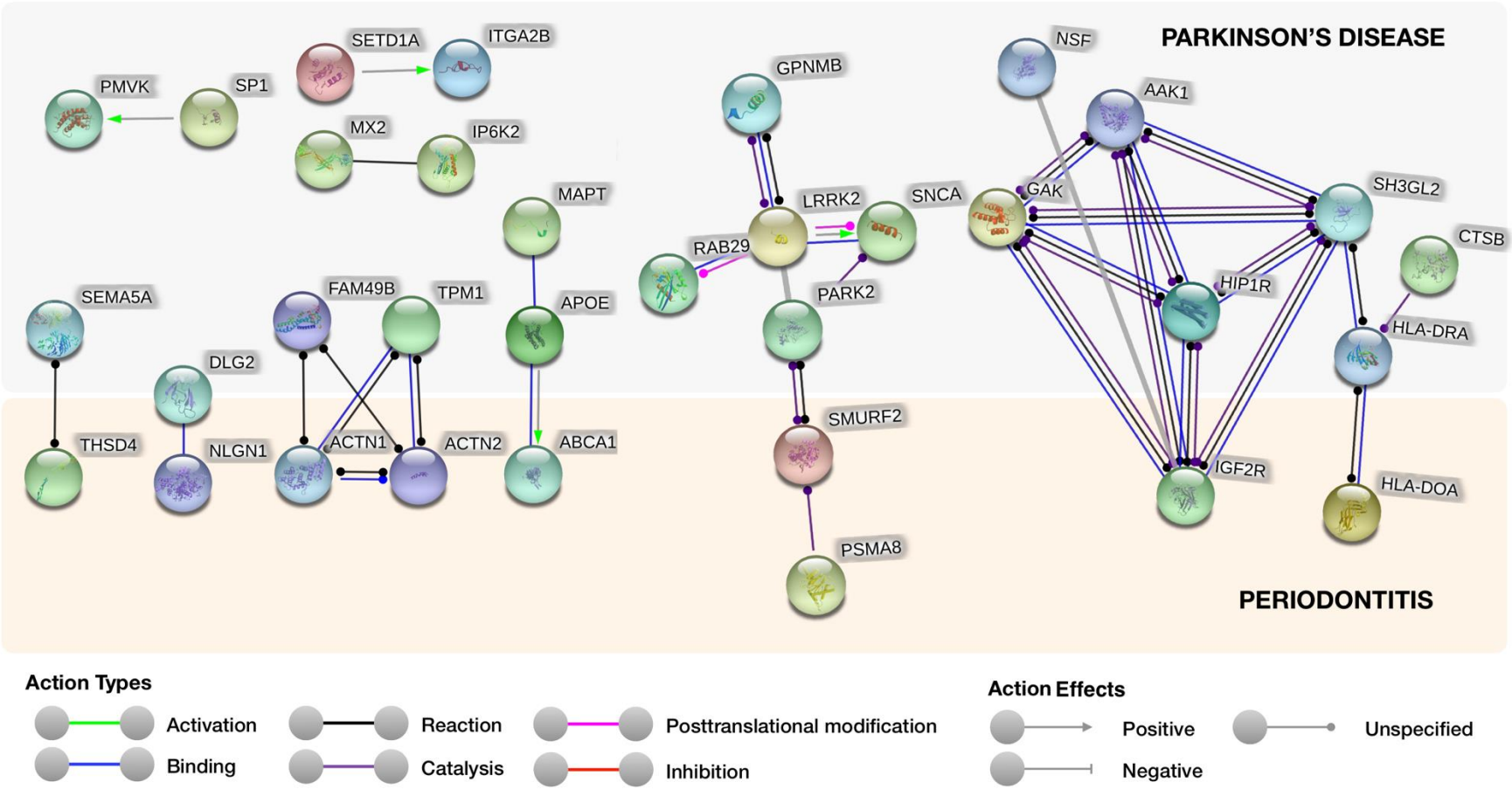

Figure 1. STRING analysis reveals protein interaction networks between Parkinson's Disease and Periodontitis proteins. We implemented the highest confidence cut-off of 0.9 in this network. In the resulting protein association network, proteins are presented as nodes which are connected by lines whose thickness represents the confidence level (0.9).

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Table 2. Details of the identified genes in the interaction between PD and periodontitis.

Gene Symbol	Name	Description	Localization
		Parkinson's Disease	
SEMA5A	Semaphorin-5A	Bifunctional axonal guidance cue regulated by sulphated proteoglycans; attractive effects result from interactions with heparan sulphated proteoglycans (HSPGs), while the inhibitory effects depend on interactions with chondroitin sulphated proteoglycans (CSPGs) (By similarity). Ligand for receptor PLXNB3. In glioma cells, SEMA5A stimulation of PLXNB3 results in the disassembly of F-actin stress fibers, disruption of focal adhesions and cellular collapse as well as inhibition of cell migration and invasion through ARHGDIA-mediated inactivation of RAC1.	- Plasma membrane - Extracellular exosome
FAM49B	Protein FAM49B	Family with sequence similarity 49 member B	- Mitochondrion
TPM1	Tropomyosin alpha-1 chain	Tropomyosin 1	- Cytoskeleton
APOE	Apolipoprotein E	Mediates the binding, internalization, and catabolism of lipoprotein particles. It can serve as a ligand for the LDL (apo B/E) receptor and for the specific apo-E receptor (chylomicron remnant) of hepatic tissues; Apolipoproteins	- Extracellular region or secreted
PARK2	E3 ubiquitin-protein ligase parkin	Functions within a multiprotein E3 ubiquitin ligase complex, catalyzing the covalent attachment of ubiquitin moieties onto substrate proteins. Mediates monoubiquitination as well as 'Lys-6', 'Lys-11', 'Lys-48'-linked and 'Lys-63'-linked polyubiquitination of substrates depending on the context.	- Mitochondrion - Nucleus - Cytosol - Endoplasmic reticulum
HIP1R	Huntingtin-interacting protein 1-related protein	Component of clathrin-coated pits and vesicles, that may link the endocytic machinery to the actin cytoskeleton. Binds 3-phosphoinositides (via ENTH domain). May act through the ENTH domain to promote cell survival by stabilizing receptor tyrosine kinases following ligand-induced endocytosis	- Perinuclear region - Endomembrane system - Clathrin-coated vesicle membrane
GAK	Cyclin-G-associated kinase	Associates with cyclin G and CDK5. Seems to act as an auxilin homolog that is involved in the uncoating of clathrin-coated vesicles by Hsc70 in non-neuronal cells. Expression oscillates slightly during the cell cycle, peaking at G1; Belongs to the protein kinase superfamily. Ser/Thr protein kinase family	- Golgi apparatus - Perinuclear region - Focal adhesion
AAK1	AP2-associated protein kinase 1	Regulates clathrin-mediated endocytosis by phosphorylating the AP2M1/mu2 subunit of the adaptor protein complex 2 (AP-2) which ensures high affinity binding of AP-2 to cargo membrane proteins during the initial stages of endocytosis. Isoform 1 and isoform 2 display similar levels of kinase activity towards AP2M1. Regulates phosphorylation of other AP-2 subunits as well as AP-2 localization and AP-2-mediated internalization of ligand complexes. Phosphorylates NUMB and regulates its cellular localization, promoting NUMB localization to endosomes.	- Plasma membrane - Clathrin-coated pit - Presynapse

SH3GL2	Endophilin-A1	Implicated in synaptic vesicle endocytosis. May recruit other proteins to membranes with high curvature. Required for BDNF-dependent dendrite outgrowth. Cooperates with SH3GL2 to mediate BDNF-NTRK2 early endocytic trafficking and signalling from early endosomes; N-BAR domain containing	- Endosome - Cytoplasm - Membrane - Presynapse
CTSB	Cathepsin B	Thiol protease which is believed to participate in intracellular degradation and turnover of proteins. Has also been implicated in tumour invasion and metastasis;	- Lysosome - Plasma Membrane - Extracellular region
HLA-DRA	HLA class II histocompatibility antigen, DR alpha chain	Binds peptides derived from antigens that access the endocytic route of antigen presenting cells (APC) and presents them on the cell surface for recognition by the CD4 T-cells. The peptide binding cleft accommodates peptides of 10-30 residues. The peptides presented by MHC class II molecules are generated mostly by degradation of proteins that access the endocytic route, where they are processed by lysosomal proteases and other hydrolases. Exogenous antigens that have been endocytosed by the APC are thus readily available for pre [...]	- Golgi apparatus - Lysosome - Plasma membrane - Endoplasmic reticulum - Endosome
NSF	Vesicle-fusing ATPase	Required for vesicle-mediated transport. Catalyses the fusion of transport vesicles within the Golgi cisternae. Is also required for transport from the endoplasmic reticulum to the Golgi stack. Seems to function as a fusion protein required for the delivery of cargo proteins to all compartments of the Golgi stack independent of vesicle origin. Interaction with AMPAR subunit GRIA2 leads to influence GRIA2 membrane cycling (By similarity); Belongs to the AAA ATPase family	- Cytoplasm
		Periodontitis	
THSD4	Thrombospondin type-1 domain-containing protein 4	Promotes FBN1 matrix assembly. Attenuates TGFB signalling, possibly by accelerating the sequestration of large latent complexes of TGFB or active TGFB by FBN1 microfibril assembly, thereby negatively regulating the expression of TGFB regulatory targets, such as POSTN (By similarity)	- Extracellular Matrix
NLGN1	Neuroligin-1	Cell surface protein involved in cell-cell-interactions via its interactions with neurexin family members. Plays a role in synapse function and synaptic signal transmission, and probably mediates its effects by recruiting and clustering other synaptic proteins. May promote the initial formation of synapses, but is not essential for this. In vitro, triggers the de novo formation of presynaptic structures. May be involved in specification of excitatory synapses.	- Extracellular Region - Plasma membrane - Post-synaptic density
ACTN1	Alpha-actinin-1	F-actin cross-linking protein which is thought to anchor actin to a variety of intracellular structures. This is a bundling protein; Belongs to the alpha-actinin family	- Plasma membrane - Cytoskeleton
ACTN2	Alpha-actinin-2	F-actin cross-linking protein which is thought to anchor actin to a variety of intracellular structures. This is a bundling protein; Actinins	- Z line

ABCA1	ATP-binding cassette sub-family A member 1	cAMP-dependent and sulfonylurea-sensitive anion transporter. Key gatekeeper influencing intracellular cholesterol transport; Belongs to the ABC transporter superfamily. ABCA family	- Endosome - Plasma Membrane - Membrane
SMURF2	E3 ubiquitin-protein ligase SMURF2	E3 ubiquitin-protein ligase which accepts ubiquitin from an E2 ubiquitin-conjugating enzyme in the form of a thioester and then directly transfers the ubiquitin to targeted substrates. Interacts with SMAD1 and SMAD7 in order to trigger their ubiquitination and proteasome-dependent degradation. In addition, interaction with SMAD7 activates autocatalytic degradation, which is prevented by interaction with SCYE1. Forms a stable complex with the TGF-beta receptor-mediated phosphorylated SMAD2 and SMAD3.	- Plasma Membrane - Nucleus - Cytoplasm - Membrane Raft
IGF2R	Cation-independent mannose-6-phosphate receptor	Transport of phosphorylated lysosomal enzymes from the Golgi complex and the cell surface to lysosomes. Lysosomal enzymes bearing phosphomannosyl residues bind specifically to mannose-6-phosphate receptors in the Golgi apparatus and the resulting receptor-ligand complex is transported to an acidic prelysosomal compartment where the low pH mediates the dissociation of the complex. This receptor also binds IGF2. Acts as a positive regulator of T-cell coactivation, by binding DPP4; CD molecules	- Lysosome
HLA-DOA	HLA class II histocompatibility antigen, DO alpha chain	Important modulator in the HLA class II restricted antigen presentation pathway by interaction with the HLA-DM molecule in B-cells. Modifies peptide exchange activity of HLA-DM; C1-set domain containing	- Lysosome - Endosome
		Parkinson's Disease and Periodontitis	
DLG2	Disks large homolog 2	Required for perception of chronic pain through NMDA receptor signalling. Regulates surface expression of NMDA receptors in dorsal horn neurons of the spinal cord. Interacts with the cytoplasmic tail of NMDA receptor subunits as well as inward rectifying potassium channels. Involved in regulation of synaptic stability at cholinergic synapses. Part of the postsynaptic protein scaffold of excitatory synapses (By similarity); Membrane associated guanylate kinases	- Plasma membrane Other locations: - Postsynaptic density - Synapse - Axon - Perikaryon

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3.2. Hydrophobicity levels of proteins of interest

Thrombospondin type 1 domain containing 4 (THSD4) as an extracellular matrix protein was deemed as a candidate to pass the blood-brain barrier. Four isoforms were reported: THSD4-201, THSD4-202, THSD4-203 and THSD4-207. The isoforms THSD4-201, THSD4-202 and THSD4-203 have no potential to pass the blood-brain barrier due to a large mass (>20 kDa). A potential candidate is the isoform THSD4-207 (10.7 kDa), however is predicted as a membrane protein. Nevertheless, RNA expression revealed significant expression of THSD4 in several brain areas, significantly related with PD, indicating that THSD4 may be produced locally rather than transported into the brain (Figure 2).

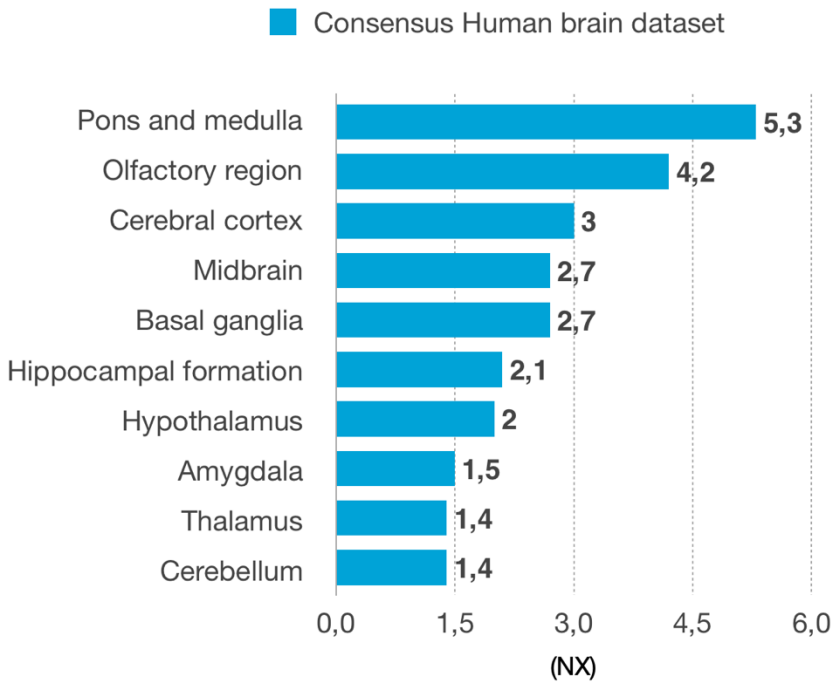

Figure 2. RNA expression of THSD4 in different brain regions according to the Consensus Human Brain Dataset.

4. Discussion

In this bioinformatic study, we predicted a potential PPI network between PD and periodontitis from catalogues of human genome-wide association studies using a bioinformatic approach. Although these PPIs require further experimental validation, they unravel new clues for downstream studies and propose biological mechanisms pathways through which these two conditions may interplay.

A strong candidate in this study is the interaction established by SMURF2, a E3 ubiquitin-protein ligase which accepts ubiquitin from an E2 ubiquitin-conjugating enzyme in the form of a thioester and then directly transfers the ubiquitin to targeted substrates [93]. According to the obtained network, SMURF2 is proposed to interact with PARK2 (E3 ubiquitin-protein ligase parkin), a protein involved in the pathway protein ubiquitination, and previously associated to pathogenic mechanisms in PD [94,95]. Emerging evidence highlighter the role of impaired ubiquitin phosphorylation-dependent mitophagy and PD pathogenesis and supports multiple potential therapeutic targets for PD drug discovery [96,97].

The proteins IGF2R and HLA-DOA also figured with potential roles in this network. IGF2R is a transport of phosphorylated lysosomal enzymes from the Golgi complex and the cell surface to

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lysosomes, and was linked to proteins located at the plasma membrane (AAK1, SH3GH2), perinuclear region (HIP1E, GAK) and others. Also, HLA-DOA, a key modulator in the HLA class II restricted antigen presentation pathway was linked to HLA-DR, that binds peptides derived from antigens that access the endocytic route). Interestingly, both IGF2R and HLA-DOA have never been investigated in periodontal medicine, though these potential interactions mainly in the lysocytic/endocytic pathways should be investigated in the interplay between PD and periodontitis.

In the same way, ABCA1, a cAMP-dependent and sulfonylurea-sensitive anion transporter present in the endosome and plasma membrane also depicted a potential link with APOE that mediates the binding, internalization, and catabolism of lipoprotein particles. A recent study showed that oxysterols increased the osteogenic activity of PDLSCs and the expression of ABCA1, increased significantly during osteogenesis [98]. Further, APOE, in particular its isoform 4, was recently proposed to increase the risk of periodontitis [99] and APOE-2 allele is associated with higher prevalence of sporadic PD [100,101]. Thus, the APOE-ABCA1 pathway might play a role in this relationship, mainly within the catabolism of triglycerides and cholesterol, highly associated with PD and periodontitis.

Additionally, THSD4 revealed a possible link with SEMA5A. THSD4 is a protein present in the extracellular region that is weakly expressed in the early stage dental follicle, but becomes readily detectable in assembled microfibril-like structures during the periodontal ligament-forming stage of the dental follicle and in organized microfibrils in the adult periodontal ligament. Also, THSD4 is up-regulated in the periodontal ligament during wound healing, for instance periodontitis lesions (Manabe et al. 2008). On the other hand, SEMA5A is involved in axonal guidance and in some conditions reduces the ability to form connections with other neurons in certain brain areas and possibly a PD preclinical marker [102–104]. Considering this possible association, we further analysed if THSD4 had the ability to pass the blood-brain barrier, though the current knowledge is that its isoforms are to large or are membrane-like proteins, however, the possibility of THSD4 transport proteins in the blood-brain barrier cannot be excluded. Still, a considerable expression of THSD4 is reported in several brain areas, particularly in the basal ganglia and midbrain, known to be PD related areas. Notwithstanding, medulla/olfactory bulbs are proposed as two starting points of PD in the brain based on Braak staging proposal [105], and they accounted for the higher accounts of THSD4 RNA. Hence, despite the areas more commonly known as PD-related (the midbrain and basal ganglia) present significant values, the reader should bear in mind that this protein of interest is present throughout the brain, all these regions are affected in PD.

The proteins ACTN1 and ACTN2, both f-actin cross-linking protein thought to anchor actin to a variety of intracellular structures, were linked with FAM49B and TPM1 present in mitochondria and cytoskeleton.

This study presents a powerful and comprehensive analysis from large outputs and large sample sizes. Nevertheless, there are some potential limitations to mention. Firstly, the number of genes represented in GWAS is always dependent on the available number of GWAS studies. Therefore, we anticipate that the increase in GWAS datasets will ultimately unveil new pathways of interaction and to disregard previous ones. Another limitation of this study is that we were unable to explore confounding factors, yet the rationale of using GWAS studies is to surpass the environment risk factors load. Despite GWAS research have revolutionized the field of complex disease genetics and have been successful in identifying novel variant–trait associations, they have limited clinical predictive value [106], though in our opinion ignoring these potentially new mechanisms would be unwise. Also, the quantity of SNPs of interest in these datasets have combined both European, Asian, African and other populations, which may limit the application of these results. Moreover, the likelihood of finding the number of interactions for each given gene/protein was not possible to clarify as there are more active genes that may have more interactions, and this should be clarified in future investigations. Despite these limitations, the sample size of this study (over 1.7 million people) makes the results compelling.

5. Conclusions

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Within the limitations of this study, our protein network cast potential protein-protein interactions between Parkinson's Disease and periodontitis. Our results may guide future studies in molecular mechanisms between Parkinson's Disease and periodontitis and may serve new potential targets for research purposes.

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