

Review

Copy Number Variation: Methods and Clinical Applications

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Abstract: Gains and losses of large segments of genomic DNA, known as copy number variants (CNVs) gained considerable interest in clinical diagnostics lately, as particular forms may lead to inherited genetic diseases. In recent decades, researchers developed a wide variety of cytogenetic and molecular methods with different detection capabilities to detect clinically relevant CNVs. In this review, we summarize methodological progress from conventional approaches to current state of the art techniques capable of detecting CNVs from a few bases up to several megabases. Although the recent rapid progress of sequencing methods has enabled precise detection of CNVs, determining their functional effect on cellular and whole-body physiology remains a challenge. Here, we provide a comprehensive list of databases and bioinformatics tools that may serve as useful assets for researchers, laboratory diagnosticians, and clinical geneticists facing the challenge of CNV detection and interpretation.

Keywords: copy number variants; cytogenetics; molecular methods; bioinformatics tools; CNV detection; CNV interpretation

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1. Introduction

Among the least understood types of genetic variation are copy number variants (CNVs), a class of unbalanced structural variants characterized by deletions, insertions, duplications or even multiplications of DNA segments ranging in size from a few dozen of bp up to several Mb. Currently, the lower limit for CNV length is 50 bps, but this value has been gradually decreasing due to continuous methodological progress. The shift is mainly due to an increased resolution of used methods, allowing for detection of a wider variety of variant lengths and for an increase of CNV detection capacity (Figure 1). Considering this remarkable shift and the fact that generally used distinguishing criteria are somewhat vaguely defined, it has also been suggested that CNVs include a wider spectrum of variants. However, for practical reasons, we will focus on the conventional concept of CNVs in this review.

Pushing the limits of CNV detection revealed that they are widespread in human populations with a 5–10% difference of genomic sequences between normal individuals [1–3]. As a significant aspect of our heterogeneity, CNVs may disrupt gene function or

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