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Polymorphic locus rs10492972 of the *KIF1B* gene association with multiple sclerosis in Russia: Case control study

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ABSTRACT

Axonal degeneration is responsible for the progression of the irreversible destruction caused by multiple sclerosis (MS) resulting ultimately in permanent disability. The KIF1B protein, a member of the kinesin family, is necessary for axon growth and myelination in vertebrates. In the recent paper, Aulchenko et al. suggested that the rs10492972[C] variant of *KIF1B* increases susceptibility to MS, but three following replication study didn't confirm this association. We studied the association of the polymorphic locus rs10492972 present in the *KIF1B* gene with genetic predisposition and its occurrence in clinical presentations of MS patients resident in western Siberia and the Sakha Republic (Yakutia), Russia. rs10492972 has been genotype in 833 samples of MS patient and 689 healthy controls. Distribution of rs10492972 genotypes corresponded with a Hardy–Weinberg distribution in both the MS patient and control groups, with the frequency of the C allele being the same in both groups (33%). Frequencies of occurrence of the genotypes were not shown to be associated with different disease courses or other characteristics of the disease, such as age at onset or duration. A complete meta-analysis of all analogous studies published to date showed that the protective effect of the rs10492972 [C] allele is statistically significant (OR = 0.95, C.I.95% [0.90–0.99], $p = 0.02$).

1. Introduction

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) that destroys myelin. It is caused by autoimmune reactions to the myelin proteins and is characterized by various degrees of demyelination and axonal damage to the CNS. It is generally thought that axonal degeneration is responsible for the progression of the irreversible destruction that leads to permanent disability [1].

The myelin sheath which is destroyed in MS, acts as an electrical insulator increasing the rate of nerve pulses along the axons that it surrounds. In addition to the transfer of nerve pulses, myelin participates in the nourishment of nerve fibers and plays a structural and protective role. Remyelination occurs simultaneously with demyelination and this is especially noticeable at the margins of active patches. The further the progression of MS, the less pronounced the remyelination process, which may be related to a significant decrease in the number of oligodendrocytes. The rate of synthesis of myelin structural components such as the myelin basic protein (MBP) can affect the remyelination processes. Lyons et al. [2] showed that the KIF1B protein, which is encoded by the *KIF1B* gene and is a member of the kinesin family involved in cellular transport, is necessary for correct localization of MBP mRNA in zebrafish (*Danio rerio*) oligodendrocytes. The researchers observed a mutation in the *KIF1B* gene, resulting in an amino-acid substitution (Thr → Pro). This substitution was situated in the alpha loop in which the interaction site with microtubules in the kinesin motor is presumably located. The mRNA required for synthesis of myelin proteins

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is found in zebrafish carrying this mutation, within oligodendrocyte cells, and not at active sites of new myelin formation. Axons grow slower in *KIF1B* gene mutants than in carriers of the wild-type *KIF1B* gene. It is notable that the zebrafish KIF1B protein is highly homologous to human KIF1B; isoforms of zebrafish and human KIF1Ba protein are 78% identical and KIF1Bb, 87%. Extending this data to mammals, it can be assumed that disruptions in expression of the *KIF1B* gene or structural polymorphisms of the protein encoded by it, can affect the demyelination/remyelination processes and therefore, the risk of developing MS and its course [2,3].

The pioneering research of Aulchenko et al. [4], which was performed using genome-wide association analysis, identified an association of the rs10492972 polymorphism in the *KIF1B* gene with MS development [Odds ratio (OR) = 1.35, (95% CI: 1.23–1.48), $p = 2.5 \times 10^{-10}$]. Despite the high OR, level of statistical significance and biological relevance, an Italian, Greece populations and populations included in the International Multiple Sclerosis Genetics Consortium (IMSGC) and in the Australia and New Zealand Multiple Sclerosis Genetics Consortium (ANZgene) could not replicate this association [5–8].

Considering the regional nature of environmental and genetic factors contributing to the development of MS, our goal was to study the role of the polymorphic locus rs10492972 situated in the *KIF1B* gene in the predisposition and course of this disease in residents of western Siberia and the Sakha Republic (Yakutia), Russia.

2. Methods

2.1. MS patient population and control group

The MS patient population was comprised of 833 people (583 women and 250 men, mean age ± SD: 36.3 ± 10.9, mean age of disease onset ± SD: 27.4 ± 9.1). A total of 555 patients had relapsing MS (RMS); 45 patients had primary progressive relapsing MS (PPMS); and 233 patients secondary progressive relapsing MS (SPMS). Patients from the following organizations were invited to participate in the study: Omsk State Medical Academy (Omsk), n = 265; State Health Facility Kemerovo Oblast Clinical Hospital (Kemerovo), n = 191; Neurology and Neurosurgery Department, Siberian Chief Medical Administration, Ministry of Health (Tomsk), n = 116; Territorial Clinical Hospital (Barnaul), n = 107; Novosibirsk Oblast State Clinical Hospital (Novosibirsk), n = 100; Republican Hospital No. 2, Ministry of Health, Sakha Republic (Yakutia) (Yakutsk), n = 54. All patients participating in the study were members of the European Russian ethnic group.

The diagnostic criteria of McDonald et al. were applied to the MS patients [9]. All patients underwent a standard clinical examination, including medical history, physical and neurological examination, general laboratory diagnostics and brain MRI. Patients were surveyed to collect information on demographics (age, sex, place of birth, nationality), medical (age of MS onset, course of disease, duration of disease on the Expanded Disability Status Scale (EDSS) [10]), and genetic status (relatives presenting with MS).

The control group (n = 689) comprised of people without inflammatory CNS disease living in Novosibirsk (n = 572) and Barnaul (n = 117) (250 men and 439 women, mean age ± SD: 32.8 ± 11.8). The study was approved by local ethics committees and all participants signed informed consent forms.

2.2. Genotyping

DNA was isolated from venous blood using a standard procedure, briefly this consisted of separation and lysis of blood cells, hydrolysis of proteins by proteinase K, purification of DNA by extraction of impurities with phenol-chloroform and precipitation of DNA with ethanol. Genotyping of the single-nucleotide substitution of rs10492972 in the *KIF1B* gene was performed by real time PCR using competing TaqMan probes (forward primer 5′-GGTGGTGAGTTTT-GAATTGGTAC-3′; reverse primers 5′-AAAAAGTTATGTGACCAGGATAG-3′; 5′-FAM-TCGCTACAATTCTTCTGGTCAGG-BHQ-3′; 5′-R6G-TCGCTA-CAATTCTCCTGGTCAGG-BHQ-3′). The PCR mixture contained DNA (40–100 ng), each primer (300 nM), TaqMan probes conjugated with FAM or R6G (100–200 nM each), dNTPs (200 μM), amplification buffer, and thermally stable Taq-polymerase (0.5 U/reaction) in a total volume of 25 μL. Amplification was performed in an iCycler iQ5 (Bio-Rad, USA) under the following conditions: initial denaturation for 3 min at 96 °C then 40 cycles consisting of denaturation at 96 °C for 8 s, then annealing of primers and subsequent elongation at 60 °C for 35 s.

2.3. Statistical data analysis

The normality of the data distribution was estimated using the Shapiro–Wilkes criterion. The null hypothesis was that the quantitative indicator had a normal distribution and the quantitative indicators were described by the median and interquartile spread (25 and 75 percentile) or mean ± SD. Age differences of patients were analyzed using the Mann–Whitney U-criterion, with the null hypothesis being that the groups did not differ. Possible associations among age of onset, disease duration, EDSS and mean progression rate were determined using linear regression analysis, whilst that of genotype with disease development was found using logistic regression analysis ['GenABEL' application in programming language R (version 2.11.0)]. Power calculations were performed with the program of Purcell et al. [11] (available at http://pngu.mgh.harvard.edu/~purcell/gpc/).

Tests for observance of the Hardy–Weinberg equilibrium were performed using the DeFinetti program on the website of the Institute of Human Genetics (Munich, Germany; http://ihg2.helmholtz-muenchen.de/cgi-bin/hw/hwa1.pl).

Meta-analysis was carried out using the 'rmeta' application in programming language R (version 2.11.0). The Cochran test was used to estimate the frequency heterogeneity of the populations library rmeta, R (version 2.11.0)].

Results were considered statistically significant for all statistical calculations if $p < 0.05$.

3. Results

Clinical characteristics of MS patients included in the study are given in Table 1. The control group corresponded in age ($p = 0.07$) and sex with the MS patient population. The sub-groups sizes, based on differing disease course had a distribution of 0.0036 and the risk allele at the polymorphic locus occurred with a frequency of 0.34, resulting in an association with an OR ≥ 1.25 to be found with 80% power at the 0.05 statistical significance level.

Table 1
Characteristics of MS patients and people included in the control group.

	MS patients	Control group	*p* value
Total number of patients	833	689	
Age (years) (mean ± SD)	36.3 ± 10.9	32.8 ± 11.8	0.07
Sex, men:women	250:583	250:439	
PPMS/SPMS/RMS	45/233/555		
Age of onset (years) (mean ± SD)	27.4 ± 9.1		
EDSS (median and quartile)	3.5 (2.0–4.0)		
Disease duration (years) (median and quartile)	7.0 (3.0–13.0)		
Rate of disease progression (median and quartile)	0.50 (0.21–1.00)		
Relatives with MS (immediate family) (%)	54/779 (0.06%)		
Smoker yes/no	132/701		
Multivitamin taker yes/no	104/729		

MS patients and control group were compared by age using the Mann–Whitney method.

The distribution of rs10492972 genotypes corresponded with a Hardy–Weinberg distribution in the MS patient and control groups ($p = 0.59$ and $p = 0.77$, respectively). The frequency of occurrence of the C allele in the control and MS patient groups was the same, 0.33. When the study participants were divided into groups according to sex, the frequency of occurrence of the C allele did not change in either the control or MS patient groups (C, 0.33; T, 0.67).

Differences in the frequencies of genotype occurrence between the MS patient population and the control group were estimated using logistic regression. Analysis was performed for three inheritance models: additive, dominant, and recessive. Furthermore, patients with different types of MS disease course were divided into subpopulations (RMS, PPMS, and SPMS). The frequencies of occurrence of the genotypes in the control group did not differ statistically significantly from those in the RMS, PPMS and SPMS subpopulations or in the population including all MS patients in our study (Table 2).

The effect of genotype on characteristics of the disease course such as age at disease onset, duration, EDSS and mean progression rate was studied by linear regression analysis, however a statistically significant effect of genotype on the clinical disease characteristics was not found (Table 3).

A meta-analysis was undertaken combining our results with those previously published [4–8]. The meta-analysis included: data from our own study, the studies by Aulchenko et al. (populations in The Netherlands, Sweden, and Canada), the studies by Martinelli-Boneschi et al. (population in Italy), studies by Booth et al. (populations in Australia, Belgium, Finland, Italy, Norway, Sweden, Great Britain, USA), studies by Koutsis et al. (population in Greece) and studies by ANZgene (population in Australia and New Zealand). All studies included in the meta-analysis, with the exception of those performed with populations from Italy, Greece and Australia, had power > 80%. In the first meta-analysis, the total OR for all studies was 1.02 (95% CI: 0.97–1.06) with a statistical significance of $p = 0.46$. However, the heterogeneity test (Q-test) revealed significant differences within the groups ($p < 6.8 \times 10^{-07}$) (Fig. 1a).

Because of the statistically significant level of heterogeneity amongst the studies included in the meta-analysis, we made an estimate of the heterogeneity of the control groups using the frequency of occurrence of the C allele (Table 4) and the Cochran test (Q-test). According to the test results, the control groups in the studies differed significantly in the frequency of the C allele ($\chi^2 = 91.95$, df = 12, $p < 0.0001$). After excluding the control group from the pilot study of Aulchenko et al., significant differences in the frequencies of occurrence of the C allele were not found according to the Q-test between the remaining control groups ($\chi^2 = 15.67$, df = 11, $p = 0.15$). Therefore, we performed a second meta-analysis, excluding from it the results of Aulchenko et al. and here the heterogeneity test (Q-test) did not find any significant differences between the studies ($p = 0.81$). Moreover, the frequency of the C allele according to this second meta-analysis results was greater in the control group than in the MS group (32.3% vs. 31.7%), not as was shown by Aulchenko et al. (total OR = 0.95 (95% CI: 0.90–0.99) with statistical significance level $p = 0.02$) (Fig. 1b).

Table 3
Association of quantitative parameters with genotype at the polymorphic locus rs 10492972 on *KIF1B* gene.

	b	SE_b	OR	p value
Age of onset	−0.289	0.47605	0.75 (0.29–6.98)	0.54
Disease duration	0.0214	0.03485	1.02 (0.95–7.67)	0.54
EDSS	0.012	0.03481	1.01 (0.95–7.53)	0.73
Rate of disease progression	−0.015	0.03807	0.99 (0.91–7.16)	0.69

b, regression coefficient, SE_b, standard error of the regression coefficient; OR and p value, odds ratio and statistical significance of the results calculated by linear regression analysis.

4. Discussion

Association of the polymorphic locus rs10492972 located in intronic area of the *KIF1B* gene with MS development is currently widely debated [4–8]. Despite the high statistical power in the completed replication studies and the potential explanatory role of kinesin KIF1B in the molecular mechanisms of disease initiation, association with the C allele of the studied locus remains unconfirmed. We also studied the effect of this polymorphic locus on the predisposition to develop MS. MS patients were divided into subpopulations depending on the type of disease course (RMS, PPMS, SPMS) for a more complete analysis of the relationship of the polymorphic locus to MS, furthermore, three inheritance models: additive, dominant, and recessive, were analyzed. However, statistically significant differences in the frequencies of occurrence of the genotypes were not found between the control group and any of the MS patient subpopulations.

We hypothesized that the polymorphic locus rs10492972 of the *KIF1B* gene may be connected with clinical characteristics of the disease such as age of disease onset, duration of the disease before participation of the patient in the study, status of patient disability (EDSS), and possibly, the rate of disease progression. However, we also did not observe an effect of this polymorphic locus on these MS characteristics in the studied patients.

Two meta-analyses were performed in order to combine data published by researchers for different populations on the association of the polymorphic locus rs10492972 of the *KIF1B* gene and MS. The first meta-analysis included results of all these studies and showed significant heterogeneity in the analyzed data. This was attributed to differences in the frequencies of occurrence of the C allele in the control groups ($p < 0.0001$). Excluding results obtained in the study by Aulchenko et al., we performed a second meta-analysis. According to the Q-test result, the heterogeneity of the data was under the allowed level and moreover, the C allele was shown to be a statistically significant protective factor for MS development according to the results of this second meta-analysis [OR = 0.95 (95% CI: 0.90–0.99), $p = 0.02$].

Table 2
Odds ratio calculation for different inheritance models.

Group	Number of patients with genotype, n			Model of genetic indicator		
				Additive	Dominant	Recessive
	T/T	T/C	C/C	OR_{AD} (C.I.:95%) p $value_{AD}$	OR_D (C.I.:95%) p $value_D$	OR_R (C.I.:95%) p $value_R$
Total MS	381	362	90	0.99 (0.84–1.16) $p = 0.88$	0.96 (0.78–1.19) $p = 0.69$	1.05 (0.76–1.47) $p = 0.75$
RMS	260	239	56	0.95 (0.79–1.12) $p = 0.53$	0.92 (0.73–1.15) $p = 0.45$	1.97 (0.67–1.42) $p = 0.90$
PPMS	18	24	3	1.03 (0.63–1.66) $p = 0.92$	1.21 (0.66–2.24) $p = 0.54$	0.62 (0.19–2.06) $p = 0.44$
SPMS	103	99	31	1.08 (0.87–1.35) $p = 0.49$	1.08 (0.87–1.35) $p = 0.49$	1.34 (0.85–2.10) $p = 0.21$
Control	308	310	71			

AD, additive inheritance model; D, dominant inheritance model; R, recessive inheritance model. OR_{AD}, odds ratio calculated using logistic regression analysis for the additive inheritance model; OR_D, odds ratio calculated using logistic regression analysis for the dominant inheritance model; OR_R, odds ratio calculated using logistic regression analysis for the recessive inheritance model.

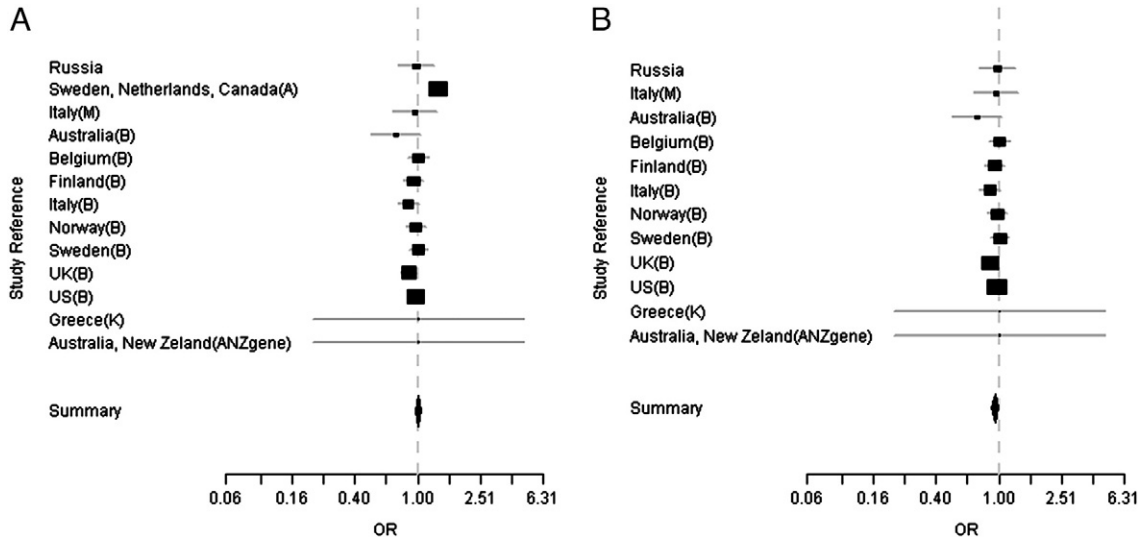

Fig. 1. Meta-analyses. A—meta-analysis including all studies. B—meta-analysis results excluding the study by Aulchenko et al. (A)—from the study by Aulchencko et al.; (B)—from the study by Booth et al.; (M)—from the study by Martinelli-Boneschi et al.; (K)—from the study by Koutsis et al.; (ANZgene)—from the study by The Australia and New Zealand Multiple Sclerosis Genetics Consortium.

Considering the involvement of KIF1B in myelination [3], such contradictory results from different researchers appears intriguing. Hintzen et al. proposed several hypotheses in order to explain these contradictory results [6]. One of these was a mistaken genotyping, which is observed very often as a result of a deviation of the genotype distribution from the Hardy–Weinberg distribution, not only in the patient population but also in the control group. Hintzen et al. noted that the genotype distribution in the study by Booth et al. in the control group for the British population did not obey the Hardy–Weinberg law ($p = 0.04$), and it was close to the statistically significant limiting value ($p = 0.08$) for the control group of the Italian population. For the Italian population, an association with the C allele was not demonstrated (OR = 0.873, 95% CI: 0.745–1.024, $p = 0.10$), however, for the British population, the C allele was a protective factor for MS development (OR = 0.879, 95% CI: 0.786–0.982, $p = 0.02$). This contradicts the results from the study by Aulchenko et al. which was an integral part of our second meta-analysis. Nevertheless, the genotype distribution in our study obeyed the Hardy–Weinberg law in both the control group and MS patient population ($p = 0.77$ and $p = 0.59$, respectively), however the OR was close to unity and did not show an association. Another hypothesis proposed by Hintzen et al. was concerning the fact that the gene may not affect predisposition to the disease but characteristics such as the age of MS onset. Hintzen et al. observed that MS patients living in The Netherlands and participating in the study exhibited differences in the age of disease onset for carriers of different genotypes that were nearly significant ($p = 0.09$). However, such a tendency was not observed for MS patients living in western Siberia and the Sakha Republic (Yakutia) ($p = 0.54$), or incidentally was there an effect of the genotype on the disability status or the rate of disease progression. The statistically significant protective effect of the C allele of the rs10492972 polymorphism obtained as a result of our meta-analysis keeps the question unanswered and does not allow the *KIF1B* gene to be dropped from the list of candidates for genetic predictors of MS risk. Notably, rs12122721 located in an intron of *KIF21B* was found to be associated with multiple sclerosis [12,13]. Moreover, rs11584383 located downstream of *KIF21B* was found to be associated with other autoimmune disease, Crohn's disease [14]. Both *KIF21B* and *KIF1B* are the members of kinesin superfamily (KIF). This fact allows to propose that genes of kinesis superfamily play role in predisposition to autoimmune disease. In summary, the disparate results from studies on large populations indicate that further research on the involvement of this region of the genome in the pathogenesis and clinical presentation of MS

Table 4
Frequencies of occurrence of C allele at the polymorphic locus rs10492972 on the *KIF1B* gene.

Cohort	MS group, n	Control group, n	Frequency of C allele in MS group	Frequency of C allele in control group	OR_C	*p* value
Russian	833	689	0.33	0.33	0.99	0.88
Italian[M]	221	222	0.34	0.33	0.96	0.81
Swedish[A]	826	997	0.34	0.29	1.30	0.0003
Dutch outbread[A]	490	426	0.34	0.27	1.42	0.0009
Canada[A]	1318	1507	0.31	0.27	1.31	0.0012
Australian[B]	159	120	0.31	0.38	0.73	0.09
Belgian[B]	795	970	0.31	0.31	1.01	0.93
Finnish[B]	793	984	0.34	0.35	0.94	0.39
Italian[B]	831	647	0.30	0.33	0.87	0.10
Norwegian[B]	738	1212	0.31	0.32	0.98	0.75
Swedish[B]	1239	736	0.32	0.31	1.01	0.84
British[B]	1384	1540	0.30	0.33	0.88	0.02
American[B]	2452	1843	0.32	0.33	0.97	0.53
Greek[K]	609	230	0.31	0.31	1.00	0.99
Australian and New Zealand Consortium[ANZgene]	3874	5723	0.32	0.32	1.00	0.99

OR_C—OR is provided of the C allele comparison with the T reference group according to a logistic regression model adjusted for age and sex.
A—from study by Aulchencko et al.; B—from study by Booth et al.; M—from study by Martinelli-Boneschi et al.; (K)—from the study by Koutsis et al.; (ANZgene)—from the study by The Australia and New Zealand Multiple Sclerosis Genetics Consortium.

is required. Re-sequencing of this genome section will probably shed light on the reasons for the opposing results and enable the functional genetic polymorphism of this gene to be found.

In conclusion, our study did not show an effect of genotype rs10492972 on MS risk and clinical characteristics of the disease in patients living in western Siberia and the Sakha Republic (Yakutia), however the meta-analysis showed a statistically significant ($p = 0.02$) protective effect of the C allele of the rs10492972 polymorphism.

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Conflict of interest

The authors declare no conflicts of interest.

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