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World J Gastroenterol 2005;11(41):6445-6449
World Journal of Gastroenterology ISSN 1007-9327

• *BASIC RESEARCH* •

Cytochrome P450 2E1 high activity polymorphism in alcohol abuse and end-organ disease

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Received: 2005-03-04 Accepted: 2005-04-02

Abstract

AIM: To investigate a possible role for a recently identified polymorphism in the gene of cytochrome P450 2E1, the presence of which is associated with high activity of the enzyme.

METHODS: Two hundred and thirty-nine alcohol consumers, ICD 10.1/.2 (ALC), and 208 normal controls were studied. PCR amplification of the CYP2E1 gene region was performed to assess polymorphic variation. Fisher's exact test was used to assess the data.

RESULTS: Twelve normal controls (5.8%) possessed the insertion. Five ALC (2.1%) had the insertion; of these 2 of 144 with alcohol induced chronic pancreatitis, none of 28 with alcoholic liver disease and 3 of 67 without end-organ disease had the polymorphism. A significantly Lower frequency of subjects possessed the insertion than normal controls [$P = 0.049$ (genotype analysis $P = 0.03$)]. To further assess, if there was a relationship to alcohol problems *per se* or end-organ disease, we compared patients with alcohol induced end-organ disease *vs* alcoholic controls without end-organ disease *vs* normal controls which again showed a significant difference [$P = 0.045$ (genotype analysis, $P = 0.011$)], further sub-group analysis did not identify which group(s) accounted for these differences.

CONCLUSION: We have shown the frequencies of this high-activity polymorphism in alcohol related patient groups for the first time. The frequency is significantly less in alcoholics than normal controls, as with high activity polymorphisms of alcohol dehydrogenase. The biological significance, and whether the relevance is solely for alcoholism or is there a relationship to end-organ disease, would benefit from the assessment in the populations with a greater frequency of this polymorphism.

Key words: CYP2E1; Alcohol; Chronic pancreatitis; Liver disease; Polymorphism

Cartmell MT, Schulz HU, O'Reilly DA, Yang BM, Kielstein V, Dunlop SP, Halangk W, Demaine AG, Kingsnorth AN. Cytochrome P450 2E1 high activity polymorphism in alcohol abuse and end-organ disease. *World J Gastroenterol* 2005; 11(41):6445-6449
http://www.wjgnet.com/1007-9327/11/6445.asp

INTRODUCTION

Cytochrome P450 2E1 (CYP2E1) is the major component of the microsomal enzyme oxidizing system, which is one of the major pathways of oxidative metabolism of ethanol[1,2] as well as a large number of xenobiotics[3]. CYP2E1 is induced to greater activity by its substrate ethanol, probably *via a* number of mechanisms, including transcriptional, post-transcriptional and post-translational[2,4,5].

CYP2E1 activity is expressed in the liver, at sites of maximal alcohol induced damage[6], and in the pancreas, where it is also induced by chronic alcohol consumption[7,8]. These two are the major sites of damage following chronic consumption of ethanol. In addition, it is found in the brain[9], also a site of ethanol induced damage.

The genetic predisposition to both alcoholism and alcohol induced end-organ damage is an area of debate. Alcohol-induced pancreatitis occurs in approximately 5% of alcoholics[10] while no, or minimal, fibrosis is found in 32% of pancreata of alcoholics[11]. Alcoholic cirrhosis occurs in around 10% and hepatitis in 10-35%[12].

The heterogeneity of the response to alcohol implicates genetic factors. Family and twin studies suggest a genetic component to alcoholism[13,14]. Some evidence suggests that the majority of genetic predisposition to psychosis and liver disease may be accounted for by disposition to alcoholism[14].

Recently, an insertion polymorphism in the promoter

region of the gene coding for the enzyme CYP2E1 has been described; sequencing has shown a 96-bp insertion as a series of eight repeats, as opposed to six in the wild type[15,16]. This corresponds to the restriction fragment length polymorphism, between positions -2270 and -1672. Presence of which is associated with higher CYP2E1 metabolic activity (employing an *in vivo* chlorazoxazone 6-hydroxylation test) in the presence of recently consumed alcohol or obesity[17]. We have therefore analyzed the frequency of this polymorphism in patients with a history of excessive alcohol consumption, with and without end-organ damage, and normal controls.

The 96-bp insertion, previously described, is a 729-bp fragment employing the PCR based analysis of Fritsche *et al*[16]. The wild type allele is 633 bp in length. In addition, a GenBank record also exists for a 48-bp deletion (accession no. J02843), corresponding to 585 bp.

MATERIALS AND METHODS

Subjects

Venous blood samples were drawn from patients giving informed consent and local research ethics committee approval was obtained. We collected samples on 239 Caucasoid subjects (ALC) fulfilling the ICD 10 criteria 10.1 and 10.2, that is harmful use and/or alcohol dependence syndrome. Cut-off for minimal consumption was 80 g alcohol per day (UK patients range 56-400 U/week; median 106 U/week) over a minimum of 2 years (UK range 2-45 years; median 10 years). Age range was 25-73 years, median 47 years. The subjects were sub-divided as follows:

Sixty-seven (36 British and 31 German) subjects without known end-organ disease, AC, collected from clients at alcohol rehabilitation centers.

One hundred and seventy-two with alcohol-related end-organ disease (AEOD). Of which, one hundred and forty-four (39 British and 105 German) patients had alcohol-induced chronic pancreatitis (AICP); all fulfilled the criteria for late- or end-stage AICP, as defined by the Zurich criteria[18]. The twenty-eight patients with alcoholic liver disease (ALD) had biopsy proven cirrhosis or a history, consistent with alcoholic hepatitis, including jaundice associated with excess alcohol consumption without other evident cause.

Two hundred and eight samples of cord blood from Caucasoids with a normal, healthy delivery taken in Derriford Hospital, Plymouth, UK were employed as normal controls.

Laboratory analysis

DNA samples were extracted from peripheral and cord blood samples employing the commercially available Nucleon II DNA extraction kits (Nucleon Biosciences, Lanarkshire, Scotland, UK) or QIAmp DNA Blood Minikits (Qiagen, Hilden, Germany).

DNA amplification was performed for the promoter region of CYP2E1 as previously described[16], employing amplimers 5'-GTG ATG GAA GCC TGA AGA ACA- and 5'-CTT TGG TGG GGT GAG AAC AG-. Reactions were carried out in a volume of 25 μ L employing 100-200 ng of genomic DNA. Following a hot start for 4 min at 94 °C, thirty cycles of: 94 °C (denaturing) for 30 s; 66 °C (annealing) for 2 min and 72 °C (extension) for 2 min were performed. This was followed by 10-min extension at 72 °C.

Products were analyzed on a 1.5% agarose gel stained with 0.01% v/v ethidium bromide, viewed under ultraviolet light and compared to 50 and 100 bp molecular weight ladders (Roche Diagnostics, Lewes, East Sussex, UK).

Statistical analysis

Two-sided Fisher's exact tests were used throughout (SPSS 9.0, SPSS Inc., Chicago, IL, USA). A P value of <0.05 was taken as significant. Where appropriate, multisided contingency tables were employed initially for comparisons, with sub-group analysis only when a statistically significant result was seen in the initial comparison. Individual sub-group analyses for end-organ disease(s) only involved comparison with AC controls. Chi square values, where expected cell numbers are greater than 5, are shown in brackets in tables. A comparison is made for the presence of the insertion polymorphism, which has the functional association[17], and for the genotype of that polymorphism.

RESULTS

Results are displayed in Table 1. of 208 normal controls 12 (5.8%) had the insertion polymorphism, and all were heterozygotes (Figure 1A). In contrast, 5 of 239 ALC subjects (2.1%) had the insertion. In the AICP group two subjects had the insertion and one of these was homozygous for the insertion. In the AC group, three subjects had the insertion. In addition, one AICP and one AC had a band which would correspond to the 48-bp deletion found in GenBank (Figure 1B), as did two normal controls. Results from the British and German groups, all European Caucasoids, were similar: three of the 136 German subjects (2.2%) and 2 of the 103 British (2%) had the insertion; two of the 31 German AC, 1 of the 36 British AC, 1 of the 105 German AICP and 1 of the 39 British AICP.

Comparing ALC to NC for the presence of the insertion polymorphism, showed that it was less abundant in the former than the latter ($P = 0.049$) (Table 2). The same comparison for genotype of the insertion was comparable ($P = 0.030$) (Table 2).

To delineate whether the difference may have been for alcohol problems *per se* or end organ disease we initially employed Fisher's exact test for the presence of the insertion using a three by two contingency table of normal controls, AC and AEOD. This revealed a statistically significant difference ($P = 0.045$), and analysis for insertion genotypes was comparable ($P = 0.011$) (Table 3). Thus, we further analyzed the sub-groups. Comparing AC with NC and comparisons within alcoholic (ALC) subgroups analysis did not reveal any significant differences, as might be expected with such a low frequency in the patient

Table 1 Full genotype data on all subjects

	Normal controls (n = 208)	ALC (n = 239)	Of ALC		Of AEOD	
			AC (n = 67)	AEOD (n = 172)	AICP (n = 144)	ALD (n = 28)
Homozygote wildtype	194	232	63	169	141	28
Heterozygote for insertion	12	4	3	1	1	0
Homozygote for insertion	0	1	0	1	1	0
Heterozygote for deletion	2	2	1	1	1	0

ALC, ICD 10.1/10.2; AC, alcoholic controls; AEOD, alcohol-related end-organ disease; AICP, alcohol induced chronic pancreatitis; ALD, alcoholic liver disease.

Table 2 Normal control and alcoholic figures and comparisons

	Normal controls n = 208 (%)	ALC n = 239 (%)	Fisher's exact test
Presence of insertion polymorphism	12 (5.8)	5 (2.1)	$P = 0.049$ ($\chi^2 = 4.110$, $P = 0.043$)
Genotype for insertion polymorphism			
Heterozygote	12 (5.8)	4 (1.7)	$P = 0.030$
Homozygote	0 (0.0)	1 (0.4)	

ALC, ICD 10.1/10.2.

Table 3 Alcoholic subgroup figures and analyses

	Normal controls n = 208 (%)	Alcoholic controls n = 67 (%)	Alcoholic end organ disease n = 172 (%)	Fisher's exact test
Presence of insertion polymorphism	12 (5.8)	3 (4.5)	2 (1.2)	$P = 0.045$
Genotype for insertion polymorphism				
Heterozygote	12 (5.8)	3 (4.5)	1 (0.6)	$P = 0.011$
Homozygote	0 (0.0)	0 (0.0)	1 (0.6)	

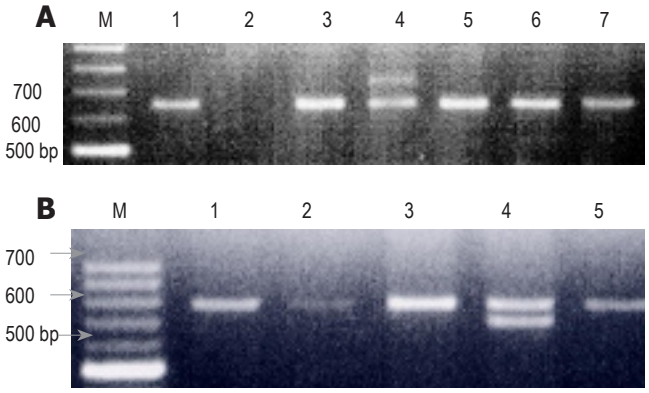

Figure 1 A: Agarose gel showing wild type homozygotes (633 bp, lanes 1, 3, 5–7) and a heterozygote for the insertion polymorphism (729 bp, lane 4). Run alongside a molecular weight marker (M); **B**:Agarose gel showing wild type homozygotes (633 bp, lanes 1–3 and 5) and a heterozygote for the deletion polymorphism (585 bp, lane 4). Run alongside a molecular weight marker (M).

groups. Although genotype analysis for AEOD compared with AC approached significance with $P = 0.068$.

DISCUSSION

Polymorphisms in CYP2E1, other than that studied here, have been looked at in previous studies, though some have used small numbers. Their association with alcoholism has been studied: no association was found for the c1/c2 alleles in most studies[19-23]. A positive association for the D form of the C/D polymorphism was found in Japanese subjects[24]. Although some studies used non-alcoholic controls, in alcohol induced end-organ disease association for these polymorphisms has been found: for ALD and the c2 allele[25-27] and fatty liver and the c2 allele[28]. However, the positive association with end-organ disease has not been found in a number of studies[19,21,29-31] and two studies found an association with the c1 allele[32,33].

The original study describing the polymorphism assessed in this study, showed greater CYP2E1 metabolic activity associated with the 96 bp insertion. In that study chlorazoxazone hydroxylation was higher in the patients with the presence of the polymorphism and who were obese or recent consumers of alcohol[17]; both circumstances when CYP2E1 is induced. The two later descriptions[15,16] delineate the pattern of 8 repeats of 42-60 bp, as opposed to 6 in the wild type. The first sequencing data showed a run of five repeats[34] (accession no. J02843), which had not been seen in the two further studies[15,16], this form would correspond to the smaller band seen in four of our 447 samples (Figure 1B).

Hu *et al*[15] did not find an increased constitutive

expression in luciferase transfection experiments, for the insertion polymorphism, which would agree with McCarver et al[17] findings of increased enzymatic activity only in the induced state (obese subjects and recent alcohol consumers).

To our knowledge, this is the first study to look at this polymorphism in patient groups. In previous studies of healthy groups of American Caucasoids, frequencies of 6.9%[17] and 4.2%[16] are seen. Another previous study found the insertion in only 2.1% of healthy Swedish subjects[15].

At low frequencies these results, on Caucasoid subjects, could all be consistent with the frequencies found in our patient, as well as our control, groups; of 5.8% controls (British), 2.2% German ALC and 2% British ALC. However, in the large numbers in our study our results do indicate a statistically significant difference, which remains when isolating the smaller numbers of only British subjects for insertion genotype between NC and ALC ($P = 0.03$). Population stratification is a confounding factor in all genetic association studies and the possibility of this is recognized, raising the question as to whether our results are biologically as well as statistically significant.

We have shown a significantly lower frequency of this polymorphism, which is associated with increased activity, in the gene coding for the enzyme CYP2E1 when comparing those with alcohol dependence or abuse and normal controls. This could be explained and be analogous to the association found in the functional variations in ADH. It has been shown that high activity forms of ADH (and low activity forms of ALDH) are associated with the protection against alcoholism in a number of studies, as previously reviewed[35]. This is believed to be due to the increased production (or decreased metabolism) of the ethanol metabolite acetaldehyde (and possibly other toxic metabolites), to which associated unpleasant side effects such as flushing are ascribed[35].

Due to the low frequency in our patient populations it was not possible to delineate whether there was only a relationship to alcohol misuse *per se*, or a relationship to end-organ disease. If a lower frequency existed in alcoholics, it could then be expected to be increased in those with end-organ disease compared to alcoholic controls. The sole homozygote was a patient with AICP and genotype analysis of those with end-organ disease *vs* AC approached significance, with $P = 0.068$. However, to infer a finding from such a result would not be justified.

Further analysis in ethnic populations with a frequency of this polymorphism which is sufficiently common to a more likely impact on susceptibility to CYP2E1-related diseases would be useful (e.g. Chinese[15], Taiwanese or African American[16] populations). This would be useful both to confirm or refute the association found here and to delineate any association with end-organ disease, rather than alcoholism *per se*.

In conclusion, the debate regarding a role for CYP2E1 in alcohol misuse and end-organ disease and a genetic component of this is further assessed. We have shown for the first time frequencies of this functional polymorphism in patient groups and there appears to be an association with this high activity polymorphism in the gene coding for cytochrome P450 2E1 and genetic protection against alcohol consumption. However, further studies are required in other populations.

ACKNOWLEDGMENTS

The authors would like to thank David Wright for his statistical input and the staff and clients of Broadreach Drug and Alcohol Treatment Centre, Plymouth.

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