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# Retroperitoneal catecholamine-producing ganglioneuroma with a birth history of monozygotic twins who both suffered from neuroblastoma during their childhoods: A case report with genome analysis

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Highlights:

We experienced a rare case of female patient with hormone-producing extra-adrenal GN.

We experienced a rare case of familiar occurrence of GN in mother and NB in twins.

Novel genome variant of familiar GN and NB can be detected by genome wide analysis.

Abbreviations: GN, ganglioneuroma; NB, neuroblastoma; CT, computed tomography; OR, odds ratio

***Introduction***

Ganglioneuroma (GN) is a rare, well-differentiated, benign tumor that is usually found in the posterior mediastinum and retroperitoneum, and commonly arises from sympathetic ganglion cells [1]. Meanwhile, hormone-producing extra-adrenal GNs are extremely rare [2]. Neuroblastoma (NB) and

GN represent tumors of neural crest origin with a continuous spectrum of maturation [1]. Familial occurrence of GN and NB in twins have been reported previously [3, 4]. Genetic susceptibility to this disorder is thought to arise via a germline mutation affecting a tumor suppressor gene, in accord with the two-hit model established for familial and sporadic retinoblastoma. Some chromosomal sites such as chromosome arms 3p24-pter, 10p12-p13, 10q25-qter, 16q12-q22, 20q13.3-qter, 1p36 and 11q have been reported to become harbor of novel tumor suppressor genes that could aid in our understanding of the predisposition to and pathogenesis of familial NB and potentially sporadic tumors as well [5]. Also, several novel genes and genetic regions, such as 2p and 12p [6], or ALK mutations [7], have been identified as genetic predisposition to familial NB by genome-wide linkage analysis. More recently, common variation at 6q16 within *HACE1* and *LIN28B* [8] or LMO1 [9] as a NB oncogene have been reported to influence susceptibility to NB. Herein, we report a female patient who developed a retroperitoneal catecholamine-producing GN with a birth history of identical twins who both suffered from NB. We performed genome analysis to identify some newly associated genome in familial GN and NB patients.

***Case report***

A 58-year-old female with stomachache, nausea and palpitation was referred to our hospital. Enhanced computed tomography (CT) scan revealed the presence of an oval-shaped, slightly-

heterogeneous and poor contrast-enhancement neoformation with a well-defined margin, located close to the upper poles of the bilateral kidneys (Fig.1A, 1B). At the age of 30 year-old, her birth history was identical twin boys who underwent surgical removal of NB at 1-year of age at another institution. The eldest son with diagnosis as stage III received chemotherapy immediately after the initial surgery, and second surgical removal of recurrent tumor at the age of 15 month-old, however, he was dead at the age of 18 month-old for the cerebral hernia due to brain metastasis. Meanwhile, the second son with diagnosis as stage IV received chemotherapy at the age of 30 month-old, and underwent the second surgery for recurrent tumor at the age of 5 year-old. Since the second surgery, the tumor has not recurred, and he is alive now. Laboratory examination indicated elevation of catecholamine hormones (noradrenaline 845 pg/ml, normal range < 450 pg/ml; dopamine 25 pg/ml, normal range < 20 pg/ml; homovanillic acid 19.4 ng/ml, normal range < 15.1 ng/ml; vanillymandelic acid 13.4 ng/ml, normal range < 8.6 ng/ml). Urinary hormone testing also showed high levels of catecholamines (noradrenaline 384 μg/day, normal range < 168 μg/day; dopamine 1451 μg/day, normal range 961 μg/day; normetanephrine 2.03 mg/day, normal range < 0.33 mg/day). Therefore, she was initially diagnosed as catecholamine-producing adrenal tumor, such as pheochromocytoma, and underwent the surgical removal. Intraoperative findings revealed that complete removal was difficult because of firm-involvement with left renal vein and splenic vein. Frozen section analysis did not reveal any evidence of malignancy and suggested the diagnosis of an extra-adrenal GN. The resected material was an

encapsulated, elastic-soft mass measuring approximately 14×12cm with a yellowish-white cut surface. Immunohistological findings showed abundant Schwann cells with mixed mature ganglion cells but without a NB component, compatible with GN (Fig.1C, 1D). We finally diagnosed this as a retroperitoneal catecholamine-producing GN. Postoperatively, her catecholamine hormone levels decreased to normal level. Follow-up CT scans have shown that the bilateral tumors, residual left-side and original right-side tumors, have no changed for approximately 4 years.

***Discussion***

While NB is mainly a sporadic tumor, 1-2% of new patients have a family history of the disease [4]. Familial transmission in NB has been rarely reported with only 146 patients from 62 families up to 2004, according to Claviez et al [3]. The pattern of familial NB is suspected to follow an autosomal-dominant trait with variable penetrance in some families. Additionally, presentation of NB in both twins is extremely rare [4]. The mechanism of tumor development in monozygotic twin remains unknown; two paths have been considered: hereditary and twin-to-twin metastasis for transplacental dissemination *in utero* [10]. Only a few families have reported the occurrence of tumor in both the parents' and their children's generation. The affected parents generally suffered from GN [3].

The genetic etiology that cause familial GN and NB remains largely unknown. To identify some newly related gene in this extremely rare and precious disorder, genome wide analysis using their

sputum samples were entrusted to the DeNA Life Science venture-company (https://mycode.jp/) based on their informed consent. As a result, 5 kinds of disease including gestational diabetes, idiopathic pulmonary fibrosis, type 2 diabetes, pancreatitis and Sjögren's syndrome in mother, and 6 kinds of disease including venous thromboembolism, β-thalassemia, idiopathic pulmonary fibrosis, sarcoidosis, prostate cancer and type 2 diabetes in her monozygotic twin boy were identified as the diseases those of onset risk were over 1.5 times compared to general Japanese population among the total of 280 examined diseases. Onset risk were measured as odds ratio (OR) based on the polymorphism of several genes closely correlated with each disease (*TERT, UBE2E2, IGF2BP2, CDKAL1, ANK1;MIR486, TCF7L2, KCNQ1, PRSS1, STAT4, CCDC181, F11, ABO, BCL11A, HBBP1, RFX6, MSMB, CCDC88B*). Consequently, same types of SNPs were confirmed in *TERT* (5p15.33 rs2736100 *A/A* genotype) that is associated with susceptibility to idiopathic pulmonary fibrosis (OR = 1.62), *IGF2BP2* (3q27.2 rs6769511 *C/C* genotype) and *KCNQ1* (11p15.4 rs2237892 *T/T* genotype) that are associated with susceptibility to type 2 diabetes (OR = 1.57) between mother and her monozygotic twin boy. A detail list of these genes/SNPs detected by this analysis is shown as Table 1. As our knowledge, there have not been reported neither that these gene variants are regarded as causative genes, nor that there is causation between familial GN and NB, and idiopathic pulmonary fibrosis, or type-2 diabetes. We recognize some limitations about the present study. First, there are epidemiologically many people who genetically have gene variants associated with type-2 diabetes in general population. Second, the

present analysis is performed only 1 familial case. However, there are quite few studies that genome analysis is performed using samples from familial cases. Therefore, these gene variants might be worthwhile candidates to examine the susceptibility to familial allochronic occurrence of GN and NB.

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***Conflict of interest***

None declared.

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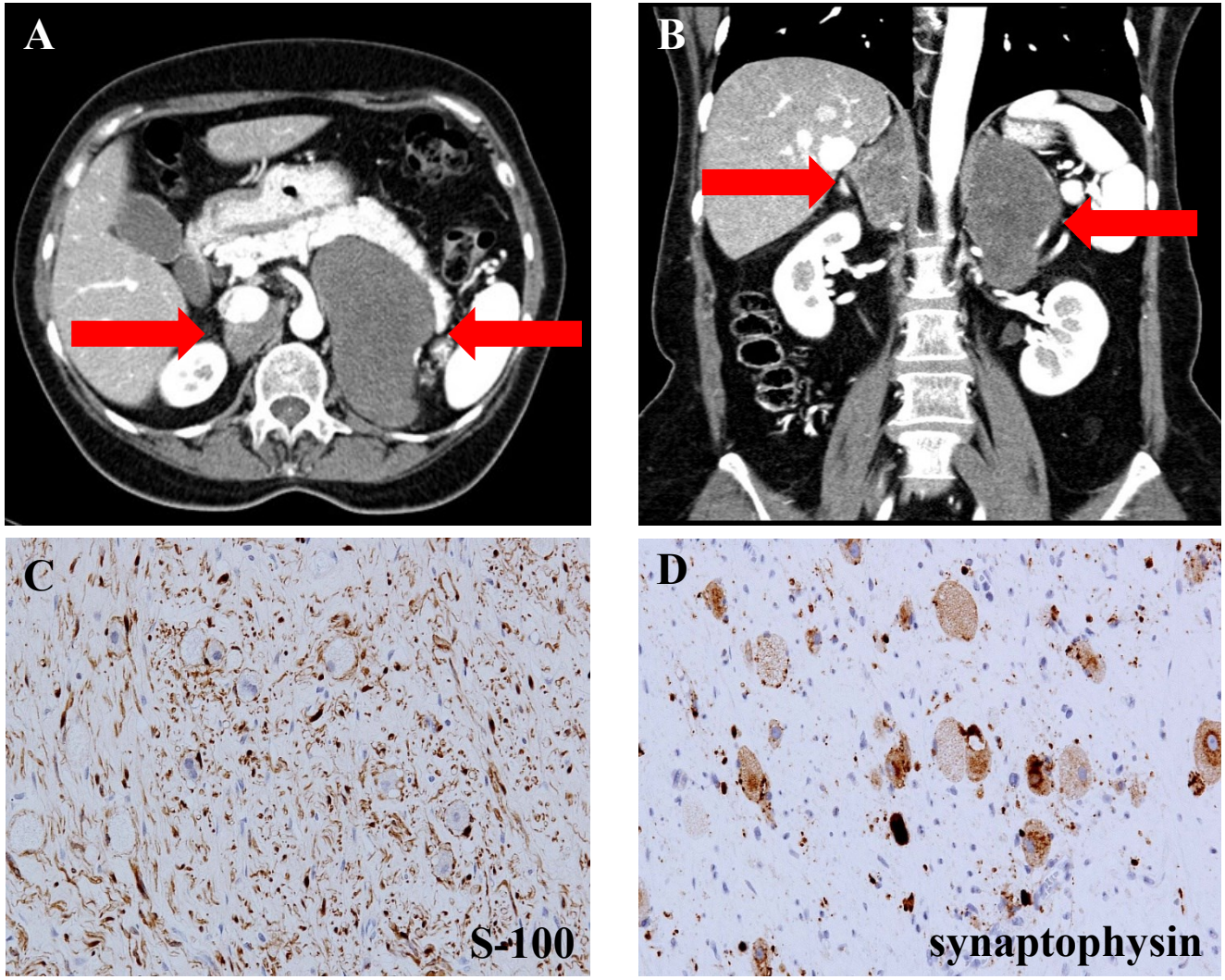


Fig. 1. (A, B) Enhanced CT scan of the abdomen revealed the presence of an oval-shaped, slightly-heterogeneous and poor contrast-enhancement neoformation with a well-defined margin, located close to the upper pole of the bilateral kidney. The left-side tumor was approximately 12cm in diameter and right-side one was 7cm. Immunohistochemical examination indicated positive staining of the ganglion and Schwann cells for S-100 (C) and synaptophysin (D).

Table 1
The type of gene polymorphism and genotype in our cases and the frequency of same SNPs in the general Japanese population.

| Gene | Gene region | SNP | Genotype | Frequency (%) |
|---|---|---|---|---|
| TERT | 5p15.33 | rs2736100 | A/A | 34.9 |
| IGF2BP2 | 3q27.2 | rs6769511 | C/C | 10.2 |
| KCNQ1 | 11p15.4 | rs2237892 | T/T | 16.6 |