**Supplementary table 1**.Previously reported renal carcinomas showing negative staining for SDHB or arising in individuals carrying germline*SDH*-x mutations.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Case *No*.** | **Study** | | **Age/Sex** | **Family history of RCC** | | **germline *SDH-*x mutation / variation** | **SDHB IHC** | | **Personal or family history of PCC/ PGL** | | | | **Other pathologies** | **Follow up** |
| **1-2** | Ricketts et al  **J Urol [22]** | | **36/M** | Brother 25yrs  Paternal uncle | | SDHB  **exon** **1** deletion | **NA** | | **None** | | | | **NA** | **DOD**  *both siblings had a systematic presentation and suffered bone metastasis* |
| **3** | Ricketts et al  **J Urol [22]** | | 27/F | Paternal grandmother | | SDHB  **exon** **1** deletion | **NA** | | **None** | | | | **NA** | **Disease free (17 mo)** |
| **4** | Ricketts et al  **J Urol [22]** | | 42/F | None | | SDHB  **exon** **1** deletion | **NA** | | **Sister**  ***carrier of the familial mutation*** | | | | **NA** | **Disease free** (3.3 mo) |
| **5** | Ricketts et al  **J Urol [22]** | | 32/F | None | | **SDHB**  c.137G>A | **NA** | | **Paternal aunt**  ***carrier of the familial mutation*** | | | | **NA** | **DOD** (6.1 mo)  *Bone metastasis* |
| **6** | Ricketts et al  **J Urol [22]** | | 61/M | None | | **SDHB**:  c.268C>T | **NA** | | **Son**  (not screened for the familial mutation) | | | | **NA** | **Disease free** (50.4mo) |
| **7** | Ricketts et al  **J Urol [22]** | | 37/M | NA | | **SDHB**  c.286+2T>A | **NA** | | **NA** | | | | **NA** | **Disease free** (30 mo) |
| **8** | Ricketts et al  **J Urol [22]** | | 28/M | None | | **SDHB**  c.379A>C | **NA** | | **None** | | | | **NA** | **Disease free** (36.2 mo) |
| **9** | Ricketts et al  **J Urol [22]** | | 19/F | None | | **SDHB**  c.541-2A>G | **NA** | | **Mother**  (not screened for the familial mutation) | | | | **NA** | **Disease free** (40.6 mo) |
| **10-11** | Ricketts et al  **J Urol [22]** | | **17**, **34\*/F** | Mother  *RCC at the age of 55/ carrying the familial mutation*  Female sibling of the maternal grandfather  *not screened for the familial mutation* | | **SDHB**  c.286G>A | **NA** | | **None** | | | | **NA** | **Disease free** (212.4 mo)  **Mother AWD** (65.8 mo)  *liver and bone metastasis* |
| **12** | Ricketts et al  **J Urol [22]** | | 15/M | None | | **SDHB**  c.268C>T | **NA** | | **Paternal *m* cousins** (siblings)  **Paternal distant *f* relative**  *all carrying the familial mutation* | | | | **NA** | **Disease free** (10.8 mo) |
| **13** | Ricketts et al  **J Urol [22]** | | 17/M | None | | **SDHB**  c.137G>A | **NA** | | **None** | | | | **NA** | **Disease free** (6.0 mo) |
| **14** | Said-Al-Naief & Ojha  **Head Neck Pathol [23]**  Ricketts et al  **J Urol [22]** | | 52/F | Paternal Uncle 60yrs  Maternal grandfather  *RCC in later years*  Mother’s sibling | | **SDHB**  c.689G>A | **NA** | | **Daughter**  **-** *pheochromocytoma age 20*  **Paternal Cousin** 53 yrs  *- head and neck PGLs & one extra-adrenal PGL*  **-** *subsequently demonstrated to carry the familial mutation* | | | | **Multiple uterine fibroids**  **Multiple benign & malignant neoplasms existed in the family**:  **Maternal niece**  adrenal ganglioneuroma at the age of 13  **Maternal aunt**  lung and brain malignancies at the age of 30  **Mother’s sibling**  RCC, lung and breast carcinoma | **Disease free** (35.5 mo) |
| **15** | Solis et al  **Clin** **Genet [24]** | | 42/F | No | | SDHB  **exon** **1**deletion | **ND** | | **Positive personal history:**  Head and Neck PGL  (carotid body)  diagnosed at the age of 39  **11** **relatives out of 41 mutation carriers in this large family**  *-8 extra-adrenal PGLs*  *-3 PCCs* | | | | **Brother** 36 yrs  - papillary thyroid cancer  **Cousin** 59 yrs  -papillary bladder cancer  **Mother’s sibling**  62 yrs  -uterine adenocarcinoma  **Maternal aunt**  72 yrs  -lung cancer | Benign disease course? |
| **16** | [Henderson](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Henderson%20A%22%5BAuthor%5D) et al  **Fam Cancer [25]** | | 65/F | No | | **SDHB**  c.600G>T | **ND** | | **Grandson**  *- demonstrated to carry the familial mutation* | | | |  |  |
| **17-18** | Fairchild  et al  **JAMA [26]**  Schimke  et al  **Am J Med Genet A [27]** | | 60/M | maternal cousin *F* 26yrs | | **SDHB**  c.418G>T | **ND** | | **Positive personal history**:  Extra-adrenal PGL 52 yrs  3 **maternal** c**ousins**  **(Siblings**: *f* 16 *f* 55 *m* 49)  *extra-adrenal PGLs* | | | | **Cousin**  left para-aortal neuroblastoma (9 mo), while extra-adrenal PGL (16 yrs) with liver metastases (21 yrs) and a multifocal RCC (26 yrs) | **DOD**  (metastatic RCC)  **Cousin**  **DOD** (multifocal RCC) 26yrs |
| **19** | Vanharanta et al  **Am J Hum Genet [28]**  Neumann et al  **JAMA [29]**  Charis Eng  **J Natl Cancer Inst [30]** | | 28/M |  | | **SDHB**  c.79C>T | **ND** | | **Mother** 55yrs  *-malignant PGL of the heart*  *- demonstrated to carry the familial mutation*  **Extra-adrenal PGL**  (PGL of the heart) | | | |  | **DOD** (6 yrs) |
| **20** | Vanharanta et al  **Am J Hum Genet** [28]  Neumann et al  **JAMA** [29]  Charis Eng  **J Natl Cancer Inst** [30] | | **26/M** | Sister  24yrs | | **SDHB**  c.713\_716delTCTC | **ND** | | **Positive personal history**:  Paraganglioma34yrs  *- this diagnosis was sequential to the respective one of RCC*  **Sister**  *-paraganglioma, which along with both renal tumors displayed somatic loss of the remaining wild type allele* | | | |  | Alive after long follow-up |
| **21** | Vanharanta et al  **Am J Hum Genet** [28]  Neumann et al  **JAMA** [29]  Charis Eng  **J Natl Cancer Inst** [30] | | **24/F** | Brother 26yrs | | **SDHB**  c.713\_716delTCTC | **ND** | | **Positive personal history**:  Paraganglioma16yrs  **Brother**  *-paraganglioma, which did not show somatic loss of the remaining wild-type allele* | | | |  | **DOD** (1y 4 months) |
| **22** | Srirangalingam et al  **Clin Endocrinol** (**Oxf**) [31]  Srirangalingam et al  **Endocr Relat Cancer [32]**  [Tuthill](http://www.ncbi.nlm.nih.gov/pubmed?term=Tuthill%20M%5BAuthor%5D&cauthor=true&cauthor_uid=21686655) et al  [**BMJ Case Rep**](http://www.ncbi.nlm.nih.gov/pubmed/21686655##) **[33]** | | 26/F |  | | **SDHB**  c.141G>A | **ND** | | **Positive personal history**::  Extra-adrenal PGL 10yrs  *Family History Negative* | | | |  | **AWD** (24 mo)  Metastatic disease  -12 mo following surgical resection (*pelvic and supraclavicular R lymph node mass*)  -15 mo following surgical resection  (*evidence of progression within the right supraclavicular lymph nodes, partial metastatic destruction of the right scapula and new splenic metastasis*)  partial response to the multi-ta  rget tyrosine kinase inhibitor *sunitinib* |
| **23-25** | Ricketts et al  **J Natl Cancer Inst [34]** | | 24/M | Father 24yrs  Paternal Uncle 73yrs  *subsequently demonstrated to carry the familial mutation* | | **SDHB**  c.136C>T | **ND** | | **None** | | | |  | … |
| **26** | Ricketts et al  **J Natl Cancer Inst [34]** | | 30/F |  | | **SDHB**  c.137G>A | **ND** | | **None** | | | |  | … |
| **27** | Ricketts et al  **J Natl Cancer Inst [34]** | | 38/M |  | | **SDHB**  c.32G>A | **ND** | | **None** | | | |  | … |
| **28** | Cascón  et al  **J Med Genet [35]** | | 17/F | None | | SDHB  **exon** **1** deletion | **ND** | | **Positive personal history**:  Extra-adrenal PGL | | | | **None** | **AWD** (10 years)  *osseous metastatic disease* |
| **29** | Cascón et al **Genes Chromosomes Cancer [36]** | | 26/M | None | | SDHB  Whole gene (**Exons 1**-**8**) deletion | **ND** | | **Positive personal history**:  Head and Neck PGL **18yrs**  **Positive family history** (pers. com. Dr **M Robledo**) | | | |  |  |
| **30** | Fleming et al  **Histopathology** **[37]** | | 28/F |  | | **SDHB**  c.759\_765 + 7del | **ND** | |  | | | |  |  |
| **31** | Fleming et al  **Histopathology** **[37]** | | 69/F |  | | **SDHB**  c.320G>A | **ND** | |  | | | |  |  |
| **32** | Jasperson et al  **Familial** Cancer [38] | | 30/M | None | | **SDHB**  c.590C>G | **ND** | | **None**  **Positive family history** (pers. com. Dr K Jasperson) | | | |  | **Disease free** (? Mo) |
| **33** | Malinoc et al  **Endocr Relat**  **Cancer [39]** | | 68/ F | No | | **SDHC**  c.3G>A | **Neg/ Pos** | | **Positive personal history**:  Head and Neck PGL **42yrs**  **Son 40yrs**  *Head and Neck PGL* | | | |  |  |
| **34-36** | Ricketts et al  **J Urol [22]** | | **49/F** | 4 cousins (*f* siblings 44 52 53/68\*\* and a male 46 yrs)  Nephew 40 yrs  carrier of the familial mutation | | **SDHC**  c.397C>T | **ND** | | **Cousin (F)**  carrier of the familial mutation that did not develop RCC  HN PGL  (carotid PGL?) | | | |  | **Disease free** (240.8 mo)  Cousin **M** DOD (133.5 mo)  Cousin **F** Disease free (62.0 mo)  Cousin **F\*\*** AWD (54.8)  Cousin **F** Dead of other cause (182.7 mo)  Nephew Disease free (12.3 mo) |
| **37** | Ricketts et al  **J Urol [22]** | | 45/ M | None | | **SDHD**  c.239G>T | **ND** | | **Positive personal history**:  PGL 17,21,28,31,45,45yrs  Extensive family history of *CBT*s (**paternal grandfather**, **father**, **paternal uncle** and two **aunts**)  **Brother**  *Pheo* | | | |  | **DOD** (18.7 mo)  (osseous, lung and retroperitoneal metastatic disease) |
| **38** | Ni et al  **Am J Hum Genet [40]** | | 62/F | No | | **SDHD**  c.34G>A | **ND** | | **None** | | | | Thyroid gland & breast: benign pathology  Uterine leiomyomas |  |
| **39** | Ni et al  **Am J Hum Genet [40]** | | 53/ F | No | | **SDHD**  c.433C>A | **ND** | | **None** | | | | Breast carcinoma  Thyroid gland: benign pathology |  |
| **40** | Gill et al  **N Engl J Med [12]**  Gill et al  **Am J Surg Pathol [4]** | | **34/F** | Nephew  *carrying the familial mutation* | | **SDHB**  c.166-170 delCCTC | **Neg** | | **Nephew**  **Extra-adrenal PGL**  (intra-abdominal) | | | | **Sister** 31 yrs  Breast cancer  *subsequently demonstrated to carry the familial mutation* | **Disease free** (30 years) |
| **41-42** | Papathomas et al  **Eur J Endocrinol[41]** | | 25/M  23/M | Brother 23 yrs  Brother 25 yrs | | **SDHB**  c.3G>A | **Neg/Neg**  **Neg** | | **Positive personal history**:  Extra-adrenal PGL (1st brother) **Negative family history** | | | |  | **AWED**/31  **AWED**/28 |
| **43** | Papathomas et al  **Eur J Endocrinol** **[41]** | | 36/M | None | | **SDHB**  **exon** **3** deletion | **Neg** | | **Positive personal history**:  HN PGLs (30/34 yrs)  **Negative family history** | | | |  | **AWD**/47  (liver & splenic metastatic disease---  intraabdominal recurrent disease) |
| **44** | Paik et al.  **J Clin Oncol**  **[16]** | | 27/M | Male second cousin  *Metastatic RCC*  (DOD 37 yrs) | | **SDHB**  c.88delC | **Neg** | | **None** | | | | **Mother**  *Asymptomatic carrier of the familial mutation* | **DOD** at age 29 yrs  2.5 years after widespread metastatic disease presentation  (bone & liver metastatic disease) |
| **45** | Gill et al  **N Engl J Med [12]**  Gill et al  **Am J Surg Pathol [4]** | | **28/M** | Maternal Aunt 34yrs  *subsequently demonstrated to carry the familial mutation* | | **SDHB**  c.166-170 delCCTC | **Neg** | | **Positive personal history:**  Extra-adrenal PGL  (intra-abdominal)  **Synchronous tumors** also showed negative staining for SDHB | | | | **Mother** 31 yrs  Breast cancer  *subsequently demonstrated to carry the familial mutation* | **Disease free** (4 years) |
| **46** | Gill et al  **N Engl J Med [12]**  Gill et al  **Am J Surg Pathol [4]** | | 21/F | None | | **SDHB**  c.268C>T | **Neg** | | **Mother** 43,45 yrs  *-subsequently demonstrated to carry the familial mutation*  *-metachronous tumors showed SDHB immunonegativity*  Multiple **HN PGL**s  carotid body (R) PGL (43yrs); jugular (L) PGL and vagal (L) PGL (45 yrs) | | | |  | **Disease free** (7 years) |
| **47** | Gill et al  **N Engl J Med [12]**  Gill et al  **Am J Surg Pathol [4]** | 22/M | | None | **SDHB**:  c.423+1G>A | | | **Neg** | | **Nephew** 19yrs  *subsequently demonstrated to carry the familial mutation*  **Extra-adrenal PGL**  (intra-abdominal/ metastatic)  **Brother** 44yrs  *-subsequently demonstrated to carry the familial mutation*  -*synchronous tumors (****PGL*** *&* ***GIST****) also showed SDHB immunonegativity*  **Extra-adrenal PGL**  (intra-abdominal) | | **Brother** 44yrs  **SDH deficient GIST** | | **DOD** (1 year)  *progressive metastatic disease* |
| **48** | [Housley](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Housley%20SL%22%5BAuthor%5D) et al  et al  **Histopathology [42]**  Gill et al  **Am J Surg Pathol [4]**  Fleming et al  **Histopathology [37]** | 58/F | | None | **SDHB**  c.72+1G>T | | | **Neg** | | **Daughter**  - *previous diagnosis of a malignant Pheo accounting for genetic screening*  *and subsequent detection of RCC in the mother*  *- demonstrated to carry the familial mutation concurrently with her mother*  **Pheochromocytoma** |  | | | **Disease free**  2 years |
| **49** | Gill et al  **Pathology [17]** | | 22/F | None | | **SDHC**  c.380A>G | **Neg** | | **None**  Her sister/mother are asymptomatic carriers of the familial mutation | | | | Gastric SDH-deficient GIST  (+ Liver metastasis)  **12/ 33 yrs**  Papillary thyroid carcinoma  **30 yrs** | Disease free (**?** **Mo**) |
| **50** | Miettinen et al **AIMM[43]** | | 40/M | None | | **Not performed (SDHB negative by IHC)** | **Neg** | | **None** | | | |  | Adrenal Metastasis |
| **51** | Miettinen et al **AIMM[43]** | | 35/M |  | | **Not performed (SDHB negative by IHC)** | **Neg** | |  | | | |  | Retropertioneal Node Metastasis |
| **52** | Miettinen et al **AIMM[43]** | | 44/M | Mother age 25 | | **Not performed (SDHB negative by IHC)** | **Neg** | | **None** | | | |  | Adrenal Metastases at presentation |
| **53** | Miettinen et al **AIMM[43]** | | 59/F |  | | **Not performed (SDHB negative by IHC)** | **Neg** | |  | | | | Gastric SDH-Deficient GIST **19 yrs**  Liver met of SDH-deficient GIST **42yrs** | ?disease free 2 years |

# 3 cases (No 2, 18 & 25) were included due to familial RCC occurrence, familial aggregation of the SDHB mutation, early age at presentation and/ or personal/familial history of PCC/PGL; two of these patients were deceased (No 18 & 25) and thus mutational analysis was not performed

\* metachronous contralateral kidney cancer recurrence 17 yrs following initial renal tumor resection

\*\* carrier of the familial mutation; metachronous contralateral disease subsequently developed in the presence of widespread metastases

(liver, lung, brain)

http://chromium.liacs.nl/lovd\_sdh/home.php?select\_db=SDHB

**ND** **N**ot **D**one