DNA copy number variations – do these big mutations have a small effect on cardiovascular risk?

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In simple terms, copy number variations or CNVs are replications or deletions in the DNA which, in humans, changes it from the normal number of two gene copies. These CNVs are caused by inherited or *de novo* structural changes such as duplications, insertions or deletions of repeated portions of genetic material (Figure 1). These duplications can vary from one to ten or more copies and range in size from 50 DNA base pairs to several millions (1). Since their discovery in 1987 by Nakamura et al (2), when they were initially named variable number tandem repeats, many studies have investigated their association with rare and common human diseases. Throughout evolution, some of these changes in copy number were beneficial such as the globin gene number duplication, while others such as the CNVs that cause Huntington's disease were not. In 2004, two landmark studies by Iafrate et al. (3) and Sebat et al. (4) found that large-scale copy-number variations, ranging in size from 100kb to 2Mb, are common throughout the human genome, and that a high proportion of them are in known genes. These findings roused several association studies between CNVs and disease.

In terms or cardiovascular disease (CVD), in 2010, findings from a large genome-wide study challenged the view that CNVs are associated with common human diseases. A large study from the Wellcome Trust Case Control Consortium using a purpose-designed array (5) genotyped 16,000 cases of common diseases and 3,000 controls and failed to identify any association between CNVs and susceptibility to common diseases including essential hypertension. However, smaller studies using sensitive technologies for quantifying copy number such as digital PCR found association between CNVs with both hypertension (6) and hypertension-induced left ventricular hypertrophy (7).

Recently, using high density single nucleotide polymorphism (SNP) arrays to screen the human genome for association with disease, two studies (8, 9) again report a substantial degree of CNVs in the human population. In addition, these two studies report a burden of these genetic changes on CVD. Glessner and colleagues, reporting on this issue, describe their use of 657,366

markers on the Illumina Infinium Quad 660 array to determine low-frequency CNV number and assess their association with 23 cardiovascular related traits. They examined the association in 10,619 unrelated subjects of European ancestry. The authors report 11 genetic loci that are associated with CVD related traits such as body mass index, high and low density lipids levels at the genome-wide significance level.

Aguirre et al. (2019), reporting in *The American Journal of Human Genetics*, describe similar findings in albeit a much bigger cohort of 472,228 individuals from the UK Biobank. They used the UK BiLEVE Axiom Array by Affymetrix and the UK Biobank Axiom Array. The authors studied genome-wide associations across 3,157 phenotypes for 7,038 common CNVs observed at 0.005% allele frequency. They show a dizzying number of associations between CNVs and traits. Of particular interest are the associations found with CNVs at two well-known syndromic loci 16p11.2 and 22q11.2, with acute coronary artery disease and high body mass index. As with SNPs, the functional consequence of these CNVs is difficult to predict. One direct consequence is a dosage effect upon the level of mRNA transcription; alternatively, these CNVs may cause other instability in the DNA with consequences beyond RNA transcription in the gene of interest. Both of these studies have limitations such as the indirect quantification of CNVs by SNP arrays or by the known selection cohort bias. However, further work is warranted to cement these findings.

So, will CNVs have a clinical utility for CVD?

The associations found in the studies described certainly suggest a role of structural variation such as CNVs in population-wide effect on common disease such as coronary artery disease. Other studies have also suggested a role for these mutations in rarer events such as sudden cardiac death (10). Further in-depth data and replication in cohorts are needed to verify the findings. However these findings are the start of a DNA variation databanks that may be used

by clinicians for disease classification and detection in the future. This is particularly relevant in the age of the whole genome sequence.

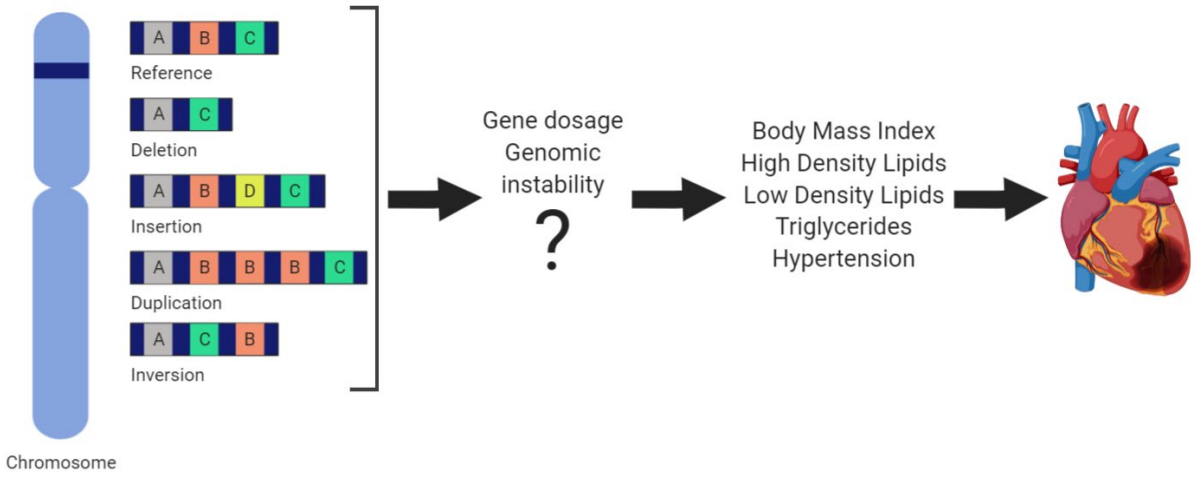

Figure 1: Chromosomal representation of copy number variations (CNVs) showing a deletion, insertion, duplication and inversion in comparison to the reference sequence. These CNVs can lead to changes in gene dosage or cause genomic instability and have been implicated in cardiovascular disease and associated to various cardiovascular disease risk factors such as body mass index, high and low density lipids, triglycerides and hypertension and end stage disease such as coronary artery disease.

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