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Expression of the BRCA2 Mechanism Gene EMSY in Breast Cancer

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ABSTRACT— In spite of the relevance of (BRCA2) breast cancer gene 2 which gene for suppression of cancer in hereditary malignancies of breast and ovarian is well recognized. The discovery of EMSY, a recent protein binding to BRCA2, as a possible Oncogene implies that the (breast cancer gene 2) system has a role in non- hereditary (sporadic) malignancies. The study's aim is determining the attendance of EMSY mutation in breast cancer. 60 patients diagnosed with breast cancer, classified according to the genotype, age, family history, aggressive type of breast cancer and other types of tumors associated with EMSY gene. This study was based in PCR sequencing to determine the attendance of EMSY mutation. Incidence of breast cancer occurred in 37 % patients aged 25-40 years old, while incidence of metastatic breast cancer was 53% of cases, incidence of linkage of EMSY gene to BRACA2 in cases of breast cancer was: 73%, incidence of linkage of EMSY gene to BRACA2 in cases of breast cancer was: 43% with positive family history of breast cancer , incidence of linkage of EMSY gene to BRACA2 in cases of stage 4 breast cancer was: 68.2 and incidence of linkage of EMSY gene to BRACA2 in cases of other types of cancer was: 22.7% with ovarian cancer. The EMSY gene has been linked to a poor outcome in cases of metastatic breast cancer. To confirm that EMSY is over presented in primary breast and ovarian tumors, more evidence is required.

KEYWORDS: sporadic breast cancer, EMSY gene, BRACA2.

1. INTRODUCTION

Like other tumor types: breast malignancy, is caused by a series of genetic and epigenetic alterations. Although it is well known that genetic abnormalities in the breast cancer genes 1 (BRCA1) and 2 (BRCA2) tumor suppressor genes cause the bulk of inherited breast and ovarian tumors, only about 5% of all breast carcinomas are caused by genetic mutations. BRCA1 and BRCA2 mutations or deletions have not been found in more prevalent non-hereditary (sporadic) type of the tumor. This is in unlike to other tumor suppressors like TP53, which is affected by both germline and somatic abnormalities [1- 4].

Although BRCA1 loss due to hyper-methylation of promoter and loss of non- homozygosity has been recorded in a small sample of breast and ovarian tumors, little information on how BRCA2 may be affected in sporadic malignancies is currently available. Hughes-Davies and colleagues published a paper in Cell recently revealed the surprising results that BRCA2 connect with the EMSY put antivenom gene connect and its effect is decreased. If this theory is correct, EMSY amplification could explain why sporadic breast tumors lack BRCA2 mutations, emphasizing the function of BRCA proteins in cancer development [5- 7].

The BRCA2gene encodes a large protein (3418 amino acids) that is in velveting repair of DNA Damage, non-heterologous recombination, remodeling of chromatin, and transcription regulation. BRCA 2isdrawntoRAD51-containing nuclear focipostmutations, for example, as it aids in Telomerase. This conclusion is supported by the fact that BRCA2 null cells from human malignancies, and cells from knockout animals, are vulnerable to ionizing radiation. When BRCA2 is combined with a heterologous DNA binding domain, it has been aimed to activate transcription. However, because all of these researches were done using overexpressed proteins and in vitro, the physiologic points that activation of domains' putative BRCA2 transactivation, The physiologic significance of that activity, as well as whether it is essential for tumor suppressor action, are unclear [8- 12].

Exogenously gene rated BRCA2 boosted transcription of genes for androgen receptor-regulation in mammalian 293 cells, according to a recent survey.

Although the significance of that result in cancer of breast is uncertain. The only real reason for the significance of the domain of BRCA2 putative transactivation comes from a mutation of germline in a breast and ovarian tumors that laminates domain of putative transactivation only due to in frame downregulation, though overall structural impacts cannot be ruled out even in this case [13].

Utilizing a yeast two-hybrid screen by Hughes-Davies and colleagues to find proteins that could react with the domain of BRCA2 transactivation and they found a new protein named EMSY. The relationship in recombinant and endogenous EMSY, BRCA2, and the consequences of this relationship, was confirmed using a reporter experiment including transactivation of BRACA2 and the fusion protein of GAL4 DNA binding domain. The fusion protein of BRCA2–GAL4 was prevented from transactivating a GAL4 promoter by co- expression of EMSY or N-terminus portion of EMSY.

These findings imply that Inhibition BRCA2'strans activation function through EMSY by connecting to domain of its transactivation directly. Based on this discovery, the authors hypothesized that EMSY could bean on proteinate inhibitsBRCA2 activity in cancer patients [14].

Due to its intracellular position, EMSY, like BRCA2, is involved in damage of DNA. After radiation which is ionized, Reports by Hughes-Davies and colleagues provided that the EMSY's recruitment into a murine fibroblast cell line' nuclear foci, This, however, not to be replicated in human cells. When DNA damage is responded with involvement of proteins for repairing a cluster in damaged areas to undertake repair tasks, nuclear foci is induced by DNA damage and is hypothesized to form. After DNA damage, EMSY foci were formed shortly and nearly complete colonization with phosphomimic histone 2AX, informed us that in early response, EMSY is involved. By using EMSY as baiting no their yeast two-hybrid screen, Hughes-Davies and colleagues found that EMSY can connect with HP1 and BS69, proteins having domain of 'Royal Family' and involve din remodeling of chromatin. BRCA2 has also been linked to chromatin remodeling as a biological process. These findings suggest that EMSY is involved in a number of cellular activities in which there is a role for BRCA2, implying that the EMSY–BRCA2 connection is physiologic and regulates BRCA2's tumor suppressor activity [15- 21].

The finding of the gene of EMSY on chromosome 11q13, which is increased in 13% of breast tumors, raised the possibility that EMSY could playa veratroles an oncogene in non-hereditary (sporadic)malignancies. Hughes-Davies and colleagues looked studied the expression of EMSY in a panel of breast cancer cell lines to see if their theory was correct.

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Using (real-time PCR, array comparative genomic hybridization, and FISH (fluorescence inset hybridization), they discovered that lavation of EMSY, it's production in a subset of breast cancer cell lines. Amplification of the EMSY gene was observed in (7.4–13%)of sporadic breast tumors, although the prevalence of EMSY in original breast tumors was not examined [22], [23].

2. Material and Method

2.1 Patient and controls

A total of 60 females were diagnosed with carcinoma of breast cancer were admitted to the Najaf Governorate's Al- Sadr Teaching Hospital. Their ages are between (40 -80) years old.

2.2 Setting

This study was done at Najaf Governorate's Al- Sadr Teaching Hospital between 23-9-2020 to 25-7-2021

2.3 Sample collection /storage

60 blood samples were taken from cases. The blood of the group was sterilized in EDTA tubes. A pair extract to genomic DNA was utilized to test the Genetic DNA Mini kit. The gene EMSY was amplified using the primer-based PCR method.:

EMS1-r (5′-ggCTgTCACggTATgACATAgg-3′),
EMSY-f (5′-AAgTTCCAAAggCCgTTgTT-3′),
EMSY-r(5′gTggTAAggAgTTggCAATgCT-3′).

The following were the PCR conditions:

- Initial denaturation at 95°C for 5 minutes.
- Denaturation at 95°C for 30 seconds in 30 cycles.
- Extension at 72°C for 1 minute after annealing at 60°C for 30 seconds.
- A 5-minute final extension at 72°C.

2.4 Statistical analysis

BEAST was used to examine the sequencing results (Basic Local Aligned Search Tool). The OR and 95 percent cl were calculated using SPSS. If OR was less than 1.5, it was considered syndicated.

3. Results

Demography study:

1- Age

Table1: showed that incidence of breast cancer occurredin37%patients aged 25-40 years old.

Age	Frequency	Percent%
25-40years	**22**	**37%**
41-55years	**19**	**32%**
56-70years	**12**	**20%**
71-85years	**6**	**10%**

86morethan	**1**	**2%**
Total	**60**	**100%**

2- Pillstoprevent pregnancy

Table 2: showed that incidence of breast cancer occurredin53%patients who received contraceptive pills.

Pillstoprevent pregnancy	**Frequency**	**Percent%**
Yes	**32**	**53%**
No	**28**	**47%**
Total	**60**	**100%**

3- Metastatic or not

Table 3: showed that incidence of metastatic breast cancer was53%of cases.

Metastatic or not	**Frequency**	**Percent%**
Yes	**32**	**53%**
No	**28**	**47%**
Total	**60**	**100%**

4- Link of gene to BRCA2

Table 4: showed that incidence of linkage of EMSYgenetoBRACA2in cases of breast cancer was :73 %

Link of gene to BRCA2	**Frequency**	**Percent%**
Yes	**44**	**73%**
No	**16**	**27%**
Total	**60**	**100%**

5- Link of EMSY gene to Family history factor:

Table 5: showed that incidence of linkage of EMSY gene to BRACA2 in casesofbreastcancerwas:43%with+vefamilyhistoryofbreastcancer while20.5 % with +ve family history of ovarian cancer.

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Family history		Frequency	Percent
Valid	Brain	2	4.5
	Breast	19	43.2
	Leukemia	4	9.1
	No	9	20.5
	Ovarian	9	20.5
	Stomach cancer	1	2.3
	Total	44	100.0

6- Link of EMSY gene to Staging factor:

Table 6: showed that incidence of linkageofEMSYgenetoBRACA2in cases of stage 4 breast cancer was :68.2

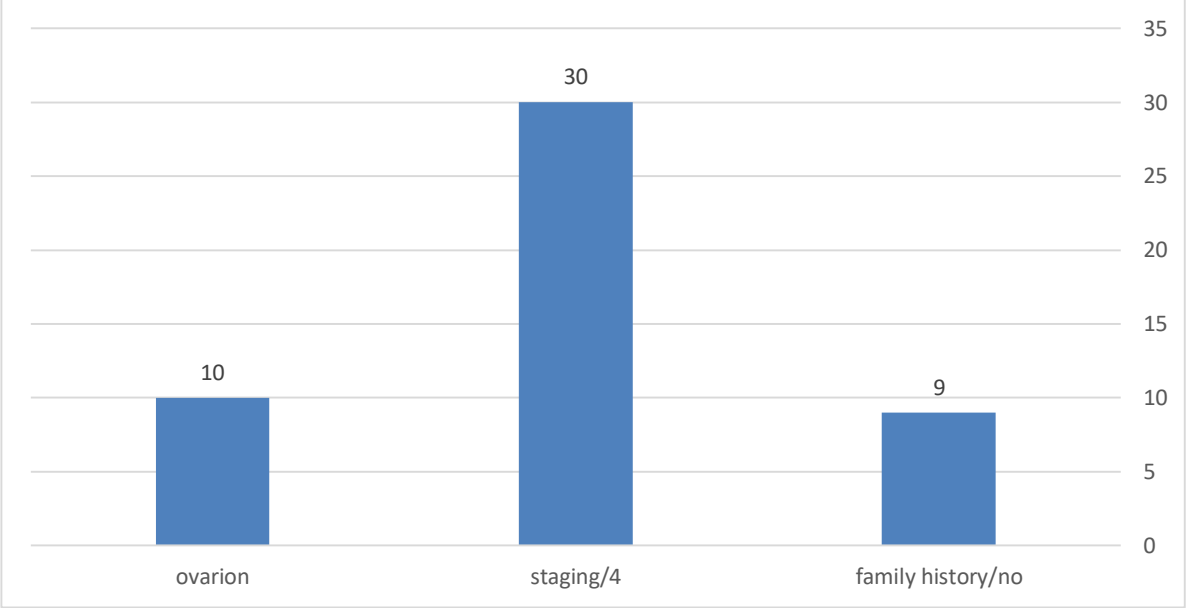
Staging		Frequency	Percent
Valid	2	4	9.1
	3	10	22.7
	4	30	68.2
	Total	44	100.0

7- Link of EMSY gene too their types of cancer:

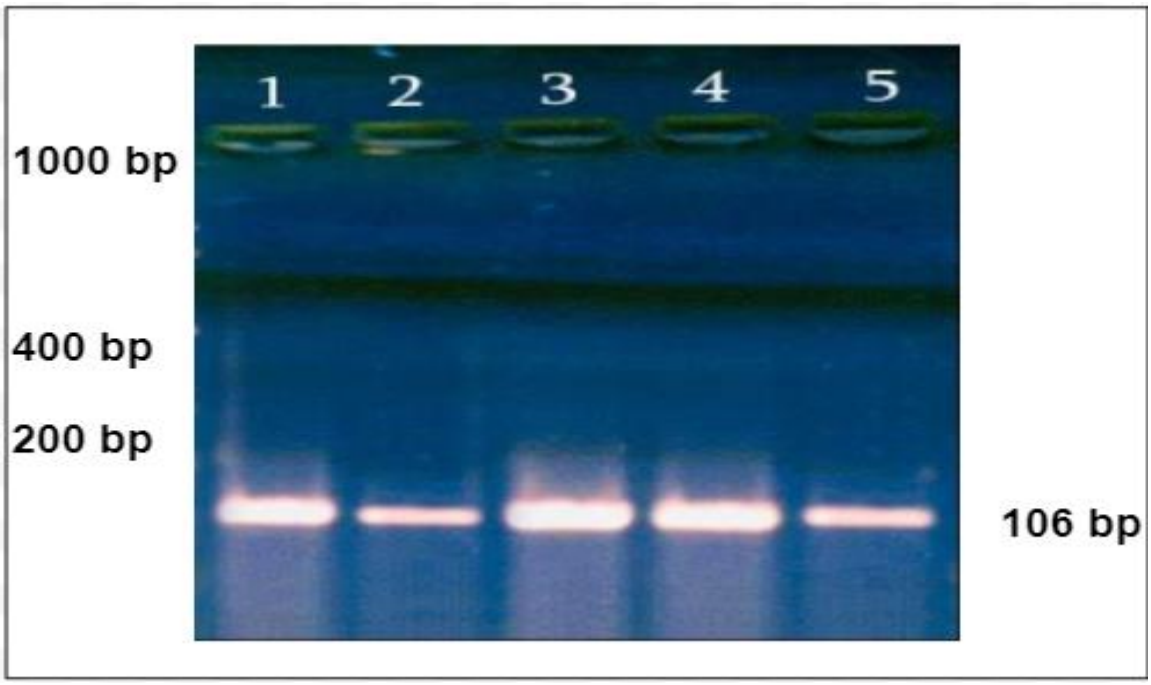
Table 7: showed that incidence of linkageofEMSYgenetoBRACA2in casesofothertypesofcancerwas:22.7%with ovariancancer,22.7% with lung cancer and with 36.4 % with no previous cancer.

Other types of cancer		Frequency	Percent
Valid	Liver	7	15.9
	liver\lung	1	2.3
	Lung	10	22.7
	No	16	36.4
	Ovarian	10	22.7

	Total	**44**	**100.0**



8- Agarose electrophoresis for PCR Product of EMSY gene:



OR: odds ratio 95%: confidence interval

4. Discussion

75% of family breast-ovarian tumor cases are due to BRCA1 or BRCA2 mutations. In these conditions, a non-homozygous germ-line mutation that causes truncation of premature proteins then followed by deletion(somatic)of the remaining allele of wild-type, resulting in entire gene function loss. On the other hand, the deletion of mutation of BRCA1 or BRCA2 in non-hereditary breast and ovarian cancers remains

unknown [24]

In our results showed that 33 % of cases with breast cancer had+ve family history of breast malignancy and 20 % with +ve family history with ovarian breast tumors, incidence of linkage of EMSY gene to BRACA2 in cases of breast cancer was:43%with+ve family history of breast cancer and 20.5 %with+ve family history of ovarian cancer.

BRCA2 may play a function in chromatin remodeling and transcriptional control, according to studies. EMSY, anew protein, connecttoexon3ofBRCC and inhibits reporter design activation. It will be especially interesting to see how overexpression of EMSY affects RAD51-dependent non heterologous recombination's rate [25].

According to, genetic events may govern EMSY in non-hereditary (sporadic) breast and ovarian tumors separately. EMSY is located onchromosome11q13.5, amplification of alocusin13% of breast tumors and 17% of ovarian tumors [26].

In our results: that incidence of link age of EMSY gene to BRACA2 in cases of breast cancer with other types of cancer was :22.7 % with ovarian cancer,22.7 % with lung cancer and with 36.4 % with no previous cancer.

It's difficult to say whether EMSY over expression is enough to cause cancer; oncogenic effects in experimental systems will have to be demonstrated. Mice withweakenedBRCA2 create lymphoid cancers, while tissue-specific targeting of TP53 causes mammary tumors, suggesting that this system can be effectively mimicked in mice [27].

EMSY amplification is linked to a worse prognosis in individuals with breast cancer, with a median disease-free life of 6.4 years in patients with gene amplification compared to 14 years in patients with diploid gene copy counts. When there was no evidence of regional lymph node metastases at the time of diagnosis, this differentiation was most obvious. (Review by Osin and Lakhani, 1999) EMSY amplification was linked to a shorter disease-free survival in both univariate and multivariate analyses [28].

While in our study showed that: incidence of linkage of EMSY gene to BRACA2 in cases of stage4 breast cancer was:68.2whilewas30%of non-metastatic breast cancer (stage 2,3). EMSY amplification in non-hereditary (sporadic)breast and ovarian tumors similar to the impact of BRCA2 mutations in hereditary breast and ovarian tumors. In chromatin assembly, HP1interacts with methylation histones, which can block these actions. The fact that EMSY's overexpression inhibits BrcA2ex3 transactivation suggests that EMSY may has a vital role in non- familial cancer [29], [30].

In our study: incidence of linkage of EMSY gene to BRACA2 in cases of breast cancer was :73 %. In some non-hereditary (sporadic)breast and ovarian tumors, overexpression of the protein EMSY may be functionally comparable to the absence of BRCA genes in family instances. The molecular consequences of the bRCA2-EMSY interactions have yet to be known understood, and proof that EMSY over expression is sufficient to cause cancer will need to be required [31].

5. Conclusion

According to EMSY, the BRCA2 gene is connected to non-hereditary (sporadic). Breast and ovarian tumor. Elevated EMSY levels suppress BRCA2 transactivation potential and cause chromosomal instabilities,

simulating BRCA2 mutation behavior in the establishment of hereditary breast/ovarian cancer. It keys for a nuclear bind to the BRCA2 N-terminal domain, which is involved in chromatin/transcription regulation, but when sporadically amplified/over expressed, it inhibits BRCA2transactivationpotentialandcauses cancer. In breast cancer patients who have progressed to metastatic illness, the EMSY gene has been related to a poor prognosis. It would be fascinating to examine if EMSY amplification is connected to breast cancer cell lines to show some of the phenotypic traits of BRCA2 deficient cells (radio sensitivity and homologous recombination impairment). More data is required to indicate that overexpression of EMSY and is amplified in primary breast and ovarian malignancies [32]. Furthermore, it would be vital to have information which breast carcinoma subtypes are affected by EMSY amplification and which the condition of EMSY is in BRCA2 negative tumors.

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