Review

A review of the JR blood group system

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The JR blood group system (ISBT 032) consists of one antigen, Jr^a, which is of high prevalence in all populations. The rare Jr(a–) phenotype has been found mostly in Japanese and other Asian populations, but also in people of northern European ancestry, in Bedouin Arabs, and in one Mexican. Anti-Jr^a has caused transfusion reactions and is involved in hemolytic disease of the fetus and newborn. The Jr^a antigen is located on ABCG2 transporter, a multipass membrane glycoprotein (also known as the breast cancer resistance protein, BCRP), which is encoded by the *ABCG2* gene on chromosome 4q22.1. The Jr(a–) phenotype mostly results from recessive inheritance of *ABCG2* null alleles caused by frameshift or nonsense changes. ***Immunohematology* 2013;29:63–68.**

Key Words: blood groups, JR, ABCG2, BCRP, Jr^a antigen

History

The high-prevalence erythrocyte blood group antigen Jr^a was first reported in 1970 by Stroup and MacIlroy[1] at the 23rd annual meeting of the American Association of Blood Banks, when it was recognized that five individuals had an antibody to the same antigen, present on all erythrocyte samples tested except those from each other. This new alloantibody—called anti-Jr^a, defining a "new" blood group antigen of high prevalence (named Jr after Rose Jacobs, one of the first five probands, and not an abbreviation of "Junior" as some believed)—showed no relation with any other blood group system. By 1974, Gellerman and Stroup[2] had identified 18 examples of anti-Jr^a, 7 of which had been made by Japanese people.

In 1994, Miyazaki and colleagues[3] published the isolation and characterization of an immunoglobulin G3 (IgG3) human monoclonal anti-Jr^a (HMR0921) produced by a heterohybridoma derived from mouse myeloma cells and Epstein-Barr virus (EBV)–transformed lymphocytes from a blood donor with anti-Jr^a. Using this human monoclonal antibody, the authors found a prevalence of 0.07 percent for the Jr(a–) phenotype in the Japanese blood donors. Nakajima and Ito[4] and Okubo[5] previously reported that the prevalence of the Jr(a–) phenotype in Japan was 0.03 and 0.12 percent, respectively. Other studies[6–10] have shown that the rare Jr(a–) phenotype occurs in various populations (northern European extraction, Bedouin Arabs, and one Mexican) but is found most often in Japanese and other people of Asian ancestry.

Anti-Jr^a is stimulated by either transfusion or pregnancy. A review of the literature indicates that anti-Jr^a may be clinically significant because it has been implicated in cases of hemolytic disease of the fetus and newborn (HDFN)[4,6,8,11–21] and hemolytic transfusion reactions (HTRs).[22–28] Anti-Jr^a has caused significant transfusion reactions as well as severe HDFN in some cases,[15–18] including two cases of fatal HDFN.[17,18]

In 1990, the Jr^a antigen was placed in the 901 series of high-incidence antigens by the International Society of Blood Transfusion (ISBT) and assigned #901005.[29]

For many years, numerous laboratories using various methods have failed to characterize Jr^a, and their attempts to immunoprecipitate and immunoblot the antigen using human anti-Jr^a were unsuccessful.

The rare Jr(a–) phenotype appeared to be inherited as an autosomal recessive trait as the children of Jr(a+) parents type Jr(a–),[2] but the gene controlling the expression of Jr^a was not known until two recent studies[30,31] that provided genetic and molecular evidence that null alleles in *ABCG2* define the Jr(a–) phenotype.

Jr Is Carried on ABCG2 Transporter and Encoded by *ABCG2* Gene

Recently, in an attempt to identify the gene responsible for Jr^a expression, two groups using different approaches[30,31] established the connection between the Jr(a–) blood group phenotype and *ABCG2*.

Zelinski and coworkers[30] conducted a homozygosity-by-descent (HBD) mapping study to identify the chromosomal region containing the gene responsible for Jr^a expression. Genomic DNA was extracted from stored samples of six Jr(a–) individuals (four probands). The authors performed analysis of single nucleotide polymorphisms (SNPs), (GeneChip Human Mapping, 250K Nsp array, Affymetrix, Santa Clara, CA) and identified a homozygous region of 397,000 bp located at chromosome 4q22.1 that contained four validated genes: *MEPE, SPPI, PKD2,* and *ABCG2,* but only the product of *ABCG2* was known to be expressed on red blood cells (RBCs). DNA sequence analysis defined three nonsense *ABCG2* alleles (c.376C>T, c.706C>T, and c.736C>T) in the six study subjects

(Table 1). The nonsense mutation c.736C>T was present in homozygous state in two subjects and the nonsense mutation c.376C>T was present in homozygous state in three subjects. The remaining individual was homozygous for the missense c.34G>A mutation and heterozygous for the nonsense mutation c.706C>T.

This study,[30] the first to use an HBD gene mapping strategy to identify a gene for a blood group system, provided genetic proof that the Jr(a–) phenotype is defined by the *ABCG2* null allele.

Because HMR0921 monoclonal antibody (MoAb)[3] reacted weakly with RBCs from humans, Saison and coworkers[31] explored the existence of Jr^a in different mammalian species by analyzing their RBCs by flow cytometry using HMR0921. They observed that cat RBCs reacted much more strongly than human RBCs and decided to identify the antigen recognized by the HMR0921 MoAb on cat RBCs. Using a lysate from cat RBCs, they immunoprecipitated a single protein of around 70 kDa, identified by mass spectrometry as abcg2, encoded by the cat ortholog (*abcg2*) of the human transporter gene *ABCG2*. They transfected K-562 cells with *ABCG2* and observed strong expression of ABCG2 as well as Jr^a at the surface of the *ABCG2*-transfected K-562 cells. Using these cells to immunoprecipitate ABCG2 with the HMR0921, they verified expression of Jr^a on RBCs and concluded that Jr^a is carried on *ABCG2*. Further studies including Western blot analysis proved that ABCG2 was absent in the RBC membrane of Jr(a–) individuals. Sequencing of *ABCG2* in a cohort of 18 unrelated Jr(a–) probands identified eight different mutations in *ABCG2:* five frameshift mutations (c.187_197delATATTATCGAA, c.542_543insA, c.791_792delTT, c.875_878dupACTT, c.1111_1112delAC) and three nonsense mutations (c.376C>T, c.706C>T, c.730C>T; Table 1). Interestingly, later the nonsense mutation c.706C>T was reported to be present in the homozygous state in six of seven Gypsy subjects and in the heterozygous state in the seventh Gypsy subject, suggesting that this nucleotide change is the basis of the Jr(a–) phenotype in this ethnic group.[31] Similarly, the nonsense mutation c.376C>T was present in the homozygous state in three unrelated Jr(a–) subjects from Korea, suggesting this is a founder mutation, too. Actually, this mutation has been extensively studied as a nonsynonymous SNP of *ABCG2* (rs72552713) in the Japanese population with an estimated allele frequency of 1.6 to 2.4 percent.[34,35] These are important data to be considered for implementation in RBC genotyping devices.

Table 1. Alleles encoding Jr(a–) and Jr(a+^{w}/–) phenotypes

Phenotype	Nucleotide change (exon)	Amino acid	Ethnicity*
Jr(a–)	c.376C>T (4)	Gln126Stop	Asian[30,31]
Jr(a–)	c.706C>T (7)	Arg236Stop	Caucasian[30]
Jr(a–)	c.34G>A (2), c.706C>T (7)	Va112Met, Arg236Stop	Asian[30]
Jr(a–)	c.736C>T (7)	Arg246Stop	Caucasian[30]
Jr(a–)	c.337C>T (4)	Arg113stop	Caucasian[32]
Jr(a–)	c.784G>T (7)	Gly262Stop	Caucasian[32]
Jr(a–)	c.34G>A (2), 1591C>T (13)	Va112Met, Gln531Stop	Caucasian[32]
Jr(a–)	c.187_197delATATTATCGAA (2)	Ile63TyrfsStop54	Caucasian[31]
Jr(a–)	c.542_543insA (6)	Phe182ValfsStop14	Caucasian[31]
Jr(a–)	c.730C>T (7)	Gln244Stop	Caucasian[31]
Jr(a–)	c.791_792delTT (7)	Leu264HisfsStop14	Caucasian[31]
Jr(a–)	c.875_878dupACTT (8)	Phe293LeufsStop8	Caucasian[31]
Jr(a–)	c.1111_1112delAC (9)	Thr371LeufsStop20	Asian[31]
Jr(a–)	c.34G>A(2), c.244_245insC (3)	Va112Met, Thr82HisfsStop38	Asian[30,32]
Jr(a–)	c.1017_1019delCTC (9)	Ser340del	Caucasian[33]
Jr(a+^{w}/–)	c.421C>A (4)	Gln141Lys	Caucasian[33]
Jr(a+^{w}/–)	c.1858G>A (16)	Asp620Asn	Caucasian[33]
Jr(a+^{w}/–)	c.1714A>C (16)	Ser572Arg	Caucasian[33]

*Most alleles have been found in only one proband. The exceptions are c.376C>T, which has been found in Japanese, Koreans, and Chinese, and c.706C>T, which has been found in Gypsies and in one Asian with a concomitant c.34G>A.[30,31]

The reports of Zelinski et al.[30] and Saison et al.,[31] published 42 years after the first examples of anti-Jr^a, provided the information that Jr^a is carried on the ABCG2 transporter and encoded by the *ABCG2* gene. Based on these results, Jr^a, previously designated ISBT 901.005, was promoted from the 901 series of high-incidence antigens to a blood group system (JR or ISBT 032) by the ISBT Working Party on Red Cell Immunogenetics and Blood Group Terminology in July 2012 (www.isbtweb.org/, Working Party on Red Cell Immunogenetics, J.R. Storry, personal communication, 2012).

ABCG2 Gene and ABCG2 Glycoprotein

ABCG2 is located on chromosome 4q22.1. It is composed of 16 exons (15 coding exons) that span approximately 68.6 kb of gDNA. The gene encodes a 655–amino acid, 72.6-kDa ABCG2 protein.[36] The amino acid sequence of the wild-type ABCG2 protein is shown in Figure 1.

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MSSSNVEVFIPVSQGNTNGFPATASNDLKAFTEGAVLSFHNICYRVKLKS 50
GFLPCRKPVEKEILSNINGIMKPGLNAILGPTGGGKSSLLDVLAARKDPS 100
GLSGDVLINGAPRPANFKCNSGYVVQDDVVMGTLTVRENLQFSAALRLAT 150
TMTNHEKNERINRVIQELGLDKVADSKVGTQFIRGVSGGERKRTSIGMEL 200
ITDPSILFLDEPTTGLDSSTANAVLLLLKRMSKQGRTIIFSIHQPRYSIF 250
KLFDSLTLLASGRLMFHGPAQEALGYFESAGYHCEAYNNPADFFLDIING 300
DSTAVALNREEDFKATEIIEPSKQDKPLIEKLAEIYVNSSFYKETKAELH 350
QLSGGEKKKKITVFKEISYTTSFCHQLRWVSKRSFKNLLGNPQASIAQII 400
VTVVLGLVIGAIYFGLKNDSTGIQNRAGVLFFLTTNQCFSSVSAVELFVV 450
EKKLFIHEYISGYYRVSSYFLGKLLSDLLPMRMLPSIIFTCIVYFMLGLK 500
PKADAFFVMMFTLMMVAYSASSMALAIAAGQSVVSVATLLMTICFVFMMI 550
FSGLLVNLTTIASWLSWLQYFSIPRYGFTALQHNEFLGQNFCPGLNATGN 600
NPCNYATCTGEEYLVKQGIDLSPWGLWKNHVALACMIVIFLTIAYLKLLF 650
LKKYS                                               655
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Fig. 1 Amino acid sequence of ABCG2 protein. Amino acid sequence taken from GenBank, accession NP_004818.2.

ABCG2 (breast cancer resistance protein [BCRP], mitoxantrone resistance protein), a well-studied molecule with more than 2000 publications, is an abbreviation for ATP-binding cassette (ABC), subfamily G, member 2. ABC transporters form one of the largest protein families encoded in the human genome, and more than 48 human ABC protein genes have been identified.[37] ABCG2 is predicted to pass through the membrane six times and has a single *N*-linked glycan. The intracellular amino terminal harbors a nucleotide-binding domain with Walker A, Walker B, and ABC signature motifs.[38] The functional molecule is likely a homodimer or homotetramer in the membrane.[39,40] Figure 2 depicts the predicted structure of the ABCG2 protein in the membrane and shows the location of amino acid changes encoded by nonsense and missense alleles.

ABCG2 has high expression in the placenta and blood–brain barrier and has low expression in epithelial cells of small and large intestines, liver ducts, colon, and lobes of the breast, in endothelial cells of veins and capillaries, in brain microvessel endothelium, and in stem cells, lung, and the apical membrane of proximal tubules of the kidney.[38,41,42]

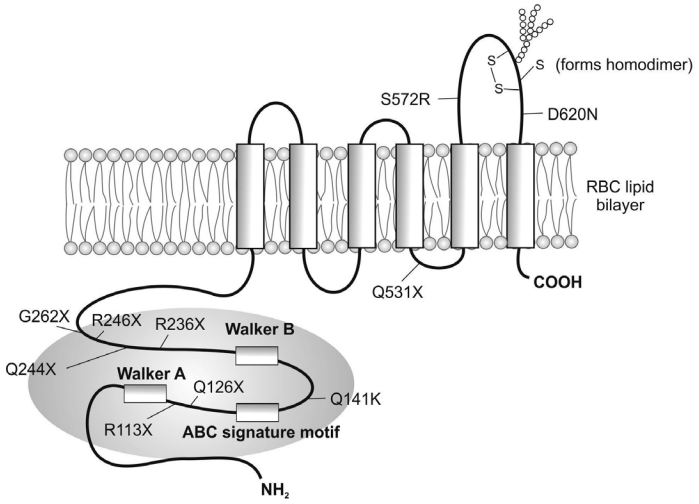

Fig. 2 Predicted topology of ABCG2 protein with location of amino acid changes encoded by nonsense and missense alleles. The single-letter code is used for amino acids. RBC = red blood cell; –S– = disulfide bond; X = stop codon.

Functional Aspects of the ABCG2 Glycoprotein

Numerous studies in *Abcg2*$^{-/-}$ mice have suggested roles for ABCG2 in a variety of physiologic processes. ABCG2, also named BCRP, is known to be an essential transporter in cell detoxification and has a wide variety of substrates.[41–44] It is a high-capacity transporter of urate,[38,45] it appears to have a role in folate[46] and porphyrin homeostasis,[47,48] it may protect normal cells from toxic agents or metabolites,[49] it may play a role in removing xenobiotics from the brain,[50] and it may be involved in brain-to-blood efflux.[51] It transports a wide variety of drugs and does not require glutathione for transport of electroneutral amphipathic compounds.[52] It also appears to play a major role in the multidrug resistance phenotype of several cancer cell lines and solid tumors, posing a problem in chemotherapy.[53,54] The Gln126Stop and Gln141Lys variants of ABCG2 are associated with an increased risk for gout.[55] In a recent paper, Tiribelli et al.[56] demonstrated that the Gln141Lys variant is associated with poor outcome in patients with acute myeloid leukemia receiving idarubicin-based chemotherapy.

Molecular Bases of Jr(a–) and Jr(a+^{w}/–) Phenotypes

The Jr(a–) phenotype results from the recessive inheritance of *ABCG2* null mutations caused by frameshift or nonsense changes, and the Jr(a+^{w}/–) phenotype results from missense nucleotide changes (Table 1, Fig. 2).[32,33]

Jr^{a} Antigen

Jr^{a} is fully developed on cord blood cells. The antigen is resistant to the treatment of RBCs with papain, trypsin, chymotrypsin, pronase, neuraminidase, and 2-aminoethylisothiouronium bromide.[57]

Clinical Significance

Anti-Jr^{a} is generally IgG (some are IgG1; some are a mixture of IgG1 and IgG3) and reacts best by the antiglobulin test, especially when ficin- or papain-treated RBCs are used.[57] IgM anti-Jr^{a} was found in the plasma of two Jr(a–) brothers who had not been transfused, and it has been detected in

untransfused Jr(a–) women during their first pregnancy.[12,13] Some anti-Jr^a may bind complement.[4,9,57] A collaborative study of irregular erythrocyte antibodies in Japan showed that anti-Jr^a is more frequently determined in pregnant patients than in nonpregnant patients.[58]

Anti-Jr^a may be stimulated by transfusion[22] or by pregnancy.[7,10] Rare cases of hemolysis associated with transfusion have been reported, mostly as delayed HTRs.[7,22–26] One patient with anti-Jr^a in the plasma developed rigors after 150 mL of serologically incompatible blood had been transfused,[24] and in another patient chromium-51 cell survival studies indicated reduced RBC survival.[7] In contrast, another patient with anti-Jr^a was transfused with three units of Jr(a+) blood in an emergency situation,[13] and no symptoms of either an immediate or a delayed HTR were seen, although the titer of anti-Jr^a increased from 32 to 2048 on the 20th day after transfusion and later fell to 64 (35 days after transfusion). Kwon et al.[27] described two cases of anti-Jr^a in the setting of incompatible transfusions, one without consequences despite multiple transfusions of Jr(a+) blood and the other leading to an acute HTR. Ogasawara and Mazuda[59] studied 20 plasma samples containing anti-Jr^a and reported that none mediated phagocytosis of RBCs (in vitro). Garratty et al.[60] reported that only one of eight anti-Jr^a samples had a positive monocyte monolayer assay, suggesting clinical significance.

Anti-Jr^a has been responsible for a positive direct antiglobulin test on RBCs from newborns and, rarely, HDFN.[4,9,12,13] A review of the literature indicates that anti-Jr^a has caused mild and even severe cases of HDFN with no evidence of hemolysis.[11–21] There is one report of a fatality associated with anti-Jr^a alloimmunization.[17] Collectively, these data suggest that Jr^a, like Kell and Gerbich,[61,62] is expressed on erythroid progenitor cells and that in these cases of HDFN, anti-Jr^a causes suppression of erythropoiesis rather than hemolysis.

Concluding Remarks

To date, nearly 1300 synonymous and nonsynonymous SNPs in the gene sequence of *ABCG2* have been described (http://www.ncbi.nlm.nih.gov/snp), and therefore, additional diversity within the JR blood group system is still expected.

Jr(a–) individuals provide a large cohort of "natural knockouts" for *ABCG2* (*ABCG2*$^{-/-}$), opening the opportunity to study the exact role and function of ABCG2 in humans under normal physiology and in pathologic conditions such as cancer.

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