Kinase Mutations in Dominant Form of Spinocerebellar Ataxia (SCA)

Hirohide Asai*
Department of Pharmacology and Experimental Therapeutics, Boston University School of Medicine, USA

To date, 31 genes associated with different forms of SCA have been identified, but the cellular and molecular bases for this pathology remain poorly defined. The autosomal dominant cerebellar ataxias (ADCA) were thought to be exclusively due to expansions of coding CAG repeats, as in the genes that underlie SCA1, SCA2, SCA3, SCA6, SCA7, SCA17, and DRPLA (dentatorubropallidolysian atrophy)—the so-called polyglutamine expansion SCAs. About 90% of genetically diagnosed ADCA is attributed to polyglutamine expansion SCAs [1]. However, mutations in two different kinase coding genes have been discovered in ADCA families: tau-tubulin-kinase 2 (TTBK2) in SCA11 and protein kinase c gamma (PKCγ) in SCA14. The roles of these two kinases are essential for post-translational modifications controlling neuronal degeneration or functional maintenance and, very interestingly, these kinases or their isoforms share common signaling pathways with another SCAs or neurodegenerative diseases. In this short communication, I introduce these two interesting ADAC causative kinases, their molecular signaling pathways leading to degeneration, and our published data on the topics.

SCA11 (tau-tubulin-kinase 2, TTBK2)

Mutations within TTBK2 cause SCA11, which is characterized by progressive cerebellar ataxia, pyramidal features, peripheral neuropathy and, on occasion, dystonia, with age of onset from the early teens to the mid-20s. TTBK2 consists of 1244 residues and apart from an N-terminal serine/threonine protein kinase domain (residues 20–280) possesses no distinctive functional domains or motifs. SCA11 truncating mutations promote TTBK2 protein expression, suppress kinase activity and lead to enhanced nuclear localization [2]. More recently, these mutant proteins inhibit ciliogenesis and it has been suggested that the cell-cycle regulators target TTBK2 to the basal body, where it modifies specific targets to initiate ciliogenesis [3].

TTBK1 is highly homologous to TTBK2 and is among the closest relatives of casein kinase in the CK1 groups. TTBK1 protein expression is significantly up-regulated in Alzheimer disease (AD) brains, and genetic variations of the TTBK1 gene are associated with late-onset AD in two cohorts of Chinese and Spanish populations. Interestingly, its highest expression is found in the perforant pathway area, the pyramidal layer of hippocampal CA1-3 fields, and the granular layer of dentate gyrus. Our laboratory created TTBK1 transgenic mice and showed enhanced activity of cyclin-dependent kinase 5 (Cdk5) and glycogen synthase kinase-3β (GSK3β), and accumulation of hyperphosphorylated tau in the brain. This suggests that TTBK1 is involved in early tauopathy development in AD brain [4].

SCA14 (Protein kinase C gamma; PKCγ)

Spinocerebellar ataxia type 14 (SCA14) is an autosomal dominant cerebellar ataxia, associated with various combinations of myoclonus, Parkinsonism and dementia. Causative mutations have been identified in the PRKCG gene encoding protein kinase Cy (PKCγ). PKCγ, comprising 697 amino acids with two N-terminal regulatory and two C-terminal catalytic domains, is a major PKC isoform in cerebellar Purkinje cells and regulates certain motor learning functions and cell morphology. We have reported an SCA14 family with a new type of mutation, i.e. a deletion of a termination-codon-containing region of the PRKCG gene, producing a mutant PKCγ protein (M697Iex) with a missense change (M697I) and a C-terminal 13-amino-acid extension (Ext13) with increased kinase activity. We also shed new light on the molecular consequences of increased kinase activities of PKCγ mutants: aprataxin (APTX), a DNA repair protein causative for autosomal recessive ataxia, was found to be a preferential substrate for mutant PKCγ, and the resultant phosphorylation inhibited its nuclear entry because of disturbed interactions with importin α, a nuclear import adaptor. Decreased nuclear APTX sensitized cells to oxidative stress by increasing unrepaired DNA damage. Phosphorylation-resistant APTX, a kinase inhibitor, and antioxidants reduced DNA damage and thus cell death [5].

Here, we briefly summarize two SCA forms caused by kinase mutants. Furthermore, these kinases and highly homologous isoforms interact or share the neurodegenerative diseases. Because regulating kinase activity can be a pharmacological therapeutic target, to characterize these kinase-mediated mechanisms of degeneration should extend the possibility of neurodegenerative disease therapy.

REFERENCES


