




Case Report of a Glioma Patient with Homozygous Missense Amino Acid Substitution in *KDR* Gene

Kalyan Ram Uppaluri¹ Himavanth Reddy Kambalachenu¹ Hima Jyothi Challa¹ Saadvik Raghuram Y.²
Deepak Sharma¹ Ramya Gadicherla¹ Srinivas Ketavath¹ Kalyani Palasamudram¹ Sri Manjari K.¹

¹GenepowerRx, Suit #2B, Plot No. 240, Nirvana, Road No. 36, Jawahar Colony, Jubilee Hills, Hyderabad, Telangana, India

²Medicover Cancer Institute, Madhapur, Hyderabad, Telangana, India

Address for correspondence Kalyan Ram Uppaluri, MD, GenepowerRx, Suit #2B, Plot No. 240, Nirvana, Road No. 36, Jawahar Colony, Jubilee Hills, Hyderabad 500033, Telangana, India
(e-mail: kalyan@khdreamlife.com).

Ind J Med Paediatr Oncol 2023;44:356–359.

Abstract

Gliomas are the most commonly seen cancers of the central nervous system with a variable genetic predisposition. Here, we report a homozygous missense variant in the *KDR* gene in a patient with recurrent glioma. The 35-year-old male patient was diagnosed with stage IV glioma with a recurrence after 10 years from a low-grade stage two glioma. The patient underwent a repeat right craniotomy and ventriculo-peritoneal shunt placement. Biopsy of the lesion showed areas of necrosis with microvascular proliferation and multinucleated tumor cells. An in-depth analysis of NGS data comprising a multigene panel of 351 genes (Agilent Cancer Core Panel) found a homozygous missense variant in exon 25 of the *KDR* gene that resulted in a substitution of an amino acid glutamine for arginine at codon 1118. The *KDR* gene or VEGF2 receptor is a type III receptor tyrosine kinase of the *VEGF* gene involved in angiogenesis. We hypothesize that the variation in the *KDR* gene may have a role in the patient's transition from grade II to grade IV glioma. While the clinical relevance of this mutation is not clear, screening mutations in the protein tyrosine and serine/threonine kinase domain of the *KDR* will provide critical insights into the development and progression of glioma in the pediatric and adult populations.

Keywords

- ▶ glioma
- ▶ Protein Kinase
- ▶ KDR

Introduction

Gliomas are the most frequent neoplasms of the central nervous system (CNS) originating from glial cells in older adults (mean age of 65 years). They are diffusely infiltrative tumors that affect the surrounding brain tissue. Glioblastoma multiforme is the most malignant type of glioma, while pilocytic astrocytoma is the least. Based on the histopathological analysis, gliomas are graded into four types (I–IV). The first type, Grade I glioma, is easily curable as it is usually benign. The second type, Grade II glioma, also called lower grade glioma (LGG), is often encountered in young adults. LGG is

characterized by seizures and lesions in the temporal, frontal, or insular lobes. Most glioma cases detected belong to Grade III or Grade IV. In the United States, there are six cases of gliomas diagnosed per 100,000 people every year.¹ In India, 1 to 4 brain tumors per 100,000 cases occur. Glioblastoma multiforme (GBM) accounts for 18% of all primary brain tumors and 45.9% of all glioma tumors (data from Population-based Cancer Registry, GCRI). Thus, overall, the epidemiological data on GBM tumors indicates that the incidence of this malignancy is increasing in India.² Genetic factors, along with environmental influence, are known to cause gliomas. LGG in a young adult

DOI <https://doi.org/10.1055/s-0043-1762919>.
ISSN 0971-5851.

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may be more genetic in etiology. As more genetic studies are being done, several new genetic biomarkers are found to be associated with specific cancers. We report a case of recurrent gliomas, with increasing severity, in a young individual found to have a germline mutation in the *KDR* gene.

Case Report

A 35-year-old man with recurrent glioma was diagnosed with LGG in 2013, for which he underwent right-sided craniotomy and radiation therapy. This time he came in with aggressive secondary GBM, likely originating from the previous LGG. The patient presented with symptoms of generalized seizures and ECOG (Eastern Cooperative Oncology Group) performance status of level 3. Magnetic resonance imaging (MRI) brain showed right frontal craniotomy changes, including meningocele, along with new lesions in the right frontal lobe. The patient underwent a repeat right craniotomy and ventriculoperitoneal shunt placement. Biopsy of the lesion showed areas of necrosis with microvascular proliferation and multinucleated tumor cells. The patient was diagnosed as *IDH* mutated, *ATRX* mutated, GBM WHO grade IV. The patient was started on antiepileptics. He was also started on the chemotherapy agent Lomustine.

The attending physician sought tumor profiling and multi-gene panel testing to aid in drug decision-making of Foods and Drug Administration (FDA)-approved therapeutic molecules for approved biomarkers because the genetic factor was assumed to be linked to carcinogenesis. They investigated the correlation between non-routinely assessed oncogenes from a panel of 351 genes (Agilent Cancer Core Panel; **►Supplementary Table S1**, available online only) and clinical, morphological, and molecular features to isolate gene

variants, which might hold a diagnostic or prognostic significance and potential relevance for treatment. The DNA was extracted from FFPE blocks using the MN NucleoSpin DNA FFPE XS kit, followed by NGS Library preparation using SureSelect XT HS2 DNA system, a hybrid capture-based technology that includes 351 genes and subjected to paired-end sequencing on Illumina Novoseq 6000 platform. A total of 9.5 GB of raw data were generated, followed by the quality screening of raw FASTQ files, adapter trimming, mapping of raw data to the hg38 reference genome and generation of Sam/Bam files. VCF file was generated using the GATK 4.2.2 pipeline. Annotation of VCF file was using Ensembl VEP and Oncotator.

Results of Gene Panel test: Variant analysis in the targeted genes found a homozygous missense variant in exon 25 of the *KDR* gene (chr4:55089425C > T; NM_002253.4) (**►Fig. 1**). The single nucleotide substitution of C > T results in an amino acid substitution of glutamine for arginine at codon 1118 (c.3353G > A; p.Arg1118Gln) (**►Fig. 2**). The observed *KDR* gene variant lies in the protein tyrosine and serine/threonine kinase domain of the KDR protein. Though there are no proven clinical studies yet, and *in silico* analysis of the *KDR* gene variant p.Arg1118Gln was found to be probably damaging by PolyPhen-2 (HumVar and HumDiv) and deleterious by SIFT.

Discussion

The *KDR* gene encodes a kinase insert domain receptor, also known as VEGFR2,³ which is a type III receptor tyrosine kinase of the *VEGF* gene involved in angiogenesis.⁴ Angiogenesis plays an essential role in the transition from early stages of cancer to metastasis or stage IV. Strategies or medications that block VEGF-KDR signaling successfully inhibit experimental tumor growth, as this is the foremost signaling step required for the

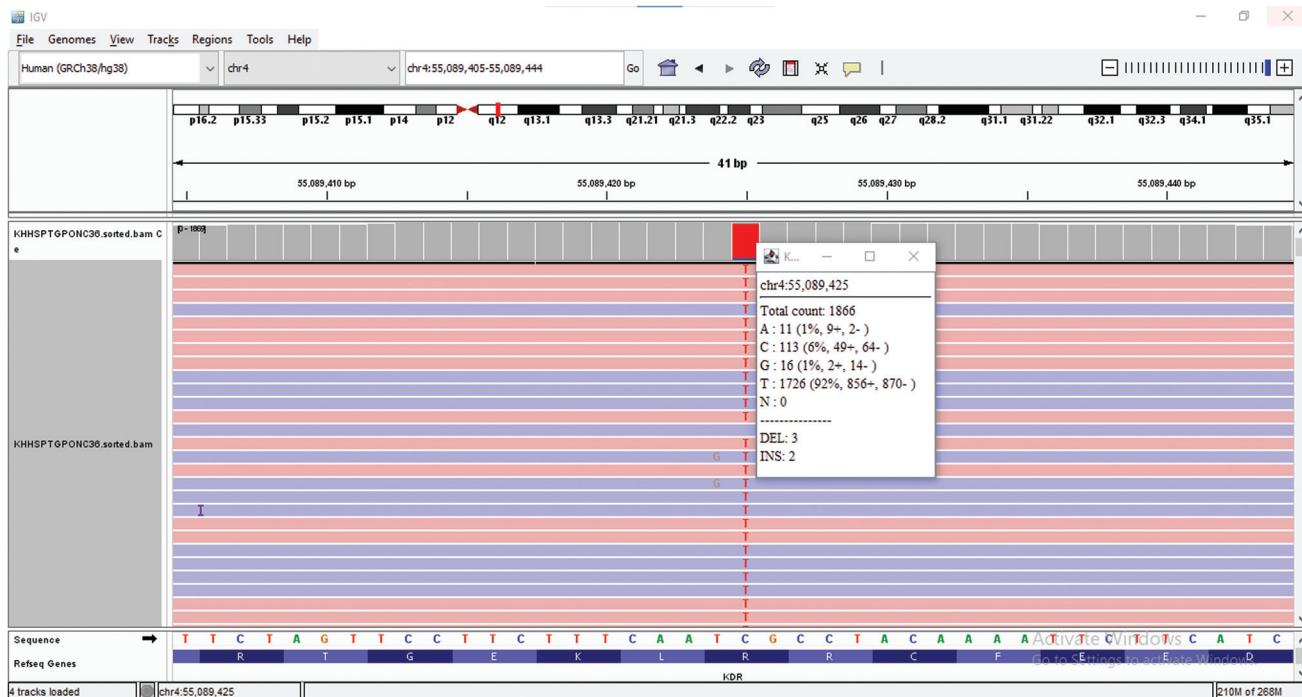


Fig. 1 KDR Gene Variant in IGV.

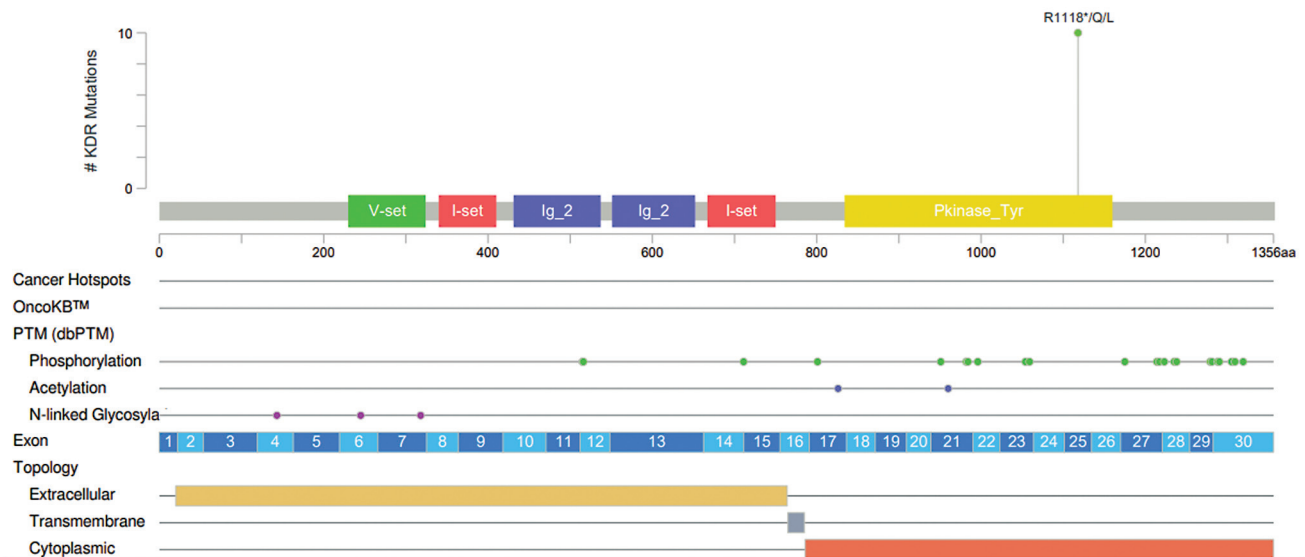


Fig. 2 Location of KDR Gene Variant (p.Arg1118Gln) (1).

proliferating tumor endothelium.⁵ It is well known that many FDA-approved drugs targeting the *KDR* gene (including apatinib, cabozantinib, pazopanib, and sorafenib) have been applied to treat renal, gastric, colorectal, and other cancers.^{6–9} A clinical trial in a Chinese cohort is going on to treat recurrent glioblastoma with apatinib.¹⁰

Association of *KDR* gene Mutations in Glioma

Mutations in the *KDR* gene have been reported in different cancer types, predominantly in melanoma and non-melanoma skin cancers (→ **Supplementary Fig. S1**, available online only). The p.Arg1118Gln variant in heterozygous conditions has previously been reported in glioblastoma, rectal adenocarcinoma, uterine endometrioid cancer, and colon adenocarcinoma (Resource: cBioportal).^{11,12} Two different mutations affecting the codon 1118 (p.Arg1118Ter and p.Arg1118Leu) have previously been reported in patients with glioblastoma multiforme, sarcoma, uterine endometrioid carcinoma, lung, and colon adenocarcinoma (The AACR Project GENIE Consortium, 2017).¹³ *KDR* p.Arg1118Ter variant is present in 0.02% of AACR GENIE cases and comprised colon adenocarcinoma, endometrial endometrioid adenocarcinoma, lung adenocarcinoma, and sarcoma and astrocytoma.^{14–16}

The limitation of this case report is that the targeted therapy associated with the *KDR* gene in gliomas is under clinical trials only. Though the detected variant was with a very high variant allele fraction, Sanger validation in paired tumor-normal specimens may strengthen the authenticity of zygosity. Hence, the present information helps facilitate further exploration of functional analyses of *KDR* mutations in gliomas.

Conclusion

This is the first report of the *KDR* gene variant in a homozygous state reported in a patient diagnosed with glioma. Screening

mutations in protein tyrosine and serine/threonine kinase domain of the *KDR* will provide critical insights into the development and progression of glioma in the pediatric and adult populations. Screening for germline mutations in pediatric cases, it is strongly recommended to conduct additional testing with paired tumour-normal specimens. Because GBM, the most aggressive type of glioma, is a vascular tumor, the *KDR* gene associated with VEGF is probably implicated in tumor growth. Therefore, in young GBM patients with germline *KDR* mutations, it might be prudent to give a trial of anti-vascular drugs along with the conventional treatment regimen.

Authors' Contributions

All authors have contributed and approved the manuscript.

Patient consent

The authors certify that they have obtained all appropriate patient consent forms

Statement of Ethics

This retrospective review of patient data did not require ethical approval under local guidelines. Written informed consent was obtained from the patient to publish this case report.

Funding

None.

Conflicts of Interest

None declared.

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