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Interleukin-1 alpha and beta, TNF-alpha and HTTLPR gene variants study on alcohol toxicity and detoxification outcome

Alessandro Serretti [a,*], Ioannis Liappas [b], Laura Mandelli [a], Diego Albani [c], Gianluigi Forloni [c], Petros Malitas [b], Christina Piperi [d], Aikaterini Zisaki [d], Elias O. Tzavellas [b], Zeta Papadopoulou-Daifoti [e], Francesca Prato [c], Sara Batelli [c], Marzia Pesaresi [c], Anastasios Kalofoutis [d]

[a] *Institute of Psychiatry, University of Bologna, Bologna, Italy*
[b] *Department of Psychiatry, Eginition Hospital, University of Athens Medical School, Athens, Greece*
[c] *Neuroscience Department. Istituto di Ricerche Farmacologiche "Mario Negri", Milan, Italy*
[d] *Laboratory of Biological Chemistry, University of Athens Medical School, Athens, Greece.*
[e] *Department of Experimental Pharmacology, University of Athens Medical School, Athens, Greece*

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Abstract

Genetic factors may influence the liability to treatment outcome and medical complications in alcoholism. In the present study we investigated the IL-1A rs1800587, IL-1B rs3087258, TNF-α rs1799724 and the HTTLPR variants in a sample of 64 alcohol dependents and 47 relatives versus a set of clinical parameters and outcome measures. Alcohol dependents had a less favorable clinical profile compared to relatives (higher cholesterol, triglycerides, glucose, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, gamma-glutamyltransferase). After detoxification, all clinical indexes improved and hepatic enzyme levels were similar in alcohol dependents and relatives, except for the GGT that remained significantly higher in alcohol dependents. Alcoholic depressive and anxiety scores were significantly reduced after detoxification. IL-1A, IL-1B, TNF-α and HTTLPR variants were not associated with any baseline clinical index or change after detoxification. In our sample IL-1A, IL-1B, TNF-α and HTTLPR do not appear as liability factors for alcohol toxicity or detoxification outcome, however the small sample size may influence the observed results.

Keywords: Interleukin; Alcohol dependence; Detoxification; Gene

Alcohol dependence is a serious health problem with a heritability of 40–50% [20]. A number of possible liability genes have been investigated in the recent years. However, recent research focused beyond the liability to alcohol behaviors to liability to treatment outcome [8] and medical complications [15]. Those traits are in fact considered relatively simpler in their genetic basis, although formal heritability studies are lacking, and the analysis of such phenotypes may facilitate the dissection of the genetic basis of alcoholism [17,25].

Pro-inflammatory cytokines, such as interleukin-1 (IL-1) and tumour necrosis factor-a (TNFa) emerged as proteins involved in a number of processes, from the pathogenesis of medical complications such as alcohol liver disease [26] to mood and anxiety symptomatology [1]. Polymorphisms within genes encoding these cytokines could therefore influence medical status and outcome of alcoholism.

IL-1 mediates reactions of acute phase response. The IL-1 gene family is located on chromosome 2q and encodes nine proteins, including IL-1Alpha and IL-1Beta, which are coded by IL-1A and IL-1B genes, respectively [27]. Cytokine expression levels are partially associated with genetic polymorphisms located mainly in the promoter and coding sequences of the genes that encode for these proteins. IL-1A has a common polymorphism in the 5′ regulatory region (a C to T transition at position -889 relative to the start site of transcription - rs1800587) with possible functional effects [23]. IL-1A T/T genotype has been associated with Alzheimer's disease [33], liver cirrhosis in patients with chronic hepatitis C [3] and with schizophrenia [13]. The same variant has been associated with depressive symptomatology and antidepressant outcome [46].

* Corresponding author. Tel.: +39 051 6584 233; fax: +39 051 521 030.
E-mail address: alessandro.serretti@unibo.it (A. Serretti).

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The IL-1B gene most studied SNPs are at position −511 C/T (rs3087258) in the promoter region and +3953 T/C within exon 5. Of those, the −511 C/T has been related to changes in the cytokine production [9]. It has been associated with alcoholic cirrhosis [37], though not confirmed [15], and with alcoholism [30].

TNF is a white cell produced proinflammatory cytokine. Stable inter-individual variations in the levels of TNF production suggest inherited individual differences and family studies show that up to 60% of the variability may be genetically determined [42]. TNF-alpha gene variants have been associated with susceptibility and outcome of various infectious, inflammatory and neoplastic diseases, but of particular interest the association with acute and chronic alcoholic pancreatitis [29].

The TNF gene cluster spans 12 kilobases (kb) and it is located on the short arm of chromosome 6. A TNF-α −850 C/T variant, located within the promoter (rs1799724), demonstrated possible functional effects [45]. It was not extensively studied but showed an association with sporadic Alzheimer's disease [22].

The serotonin transporter (5-HTT), a key protein in the serotonergic system, is encoded by the single gene SLC6A4 (17q11.1-q12, 31 kb for 14 exons). The functional polymorphism in the transcriptional control region upstream of the serotonin transporter gene coding sequence (HTTLPR) [11] is the most widely studied polymorphism in psychiatric genetics given the huge number of confirmed effects reported [35]. In particular it has been associated with substance dependence and alcoholism [10]. In a recent meta-analysis, conducted on 17 published studies, the frequency of the s allele resulted to be significantly associated with alcohol dependence [7]. Interestingly, the same short variant was also associated with alcohol dependence specific features such as anxiety [28] and alcoholic cirrhosis [31].

In the present study we investigated the IL-1A rs1800587, IL-1B rs3087258, TNF-α rs1799724 and the HTTLPR gene variants in a sample of alcohol dependent subjects and their relatives with a set of clinical parameters and outcome measures.

The sample of the study was composed by 64 subjects (males/females 49/15; medium age: 46.0 ± 9.4 years), randomly enrolled over one-year period, fulfilling the DSM-IV diagnostic criteria for alcohol abuse/dependence – "primary alcoholism" – who were admitted to the Drug and Alcohol Addiction Clinic of the Athens University Psychiatric Clinic at the Eginition Hospital in Athens, Greece for alcohol detoxification on an inpatient basis. The present sample was part of a previously reported study where the biochemical and psychopathological variables were analyzed [18] with blood samples available. The patients had been abstinent from alcohol for an average of 24.0 ± 12.2 h prior to admission to the clinic.

The patients who were included in our study had to fulfill the following criteria: absence of serious physical illness (as assessed through physical examination and routine laboratory screening), absence of other drug abuses, age between 20 and 75 years old, absence of DSM-IV axis I co-morbidity. The presence of affective symptoms was not considered to be an exclusion criterion. Alcohol abusers who fulfilled the DSM-IV diagnosis of depressive disorder were excluded from the study if a major depressive episode had been recorded prior to the onset of alcoholism. When the depressive episode was present concurrently with an alcohol-abusing period these patients were not excluded.

An additional sample composed by 47 non-alcohol dependents (males/females 8/39, medium age: 47.9 ± 11.5), who were relatives of the recruited alcoholic patients, was collected. Relatives were included in the study if they did not meet criteria for past or current alcohol abuse/dependence and major medical disturbances. Written informed consent was obtained from each participant after approval from the local ethical committee, and their participation in the project was on a voluntary basis.

Upon admission, alcohol detoxification was initiated and completed over 4–5 weeks. Detoxification comprised vitamin replacement (B, C, E) and oral administration of diazepam (10–40 mg daily in divided doses), with gradual taper off over a week. Patients then followed an inpatient standard treatment program with a short-term psychotherapy of cognitive-behavioral orientation. It consisted of both individual sessions (twice a week) and family interventions (at least once every 2 weeks).

Participants were diagnosed by the Schedules for Clinical Assessment in Neuropsychiatry (SCAN [43]) and assessed through the Composite International Diagnostic Interview (CIDI - section on alcohol consumption) [44] for their pattern of alcohol abuse, potential major life problems related to alcohol consumption and the occurrence of withdrawal symptoms in the past; a structured questionnaire similar to the one proposed by the World Health Organization [12] was also used to assess the pattern of alcohol use. This questionnaire includes items related to lifetime, past year and past month frequency and quantity of alcohol abuse. Furthermore, sociodemographic data, including age, sex, level of education, marital status, socioeconomic status, and previous psychiatric history (pre-existent diagnosis, medication, and hospitalizations) were recorded.

The biochemical profile of serum lipoproteins (cholesterol, HDL, LDL) as well as the levels of hepatic enzymes serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) and gamma-glutamyltransferase (GGT), were assessed once in relatives and twice in alcohol dependent subjects (in admission and after the completion of detoxification period) using diagnostic kits from Medicon, Germany. Hematocrit, hemoglobin and thyroid hormonal levels (FT3, FT4, TSH) were measured once in both relatives and alcohol dependents, on admission.

In alcohol dependent subjects, depressive and anxiety symptoms were assessed through the Hamilton Depression Rating Scale (HAM-D) and the Hamilton Anxiety Rating Scale (HAM-A). Overall functioning was assessed through the Global Assessment Scale (GAS). Depressive and anxiety symptoms, as well as the level of functioning, were initially evaluated within 48 h upon entering the program (1st assessment at time point 1) and sequentially assessed at the discharge, after the 4–5 weeks detoxification period.

Patients were also evaluated for social phobia by the Liebowitz Social Anxiety Scale [19], which produces measures for social and performance fear/avoidance, for general fears with the Mark & Mathews Scale [21], hypochondriac symptoms by the Pilowski scale [32], obsessive compulsive dimensions with