Cytogenetic and Genome Research

Novel Insights from Clinical Practice

Cytogenet Genome Res 2020;160:316–320
DOI: 10.1159/000509020

Received: February 28, 2020
Accepted: May 20, 2020
Published online: June 24, 2020

# Narrowing down the Common Cytogenetic Deletion 14q to a 5.6-Mb Critical Region in 1p/19q Codeletion Oligodendroglioma-Relapsed Patients Points to Two Potential Relapse-Related Genes: *SEL1L* and *STON2*

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**Established Facts**

- A deletion of 14q is common in higher-grade oligodendrogliomas and is related to poor progression.
- Relapse-related genes are unknown in patients with 1p/19q codeletion high-grade oligodendrogliomas.

**Novel Insights**

- 14q24.2q31.3 appears to be the crucial region for disease relapse in patients with 1p/19q codeletion oligodendrogliomas.
- Retrospective studies of 14q deletion along with our data are suggestive of 2 potential relapse-related genes: *SEL1L* and *STON2*.

**Keywords**
Codeletion 1p/19q · Deletion 14q · Oligodendrogliomas · *SEL1L* · *STON2*

**Abstract**
Based on a literature review and our database, we report on the smallest 14q deletion identified in a brain tumor characterized by 1p/19q codeletion low-grade oligodendroglioma. In 2013, array-comparative genomic hybridization of the brain tumor revealed 1p/19q codeletion as a sole abnormality. In 2019, the patient relapsed showing additional abnormalities including a 14q deletion of 16.5 Mb at 14q24.2q31.3. This region overlaps with 2 previously identified minimal regions, 14q21.2q24.3 and 14q31.3q32.1, based on 142 cases of glioma. The authors reported no correlation between these 2 regions and survival. By extracting these 2 regions from our patient's deletion and comparing it to 12 other cases of 1p/19q codeletion oligodendrogliomas reported in the literature, we narrowed down the 14q loss possible critical region to 5.6 Mb mapping at 14q31.1q31.2. This region contains 2 potential relapse-related genes: *SEL1L* and *STON2*.



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Patients with 1p/19q codeleted oligodendrogliomas are well-known to have a good response to chemotherapy and radiation therapy [Hu et al., 2016]. However, disease progression or recurrence is a common complication of these tumors. Published data showed that a deletion of 14q is common in higher-grade oligodendrogliomas and related to poor progression [Jeuken et al., 2002]. Currently, the gene on 14q responsible for the disease relapse remains unknown. By array-comparative genomic hybridization (array-CGH), our patient's brain tumor showed complete 1p/19q codeletion as the sole anomaly in 2013. The patient relapsed in 2019 during which array-CGH of the tumor showed additional abnormalities including an interstitial 14q deletion. Following an extensive literature review and comparison of all 14q deletions identified in relapsed/advanced oligodendroglioma patients, we here report on the smallest 14q deletion that encompasses 2 potential relapse-related genes in patients with 1p/19q codeleted oligodendrogliomas.

## Clinical Findings

A 46-year-old female who was admitted to the neurosurgical service for loss of consciousness and seizure in January 2013 underwent a CT scan of the head. The results showed a large calcified right parietal mass with vasogenic edema and right-to-left midline shift. In the meantime, MRI of the brain confirmed a minimally enhancing, cortically based right parietal lobe of 6.8 cm (anteroposterior) × 3.9 cm (transverse) × 3.7 cm (craniocaudal) mass containing calcifications with markedly increased perfusion, elevated cell membrane turnover, and neuronal loss. The differential diagnosis based on the imaging findings included oligodendroglioma with anaplastic features, intermediate to high-grade astrocytoma or oligoastrocytoma. The patient underwent craniotomy for resection of the tumor and was diagnosed as grade 2 oligodendroglioma, WHO grade II, focal high-proliferative index. The patient was tested positive for *IDH1* mutation, c.394C>T (p.R132C), detected by PCR. The patient received chemotherapy and radiation therapy after surgery. In 2019, after presenting to the emergency department for severe headache, the patient's head MRI showed a progressively increased heterogeneous/nodular enhancement at the posterior aspect of the resection cavity of approximately 2.8 × 2.6 × 3.9 cm in the anteroposterior, transverse, and craniocaudal dimensions, respectively, indicating recurrence of tumor changes. The patient had repeat right craniotomy for tumor resection on August 2019. Pathology reported the tumor as anaplastic oligodendroglioma, WHO grade III. Currently, the patient reports improvement in her left hand strength, gait, and speech.

## Pathology Findings

Microscopy of the paraffin-embedded permanent sections of the tumor detected in 2013 showed grade 2 oligodendroglioma, WHO grade II.

Microscopy of the paraffin-embedded permanent sections of the tumor dissected in 2019 highlighted an infiltrating cellular glial neoplasm with oligodendroglial morphology including medium- to small-sized tumor cells with round nucleus, mild to moderate pleomorphism, and scant cytoplasm. Calcifications were present. Focally, the tumor showed an increase in mitotic figures, up to 7 in 10 high-power fields. Microvascular proliferation and necrosis were not seen. The tumor was described as anaplastic oligodendroglioma, WHO grade III.

## Molecular Cytogenetic Results

Array-CGH with 108,000 probes designed by Agilent (Santa Clara, CA, USA) and interpreted using Genoglyphix software (PerkinElmer, UK) was performed to determine genomic losses and gains in correlation with the human genome build (hg19).

Array-CGH of the oligodendroglioma resected in 2013 showed only genomic losses of the whole chromosomearms1pand19q:1p36.33p12(835601_120504552)×1 and 19q11q13.43(27923819_59091183)×1.

Array-CGH of the recurrent oligodendroglioma in 2019 showed the previously identified clonal abnormality of 1p/19q codeletion and additional aberrations including an interstitial deletion of chromosome 14, 14q24.2 q31.3(72896946_89429196)×1 (Fig. 1), and a small interstitial deletion of chromosome 17, 17q23.3q24.1 (61746309_63241114)×1.

## Discussion

The genetic hallmark of oligodendroglial tumors is the complete loss of chromosome arms 1p and 19q. Patients with these tumors are thought to have a better prognosis than patients with mixed gliomas [Reifenberger and Louis, 2003]. Other genomic alterations are frequently found in anaplastic/high-grade tumors. These include deletions of chromosomes 4, 6q, and 14q [Jeuken et al., 2002; Reifenberger and Louis, 2003]. The latter is the most common aberration and claimed to play a role in disease relapse [Reifenberger et al., 1994; Kros et al., 1999; Jeuken et al., 2002; Kitange et al., 2005; Trost et al., 2007; Nauen et al., 2016; Hassanudin et al., 2019]. A recurrent chromosome loss indicates the presence of one or multiple genes that could be responsible for disease relapse. In search for this gene, a large study of 142 gliomas demonstrated 2 overlapping regions of 14q deletions, 14q21.2q24.3 and 14q31.3q32.1, which did not correlate with survival, histological grading and subtype, or other genetic alterations

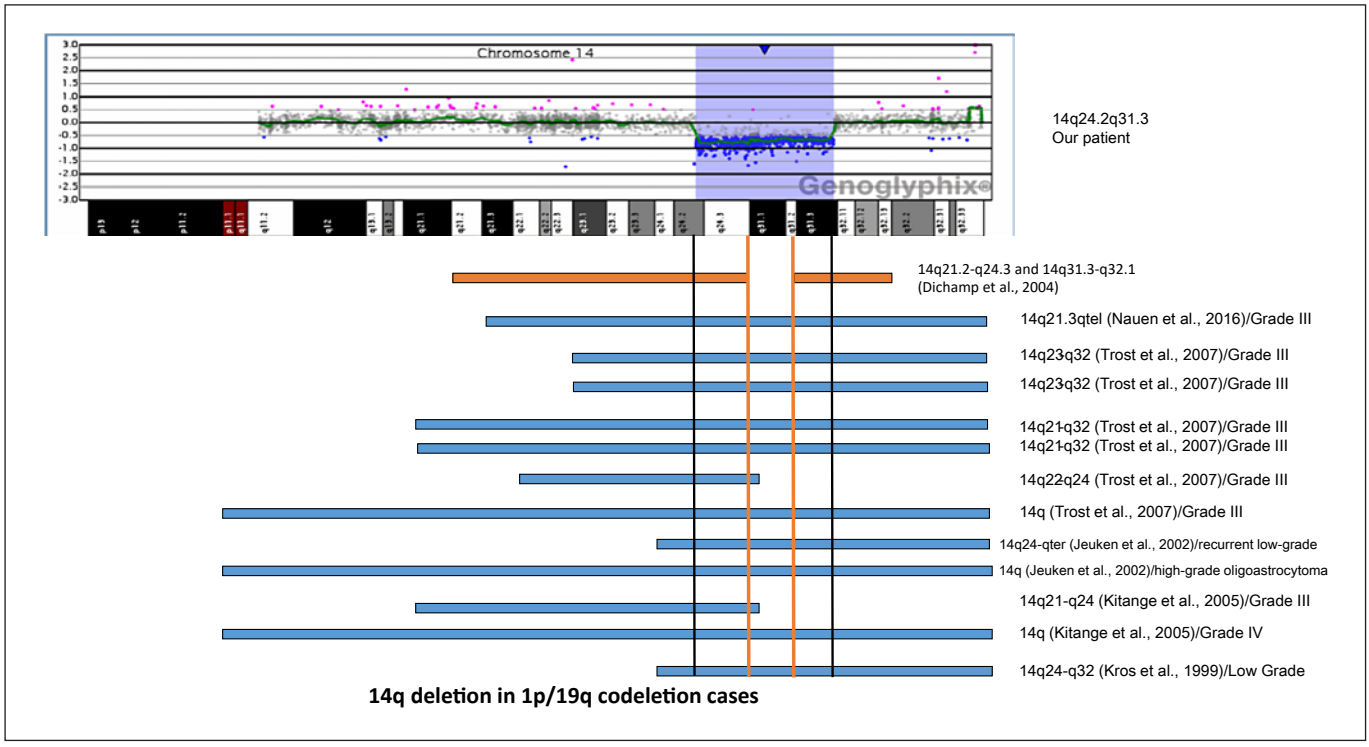


**Fig. 1.** Array-CGH plot of chromosome 14 showing the smallest interstitial deletion reported so far in oligodendrogliomas associated with 1p/19q codeletion. Below our patient's 14q deletion, all the blue bars represent the 14q deletions identified in patients described to have 1p/19q codeletion by array-CGH. The orange bars represent the exclusive regions of 14q that were found not to correlate with patient prognosis.

[Dichamp et al., 2004]. However, this study combined all different types of gliomas. In our study, we only compared the 14q deletions identified in all reported oligodendroglioma cases that had 1p/19q codeletion by array-CGH. A review of the literature published after the 2004 study revealed 12 additional cases of 14q deletions that may contribute to disease relapse or advanced stage as described by the authors. Although, these studies were performed by CGH, only the cytogenetic bands were published. Therefore, by comparing the cytogenetic bands of all these deletions to the region deleted in our patient and by excluding the non-significant regions documented by Dichamp et al. [2004] (Fig. 1, orange bars), a minimal critical 14q deletion of 5.6 Mb was assigned to 14q31.1q31.2 with the following genomic coordinates: 78,924,771–84,520,236. This appears to be the smallest deleted region of chromosome 14 identified in relapsed oligodendrogliomas that has ever been reported.

Moreover, a comparison of all 14q deletions found in gliomas without clear description of 1p/19q deletion status also revealed that our current minimal critical region is still in the 14q31.1q31.2 region (Fig. 2).

This minimal critical region of 14q31.1q31.2 encompasses 6 candidate genes: *NRXN3*, *DIO2*, *TSHR*, *GTF2A1*, *STON2*, and *SEL1L* (Fig. 3). The latter 2 genes, *STON2* and *SEL1L*, were found to be mutated in several types of cancer and may play a role in disease relapse:

*STON2* (stonin 2; OMIM 608467) encodes STON2 which interacts with the endocytic machinery proteins EPS15, EPS15R, and intersectin-1 and is a novel component of the general endocytic machinery that likely regulates vesicle endocytosis. Some studies suggested that STON2 may play an important role in schizophrenia as an AP-2-dependent endocytic sorting adaptor for synaptotagmin internalization and recirculation. Importantly, its role in tumor progression was first reported in ovarian carcinoma cell lines, in which overexpression was demonstrated in comparison with the normal ovarian cell lines [Sun et al., 2017].

*SEL1L* (suppressor of Lin12-like; OMIM 602329) encodes an endoplasmic reticulum-resident transmembrane adaptor protein for the hydroxymethylglutaryl reductase degradation protein 1 (HRD1). The SEL1L-HRD1 complex is involved in the recruitment, retrotranslocation,

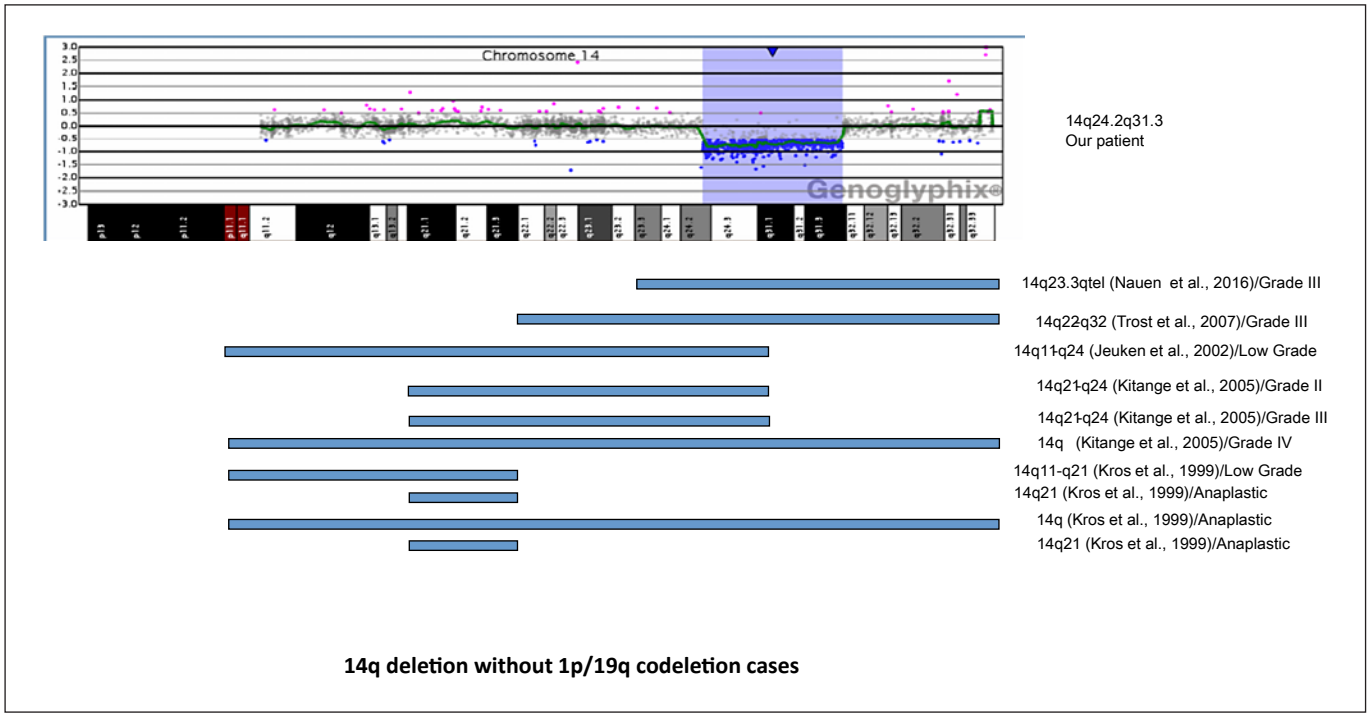


**Fig. 2.** Below our patient's 14q deletion, all the blue bars represent the 14q deletions identified in patients described to have oligodendrogliomas without 1p/19q codeletion by array-CGH.

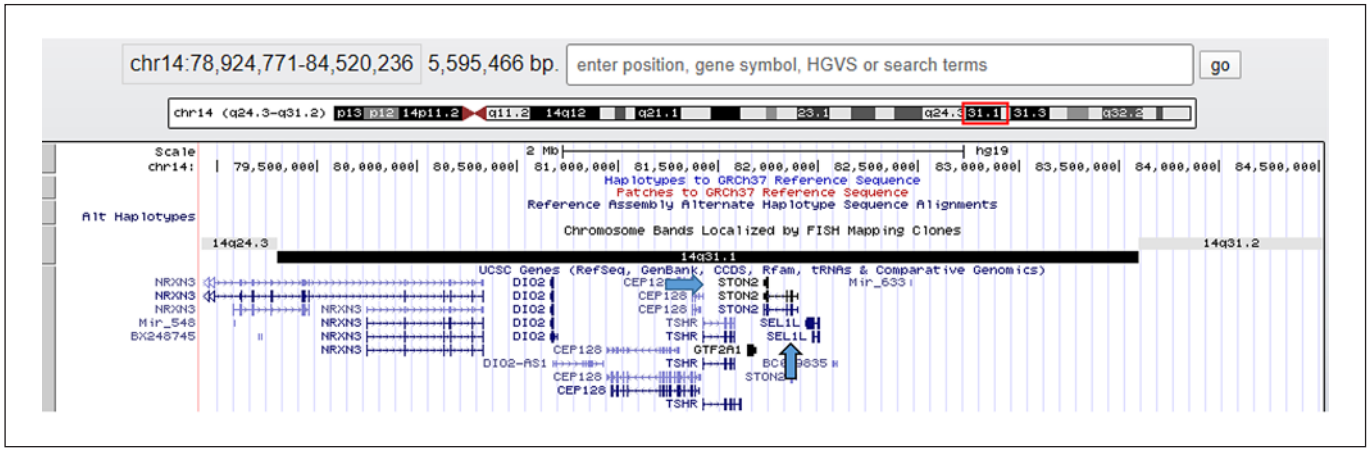


**Fig. 3.** UCSC ideogram of chromosome 14 listing all the genes found in the red square which represents the minimal critical region of 14q deletion after the exclusion of the non-significant regions described in Figure 1.

and ubiquitination of endoplasmic reticulum-associated degradation substrates. In 2006, a review article on SEL1L functions described its important role in hemostasis of cell physiology. Once the gene is affected, the cells undergo transformation leading to cancer, implying its role in tumor progression [Biunno et al., 2006]. Further, different expression regulations of *SEL1L* were identified in several human malignancies including pancreatic, colorectal, breast, gastric, esophageal, lung, and prostate cancer, i.e., downregulation in pancreatic and breast adenocarcinomas and upregulation in prostatic, lung, and cervical cancer and metastasis. Moreover, *SEL1L* is upregulated in the initial phases of colorectal cancer, suggesting a potential function in tumor progression [Mellai et al., 2020].

Recently, *SEL1L* expression appeared to be linked to glioma proliferation rate, histological malignancy grade, and to therapy response. Mellai et al. [2020] reported that overexpression of *SEL1L* in malignant gliomas is associated significantly with *TERT* promoter mutation, *EGFR* gene amplification, and other well-known negative prognostic markers for gliomas, leading the authors to suggest a role for *SEL1L* in glioma progression. Furthermore, downregulation of *SEL1L* conferred positive sensitivity to valproic acid treatment [Cattaneo et al., 2014] which may suggest a role of SEL1L in gene-target therapy.

The 17q deletion that encompasses 24 protein-coding genes is not known to be associated with oligodendroglioma relapse. Therefore, this aberration was not compared to other studies of high-grade oligodendrogliomas.

We report on the smallest cytogenetic deletion of 14q that could represent the most critical region in disease relapse in 1p/19q codeleted oligodendrogliomas. This region highlighted 2 strong candidate genes in the search for an understanding of the recurrence of high-grade oligodendrogliomas. Perhaps, a mutation analysis of *STON2* and *SEL1L* or next-generation sequencing of 14q24.3q31.1 would provide a refined mapping of the relapse-related minimal region in non-deleted 14q oligodendroglioma cases which would be necessary to confirm their primary roles in disease relapse which ultimately lead to gene-target therapy.


## Acknowledgement

The authors would like to acknowledge the technologists of the Molecular Cytogenomic lab of SSM Cardinal Glennon for performing the technical work.


## Statement of Ethics

The patient has given written informed consent to publish the results of the clinical work without any specific identification.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.


## Funding Sources

The authors have no funding sources to claim.


## Author Contributions

T.Z. gathered the data and wrote the manuscript. M.A.G. performed the pathology findings. J.R.B. designed and directed the work, supervised and edited the manuscript.

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