# DEMENTIA

FROM GENES TO PRACTICE

# Genetic Testing in Dementia

- What are the genes ?
- What are the available tests ?
- The proper use of Dementia genetic testing
- How best to offer genetic testing in dementia patients ?

# Alzheimer's disease genetics

- Classified into two subtypes depending on the age of onset

1. Early onset Alzheimer's Disease [EOAD]: **also called familial AD**
   - Starts before the age of 65 years, typically in late 40s and early 50s
   - Accounts for 1-5% AD patients
   - Most obvious family aggregation of AD patients
   - Mendelian autosomal dominant pattern of inheritance [<1% AD patients
2. Late onset Alzheimer's Disease [LOAD]: **also called sporadic AD**
   - Starts after the age of 65 years
   - Accounts for >95% of cases

# Early onset AD

- Caused by mutation into 3 genes
- Which is highly penetrant
- Genes encode protein involved in Amyloid Precursor Protein [APP] and Aβ generation

- Genes:
  - ***APP: Chromosome 21***
  - ***Presenilin 1 [PSEN1]: chromosome 14***
  - ***Presenilin 2 [PSEN2]: chromosome 1***

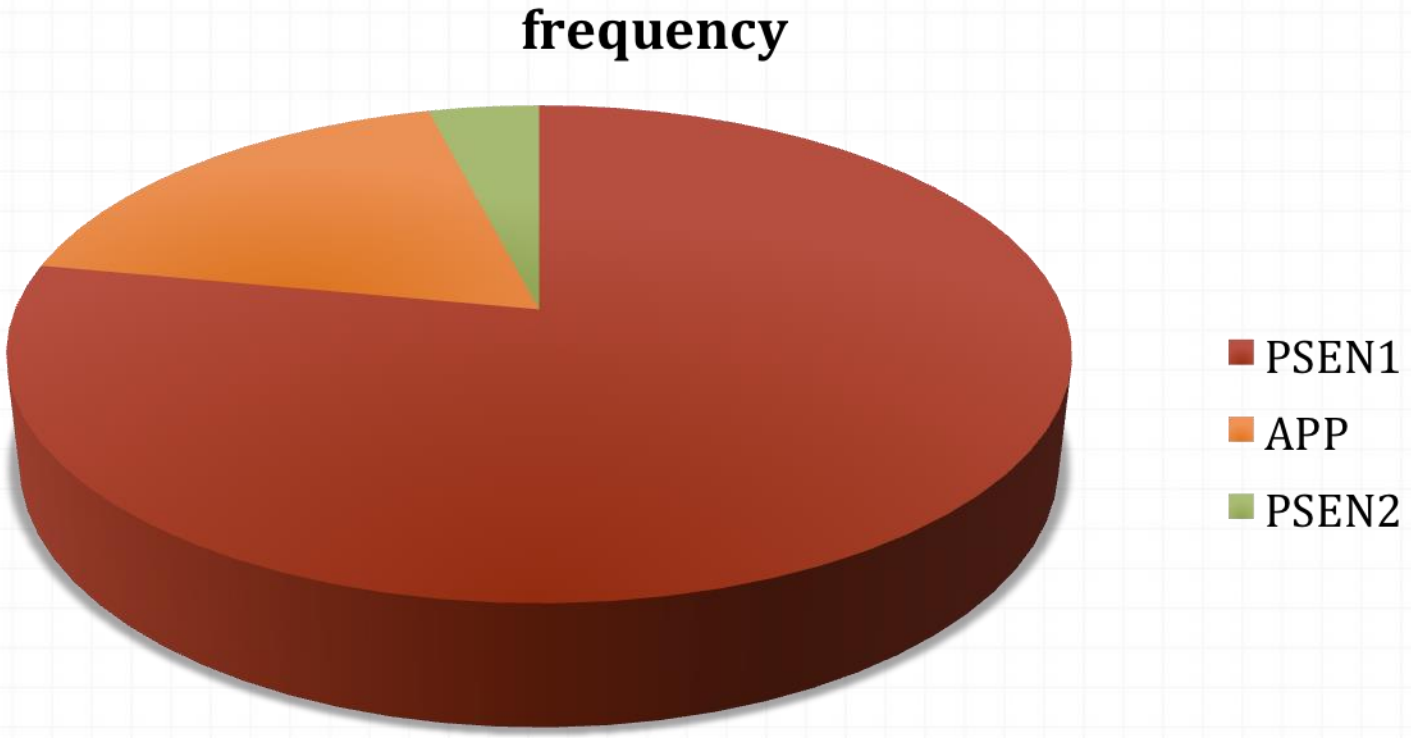
# Familial AD

- Approximately 25% of all AD is familial (i.e., two or more persons in a family have AD)
- Stringent criteria for ADEOAD is affected members in three generation with average onset prior to 60 years.
- 95% of familial AD is late-onset (after age 60-65 years) and 5% is early-onset (before age 65 years)
- 60% of early onset AD is familial
- Familial cases appear to have the same clinical and pathologic phenotypes as non-familial cases

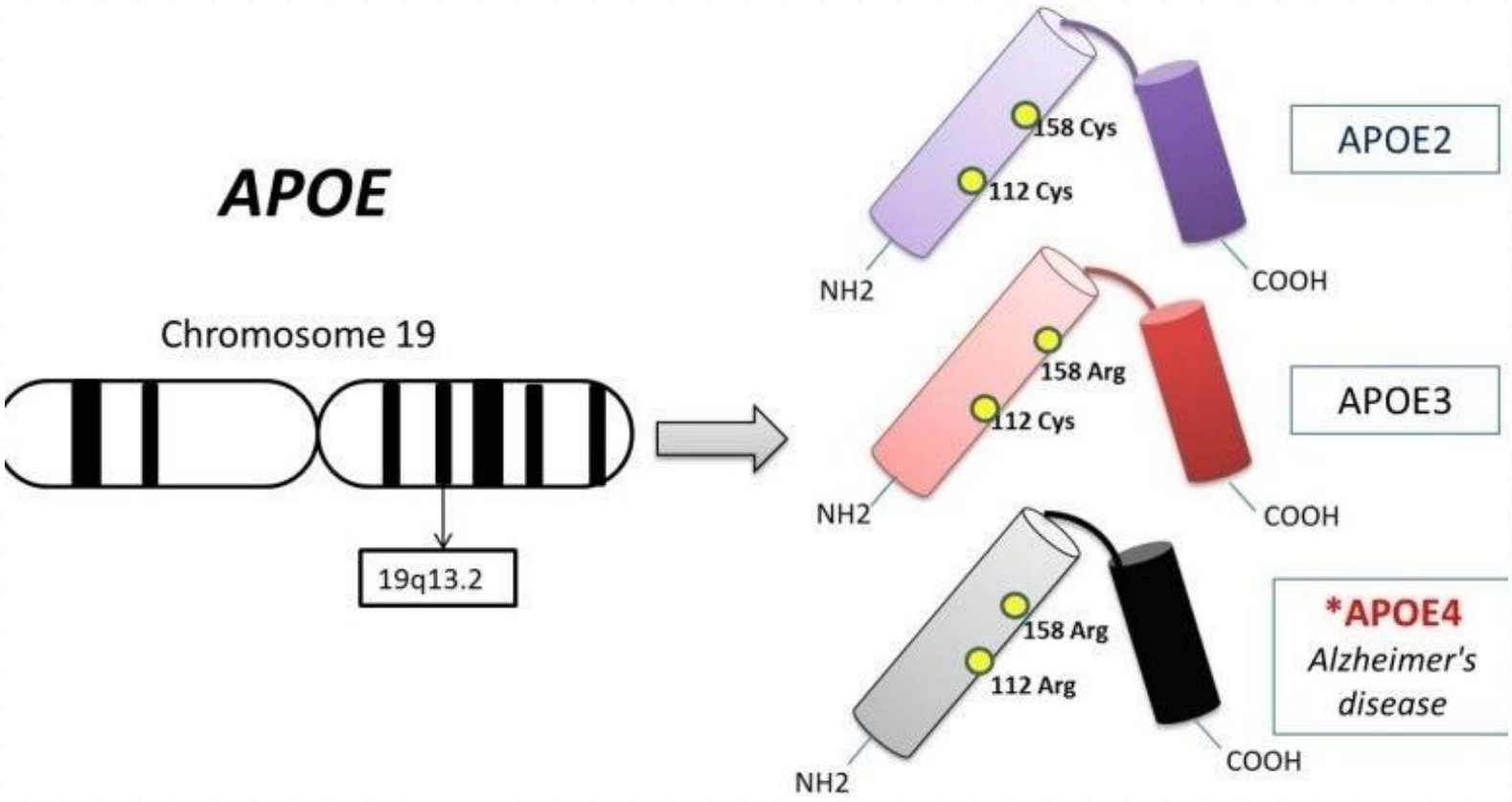
# PSEN 1 AND 2

- Mutations in the *PSEN1 and PSEN2* genes have been identified in EOAD families.
- These genes encode for presenilin 1 and presenilin 2 proteins respectively, required **for □-secretase to produce A□ from APP.**
- To date, approximately 200 different AD-related *PSEN1* mutations and 22 AD-related *PSEN2 mutations have been* detected.
- The presenilins act as aspartyl proteases that carry out □-secretase cleavage of APP to produce A□. ***Therefore, mutations in the PSEN1 and PSEN2 genes increase the ratio of A□42 to A□40.***

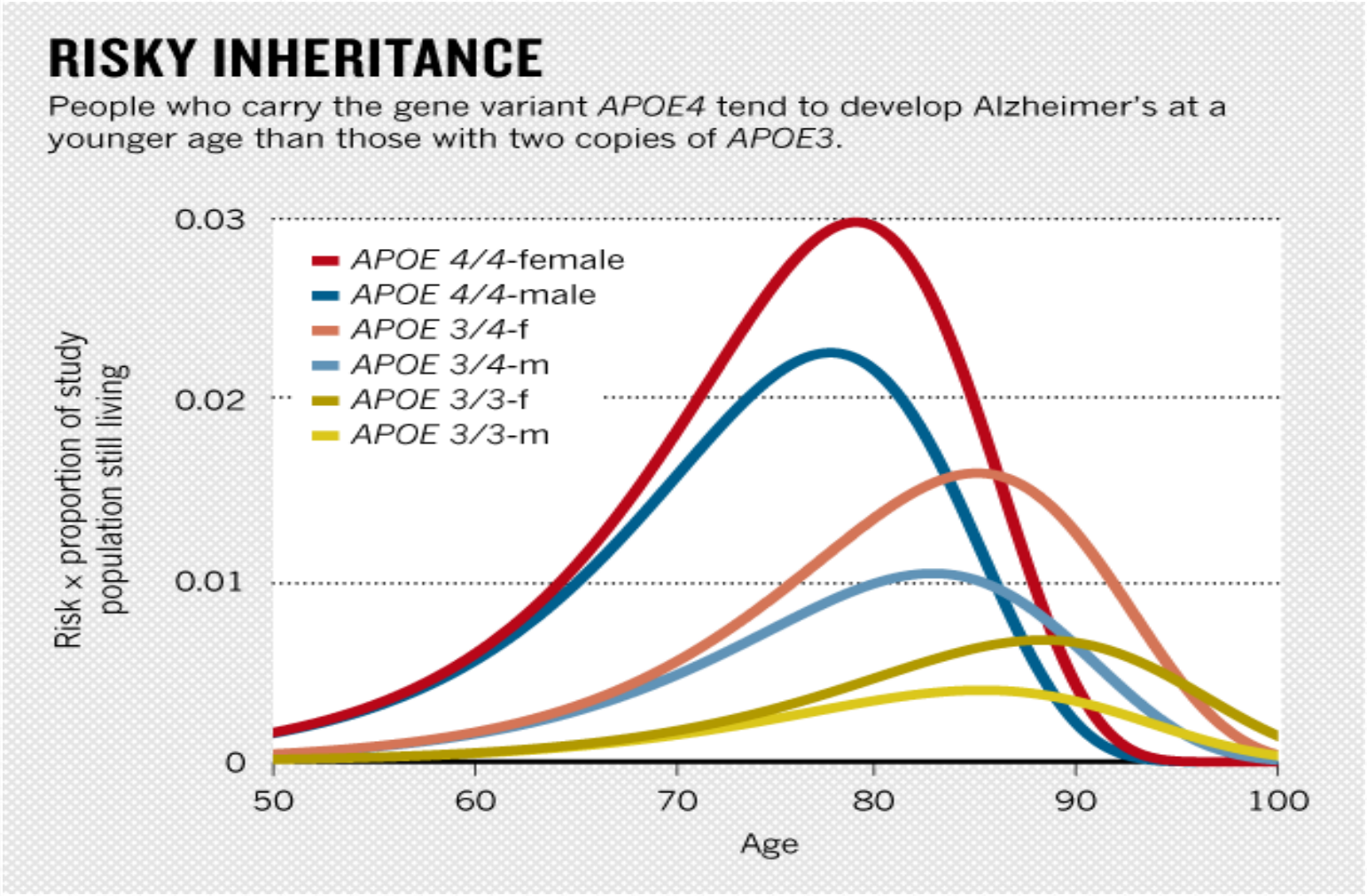
# Proportion of Genetic Cause of EOAD



# Apolipoprotein E

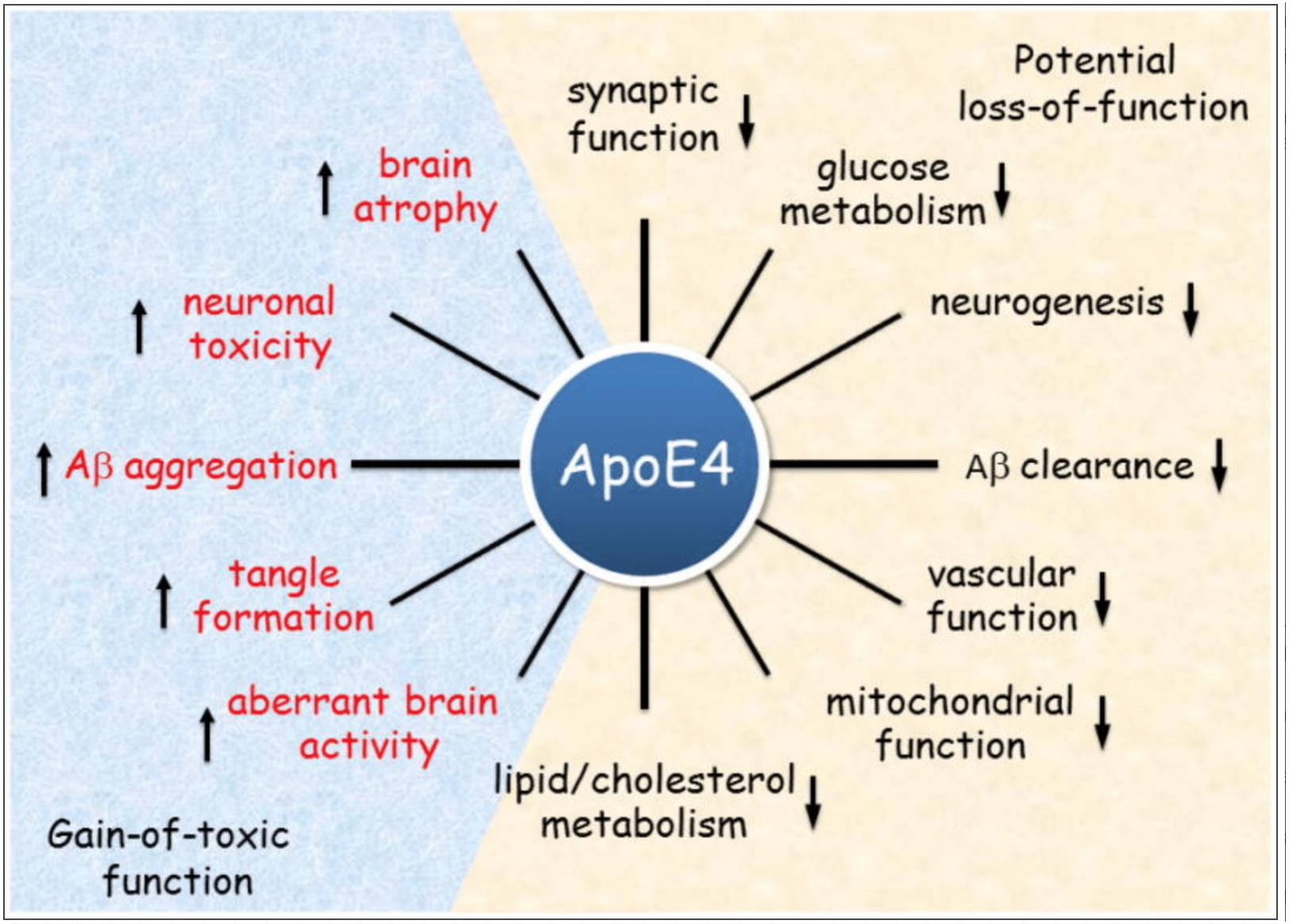


# Age of onset effect of Apo E




Nature 510, 26–28 (05 June 2014)

| Genotype | E2/E2 | E2/E3 | E2/E4 | E3/E3 | E3/E4 | E4/E4 |
|---|---|---|---|---|---|---|
| Disease Risk | 40% less likely | 40% less likely | 2.6 times more likely | Average risk | 3.2 times more likely | 14.9 times more likely |




Liu et al, Nat Rev Neurol. 2013; 9:106-118.

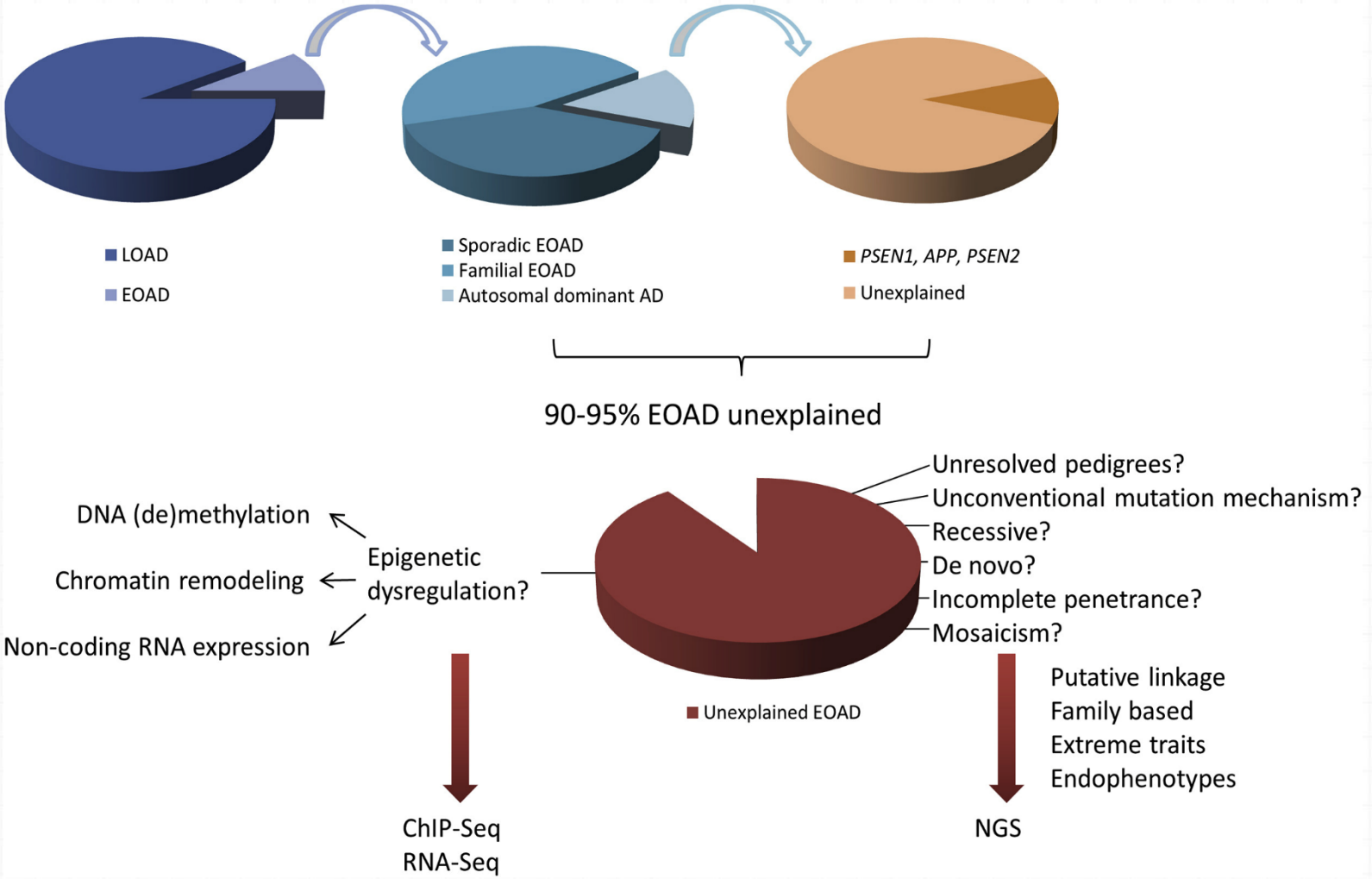
# *APOE4* and AD

- The association of the *APOE* e4 allele with AD is significant; however, *APOE* genotyping alone is neither fully specific nor sensitive.

- 25% of population is E4 carrier, 2% homozygote
- Risk is increased 3-15 times in E4 positive cases

- While *APOE* genotyping may have an adjunct role in the diagnosis of AD in symptomatic individuals, it appears to have no role at this time in predictive testing of asymptomatic individuals.

# Genetic Landscape of Alzheimer disease




R. Cacace et al. / Alzheimer's & Dementia 12 (2016) 733-748734

# Genome wide study revealed other loci for LOAD

- **GWAS [Genome wise association studies] have identified candidate genes associated with LOAD:**
- *Clusterin (CLU)*
- *Complement component receptor 1 (CR1)*
- *Phosphatidylinositol binding clathrin assembly protein (PICALM)*
- *Bridging integrator 1 (BIN1)*
- *Sialic acid binding Ig-like lectin (CD33)*
- *CD2-associated protein (CD2AP)*
- *Membrane spanning 4A gene cluster (MS4A6A/MS4A4E)*
- *Ephrin receptor A1 (EPHA1)*
- *ATP-binding cassette transporter (ABCA7)*

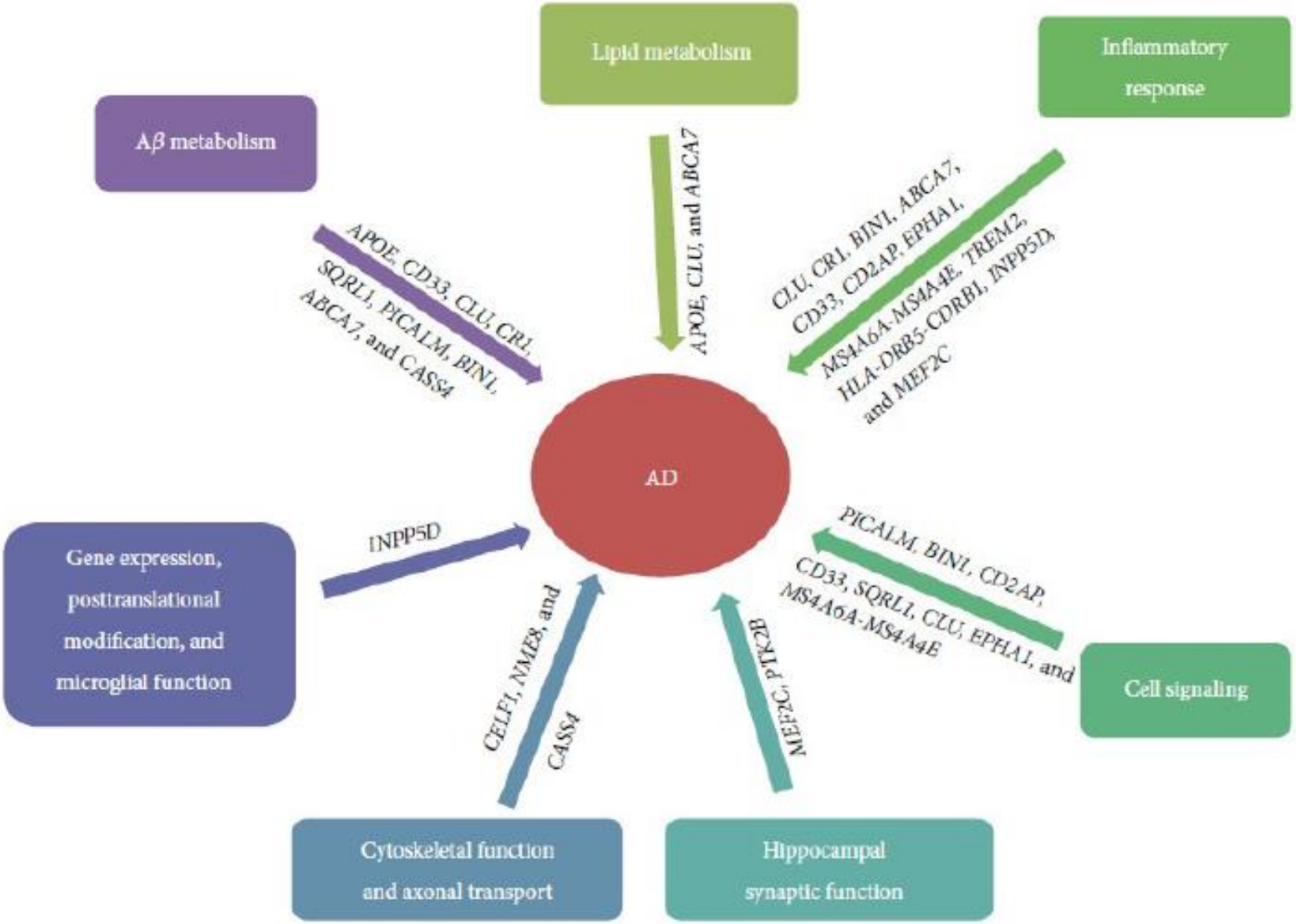
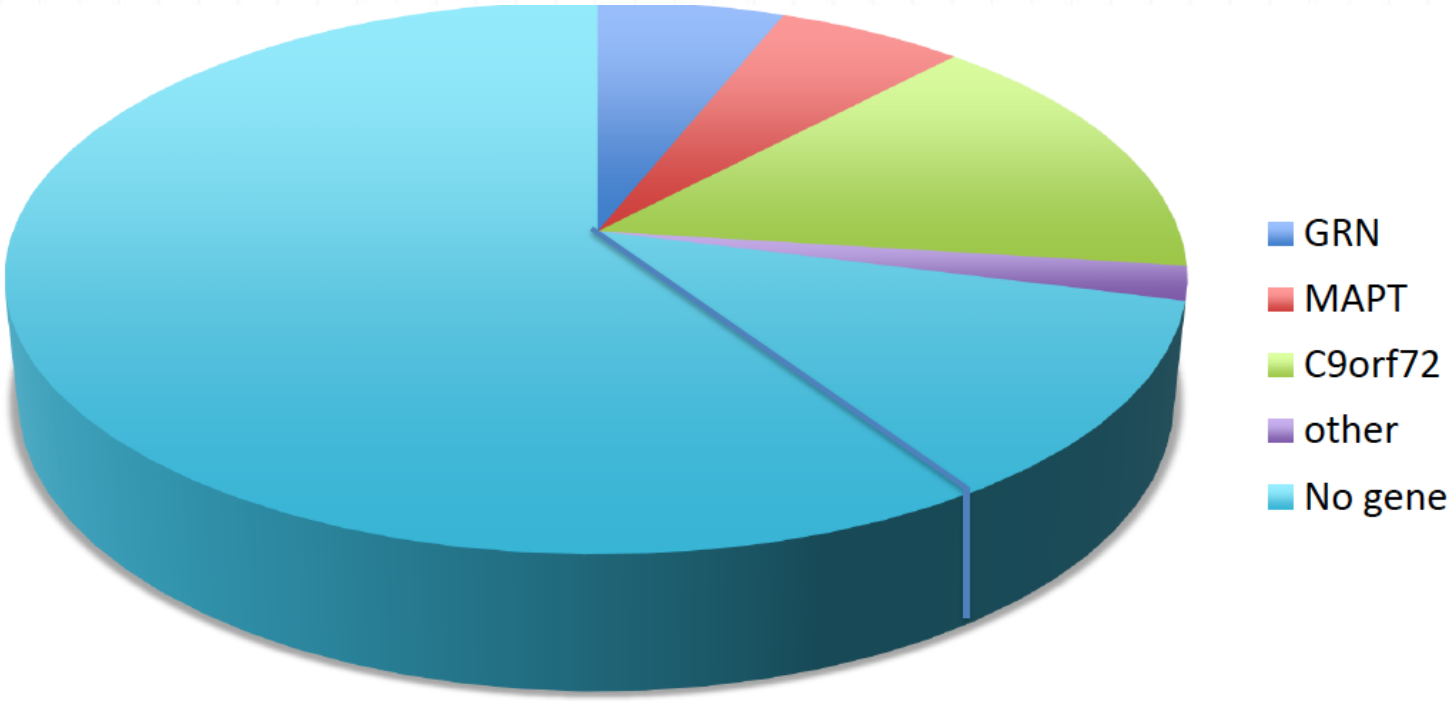



FIGURE 1: Potential pathways of susceptibility genes involved in the pathogenesis of AD.

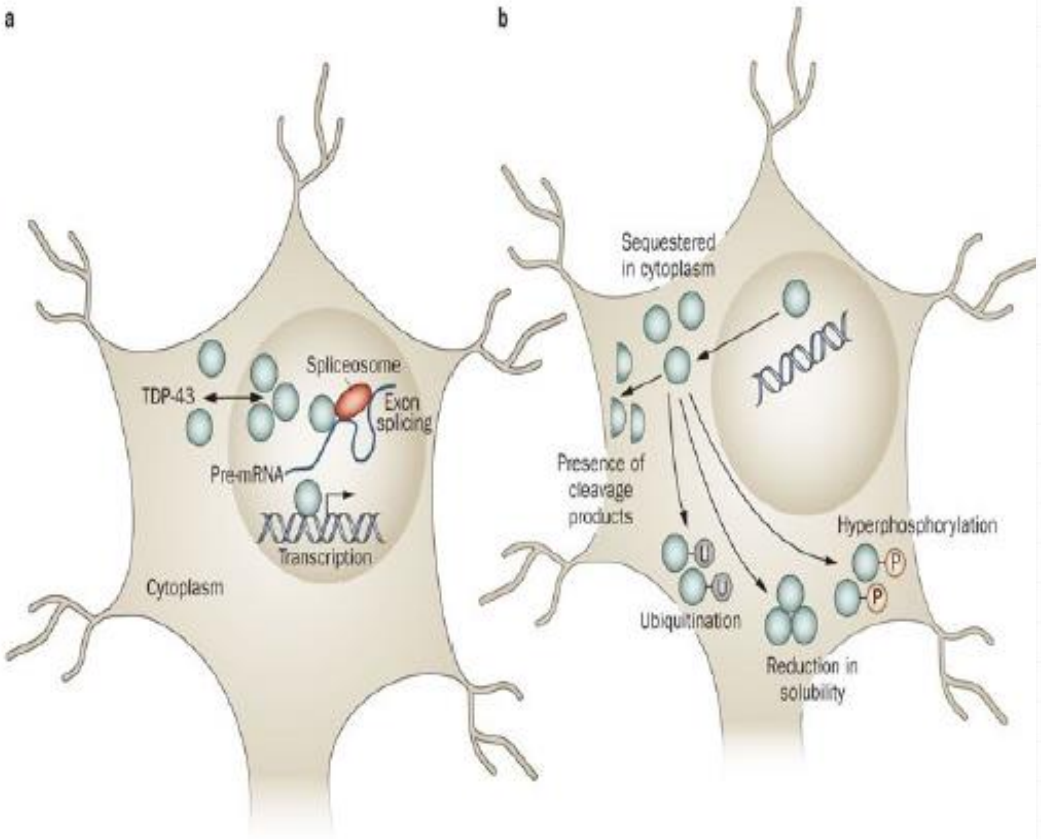
# Genetic Loci for FTD




VCP, CHMP2B, TBK1, TARDP, FUS

# PGRN Gene

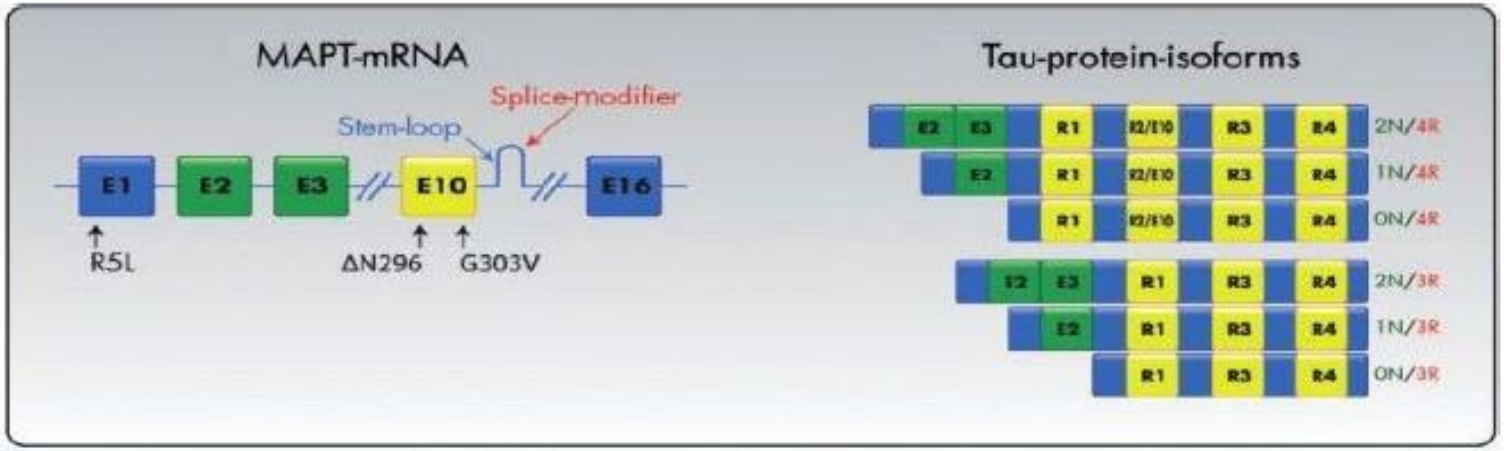
- Encodes for PGRN protein
- PGRN, expressed in neurons and activated microglia
- involved in tissue remodeling by activating signaling cascades that control cell cycle progression and cell motility
- PGRN mutations occur in 26% of familial FTD cases.
- PGRN mutation is associated with the expression of truncated and hyperphosphorylated isoforms of TDP-43 (TAR DNA binding protein 43).
- **Under pathologic conditions, TDP-43 relocates from the neuronal nucleus to the cytoplasm resulting in loss of TDP-43 nuclear functions**



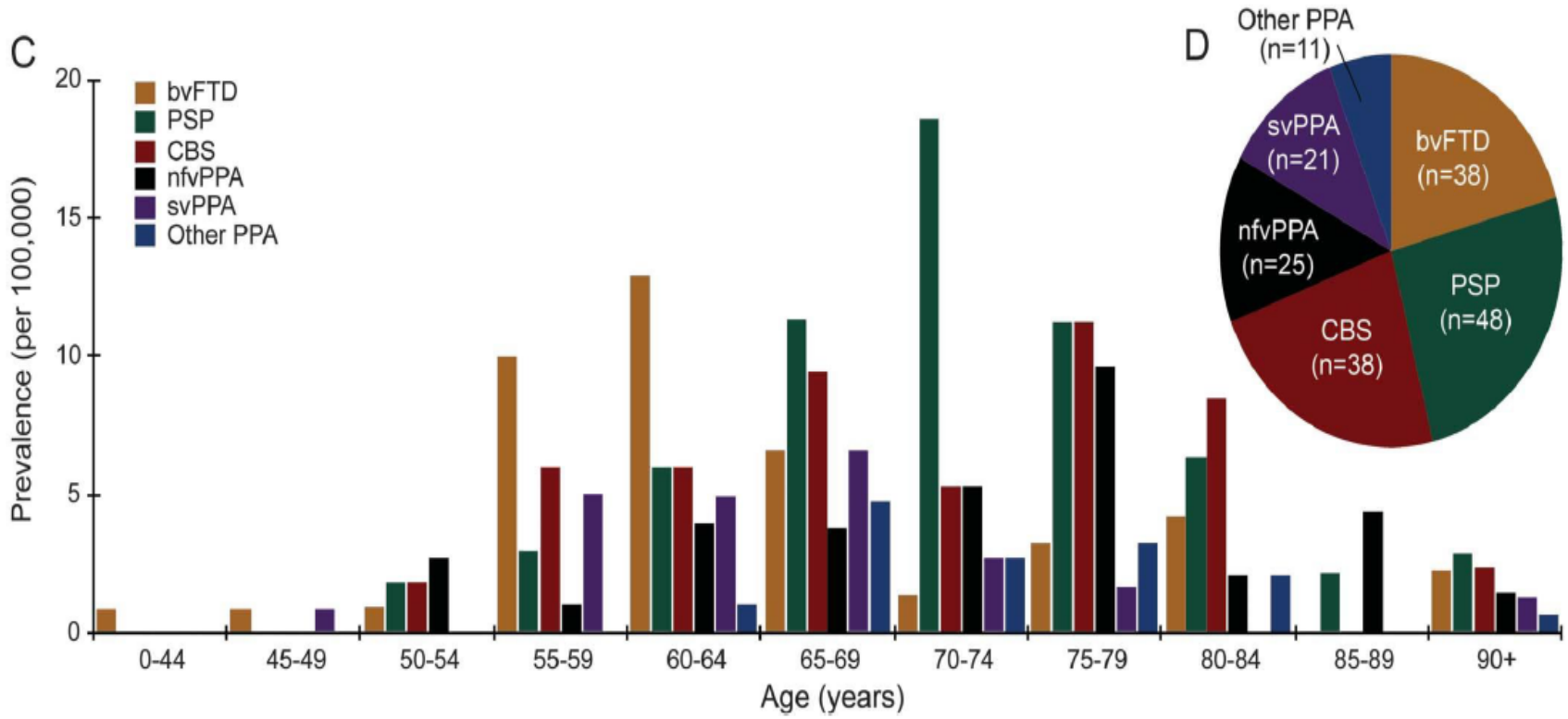

(Presence of this ubiquinated protein outside the nucleus, in cytoplasm suggest that it has some important regulatory functions in cell, and loss of which results in death of affected neurons, same mutation is seen in patients with ALS)

# MAPT Gene

- MAPT having 37 mutations within the microtubule-binding region or exon 10, produce tau isoforms with either three microtubule-binding repeats (**3R-tau**) or four repeats (**4R-tau**).
- **In Pick's disease 3R-tau accumulates.**
- Missense and deletion mutations disrupts the binding of tau to microtubules resulting in accumulation of unbound tau.
- MAPT mutations on exons 1, 9, and 11 to 13 account for the **dementia-dominant phenotype**.
- The **parkinsonism-plus–predominant phenotype** is associated with mutations within intron and exon 10, leading to the overproduction of 4R-tau isoforms.



# Syndromes and age




Coyle-Gilchrist et al. Neurology 2016

# Genotype- Phenotype Correlation

- GRN — bvFTD, PPA, TDP-43 related FTD/MND
- MAPT — bvFTD, FTD, PSP, CBS, some cases of MSA
- C9Orf72 — bvFTD, FTD/MND, MND
- VCP — FTD and Paget disease
- CHMP2B — FTD, MND, FTD/MND

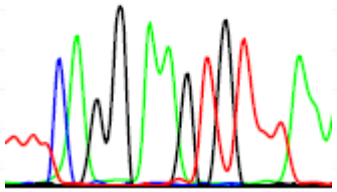
# Other genetic causes of Dementia

- Dementia with Lewy body : Synucleinopathy
- Vascular dementia : CADASIL
- Dementia with PD : Synucleinopathy, GBA
- Polyglutamine expansion diseases : HD, SCA, DRPLA

# What are the available tests ?

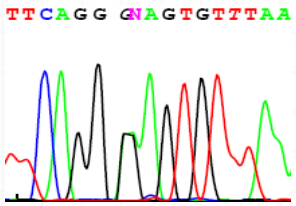
- Single gene testing
  - Whole gene screening : PCR sequencing
  - Target mutation testing : PCR
- Panel gene testing  (next generation sequencing)
  - Clinical syndrome guided panel test : AD, FTD
  - Dementia gene panel testing

TT CAGG AAGTGTTTAA



**Normal control**

**1**

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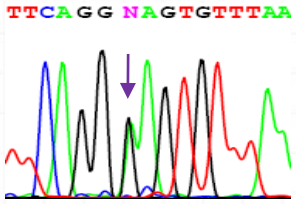


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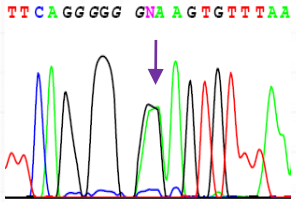


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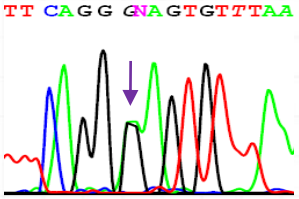
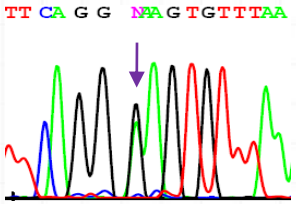



**5**

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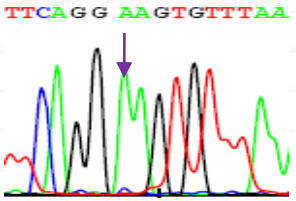


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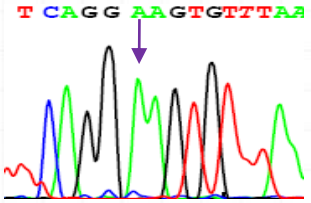
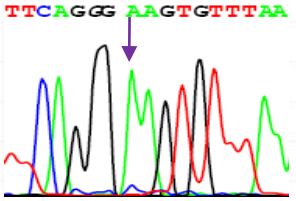
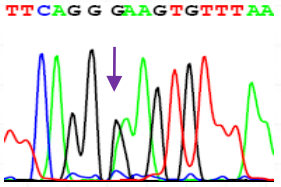


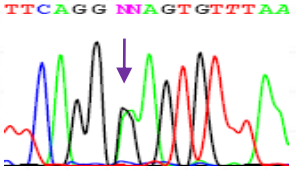

**9**



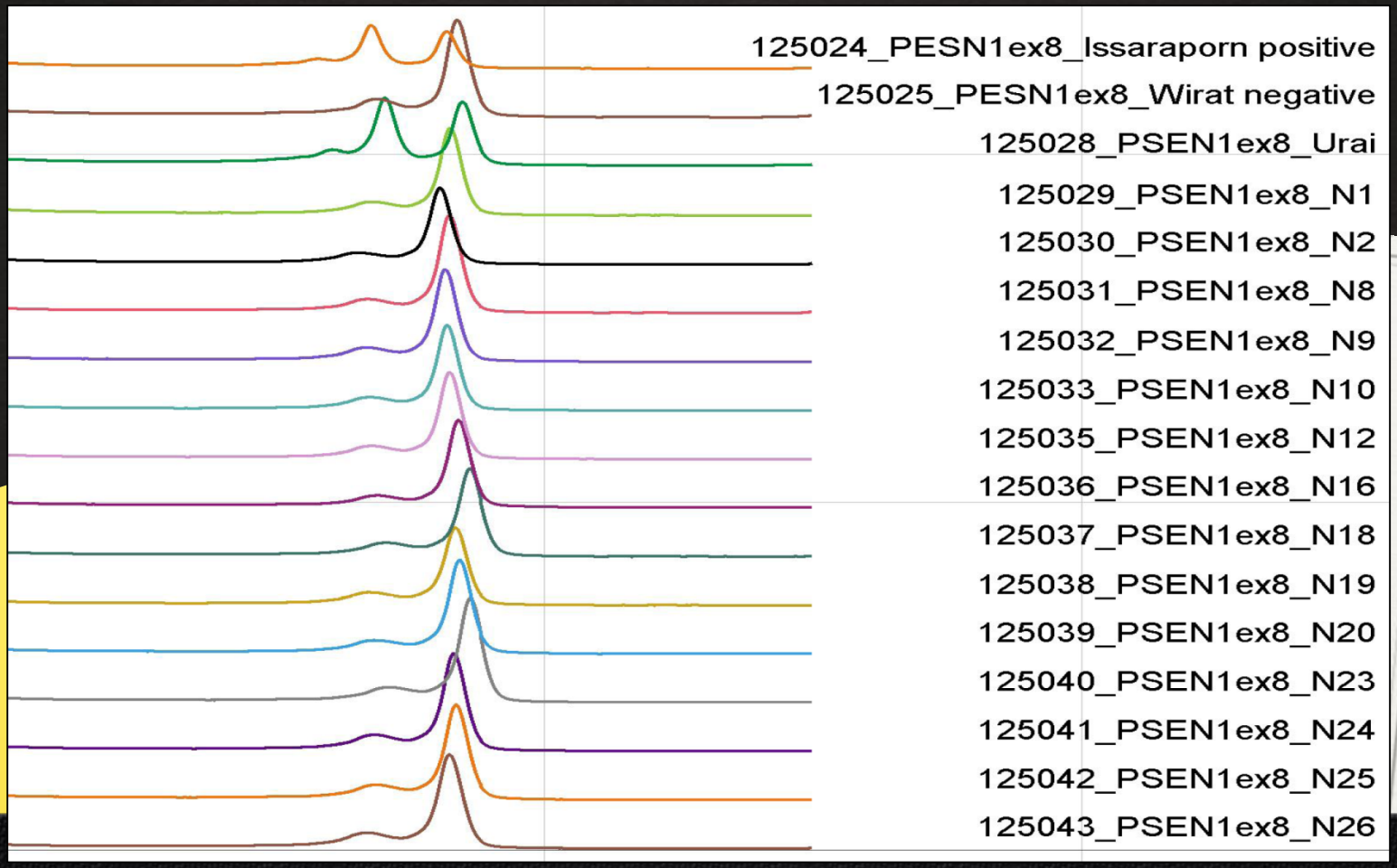

**10**




**11**



# Screening of E184G by DHPLC in 109 normal controls

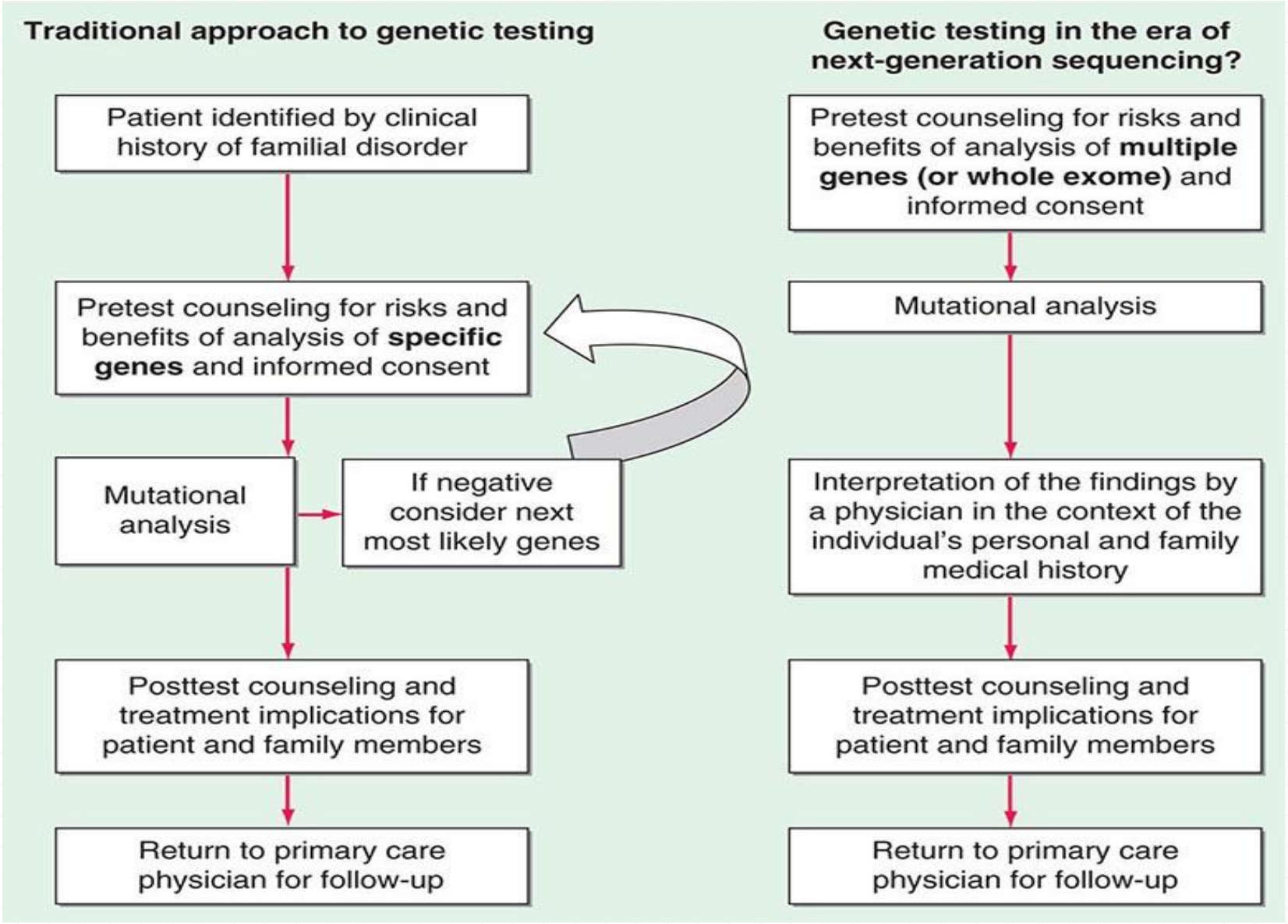


AD genes

FTD genes

Other rare genes

Single NGS Panel


Traditional approach to genetic testing
Patient identified by clinical history of familial disorder
Pretest counseling for risks and benefits of analysis of **specific genes** and informed consent
Mutational analysis
If negative consider next most likely genes
Posttest counseling and treatment implications for patient and family members
Return to primary care physician for follow-up
Genetic testing in the era of next-generation sequencing?
Pretest counseling for risks and benefits of analysis of **multiple genes (or whole exome)** and informed consent
Mutational analysis
Interpretation of the findings by a physician in the context of the individual's personal and family medical history
Posttest counseling and treatment implications for patient and family members
Return to primary care physician for follow-up

| Dementia gene 27 gene panel | | | |
|---|---|---|---|
| **Condition** | **OMIM** | **Gene** | **Primary transcript** |
| Cerebral amyloid angiopathy, APP Related | 605714 | *APP* | NM_000484.3 |
| Alzheimer disease 1, familial, AD | 104300 | *APP* | NM_000484.3 |
| Frontotemporal dementia and/or amyotrophic lateral sclerosis 2, FTDALS2 | 615911 | *CHCHD10* | NM_001301339.1 |
| Frontotemporal Dementia, Chromosome 3-Linked, FTD3 | 600795 | *CHMP2B* | NM_014043.3 |
| Leukoencephalopathy, diffuse hereditary, with spheroids, HDLS | 221820 | *CSF1R* | NM_005211.3 |
| Cerebrotendinous xanthomatosis, CTX | 213700 | *CYP27A1* | NM_000784.3 |
| Perry syndrome | 168605 | *DCTN1* | NM_004082.4 |
| Neuropathy, hereditary sensory, type IE, HSN1E | 614116 | *DNMT1* | NM_001005360.2 |
| Amyotrophic lateral sclerosis 6, with or without frontotemporal dementia, ALS6 | 608030 | *FUS* | NM_004960.3 |
| Frontotemporal lobar degeneration with TDP43 inclusions, GRN related | 607485 | *GRN* | NM_002087.3 |
| Inclusion body myopathy with early-onset Paget disease with or without frontotemporal dementia 2, IBMPFD2 | 615422 | *HNRNPA2B1* | NM_031243.2 |
| Cerebral arteriopathy, autosomal recessive, with subcortical infarcts and leukoencephalopathy, CARASIL | 600142 | *HTRA1* | NM_002775.4 |
| Cerebral amyloid angiopathy, ITM2B-related, 1 | 176500 | *ITM2B* | NM_021999.4 |
| Frontotemporal Dementia, FTD | 600274 | *MAPT* | NM_001123066.3 |
| Amyotrophic lateral sclerosis 21, ALS21 | 606070 | *MATR3* | NM_199189.2 |
| Cerebral arteriopathy with subcortical infarcts and leukoencephalopathy, CADASIL | 125310 | *NOTCH3* | NM_000435.2 |
| Gerstmann-Straussler disease, GSD | 137440 | *PRNP* | NM_000311.3 |
| Alzheimer disease, type 3, AD3 | 607822 | *PSEN1* | NM_000021.3 |
| Alzheimer disease-4, AD4 | 606889 | *PSEN2* | NM_000447.2 |
| Mast syndrome | 248900 | *SPG21* | NM_016630.6 |
| Frontotemporal dementia and/or amyotrophic lateral sclerosis 3, FTDALS3 | 616437 | *SQSTM1* | NM_003900.4 |
| Amyotrophic lateral sclerosis 10, with or without FTD, ALS10 | 612069 | *TARDBP* | NM_007375.3 |
| Frontotemporal dementia and/or amyotrophic lateral sclerosis 4, FTDALS4 | 616439 | *TBK1* | NM_013254.3 |
| Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy, PLOSL | 221770 | *TREM2* | NM_018965.3 |
| Amyotrophic lateral sclerosis 22 with or without frontotemoral dementia, ALS22 | 616208 | *TUBA4A* | NM_006000.2 |
| Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy, PLOSL | 221770 | *TYROBP* | NM_006000.2 |
| Amyotrophic lateral sclerosis 15, with or without frontotemporal dementia, ALS15 | 300857 | *UBQLN2* | NM_013444.3 |
| Amyotrophic lateral sclerosis 14, with or without frontotemporal dementia, ALS14 | 613954 | *VCP* | NM_007126.3 |

# Example of UK NGS Dementia Panel

Email: matthew.jones@manchester.ac.uk


# VARIANT CLASSIFICATION RESULT

POPULATION DATA

COMPUTATIONAL DATA

FUNCTIONAL DATA

SEGREGATION DATA

DE NOVO DATA

ALLELIC DATA

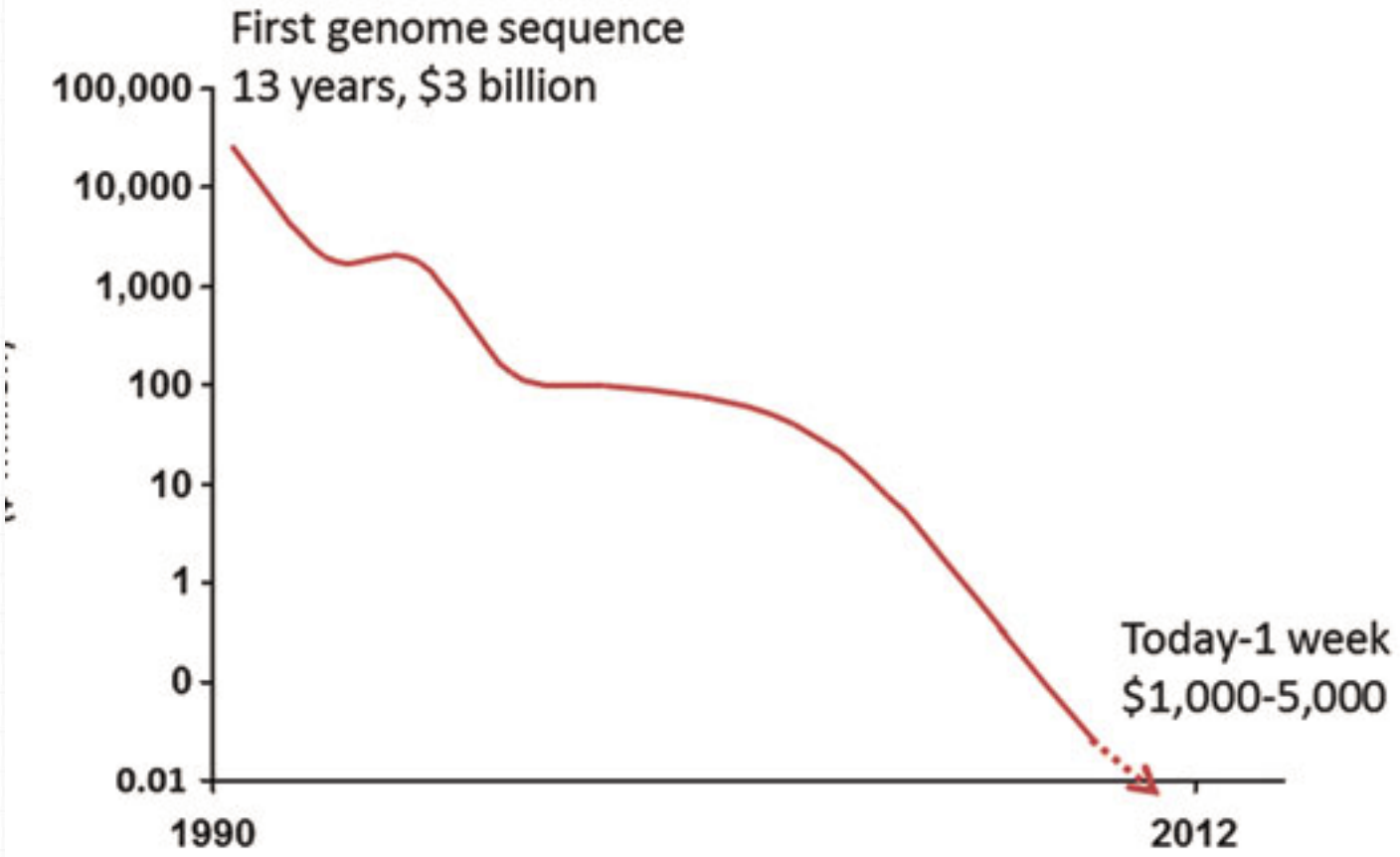
# VARIANT CLASSIFICATION

# Drawbacks of Multi-Gene Panel Testing

- Higher rate of Ambiguous Results called Variants of Uncertain Significance or VUS
- Common: The VUS rate for gene panels are 20-40%
- Normal: We will likely find a one or more variations in one or more of the genes on this test for which the clinical ramifications are unknown
- Probably nothing: 90-95% of VUS results are eventually found to be benign
- Will not change management: You will be followed based on your family history and NOT the VUS until/unless it is proven to be pathogenic
- Keep contact information up-to-date: Most labs keep an eye on their VUS results and will issue a new report if it is reclassified. Your genetic counselor will recontact you to let you know this new information.

The James
The Ohio State University
Comprehensive Cancer Center

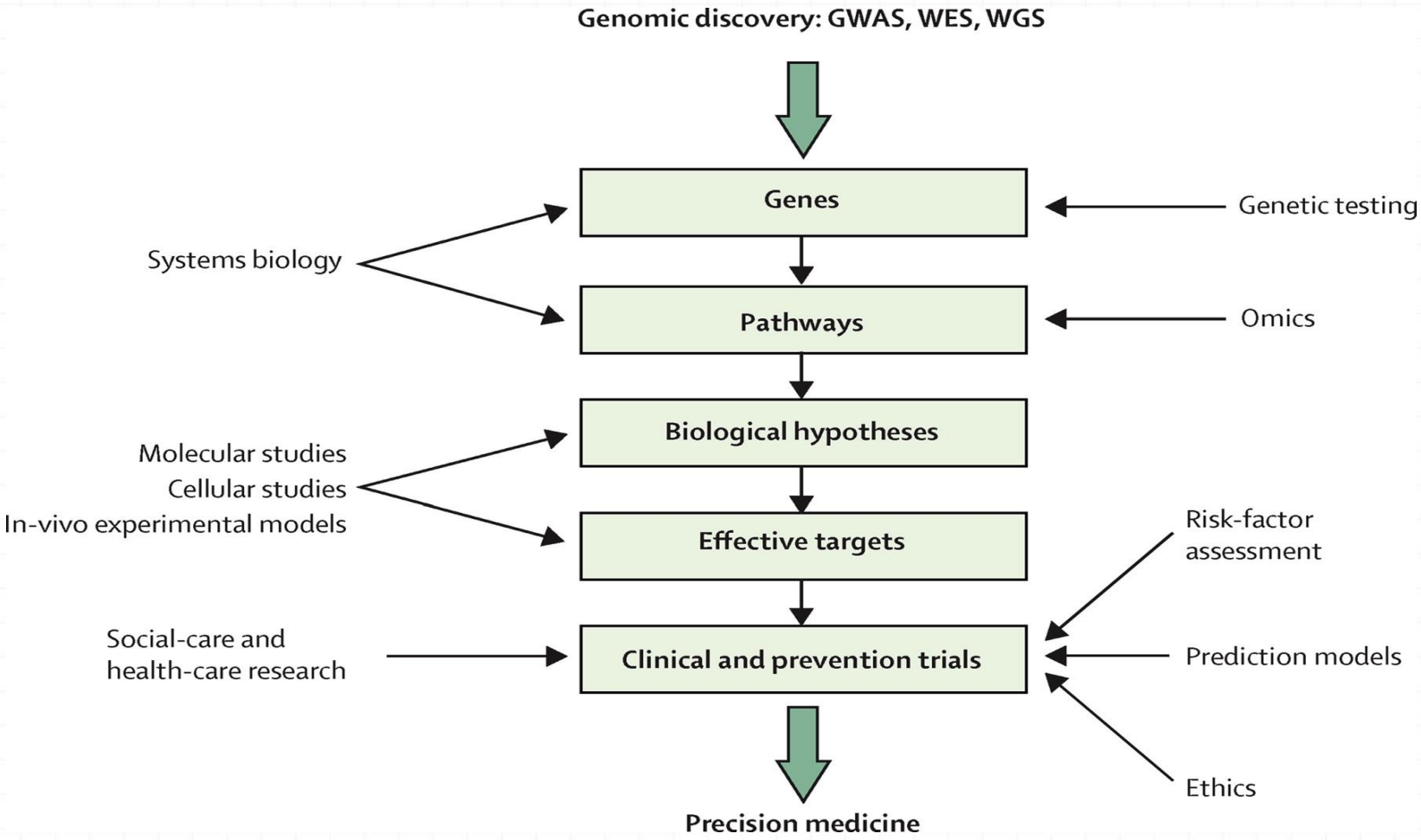
# Changing Cost of DNA Sequencing



# Why offer genetic testing ?

- Specific treatment
- Family counseling and further pre-symptomatic testing in family member
- Molecular epidemiology study

# Benefit of Genetic Study in Dementia




Lancer Neurology 2016

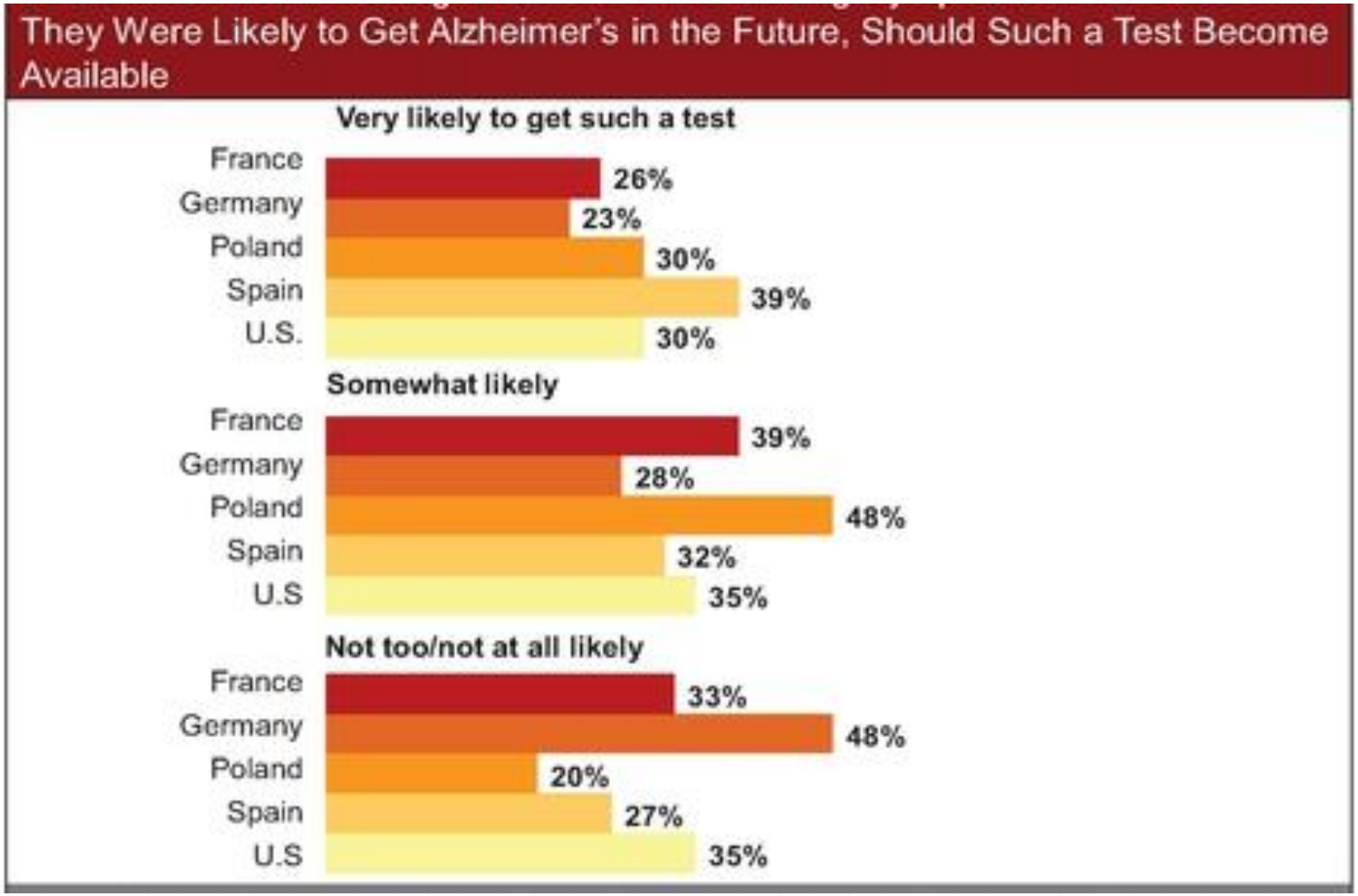
# The proper use of Dementia genetic testing

- Symptomatic Diagnosis of Familial EOAD, FTD
- Symptomatic Diagnosis of Sporadic EOAD, FTD
- Symptomatic Diagnosis of familial LOAD
- Symptomatic Diagnosis of Sporadic LOAD, sporadic FTD

- Pre-symtomatic diagnosis of the above

- RCT trial showed that testing can be successfully done

# Public Attitude for Alzheimer Testing




Alzheimer Europe 2016

# Consideration for offering Dementia Testing

- Autonomy : informed
- Non-directive
- Beneficence : pros and cons detail counseling
- Conflict of interest
- Confidentiality
- Right to know and Not to know
- Testing in young adult and children
- PND, PGD testing

# Genetic counseling in sporadic AD

- The overall lifetime risk to any individual of developing dementia is approximately 10%-12%
- First-degree relatives of a person with AD have a cumulative lifetime risk of developing AD of approximately 15%-30% (2.5 times background risk)

# Conclusion

- Genetic testing in dementia is now out of the research box
- Panel testing is likely to be recommended
- VUS will still be an issue
- Counseling must be thorough prior to testing