CASE REPORT

A Chinese family with familial paraganglioma syndrome due to succinate dehydrogenase deficiency

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We report the genetic characteristics of a family with familial paraganglioma syndrome. The index patient was diagnosed with carcinoid tumour of the bronchus at the age of 30 years then later diagnosed with bilateral phaeochromocytoma. His sister had bilateral carotid body tumours. Mutational analyses of succinate dehydrogenase B and *SDHD* on the index patient showed him to be heterozygous for the *M11* mutation of the *SDHD* gene. A genetic analysis revealed that his sister also had succinate dehydrogenase deficiency with the same mutation. Pre-symptomatic testing confirmed the genetic diagnosis, and led to a clinical diagnosis in an otherwise asymptomatic sibling. Comparison with other known cases of *M11* mutation suggests that this is a founder mutation in the Chinese population. Genetic analysis of the succinate dehydrogenase genes can provide a specific diagnosis and allow for genetic screening of at-risk individuals.

Introduction

Paragangliomas are rare tumours derived from the parasympathetic and sympathetic nervous systems. These tumours arise from embryonic neural crest derivatives, and can arise from sympathetic nervous tissues in the thorax, abdomen, Zuckerkandl body at the aortic bifurcation or adrenal medulla, or from parasympathetic tissues in the carotid body, intravagal, aortocaval or jugulolymphatic regions.[1] Sympathetic-associated paragangliomas arising from the adrenal medulla or sympathetic ganglia are usually functionally active, producing excess catecholamines, and are commonly referred to as phaeochromocytomas. The parasympathetic-associated paragangliomas arising in the head and neck are usually non-functioning. Carotid body tumours are composed of paraganglionic cells and sustentacular cells, and are therefore better referred to as paragangliomas. Approximately 10% of paragangliomas are thought to be hereditary and are inherited in an autosomal dominant pattern with incomplete penetrance. Characteristic features of hereditary paraganglioma include early age of onset, multicentricity of tumours, and familial clustering.[2] Succinate dehydrogenase (SDH) is a key enzyme that catalyses the oxidation of succinate to fumarate in the tricarboxylic acid (TCA) cycle. Functioning as mitochondrial complex II in the electron transport chain, it transfers electrons extracted from succinate to ubiquinone.[3] Recently, mutations in the subunits of SDH have been found to cause familial paraganglioma syndrome.[3,4] In this report, we describe the genetic characteristics of a family with familial paraganglioma syndrome, with identification of a mutation causing SDH deficiency.

Key words
Paraganglioma; Phaeochromocytoma; Succinate dehydrogenase

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Case report

The clinical presentation of the index case has been previously described.[5] Briefly, the patient developed episodic flushing, diarrhoea, and sweating in 1988 but did not seek medical attention initially. In February 1989, the patient developed haemoptysis, was investigated at another hospital and found to have a tumour of the right upper lobe bronchus. Histology showed a carcinoid tumour that stained positive for neuron-specific enolase. A postoperative spot urine test for 5-hydroxyindoleacetic acid was normal. The patient continued to have episodic symptoms after the operation, and was subsequently found to have bilateral phaeochromocytoma, with an elevated urinary noradrenaline of 10 421-14 609 nmol/day (reference range, 63-146 nmol/day) and bilateral adrenal tumours on magnetic resonance imaging of the abdomen. Magnetic resonance imaging of his neck and upper thorax did not reveal any paragangliomas. A metaiodobenzylguanidine scan did not reveal any focal areas of increased uptake. He was treated with phenoxybenzamine and propranolol, and managed with bilateral adrenalectomy. He was found to have a 5 x 2 x 4 cm tumour in the right adrenal and a 4.5 x 2 x 3.5 cm tumour affecting the left adrenal gland. Histology confirmed bilateral phaeochromocytomas with no evidence of vascular invasion. Repeated postoperative urine collections analysed for catecholamines were

一個華裔家庭因琥珀酸脫氫酶缺乏症而出現家族性副神經節細胞瘤綜合徵

本文描述一個出現家族性副神經節細胞瘤綜合徵的家庭的基因特點。首發病例的男性患者30歲時經診斷後發現患上支氣管類癌，之後發現雙側嗜鉻細胞瘤，而患者的姐姐則患雙側頸動脈體瘤。對患者進行琥珀酸脫氫酶B和*SDHD*突變分析發現，他的基因是*SDHD*基因中*M11*突變的雜合，而基因分析顯示他的姐姐亦有琥珀酸脫氫酶缺乏症兼有同樣的突變。對患者另一個弟弟作臨床診斷，遺傳學測試證實他亦有同樣的突變但未出現任何症狀。與其他*M11*突變的病例比較後可知，此為華裔群體裏的始建性突變，而對琥珀酸脫氫酶基因作基因分析研究是一個相當有效的診斷方法，有利於對可能患病的人作進一步的基因檢測。

normal and the patient remains well on hydrocortisone and fludrocortisone. Further questioning revealed a positive family history of paraganglioma; the family pedigree is outlined in Figure 1.

The index patient's elder sister is known to have a history of paragangliomas. She presented to another hospital in 1982 at the age of 24 years with a right-sided neck mass. This was resected and histology revealed a carotid body tumour. Three years later, she developed a mass affecting the left side of her neck. This was resected and histology again revealed a carotid body tumour. She has remained well and is currently on lansoprazole for gastro-oesophageal reflux. During a recent clinical review her blood pressure was 119/82 mm Hg and her urinary metanephrines and catecholamines were all normal. She has a son aged 22 years and a daughter aged 18 years who are both in good health.

We performed mutation analyses on DNA extracted from peripheral blood. All the coding exons and flanking introns of the *SDHB* and *SDHD* genes were amplified by polymerase chain reaction (PCR) and the PCR products were sequenced by direct DNA sequencing.[6]

The mutation analysis revealed that the index patient was heterozygous for the *M11* mutation in the *SDHD* gene (Fig 2). Following genetic testing of the proband, genetic testing was performed on the other affected sibling after counselling. The sister was found to carry the same *SDHD* mutation. After detailed counselling, pre-symptomatic testing was offered to other family members. The index patient's younger brother underwent genetic testing, and was found to carry the same mutation. This younger sibling did not have any significant medical history and his physical examination, including blood pressure was unremarkable. Screening revealed a 2-fold elevation of urinary noradrenaline suggestive of the presence of a catecholamine-secreting tumour. This patient is currently being investigated to locate the tumour. The children of the two family members with clinically apparent disease have been given genetic counselling, and are contemplating genetic testing. The elder brother of the proband is also currently contemplating screening.

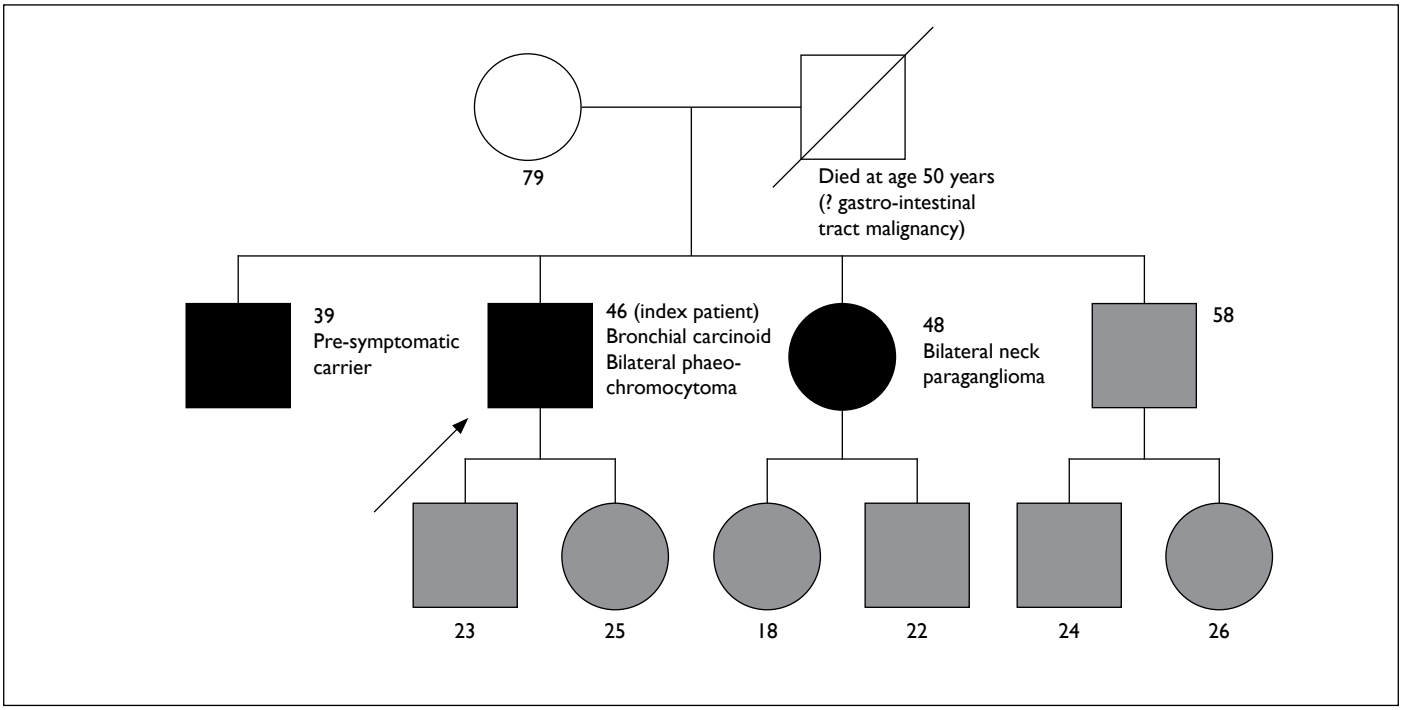

FIG 1. Pedigree of the family

Black circles/squares—individuals tested positive for *SDHD* mutation
Grey circles/squares—individuals not had genetic testing
Current age (years) of individual is displayed next to/below the symbol

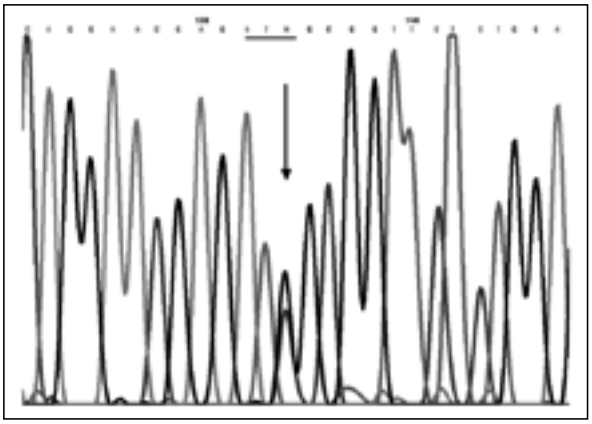

FIG 2. Sequence chromatogram showing the *SDHD* mutation in the proband

The single base G-to-C substitution in exon 1 results in replacement of the start codon (underlined), ATG to ATC. The heterozygous site is represented by the letter N

Discussion

In recent years there have been significant advances in knowledge of the molecular pathogenesis of phaeochromocytomas. Phaeochromocytomas have been recognised as occurring in association with von Hippel-Lindau disease, multiple endocrine neoplasia type 2, and neurofibromatosis in relation to germline mutations in *VHL*, *RET*, or *NF1*, respectively.[7] Phaeochromocytomas can also occur as part of a familial paraganglioma syndrome. Recently, mutations in genes encoding subunits of SDH, or mitochondrial complex II, have been identified as causing familial paragangliomas.[4] Succinate dehydrogenase is a key enzymatic complex involved in both the TCA cycle and oxidative phosphorylation as part of the mitochondrial respiratory chain. Mutations in the genes encoding three subunits of SDH (*SDHB*, *SDHC*, and *SDHD*) have been identified in subjects with familial paragangliomas.[8] Functional studies of mutations of the *SDH* gene have revealed that mutations abolish the enzymatic activity of mitochondrial complex II, resulting in activation of the hypoxia pathway.[9] It is believed that inactivation of SDH might lead to a build-up of reactive oxygen species and succinate, which together could signal the presence of hypoxia in the paraganglionic cells, leading to hyperplasia and eventual neoplastic transformation.[3] Interestingly, mutations in *SDHD* and *SDHB* have also been found to confer susceptibility in apparently non-syndromic phaeochromocytomas.[10]

The family we described suffers from SDH deficiency due to *M1I* mutation of the *SDHD* gene. This mutation has been previously reported,[11,12] and causes a G-to-C substitution at the last nucleotide of codon 1 of the *SDHD* gene, resulting in abolishment of the initiation codon. As the next methionine codon in the *SDHD* gene is not until met91, the *M1I* missense mutation is expected to produce a non-translated transcript, resulting in SDH deficiency. In a recent study on the genotype-phenotype association of a large cohort of patients with phaeochromocytoma and paraganglioma syndromes and *SDHB* and *SDHD* mutations, it was noted that *SDHD* mutation carriers had a greater propensity to develop head and neck paragangliomas and multiple tumours. Common presenting symptoms seen in carriers of *SDHD* mutations include headache, dysphonia, deafness, and hypertension. Although several of the subjects in the cohort had extra-adrenal thoracic paragangliomas, none of the patients had a carcinoid tumour.[13] It is sometimes difficult to distinguish bronchial carcinoids from phaeochromocytomas histologically, with both tumour types sharing similar morphology and both exhibiting immunoreactivity against neuron-specific enolase and S-100 protein.[14] In retrospect, it is likely that the bronchial tumour in our index patient was in fact a thoracic paraganglioma. Patients in this family had abdominal phaeochromocytomas and head and neck paragangliomas, consistent with the clinical presentation of other known patients with this mutation.[11,12]

All members of the family we described carried germline mutations of the *SDHD* gene. Our report, to the best of our knowledge, represents the first case of SDH mutation identified in China. It is known that familial paraganglioma is inherited in an autosomal dominant pattern. The *SDHD* gene demonstrates maternal imprinting and only a paternal transmission leads to paragangliomas in the offspring. We postulated that our patients must have inherited the mutation through their deceased father. This mutation has only been previously described in a Chinese family residing in Australia[11] and a Chinese family in Singapore.[8,12] Reported mutations in the *SDHD* gene are widely distributed along the entire gene, with no obvious hot spots shared by different ethnic groups.[8] The fact that our family represents the third Chinese family carrying this mutation is intriguing, and is consistent with the view that the *SDHD M1I* mutation is a founder mutation in the Chinese population.[12] This phenomenon has been noted elsewhere. Most affected Dutch families with familial paraganglioma were descendents of a single individual who was the first ancestral carrier of the gene mutation.[15]

In view of the autosomal dominant pattern of inheritance in familial paraganglioma, patients with paragangliomas and/or phaeochromocytomas should be offered genetic screening, particularly those with young-onset and multicentric manifestations. Given that different mutations are associated with tumours affecting different sites, patients presenting with catecholamine-secreting abdominal paragangliomas should be screened for *SDHB* mutations before *SDHD* mutations, whereas patients with head and neck paragangliomas should be tested for *SDHD* mutations first, followed by *SDHC* and *SDHB* genetic testing if negative.[7] Genetic testing of

one family member has clear implications for the whole family, and detailed counselling before, during, and after the testing procedure is required.

In conclusion, we describe a family with familial paragangliomas due to SDH deficiency. Genetic testing, after appropriate counselling, should be considered in subjects who present with head and neck tumours or phaeochromocytomas. Genetic testing may permit a pre-symptomatic diagnosis and subsequent management of at-risk individuals.

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