Expanding Genomic Landscapes of Pituitary Adenomas: A Case with Somatic IDH1 Mutation

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Introduction

- Pituitary adenomas are generally benign neoplasms of the anterior pituitary gland and are classified by their hormonal activity and histopathological features.
- Recurrent somatic mutations in *GNAS*, *USP8*, and *MEN1* have been implicated in pituitary tumorigenesis[1], but alterations in metabolic enzymes are exceptionally rare.
- Isocitrate dehydrogenase 1 (*IDH1*) mutations, common in gliomas and other malignancies, are extremely rare and have only been reported in single case reports.
- We describe a rare case of a pituitary adenoma harboring a **somatic *IDH1*** mutation, highlighting its potential biological and clinical relevance.

Methods and Materials

- We evaluated the clinical, pathological, and genomic characteristics of the patient.
- Whole-exome sequencing (WES) was performed on the tumor and matched peripheral blood.
- Sequencing was conducted at the Yale Center for Genome Analysis (YCGA) on Illumina NovaSeq 600 platforms, generating paired-end 2 × 101 bp reads.
- Mean target coverage was 421× for the tumor and 132× for blood.
- Downstream analyses identified somatic single-nucleotide variants (SNVs), insertion–deletions (INDELs) and copy number variations (CNVs).

Table 1. Tumor characteristics summarized from histopathological and genomic metrics

Immunohistochemistry	Positive for synaptophysin, focal positive for growth hormone, Pit-1, prolactin, ACTH Negative for TSH, LH, FSG, SF-1
Ki-67	3%
Tumor mutation burden	0.3 mut/Mb
IDH1 mutation allele frequency	40%

Results

Clinical case presentation & Histopathology

- Patient demographics:
  - an otherwise-healthy 39-year-old male
  - presented with headache, fatigue, and low libido
  - found to have a large sellar and suprasellar mass
- underwent uncomplicated endoscopic endonasal resection.
- Histopathology confirmed pituitary adenoma (Table 1).
- Ki-67 was 3%.

Genomic analysis (Somatic WES)

- tumor mutation burden of 0.3 mut/Mb, with two somatic mutations.
- **a hotspot *IDH1* mutation (p.R132C) was identified, with variant allele frequency of 40%, consistent with a clonal event.**
- *MALT1* splice acceptor variant, with variant allele frequence of 9%.
- No somatic CNVs were detected (Figure 1).
- No pathogenic germline variants associated with pituitary adenomas, other tumors, or cancer predisposition syndromes were detected.

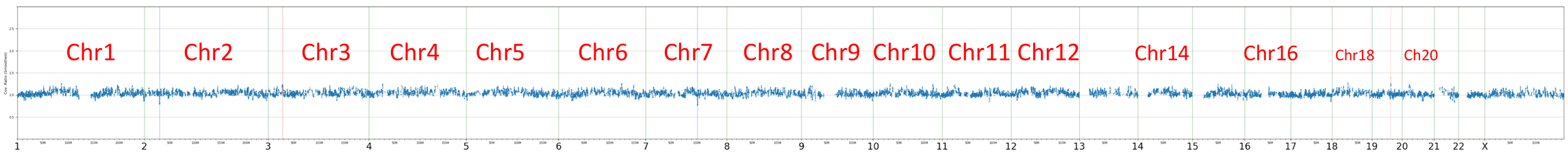

Figure 1. Normalized tumor coverage showing no large scale somatic CNVs

Discussion

- *IDH1* is a key metabolic enzyme in the tricarboxylic acid cycle, catalyzing the conversion of isocitrate to α-ketoglutarate and contributing to NADPH production.
- While essential for normal metabolism, mutations in *IDH1,* most often at codon 132, are recurrent in several cancers[2], where they generate the oncometabolite 2-hydroxyglutarate[3] and drive tumorigenesis through epigenetic reprogramming.
- The identification of a somatic *IDH1* (p.R132C) mutation in this pituitary adenoma is therefore striking and suggests a potential pathogenic role, supported by its clonal allele frequency.
- *IDH1* mutations serve as early drivers in frequently altered tumor types (gliomas, etc.) with therapeutic implications, and targeted inhibitors are already in clinical use.

Conclusions

Our finding expands the mutational spectrum of pituitary adenomas and underscores the value of genomic profiling to uncover clinically relevant alterations, even in rare cases.

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