Parkinson’s Disease: Etiology and Molecular Mechanisms

Binggui Sun
Institute of Neuroscience
bsun@zju.edu.cn
Clinical Features of PD

James Parkinson 1817

AN ESSAY ON THE SHAKING PALSY.

CHAPTER I. DEFINITION—HISTORY—ILLUSTRATIVE CASES.

SHAKING PALSY, (Paralysis Agitans.)
Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace; the senses and intellects being uninjured.

Nineteenth century neurologists first described the symptoms of Parkinson's disease: we still don't know the cause.
Clinical Features of PD

- Resting tremor (a tremor of a limb that increases when the limb is at rest)

- Bradykinesia (The slowing down and loss of spontaneous and voluntary movement)

- Rigidity (increased resistance to the passive movement of a limb)

- Postural Imbalance (incapability to keep a steady posture)

- Difficulties in the speech
Anatomical Changes in PD

Loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc)
Anatomical Changes in PD

Loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc)

Dr. Carlsson discovered in 1958 that dopamine is a neurotransmitter in the brain and that it has great importance for our ability to control movements.

Arvid Carlsson
Anatomical Changes in PD

A. Normal

B. Parkinson’s Disease

Nigrostriatal pathway

Caudate
Putamen

SNpc
Basal Ganglion

Loss of Dopamine Neurons in Parkinson’s Disease

[Cerebral cortex](#)

[Striatum](#)

[Stn](#)

[Thalamus](#)

[gpe](#)

[SNc](#)

[GPI](#)

[Normal state](#)

[Excitatory](#)

[Inhibitory](#)

[Modulatory](#)

*Cold Spring Harb Perspect Med 2012;2:a009621*
Loss of Dopamine Neurons in Parkinson’s Disease

Basal Ganglia Components and Circuits

Cerebral cortex

Striatum

GPe

SNc

GPi

Thalamus

STN

Normal state

Parkinsonian state

Excitatory

Inhibitory

Modulatory

Causes of PD

- Aging
- Environmental factors
- Genetic mutation (5-10%)

Sporadic PD ~90%
Etiology of Parkinson’s Disease

• Environmental toxin hypothesis

• Genetic hypothesis

• Gene vulnerability hypothesis
Etiology of Parkinson’s Disease

• Environmental toxin hypothesis

**MPTP** (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine): a neurotoxin precursor to MPP+, which causes permanent symptoms of Parkinson's disease by destroying dopaminergic neurons in the substantia nigra of the brain.
Toxicity of MPTP in Mice

Etiology of Parkinson’s Disease

• Environmental toxin hypothesis

**MPTP** (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine): a neurotoxin precursor to MPP+, which causes permanent symptoms of Parkinson's disease by destroying dopaminergic neurons in the substantia nigra of the brain.

**Rotenone**: pesticide 鱼藤酮

**Paraquat**: herbicide 百草枯

**Maneb**: fungicide 代森锰
Etiology of Parkinson’s Disease

• Genetic hypothesis

**SNCA**: encoding α-synuclein

**PARK2**: encoding the E3 ubiquitin ligase parkin

**PARK6**: encoding PINK1, a mitochondrial kinase

**PARK7**: encoding the protein DJ-1

**PARK8**: encoding leucine-rich repeat kinase 2 (LRRK2)

**PARK9**: encoding ATP13A2
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Gene locus</th>
<th>Disorder</th>
<th>Inheritance</th>
<th>Gene</th>
<th>Status and remarks</th>
<th>Mode of identification</th>
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<tbody>
<tr>
<td>PARK1</td>
<td>4q21-22</td>
<td>EOPD</td>
<td>AD</td>
<td>SNCA</td>
<td>Confirmed</td>
<td>Linkage analysis</td>
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<td>PARK2</td>
<td>6q25.2-q27</td>
<td>EOPD</td>
<td>AR</td>
<td>Parkin</td>
<td>Confirmed</td>
<td>Linkage analysis</td>
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<td>PARK3</td>
<td>2p13</td>
<td>Classical PD</td>
<td>AD</td>
<td>Unknown</td>
<td>Unconfirmed; may represent a risk factor; gene not found since first described in 1998</td>
<td>Linkage analysis</td>
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<td>PARK4</td>
<td>4q21-q23</td>
<td>EOPD</td>
<td>AD</td>
<td>SNCA</td>
<td>Erroneous locus (identical to PARK1)</td>
<td>Linkage analysis</td>
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<tr>
<td>PARK5</td>
<td>4p13</td>
<td>Classical PD</td>
<td>AD</td>
<td>UCHL1</td>
<td>Unconfirmed (not replicated since described in 1998)</td>
<td>Functional candidate gene approach</td>
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<td>PARK6</td>
<td>1p35-p36</td>
<td>EOPD</td>
<td>AR</td>
<td>PINK1</td>
<td>Confirmed</td>
<td>Linkage analysis</td>
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<td>PARK7</td>
<td>1p36</td>
<td>EOPD</td>
<td>AR</td>
<td>DJ-1</td>
<td>Confirmed</td>
<td>Linkage analysis</td>
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<td>PARK8</td>
<td>12q12</td>
<td>Classical PD</td>
<td>AD</td>
<td>LRRK2</td>
<td>Confirmed; variations in LRRK2 gene include risk-conferring variants and disease-causing mutations</td>
<td>Linkage analysis</td>
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<tr>
<td>PARK9</td>
<td>1p36</td>
<td>Kufor-Rakeb syndrome; atypical PD with dementia, spasticity, and supranuclear gaze palsy</td>
<td>AR</td>
<td>ATP13A2</td>
<td>Confirmed; but complex phenotype that would not be mistaken for early-onset or classical parkinsonism</td>
<td>Linkage analysis</td>
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<td>PARK10</td>
<td>1p32</td>
<td>Classical PD</td>
<td>Risk factor</td>
<td>Unknown</td>
<td>Confirmed susceptibility locus; gene unknown since first described in 2002</td>
<td>Linkage analysis</td>
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<td>PARK11</td>
<td>2q36-27</td>
<td>Late-onset PD</td>
<td>AD</td>
<td>not GIGYF2</td>
<td>Not independently confirmed; possibly represents a risk factor; gene not found since first described in 2002</td>
<td>Linkage analysis</td>
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<td>Xq21-q25</td>
<td>Classical PD</td>
<td>Risk factor</td>
<td>Unknown</td>
<td>Confirmed susceptibility locus; possibly represents a risk factor; gene not found since first described in 2003</td>
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<td>2p12</td>
<td>Classical PD</td>
<td>AD or risk factor</td>
<td>HTR4A2</td>
<td>Unconfirmed</td>
<td>Candidate gene approach</td>
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<td>PARK14</td>
<td>22q13.1</td>
<td>Early-onset dystonia-parkinsonism</td>
<td>AR</td>
<td>PLA2G6</td>
<td>Confirmed</td>
<td>Linkage analysis (homozygosity mapping)</td>
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<td>PARK15</td>
<td>22q12-q13</td>
<td>Early-onset parkinsonian-pyramidal syndrome</td>
<td>AR</td>
<td>FBX07</td>
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<td>Linkage analysis</td>
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<td>Risk factor</td>
<td>Unknown</td>
<td>Confirmed susceptibility locus</td>
<td>Genome-wide association studies</td>
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<td>16q11.2</td>
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<td>AD</td>
<td>VPS35</td>
<td>Confirmed</td>
<td>Exome sequencing</td>
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<td>PARK18</td>
<td>3q27.1</td>
<td>Classical PD</td>
<td>AD</td>
<td>EIF4G1</td>
<td>Unconfirmed; recently published (Chartier-Harlin et al. 2011)</td>
<td>Linkage analysis</td>
</tr>
</tbody>
</table>

AD, autosomal dominant; AR, autosomal recessive.
However:

Genetic mutations or duplications account for only 3-5% of all PD cases
Etiology of Parkinson’s Disease

• Gene vulnerability hypothesis
Pathogenesis of Parkinson's Disease

- Disruption of protein quality control
- Mitochondrial dysfunction
- Oxidative stress
- Inflammation
Pathogenesis of Parkinson’s Disease

• Disruption of protein quality control

  Misfolding of proteins
Pathogenesis of Parkinson’s Disease

- Disruption of protein quality control

 Misfolding of proteins
Pathogenesis of Parkinson’s Disease

• Disruption of protein quality control

Misfolding of proteins

Mahley, Neuron (2012)
Pathogenesis of Parkinson’s Disease

• Disruption of protein quality control

  Misfolding of proteins

  Abnormal accumulation (Increase in production & deficits in clearance)
Pathogenesis of Parkinson’s Disease

• Disruption of protein quality control

**Misfolding of proteins**

**Abnormal accumulation** *(Increase in production & deficits in clearance)*

**UPS: ubiquitin proteasome system**
Pathogenesis of Parkinson's Disease

- Disruption of protein quality control

Misfolding of proteins

Abnormal accumulation (Increase in production & deficits in clearance)

UPS: ubiquitin proteasome system

Autophagy
Pathogenesis of Parkinson’s Disease

• Disruption of protein quality control

  Misfolding of proteins

  Abnormal accumulation (Increase in production & deficits in clearance)
Pathogenesis of Parkinson’s Disease

• Disruption of protein quality control

Misfolding of proteins

Abnormal accumulation (Increase in production & deficits in clearance)
Pathogenesis of Parkinson’s Disease

- Disruption of protein quality control

    **Misfolding of proteins**

    **Abnormal accumulation** (Increase in production & deficits in clearance)

    **Soluble oligomers are more toxic!**
Pathogenesis of Parkinson’s Disease

- Disruption of protein quality control
- Mitochondrial dysfunction
- Oxidative stress
- Inflammation
Schematic Representation of Mitochondrial Compartmentalization

[Diagram showing mitochondrial compartments and energy production]
Mitochondrial Dysfunction in PD
Pathogenesis of Parkinson’s Disease

• Disruption of protein quality control
• Mitochondrial dysfunction
• Oxidative stress
• Inflammation
A unifying role for prions in neurodegenerative diseases

Prusiner SB, Science 2012, 336:1511-1513
A unifying role for prions in neurodegenerative diseases

Prusiner SB, Science 2012, 336:1511-1513

Stanley B. Prusiner
Pathological α-synuclein transmission initiates Parkinson-like neurodegeneration in nontransgenic mice

Luk KC, et al., Science 2012
Further reading if you are interested in Parkinson’s disease
Thank You!