

Deciphering Functional Non-Coding Conserved Regions Governing α -Synuclein Gene Regulation

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Abstract

α -Synuclein, encoded by the SNCA gene, is central to the biology of Parkinson's disease and related synucleinopathies. Although coding variation and changes in SNCA dosage have been extensively studied, regulatory variation within conserved non-coding regions remains less well characterized in individual clinical cases. We describe an illustrative case of a 58-year-old man with parkinsonism and a strong family history of Parkinson's disease in whom targeted genomic analysis identified a rare sequence change within a highly conserved non-coding region upstream of SNCA. In this sample case, comparative sequence analysis, chromatin-accessibility data and an in-vitro reporter assay were used to explore the potential regulatory significance of the region. The analysis suggested altered enhancer activity and provided a framework for interpreting non-coding variants that may influence SNCA expression. The case demonstrates how clinical genomic evaluation can be integrated with functional assays when a potentially relevant non-coding variant is identified. These findings are illustrative only and are not evidence of pathogenicity.

Keywords: α -Synuclein; SNCA; non-coding DNA; enhancer; gene regulation; Parkinson's disease; functional genomics

Introduction

Parkinson's disease is a clinically heterogeneous neurodegenerative disorder characterized by motor features including bradykinesia, rigidity and resting tremor, together with a broad range of non-motor manifestations. The SNCA gene, which encodes α -synuclein, has a well-established relationship with synucleinopathy biology. Changes affecting SNCA dosage, expression and protein aggregation have therefore attracted substantial interest in both clinical and experimental research.

The regulatory architecture surrounding SNCA extends beyond its protein-coding sequence. Conserved non-coding regions may contain enhancers, silencers, transcription-factor binding sites and other regulatory elements that influence tissue-specific gene expression. A sequence variant in such a region can be difficult to interpret because conventional clinical variant pipelines are generally more mature for coding variants than for regulatory variation.

This case is presented as a model for documenting a clinically identified non-coding variant together with exploratory functional testing. It illustrates the structure and level of detail that may be appropriate for a case report involving genomic findings, while emphasizing that functional observations alone do not establish clinical causality.

Case Presentation

A 58-year-old man was evaluated in a movement-disorders clinic for a 3-year history of progressively asymmetric bradykinesia, right-sided rigidity and intermittent resting tremor. He reported reduced arm swing and difficulty performing fine motor tasks. His medical history was otherwise unremarkable. Two first-degree relatives had reportedly been diagnosed with Parkinson's disease after the age of 60.

Neurological examination demonstrated mild hypomimia, right-predominant bradykinesia, increased tone in the right upper limb and a low-amplitude resting tremor. Cognitive screening was within the expected range for age. Brain magnetic resonance imaging showed no structural abnormality that explained the presentation. The clinical findings were considered compatible with idiopathic Parkinsonian syndrome.

Genomic Evaluation

After genetic counseling, a targeted next-generation sequencing panel was performed. No clearly pathogenic coding variant was identified in the principal Parkinsonism-associated genes included in the panel. Because of the family history and the absence of an explanatory coding variant, the analysis was extended to selected conserved non-coding regions surrounding SNCA.

A rare single-nucleotide substitution was identified within a highly conserved non-coding interval located upstream of the SNCA transcriptional region. The variant was absent from the laboratory’s internal control dataset and had a high conservation score in the illustrative analysis. In-silico annotation suggested that the altered nucleotide was positioned within a putative regulatory element.

The finding was considered a variant of uncertain clinical significance. No change in clinical management was based solely on this result.

Functional Assessment

To explore whether the identified sequence could have regulatory activity, the corresponding reference and variant DNA fragments were cloned upstream of a luciferase reporter construct. The constructs were introduced into a dopaminergic neuronal cell model and a non-neuronal control cell line. Reporter activity was measured after standardized incubation.

In the illustrative experiment, the reference sequence increased reporter activity relative to the promoter-only control in the neuronal model. The variant construct showed lower activity than the reference construct. The effect was smaller in the non-neuronal cell line, suggesting that the regulatory activity might be context dependent.

Table 1. Illustrative functional reporter results

Construct	Neuronal model	Control cell line
Promoter only	1.00 ± 0.08	1.00 ± 0.07
Reference regulatory sequence	2.18 ± 0.16	1.31 ± 0.11
Variant regulatory sequence	1.46 ± 0.12	1.20 ± 0.10

Additional Bioinformatic Review

Comparative sequence inspection demonstrated conservation of the affected nucleotide across multiple vertebrate species in the illustrative dataset. Publicly available regulatory annotations were reviewed to determine whether the interval overlapped predicted enhancer-associated chromatin features. The region was considered a plausible candidate regulatory element, but the available evidence was insufficient to assign a definitive molecular mechanism.

Clinical Course

The patient was treated according to standard clinical management for Parkinsonian symptoms. At a 12-month follow-up, motor symptoms remained stable on symptomatic therapy. The non-coding sequence finding was documented in the clinical record as a research-level observation rather than a confirmed disease-causing variant. Genetic counseling emphasized the uncertainty of the finding and the limitations of extrapolating functional assay results to individual disease risk.

Discussion

Non-coding variation presents a major interpretive challenge in clinical genomics. Unlike many coding variants, regulatory variants may alter transcription-factor binding, chromatin organization or enhancer activity without changing the amino-acid sequence of the encoded protein. For genes such as SNCA, where altered expression and dosage are biologically relevant, investigation of regulatory architecture may provide additional insight when conventional sequencing does not identify an explanatory coding variant.

In this illustrative case, the combination of conservation analysis, regulatory annotation and reporter testing suggested that the candidate interval may have transcriptional activity. The apparent reduction in reporter activity associated with the variant provides a hypothesis for further investigation, but it does not establish that the variant changes SNCA expression in the human brain or contributes to Parkinson’s disease.

Functional assays also require careful interpretation. Reporter constructs do not fully reproduce endogenous chromatin structure, three-dimensional genomic interactions or the cellular environment of human substantia nigra neurons. Additional approaches, such as endogenous gene-expression studies, chromatin profiling, allele-specific expression analysis and appropriately designed neuronal models, would be required to establish biological relevance.

The presence of a variant in a conserved region can increase biological interest but should not be equated with pathogenicity. Clinical interpretation should incorporate population frequency, segregation, phenotype, functional evidence, established disease mechanisms and other relevant evidence. In a real clinical setting, classification should follow an appropriate variant-interpretation framework and should be periodically reconsidered as evidence develops.

This case also highlights the value of integrating clinical genetics with functional genomics. When a rare non-coding variant is identified in a patient with a compatible phenotype, a structured investigation can help determine whether the region has plausible regulatory activity. Nevertheless, research findings should be clearly separated from clinically validated evidence.

Limitations

This sample case has important limitations. The functional findings are illustrative, the patient information is , and no conclusions regarding SNCA expression or Parkinson's disease causation can be drawn. In an actual report, replication, appropriate controls, detailed assay methods, statistical analysis, variant classification criteria and independent confirmation would be necessary.

Conclusion

Conserved non-coding regions surrounding disease-associated genes may represent clinically interesting targets when conventional coding-sequence analysis does not explain a patient's phenotype. A combination of genomic annotation and functional testing can generate useful hypotheses regarding regulatory mechanisms. However, functional observations should be interpreted cautiously and should not be presented as proof of pathogenicity without adequate clinical and experimental evidence.

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