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α-Synuclein: Prion or Prion-like?

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Misfolded alpha-synuclein is a corruptive seed, but is it infectious?

Alpha-synuclein is a natively unfolded or intrinsically disordered protein, but it can also assume amphipathic alpha-helical shapes in the presence of negatively-charged lipids. In Lewy body disorders, alpha-synuclein monomers aggregate into oligomers, protofibrils, and fibrils, forming part of the hallmark amyloid inclusions known as Lewy bodies and Lewy neurites. Proteins exist in biological settings in multiple conformations, often with varied biological functions, and the transitions between conformations include structures that seed the nucleated growth of aggregates [10]. After the kinetic barrier to aggregation of natively monomeric proteins is (rarely) overcome, the global free-energy minimum favors the precipitation of hydrophobically-packed protein masses [15]. Once this low-energy state is acquired, it may not be energetically feasible to proteolyze and resolve the protein mass, and, therefore, “the aggregate state always wins,” in the words of Guest *et al*. [15].

The thermodynamic principles outlined above would favor the retention of aggregated forms of alpha-synuclein in Lewy inclusions, and the aggregated alpha-synuclein could then provoke the polymerization of neighboring, native alpha-synuclein molecules into higher-order species, perhaps by imprinting its beta-sheet template onto monomers—not unlike the scrapie-associated prion protein (PrP^{Sc}). PrP^{Sc} (scrapie) is responsible for inherited and acquired forms of spongiform encephalopathy in cattle (bovine spongiform encephalopathy), sheep (scrapie), deer and elk (chronic wasting disease), and humans (Kuru, Creutzfeldt-Jakob disease, variant Creutzfeldt-Jakob disease, fatal familial insomnia, Gerstmann-Sträussler-Scheinker syndrome). The term prion, coined by Stanley Prusiner, is a

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portmanteau of two unambiguous words, “protein” and “infection.” Therefore, a prion particle is, by definition, the underlying cause of an infectious disease, rather than a secondary consequence of disease processes or a generalized stress response, and it is purely proteinaceous in nature.

In an influential series of histopathological investigations, Heiko Braak, Kelly Del Tredici, and colleagues lay the groundwork for the speculation that misfolded versions of alpha-synuclein act as “prion-like” molecules, traveling transneuronally across brain circuitry in a stereotypic fashion, leaving in their wake a “falling row of dominoes” and exposing six stages of Parkinson’s disease [4-6, 11]. The provocative “Braak hypothesis,” as it came to be known, spawned a large body of work addressing the new concepts that 1) the olfactory and gastrointestinal mucosae serve as peripheral entry points for an unnoticed invading agent, prion-like or otherwise, and 2) the alpha-synucleinopathy is then transcellularly transmitted deep into the brain, through a preestablished set of neural circuits, and is responsible for the onset of disease in Lewy body disorders.

If we assume that alpha-synuclein is not prion-like, but a bona fide prion, it then follows that a misfolding event in alpha-synuclein might be the cause of Lewy body disorders (including in patients without an inherited form of disease), rather than being a consequence of the disease process. This postulate differs in important ways from the notion that alpha-synuclein aggregation is an innocent bystander of disease or a natural protective mechanism [33, 49]. According to the latter concepts, misfolded alpha-synuclein molecules are tucked away in somal Lewy inclusions, shunted from the synapse, axon, and critical organelles. This mechanism mirrors a garbage dump full of nonrecyclable waste, built in a sheltered location that does not contaminate human living spaces. A parallel argument was dubbed the “airbag problem”, in which investigators ignorant of the actual reasons for airbag use measure a robust correlation between airbag deployment and car crashes, and conclude that airbags are the cause of the crash, rather than being specifically manufactured as a defense mechanism [26].

In previous centuries, the field of microbial infections contended with similar problems in distinguishing correlation from causation. In the words of the physician and microbiologist Robert Koch,

> “…from the mere coincidental relation of tuberculous affections and bacilli, it may not be concluded that these two phenomena have a causal relationship, notwithstanding the not inconsiderable degree of likelihood for this assumption that is derivable from the fact that the bacilli occur by preference where tuberculous processes are incipient or progressing, and that they disappear when the disease comes to a standstill.” [23]

Criteria that distinguish causal links from correlations

In his experiments that proved causality, Koch grew bacteria from patients’ sera, for months in culture, which, when injected into animals, elicited a phenotypically analogous disease, whereas animals inoculated with serum lacking any bacterium failed to display similar symptoms. Sir Austin Bradford Hill subsequently described nine criteria for causal

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associations in epidemiological studies. The latter are copied and pasted below from Fredricks and Relman [13], to encourage their application to alpha-synuclein as a potential disease-causing entity:

1. " Strength of the association (relative risk)
2. Consistency of association
3. Specificity of association (outcome is unique to the exposure)
4. Temporality (exposure precedes outcome)
5. Biological gradient (evidence of dose-response)
6. Plausibility
7. Coherence (compatibility with present knowledge)
8. Experimentation (controlled manipulation of exposure should change outcomes)
9. Analogy (causal relationship conforms to previous relationships) [13]"

According to criterion 8 and the very definition of a prion, scientists would need to show that alpha-synuclein protein itself, *in the absence of other exogenous factors* (e.g., nucleic acids, bacterial lipopolysaccharides, proinflammatory cytokines) can initiate the histological and behavioral manifestations of Lewy body disorders, and that its removal from the host organism therefore abolishes the onset of disease. In the latter context (i.e., removal from host), two key experiments demonstrate a failure of transmission of alpha-synucleinopathy to *SNCA* knockout mice [22, 42], as well as after immunodepletion of alpha-synuclein from diseased human tissue that is then transplanted into mice [42]. These two observations lend credible support to the essential nature of alpha-synuclein protein for the emergence of disease—in the animal models. They do not, however, reveal whether *other* forms of Lewy-like pathology, consisting of ubiquitin, filaments, lipids, and organelles [46], can still materialize in the absence of alpha-synuclein protein.

Some reports suggest that the loss of neurons and the cardinal neurological deficits in Lewy body disorders are triggered by factors other than alpha-synucleinopathy *per se*. First, brain structures with Lewy inclusions do not necessarily display frank neuronal loss, and, conversely, Parkinson's patients may suffer cell loss in specific regions (e.g., presupplementary motor cortex) with sparse or no burden of Lewy bodies [8, 17, 31,35]. Second, neuronal loss may transpire before Lewy inclusions appear, such as in the substantia nigra during the early Braak stages I to II (flouting Hill's criteria 3-4) [32]. Third, A53E and G51D mutations in alpha-synuclein, which are associated with inherited forms of Parkinson's disease, delay—rather than accelerate—the fibrillization of alpha-synuclein [12,14]. On the other hand, when minimal threshold levels of alpha-synucleinopathy are present, significant clinicopathological correlations are indeed observed, including of deficits in movement and cognition [2] (fulfilling Hill's criteria 1-2). Additional research is required to determine if alpha-synuclein oligomers are a more reliable source of cellular injury than the relatively mature Lewy inclusions visualized by popular histopathological methods.

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James Surmeier argued that varying degrees of vulnerability of neuronal subpopulations better explain the noncontiguous emergence of Lewy inclusions across space and time within the host, rather than prion-like transmission [47]. To date, it also remains unclear to what degree alpha-synucleinopathy contributes to— rather than correlates with—neuronal demise and an idiopathic clinical syndrome, particularly if few inclusions are present. Although behavioral deficits in patients may be triggered by surpassing a threshold of neuronal loss rather than Lewy bodies and neurites, it also seems likely that alpha-synuclein aggregates perturb axonal function, which might trigger cell death, if sufficiently chronic or intense [51].

Is the debate merely semantic?

The most significant human evidence favoring the prion-like properties of alpha-synuclein derives from transplant studies, which demonstrated that embryonic tissue engrafted into the striata of Parkinson's patients acquired Lewy inclusions over the course of a decade or more, with the inclusions increasing over time, in a roughly "dose-dependent" manner, from 3-5% of grafted cells to ~30% [24,25,27,28] (Hill's criteria 4, 5, & 8). However, whether these observations reflect the prion-like transmissibility of alpha-synuclein, or the cellular toxicity of other factors present in the diseased host brain, including inflammatory mediators, reactive oxygen and nitrogen species, and bioenergetic disequilibria, continues to be debated. No overt cell death was apparent in the transplanted human tissue, again supporting the uncoupling of Lewy inclusions from cell loss (see Hill's criteria 1-3).

After a spate of tissue transplant studies, it became important to examine whether relatively pure preparations of alpha-synuclein could induce *de novo* alpha-synucleinopathy. In a series of landmark studies from the Lee lab, Volpicelli *el al.* and Luk *el al.* collected support for the idea that recombinant, preformed fibrillar alpha-synuclein protein can induce disease in wildtype cells and animals [30,52]. Compelling evidence favoring transneuronal transport of alpha-synuclein into the brain from the periphery, including the gut, has also been collected [22, 50]. Indeed, alpha-synuclein assemblies appear to cross into the brain from the oral, intravenous, intraperitoneal, intraglossal, and intramuscular routes [7, 29, 38, 45]. Some of the latter data have been collected in transgenic animals, in which Beekes and colleagues argued the inoculum might simply increase or accelerate the preordained precipitation of forcibly-overexpressed alpha-synuclein in vulnerable brain regions, rather than representing an "infectious trigger" [3]. These transgenic animals are, after all, genetically engineered to display amyloidogenic proteins, and, despite this experimental design, do not faithfully recapitulate the human alpha-synucleinopathies anyway.

The appropriateness of the term prion versus prion-like is not an inconsequential debate, but one with significant implications for our understanding of the etiology of Lewy body disorders, and how patients and their biopsied tissues are treated in the home, clinic, hospital, surgery room, and research laboratory. In the words of Adriano Aguzzi, "prionoids sport predatory behavior akin to that of prions," but they "do not spread within communities or cause epidemics" [1]. In contrast, prions such as serum amyloid A display true elements of infectivity in geese and cheetahs, including uptake, replication in permissive hosts, and excretion [1]. It is worth noting that excretion of infectious PrP^{Sc} from the host may

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represent the mechanism of spread for scrapie and chronic wasting disease in the wild [16, 48]. However, patients are not infected by casual contact with nasally-secreted or aerosolized prions, although nasal brushings collected from the olfactory epithelia of Creutzfeldt-Jakob disease patients have prion-seeding activity in real-time quaking-induced conversion tests [34]. Rather, patients seem to acquire the transmissible disease by consuming prion-infected brain matter or being subjected to invasive medical procedures with infected biological materials or surgical instruments.

Are there inherited, sporadic, *and* acquired forms of Lewy body disorders?

Kuru was transmitted in the natural world due to ritualized mortuary cannibalism in the Fore region of New Guinea. Prions may also be transmitted across the species barrier, such as when humans consume PrP^{Sc} infected tissues. It is easy to imagine that calorically dense and prion-rich brain tissues would have been consumed at every opportunity by prehistoric hominid hunters. Even modern societies have consumed goat and sheep brains as a part of their traditional diet, including *cervelle de veau*, part of the French cuisine. The bovine spongiform encephalopathy outbreak was traced to infected cattle meat, and the Centers for Disease Control states that ~230 patients with variant Creutzfeldt-Jakob disease have been reported worldwide since 1996. In addition, >450 cases of Creutzfeldt-Jakob disease were traced to clinical treatment with cadaver-derived human growth hormone or gonadotrophin, dura mater or cornea transplantations, implantation of surgical or EEG recording tools, and blood or plasma transfusions [3]. Prion infections are, therefore, a rarity, compared to the incidence of Parkinson's disease, which affects more than 1200 individuals per 100,000 in industrialized nations [40].

It is not known why alpha-synucleinopathies do not naturally emerge in other vertebrates, whereas prion diseases clearly do. Given the human-specific nature of Lewy body disorders and the paucity of dietarily-acquired prion diseases, the statistical probability that alpha-synuclein aggregates within consumable animal products give rise to Lewy body disorders seems low (see Hill's criterion 6), even if meat consumption is correlated with a higher risk of Parkinson's disease [21]. Prospective studies on this topic are limited. On the other hand, amyloid proteins produced by gut bacteria can seed alpha-synucleinopathy in the nervous systems of vertebrate and invertebrate models [9].

If future experiments demonstrate that exposure to brain or other tissues transmits Lewy body disease, even if iatrogenic, we could state with greater confidence that there are three forms of Lewy body disorders—inherited, sporadic, and acquired. One 2013 study specifically tested this hypothesis, but failed to gather support for the idea that Parkinson's disease could be acquired from cadaver-derived human growth hormone [18]. It is unfortunate that the authors of this study did not include the terms "multiple system atrophy" in their search for iatrogenic transmission, given the work of the Prusiner lab on this condition [41]. In their report, Irwin and colleagues cited unpublished findings from the National Institutes of Health, in which there was no evidence of Parkinson's pathology in primates inoculated with diseased human tissue [18]. More recently, however, exposure to cadaver-derived human growth hormone has been associated with the development of Alzheimer's disease [19, 44].

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Conclusions

Few would insist that similar molecular processes are not at play with alpha-synuclein and PrP^{Sc}. Nevertheless, given the lack of unequivocal evidence that exposure to alpha-synuclein aggregates is the cause of a communicable form of disease in the natural environment, many authors employ the term “prion-like” for alpha-synuclein. We have learned that preclinical models of disease suffer from grave limitations, and that the most parsimonious narratives about human conditions (i.e., Occam’s razor) can be fundamentally wrong. It is exceedingly difficult to prove causality when incubation periods are long, when there are confounding effects of host factors, such as inflammation, and when reliably translatable preclinical models are largely unavailable. Further complicating matters, humans likely display robust immune responses against foreign protein aggregates, given the phylogenetically ancient nature of amyloid, and our bodies may clear protein aggregates unexpectedly well. If this were true, prionoids might struggle to gain a foothold in the human body, unless, perhaps, the concentration surpasses a threshold or aging processes diminish protein clearance.

Guest and colleagues wrote that infection is not simply a matter of biochemistry, but a “multidimensional question of biological, epidemiological, and sociological origin” [15]. Koch’s avoidance of casual use of the word infectious therefore seems instructive today. Obviously, we must avoid the application of Koch’s postulates with a “mathematical zeal not warranted in the biological world”, as maintained by Fredricks and Relman [13]. For example, disregarding the prion-like properties of alpha-synuclein might lead to accidental human disease and decelerate progress in the field of rational drug design, such as anti-alpha-synuclein vaccination therapies. On the other hand, Fredricks and Relman also concluded, “The power of Koch’s postulates comes not from their rigid application, but from the spirit of scientific rigor that they foster. The proof of disease causation rests on the concordance of scientific evidence, and Koch’s postulates serve as guidelines for collecting this evidence.”

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References

1. Aguzzi A (2009) Cell biology: Beyond the prion principle. Nature 459: 924–925 Doi 10.1038/459924a [PubMed: 19536253]
2. Beach TG, Adler CH, Lue L, Sue LI, Bachalakuri J, Henry-Watson J, Sasse J, Boyer S, Shirohi S, Brooks R et al. (2009) Unified staging system for Lewy body disorders: correlation with nigrostriatal degeneration, cognitive impairment and motor dysfunction. Acta Neuropathol 117: 613–634 Doi 10.1007/s00401-009-0538-8 [PubMed: 19399512]
3. Beekes M, Thomzig A, Schulz-Schaeffer WJ, Burger R (2014) Is there a risk of prion-like disease transmission by Alzheimer- or Parkinson-associated protein particles? Acta Neuropathol 128: 463–476 Doi 10.1007/s00401-014-1324-9 [PubMed: 25073522]

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4. Braak H, Del Tredici K, Bratzke H, Hamm-Clement J, Sandmann-Keil D, Rub U (2002) Staging of the intracerebral inclusion body pathology associated with idiopathic Parkinson's disease (preclinical and clinical stages). J Neurol 249 Suppl 3: III/1–5
5. Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E (2003) Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 24: 197–211 [PubMed: 12498954]
6. Braak H, Rub U, Gai WP, Del Tredici K (2003) Idiopathic Parkinson's disease: possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen. J Neural Transm 110: 517–536 [PubMed: 12721813]
7. Breid S, Bernis ME, Babila JT, Garza MC, Wille H, Tamguney G (2016) Neuroinvasion of alpha-Synuclein Prionoids after Intraperitoneal and Intraglossal Inoculation. J Virol 90: 9182–9193 Doi 10.1128/JVI.01399-16 [PubMed: 27489279]
8. Burke RE, Dauer WT, Vonsattel JP (2008) A critical evaluation of the Braak staging scheme for Parkinson's disease. Ann Neurol 64: 485–491 Doi 10.1002/ana.21541 [PubMed: 19067353]
9. Chen SG, Stribinskis V, Rane MJ, Demuth DR, Gozal E, Roberts AM, Jagadapillai R, Liu R, Choe K, Shivakumar B et al. (2016) Exposure to the Functional Bacterial Amyloid Protein Curli Enhances Alpha-Synuclein Aggregation in Aged Fischer 344 Rats and Caenorhabditis elegans. Sci Rep 6: 34477 Doi 10.1038/srep34477 [PubMed: 27708338]
10. Chiti F, Dobson CM (2006) Protein misfolding, functional amyloid, and human disease. Annu Rev Biochem 75: 333–366 Doi 10.1146/annurev.biochem.75.101304.123901 [PubMed: 16756495]
11. Del Tredici K, Rub U, De Vos RA, Bohl JR, Braak H (2002) Where does parkinson disease pathology begin in the brain? J Neuropathol Exp Neurol 61: 413–426 [PubMed: 12030260]
12. Fares MB, Ait-Bouziad N, Dikiy I, Mbefo MK, Jovicic A, Kiely A, Holton JL, Lee SJ, Gitler AD, Eliezer D et al. (2014) The novel Parkinson's disease linked mutation G51D attenuates in vitro aggregation and membrane binding of alpha-synuclein, and enhances its secretion and nuclear localization in cells. Human molecular genetics 23: 4491–4509 Doi 10.1093/hmg/ddu165 [PubMed: 24728187]
13. Fredricks DN, Relman DA (1996) Sequence-based identification of microbial pathogens: a reconsideration of Koch's postulates. Clin Microbiol Rev 9: 18–33 [PubMed: 8665474]
14. Ghosh D, Sahay S, Ranjan P, Salot S, Mohite GM, Singh PK, Dwivedi S, Carvalho E, Banerjee R, Kumar A et al. (2014) The newly discovered Parkinson's disease associated Finnish mutation (A53E) attenuates alpha-synuclein aggregation and membrane binding. Biochemistry 53: 6419–6421 Doi 10.1021/bi5010365 [PubMed: 25268550]
15. Guest WC, Silverman JM, Pokrishevsky E, O'Neill MA, Grad LI, Cashman NR (2011) Generalization of the prion hypothesis to other neurodegenerative diseases: an imperfect fit. J Toxicol Environ Health A 74: 1433–1459 Doi 10.1080/15287394.2011.618967 [PubMed: 22043906]
16. Haley NJ, Mathiason CK, Carver S, Zabel M, Telling GC, Hoover EA (2011) Detection of chronic wasting disease prions in salivary, urinary, and intestinal tissues of deer: potential mechanisms of prion shedding and transmission. J Virol 85: 6309–6318 Doi 10.1128/JVI.00425-11 [PubMed: 21525361]
17. Halliday GM, Macdonald V, Henderson JM (2005) A comparison of degeneration in motor thalamus and cortex between progressive supranuclear palsy and Parkinson's disease. Brain 128: 2272–2280 Doi 10.1093/brain/awh596 [PubMed: 16014651]
18. Irwin DJ, Abrams JY, Schonberger LB, Leschek EW, Mills JL, Lee VM, Trojanowski JQ (2013) Evaluation of potential infectivity of Alzheimer and Parkinson disease proteins in recipients of cadaver-derived human growth hormone. JAMA Neurol 70: 462–468 Doi 10.1001/jamaneurol.2013.1933 [PubMed: 23380910]
19. Jaunmuktane Z, Mead S, Ellis M, Wadsworth JD, Nicoll AJ, Kenny J, Launchbury F, Linehan J, Richard-Loendt A, Walker AS et al. (2015) Evidence for human transmission of amyloid-beta pathology and cerebral amyloid angiopathy. Nature 525: 247–250 Doi 10.1038/nature15369 [PubMed: 26354483]

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20. Johansen KK, Torp SH, Farrer MJ, Gustavsson EK, Aasly JO (2018) A Case of Parkinson's Disease with No Lewy Body Pathology due to a Homozygous Exon Deletion in Parkin. Case Rep Neurol Med 2018: 6838965 Doi 10.1155/2018/6838965 [PubMed: 30050705]
21. Killinger BA, Labrie V (2017) Vertebrate food products as a potential source of prion-like alpha-synuclein. NPJ Parkinsons Dis 3: 33 Doi 10.1038/s41531-017-0035-z [PubMed: 29184902]
22. Kim S, Kwon SH, Kam TI, Panicker N, Karuppagounder SS, Lee S, Lee JH, Kim WR, Kook M, Foss CA et al. (2019) Transneuronal Propagation of Pathologic alpha-Synuclein from the Gut to the Brain Models Parkinson's Disease. Neuron: Doi 10.1016/j.neuron.2019.05.035
23. Koch R, Pinner M, Pinner BR, National tuberculosis association. [from old catalog] (1932) The aetiology of tuberculosis. National tuberculosis association, City
24. Kordower JH, Chu Y, Hauser RA, Freeman TB, Olanow CW (2008) Lewy body-like pathology in long-term embryonic nigral transplants in Parkinson's disease. Nat Med 14: 504–506 Doi nm1747 [pii] 10.1038/nm1747 [PubMed: 18391962]
25. Kordower JH, Dodiya HB, Kordower AM, Terpstra B, Paumier K, Madhavan L, Sortwell C, Steece-Collier K, Collier TJ (2011) Transfer of host-derived alpha synuclein to grafted dopaminergic neurons in rat. Neurobiol Dis 43: 552–557 Doi S0969-9961(11)00155-0 [pii] 10.1016/j.nbd.2011.05.001 [PubMed: 21600984]
26. Krstic D, Knuesel I (2013) The airbag problem-a potential culprit for bench-to-bedside translational efforts: relevance for Alzheimer's disease. Acta Neuropathol Commun 1: 62 Doi 10.1186/2051-5960-1-62 [PubMed: 24252346]
27. Li JY, Englund E, Holton JL, Soulet D, Hagell P, Lees AJ, Lashley T, Quinn NP, Rehncrona S, Bjorklund A et al. (2008) Lewy bodies in grafted neurons in subjects with Parkinson's disease suggest host-to-graft disease propagation. Nat Med 14: 501–503 Doi 10.1038/nm1746 [PubMed: 18391963]
28. Li JY, Englund E, Widner H, Rehncrona S, Bjorklund A, Lindvall O, Brundin P (2010) Characterization of Lewy body pathology in 12- and 16-year-old intrastriatal mesencephalic grafts surviving in a patient with Parkinson's disease. Mov Disord 25: 1091–1096 Doi 10.1002/mds.23012 [PubMed: 20198645]
29. Lohmann S, Bernis ME, Tachu BJ, Ziemski A, Grigoletto J, Tamguney G (2019) Oral and intravenous transmission of alpha-synuclein fibrils to mice. Acta Neuropathol: Doi 10.1007/s00401-019-02037-5
30. Luk KC, Kehm V, Carroll J, Zhang B, O'Brien P, Trojanowski JQ, Lee VM (2012) Pathological alpha-synuclein transmission initiates Parkinson-like neurodegeneration in nontransgenic mice. Science 338: 949–953 Doi 10.1126/science.1227157 [PubMed: 23161999]
31. MacDonald V, Halliday GM (2002) Selective loss of pyramidal neurons in the pre-supplementary motor cortex in Parkinson's disease. Mov Disord 17: 1166–1173 Doi 10.1002/mds.10258 [PubMed: 12465053]
32. Milber JM, Noorigian JV, Morley JF, Petrovitch H, White L, Ross GW, Duda JE (2012) Lewy pathology is not the first sign of degeneration in vulnerable neurons in Parkinson disease. Neurology 79: 2307–2314 Doi 10.1212/WNL.0b013e318278fe32 [PubMed: 23152586]
33. Olanow CW, Perl DP, DeMartino GN, McNaught KS (2004) Lewy-body formation is an aggresome-related process: a hypothesis. Lancet Neurol 3: 496–503 Doi 10.1016/S1474-4422(04)00827-0 [PubMed: 15261611]
34. Orru CD, Bongianni M, Tonoli G, Ferrari S, Hughson AG, Groveman BR, Fiorini M, Pocchiari M, Monaco S, Caughey B et al. (2014) A test for Creutzfeldt-Jakob disease using nasal brushings. N Engl J Med 371: 519–529 Doi 10.1056/NEJMoa1315200 [PubMed: 25099576]
35. Parkkinen L, Kauppinen T, Pirttila T, Autere JM, Alafuzoff I (2005) Alpha-synuclein pathology does not predict extrapyramidal symptoms or dementia. Ann Neurol 57: 82–91 Doi 10.1002/ana.20321 [PubMed: 15562510]
36. Parkkinen L, O'Sullivan SS, Collins C, Petrie A, Holton JL, Revesz T, Lees AJ (2011) Disentangling the relationship between lewy bodies and nigral neuronal loss in Parkinson's disease. J Parkinsons Dis 1: 277–286 Doi 10.3233/JPD-2011-11046 [PubMed: 23939308]

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37. Parkkinen L, Pirttila T, Tervahauta M, Alafuzoff I (2005) Widespread and abundant alpha-synuclein pathology in a neurologically unimpaired subject. Neuropathology 25: 304–314 [PubMed: 16382779]
38. Peelaerts W, Bousset L, Van der Perren A, Moskalyuk A, Pulizzi R, Giugliano M, Van den Haute C, Melki R, Baekelandt V (2015) alpha-Synuclein strains cause distinct synucleinopathies after local and systemic administration. Nature 522: 340–344 Doi 10.1038/nature14547 [PubMed: 26061766]
39. Poulopoulos M, Levy OA, Alcalay RN (2012) The neuropathology of genetic Parkinson's disease. Mov Disord 27: 831–842 Doi 10.1002/mds.24962 [PubMed: 22451330]
40. Pringsheim T, Jette N, Frolkis A, Steeves TD (2014) The prevalence of Parkinson's disease: a systematic review and meta-analysis. Mov Disord 29: 1583–1590 Doi 10.1002/mds.25945 [PubMed: 24976103]
41. Prusiner SB, Woerman AL, Mordes DA, Watts JC, Rampersaud R, Berry DB, Patel S, Oehler A, Lowe JK, Kravitz SN et al. (2015) Evidence for alpha-synuclein prions causing multiple system atrophy in humans with parkinsonism. Proc Natl Acad Sci U S A 112: E5308–5317 Doi 10.1073/pnas.1514475112 [PubMed: 26324905]
42. Recasens A, Dehay B, Bove J, Carballo-Carbajal I, Dovero S, Perez-Villalba A, Fernagut PO, Blesa J, Parent A, Perier C et al. (2014) Lewy body extracts from Parkinson disease brains trigger alpha-synuclein pathology and neurodegeneration in mice and monkeys. Ann Neurol 75: 351–362 Doi 10.1002/ana.24066 [PubMed: 24243558]
43. Ross OA, Toft M, Whittle AJ, Johnson JL, Papapetropoulos S, Mash DC, Litvan I, Gordon MF, Wszolek ZK, Farrer MJ et al. (2006) Lrrk2 and Lewy body disease. Ann Neurol 59: 388–393 Doi 10.1002/ana.20731 [PubMed: 16437559]
44. Rudge P, Jaunmuktane Z, Adlard P, Bjurstrom N, Caine D, Lowe J, Norsworthy P, Hummerich H, Druyeh R, Wadsworth JD et al. (2015) Iatrogenic CJD due to pituitary-derived growth hormone with genetically determined incubation times of up to 40 years. Brain 138: 3386–3399 Doi 10.1093/brain/awv235 [PubMed: 26268531]
45. Sacino AN, Brooks M, Thomas MA, McKinney AB, Lee S, Regenhardt RW, McGarvey NH, Ayers JI, Notterpek L, Borchelt DR et al. (2014) Intramuscular injection of alpha-synuclein induces CNS alpha-synuclein pathology and a rapid-onset motor phenotype in transgenic mice. Proc Natl Acad Sci U S A 111: 10732–10737 Doi 10.1073/pnas.1321785111 [PubMed: 25002524]
46. Shahmoradian SH, Lewis AJ, Genoud C, Hench J, Moors TE, Navarro PP, Castano-Diez D, Schweighauser G, Graff-Meyer A, Goldie KN et al. (2019) Lewy pathology in Parkinson's disease consists of crowded organelles and lipid membranes. Nat Neurosci 22: 1099–1109 Doi 10.1038/s41593-019-0423-2 [PubMed: 31235907]
47. Surmeier DJ, Obeso JA, Halliday GM (2017) Parkinson's Disease Is Not Simply a Prion Disorder. J Neurosci 37: 9799–9807 Doi 10.1523/JNEUROSCI.1787-16.2017 [PubMed: 29021297]
48. Tamguney G, Miller MW, Wolfe LL, Sirochman TM, Glidden DV, Palmer C, Lemus A, DeArmond SJ, Prusiner SB (2009) Asymptomatic deer excrete infectious prions in faeces. Nature 461: 529–532 Doi 10.1038/nature08289 [PubMed: 19741608]
49. Tanaka M, Kim YM, Lee G, Junn E, Iwatsubo T, Mouradian MM (2004) Aggresomes formed by alpha-synuclein and synphilin-1 are cytoprotective. J Biol Chem 279: 4625–4631 Doi 10.1074/jbc.M310994200 M310994200 [pii] [PubMed: 14627698]
50. Van Den Berge N, Ferreira N, Gram H, Mikkelsen TW, Alstrup AKO, Casadei N, Tsung-Pin P, Riess O, Nyengaard JR, Tamguney G et al. (2019) Evidence for bidirectional and trans-synaptic parasympathetic and sympathetic propagation of alpha-synuclein in rats. Acta Neuropathol: Doi 10.1007/s00401-019-02040-w
51. Volpicelli-Daley LA (2017) Effects of alpha-synuclein on axonal transport. Neurobiol Dis 105: 321–327 Doi 10.1016/j.nbd.2016.12.008 [PubMed: 27956085]
52. Volpicelli-Daley LA, Luk KC, Patel TP, Tanik SA, Riddle DM, Stieber A, Meaney DF, Trojanowski JQ, Lee VM (2011) Exogenous alpha-synuclein fibrils induce Lewy body pathology leading to synaptic dysfunction and neuron death. Neuron 72: 57–71 Doi 10.1016/j.neuron.2011.08.033 [PubMed: 21982369]