The genetics of BWS associated tumors
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SUMMARY

The Beckwith-Wiedemann syndrome (BWS) is a syndrome which occurs with a frequency of 1:13,700. It is characterized by several features, of which the most striking is pre- and postnatal gigantism. In addition, BWS patients have a risk of 7.5% of developing certain solid childhood tumors. Tumors that are most frequently found in these patients are Wilms tumor (WT), adrenocortical carcinoma (ACC), rhabdomyosarcoma (RMS) and hepatoblastoma (HB). Genetic analyses of BWS patients showed that the disease cosegregates with chromosome region 11p15. In addition, structural abnormalities involving 11p15 have been described. Therefore, BWS patients may have a genetic defect located on this chromosome region. Since several childhood tumors occur with an increased frequency in BWS patients it is believed that these tumors develop because of the same genetic defect. Indeed it has been shown for all the tumors mentioned above that, when they occur sporadically, they also demonstrate chromosome 11p abnormalities. Thus, a common genetic pathway may be involved in the etiology of these tumors.

This thesis deals with the identification of genetic aberrations in BWS associated tumors when occurring sporadically. Two genes are analyzed in a series of WTs: The Insulin-like growth factor 2 gene (IGF2) and the HI9 gene. Both genes are located on chromosome 11p15 and both are imprinted. IGF2 is only expressed from the paternal allele, whereas HI9 is only expressed from the maternal allele. IGF2 is a growth-promoting gene, whereas HI9 may function in the maintenance of the imprinting-status of IGF2. It had already been shown that these genes display loss of imprinting (LOI) in WTs. In our analysis we determined both the level of expression of these genes and the methylation status of the H19 promoter. We found that LOI of IGF2 is linked to reduced expression and hypermethylation of H19.

Next, to detect all quantitative chromosome aberrations, we analyzed a series of WTs and HBs using comparative genomic hybridization (CGH). The results of the CGH analysis of the WTs corresponded well to data obtained using other techniques. In addition we found loss of chromosome 4q. Comparison of the results of CGH analysis of WTs and HBs revealed several common quantitative chromosome abnormalities occurring in a high percentage in both tumor-types. When including data from a CGH analysis of RMSs from the literature it became evident that gains of chromosome regions 7q, 8q and 17q are frequent in all three BWS associated tumor-types.
Finally we focused on a region on chromosome 1. We showed by loss of heterozygosity (LOH) analysis that 18% of informative WTs had become homo- or hemizygous for 1p35-36. Since this region is known to be affected in several BWS associated tumors we sought to determine the precise location of the genetic defect. For this purpose we analyzed cells from a WT and cells from a RMS which contained chromosome translocations involving region 1p35-36. We found that both breakpoints are not identical but are separated by at least 875 kb. This finding makes it unlikely that one gene is disrupted by both translocations. It is however still possible that both breakpoints disturb the regulation of the same gene. Furthermore we established that the translocation breakpoint in the RMS cells was located proximal to the PAX7 gene. This gene is involved in most, if not all, translocations in RMS cells affecting 1p36 studied to date. Our data provide the first evidence for the presence of an additional gene on 1p35-36 involved in the etiology of RMS.