La demenza frontotemporale lobare e gli aspetti di confine

Dott. Amalia C. Bruni

Centro Regionale di Neurogenetica

Lamezia Terme - ASP CZ
Frontotemporal dementia

- Complex disorder
- Several phenotypes
  - Clinically
  - Neuropathologically
  - Genetically
  - Heterogeneous
Important events in the molecular pathogenesis of FTD

* 1892: Arnold Pick describes lobar atrophy in a patient with presenile dementia and aphasia.\(^{145}\)
* 1911: Alois Alzheimer characterizes Pick bodies using silver stains.\(^{146}\)
* 1960’s: descriptions of PSP and CBD clinicopathological syndromes.\(^{147,148}\)
* 1974: different pathological subtypes of PiD disease described.\(^{149}\)
* mid 1980’s - early 1990’s: identification of tau as major component of pathological lesions in AD, PiD, PSP and CBD (reviewed in Lee et al.).\(^{150}\)
* 1990: description of FTD cases without specific histopathology (DLDH).\(^{151}\)
* mid 1990’s: identification of subset of FTD with FTLD-U pathology.\(^{152}\)
* 1998: MAPT mutations identified in some families with FTD and parkinsonism genetically linked to chromosome 17.\(^{10-12}\)
* 2004–06: recognition that most cases of DLDH are really FTLD-U and that FTLD-U is the most common FTD-associated pathology.\(^{33}\)
* 2006: description of different patterns of FTLD-U that correlate with clinical phenotypes, genetic abnormalities and biochemical properties of inclusions.\(^{115,117}\)
* 2006: discovery that GRN mutations cause autosomal dominant FTD and explain all remaining chromosome 17 linked families.\(^{14,15}\)
* 2006: TDP-43 identified as pathological protein in most cases of FTLD-U and ALS.\(^{34,35}\)
* 2008: identification of a subset of FTLD-U cases that lack TDP-43-immunoreactive pathology (aFTLD-U).\(^{153,154}\)
* 2009: discovery that most cases of tau/TDP-43-negative FTLD have FUS-immunoreactive pathology (FTLD-FUS).\(^{38-40}\)
* 2011: discovery that FTLD-FUS shows accumulation of other FET protein members TAF15 and EWS.\(^{41}\)
* 2011: FTD/ALS associated gene defect on chromosome 9p identified as repeat expansion in C9ORF72.\(^{27,28}\)
**FTD Epidemiology**

* Second most common type of presenile dementia (now several cases described >80)

* Positive family history in up to 50% of cases (mainly autosomal dominant)

**Literature**

* Andreasen, 1999 (Swedish): 3.2%

* Ratnavalli et al 2002 (Cambridge study): 15.7%

* Harvey et al, 2003 London study 12%

* **FTD Prevalence 0.02%**

* Ikeda et al 2004 (Japan study) 12.7%
### Clinical characteristics of FTLD

**Sex distribution**: 1:1

**Age at onset**: 45-65 (range 21-85)

**Duration (yrs)**: 6-8 (3 with MND)

**Prevalence**: 15/100,000

**Familial history**: 50%

**Symptoms at onset**: Behavioral changes

**Cognitive features**: Executive and language deficits

**Neurological signs**: Parkinsonism / MND

**Neuroimaging**: FT abnormalities

Neary et al 2005
DEMENTIA CASES 1997-2012

<table>
<thead>
<tr>
<th></th>
<th>Early</th>
<th>Late</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic</td>
<td>363</td>
<td>1177</td>
<td>1540</td>
</tr>
<tr>
<td>Familial</td>
<td>459</td>
<td>951</td>
<td>1410</td>
</tr>
<tr>
<td>Autosomal dominant</td>
<td>27</td>
<td>17</td>
<td>44</td>
</tr>
<tr>
<td>Total</td>
<td>849</td>
<td>2145</td>
<td>2994</td>
</tr>
</tbody>
</table>
FTD

1997-2012
2997 DEMENTIA CASES

Early

Late

Familial 49%
Sporadic 42%
Autosomal dominant 9%

Familial 49%
Sporadic 47%
Autosomal dominant 4%
ESTIMATING THE INHERITANCE OF FRONTOTEMPORAL LOBAR DEGENERATION IN THE ITALIAN POPULATION

* EO-FTD 86.3%
* (95% CI: 77.0%-95.0%)

* Hereditability LO-FTD 75.7%
(95% CI: 65.0%-86.0%).


J Alzheimers Dis. 2013 May 29. [Epub ahead of print]
One Disease Multiple Genes

**Storia Naturale**

- Malattia di Alzheimer
- Disturbi comportamentali
- Demenza frontotemporale
- Disturbi cognitivi

(onset)
<table>
<thead>
<tr>
<th>Clinical features</th>
<th>FTD</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset</td>
<td>Rarely &gt; 75 years</td>
<td>Increases markedly with age</td>
</tr>
<tr>
<td>Early behavioural problems</td>
<td>Common</td>
<td>Unusual</td>
</tr>
<tr>
<td>Socially inappropriate behaviours</td>
<td>Common early in the course</td>
<td>Usually in severe case</td>
</tr>
<tr>
<td>Memory impairment</td>
<td>Less prominent in early course</td>
<td>Early and profound impairment</td>
</tr>
<tr>
<td>Language problems</td>
<td>May have isolated language problems without memory impairment (in progressive nonfluent aphasia type)</td>
<td>Usually associated with memory impairment</td>
</tr>
<tr>
<td>Visuospatial defect</td>
<td>Rare in mild to moderately impaired case</td>
<td>Common</td>
</tr>
<tr>
<td>Motor signs</td>
<td>More common (in FTD with motor neuron disease)</td>
<td>Less common</td>
</tr>
<tr>
<td>Mood</td>
<td>Marked irritability, anhedonia, withdrawal, alexithymia (difficulties in understanding, processing, or describing emotions), euphoria, lack of guilty, apathy or suicidal ideation</td>
<td>Sadness, tears, anhedonia, apathy, guilt</td>
</tr>
<tr>
<td>Psychotic features</td>
<td>Rare persecutory delusion, usually jealous, somatic, religious, and bizarre behaviours</td>
<td>Usually have delusion of misidentification or persecutory type and usually occur in middle or late stage</td>
</tr>
<tr>
<td>Appetite, dietary change</td>
<td>Increased appetite, carbohydrate craving 80%, weight gain</td>
<td>Less common: anorexia and weight loss</td>
</tr>
</tbody>
</table>

Table 3  International consensus criteria for behavioural variant FTD (FTDC)

I. Neurodegenerative disease
The following symptom must be present to meet criteria for bvFTD
   A. Shows progressive deterioration of behaviour and/or cognition by observation or history (as provided by a knowledgeable informant).

II. Possible bvFTD
Three of the following behavioural/cognitive symptoms (A–F) must be present to meet criteria. Ascertaintment requires that symptoms be persistent or recurrent, rather than single or rare events.
   A. Early* behavioural disinhibition [one of the following symptoms (A.1–A.3) must be present]:
      A.1. Socially inappropriate behaviour
      A.2. Loss of manners or decorum
      A.3. Impulsive, rash or careless actions
   B. Early apathy or inertia [one of the following symptoms (B.1–B.2) must be present]:
      B.1. Apathy
      B.2. Inertia
   C. Early loss of sympathy or empathy [one of the following symptoms (C.1–C.2) must be present]:
      C.1. Diminished response to other people’s needs and feelings
      C.2. Diminished social interest, interrelatedness or personal warmth
   D. Early perseverative, stereotyped or compulsive/ritualistic behaviour [one of the following symptoms (D.1–D.3) must be present]:
      D.1. Simple repetitive movements
      D.2. Complex, compulsive or ritualistic behaviours
      D.3. Stereotypy of speech
   E. Hyperorality and dietary changes [one of the following symptoms (E.1–E.3) must be present]:
      E.1. Altered food preferences
      E.2. Binge eating, increased consumption of alcohol or cigarettes
      E.3. Oral exploration or consumption of inedible objects
   F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions [all of the following symptoms (F.1–F.3) must be present]:
      F.1. Deficits in executive tasks
      F.2. Relative sparing of episodic memory
      F.3. Relative sparing of visuospatial skills
**Frontotemporal lobar degeneration**

**Clinical Entities**

- Frontotemporal Dementia-Behavioral Variant (FTD-BV)
- Pick’s Disease (PD)
- Semantic Dementia (SD)
- Primary Progressive non-fluent aphasia (PPA)
- Cortico-Basal Syndrome (CBS)
- Progressive Sopranuclear Palsy (PSP)
- FTD-Motor Neuron Disease (FTD-MND)

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**Core Features**

<table>
<thead>
<tr>
<th>Core Features</th>
<th>Brain topography</th>
<th>Clinical syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behaviour</td>
<td>Aphasial + behaviour</td>
<td>Extrapyramidal + behaviour</td>
</tr>
<tr>
<td>FTD</td>
<td>Prefrontal &amp; anterior-temporal</td>
<td>Frontotemporal (left)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressive aphasia (PPA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Semantic dementia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FTD-MND</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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### Mutations per Gene

<table>
<thead>
<tr>
<th>Gene</th>
<th># Mutations</th>
<th># Families</th>
</tr>
</thead>
<tbody>
<tr>
<td>APP</td>
<td>33 (7.78%)</td>
<td>90 (6.20%)</td>
</tr>
<tr>
<td>PSEN1</td>
<td>185 (43.63%)</td>
<td>405 (27.91%)</td>
</tr>
<tr>
<td>PSEN2</td>
<td>13 (3.07%)</td>
<td>22 (1.52%)</td>
</tr>
<tr>
<td>C9orf72</td>
<td>1 (0.24%)</td>
<td>336 (23.16%)</td>
</tr>
<tr>
<td>CHMP2B</td>
<td>4 (0.94%)</td>
<td>5 (0.34%)</td>
</tr>
<tr>
<td>FUS</td>
<td>23 (5.42%)</td>
<td>49 (3.38%)</td>
</tr>
<tr>
<td>GRN</td>
<td>69 (16.27%)</td>
<td>231 (15.92%)</td>
</tr>
<tr>
<td>MAPT</td>
<td>44 (10.38%)</td>
<td>134 (9.24%)</td>
</tr>
<tr>
<td>TARDBP</td>
<td>34 (8.02%)</td>
<td>131 (9.03%)</td>
</tr>
<tr>
<td>VCP</td>
<td>18 (4.25%)</td>
<td>48 (3.31%)</td>
</tr>
</tbody>
</table>

**Total** 424 1451

Note: Mutations without pathogenic effect or of unclear nature are excluded.
<table>
<thead>
<tr>
<th>GENES</th>
<th>#Mutations</th>
<th>#Proteins</th>
<th># Families</th>
<th>#Inclusions</th>
<th>#Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAPT</td>
<td>44</td>
<td>Microtubule network</td>
<td>132</td>
<td>Tau inclusions</td>
<td>FTD-bv FTDP</td>
</tr>
<tr>
<td>GRN</td>
<td>69</td>
<td>Growth factor</td>
<td>231</td>
<td>Ub/TDP-43 inclusions</td>
<td>FTD-bv-SD-PPA CBS</td>
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<tr>
<td>VCP</td>
<td>17</td>
<td>Vesicle transport</td>
<td>41</td>
<td>Ub/VCP inclusions</td>
<td>IBMPFD-ALS</td>
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<tr>
<td>CHMP2B</td>
<td>4</td>
<td>Endosomal trafficking</td>
<td>5</td>
<td>Ub inclusions</td>
<td>ALS-FTD</td>
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<tr>
<td>TAR-TDP</td>
<td>34</td>
<td>DNA binding/regulating protein</td>
<td>92</td>
<td>TDP-43 inclusions</td>
<td>ALS - rarely FTD bv</td>
</tr>
<tr>
<td>FUS</td>
<td>23</td>
<td>DNA binding Regulating protein</td>
<td>49</td>
<td>FUS inclusions</td>
<td>ALS – rarely FTD bv</td>
</tr>
<tr>
<td>C9ORF72</td>
<td>1</td>
<td>Unknown</td>
<td>336</td>
<td>Ub inclusions</td>
<td>ALS-FTD / FTD / ALS</td>
</tr>
</tbody>
</table>
Fig. 1 The molecular and genetic classification of FTLD. Three distinct neuropathologic categories may be identified based on the molecular pathology of the misfolded protein within the inclusion: FTLD-Tau, FTLD-TDP, and FTLD-FUS; the molecular pathology of a fourth category, FTLD with epitopes of the ubiquitin–proteasome system (FTLD-UPS), remains indeterminate. 3R, 4R, 3R/4R the predominant tau isoform within the inclusion; PICK, Pick’s disease; FTLD with microtubule-associated protein tau (MAPT) mutation with inclusions of 3R, 4R, or 3R and 4R tau protein; CBD, corticobasal degeneration; PSP, progressive supranuclear palsy; AGD, argyrophilic grain disease; TOD, tangle only dementia; WMT-GGI, white matter tauopathy with globular glial inclusions; FTLD-U, FTLD with ubiquitin inclusions, now called FTLD-TDP; FTLD with progranulin (GRN) mutation; FTLD with TAR DNA-binding protein 43 (TARDBP) gene mutation; FTLD with valosin-containing protein (VCP) mutation; FTLD with C9ORF72 expansion, chromosome 9-linked FTLD with C9ORF72 hexanucleotide repeat expansion; NIFID neuronal intermediate filament inclusion disease; aFTLD-U atypical FTLD with ubiquitin inclusions; BIBD basophilic inclusion body disease; FTLD with fused in sarcoma (FUS) mutation; FTLD with charged multivesicular body protein 2B (CHMP2B) mutation. There may still be unclassified entities within each molecular pathology grouping (modified from [12]).
The profile of main genes mutation and its possible disease mechanisms in FTLD

<table>
<thead>
<tr>
<th>Gene symbol</th>
<th>MAPT</th>
<th>C9ORF72</th>
<th>PGRN</th>
<th>VCP</th>
<th>CHMP2B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full name</td>
<td>Microtubule-associated protein tau</td>
<td>Chromosome 9 open reading frame 72</td>
<td>Progranulin</td>
<td>Valosin containing protein</td>
<td>Chromatin modifying protein 2B</td>
</tr>
<tr>
<td>Chromosomal localization</td>
<td>17q21.32</td>
<td>9p21.2</td>
<td>17q21.32</td>
<td>9p13.3</td>
<td>3p11.2</td>
</tr>
</tbody>
</table>

- **MAPT** gives rise to six isoforms: three isoforms containing three amino-acid repeats (3R), and three isoforms with four repeats (4R) [79].

- Functions and possible role in the disease mechanism:
  - Mutations result in a change in ratio of 3R to 4R tau isoforms. Mutations affect the normal function of the tau protein to stabilise microtubules, increase the tendency of tau to form neurotoxic aggregates and disturb neuronal plasticity and axonal transport [80].

- Repeat expansion results in accumulation of transcripts harboring the expanded G4C2 repeat in nuclear RNA foci [70].

- Repeats expand and are expressed as three major transcripts, the expanded G4C2 ubiquitously expressed a family of ATPases complex with functions in degradation pathway.

- Encodes a component of the heteromeric ESCRT-III complex with functions in the growth factor precursor associated with the endosomal-lysosomal degradative pathway.

- A wide range of biological processes such as inflammation and wound repair, or in pathological conditions including tumorigenesis [82].

- Mutations reside at the interface between the N-domain of the D1 ATPase and all major brain regions. It is critical for development, sexual differentiation [88] and neuronal survival [89].
Frontotemporal dementia and Parkinsonism linked to chromosome 17

Missense or splice site mutations in Mapt gene cause FTDP-17

4R/3R Altered ratio

Clinical features of tauopathies

* Onset = <30 <50
* Duration <5 years  < 15
* First signs: Parkinsonism Dementia
* Personality change
* Language difficulties
* Eye movements abnormalities
* Epilepsy
* Myoclonus
* Pyramidal signs
* Amiotrophy
Clinical duration and clinical category of FTD is shown as a coloured bar in GRN mutation carriers (GRN positive), MAPT mutation carriers (MAPT positive) and wild-type GRN FTLD-U.

Most severely affected areas: frontal lobe, including motor cortex, supramarginal G.
The same mutation could be associated to different phenotypes i.e. MAPT P301S variability

- FTD phenotype and corticobasal degeneration in the same family (Bugiani et al 1999)
- Parkinsonism and epileptic seizures (Sparked, 1999)
- Parkinsonism followed by cognitive impairment (Kawamata, 2005)

onset 50.0±3.4
death 53.0±7.5

Memory impairment, troubles of language, disorientation, troubles of behaviour and personality, apathy, lack of personal and social awareness, delusions, hallucinations, psychomotor agitation, aggressivity and violence. Extrapyramidal signs rigidity, amimia, supraspinal signs. No tremor, Epilepsia, myoclonus
# 133546 Lives in Milan
Onset 46. Uninterested in home management, disinhibited. Insight absent. Frequent collapse, agitated, disoriented. After 6 yrs mutacic but able to sing old songs, echolalia, wandering. After 8 yrs completely mute, aggressive, bulimic, fatuous expression. Diagnosis FTD

#133548 Lives in Turin  onset 48. Language poor and stereotypic, childish, cognitive troubles (concentration, abstraction and planning deficits) but spatially oriented, insight absent. No delusions Diagnosis AD

onset 47.5±0.7
dead 55.5±6.4
* Haplotype analysis on families RB and Pul having the same MAPT mutation (Pro301Leu)

<table>
<thead>
<tr>
<th>Marker</th>
<th>Position</th>
<th>(RB Family)</th>
<th>(Pul. Family)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D17S951</td>
<td>(39 Mb)</td>
<td>1 3</td>
<td>4 5</td>
</tr>
<tr>
<td>D17S579</td>
<td>(40 Mb)</td>
<td>1 3</td>
<td>1 2</td>
</tr>
<tr>
<td>MAPT</td>
<td>(41 MB)</td>
<td>1 3</td>
<td>1 3</td>
</tr>
<tr>
<td>D17S920</td>
<td>(42 Mb)</td>
<td>1 3</td>
<td>1 1</td>
</tr>
<tr>
<td>D17S806</td>
<td>(43 Mb)</td>
<td>1 3</td>
<td></td>
</tr>
</tbody>
</table>

(D17S951) is different: it is possible that a single recombination event has occurred in this region.
Intrafamilial clinical variability in pathologically-proven Frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) caused by MAPT-P301L mutation.

Cupidi C. 1, AnfoM. 1, Colao R. 1, Puccio G. 1, Frangipane F. 1, Clodomiro A. 1, Conidi M.E. 1, Gallo M. 1, Bernardi L. 1, Curcio S.A.M. 1, Mirabelli M. 1, Smirne N. 1, Di Lorenzo R. 1, Maletta R. 1, Leotta A. 2, Lio S.G. 2, Bruni A.C. 1

1 Centro Regionale di Neurogenetica, ASP Catanzaro, Lamezia Terme
2 S.C. Anatomia e Iistologia Patologica e Citodiagnostica, ASP Catanzaro, Lamezia Terme

Tau-immunoreactive (AT8-ir) changes in the neuropil: neurofibrillary tangles (NFT) in the perikarya of neurons (Fig.5), Pick bodies (Fig.6), and meshwork of neuropil threads (Fig.7).

Significant tau-immunoreactivity in the glial cells in the form of coiled bodies in oligodendrocytes (Fig.8, AT8-ir; black arrow) and star-like tufted astrocytes (Fig.9, AT8-ir) with marked reactive astrogliosis in the neuropil and around vessel walls (Fig.10, GFAP-ir).

Spinal motoneurons were greatly involved (Fig.11, AT8-ir); in the cerebellum, rare NFT were present in the dentate nucleus (Fig.12, AT8-ir) but cerebellar hemispheres were spared.
A clinical pathological comparison of three families with frontotemporal dementia and identical mutations in the tau gene (*P301L*)

Thomas D. Bird,1,2,3,5 David Nochlin,4 Parvoneh Poorkaj,5 Monique Cherrier,6 Jeffrey Kaye,7 Haydeh Payami,7,8 Elaine Peskind,3,6 Thomas H. Lampe,3,5 Ellen Nemens,5 Philip J. Boyer,9 Gerard D. Schellenberg1,2,5

Summary

We investigated three separate families (designated D, F and G) with frontotemporal dementia that have the same molecular mutation in exon 10 of the tau gene (*P301L*). The families share many clinical characteristics, including behavioural aberrations, defective executive functions, language deficits, relatively preserved constructional abilities and frontotemporal atrophy on imaging studies. However, Family D has an earlier mean age of onset and shorter duration of disease than Families F and G (49.0 and 5.1 years versus 61–64 and 7.3–8.0 years, respectively). Two members of Families D and F had neuropathological studies demonstrating lobar atrophy, but the brain from Family D had prominent and diffuse circular, intraneuronal, neurofibrillary tangles not seen in Family F. The brain from Family F had ballooned neurons typical of Pick’s disease type B not found in Family D. A second autopsy from Family D showed neurofibrillary tangles in the brainstem with a distribution similar to that found in progressive supranuclear palsy. These three families demonstrate that a missense mutation in the exon 10 microtubule-binding domain of the tau protein gene can produce severe behavioural abnormalities with frontotemporal lobar atrophy and microscopic tau pathology. However, the findings in these families also emphasize that additional unidentified environmental and/or genetic factors must be producing important phenotypic variability on the background of an identical mutation. Apolipoprotein E genotype does not appear to be such a factor influencing age of onset in this disease.
Semantic dementia (SD) is a clinical subclassification of frontotemporal lobar degeneration. Patients with 'pure SD' present with semantic memory impairment preceding the frontal symptoms, and there have been no reports of familial cases.

Methods: We evaluated the clinical features of, and performed neuropsychological examinations on, the proband and two affected family members. Then we performed neuroimaging and genetic analysis of MAPT and other dementia-related genes in the proband.

Results: All three cases had semantic memory impairment with loss of word meanings as the primary early symptom. We diagnosed all cases as pure SD and identified a P301L mutation in the MAPT gene of the proband.

Conclusion: Although the P301L mutation identified here has been previously described as pathogenic for frontotemporal dementia with parkinsonism-17 (FTDP-17), the proband and his two affected relatives showed different clinical symptoms from those of typical FTDP-17 cases who carry the P301L mutation. Pathologically, pure SD usually shows a TAR DNA-binding protein proteinopathy, but the molecular understanding of SD is not well established. Although our cases were clinically pure SD, the proband has a tau gene mutation, which would lead to tauopathy. These findings suggest that reconsideration of the molecular understanding of SD is warranted.
Onset 56, she presented with hallucinations and progressive personality changes, became disinhibited with inappropriate jocularity; touching everything and everyone; stopping people on the road telling that she was seeing angels. At 56 she was untestable gradually progressed to complete mutism. Death occurred at 61
MAPT V363I mutation in a sporadic case of frontotemporal dementia
Phenotypes associated to +3 MSTD

Parkinsonism, frontal lobe signs.
Mutations in the *MAPT* gene

Compound heterozygosity of 2 novel *MAPT* mutations in frontotemporal dementia

Maria Anfossi\textsuperscript{a,1}, Romina Vuono\textsuperscript{b,1}, Raffaele Maletta\textsuperscript{a}, Kanwar Virdee\textsuperscript{c}, Maria Mirabelli\textsuperscript{a}, Rosanna Colao\textsuperscript{a}, Gianfranco Puccio\textsuperscript{a}, Livia Bernardi\textsuperscript{a}, Francesca Frangipane\textsuperscript{a}, Maura Gallo\textsuperscript{a}, Silvana Geracitano\textsuperscript{a}, Carmine Tomaino\textsuperscript{a}, Sabrina Anna Maria Curcio\textsuperscript{a}, Giuseppa Zannino\textsuperscript{d}, Francesco Lamenza\textsuperscript{d}, Charles Duyckaerts\textsuperscript{e}, Maria Grazia Spillantini\textsuperscript{c}, Maria Adele Losso\textsuperscript{b}, Amalia C. Bruni\textsuperscript{a,\#}  

\textsuperscript{a} Regional Neurogenetic Centre, ASP Catanzaro, Lamezia Terme (CS), Italy  
\textsuperscript{b} Department of Cell Biology, University of Calabria, Arcavacata di Rende CS, Italy  
\textsuperscript{c} Department of Clinical Neurosciences, Brain Repair Centre, University of Cambridge, Cambridge, UK  
\textsuperscript{d} Geriatric Unit ASP Cosenza Rossano (CS), Italy
Brain weighted 650 gr. Massive atrophy of the frontal temporal lobes with relative sparing of Rolandic and calcarine regions.

Severe atrophy of the caudate nucleus and of white matter (fig 2). Hippocampus was destroyed (fig 3, H&E).
Morphological aspect of tau labelling:
A: Neurofibrillary tangles (arrow) immunolabelled by antibody against 3R tau.
B: Pick body like inclusion stained by a polyclonal antitau antibody.
C: Astrocytic inclusion
D: Coiled body in the white matter
E and F: comparison of the same region immunolabelled by an antibody against 3R Tau (E) and against 4R Tau (F).
3R labels tangles (black arrow); a perinuclear ring is sometimes also visible. The immunolabelling obtained with 4R tau is weak or absent.
*Proband’s pedigree*
Brain tissue

Bands corresponding to the 3R transcripts are much stronger than 4R

In vitro

3R/4R ratio altered in II-1

Patient’s parents (I-1; I-2)
Brain Tissue Study

**Tau Analysis**

*Immunoblot analysis of Sarkosyl-insoluble tau: detection of increased levels of 3RTau isoforms*

**Index Brain AD**

- BR134
- AT8
- AT100
- 12E8

Pick bodies are negative for 12E8

BR134: phosphorylation-independent anti-tau antibody
AT8, AT100 e12E8: phosphorylation-dependent antibodies
Tau Analysis

**Immunoblot analysis of soluble tau:**
detection of increased levels of 3RTau isoforms

Index brain

AD brain

\[ \lambda \text{PPase} \]

BR134

BR134

4R2N → 3R2N → 4R1N → 3R1N → 4R0N → 3R0N

Brain Tissue Study
Generally intronic mutations affecting tau splicing leads to 4Rtau

In our case the increase of 3R0N is probably caused by the interaction of the two mutations with unknown mechanisms (other splicing factors?)

This compound heterozygous case reinforces the notion that sporadic cases can be caused by genetic mutations
* Onset 46. Progressive personality changes, memory loss, strong reduction of verbal fluency evolving to complete mutism,
* behavioural stereotypies, episodic myoclonus, urinary incontinence, hyperorality.
* No amyotrophy. Death at 57.
Morphological aspect of tau labelling:
A: Neurofibrillary tangles (arrow) immunolabelled by antibody against 3 R tau.
B: Pick body like inclusion stained by a polyclonal antitau antibody.
C: Astrocytic inclusion
D: Coiled body in the white matter
E and F: comparison of the same region immunolabelled by an antibody against 3R Tau (E) and against 4R Tau (F).
3R labels tangles (black arrow); a perinuclear ring is sometimes also visible. The immunolabelling obtained with 4R tau is weak or absent.

Scale bar = 20 µm for all pictures.
Onset 56, she presented with hallucinations and progressive personality changes, became disinhibited with inappropriate jocularity; touching everything and everyone; stopping people on the road telling that she was seeing angels. At 56 she was untestable gradually progressed to complete mutism. Death occurred at 61
MAPT V363I mutation in a sporadic case of frontotemporal dementia
The profile of main genes mutation and its possible disease mechanisms in FTLD

<table>
<thead>
<tr>
<th>gene symbol</th>
<th>MAPT</th>
<th>C9ORF72</th>
<th>PGRN</th>
<th>VCP</th>
<th>CHMP2B</th>
</tr>
</thead>
<tbody>
<tr>
<td>full name</td>
<td>microtubule-associated protein tau</td>
<td>chromosome 9 open reading frame 72</td>
<td>progranulin</td>
<td>callosin containing protein</td>
<td>chromatin modifying protein 2B</td>
</tr>
<tr>
<td>chromosomal localization</td>
<td>17q21.32</td>
<td>9p21.2</td>
<td>17q21.32</td>
<td>9p13.3</td>
<td>3p11.2</td>
</tr>
</tbody>
</table>

- **MAPT** gives rise to six isoforms: three isoforms containing three amino-acid repeats (3R), and three isoforms with four repeats (4R) [79].
- **C9ORF72** is ubiquitously expressed as three major transcripts, the expanded G4C2 repeat is located in the proximal regulatory region of C9ORF72 [70, 73].
- **PGRN** is expressed as progranulin, a ubiquitously expressed member of the heteromeric ESCRT-III family of ATPases complex with functions in growth factor precursor processing and the endosomal-lysosomal degradation pathway.

**Functions and possible role in the disease mechanism**

- Mutations result in a change in ratio of 3R to 4R tau isoforms. Mutations affect the normal function of the tau protein to stabilise near complete loss of the major tau phosphorylation sites such as inflammation, neuronal plasticity and axonal transport [80].
- Repeat expansion results in neurotoxic aggregates and disturb accumulation of transcripts harboring the expanded G4C2 repeat in nuclear RNA foci [70].
- Mutations reside at the interface between the D1 ATPase and all major brain regions. It is critical for development, sexual differentiation [88] and neuronal survival [89].
Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17

Matt Baker¹, Ian R. Mackenzie², Stuart M. Pickering-Brown⁵,⁶, Jennifer Gass¹, Rosa Rademakers¹; Caroline Lindholm³, Julie Snowden⁶, Jennifer Adamson¹, A. Dessa Sadovnick³,⁴, Sara Rollinson⁸, Ashley Cannon¹, Emily Dwosh¹, David Neary⁶, Stacey Melquist¹, Anna Richardson⁶, Dennis Dickson¹, Zdenek Berger¹, Jason Eriksen¹, Todd Robinson¹, Cynthia Zehr¹, Chad A. Dickey¹, Richard Crook¹, Eileen McGowan¹, David Mann⁶, Bradley Boeve⁷, Howard Feldman⁵ & Mike Hutton¹

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

Marc Cruts¹,²,⁵, Ilse Gijselinck¹,²,⁵, Julie van der Zee¹,²,⁵, Sebastiaan Engelborghs³,⁵,⁶, Hans Wils¹,²,⁵, Daniel Pirici¹,²,⁵, Rosa Rademakers¹,²,⁵, Rik Vandenberghé¹, Bart Dermaut⁹, Jean-Jacques Martin⁴,⁵, Cornelia van Duijn¹⁰, Karin Peeters¹,²,⁵, Raf Scirot⁸, Patrick Santens⁹, Tim De Pooter¹,²,⁵, Maria Mattheijssens¹,²,⁵, Marleen Van den Broeck¹,²,⁵, Ivy Cuijt¹,²,⁵, Krist¹ Vennekens¹,²,⁵, Peter P. De Deyn³,⁵,⁶, Samir Kumar-Singh¹,²,⁵ & Christine Van Broeckhoven¹,²,⁵
PGRN GENE

- PGRN is widely expressed and implicated in many processes, such as development, tumor proliferation, wound healing, inflammation.
- In peripheral tissues PGRN cleavage is ensured by elastase into several GRNs which probably have separate functions.....
- Promotes also neuronal survival and enhances neurite outgrowth in cultured neurons.

Pathogenic mechanism
Haploinsufficiency

Mutations cause a premature termination Codon that leads to nonsense –mediated mRNA decay.

This functionally NULL ALLELE reduces PGRN expression by 50%

Low plasma progranulin levels predict progranulin mutations in frontotemporal lobar degeneration

Neurology © 2008; 71:1-1

Bhandari et al., 1993; Daniel et al., 2000; Bateman and Bennett, 1998; He and Bateman, 2003; Ahmed et al., 2007
PGRN is NOT incorporated into UBI+ inclusions in FTLD-Ubi

cause PGRN is not incorporated into UBIs in FTDP-17U (11, 12), the FTLD-U disease protein
Mutations in the progranulin gene (PGRN), on chromosome 17q21, have been identified as a major cause of familial frontotemporal dementia (FTD). These cases have a characteristic pattern of neuropathology that is a distinct subtype of frontotemporal lobar degeneration with ubiquitinated inclusions (FTLD-U). There is no abnormal accumulation of PGRN protein in the brain and immunohistochemical and biochemical analysis indicates that the ubiquitinated pathological protein is TDP-43.

The neuropathology and clinical phenotype of FTD with progranulin mutations
Nuclear protein involved with the regulation of DNA expression NORMALLY contained in the nucleus, in diseased neurones leaves the nucleus and accumulates in cellular bodies.

*TDP-43

Permission from G. Giaccone
Epidemiology and clinic of PGRN

- USA/UK/France studies. PGRN mutation prevalence:
  5-11% in sporadic cases
  13-25% in familial cases

- Clinical endophenotypes:
  behavioural disturbances, language deficit and parkinsonism, then (less frequent FTD-MND). PNFA, CBDS, fvFTD (non PSP!)
* Progranulin mutations
Clinical duration and clinical category of FTD is shown as a coloured bar in GRN mutation carriers (GRN-positive), MAPT mutation carriers (MAPT-positive) and wild-type GRN FTLD-U.
## Mutations in progranulin (GRN) within the spectrum of clinical and pathological phenotypes of frontotemporal dementia

**Table: Demographic, clinical, and pathological features of hereditary FTD with MAPT, VCP, CHMP2B, GRN gene mutations, and FTD and motor neuron disease linked chromosome 9**

<table>
<thead>
<tr>
<th>Hereditary FTD variant</th>
<th>Prevalence in FTD</th>
<th>Number of mutations</th>
<th>Age at onset (years)</th>
<th>Clinical presentation</th>
<th>Neuropathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAPT mutations</td>
<td>5-15%</td>
<td>&gt;40</td>
<td>25-65</td>
<td>Behavioural changes, cognitive dysfunction, and parkinsonism (progressive supranuclear palsy, corticobasal syndrome)</td>
<td>Neuronal and glial tau-positive inclusions</td>
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<tr>
<td>VCP mutations</td>
<td>Rare</td>
<td>8</td>
<td>48-65</td>
<td>Inclusion body myositis, Paget’s disease, behavioural changes, and cognitive dysfunction</td>
<td>Ubiquitin-positive and TARDBP-positive NII and dystrophic neurites</td>
</tr>
<tr>
<td>CHMP2B mutation</td>
<td>Rare</td>
<td>5</td>
<td>&gt;50</td>
<td>Behavioural changes, cognitive dysfunction, extrapyramidal features, and motor neuron disease</td>
<td>Ubiquitin-positive, p62-positive and TARBP-negative NCI</td>
</tr>
<tr>
<td>GRN mutations</td>
<td>&gt;5-15%</td>
<td>&gt;50</td>
<td>35-89</td>
<td>FTD, Alzheimer’s disease, corticobasal syndrome, and parkinsonism</td>
<td>Ubiquitin-positive, TARDBP-positive NCI, NII, and dystrophic neurites</td>
</tr>
<tr>
<td>Chromosome 9-linked FTD</td>
<td>Unknown</td>
<td>Unknown</td>
<td>39-72</td>
<td>Motor neuron disease, behavioural changes, and cognitive dysfunction</td>
<td>Ubiquitin-positive, TARDBP-positive NCI, and glial inclusions</td>
</tr>
</tbody>
</table>

FTD= frontotemporal dementia. NCI = neuronal cytoplasmic inclusions. NII = neuronal intranuclear inclusions.
Novel PSEN1 and PGRN mutations in early-onset familial frontotemporal dementia

Livia Bernardi, Carmine Tomaino, Maria Anfossi, Maura Gallo, Silvana Geracitano, Angela Costanzo, Rosanna Colao, Gianfranco Puccio, Francesca Frangipane, Sabrina A.M. Curcio, Maria Mirabelli, Nicoletta Smirne, David Iapaolo, Raffaele Giovanni Maletta, Amalia C. Bruni

Onset 61 Playful and moriatic, alteration of eating behavior. Within 3 yrs apathetic, reduction of verbal fluency. At 69 mute, incontinent, completely dependent.

Fig. 1. Chromatograms of part of exon 5 of the PGRN gene showing the Cys139Arg mutation: (A) w.t. sequence and (B) mutated sequence.
* mutazione GRN – CYS139ARG

**Legenda:**
- / soggetti deceduti
- ■ ■ soggetti affetti da Demenza di Alzheimer
- ■ soggetti affetti da infarto del miocardio
- ◦ soggetto affetto da afasia primaria progressiva evoluta in demenza, infarto del miocardio e vasculopatia
- ◼ soggetto affetto da vasculopatia cerebrale
Association of the Variant Cys139Arg at GRN Gene to the Clinical Spectrum of Frontotemporal Lobar Degeneration

Irene Piaceri\textsuperscript{a}, Silvia Pradella\textsuperscript{a}, Chiara Cupidi\textsuperscript{b}, Serena Nannucci\textsuperscript{a}, Cristina Polito\textsuperscript{c}, Silvia Bagnoli\textsuperscript{a}, Andrea Tedde\textsuperscript{a}, Nicoletta Smirne\textsuperscript{b}, Maria Anfossi\textsuperscript{b}, Maura Gallo\textsuperscript{b}, Livia Bernardi\textsuperscript{b}, Rosanna Colao\textsuperscript{b}, Raffaele Maletta\textsuperscript{b}, Amalia Cecilia Bruni\textsuperscript{b}, Sandro Sorbi\textsuperscript{a} and Benedetta Nacmias\textsuperscript{a,}\textsuperscript{*}

\textsuperscript{a}Department of Neuroscience, Psychology, Drug Research and Child Health (NEUROFARBA), University of Florence, Florence, Italy

\textsuperscript{b}Centro Regionale di Neurogenetica, ASP Catanzaro, Lamezia Terme (CZ), Italy

\textsuperscript{c}Department of Clinical Pathophysiology, Nuclear Medicine Division, University of Florence, Florence, Italy

Handling Associate Editor: Daniela Galimberti

Table 1
Characteristics of FTLD patients carrying the Cys139Arg genetic variant

<table>
<thead>
<tr>
<th>ID Patient</th>
<th>Gender</th>
<th>Age at onset Y</th>
<th>Current age or age at death\textsuperscript{*}, Y</th>
<th>Goldman score</th>
<th>Clinical diagnosis</th>
<th>Parkinsonism</th>
<th>Symptom at onset</th>
<th>PGRN plasma level (ng/ml)</th>
<th>APOE</th>
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</thead>
<tbody>
<tr>
<td>TM1</td>
<td>F</td>
<td>55</td>
<td>59</td>
<td>4</td>
<td>Behavioral FTD</td>
<td>No</td>
<td>Memory</td>
<td>110.2</td>
<td>3/3</td>
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<tr>
<td>CI2</td>
<td>F</td>
<td>78</td>
<td>83</td>
<td>3.5</td>
<td>Semantic dementia</td>
<td>Yes</td>
<td>Language</td>
<td>97.5</td>
<td>3/3</td>
</tr>
<tr>
<td>LT3</td>
<td>M</td>
<td>80</td>
<td>87\textsuperscript{*}</td>
<td>1</td>
<td>Corticobasal syndrome</td>
<td>Yes</td>
<td>Memory</td>
<td>81.0</td>
<td>3/4</td>
</tr>
</tbody>
</table>

PGRN, progranulin protein; APOE, Apolipoprotein E
Fig. 1. Pedigree and magnetic resonance imaging (MRI) for each studied patient carrying Cys139Arg. A) Pedigree and MRI of the Patient 1 (T1). The pedigree showed absence of family history, Goldman Score: 4. Brain MRI showed white matter subcortical abnormalities with frontal atrophy. B) Pedigree and MRI of the Patient 2 (C12). The pedigree showed a family history of late-onset dementia, Goldman Score: 3.5. Brain MRI showed atrophy in the left tempo-polar and tempo-parietal areas. C) Pedigree and MRI of the Patient 3 (LT3). The pedigree of the family showed a clear family history of dementia, Goldman score: 1. Brain MRI showed diffuse cortical fronto-temporo-parietal atrophy with slight asymmetry. Arrows in the pedigrees showed probands.
A large Calabrian kindred segregating frontotemporal dementia

Biv... Family

τ negative – Chrom 3 and 9 (linkage) negative

onset 63.8 ±11.6 (40-78)
death 67.0 ±10.5 (44-80)
Symptoms in the first year

- Apathy
- Lack of critic and judgment
- Loss of personal insight
- Loss of social rules
- Disinhibition
Symptoms in the second year

- Stereotipie e perseverazioni: 8
- Incapacità di astrazione: 10
- Deficit attenzione: 10
- Rid. iniziativa verbale: 11

Pazienti
Mean onset 65.1 ± 17.1 (35-87)

APOE, tau, or TMEM106B genotypes do not modify the age-at-onset in carriers of the mutation
Epidemiology and genetics of frontotemporal dementia: a door-to-door survey in Southern Italy

Livia Bernardi, Francesca Frangipane, Nicoletta Smirne, Rosanna Colao, Gianfranco Puccio, Sabrina A.M. Curcio, Maria Mirabelli, Raffaele Maletta, Maria Anfossi, Maura Gallo, Silvana Geracitano, Maria Elena Conidi, Raffale Di Lorenzo, Alessandra Clodomiro, Chiara Cupidi, Sandra Marzano, Francesco Comito, Vincenzo Valenti, Maria Angela Zirilli, Mahdi Ghanì, Zhengrui Xi, Christine Sato, Danielle Moreno, Annelisa Borelli, Rosa Anna Leone, Peter St. George-Hyslop, Ekaterina Rogaeva, Amalia C. Bruni.
**Population >50 yrs**

702 individuals

- Questionnaire for demographic and social data (WHO-QOL)
- Anamnestic record compiled by family physician
- MMSE, ADL, IADL, verbal fluency (phonological and for categories)
- Biochemistry; DNA analyses

*Door to door survey*
* 92 subjects selected for II step

29 soggetti con demenza
<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Men</th>
<th>Women</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Dementia</td>
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<tr>
<td>50-59</td>
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<tr>
<td>60-69</td>
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<td>1</td>
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<tr>
<td>70-79</td>
<td>8</td>
<td>10.0</td>
<td>9</td>
</tr>
<tr>
<td>80-89</td>
<td>4</td>
<td>8.3</td>
<td>6</td>
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<tr>
<td>90-99</td>
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<tr>
<td>Total</td>
<td>12</td>
<td>5.3</td>
<td>17</td>
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<tr>
<td>Age (yrs)</td>
<td>Frontotemporal dementia</td>
<td>Alzheimer</td>
<td>Vascular dementia</td>
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<td></td>
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<td>90-99</td>
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<tr>
<td>Total</td>
<td>5</td>
<td>11</td>
<td>16</td>
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<td>Total &gt;50 yrs</td>
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<tr>
<td>Total &gt;50 yrs</td>
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</tbody>
</table>
FTD patients identified through the door to door survey

**Prevalence**

- 55.2% of dementing patients has FTD
- Prevalence rate of FTD is 3.1%
- FTD is twofold common in females than males (11/5)

<table>
<thead>
<tr>
<th>FTD patients</th>
<th>P6RN</th>
<th>Gender</th>
<th>Education (yrs)</th>
<th>Age</th>
<th>Onset</th>
<th>Duration at 1st examination</th>
<th>Family history</th>
<th>CT/MRI/SPECT</th>
<th>Loss of insight</th>
<th>Memory impairment</th>
<th>Disinhibition</th>
<th>Reduction of verbal output</th>
<th>Irritability</th>
<th>Perseveration</th>
<th>Apathy</th>
<th>Pyramidal signs</th>
<th>Extrapyramidal signs</th>
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<tr>
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<td>-</td>
</tr>
<tr>
<td>15</td>
<td>-</td>
<td>F</td>
<td>4</td>
<td>93</td>
<td>90</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>-</td>
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<td>-</td>
<td>F</td>
<td>0</td>
<td>72</td>
<td>72</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
</tbody>
</table>

Total: 2/16, 11F/5M, 2.8, 79.4, 76.6, 2.9, 7/16, 8/16
*PGRN mutations phenotypes*

**Mutazione INS**
Media ± Ds 64.3 ± 14.3
Range 35-87

Quadro clinico «comportamentale»
- Disinibizione
- Perdita della consapevolezza sociale
- Distraibilità
- Perdita del linguaggio fino al mutismo

**Mutazione ALA**
Media ± Ds 76 ± 2.9
Range 76-79

Quadro clinico «affettivo»
- Apatia
- Indifferenza emotiva e affettiva
- Riduzione del linguaggio ma mai perdita

**Mutazione CYS**
Età di esordio 65-77

Quadro clinico «delirante»
- Deliri paranoidei
- Disinibizione
- Agitazione
* c.1145insA

phenocopy
Nell’area studiata la prevalenza delle demenze è uguale a quella in tutte le parti del mondo (6%)
Tuttavia….  
La demenza frontotemporale ha una prevalenza altissima e mai riscontrata in altri parti del mondo.

Circa la metà dei casi identificati ha una causa genetica
Le mutazioni identificate causano la stessa malattia ma con varianti cliniche. Una stessa mutazione da origine a casi con esordio a 50 anni e altri con esordio ad 87!
La Malattia di Alzheimer è “praticamente assente” e non abbiamo spiegazione per questo fenomeno
• Questi risultati sono causati da un ambiente particolare???

• O da un substrato genetico ancora diverso?

* O da interazione geni ambiente???
*Programmi futuri*

Studiare gli effetti di geni e ambiente.

1) Censire i Bivongesi emigrati
2) Identificare soggetti affetti da demenza in fase conclamata o iniziale e diagnosticare la tipologia
3) Studio genetico molecolare
La ricerca scientifica su Bivongi
tra presente e futuro:
oggi in Calabria, domani nel mondo.

Amalta C. Bruni
Direttore Centro Regionale di Neurogenetica
Lamezia Terme
Azienda Sanitaria Provinciale di Catanzaro

Centro Culturale Bivongesi
calle 63 n. 1563 - La Plata.

20 marzo ore 20.00.
'Tangles' and 'neuropile threads', visualised by silver staining and antitau; better with ubiquitin immunoreactivity. No plaques.
Bag. Family

- Probable FTD
- SLA
- FTD - SLA
- Parkinson

Onset 49-55

+87
+51
+72
*Famiglie con SLA e FTD*

GENI IDENTIFICATI

VCP- CHPM2B – TDP – FUS - C9ORF72

ALS - Dementia

3-10% Ubi+ve Inclusions in dentate G. & Cortex

Ubi+ve Inclusions

ALS

Dementia
Fig. 1 | ALS-FTLD genes plotted to show phenotype, year of discovery and importance gauged by research outputs. The $X$ axis is a score representing the involvement of each gene in ALS or FTLD (−4 being FTLD, 0 being ALS-FTD, and +4 ALS/MND based on evidence from the ALSoD database (http://alsod.iop.kcl.ac.uk), PubMed, peer-reviewed publications and case studies. The $Y$ axis represents year of mutation identification. The circle size represents the level of research on each gene scaled by the logarithm of the number of articles from PubMed retrieved by the search command ‘((GENE>[Title/Abstract]) AND amyotrophic lateral sclerosis[Title/Abstract]) AND frontotemporal dementia[Title/Abstract]) AND genetics[MeSH Subheading]’
Non solo in casi ereditari!!!
Kaivorrine et al 2013
**Table 1.** Summary of demographic and clinical characteristics of patients with C9ORF72 repeat expansion

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Clinical diagnosis</th>
<th>FTLD subtype</th>
<th>ALS onset</th>
<th>Family history</th>
<th>Age at onset, years</th>
<th>Age, years</th>
<th>Duration, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>FTLD</td>
<td>bvFTD</td>
<td>–</td>
<td>No</td>
<td>58</td>
<td>–</td>
<td>64 (current)</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>FTLD</td>
<td>bvFTD</td>
<td>–</td>
<td>Yes</td>
<td>57</td>
<td>–</td>
<td>62 (current)</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>FTLD</td>
<td>bvFTD</td>
<td>–</td>
<td>Yes</td>
<td>64</td>
<td>–</td>
<td>75 (current)</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>FTLD</td>
<td>bvFTD</td>
<td>–</td>
<td>Yes, Yes</td>
<td>60</td>
<td>–</td>
<td>72 (current)</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>FTLD</td>
<td>bvFTD</td>
<td>–</td>
<td>Yes, No</td>
<td>54</td>
<td>–</td>
<td>66 (current)</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>FTLD</td>
<td>bvFTD</td>
<td>–</td>
<td>Yes</td>
<td>47</td>
<td>–</td>
<td>53 (current)</td>
</tr>
<tr>
<td>7</td>
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<td>FTLD</td>
<td>bvFTD</td>
<td>–</td>
<td>No</td>
<td>51</td>
<td>–</td>
<td>54 (current)</td>
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<tr>
<td>8</td>
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<td>FTLD</td>
<td>bvFTD</td>
<td>–</td>
<td>Yes</td>
<td>55</td>
<td>–</td>
<td>60 (current)</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>FTLD</td>
<td>bvFTD</td>
<td>–</td>
<td>Yes</td>
<td>54</td>
<td>–</td>
<td>60 (current)</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>FTLD</td>
<td>bvFTD</td>
<td>–</td>
<td>No</td>
<td>46</td>
<td>–</td>
<td>49 (current)</td>
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<tr>
<td>11</td>
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<td>bvFTD</td>
<td>–</td>
<td>Yes, No</td>
<td>59</td>
<td>–</td>
<td>63 (current)</td>
</tr>
<tr>
<td>12</td>
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<td>bvFTD</td>
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<td>64</td>
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<td>FTLD</td>
<td>PNFA</td>
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<td>60</td>
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<td>71 (at death)</td>
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<tr>
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<td>–</td>
<td>No</td>
<td>51</td>
<td>–</td>
<td>70 (current)</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>FTLD</td>
<td>PNFA</td>
<td>–</td>
<td>No</td>
<td>64</td>
<td>–</td>
<td>71 (at death)</td>
</tr>
<tr>
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<td>F</td>
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<td>PNFA</td>
<td>–</td>
<td>Yes, No</td>
<td>63</td>
<td>–</td>
<td>72 (at death)</td>
</tr>
<tr>
<td>17</td>
<td>F</td>
<td>FTLD-ALS</td>
<td>bvFTD</td>
<td>bulbar</td>
<td>No, No</td>
<td>59</td>
<td>60</td>
<td>62 (at death)</td>
</tr>
<tr>
<td>18</td>
<td>F</td>
<td>FTLD-ALS</td>
<td>PNFA</td>
<td>bulbar</td>
<td>No, Yes</td>
<td>54</td>
<td>55</td>
<td>58 (at death)</td>
</tr>
<tr>
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<td>PNFA</td>
<td>bulbar</td>
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<td>70</td>
<td>70</td>
<td>71 (at death)</td>
</tr>
<tr>
<td>20</td>
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<td>bvFTD</td>
<td>bulbar</td>
<td>No, No</td>
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<td>57</td>
<td>60 (at death)</td>
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<td>21</td>
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<td>bvFTD</td>
<td>spinal</td>
<td>Yes, No</td>
<td>60</td>
<td>60</td>
<td>63 (at death)</td>
</tr>
<tr>
<td>22</td>
<td>F</td>
<td>FTLD-ALS</td>
<td>bvFTD</td>
<td>bulbar</td>
<td>Yes, No</td>
<td>66</td>
<td>66</td>
<td>69 (at death)</td>
</tr>
</tbody>
</table>
Zhengrui Xi, PhD; Lorne Zinman, MD; Yakov Grinberg, PhD; Danielle Moreno, BSc; Christine Sato, MSc; Juan M. Bilbao, MD; Mahdi Ghani, MD; Isabel Hernández, MD; Agustín Ruiz, MD, PhD; Mercè Boada, MD, PhD; Francisco J. Morón, PhD; Anthony E. Lang, MD; Connie Marras, MD, PhD; Amalia Bruni, MD; Rosanna Colao, MD; Raffaele G. Maletta, MD; Gianfranco Puccio, MD; Innocenzo Rainero, MD, PhD; Lorenzo Pinessi, MD; Daniela Galimberti, PhD; Karen E. Morrison, PhD; Catriona Moorby, BSc; Joanne D. Stockton, BSc; Mario Masellis, MD; Sandra E. Black, MD; Lili-Naz Hazrati, MD; Yan Liang, MD; Jan van Haersma de With, BSc; Luis Fornazzari, MD; Roque Villagra, MD; Ricardo Rojas-García, MD, PhD; Jordi Clarimon, PhD; Richard Mayeux, MD; Janice Robertson, PhD; Peter St George-Hyslop, MD, FRCP(C); Ekaterina Rogaeva, PhD

Table 1. Sample Characteristics, Including Expansion Carriers Identified in Each Cohort

<table>
<thead>
<tr>
<th>Cohort</th>
<th>All Samples, No. (%)</th>
<th>No. of Expansion Carriers</th>
<th>Frequency of Expansion, %</th>
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<td>ALS</td>
<td>389</td>
<td>47</td>
<td>9.3</td>
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<td>Female 149 (38.3)</td>
<td>36</td>
<td>38.3</td>
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<td>Total 389</td>
<td>47</td>
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</tr>
<tr>
<td></td>
<td>Familial 47</td>
<td>18</td>
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</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>FTLD</td>
<td>520</td>
<td>211</td>
<td>5.2</td>
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<tr>
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<td>Female 258 (49.6)</td>
<td>27</td>
<td>10.4</td>
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<tr>
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<td>Total 520</td>
<td>211</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Familial 211</td>
<td>22</td>
<td></td>
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<tr>
<td></td>
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<tr>
<td>AD</td>
<td>424</td>
<td>167</td>
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</tr>
<tr>
<td></td>
<td>Female 264 (62.3)</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total 424</td>
<td>167</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Familial 167</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PD</td>
<td>289</td>
<td>116</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female 92 (31.8)</td>
<td>2</td>
<td>0.7</td>
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<tr>
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<td>Total 289</td>
<td>116</td>
<td>0.9</td>
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<tr>
<td></td>
<td>Familial 116</td>
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<td></td>
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<tr>
<td>Controls</td>
<td>602</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female 357 (59.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total 602</td>
<td></td>
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</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; ALS, amyotrophic lateral sclerosis;
Original Article

C9ORF72 repeat expansions and other FTD gene mutations in a clinical AD patient series from Mayo Clinic

Aleksandra Wojtas¹, Kristin A Heggeli², Nicole Finch¹, Matt Baker¹, Mariely DeJesus-Hernandez¹, Steven G Younkin¹, Dennis W Dickson¹, Neill R Graff-Radford², Rosa Rademakers¹

Figure 2. C9ORF72 repeat-primed PCR assay in clinical AD patients. PCR products of C9ORF72 repeat-primed PCR reactions separated on an ABI3730 DNA Analyzer and visualized by GENEMAPPER software. Electropherograms are zoomed to 4,000 relative fluorescence units to show stutter amplification. The two clinical AD patients with expanded repeats (7391 and 9979) and one non-carrier (15077) are shown. Note the strong amplification in patient 7391 around ~470bp, suggesting a large proportion of cells carrying approximately 60 GGGGCC repeats, in addition to a smaller population of cells carrying longer repeat expansions.
‘Tangles’ and ‘neuropile threads’, visualised by silver staining and antitau; better with ubiquitin immunoreactivity. No plaques.
* Inclusioni Ubi+ p62+ in corteccia, ippocampo e cervelletto
Degenerazione neurofibrillare tau+

Placche e depositi di Abeta proteina
Hippocampal sclerosis dementia with the C9ORF72 hexanucleotide repeat expansion.

Frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) are the main syndromes of the chromosome 9 ORF72 (C9ORF72)….studies have shown a substantial phenotypic diversity that includes psychiatric presentations. This study describes hippocampal sclerosis dementia (HSD) in carriers of the C9ORF72 mutation. We compared clinical and neuropathological features of HSD in carriers and noncarriers autopsied at Johns Hopkins. Carriers presented with amnesia, agitation, dissociative behavior, and impaired self-care, whereas noncarriers showed little agitation.

Neuropathological examination of carriers showed cerebellar neuronal inclusions positive for ubiquitin, p62, and ubiquilin-2, and negative for TAR DNA-binding protein 43. Noncarriers did not have cerebellar inclusions. C9ORF72 repeat-associated non-ATG translation was confirmed by immunohistochemistry. These observations broaden the C9ORF72 phenotype and place HSD in the FTD spectrum. The amnesic phenotype of HSD, which is consistent with the focal hippocampal atrophy, should be included in clinical categorizations of FTD.

Pletnikova O¹, et al 2014

Expanded C9ORF72 Hexanucleotide Repeat in Depressive Pseudodementia

Kevin F. Bieniek, BSc; Marka van Blitterswijk, MD, PhD; Matthew C. Baker, BSc; Leonard Petrucelli, PhD; Rosa Rademakers, PhD; Dennis W. Dickson, MD

**IMPORTANCE** Expanded hexanucleotide repeats in C9ORF72 are a common genetic cause of frontotemporal dementia and amyotrophic lateral sclerosis. Repeat expansions have also been detected infrequently in other disorders, including Alzheimer disease, dementia with Lewy bodies, and parkinsonian disorders.

**OBSERVATIONS** A consecutive series of 31 cases from the brain bank for neurodegenerative disorders at Mayo Clinic was screened to assess the incidence of the expanded C9ORF72 repeat in cases of depressive pseudodementia. The presence of the hexanucleotide repeat was established using immunohistochemistry with a highly disease-specific antibody (C9RANT), and was further validated in carriers using repeat-primed polymerase chain reaction and Southern blotting. Two individuals harbored the C9ORF72 repeat expansion. Both patients were men with refractory depression. One patient experienced drug-induced parkinsonism and sudden-onset dementia, while the other patient had a more insidious disease course suspected to be Alzheimer disease.

**CONCLUSIONS AND RELEVANCE** This report increases the range of clinicopathologic presentations of C9ORF72 expanded hexanucleotide repeat to include psychiatric disorders such as depressive pseudodementia.

JAMA Neurol. doi:10.1001/jamaneurol.2013.6368
Published online April 21, 2014.

* Schizophrenia or neurodegenerative disease prodrome? Outcome of a first psychotic episode in a 35-year-old woman. Khan BK et al.
Psychosis and hallucinations in frontotemporal dementia with the C9ORF72 mutation: a detailed clinical cohort.

To specify the presenting symptoms and clinical course of patients with frontotemporal dementia (FTD) and chromosome 9 open reading frame 72 (C9ORF72) repeat expansion.

BACKGROUND:
………Prior reports identified a subset of patients with FTD who had an unusually high prevalence of psychosis, although their specific symptoms had not yet been fully described.

METHODS:
From a cohort of 62 patients with FTD, we conducted a retrospective chart review of 7 patients who had C9ORF72 mutations on genetic testing, and 1 untested sibling of a C9ORF72 carrier.

RESULTS:
Detailed histories revealed a higher prevalence of psychosis, including visual and auditory hallucinations and delusions, in the 8 C9ORF72 carriers than in our patients with sporadic FTD.

CONCLUSIONS:
This cohort confirms and adds clinical details to the reports of a high prevalence of psychotic phenomena in patients who have C9ORF72 mutations as well as FTD or amyotrophic lateral sclerosis

Kertesz A¹
Cogn Behav Neurol. 2013 Sep;26(3):146-54. doi: 10.1097/WNN.0000000000000008
C9ORF72 expansion in a family with bipolar disorder.
Meisler et al 2013
Figure 1 | Proposed molecular diagnostics on the basis of clinical phenotype and pattern of brain atrophy. *Other genes: genetic screening of either TAR DNA-binding protein 43 (TARDBP) or fused in sarcoma (FUS) genes should be considered. Abbreviations: avPPA, agrammatic variant of primary progressive aphasia; bvFTD, behavioural variant frontotemporal dementia; CBS, corticobasal syndrome; FTD–MND, frontotemporal dementia with motor neuron disease; GRN, granulin; MA2TP, microtubule-associated protein tau; PSP, progressive supranuclear palsy; svPPA, semantic variant of primary progressive aphasia.

a 2-stage GWAS analyzing a total of 3,526 FTD cases and 12,538 controls with the aim of identifying common/novel loci associated with the disease
Gruppo di Lavoro
Demenza Frontotemporale
FTD - Italian Network

n° 87 centri coinvolti
87 Questionari analizzati
113 Professionisti coinvolti
La migliore conoscenza ed individuazione Della FTD ci permetterà sempre meglio di comprenderne i meccanismi patogenetici, di individuare terapie adeguate e percorsi Assistenziali specifici.
* Comune di Bivongi
(Sindaci Valenti- Riggio)
* Sandra Marzano
* Francesco Comito
* Enzo Valenti
* Maria Angela Zirilli
* Il Centro Bivongesi di La Plata
Centro Regionale NEUROGENETICA
CRN – Drs
CRN – Psychologists
* CRN – Lab
*CRN - Data Management*
* CRN – Social Services, Administration and Nurse
* CRN – Reception and Front/Back Office
Last but... not least !!!