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A Systematic Review of Genetic, Clinical, and Gender Associated Aspects of the *SNCA* Gene in Familial Parkinson's Disease

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Abstract: Parkinson's disease (PD) presents as a progressive neurological disorder that manifests through motor symptoms such as tremors and movement stiffness, which drastically affect both mobility and quality of life. This is caused by dopamine-producing cells in the brain. The worldwide prevalence is estimated at 149 cases per 100,000 persons, indicating a rise to 25.2 million by 2050. By conducting a comprehensive PubMed database search for *SNCA* AND Parkinson's from 2020 to 2025, with adult populations as the focus, the researchers identified relevant studies for data extraction and analysis. The *SNCA* gene holds critical significance because it produces alpha-synuclein, which forms toxic Lewy bodies in brain tissue. Rare *SNCA* mutations that result in gene multiplication trigger severe early-onset Parkinson's disease, while common genetic variations such as REP1 polymorphism increase idiopathic PD risk. Research indicates that individuals with longer *SNCA*-Rep1 alleles have a greater chance of developing Parkinson's disease while also experiencing worsening cognitive impairment and non-motor symptom severity. Men exhibit a 1.5-2 fold higher prevalence of Parkinson's disease and experience symptoms earlier in life compared to women, but women display tremors more frequently when diagnosed with the disease. Female patients show elevated striatal dopamine measurements while experiencing symptoms and describe a greater intensity of pain and emotional responses. The evaluation of motor symptoms like bradykinesia through gyroscope signals demonstrates potential since it aligns closely with clinical rating scales such as the Unified Parkinson's disease rating scale (UPDRS). Many non-motor symptoms, including neuropsychiatric difficulties, sleep disorders, and autonomic dysfunction, affect up to 95% of patients with hyposmia and lower quality of life before motor symptoms appear. Analysing how genetics and gender contribute to symptom development is crucial for developing improved diagnostic tools and treatment methods for Parkinson's disease.

Keywords: Systematic Review, *SNCA*, Parkinson's Disease, Unified Parkinson's disease rating scale (UPDRS).

1. Introduction

Parkinson's disease (PD) is a progressive neurological condition with symptoms including tremors, stiffness, slowness of movement, and balance issues that largely impair mobility. The condition is caused by the death of dopamine-producing cells in the brain. The condition affects millions of people worldwide and is a huge health challenge. It is estimated that there are around 149 cases of Parkinson's disease for every 100,000 persons worldwide. It is anticipated that the global population with Parkinson's disease will rise sharply over the next several years, reaching 25.2 million by 2050. Although it is challenging to obtain exact figures for Pakistan, research indicates that the prevalence is rising, which is consistent with

worldwide patterns. Several genes are reported for Parkinson's disease, including *SNCA*, LRRK2, PARK2, PINK1, and PARK7. The *SNCA* gene is one of their most crucial as it provides instructions to make Alpha-synuclein. This protein aggregates to generate Lewy bodies in Parkinson's disease, which harm nerve cells. The fourth chromosome is home to the *SNCA* gene. The nucleus converts its DNA sequence into messenger RNA (mRNA). The alpha-synuclein protein is subsequently assembled by ribosomes using the mRNA sequence after this mRNA has undergone translation in the cytoplasm. The *SNCA* gene, like all other genes, is duplicated before cell division by a process known as DNA replication, which guarantees that every new cell obtains a full copy of the genetic information. Researchers are still looking for improved treatments and a cure. Understanding the disease causes, finding biomarkers, creating novel medicines, and enhancing care are the main goals of current Parkinson's disease research. Review articles frequently address difficulties in identifying and managing motor and non-motor symptoms.

2. Methodology

Data retrieval

The PubMed database was used for the free text search '*SNCA* AND Parkinson's' accessed on 06th May 2025. Additional records were identified using PubMed Medical Subject Headings (MeSH). Two filters were applied: Publication date (2020-2025) and Age (adults) to target the main population of interest. Screening of abstracts for patients with a mutation within the *SNCA* gene and associated Parkinson's was performed. Furthermore, all duplicates of articles were removed.

Data extraction and management

All the extracted data were handled systematically using an Excel spreadsheet, which made data storage and comparison with other studies easier. The first group included the concentration on gathering basic information about the research and its participants. Parameters such as publication year, study type (e.g., cohort, case-control, GWAS), and sample size were recorded. For each participant group, data were collected on age, focusing on distinguishing between early-onset and late-onset PD and gender, documenting male-to-female ratios when available. The second group of extracted data was distributed with the clinical features of Parkinson's Disorder. The occurrence and severity of key motor symptoms such as bradykinesia, resting tremor, rigidity, postural instability, and gait abnormalities were documented, as well as taking notes of the specific scales used to evaluate motor function, such as the Unified Parkinson's Disease Rating Scale (UPDRS) and the Hoehn and Yahr (HY) scale. The data was extracted on the existence and severity of non-motor symptoms, which were classified into 10 symptom domains: cognitive, mental, sleep, sensory, speech, digestive, urine, sexual, and autonomic. Symptoms unique to each domain were documented (for example, cognitive impairment, sadness, sleep difficulties, constipation). The data was gathered to evaluate the impact of these symptoms on patients' physical and psychosocial functioning. The third group included the extraction of genetic information in which specific *SNCA* variants discovered during the investigations, including mutations, multiplications, and Rep1 allele length, were recognised and recorded. The information on pathogenic scoring or classification of these changes was also retrieved using established methodologies, including the impact of *SNCA* polymorphism on both motor and non-motor symptoms. Further investigation was also done on alpha-synuclein levels and post-translational modifications in different tissues. Many subtypes of Parkinsonism were studied, including Lewy body disease (LBD) spectrum illness, Parkinson's disease dementia (PDD), and early-onset PD.

3. Results and Discussion

Data Analysis

Genome- and Candidate Gene Wide Association Studies (GWAS)

Genome-wide association studies on the Jewish population have assisted researchers in better understanding the genetic landscape of Parkinson's disease. One such study included data from two cohorts:

The Genetic Epidemiology of Parkinson's Disease study and the Ashkenazi Jewish Study, which included 268 PD cases and 178 control samples.

The Role of the SNCA Gene

The *SNCA* was the first gene to be conclusively linked with Parkinson's disease, and is crucial for the current study condition. It is known that severe, early-onset forms of Parkinson's disease (PD) with an autosomal dominant pattern of inheritance are caused by rare mutations and multiplications of the reported gene. In addition to these uncommon instances, frequent changes in the *SNCA* locus have been repeatedly linked to a higher risk of idiopathic Parkinson's disease. The discovery of the REP1 polymorphism, a dinucleotide repeat sequence found in the *SNCA* gene's promoter region, and its link with Parkinson's disease risk were among the first signs of this association. The connection between the *SNCA* locus and Parkinson's disease has been further established by subsequent genome-wide association studies, which have found association signals extending from intron 4 to the region after the 3' UTR of the gene. Current research shows this crucial genomic region contains two to five semi-independent association signals. A thorough examination of the haplotype structure at the 17q21 region, which includes the MAPT gene, has shown the existence of several related haplotypes in addition to the discoveries surrounding *SNCA*. Three different haplotype risk backgrounds corresponding to the H2 haplotype and two subgroups of the H1 haplotype were found within this region by researchers using specialised software. Four distinct SNPs- rs9303521, rs11079711, rs12938476, and rs1880756 clearly distinguish these three risk categories. One group had a risk of 1.18 and another had a risk of 1.36.3, according to the study's estimation of the relative risk associated with these H1 haplotype subsets in comparison to the H2 haplotype. Replication data from the French cohort also confirmed this three-group model of risk at the 17q21 gene.

Demographic Characteristics in Parkinson's Disease Research

A 19-year single-centre study in the Netherlands between 2003 to 2021 examined time shifts in the demographic characteristics of Parkinson's disease research participants. A distinct dataset of summary statistics from multiple studies was analysed, and certain similar trends emerged across this period. There was no statistically significant association between the calendar year and the proportion of female participants in the study, which remained relatively steady at 39% throughout all investigations. Similarly, the average age of research participants did not vary significantly over the 19 years, remaining at 66 years. The proportion of studies that indicated the ethnic background of their participants remained unchanged significantly over time. In the studies that provided ethnic origin, the proportion of native Dutch participants remained consistently high, ranging from 97% to 100%. This implies that the study undertaken at this centre primarily included individuals of Dutch ethnicity, with low representation from other ethnic groups. Although there appeared to be an apparent pattern of an increase in the number of participants who had non-motor symptoms evaluated as a measure of outcome over time, this increase was not considered to be significant and might have taken place by chance, indicating a possibility of increasing awareness of the importance of non-motor symptoms in PD research, but possibly still lacking a systematic and statistically significant change in research focus at this center.

Table 1: Novel Candidate Genes Identified in Ashkenazi Jewish GWAS

Gene	Chromosomal Location	SNP with Strongest Evidence	Potential Role/Pathway	References
LOC100505836	Chr3*p*24	rs1694037	Unknown	(Liu et al., 2011)
LOC153328/SLC25A48	Chr5*q*31.1	rs4976493	Mitochondrial transporter, neuronal signalling, dopamine pathway	
UNC13B	9*p*13.3	rs10121009	Priming of synaptic and secretory vesicles in neurons	
SLCO3A1	15*q*26.1	rs7171137	Transporter	
WNT3	17*q*21.3	rs415430	Neurogenesis	
NSF	17*q*21.3	rs183211	Vesicular trafficking, neurotransmitter release, dopamine receptor interaction	

Gender-Specific Features of Parkinson's Disease

Research studies consistently show that men have more cases of PD, with male cases 1.5-2 times higher than female cases. Women with Parkinson's disease often develop symptoms around two years later than men. Women are more likely to experience tremor as their first symptom, whilst men are more likely to experience bradykinesia or rigidity. Interestingly, regardless of gender, patients who first appear with tremor have a slower rate of motor symptom worsening. Longer reproductive lifetime in women is associated with later onset of Parkinson's disease. SPECT imaging studies show that women had around 16% higher dopamine level markers than males at the onset and during the development of PD. This shows that higher physiological dopamine levels in women, presumably driven by oestrogens, may postpone the onset of symptomatic Parkinson's disease. This is reinforced by research correlating higher parity, later menopause age, and a longer reproductive lifetime in women to later PD onset. However, a recent meta-analysis (2011-2021) indicates that the overall male/female prevalence ratio (OPR) may be lower than previously predicted, at 1.18. The OPR was lowest in Asia, and it appeared to be falling with time. Factors such as research design, national affluence, and participant age did not fully explain the variation in prevalence ratios. The incidence and prevalence ratios for young-onset Parkinson's disease are closer to 1.27. Beyond prevalence, gender disparities occur in specific motor symptoms, with men perhaps more prone to rigidity and women more likely to acquire tremor-dominant Parkinson's disease. Women with Parkinson's disease also report increased levels of pain and sadness.

Table 2: Gender Differences in Parkinson's Disease

Parameters	Case Findings in females	Case Findings in Males	Potential outcomes	References
Prevalence	Lower	Higher (1.5-2 times)	Possible neuroprotective effects of estrogen	(Georgiev et al., 2017)
Age of Onset	Later (approx. 2 years)	Earlier	Potential influence of hormonal factors	
Presenting Symptom	More frequent tremor	More frequently, bradykinesia/rigidity	Unknown	
Motor Deterioration (Tremor-Dominant)	Slower rate	Slower rate (regardless of gender)	Tremor as a potentially more benign disease subtype	
Striatal Dopamine Levels	Higher at symptom onset	Lower at symptom onset	Possible influence of estrogen on dopamine neurotransmission	
Prevalence Ratio (Recent Meta-analysis)	Part of an OPR of 1.18	Part of an OPR of 1.18	OPR is possibly decreasing over time, lower in Asia	
Motor Symptoms	More prone to tremor-dominant PD, less rigid	Less prone to tremor-dominant PD, more rigid	Unknown	
Non-Motor Symptoms	Report more pain symptoms, score higher on depression scales		Unknown	

Hierarchy of Motor Symptoms

Structure of Motor Symptoms

Parkinson's disease (PD) can be detected by examining bradykinesia (slow mobility), resting tremor, stiffening (increased muscle tone), and postural instability. Bradykinesia can manifest as akinesia or hypokinesia, although rest tremor is typically asymmetric, pill-rolling tremor. Other motor symptoms include hypomimia, hypophonia, and gait problems. These motor characteristics result from dopamine neurone loss in the substantia nigra, with alpha-synuclein aggregation playing an important role. Levodopa medication might result in on and off periods. The UPDRS motor section evaluates these symptoms and identifies unique but related domains such as stiffness, tremor, and bradykinesia. The UPDRS factor structure can change in early Parkinson's disease, indicating that motor symptoms are progressing dynamically.

Assessing Bradykinesia Using Gyroscope Signals

The clinical PD evaluations for bradykinesia are subjective; quantitative approaches using wearable gyroscopes provide an objective assessment. Gyroscopes record angular velocity and movement angle, enabling precise kinematic analysis of operations such as finger tapping, grasping, and pronation-supination. The parameters retrieved include movement range, velocity, frequency, power, and smoothness. Studies have found substantial relationships between gyroscope-derived metrics and clinical bradykinesia scores, supporting their usage. The pronosupination task (rapid hand rotation) and peak power analysis offer promising tools for detecting and tracking Parkinson's. These methods can objectively measure motor decline, helping with early diagnosis and monitoring disease progression. These tools allow for objective motor assessment, home monitoring, and more accurate therapy efficacy evaluation in research and clinical practice.

Table 3: Parameters Extracted from Gyroscope Signals for Bradykinesia Assessment (Motor Symptoms)

Parameter	Description	Movement Analyzed	Correlation with UPDRS	References
Range/Amplitude	Extent of movement	Wrist, Finger Tapping, Whole-Hand Grasp	Significant	(Summa et al., 2017)
Velocity (Peak, RMS)	Speed of movement	Finger Tapping	Good	
Frequency	Rate of repetitive movements	Finger Tapping, Whole-Hand Grasp	-	
Power	Intensity of movement	Finger Tapping, Prono-Supination	Good	
Smoothness (SAL)	Fluidity of movement	Finger Tapping	-	
Fatigability	Rate of decrease in speed/amplitude over repetition	Finger Tapping, Prono-Supination	-	
Modified Mean Range	Product of dominant frequency and mean range (for whole-hand grasp)	Whole-Hand Grasp	Good	

The Array of Nonmotor Symptoms (NMS)

Prevalence and Impact of Non-Motor Symptoms

Parkinson's disease is becoming acknowledged as a multisystem disorder characterised by a variety of non-motor symptoms that have an important influence on quality of life and can arise before motor symptoms. These include neuropsychiatric disorders (depression, anxiety, apathy, cognitive dysfunction, hallucinations), sleep irregularities (insomnia, Rapid Eye Movement sleep behavior disorder), autonomic dysfunction (constipation, urinary problems, orthostatic hypotension), and sensory issues (hyposmia, pain). NMS usually has a greater effect focused on quality of life than motor symptoms. Nearly all PD patients have at least one NMS, with some reporting more than 16 patients. Pain, exhaustion, sleep issues, cognitive difficulty, anxiety, and sadness are all common NMS symptoms. Certain NMS (depression, constipation, hyposmia) might appear years before motor symptoms and may serve as early signs. Hyposmia, RBD, and constipation are considered potentially initial or preclinical Parkinson's disease diagnostic markers. Despite their importance, NMS are typically neglected and undertreated with motor symptoms. Some patients have non-motor fluctuations (NMF), which vary in intensity throughout the day and are usually linked to levodopa-induced motor fluctuations.

Table 4: Common Non-Motor Symptoms in Parkinson's Disease

Symptom Category	Specific Symptoms	Prevalence (Range if available)	Impact on Quality of Life	References
Neuropsychiatric	Depression, Anxiety, Apathy, Cognitive Impairment, Hallucinations, Delusions, Impulse Control Disorders	Up to 50-60% for some	Significant, sometimes dominant impact	
Sleep Disorders	Insomnia, REM Sleep Behavior Disorder, Excessive Daytime Sleepiness, Restless Legs Syndrome, Sleep Apnea	Up to 75-84%	Can be very intrusive on the quality of life	
Autonomic Dysfunction	Constipation, Urinary Problems (urgency, frequency, incontinence), Orthostatic Hypotension, Excessive Sweating, Sexual Dysfunction, Drooling, Gastrointestinal Issues (e.g., delayed gastric emptying, dysphagia, sialorrhea, hypogeusia, dyschezia, weight loss), Cardiovascular dysfunctions	30-80% for some	Can be troublesome and disabling	
Sensory Issues	Hyposmia (reduced sense of smell), Anosmia (loss of smell), Pain (various types), Fatigue, Vision Changes, Smell and Taste Issues, Skeletal & Bone Health, Skin Changes, Vertigo & Dizziness, Lightheadedness, Foot Cramps, Peripheral Neuropathy, Restless Leg Syndrome, Facial Masking (non-verbal communication change)	Up to 95% for hyposmia	Can significantly affect daily life and well-being	(K Ray Chaudhuri et al., 2014; Summa et al., 2017) 2017)
Cognitive Changes	Memory Problems, Thinking Changes, Word Finding Difficulties, Judgment Problems, Confusion, Dementia	Up to 30% for some	Can be particularly concerning and impact independence	
Other Non-Motor	Fatigue, Low Blood Pressure, Bladder and Bowel Problems, Skin and Sweating Problems, Eating, Swallowing and Managing Saliva Problems, Speech and Communication Problems, Eye Problems, Foot Care, Mouth and Dental Issues, Hallucinations and Delusions (as a symptom), Weight Management, Melanoma, Personality Changes, Psychosis, Sexual Concerns		Can contribute to the overall disease burden and require specific management strategies	

Management Strategies for Non-Motor Symptoms

Efficient PD management involves finding and fixing a wide range of NMS. Approaches include both non-pharmacological and pharmaceutical treatments. Lifestyle adjustments (diet, exercise), cognitive training, mindfulness, and complementary therapy (acupuncture, massage) are all examples of non-pharmacological treatments. Exercise, mindfulness, and cognitive training have all been shown to benefit cognitive impairment, depression, and anxiety. Pharmacological therapies are frequently required for a variety of NMS. Treatments for motor symptoms may have a beneficial or negative impact on NMS, demanding tailored therapy. The MDS provides evidence-based recommendations for NMS treatment. However, given the widespread prevalence and importance of NMS, as well as the limitations of current treatments, there is a critical need for novel therapeutic techniques. A comprehensive PD management strategy usually involves a team-based care model and support groups.

Role of SNCA Gene Polymorphisms and Methylation

SNCA-Rep1 Polymorphic Locus

The *SNCA*-Rep1 locus, a dinucleotide microsatellite in the 5' regulatory region of the *SNCA* gene (encoding alpha-synuclein), has variable repeat numbers, leading to different alleles. Longer *SNCA*-Rep1 alleles are consistently associated with increased PD risk across various populations. The length of *SNCA*-Rep1 alleles is linked to *SNCA* gene methylation status. Longer alleles are associated with hypomethylation of CpG sites in intron 1 of *SNCA*. Hypomethylation in regulatory regions often increases gene expression. It's proposed that longer *SNCA*-Rep1 variants increase PD risk by causing hypomethylation in a transcriptionally significant region, potentially leading to increased alpha-synuclein expression and accumulation. While some studies report *SNCA* hypomethylation in PD patients, others do not, indicating complex epigenetic regulation in PD. Associations between specific SNPs in the *SNCA* region and gene methylation levels have also been identified. Meta-analyses have further elucidated the role of specific *SNCA* REP1 alleles in PD risk, with some alleles (265, 269, 271-bp) showing increased risk and the 267-bp allele appearing to decrease risk, although these effects can vary across ethnicities.

Influence of SNCA Rep1 Microsatellite Length on Cognitive Evolution

Studies suggest that *SNCA* Rep1 microsatellite length influences cognitive function evolution in PD patients. Carriers of longer Rep1 alleles tend to exhibit faster decline in global cognitive function (measured by MoCA). This suggests this genetic variation contributes to cognitive impairment, a common PD non-motor symptom. Individuals with longer *SNCA* Rep1 alleles may experience greater apathy increase over time, and a more pronounced decline in attention and memory. The longer 263 base pair allele of Rep1 has been linked to increased risk of dementia and visual hallucinations in PD patients. Longer Rep1 alleles are also associated with higher overall non-motor symptom burden (higher NMSS scores) and increased depression symptoms in early PD. Some studies found that PD patients with longer Rep1 alleles have more impaired cognitive and motor function. However, the role of *SNCA* common variants in PD progression is still under investigation, with some conflicting results. Nevertheless, accumulating evidence suggests that *SNCA* Rep1 microsatellite length may play a role in influencing cognitive evolution and the overall burden of non-motor symptoms in PD.

A Major Player in Parkinson's Disease

Where Does Alpha-Synuclein in Spinal Fluid Come From?

Alpha-synuclein (α-syn) is a sticky protein that clumps together in Parkinson's, forming harmful blobs called Lewy bodies. Scientists believe tracking this protein in spinal fluid (CSF) could help diagnose and treat the disease earlier. Research shows that most α-syn in spinal fluid comes directly from brain and nerve cells, not from leaking blood. Think of it as a factory (the brain) shipping out its products (α-syn) rather than importing them. The fact that α-syn levels taper off slightly as you move down the spine, just like other brain-made proteins, further proves it's homemade by the nervous system.

Alpha-Synuclein as a Potential Biomarker

Because alpha-synuclein (α-syn) plays such a big role in Parkinson's disease (PD), scientists have been checking its levels in spinal fluid (CSF) and blood as a possible way to detect the disease early. The idea is that if α-syn builds up in the brain, traces of it might show up in these easier-to-test fluids. Most studies find that people with PD have lower levels of α-syn in their spinal fluid compared to healthy individuals. Blood tests, however, give mixed results, sometimes higher, sometimes lower. Researchers think certain forms of α-syn, like tiny clumps called oligomers, might be better warning signs than just measuring total α-syn. Other brain injuries (like concussions) can also affect these levels, making things tricky. Interestingly, while total α-syn in spinal fluid tends to be lower in PD, tiny packets called exosomes in the blood might carry more of it, opening another possible path for diagnosis. The way α-syn moves between the brain and blood is complicated but understanding it could lead to better tests.

How Alpha-Synuclein Spreads in the Brain

To figure out how PD progresses, scientists study mice by injecting them with pre-formed clumps of human α-syn (called PFFs). These clumps act like seeds, spreading and turning healthy α-syn into harmful, misfolded versions like how prion diseases work. Even though the brain's cleaning system (the choroid plexus) quickly removes these clumps from spinal fluid, they still show up in key brain areas like the striatum shortly after injection. This spread triggers inflammation and weakens the barrier between blood and spinal fluid, which might kickstart damage. A single dose doesn't immediately cause movement problems, but repeated doses over months lead to weaker grip and more α-syn clumps in the brain, without yet killing dopamine cells. This suggests that long-term exposure to these clumps could slowly harm the brain's protective systems. Different shapes of α-syn clumps might cause different types of damage, adding to the complexity of PD.

Parkinson's Dementia (PDD) vs. Lewy Body Dementia (DLB): What's the Difference?

Both PDD and DLB involve clumps of α-syn (Lewy bodies) damaging the brain, but they're diagnosed based on when dementia appears:

- PDD -Dementia starts at least a year after Parkinson's movement symptoms (like tremors).
- DLB -Dementia comes before or around the same time as movement issues.

Despite this rule, the two conditions share many symptoms: memory swings, vivid hallucinations, and movement problems. Researchers are comparing α-syn and amyloid-beta levels in spinal fluid to tell them apart, especially in unclear cases. Some experts think PDD and DLB are part of the same disease spectrum, just showing up differently. For example, PDD often has more α-syn clumps in deep brain areas, while DLB spreads them widely across the outer brain layers. This might explain why DLB causes earlier and more severe thinking problems. The debate continues, but better tests could help patients get the right treatments sooner.

4. Conclusion

Parkinson's disease is a complex condition, with genetics, gender, and environment all influencing risk. Men are more prone to it, but the difference may be narrowing, possibly due to hormonal or lifestyle changes. New technologies, such as motion sensors, can detect early movement symptoms, but non-motor disorders (such as depression and sleep problems) are frequently overlooked. Parkinson's disease is primarily caused by misfolded alpha-synuclein proteins that spread throughout the brain. Researchers are working on tools for early detection and measures to halt this spread. The overlap with Lewy body dementia is uncertain; however, the timing of symptoms distinguishes them. More diversified trials, improved symptom tracking, and treatments that address both physical and mental consequences are essential for progress. Listening to patients is critical; research must begin with their experiences.

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