|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Patient number (n=19) | Mutation | Mutation  Nucleotide | AS-change | Codon number/  AS-position | Codon-change |
| 3 | missense | 407 C → G | Ser → Trp | 65 | TCG → TGG |
| 4 | missense | 676 G → A | Val → Met | 155 | GTG → ATG |
| 48 | missense | 704 A → T | Gln → Leu | 164 | CAG → CTG |
| 7 | missense | 601 G → T | Val → Phe | 130 | GTT → TTT |
| 9 | missense | 479 T → C | Leo → Pro | 89 | CTC → CCC |
| 10 | missense | 601 G → T | Va → Phe | 130 | GTT → TTT |
| 12 | missense | 557 A → G | His → Arg | 115 | CAC → CGC |
| 14 | missense | 674 C → T | Pro → Leu | 154 | CCA → CTA |
| 23 | missense | 712 C → T | Arg → Trp | 167 | CGG → TGG |
| 25 | missense | 434 T → G | Val → Gly | 74 | GTC → GGC |
| 50 | missense | 505 T → C | Tyr → His | 98 | TAC → CAC |
| 40 | missense | 712 C → T | Arg → Trp | 167 | CGG → TGG |
| 43 | missense | 475 T → A | Trp → Arg | 88 | TGG → AGG |
| 44 | missense | 695 G → C | Arg → Pro | 161 | CGA → CCA |
| 45 | missense | 620 T → C | Phe → Ser | 136 | TTT → TCT |
| 46 | missense | 475 T → A | Trp → Arg | 88 | TGG → AGG |
| 60 | missense | 701 T → A | Leu → Hist | 163 | CTC → CAC |
| 62 | missense | 479 T → C | Leo → Pro | 89 | CTC → CCC |
| 65 | missense | 452 G → T | Ser → Ile | 80 | AGT → ATT |

**Supplementary Tables S1 - S9**

**Table S1**: 19 patients with missense mutation

**Table S2**: 9 patients with nonsense mutation

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Patient number (n=9) | Mutation | Mutation Nucleotide | AS-change | Codon number/  AS-position | Codon-change |
| 5 | nonsense | 407 C → A | Ser → Term | 65 | TGA → TAG |
| 8 | nonsense | 430 C → T | Gln → Term | 73 | CAG → TAG |
| 11 | nonsense | 550 C → T | Arg → Term | 113 | CGA → TGA |
| 33 | nonsense | 430 C → T | Gln → Term | 73 | CAG → TAG |
| 34 | nonsense | 617 T → A | Leu → Term | 135 | TTA → TAA |
| 42 | nonsense | 694 C → T | Arg → Term | 161 | CGA → TGA |
| 57 | nonsense | 761 C → A | Ser → Term | 183 | TCG → TAG |
| 61 | nonsense | 694 C → T | Arg → Term | 161 | CGA → TGA |
| 63 | nonsense | 694 C → T | Arg → Term | 161 | CGA → TGA |

**Table S3**: 9 patients with splice mutations

|  |  |  |  |
| --- | --- | --- | --- |
| Patient number (n=9) | Mutation | Mutation Nucleotide | Localisation |
| 1 | splice | 553 + 1 G → T | "+1" |
| 13 | splice | 553 + 1 G → T | "+1" |
| 22 | splice | 677 - 1 G → A | "-1" |
| 54 | splice | 677 - 2 A → G | "-2" |
| 28 | splice | 676 + 2 T → C | "+2" |
| 37 | splice | 677 - 1 G → T | "-1" |
| 38 | splice | 677 - 1 G → A | "-1" |
| 41 | splice | 676 + 2 T → C | "+2" |
| 55 | splice | 677 - 1 G → C | "-1" |

**Table S4**: 13 patients with large deletion

|  |  |  |
| --- | --- | --- |
| Patient number (n=13) | Mutation | Deletion |
| 17 | large deletion | Exon 3 |
| 19 | large deletion | Exon 1-3 |
| 20 | large deletion | Exon 1-3 |
| 21 | large deletion | Exon 1-3 |
| 27 | large deletion | Exon 1-3 |
| 29 | large deletion | Exon 1 |
| 30 | large deletion | Exon 2, 3 |
| 31 | large deletion | Exon 1-3 |
| 35 | large deletion | Exon 3 |
| 47 | large deletion | Exon 1-2 |
| 36 | large deletion | Exon 1-2 |
| 51 | large deletion | Exon 1-2 |
| 59 | large deletion | Exon 2 |

**Table S5**: 8 patients with small deletion

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Patient number  (n=8) | Mutation | Mutation Nucleotide | Codon | In frame/  frameshift |
| 49 | small deletion | 740 del G | 176 | frameshift |
| 6 | small deletion | 437-9 del TCT | 76/77 | in frame |
| 52 | small deletion | 794-5 del GT | 194 | frameshift |
| 15 | small deletion | 597 del T | 128 | frameshift |
| 18 | small deletion | 437-9 del TCT | 75/76 | in frame |
| 24 | small deletion | 437-9 del TCT | 75/76 | in frame |
| 56 | small deletion | 437-9 del TCT | 75/76 | in frame |
| 58 | small deletion | 691-92 del AG | 159/160 | frameshift |

**Table S6**: 3 patients with small insertion

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Patient number  (n=3) | Mutation | Mutation Nucleotide | Codon-position | In frame/  frameshift |
| 26 | small insertion | 417 ins. G | 68/69 | frameshift |
| 53 | small insertion | 417 ins. G | 68/69 | frameshift |
| 32 | small insertion | 529 ins. A | 105/106 | frameshift |

**Table S7**: Volume multiplication per year depending on germline mutation

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Tumour volume multiplication per year | | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
| Splice | n (tumours) | 12 | 10 | 7 | 5 | 3 |
| Mean | 3,2 | 2,4 | 2,2 | 1,6 | 1,7 |
| Median | 2.1 | 1.7 | 2.1 | 1.2 | 1.2 |
| SD | 2,2 | 1,9 | 0,7 | 0,6 | 0,6 |
| Missense | n (tumours) | 30 | 27 | 25 | 17 | 11 |
| Mean | 2,4 | 2,5 | 1,7 | 1,6 | 1,7 |
| Median | 1.9 | 1.5 | 1.4 | 1.4 | 1.5 |
| SD | 1,6 | 1,9 | 1,0 | 0,5 | 0,8 |
| Large deletion | n (tumours) | 27 | 24 | 22 | 18 | 13 |
| Mean | 2,1 | 1,7 | 1,5 | 1,4 | 1,7 |
| Median | 1.5 | 1.5 | 1.4 | 1.3 | 1.6 |
| SD | 1,6 | 1,0 | 0,3 | 0,4 | 0,5 |
| Small deletion | n (tumours) | 8 | 8 | 7 | 7 | 6 |
| Mean | 1,8 | 1,9 | 1,5 | 1,7 | 1,5 |
| Median | 1.4 | 1.4 | 1.2 | 1.4 | 1.1 |
| SD | 1,1 | 1,1 | 0,5 | 0,7 | 0,7 |
| Nonsense | n (tumours) | 14 | 14 | 14 | 6 | 5 |
| Mean | 1,7 | 1,3 | 1,5 | 1,4 | 1,5 |
| Median | 1.3 | 1.3 | 1.4 | 1.3 | 1.4 |
| SD | 1,1 | 0,2 | 0,5 | 0,2 | 0,3 |
| Small insertion | n (tumours) | 3 | 3 | 3 | \* | \* |
| Mean | 2,0 | 1,8 | 3,9 | \* | \* |
| Median | 1,3 | 2,1 | 2,8 | \* | \* |
| SD | 1,7 | 0,5 | 1,6 | \* | \* |
| Unknown mutation\*\* | | 1,7 | 11,2 | 27,7 | 65,3 | \* |
| Unknown mutation\*\* | | 2,5 | 5,1 | 8,9 | 12,9 | \* |

\*no data

\*\* VHL-diagnosis based on clinical criteria and family history

**Table S8**: Cumulative volume multiplication depending on germline mutation

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Cumulative tumour  volume multiplication | | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
| Large deletion | n (tumours) | 27 | 24 | 22 | 18 | 13 | 7 |
| Mean | 2,0 | 4,3 | 6,6 | 6,5 | 13,5 | 28,4 |
| Median | 1.5 | 2.1 | 3.0 | 3.8 | 7.7 | 9.4 |
| SD | 1,6 | 7,7 | 12,1 | 10,1 | 18,5 | 38,3 |
| Missense | n (tumours) | 30 | 27 | 25 | 17 | 11 | 9 |
| Mean | 2,4 | 6,9 | 13,8 | 11,3 | 29,0 | 49,6 |
| Median | 1.9 | 3.0 | 4.0 | 4.3 | 21.6 | 40.0 |
| SD | 1,6 | 8,9 | 23,5 | 10,7 | 30,9 | 42,7 |
| Nonsense | n (tumours) | 14 | 14 | 14 | 6 | 5 | 5 |
| Mean | 1,7 | 2,5 | 4,5 | 11,5 | 16,1 | 24,2 |
| Median | 1.3 | 1.8 | 2.3 | 3.8 | 5.8 | 9.5 |
| SD | 1,1 | 2,1 | 6,4 | 15,4 | 22,6 | 32,2 |
| Small deletion | n (tumours) | 8 | 8 | 7 | 7 | 6 | 4 |
| Mean | 1,8 | 4,3 | 8,5 | 14,1 | 14,4 | 32,2 |
| Median | 1.4 | 1.9 | 2.5 | 3.4 | 3.9 | 8.9 |
| SD | 1,1 | 4,5 | 10,6 | 18,0 | 22,6 | 44,2 |
| Splice | n (tumours) | 12 | 10 | 7 | 5 | 3 | \* |
| Mean | 3,2 | 6,9 | 18,7 | 47,1 | 143,3 | \* |
| Median | 2.1 | 5.11 | 16.0 | 27.7 | 34,5 | \* |
| SD | 2,2 | 5,1 | 18,3 | 56,0 | 176,6 | \* |
| Small insertion | n (tumours) | 3 | 3 | 3 | \* | \* | \* |
| Mean | 2,0 | 4,0 | 16,4 | \* | \* | \* |
| Median | 1,3 | 2,4 | 16,4 | \* | \* | \* |
| SD | 1,4 | 3,3 | 19,3 | \* | \* | \* |
| Unknown mutation\*\* | | 2,5 | 5,13 | 8,9 | 12,9 | \* | \* |
| Unknown mutation\*\* | | 1,7 | 11,2 | 27,7 | 65,3 | \* | \* |

\*no data

\*\* VHL-diagnosis based on clinical criteria and family history

**Table S9**: Growth parameters depending on germline mutation

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Growth parameters  Overall n=96 | | Volume doubling time (months) | Growth rate mm/year | Initital tumour diameter (mm) | Final tumour diamter (mm) | Initial tumour volume (mm3) | Final tumour volume (mm3) |
| Splice  n=12 tumours | Mean | 18,2 | 5,2 | 21,0 | 40,6 | 12492,4 | 55109,4 |
| Median | 16,7 | 4,6 | 14,9 | 40,5 | 1735,8 | 35410,3 |
| SD | 11,2 | 3,5 | 14,7 | 18,1 | 19251,2 | 60645,1 |
| Missense  n=30 tumours | Mean | 23,51 | 4,96 | 17,20 | 37,56 | 5084,11 | 42841,24 |
| Medain | 21,55 | 3,83 | 14,20 | 37,05 | 1500,11 | 26636,64 |
| SD | 19,86 | 4,41 | 8,86 | 16,09 | 8448,68 | 43916,29 |
| Large deletion  n=27 tumours | Mean | 27,0 | 3,8 | 20,5 | 37,8 | 7776,6 | 39189,3 |
| Median | 25,2 | 4,0 | 18,0 | 39,0 | 3053,6 | 31059,3 |
| SD | 17,3 | 2,1 | 9,7 | 14,0 | 9869,0 | 32120,4 |
| Small deletion  n= 8 tumours | Mean | 34,3 | 3,9 | 20,0 | 40,1 | 7283,3 | 42759,4 |
| Median | 25,3 | 3,3 | 19,5 | 39,6 | 3890,1 | 32935,5 |
| SD | 28,7 | 2,8 | 9,9 | 12,7 | 10997,8 | 37646,8 |
| Nonsense  n=14 tumours | Mean | 33,1 | 2,5 | 19,8 | 33,6 | 7478,8 | 26586,1 |
| Median | 26,3 | 2,5 | 16,5 | 29,3 | 2358,6 | 13450,6 |
| SD | 27,2 | 1,1 | 10,0 | 11,3 | 11062,3 | 25174,6 |
| Small insertion  n= 3 tumours | Mean | 17,1 | 6,0 | 20,7 | 37,5 | 4986,1 | 32266,4 |
| Median | 19,2 | 4,0 | 22,0 | 32,0 | 5575,3 | 17221,7 |
| SD | 8,9 | 4,5 | 4,2 | 10,6 | 2597,4 | 27740,3 |
| Unknown mutation\*\* | | 13,1 | 4,9 | 14,5 | 34 | 1596,26 | 20579,53 |
| Unknown mutation\*\* | | 7,9 | 2,8 | 3,8 | 15,3 | 28,73 | 1875,3 |

\*\* VHL-diagnosis based on clinical criteria and family history