Distribution of the ATP-binding cassette transporter ABCG8 IVS1-2A>G genotype and clinical characteristics of gallbladder patients in Northeastern Mexico: A pilot study

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Abstract. Biliary lithiasis is a multifactorial pathology determined by the interaction of genes and the environment, characterized by alterations in cholesterol homeostasis and in the metabolism of bile salts. A number of gene polymorphisms and mutations have been identified in the ATP-dependent cholesterol transporter (ABCG8) associated with lithiasis disease. The aim of the present study was to evaluate the association of the ABCG8 gene mutation IVS1-2A>G with cholecystolithiasis in patients from Northeast Mexico. This was a pilot study including 90 Mexican subjects diagnosed by ultrasonography, 57.8% of which presented gallstones. The studied parameters included: Lipid profile, total protein in plasma and polymerase chain reaction-restriction fragment length polymorphism genotyping. Significant differences were identified in total plasma protein, weight and BMI values, with these being these higher in subjects with gallstones ($P<0.05$). The presence of the mutant allele IVS1-2G was not detected, and the IVS1-2A wild-type allele was present in 100% of the population. Therefore, no association was apparent between the presence of the splice site mutation in ABCG8 (IVS1-2A>G) and the presence of gallstones in the evaluated subjects.

Introduction

Cholecystolithiasis is an established health problem with medical, social and economic implications due to its typically high rate of occurrence and associated complications. It is a chronic and frequent pathology of the digestive system, and is generally treated by cholecystectomy (1). Cholecystolithiasis is among the five main reasons prompting surgical intervention worldwide, and the primary reason in Mexico and other countries in Latin America (1), and thus represents the digestive disease with greatest economic burden in Western countries (2). In modern times, biliary lithiasis has been described as a multifactorial pathology, determined by the interaction of genes and the environment and characterized by alterations in cholesterol homeostasis and in the metabolism of bile salts (3). In this regard, the ATP-binding cassette gene subfamily G member 8 (ABCG8), which transports cholesterol to the canalicular membrane of hepatocytes and the brush border of enterocytes, has been described as a major genetic determinant for the development of gallstones in humans (3), and is among the most studied of ABC transporters at clinical and experimental levels (4-6).

In 2002, it was reported that Sitosterolemia may be caused by mutations in exon 5 of the ABCG8 gene (c.584T>A; Leu195Gln) in a German population (7). In fact, mutations and polymorphisms in ABCG5 and ABCG8 genes were identified in these patients (7). In other studies, the involvement of ABCG8 gene polymorphisms D19H and Y54C/T400K have been associated with the development of gallstone disease in German, Romanian, Scandinavian, Chinese and Indian populations, among others (8,9). Recently, a genome-wide association study meta-analysis conducted by Joshi *et al* (10) revealed the association of two ABCG8 gene polymorphisms, rs11887534 and rs4245791, with the risk of developing gallstones.

Furthermore, a study conducted by Hubacek *et al* (11) identified an ABCG8 gene mutation in the splicing acceptor of intron 1 (IVS1-2A>G) in patients with Sitosterolemia, inducing alternative splicing. However, to the best of our knowledge there have been no new studies describing the participation of IVS1-2A>G gene mutation in the development of Sitosterolemia and gallstone disease to date.

As gallstone lithiasis is a common pathology in Mexico, and there is a lack of published Mexican studies determining the existence of clinical, biochemical and molecular markers

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