Biochemical and Biophysical Research Communications 501 (2018) 619–627

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Over-expression of lysyl oxidase is associated with poor prognosis and response to therapy of patients with lower grade gliomas

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ARTICLE INFO

Article history:
Received 18 April 2018
Accepted 30 April 2018

Keywords:
Lysyl oxidase (*LOX*)
Lower grade gliomas (LGGs)
Biomarker
TCGA
EMT
IDH1

ABSTRACT

Lower grade gliomas (LGGs) have highly diverse clinical phenotypes. The histological grade and type are insufficient to accurately predict the clinical outcomes of patients with LGGs. Therefore, identification of biomarkers that can facilitate the prediction of clinical outcomes in LGGs is urgently needed. Gene expression of *LOX* has been identified as a biomarker for various cancers. However, the clinical significance of *LOX* expression in LGGs has not been investigated. In this study, we analyzed the glioma RNA-seq dataset from TCGA (The Cancer Genome atlas) and identified lysyl oxidase (*LOX*) as a potential biomarker for LGGs. Kaplan-Meier survival analysis revealed that high *LOX* expression is associated with worse overall survival and recurrence free survival in LGG patients. Besides, high *LOX* expression is associated with poor response to primary therapy, follow-up treatment, targeted molecular therapy, and radiation therapy. Univariate and multivariate Cox regression analyses further confirmed *LOX* expression as an independent prognostic factor for LGG patients. Finally, we observed that *LOX* expression is significantly correlated with EMT (epithelial to mesenchymal transition) and *IDH1* status in LGGs. In conclusion, our analyses suggest that *LOX* expression is a potential biomarker for prognosis and therapeutic response in LGGs.

1. Introduction

Gliomas are the most common primary brain neoplasms. Despite the standard therapy, including surgery and post-operative chemo and radiotherapy, or even targeted therapy in recent decades, the mortality rate of glioma patients remains high [1]. The World Health Organization (WHO) classification divides gliomas into four grades according to the malignant level diagnosed by pathology [2]. Lower grade gliomas (LGGs) were defined as grades II and III gliomas, which include oligodendrogliomas, oligoastrocytomas, and astrocytomas [3]. LGGs have highly diverse clinical phenotypes [4]. The prognosis of patients with LGGs is highly correlated with the WHO grade and varies depending on age and histological type [5]. Although the WHO grade and histological type are currently used by clinicians to predict the clinical outcomes of LGG patients, they remains unsatisfactory due to inter-observer variability, lack of reproducibility [6], and the existence of heterogeneity within patients who have the same WHO grade and histological subtype. Therefore, it is pivotal to identify clinically relevant molecular markers, which can be objectively measured in LGGs.

Lysyl Oxidase (*LOX*) is a secreted extracellular matrix (ECM) protein and normally required for its enzymatic function in the cross-linking of elastin and collagen in ECM. The increased *LOX* expression was originally found during normal embryonic

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https://doi.org/10.1016/j.bbrc.2018.04.228
0006-291X/

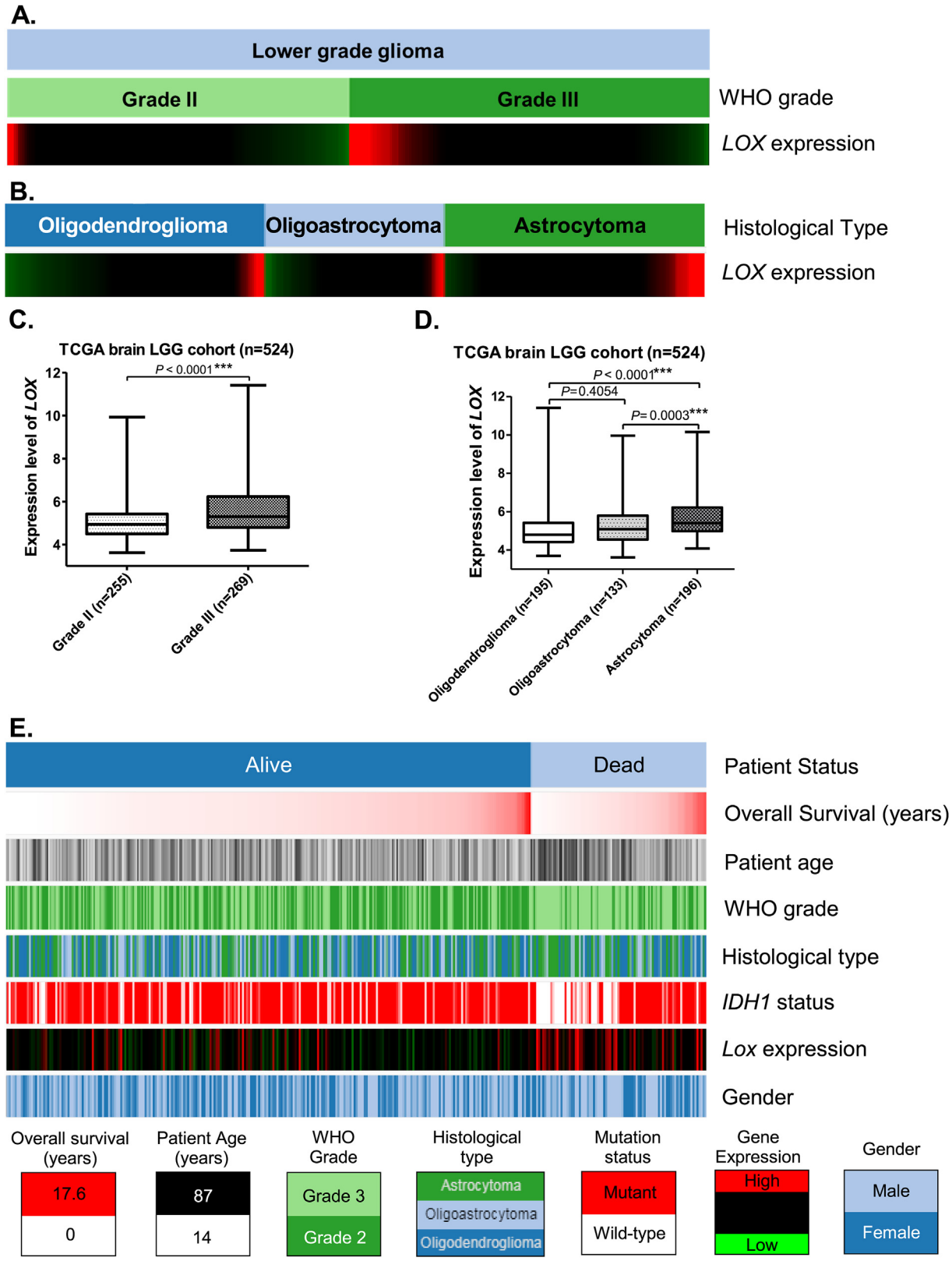

Fig. 1. The correlations between *LOX* expression and clinicopathological features in LGGs. The heat map was constructed according to the data in the TCGA brain LGG cohort. The expression levels of *LOX* were obtained by gene expression RNAseq (IlluminaHiSeq). (**A**). *LOX* expression in grade II and grade III gliomas. (**B**). *LOX* expression in oligodendrogliomas, oligoastrocytomas, and astrocytomas. (**C**). The expression levels of *LOX* in grade II and grade III gliomas. (**D**). The expression levels of *LOX* in oligodendrogliomas, oligoastrocytomas, and astrocytomas. (**E**). The correlations of *LOX* expression with patient status, survival time, age, the WHO grade, histological type, *IDH1* status, and gender.