Genes From a Translational Analysis Support a Multifactorial Nature of White Matter Hyperintensities

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**Background and Purpose**—White matter hyperintensities (WMH) of presumed vascular origin increase the risk of stroke and dementia. Despite strong WMH heritability, few gene associations have been identified. Relevant experimental models may be informative.

**Methods**—We tested the associations between genes that were differentially expressed in brains of young spontaneously hypertensive stroke–prone rats and human WMH (using volume and visual score) in 621 subjects from the Lothian Birth Cohort 1936 (LBC1936). We then attempted replication in 9361 subjects from the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE). We also tested the subjects from LBC1936 for previous genome-wide WMH associations found in subjects from CHARGE.

**Results**—Of 126 spontaneously hypertensive stroke–prone rat genes, 10 were nominally associated with WMH volume or score in subjects from LBC1936, of which 5 (AFP, ALB, GNAI1, RBM8a, and MRPL18) were associated with both WMH volume and score (P<0.05); 2 of the 10 (XPNPEP1, P=6.7×10⁻⁴; FAR1, P=0.024) plus another spontaneously hypertensive stroke–prone rat gene (USMG5, P=0.00014), on chromosomes 10, 13, and 10 respectively, were associated with WMH in subjects from CHARGE. Gene set enrichment showed significant associations for downregulated spontaneously hypertensive stroke–prone rat genes with WMH in humans. In subjects from LBC1936, we replicated CHARGE’s genome-wide WMH associations on chromosomes 17 (TRIM65 and TRIM47) and, for the first time, 1 (PMF1).

**Conclusions**—Despite not passing multiple testing thresholds individually, these genes collectively are relevant to known WMH associations, proposed WMH mechanisms, or dementia: associations with Alzheimer’s disease, late-life depression, ATP production, osmotic regulation, neurodevelopmental abnormalities, and cognitive impairment. If replicated further, they suggest a multifactorial nature for WMH and argue for more consideration of vascular contributions to dementia. *(Stroke. 2015;46:341-347. DOI: 10.1161/STROKEAHA.114.007649.)*

Key Words: genetics ■ humans ■ leukoencephalopathies ■ magnetic resonance imaging

Received October 5, 2014; final revision received November 15, 2014; accepted December 3, 2014.

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The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.114.007649/-/DC1.

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Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.114.007649

341
White matter hyperintensities (WMH) of presumed vascular origin, a major component of cerebral small vessel disease (SVD), double the risk of stroke and dementia. Despite considerable societal effect, the causes of WMH and SVD are poorly understood. Conventional vascular risk factors explain little of the WMH variance. Family studies, several rare monogenic SVD disorders, and epidemiology suggest that genetic predisposition is important.

Identification of genetic factors for SVD has been challenging. Several replicable single-nucleotide polymorphisms (SNPs) associated with WMH have been identified in 1 locus on chromosome 17q25, although the exact gene(s) and biological pathways to WMH are unclear. Few other replicable genes have been found in genome-wide association studies (GWAS), and little is known of their functional significance.

Experimental SVD models might provide insight into human SVD. The spontaneously hypertensive stroke-prone rat (SHRSP) is a relevant model of spontaneous SVD. It was selectively crossbred (1974) from Wistar-Kyoto (WKY) rats via the spontaneously hypertensive rat (SHR, 1963). Hypertension, established in SHRSP rats by 10 weeks of age, is considered to be the main cause of their brain disease. However, differences in protein and gene expression in SHRSP rats versus WKY rats at 5 weeks of age (before measurable blood pressure rises) suggest underlying susceptibilities to SVD. Compared with WKY controls, 5-week-old SHRSP rats have reduced claudin 5 (tight junction) and myelin basic protein and increased microglia (IBA1) and glial activation (GFAP); at 16 and 21 weeks, increase in smooth muscle actin was seen, thought to reflect arteriolar smooth muscle hyperplasia secondary to hypertension. SHRSP gene expression differences at 5 weeks of age were more numerous than at 16 or 21 weeks of age and included downregulation of Mmp14, Mbp, Gfap, Avp, Alb, and Igf2, upregulation of Gucy1A3, Rps9, Fos, and JunB, early-growth response, cell-signaling genes, and overexpression of genes involved in neurological diseases (stroke, depression, and blood–brain barrier leakage), rather than just hypertension. Recent gene sequencing of SHRSP rats (and 26 other rat models of common human diseases) revealed that genes that were either shared between or uniquely mutated in these rat models were significantly over-represented in human GWAS hits for hypertension or metabolism-related phenotypes, suggesting coevolution of these genes and their role in common diseases in models and humans.

In a hypothesis-driven collaborative approach, we tested for associations between genes that were differentially expressed in the brains of 5-week-old SHRSP rats and WMH in humans. We used data from 5-week-old rats because gene expression differences were more frequent at that age than at 16 or 21 weeks, and we wanted to minimize the confounding of tissue changes by secondary effects of hypertension and to optimize the chances of detecting genes related to WMH susceptibility. We focused on WMH as the most frequent feature of SVD with the most data available in replication cohorts. We first tested the subjects from Lothian Birth Cohort 1936 (LBC1936) and then attempted replication in subjects from the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium. To provide confidence in the relevance of subjects from LBC1936, we also sought CHARGE’s previously reported WMH-gene associations in the subjects from LBC1936.

### Methods

**Subjects**

The subjects from LBC1936 are community-dwelling individuals living in South East Scotland who underwent detailed cognitive, biochemical, genetic assessments, and detailed brain MRI at ∼73 years of age (n=866). The MRI acquisition, methods for assessing WMH burden and quantitatively, and proportions with WMH by either method have been reported. This study was approved by the Lothian (REC 07/MRE00/58) and Scottish Multicentre

### Table 1. Genes Associated With Cerebral Small Vessel Disease in Rats That Are Associated With WMH in Older Humans: 126 Differentially Expressed Genes Between Spontaneously Hypertensive Stroke Prone and Wild-Type Rats Were Tested for Association With WMH in Subjects From LBC1936 and 10 Genes Were Significantly Associated (P<0.05) With Either WMH Volume or Fazekas Score

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Gene</th>
<th>Start Position</th>
<th>Stop Position</th>
<th>nSNPs</th>
<th>Genotyped SNPs</th>
<th>Imputed SNPs</th>
<th>Replication: CHARGE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>WMH Volume</td>
<td>Fazekas Score</td>
<td>P Value</td>
<td>P Value</td>
<td>nSNPs</td>
<td>P Value</td>
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<tr>
<td>4</td>
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<td>74520796</td>
<td>74540356</td>
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<td>0.0021</td>
<td>0.00009</td>
<td>77</td>
</tr>
<tr>
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<td>ALB</td>
<td>74488696</td>
<td>74505834</td>
<td>11</td>
<td>0.0026</td>
<td>0.0017</td>
<td>61</td>
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<tr>
<td>7</td>
<td>GNA1</td>
<td>79602075</td>
<td>79686661</td>
<td>42</td>
<td>0.034</td>
<td>0.033</td>
<td>181</td>
</tr>
<tr>
<td>1</td>
<td>RBM6A</td>
<td>144218994</td>
<td>144222801</td>
<td>13</td>
<td>0.038</td>
<td>0.057</td>
<td>26</td>
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<tr>
<td>2</td>
<td>INPP5D</td>
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<td>233781288</td>
<td>69</td>
<td>0.041</td>
<td>0.078</td>
<td>198</td>
</tr>
<tr>
<td>10</td>
<td>XPNPEP1</td>
<td>111614513</td>
<td>111763192</td>
<td>18</td>
<td>0.042</td>
<td>0.14</td>
<td>130</td>
</tr>
<tr>
<td>9</td>
<td>NRA4A</td>
<td>101623957</td>
<td>101668994</td>
<td>13</td>
<td>0.045</td>
<td>0.16</td>
<td>62</td>
</tr>
<tr>
<td>13</td>
<td>FARP1</td>
<td>9795343</td>
<td>97900024</td>
<td>154</td>
<td>0.049</td>
<td>0.25</td>
<td>550</td>
</tr>
<tr>
<td>6</td>
<td>MRPL18</td>
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<td>160139451</td>
<td>24</td>
<td>0.059</td>
<td>0.039</td>
<td>89</td>
</tr>
<tr>
<td>1</td>
<td>SIPA1L2</td>
<td>230600334</td>
<td>230717866</td>
<td>80</td>
<td>0.087</td>
<td>0.0093</td>
<td>340</td>
</tr>
</tbody>
</table>

nSNPs is the number of SNPs considered in the gene test. CHARGE indicates Cohorts for Heart and Aging Research in Genomic Epidemiology; LBC1936, Lothian Birth Cohort 1936; SNP, single-nucleotide polymorphism; and WMH, white matter hyperintensities.
Methods in the online-only Data Supplement). We excluded 48 sub-
jects from LBC1936 with a history of stroke or dementia.

**Gene Analysis**

In the 5-week-old SHRSP rats, 162 genes were differentially ex-
pressed compared with 5-week-old WKY rats in frontal and midcor-
onal brain sections (Table II in the online-only Data Supplement).14
We used the following databases to match the SHRSP Illumina IDs
to human genes (Materials and Table II in the online-only Data
Supplement): Ensembl—http://www.ensembl.org, GeneCards—
http://www.genecards.org, Illumina ID search—http://www.gen-
Database—http://www.rgd.mcw.edu. Of the 162 SHRSP genes, 132
had an equivalent human gene, 8 transcripts were mapped to the same
gene, 20 were uncharacterized in humans, and 2 had no human ho-
mologe. Of the 132 genes, 126 were available for association testing
using the Versatile Gene-based Association Study (VEGAS) test.23
We first performed a genome-wide association analysis on subjects
from LBC1936 using PLINK software24 to test the genetic associa-
tion with WMH measurements in subjects from LBC1936.3 The VEGAS software summa-
ized the association data associated with WMH, accounting for whether these were upreg-
ulated or downregulated (online-only Data Supplement).26 corrected
for multiple testing using a false discovery rate (FDR) method.27

We applied Bonferroni correction for multiple testing (P<0.05/126
genes=0.0004). We did not include the 2 WMH phenotypes in the
Bonferroni correction as they are highly correlated (r2=0.77). Because of
the overconservative nature of Bonferroni correction for multiple testing,29 a nominal significance threshold of P value of <0.05 was
required for replication efforts.

**Results**

**SHRSP Genes in Subjects From LBC1936**

Of the 126 candidate SHRSP-derived genes, 10 were nominally
associated with WMH in subjects from LBC1936 (P<0.05; Table 1).
Using imputed or genotyped data, 5 genes were associated
with WMH volume (AFP, ALB, GNAI1 [RBMSA and INPP5D, both borderline]); 3 of these (AFP, ALB, and
GNAI1) and 2 others (MRPL18 and SIPA1L2) were associated
with WMH Fazekas scores. Three other genes were associated
with WMH volume using genotyped data only (XNPPEP1, NTRA3,
and FARP1). None of these genes individually passed
Bonferroni correction in subjects from LBC1936 (all were
P>0.0004), in part, reflecting the LBC1936 sample size.

**SHRSP Genes in Subjects From CHARGE**

Two of these 10 genes were also associated with WMH in subjects
from CHARGE (XNPPEP1, P=6.7×10−3; and
FARP1, P=0.024; Table 1). Full details of all 126 SHRSP to
LBC1936 to CHARGE gene associations are given in Table
III in the online-only Data Supplement. Several other of
the 126 SHRSP genes (outside the 10/126 described above)
showed significance at P<0.05 in subjects from CHARGE (eg,
USMG5, MED17, ZNF461, C20orf7, EGR1, ARC, NUDT14,
and MMP14) of which 1 (USMG5, P=0.000142) passed
Bonferroni correction (P<0.0004).

**Gene Set Enrichment**

Using gene set enrichment analysis, all 126 SHRSP candidate
genes were not enriched in subjects from LBC1936 for associa-
tion with WMH in the 17,681 genes tested here (WMH volume,
P=0.34; Fazekas score, P=0.81), but this would not preclude the
possibility that in either upregulated or downregulated gene sets,
there was an abundance of genes showing an enriched associ-
ation. We tested the upregulated (n=76) and downregulated (n=50)
SHRSP genes separately and found significant enrichment for
Fazekas scores in SHRSP downregulated genes (P=0.035;
FDR, 0.046) but not SHRSP upregulated genes (P=0.921; FDR,
0.899). WMH volume showed significant enrichment in down-
regulated (P=0.018; FDR, 0.025) but not upregulated (P=0.802;
FDR, 0.780) genes. In the CHARGE consortium, there was no
significant enrichment for either the total set of 126 genes
(P=0.0514), the upregulated (P=0.109; FDR, 0.266) or the
downregulated genes (P=0.173; FDR, 0.149).

**Replication of Previous CHARGE Findings in Subjects From LBC1936**

To demonstrate our ability to detect WMH-gene associations in
subjects from LBC1936, we attempted replication of CHARGE’s

(MREC/01/0/56) Research Ethics Committees; all subjects gave writ-
ten informed consent.

The subjects from LBC1936 had genome-wide SNP data on
542,050 SNPs,21 imputed to 2.5 million SNPs with HapMap2.22 There
were 621 participants (392 men) from LBC1936 with both MRI and
genetic data (mean age, 72.67 years; SD=0.73 years; Table I and
Methods in the online-only Data Supplement). We excluded 48 sub-
jects from LBC1936 with a history of stroke or dementia.

genome-wide associations with WMH24 in the subjects from the
LBC1936 Cohort in a genome-wide association analysis using the
2,534,887 SNPs imputed to HapMap2, with WMH (volume and
Fazekas score) in Mach2QTL software.25

We performed a gene set enrichment analysis25 to investigate the en-
richment of the 126 SHRSP genes in the LBC1936 and CHARGE
genes separately and found significant enrichment
for either the total set of 126 genes
(P=0.0514), the upregulated (P=0.109; FDR, 0.266) or the
downregulated genes (P=0.173; FDR, 0.149).

**Replication of CHARGE’s Previous Genome-Wide
Association in Subjects From LBC1936**

We sought CHARGE’s previous genome-wide association results for WMH in subjects from LBC1936. Of CHARGE’s
15 SNPs (P<1×10−5) associated with WMH (Table 2),7 3 SNPs replicated in subjects from LBC1936 with both WMH volume and Fazekas score at P<0.05 (rs3744028, rs1055129, and rs1052053); rs1052053, a miss-sense variant on chromosome 1 in the polyamine-modulated factor 1 gene (PMF1), has not replicated previously.

**Discussion**

We used a clinically relevant translational approach15 to identify potential new gene associations for WMH, a common cause of cognitive impairment, stroke, and dementia. We found parallels between differentially expressed genes in a young spontaneous SVD model and WMH-gene associations in older humans. Two novel genes on chromosome 10 derived from SHRSP rats were associated with WMH, XPNPEP1 in both LBC1936 and CHARGE and USMG5 in CHARGE only. Several other genes were nominally associated with WMH in LBC1936 or CHARGE although none passed multiple testing. We replicated 3 of CHARGE’s WMH-gene associations in subjects from LBC1936: 2 (rs3744028 and rs1055129) on chromosome 17q25 and 1 previously unreplicated SNP (rs1052053) on chromosome 1, a miss-sense variant in the polyamine-modulated factor 1 gene, PMF1, that has a role in the cell cycle. Jointly, these approaches yielded 6 genes (3 from the SHRSP rats and 3 replicates of a GWAS finding) and 5 further rat-derived genes based on the LBC1936 sample alone, which despite not passing multiple testing thresholds individually, as a group they are notable for their involvement in biological pathways relevant to WMH pathogenesis.2

Of the 2 SHRSP genes found in LBC1936 and CHARGE, XPNPEP1 is X-prolyl aminopeptidase (aminopeptidase P) 1, soluble, associated with biliary atresia, and located in a region on chromosome 10 that is associated with Alzheimer’s disease.30 FARP1 is Pleckstrin domain protein 1, associated with brain volume differences,31 and important in synapse development.32 The SHRSP-CHARGE–associated gene USMG5 is upregulated during skeletal muscle growth 5 homolog (also known as diabetes mellitus–associated protein in insulin sensitive tissues, or DAPIT), sits on chromosome 10, and maintains ATP synthase populations in mitochondria.33 All 5 SHRSP genes associated with both WMH volume and Fazekas score in subjects from LBC1936 (AFP, ALB, GNAI1, RBMSA, and MRPL18) are associated with white matter–relevant diseases in humans. Despite not surviving correction for multiple testing, there was a notable consistency in their association with 2 separate WMH measures. AFP encodes α-fetoprotein, a major plasma protein produced in the yolk sac and liver during fetal life. Abnormally, high amounts of α-fetoprotein are found in ataxia telangiectasia,34 also associated with abnormal white matter.35 ALB encodes albumin, a soluble monomeric protein important for maintaining plasma oncotic pressure found in cerebral WMH,36 and cerebrospinal fluid as blood–brain barrier function deteriorates with ageing and dementia.37 GNAI1 encodes guanine nucleotide–binding protein (G protein), alpha-inhibiting activity polypeptide 1, implicated with Alzheimer’s disease.38 RBMSA is an RNA binding protein that has differential expression in Alzheimer’s disease,39 associations with a range of intellectual disabilities in humans and anxiety-related behavior in mice,40 with schizophrenia, several neurodevelopmental intellectual disabilities, anxiety behavior and may target neuronal genes to regulate behaviors. WMH in old age are known associates of late-onset depression,41 and they are also associated with lower age 11 IQ.42 MRPL18 is the mitochondrial ribosomal protein L18, previously associated

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**Table 2. Association of SNPs Previously Associated With WMH in CHARGE in Subjects From LBC1936 and the Corresponding SNP Association Results Are Given for LBC1936 WMH Volume and Fazekas Score**

<table>
<thead>
<tr>
<th>SNP</th>
<th>Chromosome</th>
<th>Nearest Gene</th>
<th>Risk Allele</th>
<th>Allele Freq</th>
<th>P Value</th>
<th>Effect Allele</th>
<th>Allele Freq</th>
<th>r²</th>
<th>β</th>
<th>P Value</th>
<th>β</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>rs3744028</td>
<td>17</td>
<td>TRIM65</td>
<td>C</td>
<td>0.18</td>
<td>4.0×10−9</td>
<td>T</td>
<td>0.81</td>
<td>0.99</td>
<td>−0.217</td>
<td>0.00287</td>
<td>−0.287</td>
<td>0.000511</td>
</tr>
<tr>
<td>rs1055129</td>
<td>17</td>
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<td>G</td>
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<td>0.97</td>
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<td>0.305</td>
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<td>PDDC11</td>
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<td>6.1×10−7</td>
<td>T</td>
<td>0.63</td>
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<td>0.603</td>
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Allele frequency is the frequency of the effect allele. r² is a measure of the imputation quality to HapMap2. β is the regression coefficient. CHARGE indicates Cohorts for Heart and Aging Research in Genomic Epidemiology; LBC1936, Lothian Birth Cohort 1936; SNP, single-nucleotide polymorphism; and WMH, white matter hyperintensities.
with multiple sclerosis. These 7 SHRSP-derived genes are related to pathologies (ataxia telangiectasia, blood–brain barrier impairment, Alzheimer's disease, multiple sclerosis, depression, developmental intellectual disabilities, and brain size) that display white matter abnormalities or affect intellectual function. Impaired ATP production because of defects in USMG3, the gene that replicated from SHRSP to CHARGE, could increase susceptibility to WMH via ischemia.

The genes that were downregulated in the SHRSP were significantly enriched in subjects from LBC1936 for WMH. This may be because, in a complex disease such as SVD/WMH, several individually modest genetic defects in different components of key pathways, when present in combination, increase disease risk. This interpretation is consistent with differential protein expression seen in SHRSP and the absence, so far, of individual major human gene defects explaining either sporadic WMH or lacunar stroke.

The lack of consistent replication from SHRSP to LBC1936 to CHARGE requires caution. The power and required significance threshold of the LBC1936 was modest for GWAS, hence our hypothesis-driven approach. Genes associated with WMH in subjects from LBC1936 but not CHARGE could be false positives; other factors include greater heterogeneity of WMH assessment and greater age range in subjects from CHARGE. The narrow age range of subjects from LBC1936 minimizes the effect of age, possibly helping to expose relevant genes. CHARGE-contributing studies used several methods of quantifying WMH, different MR scanner field strengths, and generations of technology and sequences. However, WMH volume and visual scores are highly correlated, and our replication of 3 findings from CHARGE in subjects from LBC1936 suggests that our approach has some validity. The CHARGE cohorts may have used different imputation platforms or more SNPs may have failed quality assurance in subjects from LBC1936, contributing to differences between the imputation results. There are several limitations to gene-based analysis, including the omission of nonautosomal genes, the effect of noncausal SNPs to dilute association (in particular, in the presence of a strong genetic association with a single locus within or in the regulatory region of a given gene, thus missing important associations), the lack of knowledge on (and overlap of) gene boundaries, the possibility that an SNP variant may influence a gene distal to its site, thus not corresponding to a gene that it is located next to it, and the potential of the genetic data not to tag causative genetic variants. Power may have been limited (despite CHARGE's large sample size) to detect associations with some genes. We did not stratify the human cohorts by risk factors as these explained <2% of WMH variance in subjects from LBC1936, and risk-stratified genetic data were unavailable for CHARGE. We did not test gene associations with other SVD features in addition to WMH because a total SVD burden score was not available for CHARGE. Although it is a relevant model of spontaneous SVD, and of human hypertension and metabolic disorders, like any model, the SHRSP has translational limitations, arguing for additional studies at different ages and brain regions, with or without environmental stressors.

This work has the following strengths: accurate LBC1936 WMH phenotyping and genetic information in this relatively large narrow age-range older population. The Glasgow SHRSP colony is long established, with carefully controlled environments. The mRNA data were obtained from the same rats that provided protein expression data. Replication in other SHRSP colonies and examination of related strains (eg, SHR's) may be informative. The genomes of SHRSP and 26 other complex disease phenotype models were recently sequenced, showing associations between genes in rat models of hypertension and human GWAS hits for hypertension phenotypes. This provides support for our reverse-translational discovery approach, suggesting that genes in disease models have coevolved and may contribute to disease-related phenotypes in humans.

Our findings require validation. The selection of candidate genes for investigation could be widened by examining more genes from the 5-week-old SHRSP rats (Table II in the online-only Data Supplement), other models, and in larger samples of well-phenotyped humans, such as from METASTROKE and the Wellcome Trust Case-Control Consortium. This translational analysis of experimental models and human disease suggests some aspects of the genetic architecture underlying SVD, stroke, and dementia and argues for greater awareness of vascular contributions to neurodegeneration.

Figure I and Tables IV and V in the online-only Data Supplement provide the top SNP (P<1×10^-5) and gene (P<0.001) associations with WMH variables in subjects from LBC1936 for further reference.

Acknowledgments

We thank the Lothian Birth Cohort 1936 participants and research team members, Wellcome Trust Clinical Research Facility (http://www.wtcrf.ed.ac.uk, subject testing and genotyping), and Brain Research Imaging Centre (http://www.bric.ed.ac.uk, brain imaging and analyses). Cohorts for Heart and Aging Research in Genomic Epidemiology thanks the staff and participants of the Aging Gene-Environment Susceptibility-Reykjavik Study, Atherosclerosis Risk in Community Study (ARIC), Austrian Stroke Prevention Study (ASPS), Cardiovascular Health Study, and Framingham Heart and Rotterdam Studies for their important contributions. APS thanks Birgit Reinhard for her long-term administrative commitment and Ing Johann Semmler for the technical assistance at creating the DNA bank. Drs Wardlaw, Bailey, McBride, Graham, Dominiczak, Deary, Starr, Seshadri, Fornage, Ikram, Debbete, Launer, Bis, and Schmidt contributed to data collection. Dr Lopez, Harris, Hill, Yang, Bailey, McClure, McBride, Smith, Hernandez, Maniega, Bastin, and Wardlaw contributed to data analysis. Drs Wardlaw, Deary, and Seshadri contributed to study design, co-ordination, and funding. Lopez, Wardlaw, Seshadri, and Deary contributed to article preparation. Lopez, Harris, Hill, Porteous, Smith, Deary, Starr, Seshadri, Yang, Fornage, Ikram, Debbete Launer, Bis, Schmidt, Bailey, McBride, Graham, McClure, Dominiczak, Hernandez, Maniega, Bastin, and Wardlaw contributed to article review. Wardlaw was the guarantor and provided the overall concept.

Sources of Funding

Lothian Birth Cohort 1936 was funded by Age UK's Disconnected Mind programme (http://www.disconnectedmind.ed.ac.uk) and by Research Into Ageing (references 251 and 285). Whole-genome association was funded by Biotechnology and Biological Sciences Research Council (reference BB/F011994/1), brain image analysis was funded by Medical Research Council (G1001401 and 8200), and imaging was funded by Brain Research Imaging Centre (http://www.bric.ed.ac.uk), The University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology (http://www.
Disclosures

None.

References


Genes From a Translational Analysis Support a Multifactorial Nature of White Matter Hyperintensities

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Stroke. 2015;46:341-347; originally published online January 13, 2015; doi: 10.1161/STROKEAHA.114.007649

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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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SUPPLEMENTAL MATERIAL
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Index
Supplementary Methods
Supplementary tables and figures
Table I: Description of LBC1936 white matter hyperintensity (WMH) variables.
Table II: Candidate genes from SHRSP rat model. This is a list of the 162 transcripts differentially expressed between SHRSP and WKY at 5 weeks in two relevant brain regions, and the corresponding human genes where available.
Table III: Candidate gene-based association results with white matter hyperintensity variables (WMH) in the discovery cohort, LBC1936, and the replication cohort, CHARGE.
Table IV: 5 Top hits from genome wide association study with WMH variables in LBC1936 (P < 1x10-5).
Table V: Top gene-based results from LBC1936 for the WMH variables run in Vegas.
Figure I: Genome-wide association study results of WMH (a) and Fazekas score (b) on 542,050 SNPs. QQ and Manhattan plots are shown.
Supplementary Methods

Genotyping

A detailed description of the genotyping method is described elsewhere. Briefly, genotyping was performed using Illumina Human 610-Quadv1 arrays on blood-extracted DNA at the WTCRF Genetics Core. All individuals were checked for disagreement between genetic and reported gender. Relatedness between subjects was investigated and, for any related pair of individuals, one was removed. Samples with a call rate \( \leq 0.95 \), and those showing evidence of non-Caucasian ascent by multidimensional scaling (MDS), were also removed. SNPs were included in the analyses if they met the following conditions: call rate \( \geq 0.98 \), minor allele frequency \( \geq 0.01 \), and Hardy-Weinberg Equilibrium test with \( P \geq 0.001 \). The final number of genotyped SNPs included in the study was 542,050 in 1,005 individuals.

Genetic imputation

~2.5M common SNPs included in HapMap, using the HapMap phase II CEU data as the reference sample were imputed. NCBI build 36 (UCSC hg18) was used and genotype data were imputed using MACH software. Prior to imputation SNPs were removed that diverged from HWE with a significance \( p < \)1x10\(^{-3}\) and SNPs with a minor allele frequency < 0.01.

Gene mapping.

Listed below are the databases used to match the Illumina IDs from the SHRSP study to human genes as shown in Supplementary Table II.


Gene set enrichment analysis

A gene set enrichment analysis was performed to investigate the enrichment of 126 SHRSP genes in WMH gene associations. First, the gene based statistics from VEGAS were rank ordered before being \( -\log(10) \) transformed. Gene set enrichment analysis (GSEA) uses a set of candidate gene identifiers and a genome wide set of genes, ranked based on their association with a phenotype. Next, a weighted Kolmogorov-Smirnov type statistic, walks down the genome wide ranked set of genes and increases the test statistic each time it finds a gene that matches one from the candidate gene set and decreases it when it does not. The magnitude of the increase is proportional to its p value, allowing for information regarding rank and distance between ranks to be used in the calculation of enrichment. The maximum deviation from zero is assigned to the candidate gene set (this is the enrichment score or ES). The gene set is then permuted before the ES being re-calculated. The p-value describes the proportion of the 5,000 permuted enrichment scores that the observed enrichment score was greater than.
Table I: Description of LBC1936 WMH variables. Fazekas scale for periventricular lesions, Fazekas scale for deep lesions and the sum of these Fazeskas scores are described. WMH as percentage of true WMH alone in intracranial volume (ICV) are listed.

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<tr>
<th>Trait</th>
<th>Median</th>
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<th>Standard deviation</th>
<th>Minimum</th>
<th>Maximum</th>
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<td>0</td>
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</table>
Table II: Candidate genes from SHRSP rat model. This is a list of the 162 transcripts differentially expressed between SHRSP and WKY at 5 weeks in two relevant brain regions from Bailey et al. and the corresponding human genes.

<table>
<thead>
<tr>
<th><strong>SHRSP versus WKY differential gene expression at five weeks of age</strong></th>
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**Human equivalent of SHRSP differentially expressed genes**

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<th>Gene Accession</th>
<th>Gene Name</th>
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</tr>
<tr>
<td>ILMN_1357461</td>
<td>ZFP61</td>
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</tr>
</tbody>
</table>

**Similar to goliath-related E3 ubiquitin ligase 4**

**Similar to ribosomal protein L22 like 1**

**Similar to zinc finger protein 582**

**Similar to Tubulin alpha-2 chain**

**Similar to Zfp583 protein**

**RT1-A1 is HLA-B**

**Similar to Zinc finger protein 45**
**SHRSP versus WKY differential gene expression at five weeks of age.**

<table>
<thead>
<tr>
<th>Gene ID</th>
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<th>P-value</th>
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*** Human equivalent of SHRSP differentially expressed genes

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<thead>
<tr>
<th>Gene ID</th>
<th>Symbol</th>
<th>Description</th>
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<tbody>
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<td>ZCCHC9</td>
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<td>FAM32A</td>
<td>Homo sapiens family with sequence similarity 32, member A (FAM32A), mRNA.</td>
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<tr>
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<td>TM9SF4</td>
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<tr>
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### **SHRSP versus WKY differential gene expression at five weeks of age.**

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### ***Human equivalent of SHRSP differentially expressed genes***

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Uncharacterised
**SHRSP versus WKY differential gene expression at five weeks of age.**

### Human equivalent of SHRSP differentially expressed genes

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<td>ILMN_1350094</td>
<td>SDPR</td>
<td>SDPR Homo sapiens serum deprivation response (SDPR), mRNA.</td>
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<tr>
<td>ILMN_2039346</td>
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<td>HLA-DMA Homo sapiens major histocompatibility complex, class II, DM alpha (HLA-DMA), mRNA.</td>
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<td>ILMN_1349530</td>
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<tr>
<td>ILMN_1369447</td>
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<td>TPX2 Homo sapiens TPX2, microtubule-associated, homolog (Xenopus laevis) (TPX2), mRNA.</td>
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<td>XPNPEP1 Homo sapiens X-prolyl aminopeptidase (aminopeptidase P) 1, soluble (XPNPEP1), transcript variant 1, mRNA.</td>
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<tr>
<td>ILMN_1351156</td>
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<td>GNA1 Homo sapiens guanine nucleotide binding protein (G protein), alpha inhibiting activity polypeptide 1 (GNA1), transcript variant 1, mRNA.</td>
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</table>

### Uncharacterised genes
- **Shr**
- **Uncharacterised**

### Table notes
- **Uncharacterised:** Genes marked as uncharacterised or with no known function.
- ** Similar to:** Genes with similar functions or annotations.
- **Not in RefSeq:** Genes not present in the RefSeq database.

### Additional notes
- **CRSP6 = MED17:** CRSP6 is the predicted transcript variant of MED17.
- **Similar to:** Genes with similar functions or annotations.
**SHRSP versus WKY differential gene expression at five weeks of age.**

*** Human equivalent of SHRSP differentially expressed genes

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Description</th>
<th>Gene Symbol</th>
<th>Description</th>
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<td>Afp</td>
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<td>Inpp5d</td>
<td>Homo sapiens inositol polyphosphate-5-phosphatase, 145kDa (INPP5D), transcript variant 1, mRNA.</td>
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<td>Pde10a</td>
<td>Homo sapiens phosphodiesterase 10A (PDE10A), transcript variant 1, mRNA.</td>
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<td>Homo sapiens matrix metallopeptidase 14 (membrane-inserted) (MMP14), mRNA.</td>
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Uncharacterised
**SHRSP versus WKY differential gene expression at five weeks of age.**

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*** Human equivalent of SHRSP differentially expressed genes

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Table III: All candidate SHRSP gene-based results from LBC1936 and CHARGE with WMH variables. Chr is chromosome. nSNPs is the number of SNPs in the gene (+/- 50kb). Please note that the gene boundaries are overlapping as SNPs can be allocated to multiple genes, so the same SNP could be driving the signal in different genes. The results are ordered by significance.

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**Legend:**
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- **stop/strand:** Chromosome end position
- **strand:** DNA strand
- **54:** t-value
- **0.44:** p-value
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Table V Top gene-based results for the LBC1936 WMH variables analysed in Vegas (P<0.001). Chr is chromosome. nSNPs is the number of SNPs in the gene (+/- 50kb). Please note that the gene boundaries are overlapping as SNPs can be allocated to multiple genes, so the same SNP could be driving the signal in different genes. The results are ordered by significance.

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Figure I Genome-wide association study results of WMH volume (a) and Fazekas score (b) using genotyped data on 542,050 SNPs in LBC1936. QQ and Manhattan plots are shown.
References


