Title: *LRRK2* Parkinson Disease *GeneReview* – Neuropathology
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LRRK2-PD has the potential to be the "Rosetta stone" of parkinsonian disorders because: (1) all the major pathologies associated with parkinsonism have been observed; and (2) the end-stage pathology may differ even in families with the same pathogenic variant (see Table). For example:

- **p.Arg1441Cys.** Four members of Family D with this pathogenic variant had variable, pleomorphic pathology:
  - One with diffuse Lewy body disease within the cortex and brain stem;
  - One with Lewy bodies restricted to brain stem, typical of idiopathic PD;
  - One with a 4R-tauopathy with globose neurofibrillary tangles and tufted astrocytes, reminiscent of argyrophilic grain disease and progressive supranuclear palsy (PSP); and
  - One with nigral neuronal degeneration and gliosis, without coexisting pathology [Wszolek et al 2004].
- **p.Tyr1699Cys.** Two members of Family A with this pathogenic variant had ubiquitin-immunoreactive cytoplasmic and nuclear inclusions (Marinesco bodies), and a third had brain stem Lewy body disease [Zimprich et al 2004].
- **p.Gly2019Ser.** As the most common pathogenic variant, p.Gly2019Ser is present in the majority of autopsied cases in which brain stem or transitional, α-synuclein immunopositive Lewy body pathology is observed [Taylor et al 2006]. Rarely, however, nigral neuronal loss and gliosis only or alternate tauopathy or ubiquitin-immunopositive pathology are observed [Giasson et al 2006, Ross et al 2006] (see Table).
- **p.Ile2020Thr.** In four members of the Sagamihara kindred with this pathogenic variant, only moderate nigral neuronal degeneration and gliosis with no coexisting intracytoplasmic lesion pathology were observed [Funayama et al 2005]. Tau pathology has since been present in six individuals with this pathogenic variant [Ujiie et al 2012].

Table. Number of Individuals with *LRRK2* PD with Distinct Pathogenic Findings

***LRRK2* Pathogenic Variant**	**Lewy Bodies and Neurites**	**Tau and NFTs**	**Ubiquitin**	**Neuronal Loss Only**
p.Arg1441Cys	2	1	0	1
p.Tyr1699Cys	1	0	1	1
p.Gly2019Ser	13	2	1	1
p.Ile2020Thr	1	6	0	6

NFTs = neurofibrillary tangles

Zimprich et al [2004], Funayama et al [2005], Gilks et al [2005], Giasson et al [2006], Rajput et al [2006], Ross et al [2006], Ujiie et al [2012]
In some cases with neuronal loss and otherwise nonspecific findings, TDP-43 immunopositive inclusions may be observed [Covy et al 2009; Dennis Dickson, personal communication].

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