Gly322Asp and Asn127Ser single nucleotide polymorphisms (SNPs) of hMSH2 mismatch repair gene and the risk of triple-negative breast cancer in Polish women

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Abstract  Triple-negative breast cancer (TNBC) is characterised by worse clinical outcome and poor prognosis. The alterations in the oncogenes and tumor suppressor genes as well as microsatellite instability (MSI) have been associated with breast cancer development. It is knowledge that the most common mechanism inducing MSI in many cancer is genomic rearrangements found in the hMSH2 (human MutS homolog 2) gene. In this report we genotyped two polymorphisms of hMSH2 DNA repair gene in 70 TNBC patients and 70 age-matched cancer-free women using RFLP–PCR. The following polymorphisms were studied: an A/G transition at 127 positions producing an Asn/Ser substitution at codon 127 (the Asn127Ser polymorphism, rs17217772) and a G/A transition at 1032 position resulting in a Gly/Asp change at codon 322 (the Gly322Asp polymorphism, rs4987188). We found an association between the hMSH2 Asp/Asp and Gly/Asp genotypes and TNBC occurrence. Variant Asp allele of hMSH2 decreased cancer risk [odds ratio (OR) 0.11; 95 % confidence interval (CI) 0.05–0.21]. The risk of TNBC in the carriers of the Gly322Gly–Asn127Ser combined genotype was increased (OR 3.71; 95 % CI 1.36–10.10). However the risk of TNBC was not alter by polymorphism Asn127Ser of the hMSH2 gene. The Gly322Asp polymorphism of the hMSH2 gene may be linked with TNBC occurrence in Polish women.

Keywords  hMSH2 · MMR · Breast cancer · Gene polymorphism

Introduction

Over the past decade, the landscape of breast cancer has changed. Various genetic and environmental factors have been established as causes of breast cancer, which is a genetically heterogeneous disease [1–3].

Modern molecular genetics methods such as microarray techniques have divided breast cancer into several intrinsic subtypes: (1) luminal A, (2) luminal B, (3) human epidermal growth factor receptor-2 (HER-2)-enriched and (4) the “basal-like” subtype. Both luminal A and B are clinically characterized by expression of hormone receptor-related genes, whereas both HER-2-enriched and the “basal-like” subtypes are less likely to express either estrogen receptor (ER) or progesterone receptor (PgR). Moreover, the “basal-like” subtype, one of the most clinically aggressive of the subtypes, is more commonly negative for all 3 markers-ER, PgR, and HER2-hence the “triple-negative” phenotypic classification [4, 5].

Triple-negative breast cancer (TNBC) and basal-like breast cancer are not the same. Some TNBCs have basal-like genetic patterns, but not all do. While most basal-like...
breast cancers are triple-negative, a small but significant number may be hormone receptor or HER-2 positive. Basal type cancers are frequently defined by cytokeratin 5/6 and EGFRs staining.

Of the estimated 1,000,000 women of breast cancer diagnosed worldwide in 2008, it is estimated that 172,695 will harbor the triple-negative phenotype.

The alterations in the oncogenes and tumor suppressor genes as well as microsatellite instability (MSI) have been associated with breast cancer development [6–11]. It is knowledge that microsatellites, are particularly prone to replication errors associated with the type of genomic instability that results from the loss of mismatch repair (MMR) function or alterations in MMR genes [12–14].

Mismatch repair deletes mispaired bases resulting from replication errors, recombination between imperfectly matched sequences and deamination of 5-methyl-cytosine. The main MMR pathway is initiated by the recognition of a mismatch by the heterodimer consisting of the MSH2 and MSH6 proteins (also called MutSα). MutSα is responsible for the recognition of base mismatches and insertion/deletion (IDLs) in mono- to tetrancleotide repeats. This complex, MutSα, is able to recognize most base–base mismatches and short IDLs [15].

MMR is a highly conserved repair pathway that functions in improving replication fidelity by correcting replication-associated base–base and insertion/deletion mispairs. The MMR mechanisms play an important role in repair of oxidative damage by mechanisms that are not well understood [16]. MMR is essential for maintenance of genome stability [17–20].

High-frequency MSI is detected more frequently in bilateral but not in unilateral breast cancers [21, 22]. Losses of heterozygosity and/or MSI were detected in 83 % of the skin samples from breast cancer patients, which suggest a potential role of MMR in breast cancer susceptibility [22].

Indeed, recently several studies have shown that the most common mechanism inducing MSI in many cancer is the loss of the hMSH2 protein or genomic rearrangements found in the hMSH2 (human MutS homolog 2) gene [23–26].

There is also some reports associated mutations in MMR proteins genes (predominantly in hMSH2) with the initiation and progression of breast cancer [27–31].

Because a little is known on association of hMSH2 genetic variants and triple-negative breast carcinoma, we studied whether two polymorphisms of this gene: an A/G transition at 447 position producing an Asn/Ser substitution at codon 127 (the Asn127Ser polymorphism) and a G/A transition at 1032 position resulting in a Gly/Asp change at codon 322 (the Gly322Asp polymorphism) may be linked with TNBC risk in Polish women.

### Materials and methods

#### Patients

In the present study, paraffin embedded tumor tissue were obtained from 70 women with triple-negative breast carcinoma, treated at the Department of Oncology, Institute of Polish Mother’s Memorial Hospital, Lodz, Poland between 2000 and 2013. The age of the patients ranged in from 36 to 68 years (the mean age 46.2 ± 10.12). Table 1 shows clinical characteristics of patients. The median follow-up of patients still alive at the time of analysis was 38 months (range 2–70 months). DFS (the disease-free survival) was defined as the time elapsed between excision of the primary tumor and the manifestation of recurrent breast cancer or metastasis. The median DFS was 33.5 months (range 7–65 months). Overall survival (the OS) was defined as time between excision of the primary tumor and death because of cancer. The median OS

| Characteristics | Number of patients (%) | Number of controls (%) |
|-----------------|------------------------|------------------------|
| Age (years)     |                        |                        |
| <45             | 27 (39)                | 24 (34)                |
| 45–54           | 15 (21)                | 18 (26)                |
| 55–64           | 18 (26)                | 16 (23)                |
| ≥64             | 10 (14)                | 12 (17)                |
| Family history of breast cancer | |                        |
| Yes             | 25 (36)                | 22 (31)                |
| No              | 45 (64)                | 48 (69)                |
| Menarche (years)|                        |                        |
| 10              | 5 (7)                  | 3 (4)                  |
| 11              | 18 (26)                | 21 (30)                |
| 12              | 19 (27)                | 16 (23)                |
| 13              | 13 (19)                | 15 (22)                |
| 14              | 10 (14)                | 12 (17)                |
| ≥15             | 5 (7)                  | 3 (4)                  |
| Parity          |                        |                        |
| Nulliparous     | 25 (36)                | 20 (29)                |
| 1               | 15 (21)                | 20 (29)                |
| 2               | 16 (23)                | 12 (17)                |
| 3               | 9 (13)                 | 13 (18)                |
| ≥4              | 5 (7)                  | 5 (7)                  |
| Menopause status|                        |                        |
| Premenopausal   | 30 (43)                | 35 (50)                |
| Postmenopausal  | 40 (57)                | 35 (50)                |
| Use of menopausal hormones | |                        |
| Never           | 37 (53)                | 30 (43)                |
| Estrogen        | 33 (47)                | 40 (57)                |

* Family history defined as self-reporting of at least one first-degree relative with known breast cancer
was 27.3 months (range 2–70 months). The average tumor size was 20 mm (range 17–32 mm). All the tumors were graded by a method, based on the criteria of Scarf–Bloom–Richardson. This system is the most common type of cancer grade classification used today. In this system, there are three factors that the pathologists take into consideration: the frequency of cell mitosis (rate of cell division), tubule formation (percentage of cancer composed of tubular structures), and nuclear pleomorphism (change in cell size and uniformity). Each of these features is scored from 1 to 3, and then each score is added to give a final total score ranging from 3 to 9. The final total score is used to determine the grade in the following way: Grade 1 tumors have a score of 3–5 (well-differentiated), Grade 2 tumors have a score of 6–7 (moderately-differentiated), Grade 3 tumors have a score of 8–9 (poorly-differentiated).

Determinant of hMSH2–Gly322Asp genotype

Polymorphism Gly322Asp (rs4987188) of the hMSH2 gene was determined by PCR–RFLP, using primers: sense 5′-GGTCTACTAATGGAGCTGC-3′, antisense 5′-GTG GTATAATCATGTGGGTG-3′). The PCR was carried out in a PTC-100 TM (MJ Research, INC) thermal cycler. PCR amplification was performed in the final volume of 25 μl of reaction mixture, which contained 5 ng of genomic DNA, 0.2 μmol of each primer (ARK Scientific GmbH Biosystems, Darmstadt, Germany), 2.5 mM of MgCl2, 1 mM of dNTPs and 1 unit of Taq Polymerase (Qiagen GmbH, Hilden, Germany). PCR cycle conditions were the following: 95 °C for 30 s, 60 °C for 30 s and 72 °C for 30 s, repeated in 30 cycles. PCR products were electrophoresed in a 2 % agarose gel and visualised by ethidium bromide staining. The cleavage with HinflI produced fragments of 252 and 70/182 bp corresponding to the Gln and Asp alleles of the hMSH2 gene, respectively.

Determinant of Asn127Ser genotype

Polymorphism Asn127Ser (rs17217772) of the hMSH2 gene was determined by PCR–RFLP, using primers: two allele specific sense oligonucleotides 5′-TTAGGCTTCCTGGCAA-3′ for Asn variant and 5′-TTAGGCTTCGTATAATCAGTGGT-3′. The control PCR for each sample using sense primer 5′-AAAATTTTAAAG-GAGAGGCCTCAAGATTG-3′. The control PCR for each sample using sense primer 5′-AAAATTTTAAAG-GAGAGGCCTCAAGATTG-3′. The control PCR for each sample using sense primer 5′-AAAATTTTAAAG-GAGAGGCCTCAAGATTG-3′. The control PCR for each sample using sense primer 5′-AAAATTTTAAAG-GAGAGGCCTCAAGATTG-3′. The control PCR for each sample using sense primer 5′-AAAATTTTAAAG-GAGAGGCCTCAAGATTG-3′. The control PCR for each sample using sense primer 5′-AAAATTTTAAAG-GAGAGGCCTCAAGATTG-3′.
was performed. The 210 and 264 bp control PCR products were electrophoresed in a 2 % agarose gel and visualised by ethidium bromide staining.

The PCR was carried out in a PTC-100 TM (MJ Research, INC) thermal cycler. PCR amplification was performed in the final volume of 25 μl of reaction mixture, which contained 5 ng of genomic DNA, 0.2 μmol of each primer (ARK Scientific GmbH Biosystems, Darmstadt, Germany), 2.5 mM of MgCl2, 1 mM of dNTPs and 1 unit of Taq Polymerase (Qiagen GmbH, Hilden, Germany), 2.5 mM of MgCl2, 1 mM of dNTPs and 1 unit of Taq Polymerase (Qiagen GmbH, Hilden, Germany). PCR amplification was performed in 210 and 264 bp control PCR products were electrophoresed in a 2 % agarose gel and visualised by ethidium bromide staining.

**Statistical analysis**

Logistic regression analysis was used to compute odds ratio (OR) and associated 95 % confidence interval (95 % CI) relating each of the single nucleotide polymorphism (SNP) as well as combinations of SNPs and another analysed factors presented in Table 1 to the risk of TNBC. The Hardy–Weinberg equilibrium (HWE; \( p^2 + 2pq + q^2 = 1 \)), where \( p \) is the frequency of the variant allele \( (q = 1 - p) \) was tested by a goodness-of-fit Chi square test to compare the observed genotype frequencies with expected genotype frequencies in cancer-free controls. All multivariate models were adjusted for age, family history, menarche, parity, menopausal status, and use of contraceptive and menopausal hormones. \( P \) values <0.05 were considered significant. The disequilibrium coefficient \( D' \) and \( r^2 \) values for all pair-wise combinations of SNPs were obtained using www.oege.org software. All the statistical analyses were performed, using the STATISTICA 6.0 software (Statsoft, Tulsa, Oklahoma, USA).

**Table 3** Distribution of genotypes and odds ratios (OR) of the Gly322Asp and Asn127Ser polymorphisms of the hMSH2 gene in patients with TNBC and controls

| Genotype | Patients (N = 70) | Controls (N = 70) | OR (95 % CI)\(^a\) |
|----------|------------------|------------------|---------------------|
| Gly/Gly  | 61 (87)          | 25 (36)          | 1.00 ref.           |
| Gly/Asp  | 4 (6)            | 20 (28)          | **0.08 (0.02–0.26)** |
| Asp/Asp  | 5 (7)            | 25 (36)          | **0.08 (0.02–0.23)** |
| Gly      | 126 (90)         | 70 (50)          | 1.00 ref.           |
| Asp      | 14 (10)          | 70 (50)          | **0.11 (0.05–0.21)** |

Data in bold font are statistically significant

\(^a\) Adjusted for age, family history, menarche, parity, menopausal status, and use of contraceptive and menopausal hormones

The haplotypes analysis according to wild-type of Gly 322Gly–Asn127Asn showed high frequency Gly322Gly–Asn127Ser, genotype. The combined Gly322Gly–Asn127Ser genotype increased the risk of TNBC (OR = 3.71,
Discussion

Breast cancer is the leading cause of tumour-related death among women worldwide [32]. Currently therapeutic approaches are limited by the development of drug resistance and progression of the majority of tumours to a more invasive and aggressive phenotype [33]. Resistance to anticancer agents that induce DNA damage has been associated with increased expression of DNA repair genes [34, 35] and the development of aggressive/metastatic behaviour in at least four different types of tumours [36–39].

Recently, using gene expression profiling of human primary malignant melanoma, Sarasin and Kauffman [37, 38] hypothesised that aberrant expression of genes connected with DNA repair pathways is associated with increased metastatic potential.

As mentioned in “Introduction” section MMR function leads to MSI, a type of genomic instability characterized by alterations in the length of microsatellite sequences distributed throughout the genome [40]. In fact, higher levels of DNA damage and deficient DNA repair may predispose individuals to cancer [41].

Commonly occurring SNPs in DNA repair genes have also been shown to incrementally contribute to cancer risk because of their critical role in maintaining genome integrity [42].

Many genetic changes in the form of SNPs have been identified in the MMR genes, but the function of these SNPs is largely unknown. Such alterations in MMR genes may have various effects on tumor phenotype, depending on where the alteration is located within the gene.

The aim of the present study was to evaluate associations between the risk of TNBC and polymorphisms in the hMSH2 gene, encoding for key protein of MMR. In the present work we analysed two single nucleotide polymorphisms of the hMSH2 DNA repair genes and tested the association between the distributions of their genotypes with TNBC.

In our study a weak association was found between the Asp/Asp (OR 0.08; 95% CI 0.02–0.23) genotype of the Gly322Asp polymorphism with TNBC occurrence.

Vanart Asp allele of hMSH2 decreased cancer risk. Moreover, the combined Gly322Asp–Asn127Ser and Asp322Asp–Ser127Ser genotype decreased the risk of breast cancer occurrence. Gly322Gly–Asn127Ser variant was associated with an elevated risk of TNBC in the Polish population. Additionally we observe correlation between studied Gly322Asp polymorphism and breast cancer progression evaluated by tumor size and Bloom–Richardson grading.

Our data suggest a protective role of the Asp allele of the Gly322Asp polymorphism of the hMSH2 gene against...
the development of cancer and this function can be underlined by increasing the activity of MMR.

This result may suggest major contribution of the Gln322Asp polymorphism of the \textit{hMSH2} gene in cancer development but more studies performed on larger population is needed to draw a final conclusion.

A positive correlation between polymorphism of the \textit{hMSH2} gene and occurrence of cancer was reported in colorectal cancer [43–45], gastric cancer [46], lymphoma [47] and leukemia [48].

Poplawski et al. [49] suggest that 322Gly variant in the \textit{hMSH2} gene may increase the risk of breast cancer. However the role of \textit{hMSH2} polymorphisms and breast cancer development is still unknown. To date, none studies have addressed the association between alterations in this region of the \textit{hMSH2} gene and TNBC. Because a proper functioning of the \textit{hMSH2} gene is important for the genomic stability, its alternations may be associated with higher cancer susceptibility.

In the recent studies, polymorphism of \textit{hMSH2} may be associated with an elevated tumour risk in the Polish populations, regarding breast cancer [49], while there are still no data, which would be illustrating the significance of \textit{hMSH2} polymorphism for TNBC development in other populations.

In the reported study, the Asn127Ser polymorphism of \textit{hMSH2} gene was not correlated with triple-negative breast carcinoma progression. Our results are in line with the data from other reports [48]. \textit{hMSH2} Asn127Ser gene variants were found to be not associated with breast cancer risk. This polymorphism was not related, either to tumor size or grade [36].

A limitation of the study was the relatively small population of participants. The sample for the present study comprised of 70 TNBC patients. This sample is only a very small proportion of the entire population of TNBC women in the country. Therefore the obtained results can not be considered as definitive and require further, more extensive evaluations, performed on bigger groups of patients. However, our preliminary results are fairly promising, indicating a significant role of the polymorphisms of \textit{hMSH2} gene for TNBC development.

In conclusion in the present study, an association was identified between Gln322Asp polymorphism of \textit{hMSH2} the incidence of TNBC. The obtained data suggest that the reported study may be the first observation of the polymorphisms in \textit{hMSH2} genes, involved in the DNA repair pathway, to be associated with triple-negative breast carcinoma risk in the population of Polish women.

\textbf{Conflict of interest} The authors declare no conflicts of interest.

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