KIF21B as a shared susceptibility locus between inflammatory bowel disease and multiple sclerosis

An Goris, Steven Boonen, Marie-Béatrice d'Hooghe, Bénédicte Dubois

► To cite this version:

An Goris, Steven Boonen, Marie-Béatrice d'Hooghe, Bénédicte Dubois. KIF21B as a shared susceptibility locus between inflammatory bowel disease and multiple sclerosis. *Journal of Medical Genetics*, 2010, 47 (11), pp.775. 10.1136/jmg.2009.075911 . hal-00557390

HAL Id: hal-00557390

<https://hal.science/hal-00557390>

Submitted on 19 Jan 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Replication of KIF21B as a susceptibility locus for multiple sclerosis

An Goris¹, Steven Boonen², Marie-Béatrice D'hooghe³, Bénédicte Dubois¹

¹Laboratory for Neuroimmunology, Section for Experimental Neurology, Katholieke Universiteit Leuven, Herestraat 49, bus 1022, 3000 Leuven, Belgium

²Leuven University Center for Metabolic Bone Diseases and Division of Geriatric Medicine, University of Leuven, 3000 Leuven, Belgium

³National MS Center Melsbroek, Van Heylenstraat 16, 1820 Melsbroek, Belgium

Corresponding author:

An Goris

Laboratory for Neuroimmunology

Section of Experimental Neurology

O&N2, Herestraat 49, box 1022

3000 Leuven

Belgium

Phone: +32-16-33.07.72.

Fax: +32-16-33.07.70.

E-mail: an.goris@med.kuleuven.be

Keywords: multiple sclerosis, association, genetics, autoimmune disease, kinesin

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^{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)

ACKNOWLEDGEMENTS

We thank all individuals for participating in this study and are grateful to Cindy Thys, Katleen Clijsters and Ann Van Remoortel for their crucial role in patient recruitment and sampling.

This work has been supported by Wetenschappelijk Onderzoek Multiple Sclerose (WOMS). BD is a Clinical Investigator of the Research Foundation Flanders (FWO-Vlaanderen) and holds the *Bayer Chair on fundamental genetic research regarding the neuroimmunological aspects of multiple sclerosis* at the KULeuven, Leuven, Belgium.

COMPETING INTERESTS

None

"The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd to permit this article (if accepted) to be published in Journal of Medical Genetics and any other BMJ PGL products and sublicences such use and exploit all subsidiary rights, as set out in our licence

(<http://group.bmj.com/products/journals/instructions-for-authors/licence-forms>).

REFERENCES

- 1 Gregory SG, Schmidt S, Seth P, Oksenberg JR, Hart J, Prokop A, Caillier SJ, Ban M, Goris A, Barcellos LF, Lincoln R, McCauley JL, Sawcer SJ, Compston DA, Dubois B, Hauser SL, Garcia-Blanco MA, Pericak-Vance MA, Haines JL. Interleukin 7 receptor alpha chain (IL7R) shows allelic and functional association with multiple sclerosis. *Nat Genet* 2007;**39**(9):1083-91.
- 2 International Multiple Sclerosis Genetics Consortium. Risk alleles for multiple sclerosis identified by a genomewide study. *N Engl J Med* 2007;**357**(9):851-62.
- 3 Wellcome Trust Case Control Consortium, Australo-Anglo-American Spondylitis Consortium. Association scan of 14,500 nonsynonymous SNPs in four diseases identifies autoimmunity variants. *NatGenet* 2007;**39**(11):1329-37.
- 4 Ban M, Goris A, Lorentzen AR, Baker A, Mihalova T, Ingram G, Booth DR, Heard RN, Stewart GJ, Bogaert E, Dubois B, Harbo HF, Celius EG, Spurkland A, Strange R, Hawkins C, Robertson NP, Dudbridge F, Wason J, De Jager PL, Hafler D, Rioux JD, Ivinson AJ, McCauley JL, Pericak-Vance M, Oksenberg JR, Hauser SL, Sexton D, Haines J, Sawcer S. Replication analysis identifies TYK2 as a multiple sclerosis susceptibility factor. *Eur J Hum Genet* 2009;**17**:1309-13.
- 5 De Jager PL, Baecher-Allan C, Maier LM, Arthur AT, Ottoboni L, Barcellos L, McCauley JL, Sawcer S, Goris A, Saarela J, Yelensky R, Price A, Leppa V, Patterson N, de Bakker PI, Tran D, Aubin C, Pobywajlo S, Rossin E, Hu X, Ashley CW, Choy E, Rioux JD, Pericak-Vance MA, Ivinson A, Booth DR, Stewart GJ, Palotie A, Peltonen L, Dubois B, Haines JL, Weiner HL, Compston A, Hauser SL, Daly MJ, Reich D, Oksenberg JR, Hafler DA. The role of the CD58 locus in multiple sclerosis. *Proc Natl Acad Sci U S A* 2009;**106**:5264-9.
- 6 International Multiple Sclerosis Genetics Consortium. The expanding genetic overlap between multiple sclerosis and type I diabetes. *Genes Immun* 2009;**10**(1):11-4.
- 7 International Multiple Sclerosis Genetics Consortium. Refining genetic associations in multiple sclerosis. *Lancet Neurol* 2008;**7**(7):567-9.
- 8 De Jager PL, Jia X, Wang J, de Bakker PI, Ottoboni L, Aggarwal NT, Piccio L, Raychaudhuri S, Tran D, Aubin C, Briskin R, Romano S, Baranzini SE, McCauley JL, Pericak-Vance MA, Haines JL, Gibson RA, Naeglin Y, Uitdehaag B, Matthews PM, Kappos L, Polman C, McArdle WL, Strachan DP, Evans D, Cross AH, Daly MJ, Compston A, Sawcer SJ, Weiner HL, Hauser SL, Hafler DA, Oksenberg JR. Meta-analysis of genome scans and replication identify CD6, IRF8 and TNFRSF1A as new multiple sclerosis susceptibility loci. *Nat Genet* 2009;**41**(7):776-82.
- 9 The Australia and New Zealand Multiple Sclerosis Genetics Consortium (ANZGene). Genome-wide association study identifies new multiple sclerosis susceptibility loci on chromosomes 12 and 20. *Nat Genet* 2009;**41**(7):824-8.
- 10 Zhernakova A, van Diemen CC, Wijmenga C. Detecting shared pathogenesis from the shared genetics of immune-related diseases. *Nat Rev Genet* 2009;**10**(1):43-55.
- 11 Hafler JP, Maier LM, Cooper JD, Plagnol V, Hinks A, Simmonds MJ, Stevens HE, Walker NM, Healy B, Howson JM, Maisuria M, Duley S, Coleman G, Gough SC, Worthington J, Kuchroo VK, Wicker LS, Todd JA. CD226 Gly307Ser association with multiple autoimmune diseases. *Genes Immun* 2008;**10**(1):15-7.
- 12 Rubio JP, Stankovich J, Field J, Tubridy N, Marriott M, Chapman C, Bahlo M, Perera D, Johnson LJ, Tait BD, Varney MD, Speed TP, Taylor BV, Foote SJ, Butzkueven H, Kilpatrick TJ. Replication of KIAA0350, IL2RA, RPL5 and CD58 as multiple sclerosis susceptibility genes in Australians. *Genes Immun* 2008;**9**(7):624-30.
- 13 Barrett JC, Hansoul S, Nicolae DL, Cho JH, Duerr RH, Rioux JD, Brant SR, Silverberg MS, Taylor KD, Barmada MM, Bitton A, Dassopoulos T, Datta LW, Green T, Griffiths AM, Kistner EO, Murtha MT, Regueiro MD, Rotter JI, Schumm LP, Steinhardt AH, Targan SR, Xavier RJ, Libioulle C, Sandor C, Lathrop M, Belaiche J, Dewit O, Gut I, Heath S, Laukens D, Mni M, Rutgeerts P,

- Van Gossum A, Zelenika D, Franchimont D, Hugot JP, de Vos M, Vermeire S, Louis E, Cardon LR, Anderson CA, Drummond H, Nimmo E, Ahmad T, Prescott NJ, Onnie CM, Fisher SA, Marchini J, Ghorri J, Bumpstead S, Gwilliam R, Tremelling M, Deloukas P, Mansfield J, Jewell D, Satsangi J, Mathew CG, Parkes M, Georges M, Daly MJ. Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease. *Nat Genet* 2008;**40**(8):955-62.
- 14 International Multiple Sclerosis Genetics Consortium. Comprehensive Follow-up of the First Genome-Wide Association Study of Multiple Sclerosis identifies KIF21B and TMEM39A as Susceptibility Loci. *Hum Mol Genet* 2009;e-pub ahead of print.
- 15 Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, Maller J, Sklar P, de Bakker PI, Daly MJ, Sham PC. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet* 2007;**81**(3):559-75.
- 16 Franke A, Balschun T, Karlsen TH, Hedderich J, May S, Lu T, Schuldt D, Nikolaus S, Rosenstiel P, Krawczak M, Schreiber S. Replication of signals from recent studies of Crohn's disease identifies previously unknown disease loci for ulcerative colitis. *Nat Genet* 2008;**40**(6):713-5.
- 17 Anderson CA, Massey DC, Barrett JC, Prescott NJ, Tremelling M, Fisher SA, Gwilliam R, Jacob J, Nimmo ER, Drummond H, Lees CW, Onnie CM, Hanson C, Blaszczyk K, Ravindrarajah R, Hunt S, Varma D, Hammond N, Lewis G, Attlesey H, Watkins N, Ouwehand W, Strachan D, McArdle W, Lewis CM, Lobo A, Sanderson J, Jewell DP, Deloukas P, Mansfield JC, Mathew CG, Satsangi J, Parkes M. Investigation of Crohn's disease risk loci in ulcerative colitis further defines their molecular relationship. *Gastroenterology* 2009;**136**(2):523-9 e3.
- 18 Aulchenko YS, Hoppenbrouwers IA, Ramagopalan SV, Broer L, Jafari N, Hillert J, Link J, Lundstrom W, Greiner E, Dessa Sadovnick A, Goossens D, Van Broeckhoven C, Del-Favero J, Ebers GC, Oostra BA, van Duijn CM, Hintzen RQ. Genetic variation in the KIF1B locus influences susceptibility to multiple sclerosis. *Nat Genet* 2008;**40**(12):1402-3.
- 19 Marszalek JR, Weiner JA, Farlow SJ, Chun J, Goldstein LS. Novel dendritic kinesin sorting identified by different process targeting of two related kinesins: KIF21A and KIF21B. *J Cell Biol* 1999;**145**(3):469-79.
- 20 Harada M, Ishihara Y, Itoh K, Yamanaka R. Kinesin superfamily protein-derived peptides with the ability to induce glioma-reactive cytotoxic T lymphocytes in human leukocyte antigen-A24+ glioma patients. *Oncol Rep* 2007;**17**(3):629-36.
- 21 Dugas JC, Tai YC, Speed TP, Ngai J, Barres BA. Functional genomic analysis of oligodendrocyte differentiation. *J Neurosci* 2006;**26**(43):10967-83.
- 22 Hunter K, Rainbow D, Plagnol V, Todd JA, Peterson LB, Wicker LS. Interactions between Idd5.1/Ctla4 and other type 1 diabetes genes. *J Immunol* 2007;**179**(12):8341-9.