Glioma in an *AIP* mutation carrier patient

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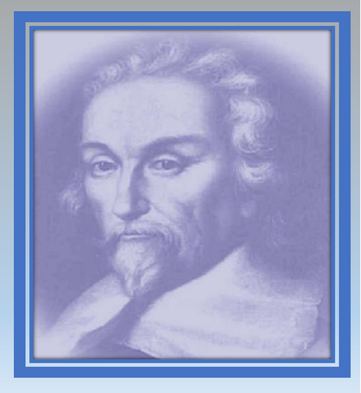

1. INTRODUCTION

Patients with mutations in the aryl hydrocarbon receptor-interacting protein *(AIP)* gene are characterised by young onset somatotroph or lactotroph macroadenomas.

AIP is believed to be a tumour suppressor gene (TSG). Loss of heterozygosity (LOH) has been discovered in pituitary adenoma samples from *AIP* mutation-positive patients and it is believed that *AIP* LOH is required for oncogenesis to occur[1].

A 53 years old male patient who was a carrier of a pathogenic *AIP* mutation (R304*), but was not affected by a pituitary adenoma (Figure 1), was identified with a low-grade glioma when clinical screening was first performed due to his carrier status (Figure 2). After 4 years of observational follow-up he was operated due to tumour enlargement.

Low grade gliomas are brain tumors arising from two different types of brain cells known as astrocytes and oligodendrocytes.

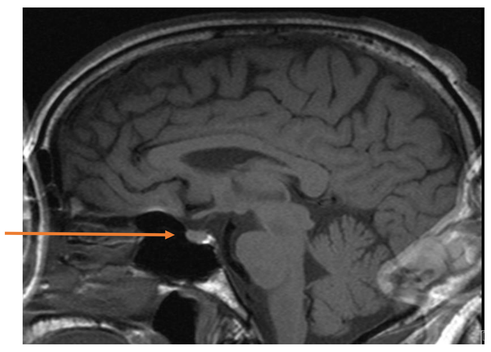

Figure 1: Sagittal MRI scan showing a normal pituitary

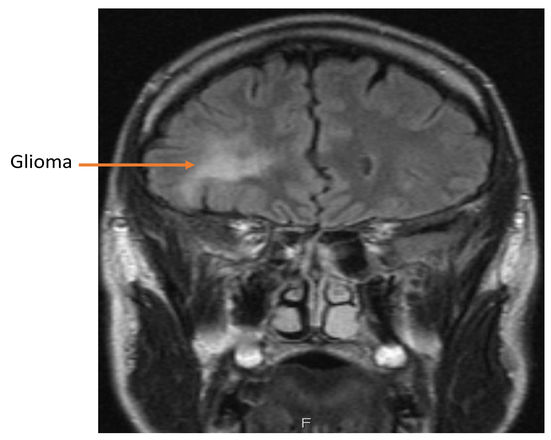

Figure 2: Coronal MRI portraying the glioma in the right hemisphere.

2. AIMS & OBJECTIVES

Aim:

Validate whether *AIP* may play a role in this patient's low grade glioma.

Objective:

To test if the glioma sample has lost the wild-type copy of *AIP* gene.

3. METHODS

DNA extraction:

DNA was extracted from the patients blood using QIAamp DNA Blood Mini Kit.

DNA was extracted from the patient's glioma tissue, marked on H&E slide by a neuropathologist avoiding surrounding non-tumorous tissue, using a QIAamp DNA FFPE Tissue Kit.

PCR:

A PCR experiment was carried out on blood-derived and glioma-derived DNA from the patient to amplify the region (exon 6) possessing the patient's *AIP* mutation (R304*). The PCR product was purified using Qiagen gel extraction kit and sent off for Sanger sequencing.

4. RESULTS

PCR bands showing amplification from blood and tumour-derived DNA (Figure 3)

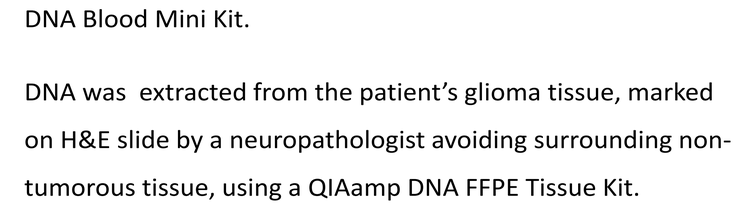

Figure 3: The agarose gel showed bands present in all of the DNA samples.

Sequence analysis:

Sequence analysis of the R304* *AIP* mutation of exon 6 performed in both glioma tissue & blood DNA showing a heterozygous mutation (highlighted in blue). No LOH was identified (Figure 4).

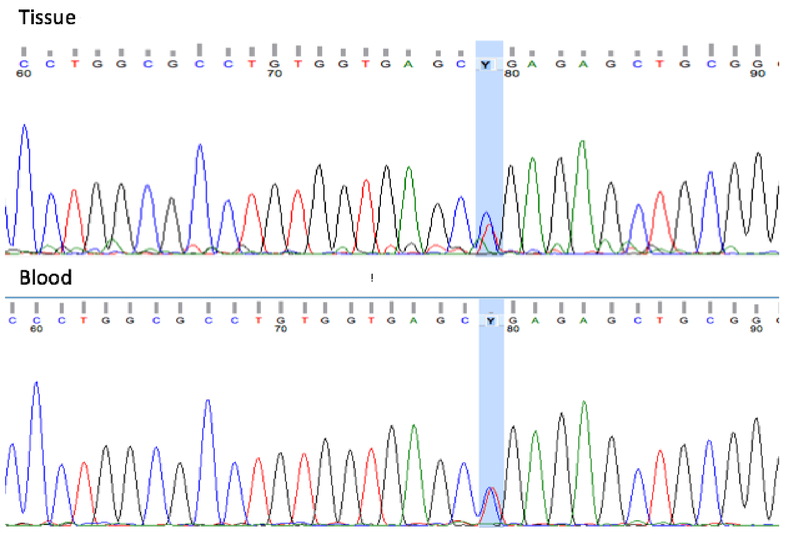

Figure 4: Sequence analysis of the R304* *AIP* mutation of exon 6.

6. DISCUSSION

The results indicate that there was no LOH of *AIP* in the patient's glioma tissue. Although the most common mechanism to lose the wild-type copy of a TSG in the tumour tissue is large deletion affecting the wild-type allele, other mechanisms could also play a role, such as another somatic mutation in other parts of the gene, or silencing of the wild-type copy with epigenetic mechanism - promoter methylation or microRNAs.

We have shown previously that a meningioma in a patient with acromegaly due to an *AIP* mutation also did not show LOH in the meningioma tissue while LOH was present in the pituitary adenoma (1) and similar data exist for other tumours (2).

AIP mutations are known to have a low penetrance. At this point there is no genetic or molecular explanation for this low penetrance. There is a possibility that other, more general cancer development genes might play a role, as there is several data available suggesting that patients with pituitary adenomas have a higher risk of other tumours (3-5). This suggests that in families where a pituitary tumour develops, other cancer predisposing variants are also present. While this patient did not have a pituitary adenoma, his brother suffered of early-onset acromegaly, clearly being one of the carrier subjects manifesting in this family. Whether there is a link between this patients glioma and the manifestation of pituitary adenoma in the brother is unclear.

7. CONCLUSION

It is unlikely that the R304* *AIP* mutation would play a role in the development of this patient's glioma.

7. REFERENCES

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