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Copy number variation in the human genome and its implication in autoimmunity

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Summary

The causes of autoimmune disease remain poorly defined. However, it is known that genetic factors contribute to disease susceptibility. Hitherto, studies have focused upon single nucleotide polymorphisms as both tools for mapping and as probable causal variants. Recent studies, using genome-wide analytical techniques, have revealed that, in the genome, segments of DNA ranging in size from kilobases to megabases can vary in copy number. These changes of DNA copy number represent an important element of genomic polymorphism in humans and in other species and may therefore make a substantial contribution to phenotypic variation and population differentiation. Furthermore, copy number variation (CNV) in genomic regions harbouring dosage-sensitive genes may cause or predispose to a variety of human genetic diseases. Several recent studies have reported an association between CNV and autoimmunity in humans such as systemic lupus, psoriasis, Crohn's disease, rheumatoid arthritis and type 1 diabetes. The use of novel analytical techniques facilitates the study of complex human genomic structures such as CNV, and allows new susceptibility loci for autoimmunity to be found that are not readily mappable by single nucleotide polymorphism-based association analyses alone.

Keywords: autoimmunity, copy number variation, gene-dosage, genome diversity

The analysis of genetic variation and population structure are important research areas in human genetic studies. Genetic variation occurs in many forms, from visible karyotypic alterations, deletions or duplications in the genome to single nucleotide changes. The human genome encodes potentially 25 000–30 000 protein-coding genes which are usually present in two copies, each inherited from the parental genomes. Recent studies have revealed that DNA segments in sizes from kilobases to megabases can vary in copy number among individuals in a population [1–6]. These changes in copy number are the result of duplications, deletions, insertions, inversions and complex combinations of rearrangements, and are termed collectively copy number variants (CNVs).

In a recent study CNVs have been mapped genome-wide in the 270 HapMap individuals from different ethnic groups [5]. From this study it has been estimated that an astonishing 12% of the genome is covered by CNVs, and this may cause more overall sequence variation between humans than single nucleotide polymorphisms (SNPs) [5]. Genomic regions containing CNV may harbour important genes and gene regulatory elements and may therefore influence substantially gene expression and phenotypic diversity [7,8]. It is thought, therefore, that CNV in gene-dosage sensitive genes may have considerable influence on disease susceptibility (or alternatively on disease resistance) in humans. Currently, 5,672 CNV loci are catalogued in the Database of Genomic Variants (http://projects.tcag.ca/variation/) [9]. The full extent of CNV across the genome remains to be established firmly; for example, it has been shown recently that bacterial artificial chromosome array studies have led to an overestimation of the size of CNVs, and therefore fine-scale analysis of the architecture of these CNVs is necessary [10]. It also seems that deletions occur less frequently than duplications [5]. The evolutionary drive in generating and maintaining CNVs, however, is not yet well explored, but it has been suggested that CNVs may be generated constantly *de novo* [11]. The predominant molecular mechanism in generating CNVs appears to be non-allelic homologous recombination events during meiosis between repeated sequences [12]. However, a recent population genetic analysis of SNPs and CNVs on HapMap samples showed that approximately

Table 1. Autoimmune diseases associated to copy number variants (CNVs) in the human genome.

Autoimmune diseases/syndrome	Genes with CNV involved	Chromosomal location	Risk associated with CNV	Reference
SLE and AASV	*FCGR3B*	1q23	Low	26,28
SLE but not with AASV	*FCGR3B*	1q23	Low	27
SLE	*C4A/C4B*	6q21	Low	37
SLE	*CCL3L1*	17q12	High and low	51
ITP	*FCGR2C*	1q23	High	30
Psoriasis	*DEFB*	8p23	High	42
Crohn disease	*DEFB*	8p23	Low	43
Rheumatoid arthritis and type 1 diabetes	*CCL3L1*	17q12	Low	50

AASV, anti-neutrophil cytoplasmic antibody (ANCA)-associated systematic vasculitis; FGCR, Fcgamma receptor; ITP, idiopathic thrombocytopenic purpura; SLE, systemic lupus erythematosus.

80% of observed copy number differences between pairs of individuals were due to common CNVs and more than 99% derived from inheritance (i.e. showed Mendelian inheritance) rather than new mutations [13]. Thus, *de novo* generation of CNVs to an individual's genome seems to be 100 times less common than the contribution of inherited CNVs [13]. Furthermore, it also seems that there is a substantial inter-population variation of CNVs among human populations [5,14–16]. For example the *CCL3L1* gene, which encodes a potent human immunodeficiency virus (HIV)-1-suppressive chemokine, shows striking geographical structuring among human populations, indicating that variability in copy number has probably contributed to adaptation to different environmental conditions [16]. Such geographical differences have contributed to the view that some CNVs may not only evolve in a neutral fashion, but may be also under selection [15,17,18]. In particular, those CNVs that have experienced positive selection may be of particular interest because of their beneficial role in adaptation in human populations.

A high proportion of CNVs are located in close proximity to or within segmental duplications, which are large blocks of highly identical sequences (> 1 kbp and > 90% sequence similarity) (reviewed in [19]). Segmental duplications may define hotspots of chromosomal rearrangement and are thus probably acting as mediators not only for normal structural variation in the genome, but also for genomic disorder [4]. Moreover, it appears that CNVs are enriched in genomic regions containing genes that encode immunity, olfactory and secreted molecules [20,21]. In particular, if dosage-sensitive immune genes (or their regulative elements) are involved in CNVs then this could contribute to diverse autoimmune diseases. Data from both human linkage analyses and rodent models of autoimmunity suggest that there are common genetic factors that underlie different autoimmune disease states [22,23]. In addition, evidence for genetics in autoimmunity arises from a number of sources, including twin studies and familial clustering, as well as formal heritability studies in some diseases. However, in linkage and genome-wide association studies little of the genetic variation is actually explained so far (usually 1–15%). The analysis of risk loci potentially harbouring CNVs provides one possible explanation for the unexplained genetic disease risk. Indeed, a number of recent studies provide the first good evidence that CNVs in the human genome are associated with some form of autoimmune disease (see Table 1).

The CNVs within a segmental duplication region located on chromosome 1q23 encompass the low-affinity Fcgamma receptor (*FCGR*) genes (Fig. 1). This low-affinity receptor family comprises three class II genes (*FCGR2A*, *FCGR2B*, *FCGR2C*) and two class III genes (*FCGR3A*, *FCGR3B*) [24]. Functionally, the gene products, FcγRs, mediate immune responses by binding specifically to the Fc portion of immunoglobulin G molecules. FcγRIIB acts as an immune inhibitory receptor, whereas the other low-affinity receptor molecules (FcγRIIA, FcγRIIIA, FcγRIIC and FcγRIIIB) act as activation molecules. These genes have been the subject of intense study in susceptibility to various autoimmune and infectious diseases (reviewed in [25]). They undoubtedly contain a number of single base-pair polymorphisms that predispose to disease. However, recent studies have highlighted the role that CNVs may also be playing in disease susceptibility.

Suggestions that CNVs at the *FCGR* locus may contribute to human disease were based in part on observations made in rodent models. The unique rat isotype *Fcgr3-rs* encodes a rat-specific cytoplasmic tail owing to a frameshift mutation in its cytoplasmic domain. This results functionally in a protein that inhibits native Fcgr3-mediated macrophage

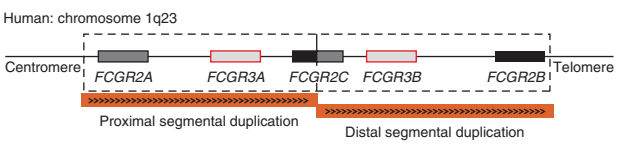

Fig. 1. Genomic organization of human Fc receptors gene organization on chromosome 1q23. The boxes with the different grey-coloured patterns show homology between the genes. Also shown are the proximal and distal segmental duplications. Copy number variants (CNVs) have been described for Fcgamma receptor genes *FCGR3A*, *FCGR2C* and *FCGR3B*.

activation. Rat strains showing deletion of *Fcgr3-rs* have overactive macrophages and are prone to immunologically mediated glomerulonephritis [26]. This study and others [27,28] revealed that low copy number at the *FCGR3B* locus (ranging between zero and four) in humans is associated with increased risk for systemic lupus erythematosus (SLE). The *FCGR3B* gene is expressed in two isoforms, NA1 and NA2, which differ by four amino acids in the membrane-distal immunoglobulin-like domain. The NA2 isoform has been found previously to be associated with anti-neutrophil cytoplasmic antibody-associated systematic vasculitis (AASV) [29]. However, CNVs in the *FCGR3B* region make it currently difficult to assess accurately the NA1/NA2 diversity in an individual. Thus, an important task in further studies will be to take CNVs into consideration to be able to assess accurately the qualitative impact of this isoform on disease susceptibility. In a recent study, AASV have been found to be associated with low *FCGR3B* gene copy number [28], although this finding was not replicated by another group of investigators [27]. It has been suggested that reduced *FCGR3B* expression is likely to contribute to the impaired clearance of immune complexes, which is a feature of SLE, explaining the association between low *FCGR3B* CNVs and SLE [27]. However, this contradictory result regarding AASV shows that additional research is necessary to clarify the functional consequences of *FCGR3B* CNVs and its relation to this autoimmune disease. There is still controversy regarding the optimal molecular assays for determination of CNV numbers. Conflicting data may, in part, represent errors in accurate CNV estimation.

The FCGR locus has been the subject of extensive study in non-systemic autoimmune disease. A recent paper reported that CNVs of the *FCGR2C* gene predisposes to idiopathic thrombocytopenic purpura (ITP) [30]. This role of *FCGR2C* polymorphism is complicated by the frequent occurrence of a SNP in exon 3 which leads to a stop codon but the expressed form, estimated in a study [24], occurred at a frequency of 0·12. CNVs in this locus lead apparently to a significantly higher proportion of expressed *FCRGR2C* alleles in ITP subjects [30]. This study also revealed that *FCRGR3A* varies in copy numbers, but compared with *FCGR3B* at a much lower frequency. The *FCRGR3A* gene was found to be associated with rheumatoid arthritis (RA) [31,32]. In particular, a strong association for RA susceptibility was found for the *FCGR3A-FCGR3B* NA2 haplotype [33]. However, it remains to be tested how the recent discovery of CNVs at this locus affects its association functionally with RA.

The major histocompatibility complex (MHC) region [in humans also called human leucocyte antigen (HLA) system] on chromosome 6 in humans is an extraordinarily gene-dense region which encodes at least 250 genes. It is divided into three classes: classes I, II and III. The class I and class II regions encode the classical antigen-presenting molecules (*HLA-A*, *-B*, *-C*; *HLA-DR*, *-DQ*, *-DP*), and class III encodes genes of which some are of immunological interest (e.g. complement factors, tumour necrosis factor, heat shock protein 70). MHC genes have been found to be associated with many different autoimmune diseases, including SLE. In previous studies (reviewed in [34]) two MHC haplotypes, *HLA-B8-C4AQO-C4B1-DR3* and *HLA-B7-C4A3-C4B1-DR2*, were identified as risk factors for SLE [35]. Within the MHC class III region CNVs for the complement *C4* have been described [36], and in the light of our current knowledge of the extent CNVs in the genome, the potential role of CNVs at the *C4* locus has been re-emphasized [37]. The complement *C4* is an effector protein of the immune system and the link between total deficiency of *C4* and human SLE was observed first in 1974 [38]. In a diploid genome, *C4* gene copy number varies between two and eight, which may be either *C4A* or *C4B*. In humans with only two copies of total *C4* genes, the risk of developing SLE increases significantly and the risk decreases with more than five copies of *C4* genes; the risk of SLE being associated preferentially with deficiency of *C4A* [37]. However, it remains to be established whether the influence of *C4* copy number is an effect independent of the flanking class III MHC region and the linkage disequilibrium between *C4A* null alleles and HLA-DRB1*0301.

Other immune genes involved in autoimmunity are beta-defensin genes. The beta-defensin genes (*DEFB*) are members of a large diverse family of anti-microbial peptides which have evolved by repeated gene duplication events and by positive selection [39–41]. This gene family is situated on three chromosomal locations (two clusters on chromosome 20 and one on chromosome 8). In a recent paper by Hollox *et al.* [42], an association between higher CNVs for *DEFB* on chromosome 8p23.1 and risk of psoriasis has been found. In addition, this gene cluster has been found to be associated with Crohn's disease (CD) [43]. In this study individuals were found to have a median of 4 (ranging from 2 to 10) gene copies per genome. However, individuals with = 3 copies of *DEFB 2* (*HBD-2*) gene had a significantly higher risk of developing colonic CD than individuals with = 4 copies. The authors concluded that a lower *HBD-2* gene copy number predisposes to colonic CD through reduced gene expression of these genes.

Many studies suggest that chemokine receptors mediate inflammatory responses and therefore have a role in pathogenesis of autoimmunity (reviewed in [44,45]). The chemokine ligand 3-like 1 (*CCL3L1*) is encoded by a variable copy-number gene on chromosome 17q12, and binds to several proinflammatory cytokine receptors, including chemokine receptor 5 (*CCR5*). The *CCR5* chemokine receptor is a major co-receptor for HIV and *CCL3L1* can inhibit or reduce HIV entry into $CD4^+$ T helper cells through competitive binding to *CCR5* [16,46]. The copy number of this gene varies among individuals, with most individuals having one to six copies in the diploid genome, owing to a hotspot for segmental duplication [16,47,48]. Low *CCL3L1* copy number is a significant risk factor for HIV infection and disease progression, while high CNV is protective ([16], but

see [49]). The mechanistic link suggests that with increased copy number more *CCL3L1* is expressed, which may lead to an increased steric blocking of the *CCR5* receptor molecule on $CD4^+$ T helper cells, thereby limiting the entry of the virus through this type of receptor molecule [16]. A recent study suggested that *CCL3L1* CNV may also influence susceptibility to RA and type 1 diabetes (T1D) because lymphocyte recruitment by β-chemokines is a feature of autoimmunity, and that the *CCR5?32* variant is associated with protection to RA and T1D [50]. Indeed, their data suggest that CNV in *CCL3L1* with increased gene expression increases the risk of developing RA and T1D because of proinflammatory effects of excess of *CCL3L1*. Furthermore, this locus may also be associated with SLE. A deviation from the average copy number has been found to be a risk factor for developing SLE; a copy number lower than or greater than two was associated with an increased risk of developing SLE in the study by [51].

Concluding remarks and future perspectives

Current efforts to type and catalogue CNVs accurately will be accompanied by more detailed analyses of the fine-scale architecture of CNV regions. As it has been pointed out recently [10], most CNVs (88%) are probably smaller in size than what is recorded in the Database of Genomic Variants [9]. Therefore, fine-mapping of CNVs is warranted which includes sequence-level resolution and the characterization of breakpoints. CNVs should also be validated using biologically relevant information such as the transmission rate of heritable CNVs from parents to offspring. This will make it possible, for example, to distinguish whether two alleles stem from the same or different ancestral mutation events. The detection of the ancestral state of CNVs may allow insights to be gained about the inheritance mode of CNVs, but may also help to understand the evolutionary force that generates and maintains CNVs at certain genomic regions in human populations. Moreover, information on the frequency of CNVs and the incorporation of CNVs into population genetics will provide a more comprehensive understanding of both the evolution of normal variation in the genome as well as variations that contribute to disease. Further studies will also have to demonstrate the functional consequences of CNVs and their direct implications for certain clinical phenotypes. However, it can be supposed a priori that the functional consequences of a CNV event maybe greater than that consequent on many single base pair sequence changes. CNV has the potential to alter significantly the expression of the gene exhibiting the CNV. CNV is an important source of variation in the genome; at present only the tip of the 'CNV iceberg' has been explored in relation to complex trait genetics. The likelihood that many genes encoding products with immune function are prone to CNV is such that these structural polymorphisms will almost certainly be important in future understanding of the molecular genetic basis of autoimmunity.

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