

Comment: *HLA-DRB*1501* associations with magnetic resonance imaging measures of grey matter pathology in multiple sclerosis

Richard L. Yates¹ & Gabriele C. DeLuca¹

¹ Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK, OX3 9DU

We read with interest the recent article published in Multiple Sclerosis and Related Disorders entitled “*HLA-DRB*1501* associations with magnetic resonance imaging measures of grey matter pathology in multiple sclerosis” (Yaldizli et al., 2016). In their study, the authors investigate whole/lesional cortical grey matter volumes and lesional/normal-appearing magnetization transfer ratio in a large cohort of MS cases and controls genotyped for *HLA-DRB1*1501*. The authors do not observe any difference in MRI-visible cortical grey matter disease and question the role of this locus on modulating cortical pathologic outcome.

Understanding the genetic contribution to MS heterogeneity is of profound clinical importance. The identification of factors that associate with disease severity would allow patient stratification for therapeutic benefit and could help to elucidate novel drug targets. The conflation of current radiographic evidence suggests that carriage of *HLA-DRB1*15* influences the extent and distribution of demyelination in both spinal cord (Sombekke et al., 2009) and cerebral white matter (Okuda et al., 2009; Tur et al., 2014). However, until now the radiographic study of genetic determinants of cerebral cortical disease has been neglected. This is despite the increasingly evident contribution of grey matter pathology to physical and cognitive disability (Calabrese et al., 2012), and the striking extent of cortical disease in progressive MS (Kutzelnigg et al., 2005). One reason for this is that conventional MRI techniques do not have sufficient

resolution to detect cortical lesions, which are typically not contrasted well with surrounding normal-appearing parenchyma (Ciccarelli et al., 2012). More advanced techniques can improve the radiographic detection of cortical lesions, such as the phase-sensitive inversion recovery sequences that have been employed by the authors of the current study. However, the use of 3T MRI limits the interpretation of this work as subpial lesions, the most abundant cortical lesion type, remain poorly detected even with the application of advanced sequences (Stadelmann et al., 2011; Harel et al., 2016).

We would like to direct the authors to a recent study by our group, in which we investigated the influence of *HLA-DRB1*15* on MS cortical pathology in a post-mortem cohort examined histologically (Yates et al., 2015). In our study, 93% of cortical lesions identified were subpial. Cortical lesional burden was more severe in MS cases that died at a younger age, and within this group demyelination was more severe in *HLA-DRB1*15* positive cases. Cortical parenchymal inflammation was also more severe in *HLA-DRB1*15* positive cases, particularly in those cases that died at a younger age. The age-dependant nature of these observations suggest that age may be a critical factor to consider in the assessment of genetic relationships with cortical pathology. Age-related senescence of inflammation and the remyelination capacity of the cortex provide possible explanations for these observations. We wonder if the authors of the current study assessed the influence of age on their findings?

We believe understanding the influence of *HLA-DRB1*15* on *in vivo* cortical disease burden is an important area of study. However, pathologic differences that associate with *HLA-DRB1*15* in the cortex will likely be difficult to discern using current MRI modalities. Whilst the use of higher field strength 7T MRI has recently been shown to more than double the detection of subpial lesions, they remain underrepresented when compared to neuropathology (Kilsdonk et al., 2016). Robust and quantitative pathologic outcomes will therefore continue to play a complementary role to MRI studies in the evaluation of how genetic variation impacts MS disease severity (DeLuca et al., 2013; Yates et al., 2015).

Acknowledgements

R.L is supported by a Ph.D studentship funded by the MRC. G.C. DeLuca is supported by the NIHR Biomedical Research Centre (BRC), Oxford and has research funding from the Oxford BRC, MRC (UK), and Merck-Serono. G.C. DeLuca has received travel expenses from Bay Schering, Biogen Idec, Genzyme, Merck Serono, and Novartis, and honoraria as an invited speaker for Bayer Schering.

References

Calabrese M., Poretto V., Favaretto A., Alessio S., Bernardi V., Romualdi C., Rinaldi F., Perini P., Gallo P., 2012. Brain. 135, 2952-61.

Ciccarelli O., Chen J.T., 2012. MS cortical lesions on double inversion recovery MRI: few but true. Neurology. 78, 296-7.

DeLuca G.C., Alterman R., Martin J.L., Mittal A., Blundell S., Bird S., Beale H., Hong L.S., Esiri M.M., 2013. Casting light on multiple sclerosis heterogeneity: the role of HLA-DRB1 on spinal cord pathology. Brain. 136, 1025-34.

Harel A., Ciccarelli A., Farrell C., Fabian M., Howard J., Riley C., Miller A., Lublin F., Inglese M., 2016. Phase-Sensitive Inversion-Recovery MRI Improves Longitudinal Cortical Lesion Detection in Progressive MS. PLoS One. 11, e0152180.

Kilsdonk I.D., Jonkman L.E., Klaver R., van Veluw S.J., Zwanenburg J.J., Kuijter J.P., Pouwels P.J., Twisk J.W., Wattjes M.P., Luijten P.R., Barkhof F.,

Geurts J.J., 2016. Increased cortical grey matter lesion detection in multiple sclerosis with 7 T MRI: a post-mortem verification study. *Brain*.

Kutzelnigg A., Lucchinetti C.F., Stadelmann C., Brück W., Rauschka H., Bergmann M., Schmidbauer M., Parisi JE., Lassmann H., 2005. Cortical demyelination and diffuse white matter injury in multiple sclerosis. *Brain*. 128, 2705-12.

Okuda D.T1, Srinivasan R., Oksenberg J.R., Goodin D.S., Baranzini S.E., Beheshtian A., Waubant E., Zamvil S.S., Leppert D., Qualley P., Lincoln R., Gomez R., Caillier S., George M., Wang J., Nelson S.J., Cree B.A., Hauser S.L., Pelletier D., 2009. Genotype-Phenotype correlations in multiple sclerosis: HLA genes influence disease severity inferred by 1HMR spectroscopy and MRI measures. *Brain*. 132, 250-9.

Sombekke M.H., Lukas C., Crusius J.B., Tejedor D., Killestein J., Arteta D., Martínez A., Uitdehaag B.M., Knol D.L., Peña A.S., Geurts J.J., De Jager P.L., Barkhof F., Vrenken H., Polman C.H., 2009. HLA-DRB1*1501 and spinal cord magnetic resonance imaging lesions in multiple sclerosis. *Arch. Neurol*. 66, 1531-6.

Stadelmann C., Wegner C., Brück W., 2011. Inflammation, demyelination, and degeneration — Recent insights from MS pathology. *Biochim Biophys Acta*. 1812, 275-82.

Tur C., Ramagopalan S., Altmann D.R., Bodini B., Cercignani M., Khaleeli Z., Miller D.H., Thompson A.J., Ciccarelli O., 2014. HLA-DRB1*15 influences the development of brain tissue damage in early PPMS. *Neurology*. 83, 1712-8.

Yaldizli Ö., Sethi V., Pardini M., Tur C., Mok KY., Muhlert N., Liu Z., Samson RS., Wheeler-Kingshott CA., Yousry TA., Houlden H., Hardy J., Miller DH., Chard DT., 2016. HLA-DRB*1501 associations with magnetic resonance imaging measures of grey matter pathology in multiple sclerosis. *Mult Scler Relat Disord*. 7, 47-52.

Yates R.L., Esiri M.M., Palace J., Mittal A., DeLuca G.C., 2015. The influence of HLA-DRB1*15 on motor cortical pathology in multiple sclerosis. *Neuropathol. Appl. Neurobiol*. 41, 371-84.