6 Summary

Genome rearrangements contribute significantly to the etiology of genetic disorders but also to human genetic diversity and disease susceptibility. For the detection of submicroscopic deletions and duplications on a genome wide level, a BAC-Array based technique for comparative genomic hybridisation (Array CGH), using a high number of overlapping BACs covering the whole genome is now being applied. The resulting data output however is of a magnitude that requires powerful management tools for handling not only large data quantities but also for coping with data quality variation.

To facilitate the analysis and management of array CGH data, I have developed a comprehensive software package called 'CGHPRO'. Using the results from the image analysis software, CGHPRO allows hybridisation features to be checked with a variety of graphical representation options, thus enabling the selection of the most suitable normalisation method for individual experiments. A variety of options is then offered to characterize individual genomic profiles from the normalized data sets. All results are visualized in an interactive interface and stored in a database. The database allows the repetitive use of the stored results in comparative analyses, e.g. for investigating chromosomal aberration patterns in specific patient cohorts. In order to take the resolution of ArrayCGH applications beyond the BAC level CGHPRO allows the design of high-resolution specific sub-arrays.

The power of CGHPRO was demonstrated in the analysis of 22 mentally retarded patients with submegabase resolution whole genome tiling path BAC array CGH, which led to the identification of 20 deletions and two duplications. Additionally, as a proof of principle for CGHPRO assisted sub-array design, the breakpoints from a balanced translocation t(1;13) were successfully fine mapped.

When comparing the breakpoint regions for the 22 mentally retarded patients with those from a set of 41 balanced translocation carriers, in 6 of 22 unbalanced aberrations, breakpoint flanking duplications with a high degree of sequence

similarity were found, suggesting that unequal crossing over might be one factor in chromosome instability. In all 41 balanced translocations however, even though breakpoint flanking duplications were observed, sequence homology between them never occured. This second finding indicates the existence of additional chromosomal instability factors which depend on or coincide with segmental duplications.

Taken Together, the results presented here demonstrate the powerful enhancement of the Array-CGH technique by the development and application of a versatile data management and ananlysis tool. It can be concluded, that the implementation of the protocols introduced here will, also for studies in large patient cohorts, greatly facilitate the identification and investigation of disease-associated chromosomal aberrations.

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