How do people inherit Parkinson disease?

- ✓ Most cases of Parkinson disease occur in people with no apparent family history of the disorder. These **sporadic cases may not be inherited**, or they may have an inheritance pattern that is unknown.
- ✓ Among **familial cases of Parkinson disease**, the inheritance pattern differs depending on the gene that is altered. If the ***LRRK2* or *SNCA* gene is involved**, the **disorder is inherited in an autosomal dominant pattern,** which means one copy of an altered gene in each cell is sufficient to cause the disorder. In most cases, an affected person has one parent with the condition.
- ✓ If the ***PARK2*, *PARK7*, or *PINK1* gene is involved, Parkinson disease is inherited in an autosomal recessive pattern**.
- ✓ This type of inheritance means that two copies of the gene in each cell are altered. Most often, the parents of an individual with **autosomal recessive Parkinson disease** each carry one copy of the altered gene but do not show signs and symptoms of the disorder.

Diagnosis

Other diagnostic tools:

1. ***Transcranial Ultrasound***
2. ***Examine deficits in olfaction***
3. ***Detection of alpha -synucelin in blood of patients with Parkinson disease***

Treatment

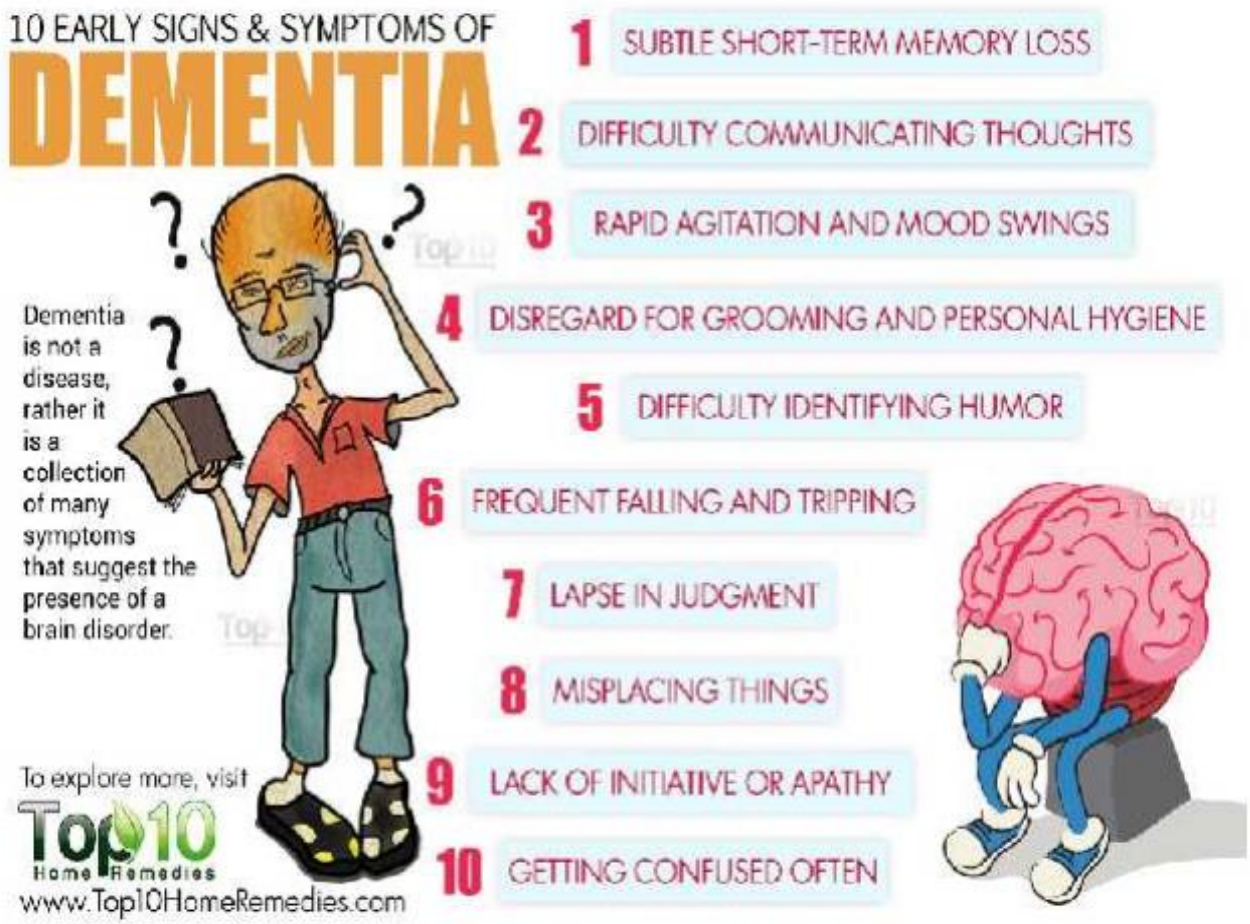
Non - Drug Treatment

1. ***Exercise***
2. ***Nutrition***
3. ***Sufficient Fiber ..... Prevent constipation***
4. ***Calcium Supplementation – Maintain Bone Structure***
5. ***Excessive dietary protein - late stages of the disease causes Erratic Responses to LEVODOPA - therapy***
6. ***Antioxidants - Neuroprotective Role Alpha - tocopherol / Vitamin E, Coenzyme Q10 ..... Scavengers ..... free radical***

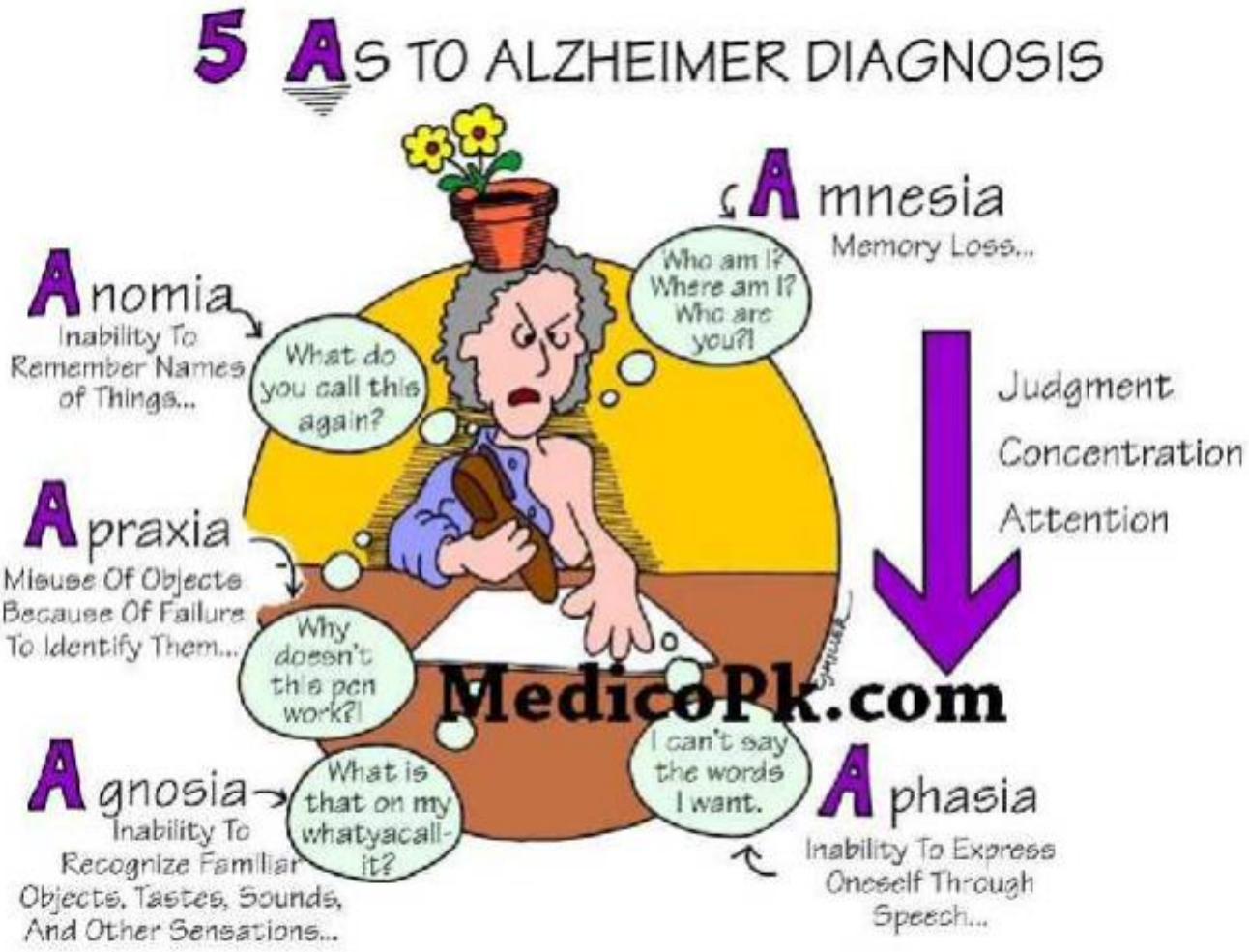
Alzheimer's disease

- ✓ Alzheimer disease is a **degenerative disease of the brain that causes dementia**, which is a gradual loss of memory, judgment, and ability to function.
- ✓ This disorder usually appears in **people older than age 65, but less common forms of the disease appear earlier in adulthood**.
- ✓ What is Alzheimer's disease
- ✓ Alzheimer's disease is an irreversible, progressive brain disease.
- ✓ It is characterized by the development of amyloid plaques and neurofibrillary, or tau, tangles; the loss of connections between nerve cells (neurons) in the brain; and the death of these nerve cells.

- ✓ There are two types of Alzheimer's—early-onset and late-onset. Both types have a genetic component.



- ✓ Memory loss is the most common sign of Alzheimer disease. Forgetfulness may be subtle at first, but the loss of memory worsens over time until it interferes with most aspects of daily living.
- ✓ Even in familiar settings, a person with Alzheimer disease may get lost or become confused.
- ✓ Routine tasks such as preparing meals, doing laundry, and performing other household chores can be challenging. Additionally, it may become difficult to recognize people and name objects. Affected people increasingly require help with dressing, eating, and personal care.



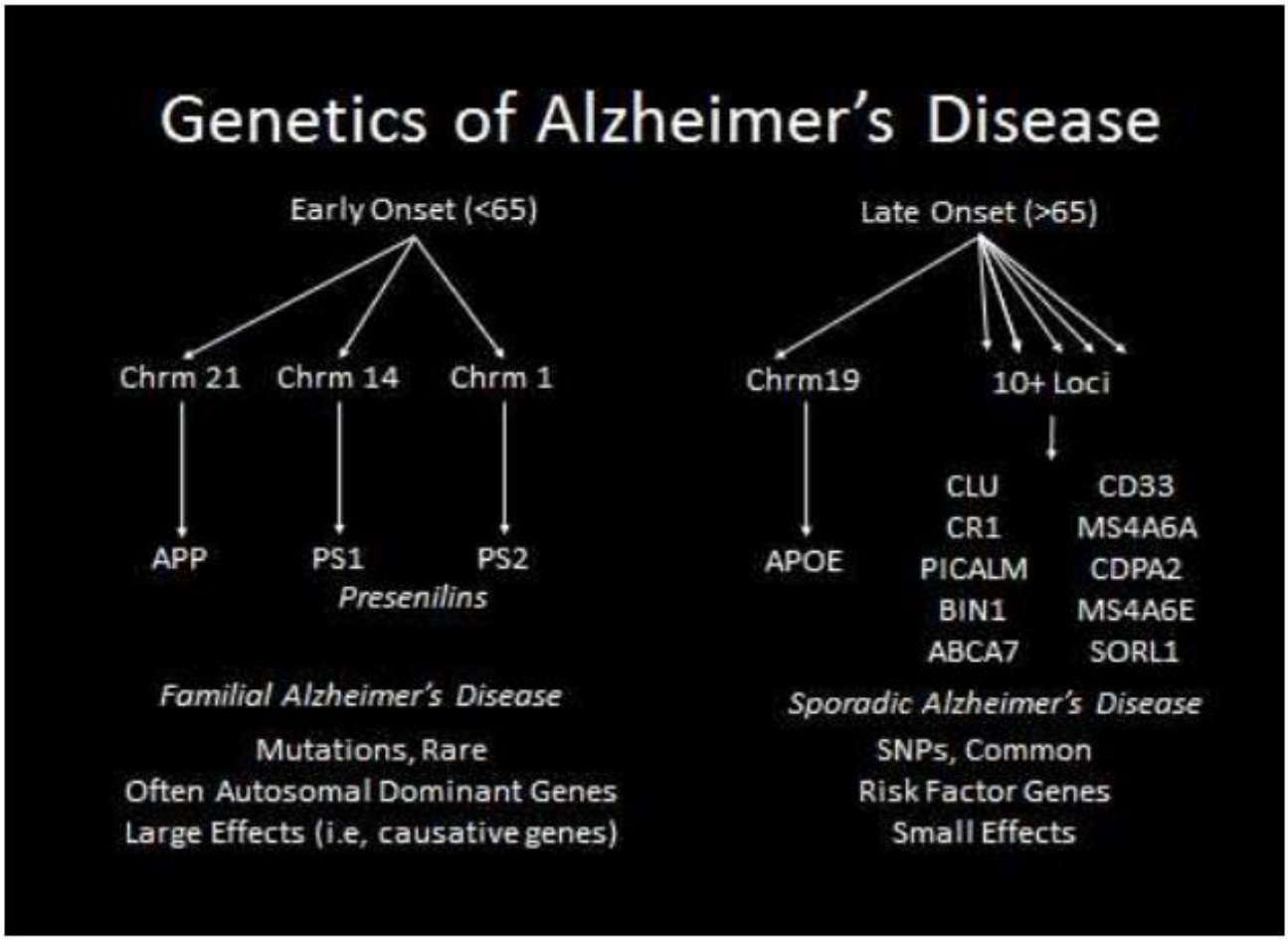
- ✓ As the disorder progresses, some people with Alzheimer disease experience personality and behavioral changes and have trouble interacting in a socially appropriate manner.
- ✓ Other common symptoms include agitation, restlessness, withdrawal, and loss of language skills. People with this disease usually require total care during the advanced stages of the disease.
- ✓ Affected individuals usually survive 8 to 10 years after the appearance of symptoms, but the course of the disease can range from 1 to 25 years.

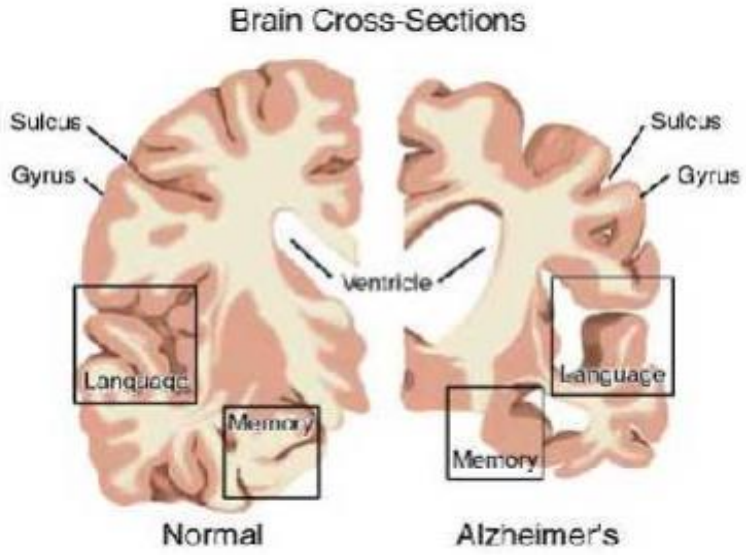
Symptoms of Alzheimer's disease

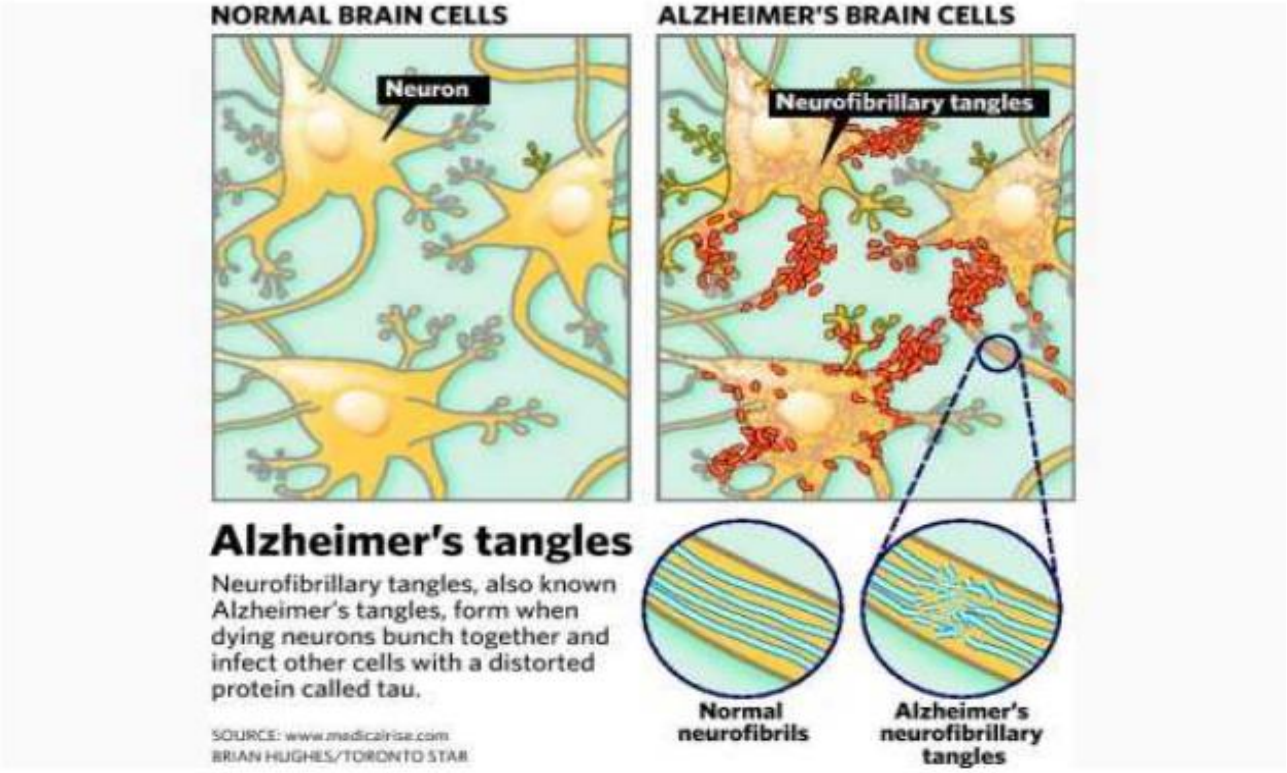
- ✓ Death usually results from **pneumonia, malnutrition, or general body wasting (inanition).**
- ✓ Alzheimer disease can be classified as **early-onset or late-onset.**
- ✓ The signs and symptoms of the early-onset form appear before age 65, while the late-onset form appears after age 65.
- ✓ The early-onset form is much less common than the late-onset form, accounting for less than 5 percent of all cases of Alzheimer disease.

Cause

- ✓ The cause for most Alzheimer's cases is still mostly unknown except for 1% to 5% of cases where genetic differences have been identified.
- ✓ Several competing hypotheses exist trying to explain the cause of the disease


Genetics of Alzheimer's Disease
Early Onset (<65)
Late Onset (>65)
Chrm 21
Chrm 14
Chrm 1
Chrm19
10+ Loci
APP
PS1
PS2
Presenilins
APOE
CLU
CR1
PICALM
BIN1
ABCA7
CD33
MS4A6A
CDPA2
MS4A6E
SORL1
Familial Alzheimer's Disease
Mutations, Rare
Often Autosomal Dominant Genes
Large Effects (i.e, causative genes)
Sporadic Alzheimer's Disease
SNPs, Common
Risk Factor Genes
Small Effects


Brain Cross-Sections
Sulcus
Gyrus
Ventricle
Language
Memory
Sulcus
Gyrus
Language
Memory
Normal
Alzheimer's



Early-Onset Alzheimer's Disease

Early-onset Alzheimer's disease occurs in people age 30 to 60 and represents less than 5 percent of all people with Alzheimer's.

Most cases are caused by an inherited change in one of three genes, resulting in a typle known as early-onset familial Alzheimer's disease, or FAD.

For others, the disease appears to develop without any specific, known cause.

- A child whose biological mother or father carries a genetic mutation for early-onset FAD has a 50/50 chance of inheriting that mutation. If the mutation is in fact inherited, the child has a very strong probability of developing early-onset FAD.
- Early-onset FAD is caused by any one of a number of different single-gene mutations onchromosomes 21, 14, and 1. Each of these mutations causes abnormal proteins to be formed.
- Mutations on chromosome 21 cause the formation of abnormal amyloid precursor protein (APP). A mutation on chromosome 14 causes abnormal

presenilin 1 to be made, and a mutation on chromosome 1 leads to abnormal presenilin 2.

- Most cases of **early-onset Alzheimer d**isease are caused by gene mutations that **can be passed from parent to child**.
- Researchers have found that this form of the disorder can result from mutations in one of three genes: ***APP*, *PSEN1*, or *PSEN2*.**
- When any of these genes is altered, **large amounts of a toxic protein fragment called amyloid beta peptide** are produced in the brain.
- This **peptide can build up** in the brain to form clumps called **amyloid plaques**, which are characteristic of Alzheimer disease.
- A buildup **of toxic amyloid beta peptide and amyloid plaques** may lead to the **death of nerve cells** and **the progressive signs and symptoms** of this disorder.
- Some **evidence indicates that people with Down syndrome have an increased risk of developing Alzheimer disease**.
- Down syndrome, a condition characterized by intellectual disability and other health problems, occurs when a person is born with an extra copy of chromosome 21 in each cell.
- As a result, people with Down syndrome **have three copies of many genes in each cell, including the *APP* gene,** instead of the usual two copies.
- Although the **connection** between Down syndrome and Alzheimer disease is **unclear**, the **production of excess amyloid beta peptide** in cells may account for the increased risk.
- People with Down syndrome **account for less than 1 percent of all cases of Alzheimer disease.**
- **Late-Onset Alzheimer's Disease-** LOAD
- Most people with Alzheimer's have the late-onset form of the disease, in which symptoms become apparent in the **mid-60s and later.**

- The causes of late-onset **Alzheimer's are not yet completely understood**, but they likely include a combination of genetic, environmental, and lifestyle factors that affect a person's risk for developing the disease.
- Researchers have not found a specific gene that directly causes the late-onset form of the disease. However, one genetic risk factor—having one form of the apolipoprotein E (APOE) geneon **chromosome 19—does** increase a person's risk.
- **How are changes in the *APOE* (**apolipoprotein E)**gene related to AD**"apolipoprotein E."

What is the normal function of the *APOE* gene?

- The *APOE* gene provides instructions for making a protein called **apolipoprotein E**.
- This protein combines **with fats (lipids) in the body to form molecules called lipoproteins**.
- **Lipoproteins are responsible for packaging cholesterol and other fats and carrying them through the bloodstream**.
- Apolipoprotein E is a major component of a specific type of lipoprotein called **very low-density lipoproteins (VLDLs)**.
- **VLDLs remove excess cholesterol from the blood** and **carry it to the liver for processing**. Maintaining normal levels of cholesterol is essential for the prevention of disorders that affect the heart and blood vessels (cardiovascular diseases), including heart attack and stroke.
- There are at **least three slightly different versions (alleles) of the *APOE* gene**. **The major alleles are called e2, e3, and e4.** The most common allele is e3, which is found in more than half of the general population
- **How are changes in the *APOE* (**apolipoprotein E)**gene related to AD**"apolipoprotein E."

- The **e4 version of the *APOE* gene increases an individual's risk** for developing late-onset Alzheimer disease. People who **inherit one copy of the *APOE* e4 allele have an increased chance of developing the disease;** those who **inherit two copies of the allele are at even greater risk**. The*APOE* e4 allele may also be associated with an earlier onset of memory loss and other symptoms.
- It is **not known how the *APOE* e4 allele is related to the risk of Alzheimer disease.** However, researchers have found that this allele is **associated with an increased number of protein clumps, called amyloid plaques**, in the brain tissue of affected people. A buildup of toxic amyloid beta peptide and amyloid plaques may lead to the death of neurons and the progressive signs and symptoms of this disorder.
- It is important to note that people with the *APOE* e4 allele inherit an increased risk of developing Alzheimer disease, not the disease itself.
- Not all people with ***Alzheimer disease have the APOE e4 allele, and not all people who have this allele will develop the disease.***
- **How are changes in the *APP* gene related to AD**

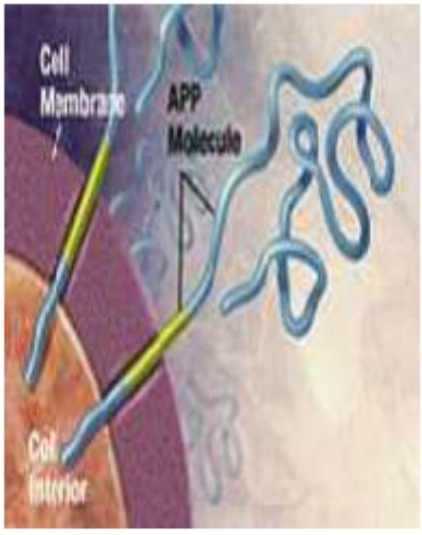
What is the normal function of the *APP* gene?

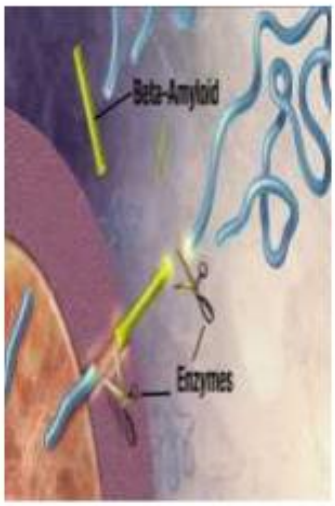
- ✓ The *APP* gene provides instructions for making a protein **called amyloid precursor protein**.
- ✓ This protein is found in many tissues and organs, including the brain and spinal cord (central nervous system).
- ✓ Little is known about the function of amyloid precursor protein.
- ✓ Researchers speculate that **it may bind to other proteins on the surface of cells or help cells attach to one another**.
- ✓ **Studies suggest that in the brain, it helps direct the movement (migration) of nerve cells (neurons) during early development.**
- ✓ Amyloid **precursor protein is cut by enzymes to create smaller fragments (peptides), some of which are released outside the cell**.

- ✓ Two of these fragments are called ***soluble amyloid precursor protein (sAPP) and amyloid beta (β) peptide***.
- ✓ Recent evidence suggests that **sAPP has growth-promoting properties and may play a role in the formation of nerve cells (neurons) in the brain** both before and after birth.
- ✓ The sAPP peptide may also **control the function of certain other proteins by turning off (inhibiting) their activity.**
- ✓ Amyloid β peptide is likely involved in the **ability of neurons to change and adapt over time (plasticity).**

- ✓ **How are changes in the *APP* gene related to AD**

- ✓ More than **50 different mutations in the *APP* gene** can cause early-onset Alzheimer disease, which begins before age 65. **These mutations are responsible for less than 10 percent of all early-onset cases of the disorder.**
- ✓ The most common ***APP* mutation changes one of the protein building blocks (amino acids) in the amyloid precursor protein**.
- ✓ This mutation replaces the amino acid valine with the amino acid isoleucine at protein position **717 (written as Val717Ile or V717I).**





- ✓ Mutations in the *APP* gene **can lead to an increased amount of the amyloid β peptide or to the production of a slightly longer and stickier form of the peptide**.
- ✓ When these **protein fragments are released from the cell, they can accumulate in the brain and form clumps called amyloid plaques**.
- ✓ These plaques are characteristic of Alzheimer disease.
- ✓ A buildup of toxic amyloid β peptide and amyloid plaques may lead to the death of neurons and the progressive signs and symptoms of this disorder.

✓ **How are changes in the *PSEN1* gene related to AD**

What is the normal function of the *PSEN1* gene?

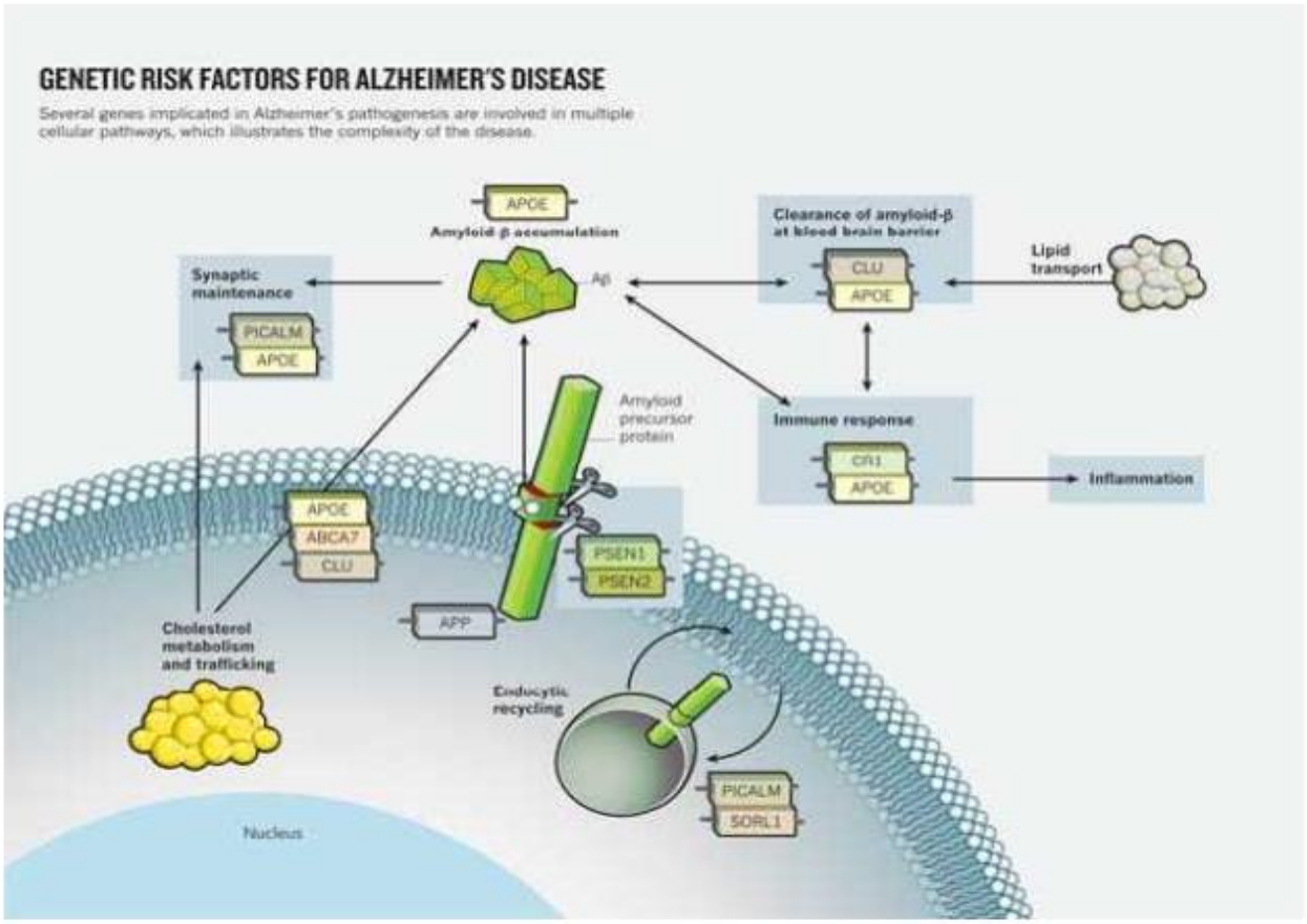
- ✓ The *PSEN1* gene provides instructions for making a protein called **presenilin 1**.
- ✓ This protein is one part (subunit) of a **complex called gamma- (γ-) secretase.**
- ✓ Presenilin 1 carries out the **major function of the complex, which is to cut apart (cleave) other proteins into smaller pieces called peptides. This process is called proteolysis, and presenilin 1 is described as the proteolytic subunit of γ-secretase.**
- ✓ The γ-secretase complex is located in the **membrane that surrounds cells, where it cleaves many different proteins that span the cell membrane (transmembrane proteins)**.
- ✓ This cleavage is ***an important step in several chemical signaling pathways that transmit signals from outside the cell into the nucleus***.
- ✓ One of these pathways, known as **Notch signaling, is essential for the normal maturation and division of hair follicle cells and other types of skin cells**. Notch signaling is also involved in normal **immune system function**.

- ✓ The γ-secretase complex **may be best known for its role in processing amyloid precursor protein (APP), which is made in the brain and other tissues**.
- ✓ γ-secretase cuts APP into smaller peptides, **including soluble amyloid precursor protein (sAPP) and several versions of amyloid-beta (β) peptide**.
- ✓ Evidence suggests that **sAPP has growth-promoting properties and may play a role in the formation of nerve cells** (neurons) in the brain both before and after birth.
- ✓ More than 150 *PSEN1* gene mutations have been identified in patients with early-onset Alzheimer disease, a degenerative brain condition that begins before age 65. Mutations in the *PSEN1* gene are the most common cause of early-onset Alzheimer disease, accounting for up to 70 percent of cases.
- ✓ Almost all ***PSEN1* gene mutations change single building blocks of DNA (nucleotides) in a particular segment of the *PSEN1* gene**. These mutations result in the **production of an abnormal presenilin 1 protein**.
- ✓ Defective presenilin 1 interferes with the **function of the γ-secretase complex**, which **alters the processing of APP and leads to the overproduction of a longer, toxic version of amyloid-β peptide.**
- ✓ Copies of this **protein fragment stick together and build up in the brain, forming clumps called amyloid plaques** that are a characteristic feature of Alzheimer disease.
- ✓ A buildup of toxic amyloid-β peptide and the formation of amyloid plaques likely lead to the death of neurons and the progressive signs and symptoms of this disorder.
- ✓ **How are changes in the *PSEN2* gene related to AD**

What is the normal function of the *PSEN2* gene?

- ✓ The *PSEN2* gene provides instructions for making a protein called presenilin 2.

- ✓ Presenilin 2 helps **process proteins that transmit chemical signals from the cell membrane into the nucleus**. Once in the nucleus, these signals turn on (activate) genes that are important for cell growth and maturation.
- ✓ Presenilin 2 is best known for its role in **processing amyloid precursor protein, which is found in the brain and other tissues**.
- ✓ Research suggests that **presenilin 2 works together with other enzymes to cut amyloid precursor protein** into smaller segments (peptides).
- ✓ One of these peptides is called **soluble amyloid precursor protein (sAPP), and another is called amyloid beta peptide.**
- ✓ Recent evidence suggests that **sAPP has growth-promoting properties** and may play a role in the formation of neurons in the brain both before and after birth.
- ✓ At least 11 mutations in the *PSEN2* gene have been shown to cause early-onset Alzheimer disease. Mutations in this gene account for less than 5 percent of all early-onset cases of the disorder.
- ✓ Two of the most common *PSEN2* mutations that cause **early-onset Alzheimer disease change single protein building blocks (amino acids) used to make presenilin 2.**
- ✓ One mutation replaces the amino acid asparagine with the amino acid isoleucine at position **141 (written as Asn141Ile or N141I).**
- ✓ The other mutation changes the amino acid methionine to the amino acid valine at position **239 (written as Met239Val or M239V).**
- ✓ These mutations appear to disrupt the **processing of amyloid precursor protein, leading to the overproduction of amyloid beta peptide.**
- ✓ This protein fragment can build up in the brain and **form clumps called amyloid plaques that are characteristic of Alzheimer disease.**
- ✓ A buildup of toxic amyloid beta peptide and amyloid plaques may lead to the death of neurons and the progressive signs and symptoms of this disorder.



Environmental/Lifestyle Factors

- ✓ Research also suggests that a host of factors beyond basic genetics may play a role in the development and course of Alzheimer's disease. There is a great deal of interest, for example, in associations between **cognitive decline and vascular and metabolic conditions such as heart disease, stroke, high blood pressure, diabetes, and obesity.** Understanding these relationships and testing them in clinical trials will help us understand whether reducing risk factors for these conditions may help with Alzheimer's as well.
- ✓ **Further, a nutritious diet, physical activity , social engagement, and mentally stimulating pursuits can all help people stay healthy as they age.**

- ✓ New research suggests the possibility that these and other factors also might help to reduce the risk of cognitive decline and Alzheimer's disease. Clinical trials of specific interventions are underway to test some of these possibilities.

✓ HYPOTHESIS RELATED TO ALZHEIMERS

✓ Cholinergic hypothesis

- ✓ The oldest, on which most currently available drug therapies are based, is the *cholinergic hypothesis*, which proposes that AD is caused by **reduced synthesis of the neurotransmitter acetylcholine**.

Amyloid hypothesis

- ✓ In 1991, the *amyloid hypothesis* postulated that **extracellular amyloid beta (A_β) deposits** are the fundamental cause of the disease.
- ✓ Support for this postulate comes from the location of the gene for the amyloid precursor protein (APP) on chromosome 21, together with the fact that people with trisomy 21 (Down Syndrome) who have an extra gene copy almost universally exhibit AD by 40 years of age.
- ✓ Also, a specific isoform of apolipoprotein, APOE4, is a major genetic risk factor for AD. Whilst apolipoproteins enhance the breakdown of beta amyloid, some isoforms are not very effective at this task (such as APOE4), leading to excess amyloid buildup in the brain.
- ✓ Further evidence comes from the finding that transgenic mice that express a mutant form of the human APP gene develop fibrillar amyloid plaques and Alzheimer's-like brain pathology with spatial learning deficits.

Tau hypothesis

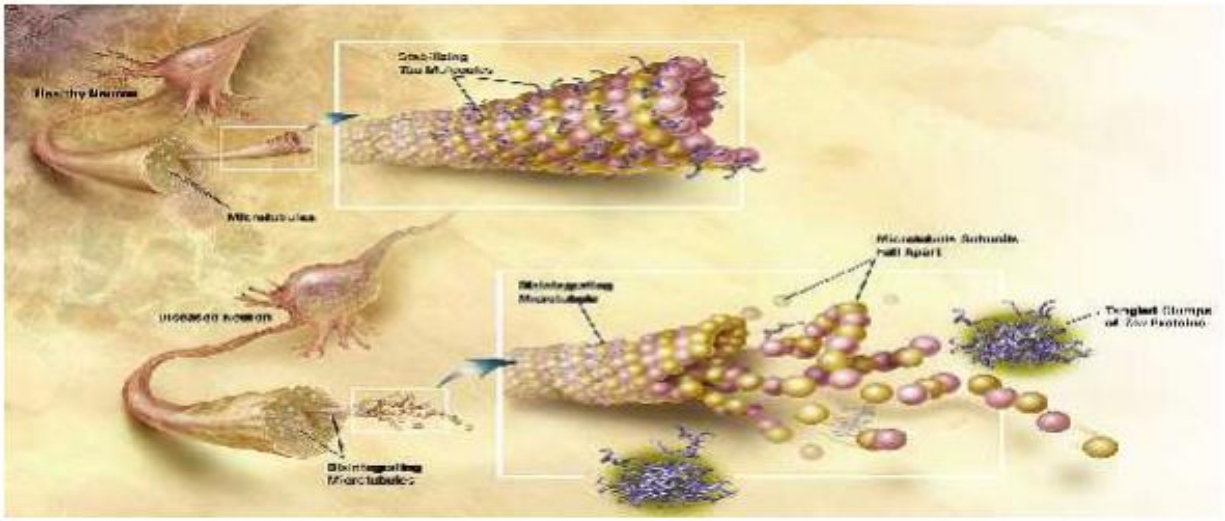
- ✓ The *tau hypothesis* proposes that tau protein

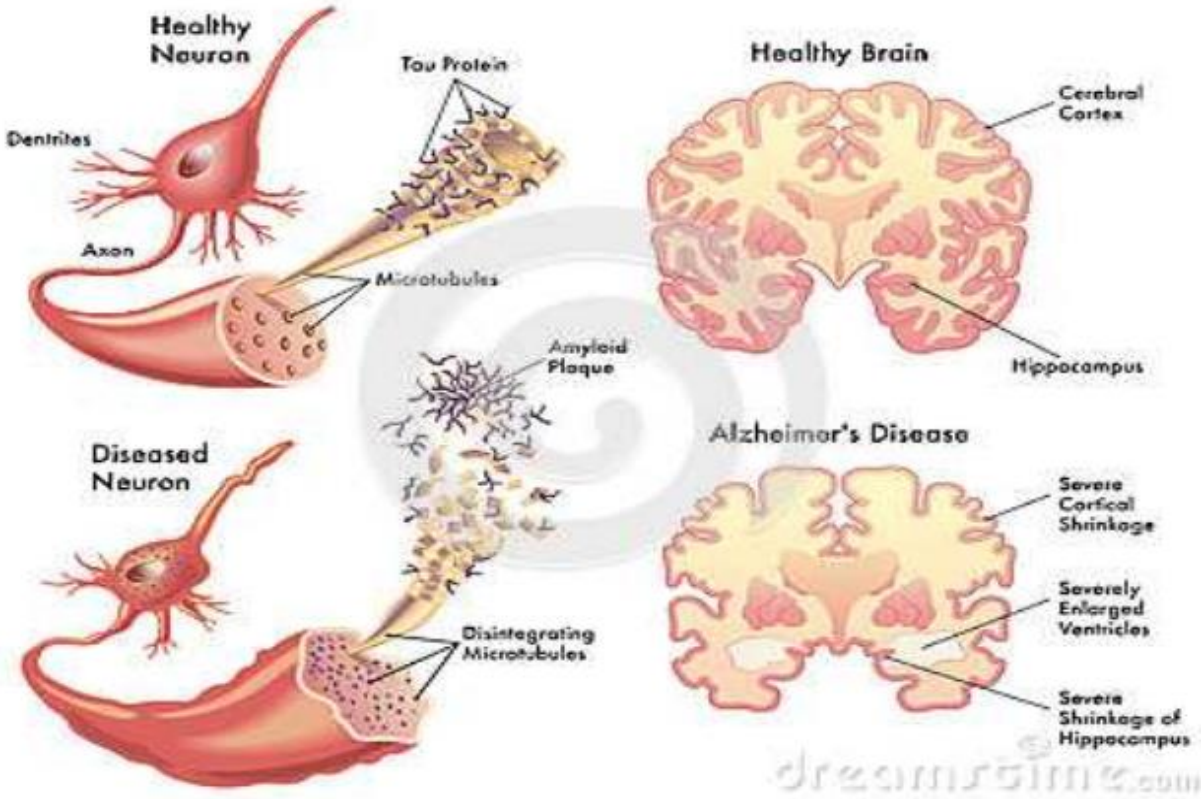
  abnormalities initiate the disease cascade.
- ✓ In this model,hyperphosphorylated tau begins to pair with other threads of tau.
- ✓ Eventually, they form neurofibrillary tangles inside nerve cell bodies.

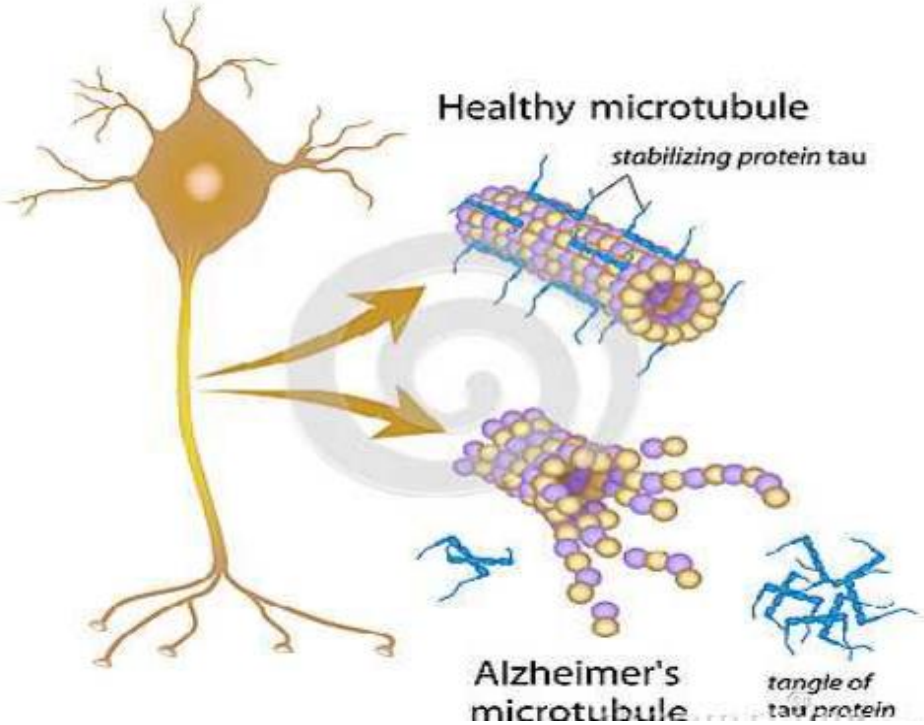
- ✓ When this occurs, the microtubules disintegrate, destroying the structure of the cell'scytoskeleton

  which collapses the **neuron's transport system**.

- ✓ This may result first in malfunctions in biochemical communication between neurons and later in the death of the cells
- ✓ Tau protein is a highly soluble microtubule-associated protein (MAP).
- ✓ In humans, these proteins are found mostly in neurons compared to non-neuronal cells.
- ✓ **Tau proteins** (or **τ proteins**, after the Greek letter by that name) are proteins that stabilize microtubules. Tau proteins interact with tubulin to stabilize microtubules and promote tubulin assembly into microtubules.
- ✓ Tau has two ways of controlling microtubule stability: isoforms and phosphorylation.
- ✓ They are abundant in neurons of the central nervous system and are less common elsewhere, but are also expressed at very low levels in CNS astrocytes and oligodendrocytes.
- ✓ Pathologies and dementias of the nervous system such as Alzheimer's disease and Parkinson's disease are associated with tau proteins that have become defective and no longer stabilize microtubules properly.




Healthy Neuron
Tau Protein
Dentrites
Axon
Microtubules
Amyloid Plaque
Diseased Neuron
Disintegrating Microtubules
Healthy Brain
Cerebral Cortex
Hippocampus
Alzheimer's Disease
Severe Cortical Shrinkage
Severely Enlarged Ventricles
Severe Shrinkage of Hippocampus


Healthy microtubule
stabilizing protein tau
Alzheimer's microtubule
tangle of tau protein

Treating Alzheimer's Disease

Alzheimer's disease is complex, and it is unlikely that any one intervention will be found to delay, prevent, or cure it. That's why current approaches in treatment and research focus on several different aspects, **including helping people maintain mental function, managing behavioral symptoms, and slowing or delaying the symptoms of disease.**

Maintaining Mental Function

- ✓ Four medications are approved by the U.S. Food and Drug Administration to treat Alzheimer's. Donepezil (Aricept®), rivastigmine (Exelon®), and galantamine (Razadyne®) are used to treat **mild to moderate Alzheimer's** (donepezil can be used for severe Alzheimer's as well). Memantine (Namenda®) is used to treat moderate to severe Alzheimer's.
- ✓ These drugs work by regulating neurotransmitters (the chemicals that transmit messages between neurons). They may help maintain thinking, memory, and speaking skills, and help with certain behavioral problems.
- ✓ However, these drugs don't change the underlying disease process, are effective for some but not all people, and may help only for a limited time.

✓ Managing Behavioral Symptoms

- ✓ Common behavioral symptoms of Alzheimer's include sleeplessness, agitation, wandering, anxiety, anger, and depression. Scientists are learning why these symptoms occur and are studying new treatments—drug and non-drug—to manage them. Treating behavioral symptomsoften makes people with Alzheimer's more comfortable and makes their care easier for caregivers.
- ✓ Slowing, Delaying, or Preventing Alzheimer's Disease
- ✓ Alzheimer's disease research has developed to a point where scientists can look beyond treating symptoms to think about addressing underlying disease processes. **In ongoing clinical trials, scientists are looking at many possible interventions, such as immunization therapy, cognitive**

training, physical activity, antioxidants, and the effects of cardiovascular and diabetes treatments.

Diagnosis

- ✓ Alzheimer's disease is usually diagnosed based on the person's medical history, history from relatives, and behavioural observations.
- ✓ Advanced medical imaging with computed tomography (CT) or magnetic resonance imaging(MRI), and with single-photon emission computed tomography (SPECT) or positron emission tomography (PET) can be used to help exclude other cerebral pathology or subtypes of dementia.
- ✓ Moreover, it may predict conversion from prodromalstages (mild cognitive impairment) to Alzheimer's disease.
- ✓ Assessment of intellectual functioning including memory testing can further characterise the state of the disease.
- ✓ Medical organisations have created diagnostic criteria to ease and standardise the diagnostic process for practising physicians.
- ✓ The diagnosis can be confirmed with very high accuracy post-mortem when brain material is available and can be examinedhistologically.