**Table S4: Summary of alternative splice variants impacting the amino terminal sequences.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Amino End** | |  |  |
| **Rhomboid Name (accession #) [total forms]** | **Species** | **Rhomboid Type** | **Effect of Splicing** |
| X5 PARL (XM\_017006803.1/XP\_005247643.1) [10 forms] | Human | PARL | Whole amino end is missing, leading to an alternate starting methionine |
|  |  |  |  |
| X2 RHBDF1 iRhom1 (XM\_017023556.1/XP\_016879045.1) [7 forms] | Human | iRhom (evolved from PARL) | Additional residues added after amino acid number 38 |
| X3 RHBDF1 iRhom1 (XM\_006720921.1/XP\_006720984.1) [7 forms] | Human | iRhom (evolved from PARL) | Additional residues added after amino acid number 38 |
| X4 RHBDF1 iRhom1 (XM\_017023557.1/XP\_016879046.1) [7 forms] | Human | iRhom (evolved from PARL) | Additional residues added after amino acid number 38 |
| X5 RHBDF1 iRhom1 (XM\_005255498.2/XP\_005255555.1) [7 forms] | Human | iRhom (evolved from PARL) | Amino terminus not present, leading to an alternate starting methionine |
| X6 RHBDF1 iRhom1 (XM\_017023558.1/XP\_016879047.1) [7 forms] | Human | iRhom (evolved from PARL) | Additional residues added after amino acid number 38 |
|  |  |  |  |
| Isoform2 RHBDF2 iRhom2 (NM\_001005498.3/XP\_001005498.2) [8 forms] | Human | iRhom (evolved from PARL) | 29 residues removed after amino acid number 49 |
| X1 RHBDF2 iRhom2 (XM\_011525250.2/XP\_011523552.1) [8 forms] | Human | iRhom (evolved from PARL) | 29 residues removed after amino acid number 49 |
| X2 RHBDF2 iRhom2 (XM\_011525251.2/XP\_011523553.1) [8 forms] | Human | iRhom (evolved from PARL) | 29 residues removed after amino acid number 49 |
| X3 RHBDF2 iRhom2 (XM\_005257670.1/XP\_005257727.1) [8 forms] | Human | iRhom (evolved from PARL) | 29 residues removed after amino acid number 49 |
| X4 RHBDF2 iRhom2 (XM\_017025079.1/XP\_016880568.1) [8 forms] | Human | iRhom (evolved from PARL) | 29 residues removed after amino acid number 49 |
| X5 RHBDF2 iRhom2 (XM\_005257669.3/XP\_005257726.1) [8 forms] | Human | iRhom (evolved from PARL) | 29 residues removed after amino acid number 49 |
| X6 RHBDF2 iRhom2 (XM\_011525249.2/XP\_011523551.1) [8 forms] | Human | iRhom (evolved from PARL) | 29 residues removed after amino acid number 49 |
|  |  |  |  |
| Isoform3 RHBDL1 (NM\_001318733.1/NP\_001305662.1) [5 forms] | Human | Secretase-type (6+1) | Alternate starting methionine that resulted in the introduction of 65 additional residues |
| X1 RHBDL1 (XM\_017023849.1/XP\_016879338.1) [5 forms] | Human | Secretase-type (6+1) | Alternate starting methionine that resulted in the introduction of 65 additional residues |
| X2 RHBDL1 (XM\_017023850.1/XP\_016879339.1) [5 forms] | Human | Secretase-type (6+1) | Alternate starting methionine that resulted in the introduction of 65 additional residues |
|  |  |  |  |
| Isoform 2 RHBDL2 (NM\_017821.4/NP\_060291.2 [2 forms] | Human | Secretase-type (6+1) | Alternate starting methionine that resulted in the removal of 80 residues |
|  |  |  |  |
| Isoform 2 RHBDL3 (NM\_001330181.1/NP\_001317110.1) [13 forms] | Human | Secretase-type (6+1) | Removal of 8 residues after amino acid number 37 |
| X2 RHBDL3 (XM\_017024275.1/XP\_016879764.1) [13 forms] | Human | Secretase-type (6+1) | Removal of 53 amino acids after the first 45 residues |
| X3 RHBDL3 (XM\_017024273.1/XP\_016879762.1) [13 forms] | Human | Secretase-type (6+1) | Removal of 8 residues after amino acid number 37 |
| X4 RHBDL3 (XM\_017024276.1/XP\_016879765.1) [13 forms] | Human | Secretase-type (6+1) | Removal of 61 amino acids after the first 37 residues |
| X6 RHBDL3 (XM\_011524443.2/XP\_011522745.1) [13 forms] | Human | Secretase-type (6+1) | Removal of 61 amino acids after the first 37 residues |
| X7 RHBDL3 (XM\_017024279.1/XP\_016879768.1) [13 forms] | Human | Secretase-type (6+1) | Alternate starting methionine that resulted in the removal of the first 98 residues |
| X8 RHBDL3 (XM\_006721734.3/XP\_006721797.1) [13 forms] | Human | Secretase-type (6+1) | Alternate starting methionine that resulted in the removal of first 42 residues |
| X9 RHBDL3 (XM\_017024274.1/XP\_016879763.1) [13 forms] | Human | Secretase-type (6+1) | Alternate starting methionine that resulted in the removal of first 42 residues |
| X10 RHBDL3 (XM\_017024278.1/XP\_016879767.1) [13 forms] | Human | Secretase-type (6+1) | Alternate starting methionine that resulted in the removal of first 98 residues |
| X11 RHBDL3 (XM\_017024277.1/XP\_016879766.1) [13 forms] | Human | Secretase-type (6+1) | Alternate starting methionine that resulted in the removal of first 98 residues |
| X12 RHBDL3 (XM\_017024280.1/XP\_016879769.1) [13 forms] | Human | Secretase-type (6+1) | Alternate starting methionine downstream resulting in the loss of the default amino end |
|  |  |  |  |
| Isoform b RHBDD2 (NM\_001040457.2/NP\_001035547.1) [6 Forms] | Human | distant relation | Alternate starting methionine that resulted in the removal of first 141 residues |
| Isoform b RHBDD2 (NM\_001346186.1/NP\_001333115.1) [6 Forms] | Human | distant relation | Alternate starting methionine that resulted in the removal of first 141 residues |
| Isoform b RHBDD2 (NM\_001346187.1/NP\_001333116.1) [6 Forms] | Human | distant relation | Alternate starting methionine that resulted in the removal of first 141 residues |
| Isoform c RHBDD2 (NM\_001346188.1/NP\_001333117.1) [6 Forms] | Human | distant relation | Removal of amino terminal sequence after the first 60 residues |
| Isoform c RHBDD2 (NM\_001346189.1/NP\_001333118.1) [6 Forms] | Human | distant relation | Removal of amino terminal sequence after the first 60 residues |
|  |  |  |  |
| X1 RHBDD3 (XM\_017028750.1/XP\_016884239.1) [5 forms] | Human | inactive distant relation | Alternate starting methionine that resulted in the removal of the first 143 residues |
| X2 RHBDD3 (XM\_006724224.3/XP\_006724287.1) [5 forms] | Human | inactive distant relation | Changes and removal of amino acids after the first 49 residues |
| X3 RHBDD3 (XM\_017028749.1/XP\_016884238.1) [5 forms] | Human | inactive distant relation | Alternate starting methionine that resulted in a unique sequence |
|  |  |  |  |
| Isoform c DERL1 (NM\_001330601.1/NP\_001317530.1) [4 forms] | Human | Rhomboid pseudoprotease | Alternate starting methionine that resulted in the removal of the first 100 residues |
| X2 DERL1 (XM\_006716657.1/XP\_006716720.1) [4 forms] | Human | Rhomboid pseudoprotease | Alternate starting methionine that resulted in the removal of the first 100 residues |
|  |  |  |  |
| Isoform b DERL2 (NM\_001304777.1/NP\_001291706.1) [3 forms] | Human | Rhomboid pseudoprotease | Sequence changes after residue number 30 |
| Isoform c DERL2 (NM\_001304779.1/NP\_0012991708.1) [3 forms] | Human | Rhomboid pseudoprotease | Sequence changes after residue number 53 |
|  |  |  |  |
| X2 DERL3 (XM\_017029082.1/XP\_016884571.1) [10 forms] | Human | Rhomboid pseudoprotease | Alternate starting methionine that resulted in the removal of the first 74 residues |
| X3 DERL3 (XM\_017029080.1/XP\_016884569.1) [10 forms] | Human | Rhomboid pseudoprotease | Deletion of 20 residues between the first residues 30 and 50 |
| X4 DERL3 (XM\_017029079.1/XP\_016884568.1) [10 forms] | Human | Rhomboid pseudoprotease | Changes in 2 amino acids between residues 30 and 33 |
| X6 DERL3 (XM\_011530505.2/XP\_011528807.1) [10 forms] | Human | Rhomboid pseudoprotease | Changes in 2 amino acids between residues 30 and 33 |
|  |  |  |  |
| Isoform 2 UBAC2 (NM\_177967.3/NP\_808882.1) [7 forms] | Human | Rhomboid pseudoprotease | Alternate starting methionine that introduced a unique sequence before residue number 130 |
| X1 UBAC2 (XM\_011521082.2/XP\_011519384.1) [7 forms] | Human | Rhomboid pseudoprotease | Alternate starting methionine that introduced a unique sequence before residue number 130 |
| X2 UBAC2 (XM\_006719948.3/XP\_006720011.1) [7 forms] | Human | Rhomboid pseudoprotease | Alternate starting methionine that resulted in the removal of the first 113 residues |
| X3 UBAC2 (XM\_011521083.2/XP\_011519385.1) [7 forms] | Human | Rhomboid pseudoprotease | Alternate starting methionine that introduced a unique sequence before residue number 130 |
| X4 UBAC2 (XM\_011521084.2/XP\_011519386.1) [7 forms] | Human | Rhomboid pseudoprotease | Alternate starting methionine that resulted in the removal of the first 113 residues |
| X5 UBAC2 (XM\_017020553.1/XP\_016876042.1) [7 forms] | Human | Rhomboid pseudoprotease | Alternate starting methionine that resulted in the removal of the first 150 residues |
|  |  |  |  |
| X1 PARL (XM\_006522312.1/XP\_006522375.1) [2 forms] | Mouse | PARL | The first 164 residues are replaced by a unique 43 residue sequence |
|  |  |  |  |
| X1 Rhbdf1 iRhom1 (XM\_006514492.1/XP\_006514555.1) [13 forms] | Mouse | iRhom (evolved from PARL) | Alternate starting methionine resulted in an extension to the amino terminus by 13 residues and an insertion of 35 residues after amino acid number 82 |
| X2 Rhbdf1 iRhom1 (XM\_006514493.1/XP\_006514556.1) [13 forms] | Mouse | iRhom (evolved from PARL) | Alternate starting methionine resulted in an extension to the amino terminus by 13 residues and an insertion of 35 residues after amino acid number 82 |
| X3 Rhbdf1 iRhom1 (XM\_006514494.1/XP\_006514557.1) [13 forms] | Mouse | iRhom (evolved from PARL) | Insertion of 35 residues after amino acid number 82 |
| X4 Rhbdf1 iRhom1 (XM\_006514495.1/XP\_006514558.1) [13 forms] | Mouse | iRhom (evolved from PARL) | Insertion of 35 residues after amino acid number 82 |
| X5 Rhbdf1 iRhom1 (XM\_006514496.1/XP\_006514559.1) [13 forms] | Mouse | iRhom (evolved from PARL) | Insertion of 35 residues after amino acid number 82 |
| X6 Rhbdf1 iRhom1 (XM\_006514497.1/XP\_006514560.1) [13 forms] | Mouse | iRhom (evolved from PARL) | Alternate starting methionine resulted in an extension to the amino terminus by 13 residues and an insertion of 35 residues after amino acid number 82 |
| X7 Rhbdf1 iRhom1 (XM\_006514498.1/XP\_006514561.1) [13 forms] | Mouse | iRhom (evolved from PARL) | Alternate starting methionine that resulted in a 13 residue extension of the amino terminus |
| X9 Rhbdf1 iRhom1 (XM\_006514500.1/XP\_006514563.1) [13 forms] | Mouse | iRhom (evolved from PARL) | Alternate starting methionine that resulted in a 13 residue extension of the amino terminus |
| X10 Rhbdf1 iRhom1 (XM\_006514501.1/XP\_006514564.1) [13 forms] | Mouse | iRhom (evolved from PARL) | Alternate starting methionine that resulted in the removal of 213 residues |
| X11 Rhbdf1 iRhom1 (XM\_006514502.1/XP\_006514565.1) [13 forms] | Mouse | iRhom (evolved from PARL) | Alternate starting methionine that resulted in the removal of 213 residues |
| X12 Rhbdf1 iRhom1 (XM\_006514503.1/XP\_006514566.1) [13 forms] | Mouse | iRhom (evolved from PARL) | Alternate starting methionine that resulted in the removal of the amino end |
|  |  |  |  |
| X1 Rhbdl1 (XM\_006524021.1/XP\_006524084.1) [3 forms] | Mouse | Secretase-type (6+1) | Alternate starting methionine that resulted in a 102 residue extension to the amino terminus |
| X2 Rhbdl1 (XM\_006524022.1/XP\_006524085.1) [3 forms] | Mouse | Secretase-type (6+1) | Alternate starting methionine that resulted in a 102 residue extension to the amino terminus and a removal of 54 residues after amino acid number 13 |
|  |  |  |  |
| X2 Rhbdl2 (XM\_006503026.1/XP\_006503089.1) [3 forms] | Mouse | Secretase-type (6+1) | A frameshift resulted in the shortening of the amino end to 9 residues |
|  |  |  |  |
| X3 Rhbdl3 (XM\_006533328.1/XP\_006533391.1) [7 forms] | Mouse | Secretase-type (6+1) | Removal of 8 residues after amino acid number 36 |
| X5 Rhbdl3 (XM\_006533330.1/XP\_006533393.1) [7 forms] | Mouse | Secretase-type (6+1) | Removal of 8 residues after amino acid number 36 |
| X6 Rhbdl3 (XM\_006533331.1/XP\_006533394.1) [7 forms] | Mouse | Secretase-type (6+1) | Removal of 53 residues removed after amino acid number 45, plus another removal of a segment from within amino end |
|  |  |  |  |
| X1 Rhbdd2 (XM\_006504416.1/XP\_006504479.1) [3 forms] | Mouse | distant relation | Alternate starting methionine that resulted in the removal of the whole amino end |
| X2 Rhbdd2 (XM\_006504417.1/XP\_006504480.1) [3 forms] | Mouse | distant relation | Alternate starting methionine that resulted in the removal of the whole amino end |
|  |  |  |  |
| Isoform 2 Derl2 (NM\_001291146.1/NP\_001278075.1) [4 forms] | Mouse | Rhomboid pseudoprotease | Alternate starting methionine that resulted in the removal of the whole amino end |
| Isoform 3 Derl2 (NM\_001291147.1/NP\_001278076.1) [4 forms] | Mouse | Rhomboid pseudoprotease | Alternate starting methionine that resulted in the removal of the whole amino end |
|  |  |  |  |
| X1 Derl3 (XM\_006514079.1/XP\_006514142.1) [2 forms] | Mouse | Rhomboid pseudoprotease | Addition of 85 extra residues upstream of the amino terminus |
|  |  |  |  |
| X2 Ubac2 (XM\_006519493.1/XP\_006519556.1) [3 forms] | Mouse | Rhomboid pseudoprotease | Alternate starting methionine that resulted in the removal of the amino end |
|  |  |  |  |
| RBL14 At3g17611 (NM\_202600.1 / NP\_974329.1) [3 forms] | Arabidopsis | Secretase (basic) | Alternate starting methionine that resulted in the removal of the amino end |
| RBL14 At3g17611 (NM\_001084701.1 / NP\_001078170.1) [3 forms] | Arabidopsis | Secretase (basic) | Alternate starting methionine that resulted in the removal of the amino end |
|  |  |  |  |
| RBL4 At3g53780 (NM\_115238.2 / NP\_566989.1) [2 forms] | Arabidopsis | Secretase type (6+1) | Alternate starting methionine that resulted in the removal of the amino end |
|  |  |  |  |
| RBL15 At3g58460 (NM\_001203197.1/NP\_001190126.1) [2 forms] | Arabidopsis | Secretase (basic) | A frameshift resulted in the addition of 23 residues at the amino terminus that changed the first 8 residues |
|  |  |  |  |
| Isoform B stet (NM\_176272.2éNP\_788450.1) [2 forms] | Drosophila | Secretase (basic) | Alternate starting methionine that resulted in the removal of the amino end |
|  |  |  |  |
| IsoformB ROM-4 (NM\_001047549.2 / NP\_001041014.1) [3 forms] | C elegans | Secretase (basic) | Alternate starting methionine that resulted in the removal of the amino end |