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Review Article

MUTATIONS AND ITS SIGNIFICANCE IN CANCER RESEARCH: A REVIEW

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ABSTRACT

Cancer is a genetic disease associated with the diverse molecular alterations resulting in several obstacles in diagnosis. Such mutations may result in improper therapy and lead to several types of resistance. Recent advances have helped in identifying existing biomarkers as well as novel ones. These biomarkers could be a number of biochemical entities including nucleic acids, proteins, sugars, lipids and small metabolites, cytogenetic and cytokinetic parameters and even tumour cells present in the biological fluid. Biomarkers have many potential applications in oncology, including risk assessment, screening, differential diagnosis, determination of prognosis, prediction of response to treatment and monitoring of progression of disease. The identification of biomarkers will help in the development of better therapeutic alternatives in turn providing benefit to the patients. In this perspective, we have identified a handful of such mutations with respect to the clinical aspects and which may help in identifying a possible role in cancer and targeting approaches in prospective research.

Keywords: Cancer, Mutations, Biomarkers, Targeting, Prognosis

INTRODUCTION

Cancer has been identified as a genetic disease possessing a number of causes eventually exerting its actions on a special class of genes referred to as cancer genes or proto-oncogenes.[1] Recently several proto-oncogenes have been identified and mapped along with the determination of their biological functions such as cell division. There are several events which alter a proto oncogenes including;

- **Point mutation**

  Which alters or selectively deletes only particular nucleotides in the gene sequence, hence activating the proto oncogene.[2]

- **Gene amplification**

  Leads to generation of additional gene copies.[2]

- **Chromosomal translocation**

  Relocation of the gene to new chromosomal regions leading to increased expression.[2]

The normal cell proliferation is controlled by the balance between growth promoting signals of proto-oncogenes and growth restraining signals of tumour suppressor genes.[3]

The conversion of normal cells to cancerous ones involves several processes including initiation, promotion and progression, hence converting them into malignant cells with invasive capabilities.[3]

Mutation is one of the major methods of changing a proto-oncogene which can be either spontaneous or induced environmentally.[4] Since the altered oncogene is present in the tumour, it is designated as a mutant clone. Normal cells balance the activity of the genes which enhance cell proliferation as well as those which result in suppression. It also regulates the process of apoptosis.[5] The accumulation of mutations in genes may result in cancerous formation of cells and according to the results obtained from the Cancer Genome Project, a majority of the cancers possess 60 or greater mutations. The main obstacle is to identify which mutation is responsible for which type of cancer.[6]

Mutations

Epidermal Growth Factor Receptor (EGFR) mutation

Cytogenetic Location

7p11.2, which is the short (p) arm of chromosome 7 at position 11.2 (Figure 1)

Molecular Location:

Base pairs 55,019,017 to 55,211,628 on chromosome 7

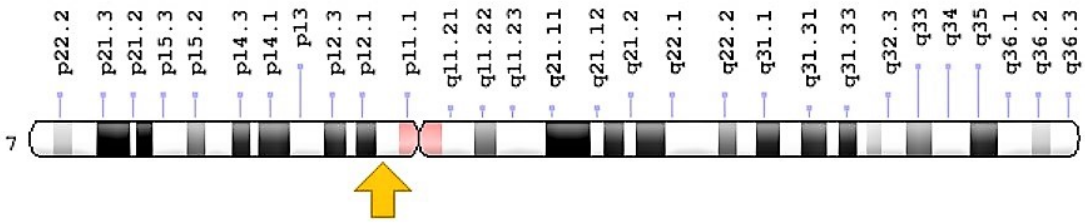

Figure 1: EGFR mutation[7]

The presence of somatic mutations was first identified from two independent studies which characterized the mutations as short deletions in exon 19 and several other point mutations in the exon region 19 and 21 (G719S, L858R and L861Q). These mutations were found to be present in 108 cancer derived cell lines and in 16 tumours within cohort of 119 primary Non-small-cell lung carcinoma samples. Among these, 15 mutations were obtained among tumour samples of Japan and 1 mutation was found in the tumour samples of the United States.

Mutations may be characterized into three main types:

Class I mutation

Short in-frame deletions that result in the loss of four to six amino acids (E746 to S752) encoded by exon 19.[8]

Class II mutation

Class II mutations are single-nucleotide substitutions that may occur throughout exons 18 to 2.[8]

Class III mutation

Class III mutations are in-frame duplications and/or insertions that occur mostly in exon 20.[8]

Studies have reported that there is an equal distribution of exon 19 deletions and L858R mutation but several recent reports have suggested the increased frequency of deletions when compared to point mutations. Recent research has identified a rare mutation in the exon 22(E884K) had shown differential sensitivity to various EGFR small molecule inhibitors.

In general, the domain of EGFR kinase is in the inactive state but once there is a mutation in the Tyrosine kinase domain region of EGFR, there is destabilization and activation of kinase activity leading to downstream signal activation.[8]

Tumour Protein 53 (TP53) mutation

Cytogenetic Location

17p13.1, which is the short (p) arm of chromosome 17 at position 13.1 (Figure 2)

Molecular Location

Base pairs 7,668,402 to 7,687,550 on chromosome 17

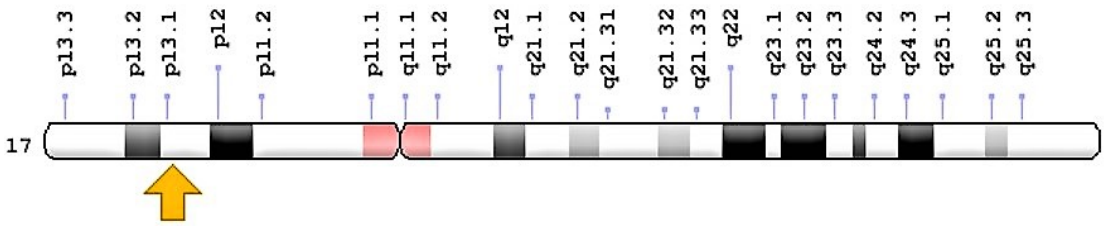

Figure 2: TP53 mutation[9]

Several research studies carried out on the mutations resulting in lung cancer have identified the loss of heterozygosity (LOH) and its frequent detection in tumour samples in the region of TP53 gene sequence in the chromosome number 17p13 leading to an outcome that it is likely to be involved in pathogenesis of cancer. This genetic abnormality has been associated with the poor prognosis and resistance to most therapies.

In Patients with Small Cell Lung Carcinoma, TP53 mutations were found to be higher in squamous cell carcinoma and least in adenocarcinomas. These were identified within the DNA binding domain in the presence or absence of allele at 17p13. Certain coding mutations occur at the early stages of lung cancer and are essential in maintaining a malignant phenotype. Statistics have shown that the incidence rates of TP53 mutations in primary and metastatic lymph nodes were around 23.2% and 21.4%. The metastasis condition of the tumour is generally formed after the mutation.[10]

PMS1 Homolog 2 (PMS2) mutation

Cytogenetic Location

7p22.1, which is the short (p) arm of chromosome 7 at position 22.1 (Figure 3)

Molecular Location

Base pairs 5,970,925 to 6,009,106 on chromosome 7

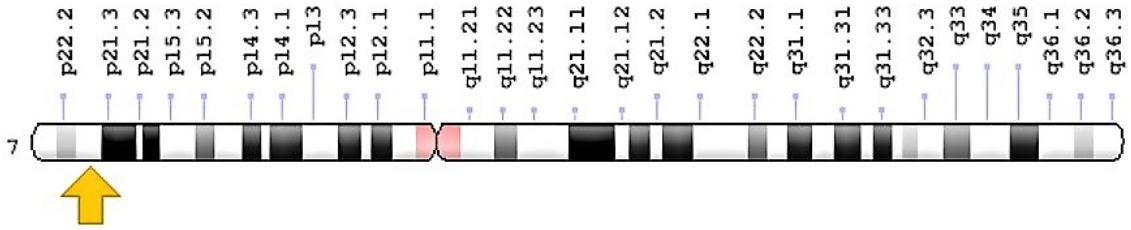

Figure 3: PMS2 mutation[11]

One of the prominent risk factors associated with colorectal and endometrial cancer is Lynch Syndrome which is a result of germ line mutation. A background of this disease is not commonly understood and is hypothesized to be as a result of mismatch repair genes including PMS2 deletion.[12] This syndrome is also found to be largely associated with other forms of cancer namely gastric, ovarian, small bowel, brain, urothelial cell, skin, pancreas, prostate, and biliary tract cancers.[13] The identification of heterozygous PMS2 mutation has been related with several complication due to the appearance of multiple pseudogenes and the lower penetrance of carriers. Previous studies performed to determine the penetrance of PMS2 carriers were determined in European cancer clinics and found 98 PMS2 families involved in the incidence of extra colonic cancer. However reliable penetrance data was not found due to several infrequencies. A study performed in Iceland found that two pathogenic variants of PMS2 were associated with colorectal, ovarian and endometrial cancer.[14]

Based on the results of a study carried out by Sanne *et al*., they identified that the PMS2 related Lynch syndrome spectrum was related to colorectal and endometrial cancer only. It also found that this particular mutation was related to a much minor risk of cancer- at 11% and 20% in case of colorectal cancer and 12% to 15% in endometrial cancer in patients at cumulative age of 70 years which is less when compared to several other Mismatch repair gene mutation which was associated with 35-55% in colorectal cancer and 10-45% in endometrial cancer.[15]

Another identification from this study showed that the carriers of PMS2 mutations who regularly underwent colonoscopy screening procedures were less susceptible to cancer development. Notably, colorectal cancer did not occur in any of the PMS2 mutation carriers undergoing regular colonoscopic screening. This, together with penetrance data estimates, could justify consideration of less-frequent colonoscopy screening for PMS2 mutation carriers.

APC membrane recruitment protein 1-WTX (AMER 1) mutation

Cytogenetic Location

Xq11.2, which is the long (q) arm of the X chromosome at position 11.2 (Figure 4)

Molecular Location

Base pairs 64,185,117 to 64,205,708 on the X chromosome

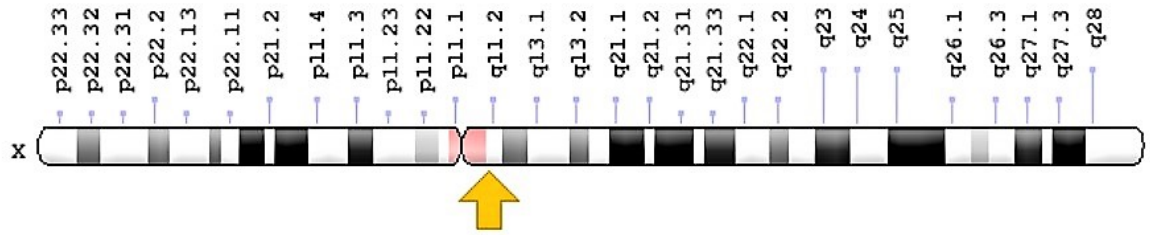

Figure 4: WTX mutation[16]

Hepatocellular carcinoma (HCC) is identified as the third leading cause of mortality around the globe and the main causes of it were identified to be Hepatitis B, C Virus and development of cirrhosis in the liver.[17] Though there has been significant development in prolonging the life span of the patient, there is no improvement in the survival after surgery.

In the identification of Wilms' tumour, a tumour suppressor gene known as new X chromosome was identified which was named as Wilms' tumour gene on the X-Chromosome (WTX). The mutations in WTX gene was hypothesized to cause damage to the β-catenin destruction complex leading to the prognosis of colorectal cancers. Studies performed had suggested it's novelty in the therapy of HCC.[18]

According to cell line studies performed by Liao *et. al*., the expression was estimated at mRNA and protein levels through Western blot technique as well as reverse transcription-polymerase chain reaction (RT-PCR) in which the mRNA level and protein levels were found to be ($P = 0.001$ for all) and ($P < 0.05$ for all). When compared to non-cancerous tissues, the gene level was lower in HCC and other analysis reports suggested the possible correlation along with TNM (Tumour, Node, Metastasis) staging and differentiation as well as metastasis of the lymph node ($P < 0.05$ for all).[19]

MutL homolog 1(MLH1) and MutS homolog 2 (MSH2) mutations

MLH1 Cytogenetic Location

3p22.2, which is the short (p) arm of chromosome 3 at position 22.2 (Figure 5)

MLH1 Molecular Location

Base pairs 36,993,350 to 37,050,846 on chromosome 3

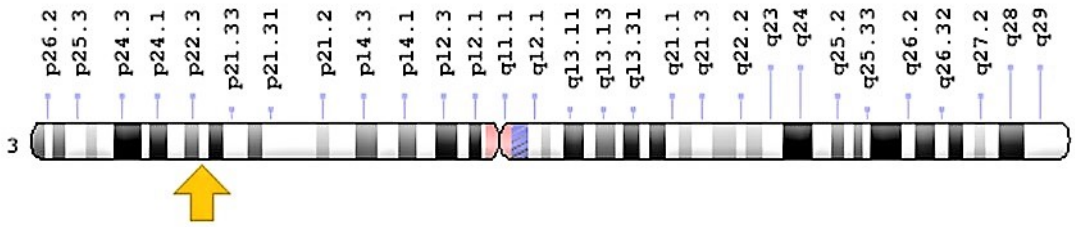

Figure 5: MLH1 mutation[20]

MSH2 Cytogenetic Location

2p21-p16.3, which is the short (p) arm of chromosome 2 between positions 21 and 16.3 (Figure 6)

MSH2 Molecular Location

Base pairs 47,403,067 to 47,634,501 on chromosome 2

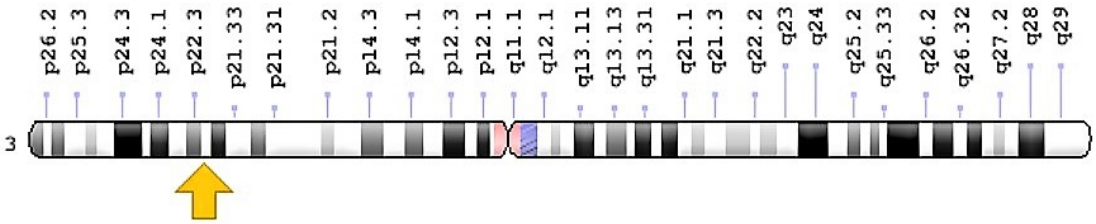

Figure 6: MSH2 mutation[21]

Dowty *et al*. carried out significant research in MLH1 and MSH2 mutations and carried out clinical studies on a total of 17,576 patients which were taken from the Colon Cancer Family Registry with 166 patients containing MLH1 mutation and 224 patients with MSH2 mutations. When compared to male and female carriers, the rate of MLH1 mutation was observed to be more in the male population and not the same in MSH2 mutation.[22]

Since the participants were obtained from populations with decreased incidences of stomach cancer, the mutation of MLH1 was found to be a lesser extent when compared to MSH2 mutation. The differences in the male population carriers of MLH1 and MSH2 mutations may be due to the following factors:

- True risk variation
- Improper Hazard ratio Estimation
- Early onset of MLH1 carrier mutation
- A higher proportion of MLH1 mutation carriers among the stomach cancer cases than MSH2 mutation carriers or a combination of these.[22]

Further assessment of possible other cancer sites, showed a higher incidence of pancreatic cancer as concluded by previous studies of Kastrinos *et al*., there was found to be no significant relation with breast or prostate cancer. However recent research has shown the possible risk of such cancers due to signs of MMR.[23]

Utilizing the polygenic model, there has been supporting evidence that Colorectal Cancer (CRC) is heterogeneous and based on the statistical analysis obtained, the risk of heterogeneity of a population of mutational carrier are in a population level risk and a minority of them are at a risk of CRC.[24]

Other environmental factors have not been studied extensively, though a few have been found to be correlated with MMR gene mutations carriers.[24]

The results obtained from this study may aid in development of genetic counselling, optimizing surveillance, identification of possible carriers from family histories.

Breast Cancer 1 and 2 (BRCA1 and BRCA2) mutations

BRCA1 Cytogenetic Location

17q21.31, which is the long (q) arm of chromosome 17 at position 21.31 (Figure 7)

BRCA1 Molecular Location

Base pairs 32,315,480 to 32,399,672 on chromosome 13

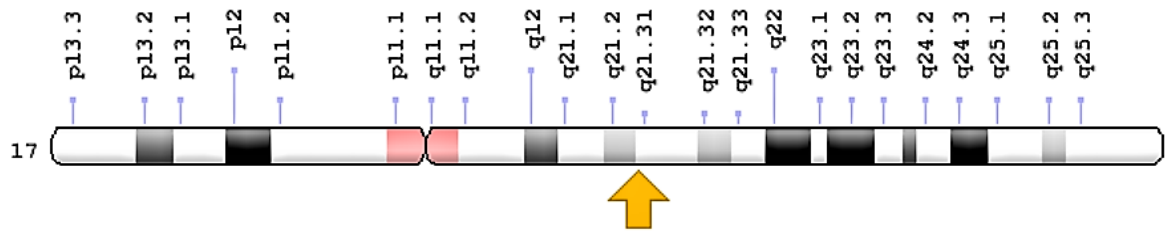

Figure 7: BRCA1 mutation[25]

BRCA2 Cytogenetic Location

13q13.1, which is the long (q) arm of chromosome13 at position 13.1 (Figure 8)

BRCA2 Molecular Location

Base pairs 43,044,295 to 43,125,364 on chromosome 17

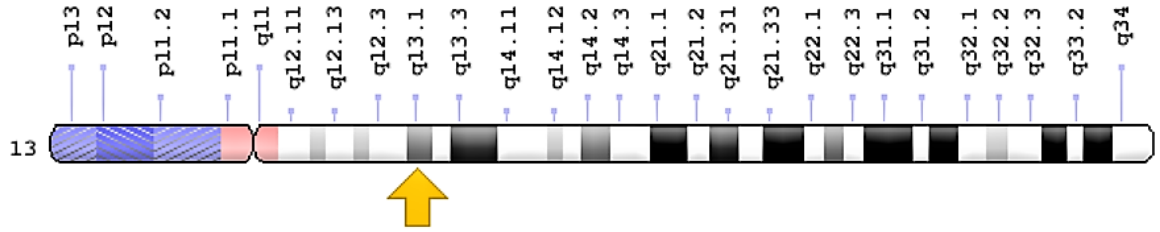

Figure 8: BRCA2 mutation[26]

Statistics have proven that the possible cause of breast cancer in women was BRCA1 mutation which eventually led to the development of ovarian cancer. In men this mutation resulted in prostate cancer in around 60-80% of the patients.

The resulting breast cancer in women causes enhances mitotic rates as well as lymphatic penetrance.[27] Most of the families observed the presence of Germ line mutation associated with the early emergence of breast cancer and in both men and women resulted in an increase in risk of colon, prostate, pancreatic, melanoma and gastric cancer.

A cohort prospective study was carried out on patients with Triple negative breast cancer by Copson *et al*., aimed to identify the possible outcome of germ line BRCA1 or BRCA2 mutation in young patients suffering from breast cancer.[28]

The study recruited patients from 125 hospitals around the UK with the age of 40 or younger during preliminary diagnosis and within 12 months of initial diagnosis. Those patients exhibiting previous invasive malignancies were excluded from the study. The mutations were analysed using the blood and the clinicopathological data and those relating to the outcomes of the patient in the long term were collected and finally follow up was done until the death of the patient or loss of follow up. Patients were recognized within the period of 12 months of diagnosis and the mutations were analysed using the blood of the patients. The other data such as clinicopathological data as well as the long-term outcomes were also assessed from medical history within 6 months, 12 months and continued till death or loss of follow up. The outcomes were studied for the survival of those patients carrying the mutations versus non-carriers of mutations to 2, 5 and 10 years of diagnosis. The study concluded that the survival proportion was similar between carriers as well as non-carriers. However, those who carried the mutation had a more advantage in survival during the preliminary few years after diagnosis. Additionally, those patients seeking additional surgery for reducing the future risks of cancer should take into consideration the preference of patients and the prognosis related to first malignancy.[28]

CONCLUSION

Cancer is a result of uncontrolled cell growth and mutations resulting in inhibition of normal control systems including apoptosis and cell cycle. The cancer cells may invade other body parts resulting in metastasis. Hence it is imminent to identify the possible mutation in the gene sequence in order to determine an appropriate therapy to improve the therapeutic outcomes of the patient. Hence this may aid in the diagnosis of the disease at a much earlier stage.

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