Genetic basis of motoric cognitive risk syndrome in the Health and Retirement Study

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Neurology® 2019;92:e1427-e1434. doi:10.1212/WNL.0000000000007141

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Abstract

Objective

To examine polygenic inheritance of motoric cognitive risk syndrome (MCR), a predementia syndrome characterized by the presence of subjective cognitive complaints and slow gait.

Methods

We analyzed 4,915 individuals, age 65 years and above, with European ancestry (mean age 75.0 ± 6.8 years, 56.6% women) in the Health and Retirement Study. Polygenic scores (PGS) were calculated as weighted sums of the effect of single nucleotide polymorphisms, with effect sizes derived from genome-wide association studies. The association between PGSs of 9 phenotypes (general cognition, body mass index [BMI], mean arterial pressure, education, Alzheimer disease [AD], neuroticism, well-being, waist circumference, and depressive symptoms) and MCR as well as its key components (cognitive complaints and slow gait) were examined by logistic regression, adjusting for age, sex, education, and genetic ancestry, and reported as odds ratios (ORs) with 95% confidence intervals (CIs).

Results

There were 260 prevalent MCR cases, 529 with slow gait, and 1,928 with subjective cognitive complaints. Higher PGSs for BMI (OR 1.22, 95% CI 1.07–1.39) and waist circumference (OR 1.23, 95% CI 1.07–1.40) were associated with MCR, and PGS of AD showed a suggestive association (OR 1.16, 95% CI 1.02–1.32). Higher PGS for neuroticism (OR 1.10, 95% CI 1.03–1.18) was associated with cognitive complaints, whereas higher well-being PGS (OR 0.92, 95% CI 0.87–0.98) was protective. PGS for BMI (OR 1.16, 95% CI 1.06–1.28), waist circumference (OR 1.19, 95% CI 1.08–1.31), and AD (OR 1.13, 95% CI 1.03–1.24) was associated with slow gait.

Conclusion

Obesity-related genetic traits increase risk of MCR syndrome; further investigation is required to identify potential therapeutic targets.

Glossary

AD = Alzheimer disease; **BMI** = body mass index; **CI** = confidence interval; **FDR** = false discovery rate; **GWAS** = genome-wide association studies; **HRS** = Health and Retirement Study; **LD** = linkage disequilibrium; **MCI** = mild cognitive impairment; **MCR** = motoric cognitive risk; **OR** = odds ratio; **PCA** = principal components analysis; **PGS** = polygenic score; **SNP** = single nucleotide polymorphism.

Motoric cognitive risk (MCR) syndrome is a predementia syndrome characterized by the presence of subjective cognitive complaints and slow gait.^{1,2} A pooled analysis of 26,802 older adults from 17 countries showed a prevalence of MCR of 9.7%.² The incidence of MCR was 65.2/1,000 person-years in 4 US-based cohorts.³ Individuals with MCR are at high risk for transitioning to dementia, both Alzheimer disease (AD)² and vascular dementia.¹ MCR has incremental predictive validity for dementia compared to its individual components of cognitive complaints or slow gait.^{1,2}

The underlying biology of MCR is not yet established. Our preliminary study showed an association of the regulatory variant in the *IL10* gene with incident MCR.⁴ While candidate gene and genome-wide association studies (GWAS) have shown variants in multiple genetic loci to be associated with dementia,^{5,6} their individual effect sizes are small. Recent studies suggest that multiple regions across the genome (polygenic inheritance) may determine cognitive phenotypes.^{7,8} Individual level genetic predisposition is reflected by the polygenic score (PGS), constructed based on effect sizes of millions of single nucleotide polymorphisms (SNPs) derived from large GWAS conducted in the phenotype of interest.⁹

Obesity, stroke, Parkinson disease, physical inactivity, and depressive symptoms were reported to increase risk for MCR, whereas education was protective.^{2,3,10} We hypothesized that the combined genetic predisposition for these phenotypes might be associated with MCR. We conducted a preliminary investigation to examine polygenic effects on MCR and its components in the Health and Retirement Study (HRS).

Methods

Study population

The HRS is a nationally representative US-based cohort study of social, economic, and health issues in individuals age 50 years and older.^{11–13} The study is supported by the National Institute on Aging (NIA U01AG009740) and Social Security Administration and is conducted at the University of Michigan. The HRS conducts core interviews every 2 years using a mixed-mode design of telephone and in-person interviews. In 2006, HRS implemented “enhanced” face-to-face interviews, which included physical performance tests as well as blood and saliva samples. Half of the HRS cohort was randomly selected to receive physical performance tests (including timed gait) as part of the enhanced interview in 2006,

and the other half in 2008. Additional information on the HRS design, sampling, clinical protocols, as well as genomic data are available on the HRS website (hrsonline.isr.umich.edu).

Ethical approval for the HRS was obtained from the University of Michigan institutional review board. The Einstein institutional review board approved this analysis.

MCR syndrome

MCR syndrome was diagnosed in HRS participants based on established criteria.^{1–3} In brief, MCR adapts definitions of mild cognitive impairment (MCI),¹⁴ substituting the objective cognitive impairment criterion based on cognitive tests used in MCI with slow gait speed. MCR is defined as presence of subjective cognitive complaints and slow gait in older individuals without dementia or mobility disability. Subjective cognitive complaints were classified based on a positive response by the participant to either of the following 2 questions on the core HRS interview: (1) “How would you rate your memory at the present time? Would you say it is excellent, very good, good, fair, or poor?” “Fair” and “poor” responses were coded as positive. (2) “Compared with the previous interview, would you say your memory is better now, about the same, or worse now than it was then?” A response of “worse” was coded as positive. Participants aged 65 years and older were timed while walking at normal pace over a 98.5-inch (8 feet) course with start and stop points marked on the floor. The mean of 2 trials was calculated. Walking times were converted to gait speed (m/s). Slow gait was defined as gait speed 1 SD or more below age- and sex-specific means.¹⁵ Age- and sex-adjusted slow gait cut scores (m/s) were as follows: men <75 years = 0.61, men ≥75 years = 0.48, women <75 years = 0.54, and women ≥75 years = 0.42. We have reported risk factors for incident slow gait in HRS using the same definition of slow gait.¹⁵ We also defined MCR in HRS using the same operational criteria.^{16,17}

Genetic data and PGS construction

Genomic data and quality control

DNA samples for the 2006 wave were collected from buccal swabs, and extracted using the Qiagen (Venlo, the Netherlands) Autopure method. In 2008, saliva samples were collected and DNA extracted with Oragene. Around 12,500 individuals in these 2 phases were genotyped for ~2.4 million SNPs using the Illumina (San Diego, CA) HumanOmni2.5-4v1 array at the Center for Inherited Disease Research. Standard quality control procedures led to removal of individuals with missing call rates (>2%), chromosomal anomalies, and

first-degree relatives. SNPs with call rates <98% and HWE p value <0.0001 were also removed. For our study, only participants with European ancestry were included to minimize population stratification issues. European ancestry (European American) was defined as individuals who reported non-Hispanic white/Caucasian ethnicity and fell within 1 SD for eigenvectors 1 and 2 in the principal components analysis (PCA) of all unrelated study participants. PCA have been further defined in the quality control report available on the HRS website (hrs.isr.umich.edu/data-products/genetic-data).

Polygenic scores

We examined the association of 9 PGS with MCR and its components, subjective cognitive complaints, and slow gait. The PGS were those associated with the following 9 phenotypes: general cognition, body mass index (BMI), mean arterial pressure, education, AD, neuroticism, subjective well-being, waist circumference, and depressive symptoms. These phenotypes were selected based on their associations with MCR or dementia in epidemiologic studies.^{2,3,10}

Polygenic scores construction

PGSs are the weighted sum of SNPs across the genome associated with the phenotype for an individual, and are calculated based on large GWAS meta-analysis studies. PGS data for various phenotypes were released by HRS in July 2017, and made accessible online (hrs.isr.umich.edu/news/hrs-polygenic-scores-2006-2010-genetic-data). All available SNPs, independent of any linkage disequilibrium (LD) or p value threshold, were used to construct PGS. MHC region in chromosome 6 (26–33 Mb) was omitted due to long range LD. PGS were calculated as weighted sums, with odds ratio (OR) or beta estimates from the GWAS meta-analysis file for

the phenotypes of the interest used to define weights. GWAS meta-analyses that did not include HRS data in discovery analysis were selected or when analysis was repeated after removing HRS participants. All the GWAS meta-analyses SNP files were converted to National Center for Biotechnology Information build 37 annotations for compatibility with HRS SNP data. In case of negative beta values (or OR < 1), the beta/OR measures are converted to positive values by flipping reference allele to contribute to phenotype-increasing PGSs. The following formula is used to derive PGSs:

$$PGSi = \sum_{j=1}^J W_j G_{ij}$$

where i is individual i ($i = 1$ to N), j is SNP j ($j = 1$ to J), W is the meta-analysis effect size for SNP j , and G is the genotype, or the number of reference alleles (0, 1, or 2), for individual i at SNP j . All the PGSs were standardized within ethnicity to a standard normal curve with mean = 0 and SD = 1. Further details on PGS construction can be accessed from the HRS website (hrs.isr.umich.edu/news/hrs-polygenic-scores-2006-2010-genetic-data).

Statistical analysis

Baseline characteristics of participants with and without MCR were compared by t test for continuous variables and χ^2 test for categorical variables (table 1). MCR was diagnosed based on data from either the 2006 or 2008 wave depending on which wave the participant completed the physical function assessment. Association of PGSs with MCR and individual components was conducted using logistic regression, and reported as ORs with 95% confidence intervals (CIs). All analyses were adjusted for age, sex, education, and 5 ancestry-specific

Table 1 Study characteristics overall and by motoric cognitive risk (MCR) status

Baseline characteristics	Overall (n = 4,915)	MCR (n = 260)	Not MCR (n = 4,655)
Age, y	74.83 ± 6.67	76.57 ± 7.67	74.73 ± 6.60
Male/female	43.4/56.6	45.8/54.2	43.2/56.8
Education, y	12.98 ± 2.52	11.96 ± 2.65	13.03 ± 2.50
Heart condition	32.7	47.3	31.9
Stroke	7.0	15.1	6.5
High blood pressure	62.8	71.8	62.3
Diabetes	18.9	26.5	18.4
Lung disease	12.9	21.5	12.4
Angina	10.1	17.3	9.6
Emotional/psychiatric problems	14.1	26.6	13.4
Vascular disease ^a	74.9	82.7	74.5
Velocity, m/s	0.80 ± 0.26	0.39 ± 0.12	0.82 ± 0.24

Values are mean ± SD or n (%).

^a Heart disease, hypertension, diabetes, or stroke.

principal components (to correct for potential bias due to population stratification). The phenotypes and trait analyzed in this study and the meta-analysis used for the construction of PGSs are described in table 2. Statistical analyses were conducted using SPSS software (version 24; IBM Corporation, Armonk, NY).

Sensitivity analysis

We did not statistically correct our primary analyses as they were empirically based with phenotypes selected based on previous studies.^{2,3,10} As a secondary approach, the results were adjusted for multiple testing using the Benjamini and Hochberg¹⁸ false discovery rate (FDR) procedure. FDR *p* values less than 0.05 were considered significant. Due to the preliminary nature of this study and to avoid missing important insights, in analyses where the FDR *p* value was more than 0.05, a *p* value less than 0.05 was described as being of suggestive significance.

To account for the presence of individuals with individual clinical MCR components (cognitive complaints or slow gait) in the non-MCR control group, we conducted sensitivity analysis excluding these individuals from the control group.

Pairwise interaction analysis was carried out between PGSs on MCR. This analysis was exploratory in nature, as such analyses require a larger sample size to have adequate statistical power. The logistic regression model contained both the individual PGSs as well as the interaction variable. All interaction analyses were adjusted for age, sex, education, and genetic ancestry.

Data availability statement

The datasets used for the primary and supplementary analyses are available from the HRS website (hrs.isr.umich.edu/data-products/access-to-public-data).

Results

Study population

Of the 9,991 HRS participants with European ancestry with PGS available, 8,958 participated in the 2006 or 2008 enhanced HRS interview, and 5,671 were age 65 and older. We excluded 756 older individuals from this analysis for the following reasons: self-reported or proxy-reported dementia diagnosis at baseline (*n* = 155), participants with total scores that were 2 SDs or below the mean on the modified Telephone Interview for Cognitive Status used to assess general mental status in HRS (*n* = 164),¹⁹ incomplete timed walk assessments due to safety concerns (*n* = 170), refusal (*n* = 39), inability to walk due to a health condition (*n* = 70), space constraints or equipment malfunction (*n* = 149), or inaccurate or missing walk time (*n* = 9). Hence, 4,915 HRS participants, age 65 years and older, formed the eligible sample.

Of the 4,915 eligible participants, 260 individuals had MCR diagnosed at either the 2006 or 2008 wave, 1,928 subjective cognitive complaints, 529 slow gait, and 2,718 were free from both slow gait and cognitive complaints. The study characteristics overall and by MCR status are presented in table 1. Overall, the mean age of participants was 75.0 ± 6.8 years (range 65–101 years). The mean years of education were 12.9 ± 2.6, and 56.6% of participants were women. There was higher prevalence of heart-related disorders, stroke, high blood pressure, diabetes, and lung disease as well as emotional/psychiatric problems in participants with MCR compared to those without MCR (table 1).

PGS analysis

MCR syndrome

The association of PGS of multiple traits with MCR adjusted for age, sex, education, and genetic ancestry is shown in table 3. Increased PGS for BMI (OR 1.22, *p* = 0.004, *p*_{FDR} = 0.027) and

Table 2 Genome-wide association studies (GWAS) meta-analysis used by the Health and Retirement Study (HRS) to derive polygenic scores for different phenotypes

	Phenotype of GWAS meta-analysis	GWAS meta-analysis, author (study, y)	Study size
1	General cognition (HRS removed)	Davies et al. ⁷ (CHARGE, 2015)	53,949
2	Body mass index	Locke et al. ⁴⁵ (GIANT, 2015)	234,069
3	Blood pressure (MAP)	Wain et al. ⁴⁶ (ICBP, 2011)	74,064
4	Educational attainment (HRS removed)	Okbay et al. ⁴⁷ (SSGAC, 2016)	293,723
5	Alzheimer disease	Lambert et al. ⁵ (IGAP, 2013)	74,046
6	Neuroticism	Okbay et al. ⁴⁸ (SSGAC, 2016)	170,911
7	Subjective wellbeing (HRS removed)	Okbay et al. ⁴⁸ (SSGAC, 2016)	298,420
8	Waist circumference	Shungin et al. ⁴⁹ (GIANT, 2015)	210,088
9	Depressive symptoms	Okbay et al. ⁴⁸ (SSGAC, 2016)	180,866

Abbreviations: CHARGE = Cohorts for Heart and Aging Research in Genomic Epidemiology; GIANT = Genetic Investigation of ANthropometric Traits; ICBP = International Consortium for Blood Pressure; IGAP = International Genomics of Alzheimer's Project; MAP = mean arterial pressure; SSGAC = Social Science Genetic Association Consortium.

Table 3 Logistic regression analysis of polygenic score (PGS) of multiple phenotypes with motoric cognitive risk syndrome adjusted for age, sex, education, and genetic ancestry

PGS	B	Significance	Exp (B)	95% CI for Exp (B)	
				Lower	Upper
General cognition	-0.059	0.384	0.942	0.824	1.077
Body mass index	0.197	0.004 ^a	1.217	1.067	1.389
Mean arterial pressure	0.021	0.747	1.021	0.901	1.157
Educational attainment	-0.031	0.639	0.969	0.850	1.105
Alzheimer disease	0.149	0.021	1.160	1.023	1.316
Neuroticism	0.071	0.369	1.073	0.920	1.252
Subjective well-being	-0.025	0.714	0.975	0.852	1.116
Waist circumference	0.203	0.003 ^a	1.225	1.073	1.399
Depressive symptoms	-0.034	0.615	0.966	0.846	1.104

Abbreviations: CI = confidence interval; FDR = false discovery rate.

^aSurvived multiple correction; p_{FDR} value < 0.05.

waist circumference (OR 1.23, $p = 0.003$, $p_{FDR} = 0.027$) were associated with MCR syndrome. Increased PGS for AD (OR 1.16, $p = 0.021$, $p_{FDR} = 0.071$) showed a trend towards increased risk of MCR. The other 6 PGS were not associated with MCR (table 3).

Sensitivity analysis excluding individuals with isolated cognitive complaints or slow gait confirmed the association of BMI (OR 1.23, 95% CI 1.07–1.41, $p = 0.003$) and waist circumference (OR 1.24, 95% CI 1.08–1.43, $p = 0.002$) PGS with MCR. Further, the association of PGS associated with AD (OR 1.17, 95% CI 1.02–1.33, $p = 0.021$) were strengthened in the sensitivity analysis (table 4).

We conducted a post hoc analysis, including the trait along with its related PGS in the logistic regression analysis for those showing significant results. Increased PGS for BMI (OR 1.16, 95% CI 1.01–1.33, $p = 0.027$) and waist circumference (OR 1.17, 95% CI 1.02–1.34, $p = 0.021$) were still associated with MCR in these models, though the level of significance was reduced.

Subjective cognitive complaints

Increased neuroticism PGS was associated with subjective cognitive complaints (OR 1.10, $p = 0.007$, $p_{FDR} 0.036$) (table 5). The PGS for subjective wellbeing was associated with reduced risk of cognitive complaints (OR 0.92, $p = 0.012$, $p_{FDR} 0.046$).

Table 4 Logistic regression analysis of polygenic score (PGS) of multiple phenotypes with motoric cognitive risk adjusted for age, sex, education, and genetic ancestry (sensitivity analysis)

PGS	B	Significance	Exp (B)	95% CI for Exp (B)	
				Lower	Upper
General cognition	-0.046	0.512	0.955	0.832	1.096
Body mass index	0.207	0.003	1.230	1.071	1.414
Mean arterial pressure	0.041	0.523	1.042	0.919	1.182
Educational attainment	-0.035	0.609	0.966	0.844	1.105
Alzheimer disease	0.153	0.021	1.166	1.024	1.328
Neuroticism	0.121	0.130	1.129	0.965	1.321
Subjective well-being	-0.075	0.290	0.928	0.807	1.066
Waist circumference	0.216	0.002	1.241	1.079	1.427
Depressive symptoms	-0.005	0.940	0.995	0.869	1.139

Abbreviation: CI = confidence interval.

In this model, healthy controls are free from slow gait or cognitive complaints.

Table 5 Logistic regression analysis of polygenic score (PGS) of multiple phenotypes with cognitive complaints adjusted for age, sex, education, and genetic ancestry

PGS	B	Significance	Exp (B)	95% CI for Exp (B)	
				Lower	Upper
General cognition	0.046	0.145	1.047	0.984	1.113
Body mass index	0.034	0.272	1.035	0.974	1.099
Mean arterial pressure	0.040	0.180	1.040	0.982	1.102
Educational attainment	0.014	0.652	1.014	0.954	1.077
Alzheimer disease	0.025	0.407	1.025	0.967	1.086
Neuroticism	0.098	0.007 ^a	1.103	1.027	1.184
Subjective well-being	−0.079	0.012 ^a	0.924	0.869	0.983
Waist circumference	0.012	0.689	1.013	0.953	1.076
Depressive symptoms	0.052	0.095	1.053	0.991	1.119

Abbreviations: CI = confidence interval; FDR = false discovery rate.

^aSurvived multiple correction; p_{FDR} value < 0.05.

There was no association between the other PGS and cognitive complaints (table 5).

Slow gait

Similar to MCR, PGS for BMI (OR 1.16, $p = 0.002$, p_{FDR} 0.027) and waist circumference (OR 1.19, $p = 0.001$, p_{FDR} 0.027) were associated with the slow gait component of MCR (table 6). AD PGS was associated with slow gait (OR 1.13, $p = 0.008$, p_{FDR} 0.036). No other PGSs were associated with slow gait (table 6).

Of all pairwise interactions between the 9 PGSs, only 2 were nominally significant. AD–neuroticism (OR 1.153, 95% CI 1.027–1.294, $p = 0.016$) as well as mean arterial pressure–

educational attainment (OR 0.880, 95% CI 0.785–0.986, $p = 0.027$) PGS interactions were associated with MCR. However, neither association survived FDR correction.

Discussion

Our study based in the nationally representative HRS cohort provides insights into the genetic predisposition of MCR syndrome. We found associations between (1) obesity-related PGS and MCR, (2) neuroticism, depressive symptoms, and subjective well-being PGS with cognitive complaints, and (3) obesity-related and AD PGS with slow gait speed. Although the study was carried out in relatively small sample size and not all associations survived corrections for multiple testing,

Table 6 Logistic regression analysis of polygenic score (PGS) of multiple phenotypes with slow gait adjusted for age, sex, education, and genetic ancestry

PGS	B	Significance	Exp (B)	95% CI for Exp (B)	
				Lower	Upper
General cognition	−0.059	0.236	0.943	0.856	1.039
Body mass index	0.152	0.002 ^a	1.164	1.057	1.281
Mean arterial pressure	0.022	0.635	1.022	0.934	1.119
Educational attainment	−0.081	0.096	0.922	0.838	1.015
Alzheimer disease	0.124	0.008 ^a	1.132	1.033	1.240
Neuroticism	0.031	0.591	1.031	0.922	1.153
Subjective well-being	0.030	0.548	1.030	0.935	1.136
Waist circumference	0.171	0.001 ^a	1.187	1.078	1.307
Depressive symptoms	−0.009	0.862	0.992	0.901	1.092

Abbreviations: CI = confidence interval; FDR = false discovery rate.

^aSurvived multiple correction; p_{FDR} value < 0.05.

all effects were in the expected directions, and the inferences were consistent with biological pathways (e.g., AD PGS was associated with MCR, brain-related PGS were more strongly associated with cognitive complaints, whereas anthropometric PGS were more strongly associated with gait). Furthermore, the MCR-associated genetic traits were consistent with the clinical risk factors identified for MCR in multiple aging cohorts.^{2,3,10} The findings from our preliminary investigation will help decipher the genetic risk shared with other complex phenotypes as well as in understanding specific biological pathways underlying MCR. To our knowledge, this is the first study that has examined individual-level genetic burden in relation to a predementia syndrome.

Higher BMI and waist circumference PGS were associated with increased risk for MCR in HRS. Support for our findings comes from both epidemiologic and genetic studies. Obesity in midlife is a strong risk factor for AD as well as vascular dementia.^{20–22} Higher midlife BMI predicted early onset of AD as well as vascular dementia.^{23–25} High BMI is also associated with reduced default mode connectivity^{26,27} as well as global and regional gray matter volume loss.²⁸ Higher BMI was associated with incident MCR in a multicenter study involving 3,128 older adults in United States³ as well as with prevalent MCR in a cross-sectional Japanese study.¹⁰ Waist circumference has been suggested as a better indicator of obesity-related health risk than BMI.²⁹ It was shown to be associated with dementia in persons 65–75 years old.³⁰ An age-related paradox in the association of obesity with dementia has been reported, with obesity being a risk factor for dementia in midlife and protective of cognition in advanced ages. However, this has less influence on our genetic results. The obesity-related genetic predisposition to MCR may be due to pleiotropic effects of SNPs related with obesity and shared pathways with dementia rather than a direct effect. At the genetic level, variations in the fat and obesity-associated *FTO* gene have been associated with dementia, mainly AD.^{31,32} *FTO* obesity-associated risk allele carriers also showed lower brain volumes compared to noncarriers.³³ Inclusion of associated traits (BMI and waist circumference) reduces but does not take away the effect of the related PGS with MCR, suggesting that other pathways might also be involved in this association. Biological studies are needed to further explore these associations.

Increased genetic predisposition for neuroticism as well as lower subjective well-being PGS were risk factors for subjective cognitive complaints in HRS. Neuroticism is one of the Big Five higher-order personality traits, and higher levels of neuroticism were associated with dementia and MCI.³⁴ Neuroticism PGS was suggestively associated with MCR in our sensitivity analysis. Midlife neuroticism was found to be associated with increased risk of AD dementia over a 38-year follow-up period in women in a population-based study.³⁵ Neuroticism was correlated with subjective cognitive complaints in the Sydney Memory and Ageing Study.³⁶ Interaction analysis showed an association of neuroticism–AD PGS pair with MCR. But this interaction needs to be validated in

a larger sample. Lower PGSs for subjective well-being were associated with increased risk for MCR in our analysis.

Our analysis revealed shared genetic predisposition for AD and obesity-associated traits with slow gait. Growing evidence supports slow gait as an early predictor of cognitive decline and dementia.³⁷ Slowing of gait has been reported to precede mild cognitive impairment syndrome as well as dementia.^{38,39} MCR syndrome was shown to predict AD as well as vascular dementia.^{1,2} In the Einstein aging study, we found that *APOE* $\epsilon 4$ allele was associated with faster gait speed decline in older men.⁴⁰ PGS of obesity-related phenotypes (BMI and waist circumference) were associated with slow gait, similar to MCR. Elevated BMI is a well-established risk factor for slow gait.^{41,42} Thus, our observation in regard to higher PGSs for BMI and waist circumference being associated with slow gait aligns with earlier studies linking obesity and gait performance. PGS for educational attainment had a suggestive protective effect on slow gait. Education, a marker of cognitive reserve, is protective for AD.⁴³

The strengths of this study include the well-defined PGS based on comparative studies carried out in HRS⁴⁴ and the use of best available estimates of genetic effects from large meta-analyses. We were consistent in defining MCR as in our previous reports.^{1–3,10} Strengths of the MCR construct are that slow gait is defined objectively, independent of clinical gait evaluations that may be prone to variable sensitivity and specificity as well as being examiner-dependent. Though slow gait is multifactorial in nature with both neurologic and non-neurologic etiologies,¹⁵ multiple studies have shown that slow gait predicts cognitive decline irrespective of the underlying etiology.³⁹ Our analytical approach was empiric; we identified phenotypes of interest from previous MCR studies.^{2,3,10} Finally, the large, well-characterized HRS sample and the systematic gait assessments are also strengths. There are limitations that need to be noted. We may have missed other unstudied phenotypes that might also influence MCR and dementia pathogenesis. The analysis was restricted to European ancestry; our findings need to be verified in other ethnicities. The analysis was cross-sectional in nature.

We found an association of obesity-related genetic traits with MCR syndrome. These observations have to be studied further to identify underlying biological mechanisms and potential therapeutic targets in dementia pathogenesis.

Study funding

This study was supported by a National Institute on Aging grant (1R56AG057548-01). The sponsors had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication history

Received by *Neurology* August 17, 2018. Accepted in final form November 21, 2018.

Appendix Authors

Name	Location	Role	Contribution
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