SHORT REPORT

Genetic screening for pheochromocytoma: should *SDHC* gene analysis be included?

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J Med Genet 2007;44:586–587. doi: 10.1136/jmg.2007.051045

PGL3 syndrome is caused by mutations in the *SDHC* gene. At present, only a few families affected by *SDHC* mutations have been reported in the literature and in each of them the clinical presentation was characterised by paragangliomas located only in the head and neck regions. No evidence of thoracic or abdominal catecholamine-secreting chromaffin tumours has been reported to date. We report the case of a 15-year-old girl with hypertension and a norepinephrine-secreting abdominal paraganglioma who was found to harbour a novel nonsense *SDHC* mutation, demonstrating that the clinical presentation of PGL3 syndrome can be more diverse than expected.

The genes predisposing to pheochromocytoma/paraganglioma include, in addition to *VHL*, *RET* and *NF1*, those encoding three subunits of mitochondrial succinate dehydrogenase (*SDH*).^{1,2}

Mutations in the *SDHB*, *SDHC* and *SDHD* genes cause PGL4, PGL3 and PGL1 syndromes, respectively. These syndromes are characterised by head/neck paragangliomas, which are parasympathetic in origin and generally not secreting. In PGL1 and PGL4, these paragangliomas are sometimes associated with chromaffin tumours, catecholamine-secreting tumours located in the abdomen or the thorax. PGL syndromes differ in penetrance (higher for PGL1 than PGL4), genetic transmission (maternal imprinting in PGL1) and malignancy (highest in PGL4). The absence of abdominal secreting tumours is considered a peculiarity of PGL3.

We report a patient with a novel germline *SDHC* mutation and an abdominal, norepinephrine-secreting paraganglioma.

A 15-yr-old girl was referred to our outpatient clinic for high blood pressure (150/95 mmHg). No relevant diseases were reported in her medical history. The clinical examination confirmed the hypertension.

Because of the patient's young age, a secondary cause was suspected and in fact, laboratory tests showed abnormal levels of urinary normetanephrine (5065 µg/day, normal range 88–440). Nuclear magnetic resonance imaging showed an abdominal mass, 5×3 cm in size. The chromaffin nature of the tumour was confirmed by ¹²³Iodine metaiodobenzylguanidine scintigraphy.

After a 10-day course of oral doxazosine (6 mg/day), the patient underwent surgery. A large compact tumour, 5 cm in size, located in the right paraaortic region, was removed. No enlarged lymph nodes were found. The postsurgical course was uneventful. At 40 days after surgery, urinary normetanephrine was normal and to date, the patient is normotensive and does not require treatment.

Although the patient's family history was negative for pheochromocytoma-associated syndromes, we suggested performing genetic analysis as the familial forms are frequent in the first two decades of life.³ The patient gave written informed consent to the study, and all necessary ethics approval was given by the local ethics committee of our university hospital.

METHODS AND RESULTS

A blood sample was taken for DNA extraction, and genetic analysis of *VHL*, *SDHB*, *SDHD* and *SDHC* genes was performed as previously reported.⁴

No mutations were found in the *VHL*, *SDHB* and *SDHD* genes. A nonsense mutation (W42X; c.126G→A) was found in the third exon of the *SDHC* gene, resulting in a stop codon and causing premature truncation (fig 1).

Because of this finding, we also performed nuclear magnetic resonance imaging of the patient's head and neck region to look for additional paragangliomas, which are considered a hallmark of PGL3 syndrome. No other lesions were found.

DISCUSSION

To our knowledge, this is the first report of an *SDHC* mutation associated with an isolated abdominal chromaffin tumour. The few *SDHC* mutation carriers identified to date had developed only head and neck paragangliomas⁵ and no *SDHC* mutations had been described in a large series of patients with apparently sporadic pheochromocytomas.³ Consequently, at present, in the presence of an abdominal secreting paraganglioma, the algorithms so far published for genetic screening in patients with pheochromocytoma suggest avoiding *SDHC* testing.⁶ It might well be that our unique finding depends on the much lower prevalence of *SDHC* mutations in comparison with those of *SDHD*, *SDHB* and other susceptibility genes for pheochromocytoma.

Abbreviation: SDH, succinate dehydrogenase

Figure 1 Electropherograms showing the W43X mutation. Wild-type (left), forward (centre) and reverse (right) sequences are shown. SDH, succinate dehydrogenase.

Nevertheless, we believe that our finding, especially if confirmed in other patients, will change the approach to genetic analysis in patients with pheochromocytoma.

ACKNOWLEDGMENTS

This paper was partly supported by a grant from MIUR (Ministero dell'Istruzione, dell'Università e della Ricerca; grant no 2006060473) and by an unrestricted grant by Villa Gisella, Florence, Italy.

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Competing interests: None declared.

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Received 17 April 2007

Revised 8 May 2007

Accepted 16 May 2007

Published Online First 8 June 2007

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