Familial Occurrence of Dementia and Parkinsonism

A Systematic Review

Martin Wilhelm Kurz^{a, c} Anna Melissa Schlitter^b Jan Petter Larsen^c Clive Ballard^e
Dag Aarsland^d

^aDepartment of Neurology, Heinrich Heine University Düsseldorf, Düsseldorf, ^bDepartment of Human Genetics, Ruhr University Bochum, Bochum, Germany; ^cDepartment of Neurology and ^dPsychiatric Clinic, Stavanger University Hospital, Stavanger, Norway; ^eWolfson Centre for Age-Related Diseases, King's College London, London, UK

Key Words

Parkinson's disease with dementia · Dementia with Lewy bodies · Cognitive decline

Abstract

Parkinson's disease with dementia (PDD) and dementia with Lewy bodies (DLB) are common clinical dementias characterized neuropathologically by the presence of cortical Lewy body pathology and with distinct clinical and neurobiological similarities. Importantly, genetic factors seem to play a key role in the pathogenesis of Parkinson's disease. In the current article, we examine the evidence for a genetic component to DLB and PDD by reviewing studies of familial PDD and DLB as well as familial coincidental PDD and DLB, and report the genes involved. There is a convincing genetic overlap between both syndromes, suggesting that they share a common etiological factor.

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Introduction

Dementia is one of the most common age-related neurodegenerative disorders in the industrialized world. Due to the progressive aging of the Western population, the incidence of late-onset neurodegenerative disorders as-

sociated with dementia are increasing dramatically. Over the last decade, exciting recent studies have identified several genes such as presenilin 1 and 2, apolipoprotein ε (APOε) and amyloid precursor protein involved in the development of Alzheimer's disease (AD) [1, 2], which have enabled enormous advances in our understanding of the molecular biology of the disease and facilitated the development of novel therapeutic approaches.

In parallel, progress in the study of the genetics of Parkinson's disease (PD) has enhanced our understanding of basic disease mechanisms, for example highlighting the central importance of α-synuclein. Mutations in the α-synuclein gene (*SNCA*) give rise to autosomal dominant PD [3], and recently a direct relationship between *SNCA* dosage and disease progression has been reported [4]. Furthermore mutations in the *parkin* gene have been found to contribute in the pathogenesis of early onset autosomal recessive parkinsonism, with a wide range of phenotypic features [5–7]. The phenotype appears due to partial or complete loss of the parkin protein. Typically nigral degeneration is not accompanied by Lewy body formation. Parkin protein acts as an E3 ubiquitin protein ligase [8] in the ubiquitin-proteasome system. However, proteomic analysis has revealed that parkin may have a neuroprotective effect by maintaining mitochondrial integrity [9–11].

The cumulative frequency of dementia in PD has been shown to be as high as 78% [12]. Although there is some inconsistency in the literature, the results from recent studies on balance indicate that limbic and cortical Lewy bodies are the main cause of dementia in PD [13–15]. Dementia is a key symptom for PD patients as it increases the risk of nursing home admission [16], mortality [17], and has a substantial impact on the quality of life. Given the prevalence of PD and the frequency of dementia in PD, the approximate frequency of PD with dementia (PDD) in the population older than 65 years is 0.5% [18]. Dementia with Lewy bodies (DLB) is the second most common form of neurodegenerative dementia following AD, accounting for 10–20% of patients with late-onset dementia [19, 20]. DLB is characterized by parkinsonism, visual hallucinations and cognitive fluctuations. The clinical, neuropsychological and neuropathological similarities of PDD and DLB underline the close relation between the two diseases and support a model where both diseases are seen as part of a spectrum of dementias with cortical Lewy bodies. According to current classification, PDD is diagnosed if PD symptoms develop before the onset of dementia, whereas DLB is diagnosed if dementia precedes or occurs simultaneously with motor symptoms [21, 22]. Little is known regarding the familial incidence and genetic predisposition of PDD and DLB.

In the current report, we analyze the available studies of genetics in PDD and DLB to determine (1) familial occurrence and genetics of dementia in PD; (2) familial occurrence and genetics in DLB; (3) whether there is evidence of genetic overlap between PDD and DLB, and (4) which genes are involved in PDD/DLB.

Methods

A systematic literature search from October to December 2005 was performed using the entire time scale of PubMed without using any language restrictions. Mixtures of the following key words with a limit to dementia or cognitive decline and familial or genes were used to perform multiple searches: Parkinson* (MeSH), Lewy body (MeSH), DLB (MeSH). We identified 822 titles and abstracts addressing familial parkinsonism and 78 titles describing familial occurrence of parkinsonism and dementia. We excluded 50 studies that did not fulfill the inclusion criteria. Of the 28 included studies, 14 focused on PDD, 7 reported people with DLB and 8 studies included family members with either PDD/DLB (one study describes two families with distinct classifications). Cases reported in multiple publications were whenever possible combined in order to avoid reiterations.

Inclusion criteria were: (1) Original study reporting of familial occurrence of Parkinsonism and prominent dementia and

(2) pathological findings compatible with PD, PDD or DLB or (3) clinical findings compatible with PD, PDD or DLB (if autopsy was not performed).

Results

Results of genetic testing are listed in brackets at the end of each section and in table 1.

Studies of Familial PDD

An early study proposed a new neurological genetic disorder, describing a family with dominant inheritance of parkinsonism combined with severe dementia [23], indicating a connection between the two syndromes. A larger study looking at general influence of genes in 71 people with sporadic PD confirmed this coincidence of dementia and parkinsonism. Older age and familial occurrence of dementia were identified as risk factors for the development of dementia in PD. Thirty percent of PD patients with dementia (17 patients) reported a familial occurrence of dementia compared to only 5.6% of PD patients without dementia. No difference was seen in environmental exposure, personal habits, or medical or surgical illness [24]. (Genetic testing not performed.)

A genetic susceptibility to a syndrome presenting with both PD and dementia was also reported in a large family (Contursi kindred) with 60 affected individuals spanning 5 generations [25–27]. Precise time of onset of dementia was not available, but developed typically after the onset of parkinsonism. Hallucinations and delusions were common. (A53T SNCA mutation.)

Concurrent PD and dementia were also apparent in a family (Iowa kindred) with 22 affected individuals spanning 6 generations [28–31]. All affected members had early-onset PD (mean onset 34 years), weight loss and rapidly progressive L-dopa-responsive parkinsonism followed by hypotension and dementia (mean age of onset, 49 years) including impairment of orientation and visuospatial dysfunction in the course of the disease. Hallucinations were reported in only 1 individual. According to current diagnostic criteria [22, 32], these patients should be classified as PDD. [Inferred haplotype on chromosome 4p (PARK4). SNCA triplication.]

Ishikawa et al. [33] and Wakabayashi et al. [34] describe a Japanese woman who married her uncle (family A). Both developed parkinsonism and the subsequent onset of dementia. Interestingly, both developed a neuroleptic malignant syndrome in the course of their disease. Their two sons developed similar parkinsonism at the

Table 1. Clinical, neuropathological and genetic results in reported families

Study by	Clinical information		Categorization		Neuropathology			Genetic findings
	affected	families	PDD	DLB	autopsied	AD	Lewy bodies	
Globe et al., 1990, 1996; Duda et al., 2002	60	1	yes	no	2	0	(+2); ^{SN + NC}	A53T SNCA mutation
Waters and Miller, 1994; Muentert et al., 1998; Farrer et al., 1999; Singleton et al., 2003	22	1	yes	no	6	0	(+6); ^{SN + NC}	Inferred haplotype on chromosome 4p (PARK4); SNCA triplication.
Ishikawa et al., 1997; Wakabayashi et al., 1998	4 (fam. A)	1	yes	no	2	0	Fam. A (+2); ^{SN + NC}	Fam. A: APOε3/4 and ε4/4
Ohara et al., 1999	4	1	yes	no	1	0	(+1); ^{SN + NC}	No mutations found
Spira et al., 2001	5	1	yes	no	2	0	(+1); ^{SN + NC} ; (1) ^{SN}	A53T SNCA mutation
Ohtake et al., 2004	1	1	yes	no	0	–	Autopsy not performed	V70M β-synuclein mutation
Galvin et al., 2002	2 (fam. 1) 2 (fam. 2)	1 1	yes no	yes yes	2 2	no (+2)	(+2) ^{SN + NC} (+2) ^{SN + NC}	No mutations found
Krüger et al., 1998, 2001	5	1	no	yes	0	–	Autopsy not performed	A30P SNCA mutation APOε3/ε3, APOε3/ε4 Tyr18 allele (<i>UCHL1</i>)
Brett et al., 2002	2	1	no	yes	2	0	(+2); ^{SN + NC}	Genetic testing not performed
Tsuang et al., 2002	8 (fam. 1) 6 (fam. 2)	1 1	no no	yes yes	3 2	(+1) (+1)	(+2) ^{SN + NC} ; (1) ^{AM} (+2) ^{SN + NC} ; (1) ^{AM}	APOε3/ε4, APOε4/ε4 APOε3/ε4, APOε4/ε4
Bonner et al., 2003; Ohtake et al., 2004	8	1	no	yes	1	(+1)	(+1); ^{SN + NC}	P123H β-synuclein mutation
Denson and Wszolek 1995; Denson et al., 1997	80	8	yes	yes	14	0	(+1); ^{SN + NC}	Linkage to chromosome 17 (PPND family)
Ishikawa et al., 1997	3 (fam. S)	1	yes	yes	0	–	Autopsy not performed	Genetic testing not performed
Inose et al., 1988; Mizutani et al., 1993, 1997	6	1	yes	yes	2	0	(+2); ^{brainstem}	Genetic testing not performed
Zarranz et al., 2004	5	1	yes	yes	1	0	(+1); ^{SN + NC}	E46K SNCA mutation

Persons affected denominated with numbers. Fam. = family; SN = substantia nigra; NC = neocortex; AM = amygdala only; *UCHL1* = ubiquitin C-terminal hydrolaseL1; SNCA = α-synuclein gene; APOε = apolipoprotein ε.

ages of 39 and 28. Parkinsonism was accompanied by autonomic failure; dementia presented several years after onset of parkinsonism and was accompanied by hallucinations and delusions. (Family A: APO ε3/4 and ε4/4.)

In another study, 1 patient died at the age of 51 after a history of dementia and parkinsonism [35]. Among 3 existing siblings, 2 were diagnosed as probable and 1 as possible DLB, although dementia (mean age of onset 45 years) developed late in the course of the disease (mean age of onset of parkinsonism, 35 years) and would be classified as PDD. The patient's sister showed compulsive behavior and the other two siblings had parkinsonism. All showed progressive dementia with a progressive para-

phasia and word finding difficulties. Psychotic features, such as persecutory delusions (all), visual hallucinations (2) and sexually disinhibited behavior (2) were also present. Treatment of parkinsonism with L-dopa was effective in 1 individual, but of limited benefit in the others. (No mutations found.)

Familial occurrence of PD and dementia was also diagnosed in an Australian family of Greek origin where 5 of 9 siblings in 1 generation were affected with a L-dopa responsive parkinsonism (mean age of onset, 45 years) and progressive cognitive decline (mean age of onset, 51 years) [36]. Additionally, severe central hypoventilation, orthostatic hypotension, prominent myoclonus and uri-

nary incontinence were present. Two individuals exhibited psychotic features including paranoia (both) and hallucinations (1). (A53T SNCA mutation.)

Finally, a recent study reported an 83-year-old man with apparently sporadic PDD [37]. PD symptoms developed at the age of 78 that responded well to L-dopa. He also displayed fluctuating dementia, visual hallucinations and cognitive impairment with unclear time of onset. A mutation in the β -synuclein gene was identified in this individual. (V70M β -synuclein mutation.)

Studies of Familial DLB

There have been only a handful of studies of the familial occurrence of DLB. Two families with co-occurrence of parkinsonism and dementia are described by Galvin et al. [38], but the subjects met the clinical criteria for DLB in only one of the families (family 2). In this family, mother and son were affected. The son presented at age 56 with a progressive cognitive decline without hallucinations. At age 61, bradykinesia and gait changes occurred followed by rigidity. He died 9 years after disease onset. His mother presented at age 85 with progressive cognitive decline including paranoid delusions. Visual hallucinations were not present. At the age of 89 years, she showed very mild rigidity and died at age 91 without prominent parkinsonism. (No mutations found.)

A German family exhibited familial PD with mean disease onset at 59.7 years with a high variability (54–76 years) [39, 40]. Five individuals in 5 generations were affected. Beside the high variability in disease onset, a milder phenotype and early onset of dementia were remarkable. All examined mutation carriers exhibited deficits in visuoconstructive functions. In 1 patient, visual hallucination developed. As cognitive decline in the affected cases begins early in the course of the disease or is the starting symptom, these cases should be considered as DLB. [A30P SNCA mutation, APO ϵ 3/ ϵ 3, APO ϵ 3/ ϵ 4, Tyr18 allele (ubiquitin C-terminal hydrolase L1).]

Two siblings from a family in Ireland developed progressive parkinsonism and dementia with visual hallucinations [41]. The first patient presented with parkinsonism and developed a fluctuating cognitive deficit with unclear time of onset, the other person experienced a slow and steady decline in cognitive and physical functions and visual hallucinations. As mental and physical decline began contemporaneously, this case should be considered as DLB. Both showed little or no response to L-dopa. Their mother died in the middle of her 4th decade, while no other neurological deficit was found in the family history. (Genetic testing not performed.)

Another report investigated 2 families with two or more autopsy-proven cases of DLB and a positive family history of dementia [42]. In family 1, 8 affected individuals in 2 generations exhibited dementia as their first neuropsychiatric symptom; 5 developed subsequent parkinsonism and 4 experienced psychiatric symptoms. In family 2, 6 affected individuals in 1 generation presented with cognitive decline, 4 developed parkinsonism but none developed hallucinations or delusions. (Family 1 and 2: APO ϵ 3/ ϵ 4, APO ϵ 4/ ϵ 4.)

Another study investigated a 64-year-old male with dementia, parkinsonism and hallucinations [37, 43]. At the age of 61, he started recognizing memory deficits and deterioration in handwriting. The cognitive decline progressed, while parkinsonism became obvious at the age of 73. His family history revealed 8 relatives with a history of dementia, including 4 with subsequent parkinsonism fulfilling consensus criteria for possible or probable DLB. (P123H β -synuclein mutation.)

Studies Reporting Families with Both PDD and DLB

Several families with DLB and PDD phenotypes have been reported. Eight large kindreds from North America have been described [44, 45]. In family G, a family with 10 affected members across 3 generations, 4 individuals were examined clinically. Four individuals had an L-dopa-responsive parkinsonism without dementia, 3 individuals presented with dementia followed by parkinsonism, and 3 developed dementia. The mean age of onset of parkinsonism was 57 years, and mean age of onset of dementia was 74 years. In family F, affected individuals presented also with dementia. Exact information about onset of dementia is not given in the other described families. [Linkage to chromosome 17 (PPND family).]

Ishikawa et al. [33] described a family (3 generations) where 1 individual reported an affected grandfather exhibiting gradually progressing bradykinesia (family S); the father developed memory loss from the age of 35 and PD symptoms from the age of 44, and thus fulfilled criteria for possible DLB. The investigated individual showed juvenile parkinsonism from the age of 34, and cognitive decline developed 6 years after onset of PD. L-dopa-induced dyskinesias and choreic movement and a neuroleptic malignant syndrome were present. (Genetic testing not performed in family S.)

Co-occurrence of DLB and PDD syndromes was reported in a family with 6 affected individuals spanning 3 generations [46, 47]. Four patients were clinically evaluated. All individuals exhibited PD features and subsequent dementia. In 2 of the patients, dementia was recog-

nized in the 1st year of PD symptoms (i.e. DLB), and in 1 patient dementia developed at a later stage of the disease [46] (i.e. PDD). In 1 patient, no information was given about onset of dementia. All patients developed autonomic failure, myoclonic jerks and two of them had general convulsions. Pyramidal tract signs were positive. (Genetic testing not performed.)

The second family (family 1) described by Galvin et al. [38] involved also mother and son. The son presented at age 45 with parkinsonism. Seven years after onset of PD symptoms, dementia was apparent accompanied by visual hallucinations, misperceptions and fluctuations. His mother was evaluated initially at the age of 75 with mild cognitive impairment leading to diagnosis of mild AD. Over the next 2 years, progressive cognitive decline with visual hallucinations and delusions occurred. Postural instability and gait impairment were present. (No mutations found.)

Finally, a 69-year-old man with parkinsonism, memory loss and agitated nocturnal sleep from the age of 67 was described (i.e. DLB) [48]. Initial response to L-dopa was good but choreic dyskinesias developed. Cognition deteriorated and he developed delusions, visual hallucinations and confusion of reality. Four siblings exhibited parkinsonism and dementia, 2 accompanied with hallucinations. In 2 individuals, cognitive impairment developed 2 years after onset of motor symptoms (i.e. PDD), and in 2 the precise onset of dementia was not described. (E46K, SNCA mutation.)

Discussion

This review of the literature identifies the familial occurrence of coincidental parkinsonism and dementia in 24 families (table 1), 12 of which involved presentations of both DLB and PDD. Differentiation between familial PDD and familial DLB often deviates from the established diagnostic guidelines [21, 22, 32], hence the published pedigree probably underestimates the overlap, which strongly suggests that at least a substantial proportion of these families have the same underlying pathophysiology. As this is clearly the situation in people with familial presentations of DLB or PDD, it is likely that the same will be true of sporadic presentations. This strongly implies that the arbitrary distinction between DLB and PDD based upon the presentation of parkinsonism prior to dementia does not reflect the molecular biology of the disease process and is contrary to the scientific evidence [49]. This point is further emphasized by reports of fam-

ilies including individuals with PDD and DLB phenotypes within the same cohort carrying the same mutation. For example, in the study by Zarranz et al. [48], all patients carried the E46K mutation but only the index patient developed dementia within the timeframe to meet diagnostic criteria for DLB. Two siblings developed cognitive decline after 2 years of onset of motor symptoms and thus have to be classified as PDD.

This point of view is strengthened by a recent study that proposes a direct correlation between SNCA dosage and disease progression, i.e. age at onset of parkinsonism and development of dementia in PD patients [4], indicating that the degree of genetic alteration is determining clinical severity. However, a recently completed study failed to identify SNCA multiplication in 101 familial PD probands, 325 sporadic PD cases and 65 patients with DLB, indicating that SNCA multiplications remain a rare cause for familial forms of PD [3, 50]. However, the pathogenic relevance of SNCA is underlined by the fact that α -synuclein is a substantial component of Lewy bodies in familial and sporadic PD [51].

Collectively, the known and unknown genetic PD cases are likely to explain no more than 5–10% of the overall PD population. However, they contribute significantly to our understanding of the molecular biology of both familial and sporadic PD cases with huge therapeutic potential for the patients. In the recent years, the number of genes contributing to the pathogenesis of PD have increased [7, 52, 53]. Interestingly, patients meeting diagnosis criteria for DLB so far display either mutations in the synuclein gene or show positive correlations with APO (table 1). α -Synuclein is the main component of Lewy bodies, and regularly the gene results in a presynaptic protein of 140 amino acids that is abundant in the brain and may have lipid binding properties [54]. Three mutations have so far been found in the SNCA that lead to the misfolding of the protein and subsequent protein aggregation in the Lewy bodies (A53T, A30P, E46K). Hypotheses based upon the molecular evidence have proposed that an underlying molecular abnormality leads to a α -synuclein aggregation and subsequent cell loss. Most families reported carry the A53T mutation with a typical presentation with early onset of parkinsonism. The mutation consists in the transversion at the nucleotide position 209 from guadenine to adenine, leading to the change of alanine to threonine in the mutant protein [3]. Dementia is seen in the later course of the disease, although it may also be the presenting feature in some individuals. Additional features may include central hypoventilation, postural hypotension, bladder incontinence and myoclo-

nus [26, 36]. The mechanisms of increased aggregation of α -synuclein in individuals carrying the A53T mutation are still not fully understood, although iron-induced mechanisms are discussed [55–57]. The A30P mutation involves the substitution of guanine to cytosine at position 88 resulting in the change of alanine to proline [40]. Affected individuals have typical L-dopa-responsive parkinsonism except for early-onset dementia. Likewise, carriers of the E46K mutation [48] usually display cognitive decline at an early stage of the disease and show extensive cortical Lewy body pathology. The E46K mutation increases phospholipid binding and assembly into filaments of α -synuclein. Thus, three different mutations in the same gene are leading to accumulation of α -synuclein and Lewy bodies, strengthening the hypothesis that α -synuclein accumulation is key to the subsequent development of dementia.

The discovery of mutations in the gene for leucine-rich kinase 2 (*LRRK2*) has, however, complicated interpretation. The current findings suggest that mutations in the *LRRK2* gene are the most common genetic cause of late-onset PD, accounting for approximately 8% of cases [58]. Affected individuals display clinical findings typical for sporadic PD without development of cognitive decline (except one case developing severe dementia after a disease duration of >20 years [59]). However, the pathomorphologic picture is remarkably variable, ranging from pure degeneration without Lewy bodies to degeneration with brainstem Lewy bodies, widespread Lewy bodies

fitting the pattern seen in DLB, and neurofibrillary tau-positive tangles [60–62]. At present, it still has to be determined how mutations in the *LRRK2* gene cause PD and why neuropathologic findings fitting DLB are not accompanied by dementia.

Consequently, other influences like neurochemical effects as the cholinergic deficit have to interplay as well, causing the clinical picture with early cognitive decline and development of neuropsychiatric deficits like hallucinations.

The APO ϵ 4 allele is associated with an increase in the number of neocortical Lewy bodies and amyloid plaques in patients with PD [63], and recent evidence supports that the APO ϵ 4 allele may be an independent risk factor in the development of Lewy bodies and dementia in PD [42, 64]. Primarily, the APO ϵ 4 allele is known to be associated with familial and sporadic late-onset AD [65, 66]. As an additional effect, coincident significant AD pathology as seen in DLB patients may increase or accelerate symptom severity. However, in the presented familial studies coincidental AD pathology is only found in the minority of people with dementia (table 1), and a recent study showed that there is no correlation between occurrence of PD and AD in the subject's family [67].

Further correlations of clinical, pathomorphological and genetic evidence are needed to elaborate further insights into the molecular biology of dementia in PD, thus creating new chances of developing novel treatment approaches.

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