2 Genome rearrangement

Human chromosomes were first observed more than 120 years ago and since then technical innovations have paved the way for progress in this field. In 1923, the study of dividing testicular cells led Thomas Painter to conclude that humans have 48 chromosomes, and the correct number of 46 was only determined in 1956, after Tjio and Levan (Tjio and Levan, 1956) had developed an improved protocol for the preparation and spreading of chromosomes. This innovation was also instrumental in defining a variety of diseases that are due to aberrant number of chromosomes, so-called numerical chromosome aberrations, such as Down Syndrome (trisomy 21), Klinefelter syndrome (47, XXY) and Turner syndrome (45, XO).

In the late 1960s and 1970s, staining protocols were developed, generating specific banding patterns along the length of each chromosome. These banding patterns allowed to distinguish all human chromosomes and greatly facilitated the recognition of chromosome structural rearrangements.

Such structural rearrangements occur when a chromosome breaks and is rejoined to another broken chromosome fragment. They can be confined to a single chromosome, resulting in a loss or gain of material (deletion/duplication), or leading to the inversion of an internal chromosome segment. If fragments of two different chromosomes are exchanged, this will result in reciprocal translocations.

Genome rearrangements play an important role in the etiology of human genetic diseases. The term ‘genomic disorder’ has been coined for a broad spectrum of diseases caused by the rearrangement of specific genomic segments , ranging in size from a few kilobases to several megabases (Lupski, 1998); (Inoue and Lupski, 2002). This group of disorders does not result from single nucleotide substitutions, but is due to recurrent chromosomal aberrations which give rise to DNA copy number changes or disruption of the structural integrity of a dosage sensitive gene(s). Very often, in these disorders, the underlying recurrent genome rearrangements are mediated by nonallelic homologous recombination between highly similar paralogous sequences.

Apart from causing a variety of well-known genomic disorders, such as DiGeorge Syndrome, Williams-Beuren Syndrome and Prader-Willi Syndrome, some of these genome rearrangements are also observed in the normal population and are considered as functionally neutral structural variants. Major types of structural variants consist of copy number polymorphisms (CNPs) and inversion polymorphisms, respectively.

Simple nucleotide substitutions have been implicated in many genetic diseases, but the majority of these are considered as functionally neutral variants. In contrast, small genome rearrangements have only recently been appreciated as an important source of genetic variation. Apart from genome rearrangements directly causing genetic diseases, other may modulate the predisposition for specific disorders. Since the early 1990s, the development of suitable tools for their detection has bridged the gap between karyotyping and molecular genetics and opened the new field of "Molecular Cytogenetics".