ascertained as described in detail previously.[2] The research protocol was approved by the ethics committee of the Medical Faculty of the University of Oulu, Finland, and the Finnish Ministry of Social Affairs and Health.

DNA from blood samples was purified using the QIAamp Blood Kit (QIAGEN) and a fragment encompassing the MTTK gene was amplified by PCR in the presence of ^{35}S-dATP. The 8344A>G mutation was detected by restriction fragment analysis using *BglI*. After digestion, the samples were electrophoresed through a 6% acrylamide gel, which was dried and autoradiographed at −72°C overnight using Kodak XAR-5 film with an intensifying screen. Amplified DNA from a subject known to harbour the mutation was included in each restriction digestion and electrophoresis. The degree of mutant heteroplasmy in this sample was 59%.

Results and Comment

We identified 818 patients with signs or symptoms that have been associated with MERRF (table 1), and samples obtained from 621 of these were examined for the 8344A>G mutation. None of the patients harboured the mutation (95% confidence intervals (CI) 0 to 3.67). The prevalence of 8344A>G in the adult population of Northern Ostrobothnia was thus calculated to be 0–1.5/100 000. The estimated frequency of 8344A>G in northern Finland is much lower than that of 3243A>G, but comparable to that found in two previous studies: 0.25/100 000 (95% CI 0.01 to 0.50) among adult patients in a single neurology centre in United Kingdom over a 10 year period,[3] and 0 to 0.25/100 000 (95% CI) in a population based study among children in western Sweden.[4] The 8344A>G mutation is not absent in Sweden or Finland, however, as the authors are aware of two families in southern Finland who possess it, and a few such families have been reported in Sweden.[4]

The frequency of 3243A>G has been found to be four times that of 8344A>G in the United Kingdom.[3] Furthermore, gene analyses in a molecular diagnostic laboratory have revealed that the ratio of these two mutations among 2000 patients with features of mitochondrial disorders is 4,[5] suggesting that the frequency ratio between the two is fairly constant. The 3243A>G MELAS mutation appears to be clearly more common than 8344A>G also among Finnish patients that was ascertained in a population based manner.

MtDNA mutations are a comparatively common cause of neurometabolic disorders in both adults and children, but they vary in prevalence. The most common mtDNA point mutations seem to be 11778G>A, 3243A>G and 3460G>A, while 8344A>G is infrequent. The 3243A>G mutation has arisen several times in a population[2] and is not faced with any strong selection pressure,[6] but the low frequency of 8344A>G suggests either that this gene is not a hot spot for mutational events, or that the mutation is rapidly eliminated in a population. Indeed, the two mutations lead to different biochemical consequences at the cellular level. The MERRF mutation impairs mitochondrial translation more severely than does the MELAS mutation.[7] Evolutionarily, these two mutations may therefore be faced with different negative selection and may explain the differences in population frequencies.

A M Remes, M Kärppä, H Rusanen, K Majamaa
Department of Neurology, University of Oulu, Oulu, Finland

A M Remes, M Kärppä, J S Moilanen, H Rusanen, I E Hassinen, K Majamaa
Department of Medical Biochemistry and Molecular Biology, University of Oulu

A M Remes, M Kärppä, J S Moilanen, H Rusanen, K Majamaa
Biocentre, University of Oulu

S Uimonen, M Sorri
Department of Otorhinolaryngology, University of Oulu

P I Salmela
Department of Internal Medicine, University of Oulu

S-L Karvonen
Department of Dermatology, University of Oulu

S-L Karvonen
Department of Dermatology, University of Helsinki, Helsinki, Finland

Correspondence to: Professor K Majamaa, Department of Neurology, University of Oulu, PO Box 5000, FIN-90014 Oulu, Finland; kari.majamaa@oulu.fi

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

1 **Chinnery PF**, Howell N, Lightowlers RN, *et al*. Molecular pathology of MELAS and MERRF. The relationship between mutation load and clinical phenotypes. *Brain* 1997;**120**:1713–21.
2 **Majamaa K**, Moilanen JS, Uimonen S, *et al*. Epidemiology of A3243G, the mutation for mitochondrial encephalopathy, lactic acidosis, and strokelike episodes: prevalence of the mutation in an adult population. *Am J Hum Genet* 1998;**63**:447–54.
3 **Chinnery PF**, Johnson MA, Wardell TM, *et al*. The epidemiology of pathogenetic mitochondrial DNA mutations. *Ann Neurol* 2000;**48**:188–93.
4 **Darin N**, Oldfors A, Moslemi A-R, *et al*. The incidence of mitochondrial encephalomyopathies in childhood: clinical features and morphological, biochemical, and DNA abnormalities. *Ann Neurol* 2001;**49**:377–83.
5 **Liang M-H**, Wong L-JC. Yield of mtDNA mutation analysis in 2,000 patients. *Am J Med Genet* 1998;**77**:395–400.
6 **Moilanen JS**, Majamaa K. Relative fitness of carriers of the mitochondrial DNA mutation 3243A>G. *Eur J Hum Genet* 2002;**9**:59–62.
7 **Chomyn A**. The myoclonic epilepsy and ragged-red fiber mutation provides new insights into human mitochondrial function and genetics. *Am J Hum Genet* 1998;**62**:745–51.

Shifts 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.[1] Studies conducted in northern European populations have considered the ACE*I allele to be a risk factor for various types of cognitive decline.[1 2] One such study in a French population found an association between the ACE*D allele and dementia,[3] while other studies in southern European populations found either a slight but significantly increased frequency of ACE*I in Alzheimer's disease patients[4] or did not detect any effect of ACE polymorphism.[5]

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.[6] We hypothesised that the variability in the strength of evidence for an association between ACE polymorphism and Alzheimer's disease was related to similar geographical variations in ACE*I 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.[1 2 4]

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 collection, 72 (7.1) 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.[6] 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.

APOE genotypes were determined as detailed elsewhere.[6] ACE genotypes were produced using established methods, followed by a quality control amplification step necessary in detecting underamplified ACE*I alleles.[1]

The statistical analysis was performed by Pearson χ^2 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 variances 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 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 (Proc-LogXact 4; Copyright 2001 by CYTEL Software Corporation, Cambridge, MA 021139). In order to correct for multiple statistical testing, the results were adjusted according to 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 of three European countries (Italy, Spain, and United Kingdom), from published studies.[1 2 4] 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 $\chi^2 = 2.09$, $p = 0.15$; controls: $\chi^2 = 2.49$, $p = 0.11$). Moreover, there was no

Table 1 Angiotensin I converting enzyme (ACE) genotype and allele distributions in Italian, Spanish, and United Kingdom populations*

Nationality	Age at onset or collection (years), mean (SD)	Genotypes (n)			Alleles (n)	
		ACE*I/*I	ACE*I/*D	ACE*D/*D	ACE*I	ACE*D
Italian AD (n=141)	71 (8.5)	17	75	49	109	173
Frequency (95% CI)		0.12 (0.08 to 0.19)	0.53 (0.45 to 0.61)	0.35 (0.27 to 0.43)	0.39 (0.33 to 0.45)	0.61 (0.56 to 0.67)
Spanish AD[4] (n=350)	72 (9.0)	70	161	119	301	399
Frequency (95% CI)		0.20 (0.16 to 0.25)	0.46 (0.41 to 0.51)	0.34 (0.29 to 0.39)	0.43 (0.39 to 0.47)	0.57 (0.53 to 0.61)
UK AD[2] (n=239)	81.2 (7.8)	60	111	68	231	247
Frequency (95% CI)		0.25 (0.20 to 0.31)	0.46 (0.40 to 0.53)	0.28 (0.23 to 0.35)	0.48 (0.44 to 0.53)	0.52 (0.47 to 0.56)
UK AD[1] (n=542)	70.3 (9.4); 82.3 (6.7); 76.6 (6.3)	127	323	92	577	507
Frequency (95% CI)		0.23 (0.20 to 0.27)	0.60 (0.55 to 0.64)	0.17 (0.14 to 0.20)	0.53 (0.50 to 0.56)	0.47 (0.44 to 0.50)
Italian controls (n=268)	72 (7.1)	32	138	98	202	334
Frequency (95% CI)		0.12 (0.08 to 0.16)	0.52 (0.46 to 0.57)	0.37 (0.42 to 0.31)	0.38 (0.34 to 0.42)	0.62 (0.58 to 0.66)
Spanish controls[4] (n=400)	21 to 65 (range)	60	176	164	296	504
Frequency (95% CI)		0.15 (0.12 to 0.19)	0.44 (0.39 to 0.49)	0.41 (0.36 to 0.46)	0.37 (0.34 to 0.40)	0.63 (0.60 to 0.66)
UK controls[2] (n=342)	82.1 (3.8)	60	203	79	323	361
Frequency (95% CI)		0.18 (0.14 to 0.22)	0.59 (0.54 to 0.64)	0.23 (0.19 to 0.28)	0.47 (0.44 to 0.51)	0.53 (0.49 to 0.57)
UK controls[1] (n=386)	73.5 (6.2); 80.8 (4.5); 77.1 (6.4)	89	180	117	358	414
Frequency (95% CI)		0.23 (0.19 to 0.28)	0.47 (0.42 to 0.52)	0.30 (0.26 to 0.35)	0.46 (0.43 to 0.50)	0.54 (0.50 to 0.57)

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/*I; DD, ACE*D/*D; ID, ACE*I/*D.

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, $\chi^2 = 2.18$, $p = 0.34$). 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 and controls showed a statistically significant decreasing trend from northern to southern regions of Europe ($z = 5.36$ $p < 0.001$; $z = 4.33$ $p < 0.001$, respectively), while there was a concomitant increase in ACE*D allele frequency (table 1). This was reflected by genotype data whereby a decreasing geographical trend from north to south was found for ACE*I/*I genotype (cases, $z = 3.92$ $p < 0.01$; controls, $z = 4.15$ $p < 0.001$) and an inverse trend for ACE*D/*D genotype (cases, $z = 3.29$ $p < 0.001$; controls, $z = 3.46$ $p < 0.001$). Interestingly, we found a statistically significant decreasing trend from northern to southern regions for the ACE*I/*D genotype, but this was observed only in Alzheimer's disease patients ($z = 3.12$ $p < 0.01$).

Comment

The present study does not support previous findings that increased Alzheimer's disease risk is associated with the ACE*I genotype and allele frequencies.[1] 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).[1]

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,[6] 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 geographic 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,[6] 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.[1–5]

F Panza, V Solfrizzi, A D'Introno, A M Colacicco, C Capurso, A Capurso
Department of Geriatrics, Centre for Aging Brain, Memory Unit, University of Bari, Policlinico, Piazza Giulio 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.dot@geriatria.uniba.it

References

1 **Kehoe PG**, Russ C, McIlory S, *et al*. Variation in DCP1, encoding ACE, is associated with susceptibility to Alzheimer disease. *Nat Genet* 1999;**21**:71–2.
2 **Narain Y**, Yip A, Murphy T, *et al*. The ACE gene and Alzheimer's disease susceptibility. *J Med Genet* 2000;**37**:695–7.
3 **Richard F**, Fromentin-David I, Ricolfi F, *et al*. The angiotensin I converting enzyme gene as a susceptibility factor for dementia. *Neurology* 2001;**56**:1593–5.
4 **Alvarez R**, Alvarez V, Lahoz CH, *et al*. Angiotensin converting enzyme and

Table 1

Enzyme	Presumed genotype at risk	Total number		% at risk		OR	CI	p
		Cases	Controls	Cases	Controls			
NAT 2	2 mutant allels	150	373	62.0	57.6	1.2	0.8 to 1.8	0.2
GSTM1	2 mutant allels	150	373	49.3	51.1	0.9	0.6 to 1.4	0.4
	No GSTM1*A allele	150	373	68.0	64.1	1.2	0.8 to 1.8	0.3
	No GSTM1*B allele	150	373	76.7	84.7	0.6	0.3 to 0.9	0.01
GSTT1	1 or 2 active alleles	150	360	84.0	79.2	1.4	0.8 to 2.4	0.1
MEH	2 Tyr113 mutations	150	336	50.0	47.6	1.0	0.7 to 1.6	0.4
MEH	2 His139 mutations	150	330	60.0	63.3	0.8	0.6 to 1.3	0.2
CYP1A1	1 or 2 6235C mutations	150	349	11.3	14.9	0.7	0.4 to 1.3	0.2
CYP1A1	1 or 2 Val462 mutations	150	348	5.3	5.7	0.8	0.3 to 1.9	0.4
CYP2C19	1 or 2 active alleles	150	340	98.0	96.5	1.8	0.5 to 10.0	0.3
CYP2D6	1 or 2 active alleles	150	373	4.7	5.9	0.8	0.5 to 3.6	0.4
CYP2E1	1 or 2 1019T mutations	150	348	2.0	5.7	0.3	0.06 to 1.2	0.04
CYP2E1	1 or 2 9930G mutations	150	328	24.7	25.9	0.9	0.6 to 1.4	0.4
CYP2E1	1 or 2 7776T mutations	150	300	12.7	12.6	1.0	0.5 to 1.9	0.6

endothelial nitric oxide synthase DNA polymorphisms and late onset Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 1999;**67**:733–6.
5 **Scacchi R**, De Bernardini L, Mantuano E, *et al*. DNA polymorphisms of apolipoprotein B and angiotensin I-converting enzyme genes and relationships with lipid levels in Italian patients with vascular dementia or Alzheimer's disease. *Dement Geriatr Cogn Disord* 1998;**9**:186–90.
6 **Panza F**, Solfrizzi V, Torres F, *et al*. Decreased frequency of apolipoprotein E ϵ4 allele from northern to southern Europe in Alzheimer's disease patients and centenarians. *Neurosci Lett* 1999;**277**:53–6.

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 controls on the genetic level and could not detect any significant difference between both groups. These results strongly support a view that—in contrast with earlier observations—hepatic foreign compound metabolism does not contribute to the pathogenesis of ALS.

Genetic studies of familial ALS have yielded at least six chromosomal loci and two disease genes ("alsin" and superoxide dismutase 1).[1–3] Mutations on the superoxide dismutase 1 initially suggested a role for free radicals in the disease process but recent results clearly argue for a gain of function mechanism. The mechanisms through which the mutant enzyme exerts toxicity and results in selective motor neuron death remain unclear. Although familial ALS accounts only for 2% of all cases, the findings on the DNA level demonstrate the significance of genetic factors.

In contrast, the cause of the sporadic form of ALS remains largely obscure. Basically, the aetiology of the disease is viewed as multifactorial with polygenic as well as ecological factors. Assuming an involvement of exogenous or endogenous toxic factors, an inter-individually different capacity for toxification or detoxification of endogenous compounds, xenobiotics including drugs could cause an inter-individually different susceptibility to develop ALS. Thus, respective enzymes and their encoding genes with functionally different alleles might be candidates for susceptibility genes for the sporadic form of ALS. Some earlier studies of the metabolic phenotype seemed to show an altered xenobiotic metabolism in ALS patients. For example, Heafield *et al*[4] described 74% slow acetylators among 14 ALS patients compared with 60% in the normal population.

We investigated a number of different genes encoding for toxifying and detoxifying enzymes that have been suspected to be causually linked to ALS: arylamine-N acetyltransferase (NAT2), the glutathione-S transferases (GSTs) M1 and T1, microsomal epoxide hydrolase (mEH) as well as the cytochrome P-450 enzymes (CYP) 1A1, 2E1, 2C19, and 2D6. For all these enzymes, well defined polymorphisms are known. All methods used have been described previously.[5] Briefly, DNA was extracted from blood samples, PCR amplified by gene specific primers, and analysed by restriction fragment length polymorphisms (RFLP).

We analysed blood of 150 patients with the diagnosis of sporadic ALS according to the revised El Escorial criteria and 373 control patients recruited in three German centres (Berlin, Homburg/Saar, and Hannover). Control patients had 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 1.1:1. 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 $CYP2E1_{1019T}$ mutation (table 1). However, in the absence of differences of activity between the isoenzymes GSTM1*A and GSTM1*B, the significance of the B-allelic over-representation among ALS patients remains uncertain. As the CYP2E1 has toxifying properties and the $CYP2E1_{1019T}$ mutation is associated with an increased enzyme activity an under-representation in the ALS population is likely to be of minor significance.

Our results are in accordance with other genotype studies analysing the enzymes GSTM1, CYP2D6, CYP1A1 and NAT2[6] as well as NAT2 and CYP2D6[7] where no significant differences between patients and control groups were found. Using a substantially larger population of ALS patients and extending these studies for other toxifying and detoxifying enzymes, we have found no significant differences between patients and control groups for the glutathione-S transferase T1, the microsomal epoxide hydrolase, and the cytochrome P-450 enzymes 2E1 and 2C19.

We conclude from our data, that an involvement of the analysed toxifying and detoxifying enzymes in the pathogenesis of ALS is most unlikely.

R Bachus
Department of Neurology, Humboldt University of Berlin, Germany

K Neubert, I Roots
Department of Clinical Pharmacology, Humboldt University of Berlin

J Prudlo
Department of Neurology, University of Homburg, University of Goettingen, Germany

J Brockmöller
Department of Clinical Pharmacology, University of Goettingen

A C Ludolph
Department of Neurology, University of Ulm, Germany

Correspondence to: Professor A C Ludolph, Department of Neurology, University of Ulm, 89075 Ulm, Steinhövelstraβe 9, Germany; albert.ludolph@rku.de

References

1 **Shaw PJ**. Genetic inroads in familial ALS. *Nat Genet* 2001;**29**:103–4.
2 **Yang Y**, Hentati A, Deng H-X, *et al*. The gene encoding alsin, a protein with three guanine-nucleotide exchange factor domains, is mutated in a form of recessive amyotrophic lateral sclerosis. *Nat Genet* 2001;**29**:160–5.
3 **Hadano S**, Hand CK, Osuga H, *et al*. A gene encoding a putative GTPase regulator is mutated in familial amyotrohic lateral sclerosis 2. *Nat Genet* 2001;**29**:166–73.
4 **Heafield MTE**, Waring RH, Sturman SG. N-Acetylation status in neurodegenerative disease. *Med Sci Res* 1990;**18**:963–4.
5 **Brockmöller J**, Cascorbi I, Kerb R, *et al*. Combined analysis of inherited polymorphisms in arylamine *N*-acetyltransferase 2, glutathione *S*-transferase M1 and T1, microsomal epoxide hydrolase, and cytochrome P450 enzymes as modulators of bladder cancer risk. *Cancer Res* 1996;**56**:3915–25.
6 **Nicholl DJ**, Bennett P, Hiller L, *et al*. A study of five candidate genes in Parkinson's disease and related neurodegenerative disorders. *Neurology* 1999;**53**:1415–21.
7 **Ray-Chaudhuri KR**, Smith CAD, Gough AC, *et al*. Debrisoquine hydroxylase gene polymorphism in Parkinson's disease and amyotrophic lateral sclerosis. [Letter]. *J Neurol Neurosurg Psychiatry* 1995;**58**:109.