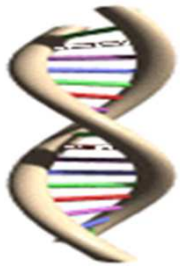
I Lincei per la Scuola
Fondazione

I LINCEI PER UNA NUOVA DIDATTICA NELLA SCUOLA: UNA RETE NAZIONALE
Polo di Firenze
A.S. 2018/2019

Titolo corso: BIOMOLECOLE: STRUTTURA E FUNZIONI

Genetica delle demenze

Benedetta Nacmias



UNIVERSITÀ
DEGLI STUDI
FIRENZE
NEUROFARBA
DIPARTIMENTO DI NEUROSCIENZE,
PSICOLOGIA, AREA DEL FARMACO
E SALUTE DEL BAMBINO

Mappature delle competenze

- Antibiotici naturali per superare il problema della farmaco-resistenza
- Lipidi biuoattivi
- Ruolo del calcio nella trasmissione del segnale cellulare
- Correlazione tra genetica e malattie neurodegenerative
- Proteine terapeutiche.

COMMENT

SUPERCOMPUTING Approximate processing will advance modelling p.32 | **AUTUMN BOOKS** Grande dame of food politics takes on the soft-drinks industry p.34 | **CLIMATE** Geoengineering debated, with erudition and poetry p.38 | **EARTH** Marking the centenary of the book that proposed continental drift p.43

1989, Pre-HGP Banbury meeting. Francis Collins & James Watson in top row.

1990, Washington University School of Medicine. Millyard Dixon & Eric Green.

1997, HGP meeting at Cold Spring Harbor. E Green, R Myers, J Witkowski & R Gibbs.

Twenty-five years of big biology

The Human Genome Project, which launched a quarter of a century ago this week, still holds lessons for the consortium-based science it ushered in, say **Eric D. Green, James D. Watson** and **Francis S. Collins.**

Twenty-five years ago, the newly created US National Center for Human Genome Research (now the National Human Genome Research Institute; NHGRI), which the three of us have each directed, joined forces with US and international partners to launch the Human Genome Project (HGP). What happened next represents one of the most historically significant scientific endeavours: a 13-year quest to sequence all three billion base pairs of the human genome.

Even just a few years ago, discussions surrounding the HGP focused mainly on what insights the project had brought or would bring to our understanding of human disease. Only now is it clear that, as well as dramatically accelerating biomedical research, the HGP initiated a new way of doing science.

As biology's first large-scale project, the HGP paved the way for numerous consortium-based research ventures. The NHGRI alone has been involved in launching more than 25 such projects since 2000. These have presented new challenges to biomedical research — demanding, for instance, that diverse groups from different countries and disciplines come together to share and analyse vast data sets.

It is easy for young researchers to forget that many of the problems they are trying to solve today had not even been thought about by their predecessors a quarter of a century ago. Equally easy to lose sight of are the insights that the HGP still offers to those pursuing big science projects. In fact, we think that the success of today's consortium-based science depends on six key lessons from the HGP.

SIX LESSONS

Embrace partnerships. By necessity, the HGP broke the mould of individual researchers toiling away in isolation to answer a small set of scientific questions. It also ran against the grain of hypothesis-driven research, focusing instead on the discovery of fundamental information that would inform many follow-on investigations.

The HGP brought together more than 2,000 researchers from many countries, disciplines and levels of seniority, with subgroups answering to different funding agencies. Success stemmed from: strong ▶

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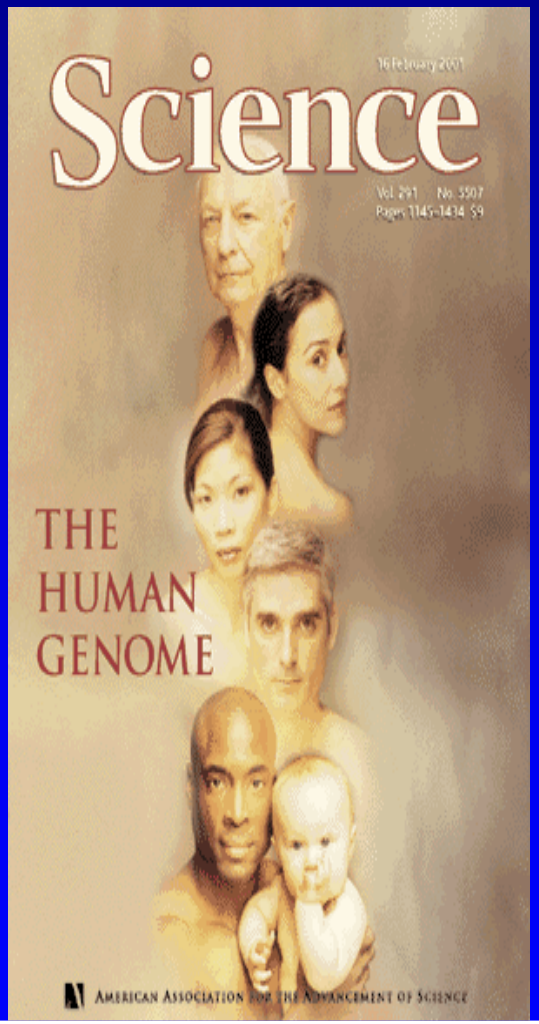
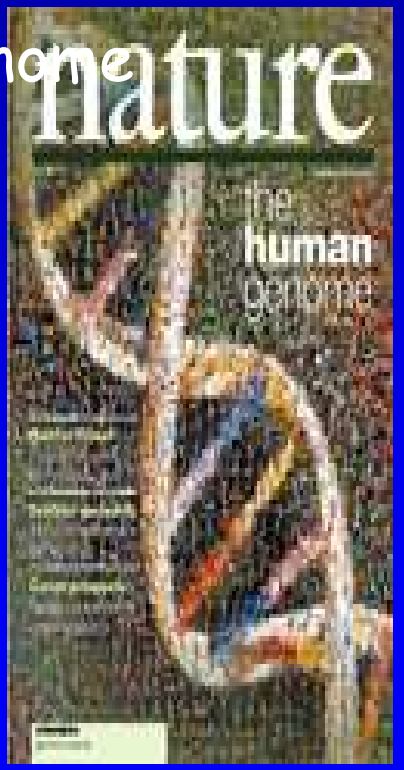
Early days: a DNA-sequencing lab in 1994.

By 2006, DNA sequencing required much less manpower.

The face of the human genome. A scientific milestone of Enormous proportions, the sequencing of the human genome will impact all of us in diverse ways-from our views of ourselves as human beings to new paradigms in medicine.



scientific announcement
of the
sequencing of
the human genome

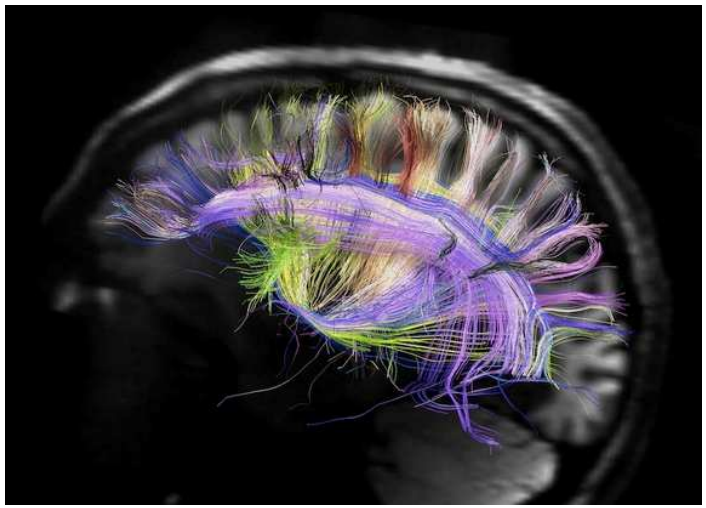


2001

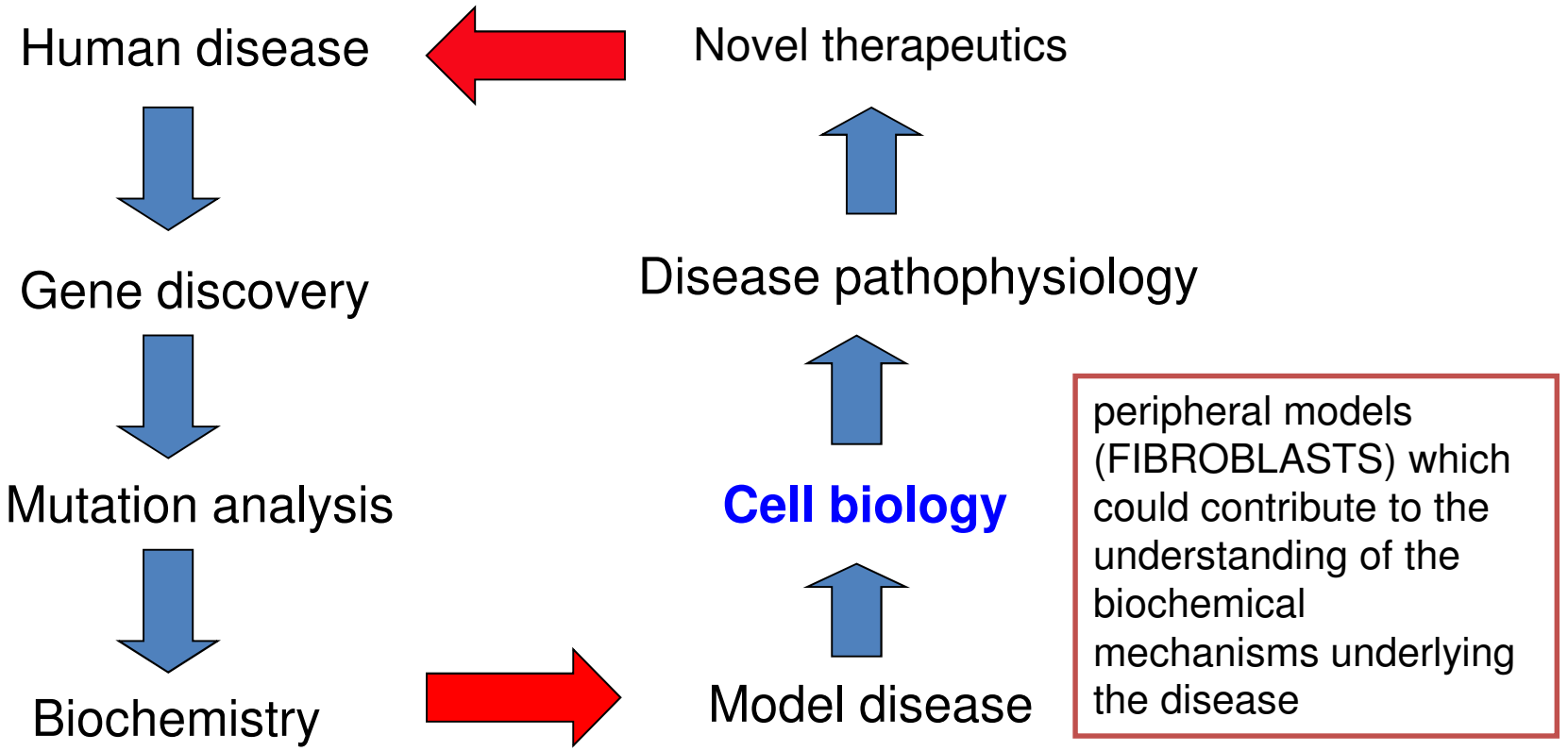
2001 Sequenziamento del genoma umano – ha rappresentato l'apice di uno sforzo decennal e comune di centinaia di scienziati dei migliori laboratori Ci ha permesso di avere una stima quasi definitiva del numero di geni (**circa 25mila)** e delle proteine codificate,

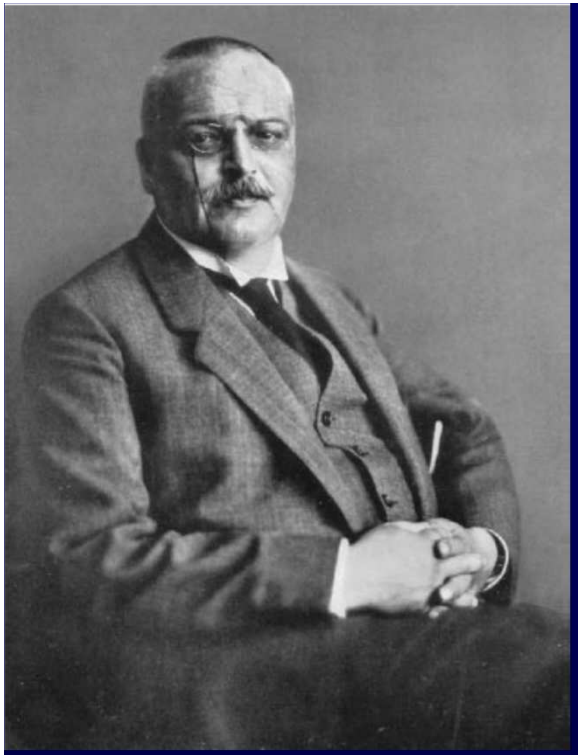
84% dei geni umani sono espressi a livello del cervello

I neurologi sono interessati
Alle nuove modalità diagnostiche
con la genetica molecolare

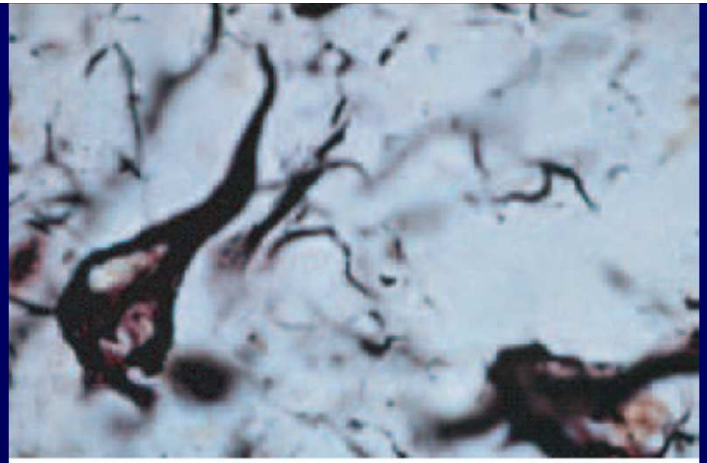


THE PROMISE OF HUMAN GENETICS

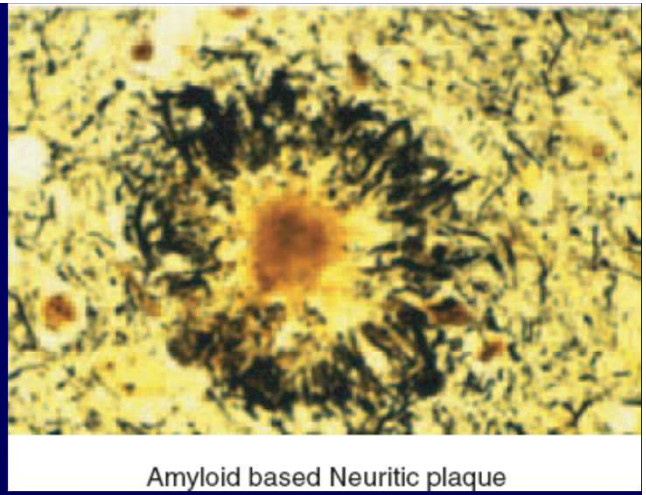




Alois Alzheimer (1864–1915).

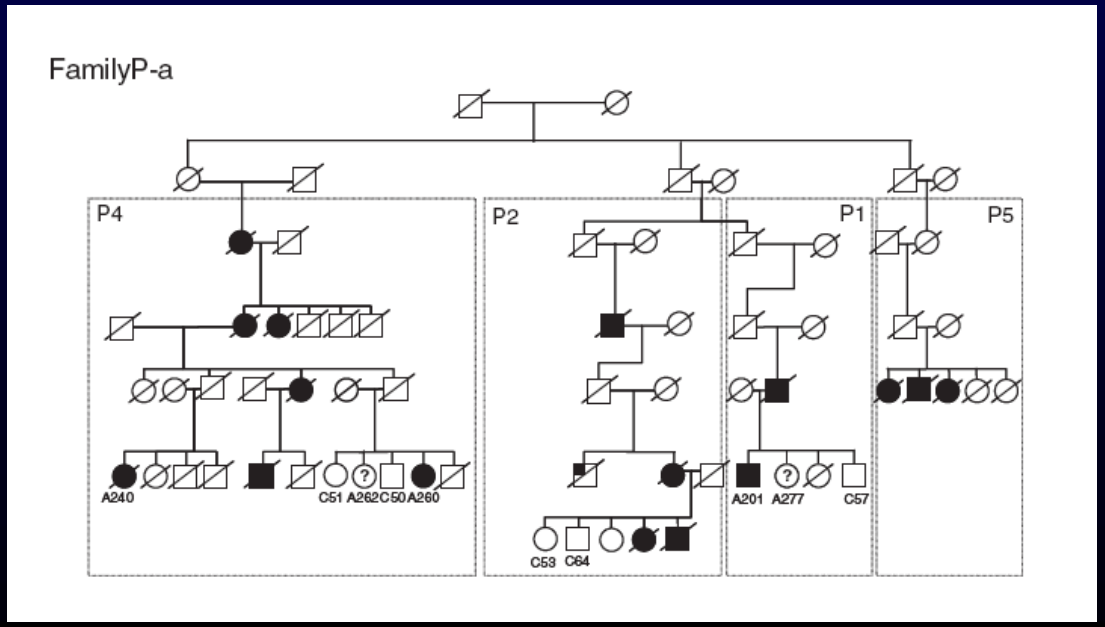


Tau based neurofibrillary tangle



Amyloid based Neuritic plaque

Genetica delle Demenze



MALATTIA DI ALZHEIMER

CASI SPORADICI	~75%
FORME FAMILIARI	~25%
• Late-Onset FAD (>65 anni)	15-25%
• Early-Onset FAD (<65 anni)	<5%

Geni e demenze

FAD

FTLD

2017

Gene	# Mutations	# Families
APP	51 (9.86 %)	121 (7.35 %)
PSEN1	219 (42.36 %)	480 (29.16 %)
PSEN2	16 (3.09 %)	34 (2.07 %)
C9orf72	1 (0.19 %)	336 (20.41 %)
CHMP2B	4 (0.77 %)	5 (0.30 %)
FUS	23 (4.45 %)	49 (2.98 %)
GRN	79 (15.28 %)	259 (15.74 %)
MAPT	44 (8.51 %)	134 (8.14 %)
TARDBP	33 (6.38 %)	134 (8.14 %)
TBK1	28 (5.42 %)	45 (2.73 %)
VCP	19 (3.68 %)	49 (2.98 %)
Total	**517**	**1646**

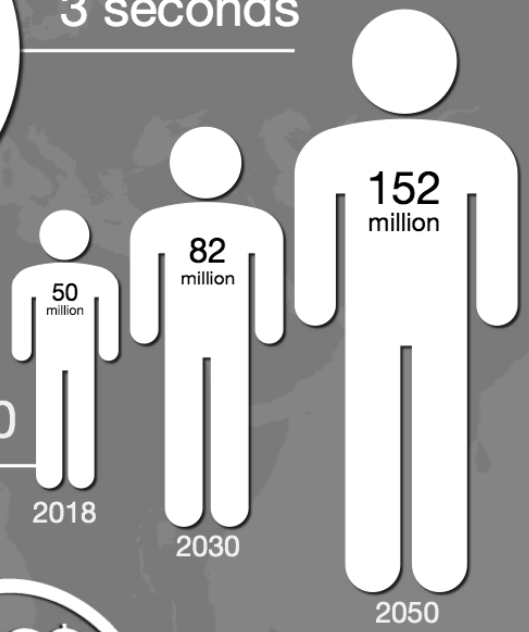
FAD Familial Alzheimer's Disease FTLD Frontotemporal lobe Degeneration

INFOGRAPHIC

The global impact of dementia

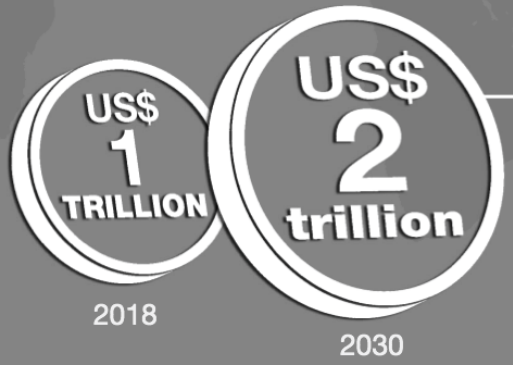
Around the world, there will be one new case of dementia

every 3 seconds



50 million people worldwide are living with dementia in 2018. This number will more than

triple to 152 million by 2050



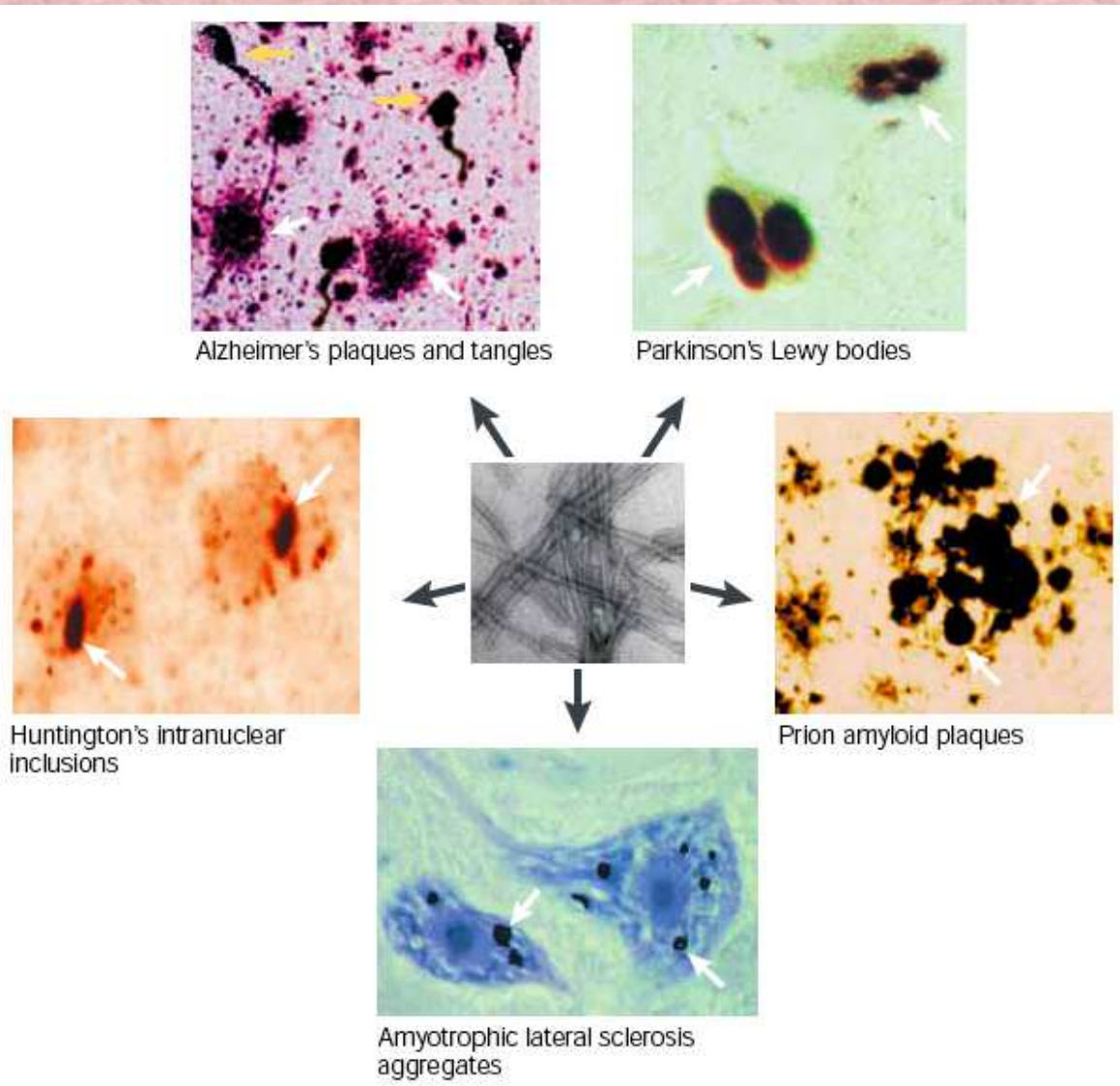
The total estimated worldwide cost of dementia in 2018 is US$1 trillion. This figure will rise to

US$ 2 trillion by 2030

"Discordance od dementia in monozygotic twins suggests that environmental factors also play a role in the development of AD"

Rapoport SI. 1991

Aggregati proteici nelle malatte neurodegenerative



La malattia di Alzheimer condivide con le altre malattie neurodegenerative alcune caratteristiche

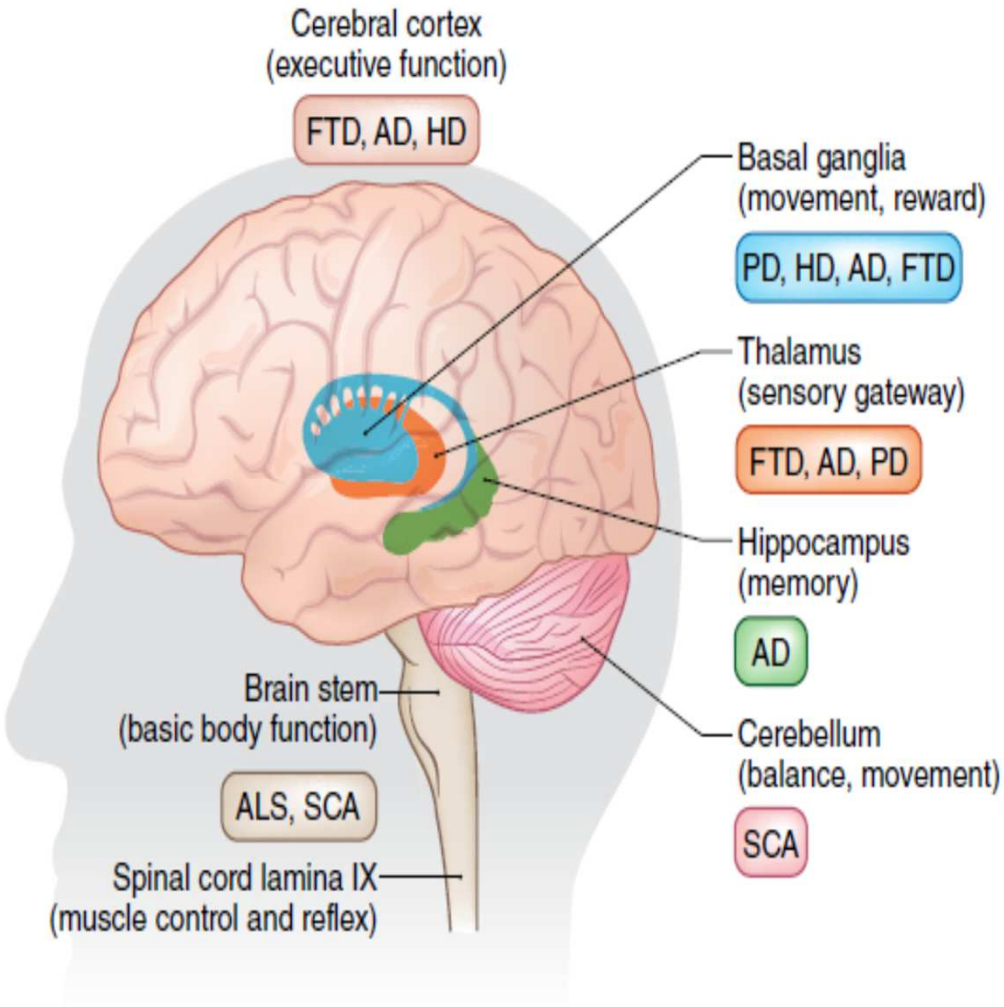


Fig. 1 | Primary brain regions affected in major neurodegenerative diseases. Clinical manifestations reflect distinct and overlapping neuronal circuits that progressively degenerate in various neurodegenerative diseases.

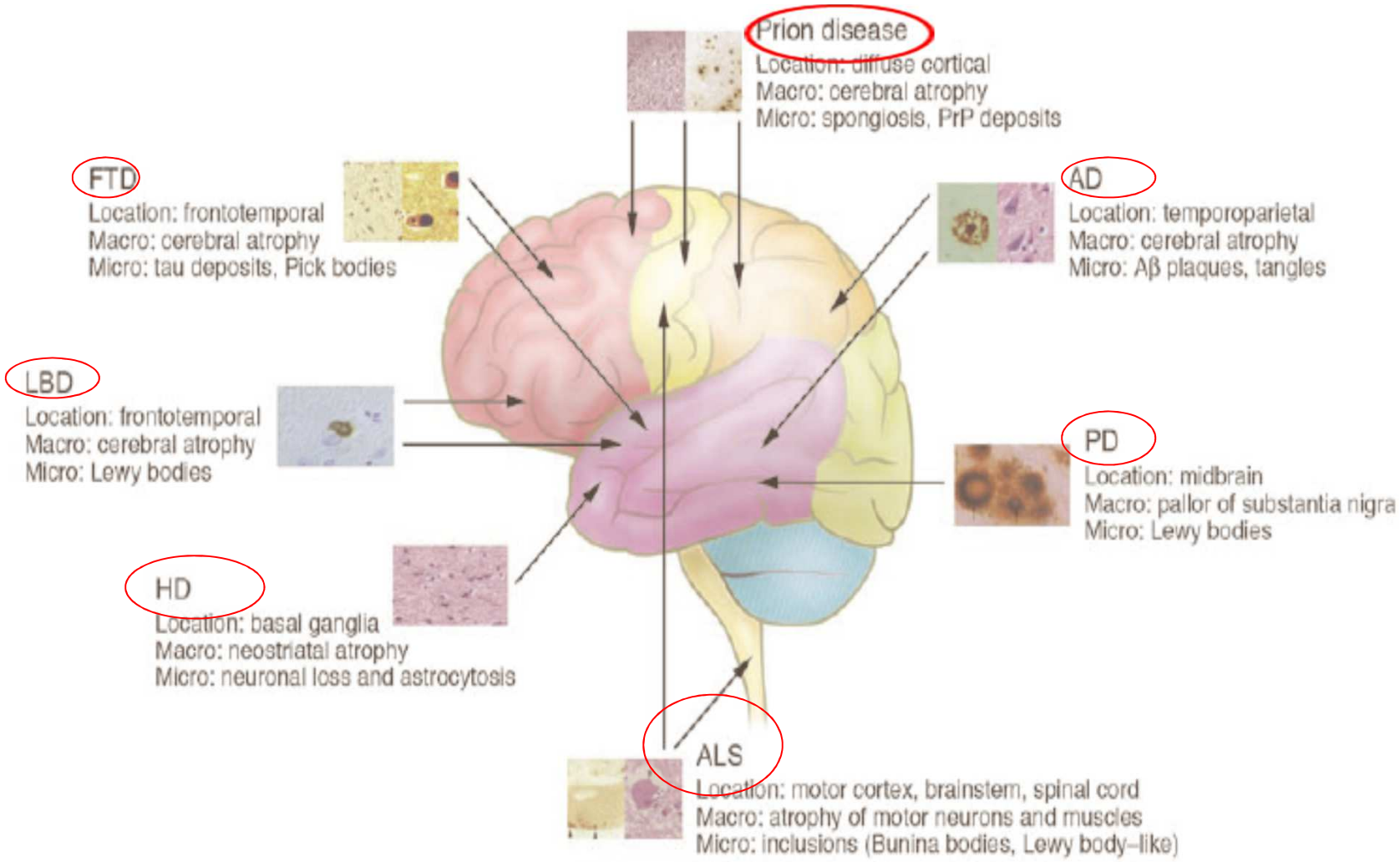
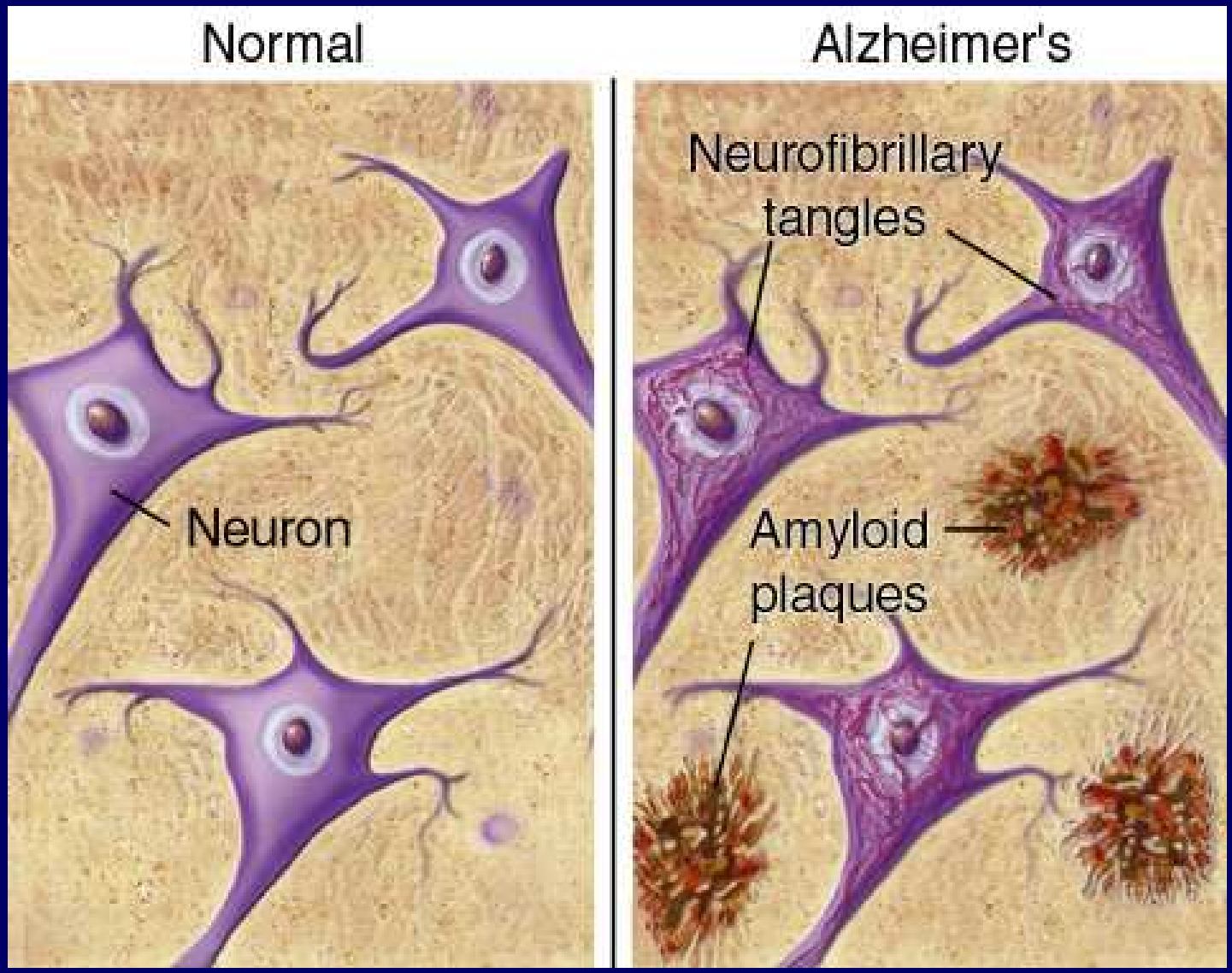
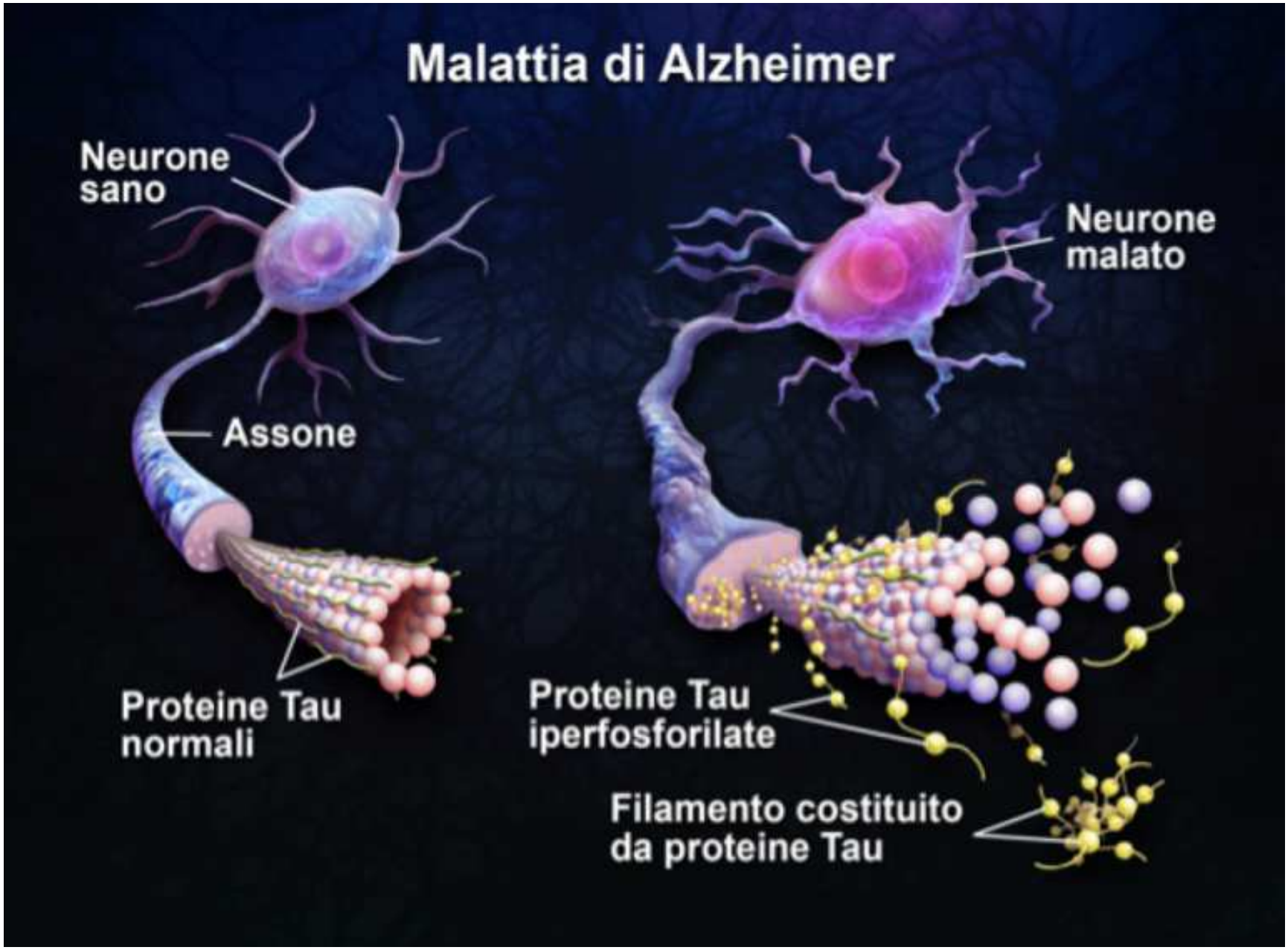


Figure 3

Overview of the anatomical location of and macroscopic and microscopic changes characteristic of the neurodegenerative disorders discussed

LE ALTERAZIONI NEUROPATOLOGICHE CARATTERISTICHE DELLA MALATTIA DI ALZHEIMER



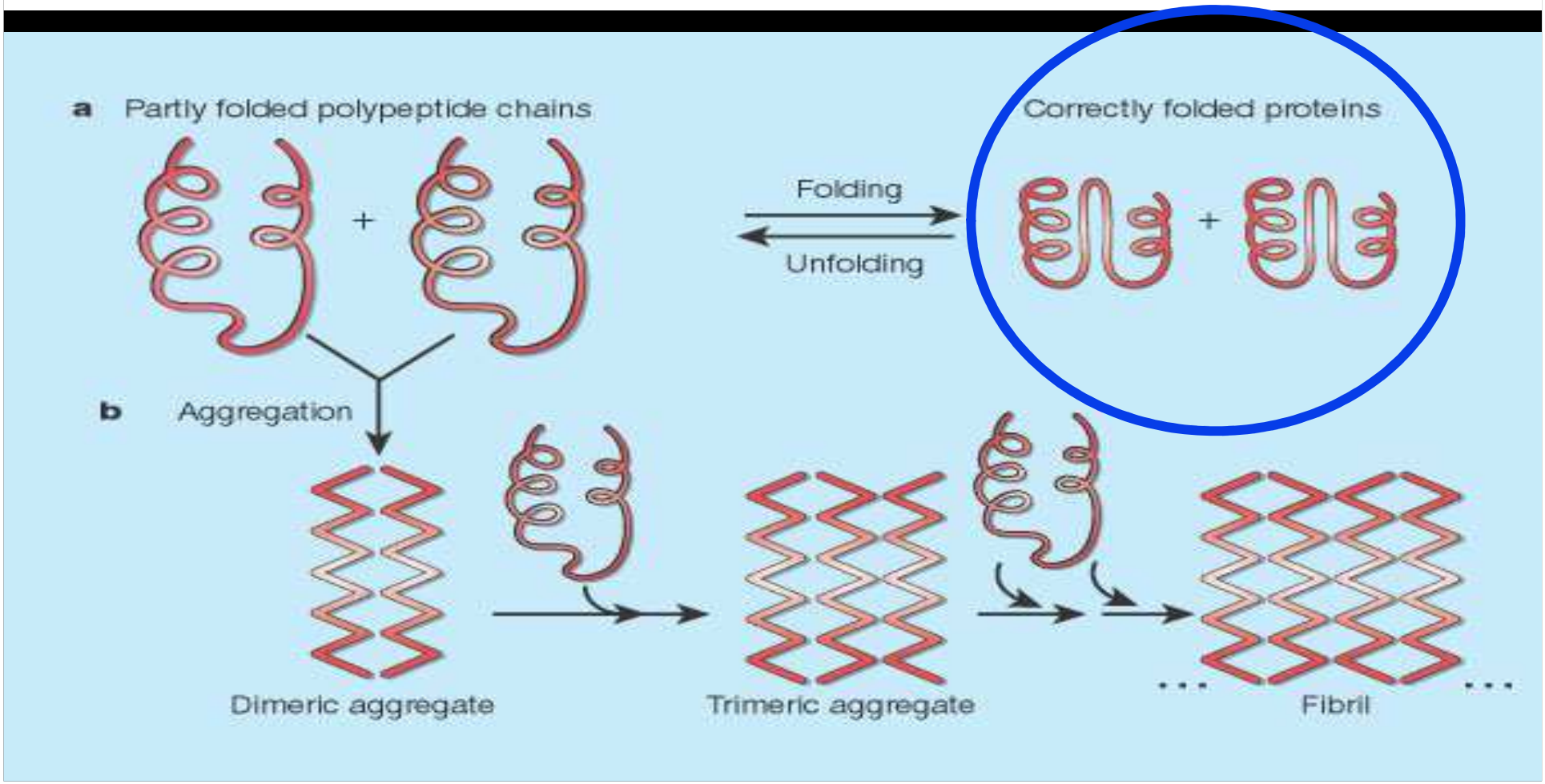

Malattia di Alzheimer
Neurone sano
Assone
Proteine Tau normali
Neurone malato
Proteine Tau iperfosforilate
Filamento costituito da proteine Tau

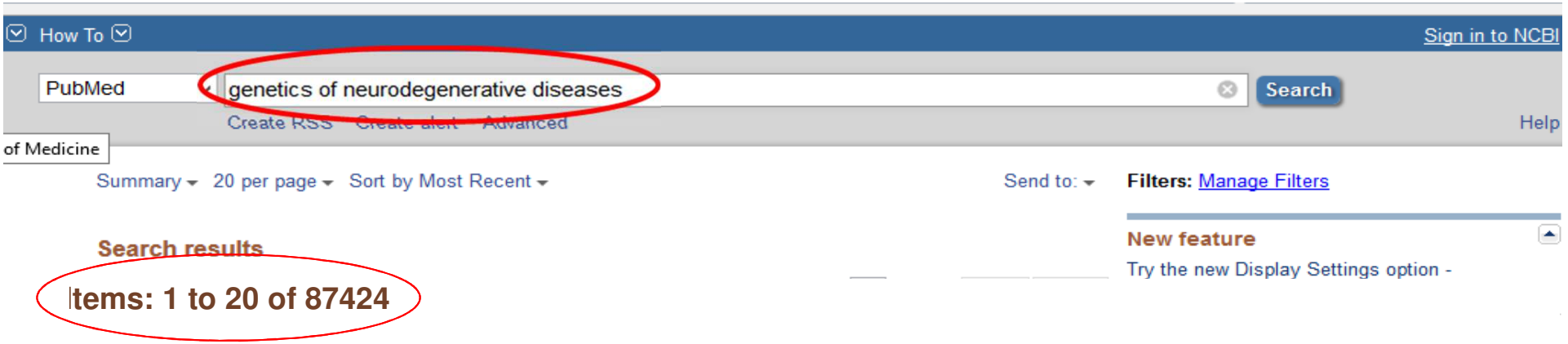
NATURE | VOL 416 | 4 APRIL 2002

news and views

Danger — misfolding proteins

R. John Ellis & Teresa J. T. Pinheiro





1. Deubiquitinase Usp12 functions noncatalytically to induce autophagy and confer neuroprotection in models of Huntington's **disease**.

   Aron R, Pellegrini P, Green EW, Maddison DC, Opoku-Nsiah K, Wong JS, Daub AC, Giorgini F, Finkbeiner S.

   Nat Commun. 2018 Sep 28;9(1):3191. doi: 10.1038/s41467-018-05653-z.

   PMID: 30266909

2. Molecular docking analysis of phytoconstituent from Momordica charantia with Guanylate Cyclase catalytic domain.

   Ghanta M, Panchanathan E, Lakkakula BVKS, Narayanaswamy A, Abhinand PA, Antony S.

   Bioinformation. 2018 Jul 31;14(7):378-383. doi: 10.6026/97320630014378. eCollection 2018.

   PMID: 30262975

3. Dynein links engulfment and execution of apoptosis via CED-4/Apaf1 in C. elegans.

   Harders RH, Morthorst TH, Lande AD, Hesselager MO, Mandrup OA, Bendixen E, Stensballe A, Olsen A.

   Cell Death Dis. 2018 Sep 27;9(10):1012. doi: 10.1038/s41419-018-1067-y.

   PMID: 30262881

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Opening up the DNA methylome of **dementia**.
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Mol Psychiatry. 2019 Feb 13. doi: 10.1038/s41380-019-0372-x. [Epub ahead of print]
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2. Biallelic VARS variants cause developmental encephalopathy with microcephaly that is recapitulated in vars knockout zebrafish.
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Nat Commun. 2019 Feb 12;10(1):708. doi: 10.1038/s41467-018-07953-w.
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3. N-homocysteinylation of tau and MAP1 is increased in autopsy specimens of Alzheimer's disease and vascular **dementia**.
Bossenmeyer-Pourié C, Smith AD, Lehmann S, Deramecourt V, Sablonnière B, Camadro JM, Pourié G, Kerek R, Helle D, Umoret R, Guéant-Rodriguez RM, Rigau V, Gabelle A, Sequeira JM, Quadros EV, Daval JL, Guéant JL

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Alzheimer's Disease and Frontotemporal **Dementia**: The Current St [Mol Diagn Ther. 2018]

Molecular **Genetics** of Frontotemporal **Dementia** Elucidated by <i>Drosophila [Int J Mol Sci. 2018]

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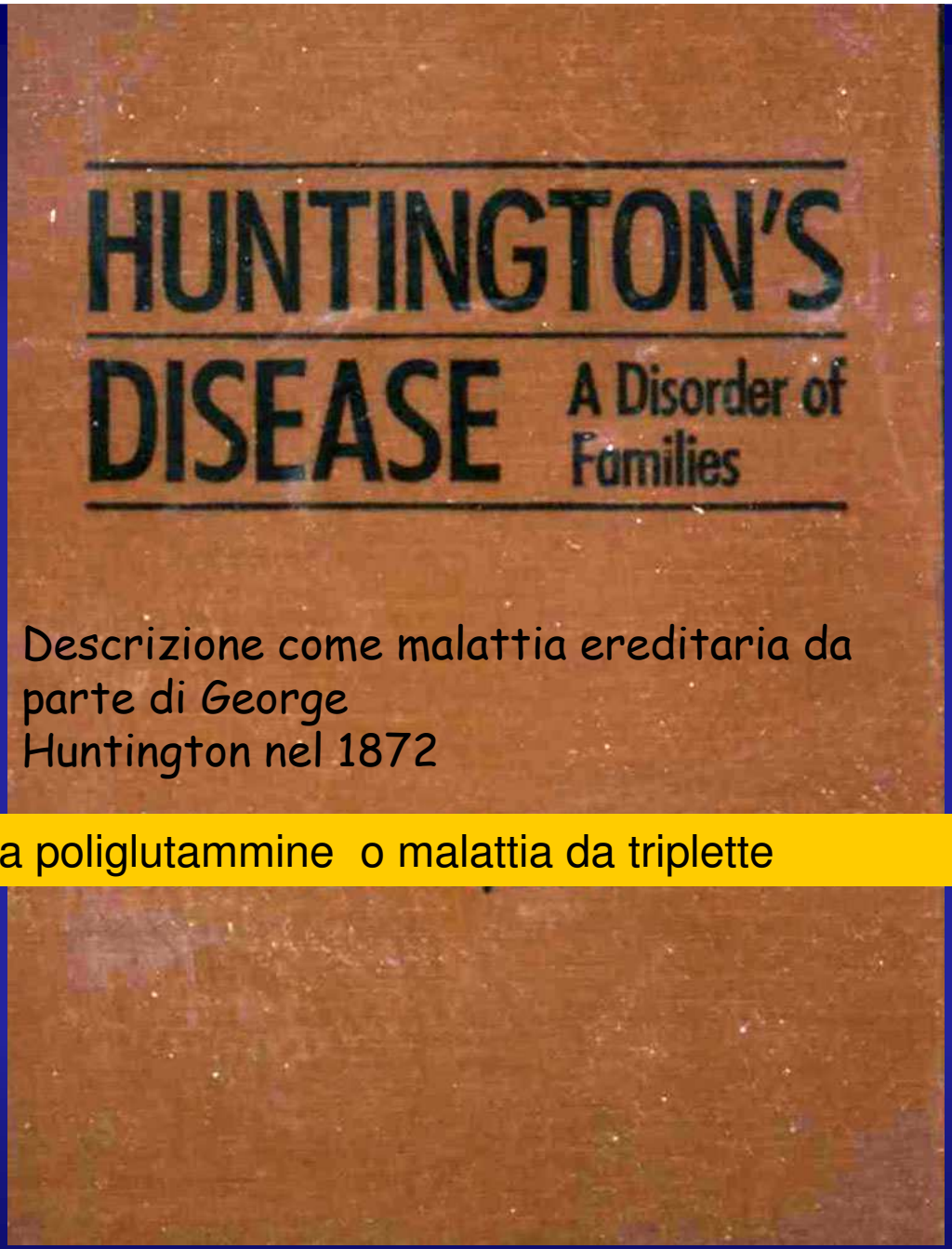
Attiva Windo
Passa a Impostaz

Tab. 5.1 **Alcuni esempi di malattie del sistema nervoso caratterizzate da diverse modalità di trasmissione genetica**

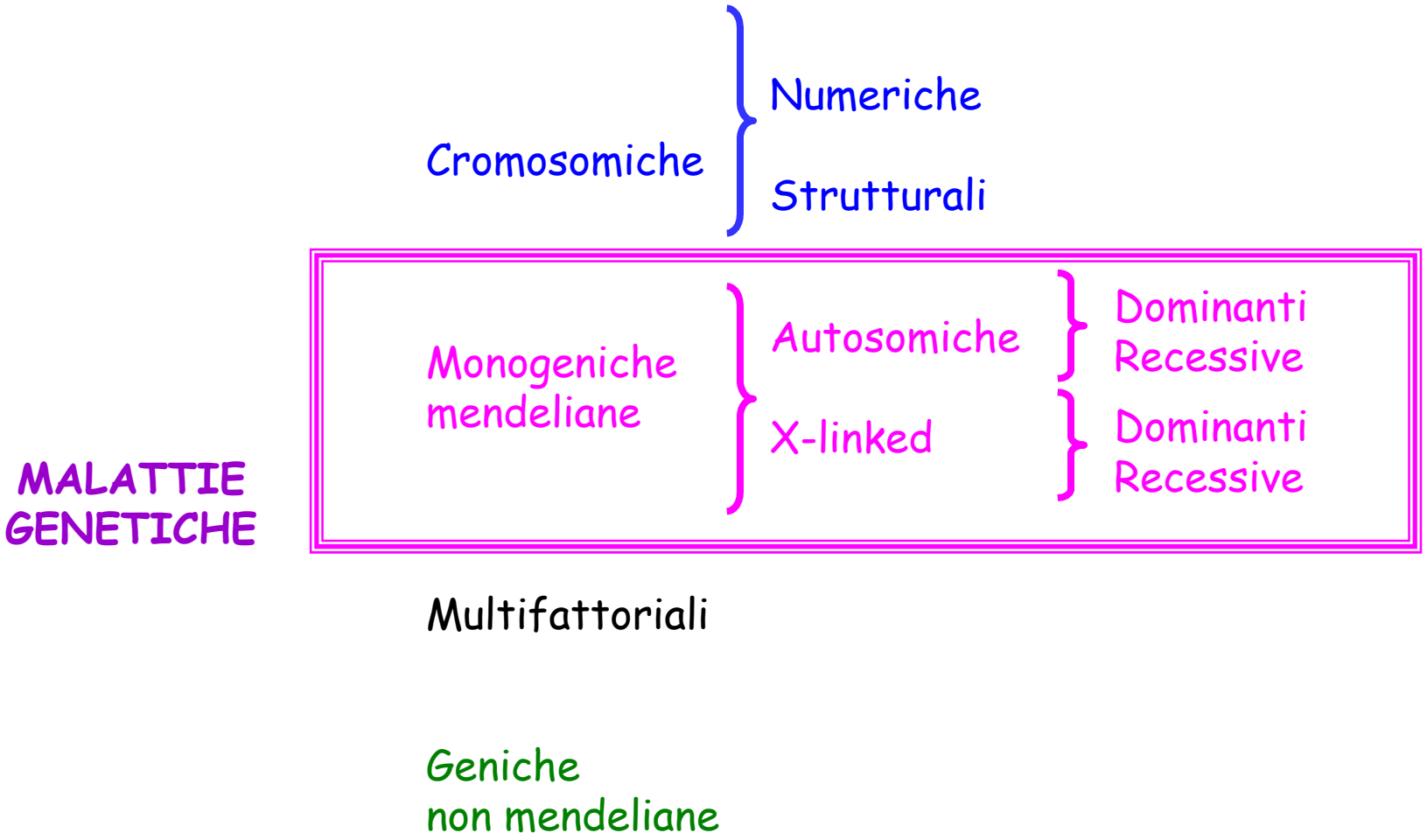
Malattie neurologiche ereditarie autosomiche dominanti
Charcot Marie Tooth Tipo 1
Retinite pigmentosa
Corea di Huntington
Neurofibromatosi tipo 1
Charcot Marie Tooth Tipo 2
Neurofibromatosi tipo 2
Malattia familiare di Alzheimer
Distrofia miotonica
Malattie neurologiche ereditarie autosomiche recessive
Atassia di Friedreich
Atassia teleangectasia
Fenilchetonuria
Malattia di Wilson
Ceroidolipofuscinosi neuronale
Malattie neurologiche ereditarie x-linked recessive
Distrofia muscolare di Duchenne e Becker
Malattia di Fabry
Ritardo mentale con X fragile
Adrenoleucodistrofia



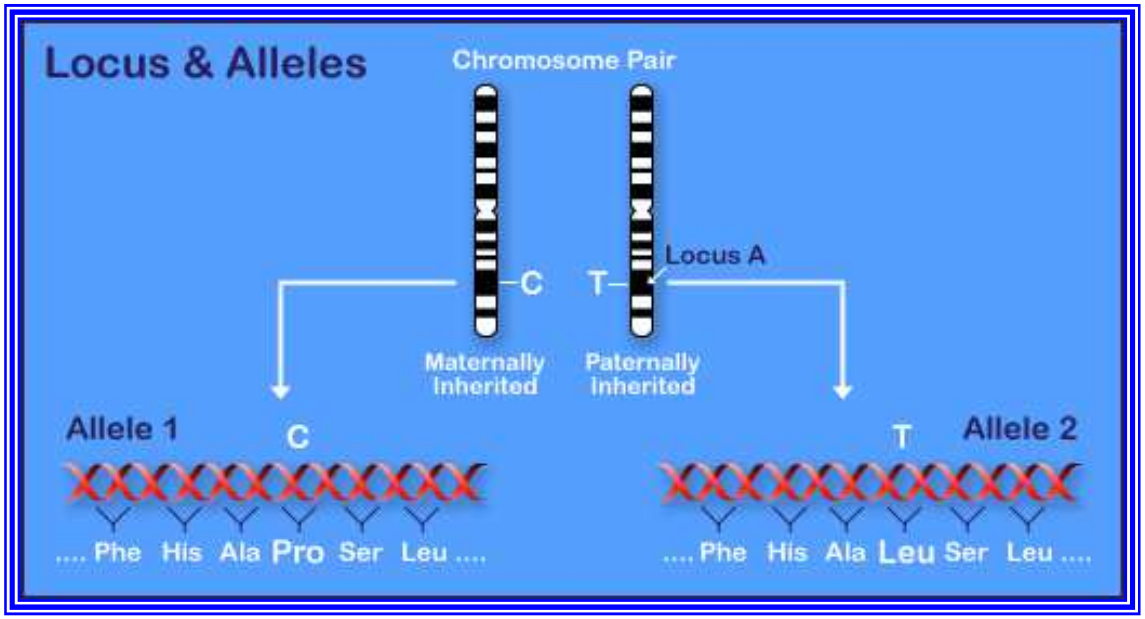
Descrizione come malattia ereditaria da parte di George Huntington nel 1872

Malattia da poliglutammine o malattia da triplette

Classificazione delle malattie genetiche



MODELLI DI TRASMISSIONE EREDITARIA



LOCUS — sito o specifica porzione su un cromosoma.
…. spesso è riferito ad un singolo gene

GENE — segmento di DNA che costituisce un'unità funzionale

GENOTIPO — composizione genetica dell'individuo

FENOTIPO — risultato dell'interazione del genotipo con i fattori ambientali; in altre parole, l'espressione osservabile di uno o più geni.

Alleli forme alternative di un gene, o di una sequen
DNA ad un certo locus.

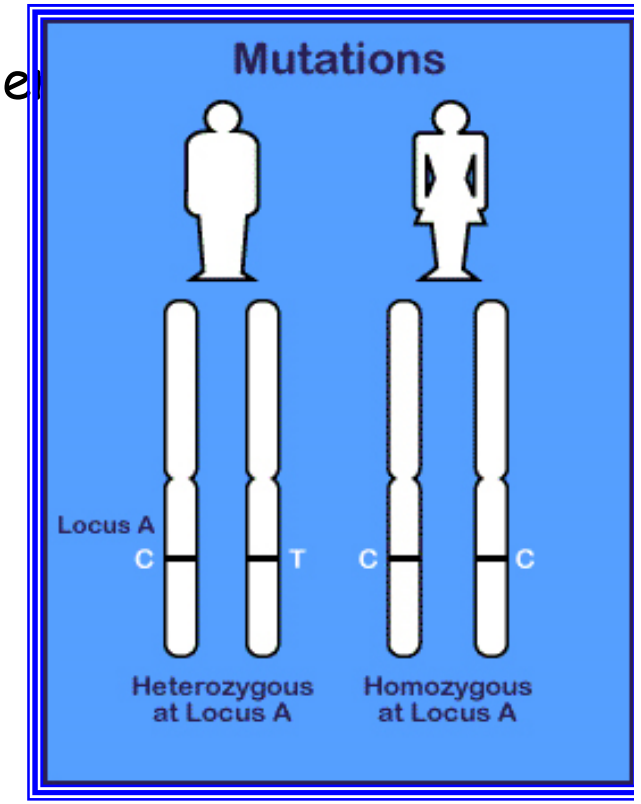
Eterozigote individuo con alleli diversi allo stesso locus (CT)

Omozigote individuo con alleli identici ad uno stesso locus (CC o TT)

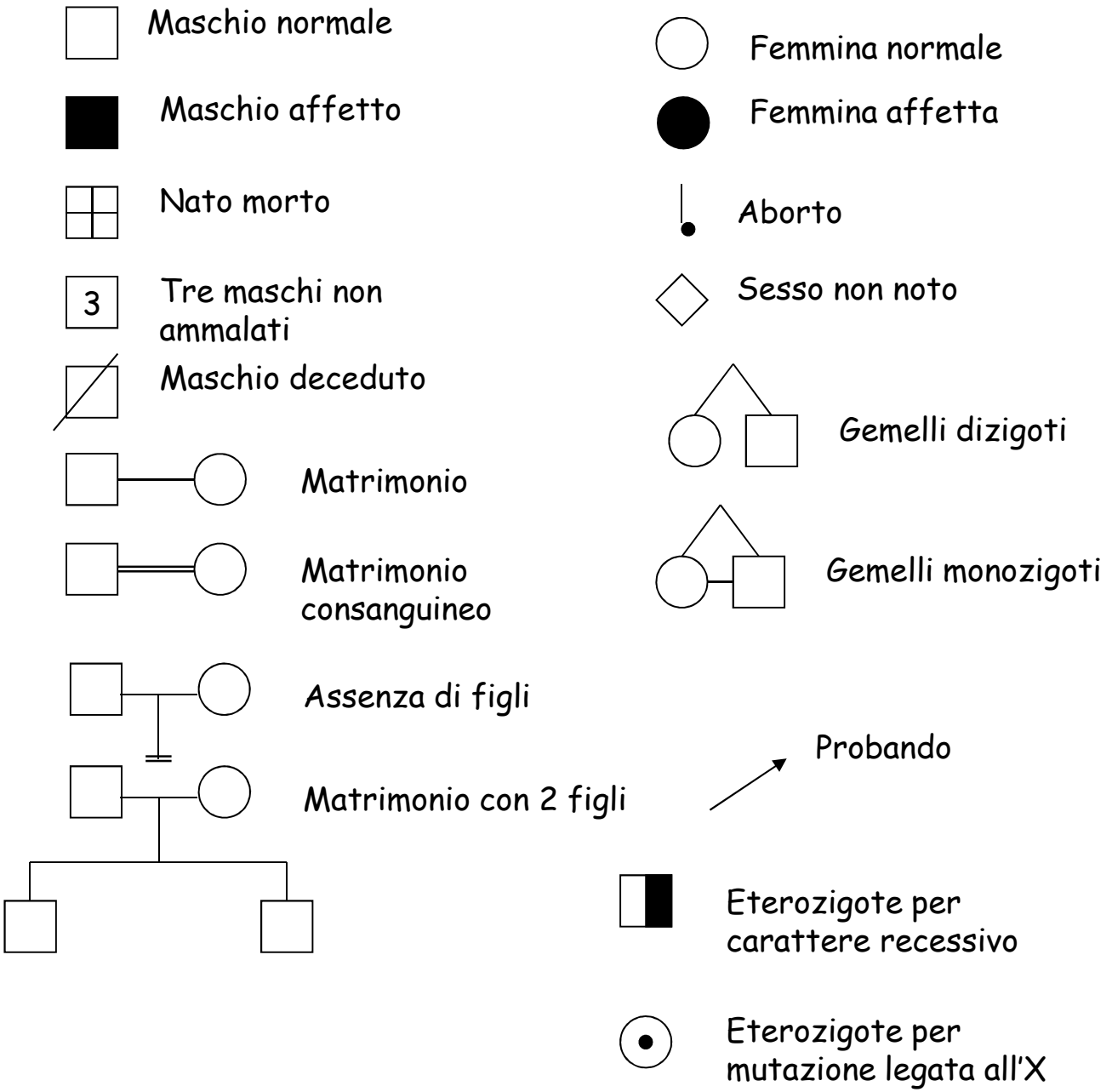
Genotipo costituzione genetica di un individuo o più specificamente gli alleli presenti ad ogni particolare locus

Mutazione alterazione della sequenza nucleotidica di una molecola di DNA

Polimorfismo variazione della sequenza nucleotidica di un gene, senza effetto fenotipico, che esiste nella popolazione con una frequenza di almeno l'1%



SIMBOLI UTILIZZATI PER LA COSTRUZIONE DI UN ALBERO GENEALOGICO

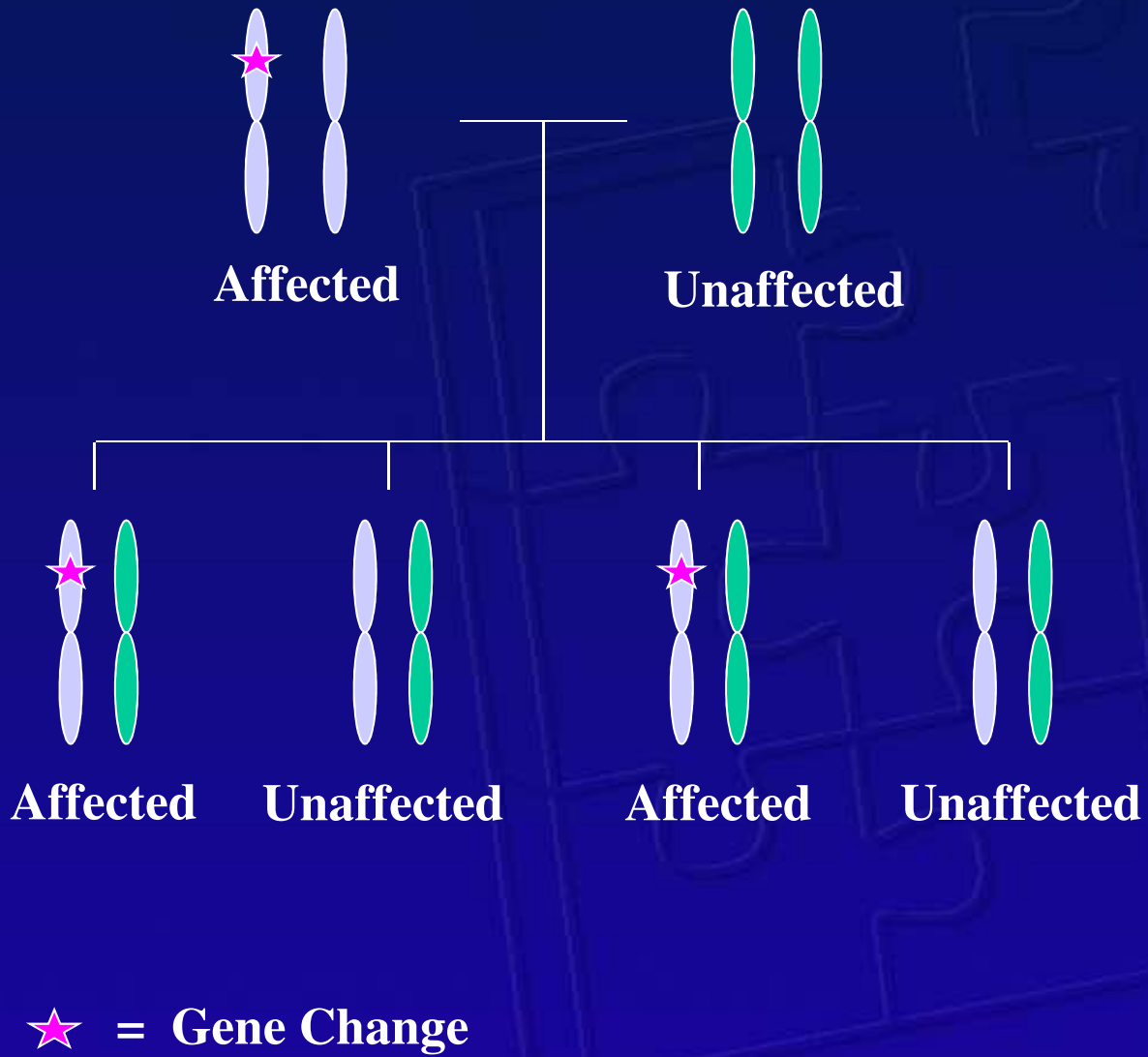


Classificazione delle malattie ad eredità mendeliana

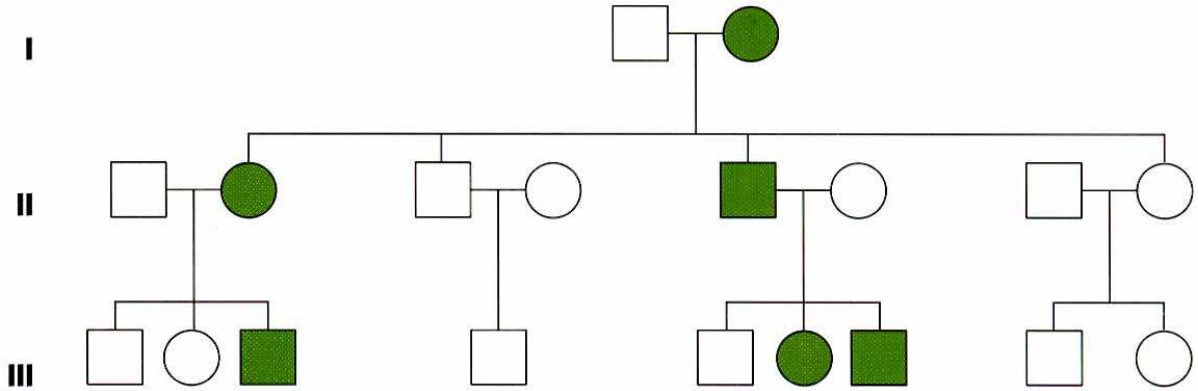
MONOGENICHE MENDELIANE

- Autosomiche
  - Dominanti
  - Recessive
- X-linked
  - Dominanti
  - Recessive

Autosomal Dominant Inheritance



Eredità autosomica dominante



Albero genealogico con esempio di trasmissione verticale di una mutazione autosomica dominante

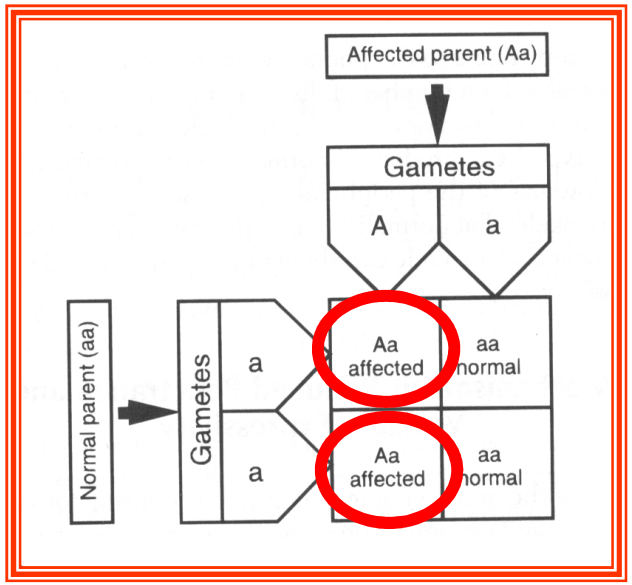
Caratteristiche di trasmissione

Singola dose dell'allele mutato (Aa) -> patologia

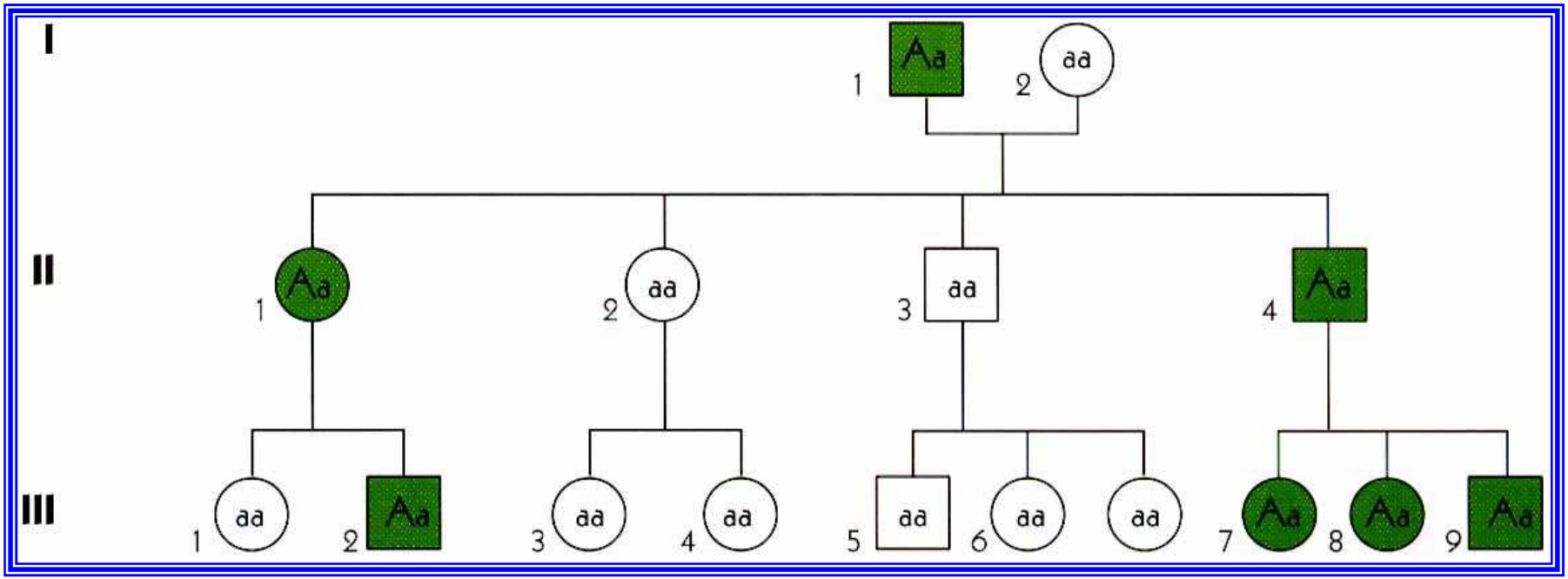
Trasmissione verticale dell' allele mutato all' interno dell' albero genealogico

Uguale rapporto maschi/femmine che ereditano l' allele mutato

Il 50% dei figli nati da genitori affetti manifestano la stessa malattia



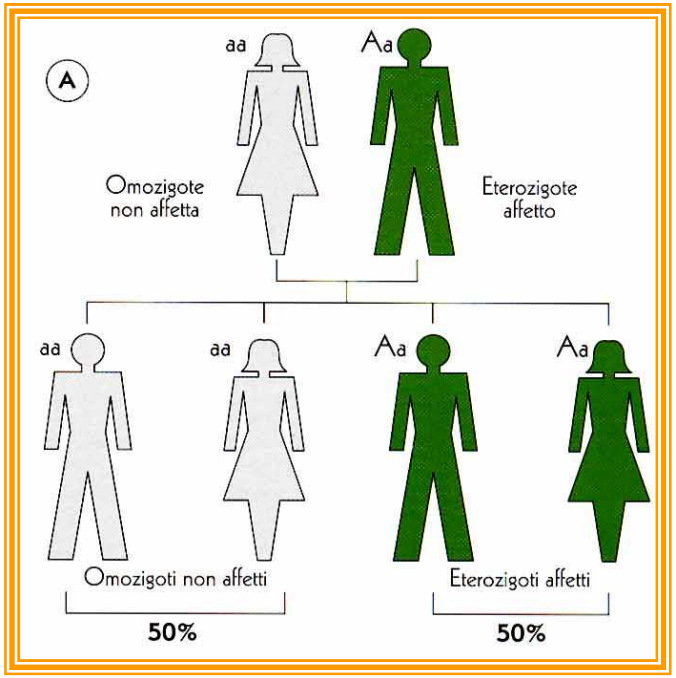
Il 50% dei figli nati da genitori affetti manifestano la stessa malattia



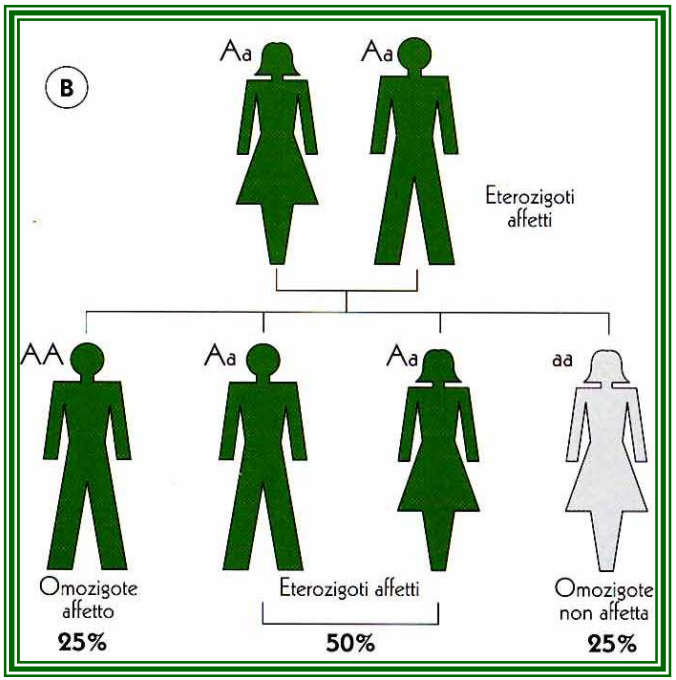
MALATTIE AUTOSOMICHE DOMINANTI.

Rischio riproduttivo

Soggetto eterozigote e partner normale



Entrambi i soggetti eterozigoti



Regole generali per malattie autosomiche dominanti

La malattia viene trasmessa di generazione in generazione, solo tramite gli individui affetti

Ciascun figlio di individuo affetto ha 1 probabilità su 2 di essere malato

I figli sani di soggetti sani avranno solo figli sani

La malattia colpisce indifferentemente maschi e femmine

Irregolarità della trasmissione autosomica dominante

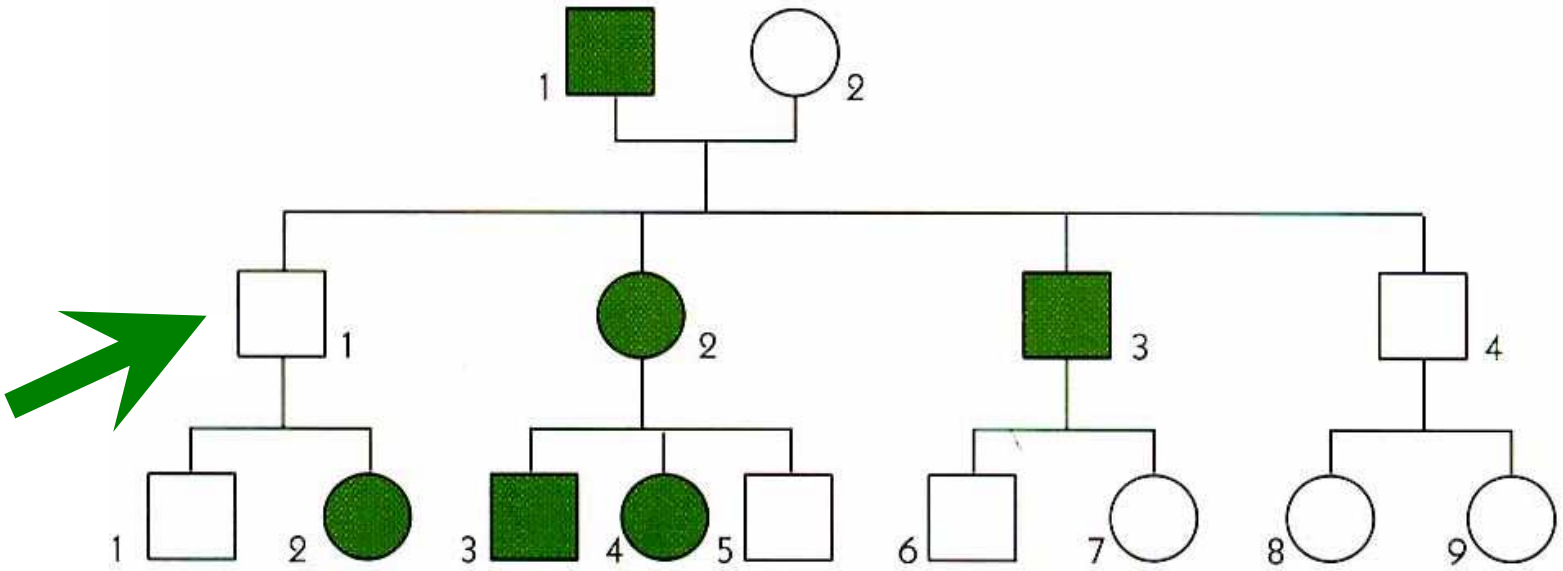
Penetranza: frequenza (probabilità) che un genotipo esprima il fenotipo (clinico) si esprime come una percentuale o una frazione di uno

Frazione di individui con un dato genotipo (Aa) che manifestano il carattere associato con quel genotipo

La penetranza incompleta di un carattere si manifesta in una proporzione di figli affetti minore di quella attesa dalle proporzioni mendeliane (comunemente il 50% e 25% nei casi di caratteri autosomici rispettivamente dominanti e recessivi)

Molte malattie autosomiche dominanti sono a penetranza incompleta: vengono all'osservazione come fenotipi che saltano una generazione

Albero genealogico con segregazione di malattia autosomica dominante: apparente salto di generazione per penetranza incompleta

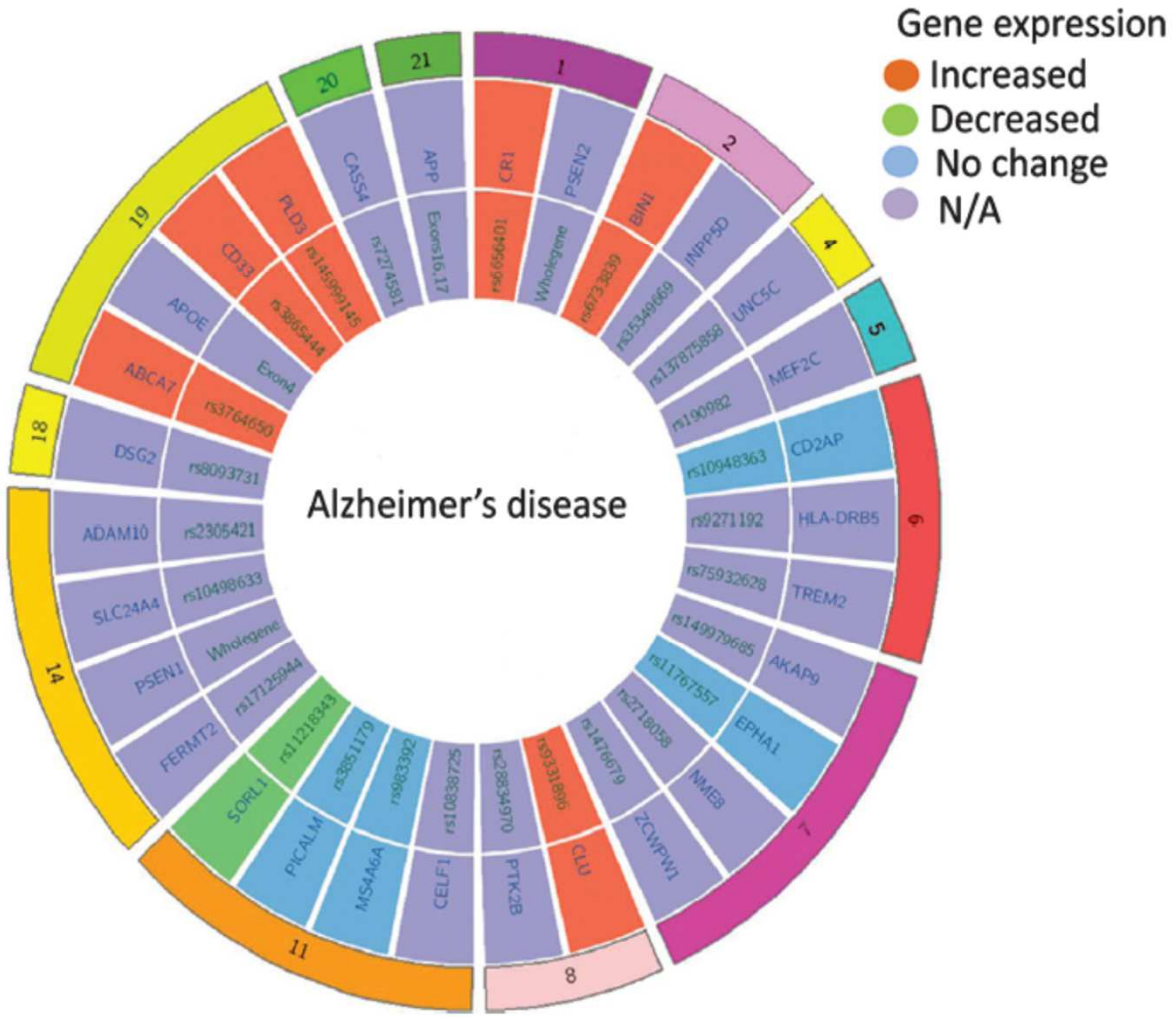


Eterogeneità genica

Lo stesso fenotipo causato da mutazioni in geni diversi

– mutazioni in geni che codificano per diverse unità o subunità di una proteina, o per proteine che interagiscono con altre proteine, o che agiscono a stadi diversi di un processo metabolico

Malattia di Alzheimer
Malattia di Parkinson
Sclerosi laterale amiotrofica



Journal of Alzheimer's Disease 58 (2017) 631–659

Circular genetic map from the software circos shows positions of genetics variants of Alzheimer's disease. The outermost circle shows the numbered autosomal chromosomes. The second circle shows genes that associated with AD. The third circle shows SNPs that
located in risk gene/locus that associated with AD

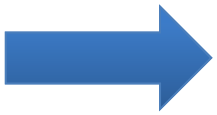
Eterogeneità allelica

Lo stesso fenotipo causato da mutazioni diverse nello stesso gene

- comune perché molte malattie sono causate da mutazioni che inducono una perdita di funzione (ogni mutazione che impedisce la produzione o la funzione del prodotto genico)

Esempi: ipercolesterolemia famigliare, varie mutazioni a livello del gene del recettore LDL provocano la perdita di recettori funzionali con conseguente accumulo di colesterolo

β- talassemia, a produrre questo fenotipo sono molte mutazioni diverse nel gene della b-globina



Tab. 5.1	**Alcuni esempi di malattie del sistema nervoso caratterizzate da diverse modalità di trasmissione genetica**

Malattie neurologiche ereditarie autosomiche dominanti
Charcot Marie Tooth Tipo 1
Retinite pigmentosa
Corea di Huntington
Neurofibromatosi tipo 1
Charcot Marie Tooth Tipo 2
Neurofibromatosi tipo 2
Malattia familiare di Alzheimer
Distrofia miotonica
Malattie neurologiche ereditarie autosomiche recessive
Atassia di Friedreich
Atassia teleangectasia
Fenilchetonuria
Malattia di Wilson
Ceroidolipofuscinosi neuronale
Malattie neurologiche ereditarie x-linked recessive
Distrofia muscolare di Duchenne e Becker
Malattia di Fabry
Ritardo mentale con X fragile
Adrenoleucodistrofia

CARATTERI AUTOSOMICI RECESSIVI

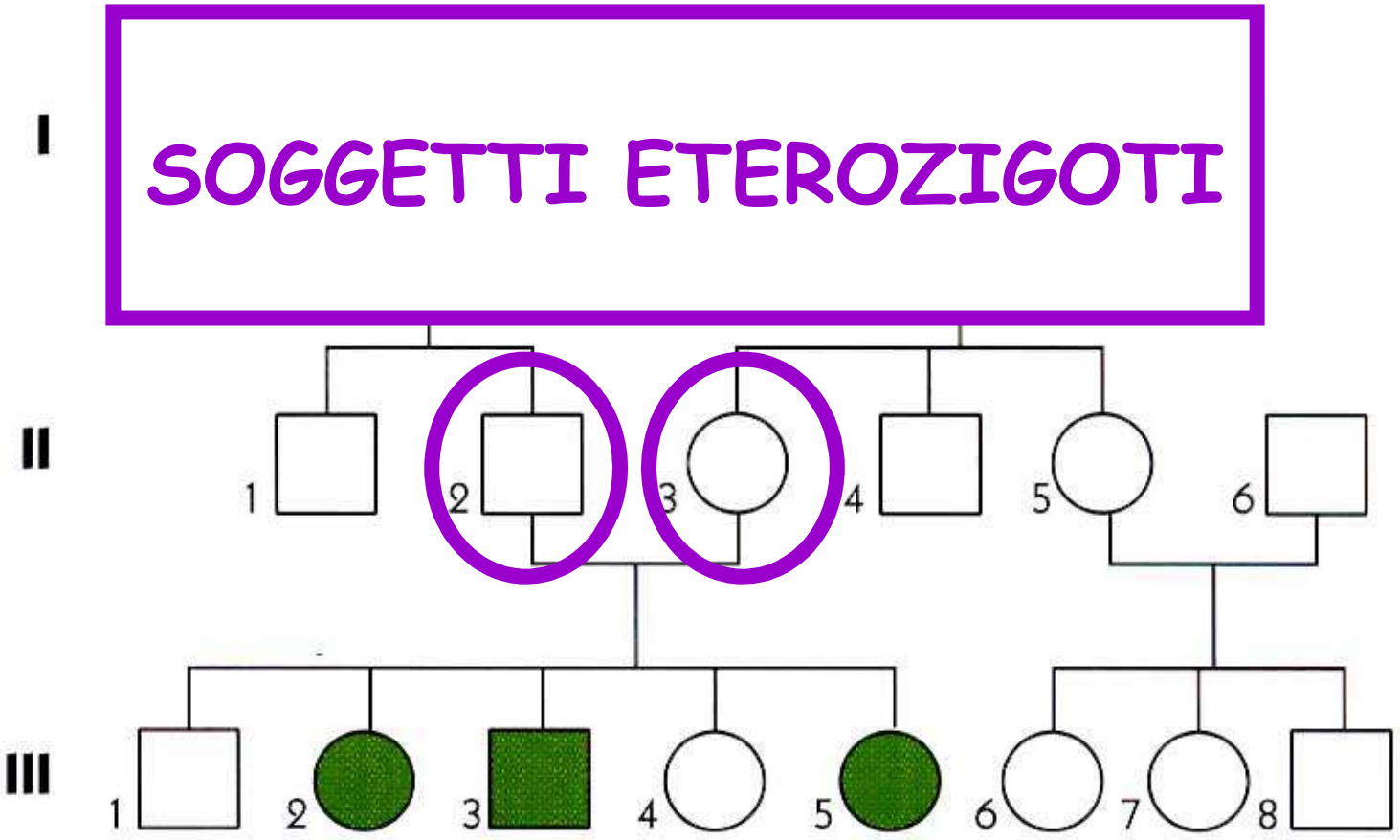
Si manifestano in omozigosi

Rischio di ricorrenza 25% da genitori entrambi eterozigoti

Più frequenti tra la prole di genitori consanguinei

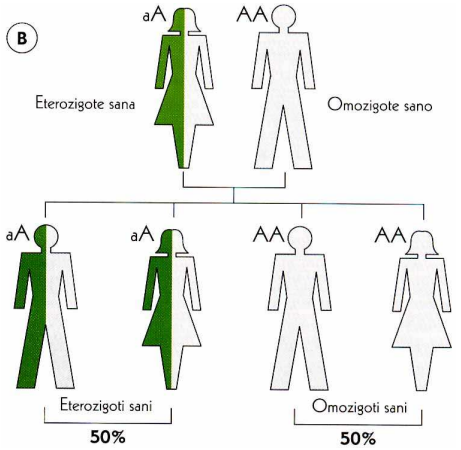
MALATTIA AUTOSOMICA RECESSIVA

esempio di albero genealogico con trasmissione orizzontale della malattia

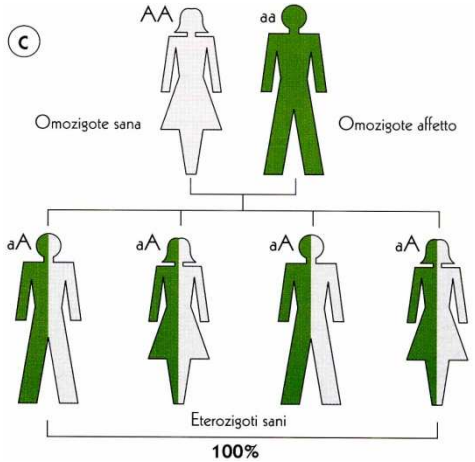


Malattie autosomiche recessive
probabilità di trasmissione dell'allele mutato e relativo rischio riproduttivo:

entrambi genitori eterozigoti



un solo genitore eterozigote.



uno dei due genitori omozigote affetto.

Regole generali per malattie autosomiche recessive

Gli eterozigoti sono normali come aspetto fenotipico, **ma portatori** del carattere mutato

Quando un individuo affetto nasce da genitori normali, si deve ritenere che entrambi i genitori siano eterozigoti e che, con media statistica $\frac{1}{4}$ della prole risulterà affetta, $\frac{1}{2}$ portatrice e $\frac{1}{4}$ normale

Quando un individuo affetto contrae matrimonio con una persona genotipicamente normale, la prole sarà genotipicamente eterozigote e fenotipicamente normale

Quando contraggono matrimonio due individui ammalati, tutta la prole risulterà affetta

La malattia colpisce indifferentemente maschi e femmine

Il rischio di ricorrenza nelle generazioni successive è basso, a meno che non si verifichino particolari circostanze che favoriscono l' unione tra due eterozigoti (consanguineità, alta frequenza del gene)

Tab. 5.1	**Alcuni esempi di malattie del sistema nervoso caratterizzate da diverse modalità di trasmissione genetica**

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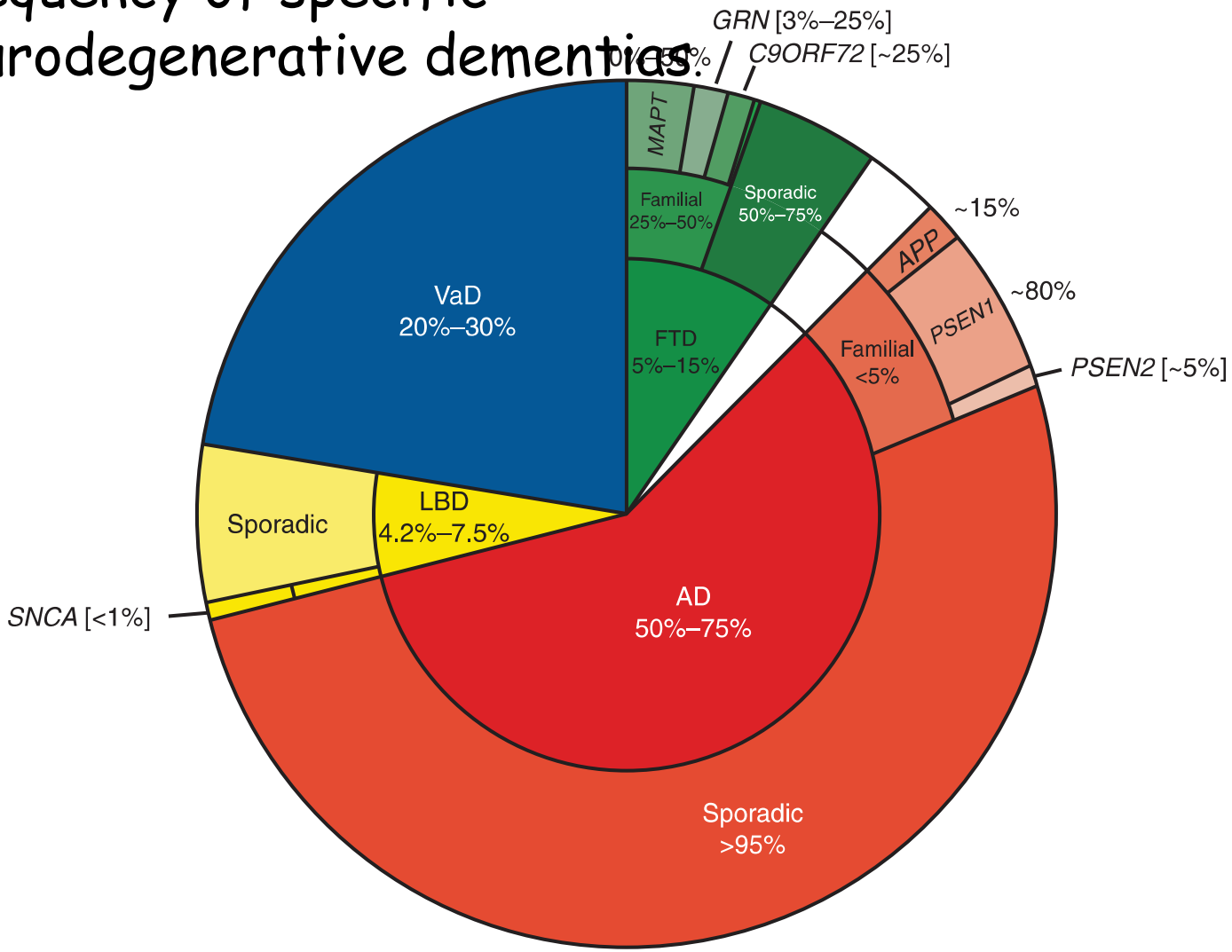
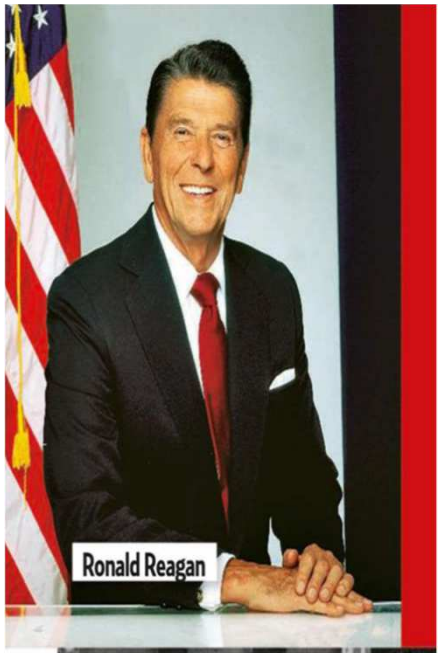
Distrofia muscolare di Duchenne e Becker
Malattia di Fabry
Ritardo mentale con X fragile
Adrenoleucodistrofia

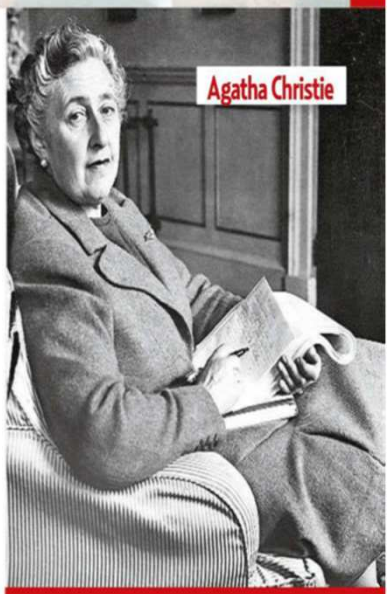
Molecular Genetics of Neurodegenerative Dementias

F.I. Hinz and D.H. Geschwind 2016

Frequency of specific neurodegenerative dementias.



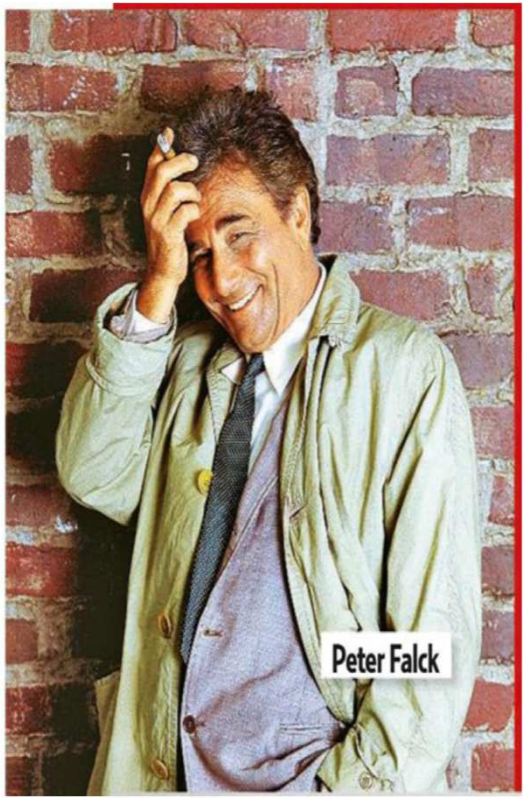


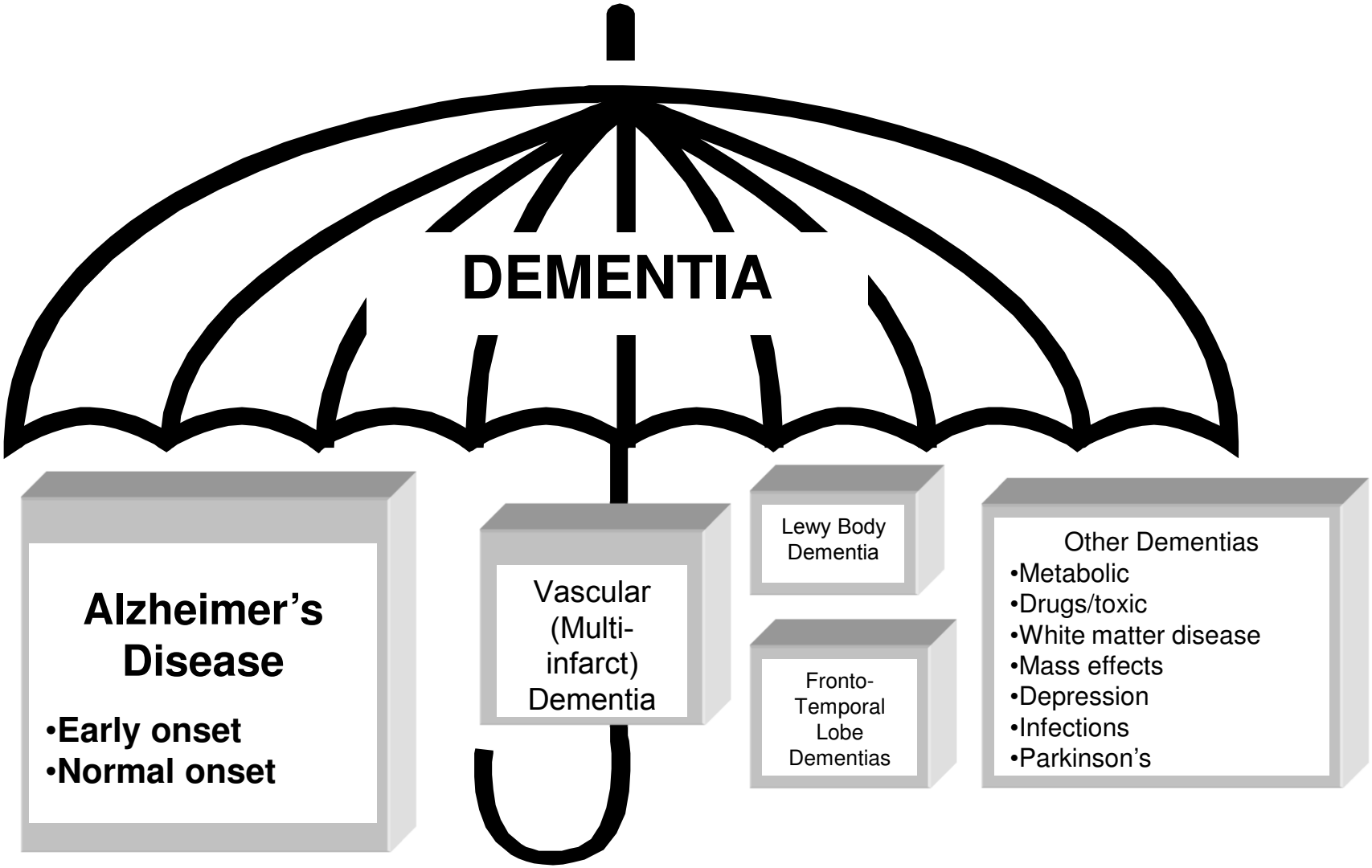


MENTI ILLUMINATE SPROFONDATE NEL BUIO
Ronald Reagan (1911-2004), presidente Usa dal 1981 al 1989, con la sua politica provocò la caduta dell'Unione Sovietica cambiando il mondo; Agatha Christie (1890-1976), la celebre scrittrice di libri gialli. Anche le loro menti sono state devastate da forme incurabili di Alzheimer.

Vite diverse: Lo stesso destino

Perter Falck, il tenente colombo
L attrice Rita Hayworth
Margaret Thatcher primo ministro inglese
Ronald Reagan, presidente usa
Agatha Christie, scrittrice




DEMENTIA
Alzheimer's Disease
•Early onset
•Normal onset
Vascular (Multi-infarct) Dementia
Lewy Body Dementia
Fronto-Temporal Lobe Dementias
Other Dementias
•Metabolic
•Drugs/toxic
•White matter disease
•Mass effects
•Depression
•Infections
•Parkinson's

La demenza è uno stato di progressivo decadimento delle funzioni cognitive riconducibile ad una patologia organica che porta il paziente ad una progressiva perdita dell"autonomia funzionale.

Con il termine demenza in genere si fa riferimento ad una condizione neurodegenerativa cronica progressiva ed irreversibile, anche se esistono condizioni demenziali totalmente o parzialmente reversibili (quelle ad esempio imputabili a cause vascolari e/o ad altre cause internistiche).

Cosa è la Demenza?

E' un processo clinico complesso che avviene in un soggetto le cui funzioni cognitive erano adeguatamente funzionanti. In un certo momento della vita adulta il funzionamento cognitivo si riduce e compaiono alterazioni comportamentale e psicologiche. Il quadro clinico è persistente nel tempo e progressivo.

Tutte le definizioni di demenza comprendono tre caratteristiche fondamentali:

1.La compromissione cognitiva deve essere acquisita.
2 Il deterioramento deve coinvolgere domini multipli delle funzioni cognitive piuttosto che risultare da un deficit neuropsicologico isolato.
3. Il paziente non deve presentare compromissione della vigilanza,

La diagnosi è convenzionalmente considerata *definita*, quando confermata autopticamente

Per molto tempo la demenza (decadimento cognitivo) è stata considerata una naturale sequela dell'invecchiamento, ovvero l'accentuazione di un normale e ineluttabile processo fisiologico

Forme primarie (60-70%) dove il processo patologico di tipo degenerativo porta di per se al quadro clinico di deficit cognitvo Che chiamiamo demenza

Forme secondarie (30-40%) che dipendono dalle modalità e caratteristiche con cui la patologia si manifesta a livello cerebrale

Nel quadro globale delle demenze neurodegenerative,
la malattia di Alzheimer (Alzheimer‟s Disease, AD) è in assoluto
la forma più frequente nella popolazione anziana (54% di tutte
le demenze neurodegenerative), seguita **dalla demenza**
con corpi di Lewy (dementia with Lewy Body, DLB) e
dalla **demenza fronto-temporal**e (Fronto-Temporal Dementia, FTD).

Le demenze ad eziologia vascolare vengono invece denominate
demenze vascolari (Vascular Dementia, VAD)
mentre le demenze ascrivibili ad altri fattori vengono
definite **demenze secondari**e.

La genetica molecolare sta portando la neurologia, ma in genere la medicina, ad un nuovo schema "mentale" operativo, una nuova nosologia basata non sui segni e sintomi né sui dati neuropatologici né sulle tradizionali classificazioni delle malattie in infettive, vascolari, neoplastiche, immunitarie, …. ma sul meccanismo molecolare e cellulare che le determina e le regola.

Le mutazioni responsabili di malattia possono verificarsi sia a livello delle
cellule somatiche che di quelle germinali

Mutazioni:

puntiformi (sostituzioni di base, delezioni di base, inserzioni di base)
Cromosomiche (delezioni, duplicazioni, inversioni, traslocazioni)
Genomiche (polisomie, soprattutto trisomie e monosomie)
Dinamiche (espansioni di triplette)

CLASSIFICAZIONE MOLECOLARE DELLE DEMENZE

Table 1. Molecular Classification of Dementing Disorders[a]

Clinical Disorder	Protein	Genes
Alzheimer disease	β-Amyloid	*PSEN1*, *PSEN2*, *APP*, *APOE*, others
Progressive supranuclear palsy	Tau	*MAPT*
Corticobasal degeneration	Tau	*MAPT*
Frontotemporal dementia	Tau	*MAPT*
	TDP-43	*TARDP*, *PGN*, *C9ORF72*
Lewy body dementia	α-Synuclein	*GBA*
Parkinson disease dementia	α-Synuclein	*SNCA*, *LRRK2*, *GBA*
Creutzfeldt-Jakob disease	Prion protein	*PRNP*
Huntington disease	Huntingtin	*HTT*

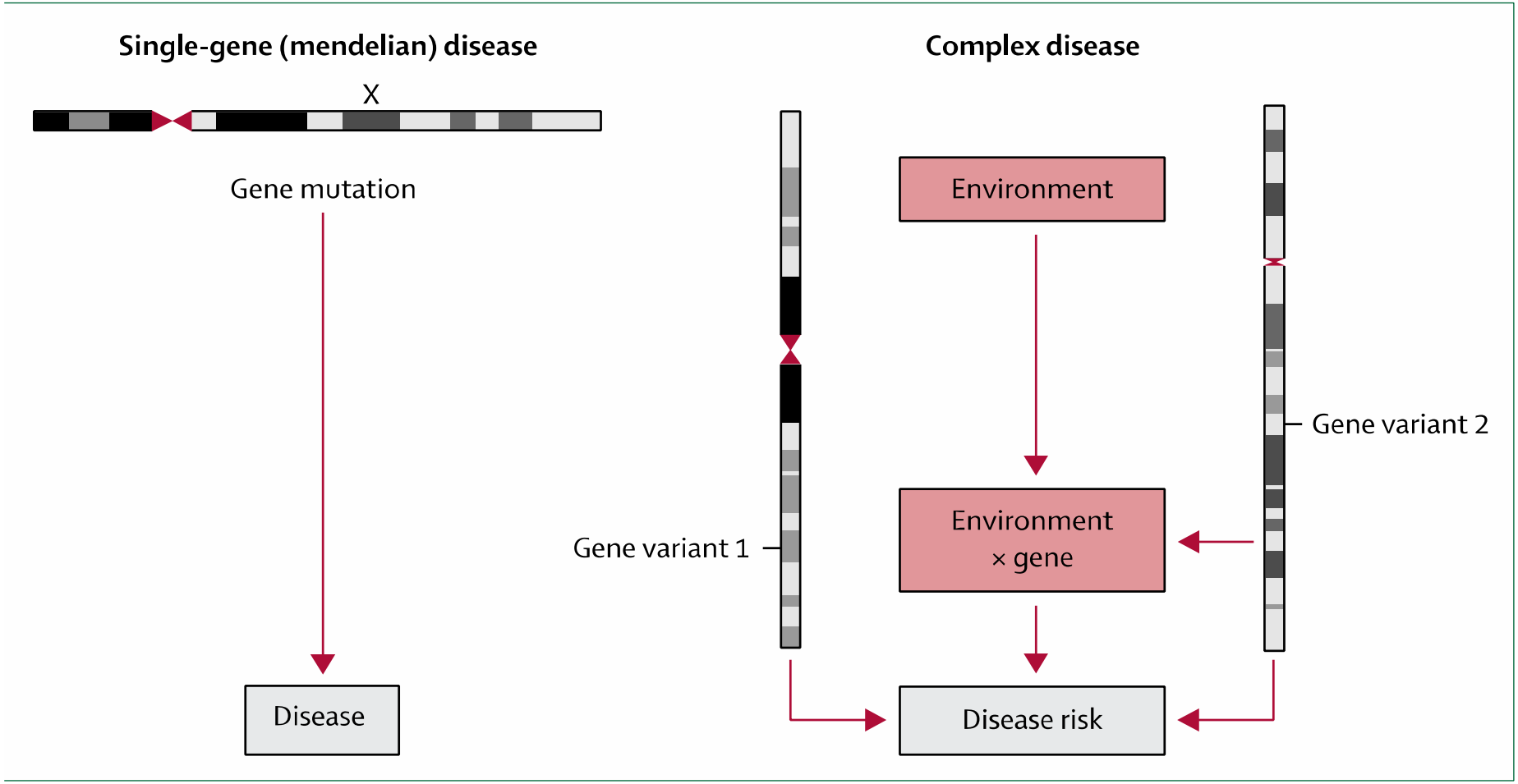
ONLINE FIRST ARCH NEUROL PUBLISHED ONLINE APRIL 2, 2012

Translational Research in Neurology

Dementia

Lawrence S. Honig, MD, PhD

Patogenesi nelle forme mendeliane e nelle malattie complesse



In una malattia mendeliana , la mutazione in un gene è necessaria e sufficiente a causare la malattia. In una malattia complessa le varianti geniche interagiscono con i fattori ambientali per aumentare il rischio di malattia.

Candidate gene

- Studio dei marcatori che cadono nella regione di un gene

Fine Mapping

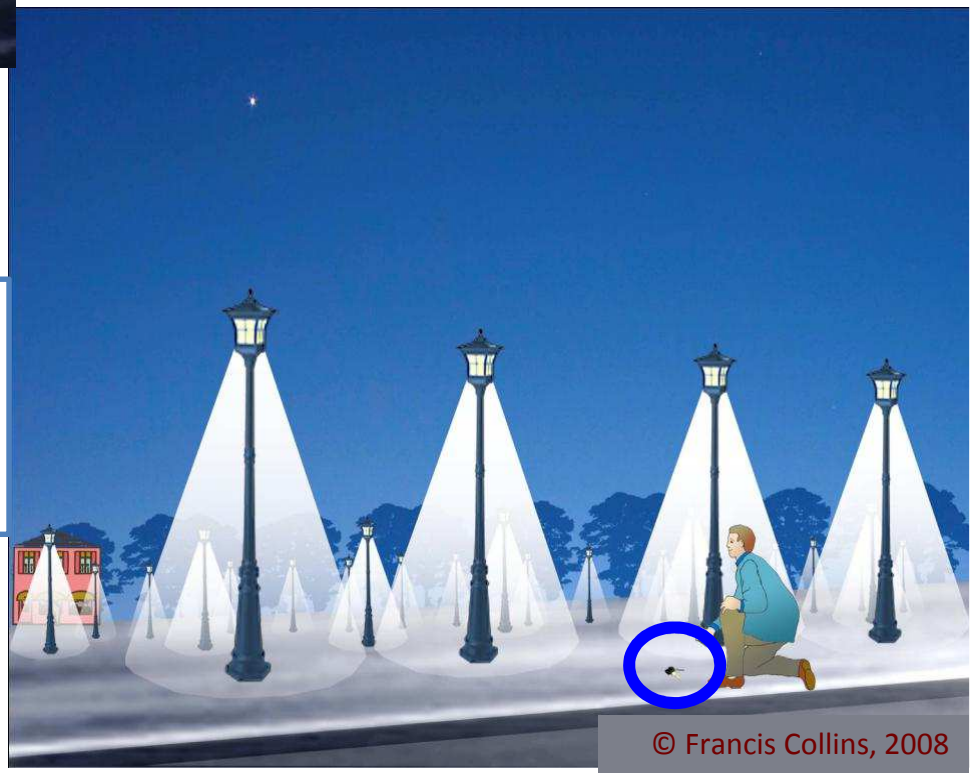
- Studio ad alta risoluzione di marcatori che cadono in un' intera zona che può contenere uno o più geni

Candidate gene

Studio di una specifica regione del genoma

Genome-Wide Studies

Studio il cui scopo è quello di identificare le varianti causali lungo tutto il genoma



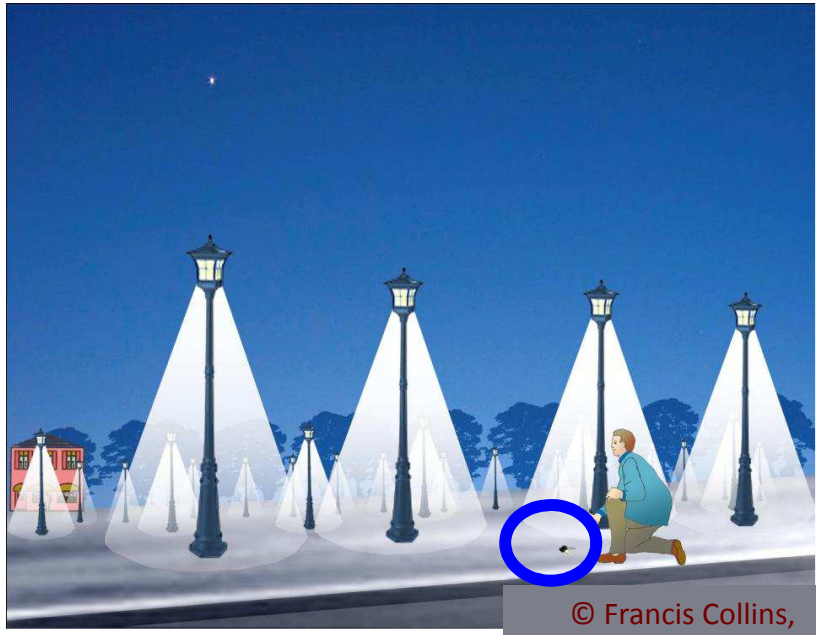
© Francis Collins, 2008

Approcci di studio

Candidate gene

Studio di una specifica regione del genoma

(richiede ipotesi *a priori)*



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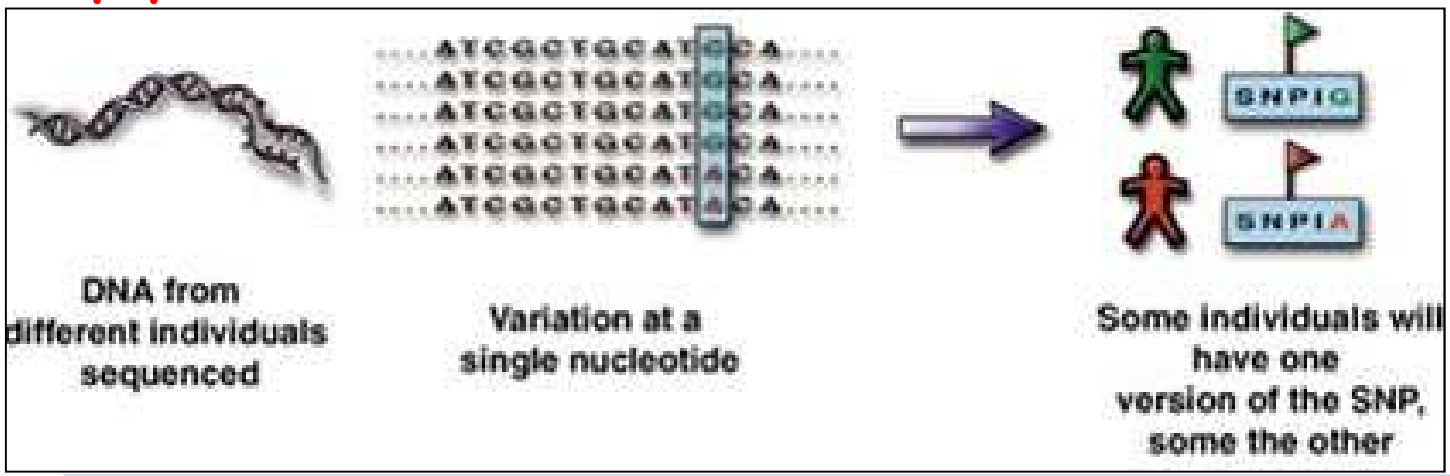
Genome-Wide Association (GWA) Studies

Studio il cui scopo è quello di identificare le varianti causali lungo tutto il genoma
(no ipotesi)

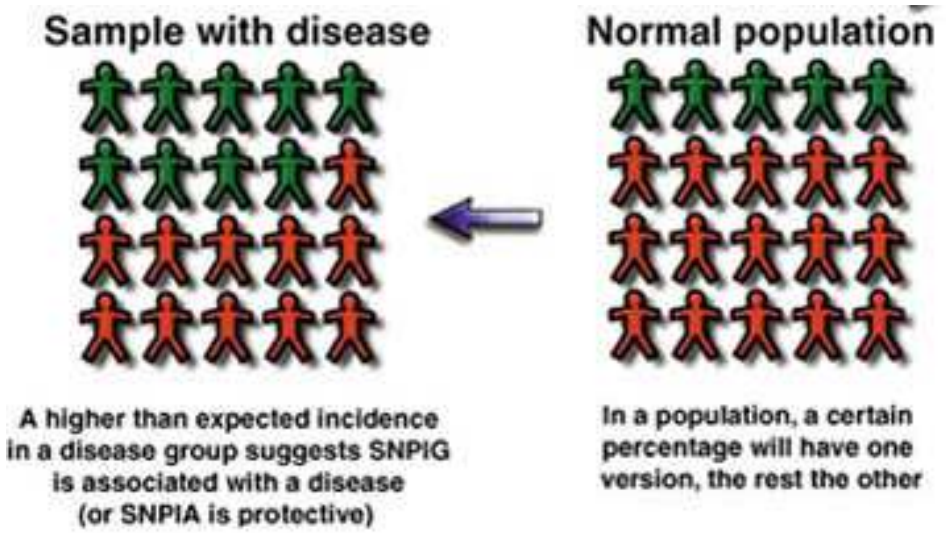
SNP (Polimorfismo a Singolo Nucleotide)

Variazione non patologica di un singolo nucleotide, osservata in almeno l' 1% della popolazione.



14 milioni di SNP attualmente convalidati nel genoma umano

Quando la frequenza di una particolare SNP differisce in modo significativo fra casi e controlli conferisce al gene, all' interno del quale si trova lo SNP , un rischio di influenzare la malattia

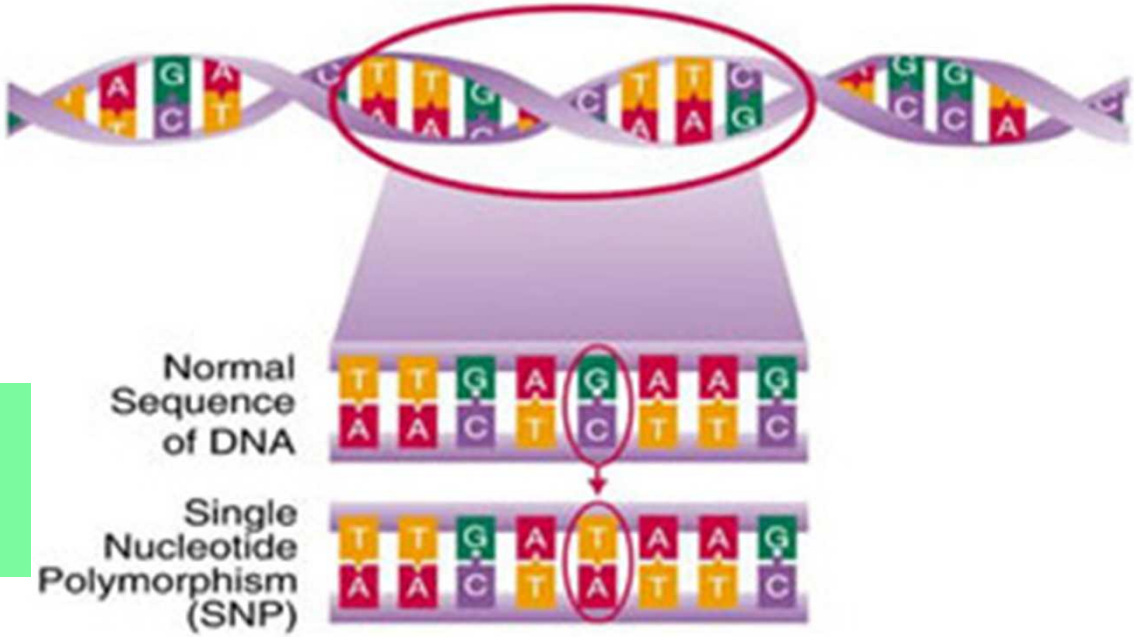


© Gibson & Muse, A Primer of Genome Science

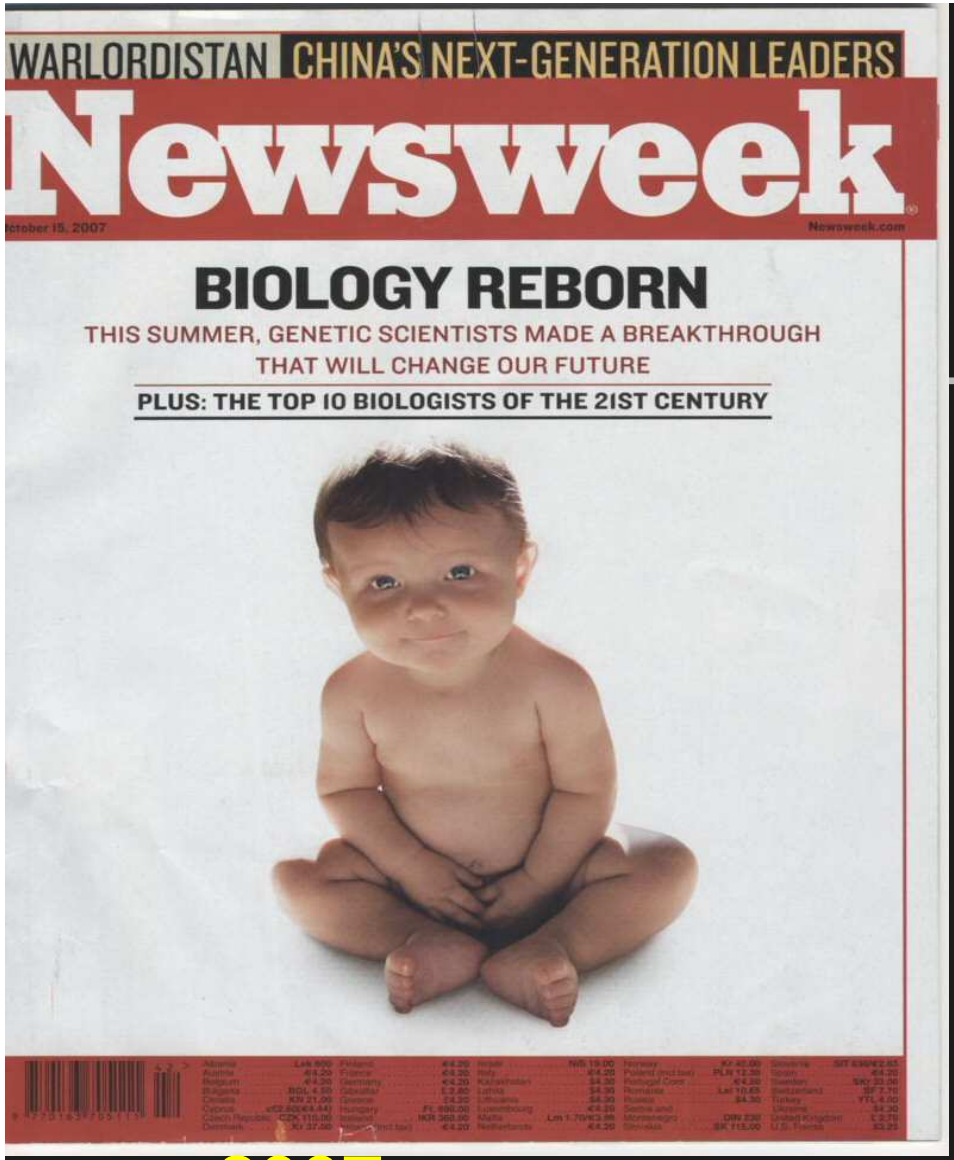
Ogni circa 1000 basi fisse del genoma esiste una possibile variazione e l'elemento che si modifica viene chiamato "snp" (single nucleotide polymorphism)

Il 99.9% del nostro genoma è identico per tutti noi mentre quel **0.1% è il solo responsabile delle nostre variazioni e specificità.**

3.000.000.000 coppie di basi nel genoma umano e 20.000 -25.000 geni.



Le quattro molecole (basi azotate) contraddistinte dalle lettere A,T,C,G. **(Adenina, Citosina, Timina, Guanina**) sono disposte in diverse sequenze di lunghezza variabile.
In un quadro di sostanziale costanza delle sequenze, esistono variazioni (polimorfismi) che cambiano una di queste in posizioni omologhe nei diversi DNA.



2007

The Year of miracles

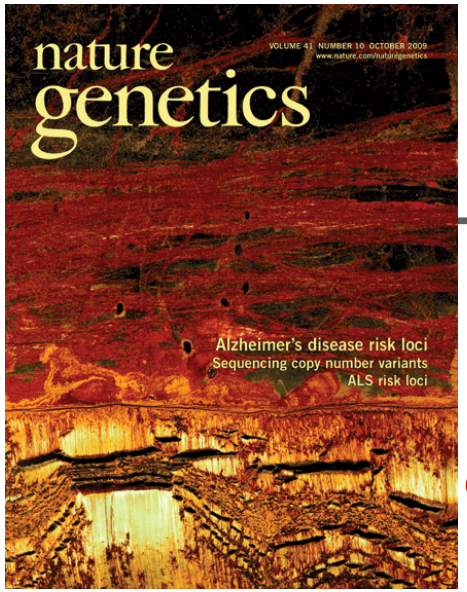
SNP's year

GWAS studiano simultaneamente molti SNPs e suggeriscono quali sono i geni che possono influenzare il rischio di malattia

In un GWA , il DNA di soggetti con e senza malattia è ibridato al chip che consente di genotipizzare dai 300.000 a 1 milione dei 14 milioni di SNP attualmente convalidati nel genoma umano.

Dato che uno SNP in una particolare regione frequentemente predice altri SNPs nelle vicinanze, i chip dei GWAS possono determinare in modo efficiente gran parte delle comuni variazioni del DNA nelle 3000000000 bp genoma umano e nei 20.000 -25.000 geni.

October 2009



LETTERS

nature genetics

Genome-wide association study identifies variants at *CLU* and *CR1* associated with Alzheimer's disease

Jean-Charles Lambert[1–3], Simon Heath[4], Gael Even[1,2], Dominique Campion[5], Kristel Sleegers[6,7], Mikko Hiltunen[8], Onofre Combarros[9], Diana Zelenika[4], Maria J Bullido[10], Béatrice Tavernier[11], Luc Letenneur[12], Karolien Bettens[6,7], Claudine Berr[13], Florence Pasquier[3,14], Nathalie Fiévet[1,2], Pascale Barberger-Gateau[12], Sebastiaan Engelborghs[7,15], Peter De Deyn[7,15], Ignacio Mateo[9], Ana Franck[16], Seppo Helisalmi[8], Elisa Porcellini[17], Olivier Hanon[18], the European Alzheimer's Disease Initiative Investigators[19], Marian M de Pancorbo[20], Corinne Lendon[21], Carole Dufouil[22,23], Céline Jaillard[24], Thierry Leveillard[24], Victoria Alvarez[25], Paolo Bosco[26], Michelangelo Mancuso[27], Francesco Panza[28], Benedetta Nacmias[29], Paola Bossù[30], Paola Piccardi[31], Giorgio Annoni[32], Davide Seripa[33], Daniela Galimberti[34], Didier Hannequin[5], Federico Licastro[17], Hilkka Soininen[8], Karen Ritchie[13], Hélène Blanché[35], Jean-François Dartigues[12], Christophe Tzourio[22,23], Ivo Gut[4], Christine Van Broeckhoven[6,7], Annick Alpérovitch[22,23], Mark Lathrop[4,35] & Philippe Amouyel[1–3,14]

6000 patients/9000 controls

LETTERS

nature genetics

Genome-wide association study identifies variants at *CLU* and *PICALM* associated with Alzheimer's disease

Denise Harold[1,45*], Richard Abraham[1,45], Paul Hollingworth[1,45], Rebecca Sims[1], Amy Gerrish[1], Marian L Hamshere[1], Jaspreet Singh Pahwa[1], Valentina Moskvina[1], Kimberley Dowzell[1], Amy Williams[1], Nicola Jones[1], Charlene Thomas[1], Alexandra Stretton[1], Angharad R Morgan[1], Simon Lovestone[2], John Powell[3], Petroula Proitsi[3], Michelle K Lupton[3], Carol Brayne[4], David C Rubinsztein[5], Michael Gill[6], Brian Lawlor[6], Aoibhinn Lynch[6], Kevin Morgan[7], Kristelle S Brown[7], Peter A Passmore[8], David Craig[8], Bernadette McGuinness[8], Stephen Todd[8], Clive Holmes[9], David Mann[10], A David Smith[11], Seth Love[12], Patrick G Kehoe[12], John Hardy[13], Simon Mead[14], Nick Fox[15], Martin Rossor[15], John Collinge[14], Wolfgang Maier[16], Frank Jessen[16], Britta Schürmann[16], Hendrik van den Bussche[17], Isabella Heuser[18], Johannes Kornhuber[19], Jens Wiltfang[20], Martin Dichgans[21,22], Lutz Frölich[23], Harald Hampel[24,25], Michael Hüll[26], Dan Rujescu[25], Alison M Goate[27], John S K Kauwe[28], Carlos Cruchaga[27], Petra Nowotny[27], John C Morris[27], Kevin Mayo[27], Kristel Sleegers[29,30], Karolien Bettens[29,30], Sebastiaan Engelborghs[30,31], Peter P De Deyn[30,31], Christine Van Broeckhoven[29,30], Gill Livingston[32], Nicholas J Bass[32], Hugh Gurling[32], Andrew McQuillin[32], Rhian Gwilliam[33], Panagiotis Deloukas[33], Ammar Al-Chalabi[34], Christopher E Shaw[34], Magda Tsolaki[35], Andrew B Singleton[36], Rita Guerreiro[36], Thomas W Mühleisen[37,38], Markus M Nöthen[37,38], Susanne Moebus[39], Karl-Heinz Jöckel[39], Norman Klopp[40], H-Erich Wichmann[40–42], Minerva M Carrasquillo[43], V Shane Pankratz[44], Steven G Younkin[43], Peter A Holmans[1], Michael O'Donovan[1], Michael J Owen[1] & Julie Williams [1]

7000 patients/9000 controls

still 59% of the AD genetic determinants to be characterised

nature genetics

VOLUME 41 | NUMBER 10 | OCTOBER 2009 NATURE GENETICS

Genome-wide association study identifies variants at *CLU* and *CR1* associated with Alzheimer's disease

Jean-Charles Lambert[1–3], Simon Heath[4], Gael Even[1,2], Dominique Campion[5], Kristel Sleegers[6,7], Mikko Hiltunen[8], Onofre Combarros[9], Diana Zelenika[4], Maria J Bullido[10], Béatrice Tavernier[11], Luc Letenneur[12], Karolien Bettens[6,7], Claudine Berr[13], Florence Pasquier[3,14], Nathalie Fiévet[1,2], Pascale Barberger-Gateau[12], Sebastiaan Engelborghs[7,15], Peter De Deyn[7,15], Ignacio Mateo[9], Ana Franck[16], Seppo Helisalmi[8], Elisa Porcellini[17], Olivier Hanon[18], the European Alzheimer's Disease Initiative Investigators[19], Marian M de Pancorbo[20], Corinne Lendon[21], Carole Dufouil[22,23], Céline Jaillard[24], Thierry Leveillard[24], Victoria Alvarez[25], Paolo Bosco[26], Michelangelo Mancuso[27], Francesco Panza[28], Benedetta Nacmias[29], Paola Bossù[30], Paola Piccardi[31], Giorgio Annoni[32], Davide Seripa[33], Daniela Galimberti[34], Didier Hannequin[5], Federico Licastro[17], Hilkka Soininen[8], Karen Ritchie[13], Hélène Blanché[35], Jean-François Dartigues[12], Christophe Tzourio[22,23], Ivo Gut[4], Christine Van Broeckhoven[6,7], Annick Alpérovitch[22,23], Mark Lathrop[4,35] & Philippe Amouyel[1–3,14]

Beatrice Arosio[-], Eliecer Coto[-], Maria Del Zompo[-], Vincent Deramecourt[-], Jacques Epelbaum[-], Paola Forti[7], Alexis Brice[8], Raffaele Ferri[9], Elio Scarpini[10], Gabriele Siciliano[11], Vincenzo Solfrizzi[12], Sandro Sorbi[13], Gianfranco Spalletta[14], Giovanni Ravaglia[7], José Sahel[15], Fernando Valdivieso[16], Saila Vepsäläinen[17], Alberto Pilotto[18]

Francia, Italia, Belgio e Spagna

Firenze e Pisa

6000 patients/9000 controls

geni di suscettibilità

Malattia di Alzheimer: geni di suscettibilità

- **Apolipoproteina E**
- AACT
- VLDL receptor
- LRP
- A2M
- PS-1
- NACP
- TNF-α
- Tau
- Ubiquitin
- NOS3
- HLA-A2
- IL-1
- BCHE-K
- BLMH
- DLST
- CYP46
- ACE
- CST3
- MTHFR
- TNFRSF6
- ESR1
- Fe65
- Cat D
- BDNF

Apolipoproteina E

5 JUNE 2014 | VOL 510 | NATURE | 27

The forgetting GENE

For decades, most researchers ignored the leading genetic risk factor for Alzheimer's disease. That is set to change.

BY LAURA SPINNEY

© 1994 Oxford University Press

Human Molecular Genetics, 1994, Vol. 3, No. 4 569–574

Apolipoprotein E, ε4 allele as a major risk factor for sporadic early and late-onset forms of Alzheimer's disease: analysis of the 19q13.2 chromosomal region

Marie-Christine Chartier-Harlin[1], Matthew Parfitt[1,2], Sylvie Legrain[3], Jordi Pérez-Tur[1], Thierry Brousseau[4], Alun Evans[5], Claudine Berr[6], Odile Vidal[4], Penelope Roques[2], Véronique Gourlet[6], Jean-Charles Fruchart[4], André Delacourte[1], Martin Rossor[2] and Philippe Amouyel[4,7,*]

APOE-ε4 count predicts age when prevalence of AD increases, then declines

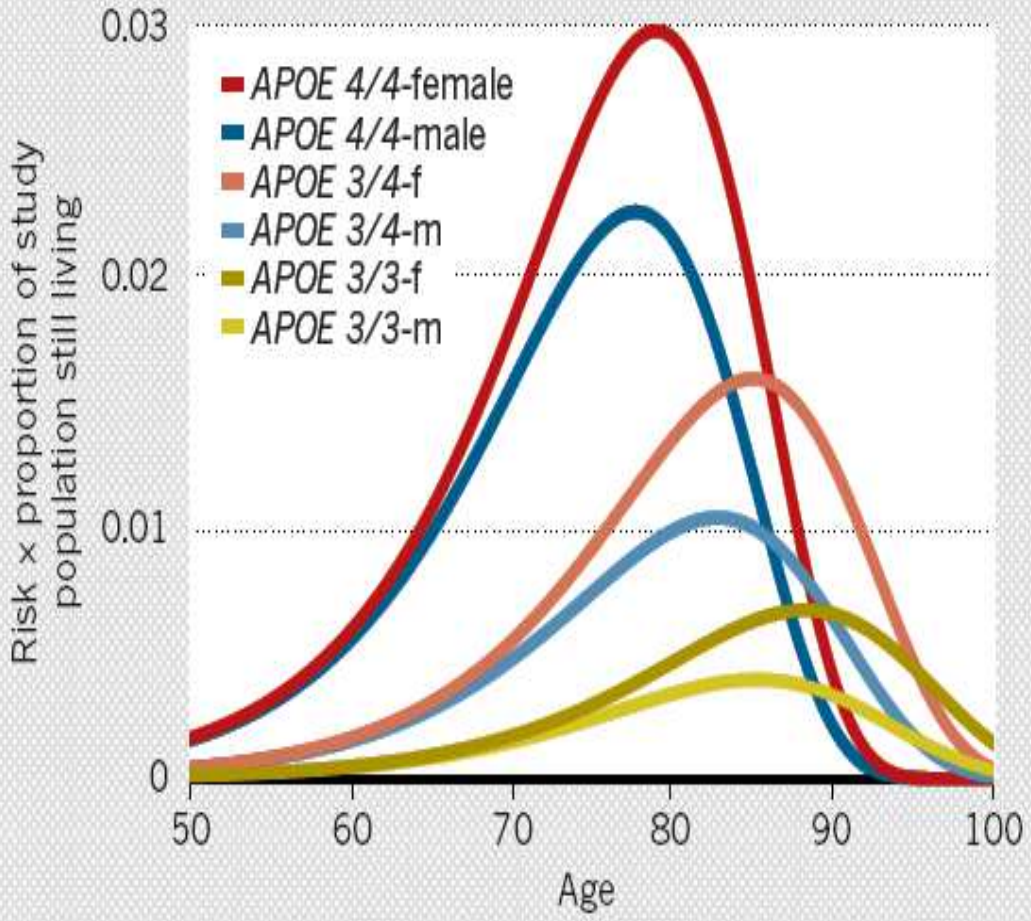
The Cache County Study

J.C.S. Breitner, MD, MPH; B.W. Wyse, PhD; J.C. Anthony, PhD; K.A. Welsh-Bohmer, PhD; D.C. Steffens, MD; M.C. Norton, MS; J.T. Tschanz, PhD; B.L. Plassman, PhD; M.R. Meyer, PhD; I. Skoog, MD; and A. Khachaturian, BS

NEUROLOGY 1999;53:321–331

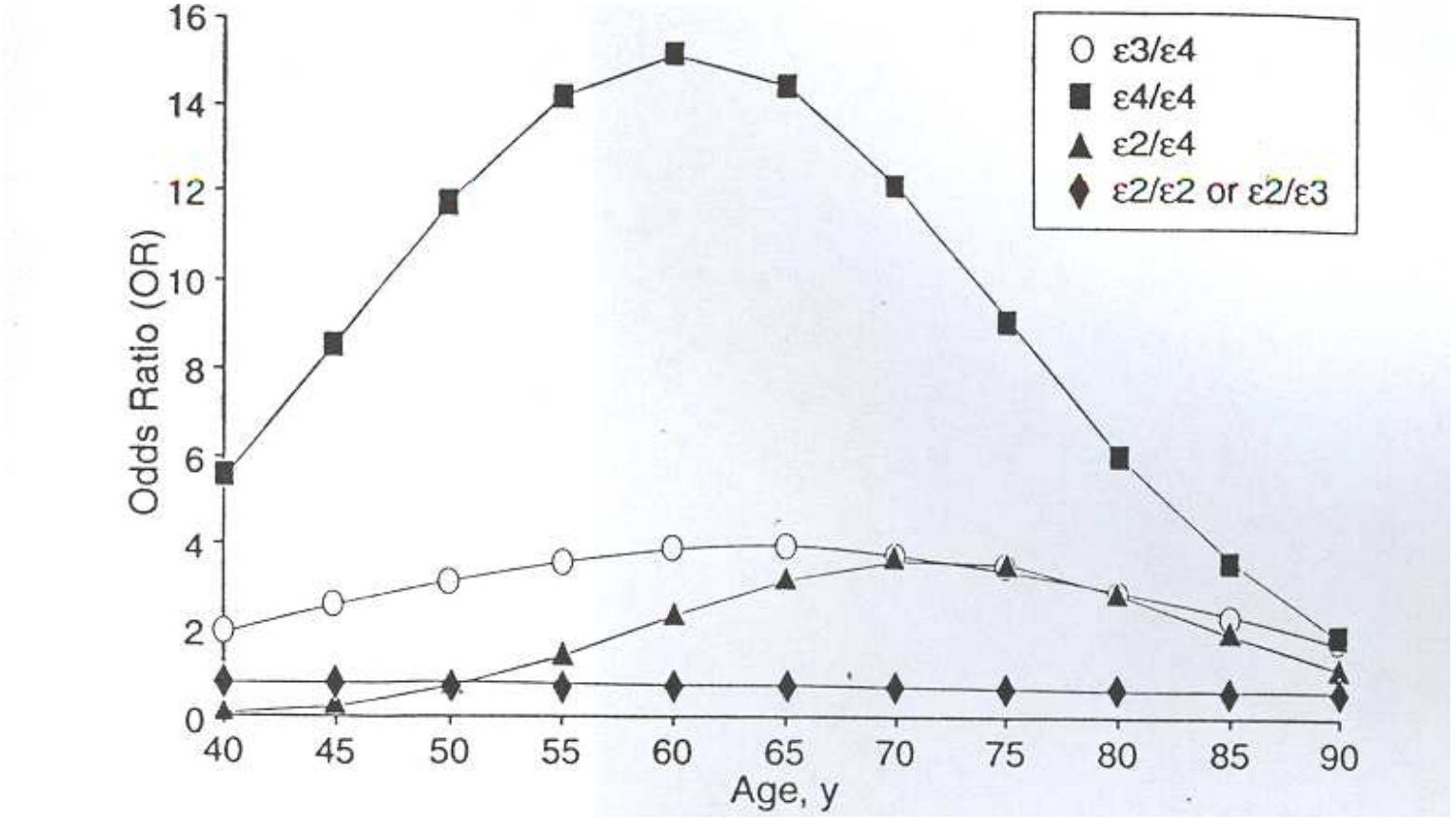
RISKY INHERITANCE

People who carry the gene variant *APOE4* tend to develop Alzheimer's at a younger age than those with two copies of *APOE3*.



APOE genotype and Alzheimer disease

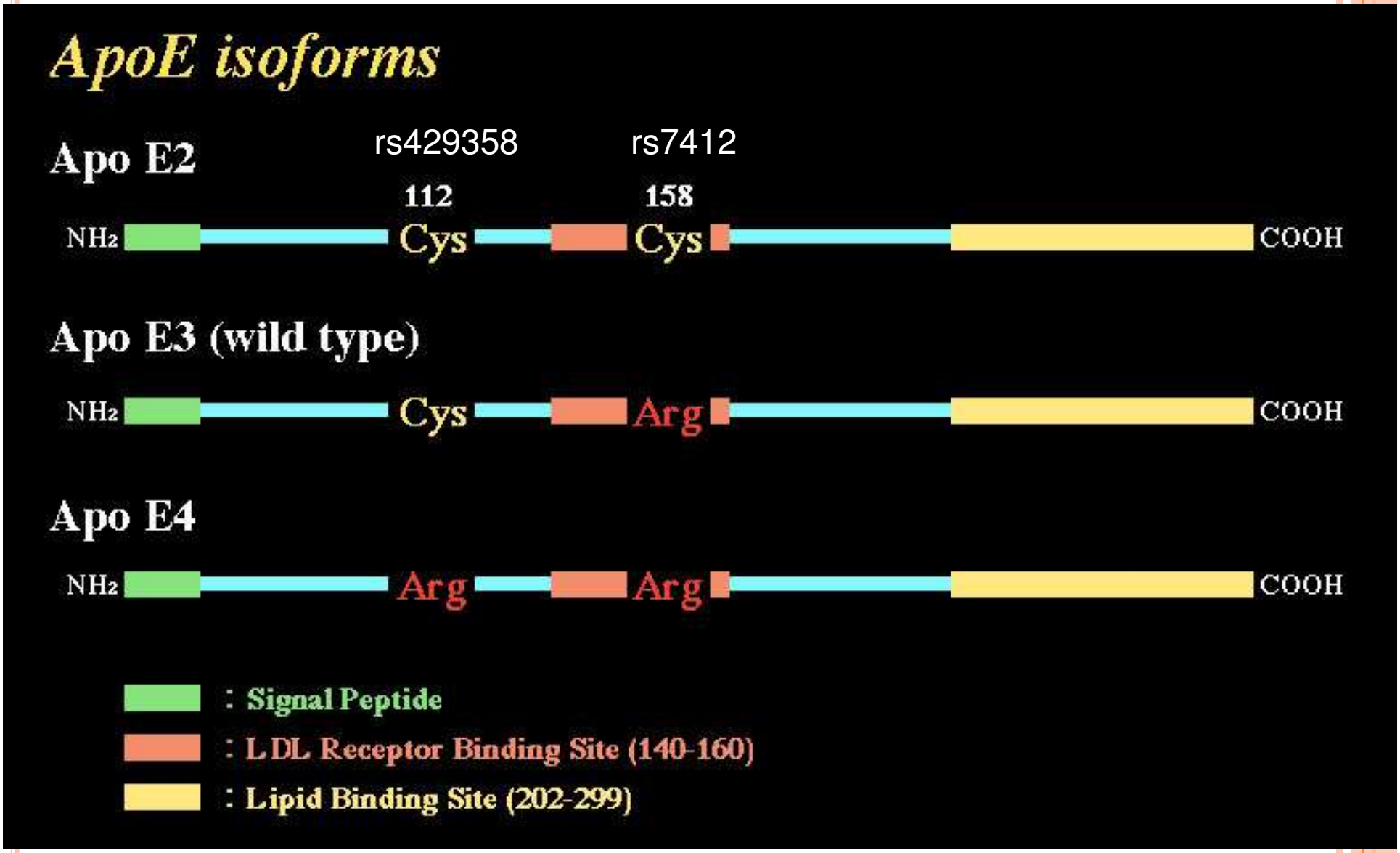
40.000 alleli



Farrer L. A., Cupples A., Haines J., Human B., Kukull W.A., Mayeux R., Myers R., Pericack-Vance M., Risch N., van Duijn C., **Sorbi S.**, and the ***ApoE and Alzheimer disease Meta Analysis Consortium***

JAMA 1997

Apolipoproteina E (ApoE chr. 19)



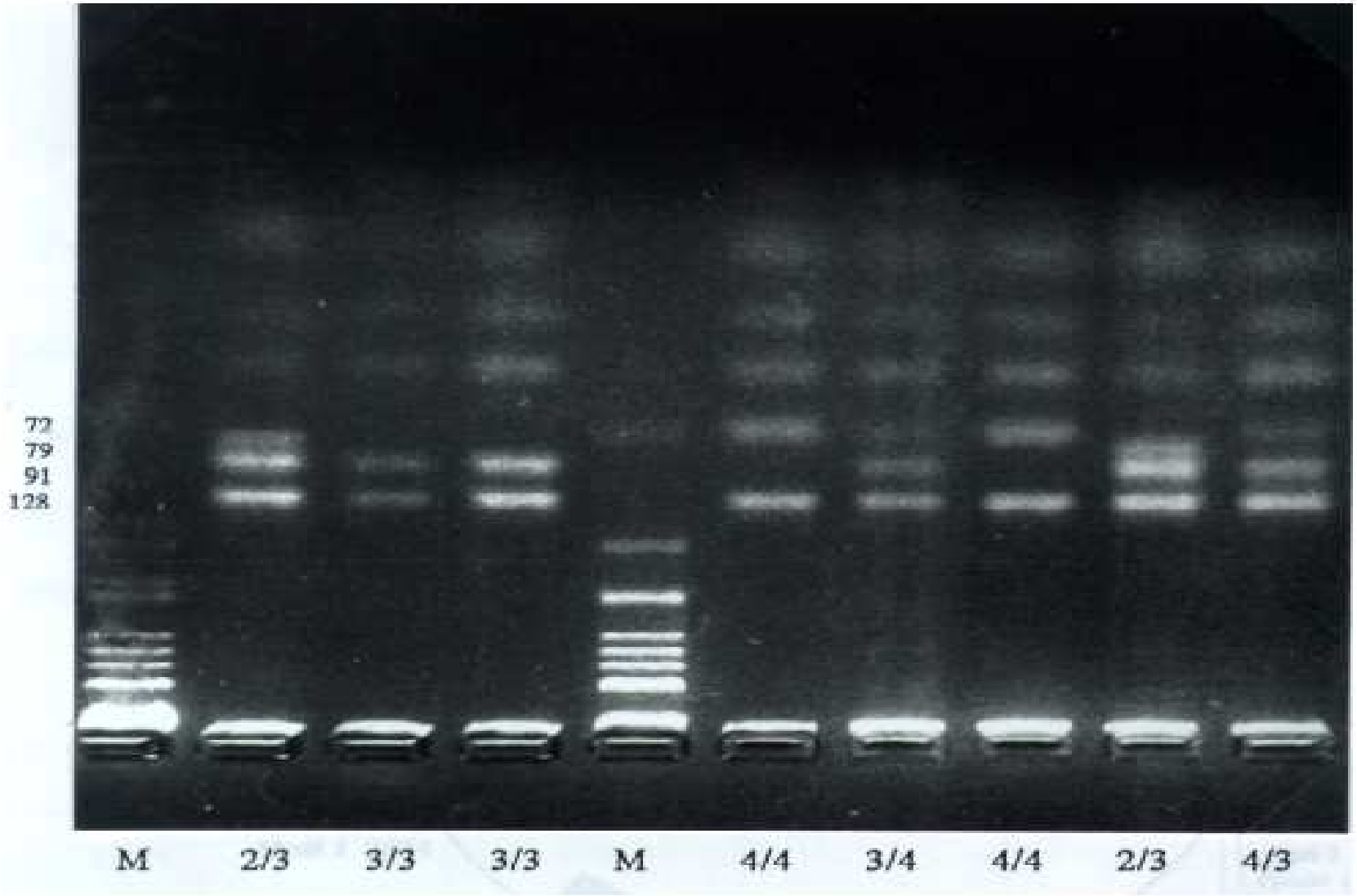
L'enzima di restrizione HhaI riconosce la sequenza:

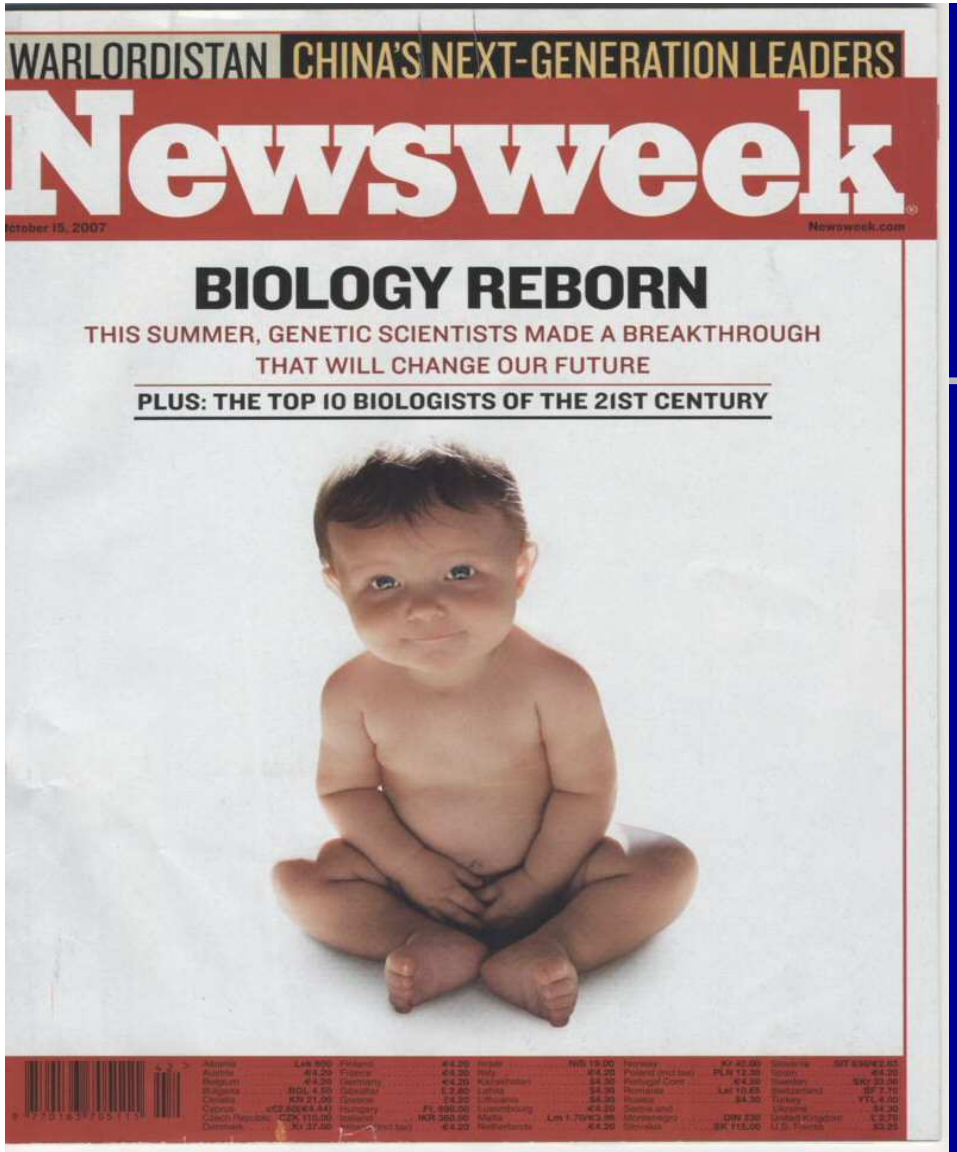
5′ ...GCG▼C...3′
3′ ...C▲GCG...3′

CGC	Arg
UGC	Cys

CGGCCGCAGGGCGCTGATGGACGAGACCATGAAGGAGTTGAAGGCCTACAAATCGGAAC
TGGAGGAACAACTGACCCCGGTGGCGGAGGAGACGCGGGCACGGCTGTCCAAGGAGCTG
CAGGCGGCGCAGGCCCGGCTGGGCGCGGACATGGAGGACGTG[C/T]GCGGCCGCCTGGTG
CAGTACCGCGGCGAGGTGCAGGCCATGCTCGGCCAGAGCACCGAGGAGCTGCGGGTGCG
CCTCGCCTCCCACCTGCGCAAGCTGCGTAAGCGGCTCCTCCGCGATGCCGATGACCTGCAG
AAG[C/T]GCCTGGCAGTGTACCAGGCCGGGGCCCGCGAGGGCGCCGAGCGCGGCCTCAGC
GCCATCCGCGAGCGCCTGGGGCCCCTGGTGGAACAGGGCCGCGTGCGGGCCGCCACTGTG
GGCTCCCTGGCCGGCCAGCCGCTACAGGAGCGGGCCCAGGCCTGGGGCGAGCGGCTGCG

PCR-RFLP (Restriction Fragment Length Polymorphism)





2007

The Year of miracles

snp's year

Negli ultimi mesi nuove tecnologie e ricerca hanno scardinato alcuni dogmi del 20 secolo. Gli scienziati sanno ora che la nozione del gene mendeliano inteso come unità di ereditarietà non regge più.

Cosa la sta sostituendo? Si ritiene che l'ereditarietà sia il risultato dell'interazione estremamente complessa tra i componenti base del genoma, distribuiti fra diversi geni, persino in vasti tratti del DNA spazzatura, che un tempo si pensava non avesse alcuno scopo. Una volta abbandonata la nozione di gene, si guarda alle lettere del DNA, le 4 basi A,T, G, C e a vedere connessioni causa effetto per numerose malattie e caratteristiche, tratti umani

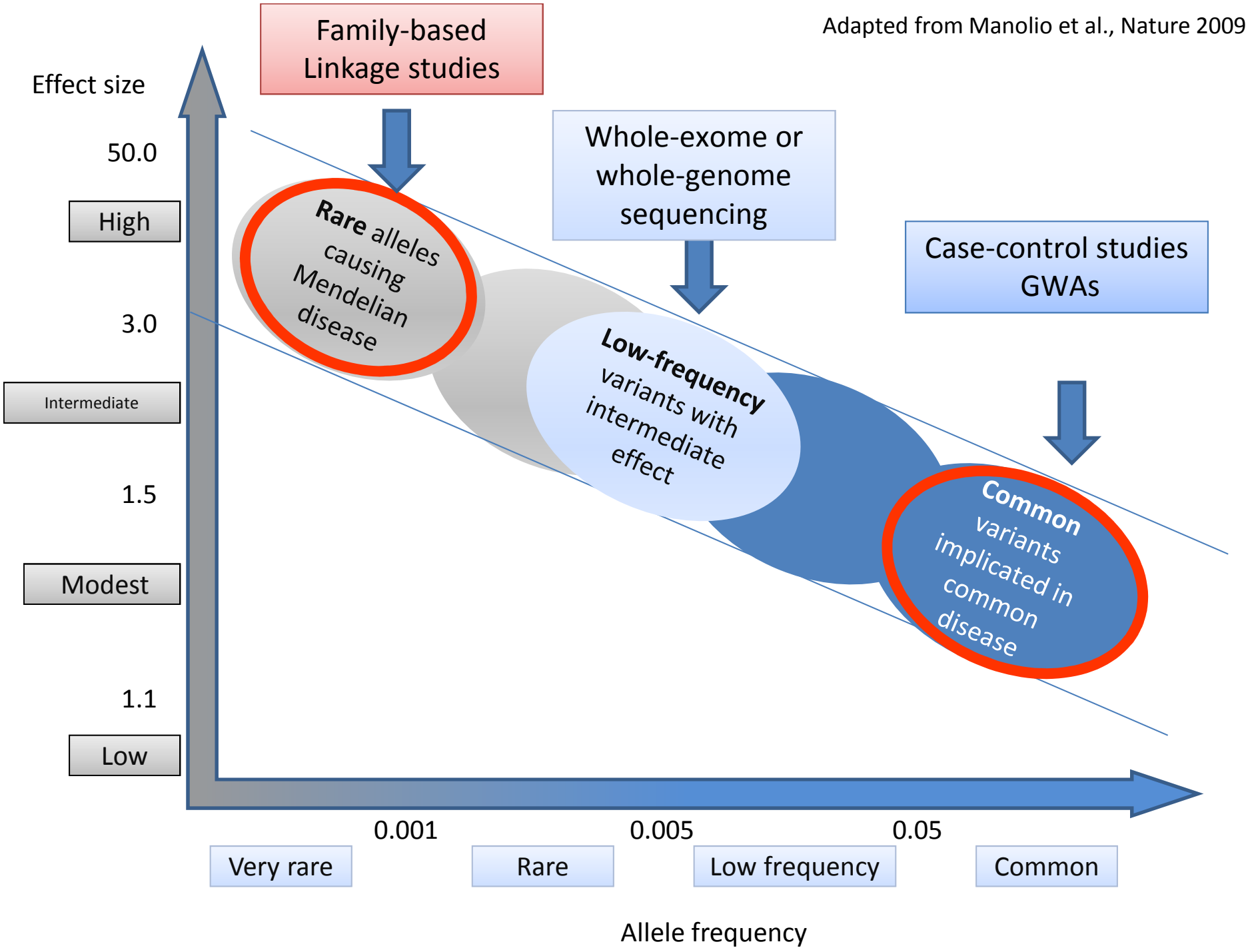
REPORTS

A Single IGF1 Allele Is a Major Determinant of Small Size in Dogs

Nathan B. Sutter, et al

SCIENCE april 2007

A single IGF1 single-nucleotide polymorphism haplotype is common to all small breeds and nearly absent from giant breeds, suggesting that the same causal sequence variant is a major contributor to body size in all small dogs


Adapted from Manolio et al., Nature 2009
Family-based Linkage studies
Whole-exome or whole-genome sequencing
Case-control studies GWAs
Effect size
50.0
High
3.0
Intermediate
1.5
Modest
1.1
Low
Rare alleles causing Mendelian disease
Low-frequency variants with intermediate effect
Common variants implicated in common disease
0.001
0.005
0.05
Very rare
Rare
Low frequency
Common
Allele frequency

Geni e demenze

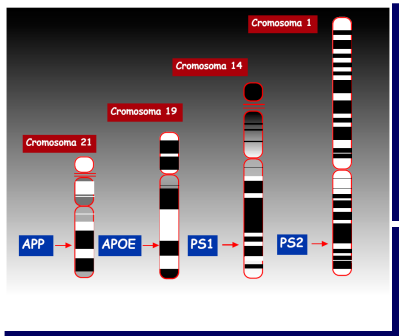
FAD

FTLD

2017

Gene	# Mutations	# Families
APP	51 (9.86 %)	121 (7.35 %)
PSEN1	219 (42.36 %)	480 (29.16 %)
PSEN2	16 (3.09 %)	34 (2.07 %)
C9orf72	1 (0.19 %)	336 (20.41 %)
CHMP2B	4 (0.77 %)	5 (0.30 %)
FUS	23 (4.45 %)	49 (2.98 %)
GRN	79 (15.28 %)	259 (15.74 %)
MAPT	44 (8.51 %)	134 (8.14 %)
TARDBP	33 (6.38 %)	134 (8.14 %)
TBK1	28 (5.42 %)	45 (2.73 %)
VCP	19 (3.68 %)	49 (2.98 %)
Total	**517**	**1646**

FAD Familial Alzheimer's Disease FTLD Frontotemporal lobe Degeneration

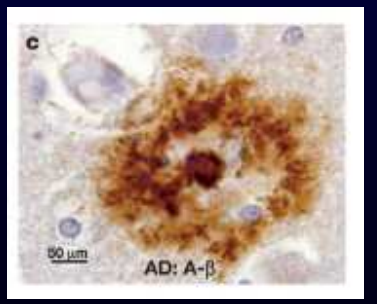


GENETICA DELLA MALATTIA DI ALZHEIMER

Forme Familiari

- **APP (21q21)** → **51 mutazioni**
  Amyloid precursor protein
- **PS1 (14q24.3)** → **219 mutazioni**
  Presenilin 1
- **PS2 (1q31-q32)** → **16 mutazioni**
  Presenilin 2

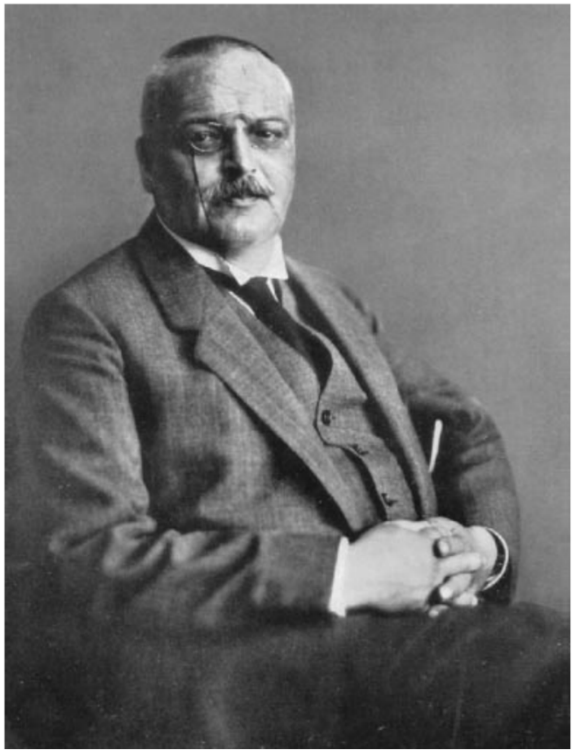
Aβ42 ↑
Principale componente delle placche amiloidi



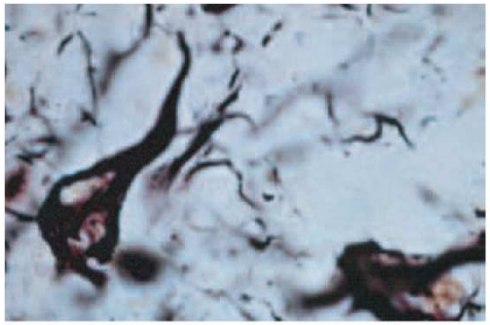
Squilibrio tra produzione e clearance di Aβ

http://molgen-www.uia.ac.be/ADMutations

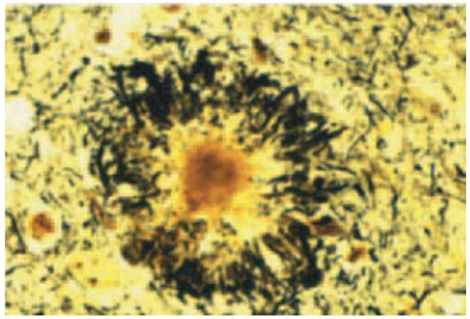
La malattia di Alzheiemer è la piu comune forma di demenza



Da punto di vista microscopico:
placche senili (proteina Beta amiloide) e
grovigli neurofibrillari (proteina tau) che sono
 i reperti neuropatologici che si riscontrano prima
Dello sviluppo dei sintomi clinici



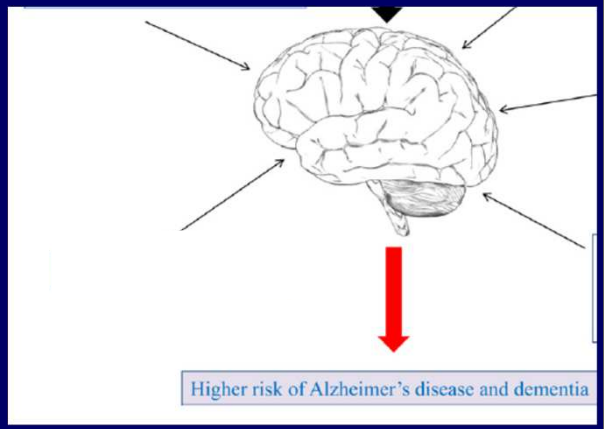
Tau based neurofibrillary tangle

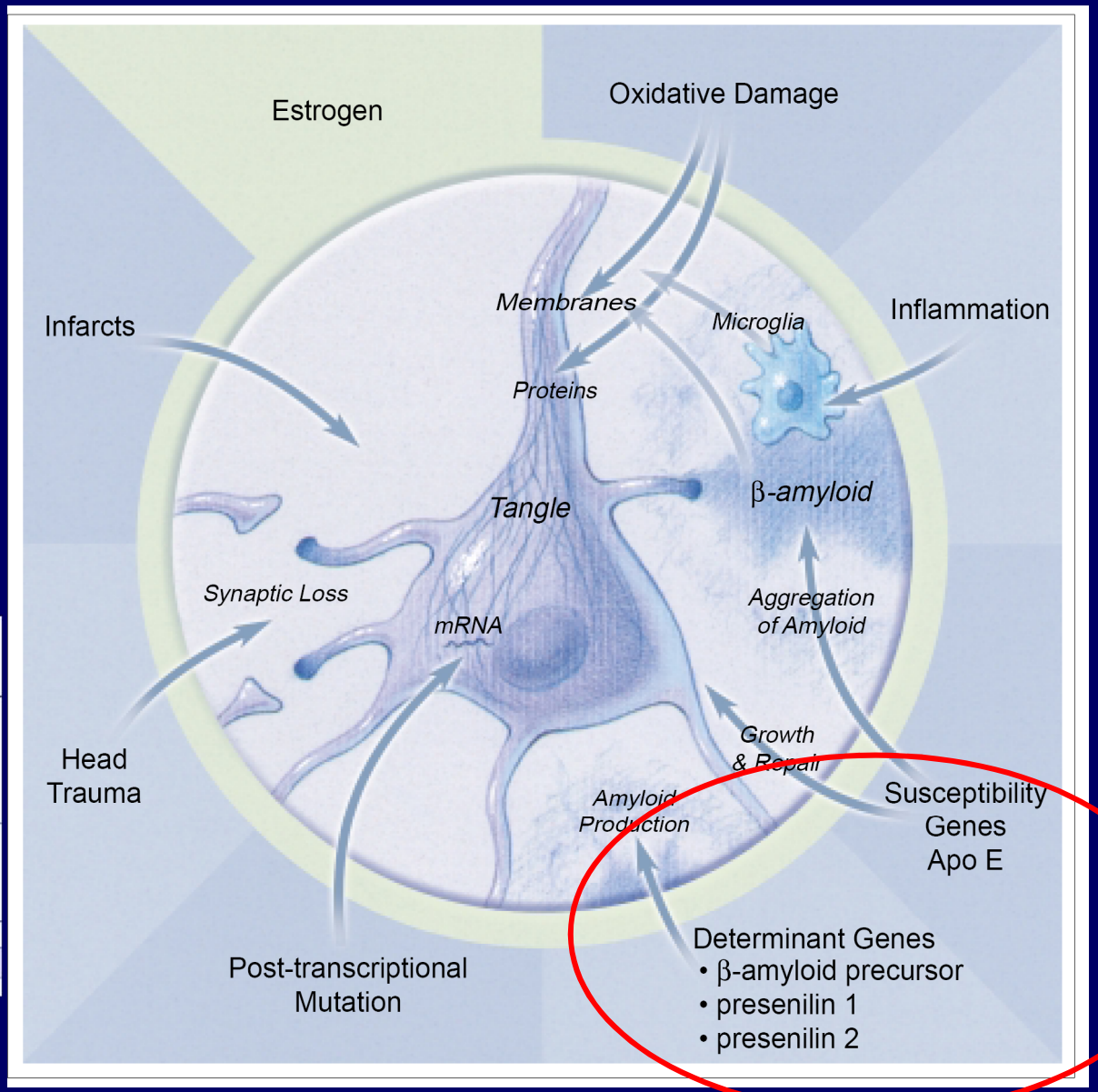


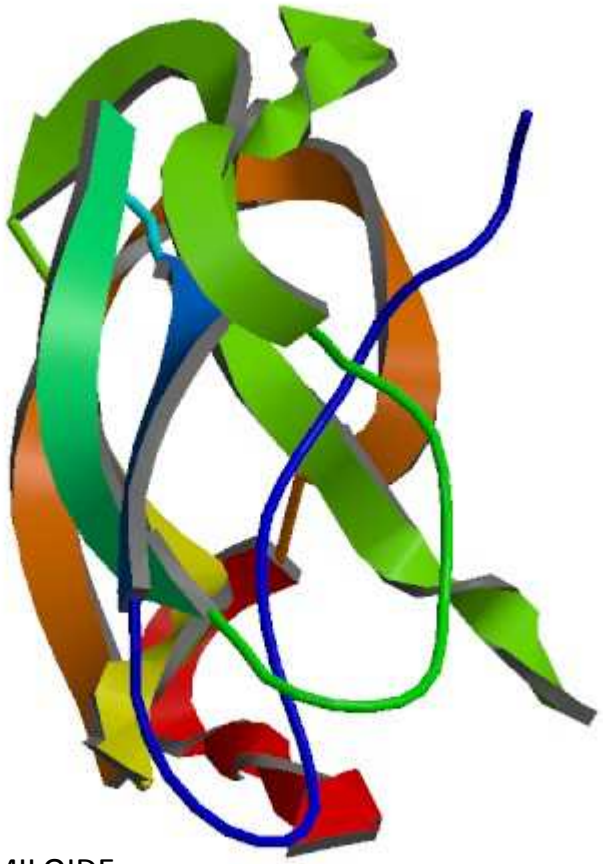
Amyloid based Neuritic plaque

La diagnosi certa di malattia è autoptica. La diagnosi clinica è sempre di probabilità

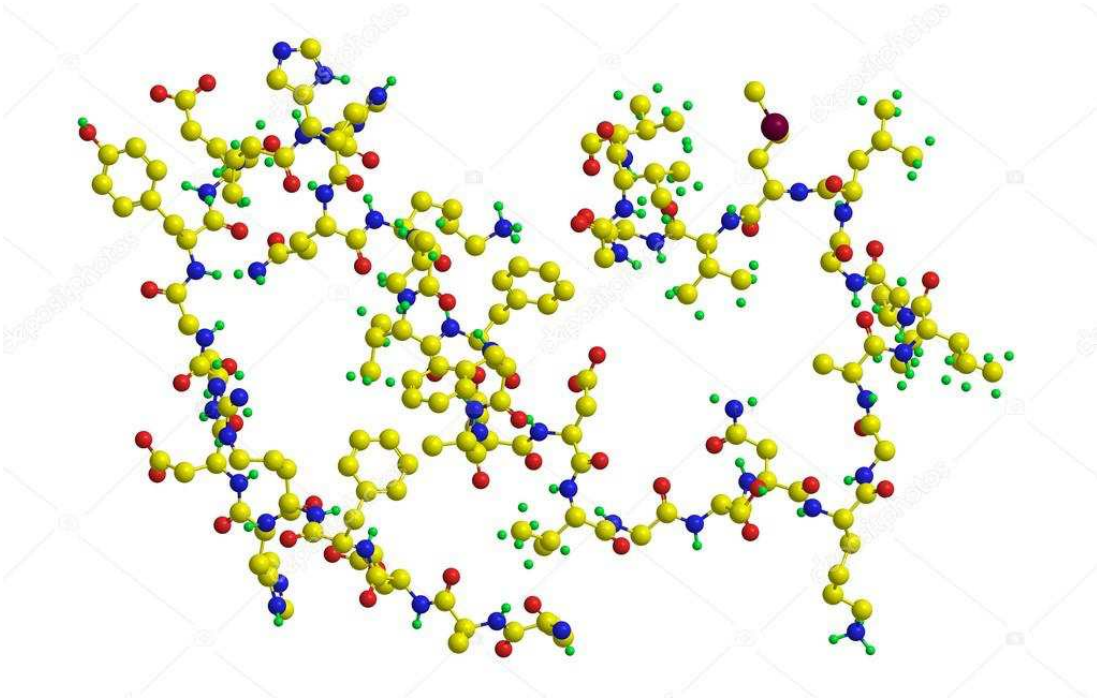
Cause della malattia di Alzhiemer







AMILOIDE



Beta amiloide struttura molecolare

10 aprile 1992: Amyloid Cascade Hypothesis

PERSPECTIVE

Science

Alzheimer's Disease: The Amyloid Cascade Hypothesis

John A. Hardy and Gerald A. Higgins

Alzheimer's disease causes dementia in many elderly people and in some individuals with Down syndrome who survive to age 50. Alzheimer's is characterized by various pathological markers in the brain—large numbers of amyloid plaques surrounded by neurons containing neurofibrillary tangles (*1*), vascular damage from extensive plaque deposition (*2*), and neuronal cell loss (*1*). Because it is not known if the amyloid plaques or the neurofibrillary tangles are the earliest lesion in the disease process, the role of these markers in the etiology of the disease is controversial.

Our hypothesis is that deposition of amyloid β protein (AβP), the main component of the (*3*) plaques, is the causative agent of Alzheimer's pathology and that the neurofibrillary tangles, cell loss, vascular damage, and dementia follow as a direct result of this deposition. AβP is a peptide product of the larger amyloid precursor protein (APP) (*4*). Because Down syndrome is caused by trisomy of the region of chromosome 21 that contains the APP gene, deposition of AβP is likely to be an early event in the disease (*5*). The AβP molecule is a 39– to 42–amino acid peptide (*4, 6*), part of which forms the hydrophobic transmembrane domain in the COOH-terminal portion of APP (Fig. 1). AβP is one of a diverse group of "amyloid" (starch-like) proteins that forms insoluble extracellular deposits. The APP gene undergoes alternative RNA splicing to produce several protein isoforms; the predominant variant in brain lacks a serine protease inhibitor domain that is present in APP molecules in cerebrospinal fluid (*9*). The APP secretase that cuts within the AβP region has an extraordinarily broad sequence specificity and recognizes the secondary structure of APP, cleaving at a defined distance from the membrane (*10*). Several recent studies suggest that APP can also be processed by the endosomal-lysosomal pathway, after recycling of membrane-bound APP and possibly via an intracellular metabolic route (*11–13*). Carboxyl-terminal fragments containing the entire AβP sequence can be derived from this alternate normal processing of APP (*12, 14*) and may eventually lead to amyloid deposition (*12, 14*) (Fig. 1).

Alzheimer's disease. These mutations all occur at codon 717 of the protein (*15, 16*) and change the native valine, located three residues from the COOH-terminal end of AβP, to isoleucine, phenylalanine, or glycine (Fig. 1). It is unclear how these mutations cause amyloid deposition, but they may inhibit the breakdown of a COOH-terminal fragment of APP that contains AβP (*15*), alter the anchoring of APP in the cell membrane, or stabilize AβP-containing amyloidogenic fragments within lysosomes (*12, 15*).

Our cascade hypothesis states that AβP itself, or APP cleavage products containing AβP, are neurotoxic and lead to neurofibrillary tangle formation and cell death. Thus, two successive events are needed to produce Alzheimer's pathology. First, AβP must be generated as an intact entity, either by accumulation of AβP or as an AβP-containing fragment of APP. Second, this molecule must facilitate or cause neuronal death and neurofibrillary tangle formation. Neve and her colleagues have reported that

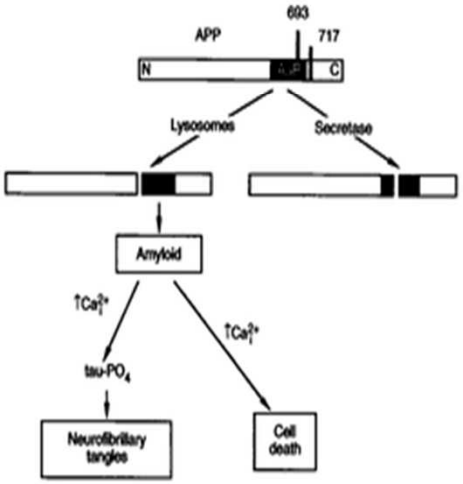
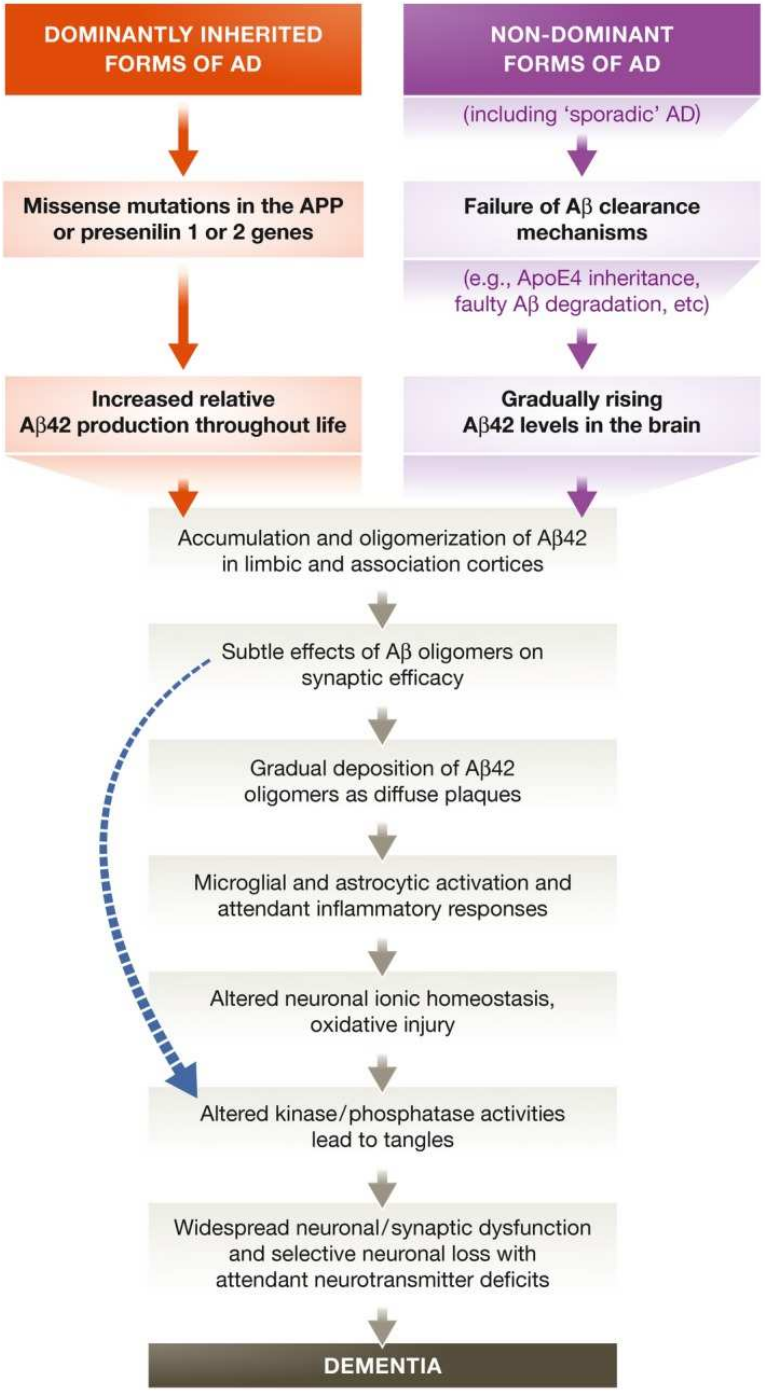


Fig. 1. The amyloid cascade hypothesis. Processing of APP can occur via two pathways: (i) Cleavage within AβP by the secretase, which generates peptide products that do not precipitate to form amyloid and (ii) cleavage in the endosomal-lysosomal compartment, resulting in intact AβP that precipitates to form amyloid and, in turn, causes neurofibrillary tangles and cell death, the hallmarks of Alzheimer's disease.



Review

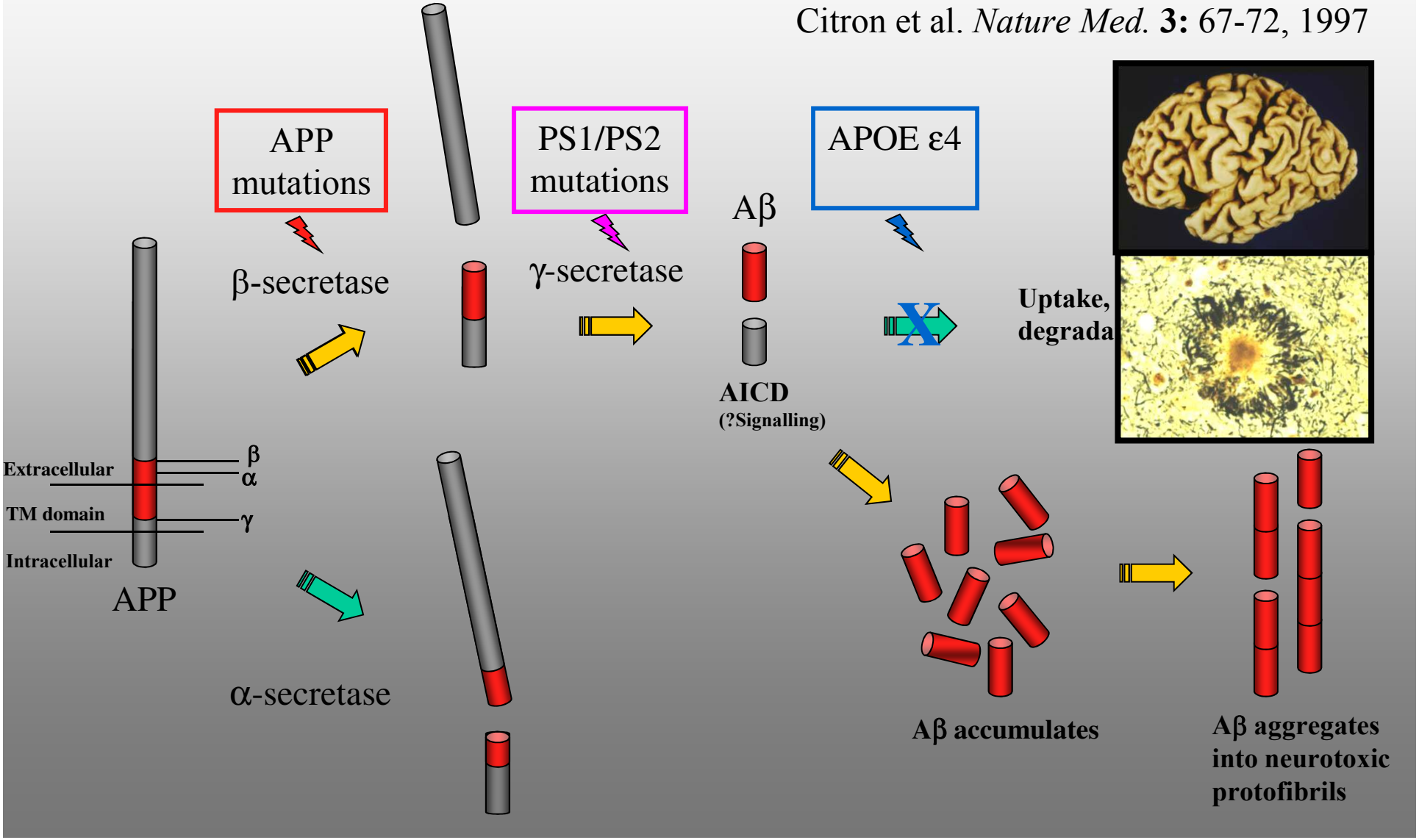
OPEN ACCESS

EMBO Molecular Medicine

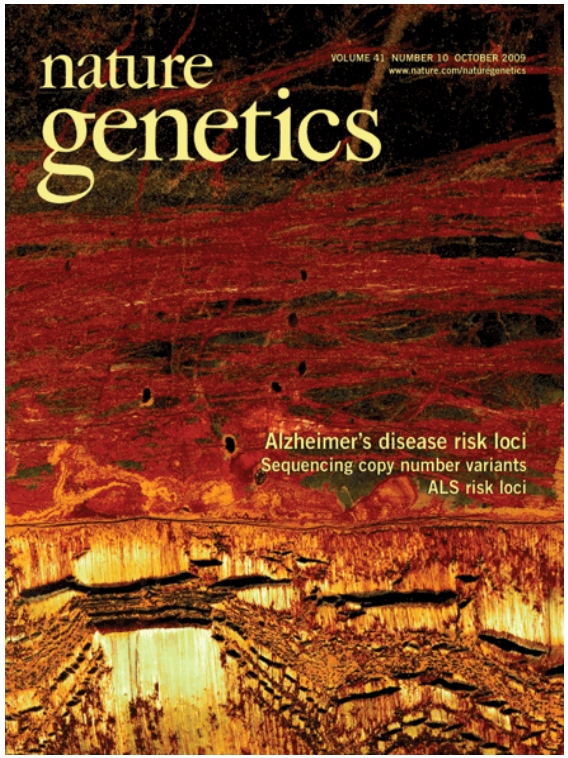
The amyloid hypothesis of Alzheimer's disease at 25 years

Dennis J Selkoe[1,†] & John Hardy[2,*,†]

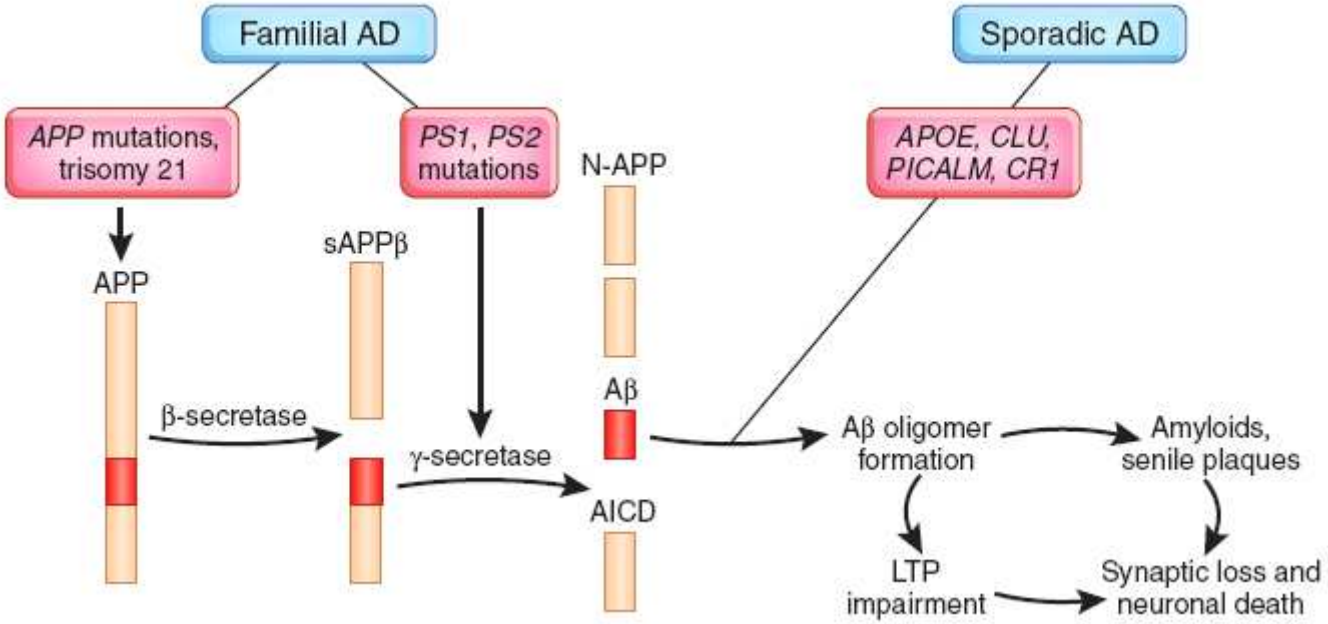
Mutations Causing Alzheimer Disease cause mis-processing of APP



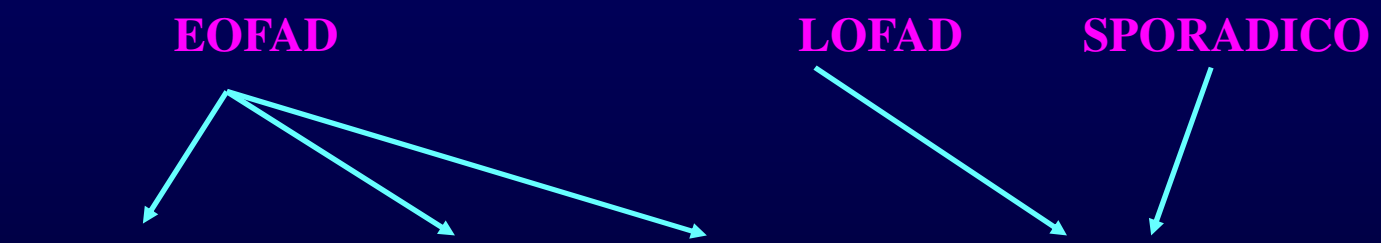
Alzheimer's disease beyond *APOE*



Michael A van Es & Leonard H van den Berg



DETERMINANTI GENETICI NELLA MALATTIA DI ALZHEIMER

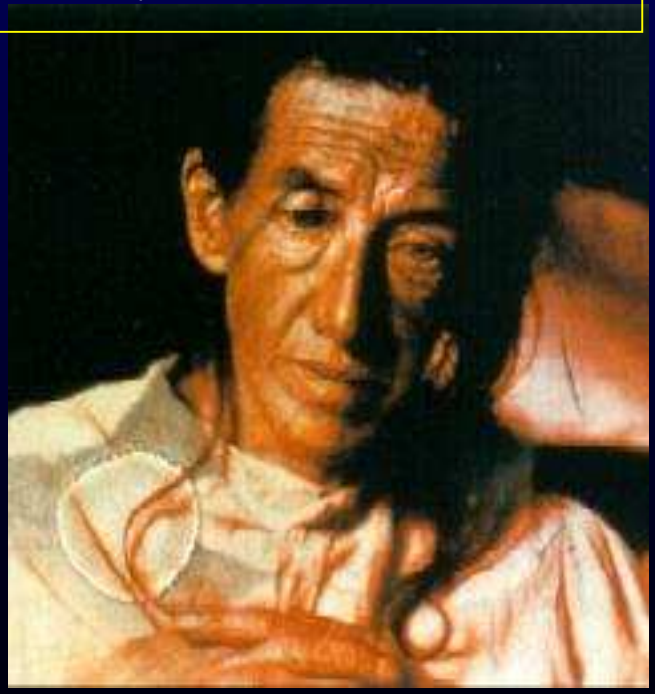


GENE PSEN1	GENE APP	GENE PSEN2	ApoE
(Chr. 14)	(Chr. 21)	(Chr. 1)	(Chr. 19)
Età 25-60 anni	Età 40-65 anni	Età 45-84 anni	>50 anni

ALTRI GENI ANCORA DA IDENTIFICARE

Nel suo articolo del 1907 "Una caratteristica malattia della corteccia cerebrale" Alois Alzheimer riporta il caso di una donna morta a 51 anni e che era stata istituzionalizzata all'età di 46 anni a Francoforte.

Auguste D.: morta a 51 anni, dopo una malattia durata circa 8 anni e caratterizzata da decadimento cognitivo sintomi focali, allucinazioni, delirio e incompetenza psico sociale



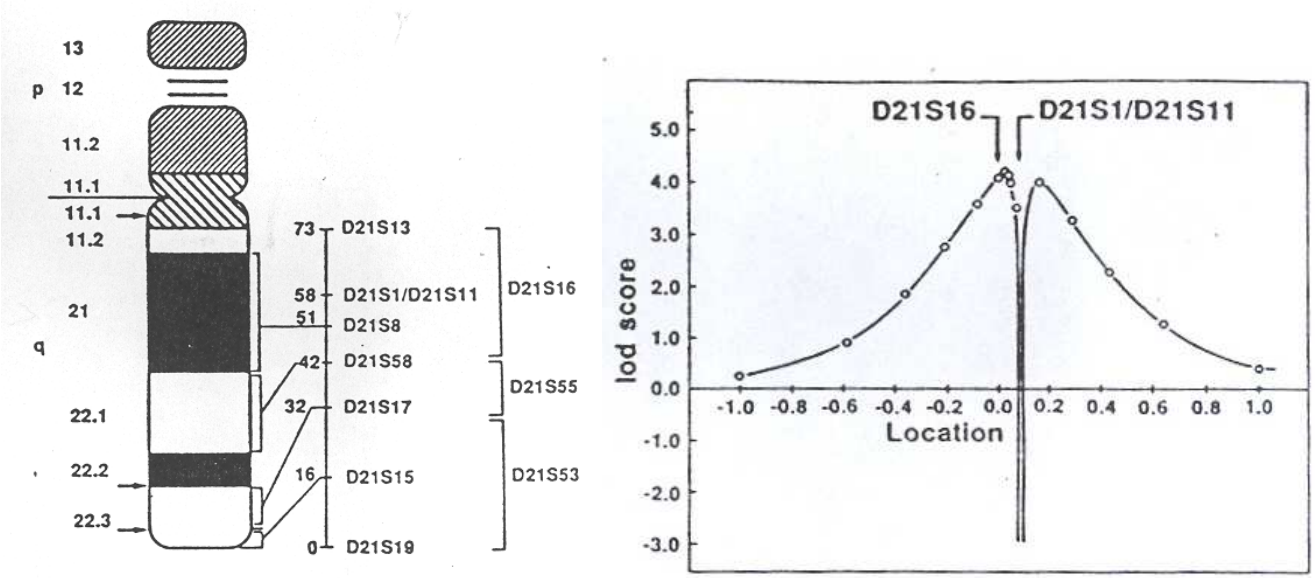
Alzheimer A.: Uber einen eigenartigen schweren Erkrankungsprozeβ der Hirnrinde. Neurologisches Centralblatt

The genetic defect causing familial Alzheimer's disease maps on chromosome 21.

St. George-Hyslop P., Tanzi R.E., Polinsky R., Haines J., Nee L., Watkins P.C., Myers R., Feldman R., Pollen D., Drachmann D., Growdon J., Bruni A., Foncin J-F., Salmon D., Frommelt P., Amaducci L., Sorbi S., Piacentini S., Stuart G.D., Hobbs W.E., Conneally M.P., Gusella J.

Science 1987, 235:885-890.

AD Genetica : 30 anni



NATURE · VOL 347 · 13 SEPTEMBER 1990

Genetic linkage studies suggest that Alzheimer's disease is not a single homogeneous disorder

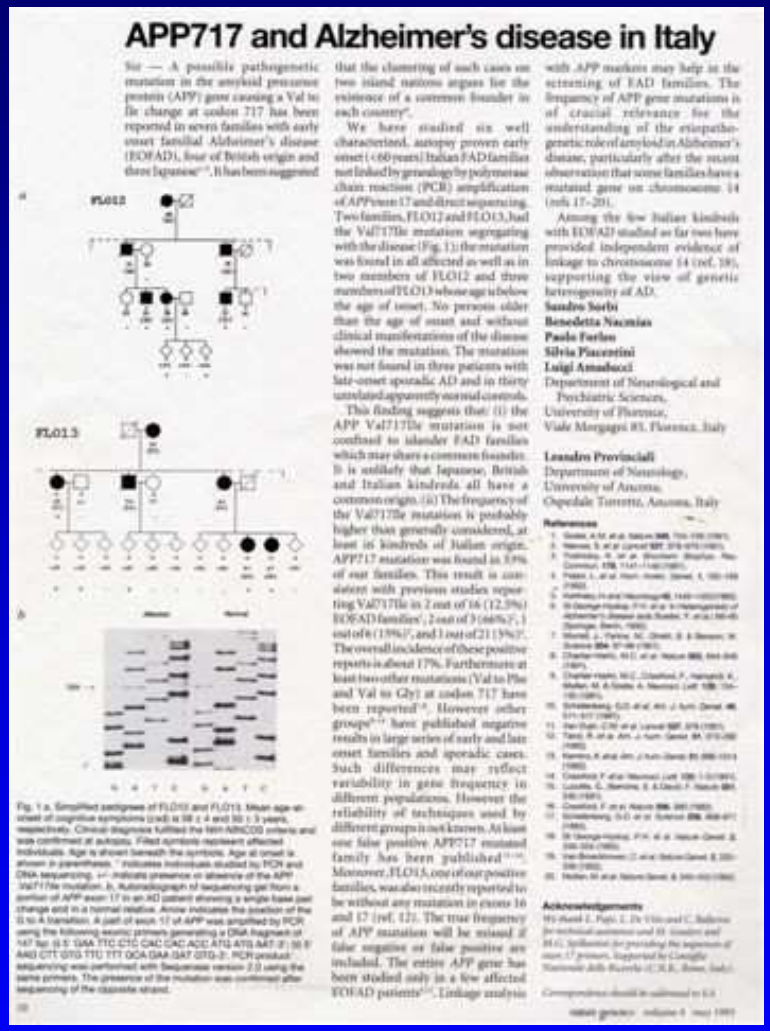
P. H. St George-Hyslop*, J. L. Haines*, L. A. Farrer†, R. Polinsky‡, C. Van Broeckhoven§, A. Goate‖, D. R. Crapper McLachlan¶, H. Orr#, A. C. Bruni**, S. Sorbi††, I. Rainero‡‡, J.-F. Foncin§§, D. Pollen‖‖, J-M. Cantu¶¶, R. Tupler##, N. Voskresenskaya***, R. Mayeux†††, J. Growdon*, V. A. Fried*, R. H. Myers†, L. Nee‡, H. Backhovens§, J-J. Martin§, M. Rossor‖, M. J. Owen‖, M. Mullan‖, M. E. Percy¶, H. Karlinsky¶, S. Rich#, L. Heston#, M. Montesi**, M. Mortilla††, N. Nacmias††, J. F. Gusella*, J. A. Hardy‖ & other members‡‡‡ of the FAD Collaborative Study group

Nature Genetics 4, 10 (1993)

APP717 and Alzheimer's disease in Italy

Sandro Sorbi, Benedetta Nacmias, Paolo Forleo, Silvia Piacentini, Leandro Provinciali, Luigi Amaducci

26 anni fa



APP717 and Alzheimer's disease in Italy

Sir — A possible pathogenetic mutation in the amyloid precursor protein (APP) gene causing a Val to Ile change at codon 717 has been reported in seven families with early onset familial Alzheimer's disease (EOFAD), four of British origin and three Japanese[1–4]. It has been suggested that the clustering of such cases on two island nations argues for the existence of a common founder in each country[4].

We have studied six well characterized, autopsy proven early onset (<60 years) Italian FAD families not linked by genealogy by polymerase chain reaction (PCR) amplification of APP exon 17 and direct sequencing. Two families, FLO12 and FLO13, had the Val717Ile mutation segregating with the disease (Fig. 1); the mutation was found in all affected as well as in two members of FLO12 and three members of FLO13 whose age is below the age of onset. No persons older than the age of onset and without clinical manifestations of the disease showed the mutation. The mutation was not found in three patients with late-onset sporadic AD and in thirty unrelated apparently normal controls.

This finding suggests that: (i) the APP Val717Ile mutation is not confined to islander FAD families which may share a common founder. It is unlikely that Japanese, British and Italian kindreds all have a common origin. (ii) The frequency of the Val717Ile mutation is probably higher than generally considered, at least in kindreds of Italian origin. *APP717* mutation was found in 3.9% of our families. This result is consistent with previous studies reporting Val717Ile in 2 out of 16 (12.5%) EOFAD families[1], 2 out of 3 (66%)[2], 1 out of 6 (17%)[3], and 1 out of 21 (5%)[4]. The overall incidence of these positive reports is about 17%. Furthermore at least two other mutations (Val to Phe and Val to Gly) at codon 717 have been reported[1,4]. However other groups[5–10] have published negative results in large series of early and late onset families and sporadic cases. Such differences may reflect variability in gene frequency in different populations. However the reliability of techniques used by different groups is not known. At least one false positive APP717 mutated family has been published[11–13]. Moreover, FLO13, one of our positive families, was also recently reported to be without any mutation in exons 16 and 17 (ref. 12). The true frequency of *APP* mutation will be missed if false negative or false positive are included. The entire *APP* gene has been studied only in a few affected EOFAD patients[1,4]. Linkage analysis with *APP* markers may help in the screening of FAD families. The frequency of APP gene mutations is of crucial relevance for the understanding of the etiopathogenetic role of amyloid in Alzheimer's disease, particularly after the recent observation that some families have a mutated gene on chromosome 14 (refs 17–20).

Among the few Italian kindreds with EOFAD studied so far two have provided independent evidence of linkage to chromosome 14 (ref. 18), supporting the view of genetic heterogeneity of AD.

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Benedetta Nacmias
Paolo Forleo
Silvia Piacentini
Luigi Amaducci
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Leandro Provinciali
Department of Neurology, University of Ancona, Ospedale Torrette, Ancona, Italy

References

Acknowledgements

APP717 and Alzheimer's disease in Italy

NATURE *Genetics*, 1993

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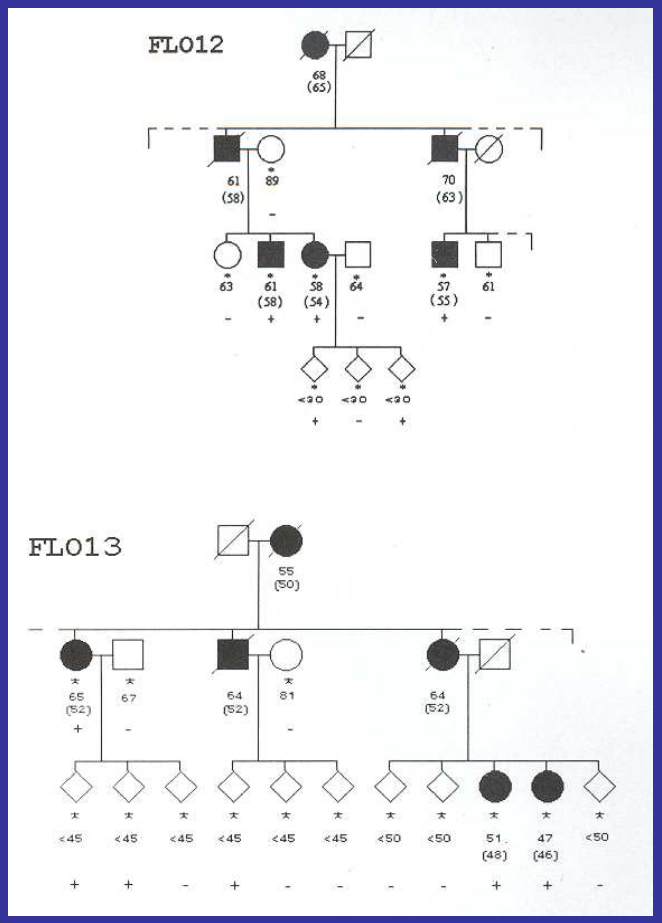
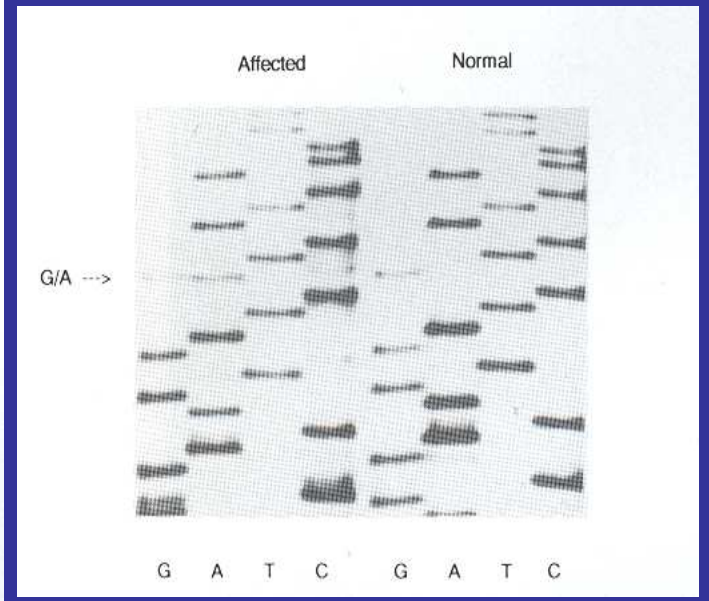
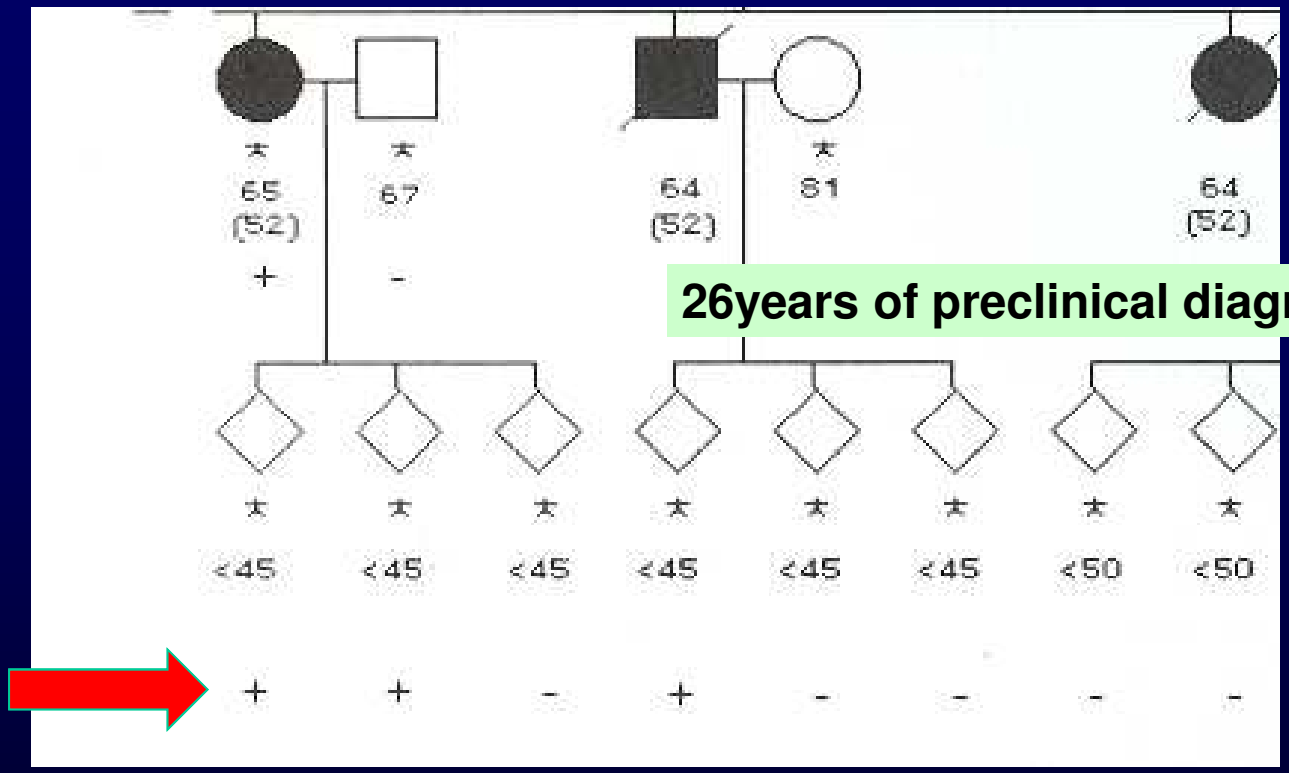
Leandro Provinciali

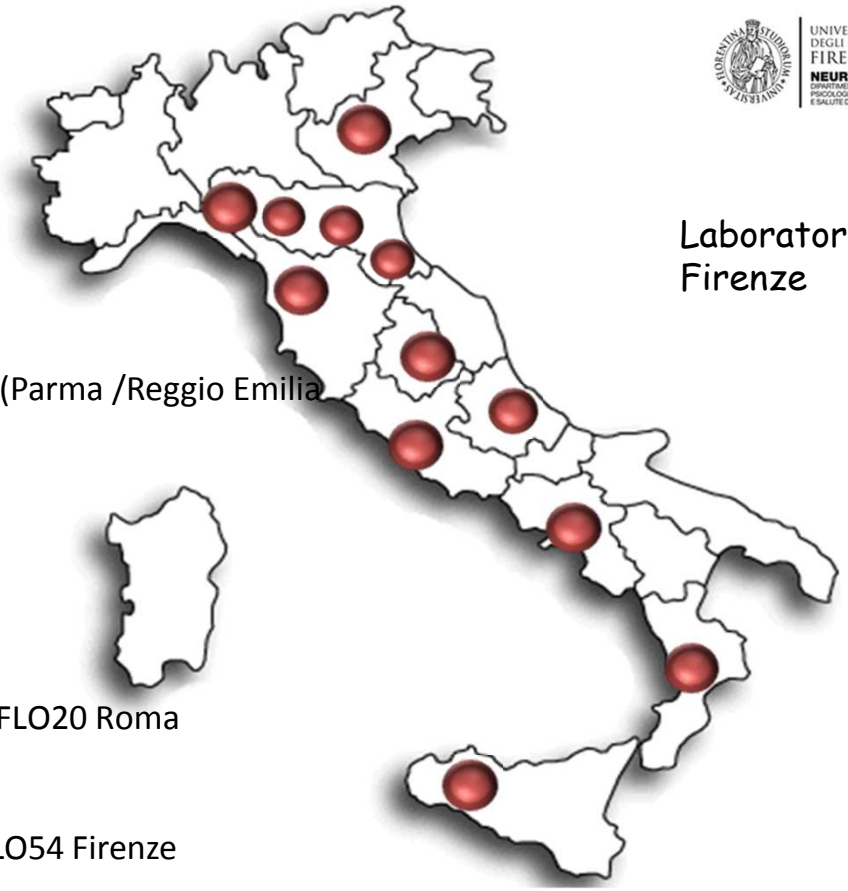





65
(52)
67
64
(52)
81
64
(52)
26years of preclinical diagnosis
<45
<45
<45
<45
<45
<45
<50
<50
+
+
-
+
-
-
-
-

G/A --->

PSEN 1



Laboratorio Neurogenetica
Firenze

Ex 4 M84V (Cosenza)
Cys92Ser: FLO2 e FLO28 (Firenze) e FLO57 (Parma /Reggio Emilia

Ex 5 Ile143Val FLO65 Modena
Met146Leu Napoli, Torino , Lamezia Terme

Ex 6 Leu166His FLO33 Bologna
Leu174Met FLO 55 Firenze
Ex 7 Met233Thr FLO25 Perugia
Ex 8 Ala260Val FLO15 Palermo e Ala260Gly FLO20 Roma
Leu262Ser FLO 76 Modena /Baggiovara
Pro 264 Leu FLO 75 Firenze
Ex 11 Leu392Val FLO 21 Firenze e Leu392 Pro FLO54 Firenze
Ile408Thr FLO 94 Pescara

Neuroscience Letters 610 (2016) 150–153

Contents lists available at ScienceDirect

Neuroscience Letters

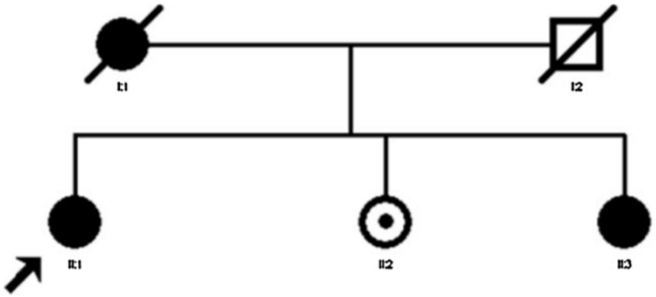
journal homepage: www.elsevier.com/locate/neulet

Research paper

Novel presenilin 1 mutation (Ile408Thr) in an Italian family with late-onset Alzheimer's disease

Andrea Tedde[a], Antonella Bartoli[b], Irene Piaceri[a], Sara Ferrara[b], Silvia Bagnoli[a], Antonio Serio[b], Sandro Sorbi[a], Benedetta Nacmias[a,*]

[a] Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Italy
[b] Villa Serena Hospital, Città S. Angelo, Pescara, Italy



PSEN 2

Laboratorio Neurogenetica
Firenze

Ex 4 Arg71Trp ? FLO 77 Firenze
Ex 5 Ser130Leu FLO 56 Reggio Emilia
Lys 161Arg ? FLO 78 Firenze
Ex 7 **Met239Val FLO10 Udine**

? Natura patogenetica non chiara

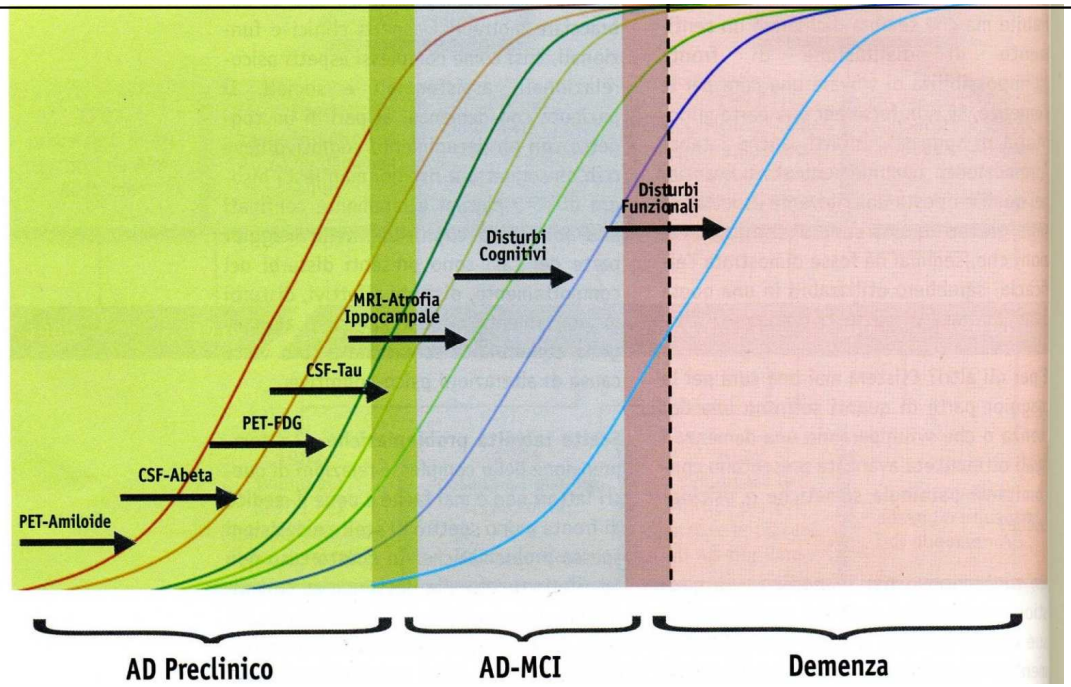
EDITORIAL

ONLINE FIRST

Treat Alzheimer Disease Before It Is Symptomatic

ARCH NEUROL/VOL 68 (NO. 10), OCT 2011

…a narrow but vital window of opportunity exists for preventing AD but it correlates with the time when patients do not yet have dementia and are not even significantly impaired with serious memory loss.



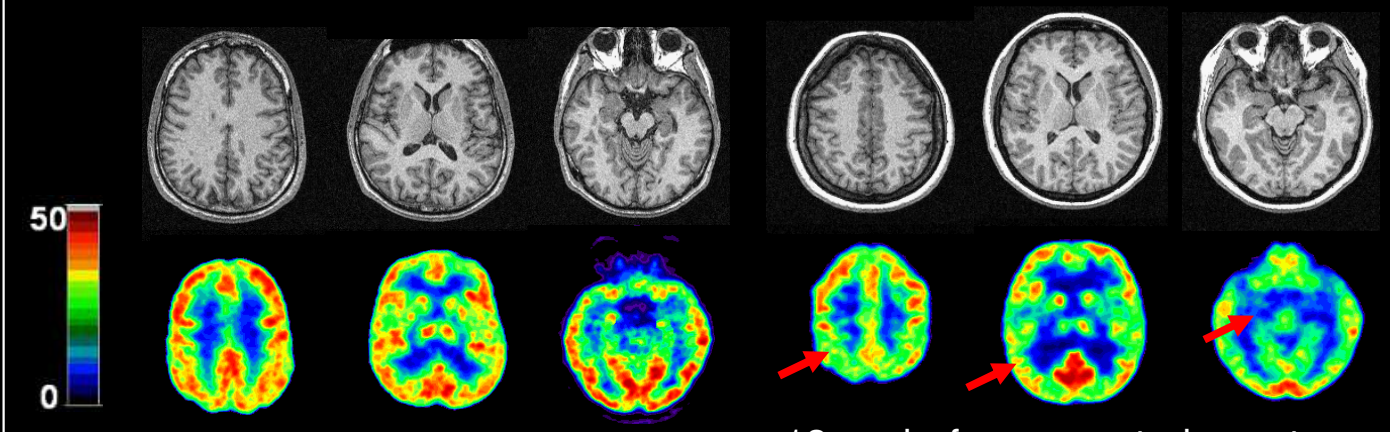
EOFAD show CMRglc reductions before symptoms

- Presymptomatic PS-1 FAD (n=7) vs matched controls (n=7)
- Age 35-49 yrs, education>10 yrs, MMSE 29-30, CDR=0
- MRI and FDG-PET scans

Studiare chi si ammalerà

F, 42 yrs, MMSE 30, CDR 0

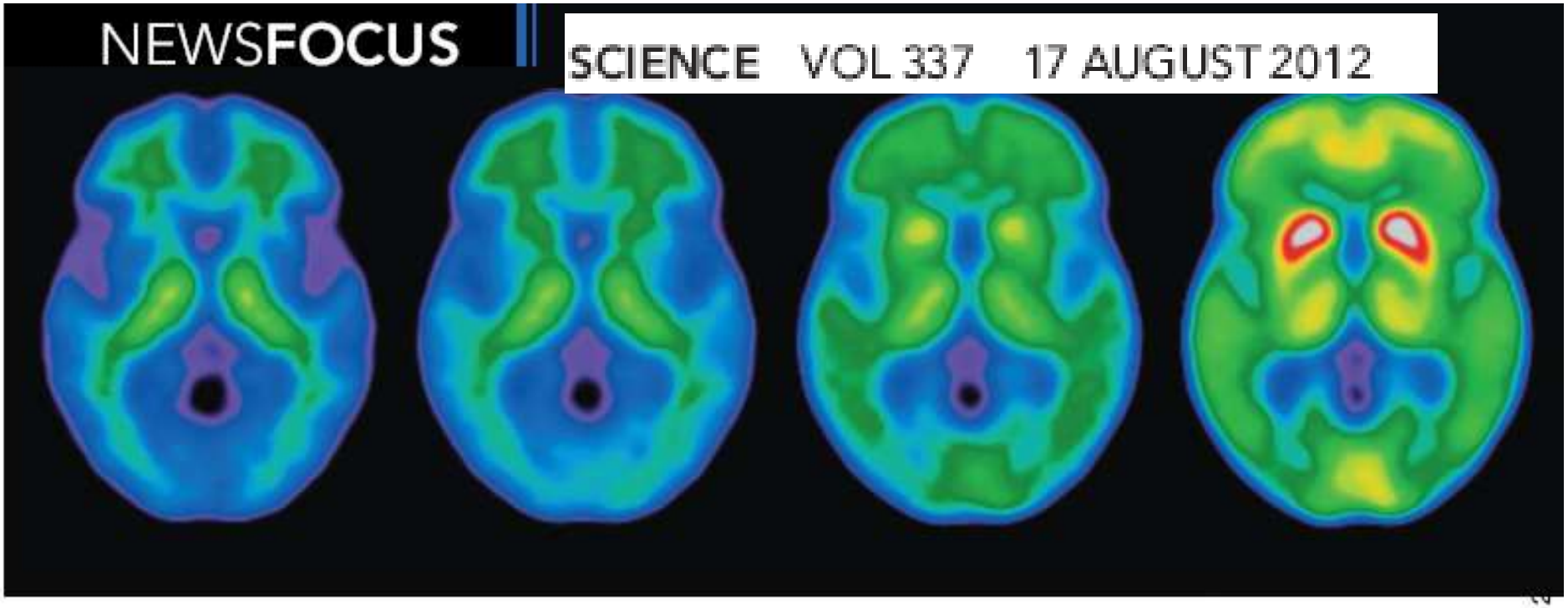
PS-1: F, 35 yrs, MMSE 30, CDR 0



13 yrs before expected onset age

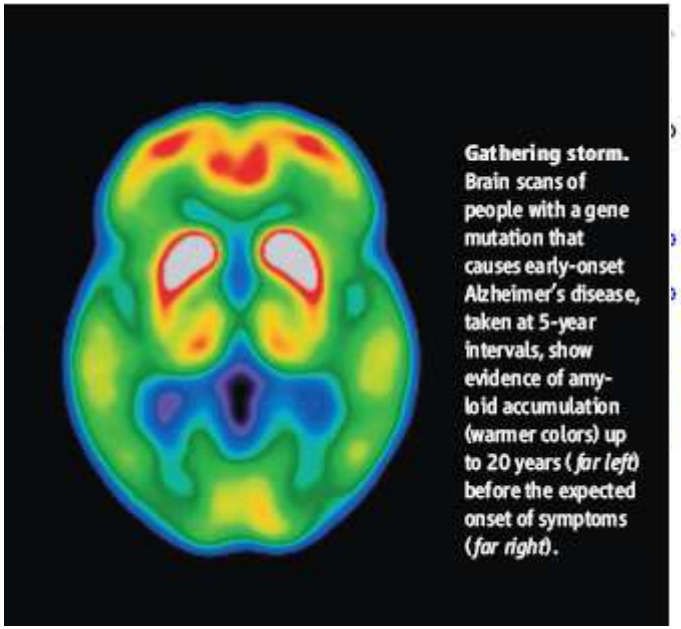
Mosconi et al, J Nucl Med 2006

SCIENCE VOL 337 17 AUGUST 2012



Stopping Alzheimer's Before It Starts

Three new clinical trials expected to begin next year will attempt to prevent dementia by treating people at risk for the disease before they develop symptoms



Gathering storm. Brain scans of people with a gene mutation that causes early-onset Alzheimer's disease, taken at 5-year intervals, show evidence of amyloid accumulation (warmer colors) up to 20 years (*far left*) before the expected onset of symptoms (*far right*).

"I'm fine; I'm just waiting for my disease"

The new and growing class of presymptomatic patients

Neurology® 2011;77:522–523

….a new trend that neurologists, medical geneticists, and other clinicians are facing in patient diagnosis—that is, the presymptomatic diagnosis of a serious and progressive disorder in an individual who is currently healthy

- Supportive care for at risk individuals and Genetic Counseling

Journal of Alzheimer's Disease 51 (2016) 277–291

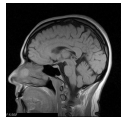
Genetic Counseling and Testing for Alzheimer's Disease and Frontotemporal Lobar Degeneration: An Italian Consensus Protocol

Martina Bocchetta[a,b], Anna Mega[a], Livia Bernardi[c], Emilio Di Maria[d], Luisa Benussi[e], Giuliano Binetti[f], Barbara Borroni[g], Rosanna Colao[c], Giuseppe Di Fede[h], Silvia Fostinelli[e], Daniela Galimberti[i], Massimo Gennarelli[j], Roberta Ghidoni[e], Irene Piaceri[k], Michela Pievani[a], Corinna Porteri[l], Veronica Redaelli[h], Giacomina Rossi[h], Silvia Suardi[h], Claudio Babiloni[m], Elio Scarpini[i], Fabrizio Tagliavini[h], Alessandro Padovani[g], Benedetta Nacmias[k], Sandro Sorbi[k], Giovanni B. Frisoni[a,n], SINdem[‡], Amalia C. Bruni[c,*]

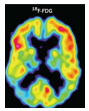
Mappatura attrezzature a disposizione: invio pazienti per specifici esami

DIAN TU
Dominantly Inherited Alzheimer Network Trials Unit

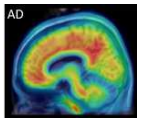
Clinical Trial



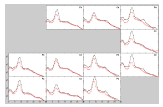
3T - MRI



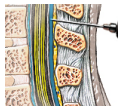
18F-FDG-PET



18F-AV-45-PET



EEG



CSF

Genetica

International Genomics of Alzheimer's Project (IGAP)

First International Collaboration on the Genetics of Alzheimer's Disease Is Launched

A Global Consortium Aims to Discover and Map all the Alzheimer's Genes

CHICAGO (Feb. 1, 2011) CHICAGOPRESSRELEASE.COM/ – The launch of the International Genomics of Alzheimer's Project (IGAP) – a collaboration formed to discover and map the genes that contribute to Alzheimer's disease – was announced today by a multi-national group of researchers. The collaborative effort, spanning universities from both Europe and the United States, will combine the knowledge, staff and resources of four consortia that conduct research on Alzheimer's disease genetics.

The four groups are:

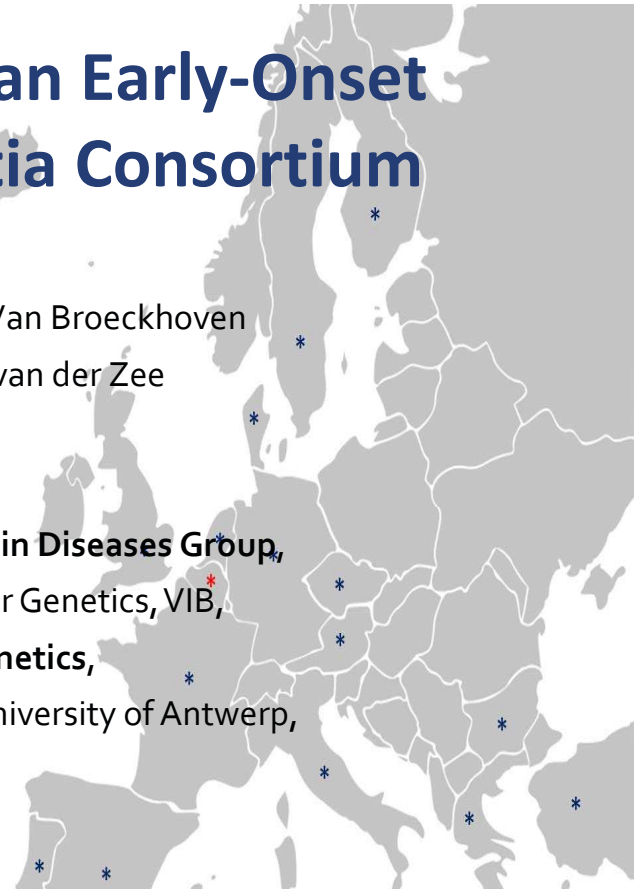
- The European Alzheimer's Disease Initiative (EADI) in France led by **Philippe Amouyel, M.D., Ph.D.**, at the **Institute Pasteur de Lille and Lille University.**

- The Alzheimer's Disease Genetics Consortium (ADGC) from the United States led by **Gerard Schellenberg, Ph.D.**, at the **University of Pennsylvania School of Medicine.**

- The Genetic and Environmental Risk in Alzheimer's Disease (GERAD) from the United Kingdom led by **Julie Williams, Ph.D.**, at **Cardiff University.**

- The neurology subgroup of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) led by **Sudha Seshadri, M.D.**, at **Boston University.**

European Early-Onset Dementia Consortium

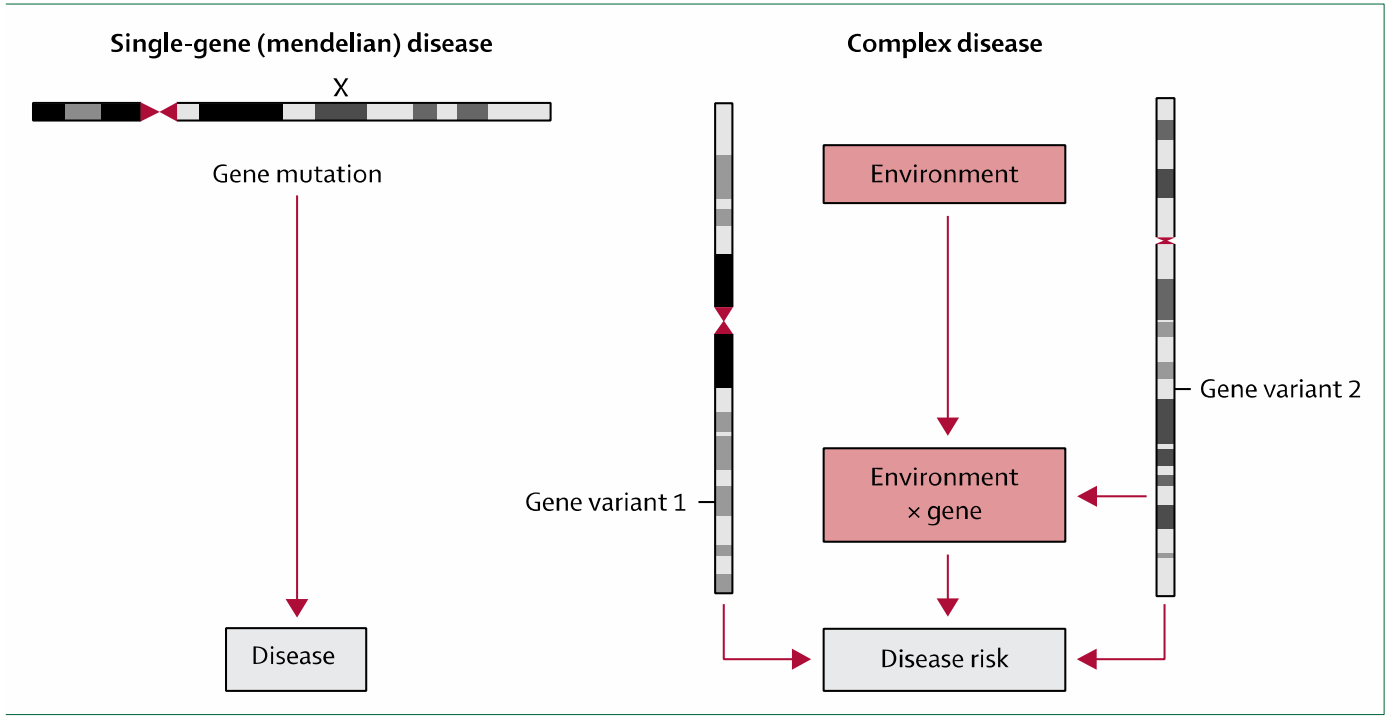


- **Coordinator:** Christine Van Broeckhoven
- **Vice-coordinator:** Julie van der Zee

- **Neurodegenerative Brain Diseases Group,**
- Department of Molecular Genetics, VIB,
- **Laboratory of Neurogenetics,**
- Institute Born-Bunge, University of Antwerp,
- Belgium

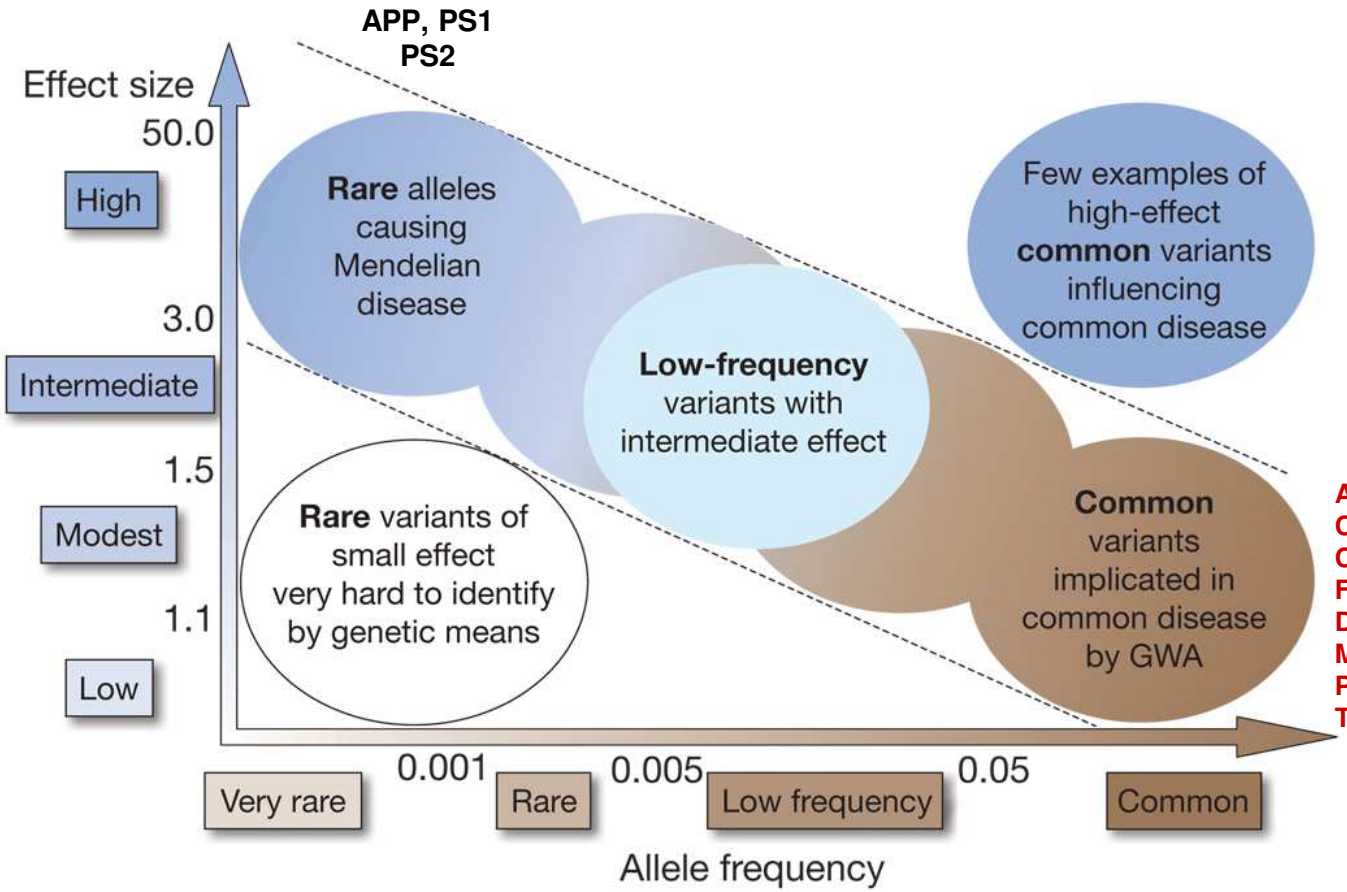
Neurodegenerative Brain Diseases Group,
Department of Molecular Genetics, VIB
Laboratory of Neurogenetics,
Institute Born-Bunge, University of Antwerpen
Belgium

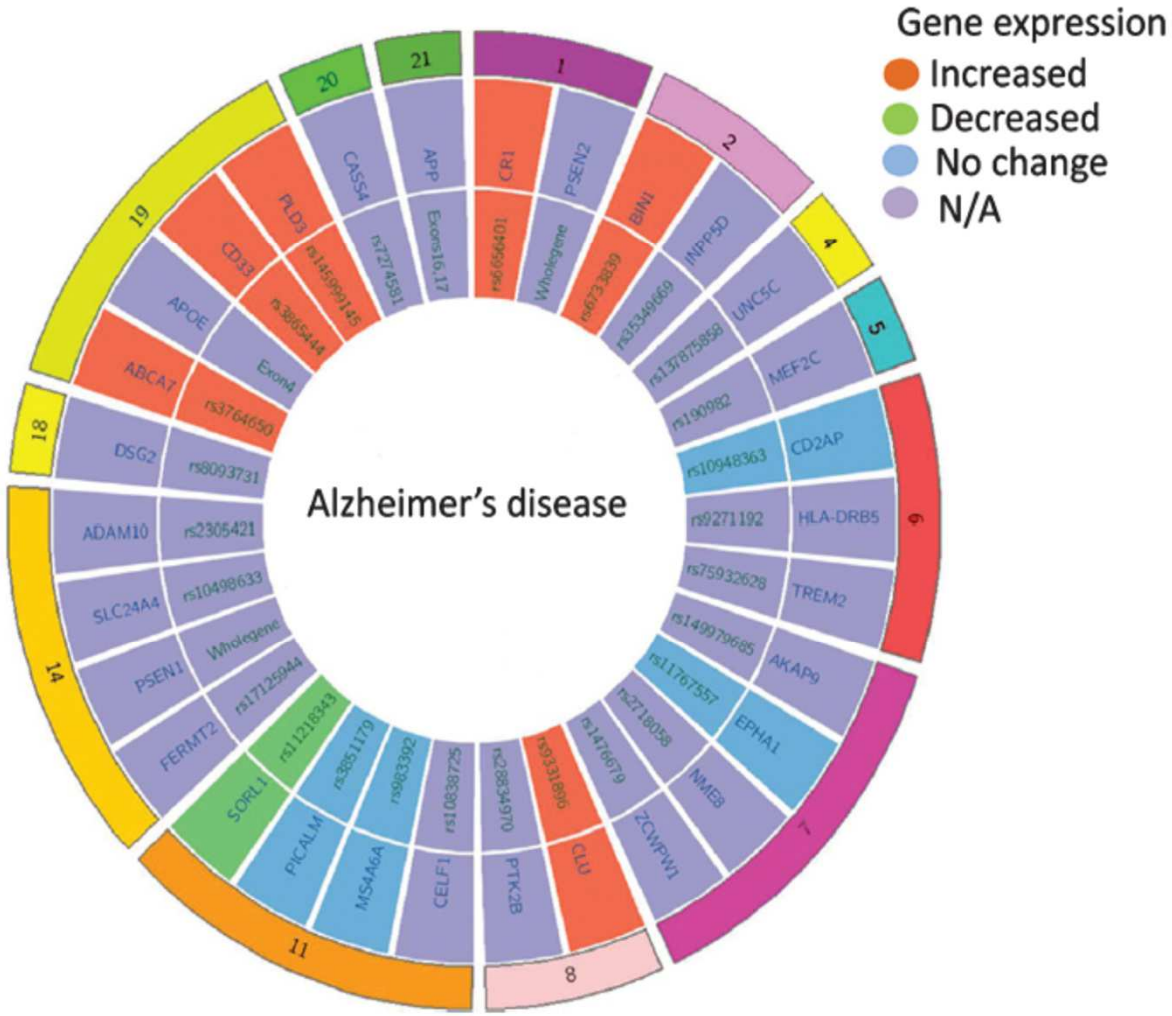
Patogenesi nelle forme mendeliane e nelle malattie complesse



In una malattia mendeliana , la mutazione in un gene è necessaria e sufficiente a causare la malattia. In una malattia complessa le varianti geniche interagiscono con i fattori ambientali per aumentare il rischio di malattia.

Genetics of Alzheimer's disease





Journal of Alzheimer's Disease 58 (2017) 631–659

Circular genetic map from the software circos shows positions of genetics variants of Alzheimer's disease. The outermost circle shows the numbered autosomal chromosomes. The second circle shows genes that
with AD. The third circle shows SNPs that
located in risk gene/locus that associated with AD

Genetic variations underlying Alzheimer's disease: evidence from genome-wide association studies and beyond

Elise Cuyvers, Kristel Sleegers

www.thelancet.com/neurology **Vol 15 July 2016**

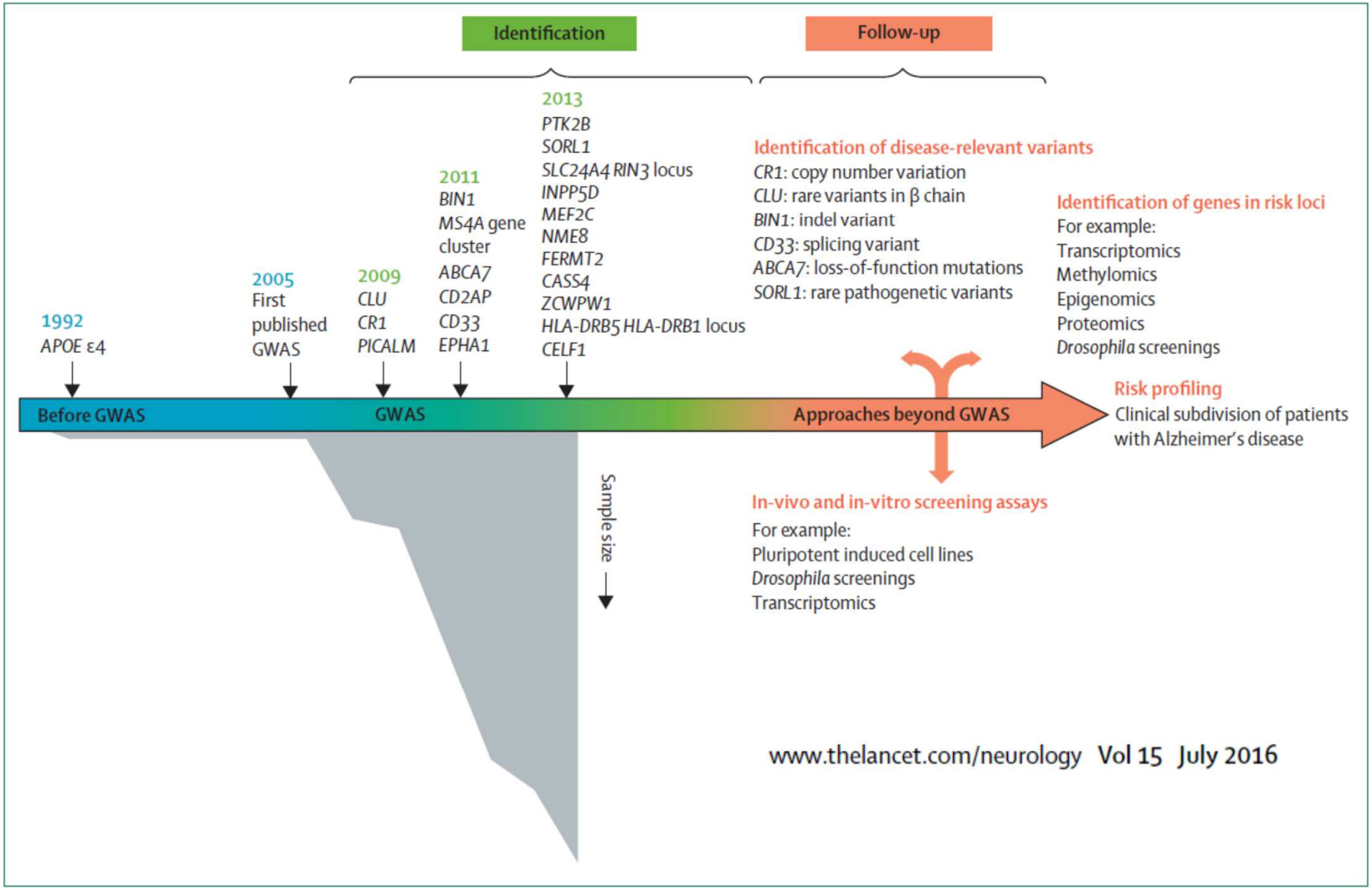
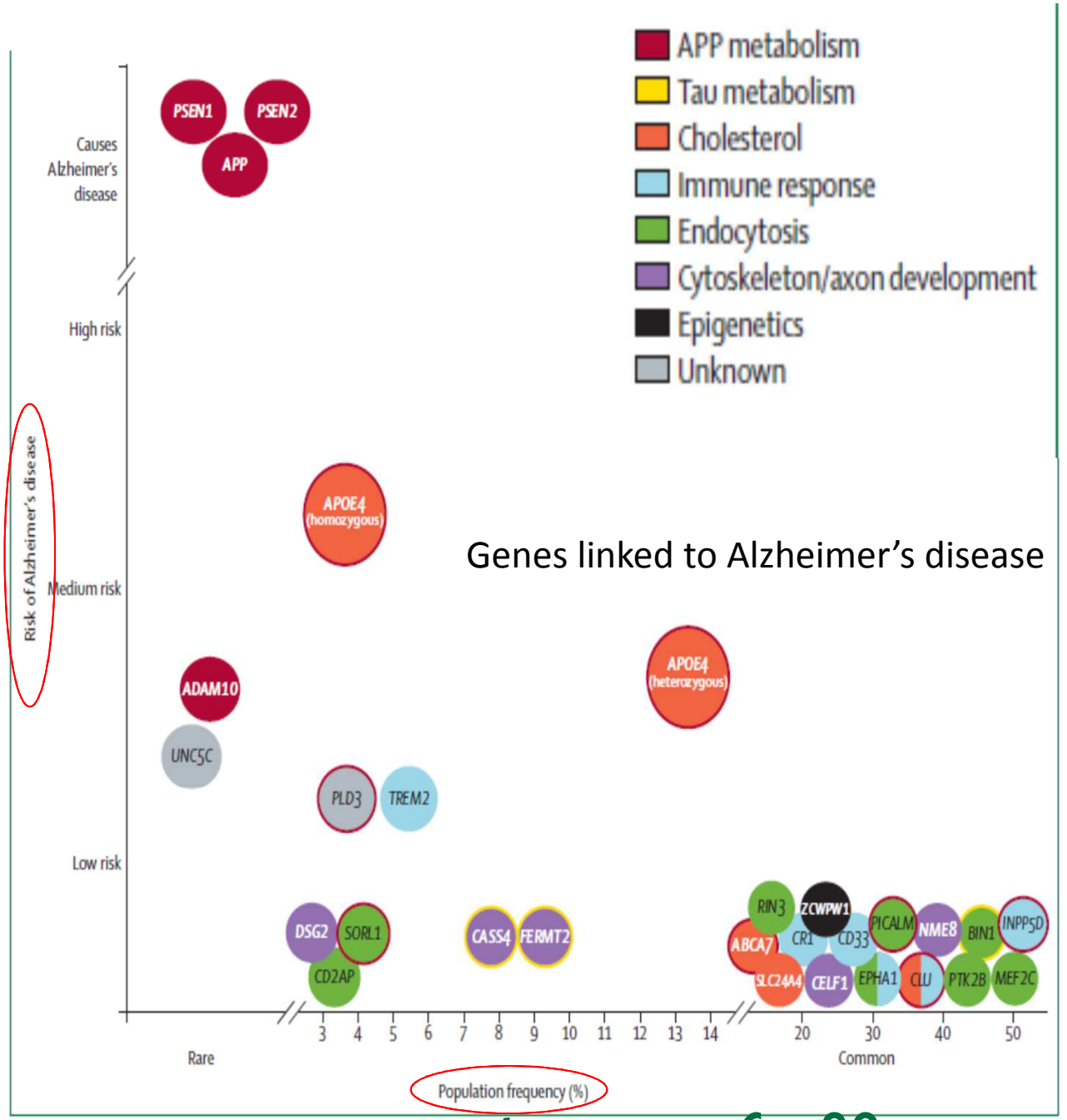


Figure 1: Progress in risk gene identification, follow-up, and relevance in Alzheimer's disease research

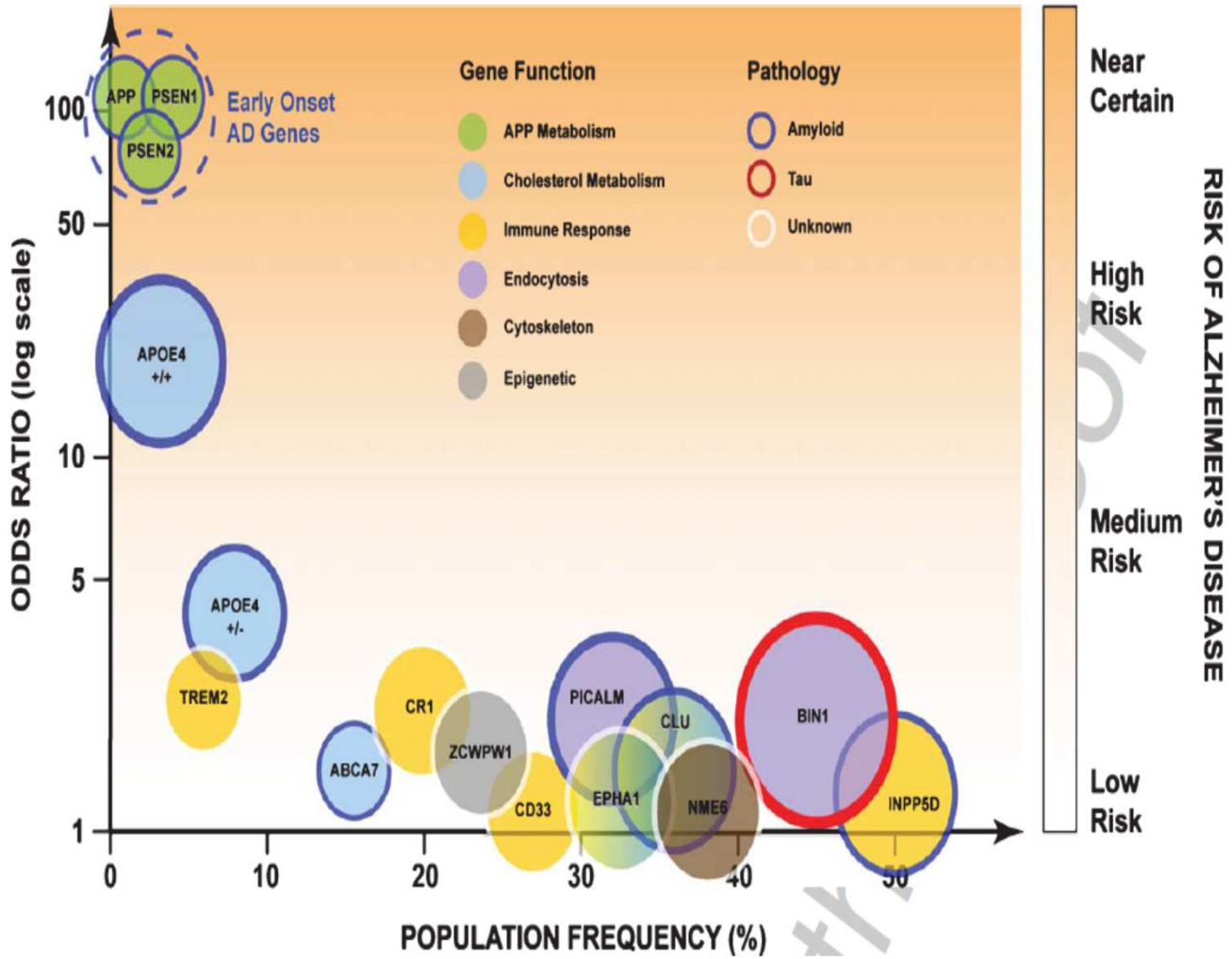


Genes linked to Alzheimer's disease

Figure: Schematic overview of genes linked to Alzheimer's disease

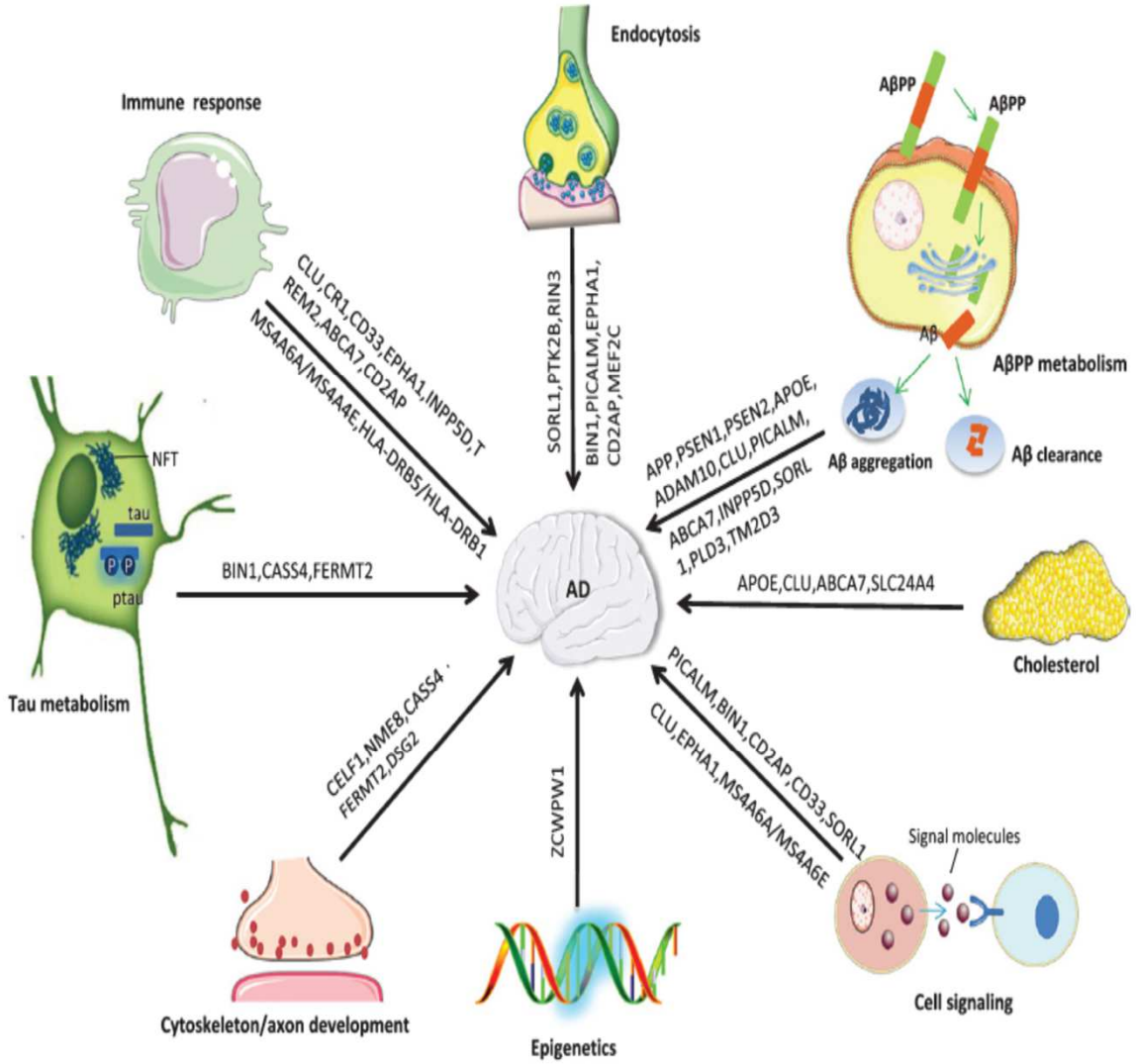
Lancet 2016; 388: 505–17

Genetic risk factors for AD and their general role in physiological function.



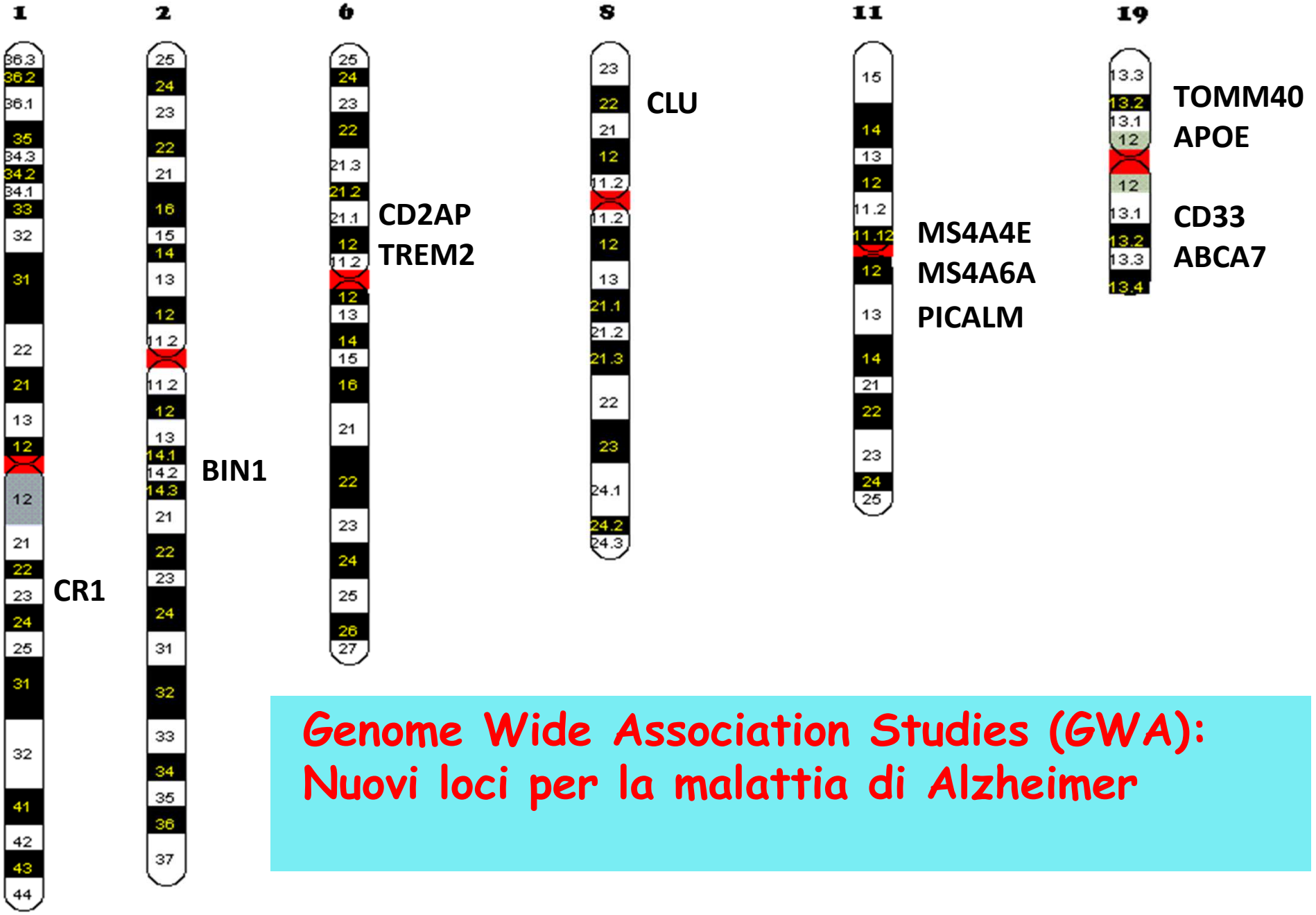
M. Robinson et al. / Recent Progress in Alzheimer Disease Research, JAD 57 (2017) 317–330

Potential pathways of susceptibility genes involved in the pathogenesis of AD



Journal of Alzheimer's Disease 58 (2017) 631–659

APP, amyloid precursor protein, Aβ, β-amyloid, NFT, neurofibrillary tangles



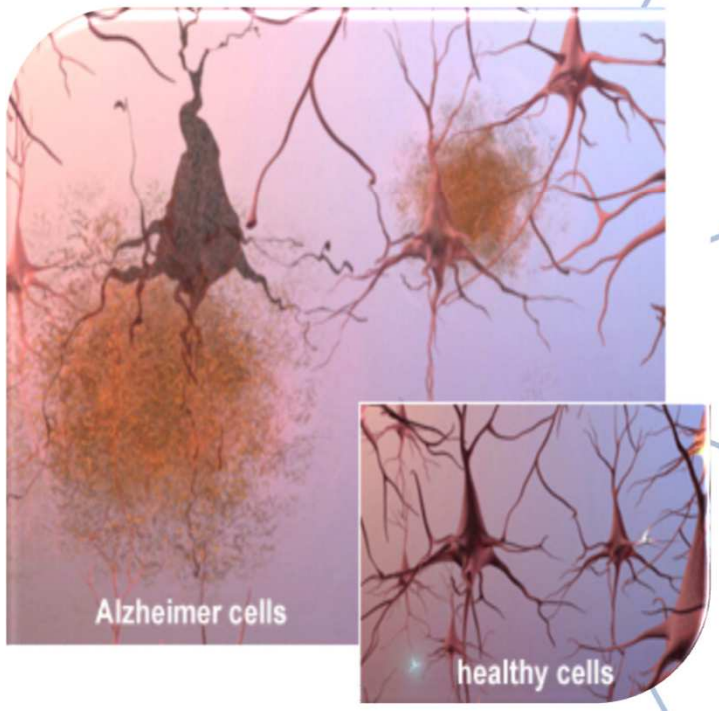
Genome Wide Association Studies (GWA): Nuovi loci per la malattia di Alzheimer

Disfunzione sinaptica

- PICALM
- BIN1
- CD2AP
- CD33

Metabolismo Lipidico

- APOE
- CLU
- ABCA7



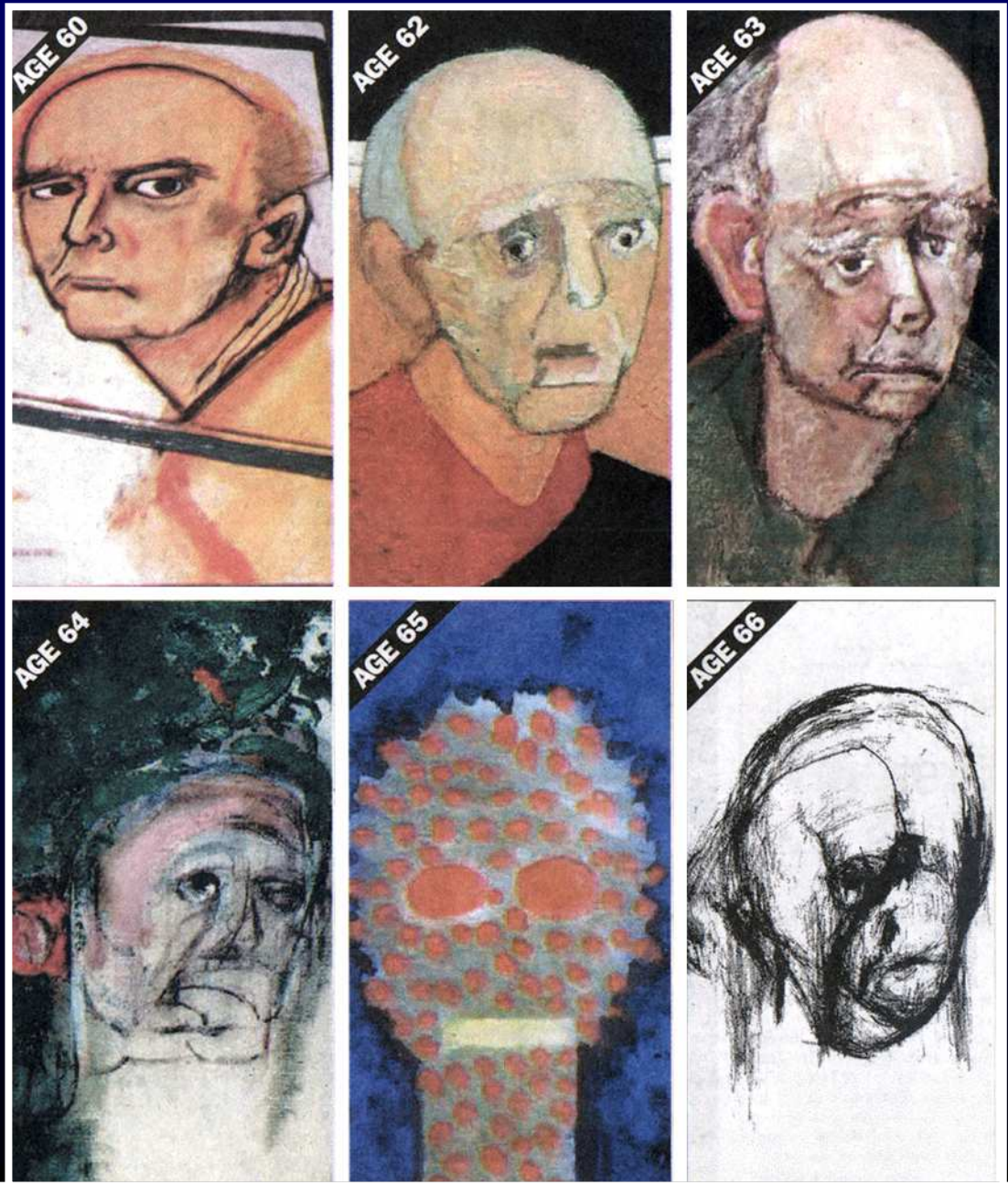
Infiammazione

- CLU
- CD33
- CR1
- EPHA1
- ABCA7

Metabolismo β amiloide

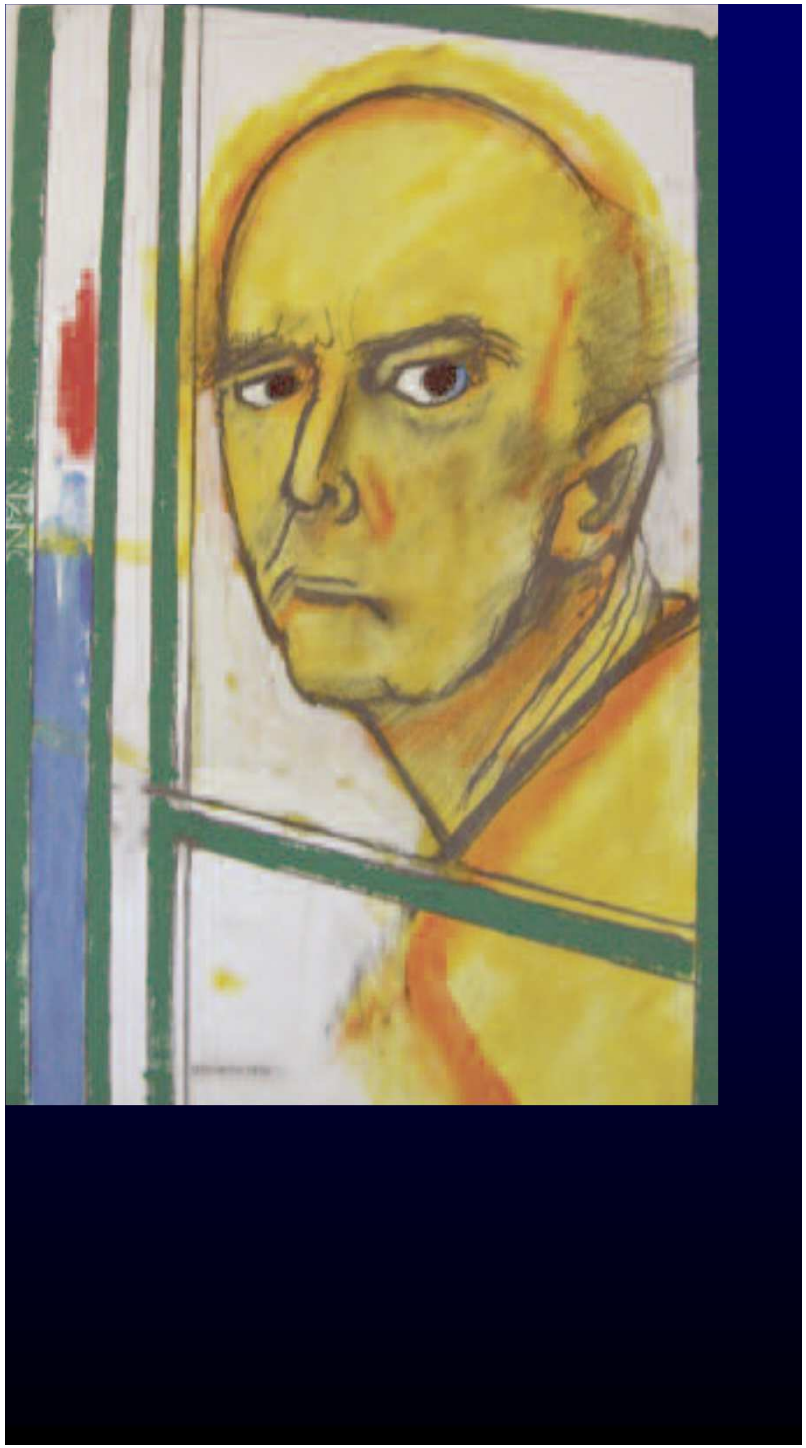
- APOE
- CLU
- ABCA7

The natural history of Alzheimer's disease



William Utermohlen

Rossor et al



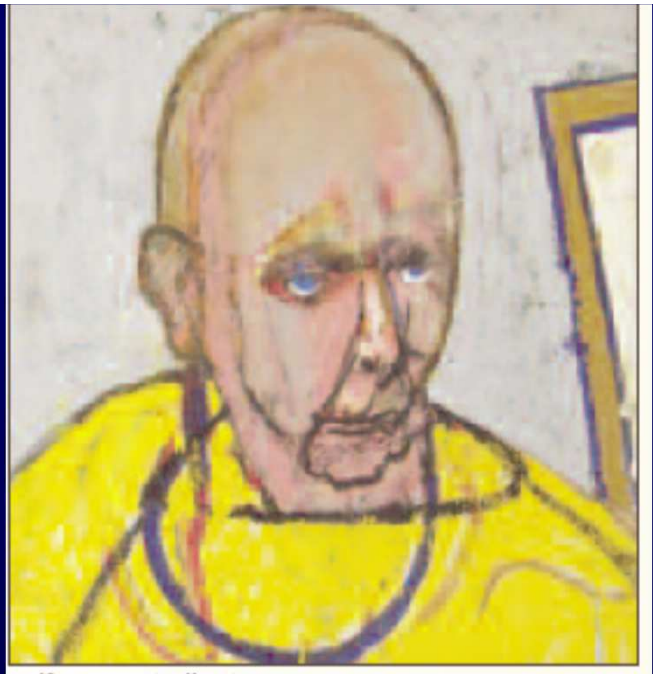
In 1995, at age 61, the painter William Utermohlen received a diagnosis of Alzheimer disease. An established artist for
more than three decades, Utermohlen used
his artistic skill to investigate, as the illness
progressed, the ways in which his mental capacity diminished and his identity distorted.
In a variety of mediums—pencil, watercolors, oils—Utermohlen's self portraits
poignantly illustrate one man's struggle to remain recognizable to himself
despite the gradual yet inexorable erosion of language, independence, creative will.
Utermohlen continued to paint, at a

The Faces of Early-Onset Alzheimer Disease

The late self-portraits of William Utermohlen.

Self Portrait 1998

Erased Self Portrait 1999

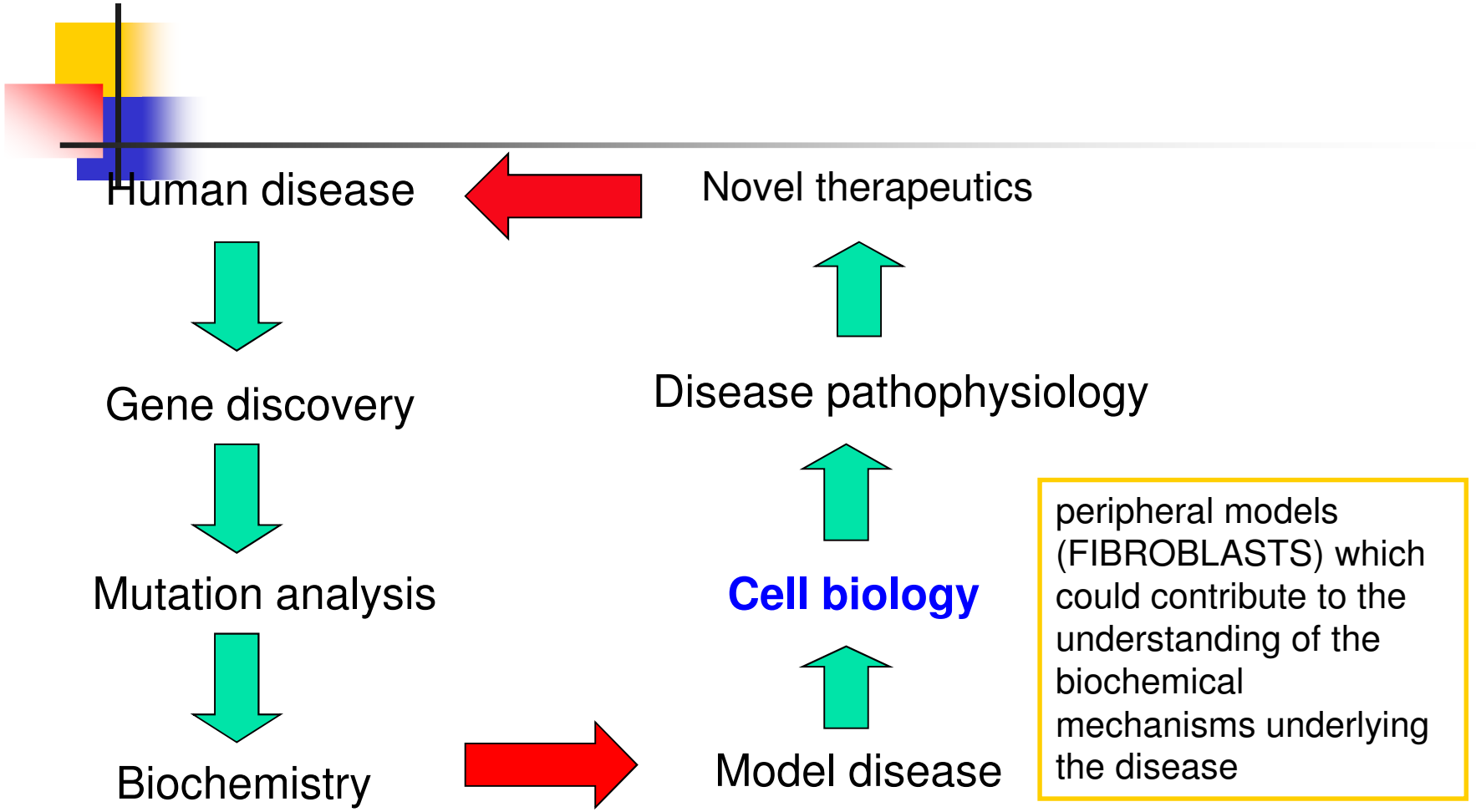


Self Portrait (yellow) 1997

Head August 30, 2000

Crutch SJ, et al. Some workmen can blame their tools: artistic change in an individual with Alzheimer's disease. *Lancet* 2001;357(9274):2129-33.

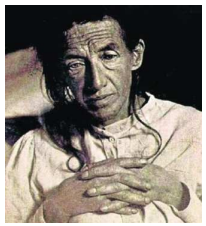
THE PROMISE OF HUMAN GENETICS

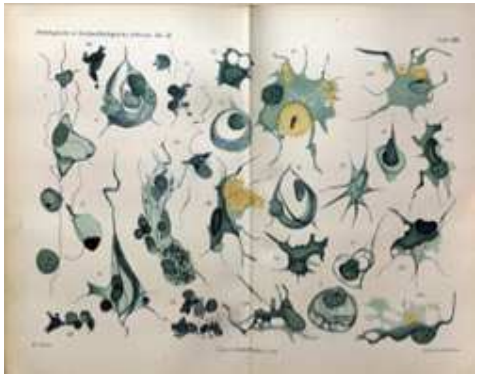


LE TAPPE DELLA MALATTIA DI ALZHEIMER

1906: Il Dr. Alois Alzheimer descrive la malattia

1909: Gaetano Perusini istologia





Alzheimer's Disease—Pathology

1984 identificazione della β-amiloide

1986 identificazione della Tau

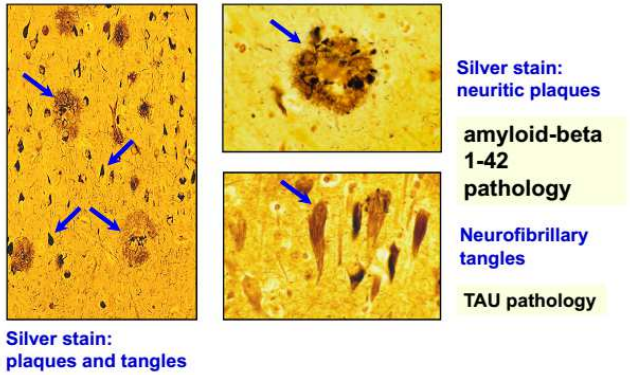
1987-1991 identificazione del "gene di causa" APP

1993 identificazione del "gene di rischio" apoE

1995 identificazione di PS1 e PS2

1995 primo modello di AD su topo transgenico

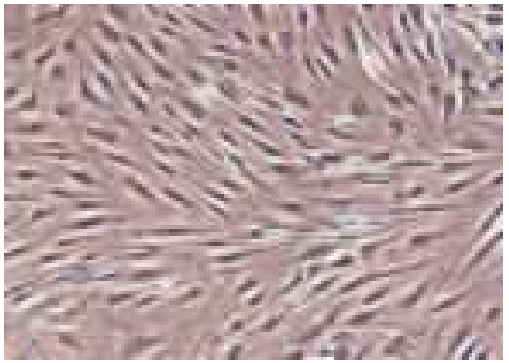
1999 successo del vaccino anti-amiloide nel topo



ALLESTIMENTO COLTURE PRIMARIE FIBROBLASTI

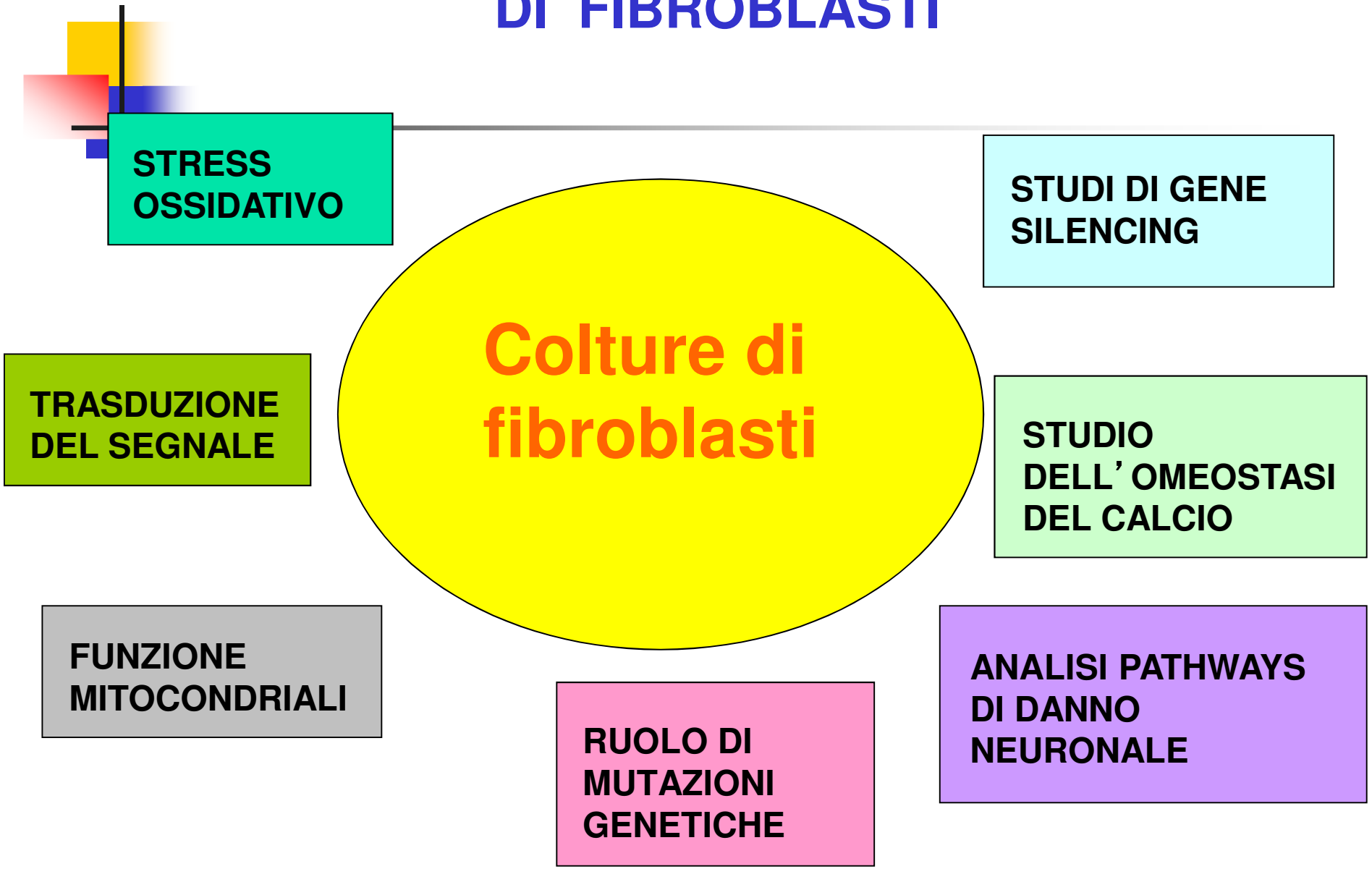
- Prelievo di cute o sottocute in anestesia locale
- Allestimento coltura di fibroblasti per indagini biochimiche, morfologiche o genetiche

BIOPSIA CUTANEA

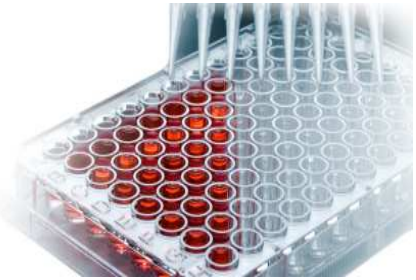


COLTURA FIBROBLASTI

POSSIBILI STUDI SU MODELLI CELLULARI DI FIBROBLASTI



Colture Cellulari Primarie



PAZIENTI CON MALATTIA DI ALZHEIMER

FAMILIARE CON ALTERAZIONE GENETICA NOTA:

- mutazione su **APP** (Val717Ile)
- mutazione su **PS-1**(met146leu)
- mutazione su **PS-1**(leu392val)
- mutazione su **PS-1**(leu392pro)
- mutazione su **PS-2** (met239val)

LINEE CELLULARI DERIVATE DA SOGGETTI SANI

Fibroblasts as peripheral models for Azheimer's disease studies

Current Alzheimer Research, 2013, *10*, 143-153

Lipid Rafts Mediate Amyloid-Induced Calcium Dyshomeostasis and Oxidative Stress in Alzheimer's Disease

Elisa Evangelisti[a], Daniel Wright[a], Mariagioia Zampagni[a], Roberta Cascella[a], Claudia Fiorillo[a], Silvia Bagnoli[b], Annalisa Relini[c], Daniela Nichino[c], Tania Scartabelli[d], Benedetta Nacmias[b], Sandro Sorbi[b] and Cristina Cecchi[a]*

Neurobiology of Aging 32 (2011) 210–222

Membrane cholesterol enrichment prevents Aβ-induced oxidative stress in Alzheimer's fibroblasts

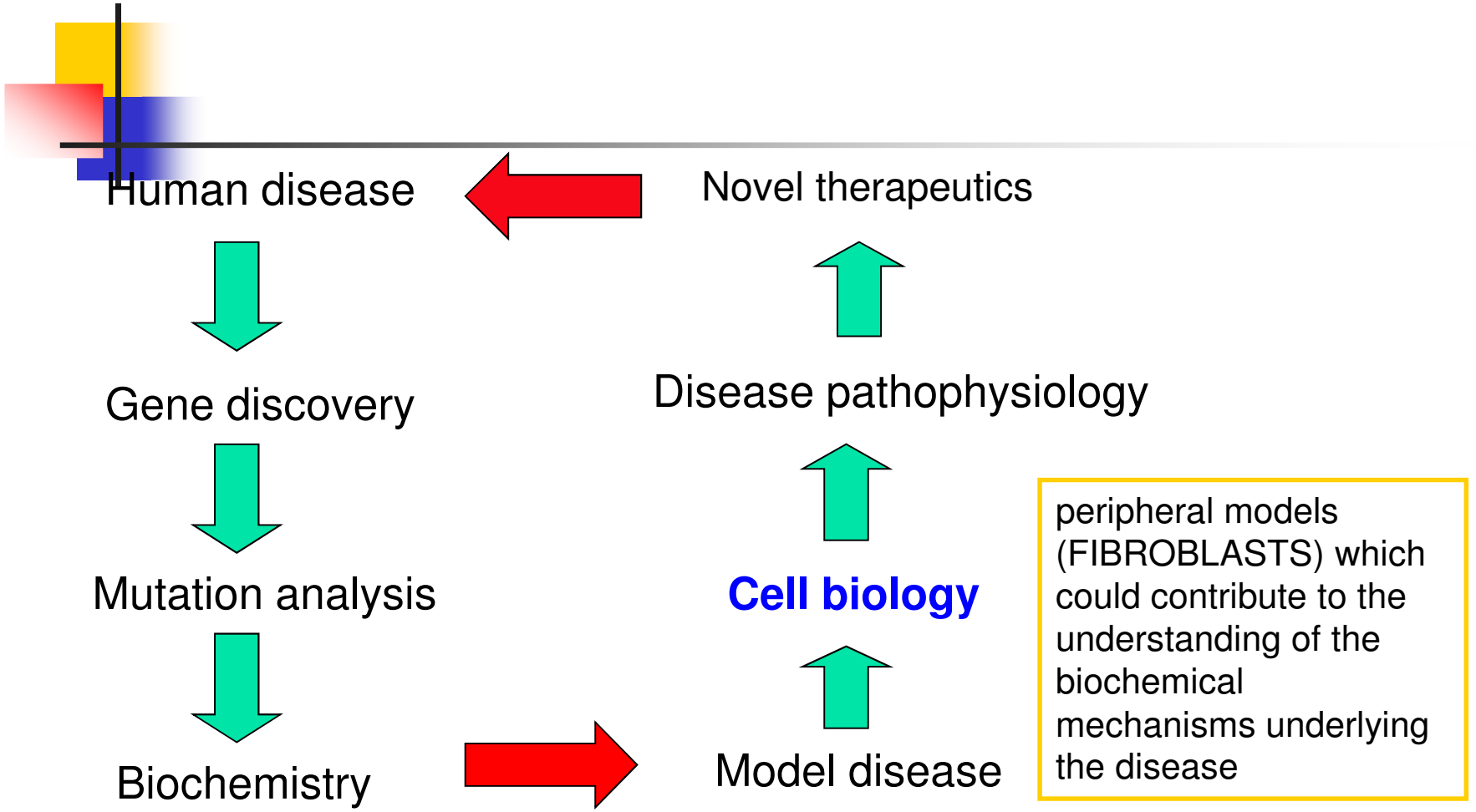
Anna Pensalfini[a,1], Mariagioia Zampagni[a], Gianfranco Liguri[a,c], Matteo Becatti[a], Elisa Evangelisti[a], Claudia Fiorillo[a], Silvia Bagnoli[b], Elena Cellini[b], Benedetta Nacmias[b], Sandro Sorbi[b], Cristina Cecchi[a,c,*]

Neurobiology of Aging 28 (2007) 863–876

Increased susceptibility to amyloid toxicity in familial Alzheimer's fibroblasts

Cristina Cecchi[a,*], Claudia Fiorillo[a], Serena Baglioni[a], Anna Pensalfini[a], Silvia Bagnoli[b], Benedetta Nacmias[b], Sandro Sorbi[b], Daniele Nosi[c], Annalisa Relini[d], Gianfranco Liguri[a]

THE PROMISE OF HUMAN GENETICS



Can Transgenic Mice Help Us?

The American Journal of Pathology, Vol. 173, No. 3, September 2008

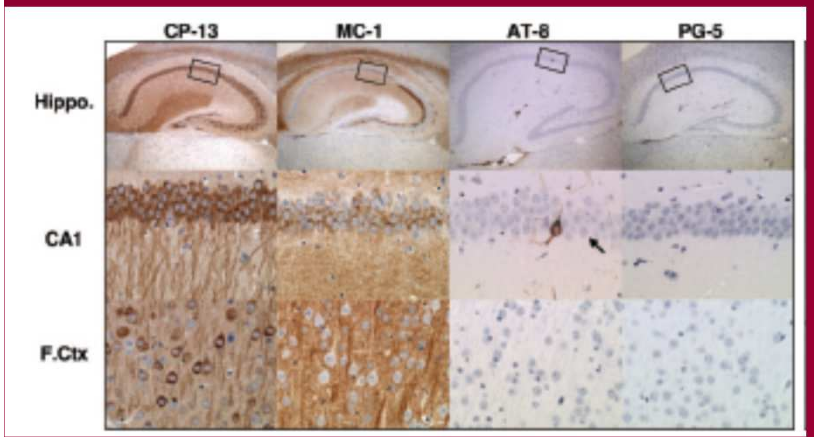
Molecular Pathogenesis of Genetic and Inherited Diseases

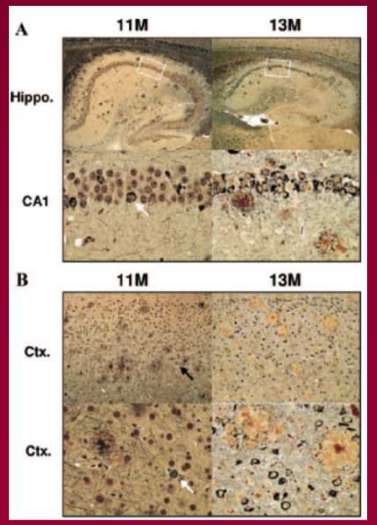
Paulson JB et al

Amyloid Plaque and Neurofibrillary Tangle Pathology in a Regulatable Mouse Model of Alzheimer's Disease

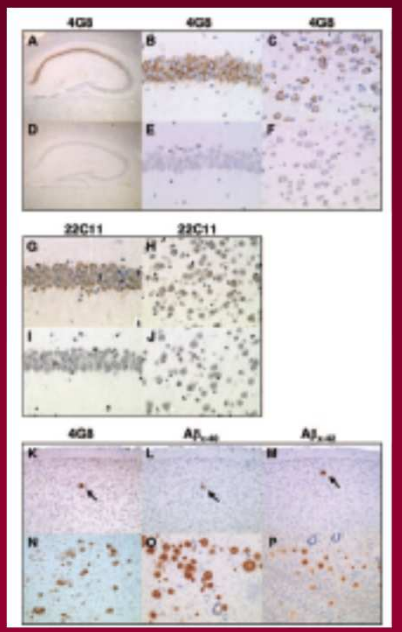
regulatable transgenic mouse that harbors both APP and tau transgenes

development of three neuropathological features of AD:
A plaques
Neurofibrillary tangles
neurodegeneration





mature plaque and NFT pathology.



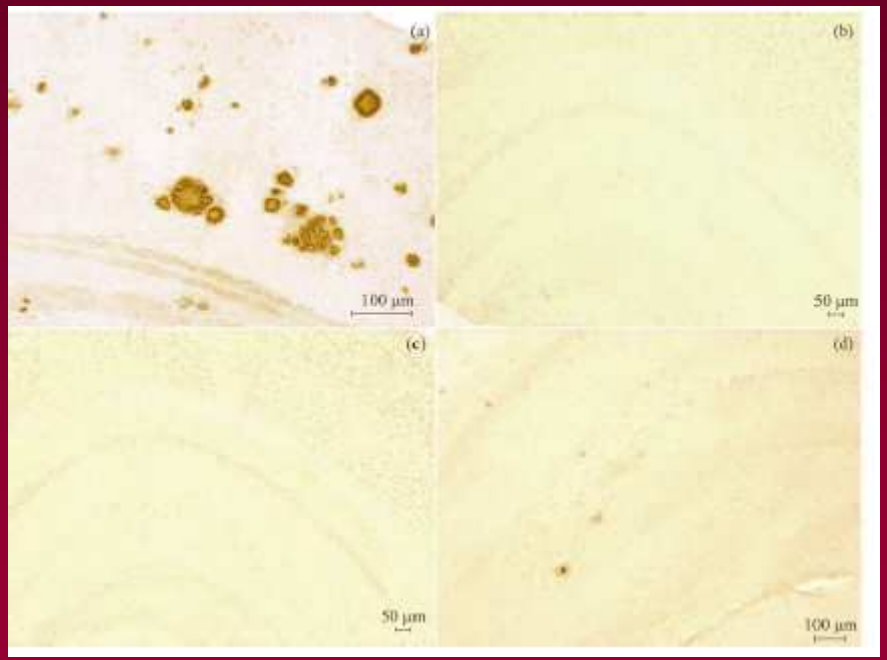
AB plaque development

Sci China C Life Sci. 2008 Aug;51(8):743-50.

© 2008 SCIENCE IN CHINA PRESS

Prevention of pathological change and cognitive degeneration of Tg2576 mice by inoculating $A\beta_{1-15}$ vaccine

HU JinJia[1], LI GuoYing[2], WANG HuaQiao[3], LIN Xian[3] & YAO ZhiBin[3†]



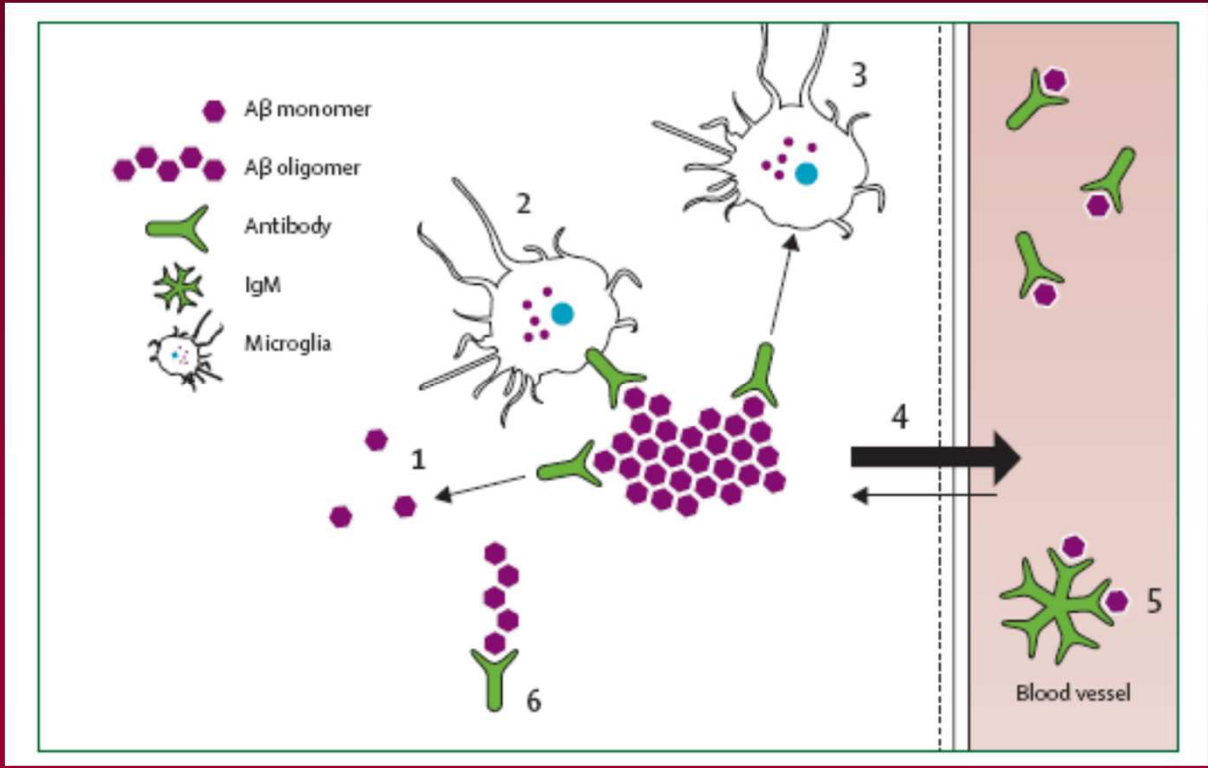
The subunit fragment of Aβ1—15 vaccine could prevent not only cognitive and behavioral degeneration but also Aβ deposition and formation of senile plaques in Tg2576 mice.

Lancet Neurol 2008; 7: 805–11

Amyloid-β immunisation for Alzheimer's disease

Thomas Wisniewski, Uwe Konietzko

Potential mechanisms of immunomodulation for amyloid-β related pathology

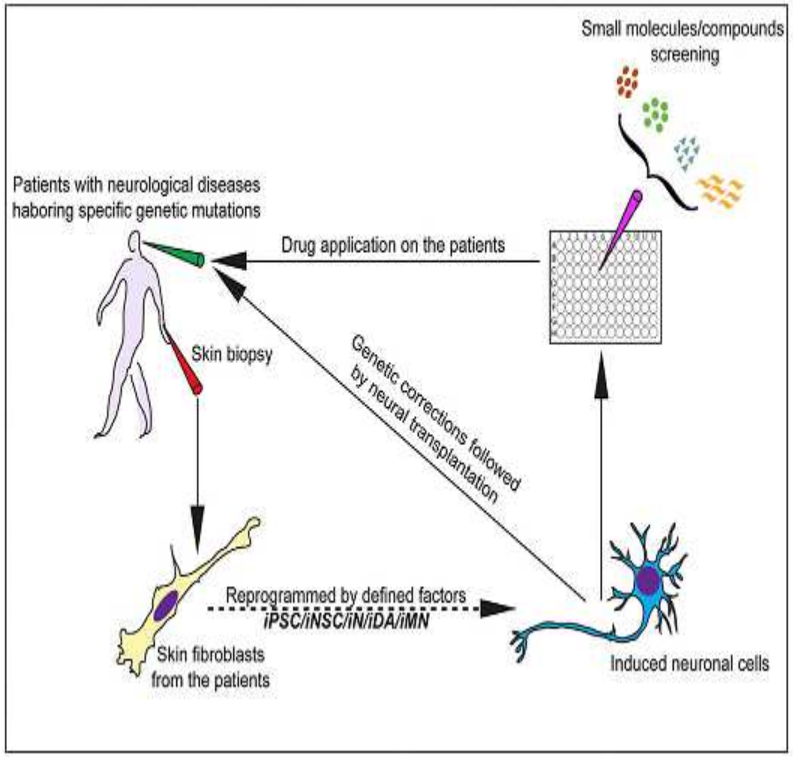


Le scienze maggio 2016

Staminali per il cervello

L'impiego di queste e di altre cellule in terapie dedicate a malattie neurodegenerative è ancora in fase di studio, ma all'orizzonte potrebbe esserci qualche novità

In particolare dai fibroblasti umani ad oggi si sono ottenuti diversi tipi neuronali:



Neuron 78, June 19, 2013

Table 2. A Summary of Directed Reprogramming Methods for the Generation of Human CNS Cell Phenotypes

Original Cells	Target Cells	Key Components for Differentiation or Reprogramming	Efficiency	Duration	Reference
Human fibroblasts	Glutamatergic/ GABAergic neurons	Ascl1, Brn2, Myt1l, Olig2, Zic1	9%	2–3 weeks	Qiang et al., 2011
		miR-9/9*, miR-124, Ascl1, Myt1l, NeuroD2	N/A	6 weeks	Yoo et al., 2011
		Ascl1, Brn2, Myt1l, NeuroD1	4%	2–5 weeks	Pang et al., 2011
		Ascl1, Brn2, Myt1l	4%	2 weeks	Pfisterer et al., 2011
		Brn2, Myt1l, miR-124	4%–11%	2–3 weeks	Ambasudhan et al., 2011
	Dopaminergic neurons	Ascl1, LmX1a, Nurr1	3%–6%	2–3 weeks	Caiazzo et al., 2011
		Ascl1, Brn2, Myt1l, Lmx1a, FoxA2	5%–10%	3–4 weeks	Pfisterer et al., 2011
	Motoneurons	Ascl1, Brn2, Myt1l, NeuroD1, Lhx3, Hb9, Isl1, Ngn2	0.05%	4–5 weeks	Chatrchyan et al., 2011
	Neural stem cells	Sox2	N/A	1–2 weeks	Ring et al., 2012

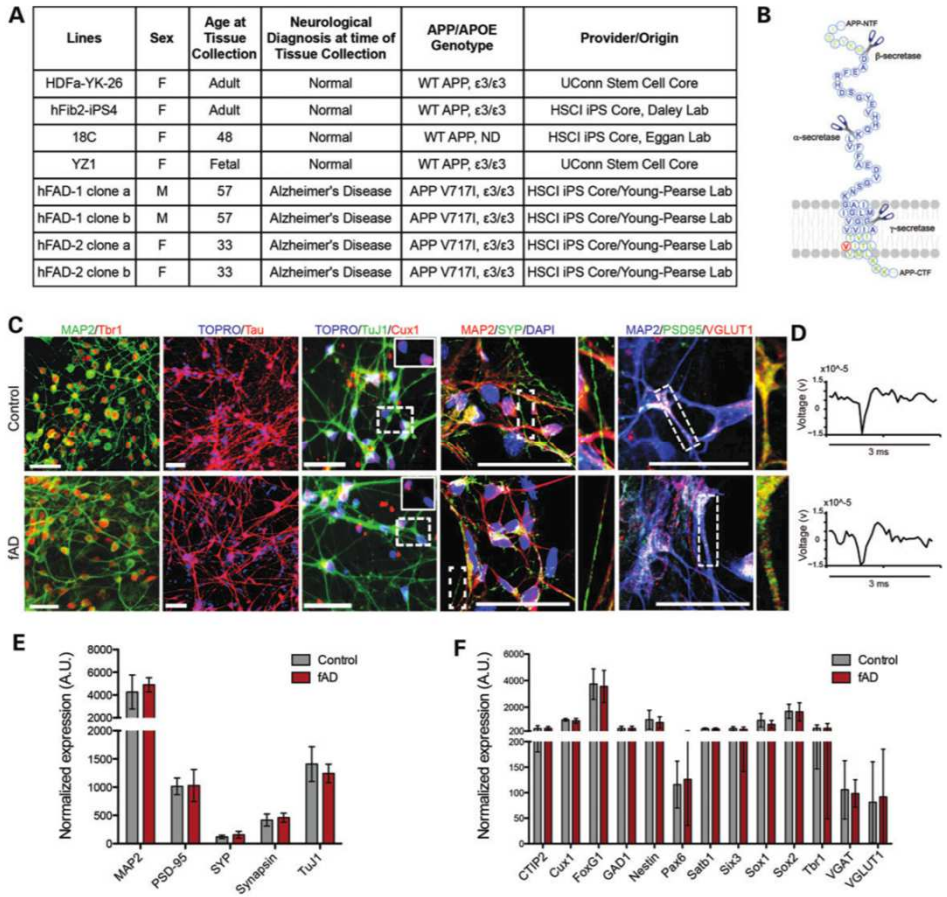
Human Molecular Genetics, 2014, Vol. 23, No. 13

The familial Alzheimer's disease APPV717I mutation alters APP processing and Tau expression in iPSC-derived neurons

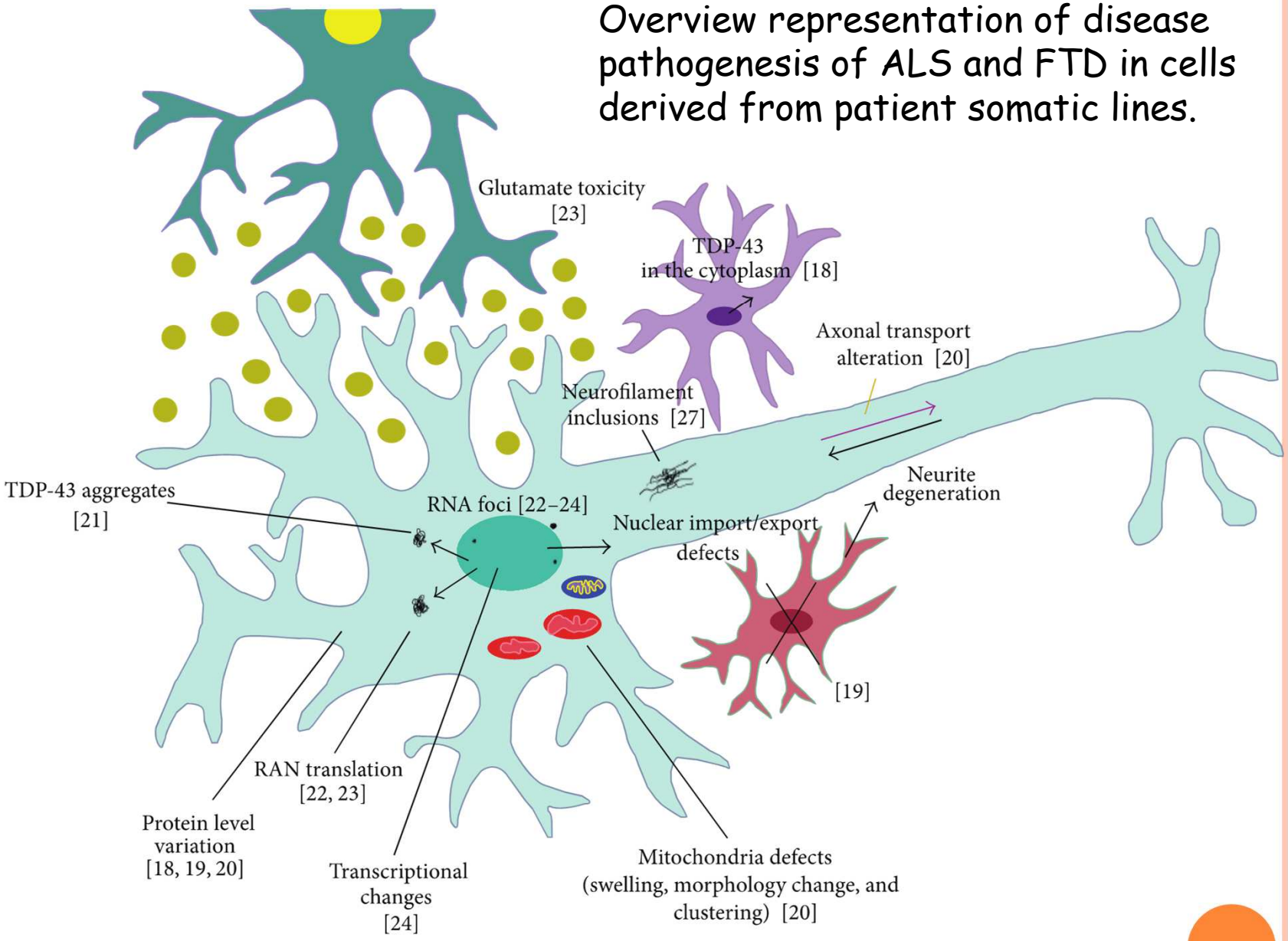
Christina R. Muratore, Heather C. Rice, Priya Srikanth, Dana G. Callahan, Taehwan Shin, Lawrence N. P. Benjamin, Dominic M. Walsh, Dennis J. Selkoe and Tracy L. Young-Pearse*

A

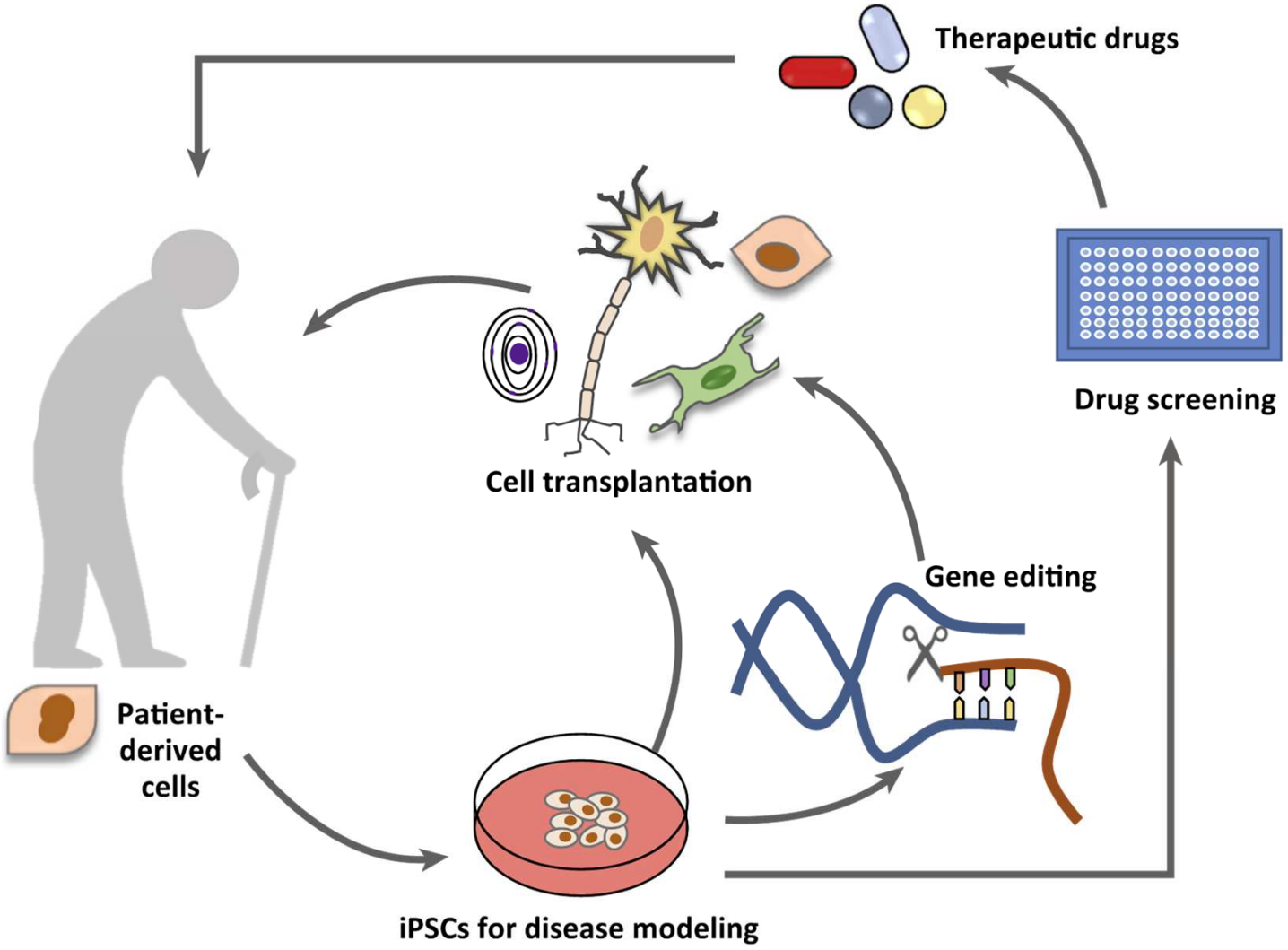
Lines	Sex	Age at Tissue Collection	Neurological Diagnosis at time of Tissue Collection	APP/APOE Genotype	Provider/Origin
HDFa-YK-26	F	Adult	Normal	WT APP, ε3/ε3	UConn Stem Cell Core
hFib2-iPS4	F	Adult	Normal	WT APP, ε3/ε3	HSCI iPS Core, Daley Lab
18C	F	48	Normal	WT APP, ND	HSCI iPS Core, Eggan Lab
YZ1	F	Fetal	Normal	WT APP, ε3/ε3	UConn Stem Cell Core
hFAD-1 clone a	M	57	Alzheimer's Disease	APP V717I, ε3/ε3	HSCI iPS Core/Young-Pearse Lab
hFAD-1 clone b	M	57	Alzheimer's Disease	APP V717I, ε3/ε3	HSCI iPS Core/Young-Pearse Lab
hFAD-2 clone a	F	33	Alzheimer's Disease	APP V717I, ε3/ε3	HSCI iPS Core/Young-Pearse Lab
hFAD-2 clone b	F	33	Alzheimer's Disease	APP V717I, ε3/ε3	HSCI iPS Core/Young-Pearse Lab



Overview representation of disease pathogenesis of ALS and FTD in cells derived from patient somatic lines.

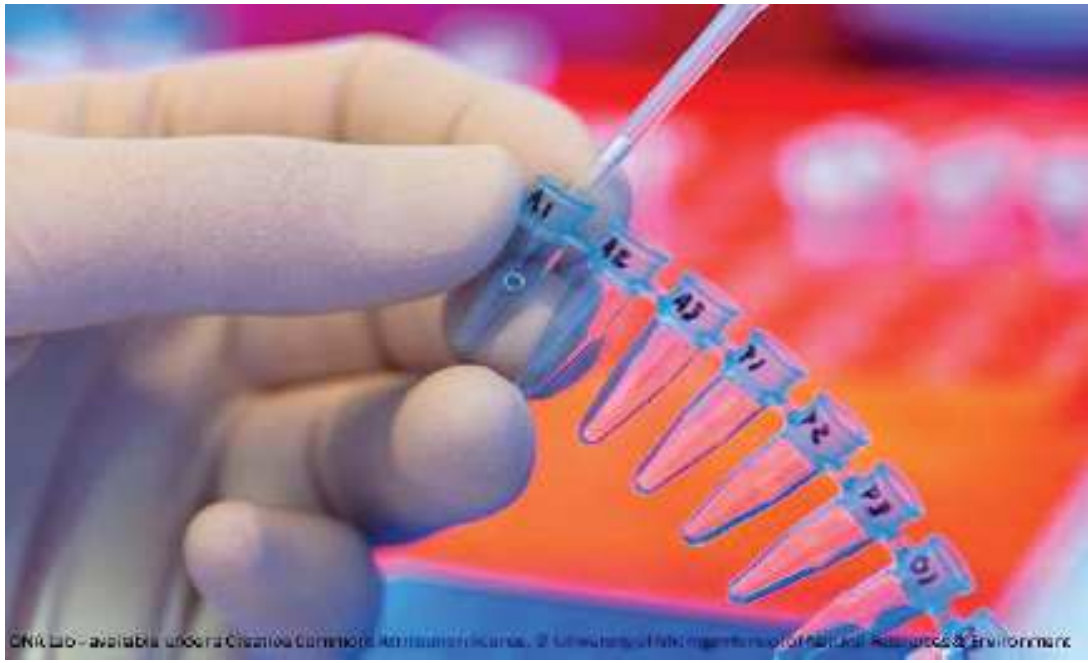


Therapeutic Potential of Patient Induced Pluripotent Stem Cells (iPSCs) in Age-Related Diseases.



Pluripotent induced stem cells

Trends in Molecular Medicine, August 2016, Vol. 22, No. 8



genetica e impatto su diagnosi e ricerca

- Supportive care for at risk individuals and Genetic Counseling

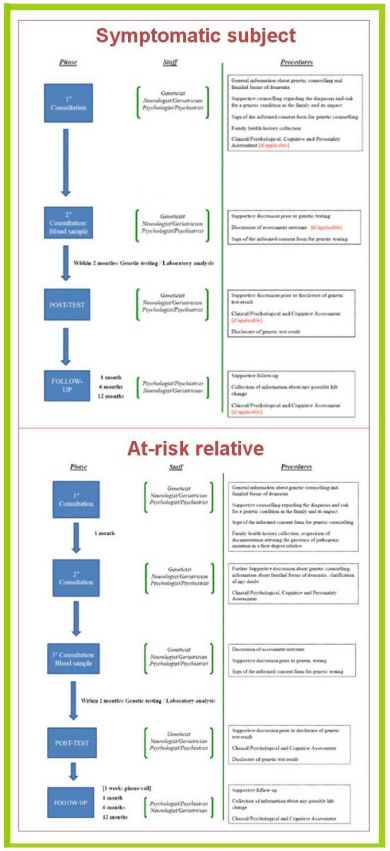
Journal of Alzheimer's Disease 51 (2016) 277–291

Genetic Counseling and Testing for Alzheimer's Disease and Frontotemporal Lobar Degeneration: An Italian Consensus Protocol

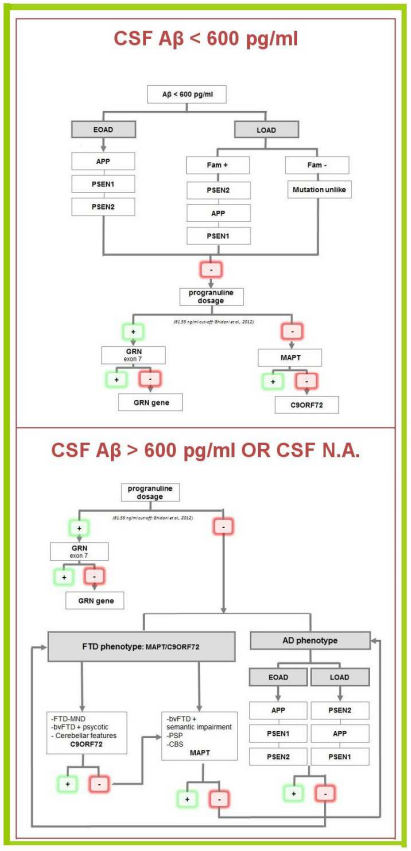
Martina Bocchetta[a,b], Anna Mega[a], Livia Bernardi[c], Emilio Di Maria[d], Luisa Benussi[e], Giuliano Binetti[f], Barbara Borroni[g], Rosanna Colao[c], Giuseppe Di Fede[h], Silvia Fostinelli[e], Daniela Galimberti[i], Massimo Gennarelli[j], Roberta Ghidoni[e], Irene Piaceri[k], Michela Pievani[a], Corinna Porteri[l], Veronica Redaelli[h], Giacomina Rossi[h], Silvia Suardi[h], Claudio Babiloni[m], Elio Scarpini[i], Fabrizio Tagliavini[h], Alessandro Padovani[g], Benedetta Nacmias[k], Sandro Sorbi[k], Giovanni B. Frisoni[a,n], SINdem[‡], Amalia C. Bruni[c,*]

Protocollo Consulenza Genetica

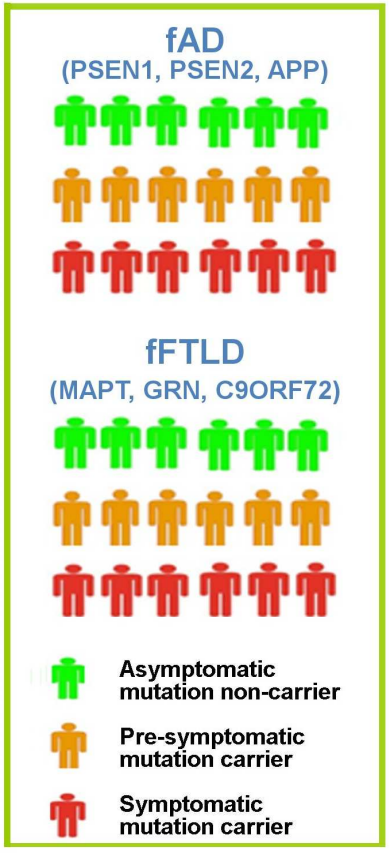
Genetic Counselling Protocol



Genetic Testing Flowchart



Target Population



Protocollo di consulenza genetica

Paziente

Figure professionali coinvolte

PRIMO INCONTRO

Spiegazione informativa sulla patologia al paziente

Genetista
Neurologo
(Psicologo/Psichiatra)

SECONDO INCONTRO

Consenso del paziente al prelievo e prelievo

Genetista
Neurologo
(Psicologo/Psichiatra)

TEST GENETICO

Biologo

POST-TEST

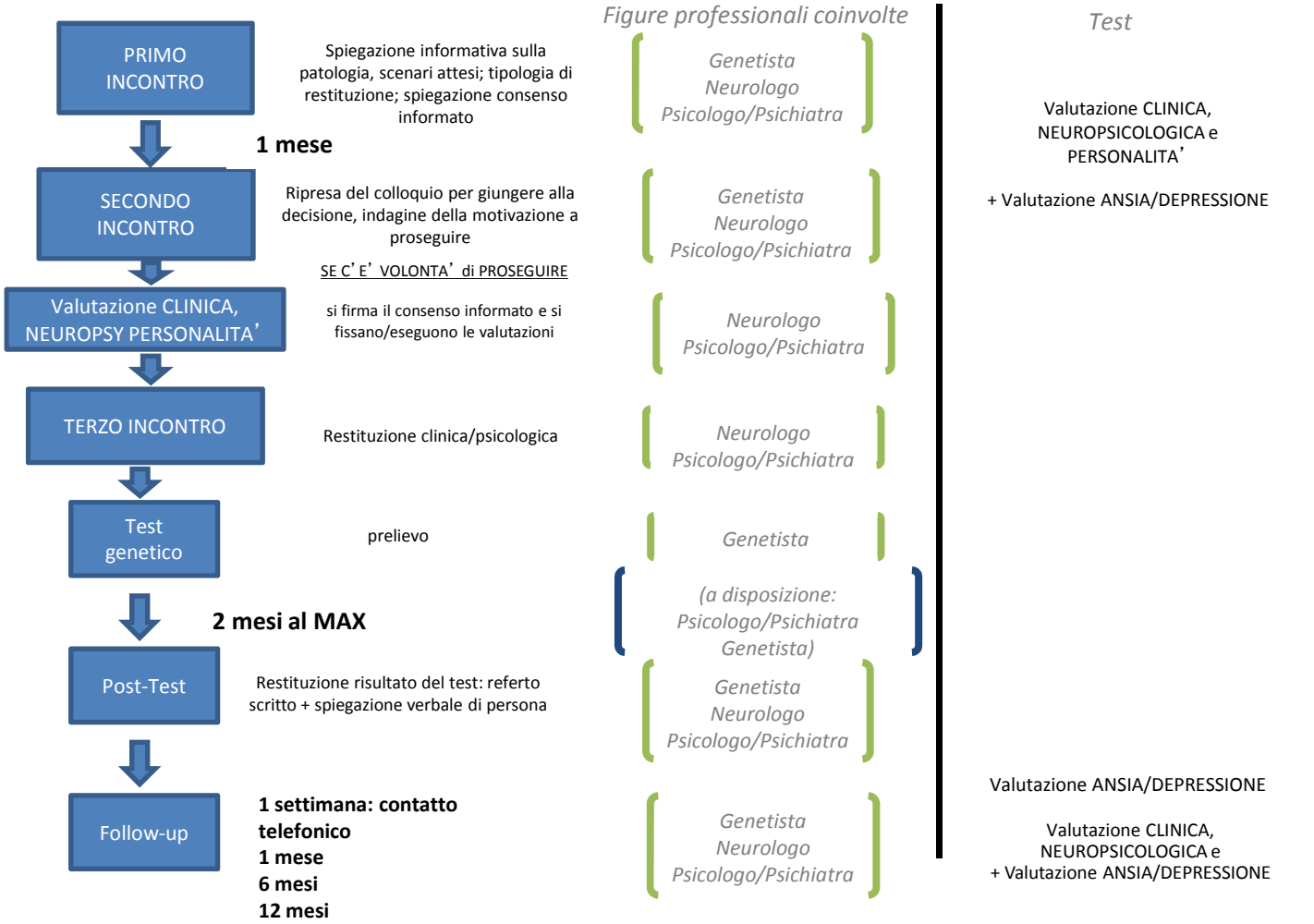
Genetista
Neurologo
(Psicologo/Psichiatra)

FOLLOW-UP

Genetista
Neurologo
(Psicologo/Psichiatra)

protocollo di consulenza genetica

Soggetto a rischio



CONSENSO INFORMATO PER INDAGINE GENETICA

Le analisi genetiche comprendono esami eseguiti sul DNA umano, sui cromosomi e su qualsiasi altro prodotto genetico allo scopo di individuare alterazioni del patrimonio genetico predisponenti allo sviluppo di malattie. Le informazioni raccolte durante il colloquio e i risultati ottenuti dalle analisi genetiche sono considerate strettamente confidenziali e sottostanno al vincolo del segreto professionale.

Il/La sottoscritto/a (nome e cognome).....

Nato/a a…… il ……

Residente in…….....PROV……..…CAP……..……

Via……..n°……tel……..

DICHIARA

Di aver ricevuto informazioni riguardo agli eventuali aspetti genetici della malattia presente nella famiglia e/o di cui è affetto.

- ☐ **ACCONSENTE**
- ☐ **NON ACCONSENTE**

al prelievo per l'esecuzione di analisi molecolare per……..

e che in conseguenza dei risultati ottenuti, possano essere condotte ulteriori analisi necessarie a scopo diagnostico

- ☐ **ACCONSENTE**
- ☐ **NON ACCONSENTE**

che il proprio materiale biologico venga utilizzato per indagini genetiche a scopo di studio e di ricerca sempre strettamente correlate alla patologia e che venga conservato presso il Laboratorio di Neurogenetica, Complesso Polivalente, viale Pieraccini 6, 50139 Firenze.

Il sottoscritto desidera che il risultato del test genetico:

- ☐ sia comunicato all'interessato tramite il medico richiedente
- ☐ non desidera sapere il risultato del test

Il trattamento dei dati personali è conforme alle disposizioni contenute nel **Decreto Legislativo 30 giugno 2003, n. 196. Codice in materia di protezione dei dati personali** e nel **Provvedimento dell'Autorità Garante del 22.02.2007 Autorizzazione al trattamento dei dati genetici**. Una copia di questo consenso informato e del foglio informativo resteranno in mio possesso.

Il sottoscritto/a si impegna a comunicare tempestivamente ogni eventuale cambiamento di opinione in merito alle dichiarazioni fatte in sede di visita.
Inoltre indico di essere a conoscenza della possibilità di REVOCARE il presente consenso in qualsiasi momento

Data……

Firma del paziente……
o Firma tutore legale/Amministratore di sostegno ……

Firma del Medico che ha raccolto il consenso……..……..

NOTE CLINICHE: ……

MEDICO REFERENTE: DR……..

REPARTO DI PROVENIENZA:……

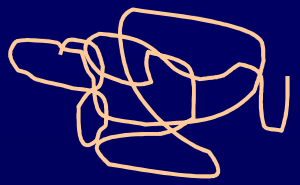
ANALISI GENETICA RICHIESTA:

- ☐ **APO E**
- ☐ **ANALISI GENETICA NEI GENI PS1, PS2 E APP PER MALATTIA DI ALZHEIMER FAMILIARE**
- ☐ **ANALISI GENETICA ATASSIE SPINOCEREBELLARI AUTOSOM. DOMINANTI**
- ☐ **ANALISI GENETICA ATASSIE AUTOSOM. RECESSIVE (Atassia di Friedreich)**
- ☐ **ANALISI GENETICA MALATTIA DI HUNTINGTON**
- ☐ **ANALISI GENETICA NEI GENI MAPT E PGRN PER DEMENZA FRONTOTEMPORALE**
- ☐ **ANALISI GENETICA SCLEROSI LATERALE AMIOTROFICA (SOD1, TDP-43)**

Spazio riservato al laboratorio	**PEDIGREE…… N. ID……**
☐ **DNA**	**Data estrazione __ /__ /___ in µl**
☐ **FIBROBLASTI**	

ANALISI GENETICA MUTAZIONI

Prelievo Sangue → **DNA genomico**



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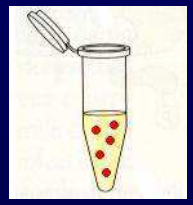
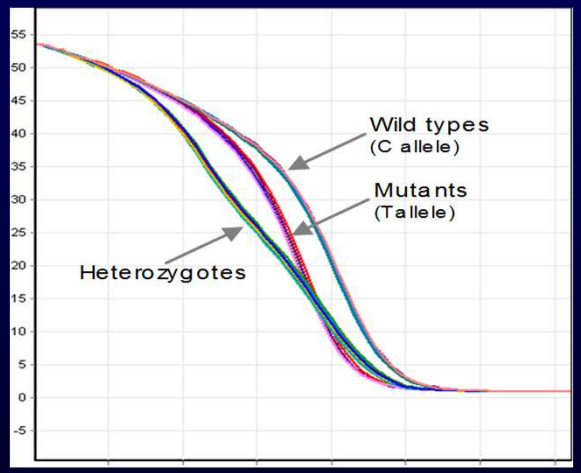
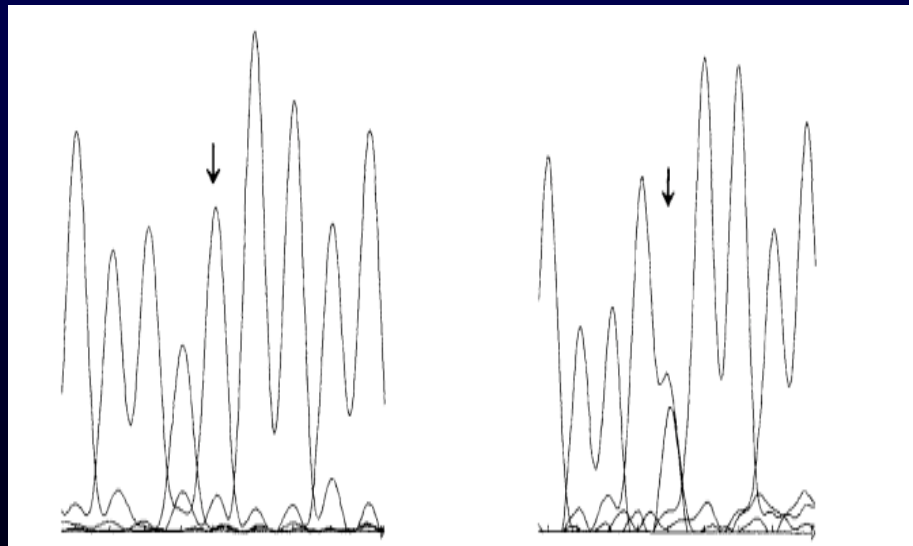
PCR



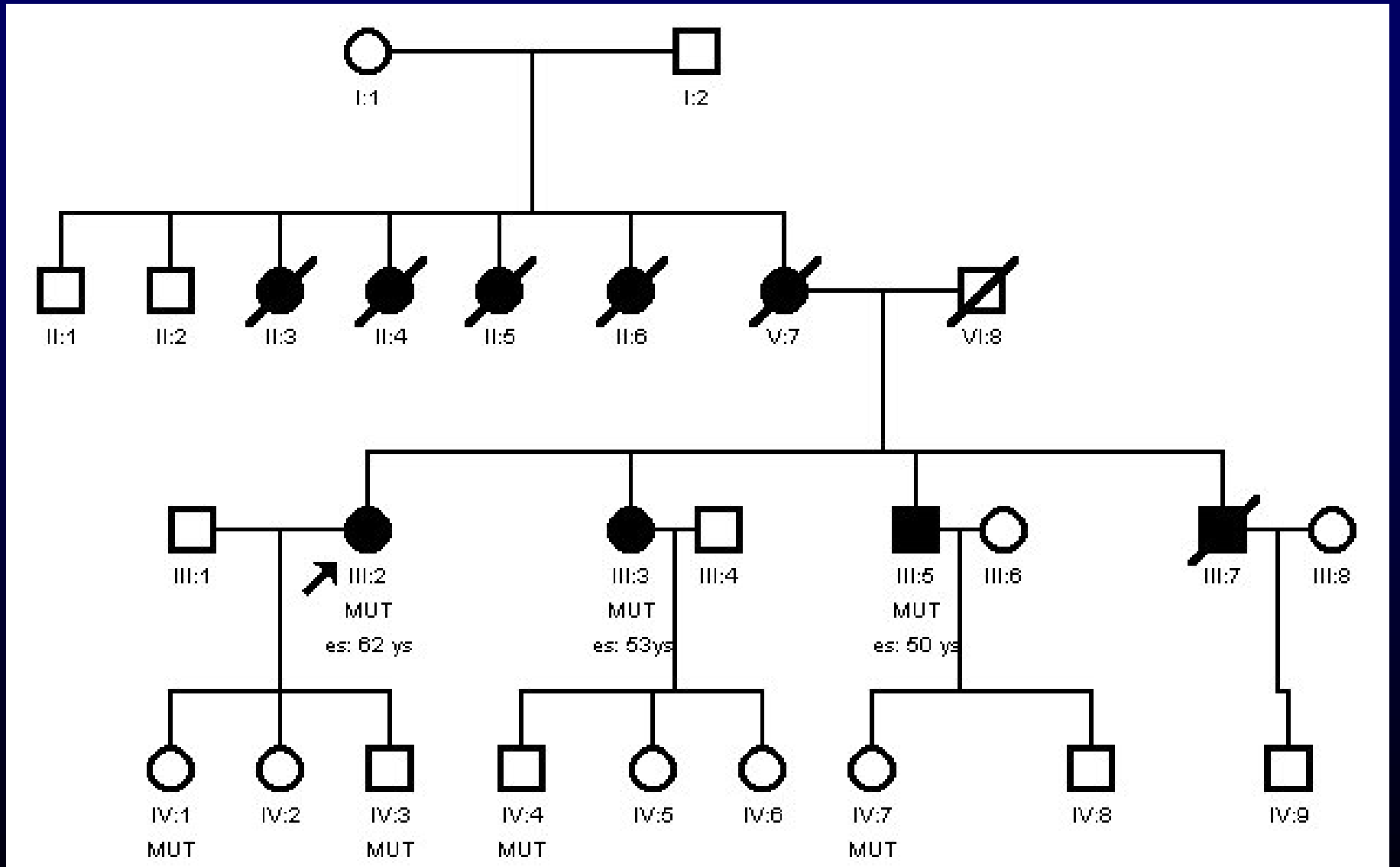
← **HRM**

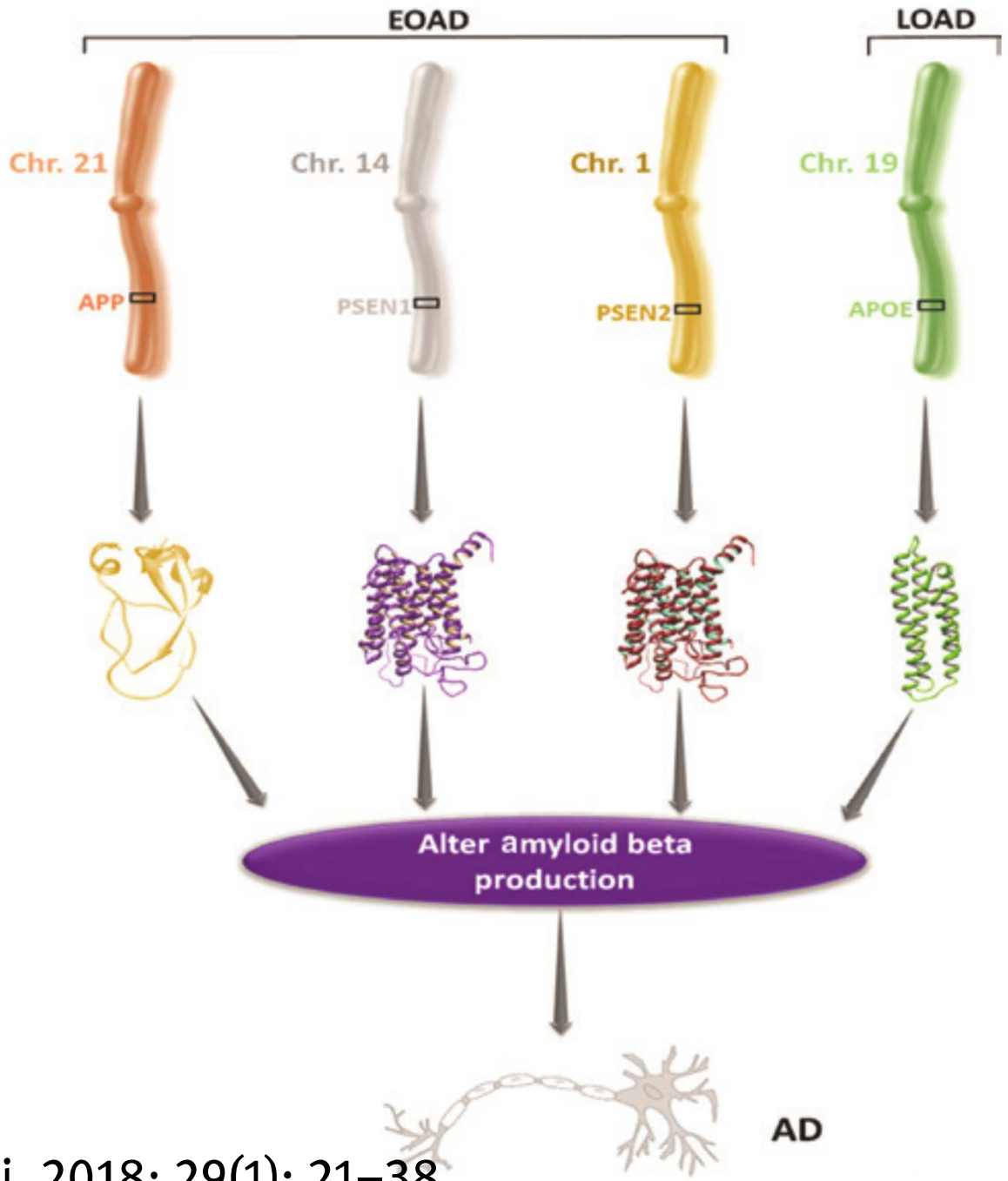


→ **Sequenziamento semi-automatico**



Flo 57
PS1 Cys92Ser





Rev. Neurosci. 2018; 29(1): 21–38

Rev. Neurosci. 2018; 29(1): 21–38

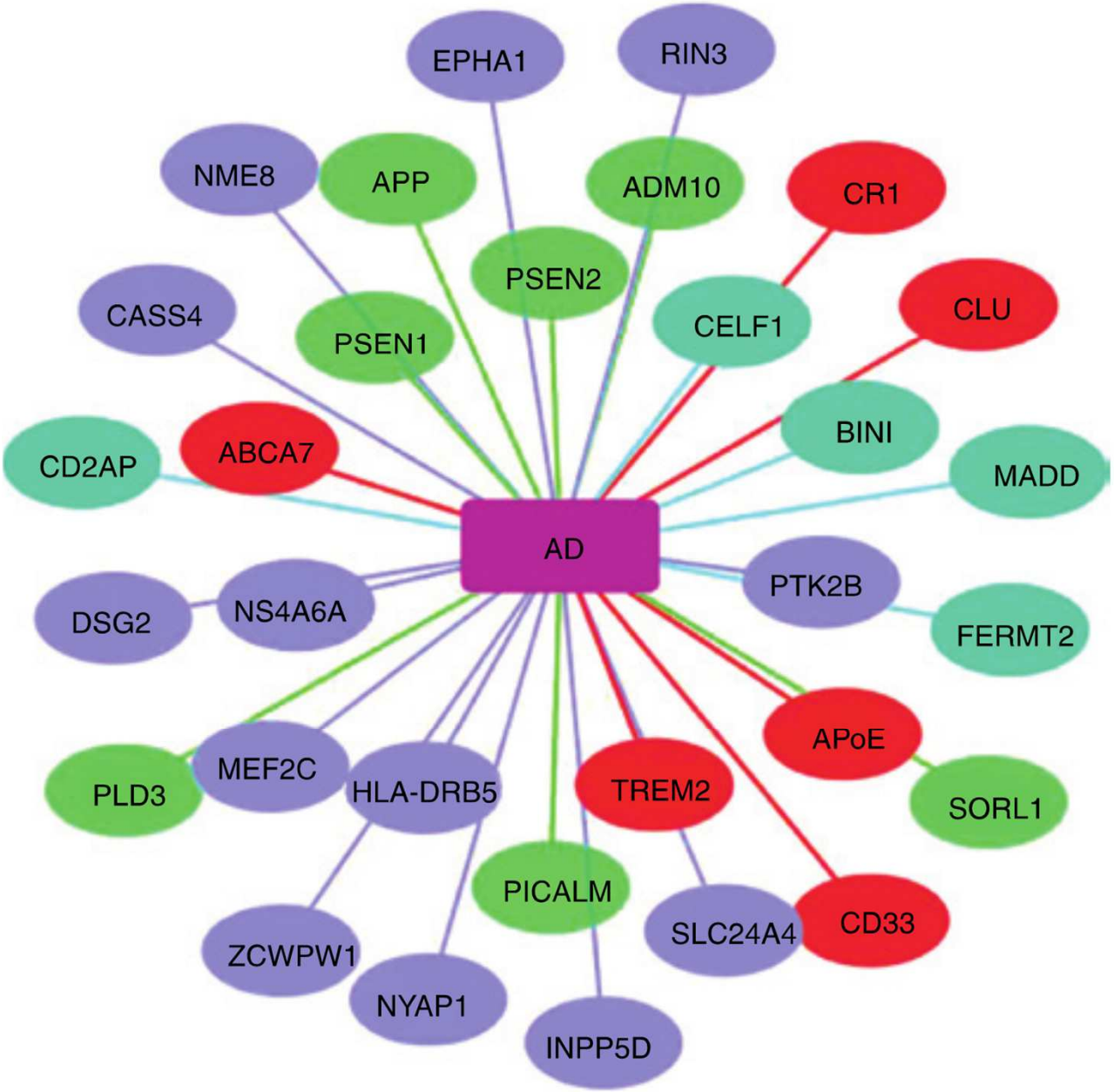
Ahmed A. Moustafa[a,*], Mubashir Hassan[a], Doaa H. Hewedi, Iman Hewedi, Julia K. Garami, Hany Al Ashwal, Nazar Zaki, Sung-Yum Seo, Vassilis Cutsuridis, Sergio L. Angulo, Joman Y. Natesh, Mohammad M. Herzallah, Dorota Frydecka, Błażej Misiak, Mohamed Salama, Wael Mohamed, Mohamad El Haj and Michael Hornberger

Genetic underpinnings in Alzheimer's disease – a review

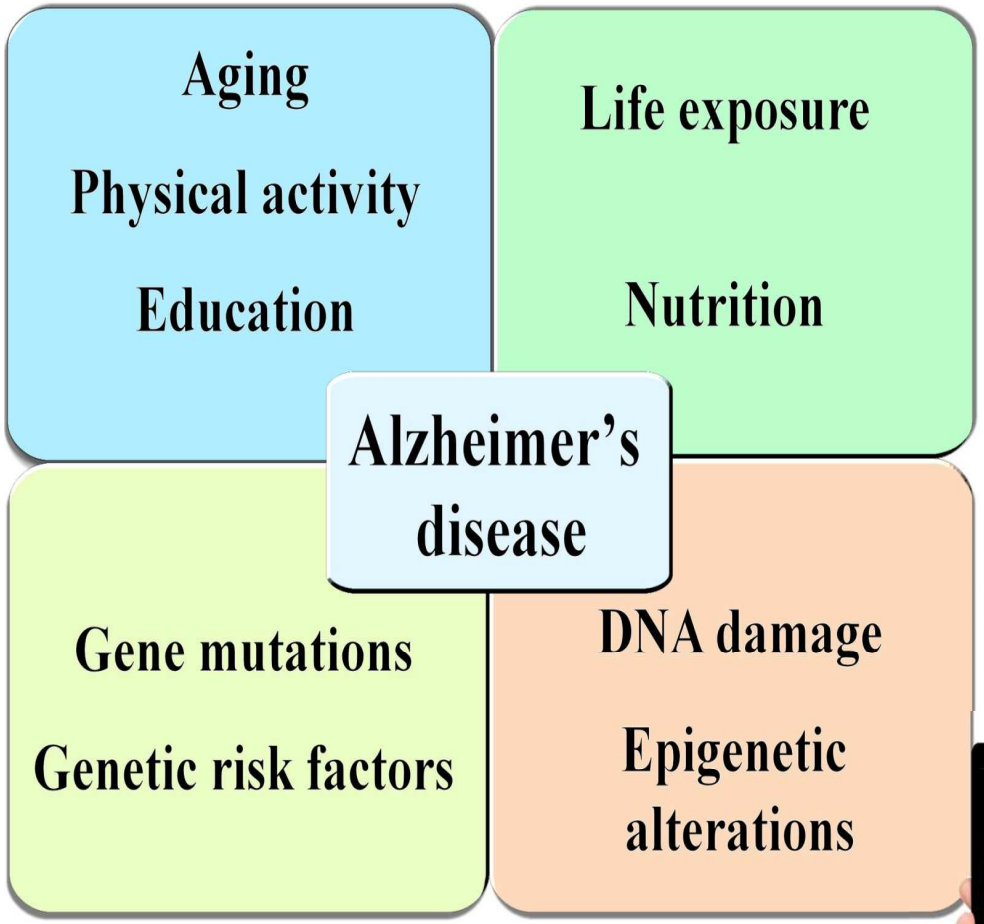
Table 1: Mutations in genes associated with AD.

Genes	Encoded proteins	Locations	Mutations	Penetrance	Prevalence
APP	Amyloid precursor protein	21q21.3	35	High	Low
PSEN1	Presenilin 1	14q24.3	165	High	Low
PSEN2	Presenilin 2	1q31-q42	13	High	Low
ApoE	Apolipoprotein-E	19q13.2	13	Low	High
ADAM10	ADAM domain 10	15q21.3	1	High	Low
CR1	Complement component 3b/4b receptor 1	1q32	8	–	–
BIN1	Bridging integrator 1	2q14	1	–	–
CD2AP	CD2-associated protein	6p12	1	–	–
EPHA1	EPH receptor A1	7q35	1	–	–
CLU	Clusterin	8p21.1	5	Low	High
MS4A6A	Membrane spanning 4-domains A6A	11q12.1	1	–	–
PICALM	Phosphatidylinositol-binding clathrin assembly protein	11q14	1	–	–
ABCA7	ATP-binding cassette subfamily A member 7	19p13.3	1	High	Low
CD33	CD33 molecule	19q13.3	1	–	–
HLA-DRB5	Major histocompatibility complex, Class II, DR Beta 5	6p21.32	8	–	–
PTK2B	Protein tyrosine kinase 2 Beta	8p21.1	1	–	–
SORL1	Sortilin-related receptor, L(DLR Class) A repeats containing	11q23.2-q24.2	6	High	Low
SLC24A4	Solute carrier family 24 member 4	14q32.12	8	–	–
RIN3	Ras and Rab interactor 3	14q32.12	1	–	–
DSG2	Desmoglein 2	18q12.1	1	–	–
INPP5D	Inositol polyphosphate-5-phosphatase D	2q37.1	1	–	–
MEF2C	Myocyte enhancer factor 2C	5q14	17	–	–
NME8	NME/NM23 family member 8	7p14.1	1	–	–
ZCWPW1	Zinc finger CW-type and PWWP domain containing 1	7q22.1	1	–	–
NYAP1	Neuronal tyrosine phosphorylated phosphoinositide-3-kinase adaptor 1	7q22.1	1	–	–
CELF1	CUGBP, Elav-like family member 1	11p11.2	1	–	–
MADD	MAP kinase activating death domain	11p11.2	1	–	–
FERMT2	Fermitin family member 2	14q22.1	1	–	–
CASS4	Cas scaffolding protein family member 4	20q13.31	1	–	–
TREM2	Triggering receptor expressed on myeloid cells 2	6p21.1	7	–	–
PLD3	Phospholipase D family member 3	19q13.2	1	–	–

Rev. Neurosci. 2018; 29(1): 21–38



NON-GENETIC FACTORS

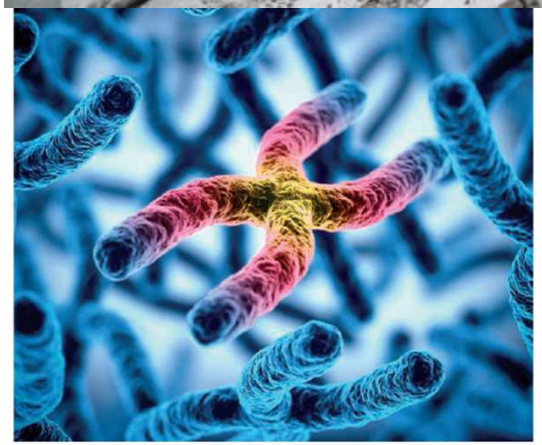


GENETIC FACTORS

Genetics of Alzheimer's Disease

Piaceri I[1], Bagnoli S[1] and Nacmias B[1]*

SMGroup



"...genes alone do not determine our futures..."

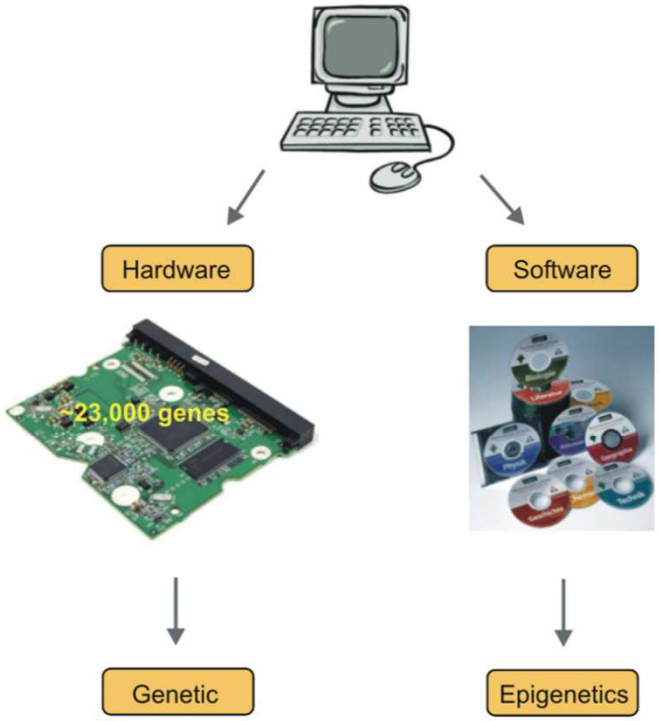


Fig. 1. Epialleles. Shown is an example of a natural non–DNA sequence–mediated multigenerational epigenetic inheritance in toad flax: breaking flower symmetry (*12*). The flower changes from bilateral symmetry (**left**) to radial symmetry (**right**) via a naturally occurring mutant. The molecular basis of this mutant is a metastable and heritable DNA methylation state of the *Lcyc* gene locus.

NATURE | **NEWS**

Astronaut twin study hints at stress of space travel

Unusual study of NASA's Scott and Mark Kelly finds gene-expression shifts during nearly a year in space.

Alexandra Witze

26 January 2017

Pat Sullivan/AP Photo

NASA astronaut Scott Kelly (left) spent a year aboard the International Space Station without his twin, Mark.

NEWS FEATURE

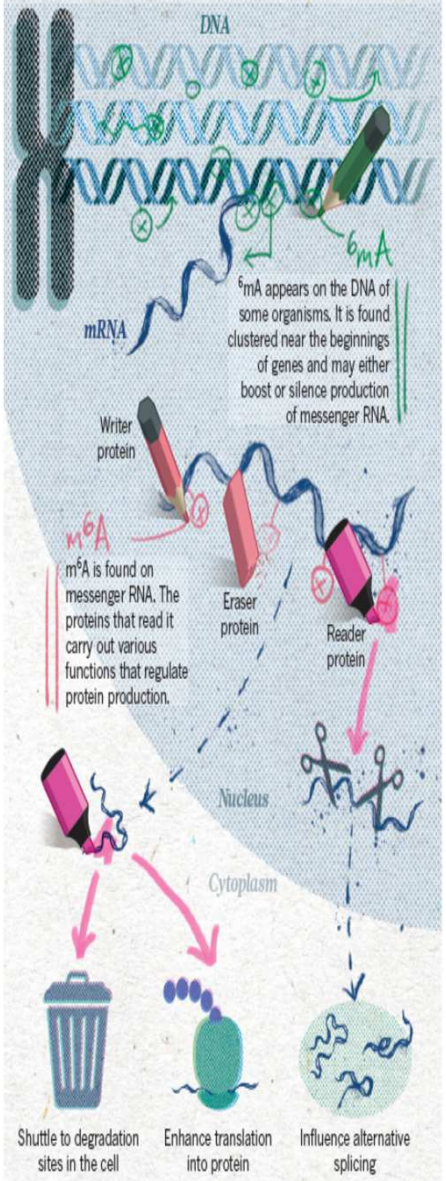
23 FEBRUARY 2017 | VOL 542 | NATURE | 407

A new twist on epigenetics

How rediscovered chemical tags on DNA and RNA are shaking up the study of gene expression.

Reading, writing and regulation

A lot of the research on epigenetic modifications has been concentrated on methyl marks on cytosine bases in DNA. Recent studies have brought methylated adenine bases in both DNA and RNA into focus. The identification of proteins that write, read or erase these marks suggests their importance in the regulation of gene expression.



Review

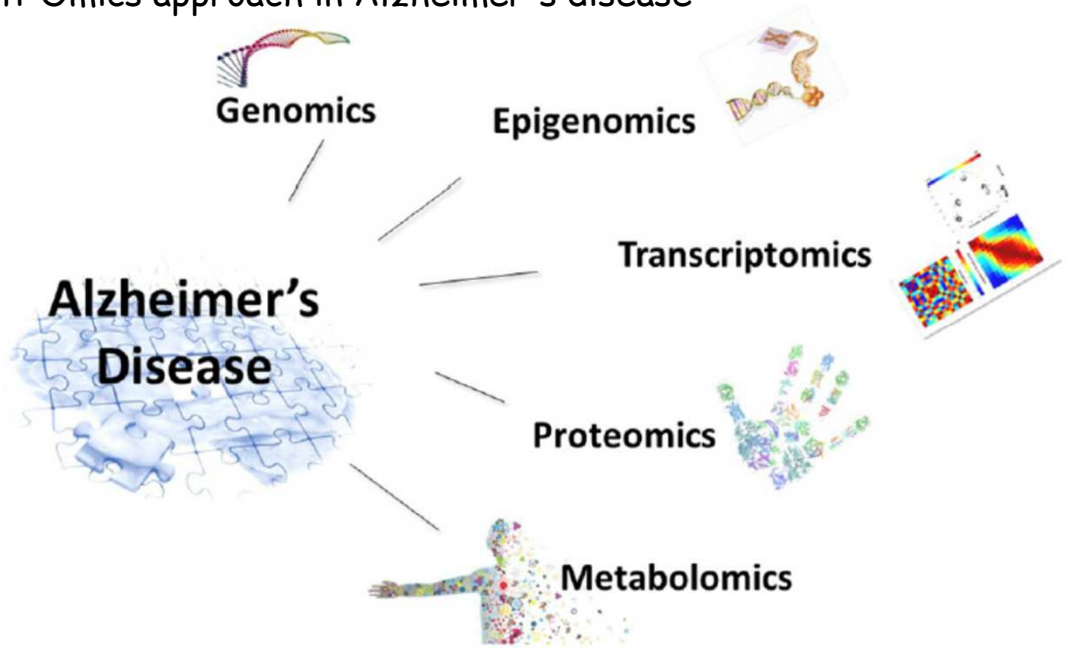
Clinical Biochemistry 59 (2018) 9–16

Alzheimer's disease in the omics era

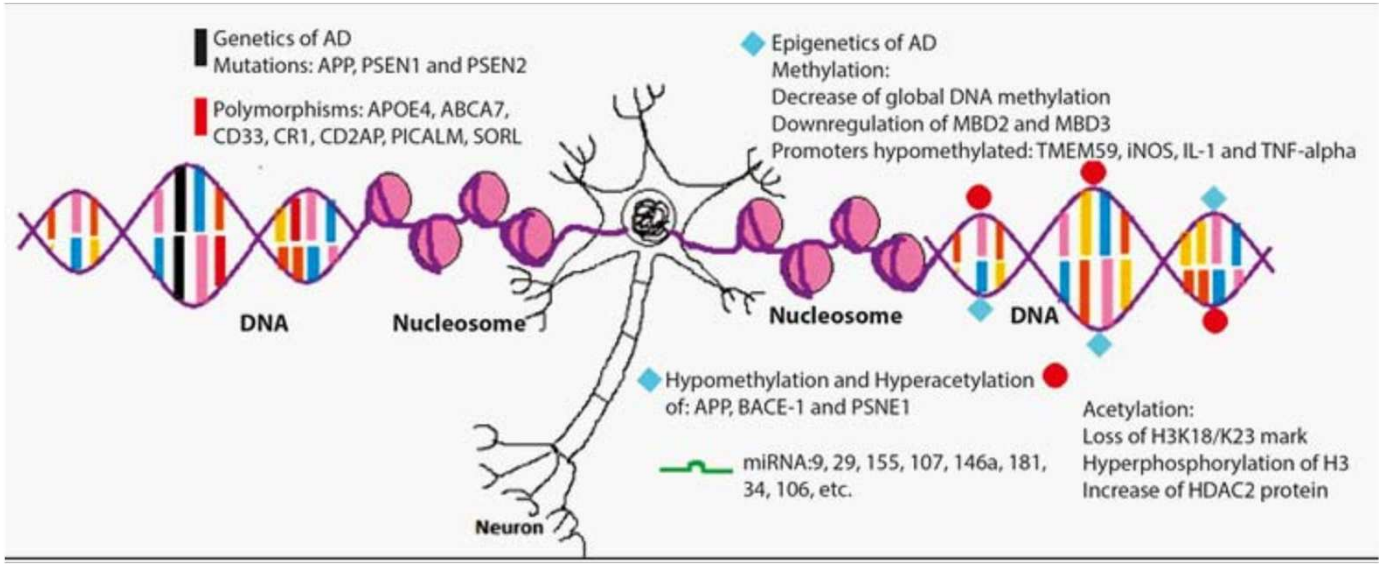
Giulia M. Sancesario[a,*], Sergio Bernardini[b]

[a] IRCCS Santa Lucia Foundation, Dept. Clinical and Behavioural Neurology, Rome, Italy
[b] Tor Vergata University General Hospital, Dept. Experimental Medicine, Rome, Italy

Multi-Omics approach in Alzheimer's disease



Genetic and epigenetic modifications in Alzheimer's disease



Alzhiemer's disease/ SMGebooks.com,

Journal of Alzheimer's Disease 65 (2018) 3–13

Journal of Alzheimer's Disease 65 (2018) 3–13
DOI 10.3233/JAD-180145
IOS Press

Review

Alzheimer's Disease: Advances in Drug Development

Morgane Piton[a], Christophe Hirtz[d], Caroline Desmetz[b], Jacqueline Milhau[b], Anne Dominique Lajoix[b], Karim Bennys[c], Sylvain Lehmann[d] and Audrey Gabelle[a,c,*]
[a]*University of Montpellier, Montpellier, France*
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[d]*Clinical Proteomics Platform, LBPC, IRMB, CHU Montpellier, Montpellier University, Montpellier, France*

Journal of Alzheimer's Disease 65 (2018) 3–13

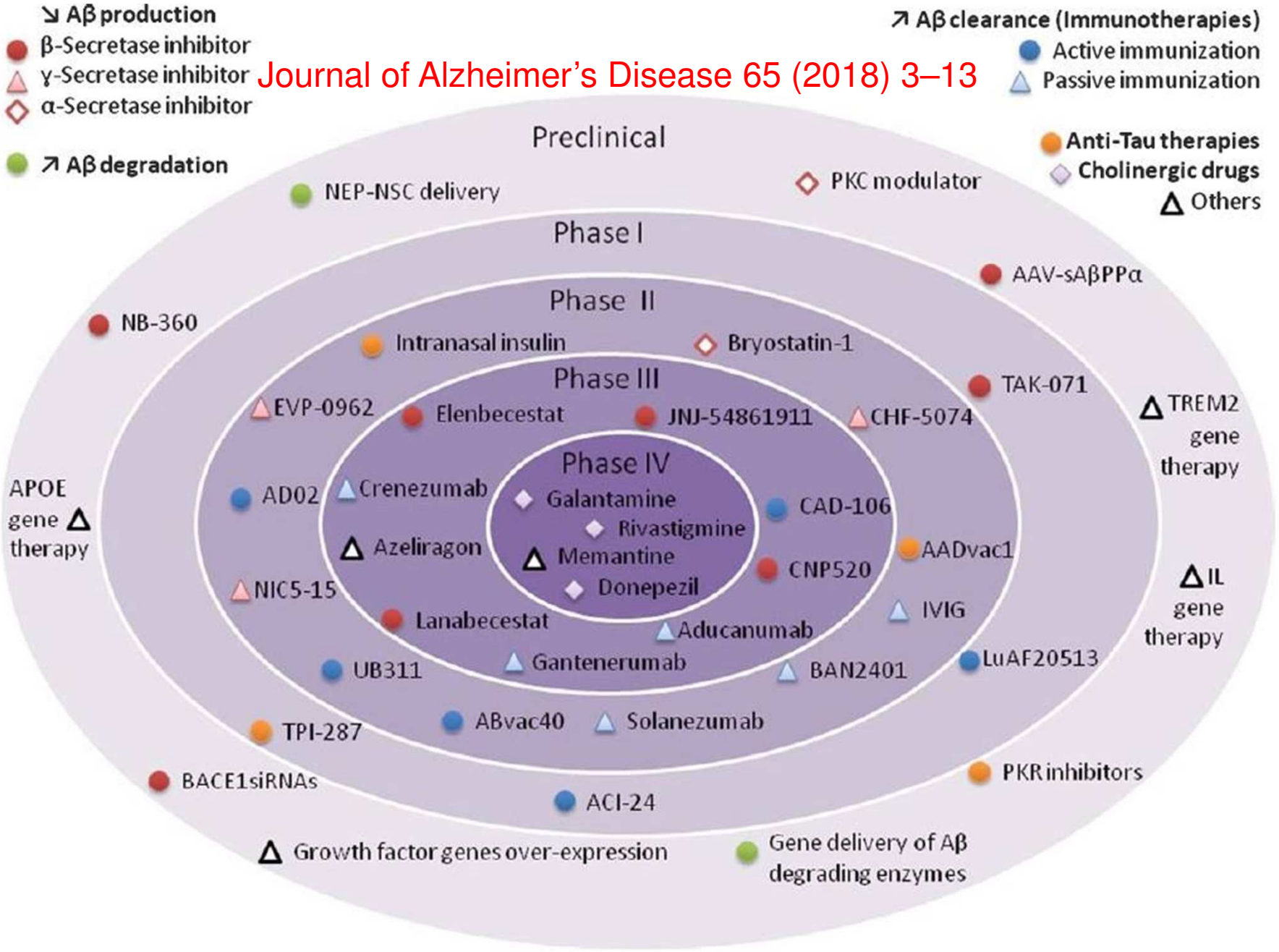
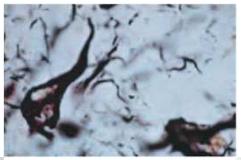
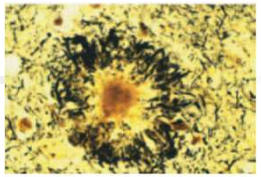


Fig. 1. Drug development in Alzheimer's disease. Drugs being investigated for Alzheimer's disease therapy, reported according to the most advanced phase of study and main therapeutic properties (including data from *in vitro* studies and animal models).

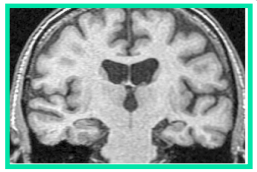
Dr Alois Alzheimer
1864 - 1915



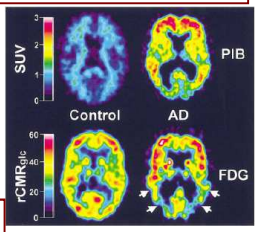
Tau based neurofibrillary tangle

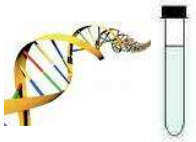


Amyloid based Neuritic plaque



MRI
FDG & PIB PET





Genetic markers

Auguste D.
First seen by Dr Alzheimer in 1901 when she was in her early 50s

Growing old gracefully