The Relation between Exon Variations of KIT Gene and Clinical Pathological Factors of Breast Cancer

Maryam Rahimi1*, Elahe Keyhani2, Farkhondeh Behjati2

1. Department of Microbiology, Karaj Branch, Islamic Azad University, Karaj, Iran
2. Genetics Research Center, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran

ABSTRACT

Background & Objective: As the most common cancer type, breast cancer has been recognized as the second mortality cause among women. The KIT proto-oncogene is one of the important factors involved in tumor development. The previous findings have demonstrated an increased copy number and overexpression of this gene under the influence of breast cancer development.

Materials & Methods: This study aimed to investigate the relationship between the copy number variation (CNV) of all exons of KIT gene and estrogen receptor (ER), progesterone receptor (PR), HER2, P53, stage, tumor size, Ki67, Annexin V, histological type, age, molecular subtype, and node status by surveying breast cancer tissues collected from 64 patients. The CNV exons and clinicopathological variables were assessed by multiplex ligation-dependent probe amplification (MLPA), hematoxylin and eosin (H&E) staining, and immunohistochemistry techniques.

Results: Sixty percent of cases in exon 17, 60% in exon 18, and nearly 67% in exon 19 with increased CNVs had a tumor size of 2-5 cm; these results were significant. Also, patients with an increased exon 7 CNV were significantly in stage 3. Other exons did not exhibit significant relation to other clinicopathological variables (P>0.05).

Conclusion: Exons 7, 17, 18, and 19 are the key coding domains of tyrosine kinase, involving the activation of various upstream transcription factors that regulate apoptosis, cell differentiation, proliferation, and angiogenesis. Variation in exons can influence drug resistance. The results of this study can contribute to the diagnosis and treatment of breast cancer, although their confirmation requires further examinations.

Keywords: KIT gene, Clinical pathology factors, Breast cancer

Introduction

The KIT gene is a proto-oncogene located at 4q12, which spans 21 exons. This gene is one of the important factors in angiogenesis and tumor proliferation. Exons 1-9 of this gene code the extracellular domain, while exons 10 and 11 are involved in coding the transmembrane and juxtamembrane domains (JM), respectively. Exons 13-21 are responsible for the split tyrosine kinase domain (1).

The KIT gene is activated by binding of its ligand, the stem cell factor. Phosphorylation cascade activation is followed by the activation of various transcription factors. Malignant tumors, such as breast cancer, could be suppressed by inhibiting the KIT gene (2, 3).

Several studies have indicated the key role of KIT overexpression in the development of various cancers, such as gastrointestinal carcinoma, leukemia, and melanoma, in which insertion/deletion nucleotide and increased copy number variation (CNV) can result in the KIT overexpression (4-9).

In contrast with other cancers, the increased copy number gene is highly frequent in breast cancer, while in other mutations are rarely observed (10-16).

Our previous study showed a 55% increment in the level of KIT expression in breast cancer tissues (17), while other studies demonstrated that nearly 28% of the samples had CNV of exons (18). Variation of exons could lead to diverse protein structures and functions without its overexpression.

On the other hand, several KIT mutations are clinicopathologically relevant to responses toward inhibitor drugs.

In gastrointestinal stromal tumors (GISTs), for example, the majority of KIT mutations are seen in exon 11 (juxtamembrane domain) and exon 17 (tyrosine kinase domain), while mutations in KIT exons 2, 8, and 9 (extracellular domain) or exons 13 and 14 (tyrosine kinase domain) are less frequent. Interestingly, patients with variations in exon 17 are...
resistant to imatinib drug (19, 20). This issue is of crucial significance in the medicinal regime of patients with KIT gene mutations.

In this regard, the current study is the first research analyzing the relationship between deletions and duplications of KIT gene exons and clinicopathological variables, such as estrogen receptor (ER), progesterone receptor (PR), HER2, P53, stage, tumor size, Ki67, Annexin V, histological type, age, molecular subtype, and node status, among Iranian women suffering from breast cancer.

**Material and Methods**

**Patients**

Tissues were collected from 64 patients with breast cancer. The study included females with primary, sporadic breast cancer with no history of treatment regardless of their age or histopathological subtype who referred to Mehrad Hospital (Tehran, Iran). DNA extraction was carried out on the tumor tissue samples obtained from tumor regions. The quality and quantity of DNAs were assessed by agarose gel electrophoresis and NanoDrop ND 2000 spectrophotometer.

**Multiplex Ligation-Dependent Probe Amplification**

KIT gene deletion and duplication were assayed using the P354-A2 kit, which investigated all CNVs of 21 exons in the KIT gene. Multiplex ligation-dependent probe amplification (MLPA) was conducted according to the protocol of the MRC Company, whose results were used for gel electrophoresis. Polymerase chain reaction (PCR) products were separated on an ABI3730XL capillary sequencer. The variation of the copy number of the KIT gene was determined using Coffalyser (ver. 140721.1958). According to the guideline of MRC, results below 0.7 or 1.3-2 were interpreted as deletion and low-level amplification of genes, respectively (Figure 1).

![Figure 1. A: MLPA result of a sample on Coffalyser software without amplification of KIT B: MLPA result of a sample on Coffalyser software, which shows amplification of KIT](image.jpg)
Histopathology

Tissue sections were prepared, stained by hematoxylin and eosin (H&E), and studied by a pathologist to confirm the tumor diagnosis and characterization. Immunohistochemical staining was carried out for ER, PR, and HER2/neu on paraffin blocks. The pathological stage of the disease was also determined. The association between the variation of exons and ER, PR, HER2, P53, stage, tumor size, Ki67, Annexin V, histological type, age, molecular subtype, and node status was statistically analyzed.

Statistical Analysis

Data analysis was achieved using SPSS 19.0 (SPSS Inc., Chicago, Ill., USA). Fisher’s exact tests were used to assess the association between the variation in the copy number of KIT and clinicopathological variables. A P-value of less than 0.05 was considered statistically significant.

Results

The mean age of studied cases was 51 years (ranging from 30 to 76 years); their histological subtypes included 95% invasive ductal carcinoma and 4.9% invasive lobular carcinoma, while their tumor size was classified < 2 cm (8.5%) and 2-5 cm (91.5%).

Further, 16.1% of the patients were classified as grade 1, whereas 74.2% and 9.7% of the cases were grades 2 and 3, respectively.

These cases had an overall mean of 7.48 for P53, 8.97 for Ki67, and 8.66 for Annexin V. Further, 6.8% of the cases were in stage 1, while 79.7% and 13.6% were in stages 2 and 3, respectively.

Also, 46.8% of the samples were HER2-positive (hence, 53.2% were HER2-negative). Moreover, 69.4% and 61.3% of the subjects were ER-positive (30.6% ER-negative) and PR-positive (38.7% PR-negative), respectively.

Tables 1, 2, and 3 present the correlation between variations in KIT exons and clinicopathological variables.

Our results showed a significant correlation between increased copy number in exons 17-19 and the enhancement of tumor size (P<0.05). Also, a significant correlation was found between increased copy number in exon 7 and the cancer stage (P<0.05).

Other exons did not show a significant relationship with other clinicopathological variables (P>0.05).

Table 1. The relation between CNV in KIT gene exons, ER, PR, HER2, and tumor size

| Tumor size | HER2 status | PR status | ER status | Exons/ Copy Number Variation |
|------------|-------------|-----------|-----------|------------------------------|
| P-value    | <2 cm       | ≥2 cm     | <2 cm     | ≥2 cm                        |<0.05) | NO | 1 |
| 0.06       | 24          | 24        | 18        | 15                           | 0.71  | 0.76 | Yes |
| 10         | 9           | 5         | 6         | 4                            | 0.76  | 1.00 | Yes |
| 0.10       | 28          | 27        | 21        | 19                           | 0.27  | 1.00 | No |
| 0.30       | 29          | 29        | 23        | 19                           | 0.26  | 1.00 | No |
| 0.30       | 29          | 29        | 23        | 19                           | 0.26  | 1.00 | No |
| 1.00       | 29          | 29        | 23        | 19                           | 0.57  | 0.39 | No |
| 0.30       | 30          | 28        | 22        | 18                           | 0.60  | 0.63 | No |

Maryam Rahimi et al., 139

Volume 5, Fall 2020 Journal of Obstetrics, Gynecology and Cancer Research
### Table: Relation between Exon Variations of KIT Gene and Clinical Pathological Features

| Tumor size | HER2 status | PR status | ER status | Exon/ Copy Number Variation |
|------------|-------------|-----------|-----------|----------------------------|
|            | Negative    | Positive  | Negative  | Positive  | 2-5cm | ≥5cm | ≤5cm | ≥5cm | ≤5cm | 2-5cm | ≥5cm | ≤5cm | ≥5cm | ≤5cm |
| 0.30       | 3           | 1         | 3         | 1         | 75%   | 25%  | 75%  | 25%  | 75%  | 25%  | 75%  | 25%  | 75%  | 25%  |
| 0.36       | 4           | 0         | 4         | 0         | 100%  | 0%   | 100% | 0%   | 100% | 0%   | 100% | 0%   | 100% | 0%   |
| 0.10       | 1           | 2         | 1         | 2         | 66.7% | 33.3%| 66.7% | 33.3%| 66.7% | 33.3%| 66.7% | 33.3%| 66.7% | 33.3%|
| 0.07       | 5           | 2         | 5         | 2         | 71.4% | 28.6%| 71.4% | 28.6%| 71.4% | 28.6%| 71.4% | 28.6%| 71.4% | 28.6%|
| 1.00       | 5           | 0         | 5         | 0         | 100%  | 0%   | 100% | 0%   | 100% | 0%   | 100% | 0%   | 100% | 0%   |
| 1.00       | 1           | 2         | 1         | 2         | 66.7% | 33.3%| 66.7% | 33.3%| 66.7% | 33.3%| 66.7% | 33.3%| 66.7% | 33.3%|
| 0.23       | 3           | 1         | 3         | 1         | 75%   | 25%  | 75%  | 25%  | 75%  | 25%  | 75%  | 25%  | 75%  | 25%  |
| 0.05       | 4           | 0         | 4         | 0         | 100%  | 0%   | 100% | 0%   | 100% | 0%   | 100% | 0%   | 100% | 0%   |
| 0.05       | 1           | 2         | 1         | 2         | 66.7% | 33.3%| 66.7% | 33.3%| 66.7% | 33.3%| 66.7% | 33.3%| 66.7% | 33.3%|
| 0.02       | 4           | 0         | 4         | 0         | 100%  | 0%   | 100% | 0%   | 100% | 0%   | 100% | 0%   | 100% | 0%   |

**Note:** The table displays the relationship between exon variations of KIT gene and clinical pathological features such as tumor size, HER2 status, PR status, and ER status. The percentages indicate the proportion of patients with specific characteristics.
Table 2. The relation between the CNV in *KIT* gene exons, stage, histological Type, Annexin V, and Ki67

| Tumor size | HER2 status | PR status | ER status | Exons/ Copy Number Variation |
|------------|-------------|-----------|-----------|------------------------------|
| **P-value** | **Negative** | **Positive** | **Negative** | **Positive** | **Negative** | **Positive** | **Negative** | **Positive** | **Variation** | **Number** |
| <2cm | 0.10 | 94.2% | 5.8% | 0.86 | 29 | 52.7% | 47.3% | 20 | 36.4% | 63.6% | 19 | 34.5% | 65.5% | NO | 20 |
| 2-5cm | 0.16 | 71.4% | 28.6% | 0.47 | 5 | 57.1% | 42.9% | 4 | 57.1% | 42.9% | 0 | 0% | 100% | NO | 21 |
| >5cm | 0.36 | 68.4% | 31.6% | 0.17 | 7 | 50.8% | 49.2% | 5 | 44.4% | 55.6% | 1 | 11.1% | 88.9% | Yes | 14 |

| Table 2. The relation between the CNV in *KIT* gene exons, stage, histological Type, Annexin V, and Ki67 |
| Ki67 | Annexin V | Histological Type | Stage | Exons/ Copy Number Variation |
| **P-value** | **Negative** | **Positive** | **Negative** | **Positive** | **Negative** | **Positive** | **Negative** | **Positive** | **Variation** | **Number** |
| *Yes* | 0.43 | 81.3% | 18.8% | 0.71 | 39 | 10 | 29 | 52.7% | 47.3% | 1.00 | 4 | 10 | 91.5% | 0.06 | 8.7 | 84.8% | 6.5% | NO | 1 |
| *Yes* | 0.58 | 81.8% | 18.2% | 0.65 | 45 | 10 | 43 | 72.8% | 27.2% | 1.00 | 4 | 50 | 92.6% | 0.56 | 13.5% | 80.8% | 5.8% | NO | 2 |
| *Yes* | 0.30 | 81.8% | 17.2% | 0.56 | 48 | 10 | 44 | 75.9% | 24.1% | 1.00 | 4 | 53 | 93% | 0.18 | 14.3% | 71.4% | 14.3% | Yes | 3 |
| *Yes* | 0.00 | 82.8% | 17.2% | 0.56 | 100% | 0% | 44 | 100% | 0% | 1.00 | 4 | 0 | 100% | 0.18 | 12.7% | 81.8% | 5.5% | NO | 4 |
| *Yes* | 0.57 | 82.1% | 17.9% | 0.61 | 46 | 10 | 44 | 78.6% | 21.4% | 1.00 | 4 | 51 | 92.7% | 0.68 | 13% | 79.6% | 7.4% | NO | 5 |
| *Yes* | 0.51 | 84.5% | 15.5% | 1.00 | 49 | 9 | 45 | 66.7% | 33.3% | 1.00 | 4 | 0 | 100% | 0.18 | 12.7% | 81.8% | 5.5% | NO | 6 |
| *Yes* | 0.51 | 75% | 25% | 1.00 | 48 | 10 | 44 | 75.9% | 24.1% | 1.00 | 4 | 53 | 93% | 0.18 | 12.7% | 81.8% | 5.5% | NO | 7 |
| *Yes* | 0.10 | 82.8% | 17.2% | 0.56 | 4 | 0 | 4 | 0 | 100% | 0% | 1.00 | 4 | 0 | 100% | 0.02 | 10.9% | 83.6% | 5.5% | NO | 8 |
| *Yes* | 0.10 | 83.1% | 16.9% | 1.00 | 4 | 0 | 4 | 0 | 100% | 0% | 1.00 | 4 | 0 | 100% | 0.10 | 12.5% | 82.1% | 5.4% | NO | 9 |
| *Yes* | 0.36 | 82.5% | 17.5% | 0.57 | 5 | 0 | 5 | 100% | 0% | 1.00 | 5 | 0 | 100% | 0.26 | 13.0% | 81.5% | 5.6% | NO | 10 |
| Ki67 | Annexin V | Histological Type | Stage |
|------|-----------|--------------------|-------|
|      | Negative  | Positive           |       |
|      | Negative  | Positive           |       |
|      | Negative  | Positive           |       |

**Exons/Copy Number Variation**

|   |   |   |   |
|---|---|---|---|
| NO | Yes | NO | Yes |
| YES | 10 | 11 | 12 |
| YES | 13 | 14 | 15 |
| YES | 16 | 17 | 18 |
| YES | 19 | 20 | 21 |

*P*-value from Fisher’s Exact Test.
### Table 3. The relation between CNV in KIT gene exons, subtype, age, and node status

| Node status | Age | Subtype | Exons/Copy Number Variation |
|-------------|-----|---------|-----------------------------|
|             |     |         |                             |
| P-value     |     |         |                             |
| Negative    | 23  | 41      | 10                          | NO |
| Positive    | 23  | 5       | 20.8%                       | Yes |
| P-value     | 0.37| 0.47    |                              |    |
| Negative    | 7   | 46      | 5                           | No  |
| Positive    | 6   | 1       | 20.8%                       | Yes |
| P-value     | 0.55| 1.00    |                              |    |
| Negative    | 27  | 11      | 13                          | No  |
| Positive    | 25  | 3       | 13                          | Yes |
| P-value     | 0.57| 0.55    |                              |    |
| Negative    | 3   | 6       | 0                           | No  |
| Positive    | 4   | 1       | 10                          | Yes |
| P-value     | 0.52| 1.00    |                              |    |
| Negative    | 28  | 28      | 0                           | No  |
| Positive    | 27  | 13      | 13                          | Yes |
| P-value     | 0.35| 0.44    |                              |    |
| Negative    | 2   | 3       | 1                           | No  |
| Positive    | 2   | 1       | 12                          | Yes |
| P-value     | 0.61| 1.00    |                              |    |
| Negative    | 29  | 49      | 12                          | No  |
| Positive    | 26  | 7       | 12                          | Yes |
| P-value     | 0.48| 0.79    |                              |    |
| Negative    | 2   | 2       | 1                           | No  |
| Positive    | 2   | 1       | 10                          | Yes |
| P-value     | 0.56| 0.75    |                              |    |
| Negative    | 26  | 46      | 0                           | No  |
| Positive    | 26  | 7       | 0                           | Yes |
| P-value     | 0.81| 1.00    |                              |    |
| Negative    | 4   | 6       | 1                           | No  |
| Positive    | 3   | 1       | 1                           | Yes |
| P-value     | 0.54| 1.00    |                              |    |
| Negative    | 27  | 4       | 1                           | No  |
| Positive    | 27  | 1       | 1                           | Yes |
| P-value     | 0.54| 1.00    |                              |    |
| Negative    | 3   | 5       | 1                           | No  |
| Positive    | 3   | 1       | 1                           | Yes |
| P-value     | 0.54| 1.00    |                              |    |
| Negative    | 28  | 5       | 1                           | No  |
| Positive    | 28  | 1       | 1                           | Yes |
| P-value     | 0.52| 1.00    |                              |    |
| Negative    | 2   | 4       | 1                           | No  |
| Positive    | 3   | 1       | 1                           | Yes |
| P-value     | 0.52| 1.00    |                              |    |

- **CNV**: Copy Number Variation
- **P-values**: Statistical significance levels
- **Subtype**: Basal Like, Luminal B, Luminal A

**Note**: Numbers represent counts or percentages as specified in the table.
Discussion

Our results indicated that 60% of cases in exon 17, 60% in exon 18, and about 67% in exon 19 had a tumor size of 2-5 cm with an increase in CNVs; no significant relation was, however, found between other exons and tumor size.

These exons are key coding domains of tyrosine kinase, involving the activation of various upstream transcription factors that regulate apoptosis, cell differentiation, proliferation, and angiogenesis (1, 20). Previous studies on phyllodes tumors have suggested an increase in exon 18 CNVs due to KIT overexpression (15). Thus, an increase in the copy number of these exons may explain the rise in kit tyrosine kinase activity with an effective role in the tumor size enhancement. On the other hand, a study on phyllodes tumors demonstrated that 2 out of 13 KIT cases possess exon 17 alterations and protein overexpression (21).

Our research confirmed other studies indicating that KIT can be a key factor in tumor development and breast cancer malignancy (22). Exon 17 is one of the most important exons in other cancer types, such as GISTs, in terms of mutation frequency (23, 24). On the other hand, variation in this exon can be due to resistance to imatinib (25-27).

In this study, almost all the patients with a normal copy number of exons 7 were in stage 2, while those with increased CNV were in stage 3; these results were significant. Exon 7 codes the key domain of receptor tyrosine kinase, whose variation may influence stage development. These findings are in line with previous results highlighting the importance of KIT variation and overexpression for stage development (28-30).

Most cases with no variation in exon 12 were HER2-positive, while those showing an increase of CNV exon
12 were HER2-negative (P>0.05). This exon encoded JM and can affect protein activity. The small sample size may be the main reason for insignificant results.

This study also demonstrated that most of the cases with increased exon 5 CNV were PR-positive, whereas those showing increased exons 15, 18, and 20 were PR-negative. One study revealed a correlation between enhanced copy numbers in exons 15 and 18 and their overexpression in phyllodes tumors (15). All the cases with the increased exons 3 and 4 were ER-negative, although it was not statistically significant (P>0.05).

Two studies showed KIT expression in 42% and 30% of triple-negative breast cancers (16, 31). Most studies have generally found that kit positivity may be more common in ductal carcinomas, HER2+, ER/PR2, and prognostically unfavorable tumors (32, 33).

Furthermore, the correlation between variation in KIT exons and node status was also addressed. The cases with a normal copy number of exons 2, 6, 8, 9, 11, and 13-21 were node-negative, while those with increased copy numbers were mostly node-positive; our results were not significant. Exons 11, 13, 17, 2, and 8 play a key role in most cancer types, such as GISTs, as their mutation rate can dramatically influence malignancy (27).

Conclusion

This study was carried out following our previous studies on the role of KIT gene CNVs and their expression in breast cancer. A significant relationship was found between the major exons involving the coding of key domains and tumor size and stage in some cancer types. These factors are indicative of the rate of tumor development. On the other hand, they are influential in diagnosis and follow-up processes. Further studies with larger populations are necessary to confirm our results.

kit-repressing drugs, such as imatinib used in the treatment of GIST, can also be employed for treating breast cancer. The variation in exon 17, i.e., in GIST, can be due to resistance to imatinib drug. Thus, further studies are needed to investigate this issue for the prevention of drug resistance. Moreover, previous studies have shown that the response to imatinib has a closer relationship with KIT mutational activation but not the expression of kit protein (27-34). Some of the mutations of this study are different from the activating mutations reported in GISTs, reflecting genetic instability in malignant tumors. In breast cancer, however, an increase was observed in the copy number of the KIT gene, unlike other cancers (4, 5, 12, 15, 35, 36).

Acknowledgments

The authors thank all those who helped them writing this article.

Conflict of Interest

All authors declare that they have no conflict of interests.

Informed consent: Informed consent was obtained from all individual participants included in the study.

References

1. Miettinen M, Lasota J. KIT (CD117): A Review on Expression in Normal and Neoplastic Tissues, and Mutations and Their Clinicopathologic Correlation. Appl Immunohistochem Mol Morphol 2005;13: 205-220 [DOI:10.1097/01.pai.0000173054.83414.22] [PMID]

2. Ribatti D, Nico B, Crivellato E, Roccaro AM, Vacca A. The history of angiogenic switch concept. Leukemia. 2007; 21(1): 44-52. [DOI:10.1038/sj.leu.2404402] [PMID]

3. Fakhrejahani E, Toi M. Antiangiogenesis Therapy for Breast Cancer: An Update and Perspectives from Clinical Trials. Jpn J Clin Oncol. 2014; 44(3): 197-207 [DOI:10.1038/jjco.hyt201] [PMID] [PMCID]

4. Tuveson D, Willis N, Jacks T, Gri J, Singer S. STI571 inactivation of the gastrointestinal stromal tumor c-KIToncoprotein: biological and clinical implications. Oncogene. 2001; 20:5054-58. [DOI:10.1038/sj.onc.1204704] [PMID]

5. Orsenigo M, Brich S, Riva C, Conca E, Bertulli R, Dileo P, Gronchi A, Casali PG, Pierotti MA, Tamborini E, Pilotti S. Fluorescence in situ hybridization analysis and immunophenotyping of c-Kit/PDGFRα and Bcl-2 expression in gastrointestinal stromal tumors. Anal Quant CytolHistol. 2010;32 (4):225-33.

6. Lasota J, Miettinen M. Clinical significance of oncogenic KIT and PDGFRα mutations in gastrointestinal stromal tumours. Histopathology. 2008; 53(3):245-266. [DOI:10.1111/j.1365-2559.2008.02977.x] [PMID]
7. Malaise M, Steinbach D, Corbacioglu S. Clinical implications of c-KIT mutations in acute myelogenous leukemia. Find out how to access preview-only content. Current Hematologic Malignancy Reports. 2009; 4(2): 77-82. [DOI:10.1007/s11899-009-0011-8] [PMID]

8. Renneville A, Roumier C, Biggio V, Nibourel O, Boissel N, Fenaux P, Preudhomme C. Cooperating gene mutations in acute myeloid leukemia: a review of the literature. Leukemia 2008; 22:915-931. [DOI:10.1038/leu.2008.19] [PMID]

9. Beadling C, Jacobson-Dunlop E, Hodi FS, Le C, Warrick A, Patterson J, Town A, Harlow A. KIT gene mutations and copy number in melanoma subtypes. Clin Cancer Res. 2008;14 (21):6821-8. [DOI:10.1158/1078-0432.CCR-08-0575] [PMID]

10. Lee JY, Park K, Lim S H, Kim H S, Yoo K H, Jung K S, Song H, Hong M. Mutational profiling of brain metastasis from breast cancer: matched pair analysis of targeted sequencing between brain metastasis and primary breast cancer. Oncotarget. 2015; 22; 6(41):43731-42. [DOI:10.18632/oncotarget.6192] [PMID] [PMCID]

11. Judith A. Gilbert, Matthew P. Goetz, Carol A. Reynolds, James N. Ingle, Karin F.Giordano. Molecular analysis of metaplastic breast carcinoma. Mol Cancer Ther. 2008; 7(4): 944-951 [DOI:10.1158/1535-7163.MCT-07-0570] [PMID] [PMCID]

12. Kondi-Pafiti A, Arkadopoulos N, Gennatas C, Michalaki V, Frangou-Plegmenou M. Expression of c-kit in common benign and malignant breast lesions. Tumori. 2010; 96: 978-984 [DOI:10.1177/548.6519] [PMID]

13. Johansson I, E. Aaltosen K, Ebbesson A, Grabau D, Wigerup C, Hedenfalk I. Increased Gene Copy Number of KIT and VEGFR2 at4q12 in Primary Breast Cancer is Related to an Aggressive Phenotype and Impaired Prognosis GENES.CHROMOSOMES & CANCER.2012; 51:375-383 [DOI:10.1002/gcc.21922] [PMID] [PMCID]

14. Jansson S, Grabau D, Falck A, Aaltonen K. The Three Receptor Tyrosine Kinases c-KIT, VEGFR2 and PDGFRa, Closely Spaced at 4q12, Show Increased Protein Expression in Triple-Negative Breast Cancer. PLOS ONE.2014; 9 (7):102176. [DOI:10.1371/journal.pone.0102176] [PMID] [PMCID]
NCCTG study. Ann Oncol 2005; 16: 1811-1816. [DOI:10.1093/annonc/mdi365] [PMID]

25. Antonescu C, Romeo S, Zhang L, Nafá K, Hornick J, Nielsen G, Mino-Kenudson M, Huang H, Mosquera J, Dei Tos P, Fletcher. C. Dedifferentiation in Gastrointestinal Stromal Tumor to an Anaplastic KIT Negative Phenotype - a Diagnostic Pitfall. Morphologic and Molecular Characterization of 8 Cases Occurring either de novo or after Imatinib Therapy. Am J Surg Pathol. 2013; 37(3): 385-392. [DOI:10.1097/PAS.0b013e31826c1761] [PMID] [PMCID]

26. Reichardt P, Hogendoorn PC, Tamborini E, Lodà M, Gronchi A, Poveda A et al, Gastrointestinal stromal tumors I: pathology, pathobiology, primary therapy, and surgical issues. Semin Oncol. 2009; 36(4): 290-301. [DOI:10.1053/j.seminoncol.2009.06.002] [PMID]

27. Martin-Broto J, Rubio L, Alemany R, Lopez-Guerrero JA, Clinical implications of KIT and PDGFRA genotyping in GIST. Clin Trans Oncol. 2010; 12(10):670-676. [DOI:10.1007/s12094-010-0576-7] [PMID]

28. Zhao F, Chen Y, Wu Q, Wang Z, Lu J, Prognostic value of CD117 in cancer: a metaanalysis. Int J Clin Exp Pathol. 2014; 7(3):1012-1021. [DOI:10.2147/DDDT.S89114] [PMID] [PMCID]

29. Babaei M A, Kamalidehghan B, Saleem M, Huri H Z, Ahmadipour F, Receptor tyrosine kinase (c-Kit) inhibitors: a potential therapeutic target in cancer cells. Drug Des Devel Ther. 2016; 10: 2443-2459. [DOI:10.2147/DDDT.S89114] [PMID] [PMCID]

30. LU H Y, ZHANG G, CHENG Q, CHEN B, CAI J, WANG X, ZHANG Y, WANG Z, LU Z, XIE F, MAO W, Expression and mutation of the c-kit gene and correlation with prognosis of small cell lung cancer. Oncolett. 2012; 4(1): 89-93. [DOI:10.3892/ol.2012.679] [PMID] [PMCID]

31. Ahmed R, Din H U, Akhtar F, Afzal S, Muhammad I, Hashmi S N, Immunohistochemical Expression of Epidermal Growth Factor Receptor and c-Kit in Triple Negative Breast Cancer. Journal of the College of Physicians and Surgeons Pakistan 2016; 26 (7): 570-572.

32. Natali PG, Nicotra MR, Sures I. Expression of c-kit receptor in normal and transformed human nonlymphoid tissues. Cancer Res. 1992; 52:6139-6143.

33. Matsuda R, Takahashi T, Nakamura S. Expression of the c-kit protein in human solid tumors and in corresponding fetal and adult normal tissues. Am J Pathol. 1993;142:339-346.

34. Lasota J. Not all c-kit mutations can be corrected by imatinib. Lab Invest 2007; 87: 317. [DOI:10.1038/labinvest.3700538]

35. Atay S, Banskota S, Crow J., Sethi G. Oncogenic KIT-containing exosomes increase gastrointestinal stromal tumor cell invasion. PNAS, 2014. 111 (2) 711-716. [DOI:10.1073/pnas.1310501111] [PMID] [PMCID]

36. McIntyre A, Summersgill B, Grygulewicz B, Gilliss AJ, Stoop J, van Gurp RJ, Dennis N, Fisher C, Huddart R, Cooper C, Clark J, Oosterhuis JW, Looijenga LH, Shipley J. Amplification and overexpression of the KIT gene is associated with progression in the seminoma subtype of testicular germ cell tumors of adolescents and adults. Cancer Res. 2005; 65 (18): 8085-9. [DOI:10.1158/0008-5472.CAN-05-0471] [PMID]

How to Cite This Article:
Rahimi M. The Relation between Exon Variations of KIT Gene and Clinical Pathological Factors of Breast Cancer. J Obstet Gynecol Cancer Res. 2020; 5 (4) :137-148