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Short Review/Commentary
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PIK3CA Gene Mutations in Major Gynecologic Cancers

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Short Review/Commentary

Gynecologic malignancies posses' major threat in women, leading to cancer in their reproductive organs, there are five main types including cervical, ovarian, uterine, vaginal and vulvar [1]. Traditionally, cancers have been viewed as diseases that are caused by the accumulation of genetic mutations, epigenetic alterations and environmental risk factors [2]. The development of sequencing era lead to identification of candidate genes, oncogenes, tumor suppressor genes which are directly associated with the disease [3]. These gynecological cancers account for 5.1 million new cancer cases among women every year globally. Out of these five malignancies cervical and ovarian cancers are more common affecting women from 30 years and above with high incidence rates [4]. In brief, cervical cancer defined as the malignant neoplasm arising from cells originating in the cervix and the cancer in any one of the ovaries are termed as ovarian cancer. Comparative Genomic Hybridization (CGH) studies have documented the amplification of 3q region in various tumor types, which found PIK3CA at 3q26 encoding the p110a catalytic subunit of phosphatidylinositol (PI) 3-kinase as an oncogene in cervical [5] and ovarian cancer [6]. This review focuses on the reported genetic mutations occurring in Phosphatidylinositol-4, 5-Bisphosphate 3-Kinase Catalytic Subunit Alpha (PIK3CA) oncogene of cervical and ovarian cancer respectively.

PIK3CA gene spanning 20 exons encodes for protein of 1068 amino acids, 9th and 20th exons are considered as mutational hot spots harboring more somatic mutations playing significant roles in various stages of cancers [7]. (Figure1) explains the chromosomal locations, exon structure, location of reported mutations at their corresponding genomic positions and the protein domains. The p110α subunit consists of five domains namely: ABD (adaptor-binding domain, RBD (Ras-binding domain), C2 domain, helical and kinase domains. The PI3K-AKT signaling pathway mainly involve in the regulation of various biological processes including cell propagation, progression and survival [8]. Abnormal activation of this pathway has been observed in various types of gynecologic cancers, causing aberrant cell-cycle progression, altered adhesion, apoptosis inhibition, motility and angiogenesis indicating the significance of PI3K pathway in carcinogenesis [9].

In cervical cancer, recent study in 2015 published from Chinese population with 771 cervical cancer patients screened for PIK3CA gene documented 13.6% subject's harbored non-synonymous mutations from the 9th and 20th exons in which most of them are found to be pathogenic [10]. A

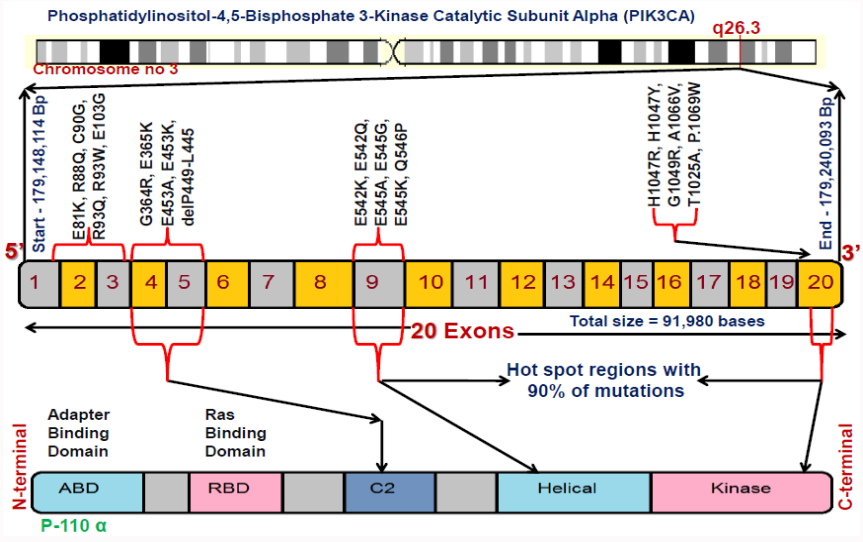

Figure 1: Exon structure of PIK3CA gene with reported mutations and their protein domains.

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study comprising 114 cervical cancer samples from Italy revealed 11% of mutations in this gene in different stages of cervical malignancy [11]. Similar study with 255 cancer patients from Sweden and China were analyzed exon 1, 9, 20 of PIK3CA gene in cervical carcinomas identified 8.15% of somatic mutations suggesting that genetic alterations of this oncogene are late events during the process of carcinogenesis [12]. The functional consequence of these mutations leads to over expression of mutant PIK3CA proteins causing the cellular transformation with phosphorylation of proteins in the AKT signaling pathway [13].

The effects of PIK3CA gene mutations in ovarian cancer were same as the cervical malignancies with higher percentage of variations in exon 9, 20 comprising the helical and kinase domains [14]. A study published in 2005 with 198 cancer patients from USA revealed 12% of mutations signifying the oncogenic role of PIK3CA gene and its pathway in ovarian cancers [15]. Similar study, comprising 182 ovarian cancer subjects from Australia documented with mutational frequency of 6%, these mutations played major role in pathogenesis of this disease. The presence of hotspot regions strongly elucidate that mutant protein may be associated with higher kinase activity and oncogenic properties [16]. In-spite of several confounding factors such as sample source, collection, preservation methods, geographical variations, ethnic background, DNA isolation, PCR methods also have an impact on mutation detection. Despite these limitations, the high frequencies of PIK3CA gene mutations have an impact on clinical applications for cancer diagnosis, prognosis of disease followed by therapeutic measures.

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