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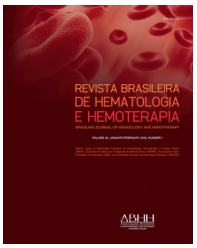

Original article

Lack of association between Kidd blood group system and chronic kidney disease

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ABSTRACT

Background: The Kidd blood group system has three antigens, Jk^a, Jk^b and Jk3, found on red blood cells and on endothelial cells of the inner lining of blood vessels in the renal medulla. These are known as urea transporter B (UT-B). Researchers have found that individuals carrying the Jk(a – b–) or Jk-null (UT-B null) phenotypes have a lower urine-concentrating capability and risk of severe renal impairment. This study evaluated the distribution of the JK phenotypes in patients with chronic kidney disease and a possible association of JK antigens with the development of renal disease.

Methods: Jk^a and Jk^b antigens were phenotyped using the gel column agglutination test (ID-cards Bio-RAD) in 197 patients with chronic kidney disease and 444 blood donors, as the control group. The phenotype and antigen frequencies between patients and controls were evaluated using the Chi-square method with Yates correction and logistic regression after adjustments for gender and age.

Results: No differences were observed between the Jk phenotype frequency distribution between patients with chronic kidney disease and blood donors [Jk(a – b+) = 22.3% and 27.2%; Jk(a + b–) = 30.5% and 24.3%; Jk(a + b+) = 47.25% and 48.4%, respectively].

Conclusion: The distribution of JK phenotypes found in the studied population is expected for Caucasians; Jk^a and Jk^b antigens and phenotypes were not found to be related to susceptibility for chronic kidney disease.

Introduction

The red blood cell (RBC) membrane contains many anchored surface proteins and proteins that cross the lipid bilayer carrying different blood group antigens. Currently, 36 systems[1] of RBC groups have been described according to the International Society of Blood Transfusion (ISBT) (http://www.isbtweb.org). Among them, the Kidd blood group system (JK; ISBT 009) has been recognized as clinically important since its identification in 1951.[2]

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Antigens of the Kidd blood group system are expressed on type 3 glycoproteins, also known as the urea transporter B (UT-B). This protein contains 389 amino acids and passes ten times through the lipid bilayer with both the N terminus and C terminus being intracellular. Three antigens have been found (Jk^a, Jk^b and Jk3) on the neighboring fourth extracellular looping and three phenotypes, Jk(a + b−), Jk(a − b+), and Jk(a + b+), are common among different populations. The Jk(a − b−) phenotype is rare in most populations. It was first found in a Filipina of Spanish and Chinese ancestry with the antibodies usually being detected after transfusions or pregnancies. After immunization, anti-Jk3 can be found in patients with the Jk(a − b−) recessive phenotype, causing acute and delayed hemolytic transfusion reactions.[3,4]

The Jk glycoprotein is coded by the *Solute carrier family 14, member A1* (*SLC14A1*) gene, a member of the urea-transporter gene family, located on chromosome 18q12-q21 and organized into 11 exons. The two major codominant alleles of the gene, *JK*A* and *JK*B*, have similar frequencies in Caucasian populations (0.51 and 0.49, respectively) and define the Jk^a and Jk^b antigens, respectively. The Jk^a/Jk^b polymorphism is defined by 838 A>G in exon 9 (Asp280Asn substitution), the other two single nucleotide polymorphisms (SNPs) cause no changes to the amino acid sequence.[5]

The Kidd antigens or UT-B are expressed on RBCs and the endothelium of the vasa recta and epithelial surfaces of the renal inner medulla, as well as in non-renal tissues and endothelial cells.[6–8] The Kidd protein is a major transporter of urea across the RBC membrane and this rapid process helps maintain the osmotic stability of the cell. Null phenotype individuals lack this transporter. Within the Kidney, the urea transporter enables the renal medulla to maintain a high concentration of both urea and urine, as well as conserve water. Individuals with the Jk(a − b−) phenotype have lower urine-concentrating ability.[9–11] In UT-B-null mice, long-term UTB deficiency was associated to severe renal dysfunction and structural damage.[12] UT-B isoforms are also important in several cellular functions, including urea nitrogen salvage in the colon, nitric oxide pathway modulation in the hippocampus, and normalization of the cardiac conduction system.[13]

Chronic kidney disease (CKD) is a major public health problem, defined as abnormalities of kidney structure and/or function, present for at least three months with implications on health.[14] The adverse outcomes of the disease include loss of kidney function, cardiovascular disease and premature death. Besides environmental factors, genetic abnormalities are also involved[15] including variations in the *MYH9* (encoding non-muscle myosin IIA heavy chain),[16] *APOL1* (apolipoprotein L1),[17–19] *NPHS1* (nephrin),[20] and *SHROOM3* (shroom family member 3)[21] genes.

The relationship between the Kidd antigens and chronic kidney disease remains unknown. Therefore, the aim of this study was to investigate the distribution of JK phenotypes in patients with the chronic kidney disease and a possible association of JK antigens with the development of renal disease.

Methods

The ethical and methodological aspects of this study were approved by the Ethics Committee of Research on Human Beings from the Maringa State University (COPEP-UEM # 1.141.385/2014, CAAE 43117115.0.0000.0104, according to the Resolution of the Brazilian Council on Health-CNS 466/12.

Subjects

This retrospective case–control study enrolled 197 unrelated patients with chronic kidney disease (CKD group) and 444 unrelated blood donors as a control group, living in the same geographical area as the patients. The individuals were attended and immunophenotyped between 2013 and 2015 at the Regional Blood Bank of Pato Branco, southwest region of Parana (located in the southern region of Brazil at 26°13′46″–09″S and 52°40′16″–09″W).

Serologic tests

Red blood cell phenotyping for Kidd blood group systems was performed on a gel card (ID-Perfil II – k-Kp^a-Kp^b-Jk^a-Jk^b-ctl) using monoclonal antibodies according to the manufacturer's instructions (Diamed ID-Cards, DiaMed® AG, Switzerland). RBCs were suspended in Bromelin solution (BioRad ID-Diluent 1) at a final concentration of 1:21 or 5%.

Statistical analysis

The antigen and phenotype frequencies were estimated and the data was tested for their fit to the Hardy–Weinberg equilibrium[22] by calculating the expected frequencies of the genotypes and comparing them with the observed values. The Student's *t*-test was used to compare differences between groups. Statistical comparisons between these groups were performed and the estimated risk of developing CKD in individuals who have genetic polymorphisms was calculated by determining the Odds Ratio (OD) with a 95% of confidence interval (CI) adjusted for gender and age. Association tests were carried out to identify the codominant, dominant, recessive, overdominant and log-additive genetic inheritance models. p-Values ≤ 0.05 by the Chi-square test with Yates correction and logistic regression were considered statistically significant. All statistical analyses were performed using the software OpenEpi program Version 2.3.1 (http://www.openepi.com) and SNPstats[23] (http://bioinfo.iconcologia.net/index.php).

Results

The Kidd phenotype frequency distribution in the studied populations was in Hardy–Weinberg equilibrium (p-value = 0.48: CKD and p-value = 0.51: controls).

The characteristics of patient and control subjects are described in Table 1. The CKD patients were between 45 and 90 years old (62.8 ± 13.9) and from both genders (male: 55.8%; female: 44.2%). Regarding ethnicity, all patients declared

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