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Germline and somatic FGFR1 abnormalities in dysembryoplastic neuroepithelial tumors

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Supplementary Appendix

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Supplementary Methods

Patients and samples

The study was approved by the Institutional Review Board (IRB) of the Faculty of Medicine of McGill University. Participants were recruited in compliance with the second edition of the Canadian Tri-Council Policy Statement of Ethical Conduct for Research Involving Humans and Eligible Persons or Designates and signed a consent form in accordance with the IRB approvals. Blood from 3 affected members from family 1 and 3 formalin fixed paraffin embedded (FFPE) blocks (2 primary tumors, one from each child plus a recurrence from the daughter) were collected. The sporadic series is composed by a total of 100 cases (29 fresh frozen tumor (FFT) samples and 71 FFPE samples). Samples from 96 persons were recruited under the diagnosis of DNET from the reference centers; age of diagnoses, sex of the patient and location of the tumor was collected with the samples. Formalin-fixed paraffin-embedded tumor samples from all patients were independently reviewed according to 2007 WHO criteria by three senior neuropathologists (S.A., M.H., W.P). In line with the WHO classification, only tumors containing the specific glioneuronal element were diagnosed as DNET. Because the concept of "non-specific" DNET (i.e. tumors showing clinical and imaging similarities with DNET but lacking the specific glioneuronal element) is controversial, also according to the current WHO classification, this diagnosis was not made. During the blinded pathology review cases were classify into three different groups: 1 - DNET cases meeting WHO criteria; 2 - Non-DNET cases for which a differential diagnosis was made, including ganglioglioma (n = 7), diffuse astrocytic tumor (n= 5), pilocytic astrocytoma (n = 3), oligodendroglial tumor (n = 2), cortical dysplasia (n = 2), low greade glioma (n = 2), meningo-angiomatosis (n = 1); 3 - Cases for which the diagnosis remained unclear because a) material was sparse, or some elements of DNET (such as nodular growth) were present but no glioneuronal element was encountered, or b) there was disagreement between the reference pathologists and a more definite diagnosis would require an extensive immunohistochemical /molecular work-up, for which no material was available. To be conservative for statistical purposes, these unclear cases were consider as non-DNETs, from here on in the text we will refer to them as that.

The Index Family

In the index family, three cases of histopathologically- confirmed DNET occurred:

Case 1: In the 46- year old father, focal seizures with eye deviation to the right heralded the diagnosis of a tumor of the left occipital cortex at the age of six years. After tumor resection, the patient experienced no tumor recurrence and remained seizure-free. Except for right-sided hemianopsia, neurological examination was normal. Histopathologically, the tumor had been interpreted as oligodendroglioma initially (DNET was not recognized as an entity at that time), but reclassified as a DNET according to WHO criteria in 2004 [36].

Case 2: In the 17 year old daughter, focal seizures with eye deviation to the right occurred at the age of 6 years. On MRI, a non-contrast-enhancing mass in the left occipital cortex was detected, which was hypointense in the T1-weighted images. After tumor resection, the girl remained seizure-free for about three years. At the age of nine years, a local recurrence was completely resected. MRI scans during the neuro-oncological follow-up showed multiple non-contrast enhancing lesions supra- as well as infra-tentorially. At the age of 16 years the patient became symptomatic again (seizures with visual aura). The MRI scans revealed a progression of the lesion in the left occipital lobe. After repeat-surgery of the occipital lesions the patient is free of seizures with lamotrigene as a seizure prophylaxis. Except for right-sided hemianopsia, neurological development, as well as examination, is normal.

Case 3: In the 19 year old son, a DNET of the right temporal cortex was diagnosed when the patient was 9 year old after a history of focal seizures. Upon tumor resection, the patient remained seizure-free for seven years. Additionally, MRI scans during the neuro-oncological follow-up showed multiple non-contrast enhancing lesions located in the right posterior horn, the left frontal cortex and both thalami. At the age of 16 years, generalized seizures occurred. MRI scans showed a relapse with progression of the manifestation in the posterior horn of the right ventricle. After partial resection of the lesion in the right

posterior horn, the patient remains free of seizures with a prophylaxis of lamotrigene. Neurological development and examination is normal.

In all, in the index family, the father suffered from one single lesion whereas both children are suffering from multiple tumor lesions.

Suppl. Figure 1 Germline expression of p.R661P in lymphocytes. Chromatograms of the mutant sequence c.1982G>C; p.R661P in individuals I.1, II.1 and II.2 in DNA and cDNA. Asterisks show the position of the mutation, dash line marked the exon-exon boundary

Suppl. Figure 2 Validation of BRAF V600E by immunohistochemical staining. Case 70 BRAF V600E mutation validation by immunohistochemistry with anti-BRAF V600E specific antibody

Suppl. Figure 3 Tyrosine Kinase Domain duplications schema. Samples with the FGFR1 tyrosine kinase domain (TKD) duplication and their breakpoints. The second TKD starts from the N-terminal of the TKD to the end of the domain. Dashed blue lines show inserted sequence as a linker between the duplicated domains. Breakpoints inside the intron between exon 9 and exon 10 probably result in skipping exon 18, and therefore directly join exon 17 and the second TKD

Suppl. Figure 4 FISH results in 4 cases with either chromosomal breakpoints or gains of the *FGFR1* locus. FISH with FGFR1 break apart probe (MetaSystems, Altlussheim, Germany) for the cases 19, 40, 60 and 23. Each column represents one case. Yellow arrows point to co-localized signals, indicating intact *FGFR1* loci. Green and red arrows indicate split signals corresponding to a break in the *FGFR1* locus. Nuclei in the dotted boxes in the first and third row are magnified in the second and fourth row

Suppl. Figure 5 Chromosomal Number Variants plot resulting from the WES analyses. Genome-wide recurrent plot of Allelic Imbalance (AI) generated by ExomaAI [58]. The Y axis indicates the frequency of chromosomal aberrations. The X axis shows genomic positions and colors represent chromosomes. The most frequent aberrations were on chromosome 7 and 22 (6 out of 46 samples)

Suppl. Figure 6 Description of mutants in cis. A) Chromatogram resulting of the cloning of *FGFR1* exons 14 and 15 from the tumoral of DNA of individual II.1. Both germline and somatic mutations were confirming to be in cis. B) Table of clones showing double mutants in cis or wildtype sequences in 4 sporadic cases and individual II.1 C) Diagram of sequential mutational events in the individual II.1. D) Diagram both possibilities of sequential mutational events that will lead to a p.K656D mutant. F) Chromatograms and proposed sequential alterations that will result in the quadruple mutant p.K655V+p.K656E. Four nucleotide changes are required to produce this mutant. Due to the large number of possible combinations, only one is proposed. Occurrence of accompanying mutations in cis that increase the oncogenic properties of the first mutation has been described in *EGFR* and *NOTCH1* [33, 96]

Suppl. Figure 7 Forward and side scatter plots of phospho-ERK measurement. a) Forward scatter plot. b) Side scatter plot. c) Histogram of phospho-ERK fluorescence intensity in the single cell populations

Suppl. Table 1 Complete series of cases in the study and their diagnoses, age, sex, and location

Suppl. Table 2 a) Significantly mutated genes in 40 sporadic DNET samples b) Variants identified in cancer-related genes from Table S4a.

Suppl. Table 3 Figure 5- associated table. Description of phenotypes

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