

Metallic Dysfunction Across Huntington's Heart And Brain In Mice And Humans

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BACKGROUND



Huntington's disease is an autosomal dominant genetic disease that affects motor and cognitive function, affecting movement and memory as well as speech, emotional regulation, and sleep

Cardiovascular symptoms are common in Huntington's disease, affecting ≥50% of individuals

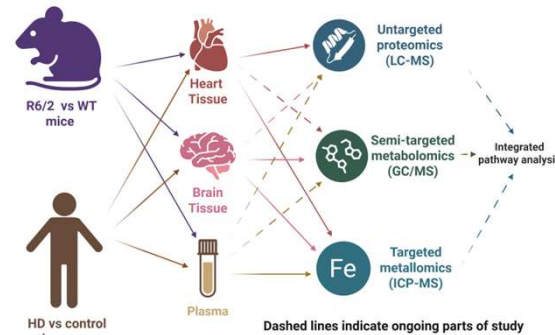


Heart failure is the second most common recorded cause of death in Huntington's

Very little research conducted into why this might be—this study aims to address this gap in knowledge



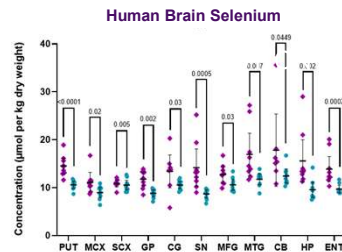
METHODS



KEY FINDINGS

- Essential metal dyshomeostasis is present throughout the HD heart and brain, but not in the plasma, indicating localised disruptions
- Patterns of metallic dysfunction are only partially replicated in the R6/2 HD mouse model heart and plasma; patterns differ in the brain
- HD human heart proteomics also indicates changes in proteins with metallic cofactors
- Next steps: proteomics in human brain and metabolomics in human heart

BRAIN & PLASMA METALS



Graph shows means±95%CI. Case-control differences determined by multiple Mann-Whitney U test. N = 9 HD cases vs 9 controls.

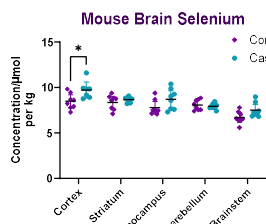
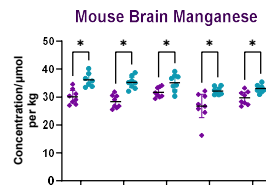
Full published
human metal
results available
online



In contrast, the R6/2 mouse brain (8 R6/2 vs 8 WT) showed differing patterns of metallic dysfunction, including localised decreases in manganese and copper, widespread increases in zinc, widespread increases in manganese and iron, and interestingly, increased Se only in the cortex.

As in the human plasma, R6/2 mouse plasma (n=8 vs 8) showed no significant case-control differences.

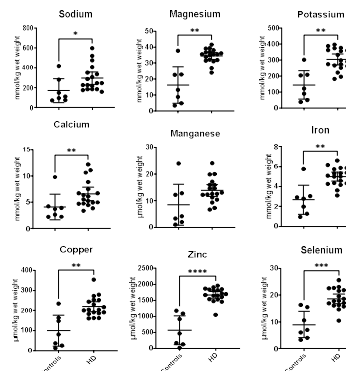
HD brains (n=9) showed several statistically significant changes compared to controls (n=9), including localised increases in calcium and zinc, localised decreases in manganese, iron, and copper, widespread increases in the sodium:potassium ratio, and most strikingly, decreased selenium across all eleven investigated brain regions. HD plasma (n=30 vs 30) showed no significant case-control differences.



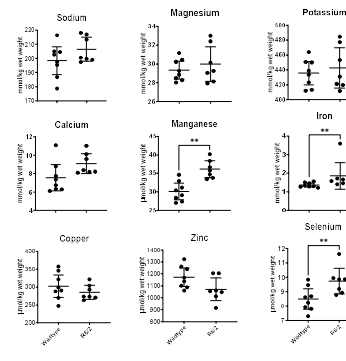
Graphs show means±95%CI. Case-control differences determined by multiple Mann-Whitney U test. N = 8 R6/2 mice vs 8 WT mice. * P<0.05.

HEART METALS

Human Heart Metals



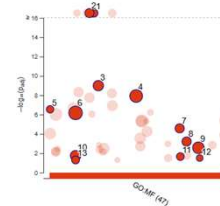
R6/2 Mouse Heart Metals



Graphs show means±95%CI. Case-control differences determined by multiple Mann-Whitney U test. N = 7 HD cases vs 21 controls and 8 R6/2 mice vs 8 WT mice, respectively. * P<0.05; ** P<0.01; *** P<0.001; **** P<0.0001.

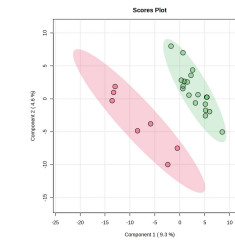
HUMAN HEART PROTEOMICS

Top Altered Pathways by Molecular Function (MF)

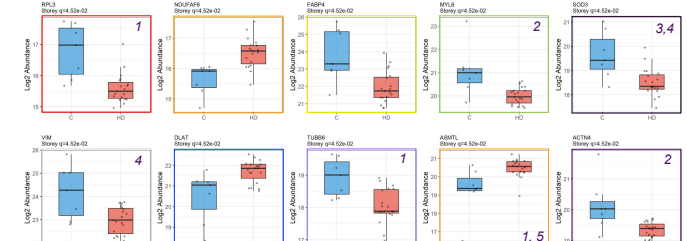


ID	Source	Term ID	Term Name	Padj (qval, 1)
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2	GO:MF	GO:0015078	proton transmembrane transporter activity	2.52E-10
3	GO:MF	GO:0016481	oxidoreductase activity	1.08E-10
4	GO:MF	GO:0036094	small molecule binding	1.79E-10
5	GO:MF	GO:0001146	microfilament motor activity	2.61E-10
6	GO:MF	GO:0005115	protein binding	4.64E-10
7	GO:MF	GO:0015015	actin filament binding	5.01E-10
8	GO:MF	GO:0011334	peptidase regulator activity	6.01E-10
9	GO:MF	GO:0073767	carbohydrate derivative binding	2.68E-10
10	GO:MF	GO:0005509	calcium ion binding	1.79E-10
11	GO:MF	GO:0011387	NaCl binding	1.79E-10
12	GO:MF	GO:0096841	cadherin binding involved in cell-cell adhesion	1.79E-10
13	GO:MF	GO:0005507	copper ion binding	6.90E-10

Good separation by PLS-DA



Top 10 Differentiated Proteins



KNOWN METALLIC COFACTORS: 1 – Magnesium, 2 – Calcium, 3 – Zinc, 4 – Copper, 5 – Manganese