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Multisystem Lewy body disease and the other parkinsonian disorders

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Here we prioritize as multisystem Lewy body disease (MLBD) those genetic forms of Parkinson's disease that point the way toward a mechanistic understanding of the majority of sporadic disease. Pathological diagnosis of genetic subtypes offers the prospect of distinguishing different mechanistic trajectories with a common mutational etiology, differing outcomes from varying allelic bases, and those disease-associated variants that can be used in gene-environment analysis. Clearly delineating parkinsonian disorders into subclasses on the basis of molecular mechanisms with well-characterized outcome expectations is the basis for refining these forms of neurodegeneration as research substrate through the use of cell models derived from affected individuals while ensuring that clinically collected data can be used for therapeutic decisions and research without increasing the noise and confusion engendered by the collection of data against a range of historically defined criteria.

Over the last half century, new discoveries and insights into Parkinson's disease (clinically defined as bradykinesia, resting tremor, and rigidity with pathology of loss of dopaminergic nigral neurons and the presence of intraneuronal inclusions known as Lewy bodies) have been plentiful, and in some instances revolutionary. These range from the recognition of the importance of the substantia nigra in the 1950s[1] to the observations of a nigrostriatal dopamine deficiency as the main cause of symptoms and signs of the disease[1–3]. This, in turn, led to the identification, in 1968, of the first effective treatment (L-dopa) for the motor symptoms of the disease[2]. In 1983, the parkinsonogenic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)[3] was discovered, leading to the creation of the first good animal model for the disease and stimulating a renaissance of interest in environmental toxins as potential causes for it. More recently, the first monogenic form of Lewy body parkinsonism similar to Parkinson's disease, caused by the NM_000345.3(*SNCA*):c.157G>A (p.Ala53Thr) mutation in the gene encoding α-synuclein[4], ignited an explosion of interest and discoveries in the genetics of Parkinson's disease. These genetic data have provided important new biological insights[5], just as the discovery of MPTP did. Notwithstanding all of these developments, however, nearly 50 years after its discovery, L-dopa still remains the most effective drug for Parkinson's disease, allowing management of some symptoms but still far from an ideal therapy[5].

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Clinical syndromes and clinical-pathological syndromes

The five clinical and histopathological features of Parkinson's disease listed above (see **Box 1**) describe only a subset of what now appears to be a broader unitary disease process[6], while a set of related parkinsonian disorders that may have entirely different pathophysiological mechanisms are swept relatively unexamined into the Parkinson's disease classification (see **Box 1**, **Supplementary Table 1** and **Supplementary Note**). Because some genetic causes and some of the molecular entities responsible for this disease mechanism are now known, many have called for reclassification of parkinsonian nosology[7–11].

Indeed, it is now clear that what has been called Parkinson's disease is part of a much more extensive process[6] that involves more than just the substantia nigra. α-synuclein-positive Lewy neurites and Lewy bodies have repeatedly been reported in multiple areas of the brain and spinal cord and in the peripheral autonomic nervous system[6,7,12]. Friedrich H. Lewy himself first identified the intracellular inclusions named after him not in the substantia nigra but the locus coeruleus, dorsomotor nucleus of the vagus and nucleus basalis of Meynert[8], and E. Herzog reported them in the peripheral autonomic nervous system as early as 1928 (ref. 9). Furthermore, it is now known that in the brain, Lewy pathology is typically first seen in the olfactory bulb and the dorsomotor nucleus of the vagus[10,11,13]. Lewy pathology then progresses in a fairly typical pattern, from brain stem through a transitional phase to a diffuse disease[11,14]. Braak has divided this ascending pathology into six stages[11], with the substantia nigra not affected until stage 3. Confusingly, the clinical penetrance of affected anatomical areas varies widely, and patients with Lewy pathology can present symptoms and signs ranging from constipation to dementia.

Two other classic Lewy body disorders, dementia with Lewy bodies (DLB) and pure autonomic failure (PAF), have been shown to have histopathological features virtually identical to those of Parkinson's disease and Parkinson's disease dementia (PDD)[15], suggesting that they are all parts of the same disease. Finally, it is difficult to overemphasize the importance of the peripheral autonomic nervous system. α-synuclein-positive Lewy bodies and Lewy neurites have been identified postmortem in a wide variety of areas of the body, ranging from the myenteric plexus of the gut to the salivary gland, in patients diagnosed with Parkinson's disease. Over 40 imaging studies have shown sympathetic denervation of the heart in virtually all patients clinically diagnosed with Parkinson's disease[16], and one recent study showed Lewy neurites in the heart in 100% of the autopsy cases[17]. Thus, given the pathological

Box 1 Definitions of MLBD, Parkinson's disease and parkinsonism

Multisystem Lewy body disease (MLBD). A clinical and neuropathological entity that presents clinically with signs and symptoms consistent with Parkinson's disease including both motor and nonmotor symptoms. Neuropathologically there is Lewy body disease with α-synuclein-positive Lewy bodies and Lewy neurites in the brain (typically following Braak staging), spinal cord and peripheral autonomic nervous system.

Parkinson's disease classic definition. A clinical pathologic complex that presents clinically with bradykinesia, resting tremor and rigidity. Neuropathologically there are α-synuclein-positive Lewy bodies, Lewy neurites and neuronal cell loss in the substantia nigra.

Parkinsonism. A clinical complex that presents with rigidity, resting tremor and bradykinesia, typically occurring with any condition that interferes with basal ganglia function. Parkinsonism can result from a variety of causes including neurodegenerative disease, toxins and structural lesions.

distribution (brain, spinal cord and peripheral autonomic nervous) and natural history of its caudal-to-rostral development pathologically, we believe that the term 'multisystem Lewy body disease' (MLBD) is the best one to describe this complex and widespread disease (see **Box 1**).

The other key point is that the significance of the term 'MLBD' contrasts with what is denoted by 'parkinsonism', which is a purely clinical term referring to the syndrome of resting tremor, bradykinesia and rigidity. Thus 'parkinsonism' refers to a symptom complex, not a disease. Indeed, there are a huge number of causes of parkinsonism beyond neurodegenerative disease, ranging from toxins to pharmacological agents and even neoplastic lesions. This distinction is very important, particularly when categorizing patients on the basis of phenotype.

Gene names are labels, not surrogate mechanisms

With associations having been demonstrated between neurodegenerative disease that have any parkinsonian features and over 35 reported genes and other risk factors[5,18,19], it is becoming harder to infer the mechanisms that connect genetic forms with sporadic Lewy body disease. For this reason, we suggest that the claiming of newly associated genes with the *PARK* label should cease. This should not create mass confusion because all of the genes, except *PARK2*, that have been associated with parkinsonism (alone or with other features) can be cited using their existing HUGO Gene Nomenclature Committee–approved or other approved gene names (such as *SNCA*, *LRRK2*, *GBA* and *DJ-1*). Because different alleles can lead to different pathology and symptoms, before any newly discovered gene variants can be confirmed as causative for MLBD, it would be important to define the clinical phenotype and the neuropathology, as well as evidence using replicated association, transmission or recurrent *de novo* mutation criteria recommended by the American College of Medical Genetics[20], before codifying it as a gene with parkinsonism-causative mutations. We provide a structure exemplifying how this could work in **Supplementary Table 1**. Each of the gene variants is categorized as to whether it causes an MLBD-like disorder or simply parkinsonism (either as a primary manifestation or as part of a more complex disease). If the disorder is a Lewy body disease, it is important to include any available data on peripheral autonomic involvement (such as cardiac imaging as shown in **Supplementary Table 1**).

Allelic variation in genetic subtypes

Interestingly, so far, all genetic forms of MLBD have shown parkinsonian features, whereas sporadic MLBD can present with a wide variety of pre- and nonmotor symptoms[21]. Also, the same mutation (for example, NM_198578.3 (*LRRK2*): c.6055G>A (p.Gly2019Ser)) can cause MLBD in some instances, while in others resulting in degeneration limited to the substantia nigra and locus coeruleus with no Lewy body pathology[22]. For three of the genes with well-established associations with MLBD, there are allelic differences in phenotype as well as differences that cannot be attributed to allelic variation (**Table 1**). Sorting these out clinically could be difficult, but assessment of the peripheral autonomic system should differentiate between MLBD and non–Lewy body parkinsonism[23], including the atypical parkinsonisms. It is critical to understand this clinically, as peripheral nervous system involvement can be determined in the clinic, and affected individuals who lack peripheral nervous system involvement may have a different disease course and require different treatments from those who do not.

Analysis of gene-environment interactions

Over the last quarter century, with a renaissance of research on the environmental determinants of typical Lewy body parkinsonism—that is, MLBD—and the explosion of genetics in the study of MLBD and other genes that cause other diseases that include parkinsonian symptoms, one might have assumed that these two disciplines would have worked closely together to unravel these disorders. However, epidemiologic studies are typically long and very expensive, and the causal possibilities are nearly infinite. On the other hand, the huge technical advances in genetics have accelerated genetic research in the Parkinson's field over the last 15 years. Unfortunately, there are challenges that make it difficult for the two disciplines to integrate in a meaningful way. For example, a PubMed search for the terms "gene-environment" and "parkinsonism" netted only 64 references, whereas "parkinsonism" and "environment" netted slightly over 1,000 references, and "genetic" and "parkinsonism" over 8,000 references. This is particularly surprising given that most researchers believe that gene-environment (GxE) interaction will be a key to solving Parkinson's disease—yet there is a poverty of research in this area as compared to genetics.

Obviously the solution is for epidemiology and genetics to collaborate from the design of experiments onward[24,25]. For example, examining an epidemiologically characterized cohort on a genetic basis showed that working with the herbicide paraquat doubled the risk of Parkinson's disease, but the risk was increased 11-fold in subjects who also had a common genetic variant (a defective *GSTT1* gene), representing one of the largest increases in risk for Parkinson's disease reported to date[26]. Obvious obstacles to be anticipated in this field relate to the number of subjects required for the studies, given that GxE effects for common variants are anticipated to be small and cohorts of hereditary mutation carriers will be limited by their rarity.

Limits and prospects of stem cell genetic models

Although the MPTP model has proved highly useful in regard to testing new drugs for symptomatic therapy for parkinsonian signs and symptoms and agents that block the side-effects of L-dopa[27,28], it is not a model of MLBD, and it has not proved useful for the discovery of drugs aimed at modifying disease progress. Of course the genetic discoveries have given birth to a myriad of transgenic models, but although these have been helpful, none appear to replicate the features of MLBD, and so their usefulness remains unclear when it comes to identifying disease-modifying agents that would be effective in the human sporadic genetic forms of the disease. This is the case even when transgenic and knockout technologies

Table 1 Multisystem Lewy body disease and parkinsonism allelic variants

Gene, allelic variant (protein variant)	Mean age at onset (years)	Disease duration (years)	Cases with pathology	Presentation of MLBD	Ref(s).
α-synuclein, *SNCA* alleles (Chr. 4q21-22, NM_000345.3)					
SNCA, c.88G>C (p.Ala30Pro)	54	15	1	PD-like syndrome with more rapidly progressive course and cognitive decline; α-synuclein-positive LBs, Lewy neurites and neuronal cell loss in substantia nigra and other areas in a distribution similar to that in MLBD.	51
SNCA, c.136G>A (p.Glu46Lys)	67	8	1	PD-like syndrome with more rapidly progressive course and dementia; α-synuclein-positive LBs, Lewy neurites and neuronal cell loss in substantia nigra and other areas in a distribution similar to that in MLBD.	52
SNCA, c.150T>G (p.His50Gln)	71	12	1	PD-like syndrome with α-synuclein-positive LBs, Lewy neurites and neuronal cell loss in substantia nigra and other areas in a distribution similar to that in MLBD.	53
SNCA, c.152G>A (p.Gly51Asp)	48.5 (s.d. 21.82)	12 (s.d. 11.34)	4	Early-onset PD-like syndrome with dementia; α-synuclein-positive LBs, Lewy neurites and neuronal cell loss in substantia nigra and other areas in a distribution similar to that in MLBD. Also TAR DNA-binding protein 43 (TDP-43) inclusions in limbic region and striatum neurons and MSA-related pathology with glial-cytoplasmic inclusions.	54
SNCA, c.157G>A (p.Ala53Thr)	45.28 (s.d. 10.73)	8.14 (s.d. 2.96)	7	PD-like syndrome; can present with early onset, dementia; α-synuclein-positive LBs, Lewy neurites and neuronal cell loss in substantia nigra and other areas in a distribution similar to that in MLBD. Additional neuropathology has been reported including neurofibrillary tangles, glial-cytoplasmic inclusions, TDP-43 immunoreactivity.	57–61
SNCA gene duplication	50.66 (s.d. 12.94)[62]	12.83 (s.d. 4.75)	6	Can present as early-onset PD-like syndrome with dementia, and autonomic failure; α-synuclein-positive LBs, Lewy neurites and neuronal cell loss in substantia nigra and other areas in a distribution similar to that in MLBD, more prominent cortical and brain-stem LBs. Size of duplication varies from 0.2 Mb to 41.2 Mb[61,62].	65–68
SNCA gene triplication	30.85 (s.d. 14.98)[62]	12.71 (s.d. 8.53)	7	Usually early-onset PD-like syndrome with dementia, and autonomic failure; α-synuclein-positive LBs, Lewy neurites and neuronal cell loss in substantia nigra and other areas in a distribution similar to that in MLBD; cortical and brainstem LBs, temporal lobe vacuolation, neuronal loss in cornu ammonis (CA2/3) area of the hippocampus have been reported.	43, 69–71
Leucine-rich repeat kinase 2, *LRRK2* alleles (Chr. 12q12, NM_198578.3)					
c.4111A>G (p.Ile1371Val)	61	10	1	PD-like syndrome, α-synuclein-positive LBs, Lewy neurites and neuronal cell loss in substantia nigra and other areas in a distribution similar to that in MLBD.	72
c.4309C>A (p.Asn1437His)	52	19	1	PD-like syndrome, α-synuclein-positive LBs, Lewy neurites and neuronal cell loss in substantia nigra and other areas in a distribution similar to that in MLBD; unusual finding of very pronounced ubiquitin-positive pathology in brainstem, temporolimbic regions and neocortex.	73
c.4321C>T/G (p.Arg1441Cys/Gly)	63.5 (s.d. 9.1)[b]	13.1 (s.d. 5.6)[b]	6	PD-like syndrome, α-synuclein-positive LBs, Lewy neurites and neuronal cell loss in substantia nigra and other areas in a distribution similar to that in MLBD in 2 cases; nigrostriatal cell loss without α-synuclein-positive LBs or Lewy neurites in 3 cases; PSP-like pathology (neurofibrillary tangles, coiled bodies and tufted astrocytes) in 1 case.	22,74–76[b]
c.5096A>G (p.Tyr1699Cys)	52.1 (s.d. 9.3)	12.6 (s.d. 7.6)	14 (3)	PD-like syndrome, α-synuclein-positive LBs, Lewy neurites and neuronal cell loss in substantia nigra and other areas in a distribution similar to that in MLBD in 1 case; nigrostriatal cell loss without α-synuclein-positive LBs or Lewy neurites in 2 cases.	22,77[c]
c.6055G>A (p.Gly2019Ser)	With LBs: 57 (s.d. 12.8); without LBs: 68.0 (s.d. 7.5)	With LBs: 21.1 (s.d. 9.7); without LBs: 13.5 (s.d. 4.2)	With LBs: 1; without LBs: 6	PD-like syndrome, α-synuclein-positive LBs, Lewy neurites and neuronal cell loss in substantia nigra and other areas in a distribution similar to that in MLBD in 11 cases (14 further cases with α-synuclein-positive LBs have been described elsewhere[78–81]); nigrostriatal cell loss without α-synuclein-positive LBs or Lewy neurites in 6 cases; neurofibrillary tangles and amyloid plaques described in some cases.	22
c.6059T>C (p.Ile2020Thr)	53.4 (s.d. 9.45)	19.9 (s.d. 8.2)	9	PD-like syndrome, α-synuclein-positive LBs, Lewy neurites and neuronal cell loss in substantia nigra and other areas in a distribution similar to that in MLBD in 1 case; nigrostriatal cell loss without α-synuclein-positive LBs or Lewy neurites in 7 cases; MSA-related pathology with glial-cytoplasmic inclusions but no neurofibrillary tangles or amyloid plaques described in 1 case.	22,82, 83[d]
Glucosidase, beta, acid, *GBA* alleles (Chr. 1q22, NM_000157.3)					
c.1226A>G (p.Asn370Ser), ~10% enzyme activity	70.33 (s.d. 7.76) (ref. 86)	15.6 (s.d. 4.7) (ref. 86)	3/16 (ref. 86)	PD-like syndrome, α-synuclein-positive LBs, Lewy neurites and neuronal cell loss in substantia nigra and other areas in a distribution similar to that in MLBD.	87
c.1448T>C (p.Leu444Pro) ~15% enzyme activity	51.2 (s.d. 8.87)(ref. 86)	15.2 (s.d. 4.8) (ref. 86)	5/16 (ref. 86)	PD-like syndrome, α-synuclein-positive LBs, Lewy neurites and neuronal cell loss in substantia nigra and other areas in a distribution similar to that in MLBD.	87
Other rare *GBA* alleles	51.5 (s.d. 9.18) (ref. 86)	11.8 (s.d. 4.7) (ref. 86)	8/16 (ref. 86)	PD-like syndrome, α-synuclein-positive LBs, Lewy neurites and neuronal cell loss in substantia nigra and other areas in a distribution similar to that in MLBD.	87

Mutation designation based on human genome variation society (HGVS) nomenclature recommendations. LBs, Lewy bodies; MSA, multiple system atrophy; PD, Parkinson's disease.

[a]Greek/Italian background. [b]Family D (p.Arg1441Cys). [c]Lincolnshire family. [d]Sagamihara family.

have been used to generate rodent versions carrying mutations that are identical to the human mutation (**Supplementary Table 2**).

One option is to turn to human cell models that are based on genetic variations that cause disease in humans. This is feasible as many clinical centers and organizations have been collecting various biospecimens for use in both discovery and drug development along with the phenotypic information that can be obtained about the affected individual donating the tissue either from medical records or as part of a clinical study. Using the Parkinson's Institute as an example, we have a research model that includes medical history, clinical evaluations, environmental risk exposure and biospecimens, and we have the ability to integrate and search across 25 years of data. The Institute has collected tissues from subjects with clinical and neuropathological diagnoses of MLBD and parkinsonism due to a variety of causes (such as multiple system atrophy) and additional diseases that show α-synuclein- and/or tau-related neuropathology (**Table 2**, upper part). Within these categories, we have also been able to collect samples from subjects with genetically causal forms of these disorders (**Table 2**, lower part).

One avenue is the use of nuclear reprogramming and induced pluripotent stem (iPS) cell technology starting from individual donors with clear clinical diagnoses. This approach could be used to create a disease model from patient-specific human cells[29]. In regard to addressing some of the challenges specific to MLBD and parkinsonism, patient-specific iPS cells could allow us to more clearly understand the differences and/or potential similarities between genetic forms of disease, including allelic variants, and to compare these to idiopathic disease. Establishing a well-defined collection of cell lines taken from patients with thoroughly characterized high-quality clinical data, including data on the peripheral manifestations of the disease (if any) and ideally with confirmative neuropathology at autopsy, is the key to the successful interpretation of findings.

In addition to the need for clinically fully characterized patient donors, several technical challenges must be addressed to reduce variability (**Supplementary Table 3**). Another critical area for improvement is the use of consistent and well-documented methods (see **Supplementary Table 3**). Multiple different neuronal differentiation protocols have been developed over the last 15 years to differentiate human embryonic stem cells, and now iPS cells, into various types of neurons. Unfortunately, it is challenging to compare neuronal differentiation protocols because of their variable methods and techniques. As a result, studies often do not replicate, and data are difficult to interpret across laboratories. The field is in need of standardized and validated iPS cell laboratory practices that can be used to generate and characterize cells and phenotypes of interest (see **Supplementary Table 3**).

Taking these precautions, and using well-characterized patient material, we are establishing a comprehensive collection of patient-specific skin cell lines and iPS cell clones (see **Table 2**, lower part). Preliminary evidence that this is feasible has been published by our group and others with regard to disease caused by mutations in the *SNCA* and *LRRK2* genes. We and others have shown there are differences between patient-derived cells and control cells derived from unaffected individuals leading to mitochondrial dysfunction, increased susceptibility to oxidative stress and reduced survival after differentiation[30–40]. By integrating longitudinal clinical assessment and brain neuropathology to establish the diagnoses of MLBD and parkinsonism, this research model reinforces its criteria and securely identifies more of the subtypes.

Mechanism and outcomes on pathology via data resources

The fundamental concept driving the Parkinson's Institute, which was founded upon this experience, is that of ensuring that information can flow quickly from the laboratory to the clinic and vice versa. For this model to work successfully, it is critical to collect the highest-quality diagnostic and clinical data, gathered by trained movement-disorder specialists caring for their patients. The second component of this model is building a data and tissue bank derived from as many affected individuals as possible and including blood, saliva, DNA, immortalized lymphocytes, skin fibroblasts and libraries of iPS cell lines, as well as ancillary clinical data (for example, imaging studies and data on environmental exposures or nonmotor symptoms of Parkinson's disease). Importantly, patients are asked to sign up for our brain donation program (see **Table 2**, upper part). Because of the availability of

Table 2 Data resources for research on MLBD and other disorders with parkinsonism

	Brain and histopathology	DNA	Fibroblasts	iPS cell donor line	Longitudinal clinical data
Brain, tissue and clinical resources					
MLBD, Parkinson's disease or parkinsonism	157 (refs. 41,88,89)	629	42	12	260
Multiple system atrophy	17 (refs. 42,90)	0	2	2	4
Progressive supranuclear palsy	24	0	1	0	6
Corticobasal degeneration	1	0	0	0	0
Fronto-temporal dementia	1	0	0	0	
Azheimer's disease without Parkinson's disease	8	0	0	0	1
Atypical parkinsonism	6	8	2	1	6
No neurological disease	23	542	18	9	Not applicable
Genetic MLBD or parkinsonism resources					
Idiopathic Parkinson's disease	146	552	14	1	241
SNCA any mutation	2 (refs. 43,91,92)	2	1 (ref. 93)	1 (ref. 30)	3
LRRK2 any mutation	2 (ref. 22)	44 (ref. 94)	15	3 (refs. 31,95)	8
GBA one allele	4 (ref. 96)	3	2	0	1
GBA both alleles	0	1	1	1	1
LRRK2/GBA compound heterozygote	0	8	4	1	1
PARK2 one allele	2 (ref. 97)	11 (ref. 98)	1	0	0
PARK2 both alleles	1 (ref. 98)	4	2	2	2
PINK1 both alleles	0	2	1	1	1 (ref. 99)
22q11 deletion	0	1	1	1	1
No neurological disease	19	542	18	3	Not applicable

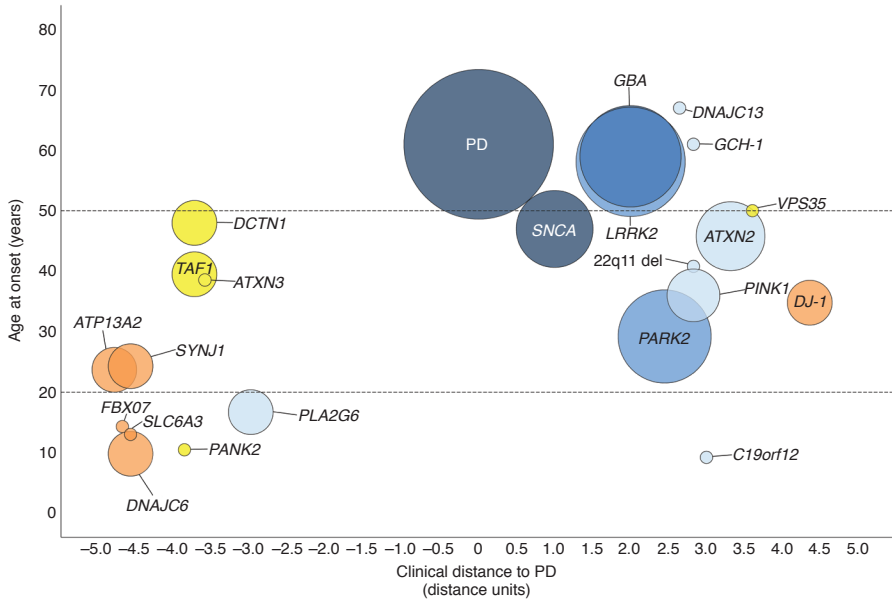

Figure 1 Bubble graph of genetic forms of parkinsonism. To more readily visualize the relationship between various forms of parkinsonism and sporadic Parkinson's disease (which we propose is MLBD), we used the information in **Supplementary Table 1** (which is organized on the basis of genetics, clinical assessments and neuropathology) to calculate the Euclidean distance of the clinical manifestations of the gene, mutation or condition listed relative to sporadic Parkinson's disease (*x* axis). The *y* axis represents the age of onset of disease, and the size of each bubble represents the relative prevalence (see **Supplementary Table 4** and **Supplementary Note** methods for details). The circle labeled "PD" refers to idiopathic PD where genotype is not known. Because there are varying degrees of robustness of neuropathological data, color shades were used to reflect this as follows: dark blue indicates Lewy body pathology in all cases; medium blue indicates variable findings with the majority of cases showing Lewy body pathology; light blue indicates Lewy body pathology in only a few cases; yellow indicates that Lewy body pathology was not found but the data are sparse or incomplete; orange indicates no data were available.

a repository of well-characterized clinical data and tissue samples, we were able to rapidly confirm that most individuals with pathologically sporadic Lewy body Parkinson's disease (MLBD) do not carry the first identified autosomal dominant *SNCA* variant[41,42]. We were also able to confirm the existence of cases caused by *SNCA* triplication as well as to run the first clinical trial aimed at modifying the course of Parkinson's disease[41–44]. By integrating clinical care and patient participation with over 70 data sources and by anchoring records to neuropathology, we can model the diseases and test hypotheses with maximal relevance to clinical delivery and improvement of care[45]. National registries such as the Danish National Patient Register and Swedish patient registries are excellent data sources for calculating the prevalence and incidence of Parkinson's disease. Data such as International Classification of Diseases (ICD) codes for diagnoses are typically collected, along with medication history and hospital treatment codes; however, these registries usually lack more detailed data types such as phenotypic, genetic, environmental and pathological data, and in most cases autopsy data are limited or unavailable[46,47].

Ordination of disease subtypes and associated genes

An analytical approach to understanding that there are several mechanistic processes at work in MLBD and other parkinsonian disorders is to examine their clustering in multidimensional space by their quantitative clinical measures. A visual representation of the data from **Supplementary Table 1**, which is organized based on consideration of genetics, clinical assessments and neuropathology, is shown in **Figure 1**. We used the 21 clinical symptoms and 8 neuropathologic categories to calculate the Euclidean distance from Parkinson's disease (see **Supplementary Table 4** and **Supplementary Note**). With the visual representation of clinical features by Euclidean distance, age distribution and robustness of evidence for pure Lewy body pathology, it becomes clear that mutations in these genes can cause very different clinical and neuropathological phenotypes.

Another way to consider using a mechanistic approach is to focus searches for interacting proteins by pathological classification (see **Supplementary Fig. 1a** and **Supplementary Note**). Our hypothesis was that querying the protein interaction networks of gene-related protein products associated with parkinsonism, using their pathological substrate as a guide, could yield important physiological interactions or sets of related genes based on common pathways whose disruption could result in Parkinson's disease. Although the majority of data queried are based on cell type–specific interactions of wild-type proteins, these might be relevant to disease processes in cells expressing the products of mutated genes through disruption of these normal physiologic interactions.

For purposes of illustrating this approach, we interrogated the public database STRING DB[48] to drive understanding of the best next steps toward identifying gene products as novel therapeutic targets. Using the information in **Supplementary Table 1**, we identified the interacting proteins from among the products of our first group of genes, which are a mix of disease alleles that are associated with some aspects of MLBD and several genes that are associated with parkinsonism but for which there is little or no data to support their association with a primary Lewy body pathology diagnosis (*LRRK2, GBA, SNCA, VPS35, DJ-1, PINK1, PARK2* and *DNAJC13*). There were multiple interactions with these proteins, but only a single interaction was found in common among the eight: human ubiquitin C (**Supplementary Fig. 1a**; UBC, yellow dot). When the protein interaction network search was limited to only genes that are associated with MLBD or possible MLBD (*LRRK2, DNAJC13, GBA,* and *PINK1*), only two common interacting proteins, UBC and Hsp70 (HSPA4), were found (**Supplementary Fig. 1b**). However, the interaction network for proteins encoded by genes best characterized to cause MLBD (*LRRK2, SNCA* and *GBA*) showed an extensive overlap in the number of common interactions (more than 50, **Supplementary Fig. 1c**; see **Supplementary Table 5** for a list of these interactions). Although databases have inherent bias based on complexities ranging from the definition of the protein-protein interaction to the number of people studying the genes[49] (which can be difficult to correct for and and whose statistical effect remains controversial), it is still useful to consider this approach. It is difficult to account for the potential inherent bias in the data sets, and for the additional potential bias resulting from reducing the number of 'interactors' from five to three; nonetheless, these findings are consistent with the approach we have taken using clinical analysis of phenotype. Although the hypothetical interaction network for the

proteins encoded in this set of genes is extensive and requires validation, conceptually, these networks illustrate how this approach could provide insights that cannot be gained from single-protein analyses.

Taken together, these illustrations highlight the potential importance of defining the underlying pathological process to understanding genetic diseases and their relevance to corresponding sporadic diseases. Many of the problems prevalent in the field show the difficulties that arise when we get this wrong.

In summary, MLBD forms a core of sporadic cases of Parkinson's disease and includes at least three genetic subtypes based upon our summaries of allelic heterogeneity, clustering of multiple quantitative clinical features and the protein-protein interactions attributable to the products of genes associated with MLBD and other parkinsonian disorders. First, our detailed examination of 25 years of patient data and samples at our Institute, in combination with a comprehensive literature review, suggests a unified entity of primary Lewy body diseases, which we propose might best be called 'multisystem Lewy body disease', that includes Parkinson's disease, DLB and PAF. Second, on the basis of the clinical, neuropathological and peripheral autonomic features of all forms of parkinsonism associated with genetic causes, only three genes fall into the category of MLBD-associated genes: *SNCA*, *LRRK2* and *GBA* (**Supplementary Table 1** and **Fig. 1**). Third, the proteins encoded by these three genes showed by far the highest number of first-degree interactors in our protein-protein network (**Supplementary Fig. 1c**). Fourth, these overlapping genes are the ones most consistently reported in GWAS studies associated with clinically characterized Parkinson's disease[5,19] (a pattern that is not consistently found in other neurodegenerative disease, such as Alzheimer's disease[50]). These approaches are largely independent in nature and exploratory (clinical and pathological observation, protein-protein interaction and genome-wide association), yet they yield the similar finding, adding solid support to our unified hypothesis of multisystem Lewy body disease. Overall, we hope to stimulate data-driven discussion of similarities and differences in the several mechanisms operating in parkinsonian movement disorders that will change the emphasis of the field to encourage the use a common language and allow this research move forward with greater clarity and speed.

Note: Supplementary information is available in the online version of the paper.

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AUTHOR CONTRIBUTIONS

All authors wrote the manuscript. J.W.L. contributed clinical and pathological aspects of MLBD, B.S. contributed concepts around genetics and stem cell modeling, L.R. contributed fundamental work on clinical data integration, R.J.N. contributed modeling of protein-interactions networks and review of animal models of Parkinson's disease, and C.B. built concepts around data integration and informatics approaches for translation into clinical applications.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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