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COLD SPRING HARBOR
Molecular Case Studies

RESEARCH REPORT

Somatic *IDH1* variant (p.R132C) in an adult male with Maffucci syndrome

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Abstract Maffucci syndrome is a rare, highly variable somatic mosaic condition, and well-known cancer-related gain-of-function variants in either the *IDH1* or *IDH2* genes have been found in the affected tissues of most reported individuals. Features include benign enchondroma and spindle-cell hemangioma, with a recognized increased risk of various malignancies. Fewer than 200 affected individuals have been reported; therefore, accurate estimates of malignancy risk are difficult to quantify and recommended surveillance guidelines are not available. The same gain-of-function *IDH1* and *IDH2* variants are also implicated in a variety of other benign and malignant tumors. An adult male presented with several soft palpable lesions on the right upper limb. Imaging and histopathology raised the possibility of Maffucci syndrome. DNA was extracted from peripheral blood lymphocytes and tissue surgically resected from a spindle-cell hemangioma. Sanger sequencing and droplet digital polymerase chain reaction (PCR) analysis of the *IDH1* gene were performed. We identified a somatic mosaic c.394C > T (p.R132C) variant in exon 5 of *IDH1*, in DNA derived from hemangioma tissue at ~17% variant allele fraction. This variant was absent in DNA derived from blood. This variant has been identified in the affected tissue of most reported individuals with Maffucci syndrome. Although this individual has a potentially targetable variant, and there is a recognized risk of malignant transformation in this condition, a decision was made not to intervene with an IDH1 inhibitor. The reasons and prospects for therapy in this condition are discussed.

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INTRODUCTION

Benign tumors of bone and blood vessels characterize Maffucci syndrome, specifically enchondroma and spindle-cell hemangioma, whereas in Ollier disease, the manifestations are limited to enchondroma. Maffucci syndrome was first defined by Carleton et al. (1942) who named it for the Italian pathologist who described the first affected individual in 1881. Carleton speculated that the combination of vascular and bony lesions reflected a common mesodermal origin, and in 2011, Pansuriya et al. (2011) and Amary et al. (2011) simultaneously identified somatic mosaic gain-of-function variants within either the *IDH1*

or *IDH2* genes in the majority of affected individuals. The same heterozygous *IDH1/2* somatic variants have also been identified in isolated enchondroma and chondrosarcoma, confirming that these genes are implicated in both syndromic and isolated benign and malignant bone tumors. Furthermore, the same spectrum of variants in these genes contributes to several other malignancies, including acute myeloid leukemia (AML), glioma, intrahepatic cholangiocarcinoma, and thyroid carcinoma, with occasional reports in paraganglioma, colorectal carcinoma, and prostate cancers (Yang et al. 2012; Tate et al. 2019) (COSMIC database; cancer.sanger.ac.uk). Precisely how these variants contribute to this wide disease spectrum remains incompletely understood.

It is reported that individuals with Maffucci syndrome appear to be at increased risk of certain cancers, although malignant transformation within spindle-cell hemangioma is rare. Therapeutic treatment options are limited and due to the rarity of the disease; controlled trials have not been conducted.

The *IDH1/2* genes have been the focus of much recent attention because of the discovery of specific inhibitors with utility reported in cancer treatment. The U.S. Federal Drug Agency (FDA) approved the first IDH inhibitor, enasidenib (Idhifa; Agios Pharmaceuticals) in August 2017, for individuals with relapsed/refractory AML and confirmed *IDH2* variant following a successful trial showing an overall 40% hematologic response rate and reasonable tolerability (Stein et al. 2017).

Currently, the potential benefits and risks of IHD1/2 inhibitors in Maffucci syndrome are unknown; however, it is possible that these agents might lead to a reduction in tumor growth or reduced risk of cancer progression within enchondroma. To date this has not been explored, likely because of the scarcity of the condition. Toxicities in individuals with relapsed/refractory AML are much more justifiable when the underlying prognosis is extremely poor. Nevertheless, for those with severe manifestations of Maffucci syndrome or in those with progression to malignancy, these agents may offer therapeutic benefit.

RESULTS

Clinical Presentation

A 36-yr-old male was referred to the Austin Health Clinical Genetics Unit via the plastic surgical team. He had noted several soft tissue lumps in the palm of the right hand, growing slowly and increasing in number over the preceding 3–4 yr (Fig. 1E,F). He had three further palpable lesions on the volar aspect of the wrist and a fourth lesion above the olecranon on the posterior upper arm. He was otherwise healthy, with no medical problems and apparently normal intellect. He had three healthy children and his extended family history was unremarkable.

Imaging (plain X-ray and magnetic resonance imaging [MRI] scan) demonstrated striking soft tissue and bony lesions in the right arm (Fig. 1A–D). Surgical resection of the palmar lesions was performed, because of increasing functional impairment of the hand and for diagnostic purposes. Histopathology showed a benign vascular tumor with vascular spaces lined by bland endothelium and intervening bland spindle-cell proliferation. These features were diagnostic of a spindle-cell hemangioma (International Society for the Study of Vascular Anomalies [ISSVA] benign vascular tumor 1 group), and together with the bony lesions, were suggestive of Maffucci syndrome (Fig. 1G,H).

Variant Screening

Sequencing of the coding exons and flanking introns of the *IDH1* gene in hemangioma-derived DNA identified a somatic c.394C > T (p.R132C) variant in exon 5 that was absent in

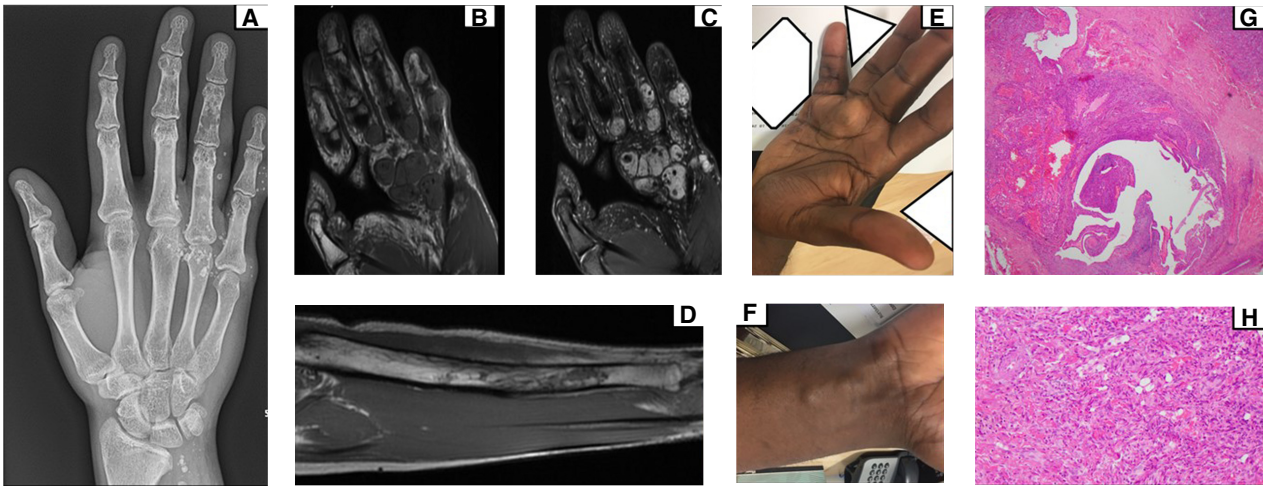

Figure 1. Radiology, clinical photographs, and histopathology of the affected individual. (*A*) Anteroposterior (AP) view of the right hand demonstrates multiple enchondromas of the third, fourth, and fifth digits. There are multiple soft tissue masses containing small round calcifications (phleboliths) within the hemangiomas. (*B*,*C*) Magnetic resonance imaging (MRI) of hand (T1 coronal/T2 coronal): multiple soft tissue masses that are T1 isointense/T2 hyperintense to muscle. There is T1 hypointensity in keeping with cartilage replacing normal marrow signal of the second to fourth proximal phalanges, third to fifth middle phalanges, and the second distal phalanx. Note expansion of the third and fourth middle phalanges caused by enchondromas. (*D*) MRI of right forearm (T1 sagittal): There is patchy heterogeneous T1 hypointensity within the medullary cavity of the ulnar diaphysis, associated with mild expansion, bowing, and shortening. T1 hypointense cartilaginous material replaces the normal T1 hyperintense bone marrow signal of the radius. (*E*) Right hand at initial presentation, demonstrating palmar masses. (*F*) Volar aspect of right wrist demonstrating soft masses (white shapes in *E* and *F* are used to conceal potentially identifying information). (*G*) Spindle-cell hemangioma. The typical combination of solid spindle-cell areas and cavernous areas is evident. (*H*) Solid areas composed of bland spindle cells along with small numbers of more epitheliod cells, some of which have large intracytoplasmic vacuoles. Slit-like vascular spaces in the solid area can be appreciated.

DNA derived from blood (Fig. 2A; Table 1). This variant has previously been identified in individuals with Maffucci syndrome (Pansuriya et al. 2011).

Determination of Somatic Mosaicism

The sequence chromatogram in Figure 2 indicated the *IDH1* p.R132C variant appeared mosaic in hemangioma tissue. Sanger sequencing is not able to accurately quantify the variant allele fraction at low levels. Therefore we used a commercially available droplet digital polymerase chain reaction (ddPCR) assay that we optimized in-house (lower limit of detection 0.1% variant allele fraction) to precisely quantify the level of mosaicism in tissue. The *IDH1* p.R132C variant was detected at 17.3% variant allele fraction in hemangioma-derived DNA and was not detected in blood-derived DNA (Fig. 2B).

DISCUSSION

We report an individual with Maffucci syndrome with development of lesions in adulthood, molecularly confirmed to be mosaic for the *IDH1* p.R132C variant using ddPCR and Sanger sequencing. This rare condition typically presents in childhood, although other adult diagnoses have been reported occasionally (Maione et al. 2016).

The clinical characteristics are specific, with the combination of spindle-cell hemangioma and enchondroma essentially pathognomonic for Maffucci syndrome. Typically, the lesions

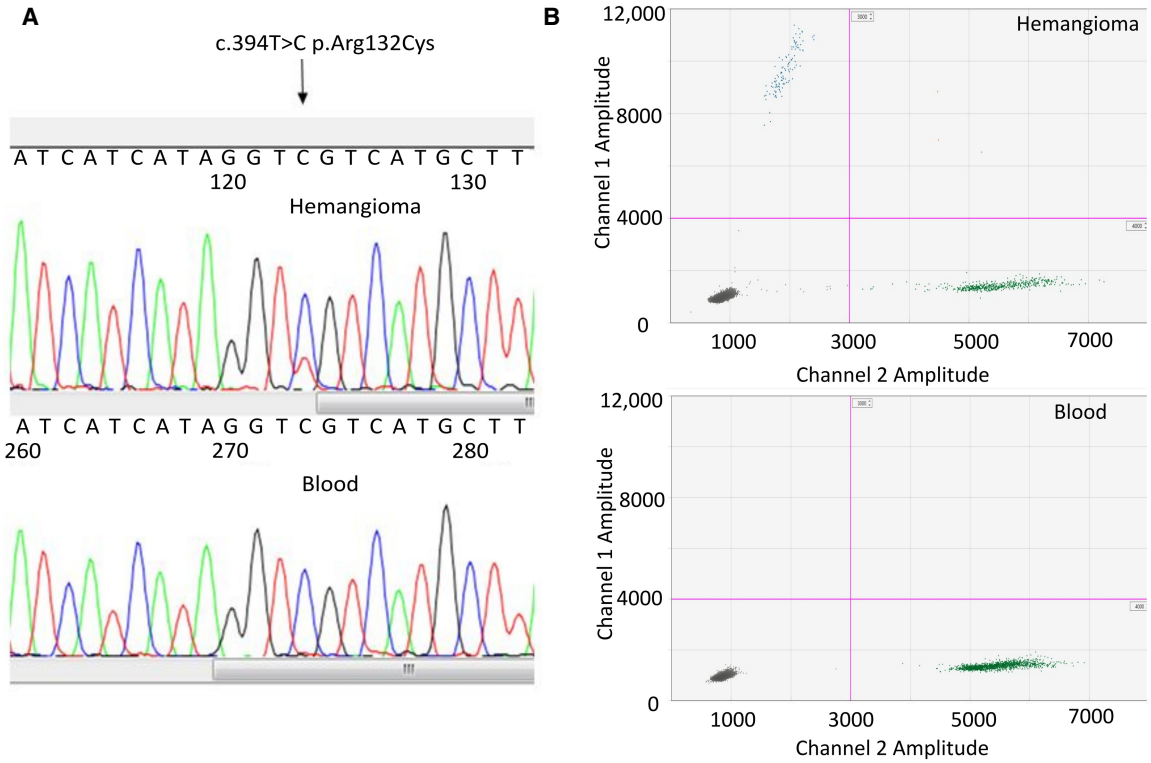

Figure 2. Sequencing and droplet digital polymerase chain reaction (ddPCR) results. (*A*) Sequence chromatograms showing the somatic *IDH1* c.394C > T; p.R132C variant in hemangioma-derived but not blood-derived DNA of an individual with Maffucci syndrome. (*B*) ddPCR readout showing droplets positive (blue) for p.R132C mutant probe in hemangioma-derived but not blood-derived DNA. Droplets for wild-type probe are green and droplets without DNA template are gray. An amplitude of 4000 was set as the positive mutant droplets threshold. Hemangioma-derived DNA: *IDH1* p.R132C concentration, 10.24 copies/µL; wild-type concentration, 48.9 copies/µL; mutant allele fraction, 17.3%. Blood-derived DNA: *IDH1* p.R132C concentration, 0 copies/µL; wild-type concentration, 138 copies/µL.

are subcutaneous and involve the extremities, but visceral vascular lesions are described, as well as skull base chondroma (Huang et al. 2017; Mandonnet et al. 2017). Clinical challenges in management include issues such as preservation of limb function, scoliosis, leg length discrepancy, pathological fracture, cosmesis, and, importantly, malignancy. Because of the scarcity of reports and lack of long-term follow-up data, the cancer risk in individuals with Maffucci syndrome has been difficult to quantify and estimates varied widely by study (Schwartz et al. 1987). However, recently El Abiad et al. (2020) reviewed data from 287 published manuscripts and also prospectively surveyed 162 individuals with Maffucci syndrome (36/162) or Olliers disease (126/162) through Facebook. This study provides the best data to date and confirms an ~30% prevalence of chondrosarcoma and a combined cancer prevalence in both conditions of ~50%. The risk of malignant transformation in vascular tumors in Maffucci syndrome was 8.5%.

Table 1. Variant table

Gene	Chromosome	HGVS DNA reference	HGVS protein reference	Variant type	Predicted effect	dbSNP/dbVar ID	Genotype
IDH1	Chr 2	NM_001282386.1: c.394C > T	p.Arg132Cys (R132C)	Missense	Substitution	rs121913499	Mosaic

Screening for malignancy in Maffucci syndrome has been suggested by several groups, but there are currently no consensus or evidence-based guidelines. Proposals have varied, including annual total body MRI with twice yearly dilated ophthalmoscopy and physical examination (McGarry 2017), and cranial MRI each 1–3 yr for skull base chondrosarcoma and glioma (Mandonnet et al. 2017). El Abiad et al. (2020) provide the most recent comprehensive recommendations for both Olliers disease and Maffucci syndrome, with 11 specific comprehensive recommendations.

Molecular Aspects

Somatic gain-of-function variants in the *IDH1* and *IDH2* genes play a role in the etiology of various benign and malignant tumors, as well as some premalignant disorders. Examples include 6%–10% of acute myeloid leukemia, >80% of glioma and secondary glioblastoma multiforme (GBM), and ~23% of intrahepatic cholangiocarcinoma, enchondroma, and osteosarcoma, as well as myelodysplastic syndrome and primary myelofibrosis (Borger et al. 2012; Dang et al. 2016; Tate et al. 2019; Bhavya et al. 2020). The presence of an *IDH1* variant is considered a favorable prognostic marker in glioma and in secondary low-grade GBM, and an indicator of favorable response to specific drug therapies such as temozolomide. However, in other cancers, such as AML and chondrosarcoma, the presence of *IDH1/2* variants confers a worse prognosis than does their absence (Molenaar et al. 2015; Zhu et al. 2020).

The IDH1 and IDH2 enzymes catalyze the conversion of isocitrate into alpha ketoglutarate (αKG) and generate NAPDH from NAD^+. Both αKG and NADPH are key elements of the tricarboxylic acid (TCA) cycle and are therefore fundamental to energy generation, cellular growth, and homeostasis; αKG is also a cofactor for a wide range of dioxygenase enzymes and therefore influences many different cellular processes. Gain-of-function variants in *IDH1/2* lead directly to increased cellular D-2-hydroxyglutarate (2HG), which is usually present at extremely low levels (Dang et al. 2016; Schaefer et al. 2018; Bhavya et al. 2020). D-2-hydroxyglutarate is considered a competitive inhibitor of αKG-catalyzed reactions, and in excess produces epigenetic dysregulation via hypermethylation, leading to impaired cellular differentiation and tumor growth. Widespread abnormalities of histone and DNA methylation have been identified in the context of *IDH1/2* variants (Pansuriya et al. 2011; Schaefer et al. 2018). Proposed mechanisms of oncogenesis of 2HG are broad and include complement pathway inhibition, epigenetic modulation, impaired DNA repair mechanisms producing genomic instability, down-regulation of tumor suppressors such as p53, mitochondrial dysfunction, and modulation of immune pathways (Dang et al. 2016; Schaefer et al. 2018; Bhavya et al. 2020). However, the precise mechanism by which the *IDH1* p.R132C variant contributes to Maffucci syndrome, and indeed to other conditions, is not currently understood.

Elevation of 2HG has been proposed as a potential biomarker of mutated *IDH1/2* and also as a potential marker of treatment response to inhibitors (Yang et al. 2012; Schaefer et al. 2018).

Treatment of Maffucci Syndrome and Consideration of New Agents

Traditional treatment of Maffucci syndrome has primarily been surgical, with intervention for functional impairment or progression to malignancy. Recently, sirolimus has been piloted in two published reports for treatment of vascular lesions—one without success, but the second was reported successful in combination with surgery (Gupta et al. 2019; Lekwuttikarn et al. 2019).

Given the new data confirming a significant risk of malignant transformation in Maffucci syndrome, we were concerned about this risk in our patient. We reviewed current knowledge

of specific IDH1/2 inhibitors to determine whether there could be emerging evidence supporting their use in this individual.

The first phase 1 trial of Enasidenib (AG-221), a specific IDH2 inhibitor, in *IDH2*$^+$ refractory/relapsed AML, demonstrated a 42% overall response rate but also found 24% of individuals had a serious treatment-related adverse event (Stein et al. 2017). Toxicities included hyperbilirubinemia, diarrhea, nausea/vomiting, prolongation of QT interval, rash, fatigue, thrombocytopenia, and IDH-related differentiation syndrome (IDH-DS) in 8% of individuals.

Ivosidenib (AG-120) was the first orally available IDH1 inhibitor shown to reduce 2HG levels and induce cellular differentiation in vitro and in human trials, although it does not show an effect against mutant *IDH2* (Popovici-Muller et al. 2018).

In an initial phase 1 study, Di Nardo et al. demonstrated an overall response rate of 41.6% of adults with relapsed/refractory AML and absence of mutant *IDH1* in 21% of those in complete remission/complete remission with partial hematological recovery, using ddPCR (DiNardo 2018). Comparison of survival data to historical controls was also highly favorable. However, toxicities were significant in >20%, including thrombocytopenia, leukocytosis, dyspnea, prolonged QT interval, and IDH-DS in 10.6% (DiNardo 2018). Further studies of ivosidenib have demonstrated complete remission/complete remission with partial hematological recovery in 42% of adults with newly diagnosed *IDH1* mutant AML (Roboz et al. 2020). An uncontrolled Phase 1 trial in *IDH1*$^+$ low-grade glioma found 66% of individuals demonstrated stable disease, the safety profile was considered acceptable, and exploratory analyses showed possible reduction in tumor volumes in some instances (Mellinghoff et al. 2020). Recently, a randomized placebo-controlled Phase 3 trial in chemotherapy-refractory intrahepatic cholangiocarcinoma showed improved disease-free survival but serious adverse effects in 30% of ivosidenib-treated individuals compared to 22% of controls (Abou-Alfa et al. 2020). An open-label Phase 1 trial in 21 individuals with advanced chondrosarcoma showed modest results of stable disease in 52%, reduction in serum 2HG levels to control levels, and minimal toxicity (Tap et al. 2020).

The U.S. FDA granted approval for use of enasidenib in *IDH2*$^+$ relapsed/refractory AML in 2017 and for ivosidenib in *IDH1*$^+$ relapsed/refractory AML in July 2018. In May 2019 the ivosidenib approval was extended to individuals with newly diagnosed AML ineligible for intensive chemotherapy, and in May of 2021 release of data from the Abou-Alfa et al. (2020) study led to the announcement of an FDA priority review for use in *IDH1*$^+$ cholangiocarcinoma.

Concerns emerged regarding toxicities that may have been underrecognized in the early studies—in particular, the potentially fatal IDH-DS. This condition is characterized by dyspnea, fever, hypotension, acute kidney injury, and pulmonary infiltrates or pericardial effusion. IDH-DS is treatable; however, recognition can be difficult and therefore use of these agents requires clinicians to be highly alert to the possibility (Birendra and DiNardo 2016). Differentiation syndrome was reported in the original landmark studies at ~11%–12%; however, a systematic analysis including active case searching conducted by the FDA suggests this may occur in as many as 19% of treated individuals (Norsworthy et al. 2020).

The great promise shown by selective IDH1/2 inhibitors for AML particularly, but also the emerging data on glioma and chondrosarcoma, certainly raises the question of whether these agents may offer benefit to individuals with Maffucci syndrome. The very small number of reported individuals means that evidence-based clinical trials in Maffucci syndrome may be difficult to achieve. However, the recent work of El Abiad et al. (2020) confirms that malignancy rates are indeed high and that, similar to other rare diseases, recruitment to research via social media platforms is effective.

Conclusions

Overall, based on the data reflecting high rates of IDH-DS, the justification for use of IDH1/2 inhibitors in Maffucci syndrome is currently lacking. In the context of a severe relapsed hematological malignancy, the risk–benefit analysis is quite different than the individual reported here, who was systemically perfectly well, but we were concerned about the potential risk of malignant transformation in the future.

A decision was made not to offer an IDH1 inhibitor in this scenario, and the patient was referred to a specialized orthopedic tumor unit, with a plan for ongoing imaging surveillance of bony lesions and regular clinical review.

In the future, if trials of these agents are considered for individuals with Maffucci syndrome, it would be appropriate to explore questions such as whether treatment may slow progression of existing benign lesions, reduce the risk of malignant transformation, or improve outcomes in those with existing malignant disease.

METHODS

Recruitment

The individual described was identified via routine clinical care through the Austin Health Clinical Genetics Unit, Heidelberg, Australia.

DNA Extraction PCR and Sanger Sequencing

Peripheral blood was collected in EDTA tubes and DNA-extracted using a QIAamp DNA Maxi Kit (QIAGEN). Surgically resected hemangioma tissue was formalin-fixed and paraffin embedded (FFPE) and DNA-extracted using a FFPE Tissue Kit.

PCR and Sanger Sequencing

The eight coding exons of the *IDH1* gene (RefSeq ID: NM_005896), including flanking introns, were sequenced. Regions were amplified using gene-specific primers designed to the reference human gene transcript (http://www.ncbi.nlm.nih.gov/gene). Primer sequences are available upon request. Amplification reactions were cycled using a standard protocol on a Veriti Thermal Cycler (Applied Biosystems). Bidirectional sequencing of all exons and flanking introns was completed with a BigDye v3.1 Terminator Cycle Sequencing Kit (Applied Biosystems), according to the manufacturer's instructions. Sequencing products were resolved using a 3730xl DNA Analyzer (Applied Biosystems). All sequencing electropherograms were compared to published cDNA sequence; nucleotide changes were detected using Codon Code Aligner (CodonCode Corporation).

Droplet Digital PCR

We used a commercially available PrimerPCR Mutation Assay (ID: dHsaCP2000054; Bio-Rad) to detect the *IDH1* c.394C > T (p.R132C) variant and corresponding wild-type allele. The lower limit of detection for this assay is 0.1% variant allele fraction. Droplet generation, PCR cycling, and droplet reading were performed according to the manufacturer's recommendations (Bio-Rad). Briefly, probes and primers were mixed with 2× ddPCR Supermix for probe (Bio-Rad) at 217 nM and 435 nM final concentrations for each probe and each of the primers, respectively, and mixed with 10 ng of DNA sample to a final volume of 23 µL. Twenty microliters of reactions were loaded in an eight-channel droplet generator cartridge (Bio-Rad), and droplets were generated with 70 µL of droplet generation oil (Bio-Rad) by using the manual QX200 Droplet Generator. Following droplet generation, samples were manually transferred to a 96-well PCR plate, heat-sealed, and amplified on a C1000

Touch thermal cycler using the following cycling conditions: 10 min at 95°C for one cycle, followed by 40 cycles of 30 sec at 94°C and of 60 sec at 55°C, one cycle of 10 min at 98°C and of infinite at 12°C. Post-PCR products were read on the QX200 droplet reader (Bio-Rad) and analyzed using the QuantaSoft software.

ADDITIONAL INFORMATION

Data Deposition and Access

The variant identified has been deposited in the following database: https://databases.lovd.nl/shared/genes/*IDH1*; variant #0000796578 (NC_000002.11:g.209113113G > A, *IDH1* (NM_005896.2):c.394C > T); individual ID: 00381525.

Ethics Statement

As a single descriptive case report, ethics board review is not required by our institution. Informed consent for publication including images was provided by the patient.

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Author Contributions

M.S.H. and Z.Y. performed molecular genetics experiments. N.J.B., C.S., A.S., and S.M. conducted clinical phenotyping, patient recruitment and consent, and intellectual input. M.S.H. provided equipment and reagents. S.I.J. made the initial histopathological diagnosis and provided input on histopathological features. S.A.M. reviewed and provided input on MRI and X-ray images. N.J.B. prepared the manuscript, and all remaining authors provided intellectual input and comments to the final manuscript.

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Competing Interest Statement

The authors have declared no competing interest.

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