A NOTCH4 missense mutation confers resistance to multiple sclerosis in Japanese

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論文題名：　A *NOTCH4* missense mutation confers resistance to multiple sclerosis in Japanese
（*NOTCH4* ミスセンス変異は日本人で多発性硬化症への疾患抵抗性を付与する）

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論　文　内　容　の　要　旨

Background: The G allele of *NOTCH4* rs422951 is protective against demyelinating disease in Japanese.

Objectives: To assess the relation of the G allele to neuromyelitis optica (NMO)/NMO spectrum disorder (NMOSD) and multiple sclerosis (MS) and the interaction between the G allele and *HLA-DRB1* alleles, and to clarify any association of the G allele with clinical features.

Methods: DNA sequencing was used to genotype 106 NMO/NMOSD patients, 118 MS patients and 152 healthy controls (HC) for rs422951.

Results: G allele frequency in MS patients, but not that in NMO/NMOSD patients, was lower than that in HC (8.9% vs. 21.7%, $p<0.0001$, OR=0.35). *HLA-DRB1*0405* was positively associated with MS (OR=2.22, $p^{corr}=0.0380$) while *DRB1*0901* was negatively associated (OR=0.32, $p^{corr}=0.0114$). Logistic regression analyses revealed that, after adjusting for gender and either *HLA-DRB1*0405* or *DRB1*0901*, rs422951 was associated with MS in the dominant model (OR=0.37, 95% CI= 0. 20 – 0.66, $p=0.0012$). Haplotype

analyses identified two susceptible and three resistant haplotypes formed from rs422951 and either *HLA-DRB1*0405* or *DRB1*0901*. There were no statistically significant differences in clinical features between G allele carriers and non-G allele carriers.
Conclusion: The G allele of *NOTCH4* rs422951 is an independent resistant allele for MS in Japanese not affecting clinical features.