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CASE REPORT

PTPRD copy number variants and Ewing's sarcoma: Strengthening the association and therapeutic implications

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Abstract

Ewing sarcoma (ES), a common pediatric primary bone neoplasm, has a well-defined genomic landscape with various predisposing genomic elements including TP53, PMS2 and RET. Additionally, germline and somatic variants in protein tyrosine phosphatase delta (*PTPRD)*, a tumor suppressor gene, have been identified in a limited number of ES patients. Here we present an ES patient, remarkable in terms of his young age and extent at presentation, found to have a *PTPRD* CNV. We explore the pathogenicity of this CNV, describe the patient's clinical course and touch upon the potential therapeutic implications in this subset of patients.

Keywords Ewing sarcoma, PTPRD, Copy number variant, Germline.

Introduction

Ewing sarcoma (ES), accounting for approximately 3% of all pediatric cancers [1], is a primary bone neoplasm presenting with a median age of 14 years [2]. While somatic *STAG2, CDKN2A* and *TP53* variants have been implicated in its pathogenesis, only rarely have deleterious predisposing germline variants been identified [3–6]. Improved understanding of the genetics of ES will hopefully lead to effective treatments with limited toxicity, which to date remain elusive [7].

Protein tyrosine phosphatase delta (*PTPRD)* is a tumor suppressor belonging to the protein tyrosine phosphatase receptors (PTPR) family with (epi)genetic abnormalities found in neuroblastomas, lung, pancreatic and colorectal carcinoma [8–11]. Recently three germline *PTPRD* variants have been implicated in ES patients [12]. Additionally, somatic investigation of ES samples has revealed a deleterious *PTPRD* variant [13].

Here we present a case of a 14 year old male presenting with an extensive ES at the age of eight months found to have a germline intragenic deletion of *PTPRD.*

Case description

At eight months, a previously-healthy boy underwent investigations into an extensive right pelvic mass, diagnosed pathologically as an ES consisting of small round blue cells and spindled cells with evidence of neuronal differentiation and dense core granules by electron microscopy. Muscle staining excluded rhabdomyosarcoma, differentiated neuroectodermal tumor and extraosseous ES. Fluorescent in situ hybridization (FISH) showed no evidence of ES locus rearrangements. After a protracted course with multiple episodes of recurrence, requiring extensive treatments with significant morbidity, the child has been in remission for the last six years (Table 1).

Family history revealed non-consanguineous parents, a maternal aunt with brain cancer at 26 years and a maternal uncle with leukemia at 50 years.

Cytogenetic analysis with array comparative genomic hybridization (aCGH), revealed a 135 kb intragenic deletion

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Table 1 Clinical course and treatment regimen.

	Site	Chemotherapy Regimen	Radiotherapy Regimen	Additional Therapy
Initial presentation (8 months)	Right pelvic primary	Vincristine, Doxorubicin, Cyclophosphamide, Ifosfamide and Etoposide	Local - 4500 cGy	Extensive surgical resection
First recurrence (5.5 years)	Lung metastasis	Cyclophosphamide, Topotecan, Vincristine, and Bevacizumab		Autologous hematopoietic stem cell transplantation
Second recurrence (7.5 years)	Lung recurrence	Vincristine, Irinotecan, and Temozolomide	Whole lung- 1500 gGy	

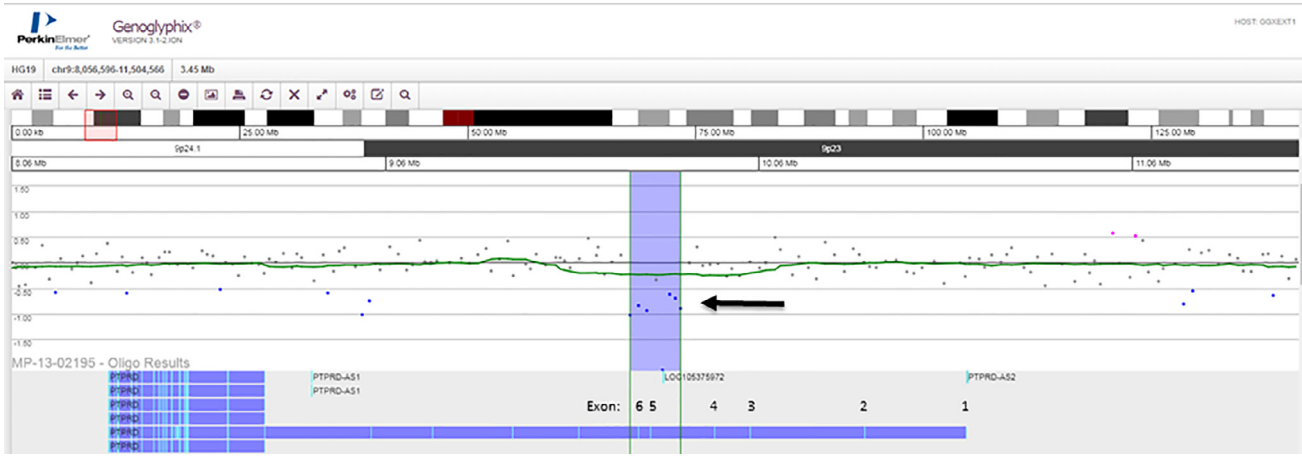

Fig. 1 Read out of aCGH results using Genoglyphix software and Agilent (CGX™-HD 4 × 180 K) CGH microarray platform revealing an intragenic deletion in *PTPRD* highlighted in blue (Arrow). This 8 oligonucleotide deletion (average value of −0,95) includes exon 5 and exon 6 of *PTPRD* (nucleotide 9712,973 - 9848,189 [UCSC 2009 hg19 assembly]). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

in *PTPRD* [arr[GRCh37] 9p23(9,712,973_9,848,189)x1] not found to be inherited from his mother (Fig. 1). Sequencing and deletion/ duplication failed to show any variant in TP53.

Discussion

Here we present a patient developing an ES, remarkable in terms of his young age and extent at presentation, found to harbor a germline copy number variant (CNV) in *PTPRD*. Given the aforementioned reports of germline and somatic studies of ES patient, this CNV, predicted be deleterious due to the complete loss of exons five and six, may have conferred ES susceptibility.

The PTPR family is implicated in tumorigenesis for at least a subset of human cancers. In terms of the association of *PTPRD* with ES, a previous study by Jiang et al. investigating a metastatic ES patient identified a germline deleterious truncating *PTPRD* variant on whole exome sequencing [12]. They further identified two additional germline variants on targeted sequencing of *PTPRD* in seven ES patients. Unfortunately, no function analysis was undertaken and mRNA expression was not measured. However, the presence of these germline variants in association with young onset ES suggests the possibility of a germline ES predisposition. Our case, presenting with an extensive ES at 8 months with an underlying likely deleterious intragenic *PTPRD* CNV further strengthens this association.

PTPRD is an unusual gene in that it has a large 5′ UTR region spliced together from 11 noncoding exons with multiple isoforms [14]. Through somatic investigations of neuroblastomas (NB), previous investigations of *PTPRD* have shown that the loss of 5′ UTR exons occurs in a large proportion of NB cell lines, with corresponding reductions in *PTPRD* mRNA levels, implying an essential function of this 5′ UTR including mRNA stability [15,16].

STAT3 phosphorylation, the downstream effector of IGF1R, is known to be activated in a large proportion of ES directly contributing to the growth of neoplastic cells [17]. Given its regulation by PTPRD mediated dephosphorylation, decreasing levels of PTPRD resulting in increased activation of STAT3 offers a plausible pathophysiologic association.

Importantly, in the paper from Jiang et al. [12], the individual with a truncating *PTPRD* germline variant had a complete response to IGF-1R monoclonal antibody alone. Moreover, one of the two patients with germline missense variants achieved a complete response with a combination of IGF-1R antibody and mTOR inhibitor therapy. Therefore, inhibiting STAT3 activation in this subset of patients may lead to improved outcomes and reduced toxicity and morbidity, as was present in our case.

Given that our case represents the fourth published report of a germline alteration in *PTPRD* in ES patients and is the first case of a documented germline *PTPRD* CNV in a pediatric ES patient, further patient acquisition will be required to conclusively associate these germline variants with a ES

predisposition. However, further investigation is warranted given the therapeutic potential in a disease with few therapeutic options and poor outcomes.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cancergen.2019.01.004.

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