

The contribution of *ABCG2* G34A and C421A polymorphisms to multiple myeloma susceptibility

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Background: Breast cancer resistance protein BCRP, belonging to superfamily G of the adenosine triphosphate-binding cassette (ABC) transporters, is an efflux pump and plays a critical role in protecting cells against xenobiotics and toxic compounds including (pro)carcinogens. BCRP is expressed in many tissues, including hematopoietic stem cells. Genetic variants such as single nucleotide polymorphisms (SNPs) can change the gene expression and/or reduce their products' activity which may affect an individual's susceptibility to xenobiotics and the development of carcinoma. These changes may affect the exposure of blood cells to toxic compounds, which increases the risk of multiple myeloma. The aim of this study was to determine polymorphisms at positions G34A and C421A of the *ABCG2* gene in multiple myeloma in the Polish population for the first time.

Materials and methods: Material for the study included DNA isolated from nucleus of cells of peripheral blood of patients diagnosed with multiple myeloma (investigated group N=181) and from healthy people (control group N=97). Research into the polymorphisms was conducted using the polymerase chain reaction-restriction fragment length polymorphism technique.

Results: The present study showed a statistically significant association between SNP C421A of the *ABCG2* gene and the risk of developing multiple myeloma ($P=0.0218$). No statistically significant relationship was found for the other parameters analyzed, such as age, gender, or type of secreted immunoglobulin.

Conclusion: Preliminary studies indicate that SNP C421A may become a potential predictor for the development of multiple myeloma.

Keywords: BCRP, polymorphism, *ABCG2*, multiple myeloma risk, plasma cell myeloma, single nucleotide polymorphism

Introduction

The *ABCG2* gene located on chromosome 4q22 encodes the 655-amino-acid breast cancer resistance protein BCRP.¹ Like other G-subfamily proteins of adenosine triphosphate-binding cassette (ABC) transporters, BCRP is a half transporter containing one nucleotide-binding domain and one transmembrane domain fused into a single polypeptide chain. BCRP has a functional form as a homodimer with a molecular mass of 144 kDa.² In humans, BCRP functions as a protective pump. Physiologically, it occurs in many normal human tissues including the placenta, liver, brain, syncytiotrophoblast, small intestine, and breast tissue.³ This protein determines the existence of barriers: the brain, the testicles, and the placenta.⁴ BCRP is suggested to provide the fundamental physiological barrier function that can protect cells. High expression of BCRP affects tissues of organs responsible for detoxification processes.⁵ BCRP is one of the major proteins responsible for the active transport of a broad spectrum of chemical compounds across extracellular and intracellular membranes, for

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example: heme, porphyrin, riboflavin, hormones (estrogens), and chemotherapeutics (methotrexate, imatinib, doxorubicin, topotecan).^{6,7} Among the substrates for BCRP there are also carcinogenic xenobiotics. The BCRP transporter, by regulating the concentration of xenobiotics in the cell, fulfills the physiological protective role for the cell against toxicity of environmentally or clinically administered drugs.⁵ BCRP plays also an important protective role for hematopoietic stem cells against xenobiotics and hypoxia.^{3,8,9}

The genetic background significantly determines the kinetic properties of BCRP, starting from the single nucleotide polymorphism (SNP) to large chromosome aberrations that change protein properties and functions leading to an increased risk of cancer.^{3,10}

SNPs are the most frequent inherited sequence variations in a particular gene and occur every 100–300 bp.¹¹ The *ABCG2* gene protein was tested for SNPs in 90 different ethnic populations. Within the *ABCG2* gene, more than 40 nonsynonymous and synonymous SNPs in promoter regions, exons, and intron sequences have been identified.^{12,13}

The two most common SNPs are G34A and C421A. The G34A polymorphism in exon 2 (rs2231137) results in an amino acid change in position 12 from valine to methionine (Val12Met). This results in the formation of a protein with a significantly reduced ability to translocate the substance across the cell membrane. The C421A polymorphism in exon 5 (rs2231142) which leads to a glutamine-to-lysine amino acid substitution is associated with low levels of BCRP expression.^{2,10,14}

Loss of the physiological function of BCRP resulting from SNPs G34A and C421A in *ABCG2* gene variants may affect susceptibility to cancer development such as acute myeloid leukemia (AML), chronic myelogenous leukemia (CML), diffuse large B-cell lymphoma, breast cancer, prostate cancer, colorectal cancer, nonpapillary renal cell cancer, pancreatic cancer, and non-small-cell lung carcinoma. Therefore, several studies have tried to identify the role of SNPs with susceptibility, survival, and treatment outcomes of carcinoma.^{15,16}

Multiple myeloma is a cancerous disease derived from a single clone of cancer cells from the bone marrow. Multiple myeloma belongs to the group of malignant monoclonal gammopathies.³ The incidence in Europe ranges between 4.5 and 5.8/100,000. In epidemiological studies in Poland carried out since the 1990s, there has been a steady increase in multiple myeloma incidence. Multiple myeloma represents 1% of all malignancies and up to 14% of hematological malignancies. The disease is slightly more common in men. The pathogenesis of multiple myeloma is not yet fully known. However, it is assumed to be a multifactorial disease where environmental, genetic, and long-term antigenic stimulation of the immune

system in the course of bacterial and viral infections interact. The risk of first-degree multiple myeloma is 3–7 times higher in kinship relatives, which supports the concept of involvement of genetic factors in the development of the disease.

Therefore, it is reasonable to assume that the genetic variants of the *ABCG2* gene can cause altered exposure of hematopoietic cells to xenobiotics and thereby reduce or increase the risk of multiple myeloma development.³

The aim of this study was to determine the potential significance of SNPs G34A and C421A of the *ABCG2* gene in the development of multiple myeloma. To the best of our knowledge, the role of this polymorphism in multiple myeloma has not so far been studied in the Polish population.

Materials and methods

Materials

Blood samples (N=181) were collected from patients (85 females, 96 males; median age of group: 63 years) with multiple myeloma diagnosed at the Clinic of Hematology, Medical University of Lodz, Poland. The control group consisted of 97 blood samples obtained from healthy individuals (58 females, 39 males, median age of group: 33 years) from the local blood bank, and geographically and ethnically matched the group of patients with multiple myeloma. The investigation was performed in accordance with the principles of the Declaration of Helsinki and was approved by the Ethical Committee of the Medical University of Lodz (No RNN/88/16/KE and RNN/285/13/KE). All patients provided a written informed consent before their inclusion in the study.

DNA isolation

DNA was isolated from peripheral blood according to the “Blood Mini” protocol (A&A Biotechnology, Gdynia, Poland). DNA samples were stored at –20°C until analysis.

Genotyping of G34A and C421A

Polymerase chain reaction

Polymerase chain reaction (PCR) for both investigated polymorphisms was performed according to the 2×PCR Super Master Mix (Biotools, Jupiter, FL, USA) protocol. The mixture for PCR reaction consisted of: 5 µL of 2×PCR Super Master Mix (which included in its composition: buffer, MgCl₂, dNTPs, *Taq* DNA polymerase); 0.5 mM of each primer, specific to the particular SNP; 50 ng of DNA template; and distilled water up to 20 µL. Negative control was included in every experiment. PCR products for both SNPs were evaluated during electrophoresis on 2% agarose gel. Products of PCR reaction for SNPs G34A and C421A had a size of 291 bp and 184 bp, respectively.

Table 1 Details of methodology used in genotyping by polymerase chain reaction analysis

Primer sequence	Annealing temperature (°C)	Restriction enzyme	Genotype	Fragment length (bp)
BCRP SNP G34A				
Forward primer: 5'-AAATGTTTCATAGCCAGTTTCTTGGA-3' Reverse primer: 5'-ACAGTAATGTCGAAGTTTTATCGCA-3'	60	<i>BseMI</i>	GG GA AA	291 291, 261, 30 261, 30
BCRP SNP C421A				
Forward primer: 5'-ATGTTGTGATGGGCACTCTG-3' Reverse primer: 5'-TGCTGATCATGATGCTTTCAG-3'	58	<i>MseI</i>	CC CA AA	100, 84 100, 84, 64, 36 84, 64, 36

Abbreviations: BCRP, breast cancer resistance protein; bp, base pair; SNP, single nucleotide polymorphism.

Restriction fragment length polymorphism

PCR products for both polymorphisms were digested by restriction enzyme specific to the studied polymorphism: *BseMI* for SNP G34A and *MseI* for SNP C421A. The digestion mixture consisted of 16 µL of PCR product, 2 µL of buffer, 0.1 µL of specified enzyme, and 1.9 µL of distilled water up to 20 µL for G34A; and 16 µL of PCR product, 2 µL of buffer, 0.5 µL of specified enzyme, and 1.5 µL of distilled water up to 20 µL. Digestion by restriction enzyme was performed for SNPs G34A and C421A, respectively, at 55°C for 16 h and at 30°C for 16 h. Genotypes for both studied polymorphisms were identified by electrophoresis (on 2% and 4% agarose gel for G34A and C421A, respectively) of amplified DNA fragments after digestion by restriction enzyme. The details of the band patterns are presented in Table 1.

Statistical analyses

All statistical analyses were performed using STATISTICA 10 (2011; StatSoft Inc., Tulsa, OK, USA). The Hardy–Weinberg equation was calculated in the experimental and control groups in the study only for SNP C421A. The χ^2 Pearson test with the Yates correction was applied to evaluate conformity between the observed and expected genotype frequencies according to the Hardy–Weinberg rule. To determine the significance of differences in genotype frequencies between the group of multiple myeloma patients and the group of healthy individuals, the χ^2 Pearson test with the Yates correction was used. In all conducted tests, $P < 0.05$ was assumed significant.

Ethics statement

The investigation was in accordance with the Declaration of Helsinki and the Good Laboratory Practice rules, and was approved by the Ethical Committee of the Medical University of Lodz (Nos RNN/88/16/KE and RNN/285/13/KE).

All patients provided a written informed consent before their inclusion in the study.

Results

This study recruited a total of 181 people diagnosed with multiple myeloma and 97 healthy people as a control group. All samples obtained from patients with multiple myeloma and from healthy individuals were included in the statistical analysis. The multiple myeloma and healthy control groups were analyzed using the Hardy–Weinberg equation model. Both groups were in Hardy–Weinberg equilibrium. Only SNP C421A of the *ABCG2* gene was significantly associated with the increased risk of multiple myeloma development ($P = 0.0218$). For SNP G34A in the *ABCG2* gene (rs2231137), none of the patients or controls was carrying the minor (A) variant. For SNP C421A (rs2231142), our data showed that 10.5% and 1.1% of the patients with multiple myeloma had CA and AA genotypes respectively, while only 2.1% and 0% patients from the healthy control group had these genotypes (Table 2).

The group of patients with multiple myeloma was divided according to gender. Then, the correlation between gender and the incidence of individual genotypes and alleles for the C421A polymorphism in the *ABCG2* gene was analyzed. No statistically significant relationship in the case of analysis for genotypes and also in case of the presence of the C allele or the A allele was found ($P = 0.1255$, $P = 0.1307$, and $P = 0.3865$ respectively).

For 84 trials, clinical data were given about the type of immunoglobulin secreted by myeloma cells. In this case, no association was found between the different genotypes of SNP C421A of the *ABCG2* gene and the type of immunoglobulin produced (Table 3).

Due to the lack of substantive association of the obtained results, they were not correlated with other available clinical

Table 2 Incidence of genotypes and alleles for G34A and C421A polymorphisms of the *ABCG2* gene in multiple myeloma patients and healthy individuals

ABCG2 SNPs	Multiple myeloma patients, N=181 (%)	Healthy individuals, N=97 (%)	P (χ^2 Pearson with the Yates correction)	OR (95% CI)
SNP C421A				
CC	160 (88.4)	95 (97.9)	0.0218	1 (–)
CA	19 (10.5)	2 (2.1)		5.64 (1.28–24.75)
AA	2 (1.1)	0 (0.0)		2.97 (0.14–62.62)
C	339 (93.6)	192 (99.0)	0.0040	1 (–)
A	23 (6.4)	2 (1.0)		6.51 (1.52–27.93)
HWE P	0.7537	1.000		
SNP G34A				
GG	181 (100.0)	97 (100.0)	NA ^a	NA ^a
GA	0 (0.0)	0 (0.0)		
AA	0 (0.0)	0 (0.0)		
G	362 (0.0)	194 (0.0)	NA ^a	NA ^a
A	0 (0.0)	0 (0.0)		
HWE P	NA	NA		

Notes: $P < 0.05$ (written italic) indicates a significant impact on the risk of multiple myeloma development. ^aDue to the obtained distribution of genotypes in the studied groups, statistical analysis was impossible.

Abbreviations: HWE, Hardy–Weinberg equilibrium; NA, not applicable; SNP, single nucleotide polymorphism.

data: disease advancement according to the Durie-Salmon classification, general condition of the patients according to the WHO, therapy regimen, or laboratory parameters such as C-reactive protein, lactate dehydrogenase, hemoglobin, albumin, and β 2-microglobulin level (because data were not available from the whole group of patients with multiple myeloma).

Discussion

Multiple myeloma remains an incurable disease with an average survival of 4–6 years. Extensive epidemiological studies have shown that the processes of detoxification and elimination of xenobiotics from cells are associated with tumors.¹⁷ BCRP acts as a pump that actively removes toxic compounds, including carcinogens from cells. SNPs can alter the expression and activity of the relevant genes and their proteins, and

predispose them to the development of tumors.⁹ Much research has been done to clarify the role of SNPs and the development of various cancers including hematologic and solid tumors.¹⁵

Thus far, there have been only a few epidemiological studies to investigate the association between G34A and C421A polymorphisms in the *ABCG2* gene and the risk of various types of cancer. The exact association between cancer susceptibility and *ABCG2* polymorphisms remains unclear. The results appear to depend on the ethnic origin and type of cancer. Previous studies have shown important differences in the frequencies of genotype of G34A and C421A. For G34A, the Han Chinese population appears to have the highest frequency (34%), while the variant allele is extremely rare in the sub-Saharan African population (<1%) and is relatively rare in the African-American (5%) and

Table 3 Incidence of genotypes of single nucleotide polymorphism C421A in the *ABCG2* gene in patients with multiple myeloma by type of immunoglobulin secreted by myeloma cells

SNP C421A	Multiple myeloma patients (N=84)				P (χ^2 Pearson with the Yates correction)
	IgG (%)	IgA (%)	IgD (%)	Light chains (%)	
CC	48 (57.1)	13 (15.4)	1 (1.2)	14 (16.7)	0.9939
CA	4 (4.8)	2 (2.4)	0 (0.0)	2 (2.4)	
AA	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
C	52	15	1	16	0.8674
A	4	2	0	2	

Caucasian populations in the United States (12%). Variant A of the G34A polymorphism in the European population, according to the dbSNP database, could account for about 5% of the population. However, it may occur at a lower level, such as in the Turkish or Dutch population. To the best of our knowledge, the G34A analysis of the *ABCG2* gene presented in this publication is the first study of this type in the Polish population.¹⁸ The allelic frequencies in the Mexican-Indian, Mexican, and Latin populations were 90%, 10%, and 40%, respectively. Importantly, the A allele of C421A is widespread in the Japanese and Chinese populations (35%). For the Caucasian population it is below 10% and it is rarest for the sub-Saharan African and African-American populations, accounting for 5%.¹⁰

The present study focused on the role of the two most common polymorphisms of the *ABCG2* gene in the development of multiple myeloma. G34A is not related to the risk of developing multiple myeloma, whereas C421A was significantly associated with multiple myeloma ($P=0.0218$).

In contrast to the obtained results, the GA and AA genotype variants of SNP G34A in the *ABCG2* gene were associated with increased toxicity in AML. On the other hand, these genotypes were linked with improved survival in AML. In the same study, the *ABCG2* C421A polymorphism was associated with decreased drug resistance and a higher risk of death when compared to the wild type.¹⁹

Kim et al²⁰ demonstrated that SNP G34A variants may be relevant in response to imatinib therapy used in CML. They showed that the GA and AA genotypes were significantly associated with the lower rate of complete cytogenetic response to imatinib. In contrast, data available in another publication showed that there was no difference in the frequencies of SNP G34A between CML patients with good response and resistance to imatinib, but the AA genotype variant of SNP C421A was associated with the lower risk of resistance development to imatinib for patients with CML.¹

Similar studies have been carried out on a group of children with acute lymphoblastic leukemia among SNPs G34A and C421A in BCRP. Only SNP G34A in the *ABCG2* gene was related to a higher risk of acute lymphoblastic leukemia, which remains in contrast to the results of the research conducted by us on a group of patients with multiple myeloma.²¹ Hu et al⁹ obtained similar results. The researchers reported that the C421A A allele increased the risk of developing diffuse large B-cell lymphoma.

Regarding studies on the role of polymorphisms within the *ABCG2* gene in solid tumors, Wu et al¹⁴ found an

increased frequency of G34A GA and AA genotypes in patients with breast cancer. The G34A allele polymorphism was significantly different in these patients and was associated with an increased risk of cancer. Similarly, the homozygous variant of the C421A AA genotype was associated with a higher risk of developing breast carcinoma.¹⁴ Another study on the role of C421A polymorphism in a group of Kurdish breast cancer patients showed that the AA genotype is significantly associated with an increased risk of developing breast cancer.²²

Similar results were obtained by Sari et al¹⁰ in a study into the role of SNPs in the BCRP transporter and susceptibility to colorectal cancer. In this study, *ABCG2* C421A was statistically significantly associated with colorectal cancer risk. In particular, patients with A alleles were much more likely to have the disease than those with C alleles. In contrast, the *ABCG2* G34A genotypes in the cases and controls did not differ significantly, and thus polymorphism was not associated with the risk of colorectal cancer.¹⁰

C421A in the *ABCG2* gene plays contrasting roles in prostate cancer. First, enhanced tumor cell proliferation results from decreasing folate efflux and increased intracellular folate levels. On the other hand, in patients treated with docetaxel intratumoral, the level of docetaxel and tumor cell sensitivity increased and so did the patients' survival time.²³ Different results for C421A and prostatic cancer were obtained by Gardner et al²⁴ as there were no significant differences in the prevalence of prostate cancer based on the genetic variability of *ABCG2* in a non-Hispanic Caucasian cohort. Hahn et al²⁵ demonstrated that hormone-refractory prostate cancer patients carrying the *ABCG2* C421A genotype were more likely to survive beyond 15 months compared with those carrying the C421A CC genotype.

In contrast, another analysis of the role of SNP C421A in the *ABCG2* gene performed by Korenaga et al²⁶ proved that the CC genotype was associated with a higher risk of developing nonpapillary renal cell cancer.

Conclusion

Our study has shown that SNP C421A of the *ABCG2* gene predisposed to an increased individual risk of developing multiple myeloma. These results encourage further research into SNP C421A in the BCRP encoding gene and the risk of developing multiple myeloma, despite the fact that the small number of examined individuals may have limited the possibility to detect the effects of SNPs on the risk of multiple myeloma. However, further studies on the relationship between polymorphism and the risk of multiple

myeloma are required to confirm our findings prior to the use of polymorphism to identify subgroups with an increased risk of multiple myeloma.

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Disclosure

The authors report no conflicts of interest in this work.

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