1 Preface

Comparative genomic hybridisation using arrays of DNA clones as targets (array CGH) is a novel and powerful technique to identify submicroscopic deletions and duplications and to study their roles in genetic disorders. Typically, very high resolution CGH arrays covering the whole human genome comprise >30,000 overlapping Bacterial Artificial Chromosomes (BAC) clones and yield a corresponding number of discrete hybridisation signals. The management and interpretation of these data poses enormous problems, not only because of their quantity, but also because of their variable quality. Recently, CGH arrays comprising 36,000 BAC clones have been generated at Max Planck Institute for Molecular Genetics, which are being employed for deletion/duplication screening in patients with mental retardation and various related disorders. As a prerequisite for these studies, I have developed a comprehensive software package for visualisation, analysis and management of array CGH data. The program, called 'CGHPRO', is also designed to support the search for genomic imbalances that are only seen in specific cohort of patients, and even more importantly, it tracks previously reported functional neutral genomic imbalances.

The second part of my project focused on the practical application of high-resolution array CGH and CGHPRO. First, by means of array CGH, copy number changes in 22 patients with mental retardation were analysed. In order to obtain insights into the molecular mechanisms of genome rearrangements, especially the impact of segmental duplications, I investigated the chromosomal breakpoint regions of these 22 patients in more detail. These data were supplemented with fine mapping data of another 41 cases with balanced translocations. Implementation of further features into CGHPRO, which allowed the automatic design of specific sub-arrays, paved the way for high-resolution array-painting. This technique combines chromosome sorting and DNA array technology and enables rapid fine mapping of breakpoints in balanced translocations.