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# *MAPT* gene rs1052553 variant is not associated with the risk for multiple sclerosis

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ABSTRACT

*Background/Objectives:* Some experimental data suggest a possible role of tau protein in the pathogenesis of multiple sclerosis (MS) and in experimental autoimmune encephalomyelitis. The aim of this study was to investigate a possible influence of the SNP rs1052553 in the *MAPT* gene in the risk for relapsing bout onset (relapsing–remitting and secondary progressive) MS.
*Methods:* We analyzed the allelic and genotype frequency of *MAPT* rs1052553, which has been associated with some neurodegenerative diseases, in 259 patients with relapsing bout onset MS and 291 healthy controls, using *TaqMan* Assays.
*Results:* *MAPT* rs1052553 allelic and genotype frequencies did not differ significantly between relapsing bout onset MS patients and controls, and were unrelated with the age of onset of MS or gender.
*Conclusions:* These results suggest that *MAPT* rs1052553 polymorphism is not related with the risk for relapsing bout onset MS.
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## 1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disorder with axonal degeneration affecting the Central Nervous system. The etiology of MS is unknown, but likely multifactorial, with an interplay of genetic, ethnic, geographical and environmental factors (infectious or chemical) [1–5]. Some authors proposed that MS is an autoimmune disorder with susceptibility influenced, if not determined, by a relatively small number of genes [1]. Findings from studies on seasonality in MS patients' birth, disease onset and exacerbations, as well as apparent temporal trends in incidence and gender ratio support an influential effect of viruses, metabolic and lifestyle factors on MS risk. Epstein–Barr virus, vitamin D status, and smoking are factors that may explain such epidemiological patterns [4].

A haplotype within the major histocompatibility region is the major risk factor for MS, but despite clear evidence for a genetic component additional risk variants were not identified until the recent advent of genome-wide association studies (GWAS). Until 2010, 11 GWAS have been conducted in MS, and together with follow-up studies these have confirmed 16 loci with genome-wide significance [6,7]. Many of these common risk variants are located at or near genes with central immunological functions (such as *interleukin 2* and *7 receptors*, *CD58*, *CD6*, *CD40*, *TNFRSF1A* and others) and the majority are associated with other autoimmune diseases [6,7]. A further report of the International Multiple Sclerosis Genetics Consortium identified at least 50 loci related with the risk for MS [8,9]. However, all loci except HLA showed

*Abbreviations:* MS, multiple sclerosis; GWAS, genome-wide association studies; *TNFRSF1A*, tumor necrosis factor receptor superfamily member 1A; CSF, cerebrospinal fluid; TPPP/p25, tubulin polymerization promoting protein 25; *MAPT*, microtubule-associated protein tau; SNP, single nucleotide polymorphism.

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**Table 1**
*MAPT* rs1052553 genotype and allelic variants of patients with multiple sclerosis (MS) and healthy volunteers. The values in each cell represent: number (percentage; 95% confidence intervals CI).

| | Genotypes | | | Alleles | |
|---|---|---|---|---|---|
| | *MAPT* rs1052553 *A/A* | *MAPT* rs1052553 *A/G* | *MAPT* rs1052553 *G/G* | *MAPT* rs1052553 *A* | *MAPT* rs1052553 *G* |
| MS patients wITH bout onset (*N* = 259, 518 alleles) | 125 (48.3; 42.2–54.3) | 117 (45.2; 39.1–51.2) | 17 (6.6; 3.5–9.6) | 367 (70.8; 66.9–74.8) | 151 (29.2; 25.2–33.1) |
| Relapsing–remitting MS (*N* = 165; 330 alleles) | 80 (48.5; 40.9–56.1) | 73 (44.2; 36.7–51.8) | 12 (7.3; 3.3–11.2) | 233 (70.6; 65.7–75.5) | 97 (29.4; 24.5–34.3) |
| Secondary progressive MS (*N* = 94; 188 alleles) | 45 (47.9; 37.8–58.0) | 44 (46.8; 36.7–56.9) | 5 (5.3; 0.8–9.9) | 134 (71.3; 64.8–77.7) | 54 (28.7; 22.3–35.2) |
| Controls (*N* = 291, 582 alleles) | 158 (54.3; 48.6–60.0) | 111 (38.1; 32.6–43.7) | 22 (7.6; 4.5–10.6) | 427 (73.4; 69.8–77.0) | 155 (26.6; 23.0–30.2) |
| Intergroup comparison values OR (95% CI); P | | | | | |
| Total bout onset MS vs. Controls | 0.79 (0.55–1.11); 0.158 | 1.34 (0.94–1.91); 0.095 | 0.86 (0.42–1.73); 0.650 | 0.88 (0.67–1.16); 0.352 | 1.13 (0.86–1.49); 0.352 |
| RRMS vs. Controls | 0.79 (0.53–1.18); 0.233 | 1.29 (0.86–1.93); 0.203 | 0.96 (0.43–2.10); 0.911 | 0.87 (0.64–1.19); 0.370 | 1.15 (0.84–1.57); 0.370 |
| SPMS vs. Controls | 0.77 (0.47–1.26); 0.279 | 1.43 (0.87–2.34); 0.137 | 0.69 (0.22–1.99); 0.460 | 0.90 (0.62–1.32); 0.575 | 1.11 (0.76–1.63); 0.575 |

modest OR in the range of 1.1–1.3 [10]. In particular the association between MS and the *HLA-DRB1*15:01* haplotype has been proven to be strong.

Although MS is the prototype of demyelinating disease, nowadays it is well known that the presence of axonal damage is an important factor in the progression of the disease [11]. Moreover, some authors showed that cerebrospinal fluid (CSF) from patients with "aggressive" MS beared soluble mediators that were able to induce axonal damage and apoptosis of neurons in culture [12]. Although the underlying molecular mechanisms for the axonal degeneration are unknown, the degree of inflammatory demyelination correlates with the extent of axonal damage, suggesting an involvement of the proinflammatory mediators in inducing axonal degeneration [11]. However, the alternative possibility that axonal regeneration should be severely impaired in MS lesions could be suggested, because an accumulation of glial scar and neurite growth inhibitors provide a non-permissive environment for regrowth of damaged axons [13].

Tau protein is considered to be important for maintaining the stability of axonal microtubules involved in the mediation of fast axonal transport of synaptic constituents. Following neuronal damage, tau is released into extracellular space and may be increased in the CSF [14]. Several neuropathological and experimental data have suggested a possible role of tau protein in the pathogenesis of MS and experimental autoimmune encephalomyelitis [15–18].

Mutations in the microtubule-associated protein tau gene (*MAPT*) cause frontotemporal dementia [19] and a *MAPT* haplotype designated as H1 has shown association with the risk for developing other degenerative conditions such as Parkinson's disease [20–25], progressive supranuclear palsy [20,26,27], corticobasal degeneration [20], and multiple system atrophy [28], whereas additional studies showed a lack of association with other neurological disorders such as restless legs syndrome [29] or essential tremor [30].

Despite *MAPT* polymorphisms are not mentioned among the possible susceptibility genes in GWAS studies, the possible role of tau protein in the pathogenesis of MS makes it reasonable to analyse the possible relationship between *MAPT* gene polymorphisms and the risk of MS. To our knowledge, there is only one report published addressing the possible role of the SNP rs9468 in this gene in MS, which included 937 trio families (an affected individual and their both parents) and showed lack of association [31]. In an attempt to identify additional factors involved in MS susceptibility, we mapped the SNP rs1052553 in the *MAPT* gene, which is indicative of the H1 haplotype, in patients with MS and in healthy subjects.

## 2. Materials and methods

### 2.1. Patients and controls

We recruited 303 unrelated Caucasian Spanish patients who fulfilled the McDonald's criteria for definite MS [32] with no other previous neurological diseases. Recruiting sources were the following: the "Multiple Sclerosis Association of Madrid"; *n* = 175 cases), the Health Areas of the Hospital La-Mancha-Centro (Alcázar de San Juan, Ciudad Real; *n* = 65 cases), and University Hospitals "Doce de Octubre" (Madrid, 32 cases), and "Príncipe de Asturias" (Alcalá de Henares, Madrid; *n* = 31 cases). Most of these patients participated in previous studies of genetic association with MS risk [33–36].

Because relapsing MS with bout onset (relapsing–remitting MS and secondary progressive MS) is quite different from pathogenesis of primary progressive MS, we analysed relapsing bout onset MS subgroup separately (165 relapsing–remitting, 94 secondary progressive; 73 men, 186 women, mean age 42.1 ± 11.3 years, mean age at onset 31.3 ± 10.0 years; mean ± SD expanded disability status scale or EDSS 3.3 ± 2.5). We also analyzed 44 patients with primary progressive MS (23 men, 22 women, mean age 54.4 ± 10.2 years, mean age at onset 43.4 ± 11.6 years mean ± SD EDSS 6.8 ± 0.9).

The control group was composed of 291 healthy unrelated Caucasian Spanish individuals age-matched with the patients (145 men, 146 women; mean age 43.8 ± 12.4 years). Controls were healthy unrelated Caucasian Spanish individuals, most of them students or staff from the University of Extremadura. The "normality" in the control group was established on the basis of an interview and biochemical measurements of blood count, routine biochemistry, and a coagulation study.

All the participants were included in the study after giving written informed consent. The protocol was approved by the Ethics Committees of the University Hospitals "Príncipe de Asturias" and "Infanta Cristina" (Badajoz). The study was conducted according to the principles expressed in the declaration of Helsinki.

### 2.2. Genotyping for rs1052553

Genotyping for rs1052553 allelic variant was performed in genomic DNA obtained from venous blood samples of participants using *TaqMan* Assays (C_7563736_10, Applied Biosciences Hispania, Alcobendas, Madrid, Spain) designed to detect the SNP rs1052553. Detection was carried out by qPCR in an Eppendorf realplex thermocycler. The amplification conditions were as follows: after a denaturation time of 10 min at 96 °C, 45 cycles of 92 °C 15 s 60 °C 90 s were carried out and fluorescence was

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