Neuroblastoma: biology and molecular and chromosomal pathology

Manfred Schwab, Frank Westermann, Barbara Hero, and Frank Berthold

Neuroblastoma is the most frequently occurring solid tumour in children, with an incidence of 1·3 cases per 100 000 children aged 0–14 years. Despite many advances during the past three decades, neuroblastoma has remained an enigmatic challenge to clinical and basic scientists. 20 years ago, the MYCN gene was found to be amplified in neuroblastomas, and research since then has focused on the search for other genetic markers. It has emerged that neuroblastoma cells, like cells of many other tumour types, often suffer from extensive, non-random genetic damage at multiple genetic loci. Elucidation of the exact molecular make-up of neuroblastomas will enable researchers to analyse how much specific markers, alone or in combination, can help to stratify disease in prospective studies; at present, stratification is based on age, stage, MYCN, and Shimada pathology. Neuroblastoma may be one of the first examples of the use of genetic tumour markers as a tool for defining tumour behaviour and to aid clinical staging.


Neuroblastoma is a malignant tumour consisting of undifferentiated neuroectodermal cells derived from the neural crest. As is characteristic of embryonic tumours, neuroblasts are histologically indistinguishable from developing neuroblastic cells in the embryo. Neuroblastoma is the most common malignant disease in children with 7·5 cases for every 100 000 infants. Furthermore, there are 1·3 new cases per 100 000 children under the age of 15 years every year, which accounts for 9·0% of all childhood cancers. 90% of children with the disease are diagnosed in the first 5 years of life.

Clinical features of neuroblastoma: regression, maturation, progression

Neuroblastoma has diverse clinical features because of its variable sites of origin, a propensity to metastasise to many distant sites, secretion of hormones, and manifestation as a paraneoplastic syndrome. The most common symptoms are pain (frequency of occurrence 34%), fever (28%), and weight loss (21%); symptoms depend on tumour mass and the extent of metastases. Some neuroblastomas, mainly those of lower stage, are asymptomatic and are detected incidentally. However, there are some rare but characteristic symptoms which are highly indicative of neuroblastoma:

- lower limb paresis due to intraspinal epidural extension of a primary paraspinal tumour (4%)
- severe diarrhoea refractory to standard treatment due to production of vasoactive intestinal peptide (VIP) by tumour cells (4%)

Correspondence: Prof Manfred Schwab, Director Division of Tumour Genetics, German Cancer Research Centre, Heidelberg, Germany. BH is a postdoctoral fellow and FB is Professor of Clinical Oncology at the University of Köln Children’s Hospital, Köln, Germany.

Figures:

Figure 1. Spontaneous neuroblastoma regression. (a) Abdominal neuroblastoma stage 3 (red arrows) of a 3-month-old infant at diagnosis. (b) Almost complete regression of the tumour (red arrows) at 13 months without any cytoreductive therapy. Regular right adrenal (green arrows).
• acute cerebellar encephalopathy characterised by cerebellar ataxia, rapid and random eye movements (opsoclonus), and myoclonic jerks due to unknown metabolic disturbances (2.8%).
• Horner syndrome, often present in patients with lesions in the cervical or upper thoracic sympathetic ganglia (1.7%).
• Hypertension, flushing, and periods of excessive sweating occasionally caused by increased concentrations of catecholamines (0-2%).

Neuroblastoma is often described as enigmatic and unpredictable because it is associated with contrasting patterns of clinical behaviour: life-threatening progression, maturation to ganglio-neuroblastoma or ganglioneuroma, and spontaneous regression. The differences are not apparent with microscopic investigation but clinically, “age” and “stage” enable physicians to predict, to some extent, the biological course of the disease. 55% of neuroblastomas in patients older than 1 year (40% in patients of all ages) present at diagnosis with metastatic disease and are usually associated with poor survival despite intensive therapy. Therapeutic improvements have been achieved in the past decade but treatment remains unsatisfactory.

However, a significant proportion of tumours (>10%) undergo complete spontaneous regression in the absence of or with minimum therapeutic intervention. The incidence of spontaneous regression in neuroblastoma is between 10 and 100 times greater than that for any other human cancer. The most striking phenomenon of spontaneous regression is when primary neuroblastoma and metastatic disease disappear without any treatment. This situation is generally associated with a clinically recognisable syndrome called 4s, defined as a small primary tumour in the abdomen or thoracic cavity accompanied with metastasis in the liver or bone marrow and skin (or both) but not in the cortical bone. Although spontaneous regression is most commonly observed in patients with stage 4s disease, it is well described in stage 1–3 neuroblastoma in children and older patients (figures 1a and 1b). Extensive screening studies in Europe, Japan, and North America suggest that the incidence of neuroblastoma detected in a screened population is increased roughly two-fold over that seen in unscreened populations, i.e., there is overdiagnosis. Therefore, children with clinically detectable low-stage disease who have a good prognosis are a small proportion of the number of children in whom neuroblastoma cells undergo apoptosis or maturation and do not show clinical signs.

Spontaneous maturation to benign ganglioneuroma is much less frequent than spontaneous regression. A systematic evaluation of the frequency of ganglioneuroma has been hampered by the lack of reporting of these benign tumours in the worldwide tumour registries. The maturation observed after treatment with chemotherapy is usually distinct but incomplete.

Screening studies have attempted to identify patients with neuroblastoma earlier in the course of their disease, with the assumption that advanced disease develops from localised disease over time. Although screening programmes detected a substantial number of patients with low-stage disease, the incidence of high-stage neuroblastoma in patients over the age of 1 year has not decreased accordingly. Therefore, it is unclear whether a significant proportion of advanced stage tumours develop from early infancy, or whether there is a subgroup of rapidly evolving metastatic disease in toddlers (1–5 years). Transition from one type to the other seems to occur rarely, if at all. However, from the clinical perspective, a better prediction of tumour behaviour at diagnosis will help to avoid overtreatment of spontaneously regressing tumours and treatment failure in high-risk patients. Currently, prognostic evaluation is based primarily on the extent of tumour spread at diagnosis and age of the patient. This classification overestimates the number of patients who need chemotherapy, because it cannot define patients with stage 1–3 tumours that are regressing.

The Shimada pathology classification has been proven to be independently prognostic in multivariate analyses. More recently, several biological markers have been incorporated to describe therapeutic risk groups. Molecular classification by detection of amplified MYCN and deletion of 1p chromosomal material underestimates the proportion of high-risk patients because only about 30% of the children with high-risk stage 4 disease have amplified MYCN and 47% have 1p alteration (table 1). Tumour histology assessments of ganglionic differentiation and the extent of Schwannian stroma have been widely used but this method is not universally accepted to be of prognostic value. The diverse biological behaviour, which is

**Table 1. Incidence of genetic abnormalities as assessed by FISH analyses in 182 patients with neuroblastoma**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Good prognosis</th>
<th>Poor prognosis</th>
<th>All (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1p36 deletion</td>
<td>11</td>
<td>5</td>
<td>32</td>
</tr>
<tr>
<td>1p36 imbalance</td>
<td>15</td>
<td>20</td>
<td>9</td>
</tr>
<tr>
<td>MYCN amplification</td>
<td>9</td>
<td>33</td>
<td>19</td>
</tr>
<tr>
<td>3p26 deletion</td>
<td>6</td>
<td>2</td>
<td>29</td>
</tr>
<tr>
<td>3p26 imbalance</td>
<td>7</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>11q23 deletion</td>
<td>7</td>
<td>7</td>
<td>36</td>
</tr>
<tr>
<td>11q23 imbalance</td>
<td>12</td>
<td>20</td>
<td>9</td>
</tr>
<tr>
<td>17p13-q23 gain</td>
<td>53</td>
<td>71</td>
<td>62</td>
</tr>
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FISH, fluorescence in-situ hybridisation.
often associated with particular genetic damage, makes neuroblastoma a paradigm for the clinical importance of genetic alterations. However, treatment failure occurs in all patient subgroups, which suggests that additional prognostic markers must be uncovered to further refine treatment decisions. In addition, studies of sites of genetic alterations will provide insights into mechanisms of malignant transformation and progression. These studies also have the potential to uncover the molecular mechanisms of spontaneous regression and differentiation in neuroblastoma.

**Changes in gene dosage**

Increases in gene dosage in neuroblastoma generally occur in three different forms: oncogene amplification resulting in several hundred gene copies, duplication and low-level gain leading to a moderate genetic imbalance; and chromosome segmental gain resulting in a three to six-fold dosage increase of the region involved.

**Amplification**

Gene amplification refers to a localised genomic change that results in an increased dosage of the gene or genes affected. Amplification is one of the major molecular pathways through which oncogenic potential of proto-oncogenes is activated during tumourigenesis. Amplified MYCN in neuroblastomas is typical of the significance of proto-oncogene amplification. Cytogenetically, the amplified status is often highlighted by the presence of conspicuous chromosomal abnormalities, either homogeneously staining regions (figure 2) or double minutes. Double minutes represent extrachromosomal manifestations and homogeneously staining regions are generally located on different chromosomes and not at the resident site (2p24) of MYCN. Amplification values in neuroblastomas may range from 10 to more than 500-fold but values of around 50 to 100-fold are generally seen in tumours. The complexity of amplified DNA encompassing MYCN can range from 100 kb to more than 1 Mb. A core 100 to 200 kb domain encompassing MYCN has been found consistently without rearrangements. In most homogeneously staining regions, DNA segments of unit size length that are several hundred kilobases—and not noticeably rearranged any differently from normal genomic organisation—are present in an ordered direct repeat head-to-tail tandem arrangement.

The size of the DNA surrounding MYCN raises the possibility that additional genes may be coamplified. Several technological strategies have been used to identify coamplified genes but MYCN has emerged as the only consistently amplified gene. However, in about 50% of MYCN-positive tumours (retinoblastomas and neuroblastomas) the DDX1 gene, which maps within 400 kb 5’ of MYCN has been found to be coamplified. There is no instance in which DDX1 has been found to be the only amplified gene. A gene referred to as neuroblastoma amplified gene (NAG) has also been found to be coamplified. It is quite possible that additional genes may
be found to be coamplified. The extent to which the coamplified genes might contribute to the maintenance of the amplified DNA or to neuroblastoma phenotype is a matter for debate.

DNA sequence analyses have not revealed mutations in the MYCN coding sequence. Amplification leads to increased expression of a wild-type protein that contributes to tumourigenesis; this theory is supported by the fact that wild-type MYCN has transforming activity in rodent and human experimental cell systems. Circumstantial evidence suggests that all copies of the amplified gene are transcriptionally active, which would explain the high level of MYCN mRNA in cells carrying amplified MYCN. The translation of this mRNA generates large amounts of a 64 kDa nuclear phosphoprotein, which is capable of forming a transcription complex in vivo by associating with several other nuclear proteins. Experimental approaches have not shown a functional difference between MYCN and MYC proteins. However, neuroblastomas only contain amplified MYCN, not MYC, and it is possible that MYCN has an unidentified role in neuronal cells. Most established neuroblastoma cell lines have amplified MYCN. The proportion of tumours with amplified MYCN is about 20–30%, with variations between different studies.

Amplification of oncogenes has been widely observed in many different types of human cancers. The architecture of amplified DNA can assume two different structures, presumably resulting from two different molecular amplification pathways. First, amplification can occur intrachromosomally, in which case it resides at the chromosomal site of the single-copy genes involved. This arrangement is exemplified by amplified 11q–13 DNA, which usually has a genomic complexity of several megabase-pairs. There is strong evidence that this type of in-situ amplification of very large DNA regions could be initiated by activation of a fragile site. Fusion of sister chromatids due to DNA repair at breakage sites could result in dicentric chromosomes, and breakage of the dicentric chromosomes during anaphase could then lead to inverted amplified structures and deletion in the daughter cells (breakage-fusion-bridge cycle; figure 3a). Additional breakage-fusion-bridge cycles will eventually result in amplification structures. The hallmark of this molecular pathway is that it occurs intrachromosomally at the resident site of the amplified DNA, and the resulting amplification structures show an inverted arrangement (figure 3b).

Second, the DNA can be amplified in a chromosomal region distant from the resident site of the single-copy gene. This arrangement seems to be consistently assumed by amplified MYCN in neuroblastoma cells. The DNA coamplified around MYCN is fairly short (several hundred kilobases) and is generally continuous. Repair replication, either at a fragile site or at any other DNA sequence, could initiate the amplification process and could result in the duplication of a DNA region around MYCN; such duplications have been observed. The duplicated copy could be excised, persist, and multiply extrachromosomally in double minutes, which are the prominent arrangement of amplified MYCN in neuroblastoma tumours, in contrast to the homogeneously staining regions in cell lines. Integration of the DNA into any chromosomal locus could destabilise this region and result in intrachromosomal amplification. The hallmark of this pathway is that homogeneously staining regions are always located in chromosomal amplification. The proportion of tumours with amplified MYCN is about 20–30%, with variations between different studies.

Figure 3a. Additional breakage-fusion-bridge cycles will eventually result in amplification structures. The hallmark of this molecular pathway is that it occurs intrachromosomally at the resident site of the amplified DNA, and the resulting amplification structures show an inverted arrangement (figure 3b).

Figure 4. Stage-related overall survival by MYCN amplification in 1706 patients with neuroblastoma. (a) Stage 1–3 disease. (b) Stage 4s disease. (c) Stage 4 disease. *p=0.01 for all curves.

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The amplified version of the MDM2 gene has been detected in neuroblastoma cells in isolated settings. In all these cases, the cells also harboured amplified MYCN. MDM2 maps to 12q14, so the two genes are non-syntenic and therefore are not coamplified. Rather, the amplified status results from two independent amplification events. It is not clear if the proteins encoded by MYCN and MDM2 cooperate in determining the neuroblastoma cell phenotype.

Amplified MYCN (from 5 to more than 100 copies) is a major prognostic factor in localised neuroblastoma and is also included in the International Neuroblastoma Staging System (INSS). In localised neuroblastomas and in stage 4s disease, 8–10% of patients present with MYCN amplified tumours (table 1). In patients with stage 4 disease, a third have amplified MYCN, although prognostically this marker seems to be less important in stage 4 neuroblastomas. Large and very rapidly growing tumours respond well to chemotherapy initially, but recur early because of the emergence of treatment resistance. The survival prognosis of these patients is worse than for those who don’t have amplified MYCN. The statistical difference is striking in patients who otherwise have good prognoses (stages 1, 2, 3, and 4s). In some studies, a significant difference has also been found in children with stage 4 tumours with a poor prognosis. A conservative estimate is that the region of 17q segmental chromosome gain results in the increased dosage of genes that could confer a growth advantage to the tumour cells. More recent studies have confirmed the 17q gain as a common chromosomal change in primary neuroblastoma tumours, and it has been noted that the breakpoint position on 17q is associated with determining the tumour phenotype. Therefore, the analysis of total DNA, for instance by Southern blotting or comparative genomic hybridisation, can only determine the molecular basis of low-level MYCN copy gain. As yet, low-copy MYCN gain has not been rigorously analysed for association with survival.

Segmental chromosome gain

Cytogenetic studies of neuroblastoma cells have shown that translocation involving 1p and 17q is a recurrent genomic change. A high proportion of tumours with this translocation (up to 70%) were found to be trisomic or hexasomic for 17q21→ter, and it has been postulated that this segmental genomic gain results in the increased dosage of genes that could confer a growth advantage to the tumour cells. More recent studies have confirmed the 17q gain as a common chromosomal change in primary neuroblastoma tumours, and it has been noted that the breakpoint position on 17q is associated with determining the tumour phenotype. A conservative estimate is that the region of 17q segmental gain spans around 20 Mb, which could translate to more than 200 genes. Therefore, it will be difficult to identify individual genes involved in determining neuroblastoma phenotype and to validate specific gene sequences, which may be suitable as predictive probes. Independent studies have identified 17q gain as an indicator of poor prognosis. Furthermore, it has been postulated that 17q gain is associated with worse prognosis even within one disease stage. The main challenge at present is to identify an informative and reliable technology to analyse the prognostic usefulness of 17q gain in large prospective multivariate clinical studies. As with many other molecular markers, problems of tumour heterogeneity and the presence of normal stroma hinder the detection of low-level molecular and chromosomal markers in tumour tissue. Modern array-based methods need to be tested to assess whether these types of analyses are a useful alternative. However, it is important to remember that although such technologies are very useful for large-scale simultaneous determination of many markers they also encounter problems in identifying molecular markers from...
Loss of genetic material

Allelic deletions have been detected at multiple genetic loci in 1p, 2q, 3p, 4p, 9p, 11q, 14q, 16p, and 19q. The molecular characterisation of these allelic deletions by use of loss-of-heterozygosity studies has led to the identification of involved regions often spanning several megabase pairs. However, the postulated “neuroblastoma suppressor genes” have remained elusive in all settings. Allelic deletions in neuroblastoma are commonly loss of heterozygosity of different regions of 1p. The strategy for identifying a small overlapping 1p deletion common to all neuroblastomas has been to determine the extent of deleted genomic material by analysing the status of highly polymorphic microsatellite loci. The most successful approach has been the use of polymerase chain reaction to identify allelic retention or loss, which results in the construction of consensus deletion regions that vary in size among different studies. A combined overlapping consensus region has been derived from these studies and although this common consensus region is sufficiently small to be useful for gene identification, it remains unclear if it encompasses the neuroblastoma suppressor gene or if it is simply an artificial construct with borders defined by data from a single tumour.

The main concern surrounding this data is that a closer inspection of a larger panel of densely spaced microsatellite loci in primary tumours clearly identifies regions of loss of heterozygosity of non-overlapping diversity in 1p36—ie, with occasionally different non-contiguous deletions in the individual tumour (unpublished data). This diversity makes the existence of a single and general “neuroblastoma suppressor gene” in 1p unlikely and raises concerns about the molecular definition of 1p-deletion. Consequently, it is unclear how molecular probes can be developed that would faithfully identify 1p-deletion.

The search for the neuroblastoma suppressor gene is based on the “two-hit” hypothesis of genetic damage of two alleles, for which retinoblastoma is prototypic. The theory states that the two alleles of the suspected neuroblastoma suppressor must be damaged for the tumour phenotype to develop. The first hit is thought to be a deletion of DNA encompassing the target gene and it has been suggested that the remaining normal allele to be damaged by a mutational or epigenetic silencing event. Extremely laborious gene identification studies of different regions of loss of heterozygosity followed by gene mutation analyses have so far failed to uncover any consistent mutation pattern. There are several explanations that could account for this failure. There could be genetic heterogeneity for particular loss-of-heterozygosity regions within neuroblastoma subtypes, and the strategy of analysing the genes of a consensus region deduced from a large number of tumours could be a major reason for failure. A hypothetical scenario could be that neuroblastomas of one biological or clinical group (group I) depend on the inactivation of one particular gene in 1p36 and neuroblastomas of another group (group II) depend on the inactivation of another gene, also in 1p36 but perhaps several megabases away from the group I gene. If loss-of-heterozygosity data are combined from these two groups, a smallest region of overlapping (SRO) deletions will be derived that is extremely unlikely to harbour the second damaged allele (figure 6a). If this hypothesis is correct there would actually be two SROs each harbouring a different gene that is damaged only in tumours of the corresponding group (figures 6b and 6c). Some studies have postulated the existence of two, or even more neuroblastoma genes in 1p. The existence of two separate 1p regions that are associated with neuroblastoma is supported by a study that identified one region at 1p36 and one at 1p22. Moreover, Hiyama and colleagues reported three regions at 1p36.1-2, 1p36.3, and 1p32-34, each associated with different subgroups of neuroblastoma. Similarly, the existence of two deleted regions has also been postulated for 9p21. Another possibility

![Image](image_url)
is that the two-hit hypothesis may not apply to neuroblastoma. Instead, haploinsufficiency resulting from the change in gene dosage because of the loss of one allele of a particular gene, or a group of genes, alone or in combination with other allelic losses could contribute to neuroblastoma development. There is increasing evidence that slight gene-dosage changes, such as segmental duplications, can contribute to human malignant and non-malignant disorders. 30,31 In neuroblastoma, genetic imbalance of 1p36 (at least two copies of chromosome 1 present with additional copies with 1p36 deletions) is associated with a poor prognosis similar to that for patients with 1p deletion or with amplified MYCN. 32 These considerations are not restricted to 1p36 and may also apply to other genetic loci where deletions have been interpreted as being indicative for the loss of a tumour suppressor gene.

Several large studies have found that 1p deletion is associated with poor prognosis. 33,34,35 However, Rubie and colleagues found that 1p analysis was reliable only in about 30% of patients, 36 and its effect on survival should be assessed further in larger prospective studies.

Deletion of genetic material from 3p26 is non-randomly associated with deletion of 11q23. 37 Although both alterations are more frequently detected in metastatic neuroblastoma (stage 4), they do not show additional prognostic influence in this group. By contrast, deletions in one or both loci reliably predict poor prognosis in patients with otherwise good prognosis neuroblastoma (stage 1–3; figure 7). 38,39 The deletion 3p26/11q23 only overlaps to a small extent with 1p deletion/amplified MYCN. 40,41 This stratification of neuroblastoma phenotypes, which show different clinical qualities, on the basis of a group of molecular markers follows a general trend. For example, three non-overlapping neuroblastoma types with distinct genetic and morphological features have been categorised as type 1 (without 17q gain, 1p deletion, and amplified MYCN), type 2 (17q gain only or combined 17q gain and 1p deletion), and type 3 (17q gain, 1p deletion, and amplification of MYCN). 42,43 Although these definitions indicate that particular combinations of genetic changes contribute to different neuroblastoma phenotypes, the informative value of defining groups of molecular parameters in clinical practice needs to be established.

Neurotrophin receptors

Neuroblastomas originate from neural crest precursor cells that are committed to differentiate into cells that make up sympathetic ganglia or the adrenal medulla. The high incidence of spontaneous regression and differentiation of favourable neuroblastomas resembles the physiological coincidence of neuronal differentiation and massive cellular suicide (apoptosis) during normal fetal and postnatal development of the nervous system. This similarity indicates that neuroblastoma cells of some tumours may retain the genetic programme of their normal counterparts. Development of sympathoadrenal cell lineage partially depends on complex neurotrophin (nerve growth factor, brain-derived neurotrophic factor, neurotrophin 4/5, and neurotrophin 3) signalling via receptors with tyrosine kinase activity (TRKA, TRKB, and TRKC). 44,45 In normal sympathetic ganglia, most of the mature neurons at the perinatal stage express TRKA at high concentrations. However, it has been reported that switching expression from TRKB or TRKC to TRKA occurs in later embryonic stages. 46 A massive physiological neuronal apoptosis occurs soon after expression of TRKA. This apoptosis is explained by the trophic theory, which states that depletion of nerve growth factor, the preferred ligand for TRKA, makes cells unable to survive. Therefore, the fate of a neuronal progenitor cell during ontogenesis to differentiate into highly specialised neurones or to be removed by an apoptotic process is mediated by a highly balanced expression of neurotrophin receptors and their ligands.

The biology of neuroblastoma seems to be affected by neurotrophic factors that are secreted by tumour cells and by stromal cells from the microenvironment. 47,48 These factors mediate cross talk between cell components within the tumour and regulate proliferation, differentiation, and death of tumour cells. High concentrations of TRKA are expressed in favourable prognosis neuroblastomas, which often show spontaneous regression. 49,50 A limited amount of nerve growth factor may be supplied from stromal cells, which partially regulates differentiation and programmed cell death of neuroblastoma cells in the same way as it does in normal sympathetic neurones. TRKA expression is strongly downregulated in neuroblastomas with aggressive behaviour, which usually have amplified MYCN. By contrast, TRKB is preferentially expressed in aggressive neuroblastomas. 51 These tumours also express the preferred TRKB ligands (brain-derived neurotrophic factor and neurotrophin 4/5), which might represent an autocrine or paracrine loop, thereby providing some survival and growth advantage. TRKC is expressed in favourable neuroblastomas at variable levels but its preferred ligand neurotrophin 3 is almost undetectable in primary neuroblastomas. 52 Some groups have incorporated the expression status of neurotrophin receptors into classification systems characterising clinical and biological subtypes of neuroblastomas. 53 Unfortunately, these classification systems do not explain the substantial number of stage 3 and 4 tumours that express TRKA; have single-copy MYCN and are associated with poor outcome.

Therapeutic improvements have been achieved during the past decade, but they are still far from satisfactory. The potential for predicting disease course and reaction to particular therapeutic regimens by use of molecular parameters may improve this situation in the future. Much is expected from large-scale surveys of gene expression profiles by use of microarray technologies and by SAGE methods, both of which seem promising. 54,55

Search strategy and selection criteria

Data for this review were identified by searches of MEDLINE and PubMed with the search terms “neuroblastoma”, “genetic alterations and neuroblastoma”, and “genetics and neuroblastoma”. Additional publications were identified from references lists of relevant articles. We also searched abstracts from the proceedings of the Advances in Neuroblastoma Research meeting, Paris, France, June 17–19, 2002.
Conclusion

The detection and systematic investigation of molecular changes will improve our understanding of the molecular basis of the histological and biological features of neuroblastoma. At present, about 30% of good-prognosis tumours and 85% of poor-prognosis tumours show at least one of the well known molecular risk factors. This figure is much closer to exact risk estimation than any other estimated clinically. The biology of a tumour seems to be much more predetermed by the individual genetic damage of the tumour cell than by clinical factors like age and stage at diagnosis. Therefore, in the near future, a limited number of important genetic characteristics may be more useful than the current neuroblastoma staging systems.

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Conflict of interest

None declared.

References


