
**Accumulation of segmental alterations determines progression in neuroblastoma.**


**Summary**

Neuroblastoma is characterized by two distinct types of genetic profiles, consisting of either numerical or segmental chromosome alterations. The latter are associated with a higher risk of relapse, even when occurring together with numerical alterations. We explored the role of segmental alterations in tumor progression and the possibility of evolution from indolent to aggressive genomic types.


**Fusion gene-negative alveolar rhabdomyosarcoma is clinically and molecularly indistinguishable from embryonal rhabdomyosarcoma.**


**Summary**

To determine whether the clinical and molecular biologic characteristics of the alveolar rhabdomyosarcoma (ARMS) and embryonal rhabdomyosarcoma (ERMS) subtypes have relevance independent of the presence or absence of the PAX/FOXO1 fusion gene.

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**Cholinergic switch associated with morphological differentiation in neuroblastoma.**

Summary

The morphology of malignant cells distinguishes between undifferentiated, poorly differentiated and differentiating neuroblastomas and constitutes a strong prognostic factor. Spontaneous or treatment-induced maturation characterizes a subset of neuroblastomas. It constitutes the basis of retinoic acid treatment to improve survival in aggressive neuroblastomas. However, the molecular events that drive differentiation are poorly understood. In the present study we have investigated the relationships between gene expression profiles and differentiation criteria in stroma-poor neuroblastomas. This study included three undifferentiated (UN), 20 poorly differentiated (PDN) and 11 differentiating (DN) neuroblastomas. These groups could be clearly separated using unsupervised clustering methods, which further enabled a major classification impact of genes involved in neural development, differentiation and function to be identified. UNs are characterized by high ASCL1, high PHOX2B, low GATA2, low TH and low DBH expressions. Most PDNs harbour a clear adrenergic phenotype, even in the presence of missense PHOX2B mutations. Finally, all DN tumours demonstrate cholinergic features. Depending upon their association with adrenergic characteristics, this enables dual ‘cholinergic/adrenergic’ and ‘fully cholinergic’ neuroblastomas to be defined. This suggests that the cholinergic switch, a final specification process that occurs physiologically in a minority of sympathetic neurons, is a critical step of differentiation in some neuroblastic tumours. This switch is associated with a down regulation of DBH that is apparently not strictly dependent upon PHOX2B. Conversely, GATA2 and TFAP2B may play critical roles in maintaining adrenergic features in poorly differentiated tumours.

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**Overall genomic pattern is a predictor of outcome in neuroblastoma.**


Summary

For a comprehensive overview of the genetic alterations of neuroblastoma, their association and clinical significance, we conducted a whole-genome DNA copy number analysis.