Title: The schizophrenia risk locus in *SLC39A8* alters brain metal transport and plasma glycosylation

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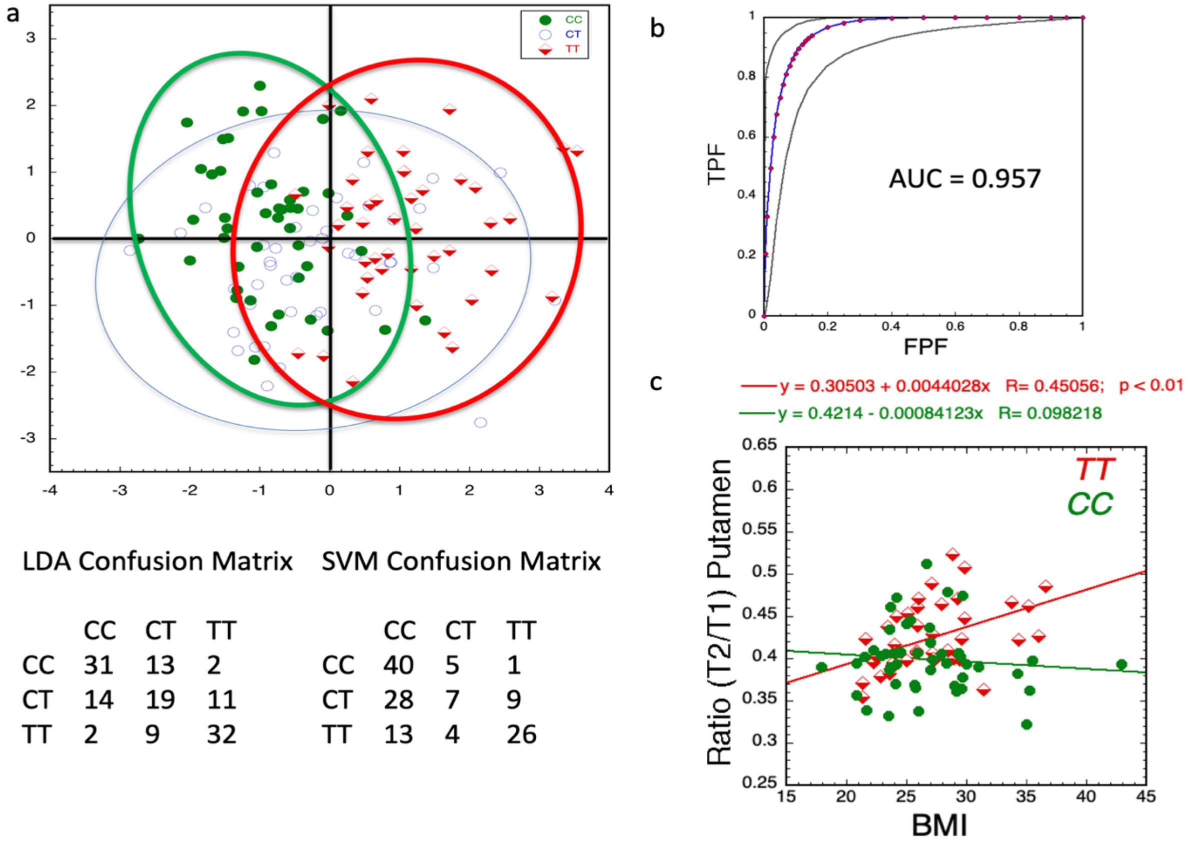


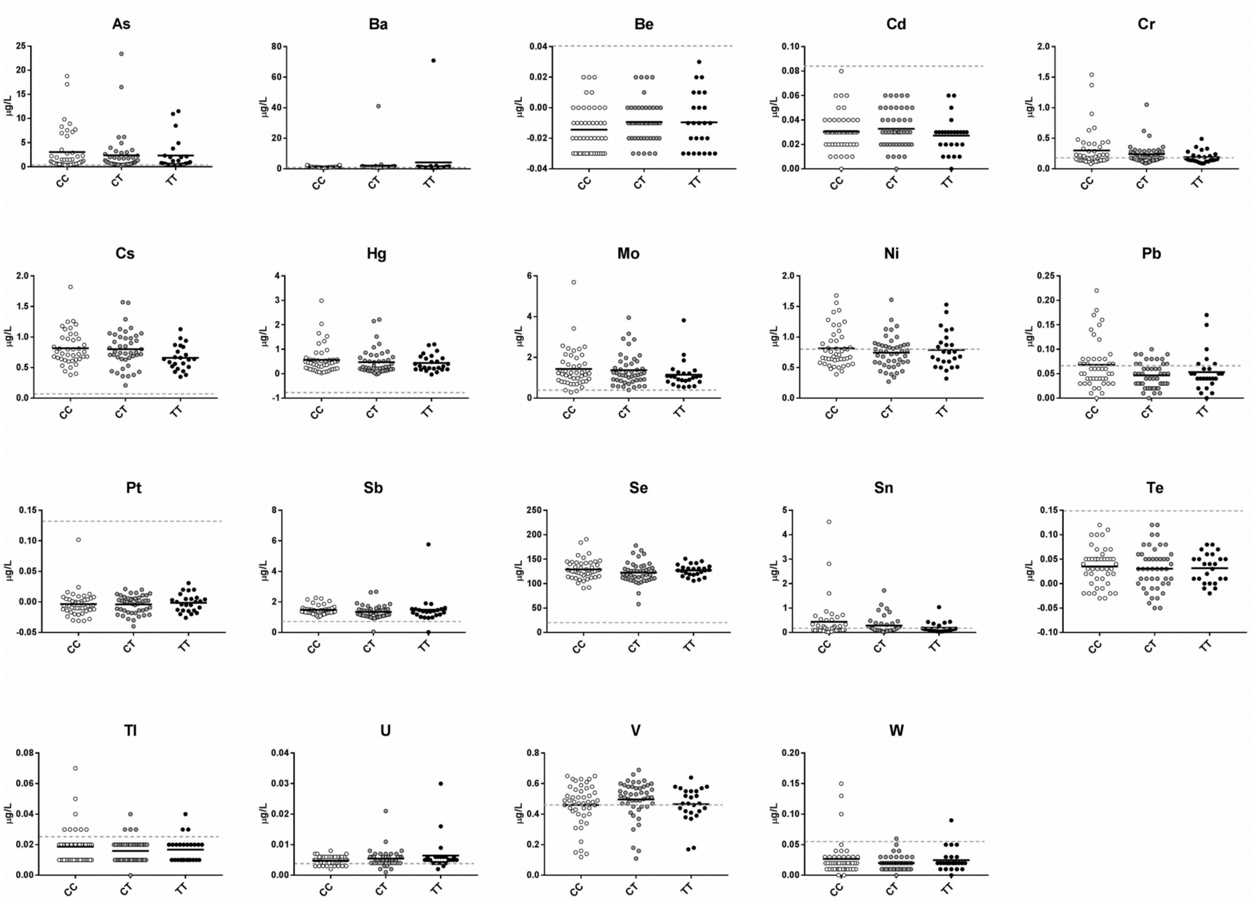
LDA Confusion Matrix

	CC	CT	TT
CC	31	13	2
CT	14	19	11
TT	2	9	32

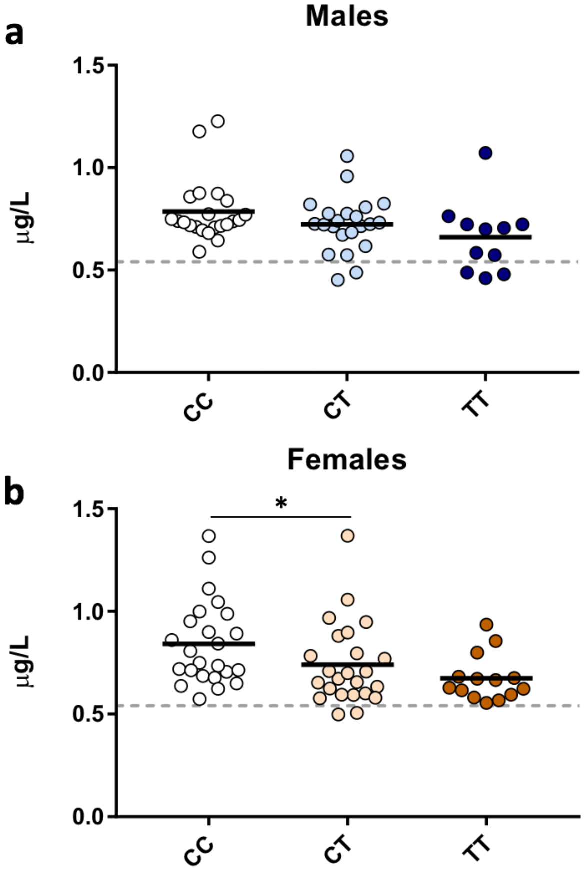
SVM Confusion Matrix

	CC	CT	TT
CC	40	5	1
CT	28	7	9
TT	13	4	26

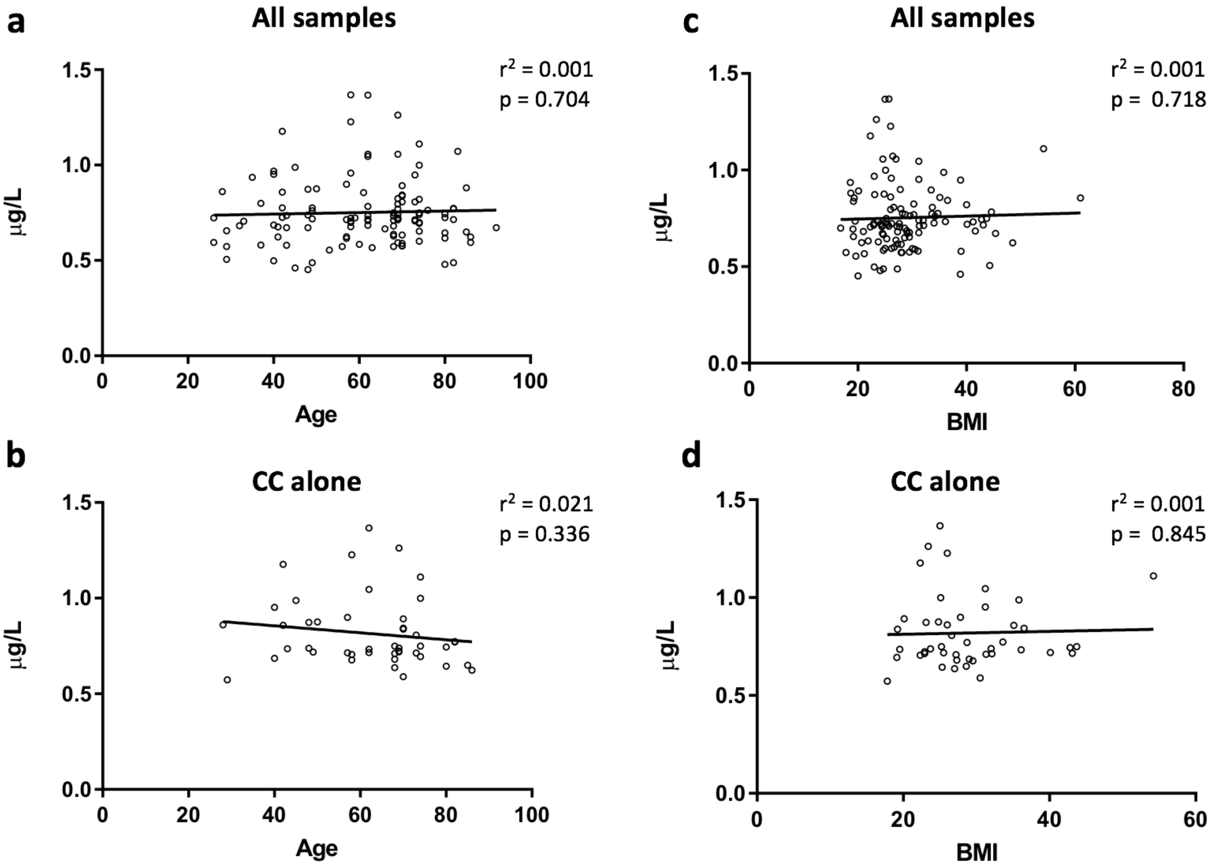
Supplementary Figure 1. **Use of MRI T2w/T1w data to classify by rs13107325 genotype.** A) Linear discriminant analysis (LDA) generated using the T2w/T1w ratio data in GPi, SN and LPut (three feature variables). There is excellent separation in along the primary axis between CC and TT genotypes, the CT carriers are spread out over the entire range (91% of the variance explained by axis one; separation along axis 2 was not significant by Wilk's lambda). We also performed support vector machines (SVM) classification with similar results as the LDA as seen in the confusion matrices using holdout analysis. B) ROC curve for binary classification between TT and CC carriers using the LDA classification. The area under the curve is 0.957 using only the three feature variables. C) We performed regression analyses using all the demographic data and the MRI data. TPF - True Positive Fraction; FPF - False Positve Fraction. The only significant effect was seen in the putamen which manifested a significant correlation with BMI (R = 0.45; p<0.01). The correlation between BMI and putamen for CC and CT carriers was not significant. CC n = 46, CT n = 44, TT n = 43.



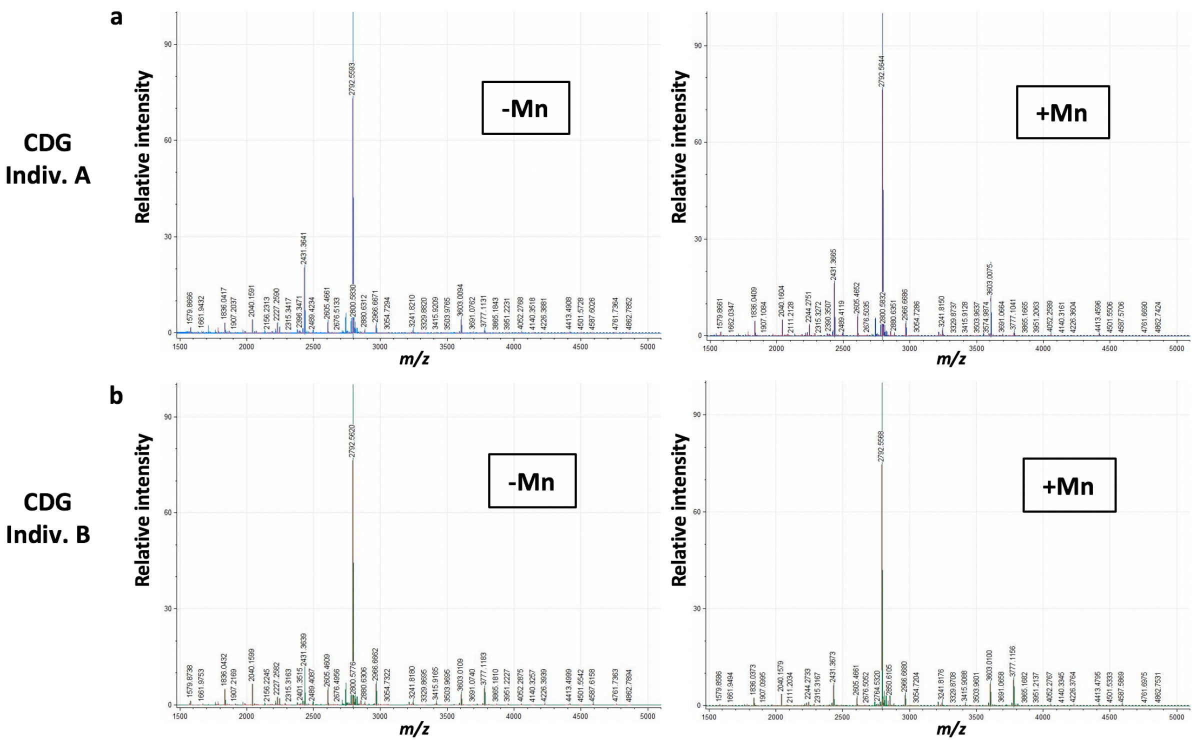
Supplementary Figure 2. **rs13107325 genotype has no effect on trace elements concentrations determined by ICP-MS except for Mn.** Data shown for each individual with black horizontal line representing mean for group. Method Detection Limit (MDL) shown as grey dashed line on each graph. (CC n = 46, CT n = 46, TT n = 25). *p-value <0.05, **p-value <0.01, ***p-value <0.001.



Supplementary Figure 3. **Serum Mn concentrations are similar in males and females based on rs13107325 genotype**. **a,** Males. **b,** Females. Data shown for each individual with black horizontal line representing mean for group. Method Detection Limit (MDL) shown as grey dashed line on each graph. (Males: CC n = 22, CT n = 22, TT n = 11) (Females: CC n = 24, CT n = 24, TT n = 14). *p-value <0.05, **p-value <0.01, ***p-value <0.001. Males: CC 0.785 μg/L vs CT 0.723 μg/L, p-value = 0.16, CC vs TT 0.661 μg/L, p-value = 0.06, CT vs TT p-value = 0.32); Females: CC 0.841 μg/L vs CT 0.740 μg/L, p-value = 0.08, CC vs TT 0.675 μg/L, p-value = 0.003, CT vs TT p-value = 0.20).



Supplementary Figure 4. **Serum Mn concentration does not correlate with age or BMI**. Linear regression of Mn concentration on age or BMI showed no significant correlation in (**a,c**) all samples or (**b,d**) CC genotype alone. Data shown for each individual result with black horizontal trend line. AGE: All samples n = 117, r^2 = 0.001, p = 0.704, Slope of best fit: 0.0004 +/- 0.0011, Slope 95% Confidence Interval: -0.0017 to 0.0025. CC Genotype n = 46, r^2 = 0.021, p = 0.336, Slope of best fit: -0.0018 +/- 0.0019, Slope 95% Confidence Interval: -0.0055 to 0.0020. BMI: All samples n = 116, r^2 = 0.001, p = 0.718, Slope of best fit: 0.0008 +/- 0.0021, Slope 95% Confidence Interval: -0.0034 to 0.0050. CC Genotype n = 46, r^2 = 0.0009, p = 0.845, Slope of best fit: 0.007 +/- 0.003, Slope 95% Confidence Interval: -0.0067 to 0.0082.



Supplementary Figure 5. Full MALDI-TOF spectra of N-glycans from severe SLC39A8 mutation carriers pre- and post- Mn supplementation. MALDI-TOF spectrum from plasma/serum of (**a**) subject A and (**b**) subject B pre- and post-Mn supplementation. X-axis scaled for m/z of 1500-5000 kd and relative signal intensity on the Y-axis.

Supplementary Tables:

UK BIOBANK	CC (n=46)	CT (n=44)	TT (n=43)
Age (SD)	61.4 (6.9)	61.3 (6.7)	61.6 (7.1)
Gender (% Female)	61%	61%	63%
BMI (SD)	26.8 (4.6)	27.1 (4.7)	27.0 (4.0)
Smoker (% Yes)	39%	39%	37%
Townsend Index (SD)	-2.1 (2.5)	-2.1 (2.4)	-2.2 (2.5)
PARTNERS BIOBANK	**CC (n=46)**	**CT (n=46)**	**TT (n=25)**
Age (SD)	62.2 (14.5)	62.2 (14.5)	54.0 (18.6)
Gender (% Female)	52%	52%	56%
BMI (SD)	28.9 (7.5)	29.2 (7.4)	26.9 (6.26)
Smoker (% Yes)	50%	46%	40%

Supplementary Table 1. Clinical comparisons between Biobank participants based on genotype.

Metal	µg/L
As	0.24
Ba	0.21
Be	0.06
Cd	0.086
Co	0.313
Cr	0.18
Cs	0.048
Cu	110
Hg	0.14
Mn	0.54
Mo	0.32
Ni	0.76
Pb	0.06
Pt	0.22
Sb	0.049
Se	14
Sn	0.12
Te	0.15
Tl	0.025
U	0.004
V	0.46
W	0.053
Zn	42

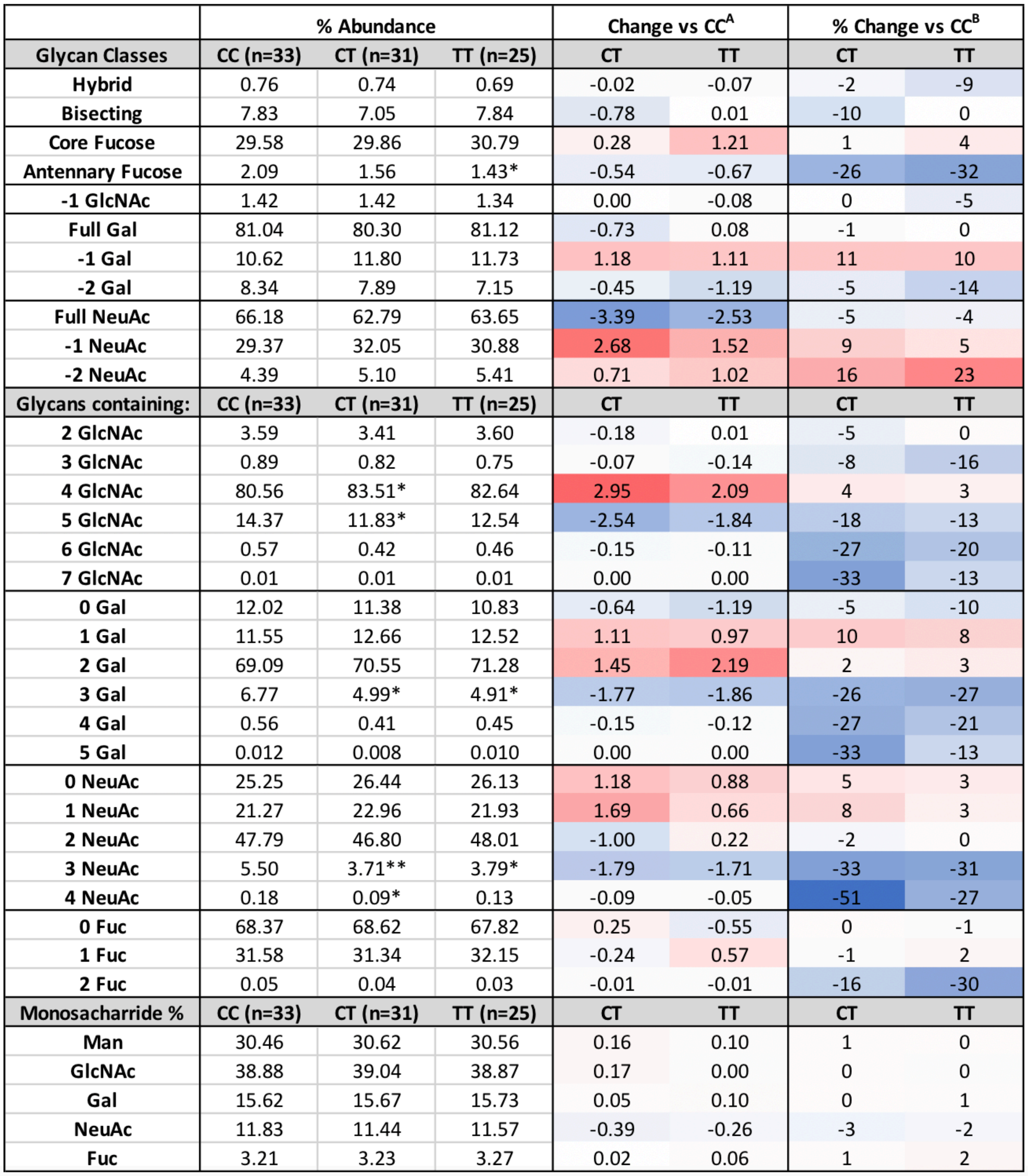
Supplementary Table 2. Serum trace element ICP-MS Method Detection Limits. Based on 7 independent runs.

Supplementary Table 3. Plasma protein N-glycan structure, name, mass, and characteristics used in study. PLEASE SEE ATTACHED EXCEL SHEET

Supplementary Table 4. Individual plasma protein N-glycan abundance based on rs13107325 genotype. #Heat maps scale: dark blue -> white -> bright red representing -50.0% -> 0 -> +50.0% for relative change. PLEASE SEE ATTACHED EXCEL SHEET

ALL	**% Abundance**			**Change vs CC^{A}**		**% Change vs CC^{B}**	
Antennarity	**CC (n=33)**	**CT (n=31)**	**TT (n=25)**	**CT**	**TT**	**CT**	**TT**
High-mannose	3.59	3.41	3.60	-0.18	0.01	-5	0
Mono-antennary	1.09	1.01	0.94	-0.08	-0.15	-7	-14
Bi-antennary	87.98	90.16**	90.09**	2.19	2.11	2	2
Tri-antennary	6.77	4.99*	4.91*	-1.77	-1.86	-26	-27
Tetra-antennary	0.57	0.42	0.46	-0.15	-0.12	-27	-20
MALE							
Antennarity	**CC (n=17)**	**CT (n=15)**	**TT (n=10)**	**CT**	**TT**	**CC vs CT**	**CC vs TT**
High-mannose	2.95	3.61	2.94	0.66	-0.01	22	0
Mono-antennary	0.96	0.96	0.94	0.01	-0.02	1	-2
Bi-antennary	87.91	90.74*	91.43	2.83	3.52	3	4
Tri-antennary	7.55	4.39**	4.28**	-3.15	-3.27	-42	-43
Tetra-antennary	0.64	0.30*	0.42	-0.34	-0.22	-53	-34
FEMALE							
Antennarity	**CC (n=16)**	**CT (n=16)**	**TT (n=12)**	**CT**	**TT**	**CC vs CT**	**CC vs TT**
High-mannose	4.27	3.23	4.07	-1.05	-0.20	-24	-5
Mono-antennary	1.24	1.06	0.95	-0.17	-0.29	-14	-24
Bi-antennary	88.05	89.62	89.14	1.58	1.09	2	1
Tri-antennary	5.94	5.55	5.36	-0.38	-0.57	-6	-10
Tetra-antennary	0.50	0.53	0.48	0.03	-0.02	5	-4

Supplementary Table 5. Gender-based sub-analysis of branching plasma protein N-glycan abundance. $^{\#}$Heat maps scale: dark blue -> white -> bright red representing -5.0-> 0 -> +5.0 for absolute abundance change. *p-value <0.05, **p-value <0.01 for % abundance of CT and TT vs CC genotype.



	% Abundance			Change vs CC[A]		% Change vs CC[B]	
Glycan Classes	**CC (n=33)**	**CT (n=31)**	**TT (n=25)**	**CT**	**TT**	**CT**	**TT**
Hybrid	0.76	0.74	0.69	-0.02	-0.07	-2	-9
Bisecting	7.83	7.05	7.84	-0.78	0.01	-10	0
Core Fucose	29.58	29.86	30.79	0.28	1.21	1	4
Antennary Fucose	2.09	1.56	1.43*	-0.54	-0.67	-26	-32
-1 GlcNAc	1.42	1.42	1.34	0.00	-0.08	0	-5
Full Gal	81.04	80.30	81.12	-0.73	0.08	-1	0
-1 Gal	10.62	11.80	11.73	1.18	1.11	11	10
-2 Gal	8.34	7.89	7.15	-0.45	-1.19	-5	-14
Full NeuAc	66.18	62.79	63.65	-3.39	-2.53	-5	-4
-1 NeuAc	29.37	32.05	30.88	2.68	1.52	9	5
-2 NeuAc	4.39	5.10	5.41	0.71	1.02	16	23
Glycans containing:	**CC (n=33)**	**CT (n=31)**	**TT (n=25)**	**CT**	**TT**	**CT**	**TT**
2 GlcNAc	3.59	3.41	3.60	-0.18	0.01	-5	0
3 GlcNAc	0.89	0.82	0.75	-0.07	-0.14	-8	-16
4 GlcNAc	80.56	83.51*	82.64	2.95	2.09	4	3
5 GlcNAc	14.37	11.83*	12.54	-2.54	-1.84	-18	-13
6 GlcNAc	0.57	0.42	0.46	-0.15	-0.11	-27	-20
7 GlcNAc	0.01	0.01	0.01	0.00	0.00	-33	-13
0 Gal	12.02	11.38	10.83	-0.64	-1.19	-5	-10
1 Gal	11.55	12.66	12.52	1.11	0.97	10	8
2 Gal	69.09	70.55	71.28	1.45	2.19	2	3
3 Gal	6.77	4.99*	4.91*	-1.77	-1.86	-26	-27
4 Gal	0.56	0.41	0.45	-0.15	-0.12	-27	-21
5 Gal	0.012	0.008	0.010	0.00	0.00	-33	-13
0 NeuAc	25.25	26.44	26.13	1.18	0.88	5	3
1 NeuAc	21.27	22.96	21.93	1.69	0.66	8	3
2 NeuAc	47.79	46.80	48.01	-1.00	0.22	-2	0
3 NeuAc	5.50	3.71**	3.79*	-1.79	-1.71	-33	-31
4 NeuAc	0.18	0.09*	0.13	-0.09	-0.05	-51	-27
0 Fuc	68.37	68.62	67.82	0.25	-0.55	0	-1
1 Fuc	31.58	31.34	32.15	-0.24	0.57	-1	2
2 Fuc	0.05	0.04	0.03	-0.01	-0.01	-16	-30
Monosacharride %	**CC (n=33)**	**CT (n=31)**	**TT (n=25)**	**CT**	**TT**	**CT**	**TT**
Man	30.46	30.62	30.56	0.16	0.10	1	0
GlcNAc	38.88	39.04	38.87	0.17	0.00	0	0
Gal	15.62	15.67	15.73	0.05	0.10	0	1
NeuAc	11.83	11.44	11.57	-0.39	-0.26	-3	-2
Fuc	3.21	3.23	3.27	0.02	0.06	1	2

Supplementary Table 6. Plasma protein N-glycan composition based on rs13107325 genotype.
[#]Heat maps scale: dark blue -> white -> bright red representing -5.0-> 0 -> +5.0 for absolute abundance change and -50.0% -> 0 -> +50.0% for relative change.

Supplementary Table 7. Individual plasma protein N-glycan abundance in severe SLC39A8 mutation carriers pre- and post-Mn supplementation. *Three masses in BOLD highlight glycans elevated in other MALDI-TOF studies of CDGs. PLEASE SEE ATTACHED EXCEL SHEET

	% Abundance				% Change + Mn[A]		Relative Change + Mn[B]	
Glycan Classes	**A**	**A + Mn**	**B**	**B + Mn**	**A + Mn**	**B + Mn**	**A + Mn**	**B + Mn**
Hybrid	0.95	0.97	0.63	0.71	0.02	0.07	2	12
Bisecting	1.10	3.90	3.26	4.35	2.80	1.10	256	34
Core Fucose	12.48	19.51	21.30	14.80	7.03	-6.50	56	-31
Antennary Fucose	0.98	1.03	4.99	7.79	0.05	2.80	5	56
-1 GlcNAc	1.91	1.03	1.44	0.48	-0.88	-0.95	-46	-66
Full Gal	90.45	90.96	88.46	93.10	0.51	4.65	1	5
-1 Gal	6.52	5.27	7.60	4.53	-1.25	-3.08	-19	-40
-2 Gal	3.03	3.77	3.94	2.37	0.74	-1.57	24	-40
Full NeuAc	73.24	73.18	77.20	83.35	-0.06	6.15	0	8
-1 NeuAc	23.73	23.06	20.14	14.55	-0.67	-5.58	-3	-28
-2 NeuAc	3.03	3.75	2.66	2.09	0.73	-0.57	24	-21
Glycans containing:	**A**	**A + Mn**	**B**	**B + Mn**	**A + Mn**	**B + Mn**	**A + Mn**	**B + Mn**
2 GlcNAc	3.76	2.39	2.28	1.31	-1.37	-0.96	-36	-42
3 GlcNAc	1.31	0.95	0.84	0.39	-0.36	-0.45	-28	-54
4 GlcNAc	88.09	81.30	84.90	78.93	-6.79	-5.97	-8	-7
5 GlcNAc	6.38	14.57	11.25	18.47	8.19	7.22	128	64
6 GlcNAc	0.46	0.78	0.72	0.89	0.32	0.16	70	22
7 GlcNAc	0.00	0.01	0.00	0.01	0.01	0.00	164	110
0 Gal	6.85	6.21	6.29	3.73	-0.64	-2.56	-9	-41
1 Gal	7.89	6.29	8.52	5.05	-1.60	-3.47	-20	-41
2 Gal	79.32	75.87	76.25	75.99	-3.45	-0.26	-4	0
3 Gal	5.48	10.84	8.22	14.35	5.36	6.13	98	75
4 Gal	0.45	0.77	0.72	0.88	0.32	0.16	70	22
5 Gal	0.00	0.01	0.00	0.01	0.01	0.00	164	110
0 NeuAc	12.99	13.34	13.59	8.58	0.35	-5.01	3	-37
1 NeuAc	23.30	19.79	16.77	11.43	-3.51	-5.34	-15	-32
2 NeuAc	59.51	57.55	62.72	66.60	-1.96	3.88	-3	6
3 NeuAc	4.10	9.03	6.63	13.02	4.94	6.39	120	96
4 NeuAc	0.11	0.29	0.29	0.37	0.18	0.08	170	29
0 Fuc	86.55	79.47	73.88	77.57	-7.09	3.69	-8	5
1 Fuc	13.43	20.53	25.96	22.28	7.09	-3.68	53	-14
2 Fuc	0.01	0.01	0.16	0.15	0.00	-0.01	-42	-4
Monosacharride %	**A**	**A + Mn**	**B**	**B + Mn**	**A + Mn**	**B + Mn**	**A + Mn**	**B + Mn**
Man	30.18	28.89	28.89	27.56	-1.29	-1.33	-4	-5
GlcNAc	37.58	37.62	37.54	37.02	0.05	-0.51	0	-1
Gal	16.92	17.21	16.79	17.61	0.29	0.82	2	5
NeuAc	13.97	14.26	14.32	15.85	0.28	1.52	2	11
Fuc	1.35	2.02	2.46	1.96	0.67	-0.49	50	-20

Supplementary Table 8. Plasma protein N-glycan composition following Mn supplementation in severe SLC39A8 mutation carriers. [#]Heat maps scale: dark blue -> white -> bright red representing -5.0-> 0 -> +5.0 for absolute abundance change and -50.0% -> 0 -> +50.0% for relative change.