**Appendix 6** Details of the most significantly enriched pathways, their p-values and genes. Genes that overlapped between pathways are highlighted in bold.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variants tested** | **Pathway** | **Gene** | **Empirical** **p-value** | **Adjusted** **p-value** |
| **Rare/novel variants predicted to be either damaging missense or nonsense variants** | Sphingolipid metabolism | ENPP7, ASAH2, B4GALT6, GBA, CERK | 0.002 | 0.15 |
| Gap junction | ITPR2, MAPK7, TUBB1, DRD1 | 0.03 | 0.70 |
| Caffeine metabolism | CYP1A2, NAT1 | 0.04 | 0.70 |
| Biosynthesis of unsaturated fatty acids | **ACOX1**, ACOT7 | 0.04 | 0.70 |
| **Rare/novel variants** | Aminoacyl-tRNA biosynthesis | GARS, EARS2, NARS, LARS2, AARS2, FARSB, YARS2, TARSL2 | 0.01 | 0.84 |
|  | Glycerophospholipid metabolism | LCAT, GPD2, **PLA2G5**, LPCAT3, AGPAT3, **PLD2**, DGKG, **PLA2G6**, ACHE, PTDSS1, **PLA2G2A** | 0.02 | 0.84 |
|  | Ether lipid metabolism | **PLD2**, AGPS, PAFAH1B1, **PLA2G6**, **PLA2G5**, **PLA2G2A** | 0.02 | 0.84 |
|  | Alpha-Linolenic acid metabolism | **PLA2G6**, **ACOX1**, **PLA2G5**, **PLA2G2A** | 0.03 | 0.84 |
| **All variants** | Steroid hormone | HSD17B1, UGT2B15, SULT1E1, CYP21A2, **CYP3A7**, SRD5A3, **CYP3A43**, **CYP3A4**, CYP1B1 | 0.01 | 0.44 |
|  | Proteasome | PSMB10, PSMB11, PSMC6, PSMC2, PSMA1, PSMB9, PSMF1, PSMA5 | 0.01 | 0.44 |
|  | Ether lipid metabolism  | **PLD2**, ENPP2, PAFAH1B1, **PLA2G6**, **PLA2G5**, PPAP2C, **PLA2G2A** | 0.01 | 0.44 |
|  | Linoleic acid metabolism | **CYP3A43**, **PLA2G6**, **PLA2G5**, **CYP3A7**, **CYP3A4**, **PLA2G2A** | 0.01 | 0.44 |