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CORRESPONDENCE

SHH medulloblastoma in a young adult with a *TCF4* germline pathogenic variation

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Pitt–Hopkins syndrome (PTHS, MIM #610954) is a rare neurodevelopmental disease due to heterozygous loss of function variants in the *TCF4* gene (transcription factor 4, MIM #602272) [1]. *TCF4* encodes a basic helix-loop-helix (bHLH) transcription factor which is highly expressed in the nervous system during early development and is involved in cellular proliferation and differentiation. To date, approximately 200 PTHS patients have been reported since the first clinical description in 1978 [1, 11, 12]. The limited number of cases described and their early age precludes establishing a comprehensive phenotype, especially regarding cancer predisposition. Here we report the case of a 27-year-old woman affected by PTHS who developed a medulloblastoma (MB).

The PTHS patient, previously reported (P12) [11], harbored a typical facial gestalt, hypotonia, hyperventilation, had delayed walking, and never acquired language. The PTHS diagnosis was confirmed by identification of the heterozygous de novo pathogenic frameshift variant c.1241del, p.(Gly414Valfs*48) in the *TCF4* gene (NM_001083962.1). The patient developed a posterior fossa tumor at the age of 27 years arising from the right cerebellar hemisphere (Fig. 1a). The tumor has been macroscopically completely resected and the anatomopathological examination established a diagnosis of classic MB with SHH immunohistochemical profile (filamin+, GAB1+, Supplementary Fig. 1). The patient was then treated using standard dose of craniospinal radiotherapy without post-radiation chemotherapy. Array-CGH performed on the tumor DNA revealed multiple copy number alterations including *GLI2* amplification, but no *MYC*/*MYCN* amplification and no loss of

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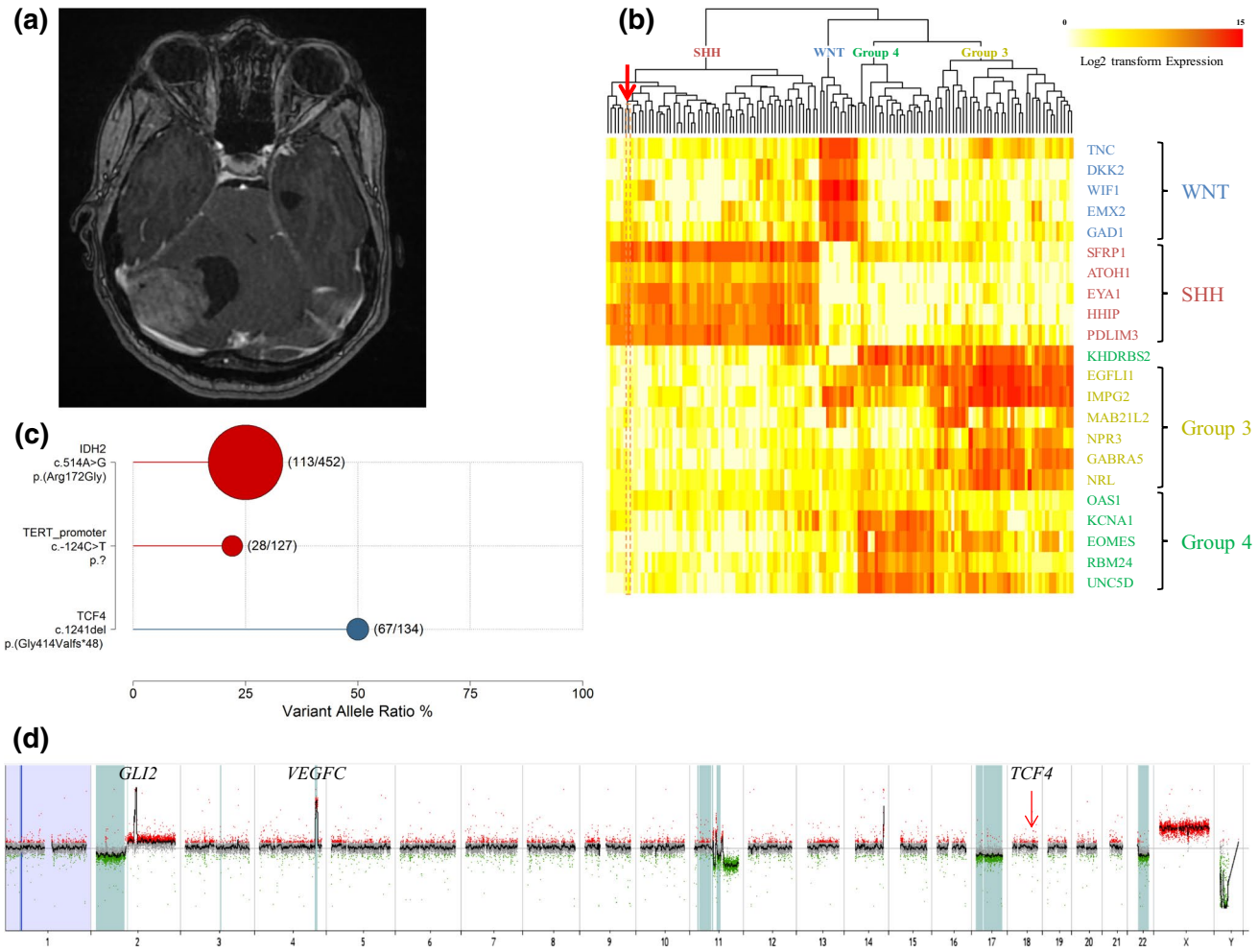

Fig. 1 Imaging and molecular features of the tumor. **a** Brain MRI axial T1 with gadolinium injection revealing a tumor in the right cerebellar hemisphere. **b** Hierarchical clustering of 113 MB from Curie dataset, based on the Nanostring signature made of 22 medulloblastoma subgroup-specific genes: the tumor reported in this correspondence is indicated by the arrow and orange dotted line box. **c** Analysis of tumor DNA by the Curie Institute custom cancer panel assessing known cancer-related genes; the two relevant mutated genes in this panel are indicated in bubbles; bubble sizes are correlated to sequencing depth at variant positions and the read count for alternative variant related to the reference nucleotide is specified in brackets. The allele ratio is specified in the *x*-axis. The *TCF4* pathogenic variation assessed by NGS is added in blue. **d** Array-CGH performed on tumor DNA revealed several copy number alterations including *GLI2* and *VEGFC* amplifications but no loss of heterozygosity at the *TCF4* locus (red arrow; 18q12.2)

heterozygosity at the *TCF4* locus (Fig. 1d). Nanostring molecular subgrouping [8] and RNAseq analysis unambiguously confirmed the SHH group (Fig. 1b). Nonetheless, based on the DKFZ classifier tool (https://www.molecularneuropathology.org) [2], the methylation analysis did not confidently match any CNS tumor class. The closest entity was SHH MB followed by IDH mutated gliomas (Supplementary Fig. 2; GSE126545). Sequencing of a custom cancer genes panel on tumor DNA identified the pathogenic variants c.-124C > T in the *TERT* promoter (NM_198253.2) and c.514A > G, p.(Arg172Gly) in the *IDH2* gene (NM_002168.3) (Fig. 1c; Supplementary Fig. 2). The *TERT* promoter variation occurred in a hot spot position which is recurrent in adult SHH MB [9]. No *TCF4* second alteration was identified in the tumor sample, neither at the genomic nor at the transcript level (GSE126545).

A recently published large-scale analysis of germline pathogenic variants associated with MB revealed that SHH MB is the most likely to arise in the context of a genetic predisposition [10]. Germline *PTCH1* and *SUFU* pathogenic variants occur in approximately 10% of SHH MB in infants and young children, while recessive diseases affecting DNA damage repair (i.e., Fanconi Anemia with bi-allelic inactivation of *PALB2* or *BRCA2*) are also associated with pediatric SHH MB. SHH MB in older patients is much less frequently associated with germline pathogenic variants, apart from rare *TP53* pathogenic variants in Li–Fraumeni syndrome. Thus, no gene is yet known to specifically predispose to adult-onset SHH MB. The case we report here raises the

hypothesis that PTHS due to germline *TCF4* pathogenic variants confers increased susceptibility to adult-onset SHH MB. However, a random association of those two rare diseases needs to be carefully ruled out.

Indeed, to date no MB has been described in PTHS patients. Nevertheless, scarcely more than 200 PTHS cases have been reported worldwide. In one of the biggest cohorts described, including 101 PTHS patients [12], only two were older than 25 years old. Hence, the susceptibility to adult-onset MB in PTHS is difficult to accurately estimate because of the small number of identified PTHS patients that have reached adulthood, which could mask a slightly elevated age-related risk.

Remarkably, in a large-scale genome wide analysis of 491 MB, eleven SHH MBs and one group 4 MB were reported to show somatic *TCF4* variants [7]. *TCF4* variants in SHH MB were mainly truncating variants (8/11) in favor of a role of TCF4 loss in SHH MB. Of note, in line with our case, all but one was heterozygous, with no second hit, strongly suggesting a haploinsufficiency mechanism for *TCF4* in promoting MB. Thus, *TCF4* may act similar to other tumor suppressors and cancer-predisposing genes, for which heterozygous truncating mutations leading to haploinsufficiency are now recurrently reported (updated review in [4]). Of note, all pathogenic *TCF4* variants were described in adult-onset tumors [7], strongly suggesting an age-related oncogenic effect of *TCF4* pathogenic variations. In line with previous studies investigating the role of *CREBBP* loss of function in MB according to developmental stages [6], Hellwig et al. describe in this issue of Acta Neuropathologica that *TCF4* abrogation increases cell proliferation only on post-natal granule cell progenitors, providing experimental evidence for an age-related oncogenic effect of *TCF4* pathogenic variations [3]. Altogether, these results suggest a bivalent effect of *TCF4* pathogenic variations, i.e., inducing a developmental disorder in the developing brain and an increased risk of malignant transformation in the adult cerebellum. This could explain the low known incidence of MB in PTHS patients, and fits with the late-onset in this case report.

Of note, all but one of the aforementioned *TCF4* mutated MB belonged to the SHH group [7], a finding consistent with previous results identifying *TCF4* recurrent pathogenic variations as one of the most frequent somatic events in adult SHH MB [5]. The strikingly unbalanced distribution of *TCF4* alterations among the four MB groups strongly suggests a specific cooperation between constitutive activation of the SHH pathway and *TCF4* loss of function. Yet how *TCF4* pathogenic variations interact and synergize with the SHH pathway remains to be more deeply investigated.

We postulate that *TCF4* germline alterations confer increased susceptibility to late-onset SHH MB. The aging of patients affected by PTHS should bring further insights into this hypothesis and would strengthen the need for further exploration of the potential synergy between TCF4 and the SHH pathway in MB.

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Compliance with ethical standards

Conflict of interest The author(s) declare that they have no conflict of interest.

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