Factors influencing the age at onset in familial frontotemporal lobar dementia: Important weight of genetics

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ABSTRACT

Objective: To quantify the effect of genetic factors and generations influencing the age at onset (AAO) in families with frontotemporal lobar dementia (FTD) due to *C9ORF72* hexanucleotide repeat expansions and *GRN* mutations.

Methods: We studied 504 affected individuals from 133 families with *C9ORF72* repeat expansions and 90 FTD families with mutations in *GRN*, 2 major genes responsible for FTD and/or amyotrophic lateral sclerosis. Intrafamilial correlations of AAO were analyzed, and variance component methods were used for heritability estimates. Generational effects on hazard rates for AAO were assessed using mixed-effects Cox proportional hazard models.

Results: A generational effect influencing AAO was detected in both *C9ORF72* and *GRN* families. Nevertheless, the estimated proportion of AAO variance explained by genetic factors was high in FTD caused by *C9ORF72* repeat expansions (44%; $p = 1.10e{-}4$), 62% when the AAO of dementia was specifically taken into account ($p = 8.10e{-}5$), and to a lesser degree in *GRN* families (26%; $p = 0.17$). Intrafamilial correlation analyses revealed a significant level of correlations in *C9ORF72* families according to the degree of kinship. A pattern of intrafamilial correlations also suggested potential X-linked modifiers acting on AAO. Nonsignificant correlation values were observed in *GRN* families.

Conclusions: Our results provide original evidence that genetic modifiers strongly influence the AAO in *C9ORF72* carriers, while their effects seem to be weaker in *GRN* families. This constitutes a rational to search for genetic biomarkers, which could help to improve genetic counseling, patient care, and monitoring of therapeutic trials. ***Neurol Genet*** **2017;3:e203; doi: 10.1212/NXG.0000000000000203**

GLOSSARY

AAO = age at onset; **ALS** = amyotrophic lateral sclerosis; **FTD** = frontotemporal lobar dementia.

Frontotemporal lobar dementia (FTD) is a rare neurodegenerative disease caused by neuronal death in the frontal and temporal lobes and represents the second cause of early-onset dementia after Alzheimer disease. FTD is associated with behavioral changes and language dysfunctions and may be associated with amyotrophic lateral sclerosis (ALS). Thanks to the use of next-generation sequencing, the identification of more than 20 FTD-associated genes allowed molecular diagnosis in more than 60%–70% of familial cases. Among these genes, mutations in *GRN* and intronic

From the INSERM U1127 (M.B., A.C., P.C., C.F., D.R., A.B., I.L.B.), CNRS UMR 7225, UPMC Université Paris 06 UMR S1127, Sorbonne Université Institut du Cerveau et de la Moelle épinière, ICM; Ecole Pratique des Hautes Etudes—EPHE (A.C.), PSL Research University; Institute of Memory and Alzheimer's Disease (IM2A) (M.H., P.C., D.R., I.L.B.), Centre of Excellence of Neurodegenerative Disease (CoEN), ICM, APHP Department of Neurology, Hopital Pitié-Salpêtrière, University Paris 6; Unité Fonctionnelle de Neurogénétique Moléculaire et Cellulaire (F.C., K. L.), Département de Génétique et Cytogénétique, AP-HP, Hôpitaux Universitaires La Pitié Salpêtrière-Charles Foix, Paris, France; Carlo Besta Neurological Institute (P.C.), IRCCS Foundation, Milano, Italy; Assistance Publique—Hôpitaux de Paris (D.R., I.L.B.), Hôpital Pitié-Salpêtrière, Centre de référence Démences Rares, Paris, France; Université de Lille (F.P.), Inserm U1171, CHU Lille, Labex DistAlz, LiCEND, France; Department of Neurology (D.H.), University Hospital, Rouen, France; Département de Neurologie (J.P.), CHU Toulouse, Equipe TONIC, INSERM, Place du Dr Baylac, France; INSERM (E.G.), UMR1078, CHU Brest, Université Bretagne Occidentale, France; and Institut de Recherche pour le Développement (IRD) (A.S.), UMR216—MERIT, Paris, France.

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Funding information and disclosures are provided at the end of the article. Go to Neurology.org/ng for full disclosure forms. The Article Processing Charge was funded by the authors.

hexanucleotide expansions in *C9ORF72* are the major causes of FTD and/or ALS.[1–4] In both genetic forms, the clinical expression of the disease can vary from an early occurrence of symptoms in the third decade of life to a virtually incomplete penetrance in elderly carriers. To date, only *TMEM106B* has been described as a potential modifier gene of FTD influencing the penetrance of the disease.[5–8] However, this association mostly concerned FTD cases caused by *GRN* mutations and did not explain all the observed variability. Therefore, the question of the variability of the age at onset (AAO) remains largely unexplained, and little is known about the global heritability of AAO in FTD. Here, we provide further insights into heritability estimates and patterns of intrafamilial correlations to evaluate the genetic component of AAO variability in FTD because this strongly influences genetic counseling, therapeutic trials, and, to a broader extent, patient care.

METHODS

Standard protocol approvals, registrations, and patient consents. All individuals were enrolled in agreement with bioethics laws (Institutional Review Board: CPP Ile de France II, project #RBM 02-59). Written informed consent was obtained from all patients (or guardians of patients) participating in the study (consent for research).

Study population. This study was initially based on a global cohort of 702 probands and affected relatives from 322 independent FTD families carrying *C9ORF72* or *GRN* mutations, assembled by the French clinical and genetic research network on FTD/FTD-ALS. AAO was defined as the age of occurrence of the first symptoms (either behavioral, language, or motor), in years, as reported by the principal informant. In most cases, a second informant was questioned independently to accurately determine the AAO, and only patients/families with concordant data were included in the study. After a careful review of all cases, 99 families were excluded because clinical information or second informant's interview was lacking, making the determination of AAO impossible or not reliable enough.

Finally, 504 probands and affected relatives from 223 families with robust data were used for the analyses, including 333 probands and affected relatives (166 women and 167 men) from 133 *C9ORF72* families as well as 171 probands and affected relatives (87 women and 84 men) from 90 *GRN* families. The AAO ranged from 30 to 91 years old (mean AAO = 58.3 ± 9.9 SD) in *C9ORF72* patients. In 236 *C9ORF72* probands and relatives, the AAO of dementia (AAO-FTD) was specifically considered in contrast to other symptoms (ALS and others) and analyzed separately, as *C9ORF72* repeat expansions could lead to both dementia and ALS. Patients with mutations of *GRN* only developed symptoms of dementia. The AAO ranged from 33 to 86 years old (mean AAO = 60.8 ± 8.5 SD). Most individuals (>97%) were of Caucasian origin. The structure of *C9ORF72* and *GRN* pedigrees is detailed in table e-1, http://links.lww.com/NXG/A4.

Statistical analyses. The heritability of traits was estimated using a variance components method as implemented in the SOLAR v8.1.4 (Sequential Oligogenic Linkage Analysis Routines) computer package.[9] Briefly, this method applies maximum likelihood estimation to a mixed-effects model that incorporates fixed effects for known covariates and variance components for genetic effects. Both AAO and AAO-FTD in *C9ORF72* patients and AAO in *GRN* patients followed a normal distribution. The heritability (h^2) of a phenotype was estimated as the ratio of additive genetic variance to the total phenotypic variance unexplained by covariates.

Familial correlation coefficients were estimated using the program FCOR of the SAGE v6.4 software package (Statistical Analysis for Genetic Epidemiology; 2016).[10] Correlations were calculated using the uniform weighting scheme. Description of affected pairs of relatives per family is provided in table e-2, http://links.lww.com/NXG/A5. As a previous study showed that penetrance may be sex dependent in patients with FTD with *C9ORF72* mutations,[11] both familial correlations and heritability estimates were calculated using residual trait values of AAO and AAO-FTD after adjusting for sex.

Anticipation was investigated in *C9ORF72* and *GRN* families using mixed-effects Cox proportional hazard regression models to test for a generational effect on the AAO. The statistical model allows the inclusion of unaffected carriers (censored data). Unaffected carriers or obligate unaffected carriers of *C9ORF72* repeat expansions or *GRN* mutations were included in this analysis and censored at the age of last evaluation. Generation and sex effects were added in the model, each patient had an individual random risk, which were correlated according to the strength of relationship using the kinship matrix. The kinship matrix was assessed on all individuals, but Cox models were fitted only on carriers (including both affected and unaffected individuals) and on families with at least 2 consecutive generations. Clinical data were available in pedigrees up to 5 consecutive generations. To get more reliable estimates of generational effects, generations with a number of informative individuals lower than 10% of total individuals included in the analysis were discarded. Finally, analyses were performed on 3 consecutive generations in *C9ORF72* families (312 individuals among 79 families) and 2 consecutive generations in *GRN* families (119 individuals among 42 families). Distribution of individuals (both censored and uncensored) according to generations is indicated in table 1. Table e-3, http://links.lww.com/NXG/A6, provides additional details about censored and uncensored statuses among FTD families. The effect of generation was tested using log-likelihood tests. Statistical analysis was performed using R 3.3.2 (The R foundation for Statistical computing) and using coxme 2.2-5 and kinship2 1.6.4 packages.

RESULTS

The heritability of traits was assayed in *C9ORF72* families using phenotypical and pedigree

Table 1 Distribution of individuals (both censored and uncensored) according to mutations and generations in FTD families selected for the generational effect analysis

Generation	*C9ORF72*	*GRN*
Earliest born	40	—
Second born	148	53
Latest born	124	66
Total	312	119

Abbreviation: FTD = frontotemporal lobar dementia.

Table 2 Intrafamilial correlation coefficients (*r*) among 348 affected relative pairs from 333 cases in 133 *C9ORF72* families and 114 affected pairs from 171 cases in 90 *GRN* families

	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

Abbreviations: AAO = age at onset; FTD = frontotemporal lobar dementia.
The number of pairs is indicated in brackets.

data for the AAO ($h^2 = 0.44 \pm 0.13$; $p = 1.10e{-}4$) and AAO-FTD ($h^2 = 0.62 \pm 0.17$; $p = 8.10e{-}5$). Table 2 resumes familial correlations among relatives. Significant correlations were observed among sibling pairs ($r = 0.46$), and nonsignificant correlations for second- and third-degree relatives that are more genetically distant ($r = 0.20$ and $r = 0.28$, respectively). Similar patterns were observed for the AAO-FTD phenotype with stronger and significant correlation values (table 2).

We did not observe any significant correlation among first-degree relatives when parent-offspring pairs were considered. This discordance between parents and offspring prompted us to analyze subtypes of parent-offspring pairs, e.g., father-offspring, mother-offspring, and sibling subtypes (table 3). A significant correlation was observed only in mother-son pairs ($r = 0.51$), conversely to mother-daughter or father-offspring pairs. Besides, brother-brother and sister-brother pairs were significantly correlated among sibling subtypes ($r = 0.58$ and $r = 0.56$, respectively) in contrast to sister-sister pairs ($r = 0.21$; nonsignificant). When AAO-FTD was considered, we observed highly significant correlations between mother-son, brother-brother, and brother-sister pairs and a moderate correlation in sister-sister pairs (table 3).

Analyses of *GRN* families revealed a nonsignificant heritability estimate of AAO ($h^2 = 0.26$) and intrafamilial correlations values (table 2). However, we observed a common thread with the analysis of *C9ORF72* families. The highest correlation values were observed for sibling pairs ($r = 0.24$), and the analysis of subtypes revealed higher correlation values for mother-son and brother-sister pairs ($r = 0.36$ and $r = 0.34$, respectively) without reaching statistical significance.

The lower parent-offspring correlation values observed in *C9ORF72* and *GRN* families compared with the sibling correlation may also underline a generational effect on AAO estimates. Cumulative proportions of disease onset in *C9ORF72* and *GRN* families according to generations are presented in figure. In both *C9ORF72* and *GRN* families, individuals in earliest-born generations have a reduced hazard ratio to develop disease compared with those in the latest-born generation ($p < 0.001$ and $p = 0.021$, respectively; table 4). Values of the hazard ratio were closer between *C9ORF72* and *GRN* families when taking into account the 2 more recent generations, i.e., the latest-born vs the second-born generations (0.45 vs 0.61, respectively; table 4). No generational effect was detected when considering the AAO of ALS (data not shown).

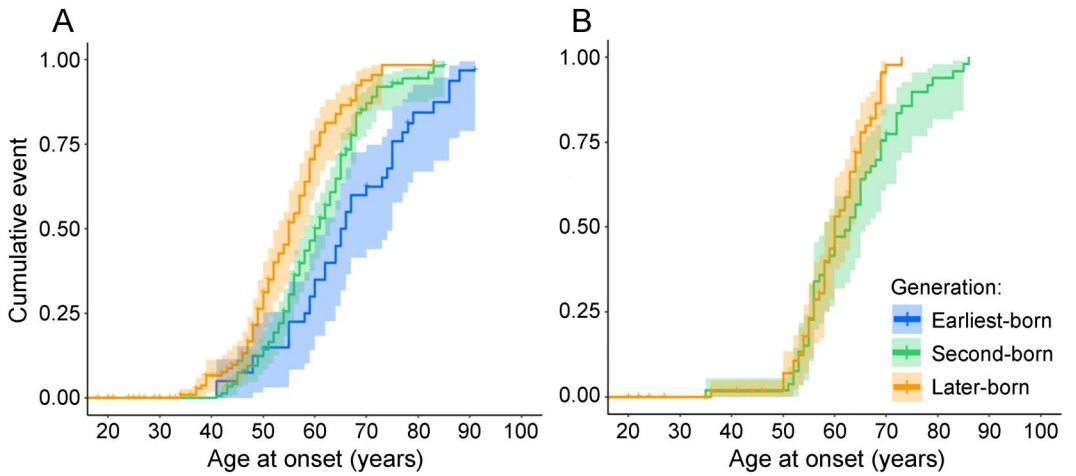
Table 3 Intrafamilial correlation coefficients (*r*) of AAO among first-degree relative subtypes in *C9ORF72* and *GRN* families

	C9 AAO		*C9* AAO-FTD		*GRN* AAO	
Pair subtypes	*r*	*p* Value	*r*	*p* Value	*r*	*p* Value
Father-son	0.03 (31)	0.89	−0.15 (19)	0.65	0.19 (13)	0.54
Mother-son	0.51 (33)	0.008	0.57 (17)	0.03	0.36 (15)	0.18
Father-daughter	0.06 (17)	0.89	0.36 (7)	0.63	0.07 (15)	0.83
Mother-daughter	−0.12 (30)	0.58	0.46 (15)	0.09	0.08 (15)	0.79
Brother-brother	0.58 (37)	0.0003	0.71 (15)	<1.10e−4	−0.17 (9)	0.62
Brother-sister	0.56 (70)	<1.10e−4	0.75 (33)	<1.10e−4	0.34 (23)	0.11
Sister-sister	0.21 (38)	0.22	0.46 (20)	0.04	0.08 (10)	0.82

Abbreviations: AAO = age at onset; FTD = frontotemporal lobar dementia.
The number of pairs is indicated in brackets.

DISCUSSION We provide the evidence for a strong genetic component influencing AAO in genetic FTD in *C9ORF72* families. Heritability estimates reached values closed to highly heritable diseases such as schizophrenia in which heritability estimates are between 0.4 and 0.8.[12] The analysis of *GRN* families revealed more contrasted results. If we cannot exclude a weaker effect of genetic factors on the AAO in the *GRN* cohort, the lower number of families (especially extended families) and patients included compared

Figure **Cumulative proportions of disease onset in familial frontotemporal lobar dementia with at least 2 successive generations**



Individuals were grouped by generations: later-born individuals belong to the youngest generation, second born and earliest born are parents and grand parents, respectively. (A) Patients with *C9ORF72* repeat expansions; (B) patients with *GRN* mutations.

with the *C9ORF72* cohort may not allow a reliable estimation of heritability.

In the *C9ORF72* population, the heritability explains between 44 and 62% of the phenotypic variance, given the phenotype considered (AAO and AAO-FTD, respectively). Results from the analysis of the AAO were very likely influenced by the AAO-FTD. First, the AAO-FTD was the most frequent available phenotype in our study. Second, the coefficient values and significance of results were consistently improved when the appearance of dementia symptoms was taken into account. Unfortunately, we did not have enough patients with isolated or associated ALS to perform similar and reliable analyses. One classic criticism of heritability estimates is that the influence of shared environment between relatives is often underestimated. However, the differences of correlation values among parent-offspring and sibling subtypes did not support a major role of a shared environment in the phenotypic correlations observed in first-degree relatives. Correlation values between brother-brother, brother-sister, and sister-sister pairs should have been homogeneous in case of a major role of a shared environment, which was not observed here. The same is true for parent-offspring pairs in which significant correlations have been observed only for mother-son pairs (table 3). If we cannot completely exclude an impact of a shared environment on our results, this role seems to be minor.

C9ORF72 mutations lead to pathogenic GGGGCC hexanucleotide expansions. Healthy controls usually carry 2 to 23 copies of the repeat, whereas patients have up to hundreds or thousands of hexanucleotide copies. Some studies evaluated whether the number of hexanucleotide repeats may influence the AAO, with contradictory conclusions.[13–15] This question is still debated, but we cannot exclude that expansion length variability may explain a part of the heritability in *C9ORF72* families. We were unable to examine the residual heritability after controlling for the *C9ORF72* repeat expansion size. Indeed, large *C9ORF72* repeat expansions cannot be sized by repeat-primed PCR, the methods classically used for molecular diagnosis. Second, the repeat length detected in peripheral lymphocytes is different and does not correlate with the repeat length in brain tissue,[14] thus precluding accurate correlations between the size of the repeat in affected tissues and the clinical parameters.

We detected lower correlation values in parent-offspring pairs in *C9ORF72* in our study. We showed that specific parent-of-origin effects in transmission of pathogenic alleles may explain such discordances in our cohort. Besides, a lower correlation of AAO among parent-offspring pairs could be due to the effect of successive generations on disease onset (anticipation) as well.

Table 4 **Generational effect analysis**

	Hazard ratio (95% CI)		
	Earliest-born generation	Second-born generation	Generational effect *p* value
C9ORF72	0.16 (0.08–0.30)	0.45 (0.30–0.67)	<0.001
GRN	—	0.61 (0.40–0.93)	0.021

Abbreviation: CI = confidence interval.
The hazard ratio of risk to develop disease in *C9ORF72* and *GRN* families was estimated with the latest-born generation as reference.

Indeed, anticipation is a well-known phenomenon influencing AAO in repeat expansion disorders such as Huntington disease or spinocerebellar ataxias.[16] This term implies that the unstable repeat expansion size tends to increase in successive generations, leading to an earlier and/or more severe expression of the disease in later-born generations. Anticipation of the AAO has been suggested in *C9ORF72* families in a clinically based study.[17] However, evidence of genetic anticipation is much more delicate to demonstrate at a molecular level in *C9ORF72* families than in other repeat expansion diseases as mentioned above. Moreover, expansions and even contractions of the repeats can happen in successive generations, as it has been shown for short *C9ORF72* expansions.[17] For these reasons, disease anticipation due to a repeat expansion phenomenon has not been conclusively demonstrated at the molecular level up to now.

We measured the generational effect on AAO in *C9ORF72* families using a mixed-effects Cox proportional hazard regression model that takes into account the degree of kinship. It is important that this model allows the inclusion of unaffected carriers (censored data) as well, which limits the right truncation bias, especially in the study of AAO compared with methods including only affected members.[18] We detected a strong generational effect on AAO, the AAO being earlier in the latest-born generation than in the ascending generation. In contrast to dynamic *C9ORF72* pathogenic repeat expansions, *GRN* mutations are stable single nucleotide variations or insertion/deletion leading to haploinsufficiency.[1,2] Strikingly, we observed a significant generational effect on AAO in *GRN* families with the same trend and the same range of the hazard ratio compared with *C9ORF72* families. So, it seems that a significant proportion of the generational effect in *C9ORF72* and in *GRN* pedigrees is likely to be due to observational biases rather than based on molecular mechanisms, as stable mutations in *GRN* cannot explain earlier AAO in successive generations.

A classic problem in studies involving AAO is a biased ascertainment of the AAO among familial cases independently of mutational effects and despite all precautions. Indeed, the first symptoms may be detected slightly earlier in younger generations when one of their parents has been affected by the same disease previously. A more efficient detection of cases due to technical or knowledge advances could also lead to detect cases earlier as before. In addition, it should be stressed that assessing precisely AAO, especially the AAO of dementia, implies more inaccuracy than assessing the clinical onset of motor symptoms of ALS in the absence of biomarkers of disease onset. To reduce this bias, we first excluded familial cases with unclear data. Second, we normalized the assessment of AAO with a define procedure used by clinicians to reduce and standardize the relative inaccuracy of AAO between patients.

However, and despite a generational effect on AAO affecting parent-offspring correlation values, it is noteworthy that the most significant correlation was observed only among mother-son pairs. The length of the pathogenic expansion may be more stable from mother to offspring rather than from father to offspring, as previously shown in other diseases due to nucleotide repeat expansions such as Huntington disease.[19] This could imply particular models of inheritance such as mitochondrial or X-linked inheritance as well. The fact that best correlation values were observed in mother-son, father-daughter, and mother-daughter pairs could imply more likely X-linked genetic modifiers. Indeed, X-linked transmission may explain higher correlation values when the X-chromosome is transmitted to the offspring. In addition, the X-chromosome inactivation that randomly affects one of the 2 X-chromosomes in women could influence the effect of potential X-linked modifiers and, subsequently, explains the reduced correlation coefficients, observed in sister-sister pairs. The hypothesis about an X-linked modifier based on statistical observations needs to be confirmed in larger populations and further investigated at the molecular level. Notably, we and others already evoked sex-mediated modifiers of *C9ORF72* disease in FTD as well as in ALS.[11,20,21] Of interest, X-linked modifiers have also been recently suggested in other repeat expansion disorders such as spinocerebellar ataxia type 2 in which the residual heritability not explained by the expansion length seems to be partially driven by X-linked factors.[22] This may suggest common genetic mechanisms modulating AAO in repeat expansion diseases.

These results derived from a familial approach are in favor of a significant genetic component influencing the AAO of FTD in patients with *C9ORF72* repeat expansions and in a lesser extent in patients with *GRN* mutations. This work justifies and reinforces the interest of searching for biomarkers and in particular genetic biomarkers influencing disease onset in FTD, thus acting on genetic counseling, therapeutic trials, and, to a broader extent, patient care.

AUTHOR CONTRIBUTIONS

Dr. Mathieu Barbier and Dr. Isabelle Le Ber: study concept and design. Dr. Agnès Camuzat, Dr. Clémence Fournier, and Dr. Fabienne Clot: acquisition of molecular data. Dr. Fabienne Clot, Dr. Paola Caroppo, Dr. Daisy Rinaldi, Dr. Florence Pasquier, Dr. Didier Hannequin, Dr. Jérémie Pariente, and Kathy Larcher: acquisition of patients' data. Dr. Mathieu Barbier, Dr. Audrey Sabbagh, Dr. Emmanuelle Génin, and Marion Houot: analysis and interpretation of data. Dr. Mathieu Barbier, Dr. Emmanuelle Génin, Dr. Audrey Sabbagh, Dr. Alexis Brice, and Dr. Isabelle Le Ber: drafting or revising the manuscript.

ACKNOWLEDGMENT

Predict-PGRN & PrevDemAls studies were conducted thanks to the Centre d'Investigation Clinique (CIC1422) at IHU-A-ICM, Paris, France. We thank clinicians from the French clinical and genetic research network on FTLD/FTLD-ALS and the Predict-PGRN-PrevDEMAls study groups (file e-4, http://links.lww.com/NXG/A7).

STUDY FUNDING

The research leading to these results has received funding from the program "Investissements d'avenir" ANR-10-IAIHU-06. This work was partially funded by Assistance Publique—Hôpitaux de Paris (Clinical Research and Development Department) Programme Hospitalier de Recherche Clinique (PHRC) FTLD-exome RCAOM-12123 (to I.L.B.), The PHRC Predict-PGRN P071229-AOM-08045 (to I.L.B.) and the ANR-PRTS PREV-DEMALS project (to I.L.B., funding and promotion by Assistance Publique—Hôpitaux de Paris and ANR).

DISCLOSURE

M. Barbier, A. Camuzat, M. Houot, F. Clot, P. Caroppo, C. Fournier, and D. Rinaldi report no disclosures. F. Pasquier has served on the scientific advisory board of Sanofi and Novartis; has served as a principal investigator for clinical trials funded by Neuus (Piramal), Forum Pharmaceuticals, Probiodrug, Lilly, Ramen, DIAN-TU, EnVivo Pharmaceutical, Roche, and Axovant; and has received research support from ANR Conseil Regional du Nord-Pas-de-Calais CNSA, Fondation Médéric Alzheimer, and Fondation Plan Alzheimer. D. Hannequin has received research support from the French Ministry of Health. J. Pariente has served on the scientific advisory boards of GE Healthcare and Lilly and has served on the editorial boards of the *Journal of Alzheimer's Disease* and *Revue Neurologique*. K. Larcher reports no disclosures. A. Brice has served on the scientific advisory boards of the FWO (Research Foundation Flanders), the ERC (European Research Council), and the BMBF (Bundesministerium für Bildung und Forschung—Berlin, Germany); has served on the editorial boards of *Neurology and Clinical Neuroscience*, *Parkinsonism and Related Disorders*, *Brain*, *Neurodegenerative Diseases*, *The Cerebellum*, and *Neurogenetics*; and has received research support from the French Research Agency (EU), the France Parkinson Association, the RDS (Roger de Spoelberch Foundation), the FDF (Fondation de France), and the FRM (Fondation pour la Recherche Médicale). E. Génin has served on the editorial boards of *Human Heredity* and *Genetic Epidemiology*. A. Sabbagh and I. Le Ber report no disclosures. Go to Neurology.org/ng for full disclosure forms.

Received July 19, 2017. Accepted in final form September 20, 2017.

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