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Molecular genetic analysis of the Kidd blood group system in a Taiwanese family with Jk_{null} phenotype

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ABSTRACT

Two common polymorphisms of 588G/A and 838G/A have been demonstrated in the *JK* gene, and the latter defines the Jk^a/Jk^b phenotypes. The Jk_{null} phenotype has been characterized as the absence of Jk^a and Jk^b antigen expression on red cells. We performed a molecular analysis of a family with the Jk_{null} phenotype and subsequently demonstrated the presence of different *JK* cDNA haplotypes. In the study, three members of a Jk_{null} family and 48 randomly-selected individuals were enrolled. The coding exons of the *JK* gene of the Jk_{null} family members were amplified by polymerase chain reaction (PCR), and the sequences were analyzed. The genomic region, encompassing exons 7~9 of the *JK* gene was PCR-amplified, cloned, and sequence-determined to elucidate the *JK* haplotype. We demonstrated that 3 missense mutations, 222C>A, 499A>G and 896G>A were in the *JK* genes of the Jk_{null} family members, in addition to the known IVS5-1g>a splice site mutation. Analysis of 48 randomly-selected individuals showed that 499A>G was a common polymorphism, besides 2 JK^{null} alleles with respective mutation of 222C>A and 896G>A being demonstrated in the Jk_{null} family. After compiling the nucleotide information of the polymorphic 499, 588, and 838 positions from the randomly-selected individuals, 5 *JK* cDNA haplotypes, constituted by the 3 polymorphic sites, were demonstrated. Among these, the JK^{a1} (499A, 588G and 838G; 46.9%), JK^{b1} (499A, 588G and 838A; 23.9%), and JK^{b2} (499G, 588G and 838A; 21.9%) were found as the 3 major haplotypes in the Taiwanese population. In conclusion, the Jk_{null} phenotypes with respective mutations of 222C>A, 896G>A and IVS5-1g>a, were identified in a Taiwanese family. The existence of 5 *JK* cDNA haplotypes with the 499A/G polymorphism was also demonstrated in the Taiwanese population.

Keywords: blood group, Kidd, *JK*, Jk_{null}

INTRODUCTION

The Kidd blood group system comprises 3 antigens, Jk^a, Jk^b, and Jk3 [1-3]. The Jk^a antigen was first described in 1951 by Allen *et al*., who identified the antibody that defined the new blood group antigen in the serum of a parturient of a baby with erythroblastosis foetalis[4]. Two years later, Plaut *et al*. demonstrated the Jk^b antigen, and showed it is antithetical to Jk^a[5]. Jk^a and Jk^b antigens are polymorphic in all popula-

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Conflict of interests

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tions tested, and define the 3 common phenotypes of the Kidd blood group system, Jk(a+b−), Jk(a+b+), and Jk(a−b+). The null phenotype of the Kidd blood group, called Jk_{null} or Jk(a−b−), in which the red cells lack all Jk antigens, has been identified, though rare, in several populations. The Jk3 antigen is common to both Jk^a− and Jk^b−positive red blood cells and is absent only on Jk_{null} red blood cells.

It is known that Jk_{null} red blood cells are resistant to lysis in 2 mol/L urea solution[6], and this phenomenon has led to the supposition that the Kidd protein might be a urea transporter. In 1999, Sidoux−Walter *et al*. cloned the *JK* gene responsible for the Kidd protein on red blood cells[7], and demonstrated that Kidd glycoprotein functions as a urea transporter. The *JK* gene (recognized by the HUGO Gene Nomenclature Committee as *SLC14A1*; solute carrier family 14, member 1) is located on chromosome 18q11−q12, and is composed of 11 exons which span over 30 kb of genomic DNA; the exon 3 region appears alternatively−spliced in the processing of *JK* mRNA transcript[8]. The coding sequence of the *JK* gene is located in exon 4~11 and encodes a polypeptide of 389 amino acids. The molecular basis for the Jk^a and Jk^b phenotypes has been demonstrated to result from the G and A difference at nucleotide 838, which leads to the amino acid alteration of Asp and Asn at residue 280 of the Kidd polypeptide, respectively[9]. Furthermore, in addition to the polymorphism of 838G/A in exon 9, a silent polymorphism of 588G/A in exon 7 has been identified in the *JK* gene, and it has been suggested that the JK^a (838G) and JK^b (838A) alleles are associated with the 588A and 588G nucleotides, respectively [10,11].

The Jk_{null} phenotype is rare in most ethnic populations across the world. For instance, incidences of 0.002% and 0.03% for Jk_{null} phenotype were demonstrated in the Finnish and Japanese population, respectively [2,12,13], and no Jk_{null} individual was identified after screening of 52,908 English and 120,000 European New Zealanders [6,14]. However, the Jk_{null} phenotype has been found to be relatively abundant in Polynesian population groups with phenotype frequencies of 0.1%~1.4%[15]. To date, several molecular bases for the JK^{null} allele have been demonstrated. The first two bases identified were the G to A mutation at the 3′−acceptor splice site of intron 5 (intervening sequence IVS5−1g>a) and the G to A mutation at the 5′−donor splice site of intron 7 (IVS7+1g>a) of the *JK* gene, which were demonstrated in a Chinese and a French Jk_{null} individual, respectively[8]. The IVS5−1g>a and IVS7+1g>a mutations lead to the skipping of exon 6 and exon 7 regions, respectively, during the processing of *JK* mRNA transcript. The $JK^{IVS5-1g>a}$ mutation was later shown to be the main molecular basis responsible for the high Jk_{null} incidences in Polynesians, and the frequency of 8.7% for the $JK^{IVS5-1g>a}$ allele was demonstrated in this population[10,16]. The Jk_{null} phenotype was identified as present in Taiwanese population groups [17]. Our recent investigation showed a wide distribution of the $JK^{IVS5-1g>a}$ allele in population groups in Taiwan and in 3 Southeast Asian populations, Fujian (southeast coast of China), Filipino, and Indonesian, and a relatively high frequency of the $JK^{IVS5-1g>a}$ allele was demonstrated in a number of Taiwanese indigenous groups, with the highest frequency of 7.8% being demonstrated for the Paiwan tribe[18]. On the other hand, the Jk_{null} phenotype in the Finnish population was demonstrated to result from homozygous 871T>C missense mutation [10,16]. In addition, nonsense mutations of 202C>T and 582C>G, missense mutation of 956C>T, and 723delA in *JK* gene [11,19], and partial deletion of *JK* locus chromosome region[19,20] have been identified to be responsible for the Jk_{null} phenotype (listed in the Blood Group Antigen Gene Mutation Database, http://www.ncbi.nlm.nih.gov/mhc/xslcgi.cgi?cmd=bgmut/home) [21].

We performed a molecular genetic analysis of a Taiwanese family with the Jk_{null} phenotype. Two JK^{null} alleles were demonstrated in this family, and further investigation identified 5 *JK* cDNA haplotypes, constituted by polymorphic nucleotides at 499, 588, and 838 positions, in the Taiwanese population.

MATERIALS AND METHODS

Samples

Three members of a Jk_{null} family and 48 randomly−selected individuals were enrolled in the present study. All of the assessed individuals belonged to the Taiwanese population, and informed consent was obtained from all participants. The use of human subjects was conducted under the tenets of the Helsinki protocol and the program was approved by the Institutional Review Board at Mackay Memorial Hospital.

Sequence analysis for the *JK* gene exon regions

Before sequence analysis, Jk phenotype was analyzed by anti−Jk^a (Gamma Biologicals Inc., Houston, TX) and anti−Jk^b (Sanquin, Amsterdam,Nethelands) reagents. Genomic DNAs of the subjects were then prepared from peripheral blood cells using the QIAamp DNA Blood Mini Kit (Qiagen GmbH, Hilden, Germany). The coding regions (exon 4~11) of the *JK* gene were divided into four segments, exon 4~5, exon 6~7, exon 8~9, and exon 10~11; each segment was amplified by polymerase chain reaction

(PCR) using designed primer pairs flanking for each specific exon region. The sequences and locations of the primer pairs and the expected PCR product sizes are shown in ***Table 1.*** Fifty ng of genomic DNA and 5 pmol of each forward and reverse primer were combined in 12.5 μL of PCR buffer containing 0.2 mmol/L of dNTP and 0.625 unit of *PfuUltra*™ hotstart DNA polymerase (Stratagene, La Jolla, CA, USA). The amplified DNA fragments were then directly sequenced using the BigDye Terminator Cycle Sequencing Kit

Table 1 **PCR primers for amplification of the coding regions of the *JK* gene**

Encompassing region	Sequence(5′→3′)	Location	Product size
Exon 4~5	JKFc: ACTGTGGGATTTGGGTTTGG	157 bp upstream to exon 4	1,248 bp
	JKRd*: CTGTAACTGATTCCCTGACC	146 bp downstream to exon 5	
Exon 6~7	JKFe: GGGACCACTGATCTAAATGC	203 bp upstream to exon 6	2,771 bp
	JKRh*: CTTAGACCCTAATGCTCTGG	153 bp downstream to exon 7	
Exon 8~9	JKFk: AGGCATGTGTTGCATGCACC	213 bp upstream to exon 8	866 bp
	JKRm*: CACACTTAGACAGCAAGTGG	113 bp downstream to exon 9	
Exon 10~11	JKFn: ATGGAGCTCCTAAGTGATGG	154 bp upstream to exon 10	1,964 bp
	JKRp*: TACCAGAGCACATCACCTGG	194 bp downstream to stop codon	

(Applied Biosystems, Foster City, CA) to examine the sequences of the exons and the adjacent splice acceptor and splice donor sites.

Molecular cloning for *JK* haplotype analysis

To determine the genotype of the *JK* cDNA haplotype, constituted by the nucleotide polymorphisms at 499, 588, and 838 positions of an individual, the genomic region encompassing exon 7 through exon 9 of the *JK* gene was amplified by nested PCR and cloned. In the first PCR amplification, 50 ng of genomic DNA and 5 pmol of each forward (ACTGCCTCTATAATAGGATTTATCCCA, 143 bp upstream to exon 7) and reverse (GGTAGGCAGAGGTGATTTTAATGCTC, antisense sequence, 163 bp downstream to exon 9) primer were combined in 12.5 μL of PCR buffer containing 0.2 mmol/L of dNTP and 0.625 unit of *PfuUltra*™ hotstart DNA polymerase. The PCR program included 2 min at 95 ℃ followed by 30 cycles of 15 sec at 95℃, 30 sec at 58℃, and 3 min at 68 ℃. A primer pair with sequences of CAGAGTATAGCGATTCCGTGTGTCAGCC (43 bp upstream to exon 7) and CTGCTTATCCTTGATTGAGATCCTGTAGTC (antisense sequence, 36 bp downstream to exon 9) was then used for the second round PCR, and one thousand fold dilution of the product from the first PCR served as template. The conditions for the second PCR were identical to those for the first PCR. The nested PCR–amplified product, ~3,400 bp, was cloned into the pCR4Blunt–TOPO vectors using a Zero Blunt TOPO PCR Cloning Kit (Invitrogen, Carlsbad, USA). The DNA sequence of each clone was determined to inspect the nucleotides at positions 499, 588, and 838, and multiple clones from one individual sample were selected and analyzed to determine the *JK* genotype of the individual.

RESULTS

Identification of 2 JK^{null} alleles in the Jk_{null} family

The mother in the family***(Fig. 1)*** was initially discovered because her serum was found to contain anti–Jk3 antibody on routine serology; further Jk phenotyping demonstrated Jk(a–b–) phenotype for the mother and her daughter and Jk(a–b+) phenotype for the father. The sequences of the coding exons

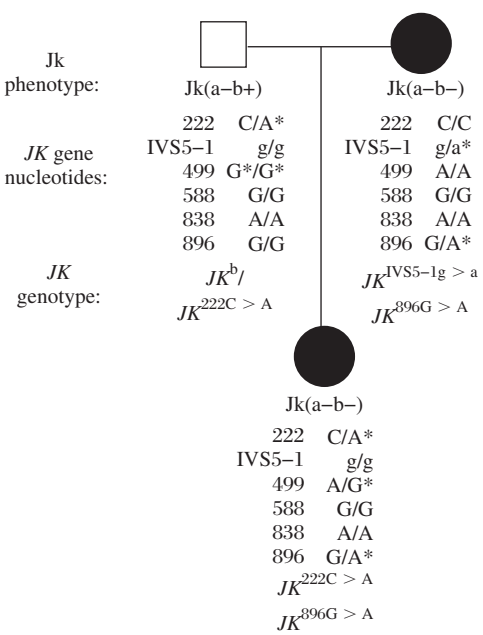

Fig. 1 **The pedigree, Jk phenotypes, and *JK* genotypes of the Jk_{null} family members**. Open and solid symbols for male (square) and female (circle) denote an individual with common Jk and Jk_{null} phenotypes, respectively. The Jk phenotype, the nucleotide changes identified in the *JK* gene and the 588 and 838 polymorphic positions, and the *JK* genotype of each member are shown under each symbol. *, the nucleotides that are different from the wild–type *JK* sequence.

(exons 4~11) and adjacent splice acceptor and splice donor sites of the *JK* genes of the 3 family members were analyzed as described in MATERIALS AND METHODS. The sequencing results demonstrated that the mother was a heterozygote with IVS5−1g>a splice site mutation and 896G>A missense mutation, as illustrated in ***Fig. 1***, while the father possessed 1 *JK* allele with a 222C>A missense mutation and was homozygous for the 499A>G nucleotide alteration. The results obtained form the daughter suggested that she harbored 1 *JK* allele with 222C>A and 499A>G alterations from her father and another *JK* allele with the 896G>A mutation from her mother. All 3 family members were shown to be homozygous for G and A nucleotides at the common polymorphisms of 588 and 838 positions, respectively. Thus, in this Jk_{null} family, in addition to the known JK^{null} mutation of IVS5−1g>a, 3 nucleotide changes of 222C>A, 499A>G, and 896G>A were identified in comparison with the wild−type *JK* coding sequence.

Genomic DNA samples prepared from 48 randomly−selected individuals (listed in ***Table 2***) were analyzed to examine the 222C>A, 499A>G, and 896G>A alterations in the general *JK* gene pool. To determine the nucleotides at positions 222 (locating exon 5), 499 (locating exon 7), and 896 (locating exon 9), the *JK* exon regions 4~5, 6~7, and 8~9 of these samples were PCR−amplified and sequence−determined. The results showed that none of the 48 randomly−sampled individuals possessed the 222C>A and 896G>A changes, demonstrating that these 2 nucleotide changes were virtually absent in the general population. However, the 499A>G alteration was found to be commonly present in the general *JK* gene pool of Taiwanese (***Table 2***). The incidences of 499A and 499G in these 48 randomly−selected individuals were 76.0% and 24.0%, respectively.

The sequence analysis results for the *JK* genes of the Jk_{null} family members and the population analysis revealed 3 different JK^{null} alleles in this family, the known $JK^{IVS5-1g>a}$ and the novel $JK^{222C>A}$ and $JK^{896G>A}$ alleles (***Fig. 2***), and the existence of a common polymorphism of 499A/G in the *JK* gene. Obviously, the Jk_{null} phenotype of the mother and daughter resulted from the genotypes of $JK^{IVS5-1g>a}/JK^{896G>A}$ and $JK^{222C>A}/JK^{896G>A}$, respectively. The $JK^{222C>A}$ and $JK^{896G>A}$ alleles both had the JK^{b} (838A) gene backbone, and the 222C>A and 896G>A mutations lead to the amino acid substitutions of Asn to Lys at residue 74 and Gly to Glu at residue 299 in the Kidd protein, respectively. As for polymorphism at the 499 position, the 499A and 499G nucleotides lead to the encoding of Met and Val amino acids at residue 167 in the Kidd protein, respectively. As shown in ***Table 2***, the Jk phenotypes of 20 of the 48 individuals were determined, and the Jk(a+) and Jk(b+) serological phenotypes of these

Table 2 **The nucleotides at 499, 588, and 838 positions, Jk phenotypes, and *JK* genotypes of randomly−selected Taiwanese individuals**

Sample	Jk phenotype	499	588	838	*JK* genotype[#]
M1	a+b−	A/A	G/G	G/G	a1/a1
M5	a+b−	A/A	G/G	G/G	a1/a1
M6	−	G/G	G/G	A/A	b2/b2
M7	a+b−	A/A	G/G	G/G	a1/a1
M9	a+b−	A/A	A/G	G/G	a1/a2
M10	a+b+	A/A	G/G	A/G	a1/b1
M12	a+b−	A/A	G/G	G/G	a1/a1
M14	a−b+	G/G	G/G	A/A	b2/b2
M16	a+b+	A/A	G/G	A/G	a1/b1
M18	a+b+	A/A	G/G	A/G	a1/b1
M20	−	A/A	G/G	G/G	a1/a1
M21	a+b+	A/A	A/G	A/G	a2/b1*
M22	−	A/A	G/G	G/G	a1/a1
M23	a+b−	A/A	G/G	G/G	a1/a1
M25	a+b−	A/A	A/G	G/G	a1/a2
M26	−	A/A	G/G	A/G	a1/b1
M27	a+b+	A/G	G/G	A/G	a1/b2*
M28	−	A/G	G/G	A/A	b1/b2
M29	a−b+	A/G	G/G	A/A	b1/b2
M31	a+b−	A/A	G/G	G/G	a1/a1
M32	a+b−	A/A	G/G	G/G	a1/a1
M35	a+b+	A/A	G/G	A/G	a1/b1
M36	a−b+	A/G	G/G	A/A	b1/b2
M37	a−b+	A/G	G/G	A/A	b1/b2
T15	−	A/A	G/G	A/G	a1/b1
T17	−	A/A	G/G	A/G	a1/b1
T18	−	A/G	G/G	A/A	b1/b2
T19	−	A/A	G/G	G/G	a1/a1
T20	−	A/A	A/G	G/G	a1/a2
T21	−	A/A	G/G	A/G	a1/b1
T22	−	A/A	G/G	G/G	a1/a1
T23	−	A/G	G/G	A/G	a1/b2*
T27	a+b+	A/G	G/G	A/G	a3/b1*
T28	−	A/A	G/G	A/A	b1/b1
T35	−	A/A	G/G	G/G	a1/a1
T40	−	A/G	G/G	A/A	b1/b2
T47	−	A/A	G/G	G/G	a1/a1
T49	−	A/A	G/G	A/G	a1/b1
T51	−	A/G	A/G	A/G	a2/b2*
T54	−	G/G	G/G	A/A	b2/b2
T55	−	G/G	G/G	A/G	a3/b2
T57	−	A/G	G/G	A/G	a1/b2*
T60	−	G/G	G/G	A/A	b2/b2
T61	−	A/G	G/G	A/A	b1/b2
T62	−	A/A	G/G	A/G	a1/b1
T63	−	A/G	G/G	A/G	a1/b2*
T71	−	A/A	G/G	A/G	a1/b1
T72	−	A/A	G/G	A/G	a1/b1

− undetermined. [#]a1, a2, a3, b1, and b2 represent the JK^{a1}, JK^{a2}, JK^{a3}, JK^{b1}, and JK^{b2} alleles, respectively. Genotypes demonstrated through cloning of the *JK* exon 7~9 region are indicated by an asterisk "*".

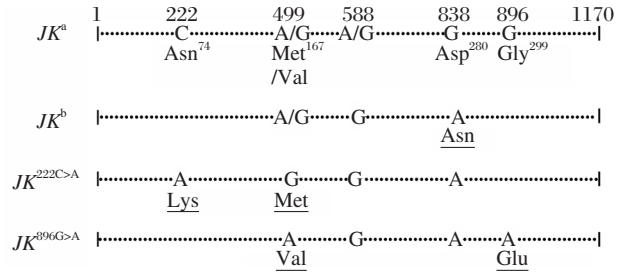

Fig. 2* Differences in nucleotides and predicted amino acids between wild-type *JK*^{a} and *JK*^{b} and the two mutant *JK* cDNAs.** The polymorphism of 499A and 499G nucleotides, leading to the encoding of Met and Val at residue 167, respectively, was found in both *JK*^{a} and *JK*^{b} alleles (detailed in the text and shown in ***Fig. 3). Besides, the *JK*$^{222C>A}$ and *JK*$^{896G>A}$ alleles were found to have the *JK*^{b} (838A) gene backbone, and to bear 499G and 499A nucleotides, respectively.

individuals were not influenced by the different genotypes at the 499 position; thus, the substitution of Met and Val at residue 167 in the Kidd protein apparently did not affect the normal Jk(a+) and Jk(b+) serological phenotypes. This finding explains the common Jk(a–b+) phenotype of the father in the Jk_{null} family, who was homozygous for the 499A>G change.

Identification of 5 *JK* cDNA haplotypes in the Taiwanese population

The known polymorphisms of the 588 and 838 positions of *JK* gene are located in the same exon regions as the 499 and 896 nucleotides, respectively. When analyzing the 499 and 896 nucleotides of the 48 randomly-selected individuals, the nucleotides at the 588 and 838 positions were also determined (***Table 2***). Consistent with previous finding, the 838G and 838A nucleotides in the *JK* gene were associated with the Jk(a+) and Jk(b+) phenotypes, respectively, and the results in the 48 randomly-selected Taiwanese individuals showed frequencies of 54.2% and 45.8% for *JK*^{a} and *JK*^{b} alleles, respectively. However, we found entirely different incidences of the 499A and 499G nucleotides (76.0% and 24.0%, respectively) and the 588G and 588A nucleotides (94.8% and 5.2%, respectively) compared to those of the 838G and 838A nucleotides. These data indicated the existence of different *JK*^{a} and *JK*^{b} gene haplotypes constituted by the 499A/G and 588G/A polymorphisms in this population.

The nucleotide information at positions 499, 588, and 838 of the 48 individuals (***Table 2***) revealed 5 different *JK* cDNA haplotypes, including 3 *JK*^{a} alleles (with 838G) and 2 *JK*^{b} alleles (with 838A), designated *JK*^{a1}, *JK*^{a2}, *Jk*^{a3}, *JK*^{b1}, and *JK*^{b2} ***(Fig. 3)***. The *JK* genotypes of the 48 individuals are shown in ***Table 2***. The genotypes of 41 of them can be directly predicted from the nucleotide information obtained by direct sequencing. However, the genotypes of the other 7 individuals (asterisked) were determined by cloning of exons 7~9 region of the *JK* gene, as described in MATERIALS AND METHODS, and the 499, 588, and 838 nucleotide positions of multiple clones from each of these individuals were sequence-determined to demonstrate their *JK* genotypes.

The frequencies of the 5 *JK* alleles in Taiwanese,

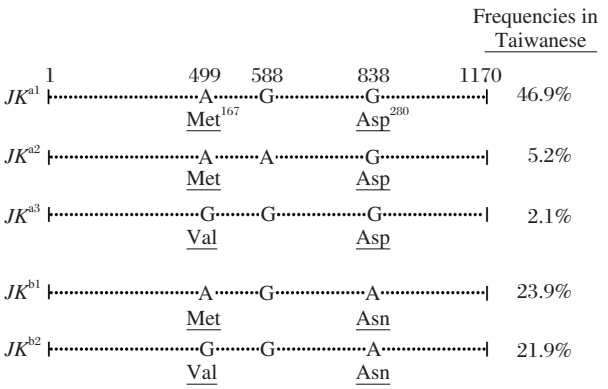

***Fig. 3* Five *JK* cDNA haplotypes and their frequencies in Taiwanese.** The 5 *JK* cDNA haplotypes are constituted by polymorphic nucleotides at 499, 588, and 838 positions.

determined from the *JK* genotypes of the 48 randomly-selected individuals, are shown in ***Fig. 3***. These results showed that *JK*^{a1}(46.9%), *JK*^{b1}(23.9%), and *JK*^{b2} (21.9%) are the 3 major *JK* alleles in this population. Among the 5 *JK* alleles, the 499A/G polymorphism was found in both of the *JK*^{a} and *JK*^{b} alleles. The 588A nucleotide is a characteristic of *JK*^{a2} allele; the 588G nucleotide is a characteristic of the other 4 *JK* alleles.

DISCUSSION

This molecular genetic study of 3 members of a Jk_{null} family found 3 different *JK*^{null} alleles, including the alleles of *JK*$^{IVS5-1g>a}$, *JK*$^{222C>A}$ and *JK*$^{896G>A}$. Furthermore, analysis of 48 randomly-selected individuals from the Taiwanese population showed that a common polymorphism of 499A/G in the *JK* gene, and its identification led to further elucidation of the existence of 5 *JK* cDNA haplotypes constituted by the polymorphic 499, 588, and 838 nucleotides in this population.

It has been demonstrated that the Kidd protein functions as a urea transporter. The topology of the Kidd protein was predicted to contain 10 transmembrane domains with 5 and 4 loops in the extracellular and cytoplasmic sides of the cell membrane, respec-

tively [22]. In the predicted topology, both the N– and C–terminal segments of the Kidd protein reside in the cytoplasmic side. However, further structural analysis is needed to elucidate the exact membrane topology of the Kidd urea transporter. According to the predicted membrane topology for the Kidd protein, the 280 amino acid position, where the Jk^a/Jk^b polymorphism of Asp/Asn alteration resides, is located on the extracellular loop, while the 167 amino acid position, which bears the common Met/Val variation led by the 499A/G polymorphism, resides in the cytoplasmic loop. This different position in the Kidd membrane structure may explain why the Met167Val variation does not present antigenicity among individuals as the Asp280Asn change does. On the other hand, the previous reported 871T>C and 956C>T mutations of the JK^{null} gene lead to the amino acid substitutions of Ser291Pro and Thr319Met, respectively. The 291 and 319 amino acid positions are located in the transmembrane domains, and it has been shown that these 2 amino acid changes lead to the diminished expression of the Kidd protein on cell membranes [11,16], which is consistent with the absence of Jk antigen expression on red blood cells of the individuals bearing these mutations. The positions of the Asn74Lys and Gly299Glu substitutions, resulted from the 222C>A and 896G>A mutations identified in the previous [23,24] and present studies, are located in the transmembrane segments. Whether the Asn74Lys and Gly299Glu amino acid changes also result in reduced expression of Kidd protein on cell membranes, thus leading to the Jk_{null} phenotype, remains to be clarified.

In the present study, the demonstration of the common polymorphism of 499A/G in the *JK* gene led to the further elucidation of the 5 *JK* cDNA haplotypes. Among the 5 *JK* alleles, the JK^{a1}, JK^{b1}, and JK^{b2} are the 3 major ones in the Taiwanese population. Together with the minor ones as JK^{a2} and JK^{a3} alleles, these 5 alleles encode 4 different Kidd urea transporters bearing amino acid combinations of Met–Asp, Val–Asp, Met–Asn, and Val–Asn at residues 167 and 280.

The 499A/G polymorphism has been registered (refSNP ID: rs2298719) in the Single Nucleotide Polymorphism (SNP) Database (dbSNP; http://www.ncbi.nlm.nih.gov/SNP/) of the National Center for Biotechnology Information (NCBI) in the United States National Library of Medicine of the National Institutes of Health. The frequencies of 499G in Asian populations (Japanese and Han Chinese) represented in the dbSNP range between 16%~25%, which are close to our results in the present study of Taiwanese participants. However, according to the dbSNP, the 499G nucleotide is virtually absent in the general *JK* gene pools of European and Africa–originated populations. Furthermore, according to the dbSNP, the 588G/A (rs2298718) and 838G/A (rs1058396) polymorphisms, though present in Asian, European, and Africa–originated populations, show quite different frequencies among these populations. The information from the dbSNP suggested that different ethnic populations possess different *JK* cDNA haplotypes and different distributions. It has been reported that the JK^a (838G) and JK^b (838A) alleles are associated with the 588A and 588G nucleotides, respectively, in the European population[11]. Nevertheless, the present study has shown this is not the case in the Taiwanese population, and information from the dbSNP also suggested this is not the case in other Asian populations. These findings further illustrated the different distribution of *JK* haplotypes in different ethnic populations.

In summary, the Jk_{null} phenotypes with respective mutations of 222C>A, 896G>A and IVS5–1g>a, were identified in a Taiwanese family. The existence of 5 *JK* cDNA haplotypes with the 499A/G polymorphism was also demonstrated in the Taiwanese population. Among these, the JK^{a1}(499A, 588G and 838G; 46.9%), JK^{b1}(499A, 588G and 838A; 23.9%), and JK^{b2}(499G, 588G and 838A; 21.9%) are the 3 major haplotypes in the Taiwanese population.

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