

ABSTRACT

Nature. 2022 Sep;609(7929):1021-1028. doi: 10.1038/s41586-022-05215-w. Epub 2022 Sep 21.

Failure of human rhombic lip differentiation underlies medulloblastoma formation.

Hendrikse LD(#)(1)(2)(3), Haldipur P(#)(4), Saulnier O(#)(1)(2), Millman J(4), Sjoboen AH(4), Erickson AW(1)(2)(5), Ong W(1)(2)(5), Gordon V(6), Coudière-Morrison L(6), Mercier AL(7), Shokouhian M(8), Suárez RA(1)(2), Ly M(1)(2)(5), Borlase S(6), Scott DS(1)(2), Vladioiu MC(1)(2)(5), Farooq H(1)(2)(5), Sirbu O(1)(2)(3), Nakashima T(9), Nambu S(9), Funakoshi Y(9), Bahcheli A(10)(11), Diaz-Mejia JJ(12), Golser J(4), Bach K(4), Phuong-Bao T(8), Skowron P(1)(2)(5), Wang EY(1)(2)(3), Kumar SA(1)(2)(5), Balin P(1)(2)(5), Visvanathan A(1)(2), Lee JJY(1)(2)(5), Ayoub R(3), Chen X(1)(2), Chen X(1)(2), Mungall KL(13), Luu B(1)(2), Bérubé P(14), Wang YC(14), Pfister SM(15)(16), Kim SK(17), Delattre O(18)(19), Bourdeaut F(18)(19), Doz F(18)(20), Maslah-Planchon J(21), Grajkowska WA(22), Loukides J(1), Dirks P(1)(2)(10)(23), Fèvre-Montange M(24)(25), Jouvet A(25), French PJ(26), Kros JM(27), Zitterbart K(28), Bailey SD(29)(30), Eberhart CG(31), Rao AAN(32), Giannini C(33), Olson JM(34), Garami M(35), Hauser P(35), Phillips JJ(36)(37), Ra YS(38), de Torres C(39), Mora J(39), Li KKW(40), Ng HK(40), Poon WS(41), Pollack IF(42), López-Aguilar E(43), Gillespie GY(44), Van Meter TE(45), Shofuda T(46), Vibhakar R(47), Thompson RC(48), Cooper MK(49), Rubin JB(50), Kumabe T(51), Jung S(52), Lach B(53)(54), Lolascon A(55)(56), Ferrucci V(55)(56), de Antonellis P(55)(56), Zollo M(55)(56), Cinalli G(57), Robinson S(58), Stearns DS(59), Van Meir EG(60), Porrati P(61), Finocchiaro G(61), Massimino M(61), Carlotti CG(62), Faria CC(63)(64), Roussel MF(65), Boop F(65), Chan JA(66), Aldinger KA(4)(67), Razavi F(68), Silvestri E(69), McLendon RE(70)(71), Thompson EM(71), Ansari M(72)(73), Garre ML(74), Chico F(75), Eguía P(75), Pérezpeña M(76), Morrissy AS(66)(77)(78), Cavalli FMG(79)(80)(81), Wu X(1)(2), Daniels C(1)(2), Rich JN(82), Jones SJM(13)(83)(84), Moore RA(13), Marra MA(13)(83), Huang X(1)(2)(10), Reimand J(3)(10)(11), Sorensen PH(85)(86), Wechsler-Reya RJ(87), Weiss WA(36)(88)(89), Pugh TJ(3)(11)(12), Garzia L(90), Kleinman CL(91)(92), Stein LD(10)(93), Jabado N(94)(95), Malkin D(3)(96), Ayrault O(7), Golden JA(97), Ellison DW(98), Doble B(8), Ramaswamy V(1)(2)(3)(96), Werbowetski-Ogilvie TE(6)(99), Suzuki H(9), Millen KJ(4), Taylor MD(100)(101)(102)(103)(104).

Author information:

(1)The Arthur and Sonia Labatt Brain Tumor Research Centre, The Hospital for Sick Children, Toronto, Ontario, Canada.

(2)Developmental and Stem Cell Biology Program, The Hospital for Sick Children, Toronto, Ontario, Canada.

(3)Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada.

(4)Center for Integrative Brain Research, Seattle Children's Research Institute, Seattle, WA, USA.

(5)Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada.

(6)Department of Biochemistry and Medical Genetics, University of Manitoba, Winnipeg, Manitoba, Canada.

(7)PSL Research University, Université Paris Sud, Université Paris-Saclay, CNRS UMR 3347, INSERM U1021, Institut Curie, Orsay, France.

(8)Department of Pediatrics and Child Health and Department of Biochemistry and Medical Genetics, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada.

(9)Division of Brain Tumor Translational Research, National Cancer Center Research Institute, Tokyo, Japan.

(10)Department of Molecular Genetics, University of Toronto, Toronto, Ontario, Canada.

- (11)Computational Biology Program, Ontario Institute for Cancer Research, Toronto, Ontario, Canada.
- (12)Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario, Canada.
- (13)Canada's Michael Smith Genome Sciences Centre, BC Cancer Agency, Vancouver, British Columbia, Canada.
- (14)McGill University Genome Centre, McGill University, Montreal, Quebec, Canada.
- (15)Division of Pediatric Neurooncology, German Cancer Research Center (DKFZ), Heidelberg, Germany.
- (16)Department of Pediatric Oncology, Hematology, Immunology and Pulmonology, University Hospital Heidelberg, Heidelberg, Germany.
- (17)Department of Neurosurgery, Division of Pediatric Neurosurgery, Seoul National University Children's Hospital, Seoul, South Korea.
- (18)SIREDO Oncology Center (Pediatric, Adolescent and Young Adults Oncology), Institut Curie, Paris, France.
- (19)INSERM U830, Institut Curie, Paris, France.
- (20)Université Paris Cité, Paris, France.
- (21)Unit of Somatic Genetics, Institut Curie, Paris, France.
- (22)Department of Pathology, The Children's Memorial Health Institute, Warsaw, Poland.
- (23)Division of Neurosurgery, The Hospital for Sick Children, Toronto, Ontario, Canada.
- (24)INSERM U1028, CNRS UMR5292, Centre de Recherche en Neurosciences, Université de Lyon, Lyon, France.
- (25)Centre de Pathologie EST, Groupement Hospitalier EST, Université de Lyon, Bron, France.
- (26)Department of Neurology, Erasmus University Medical Center, Rotterdam, Netherlands.
- (27)Department of Pathology, Erasmus University Medical Center, Rotterdam, Netherlands.
- (28)Department of Pediatric Oncology, Masaryk University School of Medicine, Brno, Czech Republic.
- (29)Department of Surgery, Division of Thoracic and Upper Gastrointestinal Surgery, Faculty of Medicine, McGill University, Montreal, Quebec, Canada.
- (30)Cancer Research Program, Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada.
- (31)Departments of Pathology, Ophthalmology and Oncology, John Hopkins University School of Medicine, Baltimore, MD, USA.
- (32)Division of Pediatric Hematology/Oncology, Mayo Clinic, Rochester, MN, USA.
- (33)Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA.
- (34)Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA.
- (35)2nd Department of Pediatrics, Semmelweis University, Budapest, Hungary.
- (36)Department of Neurological Surgery, University of California San Francisco, San Francisco, CA, USA.
- (37)Department of Pathology, University of California San Francisco, San Francisco, CA, USA.
- (38)Department of Neurosurgery, University of Ulsan, Asan Medical Center, Seoul, South Korea.
- (39)Developmental Tumor Biology Laboratory, Hospital Sant Joan de Déu, Esplugues de Llobregat, Barcelona, Spain.
- (40)Department of Anatomical and Cellular Pathology, The Chinese University of Hong Kong, Shatin, Hong Kong.
- (41)Department of Surgery, The Chinese University of Hong Kong, Shatin, Hong Kong.
- (42)Department of Neurological Surgery, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA.
- (43)Division of Pediatric Hematology/Oncology, Hospital Pediatría Centro Médico Nacional century XXI, Mexico City, Mexico.
- (44)Department of Neurosurgery, University of Alabama at Birmingham, Birmingham,

AL, USA.

(45)Pediatrics, Virginia Commonwealth University, School of Medicine, Richmond, VA, USA.

(46)Division of Stem Cell Research, Institute for Clinical Research, Osaka National Hospital, Osaka, Japan.

(47)Department of Pediatrics, University of Colorado Denver, Aurora, CO, USA.

(48)Department of Neurological Surgery, Vanderbilt Medical Center, Nashville, TN, USA.

(49)Department of Neurology, Vanderbilt Medical Center, Nashville, TN, USA.

(50)Departments of Neuroscience, Washington University School of Medicine in St Louis, St Louis, MO, USA.

(51)Department of Neurosurgery, Kitasato University School of Medicine, Sagamihara, Japan.

(52)Department of Neurosurgery, Chonnam National University Research Institute of Medical Sciences, Chonnam National University Hwasun Hospital and Medical School, Hwasun-gun, South Korea.

(53)Department of Pathology and Molecular Medicine, Division of Anatomical Pathology, McMaster University, Hamilton, Ontario, Canada.

(54)Department of Pathology and Laboratory Medicine, Hamilton General Hospital, Hamilton, Ontario, Canada.

(55)Dipartimento di Medicina Molecolare e Biotecnologie Mediche (DMMBM), University of Naples Federico II, Naples, Italy.

(56)CEINGE Biotecnologie Avanzate, Naples, Italy.

(57)Department of Pediatric Neurosurgery, Santobono-Pausilipon Children's Hospital, Naples, Italy.

(58)Division of Pediatric Neurosurgery, Case Western Reserve, Cleveland, OH, USA.

(59)Department of Pediatrics-Hematology and Oncology, Case Western Reserve, Cleveland, OH, USA.

(60)Department of Hematology and Medical Oncology, Emory University School of Medicine and Winship Cancer Institute, Atlanta, GA, USA.

(61)Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy.

(62)Department of Surgery and Anatomy, Faculty of Medicine of Ribeirão Preto, University of São Paulo, São Paulo, Brazil.

(63)Division of Neurosurgery, Centro Hospitalar Lisboa Norte (CHULN), Hospital de Santa Maria, Lisbon, Portugal.

(64)Instituto de Medicina Molecular João Lobo Antunes, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal.

(65)Department of Tumor Cell Biology, St Jude Children's Research Hospital, Memphis, TN, USA.

(66)Charbonneau Cancer Institute, University of Calgary, Calgary, Alberta, Canada.

(67)Brotman Baty Institute for Precision Medicine, Seattle, WA, USA.

(68)Assistance Publique Hôpitaux de Paris, Hôpital Necker-Enfants Malades, Paris, France.

(69)Surgical Pathology Unit, San Camillo Forlanini Hospital, Rome, Italy.

(70)Department of Pathology, Duke University, Durham, NC, USA.

(71)Department of Neurosurgery, Duke University, Durham, NC, USA.

(72)Cansearch Research Platform for Pediatric Oncology and Hematology, Faculty of Medicine, Department of Pediatrics, Gynecology and Obstetrics, University of Geneva, Geneva, Switzerland.

(73)Division of Pediatric Oncology and Hematology, Department of Women, Child and Adolescent, University Geneva Hospitals, Geneva, Switzerland.

(74)U.O. Neurochirurgia, Istituto Giannina Gaslini, Genova, Italy.

(75)Department of Neurosurgery, Hospital Infantil de Mexico Federico Gomez, Mexico City, Mexico.

(76)Instituto Nacional De Pediatría de México, Mexico City, Mexico.

(77)Department of Biochemistry and Molecular Biology, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada.

(78)Alberta Children's Hospital Research Institute, Calgary, Alberta, Canada.

(79)INSERM U900, Institut Curie, Paris, France.

(80)PSL Research University, Institut Curie, Paris, France.

- (81)CBIO-Centre for Computational Biology, PSL Research University, MINES ParisTech, Paris, France.
- (82)UPMC Hillman Cancer Center, Pittsburgh, PA, USA.
- (83)Department of Medical Genetics, University of British Columbia, Vancouver, British Columbia, Canada.
- (84)Department of Molecular Biology and Biochemistry, Simon Fraser University, Burnaby, British Columbia, Canada.
- (85)Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, British Columbia, Canada.
- (86)Department of Molecular Oncology, BC Cancer Agency, Vancouver, British Columbia, Canada.
- (87)Tumor Initiation and Maintenance Program, NCI-Designated Cancer Center, Sanford Burnham Prebys Medical Discovery Institute, La Jolla, CA, USA.
- (88)Department of Neurology, University of California San Francisco, San Francisco, CA, USA.
- (89)Department of Pediatrics, University of California San Francisco, San Francisco, CA, USA.
- (90)Cancer Research Program, McGill University Health Centre Research Institute, Montreal, Quebec, Canada.
- (91)Department of Human Genetics, McGill University, Montreal, Quebec, Canada.
- (92)Lady Davis Research Institute, Jewish General Hospital, Montreal, Quebec, Canada.
- (93)Adaptive Oncology, Ontario Institute for Cancer Research, Toronto, Ontario, Canada.
- (94)Departments of Pediatrics and Human Genetics, McGill University, Montreal, Quebec, Canada.
- (95)The Research Institute of the McGill University Health Center, Montreal, Quebec, Canada.
- (96)Division of Haematology/Oncology, Department of Pediatrics, The Hospital for Sick Children, Toronto, Ontario, Canada.
- (97)Department of Pathology, Cedars-Sinai Medical Center, Los Angeles, CA, USA.
- (98)Department of Pathology, St Jude Children's Research Hospital, Memphis, TN, USA.
- (99)CancerCare Manitoba Research Institute, Winnipeg, Manitoba, Canada.
- (100)The Arthur and Sonia Labatt Brain Tumor Research Centre, The Hospital for Sick Children, Toronto, Ontario, Canada. mdt.cns@gmail.com.
- (101)Developmental and Stem Cell Biology Program, The Hospital for Sick Children, Toronto, Ontario, Canada. mdt.cns@gmail.com.
- (102)Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada. mdt.cns@gmail.com.
- (103)Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada. mdt.cns@gmail.com.
- (104)Division of Neurosurgery, The Hospital for Sick Children, Toronto, Ontario, Canada. mdt.cns@gmail.com.
- (#)Contributed equally

Comment in

Nature. 2022 Sep;609(7929):901-903.

Medulloblastoma (MB) comprises a group of heterogeneous paediatric embryonal neoplasms of the hindbrain with strong links to early development of the hindbrain¹⁻⁴. Mutations that activate Sonic hedgehog signalling lead to Sonic hedgehog MB in the upper rhombic lip (RL) granule cell lineage⁵⁻⁸. By contrast, mutations that activate WNT signalling lead to WNT MB in the lower RL^{9,10}. However, little is known about the more commonly occurring group 4 (G4) MB, which is thought to arise in the unipolar brush cell lineage^{3,4}. Here we demonstrate that somatic mutations that cause G4 MB converge on the core binding factor alpha (CBFA) complex and mutually exclusive alterations that affect CBFA2T2, CBFA2T3, PRDM6, UTX and OTX2. CBFA2T2 is expressed early in the progenitor cells of the cerebellar RL subventricular zone in *Homo sapiens*, and G4 MB transcriptionally resembles these progenitors but are stalled in developmental time. Knockdown of OTX2 in model systems relieves this

differentiation blockade, which allows MB cells to spontaneously proceed along normal developmental differentiation trajectories. The specific nature of the split human RL, which is destined to generate most of the neurons in the human brain, and its high level of susceptible EOMES+KI67+ unipolar brush cell progenitor cells probably predisposes our species to the development of G4 MB.

© 2022. The Author(s), under exclusive licence to Springer Nature Limited.

DOI: 10.1038/s41586-022-05215-w
PMID: 36131014 [Indexed for MEDLINE]