8° CONVEGNO su:
COGNITIVITÀ E MALATTIE NEUROLOGICHE
Torino, 8 Novembre 2019
EDUCATORIO DELLA PROVVIDENZA – SALA ORPHEUS
Corso Trento, 13 – 10129 Torino

Demenze frontotemporali
Genetica

daniele.imperiale@aslcittaditorino.it

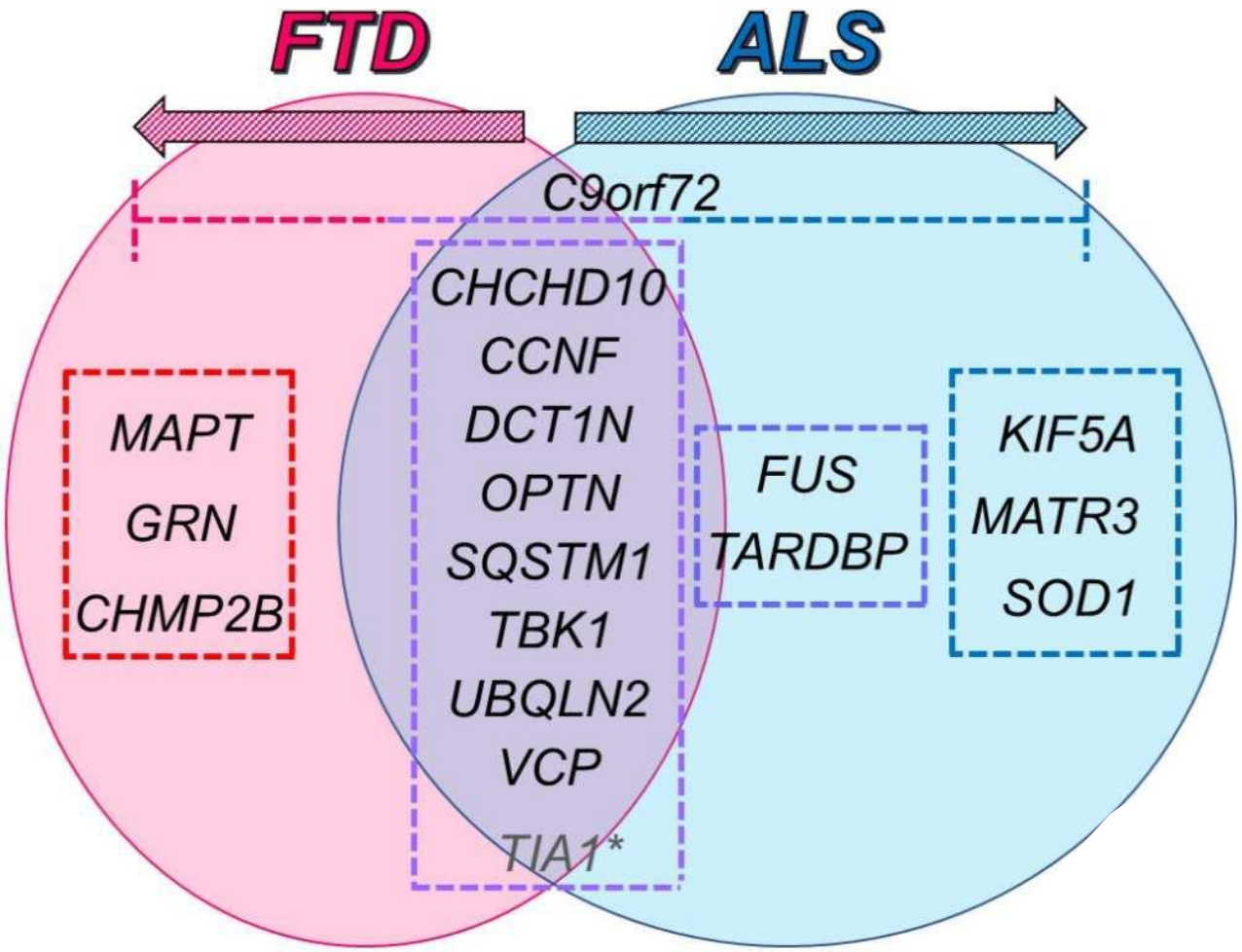
Premessa
Aspetti generali

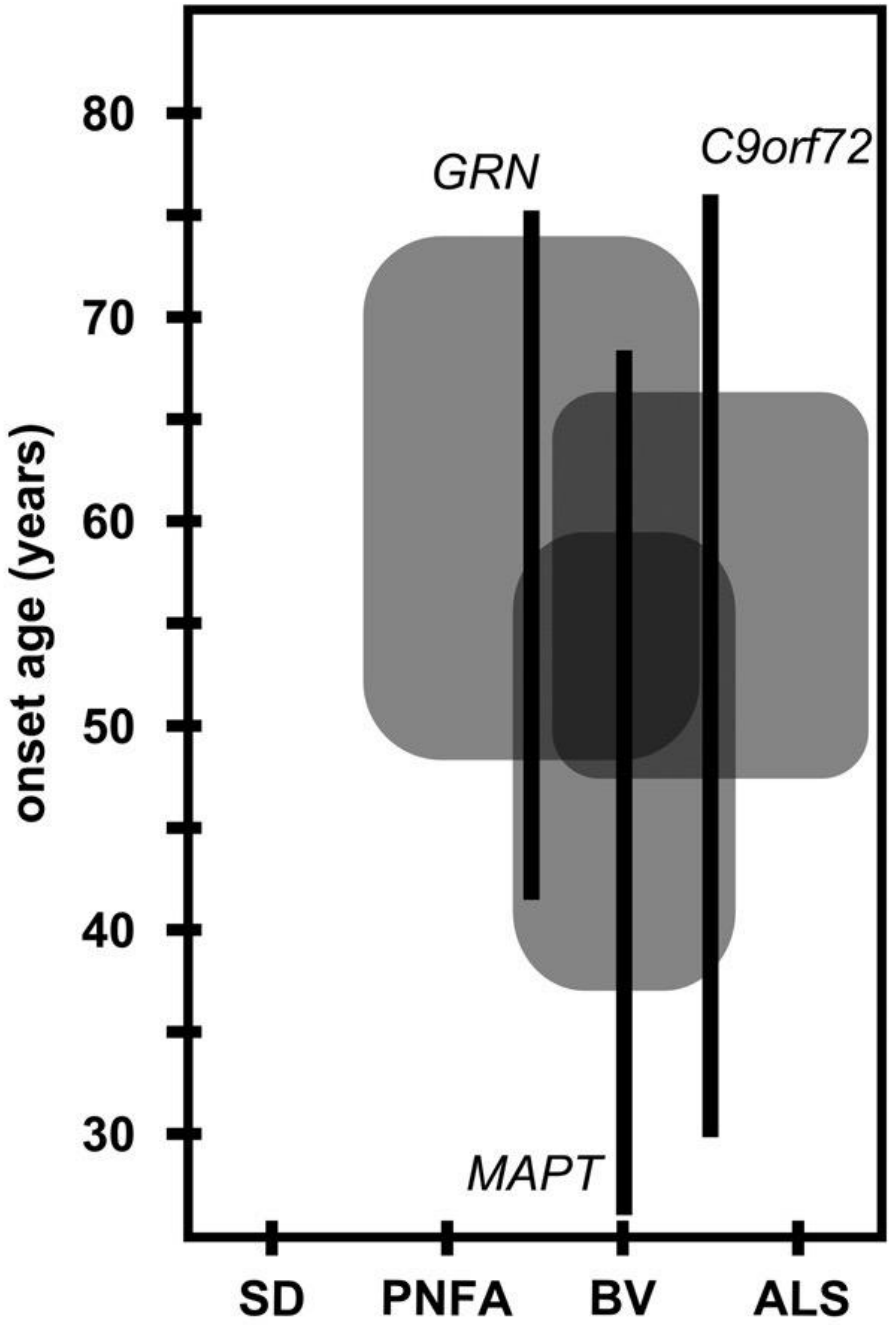
- Componente genetica rilevante
  - Storia familiare positiva nel 40-50% dei pazienti
  - Trasmissione di tipo autosomica dominante nel 20-50% delle famiglie
  - Penetranza elevata
- Differenze significative tra le varianti
  - bvFTD: fino quasi al 50% dei casi (> nei casi con MND)
  - SD: >20% dei casi
- ≈ 60% dei casi familiari presentano mutazioni di MAPT, GRN, C9orf72,
- <5%... VCP, CHMPB2, TARDBP, FUS, ITM2B o BRI2, TBK1, TBP
- Geni «modificatori»… TMEM106B
- Diagnosi non sempre agevole…
  - AD (memoria, abilità visuospaziali)
  - LBD (allucinazioni, parkisonismo, fluttuazioni)
  - VaD (decorso «a scalini», segnj pseudobulbari)
  - … HD (movimenti involontari)

Premessa
Geni coinvolti

Major phenotype	Gene	Familial cases	Sporadic cases	Clinical Presentation(s)	Brain Pathology	Reference
FTD	*CHMP2B*	<1%	NA	FTD	ubiquitin/p62	(Ferrari et al., 2011; Isaacs et al., 2011; Pottier et al., 2016)
	GRN	5-20%	1-5%		TDP43	(Chen-Plotkin et al., 2010; Pottier et al., 2016; Rohrer and Warren, 2011; Takada, 2015)
	MAPT (tau)	5-20%	0-3%		tau	(Pottier et al., 2016; Rohrer and Warren, 2011; Takada, 2015)
FTD-ALS	*CHCHD10*	<1%	NA	ALS, FTD, myopathy	NA	(Bannwarth et al., 2014)
	C9orf72	30%	~5%	ALS	TDP43/p62/repeat-dipeptides/ubiquitin	(Pottier et al., 2016; van der Zee et al., 2013)
		~25%	~5%	FTD, FTD-ALS		
		~1%	NA	AD, PD, CBS, A		
	CCNF	<1%	NA	ALS, FTD	Not reported	(Williams et al., 2016)
	DCTN1	<1%	NA	ALS, HMN7B, Perry syndrome, FTD	TDP43	(Munch et al., 2005)
	OPTN	<1%	NA	ALS, FTD	TDP43/OPTN/ubiquitin	(Pottier et al., 2015)
	SQSTM1 (p62)	<1%	NA	ALS, FTD, IBM, Pagets disease	TDP43/p62	(Gang et al., 2016; Kovacs et al., 2016; Le Ber et al., 2013)
	TBK1	1-3%	NA	ALS, FTD	TDP43/p62	(Pottier et al., 2016; Van Mossevelde et al., 2016)
	UBQLN2	<1%	NA	ALS, FTD	TDP43/p62/UBQLN2/FUS/OPTN	(Deng et al., 2011; Synofzik et al., 2012)
	VCP	~1%	NA	ALS, FTD, IBM, Pagets disease	TDP43/p62	(Ferrari et al., 2011; Gang et al., 2016)
ALS	*KIF5A*	<1%	NA	SP, ALS	TDP43	(Brenner et al., 2018)
	FUS	~4%	NA	ALS, FTD	FUS/ubiquitin/EWS/TAF15	(Mackenzie and Neumann, 2016; Nguyen et al., 2018; Urwin et al., 2010)
	MATR3	<1%	NA	ALS, myopathy	MATR3	(Johnson et al., 2014)
	SOD1	~20%	NA	ALS	SOD1/ubiquitin	(Ferrari et al., 2011; Saberi et al., 2015)
	TARDBP (TDP43)	~3-4%	NA	ALS, FTD	TDP43	(Ferrari et al., 2011; Nguyen et al., 2018)
	*TIA1**	<1%	NA	ALS, myopathy, FTD	TDP43	(Baradaran-Heravi et al., 2018; Mackenzie et al., 2017)

Premessa
Geni coinvolti





Premessa

Geni «maggiori»

Gene	Prevalence	Onset	Phenotype	MRI
MAPT	Familial 10–20%	Mean 55	Predominant frontotemporal dementia + -parkinsonism	Frontal and temporal atrophy
	Sporadic 0–3%	Range 46–65		Symmetric
GRN	Familial 5–20%	Mean 65	Behavioural most common, apathy, withdrawal	More widespread frontal, temporal atrophy with characteristic parietal atrophy
	Sporadic 1–5%	Range 35–89		Asymmetric
C9ORF72	25%	Mean 50	Behavioural + - ALS	Frontal atrophy, less temporal involvement
		Range 27–83		Symmetric

Premessa
Geni «minori»

GENE	FREQUANCY	AGE OF ONSET	SIGNS	MRI
TARDNA	<20 cases described	29–77	Behavioural	
FUS FTLD-U	Very rare	30	bvFTD,	Frontal, temporal atrophy
Intermediate filament inclusion		40–50	Rapidly progressive bvftd + pyramidal/extra pyramidal	Asymetric frontal and temporal atrophy
Basophilic inclusion body disease		Early onset	ALS	
VCP	1.6%	Mean 40	Musculoskeletal symptoms in 80%	Wide spectrum
		Range 40–60	Paget's disease 45%	No atrophy
			FTD 38%	
CHMP2B	Very rare	Mean 55	Behavioural	
		Range 46–65		
TBK1	1.1% in Belgians	Mean 63.3%	Behavioural,	
		Range 56–70	Extrapyramidal	
			Psychiatric	

Premessa
Pattern neuropatologici

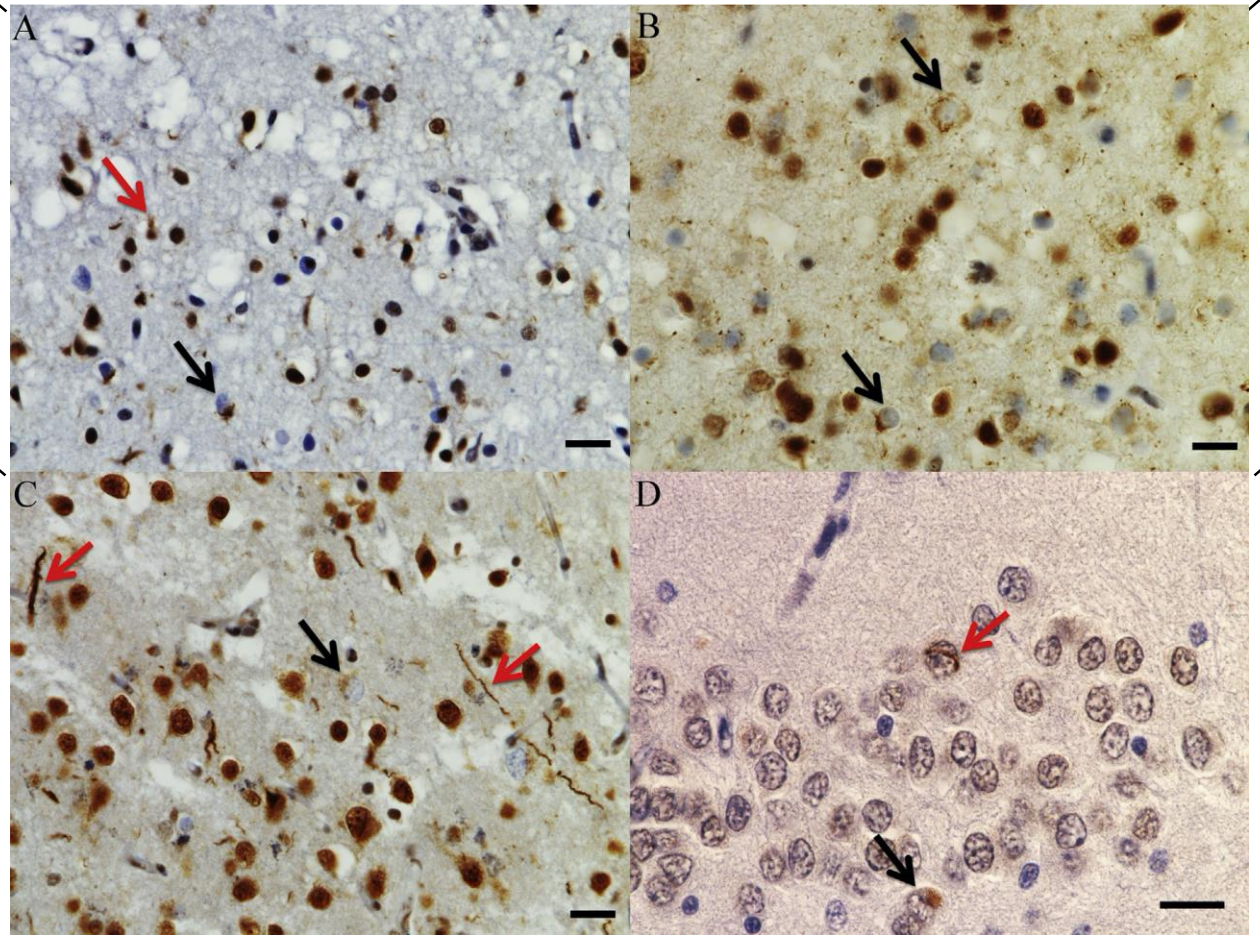
Gene symbol	Chromosomal location	Mutation frequency[a]	Number of mutations[b]	Number of independent observations[b]	Proteinopathy
C9orf72	9p21.2	10–30%	1	336	FTLD-TDP type B
GRN	17q21.32	10–25%	69	264	FTLD-TDP type A
MAPT	17q21.1	5–20%	44	138	FTLD-tau
VCP	9p13.3	<1%	17	49	FTLD-TDP type D
CHMP2B	3p11.2	<1%	4	5	FTLD-UPS
FUS	16p11.2	<1%	23	54	FTLD-FUS; aFTLD-U
TARDBP	1p36.22	<1%	34	95	FTLD-TDP

Premessa

Pattern neuropatologici

GRN
C9orf72

Sporadici
C9orf72



C9orf72

VCP

MAPT (microtubule-associated protein tau)

- Inizio anni ‘90…
- Linkage sul locus 17q21 inizialmente descritto in 13 famiglie
- FTDP-17: disinibizione, demenza, parkinsomismo, amiotrofia
- 1998: mutazioni di MAPT in alcune famiglie

letters to nature

Association of missense and 5′-splice-site mutations in *tau* with the inherited dementia FTDP-17

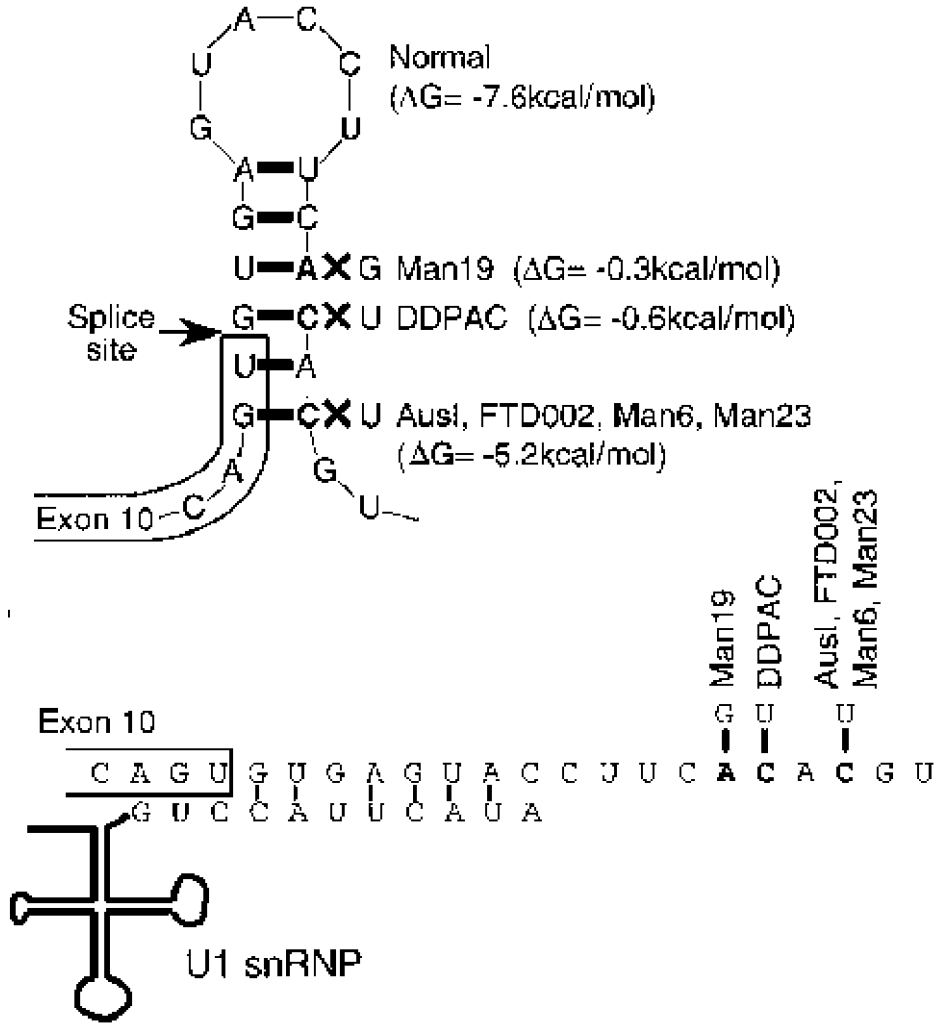
Mike Hutton*[1], Corinne L. Lendon*[2], Patrizia Rizzu*[3,4], Matt Baker[1], Susanne Froelich[3,5], Henry Houlden[1], Stuart Pickering-Brown[6], Sumi Chakraverty[2], Adrian Isaacs[1], Andrew Grover[1], Jennifer Hackett[1], Jennifer Adamson[1], Sarah Lincoln[1], Dennis Dickson[1], Peter Davies[7], Ronald C. Petersen[8], Martijn Stevens[4], Esther de Graaff[3], Erwin Wauters[3], Jeltje van Baren[3], Marcel Hillebrand[3], Marijke Joosse[3], Jennifer M. Kwon[9], Petra Nowotny[2], Lien Kuei Che[2], Joanne Norton[9], John C. Morris[9], Lee A. Reed[10], John Trojanowski[10], Hans Basun[5], Lars Lannfelt[5], Michael Neystat[11], Stanley Fahn[11], Francis Dark[12], Tony Tannenberg[13], Peter R. Dodd[14], Nick Hayward[15], John B. J. Kwok[16], Peter R. Schofield[16], Athena Andreadis[17], Julie Snowden[18], David Craufurd[19], David Neary[18], Frank Owen[6], Ben A. Oostra[3], John Hardy[1], Alison Goate[2], John van Swieten[4], David Mann[20], Timothy Lynch[11] & Peter Heutink[3]

* *These authors contributed equally to this work*

MAPT (microtubule-associated protein tau)

Family	Origin (founder)	Affecteds*	Generations	Mean onset age	Mutation
HFTD2†	Netherlands	34(15)	7	47	G272V
HFTD1†	Netherlands	49(14)	5	50	P301L
FTD003	USA	3(2)	2	45–50	P301L
Man19	UK	3(1)	2	65	Ex10 splice + 13
DDPAC†	Ireland	13(7)	3	44	Ex10 splice + 14
AusI†	Australia (UK)	28(5)	5	53	Ex10 splice + 16
FTD002†	USA	3(1)	2	40	Ex10 splice + 16
Man6	UK	2(1)	1	48	Ex10 splice + 16
Man23†	UK	10(2)	3	51	Ex10 splice + 16
FTD004	USA	10(2)	4	55	R406W

* Confirmed post mortem in brackets.
† Families with prior evidence of genetic linkage to chromosome 17.

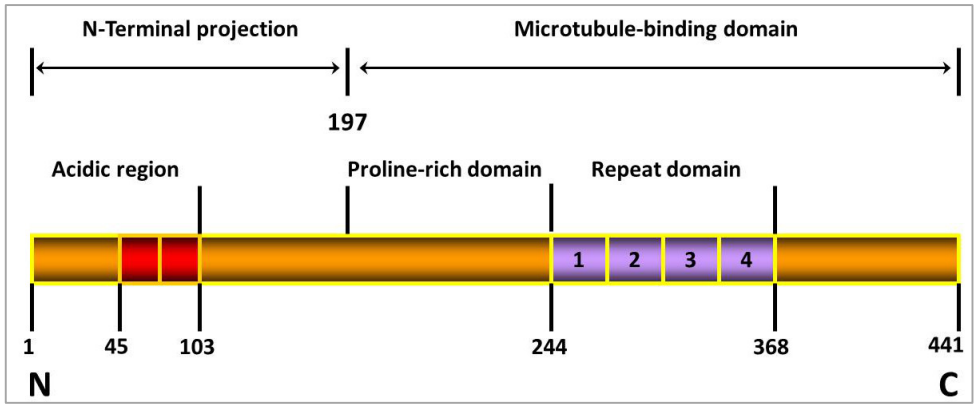


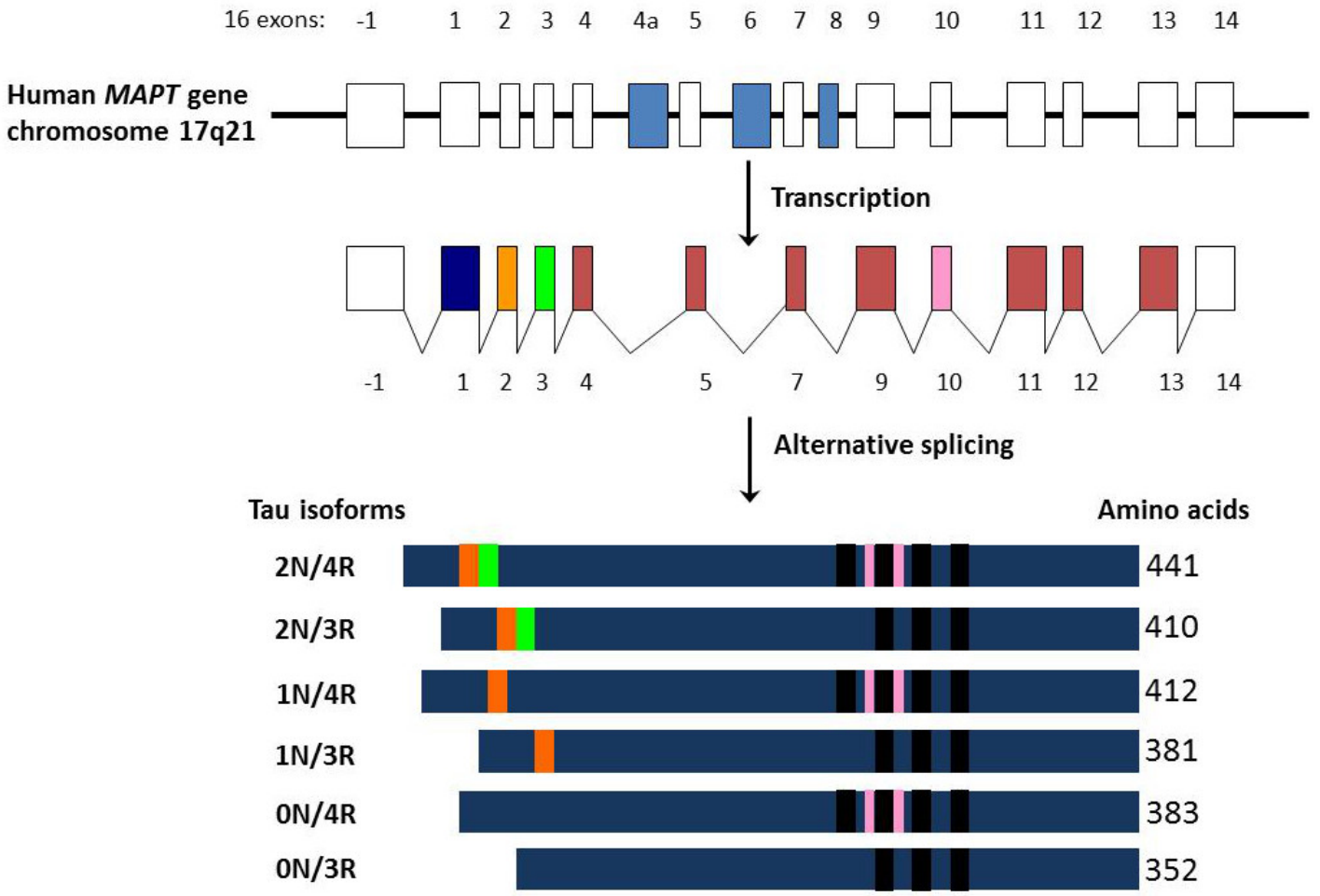
MAPT (microtubule-associated protein tau)

Mutazioni missense: esoni 9-13

Mutazioni introniche: splicing esone 10

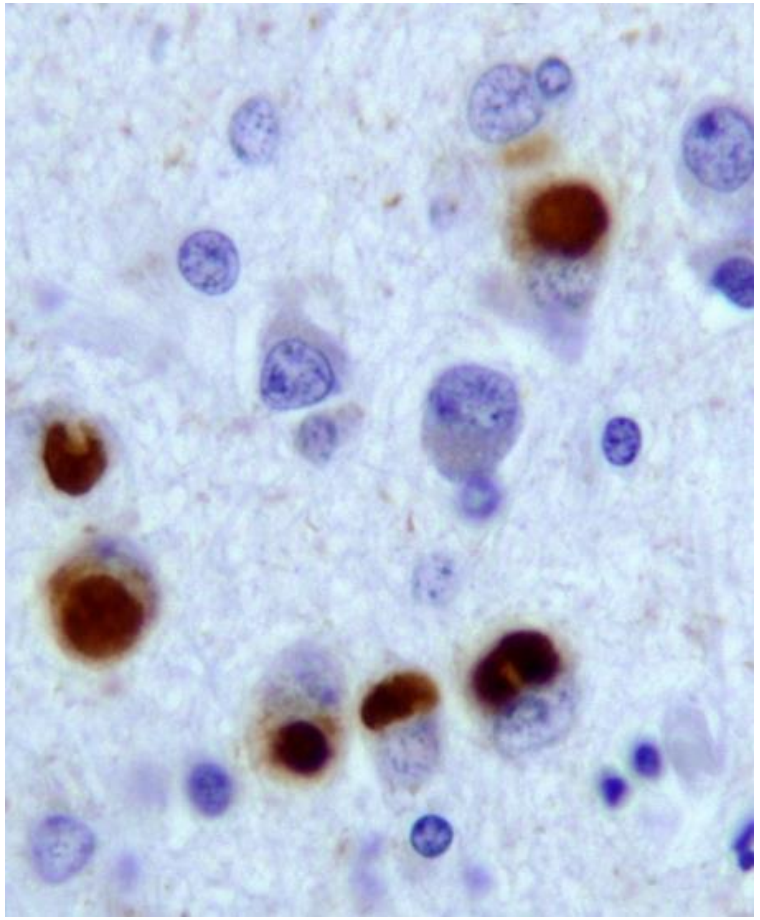
Molto più rare in altri segmenti del gene





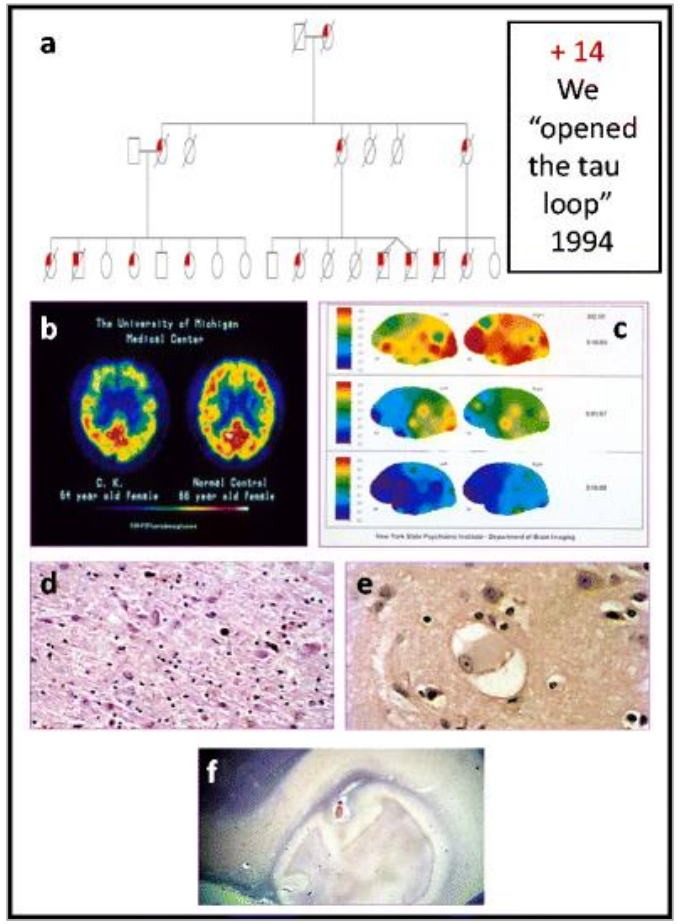
MAPT (microtubule-associated protein tau)

- Inclusioni intraneuronali di proteina tau iperfosforilata (corpi di Pick)
- Fenotipi clinici
  - bvFTD
  - PNFA
  - Altre taupatie
    - PSP
    - CBD
    - AGD



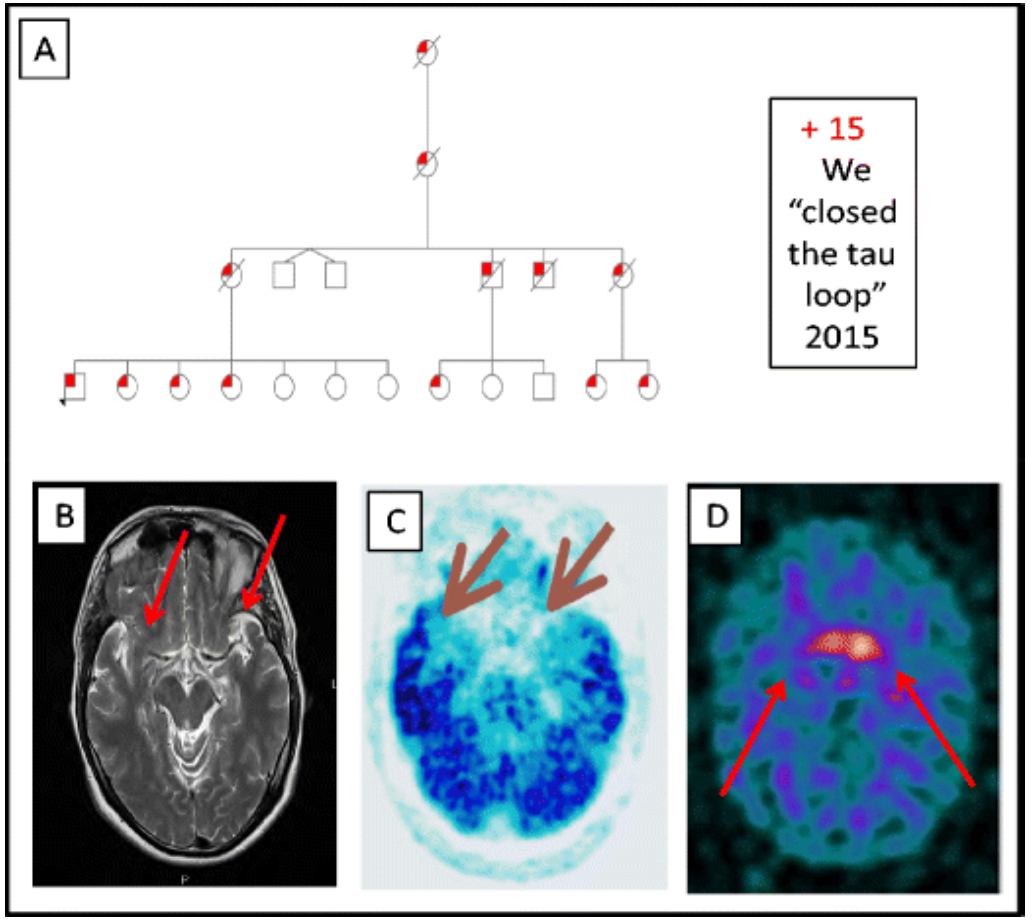
MAPT (microtubule-associated protein tau)

- Alterazioni del comportamento, demenza e/o segni extrapiramidali
  - Esordio abbastanza precoce… anche intorno ai 45 anni
  - Disinibizione, ritiro sociale, iperfagia, deficit memoria, amiotrofia
  - Ideazione paranoide
  - Bradicinesia, rigidità, instabilità posturale



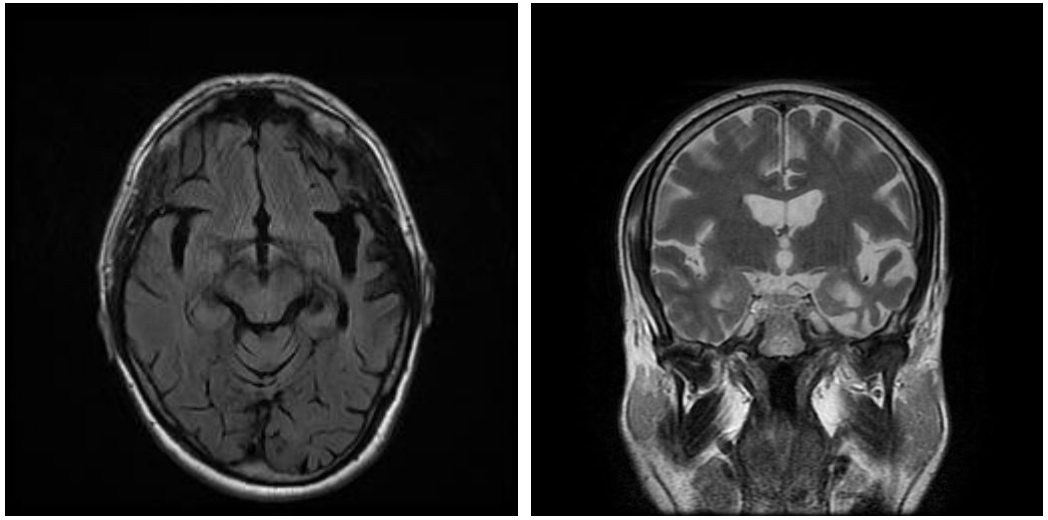
MAPT (microtubule-associated protein tau)

- Parkinsonismo e distonia senza alterazioni cognitive e comportamentali
  - Donna, 39 anni, parkinsonismo, aprassia dell'apertura delle palpebre, distonia craniocervicale



C.D., maschio, a.n. 1949

- Ricovero in SPDC nel 2012 (TSO per crisi psicotica).
- Decadimento cognitivo esordito da almeno 2 anni con disturbi comportamentali e deficit mnesici.
- Già obiettivati deficit mnesici e di linguaggio.
- Proposto ricovero per rachicentesi, rifiutato.
- Il padre sembra aver avuto disturbi simili alla stessa età.



g1330G>GT pG336H (esone 12)

DOI: 10.1093/brain/awh147 *Brain* (2004), **127,** 1415–1426

Frontotemporal dementia with Pick-type histology associated with Q336R mutation in the *tau* gene

S. M. Pickering-Brown,[1,*] M. Baker,[7,*] T. Nonaka,[8,*] K. Ikeda,[9] S. Sharma,[7] J. Mackenzie,[4] S. A. Simpson,[4] J. W. Moore,[5] J. S. Snowden,[6] R. de Silva,[2] T. Revesz,[3] M. Hasegawa,[8] M. Hutton[7] and D. M. A. Mann[6]

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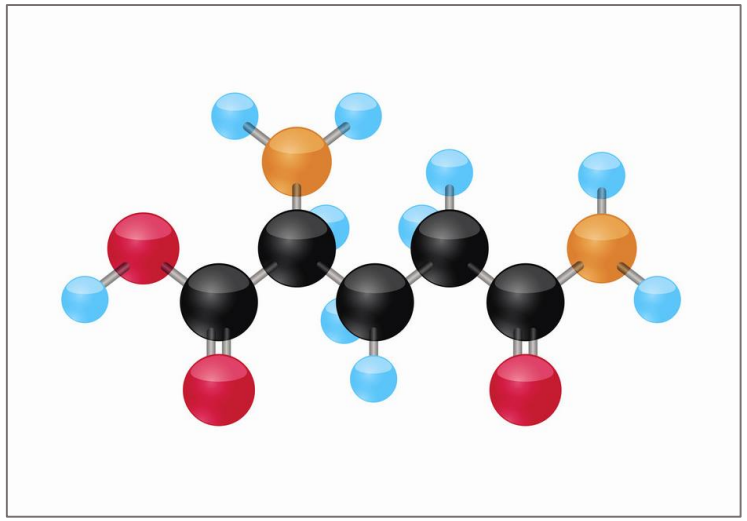
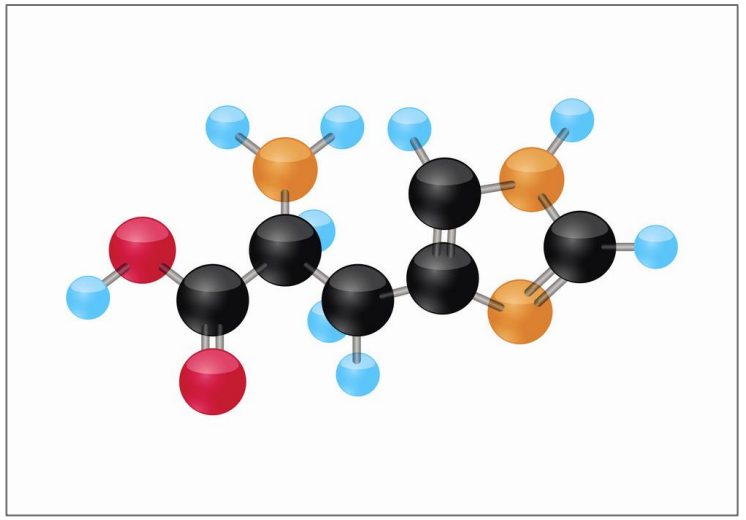
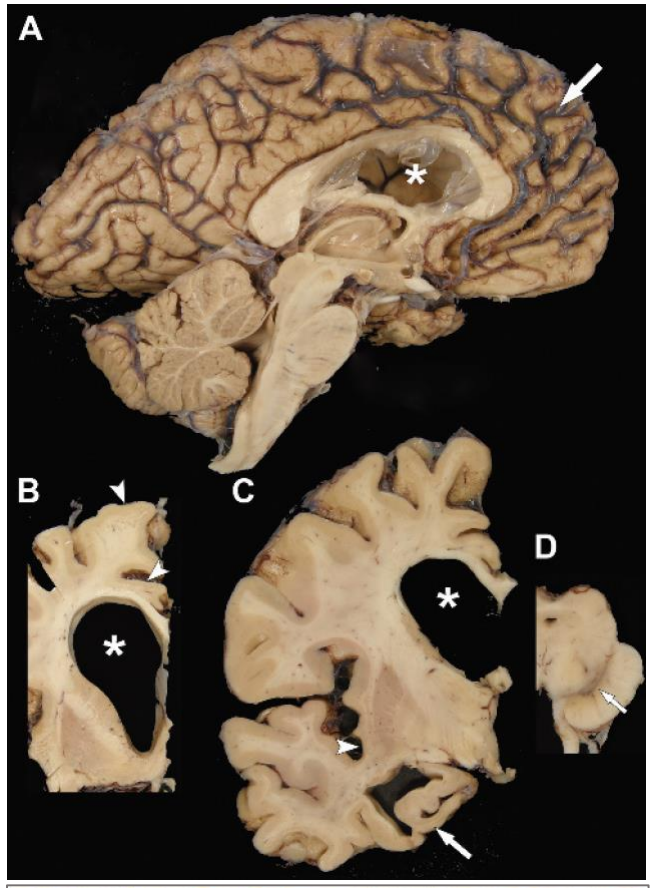
ORIGINAL ARTICLE

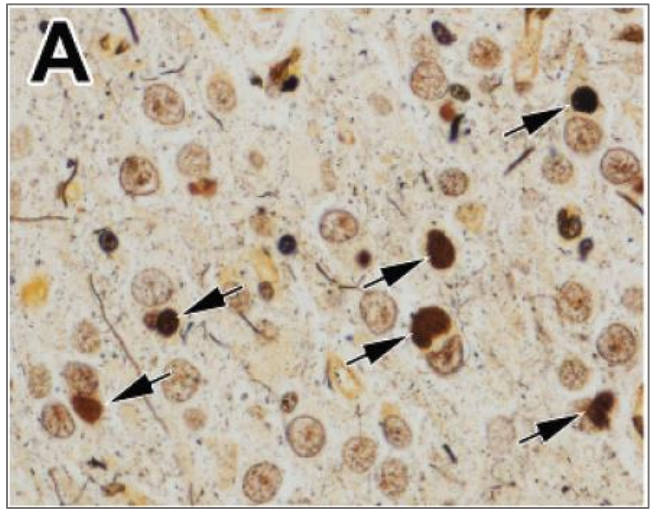
A Novel Tau Mutation in Exon 12, p.Q336H, Causes Hereditary Pick Disease

Pawel Tacik, MD, Michael DeTure, PhD, Kelly M. Hinkle, MS, Wen-Lang Lin, PhD, Monica Sanchez-Contreras, MD, PhD, Yari Carlomagno, PhD, Otto Pedraza, PhD, Rosa Rademakers, PhD, Owen A. Ross, PhD, Zbigniew K. Wszolek, PhD, and Dennis W. Dickson, MD



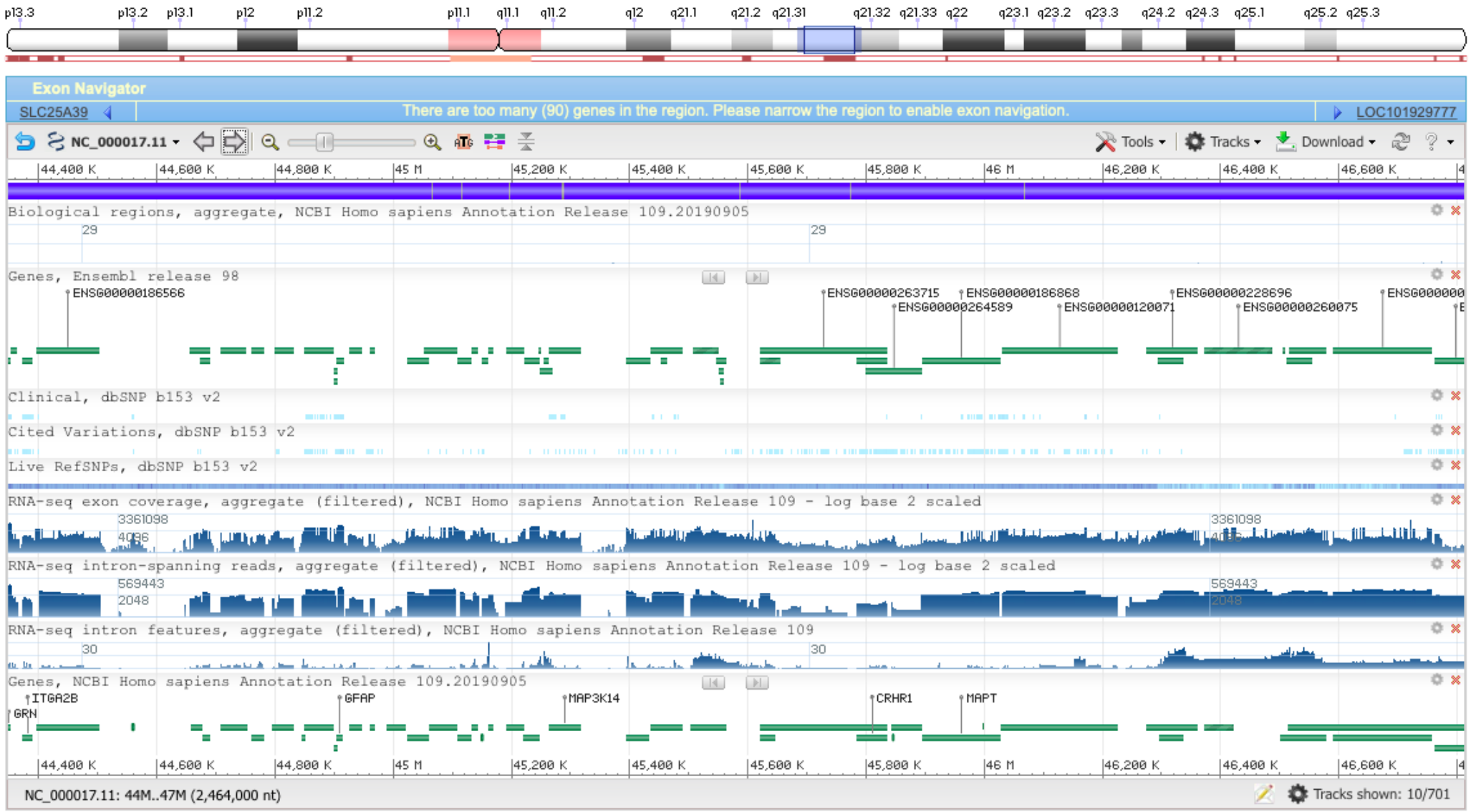






GRN (granulin)

- Diverse famiglie con linkage su 17q21 ma senza mutazioni di MAPT
- Inclusioni ubiquitina-positive ma tau-negative



GRN (granulin)

LETTERS

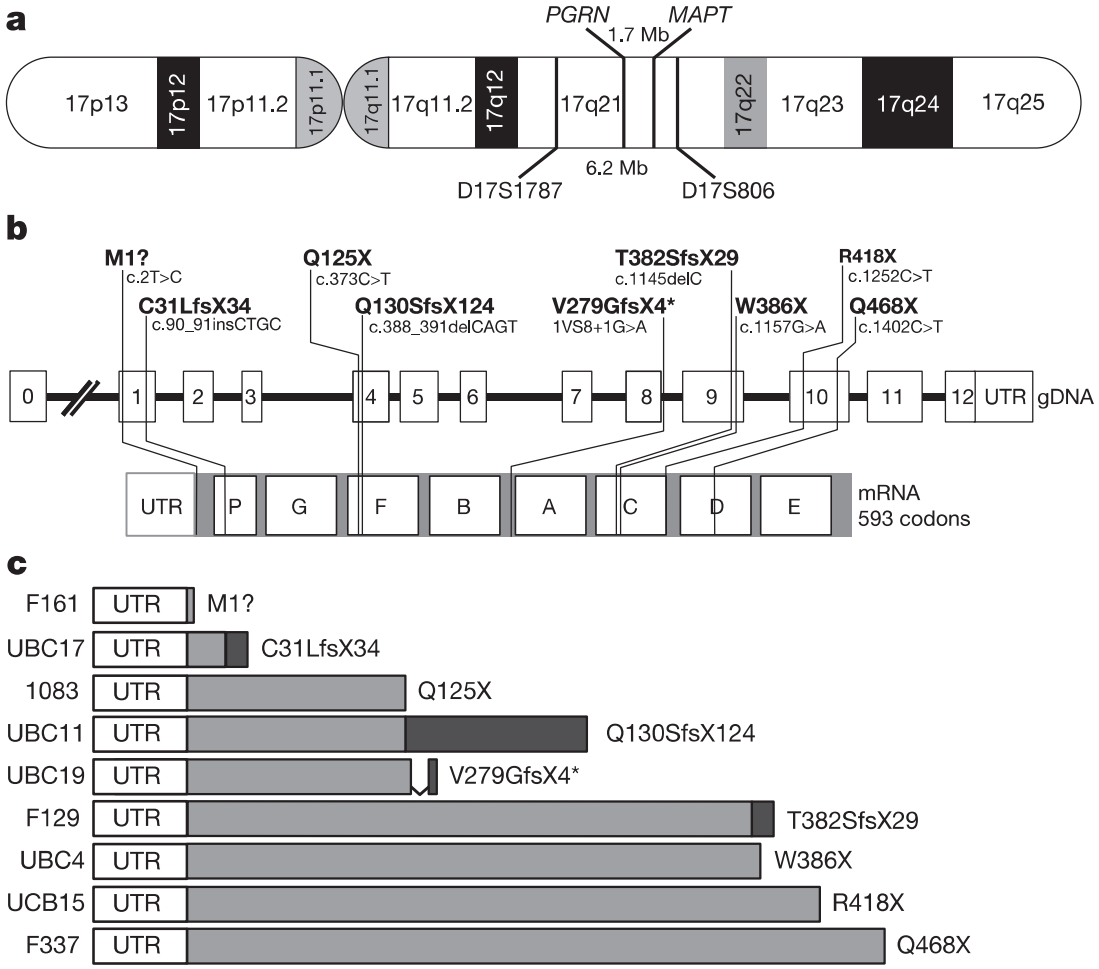
Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21

Marc Cruts[1,2,5], Ilse Gijselinck[1,2,5], Julie van der Zee[1,2,5], Sebastiaan Engelborghs[3,5,6], Hans Wils[1,2,5], Daniel Pirici[1,2,5], Rosa Rademakers[1,2,5], Rik Vandenberghe[7], Bart Dermaut[9], Jean-Jacques Martin[4,5], Cornelia van Duijn[10], Karin Peeters[1,2,5], Raf Sciot[8], Patrick Santens[9], Tim De Pooter[1,2,5], Maria Mattheijssens[1,2,5], Marleen Van den Broeck[1,2,5], Ivy Cuijt[1,2,5], Krist'l Vennekens[1,2,5], Peter P. De Deyn[3,5,6], Samir Kumar-Singh[1,2,5] & Christine Van Broeckhoven[1,2,5]

LETTERS

Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17

Matt Baker[1]*, Ian R. Mackenzie[2]*, Stuart M. Pickering-Brown[5,6]*, Jennifer Gass[1], Rosa Rademakers[1], Caroline Lindholm[3], Julie Snowden[6], Jennifer Adamson[1], A. Dessa Sadovnick[3,4], Sara Rollinson[5], Ashley Cannon[1], Emily Dwosh[4], David Neary[6], Stacey Melquist[1], Anna Richardson[6], Dennis Dickson[1], Zdenek Berger[1], Jason Eriksen[1], Todd Robinson[1], Cynthia Zehr[1], Chad A. Dickey[1], Richard Crook[1], Eileen McGowan[1], David Mann[6], Bradley Boeve[7], Howard Feldman[3] & Mike Hutton[1]

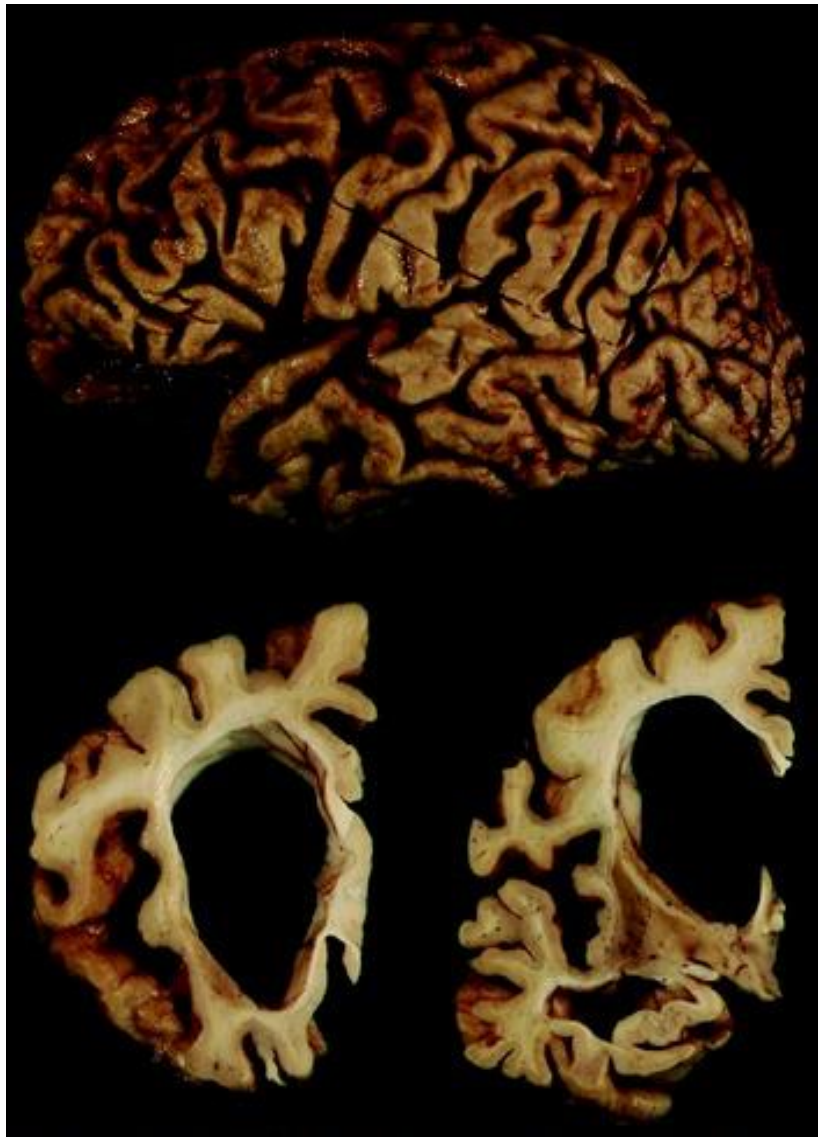


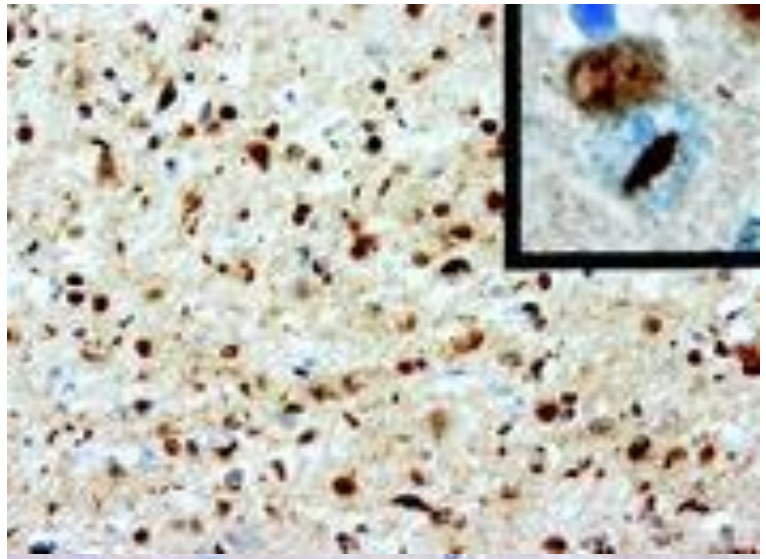
GRN (granulin)

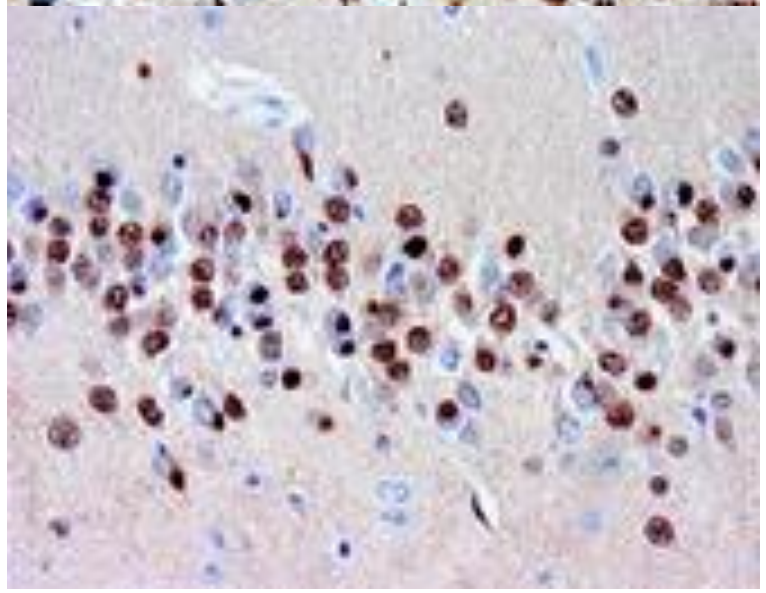
- Fattore di crescita ubiquitario
- Implicato in molteplici processi
  - Infiammazione
  - Riparazione delle ferite
  - …
  - Tumorigenesi
  - Funzione neurotrofica
- «Perdita di funzione»
- Aploinsufficienza
  - Dosaggio plasmatico di GRN
- Possibile fattore di rischio per AD
- Penetranza età dipendente
  - 50-60% a 60 anni
  - 90-95% a 70 anni
- Fino a ¼ dei pazienti con mutazioni di GRN vengono diagnosticati come FTD sporadiche

GRN (granulin)

- Numerosi neuriti distrofici ed inclusioni citoplasmatiche di TDP43, scarse inclusioni intranucleari (Tipo A)
- 40% dei casi con pattern Tipo A hanno mutazioni di GRN







GRN (granulin)

- Fenotipi clinici differenti (bvFTD, PPA, parkisonismi)
  - Apatia, ritiro sociale, disturbi del linguaggio
  - Segni extrapiramidali tardivi (40% dei casi)
    - Sindrome cortico-basale
    - Segni parkinsoniani asimmetrici
    - Occasionalmente risposta alla levodopa
    - Distonia
  - Disturbi di memoria
  - Segni parietali
  - Allucinazioni visive
  - Raramente segni di MND(circa 5%)
  - Afasia logopenica

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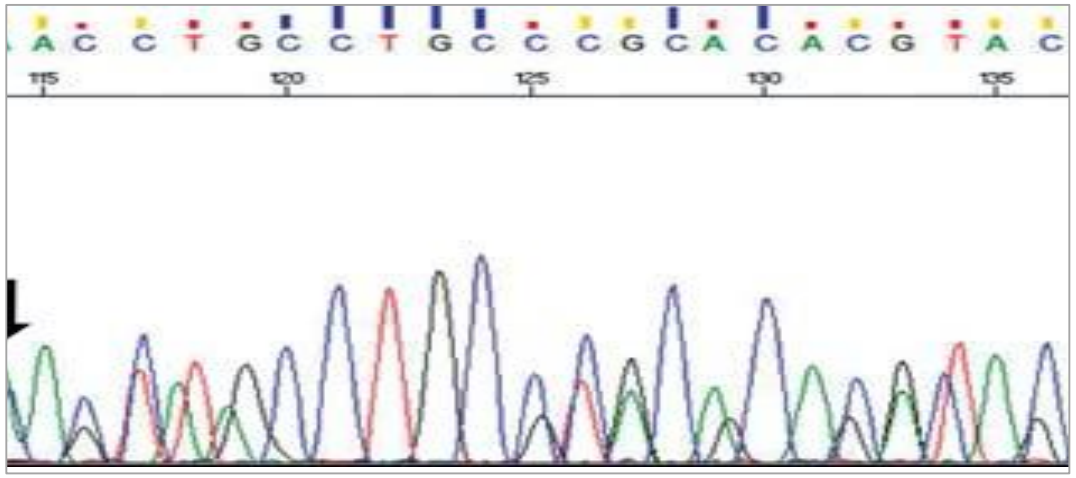
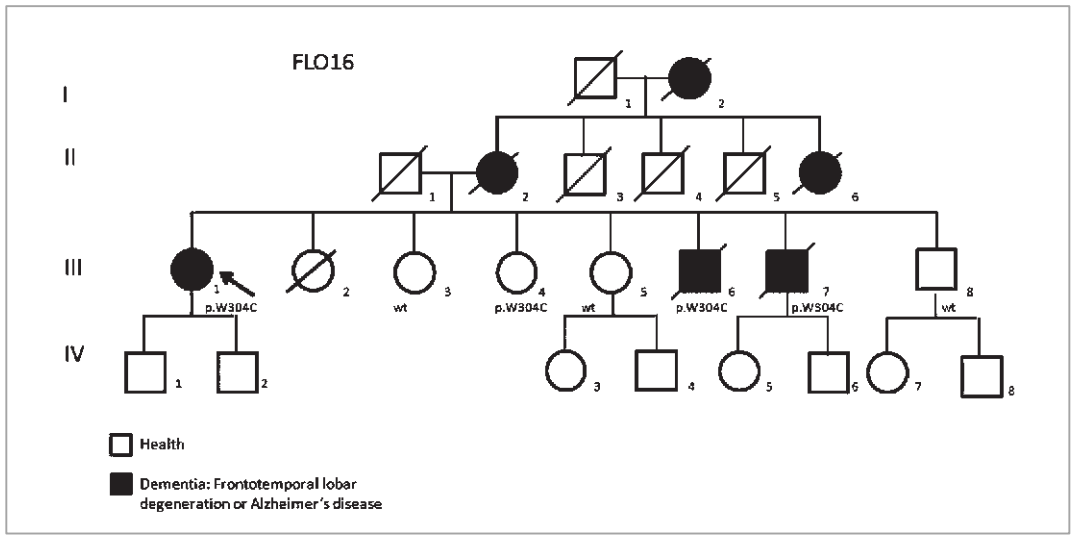
IOS Press

Novel GRN Mutations in Alzheimer's Disease and Frontotemporal Lobar Degeneration

Irene Piaceri[a], Daniele Imperiale[b], Enrico Ghidoni[c], Cristiana Atzori[b], Silvia Bagnoli[a], Camilla Ferrari[d], Silvana Ungari[e], Luca Ambrogio[e], Sandro Sorbi[a,d] and Benedetta Nacmias[a,*]
[a]*Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Italy*
[b]*Neurology Unit and Human TSE Regional Center, ASL TO2 Maria Vittoria Hospital, Turin, Italy*
[c]*UOC Neurologia, ASMN-IRRCS Reggio Emilia, Italy*
[d]*IRCCS Don Gnocchi, Florence, Italy*
[e]*ASO Neurologia, Azienda Ospedaliera S. Croce e Carle, Cuneo, Italy*

GRN (granulin)





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[a]*Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Italy*
[b]*Neurology Unit and Human TSE Regional Center, ASL TO2 Maria Vittoria Hospital, Turin, Italy*
[c]*UOC Neurologia, ASMN-IRRCS Reggio Emilia, Italy*
[d]*IRCCS Don Gnocchi, Florence, Italy*
[e]*ASO Neurologia, Azienda Ospedaliera S. Croce e Carle, Cuneo, Italy*

C9orf72

- Associazione tra FTD e MND
  - Linkage su 9q21 (2006)
  - Espansione GGGCC su C9orf72 (2011)
- Soggetti normali: 2-24 ripetizioni
  - <25 unità in popolazioni Europee e Nord-Americane
  - <15 unità in popolazioni Asiatiche
- Soggetti «patologici»: 10^2-10^3 ripetizioni
- Non è nota la minima espansione «patologica»
- In vitro correlazione inversa tra entità dell'espansione ed espressione del gene
- Mutazioni più frequenti nel Nord Europa (Scandinavia)

C9orf72

- Pattern neuropatologici variabili
  - FTD-TDP: Tipo A ≈ Tipo B >> Tipo C
  - Raramente FTD-UPS
- Quadri clinici variabili
  - Eterogeneità inter- e intra-familiare
  - FTD e MND frequentemente isolati, coesistenza nel 17-30% dei casi C9orf72
    - bvFTD in ≈ 2/3 dei casi FTD
    - PPA (nfv-PPA)
  - Sintomi psichiatrici
    - Ideazione patologica, stereotipie
    - Associazione con segni extrapiramidali
    - Sintomi tipo OCD
    - Iperfagia generalmente assente
- Fenotipi non FTD
  - AD
  - Corea di Huntington
- Età di esordio estremamente variabile (da <30 anni a >80 anni)
- Descritta «anticipazione»
  - <80 ripetizioni: in media 53 anni
  - >80 ripetizioni: in media 62 anni
  - Esordio più precoce nelle generazioni più giovani
  - Differenza anche di circa 1000 ripetizioni tra generazioni successive
  - Differente metilazione della regione CpG al 5’ di C9orf72

Geni «minori»

CHMP2B (3p11.2)

- Sistema endosoma/lisosoma, autofagia
- Mutazioni rare, STOP codon
- Pattern FTD-UPS
- bvFTD (tipo Pick)
  - Parkisonismo
  - Distonia
  - Segni piramidali
  - Mioclono
- Meno frequentemente
  - PPA
  - MND
- Esordio 45-65 anni

VCP (9p11.3)

- Sindrome specifica (IBMPFD)
  - FTD (30%)
  - Miopatia a corpi inclusi (90%)
  - Morbo di Paget (50%)
  - Esordio dei sintomi cognitivi più tardivo
- bvFTD o svPPA
  - Sintomi psichiatrici precoci
- Altre entità nosologiche
  - PD
  - AD
  - CMT2
  - HSP
- Esordio 45-65 anni

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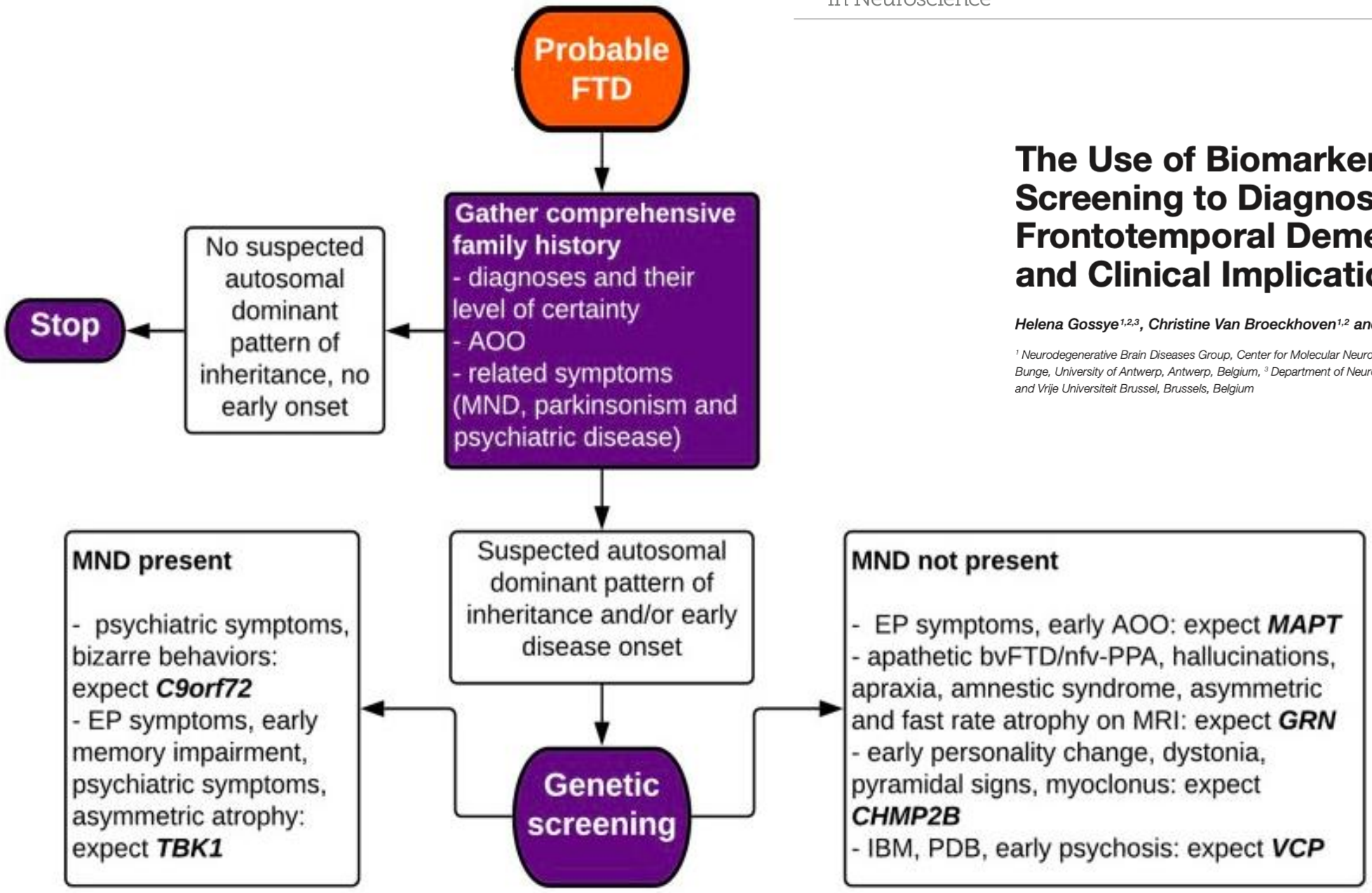

The Use of Biomarkers and Genetic Screening to Diagnose Frontotemporal Dementia: Evidence and Clinical Implications

*Helena Gossye[1,2,3], Christine Van Broeckhoven[1,2] and Sebastiaan Engelborghs[2,3]**

[1] Neurodegenerative Brain Diseases Group, Center for Molecular Neurology, VIB, Antwerp, Belgium, [2] Institute Born – Bunge, University of Antwerp, Antwerp, Belgium, [3] Department of Neurology and Center for Neurosciences, UZ Brussel and Vrije Universiteit Brussel, Brussels, Belgium