Chromosome Localization of Human Endogenous Retroviruses and Cancer Genes in Cancer Pathogenesis and Prognosis

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Introduction

Cancer development involves abnormal, multiple and independent genetic mutation of genes that regulate cell proliferation, differentiation, and survival. Intrachromosomal and interchromosomal rearrangements with ensuing gene mutations are major contributing factors to cancer pathogenesis(1). Interchromosomal rearrangement involves exchange between loci of different chromosome and may play role in immune T cells activation, gene imprinting and translocation(2). Intrachromosomal rearrangement on the hand is an exchange of gene loci located on different site, but on the same chromosome. These chromosomal genetic phenomena are reported to be implicated in expression or repression of cancer associated genes(3). However, it is important to note that chromosomal proximity also play a key role in gene function via gene promoter activities(4).

Interestingly, human endogenous retroviruses (HERVs), a HIV-like viruses domiciled in all human genome, have been reported to play important role in chromosomal rearrangements(5). These apparently quiescent viruses acronymised as HERVs are remnants of ancient retroviral infections with similarities to exogenous retroviruses vertically transmitted in to humans 25 to 40 million years ago or even earlier(6). About 8% of the entire human genome is made up of HERV sequences (7) HERVs have been reported to be actively present in human placental tissues and also implicated in cancer pathogenesis(6). The HERVs also serve several important functions that ranges from formation of placental syncytiotrophoblasts and immune defence mechanism to a role in gene transcription

HERVs contain viral enzyme polymerase (pol), the group specific antigen (gag) and glycoprotein of the Viron envelope (env) flanked by 5' and 3' long terminal repeats (LTRs). HERV-K protein transcripts are located on chromosome12q13.2, 10p12.1 (K103), 19p12 (K113), and 1p13.2, 22q11.21, 7p22 (ERV-K6), 8p23.1 (ERV-K26), 11q12.3 (ERVK-27), 19q12 (ERVK-28), 19q13.12 (ERVK-29), 1p31.1 (ERVK-1), 6p24.1 (HERV-K gag) and basically on chromosomes 3, 4, 5, 14, 15, 20, 21, 22, and Y. ERV3 is nested on chromosome 7q11.2 and HERV-H transcript proteins are found on chromosomes Xp22.3 or X Chromosome 1p, and 7q, whereas HERV-R is on human chromosome 7q11.2.

Methods

Selected HERVs, cancer genes and human chromosome sequences/data were mined from the genbank data base and high repute journal articles. A phylogenetic tree was constructed using CLUSTALX2 and bootstrapped at 2,000 bp. The sequence used include: NM_001289936.1 (HER2), AB259286.1 env (HERV-E), Y18890.1 (HERV-K complete), Y08032.1 (ERV K gag), Y10391.1 (HERV_K pol gene), NM_005430.3 (WNT1 gene), AB082923.1 (Tp53 gene), HSU08374 (cPLA2 gene), AJ010197.1 (VHL gene) and others. The chromosome locations of the genes were manually mapped using paint.inc - Microsoft Windows to create full ideogram. Positions of interest, which show the HERVs and cancer genes sitting on top or very close to each other were noted and demystified.

Results

- Results show the prostate cancer associated genes, *cPLA2,* on 1q25 and *HPC1* on 1q22-25 chromosomally co-nested with ERVK-1 on chromosome 1pcent locus (Fig 1).
- The CRC associated gene, *MLH1,* on 3p21-23 was co-located with a HERV-E transcript gene on 3p26, and 3q21.
- Wingless-related integration site 1 (Wnt-1) gene located around q13 on chromosome 12qcen was co-nested in a superimposed format with a HERV-K transcript gene on 12q13.2, and also with HERV-E env gene copy on 12p12-13 locus (Figure 1).
- The breast and endometrial cancers associated *HER2/NEU* also called *ErbB2* or *CD340* gene, on 17q11.2-12 was found co-located on the same chromosome in a superimposed format with HERV-E *env* transcript gene on 17q11.
- So also was the breast cancer associated gene, *BRCA1*, on 17q21.2 chromosomally co-nested with HERV-E pol, gag, and *env* genes on 17q11.2 locus

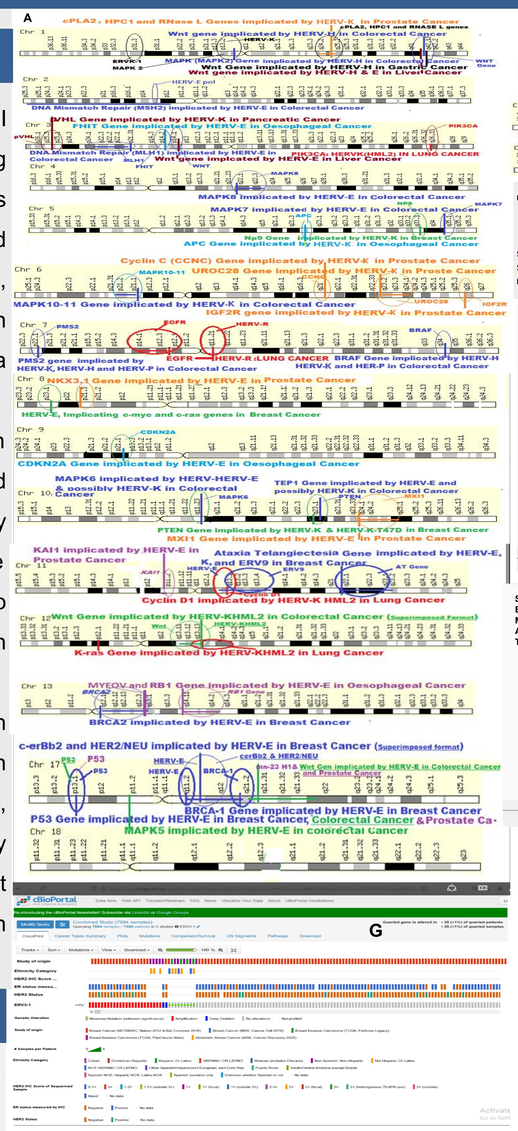

Figure 1: Relationship between different cancer associated genes, human chromosomes and human endogenous retroviruses. A) Show chromosome ideogram within which are different cancer genes and HERV subtypes were co-nested either on the same chromosome loci or close to each other on a chromosome. B) Query sequence and specific hits of HER2 gene (Accession number: P04626.1) with about 1255 amino acids and showing ATP binding sites, Receptor L domain for bilobal ligand binding site and the Protein Tyrosine Kinase (PTK) which catalyze the transfer of the gamma-phosphoryl group from ATP to tyrosine (tyr) residues in protein substrates. C) Protein ball structure of HER2/Neu (PDB: 2n2a) showing carbon, hydrogen and other molecules strongly held by Van der waals forces of attraction. The amino acids, Alanine is shown in magenta colour, Serine in yellow, threonine in red, and phenylalanine in green colouration. Abnormal disruption of these amino acids results to deregulation of genes/proteins. D-E) Nucleotide sequence during and after multiple alignment. Figure F) Molecular phylogenetic tree showing evolutionary relationship between cancer associated genes, Human endogenous retroviruses and Human chromosomes. There a significant sequence homology between Chromosome 12 and HER2; HERV-T and HERV-I; Chromosome 17 and IGF1R; HERV-E and KRAS; and BRCA1, BRCA2 and HERV-F. (G) Expression pattern of HERV-R (ERV3-1) from from cBioPortla database4,5

Discussion and Conclusions

HERVs contain viral enzyme polymerase (pol), the group specific antigen (gag) and glycoprotein of the Viron envelope (env) flanked by 5' and 3' long terminal repeats (LTRs). HERV-K protein transcripts are located on chromosome12q13.2, 10p12.1 (K103), 19p12 (K113), and 1p13.2, 22q11.21, 7p22 (ERV-K6), 8p23.1 (ERV-K26), 11q12.3 (ERVK-27), 19q12 (ERVK-28), 19q13.12 (ERVK-29), 1p31.1 (ERVK-1), 6p24.1 (HERV-K gag) and basically on chromosomes 3, 4, 5, 14, 15, 20, 21, 22, and Y. ERV3 is nested on chromosome 7q11.2 and HERV-H transcript proteins are found on chromosomes Xp22.3 or X Chromosome 1p, and 7q, whereas HERV-R is on human chromosome 7q11.2. Genetic mutation of several genes or oncogene homologues have been reported to play key roles in tumourigenesis and prognosis. Notably, tumor suppressor protein 53 (Tp53), retinoblastoma (Rb) gene breast cancer gene 1 (BRCA-1), breast cancer gene 2 (BRCA-2), ataxia telangiectasia mutated (ATM) gene, TP53, cyclin D1 (CCND1) etc. Certain genes such as PIK3CA, EGFR, CCND1 and K-Ras are respectively located on chromosome 3q26.3, 7p13, 11q13, and 12p12. Herein, we report hypothetically the relationship between cancer genes and HERVs genetic components using chromosome ideogram, DNA data mining and Phylogenetics. There may be a spate of new associations chromosomally between several cancer genes and Human endogenous retroviruses owing to the human genome sequence variations therein.

Demystifying these associations can lead to a better understanding of the aetiology of several malignant tumours which may help with diagnosis, predict drug response and identify potential new targets using newer vaccine development strategies for effective cancer therapy.This might be important in future cancer vaccine and therapy. Further studies are needed.

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