# The *APOE* ε2 Allele Increases the Risk of Earlier Age at Onset in Machado-Joseph Disease

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**ABSTRACT**

***Background.*** Machado-Joseph disease (MJD) is an autosomal dominant neurodegenerative disorder of late onset, caused by a $(CAG)_n$ expansion at the *ATXN3* gene (14q32.1). Variation in age-at-onset is partially explained by the size of the $(CAG)_n$ tract in expanded alleles. The remaining variation should be the product of other factors, namely modifier genes. The genotype at the *APOE* locus has been described as a possible modifier in different neurological disorders, namely Parkinson (PD) and Huntington disease (HD). In the CNS, apolipoprotein E constitutes an important mediator of cholesterol transport/metabolism, which is essential for synaptic integrity and neuronal function.

***Objective.*** To investigate a modulating effect of the *APOE* polymorphism on age-at-onset of MJD.

***Design and Subjects.*** The *APOE* polymorphism was typed in a series of 192 MJD patients.

***Results.*** Cases with the ε2/ε3 genotype presented an earlier onset, when compared with those with ε3/ε3 or ε3/ε4. In this series of patients, the presence of an *APOE* ε2 allele implies a decrease of nearly 5 years in the age-at-onset. When combining, in a general linear model, several other predictors, namely the presence/absence of the *APOE* ε2 allele, with the size of the $(CAG)_n$ in expanded alleles, the model was significantly improved and the explanation of onset variance was raised from 59.8% to 66.5%. Furthermore, the presence of the ε2 allele was associated with an onset below 39 years (OR=5.00; 95% CI: 1.18-21.14).

***Conclusions.*** These findings indicate that the polymorphism at the *APOE* gene plays a role as a genetic modifier of MJD phenotype.

**INTRODUCTION**

Machado-Joseph disease (MJD), also known as spinocerebellar ataxia type 3 (SCA3), is an autosomal dominant neurodegenerative disorder of late onset, caused by an expansion of a $(CAG)_n$ in the coding region of *ATXN3* (14q32.1), encoding for ataxin-3.[1, 2] MJD is the most frequent type of SCA,[3] and reaches its highest worldwide value of prevalence in the Azores islands (Portugal).[4] Wild-type *ATXN3* alleles comprise 12 to 44 CAG repeats, whereas expanded alleles consensually have more than 52 repeat units.[5, 6] MJD presents clinical heterogeneity, namely on what concerns the age-at-onset, with a mean around 40 years, but with extremes of 4[7] to 70 years.[8] Variation in the age-at-onset is only partially explained (~50-75%)[9, 10] by the size of the $(CAG)_n$ tract in the expanded *ATXN3* alleles. Familial factors may explain additional variance in age-at-onset,[11, 12] indicating that modifier genes may play a role. The hypothesis that other CAG-containing proteins could interact with the expanded ataxin-3 and influence the MJD onset was raised.[13, 14] An association between severity of fasciculations (minor signs in MJD) and the CAG length of the large SCA2 allele was found,[14] but no influence on disease onset was detected.

Apolipoprotein E (apoE) is an ubiquitous protein involved in lipid storage, transport, and metabolism.[15] *APOE* (19q13.2) has three main alleles (ε2, ε3, and ε4), encoding for isoforms E2, E3 and E4 (which differ at positions 112 and 158).[16, 17] These differences alter the protein's structure, influencing association with lipids and its binding to the receptors. While apoE3 and E4 bind to Low-Density Lipoprotein Receptors (LDLR) with similarly high affinity, apoE2 has a 50-100-fold weaker affinity.[18, 19] In CNS, ApoE is secreted by astrocytes, and is highly expressed in both intracellular and extracellular spaces,[20] constituting an important mediator of cholesterol and lipid transport in the brain (for a review see[21]), specially of cholesterol transport from

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astrocytes to neurons; furthermore, it has been suggested that apoE isoforms differentially regulate synaptic plasticity and repair.[22]

The *APOE* ɛ4 allele has been consistently associated, for example, with increased risk (e.g.[23, 24]) and a lower onset in sporadic Alzheimer disease (AD),[24] increased risk of cognitive impairment,[25, 26] as well as with a more unfavorable outcome after traumatic brain injury.[27, 28] On the other hand, the ɛ2 allele has been associated with a higher prevalence[29] and earlier onset of sporadic PD,[30, 31] increased risk of frontotemporal dementia (FTD),[32] and an earlier onset in HD.[33]

The main goal of this work was to investigate a modulating effect of *APOE* on MJD phenotype.


**METHODS**

Blood samples from 192 MJD patients (59 from the Azores, 73 from mainland Portugal and 60 from Brazil) were collected after informed consent. DNA was extracted from all samples using standard procedures. The size of the $(CAG)_n$ tract was determined following a methodology previously reported,[34] and the *APOE* polymorphism was typed according to previously described conditions.[35] For the total series of patients, data on the age-at-onset was collected as close as possible from the first complaints of gait instability or diplopia (the two most consistent initial symptoms in SCA3/MJD, according to the extensive study by Coutinho[8]). Patients with several years of disease progression were asked for the age-at-onset of the mentioned symptoms. The age reported by them was confronted with the one stated by their close relatives (usually caregivers) and, whenever possible, additional information from previous records was also taken into account, in order to get an onset as accurate as possible.

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Conformity with the Hardy-Weinberg equilibrium was tested using the exact probability without bias. An exact test of differentiation evaluated differences in *APOE* genotypic frequencies among the three groups of patients, as well as between the patients' groups and the corresponding populations of origin (previously published for the populations of Azores,[35] mainland Portugal[36, 37] and Brazil[38, 39]). All analyses were performed using the Arlequin package.[40]

Age-at-onset for the three most frequent *APOE* genotypes was adjusted for the mean number of CAGs in the expanded *ATXN3* allele, after fitting a linear regression model. Differences in the adjusted age-at-onset between *APOE* genotypes were analyzed using the *t*-test calculator of OpenEpi v.2.3.1 (www.openepi.com). Multivariate linear regression analyses were used to test the effect of several variables on age-at-onset: CAGs in expanded and normal alleles, presence/absence of the *APOE* ε2 allele, population of origin, and gender. To account for kinship among some patients of the Azorean series, a generalized estimating equation model was also applied. The risk of developing MJD before 39 years of age (mean for the present series) among patients with *APOE* ε2 allele was estimated as an odds ratio (OR), using logistic regression analysis, with onset $< 39$ yr vs. $\geq 39$ yr as the dependent variable. All analyses were performed using SPSS v. 15.0.[41]

## RESULTS

The *APOE* genotypic frequencies were in conformity with Hardy-Weinberg expectations. No significant differences were detected in the genotypic frequencies among groups of patients (Azores, mainland Portugal or Brazil), nor between the patients' groups and the corresponding populations of origin.

A summary of descriptive statistics, for the MJD patients studied, is shown in Table 1. Adjusting onset for the $(CAG)_n$ size, patients with the ε2/ε3 genotype had an earlier onset than the other two groups (Table 1). This difference was statistically significant between ε2/ε3 and ε3/ε3 (*t*-test; p=0.024), but did not reach statistical significance between ε2/ε3 and ε3/ε4 (*t*-test; p=0.097).

The $(CAG)_n$ size in the expanded *ATXN3* alleles is known to be inversely correlated with the age-at-onset of MJD (present series: r =–0.769; p<0.001). Given the earlier onset observed for *APOE* ε2/ε3 genotype, the presence/absence of the *APOE* ε2 allele was tested, in a general linear model, in addition to the $(CAG)_n$ size in expanded alleles. When the *APOE* ε2 status was taken into account (given the impossibility to dissociate the effect of ε2 from ε4, the three patients with ε2/ε4 genotype were excluded), the percentage of explanation of the onset variance was significantly increased from 59.8% to 60.9% (F=6.46; p=0.012). In this series of patients, the presence of *APOE* ε2 decreases the onset age by nearly 5 years. When adding the number of CAGs in normal *ATXN3* alleles, the model was not significantly improved; however, the population background (Azores, mainland Portugal and Brazil) (F=19.51; p<0.001) and gender of patients (F=8.26; p=0.005) majored the outcome of *APOE* ε2 (F=8.71; p=0.004), improving onset variance explanation to 66.5%. Even taking into account the fact that the subseries of patients from the Azores contained related patients, the effect of *APOE* ε2 was still statistically significant (Wald Chi-Square=7.12; p=0.008). When patients were divided according to onset mean (< 39 yr vs. ≥ 39 yr), an association was found between the presence of ε2 allele and an earlier onset (OR=5.00; 95% CI: 1.18-21.14).

**COMMENT**

The present results indicate that the *APOE* ε2 allele influences the MJD phenotype, increasing the risk for earlier onset. When the ε2 allele status was accounted (additionally to the CAG repeat size in expanded alleles), an apparent discrepancy between the approximately five years earlier onset in ε2 carriers and the minimal (but statistically significant) improvement of only about 1% in the explanation of onset variance was detected. This observation is probably due to the fact that the number of patients with the ε2 allele is not very large (n = 20). Notwithstanding, in our series of patients, the risk of developing MJD before 39 years is five times higher in carriers of the ε2 allele in comparison with the non-carriers.

The *APOE* ε4 is associated with an increased risk for AD, while the ε2 allele may be protective.[23] In contrast, having at least one copy of ε4 may protect against age-related macular degeneration or delay vision loss, while having at least one copy of ε2 may increase the risk for this disease or for an earlier onset.[42, 43] The *APOE* ε2 allele has been also associated with an earlier onset of PD[30, 31] and HD.[33] This is in agreement with the effect we now observed in MJD. Some MJD patients may present a PD-like phenotype,[44-46] which may indicate a shared neuropathological mechanism. In HD, the influence of the *APOE* genotype is still controversial (e.g.[33, 47]); nevertheless, in agreement with our results, Kehoe and co-workers[33] found that male patients with the ε2/ε3 genotype had an earlier onset than those with other *APOE* genotypes. In face of the present results, and taking into account the postulated differential efficiency of different apoE isoforms in cholesterol transport, it can be hypothesized that apoE2 may be less efficient, leading to an earlier neuronal damage and MJD onset.

Rapp *et al.*,[48] using the rat as a model, have postulated that neurons and astrocytes express different apoE receptors. Astrocytes express preferentially the LDLR, in contrast

with neurons, where the principal receptor is LRP (LDL receptor-related protein). In hippocampal astrocytes, the efficiency of apoE3 and apoE4 mediated cholesterol uptake is similar, whereas it is reduced for apoE2. This low affinity of apoE2 for LDLR in astrocytes could contribute to the altered homeostasis of cholesterol in the brain, which may ultimately be associated with the earlier manifestation of MJD in ε2 carriers.

These results support a role of *APOE* as modulator of MJD phenotypic variability, in addition to the known effect of the CAG tract size in the expanded allele.

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**Table 1:** Descriptive statistics for the MJD patients studied

| Characteristics | APOE Genotype | | | | | Total |
|---|---|---|---|---|---|---|
| | ε2/ ε3 | ε3/ ε3 | ε3/ ε4 | ε2/ ε4 | ε4/ ε4 | |
| Number of patients (%) | 20 (10.4) | 134 (69.8) | 33 (17.2) | 3 (1.6) | 2 (1.0) | 192 |
| Population | | | | | | |
| Portugal | | | | | | |
| Azores | 6 (10.2) | 42 (71.2) | 11 (18.6) | 0 (0.0) | 0 (0.0) | 59 |
| Mainland | 9 (12.3) | 52 (71.2) | 11 (15.1) | 1 (1.4) | 0 (0.0) | 73 |
| Brazil | 5 (8.3) | 40 (66.7) | 11 (18.3) | 2 (3.3) | 2 (3.3) | 60 |
| Gender | | | | | | |
| Male | 10 (10.3) | 71 (73.2) | 13 (13.4) | 2 (2.1) | 1 (1.0) | 97 |
| Female | 10 (10.5) | 63 (66.3) | 20 (21.1) | 1 (1.1) | 1 (1.1) | 95 |
| Age at onset | | | | | | |
| Mean, yr ± SE | 36.95 ± 2.83 | 39.30 ± 1.09 | 37.70 ± 1.84 | 33.33± 10.93 | 36.50 ± 16.50 | 38.66 ± 0.90 |
| Adjusted onset*, yr ± SE | 34.74 ± 2.27 | 39.16 ± 0.67 | 39.08 ± 1.11 | --- | --- | --- |
| Range, yr | 21-60 | 12-70 | 12-58 | 20-55 | 20-53 | 12-70 |
| CAG repeat length | | | | | | |
| Normal | | | | | | |
| Mean ± SE | 23.45 ± 1.02 | 21.92 ± 0.41 | 21.82 ± 0.94 | 15.67 ± 1.67 | 26.00 ± 3.00 | 22.01 ± 0.35 |
| Range | 14-34 | 14-32 | 14-37 | 14-19 | 23-29 | 14-37 |
| Expanded | | | | | | |
| Mean ± SE | 71.85 ± 0.80 | 72.75 ± 0.34 | 73.30 ± 0.54 | 74.00 ± 1.53 | 75.50 ± 3.50 | 72.80 ± 0.27 |
| Range | 65-77 | 63-82 | 69-80 | 72-77 | 72-79 | 63-82 |

*Adjusted for the mean size of expanded CAG repeats in the patient sample.