

# Mismatched Repair Genes in Breast Cancer - An Overview

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**Abstract:** Genetic basis for differential behavioral subtypes of breast cancer is being investigated extensively; one of the focus being MisMatch Repair genes, which are found to be responsible for Early onset cancers and account for their aggressive behaviour. In breast cancer MSI has been reported in varying frequencies. But, the association between MMR and breast cancer is far from clear and more focused research in the future will definitely help in tailoring the therapy for Breast Cancer.

**Keywords;** *Breast Cancer, MisMatch Repair genes.*

Carcinoma Breast, being the leading malignancy in women, has attracted a lot of attention in recent years into its pathogenesis. The search for answers regarding the etiology and behavioral patterns of breast cancers is still on and although there has been movement but one is not too sure if it is in the "forward" direction. The answer to the ultimate therapy which would be targeted and tailored lies in finding out the genetic basis of response of breast cancer to various therapies. The genetic basis of Carcinoma breast is therefore being investigated extensively world wide to find out markers delineating different behavioral subtypes. Recent research is focused primarily on HER-2NEU, CHEK-2, DBC-2, EMSY and Mismatch Repair Genes. The mismatched repair genes have been found to be responsible for the early onset cancers and also account for their aggressive behaviour.

MMR genes pathway is the most important post replicative repair process involved in maintenance of genomic instability. These genes first came into light due to the implication of their dysfunction in HNPCC syndrome. In HNPCC<sup>1</sup> syndrome MMR genes hMLH1 and hMSH2 were implicated in 30 & 50% instances respectively. MMR genes involvement is also implicated in sporadic colon, gastric, endometrial, prostatic malignancies and lymphoma. [1, 2] These genes are called *proof readers* of the genome. They correct erroneous nitrogenous base pairing occurring at the time of replication. Novel bands of DNA in the form of expansion and contraction appear in one or both alleles of microsatellites of the genome, causing microsatellite instability (MSI), hallmark of MMR dysfunction. Cells with defects in DNA repair are said to have replication error (RER positive) phenotype.

MMR genes most commonly associated with malignancy are hMSH2, hMLH1, hMSH6, hPMS2. In breast cancer MSI has been reported in varying frequencies of 5 to 30% [3]. Overall the actual number of MSI was 64 in a total of 2499 cases studied but ranged from 0% (Lohe et al 1993) to 34% (Patel et al 1994). The relationship between MMR genes dysfunction and family history in breast cancer has also seen investigated. Glebov et al [4] (1994) noted difference in instability of genome between familial and sporadic breast cancer but Jonsson et al [5] in (1995) reported that there is no significant difference of MMR dysfunction between sporadic familial and hereditary breast cancers – all falling in the range of 5-6.6%.

The clinicopathological parameters of breast cancer whose relationship has been studied with MMR dysfunction include tumour size, lymphnode positivity, histotype in situ carcinomas and histological grade. Contegiaco et al [6] in 1995 found MSI to be significantly related to tumour size, lymphnode status and histotype. Aldaz et al [7] found lobular carcinoma to be more commonly associated with MMR dysfunction. Lee et al [8] found medullary carcinoma to be uncommon in MMR dysfunction carcinoma breast. Walsh et al [9] found MSI to be associated

with higher nuclear grade in DCIS.

Many researchers have started reporting implications of MMR dysfunction in response to chemotherapy in breast cancer. Caligi et al [10] studied embryonic cell line with a 10 fold decrease in hMSH2 levels. These cells were RER negative and had no MSI, but they were found to be resistant to toxic effects of methylating agent MNNG. Instead these cells were highly sensitive to mutagenic effects of methylating agent. Cejka et al [11] have reported that human embryonic kidney cell lines, not expressing high levels of hMLH1 failed to arrest upon methylating agent MNNG treatment. Contellino et al [12] reported that MED1 gene, a base excision repair enzyme is associated with integrity of MMR system. It was found that MED1 negative phenotype had decreased cell cycle arrest and apoptosis induced by DNA damage. They also have resistance to MNNG (-) and 5-FU and a few other cytotoxic drugs.

The association between breast cancer and MMR genes is far from clear in the present scenario. A lot of focused research has to be done to clear all the doubts. However, if proven it could provide access to alternate therapy and prophylaxis for this deadly disease.

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