# Somatic loss of BCLAF-1 in an Encephalocele Secondary to Idiopathic Intracranial Hypertension

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## Case Study

We report the clinical features and somatic genomic profile of a 70-year-old female who was found to have a right-sided nasoethmoidal encephalocele after she was investigated for new seizures. Magnetic resonance imaging revealed empty sella with a likely diagnosis of IIH. She did not have a history of trauma and described long standing rhinorrhoea which had recently stopped. Her significant past medical history included history of morbid obesity. There was no known familial history of IHH. Patient underwent Endoscopic Endonasal Approach (EEA) for resection of the encephalocele, which was confirmed by pathology. The lesion and blood samples were also sent for Whole Exome Sequencing (WES).

Genetic landscapes of idiopathic intracranial hypertension (IIH) and acquired encephaloceles are poorly characterized. To date, no somatic genomic analysis studies have been conducted on IIH. Given its sporadic and late-onset nature, this study explores potential somatic genomic mutations in CSF regulation, apoptosis, and angiogenesis pathways. Figure 1 depicts the empty sella on the sagittal MRI and the R ethmoid encephalocele on the coronal.

## Methods

**Sample Processing**

- Tumor and matched blood samples were analyzed using IDT xGen Exome Research Panel Version 1 with additional spike-ins.
- Sequencing was performed at Yale Center for Genome Analysis (YCGA) on Illumina NovaSeq 600 WES systems.
- Output: 2 × 101-bp reads with a high mean coverage of 2.66.6x for tumour samples and 116.9x for blood samples

**Downstream Analysis**

- Alignment to the reference genome (Grch37), duplicate marking, and local realignment was executed using GATK (v3.4, Grch37)

**Germline Variant Detection**

- Germline SNVs and INDELs were identified using GATK HaplotypeCaller (v3.4).
- Rare germline variants were filtered based on alleles. Variants were annotated using ANNOVAR (version 2019-10-24) and VEP (v95).
- frequency <1% in control databases (e.g., gnomAD-genome and gnomAD-exome, release 170,228).

**Somatic Variant Detection**

- SNVs were identified using MuTect (v2.7).
- INDELs were identified using Indelocator (IndelGenotyperV2).
- Further filtration criteria included variant allele frequency (VAF) in matching normal and tumor samples and allele frequency <1% in control databases (e.g., 1000Genomes, ExAC, NHLBI).

## Conclusion

- To our knowledge, this is the first study investigating the somatic genomic profile of IIH, which also identified a somatic loss-of-function mutation in the **BCLAF1** gene from sampled brain tissue.

### Genetic Studies and Future Research

- MESH search identified two genetic association studies but no somatic analysis studies on IIH.
- Preprint research by Zucker et al. (DOI: 10.1101/2023.06.03.23290934) on genetic associations with IIH and papilledema using UK and FinnGen Fz9 biobanks identifying key relevant genes: **BCL2L2**, **RGCC**, **HIF3A**.

### Proposed Research Directions

- Large-scale studies such as a UK biobank genome-wide association study (GWAS) of IIH-associated encephaloceles.
- Further exploration of interactions among **HIF**, **BCL2**, and **BCLAF1** families in IIH pathophysiology.
- Investigate the phenotype linked to cell proliferation, DDR, apoptosis evasion and decreased angiogenesis.
- Suggests a potential link between abnormal cell proliferation and IIH.

## Results

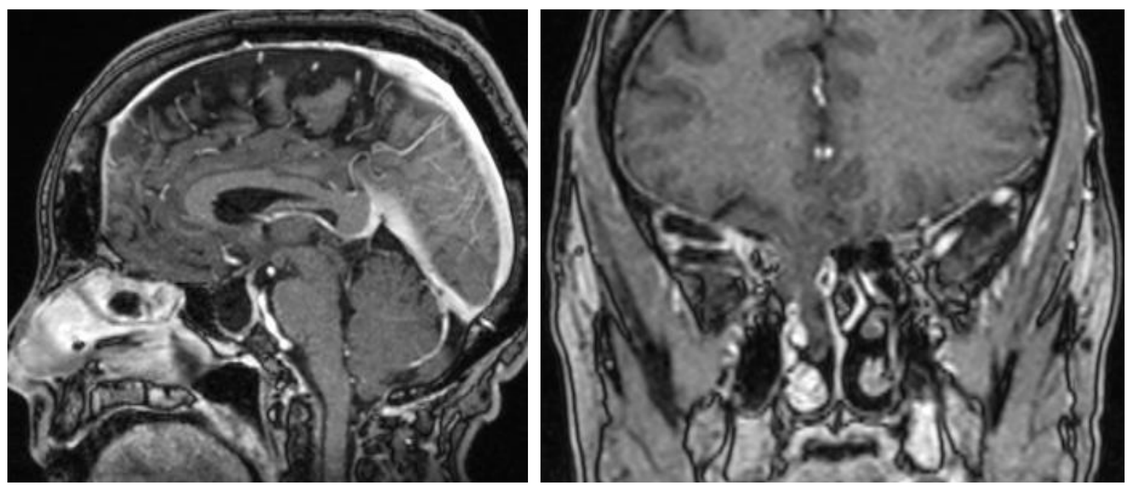

**Figure 1**

- Five somatic single nucleotide variants (SNVs) and insertions/deletions (INDELs) were detected.
- **BCLAF1 Mutation**: A stop-gain mutation in the BCLAF1 gene (NM_001077440, p.R748X) was identified.
- **Somatic CNV Analysis**: Somatic copy number variation (CNV) analysis revealed minimal genomic alterations caused by CNV events.
- **Variant Allele Frequency**: The variant allele frequency (VAF) of the BCLAF1 stop-gain mutation was calculated at 29.3%.

### BCLAF1 Gene: Characteristics and Function

**Gene Location**: Chromosome 6q23.3 with exon count of 18

**Roles in Cellular Pathways**

- Regulates the intrinsic apoptosis pathway by repressing BCL2 family proteins to promote apoptosis.
- Upregulates transcription of: **TP53**, **Bax**, **Caspase-3** and **HIF-1a**
- Involved in DNA damage response (DDR), positive transcription regulation, and negative regulation of DNA-templated transcription.
- In hypoxia, BCLAF1 binds to HIF-1a to promote angiogenesis. and reduce HIF-1a ubiquitination and degradation

**Mutation Impact**

- Stop-gain mutations in **BCLAF1** hinder cell apoptosis.
- Promote cell proliferation and growth.
- Suggest a phenotype with increased cell proliferation, evasion of apoptosis, and decreased angiogenesis.

**Dual Role**

- Exhibits either carcinogenic (colorectal cancer, acute myeloid leukaemia, hepatocellular carcinoma) or tumor suppressor behavior (colorectal adenocarcinoma, bladder cancer, multiple myeloma) depending on malignancy type.
- For example, high BCLAF1 activity showed increased survival rates in colorectal cancer but low survival rates in breast cancer
- Suggests additional regulation and biochemical functions may have a role, such as NF-kB.

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