Title

Common Genetic Variation Indicates Separate Causes for Periventricular and Deep White Matter Hyperintensities

Journal

Stroke, 51(7)

ISSN

0039-2499

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Publication Date

2020-07-01

DOI

10.1161/strokeaha.119.027544

Peer reviewed

HHS Public Access

Author manuscript

Stroke. Author manuscript; available in PMC 2021 July 01.

Published in final edited form as:

Stroke. 2020 July ; 51(7): 2111–2121. doi:10.1161/STROKEAHA.119.027544.

Common genetic variation indicates separate etiologies for periventricular and deep white matter hyperintensities

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Abstract

Background and Purpose—Periventricular (PVWMH) and deep white matter hyperintensities (DWMH) are regional classifications of white matter hyperintensities (WMH) and reflect proposed differences in etiology. In the first study to date, we undertook genome-wide association analyses (GWAS) of DWMH and PVWMH to show that these phenotypes have different genetic underpinnings.

Methods—Participants were aged 45 years and older; free of stroke and dementia. We conducted GWAS of PVWMH and DWMH in 26,654 participants from CHARGE, ENIGMA, and the UK Biobank (UKB). Regional correlations were investigated using the GWAS-pairwise method. Cross-trait genetic correlations between PVWMH, DWMH, stroke, and dementia were estimated using LDSC.

Results—In the discovery and replication analysis, for PVWMH only, we found associations on chromosomes (Chr) 2 (*NBEAL),* 10q23.1 (*TSPAN14/FAM231A),* and 10q24.33 (*SH3PXD2A).* In the much larger combined meta-analysis of all cohorts, we identified ten significant regions for PVWMH: Chr 2 (3 regions), 6, 7, 10 (2 regions), 13, 16 and 17q23.1. New loci of interest include 7q36.1 (*NOS3)* and 16q24.2. In both the discovery/replication and combined analysis, we found genome-wide significant associations for the 17q25.1 locus for both DWMH and PVWMH. Using gene-based association analysis, 19 genes across all regions where identified for PVWMH only, including the new genes: *CALCRL* (2q32.1), *KLHL24* (3q27.1), *VCAN* (5q27.1) and *POLR2F* (22q13.1). Thirteen genes in the 17q25.1 locus were significant for both phenotypes. More extensive genetic correlations were observed for PVWMH with small vessel ischemic stroke. There were no associations with dementia for either phenotype.

Conclusions—Our study confirms these phenotypes have distinct and also shared genetic architectures. Genetic analyses indicated PVWMH was more associated with ischemic stroke whilst DWMH loci were implicated in vascular, astrocyte and neuronal function. Our study confirms these phenotypes are distinct neuroimaging classifications and identifies new candidate genes associated with PVWMH only.

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See online Data Supplement.

Keywords

Genome-wide association study; white matter; neuroimaging; brain; risk factors; genomics

Introduction

Radiological white matter hyperintensities of presumed ischemic origin (WMH) are the most prevalent sign of cerebral small vessel disease (SVD) and represent 40% of all SVD disease burden[1]. They are detected as incidental lesions on T2-weighted MRI[1]. WMH are associated with increased risk for ischemic and hemorrhagic stroke, cognitive decline, and motor gait disorders [2–6]. Two regional classifications, based on their anatomical relationship to the lateral ventricles in the brain, are periventricular (PVWMH) and deep WMH (DWMH)[5, 7–9]. PVWMH have been associated with declines in cognitive performance and increased systolic and arterial pressure, while DWMH are linked to BMI, mood disorders, gait impairment and arterial hypertension[10–12]. This categorization reflects proposed differences in underlying pathophysiology[5, 7, 8]. DWMH lesions occur in the subcortex, areas primarily supplied by long microvessels, with lower estimated blood pressures, possibly subject to damage secondary to hypertension and possibly with consequent hypoperfusion.[1, 8, 13, 14]. PVWMH are related to alterations in short penetrating microvessels ending in close approximation to larger arterial blood vessels with different vascular architecture such as two leptomeningeal layers and enlarged perivascular spaces[1, 15]. They are hypothesized to be affected more directly by hypertension and risk factors associated with stroke[1, 8, 13, 14].

These sub-classifications may also reflect differences in associated underlying genetic factors[16]. Twin and family studies report that both PVWMH and DWMH have high heritability and genetic correlations[16, 17]. Recently, GWAS for total WMH volume identified a major genetic risk locus on chromosome 17q25.1[18–21] and several other loci (e.g., 10q24, 2p21, 2q33, 6q25.1)[19, 21, 22]. However, the genetic determinants of regional WMH burden, specifically DWMH and PVWMH, remain elusive.

We combined all available participants aged 45 and above with both DWMH and PVWMH measurements from the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) and the Enhancing Neuro-Imaging Genetics through Meta-Analysis (ENIGMA) consortia, and the UK Biobank (UKB). This is the only GWAS to date examining WMH subclassifications. We hypothesized that separating the two WMH subclassifications would mitigate phenotype heterogeneity, allowing us to identify additional risk loci and show that DWMH and PVWMH have different genetic underpinnings and pathophysiology.

Materials and Methods

Summary data for this meta-analysis will be available through the database of Genotypes and Phenotypes Cohorts for Heart and Aging Research in Genomic Epidemiology Summary Results site, which can be downloaded via authorized access.

Study Cohorts

Study participants (total N~26,654) were drawn from cohorts in the CHARGE and ENIGMA consortia and the UKB. Detailed methods are in the Data Supplement. All cohorts followed standardized procedures for participant inclusion, genotype calling, phenotype harmonization, covariate selection and study-level analysis. Participants were included if they had phenotype, genotype and covariate data available and were aged 45 years and over without stroke, dementia or any neurological abnormality at the time of MRI scanning. All participants provided written informed consent and each study received ethical approval to undertake this work.

Phenotype and covariates

The MRI and WMH extraction methods for each study are detailed in the Data Supplement. In brief, PVWMH and DWMH volumetric data were extracted using automated methods for all studies except HUNT, LBC and AGES, which used visual rating scales (Supplementary Table I). Hypertension was defined as systolic blood pressure ≥140mm Hg and diastolic blood pressure ≥90mm Hg or on current antihypertensive treatment.

Statistical analysis

Each study fitted linear regression models to test the association of DWMH and PVWMH (continuous measures) with individual SNPs. Additive genetic effects were assumed and the models were adjusted for age (years), sex and ICV (where applicable). In addition, principal components for population stratification and other covariates, such as familial structure, were included if necessary. Models were also fitted with hypertension as an additional covariate.

Fixed-effects, inverse-variance-weighted meta-analysis was carried out in METAL[23], with correction for genomic control. Two meta-analyses were carried out: all cohorts excluding UKB (discovery, phase I) and all cohorts (phase II). Post meta-analysis QC was also performed (see Data Supplement).

Genetic correlations with stroke and dementia

Cross-trait genetic correlation between the two sub-classifications of WMH, stroke and dementia were estimated using LDSC[24] on the GWAS summary statistics from phase II, MEGASTROKE (European ancestry-only)[25]. LD scores were based on the HapMap3 European reference panel. Regional level correlation was investigated using the GWAS-PW and HESS methods[26, 27].

Results

Detailed study descriptions are provided in Supplementary Tables I-III. The discovery cohort was comprised of ~18,234 older adults (≥45 years, 16 studies) and was primarily Caucasian, with 736 African Americans and 658 Hispanics. The predominantly Caucasian UKB was used as the replication cohort (n=8,428).

In the discovery analysis (Phase I), genome-wide significant associations (p<5e-8) were observed in the 17q25.1 region for both phenotypes (Supplementary Tables IV-V). Only the PVWMH analysis found additional genome-wide significant associations on chromosomes 2 and 10 (2 regions). Two of these regions had previously been described for total WMH burden (chr 2, *NBEAL*[19, 21], 10q24.33, *SH3PXD2A*[21]) whilst 10q23.1 had not been described. Adjusting for hypertension made little difference to our findings (Supplementary Tables VI-VII). Replication of the majority of genome-wide significant results for both phenotypes was observed after adjustment for multiple testing (DWMH p <3.6e-4, PVWMH p < 2.76e-4, Supplementary Tables VIII-IX).

Given the relatively large size of the replication cohort, a combined meta-analysis (Phase II) was undertaken using all samples (n~26,654). Removing either the small subsample of non-Caucasians, or the cohorts with visual ratings, did not substantially change the findings (beta value r^2 > 0.93). The Phase II GWAS meta-analyses identified 236 for DWMH and 513 genome-wide significant SNPs for PVWMH (Figure 1a, Table 1, Supplementary Tables X-XI respectively). Figure 1b shows the zoom plot of the single locus identified for DWMH on chr17q25.1. The associations of the identified genome-wide and suggestive associations for each phenotype for the alternate trait are also provided in Supplementary Tables X-XI. The only SNPs genome-wide significant for both phenotypes (n=209) were located on 17q25.1 (Figure 2a).

Ten chromosomal regions containing 290 genome-wide significant SNPs for PVWMH only were identified on chromosomes 2 (3 regions), 6, 7, 10 (2 regions), 13, 16 and 17q23.1 (Supplementary Results; Supplementary Table XI; Supplementary Figure I-II). Four loci had not been previously reported for associations with total WMH at the genome-wide significant level: (i) 7q36.1 (7.2kb) containing 2 exonic SNPs in the *NOS3* gene; (ii) 10q23.1 (50.5kb) containing 4 intronic SNPs in *TSPAN14* & *FAM231A;* (iii) 16q24.2 (1.2kb) containing 2 intergenic SNPs; (iv) 17q21.31 (27.2kb) containing 8 SNPs, most of which are intronic and in the *NMT1* gene. Many of these are eQTLs or participate in long-range chromatin interactions (Figure 2b). Further descriptions of the PVWMH findings are found in the Supplementary Results.

As expected, the association of the 17q25.1 locus with both phenotypes was confirmed. The size of this region, including genome-wide significant SNPs only, was similar for both DWMH (236 SNPs, BP 73757836–74025656, Figure 1b) and PVWMH (223 SNPs, BP 73757836–74024711, Supplementary Figure Ia). The top results in this locus were rs3744020 for DWMH, (p=7.06e-35, *TRIM47* intronic SNP) and rs35392904 for PVWMH (p=3.989e-28, *TRIM65* intronic SNP), which are in high linkage disequilibrium (LD, R^2=0.902) (Table 1). Many of these SNPs are eQTLs or have long-range chromatin interactions (Figure 2b-c). For further details see the Supplementary Results.

Using gene-based tests, 13 genes in the 17q25.1 locus reached genome-wide significance (p<2.66e-6) with both phenotypes (Table 2, Figure 2d, Supplementary Tables XII-XIII). For PVWMH, an additional 19 genes were identified, covering the majority of regions/loci found in the SNP-based analysis (Figure 2d, Table 2, Supplementary Table XIII). Four genes

were located in previously unidentified regions: *CALCRL* (2q32.1), *KLHL24* (3q27.1), *VCAN* (5q27.1) and *POLR2F* (22q13.1).

Heritability analyses revealed low to moderate heritability for both traits (see Supplementary Results). A high genetic correlation between DWMH and PVWMH was observed (r_g= 0.927, p=1.1e-65), indicating a shared genetic architecture. Figure 3 shows the genetic correlations with DWMH, PVWMH, stroke and Alzheimer's disease (AD). Positive genetic correlations with both phenotypes were found for 'all stroke', ischemic stroke and SVD. Intracerebral haemorrhage (ICH, all types) was correlated with DWMH only. No significant correlations were found with AD (Supplementary Table XIV).

Using GWAS-PW[26], we observed several regions with high probability (>90%) for harboring a shared genetic variant between PVWMH and DWMH (Supplementary Table XV). These regions encompass several genome-wide significant loci that were identified for PVWMH (2p16.1 (*EFEMP1*), 2q33.2 (*CARF* & *NBEAL*), 6q25.1 (*PLEKHG1*[22]), 16q24.2 (*C16orf95*), and 17q25.1 (*TRIM47*, *TRIM65*). Additionally, by using HESS[27] regional level correlation estimates were derived for those regions identified by the Bayesian approach (GWAS-PW).

Finally, we investigated local regions of a shared genetic variant between the WMH subtypes and stroke (Supplementary Table XV). A region on chromosome 7 (encompassing the PVWMH *NOS3* exonic SNP) exhibited shared genetic influence of 'all stroke' with both phenotypes. Other regions of shared influence with all stroke were observed for PVWMH only. For the sub-types of stroke, significant regions were identified for DWMH and PVWMH, but none were found for both phenotypes except the chromosome 7 region for ischemic stroke (also identified for all stroke). Similar to the GW level correlation, a positive regional level genetic correlation was observed between the WMH subtypes and stroke (all stroke, all-ischemic, cardio-embolic and small-vessel), by using HESS[27].

Discussion

In our meta-analyses using all available individuals (n=26,654, Phase II), PVWMH had significant independent associations with loci containing genes implicated in large and small vessel disease, as well as ischemic and deep hemorrhagic stroke suggesting a unique genetic and pathophysiological underpinning. While our Phase II GWAS were only slightly larger than the previous biggest GWAS on total WMH burden with 21,079 participants[21], our detection rate of significant SNPs was substantially higher[18, 19, 21]. This improved detection may be the result of reduced heterogeneity by separately analyzing the DWMH and PVWMH phenotypes.

We identified 11 independent loci for PVWMH and one locus for DWMH. Significant genes associated with WMH for the first time in PVWMH include *CALCRL*, *VCAN*, *TSPAN,* and *NOS3*. Most genes and loci previously reported as significant in total WMH.[28–32] were now found to be associated with PVWMH alone, including *PLEKHG1*[22], *SH3PXD2A*[25, 28, 33] and *COL4A2*[33]. Similarly, genes viewed as potential candidates[18, 19, 21] in prior studies we now find to be significantly associated only with PVWMH including *DYDC2* and *NEURL1*

as well as *NMT1*, *GALK1*, *H3F3B*, *UNK*, *UNC13D*, *EVPL*, *ICAL1*, *WDR12/CARF*, *NBEAL1*, and *EFEMP1*.

Many of these genes associated with PVWMH affect vascular function or vascular disease such as ischemic stroke, or coronary artery disease. The *NOS3* gene is associated with coronary artery disease, migraine, vascular dysfunction, SVD, and ischemic stroke[22, 29, 30, 34]. *PLEKHG1* is associated with dementia and ischemic stroke[35] and *SH3PXD2A* has been previously associated with total WMH and ischemic stroke[19, 25].

The most notable associated vascular gene is *COL4A2* that encodes for a subunit of type IV collagen, which has been associated with SVD, ischemic stroke, intracranial hemorrhage, and coronary artery disease[31, 35–38]. It is a proposed therapeutic target for the prevention of intracranial hemorrhage[32, 39]. The association of this vascular gene with PVWMH and deep ICH is suggestive of underlying regional gene effects of the COL4A2 gene on the microvasculature affecting the risk of vascular injury in the periventricular region. These include potential weakening of the structural integrity of the regional microvasculature by altered collagen type 4 structural integrity, dysregulated gene expression of *COL4A1* and *COL4A2*, and toxic cytosolic accumulations of COL4A2 within microvascular structural cells[40]. When comparing PVWMH and DWMH anatomy these mechanisms may enhance the direct mechanical effects of hypertension, or the other stroke risk factors, on the unique microvascular structure of the PVWMH region that also has predicted higher ambient blood pressure[1, 6, 13].

We also discovered a new set of putative PVWMH genes. These include: *TSPAN14*, which encodes one of the tetraspanins which organize a network of interactions referred to as the tetraspanin web, ADAM10 - a metalloprotease that cleaves the precursor of cell surface proteins[41], *KLHL24* encodes a ubiquitin ligase substrate receptor[42], *VCAN* encodes a large chondroitin sulfate proteoglycan that is found in the extracellular matrix. In a recent meta-analysis, *VCAN* was associated with white matter microstructural integrity[43]. These candidate genes for PVWMH may influence the immediate tissues surrounding microvessels and may contribute to SVD-associated biological changes.

The only significant locus observed for DWMH was the previously reported total WMH 17q25.1 locus[18, 19, 21, 22], which was also found for PVWMH. This locus contained the SNPs with the largest effect sizes for both phenotypes. The top genome-wide significant hits for DWMH and PVWMH (17q25.1) were either identical with the SNP recently reported by Traylor et al[22] for total WMH (PVWMH rs3744020) or in high LD (R^2>0.9) with the previously identified top ranked SNPs in the same locus (rs3744028, Fornage et al.[18], rs7214628, Verhaaren et al.[21]). Our identified SNPs were only in moderate LD (R^2≤0.396) with the top SNP (rs3760128) identified in a recent exome association analysis[19]. All of these SNPs fall within or between the previously reported *TRIM47* and *TRIM65* genes[18, 21, 22, 35]. This gene-rich locus contains genes that influence glial cell proliferation and have been hypothesized to influence gliosis, which is a histological and MRI marker of microvascular injury[1]. It includes previously identified total WMH genes, such as *TRIM47/TRIM65* (glial proliferation, astrocytoma's)[18, 21], *ACOX1* (cell replication, hepatic cancer)[18, 19, 21] and *MRPL38* (protein synthesis)[19]. Genes associated with neuronal injury

and/or neurodegenerative disorders are also found in the 17q25.1 locus, including *CDK3* (neuronal cell death in stroke)[44], *H3F3B* (schizophrenia pathogenesis) and *GALK1* (galactosemia)[45]. Interestingly, two genome-wide significant intronic *UNC13D* SNPs identified in this study and reported previously for total WMH burden[21], rs9894244 and rs7216615, have been reported as eQTLs for *GALK1* and *H3F3B* respectively[46]. The PVWMH specific loci also contained genes that potentially influence astrocytic function and gliosis, several previously reported for total WMH. These include *NBEAL1*[19, 21], *WDR12*[19], *NEURL1*[18, 19, 21], *CARF*[47], and *EFEMP1*[37]. Newly identified PVWMH genes potentially affecting astrocytic functioning include *NMT1*[48], *ICA1L*[49], *POLR2F*, *OBFC1* and *DYDC2*.

Shortcomings of this study include the potential variability due to the different WMH extraction algorithms used, with a minority of samples using visual ratings. However, this is a common problem encountered in this type of study[18, 19, 21]. Even though our results suggest improved power and reduction in potential bias through the discrimination of PVWMH from DWMH, the Euclidean methodology used by the majority of studies undoubtedly missed PVWMH lesions outside this boundary. The majority of the participants in this study were Caucasian and hence these results may not apply to other ethnicities. Sex differences have been previously reported but were not examined in the current study[50]. For the Phase II meta-analysis, we did not have an independent replication cohort. Older adults were included in this study and the majority of participants had both DWMH and PVWMH and not one or the other. However, selection of individuals with only one of subtype of these lesions present may be more appropriate to identify differences but would only be possible in younger cohorts. Future studies should aim to address these shortcomings, including continuing to improve and harmonize WMH measurement methods but also using consistent DWMH and PVWMH measurement methods across studies.

Summary/Conclusion

Our study confirms PVWMH and DWMH have distinct and shared genetic architecture. Genetic analyses indicated PVWMH was more associated with ischemic stroke and vascular function (*PLEKHG1*, *SH3PXD2*, *COL4A2, CALCRL*, *VCAN, NOS3*), while DWMH loci were implicated in vascular, astrocyte and neuronal function (TRIM47/TRIM 65, ACOX1, MRPL38, H3F3B, *GALK*, *UNC13D*, *GALK1*). New genes for PVWMH, potentially affecting the extravascular connective tissue, where also identified (*TSPAN14, ADAM10*, *KLHL24, VCAN*). Our study confirms that PVWMH and DWMH are distinct neuroimaging classifications and identifies new candidate genes associated with PVWMH only.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Acknowledgements

Sources of Funding

This work is supported by the NINDS, NIH, R01AG059874, P41EB015922, R56AG058854, U54 EB020403, R01AG022381. Medical Research Council, Age UK, Scottish Funding Council, Row Fogo Trust, The Welcome Trust, Age UK, Cross Council Lifelong Health and Wellbeing Initiative, Leverhulme Trust, National Institute for Health Research, Biotechnology and Biological Sciences Research Council, UK Medical Research Council, Icelandic Heart Association, and the Althingi, Austrian Science Fund (FWF), Australian National Health and Medical Research Council, Austrian National Bank, Anniversary Fund, European Commission FP6 STRP, European Community's 5th and 7th Framework Program, Netherlands Organization for Scientific Research, Netherlands Consortium for Healthy Aging, Russian Foundation for Basic Research, Russian Federal Agency of Scientific Organizations, Liaison Committee between the Central Norway Regional Health Authority and the Norwegian University of Science and Technology, Norwegian National Advisory Unit for functional MRI, Leipzig Research Center for Civilization Diseases (LIFE), Bristol-Myers Squibb, Netherlands Heart Foundation, French National Research Agency (ANR), Foundation Leducq, Joint Programme of Neurodegenerative Disease research, Bordeaux University, Institut Pasteur de Lille, the labex DISTALZ and the Centre National de Génotypage. Deutsche Forschungsgesellschaft (DFG) no. WI 3342/3–1 and grants from European Union, European Regional Development Fund, Free State of Saxony within the framework of the excellence initiative, LIFE-Leipzig Research Center for Civilization Diseases no. 100329290, 713–241202, 14505/2470, 14575/2470. Max Planck Society, State of Saxony, Brain Foundation, Bristol Myers Squibb, NHMRC of Australia, NHMRC of Australia, Parkinson's UK; Medical Research Council - Dementias Platform UK. Full details of funding support for each cohort are detailed in the online Data Supplement

Conflict-of-Interest/Disclosure

Jonathan Marchini is an employee of, and owns stock and stock options for, Regeneron Pharmaceuticals; Perminder Sachdev received personal fees from Biogen; Henry Brodaty, Advisory Board member, Nutricia Australia; Philippe Amouyel, advisor for Foundation Alzheimer, Occupational medicine, Oil company, and Genoscreen Biotech company; Alzheimer's Foundation, Occupational Medicine, Oil company, Genoscreen personal fees, Biotech company; Christine Fennema-Notestine, received finding from National Institutes of Health Grants NIA R01AG022381; Rebecca F. Gottesman, American Academy of Neurology, Associate Editor, Neurology; Paul Thompson, funded by NIH grant U54 EB020403 and received partial research support from Biogen, Inc., Charles DeCarli, consultant to Novartis; Markus Scholz disclosed Pfizer Inc. grants; Ralph Sacco, grant support from Boehringer Ingelheim, NINDS Grants; Neda Jahanshad received funding from the NIH grants, NIH R01AG059874,NIH R01AG059874; Joanna Wardlaw, grant support from the Medical Research Council, Age UK, Scottish Funding Council, and Row Fogo Trust during the conduct of the study and grant support from Fondation Leducq, Wellcome Trust, EPSRC, Chest Heart Stroke Scotland, British Heart Foundation, Stroke Association, Alzheimer's Society and Alzheimer's Research UK outside the submitted work.

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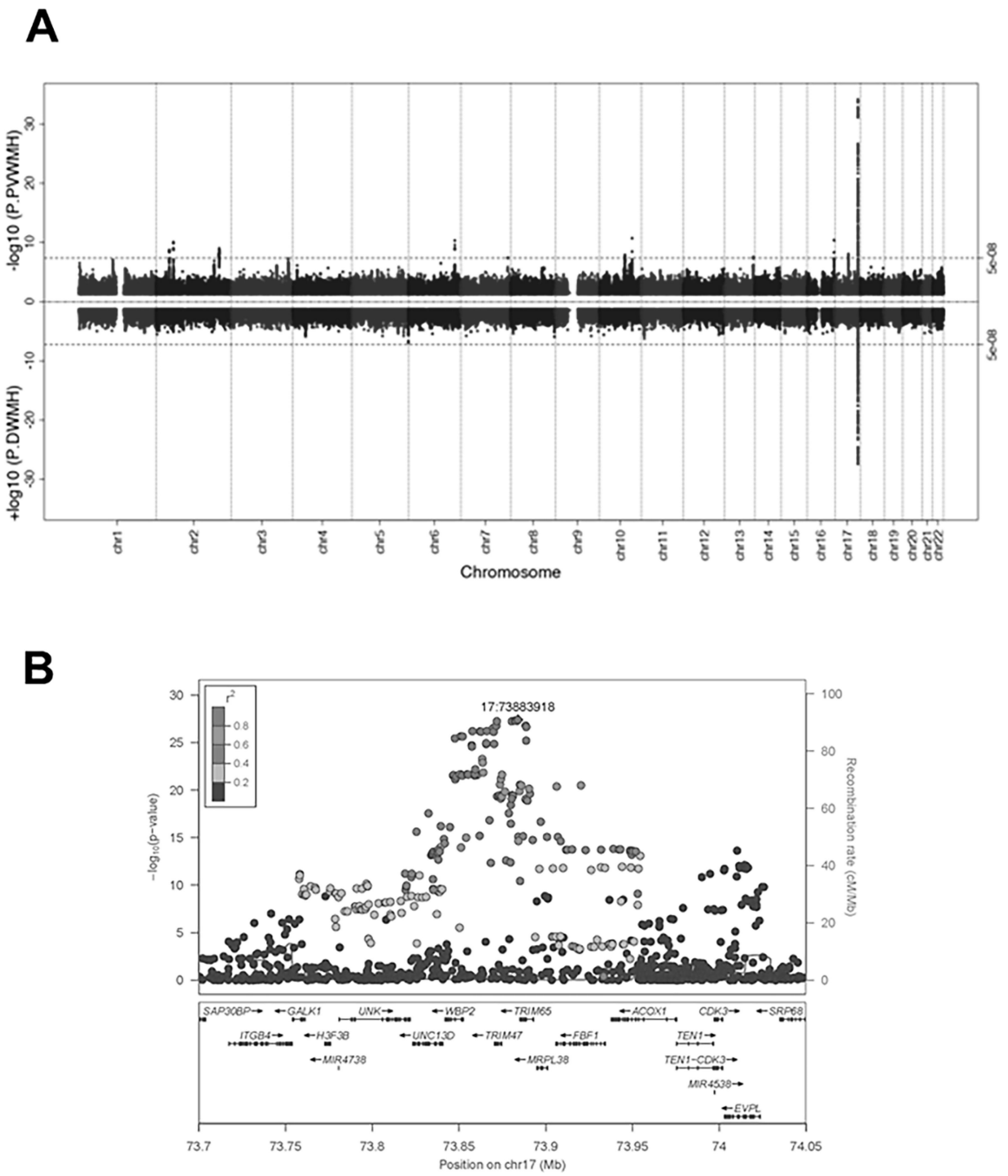

Figure 1.

(A) Phase II GWAS meta-analysis. Miami plot for PVWMH (upper panel) and DWMH (lower panel). Dashed line shows genome-wide significance threshold (p<5e-8). (B) Chr17 regional plot of genome-wide significant SNPs for DWMH. Colors of the SNPs indicate the level of LD with the top SNP (purple), rs35392904.

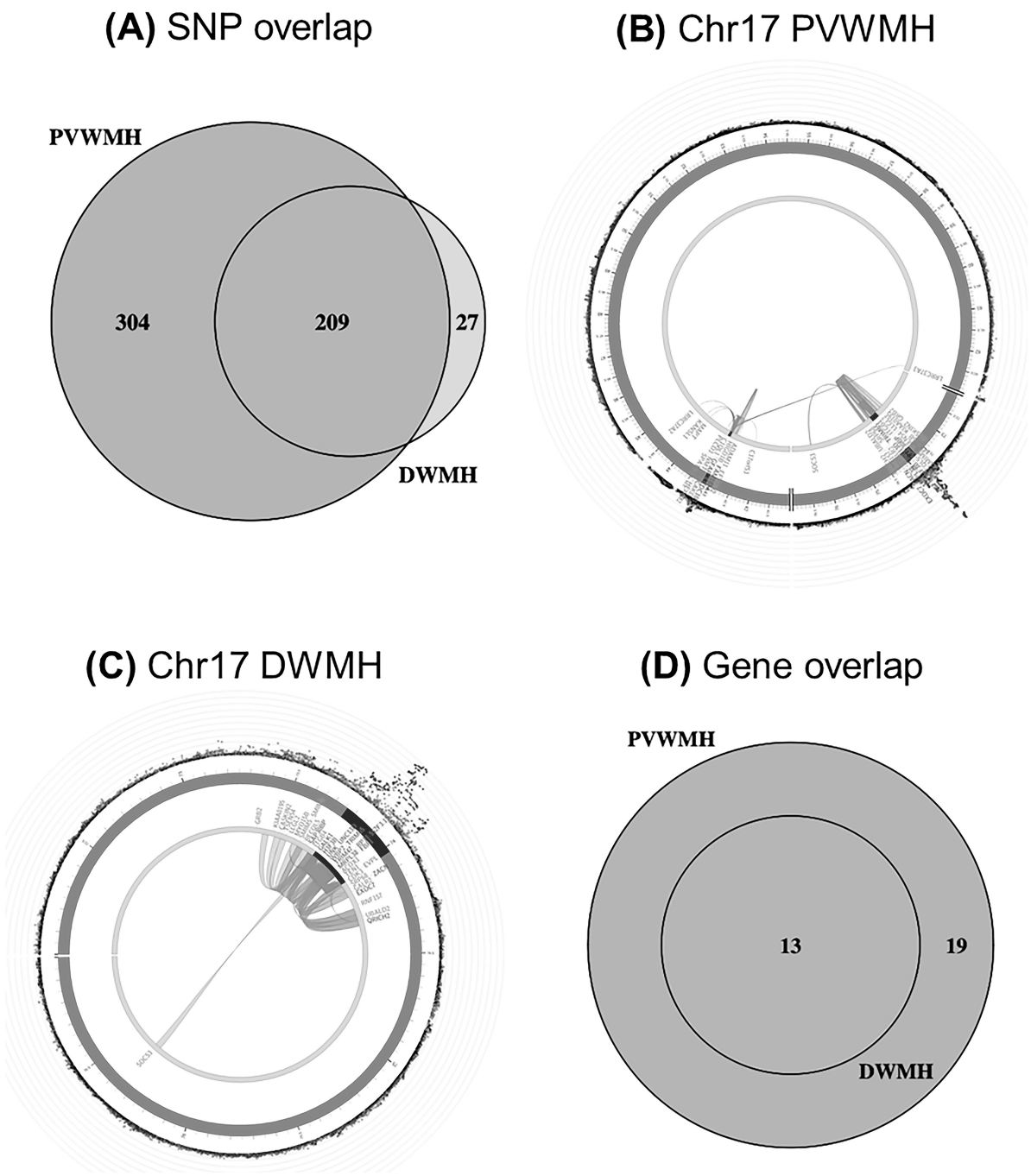

Figure 2.

(A) Overlap between genome-wide significant SNPs (p<5e-8) for DWMH and PVWMH. (B - C) Circos plots for chr17 for both phenotypes, showing two identified regions for PVWMH (B) but only one for DWMH (C). Outer ring shows SNPs <0.05 with the most significant SNPs located towards the outermost ring. SNPs in high LD with the independent significant SNPs in each locus are colored in red (r^2>0.8)-blue (r^2>0.2); no LD (grey). Genomic risk loci are colored in dark blue (2nd layer). Genes are mapped by chromatin interaction

(orange), eQTL (green) or both (red). (D) Overlap between significant genes identified by MAGMA for both phenotypes.

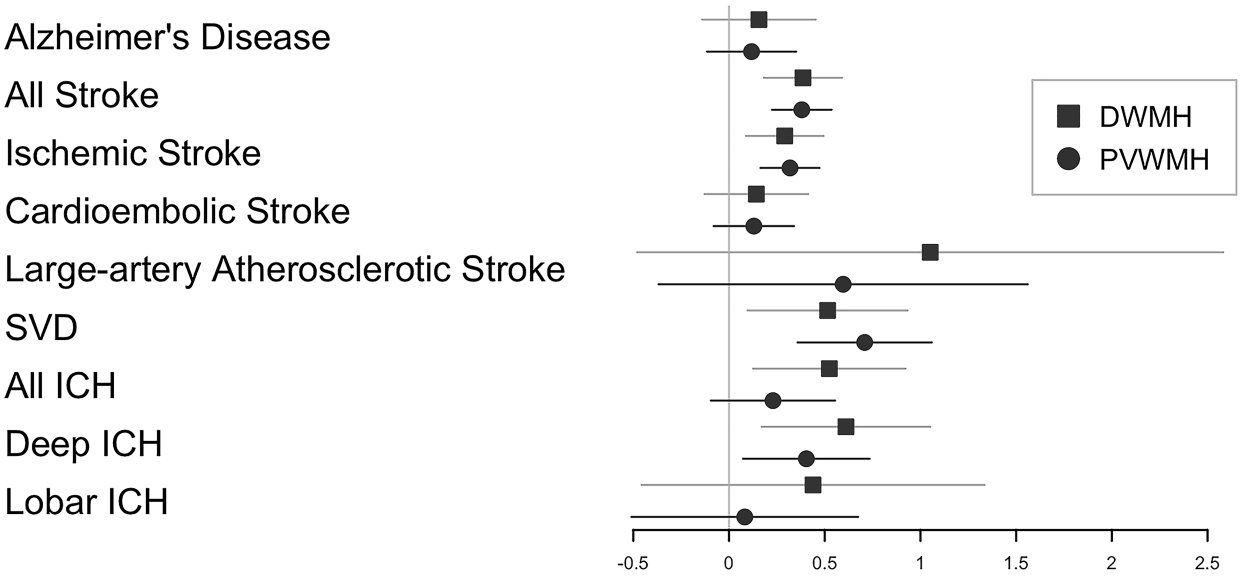

Figure 3.

Genetic correlations (r_g) between DWMH, PVWMH, Alzheimer's disease (AD) and stroke phenotypes. Horizontal bars represent standard errors and the size of the square corresponds precision. SVD = small vessel disease stroke, All ICH = All intracranial hemorrhage, Deep ICH = deep intracranial hemorrhage, Lobar ICH = lobar intracranial hemorrhage

Table 1.

Top genome-wide significant SNP results from each genomic locus identified from the Phase II GWAS meta-analysis for deep and periventricular (PV) WMH.

WMH	rsID	CHR	POS	Nearest gene	Function/Position	A1	A2	Freq (A1)	Beta (SE)	*N*	Direction	*P* value
PV	rs3744020	17q25.1	73871773	*TRIM47*	Intronic	A	G	0.1897	0.0899 (0.0073)	26438	+++-+++?++++++++++++	7.06E-35
Deep	rs35392904	17q25.1	73883918	*TRIM65*	Intronic	T	C	0.7981	−0.0765 (0.0070)	26642	-------+--------+----	3.99E-28
PV	rs3758575	10q24.33	105454881	*SH3PXD2A*	Intronic	A	G	0.4904	0.0388 (0.0058)	26654	+++-++-++++++++++++++	2.00E-11
PV	**rs12928520**	**16q24.2**	**87237568**	***C16orf95***	**Inter-genic**	**T**	**C**	**0.4252**	**0.0431 (0.0065)**	**26327**	**+++++-?-+--+++++++-++**	**4.22E-11**
PV	rs275350	6q25.1	151016058	*PLEKHG1*	Intronic	C	G	0.4202	0.0374 (0.0057)	26654	+-+-+++++-++++++---++	4.86E-11
PV	rs7596872	2p16.1	56128091	*EFEMP1*	Intronic	A	C	0.0975	0.0642 (0.0099)	25730	-++++++-+--+++???++++	8.66E-11
PV	rs72934583	2q33.2	204009057	*NBEAL1*	Intronic	T	G	0.8740	0.0529 (0.0087)	25730	-+++++++++-+++???+-++	1.03E-09
PV	rs57242328	2p21	43073247	*AC098824.6*	Intergenic	A	G	0.3317	−0.0368 (0.0061)	25730	----+----+----???-++-	1.85E-09
PV	**rs7213273**	**17q21.31**	**43155914**	***NMT1***	**Intronic**	**A**	**G**	**0.6668**	**0.0341 (0.0059)**	**26111**	**+++++-??++-++-+++++++**	**8.89E-09**
PV	**rs1993484**	**10q23.1**	**82222698**	***TSPAN14***	**Intronic**	**T**	**C**	**0.2388**	**0.0378 (0.0067)**	**26654**	**++++-+--++-++-+++++++**	**1.36E-08**
PV	rs11838776	13q34	111040681	*COL4A2*	Intronic	A	G	0.2793	0.0350	26654	-+++++-++-+++++++-+-+	2.82E-08
PV	**rs1799983**	**7q36.1**	**150696111**	***NOS3***	**Exonic**	**T**	**G**	**0.3201**	**0.0373**	**26654**	**++++++--++-++-++----+**	**3.68E-08**

Notes: Effect allele is allele 1 (A1). A2 = allele 2. SE = standard error. Those loci bolded have not been previously associated with total WMH.

Table 2.

Thirty-two significant genes were identified for PVWMH using gene-based tests (p<2.66e-6). Thirteen of these genes (chr17) were also significant for DWMH (*).

GENE	CHR	START	STOP	N SNPS	N	*p* PVWMH	*p* DWMH
WBP2	17	73841780	73852588	28	24682	3.19E-26	1.16E-21*
TRIM65	17	73876416	73893084	52	24555	7.73E-24	9.12E-19*
TRIM47	17	73870242	73874656	13	24185	1.70E-23	9.04E-19*
RP11–552F3.12	17	73894726	73926210	53	24351	2.15E-20	1.76E-15*
FBF1	17	73905655	73937221	55	24338	3.98E-17	1.23E-13*
GALK1	17	73747675	73761792	36	24307	6.34E-16	3.23E-14*
MRPL38	17	73894724	73905899	21	24481	7.62E-15	1.18E-13*
UNC13D	17	73823306	73840798	73	23788	3.10E-14	1.22E-13*
UNK	17	73780681	73821886	120	22768	3.28E-13	4.85E-10*
H3F3B	17	73772515	73781974	23	24009	4.43E-12	1.41E-10*
SH3PXD2A	10	105348285	105615301	788	24847	8.43E-12	0.21731
ACOX1	17	73937588	73975515	151	24198	7.72E-11	1.1E-09*
EVPL	17	74000583	74023533	67	24582	1.26E-10	2.82E-14*
PLEKHG1	6	150920999	151164799	1022	24922	1.59E-10	0.011765
WDR12	2	203739505	203879521	322	23753	2.53E-10	0.00104
ICA1L	2	203640690	203736708	224	23843	8.44E-10	0.001301
CARF	2	203776937	203851786	157	24076	2.41E-09	0.001763
NMT1	17	43128978	43186384	221	24766	7.18E-08	0.00034
CDK3	17	73996987	74002080	12	24433	8.54E-08	1.82E-08*
OBFC1	10	105642300	105677963	99	25461	1.41E-07	0.054127
NOS3	7	150688083	150711676	58	24608	1.73E-07	0.000371
DCAKD	17	43100708	43138473	111	25229	2.60E-07	0.000363
DYDC2	10	82104501	82127829	91	25050	2.88E-07	0.003460
NBEAL1	2	203879602	204091101	367	23413	3.83E-07	0.040539
NEURL1	10	105253736	105352309	296	25038	4.84E-07	0.098303
MAT1A	10	82031576	82049440	66	25295	4.90E-07	0.002421
TSPAN14	10	82213922	82292879	213	24731	6.73E-07	0.006605
CALCRL	2	188207856	188313187	278	24309	7.87E-07	0.000574
KLHL24	3	183353356	183402265	207	24356	1.29E-06	0.002571
POLR2F	22	38348614	38437922	105	23525	1.94E-06	0.252540
VCAN	5	82767284	82878122	316	24248	2.52E-06	0.065044
COL4A2	13	110958159	111165374	1140	24876	2.61E-06	0.365300

Notes: Those loci bolded have not been previously associated with total WMH.