Phenotypic abnormalities in childhood cancer patients; clues for molecular defects?
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Citation for published version (APA):

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Summary
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Many clinical genetic syndromes are associated with an increased risk for tumor development (Chapter 1). In these syndromes the same, constitutional molecular defect leads to both a specific clinical morphological phenotype and a predisposition for the development of specific cancers. The incidence of tumor predisposition syndromes, either established syndromes or new entities, might be much higher than currently estimated.

To test this hypothesis, we started out by defining a uniform classification system for all phenotypic abnormalities that can be scored by body surface examination, based on their (presumed) pathogenesis, in order to be able to weigh the importance of the anomalies scored in a pediatric cancer population (Chapter 2). A tree was built with 29 major areas defined by either anatomy or function, further subdivided into 98 smaller areas which were finally divided into a total of 683 single anomalies, describing all individual abnormalities and minor variants that can be scored by surface examination. Reliability of the clinical morphological examination was tested by independent scoring of 31 of the first 100 patients by two observers, showing a kappa-score for interobserver variation of 0.89.

In a three-year period a cohort of 1,073 childhood cancer patients was submitted to a detailed clinical morphological examination. We investigated the incidence of syndromes in this cohort (Chapter 3). If the primary investigator suspected a patient to have a syndrome, because of a high number of phenotypic abnormalities, specific combinations of anomalies, family history, or combinations of any of these with the primary tumor, the patient was evaluated by a second investigator. Whenever possible a diagnosis was confirmed by molecular investigations. If a patient was highly suspected to have a syndrome, but the diagnosis remained hidden despite extensive investigations the patient was categorized as having a 'private syndrome'. We diagnosed a known syndromic entity in 45 patients (4.2%) and suspected a syndrome in another 35 patients (3.3%). The percentage of 7.5% of patients with a proven or suspected syndrome is considerably higher compared to the prevalence of syndromes in the general population, indicating that constitutional molecular defects indeed are more often involved in pediatric oncogenesis than previously anticipated. We describe new syndrome - tumor associations in several entities. Alterations of chromosome-part 11p15 were found in 5 out of 14 isolated hemihyperplasia (IHH) cases, indicating that an important part of IHH cases represent one end of the spectrum of Beckwith-Wiedemann syndrome. PTEN mutational analysis in this group gave negative results. Twenty-three of the 45 detected established syndromes were detected only during this study, indicating that standard pediatric care can be insufficient to detect clinically important syndrome diagnoses in childhood cancer patients. We propose that all children diagnosed with a malignancy should be screened by a clinical geneticist or a pediatrician skilled in clinical morphology for clues pointing to an underlying congenital etiology.
Furthermore in Chapter 4 overall incidences of phenotypic abnormalities, and associations of (patterns of) phenotypic abnormalities and the different tumor types are described. One or more minor anomalies were present in 55.1% of patients compared to 14.7% in a major reference control population. Reliability of the examination was tested by independent scoring of 75 patients by two observers, showing a kappa-score for interobserver variation of 0.93. Twenty-eight phenotypic abnormalities occurred significantly more often in one specific tumor category. Multivariate logistic regression analysis revealed twenty-three phenotypic abnormalities that were significantly more often associated with certain tumor groups. Novel patterns of phenotypic abnormalities were made likely to exist for many tumor groups. In line with the high percentage of patients with a proven or suspected syndrome (Chapter 3), these results suggest that also new tumor predisposition patterns, caused by yet unrecognized genetic defects, exogenous factors, or combinations of these, are much more frequent than currently anticipated. We believe that the described associations between (patterns of) phenotypic abnormalities and specific tumors may be helpful in identifying the underlying genetic and environmental defects: new associations between tumors and known syndromes will be investigated, allowing evaluation of known genetic factors responsible for the syndrome, for their possible role in oncogenesis; tumor specific patterns of phenotypic abnormalities may show overlap with the phenotype of already known syndromes, and may point at defects in the same developmental pathway; and data mining tools may be helpful to translate tumor specific patterns of phenotypic abnormalities into candidate genes. Not only phenotypic abnormalities detectable by surface examination, but also skeletal anomalies can provide clues for underlying constitutional defects (Chapter 5). Chest radiographs of 906 childhood cancer patients, and 881 normal Caucasian pediatric controls were reviewed for the presence of 6 major rib anomaly categories, each radiograph blinded and independently scored by two observers, using strict definitions. The overall incidence of total rib anomalies in cases and controls was equal. In childhood cancer patients a significantly higher incidence of cervical rib anomalies was demonstrated in patients with acute lymphoblastic leukemia, astrocytoma, and germ cell tumors. Alterations of Hox family gene(s) expression are good candidates for this higher incidence, but also environmental factors are discussed. During the course of the studies described above, two families in the clinic caught our attention. Four members of a single family with a heterogeneous phenotype, that at first most closely fitted Bannayan-Riley-Ruvalcaba syndrome, were eventually found to have PTEN Hamartoma Tumor syndrome (Chapter 6). All four cases harbored the same PTEN mutation, predisposing them to cancer in adulthood, especially those of the breast, thyroid and endometrium. In Chapter 7 we described an unusual family with the concurrence of a neuroblastoma in a child conceived after in-vitro fertilization and maternal valproic acid use during pregnancy, and a sib with a mosaic trisomy 22. Possible mutual relations between neuroblastoma, chromosome mosaicism, valproic acid use during early pregnancy, in-vitro fertilization, and parental occupation are discussed.
In Chapter 8 we present the analysis of the *PTPN11* gene for its possible role in neuroblastoma tumorigenesis. Our hypothesis that *PTPN11* might be involved in neuroblastoma tumorigenesis was based on our diagnosis of a LEOPARD syndrome in a neuroblastoma patient and the subsequent finding of a constitutional *PTPN11* mutation in the same patient, combined with 5 previously published cases of neuroblastoma in Noonan patients. The *PTPN11* gene is known to play a role in juvenile myelo-monocytic leukemia. To test this hypothesis we are currently analyzing randomly chosen neuroblastoma tumor samples for *PTPN11* mutations (chapter 8). We found a Gly503Val mutation in exon 13 in the tumor of a stage III neuroblastoma patient. The mutation affects the active site of the protein tyrosine phosphatase domain. Lymphocytes of the patient did not show the mutation. This is the first evidence of the oncogenic role of *PTPN11* in solid tumors in general, and neuroblastoma in particular. These results show that the *PTPN11* pathway can play a causative role in neuroblastoma oncogenesis.