Whole Brain and Regional Hyperintense White Matter Volume and Blood Pressure
Overlap of Genetic Loci Produced by Bivariate, Whole-Genome Linkage Analyses

Peter Kochunov, PhD; David Glahn, PhD; Jack Lancaster, PhD; Anderson Winkler, MD;
Jack W. Kent, Jr, PhD; Rene L. Olvera, MD; Shelley A. Cole, PhD; Thomas D. Dyer, PhD;
Laura Almasy, PhD; Ravi Duggirala, PhD; Peter T. Fox, MD; John Blangero, PhD

Background and Purpose—The volume of T2-hyperintense white matter (HWM) is an important neuroimaging marker of cerebral integrity with a demonstrated high heritability. Pathophysiology studies have shown that the regional, ependymal, and subcortical HWM lesions are associated with elevated arterial pulse pressure and arterial blood pressure (BP), respectively. We performed bivariate, whole-genome linkage analyses for HWM volumes and BP measurements to identify chromosomal regions that contribute jointly to both traits in a population of healthy Mexican Americans. Our aims were to localize novel quantitative trait loci acting pleiotropically on these phenotypes and to replicate previous genetic findings on whole brain HWM volume and BP measurements.

Methods—BP measurements and volumes of whole-brain (WB), subcortical, and ependymal HWM lesions, measured from high-resolution (1 mm^3) 3-dimensional fluid-attenuated inversion recovery images, served as focal quantitative phenotypes. Data were collected from 357 (218 females; mean age=47.9±13.2 years) members of large extended families who participated in the San Antonio Family Heart Study.

Results—Bivariate genomewide linkage analyses localized a significant quantitative trait locus influencing WB and regional (ependymal) HWM volumes and pulse pressure and systolic BP to chromosomal location 1q24 between markers D1S196 and D1S1619. Several other chromosomal regions (1q42, 10q24-q26, and 15q26) exhibited suggestive linkages. The results of the post hoc analyses that excluded 55 subjects taking antihypertensive medication showed no substantive differences from the results obtained in the full cohort.

Conclusion—This study confirms several previously observed quantitative trait loci influencing BP and cerebral integrity and identifies a novel significant quantitative trait locus at chromosome 1q24. The genetic results strongly support a role for pleiotropically acting genes jointly influencing BP and cerebral white matter integrity. (*Stroke*. 2010;41:2137-2142.)

Key Words: brain ■ brain imaging ■ genetics ■ hypertension ■ leukoaraiosis ■ leukoencephalopathy ■ magnetic resonance ■ MRI

The volume of T2-hyperintense white matter (HWM) lesions[1] is an important neuroimaging marker of cerebral integrity with a large (55% to 73%) proportion of its intersubject variability attributed to genetic factors.[2–5] Increases in HWM volume are correlated with a decline in cerebral blood flow,[6] glucose metabolism,[7] and cognition.[8,9] Histopathologically, HWM lesions represent regions of accumulation of extracellular water due to focal degradation of the myelin sheath that arise from at least 2 distinct pathogenic mechanisms.[10] Ependymal lesions are the regions of periventricular gliosis and are thought to be produced by mechanical damages caused to the ependymal lining by the pulsatile movements of cerebrospinal fluid, a mechanism known as pulse-wave encephalopathy.[11] The amplitude of the pulsatile cerebrospinal fluid movements is linked to the pulse pressure (PP), the difference among arterial, systolic blood pressure (SBP)m and diastolic blood pressure (DBP). Elevated PP was shown to be associated with higher ependymal HWM volumes, even in normotensive individuals.[12,13] In contrast, subcortical HWM lesions are predominantly the regions of focal cerebral ischemia that are associated with elevated SBP and are thought to be the product of age-related stenosis and loss of permeability of capillaries due to small vessel disorders.[10,11]

Table 1. Heritability (h^2) Estimates and the Pattern of Significant Covariance for the WB and Regional HWM Volumes and 3 BP Measurements

Trait	Average±SD	h^2	*P*	Significant Covariates ($P<0.05$)	Variance Explained by Covariates
WB HWM	2.50±2.81 cm³	.72	1E-14	Age (5E-14)	28%
Subcortical HWM	.61±1.34 cm³	.66	4E-11	Age (3E-16)	27%
Ependymal HWM	1.84±2.07 cm³	.73	1E-9	Age (2E-9)	20%
SBP	122.6±16.6 mm Hg	.63	1E-6	Age (1E-3)	11%
DBP	71.3±10.8 mm Hg	.17	.04	None	0%
PP	51.3±14.2 mm Hg	.49	1E-4	Age (1E-3), age² (1E-4)	23%

Recent findings by Turner and colleagues[4] have identified overlap between genetic loci for the whole-brain (WB) HWM volume and blood pressure (BP) measurements in 488 hypertensive sibships.[4] Turner and colleagues used bivariate, whole-genome linkage analyses to identify several significant and suggestive loci for WB HWM and BP measurements, suggesting a high degree of pleiotropy between these traits. In the current article, we pursued to replicate findings by Turner and colleagues[4] using bivariate linkage analysis for WB HWM volume and BP measurements. We performed these analyses in a well-studied population of randomly selected Mexican American families. Our previous research in this population demonstrated significant heritability for HWM volumes and BP traits (Table 1) and showed that the 2 regional HWM volumes shared only a moderate (approximately 21%; $\rho_G=.46\pm0.12; P=0.001$) fraction of the genetic variance.[5,14] Furthermore, we demonstrated that although the univariate linkage analyses for the HWM and BP traits did not produce statistically significant loci, these analyses have independently showed a locus of suggestive significance on chromosome 1, q24.[5,14] An additional aim of this article is to formally test the significance of the overlap between the genes influencing the volume of HWM lesions and those determining the individual variability in arterial BP on chromosome 1 using a bivariate linkage analysis. A bivariate analysis can reveal chromosomal regions that contribute jointly to both traits either through the pleiotropic effects of the same genetic variants or the coincidental effects of closely linked genes.[4] Bivariate analysis also greatly improves the power of genetic discovery and the ability to localize causal beyond what is possible by univariate linkage analyses.[4]

Methods

Subjects and Measurements

Three hundred fifty-seven (218 females) active participants in the San Antonio Family Heart Study[15] were recruited as the part of this study. The Mexican American individuals are from large extended pedigrees selected randomly from the community. Subjects ranged in age from 19 to 85 years of age (47.9±13.2 years) and were part of 47 families (9.3±8.1 individuals/family; range, 2 to 38). Subjects were excluded for MRI contraindications, history of neurological illnesses, or major neurological event (stroke). At the time of the collection of BP measurements, 122 subjects (77 females; average age=54.8±13.0) were self-reported to have hypertension and 55 subjects (41 female, average age 58.5±12.0 years) were reported to take antihypertensive medications. Additionally, 65 subjects were reported to have Type II diabetes and 13 subjects were reported to have heart disorders. To reduce the possible confounding effects of

the antihypertensive drugs, we repeated all analyses in a cohort that excluded these subjects. This smaller cohort, after removing these individuals, consisted of 302 subjects (177 females) with the average age of 46.3±12.7 years and exhibited only slightly lower average SBP (120±16.4), DBP (70.1±10.6), and PP (50.5±13.9) values than those of the full cohort (Table 1). All subjects provided written informed consent on forms approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio (UTHSCSA).

Collection of the SBP and DBP measurements was detailed in Rutherford et al.[14] In short, SBP and DBP measurements were performed using a random-zero sphygmomanometer on the left arm. Three measurements were performed with 5-minute intervals and average of the last measurements was used as trait values. PP was calculated as the difference between SBP and DBP. Brain imaging and image analysis procedures were described in detail elsewhere.[5] Brain images were collected an average of 3.0±0.8 years (maximum=5.3 years) after the BP measurements. Hence, there is a prospective element to the brain measures. Imaging was performed at the Research Imaging Institute, UTHSCSA, using a Siemens 3-T Trio scanner and a high-resolution 8-channel head coil. Three-dimensional, T2-weighted imaging data were acquired using a high-resolution (isotropic 1 mm), turbo-spin-echo fluid-attenuated inversion recovery sequence with the following parameters: TR/TE/TI/flip angle/echo train length=5 seconds/353 ms/1.8 s/180°/221. Fluid-attenuated inversion recovery images were preprocessed by removal of nonbrain tissue, registration to the Talairach frame, and RF inhomogeneity correction. HWM regions were manually delineated in 3-dimensioal space using 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 cerebrospinal fluid structures, and subcortical in accordance with a technique described in Kochunov et al[5] and Henry Feugeas et al.[16] 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 Kammerer et al.[17] After DNA was extracted from lymphocytes, fluorescently labeled primers from the MapPairs Human Screening set (Versions 6 and 8; Research Genetics, Huntsville, Ala) and polymerase chain reaction 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, Calif) was used. The average heterozygosity index for these markers was approximately 0.76. The sex-averaged marker map was confirmed by deCODE genetics and markers not on this map were placed by interpolation based on physical location.[18]

Bivariate, Quantitative Trait Linkage Analysis

Quantitative genetic analyses were performed using a variance components methods implemented in SOLAR (sequential oligogenic linkage analysis routines).[19] Bivariate quantitative trait linkage analyses of HWM volumes and BP traits were performed to localize
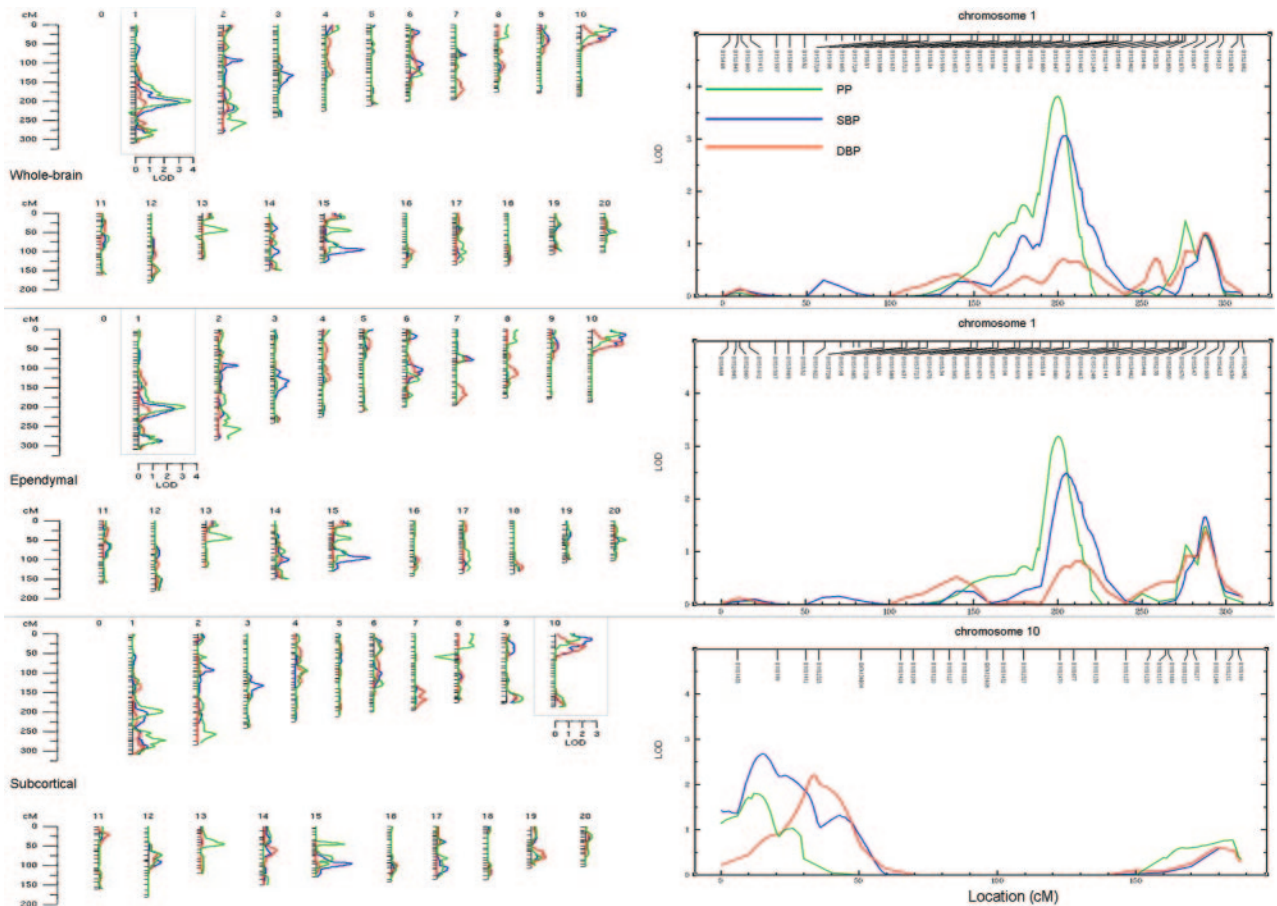
Figure. Bivariate linkage analysis results for WB (top), ependymal (middle), and subcortical (bottom) HWM volumes (bottom) and 3 measurements of arterial BP.

potential quantitative trait loci (QTLs) influencing phenotypic variation to specific chromosomal locations.[19] Model parameters were estimated using maximum likelihood. The hypothesis of significant linkage was assessed by comparing the likelihood of a classical additive polygenic model with that of a model allowing for both a polygenic component and a variance component due to linkage at a specific chromosomal location. The logarithm of odds (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. Because unmodified bivariate LOD scores typically involve an extra degree of freedom, we calculated the single locus equivalent LOD for each bivariate localization test. We chose LOD scores of 2.0 and 3.0 as the minimal requirements for the suggestive (likely to occur ≤ 1 times by chance in a genome scan) and significant scores (genomewide probability value=0.05), respectively. Similar to previous studies, HWM volumes and BP measurements were transformed using the inverse Gaussian transformation to assure normal range for kurtosis and skewness.[2–4] All genetic analyses were conducted with age, sex, age*sex, age^2, age^2*sex, and diagnostic status for Type 2 diabetes and heart disorder (encoded as 0 or 1) included as covariates.

Results

Bivarate, genomewide linkage analyses produced 3 significant (LOD >3.0) and several suggestive (LOD >2.0) QTL localizations (Figure; Table 1). The highest LOD score (LOD=3.82) was observed for the WB HWM and PP analysis at the chromosomal location 1q24, located 200 cM away from the p-terminus (Table 1). A significant linkage

(LOD=3.19) was also observed at this same location for the ependymal HWM volume and PP. Additionally, a significant linkage (LOD=3.07) between WB HWM volume and SBP was also observed at this location (Figure; Table 1). Bivariate analysis for sublobar HWM volume and BP measurements only reached suggestive levels of significance (Table 1). The highest score (LOD=2.68) was observed for SBP at chromosomal location 10q24-q26, located 15 cM away from the p-terminus (Table 1). Additionally, a suggestive linkage site was observed for both regional HWM measurements and SBP at the region of chromosome 15q26 (Table 1). There were no significant linkage results for any of the analyses that involved DBP, but a suggestive linkage site was identified on chromosome 10 for both regional HWM volume traits (Table 1).

The results of the post hoc analyses that excluded subjects taking antihypertensive medication showed no substantive differences from the results in the full cohort (Table 2). There were no new significant or suggestive genetic loci observed in the smaller cohort and there were only minute differences in the significance of the peaks. We observed a slight (but nonsignificant) increase in the LOD scores for the ependymal and PP and WB and SBP analyses, from 3.19 to 3.40 and 3.07 to 3.14, respectively. We also observed a slight (nonsignificant) reduction in the significance for the WB and PP 3 analysis from 3.82 to 3.62.

Table 2. Significant (LOD >3.0; Bold) and Suggestive (LOD >2.0) LOD Scores and Locations (on Marshfield Map, Markers) Between WB and Regional HWM Volumes and Quantitative BP Measurements

	WB HWM and			Ependymal HWM and
Chromosome	PP	SBP	DBP	PP
1	**3.82/3.62* (200; D1S196–D1S1619)**	**3.07/3.14* (203; D1S196–D1S1619)**		**3.19/3.40* (200; D1S196–D1S1619)**
10		2.41/2.35* (15; D10S1435–D10S189)		
15		2.72/2.71* (94; D15S116–D15S652)		

*LOD values were calculated from a smaller cohort, which excluded 55 subjects with hypertension.

Discussion

Our study in healthy Mexican Americans individuals aimed to replicate a finding of shared genetic loci between HWM and quantitative BP traits, previously reported by Turner et al[4] in a study of hypertensive sibships. We performed these analyses in a cohort of well-characterized population of Mexican Americans. Additional, post hoc analyses were performed in a cohort that excluded subjects taking antihypertensive medications. The genetic linkage analyses in both cohorts identified the same regions of significant and suggestive linkage and these loci overlapped with several loci reported by Turner and colleagues and with several loci previously identified by the univariate linkage analyses of BP, triglyceride levels, and atherosclerosis traits performed by this and other groups. The highest linkage value (LOD=3.82/3.62 full versus normotensive cohorts) was observed for the bivariate linkage analysis of WB HWM volume and PP. This locus (chromosome 1q24) was also significant in the bivariate analyses of the WB HWM and SBP and ependymal HWM and PP (Table 2). This locus (1q24) was previously identified by our group as a suggestive locus as a part of the univariate analysis of SBP.[14] It is known to harbor the constellation of *selectin* genes (*SELP*, *SELL*, and *SELE*) and also the coagulation factor V (*F5*) gene. In particular, the adhesion molecule P-selectin is a marker of potential endothelial dysfunction that has been implicated as a risk factor in essential hypertension[20,21] and stroke.[20,22] Additionally, platelet-derived gene expression levels of *SELP* have been observed to be strongly and positively correlated with arterial BP.[18,23] This finding was replicated in our population, in which we observed a highly significant, positive correlation between *SELP* mRNA expression levels and arterial BP.[24] No other gene transcripts in this region exhibited such a strong relationship with BP. Therefore, *SELP* appears to be a strong positional candidate gene that may be responsible for the significant QTLs on chromosome 1. Furthermore, deep sequencing and functional variants analyses will be required for true identification.

Locations of 2 suggestive linkages identified by this study overlapped with locations of suggestive linkage reported by Turner et al.[4] The first overlap was observed for the region on the chromosome 15, q26 (94 cM), where Turner and colleagues observed a suggestive QTL for the bivariate analysis of the WB HWM and mean BP. This region was previously shown to be strongly associated with hypertension and regulation of blood lipids by the genomewide association analyses of triglyceride levels.[23,24] The second overlap was

observed for the region on the chromosome 1q42 (272 cM), where Turner and colleagues observed a suggestive QTL for the bivariate analysis of WB HWM and PP. This region harbors the angiotensinogen gene and was previously implicated by a whole-genome linkage study in hypertensive individuals.[25]

However, we were unable to replicate findings by Turner and colleagues of the significant QTL on chromosomes 5 (95 cM) and 11 (19 cM). Indeed, at these chromosomal locations, our peak LOD scores were only approximately 0.1 to 0.3 (Figure). That lack of complete overlap in genetic loci between these 2 studies could be due several potential issues. Like with all complex disease genetic studies, power to localize such pleiotropic genetic effects can be limited and lead to discrepancies between studies. More fundamentally, genetic factors vary across different ethnicities. The study by Turner and colleagues was focused on populations of European ancestry, whereas 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.[26] Linkage studies of such complex phenotypes cannot be used to exclude genetic regions for important QTLs. Therefore, the lack of concordance cannot be interpreted as evidence against the hypothesis that a QTL exists in a particular genomic region. Additionally, although we identified no significant genomic regions showing joint effects on DBP and HWM volumes, we cannot rule such loci out. Similarly, the lack of identification of genomic regions jointly influencing 2 phenotypes provides no evidence on their overall pleiotropic relationship.

Our findings supported the hypothesis that ependymal and subcortical white matter lesions may have different causal genetic loci.[5,11,16,27] We previously showed that ependymal and subcortical HWM volumes shared only 21% of genetic variance, which suggested that most of the genetic variation is nonoverlapping.[5] In agreement with the pulse-wave encephalopathy mechanism of formation of the ependymal lesions, the linkage results for the bivariate, ependymal HWM volume and PP reached statistical significance (LOD=3.19). The linkage results for the subcortical HWM volume only reached suggesting significance, but the highest LOD score (LOD=2.68) was observed for the bivariate analysis with the SBP. This region, 10q24-q26, has been identified as a region of significant linkage by univariate analyses of several atherosclerosis traits,[28] therefore supporting the hypothesis of

Table 2.   Continued

	Ependymal HWM and			Subcortical HWM and	
SBP	DBP	PP		SBP	DPP
2.49/2.71* (204; D1S1619–D1S1589)		2.37/2.38* (272; D1S446–D1S235) and 2.15 (200; D1S196–D1S1619)			
2.32/2.29* (15; D10S1435–D10S189)	2.16/2.17* (36; D10S2325)			2.68/2.63* (15; D10S1435–D10S189)	2.21/2.20* (36; D10S2325)
2.56/2.54* (95; D15S116–D15S652)				2.59/2.60* (95; D15S116–D15S652)	

a small vessel-mediated origin of subcortical HWM. We did not interpret the lack of the statistically significant linkage between subcortical HWM volume and SBP as an indication that hypertension does not play a role in the formation of the subcortical HWM lesions. The pathogenesis of subcortical HWM lesion is more complex because several additional factors, including age-related, free-radical damage to oligodendrocytes, and immune system-mediated gliosis, were shown to contribute to the formation of subcortical lesions[10,29,30] and these factors can reduce the sensitivity of HWM SBP analysis. Further investigations that include BP measurements in conjunction with systemic markers of inflation, as proposed by Alzheimer's Disease Neuroimaging Initiative,[31] will be necessary to help identify the genetic factors contributing to individual risks of this complex trait.

Limitation

A limitation of this analysis is the coarse, 10 to 15 cM, chromosomal sampling of microsatellite markers. We are in the process of completing a high-density single nucleotide polymorphism analysis in this population. This step will reduce the search space to approximately 500 kb of sequence and further refine to locations of genetic loci.

Disclosures

None.

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全脑及局部性脑白质高信号体积与血压：
二变量全基因组连锁分析显示的遗传位点重叠

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背景和目的：脑白质 T2 高信号 (HWM) 体积是大脑完整性的重要的神经影像学标志，且有高度遗传性。病理生理学研究已显示局部、室管膜及皮层下的 HWM 损害分别与脉压和动脉血压相关。我们通过对健康墨西哥裔美国人的 HWM 体积和血压进行二变量全基因组连锁分析，以确定其与两者相关的染色体区域。我们的目的是明确这些表型新的基因多向性定量性状位点，并复制之前在全脑 HWM 体积和血压测量中遗传学的发现。

方法：血压测量以及高分辨率 (1 mm³) 三维液体衰减反转恢复 (FLAIR) 成像测得的全脑、皮层下及室管膜的 HWM 病损体积作为局部定量表型。数据收集于 San Antonio Family Heart 研究中多个扩大家庭的 357 位成员 (218 位女性; 平均年龄 47.9 ± 13.2 岁)。

结果：二变量全基因组连锁分析确定了影响全脑及局部 (室管膜) 的 HWM 体积及脉压和收缩压的有意义的定量性状位点，在染色体位置 1q24 的标志物 D1S196 和 D1S1619 之间。几个其他染色体区域（ 1q42, 10q24-q26 和 15q26 ）显示可能的关联。事后分析结果时排除了 55 个服用降压药者后再得出的结果 , 与整个队列研究的结果无本质区别。

结论：这一研究证实了几个预先观察的影响血压和大脑完整性的定量性状位点，并识别出位于染色体 1q24 的新的有意义的定量性状位点。这一遗传学结果强烈支持基因多向性的作用共同影响血压及脑白质的完整性。

关键词：脑，脑部成像，遗传学，高血压，脑白质疏松症，脑白质病，磁共振，核磁共振成像