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Title: Role of transcription factors ASCL1 and HES1 expression in diffuse idiopathic neuroendocrine cell hyperplasia (DIPNECH) and pulmonary carcinoids

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Body: Background Carcinoid tumours are common neuroendocrine tumours in the lung. The majority of cases appear to be solitary; multiple tumours occur in patients with diffuse idiopathic pulmonary neuroendocrine cell heperplasia (DIPNECH), characterised by multiple hyperplastic neuroendocrine (NE) cell foci throughout the lung fields. In these patients DIPNECH appears to be the precursor lesion in the development of carcinoid tumours. Aims ASCL1 (Achaete-scute homolog 1) and HES1 (Hairy and enhancer of split 1) are transcription factors important in neuroendocrine development in the lung. We hypothesised that pathways involving these genes may be deranged in patients with DIPNECH and aimed to study their expression in sporadic and DIPNECH carcinoids. Methods Formalin fixed paraffin embedded (FFPE) samples from 25 carcinoid tumour cases (19 sporadic pulmonary carcinoids, 6 DIPNECH carcinoids) were studied. Expression of ASCL1 and HES1 was studied by real time PCR and immunohistochemistry (IHC). Results ASCL1 was more highly expressed in tumour samples than background lung (p=0.0149). HES1 was more highly expressed in background lung and DIPNECH compared to tumour samples (p=0.0016). HES1 staining was positive in all carcinoid tumours with no difference between DIPNECH and sporadic cases. ASCL1 staining was positive in 4 of 6 DIPNECH carcinoids, compared to 3 of 19 sporadic carcinoids (p=0.0324). Conclusion ASCL1 expression was significantly higher in DIPNECH carcinoids compared to sporadic cases, and was also present in NE foci suggesting an alteration in the pathway of this gene in DIPNECH patients and the carcinoid tumours found in this condition.