harbor generalized genomic instability, with multiple segmental chromosomal aberrations that result in a complex karyotype with adverse prognostic implications. One peculiar form of segmental aberration described recently in aggressive neuroblastomas is called *chromothripsis* (Chapter 7), which involves localized fragmentation of a chromosome segment followed by random assembly of the fragments. In a subset of neuroblastomas, chromothripsis can result in amplification of *MYCN* or other oncogenes, or losses in tumor suppressor loci.

While *age, stage, histology,*, *MYCN status,* and *DNA ploidy* are currently the "core" criteria used for the purposes of formal risk stratification and therapeutic decision, several emerging molecular variables have been described with prognostic implications. The most pertinent ones include the following:

- *Hemizygous deletion of the distal short arm of chromosome 1* in the region of band p36 has been demonstrated in 25% to 35% of primary tumors. Loss of 1p36 in neuroblastomas has a strong correlation with *MYCN* amplification, as well as advanced disease stage, and is associated with an increased risk of disease relapse in localized tumors. *Hemizygous loss of chromosome 11q* genetic material is another adverse prognostic factor, and may be the most common deletion event in neuroblastomas.
- *The expression of specific neurotrophin receptors* is also a prognostic marker for neuroblastoma. The neurotrophin receptors are a family of tyrosine kinase receptors, notably TrkA, TrkB, and TrkC (also known as NTRK3, see earlier), that regulate the growth, survival, and differentiation of neural cells. High TrkA expression is a favorable prognostic factor in neuroblastomas, generally associated with low-stage tumors lacking *MYCN* amplification that occur in younger patients. In contrast, elevated TrkB expression is associated with unfavorable biological characteristics, including *MYCN* amplification and a higher disease stage.
- Lastly, the application of next generation sequencing techniques to unravel the neuroblastoma genome has identified recurrent mutations in genes whose products are involved in *neuritogenesis* (a process in neuronal differentiation which includes the sprouting of neurites that will subsequently lead to the formation of axons). Selected examples of mutated genes within this functional class include *alpha thalassemia / mental retardation, X-linked* (*ATRX*) and *protein tyrosine phosphatase, receptor type D* (*PTPRD*). Mutations of neuritogenesis associated genes were generally present in more aggressive, higher-stage neuroblastomas (including those arising in the absence of *MYCN* amplification), and these alterations are postulated to lead to defects in neuronal differentiation within the neoplastic cells, likely underlying their poorly differentiated histology.

Although discussion of the treatment modalities for neuroblastoma is beyond the scope of this book, we mention in passing two promising experimental approaches. The first involves the use of retinoids as an adjunct therapy for inducing the differentiation of neuroblastoma. Recall that the retinoic acid pathway plays a critical role in cellular differentiation during embryogenesis. The second is focused on tumors harboring activating *ALK* mutations because they are potentially susceptible to targeted inhibitors of the encoded kinase, and such agents are currently undergoing evaluation in clinical trials.

Finally, we should mention the current status of screening programs for neuroblastoma. Because the vast majority of neuroblastomas release catecholamines into the circulation, detection of catecholamine metabolites (VMA and HVA) in urine could, in principle, form the basis for screening for asymptomatic tumors in children. However, two large studies in Europe and North America have failed to demonstrate improved mortality rates with population screening, because most tumors detected had favorable biologic characteristics. Therefore, community-based screening programs for neuroblastomas are not currently advocated.

Wilms Tumor

Wilms tumor afflicts approximately 1 in every 10,000 children in the United States, making it the most common primary renal tumor of childhood and the fourth most common pediatric malignancy in the United States. The peak incidence for Wilms tumor is between 2 and 5 years of age, and 95% of tumors occur before the age of 10 years. Approximately 5% to 10% of Wilms tumors involve both kidneys, either simultaneously *(synchronous)* or one after the other *(metachronous).* Bilateral Wilms tumors have a median age of onset approximately 10 months earlier than tumors restricted to one kidney, and these patients are presumed to harbor a germline mutation in one of the Wilms tumor-predisposing genes (see later). The biology of this tumor illustrates several important aspects of childhood neoplasms, such as the relationship between *malformations* and *neoplasia*, the histologic similarities between *organogenesis* and *oncogenesis*, the *two-hit theory* of recessive tumor suppressor genes (Chapter 7), the role of *premalignant lesions*, and perhaps most importantly, the potential for *judicious treatment modalities* to dramatically affect prognosis and outcome. Improvements in the cure rates for Wilms tumor (from as low as 30% a few decades ago, to approximately 90% currently) represent one of the greatest successes of pediatric oncology.

Pathogenesis and Genetics. *The risk of Wilms tumor is increased with at least three recognizable groups of congenital malformations associated with distinct chromosomal loci.* Although Wilms tumors arising in this setting account for no more than 10% of cases, these *syndromic tumors* have provided important insight into the biology of this neoplasm.

- The first group of patients has the *WAGR syndrome*, characterized by *W*ilms tumor, *a*niridia, *g*enital anomalies, and mental *r*etardation. Their lifetime risk of developing Wilms tumor is approximately 33%. Individuals with WAGR syndrome carry constitutional (germline) deletions of 11p13. Studies on these patients led to the identification of the first Wilms tumor-associated gene, *WT1*, and a contiguously deleted autosomal dominant gene for aniridia, *PAX6*, both located on chromosome 11p13. Patients with deletions restricted to *PAX6*, with normal *WT1* function, develop sporadic aniridia, but they are not at increased risk for Wilms tumors. The presence of germline *WT1* deletions in WAGR