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Spectrum of structural genomic abnormalities in subjects carrying disease-associated chromosome rearrangements and their pathogenic implications

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Structural chromosomal rearrangements (SCRs) have long been recognized as a major source of human developmental anomalies, including, among others, congenital anomalies, and neurodevelopmental, intellectual and cognitive disabilities. Indeed, causal relationship between congenital anomalies and related SCRs are expected to occur in up to 40% of the affected subjects. Approaches used for detection of such SCRs evolved significantly from classical and molecular cytogenetic technologies, such as FISH and microarrays, to whole genome sequencing (WGS) with high physical and low sequence coverage, also known as large-insert WGS. The spectrum of SCRs, at DNA sequence-level resolution, in subjects carrying disease-associated SCRs, and the emerging pathogenic mechanisms will be presented. Like classical haploinsufficiency due to point mutations, disruption of the coding regions or genomic elements controlling quantitative expression of a dosage-sensitive gene will lead to a haploinsufficient phenotype. Position effect is a complex pathogenic mechanism of these SCR-associated disorders, resulting from disruption of native gene-specific and adoption of alien long-range cis-acting control elements. Haploinsufficiency or position effect on the same gene may lead to dissimilar clinical phenotypes. Certain balanced translocations can yield clinical phenotypes that are similar to microdeletion syndromes caused by hemizygosity of a major causal gene locus or of a variable number of contiguous genes. In such cases, haploinsufficiency of the causal gene with or without position effect on the contiguous genes can be considered as possible pathogenic mechanisms. Occasionally, gene fusions occur through SCRs that may lead to fusion transcripts. Although formation of such transcripts is a fundamental pathogenic mechanism behind different forms of cancer, apparently this is insignificant in SCR-associated disorders, mainly because many of such transcripts are non-functional and therefore non-pathogenic. There is no direct correlation between complexity of chromosomal rearrangements and severity of clinical phenotypes. Such genomic approach allows personalized medicine-based care and necessarily has to be accompanied by deep clinical phenotyping. The emerging picture from these SCRs data highlights the extent to which the human genome can be affected by these rearrangements, its tremendous plasticity, and the intricacy of pathogenic mechanisms leading to SCRs-associated disorders.