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Status of *IDH* mutations in chondrosarcoma of the jaws

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Abstract. The aim was to analyse the relationship between mutations of the isocitrate dehydrogenase gene (*IDH*) and clinical characteristics of chondrosarcoma of the jaw in order to provide new information on its molecular pathology. Tissue samples were collected from 25 patients diagnosed with chondrosarcoma of the jaw. *IDH* mutations were detected through polymerase chain reaction and direct sequencing. Clinicopathological data were analysed retrospectively. The study included 14 female and 11 male patients; the median patient age was 38 years. Sixteen patients had lesions in the mandible, while nine had lesions in the maxilla. The most common symptom reported was the presence of a painless, slowly enlarging mass with swelling, with or without numbness. Twenty-four patients received radical surgeries and one patient received chemoradiotherapy. The recurrence rate was 21.7%. No *IDH* mutation was found in any of the 25 samples. *IDH* mutation may not be a key event in the occurrence and development of chondrosarcoma of the jaw. However, for chondrosarcomas of a different nature and origin, the pathological significance of *IDH* mutation needs to be studied further.

Keywords: chondrosarcoma; jaw; isocitrate dehydrogenase; mutation; pathogenesis.

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Chondrosarcoma (CS) originates from the mesenchymal tissue and is one of the most common primary malignant bone tumours, accounting for 10–20% of bone sarcomas, mostly occurring in the pelvis, sternum, ribs, and limb long bones.[1] Chondrosarcoma of the jaw (CSJ) is extremely rare, accounting for only 3–4% of all cases of CS. Its clinical features, including nasal obstruction and asymptomatic or painful swelling, are non-specific and depend on the site of origin. Although CS has a high rate of malignancy and metastasis, which contributes to its poor prognosis in some cases, de Souza et al.[2] reported that 42.5% of patients with CSJ had high-grade tumours but that distant metastasis occurred in 12.9% (29/224) of cases, and 56.8% of 169 patients followed for a mean of 64 months were alive with no evidence of disease. Further, it is difficult to differentiate CSJ from chondroblastic osteosarcoma because of their overlapping symptoms and histopathology. The histogenesis of CSJ is controversial. One theory is that remnants of cartilage following failure of ossification of the nasopalatine duct may persist and cause anterior maxilla CS. Another widely propagated theory is that mesenchymal pluripotent cells undergo malignant transformation and differentiate into a chondrocytic phenotype.[3]

The principal diagnostic imaging modalities are computed tomography and magnetic resonance imaging. A definite diagnosis can be established by incisional biopsy and histopathological examination. Well-differentiated tumours resemble hyaline cartilage and

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show oval to polygonal cells within lacunar spaces surrounded by a cartilaginous matrix. The nuclei are small and uniform, with round to oval outlines and evenly distributed dense chromatin; binucleation and multinucleation frequently occur. With increasing tumour grade, the nucleoli become discernible because the chromatin opens. Nuclear atypia, increased cellularity, decreased cytoplasm volume, myxoid background, and mitoses are associated with a high tumour grade. High-grade lesions usually show > 2 mitoses per 10 high-power fields and marked cellular pleomorphism.

Recent evidence has shown that mutations in the isocitrate dehydrogenase gene (*IDH*) play an important role in the pathogenesis of CS[4,5]; however these mutations have not been reported in CSJ. The isocitrate dehydrogenases (IDH) are metabolic enzymes involved in various cellular processes, including mitochondrial oxidative phosphorylation, glutamine metabolism, lipogenesis, glucose sensing, and cellular redox regulation.[6] There are three isoforms of isocitrate dehydrogenase in humans, namely IDH1, IDH2, and IDH3.[7] Among these, IDH1 exists in the cytoplasm and peroxisomes, whereas IDH2 and IDH3 exist in the mitochondria. IDH1 and IDH2 are the main producers of reduced nicotinamide adenine dinucleotide phosphate (NADPH) in vivo and play important roles in energy generation and detoxification.[8] Therefore, a decrease or loss of IDH1 and IDH2 function in cells may negatively affect the detoxification mechanisms of the body, resulting in DNA damage and genomic instability.

The *IDH* mutations that are associated with tumours are mostly in the *IDH1* and *IDH2* genes. In 2008, Parsons et al.[9] reported the presence of *IDH1* mutations in 12% of patients with glioblastoma. *IDH1* or *IDH2* point mutations have been found to be present in approximately 50% of patients with central CS.[10] The most common point mutation in CS is *IDH1* R132C, accounting for about 40% of CS mutations; this mutation results in an increased level of D-2-hydroxyglutarate.[11] Other common point mutations in CS are *IDH1* R132G, *IDH1* R132H, *IDH2* R172S, *IDH1* R132L, and *IDH1* R132S.[12]

In view of the high *IDH1/2* mutations in CS, the World Health Organization has suggested that genetic testing may be useful in excluding chondroblastic osteosarcoma in the diagnosis of CSJ, particularly using core-needle biopsy. Thus, it is essential to reliably determine the *IDH1/2* mutation status in CSJ.

In this study, 25 cases of CSJ diagnosed between 2000 and 2020 at Peking University School of Stomatology were investigated. The clinicopathological, treatment, and follow-up data of these cases were reviewed systematically, and mutations in *IHD1* R132, *IHD2* R140, and *IHD2* R172 were explored to further understand the clinicopathological characteristics and mechanisms of occurrence and development of CSJ.

Materials and methods

Sample selection

Samples obtained from 25 patients with CSJ diagnosed in the Department of Oral Pathology, Peking University School of Stomatology between January 2000 and August 2020 were collected. All participants provided informed consent for the genetic studies. This study was approved by the Institutional Review Board of Peking University School of Stomatology (approval number: PKUSSIRB-202161009).

All paraffin-embedded tissues were examined by two senior oral pathologists after haematoxylin and eosin staining to ensure the accuracy of case selection. Clinical data including patient age, sex, CS location, symptoms, treatment strategy, and recurrence were collected and analysed retrospectively.

DNA extraction

Genomic DNA was extracted from the paraffin-embedded tissues using a QIAamp DNA extraction kit (Qiagen, Hilden, Germany), following the manufacturer's instructions. The purity and concentration of DNA were quantified using a NanoDrop ND-8000 ultraviolet spectrophotometer (Thermo Scientific, Waltham, MA, USA) to ensure that the purity of DNA was not less than 1.6 and the concentration not less than 200 mg/l to meet the experimental requirements. The DNA extract was then amplified by polymerase chain reaction (PCR) or sub-packaged and then cryopreserved at −20°C.

Touchdown (TD) PCR

The mRNA sequence of *IDH* was obtained from the National Center for Biotechnology Information Basic Local Alignment Search Tool (NCBI BLAST, https://blast.ncbi.nlm.nih.gov/Blast.cgi). Primers specific to three *IDH* mutation sites were designed and synthesized by Sangon Biotech (Shanghai, China), with the following sequences: *IDH1* R132 forward sequence 5′-GCA AAATCACATTATTGCCAAC-3′, reverse sequence 5′-CGGTCTTCAGAG AAGCCATT-3′; *IDH2* R140 forward sequence 5′-CTAGGCGTGGGATGT TTTTG-3′, reverse sequence 5′-TGTG GAAAAGTCCCAATGGA-3′; and *IDH2* R172 forward sequence 5′-CTC CACCCTGGCCTACCT-3′, reverse sequence 5′-AGCCCATCATCTGCA AAAAC-3′. The PCR was performed in a 25-μl system containing 12.5 μl Ex Taq enzyme (Takara, Shiga, Japan), 0.5 μl each of forward and reverse primers (approximately 10 pmol for each primer), 10.5 μl of ribonuclease-free water, and 100 ng DNA template.

Thermocycling conditions were optimized for each primer pair, and the following conditions were used: initial denaturation at 94°C for 5 min; 35 cycles of denaturation at 94°C for 30 s, annealing at TD 65–55°C (*IDH1* R132 and *IDH2* R140) or TD 67–57°C (*IDH2* R172) for 30 s, and elongation at 72°C for 30 s; and final extension at 72°C for 10 min.

Genetic sequencing analyses

PCR products were purified and collected using the PCR Product Purification Kit (Sangon Biotech, Shanghai, China). The purified products were subjected to sequencing by Sangon Biotech using an Applied Biosystems 3730xl DNA Analyzer (Thermo Fisher Scientific, Foster city, CA, USA). All mutations detected were confirmed by using their reverse sequences in two independent PCR experiments. The confirmed sequences were spliced using SeqMan software (DNASTAR, Madison, WI, USA).

Results

The age at admission of the 25 patients with CSJ ranged from 15 to 69 years (mean age 41.28 years, median age 38 years; Supplementary Material Table S1). Fourteen of the patients were female (56%) and 11 were male (44%).

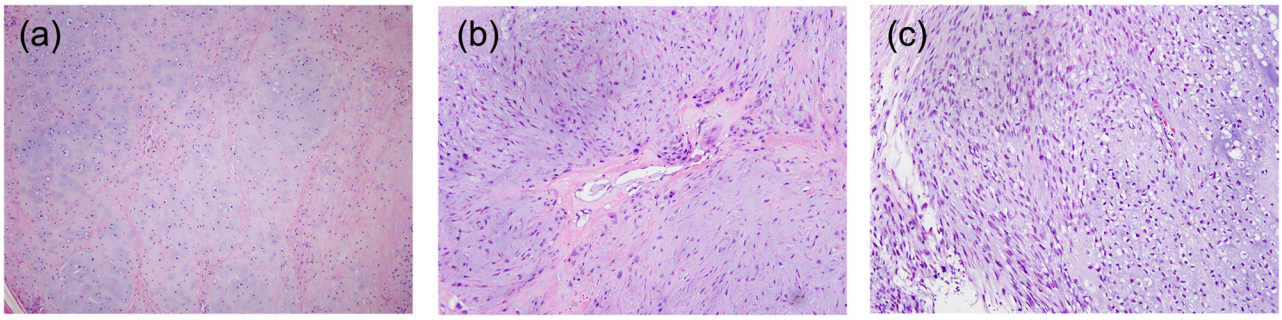

Fig. 1. (a) Grade I (low-grade) showing a lobular growth pattern, moderate cellularity, with cells embedded in hyaline cartilaginous matrix. Nuclei show condensed chromatin, while mitoses are absent. (b) Grade II showing increased cellularity with nuclei varying in size embedded within myxoid matrix. (c) Grade III (high-grade) showing higher cellularity, more mitoses and spindle cell changes.

Table 1. Clinical features of the 25 studied chondrosarcoma of the jaw cases.

Variables		
Age at surgery (years), median (range)	38 (15–69)	
	Cases	Percentage
Sex		
Female	14	56%
Male	11	44%
Location		
Mandible	16	64%
Maxilla	9	36%
Margin		
Clear	21	84%
Involved	3	12%
Not available	1	4%
Pathology grade		
I	11	44%
I–II	4	16%
II	4	16%
II–III	1	4%
III	4	16%
Mesenchymal type	1	4%
Recurrence		
No recurrence	18	72%
Recurrence	5	20%
Lost to follow-up	1	4%
Not available	1	4%
IDH mutations		
Mutant	0	0%
Wild-type	25	100%

Sixteen patients had lesions in the mandible, while nine had lesions in the maxilla. The lesions often exhibited painless swelling and slow growth, leading to facial asymmetry over time.

One patient was treated conservatively using chemoradiotherapy, while the remaining 24 underwent radical surgery. The recurrence rate was 21.7% (excluding one case of loss to follow-up and one case of biopsy). The pathology grade (histological grading) was reported for all 25 cases. Grade I (low-grade) indicates a lobular growth pattern and moderate cellularity, with cells embedded in hyaline cartilaginous matrix; nuclei show condensed chromatin, but mitoses are absent. Grade II indicates increased cellularity with nuclei varying in size and cells embedded within myxoid matrix. Grade III (high-grade) indicates higher cellularity, with increased mitoses and spindle cell changes (Fig. 1). Concerning the tumour grade, the most commonly diagnosed was grade I (n = 11, 44%), followed by the intermediate grades I–II, II, and III (each n = 4, 16%). The least commonly diagnosed grades were grade II–III and mesenchymal chondrosarcoma (each n = 1, 4%). The clinical data of the patients are reported in Table 1 and Supplementary Material Table S1, and the imaging features of a high-grade CSJ are shown in Fig. 2.

None of the 25 cases of CSJ carried any *IDH* mutation (Fig. 3). Thus, for the included cases, there was no significant correlation of age, sex, CSJ location, treatment, pathology grade, or recurrence with *IDH* mutation.

Discussion

In the maxillofacial bones, tumours with pure cartilaginous differentiation are assumed to be chondrosarcoma (CS) until proven otherwise, especially in the jawbones. Chondrosarcoma of the jaw (CSJ) is an extremely rare primary malignant bone tumour that accounts for approximately 3–4% of all CS.[13]

Studies have reported that CSJ is slightly more predominant among males.[2] In contrast, 14 of the 25 patients (56%) with CSJ included in the present study were female. The median patient age was 38 years, which corresponds with previous studies.[14] The disease can occur in any maxillofacial bone, but the maxilla and the nasal septum seem to be more frequently involved than the mandible. However, in the present study, only nine patients had maxillary lesions, with the remaining 16 having mandibular lesions. The symptoms and presentation include swelling, pain, and numbness, but these are usually non-specific.

In this study, 24 patients with CSJ underwent an extended resection, segmental or even total excision of the jaw. These methods often result in jaw defects, accompanied by the loss of teeth, which seriously affect orofacial aesthetics and function. Moreover, the recurrence rate of CSJ was 21.7% (excluding one case of loss to follow-up and one case of biopsy). The prognosis of CSJ is closely related to factors such as the location and size of the tumour, the surgical approach, and the biological characteristics of the tumour. In addition to the pathological grading of CSJ, whether the tumour is completely resected is an extremely important factor affecting the recurrence of the tumour. While most of the study patients had radical resections, the type of radical resection (extended resection, segmental or even entire excision of the jaw), whether the flap was fixed concurrently, and the year in which the operation was performed will all have had an effect on the rate of recurrence.

The current operation is far more comprehensive. Improvements in surgical equipment (ultrasonic osteotome, navigation technology) and techniques (skin flap repair) have enabled more complex procedures to be performed. Excision as a surgical notion is more easily achieved. Prior to the widespread use of free flap reconstruction, surgeons tended to prioritize jaw continuity

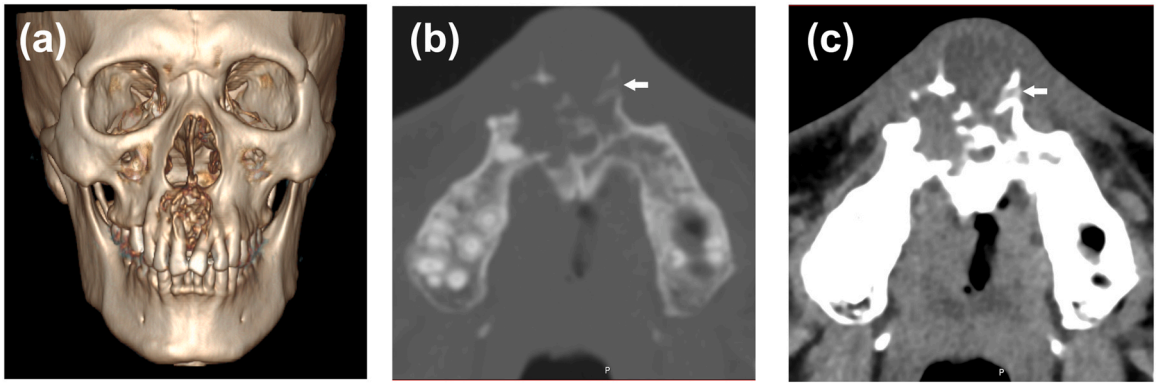

Fig. 2. (a) Three-dimensional reconstruction, and axial CT images of (b) bone and (c) soft tissue, showing an osteolytic and ill-defined lesion (arrows) in the anterior maxilla. Signs of cortical thickening and destruction, bone expansion, and soft tissue extension are observed in the images.

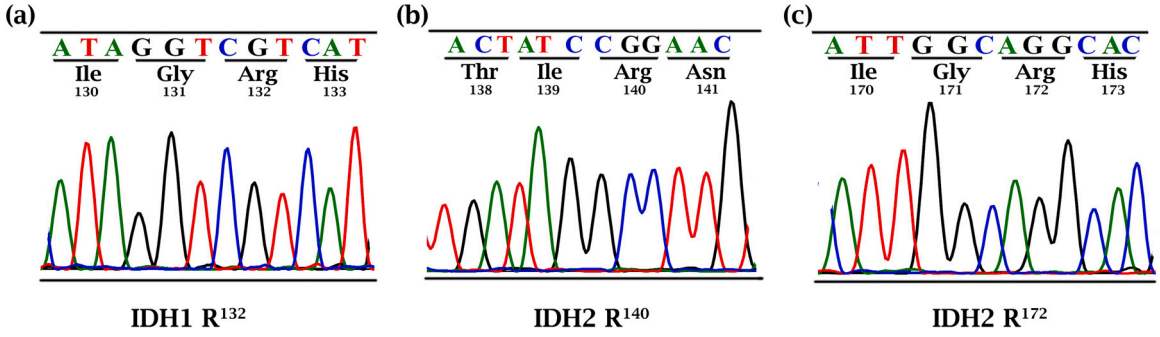

Fig. 3. (a) Wild-type *IDH1* R132 in chondrosarcoma of the jaw; (b) wild-type *IDH2* R140 in chondrosarcoma of the jaw; (c) wild-type *IDH2* R172 in chondrosarcoma of the jaw.

when conducting radical resections, limiting the scope of expanded resection. Simultaneously, as a result of the unavoidable tumour cell implantation during the procedure, relapse occurred. Therefore, CSJ cases should be treated by a multidisciplinary team, and the accuracy of the first diagnosis of CSJ patients and the use of decisive radical surgery based on a free flap during the first treatment are particularly important to reduce postoperative recurrence. It is believed that with more extensive research in this domain, therapies will achieve significant outcomes and become more effective in improving the quality of life of patients with CSJ.

To understand the pathogenesis of CSJ, it is essential to study its genetic profile. Research has indicated a close relationship between *IDH* mutation and CS formation and development. IDH is a key enzyme of the tricarboxylic acid cycle that catalyses the oxydecarboxylation of isocitrate to form α-ketoglutarate, simultaneously catalysing the reduction of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP+) into reduced NADH and NADPH.[13,15,16] NADPH, an important electron donor of glutathione, thioredoxin, and some transcription factors including nuclear factor-κB and activator factor protein-1, plays an important role in regulating the intracellular redox state. *IDH* mutation leads to the increased consumption of intracellular NADPH, which makes cells increasingly vulnerable to damage by reactive oxygen species. Studies have found that *IDH* mutation results in CS due to the destruction of the chondrocyte growth plate structure, inhibition of chondrocyte differentiation, and promotion of chondrodysplasia and multiple endophytic chondroma-like injuries,[17] indicating that *IDH* mutation has a unique effect on chondrocyte differentiation and chondroma formation. Moreover, after *IDH* enzyme mutation, α-ketoglutarate involved in the tricarboxylic acid cycle decreases and 2-hydroxyglutarate increases. 2-Hydroxyglutarate can directly inhibit the activities of several important dioxygenases such as human histone demethylase and DNA demethylase, resulting in DNA and histone hypermethylation, abnormal epigenetic regulation, and blocking of cell differentiation.[18,19]

A brief overview of *IDH* mutation rates in CS is presented in Table 2.[5,20–24] The results suggest that CS has a very high rate of *IDH* mutations. As a relatively rare subtype of CS, the status and effect of *IDH* mutation in CSJ are not clear. Tallegas et al.[20] found that 64.9% of craniofacial CS featured *IDH* mutations, with a high rate for skull base tumours (85.7%). No *IDH* mutations were observed in tumours of the facial skeleton, including five in the maxillary bones; no cases of CS in the mandible were included in their study.

The results of the present study revealed that none of the 25 CSJ cases carried *IDH* gene mutations. Therefore, the data indicate that the mutation status of *IDH1/2* cannot be used as the basis for the diagnosis or differential diagnosis of CSJ. The difference in *IDH* mutation status between CSJ and CS may be due to the unique histology

Table 2. Brief overview of *IDH* mutation rates in chondrosarcoma.

Sample size	Type	*IDH* mutation type	Mutation rate	Reference
23	High-grade	14	61%	Kerr et al., 2013[21]
39	GII and GIII	23	58.9%	Amary et al., 2011[5]
23	Dedifferentiated chondrosarcoma	13	56.5%	
1	Periosteal chondrosarcoma	1	100%	
88	Craniofacial chondrosarcomas	57	64.9%	Tallegas et al., 2019[20]
	Skull base tumours	75	85.7%	
18	Dedifferentiated chondrosarcoma	11	61.1%	Yang et al., 2020[22]
80	GI: 29; GII: 34; GIII: 17	27	34%	Lugowska et al., 2018[23]
21	Dedifferentiated chondrosarcoma	16	76%	Mohammad et al., 2020[24]

of the jaw. The facial bones are mainly derived from the neural crest cells of the first branchial arch, and the frontonasal process shows both endochondral and intramembranous ossification. The maxilla undergoes an exclusive intramembranous ossification, whereas the mandible undergoes concomitant intramembranous (body) and endochondral ossification (condyle and coronoid).

Although many studies have shown that *IDH* inhibitors have a good therapeutic effect on CS with *IDH* mutation, this strategy does not seem to significantly improve the clinical treatment of CSJ.[25] The pathogenesis of CSJ based on mutational profiling, gene expression, and DNA methylation, which activates the related carcinogenic signal pathway and finally leads to tumour occurrence and progression, needs further interpretation. New knowledge emerging from the *IDH* wild-type CSJ may provide direction for future precision therapies, including multi-omics, single cell technologies, and computational approaches. Further research is needed to identify the genes and signalling pathways relevant to CSJ, as this might improve our understanding of the biological mechanisms underlying tumourigenesis.

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Competing interests

None.

Ethical approval

This study was approved by the Institutional Review Board of Peking University School of Stomatology (approval number: PKUSS-IRB-202161009).

Patient consent

All participants provided informed consent for the genetic studies.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ijom.2022.03.003.

References

1. Jenny L, Harvinder S, Gurdeep S. Endoscopic resection of primary nasoseptal chondrosarcoma. *Med J Malaysia* 2008;**63**:335–6.
2. de Souza LL, Pontes FSC, Fonseca FP, da Mata Rezende DS, Vasconcelos VCS, Pontes HAR. Chondrosarcoma of the jaw bones: a review of 224 cases reported to date and an analysis of prognostic factors. *Int J Oral Maxillofac Surg* 2019;**48**:452–60.
3. Neff B, Sataloff RT, Storey L, Hawkshaw M, Spiegel JR. Chondrosarcoma of the skull base. *Laryngoscope* 2002;**112**:134–9.
4. Venneker S, Kruisselbrink AB, Baranski Z, Palubeckaite I. Briaire-de Bruijn IH, Oosting J, French PJ, Danen EHJ, Bovée JVMG. Beyond the influence of *IDH* mutations: exploring epigenetic vulnerabilities in chondrosarcoma. *Cancers (Basel)* 2020;**12**:3589.
5. Amary MF, Bacsi K, Maggiani F, Damato S, Halai D, Berisha F, Pollock R, O'Donnell P, Grigoriadis A, Diss T, Eskandarpour M, Presneau N, Hogendoorn PC, Futreal A, Tirabosco R, Flanagan AM. *IDH1* and *IDH2* mutations are frequent events in central chondrosarcoma and central and periosteal chondromas but not in other mesenchymal tumours. *J Pathol* 2011;**224**:334–43.
6. Medeiros BC, Fathi AT, DiNardo CD, Pollyea DA, Chan SM, Swords R. Isocitrate dehydrogenase mutations in myeloid malignancies. *Leukemia* 2017;**31**:272–81.
7. Yoshimi N, Futamura T, Bergen SE, Iwayama Y, Ishima T, Sellgren C, Ekman CJ, Jakobsson J, Pålsson E, Kakumoto K, Ohgi Y, Yoshikawa T, Landén M, Hashimoto K. Cerebrospinal fluid metabolomics identifies a key role of isocitrate dehydrogenase in bipolar disorder: evidence in support of mitochondrial dysfunction hypothesis. *Mol Psychiatry* 2016;**21**:1504–10.
8. Wang X, Inaoka DK, Shiba T, Balogun EO, Allmann S, Watanabe YI, Boshart M, Kita K, Harada S. Expression, purification, and crystallization of type 1 isocitrate dehydrogenase from *Trypanosoma brucei brucei*. *Protein Expr Purif* 2017;**138**:56–62.
9. Parsons DW, Jones S, Zhang X, Lin JC, Leary RJ, Angenendt P, Mankoo P, Carter H, Siu IM, Gallia GL, Olivi A, McLendon R, Rasheed BA, Keir S, Nikolskaya T, Nikolsky Y, Busam DA, Tekleab H, Diaz Jr LA, Hartigan J, Smith DR, Strausberg RL, Marie SK, Shinjo SM, Yan H, Riggins GJ, Bigner DD, Karchin R, Papadopoulos N, Parmigiani G, Vogelstein B, Velculescu VE, Kinzler KW. An integrated genomic analysis of human glioblastoma multiforme. *Science* 2008;**321**:1807–12.
10. Cleven AHG, Suijker J, Agrogiannis G, Briaire-de Bruijn IH, Frizzell N, Hoekstra AS, Wijers-Koster PM, Cleton-Jansen AM, Bovée JVMG. *IDH1* or *-2* mutations do not predict outcome and do not cause loss of 5-hydroxymethylcytosine or altered histone modifications in central chondrosarcomas. *Clin Sarcoma Res* 2017;**7**:8.
11. Molenaar RJ, Radivoyevitch T, Maciejewski JP, van Noorden CJ, Bleeker FE. The driver and passenger effects of isocitrate dehydrogenase 1 and 2 mutations in oncogenesis and survival prolongation. *Biochim Biophys Acta* 2014;**1846**:326–41.

12. Kaneko MK, Tsujimoto Y, Hozumi Y, Goto K, Kato Y. Novel monoclonal antibodies GMab-r1 and LMab-1 specifically recognize *IDH1*-R132G and *IDH1*-R132L mutations. *Monoclon Antib Immunodiagn Immunother* 2013;**32**:224–8.
13. El-Naggar AK, Chan JKC, Takata T, Grandis JR, Slootweg PJ. The fourth edition of the head and neck World Health Organization blue book: editors' perspectives. *Hum Pathol* 2017;**66**:10–2.
14. Mohammadinezhad C. Chondrosarcoma of the jaw. *J Craniofac Surg* 2009; **20**:2097–100.
15. Gross S, Cairns RA, Minden MD, Driggers EM, Bittinger MA, Jang HG, Sasaki M, Jin S, Schenkein DP, Su SM, Dang L, Fantin VR, Mak TW. Cancer-associated metabolite 2-hydroxyglutarate accumulates in acute myelogenous leukemia with isocitrate dehydrogenase 1 and 2 mutations. *J Exp Med* 2010; **207**:339–44.
16. Hirata M, Sasaki M, Cairns RA, Inoue S, Puviindran V, Li WY, Snow BE, Jones LD, Wei Q, Sato S, Tang YJ, Nadesan P, Rockel J, Whetstone H, Poon R, Weng A, Gross S, Straley K, Gliser C, Xu Y, Wunder J, Mak TW, Alman BA. Mutant *IDH* is sufficient to initiate enchondromatosis in mice. *Proc Natl Acad Sci U S A* 2015;**112**:2829–34.
17. Xu W, Yang H, Liu Y, Yang Y, Wang P, Kim SH, Ito S, Yang C, Wang P, Xiao MT, Liu LX, Jiang WQ, Liu J, Zhang JY, Wang B, Frye S, Zhang Y, Xu YH, Lei QY, Guan KL, Zhao SM, Xiong Y. Oncometabolite 2-hydroxyglutarate is a competitive inhibitor of alpha-ketoglutarate-dependent dioxygenases. *Cancer Cell* 2011;**19**:17–30.
18. Lu C, Ward PS, Kapoor GS, Rohle D, Turcan S, Abdel-Wahab O, Edwards CR, Khanin R, Figueroa ME, Melnick A, Wellen KE, O'Rourke DM, Berger SL, Chan TA, Levine RL, Mellinghoff IK, Thompson CB. *IDH* mutation impairs histone demethylation and results in a block to cell differentiation. *Nature* 2012; **483**:474–8.
19. Chowdhury R, Yeoh KK, Tian YM, Hillringhaus L, Bagg EA, Rose NR, Leung IK, Li XS, Woon EC, Yang M, McDonough MA, King ON, Clifton IJ, Klose RJ, Claridge TD, Ratcliffe PJ, Schofield CJ, Kawamura A. The oncometabolite 2-hydroxyglutarate inhibits histone lysine demethylases. *EMBO Rep* 2011;**12**:463–9.
20. Tallegas M, Miquelestorena-Standley É, Labit-Bouvier C, Badoual C, Francois A, Gomez-Brouchet A, Aubert S, Collin C, Tallet A, de Pinieux G. *IDH* mutation status in a series of 88 head and neck chondrosarcomas: different profile between tumors of the skull base and tumors involving the facial skeleton and the laryngotracheal tract. *Hum Pathol* 2019; **84**:183–91.
21. Kerr DA, Lopez HU, Deshpande V, Hornicek FJ, Duan Z, Zhang Y, Rosenberg AE, Borger DR, Nielsen GP. Molecular distinction of chondrosarcoma from chondroblastic osteosarcoma through *IDH1/2* mutations. *Am J Surg Pathol* 2013;**37**:787–95.
22. Yang T, Bai Y, Chen J, Sun K, Luo Y, Huang W, Zhang H. Clonality analysis and *IDH1* and *IDH2* mutation detection in both components of dedifferentiated chondrosarcoma, implicated its monoclonal origin. *J Bone Oncol* 2020; **22**:100293.
23. Lugowska I, Teterycz P, Mikula M, Kulecka M, Kluska A, Balabas A, Piatkowska M, Wagrodzki M, Pienkowski A, Rutkowski P, Ostrowski J. *IDH1/2* mutations predict shorter survival in chondrosarcoma. *J Cancer* 2018; **9**:998–1005.
24. Mohammad N, Wong D, Lum A, Lin J, Ho J, Lee CH, Yip S. Characterisation of isocitrate dehydrogenase 1/isocitrate dehydrogenase 2 gene mutation and the D-2-hydroxyglutarate oncometabolite level in dedifferentiated chondrosarcoma. *Histopathology* 2020;**76**:722–30.
25. Nakagawa M, Nakatani F, Matsunaga H, Seki T, Endo M, Ogawara Y, Machida Y, Katsumoto T, Yamagata K, Hattori A, Fujita S, Aikawa Y, Ishikawa T, Soga T, Kawai A, Chuman H, Yokoyama N, Fukushima S, Yahiro K, Kimura A, Shimada E, Hirose T, Fujiwara T, Setsu N, Matsumoto Y, Iwamoto Y, Nakashima Y, Kitabayashi I. Selective inhibition of mutant *IDH1* by DS-1001b ameliorates aberrant histone modifications and impairs tumor activity in chondrosarcoma. *Oncogene* 2019; **38**:6835–49.

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