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Histone deacetylase gene variants predict brain volume changes in multiple sclerosis

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Abstract

Neuroimaging measures hold promise for enhancing the detection of disease-related genetic variants. In this study, we use advanced multivariate regression methods to assess the predictive value of single nucleotide polymorphisms (SNPs) on several brain volumetric- and lesion-related neuroimaging measures in a well-characterized cohort of 326 patients with multiple sclerosis (MS). SNP selection was constrained to key epigenetic regulatory genes to further explore the emerging role of epigenetics in MS. Regression models consistently identified rs2522129, rs2675231, and rs2389963 as having among the highest predictive values for explaining differences related to brain volume measures. These SNPs are all contained in genes from the same superfamily, histone deacetylases, which have biological functions that are relevant to MS, neurodegeneration, and aging. Our preliminary findings generate hypotheses for testing in future independent MS data sets as well as other neurodegenerative conditions.

Keywords: Multiple sclerosis; Brain volume; Multivariate regression; Histone deacetylase; Mitochondria; Sirtuin

1. Introduction

Multiple sclerosis (MS) is an inflammatory disease involving demyelination and neurodegeneration (Hauser and Oksenberg, 2006). The disease is characterized by neurodegenerative events and autoimmune attacks against myelin in the central nervous system leading to varying degrees of relapsing or progressive neurological impairments (Vukusic and Confavreux, 2007). The clinical course and disease progression of MS is highly variable, and is likely to depend on complex heritable (genetic and epigenetic) and environmental factors (Lauer, 2010; Oksenberg and Baranzini, 2010; Urdinguio et al., 2009).

Studies are starting to unravel some of the genetic factors that influence MS disease susceptibility, of which the majority relate to immune system functions (Disanto et al., 2011). Additional genetic factors influencing specific fea-

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tures of MS disease expression, such as myelin loss, and axonal and neuronal degeneration remain largely unknown. A promising strategy for identifying possible gene variants that influence these features is to integrate intermediate measures, such as those derived from neuroimaging analyses. Radiological features derived from magnetic resonance imaging (MRI) offer in vivo measures that reflect different stages of inflammation and neurodegeneration, resulting in greatly enhanced characterization of MS disease processes (Al, 2010). These intermediate measures hold promise for enhancing the sensitivity of detecting genetic factors that influence biological mechanisms underlying MS pathogenesis.

Emerging evidence has established a preliminary role for epigenetic mechanisms in MS (reviewed by Urdinguio et al., 2009): (1) epigenetic drug targets (Aljada et al., 2010; Camelo et al., 2005; Chuang et al., 2009; Faraco et al., 2011; Kazantsev and Thompson, 2008), (2) epigenetic regulation of MS susceptibility genes (Miralvès et al., 2007), and (3) epigenetic events linking to inflammation and neurodegeneration (Kim et al., 2010). While these initial findings are encouraging, a complete understanding of the epigenetic mechanisms that specifically influence MS is far from being fully characterized.

This study utilizes a neuroimaging genetics approach to investigate potential relationships between genetic variability in genes that regulate epigenetic events in order to assess whether such mechanisms specifically influence MRI features relevant to the lesion and brain volume changes reported in the brains of MS patients. We constrain our analyses to examine genetic variability in 25 key epigenetic regulatory genes and 7 different MS-relevant brain volume- and lesion-related MRI measures using a large, well-characterized sample population of patients with MS. Given that we have no prior predictions for which genes and variants will best predict which brain measures, we explore the variability in these genes and imaging measures as a way of generating future hypotheses that can be tested in independent data sets.

While the integration of neuroimaging measures into genetic studies is likely to enhance the sensitivity of detecting relationships, this approach presents new statistical challenges (when considering multiple loci and multiple neuroimaging measures) and therefore requires advances in statistical methodologies. In this study, we apply 2 advanced multivariate regression models (Lasso regression and sparse reduced-rank regression) to account for dependencies in the data. These advanced methodologies hold promise for detecting neuroimaging and genetics relationships with greater power (Vounou et al., 2010), and thus have a higher probability of consistently identifying relevant gene variants in relation to specific determinants relevant to MS. We also report on the corresponding conventional univariate tests.

2. Methods

2.1. Cases

All patients are part of a larger cohort recruited from 2 clinical centers that participated in the GeneMSA consortium and are derived from a larger cohort that was previously published in detail (Baranzini et al., 2009, 2010). Patients visited the University Hospital in Basel and the VU University Medical Centre in Amsterdam, and patients with a diagnosis of clinically definite MS (Polman et al., 2005) were included. Because primary progressive MS may be a distinct clinical subtype we only included patients with an initial relapsing-onset of MS; relapsing-remitting MS, or secondary progressive MS. The latter was retrospectively defined by at least 6 months of worsening neurological disability not explained by clinical relapse (Hauser and Goodkin, 2001). Disability was assessed with the Expanded Disability Status Scale at baseline and follow-up after 1 year for all patients (Kurtzke, 1983). The institutional ethics review boards of the clinical centers approved the study protocol. All patients have given written informed consent before to entering into the study.

2.2. Image acquisition

Magnetic resonance (MR) imaging was performed on two 1.5 T MR systems (Amsterdam, The Netherlands: Siemens Vision; Basel, Switzerland: Siemens Avanto) at baseline and at a 1-year follow-up. Dual echo proton density T2-weighted images were acquired (repetition time [TR], 2000–4000 msec; echo time [TE], 14–20/80–108 msec), with interleaved axial 3.0-mm thick slices and an in-plane resolution of 1.0×1.0 mm^2. Also acquired were postcontrast T1-weighted spin-echo images (TR, 467–650 msec; TE, 8–17 msec); axial 3.0-mm thick slices with an in-plane resolution of 1.0×1.0 mm^2. For brain volume measurement, isotropic ($1 \times 1 \times$ mm^3) T1-weighted anatomical images were acquired (TR, 7–20.8 msec; TE 2–4 msec; inversion time [TI], 300–400 msec).

2.3. MRI measures

Images were visually inspected for the absence of movement artifacts before lesion and volume analysis. Brain volume analyses were performed at the Imaging Analysis Centre in Amsterdam and lesion marking and measurement at the University Hospital in Basel. In this study, we investigate 7 different neuroimaging measures of which 4 relate to brain volume: (1) normalized brain volume (NBV), (2) normalized gray matter volume (NGMV), (3) normalized white matter volume (NWMV), and (4) percentage brain volume change after 1 year (PBVC), and we estimate these using SIENA(X) (Smith et al., 2002) from the Functional Magnetic Resonance Imaging Building (FMRIB) Software Library, University of Oxford, Oxford, UK (version 2.2). All T1-weighted images were registered to Montreal Neurological Institute 152 standard space using the skull as a