|  |  |  |  |
| --- | --- | --- | --- |
|  |  |  |  |
| CTP | 0.04435 | -4.4949 | |  | | --- | | Cytidine triphosphate - pyrimidine nucleoside triphosphate; substrate for RNA synthesis; inhibitor of aspartate carbamoyltransferase, which is used in pyrimidine biosynthesis | |
| UTP | 0.07258 | -3.7843 | |  | | --- | | Uridine triphosphate - pyrimidine nucleoside triphosphate; substrate for synthesis of RNA during transcription; **precursor for CTP**; used in metabolism of galactose | |
| GTP | 0.10796 | -3.2114 | |  | | --- | | Guanosine triphosphate - purine nucleosdie triphosphate; substrate for synthesis of RNA during transcription; protein synthesis and gluconeogenesis energy source; signal transduction | |
| 3-phospho-serine | 0.11289 | -3.1471 | |  | | --- | | cell division, cellular differentiation, signal transfuction, and other key cellular signaling processes <https://pubmed.ncbi.nlm.nih.gov/666270/> - ALS relation | |
| dCMP | 0.12326 | -3.0202 | |  | | --- | | Deoxy-cytidine monophosphate - pyrimidine monophosphate | |
| L-cysteic acid | 0.12464 | -3.0041 | |  | | --- | | amino acid generated by oxidation of cysteine | |
| NADP+ | 0.12613 | -2.987 | |  | | --- | | ALS relation - <https://www.frontiersin.org/articles/10.3389/fcell.2022.831273/full> <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8394119/> | |
| xanthine | 0.13349 | -2.9052 | |  | | --- | | purine base; product of purine degradation pathway - subsequently converted to uric acid;  ALS relation - <https://pubmed.ncbi.nlm.nih.gov/27815397/> | |
| 6-phosphoglucono-D-lactone | 0.13938 | -2.8429 | |  | | --- | | intermediate in the PPP - ox part of the PPP goes into ribulose | |
| methylglyoxal | 0.15377 | -2.7012 | |  | | --- | | reduced derivative of pyruvic acid;  ALS relation - <https://academic.oup.com/brain/article/142/12/3771/5606749?login=true> | |
| XMP | 0.1614 | -2.6313 | |  | | --- | | Xanthosine monosphosphate - intermediate in purine metabolism | |
| uric acid | 0.17706 | -2.4977 | |  | | --- | | product of metabolic breakdown of purine nucleotides; uric acid is released in hypoxic conditions   * Acts on Sod1-OH (peroxidase) * Antioxidant; protective during stress   ALS relation - <https://pubmed.ncbi.nlm.nih.gov/26424237/>  DOI: [10.1016/j.mcn.2018.06.002](https://doi.org/10.1016/j.mcn.2018.06.002) | |
| nicotinamide | 0.17917 | -2.4806 | |  | | --- | | incorporated into NADP+ and NAD+  ALS relation - <https://pubmed.ncbi.nlm.nih.gov/33174130/> <https://clinicaltrials.gov/ct2/show/NCT05095571> | |
| CDP | 0.20237 | -2.305 | |  | | --- | | Cytidine triphosphate - pyrimidine ribonucleoside diphosphate | |
| nicotinamide riboside+ | 0.23856 | -2.0676 | |  | | --- | | ALS relation - <https://pubmed.ncbi.nlm.nih.gov/33174130/> <https://clinicaltrials.gov/ct2/show/NCT05095571> | |
| UDP | 0.25346 | -1.9802 | |  | | --- | | carrier of monosaccharides and their derivatives in a variety of reactions (bilirubin, lactose, galactose and mannose, glycogen synthesis, etc) | |
| F-1,6/2,6-DP | 0.26434 | -1.9195 | |  | | --- | | fructose glycolysis; positively modulates glycolysis - when downregulated it diverts part of glucose usage to the PPP  ALS relation - <https://elifesciences.org/articles/45114> <https://www.karger.com/Article/FullText/516926> | |
| 2-(Formamido)-N1-(5-phospho-D-ribosyl)acetamidine | 0.26574 | -1.9119 | |  | | --- | | N-glycosyl compound, a ribose monophosphate, and a carboxamidine | |
| phosphoenolpyruvate | 0.26754 | -1.9022 | |  | | --- | | enol of pyruvate and phosphate, further metabolized to pyruvic acid; involved in glycolysis and gluconeogenesis | |
| NMN | 0.2732 | -1.872 | |  | | --- | | Nicotinamide mononucleotide  ALS relation - <https://pubmed.ncbi.nlm.nih.gov/33174130/> <https://clinicaltrials.gov/ct2/show/NCT05095571> | |
| S-adenosyl-L-methionine+ | 0.27617 | -1.8564 | |  | | --- | | "SAMe" cycle precursor to methylation, aminopropylation, and transsulfuration pathways. Review: <https://academic.oup.com/ajcn/article/76/5/1151S/4824259> | |
| 2-oxoadipic acid | 0.27661 | -1.8541 | |  | | --- | | intermediate in lysine metabolism | |
| deoxycarnitine+ | 0.3108 | -1.6859 | |  | | --- | | Carnitine biosynthesis; carnitine transport long-chain farry acids into the mitochondria so they can be oxidized to produce enrgy | |
| adenylosuccinate | 0.31942 | -1.6465 | |  | | --- | | purine metabolism | |
| isonictinic acid | 0.32459 | -1.6233 | |  | | --- | | derivative of pyridine, isomer of nicotinic acid | |
| UDP-D-galactose / UDP-D-glucose | 0.32636 | -1.6154 | |  | | --- | | intermediate in carbohydrate metabolism; precursors of glycogen and glycosphingolipids | |
| AICA ribonucleotide | 0.33693 | -1.5695 | |  | | --- | | intermediate in the generation of inosine monophosphate (purine metabolism -- uric acid), can stimulate AMPK activity;  ALS relation - <https://www.sciencedirect.com/science/article/pii/S0014579315000034> | |
| Coenzyme A + | 0.34869 | -1.52 | |  | | --- | | synthesis and oxidation of fatty acids, oxidation of pyruvate in the citric acide cycle; CoA biosynthesis requires cysteine, pantothenate, and ATP. | |
| NAD+ | 0.38544 | -1.3754 |  |
| acetoin - | 0.39036 | -1.3571 | |  | | --- | | can be converted to acetyl-coA with acetoin dehydrogenase complex | |
| CDP-choline+ | 0.39476 | -1.3409 | |  | | --- | | product of the rate-imiting step in synthesis of phosphatidylcholine from chiline; plays a role in generation of phospholipids, nucleic acids, proteins, and acetylcholine - <https://pubmed.ncbi.nlm.nih.gov/7869846/> | |
| IDP | 0.39549 | -1.3383 | |  | | --- | | purine ribonucleoside diphosphate; can be converted to inosine acid | |
| pyridoxal | 0.40238 | -1.3134 | |  | | --- | | another form of viramin B6; precurse to pyridoxal 5-phosphate, which is involved in metabolism of amino acids and glycogen, synthesis of nucleic acids, hemogloblin, sphingomyelin, and other sphingolipids; syntehsis of neurotransmitters, etc | |
| GDP-L-fucose | 0.40658 | -1.2984 | |  | | --- | | nucleoside diphosphate sugar formed from GDPmannose, which provides lipopolysaccharides of bacterial cell walls and for blood group substances and other glycoproteins | |
| hypoxanthine | 0.4073 | -1.2959 | |  | | --- | | purine nucleobase; derived from adenine; uric acid pathway;  ALS relation: <https://www.nature.com/articles/s41598-021-00312-8> | |
| homogentisic acid | 0.41759 | -1.2598 | |  | | --- | | accumulation is the result of failure of the enzyme homogentisic acid 1,2-dioxygenase in the degradative pathway of tyrosine - associated with alkaptonuria; intermediate in the catabolism of aromatic amino acids such as phenylalanine and tyrosine | |
| 2,3-bisphospho-D-glycerate | 0.42422 | -1.2371 | |  | | --- | | binds to deoxygenated hemoglobin | |
| D-sedoheptulose-7-phosphate | 0.42518 | -1.2338 | |  | | --- | | PPP; formed by tkt and acted upon by transaldolase | |
| sarcosine | 0.43032 | -1.2165 | |  | | --- | | aka N-methyl-glycine intermediate in the metabolism of choline, glycine synthesis, and glycine degradation. | |
| O-succinyl-homoserine | 0.4321 | -1.2105 | |  | | --- | | homoserine o succinyltransferase catalyzed succinyl coA + L -homoserine to produce CoA and O-succinyl-homoserine | |
| ATP / dGTP | 0.43713 | -1.1939 | |  | | --- | | ALS relation - <https://www.frontiersin.org/articles/10.3389/fcell.2022.831273/full> <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8394119/> | |
| D-erythrose-4-phosphate | 0.44615 | -1.1644 | |  | | --- | | intermediate in the PPP and Calvin cycle; also a precursos in the biosynthesis of tyrosine, phenylalanine, tryptophan | |
| ethyl acetate | 0.44707 | -1.1614 | |  | | --- | | hydrolyses to give acetic acid and ethanol | |
| 6-phosphogluconic acid | 0.45164 | -1.1468 | |  | | --- | | intermediate in the PPP - ox part of the PPP | |
| vitamin B2 | 0.45603 | -1.1328 | |  | | --- | | Riboflavin, essential for formation of FMN and FAD | |
| N-acetyl-b-alanine | 0.47911 | -1.0616 |  |
| N1-acetylspermine | 0.48331 | -1.049 | |  | | --- | | acetamide; derivatibe of spermine | |
| cytidine | 0.48366 | -1.0479 | |  | | --- | | pyrimidine nucleoside; precursos for uridine; used in RNA synthesis | |
| L-arginino-succinate | 0.48399 | -1.047 | |  | | --- | | intermediate in the urea cycle; precursos to fumarate in the CAC | |
| L-NMMA | 0.48785 | -1.0355 | |  | | --- | | Methylarginine, an inhibitor of nitric oxide synthase; ALS relation - <https://www.mdpi.com/2073-4409/10/12/3554/pdf> | |
| N-acetylglucosamine 1/6-phosphate | 0.49429 | -1.0166 | |  | | --- | | component of aminosugar metabolism; GlcNAc + phosphate; indirect synthesis from glucose | |
| cystathionine | 0.49441 | -1.0162 | |  | | --- | | intermediate in the synthesis of cysteine | |
| F6P / G1P / G6P | 0.49544 | -1.0132 | |  | | --- | | glycolysis;  ND relation: <https://www.mdpi.com/1422-0067/22/11/5887/htm> | |
| homoserine / threonine / allothreonine | 2.0067 | 1.0048 | |  | | --- | | amino acid used in biosynthesis of proteins; threonine is converted to pyruvate via threonine dehydrogenase | |
| 3- / 4-hydroxyphenylacetic acid | 2.0675 | 1.0479 |  |
| F1P | 2.166 | 1.115 | |  | | --- | | glycolysis | |
| acetylcholine+ | 2.2108 | 1.1446 | |  | | --- | | excitatory in Drosophila;  ALS relation - <https://doi.org/10.1111/j.1365-2583.1994.tb00141.x> | |
| guanosine | 2.3226 | 1.2158 | |  | | --- | | purine nucleoside; can be phosphorylated --> GMP, cGMP, GDP, GTP; itself is required for RNA splicing;  ALS relation - DOI: 10.3389/fncel.2014.00282 | |
| orotic acid | 2.5479 | 1.3493 | |  | | --- | | pyrimidinemonocarboxylic acid that is a uracil bearing a carboxy substituent at posion C-6; synthesized by a mitochondrial enzyme OR a cytoplasmic enzyme of pyrimidine synthesis pathway | |
| hydroxyphenyllactic acid / HVA | 4.5414 | 2.1832 | |  | | --- | |  | | hydroxyphenyllactic acid is a tyrosine metabolite - high in patients with PKU; dopamine is converted to HVA | |
| guanine | 6.9339 | 2.7937 | |  | | --- | | pyrimidine-imidazole ring; ALS-relation - <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4159981/> | |
| deoxyuridine | 9.4844 | 3.2456 | |  | | --- | | pyrimidine nucleoside | |
| dADP | 15.31 | 3.9364 | |  | | --- | | nucleoside diphosphate | |
| cysteine-S-sulfate | 18.326 | 4.1958 | |  | | --- | | receptor agonist | |
| deoxyguanosine | 22.991 | 4.523 | |  | | --- | | purine nucleobase; ALS relation - <https://pubmed.ncbi.nlm.nih.gov/18344116/> | |
| dAMP | 25.591 | 4.6776 | |  | | --- | | ALS relation - <https://www.frontiersin.org/articles/10.3389/fphar.2021.672182/full> | |
| deoxyinosine | 28.903 | 4.8531 | |  | | --- | | purine | |

 ANOVAs:

GREEN metabolites are upregulated in G85R vs silent

**NOT RESCUED**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **f.value** | **p.value** | **WT vs G diff?** | **Rescued by OE-Tkt** | **Rescued by Tkt-Df** | **Rescued by both OE-Tkt and Tkt-Df** |
| **uric acid** | 276.3 | 2.46E-11 | YES | NO | NO | NO |
| **b-alanine** | 39.783 | 1.64E-06 | YES | NO | NO | NO |
| **nicotinamide riboside+** | 36.67 | 2.54E-06 | YES | NO | NO | NO |
| **xanthine** | 36.186 | 2.73E-06 | YES | NO | NO | NO |
| **deoxycarnitine+** | 30.886 | 6.33E-06 | YES | NO | NO | NO |
| **deoxyguanosine** | 24.292 | 2.20E-05 | YES | NO | NO | NO |
| **NMN** | 21.205 | 4.35E-05 | YES | NO | NO | NO |
| **deoxyinosine** | 20.84 | 4.75E-05 | YES | NO | NO | NO |
| **dAMP** | 18.627 | 8.24E-05 | YES | NO | NO | NO |
| **guanine** | 18.588 | 8.33E-05 | YES | NO | NO | NO |
| **phosphorylcholine+** | 15.511 | 0.00019769 | YES | NO | NO | NO |
| **3-phospho-serine** | 11.15 | 0.00087372 | YES | NO | NO | NO |
| **acrylic acid** | 8.4833 | 0.0027025 | YES | NO | NO | NO |
| **3-hydroxykynurenine** | 7.1967 | 0.0050756 | YES | NO | NO | NO |
| **cytidine** | 7.0377 | 0.0055126 | YES | NO | NO | NO |
|  |  |  |  |  |  |  |
| **dADP** | 10.595 | 0.0010868 | YES | NO | ENHANCED DEFECT | NO |
|  |  |  |  |  |  |  |
| **agmatine** | 46.579 | 6.93E-07 | NO | ENHANCED DEFECT | ENHANCED DEFECT | N/A |
| **dehydroascorbic acid** | 7.7881 | 0.0037682 | NO | N/A | ENHANCED DEFECT | N/A |
| **2-aminobutanoate / 2-/3-aminoisobutanoate** | 7.647 | 0.0040405 | NO | N/A | ENHANCED DEFECT | N/A |
| **D-sedoheptulose** | 7.5216 | 0.0043017 | NO | ENHANCED DEFECT | ENHANCED DEFECT | N/A |

**RESCUED BY OE-TKT**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | f.value | p.value | **WT vs G diff?** | **Rescued by OE-Tkt** | **Rescued by Tkt-Df** | **Rescued by both OE-Tkt and Tkt-Df** |
| **homoserine / threonine / allothreonine** | 36.009 | 2.80E-06 | YES | YES | NO | NO |
| **glutamine** | 23.462 | 2.62E-05 | YES | YES | NO | NO |
| **pyrroline hydroxycarboxylic acid** | 19.779 | 6.15E-05 | YES | YES | NO | NO |
|  |  |  |  |  |  |  |
| **asparagine** | 11.125 | 0.00088203 | YES | YES | ENHANCED DEFECT | NO |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| **glycine** | 13.4 | 0.00038784 | YES | TREND | NO | NO |
| **N-acetylaspartic acid** | 11.837 | 0.00067376 | YES | TREND | NO | NO |
| **2-oxoadipic acid** | 9.0879 | 0.0020525 | YES | TREND | NO | NO |
|  |  |  |  |  |  |  |
| **AICA ribonucleotide** | 9.1995 | 0.0019535 | YES | TREND | ENHANCED DEFECT | NO |

**RESCUED BY TKT-Df/+**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | f.value | p.value | **WT vs G diff?** | **Rescued by OE-Tkt** | **Rescued by Tkt-Df** | **Rescued by both OE-Tkt and Tkt-Df** |
| **dCMP** | 19.874 | 6.00E-05 | YES | NO | YES | NO |
| **N-acetylaspartic acid** | 12.002 | 0.00063395 | YES | NO | YES | NO |
| **D-ribose-1/5-phosphate / D-ribulose 5-phosphate** | 7.1545 | 0.0051873 | YES | NO | YES | NO |
|  |  |  |  |  |  |  |
| **N-acetyl-L-glutamic acid** | 12.56 | 0.00051857 | YES | ENHANCED DEFECT | YES | NO |

**RESCUED BY BOTH**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | f.value | p.value | **WT vs G diff?** | **Rescued by OE-Tkt** | **Rescued by Tkt-Df** | **Rescued by both OE-Tkt and Tkt-Df** |
| **hydroxyphenyllactic acid / HVA** | 10.976 | 0.00093491 | YES | TREND | TREND | TREND |
| **guanosine** | 7.7069 | 0.0039222 | YES | TREND | TREND | TREND |