**Table 5. Summary of Genes with an Over-Representation of Ultra-Rare Variants with a MAF < 0.00005 and a CADD Score > 20**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **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)** |
| *PTPRM* | Protein Tyrosine Phosphatase, Receptor Type M | None | 1) Nectin adhesion pathway  2) Cell adhesion\_Cadherin-mediated cell adhesion 3) Adherens junction  4) Adhesion  5) Cell adhesion molecules (CAMs)  6) PAK Pathway | 0.000657 | 21.389 | 6 (2.2%) | 1 (0.1%) |
| *CNKSR1* | Connector Enhancer Of Kinase Suppressor Of Ras 1 | None | 1) MAP2K and MAPK activation  2) Ceramide Pathway  3) Toll-Like receptor Signaling Pathways  4) ERK Signaling  5) Developmental Biology 6) Interleukin-3, 5 and GM-CSF signaling  7) Immune System  8) Signaling by GPCR | 0.002137 | 10.68 | 6 (2.2%) | 2 (0.21%) |
| *KDM6B* | Lysine Demethylase 6B | None | 1) Chromatin Regulation / Acetylation 2) Chromatin organization  3) Cellular Senescence  4) Activated PKN1 stimulates transcription of AR (androgen receptor) regulated genes KLK2 and KLK3 | 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%) |
| *ABCA2* | ATP Binding Cassette Subfamily A Member 2 | 1) Alzheimer Disease | 1) ABC-family proteins mediated transport 2) Lysosome 3) Transport of glucose and other sugars, bile salts and organic acids, metal ions and amine compounds | 0.002137 | 10.68 | 6 (2.2%) | 2 (0.21%) |
| *LHX9* | LIM Homeobox 9 | None | None | 0.002398 | INF | 4 (1.4%) | 0 |
| *ABR* | Active BCR-Related | none | 1) G-protein signaling\_Rac2 regulation pathway  2) Regulation of RAC1 activity  3) G-protein signaling\_Regulation of CDC42 activity  4) G-protein signaling\_Regulation of RAC1 activity 5) Regulation of RhoA activity  6) p75 NTR receptor-mediated signalling 7) Signaling by Rho GTPases 8) Interleukin-3, 5 and GM-CSF signaling  9) Signaling by GPCR | 0.002398 | INF | 4 (1.4%) | 0 |
| *ERGIC1* | Endoplasmic Reticulum-Golgi Intermediate Compartment 1 | None | None | 0.002398 | INF | 4 (1.4%) | 0 |
| *DMGDH* | Dimethylglycine Dehydrogenase | 1) Dimethylglycine Dehydrogenase Deficiency Inborn Error of Metabolism | 1) Glycine, serine and threonine metabolism 2) Glycerophospholipid biosynthesis 3) Metabolism | 0.002584 | 17.751 | 5 (1.8%) | 1 (0.1%) |