



Effects of *KRAS* Gene Mutations in Gynaecological Malignancies



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Abstract

Gynaecological disorders and malignancies affect the female reproductive system. Every woman in her life time suffers from gynaecological problem at some extent. The development and pathogenesis of gynaecological disorders is still remains unclear, several clinical and epidemiological studies have documented that they can be triggered by environmental, life-style, genetic factors and epigenetic alterations. The *KRAS* (Kristen rat sarcoma viral oncogene) gene is the commonly mutated oncogene. This gene provides instructions for making a protein called as K-Ras, which plays a vital role in cell division, differentiation and apoptosis. The frequency of mutations in this oncogene is highly reported in gynaecological cancers. This review highlights the common mutations observed in *KRAS* gene that is associated with breast, cervical, ovarian and endometrial cancer. These genetic variations can be considered with their clinical significance and might be used as diagnostic biomarkers and testing for RAS pathway mutations.

Keywords: *KRAS*; Mutation; Gynaecological malignancies; Breast cancer; Cervical cancer

Introduction

Cancer is a complex collection of diseases that interfere with regular cellular growth and death; specific molecular alterations induce a normal cell to become malignant, have the ability to invade and metastasize from the primary lesion, but the spectrum of these alterations vary substantially among cancers [1]. Gynaecological malignancies are the most common cancers in women community and hence it's an important alarming public health issue. Due to lack of awareness of this disease, pathological status and scarce of screening facilities in developing countries lead most women to report at advanced stages, adversely affecting the prognosis and clinical outcomes [2]. The risk factors of cancer in women include, family history of ovarian cancer or cancers of the uterus, breast, beyond the age of menopause, obese, have never been pregnant or had infertility problems and the usage of medication tamoxifen or use unopposed oestrogen [3]. Recently, Genome Wide Association Studies (GWAS) in major gynaecological malignancies have revealed susceptible genes such as *RAD51C*, *TP53*, *BRCA1*, *BRCA2*, *CHEK2*, *BRIP1*, *FAT10*, *MLH1*, *KRAS*, *PIK3CA* and *PTEN* associated with the disease pathogenesis [4]. This review focuses on the reported genetic mutations occurring in Kirsten Rat Sarcoma Viral Oncogene (*KRAS*) of cervical, ovarian, endometrial and breast cancer respectively.

KRAS Gene

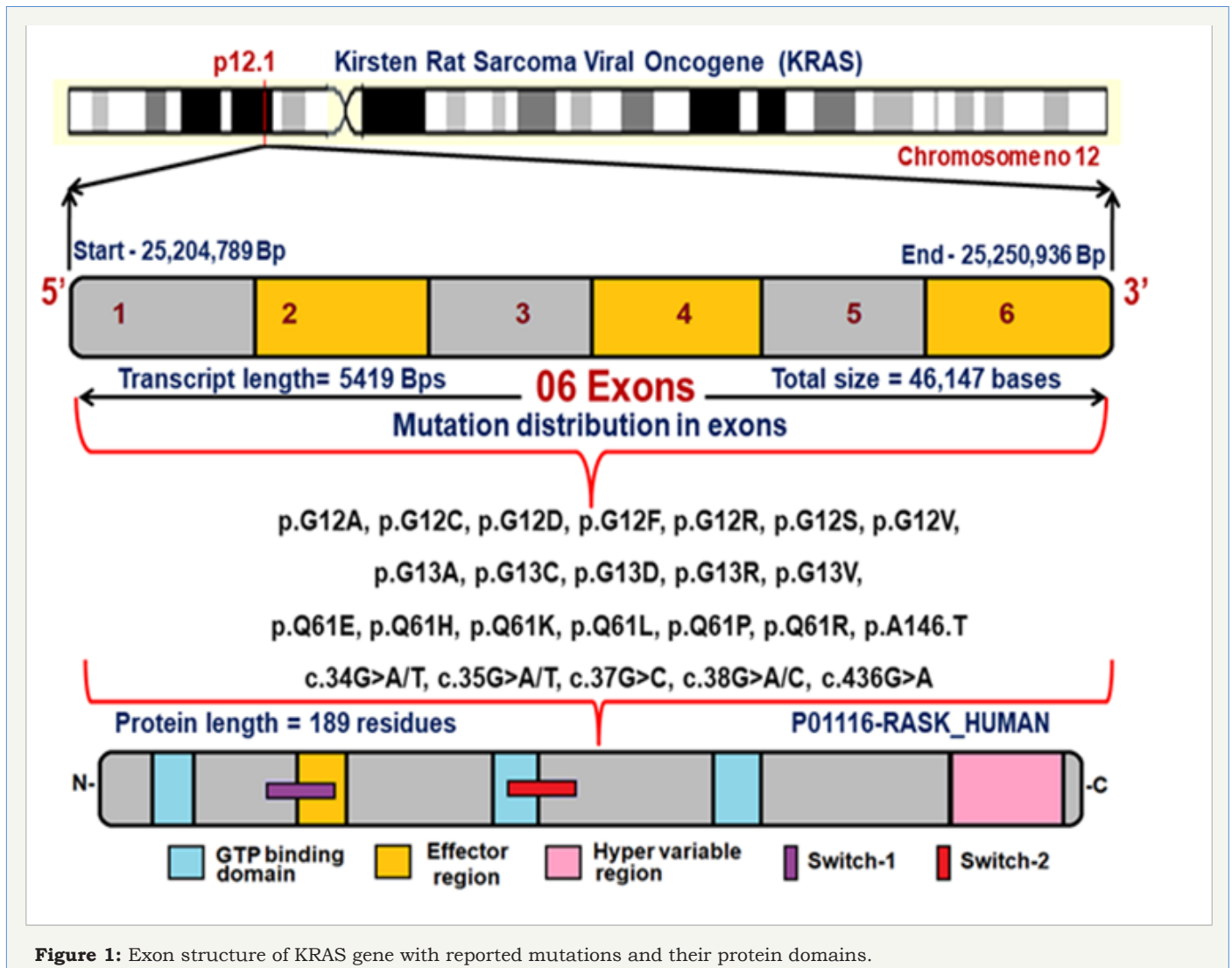
KRAS is a Protein Coding Proto-Oncogene and there are two copies of the *KRAS* gene in the human genome, designated *KRAS1* and *KRAS2*. It is located in the 12th chromosome spanning with 6 exons [5]. Figure 1 explains the chromosomal location, exon structure, position of reported mutations at their corresponding genomic positions and their protein domains. The *KRAS* gene which provides instructions for making a protein called K-Ras which belongs to small GTPase super family and Ras family. They mainly function in signal transduction pathways, RAS/MAPK pathway and limited to cell membranes consisting of an isoprenyl group on its C-terminus [6]. The K-Ras protein is a GTPase, converts a GTP molecule into GDP molecule that plays a major role in protein biosynthesis, single transduction, differentiation and translocation. The K-Ras protein acts like a molecular switch that is turned on and off by the GTP, GDP molecules [7]. It is the most frequently mutated oncogene in cancer and associated with poor diagnosis, resistance to treatment and therapy [8].

Gynaecological Cancers

The development of cancer is a multiple step process, characterized by the accumulation of environmental, life-style,

genetic factors and epigenetic alterations. In females, cancer can attack the uterus, ovaries, breast and cervix, and endometrial

tissues. These gynaecological malignancies account for 5.1 million new cancer cases among women every year globally.



KRAS Gene Mutation in Cervical Cancer

Cervical cancer is one of the leading causes for female death globally. It is the second most common gynaecologic malignancy and constitute for significant public health problem in women community [9]. The incidence of adenocarcinoma of the cervix has risen from 5 to 24% [10]. Several studies have demonstrated that adenocarcinoma confers worse prognosis with higher rates of lymph node involvement and distant metastases with decreased survival across stages compared with squamous cell carcinoma [11]. *Human Papilloma Virus (HPV)* is sexually transmitted and one of the prime etiological agent in the development of cervical cancer [12]. In addition, KRAS mutations have been identified widely in cervical adenocarcinomas and most of them were missense mutations of codon G12; these are well described by activating mutations that have found to be associated with poor prognosis in metastasis with resistance to EGFR targeted therapies in various cancers [13]. The common mutations seen in KRAS gene are G>A transition, G12D,

c.35G>A, G>T transversion, *C12GGT>TGT*, *C12GGC>GAC*, *GGT>TTT*, *GGT>TGT*, *GGT>GTT* [14]. Kras genetic variations are an active area of research with promising pre-clinical data and research is focussed on mitogen-activated protein/extracellular signal-regulated kinase (MEK) inhibitors [15].

KRAS Gene Mutation in Ovarian Cancer

Ovarian cancer (OC) is the seventh most commonly diagnosed malignancy among women worldwide [16]. According to global estimates 239,000 new cases were detected each year and 152,000 people annually die from the disease [17]. The origin and pathogenesis of OC is not well understood and, most tumours appear to be originated from other gynaecological tissues and lead to the ovary secondarily. Figure 2 illustrates the incidence age-standardized rate of ovarian cancer worldwide. This data was retrieved from the International Agency for Research on Cancer (IARC) GLOBOCAN 2012 database.

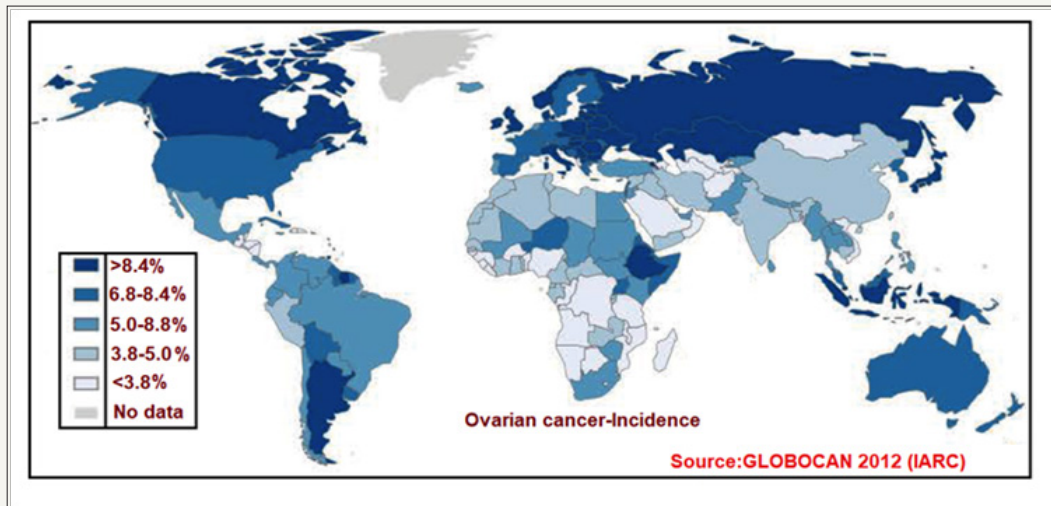


Figure 2: World map showing incidence (Age-standardized rate) of ovarian cancer.

Morphological, clinical and genetic studies have documented several hypotheses of origination; mainly for high-grade serous tumours that lack a clear progression model [18]. Numerous clinical studies have revealed the presence of mutations at codon 12 of the KRAS gene in particular association with ovarian cancer. The frequency of G12 mutations was 6.2% of ovarian cancer tissue and 14.3% in the borderline ovarian cancer [19]. The genetic variations in KRAS gene in ovarian carcinoma is consistent with the similar finding in melanoma and reveals us that KRAS mutation has equivalent effect on tumorigenesis [20].

KRAS Gene Mutation in Endometrial Cancer

Endometrial cancer is the most common pelvic gynaecological malignancy in developed nations. Endometrium is a complex tissue that lines in the uterine cavity and is composed of both glandular and stromal elements [21]. The number of new cases of endometrial cancer was 25.7/100,000 women and the mortality rate was 4.6/100,000 women per year in worldwide [22]. The cyclic proliferation, differentiation of both components is controlled and coordinated by steroid hormones produced by the ovary. In general, oestrogen promotes for the proliferation and progesterone leads to the differentiation of both components [23]. Endometrial carcinoma arises from the epithelial component and has been thought of as a single disease. However, clinico-pathological studies suggested that endometrial carcinoma could be broadly divided into two major types, referred to as type-1 and type-2 [24]. The most commonly altered oncogene in endometrial carcinoma is KRAS, which is mutated in 10-30% of cases. The mutations have been found in all grades of endometrial carcinoma and have been reported in complex atypical hyperplasia, suggesting a role for KRAS mutation in this tumour type [25].

KRAS Gene Mutation in Breast Cancer

Breast cancer is the most frequently diagnosed gynaecological malignancy in women and ranks second among causes for cancer related mortality in women community [26]. The incidence rates vary from 19.3/100,000 worldwide and the development of breast

cancer is complicated processes involving multiple factors and results from a series of genetic alterations [27]. Breast cancer is inherited and women with first-degree relative diagnosed to have breast cancer possess increase risk. The candidate genes such as BRCA1, BRCA2 harbours high frequency of mutation followed by other genes such as KRAS [28]. A study on mutational analysis in human breast cancer cell lines has revealed 18% of association with KRAS gene mutation and most of the KRAS genetic variations were localized on 12th codon and lesser at 61st codon [29]. KRAS mutations have also been reported to be the risk factor for triple negative breast cancer in premenopausal women [30].

Conclusion

In current scenario, it is important to emphasize the risk factors of gynaecological malignancies apart from highly penetrant and common genetic mutations. This review highlights the necessity to focus on KRAS gene variations, their effect on protein structure and function. Finally, these variants might be used in early diagnosis of cancer, prognosis of the disease followed by therapeutic measures so that the women community gets protected from various types of malignancies.

Conflicts of interest

There are no conflicts of interest.

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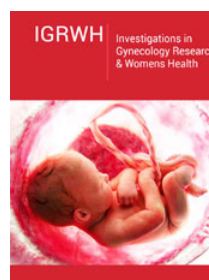
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