Copy number variation and susceptibility to human disorders (Review)

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Abstract. A large number of analyses of a new form of genetic variation, known as copy number variation (CNV), have been published recently as a new tool for understanding the genetic basis of complex traits such as diabetes, asthma, Crohn's disease, autism and bipolar disorder. Through the use of different types of genome-wide scanning procedures, CNVs have been shown to be associated with several complex and common disorders, including nervous system disorders. One of the common features of the regions associated with the complex and common disorders identified thus far is the presence of CNVs and segmental duplications. Segmental duplications lead to genome instability. Because of their location and nature (several contain genes), many CNVs have functional consequences, such as gene dosage alteration, the disruption of genes and the modulation of the activities of other genes. Therefore, these genetic variations have an influence on phenotypes, the susceptibility of an individual to disease, drug response and human genome evolution. These types of variants (gain and loss of DNA) are not restricted to humans, having also been identified in other organisms. Our current knowledge regarding CNVs and their heritability is still rudimentary, due to their location in regions of complex genomic structure and to the technical limitations of association studies. Future advances in the technology will aid in the construction of a new CNV map, used to find the genes underlying common diseases and to understand familial genetic conditions, severe developmental defects in humans and other organisms, and genome evolution.

Contents

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1. Introduction

Structural chromosome abnormalities have for a long time been known to exist at the cytogenetic and molecular level, and are associated with what are now called genome disorders. However, their importance became apparent only after the completion of the human genome project due to the use of several scanning technologies, including array-based comparative genomic hybridization (CGH). DNA, the genetic material, varies widely from person to person (1) and between human populations worldwide (2). Some individuals have variation in a single nucleotide, which is known as a single nucleotide polymorphism (SNP). The term polymorphism generally refers to genetic variants that have a minor allelic frequency (~1%) in a given population. These changes are thought to be the predominant form of the genetic variations responsible for normal phenotypic differences (our uniqueness). However, it has recently been discovered that there are individuals with deletions or multiple copies of the same gene (Fig. 1). Such changes (DNA fragments of ~1 kb or larger) are called copy number variations (CNVs) or copy number polymorphisms (3-5), and additionally appear to be widespread in normal individuals. Although the true number of CNVs and their frequency in human populations is unknown, they may result in altered levels of gene expression and, as a result, may account for significant normal phenotypic variation within a species (as they often encompass genes), susceptibility or resistance to disease, drug response, complex and common disorders and the evolution of the genome itself (6-13). This brief review summarizes some of the recent research in the field of CNVs.

2. Properties and functions

The size of DNA variation in CNVs ranges from a few kilobases to megabases (14-16). CNVs are not necessarily related to genome disorders, and can in fact be observed in healthy individuals who present no evidence of a genetic disorder (17). At present, approximately 1447 CNVs have been identified (http://projects.tcag.ca/variation). These cover 12% (of an estimated 15%) of the human genome, although this number could be slightly smaller for common human CNVs (18). Additionally, somatic mosaicism has been reported for CNVs in differentiated human tissue (19). This high degree of variability in the human genome and somatic mosaicism challenges the definition of normality (20), since it is generally

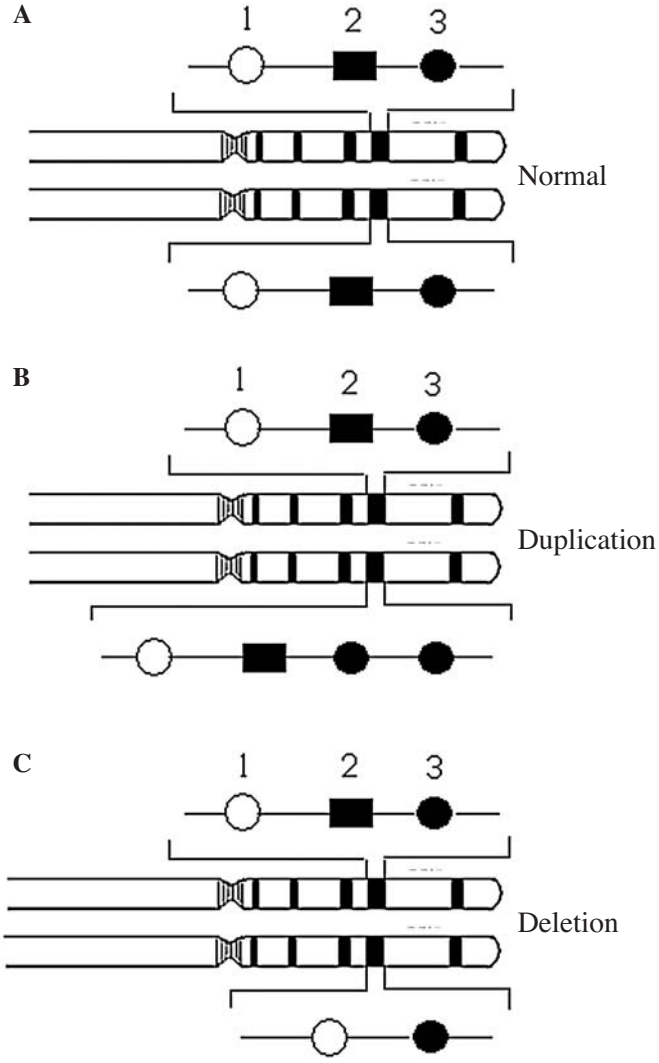

Figure 1. An example of CNV. A represents a normal pattern, while B (duplication) and C (deletion) are CNVs. Numbers 1, 2 and 3 represent genes in a chromosomal segment.

believed that normal cells are genetically identical. Large CNVs are often found to occur in regions containing large homologous repeats or segmental duplication (15,21,22), while smaller CNVs may occur because of non-homology driven mutational mechanisms. A DNA replication-based mechanism has been suggested to explain the formation of CNVs (23). According to this mechanism, the presence of many nucleotide repeats (which form an unusual structure) stalls the replication fork and then switches to a different template in any region of DNA, resulting in copy number changes. This kind of stalling and template switching may play a role in evolution by helping organisms to survive under environmental stress. Widespread CNVs are not unique to humans; they have also been identified in inbred strains of laboratory mice (24,25). In these mice, a non-allelic homologous recombination mechanism may play a role in the genesis of CNVs (26). CNVs, along with SNPs, also contribute to phenotypic variation among mouse strains. In addition, different mouse strains exhibit CNVs that are comparable to those observed in human strains. However, such variation is more locally restricted (27,28).

From an evolutionary standpoint, gene duplication is an important long-term evolutionary force (e.g., the ß-globulin gene). Supporting this is the finding that CNVs are present in the homologous regions of other closely-related species (27). This again suggests that non-allelic homologous recombination plays a role in the evolution of CNV. Interestingly, mice seem to tolerate large-scale deletions of non-gene regions much better than humans (29). When human and mouse CNVs were compared, it was found that those of humans were associated with an increased ratio of non-synonymous to synonymous substitution rates (30), suggestive of positive selection during evolution. Similarly, when the CNV regions of chimpanzees and humans were compared, many CNVs were found to occur frequently in both species, and were also found to be rich in segmental duplication. This finding is consistent with the hypothesis that CNVs are found in the homologous regions of other closely-related species (27). Furthermore, lineage-specific gene duplication and loss may occur during evolution (31-33). Analysis of structural variation in eight human genomes additionally suggests that different mutational processes may have shaped the human genome (34). It has been demonstrated, at least in the case of the *Drosophila* system, that natural selection shapes the genome-wide patterns of CNV (35,36). Since segmental duplications lead to genomic instability, they are not only associated with genome disorders, but are also involved in the continuing evolution of the genome.

CNVs may alter gene dosage without abolishing gene function, or may affect gene structure and regulation (37). Because of their mild effect on gene function, it is possible that some of the common CNVs alter phenotypes in complex and sporadic diseases (38), including nervous system disorders (39,40), and may also be behind inherited disorders (41). For instance, in non-small cell lung cancer, the EGFR copy number is found to be higher than normal (6). Additionally, individual and population differences in copy number for the gene encoding CCL3L1 (a suppressive chemokine and ligand for the human immunodeficiency virus-1 coreceptor CCR5) have been reported (7). Similarly, a lower copy number of FCGR3B can increase susceptibility to immunologically-related glomerulonephritis in humans and rats (8), with a functional correlation between CNV and protein expression (42). Copy number variation is also found to be associated with autism spectrum disorders (9,13), Crohn's disease (43) and bipolar disorder (44). A partial list of some of the other disease-related chromosomal regions containing CNVs is presented in Table I. However, the extent to which CNVs cause genetic disease is unclear. According to the literature, their contribution appears to be smaller than that of SNPs (37), and their contribution to gene expression is also independent of SNPs.

3. Technical developments and limitations

At present, it is difficult to correlate the relationship between CNVs and phenotype. This is due to insufficient collected data, and existing techniques that are not accurate enough in measuring the association between CNVs and phenotype. As well, many CNVs are located in regions of complex genomic structure. An effective genome-wide CNV genotyping method

Table I. Examples of CNVs identified in genomic regions associated with disease[a].

Disorders	Chromosomal regions	Refs.
Bipolar	3q13.3	(44)
Spinal muscular atrophy	5q13.2	(14,15,21)
Crohn's disease	8p23.1	(43)
Prader-Willi and Angelman syndrome	15q11.3	(4,5,15)
Autism	16p11.2	(13)
Charcot-Marie-tooth Angelman syndrome	17p12	(4,21)
Autism	20p13	(9)
DiGeorge/Velocardiofacial syndrome	22q11.2	(4,5,21,58)

[a]In some cases, these CNVs are also present in normal individuals.

is required. As was recently demonstrated, one possible approach is to use SNPs as markers for CNVs throughout the genome by means of the linkage disequilibrium (LD) method. This approach relies on the low recombination rate found in humans. Variants segregate on the haplotype and can hence be tagged (45). However, the method still requires a large collection of CNVs with dense SNP genotypes. Additionally, since many CNVs are located in regions of complex genomic structure, it may limit the extent to which these variants can be genotyped using tagging SNPs. Although there have been some successes in recent years (3,4,10,46), with certain of the CNVs within the duplicated regions showing LD with nearby SNPs (21,46,47) and a heritability value that did not significantly differ among the loci tested, the extent of LD between SNPs and CNVs is not at present clear (48). For instance, a region of the genome may contain high-density CNVs (21), but the density of SNPs that serve as potential tags could be much lower. The high-density CNVs may therefore not be well tagged by the SNPs (46). Markers also determine whether to focus on common polymorphisms that principally affect phenotype, or on the markers which have modifying effects on other genes or environmental factors (49). Additionally, non-Mendelian behavior may pose a problem in the use of SNPs for tagging the inheritance of CNVs.

Another equally important technical development are hybrid oligonucleotide arrays containing both SNPs and copy number probes. In this method, SNPs and CNVs are used together for association studies (50,51). Recently, microarray CGH has also been used. This method detects differences in CNVs across diverse species (27), and also assesses CNVs at multiple loci. Additionally, CNVs can be determined using oligonucleotide expression microarrays (52), bacterial artificial chromosome (BAC) arrays (17), SNP arrays and genotyping data. A review concerning the different genotyping platforms available was recently published (53). In addition, there are a variety of fine mapping techniques that researchers use to test for disease association (7,8,54,55) using a family-based (traditional) or population-based model. These methods are effective when CNVs are large, as such variations are usually taken as functional and hence causative. However, smaller CNVs that are mostly benign and can therefore not be determined as functional require statistical challenges to assess their association with diseases. Similarly, other limitations, such as insufficient recombination events, the requirement of a large pedigree, low penetrance and population stratification, must be considered in determining CNV and SNP association. Some of the methods may not be able to detect the low-penetrant variants associated with common diseases. Family-based studies are the easiest way to prevent stratification, and are therefore preferred by many investigators (49). Additionally, the quality of DNA and the sensitivity of methods such as CGH may introduce technical artifacts in association studies (56). The maintenance of high standards throughout the research process is therefore a necessity.

4. Summary and conclusion

In summary, by using array CGH and high-density customized nucleotide arrays, several regions of chromosomes containing CNVs have been identified. Research in the CNV field also suggests that large-scale variation in the human genome could be due to segmental duplications. These lead to genome instability and are hence associated with genome disorders, as well as with the evolution of the genome. They are also the hotspots of chromosomal rearrangement (17). However, our understanding of their organization and heritability is still in its infancy. Although there are many technical advances to be made in the future, the long-term goal of CNV research is to prepare a comprehensive CNV map of the human genome. This includes the correlation of variation to phenotypes and to evolutionary and mutational aspects. Since CGH and high-density oligonucleotide arrays (47,57) are cost effective and rapid, they are at present the most valuable tools for CNV research. As in many other experiments, numerous artifacts or false-positives will be encountered in CNV research. These must be minimized. In addition, high priority should be given to validation. A suitable scanning technology must be developed. When new technologies become available, primary results must be verified. Although the field is technically challenging and very expensive to accommodate within the limited amount of available resources, in the coming years it is hoped that CNV research will not only provide insight into human genetic variation, but will also contribute to a better understanding of the mechanisms of human genetic disease and evolution.

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