Inherited mutations in the SDH complex increase metastatic malignant potential of paraganglioma and pheochromocytoma tumours

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Pheochromocytomas (PCC) and paraganglioma (PGL) are neural crest tumours arising from the chromaffin producing cells of the adrenal medulla or sympathetic/parasympathetic system respectively. Recently, in part due to advances in high throughput sequencing, our understanding of the genetic predisposition to these tumours has greatly increased. To date, 13 genes have been implicated in the pathogenesis of these conditions (ten available for testing at our centre). Recent studies indicate that ~30-40% of patients with PCC/PGL may harbour a genetic predisposition to the condition. We aimed to determine the frequency that metastatic PCC/PGL was associated with mutations in known susceptibility genes.

The genetic profile of all individuals diagnosed with metastatic PCC and PGL in our centre was ascertained and compared to individuals with PCC/PGL without evidence of metastasis. Over the past 5 years 82 individuals with a diagnosis of PCC or PGL fulfilled the criteria for genetic testing. This included 16 individuals with metastatic disease. Among the patients with confirmed metastatic disease 13/16 (81%) had a genetic mutation identified in SDHB, SDHA, or SDHD predisposing to PCC and PGL. However, among those patients with no metastatic disease identified to date, only 42% (29/69) had a genetic mutation identified ($P=0.001$). Among the subjects with metastatic PCC, 11/13 had mutations (85%) in SDHB.

Our results imply that the identification of a mutation in the known PCC/PGL susceptibility genes confers an increased metastatic potential and also subjects with metastatic disease are most likely to harbour mutations in SDHB. Subjects with metastatic PGL/PCC are highly likely to have a genetic predisposition. In addition, identification of those individuals with PGL/PCC with a genetic mutation should be considered at high-risk for harbouring tumours with metastatic malignant potential.

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