Published in final edited form as:
Stroke. 2009 December ; 40(12): 3685–3690. doi:10.1161/STROKEAHA.109.565390.

Analysis of Genetic Variability And Whole Genome Linkage Of Whole-Brain, Subcortical And Ependymal Hyperintense White Matter Volume

P. Kochunov[1,3,*], **D. Glahn**[1,2], **A. Winkler**[1,2], **R. Duggirala**[3], **RL Olvera**[3], **SA Cole**[3], **TD Dyer**[3], **Almasy L**[3], **PT Fox**[1], and **J. Blangero**[3]

[1] Research Imaging Center, University of Texas Health Science Center at San Antonio

[2] Department of Psychiatry, Yale University & Olin Neuropsychiatric Research Center

[3] Southwest Foundation for Biomedical Research, San Antonio, TX

Abstract

Background and Purpose—The cerebral volume of T2-hyperintense white matter (HWM) is an important neuroimaging marker of cerebral integrity. Pathophysiology studies identified that subcortical and ependymal HWM are produced by two different mechanisms but shared a common risk factor: high arterial pulse pressure. Recent studies have demonstrated high heritability of the whole-brain (WB) HMW volume and reported significant and suggestive evidence of genetic linkage. We performed heritability and whole-genome linkage analysis to replicate previous reported findings and to study shared genetic variance, and possible overlap for specific loci, between subcortical and ependymal HWM volumes in a population of healthy Mexican Americans.

Methods—The volumes of subcortical and ependymal HWM regions were measured from high-resolution ($1mm^3$), 3D-FLAIR images acquired for 459 (283/176 females/males) active participants in the SAFH study. Subjects ranged in age from 19 to 85 years of age (47.9±13.5years) and were part of 49 families (9.4±8.5 individuals/family).

Results—The volumes of WB, subcortical and ependymal HWM were highly heritable (h^2=.72;.66;.73 respectively). The subcortical and ependymal HWM volumes shared 21% of genetic variability indicating significant pleiotropy. Genome-wide linkage analysis showed only a suggestive bivariate linkage for subcortical and ependymal HWM volumes (LOD = 2.12) on chromosome 1 at 288cM.

Conclusion—We replicated previous findings of high heritability for the WB-HWM volume. We also showed that subcortical and ependymal volume shared a significant portion of genetic variability and the bivarate linkage analysis produced a suggestive linkage near the locus previously identified in a study of WB-HWM volume and arterial pulse pressure.

Keywords

Brain Imaging; Genetics; MRI; White Matter Disease; Aging; Hyperintense White Matter; Structural imaging

*For correspondence and reprint information contact: Peter Kochunov Ph.D, Dip ABMP., University of Texas Health Science Center at San Antonio, Research Imaging Center, 7703 Floyd Curl Drive, San Antonio, Texas 78284, kochunov@uthscsa.edu, phone 210-567-8100, Fax 210-567-8152.

Conflicts of Interest

Authors have no conflicts of interest to disclose.

Background and Purpose

The volume of T2-hyperintense white matter (HWM) regions is an important neuroimaging marker of cerebral integrity. In normal aging, HWM regions begin to form during mid-adulthood (4–5thth decade of life) and their onset and progression is associated with declines in other indices of cerebral integrity[1]. Increasing volume of HWM regions is highly correlated with cerebral blood flow decline[2] and reduced glucose metabolism[3]. In addition, increasing numbers and volume of HWM regions is linked to age related cognitive declines, particularly in executive functioning[4], processing speed and general cognitive status[5]. Although the pathogenic mechanisms of HWM are unclear, histopathological and imaging findings indicate that whole-brain HWM (WB-HWM) volume includes at least two distinct mechanisms with distinct etiologies[6]. Subcortical HWM regions are more closely associated with ischemic factors[6]. In contrast, subependymal, periventricular HWM are thought to be of non-ischemic origin and potentially produced by pulse-wave encelophaty[7–9].

WB-HWM volumes are significantly influenced by genetic factors, with heritability estimates ranging between .55–.73[10–13]. Two recent genome-wide linkage studies reported significant and suggestive evidence of linkage for WB-HWM[13, 14]. DeStefano and colleagues reported significant linkage (LOD=3.69) for the WB-HWM volume at 4cM on the chromosome 4 in 747 healthy individuals from 237 families[14]. It was proposed that genes responsible for mitochondrial functioning, located near this region, may modulate volume of HWM during normal aging process. The second study performed whole-genome linkage analysis for WB-HWM in a population of 488 hypertensive adults[13]. Univariate linkage analysis only reached suggestive significance and did not overlap with genetic loci reported DeStefano and colleagues[14], possibly due to its focus on individuals with hypertension. Multivariate analysis reported many highly significant loci for WB-HWM and quantitative measurements of hypertension, suggesting a high degree of pleiotropy.

Neither of the previous studies separated the WB-HWM volume into the subcortical and ependymal components. In the current manuscript we pursued three goals: 1) to replicate findings of high heritability for WB-HWM volume; 2) to perform a novel analysis of shared genetic variance, and possible overlap for specific loci, between subcortical and ependymal HWM volumes; and 3) to search for chromosomal regions influencing HWM volume in a Mexican American population.

Methods

Subjects and measurements

459 (283/176 females/males; average age=47.9±13.5years, range=19–85years) Mexican American participants in the San Antonio Family Heart Study (SAFHS)[15] were recruited for this study. Recruited subjects were from large extended pedigree composed of 49 families with the average family size of 9.4±8.5 individuals (range=2–38). At the time of the imaging, 144 subjects were treated for hypertension, 80 subjects were treated for type II diabetes and 52 subjects had both hypertension and diabetes. Subjects were excluded for MRI contraindications, history of neurological illnesses or major neurological event (stroke). Subject's diagnosis status for hypertension and diabetes were coded as binary covariates. All subjects provided written informed consent on forms approved by the Internal Review Board of the University of Texas Health Science Center at San Antonio.

Imaging was performed at the Research Imaging Center, UTHSCSA, using a Siemens 3T Trio scanner and an eight-channel head coil. 3D T2-weighted imaging data were acquired using a high-resolution (isotropic 1mm), turbo-spin-echo Fluid Attenuated Inversion Recovery (FLAIR) sequence with the following parameters: TR/TE/TI/Flip angle/ETL=5sec/353 ms/

1.8s/180°/221. This 3D FLAIR protocol was designed to overcome limitation of 2D, thick-slice (2–5mm), imaging methods reported in prior studies of genetics of HWM[10–13]. Chosen protocol allowed for sensitive detection of smaller lesions and accurate tracing of lesion boundaries. 3D FLAIR sequence applied in the current study uses a non-selective inversion RF pulse to suppress long T1-relaxation time tissue signal, producing images with improved lesion contrast[16] that is highly advantageous over to a dual-echo sequence used in previous studies. Finally, the non-selective inversion RF pulse in 3D FLAIR sequence prevents ventricular CSF pulsation artifacts commonly seen as false-negative hyperintense regions in the 2D FLAIR sequences[17].

Measurement of HWM volume from FLAIR images is discussed elsewhere[18]. In short, FLAIR images were preprocessed by removal of non-brain tissue, registration to the T1-weighted images/Talairach frame and RF inhomogeneity correction. HWM regions were manually delineated in 3D-space using an in-house software (http://ric.uthscsa.edu/mango) by an experienced neuroanatomist with high (r^2>0.9) test-retest reproducibility. HWM regions were coded as ependymal regions, contiguous with CSF structures, and subcortical in accordance with[9]. The WB-HWM volume and the volumes of subcortical and ependymal HWM were measured for each subject.

Genotyping

The details of the genotyping procedure can be found in[19]. After DNA was extracted from lymphocytes, fluorescently labeled primers from the MapPairs Human Screening set (versions 6 and 8 (Research Genetics, Huntsville, AL, USA)) and PCR were used to amplified 417 microsatellite markers spaced at approximately 10-cM intervals across 22 autosomes. An automated DNA sequencer (ABI Model 377 with Genescan and Genotyper software; Applied Biosystems, Foster City, CA, USA) was used. The average heterozygosity index for these markers was approximately .76. The sex-averaged marker map was confirmed by deCODE genetics[20] and markers not on this map were placed by interpolation based on physical location[21].

Genotypes were subjected to extensive data cleaning with SimWalk2 software package[22]. The computation was based on maximum likelihood marker allele frequencies[23]. This statistical procedure is designed to detect inconsistencies and unlikely genotypes. An iterative process was followed to eliminate genotypes that are likely to be erroneous until no more inconsistencies or possible errors remained. Following this, the multipoint identity-by-descent matrices were estimated using the Markov chain Monte Carlo methods implemented in Loki[24]. The probabilities of multipoint identity-by-descent allele sharing among all possible pairs of related individuals were computed using the genotypes at all linked markers jointly in the computations.

Heritability and quantitative trait linkage analysis

Quantitative genetic analyses were performed using a variance components methods implemented in the SOLAR[25]. SOLAR employs maximum likelihood variance decomposition methods to determine the relative importance of genetic and environmental influences on a trait by modeling the covariance among family members as a function of genetic proximity (kinship). Heritability (h^2), the portion of phenotypic variance accounted for by additive genetic variance ($h=\sigma^2_g/\sigma^2_p$) was assessed by contrasting observed covariance matrices with the covariance matrix predicted by kinship. Bivariate genetic correlation analyses were performed to decompose phenotypic correlations (ρ_p) between regional HWM measurements into the genetic (ρ_g) and environmental (ρ_e) correlations, accounting for kinship: $\rho_p=\rho_g(h^2_1)^{1/2}(h^2_2)^{1/2}+\rho_e(1-h^2_1)^{1/2}(1-h^2_2)^{1/2}$.

Quantitative trait linkage analysis was performed to localize potential genes influencing phenotypic variation to specific chromosomal locations [25]. Model parameters were estimated using maximum likelihood. The hypothesis of significant linkage was assessed by comparing the likelihood of a classical additive polygenic model to that of a model allowing for both a polygenic component and a variance component due to linkage at a specific chromosomal location. The LOD score given by the log10 of the ratio of the likelihood of the linkage and the polygenic model served as the test statistic for genetic linkage. For this exact pedigree structure and density of markers, a LOD of 1.67 is required for suggestive significance (likely to happen by chance less than once in a genome-wide scan) and a LOD of 2.88 is required for genome-wide significance at the 0.05 level.

Similar to previous studies [10–13], HWM volumes were positively skewed. An inverse Gaussian transformation was utilized to assure normal range for kurtosis and skewness[25]. All genetic analyses were conducted with age, sex, age*sex, age^2, age^2*sex and diagnostic status for hypertension, diabetes and heart disorder (encoded as 0 or 1) included as covariates.

Results

Heritability Analysis

Whole brain (WB) HWM volume increased exponentially with age (Figure 1), consistent with previous findings by this center and others[10, 18, 26]. All measures of HWM volume were significantly influence by genetic factors. Heritability estimate for WB-HWM volume was .72±0.11, $p=1.0\times10^{-14}$. Consistent with previous reports, the age and age^2 covariates were nominally significant ($p<0.10$) for the WB-HWM volume[10, 11]. Lobar, ependymal and sublobar HWM volumes were also determined to be highly heritable (Table 1). Age was a significant covariate for both regional HWM volume measurements and age^2 approached significance for the ependymal HWM volume. Binary covariates that coded diagnosis for hypertension and diabetes did not reach statistical significance for any of the traits.

Bivariate Correlation Analysis

Genetic correlation analysis indicated that the subcortical and ependymal HWM volumes shared 21% of genetic variance (ρ_G =.46±0.12; p=.001), suggesting that some degree of pleiotropy. In contrast, the environmental correlation between HWM measurements was not significant (ρ_E=−.07±.24; p=.90). This result suggests that the observed phenotypic correlation between these two traits is driven overwhelmingly by shared genes.

Linkage Analysis

Genome-wide linkage analysis did not reveal a genome-wide significant localization for any of the HWM traits. However, suggestive linkage for subcortical and ependymal HWM volumes combined (bivariate) was found (LOD = 2.12) on chromosome 1 at 288cM near the p-terminus. Ependymal volume alone also showed suggestive linkage (LOD=1.72) at this chromosomal location. WB and subcortical HWM volumes were nominally significant (LOD=1.51 and 1.63 respectively) at this location.

Discussion

WB-HWM volume is a complex trait with a large genetic component. Histopathological findings suggest two distinct forms of HWM lesions, subcortical and ependymal [6–8]. In normal aging, subcortical HWM are though to result from ischemic and/or neuroinflamatory etiologies. Therefore, formation of subcortical HWM is thought to be the product of age-related loss of permeability of small vessels, age-related free-radical damage to oligodendrocytes and immune-system mediated gliosis[6, 27–30]. In contrast, ependymal HWM appears to be of

nonischemic origin. Histopathological findings indicate that the subependymal HWM is formed by the gliosis of periventricular WM due to the disruptions of the ependymal lining of cerebral ventricles, a condition also commonly observed in traumatic brain injuries[7–9]. The ependymal gliosis in normal aging is thought to be produced by a condition called the pulse-wave encephalopathy [7–9], which refers to the mechanical damages caused to the ependymal lining by the pulsatile movements of CSF due to the intra-cranial pulse pressure waves that produce "traumatic" micro-tears in the ependymal lining[7–9]. The magnitude of the CSF intra-cranial pulse pressure waves is linked to the gradient between systolic and diastolic arterial pressure. High arterial pulse pressure was shown to be a major risk factor for vascular damage and small vessel disease and was associated with higher ependymal HWM volumes[31, 32]. Pulse pressure is thereby could be a mechanism partially responsible for production of both subcortical and ependymal HWM. In fact, a recent whole-genome study of HWM in hypertensive individuals found evidence of significant multivariate linkage between two traits[13].

Our results in 459 generally healthy Mexican Americans individuals confirmed previous reports of significant genetic control over variation in the WB-HWM volumes [10, 11]. In addition, the heritability estimates for subcortical and ependymal HWM volume measurements were also highly significant. A significant genetic correlation supported the hypothesis that these two distinct forms of HWM lesions are partially influenced by common genetic factors. The results of the univariate whole-genome linkage analysis for the WB and regional HWM volumes did not reach statistical significance for linkage. Traits with high heritability estimates do not always produce significant linkages because heritability estimates do not provide information concerning the complexity of the underling genetic architecture[33]. The lack of significant linkage in the presents of significant heritability implies that the whole-brain and regional HWM volumes are polygenic traits with many QTLs each exerting only moderate effects. For example, normal variation in adult height is highly heritable (h^2=0.89–0.93), but current estimates suggest that up to 44 independent loci are associated with normal stature[34]. In contrast, the heritability of the neuregulin 1 transcript is somewhat lower (h^2~.50) but linkage analysis indicated a single locus (LOD=15.8) on chromosome eight[21]. However, results from bivariate linkage analysis for subcortical and ependymal volumes achieved suggestive linkage at marker 288 on chromosome 1. This finding suggests that some of the shared genetic variance between two traits reported may be related to this chromosomal region. Turner and colleagues[13] reported a suggestive linkage association for bivariate linkage analysis for the WB-HWM volume and pulse pressure (difference between systolic and diastolic BP) market 274 on chromosome 1. This hints on the nature of common genetic variance between two pools of HWM. It also supports the previously suggested hypothesis regarding the formation of ependymal gliosis and the link between ependymal and lobar HWM volumes. In contrast, the current study did not replicate findings of significant linkage on the chromosome 4 as reported in[14]. Indeed, at this chromosomal location, our peak LOD score was only ~0.3.

It is important to note that lack of overlap in genetic loci among this and other studies may be due to a number of potential issues. Genetic factors vary across different ethnicities. Prior studies of HWM were focused on populations of European ancestry while our study is the first to examine Mexican Americans, a population with significant Native American admixture. If relatively rare variants are involved in the determination of quantitative variability, we may expect considerable differences in the localization of the most important genetic loci across populations[35]. Additionally, this study and two other studies of HWM are relatively underpowered and are likely to miss important chromosomal localizations. Also, in general, linkage studies of such complex phenotypes cannot be used to exclude genetic regions for important QTLs. Thus lack of concordance cannot be interpreted as evidence against the hypothesis that a QTL exists in a particular genomic region. Finally, the cross-sectional nature of these data is suboptimal. There are well-known limitations to the conclusions that can be

made about longitudinal processes, such as aging, from cross-sectional measurements. The longitudinal studies often fail to confirm the age-related trends observed in the cross-sectional samples[36, 37] due to heterogeneity of individual aging trends. Longitudinal data from the Australian Stroke Prevention Study (ASPS) reported large intersubject differences in the rates of accumulation of HWM lesions[38]. Older subjects, subjects with higher baseline HWM volume and subjects diagnosed with neurological disorders were found to have accelerated rates of accumulation of HWM volume[39]. It is unclear to what degree longitudinal study design can confound the genetic analysis of HWM volume. Age and age^2 accounted for up to 27% of the variability in this study and others[10–13]. The individual rates of accumulation of the HWM volume rates greatly vary from a subject to subject, possibly due to individual genetic responses to aging (e.g. a genotype by age interaction). Hence, it may be useful to explicitly allow for the potential influences of genotype by age interactions. While advanced statistical genetic methods for family-based data allow for the formal detection of such interactions within cross-sectional data[35], longitudinal family studies will have much greater power to localize and ultimately identify the specific genes involved in intersubject differences in accumulation rates of HWM volume.

Acknowledgments

This research was supported by National Institute of Biomedical Imaging and Bioengineering (K01 EB006395) grant to P.K. and the National Institute of Mental Health (RO1s MH078111, MH0708143 and MH083824) to J.B. and D.G.

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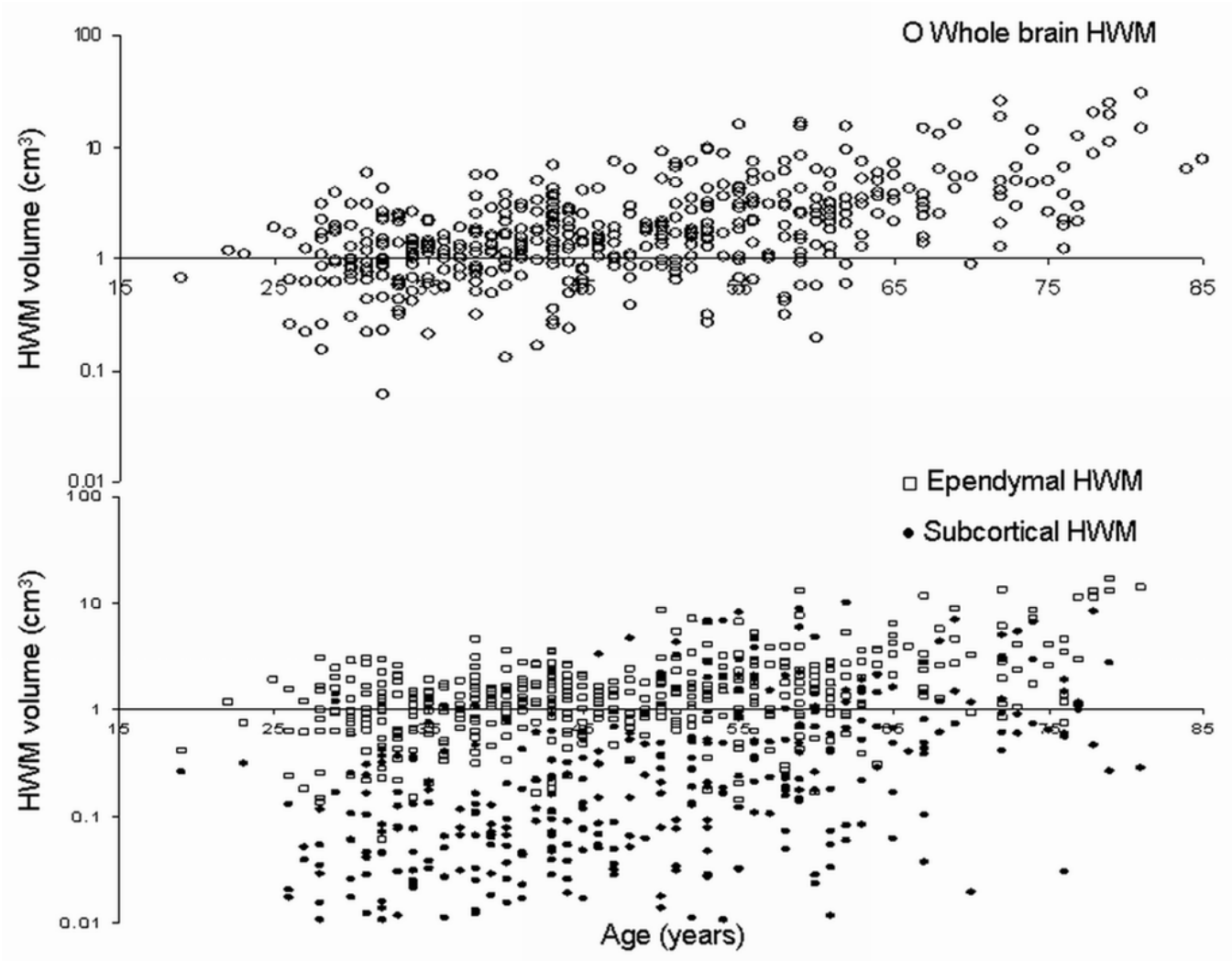

Figure 1.
Whole brain HWM raw data (top) and Ependymal (□) and Subcortical (●) HWM volumes (bottom) versus age.

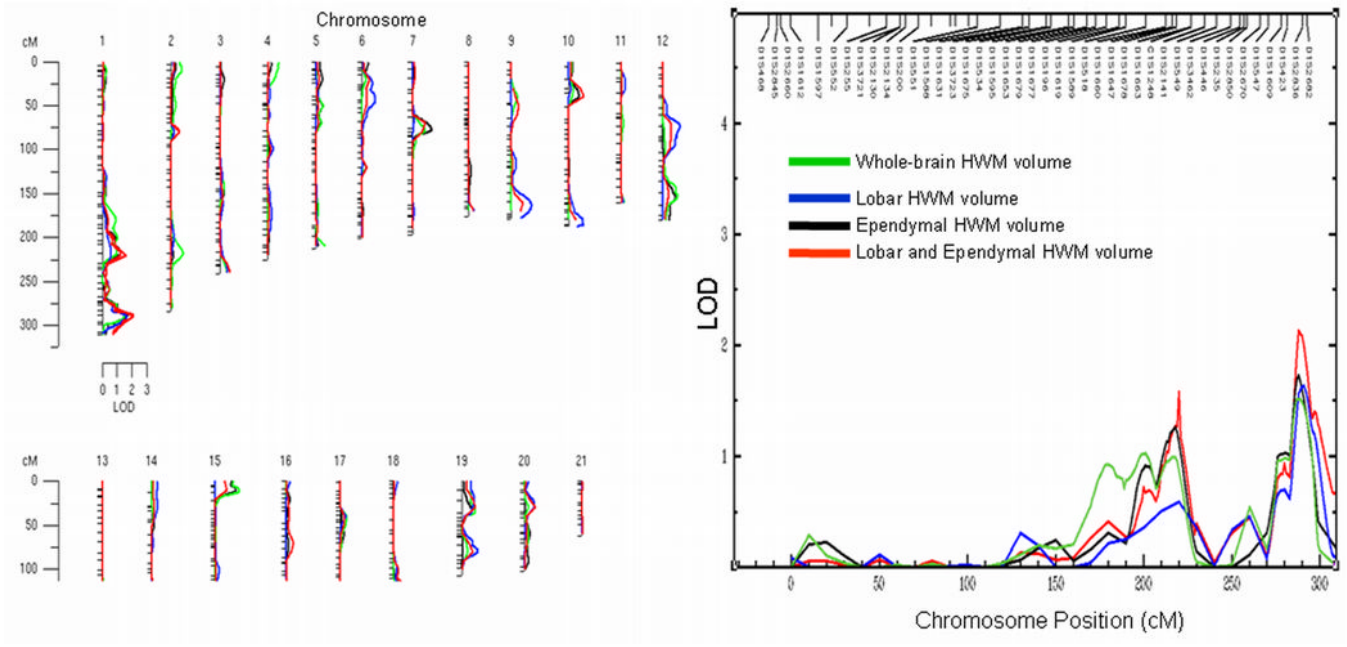

Figure 2.

Genome-wide LOD scores for the whole-brain and regional HWM volumes (left). Distribution of LOD scores for chromosome 1 is plotted along with the locations of the genetic markers (right)

Table 1

Heritability (h^2) Estimates for HWM Volume

Trait	% of Total Volume	h^2	p	Significant Covariates	Variance Explained by Covariates
Whole Brain	100.00	.72	1E-14	Age (5E-14), Age^2 (0.08)	28%
Subcortical	23.57	.66	4E-11	Age (3E-16)	27%
Ependymal	76.43	.73	1E-9	Age (2E-9), Age^2 (0.06)	20%