**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 Pathway2) 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 cofactors12) 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 autophagy2) Senescence and Autophagy3) Longevity regulating pathway - multiple species 4) AMPK signaling pathway5) p53 Pathway (RnD)6) mTOR signalling 7) Glucose / Energy Metabolism8) Neuroscience 9) Translation Insulin regulation of translation10) 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 reabsorption2) Agents Acting on the Renin-Angiotensin System Pathway, Pharmacodynamics 3) Nuclear Receptor transcription pathway4) 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 Pathway2) 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, Pharmacodynamics2) Monoamine GPCRs3) GPCRs, Other4) 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 cytoskeleton12) Circadian entrainment 13) Peptide ligand-binding receptors14) Interleukin-3, 5 and GM-CSF signaling15) 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 signaling3) 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 traffic2) 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 Signaling2) Signaling by Slit3) Interferon Pathway 4) p75 NTR receptor-mediated signalling 5) Guidance Cues and Growth Cone Motility6) 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