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| |  | | --- | | to me, Ram, Yuliya | | | |

Hi Kristi,

NMN and NAD are down.

So I would definitely do a NMN rescue. If that works then we can think of genetic rescues as well.  Let’s chat in April.

Cheers

Nav

C= Cha-Gal4/+; silent/silent

E= Cha-Gal4/+; G85Rcr/G85Rcr

A= Cha-Gal4/+; UAS-Tkt-silent/silent

F= Cha-Gal4/+; UAS-Tkt-G85Rcr/G85Rcr

B= Cha-Gal4/+; Df-8143(tkt) silent/silent

D= Cha-Gal4/+; Df-8143(tkt) G85Rcr/G85Rcr

Chart

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C= Cha-Gal4/+; silent/silent

E= Cha-Gal4/+; G85Rcr/G85Rcr

A= Cha-Gal4/+; UAS-Tkt-silent/silent

F= Cha-Gal4/+; UAS-Tkt-G85Rcr/G85Rcr

B= Cha-Gal4/+; Df-8143(tkt) silent/silent

D= Cha-Gal4/+; Df-8143(tkt) G85Rcr/G85Rcr

I ran some comparisons yesterday.  What do you think about the changes in purine metabolism?





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| |  | | --- | | **Ram Prosad Chakrabarty** | | Mar 27, 2022, 10:26 AM |  |  |
| |  | | --- | | to me, Yuliya, Navdeep | | | |

Several intermediates of purine metabolism (e.g., inosine, guanine, deoxyguanosine, dAMP, dADP, and deoxyinosine) are upregulated in pathogenic genotypes D, E, and F, and the end products of purine breakdown (e.g., xanthine, uric acid) are downregulated in pathogenic genotypes D, E, and F (you can see that from heatmap). That's why the purine metabolism pathway came up as significant in pathway analysis.

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| |  | | --- | | **Navdeep Chandel** | | Mar 27, 2022, 1:18 PM |  |  |
| |  | | --- | | to Ram, me, Yuliya | | | |

Purine metabolism might be just a reflection of trying to maintain those pools.

Key is to find way to intervene and test causality between metabolic changes and your phenotypes.

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| |  | | --- | | **Nemtsova, Yuliya** | | Mar 28, 2022, 10:46 AM |  |  |
| |  | | --- | | to Ram, me, Navdeep | | | |

Hi all,

This is great!! So cool to see metabolites changing as expected based on tkt manipulation. There are also some metabolites in the mutant genotypes that are down, which we are able to rescue with genetic suppressors, so that's great for better understanding mechanisms of rescue.

Ram, thank you for the detailed step-by-step analysis, it was very helpful. For some reason, I wasn't getting the last four metabolites that you have on the list as significant, not sure why that is, but other than that everything looks the same.

Another interesting outcome when only looking at foldchange - Cha>G85R vs Cha>sil is that RNA-synthesis substrates were down (CTP, UTP, GTP, etc.), while lots of DNA-synthesis nucleotides were up (dAM/DP, others mentioned above). Interesting to further explore, since RNA-dysregulation has been well studied in ALS pathology.

Looking forward to the discussion!

Best,

Julia