Alzheimer's disease susceptibility and Folate

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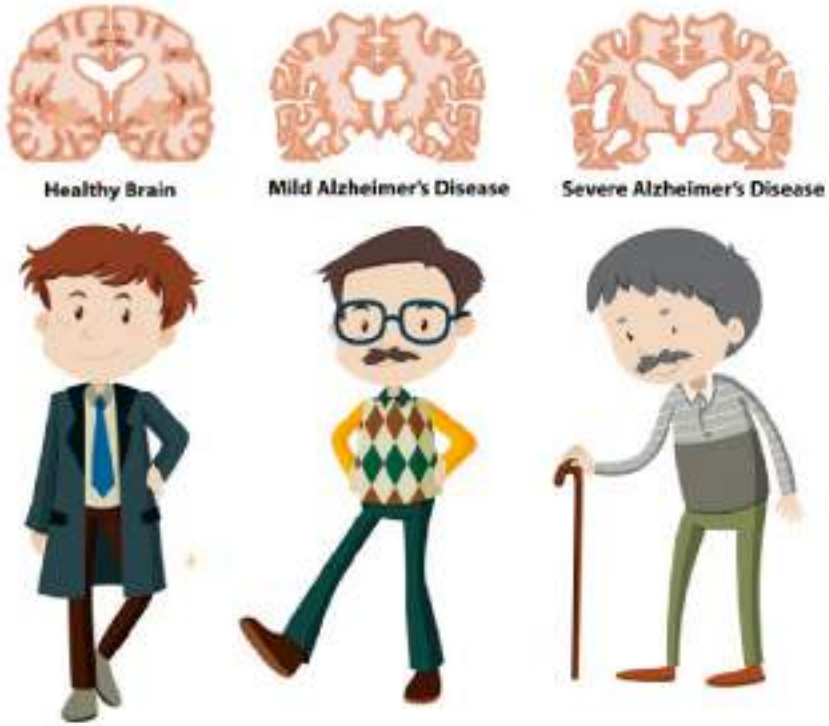
Alzheimer's Disease

- **Alzheimer's disease** is a progressive, unremitting, neurodegenerative disorder that affects wide areas of the cerebral cortex and hippocampus.

- Subtle losses of memory or changes in behaviour are the first outward signs of Alzheimer's disease.

- Despite much effort, the condition's cause remains uncertain and no effective treatment yet exists.



Progression of Alzheimer's Disease

Drew L., 2018. An age-old story of dementia. Nature 559 (7715), S2-S3. https://doi.org/10.1038/d41586-018-05718-5

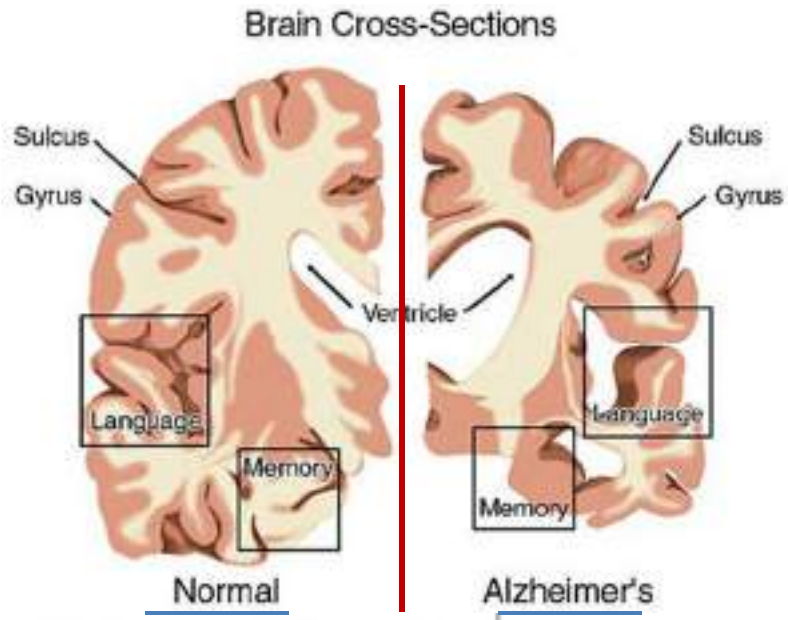
10 Symptoms of Alzheimer's

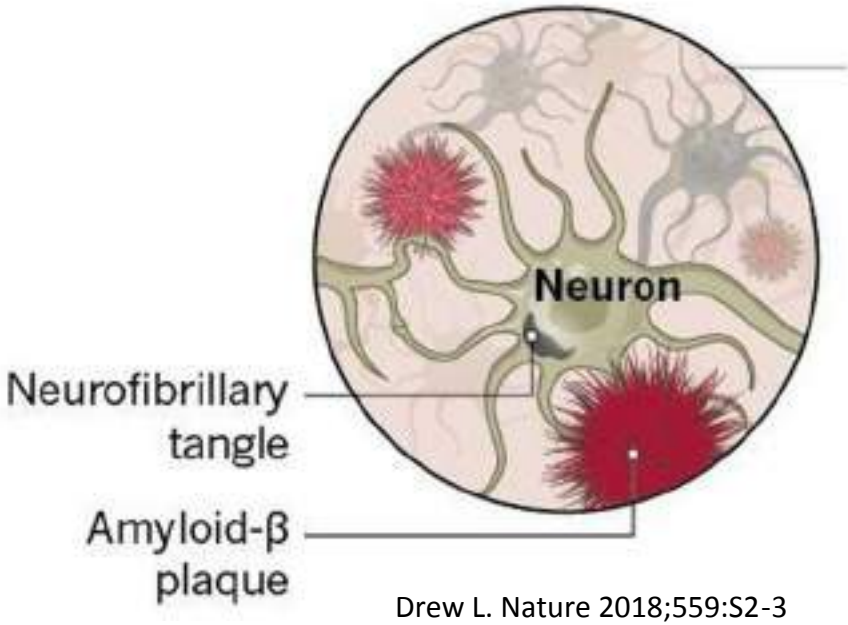
1. Memory loss that disrupts daily life
2. Challenges in planning or solving problems
3. Difficulty completing familiar tasks
4. Confusion with time or place
5. Trouble understanding visual images and spatial
6. relationships
7. New problems with words in speaking or writing
8. Misplacing things and losing the ability to retrace steps
9. Decreased or poor judgment
10. Withdrawal from work or social activities
11. Changes in mood and personality

Alzheimer's Disease

When nerve cells in key areas of the brain are damaged or destroyed.

These changes disrupt the normal flow of information between body and brain resulting in a steady decline in mental function.





MICROSCOPIC CHANGES

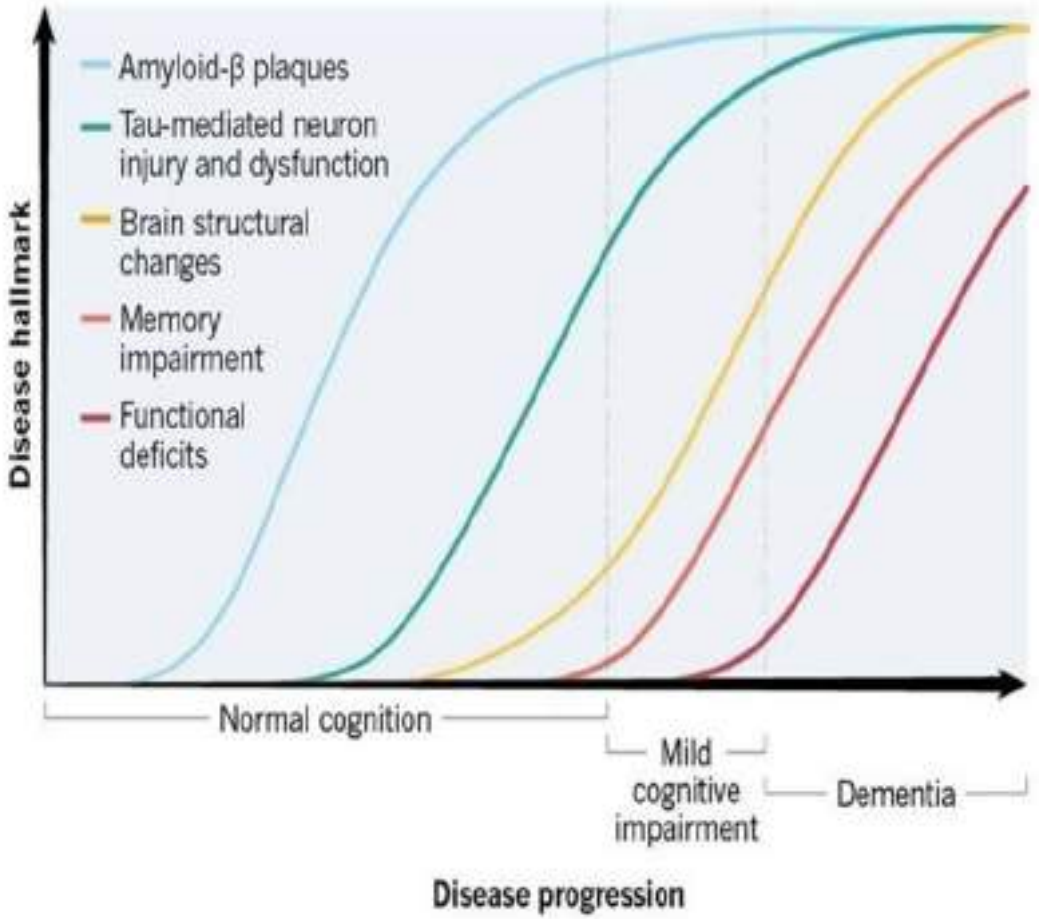
Two hallmarks of Alzheimer's disease are visible only under the microscope.

Accumulations of the peptide amyloid-β, known as plaques, form between neurons. Microtubule-associated protein tau aggregates into neurofibrillary tangles inside neurons, and these structures persist after neurons have died.

Drew L. Nature 2018;559:S2-3

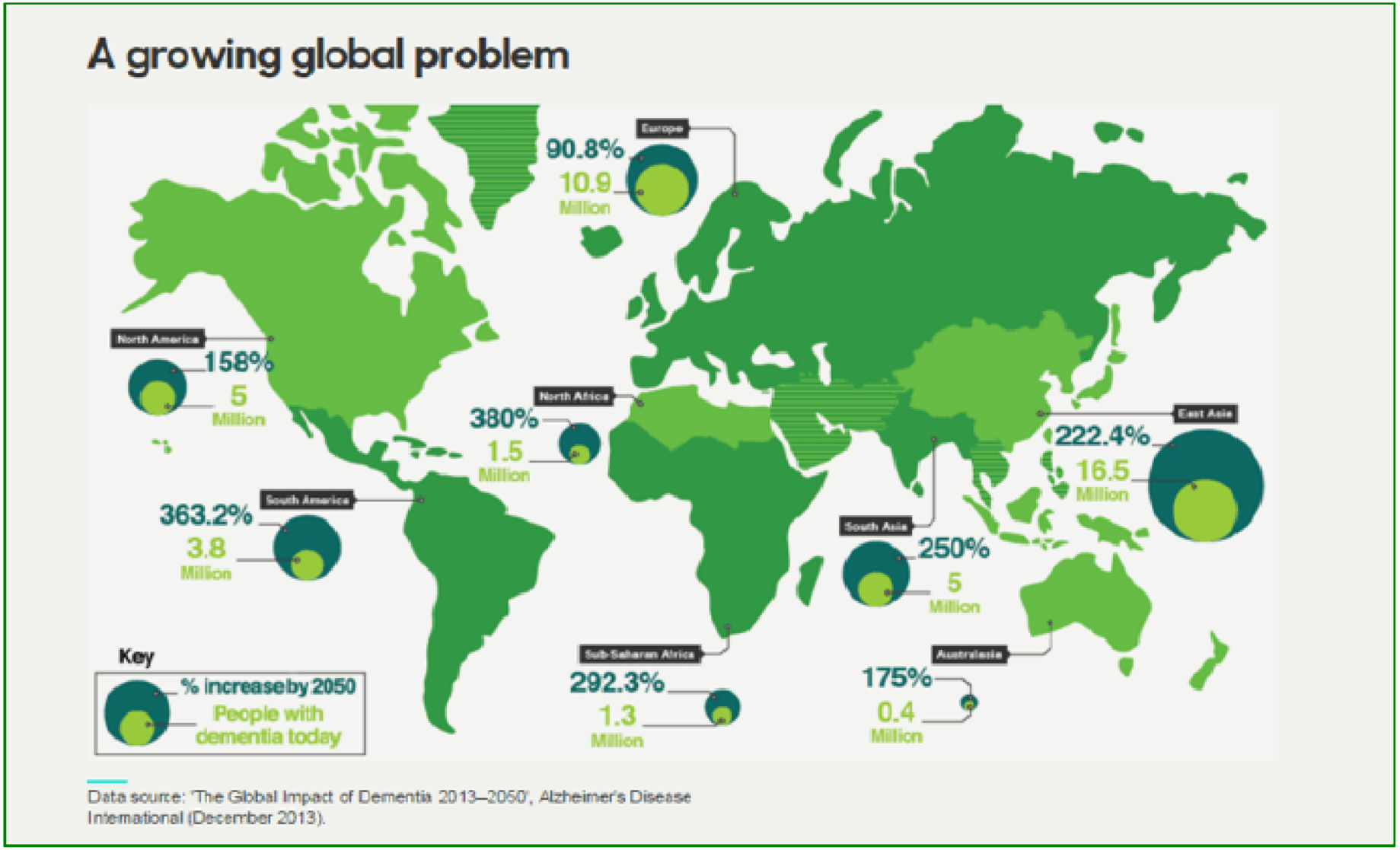
By the time that a person begins to experience the symptoms of Alzheimer's disease, the condition is already well-established in the brain.

- The accumulation of amyloid-β, generally thought to be the first step in disease progression, could precede symptoms by 10–15 years.
- Tau accumulation occurs later, much closer to the onset of neurodegeneration.



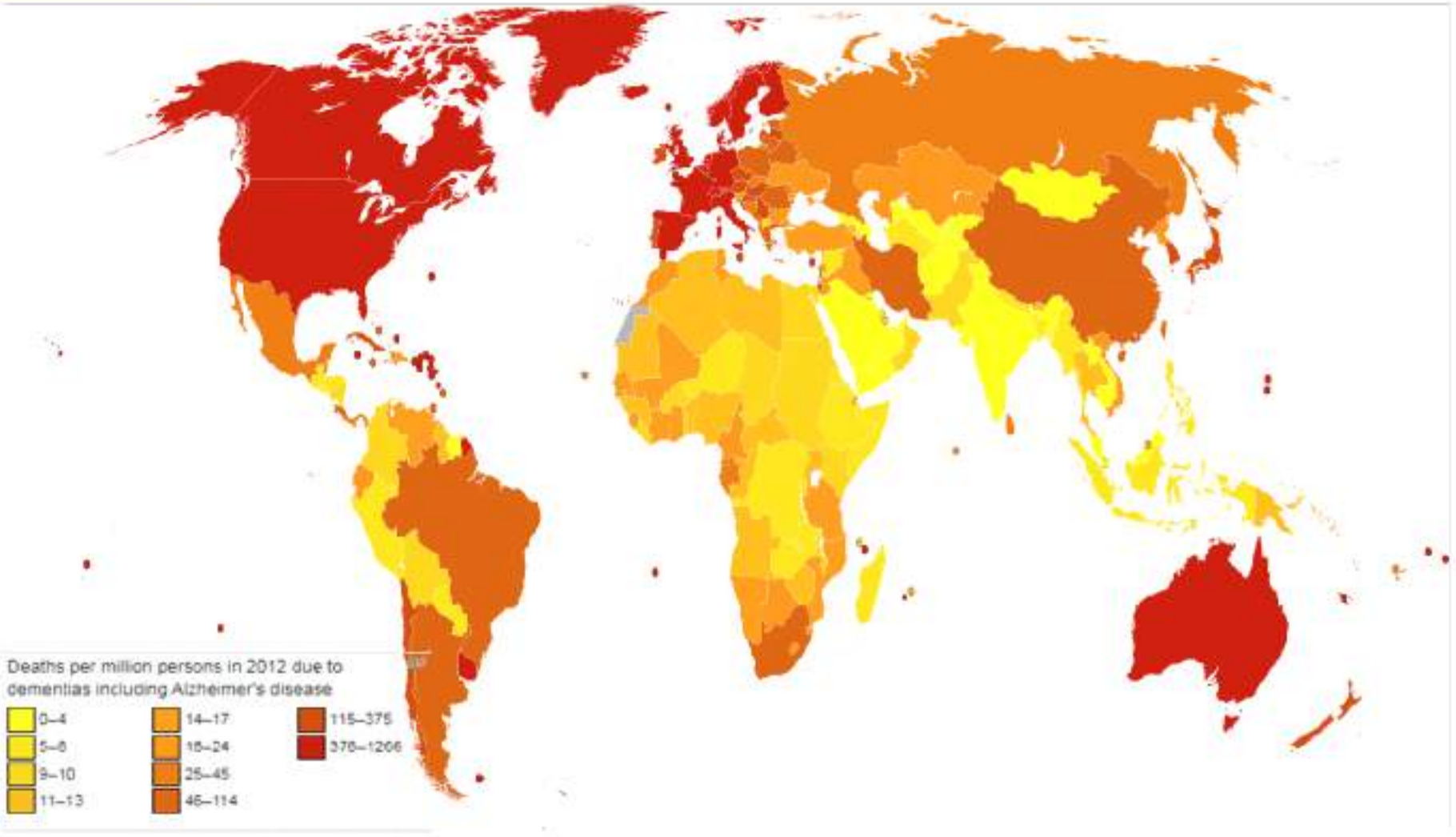
Drew L. Nature 2018;559:S2-3

Worldwide, at least 44 million people are living with AD, making the disease a global health crisis and it is increasing at an alarming rate



6TH
LEADING CAUSE OF DEATH

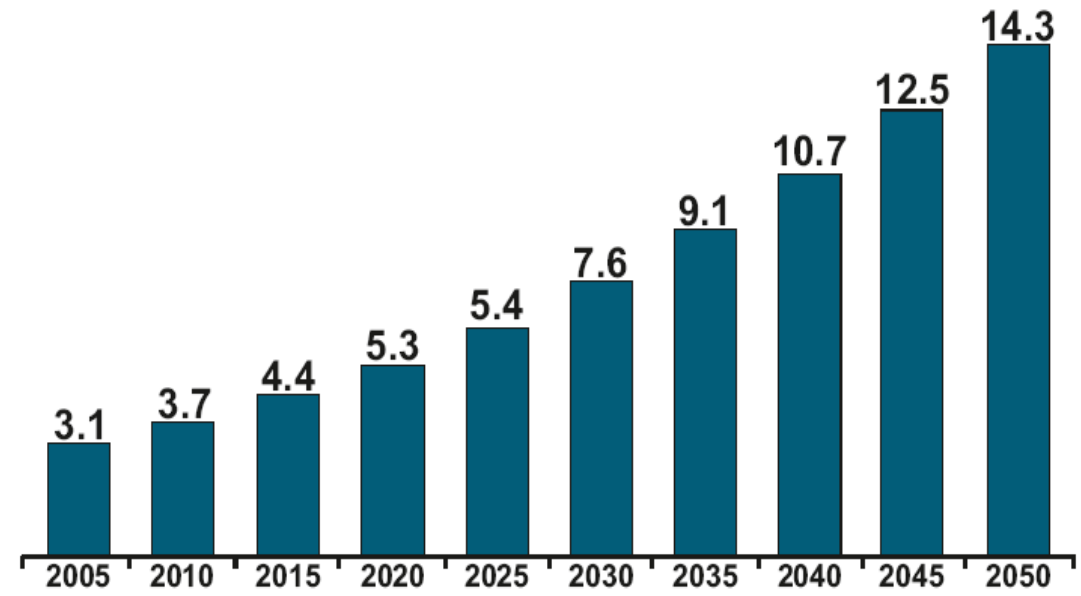
The Global Death Impact of Alzheimer's Disease



Wikipedia

India has the third highest caseload in the world, after China and the US.

Dementia – Steep increase in numbers



- **In India, more than 4 million people are estimated to be suffering from Alzheimer's and other forms of dementia.**
- **Number is expected to double by 2030**

Only 10% of cases are diagnosed

Alzheimer's and related disorders society of India (ARDSI)

अलजाइमरस एण्ड रलिटेड डसिऑरडरस सोसाइटी ऑफ इंडिया

ALZHEIMER'S & RELATED DISORDERS SOCIETY OF INDIA

ARDSI

Alzheimer's Disease International

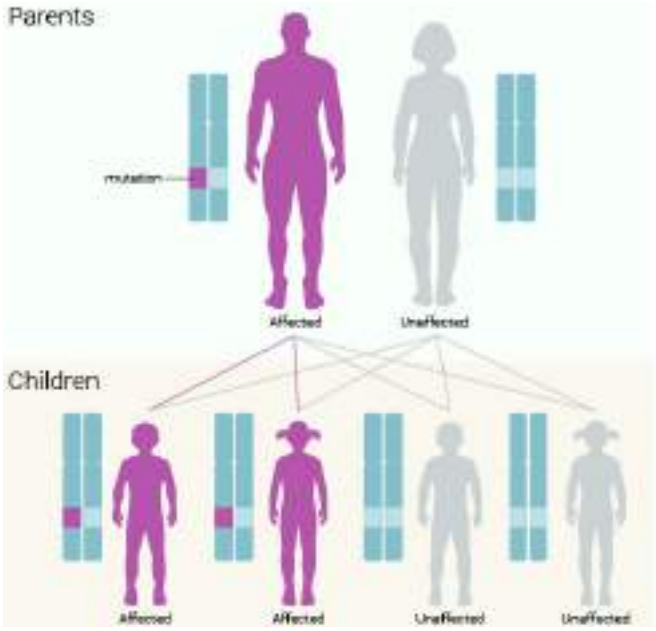
- **ARDSI National Administrative Office**
  Harmony Home, Thrissur
- **Respite Care Centre, Thrissur**
- **Cochin Harmony Home, Cochin**
- **Comprehensive Day Care Centre, Cochin**
- **Malabar Harmony Home, Calicut**
- **ARDSI - Kolkata (Calcutta) Chapter**
- **Snehasadanam, Trivandrum**
- **Day Care Centre, Delhi**
- **Nightingale Medical Trust, Bangalore**

https://www.alz.org/in/dementia-alzheimers-en.asp

RISK FACTORS

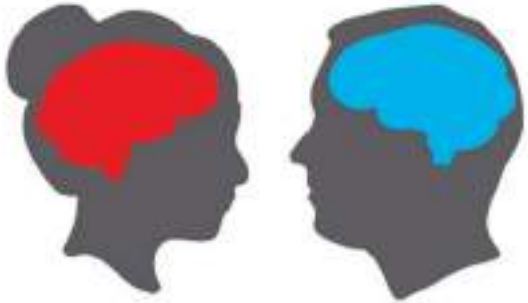
GENETICS

- Around **1%** of cases of Alzheimer's disease are caused by mutations in the genes *which affect amyloid-processing*
- *APP,*
- *PSEN1 or PSEN2,.*



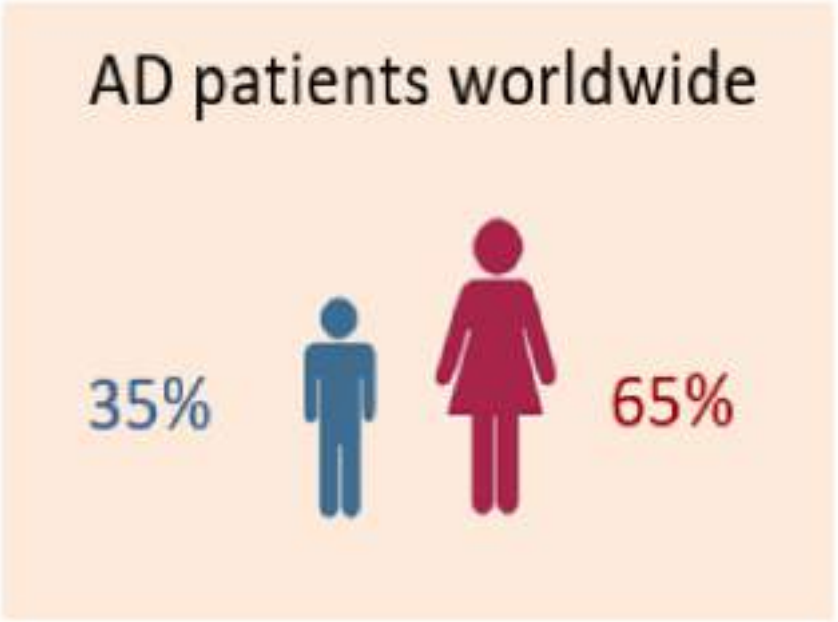
https://ghr.nlm.nih.gov/condition/alzheimer-disease#inheritance

Gender



1 in 6 **1 in 11**

chance of developing Alzheimer's disease during the remainder of their lives at age 65



The overall incidence of Alzheimer's disease in women is up to twice that of men.

https://www.brightfocus.org/alzheimers/news/scientists-shed-new-light-gender-differences-alzheimers

http://www.womensbrainproject.com/facts/

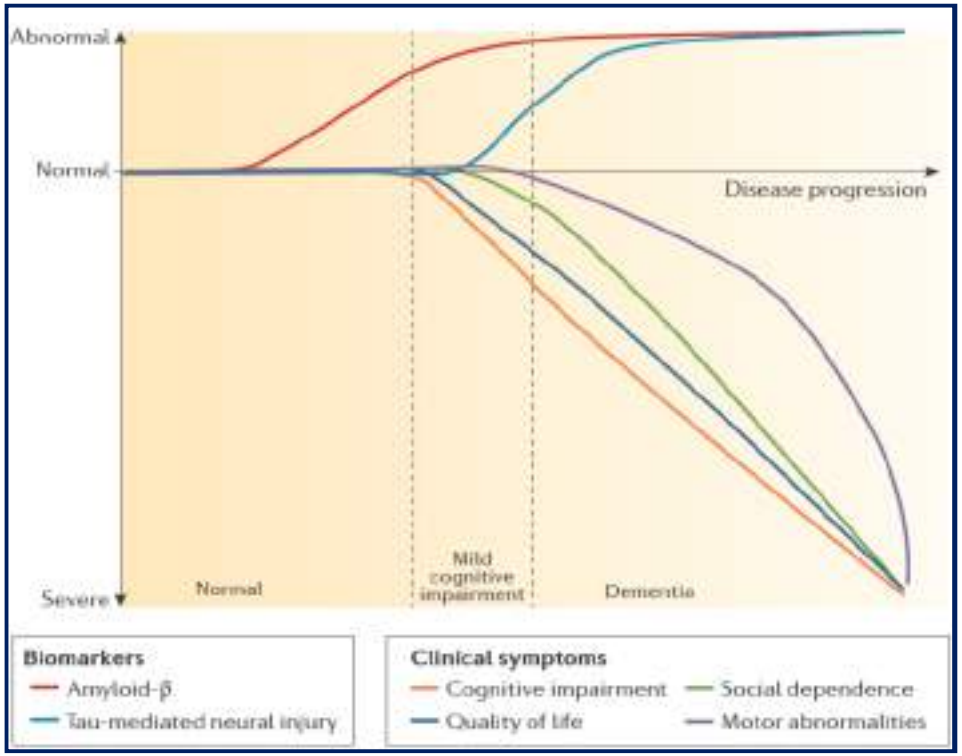
LIFESTYLE

- Potentially modifiable risk factors for Alzheimer's disease have been identified.
- Diabetes
- Obesity
- Depression
- Smoking and
- Low educational attainment.

Stages of Alzheimer Disease

Stages	Patients condition	Duration	Brain regions	Symptoms	Disease
Stage 1	Normal	7 years	Disease begins in Medial Temporal lobe	Short Term memory loss	**Mild Cognitive impairments**
Stage 2	Normal age forgetfulness				
Stage 3	Mild cognitive impairments				
Stage 4	A diagnosis of Alzheimer's disease is possible, patients have trouble with memory and every day task	2 years	Disease spreads to lateral Temporal and parital lobes	Reading problems, Poor Object recognition, Poor direction sense	**Mild Alzheimer's disease**
Stage 5	Patients can no longer live independently as their memory and ability to communicate deteriorates	2 years	Disease spreads to frontal lobe	Poor Judgement, Impulsivity, Short Attention	**Moderate Alzheimer's disease**
Stage 6	Memory is severely impaired, patients confused, Patients will need family members for personal hygiene	3 Years	Disease Spreads to Occipital lobe	Visual problems	**Severe Alzheimer's disease**
Stage 7	Patient can no longer respond to their environment and become infantile				

Quality of life of patients with Alzheimer’s disease.



Schematic depiction of relative rates of change of cognitive impairment, social dependence and motor abnormalities that adversely affect the general quality of life in people who develop dementia due to Alzheimer’s disease.

Alzheimer's disease. *Nat Rev Dis Primers* **1,** 15059 (2015)

Diagnostic and Clinical Tests for Alzheimer's Disease

Query	Pathogenesis	Pathophysiology	Biomarkers	Pathology	Clinical and cognitive
Assay	Genetic testing of risk factors and protective factors	Aβ, tau and APOE metabolism in the brain, FDG PET and functional connectivity	Biochemical measures in the CSF	Aβ and tau PET imaging, and structural MRI	CDR-SB and neurological examination, and psychometrics
Result	Mutations in *PSEN1*, *PSEN2*, *APP* or *APOE* allele (2, 3 or 4)	Overproduction or impaired clearance of Aβ and aggregation of tau in the brain Hypometabolism in the parieto-occipital cortex	Decreased Aβ42 levels, and increased T-tau and P-tau levels in the CSF	Aβ aggregation, tau aggregation, and hippocampal and cortical atrophy	Memory, attention, executive cognitive dysfunction, functional impairment and dementia staging

Aβ, amyloid-β; APOE, apolipoprotein E; APP, amyloid, precursor protein; CDR-SB, Clinical Dementia Rating-Sum of Boxes; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; P-tau, phosphorylated tau; PSEN1, presenilin 1; PSEN2, presenilin 2; T-tau, total tau.

Alzheimer's disease. *Nat Rev Dis Primers* **1,** 15059 (2015)

Confirmed genetic factors predisposing to Alzheimer's disease: relationships to the b-amyloid phenotype

Chromosome	Gene Defect	Phenotype
21	β-APP mutations	↑ Production of all Aβ peptides or $A\beta_{40}$ peptides
19	ApoE4 polymorphism	↑ Density of Aβ plaques and vascular deposits
14	Presenilin 1 mutations	↑ Production of $A\beta_{42}$ peptides
1	Presenilin 2 mutation	↑ Production of $A\beta_{42}$ peptides

β-APP, β-amyloid precursor protein; Aβ, amyloid β-protein.

Rocchi et al.,Brain Research Bulletin 61 (2003) 1–24

Alzheimer's Disease and Genes

(i)Chromosome 21, APP = amyloid precursor protein gene (-> a protease inhibitor in the membrane)

–Incorrect processing -> ~40aa beta-amyloid.

–May poison cholinergic neurons

–The inherited mutation in some families, but also in many sporatic cases of Alzheimer's

--APP Mutations Increase the Production of Ab42 Peptides

(ii)Chromsome. 14q, Presenilin 1 (PSEN1)

--Early onset, inherited

(iii) chromosome 1,Presenilin 2 (PSEN2)

Presenilin Mutations Increase the Production of Ab42 Peptides

(iv)Chrom. 19, apoE (apolipoprotein E) gene

-3 major alleles (APO E2, E3, and E4)

- Apolipoprotein e4 haplotype is a genetic risk factor

-Inheritance of ApoE4 Alleles Increases Steady-State Levels of Ab Peptides in the Brain

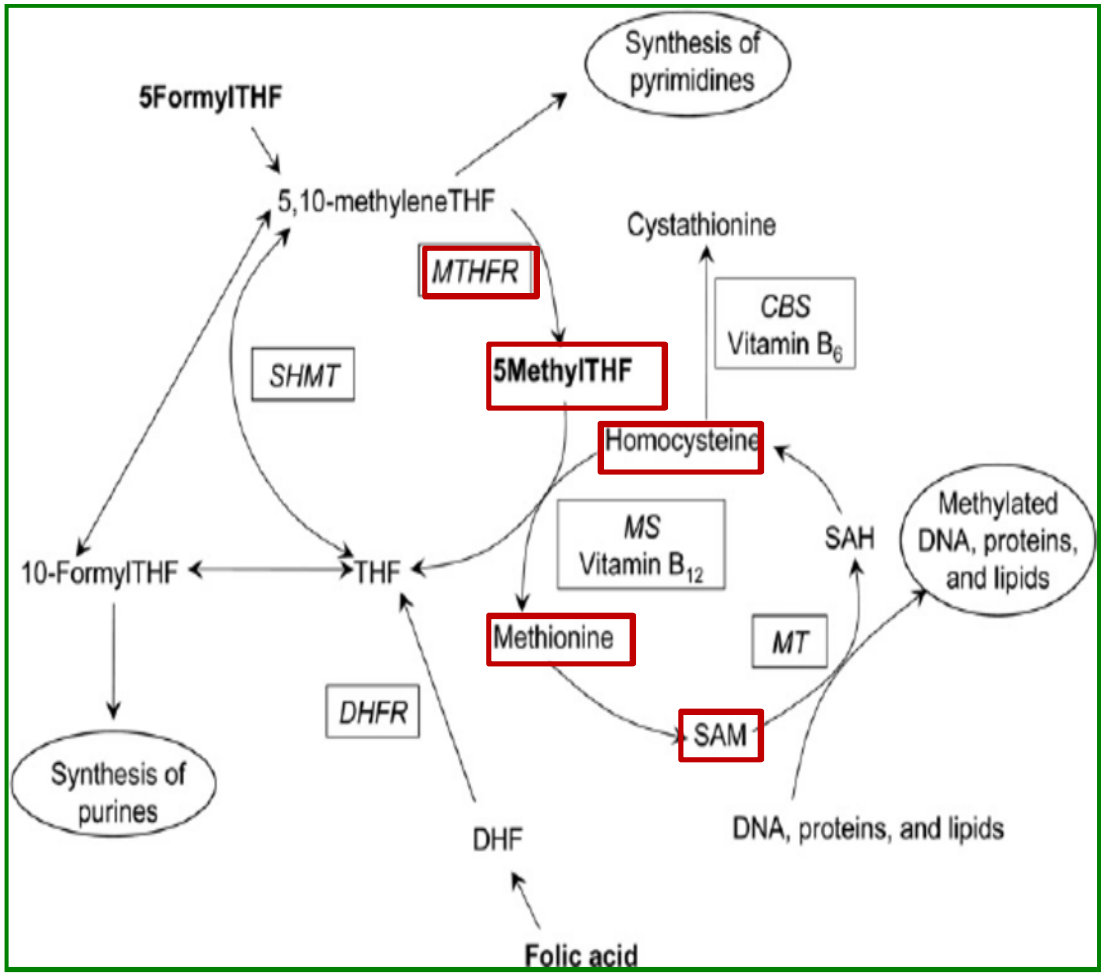
- Late onset, inherited; also sporatic

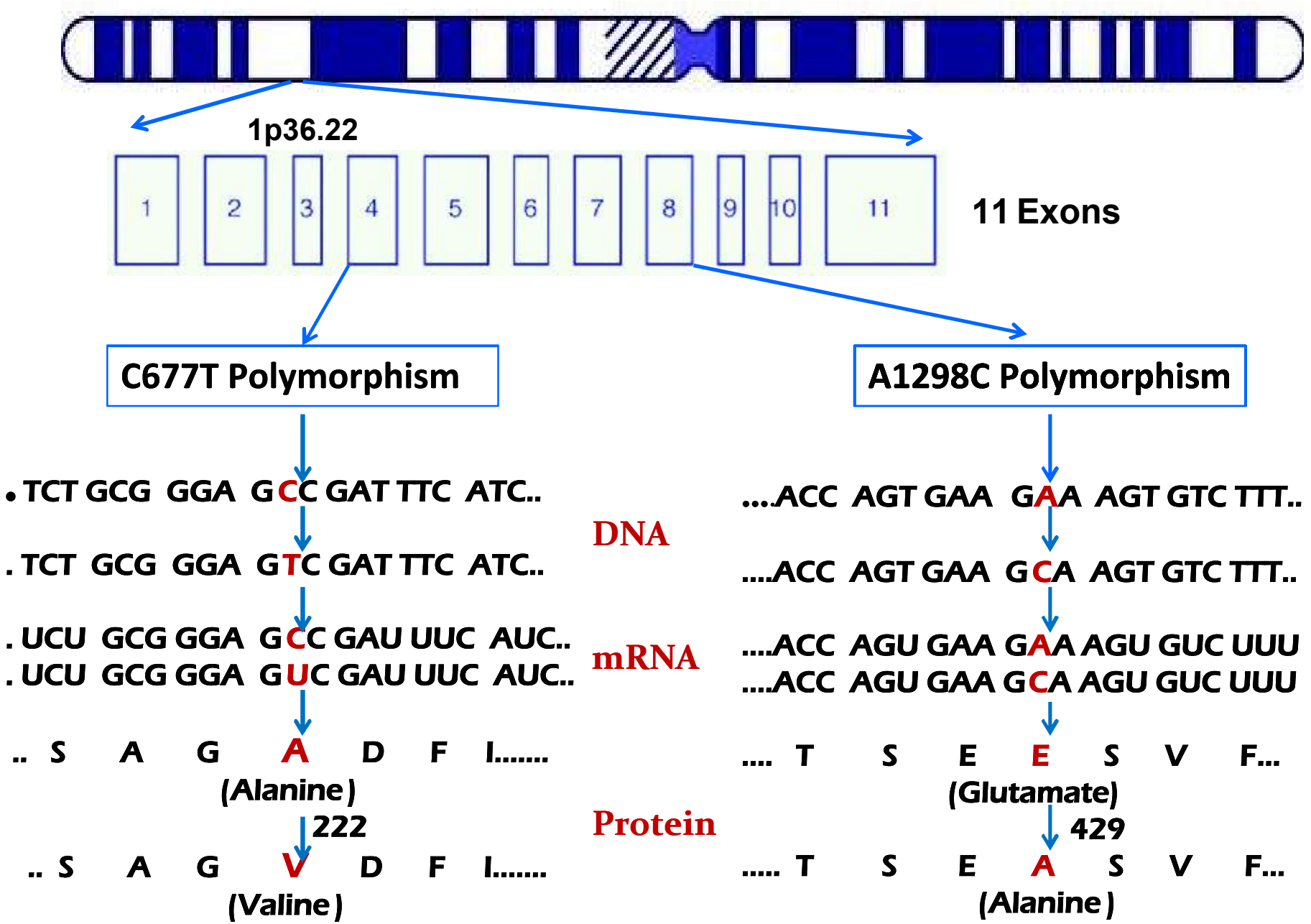
-The mutation apoE4 product binds tightly to beta-amyloid (**APO E4:** Arg112 / Arg158)

MethylenetetrahydrofolateReductase (MTHFR)

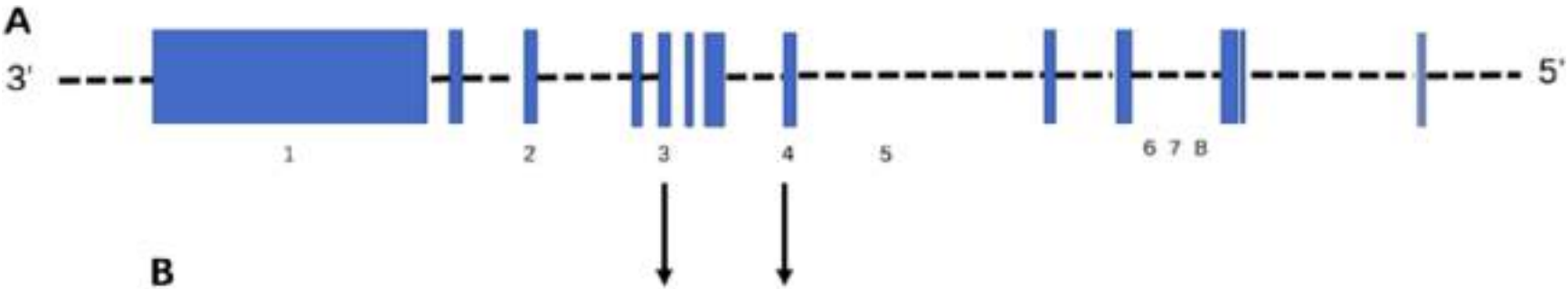
One of the most critical enzymes involved in **folate metabolism**.

- It irreversibly catalyzes the conversion of **5,10-methylenetetra hydrofolate to 5-methyltetra hydrofolate(5-THF).**
- 5-THF donates methyl group for the conversion of **homocysteine** to **methionine,** which is further converted into **S-adenosylmethionine(SAM).**
- **SAM** is the main methyl group donor for all cellular methylation reactions.
- **Human MTHFR enzyme is a 77-kilodalton protein.**




1p36.22
1
2
3
4
5
6
7
8
9
10
11
11 Exons
C677T Polymorphism
A1298C Polymorphism
• TCT GCG GGA GCC GAT TTC ATC..
. TCT GCG GGA GTC GAT TTC ATC..
. UCU GCG GGA GCC GAU UUC AUC..
. UCU GCG GGA GUC GAU UUC AUC..
.. S A G A D F I.....
(Alanine)
222
.. S A G V D F I.....
(Valine)
DNA
mRNA
Protein
....ACC AGT GAA GAA AGT GTC TTT..
....ACC AGT GAA GCA AGT GTC TTT..
....ACC AGU GAA GAA AGU GUC UUU
....ACC AGU GAA GCA AGU GUC UUU
.... T S E E S V F...
(Glutamate)
429
..... T S E A S V F...
(Alanine)

MTHFR Gene Variants



B

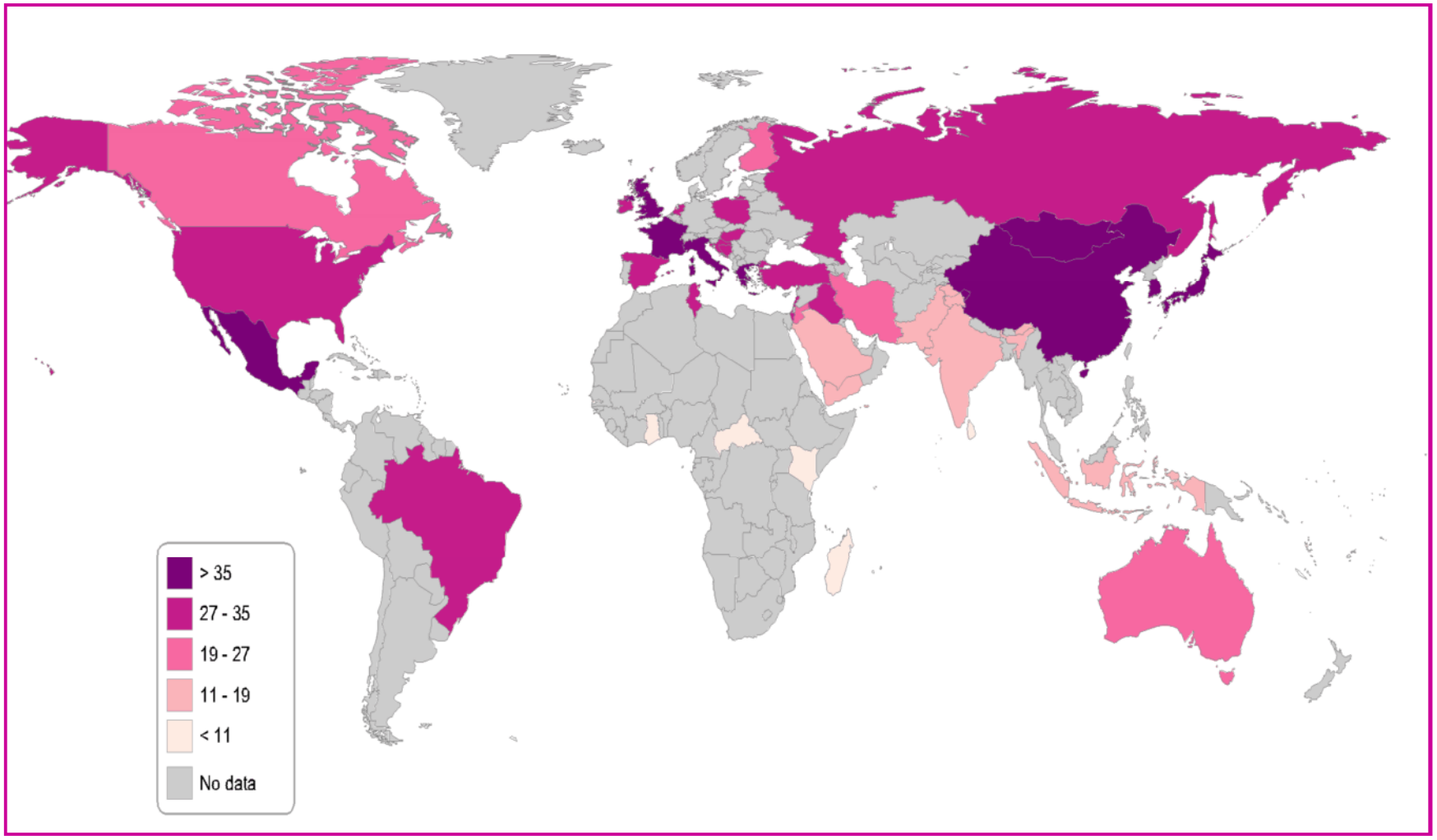
A1298C	C677T
Heterozygous 83%	Heterozygous 67%
Homozygous 61%	Homozygous 25%
Compound heterozygous (677 heterozygous+1298 heterozygous) 48%	

Enzyme activity with *MTHFR* mutations (% of normal)

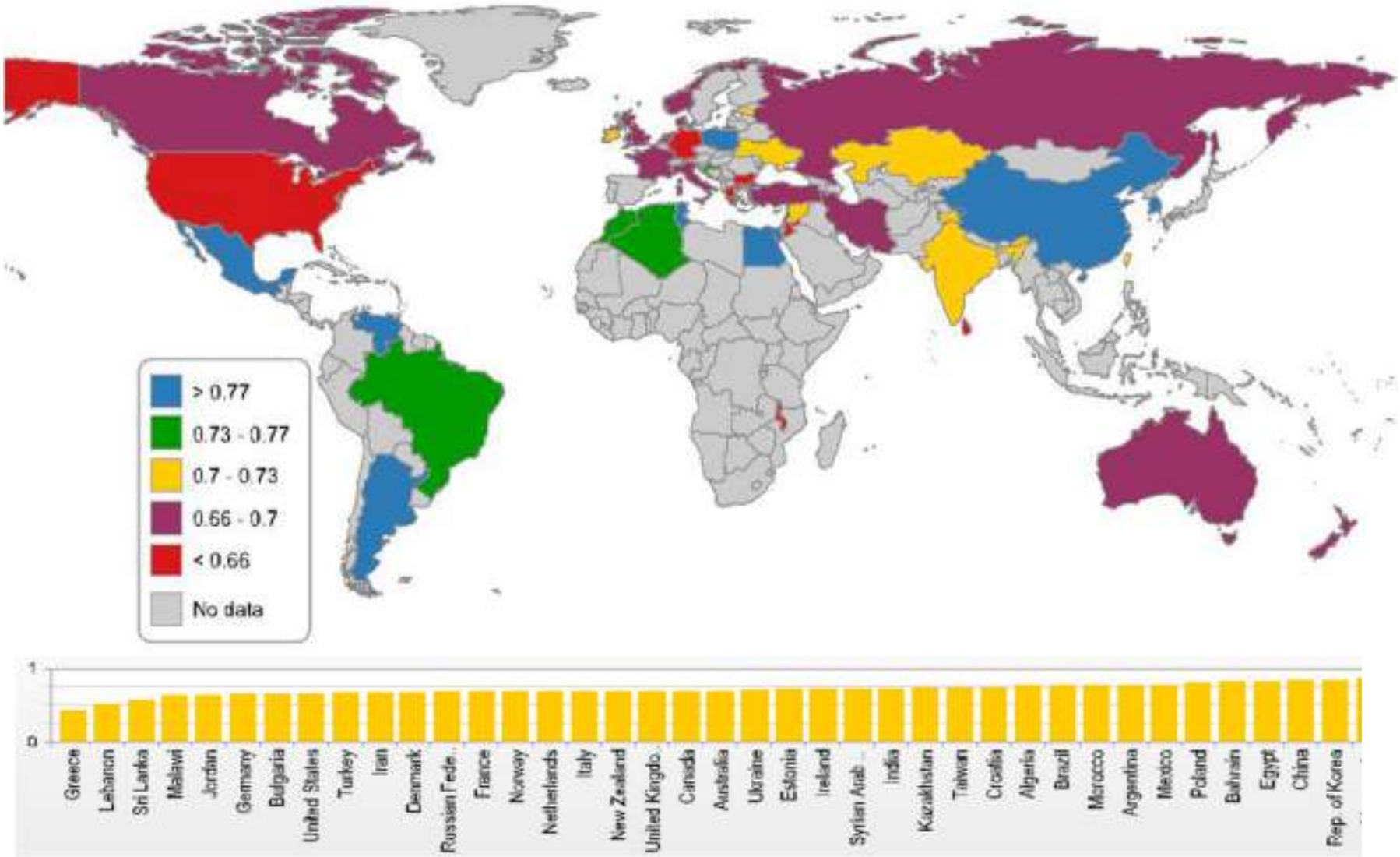
- Variant MTHFR reduces the conversion of 5, 10-methylene THF to 5-methyl THF, and elevates plasma homocysteine concentration.
- The reduction in enzyme activity associated with the C677T MTHFR polymorphism raises the dietary requirement for folic acid to maintain normal remethylation of homocysteine to methionine.

Wan et al. 2018.Transl Psychiatry. 8:242.

T allele frequency



Frequency of C allele (A1298C)



MTHFR Mutation Symptoms

Fatigue, brain fog, anxiety, depression, insomnia, headache, migraine, obesity, joint and muscle pains

MTHFR and Alzheimer Disease

Mol Neurobiol (2017) 54:1173–1186
DOI 10.1007/s12035-016-9722-8

Methylenetetrahydrofolate Reductase (MTHFR) C677T Polymorphism and Alzheimer Disease Risk: a Meta-Analysis

Vandana Rai[1]

OR (95%CI),p
TT vs CC: OR= 1.31(1.16–1.48),0.001
Association=Yes

Ind J Clin Biochem
DOI 10.1007/s12291-015-0512-2

REVIEW ARTICLE

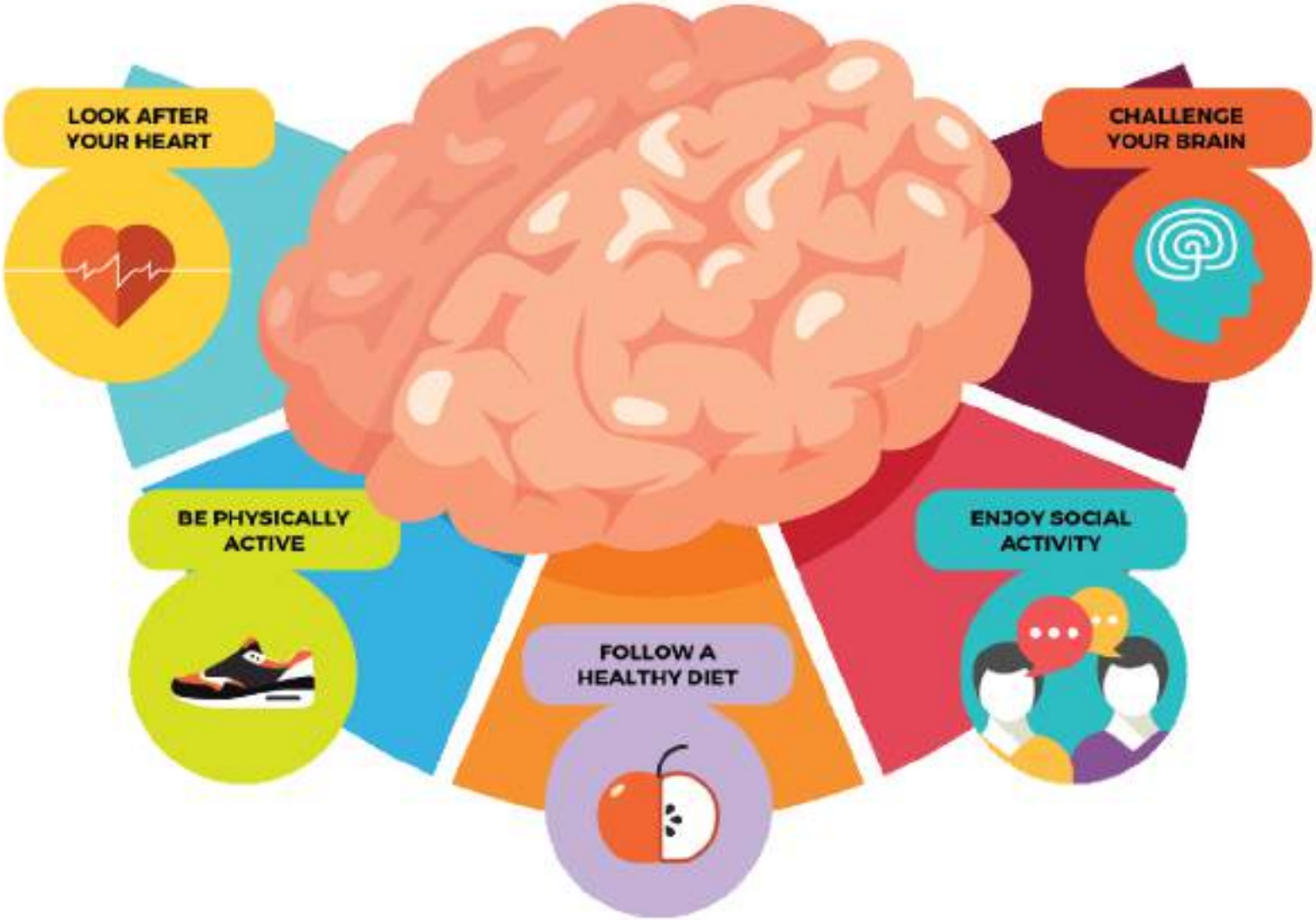
Folate Pathway Gene Methylenetetrahydrofolate Reductase C677T Polymorphism and Alzheimer Disease Risk in Asian Population

Vandana Rai[1]

Genetics and Alzheimer's Disease

	Early-Onset AD (Dominantly Inherited)	Early-Onset AD (Complex Inheritance)	Late-Onset AD (Complex Inheritance)
Cause:	Inherited Genetic Mutations	Genetic and Environmental Risk Factors	Genetic and Environmental Risk Factors
Age at Onset:	Usually 30-60 years	<65 years	>65 years
Proportion of Cases:	~1%	~4%	~95%

Five ways you can reduce your risk of AD



https://alz.org.sg/5ways/

Folate deficiency in older individuals

- **Intestinal malabsorption –**
  - Atrophic gastritis
  - Intestinal diseases (Crohn's disease, celiac disease)
  - Gastric and intestinal resection
- **Reduced dietary intake** (due to decreased sensory function and appetite, dysphagia)
- **Therapeutic drugs** (inhibitors of gastric acid secretion, antiepileptics)
- **Alcoholism**
- **Genetic polymorphisms** in enzymes involved in one-carbon metabolism

  (e.g., methylene tetrahydrofolate reductase (MTHFR))

Araújo, J.R.; Martel, F.; Borges, N.; Araújo, J.M.; Keating, E. Ageing Res. Rev. 2015, 22, 9–19

Folate deficiency symptoms

- Fatigue,
- Grey hair,
- Mouth sores,
- swollen tongue,
- Forget fullness,
- depression,
- loss of appetite,
- concentration problems,
- birth defects, and
- poor growth

Food rich in folate

- Avocado,
- Asparagus,
- Broccoli
- Cauliflower,
- Beets,
- Okra,
- Capsicum, Beans,
- Pea,
- Orange,
- Pappaya,
- Nuts and
- Lentis etc.

The United States Public Health Service recommended in 1992 that all women capable of becoming pregnant consume 400 µg folic acid daily.

In 1998, folic acid fortification of all enriched cereal grain product flour was fully implemented in the United States and Canada.

Recent estimates show that in the United States and Canada, the additional intake of about 100 to 150 µg/day of folic acid through food fortification has been effective in-

- reducing the prevalence of NTDs at birth and
- increasing blood folate concentrations in both countries.

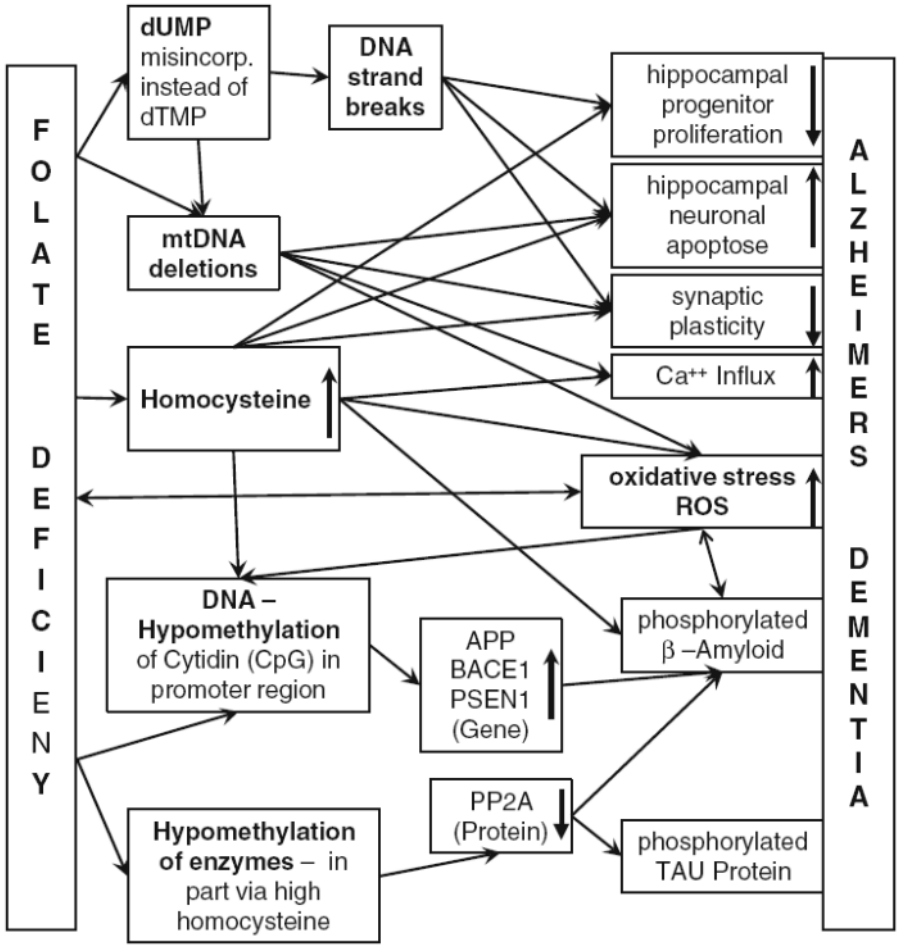
Fortification of wheat flour has a proven record of prevention in other developed countries

Wald, N.J.et al. Public Health Rev (2018) 39: 2.

Specific features make low folate a probable candidate for long-term contribution to AD development.

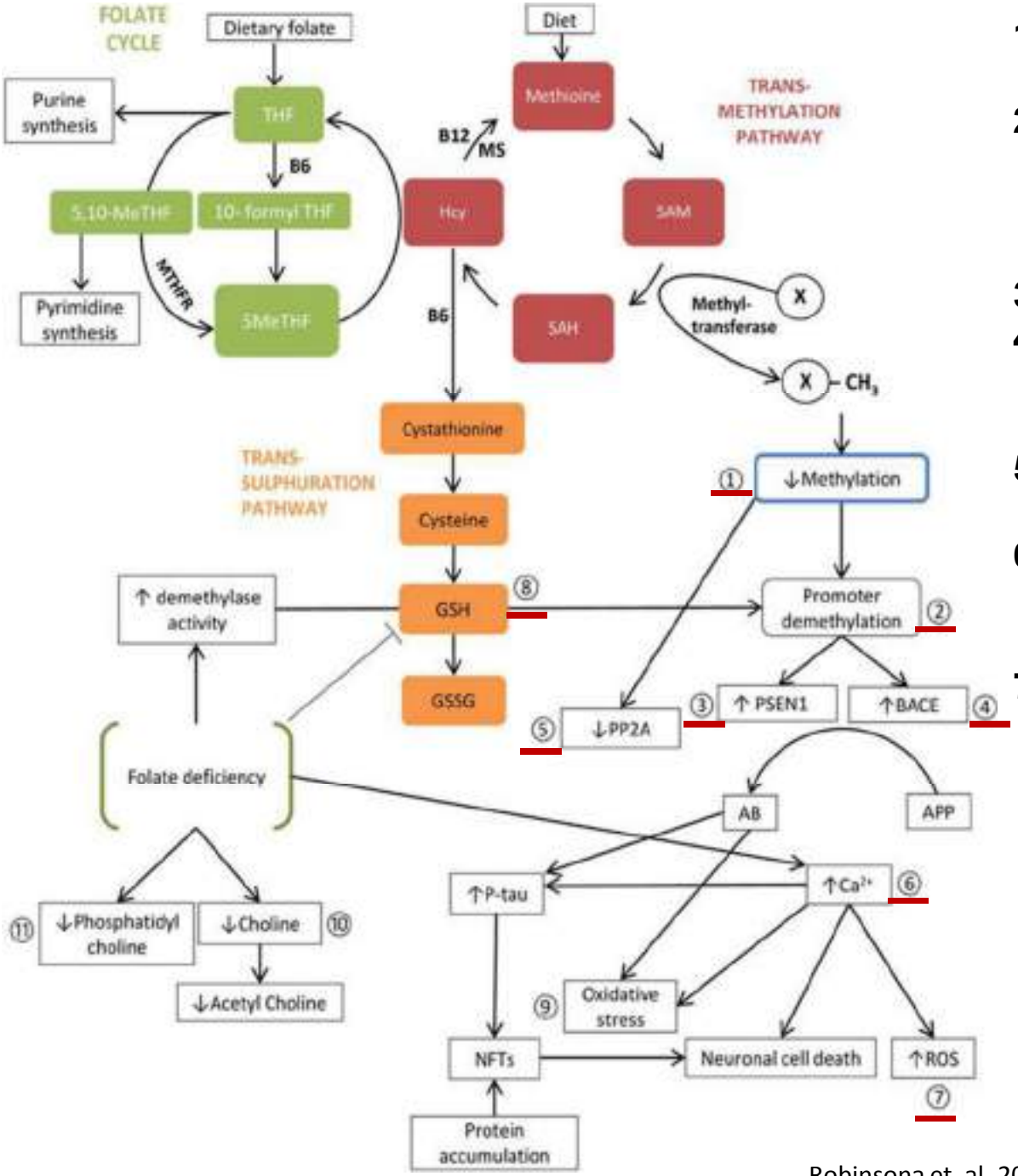
Folate deficiency induces several pathophysiologic changes supposed to be pathogenetic in Alzheimer's dementia (AD) like

1. mitochondrial dysfunction leading to oxidative stress
2. loss of calcium regulation
3. neuronal and synaptic impairment
4. accumulation of hyperphosphorylated tau and β–amyloid.



Folate deficiency and Alzheimer's dementia. For depicting this figure, the following references were used: (Fenech 2010; Fleming et al. 2011; Fuso and Scarpa 2011; Ho et al. 2003; Kruman et al. 2002; Kruman et al. 2005; Mattson and Shea 2003; Pierrot et al. 2006; Sontag et al. 2007, 2008). Only direct folate and/or homocysteine- dependent actions are considered. dUMP deoxy-uridine monophosphate, dTMP deoxy-tymidine monophosphat, mtDNA mitochondriale DNA, APP amyloid precursor protein, BACE1 beta site amyloid precursor protein cleavage enzyme 1, PSEN1 presenilin1, PP2A protein phosphatase 2A

Hinterberger, M., Fischer, P. J Neural Transm (2013) 120:211–224



1. **Folate deficiency and homocysteine**
2. **Expression of β and γ secretases increased by regulated by methyl donor availability**
3. **Tau phosphorylation**
4. **Folate deficiency alters calcium dynamics and stimulates apoptosis**
5. **Folate deficiency and increases oxidative stress**
6. **Methyl donors are required for maintenance of neurotransmitters**
7. **Evidence from epidemiological studies**

THF Tetrahdrafolate; 5,10-MeTHF 5,10-methylene tetrahydrafolate; 5 MeTHF 5-Methyl tetrahydrafolate; Hcy homocysteine; SAM S-adenosyl methionine; S-adenosyl homocysteine; MS methionine synthase; GSH glutathione; GSSG Glutathione disulphide; PP2A Protein phosphatase 2; PSEN1 Presenilin-1; BACE1 Beta-secretase 1; APP amyloid precursor protein; AB β-amyloid; P-tau phosphorylated tau; NFTs neurofibrillary tangles; ROS reactive oxygen species.

Robinsona et al.,2018)

Treatment (none)

- April 2002, mice, vaccination with beta-amyloid helps

(i)Cholinesterase inhibitors.

Inhibitors of neurotransmitter acetylcholinesterase delay symptoms but don't cure.

These drugs work by boosting levels of cell-to-cell communication by preserving a chemical messenger that is depleted in the brain by Alzheimer's disease. Commonly prescribed cholinesterase inhibitors include donepezil (Aricept), galantamine (Razadyne) and rivastigmine (Exelon).

(ii)Memantine (Namenda). This drug works in another brain cell communication network and slows the progression of symptoms with moderate to severe Alzheimer's disease.