Title

A case report of a novel germline GNAS mutation in sonic hedgehog activated medulloblastoma

Journal

Pediatric Blood & Cancer, 67(3)

ISSN

1545-5009

Authors

Crane, Jacquelyn N
Chang, Vivian Y
Yong, William H
et al.

Publication Date

2020-03-01

DOI

10.1002/pbc.28103

HHS Public Access

Author manuscript

Pediatr Blood Cancer. Author manuscript; available in PMC 2020 June 22.

Published in final edited form as:

Pediatr Blood Cancer. 2020 March ; 67(3): e28103. doi:10.1002/pbc.28103.

A case report of a novel germline *GNAS* mutation in sonic hedgehog activated medulloblastoma

Jacquelyn N. Crane[1], **Vivian Y. Chang**[1,2,3], **William H. Yong**[4], **Noriko Salamon**[5], **Hane Lee**[6,7,8] **on behalf of UCLA Clinical Genomics Center**, **Jessica Kianmahd**[9], **Naghmeh Dorrani**[7,9], **Julian A. Martinez-Agosto**[2,3,7,8,9], **Tom B. Davidson**[10]

[1]Division of Pediatric Hematology and Oncology, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, California

[2]Jonsson Comprehensive Cancer Center, University of California at Los Angeles, Los Angeles, California

[3]Children's Discovery and Innovation Institute, University of California Los Angeles Hospital, Los Angeles, California

[4]Division of Neuropathology, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, California

[5]Department of Radiology, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, California

[6]Department of Pathology and Laboratory Medicine, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, California

[7]Clinical Genomics Center, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, California

[8]Department of Human Genetics, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, California

[9]Division of Genetics, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, California

[10]Division of Hematology, Oncology and Blood and Marrow Transplantation, Children's Hospital of Los Angeles, Los Angeles, California

Correspondence: Tom B. Davidson, Division of Hematology, Oncology and Blood and Marrow Transplantation, Children's Hospital Los Angeles, 4650 Sunset Blvd., MS #54, Los Angeles, CA 90027. tdavidson@chla.usc.edu.
Present address: Tom B. Davidson, Division of Pediatric Hematology and Oncology, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

To the Editor

Medulloblastoma is the most common malignant brain tumor of childhood. Our knowledge of medulloblastoma has been advanced by the study of genetic cancer predisposition syndromes, which are associated with approximately 6% of cases.[1] We describe a case of a novel germline *GNAS* mutation in medulloblastoma, in accordance with the CARE guidelines.[2]

The patient is an 18-month-old male child with small size for age and polydactyly without other dysmorphic features who presented to an outside hospital with a 6-week history of loss of gross motor milestones and torticollis. A three-generation pedigree is shown in Figure 1A. Brain magnetic resonance imaging (MRI) as shown in Figure 1B and C revealed a 54 × 56 × 49 mm mass in the cerebellar vermis and obstructive hydrocephalus. Surgical resection and placement of a ventriculoperitoneal shunt was performed. Pathology was consistent with medulloblastoma, desmoplastic/nodular subtype, sonic hedgehog (SHH)-activated and TP53-wildtype, with TP53 status confirmed via immunohistochemistry. Brain MRI on postoperative day 6 was consistent with a subtotal resection. Spine MRI on postoperative day 29 was without evidence of metastases. No staging cerebrospinal fluid (CSF) evaluation was performed.

He began treatment on postoperative day 36 and received 5 weeks of chemotherapy including cyclophosphamide, vincristine, and methotrexate. He then transferred care to our institution. At this time, brain MRI showed complete response and CSF cytology was negative. He was treated with two cycles of cisplatin, vincristine, cyclophosphamide, etoposide, and high-dose methotrexate per Head Start 3 regimen D2, followed by three tandem cycles of carboplatin, thiotepa, and autologous stem cell rescues per CCG99703. He is now 17 months off treatment and remains small for age but in good health. Surveillance brain and spine MRIs every 3 months have been without evidence of recurrence.

Trio clinical exome sequencing was performed on peripheral blood from proband and biological parents.[3] This revealed a novel de novo heterozygous NM_000516.5:c.565–568delGACT germline *GNAS* frameshift mutation (p.Asp189Metfs*14) on the paternal allele. This variant is predicted to result in loss of function of the normally expressed paternally inherited GNAS gene product. Given concern for loss of function of GNAS, further laboratory testing was performed including parathyroid hormone, thyroid stimulating hormone, free thyroxine, insulin-like growth factor binding protein-3, luteinizing hormone, follicle stimulating hormone, serum calcium, urine calcium, and phosphate. These studies were normal, ruling out other *GNAS* associated clinical phenotypes. He was also found to have a maternally inherited hemizygous variant of uncertain significance (VUS) in *HDAC8* and a de novo heterozygous VUS in *MYLIP,* neither of which are predicted to be contributory to his phenotype.

There is only one previous report of a germline *GNAS* mutation in association with medulloblastoma. It was a 14-month-old male child patient with plate-like osteoma cutis and medulloblastoma found to have an apparently homozygous (likely hemizygous with somatic loss of heterozygosity) nonsense mutation in *GNAS* (c.838A > T; p.R280X).[4] The histologic

and molecular subtype was not reported. Germline mutations of the *GNAS* gene are associated with several other diseases.[5,6] One of these, Albright hereditary osteodystrophy, is associated with short stature but our patient did not show stigmata of other *GNAS*-associated diseases. Interestingly, Curry-Jones syndrome, caused by mutations in *SMO* leading to SHH pathway upregulation, is associated with medulloblastoma, developmental delay, and polydactyly. These features are all shared by our patient, thus may be related to downstream effects of SHH pathway activation.[7]

Somatic mutations in *GNAS* are frequent in multiple tumor types, including medulloblastoma.[8] Low or absent expression of GNAS leads to upregulation of the SHH pathway as shown in Figure 1B.[5,9–14] Aberrant activation of the SHH pathway can lead to development of SHH-activated medulloblastoma.[15] Patients with germline mutations in SHH pathway genes including *SUFU* and *PTCH1* and other germline mutations including *TP53*, *BRCA2*, and *PALB2* are associated with development of SHH-activated medulloblastoma.[1] This case illustrates how *GNAS* germline mutations may also contribute to the development of SHH-activated medulloblastoma.

While pediatric patients with SHH-activated medulloblastoma generally have an intermediate prognosis, those with *SUFU* or *PTCH1* germline mutations fare worse, and those with *TP53* germline mutations have an even poorer prognosis.[1,16] It has been shown that low *GNAS* expression in SHH-activated medulloblastomas is associated with poor prognosis[17] but further study is needed to fully elucidate the prognostic implications of germline GNAS mutations.

Limitations of this report include incomplete staging, an important prognostic factor. Additionally, tumor genotyping was not obtained due to insufficient tumor quantity at our institution, thus we could not assess co-existing somatic mutations. Nonetheless, the current knowledge of *GNAS* and its effects on the SHH pathway illuminates its importance in SHH-activated medulloblastoma and this case further supports this role. We recommend germline *GNAS* mutations be considered in patients with SHH-activated medulloblastoma and, in particular, in patients with phenotypic similarities to our patient including developmental delay, small size for age, and polydactyly. If identified, one should consider screening for other manifestations of *GNAS* mutations and consider potential prognostic implications.

ACKNOWLEDGMENTS

The authors are grateful to our patient and his family and the opportunity to participate in his care and for providing informed consent for this report. Additionally, we are grateful to Jeremy Woods, MD, for his assistance with figures.

REFERENCES

1. Waszak SM, Northcott PA, Buchhalter I, et al. Spectrum and prevalence of genetic predisposition in medulloblastoma: a retrospective genetic study and prospective validation in a clinical trial cohort. Lancet Oncol. 2018;19(6):785–798. [PubMed: 29753700]
2. Riley DS, Barber MS, Kienle GS, et al. CARE guidelines for case reports: explanation and elaboration document. J Clin Epidemiol. 2017;89:218235.
3. Lee H, Deignan JL, Dorrani N, et al. Clinical exome sequencing for genetic identification of rare Mendelian disorders. JAMA. 2014;312(18):1880–1887. [PubMed: 25326637]

4. Huh JY, Kwon MJ, Seo KY, et al. Novel nonsense GNAS mutation in a14-month-old boy with plate-like osteoma cutis and medulloblastoma. J Dermatol. 2014; 41(4):319–321. [PubMed: 24517547]
5. Ruiz i Altaba A, Sanchez P, Dahmane N. Gli and hedgehog in cancer: tumours, embryos and stem cells. Nat Rev Cancer. 2002;2(5):361–372. [PubMed: 12044012]
6. Turan S, Bastepe M. GNAS spectrum of disorders. Curr Osteoporos Rep. 2015;13(3):146–158. [PubMed: 25851935]
7. Smoll NR. Relative survival of childhood and adult medulloblastomas and primitive neuroectodermal tumors (PNETs). Cancer. 2012;118(5):1313–1322. [PubMed: 21837678]
8. Kan Z, Jaiswal BS, Stinson J, et al. Diverse somatic mutation patterns and pathway alterations in human cancers. Nature. 2010;466(7308):869–873. [PubMed: 20668451]
9. Ingham PW, Placzek M. Orchestrating ontogenesis: variations on atheme by sonic hedgehog. Nat Rev Genet. 2006; 7(11):841–850. [PubMed: 17047684]
10. Ding Q, Fukami S, Meng X, et al. Mouse suppressor of fused is a negative regulator of sonic hedgehog signaling and alters the subcellular distribution of Gli1. Curr Biol. 1999;9(19):1119–1122. [PubMed: 10531011]
11. Pan Y, Wang C, Wang B. Phosphorylation of Gli2 by protein kinaseA is required for Gli2 processing and degradation and the sonic hedgehog-regulated mouse development. Dev Biol. 2009; 326(1): 177189.
12. Rao R, Salloum R, Xin M, Lu QR. The G protein Galphas acts as atumor suppressor in sonic hedgehog signaling-driven tumorigenesis. Cell Cycle. 2016;15(10):1325–1330. [PubMed: 27052725]
13. Roussel MF, Robinson GW. Role of MYC in Medulloblastoma. Cold Spring Harb Perspect Med. 2013;3(11). 10.1101/cshperspect.a014308
14. Huse JT, Holland EC. Targeting brain cancer: advances in the molecularpathology of malignant glioma and medulloblastoma. Nat Rev Cancer. 2010;10(5):319–331. [PubMed: 20414201]
15. Gupta S, Takebe N, Lorusso P. Targeting the hedgehog pathway in cancer. Ther Adv Med Oncol. 2010;2(4):237–250. [PubMed: 21789137]
16. Guerrini-Rousseau L, Dufour C, Varlet P, et al. Germline SUFU mutation carriers and medulloblastoma: clinical characteristics, cancer risk, and prognosis. Neuro-oncology. 2018;20(8):1122–1132. [PubMed: 29186568]
17. He X, Zhang L, Chen Y, et al. The G protein alpha subunit Galphas isa tumor suppressor in sonic hedgehog-driven medulloblastoma. Nat Med. 2014;20(9):1035–1042. [PubMed: 25150496]

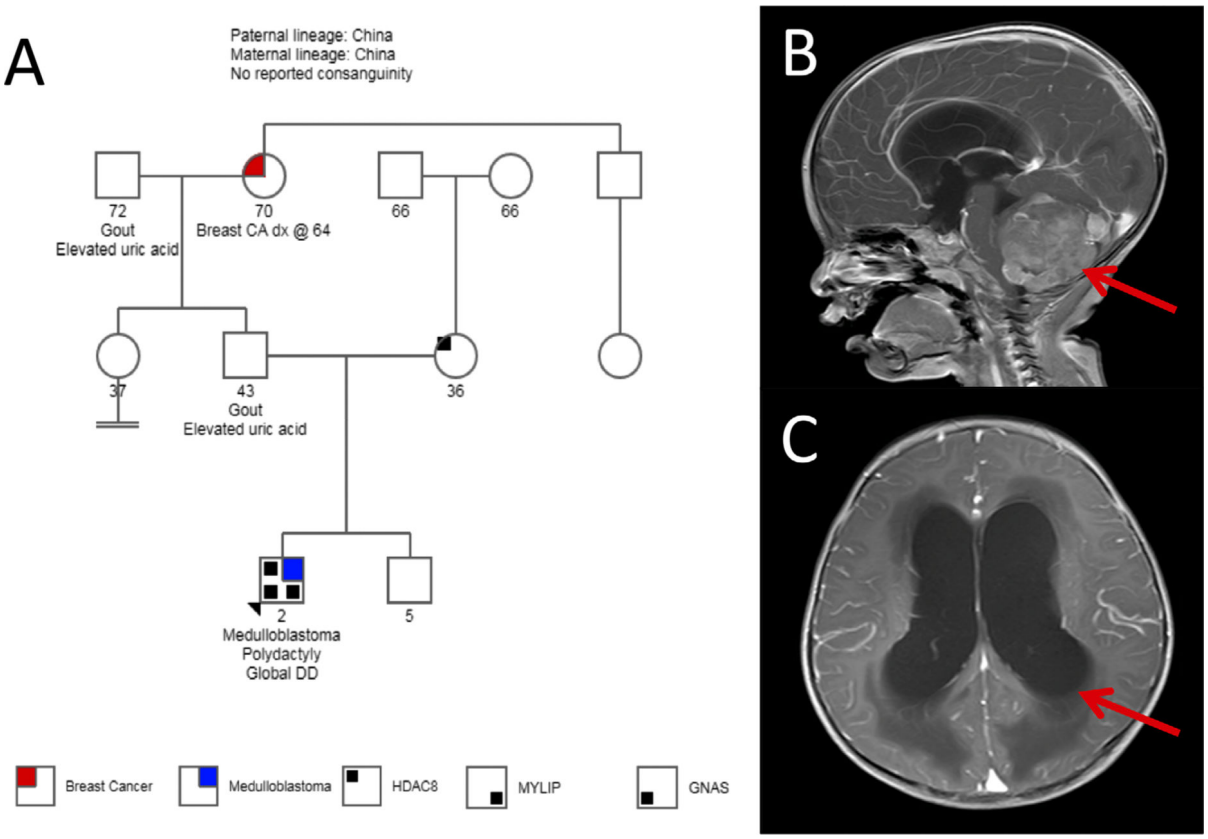

FIGURE 1.

Family history and diagnostic imaging. **A,** Three-generation pedigree. **B,** T1 sagittal view of an enhancing mass in the cerebellar vermis on initial brain MRI. **C,** Initial brain MRI T1 axial view shows enlarged lateral ventricles and transependymal flow in the periventricular white matter, suggesting obstructive hydrocephalus