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A report of succinate dehydrogenase B deficiency associated with metastatic papillary renal cell carcinoma: successful treatment with the multi-targeted tyrosine kinase inhibitor sunitinib

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[Summary] [Full text]

Loss of heterozygosity in SDHB locus on chromosome 1 in a subject with a metastatic papillary type I

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A recent case report in this journal presented the case of a subject with an SDHB mutation who developed a metastatic type II papillary renal cell carcinoma which therapeutically responded to the tyrosine kinase inhibitor, sunitinib 1 2. SDHB germline mutations account for the familial paraganglioma syndrome type 4 (PGL-4) which is characterised by predominantly extra-adrenal paragangliomas with high malignant potential 2. SDHB mutations have also been associated with renal cell carcinoma, gastro-intestinal tumours and some cases of PTEN negative Cowden-like syndromes 3-5. Though this renal cell carcinoma was presumed to be a consequence of the SDHB mutation, direct evidence to confirm this aetiological link has not been available to date. Here we report the loss of heterozygosity at the SDHB locus in chromosome 1 from metastatic tissue from this patient, confirming this supposition.

This subject developed an abdominal paraganglioma at the age of 10 years which was completely excised. Sixteen years later she developed a papillary type II renal cell carcinoma which metastasised one year following a nephrectomy. The subject experienced a partial response to second line chemotherapy with the tyrosine kinase inhibitor, sunitinib and has maintained stable disease over a year after therapy initiation. Genetic testing identified a nonsense mutation in exon 2 of the SDHB gene (c.141G>A) predicted to substitute a tryptohan residue for a premature stop codon (p.Trp47X).

We attempted to confirm the pathogenic role of SDHB in this renal cell carcinoma variant. Representative formalin-fixed, paraffin-embedded sections from an excised supraclavicular metastatic deposit were obtained. Ten micrometer sections were cut and tumoural DNA was extracted using the QIAamp DNA Mini kit (Qiagen) according to the manufacturer's instructions, with one additional round of proteinase K digestion. Loss of heterozygosity (LOH) analysis was carried out using Illumina Goldengate linkage panel (6056 SNPs). 250ng of DNA was hybridized to the arrays using the manufacturer's standard protocol. The Illumina Beadstudio software was used to indicate regions of LOH. Studies revealed loss of heterozygosity on chromosome 1p at the SDHB locus (17,217,812-17,253,252) implicating the likely role of the SDHB gene in the pathogenesis of this case of papillary renal cell carcinoma (figure1).

Since the first renal cell carcinomas were described in SDHB mutation carriers in 2004 3, there have been a limited number of further cases reported. This has been paralleled by a search in RCC registries to identify germline SDHB gene mutations. A recent review of the literature confirmed the association but it is clear that this is not a common manifestation, with a frequency of SDHB mutations in RCC of between 1- 4% 6. The majority of renal cell carcinomas associated with the SDHB mutation have been of the clear cell variety. The type II papillary morphology identified in this subject had not been noted in association with SDHB mutations previously but it is of note that this subtype is seen with mutations of the adjacent TCA cycle enzyme, fumarate hydratase, causing the hereditary leiomyomatosis and renal-cell cancer syndrome (HLRCC) 7. Type II papillary renal cell carcinomas are associated with a poorer prognosis than type I disease and matches the aggressive disease phenotype noted with SDHB associated chromaffin tumours.

Both the hypoxia inducible factor (HIF) pathway and the Von Hippel Lindau gene have been clearly implicated in the pathogenesis of renal cell

carcinoma. SDH dysfunction also appears to result in unsuppressed angiogenic stimulation via the HIF pathway. Further evidence for this link is provided by the heterogeneous staining demonstrated for HIF1α and HIF2α (Epas1) and their downstream cellular targets in tumour samples from this subject previously 1. Indeed, the patient's partial response to sunitinib, a tyrosine kinase inhibitor which targets the HIF pathway would also appear to corroborate this link.

The second hit in the normal SDHB allele therefore implicates it in the pathogenesis of renal cell carcinomas. However loss of heterozygosity in the SDHB gene is often associated with larger deletions in chromosome 1p and there is evidence to support the role of other tumour suppressor genes in this region e.g. KIF1Bβ, in which haploinsufficiency may be sufficient to promote tumourigenesis 8. In the clinical setting, SDHB mutation carriers need to be informed of the possibility, though limited, of developing renal cell carcinomas and appropriate disease surveillance in follow-up needs to be instigated. In summary, we have demonstrated evidence for loss of heterozygosity at the SDHB locus in tissue from a metastatic type II papillary renal cell carcinoma, implicating this mutation in its pathogenesis.

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Figure Legend

Figure 1: Type II papillary renal cell carcinoma – loss of heterozygosity in the SDHB locus. Loss of heterozygosity studies. Each panel gives the B allele frequency (upper) and the log R ratio plots. B(i) demonstrates a normal chromosome 1 while B(ii) shows the equivalent pattern from DNA extracted from tumour tissue. Loss of heterozygosity is demonstrated by the splitting of the indicated heterozygous calls around the 0.5 region (arrowed).

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