Institute of Human Genetics

Analyzing the Basis and Molecular Mechanisms of Human Hereditary Diseases

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In addition to the clinical services in genetic counseling and in molecular as well as cytogenetic diagnostics, the Institute of Human Genetics focuses strongly on basic science. For example, independent working groups aim at disease gene identification in selected neurogenetic diseases by analyzing the mechanisms and consequences of genetic and genomic variability, and by studying mutagenesis.

The working group of Hildegard Kehrer-Sawatzki is working on the characterization of the molecular mechanisms underlying gross genome rearrangements associated with a number of human diseases. These mechanisms include nonallelic homologous recombination (NAHR), nonhomologous end joining and microhomology-mediated replication-dependent recombination. Our work is primarily focused on the analysis of neurofibromatosis type-1 (NF1)-associated microdeletions which represent an excellent model system. NF1 is a hereditary cancer predisposition syndrome that is characterized by tumors of the peripheral nerve sheaths. Large deletions encompassing the NF1 gene and its flanking regions constitute the most frequently recurring copy number mutations causing NF1. Our work has contributed to the identification of four distinct types of large NF1 deletion (type-1, type-2, type-3 and atypical) which differ with respect to the extent of the deleted region and the location of breakpoints. The most frequent type of NF1 deletion is type-1 which encompasses 1.4 Mb; these deletions are caused by NAHR.
occurring within two recombination hotspots, 2-3 kb in length, located within low-copy repeats flanking the NF1 gene region. The vast majority of type-1 NF1 deletions appear to be of meiotic origin. The second most frequent type of NF1 deletion encompasses 1.2 Mb; the breakpoints of these type-2 deletions are located within the SUZ12 gene and its pseudogene SUZ12P, located adjacent to the NF1-REPs. Our work indicated that the majority of these type-2 deletions are caused by mitotic NAHR.

Our studies of large NF1 deletions have shown that both meiotic NAHR and mitotic NAHR occur non-randomly across the different NF1-flanking low copy repeats. The characteristic features of type-1 NF1 deletions are largely consistent with the conclusion that certain NAHR hotspots operate exclusively during meiosis and not at all during mitosis. This suggests that there are fundamental mechanistic differences between meiotic NAHR and mitotic NAHR, particularly with regard to the determinants for recombination-inducing double strand DNA breaks. Large deletions in the NF1 gene region have been found to be associated with an especially severe clinical phenotype. Thus, we observed significantly increased frequencies (relative to the general NF1 patient population) of plexiform neurofibromas (76%), subcutaneous neurofibromas (76%) and spinal neurofibromas (64%). The identification of deletion-predisposing genomic structural variants as well as disease-modifying genes is also a major research topic of the group. As in many other hereditary cancer syndromes, somatic mosaicism in NF1 exerts a considerable influence on the clinical phenotype and the transmission risk of the disease. NF1 also represents an excellent model system to study somatic mosaicism and this is currently being investigated by the group by employing a variety of different techniques and strategies that have been specially developed in order to improve mosaicism detection and mutational analysis.

(PhD project, Julia Voigt)