The genetics of BWS associated tumors
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OUTLINE OF THE THESIS

In this thesis a detailed description is given of the genetics of certain solid tumors occurring in early childhood. These tumors share a common genetic pathway on chromosome 11 since they are all associated with the Beckwith-Wiedemann syndrome (BWS), a syndrome which has been linked to chromosome 11p15. Chapter 1 gives an overview of the available data on the (epi)genetics of the most common BWS associated tumors. These tumors are Wilms tumor (WT), adrenocortical carcinoma (ACC), rhabdomyosarcoma (RMS) and hepatoblastoma (HB). It was found that these tumor-types share several common (epi)genetic aberrations. They all show abnormalities of chromosome 11p15 and mutations of the p53 gene. In addition, common duplicated chromosome regions and abnormalities of chromosome 1p were found in three out of four tumor-types. Chapter 2 deals with the aberrant imprinting and expression phenomena of the Insulin-like growth factor 2 gene (IGF2) and the H19 gene in WT. It describes hypermethylation of the promoter region of H19 and decreased expression of the gene in WTs with loss of imprinting (LOI) of IGF2. Chapter 3 gives the results of the analysis of a large series of WTs using the comparative genomic hybridization technique (CGH). CGH enabled us to make a complete inventory of chromosome regions involved in gains or losses in WT. Besides gains and losses we and others previously found with molecular and cytogenetic studies, loss of chromosome 4q was identified as a new event. In addition, this chapter also describes the involvement of chromosome 1p in WT: the shortest region of overlap (SRO) of loss of heterozygosity (LOH) using markers on 1p was determined for six WTs and one metastasis of a WT. Next, chapter 4 describes the analysis of a series of HBs using the same CGH technique. This resulted in the identification of additional common genetic aberrations found in HB, WT and RMS. These aberrations affected chromosome regions 7q, 8q and 17q. Finally, in chapter 5, a detailed description is given of the region on chromosome 1p affected by two novel translocation breakpoints in a WT and a RMS. We showed that these breakpoints are separated by at least 875 kb and do not disrupt known genes. These data provide encouraging information in the process of defining the gene(s) on 1p involved in the etiology of these childhood tumors.
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