

## Untargeted metabolic profiling identifies interactions between Huntington's disease and neuronal manganese status

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Manganese (Mn) is an essential micronutrient for development and function of the nervous system. Deficiencies in Mn transport have been implicated in the pathogenesis of Huntington's disease (HD), an autosomal dominant neurodegenerative disorder characterized by loss of medium spiny neurons of the striatum. Brain Mn levels are highest in striatum and other basal ganglia structures, the most sensitive brain regions to Mn neurotoxicity. Mouse models of HD exhibit decreased striatal Mn accumulation and HD striatal neuron models are resistant to Mn cytotoxicity. We hypothesized that the observed modulation of Mn cellular transport is associated with compensatory metabolic responses to HD pathology. Here we use an untargeted metabolomics approach by performing ultraperformance liquid chromatography-ion mobility-mass spectrometry (UPLC-IM-MS) on control and HD immortalized mouse striatal neurons to identify metabolic disruptions under three Mn exposure conditions, low (vehicle), moderate (non-cytotoxic) and high (cytotoxic). Our analysis revealed lower metabolite levels of pantothenic acid, and glutathione (GSH) in HD striatal cells relative to control cells. HD striatal cells also exhibited lower abundance and impaired induction of isobutyryl carnitine in response to increasing Mn exposure. In addition, we observed induction of metabolites in the pentose shunt pathway in HD striatal cells after high Mn exposure. These findings provide metabolic evidence of an interaction between the HD genotype and biologically relevant levels of Mn in a striatal cell model with known HD by Mn exposure interactions. The metabolic phenotypes detected support existing hypotheses that changes in energetic processes underlie the pathobiology of both HD and Mn neurotoxicity.

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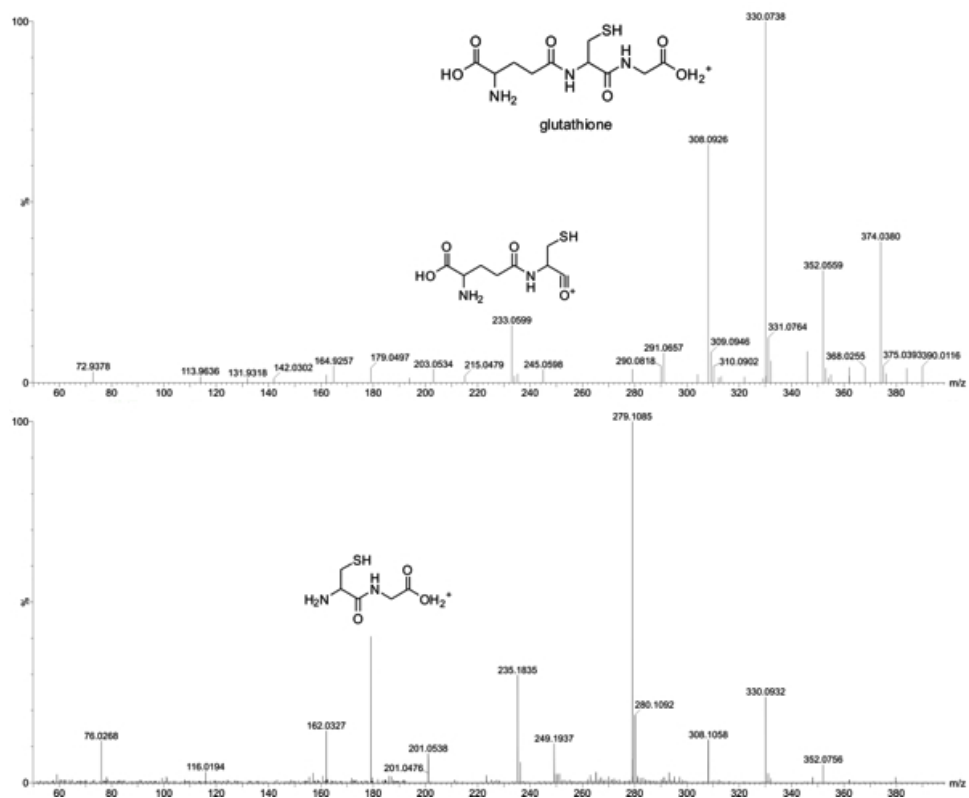
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# SUPPLEMENTAL

**Table S1.** Measured accurate masses for metabolite identifications.

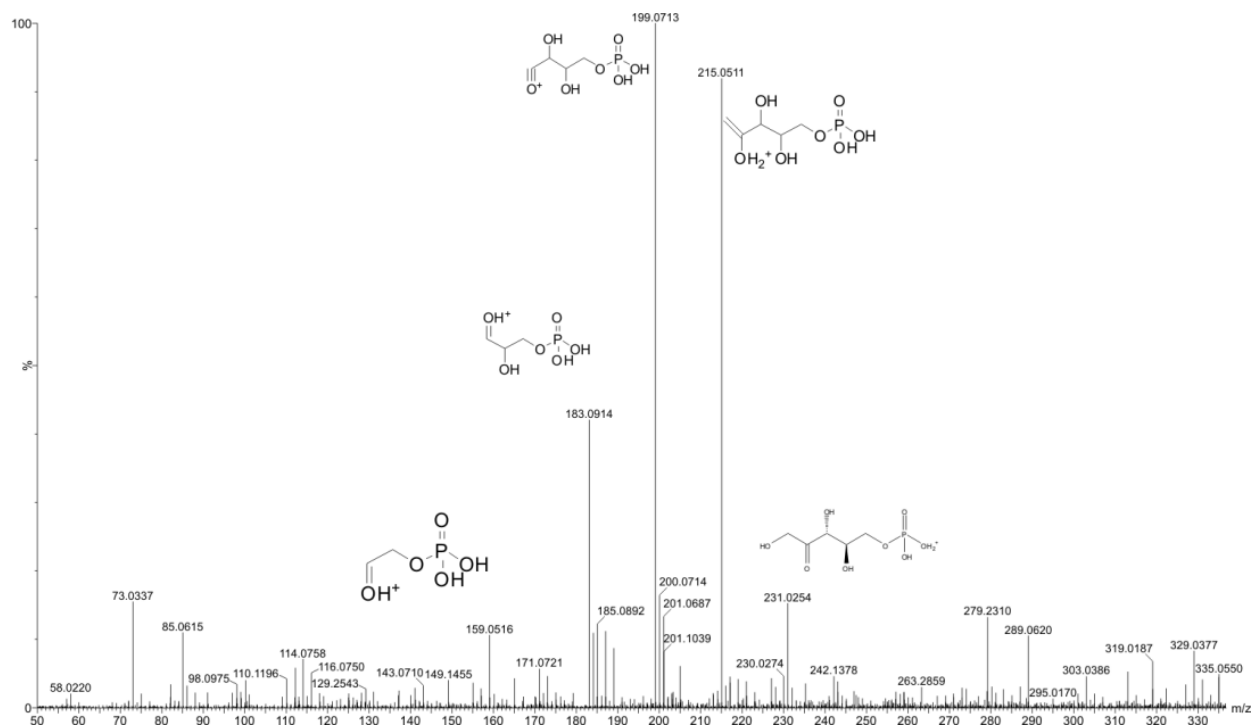
Metabolite	Measured Mass	Mass Accuracy (ppm)
Isobutyryl carnitine	232.153	6.0
Ribulose 5-phosphate	231.0254	4.3
Glutathione	308.0926	4.9
Pantothenic acid	220.1192	5.9

# SUPPLEMENTAL



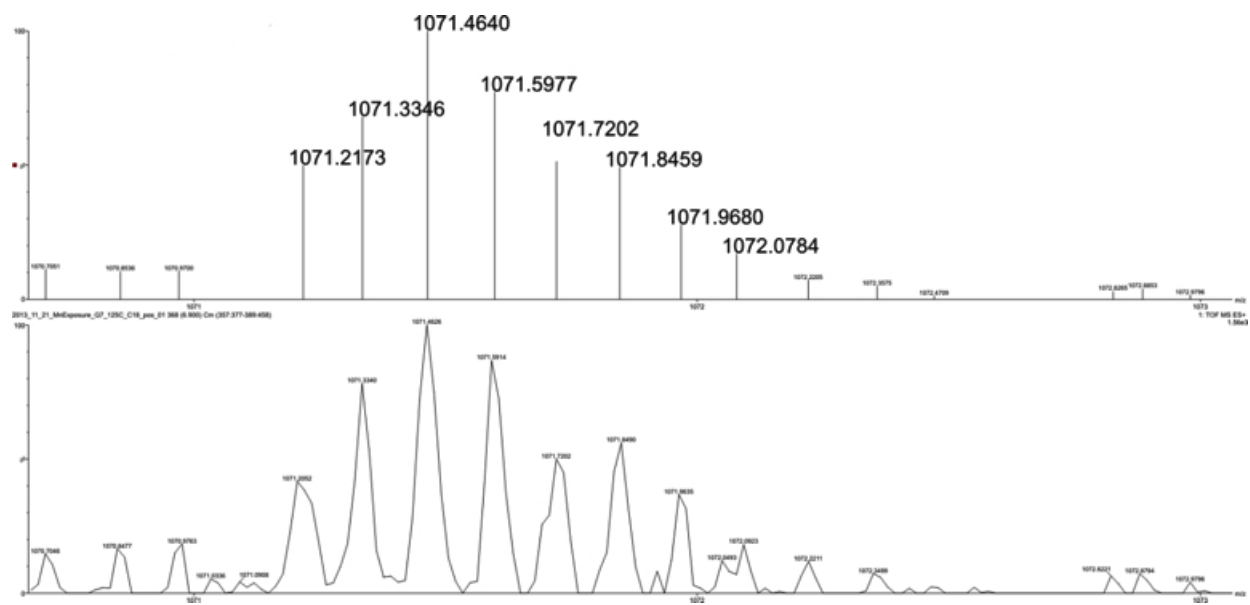
**Figure S1.** Intact (above) and mobility-selected fragmentation spectra for glutathione.

# SUPPLEMENTAL



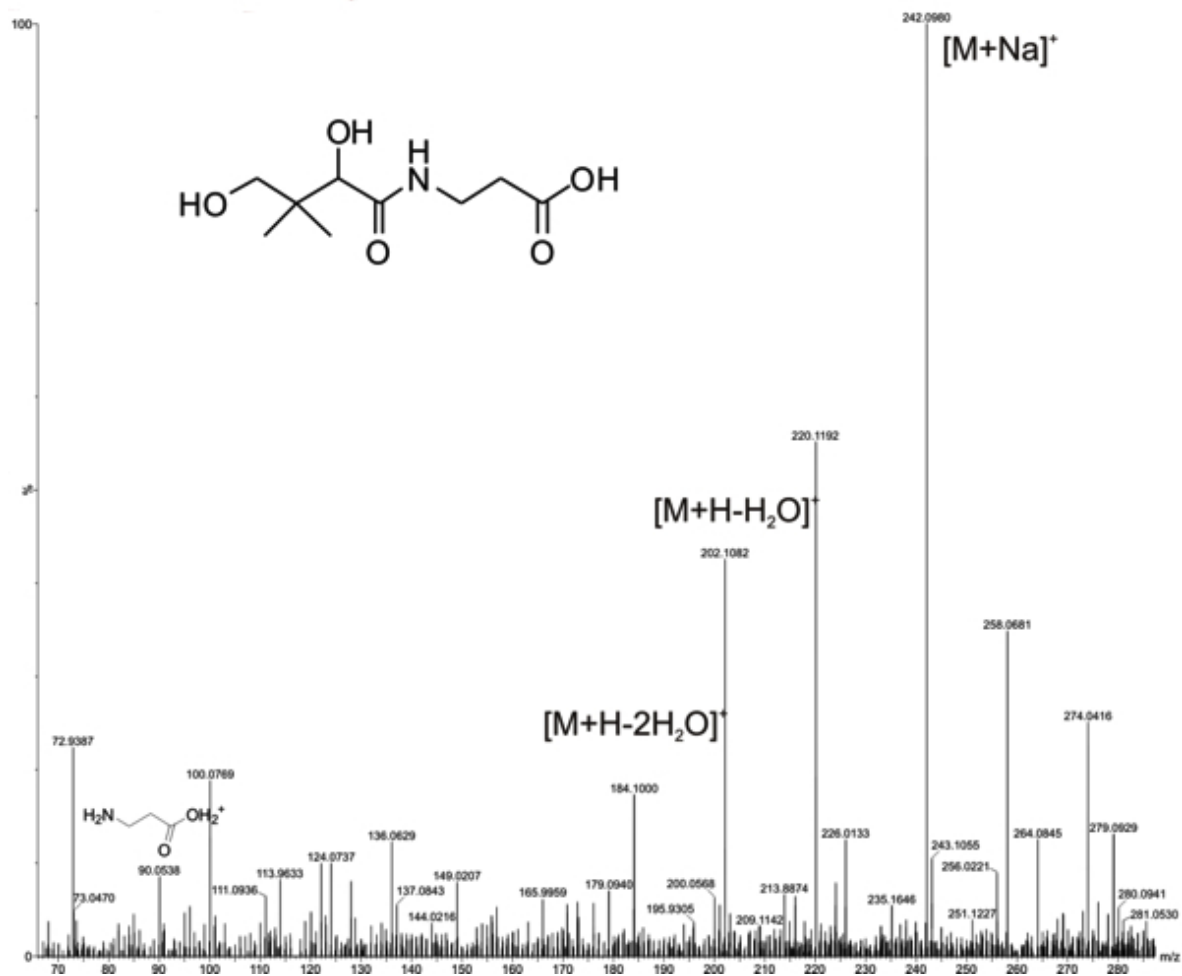
**Figure S2.** Fragmentation spectra for ribulose 5-phosphate.

# SUPPLEMENTAL



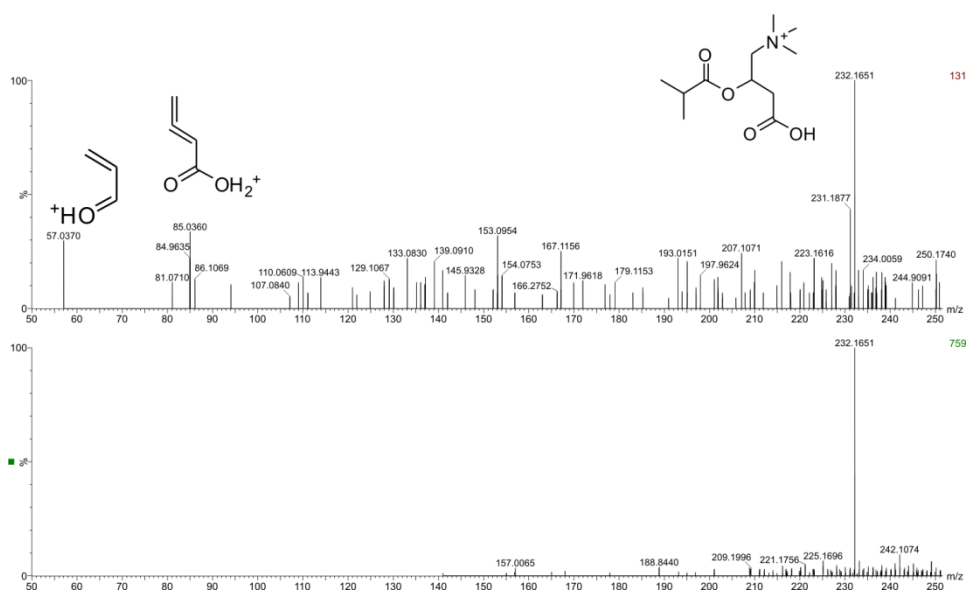
**Figure S3.** Isotopic envelope suggesting ubiquitin identification.

# SUPPLEMENTAL



**Figure S4.** Pantothenic acid fragmentation spectrum.

# SUPPLEMENTAL



**Figure S5.** Mobility-selected high (above) and low (below) energy spectra for isobutyryl carnitine.