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Review

Genomic aspects of sporadic neurodegenerative diseases

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ABSTRACT

Sporadic neurodegenerative diseases are complex in nature, that is, they involve multiple genetic and environmental factors that may play roles at the molecular level. In contrast to diseases with Mendelian inheritance, the genomic signatures of common sporadic forms of neurodegenerative diseases largely remain unknown. Over the past decade, genome-wide association studies employing common single-nucleotide polymorphisms have been intensively conducted, in which the theoretical framework is based on the "common disease–common variants" hypothesis. Another paradigm is a sequence-based association study under the "common disease–multiple rare variants" hypothesis. Because current next-generation sequencing technologies enable us to obtain virtually all the variants in human genome irrespective of allele frequencies, it is anticipated that sequence-based association studies will become the mainstream approach. In this review, we present brief overviews of molecular genetic approaches to elucidate the molecular bases of sporadic forms of neurodegenerative diseases, including Alzheimer disease, Parkinson disease, and multiple system atrophy as examples.

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1. Introduction

Neurodegenerative disease is an umbrella term for various types of disease characterized clinically by ages at onset usually in the late adulthood and by specific neurological symptoms such as cognitive decline, ataxia, parkinsonism, or motor weakness, and neuropathologically by the progressive neuronal dysfunctions usually accompanied by cell death of specific groups of neurons. Histopathologically, many neurodegenerative diseases have distinctive inclusion bodies in neurons as well as glial cells that are associated with the accumulation of misfolded and aggregated proteins, such as Lewy bodies in Parkinson disease (PD), senile plaques in Alzheimer disease (AD), TDP-43-positive inclusions in amyotrophic lateral sclerosis (ALS), and glial cytoplasmic inclusions (GCIs) in multiple system atrophy (MSA) [1].

Although palliative therapies that temporarily and partially relieve symptoms are currently available for several neurodegenerative diseases, such as choline esterase inhibitors or *N*-methyl-D-aspartate (NMDA) antagonists for AD, there remains no disease-modifying therapy that directly targets the underlying neurodegenerative processes or halts the progression of these diseases. Elucidation of the molecular bases that underlie the

Abbreviations: AD, Alzheimer disease; PD, Parkinson disease; MSA, multiple system atrophy; ALS, amyotrophic lateral sclerosis; NMDA, *N*-methyl-D-aspartate; GWASs, genome-wide association studies; SNPs, single-nucleotide polymorphisms; GCIs, glial cytoplasmic inclusions.

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pathogenesis of neurodegenerative diseases is the most fundamental basis for the development of disease-modifying therapies [2].

The majority of patients with neurodegenerative diseases have sporadic diseases without any familial occurrence, however, we infrequently encounter patients with neurodegenerative diseases presenting with rare familial forms that are consistent with Mendelian inheritance. The term "sporadic" may be oversimplistic, because many neurodegenerative diseases, such as AD, PD, or ALS, have shown a familial aggregation to a certain extent, which suggests a contribution of genetic factors to the pathogenesis of sporadic forms [3–5]. Therefore, they are complex in nature, that is, they involve multiple genetic and environmental factors that may play roles at the molecular level [6].

Regarding the familial cases with Mendelian inheritance, positional cloning strategies have been quite successful in identifying the causative genes [7]. As of April 2014, a total of 3195 genes with phenotype-causing mutations have been described in Online Mendelian Inheritance in Man (http://omim.org/statistics/geneMap) [8]. More recently, next-generation sequencing (NGS) technologies have been developed, which has further accelerated the process of finding causative genes for diseases with Mendelian inheritance over the past few years [9–17].

In contrast to diseases with the Mendelian inheritance, the genomic signatures of common sporadic forms of neurodegenerative diseases largely remain unknown. Over the past decade, genome-wide association studies (GWASs) employing common single-nucleotide polymorphisms (SNPs) have been intensively conducted to identify genomic variants associated with complex diseases [18]. The theoretical framework of GWASs is based on the "common disease-common variants" hypothesis [19–21], in which common diseases are attributable in part to relatively common variants present in more than 5% of the population. Although GWASs have successfully revealed numerous SNPs that are associated with neurodegenerative diseases, the odds ratios associated with these risk alleles are generally low and account for only a small proportion of estimated heritability. Given these results, it is expected that low-frequency variants, in particular functional variants in coding sequences, with relatively large effect sizes still remain to be identified [22]. For instance, GWASs have identified risk variants at over two dozen loci affecting the development of PD; however, only 3–5% of phenotypic variance associated with PD can be explained using all SNPs within a region identified by replicated GWASs [23]. These estimates are substantially smaller than those obtained in epidemiological studies [24,25], pointing to the compelling evidence of yet-to-be-discovered additional genetic factors. In this review, we present brief overviews of genetic research on sporadic forms of neurodegenerative diseases, including AD, PD, and MSA as examples.

2. Alzheimer disease

AD is the most common neurodegenerative disease characterized by progressive cognitive impairment, including gradual loss of memory, judgment, and ability to maintain social or occupational functioning. AD usually develops in people over 65 years of age, but the less-prevalent early-onset AD can occur much earlier in adulthood. From the viewpoint of genetics, AD occurs under two conditions: a familial AD, which is determined by mutations in a single gene, and sporadic AD. Familial AD is rare and the majority of AD cases are sporadic AD. Regarding familial AD, to date, three causative genes have been identified in autosomal dominantly inherited cases of AD, *APP* [26,27], *PSEN1* [28], and *PSEN2* [29]. Among these causative genes, mutations in *PSEN1* are the most common causes of early-onset familial AD, accounting for 18–50% of autosomal dominantly inherited cases of AD [30]. On the other hand, the molecular bases of sporadic AD are not fully elucidated, which could be caused by genetic susceptibilities, environmental exposures, and gene–environment interactions. Familial aggregation in late-onset AD has been well recognized. For example, the lifetime risk estimates for the ages of 88–90 years were 23.4–25.9% in relatives of AD patients and 19.1% in relatives of healthy controls [31,32]. A study of monozygotic and dizygotic twins without dementia, who were followed up for an average of 5 years, showed that 5.8% of subjects were newly diagnosed as having AD during the follow-up period, and of the pairs in which at least one twin developed AD, the concordance rate was 32.2% for monozygotic pairs and 8.7% for dizygotic pairs [33]. Until recently, however, the only proven genetic risk factor for late-onset AD in various ethnic groups has been the E4 allele of *APOE*, which is mapped to chromosome 19q. A meta-analysis showed that the odds ratio for E4 allele frequency in the AD and healthy control groups was 3.98 (95% confidence interval: 3.44–4.61) [34]. Originally, *APOE* conferring strong susceptibility to late-onset AD was identified by the linkage study of several late-onset AD families showing familial aggregation [35]. Because the mode of inheritance could not be determined with certainty, the affected-pedigree-member method of linkage analysis was selected [35]. Following the nonparametric linkage studies, association analysis first confirmed the role of the *APOE* E4 allele as a strong genetic risk factor for late-onset AD [36,37], as well as early-onset AD [38].

After the discovery of *APOE*, many studies highlighted the potential role of other genes in late-onset AD, and eventually a recent meta-analysis of 74,046 individuals by the International Genomics of Alzheimer's Project (IGAP) confirmed 20 AD susceptibility loci, including *CASS4*, *CELF1*, *FERMT2*, *HLA-DRB5/HLA-DRB1*, *INPP5D*, *MEF2C*, *NME8*, *PTK2B*, *SLC24A4/RIN3*, *SORL1*, *ZCWPW1*, *CR1*, *BIN1*, *CD2AP*, *EPHA1*, *CLU*, *MS4A6A*, *PICALM*, *ABCA7*, and *APOE* loci [39]. Despite the identification of an increasing number of AD susceptibility variants that are common in the general population, these variants confer a mere 0.10-fold to 0.15-fold increase or decrease in AD risk in carriers versus noncarriers of the risk alleles except for *APOE* [40]. In contrast to these finding, there could be a substantial number of rare variants with relatively large effect sizes because they were hardly detected by GWASs. For example, whole-exome sequencing analysis of multiplex families with AD and subsequent analyses of the candidate variants in large case-control data sets have recently revealed that a rare variant (an allele frequency of less than 1%), V232M in *PLD3*, segregated with AD in two unrelated families and that V232M carriers have a four-fold increased risk of developing AD compared with individuals aged over 70 years without dementia [41].

3. Parkinson disease

PD, characterized by tremor, rigidity, bradykinesia, and postural instability, is the second most common neurodegenerative disease after AD, with a median age at onset of 60 and a risk that increases with age. The prevalence of PD is estimated to be 1% in individuals older than 60 years [42]. Mendelian forms of PD show both the autosomal dominant and recessive modes of inheritance. The autosomal dominant causative genes are *SNCA* [43,44], *LRRK2* [45,46], *EIF4G1* [47], and *VPS35* [48]. The first identified causative gene *SNCA*, which encodes α-synuclein, is the principal structural component of Lewy bodies. Notably, an increased gene dosage of *SNCA* causes an autosomal dominant form of PD [44]. These findings suggest that aberrant deposition of α-synuclein in dopaminergic neurons predominantly in the substantia nigra of midbrain is the primary driving force in PD pathogenesis. The autosomal recessive PD genes are *PARK2* [49], *PINK1* [50], *DJ1* [51], *PLA2G6* [52], and *FBXO7* [53]. Recent evidence suggests that the autosomal recessive PD genes *PARK2* and *PINK1* play roles in the clearance of damaged mitochondria by autophagy [54]. Recessively transmitted

mutations in such genes possibly result in a failure to maintain mitochondrial functions, leading to a vulnerability of dopaminergic neurons [55].

Regarding sporadic PD cases, the susceptibility loci for PD have been increasingly identified by meta-analysis of various GWAS datasets [56,57]. PDGene (http://www.pdgene.org/) is an online resource that comprehensively collects and meta-analyzes results from previous genetic association studies of PD [58]. According to PDGene, the top ranked susceptibility loci are *MAPT*, *SNCA*, *GBA*, and *LRRK2*. It is intriguing that, in addition to rare variants responsible for autosomal dominant forms of PD, common polymorphisms in *SNCA* or *LRRK2* confer susceptibility to sporadic forms of PD as well [59,60].

Initially, the attention on *GBA* came from a report of several families of patients with Gaucher disease in which obligate or confirmed carriers of *GBA* mutations frequently developed parkinsonism [61]. Since then, a large number of association studies focusing on *GBA* variants have been reported, which accordingly confirmed the association of *GBA* variants with PD [62]. Note that, although the N370S variant in *GBA* is highly prevalent and predominant in the Ashkenazi Jewish population with a carrier frequency of 4–6% [63,64], it has been demonstrated that the association between *GBA* variants and PD is not exclusive to a specific population group or a specific *GBA* variant. In our study, the combined carrier frequency of the *GBA* variants that are pathogenic for Gaucher disease was as high as 9.4% in PD patients and significantly more frequent than in controls (0.37%) with a markedly high odds ratio of 28.0 (95% C.I., 7.3–238.3) for PD patients compared with controls [65]. Compared with susceptibility polymorphisms identified by GWASs with odds ratios of 1.1–1.7 [58], multiple rare variants in *GBA* represent an outstanding risk factor for PD. Indeed, the penetrance of PD in mutation carriers was estimated to be approximately 30% at 80 years of age, and one could argue that *GBA* variants are furthermore involved in familial aggregation of PD that is not following Mendelian inheritance [66]. Because there are various *GBA* variants that are individually rare, the association with PD is difficult to detect by GWASs employing common polymorphisms.

4. Multiple system atrophy

MSA is a progressive neurodegenerative disease clinically characterized by autonomic failure in addition to various combinations of parkinsonism, cerebellar ataxia, and pyramidal dysfunction. The term MSA was first introduced in 1969, to encompass the disease entities of olivopontocerebellar ataxia, striatonigral degeneration, and Shy–Drager syndrome on the basis of the neuropathological findings in these disorders [67]. Subsequently, GCIs were discovered to be the cardinal neuropathological hallmark of the disease irrespective of clinical presentation. This discovery established MSA as a distinct neurodegenerative disease and highlighted the unique glial pathology as a biological hallmark of this disease.[68] α-synuclein was subsequently discovered to be a major constituent of GCIs [68–73], which led to the notion of "α-synucleinopathies" characterized by the development of intracellular aggregates of α-synuclein primarily in oligodendroglia [74].

Clinically, the disorder is classified into two subtypes: MSA-C, characterized by predominant cerebellar ataxia, and MSA-P, characterized by predominant parkinsonism [75]. MSA-C has been reported to be more prevalent than MSA-P in the Japanese population (65–67% vs 33–35%) [76,77], whereas MSA-P has been reported to be more prevalent than MSA-C in Europe (63% vs 34%) [78] and North America (60% vs 13%) [79]. MSA has been defined as a nongenetic disorder until recently [80]. However, several multiplex MSA families have recently been reported [81–83], indicating that strong genetic factors are responsible for this rare familial clustering of MSA.

An association study of candidate polymorphisms in the European populations showed that the *SNCA* locus is associated with MSA [84–86]. In other studies in the Japanese and Korean populations, however, the association of the *SNCA* locus with MSA was not replicated [87,88]. The differences may be in part attributable to the difference in the ethnic genetic background underlying MSA pathogenesis. In another study in Japan, the copy number loss of *SHC2* was reported to be associated with MSA [89].

Recently, whole-genome sequence analysis in combination with linkage analysis has revealed that homozygous or compound heterozygous mutations in *COQ2* are responsible for familial MSA in two of the six Japanese families, which is consistent with autosomal recessive inheritance [90]. *COQ2* encodes an enzyme involved in the biosynthetic pathway of coenzyme Q_{10} (CoQ_{10}). Indeed, CoQ_{10} levels in frozen brain tissues from a patient with familial MSA carrying homozygous mutations in *COQ2* were substantially lower than those from control subjects. To determine the involvement of *COQ2* variants in sporadic MSA, an extensive mutational analysis of *COQ2* in a Japanese series consisting of 363 MSA patients and 520 control subjects, a European series consisting of 223 MSA patients and 315 controls, and a North American series consisting of 172 MSA patients and 294 controls was conducted. Of the *COQ2* variants, V393A was exclusively observed and relatively common in the Japanese population. There are four potential translation initiator codons in the exon 1 of *COQ2*. The transcription initiation site and the translation initiation site, however, have not been unequivocally determined. With this background, the first ATG codon was adopted as the start site for numbering the amino acids in this review. The allele frequencies of V393A were 35/726 (4.8%) in Japanese MSA patients and 17/1040 (1.6%) in unaffected Japanese persons, with an odds ratio of 3.05 for MSA patients compared with control subjects (95% C.I., 1.65–5.85, $p = 1.5 \times 10^{-4}$). The COQ2 enzyme activity in the lymphoblastoid cell lines from MSA patients carrying heterozygous V393A was significantly lower than that in the control cell lines. Besides V393A, various rare variants in *COQ2* were found in a case-control series. To determine the functional effect of each variant on CoQ_{10} biosynthesis, functional complementation analysis by transforming the yeast *COQ2* null strain with nonmutated or mutated human *COQ2* cDNAs was carried out. The functional complementation analysis revealed nine variants (P99H, S107T, R119H, I147T, P157S, S163F, T317A, S347C, and R387Q) to be deleterious. On combining all of the above-mentioned three case-control series, eight variants (P99H, S107T, I147T, P157S, S163F, T317A, S347C, and R387Q) were identified in 758 individuals with MSA ($n = 758$), whereas only one variant (R119H) was found among 1129 unaffected persons, giving an odds ratio of 11.97 (95% C.I., 1.60–531.5, $p = 0.0039$). The ratio of the number of MSA-C patients to that of MSA-P patients was significantly higher in carriers of deleterious *COQ2* variants than in noncarriers ($p = 0.018$), raising the possibility that the cerebellum is more vulnerable to compromised COQ2 function than other regions of the central nervous system. Intriguingly, cerebellar ataxia has been described to be a frequent clinical feature associated with CoQ10 deficiency with various backgrounds [91], further supporting the vulnerability of cerebellum to CoQ10 deficiencies.

5. Future direction

Basically, there are two general types of research paradigm in genomic aspects of sporadic neurodegenerative diseases. One involves association studies employing common SNPs as markers under the common disease–common variants hypothesis. The common disease–common variants model predicts that relatively

common and low penetrant variants that have arisen in common founders may prevail in the population and that contiguous stretches of founder haplotypes around the risk allele will maintain linkage disequilibrium within a population. In GWASs employing common SNPs, we hope to detect significant associations of one or more SNPs that are in linkage disequilibrium with a common causal variant.

The other paradigm involves sequence-based association studies under the common disease-multiple rare variants hypothesis. Because current NGS technologies enable us to obtain virtually all the variants in human genome irrespective of allele frequency, it is anticipated that sequence-based association studies will become the mainstream approach, which will elucidate low-frequency variants with relatively large effect sizes for the development of complex diseases. To accomplish this, however, there are growing concerns on the research paradigm employing sequence-based association studies. Owing to the complexity and magnitude of variants identified by whole-genome or whole-exome sequence, much larger sample sizes would be required to obtain statistical significance, particularly for low-frequency variants, as compared with conventional GWASs employing common SNPs [92,93]. Various filters for limiting the number of variants to be analyzed, including those with functional predictions, allele frequencies, and disease-related pathways, may increase the power of statistical analyses of association studies. Recent studies based on a large scale exome-sequencing have revealed that the recent explosive increase in human population size resulted in a deluge of rare functionally important variants in individual human populations [94], suggesting that contribution of rare variants may differ among population groups as illustrated in the case of V393A in *COQ2* in Japanese [90] and N370S in *GBA* in Ashkenazi Jewish [62].

To date, successes in identification of rare variants with high odds ratios have been due to the studies of multiplex families, as best illustrated by the discoveries of multiple rare variants in *GBA* in PD [61,62], *COQ2* in MSA [90], and also *APOE* and *PLD3* in AD [35,36,41] (Fig. 1). Because genetic variants with large effect sizes are expected to underlie intrafamilial clustering of patients, the search for genetic variants associated with the disease in multiplex families is a highly efficient approach to identifying low-frequency variants with large effect sizes. Furthermore, identification of such variants enables association studies focusing on specific variants, which substantially increase the power of statistical analyses bypassing the correction for multiple comparisons.

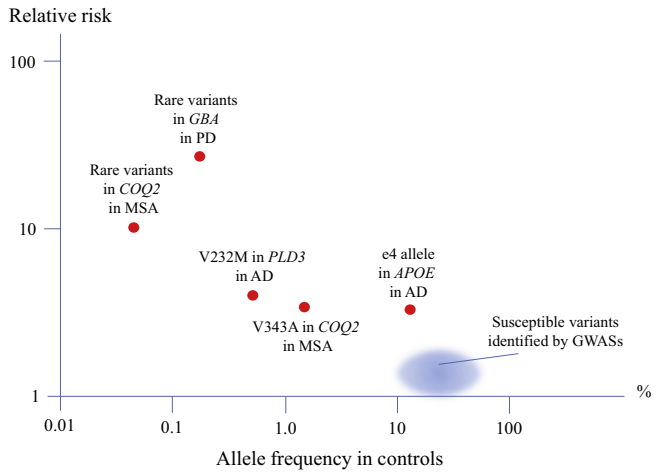

Fig. 1. Comparison of allele frequency and relative risk among disease-relevant variants.

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