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Aryl hydrocarbon receptor- interacting protein: mutational analysis and functional validation in primary pituitary cell cultures

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Recently the Aryl hydrocarbon receptor – interacting protein (AIP) gene attracted attention as a novel gene linked to familial cases of acromegaly. In Malta the predicted prevalence of pituitary adenomas is particularly high, 4.67 per 10,000 population, thus suggesting a genetic predisposition.

Fourty seven maltese patients with acromegaly were screened for germ-line mutations in the AIP gene. Pituitary tumour tissue, removed during transphenoidal surgery from eight patients was cultured using a locally optimized protocol. Functional analysis of wild-type and mutant AIP genes on cell survival and proliferation of these primary cell cultures was carried out by transfection and proliferation assays (MTT). Two variants of the AIP gene, the R304X mutant (shown to generate a non-functional truncated protein, and R9Q, the mutant identified in a Maltese patient suffering from acromegaly (Farrugia *et al.* 2008, unpublished data), were successfully transfected into the primary cells. Transfection of wild-type, R304X and R9Q variants demonstrated that the R304X variant loses the ability to reduce proliferation as compared to the wild-type AIP, an effect previously demonstrated in other cell lines but not in primary cells. Furthermore, the R9Q mutation shows an inverse behaviour, causing a significant increase in proliferation in the primary cells, hence pointing to a gain-of-function mutation in the AIP gene.

AIP protein has been postulated to interact with the cAMP pathway and cell cycle regulators. Our results provide evidence supporting a role for AIP as a tumour suppressor gene. The R9Q mutant could help clarify the role of the N-terminal of the gene, which at present remains speculative Ongoing studies utilizing immunohistochemistry, cAMP assays and q-PCR should help identify AIP alterations downstream effects and verify whether specific AIP variants may alter cAMP levels and regulate gene expression of regulators and transcription factors.

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