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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.