Breast Cancer, Thyroid Cancer and Bladder Cancer in a Family with a Novel Germline Frameshift Variant *SDHB* c.676_677del: A Case Report

SDHB Geninde Germline Yeni Bir Mutasyonun Neden Olduğu Meme, Tiroid ve Mesane Kanseri

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ABSTRACT

The succinate dehydrogenase (SDH) enzyme complex localises to the inner side of the mitochondrial membrane and participate both in the tricarboxylic acid cycle and oxidative phosphorylation. SDHB is one of the four subunits of SDH and germline mutations in the gene encoding the SDHB have an important role in the development of familial pheochromocytoma and paraganglioma (PCC/PGL). In this report, we describe a novel germline *SDHB* c.676_677del mutation in a family responsible for breast cancer, thyroid cancer and bladder cancer without the presence of the main feature, PCC/PGL. The use of whole exome sequencing helped us clarify the genetic cause of this family presenting with non-classic manifestations.

Keywords: Succinate Dehydrogenase B, Whole Exome Sequencing, Breast Cancer, Thyroid Cancer, Bladder Cancer

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ÖZET

Süksinat dehidrogenaz (SDH) enzim kompleksi mitokondri zarının iç tarafında lokalize olup hem trikarboksilik asid döngüsünde hem de oksidatif fosforilasyonda rol oynamaktadır. SDHB, SDH enzim kompleksinin dört ünitesinden biridir ve germline mutasyonları ailesel Feokromositoma/Paraganglioma (PCC/PGL) sendromuna neden olmaktadır. Bu çalışmada bir ailede en sık görülen kanser olan PCC/PGL olmadan meme kanseri, tiroid kanseri ve mesane kanserine neden olan novel *SDHB* c.676_677del mutasyonu tanımlanmıştır. Tüm ekzom dizileme, bu ailedeki sıradışı durumun genetik nedenini ortaya çıkarmada yardımcı olmuştur.

Anahtar Sözcükler: Süksinat Dehidrogenaz B, Tüm Ekzom Sekanslama, Meme Kanseri, Tiroid Kanseri, Mesane Kanseri

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INTRODUCTION

Succinate dehydrogenase B (SDHB) is an enzyme that plays a crucial role in cellular energy metabolism. Germline heterozygous mutations in the gene encoding the SDHB are predisposed to the development of hereditary pheochromocytoma/paraganglioma syndrome (PCC/PGL) (1). Several other neoplasms including renal cancer, thyroid cancer, gastrointestinal stromal tumor, breast cancer and pituitary neoplasia have been reported in SDHB mutation carriers (2).

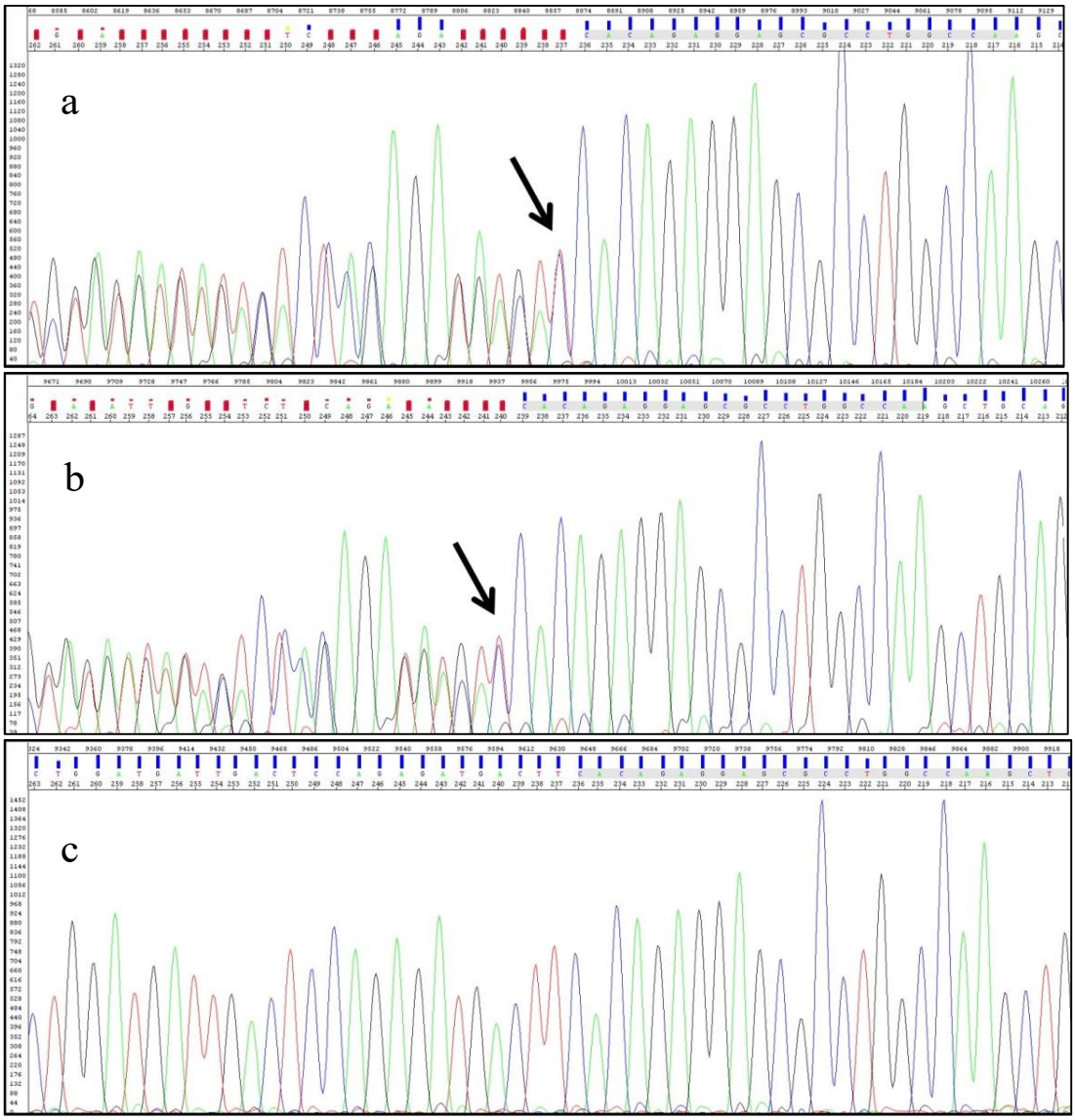
In this study, we identify a novel variant in SDHB as the genetic cause of breast cancer, thyroid cancer and bladder cancer in a family with a whole exom sequencing using next-generation sequencing (NGS) method.

CASE REPORT

A 31-year-old female in the 11 weeks of pregnancy was admitted to our genetic center for non-invasive prenatal screening test.

During the pretest genetic counseling, the patient revealed that she was diagnosed at age 26 with unilateral ductal breast carcinoma (BC) which was surgically resected. Immunohistochemical stains showed estrogen receptor, progesterone receptor and HER2/neu all negative. In addition, she received chemotherapy and radiotherapy treatment. At that time, she was genetically tested for germline mutations in BRCA1/2 genes, the results of which were unremarkable. Four years later, she developed papillary thyroid cancer (PTC) for which she underwent total thyroidectomy with radioactive iodine therapy. Her family history was positive only for a mother who was diagnosed with papillary bladder cancer at 50 years of age. Based on her significant personal and family history of cancer, we offered whole exome sequencing to assess germline variants in genes different from BRCA1/2.

Upon patient's consent, sequencing analysis was carried out using Illumina Truseq Exome Kit and Illumina Novaseq 6000 platform. Genetic testing showed that the patient carried maternally inherited a novel frameshift heterozygous variant c.676_677del in SDHB gene (Figure 1. a-c) and a previously identified missense heterozygous variant c.7816A>G in ATM gene inherited from her healthy father (Figure 1. d-f). Verification of variants detected by NGS-based screening was performed by Sanger sequencing on an ABI 3130 Genetic Analyser (Applied Biosystems).



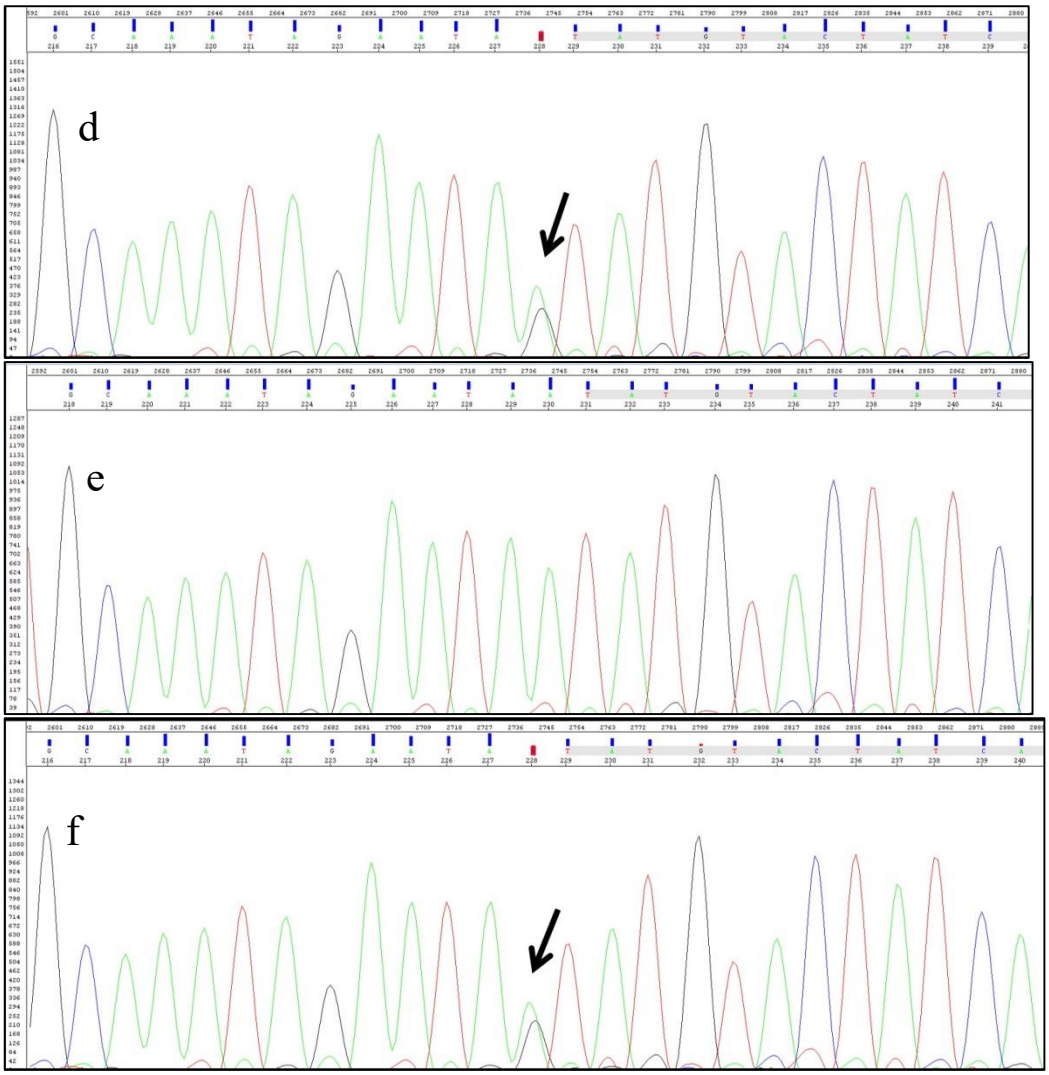


Figure 1 a-c Sequence analysis demonstrated the novel heterozygous c.676_677del variant in exon 7 of the SDHB gene in both the patient (a) and her mother (b), but not in her father (c) (arrow)
d-f Sequence analysis for part of exon 53 of ATM gene separately identified the heterozygous c.7816A>G variant in the patient (d) and her father (f), but not in her mother (e) (arrow)

DISCUSSION

Our analysis revealed that the proband harboured two heterozygous germline variants in hereditary cancer susceptibility genes. The first variant was c.676_677del (NM_ 003000.3) in the SDHB gene which has not been previously published as either a pathogenic variant or a benign variant at public databases (PubMed, ClinVar, HGMD Public). The c.676_677del variant is not observed in the broad population cohorts (The Genome Aggregation Database [gnomAD]). This variant causes a frameshift in codon 226, leading to a premature stop codon, symbolized as (p. Phe226HisfsTer29). Because this variant may lead to loss of protein function either by way of protein truncation or nonsense-mediated mRNA decay, it is likely the disease-causing mutation.

The second variant detected in ATM gene was a missense alteration called c.7816A>G (NM_ 000051.4). The nature of this variant is still to be defined. In fact, it has been described several times as of being uncertain significance in ClinVar database. Based on results from in silico analysis (SIFT, PolyPhen-2, Align-GVGD), this variant has been predicted as tolerated. Furthermore, the patient had inherited the variation from her healthy father; thus, we suggest that it has no significant impact on the patient's cancer etiology. To our knowledge, germline changes in ATM gene is associated with an increased risk of BC and PTC development, although it has not been demonstrated to lead to bladder cancer yet (3,4). It may be a genetic modifier that alter the phenotypic outcome of the primary disease-causing variant but we cannot confirm this hypothesis without functional studies.

SDHx mutated tumors other than PCC/PGL occur rarely and to our knowledge, no prospective study has been performed to determine the true prevalence of neoplasms beyond PCC/PGL. Therefore, at present, screening for these tumors does not seem to be recommended (5). The penetrance of SDHx-related PCC/PGL is incomplete and varies between 8% and 37% for asymptomatic SDHB mutation carriers across several studies (6). The Endocrine Society guidelines offer clinical surveillance for only PCC/PGL which include annual biochemistry with urine or plasma metanephrines and biennially cross-sectional imaging using either CT/MRI of skull base, neck, thorax, abdomen and pelvis (7).

Finally, due to inadequate duration of follow-up, the small size of our series of patients with this variation and genetic modifiers with variable expressivity, we cannot conclude that this variation is more likely related to breast cancer, thyroid cancer and bladder cancer. Further studies with a larger series are needed to validate this clinical association.

CONCLUSION

As the wide spectrum of the atypical malignancies for hereditary cancer syndromes, correct definition of the syndrome type might not be possible until the use of NGS-based multi-gene panel analysis.

Conflict of interest
No conflict of interest was declared by the authors.

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