R46Q Mutation in the Succinate Dehydrogenase B Gene (SDHB) in a Japanese Family with both Abdominal and Thoracic Paraganglioma Following Metastasis

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Abstract. Recently, nuclear genes encoding two mitochondrial complex II subunit proteins, SDHD and SDHB, have been found to be associated with the development of familial pheochromocytomas and paragangliomas (hereditary pheochromocytoma/paraganglioma syndrome: HPPS). Growing evidence suggests that a mutation of SDHB is highly associated with abdominal (or thoracic) paraganglioma and the following distant metastasis (malignant paraganglioma). Previously, we identified a novel heterozygous G to A point mutation at the first base of intron 3 of the SDHB gene (IVS3+1G>A) in a malignant abdominal paraganglioma from a Japanese patient. In the present study, we report another case of SDHB mutation (R46Q) in a Japanese patient with both abdominal and thoracic paraganglioma following malignant metastasis. In addition, we identified an asymptomatic carrier of SDHB mutation in this family. Our report highlights the pathogenic role of the SDHB mutation (R46Q) in malignant paraganglioma. We also discuss the desired protocol that should be adopted to follow up an asymptomatic carrier of this mutation.

Key words: SDHB, Paraganglioma, Malignant pheochromocytoma

Here, we report another case of a SDHB mutation (R46Q) in a Japanese patient with both abdominal and thoracic paraganglioma following metastasis. In addition, we identified an asymptomatic carrier of the SDHB mutation in this family. Although the pathogenic role of the R46Q mutation has been reported previously, this is the first case of an SDHB mutation (R46Q) in a Japanese patient.

**Subjects and Methods**

**Patient and his family members**

The proband, Japanese male, was previously reported by Kawai et al. as a case report [11]. In 1978, at the age of 22 yr, our subject (Fig. 1, proband) suffered from episodic headaches, truncal sweating, palpitations, and pallor. At this time, he presented with hypertension (systolic blood pressure >200 mmHg, diastolic blood pressure >140 mmHg) and was admitted to our hospital with a suspected catecholamine-secreting tumor. Urinary excretion of norepinephrine was increased during hypertensive attack as well as in 24-h collection. Preoperative chest and abdominal X-ray intravenous pyerography and pneumoretroperitoneum revealed an abnormal mass inside the cardiac shadow just above the midportion of the diaphragm. At surgery, mediastinal paraganglioma was removed. Postoperatively, however, blood pressure, as well as the 24-h urinary excretion of norepinephrine, did not fall within the normal range, indicating that another tumor still remained. Indeed, another tumor was found in the pelvic cavity. After removal of this second tumor, the 24-h urinary excretion of norepinephrine normalized and the patient was entirely free from further episodes. Subsequent histological investigations showed these two tumors to be pheochromocytomas (detailed findings of histopathological features as well as their microscopic appearance are available in the original case report [11]). Consequently, he was diagnosed with multiple paragangliomas (extra-adrenal pheochromocytomas).

Around the age of 30, the subject gradually became hypertensive. An abnormal shadow was detected by chest X-ray in the right midportion. After a second admission (1990, 38 yr), it was shown that both plasma and 24-h urinary excretion of norepinephrine were elevated, consistent with recurrent paragangliomas. After removal of a thoracic tumor, the 24-h urinary secretion of norepinephrine normalized. Histologically this tumor proved to be pheochromocytomas.

In 1994 (34 yr), 131I-MIBG revealed increased uptake in the temporal skull, strongly suggesting a distant metastasis. At this time, the subject underwent an operation to remove a tumor.

At the age of 48 yr (2004) the subject presented with lower back pain. The 24-h urinary excretion of norepinephrine was elevated and 123I-meta iodobenzylguanidine (MIBG) scintigraphy revealed discrete increased uptake in the lumbar vertebra. Magnetic resonance imaging showed lytic lesions within the lumbar vertebra (Th7, L4), consistent with distant metastasis of paragangliomas. These lesions were treated by local radiotherapy. The subject is currently alive and in good health.

The subject has three sons of whom only the third presented with hypertension (systolic blood pressure around 120–150 mmHg, diastolic blood pressure around 70–80 mmHg). After informed consent, we carried out genetic analysis of the proband as well as the three sons (details are given in Genetic analysis described below). Consequently, SDHB mutation (R46Q) was identified in the proband and his third son (see Results and Fig. 1). Given the clinical signs, together with the results of the genetic analysis, the third son was admitted to our hospital to exclude the possibility of having catecholamine-secreting tumors. The 24-h urinary excretion of norepinephrine, epinephrine, dopamine and their metabolites (e.g. metanephrine and normetanephrine) were found to be normal. Also, no tumor was detected in either CT or MIBG scintigraphy. Therefore, the subject’s third son was diagnosed as an asymptomatic carrier of the SDHB mutation (R46Q).
Genetic analysis

Participants in this study were informed about the possibility of a genetic study, its implications, and its purpose. A written informed consent was obtained from those wishing to participate in the study, and the study was approved by the ethics committee of the Medical Faculty of Tsukuba University, Tsukuba, Japan. Blood samples were collected from the participants and DNA extracted using a Blood DNA extraction kit (WAKO, Osaka, Japan).

PCR and sequence analysis

Peripheral blood for germline DNA analysis was drawn from the family members after written informed consent was obtained. Using blood DNA, the eight exons of the SDHB gene were screened with intronic primers [10]. PCR was carried out as described previously [10].

PCR amplicons were column purified and subjected to semi-automated sequencing using the above primers, dye terminator technology, and the Long-Read Tower DNA sequencer (Amersham Pharmacia Biotech) [10].

Results

SDHB mutation analysis

Direct sequencing of the eight exons of the SDHB gene in germline DNA of the subject (proband) showed a heterozygous G to A nucleotide transition in exon 2, changing arginine to glutamine at position 46 (R46Q) (Fig. 2). Furthermore, we carried out DNA analysis on his three sons, but the same R46Q mutation was only found in his third son. By contrast, no mutation of SDHB was found in the other two older sons. Although the third son presented with hypertension, his catecholamine level was normal and no tumor was detected by CT as well as MIBG, indicating that he is an asymptomatic carrier of SDHB (we defined ‘asymptomatic carrier of SDHB’ as a subject who carries the SDHB mutation but whose signs and/or symptoms are not derived from a catecholamine-producing tumor).

Discussion

In this study, we identified a germline mutation of the SDHB gene (R46Q) in a malignant paraganglioma patient, as well as in his third son, who did not suffer from paraganglioma (Fig. 2). This is the first report of a patient with SDHB gene mutation (R46Q) and an asymptomatic carrier in a Japanese family.

Current evidence suggests that the mutation of SDHB is more frequently related to abdominal (or thoracic) paraganglioma and the following distant metastasis, in agreement with our case presented here [3–8]. Therefore, it is recommended that all patients with metastatic disease, especially from paraganglioma, be tested for SDHB mutations.

Recently, a detailed description of the clinical presentations, biochemical phenotypes and genotype-phenotype correlations of patients with mutations of SDHB has been presented by Timmers et al. [12]. The biochemical phenotype was consistent with hypersecretion of both norepinephrine and dopamine in approximately 50% of the cases. Hypersecretion of norepinephrine was only found in approximately 40% of the cases. Importantly, 10% of the cases had normal catecholamine (metabolite) levels, consistent with a biochemically silent paraganglioma. No obvious genotype-phenotype correlations were identified, in agree-
ment with previous reports [3–8]. Furthermore, clinical phenotypes were found to differ significantly between family members carrying the same mutation.

Indeed, it is reported that the same SDHB mutation, including R46Q, results in remarkable variations of clinical presentation. Initially, this mutation was reported by Gimenez-Roqueplo et al., in a 55-year-old female patient with a large, highly vascularized adrenal tumor, which extended into the heart with multiple pulmonary metastases [3]. An identical mutation was identified by the same author in a 28-year-old patient with a right adrenal tumor that had extensive vascular connections with the aorta and a tumor of the Zuckerkandl body [4]. Benn et al. reported five R46Q cases, which included the two cases described previously [7]. Four out of the five cases became malignant, despite the initial location of the tumors being different between family members with the same mutation.

In a population-based study, Neumann et al. reported two SDHB (R46Q) cases [6]. Although the detailed clinical courses of these two cases remain to be clarified, the initial tumor was found as a neck paraganglioma and at the adrenal gland, both of which developed malignancy. In the present study, we identified a patient harboring the SDHB (R46Q) mutation with both abdominal and thoracic paraganglioma following distant metastasis. These findings reinforce the idea that SDHB (R46Q) mutations are closely related to malignant potential from paraganglioma/pheochromocytoma with divergent clinical phenotypes.

Another important finding of this study was to identify the same SDHB mutation (R46Q) in the third son of the proband as an asymptomatic carrier. At present, asymptomatic carriers of SDHB have been demonstrated in two large studies in the literature [6, 7]. Although there is little information available on how to follow-up and/or treat asymptomatic carriers, recommendations have been proposed as a result of these two studies [6, 7, 13]. The critical point of the recommended protocol is that all subjects must undergo periodic surveillance regardless of the presence of signs and symptoms. In the US, most SDHB mutation carriers are subject to follow-up by National Institutes of Health (NIH), where there are many clinicians experienced with pheochromocytoma and paraganglioma. Thus, we believe that in Japan SDHB mutation carriers, especially asymptomatic individuals, should be followed-up over an extended period of time at a restricted number of facilities where clinicians who specialize in pheochromocytoma and paraganglioma are working.

Further studies, especially prospective follow-up analyses of the SDHB mutation, are needed to establish routine screening for pheochromocytoma/paraganglioma, including asymptomatic carriers.

References


