HD Phenocopy Diseases Share Dysregulated Genes with HD

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ABSTRACT

Miriam Heiman's lab used translating ribosome affinity purification (TRAP) to separate striatal medium spiny neurons (MSNs) in HD mice from other brain cell types, collected RNA-seq data on the nuclei (Lee H et al., 2020), and made the data publicly available in GEO (GSE152058). The availability of gene expression data on these purified cell types, the cells most vulnerable to HD, allows us to examine whether genes known to cause HD phenocopy diseases like HDL2 or FTD-ALS are also dysregulated in HD MSNs. Schneider et al. (2016) published a list of these phenocopy diseases and their causative or associated genes. 8 of the genes were found in the HD-dysregulated MSNs, including the genes for HD, HDL1, HDL2, FTD-ALS, neuroferritinopathy, ADCY5-associated chorea, chorea-acanthocytosis, and FRRSL1-mediated chorea. We hypothesize that dysregulation of these genes all damage the proper behavior of MSNs, suggesting a mechanism that could explain the similarities in these diseases.

OBJECTIVE

Can genes dysregulated in striatal MSNs in HD explain the similarities between multiple HD phenocopy diseases?

METHODS

RNA-seq data was collected on 6-month-old male mice with Htt Q lengths of Q20 (control), Q50, Q111, Q170, or Q175, with 9 to 10 replicates in each Q length group. Differential expression was performed between each of the disease-range Q lengths compared to Q20. The significance criterion was an adjusted p-value less than 0.05. Two types of MSNs were isolated: dopamine D1 receptor neurons (expressing Drd1, labeled D1 in the results) and dopamine D2 receptor neurons (expressing Drd2, labeled D2). The differential expression results were searched to find the 20 gene symbols in the Schneider paper (2016).

REFERENCES

1. Lee H et al., *Neuron* 2020, 107:891-908.
2. Schneider SA et al., *Movement Disorders Clinical Practice* 2016, 3:342-354.

RESULTS

This is the list of HD phenocopy diseases and genes compiled by Schneider et al. (2016). Gene symbols have been updated. (TBP1 is now TBP; FTL1 is now FTL; and TITF1 is now NKX2-1.)

Condition	Synonym	Gene
HD		HTT
HDL1		PRNP
HDL2		JPH3
HDL4	SCA17	TBP
Spinocerebellar ataxias, i.e, SCA1, SCA2, SCA3, SCA8, SCA12		
DRPLA	NOD, HRS	ATN1
C9orf72 repeat expansions	Typically associated with FTD-ALS	C9orf72
Neuroferritinopathy		FTL
Benign hereditary chorea	Thyroid-lung syndrome	NKX2-1
Benign hereditary chorea, type 2		-
ADCY5-associated chorea	Familial dyskinesia with facial myokymia	ADCY5
Primary familial brain calcification	Idiopathic basal ganglia calcification, Fahr's disease	SLC20A2
		PDGFRB
		PDGFB
		XPR1
Chorea-acanthocytosis	Levine-Critchley syndrome	VPS13A
McLeod syndrome		XK
HDL3		-
RNF216-mediated neurodegeneration		RNF216)
FRRS1L-mediated chorea		FRRS1L
Wilson disease	Hepatolenticular degeneration	ATP7B
Ataxia telangiectsia	ATM syndrome	ATM
Aceruloplasminemia		CP

The log2 fold changes for these 20 genes are shown below in bold text if they were significantly changed in the disease-range Q lengths or are shown as gray "NA"s if they were never significant.

Mouse Gene	D1 Q175	D1 Q170	D1 Q111	D1 Q50	D2 Q175	D2 Q170	D2 Q111	D2 Q50
Htt	**-1.48**	**-1.61**	**-1.50**	-1.16	1.10	-1.08	**-1.33**	-1.07
Prnp	**1.54**	**1.37**	**1.25**	1.09	NA	NA	NA	NA
Jph3	**-1.24**	**-1.17**	**-1.12**	-1.02	**-1.37**	**-1.44**	-1.18	-1.21
Tbp	NA	NA	NA	NA	NA	NA	NA	NA
Atn1	NA	NA	NA	NA	NA	NA	NA	NA
C9orf72	NA	NA	NA	NA	1.33	**1.48**	1.50	1.18
Ftl1	NA	NA	NA	NA	1.39	**1.54**	1.31	-1.08
Nkx2-1	NA	NA	NA	NA	NA	NA	NA	NA
Adcy5	**-1.66**	**-1.77**	**-1.21**	1.07	**-2.07**	**-2.02**	**-1.51**	-1.09
Slc20a2	NA	NA	NA	NA	NA	NA	NA	NA
Pdgfrb	NA	NA	NA	NA	NA	NA	NA	NA
Pdgfb	NA	NA	NA	NA	NA	NA	NA	NA
Xpr1	NA	NA	NA	NA	NA	NA	NA	NA
Vps13a	NA	NA	NA	NA	**1.52**	1.02	1.35	-1.04
Xk	NA	NA	NA	NA	NA	NA	NA	NA
Rnf216	NA	NA	NA	NA	NA	NA	NA	NA
Frrs1l	NA	NA	NA	NA	-1.19	**-1.34**	-1.11	1.01
Atp7b	NA	NA	NA	NA	NA	NA	NA	NA
Atm	NA	NA	NA	NA	NA	NA	NA	NA
Cp	NA	NA	NA	NA	NA	NA	NA	NA

CONCLUSIONS

Mutant Htt was found to dysregulate the expression of 8 out of 20 genes associated with HD phenocopy diseases. These include genes that cause or are associated with HD (Htt), HDL1 (Prnp), HDL2 (Jph3), FTD-ALS (C9orf72), neuroferritinopathy (Ftl1), ADCY5-associated chorea (Adcy5), chorea-acanthocytosis (Vps13a), and FRRSL1-mediated chorea (Frrsl1). This suggests that some genetic mechanisms are shared between HD and the other diseases.