

### File S3. Wildtype and mutant *ATP1B2* exon 2 splicing patterns and predicted protein isoforms

Genetic variant: Chr5:32,551,064\_32,551,065ins227 (CanFam 3.1 assembly)  
*ATP1B2*:c.130\_131ins227 (XM\_546597.5)  
*ATP1B2*:c.130\_131insLT796559.1:g.50\_276 (XM\_546597.5)

#### (A) Exon 2 splicing patterns

CanFam 3.1, chromosome 5 genomic sequence (NC\_006587.3).

Wildtype *ATP1B2* exon 2, 129 nucleotides in black CAPITAL LETTERS (129 nt)

SINE-insertion in blue CAPITAL LETTERS

Bases retained in the transcript are highlighted in grey

#### Wildtype (without SINE insertion)

32,551,001	atcacagggg acctggaacc cctgactcc atttcctcct ccctagCCTT CATCCTCCTC	32,551,060
32,551,061	TTCTACCTCG TCTTCTATGG CTCCTCACG GCTATGTTCA CCCTCACCAT GTGGGTCATG	32,551,120
32,551,121	CTGCAGACCG TGTCTGACCA TACCCCAAG TATCAGGACC GGCTGGCCAC ACCGGgtgag	32,551,180

#### mut #1

32,551,001	atcacagggg acctggaacc cctgactcc atttcctcct ccctagCCTT CATCCTCCTC	32,551,060
32,551,061	TTCT	32,551,064
32,551,064.1	TTTTTTTTTT TTTTTTTTTT TTTTTTTTTT TTTTAAAGAT TTTATTATT TATTCATGAT	32,551,064.60
32,551,064.61	AGTCACAGAG AGAGAGAGAG GCAGAGACAC AGGCAGAGGG AGAAGCAGGC TCCACGCACT	32,551,064.120
32,551,064.121	GGGAGCCCGA TGTGGGATTC GATCCCGGT CTCCAGGATC GCGCCCTGGG CCAAAGGCAG	32,551,064.180
32,551,064.181	GCGCCAAACC GCTGCACCAC CCAGGGATCC CCTCATCCTC CTCTTCT	32,551,064.227
32,551,065	ACCTCG TCTTCTATGG CTCCTCACG GCTATGTTCA CCCTCACCAT GTGGGTCATG	32,551,120
32,551,121	CTGCAGACCG TGTCTGACCA TACCCCAAG TATCAGGACC GGCTGGCCAC ACCGGgtgag	32,551,180

#### mut #2

32,551,001	atcacagggg acctggaacc cctgactcc atttcctcct ccctagCCTT CATCCTCCTC	32,551,060
32,551,061	TTCT	32,551,064
32,551,064.1	TTTTTTTTTT TTTTTTTTTT TTTTTTTTTT TTTTAAAGAT TTTATTATT TATTCATGAT	32,551,064.60
32,551,064.61	AGTCACAGAG AGAGAGAGAG GCAGAGACAC AGGCAGAGGG AGAAGCAGGC TCCACGCACT	32,551,064.120
32,551,064.121	GGGAGCCCGA TGTGGGATTC GATCCCGGT CTCCAGGATC GCGCCCTGGG CCAAAGGCAG	32,551,064.180
32,551,064.181	GCGCCAAACC GCTGCACCAC CCAGGGATCC CCTCATCCTC CTCTTCT	32,551,064.227
32,551,065	ACCTCG TCTTCTATGG CTCCTCACG GCTATGTTCA CCCTCACCAT GTGGGTCATG	32,551,120
32,551,121	CTGCAGACCG TGTCTGACCA TACCCCAAG TATCAGGACC GGCTGGCCAC ACCGGgtgag	32,551,180

#### mut #3

(Exon 2 skipped entirely)

32,551,001	atcacagggg acctggaacc cctgactcc atttcctcct ccctagCCTT CATCCTCCTC	32,551,060
32,551,061	TTCT	32,551,064
32,551,064.1	TTTTTTTTTT TTTTTTTTTT TTTTTTTTTT TTTTAAAGAT TTTATTATT TATTCATGAT	32,551,064.60
32,551,064.61	AGTCACAGAG AGAGAGAGAG GCAGAGACAC AGGCAGAGGG AGAAGCAGGC TCCACGCACT	32,551,064.120
32,551,064.121	GGGAGCCCGA TGTGGGATTC GATCCCGGT CTCCAGGATC GCGCCCTGGG CCAAAGGCAG	32,551,064.180
32,551,064.181	GCGCCAAACC GCTGCACCAC CCAGGGATCC CCTCATCCTC CTCTTCT	32,551,064.227
32,551,065	ACCTCG TCTTCTATGG CTCCTCACG GCTATGTTCA CCCTCACCAT GTGGGTCATG	32,551,120
32,551,121	CTGCAGACCG TGTCTGACCA TACCCCAAG TATCAGGACC GGCTGGCCAC ACCGGgtgag	32,551,180

## (B) Predicted translated protein sequences

For each sequence the translation of the entire coding sequence is given. The predicted transmembrane domain is highlighted in grey. In the wildtype ATP1B2 protein amino acids 1-39 are predicted to be cytoplasmic and amino acids 68-290 are predicted to constitute the extracellular domain (Uniprot accession P14415, human ATP1B2). The peptide sequence, which was used to generate the anti-ATP1B2 antibodies corresponds to amino acids 115-141 of the wildtype protein. This sequence is underlined in all the proteins shown below.

### Wildtype (translated from wildtype allele without SINE insertion); corresponds to XP\_546597.2)

(Amino acids 38 - 80 encoded by exon 2 are shown in green.)

```
1  MVIQKEKKSC  QVVVEEWKEF  VWNPRTHQFM  GRTGTSWAFI  LFFYLVFYGF  LTAMFTLTMW  60
61  VMLQTVSDHT  PKYQDRLATP  GLMIRPKTEN  LDVIVNVSDT  ESWDQHVQKL  NKFLEPYNDS  120
121  IQAQKNDVCR  PGRYYEQPDN  GVLNYPKRAC  QFNRTLQDGC  SGIGDPHYG  YSTGQPCVFI  180
181  KMNRVINFYA  GANQSMNVTC  VGKRDEDAEN  LGNFVMPFAN  GNIDLMYFPY  YGKRFHVNYT  240
241  QPLVAVKFLN  VTPNVEVNVE  CRINAANIAT  DDERDKFAGR  VAFKLRINKT  290
```

### mut #1

(Aberrant amino acids 38-96 encoded by the SINE insertion are shown in blue, amino acids 97 – 137, which correspond to regular residues encoded by the wildtype exon 2 are shown in green.)

```
1  MVIQKEKKSC  QVVVEEWKEF  VWNPRTHQFM  GRTGTSWDFI  YLFMIVTERE  RGRDTGRGRS  60
61  RLHALGARCG  IRSRVSRIAP  WAKGRRQTAA  PPRDPLILLF  YLVFYGFLTA  MFTLTMWVML  120
121  QTVSDHTPKY  QDRLATPGLM  IRPKTENLDV  IVNVSDTESW  DQHVQKLNKF  LEPYNSIQQA  180
181  QKNDVCRPGR  YEQPDNGVL  NYPKRACQFN  RTQLGDCSGI  GDPHYGYST  GQPCVFIKMN  240
241  RVINFYAGAN  QSMNVTGK  RDEDAENLGN  FVMFPANGNI  DLMYFPYGYK  RFHVNYTQPL  300
301  VAVKFLNVTP  NVEVNVECRI  NAANIATDDE  RDKFAGRVAF  KLRINKT  347
```

### mut #2

(Aberrant amino acids 38-88 encoded by the SINE insertion are shown in blue, amino acids 89 – 129, which correspond to regular residues encoded by the wildtype exon 2 are shown in green.)

```
1  MVIQKEKKSC  QVVVEEWKEF  VWNPRTHQFM  GRTGTSWVTE  RERGRDTGRG  RSRLHALGAR  60
61  CGIRSRVSRI  APWAKGRRQT  AAPPRDPLIL  LFFYLVFYGFL  TAMFTLTMWV  MLQTVSDHTP  120
121  KYQDRLATPG  LMIRPKTENL  DVIVNVSDTE  SWDQHVQKLN  KFLEPYNSI  QAQKNDVCRP  180
181  GRYEQPDNG  VLNYPKRACQ  FNRTLQDGC  GIGDPHYGY  STGQPCVFIK  MNRVINFYAG  240
241  ANQSMNVTCV  GKRDEDAENL  GNFVMPFANG  NIDLMYFPY  GKRFHVNYTQ  PLVAVKFLNV  300
301  TPNVEVNVEC  RINAANIATD  DERDKFAGR  VAFKLRINKT  339
```

### mut #3

(This predicted protein lacks amino acids 38-80 including the transmembrane domain of the wildtype sequence.)

```
1  MVIQKEKKSC  QVVVEEWKEF  VWNPRTHQFM  GRTGTSWGLM  IRPKTENLDV  IVNVSDTESW  60
61  DQHVQKLNKF  LEPYNSIQQA  QKNDVCRPGR  YEQPDNGVL  NYPKRACQFN  RTQLGDCSGI  120
121  GDPHYGYST  GQPCVFIKMN  RVINFYAGAN  QSMNVTGK  RDEDAENLGN  FVMFPANGNI  180
181  DLMYFPYGYK  RFHVNYTQPL  VAVKFLNVTP  NVEVNVECRI  NAANIATDDE  RDKFAGRVAF  240
241  KLRINKT  247
```