Meeting report

New insights into genomic variation in health and disease

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Abstract

A report on the Genomic Disorders conference on Genomic Variation in Health and Disease, Hinxton, UK, 9-11 March, 2009.

The annual Genomic Disorders conference was held in March 2009 at the Sanger Center Genome Campus in Hinxton, UK. The scientific program was developed by Nigel Carter (Wellcome Trust Sanger Institute, Hinxton, UK), Dian Donnai (University of Manchester, UK), Helen Firth (Cambridge University, UK) and James Lupski (Baylor College of Medicine, Houston, TX, USA). This meeting covered mechanisms of genomic instability and genomic variation in common disease, brain disorders, X-chromosome disorders, and rare syndromes, as well as bioinformatics approaches, modeling approaches, and an evolutionary perspective on genomic disorders, appealing to clinicians as well as basic researchers. Across this wide variety of topics, several themes emerged in this recently revitalized field.

Understanding the mechanisms generating genomic variation and their sequence signatures

The mechanisms of genomic rearrangements are diverse, and dissection of the sequence data at breakpoints can give clues as to the underlying mechanisms. James Lupski started the meeting with a presentation focused on the mechanisms and detection of genomic rearrangements and copy number variants (CNVs). These can be classified as recurrent (with clustered breakpoints, usually within low copy repeats), non-recurrent with breakpoint grouping, and non-recurrent with little overlap. Several mechanisms underlie these classes of events: non-allelic homologous recombination (NAHR) occurs between highly homologous low copy repeats and often results in recurrent rearrangements. Non-homologous end joining (NHEJ) and fork stalling and template switching (FoSTeS) can result in non-recurrent events. NHEJ often leaves 'scars' at the site of rearrangement, including deletion or addition of nucleotides, and frequently occurs at repetitive elements or known sequence motifs, and FoSTeS often shows evidence of microhomology (for example, 2-4 base pairs) and can most simply explain complex forms of rearrangement. All of these mechanisms can occur in meiosis or mitosis. The differences in mechanism suggest that the rates of these events may vary widely across the genome, dependent on local architecture, which has implications for population and evolutionary genetics, as well as models for disease association.

These themes were touched on during other talks during the conference, including those given by Alec Jeffreys (University of Leicester, UK) focusing on hotspots of recombination and NAHR at the beta-globin locus as explored by sperm typing; Peter Campbell (Wellcome Trust Sanger Institute, Hinxton, UK) on patterns in somatic genomic rearrangements in cancer; and Lisenka Vissers (Radboud University Nijmegen Medical Centre, The Netherlands), who provided an analysis of microhomology, repetitive elements and sequence motifs present in 38 rare pathogenic CNVs ascertained clinically. Matthew Hurles

(Wellcome Trust Sanger Institute, Hinxton, UK) reported that in the Wellcome Trust Case Control Consortium (WTCCC) study of common diseases and a common pool of controls, 30-40% of events were mediated by NHEJ and an equal proportion showed microhomology; approximately 15% were variable number tandem repeats, 7% mediated by NAHR and less than 1% events of retrotransposition.

Understanding the contributions of genomic variation to human disease

Few dramatic successes have been made in identifying the contribution of CNV to common disease; in contrast, there has been much success in identifying causal genomic variants in rare disorders and in brain disorders; however, the underlying pathophysiological mechanisms are rarely obvious.

Matthew Hurles reported that in the WTCCC, there is no strong evidence for a greater rare CNV burden in disease cases versus controls or in any particular disease studied. He also observed a null distribution for common CNVs that could be detected. However, in many regions of single nucleotide polymorphism (SNP) association, there are CNVs in linkage disequilibrium with SNPs that could be the causative variation in those instances. Timothy Aitman (MRC Clinical Sciences Centre and Imperial College London, UK) and John Armour (University of Nottingham, UK) presented CNVs implicated in autoimmune disease, and Dr Armour discussed the technical challenges involved in genotyping multi-allelic and complex CNVs.

Doug Higgs (Oxford and National Haemoglobinopathy Reference Laboratory, Churchill Hospital, UK) emphasized CNV effects on flanking genes lying outside of the CNV region, including long-range effects. Similarly, position effects were observed in rare congenital malformations, as discussed by David Fitzpatrick (MRC Human Genetics Unit and Institute for Genetic and Molecular Medicine Western General Hospital, Edinburgh, UK) and Eva Klopocki (Institute of Medical Genetics, Charité Universitätsmedizin, Berlin, Germany) with regard to *SOX9*, and Pawel Stankiewicz (Baylor College of Medicine, Houston, TX, USA) with regard to *FOXF1*. In several cases, very similar phenotypes were observed with adjacent, but non-overlapping deletions in both novel and known syndromes; this was discussed by Harmut Engels (Rheinische Friedrick-Wilhelms-University, Bonn, Germany) and Femke Hannes (Center for Human Genetics, Katholieke Universiteit, Leuven, Belgium), respectively.

Several speakers in the session on brain disorders noted the wide expressivity of even highly penetrant CNVs, including shared etiology between schizophrenia, autism, mental retardation and epilepsy (Lauren Weiss, University of California San Francisco, CA, USA and Audrey Guilmatre, Inserm, Rouen, France). For this reason, the approach of reverse genomics/genetics was proposed in presentations by James Lupski and Lauren Weiss, in order to, for example, ascertain subjects with the same CNV and then look for common phenotypic manifestations. Helen Firth presented DECIPHER, a bioinformatics approach to assign a phenotype to genes or genomic regions by analysis of rare pathogenic mutations and syndromes.

Leon-Charles Tranchevent (Katholieke Universiteit Leuven, Belgium), Daniela Nitsch (Katholieke Universiteit Leuven, Belgium) and Caleb Webber (University of Oxford, UK) proposed bioinformatics approaches to identifying candidate genes of interest for specific phenotypes within large genomic rearrangements. A presentation by Maria Karayiorgou (Columbia University, New York, NY, USA) on mouse models of human 22q11 deletion attempting to explain the psychiatric phenotypes in human patients re-emphasized the complexity of disease-causing mechanisms. Single gene knock-outs of several genes in the region have been shown to cause murine phenotypes reminiscent of the cognitive deficits associated with schizophrenia in patients.

Conclusions

The identification and characterization of genomic variation has recently enjoyed much success due to high-resolution microarrays and next-generation sequencing technology. We know much more about the mechanisms and population and evolutionary characteristics of these events and we have identified many novel disease loci as compared with just a few years ago. However, this dramatic increase in the depth of our understanding of genomic rearrangements has only emphasized that we still have much to learn about the spectrum of human genomic variation and the biological and clinical implications thereof. In the immediate future, further optimization of approaches for detection, genotyping, and analysis - particularly for small, complex, and common variants - could improve our ability to detect low-penetrance contribution to human disease and population variation. Looking forward, our clinical interpretation and biological investigation must keep pace with these myriad novel genomic discoveries.

Abbreviations

CNV, copy number variant; FoSTeS, fork stalling and template switching; NAHR, non-allelic homologous recombination; NHEJ, non-homologous end joining; SNP, single nucleotide polymorphism; WTCCC, Wellcome Trust Case Control Consortium.

Competing interests

The author declares that she has no competing interests.