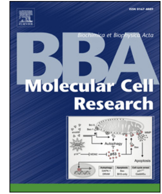
Biochimica et Biophysica Acta 1843 (2014) 2698–2704

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamcr



Review

Focal chromosomal copy number aberrations in cancer—Needles in a genome haystack

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ARTICLE INFO

Article history:
Received 11 March 2014
Received in revised form 29 July 2014
Accepted 1 August 2014
Available online 7 August 2014

Keywords:
Focal CNA
Chromosomal aberrations
Driver genes
Oncogenes
Tumor suppressor genes

ABSTRACT

The extent of focal chromosomal copy number aberrations (CNAs) in cancer has been uncovered through technical innovations, and this discovery has been critical for the identification of new cancer driver genes in genomics projects such as TCGA and ICGC. Unlike constitutive copy number variations (CNVs), focal CNAs are the result of many selection events during the evolution of cancer genomes. Therefore, it is possible that a single gene in a focal CNA gives the tumor a selective growth advantage. This concept has been instrumental in the discovery of new cancer driver genes. However, focal CNAs lack a consensus definition; therefore, we propose one based on pragmatic considerations. We also describe different strategies to identify focal CNAs and procedures to distinguish them from large CNAs and CNVs.

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Definition of key terms

Genomic aberration versus variation In this article, aberration refers to acquired changes in the tumor genome in comparison to the healthy genome; variation refers to germ line differences between healthy individuals that are inherited.

Copy number aberration (CNA) An acquired numerical change of a chromosome or chromosomal segment in comparison with a reference genome.

Focal CNA CNA of limited size, frequently enriched for cancer driver genes (described in this review).

Copy number variation (CNV) A numerical difference of a chromosomal segment present in the germ line in comparison with a reference genome. The database of genomic variants (http://dgv.tcag.ca/) states that a CNV is between 1 kb and 3 Mb [1].

Single nucleotide polymorphism arrays (SNP arrays) A type of DNA microarray initially developed for genome-wide testing of SNPs, but later applied for DNA copy number detection by comparing the fluorescence signal strength of each spot on the array to an external control reference.

Array comparative genomic hybridization (arrayCGH) A type of DNA microarray developed for copy number detection; arrayCGH compares the fluorescence signal strength of a test sample to a reference for each spot on the array.

Next generation sequencing (NGS) or massively parallel sequencing (MPS) High-throughput sequencing techniques that can be applied for copy number detection. The most commonly used method is a depth-of-coverage (DOC) method, which infers the copy number from the observed sequence depth across the genome.

Karyotyping Microscope-based test to examine chromosomes for quantitative and structural changes in cells; the techniques can be used to identify genetic problems such as the cause of a disorder or disease.

Gain and amplification Presence of multiple copies of a chromosome or chromosomal segment. An amplification is a high-level gain of a chromosomal segment (frequently defined as 8 copies) [2].

Loss/deletion Decrease in copy number of a chromosome or chromosomal segment.

Driver versus passenger Each cancer is characterized by numerous aberrations in its genome. Only a subset of these aberrations contributes to the tumor initiation and progression. Contributing aberrations are referred to as 'drivers', the non-contributing aberrations as 'passengers' [3].

1. Discovery through technical innovation

At the end of the 19th century, microscopes with a resolution that allowed visualization of chromosomes were developed. Initial reports estimated that the number of chromosomes in human cells of somatic

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http://dx.doi.org/10.1016/j.bbamcr.2014.08.001
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origin ranged from 16 to 36. Technological innovations in the early 20th century led to more accurate estimates and the assertion that, similar to chimpanzees, humans have 48 chromosomes per cell. The definitive answer that diploid human cells have 46 chromosomes came in 1955 thanks to Tijo and Levan [4], well after the discovery of the structure of DNA [5]. Before the exact number of chromosomes was determined, deviations in cell divisions, nuclear segregations and chromosome number were already observed in cancer cells (reviewed in [6]), leading to the idea that cancer is a genetic disease. (We now know cancer is marked by chromosomal aberrations, both on the numerical as well as on the structural level.) The first well-documented structural anomaly in cancer was the discovery of the "Philadelphia chromosome" [7]. This abnormally small chromosome was observed in chronic myelogenous leukemia (CML); it arises due to a reciprocal translocation between chromosomes 9 and 22, which results in the fusion of the genes *BCR* and *ABL* [8].

With the development of techniques such as chromosomal banding in the 1960s, and FISH in the early 1980s, cytogenetic analysis became more informative and gross chromosomal abnormalities, both numerical and structural, could be studied in more detail [9]. Two examples frequently observed in cancer and readily identified by chromosome banding are homogeneously staining regions (HSRs) and double minutes (DM), which are amplified inter- and extrachromosomal segments, respectively [10,11].

In the early 1990s, the development of a new technique, comparative genomic hybridization (CGH), enabled the detection of DNA copy number aberrations (CNAs) on a genome-wide scale, without the need for preparing metaphase spreads from the cells being analyzed [12–14]. The CGH technique was soon superseded by microarray-based CGH (arrayCGH), which allowed for even higher resolving power [15,16]. This technical innovation allowed the genome-wide detection of CNAs smaller than 5 Mb as well as high-resolution genome-wide detection of CNAs in formalin-fixed paraffin-embedded (FFPE) specimens (for an example, see Fig. 1). The spatial resolving power of arrays progressively increased through the introduction of new array types and higher probe density [17–21]. Individually cloned and grown DNA constructs, like phage- and bacterial artificial chromosomes (PACs and BACs), were replaced by synthetic oligonucleotides [20]; the latest commercial arrays now have over a million *in situ* synthesized oligonucleotides, enabling the detection of genomic aberrations in the kilobase range [21].

The increased spatial resolving power of chromosomal copy number detection techniques led to two discoveries. First, genomes in the healthy population contain a much larger amount of copy number

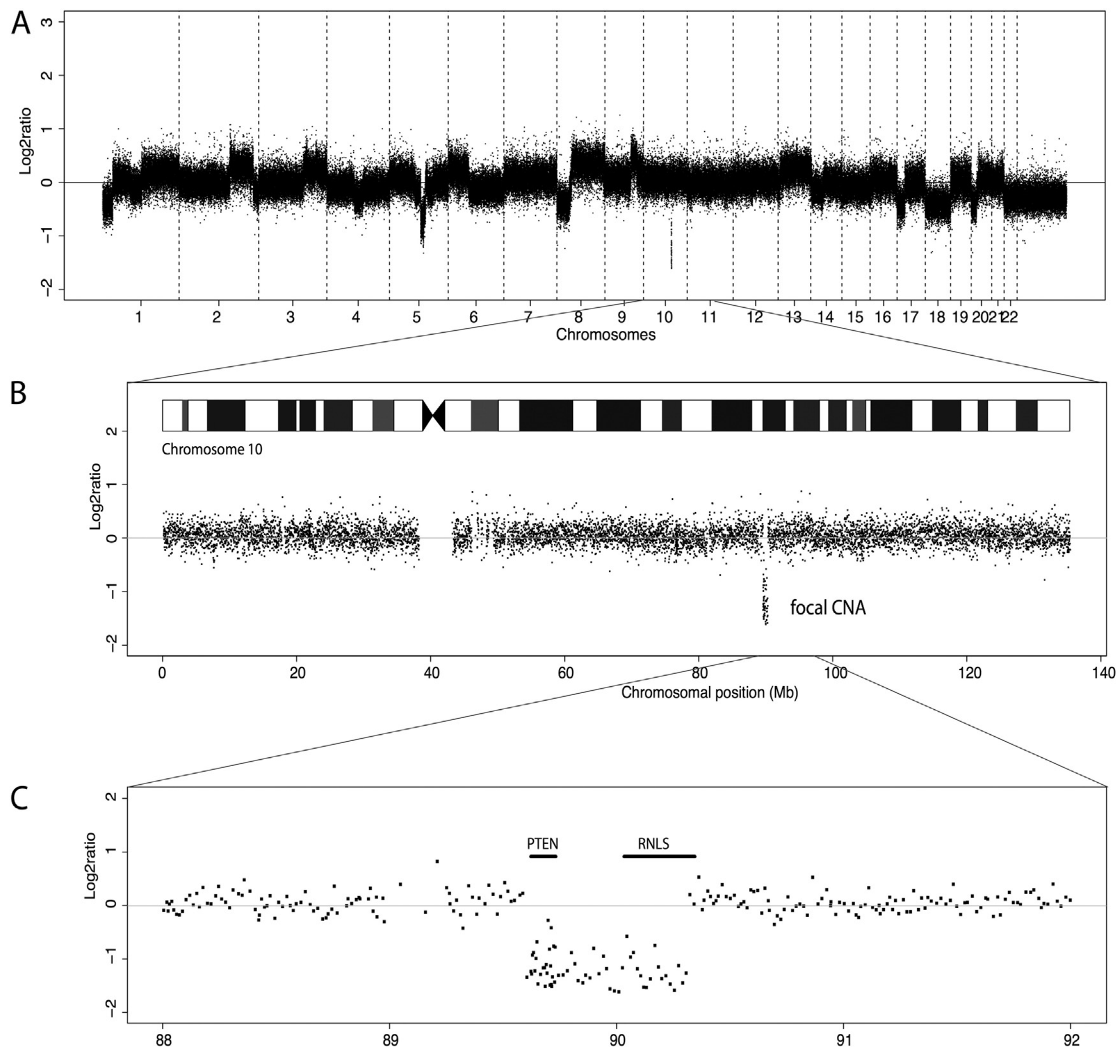

Fig. 1. Example of a focal deletion in a colon cancer specimen. Tumor DNA was isolated from FFPE archival tissue and analyzed with a 180 K CGH array (Agilent Technologies) [34]. Panel A shows the complete genome. Panel B shows chromosome 10 with a focal deletion around the 90 Mb. Panel C is a zoom-in on the region of chromosome 10 from base pair position 88 Mb to 92 Mb. In this region, a deletion of ~0.7 Mb is visible. In addition to a deletion of the well-known tumor suppressor gene *PTEN*, a second gene, *RNLS*, not previously associated with cancer, is present.

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