Istituto delle Scienze Neurologiche di Bologna

ALMA MATER STUDIORUM UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI SCIENZE BIOMEDICHE E NEUROMOTORIE

Targeted sequencing in the diagnostic of FTD/ALS spectrum diseases

NICOLA MOMETTO, *ANNA BARTOLETTI-STELLA, MICHELANGELO STANZANI-MASERATI, SAMIR ABU-RUMEILEH, SIMONE BAIARDI, FEDERICO OPPI, ROBERTO PODA, SILVIA PIRAS, ROCCO LIGUORI, PIERO PARCHI, SABINA CAPELLARI.*

Department of Biomedical and NeuroMotor Sciences (DIBINEM), Alma Mater Studiorum - University of Bologna, Bologna

IRCCS ISNB - Institute of Neurological Sciences of Bologna, Bellaria Hospital, Bologna

SINdem4Juniors

6th Winter Seminar on Dementia and Neurodegenerative Disorders

SINdem Associazione Autonoma Aderente alla SIN per le Demenze

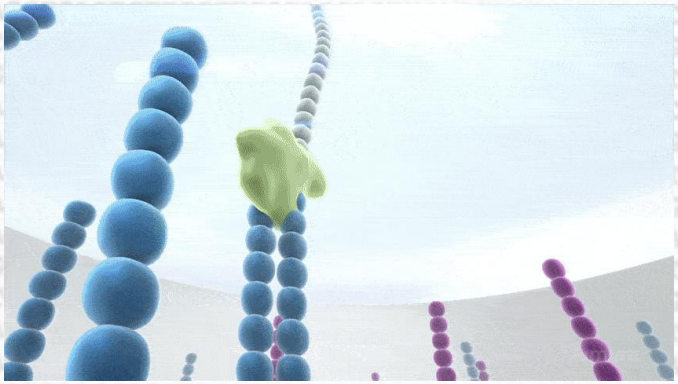
Aim of this work

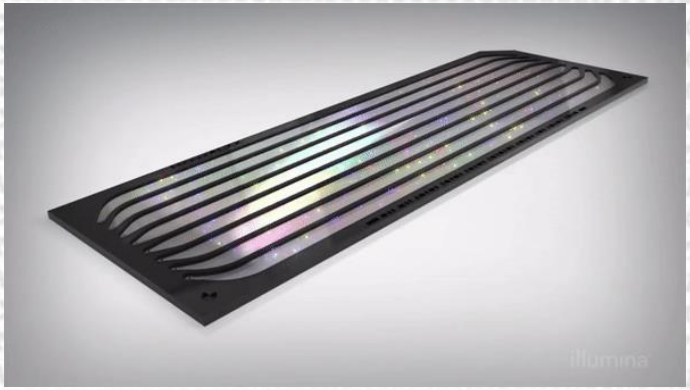
- To identify how many patients in our population carry pathogenic and novel likely-pathogenic genetic variants
- If a NGS panel could represent a cost-effective way to screen this kind of diseases in search of genetic variants

Material and Methods

- 114 patients affected by FTD spectrum diseases afferent to the Cognitive Disorders and Dementia Center of the UOC Clinica Neurologica, ISNB Bologna, underwent a comprehensive clinical examination, including personal medical, family history and neuropsychological assessment, cerebrospinal fluid (CSF) biomarkers (76% of total patients), and neuroimaging as part of diagnostic procedure.

- Targeted sequencing using a **custom-designed Next Generation Sequencing panel (Illumina MiSeq)**, covering 27 genes know to harbor mutations causative of different types of dementia. C9ORF72 RE was searched separately.





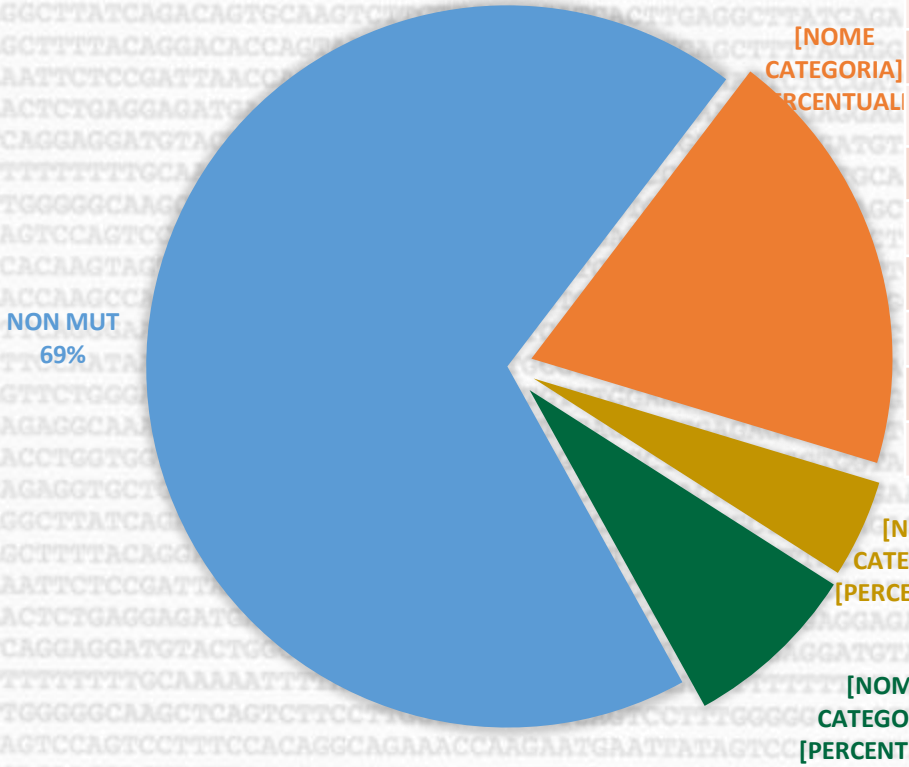
Our custom-designed Next Generation Sequencing panel

Symbol	Name	OMIM Phenotype or other Ref.
APP	amyloid beta precursor protein	AD; CAA
CHCHD10	coiled-coil-helix-coiled-coil-helix domain containing 10	?Myopathy, isolated mitochondrial, autosomal dominant; FTD/ALS; Spinal muscular atrophy, Jokela type
CHMP2B	charged multivesicular body protein 2B	ALS, Dementia
CSF1R	colony stimulating factor 1 receptor	Leukoencephalopathy, diffuse hereditary, with spheroids
DCTN1	dynactin subunit 1	Neuropathy, distal hereditary motor, type VIIB; Perry syndrome; ALS (susceptibility to)
FUS	FUS RNA binding protein	FTD/ALS; Tremor, hereditary essential
GRN	granulin	FTD; Aphasia, primary progressive
GSN	gelsolin	Amyloidosis, Finnish type
HNRNPA2B1	heterogeneous nuclear ribonucleoprotein A2/B1	?Inclusion body myopathy with early-onset Paget disease with or without FTD 2
ITM2B	integral membrane protein 2B	Dementia, familial British; Dementia, familial Danish; ?Retinal dystrophy with inner retinal dysfunction and ganglion cell abnormalities
MAPT	microtubule associated protein tau	FTD with or without parkinsonism; Pick disease; PSP; PSP atypical; Parkinson disease (susceptibility to)
NOTCH3	notch 3	?Myofibromatosis, infantile 2; Cerebral arteriopathy with subcortical infarcts and leukoencephalopathy 1; Lateral meningocele syndrome
OPTN	optineurin	Glaucoma 1, open angle, E; ALS12; Glaucoma, normal tension (susceptibility to)
PRKAR1B	protein kinase cAMP-dependent type I regulatory subunit beta	Wong et al., 2014
PRNP	prion protein	CAA, PRNP-related; Creutzfeldt-Jakob disease; Gerstmann-Straussler disease; Huntington disease-like 1; Insomnia, fatal familial; Prion disease with protracted course; Kuru (susceptibility to)
PSEN1	presenilin 1	Acne inversa, familial, 3; AD 3; AD 3 with spastic paraparesis and apraxia; AD 3 with spastic paraparesis and unusual plaques; Cardiomyopathy, dilated, 1U; FTD; Pick disease
PSEN2	presenilin 2	AD 4; Cardiomyopathy, dilated, 1V
SERPINI1	serpin family I member 1	Encephalopathy, familial, with neuroserpin inclusion bodies
SIGMAR1	sigma non-opioid intracellular receptor 1	? ALS 16 ?Spinal muscular atrophy, distal, autosomal recessive, 2
SNCA	synuclein, alpha	Dementia, Lewy body, PD 1; PD 2
SQSTM1	sesquestosome 1	Myopathy, distal, with rimmed vacuoles; FTD/ALS 3; Neurodegeneration with ataxia, dystonia, and gaze palsy, childhood-onset; Paget disease of bone 3
TARDBP	TAR DNA binding protein	ALS 10, with or without FTD
TBK1	TANK binding kinase 1	FTD/ALS 4
TREM2	Triggering receptor expressed on myeloid cells 2	Nasu-Hakola disease
TTR	Transthyretin (prealbumin)	Amyloidosis, hereditary, transthyretin-related; Carpal tunnel syndrome, familial
TYROBP	TYRO protein tyrosine kinase binding protein	Nasu-Hakola disease
VCP	Valosin-containing protein	ALS 14, with or without FTD; Charcot-Marie-Tooth disease, type 2Y; Inclusion body myopathy with early-onset Paget disease and FTD 1.

Results

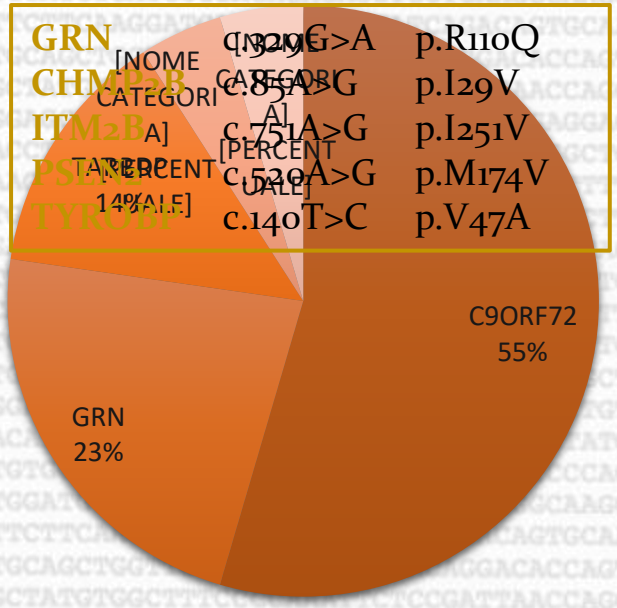
Known causative mutations

Gene	Nucleotide change	Aa change	Reported variant phenotype (ClinVar; HGMD; AD&FTDMND; other ref.)	Observed phenotype
GRN	c.2T>C	p.M1?	FTD; NR; FTD	Possible bvFTD
GRN (x2)	c.813_816del	p.T272SfsX10	NR; NR; FTLD	Probable bvFTD, FH; Probable bvFTD, FH
GRN	c.709-2A>T		NR; NR; NR; FTD (Sassi et al., 2016)	Probable bvFTD
GRN	c.796G>C	p.A266P	NR; FTD?; NR; FTD (Bernardi et al., 2012)	Probable bvFTD
FUS	c.1553G>A	p.R518K	ALS; ALS; ALS	ALS, FH
TARDBP	c.881G>C	p.G294A	FTD/MND; ALS; ALS	Probable bvFTD
TARDBP	c.883G>A	p.G295S	FTD/MND; ALS; FTD/MND	Probable bvFTD/ALS, FH
TARDBP	c.881G>T	p.G294V	FTD/MND; ALS; ALS	FTD-PPA, FH
VCP	c.277C>T	p.R93C	NR; IBMPFD; IBMPFD	IBMPFD, FH
C9ORF72 RE (x 12)				Probable bvFTD; FTD/ALS



Variants of uncertain significance

GRN	c.329G>A	p.R110Q
CHMP2B	c.85A>G	p.I29V
ITM2B	c.751A>G	p.I251V
PSEN1	c.520A>G	p.M174V
TYROBP	c.140T>C	p.V47A

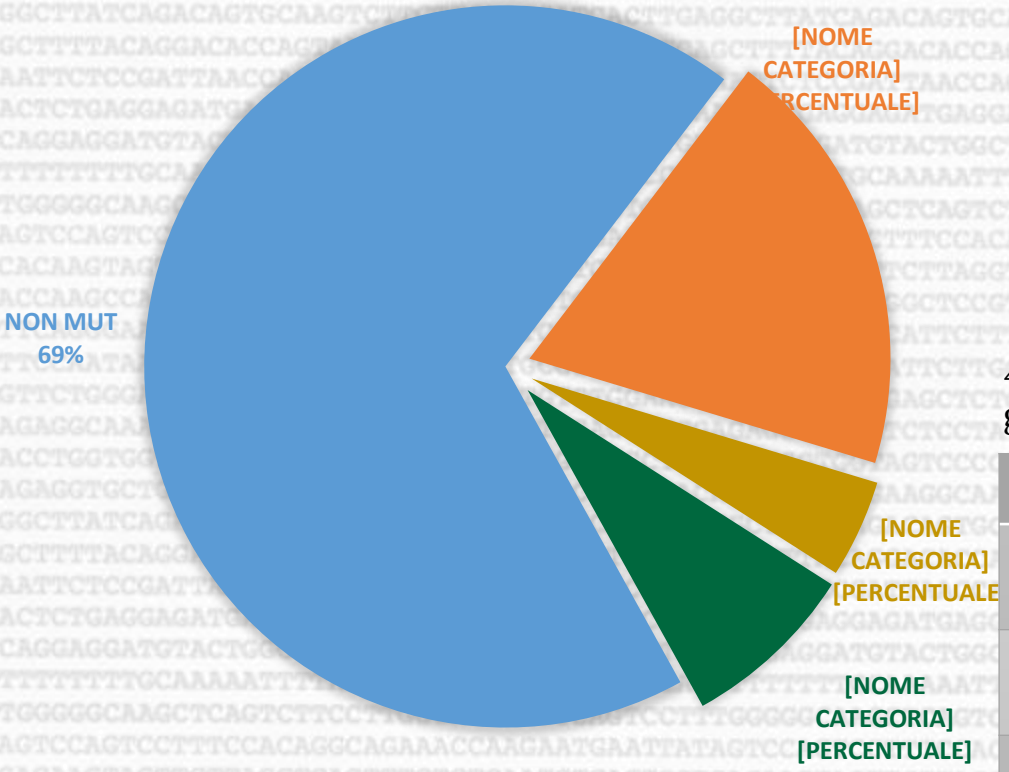


Novel likely-pathogen variants

Gene	NT change	AA change	Observed phenotype	Pathogenity tools(1)
FUS	c.G443C	p.S148T	Possible bvFTD	T/D/D/D
GRN	c.1179+3A>G		Probable bvFTD, FH	Splicing alteration
CSF1R	c.G2500C	p.V834L	Probable bvFTD	D/D/D/D
OPTN	c.C235T	p.Q79X	Possible FTD	Stop
PRKAR1B	c.C656T	p.T219M	Probable bvFTD	D/D/D/D
PRKAR1B	c.G1018A	p.V340M	ALS	D/D/D/D
DCTN1	c.C673T	p.R225W	Probable bvFTD	D/D/D/T
TREM2 (Risk factor)	c.483-2A>C		Possible bvFTD	Novel variant, Probable splicing alteration (HSF)
GSN	c.1915+2T>C		Probable bvFTD, FH	Splicing alteration
ITM2B	c.A758G	p.H253R	Probable bvFTD, FH	D/D/D/T

(1) Polyphen2, SIFT, MutationTaster, FAHTMM; results has been reported as D=damaging or disease causing; T=tolerated. Splicing alterations were assessed by Human Splicing Finder

Results



4 patients bearing more than one probable genetic cause of dementia

Observed Phenotype	Variant
Probable bvFTD, FH	GRN c.813_816del p.T272SfsX10 ITM2B c.758A>G p.H253R
Probable bvFTD, FH	FUS c.443G>C p.S148T TREM2 c.483-2A>C
Probable FTD/ALS, FH	C9orf72 Repeat expansion ITM2B c.751A>G p.I251V
Probable FTD/ALS, FH	C9orf72 Repeat expansion TYROBP c.140T>C p.V47A

Conclusions

- a significant percentage of patients affected by disease from the FTD/ALS spectrum carries a causative genetic variant.
  - This result implies that genetic testing of patients affected by this disease should be encouraged, especially when family history is significant (Turner et al., 2017).
- our results support the use of extended NGS panels as a quick, accurate and cost-effective method for the diagnosis in clinical practice

…thanks for the attention.