Supplementary Table 1. BLAST alignment for eIF2B subunits and their isoforms identified in UniProt

| The best BLAST PDB template | Max score | Total score | Query cover | E value      | Identity |
|-----------------------------|-----------|-------------|-------------|--------------|----------|
| heIF2B1-1                   | 3ECS.A    | 607         | 607         | 99%          | 98%      |
| heIF2B2-1                   | 5B04.C    | 237         | 289         | 89%          | 48%      |
| heIF2B3-1                   | 5B04.E    | 214         | 214         | 96%          | 32%      |
| heIF2B3-2                   | 5B04.E    | 198         | 198         | 97%          | 33%      |
| heIF2B3-3                   | 5B04.E    | 198         | 198         | 100%         | 33%      |
| heIF2B4-1                   | 5B04.G    | 303         | 303         | 65%          | 44%      |
| heIF2B4-2                   | 5B04.G    | 303         | 303         | 62%          | 44%      |
| heIF2B4-3                   | 5B04.G    | 303         | 303         | 65%          | 44%      |
| heIF2B5-1                   | 5B04.I    | 375         | 375         | 94%          | 33%      |

To evaluate the quality of the eIF2B structure 5B04 as a potential template for modelling of human eIF2B analog, we compared the sequences of human and yeast eIF2B, which were downloaded from the UniProt database (http://www.uniprot.org/). Isoform 1 was taken where multiple isoforms were available. The corresponding UniProt IDs of five *Homo sapiens* eIF2B subunits are Q14232-1, P49770-1, Q9NR50-1, Q9UI10-1, Q13144-1, and of *S. pombe* eIF2B subunits Q9USP0-1, Q9UT76-1, P56288-1, Q09924-1, P56287-1. The Basic Local Alignment Search Tool (BLAST) (https://blast.ncbi.nlm.nih.gov/) was used to align the sequences.
| Patient / family | Sex | DNA mutation 1 | Protein change 1 | Reference(s) mutation 1 | DNA mutation 2 | Protein change 2 | Reference(s) mutation 2 | Disease onset (group)¹ | Survival |
|-----------------|-----|---------------|-----------------|-------------------------|---------------|-----------------|------------------------|------------------------|----------|
| **EIF2B1**      |     |               |                 |                         |               |                 |                        |                        |          |
| vwm217 / F1     | m   | c.115+1G>A    | p.?             | a, c                    | c.622A>T      | p.Asn208Tyr     | b, d                   | 3 y (3)                | 11 y     |
| vwm506 / F2     | m   | c.253-23T>C   | p.Asp85Phefs*12 | c                       | c.911A>G      | p.Tyr304Cys     | d                      | 14 y (5)               | 28 y     |
| vwm796 / F3     | f   | c.483-24A>G   | p.?             |                         | c.721C>G      | p.Leu241Val     |                        | presymp. (5)           | 18 y     |
| vwm340 / F4     | m   | c.833C>G      | p.Pro278Arg     | d, e                    | homozygous    | homozygous      |                        | 5 y (4)                | 14 y     |
| vwm771 / F5     | f   | c.878C>T     | p.Pro293Leu     | homozygous              |             |                 |                        | 5 y (4)                | † 14 y   |
| **EIF2B2**      |     |               |                 |                         |               |                 |                        |                        |          |
| vwm919 / F6     | m   | c.512C>T     | p.Ser171Phe     | d, f                    | c.922G>A      | p.Val308Met     |                        | 7 y (4)                | 7 y      |
| vwm422 / F7     | f   | c.512C>T     | p.Ser171Phe     | d, f                    | c.947T>A      | p.Val316Asp     | d, g                   | 35 y (6)               | † 46 y   |
| vwm915 / F8     | f   | c.514C>T     | p.Arg172*       |                         | c.818A>G      | p.Lys273Arg     | d, g                   | † 37 y                 |          |
| vwm320 / F9     | f   | c.529_543del | p.Phe177_AlA181 | b, d                    | c.638A>G      | p.Glu213Gly     | d, g                   | 18 mo (2)              | 11 y     |
| vwm87 / F10     | f   | c.547C>T     | p.Arg183*       |                         | c.638A>G      | p.Glu213Gly     | d, g                   | 5 y (4)                | 25 y     |
| vwm235 / F11    | m   | c.548del     | p.Arg183Glnfs*9 | c, h                    | c.818A>G      | p.Lys273Arg     | d, g                   | 3 y (3)                | 5 y      |
| vwm308 / F12    | f   | c.551dup     | p.Arg185Glufs*18 | c                       | c.638A>G      | p.Glu213Gly     | d, g                   | 18 mo (2)              | 12 y     |
| vwm562 / F13    | f   | c.599G>T     | p.Gly200Val     | d, i                    | c.638A>G      | p.Glu213Gly     | d, g                   | 10 y                   |          |
| vwm539 / F14    | f   | c.599G>T     | p.Gly200Val     | d, i                    | c.638A>G      | p.Glu213Gly     | d, g                   | 18 mo (2)              | 17 y     |
| vwm659 / F15    | f   | c.599G>T     | p.Gly200Val     | d, i                    | c.638A>G      | p.Glu213Gly     | d, g                   | 18 mo (2)              | 11 y     |
| vwm353 / F16    | f   | c.599G>T     | p.Gly200Val     | d, i                    | c.638A>G      | p.Glu213Gly     | d, g                   | 2 y (3)                | 17 y     |
| vwm648 / F17    | f   | c.599G>T     | p.Gly200Val     | d, i                    | c.638A>G      | p.Glu213Gly     | d, g                   | 2 y (3)                | 11 y     |
| vwm298 / F18    | f   | c.599G>T     | p.Gly200Val     | d, i                    | c.638A>G      | p.Glu213Gly     | d, g                   | 34 y                   |          |
| vwm902 / F19    | f   | c.599G>T     | p.Gly200Val     | d, i                    | c.638A>G      | p.Glu213Gly     | d, g                   | 18 mo (2)              | 6 y      |
| vwm895 / F20    | f   | c.599G>T     | p.Gly200Val     | d, i                    | c.638A>G      | p.Glu213Gly     | d, g                   | 2 y (3)                | 9 y      |
| vwm961 / F21    | f   | c.599G>T     | p.Gly200Val     | d, i                    | c.638A>G      | p.Glu213Gly     | d, g                   | 2 y (3)                | 6 y      |
| vwm980 / F22    | f   | c.599G>T     | p.Gly200Val     | d, i                    | c.638A>G      | p.Glu213Gly     | d, g                   | 2 y (3)                | 17 y     |
| vwm1051 / F23   | f   | c.599G>T     | p.Gly200Val     | d, i                    | c.638A>G      | p.Glu213Gly     | d, g                   | 12 mo (2)              | 4 y      |
| vwm665 / F24    | m   | c.599G>T     | p.Gly200Val     | d, i                    | c.871C>T      | p.Pro291Ser     | d, i                   | 3 mo (1)               | † 6 mo   |
| vwm515 / F25    | f   | c.599G>T     | p.Gly200Val     | d, i                    | c.871C>T      | p.Pro291Ser     | d, i                   | 6 mo (1)               | † 2 y    |
| vwm1136 / F26   | f   | c.599G>T     | p.Gly200Val     | d, i                    | c.871C>T      | p.Pro291Ser     | d, i                   | 4 mo (1)               | † 3 mo   |
| vwm1135 / F26   | f   | c.599G>T     | p.Gly200Val     | d, i                    | c.871C>T      | p.Pro291Ser     | d, i                   | 3 mo (1)               | † 8 mo   |
| vwm295 / F26    | f   | c.599G>T     | p.Gly200Val     | d, i                    | c.871C>T      | p.Pro291Ser     | d, i                   | anten. (1)             | † 3 mo   |

¹ Disease onset groups: (1) antenatal, (2) puerperal, (3) neonatal, (4) infantile, (5) juvenile, (6) adult.
| Patient | Female/Male | cDNA Change | Protein Change | Age at Onset | Reference |
|---------|-------------|-------------|----------------|--------------|-----------|
| vwm726/F27 | m | c.599G>T | p.Gly200Val | d, i | c.880G>T | p.Val294Phe | d | 15 y (5) | 22 y |
| vwm848/F28 | f | c.607_612delinsTG | p.Met203Trps*2 | h, j | c.638A>G | p.Glu213Gly | d, g | 15 mo (2) | ↑ 7 y |
| vwm83/F29 | m | c.607_612delinsTG | p.Met203Trps*2 | h, j | c.986G>T | p.Gly329Val | d, g | 5 y (4) | 21 y |
| vwm376/F30 | m | c.638A>G | p.Glu213Gly | d, g | c.607_612delinsTG | p.Met203Trps*2 | h, j | 2 y (3) | 12 y |
| vwm281/F31 | m | c.638A>G | p.Glu213Gly | d, g | homozygous | homozygous | 5 y (4) | 22 y |
| vwm380/F32 | f | c.638A>G | p.Glu213Gly | d, g | homozygous | homozygous | 5 y (4) | 38 y |
| vwm591/F33 | f | c.638A>G | p.Glu213Gly | d, g | homozygous | homozygous | 3 y (3) | 14 y |
| vwm203/F34 | f | c.638A>G | p.Glu213Gly | d, g | homozygous | homozygous | 2 y (3) | 25 y |
| vwm63/F35 | f | c.638A>G | p.Glu213Gly | d, g | homozygous | homozygous | 4 y (4) | 31 y |
| vwm785/F36 | m | c.638A>G | p.Glu213Gly | d, g | homozygous | homozygous | 3 y (3) | 10 y |
| vwm764/F37 | m | c.638A>G | p.Glu213Gly | d, g | homozygous | homozygous | 6 y (4) | 13 y |
| vwm555/F38 | m | c.638A>G | p.Glu213Gly | d, g | homozygous | homozygous | 3 y (3) | 34 y |
| vwm1018/F39 | m | c.638A>G | p.Glu213Gly | d, g | homozygous | homozygous | 2 y (3) | 6 y |
| vwm371/F40 | f | c.638A>G | p.Glu213Gly | d, g | homozygous | homozygous | 4 y (4) | 29 y |
| vwm379/F40 | f | c.638A>G | p.Glu213Gly | d, g | homozygous | homozygous | 2 y (3) | 22 y |
| vwm391/F40 | f | c.638A>G | p.Glu213Gly | d, g | homozygous | homozygous | 6 y (4) | 20 y |
| vwm1133/F41 | m | c.638A>G | p.Glu213Gly | d, g | c.863T>C | p.Phe288Ser | 50 y (6) | 61 y |
| vwm1134/F41 | f | c.638A>G | p.Glu213Gly | d, g | c.863T>C | p.Phe288Ser | 42 y (6) | 56 y |
| vwm802/F42 | f | c.638A>G | p.Glu213Gly | d, g | c.947T>A | p.Val316Asp | d, g | 2 y (3) | 8 y |
| vwm206/F43 | f | c.638A>G | p.Glu213Gly | d, g | c.947T>A | p.Val316Asp | d, g | 4 y (4) | 6 y |
| vwm362/F44 | f | c.653C>T | p.Thr218Ile | d, e | homozygous | homozygous | 2 y (3) | 18 y |
| vwm939/F45 | f | c.653C>T | p.Thr218Ile | d, e | homozygous | homozygous | 18 mo (2) | 4 y |
| vwm861/F46 | m | c.817A>C | p.Lys273Gln | k | c.939_948del | p.Asp314Profs*23 | k | 10 mo (1) | ↑ 3 y |
| vwm1137/F47 | m | c.818A>T | p.Lys273Ile | homozygous | homozygous | 4 y (4) | ↑ 6 y |
| vwm867/F48 | m | c.871C>T | p.Pro291Ser | d, i | c.947T>A | p.Val316Asp | d, g | 8 mo (1) | ↑ 16 mo |
| vwm874/F49 | f | c.926A>G | p.His309Arg | homozygous | homozygous | 2 y (4) | 8 y |
| **EIF2B3** | | | | | | | | |
| vwm651/F50 | m | c.32G>T | p.Gly11Val | d, l | r.657_975del | p.Ser220Cysfs*56 | 9 mo (1) | ↑ 15 mo |
| vwm1128/F51 | m | c.40T>C | p.Ser14Pro | | | | | |
| vwm753/F52 | f | c.74A>G | p.Lys25Arg | | | | | |
| vwm1132/F53 | m | c.97A>G | p.Lys33Glu | m | homozygous | homozygous | anten. (1) | ↑ 8 mo |
| vwm1131/F53 | m | c.97A>G | p.Lys33Glu | m | homozygous | homozygous | anten. (1) | ↑ 7 mo |
| vwm691/F54 | f | c.140G>A | p.Gly47Glu | d, n | c.260C>T | p.Ala87Val | b, d | 3 y (3) | ↑ 12 y |
| vwm1076/F55 | f | c.179_187del | p.Gln60_Ala62del | | c.344A>G | p.His115Arg | 23 mo (2) | 2 y |
| VWM | F | Genotype | Mutation 1 | Mutation 2 | Mutation 3 | Status | Age at Onset | Reference |
|-----|---|----------|------------|------------|------------|--------|--------------|-----------|
| vwm47 / F56 | f | c.260C>T | p.Ala87Val | a, d | homozygous | homozygous | 17 y (5) | 29 y |
| vwm424 / F57 | f | c.260C>T | p.Ala87Val | a, d | homozygous | homozygous | 22 y (6) | 25 y |
| vwm964 / F58 | m | c.260C>T | p.Ala87Val | a, d | homozygous | homozygous | 2 y (3) | 4 y |
| vwm1129 / F59 | f | c.260C>T | p.Ala87Val | a, d, c.27G>A | p.Arg91His | d | 2 y (3) | 3 y |
| vwm810 / F60 | f | c.260C>T | p.Ala87Val | a, d | c.34A>C | p.His115Pro | 39 y (6) | 44 y |
| vwm1062 / F61 | f | c.260C>T | p.Ala87Val | a, d, c.455-1G>T | p.? | o | 3 y (3) | |
| vwm545 / F62 | m | c.272G>A | p.Arg91His | d, c.1004C>T | p.Pro335Leu | d | presymp. (4) | 9 y |
| vwm756 / F63 | m | c.319G>A | p.Asp107Asn | c.521C>A | p.Ala174Glu | 3 y (3) | 5 y |
| vwm601 / F64 | f | c.602A>G | p.Asp201Gly | d, homozygous | homozygous | | 14 mo (2) | 16 y |
| vwm1127 / F65 | m | c.602A>G | p.Asp201Gly | d, homozygous | homozygous | | 12 mo (2) | 14 mo |
| vwm625 / F65 | m | c.602A>G | p.Asp201Gly | d, homozygous | homozygous | | 12 mo (2) | 14 mo |
| vwm740 / F66 | f | c.674G>A | p.Arg225Gln | | homozygous | homozygous | 6 y (4) | 16 y |
| vwm911 / F67 | m | c.674G>A | p.Arg225Gln | a, d | homozygous | homozygous | 3 mo (1) | 10 mo |
| EIF2B4 | | | | | | | | |
| vwm688 / F71 | f | c.134A>G | p.Gln45Arg | homozygous | homozygous | | 4 y (4) | 12 y |
| vwm717 / F72 | f | c.499-1G>C | p.? | c, c.626G>A | p.Arg209Gln | c | 7 y (4) | 15 y |
| vwm748 / F72 | f | c.499-1G>C | p.? | c, c.626G>A | p.Arg209Gln | c | 6 y (4) | 8 y |
| vwm244 / F73 | f | c.683C>T | p.Ala228Val | b, d | c.1191+1G>A | p.? | a, c | 3 y (3) | 16 y |
| vwm662 / F74 | m | c.728C>T | p.Pro243Leu | d, p | c.1120C>T | p.Arg374Cys | a, d | 22 mo (2) | 23 y |
| vwm994 / F75 | f | c.728C>T | p.Pro243Leu | d, p | c.1339G>A | p.Val447Met | 13 mo (2) | 22 mo |
| vwm390 / F76 | m | c.883_885del | p.Glu295del | c, j | homozygous | homozygous | 2 y (3) | 6 y |
| vwm1126 / F77 | f | c.977_979del | p.Lys326del | c, j | homozygous | homozygous | 2 mo (1) | 9 mo |
| vwm927 / F78 | f | c.978G>C | p.Lys326Asn | homozygous | homozygous | | anten. (1) | 3 mo |
| vwm898 / F79 | m | c.1069C>T | p.Arg357Trp | d, p | homozygous | homozygous | 9 mo (1) | 3 y |
| vwm239 / F80 | m | c.1070G>A | p.Arg357Gln | a, d | c.1120C>T | p.Arg374Cys | a, d | 7 y (4) | 41 y |
| vwm709 / F81 | f | c.1090C>T | p.Arg364Trp | c.1120C>T | p.Arg374Cys | a, d | 18 mo (2) | 2 y |
| vwm312 / F82 | f | c.1120C>T | p.Arg374Cys | a, d | homozygous | homozygous | 4 y (4) | 10 y |
| vwm474 / F83 | m | c.1121G>T | p.Arg374Leu | d, c.1372+1dup | p.? | c, j | 2 mo (1) | 6 mo |
| vwm296 / F84 | f | c.1127G>A | p.Arg391Asp | d, i | homozygous | homozygous | anten. (1) | 10 mo |
| vwm930 / F85 | m | c.1352C>G | p.Ala451Gly | homozygous | homozygous | | 23 mo (2) | 4 y |
| vwm931 / F86 | m | c.1352C>G | p.Ala451Gly | homozygous | homozygous | | 22 mo (2) | 4 y |
| Sample | Mutation | State | Description | Age 1 | Age 2 |
|--------|----------|-------|-------------|-------|-------|
| vwm723 / F86 | c.1400G>T | p.Arg467Leu | homozygous | homozygous | 19 y (6) 32 y |
| vwm1125 / F87 | c.1447C>T | p.Arg483Trp | d, i | homozygous | homozygous | anten. (1) |
| vwm288 / F87 | c.1447C>T | p.Arg483Trp | d, i | homozygous | homozygous | anten. (1) |
| vwm458 / F88 | c.1465T>C | p.Tyr489His | d, q | homozygous | homozygous | 19 mo (2) 8 y |
| vwm459 / F88 | c.1465T>C | p.Tyr489His | d, q | homozygous | homozygous | 3 y (3) 9 y |
| **EIF2B5** | | | | | |
| vwm744 / F89 | c.5C>T | p.Ala2Val | d | homozygous | homozygous | 2 y (3) 10 y |
| vwm484 / F90 | c.5C>T | p.Ala2Val | d | homozygous | homozygous | 2 y (3) 7 y |
| vwm658 / F91 | c.5C>T | p.Ala2Val | d | homozygous | homozygous | 6.31A>G | p.Arg211Gly | d | 4 y (4) 12 y |
| vwm877 / F92 | c.116_130del | p.Pro39_Leu43de | homozygous | homozygous | 7 mo (1) 19 mo |
| vwm803 / F93 | c.161G>C | p.Arg54Pro | p | c.943C>T | p.Arg315Cys | d, p | 5 y (4) 29 y |
| vwm804 / F93 | c.161G>C | p.Arg54Pro | p | c.943C>T | p.Arg315Cys | d, p | 4 y (4) 27 y |
| vwm394 / F94 | c.167T>C | p.Phe56Ser | d, e | c.1360C>T | p.Pro454Ser | d, e | 5 y (4) 17 y |
| vwm1122 / F95 | c.200_206del | p.Leu67Profs*7 | c.338G>A | p.Arg113His | d, g | 22 mo (2) 3 y |
| vwm487 / F96 | c.203T>C | p.Leu68Ser | d, q | c.685-13C>G | p.Ser229_Gln255del | j | 2 y (3) |
| vwm259 / F97 | c.217G>A | p.Val73Met | d, e | homozygous | homozygous | 17 mo (2) 21 mo |
| vwm212 / F98 | c.218T>G | p.Val73Gly | b, d | c.338G>A | p.Arg113His | d, g | 7 y (4) 18 y |
| vwm213 / F98 | c.218T>G | p.Val73Gly | b, d | c.338G>A | p.Arg113His | d, g | 8 y (5) 14 y |
| vwm829 / F99 | c.230A>G | p.Asp77Gly | b, d | c.407G>A | p.Arg136His | d | 13 mo (2) |
| vwm278 / F100 | c.236C>T | p.Thr79Ile | d, e | c.338G>A | p.Arg113His | d, g | 2 y (3) |
| vwm1103 / F101 | c.241G>A | p.Glu81Lys | d, f | c.250delA | p.Thr84Leufs*24 | 2 mo (1) 7 mo |
| vwm311 / F102 | c.241G>A | p.Glu81Lys | d, f | c.338G>A | p.Arg113His | d, g | 2 y (2) |
| vwm1108 / F102 | c.241G>A | p.Glu81Lys | d, f | c.338G>A | p.Arg113His | d, g | 3 y (3) 20 y |
| vwm782 / F103 | c.247del | p.Leu83* | c.475A>G | p.Ile159Val | 18 mo (2) 9 y |
| vwm811 / F103 | c.247del | p.Leu83* | c.475A>G | p.Ile159Val | 6 y |
| vwm519 / F104 | c.251C>T | p.Thr84Ile ho | d | c.274T>A ho | p.Phe92Ile ho | d | 4 y (4) 16 y |
| vwm99 / F105 | c.271A>G | p.Thr91Ala | d, g | homozygous | homozygous | 16 y (5) |
| vwm227 / F106 | c.271A>G | p.Thr91Ala | d, g | homozygous | homozygous | 10 y (5) |
| vwm90 / F107 | c.271A>G | p.Thr91Ala | d, g | homozygous | homozygous | 3 y (3) 24 y |
| vwm645 / F108 | c.271A>G | p.Thr91Ala | d, g | homozygous | homozygous | 3 y (3) |
| vwm32 / F109 | c.271A>G | p.Thr91Ala | d, g | homozygous | homozygous | 7 y (4) 40 y |
| vwm33 / F109 | c.271A>G | p.Thr91Ala | d, g | homozygous | homozygous | 8 y (5) 39 y |
| vwm3 / F110 | c.271A>G | p.Thr91Ala | d, g | homozygous | homozygous | 5 y (4) |
| vwm4 / F110 | c.271A>G | p.Thr91Ala | d, g | homozygous | homozygous | 4 y (4) 36 y |
| Family | Sample | Mutation | Phenotype | Age | Reference |
|--------|--------|----------|-----------|-----|-----------|
| vwm1117 / F111 | m | c.271A>G | p.Thr91Ala | d, g | c.338G>A | p.Arg113His | d, g | 35 y (6) | 47 y |
| vwm1015 / F112 | f | c.271A>G | p.Thr91Ala | d, g | c.338G>A | p.Arg113His | d, g | 9 y (5) | 18 y |
| vwm1120 / F113 | f | c.271A>G | p.Thr91Ala | d, g | c.338G>A | p.Arg113His | d, g | 19 y (6) | 25 y |
| vwm1110 / F114 | m | c.271A>G | p.Thr91Ala | d, g | c.805C>G | p.Arg269Gly | d, q | 2 y (3) | † 5 y |
| vwm321 / F115 | f | c.271A>G | p.Thr91Ala | d, g | c.1015C>T | p.Arg339Trp | d, g | 22 mo (2) | † 4 y |
| vwm36 / F116 | m | c.271A>G | p.Thr91Ala | d, g | c.1015C>T | p.Arg339Trp | d, g | 21 mo (2) | † 10 y |
| vwm37 / F116 | m | c.271A>G | p.Thr91Ala | d, g | c.1015C>T | p.Arg339Trp | d, g | 2 y (3) | † 14 y |
| vwm98 / F117 | f | c.271A>G | p.Thr91Ala | d, g | c.1015C>T | p.Arg339Trp | d, g | 2 y (3) | † 5 y |
| vwm1115 / F117 | f | c.271A>G | p.Thr91Ala | d, g | c.1015C>T | p.Arg339Trp | d, g | 2 y (3) | † 6 y |
| vwm674 / F118 | m | c.271A>G | p.Thr91Ala | d, g | c.1016G>A | p.Arg339Gln | d, g | 18 mo (2) | 10 y |
| vwm201 / F119 | m | c.271A>G | p.Thr91Ala | d, g | c.1016G>C | p.Arg339Pro | x | 14 mo (2) | † 2 y |
| vwm343 / F120 | m | c.271A>G | p.Thr91Ala | d, g | c.1208C>T | p.Ala403Val | d, e | 14 mo (2) | † 12 y |
| vwm251 / F121 | f | c.271A>G | p.Thr91Ala | d, g | c.1208C>T | p.Ala403Val | d, e | 18 mo (2) | † 3 y |
| vwm576 / F122 | f | c.271A>G | p.Thr91Ala | d, g | c.1309G>A | p.Val437Met | d | 20 mo (2) | † 5 y |
| vwm492 / F123 | f | c.271A>G | p.Thr91Ala | d, g | c.1745+5G>A | p.Tyr583* | d | 33 y (6) | 57 y |
| vwm80 / F124 | m | c.271A>G | p.Thr91Ala | d, g | c.1882T>C | p.Trp628Arg | d, g | 20 mo (2) | † 12 y |
| vwm584 / F125 | m | c.314A>G | p.His105Arg | d | c.338G>A | p.Arg113His | d, g | 2 y (3) | † 12 y |
| vwm923 / F126 | m | c.318A>T | p.Leu106Phe | g | homozygous | homozygous | 12 mo (2) | 6 y |
| vwm1054 / F127 | f | c.318A>T | p.Leu106Phe | g | homozygous | homozygous | † 7 y |
| vwm272 / F128 | m | c.318A>T | p.Leu106Phe | g | homozygous | homozygous | 22 mo (2) | 4 y |
| vwm1116 / F129 | m | c.318A>T | p.Leu106Phe | g | homozygous | homozygous | 20 mo (2) | † 6 y |
| vwm668 / F129 | m | c.318A>T | p.Leu106Phe | g | homozygous | homozygous | 3 y (3) | 4 y |
| vwm799 / F130 | f | c.318A>T | p.Leu106Phe | g | homozygous | homozygous | 2 y (3) | † 16 y |
| vwm1118 / F130 | f | c.318A>T | p.Leu106Phe | g | homozygous | homozygous | 22 mo (2) | 7 y |
| vwm683 / F131 | f | c.318A>T | p.Leu106Phe | g | c.338G>A | p.Arg113His | d, g | 8 y (5) | 10 y |
| vwm699 / F132 | f | c.318A>T | p.Leu106Phe | g | c.406C>T | p.Arg136Cys | d, p | 2 y (3) | † 7 y |
| vwm220 / F133 | f | c.318A>T | p.Leu106Phe | g | c.944G>A | p.Arg315His | d, g | 2 y |
| vwm468 / F134 | m | c.318A>T | p.Leu106Phe | g | c.1946T>C | p.Ile649Thr | d, e | 3 y (3) | † 9 y |
| vwm373 / F135 | m | c.331T>C | p.Trp111Arg | d, e | c.1360C>T | p.Pro454Ser | d, e | 3 y (3) | 5 y |
| vwm586 / F136 | m | c.337C>T | p.Arg113Cys | d, p | c.338G>A | p.Arg113His | d, g | 18 y (8) | † 27 y |
| vwm1121 / F137 | f | c.337C>T | p.Arg113Cys | d, p | c.896G>A | p.Arg299His | d, g | 4 y (4) | † 9 y |
| vwm291 / F138 | f | c.338G>A | p.Arg113His | d, g | homozygous | homozygous | 25 y (6) | 55 y |
| vwm588 / F139 | f | c.338G>A | p.Arg113His | d, g | homozygous | homozygous | 2 y (3) | 41 y |
| Code     | Gender | c.338G>A | p.Arg113His | Allele | m | Age | Sex |
|----------|--------|----------|-------------|--------|---|-----|-----|
| vwm1107  | m      | c.338G>A  | p.Arg113His  | d, g   | homozygous | homozygous | 7 y (4) | 17 y |
| vwm317   | f      | c.338G>A  | p.Arg113His  | d, g   | homozygous | homozygous | 18 y (6) | 33 y |
| vwm596   | f      | c.338G>A  | p.Arg113His  | d, g   | homozygous | homozygous | 29 y (6) | 34 y |
| vwm643   | f      | c.338G>A  | p.Arg113His  | d, g   | homozygous | homozygous | 54 y (6) | 59 y |
| vwm616   | f      | c.338G>A  | p.Arg113His  | d, g   | homozygous | homozygous | 17 y (5) | 19 y |
| vwm434   | f      | c.338G>A  | p.Arg113His  | d, g   | homozygous | homozygous | 4 y (4)  | 9 y  |
| vwm634   | m      | c.338G>A  | p.Arg113His  | d, g   | homozygous | homozygous | 44 y (6) | 52 y |
| vwm1043  | f      | c.338G>A  | p.Arg113His  | d, g   | homozygous | homozygous | 43 y (6) | 46 y |
| vwm650   | m      | c.338G>A  | p.Arg113His  | d, g   | homozygous | homozygous | 24 y (6) | 43 y |
| vwm808   | f      | c.338G>A  | p.Arg113His  | d, g   | homozygous | homozygous | 8 y (5)  | 8 y  |
| vwm817   | m      | c.338G>A  | p.Arg113His  | d, g   | homozygous | homozygous | 14 y (5) | 31 y |
| vwm821   | m      | c.338G>A  | p.Arg113His  | d, g   | homozygous | homozygous | 37 y (6) | 62 y |
| vwm512   | f      | c.338G>A  | p.Arg113His  | d, g   | homozygous | homozygous | 10 y (5) | 38 y |
| vwm1021  | m      | c.338G>A  | p.Arg113His  | d, g   | homozygous | homozygous | 7 y (4)  | 31 y |
| vwm1080  | m      | c.338G>A  | p.Arg113His  | d, g   | homozygous | homozygous | 45 y (6) | 52 y |
| vwm753   | f      | c.338G>A  | p.Arg113His  | d, g   | homozygous | homozygous | 15 y (5) | 31 y |
| vwm418   | f      | c.338G>A  | p.Arg113His  | d, g   | homozygous | homozygous | 26 y (6) | 43 y |
| vwm604   | m      | c.338G>A  | p.Arg113His  | d, g   | homozygous | homozygous | 31 y (6) | 33 y |
| vwm44    | f      | c.338G>A  | p.Arg113His  | d, g   | homozygous | homozygous | 9 y (5)  | † 36 y |
| vwm266   | f      | c.338G>A  | p.Arg113His  | d, g   | homozygous | homozygous | 25 y (6) | † 30 y |
| vwm299   | m      | c.338G>A  | p.Arg113His  | d, g   | homozygous | homozygous | 3 y (3)  | 8 y  |
| vwm426   | m      | c.338G>A  | p.Arg113His  | d, g   | homozygous | homozygous | 20 y (6) | 30 y |
| vwm441   | f      | c.338G>A  | p.Arg113His  | d, g   | homozygous | homozygous | 18 mo (2) | 19 y |
| vwm480   | f      | c.338G>A  | p.Arg113His  | d, g   | homozygous | homozygous | 32 y (6) | 47 y |
| vwm570   | f      | c.338G>A  | p.Arg113His  | d, g   | homozygous | homozygous | 6 y (4)  | 15 y |
| vwm713   | f      | c.338G>A  | p.Arg113His  | d, g   | homozygous | homozygous | 16 y (5) | † 33 y |
| vwm823   | f      | c.338G>A  | p.Arg113His  | d, g   | homozygous | homozygous | 46 y (6) | 53 y |
| vwm840   | f      | c.338G>A  | p.Arg113His  | d, g   | homozygous | homozygous | 42 y (6) | 43 y |
| vwm916   | f      | c.338G>A  | p.Arg113His  | d, g   | homozygous | homozygous | 40 y (6) | † 60 y |
| vwm946   | f      | c.338G>A  | p.Arg113His  | d, g   | homozygous | homozygous | 13 y (5) | 47 y |
| vwm969   | f      | c.338G>A  | p.Arg113His  | d, g   | homozygous | homozygous | 11 y (5) | 14 y |
| vwm1055  | f      | c.338G>A  | p.Arg113His  | d, g   | homozygous | homozygous | 48 y (6) | 51 y |
| vwm697   | f      | c.338G>A  | p.Arg113His  | d, g   | homozygous | homozygous | 7 y (4)  | 22 y |
| vwm698   | m      | c.338G>A  | p.Arg113His  | d, g   | homozygous | homozygous | 6 y (4)  | 32 y |
| Accession | Name | Mutation | Genotype | Protein Change | Age 1 | Age 2 |
|-----------|------|----------|-----------|---------------|-------|-------|
| vwm793 / F173 | m | c.338G>A | d, g | p.Arg113His | 2 y (3) | 12 y |
| vwm749 / F174 | f | c.338G>A | p.Arg113His | c.407G>A | p.Arg136His | d, g | 2 y (3) | 13 y |
| vwm513 / F175 | f | c.338G>A | p.Arg113His | c.468C>G | p.Ile156Met | d, e | 2 y (3) | 32 y |
| vwm559 / F176 | m | c.338G>A | p.Arg113His | c.511A>G | p.Arg171Gly | d | 5 y (4) | 18 y |
| vwm245 / F177 | m | c.338G>A | p.Arg113His | c.592G>A | p.Glu198Lys | d, p | 39 y (6) | 49 y |
| vwm1066 / F178 | m | c.338G>A | p.Arg113His | c.685-13C>G | p.Ser229_Gln255del | j | 23 mo (2) | 3 y |
| vwm593 / F179 | m | c.338G>A | p.Arg113His | c.702G>A | p.Phe264Leufs*15 | d, g | 2 y (3) | 15 y |
| vwm274 / F180 | f | c.338G>A | p.Arg113His | c.713T>A | p.Val238Glu | 4 y (4) | 12 y |
| vwm350 / F183 | f | c.338G>A | p.Arg113His | c.793G>A | p.Ser265Tyr | 14 y (5) | 17 y |
| vwm635 / F190 | f | c.338G>A | p.Arg113His | c.806C>G | p.Arg299Glu | d, r | 9 y (5) | 46 y |
| vwm988 / F195 | f | c.338G>A | p.Arg113His | c.806G>C | p.Arg299Pro | 3 y (5) | 4 y |
| vwm526 / F192 | m | c.338G>A | p.Arg113His | c.896G>A | p.Arg299His | d, g | 5 y (4) | 35 y |
| vwm736 / F193 | m | c.338G>A | p.Arg113His | c.944G>A | p.Arg315His | d, g | 4 y (4) | 15 y |
| vwm737 / F194 | f | c.338G>A | p.Arg113His | c.944G>A | p.Arg315His | d, g | 3 y (3) | 12 y |
| vwm855 / F195 | f | c.338G>A | p.Arg113His | c.944G>A | p.Arg315His | d, g | 4 y (4) | 16 y |
| vwm1081 / F196 | m | c.338G>A | p.Arg113His | c.944G>A | p.Arg315His | d, g | 11 y (5) | 21 y |
| vwm769 / F197 | m | c.338G>A | p.Arg113His | c.947G>A | p.Arg316Gln | 2 y (3) | 6 y |
| vwm702 / F198 | m | c.338G>A | p.Arg113His | c.997del | p.Gln333Argfs*24 | c | 18 mo (2) | 9 y |
| vwm720 / F199 | m | c.338G>A | p.Arg113His | c.1015del | p.Arg339Trp | d, g | 2 y (3) | 10 y |
| vwm39 / F200 | f | c.338G>A | p.Arg113His | c.1015del | p.Arg339Trp | d, g | 3 y (3) | 7 y |
| vwm260 / F201 | f | c.338G>A | p.Arg113His | c.1015del | p.Arg339Trp | d, g | 2 y (3) | 25 y |
| vwm1106 / F202 | m | c.338G>A | p.Arg113His | c.1016del | p.Arg339Gln | d, g | 3 y (3) | 15 y |
| vwm471 / F203 | f | c.338G>A | p.Arg113His | c.1016del | p.Arg339Gln | d, g | 3 y (3) | 16 y |
| vwm607 / F204 | f | c.338G>A | p.Arg113His | c.1016del | p.Arg339Gln | d, g | 2 y (3) | 14 y |
| Sample ID / F | c.338G>A | p.Arg113His | d, g | c.1016G>A | p.Arg339Gln | d, g | 3 y (3) | 11 y |
|--------------|----------|--------------|-------|------------|------------|-------|-------|------|
| vwm1000 / F206 | c.338G>A | p.Arg113His | d, g | c.1016G>A | p.Arg339Gln | d, g | 3 y (3) | 7 y |
| vwm1112 / F207 | c.338G>A | p.Arg113His | d, g | c.1016G>A | p.Arg339Gln | d, g | 2 y (3) | † 3 y |
| vwm68 / F207 | c.338G>A | p.Arg113His | d, g | c.1016G>A | p.Arg339Gln | d, g | 18 mo (2) | † 8 y |
| vwm509 / F208 | c.338G>A | p.Arg113His | d, g | c.1022_1024del | p.Asn341del | c, j | 2 y (3) | 10 y |
| vwm620 / F209 | c.338G>A | p.Arg113His | d, g | c.1049T>C | p.Leu350Pro | d | 23 mo (2) | 4 y |
| vwm816 / F210 | c.338G>A | p.Arg113His | d, g | c.1051G>A | p.Gly351Ser | 15 y (5) | 47 y |
| vwm25 / F211 | c.338G>A | p.Arg113His | d, g | c.1157G>T | p.Gly386Val | d, g | 2 y (3) | † 7 y |
| vwm97 / F211 | c.338G>A | p.Arg113His | d, g | c.1157G>T | p.Gly386Val | d, g | 2 y (3) | † 3 y |
| vwm367 / F212 | c.338G>A | p.Arg113His | d, g | c.1208C>T | p.Ala403Val | d, e | 3 y (3) | † 10 y |
| vwm834 / F213 | c.338G>A | p.Arg113His | d, g | c.1208C>T | p.Ala403Val | d, e | 18 mo (2) | 7 y |
| vwm905 / F214 | c.338G>A | p.Arg113His | d, g | c.1208C>T | p.Ala403Val | d, e | 3 y (3) | 8 y |
| vwm19 / F215 | c.338G>A | p.Arg113His | d, g | c.1264C>T | p.Arg422* | d, g | 3 y (3) | † 16 y |
| vwm60 / F216 | c.338G>A | p.Arg113His | d, g | c.1289T>C | p.Val430Ala | d, g | 3 y (3) | † 20 y |
| vwm837 / F217 | c.338G>A | p.Arg113His | d, g | c.1289T>C | p.Val430Ala | d, g | 2 y (3) | 8 y |
| vwm1114 / F218 | c.338G>A | p.Arg113His | d, g | c.1295C>T | p.Thr432Ile | 2 y (3) | 5 y |
| vwm516 / F219 | c.338G>A | p.Arg113His | d, g | c.1360C>T | p.Pro454Ser | d, e | 36 y (6) | † 38 y |
| vwm498 / F220 | c.338G>A | p.Arg113His | d, g | c.1810C>T | p.Pro604Ser | d, e | 3 y (3) | 18 y |
| vwm255 / F221 | c.338G>A | p.Arg113His | d, g | c.1813del | p.Leu605Cysfs*21 | c, s | 2 y (3) | † 9 y |
| vwm956 / F222 | c.338G>A | p.Arg113His | d, g | c.1813del | p.Leu605Cysfs*21 | c, s | 2 y (3) | 5 y |
| vwm610 / F223 | c.338G>A | p.Arg113His | d, g | c.1824G>A | p.Met608Ile | d | 8 y (5) | 12 y |
| vwm344 / F224 | c.338G>A | p.Arg113His | d, g | c.1946T>C | p.Ile649Thr | d, e | 13 y (5) | 28 y |
| vwm1111 / F225 | c.338G>A | p.Arg113His | d, g | c.1948G>A | p.Glu650Lys | d, g | 2 y (3) | † 4 y |
| vwm9 / F225 | c.338G>A | p.Arg113His | d, g | c.1948G>A | p.Glu650Lys | d, g | 2 y (3) | † 11 y |
| vwm735 / F226 | c.338G>A | p.Arg113His | d, g | c.2051G>T | p.Trp684Ser | d | 23 mo (2) | 3 y |
| vwm438 / F227 | c.380T>C | p.Leu127Pro | d, e | c.1015C>T | p.Arg339Trp | d, g | 3 y (3) | 17 y |
| vwm1123 / F227 | c.380T>C | p.Leu127Pro | d, e | c.1015C>T | p.Arg339Trp | d, g | 5 y (4) | 17 y |
| vwm978 / F228 | c.395G>C | p.Gly132Ala | d | c.943C>T | p.Arg315Cys | d, p | 15 y (5) | † 29 y |
| vwm729 / F229 | c.406C>T | p.Arg136Cys | d, p | homozygous | homozygous | 23 mo (2) | 6 y |
| vwm822 / F230 | c.406C>T | p.Arg136Cys | d, p | homozygous | homozygous | 18 mo (2) | † 5 y |
| vwm481 / F231 | c.406C>T | p.Arg136Cys | d, p | homozygous | homozygous | 2 y (3) | 6 y |
| vwm776 / F232 | c.449T>G | p.Leu150Arg | t | c.1355A>G | p.His452Arg | t | 3 y (3) | 5 y |
| vwm1039 / F233 | c.457G>A | p.Gly153Arg | c.806G>A | p.Arg269Gln | d, u | 4 mo (1) | † 7 mo |
| vwm761 / F234 | c.562T>A | p.Ser188Thr | d | homozygous | homozygous | 3 y (3) | 9 y |
| VWM | F | Exon | Change | Protein | Affected | Age | Reference |
|-----|---|------|--------|---------|----------|-----|-----------|
| vwm959 / F234 | f | c.562T>A | p.Ser188Thr | d | homozygous | homozygous | 14 mo (2) | 7 y |
| vwm622 / F235 | f | c.578C>T | p.Pro193Leu | d, u | homozygous | homozygous | 33 y (6) | 37 y |
| vwm638 / F235 | f | c.578C>T | p.Pro193Leu | d, u | homozygous | homozygous | 25 y (6) | 38 y |
| vwm1003 / F236 | f | c.584G>A | p.Arg195His | d, v | homozygous | homozygous | 7 mo (1) | 10 mo |
| vwm812 / F237 | m | c.631A>G | p.Arg211Gly | d | c.1201C>T | p.Arg401* | 3 y (3) | 9 y |
| vwm809 / F238 | f | c.685-14A>G | p.Ser229_Gln255 | c.1543T>G | p.Trp515Gly | 20 y (6) | 29 y |
| vwm389 / F239 | m | c.806G>A | p.Arg269Gln | d, u | homozygous | homozygous | 16 mo (2) | 10 y |
| vwm1138 / F239 | m | c.806G>A | p.Arg269Gln | d, u | homozygous | homozygous | 18 mo (2) | 20 mo |
| vwm911 / F240 | m | c.806G>A | p.Arg269Gln | d, u | homozygous | homozygous | 16 mo (2) | 9 y |
| vwm1048 / F241 | f | c.806G>A | p.Arg269Gln | d, u | homozygous | homozygous | 18 mo (2) | 2 y |
| vwm970 / F242 | m | c.806G>A | p.Arg269Gln | d, u | homozygous | homozygous | 6 mo (1) | 15 mo |
| vwm1072 / F243 | m | c.860T>A | p.Ile287Asn | c.944G>A | p.Arg315His | d, g | 5 mo (1) | 10 mo |
| vwm1023 / F244 | f | c.896G>A | p.Arg299His | d, g, w | c.913A>T | p.Met305Leu | w | 19 y (6) | 26 y |
| vwm893 / F245 | m | c.913A>T | p.Met305Leu | c.1903T>C | p.Tyr635His | 7 y (4) | 13 y |
| vwm1109 / F246 | m | c.943C>G | p.Arg315Gly | d, g | homozygous | homozygous | 18 mo (2) | 4 y |
| vwm1119 / F247 | f | c.943C>G | p.Arg315Gly | d, g | homozygous | homozygous | 3 y (3) | 3 y |
| vwm18 / F248 | f | c.943C>G | p.Arg315Gly | d, g | homozygous | homozygous | 2 y (3) | 26 y |
| vwm300 / F249 | f | c.943C>G | p.Arg315Gly | d, g | homozygous | homozygous | 3 y (3) | 12 y |
| vwm451 / F249 | m | c.943C>G | p.Arg315Gly | d, g | homozygous | homozygous | 2 y (3) | 2 y |
| vwm613 / F250 | f | c.943C>T | p.Arg315Cys | d, p | c.1208C>T | p.Ala403Val | d, e | 11 mo (1) | 4 y |
| vwm951 / F251 | m | c.956A>G | p.Tyr319Cys | c.1546+1G>T | p.? | 5 mo (1) | 5 mo |
| vwm1073 / F252 | m | c.1015C>T | p.Arg339Trp | d, g | c.1208C>T | p.Ala403Val | d, e | 3 mo (1) | 9 mo |
| vwm489 / F253 | m | c.1015C>T | p.Arg339Trp | d, g | c.1360C>T | p.Pro454Ser | d, e | 8 y (5) | 10 y |
| vwm818 / F254 | m | c.1016G>C | p.Arg339Pro | x | homozygous | homozygous | 7 mo (1) | 2 y |
| vwm477 / F255 | f | c.1208C>T | p.Ala403Val | d, e | c.1360C>T | p.Pro454Ser | d, e | 3 y (3) | 9 y |
| vwm445 / F256 | m | c.1244A>G | p.Asp415Gly | d, e | c.1280C>T | p.Pro427Leu | d, p | 4 y (4) | 17 y |
| vwm1071 / F257 | f | c.1280C>T | p.Pro427Leu | d, p | homozygous | homozygous | 2 y (3) | 3 y |
| vwm881 / F258 | m | c.1280C>T | p.Pro427Leu | d, p | c.1841C>G | p.Ser614* | 8 mo (1) | 12 mo |
| vwm882 / F258 | f | c.1280C>T | p.Pro427Leu | d, p | c.1841C>G | p.Ser614* | 8 mo (1) | 16 mo |
| vwm285 / F259 | f | c.1289T>C | p.Val430Ala | d, g | c.1340C>T | p.Ser447Leu | d, i | 3 mo (1) | 7 mo |
| vwm393 / F260 | f | c.1459G>A | p.Glu487Lys | d, e | homozygous | homozygous | 42 y (6) | 51 y |
| vwm307 / F261 | m | c.1484A>G | p.Tyr495Cys | d, i | homozygous | homozygous | 7 mo (1) | 9 mo |
| vwm1113 / F261 | f | c.1484A>G | p.Tyr495Cys | d, i | homozygous | homozygous | 9 mo (1) | 9 mo |
The table is organized by ascending sequence of mutation 1 and, in case of heterozygosity, the sequence of mutation 2. Patients with similar genotypes are marked in the same colour (light or dark gray). Reference sequences of EIF2B1, EIF2B2, EIF2B3, EIF2B4 and EIF2B5 are NM_001414.3, NM_014239.3, NM_020365.3, NM_001034116.1, and NM_003907.2, respectively.

m, male; f, female; y, year; mo, months; presymp., presymptomatic; anten., antenally; †: patient deceased

1 (1) onset < 1 year, (2) onset 1 -< 2 years, (3) onset 2 - < 4 years, (4) onset 4 - <8 years, (5) onset 8 - < 18 years, (6) onset ≥ 18 years

2 This patient has 2 different homozygous mutations.

a. mutation at DNA and/or protein level amended from original publication on the basis of current HGVS guidelines and/or current transcripts (van der Knaap, M.S., et al., 2002).
b. published before in van der Knaap, M.S., et al., 2002.
c. mutation at DNA and/or protein level amended from original publication on the basis of current HGVS guidelines and/or current transcripts (van der Knaap, M.S., et al., 2010, available at http://ommbid.mhmedical.com).
d. published before in van der Knaap, M.S., et al., 2010, available at http://ommbid.mhmedical.com.
e. published before in Pronk, J.C., et al. 2006.
f. published before in Fogli, A., et al. 2003.
g. published before in Leegwater, P.A., et al., 2001.
h. mutation at DNA and/or protein level amended from original publication on the basis of current HGVS guidelines and/or current transcripts (Leegwater, P.A., et al., 2001).
i. published before in van der Knaap, M.S., et al., 2003.
j. mutation at DNA and/or protein level amended from original publication on the basis of current HGVS guidelines and/or current transcripts (Pronk, J.C., et al. 2006).
k. published before in Unal, O., et al., 2013.
l. published before in Maletkovic, J., et al., 2008.
m. published before in Song, H., et al., 2017.
n. published before Wu, Y., et al., 2009.
o. clinical case published before in Schiffmann, R., et al., 1994.
p. published before in Fogli, A., et al., 2004.
q. mutation at DNA and/or protein level amended from original publication on the basis of current HGVS guidelines and/or current transcripts (Foglii, A., et al., 2003).
r. published before in Ohlenbusch, A., et al., 2005.
s. published before in Wilson, C.J., et al., 2005.
t. published before Sharma, S., et al., 2011.u. published before in Federico, A., et al., 2006.
v. published before in Fogli, A., et al., 2002.
w. published before in Ibitoye, R.T., et al., 2016.
x. published before in Zhang, H., et al., 2015.
Supplementary Table 3. Classified missense mutations in the current cohort of VWM patients

| Mutation protein | Severity category | Location in 3D model | Functional domain |
|------------------|------------------|----------------------|-------------------|
| **EIF2B1**       |                  |                      |                   |
| c.833C>G         | p.Pro278Arg      | C                    | Other             |
| c.878C>T         | p.Pro293Leu      | C                    | Other             |
| **EIF2B2**       |                  |                      |                   |
| c.512C>T         | p.Ser171Phe      | D                    | Core*             |
| c.599G>T         | p.Gly200Val      | A                    | SI                |
| c.638A>G         | p.Glu213Gly      | C                    | SI                |
| c.653C>T         | p.Thr218Ile      | B                    | SI                |
| c.818A>T         | p.Lys273Ile      | C                    | Core*             |
| c.863T>C         | p.Phe288Ser      | D                    | SI                |
| c.871C>T         | p.Pro291Ser      | A                    | SI                |
| c.880G>T         | p.Val294Phe      | D                    | SI                |
| c.922G>A         | p.Val308Met      | A                    | SI                |
| c.926A>G         | p.His309Arg      | B                    | SI                |
| c.947T>A         | p.Val316Asp      | B                    | Core              |
| **EIF2B3**       |                  |                      |                   |
| c.74A>G          | p.Lys25Arg       | B                    | Core*             |
| c.97A>G          | p.Lys33Glu       | A                    | Core              |
| c.140G>A         | p.Gly47Glu       | A                    | SI                |
| c.260C>T         | p.Ala87Val       | D                    | Core              |
| c.272G>A         | p.Arg91His       | A                    | Core              |
| c.344A>C         | p.His115Pro      | D                    | SI                |
| c.402A>G         | p.Arg134Glu      | B                    | Core*             |
| c.441G>A         | p.Asp201Gly      | C                    | Core*             |
| c.526G>T         | p.Phe176Glu      | D                    | Exposed           |
| c.602A>G         | p.Ile229Met      | A                    | Core              |
| c.1004C>T        | p.Pro335Leu      | D                    | Exposed           |
| c.1124T>G        | p.Ile375Ser      | A                    | Core              |
| **EIF2B4**       |                  |                      |                   |
| c.134A>G         | p.Gln45Arg       | C                    | n.m.              |
| c.728C>T         | p.Pro243Leu      | A                    | Exposed           |
| c.978G>C         | p.Lys326Asn      | A                    | SI                |
| c.1069C>T        | p.Arg357Trp      | A                    | SI                |
| c.1070G>A        | p.Arg357Gln      | C                    | SI                |
| c.1090C>T        | p.Arg364Trp      | A                    | SI                |
| c.1120C>T        | p.Arg374Cys      | C                    | SI                |
| Allele | Change  | Amino Acid Change | Effect | Location |
|--------|---------|-------------------|--------|----------|
| c.1172C>A | p.Ala391Asp | A | SI | Other |
| c.1339G>A | p.Val447Met | C | SI | Other |
| c.1352C>G | p.Ala451Gly | B | SI | Other |
| c.1400G>T | p.Arg467Leu | D | SI | Other |
| c.1447C>T | p.Arg483Trp | A | SI | Other |
| c.1465T>C | p.Tyr489His | B | Core* | Other |
| c.5C>T | p.Ala2Val | B | n.m. | Other |
| c.161G>C | p.Arg54Pro | D | Exposed | NT domain |
| c.167T>C | p.Phe56Ser | B | Core | NT domain |
| c.217G>A | p.Val73Met | B | Core* | NT domain |
| c.218T>G | p.Val73Gly | D | Core* | NT domain |
| c.230A>G | p.Asp77Gly | B | Core | NT domain |
| c.236C>T | p.Thr79Ile | A | Core | NT domain |
| c.241G>A | p.Glu81Lys | A | SI | NT domain |
| c.271A>G | p.Thr91Ala | C | Core | NT domain |
| c.314A>G | p.His105Arg | A | Core* | NT domain |
| c.318A>T | p.Leu106Phe | B | Core | NT domain |
| c.331T>C | p.Trp111Arg | A | Core | NT domain |
| c.337C>T | p.Arg113Cys | D | SI | NT domain |
| c.338G>A | p.Arg113His | D | SI | NT domain |
| c.380T>C | p.Leu127Pro | D | Exposed | NT domain |
| c.395G>C | p.Gly132Ala | D | Core | NT domain |
| c.406C>T | p.Arg136Cys | B | Core | NT domain |
| c.407G>A | p.Arg136His | A | Core | NT domain |
| c.457G>A | p.Gly153Arg | A | Core | NT domain |
| c.468C>G | p.Ile156Met | A | Core | NT domain |
| c.511A>G | p.Arg171Gly | B | Core | Other |
| c.562T>A | p.Ser188Thr | B | SI | Other |
| c.584G>A | p.Arg195His | A | SI | Other |
| c.592G>A | p.Glu198Lys | D | Core* | Other |
| c.631A>G | p.Arg211Gly | C | Core | Other |
| c.713T>A | p.Val238Glu | B | SI | Other |
| c.758C>A | p.Ser253Tyr | C | Core | Other |
| c.805C>G | p.Arg269Gly | B | Core* | Other |
| c.806G>C | p.Arg269Pro | A | Core* | Other |
| c.806G>A | p.Arg269Gln | B | Core* | Other |
| c.860T>A | p.Ile287Asn | A | Core | Other |
| Position | Amino Acid Change | Severity | Location |
|----------|------------------|----------|----------|
| c.896G>A | p.Arg299His      | B        | Core*    |
| c.913A>T | p.Met305Leu      | D        | Other    |
| c.943C>T | p.Arg315Cys      | B        | SI       |
| c.943C>G | p.Arg315Gly      | B        | SI       |
| c.944G>A | p.Arg315His      | B        | SI       |
| c.947G>A | p.Arg316Gln      | A        | SI       |
| c.1015C>T| p.Arg339Trp      | A        | SI       |
| c.1016G>C| p.Arg339Pro      | A        | SI       |
| c.1016G>A| p.Arg339Gln      | A        | SI       |
| c.1049T>C| p.Leu350Pro      | A        | Core     |
| c.1051G>A| p.Gly351Ser      | D        | Core     |
| c.1157G>T| p.Gly386Val      | A        | Core     |
| c.1208C>T| p.Ala403Val      | A        | Core     |
| c.1244A>G| p.Asp415Gly      | D        | Core     |
| c.1280C>T| p.Pro427Leu      | B        | Core     |
| c.1289T>C| p.Val430Ala      | A        | Core     |
| c.1295C>T| p.Cys432Ile      | A        | Core     |
| c.1309G>A| p.Val437Met      | A        | Core     |
| c.1340T>C| p.Ser447Leu      | A        | Core     |
| c.1360C>T| p.Pro454Ser      | D        | Exposed  |
| c.1459G>A| p.Glu487Lys      | D        | n. m.    |
| c.1484A>G| p.Tyr495Cys      | A        | n. m.    |
| c.1810C>T| p.Pro604Ser      | A        | Core     |
| c.1824G>A| p.Met608Ile      | D        | Core     |
| c.1882T>C| p.Trp628Arg      | A        | Core     |
| c.1903T>C| p.Tyr635His      | A        | Core     |
| c.1946T>C| p.Ile649Thr      | C        | Core     |
| c.1948G>A| p.Glu650Lys      | A        | Core     |
| c.2051G>C| p.Trp684Ser      | A        | Core     |

1 Core: the affected amino acid is located within a subunit and faces inward. Core*: the amino acid is located within a subunit with an identified cavity around. SI: the amino acid is located at the interface of subunits. Exposed: the amino acid is exposed to a solvent without an interacting amino acid around on the current structure. NT domain: nucleotide-binding domain. CTD: catalytic domain. I-patch: motif containing isoleucine-rich hexamer repeats. N.m.: not modeled. Reference sequences of *EIF2B1*, *EIF2B2*, *EIF2B3*, *EIF2B4* and *EIF2B5* are NM_001414.3, NM_014239.3, NM_020365.3, NM_0010341161.1, and NM_003907.2, respectively.

In the three-dimensional structure of eIF2B complex, the carbon atoms of the residues containing variants are colored according to their disease severity categories: A in red, B in yellow, C in green, D in cyan.
**Supplementary Table 4. Overview of different variants in the same amino acid**

|   | Gene   | Mutation gene | Mutation protein | Disease severity category |
|---|--------|---------------|------------------|--------------------------|
| **Similar range of severity** |        |               |                  |                          |
| 1 | **EIF2B5** | c.337C>T     | p.Arg113Cys      | D                        |
|   | **EIF2B5** | c.338G>A     | p.Arg113His      | D                        |
| 2 | **EIF2B5** | c.406C>T     | p.Arg136Cys      | B                        |
|   | **EIF2B5** | c.407G>A     | p.Arg136His      | A                        |
| 3 | **EIF2B5** | c.805C>G     | p.Arg269Gly      | B                        |
|   | **EIF2B5** | c.806G>C     | p.Arg269Pro      | A                        |
|   | **EIF2B5** | c.806G>A     | p.Arg269Gln      | B                        |
| 4 | **EIF2B5** | c.943C>T     | p.Arg315Cys      | B                        |
|   | **EIF2B5** | c.943C>G     | p.Arg315Gly      | B                        |
|   | **EIF2B5** | c.944G>A     | p.Arg315His      | B                        |
| 5 | **EIF2B5** | c.1015C>T    | p.Arg339Trp      | A                        |
|   | **EIF2B5** | c.1016G>C    | p.Arg339Pro      | A                        |
|   | **EIF2B5** | c.1016G>A    | p.Arg339Gln      | A                        |
| **Dissimilar range of severity** |        |               |                  |                          |
| 1 | **EIF2B4** | c.1069C>T    | p.Arg357Trp      | A                        |
|   | **EIF2B4** | c.1070G>A    | p.Arg357Gln      | C                        |
| 2 | **EIF2B5** | c.217G>A     | p.Val73Met       | B                        |
|   | **EIF2B5** | c.218T>G     | p.Val73Gly       | D                        |

Reference sequences of **EIF2B1, EIF2B2, EIF2B3, EIF2B4 and EIF2B5** are NM_001414.3, NM_014239.3, NM_020365.3, NM_0010341161.1, and NM_003907.2, respectively.
Supplementary Table 5. Classified missense mutations in the current cohort of VWM patients

| Mutation gene | Mutation protein | Disease severity category | Location in 3D model | Functional domain | Biochemical effect | Proposed structural effects |
|---------------|------------------|---------------------------|----------------------|-------------------|-------------------|-----------------------------|
| **EIF2B1**    |                  |                           |                      |                   |                   |                             |
| c.833C>G      | p.Pro278Arg      | C                         | SI                   | Other             | No impact on complex stability or GDP release activity\(^1\) | Arg in a hydrophobic region, likely forming unfavourable contacts with nearby residues. Mutation occurs close to the elf2B\(\alpha\)/elf2B\(\delta\) interface, might affect intersubunit contacts. |
| c.878C>T      | p.Pro293Leu      | C                         | SI                   | Other             | Not assessed      | Substitution of Pro to hydrophobic Leu can allow favourable interactions with residues in the hydrophobic pocket. Pro293 is rigid and can influence secondary structure. Mutation to Leu might affect secondary structure since it lies on a short loop between a \(\beta\)-strand and an \(\alpha\)-helix. |
| **EIF2B2**    |                  |                           |                      |                   |                   |                             |
| c.512C>T      | p.Ser171Phe      | D                         | Core\(^*\)           | Other             | 10\% reduction in GDP release activity\(^2\) | Phe has a much larger and more hydrophobic side-chain than Ser. Altered folding might be required to accommodate the Phe side-chain. |
| c.599G>T      | p.Gly200Val      | A                         | SI                   | Other             | Loss of complex integrity\(^2\) | Gly200 is located in a hydrophobic region at the end of alpha helix of elf2B\(\beta\). Val might disrupt elf2B\(\beta\) fold and interaction with elf2B\(\delta\) which is close to this alpha helix. Val might interact more favorably with adjacent residues. Mutation might therefore affect subunit binding. |
| c.638A>G      | p.Glu213Gly      | C                         | SI                   | Other             | Small effect on complex stability\(^3, 4\) | No hydrogen bond interactions disrupted by this change. The substitution occurs very close to the elf2B\(\beta\)/elf2B\(\delta\) interface and ISRI\(\beta\) binding site; mutations may impact inter-subunit interactions. |
| c.653C>T      | p.Thr218Ile      | B                         | SI                   | Other             | Substitution to Ile abolishes H-bond network with adjacent residues. Might affect subunit binding due to close proximity to the elf2B\(\beta\)/elf2B\(\delta\) subunit. |
| c.818A>T      | p.Lys273Ile      | C                         | Core\(^*\)           | Other             | No effect on yeast complex stability | Substitution to hydrophobic Ile abolishes H-bond interactions with Thr236. Ile would be close to hydrophilic residues Ser31, Thr77 and Lys237 as well as hydrophobic residue Pro270, leading to unfavorable interactions. |
| c.863T>C | p.Phe288Ser | D | SI | Other | Phe288 is located in a loop of eIF2Bβ interacting with eIF2Bc. Ser is more hydrophilic and significantly smaller than Phe. Ser is located close to the eIF2Bc subunit, but not close enough to other side-chains to form any new H-bonds. |
| c.871C>T | p.Pro291Ser | A | SI | Other | Loss of complex integrity² | Pro291 is located in a loop of eIF2Bβ interacting with eIF2Bc and eIF2Bδ, it is surrounded by hydrophobic residues. Substitution to hydrophilic Ser can disrupt hydrophobic interactions. This mutation might affect subunit binding. |
| c.880G>T | p.Val294Phe | D | SI | Other | Val294 is located in a loop of eIF2Bβ facing eIF2Bδ. Relatively conservative substitution to hydrophobic Phe allows residue to maintain favorable interactions with adjacent residues in this hydrophobic pocket. However, Phe has a bulkier side-chain than Val and might therefore affect folding. Location on eIF2Bβ/eIF2Bδ interface so might affect moderately subunit binding. |
| c.922G>A | p.Val308Met | A | SI | Other | Val308 is located inside of eIF2Bβ, but that part of subunit is in a close proximity to eIF2Bc. Substitution to hydrophilic Asp in this hydrophobic region might disrupt folding and in turn affect binding to the eIF2Bc or eIF2Bδ subunits since it lies close to their interfaces. |
| c.926A>G | p.His309Arg | B | SI | Other | His309 is located in a loop of eIF2Bβ interacting with eIF2Bc and eIF2Bδ. It is interacting with side-chain of Ser307. Substitution to Arg might affect folding because it is a longer, bulkier group than His. Due to the nitrogens in side-chain, Arg might form an additional H-bond with Asn341 on eIF2Bc. Due to location at eIF2Bβ/eIF2Bδ interface might affect subunit binding. Multiple effects might lead to fairly severe phenotype. |
| c.947T>A | p.Val316Asp | B | Core | Other | Loss of complex integrity, reduced GDP release activity²,⁴ | Val316 is located inside of eIF2Bβ, but that part of subunit is in a close proximity to eIF2Bc. Substitution to hydrophilic Asp in this hydrophobic region might disrupt folding and in turn affect binding to the eIF2Bc or eIF2Bδ subunits since it lies close to their interfaces. |
| Variant | Effect | Location | Description |
|---------|--------|----------|-------------|
| c.74A>G | p.Lys25Arg | B Core* NT domain | Lys25 interacts with Asp107 of eIF2Bγ. Lys and Arg are chemically similar, but Arg has a larger side-chain than Lys. Mutation might affect the folding of NT domain, since Lys25 is located in a very narrow pocket. |
| c.97A>G | p.Lys33Glu | A Core NT domain | Lys33 forms a hydrogen bond with the backbone of Met69 of eIF2Bγ. Substitution to Glu changes the charge of the amino acid from positive to negative, which might be disruptive. |
| c.140G>A | p.Gly47Glu | A SI NT domain | Gly47 is facing several hydrophobic residues including Pro199 of eIF2Bδ. Substitution to Glu would face Glu49 & Glu50 of eIF2Bγ, which would cause repulsion between these. Substitution to Glu might introduce a new H-bond with Ser197. Might affect binding between eIF2Bγ and eIF2Bδ. |
| c.260C>T | p.Ala87Val | D Core NT domain | Ala87 is close to Arg91. Ala and Val are chemically similar, so mutation might not cause large effect. Substitution with hydrophobic Val still can make favorable interactions with nearby residues including Leu90, Leu215, Ile221 and Ile224. |
| c.272G>A | p.Arg91His | A Core NT domain | Abolishes extensive H-bond network (e.g. with side-chain of Asp88 & Asn218 of eIF2Bγ). Nitrogens of His are no longer in close proximity to any of these residues – no H-bonds possible with the His side-chain and adjacent residues which is likely to have an effect on folding. |
| c.344A>C | p.His115Pro | D SI NT domain | His115 lies at eIF2Bγ/eIF2Bδ interface. Substitution with Pro at the end of the α-helix likely to affect secondary structure. Might affect subunit binding. |
| c.602A>G | p.Asp201Gly | B Core* Other | Abolishes H-bonds with His203 and Tyr205 in eIF2Bγ. Might affect folding in this region of the eIF2Bγ subunit, presumably enough to give rise to fairly severe disease. |
| c.674G>A | p.Arg225Gln | C Core* Other | No effect on complex stability or GDP release activity, reduced binding to eIF2. Substitution to Gln abolishes the H-bond to Asp156 and polar interactions to Asp201 and Tyr205. Might affect folding in the region. |
| c.687T>G | p.Ile229Met | D Core Other | Substitution to Met might be somewhat unfavorable as it has a longer and bulkier sulphur-containing side group. Being close to the surface of the protein (rather than interior), might alter folding in this region. |
| Variation | Gene | Position | Exonic Change | Amino Acid Change | Class | Impact | Subunit/Subdomain | Impact on Subunit/Subdomain |
|-----------|------|----------|---------------|------------------|-------|--------|-------------------|-----------------------------|
| c.1004C>T | p.Pro335Leu | D | Exposed | I-patch | Exposed | Pro335 is located in a loop connecting I-patch with the rest of eIF2By subunit. This loop is solvent-exposed on the structure. |
| c.1124T>G | p.Ile375Ser | A | Core | I-patch | Core | Ile375 faces inside of hydrophobic I-patch. Substitution to polar Ser might disrupt hydrophobic interactions of Ile375 with several residues around (e.g. Ile358, Leu392). |
| **EIF2B4** | | | | | |
| c.728C>T | p.Pro243Leu | A | Exposed | Other | Exposed | Substitution to Leu abolishes rigidity caused by the Pro-Pro dipptide. Likely to result in differences in folding due to increased flexibility. Location is in loop interacting with eIF2\(\delta\). |
| c.978G>C | p.Lys326Asn | A | SI | Other | SI | Lys326 is located at the interface with subunit eIF2B\(\alpha\) (interaction with backbone of Phe239 of eIF2B\(\alpha\)). Substitution to Asn might introduce an additional H-bond with Lys400. Abolition of H-bond between Lys326 and Phe239 might affect subunit interactions and binding, with substantial impacts. |
| c.1069C>T | p.Arg357Trp | A | SI | Other | SI | Arg357 is located at the interface with eIF2B\(\varepsilon\) (interaction with His340 of eIF2B\(\varepsilon\)). Mutation of Arg to Trp is a major change of a flexible polar to a more rigid hydrophobic residue. Abolishes probable H-bond interaction between Arg357 and His340. Since Arg lies on the interface between eIF2B\(\varepsilon\) and eIF2B\(\delta\), the big bulky Trp side-chain might affect binding interfaces. Loss of complex integrity\(^2\) |
| c.1070G>A | p.Arg357Gln | C | SI | Other | SI | Arg357 is located at eIF2B\(\delta\)/eIF2B\(\varepsilon\) interface. Mutation abolishes H-bond interaction between Arg357 and His340 of eIF2B\(\varepsilon\) which might affect subunit interaction. |
| c.1090C>T | p.Arg364Trp | A | SI | Other | SI | Arg364 is located at the interface of eIF2B\(\delta\)/eIF2B\(\beta\) (interacts with backbone oxygen of Leu463 of eIF2B\(\delta\) and side-chain of Glu193 of eIF2B\(\beta\)). Substitution to Trp can alter folding in this region to accommodate its large and bulky side-chain. Also abolishes the H-bonding with adjacent residues of eIF2B\(\delta\) and eIF2B\(\beta\). Hence, might affect subunit binding between eIF2B\(\delta\) and eIF2B\(\beta\). Occurrence of multiple effects might explain phenotypic score. |
| SNP | Alleles | Protein Change | Location | Function |
|-----|---------|----------------|----------|----------|
| c.1120C>T | p.Arg374Cys | C | SI | Other |
| | | | | Arg374 is located at the interface of eIF2Bβ/eIF2Bδ (interacts with backbone oxygen of Glu299 of eIF2Bβ). Substitution with Cys abolishes this interaction. Likely moderately affects binding between eIF2Bδ and eIF2Bβ. |
| c.1172C>A | p.Ala391Asp | A | SI | Other |
| | | | | Reduced complex stability in the absence of eIF2Ba² |
| | | | | Ala391 is located at the interface of eIF2Bβ/eIF2Bδ and is surrounded by hydrophobic residues Leu386 and Ile388). Substitution to hydrophilic Asp might unfavorably affect interactions with adjacent residues. Might affect folding in this region and subsequently binding of eIF2Bβ and eIF2Be. |
| c.1339G>A | p.Val447Met | C | SI | Other |
| | | | | Val447 is located at the interface of eIF2Bβ/eIF2Bδ and makes hydrophobic interactions to the residues Leu409 and Ala410 of eIF2Bδ and Leu323 of eIF2Bβ). Substitution with Met introduces a longer, bulkier side-chain. Might interfere with interactions at the eIF2Bδ/eIF2Bβ interface. |
| c.1352C>G | p.Ala451Gly | B | SI | Other |
| | | | | Ala451 is located at the interface of eIF2Bβ/eIF2Bδ and makes hydrophobic interactions to the residues Phe452 and Val491 of eIF2Bδ and Ala224 of eIF2Bβ). Substitution with Gly (also a small residue with hydrophobic sidechain) abolishes favorable hydrophobic interactions but might only have a small effect on the eIF2Bδ/eIF2Bβ interaction. |
| c.1400G>T | p.Arg467Leu | D | SI | Other |
| | | | | Arg467 is located at the interface of eIF2Bδ/eIF2Bβ and establishes an interaction network to the residues Glu293 of eIF2Bβ and Lys294 of eIF2Be). Substitution with Leu might influence binding between the three subunits. |
| c.1447C>T | p.Arg483Trp | A | SI | Other |
| | | | | Loss of complex integrity² |
| | | | | Arg483 is located at the interface of eIF2Bδ/eIF2Bβ, close to the ISRB binding site. Arg483 protrudes into a narrow channel formed by loops in eIF2Bδ. Trp has a much bigger and bulkier side-chain than Arg, located in a solvent exposed area; likely to affect folding. This might be exacerbated by the loss of H-bond interactions in the normal structure. Substitution at this position in the subunit interface might also affect binding between eIF2Bβ and eIF2Bδ. Multiplicity of effects might explain severe phenotype. |
| SNP     | Allele 1   | Allele 2   | Location | Domain | Other |
|---------|------------|------------|----------|--------|-------|
| c.1465T>C | p.Tyr489His | Tyr489     | Core*    | Other  | Tyr489 is tightly packed within eIF2B5 subunit and makes numerous interactions with nearby residues (e.g. Arg225, His406, Val488). Substitution to His might introduce a new H-bond with Ser416. Imidazole ring of His is a smaller and more polar aromatic group than that of Tyr. Mutation might alter local folding. |
| c.161G>C | p.Arg54Pro  | Arg54      | Exposed  | NT domain | Substitution with hydrophobic proline located on solvent-exposed surface of protein might affect proper folding. |
| c.167T>C | p.Phe56Ser  | Phe56      | Core     | NT domain | Phe56 is close to I-patch and Val430 of eIF2Bε and is located in a highly hydrophobic pocket. Substitution to Ser might introduce a new H-bond with Ser56. Substitution with hydrophilic Ser into a hydrophobic pocket might cause unfavorable interactions between residues. Addition of extra H-bond might alter conformation of the local structure. Effect probably considerable. |
| c.217G>A | p.Val73Met  | Val73      | Core*    | NT domain | Met has a longer and bulkier side-chain (inclusion of sulphur) than Val. Substitution with Met might reduce unfavourable interactions between hydrophobic Val and hydrophilic residues, changing the folding of this region. Location is close to I-patch. |
| c.218T>G | p.Val73Gly  | Val73      | Core*    | NT domain | Substitution with Gly might reduce unfavourable interactions between hydrophobic Val and hydrophilic residues, changing the folding of this region. Location is close to I-patch. |
| c.230A>G | p.Asp77Gly  | Asp77      | Core     | NT domain | Asp77 is close to and possibly interacting with His105, Trp111, Glu81 and Val73 in eIF2Bε. Close to interface between eIF2Bε and eIF2Bβ. Substitution with Gly might only have a minor effect on subunit interactions between eIF2Bε and eIF2Bβ. Mutation to Gly might introduce flexibility due to its particular side-chain. |
| c.236C>T | p.Thr79Ile  | Thr79      | Core     | NT domain | Hydroxyl group of Thr79 forms H-bonds to the Leu75 and Val155 backbones in eIF2Bε and establishes numerous hydrophobic interactions to the adjacent residues. Substitution to hydrophobic Ile abolishes these interactions and might change the fold of the helix where it is located, and thus the conformation of other parts of NT domain. |
| SNP     | Mutation                        | Domain | Type  | Site | Effect of Mutation                                                                 |
|---------|---------------------------------|--------|-------|------|------------------------------------------------------------------------------------|
| c.241G>A| p.Glu81Lys                       | A      | SI    | NT domain | Glu81 is close to subunit eIF2Bβ (the mutation to a oppositely charged Lys might affect binding between eIF2Bβ and eIF2Be subunits). Lys might interact unfavorably with the other hydrophobic residues in the pocket and loss of the H-bond between Glu and Lys110 might affect folding. |
| c.271A>G| p.Thr91Ala                       | C      | Core  | NT domain | Reduced binding to complex<br>Reduced binding to complex<br>No effect on complex stability<br>Decreased binding to other subunits | Substitution from Thr to Ala might promote favorable hydrophobic interactions with adjacent residues, Ala45, Val88, Val93 and Val120 |
| c.314A>G| p.His105Arg                      | A      | Core* | NT domain | His105 forms H-bonds to Asp77 and Lys108 of eIF2Be. Substitution to larger and flexible Arg might affect these bonds and NT domain fold. |
| c.318A>T| p.Leu106Phe                      | B      | Core  | NT domain | Lower protein amount in yeast | Leu106 is hydrophobic and located in the NT domain. Phe is still hydrophobic but its bulkier side-chain might not be sterically favorable. Might alter folding in this region required to accommodate the bigger sidechain. |
| c.331T>C| p.Trp111Arg                      | A      | Core  | NT domain | Trp111 is located within core of NT domain and is in close proximity to eIF2Bβ. Substitution to Arg might introduce a new H-bond with Glu81 and with Leu80. Substitution with Arg might introduce different polar interactions. |
| c.337C>T| p.Arg113Cys                      | D      | SI    | NT domain | Arg113 is located in a loop of eIF2Be exposed to Glu16 of eIF2Bβ. The mutation might affect interaction between these subunits, but probably other interactions nearby (e.g. ionic bond between Lys110 of eIF2Be and Glu16 of eIF2Bβ) can compensate the effect of this mutation. |
| c.338G>A| p.Arg113His                      | D      | SI    | NT domain | Arg113 is located loop of eIF2Be exposed to Glu16 of eIF2Bβ. Substitution to His may introduce an additional H-bond to Ser109. The mutation might affect interaction between these subunits, but probably other interactions nearby (e.g. ionic bond between Lys110 of eIF2Be and Glu16 of eIF2Bβ) can compensate the effect of this mutation. |
| c.380T>C| p.Leu127Pro                      | D      | Exposed | NT domain | Leu127 is solvent-exposed. Substitution by hydrophobic Pro might affect secondary structure due to its rigidity. |
| c.395G>C| p.Gly132Ala                      | D      | Core  | NT domain | Gly132 is located at the core of NT domain and is surrounded by hydrophobic residues. Substitution to Ala is conservative. |
| SNP     | Change  | Location | Effect                        | Notes                                                                 |
|---------|---------|----------|-------------------------------|----------------------------------------------------------------------|
| c.406C>T | p.Arg136Cys | B Core NT domain | No effect on complex but reduced eIF2B activity<sup>6</sup> | Arg136 interacts with backbones of residues Phe260, Asn263, stabilizing a certain fold of eIF2Bε. Cys is no longer in close proximity with those residues and so H-bond network is abolished. This might lead to more flexibility in this region and altered folding. Location is close to interface with eIF2β<sup>7</sup>. |
| c.407G>A | p.Arg136His | A Core NT domain | Close to key NF motif | Arg136 interacts with backbones of residues Phe260, Asn263, stabilizing a fold of eIF2Bε. Substitution to His might introduce a possible H-bond with Thr261, depending on the orientation of the His. Remaining H-bond network is abolished. Might lead to more flexibility in this region and altered folding. Location is close to interface with eIF2β<sup>7</sup>. |
| c.457G>A | p.Gly153Arg | A Core NT domain | | Gly153 is surrounded by multiple hydrophobic residues such as Val155, Leu47 of eIF2Bε. Substitution to much bulkier hydrophilic Arg likely to disrupt the hydrophobic pocket; expected to change the conformation of this loop. |
| c.468C>G | p.Ile156Met | A Core NT domain | | Ile156 is tightly packed between multiple hydrophobic eIF2Bε residues (e.g. Val313, Tyr78, Val300, Leu70). Substitution to Met, which has a big and bulky side-chain, is likely to affect proper folding in this region. |
| c.511A>G | p.Arg171Gly | B Core Other | | Arg171 interacts with Glu167, Thr183 and His288 in eIF2Bε, which stabilizes its fold. Substitution to the much smaller Gly abolishes these bonds. |
| c.562T>A | p.Ser188Thr | B SI Other | | Ser188 is close to interface with eIF2Bβ and eIF2Bγ. The slightly larger side-chain of Thr can induce a different conformation of loop where it is located, since it is tightly packed near hydrophobic residues Leu244 and Leu245. This might affect the conformation of the loop considerably. |
| c.584G>A | p.Arg195His | A SI Other | No effect complex stability<sup>4</sup> | Arg195 is located in a loop and forms extensive H-bonding to Tyr242 and Asn200. Substitution to His changes the H-bond network and might alter the conformation of this loop. |
| c.592G>A | p.Glu198Lys | D Core* Other | | Glu198 is located at the core of eIF2Bε and interacts with Arg55 and Asn302 in eIF2Bε. Substitution to Lys likely abolishes the interaction with Asn302 and might widen the distance of the H-bond to Arg55, weakening the bond. This might affect the conformation of loops in which Glu198 and Arg55 are located. |
| Mutation | Amino Acid Change | Core | Other |
|----------|------------------|------|-------|
| c.631A>G | p.Arg211Gly      | C    | Core  |
|          |                  |      | Other |
|          |                  |      |       |
| c.713T>A | p.Val238Glu      | B    | SI    |
|          |                  |      | Other |
|          |                  |      |       |
| c.758C>A | p.Ser253Tyr      | C    | Core  |
|          |                  |      | Other |
|          |                  |      |       |
| c.805C>G | p.Arg269Gly      | B    | Core* |
|          |                  |      | Other |
|          |                  |      |       |
| c.806G>C | p.Arg269Pro      | A    | Core* |
|          |                  |      | Other |
|          |                  |      |       |
| c.806G>A | p.Arg269Gln      | B    | Core* |
|          |                  |      | Other |
|          |                  |      |       |
| c.860T>A | p.Ile287Asn      | A    | Core  |
|          |                  |      | Other |
|          |                  |      |       |
| c.896G>A | p.Arg299His      | B    | Core* |
|          |                  |      | Other |
|          |                  |      |       |
| c.913A>T | p.Met305Leu      | D    | Core* |
|          |                  |      | Other |
|          |                  |      |       |

- Arg211 forms H-bonds with Gln286 which is abolished when substituted with Gly. This might affect overall folding in this region, although effects likely modest.
- Glu has a longer and hydrophilic side-chain and is now even closer to hydrophobic residues, Leu213, Phe231, Leu230 and Ala204, which might lead to unfavorable interactions. Might disrupt eIF2Be and eIF2By interaction interface with substantial consequences.
- Ser253 makes polar contacts with nearby residues. The region is rather solvent-exposed. Substitution with Tyr might alter folding in this region to accommodate the big and bulky side-chain relative to Ser253.
- Arg269 forms H-bonds with Asp246 and His248. Mutation to a much smaller Gly abolishes H-bond network. Might lead to more flexibility in this region and alter folding.
- Arg269 forms H-bonds with Asp246 and His248. Substitution to Pro might cause a kink and alter secondary structure and therefore alter the overall structure. Loss of H-bond network might lead to more flexibility in this region and alter folding.
- Arg269 forms H-bonds with Asp246 and His248. Substitution to smaller Gln might form a new H-bond with Ser250, but existing H-bonds might be lost. Might alter fold introduce some flexibility to this region of the protein.
- Ile287 is located in a highly hydrophobic region of eIF2Be beta-sheet (near Val273, Val212, Met181). Substitution to polar Asn in this hydrophobic environment could generate unfavorable interactions that alter folding.
- Arg299 makes hydrogen/ionic bonds to with Ser51 and Asp154. Substitution to smaller His might abolish extensive hydrogen bond network and might have a significant effect on the proper folding here.
- Met305 is located close to the protein surface. Substitution to Leu which is also hydrophobic with a smaller side-chain is expected to have minimal effects.
| Variant     | Symbol      | Effect on Structure | Effect on Complex Formation in Yeast | Notes                                                                 |
|-------------|-------------|---------------------|--------------------------------------|----------------------------------------------------------------------|
| c.943C>T    | p.Arg315Cys | B                   | SI                                   | Arg315 forms an ionic interaction with Asp304 of eIF2Bβ and might also interact with side-chain of Arg312 of eIF2Bε. Substitution to Cys might affect interaction between these subunits. |
| c.943G>A    | p.Arg315Gly | B                   | SI                                   | Arg315 forms an ionic interaction with Asp304 of eIF2Bβ and might also interact with side-chain of Arg312 of eIF2Bε. Substitution with smaller Gly does not support these interactions, which might affect intersubunit binding. |
| c.944G>A    | p.Arg315His | B                   | SI                                   | Arg315 forms an ionic interaction with Asp304 of eIF2Bβ and might also interact with side-chain of Arg312 of eIF2Bε. Substitution to His might change these interactions and impact on intersubunit binding. |
| c.947G>A    | p.Arg316Gln | A                   | SI                                   | Arg339 interacts with Tyr393 of eIF2Bδ, stabilizing the eIF2Bε/δ interface. Substitution to smaller alters H-bond network and might affect intersubunit binding. |
| c.1015C>T   | p.Arg339Pro | A                   | SI                                   | Arg339 interacts with Tyr393 of eIF2Bδ and is in close proximity with eIF2Bε. Substitution to rigid Pro might affect ε/δ subunit interaction. |
| c.1016G>C   | p.Arg339Gln | A                   | SI                                   | Arg339 interacts with Tyr393 of eIF2Bδ and is in close proximity with eIF2Bα. Substitution to smaller Gln might affect ε/δ subunit interaction. |
| c.1016G>A   | p.Arg339Trp | A                   | SI                                   | Arg339 interacts with Tyr393 of eIF2Bδ and is in close proximity with eIF2Bα. Substitution to much larger Trp might affect ε/δ subunit interaction. |
| c.1049T>C   | p.Leu350Pro | A                   | Core I-patch                         | Leu350 is located at the beginning of I-patch and is close to subunit eIF2Bα. Substitution to more rigid Pro might influence secondary structure in this region. Location of Pro on flexible loop close to interface between eIF2Bε and eIF2Bα might affect subunit binding. |
| c.1051G>A   | p.Gly351Ser | D                   | Core I-patch                         | Gly351 is located on the protein surface. If Gly is substituted with Ser and its sidechain is oriented towards solvent, effects on local structure might be minimal. |
| c.1157G>T   | p.Gly386Val | A                   | Core I-patch                         | Gly386 is close to hydrophilic residue Asp387 and hydrophobic Ala403 and Ala404. Substitution to larger Val might alter conformation of adjacent residues and their interactions. Push the next repeat of I-patch (containing Ale403 and Ala404), changing its conformation. |
| c.1208C>T   | p.Ala403Val | A | Core | I-patch | The side-chain of Ala403 is very close to the residues in a next repeat of I-patch turn (e.g. Glu421 and Lys420). Substitution to Val might only have a minimal effect since they are both hydrophobic and structurally similar. Still, Val might push the next repeat of I-patch (containing Ale403 and Ala404), changing its conformation. |
| c.1244A>G   | p.Asp415Gly | D | Core | I-patch | Asp415 is oriented towards the remaining part of eIF2Bɛ. It is surrounded by polar residues, which are facing solvent. Substitution to Gly might alter conformation of the loop that contains this Asp. |
| c.1280C>T   | p.Pro427Leu | B | Core | I-patch | Pro427 is located on a loop, which faces other repeat of I-patch. Substitution to Leu might alter loop conformation and flexibility and possibly I-patch integrity. |
| c.1289T>C   | p.Val430Ala | A | Core | I-patch | Val430 is located in a hydrophobic pocket. Substitution to Ala, another hydrophobic but smaller amino acid, is likely to have a minimal effect as they are chemically similar. Mutation might affect orientation of I-patch with regards to eIF2Bɛ. |
| c.1295C>T   | p.Thr432Ile | A | Core | I-patch | Thr432 is located at the last repeat of I-patch which interacts with the rest of eIF2Bɛ. Might affect folding in this region since it is relatively close to surface of the protein too. The hydroxyl of Thr432 (absent in Ile) might be important for stabilization of I-patch position. |
| c.1309G>A   | p.Val437Met | A | Core | I-patch | Val437 is oriented inwards of I-patch repeat, making hydrophobic interactions to Leu431, Val423 and Leu443. Substitution to Met might disrupt this folding to accommodate its longer and bulkier, sulphur-containing side-chain. |
| c.1340C>T   | p.Ser447Leu | A | Core | Other   | Ser447 is oriented inwards of the last I-patch repeat and is surrounded by hydrophobic residues (Leu431, Ile443, Pro444 and Ile449). Substitution to larger Leu might form more favorable hydrophobic interactions in the pocket that can alter (I-patch) folding in this region. |
| c.1360C>T   | p.Pro454Ser | D | Exposed | Other | Pro454 is located on the protein surface. Substitution to Ser abolishes the rigidity caused by the Pro-Pro dipeptide. Likely to result in differences in folding due to increased flexibility. |
| SNP          | Allele      | Position | Effect | Amino Acid Change | Description                                                                                     |
|-------------|-------------|----------|--------|-------------------|-----------------------------------------------------------------------------------------------|
| c.1810C>T   | p.Pro604Ser | A        | Core   | CTD               | Pro604 is located towards another helix and facing other helix. Substitution to polar Ser might disrupt hydrophobic interactions with adjacent residues (Leu620, Leu621) and subsequently disrupt the fold of CTD. |
| c.1824G>A   | p.Met608Ile | D        | Core   | CTD               | Met608 is located in a loop at the end of one helix and facing another helix. Substitution to Ile, another hydrophobic amino acid, is likely to have a minimal effect as they are chemically similar. |
| c.1882T>C   | p.Trp628Arg | A        | Core   | CTD               | Tryp628 is located in a highly hydrophobic area (interacts with Val600, Phe603, Leu624, Leu651) on a helix and is facing inwards to another helix, probably stabilizing interactions between several helices. Substitution to longer and polar Arg might disrupt a number of hydrophobic interactions with nearby residues and subsequently disrupt the fold of CTD. |
| c.1903T>C   | p.Tyr635His | A        | Core   | CTD               | Tyr635 is located on a helix and facing another helix. It interacts with Asn579, Ile578, Val592, stabilizing interactions between CTD helices. Substitution to His might disrupt interactions with adjacent residues (Asn579), although this is not certain. |
| c.1946T>C   | p.Ile649Thr | C        | Core   | CTD               | Ile649 is located on a helix and facing towards other helices. It is located in a highly hydrophobic area (surrounded by Leu601, Leu667, Leu646), probably stabilizing interactions between several helices. Substitution to more polar Thr might disrupt hydrophobic interactions with nearby residues (Leu676, Leu646, Phe670) and subsequently disrupt the fold of CTD. |
| c.1948G>A   | p.Glu650Lys | A        | Core   | CTD               | Located on a helix and facing towards other helixes. Substitution to differently charged Lys might disrupt ionic interaction with residue Arg698 and subsequently disrupt the fold of CTD. |
| c.2051G>C   | p.Trp684Ser | A        | Core   | CTD               | Located on a helix and facing towards other helixes. The bulky Trp residue seems to be important for filling this pocket and stabilizing the shape of CTD. Substitution to smaller Ser might change the fold of CTD. |

Reference sequences of EIF2B1, EIF2B2, EIF2B3, EIF2B4 and EIF2B5 are NM_001414.3, NM_014239.3, NM_020365.3, NM_0010341161.1, and NM_003907.2, respectively.
1. Wortham, N.C., Proud, C.G. (2015). Biochemical effects of mutations in the gene encoding the alpha subunit of eukaryotic initiation factor (eIF) 2B associated with Vanishing White Matter disease. *BMC Medical Genetics*, 16, 64

2. Liu, R., et al. (2011). Severity of vanishing white matter disease does not correlate with deficits in eIF2B activity or the integrity of eIF2B complexes. *Human Mutation* 32, 1036-1045.

3. Richardson, J.P., Mohammad, S.S., Pavitt, G.D. (2004). Mutations causing childhood ataxia with central nervous system hypomyelination reduce eukaryotic initiation factor 2B complex formation and activity. *Molecular and Cellular Biology*, 24, 2352-2363.

4. Li, W., et al. (2004). Mutations linked to leukoencephalopathy with vanishing white matter impair the function of the eukaryotic initiation factor 2B complex in diverse ways. *Molecular and Cellular Biology*, 24, 3295-3306.

5. Wortham, N.C., et al. (2014). Analysis of the subunit organization of the eIF2B complex reveals new insights into its structure and regulation. *FASEB Journal*, 28, 2225-2237.

6. Wang, X., et al. (2012). Identification of residues that underpin interactions within the eukaryotic initiation factor (eIF2) 2B complex. *Journal of Biological Chemistry* 287, 8263-8274.

7. Kashiwagi, K., et al. (2019). Structural basis for eIF2B inhibition in integrated stress response. *Science* 364, 495-499.

8. Core means that amino acid is located within a subunit and faces inward; Core* means that amino acid is located within a subunit and that there was a cavity around identified; SI means that amino acid is located at interface of subunits; Exposed means that amino acid is exposed to a solvent and there is no interacting amino acid around on the current structure; “CTD” is catalytic domain; “NT domain” is nucleotide-binding domain.
## Supplementary Table 6. Biochemical effects of eIF2B mutations

| Mutation human | Mutation studied in yeast | Biochemical Effect | Location in 3D structure<sup>1</sup> | Functional domain | Disease severity category<sup>2</sup> |
|----------------|---------------------------|--------------------|--------------------------------------|-------------------|--------------------------------------|
| eIF2Bα         |                           |                    |                                      |                   |                                      |
| p.Pro278Arg    |                           | No effect complex stability<sup>4</sup> | SI                                    | Other             | C                                    |
| p.Gly200Val    |                           | Loss of complex integrity<sup>5,6</sup> | SI                                    | Other             | A                                    |
| p.Glu213Gly    | p.Glu239Gly               | No effect /small effect on complex in human and yeast<sup>5,7,8</sup> | SI                                    | Other             | C                                    |
| p.Pro291Ser    | p.Val316Asp               | Loss of complex integrity<sup>5,6</sup> | SI                                    | Other             | A                                    |
| p.Val341Asp    |                           | Loss of complex integrity in human<sup>5,7</sup> | Core                                 | Other             | B                                    |
| eIF2Bβ         |                           | Reduced translation initiation, increased GCN4 translation in absence of stress, grew without GCN2 in presence of 3AT in yeast<sup>8</sup> |                                      |                   |                                      |
| eIF2Bγ         |                           | No effect<sup>5,6</sup> | Core*                                | Other             | C                                    |
| p.Arg225Gln    |                           |                      |                                      |                   |                                      |
| eIF2Bδ         |                           |                      |                                      |                   |                                      |
| p.Arg357Trp    |                           | Loss of complex integrity<sup>5,6</sup> | SI                                    | Other             | A                                    |
| p.Ala391Asp    |                           | Reduced complex stability in the absence of eIF2Bα<sup>6,9</sup> | SI                                    | Other             | A                                    |
| p.Arg483Trp    |                           | Loss of complex integrity<sup>5,6</sup> | SI                                    | Other             | A                                    |
| p.Val73Gly     | p.Val57Gly               | No effect on complex but increased eIF2B activity in human<sup>6</sup> | Core*                                | NT domain         | D                                    |
| p.Thr91Ala     |                           | Reduced complex stability<sup>5</sup> | Core*                                | NT domain         | C                                    |
| p.Leu106Phe<sup>4</sup> | p.Ile90Phe              | Lower protein amount in yeast<sup>8</sup> | Core                                 | NT domain         | B                                    |
| p.Arg113His    |                           | No effect on complex but reduced eIF2B activity<sup>7</sup> | SI                                    | NT domain         | D                                    |
| p.Arg136Cys    |                           | No effect on complex but reduced eIF2B activity<sup>6</sup> | Core                                 | NT domain         | B                                    |
| p.Arg195His    |                           | No effect complex stability<sup>5</sup> | SI                                    | Other             | A                                    |
| p.Arg269Gly    |                           | No effect complex stability<sup>6</sup> | Core                                 | Other             | B                                    |
| p.Arg315Gly    |                           | No effect complex stability<sup>5</sup> | SI                                    | Other             | B                                    |
| p.Arg339Pro<sup>4</sup> | p.Arg323Pro           | No effect on complex formation in yeast<sup>6</sup> | SI                                    | Other             | A                                    |
| p.Gly386Val<sup>4</sup> | p.Gly369Val          | Lower protein amount in yeast<sup>8</sup> | Core                                 | I-patch            | A                                    |
| p.Val430Ala<sup>4</sup> | p.Ile413Ala            | Lower protein amount in yeast<sup>8</sup> | Core                                 | I-patch            | A                                    |
| p.Trp628Arg    | p.Trp618Arg             | Lower protein amount, enhanced GCN2 independent growth in yeast<sup>8</sup> | Core                                 | CTD                | A                                    |

Reference sequences of *EIF2B1, EIF2B2, EIF2B3, EIF2B4* and *EIF2B5* are NM_001414.3, NM_014239.3, NM_020365.3, NM_0010341161.1, and NM_003907.2, respectively. Exactly the same kind of enzymatic assay was used in all studies, excluding methodological differences between the published studies. In some studies, subunit interactions and binding to eIF2 were also assessed, using a consistent approach.

1. Core means that amino acid is located within a subunit and faces inward; Core* means that amino acid is located within a subunit and there was a cavity around identified; SI means that amino acid is located at interface of subunits; Exposed means that amino acid is exposed to a solvent and there is no interacting amino acid around on the current structure; CTD is catalytic domain; NT domain is nucleotide-binding domain.

2. A, ultra-severe; B, severe; C intermediate; D mild
3. Equivalent mutation in human eIF2B based on yeast mutation; biochemical effect of the mutation was not tested in human eIF2B

4. Wortham, N.C., Proud, C.G. (2015) Biochemical effects of mutations in the gene encoding the alpha subunit of eukaryotic initiation factor (eIF) 2B associated with Vanishing White Matter disease. *BMC Medical Genetics, 16,* 64.

5. Li, W., et al. (2004). Mutations linked to leukoencephalopathy with vanishing white matter impair the function of the eukaryotic initiation factor 2B complex in diverse ways. *Molecular and Cellular Biology, 24,* 3295-3306.

6. Liu, R., et al. (2011). Severity of vanishing white matter disease does not correlate with deficits in eIF2B activity or the integrity of eIF2B complexes. *Human Mutation, 32,* 1036-1045.

7. Wang, X., et al. (2012). Identification of residues that underpin interactions within the eukaryotic initiation factor (eIF2) 2B complex. *Journal of Biological Chemistry, 287,* 8263-8274.

8. Richardson, J.P., Mohammad, S.S., Pavitt, G.D. (2004). Mutations causing childhood ataxia with central nervous system hypomyelination reduce eukaryotic initiation factor 2B complex formation and activity. *Molecular and Cellular Biology, 24,* 2352-2363.

9. Wortham, N.C., et al. (2014). Analysis of the subunit organization of the eIF2B complex reveals new insights into its structure and regulation. *FASEB Journal, 28,* 2225-2237
## Supplementary Table 7. Likely benign variants

| Mutation human | dbSNP     | Allele frequency | Number of homozygotes | Type of location in 3D | Functional domain |
|----------------|-----------|------------------|-----------------------|------------------------|------------------|
| **eIF2Bα**     |           |                  |                       |                        |                  |
| p.Val59Ala     | rs199544322| 0.001            | 3                     | Exposed                |                  |
| **eIF2Bβ**     |           |                  |                       |                        |                  |
| p.Gly26Arg     | rs141355163| 0.002 (0.02 in Finland) | 4                     | Exposed                |                  |
| p.Ala127Val    | rs150617429| 0.0018           | 2                     | Exposed                |                  |
| p.Ile328Val    | rs145117455| 0.003 (0.01 in Asia) | 2                     | Exposed                |                  |
| **eIF2Bγ**     |           |                  |                       |                        |                  |
| p.Ser404Ala    | rs77068026 | 0.0211           | 178                   | Not modeled            |                  |
| **eIF2Bδ**     |           |                  |                       |                        |                  |
| p.Arg306Gly    | rs78599355 | 0.007 (0.03 in Finland) | 17                   | Exposed                |                  |
| **eIF2Bε**     |           |                  |                       |                        |                  |
| p.Ile587Val    | rs843358   | 0.39             | 7848                  | Not modeled            | CTD              |

Benign variants from online databases (1000Genomes, ESP, GnomAD, dbSNP), filtered for exonic missense variants with either minor allele frequency >0.001 and found in homozygous state in at least 2 individuals or minor allele frequency of >0.05. Reference sequences of *EIF2B1*, *EIF2B2*, *EIF2B3*, *EIF2B4* and *EIF2B5* are NM_001414.3, NM_014239.3, NM_020365.3, NM_0010341161.1, and NM_003907.2, respectively.