Ethics Watch

IMPLICATIONS OF COPY-NUMBER VARIATION IN THE HUMAN GENOME: A TIME FOR QUESTIONS

Just as bioethicists came to understand single nucleotide polymorphisms (SNPs) they are now faced with comprehending new discoveries of thousands of submicroscopic quantitative structural changes of chromosomes — including insertions, deletions and duplications — in the human genome, collectively called copy-number variants (CNVs) or polymorphisms (CNP)¹. Progress in completing genome-wide maps and databases of CNVs (for example, the **Database of Genomic Variants**) adds a new dimension to the study of genome variation. This, in turn, will affect our concept of 'normality' — it is now routinely observed that one of a pair of homologous chromosomes can be up to a million nucleotides and 20 genes shorter than the other² — with potentially profound ethical, legal and social implications (ELSI).

The discovery of CNVs as a universal feature of genomes coincides with growing interest in the influence of genomic variation on human characteristics, disease and evolution. Several ongoing or planned genotyping studies, such as the **Human Genome Organisation** Pacific Pan-Asian SNP Initiative and, of course, the **International HapMap Project**, hold interest for health-care providers, policy makers, bioethicists and the general public. Bioethicists are inextricably involved in examining social implications and developing ELSI guidelines. However, we will have to re-examine our previous conclusions and recommendations, because when earlier genomic mapping studies were designed, SNPs were the primary currency of genomic variation and little was known about CNVs and their implications.

Now, large-scale, genome-wide association or case-control studies, including those of the Wellcome Trust Case Control Consortium (15,000 samples), Broad Institute (12,000 samples), the Korean National Institute of Health (20,000 samples) and the public/private Genetic Association Information Network (GAIN), will undoubtedly incorporate CNV analyses into their designs. The **Database of Chromosomal Imbalance and Phenotype in Humans Using Ensembl Resources** (DECIPHER) project is perhaps one step ahead of others in its consideration of consent and database issues that are specific to CNVs, and might offer a precedent for future studies.

Generation of population-wide CNV catalogues means that databases that have

relied on SNPs might have to be re-evaluated. Moreover, future investigations will benefit from reliable, complementary and harmonized technologies that account for several forms of genomic variation simultaneously. This means that ELSI experts should proceed with caution and perhaps wait for more complete scientific knowledge before they consider ELSI surrounding genome variation and its applications, particularly for such potentially controversial issues as forensics and race³.

The description of CNVs has already enhanced our fundamental understanding of human evolution, disease predisposition and the body's response to drugs and other environmental influences¹. But despite several news reports and scientific editorials, the topic has not yet captured the public imagination,

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even though accumulating data indicate that CNV content might exceed that of SNPs within humans⁴, and between humans and chimpanzees.

There are several issues that could arise for ELSI experts. In a clinical research setting, how will the management and counselling of a patient and his/her family unfold with, and without, taking CNVs into account? Will ethical issues arising from analysis of CNVs simply mirror past issues encountered when using cytogenetic approaches, or will CNVs give rise to new and unforeseen complexities in genetic counselling? Should archived specimens be re-evaluated? Could patients sue if a past medical genetic diagnosis required revision in light of new knowledge afforded by CNVs?

We have argued that pharmacogenetics that is based on geographical ancestries might be harnessed to improve global health and energize the pharmaceutical industry in developing countries⁵. Can the latter benefit from harnessing knowledge of CNVs in pharmacogenomic testing and drug design? Furthermore, will industry's internalization and

use of CNVs predict how such knowledge might be more widely applied?

As we move towards the potential for personalized genome fingerprints and sequences, how might new genomic data influence conventional classifications of 'common', 'normal', 'healthy' or 'diseased'? Indeed, given our partial understanding of genomic variation, how should scientists and ELSI experts advise governments on the roles of genomics in health care?

At present, ELSI studies on CNVs are in their infancy. So we should begin by developing a conceptual framework that places the new discoveries in the wider context of contemporary discourse on genomic variation studies and their biological, health and societal implications. We need to develop a taxonomy of the research issues to be addressed jointly by scientists, social scientists, clinicians, anthropologists, philosophers, historians, lawyers and other relevant disciplines.

This is the right time for scientists and ELSI experts to work together closely. Being able to address such questions sooner rather than later will better ensure realization of the potential of scientific discoveries related to genomic CNVs.

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REFERENCES ¹Feuk, L., Carson, A. R. & Scherer, S. W. Structural variation in the human genome. *Nature Rev. Genet.* **7**, 85–97 (2006) | ²Check, E. Human genome: patchwork people. *Nature* **437**, 1084–1086 (2005) | ³Royal, C. D. M. & Dunston, G. M. Changing the paradigm from 'race' to human genome variation. *Nature Genet.* **36**, S5–S7 (2004) | ⁴Lee, C. Vive la difference! *Nature Genet.* **37**, 660–661 (2005) | ⁵Daar, A. S. & Singer, P. A. Pharmacogenetics and geographical ancestry: implications for drug development and global health. *Nature Rev. Genet.* **6**, 241–246 (2005)

FURTHER INFORMATION

Database of Chromosomal Imbalance and Phenotype in Humans Using Ensembl Resources:

<http://www.sanger.ac.uk/PostGenomics/decipher>

Database of Genomic Variants:

<http://projects.tcag.ca/variation>

Human Genome Organisation:

<http://www.hugo-international.org>

International HapMap Project: <http://www.hapmap.org>