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Genetic Gains and Losses in Neuroblastoma

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Neuroblastoma behaviour is variable and outcome partially depends on genetic factors such as the number of DNA copies at particular sites in the genome. Tumours that lack bad prognostic factors such as *MYCN* amplification or 1p deletion may progress, possible due to presently unknown genetic aberrations. Comparative genomic hybridisation (CGH) summarises DNA copy number abnormalities (CNAs) in a tumour by mapping them to their positions on normal metaphase chromosomes in a single experiment. We analysed 29 tumours from nearly equal proportions of children with stage I, II, III, IV and IV-S disease by CGH. The median and mode were 8 aberrations per tumour (range 0–15). Seven cases solely exhibited CNAs of whole chromosomes, 4 cases solely exhibited CNAs on pieces of chromosomes, 14 cases had both whole and partial CNAs and 4 cases had no CGH evidence of CNAs. There were many more partial CNAs in patients who died than in those remaining free of disease. High level amplifications were detected in 7 specimens: at 2p23 (*MYCN* region) in 5 and at 4q33-35 and 6p11.2-22.1. Two cases had localised gains including 2p23-25. Gains were frequent on chromosomes 17 (72% of cases—the common region was 17q21.3-qter), 7 (55%), 6 (35%), and 18 (31%). Losses were frequent at 14q (41%), X (35%), 11 (31%), and 1p (31%). The results indicate that partial CNAs may reflect serious disease and that 17q aberrations occur commonly in all stages of neuroblastoma and may be an initiating event.

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Targeted Expression of *MYCN* Causes Neuroblastoma in Transgenic Mice

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The ability of *MYCN* to transform neurons and its role in neuroblastoma pathogenesis have never been demonstrated directly. The address this issue, we used the tyrosine hydroxylase promotor to direct expression of *MYCN* to the neuroectoderm of transgenic mice. Several lines of such mice have developed paraspinal or abdominal masses comparable to stage 3 neuroblastoma. Tumour cells demonstrate neuronal characteristics as evidenced by neuronal morphology, neurosecretory granules, neuronal processes, and positive immunostaining for neuron specific markers. Western blotting shows elevated *MYCN* in tumour and adrenal tissue. Tumour incidence is increased significantly in animals homozygous for the *MYCN* transgene, suggesting that tumour development is dependent on *MYCN* gene dosage and mirroring clinical observations that highly amplified *MYCN* correlates with advanced malignancy. Acceleration of tumour latency in this model can be used as a selection to find new genes implicated in neuroblastoma. *MYCN* mice are being crossed to mice deleted for a number of tumour suppressors to determine if tumour formation can be accelerated. Tumour DNA is being analysed for consistent gains and losses of chromosomal regions. Tumours are also being characterised to determine at which stage in sympathetic development they become arrested. These data demonstrate that over-expression of *MYCN* as an early event can transform neurons in transgenic animals. Mice over-expressing *MYCN* represent a model for human neuroblastoma and may be useful in studying therapy for this malignancy.