**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 25yrsPaternal 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 60yrsMaternal 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 yrs3 **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-target tyrosine kinase inhibitor *sunitinib* |
| **23-25** | Ricketts et al**J Natl Cancer Inst [34]** | 24/M | Father 24yrsPaternal 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 | SDHBWhole 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 RCCHN 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 17,21,28,31,45,45yrsExtensive 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 pathologyUterine leiomyomas |  |
| **39** | Ni et al**Am J Hum Genet [40]** | 53/ F | No | **SDHD**c.433C>A | **ND** | **None** | Breast carcinomaThyroid 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 yrsBreast cancer *subsequently demonstrated to carry the familial mutation* | **Disease free** (30 years) |
| **41-42** | Papathomas et al**Eur J Endocrinol[41]** | 25/M23/M | Brother 23 yrsBrother 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 yrs2.5 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 yrsBreast 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**scarotid 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 alet 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