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Review

Role of genomics in translational research for Parkinson's disease

Kazunari Sekiyama, Yoshiki Takamatsu, Masaaki Waragai, Makoto Hashimoto *

Tokyo Metropolitan Institute of Medical Sciences, 2-1-6 Kamikitazawa, Setagaya-ku, Tokyo 156-0057, Japan

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ABSTRACT

Research on Parkinson's disease (PD) has made remarkable progress in recent decades, due largely to new genomic technologies, such as high throughput sequencing and microarray analyses. Since the discovery of a linkage of a missense mutation of the α-synuclein (αS) gene to a rare familial dominant form of PD in 1996, positional cloning and characterization of a number of familial PD risk factors have established a hypothesis that aggregation of αS may play a major role in the pathogenesis of PD. Furthermore, dozens of sensitizing alleles related to the disease have been identified by genome wide association studies (GWAS) and meta-GWAS, contributing to a better understanding of the pathological mechanisms of sporadic PD. Thus, the knowledge obtained from the association studies will be valuable for "the personal genome" of PD. Besides summarizing such progress, this paper focuses on the role of microRNAs in the field of PD research, since microRNAs might be promising as a biomarker and as a therapeutic reagent for PD. We further refer to a recent view that neurodegenerative diseases, including PD, coexist with metabolic disorders and are stimulated by type II diabetes, the most common disease among elderly populations. The development of genomic approaches may potentially contribute to therapeutic intervention for PD.

Contents

1. Introduction

First described by Dr. James Parkinson in his historic publication, "Shaking palsy", in 1817, Parkinson's disease (PD) is now known as the second most common age-related neurodegenerative disease after Alzheimer's disease (AD) in super-aged societies [1]. PD is clinically manifested by motor dysfunctions, such as rigidity, resting tremor, bradykinesia, and postural instability, as well as by non-motor symptoms, including cognitive deficits, depression, and sensory, sleep, and emotional problems [2]. These symptoms of PD appear due to a deficiency of dopamine caused by dopaminergic neuronal degeneration in the substantia nigra pars compacta. In addition to neuronal cell death, the degenerating neurons are histopathologically distinguished by the formation of Lewy bodies,

* Corresponding author. Fax: +81 3 5316 3150.
E-mail address: hashimoto-mk@igakuken.or.jp (M. Hashimoto).

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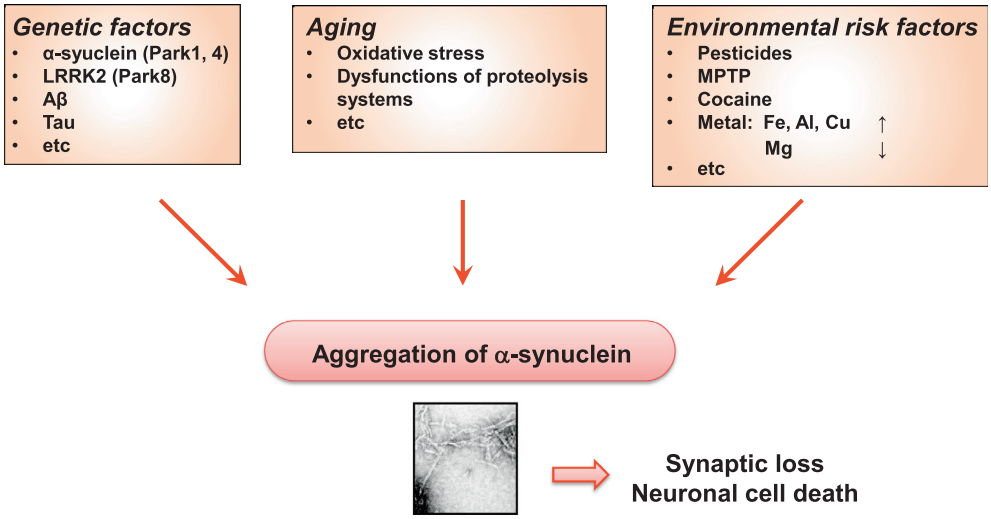

Fig. 1. Schematic of the pathogenesis of PD: αS may be situated at the center of the pathogenesis of PD.

the intracellular inclusions which are composed of various molecules, including α-synuclein (αS), ubiquitin, and neurofilaments [3]. Similar pathologies are observed in the α-synucleinopathies, such as dementia with Lewy bodies (DLB), and Lewy variants of AD, while in multiple system atrophy (MSA), Lewy bodies are frequently localized in the oligodendrocytes [3,4].

Recently, there has been much progress in understanding the pathophysiological mechanisms of PD with the development of newer technologies. Since the linkage of missense mutations in the αS gene to a rare familial dominant PD was identified [5], a wealth of new studies has been performed, leading to the established view that aggregation of αS, a presynaptic protein with unknown functions, may play a central role in the pathogenesis of PD (Fig. 1). Consistent with this notion, further studies on a number of familial PD risk factors have shown that deregulation of these molecules may result in stimulation of pathological αS aggregation [6]. Moreover, results of genome wide association studies (GWAS) have corroborated the association of sporadic PD with variety of genes including *SNCA* (a gene encoding αS), leucine-rich repeat kinase 2 (*LRRK2*), and *MAPT* (a gene encoding tau) [7]. It is expected that the knowledge obtained from these association studies will be valuable for early diagnosis/treatment of PD and for the personal PD genome in the future.

Despite the many efforts made to understand the pathogenesis of PD, there are still no treatments available that cure PD. Consequently, huge expenditures on medical and nursing care of these patients have become a serious problem for our society. Therefore, a solution to this issue has become a high priority in research on neurodegenerative diseases. In this context, since it is expected that the development of genomic approaches may play a key role in the development of a therapeutic intervention for PD, we present this important issue in this review. We first summarize the advances made using positional cloning and GWAS in PD research whereby genomic approaches have played central roles. We then discuss the possibility that the development of advanced genomic technologies, such as a next-generation sequencing and array technology, may lead to a therapeutic intervention for PD. In this respect, special attention will be paid to the relevance of microRNA (miRNA) to PD pathogenesis since accumulating evidence suggests that deregulation of miRNA expression may play an important role in the pathogenesis of PD, and manipulation of miRNA may potentially lead to a therapy. We further discuss a recent view that neurodegenerative diseases, including PD, have aspects of metabolic disorders and are exacerbated by type II diabetes mellitus (DM), the most common disease among aged-populations. We suggest that genomic studies may contribute to our understanding of the mechanism by which DM stimulates PD, leading to new therapeutic approaches for PD.

2. The mechanism of PD is revealed by genomic research (1): the synuclein family of peptides

PD research greatly benefited from the progress in molecular biology technologies when in 1996 Polymeropoulos and his associates discovered a linkage of a missense mutation (A53T) of the αS gene to a rare familial PD case (referred to as PARK1) [8] (Fig. 2). Subsequent to the A53T discovery [5], another missense mutation A30P [9] was reported in PD and E46K was reported in DLB [10] (Fig. 2). In 2013, an additional four cases of mutations, A18T, A29S, H50Q, and G51D, were reported for both PD and DLB [11–13], while another A53E mutation was found in MSA [14]

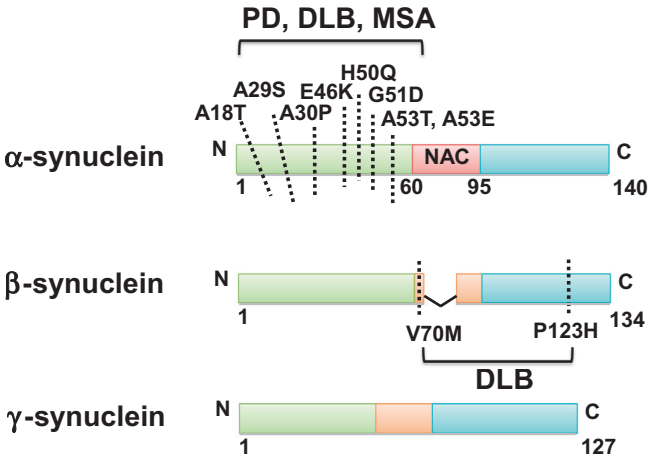

Fig. 2. Missense mutations of the synuclein peptide family (α, β, γ). Synucleins are composed of N-terminal basic regions with a repeating motif (KTKEGV) and divergent C-terminal acidic regions. The central region of α-synuclein includes a strongly hydrophobic NAC (*n*on-β-*a*myloid component of the AD amyloid) domain, whereas the majority of the corresponding region in β-synuclein is naturally deleted and the same region in γ-synuclein is less hydrophobic [21]. For α-synuclein 8 mutations (A18T, A29S, A30P, E46K, H50Q, G51D, A53T and A53E) have been found from PD, DLB and MS, respectively [17]. For β-synuclein, two mutations (V70M and P123H) have been reported in sporadic and familial DLB [17].

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