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***Replication of KIF21B as a susceptibility locus for multiple sclerosis***

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## ABSTRACT

Background: Knowledge of genetic susceptibility to autoimmune disorders is growing exponentially. One of the messages emerging from these data is the growing overlap in genetic susceptibility to different autoimmune disorders. *KIF21B* is a member of the kinesin superfamily and was recently established as a susceptibility locus for inflammatory bowel disease and for multiple sclerosis.

Results: We here replicate the association with multiple sclerosis in a Belgian study population of 791 patients and 1,098 controls.

Conclusion: As SNPs in *KIF21B* increase risk for both inflammatory bowel disease and multiple sclerosis, this suggests a common pathway in the pathogenesis of these diseases.

## **INTRODUCTION**

Multiple sclerosis (MS) is a common neurological disorder characterized by inflammation, demyelination and axonal loss. It is thought to be an autoimmune disorder directed against components of the myelin sheath. Our knowledge of susceptibility genes for MS, as for other autoimmune diseases, is growing exponentially.[1, 2, 3, 4, 5, 6, 7, 8, 9] One important conclusion emerging from these studies is the overlap in genetic susceptibility loci between different autoimmune disorders.[10] We and others previously demonstrated e.g. variation in the known type 1 diabetes risk loci *CLEC16A* and *CD226* to also influence MS susceptibility.[2, 6, 11, 12] Hence, following up susceptibility genes for one autoimmune disorder as candidate genes for another proves to be an efficient strategy.

We here started from current progress in unraveling susceptibility to Crohn's disease. In a meta-analysis of genome-wide association screens on this disease, Barrett et al. reported twenty-one novel loci as being associated with Crohn's disease.[13] One single nucleotide polymorphism (SNP), rs11584383, was located downstream of *KIF21B*, a member of the kinesin superfamily (KIF). In a recent study following up on a genome-wide association screen for MS [2], a correlated SNP, rs12122721, located in an intron of *KIF21B* was found to be associated with MS [14]. We here investigate both *KIF21B* SNPs in an independent Belgian study population of 791 MS patients and 1,098 controls.

## **METHODS**

### **Participants**

A total of 791 patients and 1,098 unrelated controls were included in this study. All individuals gave informed consent. Amongst the patients and the unrelated controls, 64% and 52% were female, respectively. Amongst the patients, 664 (84%) had bout-onset MS and 108 (14%) primary progressive MS. Average age at onset was 34±11 years.

### **Genotyping**

SNPs rs11584383 and rs12122721 were genotyped with Taqman Assays-on-Demand C\_3030223\_10 and C\_30856017\_20 according to the manufacturer's instructions and run on a 7300 SDS real-time PCR system.

### **Statistical analysis**

Analysis was done with the Plink software package version 1.06 [15].

## RESULTS AND DISCUSSION

Genotyping success rate was  $\geq 96\%$ . No deviation from Hardy-Weinberg equilibrium was observed ( $P > 0.57$ ). The two SNPs, rs11584383 and rs12122721, are correlated with an  $r^2$  of 0.83.

In particular, the T allele of SNP rs11584383 and the G allele of SNP rs12122721 are overrepresented amongst MS cases compared to controls (Table 1), an effect that is in the same direction as that reported for Crohn's disease[13], ulcerative colitis[16, 17] and for multiple sclerosis[14], respectively. The association with SNP rs12122721 reaches nominal significance with a P value of 0.01. The corresponding odds ratio is 1.21 (95% confidence interval 1.04-1.41). No association was observed with age at onset ( $P > 0.35$ ).

The SNPs investigated here are located in a 170-kb region of high linkage disequilibrium containing three genes: *C1orf106*, *KIF21B* and *CACNA1S*. Kinesin superfamily proteins (KIFs) are molecular motors and are involved in intracellular organelle transport. For another member of the KIF family, *KIF1B*, association with MS was recently reported [18]. However, this association could not be replicated in other studies (International MS Genetics Consortium, unpublished data)[9]. In contrast, the association with *KIF21B* is consistent in a study reported elsewhere [14] as well as in our independent study population. The modest effect size is comparable to that of the susceptibility genes outside of the HLA region that have been identified so far.[1, 2, 3, 4, 5, 6, 7, 8, 9]

*KIF21B* expression is detected in the lungs, brain, testes and thymus.[19, 20] In neurons, *KIF21B* is localized in the dendrites[19] and in the oligodendrocyte lineage *KIF21B* is specifically expressed in the precursor cells[21]. In the immune system expression is highest in  $CD4^+$  and  $CD8^+$  T cells,  $CD56^{\text{bright}}$  NK cells and B cells (T1Dbase, <http://www.t1dbase.org>). The function of *KIF21B* is still unknown. The fact that this gene is associated with at least two autoimmune disorders with the same direction of effect suggests that the mechanism of action may be related to an as yet unraveled function of *KIF21B* in the immune system. Notably, the mouse homologue, *Kif21b*, is located in a region linked to susceptibility (Idd5.4a) for a mouse model for diabetes[22].

In conclusion, we here report additional evidence for *KIF21B* being a susceptibility locus shared between inflammatory bowel disease and multiple sclerosis, suggesting a common pathway involved in the pathogenesis of both diseases.

**Table. Association of SNPs in *KIF21B* with MS.**

Gene	SNP	Chr	Location	Risk Allele	Risk Allele Freq cases	Risk Allele Freq ctrls	P	OR (95% CI)
<i>KIF21B</i>	rs11584383	1	199202489	T	1112/1540 (0.722)	1447/2074 (0.698)	0.11	1.13 (0.97-1.30)
<i>KIF21B</i>	rs12122721	1	200984480	G	1150/1540 (0.747)	1474/2080 (0.709)	0.01	1.21 (1.04-1.41)

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## **COMPETING INTERESTS**

None

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