Supplementary Information for

Glucuronic acid is a novel source of pentosidine, associated with schizophrenia

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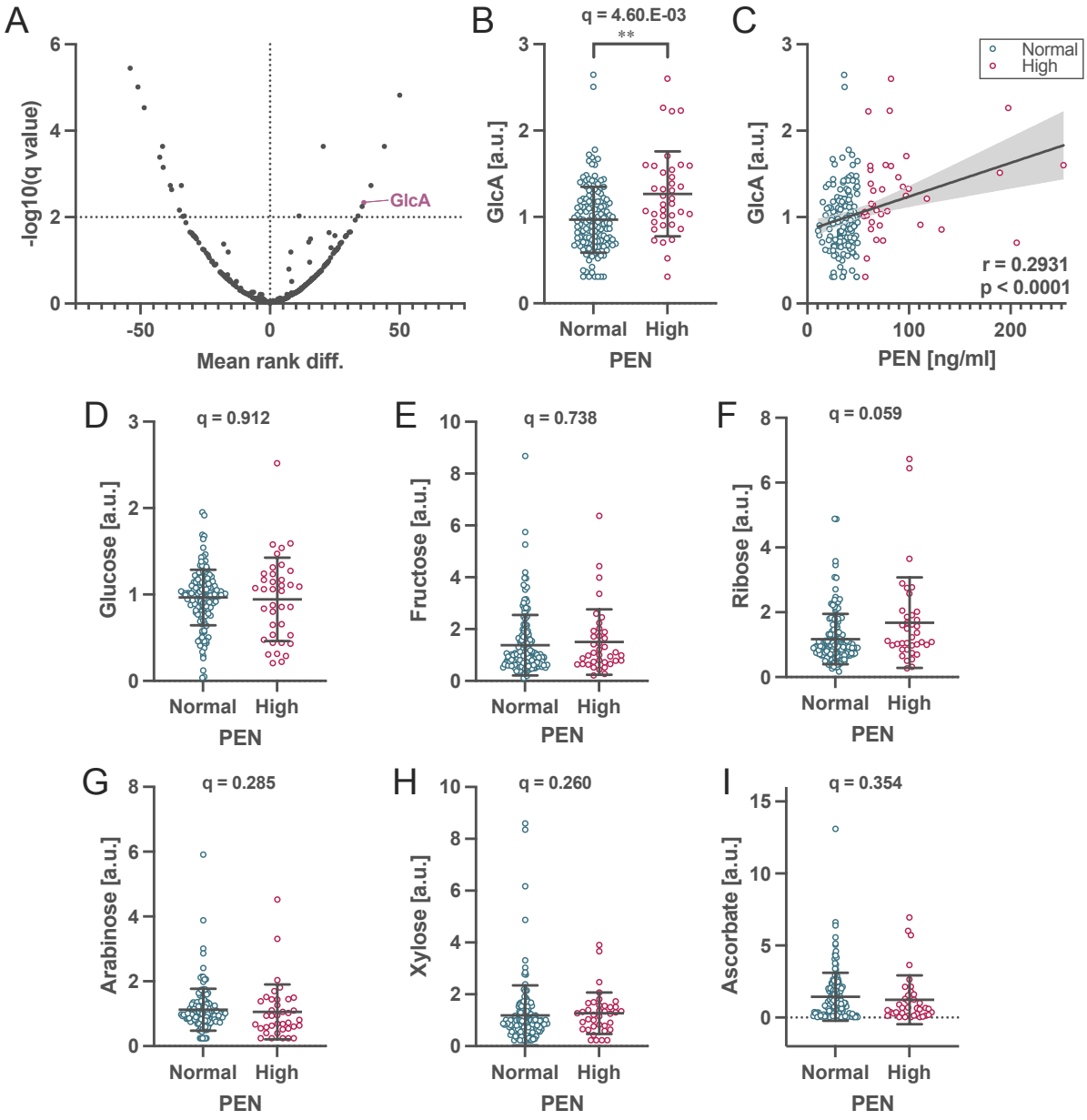
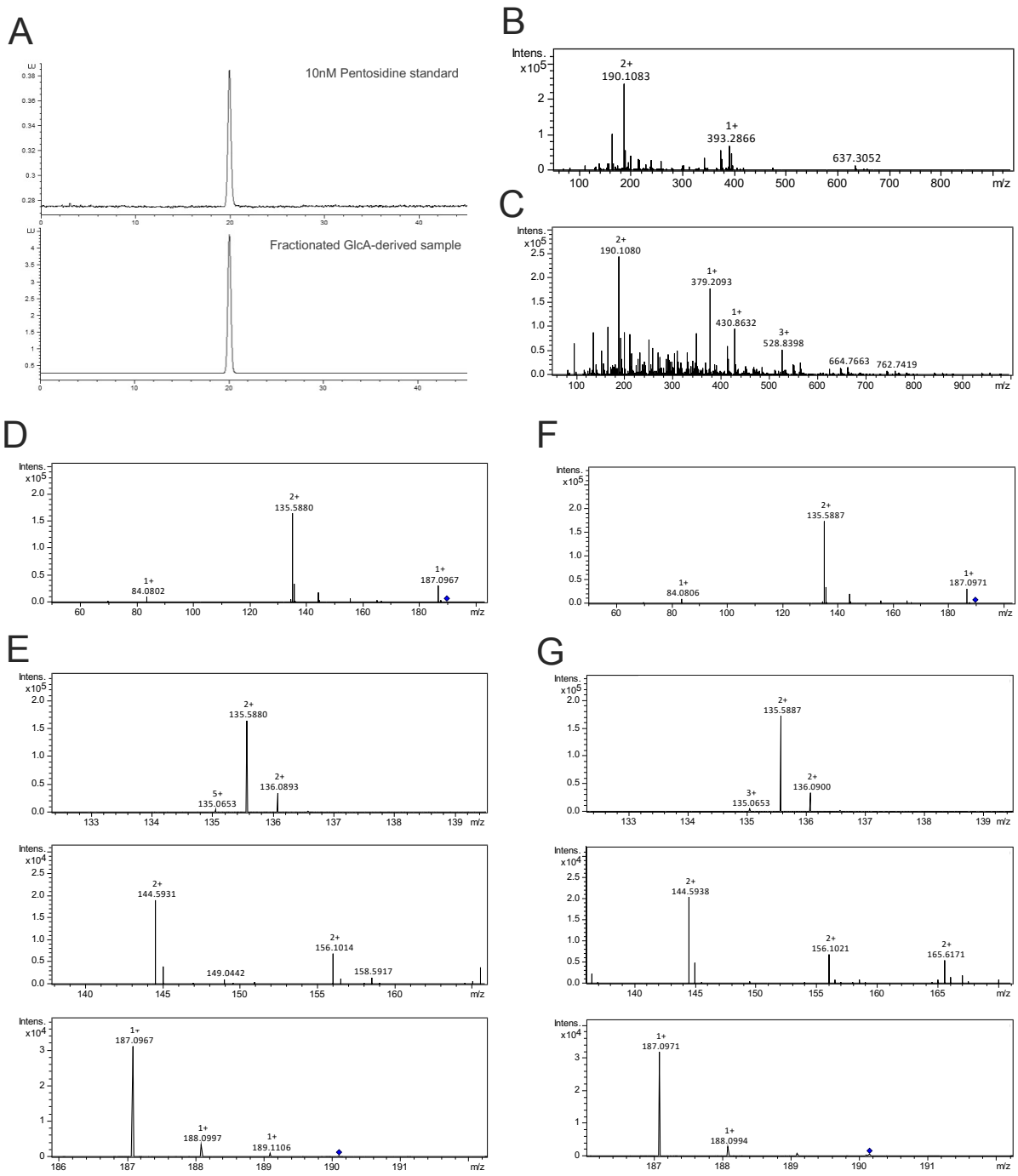
Supplementary Figures

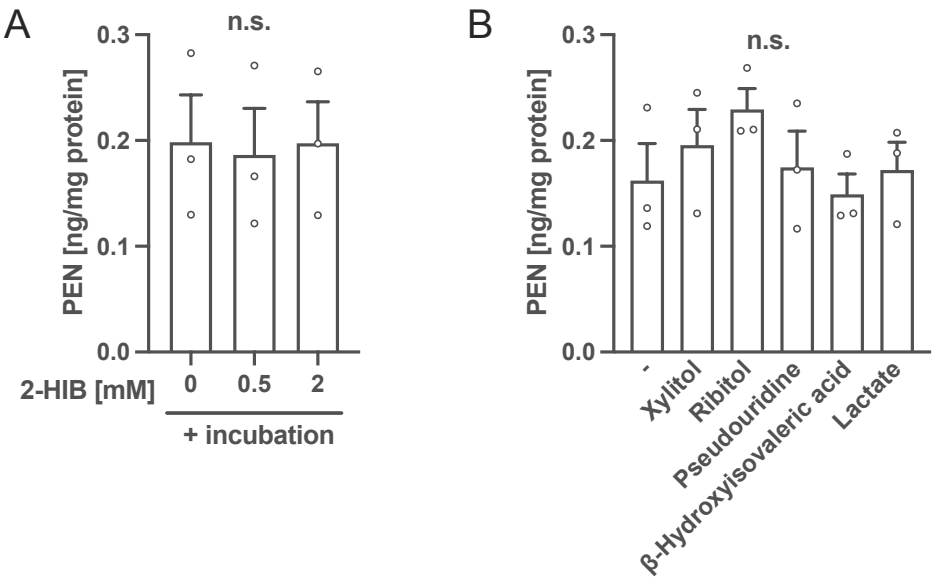


Supplementary Figure S1: Differential plasma metabolites between subjects with high and normal PEN in cohort 2

To confirm the differential plasma metabolites observed in cohort 1, metabolome analysis was performed using another independent cohort 2. (A) Volcano plot demonstrating the relationship between mean rank difference in metabolites and the FDR (i.e., the q-value) about plasma metabolites. Comparison in (B) GlcA, (D) glucose, (E) fructose, (F) ribose, (G) arabinose, (H) xylose, and (I) ascorbate between high PEN and normal PEN group. q = 4.60.E-03 using the Mann–Whitney test. The data are represented as mean ± SD. (C) Correlation between GlcA and PEN in plasma. Spearman's correlation coefficient r = 0.2931, p < 0.0001.

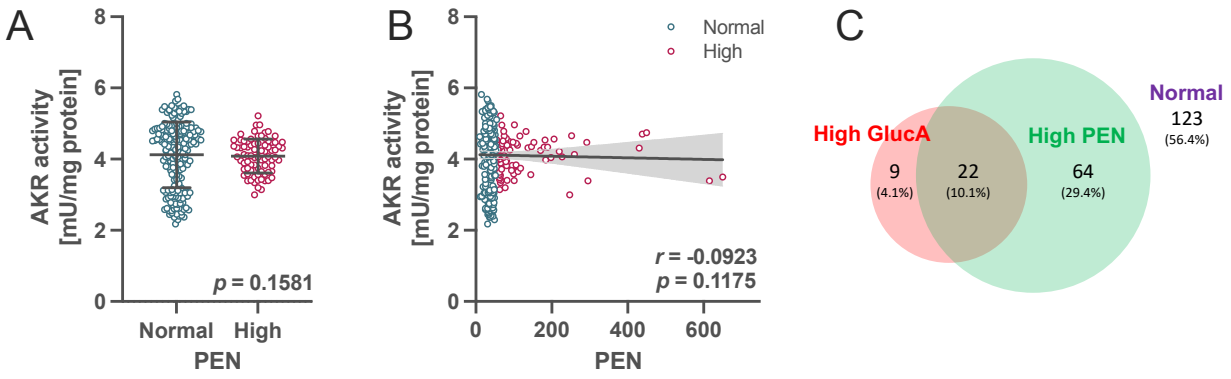


Supplementary Figure S2: Analysis of a GlcA-derived product by LC-MS/MS
(A) Chromatograms of standard PEN and fractionated GlcA-derived product synthesized by incubating GlcA with lysine and arginine. Measurement of precursor ion in (B) standard PEN and (C) the fractionated GlcA-derived product by TOF-MS. Measurement of fragment ion derived from m/z 190 in (D) standard PEN and (F) the fractionated GlcA-derived product. (E) and (G) are partially enlarged figures of (D) and (F), respectively.

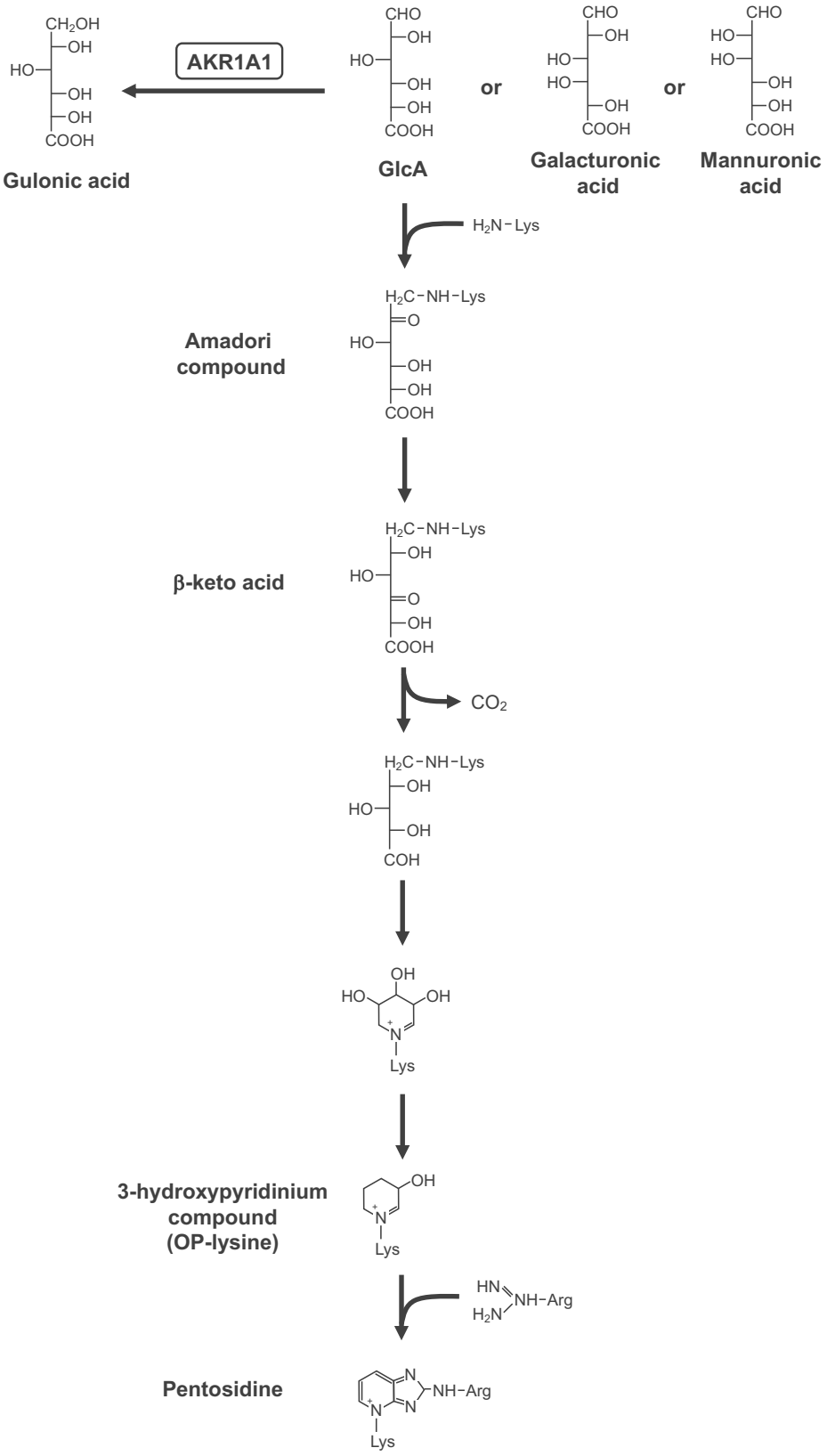


Supplementary Figure S3: PEN synthesis by incubation of metabolites upregulated in high PEN group with human plasma

Measurement of PEN in samples after incubation of (A) 2-hydroxyisobutyrate (2-HIB) at 0.5 or 2 mM dose and (B) other metabolites at 2 mM dose with human plasma. The data are presented as mean ± SEM. (A) One-way ANOVA: $F_{(2,4)} = 1.31$, $p > 0.05$, (B) One-way ANOVA: $F_{(5,12)} = 0.98$, $p > 0.05$, n.s., Tukey's test.



Supplementary Figure S4: No changes in AKR activity of high PEN group
(A) Comparison of AKR activity in whole blood cells between subjects with normal PEN and with high PEN. *p < 0.05 by Mann–Whitney test. (B) Correlation between PEN in plasma and AKR activity. Spearman's correlation coefficient r = -0.0923, p =0.11175. (C) Venn diagrams of subjects overlapped between with high GlcA and high PEN in schizophrenia are shown. The cutoff point for high plasma GlcA levels was set at 0.928 (z-score), namely, the mean + 2 SDs of healthy controls, similar to the definition of the high PEN subjects.



Supplementary Figure S5: Predicted PEN generation pathway