The Impact Of Succinate Dehydrogenase Gene (SDH) Mutations In Renal Cell Carcinoma (RCC): A Systematic Review

Seyed Mohammad Kazem Aghamir1
Ramin Heshmat2
Mehdi Ebrahimi3
Seyed Ebrahim Ketabchi4
Somayeh Parichehreh Dizaji5
Fatemeh Khatami6

1Urology Research Center, Tehran University of Medical Sciences, Tehran, Iran; 2Chronic Diseases Research Center, Endocrinology and Metabolism Population Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran; 3Department of Internal Medicine, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran; 4Department of Neurosurgery, Sina Hospital, Tehran, Iran; 5Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

Introduction: Renal cell cancer (RCC) syndrome is linked to Krebs cycle compartments and their coding genes’ alterations like succinate dehydrogenase genes (SDHx). Here we present a systematic review of the SDH genes’ mutations and their impact on both RCC diagnosis and prognosis.

Methods: This systematic review includes any study in which tissue samples of RCC are considered in correlation with the SDHx mutations, microsatellite instability (MSI), and protein expression. For this purpose, a systematic search of MEDLINE (PubMed), Scopus, Embase, and Web of Science databases was conducted and finally 5384 articles were recruited. All studies’ content was checked to find the related ones which were 145 articles, which with data extraction were limited to nineteen.

Results: The final selected nineteen studies investigating the SDHx role in RCC tumor genesis were included, among which fifteen were mutation analysis, three were just SDHx protein expression, and two were MSI and mutation analysis studies. A total of 432 RCC patients were reported by SDH mutations, and 64 patients with MSI and SDHx expression change were reported in 514 surgically resected renal epithelial tumors. The most common mutation was the single nucleotide variant rs772551056 (c.137G>A) of SDHB. For SDHC, c.380A>G presented in 48 RCC patients, and for SDHA a novel germline mutation c.2T>C: p.M1T in an occasional case of gastrointestinal stromal tumor intricate with RCC.

Conclusion: RCC as an aggressive type of kidney cancer needs some biomarkers to be diagnosed exactly. It was shown recently that the succinate dehydrogenase gene variations can provide this diagnostic and prognostic biomarker. For this purpose, SDHB rs772551056 associated with its protein expression alterations can be taken into account. It is possible that a novel mutation of SDHA (c.2T>C: p.M1T) can provide evidence of GIST associated with RCC as well.

Keywords: renal cell cancer, RCC, succinate dehydrogenases, mutation, expression, MSI

Introduction

Kidney cancers with different genetic changes have different histology and clinical significance. The genes relating to kidney cancer are usually involved in metabolic stress or nutrient stimulation pathways including Von Hippel-Lindau(VHL), mesenchymal–epithelial transition factor(MET), Folliculin(FLCN), Tuberous sclerosis(TSC1 and TSC2), Microphthalmia-associated transcription factor(MITF), Phosphatase and tensin homolog(PTEN), fumarate hydratase(FH), and succinate dehydrogenase (SDH).1,2 One of the usual forms of kidney cancers is RCC that initiates in the lining
of the proximal convoluted tubule responsible for about 90–95% of kidney cancer cases. It commonly is described by an absence of early-warning signs (which outcomes in an extraordinary proportion of patients with metastases), various medical manifestations, and fighting radiotherapy and chemotherapy with a possible impact on immunomodulation in the tumor growth suppression. RCC has the highest mortality rate of the genitourinary cancers and its prevalence has ascended steadily over the past few decades. Some recent research has proved the benefit of genomic data, principally gene expression hallmarks, as medical predictive factors in personalized cancer management.

Succinate dehydrogenase (SDH or SQR) is an enzyme complex of the inner mitochondrial membrane that contributes to the citric acid cycle as well as the electron transport chain. Succinate dehydrogenase is made of four protein subunits (SDHA, SDHB, SDHC, and SDHD) having a role in the TCA cycle and electron transport chain in mitochondria. Patients with mutations in the SDH genes are under the risk of autonomic nervous system tumors like pheochromocytomas and paragangliomas (PPGLs), both head and neck, and in the thorax and abdomen, gastrointestinal stromal tumors (GISTs), and renal cell carcinoma (RCC). The evaluation of protein expression by immunohistochemistry routinely is used to find a discriminative biomarker of benign and malignant tumors including RCC. Succinate dehydrogenase mutation in PPGL and GIST tumor cells had a microscopic result of predominantly epithelioid morphology, and epithelioid morphology, but not in RCC. In fact, renal tumors are usually known with typical morphology of identical cells with eosinophilic or oncocytic cytoplasm that have cytoplasmic vacuoles or flocculent inclusions. RCCs with additional histologic presence have been described in patients with germline mutations of succinate dehydrogenase genes, contrary to some limited histological types of RCCs with no succinate dehydrogenase mutation.

In recent years the genetic basis of RCC has been known and both genetic and epigenetic alterations of succinate dehydrogenase have been discussed. Interestingly, germline mutations of the genes coding for the succinate dehydrogenase subunits (SDHB, SDHC, and SDHD) have been identified in patients with a combination of gastrointestinal stromal tumors (GISTs) and paraganglioma (PGL). The co-occurrence of RCC with paraganglioma or pheochromocytoma suggested a succinate dehydrogenase gene mutation presence. A newly characterized specific subtype of RCC is in the new World Health Organization (WHO) classification and was published in 2016.

In spite of the fact that recently the focus of scientists is on RCC genetic and epigenetic modifications, knowledge of the clinical features and management of patients associated with the SDH mutations is limited. The current systematic review study is run with the purpose of delivering the first meticulous summary of all the available primary research over the SDH mutations, expression, and microsatellite instability (MSI) in RCC management and screening recommendations.

**Research Design And Methods**

**Search Strategy**

The study was based on an international prospective register of systematic reviews with PROSPERO 2018 code CRD42018087806 available from http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018087806. All linked works were searched from four targeted databases including: MEDLINE (PubMed), Scopus, Embase, and Web of Science. Publication dates of relevant articles were limited from 1st January 1990 to 30th March 2018. Our search syntax were “Succinic Dehydrogenase”, “SDH mutations”, “Succinic Oxidase”, “succinate-coenzyme Q reductase”, “(SQR)”, “respiratory Complex II” combined with “Collecting Duct Carcinoma”, “RCC”, “Renal Cell Adenocarcinoma”, “Kidney adenocarcinoma”, and “kidney Cancer” (Supplementary materials). In order to decrease the selection bias, two separate investigators (FK and RH) individually reviewed titles, abstracts, and available full-text articles to choose the related ones with SDH and RCC. Additional related papers were documented above searching the reference lists of selected studies. Disagreements were solved by the third independent investigator (SMKA).

**Eligibility Criteria**

All chosen studies were studied by two authors individually and based on their English full text were included or excluded. The considering inclusion criteria were: 1) participants included kidney cancer patients pathologically classified as RCC, renal epithelial tumors, or renal tumors; 2) all SDHx alteration detection techniques such as immunohistochemistry (IHC), DNA sequencing, western blotting, PCR-based methods, SNaPshot Assay, and PCR-RFLP were included; and 3) SDHx alterations were composed mutations, MSI, and protein expression. Studies were excluded if they: 1) analyzed SDHx mutations or expression in animals (in vivo studies); 2) studied them in cell culture
(in vitro studies); or (3) did not have an appropriate explanation of selected case groups.

Data Extraction And Quality Assessment
All data on population characteristics and SDHx deficiency results were extracted in the Excel file. One investigator completed the data extraction step (SPD), which was established via another investigator (FK). Due to the insufficient quantity of studies relevant to SDHx deficiencies and RCC, together with the significant variations in targeted genetic variations and study population characteristics, a meta-analysis for the current data was not applicable. The study team used the Newcastle–Ottawa Scale (NOS) scale assessment tools to assess the quality of all selected final studies. The methodologies of studies scoring 6/8 or more on the NOS were categorized as “high quality”, whereas those that scored 5/8 or lower were reported as “low quality”.

Results
Study Selection And Characteristics
The selection flow chart and results of the study selection procedure are presented in Figure 1. A total of 5384 articles was retrieved and after duplication deletion 3964 remained, in which there were 2905 from PubMed, 559 from Scopus, 325 from Web of Science, and 130 from Embase. When the review articles, in vivo/in vitro studies, and book or conference papers were deleted the total number of nineteen articles was chosen for advance considerations. A total of sixteen studies were mainly focused on SDHx mutations, three studied the SDHx protein expression without mutation analysis, and two targeted SDHx MSI with or without mutation (Table 1).

In sixteen studies, SDHB was checked for mutation, and protein expression. In these studies, SDHB was evaluated alone or simultaneously with other candidate genes like FH, TFE3 gene rearrangement, TMEM127, MAX, HIF1a, Cathepsin, PAX8, Cathepsin, CK20, and EMA. In these studies, several mutations of SDHB were checked including exonic mutations (c.137G>A), splice site acceptor or donor mutations (c.72+1G→T), exon 1 splice acceptor site or c.268C>T (p. Arg90X) in exon 3 splice site mutation, and (c.136C>T Stop) mutation of stop codons which are resulting in truncated inactive forms of the protein. Five studies were mainly focused on SDHC in which loss of heterozygosity (LOH) in two telomeric regions (D3S369, D3S1597) and five centromeric regions (D3SVHL3, D3S1337, D3SVHL7, D3SVHL8, D3S3611) more than c.380A>G mutations were tested. Especially, in an aggressive example of the Warburg Effect in succinate

![Flow chart of study selection.](Image)

Figure 1 Flow chart of study selection.
Table 1 Characterization Of Nineteen Related Studies To SDHx Genetic Modifications And Protein Expression In RCC Patients

| Target SDH | Title                                                                 | First Author          | Publication Year | Country | Sample Size | Age | Type Of Study | Detected Mutation                                                                 |
|------------|-----------------------------------------------------------------------|-----------------------|------------------|---------|-------------|-----|--------------|-----------------------------------------------------------------------------------|
| SDHB       | Renal carcinoma with giant mitochondria associated with germ-line mutation and somatic loss of the succinate dehydrogenase B gene\(^9\) | Sarah L Housley       | 2010             | UK      | 1 RCC       | 58  | Case report  | c.72+1G→T exon 1 splice acceptor site                                            |
|            | Germ line SDHB mutations and familial renal cell carcinoma\(^11\)   | Christopher Ricketts  | 2008             | UK      | 68 RCC      | 50  | Case series  | c.137G>A, c.32G>A, c.136C>T Stop                                                 |
|            | Early-onset renal cell carcinoma as a novel extraparaganglial component of SDHB-associated heritable paraganglioma\(^16\) | Sakari Vanharanta     | 2004             | Finland | 60 sporadic RCCs | 15–34 | Case series  | e R27X mutation (N8168)                                                          |
|            | Succinate dehydrogenase (SDH)-deficient renal carcinoma: a morphologically distinct entity: a clinicopathologic series of 36 tumors from 27 patients\(^10\) | Anthony J Gill        | 2014             | Australia | 36 tumors from 27 patients | 37  | Cohort       | c.137G>A                                                                  |
|            | Renal cell carcinoma with TFE3 translocation and succinate dehydrogenase B mutation\(^11\) | Anna Calió            | 2017             | USA     | 4 RCCs      | From 19 to 65 | Case series  | c.423+1G 4A, p.V140F, c.72+1G 4T                                          |
|            | Immunohistochemical characterization of fumarate hydratase (FH) and succinate dehydrogenase (SDH) in cutaneous leiomyomas for detection of familial cancer syndromes\(^12\) | Cody S Carter         | 2017             | USA     | 96 consecutive specimens of cutaneous leiomyomas from 87 RCC patients | Case/control | SDHB expression |                                        |

(Continued)
### Table 1 (Continued).

| Target SDH | Title                                                                 | First Author | Publication Year | Country | Sample Size | Age | Type Of Study | Detected Mutation |
|------------|------------------------------------------------------------------------|--------------|------------------|---------|-------------|-----|---------------|-------------------|
|            | Clinical and molecular features of renal and phaeochromocytoma/       | Ruth T Casey | 2017             | UK      | 22 probands with non-VHL RAPTAS | 30  | Case series   | N/A               |
|            | paraganglioma tumour association syndrome (RAPTAS): case series         |              |                  |         |             |     |               |                   |
|            | and literature review\(^{33}\)                                         |              |                  |         |             |     |               |                   |
|            | Succinate dehydrogenase B: a new prognostic biomarker in clear cell    | Kristine M Cornejo | 2015         | USA     | 420 surgically resected renal epithelial tumors | 62.6 (33–92) | Case series | SDHB expression |
|            | renal cell carcinoma\(^{34}\)                                         |              |                  |         |             |     |               |                   |
|            | Utility of the succinate: fumarate ratio for assessing SDH dysfunction | Edward Kim  | 2017             | Australia | 11 RCCs 18 PPGLs, 10 GISTs |     | Case/control | c.380T>G, p.Ile127Ser |
|            | in different tumor types\(^{35}\)                                      |              |                  |         |             |     |               |                   |
|            | Increased HIF1α in SDH and FH deficient tumors does not cause           | Heli J Lehtonen | 2007         | Finland | 11 RCCs, 12 ULMs 1 ULMS |     | Case series   | N/A               |
|            | microsatellite instability\(^{36}\)                                    |              |                  |         |             |     |               |                   |
|            | Renal cell carcinoma occurring in patients with prior neuroblastoma\(^{36}\) | Sara M Falconaro | 2016        | USA     | 7 RCCs  | 40–64 | Case series | SDHB expression |
|            | Renal tumors associated with germline SDHB mutation show distinctive    | Anthony J Gill | 2011         | Australia | 4 renal tumors | 32  | Case reports  | c.166-170delCCTCA in exon 2 |
|            | morphology\(^{37}\)                                                   |              |                  |         |             |     |               | c.72+1G>T         |
|            | SDHB-associated renal oncocytoma suggests a broadening of the renal     | Alex Henderson | 2009         | UK      | 11 Renal tumors | 16–73 | Case series | c.136G>T  |
|            | phenotype in hereditary paragangliomatosis\(^{38}\)                    |              |                  |         |             |     |               | c.137G>A |
|            |                                                                        |              |                  |         |             |     |               | c.79C>T  |
|            |                                                                        |              |                  |         |             |     |               | c.715_718 delTCTC |
|            |                                                                        |              |                  |         |             |     |               | c.32G>A  |
|            |                                                                        |              |                  |         |             |     |               | c.141G>A |
|            |                                                                        |              |                  |         |             |     |               | c.600G>T |
|            |                                                                        |              |                  |         |             |     |               |                   |
| Target SDH | Title | First Author | Publication Year | Country | Sample Size | Age | Type Of Study | Detected Mutation |
|------------|-------|--------------|------------------|---------|-------------|-----|---------------|--------------------|
| SDH        | Molecular genetic analysis of FH-1, FH, and SDHB candidate tumour suppressor genes in renal cell carcinoma | M R Morris | 2004 | UK | 29 RCCs | – | Case series | IVS2+33 A→R, G→A |
| SDH        | Renal carcinoma associated with succinate dehydrogenase B mutation: a new and unique subtype of renal carcinoma | Julie Y Paik | 2014 | Australia | A unique case RCC | 27 | Case report | c.88delC (p.Gln30ArgfsX47) in exon 2 |
| SDHC       | Papillary renal cell carcinoma with cytologic and molecular genetic features overlapping with renal oncocytoma: analysis of 10 cases | Kvetoslava Michalova | 2018 | Czech Republic | 147 PRCCs | 67 | Case series | N/A |
| SDHC       | Clinical and molecular features of renal and phaeochromocytoma/paraganglioma tumour association syndrome (RAPTAS): case series and literature review | Ruth T Casey | 2017 | UK | 22 probands with non-VHL RAPTAS | 30 | Case series | N/A |
| SDHC       | Increased HIF1α in SDH and FH deficient tumors does not cause microsatellite instability | Heli J Lehtonen | 2007 | Finland | 11 RCCs, 12 ULMs | 1 ULM5 | Case series | N/A |
| SDHC       | Biallelic inactivation of the SDHC gene in renal carcinoma associated with paraganglioma syndrome type 3 | Angelica Malinoc | 2012 | Germany | 35 head and neck paragangliomas | – | Case series | LOH at SDHC: 2 telomeric D3S3691, D3S1597, 5 centromeric D3S4VHL3, D3S337, D3S4VHL7, D3S4VHL8, D3S3611 |
| SDHC       | Succinate dehydrogenase (SDH)-deficient renal cell carcinoma: a morphologically distinct entity a clinicopathologic series of 36 tumors from 27 patients | Anthony J Gill | 2014 | Australia | 28 tumor samples | 37 | Cohort | SDHC c.380A>G |

(Continued)
| Target SDH | Title                                                                 | First Author            | Publication Year | Country | Sample Size                   | Age | Type Of Study | Detected Mutation |
|-----------|----------------------------------------------------------------------|-------------------------|------------------|---------|-------------------------------|-----|---------------|-------------------|
| Succinate dehydrogenase kidney cancer (SDH-RCC): an aggressive example of the Warburg Effect in cancer<sup>20</sup> | Christopher J Ricketts | 2012                   | USA              | 14 patients from SDHB mutation families | 47  | Case series   | R133X             |
| SDHA      | A novel germline mutation in SDHA identified in a rare case of gastrointestinal stromal tumor complicated with renal cell carcinoma<sup>28</sup> | Quan Jiang              | 2015             | China   | A case of GIST RCC            | 23  | Case report   | c.2T>C: p.M1T     |
|           | Early-onset renal cell carcinoma as a novel extraparaganglial component of SDHB-associated heritable paraganglioma<sup>16</sup> | Sakari Vanharanta       | 2004             | Finland | 60 sporadic RCCs              | 15–34 | Case series | N/A               |
| SDHD      | Germline SDHB mutations and familial renal cell carcinoma<sup>21</sup> | Christopher Ricketts    | 2008             | UK      | 68 RCC                        | 50  | Case series   | N/A               |
|           | Early-onset renal cell carcinoma as a novel extraparaganglial component of SDHB-associated heritable paraganglioma<sup>16</sup> | Sakari Vanharanta       | 2004             | Finland | 60 sporadic RCCs              | 15–34 | Case series | N/A               |
|           | Clinical and molecular features of renal and phaeochromocytoma/paraganglioma tumour association syndrome (RAPTAS): case series and literature review<sup>30</sup> | Ruth T Casey            | 2017             | UK      | 22 probands with non-VHL RAPTAS | 30  | Case series   | N/A               |
|           | Biallelic inactivation of the SDHC gene in renal carcinoma associated with paraganglioma syndrome type 3<sup>34</sup> | Angelica Malinoc        | 2012             | Germany | 35 head and neck paragangliomas | –   | Case series   | N/A               |
|           | Increased HIF1α in SDH and FH deficient tumors does not cause microsatellite instability<sup>40</sup> | Heli J Lehtonen         | 2007             | Finland | 11 RCCs, 12 ULMs              | 1 ULMS | Case series | N/A               |

**Abbreviations:** RAPTAS, phaeochromocytoma/paraganglioma tumor association syndrome; SDH, succinate dehydrogenase; PPGLs, phaeochromocytoma and paraganglioma; GISTs, gastrointestinal stromal tumors; RCCs, renal cell carcinomas; HLRCC, hereditary leiomyomatosis and renal cell cancer; ULM, benign uterine leiomyomas; ULMS, uterine leiomyosarcoma; HPGL, hereditary paragangliomatosis; NB, neuroblastoma; GIST RCC, gastrointestinal stromal tumor complicated with renal cell carcinoma; PRCC, papillary RCC; ccRCC, clear cell RCC; LOH, loss of heterozygosity; OPRCC, oncocytic variant of papillary renal cell carcinoma; HIF, hypoxia inducible factor; FH, fumarate hydratase; N/A, not available.
dehydrogenase kidney cancer (SDH-RCC), the germline SDHC mutation (R133X) (NM_003001.3-c.397C>T (p.Arg133Ter)) was identified. Two studies were related to SDHA (c.2T>C, p.M1T; rs864622194) resulting in substitution of Methionine with Threonine in a NM_006493.2: c.2T>C missense variant that change the amino acid sequence in protein and resulted in non-functional protein (https://www.ncbi.nlm.nih.gov/clinvar/variation/219649/).

Five studies concerned SDHD with no exact determined targeted mutations. Except for one study in sporadic RCC indicating no mutations in the three FH, FIH-1, and SDHB, others mainly suggested early-onset RCC with unusual histology (e.g., solid) must be observed to take an extended family history and SDHB mutant-related RCC in the way of better diagnosis and prognosis.35,36 In fact the weak staining, particularly in clear neoplasms, usually can be interpreted as negative by mistake.37 A total of 432 RCC patients were reported by SDH mutations, and 64 patients with MSI and SDH expression change were reported in 514 surgically resected renal epithelial tumors. The most common mutation was the single nucleotide variant rs772551056 (c.137G>A) of SDH-D with genomic location Chr1: 17044824 resulting in protein change R46Q which was reported in 106 RCC patients. After that, two mutations of c.32G>A and c.136C>T Stop were the most with 79 reported RCC patients. The mutation of c.423+1G=A was in 44 RCC patients and c.72+1G→T in 20 patients. The SDHC c.380A>G (p. His127Arg) was in 48 RCC, 18 PPGLs, and 11 GIST. The rs786201095 (c.380T>G (p. Ile127Ser)) with chromosome location Chr1: 17028643 is the common mutation found in RCC in addition to GIST and PPGL. SDHB expression in ccRCCs with high nucleolar grade (G3–G4) was considerably linked to patient’s low survival so it can be an excellent candidate biomarker for RCC diagnosis and prognosis.37 The novel germline mutation of chromosome X rs864622194 (c.2T>C: p.M1T) with genomic locus ChrX: 103776997 in SDHA was recognized in a rare case of gastrointestinal stromal tumor complicated with RCC.38

**Discussion**

RCC arises from the cells of the proximal renal tubular epithelium and has two subtypes: sporadic (non-hereditary) and hereditary.51 Inherited predisposition to RCC is dependent on cellular metabolism responsible genes.52,53 RCC is basically a metabolic disease so metabolism involving genes like SDH can trigger the cellular transformation of renal cells in reaction to sensing oxygen, iron, nutrients, and energy.1,54 The SDH enzyme is a very conserved heterotetrameric protein made up of four subunits (SDHA, SDHB, SDHC, and SDHD) in which SDHA and SDHB are catalytic subunits and SDHC and SDHD are anchored to the inner membrane.55 Recently the importance of SDH subunit mutations has been highlighted in different malignancies including RCC.56,57 There is a rare and aggressive type of RCC which is called SDH-deficient RCC (abbreviated SDH-RCC) that lately has been added to the WHO classification of renal neoplasia.58 The incidence of SDH-deficient RCC is assessed among 0.05–0.2% of all renal carcinomas and among SDH-deficient RCCs, SDHB-mutated RCC is the most frequent,59 followed by SDHC and SDHD-deficient RCC.24,40 Moreover, a patient case with SDHA-deficient RCC has been reported currently.60 Early age of onset for RCC has been observed in patients with SDHB germline mutations.61,62

Common genetic alterations of SDHB consist of a nonsense mutation (c.268C>T p.Arg90X), four missense mutations (c.137G>A p.Arg46Gln, c.286G>A p.Gly96Ser, c.379A>C p.Ile127Leu, c.689G>A p.Arg230His), two splice site altering mutations (c.286+2T>A, c.541-2A>G), and three complete deletions of the first exon of SDHB.60 The mutation c.72+1G→T which is in the exon 1 splice acceptor site resulting in production of a truncated inactive form of the protein was in RCC with giant mitochondria.39 SDHB mutation results in distinctive morphology of RCC and these RCCs have a respectable prognosis subsequently of whole excision unless there is sarcomatoid differentiation.20 The involvement of SDHB mutations in RCC recommends that SDHB mutations must be checked when renal tumors are presented in families with other tumors consistent with hereditary paraganglioma syndrome.47 The two mutations c.541-2A>G (Splice) and c.689G>A (p.Arg230His) have a role in impairing iron–sulfur cluster delivery and are highlighted in several cancers.53,64 According to our result the most common SDHB mutation was the single nucleotide variant rs772551056 (c.137G>A). SDHB is the Fe–S subunit of mitochondrial complex II including extremely consensus L(I)YR motifs essential for gaining of Fe–S clusters by recruiting the Fe–S transfer machinery.65,66 Importantly, the c.137G>A (p.Arg46Gln or R46Q) mutation occurs in the first L(I)YR motif of SDHB and can be detected in familial paraganglioma/pheochromocytoma/GIST/renal cell carcinoma tumor syndromes.67,68 KDM4/JMJD2 proteins are demethylases that target histone H3 on lysine 9 and 36, and histone H1.4 on lysine 26, and are key
epigenetic regulators of several cancer cells. However, succinate-mediated competitive suppression of 2-oxoglutarate-dependent dioxygenases, histone demethylases (JMJD), and the ten–eleven translocation (TET) family of 5-methyl cytosine (5-mC) family of hydroxylases are important in SDH-deficient tumor phenotypes. Possible succinate-induced modifications contain stabilization of HIF-\(\alpha\) propyl hydroxylase and hypermethylation of histones and DNA. The morphological study of SDH-deficient renal carcinoma represents a distinct and rare renal neoplasm, which is defined by loss of IHC staining for SDHB. It was in 2000 that the first germline mutation of SDHD was reported in HOGL families and then in link with familial PCC. Moreover, the SDHD mutations together with SDHB mutations were reported in familial PCC and HPGL. SDH-deficient PPGLs, GISTs, and RCCs keep a considerably advanced succinate:fumarate ratio versus their SDH-sufficient equivalents so metabolomic analysis is essential to directly measure SDH dysfunction linking to the numerous types of malignancies.

Germline mutation c.380A>G (p.His127Arg) of SDHC is the important mutation of this gene which is reported as a recurrent biomarker of SDH-deficient GIST and renal carcinoma. This variant was described in two brothers with head and neck paragangliomas and in a patient with papillary thyroid cancer, renal cell cancer, and GIST; both the renal tumor and GIST demonstrated absence of SDHB by IHC. This mutation was not detected in about 6,500 persons from Europeans and African Americans in the National Heart, Lung, and Blood Institute (NHLBI) Exome Sequencing Project (ESP), showing that it is not a public benign alternative in these people. Subsequently, the amino acids of Histidine and Arginine share analogous characteristics; this is measured as a conservative amino acid substitution mutation. SDHC c.380A>G happens at a conserved protein region through different species and is located at the metal attachment site for iron and in the helical transmembrane topological domain. In silico analyses predict that this polymorphism can perhaps change the protein structure and function, and suggested novel mutations in sporadic head and neck paraganglioma and familial paraganglioma and/or pheochromocytoma. Based on the currently available evidence, SDHC c.380A>G can be considered the RCC pathogenic variant. These are conflicting because germline SDHC mutations are comparatively uncommon, so it was supposed that carriers of mutations of the SDHC gene have special risk for head and neck paragangliomas more than a risk for adrenal pheochromocytoma. Therefore, not only the SDHC mutations but also the LOH and MSI were taken into consideration in RCC patients. Two telomeric (D3S3691, D3S1597) and five centromeric (D3SVHL3, D3S1337, D3SVHL7, D3SVHL8, D3S3611) were evaluated and renal carcinoma. It was reported by Malinoc et al that for the clear cell renal carcinoma LOH was established in D3S3691 and, D3S1597 as the telomeric ones and in two centromeric signs (D3SVHL3 and D3S3611) in comparison with undesirable controls so it might be a new molecular indicator for the pathogenesis of RCC and ought to be checked in both heritable and sporadic forms.

A report about SDHA by Jiang et al in 2015 diagnosed a rare case as a wild-type gastrointestinal stromal tumor (WT GIST) intricated with renal chromphobe cancer cells and distinguished an innovative germline mutation chromosome X rs864622194 (c.2T>C: p.M1T) in the position of a transcription initial codon within the SDHA gene sequence. There was another described patient of an RCC linked with an SDHA mutation. As the main catalytic subunit of SDH complex, the (c.2T>C: p.M1T) mutation certainly deactivates the entire SDH complex. It has been presented that SDHA homozygous deletion mutation of SDHA and SDHB following altered protein expression evident by IHC and decreased gene expression of SDHA noticeable by IHC faultlessly can be coordinated with SDHA mutation. Nevertheless, SDHA mutation does not result in loss of SDHA protein expression, which directs that the role of the other allele is normal, so SDHA in addition to SDHB have been recommended as diagnostic biomarkers for screening for potential SDH mutations in RCC cases.

More than genetic change there are some epigenetic modifications that change the gene expression with no change in the DNA sequences. In fact, epigenetics acts as an interface between environmental/exogenous factors, cellular responses, and pathological processes. Epigenetic signatures (DNA methylation, mRNA and microRNA expression, etc) can be biomarkers for risk stratification, early detection, and disease classification, as well as targets for therapy and chemoprevention. To better understand the interplay between etiological factors, cellular molecular characteristics, and disease evolution, the field of “molecular pathological epidemiology (MPE)” has emerged as an interdisciplinary integration of “molecular pathology” and “epidemiology”. The widespread application of epigenome (e.g., methylome) analyses will increase our understanding of disease heterogeneity, epigenotypes (CpG island methylator phenotype, LINE-1 (long interspersed nucleotide element-1; also called long
interspersed nuclear element-1; long interspersed element-1; L1) hypomethylation, etc), and host–disease interactions.  

**Conclusion**

Succinate dehydrogenase is an important metabolic enzyme in the TCA cycle and electron transport chain. Germline mutations in SDHB, SDHC, SDHA, and SDHD are associated with RCC. To our knowledge, as the first systematic review on the succinate dehydrogenase genetic alterations, we can say that the most frequently detected mutation is SDHB rs772551056 and its protein expression. Moreover, the c.380A>G mutation with four MSI markers (D3S3691, D3S1597, D3SVHL3, D3S3611) of SDHC can bring a morphologically distinct entity of RCC and be a predictor of its recurrence and aggressive behavior. The newly suggested mutation of SDHA (c.2T>C: p.M1T) can provide evidence of GIST associated with RCC as well.

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**Disclosure**

The authors report no conflicts of interest in this work.

**References**

1. Linehan WM, Srinivasan R, Schmidt LS. The genetic basis of kidney cancer: a metabolic disease. *Nat Rev Urol.* 2010 May;7(5):277–85.
2. Khatami F, Noorinayer B, Ghiassi S, Mohebi R, Hashemi M, Zali MR. Single nucleotide polymorphisms of DNA methyltransferase 1 gene and gastric cancer in Iranian patients: a case control study. *Iran J Cancer Prev.* 2008;1(3):111–118.
3. Rini BI, Campbell SC, Bex E. Renal cell carcinoma. *Lancet.* 2009;373(9669):1119–1132. doi:10.1016/S0140-6736(09)60229-4
4. Abdollahi A, Khatami F, Tavangar SM. Clear cell sarcoma: a case report and review of literature. *Int J Hematol Oncol Stem Cell Res.* 2018;12(1):65–68.
5. Talab SS, Elmi A, Emami H, et al. Protective effects of acute liver preconditioning against renal ischemia/reperfusion injury in rat: role of nitric oxide and cyclooxygenase systems. *Eur J Pharmacol.* 2012;681(1–3):94–99. doi:10.1016/j.ejphar.2012.01.042
6. Kajbafzadeh A-M, Sabetkisheh N, Sabetkisheh S, Javan-Farazmand N, Harsini S, Tavangar S-M. Protective effect of pre-conditioning against renal ischemia/reperfusion injury in rat: role of nitric oxide and cyclooxygenase systems. *Eur J Pharmacol.* 2013;696(1–3):171–177. doi:10.1016/j.ejphar.2010.08.036
7. Motzer RJ, Bander NH, Naman DM. Renal-cell carcinoma. *N Engl J Med.* 1996;335(12):865–875. doi:10.1056/NEJM199609193351207
8. Talab SS, Emami H, Elmi A, et al. Chronic lithium treatment protects the rat kidney against ischemia/reperfusion injury: the role of nitric oxide and cyclooxygenase pathways. *Eur J Pharmacol.* 2010;647(1–3):171–177. doi:10.1016/j.ejphar.2010.08.036
9. Kajbafzadeh A-M, Payavash S, Salmasi AH, Monajemzadeh M, Tavangar SM. Smooth muscle cell apoptosis and defective neural development in congenital ureteropelvic junction obstruction. *J Urol.* 2006;176(2):718–723. doi:10.1016/j.juro.2006.03.041
66. Gimenez-Roqueplo A-P, Favier J, Rustin P, et al. Functional consequences of a SDHB gene mutation in an apparently sporadic pheochromocytoma. J Clin Endocrinol Metab. 2002;87(10):4771–4774. doi:10.1210/jc.2002-020525
67. Andrews KA, Ascher DB, Pires DEV, et al. Tumour risks and genotype–phenotype correlations associated with germinal variants in succinate dehydrogenase subunit genes SDHB, SDHC and SDHD. J Med Genet. 2018;55(6):384–394. doi:10.1136/jmedgenet-2017-105127
68. Niemeijer ND, Rijken JA, Eijkelenkamp K, et al. The phenotype of SDHB germline mutation carriers: a nationwide study. Eur J Endocrinol. 2017;177(2):115–125.
69. Berry WL, Janknecht R. KDM4/JMD2 histone demethylases: epigenetic regulators in cancer cells. Cancer Res. 2013;73:2936–2942. doi:10.1158/0008-5472.CAN-12-4300
70. Rose NR, Woon EC, Kingsham GL, et al. Selective inhibitors of the JMJD2 histone demethylases underlie global epigenomic divergence in gastrointestinal stromal tumor. Cancer Discov. 2013;3:648–657. doi:10.1158/2159-8290.CD-13-0092
71. Liang Y, Vogel JL, Arbuckle JH, et al. Targeting the JMJD2 histone demethylases to epigenetically control herpesvirus infection and reactivation from latency. Sci Transl Med. 2013;5(167):167ra5–ra5. doi:10.1126/scitranslmed.3005145
72. Piruat JI, Millán-Uclés Á. Genetically modeled mice with mutations in mitochondrial metabolic enzymes for the study of cancer. Front Oncol. 2014;4:200. doi:10.3389/fonc.2014.00200
73. Selak MA, Armour SM, MacKenzie ED, et al. Succinate dehydrogenase: combined nonadenating mass spectrometric screening and crystallographic approaches. J Med Chem. 2010;53(4):1810–1818. doi:10.1021/jm901680b
74. Killian JK, Kim SY, Miettinen M, et al. Succinate dehydrogenase mutation underlies global epigenomic divergence in gastrointestinal stromal tumor. Cancer Discov. 2013;3:648–657. doi:10.1158/2159-8290.CD-13-0092
75. Letouzé É, Martinelli C, Loriot C, et al. SDH mutations establish a hypermetilator phenotype in paraganglioma. Cancer Cell. 2013;23(6):739–752. doi:10.1016/j.ccr.2013.04.018
76. Baysal BE, Ferrell RE, Willett-Brozick JE, et al. Mutations in SDHD, a mitochondrial complex II gene, in hereditary paraganglioma. Science. 2000;287(5454):848–851. doi:10.1126/science.287.5454.848
77. Hao H-X, Khalimonchuk O, Schraders M, et al. SDH5, a gene required for flavination of succinate dehydrogenase, is mutated in paraganglioma. Science. 2009;325(5944):1139–1142. doi:10.1126/science.1175689
78. Andrici J, Gill AJ, Hornick JL, editors. Next generation immunohistochemistry: emerging substitutes to genetic testing? Seminars in diagnostic pathology; 2017. Elsevier;
79. Jackson CB, Nuoffe JM, Hahn D, et al. Mutations in SDHD lead to autosomal recessive encephalomyopathy and isolated mitochondrial complex II deficiency. J Med Genet. 2013. doi:10.1136/jmedgenet-2013-101932
80. Gill AJ, Lipton L, Taylor J, et al. Germline SDHC mutation presenting as recurrent SDH deficient GIST and renal carcinoma. Pathol J RCPA. 2013;45(7):689–691.
81. Rattenberry E, Viallard L, Yeung A, et al. A comprehensive next generation sequencing–based genetic testing strategy to improve diagnosis of inherited pheochromocytoma and paraganglioma. J Clin Endocrinol Metab. 2013;98(7):E1248–E56. doi:10.1210/jc.2013-3119
82. Dorschner MO, Amendola LM, Turner EH, et al. Actionable, pathogenic incidental findings in 1,000 participants’ exomes. Am J Hum Genet. 2013;93(4):631–640. doi:10.1016/j.ajhg.2013.08.006
83. Betts MJ, Russell RB. Amino-acid properties and consequences of substitutions. Bioinf Geneticians. 2007;2:311–339.
84. Bayley J-P, van Minderhout I, Weiss MM, et al. Mutation analysis of SDHB and SDHC: novel germline mutations in sporadic head and neck paraganglioma and familial paraganglioma and/or pheochromocytoma. BMC Med Genet. 2006;7(1):1. doi:10.1186/1471-2350-7-1
85. Bayley J-P, Devilee P, Taschener PE. The SDH mutation database: an online resource for succinate dehydrogenase sequence variants involved in pheochromocytoma, paraganglioma and mitochondrial complex II deficiency. BMC Med Genet. 2005;6(1):39. doi:10.1186/1471-2350-6-39
86. Astuti D, Hart-Holden N, Latif F, et al. Genetic analysis of mitochondrial complex II subunits SDHD, SDHB and SDHC in paraganglioma and pheochromocytoma susceptibility. Clin Endocrinol (Oxf). 2003;59(6):728–733. doi:10.1046/j.1365-2265.2003.01914.x
87. Schiavi F, Boedecker CC, Bausch B, et al. Predictors and prevalence of paraganglioma syndrome associated with mutations of the SDHC gene. JAMA. 2005;294(16):2057–2063. doi:10.1001/jama.294.16.2057
88. Tufon R, Ghelani R, Srrangalingam U, et al. A novel SDHA-deficient renal cell carcinoma revealed by comprehensive genomic profiling. Endocr Relat Cancer. 2017;24(7):T91–T103.
89. Miettinen M, Lasota J. Succinate dehydrogenase deficient gastrointestinal stromal tumors (GISTs)—A review. Int J Biochem Cell Biol. 2014;53:514–519. doi:10.1016/j.biocel.2014.05.033
90. Miettinen M, Killian JK, Wang Z-F, et al. Immunohistochemical loss of succinate dehydrogenase subunit A (SDHA) in gastrointestinal stromal tumors (GISTs) signals SDHA germline mutation. Am J Surg Pathol. 2013;37(2):234. doi:10.1097/PAS.0b013e3182671178
91. Ogino S, Lochhead P, Chan AT, et al. Molecular pathological epidemiology of epigenetics: emerging integrative science to analyze environment, host, and disease. Mod Pathol. 2013;26(4):465.
92. Ogino S, Nishihara R, VanderWeele TJ, et al. The role of molecular pathological epidemiology in the study of neoplastic and non-neoplastic diseases in the era of precision medicine. Epidemiology (Cambridge, Mass). 2016;27(4):602. doi:10.1097/EDE.0000000000000471
93. Hamada T, Keum N, Nishihara R, Ogino S. Molecular pathological epidemiology: new developing frontiers of big data science to study etiologies and pathogenesis. J Gastroenterol. 2017;52(3):265–275. doi:10.1007/s00535-016-1272-3