myotrophic lateral sclerosis (ALS) is an adult-onset neurodegenerative disease characterized by progressive loss of motor neurons from the spinal cord, brainstem, and cerebral cortex that typically results in death 2 to 5 years following onset. Approximately 10% of patients with ALS have a family history, of which 15% to 20% are linked to mutations in the SOD1 gene; these patients most frequently inherit the disease in an autosomal dominant manner. Mutations in other genes including ALS2, ANG, DCTN1, SETX, VAPB, TARDBP, and FUS have also been reported in familial cases.\(^1\) The remaining 90% of cases have no obvious family history and are referred to as sporadic ALS (SALS). The etiology of these sporadic cases is considered multifactorial, with environmental and genetic factors contributing to disease susceptibility. Although candidate gene studies have identified potential risk factors for SALS, replication of these associations in different populations have often failed. Similarly, several genome-wide association studies for SALS have identified novel candidate susceptibility genes including ITTP2,\(^2\) FGGY,\(^3\) and DPP6;\(^4\) however, these associations have not been consistently replicated.\(^1\) Recently, a large-scale genome-wide association study that included 19,838 subjects showed that the variant rs12608932 located in the unc-13 homologue A gene (UNC13A) is strongly associated with SALS.\(^5\) The aim of this study is to investigate the variant as a possible risk factor for developing ALS in a French population.

**Methods.** A total of 285 patients with ALS and 285 controls were included in this study. All individuals were recruited through clinics in France and ascertained by experienced neurologists. Informed written consent was obtained from each participant and samples were collected with the approval of the relevant institutional ethic boards. All patients fulfilled the El Escorial criteria for probable or definite ALS, and familial cases were excluded. Controls were matched for age and ethnicity. The DNA was extracted from peripheral blood samples using standard methods. The rs12608932 variant was genotyped by TaqMan SNP Genotyping Assay using the Applied Biosystems 7900HT Fast Real-Time PCR machine and the Sequence Detection System (vs2.2.2; Foster City, California) for allele calling. The case-control association analysis was performed using Haploview 4.1 (Broad Institute of MIT and Harvard, Cambridge, Massachusetts).\(^6\)

**Results.** The clinical data of the study population are provided in the Table. A total of 570 samples (285 cases and 285 controls) were genotyped for rs12608932, which is located in intron 21 of the UNC13A gene on chromosome 19p13.11. The genotyping success rate was 96.6%. Hardy-Weinberg equilibrium testing was performed and revealed no significant deviation from equilibrium (\(P = .93\)). A \(\chi^2\) test on basic allele counts showed no significant association between sporadic ALS and the rs12608932 variant (\(P = .85\)).

**Comment.** A recent 2-stage genome-wide association study demonstrated that the rs12608932 variant is a risk factor for sporadic ALS.\(^5\) The rs12608932 variant is located within an intronic region of the UNC13A gene that encodes a member of the UNC13 family. The UNC13 proteins are presynaptic proteins found in central and neuromuscular synapses that regulate the release of neurotransmitters, peptides, and hormones. We evaluated this variant as a possible genetic risk factor for SALS in a French population. This revealed no significant association between SALS and the rs12608932 variant. Although the sample size of the present study is not large enough to exclude rs12608932 as a risk factor for SALS, our data does not provide evidence of an association between this variant in the UNC13A gene and susceptibility to sporadic ALS in a French homogeneous population.

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**Table. Characteristics of the Studied Populations and the Results From Association Analyses for rs12608932**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SALS</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample, No.</td>
<td>285</td>
<td>285</td>
</tr>
<tr>
<td>Sex, male/female, No.</td>
<td>175/110</td>
<td>108/177</td>
</tr>
<tr>
<td>Age, mean, ya</td>
<td>59</td>
<td>61</td>
</tr>
<tr>
<td>Site of onset, No.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal</td>
<td>189</td>
<td></td>
</tr>
<tr>
<td>Bulbar</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>Allele frequency, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>65.6</td>
<td>66.1</td>
</tr>
<tr>
<td>C</td>
<td>34.4</td>
<td>33.9</td>
</tr>
<tr>
<td>(\chi^2)</td>
<td>0.037</td>
<td></td>
</tr>
<tr>
<td>(P) Value</td>
<td>.85</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: SALS, sporadic amyotrophic lateral sclerosis.  
\(^a\)Mean age is given at onset for patients and at sampling for controls.

\(P\) values corrected using Bonferroni correction for multiple comparisons.
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COMMENTS AND OPINIONS

Long-term Follow-up of Monomelic Amyotrophy of the Upper Limb

I read with great interest the article by Van den Berg-Vos et al1 that described a prospective study of 32 patients with lower motor neuron syndrome with duration of disease of 4 years or more who were followed up for 72 months to identify the group of patients who have either slow progression or attain a stationary course for many years and do not progress to having amyotrophic lateral sclerosis. The authors describe a favorable prognosis in 8 patients with segmental distribution of muscle involvement. No significant change in muscle strength was observed but there was spread to adjoining segments in one patient and to contralateral side in another.

In this context, I wish to draw attention to 2 articles; the first is by Barontini et al2 from Italy and included 3 patients with focal amyotrophy who were followed up clinically and neurophysiologically for 13 to 15 years and whose disease course remained stationary after an initial progressive course of 2 years. The second is our long-term follow-up study3 of 44 patients from India with monomelic amyotrophy of the upper limb with illness duration of 5 years or more, with the objectives to determine whether (1) atrophy and weakness progresses beyond this period, (2) the illness spreads to the other limbs and (3) the disease progresses to amyotrophic lateral sclerosis. The clinical features of monomelic amyotrophy have been described, and the essential features are focal atrophy of muscles of upper limb in adults, mainly restricted to the C8 to T1 segments, although in a few patients, proximal muscles may be involved with no evidence of upper motor neuron signs.4,5 Our study was prospective, with a mean follow-up period of 9.7 years. The salient findings were absence of progression of atrophy and weakness in the affected limb for more than 3 years, with the exception of 2 patients in whom there was progression for 6 years in one patient and 8 years in another, with a subsequent stationary course. In 7 patients, at presentation, there was mild clinical involvement or neurogenic changes on electromyography of the contralateral limb; however, there was gross asymmetry between the two limbs. During follow-up, 1 additional patient developed mild atrophy and weakness in the contralateral limb. There was no progression to the lower limbs in all the 44 patients and, reassuringly, none progressed to develop upper motor signs or amyotrophic lateral sclerosis.

The observations of Van den Berg-Vos RM et al1 on the natural history of segmental distal muscular atrophy are similar to Barontini and colleagues2 and our3 findings in patients with monomelic amyotrophy, which is also a segmental muscular atrophy.

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In reply

We thank colleague Gourie-Devi for her valuable comments on our study.1 The large group of patients she described in her follow-up study2 shares many similarities with our patients such as the relatively long duration of the follow-up, the marked preponderance of affected men, and the stationary disease course. In the nomenclature of lower motor...