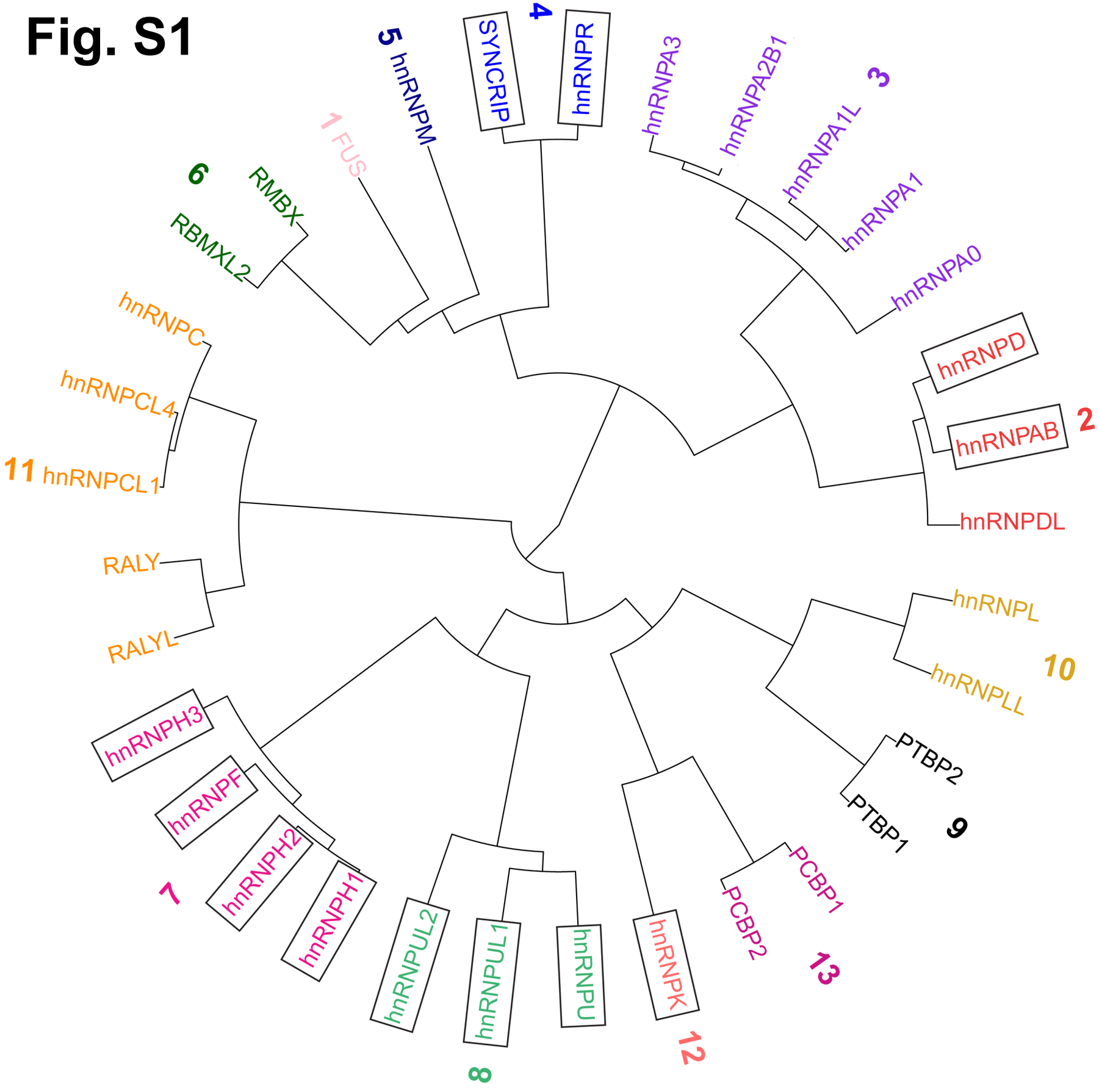
Fig. S1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5
hnRNPM
1
FUS
6
RMBX
RBMXL2
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3
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hnRNPC
hnRNPCL4
11
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RALY
RALYL
hnRNPD
hnRNPAB
2
hnRNPDL
hnRNPL
10
hnRNPLL
PTBP2
PTBP1
9
PCBP1
PCBP2
13
hnRNPK
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8
hnRNPH1
hnRNPH2
hnRNPF
hnRNPH3
7

Fig. S2

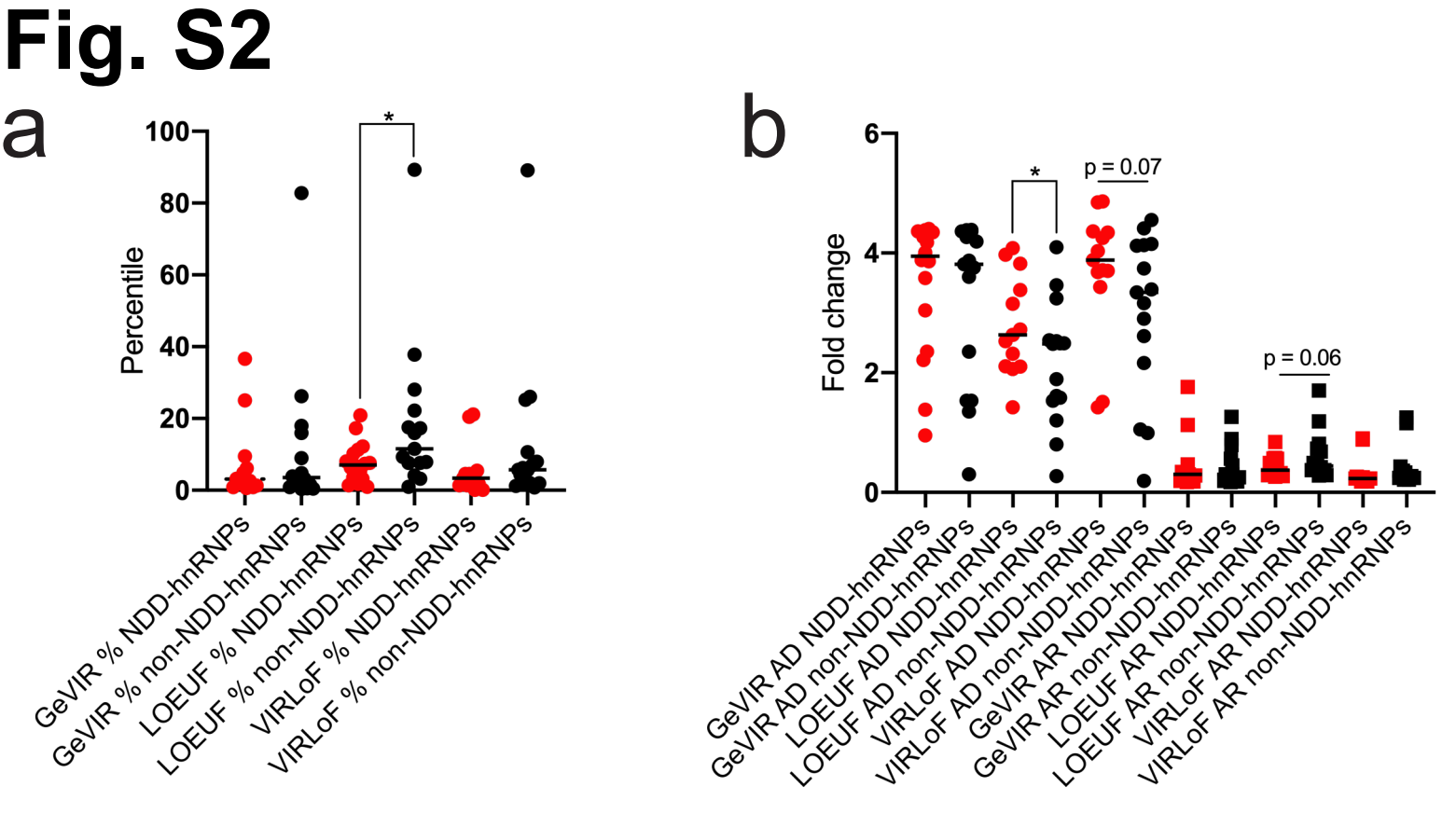
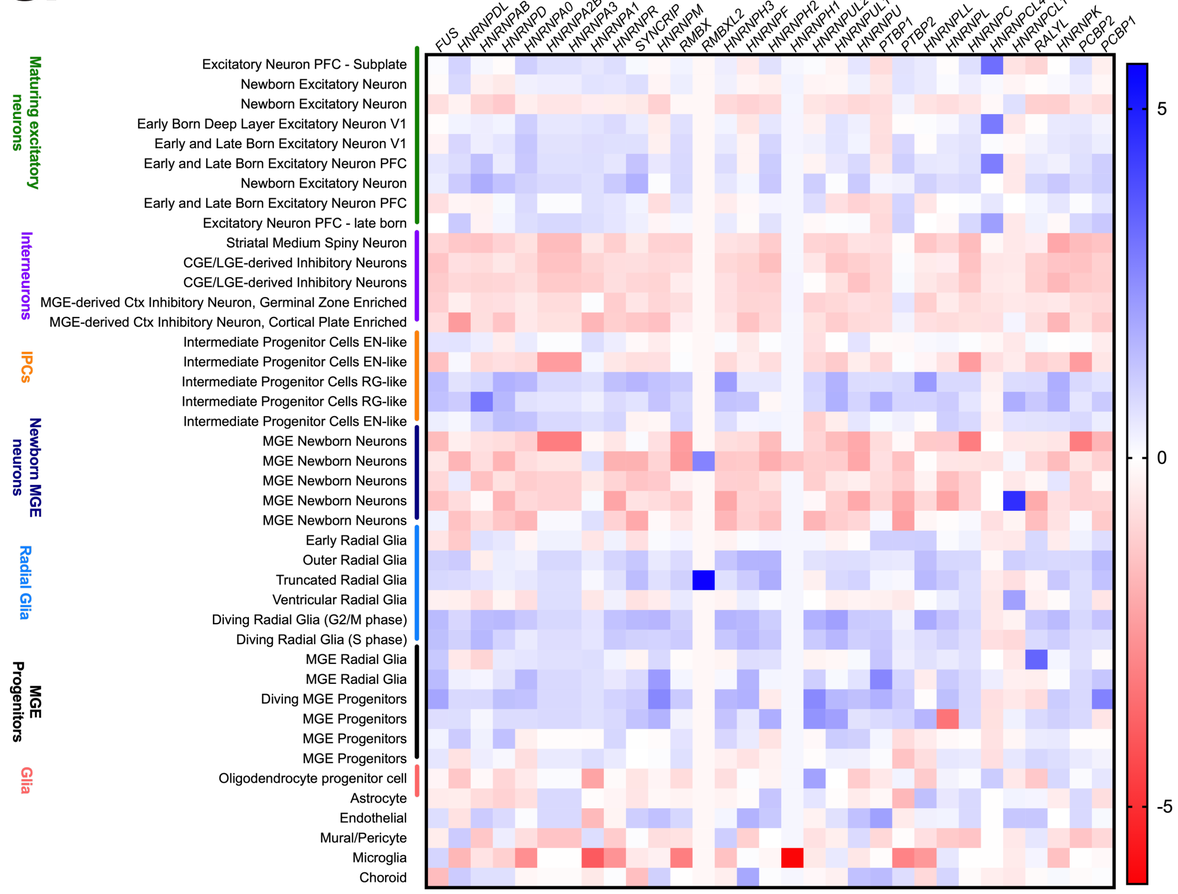

a
Percentile
100
80
60
40
20
0
*
GeVIR % NDD-hnRNPs
GeVIR % non-NDD-hnRNPs
LOEUF % NDD-hnRNPs
LOEUF % non-NDD-hnRNPs
VIRLoF % NDD-hnRNPs
VIRLoF % non-NDD-hnRNPs
b
Fold change
6
4
2
0
*
p = 0.07
p = 0.06
GeVIR AD NDD-hnRNPs
GeVIR AD non-NDD-hnRNPs
LOEUF AD NDD-hnRNPs
LOEUF AD non-NDD-hnRNPs
VIRLoF AD NDD-hnRNPs
VIRLoF AD non-NDD-hnRNPs
GeVIR AR NDD-hnRNPs
GeVIR AR non-NDD-hnRNPs
LOEUF AR NDD-hnRNPs
LOEUF AR non-NDD-hnRNPs
VIRLoF AR NDD-hnRNPs
VIRLoF AR non-NDD-hnRNPs

Fig. S3

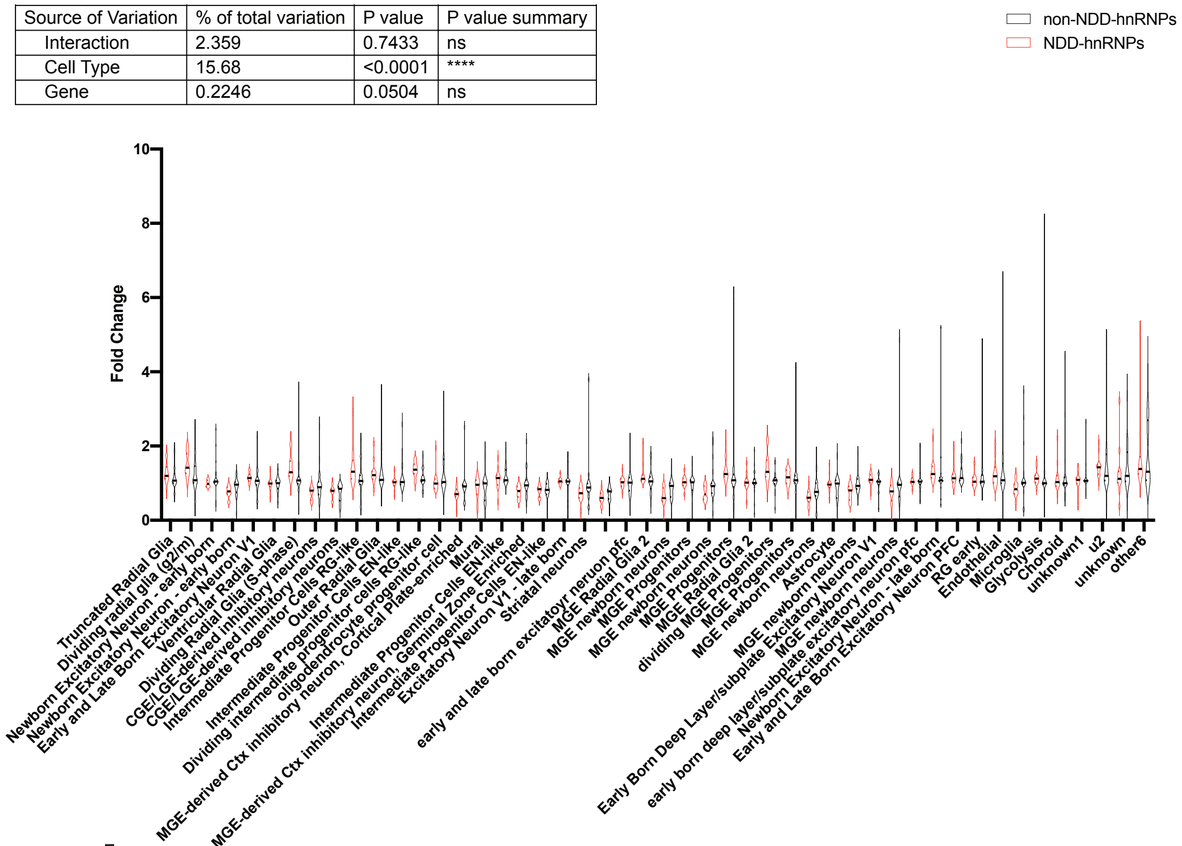
a



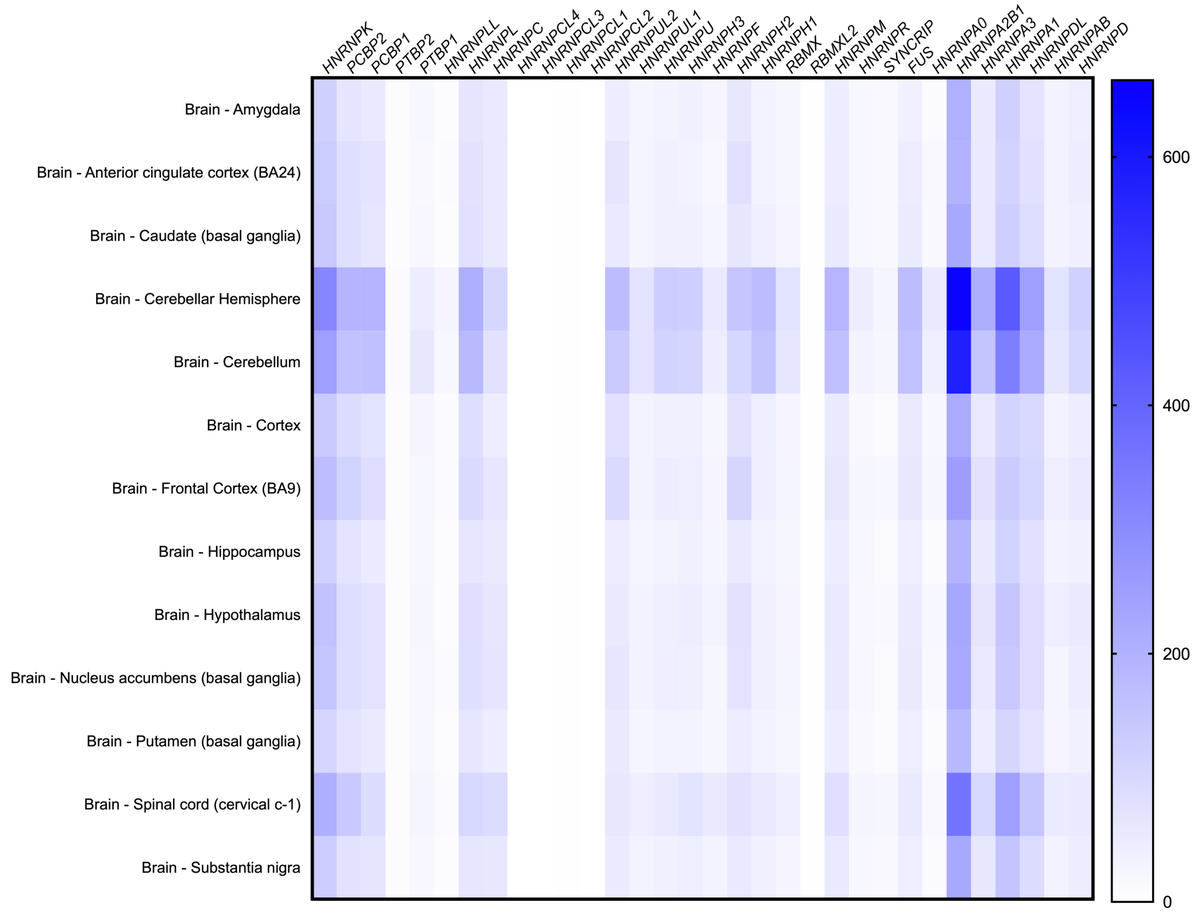
b

Two-way ANOVA statistics

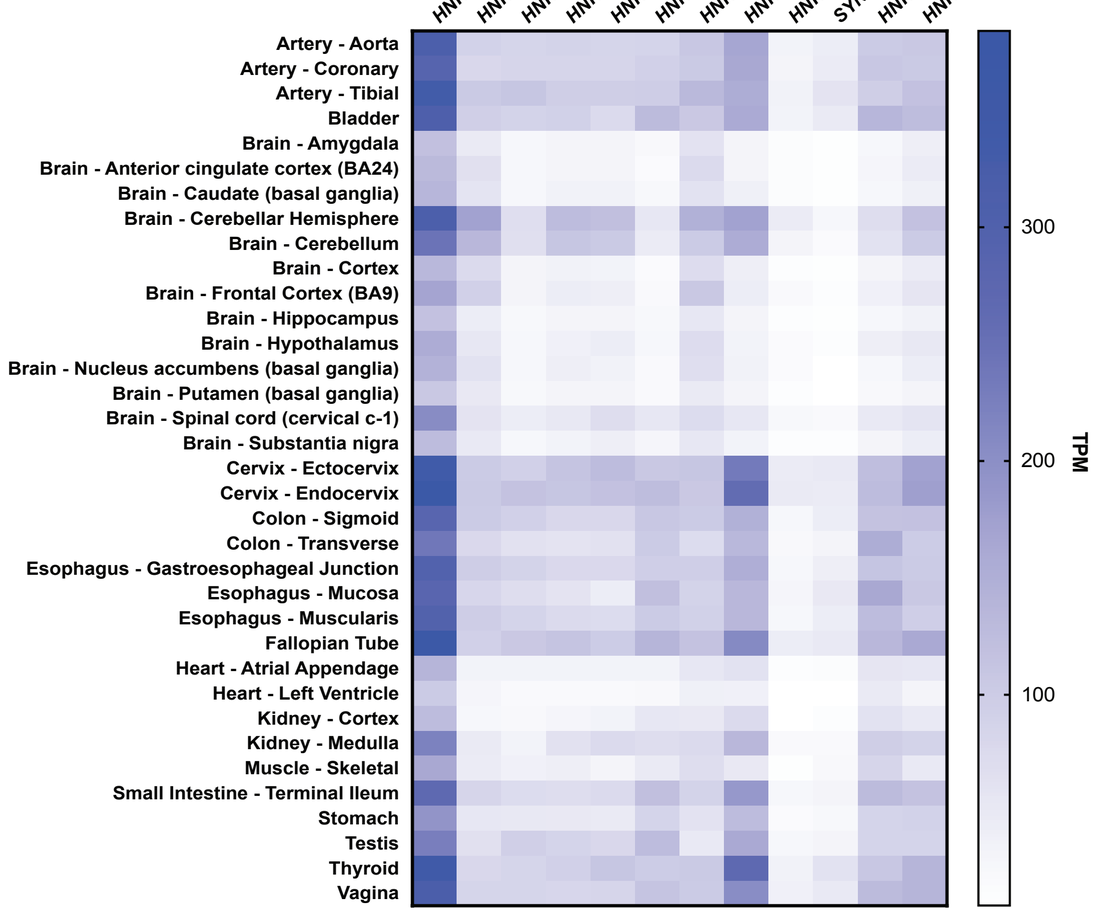
Source of Variation	% of total variation	P value	P value summary
Interaction	2.359	0.7433	ns
Cell Type	15.68	<0.0001	****
Gene	0.2246	0.0504	ns

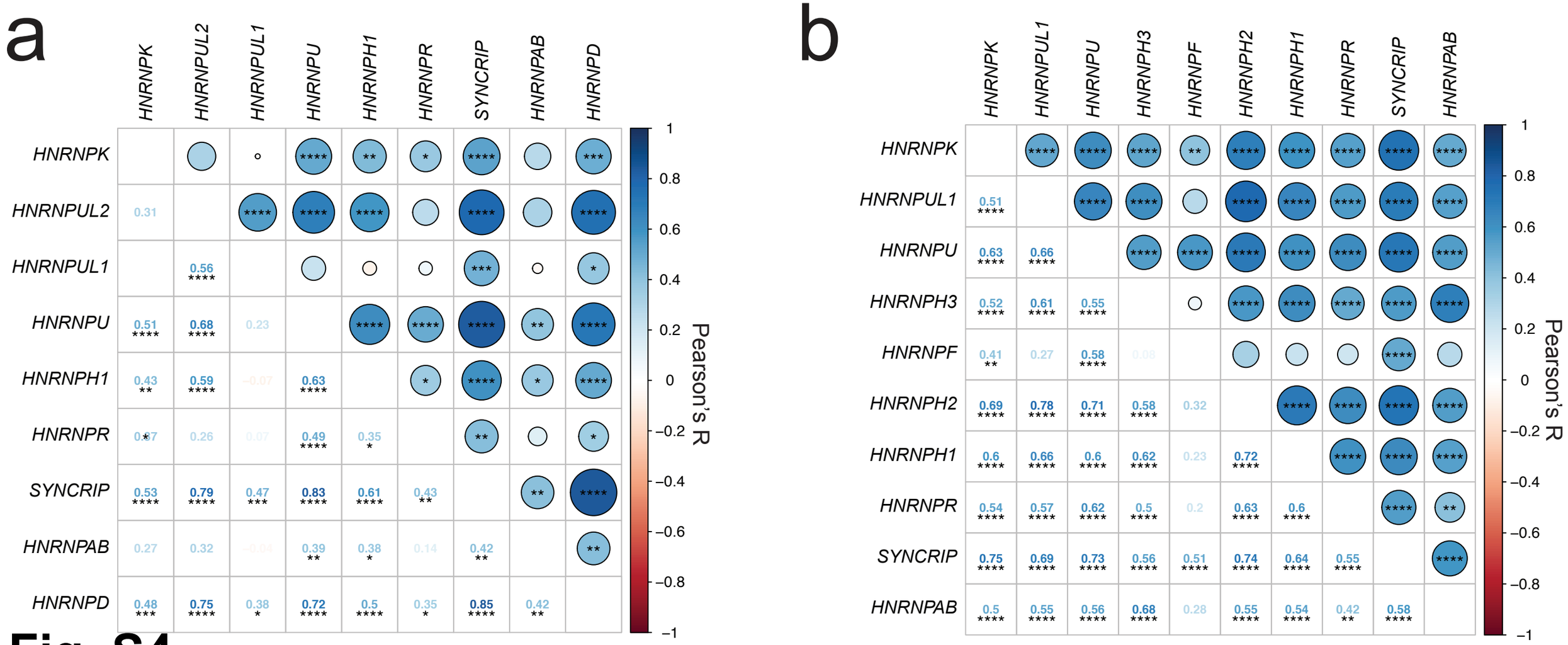


c



d

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HNRNPU
HNRNPH1
HNRNPR
SYNCRIP
HNRNPAB
HNRNPD
Pearson's R
1
0.8
0.6
0.4
0.2
0
−0.2
−0.4
−0.6
−0.8
−1
b
HNRNPK
HNRNPUL1
HNRNPU
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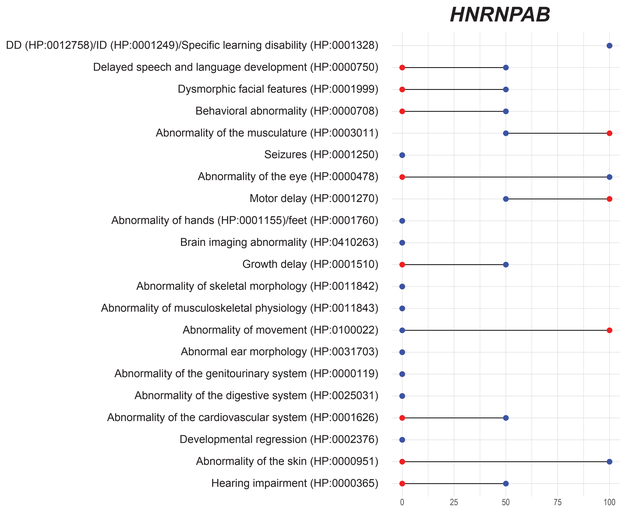
HNRNPF
HNRNPH2
HNRNPH1
HNRNPR
SYNCRIP
HNRNPAB
Pearson's R

Fig. S4

Fig. S5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Abnormality of hands (HP:0001155)/feet (HP:0001760)
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Growth delay (HP:0001510)
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Abnormality of musculoskeletal physiology (HP:0011843)
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Abnormal ear morphology (HP:0031703)
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Abnormality of the digestive system (HP:0025031)
Abnormality of the cardiovascular system (HP:0001626)
Developmental regression (HP:0002376)
Abnormality of the skin (HP:0000951)
Hearing impairment (HP:0000365)
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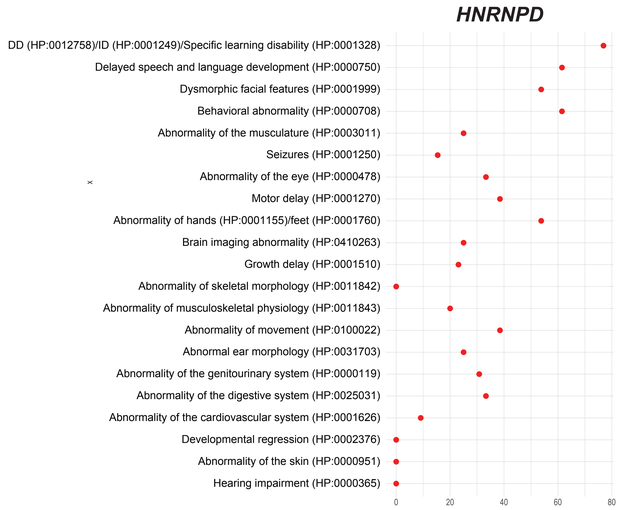
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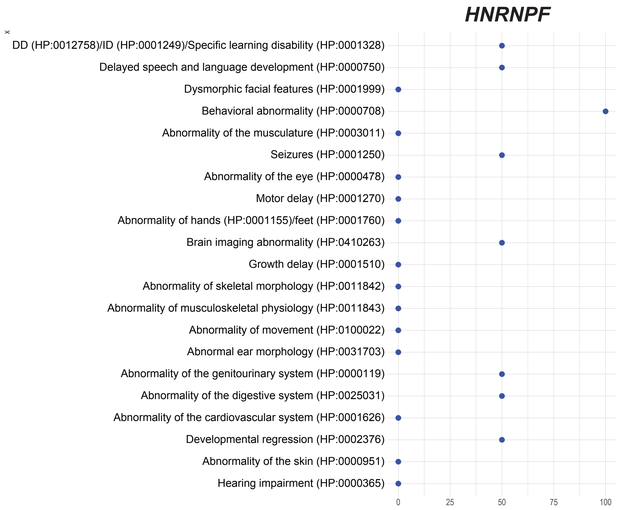
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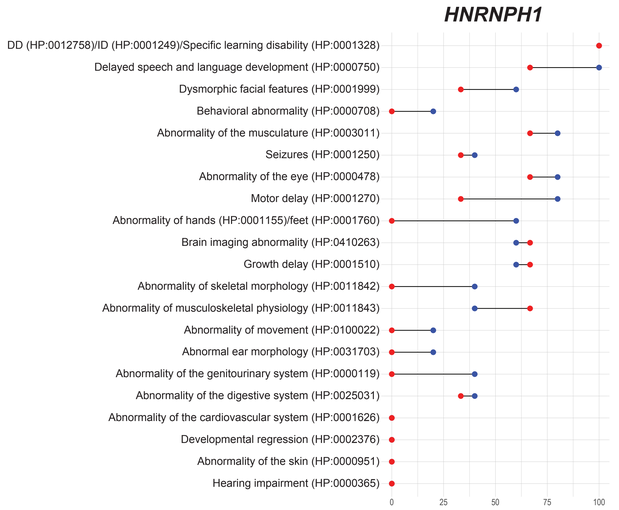
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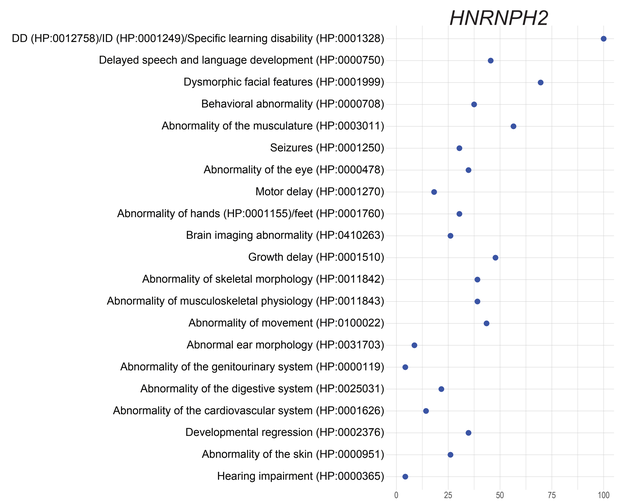
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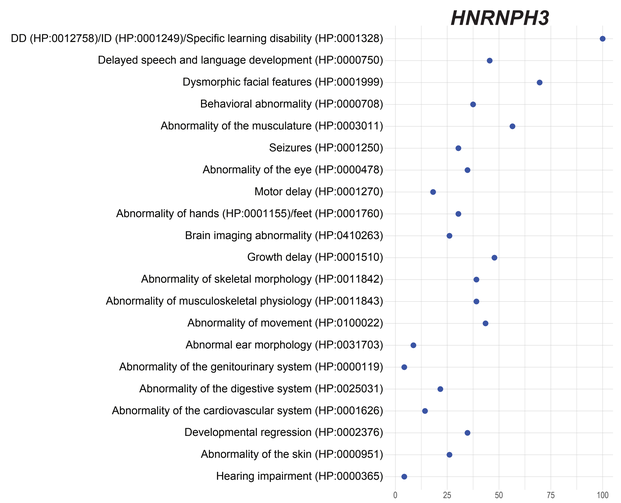
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Abnormality of the digestive system (HP:0025031)
Abnormality of the cardiovascular system (HP:0001626)
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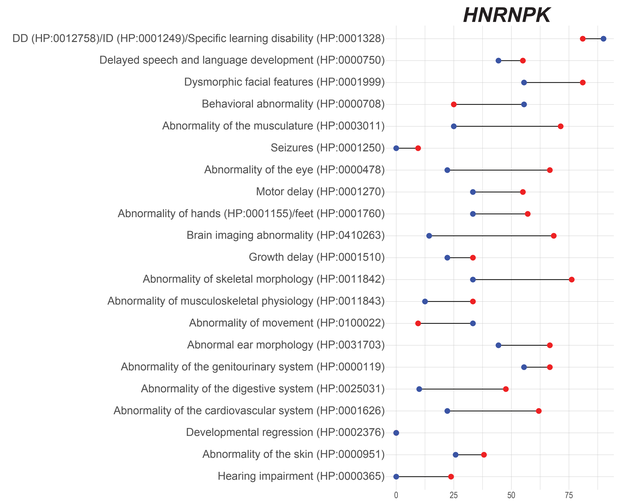
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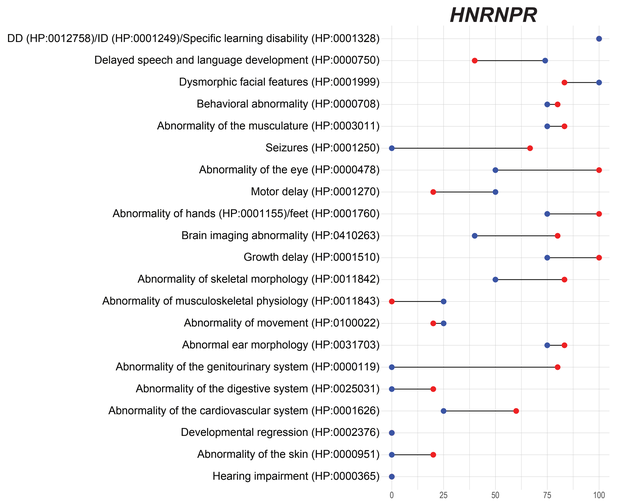
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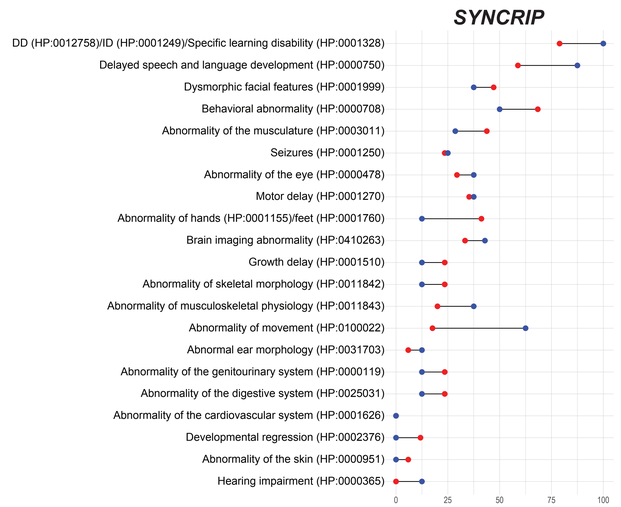
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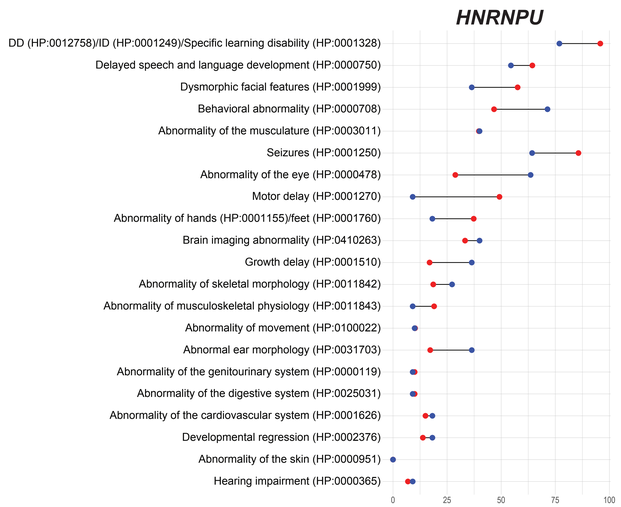
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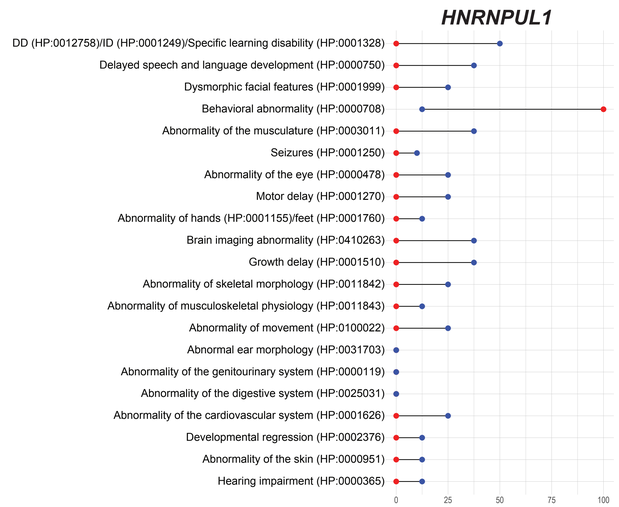
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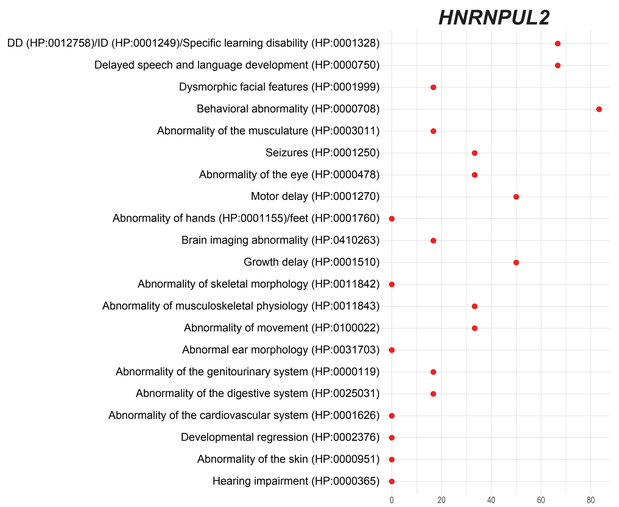
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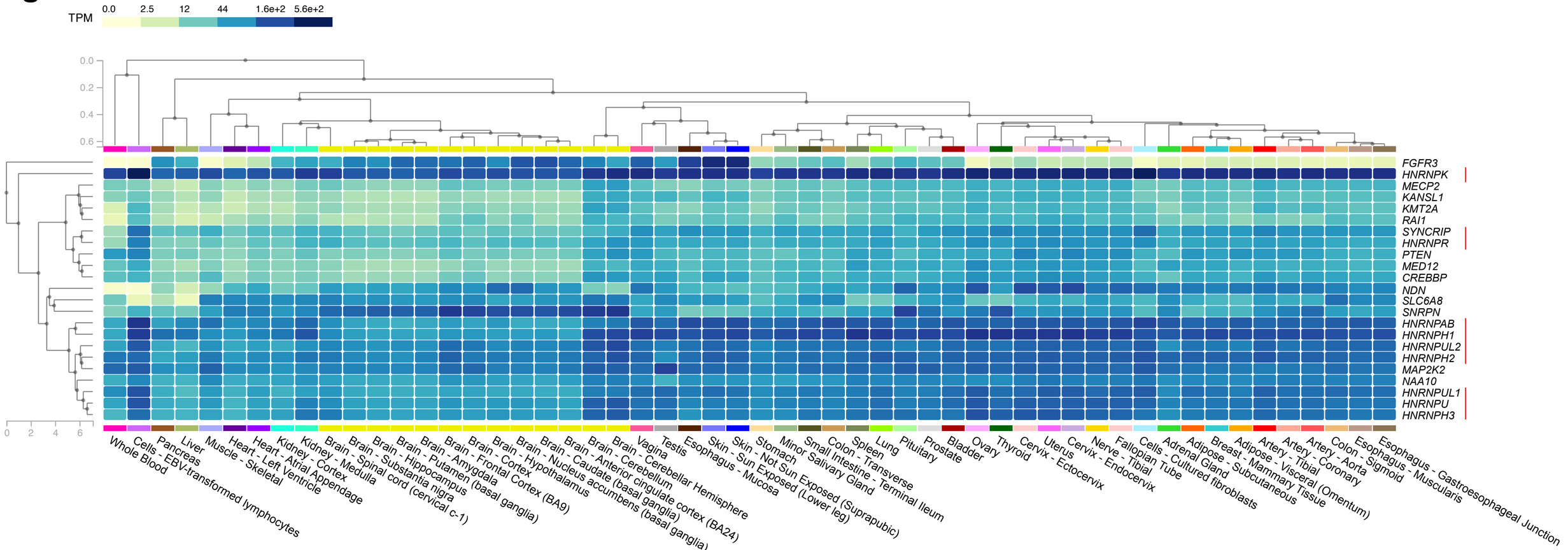
Fig. S6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0.6
0
2
4
6
FGFR3
HNRNPK
MECP2
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KMT2A
RAI1
SYNCRIP
HNRNPR
PTEN
MED12
CREBBP
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HNRNPAB
HNRNPH1
HNRNPUL2
HNRNPH2
MAP2K2
NAA10
HNRNPUL1
HNRNPU
HNRNPH3
Whole Blood
Cells - EBV-transformed lymphocytes
Pancreas
Liver
Muscle - Skeletal
Heart - Left Ventricle
Heart - Atrial Appendage
Kidney - Cortex
Kidney - Medulla
Brain - Spinal cord (cervical c-1)
Brain - Substantia nigra
Brain - Hippocampus
Brain - Putamen (basal ganglia)
Brain - Amygdala
Brain - Cortex
Brain - Frontal Cortex (BA9)
Brain - Hypothalamus
Brain - Nucleus accumbens (basal ganglia)
Brain - Caudate (basal ganglia)
Brain - Anterior cingulate cortex (BA24)
Brain - Cerebellum
Brain - Cerebellar Hemisphere
Vagina
Testis
Esophagus - Mucosa
Skin - Sun Exposed (Lower leg)
Skin - Not Sun Exposed (Suprapubic)
Stomach
Minor Salivary Gland
Small Intestine - Terminal Ileum
Colon - Transverse
Spleen
Lung
Pituitary
Prostate
Bladder
Ovary
Thyroid
Cervix - Ectocervix
Uterus
Cervix - Endocervix
Nerve - Tibial
Fallopian Tube
Cells - Cultured fibroblasts
Adrenal Gland
Adipose - Subcutaneous
Breast - Mammary Tissue
Adipose - Visceral (Omentum)
Artery - Tibial
Artery - Coronary
Artery - Aorta
Colon - Sigmoid
Esophagus - Muscularis
Esophagus - Gastroesophageal Junction

Fig. S1. Dendrogram of hnRNPs based on multiple sequence alignment of canonical amino acid sequences. Colors match those seen in Figure 2. NDD hnRNPs are shown in black boxes.

Fig. S2. Pathogenicity assessment of variation in hnRNPs. A) Gene Variation Intolerance Ranking (GeVIR), loss-of-function observed/expected upper bound fraction (LOEUF), and Variation Intolerant Region Loss-of-Function (VIRLoF) percentiles. Average LOEUF percentile is significantly higher for NDD *HNRNP*s (n = 13) compared to other *HNRNP*s (n = 15). B) Average fold change for GeVIR, LEOUF, and VIRLoF for autosomal dominant (AD) and autosomal recessive (AR) variants. Average LEOUF fold change for AD mutations is significantly higher for NDD *HNRNP*s compared to other *HNRNP*s, with the AD VIRLoF fold change trending in the same direction. The AR LEOUF fold change is trending towards being significantly higher among other *HNRNP*s compared to NDD *HNRNP*s. One-way t-test. * $p < 0.05$

Fig. S3. Expression of *HNRNP*s among adult tissues and the developing human cortex. A) Heatmap of all *HNRNP* expression in developing cortex tissues.
B) Comparison of fold expression of NDD *HNRNP*s to non-NDD *HNRNP*s. C) Heatmap of all *HNRNP* expression (transcript level expression) in adult brain tissues from GTEx.
D) Heatmap of NDD *HNRNP* expression (transcript level expression) in all tissues from GTEx.

Fig. S4. Phenotypic correlations for LGD and missense variant probands.

A) Correlation matrix of phenotypes across *HNRNP* probands with LGD variation (genes with only missense variation excluded) and B) severe missense variation (genes with only LGD variation excluded. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$.

Fig. S5. Phenotypic comparisons between LGD and missense variants by *HNRNP*.

Fig. S6. GTEx expression of NDD *HNRNP*s and genes associated with similarly presenting disorders.