

**Genome-wide gene expression profiling identifies overlap with malignant adrenocortical tumours and novel mechanisms of inefficient steroidogenesis in familial ACTH-independent macronodular adrenal hyperplasia.**

**Abstract**

ACTH-independent macronodular adrenal hyperplasia (AIMAH) is a rare cause of sporadic or familial late-onset Cushing's syndrome. It is a cytologically benign disease, of unknown pathogenesis, and characterised by inefficient steroidogenesis, ascribed to differential cellular localisation of steroidogenic enzymes. The objectives were to determine the molecular mechanisms involved in the pathogenesis of familial AIMAH tumours and the mechanisms of their inefficient steroidogenesis. Using Affymetrix Human GeneChip® HumanGene 1.0 ST arrays, we compared the genome-wide gene expression profile of two AIMAH nodules from each of three affected siblings with normal adrenal cortex and analysed the data for differential expression and using Ingenuity Pathway Analysis, Gene Set Enrichment Analysis and Motif Activity Response Analysis. Expression profiling identified: (i) that amongst the most highly differentially expressed genes were ones known to have involvement in tumorigenesis and metastasis; (ii) enrichment for differentially expressed genes in sporadic AIMAH and other benign and malignant adrenocortical tumours and (iii) reduced activity of key transcriptional regulators (Steroidogenic factor-1, SF-1 and transcription factor Sp1, Sp1) of steroidogenic enzymes. Genome-wide gene expression studies of familial AIMAH nodules have identified overlap with malignant adrenocortical tumours, which is intriguing given the benign biological behaviour of these tumours. This requires further study. Novel mechanisms of inefficient steroidogenesis were also identified.

Keyword: Gene expression; ACTH; AIMAH.