Chr8p23 region implicated in genetic basis for demyelination in multiple sclerosis patients

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OBJECTIVE

- Do pre-existing inter-patient differences or the ongoing disease process primarily influence MTR?
- Can genetics explain inter-patient differences in MTR?

INTRODUCTION

- Decreased magnetization transfer ratio (MTR) correlates with reduced myelin content.[1,2]
- MTR distinguishes between de- and remyelinated lesions[1] and qualifies as a feasible outcome measure for remyelinating drug trials.[3,4]
- Remyelination is considerable in some cases while virtually absent in others.[5]
- Subtle reductions in MTR are apparent early in MS[6] and correlate negatively with cognitive function and disability.[7,8]

METHODS

- We collected a longitudinal cohort of 33 multiple sclerosis patients and extended it cross-sectionally to 213 individuals.
- We measured MTR histogram measures (median, peak height) in lesions, normal appearing white matter (NAWM) and grey matter (NAGM), total brain, grey matter, white matter and lesion volume.
- We performed a genome-wide association study with individual MRI traits and with MTR across multiple tissue classes taking into account covariance.

RESULTS

High inter-patient with low variation over time characterizes MRI traits – Longitudinal cohort

- We obtained two to five scans with the same scanner protocol and with an average interval of 13.2 ± 7.9 months between the first and second scan (**Fig. 1**).
- Ongoing disease activity (i.e. follow-up time) and pre-existing inter-patient differences (i.e. a unique patient identifier code) both determined 70% of the variance in MTR traits ($P \leq 1.85 \times 10^{-7}$) (**Fig. 2A**).
- Inter-patient differences were the main determinant (≥ 99%) while obvious variables (age, gender and disease duration) explained much less (max. 13%) of this variation (**Fig. 2B**).

The multiple sclerosis genetic risk score is not associated with MRI traits – Cross-sectional cohort

- The genetic risk score of all susceptibility-related variants was not convincingly associated with MTR ($P \geq 0.02$).

A genome-wide association screen for variants controlling demyelination – Cross-sectional cohort

- We identified two independent novel associations (rs6982453, $P = 8.87 \times 10^{-6}$; rs3729856, $P = 2.17 \times 10^{-5}$) on chr8p23 near *FDFT1* and *CTSB* with peak height MTR in NAWM, NAGM and lesions (**Fig. 3**).
- The effect size in the univariate analysis was consistent across tissues with the rs6982453*C allele decreasing peak height in all three tissues ($-0.31 \leq \text{beta} \leq -0.37$; $3.09 \times 10^{-4} \leq P \leq 1.69 \times 10^{-5}$) (**Fig. 3**).

References: [1]Ann Neurol 2004;56:407-415; [2]Ann Neurol 2011;70:764-773; [3]Mult Scler 2010;16:660-669; [4]Nat Rev Neurol 2009;5:256-266; [5]Brain 2006;129:3165-3172; [6]Brain 2005;128:2911-2925; [7]Mult Scler 2009;15:668-677; [8]Neurology 2013;81:1759-1767.

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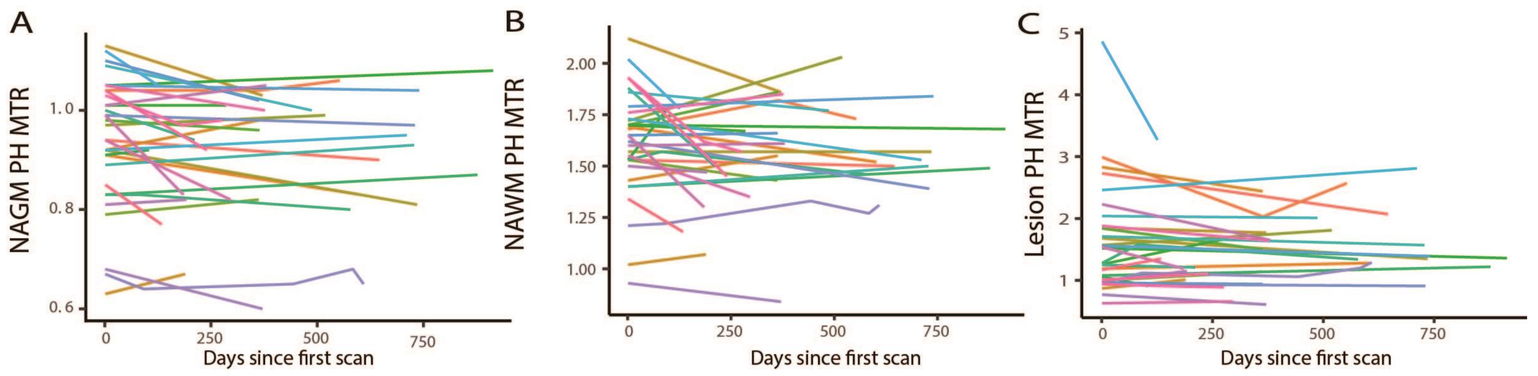
CONCLUSIONS

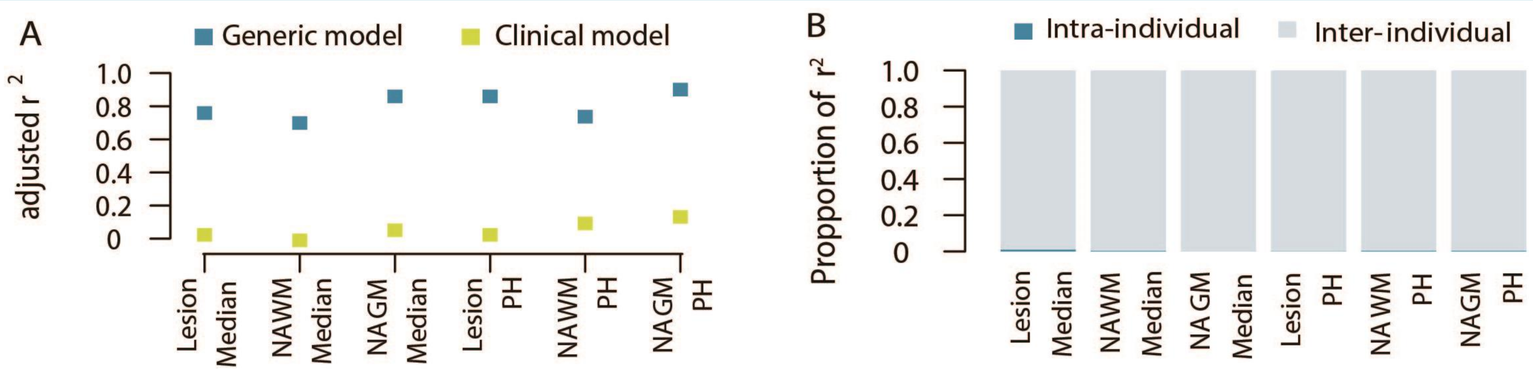
- MTR and volumetric traits reflect inter-individual variation in biology rather than in disease activity.
- Genetic factors influencing susceptibility do not explain phenotypical heterogeneity.
- SNPs near *FDFT1* and *CTSB,* involved in cholesterol biosynthesis and/or the local inflammatory response, influence MTR-quantified de- and remyelination.

FIGURE 1



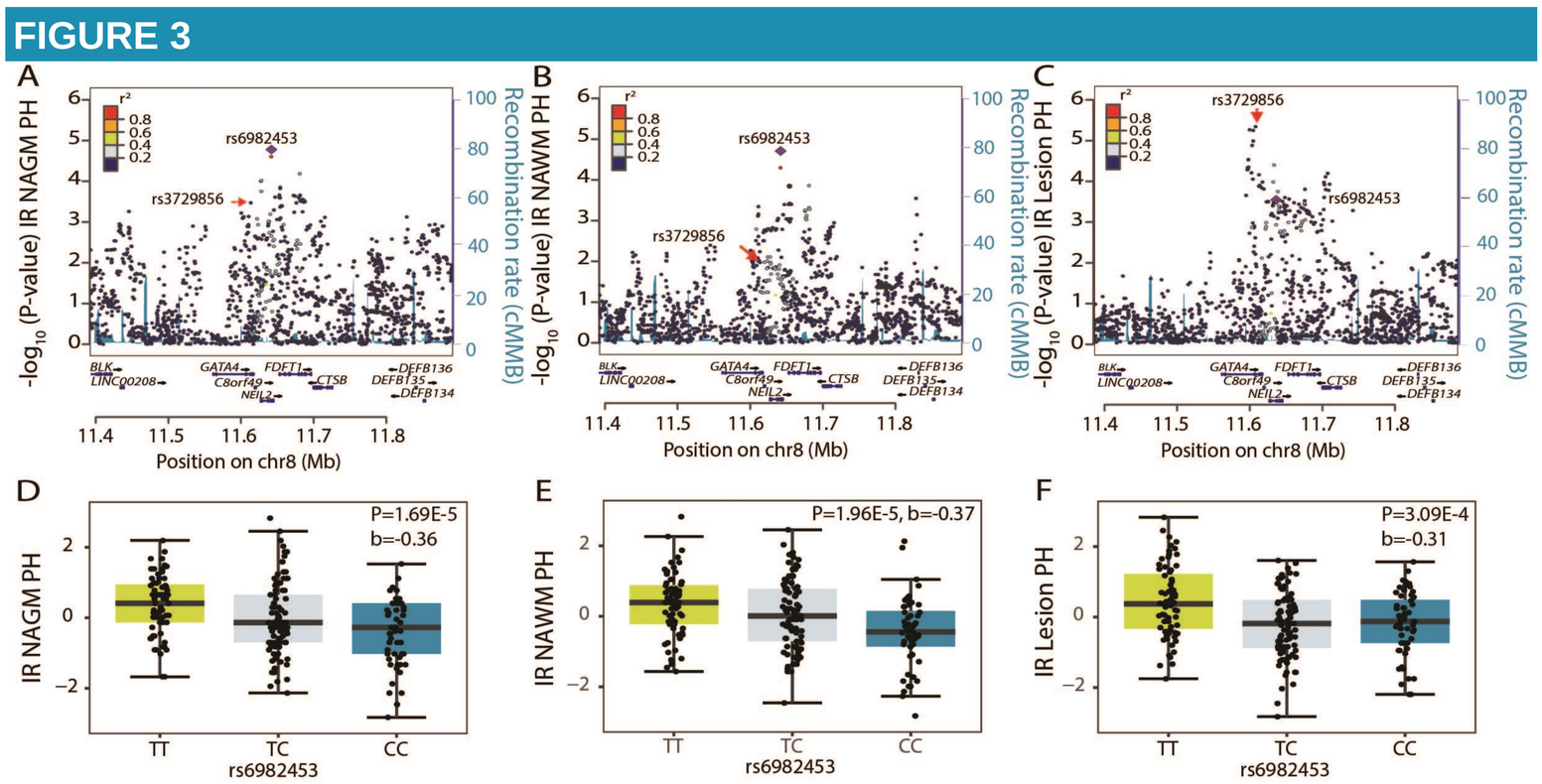
Longitudinal variation in MTR. Longitudinal evolution of peak height MTR in each tissue class (**A.** NAGM, **B.** NAWM, **C.** lesions). The same colour represents each individual patient (N = 33) throughout the graphs. All patients were scanned using the same scanner.

FIGURE 2



Contribution of inter- and intra-individual variance in longitudinal MTR. In the longitudinal cohort (N = 33) we visualized the **A.** percentage of MTR variance explained (= adjusted r^2) in a generic model (dark blue) including a unique patient identifier code (i.e. inter-individual variation) and follow-up time (i.e. intra-individual variation) and a clinical model (green) including gender, age and disease duration (i.e. known variables of inter-individual variation) and follow-up time. **B.** Relative contributions of inter- and intra-individual variation over time to the explained total variance in the generic model.

FIGURE 3



Regional association plot and association with MTR traits for rs6982453. Regional association plot of rs6982453 with **A.** inverse ranked (IR) peak height MTR in NAGM, **B.** NAWM and **C.** lesions. Each point represents a SNP plotted with the P-value (on a –log10 scale) as a function of genomic position (hg19/GRCh38.p10). The lead SNP corresponds to the purple diamond and the independent signal rs3729856 is indicated with a red arrow. The colour coding of all other SNPs (circles) indicates linkage disequilibrium with the lead SNP. MTR values for rs6982453 are visualized through boxplots for **D.** IR peak height MTR in NAGM, **E.** NAWM and **F.** lesions. P value and beta result from a regression analysis with rs6982453*C as the effect allele.