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Analysis of the *KIFAP3* gene in amyotrophic lateral sclerosis: a multicenter survival study

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Disclosure statement

All authors declare no conflicts of interest.

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Abstract

Sporadic amyotrophic lateral sclerosis is a multifactorial disease of environmental and genetic origin. In a previous large multicenter genome wide study, common genetic variation in the Kinesin-Associated Protein 3 *(KIFAP3)* gene (rs1541160) was reported to have a significant effect on survival in amyotrophic lateral sclerosis patients. However, this could not be replicated in 3 smaller independent cohorts. We conducted a large multicenter multivariate survival analysis (n = 2362) on the effect of genetic variation in rs1541160. The previously reported beneficial genotype did not show a significant improvement in survival in this patient group.

Keywords

Amyotrophic lateral sclerosis; Kinesin-associated protein 3 gene; KIFAP3; Genome-wide association study

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a devastating progressive neurodegenerative disease of upper and lower motor neurons. Although multiple genome wide association studies (GWAS) have found single nucleotide polymorphisms (SNPs) associated with the disease, most findings have not been replicated in other cohorts. A GWAS with survival analysis on 1014 patients from England, the United States, and the Netherlands showed that the CC genotype of the SNP rs1541160 located within the *KIFAP3* gene was associated with a 14 months longer survival in ALS (Landers et al., 2009). This effect could not be replicated in 2 smaller Italian studies (Orsetti et al., 2011; Traynor et al., 2010) (n = 228 and 504) and 1 Chinese study (Chen et al., 2012) (n = 395). In ALS, a possible survival benefit of 14 months is considerable, and therefore it is important to assess the association of rs1541160 in a large multicenter study. We have performed a survival analysis study including 2362 ALS patients from 9 cohorts in 6 different countries in Europe.

2. Methods

Patients were included from different GWAS from Belgium, Germany, Ireland, Italy, the Netherlands, and Sweden. The survival data of these patients have not been published previously. In addition, Taqman analysis for rs1541160 was performed on samples that were not included in any previous GWAS (from the second Belgian sample, the 2 Italian samples and the German samples).

3. Results

The baseline characteristics of the 2362 patients are shown in Supplementary Table 1. In 1220 patients (51.7%) the TT-genotype in rs1541160 was found in 949 patients (40.2%) the CT-genotype was found and in 192 patients (8.1%) the CC genotype was found. The clinical characteristics of the 3-genotype groups were comparable (Supplementary Table 2). The median survival time was 28.8 months for the TT genotype, 28.7 months for the CT genotype, and 31.2 months for the CC genotype. Using Kaplan—Meier survival analysis (Supplementary Fig. 1), the rare homozygotic genotype (CC) was compared with the other 2 genotypes (CT and TT). A Log Rank (Mantel-Cox) analysis showed no significant difference in survival between the genotypes, neither in a censored analysis of all patients (n = 2362, $p = 0.26$), nor in a deceased-only analysis (n = 1627, $p = 0.60$). A Cox regression survival analysis comparing the CC genotype with the TT genotype or with the combined CT/TT genotypes showed no significant results. Also the hazard ratios adjusted for gender, age at onset, and site of onset of the disease showed no significant result (Supplementary Table 3). The addition of country as a variable in the survival analysis did not change the outcome. Survival was determined per individual country. No country showed a significant survival benefit in the Kaplan—Meier analysis or Cox regression (Supplementary Fig. 2). In the Dutch cohort we could distinguish prevalent and incident cases (Supplementary Table 4). When compared separately in a Kaplan—Meier survival analysis neither the prevalent cohort (n = 203, $p = 0.36$) nor the incident cohort (n = 320, $p = 0.12$) showed a significant association between rs1541160 genotypes and survival.

4. Discussion

In a large, independent multicenter cohort study we have shown that there is no significant association with survival for rs1541160 in the *KIFAP3* gene. These results support the previous result in the Italian and Chinese cohorts (Orsetti et al., 2011; Traynor et al., 2010; Chen et al., 2012) and suggest a false positive survival benefit in the initial multicenter genome-wide study (Landers et al., 2009).

However, it is also possible that the difference in effect of the CC genotype on survival is caused by a country specific effect. In the original GWAS there was a difference in survival between the US and English patients on the one hand and the patients from the Netherlands on the other, the latter having the lowest survival benefit. In the present study no US or UK subjects were included.

Another possibility is that the previous study suffered from an ascertainment bias in genome wide association studies, known as the “winner’s curse”. If in such a study the effect of a significant associated genotype is tested on the same population it will usually result in an outcome that is overestimated (Goring et al., 2001). Therefore, it is possible that the effect of the minor allele is only small. This study is powered for an effect as described in the previous GWAS (power >0.99), but a smaller effect of only a few months or less would need more patients to achieve sufficient power. However, the clinical and biological relevance of such a small survival benefit is questionable.

In this large independent cohort of ALS patients the survival benefit of SNP rs1541160 in the *KIFAP3* gene could not be replicated. It remains a challenge to find SNPs in GWAS that show robust associations with disease status or survival in ALS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

See Supplementary Material.