Rapid Identification of New Biomarkers for the Classification of GM1 Type 2 Gangliosidosis using an Unbiased ¹H NMR-Linked Metabolomics Strategy

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SUPPLEMENTARY MATERIALS

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Section S1: Scientific Literature Data Available on the Maximal Blood Plasma Concentrations of Drugs Received by the GM1T2 Patient Cohort

These values are: miglustat, *ca.* 10 µmol./L [S1]; valproate, *ca.* 1.0 mmol./L [S2]; clonidine, sub-µmol./L [S3]; lamotrigine, *ca.* 5 µmol./L [S4]; tolperisone, *ca.* 0.5 µmol./L [S5]; levetiracetam, *ca.* 300-400 µmol./L [S6]; albuterol sulphate, sub-µmol./L [S7]; lamotrigine, *ca.* 5 µmol./L [S8]; cyclopentolate, sub-µmol./L [S9]; and diazepam, approaching 10 µmol./L [S10].

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Supplementary Materials Table

Table S1. Tabular representation of dysfunctional PMS enzymes, and metabolite transport and transfer processes indicated for involvement in GM1T2 pathology. Clearly, BCAA catabolism represents a major feature of the pathogenesis of this disease.

Enzyme/Process	Total	Hits	Q	FDR p	Pathway
	Compounds		Statistic	value	
2-Oxoisovalerate	2	1	80.32	7.35 x 10 ⁻¹³	BCAA degradation
dehydrogenase					0
(acylating: 3-methyl-					
2-oxobutanoate),					
mitochondrial					
3-Amino-isobutyrate	2	1	80.32	7.35 x 10 ⁻¹³	BCAA degradation
transport					
3-Amino-isobutyrate	2	1	80.32	7.35 x 10 ⁻¹³	BCAA degradation
transport,					
mitochondrial					
3-Hydroxyacyl-CoA	2	1	80.32	7.35 x 10 ⁻¹³	Butanoate metabolism
dehydratase (3-					
hydroxyisobutyryl-					
CoA) (mitochondria)					
3-	2	1	80.32	7.35 x 10 ⁻¹³	BCAA degradation
Hydroxyisobutyrate					
dehydrogenase,					
mitochondrial					
3-Hydroxyisobutyryl-	2	1	80.32	7.35 x 10 ⁻¹³	BCAA degradation/ β -Alanine
CoA hydrolase,					metabolism/Propanoate
mitochondrial	-				metabolism
Acyl-CoA	2	1	80.32	7.35 x 10 ⁻¹³	First stage of FA metabolism
dehydrogenase					
(isobutyryl-CoA),					
mitochondrial	2	1	00.22	7.25 10.13	
L-3-Amino-	2	1	80.32	$/.35 \ge 10^{-13}$	BCAA degradation
isobutanoate					
exchange	2	1	20.22	7.25 - 10.13	DCAA des redation
L-J-	2	1	80.32	7.35 X 10 ⁻¹⁵	BCAA degradation
transaminaso					
mitochondrial					
Malopate	2	1	80.32	7.35×10^{-13}	Inosital metabolism / Alanine
semialdebyde	2	1	00.52	7.55 X 10	and Aspartate metabolism $/\beta_{-}$
dehvdrogenase					Alapine
(acetylating)					metabolism/Propanoate
mitochondrial					metabolism
Methylmalonate-	2	1	80.32	7.35 x 10 ⁻¹³	Inositol metabolism/BCAA
semialdehyde	=			1.00 A 10	degradation/Propanoate
dehydrogenase					metabolism.
Methylmalonyl-CoA	8	1	25.86	0.012	Degradation of odd-chain FAs.
mutase					valine, isoleucine, methionine,
					threonine and cholesterol.

					Funneling of metabolites arising from these amino acids into the TCA cycle.
Propionyl-CoA carboxylase, mitochondrial	8	1	25.86	0.012	Propionyl CoA (PCoA) is the end- product of metabolism of odd-chain FAs, and a methyl- branched FA metabolite.
					PCoA is a major valine metabolite, and along with acetyl-CoA, is also a metabolite of isoleucine and methionine.