Parkinsonism and Related Disorders xxx (2015) 1–5

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Phenotypic spectrum of alpha-synuclein mutations: New insights from patients and cellular models

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ARTICLE INFO

Article history:
Received 11 August 2015
Accepted 14 August 2015

Keywords:
SNCA
Alpha-synuclein
Mutations
Genotype-phenotype correlates

ABSTRACT

The identification of the p.A53T mutation in the *SNCA* gene encoding alpha-synuclein (alpha-syn), as causative of autosomal dominant Parkinson disease (PD) represented a fundamental milestone, which paved the way to the extremely prolific field of PD genetics. Despite being the oldest player in this field and only a rare cause of inherited PD, research on alpha-syn has remained incredibly active over nearly twenty decades, leading to identify alpha-syn aggregation as a key mechanism in PD pathogenesis.

The past two years have witnessed new exciting findings, with the discovery of at least three novel pathogenic mutations (p.H50Q, p.G51D and p.A53E) causative of complex parkinsonian phenotypes, and the identification of additional patients carrying "old" *SNCA* mutations (p.A53T, p.A30P, p.E46K and whole gene multiplications), which has allowed to further expand their phenotypic spectrum. This review aims at providing a clinical and functional update on the most recent findings in alpha-syn genetics, at the same time discussing novel avenues of *SNCA* research such as those on somatic mutations and epigenetic mechanisms.

1. Introduction

The central role of alpha-synuclein (alpha-syn) in Parkinson disease (PD) pathogenesis emerged nearly twenty years ago, with the identification of the p.A53T mutation as the first genetic cause of inherited PD in an Italian-Greek family, the Contursi kindred [1]. A year later, this previously neglected protein was found in its aggregated form to be the most abundant component of Lewy bodies, Lewy neurites and glial cell inclusions, thereby creating a direct and unexpected link between PD, multiple system atrophy (MSA) and Lewy Body Dementia (LBD). These disorders were then collectively termed "synucleinopathies" [2]. In subsequent years, research on alpha-syn flourished, leading to the identification of two other rare mutations (p.A30P and p.E46K) and whole gene multiplications as causative of autosomal dominant PD, and of several polymorphic variants as risk factors for sporadic PD [3].

Alpha-syn is a 140 amino acid protein encoded by the *SNCA* gene on chromosome 4q22.1. It is highly expressed in neural tissues, representing more than 1% of the total brain protein content, where it predominantly localizes to presynaptic terminals. Although its physiologic function is not fully characterized yet, alpha-syn has been implicated in synaptic plasticity, vesicle dynamics and dopamine metabolism. Moreover, a large wealth of functional studies on *in vitro* and *in vivo* models have unequivocally demonstrated that accumulation and aggregation of wild type alpha-syn has a deleterious impact on a number of key mechanisms, including mitochondrial homeostasis and dynamics, endoplasmic reticulum stress and functioning of the two major cellular clearance pathways, namely the ubiquitin-proteasome system and autophagy [4,5]. As expected, the few identified *SNCA* pathogenic mutations were all found to increase alpha-syn toxicity; yet, for many years, genetic screenings in large PD cohorts yielded negative results, making *SNCA* mutations one of the rarest causes of inherited PD. Only recently genetic research on alpha-syn has taken a new spur, with the identification of some new mutations and the expansion of the phenotypic spectrum of those previously reported.

This review aims to provide an update on the most recent clinical, genetic and functional discoveries related to *SNCA* mutations, including "old mutations" (those identified between 1997

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http://dx.doi.org/10.1016/j.parkreldis.2015.08.015
1353-8020/

and 2004) and “new mutations” (described over the past two years) (Fig. 1).

2. New phenotypes for old mutations

2.1. SNCA point mutations

“Old” *SNCA* point mutations include p.A53T, p.A30P and p.E46K. The p.A53T mutation definitely bears the greatest historical value, being the first mutation ever identified to cause a monogenic form of PD [1]. Since its first description in 1997 in the large Contursi kindred, this same mutation has been reported in over 60 familial and sporadic cases, mostly with Greek or Italian background (due to a founder effect), but also from Poland, Korea and Sweden. The other two mutations were considered much rarer, being described in a single German and Basque kindred, respectively [5,6].

Among the known genes causative of mendelian PD, *SNCA* is the only one for which specific genotype-phenotype correlates have been proposed. In fact, most p.A53T mutation carriers develop PD with onset in the fourth to sixth decade (on average 10 years earlier than other *SNCA* mutations), rapid progression (mean time from onset to death was 8 $\pm$ 4 years), and variable occurrence of cognitive, psychiatric and autonomic disorders. In the German family carrying the p.A30P mutation, PD had a later onset in the sixth to eight decade; cognitive impairment was reported in two out of four patients, in the absence of other non-motor signs. Finally, a severe, highly penetrant parkinsonism with frequent occurrence of dementia, dysautonomia, depression and fluctuating alertness has been reported in members of the Spanish family carrying the p.E46K mutation (reviewed in Ref. [6]).

In the past two years, the identification of novel mutated patients has expanded the phenotypic spectrum of “old” *SNCA* mutations, challenging at least in part the existing genotype-phenotype correlates. For instance, we recently assessed a new branch of the Contursi kindred carrying the p.A53T mutation, which was followed-up for over 10 years. Affected members showed a longer disease duration than previously reported (up to 19 years from onset to death) and marked intra-familial variability as regard the age at onset, disease severity and occurrence of non-motor features. Interestingly, odor identification ability and DAT-scan were abnormal not only in patients but also in one 28-year-old asymptomatic carrier, suggesting a subclinical or preclinical dopaminergic dysfunction related to the presence of the mutation (Ricciardi et al., submitted).

Recently, Pimentel and co-workers reported a Bolivian family of Spanish origin carrying the p.E46K mutation, with a PD phenotype clearly less aggressive than that originally described in the Basque kindred. In particular, no relevant cognitive, autonomic or psychiatric dysfunctions were present in the proband after 7 years from disease onset [7]. New data have also emerged from a reassessment of the original p.E46K Basque family. A longitudinal neuropsychological study performed on available patients showed fluctuating frontal lobe deficits and posterior cortical dysfunction as early cognitive features associated to the p.E46K mutation [8]. Furthermore, selective cardiac sympathetic denervation was found in five of six carriers (including one asymptomatic subject) who underwent MIBG scintigraphy [9].

2.2. SNCA gene multiplications

Multiplications of the whole *SNCA* gene have long been recognized as causative of inherited PD. Since 2003, *SNCA* triplications were reported in 29 patients belonging to seven families; *SNCA* duplications are far more common, being detected in several familial and sporadic patients worldwide. The presence of extra copies of the *SNCA* gene results in overexpression of wild type alpha-syn, leading to increased formation of toxic aggregates and widespread neuronal damage [5].

Similarly to missense mutations, *SNCA* multiplications are also responsible of different phenotypes, whose severity seems to correlate with the overall number of gene copies. In general, the presence of four *SNCA* copies (as in case of heterozygous triplications or homozygous duplications) causes a fully penetrant, severe parkinsonian syndrome, in which motor impairment is invariably associated with sleep disorders, cognitive decline and psychiatric disturbances. Autonomic dysfunctions may also be present. Conversely, the clinical presentation of *SNCA* heterozygous duplications is much more variable, ranging from a benign form of late onset parkinsonism indistinguishable from idiopathic PD to a more aggressive, early onset hypokinetic disease with prominent non-motor features, resembling *SNCA* triplications. Asymptomatic carriers have also been described, indicating reduced penetrance [6,10,11].

Recent clinical studies corroborated and expanded these genotype-phenotype correlates. In particular, the report of long-term 12-years follow-up for the Iowa family, a second patient carrying homozygous *SNCA* duplications and a further kindred with *SNCA* triplication endorsed early cognitive dysfunction and

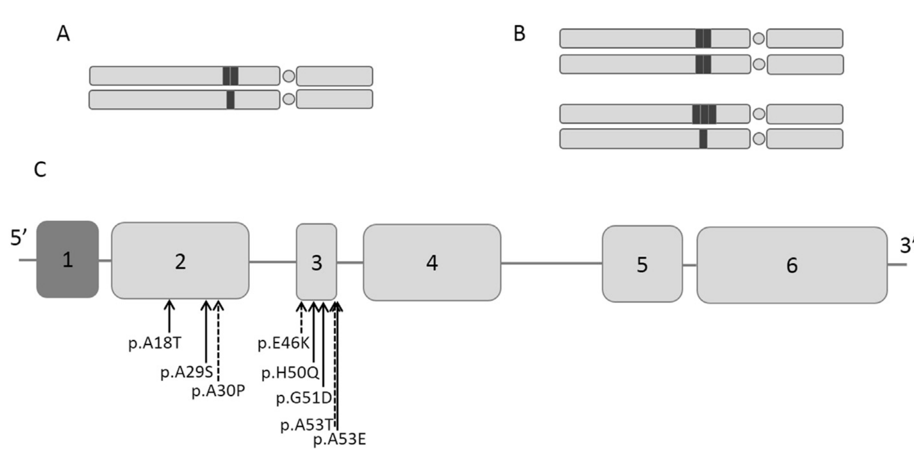

Fig. 1. Schematics of chromosome 4 with *SNCA* gene multiplications (dark grey rectangles), and of alpha-syn protein, with representation of known mutations. A) *SNCA* heterozygous duplication; B) *SNCA* heterozygous triplication or *SNCA* homozygous duplication, both resulting in the presence of four gene copies; C) “old” (dashed arrows) and “new” (full arrows) missense mutations. Exon 1 is non-coding.