The Genetics of Dementia With Lewy Bodies

What Are We Missing?

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Dementia with Lewy bodies is a complex brain disorder and a key member of the Lewy body disease spectrum. Its genetic etiology is unclear, and information is scattered. However, the results of molecular genetic studies imply a genetic and mechanistic overlap with Alzheimer disease, Parkinson disease with dementia, and Parkinson disease. In this review, we provide a comprehensive overview of the current studies on dementia with Lewy bodies heritability, genetic etiology, and genetic heterogeneity. We conclude with a critical discussion of the missing heritability in dementia with Lewy bodies and encourage scientists to further explore the underlying mechanisms of this disease.

phenotype of dementia and parkinsonism is inherited in a mendelian manner (Table).

Large multigenerational families segregating neurodegenerative brain diseases have been critical in the identification of disease-causing genes. However, only one genome-wide linkage study for DLB has been reported to date. In an autosomal dominant family with autopsy-confirmed DLB, Bogaerts et al mapped the first chromosomal locus for DLB at 2q35-q36. In-depth molecular genetic follow-up investigations, including comprehensive sequencing of all positional candidate genes and high-resolution copy number variation analyses, did not reveal a simple pathogenic or gene dosage mutation that cosegregated with DLB in this pedigree.

Most likely, the mutation underlying DLB in this family is more complex than what is usually envisaged for monogenic disorders.

**GENETIC DETERMINANTS OF DLB**

Molecular genetic investigations in cohorts of unrelated and largely sporadic patients with DLB have revealed genetic variations in genes that are involved in the pathogenic pathways leading to related neurodegenerative disorders. These include PD (α-synuclein gene [SNCA]) and AD (amyloid precursor protein gene [APP], presenilin 1 gene [PSEN1], and presenilin 2 gene [PSEN2]).

**SYNUCLEIN FAMILY**

Although rare, mutations in SNCA have been unequivocally implicated in familial PD (http://www.molgen.vib.ua.be/PDMutDB/). However, many patients carrying SNCA missense mutations or gene multiplications show neurological features beyond the realm of idiopathic PD, such as cognitive decline, dementia, hallucinations, and autonomic dysfunction. With the caveat that few SNCA mutation carriers have been described, some evidence suggests a genotype-phenotype correlation. Although SNCA duplications and the missense mutation p.A30P are rarely associated with the presence of dementia, SNCA triplications and the missense mutations p.E46K and p.A53T are associated with clinical and pathological phenotypes ranging from PD to PD with dementia to DLB.
α-Synuclein is a member of a family of presynaptic proteins and is potentially involved in neurotransmitter release and vesicle turnover at the presynaptic terminals. Both p.A53T and p.E46K have been shown to promote the propensity of SNCA to polymerize into amyloid in vitro. On the other hand, p.A30P seems to affect SNCA properties independent of protein aggregation. The synuclein family also includes β-synuclein (SNCB) and γ-synuclein (SNCG). In vitro and in vivo investigations have shown that wild-type SNCB may have a protective role in SNCA toxic effects by reducing the formation of LBs. Transgenic mice expressing high neuronal levels of SNCG developed specific hallmarks of synucleinopathies and motor deficits. These functional data support a role for SNCB and SNCG as candidate genes for DLB. Patient-control association investigations in patients with autopsy-proven DLB indicated that genetic variability in all synuclein paralogs influences risk for the disease. Also, patient-specific missense mutations in SNCB (p.V70M and p.P123H) were detected in 2 unrelated patients with DLB, one with a positive family history of DLB. Although limited genetic evidence for pathogenicity of these mutations could be provided, subsequent overexpression investigations revealed enhanced lysosomal pathology. Notably, the autophagy-lysosomal pathway is known to have a crucial role in the clearance of amyloidogenic proteins, such as SNCA. Although genetic variations in synuclein genes are rare, the results of genetic and functional investigations propose a role for all members of the synuclein family in the development of DLB. However, these observations need to be confirmed and validated in larger clinical series.

AMYLOID PRECURSOR PROTEIN AND SECRETASE PROCESSING

Mutations in 3 genes (APP, PSEN1, and PSEN2) are well-established causes of monogenic forms of AD (http://www.molgen.ua.ac.be/ADMutations). In families segregating an AD mutation, a variable degree of concomitant Aβ and LB pathology is often observed, and patients are seen with a complex clinical phenotype along the spectrum of AD and DLB. In 2 unrelated kindreds with APP duplication, a large diversity in clinical and neuropathological presentation was reported, including typical DLB.

Increased expression of APP per se and point mutations near the β-secretase (p.K670M/p.N671I) and γ-secretase (p.V717I) cleavage sites can result in significant LB pathology (Figure 2).

A similar widespread presence of LBs is becoming increasingly evident among familial patients carrying PSEN mutations as well (Figure 3). To date, only one familial patient has been described with a combined clinicopathological phenotype of DLB and variant AD carrying a mutation in PSEN1 (p.ΔT440). Stable expression of the p.ΔT440 mutant in cell lines not only leads to a marked elevation of the Aβ1-42 peptide ratio but also brings about an enhanced Ser129 phosphorylation of SNCA. An increase in the relative proportion of Aβ1-42 is known to augment nucleation and fibrillogenesis of Aβ, while phosphorylation of SNCA at Ser129 is the key event responsible for the formation of LBs and Lewy neurites.
genetic etiology of DLB, although to a limited extent. Nevertheless, such data support the clinical and genetic heterogeneity of different members of the LBD spectrum.

GENETIC SUSCEPTIBILITY FACTORS

Results of genotyping investigations of the glucocerebrosidase gene (GBA) in several cohorts of individuals with parkinsonism have revealed an increased frequency of heterozygous GBA variant carriers among patients with parkinsonism compared with healthy control individuals. Notably, a higher mutation rate in patients having DLB compared with matched PD series has been reported.

Also, GBA mutations tend to be more frequently associated with more diffuse neocortical LBs as seen in DLB brains. Although the mechanisms for the gene’s association with increased synucleinopathy risk need to be further explored, recent functional experiments demonstrated that DLB-linked GBA mutations influence SNCA processing and its steady-state levels, likely increasing the host’s susceptibility to a late-onset synucleinopathy, such as DLB.

The apolipoprotein E (APOE) ε4 allele is a long-standing risk factor for early-onset and late-onset AD. Notably, the results of investigations in clinically and neuropathologically confirmed DLB cohorts have demonstrated that the APOE ε4 allele is overrepresented in patients with DLB compared with healthy control individuals to the extent of the relative risk observed for AD (up to 3-fold increased risk). These data support a role for the APOE ε4 isoform as a biological marker for DLB and again support similarities in the pathogenesis of DLB and AD. Apolipoprotein E is believed to affect risk for both diseases through isoform-dependent modulation of Aβ accumulation and metabolism. The association found in DLB might be attributable to the fact that APOE ε4 increases the likelihood of Aβ deposition, which is present in many patients with DLB along with SNCA accumulation.

CONCLUDING REMARKS ABOUT THE MISSING HERITABILITY IN DLB

Dementia with Lewy bodies was first recognized as a disease entity only 15 years ago, and research in the field of molecular genetics has been lagging behind that of AD and PD. Although literature on the molecular genetics of DLB is scarce, the occurrence of familial aggregation of DLB and the identification of mutations in genes implicated in related neurodegenerative disorders support a role for genetic factors in the etiology of DLB. Yet, the mutations reported thus far have been identified in few patients with DLB. Moreover, the question remains whether these rare variants represent causal mutations or merely risk alleles. Studies in extended clinical or pathological DLB series are needed to determine the real contribution of these genes to the development of the disease.
A major DLB gene has not yet been uncovered. To date, few multigenerational families with DLB have been sampled for molecular genetic research, and they often lack the genetic power to identify novel genes using linkage analysis and positional cloning strategies. Therefore, the mapping of the first familial DLB locus on chromosome 2 holds great promise to identify the pathways involved in the underlying disease process. On the other hand, recent advances in high-throughput sequence capture methods and next-generation sequencing technologies enable geneticists today to find new genetic defects for mendelian disorders in small families even in the absence of previously mapped linkage regions. These approaches will certainly lead to the identification of additional causal genes and will create exciting research opportunities.

The scarcity of identified genetic factors for DLB might be related to the fact that the mutation spectrum in known and novel genes underlying this disorder is biologically more complex than is usually envisaged for monogenic disorders. Mutations causing DLB may be genetic variants influencing the level of functional proteins or RNAs rather than affecting their function. These mutations often reside in genomic regions frequently discarded when performing routine gene-based mutation analyses and require alternative mutation discovery procedures. Today, intronic and intergenic sequences are perceived to harbor crucial splicing machinery elements and other conserved but regulatory important motifs. Results of investigations have already shown that mutations affecting these regulatory elements can lead to disease. Also, deep intrinsic variations resulting in alternative splice products, inclusion of pseudoxons, and truncated proteins are becoming more evident for a multitude of diseases.

Epigenetic modifications are crucial for the regulation of human gene expression, and defects in these processes could add a new layer of complexity to the genetic etiology of complex diseases, such as DLB. The methylation patterns of DNA are known to be distorted in several heritable neurological disorders, giving rise to either hypermethylated or hypomethylated sites. These changes can induce abnormal activation or repression of gene expression and lead to disease. In PD, a recent study revealed an epigenetic type of regulation in the SNCA gene. The p.A53T mutation in SNCA causes an overall imbalance of allelic expression by epigenetically silencing the mutant allele, while the wild-type allele was expressed at increased levels equivalent to those seen for SNCA duplications. The study showed that even missense mutations may induce epigenetic deregulation, which may have an important role in neurodegenerative diseases. Because epigenetic changes are tissue specific and undergo dynamic changes over time, the study of epigenetics in the LBD spectrum is challenging for the following 2 reasons: (1) the need for brain tissue to investigate and (2) the need for sampling at different time points to interrogate the temporal changes to distinguish the cause or the consequence. Research on epigenetic effects in the LBD spectrum is just recently initiated, and few definitive clues have been found to date.

To discover what we are missing, a multidisciplinary approach is needed, including next-generation sequencing, transcriptomics, proteomics, DNA methylation, and histone modification mapping. Metabolomics may become the ultimate tactic to maximize the chance of uncovering novel gene defects.

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REFERENCES


