Supplementary data

Multiple hit hypotheses for dopamine neuron loss in Parkinson’s disease

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Table S1. Genes determined and/or suggested to cause or be a susceptibility factor underlying inherited ‘primary parkinsonism’

<table>
<thead>
<tr>
<th>PARK designation / OMIM accession</th>
<th>Protein</th>
<th>Mode of inheritance</th>
<th>Initial gene identification</th>
<th>Currently known prevalence</th>
<th>Suggested normal function</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARK1 168601</td>
<td>α-Synuclein</td>
<td>Autosomal dominant</td>
<td>[1]</td>
<td>13 families from Italy, Germany, and Greece; three pathogenic mutations to date</td>
<td>Inhibits synaptic vesicle priming [2]</td>
</tr>
<tr>
<td>PARK2 600116</td>
<td>Parkin</td>
<td>Autosomal recessive in early onset forms, susceptibility factor in adult</td>
<td>[3]</td>
<td>Very common in juvenile PD</td>
<td>Ubiquitin E3 ligase [4]; it might be involved in Lewy body formation, as these are absent in recessive juvenile form</td>
</tr>
<tr>
<td>PARK3 602404</td>
<td>2p13 Strongly suspected to be sepiapterin</td>
<td>Autosomal dominant</td>
<td>Sepiapterin mutation causes a DOPA-responsive dystonia [5]</td>
<td>Six families from Denmark and Germany</td>
<td>Sepiapterin converts 6-pyrovyl-tetrahydropterin into tetrahydrobiopterin</td>
</tr>
<tr>
<td>PARK4 163890</td>
<td>α-Synuclein duplications</td>
<td>Autosomal dominant</td>
<td>[6]</td>
<td>Seven families in</td>
<td>Inhibits synaptic vesicle priming</td>
</tr>
</tbody>
</table>
| PARK5 191342 | Ubiquitin c-terminal hydrolase L1 (UCHL1) | Possibly autosomal dominant | Single sibling pair in Germany | Hydrolyzes polyubiquitin
| PARK6 605909 | PTEN-induced putative kinase 1 (PINK1) | Autosomal recessive early onset | Three related families in Sicily | Mitochondrial serine/threonine kinase [9]
| PARK7 606324 | DJ-1 | Autosomal recessive | Families in Holland, Italy and Uruguay | Sumoylation pathway; endogenous antioxidant [11]
| PARK8 609007 607060 | LRRK2: dardarin protein | Autosomal dominant | Very common in north African and mideastern populations | Kinase with GTPase activity [14,15]
| PARK9 610513 606693 | ATP13A2 | Autosomal recessive | One Jordanian and one Chilean family | Lysosomal transporter and ATPase of unknown substrate [17]
| PARK10 606852 | Unknown: 1p32 | Autosomal susceptibility factor; suggested to affect age of onset | Not identified | Based on large population studies in Iceland: unclear | Not known
| PARK11 607688 | Unknown: 2q36-q37 | Autosomal dominant | Not identified | Identified in sib pair, but might be common in familial PD | Not known
| PARK12 300557 | Unknown: Xq21-q25 | X-linked | Not identified | Unclear | Not known
| PARK13 610297 | Omi/HtrA2; serine protease-25 (PRSS25) | Autosomal dominant | Detected in four patients in Germany | Serine protease targeted to mitochondria
| 230800 | β-Glucocerebrosidase | Autosomal susceptibility factor; recessive for Gaucher’s | Associated with Gaucher disease type 1, the most common | Many families, particularly Ashkenazi families | Hydrolase (breakdown of glucosylceramide) within lysosomal
<table>
<thead>
<tr>
<th>Gene ID</th>
<th>Gene Name</th>
<th>Disease Type</th>
<th>Description</th>
<th>Degradation</th>
</tr>
</thead>
<tbody>
<tr>
<td>174763</td>
<td>Mitochondrial polymerase gamma (POLG)</td>
<td>Autosomal susceptibility factor</td>
<td>Often associated with progressive external ophthalmoplegia [20,21]</td>
<td>Eight families in northern Europe and the USA Replication of mitochondrial DNA</td>
</tr>
<tr>
<td>603779</td>
<td>Synphilin-1</td>
<td>Autosomal dominant</td>
<td>[22]</td>
<td>Two patients from Germany with apparent sporadic disease Interacting factor with α-syn [23] and is ubiquitinated by parkin [24]</td>
</tr>
<tr>
<td>601828</td>
<td>NR4A2; NURR1</td>
<td>Autosomal susceptibility factor</td>
<td>[25]</td>
<td>Unclear Development of DA neurons</td>
</tr>
<tr>
<td>124030</td>
<td>Cytochrome P450, subfamily IID, piolypeptide 6 (CPD6)</td>
<td>Risk factor associated with pesticide exposure</td>
<td>[26]</td>
<td>Mutations might require pesticide exposure for toxic properties First phase in the metabolism and elimination of numerous endogenous and exogenous molecules</td>
</tr>
<tr>
<td>157140</td>
<td>Tau: MAPT H1</td>
<td>Autosomal susceptibility factor</td>
<td>Associated with multiple diseases by multiple studies, associated with frontotemporal dementia with parkinsonism [27]</td>
<td>Unclear Organization and assembly of microtubules</td>
</tr>
<tr>
<td>605558</td>
<td>Fibroblast growth factor 20 (FGF20)</td>
<td>Risk factor</td>
<td>Strong association in a large family study [28]</td>
<td>Unclear Growth factor that might regulate oxidative stress in dopamine neurons [29]</td>
</tr>
<tr>
<td>556500</td>
<td>Mitochondrial mutations (?)</td>
<td>Mitochondrial inheritance</td>
<td>Unclear</td>
<td>Unclear Unclear</td>
</tr>
</tbody>
</table>

*aPlease note that this table lists suggested genes whether or not the current evidence supporting a particular gene is convincing.

*bA current list of genes designated as “PARK” genes is at Online Mendelian Inheritance in Man website (OMIM: www.ncbi.nlm.nih.gov/omim/) accession 168600.
References