**Table 4. Summary of Genes with an Over-Representation of Ultra-Rare Variants with a MAF < 0.00005**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Gene ID** | **Gene/Protein Name** | **OMIM Disease Associations** | **PathCards SuperPathways** | **pValue** | **Odds Ratio (OR)** | **Number of Variant Positive Cases (n=278)** | **Number of Variant Positive Controls (n=973)** |
| *LRP1* | LDL Receptor Related Protein 1 | 1) Association with Alzheimer disease 2) Association with Abdominal Aortic Aneurysm 3) Intellectual Disability | 1) Statin Pathway 2) A-beta Pathways: Uptake and Degradation  3) Alzheimers Disease Pathway  4) Malaria  5) PDGFR-beta signaling pathway  6) amb2 Integrin signaling  7) Binding and Uptake of Ligands by Scavenger Receptors  8) Blood-Brain Barrier and Immune Cell Transmigration: Pathways Overview  9) Metabolism of fat-soluble vitamins  10) Non-Canonical Wnt Pathway  11) Metabolism of water-soluble vitamins and cofactors 12) Wnt signaling pathway (KEGG)  13) Alzheimer's disease  14) Vesicle-mediated transport  15) Signaling by GPCR  16) Metabolism | 0.000269 | 3.8948 | 16 (5.8%) | 15 (1.5%) |
| *LHX9* | LIM Homeobox 9 | None | None | 0.000527 | INF | 5 (1.8%) | 0 |
| *PDS5A* | PDS5 Cohesin Associated Factor A | None | None | 0.000657 | 21.389 | 6 (2.2%) | 1 (0.1%) |
| *ULK1* | Unc-51 Like Autophagy Activating Kinase 1 | None | 1) Regulation of autophagy 2) Senescence and Autophagy 3) Longevity regulating pathway - multiple species  4) AMPK signaling pathway 5) p53 Pathway (RnD) 6) mTOR signalling  7) Glucose / Energy Metabolism 8) Neuroscience  9) Translation Insulin regulation of translation 10) Cellular Senescence | 0.002137 | 10.68 | 6 (2.2%) | 2 (0.21%) |
| *NR3C2* | Nuclear Receptor Subfamily 3 Group C Member 2 | 1) Pseudohypoaldosteronism Type I, Autosomal Dominant  2) Hypertension, Early-Onset, Autosomal Dominant, with Severe Exacerbation in Pregnancy | 1) Aldosterone-regulated sodium reabsorption 2) Agents Acting on the Renin-Angiotensin System Pathway, Pharmacodynamics  3) Nuclear Receptor transcription pathway 4) Gene Expression | 0.002137 | 10.68 | 6 (2.2%) | 2 (0.21%) |
| *OR4C6* | Olfactory Receptor Family 4 Subfamily C Member 6 | None | 1) Olfactory Signaling Pathway 2) Signaling by GPCR | 0.002398 | INF | 4 (1.4%) | 0 |
| *CHRM3* | Cholinergic Receptor Muscarinic 3 | 1) Purne Belly Syndrome (autosomal recessive) | 1) Proton Pump Inhibitor Pathway, Pharmacodynamics 2) Monoamine GPCRs 3) GPCRs, Other 4) Taste transduction  5) Pancreatic secretion  6) Integration of energy metabolism  7) Salivary secretion  8) Insulin secretion  9) Myometrial Relaxation and Contraction Pathways  10) Calcium signaling pathway  11) Regulation of actin cytoskeleton 12) Circadian entrainment  13) Peptide ligand-binding receptors 14) Interleukin-3, 5 and GM-CSF signaling 15) Signaling by GPCR  16) Metabolism | 0.002398 | INF | 4 (1.4%) | 0 |
| *CYB5D1* | Cytochrome B5 Domain Containing 1 | None | None | 0.002398 | INF | 4 (1.4%) | 0 |
| *GBP2* | Guanylate Binding Protein 2 | None | 1) Immune response IFN alpha/beta signaling pathway  2) Interferon gamma signaling 3) Interleukin-3, 5 and GM-CSF signaling  4) Immune System | 0.002398 | INF | 4 (1.4%) | 0 |
| *ZNF506* | Zinc Finger Protein 506 | None | 1) Gene Expression | 0.002398 | INF | 4 (1.4%) | 0 |
| *IFRD2* | Interferon-Related Developmental Regulator 2 | None | None | 0.002398 | INF | 4 (1.4%) | 0 |
| *BICD2* | BICD Cargo Adaptor 2 | 1) Autosomal dominant lower extremity-predominant spinal muscular atrophy-2 | 1) COPI-independent Golgi-to-ER retrograde traffic 2) Golgi-to-ER retrograde transport  3) Vesicle-mediated transport | 0.002398 | INF | 4 (1.4%) | 0 |
| *KDM4DL* | Lysine Demethylase 4E | None | None | 0.002584 | 17.751 | 5 (1.8%) | 1 (0.1%) |
| *TNFRSF10D* | Tumor Necrosis Factor Receptor Superfamily Member 10d | None | None | 0.002584 | 17.751 | 5 (1.8%) | 1 (0.1%) |
| *CTIF* | CBP80/20-Dependent Translation Initiation Factor | None | None | 0.003588 | 6.2452 | 7 (2.5%) | 4 (0.4%) |
| *COL20A1* | Collagen Type XX Alpha 1 | None | 1) Collagen biosynthesis and modifying enzymes  2) Degradation of the extracellular matrix  3) Integrin Pathway  4) Phospholipase-C Pathway  5) ERK Signaling | 0.003588 | 6.2452 | 7 (2.5%) | 4 (0.4%) |
| *ARHGEF16* | Rho Guanine Nucleotide Exchange Factor 16 | None | 1) NgR-p75(NTR)-Mediated Signaling 2) Signaling by Slit 3) Interferon Pathway  4) p75 NTR receptor-mediated signalling  5) Guidance Cues and Growth Cone Motility 6) G-AlphaQ Signaling  7) RhoGDI Pathway  8) fMLP Pathway  9) Actin Nucleation by ARP-WASP Complex  10) Signaling by Rho GTPases  11) TGF-Beta Pathway  12) Phospholipase-C Pathway  13) GPCR Pathway  14) Apoptotic Pathways in Synovial Fibroblasts  15) Interleukin-3, 5 and GM-CSF signaling  16) ERK Signaling  17) Signaling by GPCR | 0.004595 | 4.7675 | 8 (2.9%) | 6 (0.62%) |

INF = infinite