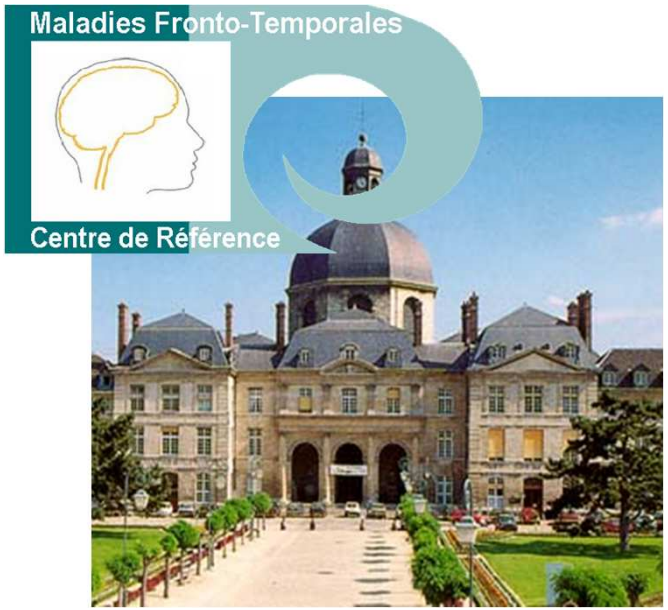
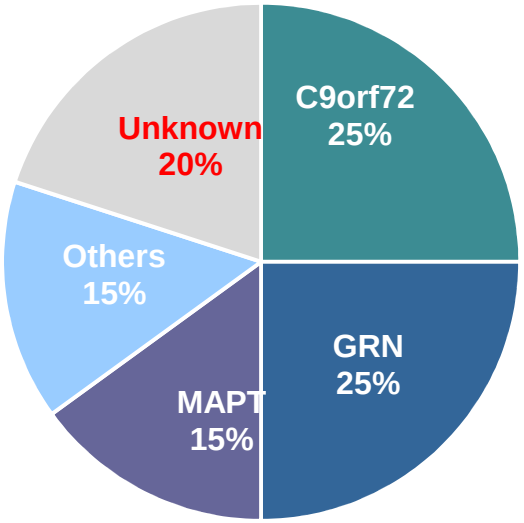


5ème reunion du réseau national Centre de reference-centres de compétences

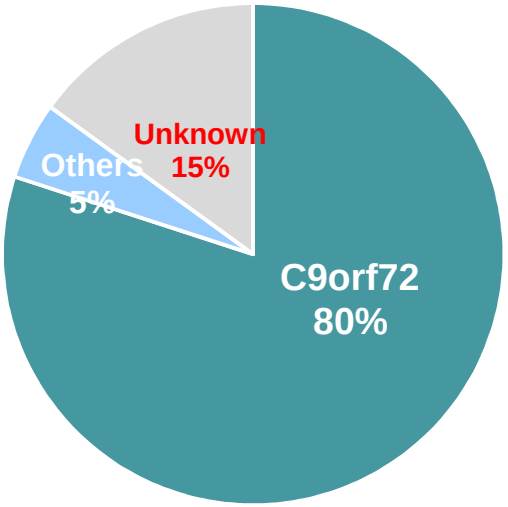
- **Projets génétiques**
- **Essais thérapeutiques**
- **Etude de la phase préclinique des DLFT**

Isabelle Le Ber

Projects in GRN and c9orf72 families



Familial FTLD



Familial FTLD/ALS

Others: *VCP, TARDBP, FUS/TLS, SQSTM1, CSF1R, CHMP2B, hnRNPA1, hnRNPA2B1, CHCHD10, ANG, UBQLN2, MATR3, PFN1, TBK1, CCNF…*

1) Presymptomatic stage of FTLD
2) Genetic modifiers of the phenotype

Emerging therapeutics in genetic forms of FTD

FORUM therapeutic trial in GRN disease

Phase 2a/2b
FRM-0334 (histone deacetylase inhibitor) vs placebo, 1 month
Pharmacodynamic, tolerance, efficacity

Criteria of evaluation:
Progranuline level in plasma and CSF

14 sites
United states and Europe
France : Paris, Bordeaux, Rouen, Lille

Inclusion criteria:
Patients with *GRN* mutation and CDR<1
Asymptomatic *GRN* carriers

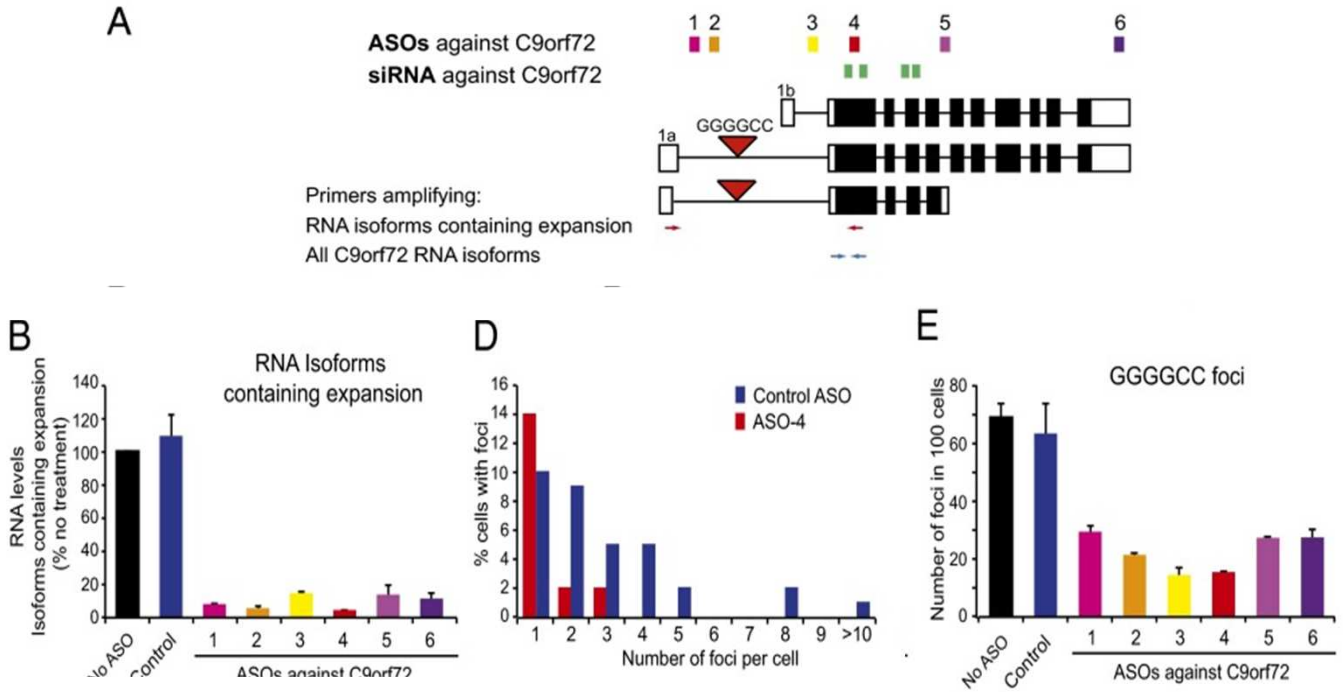
Recruitment:
4 participants in France

PNAS
www.pnas.org

Emerging therapeutics in genetic forms of FTD

Targeted degradation of sense and antisense *C9orf72* RNA foci as therapy for ALS and frontotemporal degeneration

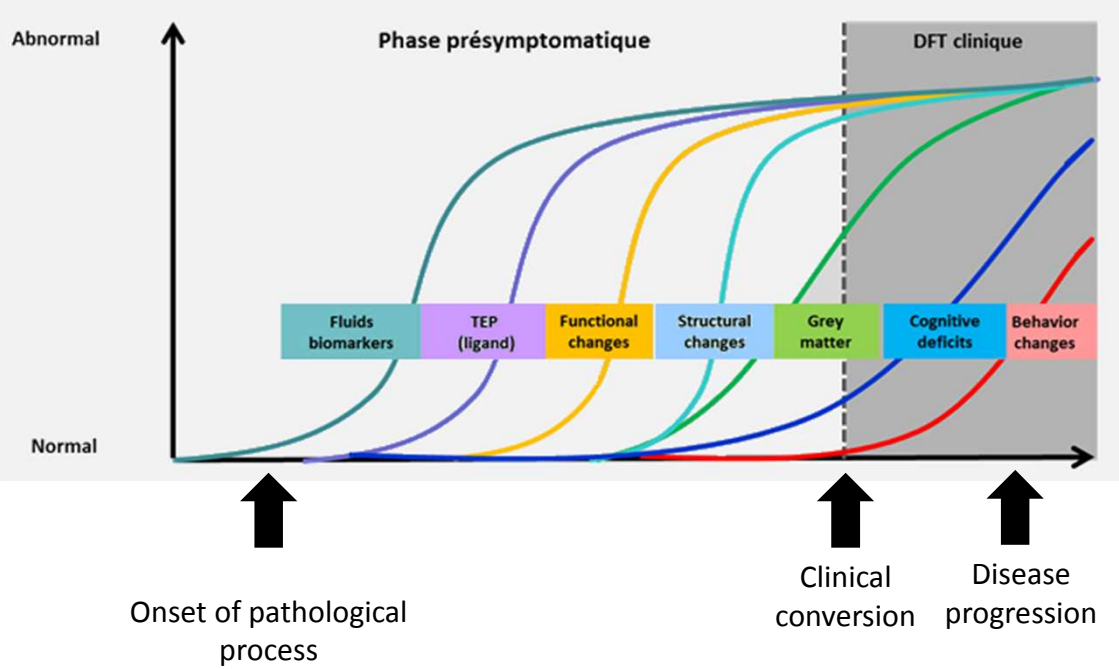
Clotilde Lagier-Tourenne, Michael Baughn, [...], and John Ravits



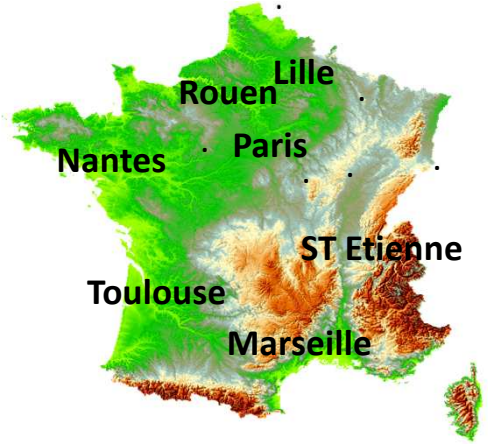
Prospective studies in GRN and c9orf72 presymptomatic carriers

- No specific markers available
- Age at onset/phenotype are variable/unpredictable

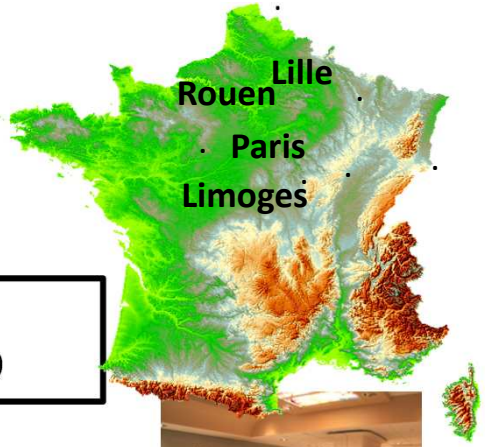
AIMS: identify markers/predictors of
→ Onset of pathologic process
→ Disease conversion
→ Disease progression
→ Clinical phenotypes (FTLD/ALS)



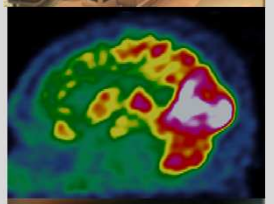
Prospective studies in GRN and c9orf72 presymptomatic carriers



GRN Families
PHRC Predict-PGRN 2010-2022



c9orf72 Families
ANR PrevDemALS 2015-2019



3 visites/participants : 0, 20, 50 months

- Behavioral, cognition & neurological evaluation
- MRI 3T imaging /FDG-PET imaging
- Biological samples (DNA, RNA, cell lines, plasma)

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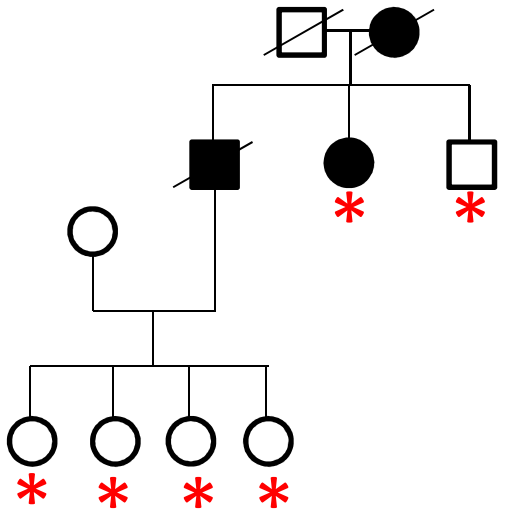
Les Programmes Hospitaliers de Recherche Clinique (PHRC)

Predict-PGRN: 64 inclusions
PrevDemals : 46 inclusions

Prospective studies in GRN and c9orf72 presymptomatic carriers

Inclusion criteria

- Age>18 years
- First-degree relative of a mutation carrier (50% at-risk)
- No intercurrent neurological disease (MS, stroke etc)
- Fleunt French speaking



Exclusion criteria

- Clinical symptoms of FTLD or ALS
- Contraindication to MRI
- Contraindication to FDG-PET
- Chronic alcoholism
- Pregnancy

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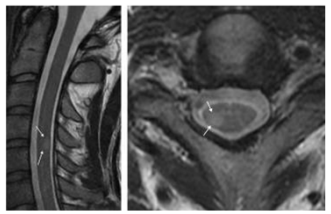
Les Programmes Hospitaliers de Recherche Clinique (PHRC)

Identify neuroanatomical/structural markers of disease onset & progression

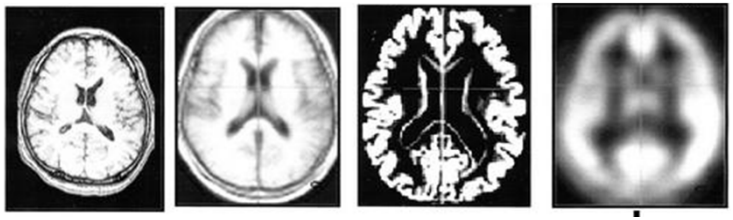
Team O Colliot – ARAMIS team, ICM

1) 3D T1-weighted sequences, with axial or sagittal slices
2) 2D FLAIR sequence
3) 3D volumic T2-weighted sequences, sagittal slices.
4) T2* sequence (T2-weighted gradient echo sequence)
5) BOLD sequence Gradient echo EPI sequence with axial slices (resting state eyes closed)
6) Diffusion tensor imaging

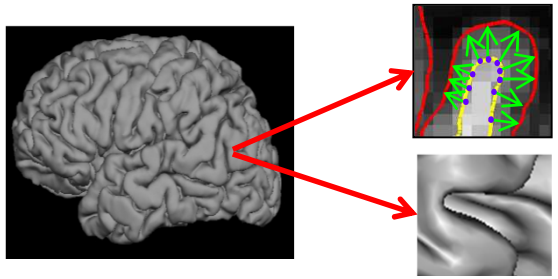
Team Dr PF Pradat– LIF team, UPMC



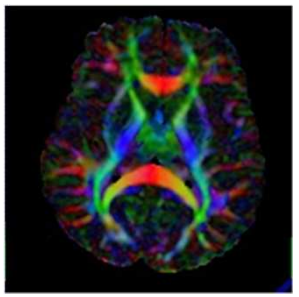
Voxel Based Morphometry



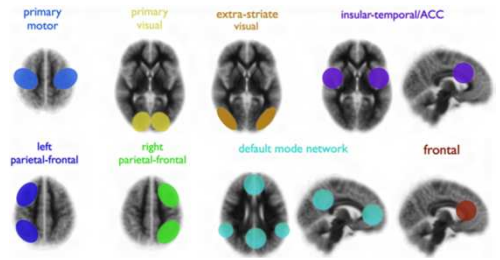
Cortical thickness and fold opening



DTI



Resting state fMRI



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Les Programmes Hospitaliers de Recherche Clinique (PHRC)

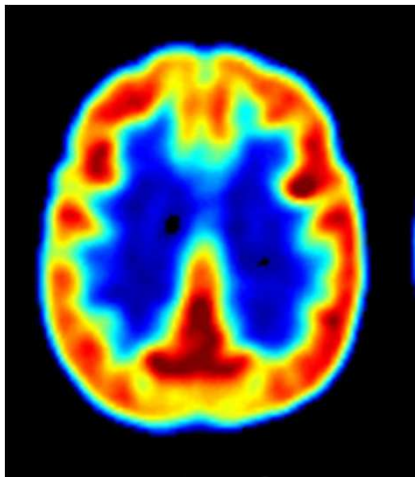
Characterize early brain metabolism changes

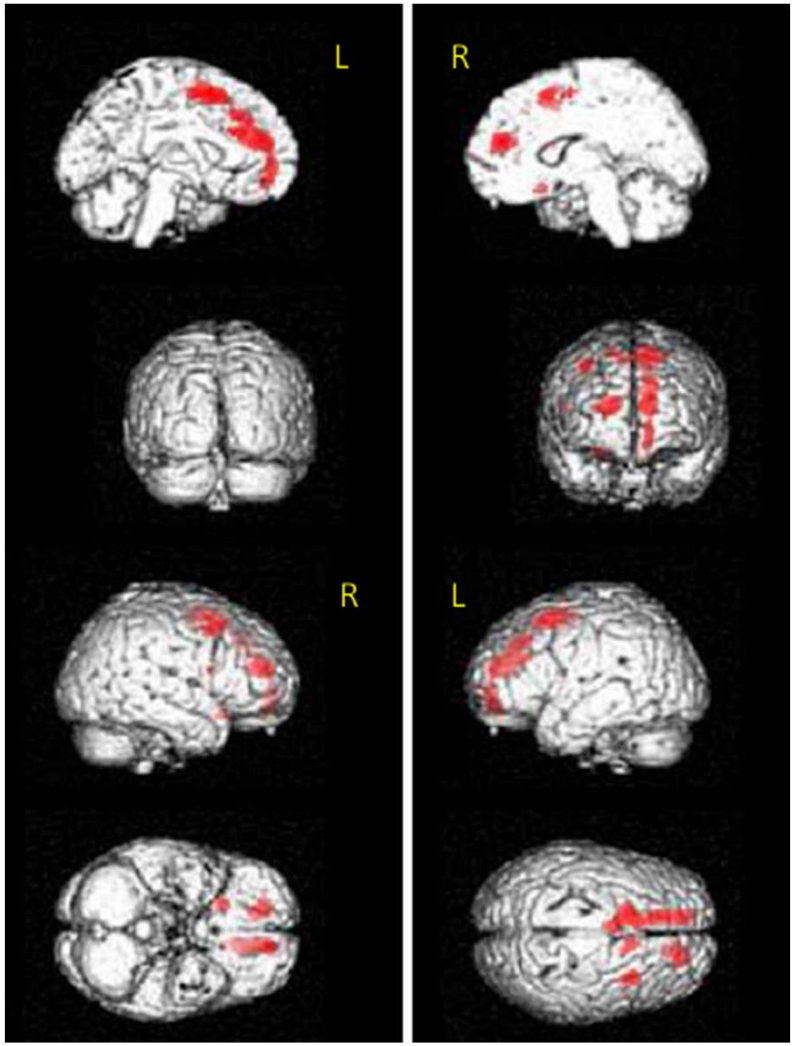
Team Dr M-O Habert– LIF team, UPMC

1) 18F-Fluorodeoxyglucose PET
   2 Mbq/kg of 18F-FDG
   15min 3D acquisition

2) Whole brain voxel-wize analysis (SPM8)

3) Volume of interest analysis (VOIs)





Frontal and social cognition

Team R Levy & B Dubois
– FrontalLab -ICM

A Guignebert, E Benchetrit, S Sayah.

1) Global cognitive efficiency : MMSE, MDRS

2) Executive functions : FAB, WCST, TMT

3) Memory : FCRT

4) Categorical fluency & phonetic fluency, denomination, Semantical words coupling

5) Visual gnosies : Semantical coupling images

6) Gestual praxies

7) Visuospatial abilities : Rey figure copy , barrage test, VOSQP

8) ToM, social cognition and Emotional recognition (Ekman test, Faux pas test, Starsktein, Rolls)

Psychiatric scales

1) DIGS

2) PSAS/SANS

3) Y-BOCS

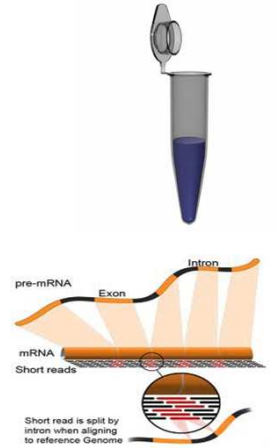
V Anquetil

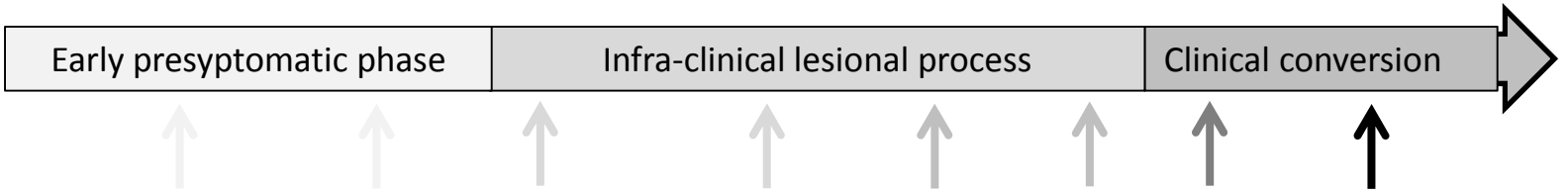
Identification of peripheral biomarkers

> Predict the conversion of the presymptomatic to the clinical stage of FTD/ALS

> New, good, specific, robust, biomarkers needed

Sequencing of RNAs in lymphocytes of carriers at PS/S stage

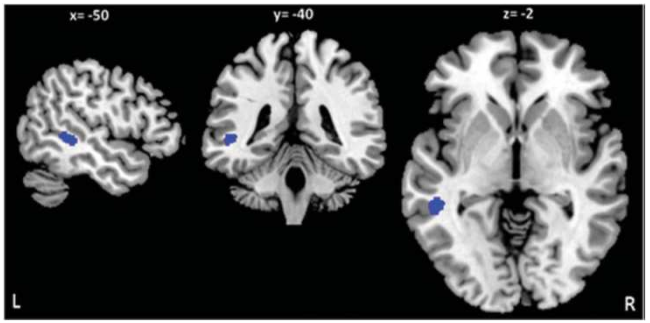




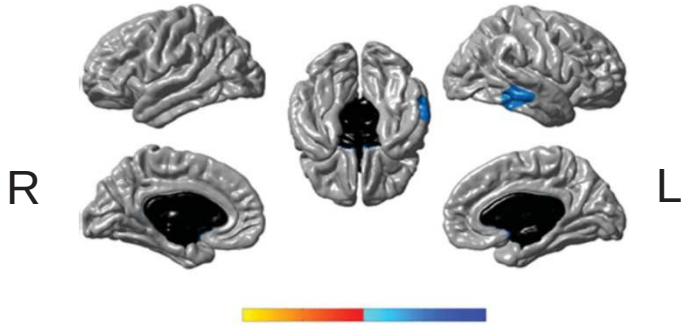
Biological signature of pathological process onset & clinical disease conversion

P Caroppo

Preliminary results – Early metabolic and structural changes in lateral (middle) temporal lobe precede cognitive and clinical symptoms in *GRN* disease



PET-FDG hypometabolism in *GRN+* compared to *GRN- at baseline* ($p < 0.001$ uncorrected).

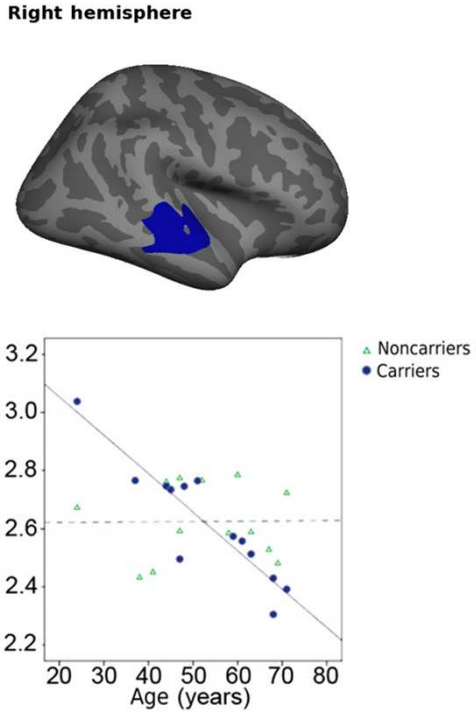


MRI - Cortical thickness changes in presymptomatic *GRN+* over a 20-months follow-up period ($p < 0.05$ corrected).

Mean age in *GRN* carriers =45 ys
≈ 20 years before disease onset

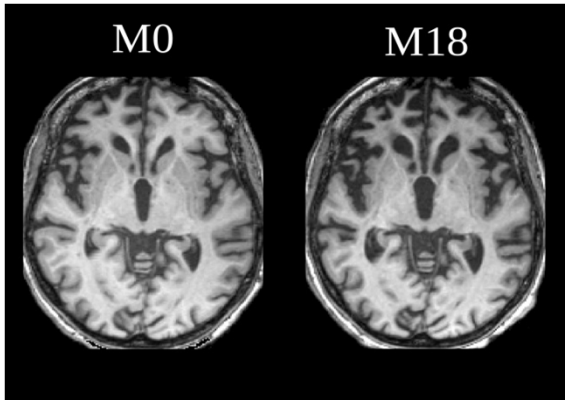
Distinctive age-related temporal cortical thinning in asymptomatic granulin gene mutation carriers

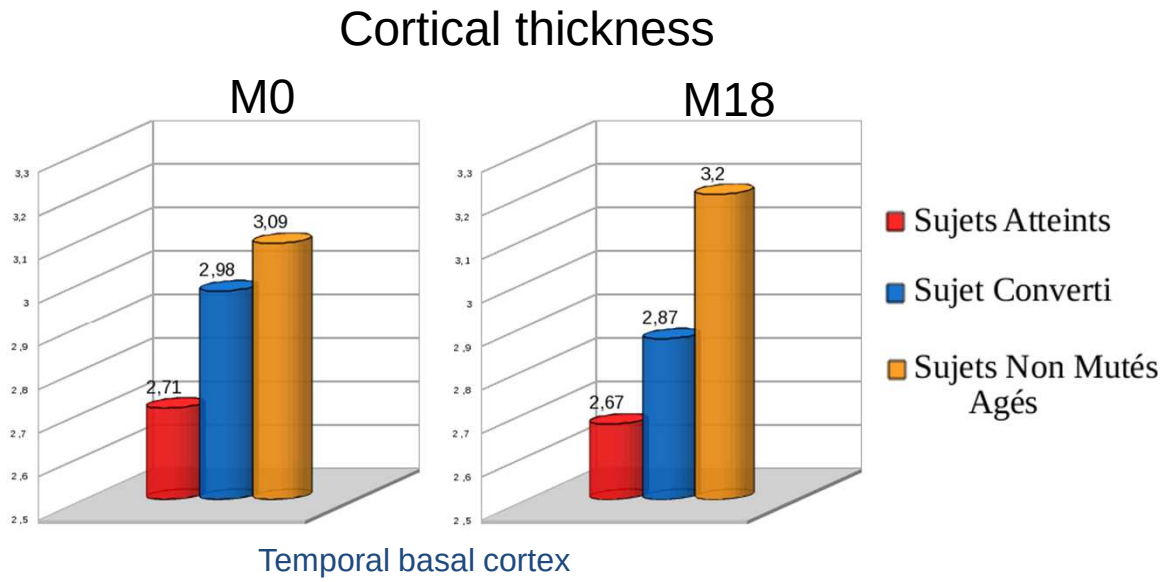
Fermín Moreno[a,b,c,*,1], Roser Sala-Llonch[d,e,1], Myriam Barandiaran[a,b,c], Raquel Sánchez-Valle[e,f], Ainara Estanga[b,c], David Bartrés-Faz[d,e], Andone Sistiaga[b,c,g], Ainhoa Alzualde[b,c], Esther Fernández[h], José Félix Martí Massó[a,b,c], Adolfo López de Munain[a,b,c], Begoña Indakoetxea[a,b,c]



Caroppo et al., 2015

Cortical atrophy measurement: results



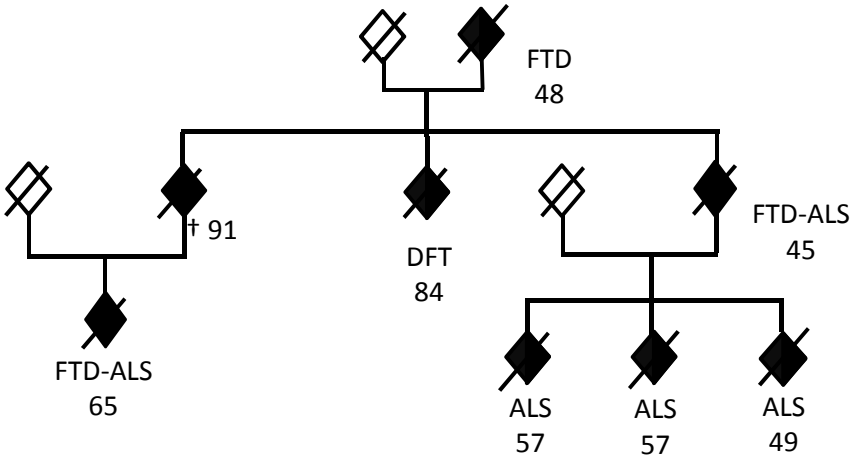


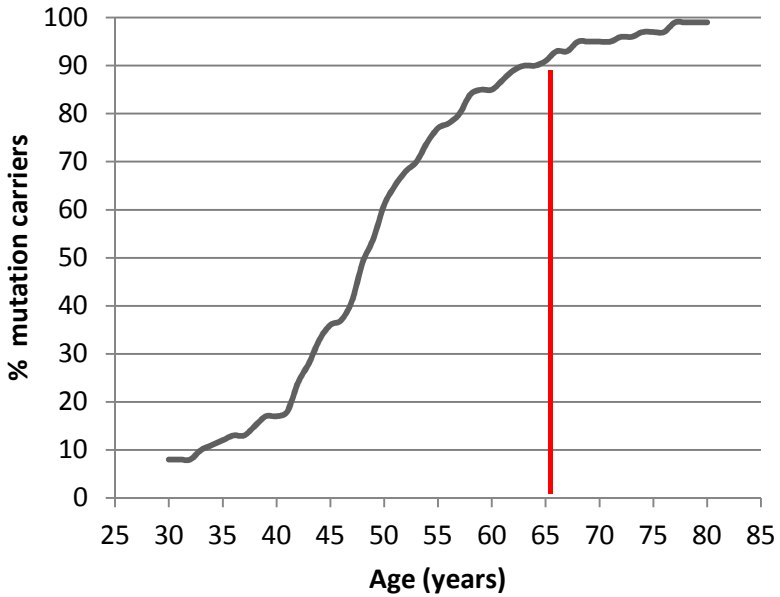
	External Frontal Lobe		Internal Frontal Lobe		External Temporal Lobe		Basal Temporal Lobe		Parietal Lobe	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Decrease of the Grey Matter thickness for the converted subject	-5,96%	-9,10%	-4,90%	-8,77%	-3,57%	-3,68%	-1,33%	-4,24%	-1,17%	-2,84%

Table 1: Markers of progressive atrophy for the initially asymptomatic subject who converted to FTD during the 18 month follow-up. Annualized percent change in fold opening and gray matter thickness averaged over different brain regions.

Unravel clinical variability GRN and c9orf72 families

Phenotypic variability in c9orf72 families

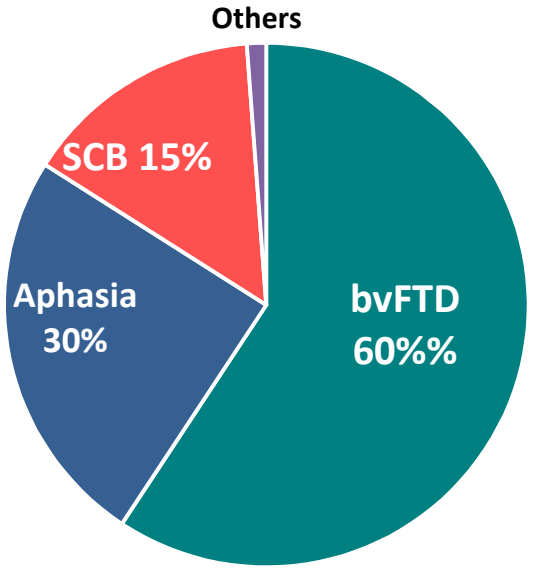


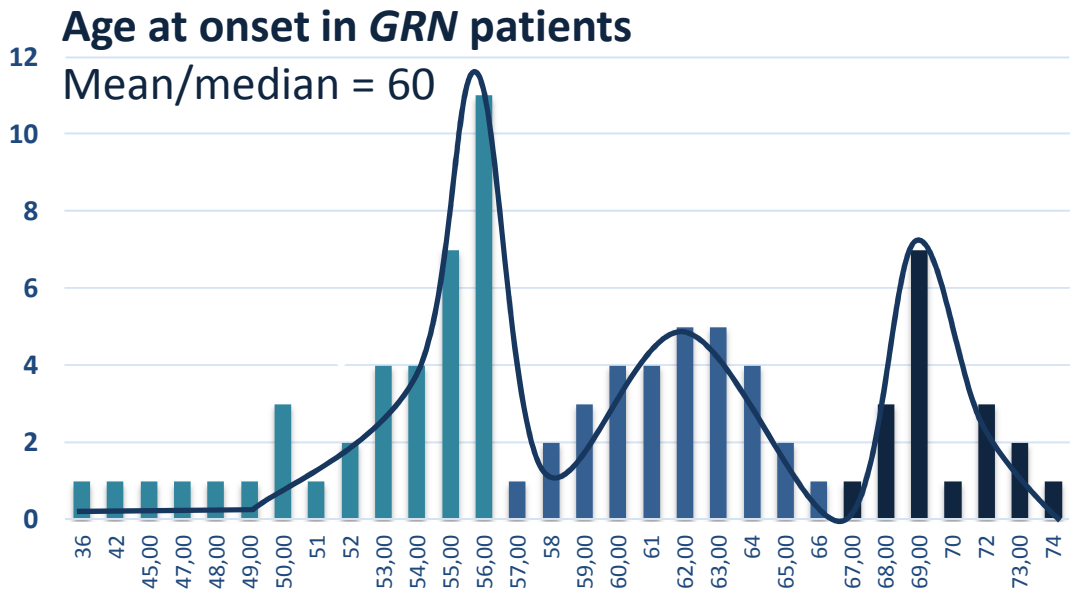


Liability curve for *C9ORF72* mutation carriers.
224 mutation carriers

Unravel clinical variability GRN and c9orf72 families

Phenotypic variability in GRN families

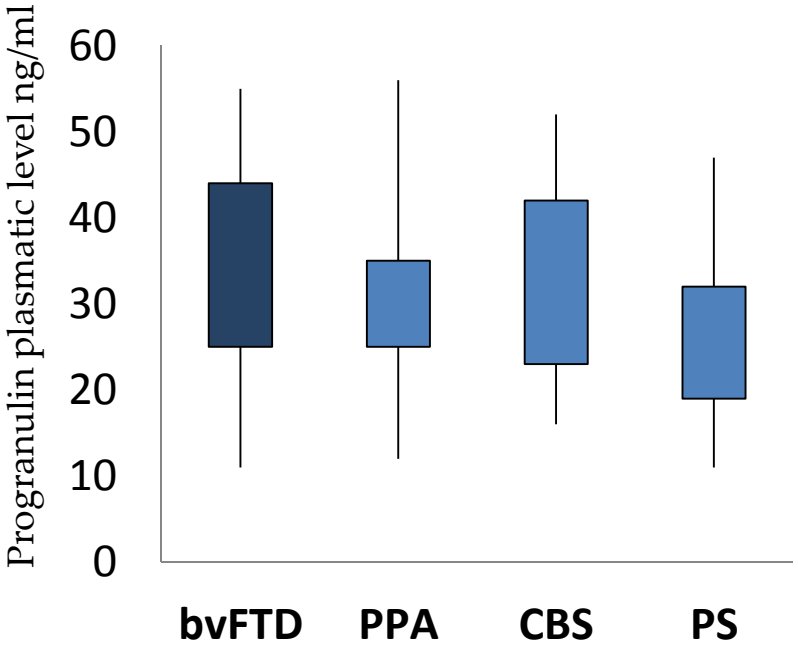


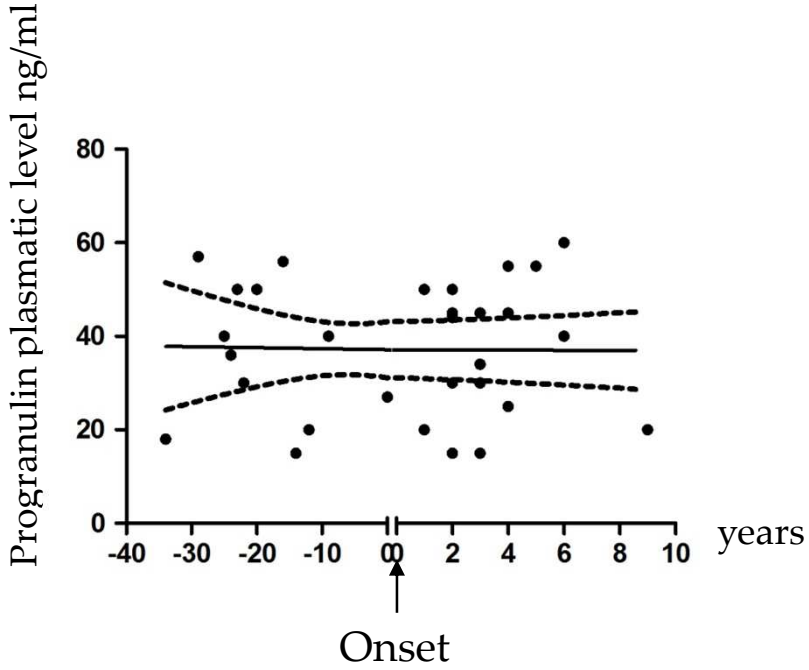


Which factors contribute to the clinical variability ?

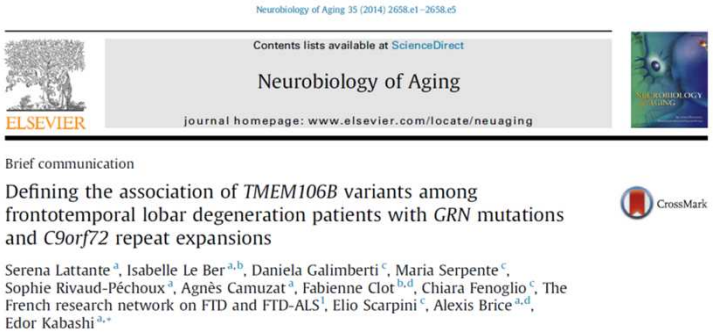
- **Genetic ?**
- Environmental ?
- Stochastic ?

In search of modifiers in FTLD: State of the art





- **Plasmatic progranulin is not predictive of the phenotype**
- ***TMEM106B* rs1990622 is also excluded as a modifier (Lattante *et al.* 2014)**



Neurobiology of Aging 35 (2014) 2658.e1–2658.e5

Contents lists available at ScienceDirect

Neurobiology of Aging

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

Brief communication

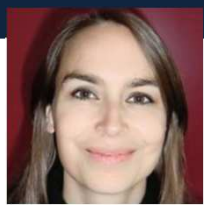
Defining the association of *TMEM106B* variants among frontotemporal lobar degeneration patients with *GRN* mutations and *C9orf72* repeat expansions

Serena Lattante[a], Isabelle Le Ber[a,b], Daniela Galimberti[c], Maria Serpente[c], Sophie Rivaud-Péchoux[a], Agnès Camuzat[a], Fabienne Clot[b,d], Chiara Fenoglio[c], The French research network on FTD and FTD-ALS[1], Elio Scarpini[c], Alexis Brice[a,d], Edor Kabashi[a,*]

Unravel clinical variability GRN and c9orf72 families

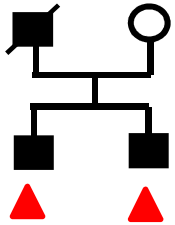
M. Barbier

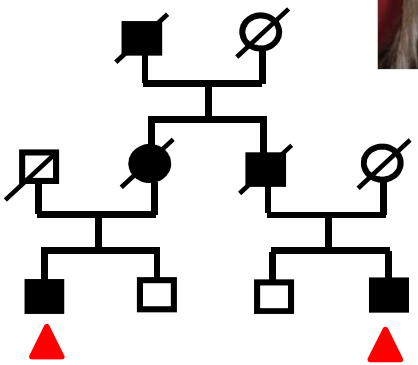
D. Rinaldi



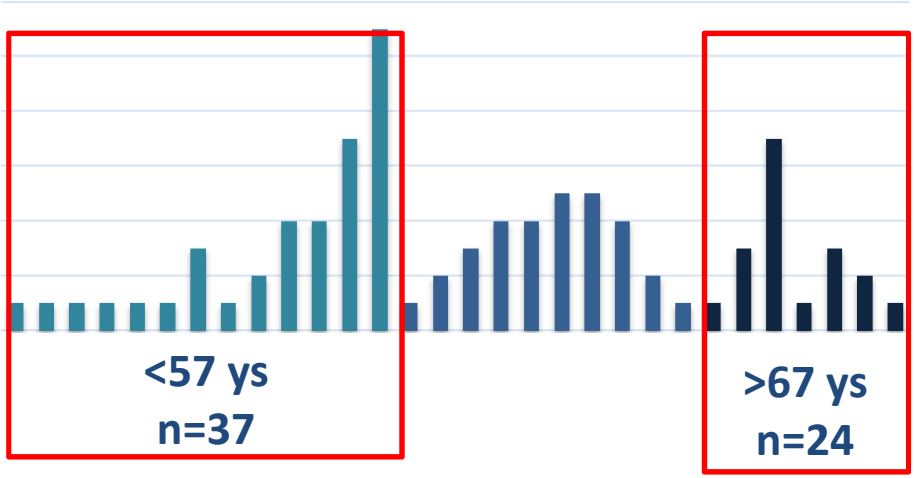
Present population

Heritability and familial correlation analyses *(SOLAR/SAGE)*





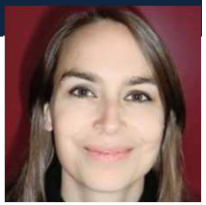
WES on extreme phenotypes



Mathieu Barbier/ Coll A. Sabbagh, E Genin, Hervé Perdry

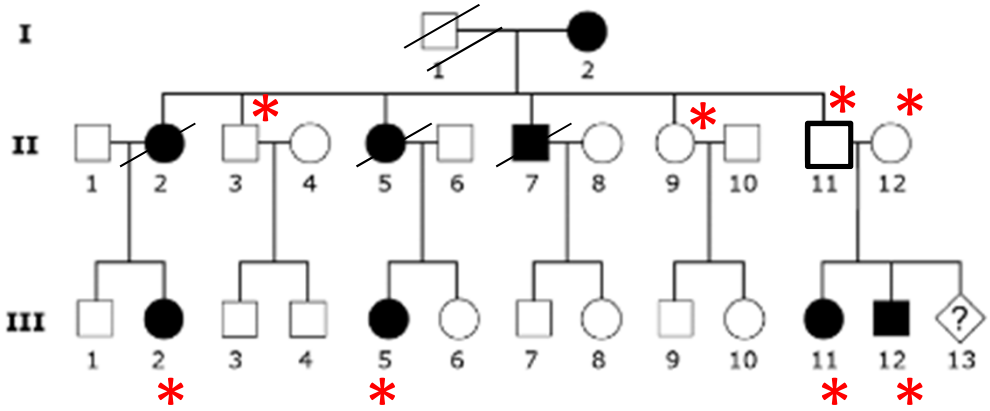
Unravel clinical variability GRN and c9orf72 families

M. Barbier



Extend Population ?

- Enrich extreme phenotypes
- Mapping
- Concordant *vs.* Discordant sibling pairs



•Detailed clinical informations

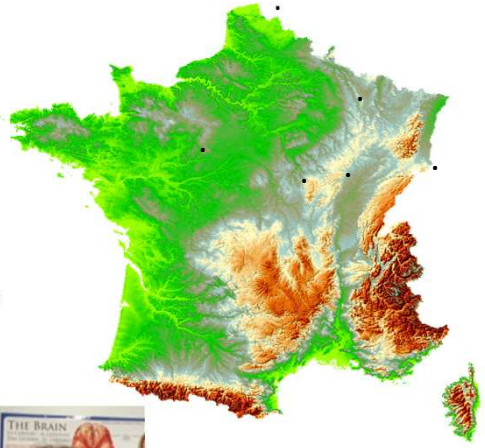
• Informations on age at onset of relatives

•Samples of patients/families with GRN and c9orf72 mutations +++++

The ‘FTLD genetic’ Team

V Anquetil
Post-doctorant

P Caroppo
Neurologue



M. Barbier
post-doctorant

D Rinaldi
Arc CNR-DR

A. Camuzat, IE

C Fournier
Post-doctorante

M. Latouche
MCU-PH