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The Correlation between Genetic Variation for SNCA Gene with Parkinson's Disease

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ABSTRACT

The purpose of the present research was to investigate the relationship between the variation of SNCA sequences and Parkinson's syndrome by collecting 120 specimens of blood from both patients as well as normal people who visited Ibn Sina Teaching Hospital in Mosul from Dec to June 2023-2024. The specimens were separated between different categories, including the Parkinson's (patient) group donated symbol P, which contained thirty specimens split into two distinct age-based subgroups, P1 (ages 50-65) and P2 (ages 66-80). Each had 15 blood samples, and the Parkinson's family record group contributed symbol F had thirty specimens of persons around the ages of 25 and 50 as well to controls group C, which had sixty specimens of people who were healthy split into three subgroups: C1 (50-65 years old) C2 (ages 66-80) and subgroup C3 (ages 25-50). Results of our study After comparison between these groups showed for the first time mutation in different location in the SNCA gene parts after specific primers designed in different parts of this gene utilized PCR technique. Most of these mutations are point mutation in the amplicon sequences of the specific gene parts in extracted DNA from blood samples of family group (F) and Parkinson's group (P) compared with the sequences of the healthy group (C) blood samples.

This research concluded according to its results that SNCA gene had an important role in the Parkinson's disease early diagnostic due to the point mutation that occurred in family history group F which could be utilized as early diagnostic marker.

Keywords: Alpha-synuclein, point mutation, primer designed.

INTRODUCTION

Parkinson's is a neurological condition characterized by the loss of dopamine cells with increasing loss of neurons. Alzheimer's disease (AD) is the most common neurodegenerative disease, followed by PD. It is a chronic, progressive disease that mainly affects movement, but can also lead to non-motor symptoms such as sleep disorders, cognitive impairment, and dementia (Aarsland *et al*., 2021).

Dopamine (DA) deficiency within the midbrain is a consequence of the disorder, which results from the death of dopamine (DA) neurons in the substantia nigra (SN), an area located in the middle of the brain. Lewy bodies (LBs), cytoplasmic inclusions carrying proteins such as alpha-synuclein found in neurons in affected brain regions, are a hallmark of Parkinson's neurological disorder. These protein aggregates affect limbic and substantia nigra neuronal circuits in the substantia nigra, and the loss of these dopaminergic neurons in the substantia nigra (SNpc). The exact cause of Parkinson's disease remains a mystery, although some cases have been linked to genetic factors caused by mutations in specific genes or oxidative stress (Ahmed *et al*., 2011; Al-Ani and Al-kattan, 2017; Calabresi *et al*., 2023).

The most important gene in autosomal dominant family types is the alpha-synuclein gene (SNCA). Alpha-synuclein, a small protein encoded by this gene, is highly expressed in the cerebral cortex and less so in the muscles and heart. It is mostly observed in the brain and nerve endings in specific structures known as presynaptic terminals, which in the normal nervous system release neurotransmitters from synaptic vesicles. In order to properly coordinate movements and regulate body and brain processes, alpha-synuclein facilitates the transfer of messages from nerves between neurons across the nervous system and the brain (Miller *et al*., 2021). It is a major component of Lewy bodies (LBs), and this type of protein accumulates in clumps within the brain neurons of individuals with Parkinson's disease (PD) (Gratton *et al*., 2019).

Alpha, beta, and gamma-synuclein are members of the synuclein family, which additionally includes alpha-synuclein. The SNCA gene, which contains twelve exons, is located on chromosome 4q22.1. The alpha-synuclein protein is made up of 140 amino acids. It is synthesized by presynaptic cells. It is associated with the development of Parkinson's disease both neurologically and through genetics, and any genetic change in the gene that codes for and expresses this protein has a role in the onset of Parkinson's disease. Alpha-synuclein normally occurs in specialized structures called nerve endings located at the highest point of nerve cells. Presynaptic endings produce chemicals called transmitters or neurotransmitters from synaptic vesicles. The production of neurotransmitters makes it easier for neurons to communicate with each other and is essential for the normal functioning of the nervous system (Federoff *et al*., 2015; Mohammed and Rabia, 2021). Besides controlling dopamine (DA), alpha-synuclein also contributes to vesicle maintenance in presynaptic neurons (Roseborough *et al*., 2017; Atarbashi and Daghestani, 2023). In addition, it is essential for the movement of microtubules within the cell structure, helping to maintain cell shape (Vekrellis *et al*., 2011). The aforementioned protein contributes to the appearance of Lewy bodies (LBs), a hallmark of the disorder (Al-Sofi, 2012; Lang and Kalia, 2015). Hereditary or familial Parkinson's disease (PD) is associated with the SNCA gene in the case of a triple missense mutation (A30p, E46K and A53T) (Giasson *et al*., 2002).

The role of alpha-synuclein intensifications as people age and brain activity increases. This is thought to have a role in neurodegeneration and the eradication of dangerous protein aggregates that are disordered and misfolded in order to maintain function (Vargas *et al*., 2017; Li *et al*., 2024).

This research aimed to found an important molecular test that considered as an-indicators for Parkinson disease recommended to be performed in the hospital to detect this disease.

MATERIALS AND METHODS

Chemical Material Used

Used DNA extraction kit from Bio add company and the ready-made measurement kit Promega GO taq master mix as the (Table 1)

Table (1): Promega GO taq master mix used in PCR

No.	Quantity	ul material	
1	Master mix	12.5	Promega GO taq master mix
2	Primer Forword (20 picomole) 10 pm	2.5	
3	Primer reverse (20 picomole) 10 pm	2.5	
4	DNA templet	5	
5	PCR water	2.5	

Blood samples

120 blood samples were collected from patients and healthy male people presenting to the Hospital of ibn Sina Teaching in Mosul city from the month Dec to jun (2023-2024 AD), depending on the field supervisor and the doctor specialized in diagnosing disease cases and after obtaining official approval from the Nineveh Health Department. These samples had been divided into several group, Parkinson group, donated symbol P that included (30) samples divided into two subgroups according to age, P1 aged (50-65) years and P2 aged (66-80) years 15 blood sample for each, while Parkinson's family group donated symbol F, included (30) samples aged between (25-50) years, in addition to Control group C which comprised (60) specimens of healthy individuals split into three distinct categories: C1 (ages 50-65), C2 (ages 66-80), and C3 (ages 25-50).

DNA extraction

DNA had been extracted by DNA extraction kit from bio add company and the ready-made measurement kit Promega from all blood samples groups (patients, healthy individuals, and family records). The concentration and purity of DNA extracted from the total blood samples used in the current study were estimated using a Nano-Photometer

Primer design:

we use primer-blast from national center for biotechnology information (NCBI) for design parts from alpha synuclein gene. This primer used to amplify the part of the *SNCA* gene which includes 3 and 4 exons as (Table 2).

Table (2): Primer design from NCBI.

No.	Primer	Sequence	number	Amplicon Bp	References
1.	*SNCA* part	Primer1: AGGGCTTTCCGACTTGAGGA	20	259	This study
		Primer2: CTCTCCACTGATTCCATGGTGG	22		

Polymerase chain reaction (PCR):

Table (3): Reaction steps in PCR technique.

No.	Step	Tm(C°)	Time	No. of cycle
1	Polymerase activation	95	10 min	1
2	Denaturation	95	1 min	35
3	Annealing	64	1 min	
4	Extension	72	1 min	
5	Terminal Extention	72	5min	1

After Amplification of specific sequences of SNCA gene parts the amplicon sequences had been sent for DNA sequencing

RESULTS AND DISCUSSION

DNA extraction from whole blood

High purity DNA extracted from blood samples ranged between (1.7-1.9) and concentration was30 ng/µl by using Nano drop instrument. Fig. (1) revealed PCR electrophoresis results of the designed part of the *SNCA* gene part 2 amplified DNA fragments of all groups had a molecular weight of 295 bp All amplified DNA fragments were uncontaminated according to comparison with the negative control group NC. The *SNCA* gene has a major role in the pathogenesis of PD and early detection of mutations develops therapeutic strategies for this disease (Guhathakurta *et al*., 2022).

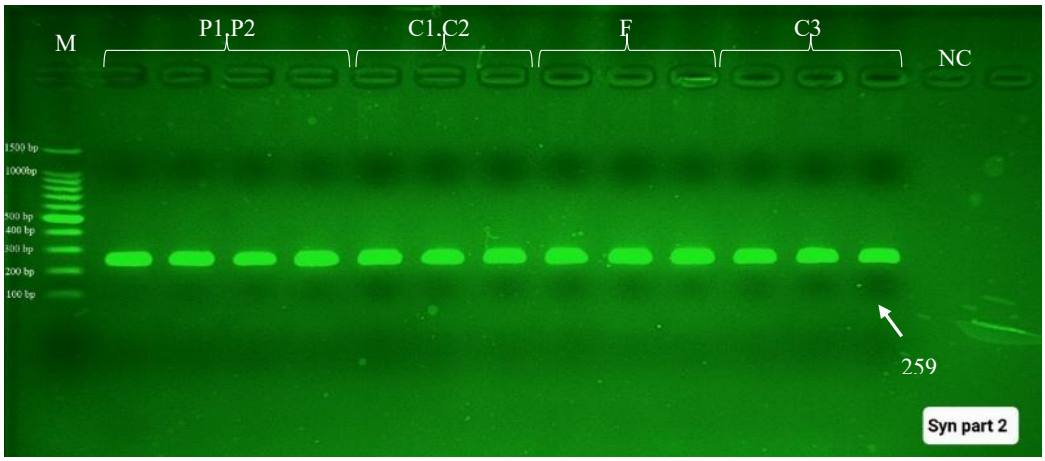

Fig. 1: PCR amplicon of syncline part 2 sequence after specific primer designed, M:100 bp marker, NC: Control negative, P1, P2 … C1, C2 … F … C3 … Band size: 259bp.

The results for the designed part of the gene showed that no mutations occurred in the healthy group, as shown in Fig. (2), compared to the nitrogenous base sequences of this gene in NCBI in Fig. (3).

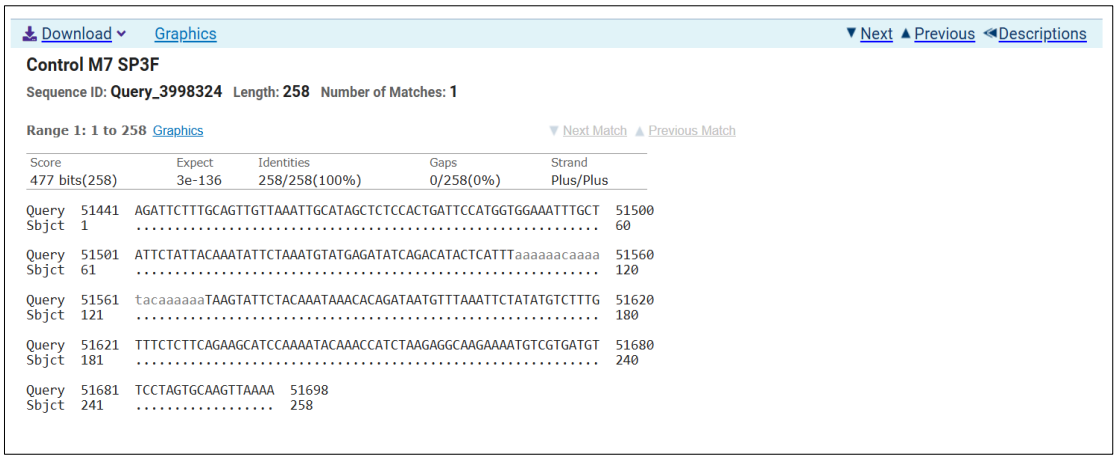

Fig. 2: Amplicon base sequences of *SNCA* part 2 in control

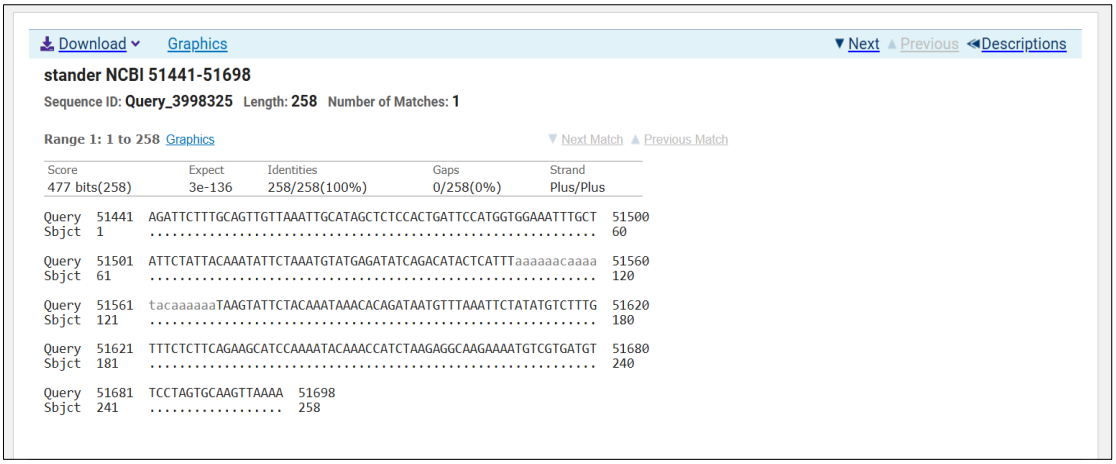

Fig. 3: Amplicon of *SNCA* Part 2 base sequences compared with standard NCBI sequences.

The results showed that the designed part of the SNCA gene had 6 mutations in the nitrogenous base sequences of the family history group, as shown in Fig. (4), and (Table 4) that showed these mutations, their type and location. Researchers (Yang *et al*., 2023) indicated that the duplication of the *SNCA* gene in the region that includes exon 2 and the presence of 3777 nucleotides, and according to the sequence technique, the occurrence of these mutations led to the appearance of Parkinson's disease symptoms, which are present in individuals who have a family record. Predicting the occurrence of the disease from the beginning and discovering mutations in the family record group contributes to providing early treatment (Duan *et al*., 2023).

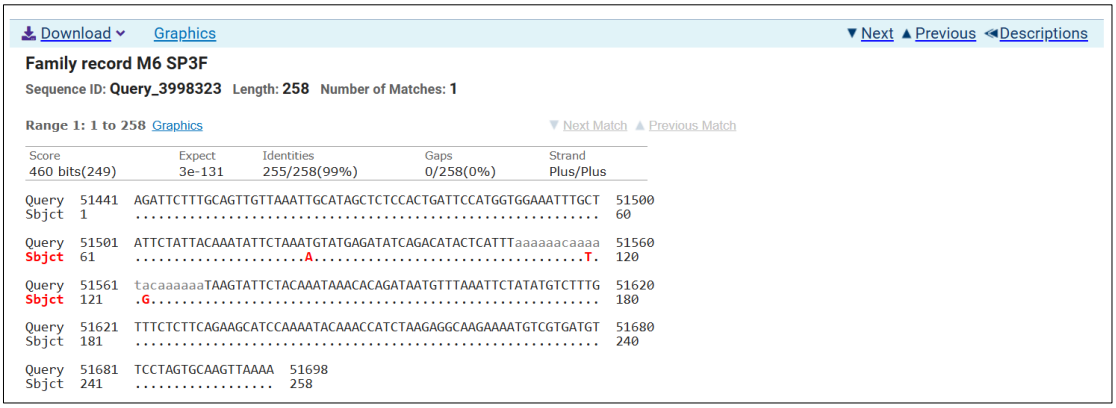

Fig. 4: Amplicon base sequences of *SNCA* part2 in the DNA extracted from family record blood samples group.

Table (4): The variation that occurred in the *SNCA* part2 amplicon sequences of family record group (F).

No.	Nitrogen base	Mutation type	Location
1	T-----A	Transversion	51523
2	A------T	Transversion	51559
3	A----G	Transsion	51562
4	T----A	Transversion	51523
5	A-----T	Transversion	51559
6	A-----G	Transsion	51562

While the results of the patient sample showed the presence of 7 mutations within the base sequences as shown in Fig. (5), and these mutations were arranged, their type and location were

according to (Table 5), our results showed these clinical and genetic characteristics of Parkinson's disease and provided strong evidence for genetic prediction and importance in future disease diagnosis (Goedert *et al*., 2017).

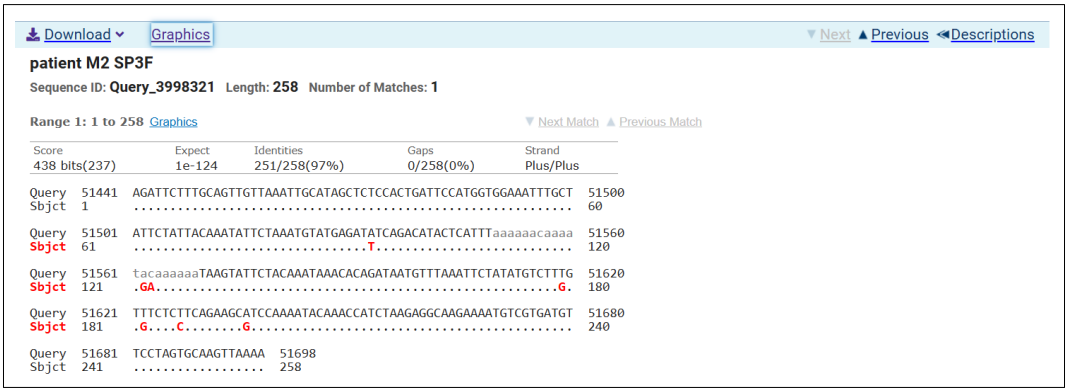

Fig. 5: Variation in the amplicon base sequences of *SNCA* part 2 of patient's group.

Table (5): Variation in *SNCA* gene sequences that occurred in the patient group:

	Nitrogen base	Mutation type	Location
1	A----T	Transversion	51533
2	A------G	Transsion	51562
3	C----A	Transversion	51563
4	T----G	Transversion	51619
5	T-----G	. Transversion	51622
6	T-----C	Transsion	51627
7	A-----G	Transsion	51636

>patient M2 SP3F
AGATTCTTTGCAGTTGTTAAATTGCATAGCTCTCCACTGATTCCATGGTGGAAATTTGC
TATTCTATTACAAATATTCTAAATGTATGAGATTTCAGACATACTCATTTAAAAAACAA
AATGAAAAAAATAAGTATTCTACAAATAAACACAGATAATGTTTAAATTCTATATGTC
TTGGTGTCTCCTCAGAAGCGTCCAAAATACAAACCATCTAAGAGGCAAGAAAATGTCG
TGATGTTCCTAGTGCAAGTTAAAA
>Family record M5 SP3F
AGATTCTTTGCAGTTGTTAAATTGCATAGCTCTCCACTGATTCCATGGTGGAAATTTGC
TATTCTATTACAAATATTCTAAAAGTATGAGATATCAGACATACTCATTTAAAAAACAA
TATGCAAAAAATAAGTATTCTACAAATAAACACAGATAATGTTTAAATTCTATATGTCT
TTGTTTCTCTTCAGAAGCATCCAAAATACAAACCATCTAAGAGGCAAGAAAATGTCGT
GATGTTCCTAGTGCAAGTTAAAA
>Family record M6 SP3F
AGATTCTTTGCAGTTGTTAAATTGCATAGCTCTCCACTGATTCCATGGTGGAAATTTGC
TATTCTATTACAAATATTCTAAAAGTATGAGATATCAGACATACTCATTTAAAAAACAA
TATGCAAAAAATAAGTATTCTACAAATAAACACAGATAATGTTTAAATTCTATATGTCT
TTGTTTCTCTTCAGAAGCATCCAAAATACAAACCATCTAAGAGGCAAGAAAATGTCGT
GATGTTCCTAGTGCAAGTTAAAA
>Control M7 SP3F
AGATTCTTTGCAGTTGTTAAATTGCATAGCTCTCCACTGATTCCATGGTGGAAATTTGC
TATTCTATTACAAATATTCTAAATGTATGAGATATCAGACATACTCATTTAAAAAACAA
AATACAAAAAATAAGTATTCTACAAATAAACACAGATAATGTTTAAATTCTATATGTCT

TTGTTTCTCTTCAGAAGCATCCAAAATACAAACCATCTAAGAGGCAAGAAAATGTCGT
GATGTTCCTAGTGCAAGTTAAAA
>stander NCBI 51441-51698 (NG_011851.1)
AGATTCTTTGCAGTTGTTAAATTGCATAGCTCTCCACTGATTCCATGGTGGAAATTTGC
TATTCTATTACAAATATTCTAAATGTATGAGATATCAGACATACTCATTTAAAAAACAA
AATACAAAAAATAAGTATTCTACAAATAAACACAGATAATGTTTAAATTCTATATGTCT
TTGTTTCTCTTCAGAAGCATCCAAAATACAAACCATCTAAGAGGCAAGAAAATGTCGT
GATGTTCCTAGTGCAAGTTAAAA

By examining the genealogical tree and genetic proximity between the groups under study as Fig. (6) showed that there is a difference between family record group and the healthy controls and NCBI 0.005 and 0.004, and that there was a difference between patients, healthy controls and standard NCBI Seq 0.016, The current results indicate that this designed part of the *SNCA* gene has produced numerous mutations that could be used in molecular diagnosis.

It would be preferable to study the entire gene, identify the exons in the gene for the studied regions, confirm the occurrence of the mutation within the exon, and determine the amino acid and genetic code. Most of the younger generations had mutations compared to the older ones of the same generation, despite the repeated and identical regions in the genealogy tree (Szwedo *et al*., 2021; Duan *et al*., 2023; Hameed and Hamed, 2023).

Fig. 6: Genetic distance between groups and NCBI standard sequences

CONCLUSIONS

According to the results of this research we concluded that the *SNCA* gene is very important to diagnosed Parkinson disease such as there are many mutation had been occurred in this gene that contributed to this disease and may be utilized as an important marker for Parkinson disease early diagnosis and recommended to utilized in hospital as an early molecular biomarker specially in the family members that had family recorded infection of this illness.

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العلاقة بين التباين الوراثي لجين *SNCA* مع مرض باركنسون

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الملخص

هدف هذا البحث إلى دراسة جين ألفا–ساينيوكلين (SNCA) المرتبط بمرض باركنسون من خلال جمع 120 عينة دم من الذكور الأصحاء والمرضى، المراجعين لمستشفى ابن سينا التعليمي في مدينة الموصل، خلال الفترة من كانون الأول إلى حزيران 2023–2024، وقد قسمت هذه العينات إلى عدة مجاميع، مجموعة مرضى باركنسون، رمزها P وتضمنت (30) عينة مقسمة إلى مجموعتين فرعيتين حسب العمر، مجموعة P1(50-65) سنة وP2(66-80) سنة بواقع 15 عينة دم لكل مجموعة، بينما مجموعة السجل العائلي رمزها F وتضمنت (30) عينة تتراوح أعمارهم بين (25–50) سنة، بالإضافة إلى مجموعة الأصحاء C وتضمنت (60) عينة من الأشخاص الأصحاء مقسمة إلى ثلاث مجموعات فرعية، C1(50-65) سنة يتم مقارنتها مع مجموعة P1 وC2(66-80) سنة يتم مقارنتها مع مجموعة p2 وC3 المجموعة الفرعية (25–50) سنة يتم مقارنتها مع مجموعة F. أظهرت نتائج هذا البحث وجود طفرات في مواقع مختلفة في الجزء المصمم من *SNCA* وبعض هذه الطفرات كانت طفرات نقطية ظهرت في مجموعات السجل العائلي F ومجموعة مرضى باركنسون P. ولا يوجد طفرة مقارنة بمجموعة الاصحاء C.

الكلمات الدالة: الفا–ساينوكلين، مرض باركنسون، الطفرات، تصميم البادئ