Postgraduate Interuniversity Course Human Genetics 03/12/2021

NEURODEGENERATIVE BRAIN DISORDERS

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CENTRUM MEDISCHE GENETICA GENT

OUTLINE

- Introduction
- Alzheimer's disease
- Related disorders: frontotemporal dementia –ALS spectrum
- mtDNA disorders

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- **Introduction**
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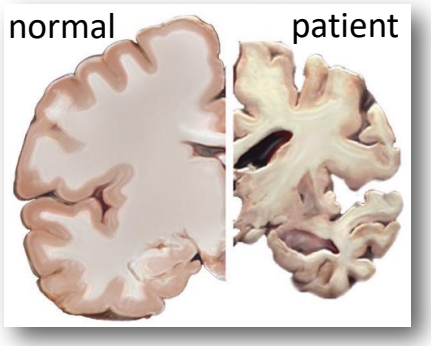
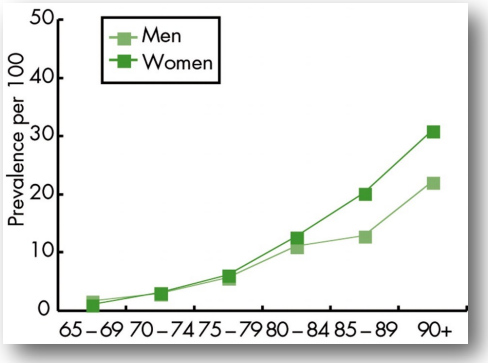
NEURODEGENERATIVE BRAIN DISORDERS





✓**progressive** loss of neurons, neuronal function

✓ **many subtypes**:

- frequent: Alzheimer (60-70%), frontotemporal dementia (<5%), Parkinson (10%)
- rare: prion disorders, motor neuron disease, Huntington's disease, …

✓**societal problem** is huge:

- Aging population – 65+ :
  - ➢16% (2015) → 25% (2030)
- dementia:
  - ➢ 44 million (2014) → 66 million (2030)

✓**limited therapeutic options**

✓**genetically heterogeneous**

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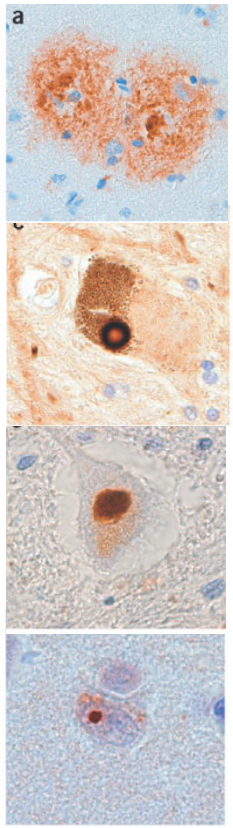
NEURODEGENERATIVE BRAIN DISORDERS

- Chronic and progressive disorders
- Progressive and selective loss of neurons
  Motor, sensorial and cognitive system
- Nosological classification following pattern of neuronal loss and **disease-specific cellular markers**
  "Proteinopathies"

  AD: senile plaques, neurofibrillary 'tangles'
  neuronal loss
  PD: Lewy bodies, depletion of dopaminergic neurons
  ALS: cellular inclusions, axon swelling of
  motor neurons
  HD: nuclear inclusions, loss of striatal neurons



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Martin J.B., NEJM 340:1970-1980 (1999)

NEURODEGENERATIVE BRAIN DISORDERS

- Causes
  - Genetic factors

    -**Mendelian** inheritance – monogenic:

    rare familial forms of common disorders

    classic monogenic e.g. repeat expansion disorder

    -**Multifactorial** - common disorders:

    several genes contribute to disease

    variation in age of onset and progression point to different pathogenetic mechanisms (e.g. AD)

  - Environment: ?, toxic or metabolic processes, infection, unknown

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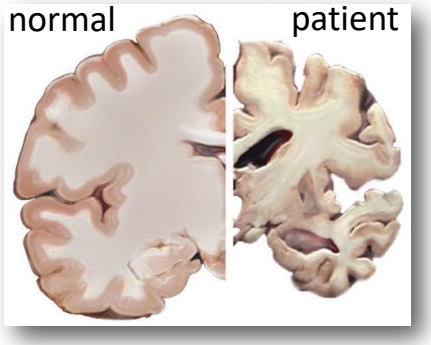
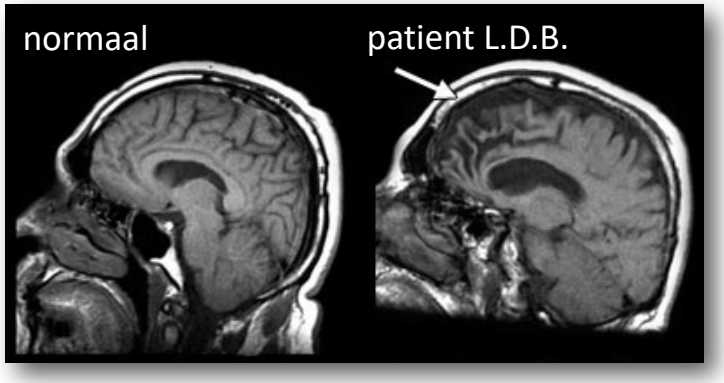
PATIENT L.D.B.



- ✓ male, 56 years, negative neuropsychiatric history
- ✓ admitted to emergency psychiatric service after car accident:
  - restless, incoherent thinking, stereotypical vocabulary, word finding problems
  - known to the police: shoplifting, aggressiveness, dangerous driving behavior
- ✓ According to brother: last 3 yrs increasing compulsive behavior, conflicts, emotional flattening, contentless speech, memory problems
- ✓ Brain imaging: atrophy of the frontal and temporal lobes
- ✓ **mother, maternal grantfather both demented < 65 yrs**



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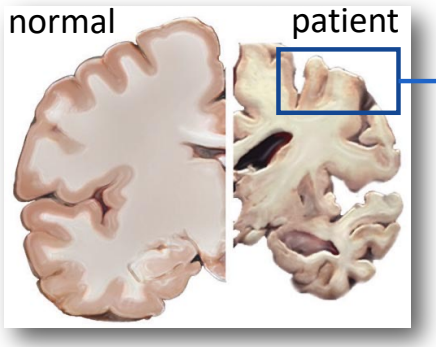
→ diagnosis **early-onset dementia: subtype?**

UNDER THE MICROSCOPE…



neuropathologist

frontal lobe dementia or Alzheimer ?

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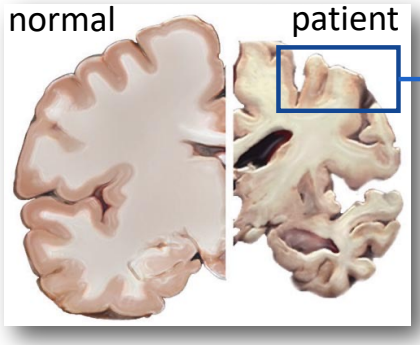
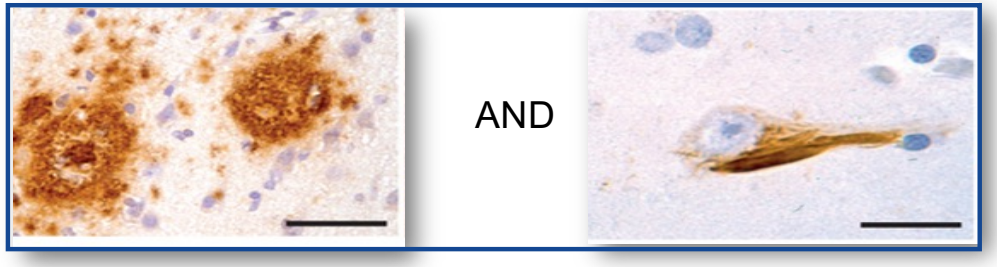
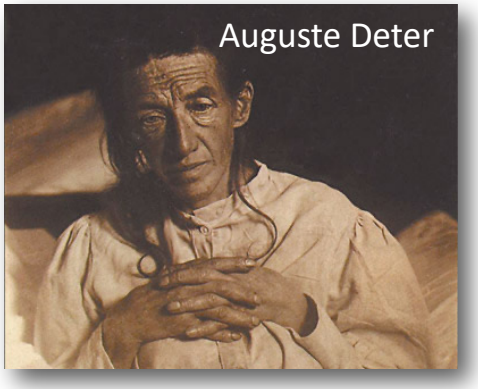


Alzheimer's disease

Amyloid plaques AND **Tau tangles**



Aloïs Alzheimer
(1864-1915)



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Alzheimer A. **Über eine eigenartige Erkrankung der Hirnrinde.** *Allgemeine Zeitschrift für Psychiatrie und Psychisch-gerichtliche Medizin*. 1907 Jan ; 64:146-8.

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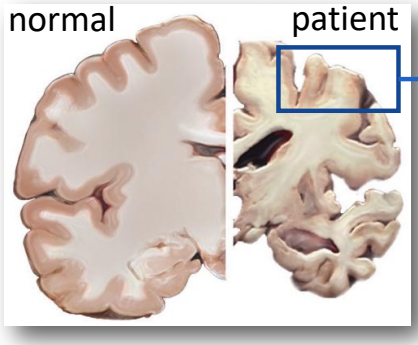


Aloïs Alzheimer (1864-1915)

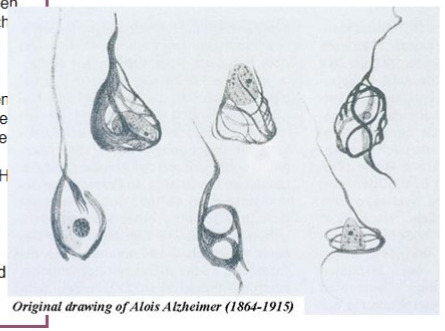
Alzheimer A.
Über eine eigenartige Erkrankung der Hirnrinde
Allgemeine Zeitschrift fur Psychiatrie und Psychisch-gerichtliche Medizin.
1907 Jan ; 64:146-8.

"Die Sektion ergab ein gleichmäßig atrophisches Gehirn ohne makroskopische Herde. Die größeren Hirngefäße sind arteriosklerotisch verändert.
An Präparaten. die mit der Bielschowskyschen Silbermethode angefertigt sind, zeigen sich sehr merkwürdige Veränderungen der Neurofibrillen. Im Innern einer im übrigen noch normal erscheinenden Zelle treten zunächst eine oder einige Fibrillen durch ihre besondere Dicke und besondere Imprägnierbarkeit stark hervor. Im weiteren Verlauf zeigen sich dann viele nebeneinander verlaufende Fibrillen in der gleichen Weise verändert. Dann legen sie sich zu dichten Bündeln zusammen und treten allmählich an die Oberfläche der Zelle. Schließlich zerfällt der Kern und die Zelle, und nur ein aufgekn[illegible]eltes Bündel von Fibrillen zeigt den Ort, an dem früher[illegible] Ganglienzelle gelegen hat.
Da sich diese Fibrillen mit anderen Farb[illegible]lassen normale Neurofibrillen, muß eine che[illegible]ndung de Fibrillensubstanz stattgefunden h[illegible]ürfte wohl die Ursache sein, daß die Fibrille[illegible]ng der Zelle uberdauern. Die Umwandl[illegible]en scheint Hand in H zu gehen mit der Einlageru[illegible]noch nicht näher erforschten pathologischen S[illegible]wechselproduktes in die Ganglienzelle. Etwa 1/4 bis 1/3 aller Ganglienzellen der Hirnrinde zeigt solche Veränderungen. Zahlreiche Ganglienzellen, besonders in den oberen Zellschichten. sind ganz verschwunden."

"Über die ganze Rinde zers[illegible]ers zahlreich in den oberen[illegible]det man miliare Herdch[illegible]ch Einlagerung ein[illegible]n Stoffes in die Hirnrinde[illegible]. Er läßt sich schon ob[illegible]kennen. ist aber Färb[illegible]ber sehr refractär."

Amyloid plaques

Tau tangles



Original drawing of Alois Alzheimer (1864-1915)

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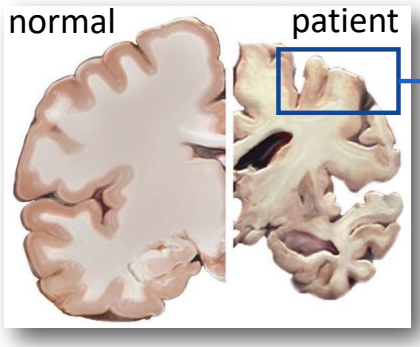
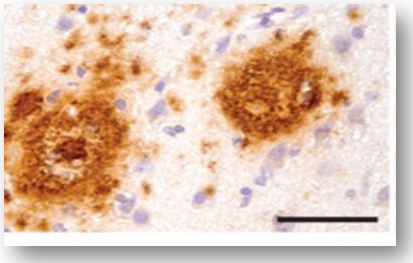
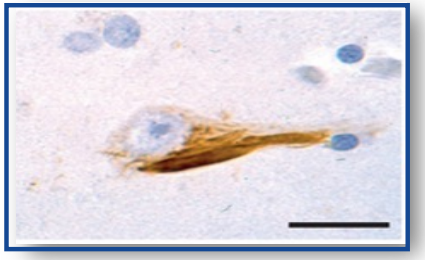


Frontal lobe dementia

Amyloid plaques



Tau tangles



Arnold Pick
(1851-1924)

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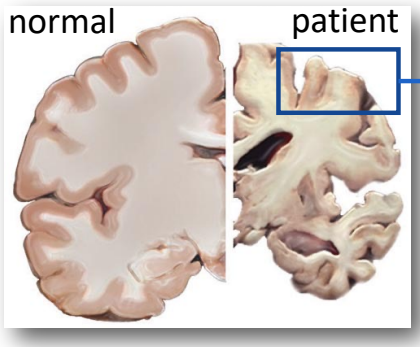

Frontal lobe dementia

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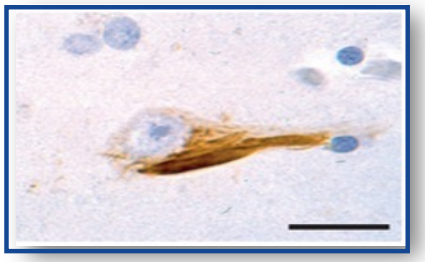

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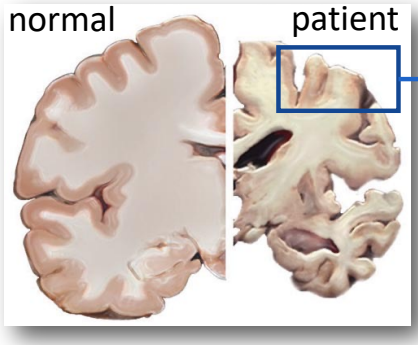

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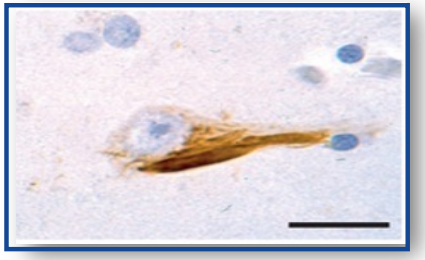

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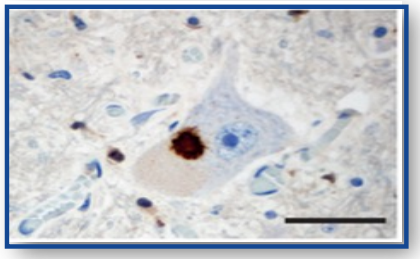

TDP-43 inclusions

Arnold Pick
(1851-1924)

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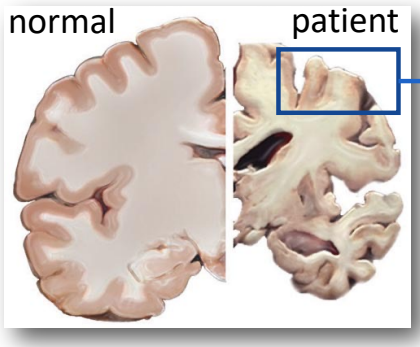
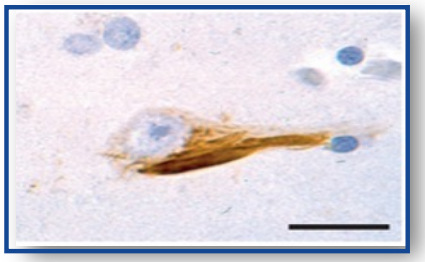


Frontal lobe dementia

Patient L.D.B.

Tau tangles



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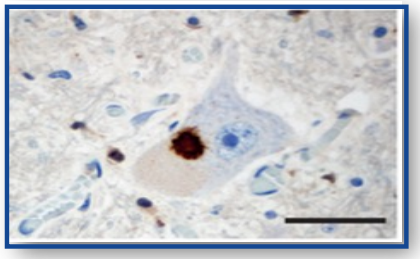

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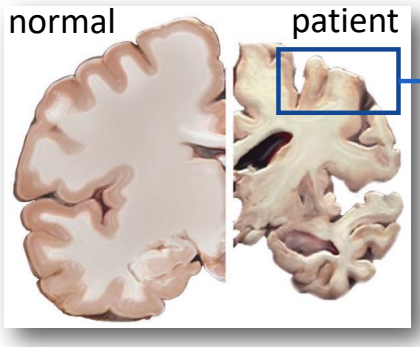

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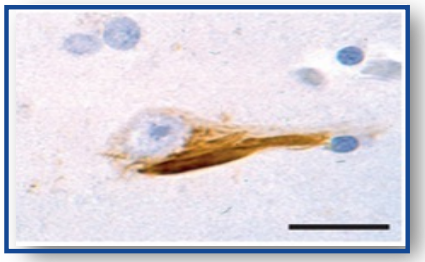

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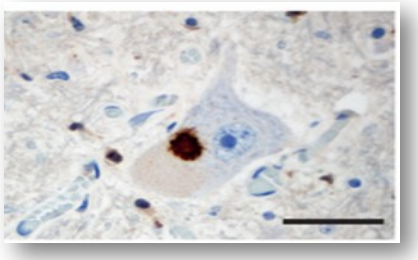

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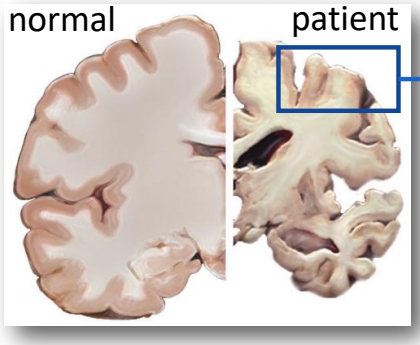
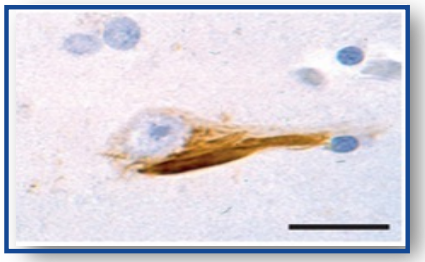


Frontal lobe dementia

Tau tangles



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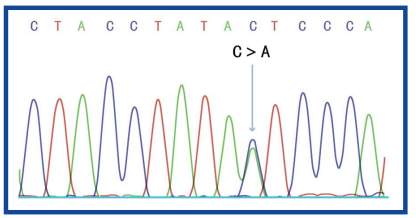

Arnold Pick
(1851-1924)

defect in the Tau gene (*MAPT* p.P301L)

→ **Tau-positive familial frontal lobe dementia**

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OUTLINE

- Introduction
- **Alzheimer's disease**
- Related disorders: frontotemporal dementia –ALS spectrum
- mtDNA disorders

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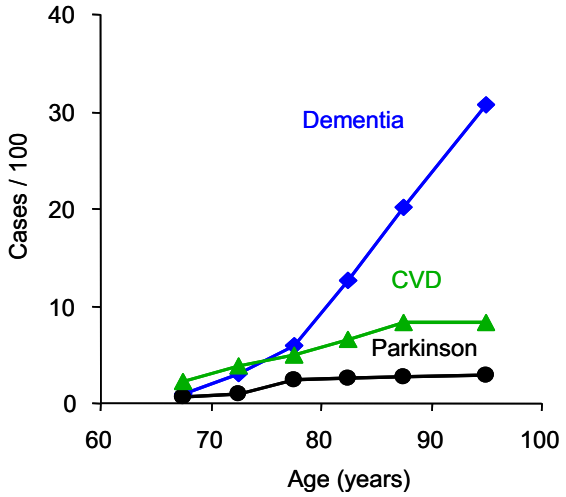
ALZHEIMER'S DISEASE

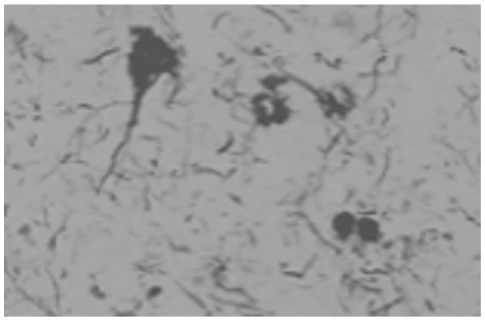
Prevalence strongly increases with age

70% are Alzheimer's disease cases
(860,000 cases in France in 2005)



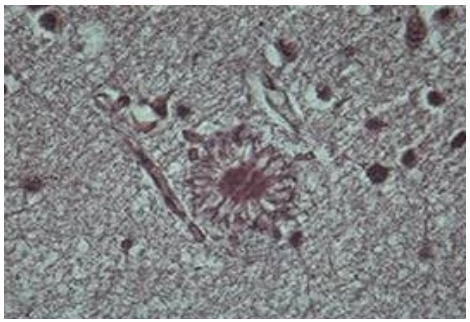
Alzheimer's disease (AD) => characterized in the brain by :

Neurofibrillary degeneration



Intraneuronal accumulation of hyperphosphorylated Tau

Amyloid deposition

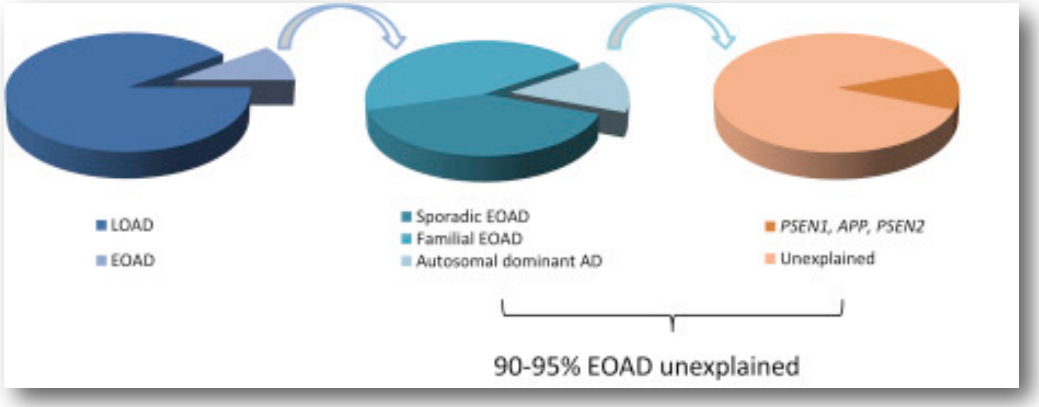


Extracellular accumulation of amyloid peptides

ALZHEIMER'S DISEASE

Disease characteristics

- adult-onset slowly progressive dementia (memory, cognition, personality)
- most frequent form of dementia
- >60 y: 5-10%, >85 y: 45%
- 4 mill/y, 100.000 +/y in US, cost 60 miljard US dollar
- 25% of cases familial
  - mostly late onset
  - < 2% early-onset familial AD (EOFAD) symptoms typically < 65 y



Cacace et al, 2016

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ALZHEIMER'S DISEASE

Clinical features

• dementia, typically begins with subtle and poorly recognized failure of memory

• other common symptoms: anxiety, confusion, poor judgment, language disturbance, agitation, withdrawal, and hallucinations

• occasional symptoms: seizures, Parkinsonian features, increased muscle tone, myoclonus, incontinence, mutism

• death usually results from general inanition, malnutrition, pneumonia

• typical clinical duration of the disease: 8-10 yrs, range: 1- 25 yrs

• post mortem: macroscopic - microscopic

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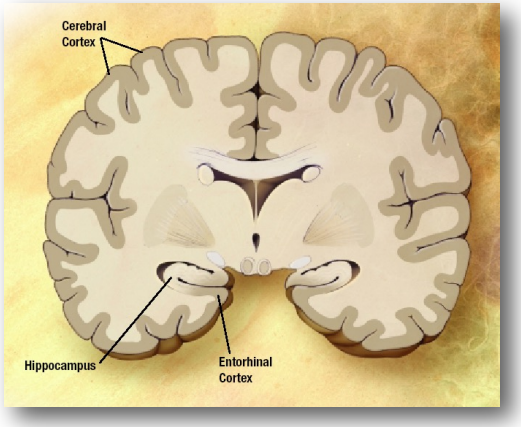
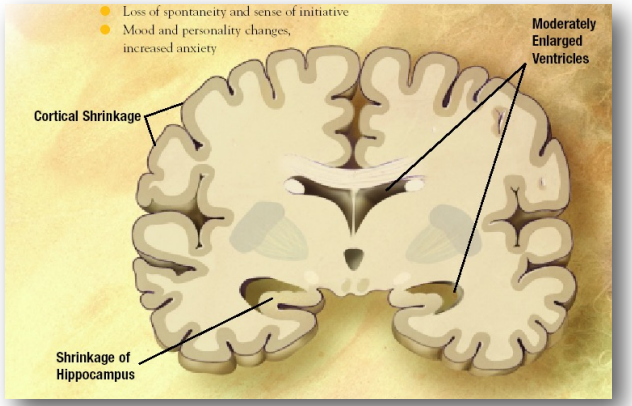
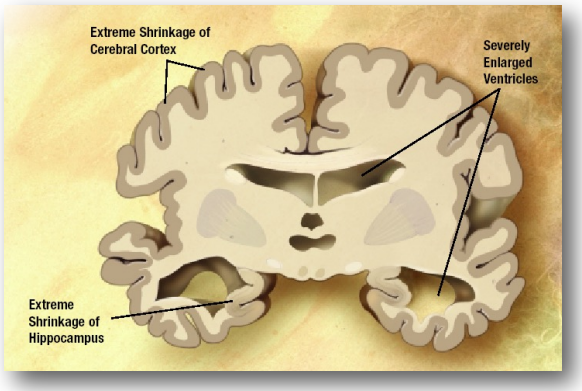
ALZHEIMER'S DISEASE



near and connected to hippocampus



learning processes, short term memory and conversion to long term memory in other parts (olfactory bulb, amygdala, nucleus basalis)



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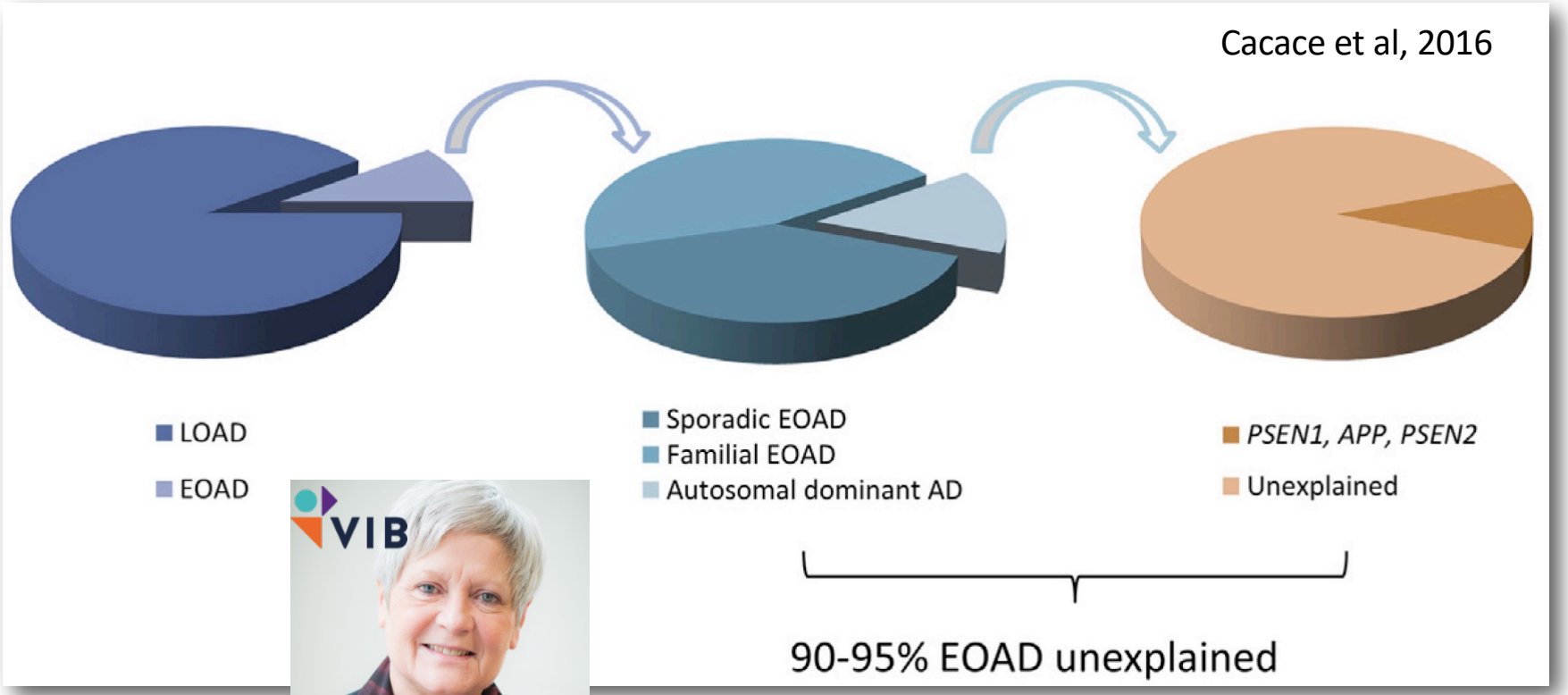
ALZHEIMER'S DISEASE - GENETICS



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Christine Van Broeckhoven

ALZHEIMER'S DISEASE - GENETICS

Table 1
Genetic heterogeneity in Alzheimer's disease (AD): Known causal early-onset AD gene

Gene	Chromosome	Inheritance	Gene identification	Mutation spectrum	Mutations (N)
APP	21q21.1–21q21.3	Autosomal dominant Autosomal recessive Protective	Linkage analysis	Missense Gene Duplication Amino acid deletion	54*
PSEN1	14q24.3	Autosomal dominant *de novo*	Linkage analysis	Missense Small indels Genomic deletions	215
PSEN2	1q31–q42	Autosomal dominant	Linkage and homology mapping	Missense	31

*The total number of *APP* mutations includes two causal recessive mutations.

Cacace et al, 2016

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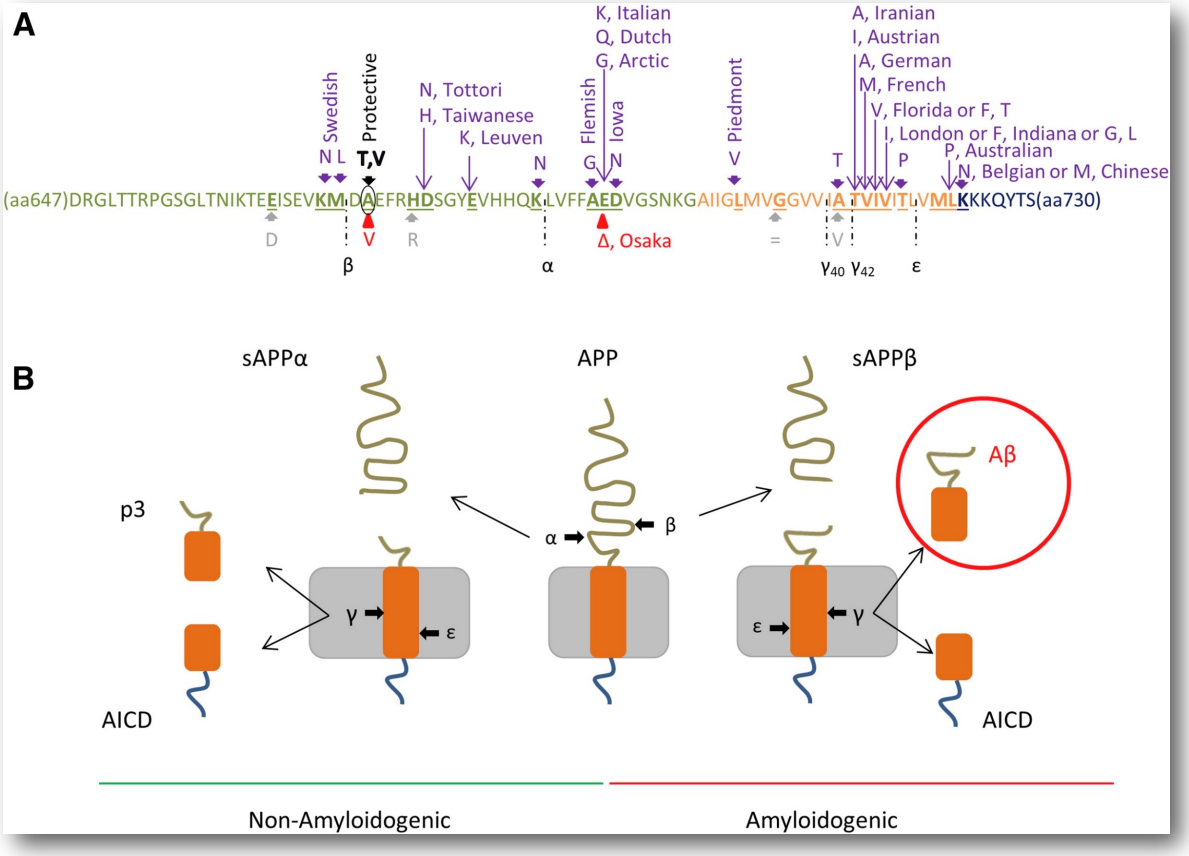
ALZHEIMER'S DISEASE - APP



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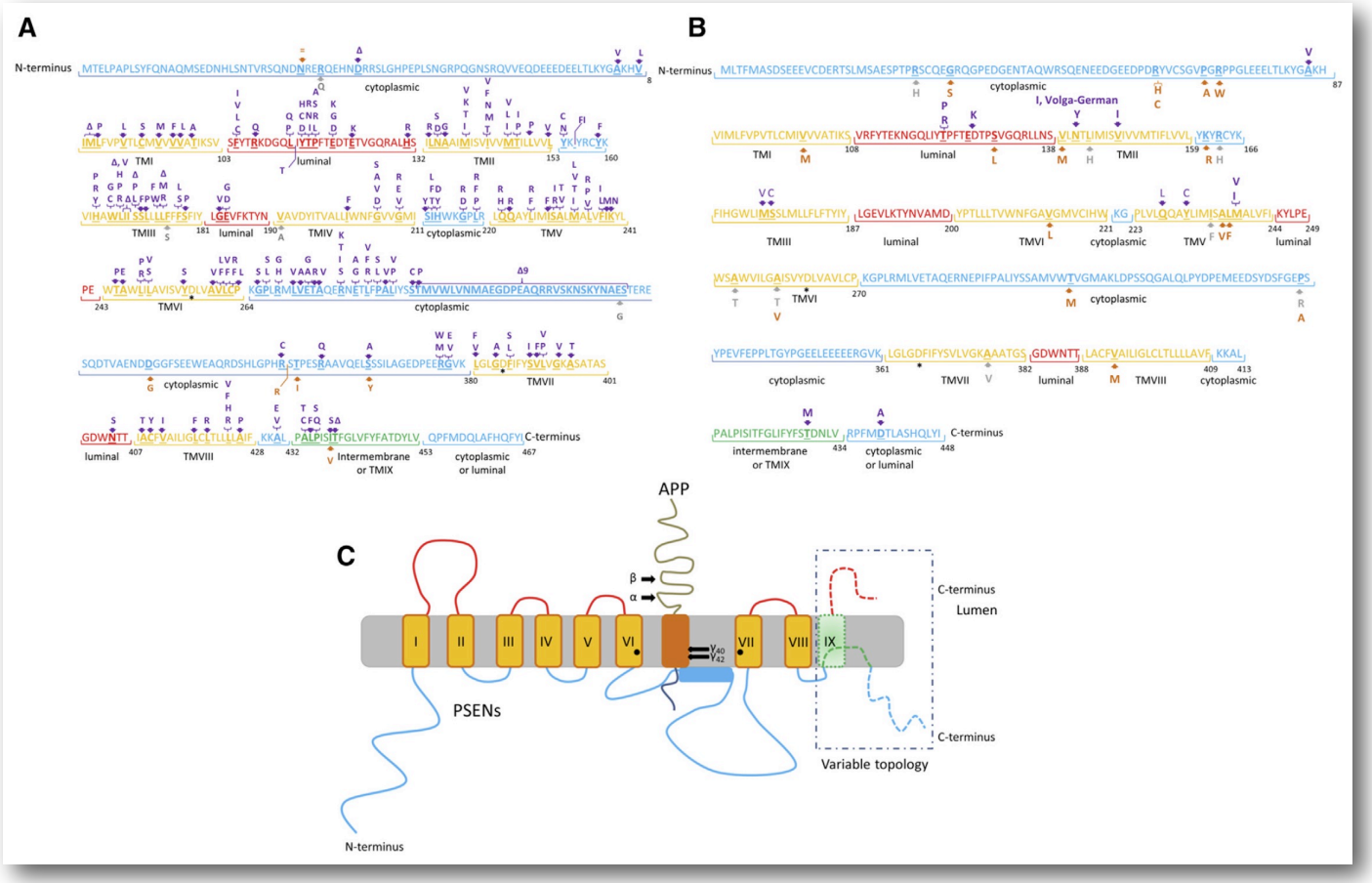
Cacace et al, 2016

ALZHEIMER'S DISEASE – PSEN1/2



Cacace et al, 2016

ALZHEIMER'S DISEASE – APP - PSEN1/2 LINK

NATURE | VOL 391 | 22 JANUARY 1998

Deficiency of presenilin-1 inhibits the normal cleavage of amyloid precursor protein

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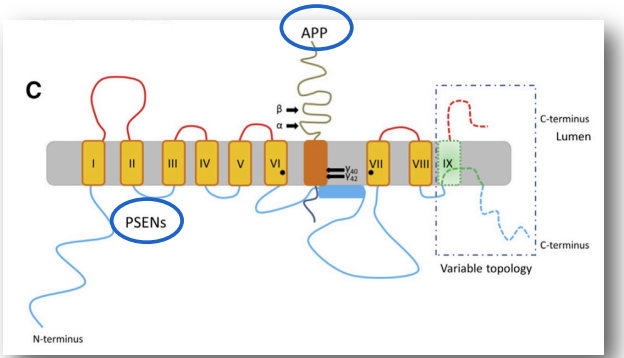
§ *Innogenetics NV, Industriepark Zw.7, 9057 Gent, Belgium*
‡ *Zentrum Biochemie und Molekular Zellbiologie, Abteilung Biochemie II, Universität Göttingen, 37073 Göttingen, Germany*
† *These authors contributed equally to this work.*

Point mutations in the presenilin-1 gene (*PS1*) are a major cause of familial Alzheimer's disease. They result in a selective increase in the production of the amyloidogenic peptide amyloid-β(1–42) by proteolytic processing of the amyloid precursor protein (APP)[1–4]. Here we investigate whether PS1 is also involved in normal APP processing in neuronal cultures derived from PS1-deficient mouse embryos. Cleavage by α- and β-secretase[5] of the extracellular domain of APP was not affected by the absence of PS1, whereas cleavage by γ-secretase of the transmembrane domain of APP was prevented, causing carboxyl-terminal fragments of APP to accumulate and a fivefold drop in the production of amyloid peptide. Pulse-chase experiments indicated that PS1 deficiency specifically decreased the turnover of the membrane-associated fragments of APP. As in the regulation of cholesterol metabolism by proteolysis of a membrane-bound transcription factor[6], PS1 appears to facilitate a proteolytic activity that cleaves the integral membrane domain of APP. Our results indicate that mutations in *PS1* that manifest clinically cause a gain of function and that inhibition of PS1 activity is a potential target for anti-amyloidogenic therapy in Alzheimer's disease.

Bart De Strooper



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ALZHEIMER'S DISEASE – APP - PSEN1/2 LINK

Genetic counseling

- first degree relatives of individuals with sporadic AD have about a 20% lifetime risk of developing AD
- presumably, when several individuals in a family have AD, the risk is further increased
- EOFAD is inherited in an autosomal dominant manner The risk to offspring of individuals with EOFAD is 50%

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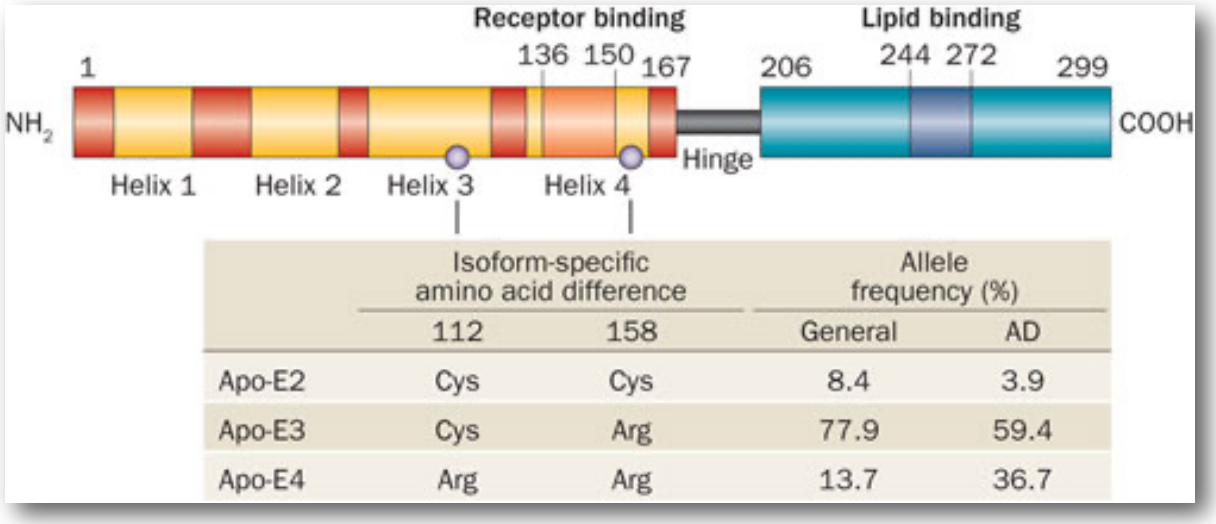
LATE-ONSET ALZHEIMER'S DISEASE GENETICS: APOE

Liu et al, 2013



	Isoform-specific amino acid difference		Allele frequency (%)	
	112	158	General	AD
Apo-E2	Cys	Cys	8.4	3.9
Apo-E3	Cys	Arg	77.9	59.4
Apo-E4	Arg	Arg	13.7	36.7

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

Credit: alzdiscovery.org/

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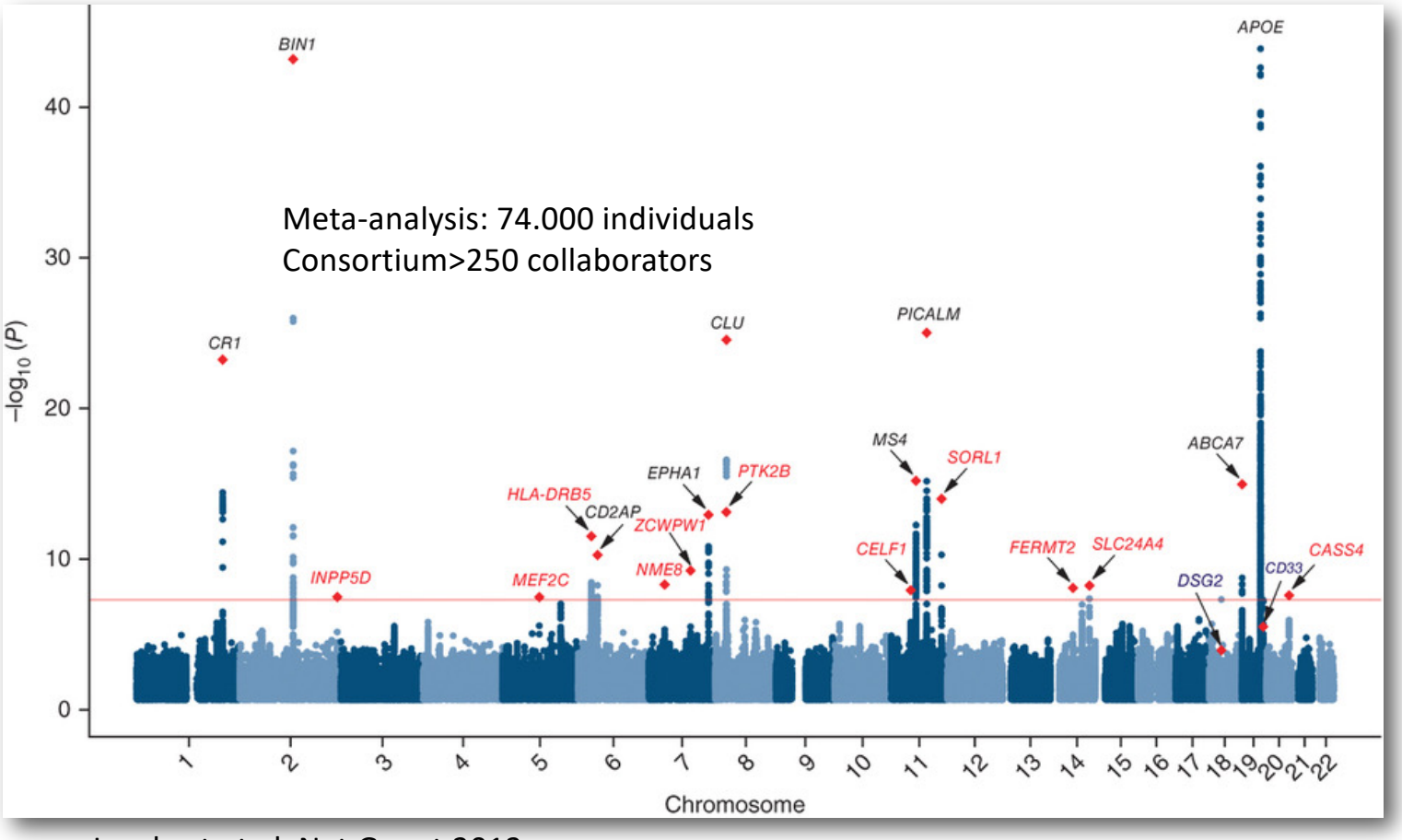
LATE-ONSET ALZHEIMER'S DISEASE GENETICS: GWAS



Lambert et al, Nat Genet 2013

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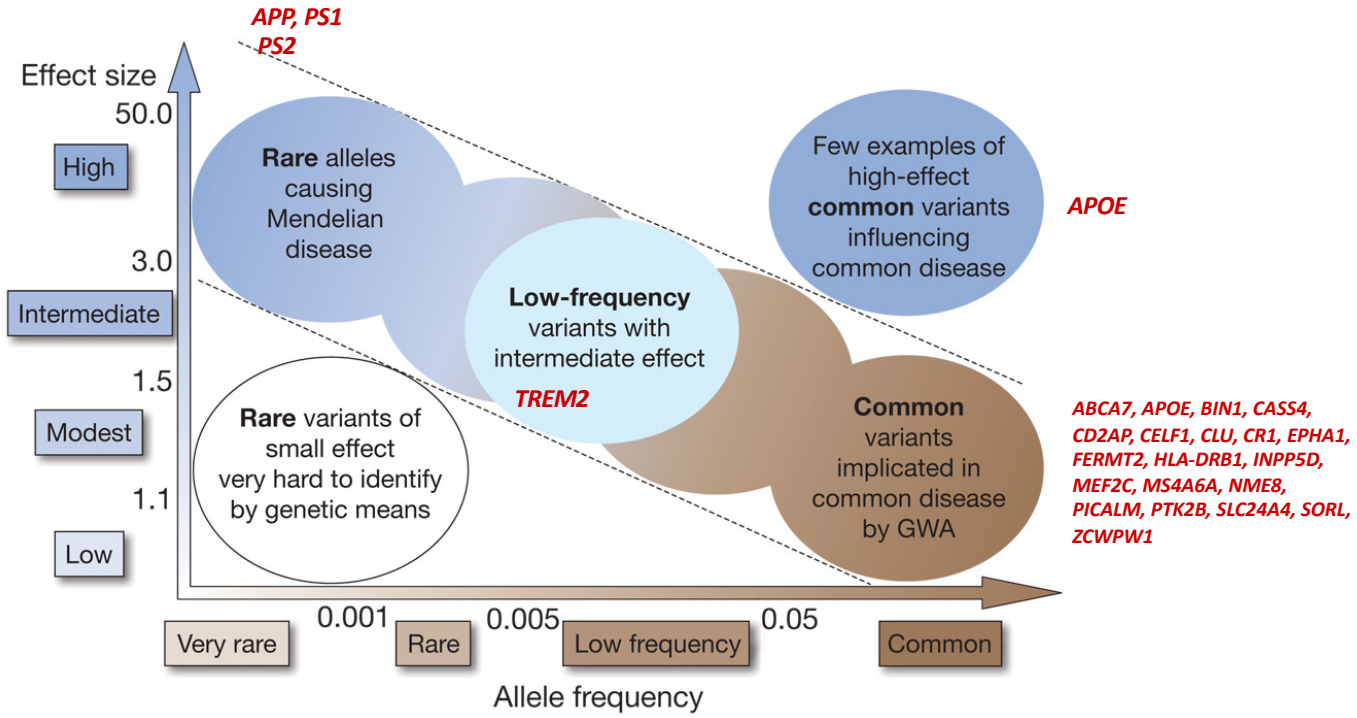
ALZHEIMER'S DISEASE GWAS – GENETIC LANDSCAPE



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Less than 1% of the cases are monogenic forms.
The genetic attributable risk has been estimated between 60 and 80% and to date, 22 loci have been associated with AD risk.

OUTLINE

- Introduction
- Alzheimer's disease
- **Related disorders: frontotemporal dementia –ALS spectrum**
- mtDNA disorders

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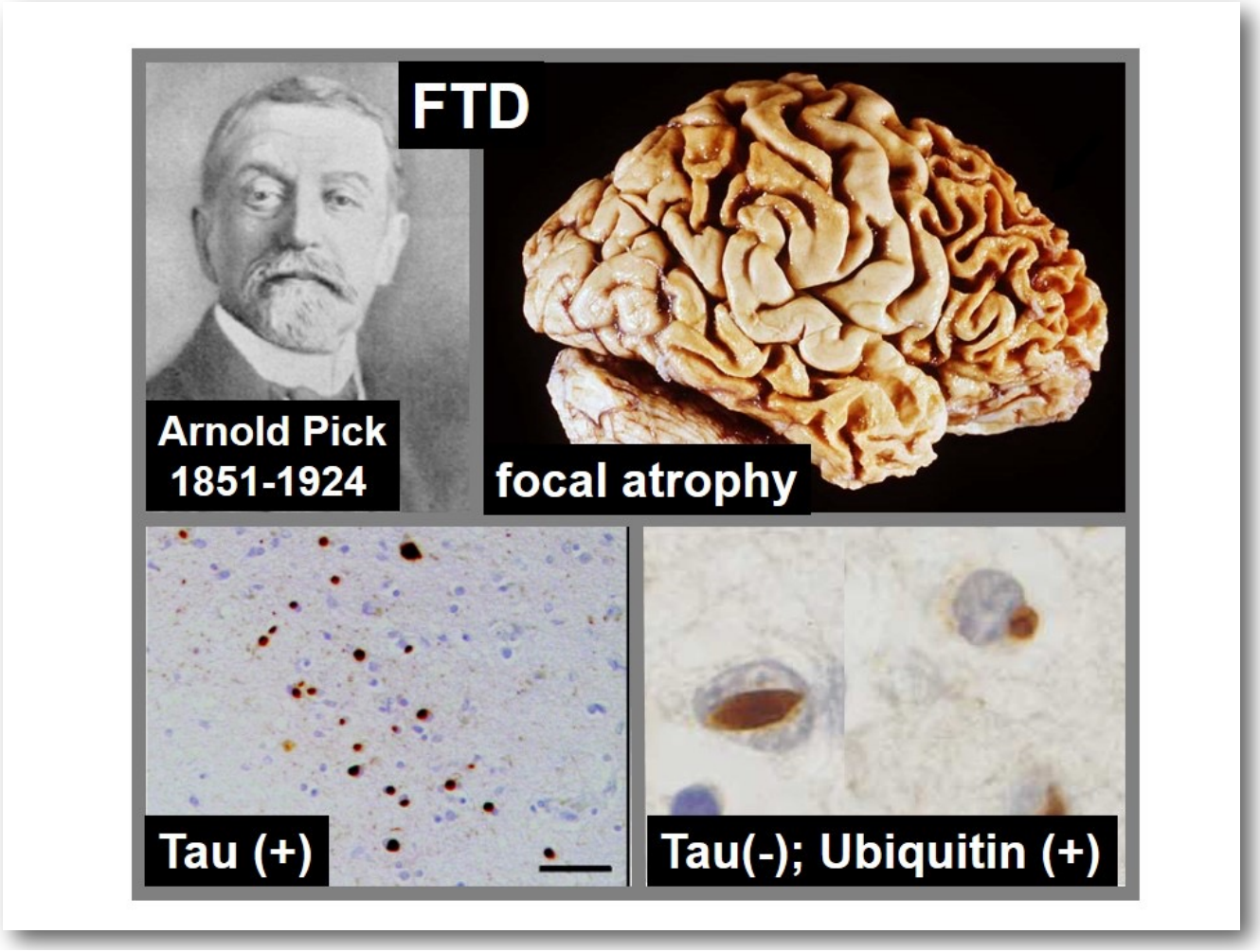
FTD – ALS SPECTRUM



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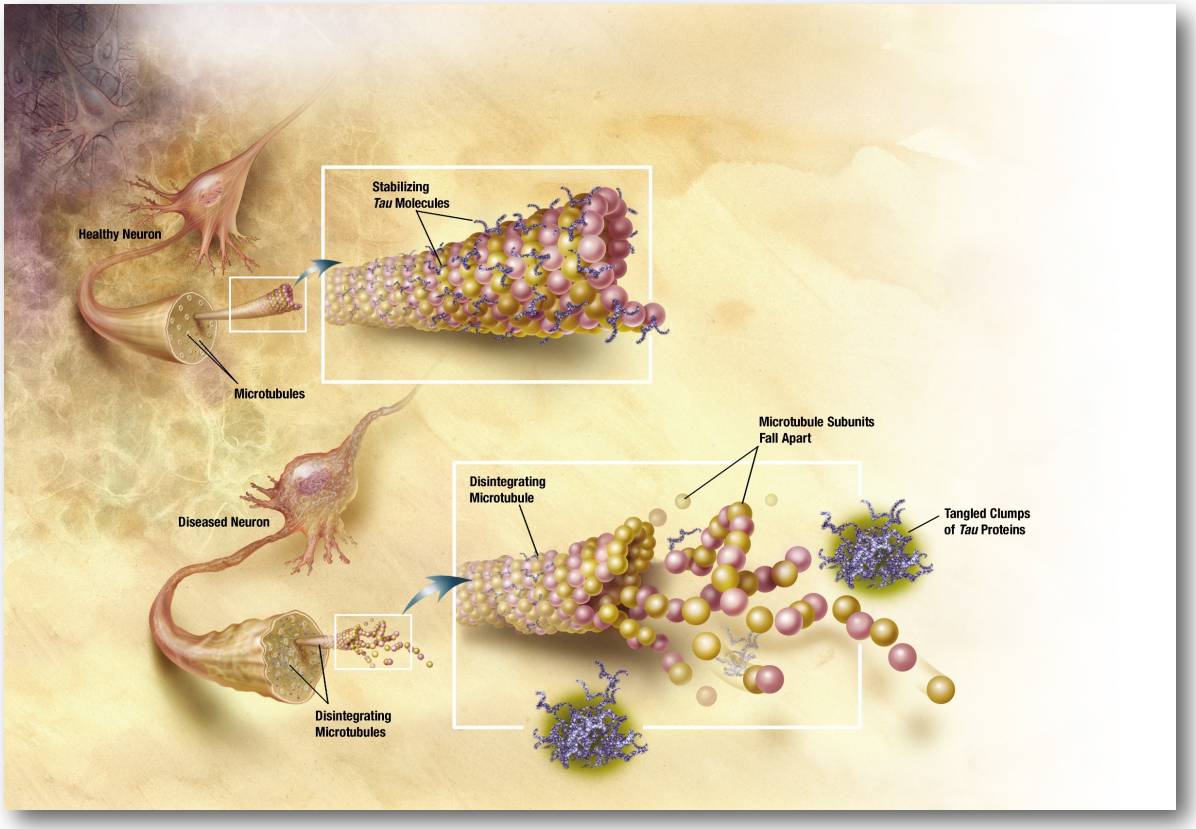
FTD – ALS SPECTRUM



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Although tau neurofibrillary tangles appear to be one of the causes of the neuronal degeneration in AD, mutations in the tau gene are associated not with AD, but with another autosomal dominant dementia, FTD

MAJOR NEURODEGENERATIVE DISEASES = PROTEINOPATHIES

- Parkinson's disease:
  - Lewy bodies (**a-synuclein**)
- Alzheimer's disease:
  - Amyloid plaques (**Ab peptide**)
  - Tau tangles (**tau**)
- Frontotemporal dementia
  - Tau tangles/Pick bodies (**tau**)
  - Ubiquitin(+) inclusions (**TDP-43**)
- Amyotrophic lateral sclerosis
  - Ubiquitin(+) inclusions (**TDP-43)**

2006

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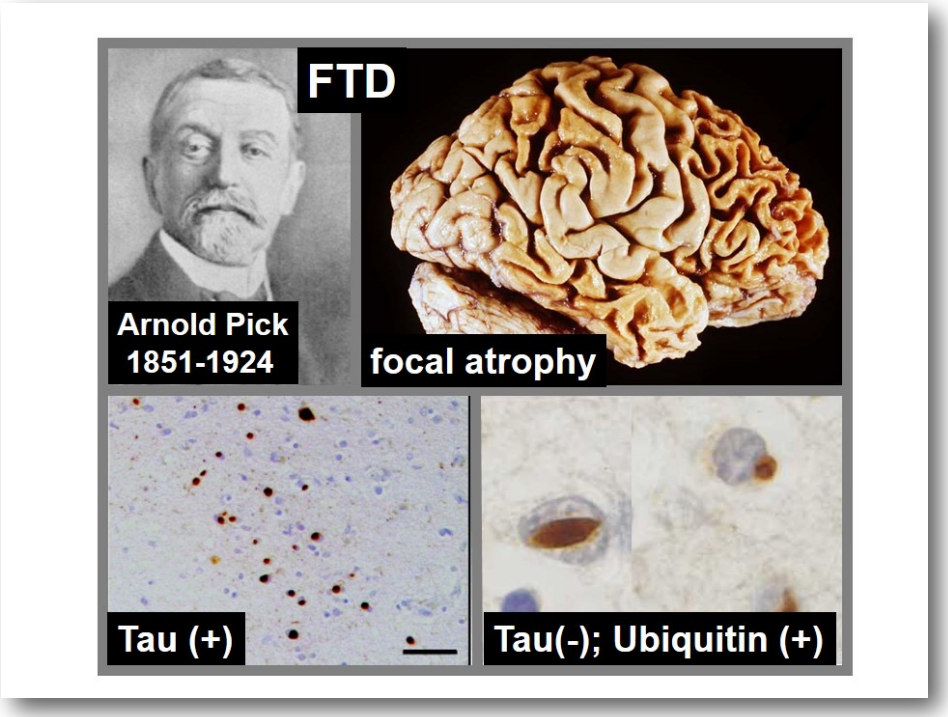
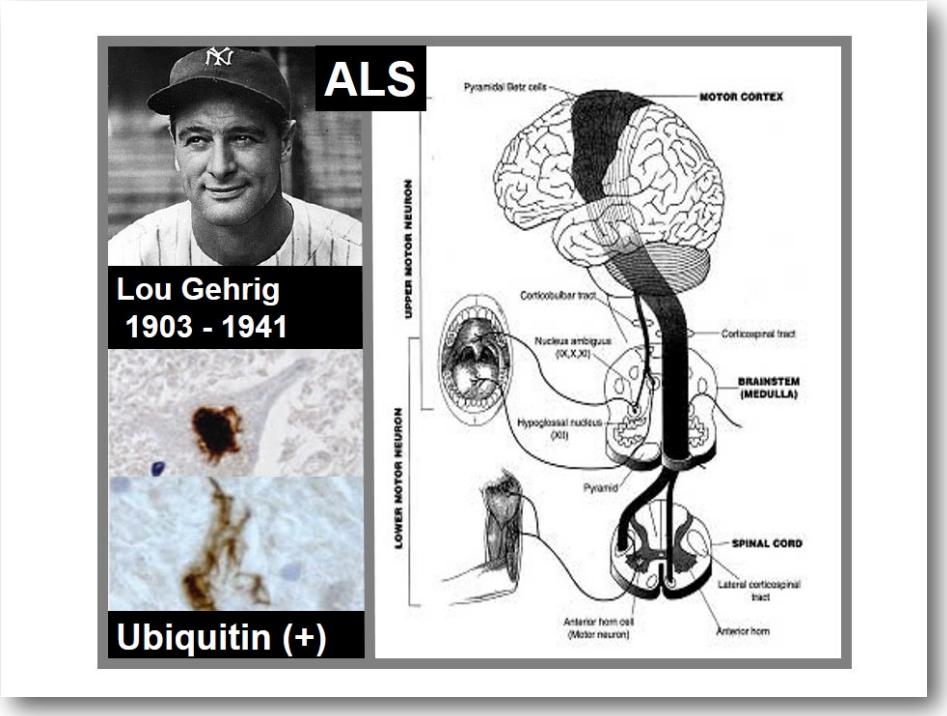
FTD – ALS SPECTRUM





TDP-43

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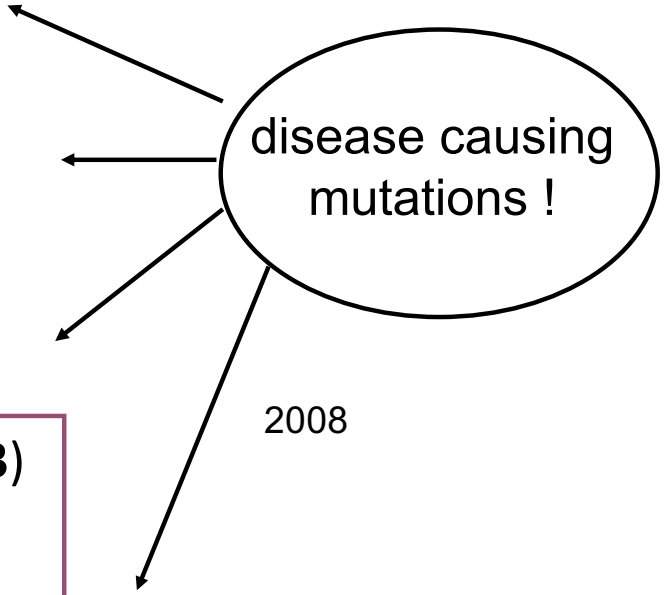
MAJOR NEURODEGENERATIVE DISEASES = PROTEINOPATHIES

- Parkinson's disease:
  - Lewy bodies (**a-synuclein**)
- Alzheimer's disease:
  - Amyloid plaques (**Aβ peptide**)
  - Tau tangles (**tau**)
- Frontotemporal dementia
  - Tau tangles/Pick bodies (**tau**)
  - Ubiquitin(+) inclusions (**TDP-43**)
- Amyotrophic lateral sclerosis
  - Ubiquitin(+) inclusions (**TDP-43)**



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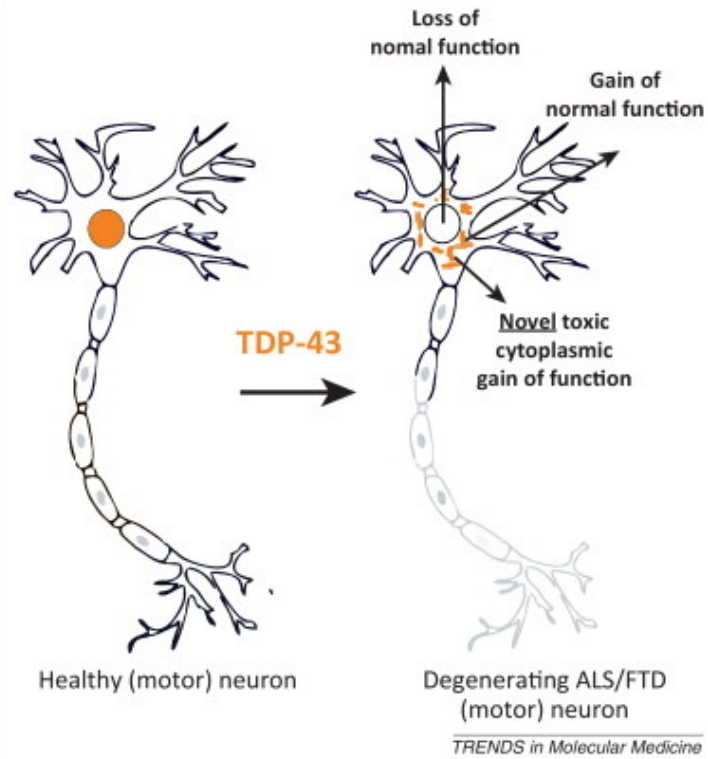
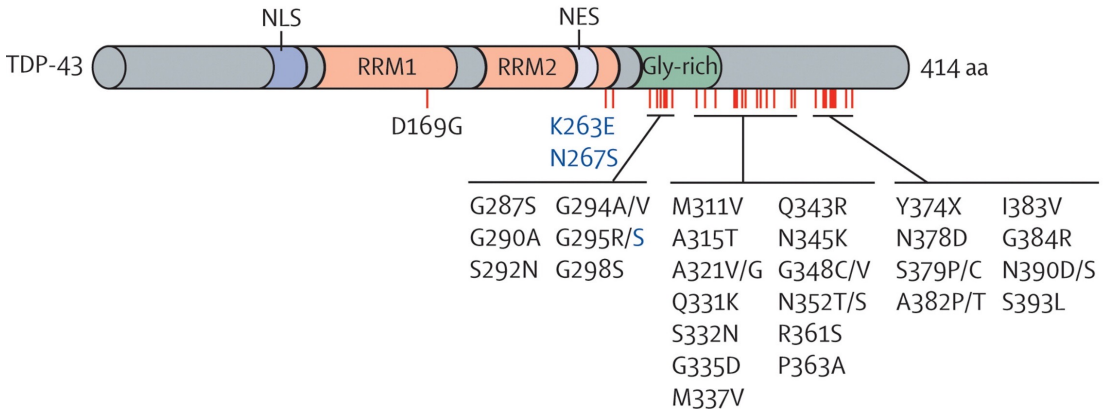
FTD – ALS SPECTRUM: TDP-43





ALS-causing mutations

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ALS-FTD GENETICS: C9ORF72 HEXANUCLEOTIDE EXPANSIONS

Neuron 2011

Expanded GGGGCC Hexanucleotide Repeat in Noncoding Region of *C9ORF72* Causes Chromosome 9p-Linked FTD and ALS

Mariely DeJesus-Hernandez,[1,10] Ian R. Mackenzie,[2,10,*] Bradley F. Boeve,[3] Adam L. Boxer,[4] Matt Baker,[1] Nicola J. Rutherford,[1] Alexandra M. Nicholson,[1] NiCole A. Finch,[1] Heather Flynn,[5] Jennifer Adamson,[1] Naomi Kouri,[1] Aleksandra Wojtas,[1] Pheth Sengdy,[6] Ging-Yuek R. Hsiung,[6] Anna Karydas,[4] William W. Seeley,[4] Keith A. Josephs,[3] Giovanni Coppola,[7] Daniel H. Geschwind,[7] Zbigniew K. Wszolek,[8] Howard Feldman,[6,9] David S. Knopman,[3] Ronald C. Petersen,[3] Bruce L. Miller,[4] Dennis W. Dickson,[1] Kevin B. Boylan,[8] Neill R. Graff-Radford,[8] and Rosa Rademakers[1,*]

A Hexanucleotide Repeat Expansion in *C9ORF72* Is the Cause of Chromosome 9p21-Linked ALS-FTD

Alan E. Renton,[1,38] Elisa Majounie,[2,38] Adrian Waite,[3,38] Javier Simón-Sánchez,[4,5,38] Sara Rollinson,[6,38] J. Raphael Gibbs,[7,8,38] Jennifer C. Schymick,[1,38] Hannu Laaksovirta,[9,38] John C. van Swieten,[4,5,38] Liisa Myllykangas,[10] Hannu Kalimo,[10] Anders Paetau,[10] Yevgeniya Abramzon,[1] Anne M. Remes,[11] Alice Kaganovich,[12] Sonja W. Scholz,[2,13,14] Jamie Duckworth,[7] Jinhui Ding,[7] Daniel W. Harmer,[15] Dena G. Hernandez,[2,8] Janel O. Johnson,[1,8] Kin Mok,[8] Mina Ryten,[8] Danyah Trabzuni,[8] Rita J. Guerreiro,[8] Richard W. Orrell,[16] James Neal,[17] Alex Murray,[18] Justin Pearson,[3] Iris E. Jansen,[4] David Sondervan,[4] Harro Seelaar,[5] Derek Blake,[3] Kate Young,[6] Nicola Halliwell,[6] Janis Bennion Callister,[6] Greg Toulson,[6] Anna Richardson,[19] Alex Gerhard,[19] Julie Snowden,[19] David Mann,[19] David Neary,[19] Michael A. Nalls,[2] Terhi Peuralinna,[9] Lilja Jansson,[9] Veli-Matti Isoviita,[9] Anna-Lotta Kaivorinne,[11] Maarit Hölttä-Vuori,[20] Elina Ikonen,[20] Raimo Sulkava,[21] Michael Benatar,[22] Joanne Wuu,[23] Adriano Chiò,[24] Gabriella Restagno,[25] Giuseppe Borghero,[26] Mario Sabatelli,[27] The ITALSGEN Consortium,[28] David Heckerman,[29] Ekaterina Rogaeva,[30] Lorne Zinman,[31] Jeffrey D. Rothstein,[14] Michael Sendtner,[32] Carsten Drepper,[32] Evan E. Eichler,[33] Can Alkan,[33] Ziedulla Abdullaev,[34] Svetlana D. Pack,[34] Amalia Dutra,[35] Evgenia Pak,[35] John Hardy,[8] Andrew Singleton,[2] Nigel M. Williams,[3,38] Peter Heutink,[4,38] Stuart Pickering-Brown,[6,38] Huw R. Morris,[3,36,37,38] Pentti J. Tienari,[9,38] and Bryan J. Traynor[1,14,38,*]

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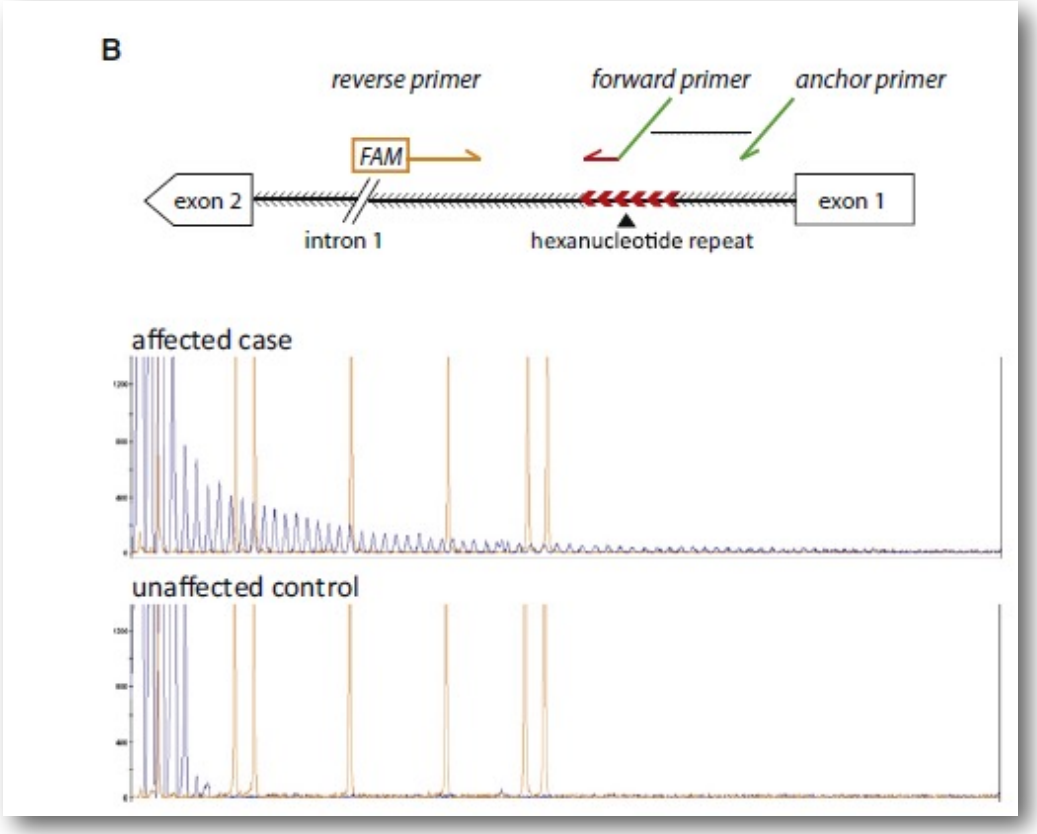
ALS-FTD GENETICS: C9ORF72 HEXANUCLEOTIDE EXPANSIONS



Normal alleles:
<25 G4C2 repeats

Pathogenic (high penetrance):
>65 G4C2 repeats
(up to 4000)

Anticipation ?

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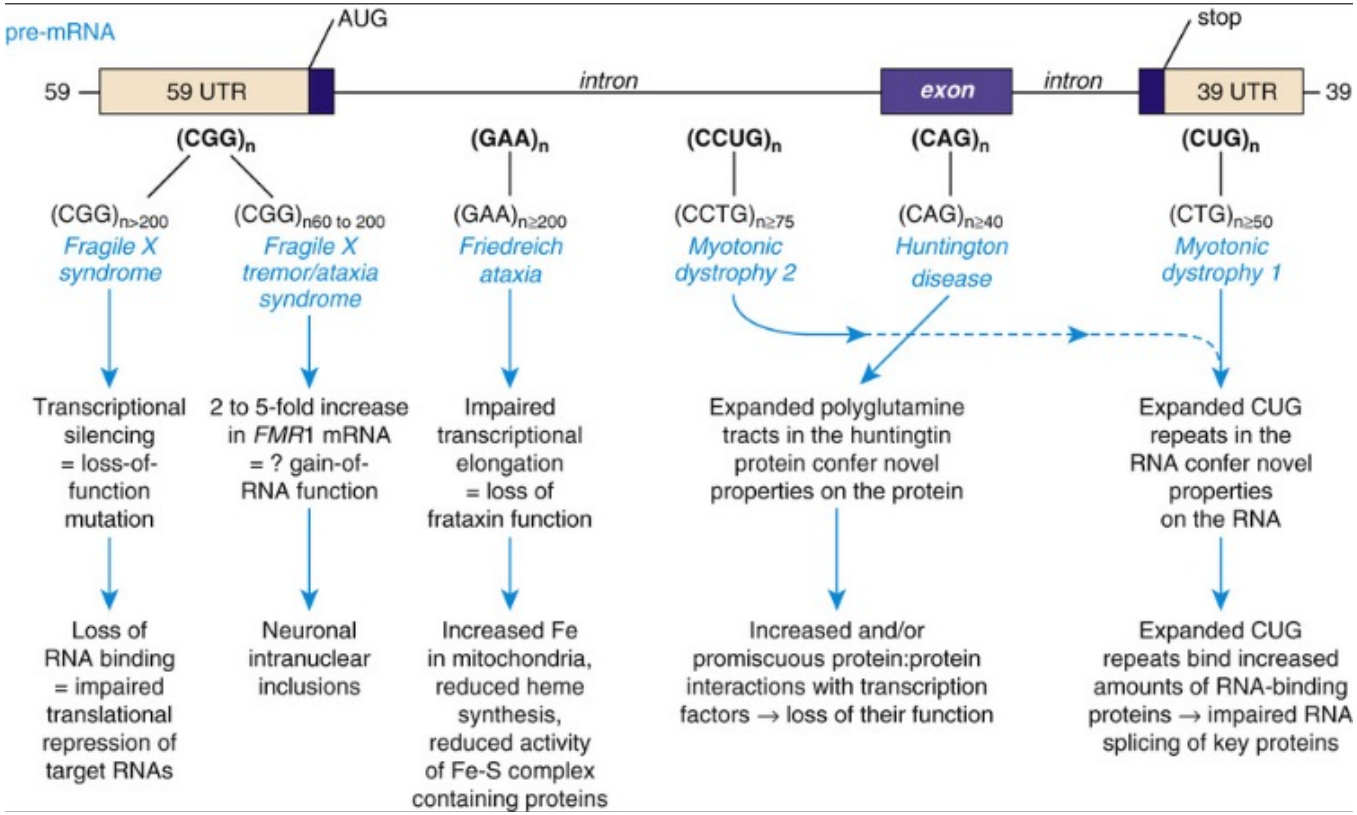
REPEAT EXPANSION DISORDERS



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ALS-FTD GENETICS

Table 1 Major ALS/FTD genes

ALS/FTD	Gene	Mutation	Protein/function	Disease contribution
ALS	SOD1	Missense	Superoxide dismutase 1/oxidative stress	fALS 12%, sALS ~1%
ALS	OPN		Optineurin/vesicle trafficking	fALS <1%, sALS <1%
ALS/FTD	C9orf72	Non-coding GGGGCC expansion	C9orf72/GDP-GTP nucleotide exchange factor	fALS 40%, sALS 7% sFTD 25%, sFTD 6%
ALS/FTD	TARDBP	Missense/nonsense	TDP-43/RNA-binding, processing	fALS 5%, sALS <1% fFTD 1%
ALS/FTD	FUS	Missense/nonsense	FUS/RNA-binding, processing	fALS 4%, sALS <1%
ALS/FTD	VCP	Missense	Valosin-containing protein/proteasome, vesicle trafficking	fALS 1% fFTD <1%
ALS/FTD	UBQLN1	Missense	Ubiquilin-1/protein degradation	X linked ALS/FTD <1%, sALS 2%
ALS/FTD	SQSTM1	Missense/deletion	p62/protein degradation	fALS ~1%, sALS 4% fFTD 2%
ALS/FTD	CHMP2B	Missense	Charged multivesicular protein 2B/vesicle trafficking	fFTD <1%
FTD	MAPT	Missense and splice-site	Tau/microtubule binding and stabilisation	fFTD ~10%
FTD	GRN	Missense	Granulin/tissue repair	fFTD ~20%, sFTD 5%

ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia; FUS, fused in sarcoma; f, familial; GRN, *granulin*; MAPT, microtubule-associated protein tau; s, sporadic; VCP, valosin-containing protein.

OUTLINE

- Introduction
- Alzheimer's disease
- Related disorders: frontotemporal dementia –ALS spectrum
- **mtDNA disorders**

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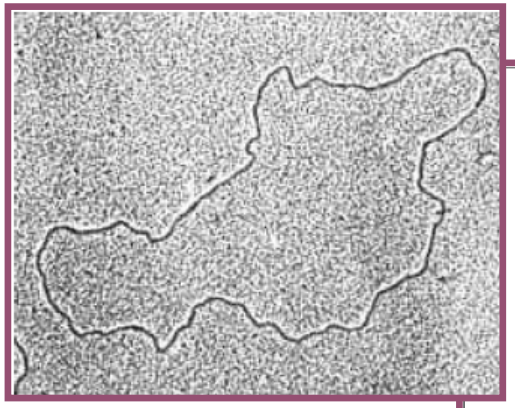
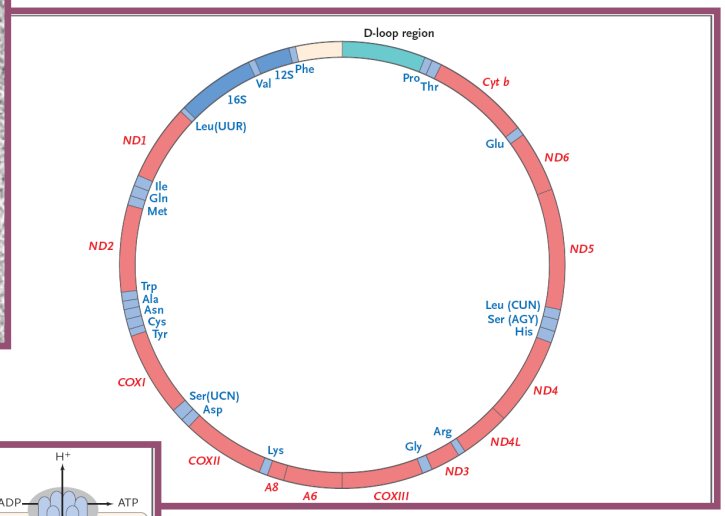
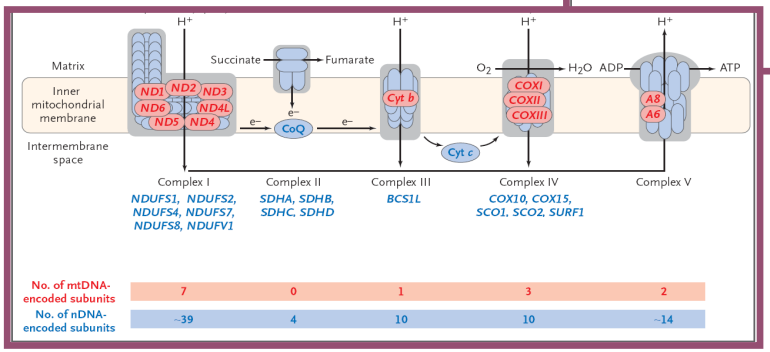
DISEASES OF MITOCHONDRIAL DNA (mtDNA)





Oxidative phophorylation and ATP synthesis



- >1200 gene products (nuclear + mtDNA-derived)
- mtDNA: **37** genes, no introns, very compact, 16.6 kb, 22 tRNAs, 2 rRNAs, 13 subunits of the RC
- hundreds of mitochondria/cell, >1000 mtDNAs/cell, 3-10 mtDNAs/mitochondrion

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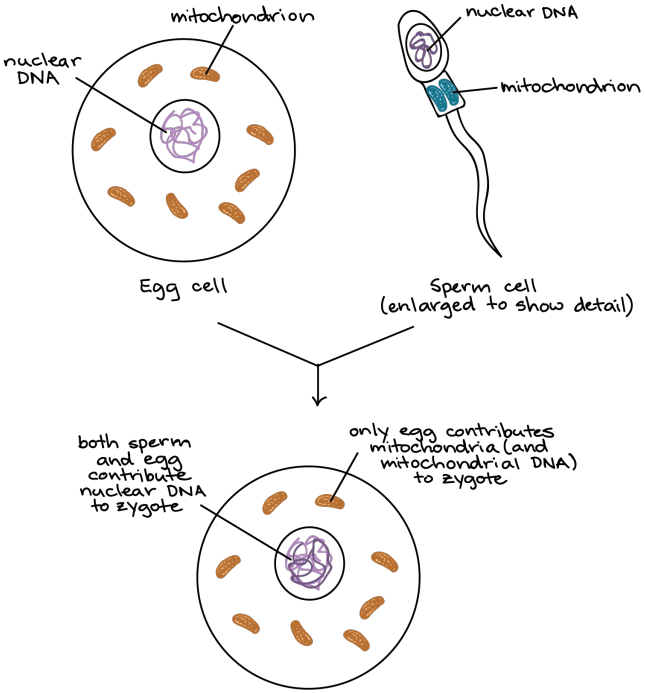
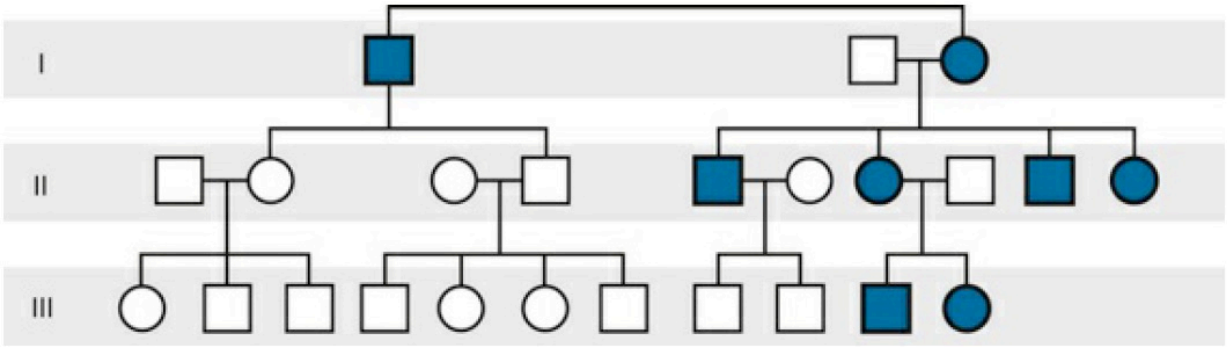
MATERNAL INHERITANCE





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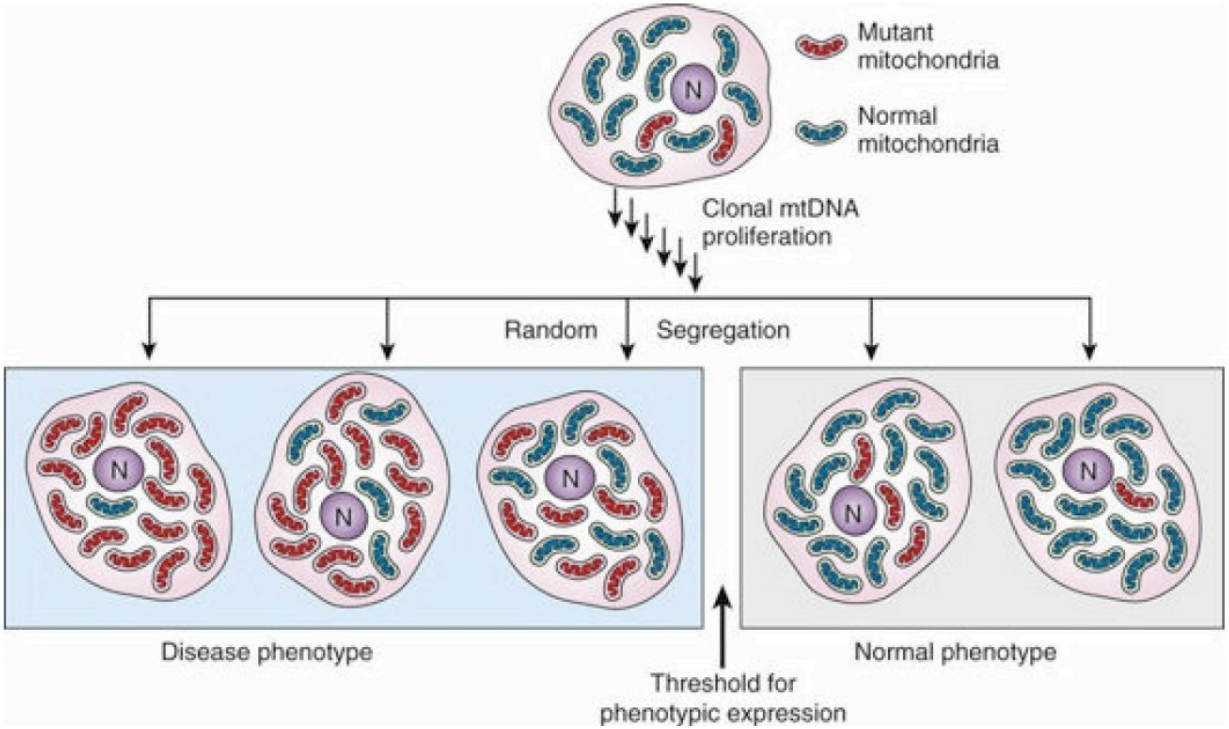
REPLICATIVE SEGREGATION, HETEROPLASMY, HOMOPLASMY



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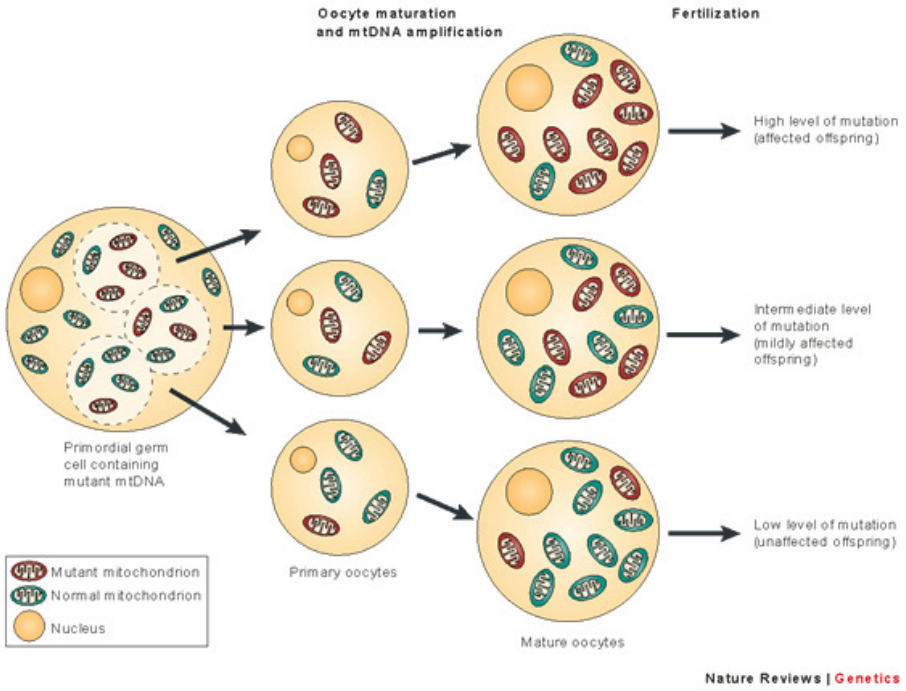
MITOCHONDRIAL GENETIC BOTTLENECK IN OOCYTES



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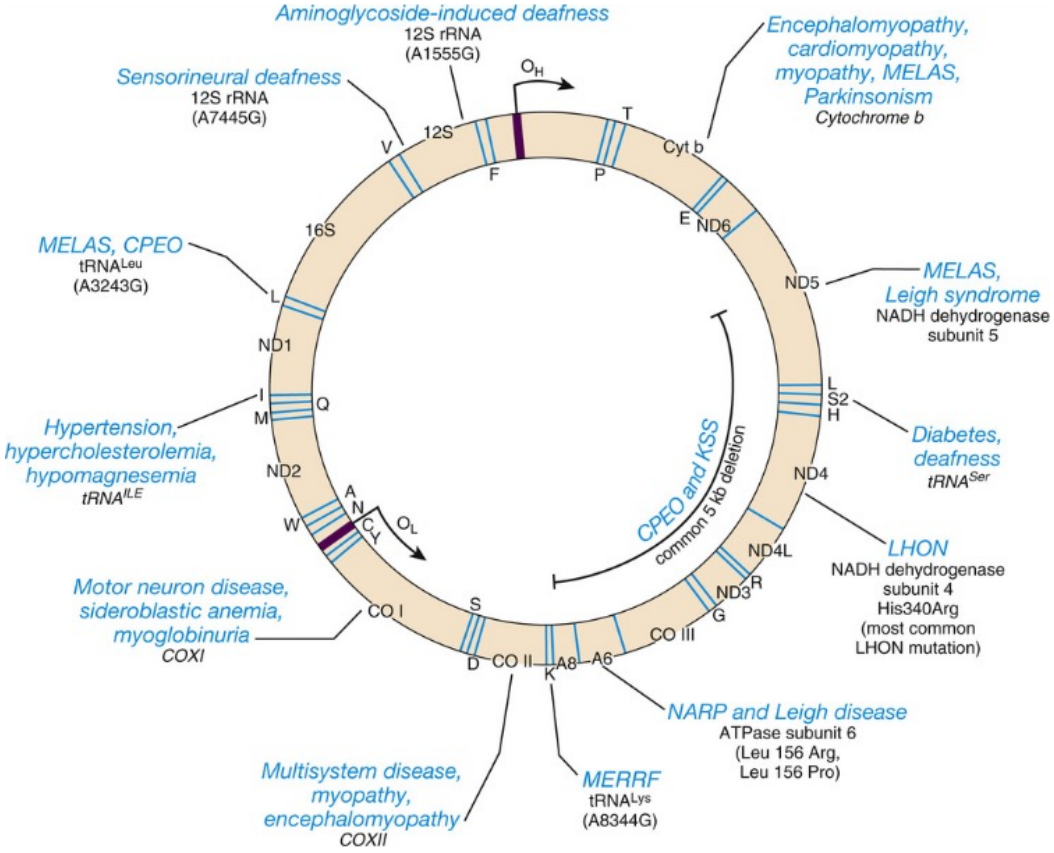
restriction → amplification

MUTATION IN mtDNA AND DISEASE



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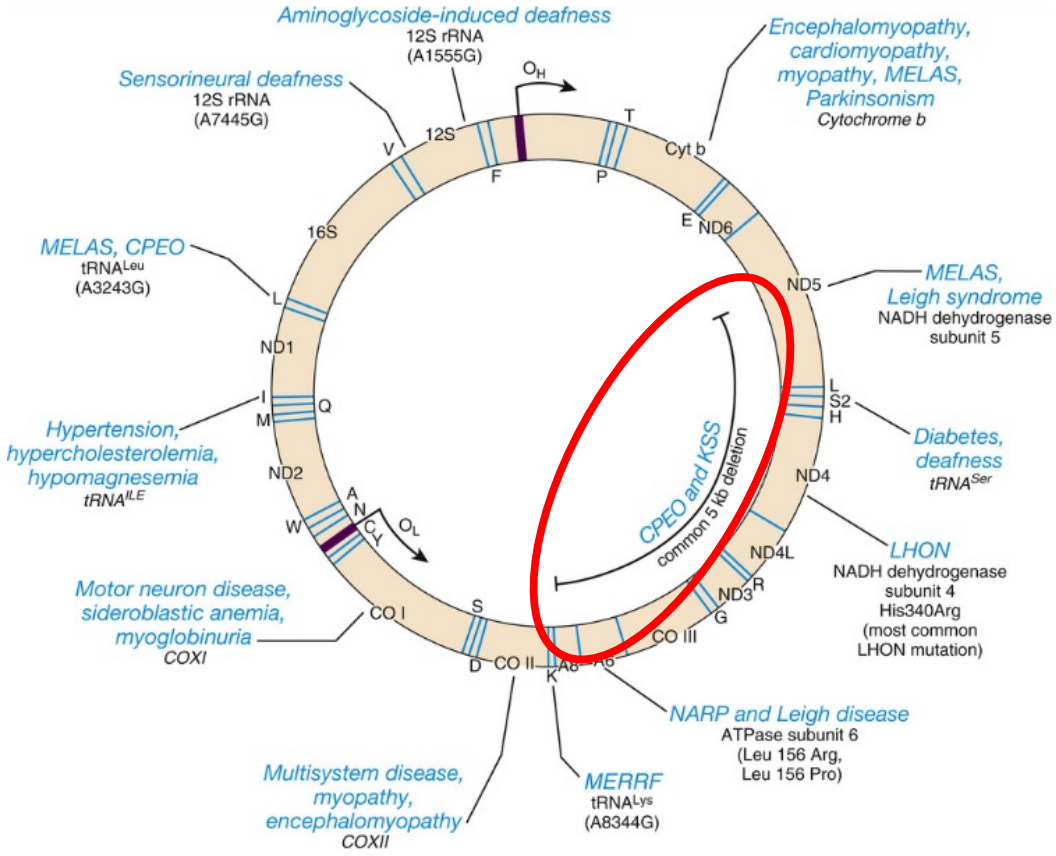
MUTATION IN mtDNA AND DISEASE



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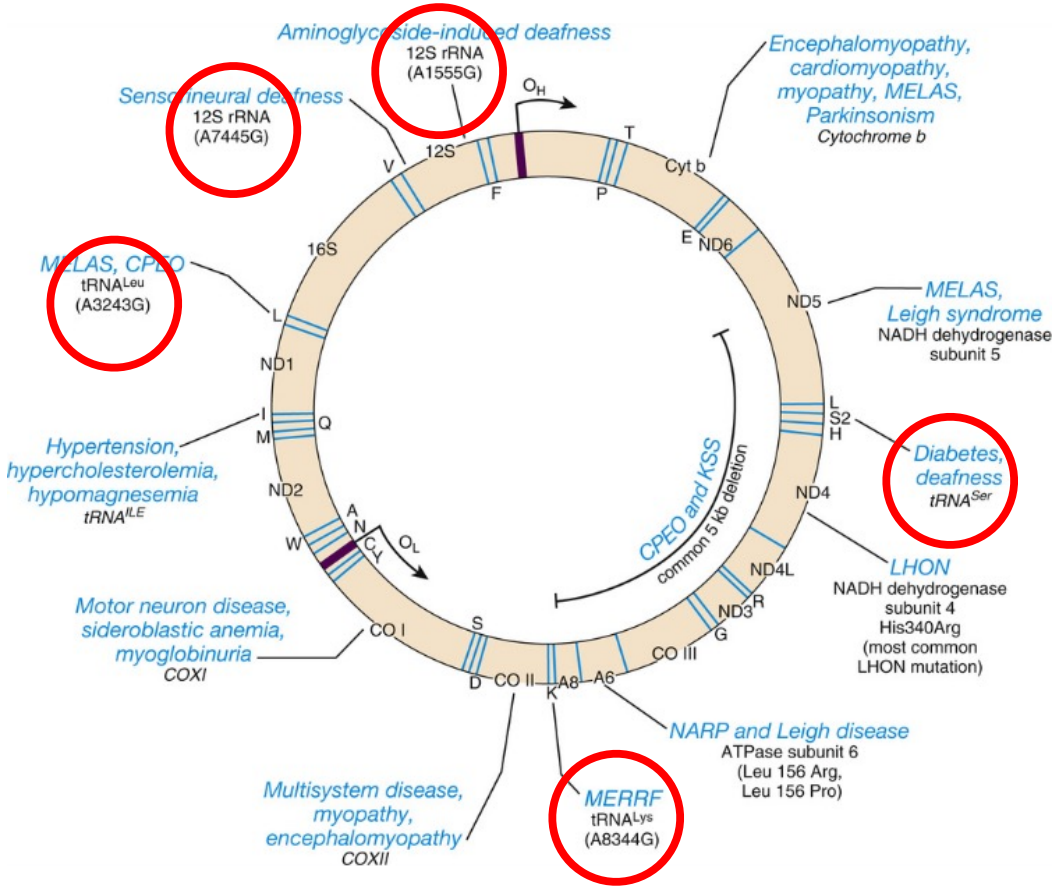
MUTATION IN mtDNA AND DISEASE



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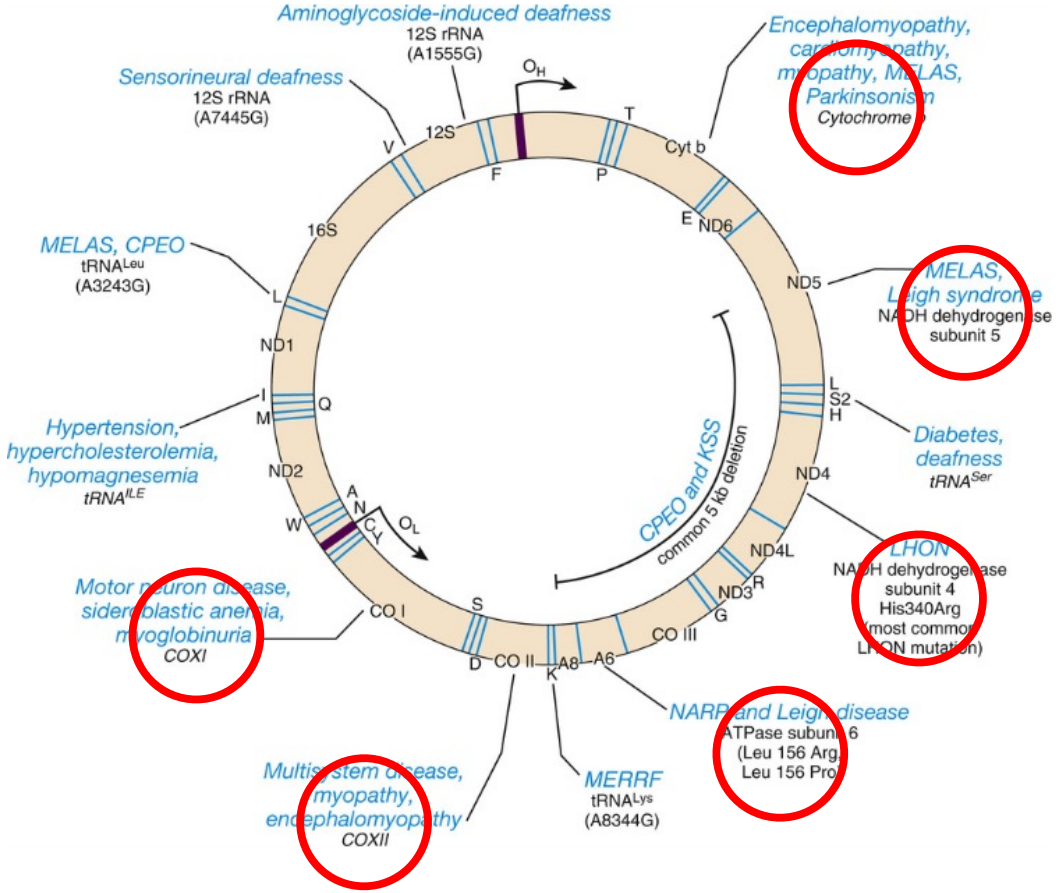
MUTATION IN mtDNA AND DISEASE



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PHENOTYPES OF MITOCHONDRIAL DISORDRES

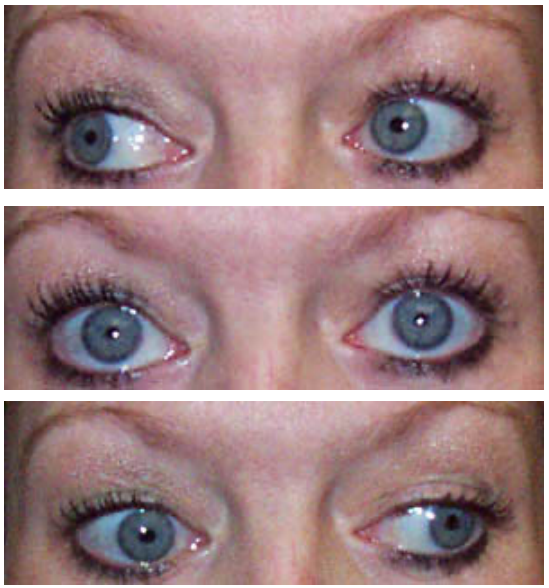
- Oxidative Phosphorylation and **mtDNA** disease:
  - Mainly **adults**!
  - decreased ATP production: cell dysfunction and death (possible additional role of ROS - byproduct)
  - **phenotypic theshold** effect:
    - ~60% for deletions
    - ~80-90% for other mutations
  - **Neuromuscular**: encephalopathy, myopathy (ragged red fibers), ataxia, retinal degeneration, ophtalmoplegia.
  - Other (broad!): liver, bone marrow, diabetes, deafness, …
  - 1/8.000-10.000

MUTATION IN mtDNA AND DISEASE

Disease	Phenotypes—Largely Neurological	Most Frequent Mutation in mtDNA Molecule	Homoplasmy vs. Heteroplasmy	Inheritance
Leber hereditary optic neuropathy (LHON)	Rapid onset of blindness in young adult life due to optic nerve atrophy; some recovery of vision, depending on the mutation. Strong sex bias: ≈50% of male carriers have visual loss vs. ≈10% of females.	Substitution 11778A>G in the ND4 subunit of complex I of the electron transport chain; this mutation, with two others, accounts for more than 90% of cases.	Largely homoplasmic	Maternal
Leigh syndrome	Early-onset progressive neurodegeneration with hypotonia, developmental delay, optic atrophy, and respiratory abnormalities	Point mutations in the ATPase subunit 6 gene	Heteroplasmic	Maternal
MELAS	Myopathy, mitochondrial encephalomyopathy, lactic acidosis, and stroke like episodes; may present only as diabetes mellitus and deafness	Point mutations in $tRNA^{Leu(UUR)}$, a mutation hot spot, most commonly 3243A>G	Heteroplasmic	Maternal
MERRF (Case 33)	Myoclonic epilepsy with ragged-red muscle fibers, myopathy, ataxia, sensorineural deafness, dementia	Point mutations in $tRNA^{Lys}$, most commonly 8344A>G	Heteroplasmic	Maternal
Deafness	Progressive sensorineural deafness, often induced by aminoglycoside antibiotics; nonsyndromic sensorineural deafness	1555A>G mutation in the 12S rRNA gene	Homoplasmic	Maternal
		7445A>G mutation in the 12S rRNA gene	Homoplasmic	Maternal
Kearns-Sayre syndrome (KSS)	Progressive myopathy, progressive external ophthalmoplegia of early onset, cardiomyopathy, heart block, ptosis, retinal pigmentation, ataxia, diabetes	The ≈5-kb large deletion (see Fig. 12-26)	Heteroplasmic	Generally sporadic, likely due to maternal gonadal mosaicism

CHRONIC PROGRESSIVE EXTERNAL OPHTALMOPLEGIA (CPEO)

droopy eyelids



weakness of the extraocular muscles

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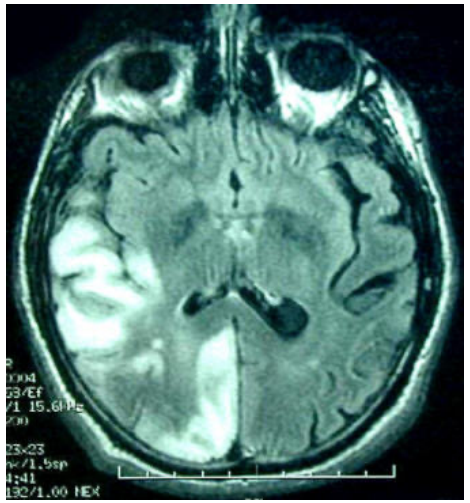
PHENOTYPIC VARIATION IN mtDNA DISEASES

- Heteroplasmy:
  - unpredictable and variable fraction of mutant mtDNA in any particular tissue
  - progessive lifetime decrease in blood possible
  - 25% difference between tissues
  - Example 3243A>G:
    - Classical MELAS
    - Isolated diabetes, deafness, cPEO



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INTERACTIONS BETWEEN MITOCHONDRIAL AND NUCLEAR GENOMES

- A.D. transmitted deletions in mtDNA:
  - Twinkle mutations (mtDNA-specific helicase)
  - *POLG* mutations (mtDNA-specific DNA polymerase)

- mtDNA depletion syndromes
  - 8 nuclear genes

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Table 1. Nuclear Mitochondrial Disease Genes – Mechanisms[a,b]

Mechanism	Examples of known disease genes
Structural subunits of respiratory chain and ATP synthase	Complex I: *NDUFS1*, *NDUFS2*, *NDUFS3*, *NDUFS4*, *NDUFS6*, *NDUFS7*, *NDUFS8*, *NDUFV1*, *NDUFV2*, *NDUFA1*^{XLR}, *NDUFA2*, *NDUFA4*, *NDUFA6*, *NDUFA9*, *NDUFA10*, *NDUFA11* Complex II: *SDHA*$^{AD/AR}$, *SDHB*, *SDHD* Complex III: *TTC19*, *UQCRB*, *CYC1*, *UQCC2* Complex IV: *COX14*, *COX15*, *COX20*, *XOC6A1*, *COX6B1*, *COX7B*^{XLD}, *TACO1*, *PET100* ATP synthase: *ATP5D*, *ATP5E*, *TMEM70*, *ATP5MD*, *ATP5A1*
Assembly factors	*NDUFAF1*, *NDUFAF2*, *NDUFAF3*, *NDUFAF4*, *NDUFAF5*, *NDUFAF6*, *NDUFAF8*, *FOXRED1*, *SCO1*, *SCO2*, *ATPAF2*
Coenzyme Q biosynthesis	*PDSS1*, *PDSS2*, *COQ2*, *COQ4*, *COQ6*, *COQ8A*, *COQ8B*, *COQ9*
Mitochondrial structure (fusion and fission)	*OPA1*$^{AD/AR}$, *MFN2*$^{AD/AR}$
Secondary mtDNA deletions and SNVs	*POLG*$^{AD/AR}$, *POLG2*^{AD}, *TYMP*, *SLC25A4*$^{AD/AR}$, *TWNK*$^{AD/AR}$, *GFER*, *RNASEH1*, *MGME1*, *DNA2*
mtDNA depletion	*SUCLA2*, *SUCLG1*, *FBXL4*, *TYMP*, *TFAM*, *DGUOK*, *RRM2B*$^{AD/AR}$, *MPV17*
Protein synthesis machinery	tRNA modification: *MTO1*, *GTP3BP*, *TRMU*, *PUS1*, *MTFMT* Mitoribosomal proteins: *MRPS2*, *MRPS22*, *MRPS34*, *MRPL3*, *MRPL44*
Aminoacyl tRNA synthetases	*AARS2*, *DARS2*, *EARS2*, *RARS2*, *YARS2*, *FARS2*, *LARS2*, *VARS2*, *CARS2*, *PARS2*, *NARS2*, *KARS*, *SARS2*, *MARS2*
Protein import/quality control	*SPG7*$^{AD/AR}$, *TIMM50*, *TIMM8A*^{XLR}
TCA cycle-related enzymes	*PDHA1*^{XLR}, *PC*

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Review

Mitochondrial Diseases: A Diagnostic Revolution

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Rita Horvath,[1] and Patrick F. Chinnery[1,2,*]

Mitochondrial disorders have emerged as a common cause of inherited disease, but are traditionally viewed as being difficult to diagnose clinically, and even more difficult to comprehensively characterize at the molecular level. However, new sequencing approaches, particularly whole-genome sequencing (WGS), have dramatically changed the landscape. The combined analysis of nuclear and mitochondrial DNA (mtDNA) allows rapid diagnosis for the vast majority of patients, but new challenges have emerged. We review recent discoveries that will benefit patients and families, and highlight emerging questions that remain to be resolved.

Highlights

Reaching a molecular diagnosis in a patient with mitochondrial disease can be a complex process, both clinically and genetically.

The diagnostic process for mitochondrial disease is undergoing a dramatic transition, moving away from a histological and biochemical approach to a primarily genetic approach.

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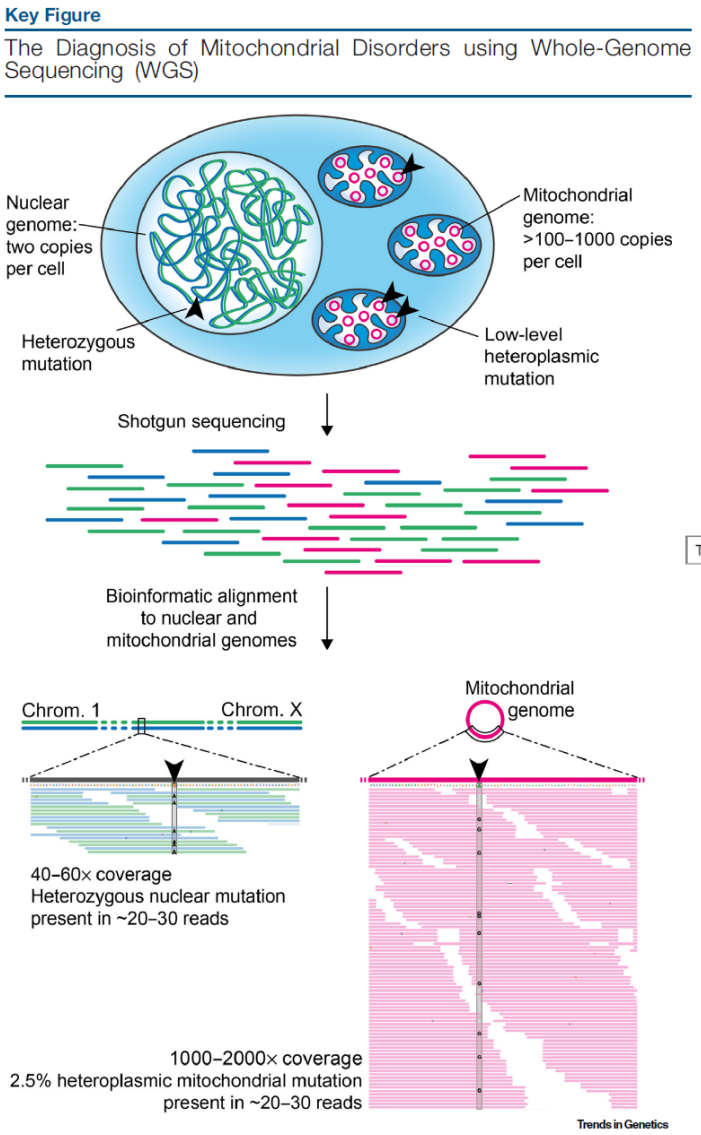

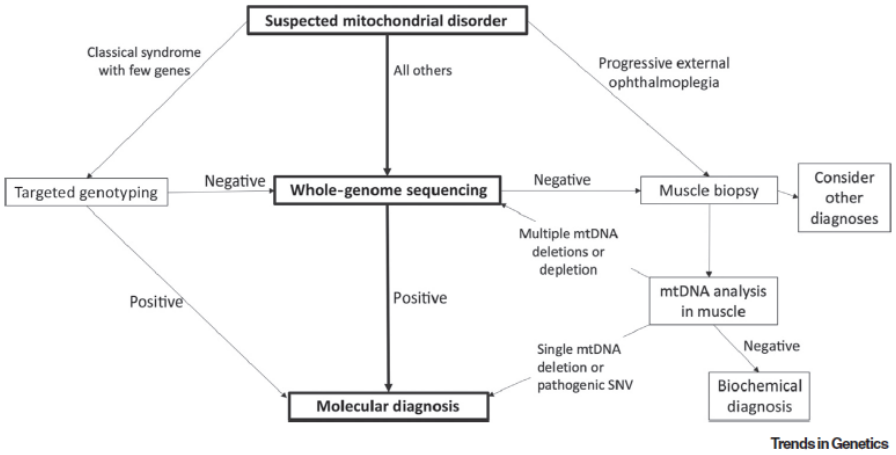

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