Identification of Candidate Transcription Factors that Bind to the ASCN Gene, Associated with Parkinson's Disease, Using Bioinformatics Analysis

Muna A. Abdal Rhida

Wasit University, College of Science, Department of Biology.

Abstract

Parkinson's disease (PD) is a neurodegenerative illness marked by progressive damage of dopaminergic neurons in the substantia nigra. Synuclein- α protein plays a key role in this term by aggregating in clumps of Lewy bodies causing PD. Despite unclear etiology of PD, growing indications show that PD pathogenesis is associated with gene expression dysregulation. Transcription factors (TFs) are the key players in regulating gene expression. In this study, we employed a bioinformatics tool to predict TF binding to Synuclein- α (SNCA)gene utilizing DNA sequences, epigenetic modifications, TF binding motifs, and creating machine learning algorithms. PROMO database was utilized to identify candidate TFs. Here we found TFs that act as regulators of neuronal function and dopaminergic signaling pathways, including members of the Forkhead box family, and nuclear factor-kappa B family members such as c-Jun, and STATs family. These findings provide a better understanding of the molecular mechanisms underlying PD disease and determine potential therapeutic targets.

Keywords: ASCN, Parkinson's Disease, Bioinformatics, PROMO, Transcription Factors.

1. Introduction

PD is a degenerative neurological disorder that largely impacts an individual's ability to move [1]. This disease affects millions of people globally. It is characterized

by the progressive deterioration of neurons that produce dopamine in the substantia nigra part of the brain. The symptoms of the decrease in neurons dopamine are represented by rigidity, bradykinesia, tremors, and problems with balance and synchronization due to its role in regulatory movement and coordination. Not only motor symptoms, but also non-motor symptoms might appear on the patients such as cognitive impairment, sleep problems, changes in mood, and autonomic dysfunction like fluctuations in blood pressure and gastrointestinal issues [2]. The exact reason behind PD is still ambiguous, however, it is thought to result from a combination of genetic and environmental stimuli. Some genetic mutations are linked with familial variations of the disease. However, most cases arise randomly. Some environmental factors such as exposure to toxins or pesticides might contribute to the heightened risk of emerging PD [3]. On the other hand, the neurons that produce dopamine, an important neurotransmitter for controlling movement, gradually break down in PD. The specific reason of this decline is not identified, but the presence of Lewy bodies comprising misfolded (SNCA) is a vital factor [4]. These clusters of protein restrict the regular cell processes, causing glitches in nerve cells and, eventually, the decease of the cell [5,6]. The important role of (SNCA) in PD pathology has made it a promising target for potential therapy [7]. Yet, generating effective therapies presents major obstacles.

2

Efforts to reduce (SNCA) clumping or expand its removal have been fruitful in animal studies but have not confirmed to be operative in human trials. It is also still a challenging work to target (SNCA) without interfering with its biological function. Despite these complications, researchers are still positive about the promises of advanced therapeutic strategies. Progressions in gene therapy, antibody-based treatments, and molecule inhibitors offer small new approaches for addressing (SNCA) pathology [8]. Moreover, current medicines and examining complex treatment options could enhance benefits in addressing the progress of PD [9]. Recent advancements in genomics and computational biology have encouraged investigations into the complicated molecular mechanisms underlying PD pathogenesis, with a precise focus on transcriptional regulation [10]. The dysregulation of gene expression has arisen as a dominant feature in the complex scenery of PD pathology. TFs, as master regulators of gene expression, employ accurate control over the transcriptional machinery, arranging the elaborate networks of gene regulation that support cellular function [11]. Considerate the interplay between TFs and genes implicated in PD holds noteworthy promise for unraveling the molecular details of the

disease and identifying de novo therapeutic targets. For instance, a recent study suggests that the activation of NF1 transcription by FOXA1 leads to the inhibition of the MAPK signaling pathway which eventually ameliorate neuronal damage and motor disability in PD. These results could present innovative concepts in the area of PD administration [12].

Predicting TFs binding to PD-associated genes signifies a cutting-edge tactic to decipher the regulatory architecture of PD. By utilizing genomic data, such as DNA sequences, epigenetic modifications, and TF binding motifs, predictive models can infer putative TF-gene interactions specific to PD, providing respected insights into the transcriptional dysregulation that is fundamental for disease progression. This study sets the stage for discovering the predictive TFs binding to (SNCA) gene implicated in PD, using PROMO database, highlighting its potential to reveal new regulatory mechanisms and therapeutic approaches involved in this overwhelming neurological disorder.

2. Methodology

2.1 The using of PROMO version 3.0 to predict TFs binding to (SNCA) gene.

Comprehending and modeling the gene expression regulatory networks in cells and tissues is one of the most difficult parts of genome biology. Thus, identifying transcription factor binding sites in DNA sequences precisely is a critical process. In order to anticipate binding sites in sequences, researcher can utilize existing knowledge of target sequences in gene regulatory regions to several databases store sets of known binding sites. For instance, TRANSFAC which has the most inclusive collection of DNA binding sites in eukaryotes. The active way to represent binding sites is through positional weight matrices, as they capture the frequency of nucleotides in recognition sites, considering the inherent variability in protein recognition signals. Weight matrices are designed in PROMO by using binding sites from TRANSFAC to find potential binding sites in sequences [13]. There are multiple tools available for predicting transcription binding locations with weight factor matrices. However, PROMO stands out due to its exceptional characteristics. PROMO has many options, such as choosing sites from any species or group of interest, generating matrices automatically for the selected taxonomic level, giving details on other regulated likewise, genes and comparing multiple sequences at once [14].

The initial step in RPOMO database involves selecting the species or taxonomic level for both factors and binding sites. This step is made possible with the aid of a Java applet that can be available from the main menu under 'SelectSpecies'. In this study, human species was selected and then the matrices were created dynamically which was afterword by utilizing examined the 'ViewMatrices' function as shown in figure 3, A-D. The Homo sapiens (SNCA) RefSeqGene sequence was retrieved from NCBI (Reference Sequence: NG 011851.1), then, this sequence was typed in the 'SearchSites' form page as shown in figure 2. The query sequence was examined for regions that closely resemble the matrices [15]. In order to speed up the search, automata were used to cover every potential subsequences from the query sequence that meet or exceed the similarity threshold to any of the matrices figure 3. The outcome included a graphical depiction of the anticipated binding sites, projected values for evaluating the importance of the matches, and genes list that were recognized to be controlled by the TFs identified in the predictions. These genes were shown separately or in combination. Data from other genes are extremely advantageous, as detecting useful connections between these

4

genes and the gene in focus could designate important findings. PROMO main menu has an additional option to view the uniqueness of matrices obtained from several organism types, known as 'MatrixSpecificity', as well as a help page [16].

3. Results

Exploitation an inclusive dataset containing genomic sequences, epigenetic marks, and TF binding motifs, we created predictive models to elucidate TF-gene interactions related to PD pathogenesis. The Homo sapiens (SNCA) RefSeqGene sequence retrieved was from NCBI (Reference Sequence: NG 011851.1). This sequence was submitted to PROMO Database to identify putative TF biding sites on SNCA gene sequence. We were able to identify candidate TFs based on the incidence of enriched TF binding motifs. These TFs include GR-a, TFIID, SRY, TCF-4E, GR, AP-2 α -A, NFI/CTF, C/EBP β , ENKTF-1, FOXP3, PR B, PR A, c-Ets-2, IRF-1, NF-AT1, ATF3, IRF-2, GR-β, NF-1, Pax-5, p53, C/EBPa, LEF-1, c-Jun, GATA-1, RXR-asynuclein, c-Myb, STAT5A, HNF-3α-, TFII-I STAT4, c-Ets-1, Elk-1, PU.1, T3R-beta1, YY1, NF-AT2, STAT1β, HNF-4α, and TCF-4. Some of these TFs are regulators of neuronal functions and many are

dopaminergic signaling pathways regulators

as demonstrated in figure1.

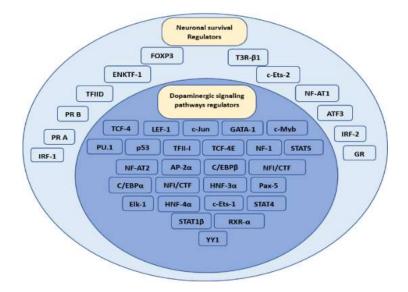


Figure 1: A schematic shows Regulators of neuronal function and dopaminergic signaling pathways as top TF candidates regulating ASCN gene involved in PD.

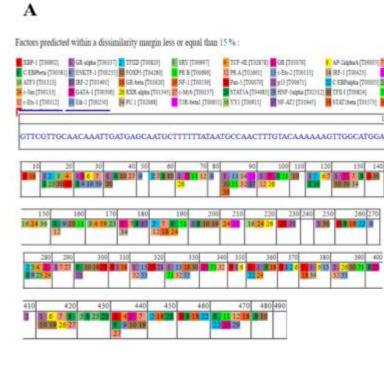
2 151 CTF (TAN)

SF-471 (100658)

LET-4 [T02901]

STAT+ HULLT

NOT-4alpha (100828)



B

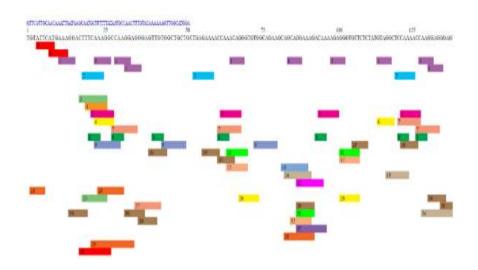


Figure 2: PROMO 'SearchSites' output. A. The regulatory region of human (SNCA)gene. Only those binding site predictions that appear in the sequences are shown, as boxes of different color and number. B. The image below, where the sequences are shown, is the result of selecting 'Zoom' in the main results page.

A			
Marganet asymptotic		time(100) support	
ten ter te			
		Canada agent al sub	
Water State		2 + 4 4 + 4 7 + 2 7 + 2	
		hanna ann an an an ann an an an an an an	
		SCALTAL CLAIPET SCALTER THE TAILET ALTERT THE GAM IT HER THE GO COLUMN AND ALLER TO THE CALCULATION IN HER THE GO COLUMN AND ALLER THE THE THE THE IN HER THE THE THE HER THE THE THE THE IN HER THE THE THE THE THE THE THE THE	
	10.0 (0.0) (0.0) (0.0) 10. (0.0) (0.0)		
TR(200) togethere	THE AREA THE THE ATTACK BARANET TO CARE THE CAR THEN INTERNATIONAL MERICAN	Paral Sana Tanàna di Angelanda ang	
1 +		The same starting of a second se	515215555
A Mythew In public .		historic operation have	
ectructoriariaalitistraariaatus chittoriaatus filosof iijae	CONTINUECTION CONTINUES 11110-000 AUCCASH CETTER A FOLIA AUCCASH CETTER	PN-9 (Doern)	
Control of anti-		OTTOTTICAACAANTONIAACAANOCTITITADADOCCAA	
(Secondaria)		Concerns reprint of article	
NUMBER AND ADDRESS	REFEAR TRUTH ASSAULTER ATTRACTOR STATES		
	3 210 25.2 26.8 4° 480. 480 986 983 4849 4849 4849 1998 4842 1918 1919 1919	(W. A.(2004)) suggestioning	
Consum: regimes and motiv.		ATTENTION AND ANY TRADUCTION AND CONTRACTOR	
		Colonina regiment and array	
a (1111) Propulsion			
E		an pident is	TITLE ALLASETTER AND TAR DEAL TAR DEAL TO ADD A DEALERA TO MAN
		inani Nati Nati	1 11 11 11 11 11 11 11 11 11 11 11 11 1
A the super constants			
		14 DIF-4 (100423) was good and as	
in sur Consuming augusta and autors	the part and the last	the second s	TEATAATOCCAACTITIETACAAAAAAHITTEOCATOOA AGCADOAAA
		Personal Regilt Regilt Regilt	Lan Martin Martin Martin
Contractor Contractor	and the product of th	Consension sequence and asserts:	
		1 1121000000 010710100000 0107101000000 01110000000 01110000000	

Journal of Wasit for Science and Medicine 2024: 17, (3), 1-16

В			
547-473 (100950) www.postkood.au		Pan.d [1000/0] was predicted in	
OTTOTTOCAACAAADTGATGAGCAADCTTTTTTATAADGCAACTTTGTACAAAAAADTTGGCADG			
(c) a state of the second sec second second sec	427% 2.07% 2.00% 2.00%	Desime Heat	ALCTITUTALAAAAAGTITOOCADGGA GDAOCOC D 59 59 10 10 10 105 104 105 105 104 105
Constants segretate and anticia:		14.per	42% (14) (24)
0 0 0 0 1 1 1 1 5 1 0 0 0 0 1 0 0 1 2 0 0 0 0 0 1 1 1 3 5 0 0 0 0 1 1 3 5 0 0 0 0 1 1 3 5		Commun segence out marks:	
atty [191111] was poolised in		0113080	
OTCOTTOCAACAAATTO/DIMOCARDICTITITIATA/DICCAACTTO/ACAAAAAOTTOICA/OHA TOAC	CAREA TENEAGEA	Example 1	
Same Ar Name Ar Name Ar	104 8.70P	21 p53 [780651]] was postered as	
Convent represented autits		OTTENTIOCAACAAAPTOADOAOCAAPOCTTTTTTATAAPOO	CAACITTOTACAAAAAADITTOOCATGGA GEAGCCC GOOCAAG GOAGCCC
60301027		Dealery	676 IQA 726
2 24042310 21002000		Rape Epe	1047 9969 1176 1077 1074 1075
THE REPORT OF		Converses sequence and matrix.	
min predicted in.			
UTTUUTTUCAACAAATTUADIAQCAADOCTTTTTTATAATOCCAAUTTUUTACAAAAADTTOOCAJ	IGGA AADTGA	2011000	
na conservation de la conservation Transmission	10 M 1005	1 1112 0 0 0 0	
18 rupuli No ann	1.12/W 8.16734	R + T G K K K	
Convenies represented party to		CEEPique (2002) ma proband as	
5 3 8 6 7 3 6 6 9 9 0 0 9			
		OTICOTTOCAACAAATIGAIGAGAAGOCTTTTTTAIJAQOCCAAC	TITIGEN ANALASITI SOCIETAS A CATOCA SACANDS CATTOCT ACCART THE REAL STREET ST
BACKNOWSKIC		Sound- Hould	275 376 346 485 1278 1291 1292 1292 1292
Ban (TRR) wantable		Hart	100 108 178 428
a solution of the solution of		Consequent surpresses and matrix.	
na karakaran karakar Karakarakaran karakaran karakaran karakaran karakaran karakaran karakaran karakaran karakaran karakaran karakar		1846930	
		100031	
A 10 10 10 10 10 10 10 10		B 2985922	
men obser al anti:		1000000	
n nu l		21 LEF-1 [70290/] Sus particul in	
0981 9881		OTTOOTTOCAACGAATTOATOAGCAATOCTITTTTTTTTAAATOCCAACT	TTOTACAAAAAOTTOICADOGA ITICAAAO GACCAAAO CTITOICA OTACAAA
03711		Tamin .	6 216 100 200 1 105 106 105 206
		Deal Dar	1094 1453 1454 1454 1005 1005 1467 1468
58 + (2003) we periodia:			
norma ma mandianas negatini talagostan titutik annan modelan andritan botilian negatina titudida titudida t	TRANSIC THEFT IN TRACTIN	Common accorde and matter	
1 10 20 10 10	5 34 44 A	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	
en 10, 10, 10, 10, 10, 10, 10, 10, 10, 10,	15 18 18 18 19 18	0 0 0 00110	
e 100 100 100 100 100	14 15 24	0 16 18 10 P 2 B 1	
state appear of brits		a da (2001) bepetieda	
1111121)			
88981276			AAAAAAETTIIKCATIIIIA 200CAW TIAACAAA TOXCOVE TIAACAAE TITUDTa TOXCAW A. 0.0 0.0 120 227 3.0 M III 100 100 100 100 100 100 100
7798681.0		Roote Root Root	201 EUR. 2006 EVE. 201 Aut. 1978 EUR. 2008 EVE. 2010 EUR. 2020 EUR. 2020 EUR. 2021
TORONIA		Counters improve nationality	

2024: 17, (3), 1-16

С		
GAIA-1 [T0000] was posterned as		rent (and a bandary a
UTCOTTOCAACAAATTOADUNGCAADUCTITTTATAATOCCAAC	TTTGTACAAAAAGTTGGCCGOGA AAGGA TATCAA 250°CAA 90 90 00 00 00 00 128, 149, 149, 149, 128, 149, 149, 149, 128, 149, 149, 149,	entresten na Auto Internan Auto International Auto Internatio Auto International Auto International Auto International Auto International Auto International Auto Internationa Auto International Auto International Auto International Auto International Auto International Auto Internationa Auto Inte
ACHELING SHERE AND REACTLY		
8 54 6 0 11 6 0 0 54 8 9 5 0 5 0 5 12 36 0 26 0 15 4 T14 10 11 12 15 15 15 15 15 15 15 15 15 15		
858.ogto [1113-2] *u protout is		Vienne appent of serve
ПТСОГТОГАНСКАНТОНТОНОСНИГОСТИТТИЧАНТОССАНСТИТОТИСА наполности	AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	The second secon
incoment supposed and the		натапас, на на полоторат тата пола състато състато с на полосната стали на пола пола с Солико с Солико с Солико 10 и и и и и и и и и и и и и и и и и и и
1 2 4 8 0 0 0 8 4 4 4 4 4 4 5 3 8 6 0 0 4 2 8 8 6 0 10 10 10 10 10 10 10 10 10 1		Name 104, 128, 100, Hapin 100, 100, 100, 100, Face 100, 100, 100, 100,
2 (5.335 (100127) an inegration		- KANANGKARA
VETCOTTINGAM ANALTINGTONICANTOCTITITE/GAN/SOCAN/2110/A	CAMAAAAATTIDOCATODIA SOGNOTIO ACCADITIO CAMETTIL CAMADITIO 8 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.	PUICE
N yali N ya	175 1980 448 844 1970 1954 1954 1994 1984 1975 1975 1984	латтоглосын алагтолдоны албосттатталдагоосын тэтийн алаамитээн арол алболоодоо байлаантаа тэтолоодоос албол албо
Normani imprese auf antiti		Bases BG 200, F.X. Klast 1200 1300 4600 Base 1200 1300 4600
0.4.5.6.0.5.1.0 0.4.5.6.0.5.1.0 0.4.5.6.0.5.1.0 0.4.5.6.0.5.1.0 0.4.5.6.0.5.1.0 0.4.5.6.0.5.1.0 0.4.5.6.0.5.1.0 VEAUXAL[164:00] was predicted as:		Concerns appeared with 1 / 4 / 4 / 4 / 4 / 2 / 1 / 1 1 / 4 / 4 / 4 / 2 / 1 / 1 4 / 1 / 4 / 4 / 2 / 1 / 1 4 / 1 / 4 / 4 / 2 / 1 / 1 4 / 1 / 4 / 4 / 2 / 1 / 1 4 / 1 / 4 / 4 / 2 / 1 / 1 4 / 4 / 4 / 2 / 1 / 1 4 / 4 / 4 / 2 / 1 / 1 4 / 4 / 4 / 2 / 1 / 1 4 / 4 / 4 / 2 / 1 / 1 4 / 4 / 4 / 2 / 1 / 1 4 / 4 / 4 / 2 / 1 / 1 4 / 4 / 4 / 2 / 1 / 1 4 / 4 / 4 / 2 / 1 / 1 4 / 4 / 4 / 2 / 1 / 1 4 / 4 / 4 / 2 / 1 / 1 4 / 4 / 4 / 2 / 1 / 1 4 / 2 / 1 / 1 4 / 2 / 1 / 1 4 / 2 / 1 4 / 2 / 1 / 1 4 / 2 / 1 / 1 4 / 2 / 1 / 1 4 / 1 4 / 1 / 1 4 /
ITTOUTIQUAACAAATSOADAACAATOCTITITIASAATOCUAACTI	TOTACAAAAAAAATTIOGCATIOGA AACTTICTUOTAC TTABAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	T/R-sens([T00531]] was produced as
	122% 122% 12346 12346 12347 12347	оттеоттосласалатодтолосалосттетнылагоссалетноглеалаламитоослоод саотоот
neer	100	Toleaner, 1175 M. spen H. jane, 2000
		Consistant requirement weak market: 0.004.002.001 0.04.002.001 0.04.002.001 0.004.000 0.004.0000 0.004.00000 0.004.0000 0.004.0000 0.004.00000 0.004.0000 0.004.00000 0.004.00000 0.004.00000 0.004.00000 0.004.0000000000
34 1057-34ptor [102912] was predicted in:		
OTICOTIGCAACAAATTGATGAGCAATGCTTTTTEALA		M YYL (1999) 31 was predicted in:
Tarantinen 15 aparly 17 genes	ALERS E.SPAS E.JPRE	OTTEOTEDCAACAAATUATGAGCAACOCTITETTATAATOCCAACTITOTACAAAAAGTOGCATGGA ATOO u ur Shannii Shannii Shannii
minum repeace and match:		0 mili 10 mili 10 mili 10 mili
1 1 2 3 3 3 0 2 0 1 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 2 0 1 0 0 0 3 1 7 4 4 4 4 4 4 4		Community supportune and matrix:
ELINER NEWSA		
effection of automation and the contract of the contract of		
Tanit Rank		15 C
Communication Collares		
240483 547483 821388		

2024: 17, (3), 1-16

D			
71 NF-AT2 [701942] **** predicted in:		RNF-Jalpha (79552) ver produtet in	
OTTO OTTO CAACAAATTO ATGAO CAATGE TTTTTTATAATO CCAALTITO TACAAAAAAOTTO OCATOO A	DOAAAOACAA	GERGETEGCAACAAAFTGATGAGCAATGCTTTTTLEEAATGCCAACTTTGEACAAAAAAGTGGGCATGGA GA	ANDOCCANDOA
Dominy House Maper	11.12% (****** 1.110%	Real Real Real	1026. 14275 14277
Constant septeme and anothe		Connected suggester and somethy	
2432200000 1000100000 200100000 2010000000 2010000000 201000000000 20100000000000			
STATISTS (1985) weigenitent at		TTP-4 [TR(915] was predicted as	
GTTCGTTBCAACAAATTEADGAGCAATGCTTTTTEATAADGCCAACTTTGTACAAAAAAGTTGGCATGGA	CASGAAAG	GITCUTTQCAACAAAFTQAPQAQCAAFGCTTTTTTAESATGCCAACTTTGTACAAAAAGTTQGCAFGGA	CTITICAAAOG
Tanalat) Al cash Russi	105	familier Rosei Rosei	2015 2229 2307
Counting represent and matters		Concerning requirements and matrix	
2 00 00 00 1 4 0 2 1 0 00 0 2 1 4 1 0 0 0 0 0 0 0 0 1 2 0 3 3 3 0 0 4 0 0 1 0 3 3 3 0 0 0 0 0 1 0 3 3 3 0 0 0 0 0 1 0 3 3 3 0 0 0 0 0 0 0 0 0 1 0 3 3 3 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0			

E

Distribution of the nucleotides over the given chain:

A	33.7%	
с	17.6%	
G	30.7%	
т	19:5%	

Figure 3: A-D, the details of the (SNCA) gene-bindings sites predictions on the sequences. They also show the weight matrix for the (SNCA) gene recognition sites and random expectations (RE) values for the different levels of sequence-matrix similarity. The RE is calculated with a model that considers that all nucleotides are equally probable and with a model that considers the nucleotide composition in the query sequence (in the picture represented by blue bars below matrix) (E).

4. Discussion

Predicting of transcription factor (TF) binding to genes involved in PD denotes a momentous step forward in unraveling the intricate regulatory mechanisms fundamental in disease pathogenesis [17,18]. Our study sheds light on the regulatory site of ASCN involved in PD by identifying putative TFgene interactions and explaining their functional significance. Here, we investigate the contents of our findings, their significance to PD biology, and the potential translational implications for developing a therapy. One of the vital insights achieved from our predictive modeling is the identification of putative TFs that may play essential roles in governing PD-associated ASCN transcriptional dysregulation.

Utilizing computational analyses and applying multi-omics data, we revealed TFs with known involvement in neuronal function and dopaminergic signaling pathways. Among these, members of the Forkhead box (FOX) family and Nuclear Factor-kappa B (NF-KB that emerged as regulators, prominent proposing their possible contribution to PD pathophysiology figure 1.

Most TFs were those that play a crucial role in regulating gene expression in different cells including response, immune metabolism, cellular processes, and/or stress adaptation and apoptosis. These TFs cover C/EBPB (CCAAT/enhancer-binding protein beta), CCAAT/enhancer-binding protein $(SNCA)(C/EBP\alpha)$, Interferon Regulatory Factor 2 (IRF-2), c-Jun, AP-2a, Interferon regulatory factor 1 (IRF-1), Nuclear Factor of Activated T cells 2 (NF-AT2), Activating Transcription Factor 3 (ATF3), Nuclear factor of activated T-cells 1 (NFAT1), Elk-1 (Ets Like-1), Yin Yang 1 (YY1), Forkhead Box A1 (FoxA1), c-MYB, the glucocorticoid $(SNCA)(GR-\alpha-synuclein),$ receptor Activating TFs such as ATF3 and TF4, in addition to signal transducers like STAT4 or STAT5A, all contribute in gene activation processes directing cell differentiation as they bind to specific promoters located

within most genes' 5' regions [19-22]. developmental Further regulators that essentially act transiently at several stages include repressors such PAX5, which encodes a B-cell-specific activator protein (BSAP) [23], HNF3α (a protein linked with the differentiation of lung cells) [24], RXRa (a protein that cooperates with other nuclear receptors) or NFI, which is a transcription factor regularly originate in the brain. Despite frequent accounts around its role within cancer processes only growing evidence suggests otherwise its involvement in neurological disorders, including PD [25].

Specific proteins like FOXP3 participate in the formation and activation of T regulatory cells [26]. Moreover, TCF-4E and LEF- has been suggested to be involved in the Wnt signaling pathway whose other functions help in maintaining the normal tissues in developed organisms and early stages of existence or disorders such as those related to the brain or cancer [27]. P53 entails a paradigm of a cancer suppressor protein controlling gene restoration, aging process among other functions like cell cycle control [28]. While TFIID takes part in a series of reactions leading to formation of a certain substance [29]. PU.1 on the other hand is a key factor in hematopoiesis, the development of immune cells and in governing their

function [30]. Thyroid hormones (THs) the transcription control gene by TR β 1(nuclear receptor) [31]. In diverse regions including liver and pancreas HNF-4a belongs to superfamily of nuclear receptors controls expression patterns [32]. The SRY factor has been confirmed to play a major role by directing bipotential gonad differentiation leading to testis and eventually male sex determination [33]. STAT1 β is a member of the STAT protein family that acts as a transcription factor in response to cytokines and growth factors [34]. While these proposed links endorse potential connections between the predicted TFs and PD, so far, there is no direct evidence of involvement of all these TFs in PD pathogenesis. Future work of experimental validation by TF-gene interactions through ChIP-seq and luciferase reporter assays will confirm their functional significance, providing mechanistic insights into the transcriptional regulation of PDassociated genes. Besides, additional studies investigating the denoted TFs roles in inflammation, oxidative stress, protein aggregation, and mitochondrial function in PD models may provide further visions into their implication in PD. These findings underscore the potential of predictive methods in elucidating disease mechanisms and identifying candidate therapeutic targets.

5. Conclusion

PD endures to present a challenge to the medical community, affecting millions worldwide with no cure in sight. However, the discovery of ASCN's key role has provided a deeper understanding of the disease's mechanisms. Unraveling the complexities of (SNCA) pathology holds the promise to emerging more effective treatments that could slow or halt PD progression. While the journey towards a cure remains laborious, the quest to decode the (SNCA) mystery offers hope for millions affected by this distressing neurological disorder. In this study, we exploited bioinformatics tools to predict the TFs that bind to the (SNCA) gene associated with PD. Knowing these TFs might explain the molecular based mechanisms behind it and determine potential therapeutic targets for PD. Future work will require a validation of these TF-gene interactions through ChIP-seq and luciferase reporter assays to confirm their functional implication, providing mechanistic insights into the transcriptional regulation of PD-associated genes.

6. References

- Messeguer X., Escudero R., Dom D., Farré D., Farré F., Nez O., Martinez J., and M. Mar Alba., (2002). PROMO: detection of known transcription regulatory elements using species-tailored searches. Bioinformatics Applications Note. 18, 2, 333-334.
- Wang Y., Zhao Y., Pan H., Zeng Q., Zhou X., Xiang Y., Zhou Z., Xu Q., Sun Q., Tan J., Yan X., Li J., Guo J., Tang B., Yu Q., and Liu Z., (2023). Genetic analysis of dystonia-related genes in Parkinson's disease. Front Aging Neurosci. 15, 1-11.
- Narayan S., Liew Z., Bronstein J. M., and Ritz B., (2017). Occupational pesticide use and Parkinson's disease in the Parkinson Environment Gene (PEG) study. Environment international. 107, 266-273.
- Calabresi P., Mechelli A., Natale G., Volpicelli-Daley L., Di Lazzaro G., and Ghiglieri V., (2023). Alphasynuclein in Parkinson's disease and other synucleinopathies: from overt neurodegeneration back to early synaptic dysfunction. Cell Death and Disease. Springer Nature. 14, 176.

- Gómez-Benito, M., Granado, N., García-Sanz, P., Michel, A., Dumoulin, M., and Moratalla, R., (2020). Modeling Parkinson's Disease With the Alpha-Synuclein Protein. Frontiers in pharmacology. 11, 356.
- Leonidas Stefanis, (2012). α-Synuclein in Parkinson's disease. Cold Spring Harbor Perspectives in Medicine, 4, a009399.
- Meade R. M., Fairlie D. P., and Mason J. M., (2019). Alpha-synuclein structure and Parkinson's disease -Lessons and emerging principles. Molecular Neurodegeneration. 14, 29.
- Calabresi P., Di Lazzaro G., Marino G., Campanelli F., and Ghiglieri V., (2023). Advances in understanding the function of alpha-synuclein: implications for Parkinson's disease. Brain. 146, 9, 3587-3597.
- Tonges L., and Zella M., (2019). Antibody-based immunotherapies for Parkinsonian syndromes. Neural Regeneration Research. 14, 1903-1904.
- Zhao Y., Qin L., Pan H., Song T., Wang Y., Zhou X., Xiang Y., Li J., Liu Z., Sun Q., Guo J., Yan X., Tang B.,

and Xu Q., (2024). Genetic analysis of transcription factors in dopaminergic neuronal development in Parkinson's disease. Chinese medical journal. 137, 4, 450-456.

- Tiwari C., Pal R., (2017). The potential role of neuroinflammation and transcription factors in Parkinson disease. Dialogues in Clinical Neuroscience. 19, 1, 71-80.
- Farré D., Roset R., Huerta M., Adsuara J. E., Roselló L., Albà M. M., and Messeguer X. (2003). Identification of patterns in biological sequences at the ALGGEN server: PROMO and MALGEN. Nucleic Acids Research. 31, 13, 3651-3653.
- Hannenhalli S., and Levy S., (2002).
 Predicting transcription factor synergism. Nucleic Acids Research. 30, 19, 4278-4284.
- Kaur S., Vashistt J., and Changotra H., (2024). Computational Investigation of Regulatory Region SNPs of Autophagy Gene BECN1. Defence Life Science Journal. 9, 1, 27-34.
- Quandt K., Frech K., Karas H., Wingender E., and Werner T., (1995).
 MatInd and MatInspector: new fast and versatile tools for detection of

consensus matches in nucleotide sequence data. Nucleic Acids Research. 23, 23, 4878-4884.

- Martínez-Vicente P., Poblador F., Leitner J., Farré D., Steinberger P., Engel P., and Angulo A. (2022). Discovery of the first PD-1 ligand encoded by a pathogen. Frontiers in immunology, 13, 1007334.
- Lambert S. A., Jolma A., Campitelli
 L. F., Das P. K., Yin Y., Albu M., Chen
 X., Taipale J., Hughes T. R., and
 Weirauch M. T., (2018). The Human
 Transcription Factors. Cell. 172, 4,
 650-665.
- Kim G. B., Gao, Y., Palsson, B. O., and Lee, S. Y. (2021). DeepTFactor: A deep learning-based tool for the prediction of transcription factors. Proceedings of the National Academy of Sciences of the United States of America. 118, 2, e2021171118.
- Tanaka T., Yoshida N., Kishimoto T., and Akira S., (1997). Defective adipocyte differentiation in mice lacking the C/EBPbeta and/or C/EBPdelta gene. The EMBO journal. 16, 24, 7432-7443.
- Koleva R. I., Ficarro S. B., Radomska H. S., Carrasco-Alfonso M. J., Alberta J. A., Webber J. T., Luckey C.

J., Marcucci G., Tenen D. G., and Marto J. A. (2012). C/EBPα and DEK coordinately regulate myeloid differentiation. Blood. 119, 21, 4878-4888.

- Persyn E., Wahlen S., Kiekens L., Van 21. Loocke W., Siwe H., Van Ammel E., De Vos Z., Van Nieuwerburgh F., Р., Taghon Matthys Т., Vandekerckhove B., Van Vlierberghe P., and Leclercq G., (2022). IRF2 is for development required and functional maturation of human NK cells. Frontiers in immunology. 13, 1038821.
- Meng Q., and Xia, Y. (2011). c-Jun, at the crossroad of the signaling network. Protein and cell. 2, 11, 889-898.
- 23. McManus S., Ebert A., Salvagiotto G., Medvedovic J., Sun Q., Tamir I., Jaritz M., Tagoh H., and Busslinger M., (2011). The transcription factor Pax5 regulates its target genes by recruiting chromatin-modifying proteins in committed B cells. The EMBO journal. 30, 12, 2388-2404.
- Klaus H Kaestner., (2000). The Hepatocyte Nuclear Factor 3 (HNF3 or FOXA) Family in Metabolism,

Trends in Endocrinology and Metabolism. 11, 7, 281-285.

- 25. Zati Zehni A, Batz F, Cavaillès V, Sixou S, Kaltofen T, Keckstein S, Helene Hildegard Heidegger, Ditsch N., Mahner S., Jeschke U., and Vilsmaier T., (2021). Cytoplasmic localization of rxrα determines outcome in breast cancer. Cancers (Basel). 13, 15, 3756.
- Frattini V., Pisati F., Speranza M. C., Poliani P. L., Frigé G., Cantini G., Kapetis D., Cominelli M., Rossi A., Finocchiaro G., and Pellegatta S., (2012). FOXP3, a novel glioblastoma oncosuppressor, affects proliferation and migration. Oncotarget. 3, 10, 1146-1157.
- 27. Hrckulak D., Janeckova L., Lanikova L., Kriz V., Horazna M., Babosova O., Vojtechova M., Galuskova K., Sloncova E., and Korinek V., (2018). Wnt Effector TCF4 Is Dispensable for Wnt Signaling in Human Cancer Cells. Genes. 9, 9, 439.
- Reisman D., Takahashi P., Polson A., and Boggs K., (2012). Transcriptional Regulation of the p53 Tumor Suppressor Gene in S-Phase of the Cell-Cycle and the Cellular Response

to DNA Damage. Biochemistry research international. 808934.

- Patel A. B., Greber B. J., and Nogales
 E., (2020). Recent insights into the structure of TFIID, its assembly, and its binding to core promoter. Current opinion in structural biology, 61, 17-24.
- Rothenberg E V., Hosokawa H, and Ungerbäck J. (2019). Mechanisms of action of hematopoietic transcription factor PU.1 in initiation of T-cell development. Front Immunol. 10, 228.
- 31. Asghar M. Y., Knuutinen T., Holm E., Nordström T., Nguyen V. D., Zhou Y., and Törnquist K. (2022). Suppression of Calcium Entry Modulates the Expression of TRβ1 and Runx2 in Thyroid Cancer Cells, Two Transcription Factors That Regulate Invasion, Proliferation and Thyroid-Specific Protein Levels. Cancers, 14(23), 5838.

- Walesky C., and Apte U., (2015).
 Role of hepatocyte nuclear factor 4α (HNF4α) in cell proliferation and cancer. Gene expression. 16, 3, 101-108.
- 33. Matsuzawa-Watanabe Y., Inoue J. I., and Semba K., (2003). Transcriptional activity of testisdetermining factor SRY is modulated by the Wilms' tumor 1 gene product, WT1. Oncogene. 22, 39, 7900-7904.
- Semper C., Leitner N. R., Lassnig C., 34. Т., Parrini М., Mahlakõiv Rammerstorfer M., Lorenz K., Rigler D., Müller S., Kolbe T., Vogl C., Rülicke T., Staeheli P., Decker T., Müller M., and Strobl B. (2014). STAT1 β is not dominant negative and is capable of contributing to gamma interferon-dependent innate immunity. Molecular and cellular biology. 34, 12, 2235-2248.

16