

Germline Platelet-derived growth factor receptor beta p.R987W pathogenic variant in 2 children with brain tumors

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Platelet-Derived Growth Factor Receptor Beta (PDGFRB) is critically implicated in development. Constitutional pathogenic variants (CPVs) in the gene encoding this receptor result in several inherited syndromes, including primary familial brain calcifications (PFBC) or infantile myofibromatosis, but have not been associated with brain tumors. Here, we describe a 9-year-old male with a DCTN1-ALK fused inflammatory myofibroblastic tumor of the brain and an 11-year-old female with a TRIM24-MET fused occipital glioneural tumor. Both probands carry the same constitutive PDGFRB c.2959C>T (p. Arg987Trp) CPV, raising the possibility that this variant, previously described in PFBC, may also promote tumor formation including in the brain.

Platelet-derived growth factor receptors (PDGFR) are a family of receptor tyrosine kinases that exist as alpha and beta isoforms encoded by 2 genes, *PDGFRA* and *PDGFRB*, respectively.¹ Somatic *PDGFRA* gain-of-function (GOF) variants, overexpression, and amplifications are commonly found in gliomas¹ while constitutional GOF variants predispose to gastrointestinal stromal tumors (GISTs) and inflammatory fibroid polyps.² Both somatic and constitutive pathogenic variants (PVs) and CPVs in *PDGFRB* have been described in myofibroma development³ and GOF CPVs were identified in several rare disorders such as infantile myofibromatosis and Kosaki overgrowth syndrome among others,¹ but alterations in this receptor have not been reported in either GISTs or brain tumors. Loss-of-function (LOF) *PDGFRB* CPVs predispose to primary familial brain calcifications (PFBC), a rare autosomal dominant disease, with unknown penetrance.⁴ This includes

a specific constitutive LOF variant, *PDGFRB* c.2959C>T (p. Arg987Trp), hereafter referred to as R987W, which was first identified in a sporadic case of PFBC (ie, no CT scans of family members available to confirm or refute segregation).⁵ Here, we describe 2 children with brain tumors who carry constitutive R987W *PDGFRB* CPV and have no PFBC.

The study was approved by the Quebec Research Ethics Board. Informed consent was obtained for both cases. DNA/RNA were extracted using standard protocols. RNA sequencing (RNAseq) on tumor samples was performed using TruSeq Stranded Total RNA libraries and the Ribo-Zero Gold Kit according to Illumina's protocol. Libraries were sequenced (~70–175 million reads, paired-end 2 × 100 bp) on a Novaseq6000. All fusions and constitutional *PDGFRB* variants were validated in a CLIA-certified laboratory. Sanger sequencing was performed on all samples to validate specifically the *PDGFRB* R987W mutation and resulting chromatograms were visualized using SnapGene software. DNA methylation were performed using the EPIC platform and analyzed using the DKFZ DNA methylation classifier of CNS tumors. The version used is specified for each case.

Case 1: a 9-year-old French-Canadian male was treated in 2016 for a WNT-activated medulloblastoma, diagnosed on typical β-catenin nuclear staining, monosomy 6, and DNA methylation classification (score of 0.99 using v11b4). Four years after remission, a new left frontal mass was identified on a control MRI. Following gross total resection, pathology indicated an inflammatory myofibroblastic tumor (IMT) of the brain. The patient is currently in remission 2 years post-surgery. Family

history indicated that parents are non-consanguineous, and apparently healthy as are his other siblings. A wide range of different primary cancers were reported in relatives from both the paternal and maternal sides (Figure 1A). RNAseq performed on the IMT revealed an in-frame Dynactin subunit 1 - Anaplastic lymphoma kinase (DCTN1-ALK) fusion (ex26–ex20), validated by Fluorescence In Situ Hybridization (FISH), and a heterozygous PV, c.2959C>T: p.R987W *PDGFRB* mutation. Sequencing of the proband's blood DNA revealed the *PDGFRB* R987W variant to be constitutive (Figure 1B). Further familial testing showed the father to be also a carrier of this variant (Figure 1A).

Case 2: an 11-year-old French-Canadian female was admitted with generalized seizures following a 3-month story of headaches. MRI showed a hemorrhagic heterogenous right occipital lesion and the initial Computed tomography (CT) scan of the brain identified intra-tumoral calcifications. Following gross total resection, a diagnosis of glioneuronal tumor was made, which was further classified by DNA methylation as dysembryoplastic neuro-epithelial tumor (DNET, score of 0.90 v12.5). Copy number variation profile indicated a gain in whole chromosome 7 and no other alterations. Parents were non-consanguineous, and in good health. An uncle of the mother and an uncle of the father died of cancer (Figure 1A). The patient is currently nine months post-surgery with no clinical/radiological sign of disease. A Tripartite motif-containing 24 (TRIM24)-Mesenchymal epithelial transition (MET) fusion and the *PDGFRB* R987W mutation were identified by RNAseq in the DNET, and this *PDGFRB* mutation was also detected in the blood (Figure 1B). Family testing indicated that the otherwise healthy father and sister also carry the same *PDGFRB* variant.

We describe here 2 children with brain tumors carrying the same constitutive *PDGFRB* R987W mutation. This variant has previously been reported in PFBC, a disease both patients do not have on imaging, and was shown to cause protein instability and to impair MAPK, AKT, and PLC γ signaling in *in vitro* studies.⁶ Both brain tumors reported herein had gene fusions involving DCTN1-ALK in Case 1 and TRIM24-MET in case 2. In IMT, 60% of cases carry Anaplastic lymphoma kinase (ALK) alterations,⁷ and the DCTN1-ALK fusion we identify leads to oncogenic constitutive ligand-independent ALK activation, in keeping with this diagnosis. Interestingly, data acquired in other ALK-mutant tumors indicate that PDGFRB inhibition led to prolonged survival and increased efficacy of an ALK-inhibitor,⁸ suggesting a possible crosstalk between both pathways. TRIM24-MET fusions are potent oncogenes commonly observed in cancer including in high-grade gliomas⁹ and its presence in a DNET is unusual and warrants close clinical follow-up. Notably, the highly vascular nature of both the IMT and the DNET further raises the possibility of a crosstalk between PDGFRB signaling, which is crucial in vasculogenesis, and the acquisition of the ALK or the MET fusions. These may represent a compensatory mechanism in specific cells where PDGFRB signaling is needed but not optimal based on the R987W mutation. This hypothesis remains speculative and warrants further in-depth investigation in appropriate model systems.

This report suggests that brain tumors can potentially be added to the list of disorders caused by PDGFRB CPVs. However, further work and more cases are required to confirm they promote tumor formation, and to assess

penetrance as family members were carriers but otherwise asymptomatic. Last, although tyrosine kinase inhibitors such as imatinib remain effective against most *PDGFRB* GOF mutations,¹⁰ disorders such as PFBC with LOF CPVs in *PDGFRB* still require effective treatment methods. *PDGFRB* is a pleiotropic gene as evidenced by the wide spectrum of human diseases caused by both its GOF and LOF variants. This underscores the importance of additional functional characterization studies and the determination of specific pathways involved in PDGFRB-related tumorigenesis, as the exact mechanisms by which PDGFRB causes such a plethora of diseases remain uncertain.

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Authorship

Study conception and design: W.D.F. and N.J., data collection: S.R., V.L., L.C., analysis and interpretation of results: H.H., D.F., S.L., D.S., A.G., J.K., draft manuscript preparation: H.H., S.R. All authors have been involved in the writing of the manuscript at draft and any revision stages and have read and approved the final version.

Conflict of Interest

Authors declare there is no conflict of interest.

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