A family-based approach to identify genetic modifiers of the age at onset in Frontotemporal Lobar Dementia (FTLD)

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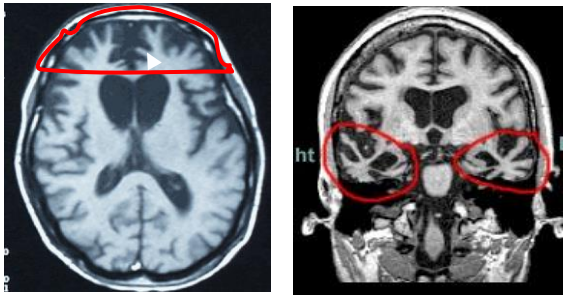
Réunion nationale du centre de référence et des centres de compétences
DEMENCES RARES OU PRECOCES – 29 juin 2018

Centre de Référence Démences Rares ou Précoces

Frontotemporal Lobar Dementia (FTLD) & Genetics

FTLD

- 4-10 cases/100,000 inhabitants
- Second most common pre-senile dementia
- Mean age at onset ~ 60 y
- Progressive neuronal loss
- Progressive degeneration of frontal and temporal cortices



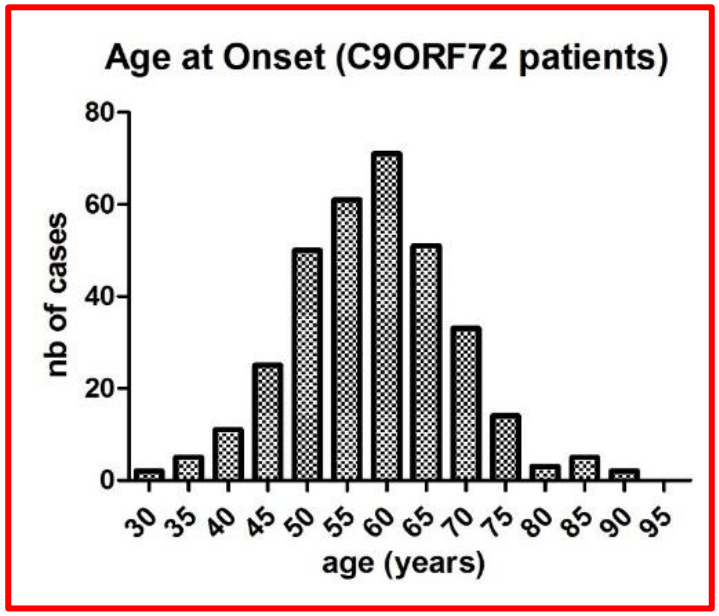
- Behavior disorders: apathy, disinhibition, stereotyped behaviors, loss of empathy…
- Language disorders
- Amyotrophic Lateral Sclerosis (ALS) in 15%

Genetic landscape of FTLD

- 40% of cases with a familial history
- Heterogeneity (>20 genes, AD++ inheritance)
- 3 major genes:
  - MAPT ⇒ « pure » FTLD
  - *GRN* ⇒ « pure » FTLD
  - *C9orf72* ⇒ Expansion, FTLD and/or ALS

- Known genes explain 80% of familial FTLD.
- The phenotypical variability remains largely unexplained.

Variability of the Age at Onset (AO) in familial FTLD
- State of the art -



- Not explained by causal mutations.
- Variability of AO impairs patients 'care (genetic counseling, set-up of therapeutic trials).
- Previous searches for genetic biomarkers influencing AO (mainly performed with *GRN* patients):
  - Used approaches with unrelated individuals (GWAS-like).
  - *TMEM106B*, +/- replicated.
  - Used candidate genes approaches (especially for *C9orf72*, only *TMEM106B* was tested).

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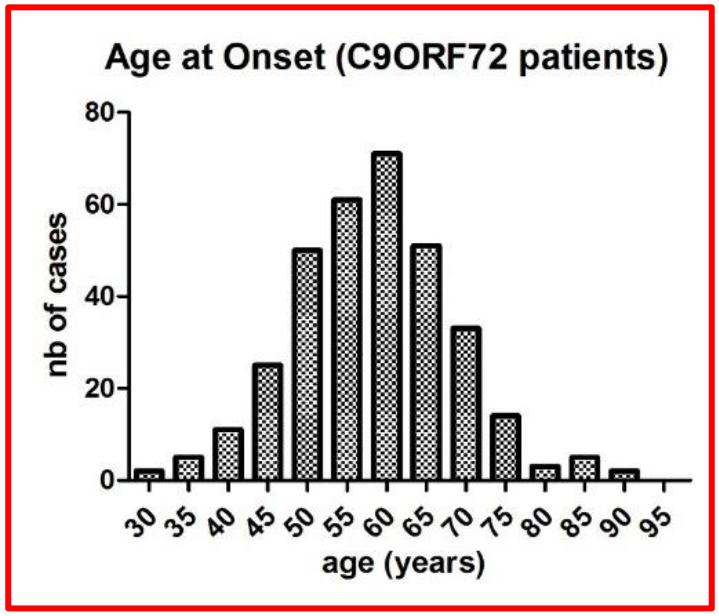

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➢ **We initiated a family-based approach without *a priori* to highlight genetic modifiers of AO:**
  - ➢ **need less individuals, less statistical corrections, adapted to rare diseases.**
  - ➢ **But need specific genetic statistical knowledges, and adapted data.**

Variability of the Age at Onset (AO) in familial FTLD
In search of Genetic markers

Collection of 504 carriers with phenotypic and pedigree data from 133 *C9orf72* and 90 *GRN* familial FTLD thanks to the French Reference Centre for Rare or Early Dementia

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Do genetic factors (broad sense) influence AO ?

↓

Heritability estimates using Variance component methods

Intra-familial correlations of the AO

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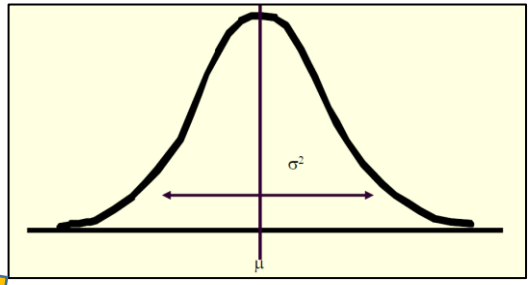
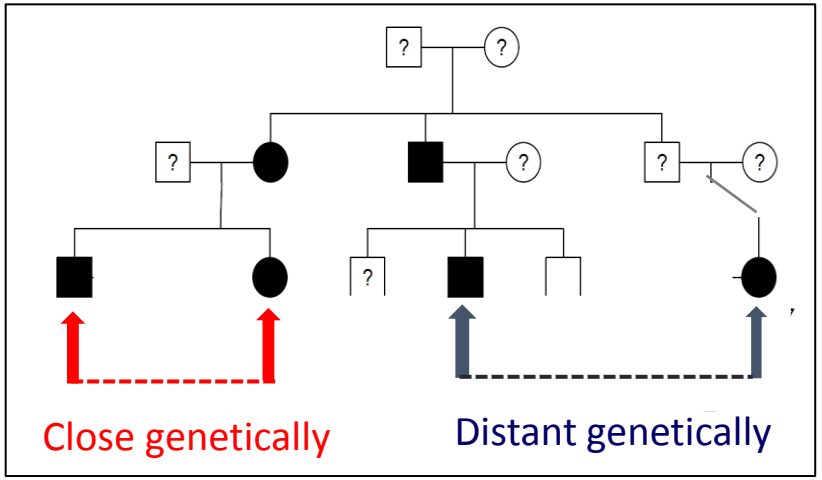


$$\sigma_p^2 = \sigma_g^2 + \sigma_e^2$$

$$h^2 = \frac{\sigma_g^2}{\sigma_p^2}$$

Intra-familial correlations of the AO



Heritability estimates & intra-familial correlations of AO

Selection of 504 probands and affected relatives from 223 families
(133 *C9orf72* and 90 *GRN* families)

Heritability estimates

C9orf72:
0.44 ± 0.13; p = 1.10^{e-4} (AO)
0.62 ± 0.17; p = 8.10^{e-5} (AO-FTD)

GRN:
0.26 ± 0.28; NS

Intra-familial correlations between pair of relatives
***r* (nb of pairs)**

	Parent-offspring		Sibling		Avuncular		Cousin	
	r	*p* Value	*r*	*p* Value	*r*	*p* Value	*r*	*p* Value
C9ORF72								
AAO	0.12 (111)	0.36	0.46 (145)	<1.10e−4	0.20 (59)	0.39	0.28 (33)	0.24
AAO-FTD	0.33 (58)	0.06	0.66 (68)	<1.10e−4	0.51 (20)	0.12	0.44 (12)	0.19
GRN								
AAO	0.13 (58)	0.21	0.24 (42)	0.13	−0.58 (8)	0.11	−0.48 (4)	0.31

Barbier *et al*. 2017

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***r* (nb of pairs)**

	C9 AAO		C9 AAO-FTD	
Pair subtypes	*r*	*p* Value	*r*	*p* Value
Father-son	0.03 (31)	0.89	−0.15 (19)	0.65
Mother-son	0.51 (33)	0.008	0.57 (17)	0.03
Father-daughter	0.06 (17)	0.89	0.36 (7)	0.63
Mother-daughter	−0.12 (30)	0.58	0.46 (15)	0.09

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Brother-brother	0.58 (37)	0.0003	0.71 (15)	<1.10e−4
Brother-sister	0.56 (70)	<1.10e−4	0.75 (33)	<1.10e−4
Sister-sister	0.21 (38)	0.22	0.46 (20)	0.04

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X-linked modifier?

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- This descriptive approach led to show:
  - High and significant heritability of AO in *C9orf72* families (up to 62%).
  - Intra-familial correlations tend to correlate with kinship coefficient.
  - Intra-familial correlations in subtypes (father-son, mother-son etc.) suggested that at least one X-linked modifier may influence AO.

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Which genetic factors influence AO ?

Whole Genome Genotyping Linkage & Association analyses

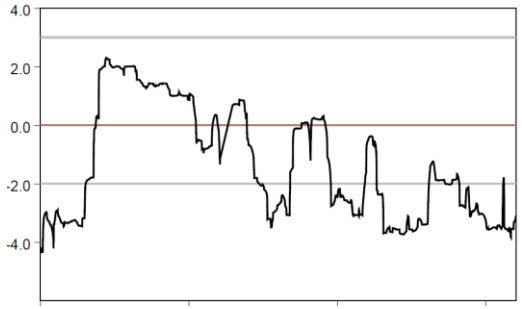
To localize genetic regions of interest

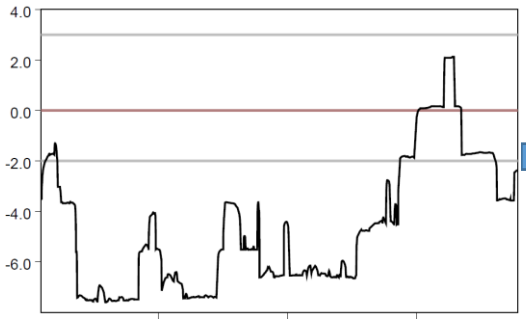
To highlight genetic variations associated with AO

Linkage using concordant / discordant pairs of relatives

- 34 families with *C9orf72* pathogenic expansion.
- 23 **concordant pairs of relatives (difference of AO <2y).**
- 35 **discordant pairs of relatives (difference of AO >10y).**

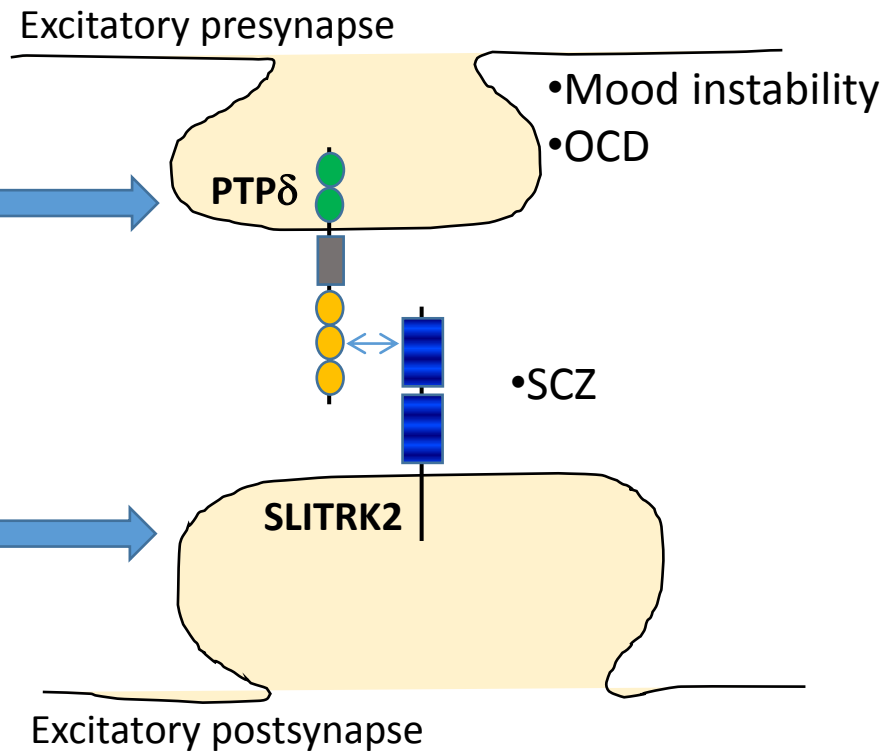
- 2 *loci* with suggestive linkage:
  - Chr. X q27.3 (max LOD=2.1)
  - Chr. 9 p23 (max LOD=2.5)





PTPRD locus

SLITRK2 locus



➢ The 2 *loci* identified include 2 genes coding for proteins interacting *in vivo*.

➢ No suggestive LOD scores in *GRN* families.

Association using concordant / discordant pairs of relatives

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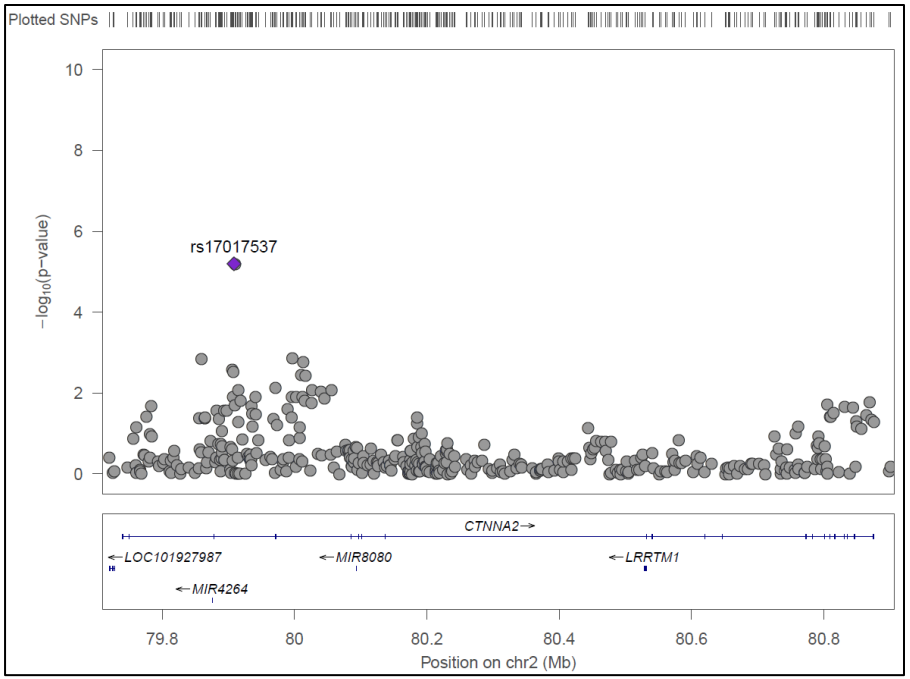
- 23 **concordant pairs of relatives (difference of AO <2y).**
- 35 **discordant pairs of relatives (difference of AO >10y).**

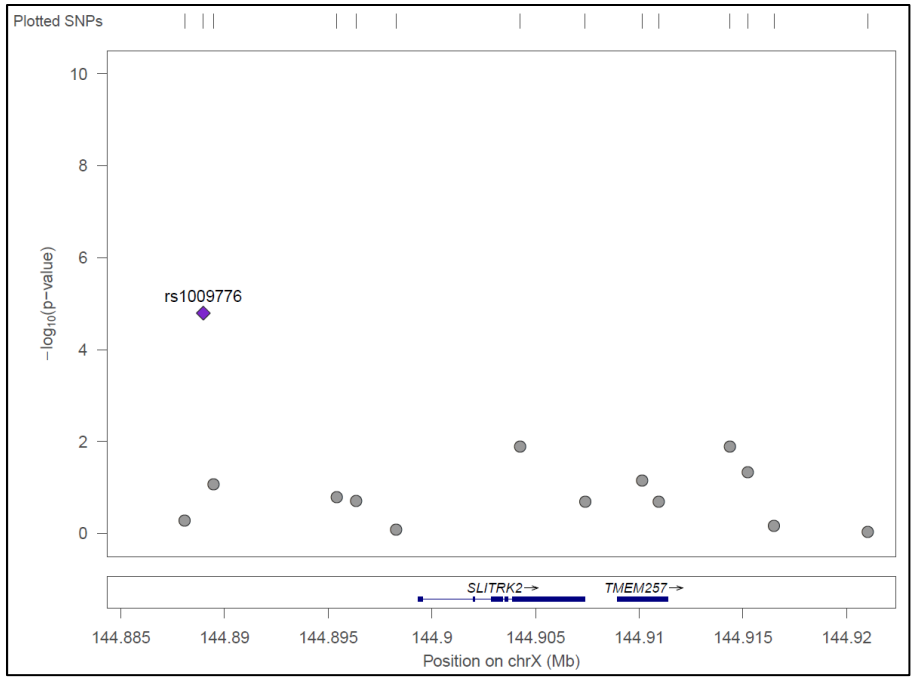
Autosome:

- 2 *loci* with suggestive scores (p-value < 10^{e-5}).
- 2 variations with a located in *CTNNA2*/*LRRTM1.*
- Excitatory synapse, associated with SCZ and psychosis.



X-chromosome:

- 1 variation with a p-value < 10^{e-5} located upstream of *SLITRK2*.



A family-based approach in familial-FTLD - Conclusion

Usefulness of using clinical data, information, and biological samples :

- High heritability of AO in familial FTLD (higher in *C9orf72* than in *GRN* families)
- Pattern of intra-familial correlation of the AO which evokes X-linked modifiers in *C9orf72* families
- Linkage & association analyses highlighted the synapse and synaptic adhesion proteins
  - ➢ Do variable synaptic dysfunctions influence the AO ?

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- Linkage & association analyses highlighted the synapse and synaptic adhesion proteins
  - Do variable synaptic dysfunctions influence the AO ?

- Next steps:

  - Increase number of families / pairs, improve our familial analyses:
    - We are getting data from consortium (IFGC, R. Ferrari, UCL, London).
    - **Despite the identification of causal genes, we still need patients' samples who fit our criteria to enrich our population (*GRN*, *C9orf72*, concordant/discordant sib-pairs, extreme AO).**

  - Cross with results from whole exome sequencing of unrelated cases with extreme AO.
    - *GRN* patients with AO<55y or AO>68y.
    - *C9orf72* patients with AO<50y or AO>67y.

  - We are planning functional analyses.

Thanks to…

UMR_S 1127, ICM, Paris
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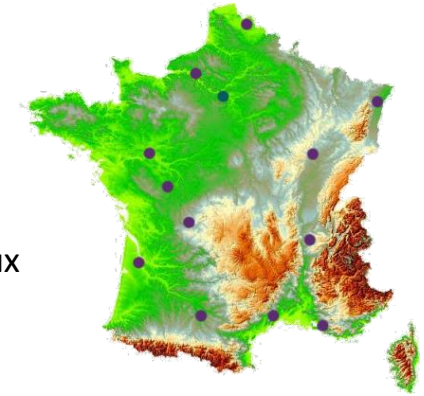
French clinical & genetic research network on FTD/FTD-ALS



- Amiens
- Angers
- Bordeaux
- Dijon
- Lille
- Limoges
- Lyon / St Etienne / Grenoble
- Nantes
- Paris
- Marseille
- Montpellier
- Poitiers
- Rennes/St Brieuc
- Rouen
- Strasbourg/Colmar
- Toulouse
- Guadeloupe

C9orf72 G_4C_2 repeats number, AO, and age at collection in blood

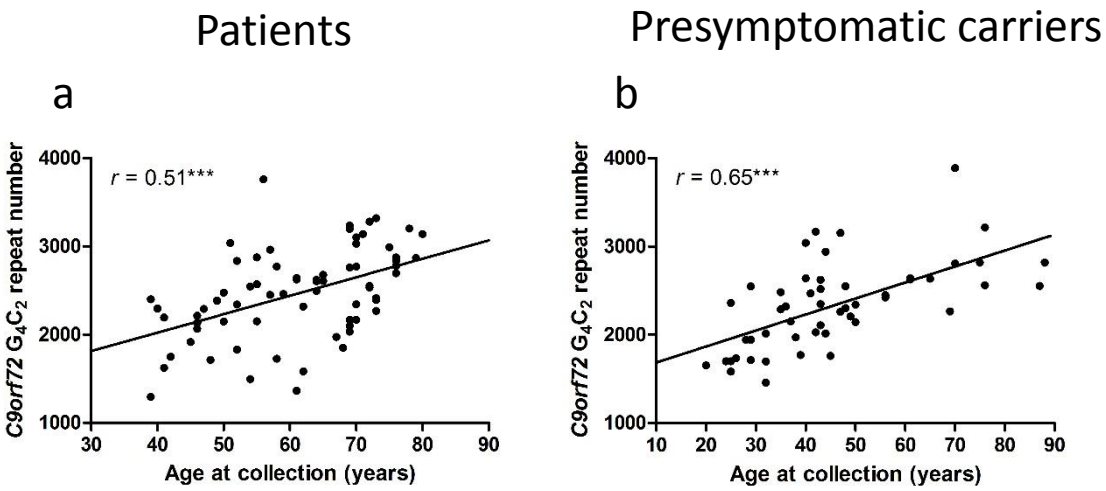


Figure 2. Correlations between *C9orf72* G_4C_2 repeat number and age at collection in patients (**a**) and in presymptomatic carriers (**b**). A regression line and Spearman's *r* are indicated. Asterisks represent p-value significance (***p < 0.0001).

Barbier *et al*. 2018, submitted