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

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Background: Magnetization transfer ratio (MTR) and brain volumetric imaging capture demyelination (especially MTR), axonal degeneration and/or inflammation. The factors shaping variation in these traits are largely unknown while neuroprotective therapies represent an unmet clinical need in multiple sclerosis. We investigate whether MRI traits are primarily influenced by pre-existing inter-patient differences or by the ongoing disease process and whether genetics can explain inter-patient differences.

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) and 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.

Results: Longitudinally, ongoing disease activity and inter-patient differences determined 70% of the variance in MRI traits ($P \leq 1.85 \times 10^{-7}$). Inter-patient differences were the main determinant (≥ 99%) but obvious variables (age, gender and disease duration) explained much less (maximum 34%) of this variation. Cross-sectionally, we observed a high correlation of median and peak height MTR across lesions, NAGM and NAWM implying a shared pathway. The genetic risk score of all susceptibility-related variants was not convincingly associated with MTR ($P \geq 0.02$) or volumetric indices ($P \geq 0.23$). Conversely, we identified two independent novel associations ($P = 8.87 \times 10^{-6}$; $P = 2.17 \times 10^{-5}$) on chr8p23 near *FDFT1* and *CTSB* with lower peak height MTR in NAWM, NAGM and lesions.

Conclusions: MTR and volumetric traits reflect individual variation in biology rather than being proxies for disease activity. Our results point to genetic variation near *FDFT1* and *CTSB,* involved in cholesterol biosynthesis and/or the local inflammatory response, influencing de- and remyelination. These findings translate evidence from demyelination in animal models to humans.