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Longitudinal cognitive decline in autosomal-dominant Alzheimer's disease varies with mutations in *APP* and *PSEN1* genes

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ABSTRACT

The purpose was to compare longitudinal cognitive changes in *APP* and *PSEN1* gene mutation carriers and noncarriers from four autosomal-dominant Alzheimer's disease (ADAD) families across preclinical and early clinical stages of disease. Carriers (n = 34) with four different mutations ($PSEN1_{M146V}$, $PSEN1_{H163Y}$, APP_{SWE}, and APP_{ARC}) and noncarriers (n = 41) were followed up longitudinally with repeated cognitive assessments starting many years before the expected clinical onset. The relationship between cognition and years to expected clinical onset, education, age, and type of mutation was analyzed using mixed-effects models. Results showed an education-dependent and time-related cognitive decline with linear and quadratic predictors in mutation carriers. Cognitive decline began close to the expected clinical onset and was relatively rapid afterward in *PSEN1* mutation carriers, whereas decline was slower and started earlier than 10 years before expected clinical onset in *APP* mutation carriers. In noncarriers, the decline was minimal across time in accordance with normal aging. These results suggest that phenotypes for onset and rate of cognitive decline vary with *PSEN1* and *APP* genes, suggesting a behavioral heterogeneity in ADAD.

1. Introduction

Early-onset autosomal-dominant Alzheimer's disease (ADAD) caused by mutations in the presenilin 1 (*PSEN1*), presenilin 2, and amyloid precursor protein (*APP*) genes allows the investigation of the disease course from early presymptomatic stages. Previous studies on the time course of cognitive decline in ADAD have demonstrated that cognitive changes appear years before the clinical onset of Alzheimer's disease (AD) (Aguirre-Acevedo et al., 2016; Almkvist et al., 2017; Bateman et al., 2012; Fagan et al., 2014; Fleisher et al., 2015; Storandt et al., 2014; Wang et al., 2015; Yau et al., 2015) following curvilinear (Almkvist et al., 2017; Bateman et al., 2012; Fleisher et al., 2015; Jack and Holtzman, 2013; Yau et al., 2015), linear (Fagan et al., 2014; Storandt et al., 2014; Wang et al., 2015), or biphasic linear trajectories (Aguirre-Acevedo et al., 2016).

In studies of ADAD, carriers of mutations in different genes have been aggregated because the neuropathology and pathogenesis of ADAD caused by different mutations are considered to be similar (Hunter and Brayne, 2018; O'Brien and Wong, 2011). However, there is evidence that downstream processing of *APP* results in different distribution of Aβ metabolites ($Aβ_{38}$, $Aβ_{40}$, $sAβ_{α}$ and $sAβ_{β}$, $Aβ_{42}$), which could cause functional diversity (Hunter and Brayne, 2018; Rasmussen et al., 2017; Shepherd et al., 2009; Thordardottir et al., 2017). Mutation carriers in the *APP* gene have higher amounts of $Aβ_{40}$ in the cerebrospinal fluid and presence of cerebral amyloid angiopathy than mutation carriers in the *PSEN1* gene (Hunter and Brayne, 2018; Shepherd et al., 2009). Furthermore, clinical features of the different ADAD mutations differ, despite disease severity being similar (Ryan et al., 2016; Scahill et al., 2013; Tang et al., 2016).

In a previous cross-sectional study of cognition in ADAD (Almkvist et al., 2017) consisting of 79 participants (35 mutation carriers and 44 noncarriers from five families) evaluated for multiple cognitive tests only at baseline, the main effect of gene (*APP* vs. *PSEN1*) and the interaction of gene-by-time to expected clinical onset were not significant in any cognitive test. This result may be due to inherent limitations and lower statistical power of cross-sectional compared with longitudinal study designs, which motivated a longitudinal follow-up investigation.

The present study is a longitudinal investigation of cognition in the same cohort for which the cross-sectional data were previously

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reported (Almkvist et al., 2017). In this present study, 75 participants (34 mutation carriers and 41 noncarriers from four families) underwent multiple longitudinal follow-ups, in total 200 examinations. It was hypothesized that differences in the ADAD genotype may cause variability in the respective cognitive phenotype. Based on this hypothesis, the aim was to compare the longitudinal cognitive changes in carriers of mutations in *APP* and *PSEN1* genes by studying cognitive function measured for over 20 years in carriers and noncarriers of four ADAD families.

2. Material and methods

2.1. Participants

Adult members of four families carrying an early-onset ADAD mutation were invited to a comprehensive clinical examination at the Memory Clinic, Karolinska University Hospital Huddinge, Sweden, starting in 1993. One family carried the Swedish *APP* mutation (APP_{SWE}: K670N/M671L, n = 22; Axelman et al., 1994), another family carried the Arctic *APP* mutation (APP_{ARC}, E693G, n = 24; Nilsberth et al., 2001), and two families carried a mutation in the *PSEN1* gene: M146V (n = 16; Haltia et al., 1994) or H163Y (n = 13; Axelman et al., 1998). All adult individuals in each family were invited to a clinical examination, and all of those who accepted to participate were examined. After each visit, the participants were invited to a follow-up and again all who accepted were examined, and there was no selection bias. The study cohort comprised participants from families with a mutation in the *APP* or *PSEN1* genes (61% *APP* and 39% *PSEN1*); the proportions of the four mutations were 29%, 32%, 21%, and 18% (APP_{SWE}, APP_{ARC}, $PSEN1_{M146V}$, and $PSEN1_{H163Y}$, respectively). The mutation status (carrier vs. noncarrier) was unknown to both the professionals involved in the examinations and the participants, except for three asymptomatic participants, who opted for genetic testing after completion of several clinical examinations. In total, the study included 34 mutation carriers and 41 noncarriers; 200 examinations were carried out, and most of the participants (69%) underwent follow-up examinations including neuropsychological assessments. All individuals in the present longitudinal study participated in a previous cross-sectional study (Almkvist et al., 2017).

All participants provided written informed consent to participate in the study, which was conducted according to the Declaration of Helsinki and subsequent revisions. Ethical approval was obtained from the regional Human Ethics Committee of Stockholm and the Faculty of Medicine and Radiation Hazard Ethics Committee of Uppsala University Hospital, Sweden.

2.2. Age at onset of clinical symptoms

Each family was characterized by an average age at onset of clinical symptoms, as follows: 36 ± 3 years for $PSEN1_{M146V}$ (Haltia et al., 1994), 51 ± 7 years for $PSEN1_{H163Y}$ (Axelman et al., 1998; Thordardottir et al., 2015), 54 ± 5 years for APP_{SWE} (Axelman et al., 1994; Thordardottir et al., 2015), and 56 ± 3 years for APP_{ARC} (Nilsberth et al., 2001; Thordardottir et al., 2015). For each individual participant, both mutation carriers and noncarriers, years to expected clinical onset (YECO) was calculated as the individual's age at the time of the examination minus the mean family-specific age at clinical onset, in agreement with previous publications (Axelman et al., 1994, 1998; Haltia et al., 1994; Nilsberth et al., 2001; Thordardottir et al., 2015). The actual age at clinical onset of mutation carriers who were symptomatic at baseline or who became symptomatic over the course of the study was found to be highly correlated to the mean family-specific age at clinical onset (Pearson's r = 0.87; $p < 0.001$). The present study has used YECO calculated based on the family-specific age at clinical onset for consistency with our previous studies (Almkvist et al., 2017) and because a previous meta-analysis supports mean family history of age at onset as a reliable method (Ryman et al., 2014). However, to investigate if our results were robust, we also replicated our longitudinal findings by estimating YECO with respect to the observed age at clinical onset for those mutation carriers when that information was known (see Results).

2.3. Background characteristics

The background characteristics of the participants are presented in Table 1. Two-way (mutation status [carrier vs. noncarrier], specific mutation [4 types]) analyses of variance of baseline factors showed that there was no significant difference between mutation carriers and noncarriers regarding age, gender, education, YECO, and follow-up time (all p's > 0.1). Furthermore, there was no significant difference between the four mutations regarding education and follow-up time (p's > 0.1); the results remained nonsignificant after correction for multiple comparisons (Benjamini and Hochberg, 1995). The $PSEN1_{M146V}$ participants were significantly younger ($p < 0.001$) and closer to the expected clinical onset ($p < 0.01$) than participants from the other mutations. The $PSEN1_{H163Y}$ participants were less frequently females ($p < 0.01$) and had a longer follow-up time than those with the other three mutations (p's < 0.05). Owing to that individual mutation groups were not ideally balanced in terms of gender (*PSEN1* H163Y lacking female participants), it was not statistically feasible to include gender as a factor in subsequent analyses. Finally, there was no significant interaction between mutation status (carriers vs. noncarriers) and the four mutation types regarding age, gender, education, and YECO (all p's > 0.1), whereas the interaction was significant for follow-up time ($p < 0.05$). In summary, there were some differences in background characteristics, although not systematically related to mutation status, specific mutation type, or mutation status-by-type interaction, which lends support to the comparability of carriers and noncarriers across mutation types.

2.4. Diagnosis

The clinical diagnosis was made by consensus in a meeting of medical professionals (geriatricians, neurologists, psychologists, nurses, and speech pathologists) and was based on all available

Table 1
Baseline demographic characteristics, premorbid cognitive function (IQ), years to expected clinical onset (YECO), and follow-up time of mutation carriers and noncarriers of four ADAD families

Characteristics	$PSEN1_{M146V}$	$PSEN1_{H163Y}$	APP_{SWE}	APP_{ARC}
Mutation carriers				
N (female/male)	4 (2/2)	7 (0/7)	9 (5/4)	14 (4/10)
Age (M ± SD), y	36.4 ± 9.1	33.6 ± 7.4	45.7 ± 10.5	52.4 ± 7.8
Education (M ± SD), y	11.0 ± 4.0	11.6 ± 1.6	10.4 ± 1.8	11.1 ± 3.4
Premorbid IQ (M ± SD)	100.8 ± 15.3	105.3 ± 4.5	98.2 ± 5.1	102.1 ± 11.2
YECO, y	−0.5 ± 8.6	−13.1 ± 12.7	−10.2 ± 8.2	−3.6 ± 7.8
Follow-up time, y	4.1 ± 1.5	6.3 ± 6.8	8.7 ± 6.4	6.0 ± 2.7
Mutation noncarriers				
N (female/male)	12 (8/4)	6 (0/6)	13 (6/7)	10 (4/6)
Age (M ± SD), y	33.6 ± 11.5	37.9 ± 12.7	43.8 ± 8.2	49.2 ± 8.4
Education (M ± SD), y	9.8 ± 1.4	10.3 ± 1.5	10.9 ± 3.2	10.9 ± 2.3
Premorbid IQ (M ± SD)	96.1 ± 4.9	101.9 ± 4.2	100.0 ± 9.5	100.8 ± 7.3
YECO, y	−2.5 ± 8.6	−17.4 ± 7.4	−8.3 ± 10.5	−6.9 ± 8.4
Follow-up time, y	3.8 ± 1.6	5.3 ± 6.8	10.6 ± 7.1	7.7 ± 4.2

Key: IQ, intelligence quotient; M, mean; SD, standard deviation.

examination reports, excluding information on the mutation status. At baseline, six individuals were diagnosed as being demented according to the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 1994) and as having AD according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria (McKhann et al., 1984); all six were mutation carriers. At baseline, two mutation carriers were diagnosed as having mild cognitive impairment (MCI; Petersen, 2004). All the other individuals were asymptomatic.

At the time of the last follow-up examination, 11 mutation carriers had been diagnosed as having AD, three as having MCI and 9 were still asymptomatic carriers. No noncarrier was diagnosed with AD, MCI, or any other disease affecting the brain, either at baseline or at any follow-up examination. Two healthy noncarriers had had lifelong selective nonprogressive cognitive difficulties because of specific syndromes (dyslexia and spatial disorientation). The data for these two participants were retained in the study but excluded for selectively impaired tests caused by the specific syndrome.

2.5. Procedure

Each examination included a comprehensive clinical evaluation of somatic, neurological, and psychiatric status and cognitive function, blood samples, and brain magnetic resonance images. Although clinical examinations started as far back as 1993, essentially the same protocol was followed throughout the study.

2.6. Assessment of cognitive function

Premorbid global cognitive function was assessed using a regression formula with demographic information and reading test results (Almkvist and Tallberg, 2009). Present global cognitive function was assessed using five separate subtests (the Information, Digit Span, Similarities, Block Design, and Digit Symbol tests) from the Wechsler Adult Intelligence Scale Revised (Bartfai et al., 1994; Wechsler, 1981). Short-term memory/attention was assessed using the Digit Span Forward test and the Corsi Span test (Lezak et al., 2004). The Rey Auditory Verbal Learning test (RAVL learning) was used to assess verbal episodic memory, the free recall score after 30 minutes (RAVL retention) was used to assess retention (Lezak et al., 2004), and the Rey-Osterrieth 30 minutes retention (RO retention) was used to assess visuospatial episodic memory (Lezak et al., 2004). Executive function was assessed using the Digit Symbol and Trail Making tests A and B (TMTA and TMTB, respectively) (Lezak et al., 2004). Raw scores were converted to z-scores using a reference group of healthy adults at Karolinska University Hospital, Huddinge (Bergman et al., 2007).

2.7. Statistical analysis

Descriptive statistics were used to analyze baseline information. Longitudinal neuropsychology data were analyzed using mixed-effects models, implemented in two steps.

In step 1, mixed-effects models were used to describe longitudinal cognition separately in carriers and in noncarriers, where each of the neuropsychology tests was used as the dependent variable, and YECO, $YECO^2$ (the quadratic term YECO*YECO), education, and age were fixed-effects predictors; all models included a random intercept at the subject level to account for longitudinal within-individual correlations.

In step 2, gene (*PSEN1* vs. *APP*) and gene-by-YECO interaction were used as fixed-effects predictors in addition to YECO, $YECO^2$, education, and age in models analyzing mutation carriers and noncarriers separately for each cognitive test; all models included a random intercept at the subject level to account for longitudinal within-individual correlations.

The results of mixed-effect models on one test of episodic memory (RAVL learning) were illustrated using smoothing natural spline curves to display the longitudinal trajectories of RAVL learning with respect to YECO for mutation carriers and noncarriers (Fig. 1). The gene-dependent trajectories (*PSEN1* and *APP*) of longitudinal decline in mutation carriers in comparison with all noncarriers were illustrated in Fig. 2, in which smoothing natural spline curves with respect to YECO were used to display the trajectories of four cognitive tests in which the gene-by-YECO interaction was significant (RAVL learning, Digit Symbol, Block Design, and Corsi Span) in mutation carriers. The respective time points at which the temporal trajectories of mutation carriers in *PSEN1* and *APP* genes started to diverge from that of noncarriers were estimated as the time at which the corresponding 95% confidence bands around the smoothing spline fitting curves no longer overlapped.

In all mixed-effects models, the covariance matrix of the residuals was modeled by an unstructured matrix, implemented using restricted maximum likelihood estimation. Statistical significance was set at $p < 0.05$. All mixed-effects models were implemented in the NLME (non-linear mixed-effects) package in R (version 3.3.3, The R foundation for Statistical Computing, http://www.r-project.org/). Visualizations were created using the ggplot2 package in R.

3. Results

3.1. Premorbid and baseline cognitive function in ADAD carriers and noncarriers

The mean values of estimated premorbid cognitive function (IQ scale) for carriers and noncarriers in the four ADAD families are presented in Table 1. Two-way (mutation status [carrier vs. noncarrier] and specific mutation [four types]) analyses of variance showed that the estimated premorbid global cognitive function was not significantly different because of either mutation status, or mutation type, or mutation status-by-type interaction. Furthermore, the carriers and noncarriers of the four mutations were comparable in the majority of specific cognitive tests at baseline. However, the interaction between mutation status (carrier vs.

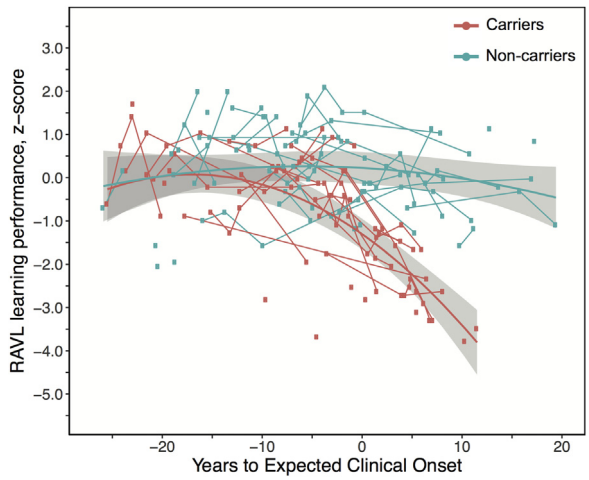

Fig. 1. Trajectories of longitudinal cognitive decline in carriers and noncarriers of four autosomal-dominant Alzheimer's disease mutations (APP_{SWE}, APP_{ARC}, $PSEN1_{M146V}$, or $PSEN1_{H163Y}$) for a test of episodic memory (RAVL learning). Test results are presented as z-scores versus years to expected family-specific clinical onset (YECO). Abbreviations: RAVL, Rey Auditory Verbal Learning; YECO, years to expected clinical onset.

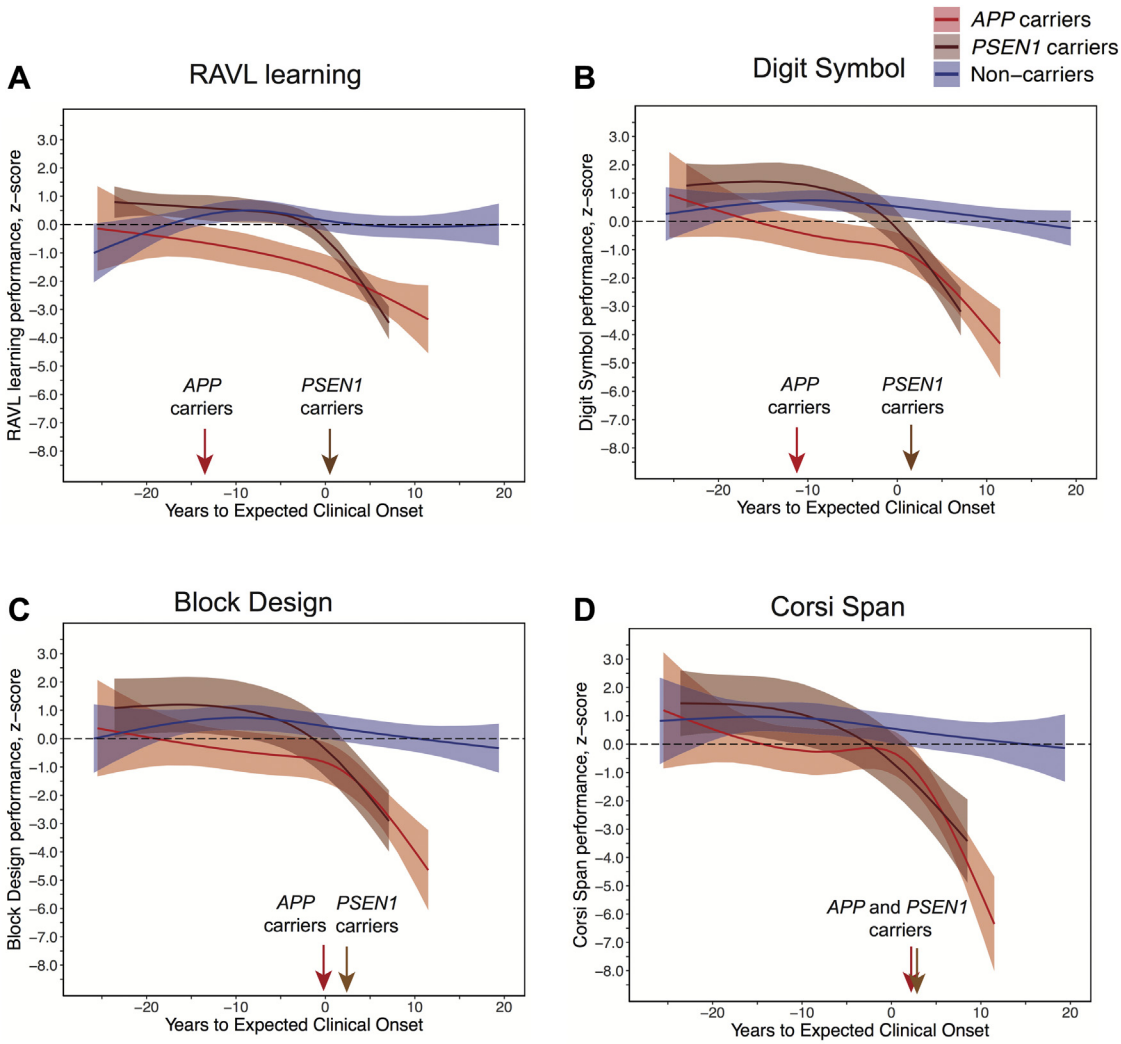

Fig. 2. Gene-dependent (*PSEN1* vs. *APP*) trajectories of longitudinal cognitive decline in carriers of four autosomal-dominant Alzheimer's disease mutations (APP_{SWE}, APP_{ARC}, $PSEN1_{M146V}$, or $PSEN1_{H163Y}$) for the following tests: episodic memory (RAVL learning, panel A), executive function (Digit Symbol, panel B), visuospatial function (Block Design, panel C), and working memory (Corsi Span, panel D) in comparison to the trajectory for all noncarriers from the same four families. Test results are presented as z-scores versus years to expected family-specific clinical onset (YECO). Abbreviations: *APP*, amyloid precursor protein; *PSEN1*, presenilin 1; RAVL, Rey Auditory Verbal Learning; YECO, years to expected clinical onset.

noncarrier) and gene (*APP* vs. *PSEN1*) was significant in two tests of episodic memory (RAVL learning and RO retention).

3.2. Tracking longitudinal cognitive decline in ADAD carriers and noncarriers

The longitudinal cognitive results for each test were modeled separately for mutation carriers and noncarriers as a function of YECO, $YECO^2$, age, and education; see Table 2. The pattern of the results suggests that cognitive performance is differentially influenced by YECO, $YECO^2$, age, and education in carriers and noncarriers. For carriers, YECO and $YECO^2$ were significantly and negatively associated with all the 12 cognitive tests. Education was significantly and positively associated with nine tests, whereas age was not significantly associated with any test. For noncarriers, the significant associations between tests and the time-related predictors (YECO and $YECO^2$) were few, two for YECO (one positive and one negative) and four for $YECO^2$ (negative) and the strength of association was less powerful for noncarriers than carriers. Education was significantly positively associated with seven tests, and age was negatively associated with four tests (Corsi Span, RAVL learning, RO retention, and Digit Symbol). The longitudinal trajectories of RAVL learning across YECO for carriers and illustrated in Fig. 1 show a time-related differentiation between carriers and noncarriers as well as interindividual heterogeneity in decline within both carriers and noncarriers.

3.3. Comparing longitudinal cognitive decline in PSEN1 and APP genes

To investigate whether the heterogeneity of cognitive decline in carriers was caused by gene differences, the previous mixed-effects model analyses were modified by adding the specific gene (*PSEN1* vs. *APP*) and the gene-by-YECO interaction as fixed factors. An overview of the outcome is presented in Table 3. YECO was a significant negative predictor in nine tests (the exceptions were Corsi Span, TMTA, and TMTB) for carriers and in four tests (Information, Similarities, RAVL retention, and Digit Symbol) for noncarriers. $YECO^2$ was a significant negative predictor in all 12 tests for carriers and in three tests (Similarities, Block Design, and TMTB) for

Table 2
Results of mixed-effect models applied to neuropsychological test results (z-scores) as a function of four independent predictors: YECO, YECO^2, education, and age in mutation carriers and noncarriers of four ADAD mutations

Test	YECO, estimate [SE]	YECO^2, estimate [SE]	Education, estimate [SE]	Age, estimate [SE]
Mutation carriers				
Information	−0.113 [0.030]***	−0.004 [0.001]***	+0.368 [0.061]***	ns
Similarities	−0.139 [0.040]***	−0.005 [0.002]***	+0.242 [0.082]**	ns
Block Design	−0.161 [0.042]***	−0.005 [0.001]***	+0.342 [0.074]***	ns
RO copying	−0.160 [0.039]***	−0.006 [0.001]***	+0.205 [0.067]**	ns
Digit Span	−0.073 [0.029]*	−0.003 [0.001]**	+0.159 [0.058]**	ns
Corsi Span	−0.150 [0.053]**	−0.005 [0.001]***	ns	ns
RAVL learning	−0.139 [0.031]***	−0.005 [0.001]***	+0.159 [0.059]*	ns
RAVL retention	−0.157 [0.037]***	−0.006 [0.001]***	ns	ns
RO retention	−0.174 [0.040]***	−0.006 [0.001]***	ns	ns
Digit Symbol	−0.156 [0.034]***	−0.005 [0.001]***	+0.252 [0.068]***	ns
TMTA	−0.104 [0.041]*	−0.005 [0.002]**	+0.231 [0.066]***	ns
TMTB	−0.114 [0.050]*	−0.008 [0.002]***	+0.283 [0.091]**	ns
Mutation noncarriers				
Information	ns	ns	+0.274 [0.073]***	ns
Similarities	ns	−0.002 [0.001]*	+0.216 [0.061]***	ns
Block Design	ns	ns	+0.243 [0.069]***	ns
RO copying	ns	ns	ns	ns
Digit Span	ns	−0.002 [0.001]**	+0.179 [0.054]**	ns
Corsi Span	−0.055 [0.028]*	ns	ns	−0.086 [0.024]***
RAVL learning	ns	ns	ns	−0.042 [0.018]*
RAVL retention	ns	ns	ns	ns
RO retention	ns	ns	ns	−0.049 [0.019]*
Digit Symbol	+0.041 [0.016]*	−0.001 [0.001]*	+0.190 [0.050]***	−0.068 [0.014]***
TMTA	ns	ns	+0.107 [0.038]**	ns
TMTB	ns	−0.001 [0.001]*	+0.124 [0.048]*	ns

For each predictor, the corresponding estimates, standard error (SE) within brackets, and statistical significance (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$) are presented.
Key: RAVL, Rey Auditory Verbal Learning; RO, Rey-Osterrieth; TMTA, Trail Making Test A; TMTB, Trail Making Test B; YECO, years to expected clinical onset.

noncarriers. All associations with YECO and YECO^2 showed that test performance decreased in a time-related manner. Education was a significant positive predictor in nine tests for carriers and in seven tests for noncarriers, implying that higher education was a favorable factor for performance in general. Increasing age was a significant positive predictor in the same two tests (Information and Similarities) for carriers and noncarriers. In addition, two tests (Corsi Span and Digit Symbol) were significantly and negatively related to age for noncarriers. The gene effect was significant in two tests (Similarities and Block Design) for carriers and in one test (Similarities) for noncarriers. Finally, the gene-by-YECO interaction was significant and positive in four tests (Block Design, Corsi Span, RAVL learning, and Digit Symbol) for carriers and in one test (RAVL retention) for noncarriers. These findings indicate that carriers with *APP* versus *PSEN1* genes differ in the temporal progression of cognition in relation to YECO.

The gene-by-YECO interaction effect in *PSEN1* and *APP* mutation carriers compared with all noncarriers is illustrated in Fig. 2 in four tests: RAVL learning (panel A), Digit Symbol (panel B), Block Design (panel C), and Corsi Span (panel D). As seen in Fig. 2, the longitudinal cognitive decline began 14 and 12 years ahead of expected clinical onset for episodic memory (RAVL learning) and executive function (Digit Symbol), respectively, in *APP* mutation carriers compared with the trajectory for noncarriers. In *PSEN1* mutation carriers, this time point occurred close to the expected clinical onset in both tests. For both *PSEN1* and *APP* mutation carriers, there was a sequential order of affected cognitive domains, with changes first observed in episodic memory (RAVL learning) and then in executive function (Digit Symbol), followed by visuospatial function (Block Design) and working memory/attention (Corsi Span).

Supplementary Fig. 1 depicts the individual longitudinal trajectories of mutation carriers within each of the four individual families compared with all noncarriers for RAVL learning (panel a) and Digit Symbol (panel b). Statistical models incorporating interaction analyses between individual mutation types (Supplementary Table 1) showed that APPswe and APParc followed similar trajectories, which were significantly differentiated from those of PSEN1 M146V and PSEN1 H163Y mutation carriers, as also illustrated in Supplementary Fig. 1.

All longitudinal analyses for the group of mutation carriers as a whole, and to investigate the (*APP* vs. *PSEN1*)*YECO interaction in mutation carriers, were replicated with YECO estimated with respect to the observed age at clinical onset in subjects who become symptomatic carriers, and both methods resulted in essentially the same findings (Supplementary Tables 2 and 3; Supplementary Fig. 2). In addition, and to investigate if our results were driven by symptomatic mutation carriers, the aforementioned longitudinal analyses were repeated by excluding the longitudinal trajectories of eight mutation carriers who were symptomatic at baseline (Supplementary Tables 4 and 5; Supplementary Fig. 3), resulting in essentially the same findings.

4. Discussion

The four families with a specific mutation in ADAD ($PSEN1_{M146V}$, $PSEN1_{H163Y}$, APP_{SWE}, and APP_{ARC}) in this longitudinal study of cognitive performance were comparable in estimated premorbid global cognitive function. Furthermore, the carriers and noncarriers of the four mutations were comparable in the majority of specific cognitive tests at baseline. However, the interaction between mutation status (carrier vs. noncarrier) and gene (*APP* vs. *PSEN1*) was significant in two tests of episodic memory (RAVL learning and RO retention) and one test of executive function (Digit Symbol), indicating a possible cognitive differentiation related to the specific gene many years ahead of the expected clinical onset. This gene-by-phenotype finding has not been reported previously to our knowledge, and it was not observed in the previously reported cross-sectional study on cognition from the same cohort (involving a total of 79 cross-sectional observations for each cognitive test) (Almkvist et al., 2017). The reason for this difference may be due to the increased statistical power in the present longitudinal study (200 observations in each cognitive test), which incorporates intraindividual variation in cognition.

Table 3
Results of mixed-effects models applied to neuropsychological test results (z-scores) in mutation carriers and noncarriers including gene-by-YECO interaction

Test	YECO, estimate [SE]	$YECO^2$, estimate [SE]	Education, estimate [SE]	Age, estimate [SE]	Gene, estimate [SE]	Gene x YECO, estimate [SE]
Mutation carriers						
Information	−0.141 [0.038]***	−0.004 [0.001]***	+0.369 [0.057]***	+0.079 [0.035]*	ns	ns
Similarities	−0.213 [0.050]***	−0.005 [0.001]***	+0.222 [0.075]**	+0.113 [0.046]*	+1.46 [0.598]*	ns
Block Design	−0.221 [0.045]***	−0.006 [0.001]***	+0.348 [0.067]***	ns	+1.23 [0.545]*	−0.064 [0.022]**
RO copying	−0.171 [0.052]**	−0.006 [0.001]***	+0.215 [0.071]*	ns	ns	ns
Digit Span	−0.091 [0.038]*	−0.004 [0.001]***	+0.161 [0.056]*	ns	ns	ns
Corsi Span	ns	−0.007 [0.002]***	ns	ns	ns	−0.084 [0.034]**
RAVL learning	−0.154 [0.039]***	−0.007 [0.001]***	+0.178 [0.058]**	ns	ns	−0.062 [0.023]**
RAVL retention	−0.168 [0.047]***	−0.006 [0.001]***	ns	ns	ns	ns
RO retention	−0.222 [0.052]***	−0.006 [0.001]***	ns	ns	ns	ns
Digit Symbol	−0.159 [0.048]**	−0.007 [0.001]***	+0.274 [0.070]***	ns	ns	−0.058 [0.023]**
TMTA	ns	−0.005 [0.002]**	+0.244 [0.068]***	ns	ns	ns
TMTB	ns	−0.001 [0.001]*	+0.124 [0.049]*	ns	ns	ns
Mutation noncarriers						
Information	−0.083 [0.037]*	ns	+0.282 [0.074]***	+0.075 [0.035]*	ns	ns
Similarities	−0.112 [0.032]***	−0.002 [0.001]**	+0.227 [0.058]***	+0.103 [0.029]***	+1.56 [0.507]**	ns
Block Design	ns	−0.002 [0.001]*	+0.254 [0.067]***	ns	ns	ns
RO copying	ns	ns	ns	ns	ns	ns
Digit Span	ns	ns	+0.179 [0.054]**	ns	ns	ns
Corsi Span	ns	ns	ns	−0.117 [0.042]**	ns	ns
RAVL learning	ns	ns	ns	ns	ns	ns
RAVL retention	−0.072 [0.035]*	ns	ns	ns	ns	−0.041 [0.020]*
RO retention	ns	ns	ns	ns	ns	ns
Digit Symbol	−0.054 [0.027]*	ns	+0.188 [0.050]***	−0.087 [0.025]***	ns	ns
TMTA	ns	ns	+0.103 [0.038]**	ns	ns	ns
TMTB	Ns	−0.001 [0.001]*	+0.124 [0.049]**	ns	ns	ns

The table presents the corresponding estimates, the standard error (SE) within brackets, and the statistical significance (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$).
Key: RAVL, Rey Auditory Verbal Learning; RO, Rey-Osterrieth; TMTA, Trail Making Test A; TMTB, Trail Making Test B; YECO, years to expected clinical onset.

The longitudinal analysis of cognitive trajectories showed that the decline across preclinical and clinical stages was well reproduced using linear (YECO) and curvilinear ($YECO^2$) time measures, years of education, and age in mutation carriers. These findings fit well with previous research on mutation carriers (Almkvist et al., 2017; Bateman et al., 2012; Fagan et al., 2014; Fleisher et al., 2015; McDade et al., 2018; Storandt et al., 2014; Yau et al., 2015). The significant curvilinear predictor of decline has been observed in ADAD mutation carriers in previous research, although it has not been commonly incorporated into statistical models (Bateman et al., 2012; Fleisher et al., 2015). For noncarriers, the longitudinal cognitive changes were relatively small and not significantly related to the time measures for the majority of cognitive tests clearly indicating divergent trajectories of cognitive change across time in carriers versus noncarriers (Almkvist et al., 2017; Bateman et al., 2012; Fagan et al., 2014; Fleisher et al., 2015; Storandt et al., 2014; Yau et al., 2015). The minor cognitive changes in noncarriers are in agreement with longitudinal studies of healthy cognitive aging (Glorioso and Sibille, 201; Schaie and Willis, 2010).

The favorable impact of education observed in both carriers and noncarriers in the present as well as in the previous cross-sectional study (Almkvist et al., 2017), where extended education appears to counter the effects of both brain neuropathology and normal aging, has been observed previously in sporadic cohorts, but its effect is not well known in ADAD. Our study provides evidence that cognitive reserve (Stern, 2009) is a significant factor in ADAD and that this phenomenon explains part of the interindividual variability in cognitive performance in both familial and sporadic AD, brain disease in general as well as in healthy aging (Amieva et al., 2014; Barulli and Stern, 2013; Bergman et al., 2007; Stern, 2009).

So far, the present study has demonstrated that cognitive decline in the present cohort is related to disease advancement as evaluated by YECO and $YECO^2$ and disease counteraction by education, consistent with our previous findings in the cross-sectional study of the same cohort (Almkvist et al., 2017). Increasing age was a significant and negative predictor particularly in noncarriers and in specific tests related to memory and executive function typically showing decline in normal aging (Bergman et al., 2007). However, there was still interindividual variation in cognitive decline that could be taken into account by analyzing the possible influence by gene (*PSEN1* and *APP*) and gene-by-YECO interaction.

The gene and gene-by-YECO analyses showed that cognitive trajectories across time for carriers of *PSEN1* and *APP* genes were different and began to diverge in the preclinical stage of disease at different times, earliest in *APP* gene carriers and close to the expected clinical onset in *PSEN1* carriers. The earliest signs were seen in episodic memory, followed by executive function, visuospatial ability, and then other domains following a similar sequence in *PSEN1* and *APP* gene carriers. The beginning of dissociated gene-dependent trajectories was 14 years before the expected clinical onset for episodic memory (RAVL learning) and 12 years before the expected clinical onset for executive function (Digit Symbol) in carriers of the *APP* gene, whereas carriers of the *PSEN1* gene began declining in both domains at about the expected clinical onset. A similar estimate of the earliest cognitive change, especially affecting episodic memory or memory generalization, has been reported for presymptomatic carriers in previous studies regarding ADAD (Almkvist et al., 2017; Bateman et al., 2012; Guzman-Velez et al., 2018; McDade et al., 2018; Petok et al., 2018; Wang et al., 2015), although not related to a specific gene or mutation. This estimate seems to correspond to the time point of metabolic and structural changes in ADAD as reported recently (Gordon et al., 2018). The present finding of early cognitive change in *APP* gene carriers suggests that models of preclinical changes in ADAD need modification by taking possible gene effects into account (Jack and Holtzman, 2013). In summary, the analyses of gene and gene-by-YECO interaction lend support to the fact that there is a gene-related variation in cognitive phenotypes of ADAD. This significant gene-dependent effect was replicated when all statistical analyses were repeated by using the observed age at clinical onset in those mutation carriers who were symptomatic or became symptomatic during the study, adding robustness to the findings. In addition, the gene-dependent effect was also significant when removing from the analyses the longitudinal trajectories of eight mutation carriers who were

symptomatic at baseline, thus indicating that the gene-dependent effect is not driven by the symptomatic stage of the disease. This gene-dependent effect represents a new finding that may have clinical implications. In contrast, our previous cross-sectional study in the same cohort investigated only at baseline (Almkvist et al., 2017) did not find a significant difference in the cognitive trajectories of *APP* versus *PSEN1* mutation carriers. The difference between longitudinal and cross-sectional studies regarding gene-dependent effects when the participants are almost the same may be due to the increased statistical power in the longitudinal study and the unfavorable influence from interindividual variability in the cross-sectional study. Longitudinal studies have been reported to be more accurate for determining the temporal trajectories of biomarkers, whereas cross-sectional studies are more influenced by intersubject variability (Gordon et al., 2018; McDade et al., 2018; Xu et al., 2014). Thus, the different findings between the present and our previous study (Almkvist et al., 2017) are likely due to the increased statistical power of the longitudinal over the cross-sectional design.

The findings that the onset and rate of cognitive decline vary in carriers with different mutations may be related to variations in downstream *APP* metabolites leading to variations in physiological function (Hunter and Brayne, 2018; O'Brien and Wong, 2011; Shepherd et al., 2009; Thordardottir et al., 2017) and phenotypes. These findings correspond to neuropathological data describing the distribution of neurofibrillary tangles in the brain during the course of the disease (Braak and Braak, 1991). Differences in symptomatology are well known, as *APP* carriers typically have a later onset of symptoms in chronological age (earlier in terms of YECO) than *PSEN1* carriers, who have an earlier onset in chronological age (later in terms of YECO). The amnestic disturbance is more prominent in *APP* carriers (Hunter and Brayne, 2018; Rasmussen et al., 2017; Shepherd et al., 2009; Thordardottir et al., 2017), whereas *PSEN1* carriers often show motor symptoms (Rasmussen et al., 2017; Ringman et al., 2014; Shepherd et al., 2009; Tang et al., 2016).

Limitations of the present study include a relatively small sample size, relative imbalance in gender distribution across mutations, and that only four ADAD mutations were investigated, thus implying uncertainty in the extent to which our findings may be generalizable to other ADAD mutations or to sporadic AD. Nevertheless, all participants were drawn from a single center and were evaluated longitudinally following the same procedures, which lend support to the reliability of methods used. The main strength of the present study is its longitudinal design, which made it possible to track the cognitive changes across about 20 years in some individuals and to follow changes in very early disease course when carriers are asymptomatic as well as the early part of the clinical stage when carriers are in the mild dementia stage. Most available studies in ADAD have investigated cohorts with a majority of members from *PSEN1* families, whereas our cohort consisted of individuals from *PSEN1* and *APP* families. The noncarriers underwent the same examinations as carriers, which confirmed their healthy status. Furthermore, several factors were combined to predict cognitive decline including linear and curvilinear time, education, age, and genes as predictors; this represents a new approach and adds to previous knowledge. Still, there may be other relevant factors to be investigated in future studies. Future longitudinal studies in ADAD cohorts comparing ADAD and sporadic AD will be valuable to investigate the generalizability of our findings and their implications toward our understanding of the temporal trajectory of Alzheimer's disease.

5. Conclusion

The cognitive decline in mutation carriers and noncarriers was clearly differentiated already in the preclinical stage. In addition, a gene-related differentiation of the cognitive phenotypes in the temporal measures of decline was observed between *APP* and *PSEN1* mutation carriers. The onset of cognitive decline was earlier in *APP* than *PSEN1* mutation carriers, and the rate of decline was slower in *APP* than *PSEN1* mutation carriers. This pattern of results demonstrated a novel gene-dependent variation of cognitive phenotypes that may be important to consider for prevention, clinical practice, and future treatment trials.

Disclosure

The authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurobiolaging.2019.06.010.

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