**Supplementary Material**

**Elongin C (*ELOC/TCEB1*) associated von Hippel-Lindau disease**

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**Supplementary Figures**

## **Supplementary Figure 1:** Comparison of WES alignments of DNA extracted from proband´s kidney tumour specimen and blood (germline).

The Binary Alignment Map (BAM) files were viewed with the Integrative Genomics Viewer (IGV) (1).

# Graphical user interface, application, Word Description automatically generated

WT= wild type allele, ALT= alternative allele

# **Supplementary Tables**

## **Supplementary Table 1:** Rare *de novo* variants in proband.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Gene | Consequence | HGVSc[[1]](#footnote-1) | HGVSp[[2]](#footnote-2) | dbSNP[[3]](#footnote-3) | gnomAD\_ALL[[4]](#footnote-4) |
| *CRIPAK* | frameshift insertion | c.51\_52insTGCCCATGTGGAGTGCCCGCCTGCTCACACA | p.T17fs | rs750778284 | 0 |
| *FGFRL1* | frameshift deletion | c.1435\_1436del | p.H479fs | rs145808953 | 1.10x10-3 |
| *TMEM185B* | frameshift deletion | c.1023delT | p.P341fs |  | 0 |
| *HEG1* | nonsynonymous SNV | c.1232G>A | p.R411H | rs538286740 | 6.45x10-5 |
| *PABPC1* | nonsynonymous SNV | c.541G>A | p.A181T | rs201575415 | 9.76x10-5 |
| *PABPC1* | nonsynonymous SNV | c.619C>T | p.L207F | rs200538577 | 9.76x10-5 |
| *HLA-DRB5* | nonsynonymous SNV | c.197A>C | p.D66A | rs200042906 | 2.70x10-3 |
| *PABPC1* | nonsynonymous SNV | c.617G>A | p.R206H | rs201157005 | 6.51x10-5 |
| *PDE4DIP* | nonsynonymous SNV | c.4186C>T | p.R1396W | rs2798901 | 0 |
| *ATAD3B* | nonsynonymous SNV | c.1907G>C | p.G636A | rs553799027 | 9.73x10-5 |
| *CELF3* | nonframeshift deletion | c.1098\_1100del | p.366\_367del | rs777856157 | 6.52x10-5 |
| *HRNR* | nonsynonymous SNV | c.5161G>A | p.G1721S |  | 0 |
| *OTOP1* | nonsynonymous SNV | c.310C>A | p.L104M | rs200554408 | 0 |
| *SSPO* | stopgain | c.11582dupA | p.Y3861\_C3862delinsX |  | 0 |
| *PAXIP1* | nonframeshift deletion | c.1642\_1644del | p.548\_548del | rs141168451 | 6.54x10-5 |
| *ELOC* | nonsynonymous SNV | c.236A>G | p.Y79C |  | 0 |

**Supplementary Table 2:** List of deep intronic and promoter variants in *VHL* excluded from the proband.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Variants | dbSNP | Type of variant | Consequence | Phenotype | Publication |
| NM\_000551.4(VHL):c.340+770T>C | rs1346312258 | cryptic exon (E1') variant in intron 1 | splicing dysregulation | erythrocytosis | Lenglet et. al. 2018 (2) |
| NM\_000551.4(VHL):c.340+694\_340+711dup | rs1575923363 | cryptic exon (E1') variant in intron 1 | splicing dysregulation | erythrocytosis | Lenglet et. al. 2018 (2) |
| NM\_000551.4(VHL):c.340+574A>T | rs98274567 | cryptic exon (E1') variant in intron 1 | splicing dysregulation | erythrocytosis | Lenglet et. al. 2018 (2) |
| NM\_000551.4(VHL):c.340+816A>C | rs1031288121 | cryptic exon (E1') variant in intron 1 | splicing dysregulation | erythrocytosis | Lenglet et. al. 2018 (2) |
| NM\_000551.4(VHL):c.340+617C>G | rs1575923261 | cryptic exon (E1') variant in intron 1 | splicing dysregulation | VHL syndrome | Lenglet et. al. 2018 (2) |
| NM\_000551.4(VHL):c.340+648T>C | rs73024533 | cryptic exon (E1') variant in intron 1 | splicing dysregulation | VHL syndrome | Lenglet et. al. 2018 (2) |
| NM\_000551.4(VHL):c.340+665G>C | rs1696160266 | nearby variant to c.340+648T>C | splicing dysregulation | functional work evidence only | Lenglet et. al. 2018 (2) |
| NM\_000551.4(VHL):c.429C>T (p.Asp143=) | rs773556807 | synonymous variants in exon 2 that induce exon skipping | exon skipping | erythrocytosis | Lenglet et. al. 2018 (2) |
| NM\_000551.4(VHL):c.414A>G (p.Pro138=) | rs869025648 | synonymous variants in exon 2 that induce exon skipping | exon skipping | VHL syndrome, phaeochromocytoma | Lenglet et. al. 2018, Flores et. al. 2019 (2, 3) |
| NM\_000551.4(VHL):c.413C>T (p.Pro138Leu) | rs780178275 | nearby variant to c.414A>G | splicing dysregulation | functional work evidence only | Lenglet et. al. 2018 (2) |
| NM\_000551.3(VHL):c.-75\_-55del | rs727503744 | promoter/5'UTR variant | promoter/5'UTR variant | VHL syndrome | Zatyka et. al. 2002 (4) |
| NM\_000551.4(VHL):c.-54\_-35dup | rs730882036 | promoter/5'UTR variant | does not appear to affect the start codon or the Kozak translational consensus sequence. | VHL syndrome | Landrum et. al. 2016 (5); Accession: SCV000211830.2 |
| NM\_000551.3(VHL):c.-77\_-32del | rs1553619239 | 5'UTR variant including the promoter | Reduced *VHL* expression | VHL syndrome | Albanyan et. al. 2019 (6) |
| NM\_000551.4(VHL):c.-61\_-51dup | rs727503743 | upstream 5'UTR variant | Mild reduction in *VHL* expression | VHL-like disease | Albanyan et. al. 2019 (6) |

## **Supplementary Table 3:** Phenotypes of individuals with multiple VHL-related tumours or a single VHL-related tumour plus a family history of a VHL-related tumour tested for germline ELOC variants.

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **ID** | | **Class** | | **Sex** | | **Age** | | **Clinical details** | | **Testing** | |
| Fam\_1 | | VHLSp | | N/A | | N/A | | Familial RCC | | WES | |
| Fam\_2 | | VHLSp | | N/A | | 71 | | Familial RCC | | WES | |
| Fam\_3 | | VHLSp | | N/A | | N/A | | Familial RCC | | WES | |
| Fam\_4 | | VHLSp | | F | | 60 | | Familial RCC | | WES | |
| Fam\_5 | | VHLSp | | M | | 62 | | Familial RCC | | WES | |
| Fam\_6 | | VHLSp | | N/A | | 55 | | Familial RCC | | WES | |
| Fam\_7 | | VHLSp | | N/A | | 56 | | Familial RCC | | WES | |
| Fam\_8 | | VHLSp | | N/A | | 57 | | Familial RCC | | WES | |
| Fam\_9 | | VHLSp | | N/A | | 64 | | Familial RCC | | WES | |
| Fam\_10 | | VHLSp | | N/A | | 56 | | Familial RCC | | WES | |
| Fam\_11 | | VHLSp | | F | | 60 | | Bilateral/multifocal RCC | | WES | |
| Fam\_12 | | VHLSp | | M | | 52 | | Familial RCC | | WES | |
| Fam\_13 | | VHLSp | | F | | 52 | | Familial RCC | | WES | |
| Fam\_15 | | VHLSp | | M | | 58 | | Bilateral/multifocal RCC | | WES | |
| Fam\_16 | | VHLSp | | M | | 48 | | Bilateral/multifocal RCC | | WES | |
| Fam\_17 | | VHLSp | | M | | 41 | | Familial RCC | | WES | |
| Fam\_18 | | VHLSp | | M | | 49 | | Bilateral/multifocal RCC | | WES | |
| Fam\_19 | | VHLSp | | F | | 47 | | Familial RCC | | WES | |
| Fam\_20 | | VHLSp | | N/A | | 51 | | Bilateral/multifocal RCC | | WES | |
| Fam\_21 | | VHLSp | | M | | 49 | | Familial RCC | | WES | |
| Fam\_22 | | VHLSp | | F | | 32 | | Bilateral/multifocal RCC | | WES | |
| Fam\_23 | | VHLSp | | M | | 49 | | Familial RCC | | WES | |
| Fam\_24 | | VHLSp | | M | | 40 | | Familial RCC | | WES | |
| Fam\_25 | | VHLSp | | M | | 38 | | Bilateral/multifocal RCC | | WES | |
| Fam\_26 | | VHLSp | | F | | 40 | | Bilateral/multifocal RCC | | WES | |
| Fam\_27 | | VHLSp | | M | | 41 | | Familial RCC | | WES | |
| Fam\_28 | | VHLSp | | M | | 31 | | Bilateral/multifocal RCC | | WES | |
| Fam\_29 | | VHLSp | | N/A | | 30 | | Familial RCC | | WES | |
| Fam\_30 | | VHLSp | | M | | 45 | | Bilateral/multifocal RCC | | WES | |
| Fam\_31 | | VHLSp | | M | | 53 | | Bilateral/multifocal RCC | | WES | |
| Fam\_32 | | VHLSp | | M | | 38 | | Familial RCC | | WES | |
| Fam\_33 | | VHLSp | | M | | 48 | | Bilateral/multifocal RCC | | WES | |
| Fam\_34 | | VHLSp | | M | | 42 | | Familial RCC | | WES | |
| Fam\_35 | | VHLSp | | M | | 34 | | Familial RCC | | WES | |
| Fam\_36 | | VHLSp | | M | | 54 | | Familial RCC | | WES | |
| Fam\_37 | | VHLSp | | M | | 48 | | Bilateral/multifocal RCC | | WES | |
| Fam\_38 | | VHLSp | | N/A | | 45 | | Familial RCC | | WES | |
| Fam\_39 | | VHLSp | | F | | 61 | | Bilateral/multifocal RCC | | WES | |
| Fam\_40 | | VHLSp | | M | | 50 | | Bilateral/multifocal RCC | | WES | |
| Fam\_41 | | VHLSp | | F | | 50 | | Familial RCC | | WES | |
| Fam\_42 | | VHLSp | | M | | 39 | | Familial RCC | | WES | |
| Fam\_43 | | VHLSp | | M | | 30 | | Familial RCC | | WES | |
| Fam\_44 | VHLSp | | N/A | | 74 | | Familial RCC | | WES | |
| Fam\_45 | VHLSp | | M | | 48 | | Familial RCC | | WES | |
| Fam\_46 | VHLSp | | M | | 61 | | Familial RCC | | WES | |
| Fam\_47 | VHLSp | | F | | 47 | | Bilateral/multifocal RCC | | WES | |
| Fam\_48 | VHLSp | | M | | 72 | | Bilateral/multifocal RCC | | WES | |
| Fam\_49 | VHLSp | | M | | 57 | | Familial RCC | | WES | |
| Fam\_50 | VHLSp | | F | | 40 | | Bilateral/multifocal RCC | | WES | |
| Fam\_51 | VHLSp | | M | | 69 | | Familial RCC | | WES | |
| Fam\_52 | VHLSp | | M | | 42 | | Bilateral/multifocal RCC | | WES | |
| Fam\_53 | VHLSp | | M | | 46 | | Bilateral/multifocal RCC | | WES | |
| Fam\_54 | VHLSp | | M | | 46 | | Bilateral/multifocal RCC | | WES | |
| Fam\_55 | VHLSp | | F | | 11 | | Familial RCC | | WES | |
| Fam\_56 | VHLSp | | M | | 37 | | Bilateral/multifocal RCC | | WES | |
| Fam\_57 | VHLSp | | M | | 63 | | PHEO, RCC | | WES | |
| Fam\_58 | VHLSp | | F | | 46 | | Familial PHEO | | WES | |
| Fam\_59 | VHLSp | | F | | 52 | | Familial PHEO | | WES | |
| Fam\_60 | VHLSp | | F | | 41 | | Bilateral/multifocal RCC | | WES | |
| Fam\_61 | VHLSp | | F | | 45 | | Bilateral/multifocal RCC | | WES | |
| Fam\_62 | VHLSp | | N/A | | N/A | | Familial RCC | | WES | |
| Fam\_63 | VHLSp | | N/A | | 62 | | Bilateral/multifocal RCC | | WES | |
| Fam\_64 | VHLSp | | N/A | | 55 | | Bilateral/multifocal RCC | | WES | |
| Fam\_65 | VHLSp | | N/A | | 47 | | Familial RCC | | WES | |
| Fam\_66 | VHLSp | | N/A | | 59 | | Bilateral/multifocal RCC | | WES | |
| Fam\_67 | VHLSp | | M | | N/A | | HB, PHEO | | Targeted | |
| Fam\_68 | VHLSp | | F | | N/A | | RA, HB | | Targeted | |
| Fam\_69 | VHLSp | | M | | N/A | | HB, RCC | | Targeted | |
| Fam\_70 | VHLSp | | N/A | | N/A | | RA,HB | | Targeted | |
| Fam\_71 | VHLSp | | N/A | | N/A | | Clinical VHL diagnosis | | Targeted | |
| Fam\_72 | VHLSp | | N/A | | N/A | | Clinical VHL diagnosis | | Targeted | |
| Fam\_73 | VHLSp | | N/A | | N/A | | Clinical VHL diagnosis | | Targeted | |
| Fam\_74 | VHLSp | | N/A | | N/A | | Clinical VHL diagnosis | | Targeted | |
| Fam\_75 | VHLSp | | N/A | | N/A | | Clinical VHL diagnosis | | Targeted | |
| Fam\_76 | VHLSp | | N/A | | N/A | | Clinical VHL diagnosis | | Targeted | |
| Fam\_77 | VHLSp | | N/A | | N/A | | Clinical VHL diagnosis | | Targeted | |
| Fam\_78 | VHLSp | | N/A | | N/A | | Clinical VHL diagnosis | | Targeted | |
| Fam\_79 | VHLSp | | N/A | | N/A | | Clinical VHL diagnosis | | Targeted | |
| Fam\_80 | VHLSp | | N/A | | N/A | | Clinical VHL diagnosis | | Targeted | |
| Fam\_81 | VHLSp | | N/A | | N/A | | Clinical VHL diagnosis | | Targeted | |
| Fam\_82 | VHLSp | | N/A | | N/A | | Clinical VHL diagnosis | | Targeted | |
| Fam\_83 | VHLSp | | N/A | | N/A | | Clinical VHL diagnosis | | Targeted | |
| Fam\_84 | VHLSp | | N/A | | N/A | | Clinical VHL diagnosis | | Targeted | |
| Fam\_85 | VHLSp | | N/A | | N/A | | Clinical VHL diagnosis | | Targeted | |
| Fam\_86 | VHLSp | | N/A | | N/A | | Clinical VHL diagnosis | | Targeted | |
| Fam\_87 | VHLSp | | N/A | | N/A | | Clinical VHL diagnosis | | Targeted | |
| Fam\_88 | VHLSp | | N/A | | N/A | | Clinical VHL diagnosis | | Targeted | |
| Fam\_89 | VHLSp | | N/A | | N/A | | Clinical VHL diagnosis | | Targeted | |
| Fam\_90 | VHLSp | | N/A | | N/A | | Clinical VHL diagnosis | | Targeted | |
| Fam\_91 | VHLSp | | N/A | | N/A | | Clinical VHL diagnosis | | Targeted | |

VHLSp=VHL spectrum phenotype, PHEO= pheochromocytoma, RCC= renal cell carcinoma, HB=haemangioblastoma, RA=retinal angioma

## **Supplementary Table 4:** RCC somatic *ELOC* variants reported in different studies.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Cohort | Variant | Variant type | Count | Publication |
| TCGA[[5]](#footnote-5) | Y79C | missense | 3 | Ricketts et. el. 2018 (7) |
| TCGA | Y79N | missense | 1 | Ricketts et. el. 2018 (7) |
| TCGA | Y79S | missense | 1 | Ricketts et. el. 2018 (7) |
| TCGA | Y79F | missense | 1 | Ricketts et. el. 2018 (7) |
| TCGA | Y79\* | nonsense | 1 | Ricketts et. el. 2018 (7) |
| TCGA | Y79\* | nonsense | 1 | Ricketts et. el. 2018 (7) |
| TCGA | C112Vfs\*3 | frameshift deletion | 1 | Ricketts et. el. 2018 (7) |
| Sato *et al* 2013 | Y79C | missense | 6 | Sato et. al. 2013 (8) |
| Sato *et al* 2013 | Y79S | missense | 1 | Sato et. al. 2013 (8) |
| Sato *et al* 2013 | A100P | missense | 1 | Sato et. al. 2013 (8) |
| TRACERx Renal[[6]](#footnote-6) | K114R | missense | 1 | Hakimi et. al. 2015 (9) |
| TRACERx Renal | I95N | missense | 1 | Mitchell et. al. 2018 (10) |
| MSKCC[[7]](#footnote-7) | Y79C/S/L/N | missense | 5 | DiNatale et. al. 2021 (11) |

## **Supplementary Table 5:** RCC somatic *ELOC* variants from the 100,000 Genomes Project.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Case no | Gene | HGVSc[[8]](#footnote-8) | HGVSp[[9]](#footnote-9) | CHR POS (GRCh38) | REF | ALT | Consequence |
| Case 1 | ELOC | ENST00000284811.12:  c.236A>G | ENSP00000284811.8:  p.Tyr79Cys | 8:73946733 | T | C | missense |
| Case 2 | ELOC | ENST00000284811.12:  c.236A>G | ENSP00000284811.8:  p.Tyr79Cys | 8:73946733 | T | C | missense |
| Case 3 | ELOC | ENST00000284811.12:  c.236A>G | ENSP00000284811.8: p.Tyr79Cys | 8:73946733 | T | C | missense |
| Case 4 | ELOC | ENST00000284811.12:  c.236A>G | ENSP00000284811.8: p.Tyr79Cys | 8:73946733 | T | C | missense |
| Case 5 | ELOC | ENST00000284811.12: c.274G>A | ENSP00000284811.8: p.Glu92Lys | 8:73946695 | C | T | missense |
| Case 6 | ELOC | ENST00000284811.12:  c.74A>T | ENSP00000284811.8: p.Asp25Val | 8:73955985 | T | A | missense |
| Case 7 | ELOC | ENST00000284811.12:  c.311T>A | ENSP00000284811.8: p.Leu104Gln | 8:73946658 | A | T | missense |
| Case 8 | ELOC | ENST00000284811.12:  c.261\_272del | ENSP00000284811.8:  p.Thr88\_Pro91del | 8:73946696 | AGGAATCTCGGTG | A | Inframe deletion |

# **Supplementary References**

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1. Human Genome Variation Society coding sequence name [↑](#footnote-ref-1)
2. Human Genome Variation Society protein sequence name [↑](#footnote-ref-2)
3. Single Nucleotide Polymorphism Database number [↑](#footnote-ref-3)
4. maximum allele frequency from all ethnicities in gnomAD database [↑](#footnote-ref-4)
5. TRACERx Renal= TRAcking Cancer Evolution through therapy (Rx) Renal cohort [↑](#footnote-ref-5)
6. MSKCC= Memorial Sloan Kettering Cancer Centre [↑](#footnote-ref-6)
7. PMID= Pubmed ID [↑](#footnote-ref-7)
8. Human Genome Variation Society coding sequence name [↑](#footnote-ref-8)
9. Human Genome Variation Society protein sequence name [↑](#footnote-ref-9)