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Review article

An update on the genetics of dementia with Lewy bodies

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ABSTRACT

The genetic architecture of dementia with Lewy bodies (DLB) is increasingly taking shape. Initially, genetic research focused mainly on linkage and candidate gene studies in small series of DLB patients. More recently, association and exome sequencing studies in larger groups have been conducted, and have shown that several variants in *GBA* and the *APOE* ε4 allele are important genetic risk factors for DLB. However, genetic research in DLB is still in its infancy. So far, many genetic studies have been biased and performed in clinically and pathologically heterogeneous populations. Therefore, it is likely that multiple DLB-specific genetic determinants still have to be identified. To further our understanding of the role of genetics in DLB, future genetic studies should be unbiased and performed in large series of DLB patients, ideally with both a clinical diagnosis and pathological confirmation. The combination of genomic techniques with other research modalities, such as proteomic research, is a promising approach to identify novel genetic determinants. More knowledge about the genetics of DLB will increase our understanding of the pathophysiology of the disease and its relation with Parkinson's Disease and Alzheimer's Disease, and may eventually lead to the development of disease modifying treatments.

1. Introduction

Dementia with Lewy bodies (DLB) is a common neurodegenerative disease in the elderly [1]. DLB is characterized by progressive cognitive decline with variable combinations of fluctuating cognition, parkinsonism, visual hallucinations, neuroleptic sensitivity and rapid eye movement (REM)-sleep behavior disorders [2]. Clinical features of DLB are not specific to the disease and overlap with those of Parkinson's Disease (PD) and Alzheimer's Disease (AD) [1]. In addition, neuropathological features also overlap between these diseases. Cortical Lewy bodies and neurites, which mainly comprise abnormal aggregated α-synuclein [3], are the pathological hallmarks of DLB, but are also observed in advanced PD and Parkinson's Disease Dementia (PDD) [4]. Furthermore, AD pathology is present in most DLB patients [4–6], which may aggravate the clinical manifestation of the disease and may increase the risk of mortality [7–9]. Due to these overlapping features, DLB is often considered as part of a spectrum with DLB placed between PD and AD [10] (Fig. 1).

Over the last years, the genetic architecture of DLB is increasingly taking shape [10–13]. Defects in genes associated with PD (such as *α-synuclein* (*SNCA*) [14–17], *leucine-rich repeat kinase* 2 (*LRRK2*) [18] and *glucocerebrosidase* (*GBA*) [19–21]) or AD (such as *presenilin 1* (*PSEN1*) [22–24], *presenilin 2* (*PSEN2*) [13,24,25], *amyloid precursor protein* (*APP*) [11,26], *apolipoprotein E* (*APOE*) [11,13,24,27–30] and *microtubule associated protein tau* (*MAPT*) [31]) have also been associated with DLB. In addition to the clinical and pathological overlap, these findings also suggest a genetic overlap of DLB with PD and AD [10] (Fig. 1).

In this article, we present a comprehensive overview of the genetics of DLB and discuss the genetic overlap of DLB with PD and

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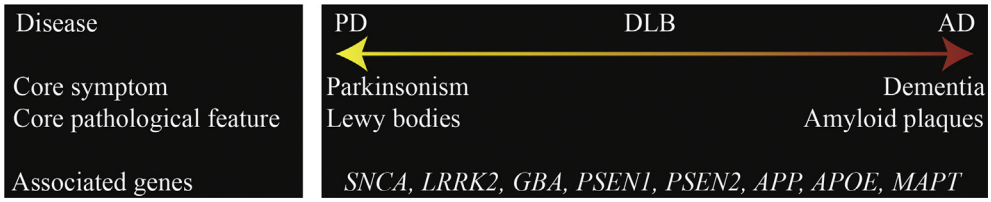

Fig. 1. Disease spectrum of PD-DLB-AD (simplified representation).

AD. In addition, we describe promising genetic research methods, which in the near future will further our understanding about the pathophysiology of DLB and the clinicopathological spectrum between DLB, PD and AD.

2. Genetics of DLB

Multiple studies have been published on the genetics of DLB. The first genetic studies involving DLB patients mainly focused on families with multiple affected members with variable phenotypes ranging from DLB to PD and AD [14–18,22–26,32–36]. These studies used linkage analysis or a candidate gene approach to find rare variants (usually defined as variants with an allele frequency of less than 1% in the general population) with a large risk of disease development [37,38]. In such families, two disease-associated loci (2q35-q36 and 2p13 [35,36]) and twelve disease-associated rare variants in six genes have been identified [11,13–18,22–26,32,34] (Table 1).

Rare disease-associated variants have also been identified by candidate gene studies in series of unrelated DLB patients [13,19–21,24,39–47] (Supplementary Table 1). Some of these variants reside in genes previously associated with DLB in familial studies, which supports a role for these genes in DLB. Interestingly, rare disease-associated variants in *GBA* are often observed in unrelated DLB patients [19–21,39–41,43].

Association studies in large cohorts of patients and controls generally take the approach of identifying common variants (usually defined as variants with an allele frequency of more than 1% in the general population) with a small to intermediate risk of disease development [37,38]. These studies with candidate genes have shown an association between DLB and, among others, the *APOE* ε4 allele [11,13,24,27–30] and the *MAPT* H1G haplotype [31]. A genome wide association (GWA) study, which is hypothesis free and typically identifies new disease-associated loci [37,38], has not yet been reported for DLB. Other relatively new and unbiased genetic approaches [37,38], such as whole exome and genome sequencing studies, have also not yet been reported.

Genes associated with DLB are discussed in more detail in the next sections.

2.1. Rare variants in SNCA

Several defects in *SNCA* (p.E46K, p.A53T variant and duplication) have been described in DLB patients with family members diagnosed with PD or PDD [14–17] (Table 1). A *SNCA* duplication was also found in a DLB patient without affected family members [24] (Supplementary Table 1). These defects were previously identified in multiple familial PD patients and are considered pathogenic [14,16,48,49]. Although evidence is scarce, there are some indications that specific genetic variability within *SNCA* could lead to different phenotypes in the PD-DLB spectrum. For example, the p.A30P variant [50] and duplications of *SNCA* are more often associated with PD and sometimes with PDD with a long disease course [51,52], whereas the p.E46K variant, the p.A53T variant and triplications are associated with PD and DLB with an early age of onset, severe clinical symptoms and a short survival [53]. The difference of phenotype with the type of variant may be related to the position of the variant and its impact on protein function [14]. Similarly, the kind of multiplication and genomic range of the *SNCA* multiplication may influence the clinical phenotype [17].

Table 1
Rare disease-associated genetic variants in familial DLB.

Genetic characteristics				Clinical diagnosis	Family history				Pathological characteristics			References
Gene	Protein	Chromosome location	Protein change		DLB	PD/ PDD	AD or unspecified dementia	Number of affected family members	Autopsy performed	Cortical Lewy pathology	AD pathology	
SNCA	α-synuclein	4q22.1	E46K	DLB**	no	yes	no	12	yes	yes	no	[14]
			A53T	DLB**	no	yes	no	3	yes	yes	no	[15]
				DLB	no	yes	no	4	no	NA	NA	[16]
			duplication	DLB	no	yes	no	1	no	NA	NA	[17]
LRRK2	leucine-rich kinase 2	12q12	G2019S	DLB	no	yes	no	4	yes	yes	yes	[18]
PSEN1	presenilin 1	14q24.2	T440 deletion*	DLB**	no	yes	no	2	no	NA	NA	[22,23]
			A79V	DLB	no	no	yes	1	no	NA	NA	[24]
PSEN2	presenilin 2	1q42.13	A85V	DLB	yes	no	yes	5	yes	yes	yes	[25]
			R71W	DLB	no	no	yes	1	no	NA	NA	[24]
			D439A	DLB	no	yes	no	1	yes	yes	yes	[13]
APP	amyloid precursor protein	21q21.3	V717I	DLB/AD	UN	UN	UN	>1	yes	yes	yes	[11]
			duplication	DLB	no	no	yes	2	yes	yes	yes	[26]
SNCB	β-synuclein	5q35.2	P123H	DLB	yes	no	yes	7	yes	yes	yes	[32,34]

*Confirmed in a son with PD and dementia. ** Based on the clinical criteria by McKeith et al., 2005, however no definite diagnosis was mentioned in article. DLB: Dementia with Lewy bodies, PD: Parkinson's Disease, PDD: Parkinson's Disease Dementia, AD: Alzheimer's Disease, UN: Unknown, NA: Not available.

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