Crohn’s associated NOD2 gene variants are not involved in determining susceptibility to multiple sclerosis

Autoimmune diseases, such as multiple sclerosis and Crohn’s disease, are believed to result from the effects of environmental agents acting on genetically susceptible individuals. Evidence from segregation analysis and systematic whole genome linkage studies indicates that the nature of this susceptibility is complex, involving several genes which individually confer only modest excess risk. Reassessment of the analysis in the relatives of affected individuals together with the comparison of whole genome linkage studies across these diseases shows that there are likely to be both genes conferring an autoimmune diathesis in general and others determining precisely which autoimmune phenotype may result. On this basis it is reasonable to hypothesise that genes shown to be relevant in one autoimmune disease may be of importance in another and therefore offer themselves as potential candidates.

During the last few years striking progress has been made in unravelling the genetic basis of susceptibility to Crohn’s disease. Significant evidence for linkage in the pericentromeric region of chromosome 16 has been found, following on from which two independent groups have used association mapping and the other following a candidate gene approach, identified the relevant gene as NOD2. Three variants of this gene (IBD8, IBD12, IBD13) were shown to influence susceptibility to Crohn’s disease. IBD8 is a missense mutation in exon 3 (2023C>T, R675W); IBD12 is a missense mutation in exon 7 (2641G>C, G188R); and IBD13 is a frameshift variant in exon 10 (2996insC, 9806981X). Although precise functions of the NOD2 gene are not fully known it is believed to have important immunological activity, particularly in maintaining symbiosis between the gut lining and its commensal bacteria.

Given the established importance of these variants in determining susceptibility to one autoimmune disease (Crohn’s disease), we embarked on a role in a second by genotyping patients participating in this genetic analysis of multiple sclerosis. The work was supported by the Wellcome Trust (grant 057097).

S Sawyer, M Maranian, A Hensiek, R Roxburgh, J Gray, A Compston
University of Cambridge Neurology unit, Addenbrooke’s Hospital, Hills Road, Cambridge, CB2 0QQ, UK

Competing interests: none declared

Correspondence to: Professor Alastair Compston; alastair.compston@medschl.cam.ac.uk

References

Favourable outcome of a brain trauma patient despite bilateral loss of cortical somatosensory evoked potential during thiopental sedation

We would like to present an observation that somewhat questions the predictive value of somatosensory evoked potentials on the outcome of brain trauma patients treated with thiopental sedation.

A 30-year-old woman suffered a high velocity car accident resulting in a diffuse brain injury. Her Glasgow coma scale score on admission was 3 (9/15), with preserved pupillary reflexes and gross motor function. Computed tomography of the head showed a traumatic disjunction of the lamboid suture and multiple left frontobasal and temporal cerebral contusions. The patient was sedated with propofol, intubated, and monitored for intracerebral pressure (ICP) through an external ventricular drain. Her clinical condition rapidly worsened because of brain swelling around the contusions, and cerebrospinal fluid drainage, manitol boluses, and mild hyperventilation were started. Three days after admission, a further ICP increase was treated with thiopental coma (10 mg/kg/h × 24 h loading dose followed by 3 mg/kg/h maintenance dose to obtain a burst suppression EEG pattern). On day 7, the patient developed a left sided mydriasis and a left temporal partial lobectomy was performed to remove contused brain. The ICP returned to normal and thiopental administration was stopped on day 8. On day 10, the EEG was isoelectrical and on day 11, somatosensory evoked potentials (SSEP) of the median nerve showed no cortical response (N20) despite normal brachial plexus (Erb) and lemniscal (P14) potentials. Levels of thiopental and phenobarbital, its main metabolite, were then respectively 65 ng/ml and 56 ng/l. The patient remained afebrile (GCS 3/15) and without brain stem reflexes, including a normal flow Doppler however showed normal flow patterns and the brain CT scan did not reveal any post-herniation ischaemic lesion. On day 21, the patient opened her eyes. The serum concentration of thiopental was then 12 ng/ml whereas that of phenobarbital remained around 40 ng/ml until day 23. A 1–2 Hz low amplitude EEG activity with right sided predominance was observed, and the SSEP cortical peak N20 recovered on day 22 when the thiopental concentration was 5.9 ng/ml. A steady improvement followed. On discharge to a rehabilitation facility (day 57), the patient could follow simple commands but suffered mixed dysphasia and general weakness. At four months, she presented no residual motor deficit, an improved verbal expression and comprehension, and a moderate frontal lobe deficit. At two years, the patient only still suffered some episodes of irritable mood, and although she had not resumed her previous job, she was active as a farm worker, read and wrote, drove her car, and could live an independent and social life, with a Glasgow outcome score (GOS) of 5/5.

SSEP are commonly used to monitor coma-toxic patients even under barbiturate sedation. Indeed, although their morphological outcome can become changed, short latency SSEPs

Table 1

<table>
<thead>
<tr>
<th>Variant</th>
<th>Multiple sclerosis (%)</th>
<th>Controls (%)</th>
<th>Published control frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBD8*</td>
<td>54 (4.8)</td>
<td>34 (6.2)</td>
<td>4</td>
</tr>
<tr>
<td>IBD12</td>
<td>11 (0.9)</td>
<td>6 (0.9)</td>
<td>1</td>
</tr>
<tr>
<td>IBD13</td>
<td>28 (2.3)</td>
<td>8 (1.2)</td>
<td>2</td>
</tr>
</tbody>
</table>

*The primary PCR for this assay was relatively unreliable such that typing success rate was 90% for cases and 80% for controls. Both of the other assays had typing success rates of greater than 95%. The manufacturer’s standard reaction conditions were used for all reactions except the primary amplification of IBD8 where a lower annealing temperature of 50°C was used along with four additional PCR cycles.

Primary PCR primers
IBD8: ACCTTCAGACAGCAGAAGCAGG and GCTCCCCCCTACCTGTAACC
IBD12: AGTTCGTTAAGTAAGAAAGCCA and CCGACGCCTTCTTCTCC
IBD13: TCTACCACTGTATCTTCCTTCCT and GAATGTACAGATCAAGGG

Extension primers
IBD6: TTTTTTTTGTACAGAAGGCGGCCTGCTC
IBD12: TGCCCTTTTACTGATGTGG
IBD13: TTTTTTGTGTTGCTACATCCTTCACAGGG

Acknowledgements
We thank members of the Association of British Neurologists and the Multiple Sclerosis Society of Great Britain and Northern Ireland for notifying us of cases. Members of the International collaboration (P14) wrote, drove her car, and could live an independent and social life, with a Glasgow outcome score (GOS) of 5/5.
in humans supposedly do not disappear in response to barbiturate doses sufficient to render the EEG isoelectric and the neurological examination similar to brain stem death. 1,2 The bilateral loss of SSEP N20 responses is regarded as a predictor of ominous outcome after a trauma. There are only a few reports on the recovery of initially absent or lost N20 potentials after severe brain injury with increased ICP some of them with a good outcome as was the case in our patient.1,2 In our case, the disappearance of the cortical evoked responses correlated with both the ICP increase and the induction of thiopental coma. As their reappearance closely matched the elimination of thiopental from the bloodstream and was quite delayed relative to the normalisation of the ICP, our observation suggests that barbiturates may contribute to the suppression of N20 evoked potentials in brain trauma patients. Awaiting further observations, caution is thus warranted on the use of SSEP to monitor the clinical evolution and predict the outcome of such patients under barbiturate coma.

Funding: PAR and SL are post-doctoral researchers at the Fonds National de la Recherche Scientifique (FNRS).

P A Robe, A Dubuisson
Service of Neurosurgery, University Hospital of Liège, Liège, Belgium

S Bartsch, P Damas
Service of Critical Care Medicine, University Hospital of Liège

S Laureys
Service of Neurology, University Hospital of Liège

Correspondence to: Dr P A Robe, Department of Neurosurgery, CHU de Liège, Domaine universitaire du Sart Tilman, B35, 4000 Liège, Belgium; pierre.robe@ulg.ac.be

References


Epidemiology of the mitochondrial DNA 8344A>G mutation for the myoclonic epilepsy and ragged red fibres (MERRF) syndrome

The myoclonic epilepsy and ragged red fibres (MERRF) syndrome is a maternally inherited progressive mitochondrial encephalomyopathy caused by a 8344A>G mutation in the MTTK gene that encodes mitochondrial tRNA for lysine. Its common clinical features include myoclonic and tonic-clonic seizures, ataxia, and myopathy, but other features have also been reported, including lipoma, diabetes mellitus, optic atrophy, peripheral neuropathy, hearing loss, and dementia.

The population frequencies of pathogenic mutations in mitochondrial DNA (mtDNA) are not well known, but the Finnish health-care organisation provides good opportunities for carry out studies on molecular epidemiology. We have previously determined the frequency of 3243A>G, the most common cause of the MELAS syndrome (mitochondrial encephalomyopathy, lactic acids, and stroke-like episodes), to be 16.0/100 000 in the adult population of Northern Ostrobothnia.1 We report here on the identification of patient groups with common clinical features of the MERRF syndrome, in a comparable population and the resulting determination of the prevalence of the 8433A>G mtDNA mutation.

Patients and methods

The prevalence area considered here is the province of Northern Ostrobothnia in northern Finland, with a total population of 335 893 on 31 December 1994 (prevalence date), including 342 884 persons ≥20 years of age. Adult patients with diagnoses that are commonly associated with the 8344A>G mutation were identified as being at risk with respect to mitochondrial disorders, and we therefore screened the population for patients ≥20 years of age who had disorders such as ataxia, diabetes mellitus, epilepsy, lipoma, myopathy, ophthalmoplegia, optic atrophy, peripheral neuropathy, and sensorineural hearing impairment (table 1). These were

---

### Table 1 Criteria used in the screening of the patient groups

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Selection criterion 1</th>
<th>Number of patients identified</th>
<th>Selection criterion 2</th>
<th>Number of patients identified</th>
<th>Number (%) of samples received</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axatia</td>
<td>Any axatia, unknown aetiology</td>
<td>79</td>
<td>Idiopathic cerebellar axatia, age ≥20 years at visit</td>
<td>39</td>
<td>26 (67)</td>
</tr>
<tr>
<td>Diabetes*</td>
<td>Insulin treatment started at age 20–45 years</td>
<td>479</td>
<td>Family history of mitochondrial phenotype†</td>
<td>169</td>
<td>143 (85)</td>
</tr>
<tr>
<td>Epilepsy†</td>
<td>Age ≥20 years at visit, response to family history questionnaire</td>
<td>945</td>
<td>Family history of mitochondrial phenotype†</td>
<td>223</td>
<td>165 (74)</td>
</tr>
<tr>
<td>Hearing loss§</td>
<td>Sensoryneural hearing impairment, hearing aid obtained at age ≥45 years, current age ≥20 years</td>
<td>242</td>
<td>Family history of mitochondrial phenotype†</td>
<td>108</td>
<td>82 (76)</td>
</tr>
<tr>
<td>Lipoma</td>
<td>Any lipoma</td>
<td>621</td>
<td>Axial or multiple lipomas, age ≥20 years at visit</td>
<td>150</td>
<td>107 (71)</td>
</tr>
<tr>
<td>Myopathy</td>
<td>Any myopathy with clinical and EMG verification, age ≥20 years at visit</td>
<td>146</td>
<td>Myopathy of unknown aetiology or any muscle dystrophy†</td>
<td>41</td>
<td>32 (78)</td>
</tr>
<tr>
<td>Neuroptathy</td>
<td>Any electrophysiologically defined idiopathic neuropathy, age ≥20 years at visit</td>
<td>138</td>
<td>Familial neuropathy or family history of mitochondrial phenotype†</td>
<td>31</td>
<td>21 (68)</td>
</tr>
<tr>
<td>Ophthalmoplegia</td>
<td>Double vision or ptosis, any age</td>
<td>799</td>
<td>Definite ophthalmoplegia or symmetric ptosis, age ≥20 years at examination</td>
<td>15</td>
<td>15 (100)</td>
</tr>
<tr>
<td>Optic atrophy</td>
<td>Decrease in visual acuity or optic disc abnormality, any cause, any age</td>
<td>1542</td>
<td>Optic atrophy of unknown aetiology* *, current age ≥20 years</td>
<td>42</td>
<td>30 (71)</td>
</tr>
<tr>
<td>Total</td>
<td>Any ataxia, unknown aetiology</td>
<td>4991</td>
<td>Total</td>
<td>818</td>
<td>621 (76)</td>
</tr>
</tbody>
</table>

OUH, Oulu University Hospital. Computer search at OUH was first performed to identify patients with specific discharge diagnoses that had been filed according to Finnish version of the International Statistical Classification of Diseases and Related Health Problems. Specific selection criteria were then applied to select patients with definite diagnoses. *Patients with insulin dependent diabetes mellitus obtain needles, syringes, insulin pens, and glucose sticks free of charge from the public health care units, and the supplies used are recorded. These patients were identified from the records of 40 of the 42 local authority health care units. Discharge diagnoses at one of the two regional hospitals in the area and the diabetes register of the other also were reviewed. †Patients with any combination of diabetes mellitus, sensorineural hearing impairment or epilepsy in first or second degree maternal relatives were included. ‡Most adult patients with epilepsy make regular follow up visits to the outpatient clinic of the department of neurology at OUH at least once a year. During a one year period, a physician involved in the study checked the charts of the patients visiting the clinic every day. The diagnosis of epilepsy was confirmed on this occasion, and patients receiving regular antiepileptic medication were included. No distinction was made between the types or aetiologies of epilepsy. §The cost of hearing aids is refunded in full by the public health service, and aids are supplied in the region only by the department of otolaryngology at OUH. The register of hearing aids supplied was reviewed and patients were ascertained on the basis of the following clinical criteria: symmetric sensorineural hearing impairment with pure tone average of frequencies 0.5, 1, 2, and 4 kHz, a difference between the ears ≤10 dB, and use of a hearing aid at age <45 years. ¶Chuchenne muscular dystrophy and other myopathies with definite molecular genetic diagnosis were excluded. **Demyelinating diseases and ischaemic diseases were excluded.

www.jnnp.com
Acknowledgements

The authors thank Ms Anja Heikkinen for her expert technical assistance. This study was supported by grants from the Medical Research Council of the Academy of Finland and the Sigrid Juselius Foundation.

References


Shifting in angiotensin I converting enzyme insertion allele frequency across Europe: implications for Alzheimer’s disease risk

Early studies suggested that angiotensin I converting enzyme (peptidyl-dipeptidase A) 1 (ACE) gene polymorphism is associated with an increased risk of coronary artery disease and, more recently, with sporadic late onset Alzheimer’s disease. Studies conducted in northern European populations consistently suggested that ACE1/1 genotype was a risk factor for various types of cognitive decline. One such study in a French population found an association between the ACE2/D allele and dementia, while other studies in southern European populations found either a slight but significantly increased frequency of ACE1 in Alzheimer’s disease patients or did not detect any effect of ACE polymorphism.

Our group recently reported the novel finding that apolipoprotein E (APOE) ε4 allele shows a geographical trend, decreasing in frequency from northern to southern Europe. We hypothesised that the variability in the strength of evidence for an association between ACE polymorphism and Alzheimer’s disease is related to similar geographical variations in ACE1 frequency. We investigated whether there was evidence in southern Italy of an association between the ACE polymorphism and increased risk of Alzheimer’s disease. Secondly, we compared our results with the findings from published studies on other European populations.

Between June 1998 and October 2001, we consecutively examined in our centre 141 patients with Alzheimer’s disease (51 men, 90 women; mean (SD) age at onset, 71 (8.5) years, and 268 unrelated caregivers, spouses, friends, neighbours, or volunteers (118 men, 150 women; mean age at onset, 72 (9) years). A clinical diagnosis of probable Alzheimer’s disease was made according to the criteria of the National Institute for Neurological and Communicative Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association, and the group of non-demented elderly control subjects was sex and age matched. The ascertainment, diagnosis, and collection of cases and controls are described in detail elsewhere. The age at onset of Alzheimer’s disease symptoms was estimated from semistructured interviews with the patients’ caregivers. The study protocol was approved by the ethics committee of the University of Bari. After a complete explanation of the study, written informed consent was obtained from all the subjects or their relatives. ACE genotypes were determined as detailed elsewhere. ACE genotypes were produced using established methods, followed by a quality control amplification step necessary in detecting underamplified ACE2/2 alleles.

The statistical analysis was performed by Pearson χ² test to make genotype and allele comparisons as well as test for agreement of data with Hardy-Weinberg principles. Allele frequencies were determined by allele counting. To express variabilities of the allele frequencies, we used 95% CIs, calculated by Wilson’s formulas. The differences among age at onset of Alzheimer’s disease symptoms in relation to different ACE genotypes were calculated with Mann-Whitney U test. To evaluate whether the association between Alzheimer’s disease and ACE genotypes were homogeneous in all APOE strata we used a permutation based exact logistic model by LogXact procedure implemented in the SAS system (ProcLogXact; Copyright 2001 by CYTEL Software Corporation, Cambridge, MA 021139). In order to correct for multiple statistical testing, the results were adjusted according to 0.05 Bonferroni inequality. The Cochran-Armitage trend test was carried out to evaluate the geographical trend among ACE allele and genotype frequencies in Alzheimer’s disease patients and controls from three European countries (Spain, Spain, and United Kingdom), from published studies. The data were analysed by SAS FREQ procedure (version 8.2).

Table 1 shows ACE allele and genotypes frequencies in Alzheimer’s disease patients and controls in southern Italy. The frequencies of the different ACE genotypes in our population were in Hardy–Weinberg equilibrium (HWE) (cases: Pearson χ² = 2.09, p = 0.13; controls: χ² = 2.49, p = 0.11). Moreover, there was no
Table 1  Angiotensin I converting enzyme (ACE) genotype and allele distributions in Italian, Spanish, and United Kingdom populations

<table>
<thead>
<tr>
<th>Nationality</th>
<th>Age at onset or collection (years), mean (SD)</th>
<th>Genotypes (n)</th>
<th>Alleles (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ACE*I/*I</td>
<td>ACE*I/*D</td>
</tr>
<tr>
<td>Italian AD (n=141)</td>
<td>71 (8.5)</td>
<td>17</td>
<td>75</td>
</tr>
<tr>
<td>Frequency (95% CI)</td>
<td>0.12 (0.08 to 0.19)</td>
<td>0.53 (0.45 to 0.61)</td>
<td>0.35 (0.27 to 0.43)</td>
</tr>
<tr>
<td>Spanish AD (n=350)</td>
<td>72 (9.0)</td>
<td>70</td>
<td>161</td>
</tr>
<tr>
<td>Frequency (95% CI)</td>
<td>0.20 (0.16 to 0.25)</td>
<td>0.46 (0.34 to 0.51)</td>
<td>0.29 (0.29 to 0.39)</td>
</tr>
<tr>
<td>UK AD (n=239)</td>
<td>81.2 (7.8)</td>
<td>60</td>
<td>111</td>
</tr>
<tr>
<td>Frequency (95% CI)</td>
<td>0.25 (0.20 to 0.31)</td>
<td>0.46 (0.28 to 0.35)</td>
<td>0.23 (0.23 to 0.35)</td>
</tr>
<tr>
<td>UK AD (n=542)</td>
<td>70.3 (9.4); 82.3 (6.7); 76.6 (6.3)</td>
<td>127</td>
<td>323</td>
</tr>
<tr>
<td>Frequency (95% CI)</td>
<td>0.23 (0.20 to 0.27)</td>
<td>0.60 (0.55 to 0.64)</td>
<td>0.17 (0.14 to 0.20)</td>
</tr>
<tr>
<td>Italian controls (n=268)</td>
<td>72 (7.1)</td>
<td>32</td>
<td>138</td>
</tr>
<tr>
<td>Frequency (95% CI)</td>
<td>0.12 (0.08 to 0.16)</td>
<td>0.52 (0.46 to 0.57)</td>
<td>0.37 (0.36 to 0.46)</td>
</tr>
<tr>
<td>Spanish controls (n=400)</td>
<td>21 to 65 (range)</td>
<td>60</td>
<td>176</td>
</tr>
<tr>
<td>Frequency (95% CI)</td>
<td>0.15 (0.12 to 0.19)</td>
<td>0.44 (0.42 to 0.31)</td>
<td>0.37 (0.34 to 0.40)</td>
</tr>
<tr>
<td>UK controls (n=342)</td>
<td>82.1 (3.8)</td>
<td>60</td>
<td>203</td>
</tr>
<tr>
<td>Frequency (95% CI)</td>
<td>0.18 (0.14 to 0.22)</td>
<td>0.59 (0.54 to 0.64)</td>
<td>0.47 (0.49 to 0.57)</td>
</tr>
<tr>
<td>UK controls</td>
<td>73.5 (6.2); 80.8 (4.5); 77.1 (6.4)</td>
<td>89</td>
<td>180</td>
</tr>
<tr>
<td>Frequency (95% CI)</td>
<td>0.23 (0.19 to 0.28)</td>
<td>0.47 (0.42 to 0.52)</td>
<td>0.30 (0.26 to 0.35)</td>
</tr>
</tbody>
</table>

n, number of individuals genotyped.

*Criteria for selection of published ACE frequencies were the sampling amplitude (>100 subjects) and the diagnosis of Alzheimer’s disease made according to the same clinical criteria.

ACE, angiotensin I converting enzyme; AD, Alzheimer’s disease; CI, confidence interval; I, ACE*I; D, ACE*D; II, ACE*I/II; DD, ACE*D/DD; ID, ACE*I/ID.

Evidence that the genotypic counts of Alzheimer’s disease patients and controls were not under HWE (Alzheimer’s disease patients under HWE, given the controls were under HWE: likelihood ratio, χ² = 2.18, p = 0.34). No significant differences were found in ACE genotype frequencies between patients with Alzheimer’s disease and controls in this southern Italian population. We did not find any statistically significant differences in rates between ACE alleles and Alzheimer’s disease among APOE allele strata, nor did we observe any lack of homogeneity among response differences (data not shown). Interestingly, Alzheimer patients with the ACE*I/*I genotype were on average 3.6 years younger at onset than those with the ACE*D/*D genotype (mean (SD) age at onset: ACE*D/*D, 72.1 (6.8) years; ACE*I/*D, 70.3 (8.1) years; ACE*I/*I, 68.5 (7.3) years). However, this difference did not reach statistical significance (z = 1.49; Bonferroni p > 0.05).

The ACE*I allele frequency in Alzheimer’s disease patients (z = 3.12 p < 0.01). The present study does not support previous findings that increased Alzheimer’s disease risk is associated with the ACE*I allele and allele frequencies. The age at onset of Alzheimer’s disease patients with the ACE*I/*I genotype appeared to be lower than in those with the ACE*D/*D genotype. Though this was not statistically significant, it suggests that the presence of an ACE*I allele might bring forward the onset of the disease without being linked to an increased overall risk of it occurring. Our findings support those of a previous report in which no evidence of an interaction between ACE alleles and age at onset, sex, and family history was found (data not shown).

It is becoming apparent that the possible association between the ACE polymorphism and increased Alzheimer’s disease risk is complex. The variation in results between different studies may simply reflect the inherent susceptibility of such association studies to type I and type II statistical errors. Another possible explanation may be the direct result of geographical genetic variation which we have hypothesised. Indeed, as with our previous findings with APOE, we report here that the putative association between ACE gene variants and increased risk of Alzheimer’s disease may be influenced by geographical genetic variations (table 1). The different and conflicting patterns of association of ACE polymorphism and Alzheimer’s disease in populations worldwide may be explained by similar geographical trends or indeed another Alzheimer’s disease susceptibility locus located elsewhere in ACE or a nearby gene. Furthermore, the same ACE gene may have pleiotropic age and sex dependent effects on Alzheimer’s disease. Though the strength of association of APOE e4 with Alzheimer’s disease seems not to be influenced by the low prevalence of e4 in southern Europe, the decrease of the ACE*I allele frequency could be related to the different patterns of association between this polymorphism and Alzheimer’s disease in various European studies.

F Panza, V Solfrizzi, A D’Introno, A M Colaciccio, C Capurso, A Capurso
Department of Geriatrics, Centre for Aging Brain, Memory Unit, University of Bari, Policlinico, Piazza Guglielmo Cesare 11, 70124 Bari, Italy

P G Kehoe
Department of Care of the Elderly, University of Bristol, Frenchay Hospital, Bristol, UK

Competing interests: none declared

Correspondence to: Dr Francesco Panza; geriat.dolf@geriatriu.uniba.it

References


Polymorphisms of toxifying and detoxifying hepatic enzymes in amyotrophic lateral sclerosis

A contribution of hepatic enzymes responsible for detoxification and toxification of xenobiotics and endogenous compounds has been suspected to contribute to the pathogenesis of amyotrophic lateral sclerosis (ALS). We studied 12 potentially relevant enzymes in 150 ALS patients and 373 control patients with non-neurological diagnoses and were of white origin. The mean age of the patients was 55.6 years. The ratio of men to women was 1:1. In 26.7% of the patients the disease was of bulbar, in 73.3% of spinal onset.

Our RFLP analysis could not reveal any significant over-representation of a polymorphism (table 1) that has been associated with an altered metabolism for the encoded enzymes in ALS patients. In contrast with our hypothesis, we found a significant over-representation of the GST M1*B allele with 24% in the patients group versus 15.3% in the control group and a significant under-representation of the CYP2E1* mut mutation (table 1).

References

Polymorphisms of toxifying and detoxifying hepatic enzymes in amyotrophic lateral sclerosis

R Bachus, K Neubert, I Roots, J Prudlo, J Brockmöller and A C Ludolph

J Neurol Neurosurg Psychiatry 2003 74: 1161
doi: 10.1136/jnnp.74.8.1161

Updated information and services can be found at:
http://jnnp.bmj.com/content/74/8/1161

These include:

References
This article cites 6 articles, 2 of which you can access for free at:
http://jnnp.bmj.com/content/74/8/1161#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/