Insufficient evidence for pathogenicity of SNCA His50Gln (H50Q) in Parkinson's disease

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Highlights

• Publicly available data show that *SNCA* His50Gln has a frequency of ~0.01% in Europeans

• *SNCA* His50Gln was reported to cause Parkinson's disease, but it is too common to do so

• There is no evidence of variant enrichment in Parkinson's disease cases compared to controls

Abstract

SNCA missense mutations are a rare cause of autosomal dominant Parkinson's disease (PD). To date, six missense mutations in *SNCA* have been nominated as causal. Here, we assess the frequency of these six mutations in public population databases and PD case-control datasets in order to determine their true pathogenicity. We found that one of the six reported *SNCA* mutations, His50Gln, was consistently identified in large population databases and no enrichment was evident in PD cases compared to controls. These results suggest that His50Gln is probably not a pathogenic variant. This information is important to provide counseling for His50Gln carriers and has implications for the interpretation of His50Gln α-synuclein functional investigations.

Introduction

Parkinson's disease (PD) disease is one of the most common neurodegenerative disorders. The pathological hallmark of PD are Lewy bodies, which are neuronal cytoplasmic inclusions consisting of misfolded α-synuclein encoded by the *SNCA* gene (Spillantini et al., 1997). To date, six missense mutations in the *SNCA* gene have been reported to cause PD: three well established mutations (Ala30Pro, Glu46Lys and Ala53Thr) and three more recently described mutations (His50Gln, Gly51Asp and Ala53Glu) (Figure 1 and Table 1). Whilst atypical presentations and a later onset have been reported, *SNCA* mutation carriers typically develop autosomal dominant early-onset PD characterized by a severe, rapidly progressive course and cognitive decline that commonly progresses to Lewy body dementia (Papadimitriou et al., 2016; Trinh et al., 2014). A fuller understanding of exactly which mutations are truly causal for PD will help direct research on the pathophysiology of PD driven by *SNCA* mutations, and is of crucial importance for counseling of mutation carriers and their family members. Here, we explore the frequency and spectrum of these different *SNCA* mutations in several large public datasets, and then examine their presence in several large PD case-control datasets.

Results

The only *SNCA* missense mutation identified in the population databases was His50Gln (Table 1). To assess whether the His50Gln mutation is found in PD cases, we accessed several PD case/control datasets, which cumulatively totaled 11,095 PD cases and 12,615 controls. From these data, we identified two controls and one case carrying the *SNCA* His50Gln mutation. Additionally, two PD cases carrying Ala53Thr and a single PD case with Gly51Asp mutation were found (Table 2 and Supplementary data). We next assessed pathogenicity prediction

algorithms for all six *SNCA* mutations and overall *SNCA* His50Gln scored poorly compared to the other five *SNCA* mutations (Figure 1, Table 1 and Supplementary data). For comparison, we used the known pathogenic *LRRK2* Gly2019Ser mutation as it is also present in the general population (Table 2)**.** Unlike for *SNCA* His50Gln, analysis in PD case-control datasets revealed a consistent increase in the frequency of *LRRK2* Gly2019Ser mutation carriers amongst PD cases than controls (Table 2).

Discussion

Here, we examined the presence of reported pathogenic *SNCA* missense mutations in large population control databases and identified that His50Gln is relatively frequent in both the European and African population. In contrast, the other five reported pathogenic mutations were not observed in these control databases. Follow-up analysis in large PD case-control cohorts identified two additional control individuals carrying this variant, representing a similar frequency to the public population databases. We identified the His50Gln mutation in a homozygous state in one sporadic early-onset PD case with an age at onset at 32 years and two heterozygous controls with last known ages of 62 and 89. Notably, two other *SNCA* mutations, Ala53Thr and Gly51Asp, were found twice and once respectively in cases, demonstrating the power of our large dataset to detect rare mutations in the *SNCA* gene. The *SNCA* His50Gln case presented with a classic PD phenotype and was free of dementia and cognitive decline after almost 10 years of disease, which is unusual for patients with pathogenic *SNCA* missense mutations (Papadimitriou et al., 2016). Currently, with the lack of other homozygous cases or controls there is insufficient evidence to conclude that the His50Gln mutation is pathogenic in a homozygous state. One possibility is that the His50Gln mutation has reduced penetrance, as has

been reported for other PD mutations, such as *LRRK2* Gly2019Ser (Healy et al., 2008; Latourelle et al., 2008). However, the lack of enrichment of *SNCA* His50Gln in PD cases versus controls argues against this and this contrasts with the enrichment observed for the *LRRK2* Gly2019Ser mutation, Table 2. Assuming a life-time risk of 1.3-2% (depending on sex) to be diagnosed with PD (Elbaz et al., 2002), one would expect ~2,600 individuals from gnomAD to develop PD. If the *SNCA* His50Gln mutation is indeed pathogenic, fully penetrant and inherited in an autosomal dominant fashion, the 22 carriers of this allele would represent around ~1% of all PD cases. Similarly, we would expect to identify over 100 PD patients in our PD case cohorts. This was not observed and argues against pathogenicity of this vairant. In general, segregation data, case-control enrichments, absence in population databases and pathogenicity prediction algorithms are considered important criteria for establishing the causality of sequence variants for genetic disease (MacArthur et al., 2014; Richards et al., 2015), however the *SNCA* His50Gln mutation does not fulfill any of these criteria (Table1). In conclusion, while it is tempting to speculate about the pathogenicity of *SNCA* His50Gln, especially given limited *in vitro* evidence indicating an increased propensity to form α-synuclein fibrils (Rutherford et al., 2014), we conclude that insufficient evidence exists to nominate the His50Gln mutation as a causative mutation or high risk mutation. This finding has important implications for the interpretation of functional investigations of His50Gln mutated α-synuclein isoforms as well as for future study design. Furthermore, when identifying the *SNCA* His50Gln mutation in either a patient or an asymptomatic individual, caution should be used by clinicians and genetic counselors, as genetic evidence suggests this is a rare benign variant.

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Gene: amino acid change	rs number	chr:bp (hg19)	gnomAD (frequency)	HRC (frequency)	SIFT (score)	Polyphen2 (score)	CADD phred	DANN score	GERP++ RS
SNCA: Ala30Pro (Kruger et al., 1998)	rs104893878	4:90756731	0	0	D (0.001)	D (0.996)	32	0.998	4.28
SNCA: Glu46Lys (Zarranz et al., 2004)	rs104893875	4:90749321	0	0	D (0.006)	B (0.426)	26.4	0.998	3.55
SCNA: His50Gln (Appel-Cresswell et al., 2013; Proukakis et al., 2013)	rs201106962	4:90749307	22 (0.0079%)	7 (0.011%)	T (1)	B (0.012)	0.007	0.425	-2.19
SNCA: Gly51Asp (Kiely et al., 2013; Lesage et al., 2013)	rs431905511	4:90749305	0	0	D (0.004)	D (0.999)	23.9	0.996	3.55
SNCA: Ala53Glu (Pasanen et al., 2014)	n/a	4:90749299	0	0	D (0.007)	B (0.015)	15.99	0.952	4.39
SNCA: Ala53Thr (Polymeropoulos et al., 1997)	rs104893877	4:90749300	0	0	T (1)	B (0)	10.48	0.203	3.12
LRRK2: Gly2019Ser (Gilks et al., 2005)	rs34637584	12:40734202	136 (0.049%)	13 (0.020%)	D (0)	D (1)	35	0.998	5.69

Table 1: Prevalence of six reported pathogenic *SNCA* mutations and *LRRK2* Gly2019Ser in large population databases and pathogenicity algorithm scores. Twenty-two individuals in gnomAD (3 Africans and 19 Europeans, n=138,587) and seven individuals in HRC (all Europeans, n=32,488) were heterozygous for *SNCA* His50Gln (Lek et al., 2016; McCarthy et al., 2016). The *LRRK2* Gly2019Ser mutation was found in 136 individuals in gnomAD (3 African, 8 Latino, 118 European [including Ashkenazi Jewish] and 7 other) and 13 individuals in the HRC (all Europeans). gnomAD = Genome Aggregation Database, HRC = Haplotype Reference Consortium, D = damaging, T = tolerant, B = benign.

Dataset	Population description	No. controls	No. cases	His50Gln alleles in controls (frequency)	His50Gln alleles in cases (frequency)	Gly2019Ser alleles in controls (frequency)	Gly2019Ser alleles in cases (frequency)	Average sequencing coverage at *SNCA* locus
IPDGC whole-exome sequencing	Mainly European ancestry	5,774	2,440	1 (0.0087%)	0	4 (0.0346%)	25 (0.51%)	>35x
IPDGC resequencing data	Mainly European ancestry	2,391	3,481	1 (0.021%)	0	0	56 (0.80%)	>60x
McGill resequencing data[1]	Mainly European and Jewish ancestry	2,460	2,175	0	0	11 (0.22%)	125 (2.9%)	>300x
COURAGE-PD resequencing data[2]	Both Asian and European ancestry	1,490	1,490	0	0	0	6 (0.20%)	>400x
French PDG group resequencing data	Mainly of French European origin	500	1,509	0	2 (1 case in HMZ state) (0.07%)	0	42 (1 HMZ + 40 HTZ) (1.39%)	>260x
Total		12,615	11,095	2 (0.0079%)	0 (0.0090%)	15 (0.059%)	254 (1.1%)	

Table 2: Frequency of *SNCA* His50Gln and *LRRK2* Gly2019Ser in large PD case/control datasets. HMZ = homozygous and HTZ = Heterozygous. [1] Samples included cohorts from Quebec, France, Israel and Columbia University NY (Alcalay et al., 2015). [2]Allele counts in the COURAGE-PD dataset were called from sequencing of DNA pools representing 10 cases or 10 controls. Average coverage is given per sample pool. For subsets of COURAGE-PD participants with available data on *LRRK2* Gly2019Ser status, known mutation carriers have been excluded from the resequencing study.

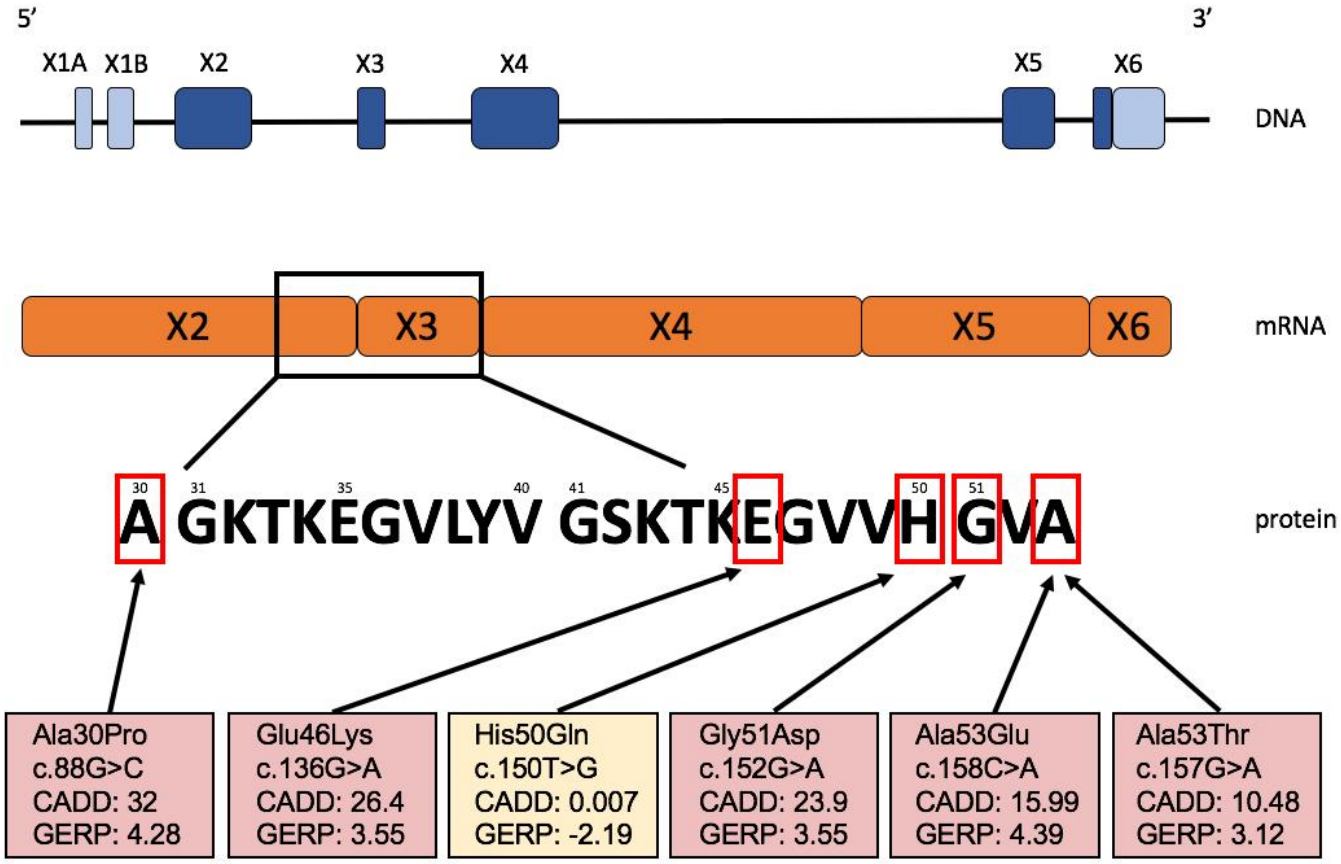

Figure 1: Overview of the *SNCA* gene on DNA, mRNA and protein level. The *SNCA* gene has six exons of which several are non-coding (light-blue). NB the *SNCA* gene is located on the antisense strand of the human genome. On mRNA level five exons are left totaling 423 nucleotides (NM_000345) which result in a 141-amino acid protein. All six missense mutations are located in exon two and three in relatively close proximity. When comparing pathogenicity algorithm scores (CADD (Quang et al., 2015), GERP (Davydov et al., 2010)) between the six missense variants, His50Gln scores very poor compared to the other five missense mutations.