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White matter hyperintensities and vascular risk factors in monozygotic twins

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ABSTRACT

Cerebral white matter hyperintensities (WMHs) have been associated with vascular risk factors, both of which are under genetic influence. We examined in a monozygotic twin sample whether the association between vascular risk and WMHs is influenced by overlapping genetic factors. We included 195 cognitively normal monozygotic twins (age = 70 ± 7 years), including 94 complete pairs. Regional WMH load was estimated using an automated algorithm. Vascular risk was summarized with the Framingham score. The within–twin pair correlation for total WMHs was 0.76 and for Framingham score was 0.77. Within participants, Framingham score was associated with total and periventricular WMHs (r = 0.32). Framingham score in 1 twin was also associated with total WMHs in the co-twin (r = 0.26). Up to 83% of the relation between both traits could be explained by shared genetic effects. In conclusion, monozygotic twins have highly similar vascular risk and WMH burden, confirming a genetic background for these traits. The association between both traits is largely driven by overlapping genetic factors.

1. Introduction

Cerebral white matter hyperintensities (WMHs) on fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) scans are a common finding in older adults (Launer, 2004) and are associated with risk of cognitive decline (De Groot et al., 2002; Debette and Markus, 2010; Prins et al., 2004). They are found in the periventricular and deep white matter. Although the etiology of WMHs is not yet fully understood, they are often considered to be a manifestation of small vessel disease. WMHs have been associated with the presence of various vascular risk factors, such as hypertension, diabetes, and smoking (Dickie et al., 2016; Habes et al., 2016; Wardlaw et al., 2015).

The occurrence of WMHs is under genetic influence. Previous family and twin studies have found heritability estimates of 0.55–0.81 for total WMH load (Atwood et al., 2004; Carmelli et al., 1998; Fennema-Notestine et al., 2016; Sachdev et al., 2016; Turner et al., 2004). Heritability studies have also found a moderate-to-strong genetic influence on the presence of various vascular risk factors such as blood pressure and hypertension (Evans et al., 2003; Kupper et al., 2005), impaired glucose tolerance (Poulsen et al., 1999), serum cholesterol and high-density lipoprotein (HDL) levels (Elder et al., 2009; Goode et al., 2007; Rahman et al., 2009), and smoking (Vink et al., 2005). It is not yet clear whether vascular risk factors are independently associated with increased WMHs or whether there are common underlying genetic factors that influence both vascular risk factors and the presence of WMHs.

Monozygotic twins are genetically identical and partly share environmental factors. Similarity of a trait within monozygotic twin pairs can be due to either genetic factors or shared environmental factors, whereas differences result from nonshared environmental factors. To disentangle the contribution of genetic and shared environmental factors to a trait, classic twin design studies also include dizygotic twins, who share 50% of their segregating genes and are assumed to have a similar amount of shared environmental

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factors as monozygotic twins. In our study, we included only monozygotic twin pairs. Previous studies including monozygotic and dizygotic twins have shown that the presence of WMHs is best explained by a model including genetic effects and nonshared environmental factors, eliminating shared environmental influences from the model (Carmelli et al., 1998; Fennema-Notestine et al., 2016; Sachdev et al., 2016). Similarly, twin studies have found that shared environmental influences do not predict vascular risk factors such as blood pressure and hypertension (Evans et al., 2003; Kupper et al., 2005; Panizzon et al., 2015), impaired glucose tolerance (Poulsen et al., 1999), and serum cholesterol and HDL levels (Elder et al., 2009; Rahman et al., 2009), although not in all studies (Jermendy et al., 2011). Together, this suggests that similarity in WMHs and vascular risk factors within monozygotic twin pairs is most likely attributable to genetic factors.

In this study, we have first examined the correlation of vascular risk factors and WMH volume, location, and pattern within cognitively normal older adult monozygotic twin pairs. We then assessed whether overlapping genetic factors could underlie the association between vascular risk factors and WMHs by examining the similarity within monozygotic twin pairs for these traits. As a summary measure for vascular risk factors, we used the Framingham score (D'Agostino et al., 2008; Habes et al., 2016), but we also tested correlation for each vascular risk factor included in this score with WMHs. As differences in heritability estimates of WMHs have been found between males and females, we also examined gender differences in these traits (Atwood et al., 2004; Sachdev et al., 2016).

2. Materials and methods

2.1. Participants

Monozygotic twins were included from the Amsterdam substudy of the European Medical Information Framework for Alzheimer's Disease PreclinAD cohort, a longitudinal study on risk factors for amyloid pathology and cognitive decline in cognitively normal older adults. Inclusion criteria were having age above 60 years, a delayed recall score of >-1.5 SD of age-adjusted normative data on the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) 10-word list (Morris et al., 1989), a global Clinical Dementia Rating score of 0 (Morris, 1993), Telephone Interview for Cognitive Status modified (TICS-m) score of 23 or higher (de Jager et al., 2003), and a 15-item Geriatric Depression Scale score of <11 (Yesavage et al., 1982). Exclusion criteria were any significant neurologic, systemic, or psychiatric disorder that could cause cognitive impairment. Participants were recruited between December 2014 and August 2016 from the Netherlands Twin Registry (Boomsma et al., 2006; Willemsen et al., 2013). All participants were asked to collect mucosal cell samples for DNA extraction to confirm zygosity. From the Amsterdam PreclinAD cohort, we excluded 6 participants due to missing MRI data (1 due to claustrophobia, 1 due to technical issues with the scanner, and 4 due to participant refusal to visit the hospital), 1 participant due to the presence of multiple sclerosis-like lesions on MRI, and 1 dizygotic twin pair. For the present study, we used 195 participants, of which 94 were complete monozygotic twin pairs and 7 single participants. The study was approved by the VU University Medical Center's ethics committee, and all participants gave written informed consent.

2.2. Clinical and vascular risk assessment

Clinical data were collected during a face-to-face interview for medical history, medication intake, smoking habits, and educational attainment. All participants also underwent physical examinations. Blood pressure was measured 3 times in a lying position with a 5-minute interval between measurements, and the mean of these 3 measurements was used for the analysis. After a minimum 2-hour fasting period, participants underwent a blood-draw to determine lipid profile and glycated hemoglobin in the morning. The cardiovascular risk profile for each participant was summarized using the Framingham score index, which includes the following factors: age, gender, total cholesterol, HDL, systolic blood pressure, antihypertensive medication use, diabetes mellitus, and smoking (D'Agostino et al., 2008). This risk index represents the 10-year risk of a major cardiovascular event. All clinical, cognitive, and MRI measurements were performed within 6 months (median 16 days).

2.3. Image acquisition

Whole-brain scans were obtained using a single 3T scanner (Philips Ingenuity Time-of-Flight PET/MRI scanner) using an 8-channel head coil. Isotropic structural 3D T1-weighted images were acquired using a sagittal turbo field echo sequence (1.00 mm^3 isotropic voxels, repetition time = 7.9 ms, echo time = 4.5 ms, and flip angle = 8°); 3D sagittal FLAIR sequences (1.12 mm^3 isotropic voxels, repetition time = 4800 ms, echo time = 279 ms, and inversion time = 1650 ms) were acquired for the analysis of WMHs. The MR protocol also included susceptibility weighted imaging. All MRI scans were visually assessed by an experienced neuroradiologist for incidental findings.

2.4. MRI analysis

All MRI scans were visually rated by a single experienced rater (MtK) who was blind to twin pairing at the time of rating. WMHs were visually assessed on the 3D FLAIR images using the 4-point Fazekas scale for deep WMHs (none, punctuate, early confluent, and confluent; Fazekas et al., 1987). Lacunes were defined as deep lesions between 3 and 15 mm with cerebrospinal fluid–like signal on T1-weighted and FLAIR images. Microbleeds were assessed on susceptibility weighted images and defined as rounded hypointense homogeneous foci of up to 10 mm in the brain parenchyma. Medial temporal lobe atrophy was assessed on coronal reconstructions of the T1-weighted images using the 5-point Scheltens' scale (Scheltens et al., 1992). Global cortical atrophy was rated on transversal FLAIR images using a 4-point scale (Pasquier et al., 1996).

Quantitative WMH load was estimated jointly from both 3D T1 and 3D FLAIR scans using a previously described algorithm (Sudre et al., 2015). Details of the WMH lesion segmentation are provided in the Supplementary Methods. To visually represent the distribution of WMHs in the brain, a coordinate frame (bullseye) was designed to characterize the location based on the normalized distance between the ventricular surface and cortex (4 layers) and the left/right cortical lobes (frontal, parietal, temporal, and occipital) or basal ganglia. Overall 36 regions (4 layers, 9 lobar regions) were defined to characterize the location of WMHs. Fig. 1 illustrates the definition of layers and lobar regions and presents an example of a bullseye representation of this local information. Infratentorial structures (i.e., brain stem and cerebellum) were not taken into account because of the low WMH lesion load in these regions in this cohort. All WMH segmentations were visually inspected, and none had to be excluded.

2.5. Statistical analysis

All statistical analyses were performed in R (R, version 3.3.1; http://www.R-project.org).