Letter to the Editor

Codon 172 in the *IDH2* gene is a mutational hotspot in tall cell carcinoma with reversed polarity of the breast

Eiichi Sasaki^, Katsuhiro Masago

Department of Pathology and Molecular Diagnostics, Aichi Cancer Center Hospital, Nagoya, Japan

Correspondence to: Eiichi Sasaki. Department of Pathology and Molecular Diagnostics, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya, Aichi, 464-8681, Japan. Email: sasakia1es@gmail.com.

Comment on: Zhang X, Wu H, Wang Z, *et al.* Tall cell carcinoma of the breast with reverse polarity: case report with gene sequencing and literature review. Gland Surg 2021;10:837-43.

Submitted Feb 18, 2022. Accepted for publication Apr 22, 2022.
doi: 10.21037/gs-22-115
View this article at: https://dx.doi.org/10.21037/gs-22-115

We read with interest the case report by Zhang *et al.* (1) in a previous issue of *Gland Surgery* (February 2021) that described a case of tall cell carcinoma with reversed polarity of the breast (TCCRP) with a genetic analysis using targeted next-generation sequencing (1). Histologically, the tumor presented by Zhang *et al.* (1) appeared to show typical histologic features of TCCRP characterized by tall columnar cells with reversed nuclear polarity, arranged in solid and solid papillary patterns (2). In addition, an *IDH2* mutation was detected in the breast tumor, genetically supporting a diagnosis of TCCRP. TCCRP is a distinct breast cancer subtype characterized by frequent *IDH2* mutations (in 80–90% of cases), while *IDH2* mutations are extremely rare in unselected breast cancer cases (3,4). In the paper by Zhang *et al.* (1), the results of *IDH2* mutation detection were shown in Figure 4A. The authors interpreted the genetic result as *IDH2* p.R120G, a novel mutation, rather than *IDH2* R172 and described the need to consider the presence of an *IDH2* mutation at other sites than codon 172 in the discussion section.

IDH2 mutations have been reported in various tumors, such as glioma, acute myeloid leukemia, cartilaginous tumor, cholangiocarcinoma, angioimmunoblastic T-cell lymphoma, and sinonasal undifferentiated carcinoma and are assumed to play an important role in the carcinogenesis of these tumors (5-7). A mutational hotspot region in the *IDH2* gene is codon 140 in acute myeloid leukemia, while the great majority of *IDH2* mutations in the remaining histologic types occur at codon 172 (5,7). To our knowledge, an *IDH2* mutation at codon 120 has not been reported (or else is extremely rare), regardless of the histologic type. Therefore, we verified the results of DNA sequencing in the study by Zhang *et al.* (1) and realized that the mutation interpreted as p.R120G by the authors was actually p.R172G, one of most common *IDH2* R172 mutations in TCCRP, along with p.R172S and p.R172T (*Figure 1*) (3,9).

To date, approximately 60 cases of TCCRP with sequencing analyses for the *IDH2* gene have been reported in the English literature (3,9,10). The mutational regions previously reported in *IDH2*-mutated TCCRP cases are limited to codon 172, although, due to the relatively small number of TCCRP cases reported thus far, the presence of exceptional TCCRP cases with other types of *IDH2* mutations than R172 cannot be absolutely denied. Several commercially available immunohistochemical mono-specific and multi-specific antibodies against *IDH2* mutations at codon 172 have been developed (11), and the diagnostic utility of IDH2 R172 immunohistochemistry for *IDH2* R172-mutated tumors, including TCCRP, has been shown in previous studies (9,10). Therefore, the IDH2 R172

^ ORCID: 0000-0002-6385-8341.

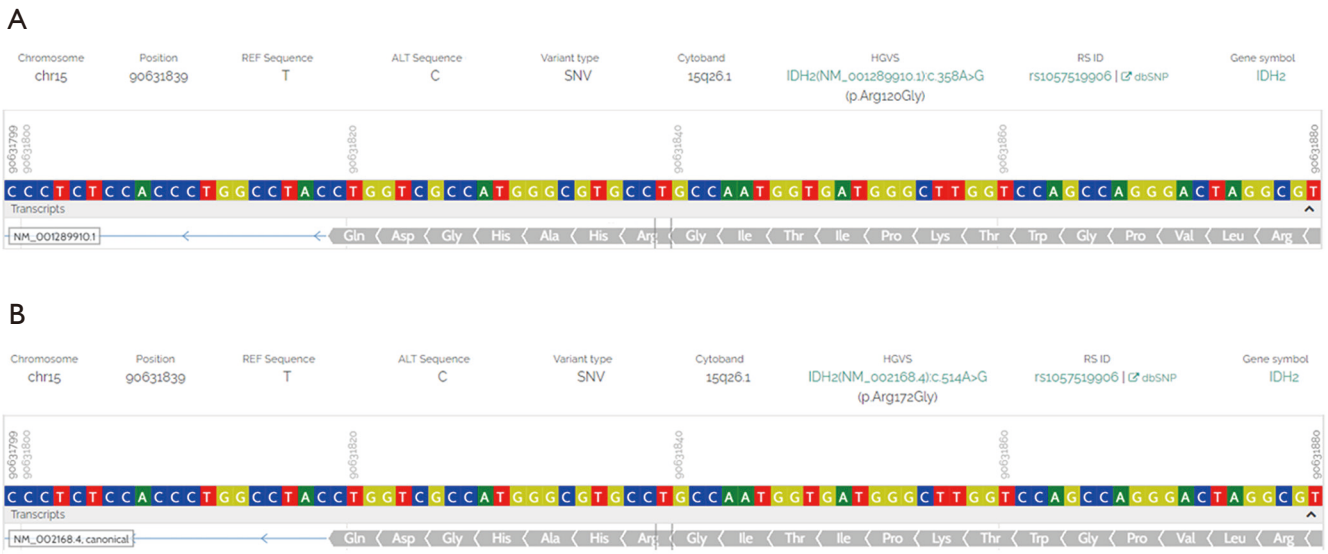

Figure 1 The mutation in this report was analyzed with the VarSome browser (https://varsome.com/) (8). (A) IDH2:c.358A>G (p.Arg120Gly) resulted from an analysis with the transcript ID (NM_001289910.1) given in the paper by Zhang *et al.* (1) (B) IDH2:c.514A>G (p.Arg172Gly) resulted from an analysis with the transcript ID (NM_002168.4). The results of these two sequences are identical, and which transcripts are used as references can influence the identification of codon numbers.

immunohistochemistry for TCCRP presented by Zhang *et al.* (1) may help confirm the presence of an *IDH2* R172 mutation (not a novel mutation).

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was a standard submission to the journal. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-22-115/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Zhang X, Wu H, Wang Z, et al. Tall cell carcinoma of the breast with reverse polarity: case report with gene sequencing and literature review. Gland Surg 2021;10:837-43.
2. Wei Y, Ding L, Song X, et al. Tall cell carcinoma with reversed polarity: case report with gene sequencing and literature review. Gland Surg 2021;10:3147-54.
3. Chiang S, Weigelt B, Wen HC, et al. IDH2 Mutations Define a Unique Subtype of Breast Cancer with Altered Nuclear Polarity. Cancer Res 2016;76:7118-29.
4. Yang W, Bu H, Foschini M, et al. Tall cell carcinoma with reversed polarity. In: Allison K, Brogi E, Ellis I, et al., editors. Breast Tumours. Lyon, France: International Agency for Research on Cancer, 2019:153-4.

5. Yang H, Ye D, Guan KL, et al. IDH1 and IDH2 mutations in tumorigenesis: mechanistic insights and clinical perspectives. Clin Cancer Res 2012;18:5562-71.
6. Cairns RA, Iqbal J, Lemonnier F, et al. IDH2 mutations are frequent in angioimmunoblastic T-cell lymphoma. Blood 2012;119:1901-3.
7. Dogan S, Chute DJ, Xu B, et al. Frequent IDH2 R172 mutations in undifferentiated and poorly-differentiated sinonasal carcinomas. J Pathol 2017;242:400-8.
8. Kopanos C, Tsiolkas V, Kouris A, et al. VarSome: the human genomic variant search engine. Bioinformatics. 2019;35:1978-80.
9. Alsadoun N, MacGrogan G, Truntzer C, et al. Solid papillary carcinoma with reverse polarity of the breast harbors specific morphologic, immunohistochemical and molecular profile in comparison with other benign or malignant papillary lesions of the breast: a comparative study of 9 additional cases. Mod Pathol 2018;31:1367-80.
10. Pareja F, da Silva EM, Frosina D, et al. Immunohistochemical analysis of IDH2 R172 hotspot mutations in breast papillary neoplasms: applications in the diagnosis of tall cell carcinoma with reverse polarity. Mod Pathol 2020;33:1056-64.
11. Kato Y. Specific monoclonal antibodies against IDH1/2 mutations as diagnostic tools for gliomas. Brain Tumor Pathol 2015;32:3-11.

Cite this article as: Sasaki E, Masago K. Codon 172 in the *IDH2* gene is a mutational hotspot in tall cell carcinoma with reversed polarity of the breast. Gland Surg 2022;11(6):1127-1129. doi: 10.21037/gs-22-115