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Featured Article

Genetic risk of neurodegenerative diseases is associated with mild cognitive impairment and conversion to dementia

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Abstract

Introduction: Neurodegenerative diseases are a major cause of cognitive impairment and can ultimately lead to dementia. Genome-wide association studies have uncovered many genetic variants conferring risk of neurodegenerative diseases, but their role in cognitive impairment remains unexplored.

Methods: In the prospective, population-based Rotterdam Study, 3605 nondemented persons aged ≥55 years were genotyped, screened for mild cognitive impairment (MCI) in 2002 to 2005 and underwent continuous follow-up for dementia until 2012. Weighted polygenic risk scores of genetic variants for Alzheimer's disease (AD), Parkinson's disease (PD), and the frontotemporal lobar degeneration/amyotrophic lateral sclerosis disease spectrum (FTLD/ALS) were constructed and investigated for association with MCI and the subsequent conversion to dementia.

Results: In total, 360 (10.0%) persons had MCI, of whom 147 (4.1%) were amnestic and 213 (5.9%) nonamnestic. The AD risk score was associated with both MCI subtypes (odds ratio for all MCI 1.15 [95% CI, 1.03–1.28]), whereas PD and FTLD/ALS risk scores were associated only with nonamnestic MCI (odds ratios 1.15 [1.00–1.32] and 1.19 [1.03–1.37], respectively). The AD risk score, but not PD and FTLD/ALS risk scores, was associated with an increased risk of dementia (hazard ratio 1.55 [1.37–1.77]).

Discussion: Genetic evidence supports the view that multiple neurodegenerative pathways lead to MCI and that the subsequent conversion to dementia, primarily of the AD subtype, is mainly due to the AD pathway(s).

Keywords: Mild cognitive impairment; Genetics; Dementia; Alzheimer's disease; Parkinson's disease; Frontotemporal lobar degeneration; Amyotrophic lateral sclerosis

1. Introduction

Aging populations worldwide face an increasing burden of neurodegenerative diseases [1]. Major diseases, in terms of mortality, morbidity, and health care costs, include Alzheimer's disease (AD), Parkinson's disease (PD), frontotemporal lobar degeneration (FTLD), and amyotrophic lateral sclerosis (ALS). Cognitive impairment is the most prominent in AD [2,3] and FTLD [4], but it is also an important feature of PD [5] and ALS [6]. Our genetic understanding of these neurodegenerative diseases has improved considerably over the past years through large-scale genome-wide association studies that have identified a large number of novel risk variants [7–12]. However, due to the

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hypothesis-free design of genome-wide association studies, it remains largely unknown how these genetic variants lead to cognitive decline and ultimately clinical disease.

The severe deterioration in cognitive function seen in neurodegenerative diseases is often preceded by a preclinical stage with only subtle cognitive deficits that deteriorate over time. Mild cognitive impairment (MCI) describes this intermediate state and is variable in both its clinical presentation and conversion to dementia [3]. Given that MCI provides a window of opportunity for preventive or therapeutic interventions, it is important to uncover risk factors for MCI and factors that lead to the conversion of MCI to dementia. The diagnosis of MCI is made on clinical grounds and, although cognitive abilities are highly heritable [13], the genetic basis of MCI remains largely unknown [2]. Apolipoprotein E (*APOE*), the major risk gene in AD, is known to play a role in MCI [14], but whether other, recently identified genetic variants for neurodegenerative diseases are also involved has yet to be determined.

In this study, we investigated the effect of genetic risk variants of AD, PD, FTLD, and ALS on MCI status and the subsequent conversion of MCI to dementia.

2. Methods

2.1. Setting

The Rotterdam Study is an ongoing population-based cohort study in the Netherlands investigating diseases in the elderly and currently consists of 14,926 residents of Rotterdam who were aged 45 years or more at baseline [15]. The initial cohort was started in 1990 and expanded in 2000 and 2005. The whole population is subject to a set of multidisciplinary examinations every 4 years. Genotyping was performed in 11,496 participants at study entry. MCI status was assessed only between 2002 and 2005, and was available in 4198 participants. This resulted in a final study population of 3605 nondemented persons with information available on both genome-wide genotyping and MCI status, who were subsequently followed up for the development of dementia until 2012. The Rotterdam Study has been approved by the medical ethics committee according to the Population Study Act Rotterdam Study, executed by the Ministry of Health, Welfare and Sports of the Netherlands. A written informed consent was obtained from all participants.

2.2. Genotyping

The Illumina 550K and 550K duo arrays were used for genotyping. We removed samples with call rate lower than 97.5%, gender mismatch, excess autosomal heterozygosity, duplicates or family relations and ethnic outliers, and variants with call rate lower than 95.0%, failing missingness test, Hardy-Weinberg equilibrium P-value $<10^{-6}$, and minor allele frequency $<1\%$. Genotypes were imputed using Markov Chain Haplotyping (MaCH)/minimac software to the 1000 Genomes phase I version 3 reference panel (all population). *APOE* ε4 genotyping was performed separately using polymerase chain reaction and was available in 3524 (97.8%) participants [16].

2.3. Genetic risk scores

We searched the literature for genetic variants for AD, PD, FTLD, and ALS. Given our population-based setting, we focused on sporadic mutations and therefore excluded mutations of familial disease (e.g., presenilin 1 [PSEN1], presenilin 2 [PSEN2], amyloid precursor protein [APP] in AD and granulin [GRN] in FTLD). Because various candidate gene studies have been performed that implicated hundreds of variants in these four neurodegenerative diseases, we have tried to minimize false-positives by including only those variants that were genome-wide significant in the largest meta-analysis of that disease. We chose to use this objective threshold and did not base decisions on functional work that potentially corroborated the findings. Notable loci that did not pass this strict threshold were CD33 and angiotensin-converting enzyme (ACE). Other variants that were considered but not included were not genotyped nor imputed with sufficient quality ($R^2 < 0.5$) in our data set, and a suitable proxy variant was absent: these were typically rare (triggering receptor expressed on myeloid cells 2 [TREM2], phospholipase D family, member 3 [PLD3], β-Glucocerebrosidase [GBA]) or in the poorly covered), human leukocyte antigen (HLA) region (AD: rs111418223, PD: rs115736749, rs9275326).

For our analyses we identified 19 variants for AD, 25 variants for PD, one variant for FTLD, and two variants for ALS (Table 1) [7–12,17–19]. Because FTLD and ALS are considered extremes of the same disease spectrum, and the FTLD variant is also implicated in ALS, we decided to pool the three variants together for increased power. The variant rs3849943 is tagging the C9orf72 hexanucleotide expansion, which itself was not assessed in our study [9].

Genetic risk scores were constructed by multiplying the number of risk alleles by their reported odds ratio (after natural logarithm transformation) for the disease, and summing this weighted allele score of each variant up into a disease risk score for AD, PD, and FTLD/ALS. Similarly, a combined genetic risk score of all neurodegenerative disease variants was created.

2.4. MCI screening

From 2002 to 2005 onward, we implemented extensive cognitive testing to allow for the screening of MCI. All participants of the three Rotterdam Study subcohorts who were alive in 2002 to 2005 were invited to undergo these tests and assessed for MCI. However, as the third subcohort of the Rotterdam Study is comprised of relatively young participants (45 years and more), but still would yield a considerable number of screen-positives for MCI, it was not included in this study population at risk.

Table 1
List of known genetic variants that increase risk of neurodegenerative diseases

Disease	RS ID	Chr.	Position	Locus	Allele 1	Allele 2	OR
AD	rs6656401	1	207692049	CR1	A	G	1.18
AD	rs6733839	2	127892810	BIN1	T	C	1.22
AD	rs35349669	2	234068476	INPP5D	T	C	1.08
AD	rs190982	5	88223420	MEF2C	G	A	0.93
AD	rs10948363	6	47487762	CD2AP	G	A	1.10
AD	rs2718058	7	37841534	NME8	G	A	0.93
AD	rs1476679	7	100004446	ZCWPW1	C	T	0.91
AD	rs11771145	7	143110762	EPHA1	A	G	0.90
AD	rs28834970	8	27195121	PTK2B	C	T	1.10
AD	rs9331896	8	27467686	CLU	C	T	0.86
AD	rs10838725	11	47557871	CELF1	C	T	1.08
AD	rs983392	11	59923508	MS4A6A	G	A	0.90
AD	rs10792832	11	85867875	PICALM	A	G	0.87
AD	rs11218343	11	121435587	SORL1	C	T	0.77
AD	rs17125944	14	53400629	FERMT2	C	T	1.14
AD	rs10498633	14	92926952	SLC24A4	T	G	0.91
AD	rs4147929	19	1063443	ABCA7	A	G	1.15
AD	rs429358/rs7412	19	45411941/45412079	APOE	ε4	ε2/3	3.69
AD	rs7274581	20	55018260	CASS4	C	T	0.88
PD	rs114138760	1	154898185	GBA	C	G	1.57
PD	rs35749011	1	155135036	GBA	A	G	1.76
PD	rs823118	1	205723572	RAB7L1	T	C	1.13
PD	rs10797576	1	232664611	SIPA1L2	T	C	1.14
PD	rs6430538	2	135539967	ACMSD	T	C	0.87
PD	rs1474055	2	169110394	STK39	T	C	1.21
PD	rs12637471	3	182762437	MCCC1	A	G	0.84
PD	rs34884217	4	944210	TMEM175	A	C	1.25
PD	rs34311866	4	951947	TMEM175	T	C	0.78
PD	rs11724635	4	15737101	BST1	A	C	1.12
PD	rs6812193	4	77198986	FAM47 E	T	C	0.90
PD	rs356182	4	90626111	SNCA	A	G	0.74
PD	rs7681154	4	90763703	SNCA	A	C	0.84
PD	rs199347	7	23293746	GPNMB	A	G	1.12
PD	rs591323	8	16697091	FGF20	A	G	0.92
PD	rs117896735	10	121536327	INPP5F	A	G	1.77
PD	rs329648	11	133765367	MIR4697	T	C	1.10
PD	rs76904798	12	40614434	LRRK2	T	C	1.17
PD	rs11060180	12	123303586	CCDC62	A	G	1.10
PD	rs11158026	14	55348869	GCH1	T	C	0.89
PD	rs2414739	15	61994134	VPS13 C	A	G	1.11
PD	rs14235	16	31121793	STX1B	A	G	1.09
PD	rs11868035	17	17715101	SREBF	A	G	0.94
PD	rs12456492	18	40673380	RIT2	A	G	0.91
PD	rs8118008	20	3168166	DDRGK1	A	G	1.11
FTLD	rs1990622	7	12283787	TMEM106 B	G	A	0.61
ALS	rs3849943	9	27543382	C9ORF72	C	T	1.17
ALS	rs34517613	17	26610252	SARM1	T	C	0.83

Abbreviations: AD, Alzheimer's disease; PD, Parkinson's disease; ALS, amyotrophic lateral sclerosis; FTLD, frontotemporal lobar degeneration; Chr., chromosome; MCI, mild cognitive impairment; OR, odds ratio; RA, risk allele.

MCI was defined as the presence of both subjectively and objectively measured cognitive impairment, in the absence of dementia [3].

Subjective cognitive impairment was considered present if persons reported complaints on any of three questions on memory (difficulty remembering, forgetting what one had planned to do, and difficulty finding words) or three questions on everyday functioning (difficulty managing finances, problems using a telephone, and difficulty getting dressed). Objective measures of cognitive functioning were neuropsychological tests (Letter-Digit Substitution Task, Stroop test, Verbal Fluency Test, and the 15-Word verbal Learning Test based on Rey's recall of words) that were incorporated into robust compound scores of memory function, information-processing speed, and executive function, as described previously [20]. Scores lower than 1.5 SD of the age- and education-adjusted means were considered indicative of objective cognitive impairment. MCI was further classified as "amnestic" in case of an objective memory deficit (irrespective of other domains), or as "nonamnestic" if only

other cognitive domains were affected. The MCI assessment in the Rotterdam Study was previously described in more detail [21].

2.5. Assessment of dementia

Participants were screened for dementia at each of the Rotterdam Study examination rounds and additionally by using information obtained from the general practitioners and regional outpatient care centers (follow-up completed until January 2012) [15]. Mini-Mental State Examination (MMSE) [22] and the Geriatric Mental Schedule (GMS) [23] were used to identify high-risk individuals (MMSE <26 or GMS >0) for an additional interview with the Cambridge Examination for Mental Disorders in the Elderly [24]. When required, further neuropsychological testing and neuroimaging were used by a consensus panel for diagnosis according to the established criteria for dementia (Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised) and Alzheimer's Disease (National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association) [25,26].

2.6. Statistical analyses

Genetic risk scores were transformed into z-scores to facilitate comparisons of their effect per standard deviation increase across each score. Logistic regression models were used to examine associations between the risk scores and MCI status. To evaluate the conversion of MCI to dementia and incident dementia in cognitively normal persons separately, Cox proportional hazard models stratified for MCI status were used. Additionally, the effects of individual variants were explored and considered significant after Bonferroni correction for the number of tested variants (P =.05/47 = .0011). Regression models were adjusted for age and sex, and additionally for vascular risk factors. Furthermore, potential interaction between the genetic risk scores and age-at-onset of MCI and dementia was examined.

To determine diagnostic and predictive accuracy of the genetic risk scores, the area under the receiver operating curve was calculated for a basic model including age and sex, and compared with a model additionally incorporating the genetic risk scores. All analyses were performed with SPSS version 22, IBM.

3. Results

3.1. Population characteristics

Mean (standard deviation [SD]) age was 71.9 (7.2) years and 2057 (57.1%) were women. A total of 360 (10.0%) participants met the criteria for MCI, of whom 147 (4.1%) were with amnestic and 213 (5.9%) with nonamnestic MCI. Mean (SD) follow-up was 6.0 (1.5) years, during which 191 persons were diagnosed with dementia, of whom 156 were with AD. A detailed description of the population characteristics can be found in Table 2.

Table 2
Study population characteristics

Characteristic	Total (N = 3605)
Demographics	
Age, yrs	71.9 (7.2)
Females	2057 (58.2%)
Educational level	
Primary education	360 (10.1%)
Lower vocational education	1022 (28.7%)
Lower secondary education	585 (16.4%)
Intermediate vocational education	967 (27.1%)
General secondary education	145 (4.1%)
Higher vocational education	438 (12.3%)
University	49 (1.4%)
Vascular risk factors	
Hypertension	2912 (81.0%)
Diabetes mellitus	529 (14.7%)
Waist circumference, cm	93.6 (11.8)
Total cholesterol, mmol/L	5.61 (0.99)
HDL-cholesterol, mmol/L	1.45 (0.40)
Smoking	
Never	1054 (29.2%)
Former	1998 (55.4%)
Current	553 (15.3%)
Cognition	
Letter-digit substitution task, no. of items/min	27.1 (6.8)
Stroop test (color word interference), s	56.4 (21.0)
Verbal fluency test, no. of animals/min	20.9 (5.1)
15-word verbal learning test, no. of words	6.54 (2.69)
Diagnosis	
MCI	360 (10.0%)
Amnestic	147 (4.1%)
Nonamnestic	213 (5.9%)
Dementia	
Incident cases	191 (5.3%)
Follow-up time, yrs	6.04 (1.50)

Abbreviations: HDL, high-density lipoprotein; MCI, mild cognitive impairment.

NOTE. Values are mean (SD) or number (percentage). Missing values are present in educational level (n = 39), hypertension (n = 9), waist circumference (n = 9), and cholesterol levels (n = 59).

3.2. MCI status

The association with MCI status was significant for the genetic risk score of AD (odds ratio or OR = 1.15 [1.03–1.28]) and suggestive for PD (1.10 [0.99–1.23]) and FTLD/ALS (1.09 [0.98–1.22]). Investigating subtypes of MCI separately, we found an association with amnestic MCI for the risk score of AD only (1.16 [0.99–1.36]) which attenuated after excluding *APOE* from the risk score (1.11 [0.94–1.31]). In contrast, risk scores of AD, PD, and FTLD/ALS were all associated with the subtype of nonamnestic MCI (see Table 3). The combined risk score for all neurodegenerative diseases together was significantly associated with MCI, particularly nonamnestic MCI. The associations were similar after an additional adjustment for education and vascular risk factors (see Supplementary Table 1).

Table 3
Associations of genetic risk scores for neurodegenerative diseases with mild cognitive impairment

Genetic risk score, per SD	OR for MCI	*P*-value	OR for amnestic MCI	*P*-value	OR for nonamnestic MCI	*P*-value
Alzheimer disease	1.15 (1.03–1.28)	.011	1.16 (0.99–1.36)	.062	1.14 (0.99–1.31)	.063
Alzheimer disease without *APOE*	1.19 (1.07–1.33)	.002	1.11 (0.94–1.31)	.223	1.25 (1.09–1.44)	.002
Parkinson disease	1.10 (0.99–1.23)	.081	1.02 (0.86–1.20)	.830	1.16 (1.01–1.33)	.037
FTLD/ALS	1.09 (0.98–1.22)	.130	0.97 (0.82–1.14)	.680	1.19 (1.03–1.37)	.019
Combined risk score	1.20 (1.08–1.34)	.001	1.13 (0.96–1.33)	.142	1.26 (1.09–1.44)	.001

Abbreviations: SD, standard deviation; OR, odds ratio; MCI, mild cognitive impairment; *APOE*, apolopoprotein E; FTLD/ALS, frontotemporal lobar degeneration/amyotrophic lateral sclerosis.

NOTE. Values are odds ratios with 95% confidence intervals per SD of genetic risk score, adjusted for age and sex.

Investigating the objective and subjective complaints that make up the MCI diagnosis separately revealed that the AD score associated strongly with subjective memory complaints (Table 4). The AD score without *APOE* and PD and FTLD/ALS primarily affected objective measures of cognitive complaints, particularly information-processing speed and executive function, although the PD score also associated with problems getting dressed. No significant interactions were detected between the risk scores and age-at-onset of MCI. In single variant analyses, AD risk variant rs6733839 near *BIN1* was associated with MCI after Bonferroni correction (see Supplementary Table 2 for all single variant results).

3.3. Conversion to dementia

The risk score for AD, but not for PD and FTLD/ALS, was associated with incident dementia. This association was particularly pronounced for the conversion from MCI (1.59 [1.23–2.05]). Exclusion of *APOE* attenuated the association of the AD risk score with incident dementia, which remained only borderline significant among persons without MCI (1.21 [1.02–1.43]). The combined genetic risk score was highly significantly associated with incident dementia. The associations were similar after additional adjustment for vascular risk factors (see Supplementary Table 3). There was a significant interaction between the AD genetic risk score and age-at-onset of dementia (P =.003), which indicated a stronger genetic effect when age at onset was lower.

Among all variants individually, only *APOE* survived multiple testing. Other AD variants that were related to incident dementia were rs983392 (*MS4A6A*), rs10948363 (*CD2AP*), and rs9331896 (*CLU*). Interestingly, rs6733839 (*BIN1*) which was associated with MCI, was not associated with incident dementia. The results of the genetic risk scores are summarized in Table 5 and of single variants in Supplementary Table 4. Additionally, the AD risk score without *APOE* was examined after the stratification for *APOE* ε4 carrier status (see Supplementary Table 5).

3.4. Diagnosis and predictive accuracy

The addition of the genetic risk scores to models of age and sex for diagnosing MCI and predicting dementia resulted in small increases of <0.025 of the area under the receiver operating curve (see Table 6).

4. Discussion

We found in a population-based cohort study that a genetic risk score for AD was associated with amnestic and nonamnestic MCI, whereas genetic risk scores for PD and FTLD/ALS only associated with nonamnestic MCI. Furthermore, only the genetic risk score for AD was associated with incident dementia, which attenuated after the exclusion of *APOE*. The diagnostic and predictive accuracy of these risk scores was only modest.

We found that the genetic susceptibility to various neurodegenerative diseases associates with MCI. The clinical concept of MCI could therefore reflect an underlying heterogeneity of disease pathways leading to the deterioration of cognitive functions. Amnestic MCI, the subtype which increases the risk of AD, was associated with *APOE*, but the novel AD risk variants identified through genome-wide association studies were related more to the nonamnestic subtype. AD genes might thus influence different cognitive domains, with the common feature of (jointly) increasing the risk of AD. The role *APOE* of in AD is well-documented, and is often used as a model for "typical" AD: neurodegeneration starting in the medial temporal lobe, giving episodic memory problems, amnestic MCI, and then leading to dementia. It is therefore interesting to see that the novel genetic loci are acting differently from *APOE*, and the underlying pathophysiological mechanism(s) might also be different and thus result in this atypical presentation. Studying the novel loci separately and in combination could complement our current knowledge of the pathophysiology, and might eventually even warrant more detailed subtyping of the heterogeneous entity of AD. Nonamnestic MCI was associated with various genetic risk factors of PD and FTLD/ALS, which indicates that the further characterization of MCI subgroups might also be appropriate.

Alternatively, these associations could be explained by persons with incipient disease who were classified as having MCI. However, all persons meeting the criteria for dementia, including causes of AD, PD, and FTLD, were excluded from the analyses with MCI, and a minimal contribution of ALS is

Table 4
Associations of genetic risk scores for neurodegenerative diseases with objective and subjective cognitive complaints

Genetic risk score, per SD	OR (95% CI) for subjective memory complaints			OR (95% CI) for subjective everyday functioning complaints			OR (95% CI) for objective cognitive complaints		
	Difficulty remembering	Forgetting plans	Finding words	Managing finances	Using telephone	Getting dressed	Memory function	Information-processing	Executive function
AD	1.12 (1.05–1.20)	1.12 (1.04–1.20)	1.09 (1.01–1.17)	1.08 (0.96–1.21)	0.97 (0.60–1.59)	0.93 (0.74–1.15)	1.12 (0.98–1.28)	1.03 (0.90–1.18)	1.07 (0.94–1.22)
AD without *APOE*	1.08 (1.01–1.16)	1.05 (0.98–1.12)	1.01 (0.94–1.09)	1.12 (1.00–1.25)	0.86 (0.55–1.33)	1.01 (0.83–1.24)	1.10 (0.96–1.26)	1.22 (1.06–1.39)	1.13 (0.98–1.29)
PD	0.97 (0.91–1.04)	1.01 (0.94–1.09)	0.97 (0.91–1.05)	0.98 (0.87–1.10)	0.80 (0.52–1.24)	1.32 (1.08–1.60)	1.04 (0.91–1.20)	1.16 (1.02–1.32)	1.11 (0.98–1.27)
FTLD/ALS	1.05 (0.98–1.12)	1.02 (0.95–1.09)	1.03 (0.96–1.10)	0.96 (0.85–1.07)	0.96 (0.62–1.49)	1.07 (0.87–1.31)	1.02 (0.89–1.17)	1.07 (0.94–1.23)	1.11 (0.97–1.28)
Combined risk score	1.10 (1.03–1.18)	1.11 (1.03–1.19)	1.07 (1.00–1.15)	1.02 (0.91–1.14)	0.88 (0.54–1.43)	1.12 (0.91–1.36)	1.13 (0.99–1.29)	1.13 (0.99–1.29)	1.15 (1.01–1.32)

Abbreviations: SD, standard deviation; OR, odds ratio; CI, confidence interval; MCI, mild cognitive impairment; *APOE*, apolipoprotein E; FTLD/ALS, frontotemporal lobar degeneration/amyotrophic lateral sclerosis.

NOTE. Values are odds ratios with 95% confidence intervals per SD of genetic risk score, adjusted for age and sex.

expected because of our community-based setting. Unfortunately, family members or caregivers were generally not present during the center visits, and could therefore not be asked about subjective cognitive complaints of the participant. Also, visuospatial functions were not explicitly assessed. However, given the extensive collection of both interview data and cognitive tests for each participant, it seems unlikely that this would results in a substantial number of undiagnosed MCI cases. Another consideration is that we were unable to assess incident MCI, because MCI screening was only performed at the baseline of our study. However, because genetic variants reflect life-long exposure, reverse causality or unmeasured confounding is highly unlikely.

A potential limitation is that we have not completed follow-up of participants until the end of their lifetimes, which would correspond to an expected 30 years of additional follow-up. Although mean age was already 72 years at baseline, and Cox proportional hazard models took the variation in starting age and follow-up time into account, we further evaluated whether age-at-onset modifies the association of the risk scores, which was true only for the AD risk score including *APOE*. Nonetheless, competing risks are a potential source of bias, and this bias remains even after following persons until the end of their lifetimes.

MCI is often called an intermediate stage, implicitly suggesting that it is merely an earlier form of dementia with more cognitive functions still remaining intact, but this might not be an adequate representation of MCI. Although risk factors between neurodegenerative diseases and MCI overlap, many people with MCI remain stable or can even return to normal [2,3]. In our study, the AD genetic risk score was indeed associated with both MCI and incident dementia, but examining the individual risk variants separately suggests that each of these two processes could be driven by different factors; e.g., *BIN1* contributes more to initiating MCI (OR = 1.32, $P < .001$) than to conversion to AD (OR = 1.13, $P = .31$). If validated in other studies, these findings could help prioritize certain AD targets for early intervention. Because only part of the MCI population develops dementia, the heterogeneity of this group could therefore provide an explanation why some genes only predispose to MCI, namely that this factor for example mostly causes a stable MCI subtype. Also, the dementia trajectory spans decades, and even infant changes have recently been implicated [27]. Rather than a single process that is responsible for all dementia pathology across its various stages, different processes might either predispose to, initiate, or propagate cognitive decline. Which process is affected by a gene, and in particular **when** in the dementia trajectory this process is relevant, might thus be reflected in stronger associations with MCI, that are less prominent later (conversion to dementia), such as with *BIN1*.

We note that most of our dementia cases were due to AD. Therefore, we were unable to detect any association of the

Table 5
Associations of genetic risk scores for neurodegenerative diseases with incident dementia in the total population and stratified by mild cognitive impairment status

	Hazard ratio for conversion to dementia, per SD increase of the genetic risk score (95% confidence interval)					
Genetic risk score, per SD	Total population (n/N = 191/3605)	*P*	Persons with MCI (n/N = 55/360)	*P*	Cognitively normal persons (n/N = 136/3245)	*P*
AD	1.56 (1.37–1.78)	<.001	1.59 (1.23–2.05)	<.001	1.53 (1.31–1.78)	<.001
AD without *APOE*	1.15 (1.00–1.32)	.058	1.03 (0.79–1.34)	.811	1.21 (1.02–1.43)	.027
PD	0.90 (0.79–1.04)	.159	0.95 (0.74–1.21)	.669	0.89 (0.75–1.05)	.162
FTLD/ALS	0.92 (0.80–1.06)	.265	0.86 (0.66–1.12)	.264	0.96 (0.81–1.14)	.634
Combined risk score	1.34 (1.16–1.55)	<.001	1.35 (1.01–1.79)	.040	1.33 (1.12–1.57)	.001

Abbreviations: n, number of persons converting to dementia; N, cohort at risk; SD, standard deviation; AD, Alzheimer's disease; PD, Parkinson's disease; MCI, mild cognitive impairment; *APOE* ε4, apolipoprotein E; FTLD/ALS, frontotemporal lobar degeneration/amyotrophic lateral sclerosis.
NOTE. All analyses are adjusted for age, sex, and MCI-status if applicable.

other genetic risk scores with dementia due to PD or FTLD/ALS. It is possible that separate genetic risk scores increase the risk of disease-specific dementia subtypes only, but this needs to be studied further. An important consideration is that variant rs3849943 is tagging the GGGGCC expansion within open reading frame 72 (C9orf72), which was shown to be responsible for this GWAS signal on chromosome 9 [9]. This expansion is present in 4% to 21% of sporadic ALS cases [28,29]. Phenotypes of neurodegenerative diseases are uncommon when less than 20 expansions are present, and it usually requires more than 50 expansions for ALS cases to develop dementia. Because we were unable to assess the exact number expansions, and given our population-based setting, it is possible that the average number of expansions was low in this study. Future efforts should therefore investigate this locus in more detail to understand its role in MCI and the subsequent conversion to dementia.

Our diagnostic and prediction models incorporating the genetic risk scores resulted in marginal improvement of diagnosing MCI and predicting dementia. This is in line with two previous studies that used a smaller set of variants [30,31]. It has been questioned if a sufficient level of accuracy will ever be achieved for complex diseases, as unraveling their complete causal pathways may be impossible [32]. However, further genetic discoveries in combination with other risk factors might eventually prove the clinical utility of polygenic risk scores, as has been shown for age-related macular degeneration and height [33,34]. Importantly, the genetic variants that are currently known explain only little of the variance in disease risk of AD, PD, FTLD, and ALS. Uncovering the "missing heritability" through larger GWAS and the novel focus on rare variants could improve the clinical utility of genetic risk scores. Additionally, the current genetic variants could have a larger effect through gene-gene and gene-environment interaction. The stratification for *APOE* ε4 carrier status showed differences in associations of the various risk scores, but this needs to be explored further. Moreover, nongenetic factors could aid in more accurately diagnosing MCI and predicting dementia by themselves.

In conclusion, MCI is genetically heterogeneous, whereas dementia develops through disease-specific mechanisms. Future research should focus on disentangling different genetic causes of MCI and the subsequent conversion to dementia.

Table 6
Areas under the curve for diagnosing mild cognitive impairment and predicting dementia using models incorporating genetic risk scores for neurodegenerative diseases

	Area under the curve for MCI status (95% confidence interval)			Area under the curve for conversion to dementia (95% confidence interval)		
	All (n/N = 360/3605)	Amnestic (n/N = 147/3392)	Nonamnestic (n/N = 213/3458)	Total population (n/N = 191/3605)	Persons with MCI (n/N = 55/360)	Cognitively normal persons (n/N = 136/3245)
Basic model: age and sex	0.578 (0.547–0.609)	0.577 (0.528–0.626)	0.603 (0.563–0.644)	0.783 (0.751–0.815)	0.734 (0.666–0.802)	0.781 (0.744–0.818)
+AD	0.588 (0.556–0.620)	0.592 (0.545–0.640)	0.614 (0.571–0.656)	0.801 (0.770–0.833)	0.744 (0.676–0.813)	0.803 (0.767–0.838)
+AD without *APOE*	0.593 (0.562–0.625)	0.589 (0.541–0.636)	0.625 (0.585–0.665)	0.785 (0.752–0.817)	0.735 (0.667–0.803)	0.782 (0.745–0.819)
+PD	0.582 (0.551–0.613)	0.577 (0.529–0.625)	0.612 (0.573–0.651)	0.782 (0.750–0.814)	0.734 (0.666–0.802)	0.780 (0.742–0.817)
+FTLD/ALS	0.579 (0.547–0.611)	0.584 (0.536–0.631)	0.612 (0.571–0.653)	0.785 (0.753–0.817)	0.743 (0.678–0.808)	0.782 (0.745–0.819)
+Combined risk score	0.594 (0.562–0.626)	0.590 (0.543–0.637)	0.627 (0.585–0.669)	0.791 (0.759–0.823)	0.733 (0.662–0.804)	0.792 (0.756–0.828)

Abbreviations: MCI, mild cognitive impairment; AD, Alzheimer's disease; *APOE*, apolipoprotein E; PD, Parkinson's disease; FTLD, frontotemporal lobar degeneration; ALS, amyotrophic lateral sclerosis.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jalz.2014.12.008.

RESEARCH IN CONTEXT

1. Systematic review: We searched the literature for genetic variants associated with neurodegenerative diseases (Alzheimer's disease [AD], Parkinson's disease [PD], frontotemporal lobar degeneration, and amyotrophic lateral sclerosis) and mild cognitive impairment (MCI) using PubMed and Google Scholar. Although over 40 variants have been associated with neurodegenerative diseases, no genetic risk factors of MCI are known besides the apolipoprotein E (*APOE*) ε4 allele.
2. Interpretation: In a large prospective, population-based cohort study, we investigated whether genetic variants for neurodegenerative diseases also contribute to MCI and the subsequent conversion to dementia. All variants in aggregate were associated with MCI, but only the AD variants also increased risk of dementia, which was mainly of the Alzheimer's type. This suggests that MCI is genetically heterogeneous, whereas dementia develops through disease-specific mechanisms.
3. Future directions: In addition to replication of these findings for the genetic variants in aggregate, exploring the effects of single variants could help prioritize therapeutical targets by determining which genes already influence cognition early in the disease process.

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