• Parkinson's disease was first formally described in "An Essay on the Shaking Palsy," published in 1817 by a London physician named James Parkinson
• It has probably existed for many thousands of years.
• Symptoms and potential therapies mentioned in:
  • Ayurveda, the system of medicine practiced in India as early as 5000 BC.
  • First Chinese medical text, Nei Jing, which appeared 2500 years ago.

• Parkinson's is a neurodegenerative disease.
• Movement is normally controlled by dopamine, a chemical that carries signals between the nerves in the brain.
• When cells that normally produce dopamine die, the symptoms of Parkinson's appear.

M – muscle rigidity
I – impaired balance
S – slowness and stiffness
T - tremor

• Soft speech
• Problems with handwriting (small)
• Reduced facial expression
• Shuffling when walking
• Muscle pain
• Stooped posture
### Other Non-motor Symptoms
- Constipation
- Sleep disturbances
- Fatigue
- Bladder urgency and frequency
- Dizziness on standing
- Depression: feeling sad, having less energy or losing interest in activities
- Memory problems

### Progression of Parkinson's Disease
- Currently, there is no cure
- Progresses at different rates for each person
- Medication will need to be adjusted as symptoms change
- Other non-motor symptoms may appear such as depression, difficulty swallowing, sexual problems, or cognitive changes
- May progress more quickly in people who are older when symptoms begin
- May progress more slowly when the main symptom is tremor
- Parkinson's is not a mental disease, although 30% of people with Parkinson's will eventually develop dementia

### Epidemiology
- Estimated 1 million patients in US
- 2nd most common age-related neurodegenerative disorder
- 2nd in frequency only to Alzheimer’s disease
- World-wide estimates vary
  - 15/100,000 in China
  - 657/100,000 in Argentina
  - 100 - 250/100,000 in North America and Europe
- Prevalence is predicted to triple over the next 50 years as average age of population increases.

### Incidence & Risk Factors
- China: 1.5/100,000
- Finland: 14.8/100,000
- US: 20/100,000
- Variations may be due to different diagnostic criteria and methods of case ascertainment in studies
- Lifetime risk of PD: 1 in 40
- Both men and women, from all ethnic backgrounds are affected. Slightly more common in men than in women;
  - Estimated 12-15 men for every 10 women
- Not only found in older people – it can affect people as young as 30 or 40, although average age of onset is 60.
- Free radicals, accelerated aging, environmental toxins, and genetic predisposition.
- Genetic predisposition
- Environmental factors (toxins)
Pathophysiology

Results from the loss of dopaminergic neurons of the basal ganglia
Specifically affects the pathway going from the substantia nigra to the striatum
As with most brain tissue, the neurons atrophy with age
If this loss of neurons becomes too great to reduce dopamine levels by about 90% then Parkinson’s symptoms result

Movement disorders arise from this disfunctioning of the nigrostriatal pathway
Normally input from the substantia nigra to the striatum can promote movement, both by the excitation of direct pathway and inhibition of an indirect pathway
In Parkinson’s patients loss of dopaminergic neurons in this pathway, resulting in increased difficulty initiating movements
The movement pathway involved is related to those movements guided by internal cues and movements guided by external cues are unaffected

Drug-induced Parkinsonism
The use of dopamine 2 receptor antagonists in the treatment of psychotic disorders, such as schizophrenia, can result in some serious side effects.
When these drugs block D2 receptors in the nigrostriatal pathway, disorders of movement resembling Parkinson’s disease can result.
These side effects are known as Extrapyramidal Symptoms (EPS)

Chemical Model of Parkinson’s
There are many hypotheses for the cause of Parkinson’s disease, the most notable being environmental factors such as exposure to toxins.
A model has been developed for use in monkeys using the chemical MPTP (1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine)
MPTP, a contaminant in synthetically made heroin, was first discovered in drug addicts that showed Parkinson’s symptoms
MPTP is metabolized by monoamine oxidase, which is highly concentrated in dopaminergic neurons, to MPP+
MPP+ concentrates in substantia nigra neurons by binding to neuromelanin and causes cell toxicity by disrupting the electron transport chain in mitochondria.
As a result, exposure to MPTP leads to Parkinson’s disease and can be used in animal models to study the disease

Mechanisms for Neuronal Degeneration
Many hypotheses as to the biochemical mechanisms that lead to neuronal cell death occurring in Parkinson’s disease.
Role of mitochondrial dysfunction and oxidative stress in contributing to neuronal cell death in the substantia nigra.
Inhibitors of Complex I of the mitochondrial electron transport chain have been shown to reproduce the pathological features of the disease.
Mis-folding and abnormal degradation of proteins within the cell has also been associated with increased dopaminergic neuronal death.
Increased levels of the enzyme monoamine oxidase (MAO) results in increased generation of H2O2 which cause oxidative damage to mitochondria in the neuron.
Increased levels of ferrous iron, which facilitates the conversion of H2O2 to reactive and damaging hydroxyl radicals, were observed in dopaminergic neurons of Parkinson’s patients.
Lower levels of protective mechanisms against oxidative agents such as glutathione peroxidase were observed in the substantia nigra of patients with Parkinson’s disease.

Treatment Options
Non-pharmacologic – education, exercise, nutrition, support
Physical therapy helps mobility, flexibility and balance
Occupational therapy helps with daily activities
Speech therapy helps with voice control
Exercise helps muscles and joints and improves overall health and well-being

Drug therapy is only for symptom management, there is no drug that can cure or slow the progression of the disease.
Non-pharmacologic – education, exercise, nutrition, support
Physical therapy helps mobility, flexibility and balance
Occupational therapy helps with daily activities
Speech therapy helps with voice control
Exercise helps muscles and joints and improves overall health and well-being
**Treatment Options**

- **MAO type B inhibitors:** prevents dopamine metabolism within the brain
  - Usually first drug of choice if disease in early stages
  - May be neuroprotective
- **Dopamine agonists:** directly stimulate dopamine receptors.
  - Also an initial drug of choice if the patient is functionally young
- **Dopamine replacement therapy:** Levodopa immediate precursor to dopamine, converted to dopamine in brain
  - When more symptom relief is required
  - Effect wears off over time
  - Patients can develop motor fluctuations (levodopa induced dyskinesias)

- **COMT (catechol-O-methyltransferase) inhibitors:** used in conjunction with levodopa
  - Reduces motor fluctuations caused by levodopa
- **Amantadine:** Used with levodopa, for antidyskinesia effect, MOA unknown
- **Anticholinergics:** blocks acetylcholine effects (i.e. tremor) that are increased in the absence of dopamine
- **Surgery:** deep brain stimulation of the subthalamic nucleus for severe disabling dyskinesias.

**Limitations of epidemiological studies in familial cases**

- Clinical manifestations may not develop in pre-symptomatic sibling for a number of years.
- Duration and time to follow-up important.
- Aetiology is very likely a complex mixture of environmental and genetic factors.
  - Environmental factors eg pesticide/chemical exposure may be difficult to detail if it occurred many years beforehand.

**Genetics & Pathogenesis**

- While the known genes for PD are responsible for only a minority of cases, they have provided extraordinary insight into the molecular pathology of the disease.

- Roughly one-fifth of Parkinson's disease patients have at least one relative with parkinsonian symptoms.
  - Suggests that a genetic factor may be involved.
  - Several genes that cause symptoms in younger patients have been identified.
  - Most researchers believe, however, that most cases are not caused by genetic factors alone.

- Genetic research studies over the past decade have uncovered a total of 10 genes associated with PD.
  - For most cases of PD, however, these genes are not thought to play a role.
  - Small as their role may be, genes provide a crucial opportunity for us to study how the brain works.
Because most patients do not have a clear history of either familial or environmental risk factors, the disorder may be due to a combination of genetic and environmental "influences" or "causes".

In a small number of cases worldwide there is a strong inheritance pattern. A genetic predisposition for Parkinson's disease is possible, with the onset of disease and its gradual development dependent on a trigger, such as trauma, other illness, or exposure to an environmental toxin.

In large epidemiological studies, researchers have found that people with an affected first-degree relative, such as a parent or sibling, have a two-to-three fold increased risk of developing Parkinson's, as compared to the general population. The vast majority of Parkinson's cases are not directly inherited, but researchers have discovered several genes that can cause the disease in a small number of families. Because genetic forms of a disease can be studied in great detail in the laboratory, and because understanding the rare genetic forms of Parkinson's disease may help to understand more common forms of the disease, genetic aspects of PD are currently the subject of intense research.

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Genetic testing in the general PD population - at the current stage of scientific knowledge - is not going to be helpful. Researchers are still trying to determine which genetic factors contribute to the development of PD for the average patient. This is a very challenging task because we suspect that the interaction of genes with each other and with the environment is probably unique to each individual. Until we gain this level of knowledge, we are a long way off from being able to offer the public PD genetic testing and accurate risk information for family members.

The recent identification of genes that cause PD in a small group of PD families is helping us to understand the processes that lead to the development of PD. Future research will undoubtedly reveal additional PD-associated genes and susceptibility factors, which will help us to further understand the cause of PD and lead to better diagnosis and treatment.

Autosomal dominant inheritance. Located on chromosome 4q21-q23

α-Synuclein is a 140 amino acid length presynaptic protein found in abundance in the human brain, particularly in the substantia nigra, hypothalamus and olfactory neurons. It is an unfolded protein in solution but assumes an alpha helical configuration within lipid containing vesicles and in high concentrations may aggregate into beta sheets typical of amyloid fibrils.

α-Synuclein is normally degraded by the ubiquitin-proteasome system, a pathway that clears unwanted cytotoxic proteins from neuronal cells.

The ubiquitin system consists of three enzymes – a ubiquitin activating enzyme (E1) that binds ubiquitin molecules and sequentially transfers them to a ubiquitin conjugating enzyme (E2) and a ubiquitin ligase (E3). E3 is attached to a target protein that in turn becomes polyubiquininated enabling it to undergo proteolysis by a 26S proteasome.
**α-Synuclein & Lewy bodies**

A possible mechanism of neurotoxicity from mutations of the α-synuclein gene is the production of proteins that are more prone to self-aggregation or alternatively the production misfolded proteins that cannot be degraded.

α-Synuclein is a major constituent of Lewy bodies. Two opposing theories for a Lewy body: (i) toxic aggregation of proteins that contributes directly to neuronal death, and (ii) protective aggregation that 'clears' excess unfolded or misfolded α-synuclein.

**α-Synuclein gene mutations**

Two mutations have been identified:

- (i) a G209A substitution in exon 4 resulting in an Ala53Thr mutation which has been found in at least 13 Italian-Greek families including one Australian family of Greek origin, and

- (ii) G88C substitution in exon 3 resulting in an Ala30Pr mutation found in a single German family.

**Phenotype of α-Synuclein gene mutation**

Levodopa responsiveness, a significantly younger age at presentation (average 10 years younger than sporadic), more rapid clinical course, longer duration of disease, lower frequency of tremor (10%) and higher prevalence of dementia.

Additional clinical features described in the Australian Greek family with an Ala53Thr mutation include central hypoventilation, postural hypotension, urinary incontinence and myoclonus.

**Parkin**

465 amino acid protein that contains a ubiquitin homologous domain in its amino-terminus and two RING finger domains in its carboxy-terminus. Proteins with RING finger domains have a ubiquitin ligase function, thus linking parkin to the ubiquitin-proteasome system.

It is postulated that parkin interacts with substrate proteins and by acting as a ubiquitin ligase is involved in their degradation.

Parkin is postulated to interact with a novel glycosylated isoform of α-Synuclein. Mutated parkin cannot bind and hence this α-Synuclein isoform accumulates.

**Parkin gene mutations**

Autosomal recessively inherited mutations of the parkin gene on chromosome 6q25.2-q27.

Pathological hallmarks of autosomally recessive early-onset Parkinson’s disease due to parkin mutations include loss of nigral and locus coeruleus neurons and the absence of Lewy body formation.

The lack of Lewy bodies is consistent with an inability of the ubiquitin-proteasome pathway to form ubiquinated aggregates of α-synuclein.

A number of different homozygous point mutations, gene deletions and multiplications have been detected in patients with parkin gene mutation.

There are no major clinical differences between the different types of mutations, that is, parkin cases do not represent a phenotypically distinct group.
Parkin gene polymorphisms

- Three polymorphisms exist:
  - G to A transition in exon 4,
  - C to T transition in exon 10 (R/W366)
  - G to C transition in exon 10 (V/L380).

- Conflicting data – Japanese study found protective association with R/W366, European study found increased risk of early onset PD with V/L380 and Chinese Taiwan study found no association.

Early age of onset (23 patients age of onset < 40 years age: mean age of onset 24 years)

- Slow progression – mean duration of disease 24.5 years
- Levodopa responsiveness including good response to anticholinergics and sensitivity to low doses.
- Early susceptibility to levodopa-induced dyskinesias.
- Tremor in 70% at onset but developed in 92%. Frequently begins in legs. Bradykinesia 44% and rigidity 13% at onset but developed in 100%.

Dystonia is presenting symptom in 41% involving feet in 7 (1 of whom had pure exercise induced dystonia), hands in 2, neck and trunk (1 each). Dystonia developed in 78% at some point prior to treatment.

- Diurnal fluctuations, sleep benefit (63%), falls (30% within 5 years) and hyper-reflexia (8%) also occur.
- Autonomic symptoms common – urgency 45%, impotence in amles 28% and orthostatic faintness 13%
- Cognition is normal with mean MMSE 28 in all but one patient with past history cerebral palsy.

In a study of 73 families with early onset (age < 45 years) Parkinson’s disease, 49% had parkin mutations.

- In a study of 100 patients with sporadic Parkinson’s disease and age of onset < 45 years (NEJM 2000), parkin mutations were detected in 70% who presented at age < 20 years but only 3% who presented at age > 30 years.
- In recent French/European study of isolated parkinsonism in 146 pts with age onset <45 years (Brain 2003), parkin mutation found in 20 including 3 new exon rearrangements and two new missense mutations. 9/20 single mutations.

Other loci include
- PARK 3: AD - chromosome 2p13,
- PARK 4: AD - chromosome 4p14-16.3,
- PARK 6: AR – chromosome 1p35-36,
- PARK 7: AR – chromosome 1p35-36,
- PARK 8: AD - chromosome 12p11.2-q13.1

- Linkage to chromosomes 17q and 9q has also been found in families with late onset Parkinson’s disease.

Combining results of two large series, frequency of parkin mutations is 15% (38/246) in patients with early onset parkinsonism (age onset < 45 years).

- Mutations detected in 67% < age 20 years and 7% with onset after 29 years.
- Single mutations are common (9/20 in study 2).

- How many undiscovered mutations are there in other regions of parkin gene?
- Are single mutations sufficient to cause phenotype?
- What is the frequency of parkin mutations in late onset disease?
Ubiquitin carboxy-terminal hydrolase-L1 gene mutation

- Ubiquitin carboxy-terminal hydrolase-L1 is a de-ubiquitinating enzyme that hydrolyses the C-terminal of ubiquitin to generate ubiquitin monomers that can be reutilized for further "target" protein clearance.
- Gene located on chromosome 4p14-15.1.
- Autosomal dominantly inherited mutation with incomplete penetrance identified in 2 German siblings.
- Very rare.

Genetic polymorphisms

- Many genetic loci have variations at a nucleotide site in normal individuals.
- A polymorphism is defined as one at which the most common gene variation (or allele) has a frequency of less than 99%.
- A number of candidate genes have been investigated for an association with Parkinson’s disease including:
  - Cytochrome P450 1A1 and 2D6,
  - N-acetyltransferase 2 (NAT2),
  - Monoamine oxidase-B (MAO-B),
  - The dopamine transporter gene (DAT)
  - Glutathione s-transferase M1

CYP1A1 metabolises a range of polycyclic aromatic hydrocarbons including those found in cigarette smoke. A negative association between smoking and Parkinson’s disease has been found in a number of clinical studies, which suggests that CYP1A1 gene polymorphisms may influence the relative risk for Parkinson’s disease.

- A Japanese study reported a positive association between the CYP1A1 GG genotype and PD. In contrast, a Chinese study did not find such an association.

CYP2D6-debrisoquine hydroxylase, which is located on chromosome 22q13.1, metabolises 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine or MPTP.

- 5-10% of Caucasians and < 1% Chinese/Japanese are poor metabolisers due to a homozygous possession of a CYP2D6 B allele (G1934A substitution).
- CYP2D6 B has two-fold ↑ risk of PD in Japanese patients and in a French population with late onset (>60 years) sporadic Parkinson’s disease. However, no association found in two German studies.

NAT2

- NAT2, which maps to chromosome 8p22, is another polymorphic gene associated with drug and xenobiotic metabolism.
- Approximately 50% of Caucasians are slow acetylators.
- Increased frequency of the two most common slow acetylation gene polymorphisms NAT2*5B and NAT2*6A in one study of Caucasian patients with early onset (age <50 years) Parkinson’s disease although not associated in older patients in this study and not replicated in a Netherlands study.

MAO-B

- Monoamine oxidase B (MAO-B) is a candidate gene in PD by virtue of its role in the metabolism of dopamine and conversion of MPTP to the active neurotoxic metabolite 1-methyl-4-phenylpyridinium ion (MPP+).
- MAO-A and MAO-B are two distinct isoforms of MAO encoded by different genes on the X-chromosome.
- An Australian study found an association between PD and a polymorphic GT repeat sequence (normal range 168 to 190 base pairs) in intron 2 with longer repeat units (186 and 188 base pairs) significantly associated with PD.
- Located on chromosome 15p15.3. Involved in the presynaptic uptake of dopamine by dopaminergic neurons. Can transport toxins, eg MPTP, into substantia nigra.

- The 3'-untranslated region of the gene contains a 40 base pair variable number tandem repeat. A 10-copy allele accounts for approximately 90% of alleles in Chinese subjects and 70% in Caucasian and black populations.

- A rare 11-copy allele has been reported to increase the risk of PD in Caucasians. Significance as found in only 0.25% of normal Caucasians.

- Glutathione-S-transferases (involved in metabolism of pesticides);
- dopamine D2 and D4 receptor genes;
- ACE gene;
- Nurr gene (on chromosome 2 which increases transcription of DAT and tyrosine hydroxylase);
- Mitochondrial gene tRNA
- APOE

- Prevalence of PD is lowest in China, Japan and Africa and highest in Western industrialised countries especially USA and Europe.

- The age-specific prevalence of PD is 5-10 fold lower in mainland China when compared to Europe although the prevalence rate in more developed ethnic Chinese regions such as Taiwan and Hong Kong is higher.

- Many of abovementioned candidate genes negative in Chinese populations.

- Exposure to chemicals
- Physical trauma
- Infections
- Nutrition

- Farming and rural living are generally regarded as risk factors for PD in Westernised countries. On the contrary, there is no association with PD in mainland China.

- In a Taiwanese study, rural living and farming (especially rice growing) as well as the use of herbicides/pesticides were associated with a greater risk for PD. Occupational use of herbicides/pesticides and paraquat were two main risk factors on multivariate analysis.

- The relative low usage of pesticides/herbicides by mainland Chinese farmers (at least in the past) may contribute to the lower prevalence found.

- There is considerable difficulty in accurately recording dietary intake, thus making it difficult to be certain of the results of ascertainment of diet in PD.

- Vitamin E consumption has been reported to be significantly lower among PD patients. This result is supported by experimental evidence of reduced putamen F-dopa uptake in PET scans of patients with vitamin E deficiency. Other studies suggest that vitamin E consumption, through diet or supplementation, does not provide significant protective effect.
- Consumption of tea amongst Chinese as well as coffee drinking amongst Caucasians has been found to be protective against PD. Tea drinking has been reported as a protective factor for PD in Hong Kong Chinese.
- Consumption of herbal tea and fruits from the Annonaceae family containing neurotoxic alkaloids has been associated with atypical parkinsonism and progressive supranuclear palsy in the French West Indies.
- Protective effect of tea? potent anti-oxidant property. Other alternative explanation? tea and coffee contain similar protective micronutrients, such as caffeine.

- Smoking has been consistently although not universally reported to be a protective factor.
- The protective effect of smoking may be confounded by the possibility that people who smoke have greater mortality than those who do not. However, given the consistency of the inverse relationship and the supporting evidence of protective effects of nicotine on MPTP induced cell loss in substantia nigra of mice, it strengthens the protective hypothesis.

- Caucasian studies have shown that genetic polymorphism of MAO-B modifies the association of smoking and PD in that smoking may increase the risk of association with PD in one genotype but may reduce the risk in another.
- Similarly, glutathione transferase polymorphisms interact with pesticide in increasing the risk for PD. One study also has found that the protective effect of smoking is lost among patients with genotype GSTM1*0.
- Chan et al found that the protective effect of tea drinking masks the increased risk of MAO-B polymorphism for PD in Chinese.

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<th>Hereditary PD</th>
<th>With Genetic Defects</th>
<th>Neurotoxins</th>
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<tr>
<td>Genetic</td>
<td>eg. α-synuclein</td>
<td>eg. pesticide herbicide</td>
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Genetic Susceptibility
eg. CYP2D6 mutant gene → poor metabolism of xenobiotics & neurotoxins

Protective factors
eg. smoking, tea

Neuronal damage

Amino acid abbreviations

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<th>Amino acid</th>
<th>Translational action</th>
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