**Table S2.** List of the new variants in rare LS nuclear genes identified in the study.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Gene** | **Variant** | **gnomAD frequency** | **SpliceAI (delta score)** | **ACMG criteria** | **Classification** | **Zygosity** |
| *COX10* | c.1037C>T (p.Ser346Leu) | 0 | 0.0 | PP3, PM2 | Uncertain Significance | hom |
| *COX10* | c.878C>T (p.Ala293Val) | 0 | 0.0 | PP3, PM2 | Uncertain Significance | het |
| *COX10* | c.1061G>A (p.Arg354Gln) | 0.0000362 | 0.1 for AL | PM2, BP4 | Uncertain Significance | het |
| *GFM2* | c.1124T>C (p.Leu375Pro) | 0 | 0.03 for AL | PM2, PP3 | Uncertain Significance | het |
| *GFM2* | c.240T>G (p.Asp80Glu) | 0 | 0.05 for AL | PP3, PM2 | Uncertain Significance | het |
| *IARS2* | c.2669T>G (p.Leu890Arg) | 0.00000795 | 0.0 | PP3, PM2 | Uncertain Significance | het |
| *IARS2* | c.547\_550del (p.Lys183LeufsTer21) | 0.00000403 | 0.0 | PVS1, PM2 | Likely Pathogenic | het |
| *NARS2* | c.595-1G>A | 0 | 0.93 for AG  0.99 for AL | PVS1, PM2, PM3 | Pathogenic | het |
| *NARS2* | c.959+1505T>G | 0 | 0.67 for AG  0.75 for DG | PM2, PS3, PM3 (supportive) | Likely Pathogenic | het |
| *NARS2* | g.78187758\_78197406del | 0 | - | - | Likely Pathogenic | het |
| *NDUFA10* | c.604dup (p.His202ProfsTer25) | 0.0000318 | 0.02 for DL | PVS1, PM2 | Likely Pathogenic | het |
| *NDUFA10* | c.557A>C (p.His186Pro) | 0 | 0.01 for AL  0.01 for DL | PP3, PM2 | Uncertain Significance | het |
| *NDUFAF5* | c.743A>C (p.Tyr248Ser) | 0 | 0.0 | PP3, PM2 | Uncertain Significance | hom |
| *NDUFAF6* | c.634G>A (p.Gly212Ser) | 0 | 0.05 for AL | PP3, PM2 | Uncertain Significance | het |
| *NDUFAF6* | c.907C>T (p.Arg303Ter) | 0.0000683 | 0.06 for AL  0.01 for DG | PP3, PM2 | Uncertain Significance | het |
| *NDUFS2* | c.245T>A (p.Leu82Gln) | 0 | 0.0 | PP3, PM2 | Uncertain Significance | het |
| *NDUFS2* | c.412C>T (p.Arg138Trp) | 0 | 0.2 for AG | PP3, PM2, PM5 | Uncertain Significance | het |
| *NDUFS8* | c.307C>T (p.Arg103Trp) | 0.00000819 | 0.0 | PVS1, PM1, PM2 | Likely Pathogenic | het |
| *NDUFS8* | c.585G>A (p.Trp195Ter) | 0 | 0.0 | PP3, PM2 | Uncertain Significance | het |
| *NDUFV1* | c.475C>T (p.Arg159Ter) | 0.0000203 | 0.0 | PVS1, PM2, PM3 | Pathogenic | het |
| *PDHA1* | c.1158\_1159insCAGTGGATCAAGTTTA (p.Lys387GlnfsTer50) | 0 | 0.0 | PVS1, PM2 | Likely pathogenic | hem |
| *PDHA1* | c.1102\_1103insTCTACT (p.Tyr369\_Ser370insPheTyr) | 0 | 0.0 | PM2, PM4 | Uncertain Significance | hem |
| *PDHB* | c.615G>A (p.Met205Ile) | 0 | 0.0 | PM2 | Uncertain Significance | het |
| *PDHB* | c.121C>T (p.Gln41Ter) | 0 | 0.07 for AG  0.05 for AL  0.02 for DL | PVS1, PM2 | Likely Pathogenic | het |
| *PMPCB* | c.355C>A (p.Leu119Met) | 0.000119 | 0.0 | PM2, BP4 | Uncertain Significance | het |
| *SCO2* | c.227\_230del (p.Leu76ProfsTer2) | 0.0000164 | 0.0 | PVS1, PM2, PM3 | Pathogenic | het |
| *SCO2* | c.533C>T (p.Ala178Val) | 0 | 0.0 | PP3, PM2, PM3 | Uncertain Significance | het |
| *SCO2* | c.202G>A (p.Gly68Arg) | 0 | 0.01 for AG | PP3, PM2, PM3 | Uncertain Significance | het |
| *SCO2* | c.763C>T (p.Arg255Trp) | 0.00000796 | 0.0 | PM2, PM3, BP4 | Uncertain Significance | het |
| *SLC19A3* | c.1253A>C (p.Gln418Pro) | 0 | 0.0 | PP3, PM2, PM5 | Uncertain Significance | hom |
| *SUCLG1* | c.665T>C (p.Leu222Ser) | 0 | 0.17 for DG  0.08 for DL | PP3, PM2 | Uncertain Significance | hom |
| *SURF1* | c.703A>G (p.Met235Val) | 0.00000398 | 0.02 for DG | PP3, PM2, PM3, PM5 | Likely Pathogenic | het |
| *SURF1* | c.584G>T (p.Gly195Val) | 0.00000801 | 0.04 for AG  0.04 for DG | PP3, PM2, PM3, PM5 | Likely Pathogenic | het |
| *SURF1* | c.779G>A (p.Gly260Glu) | 0 | 0.0 | PP3, PM1, PM2, PM3 | Likely Pathogenic | het |
| *SURF1* | c.554\_555insA (p.Lys186GlufsTer5) | 0 | 0.02 for AG  0.1 for AL  0.14 for DL | PVS1, PM2, PM3 | Pathogenic | het |
| *SURF1* | c.49G>T (p.Gly17Ter) | 0 | 0.02 for DG  0.04 for DL | PVS1, PM2 | Likely Pathogenic | hom |
| *SURF1* | c.65del (p.Ser22ThrfsTer50) | 0 | 0.11 for AG  0.01 for DL | PVS1, PM2 | Likely Pathogenic | hom |
| *SURF1* | c.227T>A (p.Leu76Ter) | 0 | 0.01 for AG, AL, DG  0.03 for DL | PVS1, PM2 | Likely Pathogenic | hom |
| *SURF1* | c.515+2T>C | 0.00000399 | 0.2 for DG  0.96 for DL | PVS1, PM2, PM3 | Likely Pathogenic | het |
| *SURF1* | c.187C>T (p.Gln63Ter) | 0 | 0.01 for DL | PVS1, PM2, PM3 | Pathogenic | het |
| *SURF1* | c.856T>C (p.Ser286Pro) | 0 | 0.0 | PP3, PM1, PM2, PM3 | Likely pathogenic | het |
| *SURF1* | c.584G>A (p.Gly195Asp) | 0 | 0.07 for AG  0.07 for DG | PP3, PM2, PM3, PM5 | Likely Pathogenic | het |
| *SURF1* | c.833+1del | 0 | 0.8 for DG  0.97 for DL | PVS1, PM2, PM3 | Likely Pathogenic | het |
| *SURF1* | c.899\_902del (p.Val300AspfsTer44) | 0 | 0.0 | BP3, PM1, PM2, PM3 | Likely pathogenic | het |
| *SURF1* | c.491C>T (p.Thr164Ile) | 0.0000279 | 0.0 | PP3, PP5, PM2, PM3 | Likely pathogenic | het |
| *SURF1* | Complex rearrangement | 0 | - | PVS1, PM2, PM3 | Pathogenic | het |
| *VPS13D* | c.8687C>T (p.Thr2896Met) | 0.0000119 | 0.0 | PP3, PM2 | Uncertain Significance | het |
| *VPS13D* | c.12662+1059C>G | 0 | 1.0 for DG | PM2, PS3, PM3 (supportive) | Likely Pathogenic | het |

Bioinformatic analysis: SpliceAI DS, delta score (indicates the probability of the genomic region to gain or lose the properties of splicing site); AG, acceptor gain; AL, acceptor loss; DG, donor gain; DL, donor loss. Standard cutoffs for bioinformatic tools: SpliceAI, delta score > 0.5. Zygosity: hom – homozygote, heterozygote, hemizygote.