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TERT promoter mutation and *HER2* gene amplification in malignant peripheral nerve sheath tumours: is there a molecular signature playing role in malignant transformation?

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There is no conflict of interest.

Introduction

- Peripheral nerve sheath tumors are a group of relatively rare soft tissue neoplasms, which include neurofibromas, schwannomas and malignant peripheral nerve sheath tumors (MPNST).

- MPNSTs are rare neoplasms that constitute about %5 of all malignant tumors of soft tissue.

- Benign and malignant peripheral nerve sheath tumors may occur sporadically or related to neurofibromatosis.

Introduction

- MPNSTs are neural crest originated tumours with agressive behavior and poor prognosis, sometimes related with *NF-1* that is tumor supressor gene.

- The risk of developing MPNST in a patient with *NF-1* gene is up to 10%.

Introduction

- While sporadic neurofibromas are benign, some neurofibromas related with neurofibromatosis are able to transform to MPNSTs.

- Thus, it has been thought that biological behaviour of both neurofibromas may change due to different genetic mutations.

Introduction

- Loss of NF-1 protein function leads to increased RAS signaling.

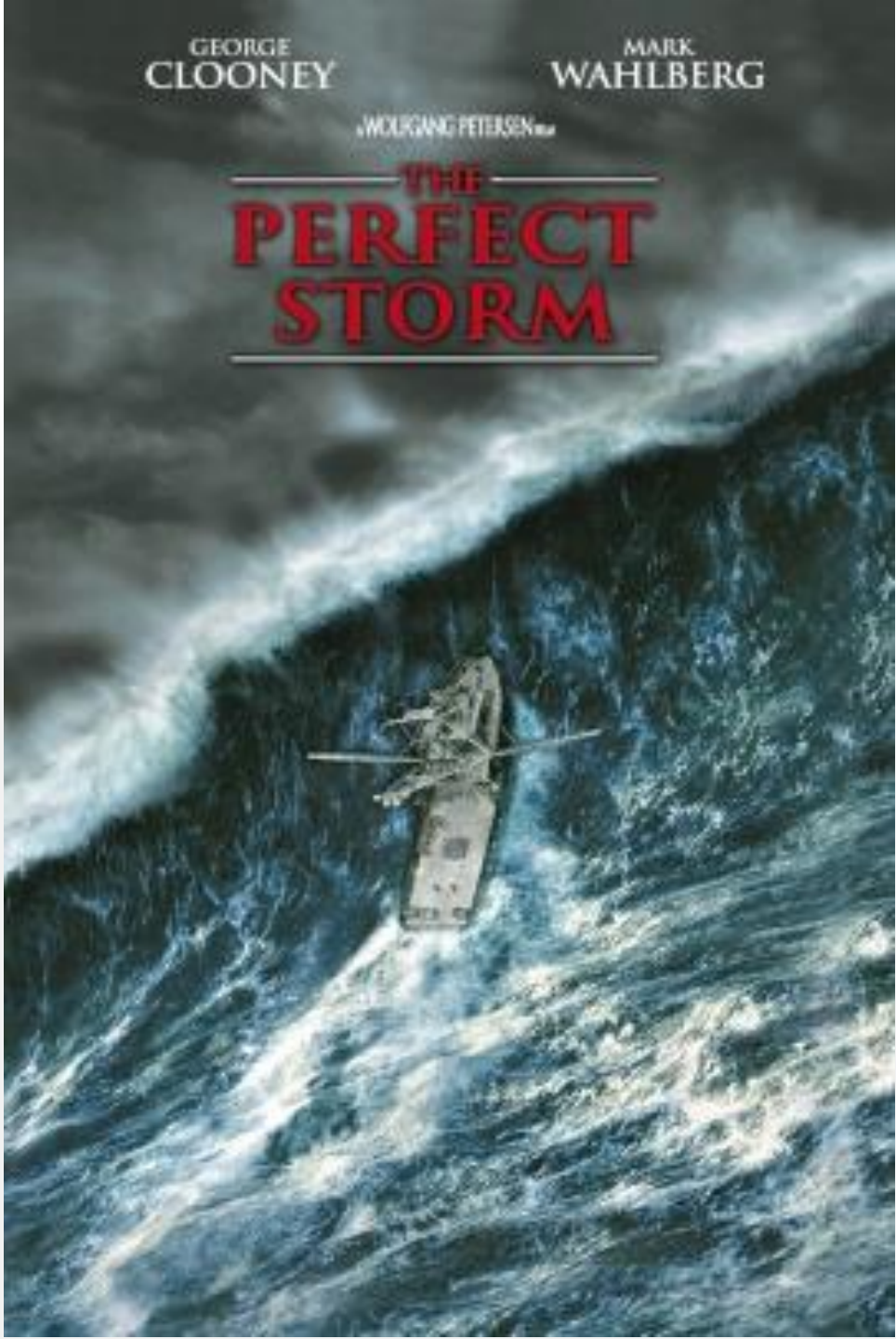
- BRAF kinase molecule is also a downstream RAS effector and its mutations are found in numerous cancers.

Introduction

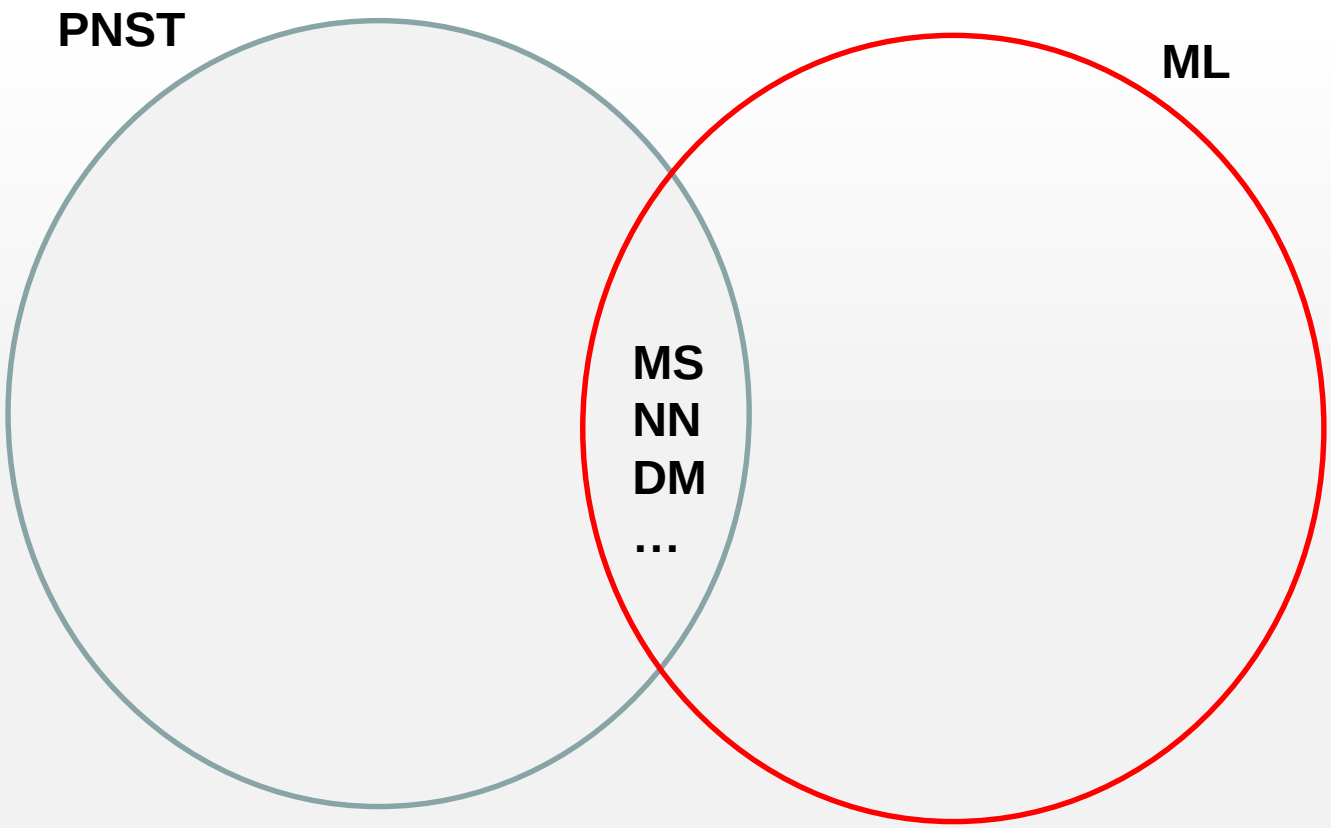
- Tumors of neuroectodermal origin such as gliomas or melanomas frequently compose hot spot mutations in the promoter region of telomerase reverse transcriptase (*TERT*).
- It is suggestive that *TERT* mutation may be one of the key molecules in the pathogenesis of MPNSTs.

BRAF (+) → **Ordinary Melanocytic Nevus** (subject to senesence)

Perfect storm (*BRAF* (+), *TERT* (+), many other genes mutation, amp, methylation, LOH, chromosomal imbalance etc…→ **melanoma**



Introduction



Sometimes, similar morphological and immunohistochemical features can be found between PNSTs and MLs.

Introduction

- Epidermal growth factor receptor (EGFR) tyrosine kinase is a member of the ErbB family receptors.

- The family comprises four receptors: EGFR, HER-2, HER-3 and HER-4.

Introduction

- *EGFR* has been implicated with malign transformation in MPNSTs and its expression is a key targetable oncogenic event.

- It has been suggested that overexpression of EGFR is associated with poor prognosis.

Introduction

- Membranous HER2 immunoexpression and gene amplification shows good correlation in breast tumor.

- Due to evaluation difficulty membranous immunopositivity in soft tissue tumors, we had to prefer CISH.

Introduction

- Unless the mechanisms of tumorigenesis NF related cases are better understood, still remained unclear in sporadic cases.
- Therefore, there is a need to investigate genetic route of tumor in both neurofibromas to open a way for targeted therapies in the future.

Introduction

- The aim of this study is
  - to investigate the frequency of *BRAF, TERT* mutation and *HER2* gene amplification in sporadic neurofibromas, neurofibromas associated with NF and MPNSTs,
  - to detect the role of these mutations in malignant transformation.

Materials and Methods

- A total of 75 patients were included in the study.
  - 25 neurofibromas associated with NF, 25 sporadic ones and 25 MPNSTs were analyzed.
- Mutations in the promoter region of the *TERT* and *BRAF* gene were analyzed by using PCR-based Sanger sequencing.
- *HER2* gene amplification (Dual ISH DNA Probe Cocktail test) and BRAF immunoexpression were also analyzed.

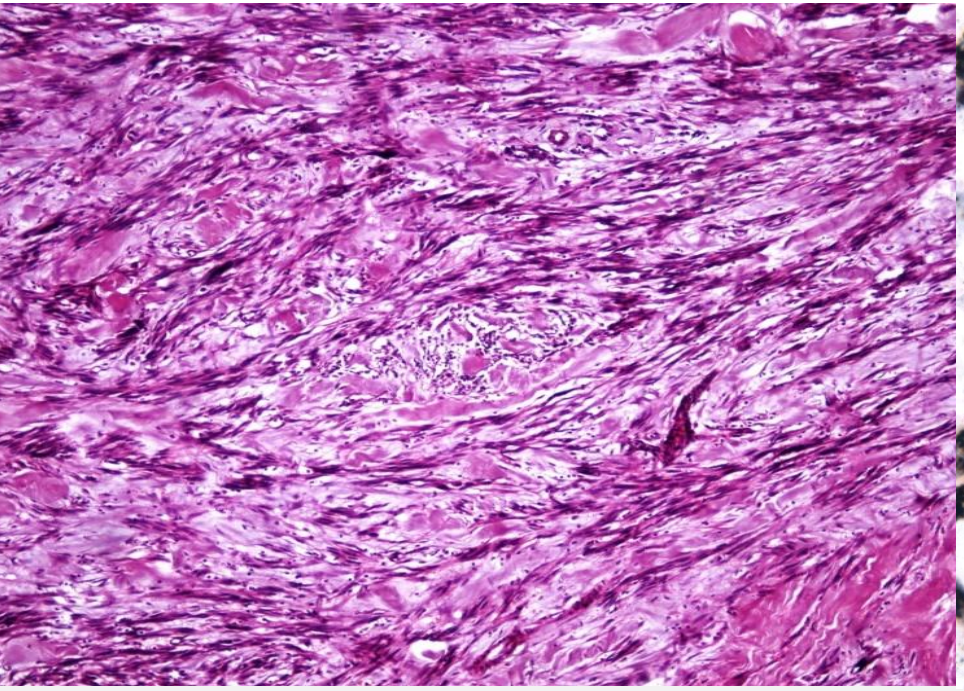
Results

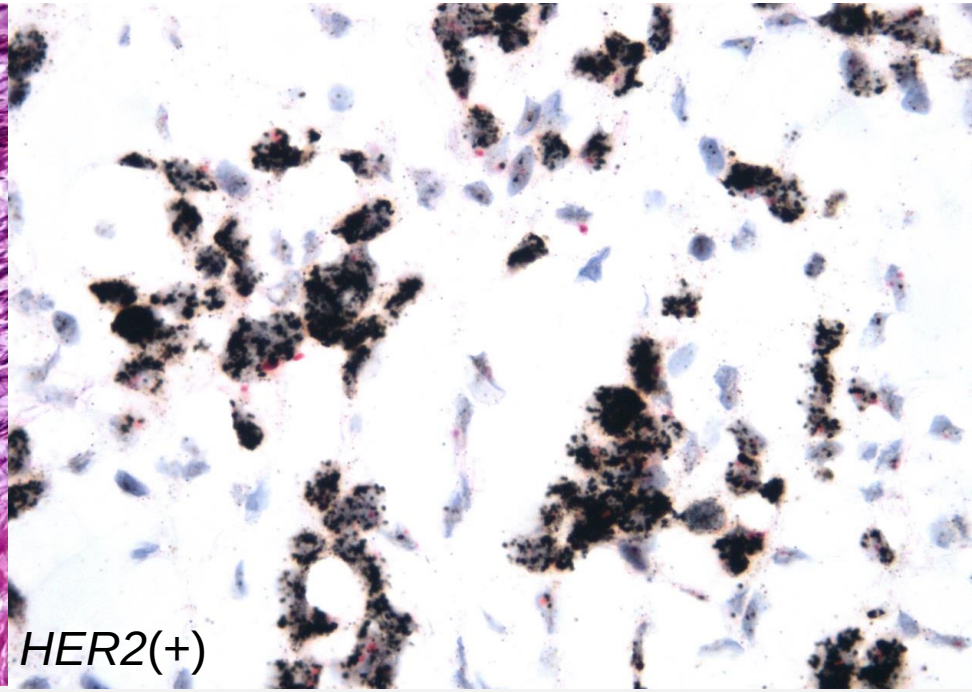
- There were gene amplification of *HER2* in 10/25 (40%) MPNST cases.
- We identified *TERT* promoter mutation only in one sporadic MPNST (4%) and no *BRAF* mutation in any case.
- No mutations or gene amplifications detected in all neurofibromas (sporadic or NF-1 related) compare to MPNSTs ($p<0,001$).

Case MPNST	Age	Gender	Localization	HER2 Amplification	TERT mutation	BRAF mutation	BRAF immunexpression
1	71	F	Sacral region	+	-	-	-
2	55	M	Paravertebral (C6-7)	-	-	-	-
3	38	F	Mediasten	-	-	-	-
4	56	F	Left glutea	-	-	-	-
5	87	M	Left inferior eyelid	+	-	-	-
6	62	F	Paravertebral (C2-6)	-	-	-	-
7	63	M	Right leg	-	-	-	-
8	57	M	Right cruris	+	-	-	-
9	48	F	Right cruris	-	-	-	-
10	53	M	Left foot ankle	-	-		-
11	34	F	Retroperitoneum	+	-	-	-
12	48	F	Left hand	-	-	-	-
13	63	F	Paravertebral (C6-7-T1)	-	-	-	-
14	18	F	Paravertebral (L3-5)	-	-	-	-
15	77	M	Neck	+	+	-	-
16	76	F	Retroperitoneum	-	-	-	-
17	63	F	Abdomen	-	-	-	-
18	81	M	Paravertebral (L4-5-S1)	+	-	-	-
19	36	F	Pleura	-	-	-	-
20	28	F	Right shoulder	+	-	-	-
21	7	F	Paravertebral (T5-7)	-	-	-	-
22	64	M	Right elbow	-	-	-	-
23	63	M	Rectum	+	-	-	-
24	58	M	Left leg	+	-	-	-
25	52	M	Hip	+	-	-	-

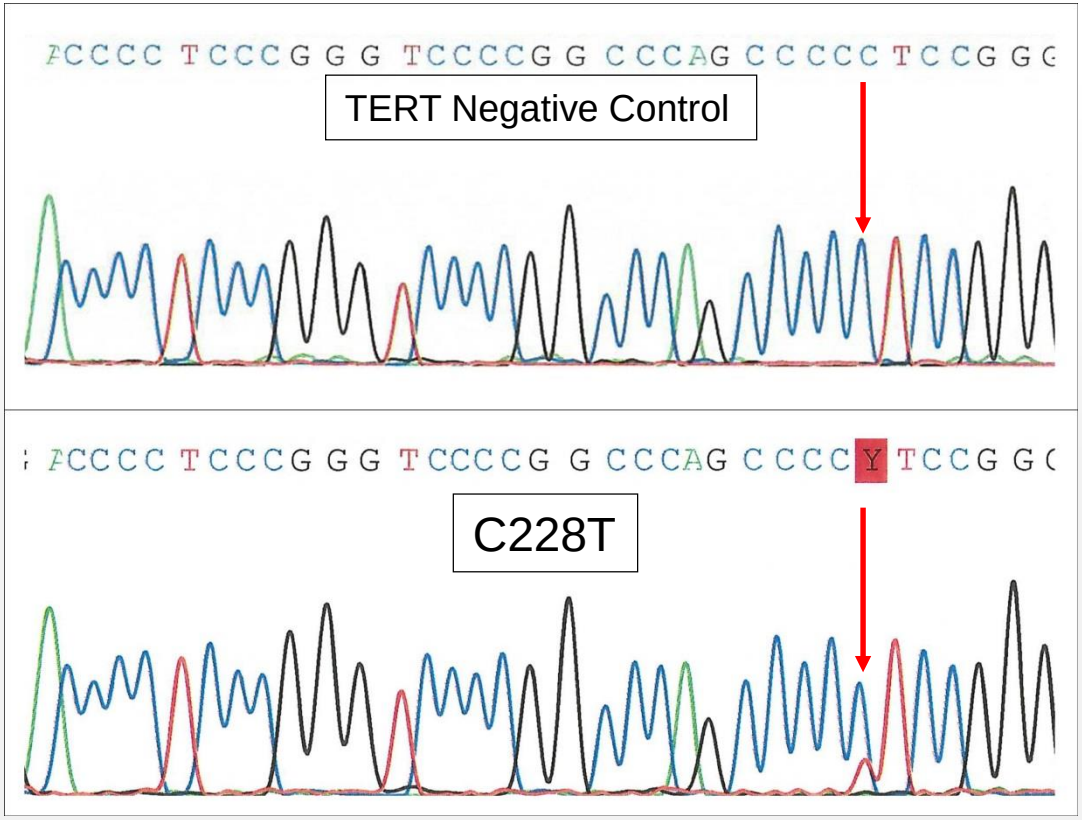
77 year old male patient with *Her2* gene amplification had also *TERT* promoter mutation.

Results





Results



C228T mutation was detected.

Discussion

- Complete surgical excision represents main curative therapy in MPNSTs with adjuvant chemo and radiation therapy.

- Nevertheless, 5-year survival rates are poor; local recurrence and metastasis are common.

Discussion

- These findings indicates an urgent need for improved and targeted therapy options for these patients.

- Pathogenesis of MPNSTs are poorly understood and limited data exists in literature about these tumours' molecular background.

Discussion

- EGFR positivity with immunohistochemical methods with good staining sensitivity in MPNSTs has been demonstrated in numerous reports in the literature.

- However, less study investigate *HER2* gene amplification.

Discussion

- Perry et al. has previously reported *EGFR* amplification in 5 out of 17 patients in MPNSTs.*

- Holtkamp et al. reported increased EGFR dosage in 28% of MPNSTs.**

- *Perry A, Kunz SN, Fuller CE, Banerjee R, Marley EF, Liapis H, Watson MA, Gutmann DH**. Differential NF1, p16, and EGFR patterns by interphase cytogenetics (FISH) in malignant peripheral nerve sheath tumor (MPNST) and morphologically similar spindle cell neoplasms**. J Neuropathol Exp Neurol. 2002 Aug;61(8):702-9
- **Nikola Holtkamp, Elke Malzer, Jan Zietsch, Ali Fuat Okuducu, Jana Mucha, Christian Mawrin, Victor-F. Mautner, Hans-Ulrich Schildhaus, and Andreas von **Deimling EGFR and erbB2 in malignant peripheral nerve sheath tumors and implications for targeted therapy** Neuro Oncol. 2008 Dec; 10(6): 946–957.

Discussion

- We found *HER2* amplification in 10/25 MPNSTs (40%).

- No amplification detected in all neurofibromas (NF-1 associated or sporadic).

Discussion

- *TERT* promoter mutations have been found in many of cancers.
- There are few studies that evaluated *TERT* promoter mutations in MPNSTs.
- *TERT* gene have been demonstrated to be absent in benign tumors and normal subjects, implicating their potentially critical roles in human carcinogenesis.
- In our study, only one sporadic MPNST case possessed *TERT* mutation.

Discussion

- Dubbink et al. reported no *TERT* promoter mutations in 17 samples of benign PNSTs (16 neurofibroma, 1 schwannoma).
- They identified *TERT* promoter mutations in 10% (9/94) of MPNSTs.
- Also no *BRAF* mutations were observed in 12 BPNSTs (11 neurofibroma, 1 schwannoma) and no *BRAF* mutations were observed in 4 successfully tested metastases.

- Dubbink H.J., Bakels H., Post E., Zwarthoff E.C., Verdijk R.M. **TERT promoter mutations and BRAF mutations are rare in sporadic, and TERT promoter mutations are absent in NF-1 related malignant peripheral nerve sheath tumours** J Neurooncol (2014) 120:267-272

Discussion

- We showed similar findings with Dubbink et al. and Serrano et al.
- Serrano et al. found 4 *BRAF* mutations in 40 schwannomas, but no mutations in none of 16 neurofibromas.
- In contrast with our study, Serrano et al. reported one *BRAF V600E* mutation in 13 sporadic MPNSTs.

- Serrano C., Simonetti S., Hernandez-Losa J., Valverde C., Carrato C., Bague S., Orellana R., Somoza R.,Moline T., Carles J., Huguet P., Romagosa C& Ramon y Cajal S. **BRAF V600E and KRAS G12S mutations in peripheral nerve sheath tumours.** Histopathology 2013 Feb;62(3):499-504. doi: 10.1111/his.12021.

Conclusion

- There are very few studies assessing *BRAF* and *TERT* promoter mutations and increasing *HER2* gene dosage in patients with MPNST.
- There is no enough data in literature to determine a molecular signature playing key role in malign transformation for both sporadic and NF-1 related cases.

Conclusion

- The leading key molecule in pathogenesis of MPNSTs still remains unclear.

- Targetable specific therapies still can not be implemented in MPNSTs and there is no preventive therapies to stop malign transformation of neurofibromas.


Thank you for your patience
Topuk plateau, Duzce