

## EDITORIAL



## Neuroblastoma — Linking a Common Allele to a Rare Disease

Brian H. Kushner, M.D., and Nai-Kong V. Cheung, M.D., Ph.D.

Neuroblastoma has a notorious reputation among solid tumors of childhood because of its frequently massive and widespread tumor burden. Yet stage for stage, this embryonal neoplasm of the sympathetic nervous system has become the most curable of the common pediatric solid tumors.<sup>1</sup> More than 90% of patients with localized neuroblastomas, including those with spread to the regional lymph nodes, will survive, often with little or no cytotoxic therapy. Rates of cure of metastatic neuroblastoma exceed 90% among infants (who are usually treated with low-dose chemotherapy) and are approximately 25% among toddlers; in contrast, osteomedullary metastases associated with other pediatric solid tumors confer less than a 5% chance of cure.

The long-held view that many cases of neuroblastoma spontaneously regress or mature into asymptomatic ganglioneuroma was confirmed by the results of urine catecholamine screening programs in infants. The programs yielded 50 to 100% more patients with neuroblastoma (virtually all had low-risk forms of the disease) than in unscreened populations, and these programs did not reduce the incidence of high-risk disease.<sup>2</sup> These findings suggest that control populations will have substantial numbers of silent neuroblastomas, a possible confounding factor in investigating genetic associations.

Numerous recurring aberrations of specific chromosomal regions and genetic loci are distinguishing features of tumor cells in patients who have high-risk neuroblastoma (approximately 50% of all patients with the disease), but they are uncommon in patients with low-risk disease (approximately 30% of patients).<sup>1,3</sup> The presence of these chromosomal abnormalities — including involvement of the *MYCN* proto-oncogene, 1p, 2p,

11q, 14q, or 17q — conveys prognostic insights that aid in risk-based care of the remaining 15 to 20% of patients with neuroblastoma. Despite the radically different chromosomal compositions among clinical subgroups, a model of tumorigenesis has been proposed to encompass all forms of this disease, centered on a common precursor and a common tumor-initiating mutation.<sup>3</sup>

The search for an inborn susceptibility to neuroblastoma was spurred by Knudsen's hypothesis that biallelic mutations inactivate a tumor-suppressor gene. This two-hit model was validated in retinoblastoma, with an abnormal constitutional karyotype leading to the discovery of the *RBI* tumor-suppressor gene.<sup>4</sup> However, studies aimed at documenting a similar scenario for neuroblastoma have proved inconclusive. Thus, the somatic genetic aberrations with confirmed or suspected relevance to prognosis are distinctly rare in constitutional karyotypes of patients with neuroblastoma,<sup>5</sup> including the few who have relatives with neuroblastoma (familial cases)<sup>6,7</sup> or a genetic disorder of neural-crest origin (e.g., Hirschsprung's disease, neurofibromatosis type 1, or congenital central hypoventilation syndrome).<sup>8-10</sup> Conversely, the constitutional genetic defects of those neurocristopathies are uncommon in other cases of neuroblastoma, whether familial or sporadic.<sup>9,10</sup> Data from studies of familial neuroblastoma underscore the complexity of genetic predisposition in neuroblastoma: different inherited tumor-initiating chromosomal regions (e.g., 2p, 4p, 12p, and 16p) are implicated in different pedigrees (interfamily variance),<sup>6,7,9</sup> and patients in the same pedigree have widely disparate clinical and biologic findings (intrafamily variance).<sup>8</sup>

These discordant observations point to multi-

ple tumor-predisposing genes, variable penetrance or tumorigenic potency of different mutations affecting those genes, and phenotypic effects of acquired somatic mutations or epigenetic modifications. The sole large genetic epidemiologic study of neuroblastoma revealed a family history in 1.2% of the patients, and it suggested predisposing genetic factors that are dominantly inherited with low penetrance.<sup>11</sup>

In this issue of the *Journal*, Maris et al.<sup>12</sup> report on a study that is noteworthy for several reasons. First, it implicates three closely linked single-nucleotide polymorphisms (SNPs) at chromosome band 6p22 in the initiation of neuroblastoma. This genomewide assessment of 464,934 SNPs, which constitute the most common forms of genetic variation, did not implicate any candidate genes from past reports. The results, however, may in part reflect the choice of study groups and statistical threshold. Second, the study involved sizable cohorts of patients (a total of 1752 patients) with a representative distribution of clinical and biologic characteristics. The size of this study is impressive given the rarity of neuroblastoma; there are 700 cases per year in the United States.<sup>3</sup> The large control populations (the total number of control subjects was 4171) and the matching of cases and controls for ancestral origin lend credence to the study's results. Third, the study highlights the technological advances that allow rapid genomewide analyses of large collections of samples. Recent reports on candidate-locus or genomewide studies have, with the exception of a few small studies of kindreds, concerned tumor tissue.<sup>13</sup> In contrast, the current article presents data derived from the use of a high-resolution SNP platform for investigating the constitutional chromosomal content in a very large cohort of patients with nonfamilial neuroblastoma, with no guiding hypothesis.

There are challenges in trying to establish a meaningful association between common alleles of weak effect and complex diseases.<sup>14</sup> The homozygosity of at-risk chromosome 6p22 alleles is highly prevalent, occurring in 18 to 20% of controls, as compared with 21 to 41% of patients. The odds ratios are in the 1.5 to 2.2 range; these are of uncertain clinical use.<sup>14,15</sup> In addition, neuroblastoma is found in only 1 of 100,000 children younger than 15 years of age (0.001%).<sup>1</sup> The absolute risk conferred by the susceptibility

allele is extremely small. Moreover, the risk that neuroblastoma may recur in families is estimated to be very low (0.004 to 1%).<sup>11</sup>

The rarity of neuroblastoma, its variable natural history, the adverse clinical sequelae in past urinary screening programs,<sup>2</sup> and the high prevalence but low penetrance of neuroblastoma-associated chromosome 6p22 variants clearly rule out any value at present for genetic screening. The low absolute risk should be reassuring to the parents of a child carrying a variant. Testing of the chromosome 6p22 status of siblings and unborn babies should be discouraged. The undesired consequences of presymptomatic testing for a hereditary risk of cancer are raising alarm.<sup>14</sup>

Although the chromosome 6p22 status has little clinical use for preventive measures, it may have a role in prognostication. Variants on chromosome 6p22 were linked to clinically aggressive forms of neuroblastoma and the powerful adverse biologic prognostic marker, *MYCN* amplification. A significant association was found for homozygosity for the at-risk alleles and the decreased probability of event-free survival, but overall survival might be a more meaningful end point, since patients without high-risk neuroblastoma often have disease progressions that are minor (occurring during observation follow-up) and curable. Also, a multivariate analysis is warranted in assessing outlook.

Validation of the results could be accomplished by an assay of samples from patients in ethnic groups that were not included in this study, but limited numbers of patients may preclude extensive replicative efforts. Laboratory research may therefore be crucial for helping to integrate the chromosome 6p22 variants into the clinical and biologic phenomena that characterize this enigmatic disease.<sup>3</sup> Learning about the functions of the new candidate predisposing genes, *FLJ22536* and *FLJ44180* (the genes associated with the implicated SNPs at 6p22), and how they may influence susceptibility is an exciting prospect.

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From the Department of Pediatrics, Memorial Sloan-Kettering Cancer Center, New York.

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