**Table S7: Summary of alternative splice variants impacting the L5 cap region.**

|  |  |  |  |
| --- | --- | --- | --- |
| **L5 Cap & TMD5** | |  |  |
| **Rhomboid Name (accession #'s) [total forms]** | **Species** | **Rhomboid Type** | **Effect of Splicing** |
| Isoform 5 (NM\_001324438.1/NP\_001311367.1) [10 forms] | Human | PARL | L5 Cap is deleted due to early termination |
|  |  |  |  |
| X6 RHBDF1 iRhom1 (XM\_017023558.1/XP\_016879047.1) [7 forms] | Human | iRhom (evolved from PARL) | L5 Cap is deleted due to early termination |
|  |  |  |  |
| X1 RHBDL1 (XM\_017023849.1/XP\_016879338.1) [5 forms] | Human | Secretase-type (6+1) | A frameshift changes the carboxyl terminal sequence |
| X2 RHBDL1 (XM\_017023850.1/XP\_016879339.1) [5 forms] | Human | Secretase-type (6+1) | A frameshift resulted in early termination |
|  |  |  |  |
| X1 RHBDL3 (XM\_017024272.1/XP\_016879761.1) [14 forms] | Human | Secretase-type (6+1) | A frameshift changes the carboxyl terminal sequence |
| X2 RHBDL3 (XM\_017024275.1/XP\_016879764.1) [14 forms] | Human | Secretase-type (6+1) | A frameshift changes the carboxyl terminal sequence |
| X3 RHBDL3 (XM\_017024273.1/XP\_016879762.1) [14 forms] | Human | Secretase-type (6+1) | A frameshift changes the carboxyl terminal sequence |
| X4 RHBDL3 (XM\_017024276.1/XP\_016879765.1) [14 forms] | Human | Secretase-type (6+1) | A frameshift changes the carboxyl terminal sequence |
| X9 RHBDL3 (XM\_017024274.1/XP\_016879763.1) [14 forms] | Human | Secretase-type (6+1) | A frameshift changes the carboxyl terminal sequence |
| X10 RHBDL3 (XM\_017024278.1/XP\_016879767.1) [14 forms] | Human | Secretase-type (6+1) | A frameshift changes the carboxyl terminal sequence |
| X11 RHBDL3 (XM\_017024277.1/XP\_016879766.1) [14 forms] | Human | Secretase-type (6+1) | A frameshift changes the carboxyl terminal sequence |
| X12 RHBDL3 (XM\_017024280.1/XP\_016879769.1) [14 forms] | Human | Secretase-type (6+1) | A frameshift changes the carboxyl terminal sequence |
|  |  |  |  |
| Isoform c DERL2 (NM\_001304779.1/NP\_001291708.1) [3 forms] | Human | Rhomboid pseudoprotease | Early termination resulted in the deletion of the L5 cap |
|  |  |  |  |
| X3 DERL3 (XM\_017029080.1/XP\_016884569.1) [10 forms] | Human | Rhomboid pseudoprotease | A frameshift resulted in changes to the sequence |
| X4 DERL3 (XM\_017029079.1/XP\_016884568.1) [10 forms] | Human | Rhomboid pseudoprotease | A frameshift resulted in changes to the sequence |
| X5 DERL3 (XM\_017029078.1/XP\_016884567.1) [10 forms] | Human | Rhomboid pseudoprotease | A frameshift resulted in changes to the sequence |
| X7 DERL3 (XM\_017029081.1/XP\_016884570.1) [10 forms] | Human | Rhomboid pseudoprotease | A frameshift resulted in changes to the sequence |
|  |  |  |  |
| X1 Rhbdf1 iRhom1 (XM\_006514492.1/XP\_006514555.1) [13 forms] | Mouse | iRhom (evolved from PARL) | 12 residues deleted from TMD5 and 3 residues deleted from the L5 cap. TMD5 residues that remain are unique |
| X2 Rhbdf1 iRhom1 (XM\_006514493.1/XP\_006514556.1) [13 forms] | Mouse | iRhom (evolved from PARL) | 9 residues deleted from TMD5 and 3 residues deleted from the L5 cap |
| X3 Rhbdf1 iRhom1 (XM\_006514494.1/XP\_006514557.1) [13 forms] | Mouse | iRhom (evolved from PARL) | 12 residues deleted from TMD5 and 3 residues deleted from the L5 cap. TMD5 residues that remain are unique |
| X4 Rhbdf1 iRhom1 (XM\_006514495.1/XP\_006514558.1) [13 forms] | Mouse | iRhom (evolved from PARL) | 12 residues deleted from TMD5 and 3 residues deleted from the L5 cap. TMD5 residues that remain are unique |
| X5 Rhbdf1 iRhom1 (XM\_006514496.1/XP\_006514559.1) [13 forms] | Mouse | iRhom (evolved from PARL) | 12 residues deleted from TMD5 and 3 residues deleted from the L5 cap. TMD5 residues that remain are unique |
| X7 Rhbdf1 iRhom1 (XM\_006514498.1/XP\_006514561.1) [13 forms] | Mouse | iRhom (evolved from PARL) | 12 residues deleted from TMD5 and 3 residues deleted from the L5 cap. TMD5 residues that remain are unique |
| X8 Rhbdf1 iRhom1 (XM\_006514499.1/XP\_006514562.1) [13 forms] | Mouse | iRhom (evolved from PARL) | 12 residues deleted from TMD5 and 3 residues deleted from the L5 cap. TMD5 residues that remain are unique |
| X10 Rhbdf1 iRhom1 (XM\_006514501.1/XP\_006514564.1) [13 forms] | Mouse | iRhom (evolved from PARL) | 12 residues deleted from TMD5 and 3 residues deleted from the L5 cap. TMD5 residues that remain are unique |
| X12 Rhbdf1 iRhom1 (XM\_006514503.1/XP\_006514566.1) [13 forms] | Mouse | iRhom (evolved from PARL) | 12 residues deleted from TMD5 and 3 residues deleted from the L5 cap. TMD5 residues that remain are unique |
|  |  |  |  |
| X1 Rhbdf2 iRhom2 (XM\_006533108.1/XP\_006533171.1) [3 forms] | Mouse | iRhom (evolved from PARL) | A frameshift within TMD2 that resulted in changes to the downstream residues |
|  |  |  |  |
| X1 Rhbdl3 (XM\_006533326.1/XP\_006533389.1) [7 forms] | Mouse | Secretase-type (6+1) | A frameshift within TMD2 that resulted in changes to the downstream residues |
| X2 Rhbdl3 (XM\_006533327.1/XP\_006533390.1) [7 forms] | Mouse | Secretase-type (6+1) | A frameshift within TMD2 that resulted in changes to the downstream residues |
| X3 Rhbdl3 (XM\_006533328.1/XP\_006533391.1) [7 forms] | Mouse | Secretase-type (6+1) | A frameshift within TMD2 that resulted in changes to the downstream residues |
| X6 Rhbdl3 (XM\_006533331.1/XP\_006533394.1) [7 forms] | Mouse | Secretase-type (6+1) | A frameshift within TMD2 that resulted in changes to the downstream residues |
|  |  |  |  |
| RBL1 At2g29050 (NM\_001084504.1/NP\_001077973.1) [2 forms] | Arabidopsis | Secretase-type (6+1) | The Linker between TMD4 and the gate contained an additional 28 residues |
|  |  |  |  |
| RBL3 At5g07250 (NM\_001125710.1/NP\_001119182.1) [2 forms] | Arabidopsis | Secretase-type (6+1) | Gate (and catalytic TMD 6 with H) was spliced out |
|  |  |  |  |
| IsoformB ROM-4 (NM\_001047549.2 / NP\_001041014.1) [3 forms] | C elegans | Secretase (basic) | Alternate start methionine and a frameshift within the L1 loop resulted in unrelated residues and a restoration of the downstream sequence |