NTRK gene fusion

A mutation (change) occurs when a piece of the chromosome containing a gene called NTRK breaks off and joins with a gene on another chromosome. NTRK gene fusions lead to abnormal proteins called TRK fusion proteins, which may cause cancer cells to grow. NTRK gene fusions may be found in some types of cancer, including cancers of the brain, head, neck, thyroid, soft tissue, lung, and colon. Also called neurotrophic tyrosine receptor kinase gene fusion.

Ahmed M, De Praeter M, Verlooy J, Schoonjans AS, Dekeyzer S, Vanden Bossche S, Lammens M, Pauwels P. A case report of a novel NTRK gene fusion in pleomorphic xanthoastrocytoma. Clin Neuropathol. 2022 May 16. doi: 10.5414/NP301455. Epub ahead of print. PMID: 35575416.

NTRK gene fusions have been described in a wide variety of central nervous system (CNS) and soft tissue tumors, including the provisional tumor type “spindle cell neoplasm, NTRK-rearranged” (SCN-NTRK), added to the 2020 World Health Organization Classification of Soft Tissue Tumors. Because of histopathological and molecular overlaps with other soft tissue entities, controversy remains concerning the lineage and terminology of SCN-NTRK.

A study included 16 mesenchymal tumors displaying kinase gene fusions (NTRK fusions and one MET fusion) initially diagnosed as infantile fibrosarcomas (IFS), SCN-NTRK, and adult-type fibrosarcomas from the soft tissue, viscera, and CNS. We used immunohistochemistry, DNA methylation profiling, whole RNA sequencing, and ultrastructural analysis to characterize them. Unsupervised t-distributed stochastic neighbor embedding analysis showed that 11 cases (2 CNS tumors and 9 extra-CNS) formed a unique and new methylation cluster, while all tumors but one, initially diagnosed as IFS, clustered in a distinct methylation class. All the tumors except one formed a single cluster within the hierarchical clustering of whole RNA-sequencing data. Tumors from the novel methylation class co-expressed CD34 and S100, had variable histopathological grades, and frequently displayed a CDKN2A deletion. Ultrastructural analyses evidenced a myofibroblastic differentiation.

The findings confirm that SCN-NTRK shares similar features in adults and children and in all locations combine an infiltrative pattern, distinct epigenetic and transcriptomic profiles, and ultrastructural evidence of a myofibroblastic lineage. Further studies may support the use of new terminology to better describe their myofibroblastic nature [1)].

A case of molecularly defined isocitrate dehydrogenase (IDH)-mutant astrocytoma that recurred twice with aggressive behavior and increased anaplastic morphology. Primary and recurrent tumors were analyzed using custom-made DNA-based cancer gene and RNA-based fusion panels for next-generation sequencing (NGS). NGS analyses revealed that recurrent astrocytoma, in addition to IDH1 and tumor protein 53 mutations detected in the primary lesion, harbored cyclin-dependent kinase inhibitor (CDKN) 2 A/B homozygous deletion and neurotrophic tropomyosin receptor kinase 2 (NTRK2) fusion genes that consisted of golgin A1- and cyclin-dependent kinase 5 regulatory subunits associated protein 2-NTRK2 fusions. Anaplasia and necrosis were observed in the recurrent tumors, but not in the primary lesion. Therefore, the integrative diagnosis was primary IDH-mutant

astrocytoma grade 2 and recurrent IDH-mutant astrocytoma grade 4 with NTRK2 fusions. This is a worthwhile report describing a case of IDH-mutant astrocytoma that showed genomic evolution during tumor recurrence. The report suggests that NTRK fusion and CDKN2A/B homozygous deletion promote high-grade transformation and indicate an unfavorable prognosis of IDH-mutant astrocytoma [2]

[1]
Tauziède-Espariat A, Duchesne M, Baud J, Le Quang M, Bochaton D, Azmani R, Croce S, Hostein I, Kesrouani C, Guillemot D, Pierron G, Bourdeaut F, Cardoen L, Hasty L, Lechapt E, Métais A, Chrétien F, Puget S, Varlet P, Le Loarer F. NTRK-rearranged spindle cell neoplasms are ubiquitous tumors of myofibroblastic lineage with a distinct methylation class. Histopathology. 2022 Nov 22. doi: 10.1111/his.14842. Epub ahead of print. PMID: 36413100.

[2]
Kirishima M, Akahane T, Higa N, Suzuki S, Ueno S, Yonezawa H, Uchida H, Hanaya R, Yoshimoto K, Shimajiri S, Kitazono I, Tanimoto A. IDH-mutant astrocytoma with an evolutional progression to CDKN2A/B homozygous deletion and NTRK fusion during recurrence: A case report. Pathol Res Pract. 2022 Nov;239:154163. doi: 10.1016/j.prp.2022.154163. Epub 2022 Oct 15. PMID: 36265224.