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

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 pheochromocytoma. 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. Sympathetic-associated paragangliomas arising from the adrenal medulla or sympathetic ganglia are usually functionally active, producing excess catecholamines, and are commonly referred to as pheochromocytomas. 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 pheochromocytomas. The characteristic features of hereditary paraganglioma include early age of onset, multicentricity of tumours, and familial clustering. 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. Recently, mutations in the subunits of SDH have been found to cause familial paraganglioma syndrome. In this report, we describe the genetic characteristics of a family with familial paraganglioma syndrome, with identification of a mutation causing SDH deficiency.

Case report

The clinical presentation of the index case has been previously described. 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 pheochromocytoma, 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 pheochromocytomas with no evidence of vascular invasion. Repeated postoperative urine collections analysed for catecholamines were...
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 M1I 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

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该病例的姐姐被确认为有多形性副神经节细胞瘤病史。1982年，24岁时，在另一家医院接受了右侧颈部肿块的切除术，病理结果显示为颈动脉体瘤。三年后，她又出现了左侧颈部肿块，再次进行切除手术，病理结果显示为颈动脉体瘤。随后，她一直健康，目前因胃食管反流而服用兰索拉唑。最近的临床复查中，她的血压为119/82 mm Hg，尿液中的甲氧肾上腺素和儿茶酚胺均正常。她有一个22岁的儿子和一个18岁的女儿，均健康。我们对抽取的外周血DNA进行了突变分析。SDHB和SDHD基因的全部编码外显子及外显子的邻近内含子被聚合酶链反应扩增，PCR产物直接测序。

突变分析显示，患者为SDHD基因中M1I突变的杂合子。患者和其姐姐都具有多形性副神经节细胞瘤缺乏症类似突变。对患者和其弟弟进行临床诊断，遗传学检测证实他们都有相同的突变。患者和患者姐姐的病例比较后可知，此为多形性副神经节细胞瘤病的典型突变，而对多形性副神经节细胞瘤基因的突变分析研究是一个相对有效的诊断方法，有利于对可能患病的人作进一步的基因检测。
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. 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. 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. 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. 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. Interestingly, mutations in SDHD and SDHB have also been found to confer susceptibility in apparently non-syndromic phaeochromocytomas.

The family we described suffers from SDH deficiency due to M1I mutation of the SDHD gene. This mutation has been previously reported, 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. 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. 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.

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 and a Chinese family in Singapore. Reported mutations in the SDHD gene are widely distributed along the entire gene, with no obvious hot spots shared by different ethnic groups. 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. 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.

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 SDHD genetic testing if negative. 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 presymptomatic diagnosis and subsequent management of at-risk individuals.

References