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ORIGINAL ARTICLE

Analysis of the relationship between interleukin polymorphisms within miRNA-binding regions and alcoholic liver disease☆

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KEYWORDS
Interleukin;
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Abstract
Introduction: Alcohol consumption promotes inflammation through the Toll-like receptor 4 (TLR4)/nuclear factor (NF)-κB pathway, leading to organic damage. Some micro-RNA (miRNA) molecules modulate this inflammatory response by downregulating TLR4/NF-κB pathway mediators, like interleukins (ILs). Thus, polymorphisms within IL genes located near miRNA binding sites could modify the risk of ethanol-induced damage. The present study analyzed potential relationships between alcoholism or alcoholic liver disease (ALD) and *IL12B* 2124 G>T (rs1368439), *IL16* 5000 C>T (rs1131445), *IL1R1* 3114 C>T (rs3917328), and *NFKB1* 3400 A>G (rs4648143) polymorphisms.
Patients and methods: The study included 301 male alcoholic patients and 156 male healthy volunteers. Polymorphisms were genotyped using TaqMan® PCR assays for allelic discrimination. Allele and genotype frequencies were compared between groups. Logistic regression analysis was performed to analyze the inheritance model.
Results: Analysis of the *IL1R1* (rs3917328) polymorphism showed that the proportion of allele T carriers (CT and TT genotypes) was higher in healthy controls (9.7%) than in alcoholic patients (6.5%; $p = .042$). However, multivariable logistic regression analyses did not yield a significant result. No differences between groups were found for other analyzed polymorphisms.

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Conclusions: Our study describes, for the first time, the expected frequencies of certain polymorphisms within miRNA-binding sites in alcoholic patients with and without ALD. Further studies should be developed to clarify the potential relevance of these polymorphisms in alcoholism and ALD development.

PALABRAS CLAVE
Interleucina;
Polimorfismo genético;
Enfermedad hepática alcohólica;
Alcoholismo;
Respuesta inflamatoria

Análisis de la relación entre polimorfismos en regiones diana de micro-ARN y la enfermedad hepática alcohólica

Resumen
Introducción: El consumo de alcohol induce una respuesta inflamatoria mediada por los receptores de tipo Toll 4 (TLR4) y el factor nuclear (NF)-κB, originando daño orgánico. Algunos micro-ARN (miARN) modulan la respuesta inflamatoria mediante retroalimentación negativa de mediadores como las interleucinas (IL). Así pues, polimorfismos en los genes de algunas IL localizados cerca de las dianas de los miARN podrían modificar el riesgo de daño orgánico inducido por el alcohol. Este estudio analizó la posible relación entre el alcoholismo o la enfermedad hepática alcohólica (EHA) y los polimorfismos *IL12B* 2124 G>T (rs1368439), *IL16* 5000 C>T (rs1131445), *IL1R1* 3114 C>T (rs3917328) y *NFKB1* 3400 A>G (rs4648143).
Pacientes y métodos: Se incluyeron 301 pacientes alcohólicos varones y 156 voluntarios sanos varones. Los polimorfismos fueron genotipados mediante discriminación alélica utilizando el sistema de PCR TaqMan®. Se compararon las frecuencias alélicas y genotípicas entre grupos y se realizó un análisis de regresión logística para dilucidar el modelo de herencia.
Resultados: El análisis del polimorfismo de *IL1R1* (rs3917328) mostró que la proporción de portadores del alelo T (genotipos CT y TT) era mayor en los controles sanos (9,7%) que en pacientes alcohólicos (6,5%, p = 0,042). Sin embargo el análisis de regresión logística no mostró resultados significativos. No se encontraron diferencias significativas entre grupos con respecto al resto de polimorfismos estudiados.
Conclusiones: Nuestro estudio describe, por primera vez, las frecuencias esperadas de polimorfismos en regiones diana de miARN en pacientes alcohólicos con y sin EHA. Serán necesarios nuevos estudios para aclarar la relevancia de estos polimorfismos en el desarrollo de alcoholismo o EHA.

Background

Genetic predisposition plays a key role in susceptibility to alcoholism[1] and ethanol-induced organ damage.[2] Previous association studies on alcoholism susceptibility have focused on candidate genes with potential involvement in brain reward systems.[3] Genetic studies on alcoholic liver disease (ALD) have mainly analyzed variants in genes encoding liver enzymes[4,5] and inflammatory response mediators.[6] However, in both cases, the complete profiles of the genetic variants underlying disease susceptibility remain unknown.

Single nucleotide polymorphisms (SNPs) in interleukin (IL)-encoding genes and interleukin receptors have been studied because of their potential relationship with the alcohol-induced inflammatory response. In particular, researchers have studied SNPs within IL-encoding genes involved in the Toll-like receptor 4 (TLR4) and nuclear factor (NF)-κB[7–9] pathway, which is activated by bacterial lipopolysaccharide (LPS). Alcohol consumption increases LPS blood levels,[10] and TLR4/NF-κB pathway activation determines the secretion of certain inflammatory cytokines, such as tumor necrosis factor (TNF)-α, which, in turn, are able to activate apoptosis, increase oxidative stress and cause liver damage through Kupffer cell activation.[11–13] The relevance of this pathway in ALD pathogenesis has been clearly established,[14] and its potential association with alcohol dependence has also been studied.[15]

Certain micro-RNA (miRNA) molecules play important roles in inflammation by downregulating TLR4/NF-κB pathway mediators.[16] Accordingly, SNPs within miRNA genes or within IL-encoding genes located near a specific miRNA binding site could modify the inflammatory response to diverse stimuli, including alcohol intake.[17] Specifically,